TITLE PAGE

CLINICAL STUDY REPORT NO: 1100702

STUDY INFORMATION

TITLE:	**OTILIA – Ovarian cancer treatment first-line with Avastin®** **Non-interventional surveillance study (NIS) on first-line (FL) Bevacizumab (Avastin®) in combination with carboplatin/paclitaxel in patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer**
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CLINICAL STUDY REPORT APPROVAL

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TABLE OF CONTENTS

1. SYNOPSIS/ABSTRACT

Title

Avastin® – OTILIA – Ovarian cancer treatment first-line with Avastin®

Non-interventional surveillance study (NIS) on first-line (FL) Bevacizumab (Avastin®) in combination with carboplatin/paclitaxel in patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer

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Keywords

Bevacizumab (Avastin®), advanced epithelial ovarian cancer/fallopian tube cancer/primary peritoneal carcinoma, quality of life, Germany, non-interventional surveillance study

Research Question and Objectives

The NIS was designed to evaluate the effectiveness, safety, tolerability and patient reported quality of life (QoL) of first-line bevacizumab (Avastin®) treatment in combination with carboplatin/paclitaxel according to the Summary of Product Characteristics (SmPC) in patients with advanced epithelial ovarian cancer (EOC), fallopian tube cancer (FTC) and primary peritoneal carcinoma (PPC) in daily routine clinical practice in Germany.

A second study phase investigated whether routine clinical practice showed the same effectiveness and safety of bevacizumab (Avastin®) in patients aged ≥70 years as had been determined in randomized clinical trials.

Study objectives

- Effectiveness
  - The main parameter of interest: progression-free survival (PFS)
  - Overall response rate (ORR)
  - Overall survival (OS)

- Safety and tolerability

- Frequencies of (serious) adverse events (AEs) and adverse drug reactions (ADRs) overall and on Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) level with a special focus on arterial hypertension, arterial thromboembolism, gastrointestinal perforations and proteinuria.

- Other objectives
  - Decisive factors for choice of treatment
  - Treatment duration of studied medicinal product
  - Modifications of treatment and reasons thereof
  - Treatment discontinuations and reasons thereof
  - QoL over time assessed by European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaires (QLQ) QLQ-C30 and QLQ-OV28

Study design

This study was a multicenter, non-interventional post-marketing surveillance study conducted in Germany in accordance with section 67 paragraph 6 of the German Medicinal Products Act (Arzneimittelgesetz; AMG), which involved primary data collection.

Target Population

Patients were recruited from 02 February 2012 (first-patient-in, FPI) through 31 December 2016 (last-patient-in, LPI) in 240 study sites across Germany including oncologists and gynecologists in hospitals, outpatient clinics, office-based oncologists and office-based gynecologists (322 sites participated, of these, 82 were non-recruiting). Eligible patients had newly diagnosed advanced EOC, FTC or PPC (FIGO stage IIIB-IV classified by the treating physician according to the respective currently valid version of the FIGO staging system dated 1988 (1,2) or 2014 (3)) with indication for a carboplatin/paclitaxel chemotherapy in combination with bevacizumab (Avastin®) according to SmPC as first-line treatment. In the first phase of the study, eligible patients had to be aged ≥18 years. The second study phase focused on an age-specific subgroup analysis and thus only included patients aged ≥70 years. The maximum duration of documentation period per patient was 27 months after enrollment, comprising a period of intensive documentation during treatment with bevacizumab (Avastin®) for up to 15 months or until premature discontinuation due to progression, and a follow-up (FU) period with less intensive documentation every 6 months for a maximum of 12 months. The individual FU period was independent of whether the treatment was still ongoing, already terminated or had been changed to a different treatment. Database lock was performed on 27 September 2019.

Study size

In this study 1,090 of patients have been enrolled from 240 sites. Of these, 266 patients were excluded from final data analysis as they did not meet the inclusion criteria, did not receive at least one dose of bevacizumab (Avastin®) or were treated “off-label” at study start.

Studied medicinal product

Avastin® (bevacizumab)

Variables

The following variables were captured from medical records as per documentation procedure in routine clinical practice:

- Demographic characteristics and medical history
- Diagnosis of advanced EOC, FTC or PPC
- Tumor anamnesis including tumor stage, type of histological classification, histologic grading
- Primary surgery method, residual tumor burden
- Prior therapies
- Concomitant medication
- Anamnesis and treatment of hypertension, if present
- Selected hematologic and biochemical laboratory
- Tumor marker: cancer antigen 125 (CA-125)
- Information on physician’s criteria to select the treatment
- Bevacizumab (Avastin®) therapy (combination therapy with carboplatin/paclitaxel) including treatment duration, reason for treatment discontinuation and modifications
- Tumor assessment according to physicians’ local practice
- Evaluation of treatment from physician’s point of view
- Supportive therapy
- Data on concomitant palliative radiotherapy
- AEs including AEs requiring expedited reporting, serious AEs (SAEs), ADRs, serious ADRs (SADRs) with special regard to the management of bevacizumab-related adverse events. Pregnancies including management and outcome.
- Subsequent antitumor therapy
- Disease and survival status

Data Sources

The electronic data capture system was provided by iOMEDICO AG, i.e. the contract research organization (CRO) which supported the study as full-service provider. Data were derived from electronic Case Report Form (eCRF)-entries made by the sites as part of routine clinical practice. Data were transferred from source documents (i.e. patient's medical records) to the eCRF. All steps of quality checks were performed and recorded according to iOMEDICO- and Roche-specific standard operating procedures (SOPs).

Paper-based QLQs (EORTC QLQ-C30 and QLQ-OV28) answered at baseline and during treatment were send back to the iOMEDICO AG by the patient. Receipt, tracking and scan of the questionnaires was performed by iOMEDICO AG. Paper-based patient questionnaires served as source documents. Scanned data from questionnaires were saved on a separate scan database.

Statistical and Epidemiological Methods

The analysis of this non-interventional study will be exploratory and primarily use descriptive statistical methods. Due to the exploratory nature of the NIS, there was no adjustment for multiplicity. All analyses were performed for the Core analysis population (CAP) and age subgroup. Selected analyses were also provided for the surgery subgroup.

The primary endpoint PFS was defined as the time from the first administration of bevacizumab (Avastin®) to disease progression or death from any cause. PFS was analyzed by Kaplan-Meier survival methodology. The absolute and relative frequencies of events (i.e. disease progression or death) are given. Median as well as first quartile (Q1) and third quartile (Q3) are presented along with their 95% confidence interval (CI). In addition, PFS rates are reported for the months 6, 12 and 18. In order to assess the effect of selected covariates on PFS, a multivariate Cox regression was performed.

Secondary Outcome measures were ORR and OS, frequencies of (serious) AEs and ADRs. ORR was defined as the percentage of patients in whom a partial or complete remission of tumor could be achieved. OS was defined as the time from first administration of bevacizumab (Avastin®) to the date of death from any cause.

All time-to-event data (PFS, OS, treatment duration) were analyzed by using the Kaplan-Meier method. Data is presented by number of events, median, Q1 and Q3 and time-rates (e.g. 6-month rate) as appropriate, together with 95% CI.

Frequencies of (serious) AEs and ADRs were reported for overall and on MedDRA PT level and included a special focus on arterial hypertension, arterial thromboembolism, gastrointestinal perforations and proteinuria.

Analysis populations

- Study population (CAP): All analyses were performed for the CAP, which consisted of all eligible patients included in the study who received at least one dose of bevacizumab (Avastin®). Patients with "off-label" use of bevacizumab (Avastin®) during the study were only included in this analysis population if administration of bevacizumab (Avastin®) was "in-label" at their study start. Patients with "off-label" use of bevacizumab (Avastin®) at study start were excluded from this analysis population but AEs of these patients were compiled in a listing. The patient assignment to the CAP was performed at the Data Review Meeting prior to database hard lock. The only exception where the CAP was not used was the QoL analyses. QoL analyses were performed with all patients of the CAP who were willing to participate in the QoL assessment and had signed a valid ICF.

Subgroups

- Age subgroup: A subgroup analysis denoted as "age subgroup" was performed in addition to the analyses on CAP in total. The analyses were conducted stratified by age at enrollment (<70 / ≥70 years).

- Surgery subgroup: A subgroup analysis denoted as "surgery subgroup" was performed in addition to the analyses on CAP in total. Specified analyses were conducted stratified by prior surgery (yes/no).

Results

Patient disposition and reasons for exclusion from CAP: Total and Age subgroup

	Total	Patients <70 years	Patients ≥70 years
Number of patients enrolled	1,090 (100.0)	583 (100.0)	507 (100.0)
Number of patients treated with bevacizumab (Avastin®)	1,041 (95.5)	560 (96.1)	481 (94.9)
Number of patients in CAP (n, %)	824 (75.6)	453 (77.7)	371 (73.2)
Number of patients excluded from CAP (n, %)[1]	266 (24.4)	130 (22.3)	136 (26.8)

	Total	Patients <70 years	Patients ≥70 years
Reasons for exclusion from CAP (n, %)[1]			
Avastin® not in combination with carboplatin or paclitaxel	17 (1.6)	12 (2.1)	5 (1.0)
Avastin® monotherapy from 1st Avastin® cycle	10 (0.9)	4 (0.7)	6 (1.2)
Dose I – 1st Avastin® dose not according to SmPC (>15 mg/kg)	7 (0.6)	2 (0.3)	5 (1.0)
Dose II – 1st Avastin® dose not according to SmPC (<15 mg/kg)	77 (7.1)	37 (6.3)	40 (7.9)
FIGO staging I – FIGO stadium IIIA	1 (0.1)	1 (0.2)	
FIGO staging I – FIGO stadium <IIIB	13 (1.2)	6 (1.0)	7 (1.4)
Frequency of Avastin® not according to SmPC	79 (7.2)	35 (6.0)	44 (8.7)
Indication	5 (0.5)	1 (0.2)	4 (0.8)
No IMP given	49 (4.5)	23 (3.9)	26 (5.1)
No cycle with all three substances	107 (9.8)	49 (8.4)	58 (11.4)
Prior Therapies I – Avastin® therapy before operation	1 (0.1)	1 (0.2)	
Prior Therapies II – First line therapy > one month	9 (0.8)	6 (1.0)	3 (0.6)
Retrospective enrollment (>42 days)	4 (0.4)	2 (0.3)	2 (0.4)

CAP = Core analysis population; FIGO = Fédération Internationale de Gynécologie et d'Obstétrique; IMP = Investigational medicinal product; N/n = Number; SmPC = Summary of product characteristics.
[1]Reasons for exclusion from CAP are explained in more detail in the minutes of the data review meeting. Multiple reasons for exclusion from CAP possible.

Demographics and baseline characteristics

In the CAP the median age (Minimum-Maximum (Min-Max)) of the patients at start of therapy was 68 years (25.9-83.4 years). At start of therapy 45.3% (n=373) of patients were aged ≥70 years (two patients were aged <70 years at enrollment but had already reached an age of ≥70 years at the start of therapy. Hence, in the CAP two more patients are aged ≥70 years at start of therapy (n=373) in comparison to the subgroup of patients aged ≥70 years (n=371) for which age at enrollment is decisive). Most patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (n=297; 38.2%) or 1 (n=389; 50.0%). 365 patients (44.3%) had ongoing comorbidities at start of first bevacizumab (Avastin®) administration and persistent arterial hypertension was present in 339 patients (41.1%). Most patients had a Charlson Comorbidity Index of 0 (n=644; 78.2%). The most frequent type of tumor was epithelial ovarian carcinoma (n=662; 80.3%) and serous tumors were the most frequent histological type (n=606; 77.8%). Tumors were mostly diagnosed at Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stage IIIC (n=472; 57.3%) and with poor differentiation (G3: n=565; 68.6%) (tumor stage was determined by the treating physician according to the respective currently valid version of the FIGO staging system dated 1988 (1,2) or 2014 (3)).

Demographics and baseline characteristics – Age subgroups

The median age (Min-Max) at start of therapy in the subgroup of patients <70 years was 58.4 years (25.9-70.2 years) whereas it was 74.6 years (70.1-83.4 years) in patients ≥70 years (age at enrollment could be younger than age at therapy start, thus two patients were included in the subgroup of patients <70 years, although they were ≥70 years at therapy start). In the subgroup of patients ≥70 years less patients had an ECOG performance status of 0 (28.6% vs. 45.7%) and more patients had an ECOG performance status of 1 (56.9% vs. 44.6%), 2 (12.0% vs. 8.3%) or 3 (2.6% vs. 1.4%). Older patients had more medical conditions ongoing at first bevacizumab (Avastin®) administration (60.1% vs. 31.3%) and more persistent arterial hypertension (55.8% vs. 29.1%). Accordingly, in the subgroup of patients ≥70 years less patients had a Charlson Comorbidity Index of 0 (75.5% vs. 80.4%). In both age subgroups of patients <70 and ≥70 years the most frequent type of tumor was epithelial ovarian carcinoma (81.0% vs. 79.5%) and serous tumors were the most frequent histological type (75.7% vs. 80.5%). In both age subgroups tumors were mostly diagnosed at FIGO stage IIIC (58.5% vs. 55.8%) and with poor differentiation (G3: 68.9% vs. 68.2%).

Bevacizumab (Avastin®) therapy

	Age subgroup		
	CAP	Patients <70 years	Patients ≥70 years
Patients, N	824	453	371
Treatment duration[1]			
Events, n (%)	453 (55.0%)	227 (50.1%)	226 (60.9%)
25% quantile [95% CI]	6.7 [5.7, 7.8]	7.9 [6.4, 9.1]	4.9 [4.1, 6.7]
Median [95% CI]	13.8 [12.7, 14.5]	14.6 [13.9, 15.2]	12.5 [11.1, 13.8]
75% quantile [95% CI]	NA [17.5, NA]	NA [18.0, NA]	17.5 [16.1, NA]
Total number of administrations			
n applications	12,431	7,153	5,278
Median	18.0	19.0	17.0
Min	1.0	1.0	1.0
Max	25.0	25.0	24.0
Total (cumulative) dose (mg/kg)			
Median	267.1	284.7	239.3
Min	14.7	14.8	14.7
Max	381.5	381.5	374.9
Dose intensity (mg/kg per week)			
Median	5.1	5.1	5.1
Min	2.3	2.3	2.4
Max[2]	108.1	108.1	106.8
Any treatment modification	653 (79.2%)	361 (79.7%)	292 (78.7%)

	Age subgroup		
	CAP	Patients <70 years	Patients ≥70 years
Patients, N	824	453	371
Kind of treatment modification[3]			
Dose increase	50 (6.1%)	32 (7.1%)	18 (4.9%)
Dose reduction	57 (6.9%)	22 (4.9%)	35 (9.4%)
Therapy delay[4]	227 (27.5%)	122 (26.9%)	105 (28.3%)
Therapy interruption[4]	556 (67.5%)	303 (66.9%)	253 (68.2%)
Reason for treatment modification[3]			
Patient's wish	148 (18.0%)	81 (17.9%)	67 (18.1%)
Physician decision	590 (71.6%)	328 (72.4%)	262 (70.6%)
Toxicity	110 (13.3%)	55 (12.1%)	55 (14.8%)
Visit created by mistake	21 (2.5%)	8 (1.8%)	13 (3.5%)

CAP = Core analysis population; CI = Confidence interval; Max = Maximum; Min = Minimum; N/n = Number; NA = Not reached.
[1]Treatment duration of bevacizumab (Avastin®) was estimated using the Kaplan-Meier method. [2]Maximum dose intensity of bevacizumab (Avastin®) seems to be a mistake in documentation. [3]Multiple observations provided. [4]There was no definition of therapy delay and therapy interruption or the difference of these two modifications provided in the observational plan or eCRF. It was at the discretion of the documenting person which of the two terms he/she chose for the treatment modification.

Carboplatin and Paclitaxel therapy

	CAP	
	Carboplatin	Paclitaxel
Patients, N	824	824
Treatment duration[1]		
Median	3.5	3.5
Min	0.0	0.0
Max	17.7	14.1
Total (cumulative) dose (mg)		
Median	30.0	1,050.0
Min	4.0	120.0
Max	2,893.0	1,575.0
Any treatment modification	354 (43.0%)	387 (47.0%)
Kind of treatment modification[2]		
Dose increase	31 (3.8%)	12 (1.5%)
Dose reduction	98 (11.9%)	110 (13.3%)
Therapy delay[3]	124 (15.0%)	112 (13.6%)
Therapy interruption[3]	198 (24.0%)	246 (29.9%)
Reason for treatment modification[2]		
Patient's wish	46 (5.6%)	44 (5.3%)
Physician decision	253 (30.7%)	258 (31.3%)
Toxicity	100 (12.1%)	141 (17.1%)
Visit created by mistake	9 (1.1%)	8 (1.0%)

CAP = Core analysis population; Max = Maximum; Min = Minimum; N/n = Number.
[1]Treatment duration displayed in months. Patients who received only one dose of carboplatin/paclitaxel the treatment duration is 0.03 displayed as 0. [2]Multiple observations provided. [3]There was no definition of therapy delay and therapy interruption or the difference of these two modifications provided in the observational plan or eCRF. It was at the discretion of the documenting person which of the two terms he/she chose for the treatment modification.

Effectiveness

	Age subgroup		
	CAP	Patients <70 years	Patients ≥70 years
Patients, N	824	453	371
Progression-free survival[1]			
Events, n [%][2]	368 (44.7%)	200 (44.2%)	168 (45.3%)
25% quantile [95% CI]	14.1 [12.5, 14.8]	14.3 [12.4, 15.9]	13.8 [11.7, 14.8]
Median [95% CI]	19.4 [18.7, 20.3]	20.0 [18.7, 21.2]	19.3 [17.6, 20.2]
75% quantile [95% CI]	23.6 [22.4, 24.8]	23.9 [22.4, 26.3]	23.3 [21.5, 24.6]
6-month rate [95%-CI]	95.2% [93.4, 96.5]	97.2% [95.1, 98.4]	92.6% [89.3, 95.0]
12-month rate [95%-CI]	79.5% [76.4, 82.3]	80.2% [75.9, 83.9]	78.7% [73.7, 82.8]
18-month rate [95%-CI]	57.5% [52.9, 61.8]	60.1% [54.0, 65.7]	54.2% [47.2, 60.6]
Overall survival[1]			
Events, n (%)[3]	181 (22.0%)	86 (19.0%)	95 (25.6%)
25% quantile [95% CI]	19.3 [17.8, 20.4]	20.3 [18.2, 22.5]	18.6 [16.7, 20.0]
Median [95% CI]	24.6 [23.7, 26.3]	26.7 [23.9, 39.8]	22.9 [21.7, 25.5]
75% quantile [95% CI]	31.5 [27.8, 47.0]	39.8 [28.9, 54.1]	27.1 [25.6, 35.2]
12-month rate [95%-CI]	91.1% [88.7, 93.0]	92.3% [89.1, 94.5]	89.6% [85.6, 92.5]
18-month rate [95%-CI]	78.5% [74.4, 82.1]	81.0% [75.4, 85.4]	75.5% [68.8, 80.9]
24-month rate [95%-CI]	53.3% [46.1, 59.8]	59.5% [49.7, 68.1]	45.5% [35.2, 55.3]
Best response			
N (non-missing)	707	392	315
CR	307 (43.4%)	195 (49.7%)	112 (35.6%)
PR	203 (28.7%)	106 (27.0%)	97 (30.8%)
ORR	510 (72.1%)	301 (76.8%)	209 (66.3%)
SD	153 (21.6%)	66 (16.8%)	87 (27.6%)
PD	27 (3.8%)	16 (4.1%)	11 (3.5%)
Not evaluable	17 (2.4%)	9 (2.3%)	8 (2.5%)
Missing	117	61	56

CAP = Core analysis population; CI = Confidence interval; CR = Complete response; N/n = Number; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease.
[1]Progression-free survival and overall survival was estimated using the Kaplan-Meier method. [2]Due to the low number of events PFS data have to be interpreted with caution. [3]Due to the low number of events the present OS data are no reliable estimators.

Safety

Number of Patients with (serious) Treatment-emergent adverse event (TEAEs)

	Total[1] (N = 824)	Cases
Patients reported with respective TEAE, n (%), n (cases)		
Any TEAE	616 (74.8%)	3,645
Any serious TEAE	222 (26.9%)	438
Any TEAE with CTCAE severity grade ≥ grade 3	317 (38.5%)	583
Any causally related TEAE[2]	330 (40.0%)	1,036
Any causally related serious TEAE[2]	72 (8.7%)	96
Any TEAE leading to discontinuation of bevacizumab (Avastin®) treatment[3]	145 (17.6%)	206

CTCAE = Common Terminology Criteria for Adverse Events; N/n = Number; TEAE = Treatment-emergent adverse event.
[1]Patients can occur in more than one category of the table. [2]Causally related TEAEs were defined as those with a possible, probable or definite relationship to bevacizumab (Avastin®). [3]TEAE leading to discontinuation of bevacizumab (Avastin®) treatment = TEAE documented as underlying adverse event for end of treatment (EOT). The number of TEAEs leading to discontinuation of bevacizumab (Avastin®) treatment might differ from the number of AEs documented as reason for end of treatment due to AEs not classified as treatment-emergent, however documented as underlying AE for EOT.

Most frequent (serious) TEAEs

- Overall 616 (74.8%) patients were reported with a Treatment-emergent adverse event (TEAE) (any Common Terminology Criteria for Adverse Events (CTCAE) grade).
    - The most frequently reported TEAEs (≥10% of patients) were hypertension (n=141; 17.1%; TEAE of particular interest), fatigue (n=132; 16.0%), polyneuropathy (n=120; 14.6%), nausea (n=112; 13.6%), anemia (n=100; 12.1%); constipation (n=92; 11.2%), alopecia (n=82; 10.0%), and diarrhea (n=82; 10.0%).
    - With regards to the other TEAEs of particular interest (other than hypertension reported above), proteinuria was reported in 35 (4.2%) patients, large intestine perforation in 6 (0.7%) patients, intestinal perforation in 3 (0.4%) patients, gastric perforation in 2 (0.2%) patients and arterial embolism in 1 (0.1%) patient.
- Overall 222 (26.9%) patients were reported with a serious TEAE.
    - The most frequently reported serious TEAEs (≥1.0% of patients) were pyrexia (n=15; 1.8%), general physical health deterioration (n=14; 1.7%), abdominal pain (n=13; 1.6%), ileus (n=13; 1.6%), hypertension (n=11; 1.3%; TEAE of particular interest), urinary tract infection (n=10; 1.2%), dyspnea (n=8; 1.0%) and leukopenia (n=8; 1.0%).
    - Regarding the other TEAEs of particular interest (other than hypertension reported above), 5 (0.6%) patients were reported with a serious large intestine perforation, 3 (0.4%) patients with a serious intestinal perforation, 2 (0.2%) patients with a

serious gastric perforation and 2 (0.2%) patients with serious proteinuria. No patients were documented with a serious arterial embolism.

Number of Patients with (serious) causally related TEAEs

	Total[1] (N = 824)	Cases
Patients reported with respective (serious) causally related TEAE, n (%), n (cases)		
Any TEAE	*616 (74.8%)*	*3,645*
Any causally related TEAE[2]	330 (40.0%)	1,036
Any causally related serious TEAE[2]	72 (8.7%)	96
Any causally related fatal TEAE[2]	5 (0.6%)	6

N/n = Number; TEAE = Treatment-emergent adverse event.
[1]Patients can occur in more than one category of the table. [2]Causally related TEAEs were defined as those with a possible, probable or definite relationship to bevacizumab (Avastin®).

Most frequent (serious) causally related TEAEs

- Overall, 330 (40.0%) patients were reported with TEAEs assessed as causally related to bevacizumab (Avastin®).
    - The most frequently reported causally related TEAEs (≥5% of patients) were hypertension (n=102; 12.4%; TEAE of particular interest) and fatigue (n=58; 7.0%).
    - With regards to the other TEAEs of particular interest (other than hypertension reported above), 28 (3.4%) patients were reported with proteinuria, 4 (0.5%) patients with large intestine perforation, 1 (0.1%) patient with intestinal perforation, 1 (0.1%) with gastric perforation and 1 (0.1%) patient with arterial embolism, all events of which were causally related to bevacizumab (Avastin®).

Number of Deaths and Fatal TEAEs

Total CAP *(N=824)*	Patients[1] N (%)	Cases N
Total number of deaths, n, %	181 (22.0%)	
Patients reported with fatal TEAE, n, %, n (cases)		
Any TEAE	*616 (74.8%)*	*3,645*
All fatal TEAE[2]	30 (3.6%)	43
Fatal causally related TEAE[3]	5 (0.6%)	6
Fatal non-related TEAE[3]	24 (2.9%)	29
Fatal TEAE – causality unknown[3]	5 (0.6%)	8

CAP = Core analysis population; N/n = Number; TEAE = Treatment-emergent adverse event.

[1]Patients can occur in more than one category of the table. [2]For one patient (pat ID 215001), the same fatal TEAE (ileus) was reported twice, once as related to bevacizumab (Avastin®) with CTCAE severity grade 4 and once as non-related with CTCAE severity grade 5. [3]Causally related TEAEs were defined as those with a possible, probable or definite relationship to bevacizumab (Avastin®).

Most frequent fatal TEAEs

- In the total population, 30 (3.6%) patients were reported with fatal TEAEs.
    - The most frequently reported fatal events (≥0.5% of patients) were death (n=6; 0.7%) and malignant neoplasm progression (n=4; 0.5%).
    - With regards to TEAEs of particular interest, a fatal intestinal perforation was reported in 3 (0.4%) patients, whereas no fatal events of large intestine perforation, gastric perforation, arterial embolism, hypertension, or proteinuria were documented.

Most frequent fatal causally related TEAEs

- Five (0.6%) patients were documented with a fatal TEAE related to bevacizumab (Avastin®) with reported PTs as follows (6 events in total).
    - Cerebrovascular accident
    - Intestinal perforation
    - Urosepsis
    - Acute kidney injury
    - Ileus
    - Death
- Of these 6 fatal causally related TEAEs, one patient was reported with 2 fatal events (urosepsis and acute kidney injury).

Conclusions

The data obtained in the non-interventional study OTILIA (NCT01697488) provide a valuable and important estimate of how clinical efficacy documented in controlled, randomized clinical trials translates into effectiveness in routine clinical practice in Germany.

While OTILIA demonstrates that first-line bevacizumab (Avastin®) therapy in combination with carboplatin/paclitaxel in patients with newly diagnosed FIGO stage IIIB-IV EOC, FTC and PPC is effective in routine clinical practice, a direct comparison with the results obtained in the pivotal

trials is subject to limitations due to differences in patient characteristics and study settings including clear cut inclusion and exclusion criteria, assessment schemes and assessment specifications.

The safety information reported in this study is consistent with the known safety profile of bevacizumab (Avastin®). No new safety signals emerged.

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
AMG	German Medicinal Products Act (deutsches Arzneimittelgesetz)
BMI	Body mass index
CAP	Core analysis population
CA-125	Cancer antigen 125
CDB	Clinical database CRO
CI	Confidence interval
CR	Complete response
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Database lock
DMP	Data management plan
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EOC	Epithelial ovarian cancer
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End of treatment
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
FL	First-line
FPI	First-patient-in
FTC	Fallopian tube cancer
FU	Follow-Up
GCIG	Gynaecologic cancer intergroup
G-CSF	Granulocyte-colony stimulating factor
HR	Hazard ratio
ICF	Informed consent form
IMP	Investigational medicinal product
IRC	Independent review of radiologic and clinical data
LoE	Lack of Efficacy
LPI	Last-patient-in
LVEF	Left Ventricular Ejection Fraction

Abbreviation	Definition
MAH	Marketing authorization holder
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
NA	Not applicable / Not reached
NCI	National Cancer Institute
NIO	Niedergelassener internistischer Onkologe / Office-based medical oncologist
NIS	Non-interventional study
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PPC	Primary peritoneal carcinoma
PR	Partial response
PT	Preferred term
QLQ	Quality of life questionnaire
QoL	Quality of Life
Q1	First quartile
Q3	Third quartile
RECIST	Response Evaluation Criteria In Solid Tumors
SADR	Serious adverse drug reaction
SAE	Serious adverse event
(S)AE	(Serious) Adverse event
SAERT	Serious Adverse Event Reconciliation Tool
SAP	Statistical analysis plan
SD	Stable disease
SD / StD	Standard deviation
SDB	Safety database Roche
SmPC	Summary of Product Characteristics
SOC	System organ class
SOP	Standard operating procedure
STIAMP	Suspected Transmission of Infectious Agent by Medicinal Product
TEAE	Treatment-emergent adverse event
TFL	Tables, Figures, Listings
TMF	Trial master file

Abbreviation	Definition
VEGF	Vascular endothelial growth factor

3. MILESTONES

Table 3-1 Study milestones

Milestone	Actual Date	Comments, if any
Start of data collection	02 February 2012	FPI
End of data collection	31 March 2019	Last follow-up of last patient
Study status report 1	14 June 2012	
Study status report 2	03 August 2012	
Study status report 3	03 September 2012	
Study status report 4	02 October 2012	
Study status report 5	05 November 2012	
Study status report 6	07 November 2012	
Study status report 7	03 December 2012	
Study status report 8	02 January 2013	
Study status report 9	04 February 2013	
Study status report 10	01 March 2013	
Study status report 11	02 April 2013	
Study status report 12	02 May 2013	
Study status report 13	03 June 2013	
Study status report 14	01 July 2013	
Study status report 15	29 July 2013	
Study status report 16	29 August 2013	
Study status report 17	27 September 2013	
Study status report 18	29 October 2013	
Study status report 19	02 December 2013	
Study status report 20	02 January 2014	
Study status report 21	03 February 2014	
Study status report 22	03 March 2014	
Study status report 23	01 April 2014	
Study status report 24	03 May 2014	
Study status report 25	02 June 2014	
Study status report 26	01 July 2014	
Study status report 27	01 August 2014	
Study status report 28	01 September 2014	
Study status report 29	01 October 2014	
Study status report 30	03 November 2014	

Study status report 31	01 December 2014
Study status report 32	02 January 2015
Study status report 33	02 February 2015
Study status report 34	02 March 2015
Study status report 35	01 April 2015
Study status report 36	04 May 2015
Study status report 37	01 June 2015
Study status report 38	01 July 2015
Study status report 39	03 August 2015
Study status report 40	05 August 2015
Study status report 41	01 September 2015
Study status report 42	01 October 2015
Study status report 43 / study progress report 1	02 November 2015
Study status report 44 / study progress report 2	01 December 2015
Study status report 45 / study progress report 3	04 January 2016
Study status report 46 / study progress report 4	01 February 2016
Study status report 47 / study progress report 5	01 March 2016
Study status report 48 / study progress report 6	01 April 2016
Study status report 49 / study progress report 7	02 May 2016
Study status report 50 / study progress report 8	01 June 2016
Study status report 51 / study progress report 9	01 July 2016
Study status report 52 / study progress report 10	01 August 2016
Study status report 53 / study progress report 11	01 September 2016
Study status report 54 / study progress report 12	04 October 2016
Study status report 55 / study progress report 13	02 November 2016
Study status report 56 / study progress report 14	01 December 2016
Study status report 57 / study progress report 15	02 January 2017

Study status report 58 / study progress report 16	09 January 2017
Study status report 59 / study progress report 17	01 February 2017
Study status report 60 / study progress report 18	01 March 2017
Study status report 61 / study progress report 19	03 April 2017
Study status report 62 / study progress report 20	02 May 2017
Study status report 63 / study progress report 21	01 June 2017
Study status report 64 / study progress report 22	03 July 2017
Study status report 65 / study progress report 23	01 August 2017
Study status report 66 / study progress report 24	01 September 2017
Study status report 67 / study progress report 25	04 October 2017
Study status report 68 / study progress report 26	02 November 2017
Study status report 69 / study progress report 27	01 December 2017
Study status report 70 / study progress report 28	02 January 2018
Study status report 71 / study progress report 29	01 February 2018
Study status report 72 / study progress report 30	01 March 2018
Study status report 73 / study progress report 31	03 April 2018
Study status report 74 / study progress report 32	02 May 2018
Study status report 75 / study progress report 33	04 June 2018
Study status report 76 / study progress report 34	03 July 2018
Study status report 77 / study progress report 35	01 August 2018
Study status report 78 / study progress report 36	04 September 2018
Study status report 79 / study progress report 37	01 October 2018

Study status report 80 / study progress report 38	05 November 2018	
Study status report 81 / study progress report 39	04 December 2018	
Study progress report 40	12 December 2018	
Study status report 82 / study progress report 41	07 January 2019	
Study status report 83 / study progress report 42	01 February 2019	
Study status report 84 / study progress report 43	04 March 2019	
Study status report 85 / study progress report 44	01 April 2019	
Study status report 86 / study progress report 45	03 May 2019	
Study status report 87 / study progress report 46	05 June 2019	
Study status report 88 / study progress report 47	02 July 2019	
Study status report 89 / study progress report 48	02 August 2019	
Study status report 90 / study progress report 49	03 September 2019	
Study status report 91 / study progress report 50	01 October 2019	
Study status report 92 / study progress report 51	05 November 2019	
Study status report 93 / study progress report 52	07 January 2020	
Interim report 1	30 June 2014	The date of respective interim report reflects the time point for database cut.
Interim report 2	06 January 2016	
Interim report 3	31 January 2017	
Final report of study results	18 May 2020	DBL: 27 September 2019

DBL = Database lock; FPI = First-patient-in

4. RATIONALE AND BACKGROUND

Ovarian cancer represents the eighth most common cancer type among women worldwide, with 295,414 new cases of ovarian cancer and 184,799 cancer deaths in 2018 (4). While morbidity rates increase up to the age of 85, 5-10% of cases are already diagnosed at an age <45 years (5). Despite therapeutic advances, especially in the treatment of earlier

stages of ovarian cancer, the increase in overall survival (OS) remains poor and high mortality rates persist. While 5-year survival rates may range up to 90% for patients in the early stage (I), it may be only 10% for patients in an advanced stage (III/IV) (6).

The disease stage at time of primary diagnosis has a major influence on prognosis (6). However, symptoms in ovarian cancer are often unspecific which makes a clear association to ovarian cancer difficult (7,8). Approximately 75 % of cases are diagnosed at an advanced stage (5). At this stage however, therapeutic efficacy is limited (9). For nearly all patients at an advanced stage (≥FIGO IIb (Fédération Internationale de Gynécologie et d'Obstétrique)), the disease will become progressive and thus often incurable, depending on the risk profile (9). Thus, the therapeutic need is particularly high for patients at an advanced stage.

At the time the non-interventional study (NIS) OTILIA was set up, the standard primary therapy consisted of an ideally complete tumor resection, followed by a platinum- and taxan-based chemotherapy (10). The combination therapy of Carboplatin and Paclitaxel represented the standard therapy regime for patients with advanced ovarian cancer (10).

Bevacizumab (Avastin®) is a recombinant humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF) and inhibits the processes mediated by this pro-angiogenic factor (11) and thus vascularization. By reducing the permeability of tumor-associated capillaries and the interstitial pressure, the perfusion with chemotherapeutic agents improves, thus increasing therapeutic efficacy (12). Since VEGF holds a key role in the female reproductive cycle, ovarian cancer is a VEGF-controlled disease (13). It was shown that VEGF expression of tumor cells is associated with the formation of ascites, malignant progression and worse survival prognosis of patients (14,15).

Bevacizumab (Avastin®) has been tested in more than 1,000 phase I-IV trials with more than 40,000 patients for a multitude of tumors as monotherapy or in combination with chemotherapy. The combination of bevacizumab (Avastin®) plus chemotherapy has improved the progression-free survival (PFS) and/or OS for metastatic colorectal cancer, metastatic breast cancer, metastatic renal cell carcinoma and advanced non-small cell lung cancer. Based on these trials, bevacizumab (Avastin®) was approved in more than 100 countries for the treatment of specific forms of colon cancer, breast cancer, lung

cancer, renal cell carcinoma, cervical cancer, and recurrent ovarian cancer. For advanced ovarian cancer (stage IIIB-IV), the combination of bevacizumab (Avastin®) plus carboplatin/paclitaxel was approved in December 2011. Until today, more than 1 million patients have been treated with Avastin®.

Multiple phase II trials investigated the potential of bevacizumab (Avastin®) in ovarian carcinoma as both monotherapy and combination therapy (16–21). Objectives were feasibility, safety and efficacy. The good tolerance and response rates proven by these phase II trials initiated phase III trials.

Fifteen years after the implementation of paclitaxel, three positive clinical phase III trials on bevacizumab (Avastin®) demonstrated a first clinically relevant improvement for patients with epithelial ovarian cancer (EOC), fallopian tube cancer (FTC) and primary peritoneal carcinoma (PPC) (22–26). The GOG-0218 and the ICON7 trials investigated whether a continuous administration of bevacizumab (Avastin®) plus carboplatin and paclitaxel improved PFS and OS (22–25).

GOG-0218 was a prospective, randomized, double-blind, placebo-controlled, multicenter phase III trial. Patients (n=1,873) with advanced, non-recurrent EOC, PPC or primary FTC of FIGO stages III/IV received primary therapy consisting of carboplatin/paclitaxel ± bevacizumab (Avastin®) (15 mg/kg of body weight i.v. q3w). After primary surgery, patients were randomized into the three arms: Patients in arm 1 received six cycles of standard chemotherapy carboplatin/paclitaxel, patients in arm 2 received six cycles of carboplatin/paclitaxel plus 5 cycles of bevacizumab (Avastin®), while for patients in arm 3, 22 cycles of bevacizumab (Avastin®) were given additionally to chemotherapy. The trial reached its primary endpoint PFS. For patients that received bevacizumab (Avastin®) for 15 months (arm 3), median PFS was increased significantly to arm 1 by 3.8 months (6 months in the independent review of radiologic and clinical data, IRC) (hazard ratio (HR) =0.717, p<0.0001) (22,23). This benefit was observed for all subgroups. In contrast to this, arm 2 showed no improvement in PFS compared to arm 1.

AGO-OVAR11/ICON7/BO17707 was a randomized two-arm phase III trial enrolling 1,528 patients with early (high-risk) or advanced ovarian cancer. Patients received 6 cycles of carboplatin/paclitaxel, which was combined with bevacizumab (7.5 mg/kg of body weight i.v q3w) for 18 cycles in the experimental arm. The early combination of bevacizumab

(Avastin®) and chemotherapy, followed by continuous application of bevacizumab (Avastin®) for 12 months, resulted in a significant increase in PFS by 1.7 months, compared to the control arm (HR 0.81, p<0.0041) (24,25). PFS benefit was shown for all subgroups. At the end of the trial on March 31, 2013 the difference in OS between randomized groups was neither clinically nor statistically significant (log-rank test p=0.85). In the high-risk patients (stage IV disease, inoperable stage III disease, or suboptimally debulked (>1 cm) stage III disease) evidence suggested longer OS in those who had received bevacizumab (p=0.03) (27).

In the year 2010, combination therapy of carboplatin, paclitaxel and bevacizumab (Avastin®) was recommended by the gynaecologic cancer intergroup (GCIG) as standard therapeutic option within the framework of clinical trials (28). The approval of bevacizumab (Avastin®) for the therapy of ovarian cancer patients represents a major therapeutic innovation.

5. RESEARCH QUESTIONS AND OBJECTIVES

The main objective of this NIS was the collection of data regarding effectiveness, safety and tolerance of bevacizumab (Avastin®) in combination with carboplatin/paclitaxel according to the summary of product characteristics (SmPC) (29) in clinical routine treatment of EOC, FTC and PPC. Further aims were the recording of quality of life (QoL) as well as the evaluation of selection criteria and therapeutic decision processes.

A second study phase (beginning July 2014) investigated whether efficiency and tolerance of bevacizumab (Avastin®) reported by randomized controlled clinical trials can be verified for patients ≥70 years in routine oncology practice.

What are the decision-making factors and patient characteristics for bevacizumab (Avastin®) treatment?

To capture the influencing factors and more information concerning the therapeutic process, the following questions were analyzed:

- Demography and medical history of the patients
- Evaluation of potential predictive/prognostic variables: Eastern Cooperative Oncology Group (ECOG) Performance Status, concomitant diseases, tumor

stage, histological classification (type) and grading, method of primary surgery, postoperative residual tumor burden

- Decision-making factors of the physician for selection of treatment

- How efficient is bevacizumab (Avastin®) combination therapy, measured by time-based effectiveness parameters (PFS, OS)?

- How long is the actual treatment duration with bevacizumab (Avastin®)? What is the frequency of treatment modifications and interruptions and what are the reasons for it? What are the reasons for treatment discontinuation?

- How safe and tolerable is the treatment with bevacizumab (Avastin®) when administered in clinical routine?

- How often are hypertension or proteinuria detected under treatment with the combination therapy in daily routine?

- Overall QoL and domain-related QoL during bevacizumab (Avastin®) treatment: How are potential adverse events (AEs) perceived from the viewpoint of patients during the course of treatment? (European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ) QLQ-C30 and QLQ-OV28)

For this, the aim of the analysis at hand was the documentation of bevacizumab (Avastin®) administration in clinical routine of ovarian cancer treatment. This NIS had no impact on treatment choice and conduct, diagnostics and examination frequency.

6. AMENDMENTS AND UPDATES TO PROTOCOL

Number	Date	Section of Study Protocol	Amendment or Update	Reason
1	06 February 2014	Section 1: Contact details Section 2: List of abbreviations Section 7.4: Guidelines for safety reporting, Registration deadlines for safety reporting Section 8.4: Planned interim analyses Section 10: Ethical and legal basis	Amendment 1 Observational plan v 2.0 Update of contact details, list of abbreviations, guidelines for safety reporting as well as ethical and legal basis Addition of interim analyses	Safety update
2	25 July 2014	Section 8: Biometrical aspects	Amendment 2 Observational plan v 3.0 Increase of patient number to 1,190 Increase of study centers to 350 Inclusion of patients ≥70 years Increase in study duration Retrospective inclusion (up to one cycle) feasible	Age-specific subgroup analysis requires increase in number of cases and number of study centers

7. RESEARCH METHODS

7.1 STUDY DESIGN

The NIS OTILIA was a non-comparative, multi-center, single-arm NIS. It was conducted according to section 67 paragraph 6 of the German Medicinal Products Act (AMG, Arzneimittelgesetz). Main objectives were effectiveness, safety and tolerance of bevacizumab (Avastin®) in combination with carboplatin/paclitaxel according to the SmPC in clinical routine treatment of EOC, FTC and PPC. Further aims were the recording of QoL as well as the evaluation of selection criteria and therapeutic decision processes. In total, 1,090 patients from Germany were included into the study. Eligibility criteria were defined according to the SmPC of Avastin® (29).

The treatment of ovarian cancer requires a remarkable oncological therapeutic experience. The study involved oncologists and gynecologists in clinics, outpatient clinics and office-based oncologists and gynecologists providing a representative depiction of physicians of this indication. In total, 350 centers were planned to be included and 321 centers eventually participated in the study. Site selection was performed by the Medical Department of Roche Pharma AG (Grenzach-Wyhlen, Germany).

Both therapeutic and diagnostic aspects were non-interventional, the NIS had no influence on the approach chosen by the participating physicians. It was exclusively the physician's choice which patient should receive treatment. Furthermore, he decided on the diagnostic measures, the patient's surveillance and the concomitant therapy. Appointments were individually defined for a patient and time points of documentation were not pre-specified.

The choice of this methodical approach was a direct result of the main aim of collecting data reflecting clinical routine. This non-intervening approach was planned to confirm for clinical routine the clinically relevant advancements that had been shown in phase III clinical trials on the primary treatment in ovarian cancer patients (22–25). For this, data regarding effectiveness, safety and tolerance as well as patient reported QoL was collected.

The sponsor of the study was Roche Pharma AG (Grenzach-Wyhlen, Germany). iOMEDICO AG (contract research organization (CRO), Freiburg, Germany) supported the study as full-service provider. The responsible parties and study administrative structure of the study are presented in Table 1 in Annex 3. Additional Information.

7.2 SETTING

The NIS started with first-patient-in (FPI) in February 2012 and ended in March 2019 with last follow-up (FU) of the last patient. The individual duration of documentation for a patient was up to 27 months. During treatment with bevacizumab (Avastin®), intensive documentation was carried out for each cycle for up to 15 months. In case progression was detected, treatment with bevacizumab (Avastin®) was discontinued or the period of 15 months of intensive documentation was reached, a less intensive FU documentation was conducted during a period of 12 months. In this period, documentation was provided every six months. The duration of this period was independent of whether the treatment was still ongoing, already terminated or in the meantime had been switched to a different

treatment. Irrespective of the treatment decision, the less intensive documentation had to end after 27 months at the latest for each patient. For patients with a premature treatment discontinuation, less intensive documentation had to end 12 months after discontinuation.

A premature discontinuation of the NIS was feasible in the case of insufficient recruitment (e.g. if the scheduled number of patients ≥70 years was not reached until the end of 2015) or in the case of novel medical findings that were incompatible with a study continuation. In the case of a premature discontinuation, the data would have been completely analyzed and a final report would have been prepared.

7.3 PATIENTS

Eligible patients were those with a new diagnosis of advanced EOC, FTC or PPC that needed front-line carboplatin/paclitaxel chemotherapy treatment and for which the treating physician made the individual decision for a treatment with bevacizumab (Avastin®).

The treating physician at the respective study site was responsible for obtaining written informed consent from each patient participating in this study after adequate explanations of the aims, methods and objectives of the study prior to study participation. The signed informed consent form (ICF) was retained by the study site as part of the study records and the date of consent was documented in the electronic Case Report Form (eCRF). A representative ICF and example CRF screenshots are provided as stand-alone documents in Table 1 Annex 1. List of stand-alone documents. The treating physician assured the anonymity of the patients (pseudonymized data) and confidentiality of data being strictly maintained and protected from unauthorized parties. Only a unique identifier and a unique study identification code were recorded on any study-related document or used for eCRF entries. Signed ICFs and patient identification lists were kept strictly confidential at the study site.

The treating physician had to document the treatment data for the agreed patient number to which he had assigned a treatment with bevacizumab (Avastin®) within the framework of approval due to therapeutic need, within three years after receipt of documentation files. A retrospective inclusion of patients up to one cycle was feasible, i.e. a treating physician was allowed to include a patient who had already received a maximum of one treatment cycle at the time of written informed consent. The treating physician had to document this cycle in the eCRF retrospectively. This first treatment cycle represented the start of the

primary therapy that means even if treatment started with carboplatin/paclitaxel only and bevacizumab (Avastin®) was planned to be added at a later time point, this first treatment cycle corresponded to the first cycle to be documented. Only patients with a treatment according to current approval were allowed to be documented. Thus, the documentation of “Off Label Use” was excluded. Prior to enrollment of a patient, the participating physician verified that the patient fulfilled the inclusion / exclusion criteria (please refer to section 7.3.1).

7.3.1 Inclusion and Exclusion Criteria

Patients were eligible for inclusion if they met the following inclusion criteria:

- Study phase 1: age ≥ 18 years
- Study phase 2: age ≥70 years (based on the modified research question that started in July 2014 and focused on an age-specific subgroup analysis)
- Signed ICF after information on the NIS was given to the patient
- Patients with a new diagnosis of advanced EOC, FTC or PPC that need first-line therapy with carboplatin/paclitaxel in combination with bevacizumab (Avastin®)

Exclusion criteria were the following:

- Contraindications for treatment with bevacizumab (Avastin®) according to the current SmPC.

7.4 VARIABLES

The treating physician had to document his decisions and conducted measures in the online documentation form. The documentation files tried to reflect the usual treatment procedure most accurately as possible to facilitate documentation. These files were not to be misunderstood as treatment guideline.

The study schedule in Table 7-1 delineates the schedule for all study activities, assessments and data capture as per final study protocol v3.0, dated 25 July 2014 (Table 1; Annex 1. List of stand-alone documents). Scheduled time points for these are marked with an “x”.

Table 7-1 Variables – study schedule of activities and assessments

	Baseline documentation	15-months intensive documentation period (documentation each cycle)	At the end of intensive documentation or at premature termination
Registration	x		
Patient informed consent	x		
Demographic data[1]	x	x[2]	x[2]
Previous disease	x		
Comorbidities	x		
Tumor anamnesis[3]	x		
Primary surgery[4]	x		
Pretreatment	x		
Selected hematologic and clinical chemistry laboratory parameters (optional)	x	x	x
Tumor marker CA-125	x	x	x
Anamnesis and treatment of hypertension, if present	x		
Information on physician's choice of treatment	x		
Tumor evaluation		x	x
Concomitant medication	x	x	x
Existing supportive therapy		x	x
(S)AEs[5]		x	X[6]
Situations requiring expedited reporting[7]		x	x
AEs of special interest[5]		x	x
Pregnancy[5]	x		x
Information on bevacizumab (Avastin®) application		x	x
Data on concomitant palliative radiotherapy, if applicable			x
Evaluation of treatment from physician's point of view			x
End of treatment			x
Reason for premature termination			x
Provided by patient			
QoL: Questionnaires EORTC QLQ-C30 and QLQ-OV28[8]	x	x[9]	

AE = adverse event; CA-125 = Cancer antigen 125; EORTC = European Organisation for Research and Treatment of Cancer, QLQ = Quality of life questionnaire; QoL = Quality of life; (S)AE = (Serious) adverse event.

[1]Demographic and anamnestic data of the patient including year of birth, baseline questionnaire number and information on patient status (weight, size, Performance Status); [2]information on patient status only (weight and performance status);[3]at initial diagnosis and at treatment start; [4]including correct staging, histology, grading and postoperative tumor residual; [5](S)AEs and pregnancy were to be documented from date of patient inclusion until 90 days after completion of the treatment phase (end of Bevacizumab (Avastin®) therapy). [6]persisting (S)AEs; [7]Including quality deficiencies, counterfeits (or suspicion), and occupational exposure. These were to be reported even in the absence of an AE. [8]see Table 1 Annex 1. List of stand-alone documents; [9]at the weeks 12, 24, 39, 66 after inclusion.

After treatment termination or upon premature termination of the treatment documentation period (intensive documentation period), further course of treatment was documented by the medical practice / health care center / hospital in half-yearly documentation intervals for 12 months, including the following information:

- Information on patient status (progression status / death)
- Basic information on further medicinal antitumor therapy
- Results of the last tumor evaluation

7.4.1 Primary Effectiveness Variable

The primary effectiveness variable was PFS, defined as the time from first administration of the studied medicinal product to the date of progression or death from any cause, whichever came first. The assessment of disease progression was based on the response assessments collected in each cycle and the FU phase.

Surviving non-progressing subjects or subjects whose first disease progression or death took place after onset of a subsequent therapy (including switch of chemotherapeutic combination during bevacizumab (Avastin®) treatment) were censored on the last available contact date prior to onset of the subsequent therapy.

7.4.2 Secondary Effectiveness Variable

The secondary effectiveness variables in this study were as follows:

- ORR, defined as the percentage of patients in whom a partial or complete remission of tumor could be achieved as best response
- OS, defined as time from first administration of the studied medicinal product to the date of death from any cause. Data of patients alive at their individual end of study were censored at date of last contact or, if last contact date is not available, at the later date of last follow-up visit or date of end of treatment visit.

7.4.3 Safety Variables

The safety variables in this study were frequencies of (serious) AEs and adverse drug reactions (ADR) overall and on Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) level with a special focus on arterial hypertension, arterial thromboembolism, gastrointestinal perforations and proteinuria.

All AEs were to be documented on the designated page in the eCRF during the NIS and up to 90 days after termination of treatment phase (FU), independent of their degree of severity.

Events that were not to be documented in an accelerated reporting procedure had to be recorded in the documentation form within 30 days:

An AE represented any adverse incident that emerged during administration of medication, which did not necessarily imply a causal relation to treatment. They included the following events:

- Abnormal laboratory values, with and without association to an AE (abnormal laboratory findings), provided they
    - were accompanied by clinical symptoms
    - resulted in a change of treatment (dose adjustment, treatment interruption, treatment discontinuation)
    - required medical intervention
    - were assessed as clinically relevant by the physician

- Special situations, i.e. overdose, abuse, misuse and medication error or near-misses
- Suspected Transmission of Infectious Agent by Medicinal Product (STIAMP)
- Drug Interactions with other products
- Product Quality and/or Technical Complaints
- Reports Involving Suspect Counterfeit or Counterfeit Drugs (Falsified Medicinal Products)
- Lack of Efficacy (LoE)
- Progression of Disease was recorded as endpoint in this study setting and included in the final report and thus, no additional documentation in form of AE

documentation was needed. Instead, the event was documented in the eCRF in the section final tumor assessment or progress documentation.

For documentation of AEs, at least the following data had to be collected:

- Description of the event
- Start date and end date
- Classification of the event (following the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) criteria, to enable a standardized documentation of serious AEs (SAEs) with type and degree of severity)
- Seriousness criteria
- Outcome of the event
- Causal relationship with the treatment
- Treatment

The evaluation of the physician whether an AE had to be graded as serious had to be documented in the documentation form.

According to Roche standard, the sponsor had to be informed on every individual event documented as AE within 24 hours if the following criteria were met:

- SAEs, defined as event that
    - results in death or is life-threatening
    - requires inpatient treatment or prolongation thereof
    - results in persistent or serious disability or invalidity
    - results in a congenital anomaly or in a birth defect
    - is medically significant (*)

(*) Medically significant are AEs that are not immediately fatal, life-threating or leading to an immediate inpatient treatment but do considerably affect a patient. AEs are also medically significant if they require an intervention/treatment in order to prevent a condition that complies with the criteria stated in the SAE definition.

The following events had to be reported in an accelerated reporting procedure, independent of a potential documentation of an AE:

- Product Quality and/or Technical Complaints

- Reports Involving Suspect Counterfeit or Counterfeit Drugs (Falsified Medicinal Products)
- Occupational exposure (e.g. needlestick injury of medical staff)

For these, the bilingual AE notification sheet “German Local Drug Safety Bilingual RO-GNE: Adverse Event Form (English/German)” had to be used (see table 1 Annex 1. List of stand-alone documents).

A pregnancy (pregnancy / breastfeeding period, exposure of the father) had to be reported in the documentation form for up to 90 days after termination of treatment phase according to Roche standard. Additionally, the physician had to report Roche the pregnancy within 24 hours on the designated reporting form “German Local Drug Safety Bilingual RO-GNE: Pregnancy Report Form (English/German)” (see table 1 Annex 1. List of stand-alone documents).

Pregnancies (pregnancies / breastfeeding period) always had to be reported separately from potentially concomitantly detected AEs / ADRs. i.e. they were not to be documented in the same box or on the same sheet. The physician had to give advice to the patient regarding the risks of a pregnancy continuation including potential effects on the fetus. Pregnancies had to be followed up.

For the recording of pregnancies (pregnancies / breastfeeding period), at least the following data had to be collected:

- Information on the pregnancy and the course of pregnancy
- Pregnancy outcome (fetus)
- Seriousness criteria (fetus)
- Causal relationship with treatment
- Information on the infant

7.4.4 Other Variables of Interest

Other variables in this study were as follows:

- Decisive factors for choice of treatment

- Treatment duration of studied medicinal product, defined as time from first to last administration in the intensive treatment documentation period.

If reason for end of treatment observation implies that treatment documentation is not complete (“lost to follow-up”, “patient wished end of therapy (not due to toxicity)”, “patient wished end of observation”) then the duration was censored at the last documented administration of the respective front-line medication.

- Modifications of treatment and reasons thereof
- Treatment discontinuations and reasons thereof
- QoL over time assessed by QLQs EORTC QLQ-C30 and QLQ-OV28

7.5 DATA SOURCE(S) AND MEASUREMENT

The electronic data capture (EDC) system (*iostudy office edc*) used in this study was provided to the study sites by iOMEDICO AG. The data were derived from eCRF-entries made by the study sites as part of routine clinical practice. Data were transferred from source documents (i.e. patient’s medical records) to the eCRF. Data were fully pseudonymized and all information collected in this study was treated strictly confidentially.

The database quality was validated by review and cleaning of data entered in the eCRF. Completed eCRF data entries were checked for compliance with study protocol and for completeness, consistency and accuracy. The data analysis only began once an accurate, validated dataset had been assured. All steps of quality checks were performed and recorded according to iOMEDICO- and Roche-specific standard operating procedures (SOPs).

For data analysis, a statistical analysis plan (SAP) was developed and approved both by iOMEDICO AG (CRO) and the sponsor of the study (Roche Pharma AG). Final data analysis was based on the final SAP v2.0, dated 12 September 2019. The SAP described the variables to be used for data analysis in detail according to the defined endpoints. The NCI’s standardized definitions for CTCAE version 4.0 were used for severity grading of all AEs and MedDRA v22.0 for classification of reported terms within respective system organ class (SOC) and PT.

7.6 BIAS

Patients were included according to the respective treating physician’s discretion whereas a retrospective inclusion was allowed for up to one treatment cycle with bevacizumab

(Avastin®) at the time of written consent. The medical decision and course of treatment with bevacizumab (Avastin®) and further lines reflect exclusively the decision of the respective treating physician in routine clinical practice. Therefore, great efforts were made to ensure inclusion and exclusion criteria were met and high data quality was assured during data collection. Review and cleaning of data entered in the eCRF was performed to ensure data quality.

The performance of a tumor evaluation according to Response Evaluation Criteria In Solid Tumors (RECIST) was exclusively at the physician's discretion. It should be conducted upon clinical note of disease progression. ORR analysis was not standardized according to RECIST, which reflects clinical routine but may evoke bias.

Since response was documented throughout the study and best response additionally at end of treatment (EOT), documentation might be inconsistent. For this analysis, best response from the end of study screen was only used if no other documentation of response was available.

Due to a short documentation period per patient of maximum 27 months in this study, there were low numbers of events for PFS (44.7%) and OS (22.0%) and a high number of censored cases. This resulted in a bias of OS data and limits the interpretability of the PFS and OS data.

The study did not include imputation of missing data records. For partially unknown dates, the most conservative imputation method was used. For further details, please refer to the final SAP v2.0, dated 12 September 2019. The NIS setting of this study per se may have led to underreporting of AEs. AE with missing onset were classified as "treatment-emergent" unless a stop date before first intake of bevacizumab (Avastin®) was reported. AE with partially unknown onset date were classified as "treatment-emergent", unless not contradictory to the available information about start year and/or start month. This may have resulted in an overestimation of treatment-emergent AEs (TEAEs). For listings, no data was imputed. In case of partial dates, the known part of the date was displayed.

In the eCRF treatment could be documented for 15 months. After end of this treatment documentation period, further antineoplastic therapy had to be entered in the FU documentation. If bevacizumab (Avastin®) treatment was continued beyond 15 months, this might have been documented in the FU documentation. However, it is not possible to

clearly decipher if bevacizumab (Avastin®) documented in the FU period is continuation of first-line therapy or a subsequent therapy line. Therefore, subjects with ongoing bevacizumab (Avastin®) treatment in the FU phase were censored after 15 months of treatment. Application of bevacizumab (Avastin®) in second- or further-line therapy would be assigned as off-label use.

Despite multiple FU queries, there were 678 open (unresolved) queries at the time of database lock (DBL), which was performed on 27 September 2019, resulting in incomplete or missing data entries in the eCRF as well as discrepancy between the safety database Roche (SDB) and clinical database CRO (CDB). Consequently, this might potentially affect several study endpoints (bias). The most commonly unresolved queries concerned tumor therapy (n=202; 29.8%). Furthermore, there were 140 (20.6%) open queries regarding (serious) AEs. Table 7-2 further details the number of queries across categories and the query processing status. For full details on all open queries, please refer to the corresponding stand-alone document (Table 1, Annex 1. List of stand-alone documents).

Table 7-2 Number and categories of open queries at time of database lock

	Number of open queries at the time of database lock[1]	
	n	%
Total number of open queries	678	100
Categories		
Arterial hypertension – Anamnesis	5	0.7
Concomitant medication	13	1.9
End of treatment documentation	40	5.9
Laboratory parameters	8	1.2
Patient status	32	4.7
Physician's assessment of treatment	11	1.6
Previous and concomitant diseases	19	2.8
Previous therapies	12	1.8
Progress documentation – General	24	3.5
Progress documentation – Antineoplastic therapy	10	1.5
Registration	9	1.3
(Serious) adverse event	140	20.6
Supportive therapy / palliative radiotherapy	8	1.2
Tumor anamnesis	18	2.7
Tumor assessment	20	2.9

	Number of open queries at the time of database lock[1]	
	n	%
Tumor marker CA 125	5	0.7
Tumor therapy	202	29.8
Queries not allocated to any category	102	15.0
Query processing status		
Queries with answer of the site	69	10.2
Queries without answer of the site	609	89.8
Queries without answer of the site	609	
Query with safety-tag	43	7.1
Queries in the category (serious) adverse event	111	18.2

[Source:OTILIA_offene_Queries_zu_DB_Lock; Table 1, Annex 1. List of stand-alone documents].
CA-125 = Cancer antigen 125; N/n = Number.
[1]Database lock was performed on 27 September 2019.

Some filled in questionnaires may not be used for analysis due to non-accurate ICF. In November 2016, it was detected that ICFs valid from 25 July 2014 were inappropriate. After detection, the ICF was revised and all patients who consented on the erroneous form were asked to sign an addendum to their ICF retrospectively allowing questionnaire collection. Only questionnaires of patients with a valid ICF were allowed to be used for analysis. This approach may have introduced survivorship bias into the data.

After amendment 2 of the observational plan dated 25 July 2014 retrospective patient inclusion for up to one cycle was feasible. However, neither in the observational plan nor via site communication retrospectively included patients were excluded from the QLQ project. Retrospectively included patients may have filled in their baseline questionnaire after first study treatment and this may have introduced a bias into the baseline QoL data.

7.7 DATA TRANSFORMATION

Data were collected via eCRFs (eCRF, iostudy office edc 5.0) containing data as available from routine clinical practice, which were transmitted to a database. Data were transferred from source documents (i.e. patient's medical records) to the eCRF. The eCRF contained a data dictionary providing a detailed description of each variable used in this NIS.

7.7.1 Duration of therapy

Duration of therapy for bevacizumab (Avastin®) and for the whole front-line treatment (bevacizumab (Avastin®), carboplatin and paclitaxel) were calculated using the Kaplan-Meier method. The treatment duration was defined as

duration [months] = (date of last documented – date of first administration of respective medication +1)/30.4375.

Patients were censored at the last documented administration if the reason for EOT observation implied that treatment documentation was not complete (“lost to follow-up”, “patient wished end of therapy (not due to toxicity)”, “patient wished end of observation”).

Duration of therapy is presented using Kaplan-Meier statistics including the number of events, median, first (Q1) and third quartile (Q3) together with respective 95% confidence interval (CI), as well as a survival plot. For handling of partial dates, refer to the SAP v2.0, dated 12 September 2019, section 3.6.

For carboplatin and paclitaxel exact durations were calculated. The treatment duration was defined as

duration [months] = (date of last documented – date of first administration of respective medication +1)/30.4375.

Duration of therapy is presented using descriptive statistics including n, mean, standard deviation (SD), median, Minimum (Min), Maximum (Max), Q1 and Q3. For handling of partial dates, refer to the SAP v2.0, dated 12 September 2019, section 3.6.

Additionally, the following parameters were presented using descriptive statistics:

- Total number of bevacizumab (Avastin®) administrations per patient (n applications, mean, SD, median, Min, Max, Q1, Q3)
- Total dose for each front-line medication (n applications, mean, SD, median, Min, Max, Q1, Q3)

- Dose intensity (only for bevacizumab (Avastin®)), defined as total dose (mg/kg) divided by treatment duration (weeks) (n applications, mean, SD, median, Min, Max, Q1, Q3)

- Any modification for each front-line medication (n, %)

- Kind of modifications for each front-line medication (n, %)

- Reason for modification for each front-line medication (n, %)

- Treatment discontinuations and reasons thereof

Administrations of any front-line medication documented after switch to a further chemotherapeutic partner (other than carboplatin and paclitaxel) were not considered front-line and therefore excluded from these analyses. Analyses were conducted for the core analysis population (CAP) and for the age subgroup. Treatment durations, total doses and total number of bevacizumab (Avastin®) administrations were also analyzed for the surgery subgroup.

7.7.2 Safety Analyses

7.7.2.1 Adverse events

AEs occurring during treatment phase or within 90 days after EOT were captured in the eCRF. AE grading was conducted by the investigator according to CTCAE, version 4.0. Coding was performed by iOMEDICO using the current version 22.0 of MedDRA dictionary.

AE summary tables are restricted to TEAE, i.e. AE with an onset at or after the day of first intake of bevacizumab (Avastin®) and not later than 90 days after the last dose of bevacizumab (Avastin®). In case of missing / partially available start dates, the “worst case” principle was applied as described in the final SAP v2.0, dated 12 September 2019, section 3.6. Causally related AEs, referenced as ADR, are defined as those with a possible, probable or definite relationship to bevacizumab (Avastin®) as assessed by the investigator.

AEs are presented displaying the absolute and relative frequency of patients with at least one respective event (incidences) and the corresponding count of events (occurrences). Percentages refer to all patients in the CAP or the age subgroup, respectively. The CAP

was defined as all eligible patients included in the study who received at least one dose of bevacizumab (Avastin®). Patients were assigned to the CAP at the Data Review Meeting prior to database hard lock (see DRM minutes Table 1 Annex 1. List of stand-alone documents).

An overview of TEAEs is presented including any TEAE, any serious TEAE, any TEAE with intensity ≥ grade 3, any causally related TEAE, any causally related serious TEAE, any TEAE leading to discontinuation of bevacizumab (Avastin®) treatment and any TEAE leading to death.

Additionally, TEAEs are grouped by MedDRA SOC and PT. Separate tables are available for any TEAE, any serious TEAE, any TEAE with intensity ≥ grade 3, any causally related TEAE, any TEAE leading to discontinuation of bevacizumab (Avastin®) treatment and any TEAE leading to death. Entries were sorted by decreasing total counts for SOC and PT, respectively. Furthermore, TEAE are presented by intensity, considering the most severe intensity on the PT level. TEAE are displayed via PT and SOC. All summary tables are presented for the CAP and the age subgroup.

All recorded AEs are listed, displaying the verbatim, MedDRA SOC and PT, start/stop day including duration, intensity, seriousness (including reasons therefore), relationship to bevacizumab (Avastin®) or other medicinal products, impact on bevacizumab (Avastin®) / other medicinal products, non-drug treatment of AE, relevant laboratory results, and outcome. AEs not considered as treatment-emergent are flagged in the data listings. Additionally, site ID, subject ID, age and first administration of bevacizumab (Avastin®) are included in the listings. Sorting within a subject was done by start date. The listing was generated for patients included in and excluded from the CAP, respectively.

7.7.2.2 Laboratory parameters

Laboratory parameters were captured as per clinical routine by local laboratories. Data on laboratory parameters was listed for patients included in the CAP and included site ID, subject ID, age, date of first bevacizumab (Avastin®) administration, visit (cycle), date of laboratory analysis, results of laboratory analysis for specific parameters (categorized as being lower / higher than a specific limit), assessment of clinical relevance.

7.7.2.3 Vital signs

A shift table displaying absolute and relative frequencies for the following blood pressure categories is provided for baseline vs. worst on treatment:

- Systolic ≤120 mm Hg and diastolic ≤80 mm Hg [best]
- (systolic ≥121 mm Hg or diastolic ≥81 mm Hg) and systolic <140 mm Hg and diastolic <90 mm Hg
- Systolic ≥140 mm Hg or diastolic ≥90 mm Hg [worst]

Blood pressure data (systolic and diastolic) are listed for the CAP together with site ID, subject ID, age, date of first administration of bevacizumab (Avastin®), visit (cycle), date of blood pressure assessment, systolic and diastolic blood pressure.

7.7.2.4 Cardiac Assessments

Data on cardiac assessments is presented via by-patient listing for the CAP, including site ID, subject ID, age, date of first administration of bevacizumab (Avastin®), date of cardiac diagnostics, visit (cycle), Left Ventricular Ejection Fraction (LVEF) [%], result of analysis including specification of result (if applicable), method of LVEF assessment.

7.7.3 Effectiveness Analyses

7.7.3.1 Progression-free survival

PFS was defined as the time from first administration of bevacizumab (Avastin®) until the date of disease progression or the date of death from any cause, whichever came first. It was transformed into months as follows:

- PFS [months] = (minimum (date of disease progression, date of death) – date of first administration of bevacizumab (Avastin®) + 1)/30.4375

  If the start day was missing, it was set to the last day of the respective month unless not contradictory to the available end date (if contradictory, the start date was set to the same as the end date). In case the end date was missing, it was set to the first day of the respective month unless not contradictory to the available start date (if contradictory, the end date was set to be the same as the start date). If the month of the date was missing, the respective date was set to be missing.

Primary analysis for PFS is based on the CAP. All PFS analyses except the Cox regression analysis are also provided for the age subgroup. Due to exploratory nature of the NIS, no adjustment for multiplicity was done. Assessment of disease progression was based on the response assessments collected in each cycle. Surviving non-progressing patients or those with first disease progression or death after onset of a subsequent therapy (including switch of chemotherapeutic combination during bevacizumab (Avastin®) treatment) were censored on the last available contact date prior to onset of the subsequent therapy.

PFS was analyzed with Kaplan-Meier survival methodology. The absolute and relative frequencies of events (i.e. disease progression or death) are given. Median and quartiles are presented with 95% CI based on the method of Brookmeyer and Crowley (Brookmeyer and Crowley 1982) (30) as well as PFS rates for 6, 12 and 18 months. Kaplan-Meier estimates are displayed in table format and graphically in Kaplan-Meier plots.

7.7.3.2 Best Response and Overall Response Rate

Best response was defined as the best documented response under bevacizumab-based front-line therapy. Best response, documented at EOT, was only used if no other documentation of response was available.

ORR was defined as the percentage of patients in whom a partial or complete remission of tumor was achieved as best response.

Best response and ORR are presented as absolute and relative frequencies. The analyses were conducted for the CAP and the age subgroup.

7.7.3.3 Overall survival

OS was defined as the time from first administration of bevacizumab (Avastin®) until death from any cause. It was calculated as follows:

OS [months] = (date of death – date of first administration of bevacizumab (Avastin®) + 1)/30.4375

OS analysis was conducted for the CAP. All analyses except for the Cox model were additionally provided for the age subgroup. Data of patients alive at their individual end of study were censored at date of last contact or, if the last contact date was not available, at the later date of last FU visit or date of EOT visit.

OS was analyzed with Kaplan-Meier survival methodology. The absolute and relative frequencies of events (i.e. documented deaths) are given. Median and quartiles are presented with their 95% CI based on the method of Brookmeyer and Crowley (Brookmeyer and Crowley 1982) (30) as well as OS rates for 12, 18 and 24 months. Kaplan-Meier estimates are displayed in table format and graphically in Kaplan-Meier plots.

7.7.4 Other Analyses

7.7.4.1 Demographics, baseline characteristics and medical history

Demographics, baseline characteristics and medical history are displayed for the CAP and the age subgroup. For a detailed listing of analyzed parameters, please refer to the final SAP v2.0, dated 12 September 2019.

7.7.4.2 Decisive factors for choice of treatment

The person / institution who decided about front-line treatment as well as factors that were decisive for front-line treatment choice are presented via absolute and relative frequencies.

7.7.4.3 Previous and concomitant medications/therapies

Previous radiotherapies (within primary treatment) are presented with absolute and relative frequencies for the CAP and the age subgroup.

Concomitant medication as well as supportive medication (like granulocyte-colony stimulating factors (G-CSF), erythropoietin, antiemetics etc. which were documented on a special eCRF separated from other concomitant medications) are listed on by-patient basis including patient ID, site ID, age, date of first administration of bevacizumab (Avastin®) and

1. *For medications documented on the concomitant medication form:*
   Any concomitant medication (yes/no), medication (verbatim text), dose, dose unit, frequency, route, start date, stop date, ongoing flag, concomitant to bevacizumab (Avastin®) flag (i.e. stop date after first administration of bevacizumab (Avastin®) or ongoing), prophylactic use (yes/no), indication

2. *For medications documented on the supportive medication form:*
   Any supportive medication (yes/no), medication (verbatim text), dose (mg), route, start date, stop date, ongoing flag, concomitant to bevacizumab (Avastin®) flag (i.e. stop date after first administration of bevacizumab (Avastin®) or ongoing), reason for use.

Concomitant radiotherapies are also listed on a by-patient basis. The listing comprises the following parameters: patient ID, site ID, age, first administration of any front-line medication, first administration of bevacizumab (Avastin®), concomitant radiation (yes/no), sites of radiation, start date, end date, total dose [Gy].

7.7.4.4 Quality of life

For QoL assessment, the validated questionnaires EORTC QLQ-C30 (version 3.0; 30 items) and QLQ-OV28 (28 items) were used. The EORTC QLQ-C30 assesses general QoL and gives information on a global health status, five functional scales and nine symptom scales. The EORTC QLQ-OV28, the ovarian cancer specific module supplementing the QLQ-C30 questionnaire, comprises six ovarian cancer specific symptom scales (addressing disease was well as treatment side effects) and four single items.

Scoring of the questionnaires was performed according to the respective manual (EORTC QLQ-C30 Scoring Manual (31)). Scores were only calculated if at least half of the corresponding items were answered. Missing items were imputed by the average of the answered items, if answers for at least half of the items of a score were available. If more than half of the items of a score were missing, the score was set to missing.

Patients that gave consent to participate in the QoL assessment were asked to complete the questionnaires at baseline and 12, 24, 39 and 66 weeks after enrollment. The number of patients willing to participate in the QoL assessment and the number of patients with filled in questionnaire (at least one answer given) per time point is given. All scores derived from the two questionnaires are summarized descriptively by time point. Furthermore, change from baseline was calculated for all time points and all scores and displayed the same way. The used statistics comprise the number of observations, mean, SD, median, Min, Max, Q1 and Q3. Exploratory two-sided paired t-tests for the global health status (EORTC QLQ-C30) compare the QoL for each post-baseline time point vs. baseline level, respectively. Change from baseline is additionally plotted in line plots. Answers to single items, which are not included in a score, are presented with absolute and relative frequencies for each time point. QoL data is presented for the CAP and the age subgroup.

7.7.4.5 Physician's assessment of therapy

Parameters of physician's assessment (assessment of treatment compared to expectations overall, reasons behind the assessment made) are presented with absolute and relative frequencies for the CAP and the age subgroup.

7.7.4.6 Subsequent antineoplastic therapy

Medications used for subsequent antineoplastic therapies are given with absolute and relative frequencies for the CAP and the age subgroup.

7.7.4.7 Tumor marker Cancer antigen 125 (CA-125)

The course of Cancer antigen 125 (CA-125) level is displayed in by-patient listings for CAP, including site ID, subject ID, age, date of first administration of bevacizumab (Avastin®), date of CA-125 assessment, visit (cycle) and CA-125 level (U/mL).

7.7.5 Sensitivity Analyses

No sensitivity analyses were performed.

7.7.6 Interim and Final Analysis and Timing of Analyses

Three interim analyses were conducted, for which separate SAPs were created as indicated below:

- First interim analysis: database cut on 30 June 2014. "Statistischer Analyseplan Erste Zwischenauswertung", version 1.0, 02 October 2014

- Second interim analysis: database cut on 06 January 2016. „Statistischer Analyseplan Zweite Zwischenauswertung", version 1.0, 08 February 2016 and „Statistischer Analyseplan Zusatzanalysen zur zweiten Zwischenauswertung", version 1.0, 01 December 2016

- Third interim analysis: database cut on 31 January 2017. „Statistischer Analyseplan Dritte Zwischenauswertung", version 3.1, 08 May 2017

All three interim reports can be found in the Roche Trial Master File (TMF; Table 1; Annex 1. List of stand-alone documents). The interim data have been presented at international conferences (32–40).

As per final study protocol v3.0, dated 25 July 2014 (Table 1, **ANNEX 1. LIST OF STAND-ALONE DOCUMENTS**), the final report of this study (final analysis) was planned for 12 months after termination of study or premature termination of study.

7.8 STATISTICAL METHODS

All statistical analyses performed to address the objectives (endpoints) in this NIS as well as the nature and extent of data presentation are detailed in the final SAP v2.0, dated 12 September 2019 (Table 1; Annex 1. List of stand-alone documents). For each of the three interim analyses and the final analyses a separate SAP was created (Table 1; Annex 1. List of stand-alone documents).

The analysis of this NIS was exploratory and primarily used descriptive statistical methods. In addition, p-values and CI were used in selected analyses to highlight interesting aspects of the data but are interpreted in an exploratory manner.

For continuous data the sample size, mean, SD, median, Min, Max and upper and lower quartiles (Q1, Q3) are presented.

Categorical data are displayed by absolute and relative frequencies (percentages). Percentages are based on all non-missing values. Missing values are displayed only by absolute frequencies.

Time-to-event data (PFS, OS, Treatment duration) were analyzed using Kaplan-Meier method. Data are presented by number of events, median, Q1 and Q3, and time-rates (e.g. 6-month rate) as appropriate, together with respective 95% CI (a log-log transformation was employed for calculation of CI based on the method of Brookmeyer and Crowley (Brookmeyer and Crowley 1982) (30)).

Multivariate Cox regression was performed to assess the effect of selected covariates on PFS or OS, including the following covariates/categorizations:

- age (<70 years / ≥70 years)
- ECOG status at baseline (<2 / ≥2 / unknown)
- Body mass index (BMI) at baseline (≤20 kg/m² / >20- ≤25 kg/m² / >25 - ≤30 kg/m² / >30 kg/m² / unknown)

- residual disease at baseline (≥1 cm / no visible residuum / unknown)
- FIGO stage at baseline (IIIB, IIIC, IV)
- ascites at baseline (>0-500 mL / >500 mL / 0 mL, unknown)
- grading at baseline (G1, G2 /G3, G4 / GX)

7.8.1 Amendments to the Statistical Analysis Plan

For each of the three interim analyses, additional analyses and for the final analysis a separate SAP was prepared. Each SAP contains the analyses that were carried out in the respective interim analysis or in the final analysis (see Table 1, Annex 1. List of stand-alone documents). There were no amendments to the following SAPs.

First interim analysis

- ML27765_Otilia_SAP_Interim1_v1.0_final, dated 02 October 2014

Second interim analysis

- ML27765_Otilia_SAP_Interim2_v1.0, dated 08 February 2016
- OTILIA SAP zur Zusatzanalyse 2.IA_signiert_20161222, dated 01 December 2016

Third interim analysis

- ML27765_Otilia_SAP_Interim3_Version3.1_20170508, dated 08 May 2017

Final analysis

- OTILIA_SAP_v2_clean, dated 12 September 2019

7.8.2 Statistical Considerations and Planned Sample Size

The primary effectiveness parameter in this study (PFS) was selected based on the sample size calculation. As per final observational plan v3.0, dated 25 July 2014 (Table 1, Annex 1. List of stand-alone documents), this NIS was planned to enroll 1,190 patients in about 350 study sites (study protocol amendment 2). With the last-patient-in (LPI) taking place on 31 December 2016, 1,090 patients had been recruited in 240 sites across Germany (322 sites participated, of these, 82 were non-recruiting); of these patients 266 were excluded from final analyses as they did not meet inclusion criteria. The CAP was used for all statistical analyses except for QoL analyses. QoL analyses were performed

with all patients of the CAP who were willing to participate in the QoL assessment and had signed a valid ICF.

- Study population (CAP): All analyses were performed for the CAP which consisted of all eligible patients included in the study who received at least one dose of bevacizumab (Avastin®). Patients with “off-label” use of bevacizumab (Avastin®) during the study were only included in this analysis population if administration of bevacizumab (Avastin®) was “in-label” at their study start. Patients with “off-label” use of bevacizumab (Avastin®) at study start were excluded from this analysis population but AEs of these patients were compiled in a listing. The patient assignment to the CAP was performed at the Data Review Meeting prior to database hard lock (see DRM minutes Table 1 Annex 1. List of stand-alone documents).

Furthermore, the following subgroups were analyzed:

- Age subgroup: A subgroup analysis denoted as “age subgroup” was performed in addition to the analyses on CAP in total. The analyses were conducted stratified by age at enrollment (<70 / ≥70 years).

- Surgery subgroup: A subgroup analysis denoted as “surgery subgroup” was performed in addition to the analyses on CAP in total. Specified analyses were conducted stratified by prior surgery (yes/no).

Free-text entries were evaluated as documented. No statistical methods were used to replace missing values. Essential missing values (i.e., informed consent, relevant inclusion and exclusion criteria, no administration of study drug) led to the exclusion of the patient from the analytical data set (i.e., patient not evaluable). The amount of missing values will be presented as percentage of the overall sample or according subgroup. For partially unknown dates, the most conservative imputation method was used.

7.8.3 Sample size justification

The sample size justification according to final SAP, v2.0 dated 12 September 2019 (Table 1, Annex 1. List of stand-alone documents), was as follows:

"Primary objective of this NIS refers to PFS of the total study population as well as of the subgroup of elderly patients (age ≥70 years).

Sample size estimation is based on the assumption of an exponentially distributed (parametric) survival function for PFS. Median PFS of the total population is expected to be 19 months (based on results from ICON7 (24) *and GOG218* (22)*. Given an observational period of 27 months per patient, a total of n=730 patients is necessary to achieve that a two-sided 95% CI for median PFS is not exceeding the median by more than ±2 months. Expecting a drop-out rate of 10%, 800 patients in the total population should be sufficient to achieve the desired accuracy. Since this sample size estimation is based on the assumption of a parametric model but analysis will be conducted using the (non-parametric) Kaplan-Meier estimate, accuracy will be slightly lower (about ±3 months). An accuracy of ±3 months is considered as minimal clinical difference for PFS by experts consistently.*

To allow subgroup analysis addressing PFS in patients aged ≥70 years, amendment No. 2 limited the enrollment to this subpopulation. While in the trial GOG-218 (22) *patients of all age-groups profited similarly from bevacizumab (Avastin®), the trial ICON7* (24)*, the phase II trial OCTAVIA* (41) *and trials in other tumor entities gave some indication for the benefit being less in this subpopulation. Based on these data, a median PFS of 18 months will be assumed in this subgroup for sample size estimation. The difference of 1 month in the assumptions on median PFS in the total and the elderly population is of clinically irrelevant quantity.*

To limit the width of a two-sided 95% CI for the assumed median PFS (18 months) to ±3 months in this subpopulation, data from about 580 patients are necessary. To take into account a drop-out rate of 10%, 640 patients in this subpopulation need to be enrolled. At date of amendment No. 2, 250 elder (age ≥70 years) and 300 younger patients were already enrolled. Therefore, from this point in time, further 390 elderly patients were needed, leading to a total sample size of 1,190 patients.

This sample size also allows sufficient accuracy for the estimation of the incidence of rare SAE under treatment consisting of bevacizumab (Avastin®) in combination with carboplatin and paclitaxel in routine clinical use. The planned sample size of 1,190 patients allows to observe SAE with an incidence of 0.3% with a probability of 95%.

Concerning SAE of specific interest in the context of the study objectives, sample size is adequate to give statements about the frequency of hypertension (expected incidence 22.9% [≥ grade 2] (22) *– 25.9%* (25)*), arterial thromboembolism (incidence of 0.7%* (22) *– 3.6% [all grades]* (25)*) and gastrointestinal perforations (incidence 1.3% [all grades]* (25) *– 2.6% [grade≥2]* (22)*).*

With an expected return rate of about 70% for the EORTC QLQ-C30 and QLQ-OV28 questionnaires, the sample size of the total population (n=1,190) as well as of the subpopulation of elderly patients (n=640) allows to discover a minimal clinically relevant average change of 5 points in the Quality-of-Life scale compared to baseline level using a two-sided t-test for paired samples and a significance level of 5% with a power of >90% (assumptions: SD = 35, r = 0.6).”

7.9 QUALITY CONTROL

For data capturing and data management, Java-based validated software (i.e. *iostudy office edc*) was deployed. The eCRFs for data capturing included online validation of eCRFs during data capturing, e.g. check on range, plausibility, typing errors. In addition to the system-based plausibility checks, computerized and manual consistency checks were undertaken, i.e. logical checks on data entries to check for inconsistencies. A formal query process was implemented to solve inconsistencies in documented data. Automated as well as manual queries were generated and sent to the sites for resolution according to predefined rules (for details please refer to the data management plan (DMP)). The DMP defined how to deal with missing data and invalid entries, how data should be cleaned, and to which level of error would be acceptable. The DMP described how data were to be tracked and coded, how query reports should be generated and resolved, and how data should be stored and secured. Finally, the DMP described a quality assurance system for data entry. All steps of quality checks were performed and recorded according to iOMEDICO- and Roche-specific SOPs.

8. RESULTS

The data presented are based on the final Tables (v3.0, dated 22 January 2020), Figures (v2.0, dated 22 January 2020), and Listings (v2.0, dated 06 December 2019) (TFLs) (Table 1; Annex 1. List of stand-alone documents). Source table(s) and figures(s) are indicated below each depicted table and figure in the report, respectively. In the same way,

source Listings are being referred to (below the table or in the text body) in certain cases where further information to the data presented are provided.

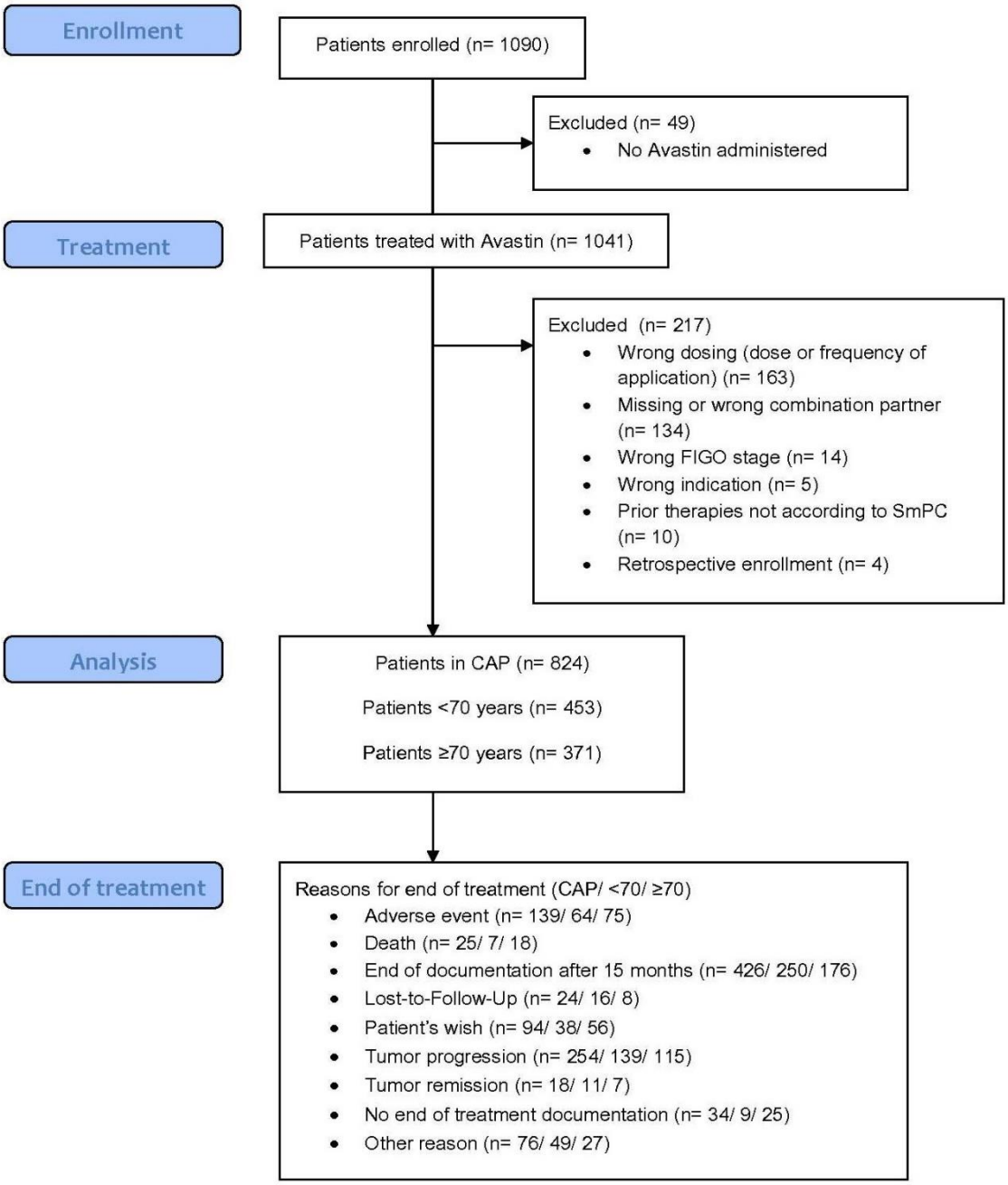
8.1 PATIENT POPULATION

8.1.1 Patient Disposition Overall and in Subgroups

Patients were recruited from 02 February 2012 (FPI) through 31 December 2016 (LPI) in 240 study sites across Germany. In total, 1,090 patients were registered in the EDC with signed ICF and included into the study (Figure 8-1), of these 266 were excluded from the CAP (N=824). The number of patients in the CAP, age subgroup and surgery subgroup used in the analysis of different objectives are detailed in

Table 8-1 and Table 8-2.

Figure 8-1 CONSORT flow diagram



CAP = Core analysis population; FIGO = Fédération Internationale de Gynécologie et d'Obstétrique; N/n = Number; SmPC = Summary of product characteristics.

Table 8-1 Patient disposition: Total and Age subgroup[1]

	Total	Patients <70 years	Patients ≥70 years
Number of patients enrolled	1,090 (100.0)	583 (100.0)	507 (100.0)
Number of patients treated with bevacizumab (Avastin®)	1,041 (95.5)	560 (96.1)	481 (94.9)
Number of patients in CAP (n, %)	824 (75.6)	453 (77.7)	371 (73.2)
Number of patients excluded from CAP (n, %)[2]	266 (24.4)	130 (22.3)	136 (26.8)

[Source: OTILIA_Tables_Final_4_20200420: Table 14.1.1].
CAP = Core analysis population; N/n = Number.
[1]Definition of CAP and subgroups is provided in chapter 7.8.2 Statistical Considerations and Planned Sample Size;
[2]Reasons for exclusion from CAP are explained in more detail in the minutes of the data review meeting. Multiple reasons for exclusion from CAP possible.

Table 8-2 Patient disposition – subgroups[1] (CAP)

	CAP
Total number of patients, N	824
Number of patients in respective subgroup, N	
Age	
Patients <70 years	453
Patients ≥70 years	371
Surgery	
Patients without primary surgery	45
Patients with primary surgery	779

[Source: OTILIA_Tables_Final_4_20200420: Table 14.1.1 and Table 14.2.1].
CAP = Core analysis population; N/n = Number.
[1]Definition of subgroups is provided in chapter 7.8.2 Statistical Considerations and Planned Sample Size.

8.1.2 Reasons for Exclusion from the Analysis Population

The most common reason for exclusion of patients (n=266; 24.4%) from the CAP (N=824) was that patients had no cycle in which all three substances were administered (n=107; 9.8%; Table 8-3). Likewise, this was also the most common reason for exclusion of patients from the CAP in both age subgroups (<70 years n=49; 8.4% and ≥70 years n=58; 11.4%; Table 8-3).

In the CAP the two most common reasons for end of treatment documentation were end of documentation after 15 months (n=349; 42.4%) and tumor progression (n=196; 23.8%). These two were also the most common reasons for end of treatment documentation in both age subgroups (end of documentation after 15 months: <70 years n=213; 47.0% and n=136; 36.7%; tumor progression: <70 years n=105; 23.2% and ≥70 years n=91; 24.5%; Table 8-3).

Table 8-3 Reasons for exclusion from the analysis population

	Total	Patients <70 years	Patients ≥70 years
Number of patients enrolled	1,090 (100.0)	583 (100.0)	507 (100.0)
Number of patients in CAP	824 (75.6)	453 (77.7)	371 (73.2)
Number of patients excluded from CAP	266 (24.4)	130 (22.3)	136 (26.8)
Reasons for exclusion from CAP (n, %)[1]			
Avastin® not in combination with carboplatin or paclitaxel	17 (1.6)	12 (2.1)	5 (1.0)
Avastin® monotherapy from 1st Avastin® cycle	10 (0.9)	4 (0.7)	6 (1.2)
Dose I – 1st Avastin® dose not according to SmPC (>15 mg/kg)	7 (0.6)	2 (0.3)	5 (1.0)
Dose II – 1st Avastin® dose not according to SmPC (<15 mg/kg)	77 (7.1)	37 (6.3)	40 (7.9)
FIGO staging I – FIGO stadium IIIA	1 (0.1)	1 (0.2)	
FIGO staging I – FIGO stadium <IIIB	13 (1.2)	6 (1.0)	7 (1.4)
Frequency of Avastin® not according to SmPC	79 (7.2)	35 (6.0)	44 (8.7)
Indication	5 (0.5)	1 (0.2)	4 (0.8)
No IMP given	49 (4.5)	23 (3.9)	26 (5.1)
No cycle with all three substances	107 (9.8)	49 (8.4)	58 (11.4)
Prior Therapies I – Avastin® therapy before operation	1 (0.1)	1 (0.2)	
Prior Therapies II – First line therapy > one month	9 (0.8)	6 (1.0)	3 (0.6)
Retrospective enrollment	4 (0.4)	2 (0.3)	2 (0.4)
Reasons for end of treatment documentation (n, %)			
Number of patients in CAP	824 (100.0)	453 (100.0)	371 (100.0)
AE not related to therapy[2]	25 (3.0)	8 (1.8)	17 (4.6)
AE related to therapy[2]	40 (4.9)	11 (2.4)	29 (7.8)
Adverse event[2]	44 (5.3)	30 (6.6)	14 (3.8)
Death	16 (1.9)	5 (1.1)	11 (3.0)
End of documentation after 15 months	349 (42.4)	213 (47.0)	136 (36.7)
Lost-to-Follow-up	15 (1.8)	10 (2.2)	5 (1.3)
Other reason (specification)	48 (5.8)	31 (6.8)	17 (4.6)
Patient's wish	7 (0.8)	3 (0.7)	4 (1.1)
Patient's wish (no toxicity)	53 (6.4)	24 (5.3)	29 (7.8)
Tumor progression	196 (23.8)	105 (23.2)	91 (24.5)
Tumor remission	13 (1.6)	7 (1.5)	6 (1.6)
No EOT documentation	18 (2.2)	6 (1.3)	12 (3.2)

[Source: OTILIA_Tables_Final_4_20200420: Table 14.1.1].
AE = Adverse event; CAP = Core analysis population; EOT = End of treatment; FIGO = Fédération Internationale de Gynécologie et d'Obstétrique; IMP = Investigational medicinal product; N/n = Number; SmPC = Summary of product characteristics.
[1]Reasons for exclusion from CAP are explained in more detail in the minutes of the data review meeting. Multiple reasons for exclusion from CAP possible. [2]In an eCRF update the reason for end of treatment documentation "Adverse event" was replaced by "AE not related to therapy" and "AE related to therapy" on 01 October 2013.

8.1.2.1 Comparison of the analysis population in third interim analysis and final analysis

The database cut for the third interim analysis was performed on 31 January 2017. At this time 1,085 patients were enrolled. The database lock for the final analysis was performed more than two and a half years later on 27 September 2019 after enrollment of 1,090

patients in total (Table 8-4). In the time between third interim analysis and final analysis patients were further observed and corresponding data were documented. Moreover, the data entered in the eCRF were checked for compliance with the observational plan and for completeness, consistency and accuracy. Due to updating, review and cleaning of the entered data, the data set of the final analysis is no longer up to the status of the interim analysis. For these reasons, the number of patients excluded from the analysis population (277 vs. 266) and the number of patients in the analysis population (808 vs. 824) differ between the third interim analysis and the final analysis. The patient number of patients <70 years (426 vs. 453) and ≥70 years (382 vs. 371) also differ between the third interim analysis and the final analysis. In the final analysis more patient were excluded due to missing or wrong combination partner (n=95; 8.7% vs. n=134, 12.3%) wrong dosing (n=87; 8.0% vs. n=163; 15.0%) or missing administration of bevacizumab (Avastin®) (n=29; 2.7% vs. n=49; 4.5%). In contrast, less patients were excluded due to retrospective enrollment (n=69; 6.3% vs. n=4; 0.4%), wrong prior therapies (n=36; 3.3% vs. n=10; 0.9%) or wrong FIGO stage (n=34; 3.1% vs. n=14; 1.3%) (Table 8-4).

Table 8-4 Comparison of the analysis population in third interim analysis and final analysis

Third interim analysis	N (%)	Final analysis	N (%)
Total number of enrolled patients	1,085 (100.0)	Total number of enrolled patients	1,090 (100.0)
Number of excluded patients	277 (25.4)	Number of excluded patients	266 (24.4)
Number of patients in Per Protocol Population	808 (74.1)	Number of patients in CAP	824 (75.6)
Patients <70 years	426 (39.1)	Patients <70 years	453 (41.6)
Patients ≥70 years	382 (35.0)	Patients ≥70 years	371 (34.0)
Reasons for exclusion		**Reasons for exclusion**	
No cycle with bevacizumab (Avastin®) + carboplatin + paclitaxel	95 (8.7)	Missing or wrong combination partner	134 (12.3)
Bevacizumab (Avastin®) dose to low/high/not determinable	87 (8.0)	Wrong dosing (dose or frequency of application)	163 (15.0)
Retrospective inclusion	69 (6.3)	Retrospective enrollment	4 (0.4)
Received prior therapy	36 (3.3)	Prior therapies not according to SmPC	10 (0.9)
FIGO stage not appropriate/unknown	34 (3.1)	Wrong FIGO stage	14 (1.3)

Third interim analysis	N (%)	Final analysis	N (%)
No treatment visit	29 (2.7)	No bevacizumab (Avastin®) administered	49 (4.5)
Off-label substance at the beginning of the therapy	16 (1.5)	-	-
Tumor subtype unknown	15 (1.4)	Wrong indication	5 (0.5)

[Source: Otilia_Interimsanalyse3_Tables_Part_I_v1.2_20170508: Table 1.2; OTILIA_Tables_Final_4_20200420: Table 14.1.1].
CAP = Core analysis population; FIGO = Fédération Internationale de Gynécologie et d'Obstétrique; N/n = Number; SmPC = Summary of product characteristics.
Multiple reasons for exclusion from CAP possible.

8.1.3 Deactivation / Removal of Patients from the EDC During the study

During the study, 72 patients have been "deactivated" and removed (deletion of registration entries) from the EDC. Thereof, 54 patients were Screening failures (75%), 16 patients were incorrectly registered in the EDC (22.2%) and 2 patients were registered as duplicate (Table 8-5). Since these 72 patients have been removed from the EDC, they are not included in the 1,090 enrolled patients.

Table 8-5 Reasons for removal of patients from the EDC

Reasons for removal of patients from the EDC	N (%)
All deleted patients, N	72
Reasons, n (%)	
Screening failure	54 (75.0%)
Patient was mistakenly registered in eCRF	16 (22.2%)
Duplicate registration entry	2 (2.8%)

[Source: ML27765_Otilia_Geloeschte_Patienten_20171018; Table 1, Annex 1. List of stand-alone documents].
eCRF = electronic case report from; EDC = Electronic data capture; N/n = Number.

8.2 DESCRIPTIVE DATA

8.2.1 Demographics, baseline characteristics and medical history

The demographic and other characteristics of the patients at baseline in the CAP and the age subgroups are summarized in Table 8-6.

In the CAP the median age (Min-Max) of the patients at start of therapy was 68.0 years (25.9-83.4 years). At start of therapy 45.3% (n=373) of patients were aged ≥70 years (two patients were aged <70 years at enrollment but had already reached an age of ≥70 years at the start of therapy. Hence, in the CAP two more patients are aged ≥70 years at start

of therapy (n=373) in comparison to the subgroup of patients aged ≥70 years (n=371) for which age at enrollment is decisive). Most patients had an ECOG performance status of 0 (n=297; 38.2%) or 1 (n=389; 50.0%). There were no patients with an ECOG performance status of 4. Medical conditions ongoing at first bevacizumab (Avastin®) administration were present in 365 patients (44.3%) and persistent arterial hypertension was present in 339 patients (41.1%). Nonetheless, most patients had a Charlson Comorbidity Index of 0 (n=644; 78.2%). The most frequent type of tumor was epithelial ovarian carcinoma (n=662; 80.3%) and serous tumors were the most frequent histological type (n=606; 77.8%). Tumors were mostly diagnosed at FIGO stage IIIC (n=472; 57.3%) and with poor differentiation (G3: n=565; 68.6%) (tumor stage was determined by the treating physician according to the respective currently valid version of the FIGO staging system dated 1988 (1,2) or 2014 (3)).

The median age (Min-Max) at start of therapy in the subgroup of patients <70 years was 58.4 years (25.9-70.2 years) whereas it was 74.6 years (70.1-83.4 years) in patients ≥70 years (age at enrollment could be younger than age at therapy start and hence patients could be in the age group <70 years even if they are more than 70 years at therapy start). In the subgroup of patients ≥70 years less patients had an ECOG performance status of 0 (28.6% vs. 45.7%) and more patients had an ECOG performance status of 1 (56.9% vs. 44.6%), 2 (12.0% vs. 8.3%) or 3 (2.6% vs. 1.4%). Older patients had more medical conditions ongoing at first bevacizumab (Avastin®) administration (60.1% vs. 31.3%) and more persistent arterial hypertension (55.8% vs. 29.1%). Accordingly, in the subgroup of patients ≥70 years less patients had a Charlson Comorbidity Index of 0 (75.5% vs. 80.4%). In both age subgroups of patients <70 and ≥70 years the most frequent type of tumor was epithelial ovarian carcinoma (81.0% vs. 79.5%) and serous tumors were the most frequent histological type (75.7% vs. 80.5%). In both age subgroups tumors were mostly diagnosed at FIGO stage IIIC (58.5% vs. 55.8%) and with poor differentiation (G3: 68.9% vs. 68.2%).

Table 8-6 Demographics, baseline characteristics and medical history

Parameter		CAP	Patients <70 years	Patients ≥70 years
Total number of patients enrolled, N		*824*	*453*	*371*
Age at start of therapy, years[1]				
	N	824	453	371
	Mean	65.4	57.6	74.9
	StD	10.85	8.43	3.16
	Median	68.0	58.4	74.6

Parameter	CAP	Patients <70 years	Patients ≥70 years
25% quantile	57.3	52.3	72.2
75% quantile	74.2	64.5	76.9
Min	25.9	25.9	70.1
Max	83.4	70.2	83.4
Age at start of therapy in decades, n, (%)[1]			
<50 years	90 (10.9)	90 (19.9)	0 (0)
50 - <60 years	163 (19.8)	163 (36.0)	0 (0)
60 - <70 years	198 (24.0)	198 (43.7)	0 (0)
70 - <80 years	347 (42.1)	2 (0.4)	345 (93.0)
≥80 years	26 (3.2)	0 (0)	26 (7.0)
Weight, kg			
N	802	444	358
Median	65.0	64.0	65.0
Min	41.0	41.0	41.0
Max	120.0	120.0	107.0
BMI, kg/m²			
N	802	444	358
Median	24.2	23.9	24.6
Min	15.6	16.2	15.6
Max	43.5	43.5	42.3
BMI category, n (%)			
≤ 20 kg/m²	126 (15.3)	80 (17.7)	46 (12.4)
> 20 - ≤ 25 kg/m²	343 (41.6)	180 (39.7)	163 (43.9)
> 25 - ≤ 30 kg/m²	242 (29.4)	133 (29.4)	109 (29.4)
> 30 kg/m²	113 (13.7)	60 (13.2)	53 (14.3)
Missing	22	9	13
ECOG performance status, n, (%)			
N	778	435	343
0	297 (38.2)	199 (45.7)	98 (28.6)
1	389 (50.0)	194 (44.6)	195 (56.9)
2	77 (9.9)	36 (8.3)	41 (12.0)
3	15 (1.9)	6 (1.4)	9 (2.6)
missing	46	18	28
Medical conditions with stop date prior to first bevacizumab (Avastin®) administration, n (%)	92 (11.2)	49 (10.8)	43 (11.6)
Medical conditions ongoing at first bevacizumab (Avastin®) administration, n (%)	365 (44.3)	142 (31.3)	223 (60.1)
Persistent arterial hypertension, n (%)			
Yes	339 (41.1)	132 (29.1)	207 (55.8)
No	485 (58.9)	321 (70.9)	164 (44.2)
Medical treatment of persistent arterial hypertension			
Yes	312 (92.0)	117 (88.6)	195 (94.2)
No	27 (8.0)	15 (11.4)	12 (5.8)
Time from primary diagnosis to start of front-line treatment, months			
N	820	450	370
Mean	4.1	4.8	3.3

Parameter	CAP	Patients <70 years	Patients ≥70 years
StD	11.47	13.33	8.63
Median	1.9	1.9	1.9
25% quantile	1.4	1.4	1.4
75% quantile	2.6	2.6	2.6
Min	0.3	0.3	0.3
Max	115.6	115.6	91.3
Time from primary surgery to start of front-line treatment, months			
N	777	439	338
Mean	3.8	4.4	3.0
StD	10.94	12.75	7.94
Median	1.7	1.7	1.8
25% quantile	1.3	1.3	1.4
75% quantile	2.3	2.3	2.2
Min	0.0	0.0	0.0
Max	115.3	115.3	91.3
Localization of surgery[2]			
Adnexa	624 (75.7%)	352 (77.7%)	272 (73.3%)
Appendix	144 (17.5%)	85 (18.8%)	59 (15.9%)
Diaphragm peritoneum	118 (14.3%)	65 (14.3%)	53 (14.3%)
Liver	42 (5.1%)	27 (6.0%)	15 (4.0%)
Lung	5 (0.6%)	2 (0.4%)	3 (0.8%)
Lymph node para-aortal	291 (35.3%)	185 (40.8%)	106 (28.6%)
Lymph node pelvin	300 (36.4%)	193 (42.6%)	107 (28.8%)
Omentum	550 (66.7%)	315 (69.5%)	235 (63.3%)
Ovarian	527 (64.0%)	312 (68.9%)	215 (58.0%)
Pancreas	12 (1.5%)	10 (2.2%)	2 (0.5%)
Peritoneum	438 (53.2%)	252 (55.6%)	186 (50.1%)
Small and large intestine	280 (34.0%)	161 (35.5%)	119 (32.1%)
Spleen	30 (3.6%)	20 (4.4%)	10 (2.7%)
Uterus	412 (50.0%)	253 (55.8%)	159 (42.9%)
Other	169 (20.5%)	100 (22.1%)	69 (18.6%)
No surgery	45 (5.5%)	13 (2.9%)	32 (8.6%)
Type of tumor, n (%)			
Epithelial ovarian carcinoma	662 (80.3%)	367 (81.0%)	295 (79.5%)
Fallopian tube carcinoma	58 (7.0%)	27 (6.0%)	31 (8.4%)
Peritoneal carcinoma	104 (12.6%)	59 (13.0%)	45 (12.1%)
FIGO stage, n (%)			
IIIB	116 (14.1%)	65 (14.3%)	51 (13.7%)
IIIC	472 (57.3%)	265 (58.5%)	207 (55.8%)
IV	236 (28.6%)	123 (27.2%)	113 (30.5%)
Grading, n (%)			
G1 – well differentiated (low grade)	22 (2.7%)	13 (2.9%)	9 (2.4%)
G2 – moderately differentiated (intermediate grade)	153 (18.6%)	99 (21.9%)	54 (14.6%)
G3 – poorly differentiated (high grade)	565 (68.6%)	312 (68.9%)	253 (68.2%)
G4 – undifferentiated (high grade)	12 (1.5%)	2 (0.4%)	10 (2.7%)
GX – grade cannot be assessed	72 (8.7%)	27 (6.0%)	45 (12.1%)
Histological type, n (%)			

Parameter	CAP	Patients <70 years	Patients ≥70 years
N	779	440	339
Clear cell	13 (1.7%)	9 (2.0%)	4 (1.2%)
Endometroid	22 (2.8%)	14 (3.2%)	8 (2.4%)
Mucinous	19 (2.4%)	13 (3.0%)	6 (1.8%)
Serous	606 (77.8%)	333 (75.7%)	273 (80.5%)
Undifferentiated	24 (3.1%)	13 (3.0%)	11 (3.2%)
Other	95 (12.2%)	58 (13.2%)	37 (10.9%)
Missing	45	13	32
Ascites, n (%)			
N	710	406	304
0 mL	6 (0.8%)	3 (0.7%)	3 (1.0%)
>0-500 mL	12 (1.7%)	6 (1.5%)	6 (2.0%)
>500 mL	100 (14.1%)	58 (14.3%)	42 (13.8%)
Unknown	592 (83.4%)	339 (83.5%)	253 (83.2%)
Missing	114	47	67
Residual disease, n (%)			
N	779	440	339
R0 – no residual tumor	229 (29.4%)	139 (31.6%)	90 (26.5%)
R1 – microscopic residual tumor (⩽1 cm)	175 (22.5%)	106 (24.1%)	69 (20.4%)
R2 – macroscopic residual tumor (>1 cm)	192 (24.6%)	99 (22.5%)	93 (27.4%)
RX – the presence of residual tumor cannot be assessed	183 (23.5%)	96 (21.8%)	87 (25.7%)
Missing	45	13	32
Baseline CA125, U/ml			
N	736	421	315
Median	174.0	164.0	189.0
25% quantile	50.3	44.0	60.3
75% quantile	532.9	496.0	581.3
Charlson Comorbidity Index[3]			
0	644 (78.2%)	364 (80.4%)	280 (75.5%)
1	31 (3.8%)	14 (3.1%)	17 (4.6%)
2	123 (14.9%)	62 (13.7%)	61 (16.4%)
≥3	26 (3.2%)	13 (2.9%)	13 (3.5%)
Blood pressure at baseline[4]			
N (non-missing)	599	347	252
Normal blood pressure	215 (35.9%)	131 (37.8%)	84 (33.3%)
Prehypertension	183 (30.6%)	109 (31.4%)	74 (29.4%)
High blood pressure	201 (33.6%)	107 (30.8%)	94 (37.3%)
Missing	225	106	119
Electrocardiogram at baseline			
N (non-missing)	339	132	207
Normal	163 (48.1%)	71 (53.8%)	92 (44.4%)
Minor dysrhythmia or ST changes	13 (3.8%)	3 (2.3%)	10 (4.8%)
Therapy-requiring dysrhythmia or ST changes	6 (1.8%)	2 (1.5%)	4 (1.9%)
Not done	157 (46.3%)	56 (42.4%)	101 (48.8%)
Missing	485	321	164
Echocardiography at baseline			
N (non-missing)	339	132	207
Normal	95 (28.0%)	35 (26.5%)	60 (29.0%)
Pathological	22 (6.5%)	3 (2.3%)	19 (9.2%)

Parameter	CAP	Patients <70 years	Patients ≥70 years
Not done	222 (65.5%)	94 (71.2%)	128 (61.8%)
Missing	485	321	164
Doppler sonography of extracardiac vessels at baseline			
N (non-missing)	339	132	207
Normal	12 (3.5%)	4 (3.0%)	8 (3.9%)
Mild stenoses	2 (0.6%)	1 (0.8%)	1 (0.5%)
Not done	325 (95.9%)	127 (96.2%)	198 (95.7%)
Missing	485	321	164

[Source: OTILIA_Tables_Final_4_20200420: Table 14.1.2; Table 14.1.3, Table 14.1.10, Table 14.1.11, Table 14.1.12, Table 14.1.13, Table 14.1.14, Table 14.1.15, Table 14.1.16, Table 14.1.17].
BMI = Body mass index; CAP = Core analysis population; CA-125 = Cancer antigen 125; ECOG = Eastern Cooperative Oncology Group; FIGO = Fédération Internationale de Gynécologie et d'Obstétrique; Max = Maximum; Min = Minimum, N/n = Number; StD = Standard deviation.
[1]Age at enrollment could be younger than age at therapy start. Therefore, patients could be in the age group <70 even if they are more than 70 at therapy start. [2]Localization of surgery: Multiple answers possible and not pre-specified answers counted as other. [3]Charlson Comorbidity Index was calculated for previous and concomitant diseases together. [4]Normal blood pressure: systolic ≤ 120 mmHg and diastolic ≤80 mmHg. Prehypertension: (systolic ≥ 121 mmHg or diastolic ≥ 81 mmHg) and systolic < 140 mmHg and diastolic < 90 mmHg. High blood pressure: systolic ≥ 140 mmHg or diastolic ≥ 90 mmHg.

In the CAP the median weight at baseline was 65.0 kg and the median of the last documented weight was 65.9 kg. The median of the lowest documented weight in the CAP was 62.0 kg (Table 8-7). In the subgroup of patients <70 years the median weight at baseline was 64.0 kg and the median of the last documented weight was 66.3 kg. The median of the lowest documented weight in the subgroup of patients <70 years was 62.0 kg (Table 8-7). In the subgroup of patients ≥70 years the median weight at baseline and the median of the last documented weight were both 65.0 kg. The median of the lowest documented weight in the subgroup of patients ≥70 years was 62.0 kg (Table 8-7).

Table 8-7 Weight (at baseline, last and lowest documented)

Weight, kg		At Baseline	Last documented	Lowest documented
CAP				
	N	802	824	824
	Median	65.0	65.9	62.0
	25% quantile	58.0	59.0	55.0
	75% quantile	75.0	75.0	70.4
Patients <70 years				
	N	444	453	453
	Median	64.0	66.3	62.0
	25% quantile	57.0	59.0	55.0
	75% quantile	76.0	77.0	72.0
Patients ≥70 years				
	N	358	371	371
	Median	65.0	65.0	62.0
	25% quantile	58.9	58.0	55.0

Weight, kg	At Baseline	Last documented	Lowest documented
75% quantile	74.0	72.0	70.0

[Source: OTILIA_Tables_Final_4_20200420: Table 14.1.4].
CAP = Core analysis population; Max = Maximum; Min = Minimum; N/n = Number; StD = Standard deviation.

In the CAP the median BMI at baseline was 24.2 kg/m^2 and the median of the last documented BMI was 24.8 kg/m^2. The median of the lowest documented BMI in the CAP was 23.3 kg/m^2 (Table 8-8). In the subgroup of patients <70 years the median BMI at baseline was 23.9 kg/m^2 and the median of the last documented BMI was 25.1 kg/m^2. The median of the lowest documented BMI in the subgroup of patients <70 years was 23.3 kg/m^2 (Table 8-8). In the subgroup of patients ≥70 years the median BMI at baseline and the median of the last documented BMI were both 24.6 kg/m^2. The median of the lowest documented BMI in the subgroup of patients ≥70 years was 23.3 kg/m^2 (Table 8-8).

Table 8-8 Body mass index (at baseline, last and lowest documented)

Body mass index, kg/m²	At Baseline	Last documented	Lowest documented
CAP			
N	802	813	813
Median	24.2	24.8	23.3
25% quantile	21.6	21.9	20.6
75% quantile	27.9	27.8	26.4
Patients <70 years			
N	444	448	448
Median	23.9	25.1	23.3
25% quantile	21.3	21.9	20.3
75% quantile	27.6	28.4	26.8
Patients ≥70 years			
N	358	365	365
Median	24.6	24.6	23.3
25% quantile	21.9	22.0	21.0
75% quantile	27.9	27.2	26.0

[Source: OTILIA_Tables_Final_4_20200420: Table 14.1.5].
CAP = Core analysis population; Max = Maximum; Min = Minimum; N/n = Number; StD = Standard deviation.

8.2.2 Previous diseases

In the CAP the most frequent previous disease stopping prior to first administration of bevacizumab (Avastin®) was another tumor (n=23; 2.8%). Chronic gastrointestinal disease and myocardial infarction were the second most frequent previous diseases (each n=3; 0.4%) (Table 8-9).

In the subgroup of patients <70 years other tumors were also the most frequent previous disease (n=10; 2.2.%) followed by chronic gastrointestinal disease, chronic pulmonary disease, coronary artery disease, heart failure and metastatic solid tumor (each n=1, 0.2%). In the subgroup of patients ≥70 years previous diseases were more frequent compared to patients <70 years: other tumor (n=13, 3.5%), myocardial infarction (n=3; 0.8%), chronic gastrointestinal disease (n=2; 0.5%) followed by arthritis, cerebrovascular disease, chronic pulmonary disease, depression / psychological disorder, diabetes mellitus (without end organ damage) and mild liver disease (each n=1; 0.3) (Table 8-9).

Table 8-9 Previous diseases

	N	%
CAP		
Other tumor	23	2.8%
Chronic gastrointestinal disease	3	0.4%
Myocardial infarction	3	0.4%
Chronic pulmonary disease	2	0.2%
Arthritis	1	0.1%
Cerebrovascular disease	1	0.1%
Coronary artery disease	1	0.1%
Depression / psychological disorder	1	0.1%
Diabetes mellitus (without end organ damage)	1	0.1%
Heart failure	1	0.1%
Metastatic solid tumor	1	0.1%
Mild liver disease	1	0.1%
Patients <70 years	453	
Other tumor	10	2.2%
Chronic gastrointestinal disease	1	0.2%
Chronic pulmonary disease	1	0.2%
Coronary artery disease	1	0.2%
Heart failure	1	0.2%
Metastatic solid tumor	1	0.2%
Patients ≥70 years	371	
Other tumor	13	3.5%
Myocardial infarction	3	0.8%
Chronic gastrointestinal disease	2	0.5%
Arthritis	1	0.3%
Cerebrovascular disease	1	0.3%
Chronic pulmonary disease	1	0.3%
Depression / psychological disorder	1	0.3%
Diabetes mellitus (without end organ damage)	1	0.3%
Mild liver disease	1	0.3%

[Source: OTILIA_Tables_Final_4_20200420: Table 14.1.8a, Table 14.1.8b, Table 14.1.8c].
CAP = Core analysis population¸ N/n = Number.
Previous was calculated as stop date prior to first administration of bevacizumab (Avastin®). Multiple answers possible. Entry of comorbidities as free-text was also possible the eCRF. Free-text entries on comorbidities were compiled in listing 16.2.4.1 (Other comorbidities) (verbatim)) but were not further processed.

8.2.3 Concomitant diseases

In the CAP the most common concomitant diseases (>5%) ongoing at first administration of bevacizumab (Avastin®) were diabetes mellitus (without end organ damage) (n=75;

9.1%), coronary artery disease (n=54; 6.6%) and depression / psychological disorder (n=48; 5.8%) (Table 8-10).

In the subgroup of patients <70 years the most common concomitant diseases (>5%) were depression / psychological disorder (n=31; 6.8%) and diabetes mellitus (without end organ damage) (n=29; 6.4%). In contrast, in the subgroup of patients ≥70 years the most common concomitant diseases were diabetes mellitus (without end organ damage) (n=46; 12.4%) and coronary artery disease (n=41; 11.1%) (Table 8-10).

Table 8-10 Most common concomitant diseases (>1.0%)

	N	%
CAP	824	
Diabetes mellitus (without end organ damage)	75	9.1%
Coronary artery disease	54	6.6%
Depression / psychological disorder	48	5.8%
Other tumor	40	4.9%
Chronic gastrointestinal disease	24	2.9%
Heart failure	24	2.9%
Arthritis	22	2.7%
Chronic pulmonary disease	22	2.7%
Alopecia	16	1.9%
Mild liver disease	12	1.5%
Moderate to severe renal disease	11	1.3%
Hearing loss	10	1.2%
Polyneuropathy	10	1.2%
Patients <70 years	453	
Depression / psychological disorder	31	6.8%
Diabetes mellitus (without end organ damage)	29	6.4%
Other tumor	22	4.9%
Coronary artery disease	13	2.9%
Chronic pulmonary disease	11	2.4%
Alopecia	9	2.0%
Arthritis	9	2.0%
Chronic gastrointestinal disease	7	1.5%
Heart failure	6	1.3%
Mild liver disease	5	1.1%
Peripheral artery disease	5	1.1%
Patients ≥70 years	371	
Diabetes mellitus (without end organ damage)	46	12.4%
Coronary artery disease	41	11.1%
Heart failure	18	4.9%
Other tumor	18	4.9%
Chronic gastrointestinal disease	17	4.6%
Depression / psychological disorder	17	4.6%
Arthritis	13	3.5%
Chronic pulmonary disease	11	3.0%
Hearing loss	9	2.4%
Alopecia	7	1.9%
Mild liver disease	7	1.9%
Moderate to severe renal disease	7	1.9%
Polyneuropathy	7	1.9%
Cerebrovascular disease	5	1.3%
Diabetes mellitus with end organ damage	5	1.3%

[Source: OTILIA_Tables_Final_4_20200420: Table 14.1.9a, Table 14.1.9b, Table 14.1.9c.]
CAP = Core analysis population; N/n = Number.
Multiple answers possible. Concomitant disease denotes disease that is ongoing at first administration of bevacizumab (Avastin®). Diseases without dates are rated as concomitant diseases. Entry of comorbidities as free-text was also possible the eCRF. Free-text entries on comorbidities were compiled in listing 16.2.4.1 (Other comorbidities) (verbatim)) but were not further processed.

8.3 OUTCOME DATA

The final analyses were performed with a dataset of 824 patients (CAP). Please refer to chapter 7.8.2 for definition of subgroups.

Outcome data were:

Description of effectiveness and safety of bevacizumab (Avastin®) in patients with ovarian cancer treated with bevacizumab (Avastin®) in combination with carboplatin and paclitaxel in the first-line setting.

- Effectiveness: PFS, best response, ORR, OS
- Decisive factors for choice of treatment: institution and decisive factors
- Therapy details:
    - treatment duration (bevacizumab (Avastin®), carboplatin, paclitaxel, front-line treatment)
    - Total number of bevacizumab (Avastin®) administrations
    - Total dose (bevacizumab (Avastin®), carboplatin, paclitaxel)
    - Dose intensity of bevacizumab (Avastin®)
- Modifications of treatment and reasons thereof
    - Any treatment modification
    - Kind of and reason for treatment modification (bevacizumab (Avastin®), carboplatin, paclitaxel)
- Treatment discontinuations and reasons thereof
- Previous radiotherapy
- QoL over time

- Physician's assessment of treatment
- Subsequent antineoplastic medications
- ECOG Performance status during study
- Blood pressure during study
- AEs and adverse reactions

8.4 MAIN RESULTS

8.4.1 Effectiveness objectives

8.4.1.1 Progression-free survival

In the CAP (N=824), 368 (44.7%) patients experienced an event (progressive disease (PD) or death) during first-line bevacizumab (Avastin®) therapy. The median PFS was 19.4 months (18.7 - 20.3 months) as detailed in Table 8-11 and Figure 8-2. 6-, 12- and 18-month rates were 95.2% (93.4% - 96.5%), 79.5% (76.4% - 82.3%) and 57.5% (52.9% - 61.8%). Due to the low number of events PFS data have to be interpreted with caution.

In the subgroup of patients <70 years (N=453), 200 (44.2%) patients experienced an event (PD or death) during first-line bevacizumab (Avastin®) therapy. The median PFS was 20.0 months (18.7 - 21.2 months) (Table 8-11 and Figure 8-3). 6-, 12- and 18-month rates were 97.2% (95.1% - 98.4%), 80.2% (75.9% - 83.9%) and 60.1% (54.0% - 65.7%). Similarly, in the subgroup of patients ≥70 years (N=371), 168 (45.3%) patients experienced an event and the median PFS was 19.3 months (17.6 - 20.2 months) (Table 8-11 and Figure 8-3). 6-, 12- and 18-month rates were 92.6% (89.3% - 95.0%), 78.7% (73.7% - 82.8%) and 54.2% (47.2% - 60.6%).

In the subgroup of patients without prior surgery (N=45), 27 (60.0%) patients experienced an event (PD or death) during first-line bevacizumab (Avastin®) therapy. The median PFS was 19.4 months (14.2 - 22.2 months) (Table 8-11 and Figure 8-4). 6-, 12- and 18-month rates were 95.4% (83.0% - 98.8%), 80.8% (65.2% - 89.9%) and 50.6% (32.5% - 66.1%). Likewise, in the subgroup of patients with prior surgery (N=779), 341 (43.8%) patients experienced an event and the median PFS was 19.6 months (18.7 - 20.3 months) (Table 8-11 and Figure 8-4). 6-, 12- and 18-month rates were 95.1% (93.3% - 96.5%), 79.5% (76.2% - 82.4%) and 58.0% (53.2% - 62.4%). However, comparability of these subgroups is limited since the number of patients in the subgroup of patients without prior surgery

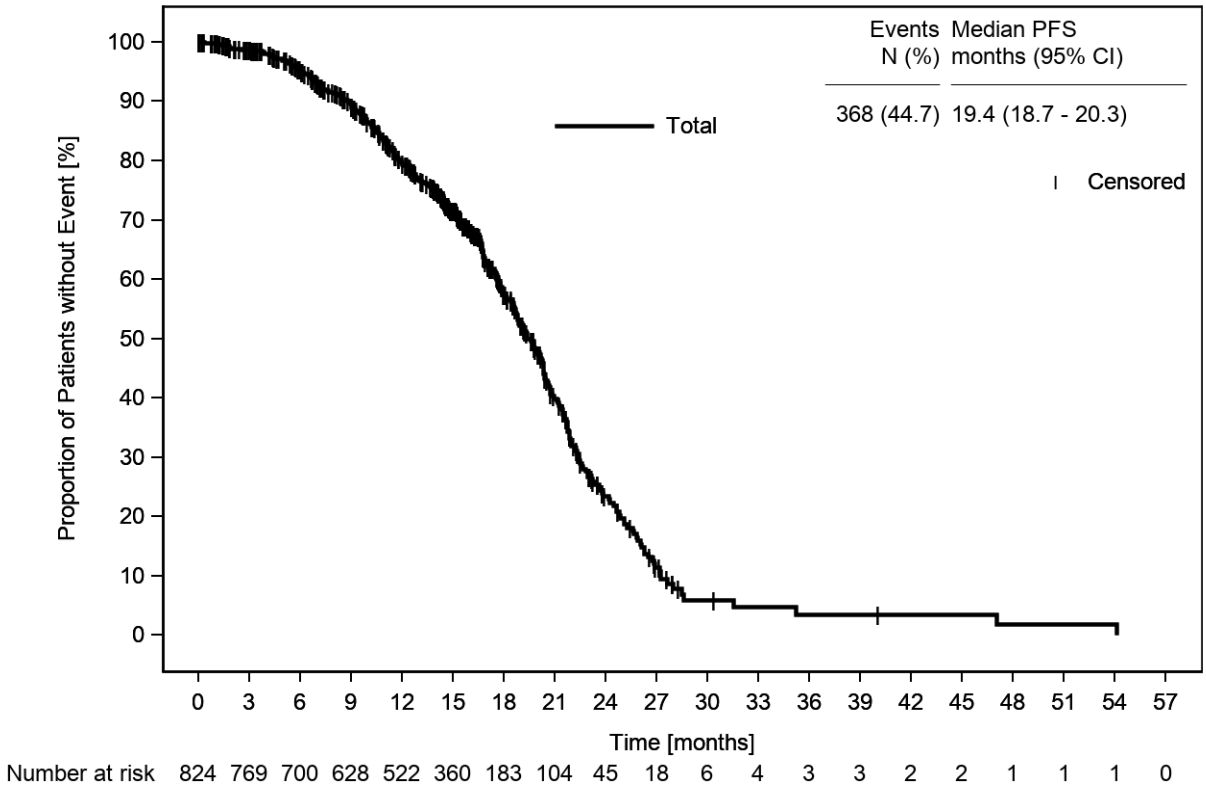
(N=45) was very small in comparison to the subgroup of patients with prior surgery (N=779).

Table 8-11 Progression-free survival (months)[1] – Kaplan-Meier statistics

		Age subgroup		Surgery subgroup	
	CAP	Patients <70 years	Patients ≥70 years	No prior surgery	Prior surgery
Patients, N	824	453	371	45	779
Events, n [%][2]	368 (44.7%)	200 (44.2%)	168 (45.3%)	27 (60.0%)	341 (43.8%)
25% quantile [95% CI]	14.1 [12.5, 14.8]	14.3 [12.4, 15.9]	13.8 [11.7, 14.8]	12.5 [9.9, 16.6]	14.1 [12.6, 15.2]
Median [95% CI]	19.4 [18.7, 20.3]	20.0 [18.7, 21.2]	19.3 [17.6, 20.2]	19.4 [14.2, 22.2]	19.6 [18.7, 20.3]
75% quantile [95% CI]	23.6 [22.4, 24.8]	23.9 [22.4, 26.3]	23.3 [21.5, 24.6]	22.4 [19.8, NA]	23.7 [22.4, 25.1]
6-month rate [95%-CI]	95.2% [93.4, 96.5]	97.2% [95.1, 98.4]	92.6% [89.3, 95.0]	95.4% [83.0, 98.8]	95.1% [93.3, 96.5]
12-month rate [95%-CI]	79.5% [76.4, 82.3]	80.2% [75.9, 83.9]	78.7% [73.7, 82.8]	80.8% [65.2, 89.9]	79.5% [76.2, 82.4]
18-month rate [95%-CI]	57.5% [52.9, 61.8]	60.1% [54.0, 65.7]	54.2% [47.2, 60.6]	50.6% [32.5, 66.1]	58.0% [53.2, 62.4]

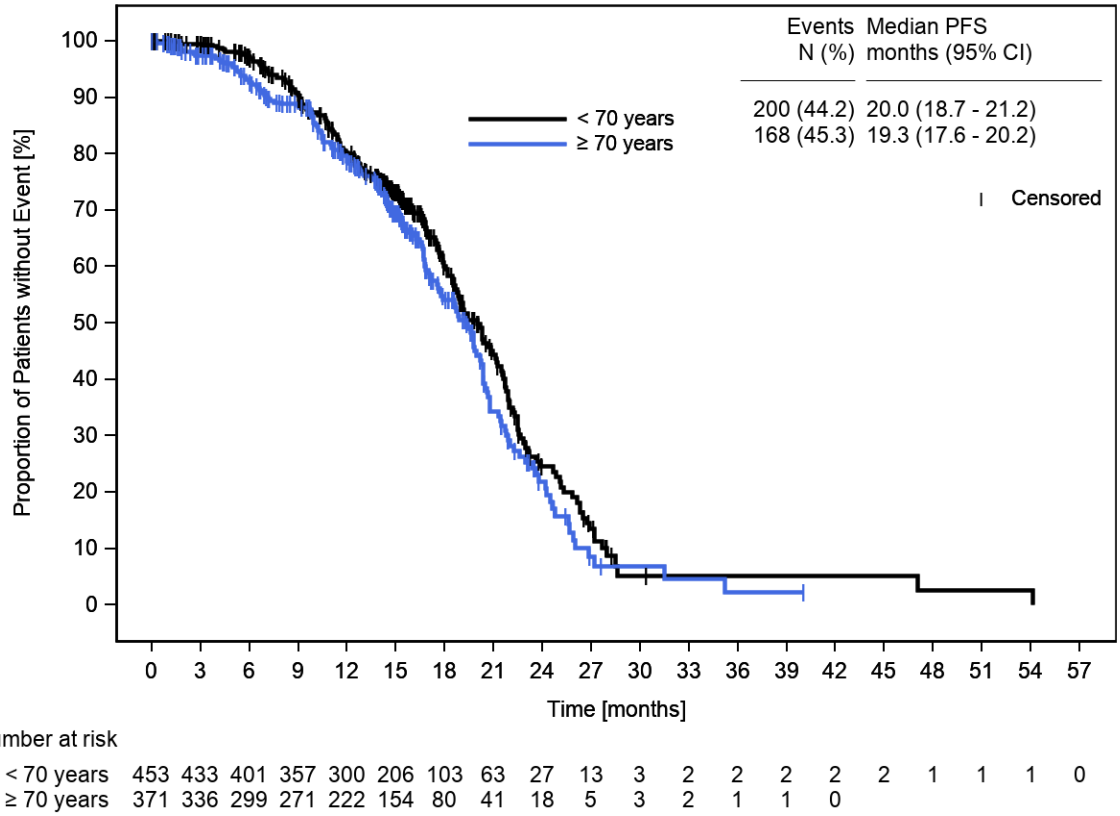
[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.1].
CAP = Core analysis population; CI = Confidence interval; N/n = Number; NA = Not applicable / Not reached.
[1]Progression-free survival was estimated using the Kaplan-Meier method. [2]Due to the low number of events PFS data have to be interpreted with caution.

Figure 8-2 Progression-free survival overall (CAP)



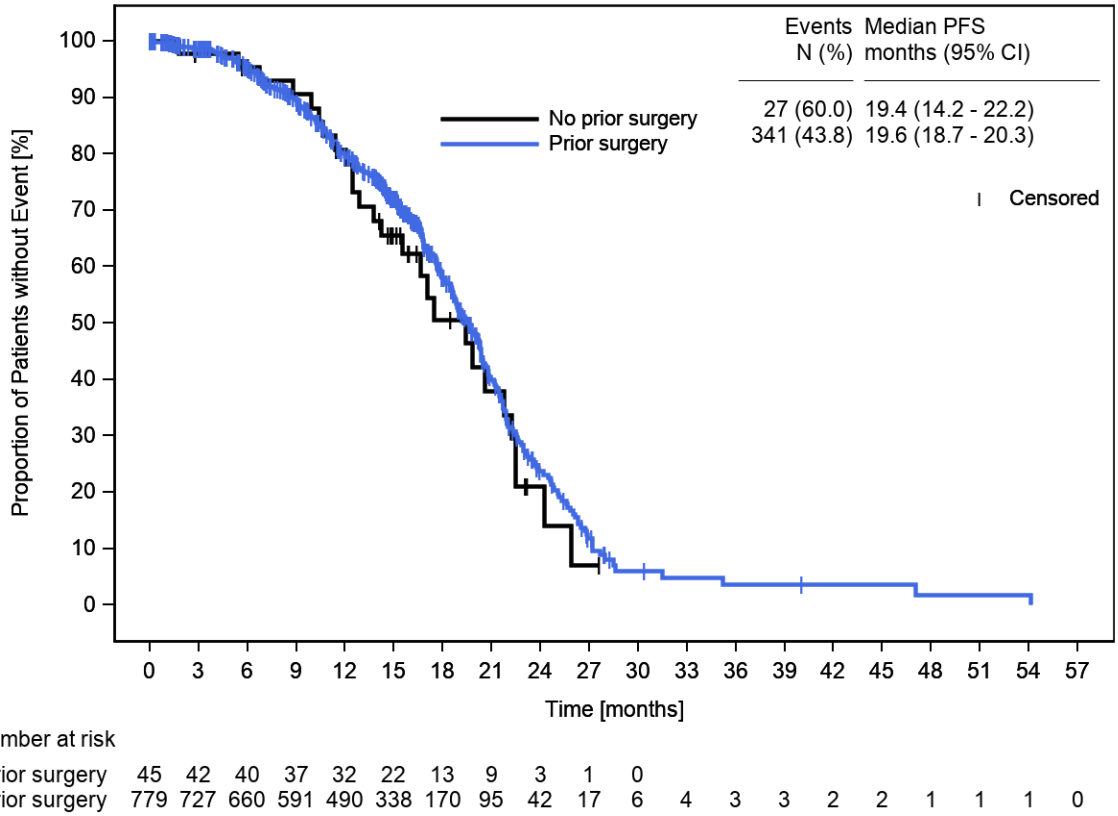
[Source: OTILIA_Figures_Final_3_20200127: Figure 2.1.1].
CAP = Core analysis population; CI = Confidence interval; N/n = Number; PFS = Progression-free survival.
Progression-free survival was estimated using the Kaplan-Meier method. Due to the low number of events PFS data have to be interpreted with caution.

Figure 8-3 Progression-free survival by age



[Source: OTILIA_Figures_Final_3_20200127: Figure 2.1.2].
CI = Confidence interval; N/n = Number; PFS = Progression-free survival.
Progression-free survival was estimated using the Kaplan-Meier method. Due to the low number of events PFS data have to be interpreted with caution.

Figure 8-4 Progression-free survival by prior surgery



[Source: OTILIA_Figures_Final_3_20200127: Figure 2.1.3].
CI = Confidence interval; N/n = Number; PFS = Progression-free survival.
Progression-free survival was estimated using the Kaplan-Meier method. Due to the low number of events PFS data have to be interpreted with caution.

8.4.1.1.1 Cox regression model

A multivariable Cox regression analysis was performed to identify potential independent factors (baseline demographics and clinical characteristics), which might have an impact on the PFS (Table 8-12). This analysis showed that patients without visible residual disease at baseline had a better outcome (PFS) as compared to patients with residual disease ≥1 cm at baseline (HR = 0.59; 95% CI: 0.45 - 0.78; p<.001).

Table 8-12 Progression-free survival – Cox regression model

	Hazard ratio	95% CI	p-value
ECOG performance status group			
> 1 vs. 0-1	1.05	[0.75, 1.49]	0.763
Unknown vs. 0-1	1.10	[0.69, 1.75]	0.700
Body mass index group			
≤ 20 vs. > 20-25	1.06	[0.76, 1.49]	0.718

	Hazard ratio	95% CI	p-value
> 25-30 vs. > 20-25	0.94	[0.72, 1.21]	0.614
> 30 vs. > 20-25	1.11	[0.82, 1.51]	0.500
Unknown vs. > 20-25	0.65	[0.33, 1.25]	0.196
Age subgroup			
≥ 70 vs. < 70	1.16	[0.94, 1.44]	0.175
Residual disease at baseline group			
No visible residuum vs. ⩾ 1 cm	0.59	[0.45, 0.78]	<.001
Unknown vs. ≥ 1 cm	0.80	[0.60, 1.07]	0.139
FIGO stage group			
IIIB vs. IIIC/IV	0.79	[0.56, 1.11]	0.177
Ascites at baseline group			
0 ml vs. > 0-500 ml	1.53	[0.53, 4.44]	0.429
> 500 ml vs. > 0-500 ml	1.11	[0.74, 1.67]	0.611
Unknown vs. > 0-500 ml	0.97	[0.68, 1.36]	0.840
Grading at baseline group			
G1 vs. G2/G3	0.74	[0.32, 1.68]	0.467
G4/GX vs. G2/G3	0.88	[0.61, 1.25]	0.466
Prior surgery subgroup			
No prior surgery vs. prior surgery	1.25	[0.77, 2.02]	0.368
Global likelihood ratio test			0.022

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.2].
CI = Confidence interval; ECOG = Eastern Cooperative Oncology Group; FIGO = Fédération Internationale de Gynécologie et d'Obstétrique.

8.4.1.2 Best response and overall response rate

In the CAP 307 patients (43.4%) had a complete response (CR) and 203 patients (28.7%) had a partial response (PR) resulting in an ORR of 72.1% (n=510) (Table 8-13).

Comparing the age subgroups, CR occurred much more often in patients <70 years than ≥70 years (49.7% vs. 35.6%) whereas PR occurred somewhat more often in patients ≥70 years than <70 years (30.8% vs. 27.0%). This results in a higher ORR in younger patients (76.8% vs. 66.3%) (Table 8-13).

In the surgery subgroups, CR occurred more often in patients without than with prior surgery (43.9% vs. 35.0%) whereas PR occurred more often in patients with than without prior surgery (40.0% vs. 28.0%). Nonetheless, the ORR was similar in both subgroups without and with prior surgery (72.0% vs. 75.0%) (Table 8-13). However, the number of patients in the subgroup of patients without prior surgery (N=45) was very small in comparison to the subgroup of patients with prior surgery (N=779), which limits the comparability of these subgroups.

Table 8-13 Best response and overall response rate

		Age subgroup		Surgery subgroup	
	CAP	Patients <70 years	Patients ≥70 years	No prior surgery	Prior surgery
Patients, N	824	453	371	45	779
Best response					
N (non-missing)	707	392	315	40	667
CR	307 (43.4%)	195 (49.7%)	112 (35.6%)	14 (35.0%)	293 (43.9%)
PR	203 (28.7%)	106 (27.0%)	97 (30.8%)	16 (40.0%)	187 (28.0%)
ORR	510 (72.1%)	301 (76.8%)	209 (66.3%)	30 (75.0%)	480 (72.0%)
SD	153 (21.6%)	66 (16.8%)	87 (27.6%)	8 (20.0%)	145 (21.7%)
PD	27 (3.8%)	16 (4.1%)	11 (3.5%)	2 (5.0%)	25 (3.7%)
Not evaluable	17 (2.4%)	9 (2.3%)	8 (2.5%)	0 (0.0%)	17 (2.5%)
Missing	117	61	56	5	112

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.3a, Table 14.2.3b, 14.2.3c].
CAP = Core analysis population; CR = Complete response; N/n = Number; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease.

8.4.1.3 Overall survival

In the CAP (N=824), 181 patients (22.0%) experienced an event (death) during first-line bevacizumab (Avastin®) therapy. The median OS was 24.6 months (23.7 - 26.3 months) as depicted in Table 8-14 and Figure 8-5. The 12-month OS rate was 91.1% (88.7% - 93.0%), whereas the 18-month, and 24-month OS rates were 78.5% (74.4% - 82.1%) and 53.3% (46.1% - 59.8%), respectively. However, the number patients who experienced an event (22.0%) was very low. Consequently, a very high number of patients (78.0%) was alive at their individual end of study and they were censored before any event was observed. Moreover, while events become more frequent after 18 months of survival, censoring often occurred within the first 18 months. Due to the low number of events and the high number of censored patients OS is no reliable estimator. Interpretation of the OS data and comparison of OS data to results of other trials is not possible.

In the subgroup of patients <70 years (N=453), 86 patients (19.0%) experienced an event (death) during first-line bevacizumab (Avastin®) therapy. The median OS was 26.7 months (23.9 – 39.8 months) as depicted in Table 8-14 and Figure 8-6. The 12-month OS rate was 92.3% (89.1% - 94.5%), whereas the 18-month, and 24-month OS rates were 81.0% (75.4% - 85.4%) and 59.5% (49.7% - 68.1%), respectively. In the subgroup of patients ≥70 years (N=371), 95 patients (25.6%) experienced an event and the median OS was 22.9 months (21.7 – 25.5 months) as depicted in Table 8-14 and Figure 8-6. The 12-month OS rate was 89.6% (85.6% - 92.5%), whereas the 18-month, and 24-month OS rates were 75.5% (68.8% - 80.9%) and 45.5% (35.2% - 55.3%), respectively. In both age subgroups the number patients who experienced an event was very low (<70 years 19.0%; ≥70 years 25.6%) and the number of censored patients was very high (<70 years 81.0%; ≥70 years 74.4%). Hence, in both age subgroups OS is no reliable estimator. Comparison of the OS data between the subgroups and interpretation of the OS data in these subgroups is not possible.

In the subgroup of patients without prior surgery (N=45), 13 patients (28.9%) experienced an event (death) during first-line bevacizumab (Avastin®) therapy. The median OS was 26.6 months (19.1 – not reached (NA) months) as depicted in Table 8-14 and Figure 8-7. The 12-month OS rate was 95.3% (82.3% - 98.8%), whereas the 18-month, and 24-month OS rates were 73.9% (53.2% - 86.5%) and 52.5% (29.9% - 70.9%), respectively. In the subgroup of patients with prior surgery (N=779), 168 patients (21.6%) experienced an event and the median OS was 24.6 months (23.8 – 26.3 months) as depicted in Table

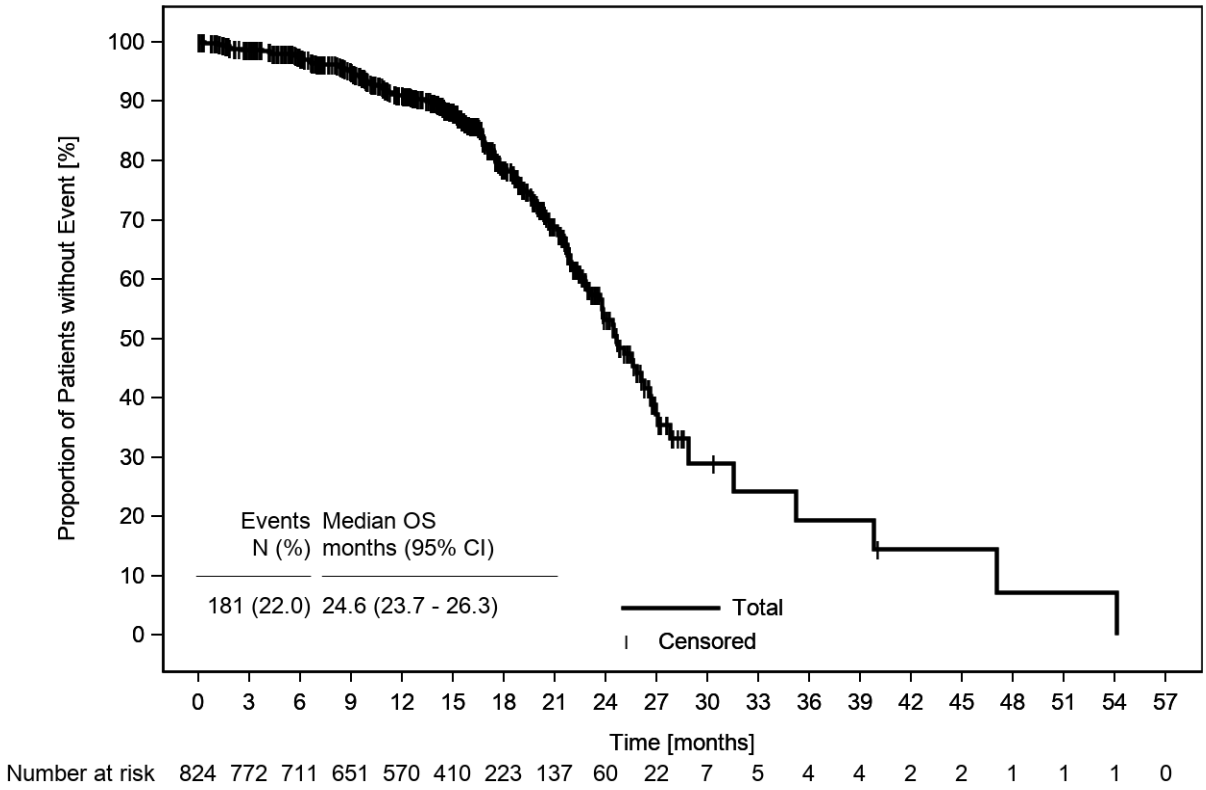
8-14 and Figure 8-7. The 12-month OS rate was 90.8% (88.3% - 92.8%), whereas the 18-month, and 24-month OS rates were 78.9% (74.6% - 82.5%) and 53.5% (46.0% -60.4%), respectively. In both surgery subgroups the number patients who experienced an event was very low (without prior surgery 28.9%; with prior surgery 21.6%) and the number of censored patients was very high (without prior surgery 71.1%; with prior surgery 78.4%). Hence, in both surgery subgroups OS is no reliable estimator. Furthermore, the number of patients in the subgroup of patients without prior surgery (N=45) was very small in comparison to the subgroup of patients with prior surgery (N=779). Thus, comparison of the OS data between the subgroups and interpretation of the OS data in these subgroups is not possible.

Table 8-14 Overall survival (months)[1] – Kaplan-Meier statistics

	Age subgroup			Surgery subgroup	
	CAP	Patients <70 years	Patients ≥70 years	No prior surgery	Prior surgery
Patients, N	824	453	371	45	779
Events, n (%)[2]	181 (22.0%)	86 (19.0%)	95 (25.6%)	13 (28.9%)	168 (21.6%)
25% quantile [95% CI]	19.3 [17.8, 20.4]	20.3 [18.2, 22.5]	18.6 [16.7, 20.0]	17.4 [14.5, 21.9]	19.5 [17.9, 20.7]
Median [95% CI]	24.6 [23.7, 26.3]	26.7 [23.9, 39.8]	22.9 [21.7, 25.5]	26.6 [19.1, NA]	24.6 [23.8, 26.3]
75% quantile [95% CI]	31.5 [27.8, 47.0]	39.8 [28.9, 54.1]	27.1 [25.6, 35.2]	NA [26.6, NA]	31.5 [27.8, 54.1]
12-month rate [95%-CI]	91.1% [88.7, 93.0]	92.3% [89.1, 94.5]	89.6% [85.6, 92.5]	95.3% [82.3, 98.8]	90.8% [88.3, 92.8]
18-month rate [95%-CI]	78.5% [74.4, 82.1]	81.0% [75.4, 85.4]	75.5% [68.8, 80.9]	73.9% [53.2, 86.5]	78.9% [74.6, 82.5]
24-month rate [95%-CI]	53.3% [46.1, 59.8]	59.5% [49.7, 68.1]	45.5% [35.2, 55.3]	52.5% [29.9, 70.9]	53.5% [46.0, 60.4]

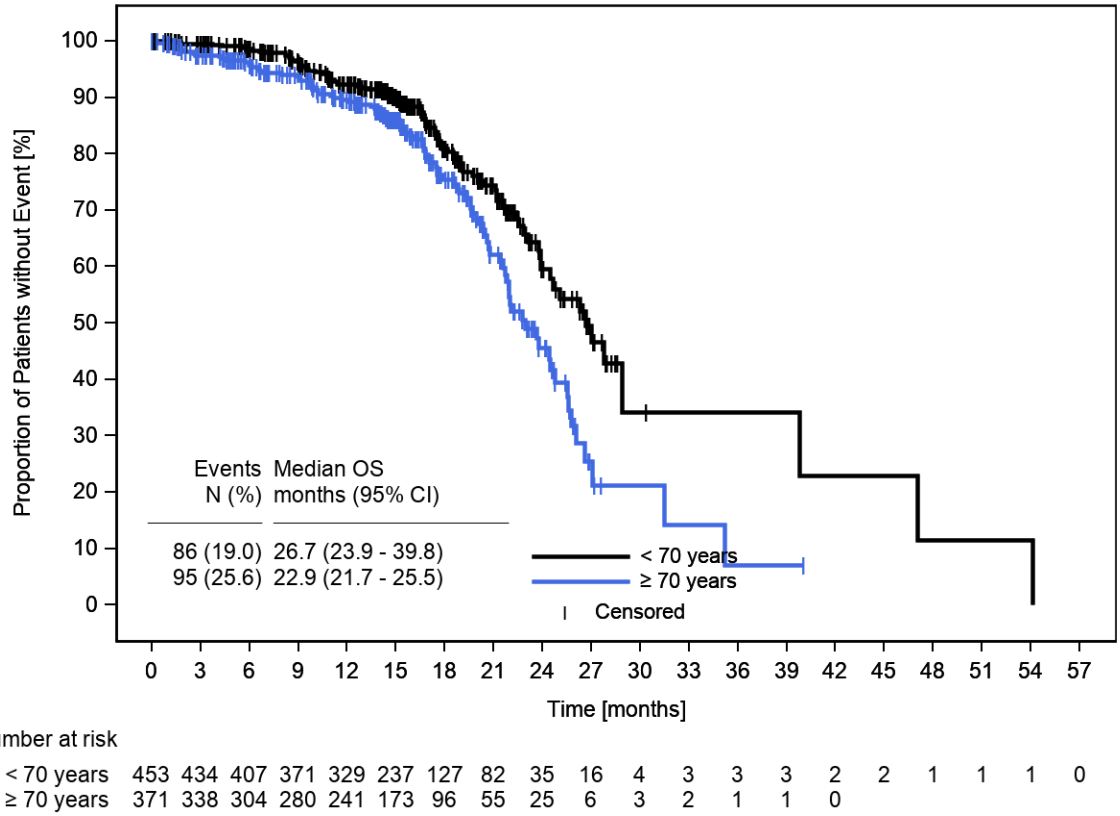
[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.4].
CAP = Core analysis population; CI = Confidence interval; N/n = Number; NA = Not reached.
[1]Overall survival was estimated using the Kaplan-Meier method. [2]Due to the low number of events the present OS data are no reliable estimators.

Figure 8-5 Overall survival overall (CAP)



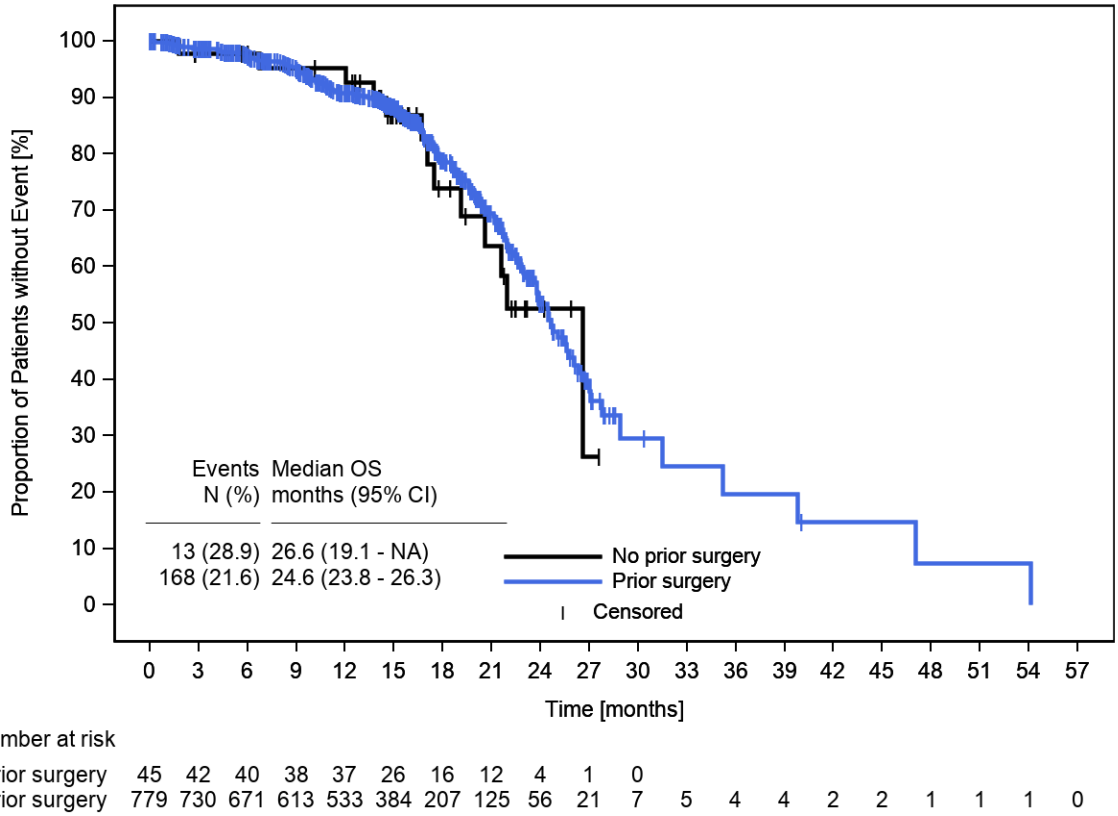
[Source: OTILIA_Figures_Final_3_20200127: Figure 2.2.1].
CAP = Core analysis population; CI = Confidence interval; N/n = Number; OS = Overall survival.
Overall survival was estimated using the Kaplan-Meier method. Due to the low number of events the present OS data are no reliable estimators.

Figure 8-6 Overall survival by age



[Source: OTILIA_Figures_Final_3_20200127: Figure 2.2.2].
CI = Confidence interval; N/n = Number; OS = Overall survival.
Overall survival was estimated using the Kaplan-Meier method. Due to the low number of events the present OS data are no reliable estimators.

Figure 8-7 Overall survival by prior surgery



[Source: OTILIA_Figures_Final_3_20200127: Figure 2.2.3].
CI = Confidence interval; N/n = Number; NA = Not reached; OS = Overall survival.
Overall survival was estimated using the Kaplan-Meier method. Due to the low number of events the present OS data are no reliable estimators.

8.4.1.3.1 Cox regression model

A multivariable Cox regression analysis was performed to identify potential independent factors (baseline demographics and clinical characteristics), which might have an impact on the OS (Table 8-15). This analysis showed that patients with an ECOG performance status of >1 had a worse outcome (OS) as compared to patients with an ECOG performance status of 0-1 (HR = 1.76; 95% CI: 1.16 - 2.67; p=0.008). Patients ≥70 years also had a worse OS as compared to patients <70 years (HR = 1.56; 95% CI: 1.15-2.13; p=0.004). In contrast, patients without visible residual disease at baseline had a better OS in comparison to patients with residual disease ≥1 cm (HR =0.58; 95% CI: 0.38-9-0.87; p=0.009) (Table 8-15).

Table 8-15 Overall survival – Cox regression model

	Hazard ratio	95% CI	p-value
ECOG performance status group			
> 1 vs. 0-1	1.76	[1.16, 2.67]	0.008
Unknown vs. 0-1	0.82	[0.39, 1.71]	0.588
Body mass index group			
≤ 20 vs. > 20-25	1.51	[0.96, 2.38]	0.075
> 25-30 vs. > 20-25	0.98	[0.67, 1.42]	0.903
> 30 vs. > 20-25	1.04	[0.67, 1.62]	0.848
Unknown vs. > 20-25	1.23	[0.55, 2.75]	0.610
Age subgroup			
≥ 70 vs. < 70	1.56	[1.15, 2.13]	0.004
Residual disease at baseline group			
No visible residuum vs. ⩾ 1 cm	0.58	[0.38, 0.87]	0.009
Unknown vs. ≥ 1 cm	0.89	[0.60, 1.33]	0.574
FIGO stage group			
IIIB vs. IIIC/IV	0.78	[0.46, 1.32]	0.352
Ascites at baseline group			
0 ml vs. > 0-500 ml	0.91	[0.12, 7.08]	0.925
> 500 ml vs. > 0-500 ml	1.28	[0.73, 2.24]	0.395
Unknown vs. > 0-500 ml	0.95	[0.57, 1.56]	0.830
Grading at baseline group			
G1 vs. G2/G3	1.24	[0.45, 3.44]	0.678
G4/GX vs. G2/G3	0.96	[0.57, 1.60]	0.862
Prior surgery subgroup			
No prior surgery vs. prior surgery	1.10	[0.55, 2.21]	0.782
Global likelihood ratio test			0.007

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.5].
CI = Confidence interval; ECOG = Eastern Cooperative Oncology Group; FIGO = Fédération Internationale de Gynécologie et d'Obstétrique.

8.4.2 Decisive factors for choice of treatment

In the CAP a tumor board decides in most cases about the therapy (n=561; 68.1%). The most common decisive factors (>25%) are guideline (n=695; 84.3%), efficacy of therapy (n=571; 69.3%), study results (n=404; 49.0%); tolerability of therapy (n=265; 32.2%), general condition of patient (n=246; 29.9%) and age of patient (n=214; 26.0%) (Table 8-16).

Similarly, in both age subgroups of patients <70 and ≥70 years a tumor board decides in most cases about the therapy (67.3% vs. 69.0%). In both age subgroups the guideline is the most frequent decisive factor (84.1% vs. 84.6%). In the subgroup of patients <70 years efficacy of therapy and study results are somewhat more frequent reasons for decision

than in the subgroup of patients ≥70 years (70.6% vs. 67.7% and 52.1% vs. 45.3%). In contrast, tolerability of therapy is a more frequent decisive factor in the subgroup of patients ≥70 years compared to patients <70 years (36.4% vs. 28.7%). Interestingly, general condition and age of patient and age are equally frequent decisive factors in both subgroups of patients <70 and ≥70 years (29.4% vs. 30.5% and 26.5% vs. 25.3%) (Table 8-16).

Table 8-16 Therapy Decision – Institution and decisive factors

	CAP (N=824)	Patients <70 years (N=453)	Patients ≥70 years (N=371)
Therapy Decision – Institution, n (%)			
Clinic physician	52 (6.3%)	27 (6.0%)	25 (6.7%)
Gynecologist	76 (9.2%)	42 (9.3%)	34 (9.2%)
NIO	80 (9.7%)	48 (10.6%)	32 (8.6%)
Oncologic consultation	49 (5.9%)	28 (6.2%)	21 (5.7%)
Tumor board	561 (68.1%)	305 (67.3%)	256 (69.0%)
Other	6 (0.7%)	3 (0.7%)	3 (0.8%)
Therapy Decision - Decisive factors, n (%)			
Age of patient	214 (26.0%)	120 (26.5%)	94 (25.3%)
Comorbidity	52 (6.3%)	24 (5.3%)	28 (7.5%)
Concomitant medication	18 (2.2%)	6 (1.3%)	12 (3.2%)
Distance clinic to home	21 (2.5%)	9 (2.0%)	12 (3.2%)
Efficacy of therapy	571 (69.3%)	320 (70.6%)	251 (67.7%)
General condition of patient	246 (29.9%)	133 (29.4%)	113 (30.5%)
Guideline	695 (84.3%)	381 (84.1%)	314 (84.6%)
Patient wish	86 (10.4%)	41 (9.1%)	45 (12.1%)
Study results	404 (49.0%)	236 (52.1%)	168 (45.3%)
Tolerability of therapy	265 (32.2%)	130 (28.7%)	135 (36.4%)
Other	6 (0.7%)	1 (0.2%)	5 (1.3%)

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.6].
CAP = Core analysis population; N/n = Number; NIO Niedergelassener internistischer Onkologe / Office-based medical oncologist.
Multiple answers provided for decisive factors.

8.4.3 Treatment duration

8.4.3.1 Treatment duration of the studied medicinal product

The treatment duration of bevacizumab (Avastin®) was estimated using the Kaplan-Meier method. In the CAP the median duration (95% CI) of bevacizumab (Avastin®) treatment was 13.8 months (12.7 – 14.5 months). In the subgroups of patients <70 and ≥70 years the median duration (95%CI) of bevacizumab (Avastin®) treatment was 14.6 months (13.9 – 15.2 months) and 12.5 months (11.1 – 13.8 months), respectively. In the subgroups of

patients without and with prior surgery the median treatment duration of bevacizumab (Avastin®) was 14.0 months (10.6 – 17.1 months) and 13.8 months (12.7 – 14.5 months) (Table 8-17). However, due to the small number of patients in the subgroup of patients without prior surgery (N=45) in comparison to the subgroup of patients with prior surgery (N=779) the comparability of these subgroups is limited.

Table 8-17 Treatment duration bevacizumab (Avastin®) (months) – Kaplan-Meier statistics

	Age subgroup			Surgery subgroup	
	CAP	Patients <70 years	Patients ≥70 years	No prior surgery	Prior surgery
Patients, N	824	453	371	45	779
Events, n (%)	453 (55.0%)	227 (50.1%)	226 (60.9%)	26 (57.8%)	427 (54.8%)
25% quantile [95% CI]	6.7 [5.7, 7.8]	7.9 [6.4, 9.1]	4.9 [4.1, 6.7]	8.8 [4.2, 11.0]	6.5 [5.6, 7.7]
Median [95% CI]	13.8 [12.7, 14.5]	14.6 [13.9, 15.2]	12.5 [11.1, 13.8]	14.0 [10.6, 17.1]	13.8 [12.7, 14.5]
75% quantile [95% CI]	NA [17.5, NA]	NA [18.0, NA]	17.5 [16.1, NA]	17.1 [15.7, 17.1]	NA [17.5, NA]

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.7].
CAP = Core analysis population; CI = Confidence interval; N/n = Number; NA = Not reached.
Treatment duration of bevacizumab (Avastin®) was estimated using the Kaplan-Meier method.

8.4.3.2 Treatment duration of carboplatin

In the CAP the median duration of carboplatin treatment was 3.5 months. In both subgroups of patients <70 and ≥70 years the median duration of carboplatin treatment was 3.5 months. In both subgroups of patients without and with prior surgery the median treatment duration of carboplatin was also 3.5 months (Table 8-18). However, the number of patients in the subgroup of patients without prior surgery (N=45) was very small in comparison to the subgroup of patients with prior surgery (N=779), which limits the comparability of these subgroups.

Table 8-18 Treatment duration carboplatin (months)

		Age subgroup		Surgery subgroup	
	CAP	Patients <70 years	Patients ≥70 years	No prior surgery	Prior surgery
Patients, N	824	453	371	45	779
Mean	3.4	3.4	3.4	3.2	3.4
StD	1.47	1.32	1.64	0.99	1.50
Median	3.5	3.5	3.5	3.5	3.5
25% quantile	3.0	3.4	2.9	3.0	3.0
75% quantile	3.7	3.7	3.7	3.7	3.7
Min	0.0	0.0	0.0	0.0	0.0
Max	17.7	15.5	17.7	4.9	17.7

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.8a; Table 14.2.8b; Table 14.2.8c].
CAP = Core analysis population; Max = Maximum; Min = Minimum; N/n = Number; StD = Standard deviation.
Treatment duration displayed in months. Patients who received only one dose of carboplatin the treatment duration is 0.03 displayed as 0.

8.4.3.3 Treatment duration of paclitaxel

In the CAP the median duration of paclitaxel treatment was 3.5 months. In both subgroups of patients <70 and ≥70 years the median duration of paclitaxel treatment was 3.5 months. In both subgroups of patients without and with prior surgery the median treatment duration of paclitaxel was also 3.5 months (Table 8-19). However, comparability of these subgroups is limited since the number of patients in the subgroup of patients without prior surgery (N=45) was very small in comparison to the subgroup of patients with prior surgery (N=779).

Table 8-19 Treatment duration paclitaxel (months)

	Age subgroup			Surgery subgroup	
	CAP	Patients <70 years	Patients ≥70 years	No prior surgery	Prior surgery
Patients, N	824	453	371	45	779
Mean	3.2	3.3	3.1	3.0	3.2
StD	1.08	1.01	1.16	1.11	1.08
Median	3.5	3.5	3.5	3.5	3.5
25% quantile	2.8	3.0	2.8	2.1	2.8
75% quantile	3.6	3.7	3.6	3.6	3.6
Min	0.0	0.0	0.0	0.0	0.0
Max	14.1	12.7	14.1	4.9	14.1

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.9a; Table 14.2.9b; Table 14.2.9c].
CAP = Core analysis population; Max = Maximum; Min = Minimum; N/n = Number; StD = Standard deviation.
Treatment duration displayed in months. Patients who received only one dose of paclitaxel the treatment duration is 0.03 displayed as 0.

8.4.3.4 Treatment duration of front-line treatment

The total duration of front-line treatment was estimated using the Kaplan-Meier method. In the CAP the median duration (95% CI) of front-line treatment was 14.5 months (13.4 – 15.0 months). In the subgroups of patients <70 and ≥70 years the median duration (95%CI) of front-line treatment was 15.2 months (14.5 – 15.8 months) and 13.1 months (11.8 – 14.5 months), respectively. In the subgroups of patients without and with prior surgery the median duration of front-line treatment was 14.0 months (11.3 – 17.1 months) and 14.5 months (13.4 – 15.0 months) (Table 8-20). However, the number of patients in the subgroup of patients without prior surgery (N=45) was very small in comparison to the subgroup of patients with prior surgery (N=779), which limits the comparability of these subgroups.

Table 8-20 Total duration of front-line treatment (months) – Kaplan-Meier statistics

		Age subgroup		Surgery subgroup	
	CAP	Patients <70 years	Patients ≥70 years	No prior surgery	Prior surgery
Patients, N	824	453	371	45	779
Events, n (%)	453 (55.0%)	227 (50.1%)	226 (60.9%)	26 (57.8%)	427 (54.8%)
25% quantile [95% CI]	7.5 [6.2, 8.3]	8.6 [7.3, 9.7]	5.6 [4.6, 7.5]	9.7 [4.8, 11.8]	7.3 [6.2, 8.3]
Median [95% CI]	14.5 [13.4, 15.0]	15.2 [14.5, 15.8]	13.1 [11.8, 14.5]	14.0 [11.3, 17.1]	14.5 [13.4, 15.0]
75% quantile [95% CI]	NA [18.0, NA]	NA [18.0, NA]	NA [17.1, NA]	17.1 [15.7, 17.1]	NA [18.0, NA]

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.10].
CAP = Core analysis population; CI = Confidence interval; N/n = Number; NA = Not reached.
Total duration of front-line treatment was estimated using the Kaplan-Meier method.

8.4.4 Total number of bevacizumab (Avastin®) administrations

In the CAP 824 patients received in total 12,431 bevacizumab (Avastin®) administrations. The median number of administrations (Min – Max) was 18.0 (1.0 – 25.0) (Table 8-21).

In the age subgroup <70 years 453 patients received in total 7,153 bevacizumab (Avastin®) administrations. The median number of administrations (Min – Max) was 19.0 (1.0 – 25.0). In the age subgroup ≥70 years 371 patients received in total 5,278 bevacizumab (Avastin®) administrations. The median number of administrations (Min – Max) was 17.0 (1.0 – 24.0) (Table 8-21).

In the surgery subgroup without prior surgery 45 patients received in total 713 bevacizumab (Avastin®) administrations. The median number of administrations (Min – Max) was 19.0 (1.0 – 24.0). In the surgery subgroup with prior surgery 779 patients received in total 11,718 bevacizumab (Avastin®) administrations. The median number of administrations (Min – Max) was 18.0 (1.0 – 25.0) (Table 8-21). However, due to the small number of patients in the subgroup of patients without prior surgery (N=45) in comparison to the subgroup of patients with prior surgery (N=779), comparability of these subgroups is limited.

Table 8-21 Total number of bevacizumab (Avastin®) administrations

	Age subgroup			Surgery subgroup	
	CAP	Patients <70 years	Patients ≥70 years	No prior surgery	Prior surgery
Patients, N	824	453	371	45	779
n applications	12,431	7,153	5,278	713	11,718
Mean	15.1	15.8	14.2	15.8	15.0
StD	6.96	6.67	7.21	6.83	6.97
Median	18.0	19.0	17.0	19.0	18.0
25% quantile	9.0	11.0	7.0	12.0	9.0
75% quantile	21.0	21.0	21.0	22.0	21.0
Min	1.0	1.0	1.0	1.0	1.0
Max	25.0	25.0	24.0	24.0	25.0

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.11a; Table 14.2.11b; Table 14.2.11c].
CAP = Core analysis population; Max = Maximum; Min = Minimum; N/n = Number; StD = Standard deviation.

8.4.5 Total dose of bevacizumab (Avastin®)

In the CAP the median total dose of bevacizumab (Avastin®) (Min – Max) was 267.1 mg/kg (14.7 – 381.5 mg/kg) (Table 8-22).

In the subgroup of patients <70 years the median total dose of bevacizumab (Avastin®) (Min – Max) of 284.7 mg/kg (14.8 – 381.5 mg/kg) was higher compared to the median total dose of bevacizumab (Avastin®) (Min – Max) of 239.3 mg/kg (14.7 – 374.9 mg/kg) in the subgroup of patients ≥70 years (Table 8-22).

In the subgroups of patients without and with prior surgery the median total dose of bevacizumab (Avastin®) (Min – Max) was 276.5 mg/kg (14.9 – 374.9 mg/kg) and 266.0 mg/kg (14.7 – 381.5 mg/kg), respectively (Table 8-22). However, the number of patients in the subgroup of patients without prior surgery (N=45) was very small in comparison to the subgroup of patients with prior surgery (N=779), which limits the comparability of these subgroups.

Table 8-22 Total (cumulative) dose of bevacizumab (Avastin®) (mg/kg)

	Age subgroup			Surgery subgroup	
	CAP	Patients <70 years	Patients ≥70 years	No prior surgery	Prior surgery
Patients, N	824	453	371	45	779
n applications	12,431	7,153	5,278	713	11,718
Mean	224.0	235.1	210.5	238.0	223.2
StD	103.52	99.48	106.83	102.78	103.57
Median	267.1	284.7	239.3	276.5	266.0
25% quantile	135.9	157.8	105.8	177.2	135.0
75% quantile	314.0	314.7	310.1	325.8	313.5
Min	14.7	14.8	14.7	14.9	14.7
Max	381.5	381.5	374.9	374.9	381.5

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.12a; Table 14.2.12b; Table 14.2.12c].
CAP = Core analysis population; Max = Maximum; Min = Minimum; N/n = Number; StD = Standard deviation.

8.4.6 Total dose of carboplatin

The median total dose of carboplatin (Min – Max) was 30.0 mg (4.0 – 2,893.0 mg) (Table 8-23).

In both age subgroups of patients <70 and ≥70 years the median total dose of carboplatin was 30.0 mg (5.0 – 2,893.0 mg and 4.0 – 600.0 mg) (Table 8-23).

Likewise, in both surgery subgroups of patients without and with prior surgery the median total dose of carboplatin was 30.0 mg (5.0 – 40.0 mg and 4.0 – 2,893.0 mg) (Table 8-23). However, comparability of these subgroups is limited since the number of patients in the subgroup of patients without prior surgery (N=45) was very small in comparison to the subgroup of patients with prior surgery (N=779).

Table 8-23 Total (cumulative) dose of carboplatin (mg)

		Age subgroup		Surgery subgroup	
	CAP	Patients <70 years	Patients ≥70 years	No prior surgery	Prior surgery
Patients, N	824	453	371	45	779
n applications	4,656	2,552	2,104	252	4,404
Mean	38.3	46.4	28.5	26.9	39.0
StD	155.13	207.15	30.52	7.30	159.52
Median	30.0	30.0	30.0	30.0	30.0
25% quantile	25.0	25.0	25.0	25.0	25.0
75% quantile	30.0	30.0	30.0	30.0	30.0
Min	4.0	5.0	4.0	5.0	4.0
Max	2,893.0	2,893.0	600.0	40.0	2,893.0

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.13a; Table 14.2.13b; Table 14.2.13c].
CAP = Core analysis population; Max = Maximum; Min = Minimum; N/n = Number; StD = Standard deviation.

8.4.7 Total dose of paclitaxel

The median total dose of paclitaxel (Min – Max) was 1,050.0 mg/m^2 (120.0 – 1,575.0 mg/m^2) (Table 8-24).

In both age subgroups of patients <70 and ≥70 years the median total dose of paclitaxel was 1,050.0 mg/m^2 (122.0 – 1,575.0 mg/m^2 and 120.0 – 1,440.0 mg/m^2) (Table 8-24).

Likewise, in both surgery subgroups of patients without and with prior surgery the median total dose of paclitaxel was 1,050.0 mg/m^2 (175.0 – 1,200.0 mg/m^2 and 120.0 – 1,575.0 mg/m^2) (Table 8-24). However, the number of patients in the subgroup of patients without prior surgery (N=45) was very small in comparison to the subgroup of patients with prior surgery (N=779), which limits the comparability of these subgroups.

Table 8-24 Total (cumulative) dose of paclitaxel (mg/m²)

		Age subgroup		Surgery subgroup	
	CAP	Patients <70 years	Patients ≥70 years	No prior surgery	Prior surgery
Patients, N	824	453	371	45	779
n applications	4,546	2,550	1,996	238	4,308
Mean	919.4	955.3	875.5	873.4	922.0
StD	231.21	209.18	248.95	257.07	229.56
Median	1,050.0	1,050.0	1,050.0	1,050.0	1,050.0
25% quantile	875.0	875.0	700.0	700.0	875.0
75% quantile	1,050.0	1,050.0	1,050.0	1,050.0	1,050.0
Min	120.0	122.0	120.0	175.0	120.0
Max	1,575.0	1,575.0	1,440.0	1,200.0	1,575.0

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.14a; Table 14.2.14b; Table 14.2.14c].
CAP = Core analysis population; Max = Maximum; Min = Minimum; N/n = Number; StD = Standard deviation.

8.4.8 Dose intensity of bevacizumab (Avastin®)

In the CAP the median dose intensity of bevacizumab (Avastin®) was 5.1 mg/kg per week (Table 8-25).

In both age subgroups of patients <70 and ≥70 years the median dose intensity of bevacizumab (Avastin®) was 5.1 mg/kg per week (Table 8-25).

Table 8-25 Dose intensity of bevacizumab (Avastin®) (mg/kg per week)

	CAP	Patients <70 years	Patients ≥70 years
N	824	453	371
n applications	12,431	7,153	5,278
Mean	8.4	7.8	9.2
StD	17.80	16.12	19.65
Median	5.1	5.1	5.1
25% quantile	4.8	4.8	4.7
75% quantile	5.4	5.3	5.5
Min	2.3	2.3	2.4
Max[1]	108.1	108.1	106.8

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.15a; Table 14.2.15b].
CAP = Core analysis population; Max = Maximum; Min = Minimum; N/n = Number; StD = Standard deviation.
[1]Maximum dose intensity of bevacizumab (Avastin®) seems to be a mistake in documentation.

8.4.9 Modifications of treatment and reasons thereof

8.4.9.1 Any treatment modification

In the CAP 79.2%, 43.0%, and 47.0% of patients had any modification of bevacizumab (Avastin®), carboplatin, and paclitaxel treatment, respectively (Table 8-26).

In the subgroups of patients <70 and ≥70 years the frequency of bevacizumab (Avastin®) modifications was similar (79.7% vs. 78.7%). However, treatment modifications of carboplatin and paclitaxel occurred more frequently in patients ≥70 years compared to patients <70 years (45.3% vs. 41.1% and 52.6% vs. 42.4%) (Table 8-26).

Table 8-26 Any treatment modification

	CAP (N=824)	Patients <70 years (N=453)	Patients ≥70 years (N=371)
Any treatment modification bevacizumab (Avastin®)	653 (79.2%)	361 (79.7%)	292 (78.7%)
Any treatment modification carboplatin	354 (43.0%)	186 (41.1%)	168 (45.3%)
Any treatment modification paclitaxel	387 (47.0%)	192 (42.4%)	195 (52.6%)

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.16a; Table 14.2.16b].
CAP = Core analysis population; N/n = Number.

8.4.9.2 Kind of treatment modification of bevacizumab (Avastin®)

In the CAP therapy interruption and therapy delay were the two most frequent kinds of treatment modification of bevacizumab (Avastin®) occurring in 67.5% (n=556) and 27.5% (n=227) of patients (Table 8-27).

Likewise, in both age subgroups of patients <70 and ≥70 years the two most frequent kinds of treatment modification of bevacizumab (Avastin®) were therapy interruption (n=303; 66.9% vs. n=253 ; 68.2%) and therapy delay (n=122; 26.9% vs. n=105; 28.3%) (Table 8-27).

Table 8-27 Kind of treatment modification of bevacizumab (Avastin®)[1]

	CAP (N=824)	Patients <70 years (N=453)	Patients ≥70 years (N=371)
Dose increase	50 (6.1%)	32 (7.1%)	18 (4.9%)
Dose reduction	57 (6.9%)	22 (4.9%)	35 (9.4%)
Therapy delay[2]	227 (27.5%)	122 (26.9%)	105 (28.3%)
Therapy interruption[2]	556 (67.5%)	303 (66.9%)	253 (68.2%)

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.19a; Table 14.2.19b].
CAP = Core analysis population; N/n = Number.
[1]Multiple observations provided. [2]There was no definition of therapy delay and therapy interruption or the difference of these two modifications provided in the observational plan or eCRF. It was at the discretion of the documenting person which of the two terms he/she chose for the treatment modification.

8.4.9.3 Reason for treatment modification of bevacizumab (Avastin®)

In the CAP the most frequent reason for treatment modification of bevacizumab (Avastin®) was physician decision (n=590; 71.6%). Patient's wish and toxicity were reasons for modification of bevacizumab (Avastin®) treatment in 18.0% (n=148) and 13.3% (n=110) of patients (Table 8-28).

In both age subgroups of patients <70 and ≥70 years physician decision was the most frequent reason for treatment modification of bevacizumab (Avastin®) treatment (n=328; 72.4% vs. n=262; 70.6%). Toxicity was somewhat more frequent the reason for treatment modification in patients ≥70 years compared to patients <70 years (n=55; 14.8% vs. n=55; 12.1%). The frequency of patient's wish as reason for treatment modifications was almost the same in both age subgroups of patients <70 and ≥70 years (n=81, 17.9% vs. n=67; 18.1%) (Table 8-28).

Table 8-28 Reason for treatment modification of bevacizumab (Avastin®)

	CAP (N=824)	Patients <70 years (N=453)	Patients ≥70 years (N=371)
Patient's wish	148 (18.0%)	81 (17.9%)	67 (18.1%)
Physician decision	590 (71.6%)	328 (72.4%)	262 (70.6%)
Toxicity	110 (13.3%)	55 (12.1%)	55 (14.8%)
Visit created by mistake	21 (2.5%)	8 (1.8%)	13 (3.5%)

[Source: OTILIA_Tables_Final_3_20200122: Table 14.2.19c; Table 14.2.19d].
CAP = Core analysis population; N/n = Number.
Multiple observations provided.

8.4.9.4 Kind of treatment modification of carboplatin

In the CAP the most common kinds of carboplatin treatment modification were therapy interruption (n=198; 24.0%), therapy delay (n=124; 15.0%) and dose reduction (n=98; 11.9%) (Table 8-29).

Similarly, in both age subgroups of patients <70 and ≥70 years the most common kinds of carboplatin treatment modification were therapy interruption (n=109; 24.1% vs. n=89; 24.0%), therapy delay (n=66; 14.6% vs. n=58; 15.6%) and dose reduction (n=45; 9.9% vs. n=53; 14.3%) (Table 8-29).

Table 8-29 Kind of treatment modification of carboplatin[1]

	CAP (N=824)	Patients <70 years (N=453)	Patients ≥70 years (N=371)
Dose increase	31 (3.8%)	22 (4.9%)	9 (2.4%)
Dose reduction	98 (11.9%)	45 (9.9%)	53 (14.3%)
Therapy delay[2]	124 (15.0%)	66 (14.6%)	58 (15.6%)
Therapy interruption[2]	198 (24.0%)	109 (24.1%)	89 (24.0%)

[Source: OTILIA_Tables_Final_3_20200122: Table 14.2.20a; Table 14.2.20b].
CAP = Core analysis population; N/n = Number.
[1]Multiple observations provided. [2]There was no definition of therapy delay and therapy interruption or the difference of these two modifications provided in the observational plan or eCRF. It was at the discretion of the documenting person which of the two terms he/she chose for the treatment modification.

8.4.9.5 Reason for treatment modification of carboplatin

In the CAP the most frequent reason for treatment modification of carboplatin was physician decision (n=253; 30.7%). Toxicity and patient's wish were reasons for modification of carboplatin treatment in 12.1% (n=100) and 5.6% (n=46) of patients (Table 8-30).

In both age subgroups of patients <70 and ≥70 years physician decision was the most frequent reason for treatment modification of carboplatin treatment (n=141; 31.1% vs. n=112; 30.2%). Toxicity and patient's wish was somewhat more frequent the reason for treatment modification in patients ≥70 years compared to patients <70 years (n=50; 13.5% vs. n=50; 11.0% and n=24, 6.5% vs. n=22; 4.9%) (Table 8-30).

Table 8-30 Reason for treatment modification of carboplatin

	CAP (N=824)	Patients <70 years (N=453)	Patients ≥70 years (N=371)
Patient's wish	46 (5.6%)	22 (4.9%)	24 (6.5%)
Physician decision	253 (30.7%)	141 (31.1%)	112 (30.2%)
Toxicity	100 (12.1%)	50 (11.0%)	50 (13.5%)
Visit created by mistake	9 (1.1%)	2 (0.4%)	7 (1.9%)

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.20c; Table 14.2.20d].
CAP = Core analysis population; N/n = Number.
Multiple observations provided.

8.4.9.6 Kind of treatment modification of paclitaxel

In the CAP the most common kinds of paclitaxel treatment modification were therapy interruption (n=246; 29.9%), therapy delay (n=112; 13.6%) and dose reduction (n=110; 13.3%) (Table 8-31).

In the subgroup of patients ≥70 years therapy interruption (n=124; 33.4% vs. n=122; 26.9%) and dose reduction (n=67; 18.1% vs. n=43; 9.5%.) of paclitaxel occurred more frequently in comparison to the subgroup of patients <70 years. The frequency of therapy delay was almost the same in both age subgroups of patients <70 and ≥70 years (n=62; 13.7% vs. n=50; 13.5%) (Table 8-31).

Table 8-31 Kind of treatment modification of paclitaxel[1]

	CAP (N=824)	Patients <70 years (N=453)	Patients ≥70 years (N=371
Dose increase	12 (1.5%)	7 (1.5%)	5 (1.3%)
Dose reduction	110 (13.3%)	43 (9.5%)	67 (18.1%)
Therapy delay[2]	112 (13.6%)	62 (13.7%)	50 (13.5%)
Therapy interruption[2]	246 (29.9%)	122 (26.9%)	124 (33.4%)

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.21a; Table 14.2.21b].
CAP = Core analysis population; N/n = Number.
[1]Multiple observations provided. [2]There was no definition of therapy delay and therapy interruption or the difference of these two modifications provided in the observational plan or eCRF. It was at the discretion of the documenting person which of the two terms he/she chose for the treatment modification.

8.4.9.7 Reason for treatment modification of paclitaxel

In the CAP the most frequent reason for treatment modification of paclitaxel was physician decision (n=258; 31.3%). Toxicity and patient's wish were reasons for modification of paclitaxel treatment in 17.1% (n=141) and 5.3% (n=44) of patients (Table 8-32).

In the subgroup of patients <70 and ≥70 years the frequency of physician decision (n=138; 30.5% vs. n=120; 32.3%) and patients wish (n=21; 4,6% vs. n=23; 6.2%) as reasons for modification of paclitaxel treatment were similar. However, toxicity was documented more frequently in the subgroup of patients ≥70 years compared to <70 years (n=82; 22.1% vs. n=59; 13.0%) (Table 8-32).

Table 8-32 Reason for treatment modification of paclitaxel

	CAP (N=824)	Patients <70 years (N=453)	Patients ≥70 years (N=371)
Patient's wish	44 (5.3%)	21 (4.6%)	23 (6.2%)
Physician decision	258 (31.3%)	138 (30.5%)	120 (32.3%)
Toxicity	141 (17.1%)	59 (13.0%)	82 (22.1%)
Visit created by mistake	8 (1.0%)	2 (0.4%)	6 (1.6%)

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.21c; Table 14.2.21d].
CAP = Core analysis population; N/n = Number.
Multiple observations provided.

8.4.10 Reasons for end of treatment documentation

In the CAP the two most common reasons for end of treatment documentation were end of documentation after 15 months (n=349; 42.4%) and tumor progression (n=196; 23.8%). These two were also the most common reasons for end of treatment documentation in both age subgroups (end of documentation after 15 months: <70 years n=213; 47.0% and n=136; 36.7%, tumor progression: <70 years n=105; 23.2% and ≥70 years n=91; 24.5%; Table 8-33).

Table 8-33 Reasons for end of treatment documentation

	Total	Patients <70 years	Patients ≥70 years
Total number of patients	824	453	371
Reasons for end of treatment documentation (n, %)			
AE not related to therapy[1]	25 (3.0)	8 (1.8)	17 (4.6)
AE related to therapy[1]	40 (4.9)	11 (2.4)	29 (7.8)
Adverse event[1]	44 (5.3)	30 (6.6)	14 (3.8)
Death	16 (1.9)	5 (1.1)	11 (3.0)
End of documentation after 15 months	349 (42.4)	213 (47.0)	136 (36.7)
Lost-to-Follow-up	15 (1.8)	10 (2.2)	5 (1.3)

	Total	Patients <70 years	Patients ≥70 years
Other reason (specification)	48 (5.8)	31 (6.8)	17 (4.6)
Patient's wish	7 (0.8)	3 (0.7)	4 (1.1)
Patient's wish (no toxicity)	53 (6.4)	24 (5.3)	29 (7.8)
Tumor progression	196 (23.8)	105 (23.2)	91 (24.5)
Tumor remission	13 (1.6)	7 (1.5)	6 (1.6)
No EOT documentation	18 (2.2)	6 (1.3)	12 (3.2)

[Source: OTILIA_Tables_Final_4_20200420: Table 14.1.1].
AE = Adverse event; EOT = end of treatment; N/n = Number.
[1]In an eCRF update the reason for end of treatment documentation "Adverse event" was replaced by "AE not related to therapy" and "AE related to therapy" on 01 October 2013.

8.4.11 Previous radiotherapy

In the CAP only 0.9% of patients (n=7) received a previous radiotherapy whereas 97.6% of patients (n=802) did not (Table 8-34).

In the subgroups of patients <70 and ≥70 years 1.1% (n=5) and 0.5% (n=2) received a previous radiotherapy. The majority of patients did not receive a previous radiotherapy (n=441; 97.8% and n=361; 97.3%) (Table 8-34).

Table 8-34 Previous radiotherapy

	CAP (N=824)	Patients <70 years (N=453)	Patients ≥70 years (N=371)
N (non-missing)	822	451	371
Yes	7 (0.9%)	5 (1.1%)	2 (0.5%)
No	802 (97.6%)	441 (97.8%)	361 (97.3%)
Unknown	13 (1.6%)	5 (1.1%)	8 (2.2%)
Missing	2	2	0

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.22a; Table 14.2.22b].
CAP = Core analysis population; N/n = Number.

8.4.12 Quality of life over time

QoL was assessed by the validated EORTC questionnaires QLQ-C30 and QLQ-OV28. Patients answered these questionnaires at baseline as well as 12, 24, 39 and 66 weeks after inclusion.

After amendment 2 of the observational plan dated 25 July 2014 retrospective patient inclusion for up to one cycle was feasible but retrospectively included patients were not excluded from the QLQ project. Retrospectively included patients may have filled in their

baseline questionnaire after first study treatment and this may introduce a bias into the baseline QoL data.

Due to a non-accurate ICF some filled in questionnaires cannot be used for analysis. Only questionnaires of patients with a valid ICF were allowed to be used for analysis. This approach may introduce a survivorship bias into the data. Taken this into account, 493 patients in the CAP were willing to participate in the QoL assessment and had signed a valid ICF. In the subgroups of patients <70 and ≥70 years 360 and 133 patients with valid ICF participated in the QoL assessment, respectively (Table 8-35).

Table 8-35 Patient population for QLQ analyses

	N
CAP	493
Patients <70 years	360
Patients ≥70 years	133

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.23].
CAP = Core analysis population; N/n = Number; QLQ = Quality of life questionnaire.
Due to non-accurate informed consent forms (ICF) some filled in questionnaires cannot be used for analysis. The total population for questionnaire analyses includes all patients of CAP with a valid ICF and willing to participate in the quality of life assessment.

Besides the questionnaire return rate the following chapters will describe the global health status and important items of the EORTC QLQ-C30 and QLQ-OV28 questionnaires with obvious changes over time.

8.4.12.1 Return rate of questionnaires

The two questionnaires EORTC QLQ-C30 and QLQ-OV28 were handed out to the patient as a stitched together document. For the patient it was not apparent where the one questionnaire ends, and the other questionnaire starts. Accordingly, both questionnaires were sent back by the patient as one connected document. Hence, questionnaire return rates are displayed for both questionnaires together in Table 8-36.

At baseline 64.6% of questionnaires (n=405) returned in the CAP. In the course of the study the questionnaire return rate declined to 41.1% (n=258) in week 66 after inclusion. Similarly, in the subgroup of patients <70 years 68.3% (n=308) of questionnaires returned at baseline and this declined to 44.1% (n=199) in week 66. In comparison, in the subgroup of patients ≥70 years only 55.1% (n=97) of questionnaires returned at baseline and in the course of study the return rate decreased to 33.5% (n=59) in week 66 (Table 8-36).

Table 8-36 Return rate of EORTC QLQ-C30 + QLQ-OV28 questionnaires

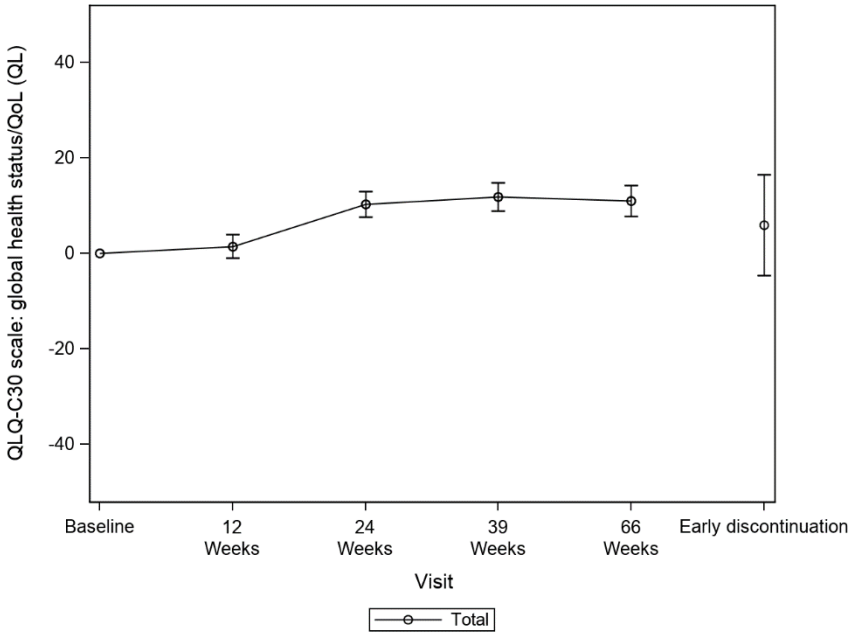
	Baseline	12 weeks	24 weeks	39 weeks	66 weeks	Early discontinuation
CAP (N=493)	405 (64.6%)	394 (62.8%)	365 (58.2%)	327 (52.2%)	258 (41.1%)	35 (5.6%)
Patients <70 years (N=360)	308 (68.3%)	301 (66.7%)	283 (62.7%)	249 (55.2%)	199 (44.1%)	26 (5.8%)
Patients ≥70 years (N=133)	97 (55.1%)	93 (52.8%)	82 (46.6%)	78 (44.3%)	59 (33.5%)	9 (5.1%)

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.23].
CAP = Core analysis population; EORTC = European Organisation for Research and Treatment of Cancer; N/n = Number; QLQ = Quality of life questionnaire.
Due to non-accurate informed consent forms (ICF) some filled in questionnaires cannot be used for analysis. The total population for questionnaire analyses includes all patients of CAP with a valid ICF and willing to participate in the quality of life assessment.

8.4.12.2 EORTC QLQ-C30: Global health status

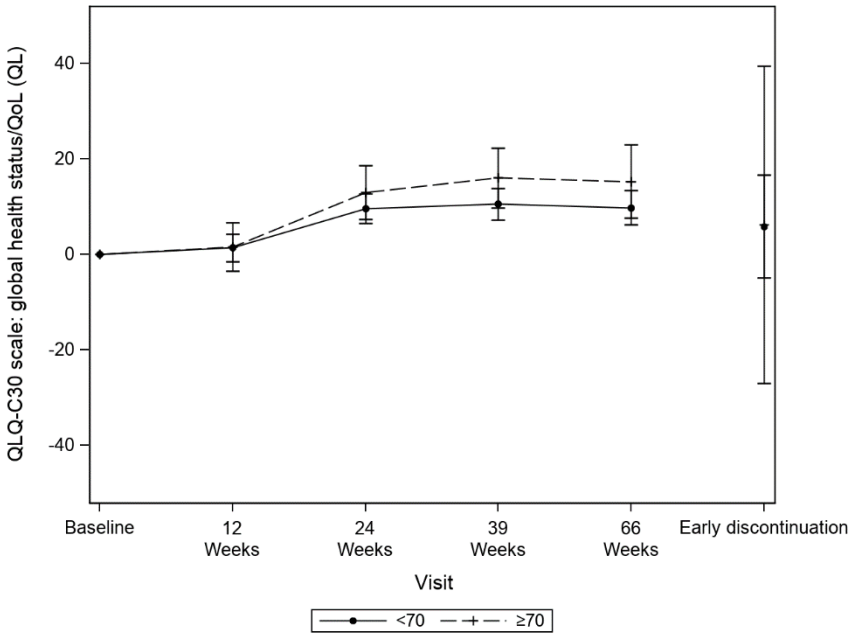
In the CAP the global health status improved by about 10 points from baseline to week 24 and then stayed at this level until week 66 (Figure 8-8 and Table 8-37). The same course of the global health status was observed in both age subgroups whereby the global health status improved somewhat more in the subgroup of patients ≥70 years (Figure 8-9 and Table 8-37).

Figure 8-8 EORTC QLQ-C30: Change from baseline in Global health status (mean) - CAP



[Source: OTILIA_Figures_Final_3_20200127: Figure 14.2.5a].
CAP = Core analysis population; EORTC = European Organisation for Research and Treatment of Cancer; QLQ = Quality of life questionnaire; QoL = quality of life.
A high score for the global health status represents a high quality of life.

Figure 8-9 EORTC QLQ-C30: Change from baseline in Global health status (mean) - Age subgroups



[Source: OTILIA_Figures_Final_3_20200127: Figure 14.2.5aa].
EORTC = European Organisation for Research and Treatment of Cancer ; QLQ = Quality of life questionnaire; QoL = quality of life.
A high score for the global health status represents a high quality of life.

Table 8-37 EORTC QLQ-C30: Change from baseline in Global health status

	12 weeks	24 weeks	39 weeks	66 weeks	Early discontinuation
CAP (N=493)					
N	353	327	294	231	31
Mean	1.4	10.3	11.8	11.0	5.9
StD	23.70	24.68	25.41	25.21	28.72
Median	0.0	8.3	8.3	8.3	8.3
25% quantile	-16.7	0.0	0.0	0.0	-16.7
75% quantile	16.7	25.0	33.3	33.3	25.0
Min	-83.3	-58.3	-83.3	-66.7	-41.7
Max	83.3	83.3	83.3	83.3	66.7
Patients <70 years (N=360)					
N	271	257	226	178	23
Mean	1.4	9.6	10.5	9.7	5.8
StD	23.93	24.93	25.17	24.30	24.93
Median	0.0	8.3	8.3	8.3	8.3
25% quantile	-16.7	0.0	0.0	-8.3	-8.3
75% quantile	16.7	25.0	25.0	25.0	25.0
Min	-83.3	-58.3	-83.3	-50.0	-41.7
Max	83.3	83.3	83.3	83.3	41.7

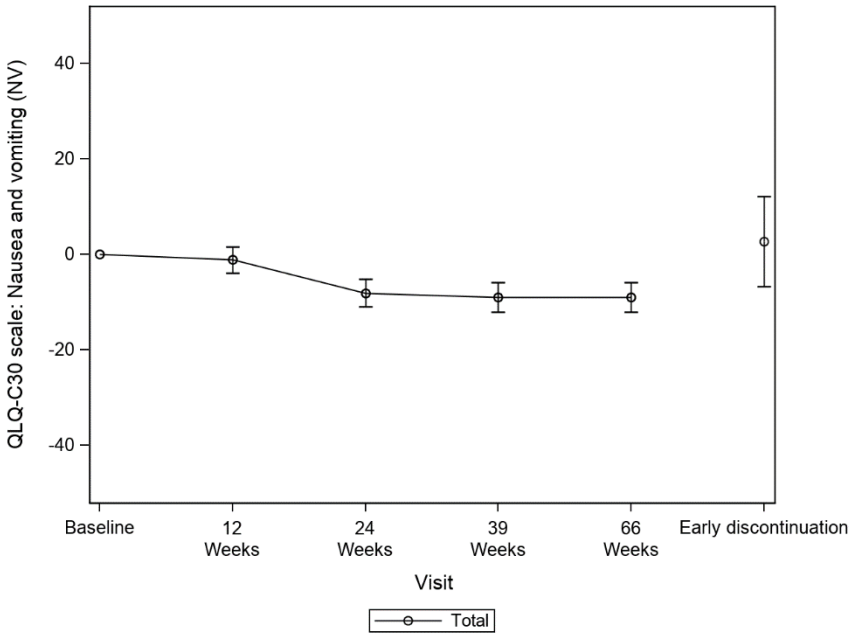
	12 weeks	24 weeks	39 weeks	66 weeks	Early discontinuation
Patients ≥70 years (N=133)					
N	82	70	68	53	8
Mean	1.6	13.0	16.1	15.3	6.3
StD	23.07	23.72	25.93	27.87	39.78
Median	0.0	8.3	16.7	16.7	-4.2
25% quantile	-16.7	0.0	-8.3	0.0	-25.0
75% quantile	16.7	33.3	37.5	33.3	37.5
Min	-58.3	-33.3	-50.0	-66.7	-33.3
Max	58.3	83.3	66.7	83.3	66.7

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.27a; Table 14.2.27b, Table 14.2.27c].
CAP = Core analysis population; EORTC = European Organisation for Research and Treatment of Cancer; Max = Maximum; Min = Minimum; N/n = Number; StD = Standard deviation.
Due to non-accurate informed consent forms (ICF) some filled in questionnaires cannot be used for analysis. The total population for questionnaire analyses includes all patients of CAP with a valid ICF and willing to participate in the quality of life assessment. A high score for the global health status represents a high quality of life.

8.4.12.3 EORTC QLQ-C30: Nausea and vomiting

In the CAP nausea and vomiting improved by about 9 points from baseline to week 24 and then stayed at this level until week 66 (Figure 8-10 and Table 8-38). A similar course of nausea and vomiting was observed in both age subgroups. However, nausea and vomiting improved more in the subgroup of patients ≥70 years (Figure 8-11 and Table 8-38).

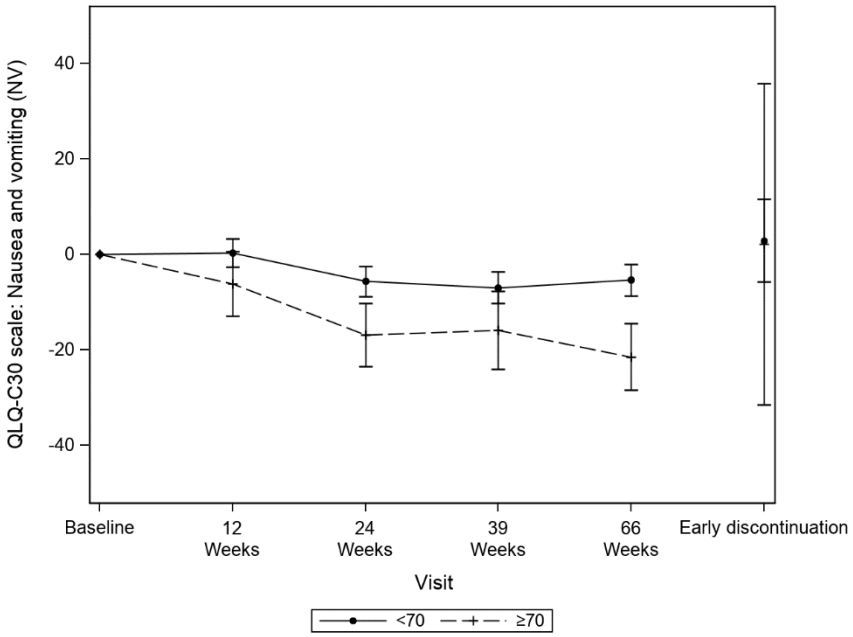
Figure 8-10 EORTC QLQ-C30: Change from baseline in Nausea and vomiting (mean) - CAP



[Source: OTILIA_Figures_Final_3_20200127: Figure 14.2.5h].

CAP = Core analysis population; EORTC = European Organisation for Research and Treatment of Cancer; QLQ = Quality of life questionnaire.
A high sore for a symptom scale/item represents a high level of symptomatology/problems.

Figure 8-11 EORTC QLQ-C30: Change from baseline in Nausea and vomiting (mean) – Age subgroups



[Source: OTILIA_Figures_Final_3_20200127: Figure 14.2.5ah].
EORTC = European Organisation for Research and Treatment of Cancer; QLQ = Quality of life questionnaire.
A high sore for a symptom scale/item represents a high level of symptomatology/problems.

Table 8-38 EORTC QLQ-C30: Change from baseline in nausea and vomiting

	12 weeks	24 weeks	39 weeks	66 weeks	Early discontinuation
CAP (N=493)					
N	355	329	291	232	31
Mean	-1.2	-8.1	-9.0	-9.0	2.7
StD	26.68	26.96	27.34	24.02	25.85
Median	0.0	0.0	0.0	0.0	0.0
25% quantile	-16.7	-16.7	-16.7	-16.7	-16.7
75% quantile	16.7	0.0	0.0	0.0	16.7
Min	-100.0	-100.0	-100.0	-83.3	-83.3
Max	100.0	100.0	100.0	100.0	50.0
Patients <70 years (N=360)					
N	274	258	225	180	23
Mean	0.3	-5.7	-7.0	-5.4	2.9
StD	25.34	26.18	25.07	22.47	19.88
Median	0.0	0.0	0.0	0.0	0.0
25% quantile	0.0	-16.7	-16.7	-16.7	-16.7

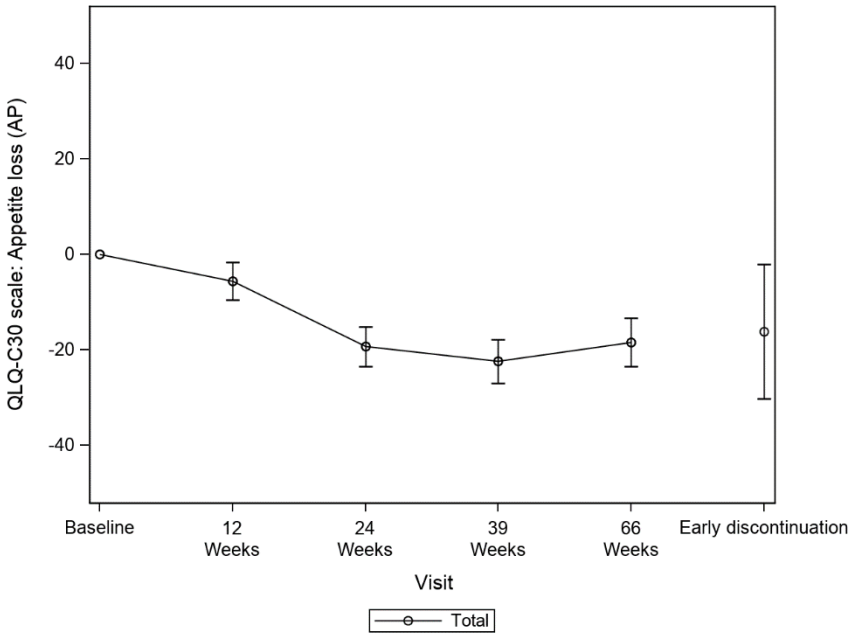
	12 weeks	24 weeks	39 weeks	66 weeks	Early discontinuation
75% quantile	16.7	0.0	0.0	0.0	16.7
Min	-100.0	-100.0	-100.0	-83.3	-33.3
Max	100.0	100.0	100.0	100.0	33.3
Patients ≥70 years (N=133)					
N	81	71	66	52	8
Mean	-6.2	-16.9	-15.9	-21.5	2.1
StD	30.44	28.10	33.26	25.21	40.27
Median	0.0	0.0	0.0	-16.7	8.3
25% quantile	-16.7	-33.3	-33.3	-33.3	-8.3
75% quantile	16.7	0.0	0.0	0.0	25.0
Min	-100.0	-100.0	-100.0	-83.3	-83.3
Max	66.7	33.3	100.0	16.7	50.0

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.27a; Table 14.2.27b, Table 14.2.27c].
CAP = Core analysis population; EORTC = European Organisation for Research and Treatment of Cancer; Max = Maximum; Min = Minimum; N/n = Number; StD = Standard deviation.
Due to non-accurate informed consent forms (ICF) some filled in questionnaires cannot be used for analysis. The total population for questionnaire analyses includes all patients of CAP with a valid ICF and willing to participate in the quality of life assessment. A high sore for a symptom scale/item represents a high level of symptomatology/problems.

8.4.12.4 EORTC QLQ-C30: Appetite loss

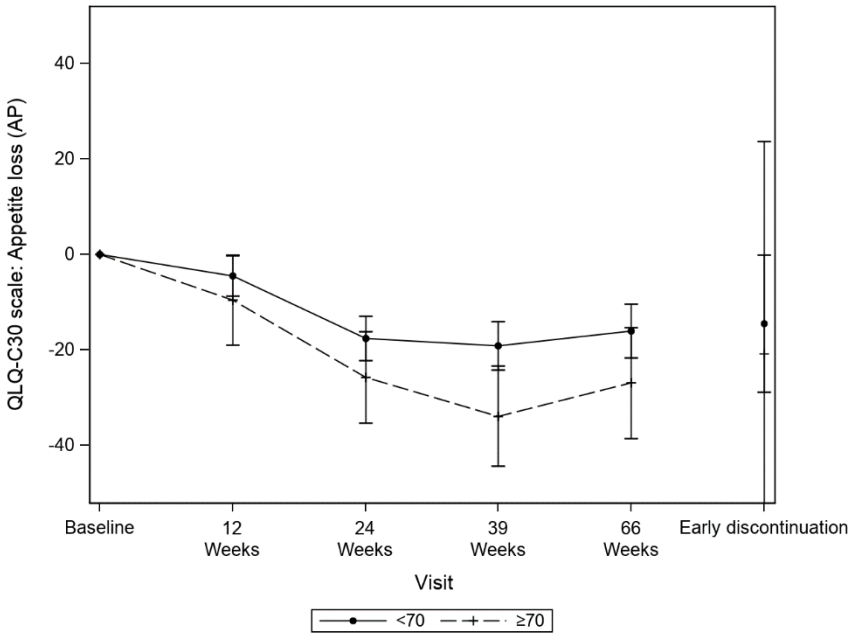
In the CAP appetite loss improved over time by about 20 points (Figure 8-12 and Table 8-39). In the subgroup of patients ≥70 years the improvement in appetite loss was more pronounced in comparison to the subgroup of patients <70 years. (Figure 8-13 and Table 8-39).

Figure 8-12 EORTC QLQ-C30: Change from baseline in Appetite loss (mean) - CAP



[Source: OTILIA_Figures_Final_3_20200127: Figure 14.2.5l].
CAP = Core analysis population; EORTC = European Organisation for Research and Treatment of Cancer; QLQ = Quality of life questionnaire.
A high sore for a symptom scale/item represents a high level of symptomatology/problems.

Figure 8-13 EORTC QLQ-C30: Change from baseline in Appetite loss (mean) – Age subgroups



[Source: OTILIA_Figures_Final_3_20200127: Figure 14.2.5al].
EORTC = European Organisation for Research and Treatment of Cancer; QLQ = Quality of life questionnaire.
A high sore for a symptom scale/item represents a high level of symptomatology/problems.

Table 8-39 EORTC QLQ-C30: Change from baseline in Appetite loss

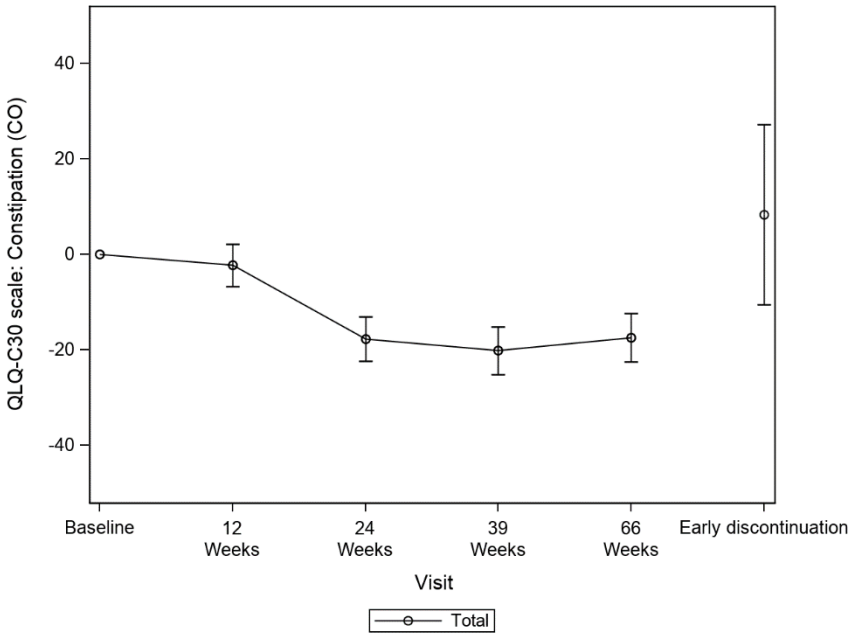
	12 weeks	24 weeks	39 weeks	66 weeks	Early discontinuation
CAP (N=493)					
N	355	328	290	233	31
Mean	-5.6	-19.3	-22.4	-18.5	-16.1
StD	37.58	38.31	39.60	39.49	38.37
Median	0.0	0.0	0.0	0.0	0.0
25% quantile	-33.3	-33.3	-33.3	-33.3	-33.3
75% quantile	0.0	0.0	0.0	0.0	0.0
Min	-100.0	-100.0	-100.0	-100.0	-100.0
Max	100.0	100.0	100.0	100.0	33.3
Patients <70 years (N=360)					
N	275	258	226	181	23
Mean	-4.5	-17.6	-19.2	-16.0	-14.5
StD	36.02	37.68	38.44	38.58	33.07
Median	0.0	0.0	0.0	0.0	0.0
25% quantile	-33.3	-33.3	-33.3	-33.3	-33.3
75% quantile	0.0	0.0	0.0	0.0	0.0
Min	-100.0	-100.0	-100.0	-100.0	-66.7
Max	100.0	100.0	100.0	100.0	33.3
Patients ≥70 years (N=133)					
N	80	70	64	52	8
Mean	-9.6	-25.7	-33.9	-26.9	-20.8
StD	42.49	40.20	41.78	41.77	53.27
Median	0.0	-33.3	-33.3	-33.3	0.0
25% quantile	-33.3	-66.7	-66.7	-33.3	-66.7
75% quantile	0.0	0.0	0.0	0.0	16.7
Min	-100.0	-100.0	-100.0	-100.0	-100.0
Max	100.0	33.3	33.3	100.0	33.3

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.27a; Table 14.2.27b, Table 14.2.27c].
CAP = Core analysis population; EORTC = European Organisation for Research and Treatment of Cancer; Max = Maximum; Min = Minimum; N/n = Number; StD = Standard deviation.
Due to non-accurate informed consent forms (ICF) some filled in questionnaires cannot be used for analysis. The total population for questionnaire analyses includes all patients of CAP with a valid ICF and willing to participate in the quality of life assessment. A high sore for a symptom scale/item represents a high level of symptomatology/problems.

8.4.12.5 EORTC QLQ-C30: Constipation

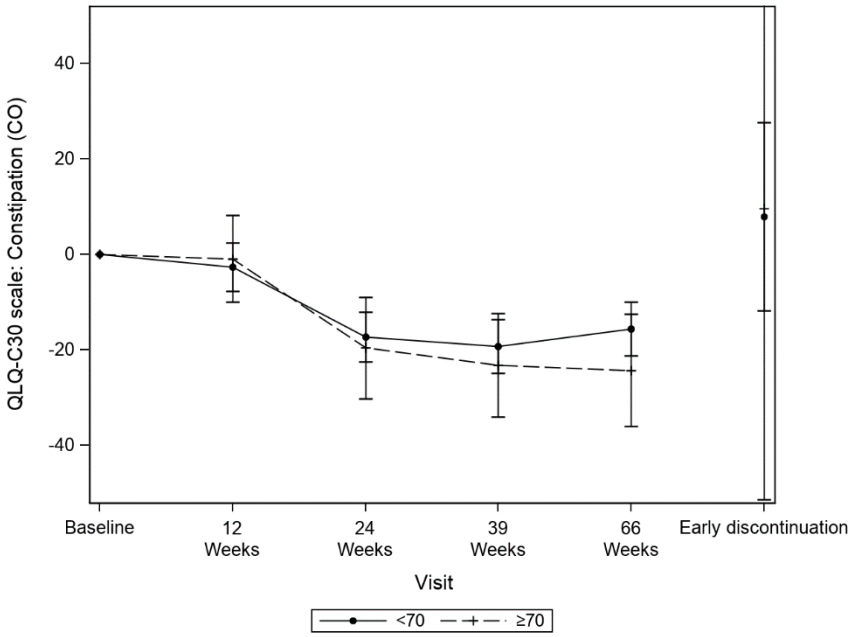
In the CAP constipation improved by about 20 points from baseline to week 24 and then stayed at this level until week 66 (Figure 8-14 and Table 8-40). A similar course of constipation was observed in both age subgroups (Figure 8-15 and Table 8-40).

Figure 8-14 EORTC QLQ-C30: Change from baseline in Constipation (mean) - CAP



[Source: OTILIA_Figures_Final_3_20200127: Figure 14.2.5m].
CAP = Core analysis population; EORTC = European Organisation for Research and Treatment of Cancer; QLQ = Quality of life questionnaire.
A high sore for a symptom scale/item represents a high level of symptomatology/problems.

Figure 8-15 EORTC QLQ-C30: Change from baseline in Constipation (mean) – Age subgroups



[Source: OTILIA_Figures_Final_3_20200127: Figure 14.2.5am].
EORTC = European Organisation for Research and Treatment of Cancer; QLQ = Quality of life questionnaire.
A high sore for a symptom scale/item represents a high level of symptomatology/problems.

Table 8-40 EORTC QLQ-C30: Change from baseline in constipation

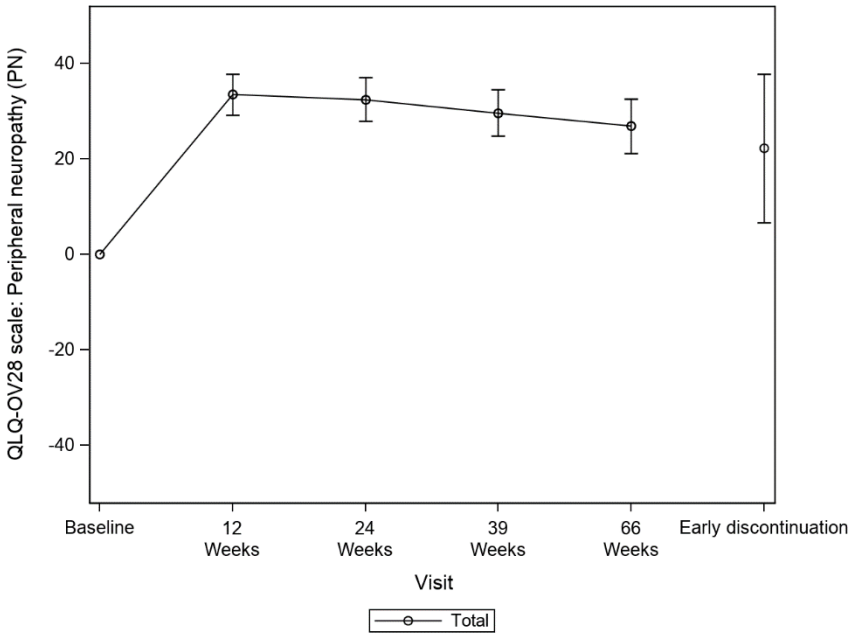
	12 weeks	24 weeks	39 weeks	66 weeks	Early discontinuation
CAP (N=493)					
N	338	317	281	225	28
Mean	-2.3	-17.8	-20.2	-17.5	8.3
StD	41.22	41.97	42.41	38.58	48.54
Median	0.0	0.0	0.0	0.0	0.0
25% quantile	-33.3	-33.3	-33.3	-33.3	-16.7
75% quantile	0.0	0.0	0.0	0.0	33.3
Min	-100.0	-100.0	-100.0	-100.0	-100.0
Max	100.0	100.0	100.0	66.7	100.0
Patients <70 years (N=360)					
N	264	249	218	177	21
Mean	-2.7	-17.3	-19.3	-15.6	7.9
StD	41.79	41.49	42.28	37.95	43.34
Median	0.0	0.0	0.0	0.0	0.0
25% quantile	-33.3	-33.3	-33.3	-33.3	0.0
75% quantile	16.7	0.0	0.0	0.0	33.3
Min	-100.0	-100.0	-100.0	-100.0	-66.7
Max	100.0	100.0	100.0	66.7	100.0
Patients ≥70 years (N=133)					
N	74	68	63	48	7
Mean	-0.9	-19.6	-23.3	-24.3	9.5
StD	39.39	43.95	43.02	40.53	65.87
Median	0.0	0.0	-33.3	-33.3	0.0
25% quantile	-33.3	-33.3	-33.3	-50.0	-33.3
75% quantile	0.0	0.0	0.0	0.0	66.7
Min	-100.0	-100.0	-100.0	-100.0	-100.0
Max	100.0	100.0	66.7	66.7	100.0

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.27a; Table 14.2.27b, Table 14.2.27c].
CAP = Core analysis population; EORTC = European Organisation for Research and Treatment of Cancer; Max = Maximum; Min = Minimum; N/n = Number; StD = Standard deviation.
Due to non-accurate informed consent forms (ICF) some filled in questionnaires cannot be used for analysis. The total population for questionnaire analyses includes all patients of CAP with a valid ICF and willing to participate in the quality of life assessment. A high sore for a symptom scale/item represents a high level of symptomatology/problems.

8.4.12.6 EORTC QLQ-OV28: Peripheral neuropathy

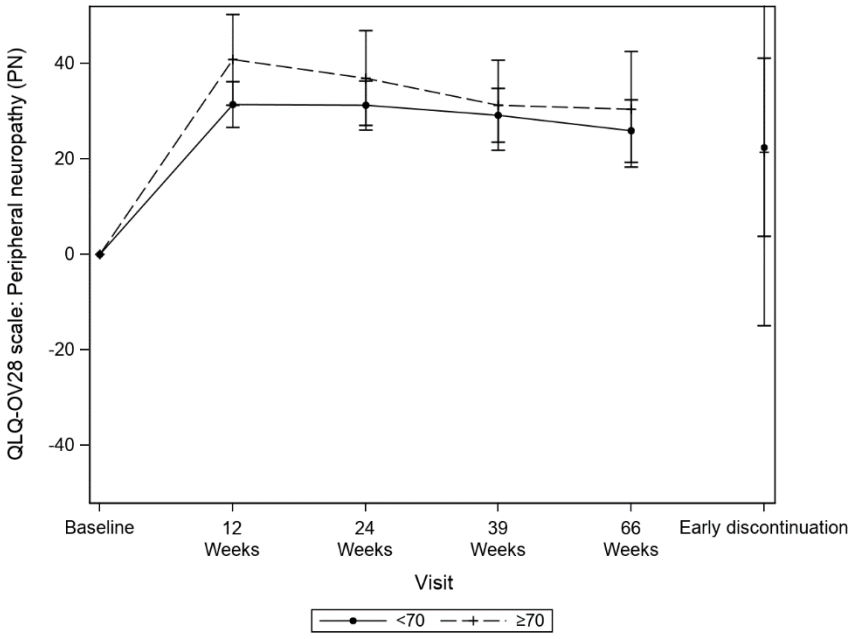
In the CAP peripheral neuropathy considerably worsened by about 30 points from baseline to week 12 and then stayed at this level until week 66 (Figure 8-16 and Table 8-41). A similar deterioration of peripheral neuropathy was observed in both age subgroups (Figure 8-17 and Table 8-41).

Figure 8-16 EORTC QLQ-OV28: Change from baseline in Peripheral neuropathy (mean) – CAP



[Source: OTILIA_Figures_Final_3_20200127: Figure 14.2.6b].
CAP = Core analysis population; EORTC = European Organisation for Research and Treatment of Cancer; QLQ = Quality of life questionnaire.
A high sore for a symptom scale/item represents a high level of symptomatology/problems.

Figure 8-17 EORTC QLQ-OV28: Change from baseline in Peripheral neuropathy (mean) – Age subgroups



[Source: OTILIA_Figures_Final_3_20200127: Figure 14.2.6ab].
EORTC = European Organisation for Research and Treatment of Cancer; QLQ = Quality of life questionnaire.
A high sore for a symptom scale/item represents a high level of symptomatology/problems.

Table 8-41 EORTC QLQ-OV28: Change from baseline in peripheral neuropathy

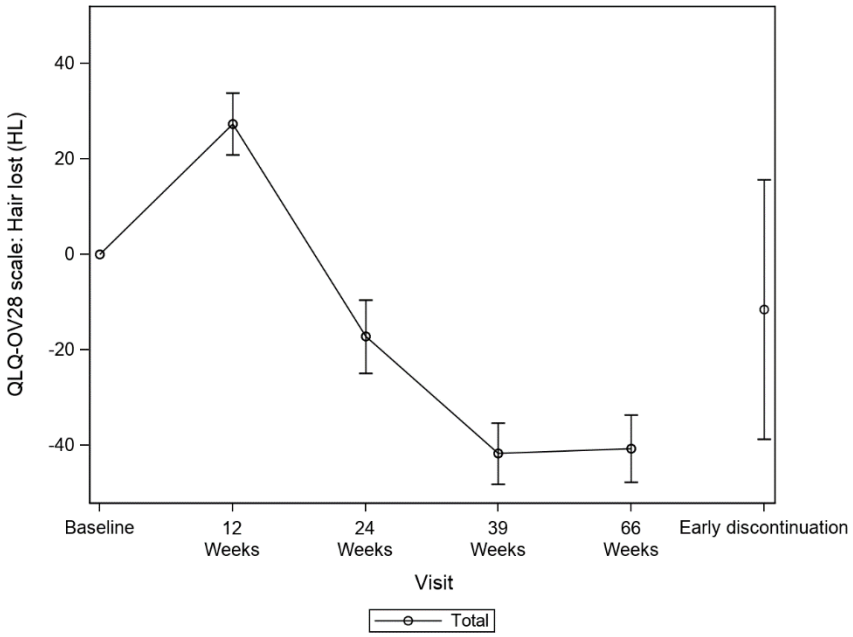
	12 weeks	24 weeks	39 weeks	66 weeks	Early discontinuation
CAP (N=493)					
N	351	326	288	230	30
Mean	33.5	32.5	29.6	26.9	22.2
StD	40.54	41.72	41.78	44.06	41.60
Median	33.3	33.3	16.7	16.7	25.0
25% quantile	0.0	0.0	0.0	0.0	0.0
75% quantile	66.7	66.7	66.7	66.7	50.0
Min	-100.0	-100.0	-83.3	-100.0	-83.3
Max	100.0	100.0	100.0	100.0	100.0
Patients <70 years (N=360)					
N	273	257	224	179	23
Mean	31.4	31.3	29.2	25.9	22.5
StD	39.92	41.85	42.94	44.42	43.11
Median	33.3	33.3	16.7	16.7	33.3
25% quantile	0.0	0.0	0.0	0.0	0.0
75% quantile	66.7	66.7	66.7	66.7	66.7
Min	-100.0	-100.0	-83.3	-100.0	-83.3
Max	100.0	100.0	100.0	100.0	100.0
Patients ≥70 years (N=133)					
N	78	69	64	51	7
Mean	40.8	37.0	31.3	30.4	21.4
StD	42.10	41.21	37.74	43.04	39.34
Median	33.3	33.3	33.3	16.7	0.0
25% quantile	0.0	0.0	0.0	0.0	0.0
75% quantile	83.3	66.7	58.3	66.7	33.3
Min	-66.7	-50.0	-50.0	-66.7	-16.7
Max	100.0	100.0	100.0	100.0	100.0

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.28a; Table 14.2.28b, Table 14.2.28c].
CAP = Core analysis population; EORTC = European Organisation for Research and Treatment of Cancer; Max = Maximum; Min = Minimum; N/n = Number; StD = Standard deviation.
Due to non-accurate informed consent forms (ICF) some filled in questionnaires cannot be used for analysis. The total population for questionnaire analyses includes all patients of CAP with a valid ICF and willing to participate in the quality of life assessment. A high sore for a symptom scale/item represents a high level of symptomatology/problems.

8.4.12.7 EORTC QLQ-OV28: Alopecia

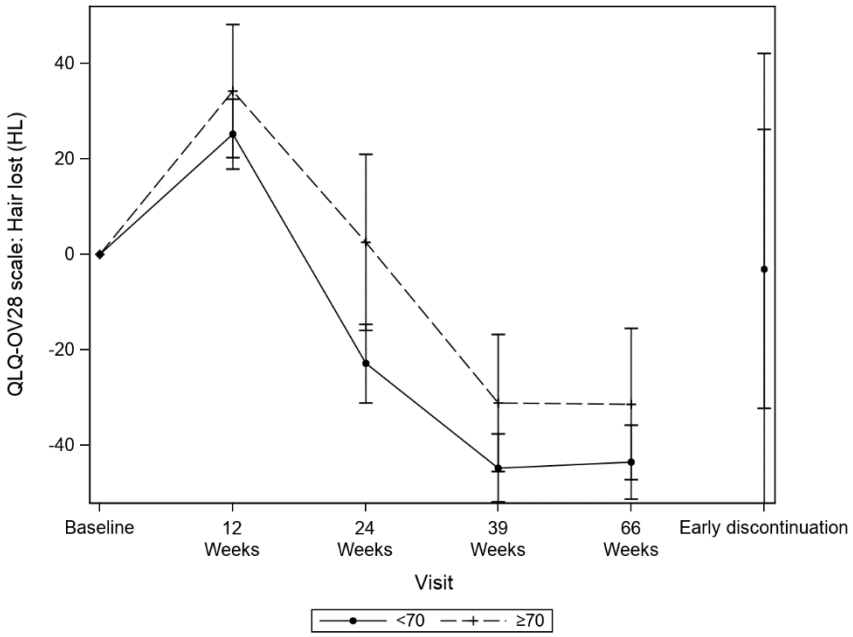
In the CAP alopecia considerably worsened by about 30 points from baseline to week 12 but then improved beyond the baseline value until week 66 (Figure 8-18 and Table 8-42). A similar course of alopecia was observed in both age subgroups (Figure 8-19 and Table 8-42).

Figure 8-18 EORTC QLQ-OV28: Change from baseline in Alopecia (mean) – CAP



[Source: OTILIA_Figures_Final_3_20200127: Figure 14.2.6h].
CAP = Core analysis population; EORTC = European Organisation for Research and Treatment of Cancer; QLQ = Quality of life questionnaire.
A high sore for a symptom scale/item represents a high level of symptomatology/problems.

Figure 8-19 EORTC QLQ-OV28: Change from baseline in Alopecia (mean) – Age subgroups



[Source: OTILIA_Figures_Final_3_20200127: Figure 14.2.6ah].
EORTC = European Organisation for Research and Treatment of Cancer; QLQ = Quality of life questionnaire.
A high sore for a symptom scale/item represents a high level of symptomatology/problems.

Table 8-42 EORTC QLQ-OV28: Change from baseline in alopecia

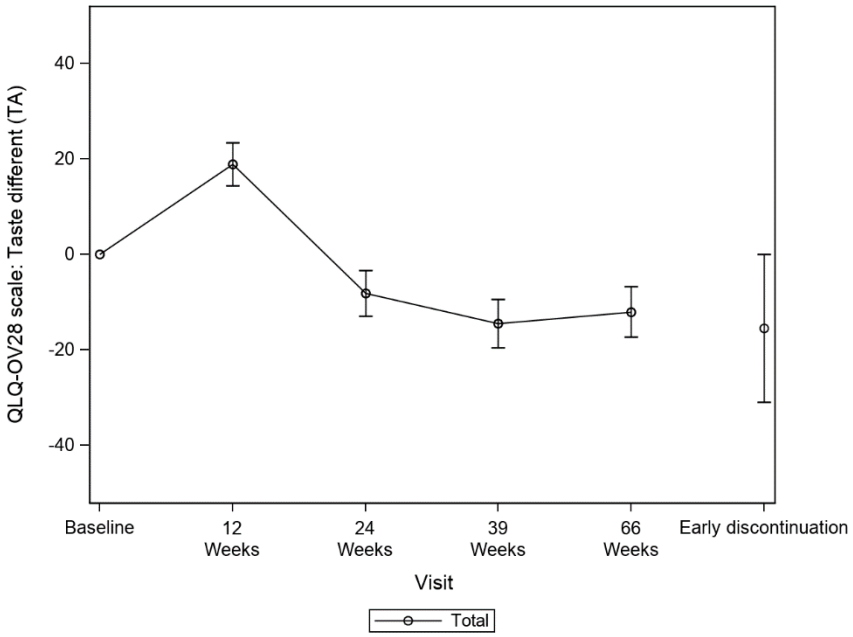
	12 weeks	24 weeks	39 weeks	66 weeks	Early discontinuation
CAP (N=493)					
N	325	298	274	218	26
Mean	27.3	-17.2	-41.7	-40.7	-11.5
StD	59.21	66.96	53.36	52.26	67.29
Median	0.0	0.0	-33.3	-33.3	0.0
25% quantile	0.0	-100.0	-100.0	-100.0	-100.0
75% quantile	100.0	0.0	0.0	0.0	33.3
Min	-100.0	-100.0	-100.0	-100.0	-100.0
Max	100.0	100.0	100.0	100.0	100.0
Patients <70 years (N=360)					
N	251	232	214	168	22
Mean	25.2	-22.8	-44.7	-43.5	-3.0
StD	58.96	63.49	52.49	51.04	65.80
Median	0.0	0.0	-50.0	-33.3	0.0
25% quantile	0.0	-100.0	-100.0	-100.0	-33.3
75% quantile	100.0	0.0	0.0	0.0	33.3
Min	-100.0	-100.0	-100.0	-100.0	-100.0
Max	100.0	100.0	100.0	100.0	100.0
Patients ≥70 years (N=133)					
N	74	66	60	50	4
Mean	34.2	2.5	-31.1	-31.3	-58.3
StD	59.93	75.18	55.53	55.70	63.10
Median	0.0	0.0	0.0	0.0	-83.3
25% quantile	0.0	-66.7	-100.0	-100.0	-100.0
75% quantile	100.0	100.0	0.0	0.0	-16.7
Min	-100.0	-100.0	-100.0	-100.0	-100.0
Max	100.0	100.0	100.0	100.0	33.3

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.28a; Table 14.2.28b, Table 14.2.28c].
CAP = Core analysis population; EORTC = European Organisation for Research and Treatment of Cancer; Max = Maximum; Min = Minimum; N/n = Number; StD = Standard deviation.
Due to non-accurate informed consent forms (ICF) some filled in questionnaires cannot be used for analysis. The total population for questionnaire analyses includes all patients of CAP with a valid ICF and willing to participate in the quality of life assessment. A high sore for a symptom scale/item represents a high level of symptomatology/problems.

8.4.12.8 EORTC QLQ-OV28: Changes in taste

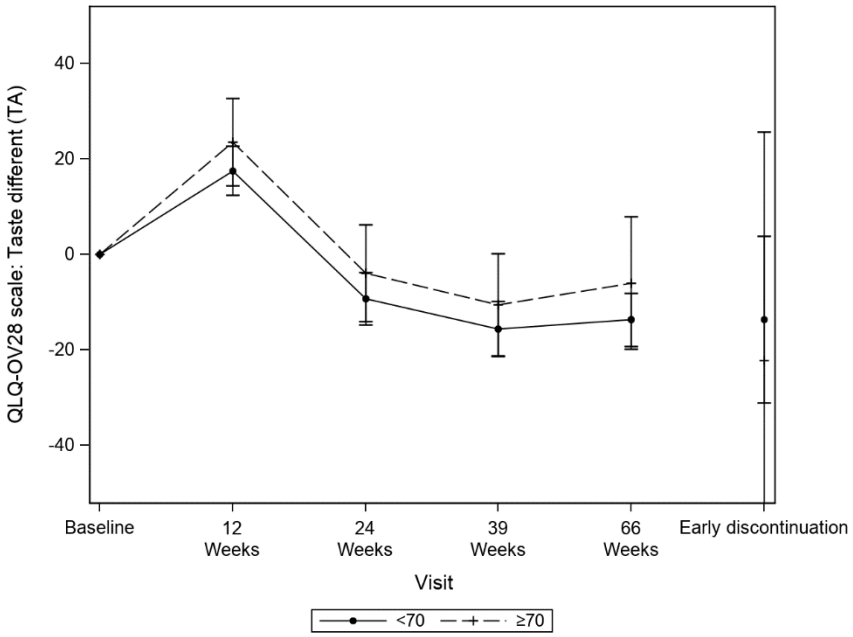
In the CAP changes in taste considerably worsened by about 20 points from baseline to week 12 but then improved beyond the baseline value until week 66 (Figure 8-20 and Table 8-43). A similar course of changes in taste was observed in both age subgroups (Figure 8-21 and Table 8-43).

Figure 8-20 EORTC QLQ-OV28: Change from baseline in changes in taste (mean) – CAP



[Source: OTILIA_Figures_Final_3_20200127: Figure 14.2.6j].
CAP = Core analysis population; EORTC = European Organisation for Research and Treatment of Cancer; QLQ = Quality of life questionnaire.
A high sore for a symptom scale/item represents a high level of symptomatology/problems.

Figure 8-21 EORTC QLQ-OV28: Change from baseline in changes in taste (mean) – Age subgroups



[Source: OTILIA_Figures_Final_3_20200127: Figure 14.2.6aj].
EORTC = European Organisation for Research and Treatment of Cancer; QLQ = Quality of life questionnaire.
A high sore for a symptom scale/item represents a high level of symptomatology/problems.

Table 8-43 EORTC QLQ-OV28: Change from baseline in changes in taste

	12 weeks	24 weeks	39 weeks	66 weeks	Early discontinuation
CAP (N=493)					
N	350	324	288	230	28
Mean	18.9	-8.1	-14.5	-12.0	-15.5
StD	42.67	44.19	43.50	40.44	40.04
Median	0.0	0.0	0.0	0.0	0.0
25% quantile	0.0	-33.3	-33.3	-33.3	-33.3
75% quantile	33.3	33.3	0.0	0.0	0.0
Min	-100.0	-100.0	-100.0	-100.0	-100.0
Max	100.0	100.0	100.0	100.0	66.7
Patients <70 years (N=360)					
N	272	256	225	180	22
Mean	17.5	-9.2	-15.6	-13.7	-13.6
StD	43.23	44.83	43.76	37.75	39.39
Median	0.0	0.0	0.0	0.0	0.0
25% quantile	0.0	-33.3	-33.3	-33.3	-33.3
75% quantile	33.3	16.7	0.0	0.0	0.0
Min	-100.0	-100.0	-100.0	-100.0	-100.0
Max	100.0	100.0	100.0	100.0	66.7
Patients ≥70 years (N=133)					
N	78	68	63	50	6
Mean	23.5	-3.9	-10.6	-6.0	-22.2
StD	40.60	41.74	42.68	48.88	45.54
Median	16.7	0.0	0.0	0.0	-33.3
25% quantile	0.0	-33.3	-33.3	-33.3	-66.7
75% quantile	33.3	33.3	0.0	33.3	33.3
Min	-66.7	-100.0	-100.0	-100.0	-66.7
Max	100.0	100.0	100.0	100.0	33.3

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.28a; Table 14.2.28b, Table 14.2.28c].
CAP = Core analysis population; EORTC = European Organisation for Research and Treatment of Cancer; Max = Maximum; Min = Minimum; N/n = Number; StD = Standard deviation.
Due to non-accurate informed consent forms (ICF) some filled in questionnaires cannot be used for analysis. The total population for questionnaire analyses includes all patients of CAP with a valid ICF and willing to participate in the quality of life assessment. A high sore for a symptom scale/item represents a high level of symptomatology/problems.

8.4.13 Physician's assessment of treatment

In the CAP about the half of physicians assessed the therapy as "good" (n=390; 49.2%). About one quarter of physicians assessed the therapy as "very good" (n=201; 25.4%). In 18.3% of cases (n=145) the physicians assessed the therapy as "moderate". Reasons for this assessment by the physicians were that effectiveness, tolerability, and patient

compliance were as expected in 64.9% (n=484), 64.6% (n=477), and 72.2% (n=481), respectively (Table 8-44).

The same holds true for both age subgroups. In the subgroup of patients <70 years the physicians assessed the therapy in 49.3% (n=217) of cases as “good”, in 26.6% (n=117) as “very good” and in 16.6% (n=73) as “moderate”. Reasons for this assessment by the physicians were that effectiveness, tolerability, and patient compliance were as expected in 63.5% (n=264), 64.4% (n=264), and 70.8% (n=262), respectively. In the subgroup of patients ≥70 years the physicians assessed the therapy in 49.1% (n=173) of cases as “good”, in 23.9% (n=84) as “very good” and in 20.5% (n=72) as “moderate”. Reasons for this assessment by the physicians were that effectiveness, tolerability, and patient compliance were as expected in 66.7% (n=220), 64.9% (n=213), and 74.0% (n=219), respectively (Table 8-44).

Table 8-44 Physician’s assessment of treatment

	CAP	Patients <70 years	Patients ≥70 years
Therapy satisfaction			
N (non-missing)	792	440	352
Excellent	32 (4.0%)	19 (4.3%)	13 (3.7%)
Very good	201 (25.4%)	117 (26.6%)	84 (23.9%)
Good	390 (49.2%)	217 (49.3%)	173 (49.1%)
Moderate	145 (18.3%)	73 (16.6%)	72 (20.5%)
Poor	24 (3.0%)	14 (3.2%)	10 (2.8%)
Missing	32	13	19
Reason for evaluation – Effectiveness			
N (non-missing)	746	416	330
Much better than expected	40 (5.4%)	26 (6.3%)	14 (4.2%)
A little better than expected	85 (11.4%)	49 (11.8%)	36 (10.9%)
As expected	484 (64.9%)	264 (63.5%)	220 (66.7%)
A little worse than expected	104 (13.9%)	56 (13.5%)	48 (14.5%)
Much worse than expected	33 (4.4%)	21 (5.0%)	12 (3.6%)
Missing	78	37	41
Reason for evaluation – Tolerability			
N (non-missing)	738	410	328
Much better than expected	41 (5.6%)	29 (7.1%)	12 (3.7%)
A little better than expected	115 (15.6%)	72 (17.6%)	43 (13.1%)
As expected	477 (64.6%)	264 (64.4%)	213 (64.9%)
A little worse than expected	78 (10.6%)	37 (9.0%)	41 (12.5%)
Much worse than expected	27 (3.7%)	8 (2.0%)	19 (5.8%)
Missing	86	43	43

	CAP	Patients <70 years	Patients ≥70 years
Reason for evaluation – Patient compliance			
N (non-missing)	666	370	296
Much better than expected	62 (9.3%)	39 (10.5%)	23 (7.8%)
A little better than expected	75 (11.3%)	48 (13.0%)	27 (9.1%)
As expected	481 (72.2%)	262 (70.8%)	219 (74.0%)
A little worse than expected	35 (5.3%)	14 (3.8%)	21 (7.1%)
Much worse than expected	13 (2.0%)	7 (1.9%)	6 (2.0%)
Missing	158	83	75
Reason for evaluation – Other			
N (non-missing)	63	34	29
Much better than expected	3 (4.8%)	2 (5.9%)	1 (3.4%)
A little better than expected	2 (3.2%)	1 (2.9%)	1 (3.4%)
As expected	40 (63.5%)	23 (67.6%)	17 (58.6%)
A little worse than expected	13 (20.6%)	6 (17.6%)	7 (24.1%)
Much worse than expected	5 (7.9%)	2 (5.9%)	3 (10.3%)
Missing	761	419	342

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.29a; Table 14.2.29b].
CAP = Core analysis population; N/n = Number.

8.4.14 Subsequent antineoplastic medications

In the CAP the most common (≥5%) subsequent antineoplastic substances were carboplatin (n=153; 18.6%), doxorubicin (n=121; 14.7%), gemcitabine (n=93; 11.3%), bevacizumab (Avastin®) (n=67; 8.1%), paclitaxel (n=42; 5.1%) and topotecan (n=42; 5.1%) (Table 8-45).

Carboplatin (n=86; 19.0%), doxorubicin (n=69; 15.2%), gemcitabine (n=59; 13.0%), bevacizumab (Avastin®) (n=45; 9.9%), paclitaxel (n=29; 6.4%) and topotecan (n=25; 5.5%) were the most frequently used (≥5%) subsequent antineoplastic substances also in the subgroup of patients <70 years. Similarly, carboplatin (n=67; 18.1%), doxorubicin (n=52; 14.0%), gemcitabine (n=34; 9.2%) and bevacizumab (Avastin®) (n=22; 5.9%) were commonly applied in the subgroup of patients ≥70 years, (Table 8-45).

In the subgroup of patients without prior surgery the most common (≥5%) subsequent antineoplastic substances were carboplatin (n=10; 22.2%), doxorubicin (n=10; 22.2%), gemcitabine (n=6; 13.3%), paclitaxel (n=4; 8.9%), bevacizumab (Avastin®) (n=3; 6.7%) and topotecan (n=3; 6.7%). Likewise, carboplatin (n=143; 18.4%), doxorubicin (n=111; 14.2%), gemcitabine (n=87; 11.2%), bevacizumab (Avastin®) (n=64; 8.2%) and topotecan

(n=39; 5.0%) were the most frequently used (≥5%) subsequent antineoplastic substances also in the subgroup of patients with prior surgery (Table 8-45). However, due to the small number of patients in the subgroup of patients without prior surgery (N=45) in comparison to the subgroup of patients with prior surgery (N=779) comparability of these subgroups is limited.

Treatment of bevacizumab (Avastin®) in a subsequent therapy line would be assigned as off-label use. However, bevacizumab (Avastin®) entered as further antineoplastic therapy in the FU documentation could also be treatment with bevacizumab (Avastin®) beyond the planned duration of treatment documentation of 15 months as described in chapter 7.6 Bias.

Table 8-45 Subsequent antineoplastic medications

		Age subgroup		Surgery subgroup	
	CAP	Patients <70 years	Patients ≥70 years	No prior surgery	Prior surgery
Bevacizumab (Avastin®)	67 (8.1%)	45 (9.9%)	22 (5.9%)	3 (6.7%)	64 (8.2%)
Carboplatin	153 (18.6%)	86 (19.0%)	67 (18.1%)	10 (22.2%)	143 (18.4%)
Carboplatin/Docetaxel/Trastuzumab	1 (0.1%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Carboplatin/Doxorubicin	5 (0.6%)	1 (0.2%)	4 (1.1%)	0 (0.0%)	5 (0.6%)
Carboplatin/Gemcitabine	14 (1.7%)	10 (2.2%)	4 (1.1%)	3 (6.7%)	11 (1.4%)
Carboplatin/Paclitaxel	7 (0.8%)	5 (1.1%)	2 (0.5%)	0 (0.0%)	7 (0.9%)
Cisplatin	9 (1.1%)	8 (1.8%)	1 (0.3%)	1 (2.2%)	8 (1.0%)
Cisplatin/Gemcitabine	1 (0.1%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Cyclophosphamide	3 (0.4%)	3 (0.7%)	0 (0.0%)	0 (0.0%)	3 (0.4%)
Cytarabine	1 (0.1%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Docetaxel	4 (0.5%)	2 (0.4%)	2 (0.5%)	0 (0.0%)	4 (0.5%)
Doxorubicin	121 (14.7%)	69 (15.2%)	52 (14.0%)	10 (22.2%)	111 (14.2%)
Etoposide	1 (0.1%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Extern, Substanz Unbekannt	1 (0.1%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.1%)
Farletuzumab	1 (0.1%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Fluorouracil	(0.1%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Gemcitabine	93 (11.3%)	59 (13.0%)	34 (9.2%)	6 (13.3%)	87 (11.2%)
Methotrexate	1 (0.1%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Niraparib	1 (0.1%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.1%)
Olaparib	5 (0.6%)	4 (0.9%)	1 (0.3%)	1 (2.2%)	4 (0.5%)
Olaparib/Placebo	1 (0.1%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.1%)
Paclitaxel	42 (5.1%)	29 (6.4%)	13 (3.5%)	4 (8.9%)	38 (4.9%)
Panitumumab	2 (0.2%)	2 (0.4%)	0 (0.0%)	0 (0.0%)	2 (0.3%)
Ramucirumab	1 (0.1%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.1%)

		Age subgroup		Surgery subgroup	
	CAP	Patients <70 years	Patients ≥70 years	No prior surgery	Prior surgery
Tamoxifen	5 (0.6%)	4 (0.9%)	1 (0.3%)	0 (0.0%)	5 (0.6%)
Topotecan	42 (5.1%)	25 (5.5%)	17 (4.6%)	3 (6.7%)	39 (5.0%)
Trabectedin	25 (3.0%)	18 (4.0%)	7 (1.9%)	2 (4.4%)	23 (3.0%)
Trastuzumab	1 (0.1%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Treosulfan	24 (2.9%)	12 (2.6%)	12 (3.2%)	1 (2.2%)	23 (3.0%)
Trofosfamide	2 (0.2%)	0 (0.0%)	2 (0.5%)	0 (0.0%)	2 (0.3%)
Unbekannt	2 (0.2%)	2 (0.4%)	0 (0.0%)	0 (0.0%)	2 (0.3%)
Vinorelbine	1 (0.1%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.1%)

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.30a; Table 14.2.30b; Table 14.2.30c].
CAP = Core analysis population.

8.5 OTHER ANALYSES

8.5.1 ECOG performance status during study

8.5.1.1 Shift in ECOG performance status baseline vs. worst on treatment

In the following the most common shifts (≥1%) in ECOG performance status at baseline compared to worst on treatment will be described.

In the CAP the ECOG performance status remained equal for ECOG 0 in 17.0%, ECOG 1 in 36.6%, ECOG 2 in 4.6% and ECOG 3 in 1.0 % of patients. The ECOG performance status worsened from 0 to 1 in 17.9%, from 0 to 2 in 3.5% and from 1 to 2 in 7.0% of patients. The ECOG performance status improved from 1 to 0 in 4.1% and from 2 to 1 in 4.5% of patients (Table 8-46). In total the ECOG performance status remained equal in 59.2% worsened in 30.7% and improved in 9.9% of patients.

In the subgroup of patients <70 years the ECOG performance status remained equal for ECOG 0 in 21.5%, ECOG 1 in 33.2% and ECOG 2 in 4.1% of patients. The ECOG performance status worsened from 0 to 1 in 21.0%, from 0 to 2 in 3.2% and from 1 to 2 in 6.3% of patients. The ECOG performance status improved from 1 to 0 in 4.1% and from 2 to 1 in 3.4% of patients (Table 8-47). In total the ECOG performance status remained equal in 59.3% worsened in 32.1% and improved in 8.5% of patients.

In the subgroup of patients ≥70 years the ECOG performance status remained equal for ECOG 0 in 11.0%, ECOG 1 in 41.3%, ECOG 2 in 5.3% and ECOG 3 in 1.7% of patients. The ECOG performance status worsened from 0 to 1 in 13.7%, from 0 to 2 in 4.0%, from 0 to 3 in 1.0% and from 1 to 2 in 8.0% of patients. The ECOG performance status improved from 1 to 0 in 4.0% and from 2 to 1 in 6.0% of patients (Table 8-48). In total the ECOG performance status remained equal in 59.3% worsened in 29.0% and improved in 11.7% of patients.

Table 8-46 Shift in ECOG performance status baseline vs. worst on treatment - CAP

	Baseline							
Worst on treatment	**0**	**1**	**2**	**3**	**4**	**Non-Missing**	**Missing**	**Total**
0	121 (17.0%)	29 (4.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	151 (21.3%)	6	157
1	127 (17.9%)	260 (36.6%)	32 (4.5%)	4 (0.6%)	0 (0.0%)	423 (59.6%)	18	441
2	25 (3.5%)	50 (7.0%)	33 (4.6%)	4 (0.6%)	0 (0.0%)	112 (15.8%)	3	115
3	4 (0.6%)	6 (0.8%)	5 (0.7%)	7 (1.0%)	0 (0.0%)	22 (3.1%)	0	22
4	1 (0.1%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	2 (0.3%)	0	2
Non-missing	278 (39.2%)	345 (48.6%)	72 (10.1%)	15 (2.1%)	0 (0.0%)	710 (100.0%)	27	737
Missing	19	44	5	0	0	68	19	87
Total	297	389	77	15	0	778	46	824

[Source: OTILIA_Tables_Final_4_20200420: Table 14.1.6a].
CAP = Core analysis population; ECOG = Eastern Cooperative Oncology Group.

Table 8-47 Shift in ECOG performance status baseline vs. worst on treatment - Patients <70 years

	Baseline							
Worst on treatment	**0**	**1**	**2**	**3**	**4**	**Non-Missing**	**Missing**	**Total**
0	88 (21.5%)	17 (4.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	105 (25.6%)	2	107
1	86 (21.0%)	136 (33.2%)	14 (3.4%)	2 (0.5%)	0 (0.0%)	238 (58.0%)	8	246
2	13 (3.2%)	26 (6.3%)	17 (4.1%)	2 (0.5%)	0 (0.0%)	58 (14.1%)	0	58
3	1 (0.2%)	2 (0.5%)	3 (0.7%)	2 (0.5%)	0 (0.0%)	8 (2.0%)	0	8
4	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0	1
Non-missing	189 (46.1%)	181 (44.1%)	34 (8.3%)	6 (1.5%)	0 (0.0%)	410 (100.0%)	10	420
Missing	10	13	2	0	0	25	8	33
Total	199	194	36	6	0	435	18	453

[Source: OTILIA_Tables_Final_4_20200420: Table 14.1.6b].
ECOG = Eastern Cooperative Oncology Group.

Table 8-48 Shift in ECOG performance status baseline vs. worst on treatment – Patients ≥70 years

	Baseline							
Worst on treatment	**0**	**1**	**2**	**3**	**4**	**Non-Missing**	**Missing**	**Total**
0	33 (11.0%)	12 (4.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	46 (15.3%)	4	50
1	41 (13.7%)	124 (41.3%)	18 (6.0%)	2 (0.7%)	0 (0.0%)	185 (61.7%)	10	195
2	12 (4.0%)	24 (8.0%)	16 (5.3%)	2 (0.7%)	0 (0.0%)	54 (18.0%)	3	57
3	3 (1.0%)	4 (1.3%)	2 (0.7%)	5 (1.7%)	0 (0.0%)	14 (4.7%)	0	14
4	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	0	1
Non-missing	89 (29.7%)	164 (54.7%)	38 (12.7%)	9 (3.0%)	0 (0.0%)	300 (100.0%)	17	317
Missing	9	31	3	0	0	43	11	54
Total	98	195	41	9	0	343	28	371

[Source: OTILIA_Tables_Final_4_20200420: Table 14.1.6c].
ECOG = Eastern Cooperative Oncology Group.

8.5.1.2 Shift in ECOG performance status baseline vs. end of treatment

In the following the most common shifts (≥1%) in ECOG performance status at baseline compared to EOT will be described.

In the CAP the ECOG performance status remained equal for ECOG 0 in 23.9%, ECOG 1 in 26.5% and ECOG 2 in 2.6% of patients. The ECOG performance status worsened from 0 to 1 in 11.8%, from 0 to 2 in 2.0%, from 1 to 2 in 4.6%, from 1 to 3 in 2.0% and from 2 to 3 in 1.4% of patients. The ECOG performance status improved from 1 to 0 in 17.1% and from 2 to 1 in 4.0% and from 2 to 0 in 2.0% of patients (Table 8-49). In total the ECOG performance status remained equal in 53.0% worsened in 22.2% and improved in 24.7% of patients.

In the subgroup of patients <70 years the ECOG performance status remained equal for ECOG 0 in 30.6%, ECOG 1 in 24.1% and ECOG 2 in 2.1% of patients. The ECOG performance status worsened from 0 to 1 in 12.7%, from 0 to 2 in 1.7% and from 1 to 2 in 3.4% of patients. The ECOG performance status improved from 1 to 0 in 17.2%, from 2 to 1 in 4.1%, from 2 to 0 in 1.4% and from 3 to 1 in 1.0% of patients (Table 8-50). In total the ECOG performance status remained equal in 56.8% worsened in 19.5% and improved in 23.7% of patients.

In the subgroup of patients ≥70 years the ECOG performance status remained equal for ECOG 0 in 14.5%, ECOG 1 in 30.0% and ECOG 2 in 3.4% of patients. The ECOG performance status worsened from 0 to 1 in 10.6%, from 0 to 2 in 2.4%, from 1 to 2 in 6.3%, from 1 to 3 in 3.9%, from 2 to 3 in 2.4% of patients. The ECOG performance status improved from 1 to 0 in 16.9%, from 2 to 1 in 3.9%, from 2 to 0 in 2.9% and from 3 to 2 in 1.4% of patients (Table 8-51). In total the ECOG performance status remained equal in 47.9% worsened in 26.1% and improved in 26.1% of patients.

Table 8-49 Shift in ECOG performance status baseline vs. end of treatment - CAP

	Baseline							
End of treatment	**0**	**1**	**2**	**3**	**4**	**Non-Missing**	**Missing**	**Total**
0	119 (23.9%)	85 (17.1%)	10 (2.0%)	1 (0.2%)	0 (0.0%)	215 (43.2%)	12	227
1	59 (11.8%)	132 (26.5%)	20 (4.0%)	4 (0.8%)	0 (0.0%)	215 (43.2%)	9	224
2	10 (2.0%)	23 (4.6%)	13 (2.6%)	3 (0.6%)	0 (0.0%)	49 (9.8%)	3	52
3	1 (0.2%)	10 (2.0%)	7 (1.4%)	0 (0.0%)	0 (0.0%)	18 (3.6%)	0	18
4	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0	1
Non-missing	189 (38.0%)	251 (50.4%)	50 (10.0%)	8 (1.6%)	0 (0.0%)	498 (100.0%)	24	522
Missing	108	138	27	7	0	280	22	302
Total	297	389	77	15	0	778	46	824

[Source: OTILIA_Tables_Final_4_20200420: Table 14.1.7a].
CAP = Core analysis population; ECOG = Eastern Cooperative Oncology Group.

Table 8-50 Shift in ECOG performance status baseline vs. end of treatment - Patients <70 years

	Baseline							
End of treatment	**0**	**1**	**2**	**3**	**4**	**Non-Missing**	**Missing**	**Total**
0	89 (30.6%)	50 (17.2%)	4 (1.4%)	0 (0.0%)	0 (0.0%)	143 (49.1%)	6	149
1	37 (12.7%)	70 (24.1%)	12 (4.1%)	3 (1.0%)	0 (0.0%)	122 (41.9%)	4	126
2	5 (1.7%)	10 (3.4%)	6 (2.1%)	0 (0.0%)	0 (0.0%)	21 (7.2%)	1	22
3	1 (0.3%)	2 (0.7%)	2 (0.7%)	0 (0.0%)	0 (0.0%)	5 (1.7%)	0	5
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0	0
Non-missing	132 (45.4%)	132 (45.4%)	24 (8.2%)	3 (1.0%)	0 (0.0%)	291 (100.0%)	11	302
Missing	67	62	12	3	0	144	7	151
Total	199	194	36	6	0	435	18	453

[Source: OTILIA_Tables_Final_4_20200420: Table 14.1.7b].
ECOG = Eastern Cooperative Oncology Group.

Table 8-51 Shift in ECOG performance status baseline vs. end of treatment - Patients ≥70 years

	Baseline							
End of treatment	**0**	**1**	**2**	**3**	**4**	**Non-Missing**	**Missing**	**Total**
0	30 (14.5%)	35 (16.9%)	6 (2.9%)	1 (0.5%)	0 (0.0%)	72 (34.8%)	6	78
1	22 (10.6%)	62 (30.0%)	8 (3.9%)	1 (0.5%)	0 (0.0%)	93 (44.9%)	5	98
2	5 (2.4%)	13 (6.3%)	7 (3.4%)	3 (1.4%)	0 (0.0%)	28 (13.5%)	2	30
3	0 (0.0%)	8 (3.9%)	5 (2.4%)	0 (0.0%)	0 (0.0%)	13 (6.3%)	0	13
4	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0	1
Non-missing	57 (27.5%)	119 (57.5%)	26 (12.6%)	5 (2.4%)	0 (0.0%)	207 (100.0%)	13	220
Missing	41	76	15	4	0	136	15	151
Total	98	195	41	9	0	343	28	371

[Source: OTILIA_Tables_Final_4_20200420: Table 14.1.7c].
ECOG = Eastern Cooperative Oncology Group.

8.5.2 Blood pressure during study

8.5.2.1 Shift in blood pressure baseline vs. worst on treatment

In the CAP 4.0%, 2.6%, and 31.3% of patients remained at normal blood pressure, prehypertension and high blood pressure from baseline to worst on treatment. Normal blood pressure worsened to prehypertension and high blood pressure in 4.4% and 28.1% of patients. Prehypertension worsened to high blood pressure in 27.6% of patients. Prehypertension improved to normal blood pressure in 0.2% of patients, high blood pressure improved to prehypertension in 1.7% and to normal blood pressure in 0.2% of patients. In total the blood pressure remained equal in 37.9% worsened in 60.1% and improved in 2.1% of patients (Table 8-52).

In the subgroup of patients <70 years 4.6%, 2.8%, and 28.2% of patients remained at normal blood pressure, prehypertension and high blood pressure from baseline to worst on treatment. Normal blood pressure worsened to prehypertension and high blood pressure in 4.3% and 29.4% of patients. Prehypertension worsened to high blood pressure in 28.5% of patients. Prehypertension improved to normal blood pressure in 0.3% of patients, high blood pressure improved to prehypertension in 1.9% and to normal blood pressure in 0.0% of patients. In total the blood pressure remained equal in 35.6% worsened in 62.2% and improved in 2.2% of patients (

Table 8-53).

In the subgroup of patients ≥70 years 3.2%, 2.3%, and 35.7% of patients remained at normal blood pressure, prehypertension and high blood pressure from baseline to worst on treatment. Normal blood pressure worsened to prehypertension and high blood pressure in 4.5% and 26.2% of patients. Prehypertension worsened to high blood pressure in 26.2% of patients. Prehypertension improved to normal blood pressure in 0.0% of patients, high blood pressure improved to prehypertension in 1.4% and to normal blood pressure in 0.5% of patients. In total the blood pressure remained equal in 41.2% worsened in 56.9% and improved in 1.9% of patients (Table 8-54).

Table 8-52 Shift in blood pressure status baseline vs. worst on treatment - CAP

	Baseline					
Worst on treatment	**Normal Blood Pressure**	**Prehypertension**	**High Blood Pressure**	**Non-Missing**	**Missing**	**Total**
Normal Blood Pressure	22 (4.0%)	1 (0.2%)	1 (0.2%)	24 (4.4%)	6	30
Prehypertension	24 (4.4%)	14 (2.6%)	9 (1.7%)	47 (8.6%)	15	62
High Blood Pressure	153 (28.1%)	150 (27.6%)	170 (31.3%)	473 (86.9%)	149	622
Non-missing	199 (36.6%)	165 (30.3%)	180 (33.1%)	544 (100.0%)	170	714
Missing	16	18	21	55	55	110
Total	215	183	201	599	225	824

[Source: OTILIA_Tables_Final_4_20200420: Table 14.3.7a].
CAP = Core analysis population.

Table 8-53 Shift in blood pressure status baseline vs. worst on treatment – Patients <70 years

	Baseline					
Worst on treatment	**Normal Blood Pressure**	**Prehypertension**	**High Blood Pressure**	**Non-Missing**	**Missing**	**Total**
Normal Blood Pressure	15 (4.6%)	1 (0.3%)	0 (0.0%)	16 (5.0%)	4	20
Prehypertension	14 (4.3%)	9 (2.8%)	6 (1.9%)	29 (9.0%)	13	42
High Blood Pressure	95 (29.4%)	92 (28.5%)	91 (28.2%)	278 (86.1%)	65	343
Non-missing	124 (38.4%)	102 (31.6%)	97 (30.0%)	323 (100.0%)	82	405
Missing	7	7	10	24	24	48
Total	131	109	107	347	106	453

[Source: OTILIA_Tables_Final_4_20200420: Table 14.3.7b].

Table 8-54 Shift in blood pressure status baseline vs. worst on treatment – Patients ≥70 years

	Baseline					
Worst on treatment	**Normal Blood Pressure**	**Prehypertension**	**High Blood Pressure**	**Non-Missing**	**Missing**	**Total**
Normal Blood Pressure	7 (3.2%)	0 (0.0%)	1 (0.5%)	8 (3.6%)	2	10
Prehypertension	10 (4.5%)	5 (2.3%)	3 (1.4%)	18 (8.1%)	2	20
High Blood Pressure	58 (26.2%)	58 (26.2%)	79 (35.7%)	195 (88.2%)	84	279
Non-missing	75 (33.9%)	63 (28.5%)	83 (37.6%)	221 (100.0%)	88	309
Missing	9	11	11	31	31	62
Total	84	74	94	252	119	371

[Source: OTILIA_Tables_Final_4_20200420: Table 14.3.7c].

8.6 ADVERSE EVENTS AND ADVERSE REACTIONS

The collected safety data comprise AEs including AEs of particular interest and AEs requiring expedited reporting, SAEs, causally related (serious) adverse event ((S)AEs), and fatal SAEs (regardless of causality). Fatal events can be either fatal, causally related SAE (assessed as related to bevacizumab (Avastin®) treatment) or fatal non-related SAE (assessed as not related to bevacizumab (Avastin®)). Causally related (S)AEs were defined as those with a possible, probable or definite relationship to bevacizumab (Avastin®). The collection of AEs and SAEs reflects the real-world situation in which the respective treating physicians with best knowledge of their patients assessed whether an observed event could be related to bevacizumab (Avastin®).

An AE was considered as a TEAE when assessed as an event having emerged during treatment (on-treatment period) or during the 90-day safety FU period following discontinuation of bevacizumab (Avastin®) therapy, having been absent during the pre-treatment period or worsened relative to the pre-treatment state.

The NCI's standardized definitions for CTCAE v4.0 were used for severity grading of all AEs and MedDRA v22.0 for classification of reported terms within respective SOC and PT.

8.6.1 Discrepancies Between Safety Database Roche (SDB) and Clinical Database CRO (CDB) – Final Reconciliation

For a NIS, it is an integral part of Roche´s Safety and Data Quality Management to review all data including free-text entries for possible hidden AEs, to review and re-evaluate seriousness assessments of AEs in terms of need of seriousness upgrade provided by investigators through single case reviews by experienced medical experts in drug safety, and to review all causality assessments. For this review process, a Serious Adverse Event Reconciliation Tool (SAERT) was used. Depending on respective assessment outcomes, discrepancies between the seriousness of AEs as reported by the respective treating physician versus the seriousness as assessed by Roche followed by a Company upgrade of respective events (i.e. from non-serious to serious) may occur. Causality assessments might differ in terms of changing "causality, not reported" to "causality, unknown", or "not related" to "related" as per Roche (Company) assessment. Another aspect of review is related to PT coding and SOC allocation of PTs.

The complete list of discrepancies between the SDB and the CDB in this NIS is available as a separate electronic file, dated 17 December 2019 (Table 1; **ANNEX 1. LIST OF**

STAND-ALONE DOCUMENTS). It needs to be stressed, that discrepancies for one single event might be attributed to several reasons. The differences between the CDB and the Company´s SDB have been subject of thorough evaluation and scientific discussion.

Overall, 985 discrepancies between the SDB and the CDB were identified following final reconciliation. These are described briefly in the following paragraphs.

In total, 47 (4.8%) discrepancies were identified with regards to different causality including 1 (0.1%) discrepancy where the event (fistula) was recorded as not related in the CDB and as related in the SDB. Furthermore, 11 (1.1%) events were recorded as related in the CDB while in the SDB they were recorded as not related / unknown / not applicable.

Regarding discrepant events with different seriousness (n=59; 6.0%), these included 1 (0.1%) case of death recorded with “seriousness, unknown” in the CDB, 57 (5.8%) events flagged as non-serious in the CDB and 1 (0.1%) event flagged as serious in the CDB.

Further discrepant events included “different PT, different SOC” (n=4; 0.4%), “different PT, same SOC” (n=26; 2.6%) and “wrong term in SDB” (n=1; 0.1%).

Overall, 150 (15.2%) events were identified as being missing in the SDB including 5 (0.5%) events concerning the primary endpoint.

In total, 698 (70.9%) events were identified as being missing in the CDB including “deleted by site” (n=3; 0.3%), “event renamed” (n=1; 0.1%), “no patient number” (n=1; 0.1%), “non-serious, non-related” (n=2; 0.2%), “primary endpoint” (n=16; 1.6%), “supportive therapy” (n=9; 0.9%), “upgraded in SDB” (n=2; 0.2%) and “not applicable, not related” (n=38; 3.9%). The remaining discrepant events, which were missing in the CDB were sorted by SOC:

- Blood and lymphatic system disorders: n=86 (8.7%)
- Cardiac disorders: n=10 (1.0%)
- Eye disorder: n=1 (0.1%)
- Gastrointestinal disorders: n=271 (27.5%, including vomiting (n=217; 22.0%))
- General disorders: n=57 (5.8%, including pain (n=15; 1.5%), death (n=13; 1.3%))
- Hepatobiliary disorders: n=4 (0.4%)
- Infections and infestations: n=16 (1.6%)

- Immune system disorders: n=28 (2.8%; all events hypersensitivity)
- Injury, poisoning: n=9 (0.9%)
- Investigations: n=36 (3.7%)
- Metabolism and nutrition disorders: n=5 (0.5%)
- Musculoskeletal disorders: n=12 (1.2%)
- Neoplasms benign: n=11 (1.1%)
- Nervous system disorders: n=20 (2.0%)
- Psychiatric disorders: n=6 (0.6%)
- Renal and urinary disorders: n=16 (1.6%)
- Reproductive system disorders: n=2 (0.2%)
- Respiratory and thoracic disorders: n=9 (0.9%)
- Skin disorders: n=8 (0.8%)
- Surgical procedures: n=3 (0.3%)
- Vascular disorders: n=16 (1.6%, including hypertension (n=8; 0.8%))

8.6.2 Overview of Treatment-Emergent Adverse Events

Overall, 616 (74.8%) patients were reported with a TEAE of any CTCAE grade; 317 (38.5%) patients were documented with a TEAE of CTCAE grade ≥3 (Table 8-55). A serious TEAE was reported in 222 (26.9%) patients, whereby a causally related serious TEAE was documented in 72 (8.7%) patients. In total, 30 (3.6%) patients were reported with a fatal TEAE (43 cases in total), of these, 5 (0.6%) patients were documented with a fatal TEAE related to bevacizumab (Avastin®) (6 cases in total). For further details on the reported fatal TEAEs, please refer to Table 8-64 and Table 8-65.

Table 8-55 Overview of treatment-emergent adverse events – total population (CAP)

	Total[1] (N = 824)	Cases
Patients reported with respective TEAE, n (%), n (cases)		
Any TEAE	616 (74.8%)	3,645
Any serious TEAE	222 (26.9%)	438
Any TEAE with CTCAE severity grade ≥ grade 3	317 (38.5%)	583
Any causally related TEAE[2]	330 (40.0%)	1,036
Any causally related serious TEAE[2]	72 (8.7%)	96
Any TEAE leading to discontinuation of bevacizumab (Avastin®) treatment[3]	145 (17.6%)	206
Any fatal TEAE[4]	30 (3.6%)	43
Any causally related fatal TEAE[2]	5 (0.6%)	6

[Source: OTILIA_Tables_Final_4_20200420: Table 14.3.1a; OTILIA_Listings_Final_2_20191206; Listing 16.2.7.1: Adverse events].
CAP = Core analysis population; CTCAE = Common Terminology Criteria for Adverse Events; N/n = Number;

TEAE = Treatment-emergent adverse event.
[1]Patients can occur in more than one category of the table. [2]Causally related TEAEs were defined as those with a possible, probable or definite relationship to bevacizumab (Avastin®). [3]TEAE leading to discontinuation of bevacizumab (Avastin®) treatment = TEAE documented as underlying adverse event for end of treatment (EOT). The number of TEAEs leading to discontinuation of bevacizumab (Avastin®) treatment might differ from the number of AEs documented as reason for end of treatment due to AEs not classified as treatment-emergent, however documented as underlying AE for EOT. [4]For one patient (pat ID 215001), the same fatal TEAE (ileus) was reported twice, once as related to bevacizumab (Avastin®) with CTCAE severity grade 4 and once as non-related with CTCAE severity grade 5.

8.6.2.1 Overview of Treatment-Emergent Adverse Events – Age Subgroup

The proportion of patients with any TEAE was higher in the subgroup of patients aged ≥70 years as compared to the subgroup of patients aged <70 years (n=288; 77.6% vs. n=328; 72.4%) as was the proportion of patients reported with serious TEAEs (n=122; 32.9% vs. n=100; 22.1%) as detailed in Table 8-56. The proportion of patients with any causally related TEAE was higher in the subgroup of patients aged <70 years as compared to the subgroup of patients aged ≥70 years (n=192; 42.4% vs. n=138; 37.2%), whereas in the latter subgroup the highest proportion of patients with any causally related serious TEAE was found (n=35; 9.4% vs. n=37; 8.2%). Fatal TEAEs were somewhat more commonly reported in patients aged ≥70 years versus patients aged <70 years (n=18; 4.9% vs. n=12; 2.6%).

Table 8-56 Overview of treatment-emergent adverse events – age subgroup (CAP)

	<70 years Total[1] (N = 453)	Cases	≥70 years Total[1] (N = 371)	Cases
Patients reported with respective TEAE, n (%), n (cases)				
Any TEAE	328 (72.4%)	1,952	288 (77.6%)	1,693
Any serious TEAE	100 (22.1%)	187	122 (32.9%)	251
Any TEAE with CTCAE severity grade ≥ grade 3	150 (33.1%)	267	167 (45.0%)	316
Any causally related TEAE[2]	192 (42.4%)	671	138 (37.2%)	365
Any causally related serious TEAE[2]	37 (8.2%)	53	35 (9.4%)	43
Any TEAE leading to discontinuation of bevacizumab (Avastin®) treatment[3]	66 (14.6%)	102	79 (21.3%)	104
Any TEAE leading to death	12 (2.6%)	20	18 (4.9%)	23

[Source: OTILIA_Tables_Final_4_20200420: Table 14.3.1b].
CAP = Core analysis population; CTCAE = Common Terminology Criteria for Adverse Events; N/n = Number; TEAE = Treatment-emergent adverse event.
[1]Patients can occur in more than one category of the table. [2]Causally related TEAEs were defined as those with a possible, probable or definite relationship to bevacizumab (Avastin®). [3]TEAE leading to discontinuation of bevacizumab (Avastin®) treatment = TEAE documented as underlying adverse event for end of treatment (EOT). The number of TEAEs leading to discontinuation of bevacizumab (Avastin®) treatment might differ from the number of AEs documented as reason for end of treatment due to AEs not classified as treatment-emergent, however documented as underlying AE for EOT.

8.6.2.2 Overview of Treatment-Emergent Adverse Events – Surgery Subgroup

The proportion of patients with any TEAE was higher in the subgroup of patients with prior surgery as compared to the subgroup of patients with no prior surgery (n=587; 75.4% vs. n=29; 64.4%), while in the latter subgroup the highest proportion of patients reported with serious TEAEs was found (n=14; 31.1% vs. n=208; 26.7%) as shown in Table 8-57. The proportion of patients with any causally related TEAE was highest in the subgroup of patients with prior surgery as compared to the subgroup of patients with no prior surgery (n=320; 41.1% vs. n=10; 22.2%) as was the proportion of patients reported with any causally related serious TEAE (n=69; 8.9% vs. n=3; 6.7%). The relative frequency of fatal TEAEs was highest in the subgroup of patients with no prior surgery versus the subgroup of patients with prior surgery (n=3; 6.7% vs. n=27; 3.5%). However, the number of patients in the subgroup of patients without prior surgery (N=45) was very small in comparison to the subgroup of patients with prior surgery (N=779), which limits the comparability of these subgroups.

Table 8-57 Overview of treatment-emergent adverse events – surgery subgroup (CAP)

	No prior surgery Total[1] (N = 45)	Cases	Prior surgery Total[1] (N = 779)	Cases
Patients reported with respective TEAE, n (%), n (cases)				
Any TEAE	29 (64.4%)	140	587 (75.4%)	3,505
Any serious TEAE	14 (31.1%)	27	208 (26.7%)	411
Any TEAE with CTCAE severity grade ≥ grade 3	19 (42.2%)	38	298 (38.3%)	545
Any causally related TEAE[2]	10 (22.2%)	18	320 (41.1%)	1,018
Any causally related serious TEAE[2]	3 (6.7%)	3	69 (8.9%)	93
Any TEAE leading to discontinuation of bevacizumab (Avastin®) treatment[3]	6 (13.3%)	13	139 (17.8%)	193
Any TEAE leading to death	3 (6.7%)	6	27 (3.5%)	37

[Source: OTILIA_Tables_Final_4_20200420: Table 14.3.1c].
CAP = Core analysis population; CTCAE = Common Terminology Criteria for Adverse Events; N/n = Number; TEAE = Treatment-emergent adverse event.
[1]Patients can occur in more than one category of the table. [2]Causally related TEAEs were defined as those with a possible, probable or definite relationship to bevacizumab (Avastin®). [3]TEAE leading to discontinuation of bevacizumab (Avastin®) treatment = TEAE documented as underlying adverse event for end of treatment (EOT). The number of TEAEs leading to discontinuation of bevacizumab (Avastin®) treatment might differ from the number of AEs documented as reason for end of treatment due to AEs not classified as treatment-emergent, however documented as underlying AE for EOT.

8.6.3 Treatment-Emergent Adverse Events (SOC/PT) – Total and by Subgroup

The documented TEAEs (SOC/PT) in the total population and by subgroup are summarized in Table 8-58. Overall, 616 (74.8%) patients were reported with a TEAE

where the most frequently reported events (≥10% of patients) were hypertension (n=141; 17.1%; TEAE of particular interest), fatigue (n=132; 16.0%), polyneuropathy (n=120; 14.6%), nausea (n=112; 13.6%), anemia (n=100; 12.1%); constipation (n=92; 11.2%), alopecia (n=82; 10.0%), and diarrhea (n=82; 10.0%). With regards to the other TEAEs of particular interest (other than hypertension reported above), proteinuria was reported in 35 (4.2%) patients, large intestine perforation in 6 (0.7%) patients, intestinal perforation in 3 (0.4%) patients, gastric perforation in 2 (0.2%) patients and arterial embolism in 1 (0.1%) patient. The proportion of patients with any TEAE was higher in the subgroup of patients aged ≥70 years as compared to the subgroup of patients aged <70 years (n=288; 77.6% vs. n=328; 72.4%). The most commonly reported TEAEs (≥10% of patients) in the subgroup of patients aged <70 years were fatigue (n=76; 16.8%), hypertension (n=71; 15.7%; TEAE of particular interest), nausea (n=66; 14.6%), alopecia (n=57; 12.6%), constipation (n=55; 12.1%), diarrhea (n=49; 10.8%) and polyneuropathy (n=48; 10.6%). With regards to the other TEAEs of particular interest (other than hypertension reported above), proteinuria was reported in 19 (4.2%) patients, large intestine perforation in 4 (0.9%) patients, intestinal perforation in 1 (0.2%) patient and gastric perforation in 1 (0.2%) patient. Arterial embolism was not reported in the subgroup of patients aged <70 years. In the subgroup of patients aged ≥70 years, the most frequent TEAEs (≥10% of patients) were polyneuropathy (n=72; 19.4%), hypertension (n=70; 18.9%; TEAE of particular interest), anemia (n=60; 16.2%), fatigue (n=56; 15.1%), nausea (n=46; 12.4%), urinary tract infection (n=41; 11.1%) and constipation (n=37; 10.0%). As for the other TEAEs of particular interest (other than hypertension reported above), proteinuria was reported in 16 (4.3%) patients, large intestine perforation in 2 (0.5%) patients, intestinal perforation in 2 (0.5%) patients, gastric perforation in 1 (0.3%) patient and arterial embolism in 1 (0.3%) patient.

The proportion of patients with any TEAE was higher in the subgroup of patients with prior surgery as compared to the subgroup of patients with no prior surgery (n=587; 75.4% vs. n=29; 64.4%). The most common TEAEs (≥10% of patients) in the subgroup of patients with no prior surgery were fatigue (n=7; 15.6%), nausea (n=7; 15.6%), hypertension (n=5; 11.1%; TEAE of particular interest), polyneuropathy (n=5; 11.1%), and vomiting (n=5; 11.1%). Regarding the other TEAEs of particular interest (other than hypertension reported above), large intestine perforation was reported in 1 (2.2%) patient, intestinal perforation in 2 (4.4%) patients and gastric perforation in 1 (2.2%) patient. Arterial

embolism and proteinuria were not reported in the subgroup of patients with no prior surgery. In the subgroup of patients with prior surgery, the most frequent TEAEs (≥10% of patients) were hypertension (n=136; 17.5%; TEAE of particular interest), fatigue (n=125; 16.0%), polyneuropathy (n=115; 14.8%), nausea (n=105; 13.5%), anemia (n=97; 12.5%), constipation (n=89; 11.4%), alopecia (n=79; 10.1%), and diarrhea (n=79; 10.1%). As for the other TEAEs of particular interest (other than hypertension reported above), proteinuria was reported in 35 (4.5%) patients, large intestine perforation in 5 (0.6%) patients, intestinal perforation in 1 (0.1%) patient, gastric perforation in 1 (0.1%) patient and arterial embolism in 1 (0.1%) patient. However, comparability of these subgroups is limited because the number of patients in the subgroup of patients without prior surgery (N=45) was very small in comparison to the subgroup of patients with prior surgery (N=779).

Table 8-58 Treatment-emergent adverse events (MedDRA PT by SOC) – total and by subgroup (CAP)

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
Patients with any event, n, %, n (cases)		616 (74.8%)	3,118	328 (72.4%)	1,652	288 (77.6%)	1,466	29 (64.4%)	124	587 (75.4%)	2,994
Gastrointestinal disorders	*Any event*	315 (38.2%)	604	179 (39.5%)	355	136 (36.7%)	249	14 (31.1%)	33	301 (38.6%)	571
	Nausea	112 (13.6%)	112	66 (14.6%)	66	46 (12.4%)	46	7 (15.6%)	7	105 (13.5%)	105
	Constipation	92 (11.2%)	92	55 (12.1%)	55	37 (10.0%)	37	3 (6.7%)	3	89 (11.4%)	89
	Diarrhoea	82 (10.0%)	82	49 (10.8%)	49	33 (8.9%)	33	3 (6.7%)	3	79 (10.1%)	79
	Vomiting	66 (8.0%)	66	37 (8.2%)	37	29 (7.8%)	29	5 (11.1%)	5	61 (7.8%)	61
	Abdominal pain	44 (5.3%)	44	20 (4.4%)	20	24 (6.5%)	24	2 (4.4%)	2	42 (5.4%)	42
	Abdominal pain upper	32 (3.9%)	32	25 (5.5%)	25	7 (1.9%)	7	1 (2.2%)	1	31 (4.0%)	31
	Stomatitis	29 (3.5%)	29	21 (4.6%)	21	8 (2.2%)	8			29 (3.7%)	29
	Ascites	14 (1.7%)	14	7 (1.5%)	7	7 (1.9%)	7			14 (1.8%)	14
	Ileus	14 (1.7%)	14	10 (2.2%)	10	4 (1.1%)	4	3 (6.7%)	3	11 (1.4%)	11
	Dyspepsia	10 (1.2%)	10	7 (1.5%)	7	3 (0.8%)	3	1 (2.2%)	1	9 (1.2%)	9
	Subileus	9 (1.1%)	9	4 (0.9%)	4	5 (1.3%)	5			9 (1.2%)	9
	Large intestine perforation	6 (0.7%)	6	4 (0.9%)	4	2 (0.5%)	2	1 (2.2%)	1	5 (0.6%)	5
	Abdominal distension	4 (0.5%)	4	1 (0.2%)	1	3 (0.8%)	3			4 (0.5%)	4
	Dysphagia	4 (0.5%)	4	3 (0.7%)	3	1 (0.3%)	1			4 (0.5%)	4
	Gingival bleeding	4 (0.5%)	4	2 (0.4%)	2	2 (0.5%)	2			4 (0.5%)	4
	Toothache	4 (0.5%)	4	2 (0.4%)	2	2 (0.5%)	2			4 (0.5%)	4
	Abdominal discomfort	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1			3 (0.4%)	3
	Abdominal hernia	3 (0.4%)	3	1 (0.2%)	1	2 (0.5%)	2			3 (0.4%)	3
	Abdominal pain lower	3 (0.4%)	3	3 (0.7%)	3			1 (2.2%)	1	2 (0.3%)	2

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Aphthous ulcer	3 (0.4%)	3	3 (0.7%)	3					3 (0.4%)	3
	Dry mouth	3 (0.4%)	3	1 (0.2%)	1	2 (0.5%)	2			3 (0.4%)	3
	Faecaloma	3 (0.4%)	3	3 (0.7%)	3					3 (0.4%)	3
	Gastrointestinal disorder	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1			3 (0.4%)	3
	Intestinal perforation	3 (0.4%)	3	1 (0.2%)	1	2 (0.5%)	2	2 (4.4%)	2	1 (0.1%)	1
	Anal incontinence	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Colitis	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Flatulence	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1	1 (2.2%)	1	1 (0.1%)	1
	Gastric perforation	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1	1 (2.2%)	1	1 (0.1%)	1
	Gastritis	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Gastrointestinal haemorrhage	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Gastrooesophageal reflux disease	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Haematochezia	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Haemorrhoids	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Mechanical ileus	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Anal haemorrhage	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Anal pruritus	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Defaecation urgency	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Diarrhoea haemorrhagic	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Diverticulum intestinal	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Duodenal obstruction	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Duodenitis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Duodenogastric reflux	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Dyschezia	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Enterocolitis haemorrhagic	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Enterocutaneous fistula	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Frequent bowel movements	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Gastric ulcer	1 (0.1%)	1	1 (0.2%)	1			1 (2.2%)	1		
	Gastrointestinal motility disorder	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
	Gastrointestinal wall thickening	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Gingival erythema	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Haemorrhoidal haemorrhage	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Hiatus hernia	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Hyperchlorhydria	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Impaired gastric emptying	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Intestinal haemorrhage	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Intestinal ischaemia	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Intestinal obstruction	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Oesophagitis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Oral discomfort	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Oral dysaesthesia	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Oral mucosal blistering	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Pancreatitis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Proctalgia	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Short-bowel syndrome	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Small intestinal haemorrhage	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Tongue coated	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Tongue ulceration	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Tooth disorder	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Nervous system disorders	*Any event*	282 (34.2%)	365	143 (31.6%)	180	139 (37.5%)	185	9 (20.0%)	10	273 (35.0%)	355
	Polyneuropathy	120 (14.6%)	120	48 (10.6%)	48	72 (19.4%)	72	5 (11.1%)	5	115 (14.8%)	115
	Paraesthesia	50 (6.1%)	50	35 (7.7%)	35	15 (4.0%)	15			50 (6.4%)	50
	Headache	36 (4.4%)	36	21 (4.6%)	21	15 (4.0%)	15			36 (4.6%)	36
	Neuropathy peripheral	33 (4.0%)	33	17 (3.8%)	17	16 (4.3%)	16	2 (4.4%)	2	31 (4.0%)	31
	Dizziness	26 (3.2%)	26	9 (2.0%)	9	17 (4.6%)	17	2 (4.4%)	2	24 (3.1%)	24
	Peripheral sensory neuropathy	17 (2.1%)	17	10 (2.2%)	10	7 (1.9%)	7			17 (2.2%)	17
	Hypoaesthesia	9 (1.1%)	9	4 (0.9%)	4	5 (1.3%)	5			9 (1.2%)	9
	Dysgeusia	8 (1.0%)	8	5 (1.1%)	5	3 (0.8%)	3			8 (1.0%)	8
	Syncope	7 (0.8%)	7	3 (0.7%)	3	4 (1.1%)	4			7 (0.9%)	7
	Migraine	5 (0.6%)	5	4 (0.9%)	4	1 (0.3%)	1			5 (0.6%)	5
	Neuralgia	5 (0.6%)	5	2 (0.4%)	2	3 (0.8%)	3			5 (0.6%)	5
	Aphasia	4 (0.5%)	4	1 (0.2%)	1	3 (0.8%)	3			4 (0.5%)	4
	Sensory disturbance	4 (0.5%)	4	4 (0.9%)	4					4 (0.5%)	4

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Transient ischaemic attack	4 (0.5%)	4	2 (0.4%)	2	2 (0.5%)	2			4 (0.5%)	4
	Cerebrovascular accident	3 (0.4%)	3			3 (0.8%)	3			3 (0.4%)	3
	Dysaesthesia	3 (0.4%)	3	1 (0.2%)	1	2 (0.5%)	2			3 (0.4%)	3
	Memory impairment	3 (0.4%)	3			3 (0.8%)	3			3 (0.4%)	3
	Neurotoxicity	3 (0.4%)	3	3 (0.7%)	3					3 (0.4%)	3
	Burning sensation	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Hemiparesis	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Ischaemic cerebral infarction	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Ageusia	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Athetosis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Carpal tunnel syndrome	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Cerebral infarction	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Disturbance in attention	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Dysarthria	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Generalised tonic-clonic seizure	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	IVth nerve paresis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Loss of consciousness	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
	Monoparesis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Noninfective encephalitis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Paresis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Partial seizures	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Peripheral motor neuropathy	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Peripheral paralysis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Restless legs syndrome	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Status epilepticus	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Tremor	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Trigeminal neuralgia	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
General disorders and administration site conditions	*Any event*	256 (31.1%)	369	133 (29.4%)	186	123 (33.2%)	183	10 (22.2%)	12	246 (31.6%)	357
	Fatigue	132 (16.0%)	132	76 (16.8%)	76	56 (15.1%)	56	7 (15.6%)	7	125 (16.0%)	125
	Pain	41 (5.0%)	41	22 (4.9%)	22	19 (5.1%)	19			41 (5.3%)	41
	Mucosal inflammation	31 (3.8%)	31	17 (3.8%)	17	14 (3.8%)	14			31 (4.0%)	31
	Pyrexia	31 (3.8%)	31	15 (3.3%)	15	16 (4.3%)	16	1 (2.2%)	1	30 (3.9%)	30
	General physical health deterioration	28 (3.4%)	28	8 (1.8%)	8	20 (5.4%)	20			28 (3.6%)	28
	Oedema peripheral	13 (1.6%)	13	3 (0.7%)	3	10 (2.7%)	10	2 (4.4%)	2	11 (1.4%)	11
	Asthenia	11 (1.3%)	11	4 (0.9%)	4	7 (1.9%)	7			11 (1.4%)	11
	Impaired healing	10 (1.2%)	10	6 (1.3%)	6	4 (1.1%)	4			10 (1.3%)	10
	Influenza like illness	10 (1.2%)	10	7 (1.5%)	7	3 (0.8%)	3			10 (1.3%)	10
	Oedema	9 (1.1%)	9	4 (0.9%)	4	5 (1.3%)	5			9 (1.2%)	9
	Chills	6 (0.7%)	6	2 (0.4%)	2	4 (1.1%)	4			6 (0.8%)	6
	Death	6 (0.7%)	6	2 (0.4%)	2	4 (1.1%)	4			6 (0.8%)	6

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Extravasation	6 (0.7%)	6	3 (0.7%)	3	3 (0.8%)	3	1 (2.2%)	1	5 (0.6%)	5
	Chest pain	5 (0.6%)	5	1 (0.2%)	1	4 (1.1%)	4			5 (0.6%)	5
	Mucosal dryness	3 (0.4%)	3	3 (0.7%)	3					3 (0.4%)	3
	Peripheral swelling	3 (0.4%)	3	1 (0.2%)	1	2 (0.5%)	2			3 (0.4%)	3
	Catheter site inflammation	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Chest discomfort	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Feeling cold	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Gait disturbance	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Inflammation	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Malaise	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Multiple organ dysfunction syndrome	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Unevaluable event	2 (0.2%)	2			2 (0.5%)	2	1 (2.2%)	1	1 (0.1%)	1
	Adverse drug reaction	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Device related thrombosis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Exercise tolerance decreased	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Feeling abnormal	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Hernia	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Local swelling	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Mucous membrane disorder	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Temperature intolerance	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
Vascular disorders	*Any event*	188 (22.8%)	222	97 (21.4%)	111	91 (24.5%)	111	7 (15.6%)	9	181 (23.2%)	213
	Hypertension	141 (17.1%)	141	71 (15.7%)	71	70 (18.9%)	70	5 (11.1%)	5	136 (17.5%)	136
	Hypertensive crisis	13 (1.6%)	13	4 (0.9%)	4	9 (2.4%)	9	2 (4.4%)	2	11 (1.4%)	11
	Hot flush	12 (1.5%)	12	9 (2.0%)	9	3 (0.8%)	3			12 (1.5%)	12
	Lymphocele	10 (1.2%)	10	6 (1.3%)	6	4 (1.1%)	4			10 (1.3%)	10
	Thrombosis	10 (1.2%)	10	5 (1.1%)	5	5 (1.3%)	5	1 (2.2%)	1	9 (1.2%)	9
	Haematoma	6 (0.7%)	6	1 (0.2%)	1	5 (1.3%)	5			6 (0.8%)	6
	Deep vein thrombosis	5 (0.6%)	5	2 (0.4%)	2	3 (0.8%)	3			5 (0.6%)	5
	Flushing	5 (0.6%)	5	4 (0.9%)	4	1 (0.3%)	1			5 (0.6%)	5
	Hypotension	3 (0.4%)	3	1 (0.2%)	1	2 (0.5%)	2	1 (2.2%)	1	2 (0.3%)	2
	Circulatory collapse	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Lymphoedema	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Thrombophlebitis	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Venous thrombosis limb	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Angiopathy	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Embolism	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Embolism arterial	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Embolism venous	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Jugular vein thrombosis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Labile blood pressure	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Peripheral arterial occlusive disease	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Vein disorder	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Vena cava thrombosis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Blood and lymphatic system disorders	*Any event*	181 (22.0%)	267	87 (19.2%)	126	94 (25.3%)	141	10 (22.2%)	13	171 (22.0%)	254
	Anaemia	100 (12.1%)	100	40 (8.8%)	40	60 (16.2%)	60	3 (6.7%)	3	97 (12.5%)	97
	Leukopenia	71 (8.6%)	71	40 (8.8%)	40	31 (8.4%)	31	3 (6.7%)	3	68 (8.7%)	68
	Thrombocytopenia	57 (6.9%)	57	29 (6.4%)	29	28 (7.5%)	28	4 (8.9%)	4	53 (6.8%)	53
	Neutropenia	26 (3.2%)	26	12 (2.6%)	12	14 (3.8%)	14	3 (6.7%)	3	23 (3.0%)	23
	Pancytopenia	5 (0.6%)	5	1 (0.2%)	1	4 (1.1%)	4			5 (0.6%)	5
	Febrile neutropenia	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1			3 (0.4%)	3
	Bone marrow failure	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Haemorrhagic diathesis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Leukocytosis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Thrombocytosis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	White blood cell disorder	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Infections and infestations	*Any event*	174 (21.1%)	231	83 (18.3%)	106	91 (24.5%)	125	7 (15.6%)	11	167 (21.4%)	220
	Urinary tract infection	58 (7.0%)	58	17 (3.8%)	17	41 (11.1%)	41	2 (4.4%)	2	56 (7.2%)	56
	Cystitis	27 (3.3%)	27	16 (3.5%)	16	11 (3.0%)	11	2 (4.4%)	2	25 (3.2%)	25
	Nasopharyngitis	19 (2.3%)	19	10 (2.2%)	10	9 (2.4%)	9	2 (4.4%)	2	17 (2.2%)	17
	Infection	13 (1.6%)	13	3 (0.7%)	3	10 (2.7%)	10	1 (2.2%)	1	12 (1.5%)	12
	Bronchitis	9 (1.1%)	9	5 (1.1%)	5	4 (1.1%)	4			9 (1.2%)	9
	Device related infection	6 (0.7%)	6	2 (0.4%)	2	4 (1.1%)	4			6 (0.8%)	6

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Sepsis	6 (0.7%)	6	3 (0.7%)	3	3 (0.8%)	3			6 (0.8%)	6
	Influenza	5 (0.6%)	5	3 (0.7%)	3	2 (0.5%)	2	1 (2.2%)	1	4 (0.5%)	4
	Pneumonia	5 (0.6%)	5	1 (0.2%)	1	4 (1.1%)	4			5 (0.6%)	5
	Urosepsis	5 (0.6%)	5	5 (1.1%)	5					5 (0.6%)	5
	Herpes zoster	4 (0.5%)	4	2 (0.4%)	2	2 (0.5%)	2			4 (0.5%)	4
	Sinusitis	4 (0.5%)	4	1 (0.2%)	1	3 (0.8%)	3			4 (0.5%)	4
	Upper respiratory tract infection	4 (0.5%)	4	1 (0.2%)	1	3 (0.8%)	3	1 (2.2%)	1	3 (0.4%)	3
	Erysipelas	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1			3 (0.4%)	3
	Febrile infection	3 (0.4%)	3	3 (0.7%)	3					3 (0.4%)	3
	Gastrointestinal infection	3 (0.4%)	3	1 (0.2%)	1	2 (0.5%)	2			3 (0.4%)	3
	Oral herpes	3 (0.4%)	3	3 (0.7%)	3					3 (0.4%)	3
	Pharyngitis	3 (0.4%)	3	1 (0.2%)	1	2 (0.5%)	2			3 (0.4%)	3
	Rash pustular	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1			3 (0.4%)	3
	Rhinitis	3 (0.4%)	3			3 (0.8%)	3			3 (0.4%)	3
	Viral upper respiratory tract infection	3 (0.4%)	3			3 (0.8%)	3			3 (0.4%)	3
	Abdominal abscess	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Anorectal infection	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Conjunctivitis	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Enteritis infectious	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Gastroenteritis	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Peritonitis	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1	1 (2.2%)	1	1 (0.1%)	1
	Respiratory tract infection	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Tooth infection	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Abdominal wall abscess	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Abscess	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Anal abscess	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Atypical pneumonia	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Candida infection	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Catheter site infection	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Diverticulitis	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
	Enterobiasis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Enterocolitis infectious	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Escherichia infection	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Genital herpes zoster	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Groin abscess	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Herpes virus infection	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Herpes zoster oticus	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Infected lymphocele	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Laryngitis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Lung infection	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Neuroborreliosis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Oesophageal candidiasis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Pelvic abscess	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Pulpitis dental	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Pyelonephritis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Urinary tract infection bacterial	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Vaginal infection	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Vestibular neuronitis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Vulvovaginal mycotic infection	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Musculoskeletal and connective tissue disorders	*Any event*	164 (19.9%)	229	108 (23.8%)	158	56 (15.1%)	71	3 (6.7%)	3	161 (20.7%)	226
	Arthralgia	54 (6.6%)	54	36 (7.9%)	36	18 (4.9%)	18			54 (6.9%)	54
	Bone pain	39 (4.7%)	39	24 (5.3%)	24	15 (4.0%)	15	1 (2.2%)	1	38 (4.9%)	38
	Pain in extremity	34 (4.1%)	34	20 (4.4%)	20	14 (3.8%)	14			34 (4.4%)	34
	Back pain	26 (3.2%)	26	16 (3.5%)	16	10 (2.7%)	10			26 (3.3%)	26
	Myalgia	23 (2.8%)	23	19 (4.2%)	19	4 (1.1%)	4			23 (3.0%)	23
	Musculoskeletal pain	9 (1.1%)	9	6 (1.3%)	6	3 (0.8%)	3	1 (2.2%)	1	8 (1.0%)	8
	Spinal pain	6 (0.7%)	6	5 (1.1%)	5	1 (0.3%)	1			6 (0.8%)	6
	Muscle spasms	5 (0.6%)	5	5 (1.1%)	5					5 (0.6%)	5
	Musculoskeletal chest pain	4 (0.5%)	4	3 (0.7%)	3	1 (0.3%)	1			4 (0.5%)	4
	Neck pain	3 (0.4%)	3	3 (0.7%)	3					3 (0.4%)	3
	Osteoarthritis	3 (0.4%)	3	1 (0.2%)	1	2 (0.5%)	2			3 (0.4%)	3
	Arthropathy	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Fistula	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Joint swelling	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Limb discomfort	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Muscle tightness	2 (0.2%)	2	2 (0.4%)	2			1 (2.2%)	1	1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Osteoporosis	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Bursitis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Intervertebral disc protrusion	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Morphoea	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Muscular weakness	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Musculoskeletal discomfort	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Musculoskeletal disorder	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Musculoskeletal stiffness	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Osteitis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Rhabdomyolysis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Rheumatic disorder	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Rotator cuff syndrome	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Skin and subcutaneous tissue disorders	*Any event*	136 (16.5%)	180	88 (19.4%)	118	48 (12.9%)	62	5 (11.1%)	6	131 (16.8%)	174
	Alopecia	82 (10.0%)	82	57 (12.6%)	57	25 (6.7%)	25	3 (6.7%)	3	79 (10.1%)	79
	Dry skin	21 (2.5%)	21	17 (3.8%)	17	4 (1.1%)	4			21 (2.7%)	21
	Palmar-plantar erythrodysaesthesia syndrome	11 (1.3%)	11	4 (0.9%)	4	7 (1.9%)	7			11 (1.4%)	11
	Pruritus	9 (1.1%)	9	7 (1.5%)	7	2 (0.5%)	2	1 (2.2%)	1	8 (1.0%)	8
	Rash	9 (1.1%)	9	7 (1.5%)	7	2 (0.5%)	2			9 (1.2%)	9
	Nail disorder	8 (1.0%)	8	4 (0.9%)	4	4 (1.1%)	4			8 (1.0%)	8

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Erythema	7 (0.8%)	7	6 (1.3%)	6	1 (0.3%)	1	1 (2.2%)	1	6 (0.8%)	6
	Hyperhidrosis	4 (0.5%)	4	1 (0.2%)	1	3 (0.8%)	3	1 (2.2%)	1	3 (0.4%)	3
	Onychoclasis	4 (0.5%)	4	1 (0.2%)	1	3 (0.8%)	3			4 (0.5%)	4
	Skin ulcer	3 (0.4%)	3			3 (0.8%)	3			3 (0.4%)	3
	Dermatitis acneiform	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Nail discolouration	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Night sweats	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Scar pain	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Skin disorder	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Blister	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Decubitus ulcer	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Eczema	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Hidradenitis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Onychomadesis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Pruritus generalised	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Psoriasis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Rosacea	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Skin discomfort	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Skin fissures	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Swelling face	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Urticaria	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Respiratory, thoracic and mediastinal disorders	*Any event*	119 (14.4%)	148	50 (11.0%)	66	69 (18.6%)	82	4 (8.9%)	4	115 (14.8%)	144

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Dyspnoea	54 (6.6%)	54	25 (5.5%)	25	29 (7.8%)	29	1 (2.2%)	1	53 (6.8%)	53
	Epistaxis	30 (3.6%)	30	16 (3.5%)	16	14 (3.8%)	14			30 (3.9%)	30
	Pleural effusion	12 (1.5%)	12	4 (0.9%)	4	8 (2.2%)	8	2 (4.4%)	2	10 (1.3%)	10
	Cough	11 (1.3%)	11	3 (0.7%)	3	8 (2.2%)	8			11 (1.4%)	11
	Dysphonia	9 (1.1%)	9	3 (0.7%)	3	6 (1.6%)	6			9 (1.2%)	9
	Pulmonary embolism	9 (1.1%)	9	4 (0.9%)	4	5 (1.3%)	5			9 (1.2%)	9
	Dyspnoea exertional	7 (0.8%)	7	3 (0.7%)	3	4 (1.1%)	4	1 (2.2%)	1	6 (0.8%)	6
	Oropharyngeal pain	3 (0.4%)	3	1 (0.2%)	1	2 (0.5%)	2			3 (0.4%)	3
	Asphyxia	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Aspiration	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Chronic obstructive pulmonary disease	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Hypoxia	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Nasal dryness	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Painful respiration	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Pleurisy	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Pneumonia aspiration	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Productive cough	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Rhinitis allergic	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Rhinorrhoea	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Sinus disorder	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Vocal cord inflammation	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
Renal and urinary disorders	*Any event*	62 (7.5%)	69	30 (6.6%)	33	32 (8.6%)	36	1 (2.2%)	1	61 (7.8%)	68
	Proteinuria	35 (4.2%)	35	19 (4.2%)	19	16 (4.3%)	16			35 (4.5%)	35
	Hydronephrosis	5 (0.6%)	5	5 (1.1%)	5					5 (0.6%)	5
	Haematuria	4 (0.5%)	4			4 (1.1%)	4			4 (0.5%)	4
	Acute kidney injury	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1			3 (0.4%)	3
	Urinary incontinence	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1	1 (2.2%)	1	2 (0.3%)	2
	Cystitis noninfective	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Dysuria	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Prerenal failure	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Urinary tract obstruction	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Bladder discomfort	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Bladder irritation	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Cystitis haemorrhagic	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Incontinence	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Nephrotic syndrome	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Pollakiuria	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Renal failure	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Stress urinary incontinence	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Urinary bladder haemorrhage	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Urinary retention	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Urinary tract disorder	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
Investigations	*Any event*	58 (7.0%)	82	30 (6.6%)	39	28 (7.5%)	43	3 (6.7%)	3	55 (7.1%)	79
	Blood creatinine increased	11 (1.3%)	11	6 (1.3%)	6	5 (1.3%)	5	1 (2.2%)	1	10 (1.3%)	10
	Weight decreased	7 (0.8%)	7	3 (0.7%)	3	4 (1.1%)	4	1 (2.2%)	1	6 (0.8%)	6
	Alanine aminotransferase increased	5 (0.6%)	5	3 (0.7%)	3	2 (0.5%)	2			5 (0.6%)	5
	Gamma-glutamyltransferase increased	5 (0.6%)	5	3 (0.7%)	3	2 (0.5%)	2			5 (0.6%)	5
	Blood alkaline phosphatase increased	4 (0.5%)	4	2 (0.4%)	2	2 (0.5%)	2			4 (0.5%)	4
	Blood pressure increased	4 (0.5%)	4	2 (0.4%)	2	2 (0.5%)	2			4 (0.5%)	4
	C-reactive protein increased	4 (0.5%)	4	2 (0.4%)	2	2 (0.5%)	2	1 (2.2%)	1	3 (0.4%)	3
	Haemoglobin decreased	4 (0.5%)	4	3 (0.7%)	3	1 (0.3%)	1			4 (0.5%)	4
	White blood cell count decreased	4 (0.5%)	4	1 (0.2%)	1	3 (0.8%)	3			4 (0.5%)	4
	Aspartate aminotransferase increased	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1			3 (0.4%)	3
	Neutrophil count decreased	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1			3 (0.4%)	3
	Blood creatine increased	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Blood creatinine abnormal	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Liver function test increased	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Platelet count decreased	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Protein urine present	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Biopsy bone marrow	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Blood alkaline phosphatase	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Blood lactate dehydrogenase increased	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Blood potassium decreased	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Blood sodium decreased	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Blood urine present	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Body temperature increased	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	General physical condition	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Hepatic enzyme increased	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Lymphocyte count decreased	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Nitrite urine present	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Nutritional condition abnormal	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Protein total decreased	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Red blood cells urine	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Sensory level abnormal	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Tumour marker increased	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Urological examination	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Vitamin B12 decreased	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Psychiatric disorders	*Any event*	55 (6.7%)	68	32 (7.1%)	42	23 (6.2%)	26			55 (7.1%)	68
	Insomnia	18 (2.2%)	18	12 (2.6%)	12	6 (1.6%)	6			18 (2.3%)	18
	Depression	15 (1.8%)	15	12 (2.6%)	12	3 (0.8%)	3			15 (1.9%)	15
	Sleep disorder	14 (1.7%)	14	6 (1.3%)	6	8 (2.2%)	8			14 (1.8%)	14
	Restlessness	4 (0.5%)	4	2 (0.4%)	2	2 (0.5%)	2			4 (0.5%)	4
	Depressed mood	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1			3 (0.4%)	3
	Nervousness	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Stress	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Anxiety	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Confusional state	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Disorientation	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Emotional distress	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Hallucination, auditory	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Hallucination, visual	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Irritability	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Listless	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Psychiatric decompensation	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Psychotic disorder	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Metabolism and nutrition disorders	*Any event*	52 (6.3%)	59	21 (4.6%)	23	31 (8.4%)	36	5 (((((11.1%)	6	47 (6.0%)	53
	Decreased appetite	23 (2.8%)	23	9 (2.0%)	9	14 (3.8%)	14	3 (6.7%)	3	20 (2.6%)	20
	Dehydration	9 (1.1%)	9	1 (0.2%)	1	8 (2.2%)	8	2 (4.4%)	2	7 (0.9%)	7
	Hyperkalaemia	6 (0.7%)	6	4 (0.9%)	4	2 (0.5%)	2			6 (0.8%)	6
	Vitamin D deficiency	4 (0.5%)	4	1 (0.2%)	1	3 (0.8%)	3			4 (0.5%)	4
	Hypokalaemia	3 (0.4%)	3	1 (0.2%)	1	2 (0.5%)	2			3 (0.4%)	3
	Hyponatraemia	3 (0.4%)	3	1 (0.2%)	1	2 (0.5%)	2	1 (2.2%)	1	2 (0.3%)	2
	Hypercholesterolaemia	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Type 2 diabetes mellitus	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Abnormal loss of weight	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Fluid retention	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Hypocalcaemia	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Hypovolaemia	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Iron deficiency	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Metabolic acidosis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Type 1 diabetes mellitus	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Injury, poisoning and procedural complications	*Any event*	37 (4.5%)	42	13 (2.9%)	15	24 (6.5%)	27	2 (4.4%)	2	35 (4.5%)	40
	Fall	7 (0.8%)	7			7 (1.9%)	7			7 (0.9%)	7

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Incisional hernia	4 (0.5%)	4	2 (0.4%)	2	2 (0.5%)	2			4 (0.5%)	4
	Failure to anastomose	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Rib fracture	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Thoracic vertebral fracture	2 (0.2%)	2			2 (0.5%)	2	1 (2.2%)	1	1 (0.1%)	1
	Wound complication	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Anastomotic complication	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Ankle fracture	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Concussion	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Contusion	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Excoriation	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Face injury	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Foot fracture	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Fractured sacrum	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Head injury	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Incarcerated incisional hernia	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Infusion related reaction	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Joint dislocation	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
	Ligament rupture	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Lower limb fracture	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Lumbar vertebral fracture	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Stoma site haemorrhage	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Stoma site pain	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Thermal burn	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Tooth fracture	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Toxicity to various agents	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Wound dehiscence	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Wound haemorrhage	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Wrist fracture	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Cardiac disorders	*Any event*	36 (4.4%)	38	22 (4.9%)	23	14 (3.8%)	15	3 (6.7%)	3	33 (4.2%)	35
	Tachycardia	9 (1.1%)	9	7 (1.5%)	7	2 (0.5%)	2			9 (1.2%)	9
	Palpitations	8 (1.0%)	8	8 (1.8%)	8					8 (1.0%)	8
	Cardiovascular disorder	4 (0.5%)	4	1 (0.2%)	1	3 (0.8%)	3	1 (2.2%)	1	3 (0.4%)	3
	Angina pectoris	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1			3 (0.4%)	3
	Atrial fibrillation	2 (0.2%)	2			2 (0.5%)	2	1 (2.2%)	1	1 (0.1%)	1
	Left ventricular dysfunction	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Atrial flutter	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Atrial tachycardia	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Cardiac failure	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
	Coronary artery disease	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Diastolic dysfunction	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Left ventricular hypertrophy	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Pericardial effusion	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Sinus tachycardia	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Stress cardiomyopathy	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Ventricular extrasystoles	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Immune system disorders	*Any event*	35 (4.2%)	35	23 (5.1%)	23	12 (3.2%)	12	2 (4.4%)	2	33 (4.2%)	33
	Hypersensitivity	19 (2.3%)	19	12 (2.6%)	12	7 (1.9%)	7	1 (2.2%)	1	18 (2.3%)	18
	Drug hypersensitivity	9 (1.1%)	9	5 (1.1%)	5	4 (1.1%)	4			9 (1.2%)	9
	Anaphylactic reaction	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Seasonal allergy	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Allergy to arthropod sting	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Contrast media allergy	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
	Sarcoidosis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	*Any event*	25 (3.0%)	28	13 (2.9%)	15	12 (3.2%)	13	1 (2.2%)	2	24 (3.1%)	26
	Malignant neoplasm progression	10 (1.2%)	10	6 (1.3%)	6	4 (1.1%)	4			10 (1.3%)	10
	Malignant pleural effusion	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Metastases to liver	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Metastases to meninges	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1	1 (2.2%)	1	1 (0.1%)	1
	Metastases to peritoneum	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Abdominal wall neoplasm benign	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Basal cell carcinoma	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Breast cancer	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Breast cancer recurrent	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Cancer pain	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Malignant melanoma	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Metastases to central nervous system	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
	Neoplasm progression	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Neoplasm recurrence	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Tumour haemorrhage	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Surgical and medical procedures	*Any event*	21 (2.5%)	22	9 (2.0%)	9	12 (3.2%)	13	1 (2.2%)	2	20 (2.6%)	20
	Tooth extraction	4 (0.5%)	4	2 (0.4%)	2	2 (0.5%)	2			4 (0.5%)	4
	Central venous catheterisation	3 (0.4%)	3	1 (0.2%)	1	2 (0.5%)	2			3 (0.4%)	3
	Dental care	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Anti-infective therapy	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Cancer surgery	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
	Dental operation	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Enterostomy closure	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Gastrectomy	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Hospice care	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Ileostomy	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Incisional hernia repair	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Limb operation	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Liver ablation	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
	Removal of foreign body	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Splint application	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Surgery	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Ear and labyrinth disorders	*Any event*	17 (2.1%)	18	7 (1.5%)	7	10 (2.7%)	11			17 (2.2%)	18
	Vertigo	12 (1.5%)	12	6 (1.3%)	6	6 (1.6%)	6			12 (1.5%)	12
	Hypoacusis	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Tinnitus	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Ear disorder	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Ear pain	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Eye disorders	*Any event*	16 (1.9%)	20	5 (1.1%)	6	11 (3.0%)	14	1 (2.2%)	1	15 (1.9%)	19
	Visual impairment	4 (0.5%)	4	1 (0.2%)	1	3 (0.8%)	3			4 (0.5%)	4
	Eye disorder	3 (0.4%)	3			3 (0.8%)	3			3 (0.4%)	3
	Visual acuity reduced	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1			3 (0.4%)	3
	Asthenopia	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Blindness	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Cataract	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Entropion	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Eye haemorrhage	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Eye inflammation	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Eye swelling	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Eyelid function disorder	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
	Retinal detachment	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Ulcerative keratitis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Reproductive system and breast disorders	*Any event*	9 (1.1%)	10	4 (0.9%)	4	5 (1.3%)	6			9 (1.2%)	10
	Pelvic pain	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Vaginal disorder	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Vaginal fistula	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Breast pain	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Nipple exudate bloody	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Vaginal discharge	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Vaginal haemorrhage	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Hepatobiliary disorders	*Any event*	6 (0.7%)	6	3 (0.7%)	3	3 (0.8%)	3	1 (2.2%)	1	5 (0.6%)	5
	Autoimmune hepatitis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Bile duct stone	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
	Cholecystitis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Cholelithiasis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Hepatotoxicity	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Portal vein thrombosis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
Endocrine disorders	*Any event*	4 (0.5%)	4	3 (0.7%)	3	1 (0.3%)	1			4 (0.5%)	4
	Hypothyroidism	4 (0.5%)	4	3 (0.7%)	3	1 (0.3%)	1			4 (0.5%)	4
Product issues	*Any event*	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Device dislocation	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Device malfunction	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1

[Source: OTILIA_Tables_Final_4_20200420: Table 14.3.2].
CAP = Core analysis population; MedDRA = Medical Dictionary for Regulatory Activities; N/n = Number; PT = Preferred term; SOC = System organ class.
On-treatment phase: from first application of study medication until 90 days after end of treatment.
SOCs are sorted by decreasing total counts, PTs within SOCs are sorted by decreasing counts.
Adverse event terms have been coded using MedDRA version 22.0.

8.6.3.1 Treatment-Emergent Adverse Events of CTCAE Severity Grade ≥3 (SOC/PT) – Total and by Subgroup

The documented TEAEs (SOC/PT) of CTCAE severity grade ≥3 in the total population and by subgroup are summarized in Table 8-59. Overall, 317 (38.5%) patients were reported with a TEAE of CTCAE severity grade ≥3 where the most frequently reported event (≥5% of patients) was hypertension (n=72; 8.7%; TEAE of particular interest). With regards to the other TEAEs of particular interest documented with CTCAE severity grade ≥3, 4 (0.5%) patients were reported with proteinuria, 5 (0.6%) patients with large intestine perforation, 3 (0.4%) patients with intestinal perforation, 2 (0.2%) patients with gastric perforation and 1 (0.1%) patient with arterial embolism.

A higher proportion of patients reported with TEAEs of CTCAE severity grade ≥3 was observed in the subgroup of patients aged ≥70 years as compared to the subgroup of patients aged <70 years (n=167; 45.0% vs. n=150; 33.1%) where the most frequently reported event (≥5% of patients) was hypertension (TEAE of particular interest) both in the subgroups of patients aged ≥70 years (n=43; 11.6%) and patients aged <70 years (n=29; 6.4%). With regards to the other TEAEs of particular interest (other than hypertension reported above) documented with CTCAE severity grade ≥3, 3 (0.7%) patients were reported with proteinuria, 3 (0.7%) patients with large intestine perforation, 1 (0.2%) patient with intestinal perforation and 1 (0.2%) patient with gastric perforation in the subgroup of patients aged <70 years, whereas no patients in this subgroup were documented with arterial embolism of CTCAE severity grade ≥3. In the subgroup of patients aged ≥70 years, 2 (0.5%) patients were reported with large intestine perforation, 2 (0.5%) patients with intestinal perforation, 1 (0.3%) patient with gastric perforation, 1 (0.3%) patient with arterial embolism and 1 (0.3%) patient with proteinuria, all events of which were documented with CTCAE severity grade ≥3.

A higher proportion of patients reported with TEAEs of CTCAE severity grade ≥3 was observed in the subgroup of patients with no prior surgery as compared to the subgroup of patients with prior surgery (n=19; 42.2% vs. n=298; 38.3%) where the most frequently reported event (≥5% of patients) was hypertension (TEAE of particular interest) both in the subgroups of patients with no prior surgery (n=3; 6.7%) and patients with prior surgery (n=69; 8.9%). Regarding the other TEAEs of particular interest (other than hypertension reported above) documented with CTCAE severity grade ≥3, 1 (2.2%) patient was reported with large intestine perforation, 2 (4.4%) patients with intestinal perforation and

1 (2.2%) patient with gastric perforation in the subgroup of patients with no prior surgery, whereas in this subgroup there were no patients documented with proteinuria or arterial embolism of CTCAE severity grade ≥3. In the subgroup of patients with prior surgery, 4 (0.5%) patients were reported with proteinuria, 1 (0.1%) patient with arterial embolism, 4 (0.5%) patients with large intestine perforation, 1 (0.1%) patient with intestinal perforation and 1 (0.1%) patient with gastric perforation, all events of which were documented with CTCAE severity grade ≥3. However, the number of patients in the subgroup of patients without prior surgery (N=45) was very small in comparison to the subgroup of patients with prior surgery (N=779), which limits the comparability of these subgroups.

Table 8-59 Treatment-emergent adverse events of CTCAE severity grade ≥3 (MedDRA PT by SOC) – total and by subgroup (CAP)

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
Patients with any event, n, %, n (cases)		317 (38.5%)	529	150 (33.1%)	238	167 (45.0%)	291	19 (42.2%)	38	298 (38.3%)	491
Vascular disorders	*Any event*	94 (11.4%)	101	40 (8.8%)	41	54 (14.6%)	60	5 (11.1%)	6	89 (11.4%)	95
	Hypertension	72 (8.7%)	72	29 (6.4%)	29	43 (11.6%)	43	3 (6.7%)	3	69 (8.9%)	69
	Hypertensive crisis	12 (1.5%)	12	3 (0.7%)	3	9 (2.4%)	9	2 (4.4%)	2	10 (1.3%)	10
	Lymphocele	5 (0.6%)	5	4 (0.9%)	4	1 (0.3%)	1			5 (0.6%)	5
	Deep vein thrombosis	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Angiopathy	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Circulatory collapse	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Embolism arterial	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Embolism venous	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Haematoma	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Hypotension	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
	Jugular vein thrombosis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Peripheral arterial occlusive disease	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Thrombosis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Vena cava thrombosis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Blood and lymphatic system disorders	*Any event*	61 (7.4%)	72	32 (7.1%)	34	29 (7.8%)	38	5 (11.1%)	6	56 (7.2%)	66
	Anaemia	21 (2.5%)	21	9 (2.0%)	9	12 (3.2%)	12			21 (2.7%)	21
	Leukopenia	20 (2.4%)	20	11 (2.4%)	11	9 (2.4%)	9	1 (2.2%)	1	19 (2.4%)	19
	Thrombocytopenia	14 (1.7%)	14	5 (1.1%)	5	9 (2.4%)	9	2 (4.4%)	2	12 (1.5%)	12

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Neutropenia	10 (1.2%)	10	5 (1.1%)	5	5 (1.3%)	5	3 (6.7%)	3	7 (0.9%)	7
	Febrile neutropenia	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1			3 (0.4%)	3
	Pancytopenia	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Bone marrow failure	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	White blood cell disorder	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Gastrointestinal disorders	*Any event*	60 (7.3%)	70	30 (6.6%)	36	30 (8.1%)	34	6 (13.3%)	9	54 (6.9%)	61
	Ileus	11 (1.3%)	11	7 (1.5%)	7	4 (1.1%)	4	2 (4.4%)	2	9 (1.2%)	9
	Abdominal pain	8 (1.0%)	8	3 (0.7%)	3	5 (1.3%)	5			8 (1.0%)	8
	Ascites	5 (0.6%)	5	2 (0.4%)	2	3 (0.8%)	3			5 (0.6%)	5
	Constipation	5 (0.6%)	5	4 (0.9%)	4	1 (0.3%)	1			5 (0.6%)	5
	Large intestine perforation	5 (0.6%)	5	3 (0.7%)	3	2 (0.5%)	2	1 (2.2%)	1	4 (0.5%)	4
	Diarrhoea	4 (0.5%)	4	2 (0.4%)	2	2 (0.5%)	2			4 (0.5%)	4
	Subileus	4 (0.5%)	4			4 (1.1%)	4			4 (0.5%)	4
	Intestinal perforation	3 (0.4%)	3	1 (0.2%)	1	2 (0.5%)	2	2 (4.4%)	2	1 (0.1%)	1
	Vomiting	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1			3 (0.4%)	3
	Abdominal pain upper	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Gastric perforation	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1	1 (2.2%)	1	1 (0.1%)	1
	Mechanical ileus	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Nausea	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1	1 (2.2%)	1	1 (0.1%)	1
	Abdominal discomfort	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Abdominal pain lower	1 (0.1%)	1	1 (0.2%)	1			1 (2.2%)	1		
	Anal haemorrhage	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Colitis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Duodenal obstruction	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Enterocolitis haemorrhagic	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Gastric ulcer	1 (0.1%)	1	1 (0.2%)	1			1 (2.2%)	1		
	Gastrointestinal haemorrhage	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Gastrointestinal wall thickening	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Impaired gastric emptying	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Intestinal ischaemia	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Pancreatitis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Small intestinal haemorrhage	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Toothache	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Infections and infestations	*Any event*	53 (6.4%)	58	25 (5.5%)	28	28 (7.5%)	30	4 (8.9%)	4	49 (6.3%)	54
	Urinary tract infection	13 (1.6%)	13	5 (1.1%)	5	8 (2.2%)	8	1 (2.2%)	1	12 (1.5%)	12
	Sepsis	6 (0.7%)	6	3 (0.7%)	3	3 (0.8%)	3			6 (0.8%)	6
	Device related infection	5 (0.6%)	5	1 (0.2%)	1	4 (1.1%)	4			5 (0.6%)	5
	Cystitis	4 (0.5%)	4	3 (0.7%)	3	1 (0.3%)	1	1 (2.2%)	1	3 (0.4%)	3
	Urosepsis	4 (0.5%)	4	4 (0.9%)	4					4 (0.5%)	4
	Pneumonia	3 (0.4%)	3			3 (0.8%)	3			3 (0.4%)	3
	Febrile infection	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Herpes zoster	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Infection	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Influenza	2 (0.2%)	2			2 (0.5%)	2	1 (2.2%)	1	1 (0.1%)	1
	Peritonitis	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1	1 (2.2%)	1	1 (0.1%)	1
	Abdominal abscess	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Anal abscess	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Anorectal infection	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Enterobiasis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Gastroenteritis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Gastrointestinal infection	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Herpes virus infection	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Herpes zoster oticus	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Infected lymphocele	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Neuroborreliosis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Pelvic abscess	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Respiratory tract infection	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Tooth infection	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
General disorders and administration site conditions	*Any event*	47 (5.7%)	53	18 (4.0%)	21	29 (7.8%)	32	2 (4.4%)	2	45 (5.8%)	51
	General physical health deterioration	12 (1.5%)	12	3 (0.7%)	3	9 (2.4%)	9			12 (1.5%)	12
	Fatigue	10 (1.2%)	10	6 (1.3%)	6	4 (1.1%)	4	1 (2.2%)	1	9 (1.2%)	9
	Pyrexia	7 (0.8%)	7	2 (0.4%)	2	5 (1.3%)	5	1 (2.2%)	1	6 (0.8%)	6
	Death	6 (0.7%)	6	2 (0.4%)	2	4 (1.1%)	4			6 (0.8%)	6
	Asthenia	3 (0.4%)	3	1 (0.2%)	1	2 (0.5%)	2			3 (0.4%)	3
	Impaired healing	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1			3 (0.4%)	3
	Pain	3 (0.4%)	3	1 (0.2%)	1	2 (0.5%)	2			3 (0.4%)	3
	Multiple organ dysfunction syndrome	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Catheter site inflammation	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Chest pain	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Extravasation	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Influenza like illness	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Mucosal inflammation	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Peripheral swelling	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Unevaluable event	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Nervous system disorders	*Any event*	35 (4.2%)	40	13 (2.9%)	15	22 (5.9%)	25	2 (4.4%)	2	33 (4.2%)	38
	Polyneuropathy	14 (1.7%)	14	3 (0.7%)	3	11 (3.0%)	11			14 (1.8%)	14
	Cerebrovascular accident	3 (0.4%)	3			3 (0.8%)	3			3 (0.4%)	3
	Dizziness	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1	1 (2.2%)	1	1 (0.1%)	1
	Headache	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Ischaemic cerebral infarction	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Peripheral sensory neuropathy	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Syncope	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Aphasia	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Athetosis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Carpal tunnel syndrome	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Cerebral infarction	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Hemiparesis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Hypoaesthesia	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Loss of consciousness	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
	Migraine	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Noninfective encephalitis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Partial seizures	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Peripheral paralysis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Status epilepticus	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Transient ischaemic attack	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Respiratory, thoracic and mediastinal disorders	*Any event*	18 (2.2%)	21	9 (2.0%)	9	9 (2.4%)	12			18 (2.3%)	21
	Dyspnoea	8 (1.0%)	8	3 (0.7%)	3	5 (1.3%)	5			8 (1.0%)	8
	Pulmonary embolism	8 (1.0%)	8	4 (0.9%)	4	4 (1.1%)	4			8 (1.0%)	8
	Asphyxia	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Aspiration	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Hypoxia	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Pleural effusion	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Pleurisy	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Injury, poisoning and procedural complications	*Any event*	16 (1.9%)	16	3 (0.7%)	3	13 (3.5%)	13	1 (2.2%)	1	15 (1.9%)	15
	Fall	3 (0.4%)	3			3 (0.8%)	3			3 (0.4%)	3
	Rib fracture	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Anastomotic complication	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Ankle fracture	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Concussion	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Contusion	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Face injury	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Failure to anastomose	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Incisional hernia	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Joint dislocation	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
	Lower limb fracture	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Stoma site pain	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Wound dehiscence	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	*Any event*	15 (1.8%)	17	8 (1.8%)	9	7 (1.9%)	8	1 (2.2%)	2	14 (1.8%)	15
	Malignant neoplasm progression	6 (0.7%)	6	3 (0.7%)	3	3 (0.8%)	3			6 (0.8%)	6
	Metastases to meninges	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1	1 (2.2%)	1	1 (0.1%)	1
	Metastases to peritoneum	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Breast cancer	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Malignant melanoma	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Malignant pleural effusion	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Metastases to central nervous system	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
	Metastases to liver	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Neoplasm progression	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Tumour haemorrhage	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Investigations	*Any event*	14 (1.7%)	18	10 (2.2%)	13	4 (1.1%)	5			14 (1.8%)	18
	Gamma-glutamyltransferase increased	3 (0.4%)	3	1 (0.2%)	1	2 (0.5%)	2			3 (0.4%)	3
	Neutrophil count decreased	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1			3 (0.4%)	3

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Alanine aminotransferase increased	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Aspartate aminotransferase increased	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Blood alkaline phosphatase increased	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Blood pressure increased	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Hepatic enzyme increased	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Liver function test increased	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Platelet count decreased	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Protein urine present	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Urological examination	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Weight decreased	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	White blood cell count decreased	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Metabolism and nutrition disorders	*Any event*	14 (1.7%)	15	3 (0.7%)	4	11 (3.0%)	11	2 (4.4%)	2	12 (1.5%)	13
	Dehydration	7 (0.8%)	7	1 (0.2%)	1	6 (1.6%)	6	1 (2.2%)	1	6 (0.8%)	6
	Decreased appetite	2 (0.2%)	2			2 (0.5%)	2	1 (2.2%)	1	1 (0.1%)	1
	Hyponatraemia	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Hyperkalaemia	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Hypocalcaemia	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Hypovolaemia	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Type 2 diabetes mellitus	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Renal and urinary disorders	*Any event*	14 (1.7%)	14	11 (2.4%)	11	3 (0.8%)	3			14 (1.8%)	14
	Proteinuria	4 (0.5%)	4	3 (0.7%)	3	1 (0.3%)	1			4 (0.5%)	4
	Acute kidney injury	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1			3 (0.4%)	3
	Hydronephrosis	3 (0.4%)	3	3 (0.7%)	3					3 (0.4%)	3
	Cystitis noninfective	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Nephrotic syndrome	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Prerenal failure	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Urinary bladder haemorrhage	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Cardiac disorders	*Any event*	6 (0.7%)	6	2 (0.4%)	2	4 (1.1%)	4	2 (4.4%)	2	4 (0.5%)	4
	Atrial fibrillation	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
	Atrial flutter	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Cardiac failure	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
	Coronary artery disease	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Left ventricular dysfunction	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Ventricular extrasystoles	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Musculoskeletal and connective tissue disorders	*Any event*	6 (0.7%)	6	4 (0.9%)	4	2 (0.5%)	2			6 (0.8%)	6
	Back pain	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Bone pain	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Fistula	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Osteoarthritis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Rhabdomyolysis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Spinal pain	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Hepatobiliary disorders	*Any event*	4 (0.5%)	4	2 (0.4%)	2	2 (0.5%)	2			4 (0.5%)	4
	Cholecystitis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Cholelithiasis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Hepatotoxicity	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Portal vein thrombosis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Psychiatric disorders	*Any event*	4 (0.5%)	4	2 (0.4%)	2	2 (0.5%)	2			4 (0.5%)	4
	Insomnia	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Confusional state	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Depression	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Surgical and medical procedures	*Any event*	4 (0.5%)	4	1 (0.2%)	1	3 (0.8%)	3	1 (2.2%)	1	3 (0.4%)	3
	Gastrectomy	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Ileostomy	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Incisional hernia repair	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Liver ablation	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
Skin and subcutaneous tissue disorders	*Any event*	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1			3 (0.4%)	3
	Alopecia	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Dry skin	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Skin ulcer	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Eye disorders	*Any event*	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Cataract	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Entropion	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Immune system disorders	*Any event*	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1	1 (2.2%)	1	1 (0.1%)	1
	Anaphylactic reaction	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Contrast media allergy	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
Reproductive system and breast disorders	*Any event*	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Vaginal fistula	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Vaginal haemorrhage	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Product issues	*Any event*	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Device malfunction	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1

[Source: OTILIA_Tables_Final_4_20200420: Table 14.3.4].
CAP = Core analysis population; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; N/n = Number; PT = Preferred term; SOC = System organ class.
On-treatment phase: from first application of study medication until 90 days after end of treatment.
SOCs are sorted by decreasing total counts, PTs within SOCs are sorted by decreasing counts.
Adverse event terms have been coded using MedDRA version 22.0.

8.6.4 Serious Treatment-Emergent Adverse Events (SOC/PT) – Total and by Subgroup

The documented serious TEAEs (SOC/PT) in the total population and by subgroup are summarized in Table 8-60. Overall 222 (26.9%) patients were reported with a serious TEAE where the most frequently reported events (≥1.0% of patients) were pyrexia (n=15; 1.8%), general physical health deterioration (n=14; 1.7%), abdominal pain (n=13; 1.6%), ileus (n=13; 1.6%), hypertension (n=11; 1.3%; TEAE of particular interest), urinary tract infection (n=10; 1.2%), dyspnea (n=8; 1.0%) and leukopenia (n=8; 1.0%). Regarding the other TEAEs of particular interest (other than hypertension reported above), 5 (0.6%) patients were reported with a serious large intestine perforation, 3 (0.4%) patients with a serious intestinal perforation, 2 (0.2%) patients with a serious gastric perforation and 2 (0.2%) patients with serious proteinuria. No patients were documented with a serious arterial embolism.

The proportion of patients with any serious TEAE was higher in the subgroup of patients aged ≥70 years as compared to the subgroup of patients aged <70 years (n=122; 32.9% vs. n=100; 22.1%). In the subgroup of patients aged <70 years, the most commonly reported serious TEAEs (≥1.0% of patients) were ileus (n=9; 2.0%), pyrexia (n=6; 1.3%), abdominal pain (n=6; 1.3%), leukopenia (n=6; 1.3%) and urosepsis (n=5; 1.1%). With regards to the TEAEs of particular interest, 3 (0.7%) patients were reported with serious hypertension, 3 (0.7%) patients with a serious large intestine perforation, 1 (0.2%) patient with a serious intestinal perforation, 1 (0.2%) patient with a serious gastric perforation and 1 (0.2%) patient with serious proteinuria. In the subgroup of patients aged ≥70 years, the most frequently reported serious TEAEs (≥1.0% of patients) were general physical health deterioration (n=11; 3.0%), pyrexia (n=9; 2.4%), hypertension (n=8; 2.2%; TEAE of particular interest), abdominal pain (n=7; 1.9%), dyspnea (n=6; 1.6%), urinary tract infection (n=6; 1.6%), dehydration (n=5; 1.3%), fatigue (n=5; 1.3%), ascites (n=4; 1.1%), death (n=4; 1.1%), device related infection (n=4; 1.1%), hypertensive crisis (n=4; 1.1%), ileus (n=4; 1.1%), malignant neoplasm progression (n=4; 1.1%), pancytopenia (n=4; 1.1%), subileus (n=4; 1.1%) and vomiting (n=4; 1.1%). Regarding the other TEAEs of particular interest (other than hypertension reported above), 2 (0.5%) patients were reported with a serious large intestine perforation, 2 (0.5%) patients with a serious intestinal perforation, 1 (0.3%) with a serious gastric perforation and 1 (0.3%) patient with serious proteinuria.

The proportion of patients with any serious TEAE was higher in the subgroup of patients with no prior surgery as compared to the subgroup of patients with prior surgery (n=14; 31.1% vs. n=208; 26.7%). In the subgroup of patients with no prior surgery, all serious TEAEs were observed at a relative frequency ≥1.0%. With regards to TEAEs of particular interest, 1 (2.2%) were reported with a serious large intestine perforation, 2 (4.4%) patients with a serious intestinal perforation, 1 (2.2%) with a serious gastric perforation and 1 (2.2%) patient with serious hypertension (n=1; 2.2%), whereas no patients in this subgroup were reported with serious proteinuria. In the subgroup of patients with prior surgery, the most frequently reported serious TEAEs (≥1.0% of patients) were general physical health deterioration (n=14; 1.8%), pyrexia (n=14; 1.8%), abdominal pain (n=13; 1.7%), hypertension (n=10; 1.3%; TEAE of particular interest), ileus (n=10; 1.3%), urinary tract infection (n=10; 1.3%) and dyspnea (n=8; 1.0%). Regarding the other TEAEs of particular interest (other than hypertension reported above), 2 (0.3%) patients were reported with serious proteinuria, 4 (0.5%) patients with a serious large intestine perforation, 1 (0.1%) patient with a serious intestinal perforation and 1 (0.1%) with a serious gastric perforation. However, the number of patients in the subgroup of patients without prior surgery (N=45) was very small in comparison to the subgroup of patients with prior surgery (N=779), which limits the comparability of these subgroups.

Table 8-60 Serious treatment-emergent adverse events (MedDRA PT by SOC) – total and by subgroup (CAP)

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
Patients with any event, n, %, n (cases)		222 (26.9%)	413	100 (22.1%)	173	122 (32.9%)	240	14 (31.1%)	26	208 (26.7%)	387
Gastrointestinal disorders	*Any event*	72 (8.7%)	86	34 (7.5%)	42	38 (10.2%)	44	6 (13.3%)	10	66 (8.5%)	76
	Abdominal pain	13 (1.6%)	13	6 (1.3%)	6	7 (1.9%)	7			13 (1.7%)	13
	Ileus	13 (1.6%)	13	9 (2.0%)	9	4 (1.1%)	4	3 (6.7%)	3	10 (1.3%)	10
	Vomiting	7 (0.8%)	7	3 (0.7%)	3	4 (1.1%)	4	1 (2.2%)	1	6 (0.8%)	6
	Ascites	6 (0.7%)	6	2 (0.4%)	2	4 (1.1%)	4			6 (0.8%)	6
	Large intestine perforation	6 (0.7%)	6	4 (0.9%)	4	2 (0.5%)	2	1 (2.2%)	1	5 (0.6%)	5
	Subileus	6 (0.7%)	6	2 (0.4%)	2	4 (1.1%)	4			6 (0.8%)	6
	Nausea	4 (0.5%)	4	1 (0.2%)	1	3 (0.8%)	3			4 (0.5%)	4
	Diarrhoea	3 (0.4%)	3	1 (0.2%)	1	2 (0.5%)	2			3 (0.4%)	3
	Intestinal perforation	3 (0.4%)	3	1 (0.2%)	1	2 (0.5%)	2	2 (4.4%)	2	1 (0.1%)	1
	Abdominal pain upper	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Constipation	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Gastric perforation	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1	1 (2.2%)	1	1 (0.1%)	1
	Gastrointestinal haemorrhage	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Mechanical ileus	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Abdominal discomfort	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Abdominal pain lower	1 (0.1%)	1	1 (0.2%)	1			1 (2.2%)	1		
	Anal haemorrhage	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Diarrhoea haemorrhagic	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Duodenal obstruction	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Enterocutaneous fistula	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Faecaloma	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Gastric ulcer	1 (0.1%)	1	1 (0.2%)	1			1 (2.2%)	1		
	Gastrointestinal wall thickening	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Haemorrhoidal haemorrhage	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Impaired gastric emptying	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Intestinal ischaemia	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Intestinal obstruction	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Pancreatitis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Small intestinal haemorrhage	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Infections and infestations	*Any event*	50 (6.1%)	57	24 (5.3%)	27	26 (7.0%)	30	2 (4.4%)	2	48 (6.2%)	55
	Urinary tract infection	10 (1.2%)	10	4 (0.9%)	4	6 (1.6%)	6			10 (1.3%)	10
	Sepsis	6 (0.7%)	6	3 (0.7%)	3	3 (0.8%)	3			6 (0.8%)	6
	Urosepsis	5 (0.6%)	5	5 (1.1%)	5					5 (0.6%)	5
	Device related infection	4 (0.5%)	4			4 (1.1%)	4			4 (0.5%)	4
	Pneumonia	4 (0.5%)	4	1 (0.2%)	1	3 (0.8%)	3			4 (0.5%)	4
	Febrile infection	3 (0.4%)	3	3 (0.7%)	3					3 (0.4%)	3
	Gastrointestinal infection	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Influenza	2 (0.2%)	2			2 (0.5%)	2	1 (2.2%)	1	1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Peritonitis	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1	1 (2.2%)	1	1 (0.1%)	1
	Abdominal abscess	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Abdominal wall abscess	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Anal abscess	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Anorectal infection	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Bronchitis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Cystitis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Enterobiasis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Erysipelas	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Gastroenteritis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Herpes zoster	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Herpes zoster oticus	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Infected lymphocele	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Infection	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Lung infection	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Nasopharyngitis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Pelvic abscess	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Pyelonephritis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Respiratory tract infection	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Vestibular neuronitis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
General disorders and administration site conditions	*Any event*	42 (5.1%)	51	15 (3.3%)	16	27 (7.3%)	35	2 (4.4%)	3	40 (5.1%)	48
	Pyrexia	15 (1.8%)	15	6 (1.3%)	6	9 (2.4%)	9	1 (2.2%)	1	14 (1.8%)	14

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	General physical health deterioration	14 (1.7%)	14	3 (0.7%)	3	11 (3.0%)	11			14 (1.8%)	14
	Death	6 (0.7%)	6	2 (0.4%)	2	4 (1.1%)	4			6 (0.8%)	6
	Fatigue	5 (0.6%)	5			5 (1.3%)	5	1 (2.2%)	1	4 (0.5%)	4
	Impaired healing	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1			3 (0.4%)	3
	Chest pain	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Multiple organ dysfunction syndrome	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Asthenia	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Extravasation	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Influenza like illness	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Unevaluable event	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
Vascular disorders	*Any event*	36 (4.4%)	37	16 (3.5%)	16	20 (5.4%)	21	2 (4.4%)	2	34 (4.4%)	35
	Hypertension	11 (1.3%)	11	3 (0.7%)	3	8 (2.2%)	8	1 (2.2%)	1	10 (1.3%)	10
	Hypertensive crisis	7 (0.8%)	7	3 (0.7%)	3	4 (1.1%)	4			7 (0.9%)	7
	Thrombosis	5 (0.6%)	5	2 (0.4%)	2	3 (0.8%)	3			5 (0.6%)	5
	Lymphocele	4 (0.5%)	4	3 (0.7%)	3	1 (0.3%)	1			4 (0.5%)	4
	Deep vein thrombosis	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1			3 (0.4%)	3
	Angiopathy	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Circulatory collapse	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Haematoma	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Hypotension	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
	Peripheral arterial occlusive disease	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Vena cava thrombosis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Venous thrombosis limb	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Nervous system disorders	*Any event*	26 (3.2%)	34	7 (1.5%)	9	19 (5.1%)	25	1 (2.2%)	1	25 (3.2%)	33
	Aphasia	3 (0.4%)	3	1 (0.2%)	1	2 (0.5%)	2			3 (0.4%)	3
	Cerebrovascular accident	3 (0.4%)	3			3 (0.8%)	3			3 (0.4%)	3
	Syncope	3 (0.4%)	3	1 (0.2%)	1	2 (0.5%)	2			3 (0.4%)	3
	Hemiparesis	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Ischaemic cerebral infarction	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Migraine	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Polyneuropathy	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Transient ischaemic attack	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Athetosis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Cerebral infarction	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Disturbance in attention	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Dysaesthesia	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Dysarthria	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Generalised tonic-clonic seizure	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Headache	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Hypoaesthesia	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	IVth nerve paresis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Loss of consciousness	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
	Monoparesis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Noninfective encephalitis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Partial seizures	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Peripheral paralysis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Status epilepticus	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Blood and lymphatic system disorders	*Any event*	21 (2.5%)	24	13 (2.9%)	15	8 (2.2%)	9	1 (2.2%)	2	20 (2.6%)	22
	Leukopenia	8 (1.0%)	8	6 (1.3%)	6	2 (0.5%)	2	1 (2.2%)	1	7 (0.9%)	7
	Anaemia	5 (0.6%)	5	3 (0.7%)	3	2 (0.5%)	2			5 (0.6%)	5
	Pancytopenia	5 (0.6%)	5	1 (0.2%)	1	4 (1.1%)	4			5 (0.6%)	5
	Thrombocytopenia	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1	1 (2.2%)	1	2 (0.3%)	2
	Febrile neutropenia	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Bone marrow failure	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	*Any event*	18 (2.2%)	20	8 (1.8%)	9	10 (2.7%)	11	1 (2.2%)	2	17 (2.2%)	18
	Malignant neoplasm progression	7 (0.8%)	7	3 (0.7%)	3	4 (1.1%)	4			7 (0.9%)	7
	Metastases to meninges	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1	1 (2.2%)	1	1 (0.1%)	1
	Metastases to peritoneum	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Abdominal wall neoplasm benign	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Breast cancer	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Cancer pain	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Malignant melanoma	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Malignant pleural effusion	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Metastases to central nervous system	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
	Metastases to liver	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Neoplasm progression	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Tumour haemorrhage	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Respiratory, thoracic and mediastinal disorders	*Any event*	17 (2.1%)	20	6 (1.3%)	6	11 (3.0%)	14			17 (2.2%)	20
	Dyspnoea	8 (1.0%)	8	2 (0.4%)	2	6 (1.6%)	6			8 (1.0%)	8
	Pulmonary embolism	4 (0.5%)	4	2 (0.4%)	2	2 (0.5%)	2			4 (0.5%)	4
	Pleural effusion	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Asphyxia	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Aspiration	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Chronic obstructive pulmonary disease	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Hypoxia	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Pleurisy	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Pneumonia aspiration	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Injury, poisoning and procedural complications	*Any event*	16 (1.9%)	16	4 (0.9%)	4	12 (3.2%)	12	1 (2.2%)	1	15 (1.9%)	15
	Fall	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Anastomotic complication	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Ankle fracture	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Concussion	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Contusion	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Face injury	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Failure to anastomose	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Incarcerated incisional hernia	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Incisional hernia	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Joint dislocation	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
	Lower limb fracture	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Lumbar vertebral fracture	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Stoma site pain	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Thoracic vertebral fracture	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Wound dehiscence	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Renal and urinary disorders	*Any event*	12 (1.5%)	12	8 (1.8%)	8	4 (1.1%)	4			12 (1.5%)	12

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Hydronephrosis	4 (0.5%)	4	4 (0.9%)	4					4 (0.5%)	4
	Acute kidney injury	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Prerenal failure	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Proteinuria	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Urinary bladder haemorrhage	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Urinary tract obstruction	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Cardiac disorders	*Any event*	11 (1.3%)	11	6 (1.3%)	6	5 (1.3%)	5	1 (2.2%)	1	10 (1.3%)	10
	Tachycardia	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1			3 (0.4%)	3
	Atrial flutter	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Atrial tachycardia	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Cardiac failure	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
	Cardiovascular disorder	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Coronary artery disease	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Diastolic dysfunction	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Left ventricular dysfunction	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Ventricular extrasystoles	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Metabolism and nutrition disorders	*Any event*	11 (1.3%)	11	4 (0.9%)	4	7 (1.9%)	7			11 (1.4%)	11
	Dehydration	6 (0.7%)	6	1 (0.2%)	1	5 (1.3%)	5			6 (0.8%)	6
	Decreased appetite	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Hyperkalaemia	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Hypokalaemia	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Hypovolaemia	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Metabolic acidosis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Musculoskeletal and connective tissue disorders	*Any event*	6 (0.7%)	7	1 (0.2%)	1	5 (1.3%)	6			6 (0.8%)	7
	Arthralgia	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Pain in extremity	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Fistula	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Joint swelling	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Rhabdomyolysis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Psychiatric disorders	*Any event*	5 (0.6%)	6	2 (0.4%)	2	3 (0.8%)	4			5 (0.6%)	6
	Confusional state	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Disorientation	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Hallucination, auditory	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Hallucination, visual	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Psychotic disorder	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Stress	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Investigations	*Any event*	4 (0.5%)	4	3 (0.7%)	3	1 (0.3%)	1			4 (0.5%)	4
	Biopsy bone marrow	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Blood creatinine increased	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Liver function test increased	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Weight decreased	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Hepatobiliary disorders	*Any event*	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1			3 (0.4%)	3

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Autoimmune hepatitis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Cholecystitis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Hepatotoxicity	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Reproductive system and breast disorders	*Any event*	3 (0.4%)	4			3 (0.8%)	4			3 (0.4%)	4
	Vaginal fistula	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Vaginal disorder	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Vaginal haemorrhage	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Surgical and medical procedures	*Any event*	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1	1 (2.2%)	1	2 (0.3%)	2
	Gastrectomy	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Liver ablation	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
	Removal of foreign body	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Immune system disorders	*Any event*	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1	1 (2.2%)	1	1 (0.1%)	1
	Contrast media allergy	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
	Hypersensitivity	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Skin and subcutaneous tissue disorders	*Any event*	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Skin ulcer	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
Eye disorders	*Any event*	1 (0.1%)	2			1 (0.3%)	2			1 (0.1%)	2
	Entropion	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Ulcerative keratitis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Product issues	*Any event*	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Device malfunction	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1

[Source: OTILIA_Tables_Final_4_20200420: Table 14.3.3].
CAP = Core analysis population; MedDRA = Medical Dictionary for Regulatory Activities; N/n = Number; PT = Preferred term; SOC = System organ class.
On-treatment phase: from first application of study medication until 90 days after end of treatment.
SOCs are sorted by decreasing total counts, PTs within SOCs are sorted by decreasing counts.
Adverse event terms have been coded using MedDRA version 22.0.

8.6.5 Causally Related Treatment-Emergent Adverse Events (SOC/PT) – Total and by Subgroup

The documented TEAEs (SOC/PT) causally related to bevacizumab (Avastin®) in the total population and by subgroup are summarized in Table 8-61. Overall, 330 (40.0%) patients were reported with TEAEs assessed as causally related to bevacizumab (Avastin®) where the most frequently reported events (≥5% of patients) were hypertension (n=102; 12.4%; TEAE of particular interest) and fatigue (n=58; 7.0%). With regards to the other TEAEs of particular interest (other than hypertension reported above), 28 (3.4%) patients were reported with proteinuria, 4 (0.5%) patients with large intestine perforation, 1 (0.1%) patient with intestinal perforation, 1 (0,.1%) with gastric perforation and 1 (0.1%) patient with arterial embolism, all events of which were causally related to bevacizumab (Avastin®).

The proportion of patients with any causally related TEAE attributable bevacizumab (Avastin®) was higher in the subgroup of patients aged <70 years as compared to the subgroup of patients aged ≥70 years (n=192; 42.4% vs. n=138; 37.2%). The most frequently reported TEAEs (≥5% of patients) causally related to bevacizumab (Avastin®) in the subgroup of patients aged <70 years were hypertension (n=53; 11.7%; TEAE of particular interest) and fatigue (n=40; 8.8%). Regarding the other TEAEs of particular interest (other than hypertension reported above), 15 (3.3%) patients were reported with proteinuria, 3 (0.7%) patients with large intestine perforation and 1 (0.2%) patient with intestinal perforation, all events of which were causally related to bevacizumab (Avastin®). There were no causally related TEAEs of arterial embolism or gastric perforation in patients aged <70 years. In the subgroup of patients aged ≥70 years, the most frequent TEAE (≥5% of patients) causally related to bevacizumab (Avastin®) was hypertension (n=49; 13.2%; TEAE of particular interest). As to the other TEAEs of particular interest (other than hypertension reported above), 13 (3.5%) patients were reported with proteinuria, 1 (0.3%) patient with large intestine perforation, 1 (0.3%) patient with gastric perforation and 1 (0.1%) patient with arterial embolism, all events of which were causally related to bevacizumab (Avastin®). There were no patients aged ≥70 years, who were reported with causally related intestinal perforation.

The proportion of patients with any causally related TEAE attributable to bevacizumab (Avastin®) was highest in the subgroup of patients with prior surgery as compared to the subgroup of patients with no prior surgery (n=320; 41.1% vs. n=10; 22.2%). In the subgroup of patients with no prior surgery, the most frequently reported TEAEs (≥5% of

patients) causally related to bevacizumab (Avastin®) were hot flush (n=3; 6.7%) and hypertension (n=3; 6.7%; TEAE of particular interest). With regards to the other TEAEs of particular interest (other than hypertension reported above), 1 (2.2%) patient was reported with intestinal perforation assessed as causally related to bevacizumab (Avastin®), while there were no patients documented with causally related proteinuria, large intestine perforation, gastric perforation or arterial embolism. In the subgroup of patients with prior surgery, the most common TEAEs (≥5% of patients) causally related to bevacizumab (Avastin®) were hypertension (n=99; 12.7%; TEAE of particular interest) and fatigue (n=57; 7.3%). Regarding the other TEAEs of particular interest (other than hypertension reported above), 28 (3.6%) patients were reported with proteinuria, 4 (0.5%) patients with large intestine perforation, 1 (0.1%) with gastric perforation and 1 (0.1%) patient with arterial embolism, all events of which were causally related to bevacizumab (Avastin®), whereas there were no causally related TEAEs of intestinal perforation. However, due to the small number of patients in the subgroup of patients without prior surgery (N=45) in comparison to the subgroup of patients with prior surgery (N=779), comparability of these subgroups is limited.

Table 8-61 Any causally related treatment-emergent adverse events[1] (MedDRA PT by SOC) – total and by subgroup (CAP)

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
Patients with any event, n, %, n (cases)		330 (40.0%)	878	192 (42.4%)	568	138 (37.2%)	310	10 (22.2%)	18	320 (41.1%)	860
Vascular disorders	*Any event*	124 (15.0%)	132	66 (14.6%)	70	58 (15.6%)	62	3 (6.7%)	3	121 (15.5%)	129
	Hypertension	102 (12.4%)	102	53 (11.7%)	53	49 (13.2%)	49	3 (6.7%)	3	99 (12.7%)	99
	Hot flush	6 (0.7%)	6	4 (0.9%)	4	2 (0.5%)	2			6 (0.8%)	6
	Hypertensive crisis	6 (0.7%)	6	2 (0.4%)	2	4 (1.1%)	4			6 (0.8%)	6
	Thrombosis	6 (0.7%)	6	4 (0.9%)	4	2 (0.5%)	2			6 (0.8%)	6
	Deep vein thrombosis	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1			3 (0.4%)	3
	Haematoma	3 (0.4%)	3	1 (0.2%)	1	2 (0.5%)	2			3 (0.4%)	3
	Embolism	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Embolism arterial	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Embolism venous	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Hypotension	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Thrombophlebitis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Venous thrombosis limb	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Gastrointestinal disorders	*Any event*	110 (13.3%)	186	73 (16.1%)	124	37 (10.0%)	62	3 (6.7%)	5	107 (13.7%)	181
	Diarrhoea	32 (3.9%)	32	22 (4.9%)	22	10 (2.7%)	10	1 (2.2%)	1	31 (4.0%)	31
	Constipation	30 (3.6%)	30	20 (4.4%)	20	10 (2.7%)	10	1 (2.2%)	1	29 (3.7%)	29
	Nausea	30 (3.6%)	30	18 (4.0%)	18	12 (3.2%)	12	1 (2.2%)	1	29 (3.7%)	29
	Vomiting	20 (2.4%)	20	12 (2.6%)	12	8 (2.2%)	8	1 (2.2%)	1	19 (2.4%)	19
	Stomatitis	19 (2.3%)	19	13 (2.9%)	13	6 (1.6%)	6			19 (2.4%)	19
	Abdominal pain upper	11 (1.3%)	11	10 (2.2%)	10	1 (0.3%)	1			11 (1.4%)	11
	Abdominal pain	9 (1.1%)	9	5 (1.1%)	5	4 (1.1%)	4			9 (1.2%)	9
	Large intestine perforation	4 (0.5%)	4	3 (0.7%)	3	1 (0.3%)	1			4 (0.5%)	4

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Abdominal pain lower	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Aphthous ulcer	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Dry mouth	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Gastrointestinal disorder	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Haematochezia	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Ileus	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Mechanical ileus	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Abdominal distension	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Colitis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Dyspepsia	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Enterocutaneous fistula	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Gastric perforation	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Gastrointestinal haemorrhage	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Gastrointestinal wall thickening	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Gingival bleeding	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Haemorrhoids	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Hyperchlorhydria	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Intestinal haemorrhage	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Intestinal perforation	1 (0.1%)	1	1 (0.2%)	1			1 (2.2%)	1		
	Proctalgia	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Subileus	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Tongue ulceration	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Tooth disorder	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Toothache	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
General disorders and administration site conditions	*Any event*	88 (10.7%)	103	59 (13.0%)	68	29 (7.8%)	35	2 (4.4%)	2	86 (11.0%)	101
	Fatigue	58 (7.0%)	58	40 (8.8%)	40	18 (4.9%)	18	1 (2.2%)	1	57 (7.3%)	57
	Mucosal inflammation	7 (0.8%)	7	5 (1.1%)	5	2 (0.5%)	2			7 (0.9%)	7
	Pain	7 (0.8%)	7	3 (0.7%)	3	4 (1.1%)	4			7 (0.9%)	7
	Asthenia	6 (0.7%)	6	4 (0.9%)	4	2 (0.5%)	2			6 (0.8%)	6
	Impaired healing	6 (0.7%)	6	5 (1.1%)	5	1 (0.3%)	1			6 (0.8%)	6
	Pyrexia	4 (0.5%)	4	2 (0.4%)	2	2 (0.5%)	2			4 (0.5%)	4
	Chills	3 (0.4%)	3	1 (0.2%)	1	2 (0.5%)	2			3 (0.4%)	3
	General physical health deterioration	3 (0.4%)	3	1 (0.2%)	1	2 (0.5%)	2			3 (0.4%)	3
	Catheter site inflammation	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Chest discomfort	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Death	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Inflammation	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Mucous membrane disorder	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Oedema	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Oedema peripheral	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Peripheral swelling	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Unevaluable event	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
Nervous system disorders	*Any event*	70 (8.5%)	86	45 (9.9%)	54	25 (6.7%)	32	1 (2.2%)	1	69 (8.9%)	85
	Paraesthesia	18 (2.2%)	18	15 (3.3%)	15	3 (0.8%)	3			18 (2.3%)	18
	Headache	17 (2.1%)	17	12 (2.6%)	12	5 (1.3%)	5			17 (2.2%)	17
	Polyneuropathy	12 (1.5%)	12	6 (1.3%)	6	6 (1.6%)	6			12 (1.5%)	12
	Neuropathy peripheral	8 (1.0%)	8	4 (0.9%)	4	4 (1.1%)	4	1 (2.2%)	1	7 (0.9%)	7

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Peripheral sensory neuropathy	5 (0.6%)	5	5 (1.1%)	5					5 (0.6%)	5
	Dizziness	4 (0.5%)	4	3 (0.7%)	3	1 (0.3%)	1			4 (0.5%)	4
	Dysgeusia	3 (0.4%)	3	1 (0.2%)	1	2 (0.5%)	2			3 (0.4%)	3
	Sensory disturbance	3 (0.4%)	3	3 (0.7%)	3					3 (0.4%)	3
	Syncope	3 (0.4%)	3	1 (0.2%)	1	2 (0.5%)	2			3 (0.4%)	3
	Aphasia	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Cerebrovascular accident	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Hypoaesthesia	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Transient ischaemic attack	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Cerebral infarction	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Dysarthria	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Generalised tonic-clonic seizure	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Hemiparesis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Ischaemic cerebral infarction	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Musculoskeletal and connective tissue disorders	*Any event*	52 (6.3%)	68	37 (8.2%)	49	15 (4.0%)	19			52 (6.7%)	68
	Arthralgia	18 (2.2%)	18	12 (2.6%)	12	6 (1.6%)	6			18 (2.3%)	18
	Bone pain	16 (1.9%)	16	12 (2.6%)	12	4 (1.1%)	4			16 (2.1%)	16
	Pain in extremity	11 (1.3%)	11	6 (1.3%)	6	5 (1.3%)	5			11 (1.4%)	11
	Myalgia	10 (1.2%)	10	8 (1.8%)	8	2 (0.5%)	2			10 (1.3%)	10
	Back pain	6 (0.7%)	6	5 (1.1%)	5	1 (0.3%)	1			6 (0.8%)	6
	Muscle spasms	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Musculoskeletal pain	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Fistula	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Muscle tightness	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Osteitis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Skin and subcutaneous tissue disorders	*Any event*	45 (5.5%)	52	34 (7.5%)	40	11 (3.0%)	12	1 (2.2%)	1	44 (5.6%)	51
	Alopecia	16 (1.9%)	16	12 (2.6%)	12	4 (1.1%)	4	1 (2.2%)	1	15 (1.9%)	15
	Dry skin	10 (1.2%)	10	9 (2.0%)	9	1 (0.3%)	1			10 (1.3%)	10
	Nail disorder	5 (0.6%)	5	3 (0.7%)	3	2 (0.5%)	2			5 (0.6%)	5
	Rash	4 (0.5%)	4	4 (0.9%)	4					4 (0.5%)	4
	Palmar-plantar erythrodysaesthesia syndrome	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1			3 (0.4%)	3
	Pruritus	3 (0.4%)	3	3 (0.7%)	3					3 (0.4%)	3
	Skin disorder	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Skin ulcer	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Dermatitis acneiform	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Erythema	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Hyperhidrosis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Nail discolouration	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Onychoclasis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Pruritus generalised	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Urticaria	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Respiratory, thoracic and mediastinal disorders	*Any event*	44 (5.3%)	51	26 (5.7%)	33	18 (4.9%)	18			44 (5.6%)	51
	Epistaxis	19 (2.3%)	19	12 (2.6%)	12	7 (1.9%)	7			19 (2.4%)	19
	Dyspnoea	18 (2.2%)	18	11 (2.4%)	11	7 (1.9%)	7			18 (2.3%)	18
	Pulmonary embolism	6 (0.7%)	6	3 (0.7%)	3	3 (0.8%)	3			6 (0.8%)	6
	Dysphonia	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Cough	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Dyspnoea exertional	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Nasal dryness	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Painful respiration	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Productive cough	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Rhinorrhoea	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Infections and infestations	*Any event*	34 (4.1%)	38	23 (5.1%)	25	11 (3.0%)	13	1 (2.2%)	1	33 (4.2%)	37
	Cystitis	6 (0.7%)	6	5 (1.1%)	5	1 (0.3%)	1	1 (2.2%)	1	5 (0.6%)	5
	Urinary tract infection	6 (0.7%)	6	3 (0.7%)	3	3 (0.8%)	3			6 (0.8%)	6
	Bronchitis	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1			3 (0.4%)	3
	Infection	3 (0.4%)	3	1 (0.2%)	1	2 (0.5%)	2			3 (0.4%)	3
	Anorectal infection	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Enteritis infectious	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Nasopharyngitis	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Rash pustular	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Urosepsis	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Abdominal abscess	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Abdominal wall abscess	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Enterobiasis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Febrile infection	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Gastroenteritis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Gastrointestinal infection	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Influenza	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Oral herpes	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Pharyngitis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Sepsis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
Renal and urinary disorders	*Any event*	33 (4.0%)	34	18 (4.0%)	18	15 (4.0%)	16			33 (4.2%)	34
	Proteinuria	28 (3.4%)	28	15 (3.3%)	15	13 (3.5%)	13			28 (3.6%)	28
	Acute kidney injury	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Haematuria	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Nephrotic syndrome	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Renal failure	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Urinary bladder haemorrhage	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Blood and lymphatic system disorders	*Any event*	30 (3.6%)	35	21 (4.6%)	25	9 (2.4%)	10	3 (6.7%)	4	27 (3.5%)	31
	Anaemia	10 (1.2%)	10	6 (1.3%)	6	4 (1.1%)	4			10 (1.3%)	10
	Leukopenia	9 (1.1%)	9	6 (1.3%)	6	3 (0.8%)	3	1 (2.2%)	1	8 (1.0%)	8
	Thrombocytopenia	9 (1.1%)	9	8 (1.8%)	8	1 (0.3%)	1	1 (2.2%)	1	8 (1.0%)	8
	Neutropenia	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1	2 (4.4%)	2	1 (0.1%)	1
	Febrile neutropenia	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Leukocytosis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Pancytopenia	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	White blood cell disorder	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Psychiatric disorders	*Any event*	19 (2.3%)	23	15 (3.3%)	19	4 (1.1%)	4			19 (2.4%)	23
	Insomnia	8 (1.0%)	8	6 (1.3%)	6	2 (0.5%)	2			8 (1.0%)	8
	Depression	6 (0.7%)	6	6 (1.3%)	6					6 (0.8%)	6
	Sleep disorder	4 (0.5%)	4	3 (0.7%)	3	1 (0.3%)	1			4 (0.5%)	4
	Restlessness	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1			3 (0.4%)	3
	Depressed mood	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Stress	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Investigations	*Any event*	17 (2.1%)	19	10 (2.2%)	12	7 (1.9%)	7			17 (2.2%)	19

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Blood creatinine increased	4 (0.5%)	4	3 (0.7%)	3	1 (0.3%)	1			4 (0.5%)	4
	Blood pressure increased	4 (0.5%)	4	2 (0.4%)	2	2 (0.5%)	2			4 (0.5%)	4
	Protein urine present	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Alanine aminotransferase increased	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Aspartate aminotransferase increased	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Blood alkaline phosphatase increased	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	C-reactive protein increased	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Gamma-glutamyltransferase increased	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Lymphocyte count decreased	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Neutrophil count decreased	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Nitrite urine present	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	White blood cell count decreased	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Cardiac disorders	*Any event*	15 (1.8%)	15	11 (2.4%)	11	4 (1.1%)	4			15 (1.9%)	15
	Tachycardia	6 (0.7%)	6	4 (0.9%)	4	2 (0.5%)	2			6 (0.8%)	6
	Palpitations	5 (0.6%)	5	5 (1.1%)	5					5 (0.6%)	5
	Angina pectoris	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Cardiovascular disorder	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Coronary artery disease	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Left ventricular dysfunction	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Metabolism and nutrition disorders	*Any event*	12 (1.5%)	13	8 (1.8%)	9	4 (1.1%)	4	1 (2.2%)	1	11 (1.4%)	12
	Decreased appetite	8 (1.0%)	8	5 (1.1%)	5	3 (0.8%)	3	1 (2.2%)	1	7 (0.9%)	7
	Hyperkalaemia	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Dehydration	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Fluid retention	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Type 1 diabetes mellitus	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Injury, poisoning and procedural complications	*Any event*	8 (1.0%)	8	4 (0.9%)	4	4 (1.1%)	4			8 (1.0%)	8
	Anastomotic complication	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Concussion	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Excoriation	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Fall	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Stoma site haemorrhage	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Wound dehiscence	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Wound haemorrhage	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Wrist fracture	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Ear and labyrinth disorders	*Any event*	5 (0.6%)	5	2 (0.4%)	2	3 (0.8%)	3			5 (0.6%)	5

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Vertigo	4 (0.5%)	4	2 (0.4%)	2	2 (0.5%)	2			4 (0.5%)	4
	Ear disorder	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Eye disorders	*Any event*	3 (0.4%)	5	2 (0.4%)	2	1 (0.3%)	3			3 (0.4%)	5
	Visual impairment	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Asthenopia	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Eye disorder	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Eye inflammation	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Immune system disorders	*Any event*	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Hypersensitivity	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Seasonal allergy	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Reproductive system and breast disorders	*Any event*	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Vaginal disorder	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Vaginal fistula	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Surgical and medical procedures	*Any event*	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Dental care	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1

[Source: OTILIA_Tables_Final_4_20200420: Table 14.3.5].
CAP = Core analysis population; MedDRA = Medical Dictionary for Regulatory Activities; N/n = Number; PT = Preferred term; SOC = System organ class.
On-treatment phase: from first application of study medication until 90 days after end of treatment.
SOCs are sorted by decreasing total counts, PTs within SOCs are sorted by decreasing counts.
Adverse event terms have been coded using MedDRA version 22.0.
[1]Causally related TEAEs were defined as those with a possible, probable or definite relationship to bevacizumab (Avastin®).

8.6.6 Treatment-Emergent Adverse Events Leading to Discontinuation of Bevacizumab (Avastin®) Treatment (SOC/PT) – Total and by Subgroup

The documented TEAEs (SOC/PT) leading to discontinuation of bevacizumab (Avastin®) treatment in the total population and by subgroup are summarized in Table 8-62. Overall, 145 (17.6%) patients were reported with a TEAE leading to discontinuation of bevacizumab (Avastin®) treatment where the most frequently reported events (≥1.0% of patients) were hypertension (n=21; 2.5%) and proteinuria (n=10; 1.2%), both events of which were TEAEs of particular interest. Regarding the other TEAEs of particular interest, 5 (0.6%) patients were reported with large intestine perforation, 2 (0.2%) with gastric perforation and 1 (0.1%) patient was reported with arterial embolism having resulted in discontinuation of bevacizumab (Avastin®), while no such event was reported for intestinal perforation.

A higher proportion of patients with TEAEs leading to discontinuation of therapy with bevacizumab (Avastin®) was found in the subgroup of patients aged ≥70 years as compared to the subgroup of patients aged <70 years (n=79; 21.3% vs. n=66; 14.6%), where the most frequent (≥1.0% of patients) TEAEs in patients aged ≥70 years were hypertension (n=12; 3.2%; TEAE of particular interest), polyneuropathy (n=6; 1.6%), general physical health deterioration (n=5; 1.3%), malignant neoplasm progression (n=4; 1.1%) and proteinuria (n=4; 1.1%; TEAE of particular interest). Regarding the other TEAEs of particular interest (other than the hypertension and proteinuria reported above), 2 (0.5%) patients were reported with large intestine perforation, 1 (0.3%) patient with gastric perforation and 1 (0.3%) patient was reported with arterial embolism having resulted in discontinuation of bevacizumab (Avastin®). In the subgroup of patients aged <70 years, the most commonly reported (≥1.0% of patients) TEAEs having led to discontinuation of bevacizumab (Avastin®) treatment were hypertension (n=9; 2.0%) and proteinuria (n=6; 1.3%), both events of which were TEAEs of particular interest. Regarding the other TEAEs of particular interest (other than the hypertension and proteinuria reported above), 3 (0.7%) patients were reported with large intestine perforation and 1 (0.2%) patient with gastric perforation having resulted in discontinuation of bevacizumab (Avastin®). There were no patients aged <70 years, who were reported with intestinal perforation or arterial embolism having led to discontinuation of therapy with bevacizumab (Avastin®).

A higher proportion of patients with TEAEs leading to discontinuation of therapy with bevacizumab (Avastin®) was observed in the subgroup of patients with prior surgery as compared to the subgroup of patients with no prior surgery (n=139; 17.8% vs. n=6; 13.3%). In the subgroup of patients with no prior surgery, all the reported TEAEs leading to discontinuation of bevacizumab (Avastin®) treatment were observed at a relative frequency ≥1.0%. Regarding the TEAEs of particular interest, 1 (2.2%) patient was reported with large intestine perforation and 1 (2.2%) patient with gastric perforation having resulted in discontinuation of bevacizumab (Avastin®). There were no patients with no prior surgery, who were reported with hypertension, proteinuria, intestinal perforation or arterial embolism having led to discontinuation of therapy with bevacizumab (Avastin®). In the subgroup of patients with prior surgery, the most frequently reported (≥1.0% of patients) TEAEs having led to discontinuation of bevacizumab (Avastin®) treatment were hypertension (n=21; 2.7%) and proteinuria (n=10; 1.3%), both events of which were TEAEs of particular interest. Regarding the other TEAEs of particular interest, 4 (0.5%) patients were reported with large intestine perforation, 1 (0.1%) with gastric perforation and 1 (0.1%) patient was reported with arterial embolism having resulted in discontinuation of bevacizumab (Avastin®). However, the number of patients in the subgroup of patients without prior surgery (N=45) was very small in comparison to the subgroup of patients with prior surgery (N=779), which limits the comparability of these subgroups.

Table 8-62 Treatment-emergent adverse events leading to discontinuation of bevacizumab (Avastin®) treatment (MedDRA PT by SOC) – total and by subgroup (CAP)

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
Patients with any event, *n, %, n (cases)*		145 (17.6%)	203	66 (14.6%)	100	79 (21.3%)	103	6 (13.3%)	13	139 (17.8%)	190
Vascular disorders	*Any event*	33 (4.0%)	33	16 (3.5%)	16	17 (4.6%)	17			33 (4.2%)	33
	Hypertension	21 (2.5%)	21	9 (2.0%)	9	12 (3.2%)	12			21 (2.7%)	21
	Deep vein thrombosis	5 (0.6%)	5	2 (0.4%)	2	3 (0.8%)	3			5 (0.6%)	5
	Thrombosis	4 (0.5%)	4	3 (0.7%)	3	1 (0.3%)	1			4 (0.5%)	4
	Embolism arterial	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Hypertensive crisis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Venous thrombosis limb	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Gastrointestinal disorders	*Any event*	27 (3.3%)	35	15 (3.3%)	21	12 (3.2%)	14	2 (4.4%)	5	25 (3.2%)	30
	Ileus	6 (0.7%)	6	4 (0.9%)	4	2 (0.5%)	2	2 (4.4%)	2	4 (0.5%)	4
	Large intestine perforation	5 (0.6%)	5	3 (0.7%)	3	2 (0.5%)	2	1 (2.2%)	1	4 (0.5%)	4
	Abdominal pain	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Ascites	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Gastric perforation	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1	1 (2.2%)	1	1 (0.1%)	1
	Subileus	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Abdominal pain upper	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Colitis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Diarrhoea	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Diverticulum intestinal	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Duodenal obstruction	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Dyschezia	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Enterocutaneous fistula	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Gastric ulcer	1 (0.1%)	1	1 (0.2%)	1			1 (2.2%)	1		
	Gastrointestinal wall thickening	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Haemorrhoids	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Impaired gastric emptying	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Intestinal obstruction	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Mechanical ileus	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Nausea	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Short-bowel syndrome	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Vomiting	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
General disorders and administration site conditions	*Any event*	19 (2.3%)	21	9 (2.0%)	11	10 (2.7%)	10	1 (2.2%)	1	18 (2.3%)	20
	General physical health deterioration	7 (0.8%)	7	2 (0.4%)	2	5 (1.3%)	5			7 (0.9%)	7
	Impaired healing	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1			3 (0.4%)	3
	Asthenia	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Fatigue	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Chest discomfort	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Chills	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Death	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Oedema peripheral	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Pain	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Pyrexia	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Unevaluable event	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
Nervous system disorders	*Any event*	19 (2.3%)	23	4 (0.9%)	4	15 (4.0%)	19	1 (2.2%)	1	18 (2.3%)	22
	Polyneuropathy	6 (0.7%)	6			6 (1.6%)	6			6 (0.8%)	6
	Transient ischaemic attack	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1			3 (0.4%)	3
	Cerebrovascular accident	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Ischaemic cerebral infarction	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Aphasia	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Dizziness	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
	Dysarthria	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Headache	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Hemiparesis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Hypoaesthesia	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Monoparesis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Partial seizures	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Peripheral paralysis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Status epilepticus	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Infections and infestations	*Any event*	14 (1.7%)	15	8 (1.8%)	8	6 (1.6%)	7	1 (2.2%)	1	13 (1.7%)	14
	Peritonitis	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1	1 (2.2%)	1	1 (0.1%)	1
	Pneumonia	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Sepsis	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Urinary tract infection	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Abdominal abscess	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Anal abscess	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Enterobiasis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Febrile infection	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Gastroenteritis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Herpes zoster oticus	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Urosepsis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Renal and urinary disorders	*Any event*	12 (1.5%)	12	8 (1.8%)	8	4 (1.1%)	4			12 (1.5%)	12
	Proteinuria	10 (1.2%)	10	6 (1.3%)	6	4 (1.1%)	4			10 (1.3%)	10
	Acute kidney injury	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	*Any event*	11 (1.3%)	13	4 (0.9%)	5	7 (1.9%)	8	1 (2.2%)	2	10 (1.3%)	11
	Malignant neoplasm progression	7 (0.8%)	7	3 (0.7%)	3	4 (1.1%)	4			7 (0.9%)	7
	Cancer pain	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Malignant pleural effusion	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Metastases to central nervous system	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
	Metastases to liver	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Metastases to meninges	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
	Metastases to peritoneum	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Respiratory, thoracic and mediastinal disorders	*Any event*	10 (1.2%)	10	5 (1.1%)	5	5 (1.3%)	5	1 (2.2%)	1	9 (1.2%)	9

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Pulmonary embolism	5 (0.6%)	5	3 (0.7%)	3	2 (0.5%)	2			5 (0.6%)	5
	Dyspnoea	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Pleural effusion	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1	1 (2.2%)	1	1 (0.1%)	1
	Epistaxis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Injury, poisoning and procedural complications	*Any event*	7 (0.8%)	7	2 (0.4%)	2	5 (1.3%)	5			7 (0.9%)	7
	Failure to anastomose	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Anastomotic complication	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Ankle fracture	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Incisional hernia	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Stoma site pain	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Thoracic vertebral fracture	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Musculoskeletal and connective tissue disorders	*Any event*	7 (0.8%)	8	4 (0.9%)	4	3 (0.8%)	4			7 (0.9%)	8
	Arthralgia	3 (0.4%)	3	1 (0.2%)	1	2 (0.5%)	2			3 (0.4%)	3
	Back pain	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Fistula	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Rhabdomyolysis	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Cardiac disorders	*Any event*	5 (0.6%)	5	4 (0.9%)	4	1 (0.3%)	1			5 (0.6%)	5
	Palpitations	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Coronary artery disease	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Diastolic dysfunction	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Left ventricular dysfunction	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Skin and subcutaneous tissue disorders	*Any event*	5 (0.6%)	5	2 (0.4%)	2	3 (0.8%)	3			5 (0.6%)	5
	Skin ulcer	3 (0.4%)	3			3 (0.8%)	3			3 (0.4%)	3
	Hidradenitis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Pruritus generalised	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Blood and lymphatic system disorders	*Any event*	3 (0.4%)	5	2 (0.4%)	4	1 (0.3%)	1	1 (2.2%)	2	2 (0.3%)	3
	Leukopenia	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1	1 (2.2%)	1	2 (0.3%)	2
	Thrombocytopenia	2 (0.2%)	2	2 (0.4%)	2			1 (2.2%)	1	1 (0.1%)	1
Investigations	*Any event*	3 (0.4%)	3	2 (0.4%)	2	1 (0.3%)	1			3 (0.4%)	3
	Liver function test increased	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Protein urine present	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Weight decreased	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Reproductive system and breast disorders	*Any event*	3 (0.4%)	3			3 (0.8%)	3			3 (0.4%)	3
	Vaginal fistula	2 (0.2%)	2			2 (0.5%)	2			2 (0.3%)	2
	Vaginal haemorrhage	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Metabolism and nutrition disorders	*Any event*	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Dehydration	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Hypokalaemia	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Hepatobiliary disorders	*Any event*	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Autoimmune hepatitis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Immune system disorders	*Any event*	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Sarcoidosis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Surgical and medical procedures	*Any event*	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Removal of foreign body	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1

[Source: OTILIA_Tables_Final_4_20200420: Table 14.3.6].
CAP = Core analysis population; MedDRA = Medical Dictionary for Regulatory Activities; N/n = Number; PT = Preferred term; SOC = System organ class.
On-treatment phase: from first application of study medication until 90 days after end of treatment.
SOCs are sorted by decreasing total counts, PTs within SOCs are sorted by decreasing counts.
Adverse event terms have been coded using MedDRA version 22.0.

8.6.7 Overview of Number of Deaths and Fatal Treatment-Emergent Adverse Events – Total Population

In total, death of 181 (22.0%) patients has been reported during the study, of these, 30 (3.6%) patients were documented with a fatal TEAE, of which the fatal event was reported as related to bevacizumab (Avastin®) in 5 (0.6%) patients (6 cases in total) (Table 8-63).

Table 8-63 Overview of number of deaths and fatal treatment-emergent adverse events – total population (CAP)

Total CAP *(N=824)*	Patients[1] N (%)	Cases N
Total number of deaths, n, %	181 (22.0%)	
Patients reported with fatal TEAE, n, %, n (cases)		
Any TEAE	*616 (74.8%)*	*3,645*
All fatal TEAE[2]	30 (3.6%)	43
Fatal causally related TEAE[3]	5 (0.6%)	6
Fatal non-related TEAE[3]	24 (2.9%)	29
Fatal TEAE – causality unknown[3]	5 (0.6%)	8

[Source: OTILIA_Listings_Final_2_20191206; Listing 16.2.7.1: Adverse events].
CAP = Core analysis population; CTCAE = Common Terminology Criteria for Adverse Events; N/n = Number; TEAE = Treatment-emergent adverse event.
[1]Patients can occur in more than one category of the table. [2]For one patient (pat ID 215001), the same fatal TEAE (ileus) was reported twice, once as related to bevacizumab (Avastin®) with CTCAE severity grade 4 and once as non-related with CTCAE severity grade 5. [3]Causally related TEAEs were defined as those with a possible, probable or definite relationship to bevacizumab (Avastin®).

8.6.7.1 Fatal Treatment-Emergent Adverse Events (SOC/PT) – Total and by Subgroup

The fatal TEAEs (SOC/PT) in the total population and by subgroup are summarized in Table 8-64. In the total population, 30 (3.6%) patients were reported with fatal TEAEs where the most frequently reported fatal events (≥0.5% of patients) were death (n=6; 0.7%) and malignant neoplasm progression (n=4; 0.5%). With regards to TEAEs of particular interest, a fatal intestinal perforation was reported in 3 (0.4%) patients, whereas no fatal events of large intestine perforation, gastric perforation, arterial embolism, hypertension, or proteinuria were documented.

A higher proportion of patients with fatal TEAEs was observed in the subgroup of patients aged ≥70 years as compared to the subgroup of patients aged <70 years (n=18; 4.9% vs. n=12; 2.6%). The most commonly reported fatal TEAEs (≥0.5% of patients) in patients aged ≥70 years were death (n=4; 1.1%), general physical health deterioration (n=3; 0.8%), intestinal perforation (n=2; 0.5%; TEAE of particular interest) and malignant neoplasm progression (n=2; 0.5%). In patients aged <70 years none of the fatal TEAEs were

reported in ≥0.5% of patients (a fatal intestinal perforation was documented in 1 (0.2%) patient).

A higher proportion of patients with fatal TEAEs was observed in the subgroup of patients with no prior surgery as compared to the subgroup of patients with prior surgery (n=3; 6.7% vs. n=27; 3.5%). In the subgroup of patients with no prior surgery, all the reported fatal TEAEs were observed at a relative frequency ≥0.5% patients including intestinal perforation (n=2; 4.4%; TEAE of particular interest), metastasis to meninges, metastases to central nervous system, leukopenia and thrombocytopenia (each n=1; 2.2%). In the subgroup of patients with prior surgery, the most frequently reported fatal TEAEs (≥0.5% of patients) were death (n=6; 0.8%) and malignant neoplasm progression (n=4; 0.5%). A fatal intestinal perforation was documented in 1 (0.1%) patient). However, the number of patients in the subgroup of patients without prior surgery (N=45) was very small in comparison to the subgroup of patients with prior surgery (N=779), which limits the comparability of these subgroups.

For further details on the reported fatal TEAEs in the total population, please refer to Table 8-65.

Table 8-64 Fatal treatment-emergent adverse events (MedDRA PT by SOC) – total and by subgroup (CAP)

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
Patients with any fatal event, n, %, n (cases)		30 (3.6%)	43	12 (2.6%)	20	18 (4.9%)	23	3 (6.7%)	6	27 (3.5%)	37
General disorders and administration site conditions	*Any event*	12 (1.5%)	12	4 (0.9%)	4	8 (2.2%)	8			12 (1.5%)	12
	Death	6 (0.7%)	6	2 (0.4%)	2	4 (1.1%)	4			6 (0.8%)	6
	General physical health deterioration	3 (0.4%)	3			3 (0.8%)	3			3 (0.4%)	3
	Multiple organ dysfunction syndrome	2 (0.2%)	2	2 (0.4%)	2					2 (0.3%)	2
	Impaired healing	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Gastrointestinal disorders[1]	*Any event*	9 (1.1%)	11	4 (0.9%)	4	5 (1.3%)	7	2 (4.4%)	2	7 (0.9%)	9
	Ileus	3 (0.4%)	4	2 (0.4%)	3	1 (0.3%)	1			3 (0.4%)	4
	Intestinal perforation	3 (0.4%)	3	1 (0.2%)	1	2 (0.5%)	2	2 (4.4%)	2	1 (0.1%)	1
	Ascites	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Diarrhoea	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Duodenal obstruction	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Intestinal ischaemia	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Vomiting	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	*Any event*	9 (1.1%)	11	5 (1.1%)	6	4 (1.1%)	5	1 (2.2%)	2	8 (1.0%)	9
	Malignant neoplasm progression	4 (0.5%)	4	2 (0.4%)	2	2 (0.5%)	2			4 (0.5%)	4
	Metastases to meninges	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1	1 (2.2%)	1	1 (0.1%)	1

MedDRA SOC	MedDRA PT	Total Patients N=824	Cases	<70 years Patients N=453	Cases	≥70 years Patients N=371	Cases	No prior surgery Patients N=45	Cases	Prior surgery Patients N=779	Cases
	Metastases to peritoneum	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Malignant pleural effusion	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Metastases to central nervous system	1 (0.1%)	1			1 (0.3%)	1	1 (2.2%)	1		
	Neoplasm progression	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Infections and infestations	*Any event*	2 (0.2%)	2	1 (0.2%)	1	1 (0.3%)	1			2 (0.3%)	2
	Pneumonia	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Urosepsis	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Blood and lymphatic system disorders	*Any event*	1 (0.1%)	2	1 (0.2%)	2			1 (2.2%)	2		
	Leukopenia	1 (0.1%)	1	1 (0.2%)	1			1 (2.2%)	1		
	Thrombocytopenia	1 (0.1%)	1	1 (0.2%)	1			1 (2.2%)	1		
Hepatobiliary disorders	*Any event*	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Hepatotoxicity	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Nervous system disorders	*Any event*	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
	Cerebrovascular accident	1 (0.1%)	1			1 (0.3%)	1			1 (0.1%)	1
Renal and urinary disorders	*Any event*	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Acute kidney injury	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
Vascular disorders	*Any event*	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1
	Angiopathy	1 (0.1%)	1	1 (0.2%)	1					1 (0.1%)	1

[Source: OTILIA_Tables_Final_4_20200420: Table 14.3.6b].
CAP = Core analysis population; MedDRA = Medical Dictionary for Regulatory Activities; N/n = Number; PT = Preferred term; SOC = System organ class.
On-treatment phase: from first application of study medication until 90 days after end of treatment.

SOCs are sorted by decreasing total counts, PTs within SOCs are sorted by decreasing counts.
Adverse event terms have been coded using MedDRA version 22.0.
[1]For one patient (pat ID 215001), the same fatal TEAE (ileus) was reported twice, once as related to bevacizumab (Avastin®) with CTCAE severity grade 4 and once as non-related with CTCAE severity grade 5.

8.6.7.2 Fatal Treatment-Emergent Adverse Events – Patient-Listing (Total Population)

Further information on the fatal TEAEs for each affected patient are provided in Table 8-65 including pat IDs, dates of first administration, start and end dates of respective TEAE, PT term and causality, which has been sorted by SOC. Please, note that some patients were reported with more than one fatal event within the same SOC or within different SOCs.

Five (0.6%) patients were documented with a fatal TEAE related to bevacizumab (Avastin®) (6 cases in total).

With regards to TEAEs of particular interest, a fatal intestinal perforation was reported in 3 (0.4%) patients (pat IDs 8002, 40002 and 137004).

Table 8-65 Fatal TEAEs – patient-listing [N=30 patients; n=43 events] (CAP)]

Patient ID	Date of first administration	Preferred Term	System Organ Class	Start date of adverse event	End date of adverse event	Causality to Bevacizumab (Avastin®)	Action taken with Bevacizumab (Avastin®)
8002	2013-03-04	Leukopenia	Blood and lymphatic system disorders	2013-04-19	2013-04-27	Not related	Drug Withdrawn
8002	2013-03-04	Thrombocytopenia	Blood and lymphatic system disorders	2013-04-19	2013-04-27	Not related	Drug Withdrawn
77007	2013-09-04	Intestinal ischaemia	Gastrointestinal disorders	2013-11-19	2013-11-19	Not related	None
8002	2013-03-04	Intestinal perforation	Gastrointestinal disorders	2013-04-19	2013-04-27	Probable	Other
40002	2012-12-05	Intestinal perforation	Gastrointestinal disorders	2013-09-23	2013-09-29	Not related	None
215001	2013-03-25	Ileus	Gastrointestinal disorders	2013-06-27	2013-07-16	YES	None
215001	2013-03-25	Ileus	Gastrointestinal disorders	2013-07-16	2013-07-16	Not related	None
137004	2013-04-25	Intestinal perforation	Gastrointestinal disorders	2014-04-22	2014-04-26	Not related	None
245009	2014-03-13	Ileus	Gastrointestinal disorders	2014-09-06	2014-09-29	Unknown	Drug Withdrawn
22006	2013-03-06	Ileus	Gastrointestinal disorders	2014-02-13	2014-02-22	Unknown	Temporary interruption
22006	2013-03-06	Vomiting	Gastrointestinal disorders	2014-02-13	2014-02-22	Unknown	Temporary interruption
22006	2013-03-06	Diarrhoea	Gastrointestinal disorders	2014-02-13	2014-02-22	Unknown	Temporary interruption
76013	2014-10-09	Ascites	Gastrointestinal disorders	2015-09-01	2015-09-12	Not related	None

Patient ID	Date of first administration	Preferred Term	System Organ Class	Start date of adverse event	End date of adverse event	Causality to Bevacizumab (Avastin®)	Action taken with Bevacizumab (Avastin®)
125004	2013-11-19	Duodenal obstruction	Gastrointestinal disorders	2014-10-22	2014-10-31	Not related	Drug Withdrawn
242001	2013-06-27	Death	General disorders and administration site conditions	2013-08-20	2013-08-20	Unknown	None
270004	2016-12-20	Death	General disorders and administration site conditions	2017-05-06	2017-05-06	Not related	None
38007	2016-08-04	Death	General disorders and administration site conditions	2017-10-08	2017-10-08	Not related	None
98004	2013-08-28	Multiple organ dysfunction syndrome	General disorders and administration site conditions	2013-09-30	2013-10-08	Not related	None
185002	2012-10-23	Impaired healing	General disorders and administration site conditions	2012-11-14	2013-01-11	Not related	Temporary interruption
156005	2014-01-07	Death	General disorders and administration site conditions	2014-10-25	2014-10-25	Possible	Dose reduction followed by permanent discontinuation
22006	2013-03-06	General physical health deterioration	General disorders and administration site conditions	2014-02-10	2014-02-22	Not related	Temporary interruption
76020	2016-10-17	Death	General disorders and administration site conditions	2016-10-26	2016-10-26	Not related	None
125004	2013-11-19	Multiple organ dysfunction syndrome	General disorders and administration site conditions	2014-10-06	2014-10-31	Not related	Temporary interruption
195001	2013-01-22	Death	General disorders and administration site conditions	2014-06-16	2014-06-16	Unknown	None
261005	2016-11-22	General physical health deterioration	General disorders and administration site conditions	2017-04-11	2017-05-15	Not related	Drug Withdrawn

Patient ID	Date of first administration	Preferred Term	System Organ Class	Start date of adverse event	End date of adverse event	Causality to Bevacizumab (Avastin®)	Action taken with Bevacizumab (Avastin®)
261006	2016-11-04	General physical health deterioration	General disorders and administration site conditions	2016-12-21	2016-12-21	Not related	Drug Withdrawn
143007	2014-02-13	Hepatotoxicity	Hepatobiliary disorders	2014-05-08	2014-08-13	Not related	None
98004	2013-08-28	Urosepsis	Infections and infestations	2013-09-30	2013-10-08	Probable	Drug Withdrawn
22011	2015-12-02	Pneumonia	Infections and infestations	2016-04-05	2016-04-05	Not related	Drug Withdrawn
154004	2013-03-07	Malignant neoplasm progression	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2013-09-16	2014-01-20	Not related	Drug Withdrawn
21008	2013-07-24	Metastases to meninges	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2014-04-03		Not related	None
6020	2013-12-04	Malignant neoplasm progression	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2015-03-18	2015-04-30	Not related	None
121003	2014-12-30	Metastases to peritoneum	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2016-01-05	2016-04-06	Not related	None
134001	2012-07-10	Malignant neoplasm progression	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2012-08-06	2012-09-03	Not related	Drug Withdrawn
22006	2013-03-06	Malignant neoplasm progression	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2014-02-10	2014-02-22	Unknown	Drug Withdrawn
125004	2013-11-19	Metastases to peritoneum	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2014-10-22	2014-10-31	Not related	Drug Withdrawn
125004	2013-11-19	Malignant pleural effusion	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2014-10-23	2014-10-31	Not related	Drug Withdrawn

Patient ID	Date of first administration	Preferred Term	System Organ Class	Start date of adverse event	End date of adverse event	Causality to Bevacizumab (Avastin®)	Action taken with Bevacizumab (Avastin®)
120003	2014-03-26	Neoplasm progression	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2014-12-25	2014-12-25	Not related	None
77005	2013-05-17	Metastases to central nervous system	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2013-10-15	2013-12-06	Not related	Drug Withdrawn
77005	2013-05-17	Metastases to meninges	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2013-10-15	2013-12-06	Not related	Drug Withdrawn
184007	2014-09-24	Cerebrovascular accident	Nervous system disorders	2014-10-19	2014-10-28	Probable	Drug Withdrawn
98004	2013-08-28	Acute kidney injury	Renal and urinary disorders	2013-10-08	2013-10-08	Probable	Drug Withdrawn
60001	2013-03-27	Angiopathy	Vascular disorders	2013-12-18	2013-12-18	Unknown	None

[Source: OTILIA_Listings_Final_2_20191206; Listing 16.2.7.1: Adverse events].
CAP = Core analysis population; TEAE = Treatment emergent adverse event.

9. DISCUSSION

9.1 KEY RESULTS

This NIS evaluated the effectiveness, safety, tolerability and patient-reported QoL of first-line bevacizumab (Avastin®) treatment in combination with carboplatin/paclitaxel in patients with advanced EOC, FTC and PPC in daily routine clinical practice in Germany. Patients were recruited from 02 February 2012 through 31 December 2016 in 240 active study sites across Germany including oncologists and gynecologists in hospitals and outpatient clinics as well as office-based oncologists and gynecologists.

In the first study phase (February 2012-June 2014), patients ≥18 years were enrolled. In the second study phase (beginning July 2014) only patients ≥70 years were included.

The report includes data from 824 patients in the CAP, thereof 453 patients in the subgroup of patients <70 years and 371 patients in the subgroup of patients ≥70 years.

9.1.1 Demographics and baseline characteristics

The most important patient and tumor characteristics of the CAP and age subgroups are summarized in

Table 9-1. Patients aged ≥70 years were not only older in comparison to patients aged <70 years, but also had a worse performance status and more comorbidities such as arterial hypertension (

Table 9-1). For detailed discussion and interpretation of baseline characteristic please refer to chapter 9.3.1 Demographics and baseline characteristics.

Table 9-1 Demographics and baseline characteristics

Parameter	CAP	Patients <70 years	Patients ≥70 years
Total number of patients enrolled, N	*824*	*453*	*371*
Age at start of therapy, years[1]			
Median	68.0	58.4	74.6
Min - Max	25.9-83.4	25.9-70.2	70.1-83.4
Age at start of therapy <70 / ≥70 years, n, (%)[1]			
<70 years	451 (54.7%)	451 (99.6%)	0 (0%)
≥70 years	373 (45.3%)	2 (0.4%)	371 (100%)
ECOG performance status, n, (%)			
0	297 (38.2)	199 (45.7)	98 (28.6)
1	389 (50.0)	194 (44.6)	195 (56.9)
2	77 (9.9)	36 (8.3)	41 (12.0)
3	15 (1.9)	6 (1.4)	9 (2.6)
Missing	46	18	28
Ongoing comorbidities, n (%)	365 (44.3)	142 (31.3)	223 (60.1)
Persistent arterial hypertension, n (%)	339 (41.1)	132 (29.1)	207 (55.8)
Charlson Comorbidity Index[2]			
0	644 (78.2%)	364 (80.4%)	280 (75.5%)
≥1	180 (21.8%)	89 (19.6%)	91 (24.5%)
Type of tumor, n (%)			
Epithelial ovarian carcinoma	662 (80.3%)	367 (81.0%)	295 (79.5%)
Fallopian tube carcinoma	58 (7.0%)	27 (6.0%)	31 (8.4%)
Peritoneal carcinoma	104 (12.6%)	59 (13.0%)	45 (12.1%)
FIGO stage, n (%)			
IIIB	116 (14.1%)	65 (14.3%)	51 (13.7%)
IIIC	472 (57.3%)	265 (58.5%)	207 (55.8%)
IV	236 (28.6%)	123 (27.2%)	113 (30.5%)
Grading, n (%)			
G1	22 (2.7%)	13 (2.9%)	9 (2.4%)
G2	153 (18.6%)	99 (21.9%)	54 (14.6%)
G3	565 (68.6%)	312 (68.9%)	253 (68.2%)
G4	12 (1.5%)	2 (0.4%)	10 (2.7%)
Grading unknown	72 (8.7%)	27 (6.0%)	45 (12.1%)
Histological type, n (%)			
Clear cell	13 (1.7%)	9 (2.0%)	4 (1.2%)
Endometroid	22 (2.8%)	14 (3.2%)	8 (2.4%)
Mucinous	19 (2.4%)	13 (3.0%)	6 (1.8%)
Serous	606 (77.8%)	333 (75.7%)	273 (80.5%)
Undifferentiated	24 (3.1%)	13 (3.0%)	11 (3.2%)
Other	95 (12.2%)	58 (13.2%)	37 (10.9%)
Missing	45	13	32

[Source: OTILIA_Tables_Final_4_20200420: Table 14.1.2; Table 14.1.10].
CAP = Core analysis population; ECOG = Eastern Cooperative Oncology Group; FIGO = Fédération Internationale de Gynécologie et d'Obstétrique; Max = Maximum; Min = Minimum; N/n = Number.
[1]Age at enrollment could be younger than age at therapy start. Therefore, patients could be in the age group <70 even if they are more than 70 at therapy start. [2]Charlson Comorbidity Index was calculated for previous and concomitant diseases together.

9.1.2 Effectiveness

Effectiveness in terms of PFS, OS and ORR in the CAP as well as age and surgery subgroups is shown in Table 9-2. PFS and OS were similar in the CAP and between age and surgery subgroups. However interpretation and comparability of these effectiveness parameters is limited due to low number of events and different size of surgery subgroups as elaborated and discussed in chapter 9.2 Limitations and 9.3.2 Effectiveness.

Table 9-2 Progression-free survival, overall survival and ORR

		Age subgroup		Surgery subgroup	
	CAP	Patients <70 years	Patients ≥70 years	No prior surgery	Prior surgery
Patients, N	824	453	371	45	779
Progression-free survival[1]					
Events, n [%][2]	368 (44.7%)	200 (44.2%)	168 (45.3%)	27 (60.0%)	341 (43.8%)
Median [95% CI]	19.4 [18.7, 20.3]	20.0 [18.7, 21.2]	19.3 [17.6, 20.2]	19.4 [14.2, 22.2]	19.6 [18.7, 20.3]
Overall survival[1]					
Events, n (%)[3]	181 (22.0%)	86 (19.0%)	95 (25.6%)	13 (28.9%)	168 (21.6%)
Median [95% CI]	24.6 [23.7, 26.3]	26.7 [23.9, 39.8]	22.9 [21.7, 25.5]	26.6 [19.1, NA]	24.6 [23.8, 26.3]
ORR	510 (72.1%)	301 (76.8%)	209 (66.3%)	30 (75.0%)	480 (72.0%)

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.1; Table 14.2.3a, Table 14.2.3b, 14.2.3c; Table 14.2.4].
CAP = Core analysis population; CI = Confidence interval; CR = Complete response; N/n = Number; NA = Not reached; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease.
[1]Progression-free survival and overall survival were estimated using the Kaplan-Meier method. [2]Due to the low number of events PFS data have to be interpreted with caution. [3]Due to the low number of events the present OS data are no reliable estimators.

9.1.3 Therapy details

9.1.3.1 Decisive factors for choice of treatment

Table 9-3 gives an overview of the most common institution that decides about the therapy and of the most common decisive factors in the CAP and age subgroups.

Table 9-3 Most common deciding institution and most common decisive factors

	CAP (N=824)	Patients <70 years (N=453)	Patients ≥70 years (N=371)
Therapy Decision – The most common institution, n (%)			
Tumor board	561 (68.1%)	305 (67.3%)	256 (69.0%)
Therapy Decision – Most common decisive factors (>25%), n (%)			
Guideline	695 (84.3%)	381 (84.1%)	314 (84.6%)
Efficacy of therapy	571 (69.3%)	320 (70.6%)	251 (67.7%)
Study results	404 (49.0%)	236 (52.1%)	168 (45.3%)
Tolerability of therapy	265 (32.2%)	130 (28.7%)	135 (36.4%)
General condition of patient	246 (29.9%)	133 (29.4%)	113 (30.5%)
Age of patient	214 (26.0%)	120 (26.5%)	94 (25.3%)

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.6].
CAP = Core analysis population; N/n = Number.
Multiple answers provided for decisive factors.

9.1.3.2 Bevacizumab (Avastin®) therapy

Details on bevacizumab (Avastin®) treatment in CAP and age subgroups are summarized in Table 9-4. Median bevacizumab (Avastin®) treatment duration is somewhat longer in patients aged <70 years in comparison to patients aged ≥70 years (14.6 vs. 12.5 months) while median dose intensity is the same (5.1 months). For detailed discussion of bevacizumab (Avastin®) treatment details and comparison to the recommendations of the SmPC please refer to chapter 9.3.3.2 Bevacizumab (Avastin®) therapy.

Table 9-4 Details on bevacizumab (Avastin®) therapy

	Age subgroup		
	CAP	Patients <70 years	Patients ≥70 years
Patients, N	824	453	371
Treatment duration[1]			
Events, n (%)	453 (55.0%)	227 (50.1%)	226 (60.9%)
Median [95% CI]	13.8 [12.7, 14.5]	14.6 [13.9, 15.2]	12.5 [11.1, 13.8]
Total number of administrations			
n applications	12,431	7,153	5,278
Median	18.0	19.0	17.0
Min-Max	1.0-25.0	1.0-25.0	1.0-24.0
Dose intensity (mg/kg per week)			
Median	5.1	5.1	5.1
Min-Max[2]	2.3-108.1	2.3-108.1	2.4-106.8
Any treatment modification	653 (79.2%)	361 (79.7%)	292 (78.7%)
Kind of treatment modification[3]			
Therapy interruption[4]	556 (67.5%)	303 (66.9%)	253 (68.2%)
Therapy delay[4]	227 (27.5%)	122 (26.9%)	105 (28.3%)
Dose reduction	57 (6.9%)	22 (4.9%)	35 (9.4%)
Dose increase	50 (6.1%)	32 (7.1%)	18 (4.9%)
Reason for treatment modification[3]			
Physician decision	590 (71.6%)	328 (72.4%)	262 (70.6%)
Patient's wish	148 (18.0%)	81 (17.9%)	67 (18.1%)
Toxicity	110 (13.3%)	55 (12.1%)	55 (14.8%)
Visit created by mistake	21 (2.5%)	8 (1.8%)	13 (3.5%)

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.7; Table 14.2.11a; Table 14.2.11b; Table 14.2.15a; Table 14.2.15b; Table 14.2.16a; Table 14.2.16b; Table 14.2.19a; Table 14.2.19b¸ Table 14.2.19c; Table 14.2.19d].
CAP = Core analysis population; CI = Confidence interval; Max = Maximum; Min = Minimum; N/n = Number; NA = Not reached.
[1]Treatment duration of bevacizumab (Avastin®) was estimated using the Kaplan-Meier method. [2]Maximum dose intensity of bevacizumab (Avastin®) seems to be a mistake in documentation. [3]Multiple observations provided. [4]There was no definition of therapy delay and therapy interruption or the difference of these two modifications provided in the observational plan or eCRF. It was at the discretion of the documenting person which of the two terms he/she chose for the treatment modification.

9.1.3.3 Concomitant chemotherapy

9.1.3.3.1 Carboplatin therapy

Table 9-5 gives an overview on carboplatin therapy in the CAP and age subgroups. Median carboplatin duration is the same in the CAP and age subgroups (3.5 months). For detailed discussion of carboplatin treatment details and comparison to the recommendations of the SmPC please refer to chapter 9.3.3.3 Concomitant chemotherapy.

Table 9-5 Details on carboplatin therapy

		Age subgroup	
	CAP	Patients <70 years	Patients ≥70 years
Patients, N	824	453	371
Treatment duration[1]			
Median	3.5	3.5	3.5
Min-Max	0.0-17.7	0.0-15.5	0.0-17.7
Any treatment modification	354 (43.0%)	186 (41.1%)	168 (45.3%)
Kind of treatment modification[2]			
Therapy interruption[3]	198 (24.0%)	109 (24.1%)	89 (24.0%)
Therapy delay[3]	124 (15.0%)	66 (14.6%)	58 (15.6%)
Dose reduction	98 (11.9%)	45 (9.9%)	53 (14.3%)
Dose increase	31 (3.8%)	22 (4.9%)	9 (2.4%)
Reason for treatment modification[2]			
Physician decision	253 (30.7%)	141 (31.1%)	112 (30.2%)
Toxicity	100 (12.1%)	50 (11.0%)	50 (13.5%)
Patient's wish	46 (5.6%)	22 (4.9%)	24 (6.5%)
Visit created by mistake	9 (1.1%)	2 (0.4%)	7 (1.9%)

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.8a; Table 14.2.8b; Table 14.2.16a; Table 14.2.16b; Table 14.2.20a; Table 14.2.20b; Table 14.2.20c; Table 14.2.20d].
CAP = Core analysis population; Max = Maximum; Min = Minimum; N/n = Number.
[1]Treatment duration displayed in months. Patients who received only one dose of carboplatin the treatment duration is 0.03 displayed as 0. [2]Multiple observations provided. [3]There was no definition of therapy delay and therapy interruption or the difference of these two modifications provided in the observational plan or eCRF. It was at the discretion of the documenting person which of the two terms he/she chose for the treatment modification.

9.1.3.3.2 Paclitaxel therapy

The most important details on paclitaxel therapy in the CAP and age subgroups are given in Table 9-6. Median paclitaxel duration is the same in the CAP and age subgroups (3.5 months). Further paclitaxel treatment details are discussed and compared to the recommendations of the SmPC in chapter 9.3.3.3 Concomitant chemotherapy.

Table 9-6 Details on paclitaxel therapy

	Age subgroup		
	CAP	Patients <70 years	Patients ≥70 years
Patients, N	824	453	371
Treatment duration[1]			
Median	3.5	3.5	3.5
Min-Max	0.0-14.1	0.0-12.7	0.0-14.1
Any treatment modification	387 (47.0%)	192 (42.4%)	195 (52.6%)
Kind of treatment modification[2]			
Therapy interruption[3]	246 (29.9%)	122 (26.9%)	124 (33.4%)
Therapy delay[3]	112 (13.6%)	62 (13.7%)	50 (13.5%)
Dose reduction	110 (13.3%)	43 (9.5%)	67 (18.1%)
Dose increase	12 (1.5%)	7 (1.5%)	5 (1.3%)
Reason for treatment modification[2]			
Physician decision	258 (31.3%)	138 (30.5%)	120 (32.3%)
Toxicity	141 (17.1%)	59 (13.0%)	82 (22.1%)
Patient's wish	44 (5.3%)	21 (4.6%)	23 (6.2%)
Visit created by mistake	8 (1.0%)	2 (0.4%)	6 (1.6%)

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.9a; Table 14.2.9b; Table 14.2.16a; Table 14.2.16b; Table 14.2.21a; Table 14.2.21b; Table 14.2.21c; Table 14.2.21d].
CAP = Core analysis population; Max = Maximum; Min = Minimum; N/n = Number.
[1]Treatment duration displayed in months. Patients who received only one dose of paclitaxel the treatment duration is 0.03 displayed as 0. [2]Multiple observations provided. [3]There was no definition of therapy delay and therapy interruption or the difference of these two modifications provided in the observational plan or eCRF. It was at the discretion of the documenting person which of the two terms he/she chose for the treatment modification.

9.1.3.4 Reasons for end of treatment documentation

Reasons for end of treatment documentation in CAP and age subgroups sorted by decreasing counts are given in Table 9-7.

Table 9-7 Reasons for end of treatment documentation

	Total	Patients <70 years	Patients ≥70 years
Total number of patients	824	453	371
Reasons for end of treatment documentation (n, %)			
End of documentation after 15 months	349 (42.4)	213 (47.0)	136 (36.7)
Tumor progression	196 (23.8)	105 (23.2)	91 (24.5)
Patient's wish (no toxicity)	53 (6.4)	24 (5.3)	29 (7.8)
Adverse event[1]	44 (5.3)	30 (6.6)	14 (3.8)
AE related to therapy[1]	40 (4.9)	11 (2.4)	29 (7.8)
AE not related to therapy[1]	25 (3.0)	8 (1.8)	17 (4.6)
Death	16 (1.9)	5 (1.1)	11 (3.0)
Lost-to-Follow-up	15 (1.8)	10 (2.2)	5 (1.3)
Tumor remission	13 (1.6)	7 (1.5)	6 (1.6)
Patient's wish	7 (0.8)	3 (0.7)	4 (1.1)
Other reason (specification)	48 (5.8)	31 (6.8)	17 (4.6)
No EOT documentation	18 (2.2)	6 (1.3)	12 (3.2)

[Source: OTILIA_Tables_Final_4_20200420: Table 14.1.1].
AE = Adverse event; EOT = end of treatment; N/n = Number.
[1]In an eCRF update the reason for end of treatment documentation "Adverse event" was replaced by "AE not related to therapy" and "AE related to therapy" on 01 October 2013.

9.1.4 Safety

9.1.4.1 Discrepancies between Safety Database Roche (SDB) and Clinical Database CRO (CDB)

- Total number of discrepancies between the SDB and the CDB: n=985
    - Different causality: n=47 (4.8%)
        - Not related in CDB, related in SDB: fistula; n=1 (0.1%)
    - Different seriousness: n=59 (6.0%)
        - Seriousness unknown in CDB: case of death; n=1 (0.1%)
        - Non-serious in CDB: n=57 (5.8%)
    - Wrong term in SDB: n=1 (0.1%)
    - Missing in SDB: n=150 (15.2%)
        - Primary endpoint: n=5 (0.5%)
    - Missing in CDB: n=698 (70.9%)
        - Primary endpoint: n=16 (1.6%)
        - Supportive therapy: n=9 (0.9%)
        - Upgraded in SDB: n=2 (0.2%)
        - SOC: Blood and lymphatic system disorders: n=86 (8.7%)
        - SOC: Gastrointestinal disorders: n=271 (27.5%, including vomiting (n=217; 22.0%))
        - SOC: General disorders: n=57 (5.8%, including pain (n=15; 1.5%), death (n=13; 1.3%))
        - Immune system disorders: n=28 (2.8%; all events hypersensitivity)
        - SOC: Neoplasms benign: n=11 (1.1%)
        - SOC: Vascular disorders: n=16 (1.6%, including hypertension (n=8; 0.8%))

9.1.4.2 Overview of Treatment-Emergent Adverse Events

Table 9-8 gives an overview of the TEAEs in the CAP and age subgroups.

Table 9-8 Overview of Treatment-Emergent Adverse Events

	CAP (N=824)			
	Patients[1] N (%)	Cases N		
Patients reported with respective TEAE, n (%), n (cases)				
Any TEAE	616 (74.8%)	3,645		
Any serious TEAE	222 (26.9%)	438		
Any TEAE with CTCAE severity grade ≥ grade 3	317 (38.5%)	583		
Any causally related TEAE[2]	330 (40.0%)	1,036		
Any causally related serious TEAE[2]	72 (8.7%)	96		
Any TEAE leading to discontinuation of bevacizumab (Avastin®) treatment[3]	145 (17.6%)	206		
All fatal TEAE[4]	30 (3.6%)	43		
Fatal causally related TEAE[2]	5 (0.6%)	6		
Fatal non-related TEAE[2]	24 (2.9%)	29		
Fatal TEAE – causality unknown[2]	5 (0.6%)	8		
	Patients <70 years (N=453)		Patients ≥70 years (N=371)	
	Patients[1] N (%)	Cases N	Patients[1] N (%)	Cases N
Patients reported with respective TEAE, n (%), n (cases)				
Any TEAE	328 (72.4%)	1,952	288 (77.6%)	1,693
Any serious TEAE	100 (22.1%)	187	122 (32.9%)	251
Any TEAE with CTCAE severity grade ≥ grade 3	150 (33.1%)	267	167 (45.0%)	316
Any causally related TEAE[2]	192 (42.4%)	671	138 (37.2%)	365
Any causally related serious TEAE[2]	37 (8.2%)	53	35 (9.4%)	43
Any TEAE leading to discontinuation of bevacizumab (Avastin®) treatment[3]	66 (14.6%)	102	79 (21.3%)	104
All fatal TEAE[4]	12 (2.6%)	20	18 (4.9%)	23

[Source: OTILIA_Tables_Final_4_20200420: Table 14.3.1a; OTILIA_Listings_Final_2_20191206; Listing 16.2.7.1: Adverse events].

CTCAE = Common Terminology Criteria for Adverse Events; N/n = Number; TEAE = Treatment-emergent adverse event. [1]Patients can occur in more than one category of the table. [2]Causally related TEAEs were defined as those with a possible, probable or definite relationship to bevacizumab (Avastin®). [3]TEAE leading to discontinuation of bevacizumab (Avastin®) treatment = TEAE documented as underlying adverse event for end of treatment (EOT). The number of TEAEs leading to discontinuation of bevacizumab (Avastin®) treatment might differ from the number of AEs documented as reason for end of treatment due to AEs not classified as treatment-emergent, however documented as underlying AE for EOT. [4]For one patient (pat ID 215001), the same fatal TEAE (ileus) was reported twice, once as related to bevacizumab (Avastin®) with CTCAE severity grade 4 and once as non-related with CTCAE severity grade 5.

9.1.4.3 Most common TEAEs, serious TEAEs, causally related TEAEs and fatal TEAEs

The most common TEAEs as well as serious, causally related and fatal TEAEs are shown in Table 9-9. Hypertension was the most frequent TEAE (17.1%) and the most frequent causally related TEAE (12.4%). However, only in 1.3% of patients hypertension was serious and there was no fatal hypertension. Hypertension is a TEAE of particular interest.

Table 9-9 Most common TEAEs, serious TEAEs, causally related TEAEs and fatal TEAEs

	CAP (N=824)	Patients <70 years (N=453)	Patients ≥70 years (N=371)
	N (%)	N (%)	N (%)
TEAEs (≥10% in CAP or age subgroup)			
Hypertension	141 (17.1%)	71 (15.7%)	70 (18.9%)
Fatigue	132 (16.0%)	76 (16.8%)	56 (15.1%)
Polyneuropathy	120 (14.6%)	48 (10.6%)	72 (19.4%)
Nausea	112 (13.6%)	66 (14.6%)	46 (12.4%)
Anemia	100 (12.1%)	40 (8.8%)	60 (16.2%)
Constipation	92 (11.2%)	55 (12.1%)	37 (10.0%)
Alopecia	82 (10.0%)	57 (12.6%)	25 (6.7%)
Diarrhea	82 (10.0%)	49 (10.8%)	33 (8.9%)
Urinary tract infection	58 (7.0%)	17 (3.8%)	41 (11.1%)
Serious TEAEs (≥1% in CAP or age subgroup)			
Pyrexia	15 (1.8%)	6 (1.3%)	9 (2.4%)
General physical health deterioration	14 (1.7%)	3 (0.7%)	11 (3.0%)
Abdominal pain	13 (1.6%)	6 (1.3%)	7 (1.9%)
Ileus	13 (1.6%)	9 (2.0%)	4 (1.1%)
Hypertension	11 (1.3%)	3 (0.7%)	8 (2.2%)
Urinary tract infection	10 (1.2%)	4 (0.9%)	6 (1.6%)
Dyspnea	8 (1.0%)	2 (0.4%)	6 (1.6%)
Leukopenia	8 (1.0%)	6 (1.3%)	2 (0.5%)
Urosepsis	5 (0.6%)	5 (1.1%)	0 (0.0%)
Dehydration	6 (0.7%)	1 (0.2%)	5 (1.3%)
Fatigue	5 (0.6%)	0 (0.0%)	5 (1.3%)
Ascites	6 (0.7%)	2 (0.4%)	4 (1.1%)
Death	6 (0.7%)	2 (0.4%)	4 (1.1%)
Device related infection	4 (0.5%)	0 (0.0%)	4 (1.1%)
Hypertensive crisis	7 (0.8%)	3 (0.7%)	4 (1.1%)
Malignant neoplasm progression	7 (0.8%)	3 (0.7%)	4 (1.1%)
Pancytopenia	5 (0.6%)	1 (0.2%)	4 (1.1%)
Subileus	6 (0.7%)	2 (0.4%)	4 (1.1%)
Vomiting	7 (0.8%)	3 (0.7%)	4 (1.1%)
Causally related TEAEs (≥5% in CAP or age subgroup)			
Hypertension	102 (12.4%)	53 (11.7%)	49 (13.2%)
Fatigue	58 (7.0%)	40 (8.8%)	18 (4.9%)
Fatal TEAEs (≥0.5% in CAP or age subgroup)			
Death	6 (0.7%)	2 (0.4%)	4 (1.1%)
Malignant neoplasm progression	4 (0.5%)	2 (0.4%)	2 (0.5%)
General physical health deterioration	3 (0.4%)	0 (0.0%)	3 (0.8%)
Intestinal perforation	3 (0.4%)	1 (0.2%)	2 (0.5%)

[Source: OTILIA_Tables_Final_4_20200420: Table 14.3.2; Table 14.3.3; Table 14.3.5; Table 14.3.6b].

CAP = Core analysis population; MedDRA = Medical Dictionary for Regulatory Activities; N/n = Number; PT = Preferred term.
On-treatment phase: from first application of study medication until 90 days after end of treatment.MedDRA PTs are sorted by decreasing counts. Adverse event terms have been coded using MedDRA version 22.0.

9.1.4.3.1 Most frequent fatal causally related TEAEs

- Five (0.6%) patients were documented with a fatal TEAE related to bevacizumab (Avastin®) (6 cases in total) with reported PTs as follows (6 events in total).
    - Cerebrovascular accident
    - Intestinal perforation
    - Urosepsis
    - Acute kidney injury
    - Ileus
    - Death
- Of these 6 fatal causally related TEAEs, one patient was reported with 2 fatal events (Urosepsis and Acute kidney injury).

9.1.4.4 TEAEs of particular interest

Table 9-10 gives an overview of the TEAEs of particular interest hypertension, proteinuria, large intestine perforation, intestinal perforation, gastric perforation and arterial embolism. The most common TEAE of particular interest was Hypertension in the CAP (17.1%) and age subgroups (15.7% and 18.9%). Intestinal perforation was the only TEAE of particular interest leading to death (CAP: 0.4%)

Table 9-10 TEAEs of particular interest

	CAP (N=824) Patients N (%)	Patients <70 years (N=453) Patients N (%)	Patients ≥70 years (N=371) Patients N (%)
TEAEs of particular interest			
Hypertension	141 (17.1%)	71 (15.7%)	70 (18.9%)
Proteinuria	35 (4.2%)	19 (4.2%)	16 (4.3%)
Large intestine perforation	6 (0.7%)	4 (0.9%)	2 (0.5%)
Intestinal perforation	3 (0.4%)	1 (0.2%)	2 (0.5%)
Gastric perforation	2 (0.2%)	1 (0.2%)	1 (0.3%)
Embolism arterial	1 (0.1%)	0 (0.0%)	1 (0.3%)
Serious TEAEs of particular interest			
Hypertension	11 (1.3%)	3 (0.7%)	8 (2.2%)
Large intestine perforation	6 (0.7%)	4 (0.9%)	2 (0.5%)
Intestinal perforation	3 (0.4%)	1 (0.2%)	2 (0.5%)
Gastric perforation	2 (0.2%)	1 (0.2%)	1 (0.3%)
Proteinuria	2 (0.2%)	1 (0.2%)	1 (0.3%)
Embolism arterial	0 (0.0%)	0 (0.0%)	0 (0.0%)
Causally related TEAEs of particular interest			
Hypertension	102 (12.4%)	53 (11.7%)	49 (13.2%)
Proteinuria	28 (3.4%)	15 (3.3%)	13 (3.5%)
Large intestine perforation	4 (0.5%)	3 (0.7%)	1 (0.3%)
Intestinal perforation	1 (0.1%)	1 (0.2%)	0 (0.0%)
Gastric perforation	1 (0.1%)	0 (0.0%)	1 (0.3%)
Embolism arterial	1 (0.1%)	0 (0.0%)	1 (0.3%)
Fatal TEAEs of particular interest			
Hypertension	0 (0.0%)	0 (0.0%)	0 (0.0%)
Large intestine perforation	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intestinal perforation	3 (0.4%)	1 (0.2%)	2 (0.5%)
Gastric perforation	0 (0.0%)	0 (0.0%)	0 (0.0%)
Proteinuria	0 (0.0%)	0 (0.0%)	0 (0.0%)

[Source: OTILIA_Tables_Final_4_20200420: Table 14.3.2; Table 14.3.3; Table 14.3.5; Table 14.3.6b].
CAP = Core analysis population; MedDRA = Medical Dictionary for Regulatory Activities; N/n = Number; PT = Preferred term.
On-treatment phase: from first application of study medication until 90 days after end of treatment.
MedDRA PTs are sorted by decreasing counts.
Adverse event terms have been coded using MedDRA version 22.0.

9.2 LIMITATIONS

- As data were collected in routine clinical practice with the current version of the SmPC of bevacizumab (Avastin®) (29), bias in reporting may have occurred (e.g., underreporting of AEs).

- The NIS setting of this study *per se* limits comparability to clinical trial data.

- In the second study phase (beginning July 2014) only patients ≥70 years were included. This further limits comparability to clinical trial data.

- No on-site monitoring and source data verification were performed.

- Tumor assessment was not standardized according to RECIST (tumor assessment as per RECIST was optional only), which may be a potential bias to PFS and ORR.

- Patients were excluded from the CAP due to violation of the inclusion or exclusion criteria as per the DRM protocol, reducing the sample size of the final analysis by 24.4% (n=266).

- There was a high number of open queries at the time of DBL (n=678), resulting in incomplete or missing data entries in the eCRF as well as discrepancy between the SDB and CDB.

- Due to a short documentation period per patient of maximum 27 months, there are low numbers of events for PFS (44.7%), which limits the interpretability of this time-to-event data.

- Due to a short documentation period per patient of maximum 27 months, the number patients in the CAP who experienced an event (22.0%) for OS analysis was very low. Consequently, a very high number of patients (78.0%) was alive at their individual end of study and they were censored before any event was observed. Moreover, while events become more frequent after 18 months of survival, censoring often occurred within the first 18 months. Due to the low number of events and the high number of censored patients the OS is no reliable estimator. Interpretation of the OS data and comparison of OS data to results of

other trials is not possible. Likewise, in the age and surgery subgroups the number patients who experienced an event was very low and the number of censored patients was very high. Hence, in the age and surgery subgroups OS is also no reliable estimator. Interpretation of the OS data in these subgroups and comparison of OS data between the subgroups is not possible.

- The number of patients in the subgroup of patients without prior surgery (N=45) was rather small in comparison to the subgroup of patients with prior surgery (N=779), which limits the comparability of these subgroups.

- At baseline 64.6% of questionnaires (n=405) returned and this declined to 41.1% (n=258) in week 66 after inclusion in the CAP. The moderate return rate and the possibility that at later times mainly patients who are doing well return questionnaires limits the interpretability of the QoL data.

- Due to non-accurate ICF all patients who consented on the erroneous form were asked to sign an addendum to their ICF retrospectively allowing questionnaire collection. Only questionnaires of patients with a valid ICF were allowed to be used for analysis. This approach may have introduced survivorship bias into the data

- After amendment 2 of the observational plan dated 25 July 2014 retrospective patient inclusion for up to one cycle was feasible but retrospectively included patients were not excluded from the QLQ project. Retrospectively included patients may have filled in their baseline questionnaire after first study treatment and this may have introduced a bias into the baseline QoL data.

9.3 INTERPRETATION

Comparison of the data obtained in this NIS with data in the pivotal trials is limited as the NIS setting of this study *per se* limits the comparability to clinical trial data.

9.3.1 Demographics and baseline characteristics

The OTILIA NIS was divided into two phases. In the first study phase, eligible patients had to be aged ≥18 years. The second study phase focused on an age-specific subgroup analysis and thus only patients aged ≥70 years were included in this phase. Due to this approach 45.3% of patients in the CAP were aged ≥70 years resulting in a median age of 68.0 years. In contrast, patients of the GOG-0218 and ICON7 phase III trials in the

experimental arms receiving bevacizumab-throughout therapy were noticeably younger with median ages of 60 and 57 years (22,24,27). Furthermore, in the present NIS less patients in the CAP had an ECOG performance status of 0 and more patients had an ECOG performance status of 1 or 2 in comparison to GOG-0218 and ICON7 trials (ECOG 0: 38.2% vs. 49.0% and 45%; ECOG 1: 50.0% vs. 42.9% and 49.0%, ECOG 2: 9.9% vs. 8.2% and 6.0%) (22,24,27). Regarding age and ECOG performance status the subgroup of patients <70 years with a median age of 58.4 years and ECOG performance status of 0, 1 and 2 in 45.7%, 44.6% and 8.3% is rather comparable with the patients of the GOG-0218 and ICON7 trials. In contrast, the patients in the subgroup of patients ≥70 years with a median age of 74.6 years and ECOG performance status of 0, 1 and 2 in 28.6%, 56.9% and 12.0% clearly represent an older patient population with worse performance status.

Furthermore, patients aged ≥70 years had more medical conditions ongoing at first bevacizumab (Avastin®) administration (60.1% vs. 31.3%) and more persistent arterial hypertension (55.8% vs. 29.1%) in comparison to patients aged <70 years. Accordingly, in the subgroup of patients ≥70 years less patients had a Charlson Comorbidity Index of 0 (75.5% vs. 80.4%). Since the subgroup of patients ≥70 years accounts for 45.3% of the CAP, it is supposed that the patients in the CAP are more comorbid than the patients of the GOG-0218 and ICON7 trials. However data on comorbidities are not published for these two phase III trials (22,24,27).

In both age subgroups of patients <70 and ≥70 years the most frequent type of tumor was epithelial ovarian carcinoma (81.0% and 79.5%) and serous tumors were the most frequent histological type (75.7% and 80.5%). In both age subgroups tumors were mostly diagnosed at FIGO stage IIIC (58.5% and 55.8%) and with poor differentiation (G3: 68.9% and 68.2%) (tumor stage was determined by the treating physician according to the respective currently valid version of the FIGO staging system dated 1988 (1,2) or 2014 (3)). Similarly, in the GOG-0218 and ICON7 trials epithelial ovarian carcinoma (ICON7 only: 88.0%) and serous tumor (GOG-0218 and ICON7: 84.1% and 69%) were the most frequent tumor and histological types (22,24,27). Furthermore, most tumors were diagnosed at FIGO stage IIIC (ICON7 only: 57.0%) and with poor differentiation (GOG-0218 and ICON7: G3: 73.8% and 71.0%) (22,24,27). Hence, there are no obvious differences in tumor characteristics between the patients in the present NIS and in the GOG-0218 and ICON7 trials.

Thus, the overall patient population in the present NIS was older and had a worse performance status than patients of the GOG-0218 and ICON7 trials. Most likely, this also comes along with more comorbidities.

9.3.2 Effectiveness

The median PFS in the CAP observed in this NIS was 19.4 months and 44.7% of patients experienced an event (PD or death) during first-line bevacizumab (Avastin®) therapy. In the subgroup of patients <70 and ≥70 years 44.2% and 45.3% of patients experienced and event and the median PFS was 20.0 and 19.3 months, respectively. The median PFS in the subgroup of patients without and with prior surgery was 19.4 and 19.6 months, respectively. In the surgery subgroups 60.0% and 43.8% of patients experienced and event. One reason why the number of events was only about 45% in the CAP and in the subgroups might be that the patients were only observed for a maximum of 27 months per patient. Hence, due to the low number of events PFS data have to be interpreted with caution. Nonetheless, the present data suggest that bevacizumab (Avastin®) is almost equally effective in older and more comorbid patients aged ≥70 years with worse performance status as in younger patients aged <70 years. There was also no difference in the PFS in patients with and without prior surgery but the small number of patients in the subgroup of patients without prior surgery (N=45) further limits interpretability. Furthermore, the median PFS in the CAP as well as age and surgery subgroups was longer than the median PFS of 14.1 months in the experimental arm with bevacizumab-throughout therapy of the GOG-0218 trial but similar to the median PFS of 19.9 months in the experimental arm of the ICON7 trial (22,27). However, the comparability of the data obtained in this NIS with results reported in controlled, randomized clinical trials is subject to limitations due to differences in patient characteristics as described above and study settings including clear cut inclusion and exclusion criteria, assessment schemes and assessment specifications (22,24,27).

A multivariable Cox regression analysis showed that patients without visible residual disease at baseline had a better outcome (PFS) as compared to patients with residual disease ≥1 cm at baseline (HR = 0.59; 95% CI: 0.45 - 0.78; p<.001). Interestingly, in this analyses age and ECOG performance status were no factors with impact on PFS. This result is in line with the equal PFS in both age subgroups.

The third interim analysis of the OTILIA NIS explored the impact of pre-existing comorbidities on clinical outcome in patients receiving first-line bevacizumab (Avastin®) in combination with chemotherapy (40). Therefore, effectiveness in subgroups of patients with diabetes mellitus, ongoing hypertension or cardiovascular comorbidities (coronary heart disease, heart failure, arrhythmia, ongoing HTN, thromboembolic event) was analyzed. However, there were no relevant differences in PFS between the various comorbidity subgroups and the overall population (all patients: 21.3 months; diabetes mellitus: 20.2 months; ongoing hypertension: 21.3 months; cardiovascular comorbidities: 21.3 months) (40). A multivariable Cox regression analysis showed that diabetes mellitus and hypertension were no factors with impact on PFS (40). The results of the third interim analysis showing similar PFS in patients with comorbidities to the overall population are in line with the present results showing that the PFS in patients aged ≥70 years with more comorbidities was comparable to patients aged <70 years.

The ORR in the CAP of the present NIS was 72.1%. Although the PFS in both age subgroups was almost the same, the ORR was higher in patients aged <70 years in comparison to patients ≥70 years (76.8% vs. 66.3%). In the subgroup of patients without and with surgery the ORR was very similar (72.0% vs. 75.0%). However, the small number of patients in the subgroup of patients without prior surgery (N=45) limits the comparability of these subgroups. In the ICON7 trial the ORR was 67% (24). Thus, in the CAP and all subgroups except the subgroup of patients aged ≥70 years the ORR is higher than in the ICON7 trial. In the subgroup of patients aged ≥70 years the ORR is still very similar to the ORR of the ICON7 trial (66.3% vs. 67%) (24).

In the GOG-0218 and ICON7 trials the median OS was 39.7 and 58.0 months, respectively (22,27). However, in the NIS OTILIA patients were observed during treatment with bevacizumab (Avastin®) for up to 15 months or until premature discontinuation and followed-up for 12 months resulting in a total observation period per patient of only maximum 27 months. Therewith, the observation period used in the NIS OTILIA was too short for OS analyses. Consequently, in the CAP only 22.0% of patients experienced an event (death) during first-line bevacizumab (Avastin®) therapy. Hence, the median OS of 24.6 months in the CAP is no reliable estimator. Likewise, in the subgroups of patients <70 and ≥70 years as well as of patients without and with surgery the number of events was very low (age subgroups: 19.0% and 25.6%; surgery subgroups: 28.9% and 21.6%)

and therefore the median OS of the subgroups are also no reliable estimators (age subgroups: 26.7 and 22.9 months; surgery subgroups: 26.6 and 24.6 months).

In conclusion, PFS and ORR of the present study show that bevacizumab (Avastin®) is not only effective in routine clinical practice but also in older patients aged ≥70 years.

9.3.3 Therapy details

9.3.3.1 Decisive factors for choice of treatment

Overall, a tumor board decides about the actual therapy regimen in about two thirds of patients. Guideline (84.3%), efficacy of therapy (69.3%), study results (49.0%); tolerability of therapy (32.2%), general condition of patient (29.9%) and age of patient (26.0%) are the most common decisive factors (>25%) for this. Likewise, in both age subgroups the guideline is the most frequent decisive factor (84.1% vs. 84.6%). However, in the subgroup of patients <70 years efficacy of therapy and study results are somewhat more frequent reasons for decision than in the subgroup of patients ≥70 years (70.6% vs. 67.7% and 52.1% vs. 45.3%). In contrast, tolerability of therapy is a more frequent decisive factor in the subgroup of patients ≥70 years compared to patients <70 years (36.4% vs. 28.7%). Interestingly, general condition and age of patient and age are equally frequent decisive factors in both subgroups of patients <70 and ≥70 years (29.4% vs. 30.5% and 26.5% vs. 25.3%).

In summary, for the treating physician it was important to follow the guidelines to provide the most efficient therapy for their patients. Especially for older patients, tolerability of therapy gained more importance.

9.3.3.2 Bevacizumab (Avastin®) therapy

In the CAP the median bevacizumab (Avastin®) treatment duration was 13.8 months and the patients received a median number of 18 administrations. The median treatment duration and number of administrations are in line with the recommended treatment duration of maximum 15 months and the recommended three-weekly schedule of the current SmPC (29). Furthermore, the median number of administrations herein is comparable to clinical trial results. In the pivotal ICON7 trial patients who started chemotherapy at/before and more than 4 weeks after surgery received a median of 16 and 17 cycles, respectively (24). In the subgroup of patients <70 years the median treatment duration was about 2 months longer than in the subgroup of patients ≥70 years (14.6 vs. 12.5 months) and in the median younger patients received 2 administrations

more than older patients (19.0 vs. 17.0 administrations). Thus, the median treatment duration and the number of administrations were even closer to the recommended maximum treatment duration of 15 months with a three-weekly schedule in patients aged <70 years. In the CAP and the age subgroups the median dose intensity was 5.1 mg/kg per week. This is also in line with the recommended dose of 15 mg/kg every three weeks of the current SmPC (29).

Optimal therapy management is paramount to achieve best possible outcomes for patients. This may include temporary therapy interruptions, therapy delay and dose modifications to address e.g. AEs or ADRs. In the CAP 79.2% of patients had any modification of bevacizumab (Avastin®). Comparing patients aged <70 and ≥70 years the frequency of bevacizumab (Avastin®) modifications was almost the same (79.7% and 78.7%). The two most frequent kinds of treatment modification of bevacizumab (Avastin®) in the CAP and the age subgroups were therapy interruption (CAP: 67.5%; <70 years: 66.9%; ≥70 years: 68.2%) and therapy delay (CAP: 27.5%; <70 years: 26.9%; ≥70 years: 28.3%). However, there was no definition of therapy delay and therapy interruption or the difference of these two modifications provided in the observational plan or eCRF. Hence, it was at the discretion of the documenting person which of the two terms he/she chose for the treatment modification. In the CAP and age subgroups the most frequent reason for treatment modification of bevacizumab (Avastin®) was physician decision (CAP: 71.6%; <70 years: 72.4%; ≥70 years: 70.6%). Interestingly, in the CAP toxicity was the reason for treatment modification in only 13.3% of patients but this was somewhat more frequent in patients aged ≥70 years compared to patients aged <70 years (14.8% vs. 12.1%). Hence, the results of the present study suggest that the therapy was frequently interrupted but only in few cases toxicity was the underlying reason. Instead, physician decision was the reason in most cases. Since there is no further information about the reason behind the physician decision for treatment modification, these data have to be interpreted with caution. It is also possible that AEs or ADRs are the reasons behind the physician decision for treatment modification.

In summary, dose and treatment duration of bevacizumab (Avastin®) recommended by the current SmPC were implemented in routine clinical practice. To achieve best possible outcomes treatment modifications were necessary in most patients.

9.3.3.3 Concomitant chemotherapy

According to the current SmPC of bevacizumab (Avastin®) (29) it is administered in addition to carboplatin and paclitaxel for up to 6 cycles. Six cycles in a three-weekly schedule result in a treatment duration of 4.1 months in best case. In the CAP and age subgroups the median treatment duration of carboplatin and paclitaxel was 3.5 months and hence somewhat shorter than the intended 4.1 months of treatment.

For the concomitant chemotherapy optimal therapy management including treatment modifications is essential to achieve best possible outcomes for patients, too. In the CAP 43.0% and 47.0% of patients had any treatment modification of carboplatin and paclitaxel treatment, respectively. Hence, there are less treatment modifications of carboplatin and paclitaxel than of bevacizumab (Avastin®), but treatment duration of chemotherapy is much shorter than treatment duration of bevacizumab (Avastin®). In contrast to bevacizumab (Avastin®), treatment modifications of chemotherapy more often occurred in patients aged ≥70 years in comparison to patients aged <70 years especially for paclitaxel (carboplatin: 45.3% vs. 41.1%; paclitaxel: 52.6% vs. 42.4%). In the CAP therapy interruption (24.0% and 29.9%), therapy delay (15.0% and 13.6%) and dose reduction (11.9% and 13.3%) were the most frequent kinds of treatment modifications of carboplatin and paclitaxel. However, one hast to keep in mind that there was no definition of therapy delay and therapy interruption or the difference of these two modifications given in the observational plan or eCRF. Hence, it was at the discretion of the documenting person which of the two terms he/she chose for the treatment modification. The reasons for these modifications of carboplatin and paclitaxel treatment were mainly physician decision (30.7% and 31.3%) and toxicity (12.1% and 17.1%). Interestingly, especially for paclitaxel dose reduction (18.1% vs. 9.5%) and toxicity (22.1% vs.13.0%) were more frequently kind and reason for treatment modification in patients aged ≥70 years in comparison to patients aged <70 years.

Thus, treatment duration of carboplatin and paclitaxel were somewhat shorter than recommended by the current SmPC of bevacizumab (Avastin®). In patients aged ≥70 years paclitaxel treatment had to be modified more often in comparison to younger patients. Dose reduction and toxicity were more frequently kind and reason for modification of paclitaxel treatment in patients aged ≥70 than <70 years.

9.3.3.4 Reasons for end of treatment documentation

In the CAP and the age subgroups the two most common reasons for end of treatment documentation were end of documentation after 15 months in about 40% of the patients and tumor progression in about one quarter of the patients. Interestingly, AE related to therapy was more often the reason for end of treatment documentation in patients aged ≥70 than <70 years (7.8% vs. 2.4%). Overall, death was the reason for end of treatment documentation in only 1.9% of patients. These reasons for end of treatment documentation suggest that about 40% of the patients received the bevacizumab (Avastin®) treatment for the recommended duration of 15 months. This is in accordance with the median bevacizumab (Avastin®) treatment duration of 13.8 months. The frequency of tumor progression as reason for EOT is comparable to the results of the GOG-0218 trial in which disease progression was the reason for premature treatment discontinuation in 26% of patients in the bevacizumab throughout group (22). Furthermore, the frequency of progression and death as reason for end of treatment documentation are in line with the low number of events in the present PFS and OS analysis.

9.3.4 Safety

9.3.4.1 Discrepancies Between Safety Database Roche (SDB) and Clinical Database CRO (CDB)

Overall, 985 discrepancies between the SDB and the CDB were identified following final reconciliation, of these, 47 (4.8%) discrepancies were identified with regards to different causality. Notably, one of these discrepant events (fistula; SAERT line number 754/755) was recorded as not related in the CDB and as related in the SDB. However, this is not critical as fistula is a known side-effect of Avastin® therapy as per current version of the SmPC of Avastin® (29), bearing in mind that the data in the CSR are presented in a conservative manner, i.e., the TFLs are based on the data recorded in the CDB only.

Of note, there were 59 (6.0%) discrepant cases regarding different seriousness. One of these was a case of death (SAERT line number 403/404; cause of death unknown) recorded with “seriousness, unknown” in the CDB, though this event was to be flagged as serious as any fatal event is to be considered as serious and recorded as such. Furthermore, 57 events were flagged as “non-serious” in the CDB, which were upgraded to “serious” through the Roche Safety review process.

The discrepant case concerning wrong term in SDB corresponded to an event of Avastin®-related visual impairment, which had been recorded as viral infection in the SDB (SAERT line number 651/652). Eye disorders are a known side-effect of Avastin® therapy as per current version of the SmPC of Avastin® (29).

In total, 150 (15.2%) events were missing in the SDB including 5 events concerning the primary endpoint (PFS, though, not to be reported as an AE); however, this is not critical as the data in the CSR are presented in a conservative manner.

As aforementioned, the data in the CSR are presented in a conservative manner, which is important to put in context with certain cases, which were missing in the CDB. In the CDB, 16 cases were missing concerning the primary endpoint (PFS). This is not a safety issue as it concerns the primary endpoint, which was not to be recorded as an AE. There were 9 cases regarding supportive therapy missing in the CDB, however, this is not to be considered as a safety issue as these events represent no new findings as per current version of the SmPC of Avastin® (29). Notably, the 2 cases “upgraded in SDB” which were missing in the CDB correspond to SAERT line number 752 (umbilical hernia; Company causality: not related) and SAERT line number 753 (intestinal prolapse; Company causality: not reported). These two cases are however not included in the CSR as they were missing in the CDB.

Furthermore, the 86 cases within the SOC “blood and lymphatic system disorders” which were missing in the CDB are all a known side effects of chemotherapy (e.g., anemia (SAERT line number 336), leukopenia (SAERT line number 407), neutropenia (SAERT line number 630)). The 271 cases within the SOC “gastrointestinal disorders” which were missing in the CDB include 217 events of vomiting, which is a very common side-effect of Avastin® therapy (29) but also of chemotherapy. Other very common side-effects of Avastin® therapy are hypertension and hypersensitivity (29), respectively, which correspond to 8 of the 16 cases within the SOC “vascular disorders” and all the 28 cases within the SOC “immune system disorders”, all of which were missing in the CDB. Therefore, the fact that the above-mentioned cases are all known side-effects of Avastin® therapy but not included in the CSR is not to be considered as critical.

In the CDB, there were 11 cases missing within the SOC neoplasms benign. However, no systematic occurrence was discernible in these 11 cases.

Of note, there were 15 cases of pain and 13 cases of death missing in the CDB. Of great importance to mention in this context is the fact that all 13 death cases are included in the TFLs and therefore also in the CSR since there were 2 places in the eCRF where the death of a patient could be recorded: on the AE reporting form and on the follow-up page (patient status). During the final reconciliation, queries were generated as to add a SAE in cases where the patient status indicated that the patient had died. In the 13 aforementioned death cases, the study site had refused to record the corresponding SAE. Therefore, this should be considered as an underreporting of fatal SAEs.

Taken together, safety results including the differences between the clinical and the Company´s SDB have been subject of thorough evaluation and scientific discussion. This included an assessment of (S)AE rates in the CDB versus the SDB, a judgement of the differences in the types of (S)AEs in both databases and the impact of discrepancies for the safety profile of the NIS and/or the risk-benefit profile of the product Avastin®. No noticeable safety aspects could be identified between the two safety databases

9.3.4.2 Adverse Drug Reactions and Fatalities

This NIS captured safety information the respective treating physician judged as non-related or causally related (serious) TEAEs, which were defined as having a possible, probable or definite relationship to bevacizumab (Avastin®).

In this study, the most frequently reported causally related TEAEs (≥5% of patients) were hypertension (12.4%; TEAE of particular interest) and fatigue (7.0%)

In this NIS, hypertension, proteinuria, gastrointestinal perforation and arterial embolism were TEAEs of particular interest. With regards to these TEAEs of particular interest (other than hypertension reported above), 28 (3.4%) patients were reported with proteinuria, 4 (0.5%) patients with large intestine perforation, 1 (0.1%) patient with intestinal perforation, 1 (0,.1%) with gastric perforation and 1 (0.1%) patient with arterial embolism, all events of which were causally related to bevacizumab (Avastin®).

In total, 181 patients were reported having died during the study, of these, 30 patients were documented with a fatal TEAE, of which the fatal event was reported as related to bevacizumab (Avastin®) in 5 patients (6 cases in total). The most frequently reported fatal events (≥0.5% of patients) were death (0.7%) and malignant neoplasm progression (0.5%). With regards to TEAEs of particular interest, a fatal intestinal perforation was reported in

3 (0.4%) patients, whereas no fatal events of large intestine perforation, gastric perforation, arterial embolism, hypertension, or proteinuria were documented. Five (0.6%) patients were documented with a fatal TEAE related to bevacizumab (Avastin®) (6 cases in total) with the following reported PTs: cerebrovascular accident, intestinal perforation, urosepsis, acute kidney injury, ileus and death. Of these 6 fatal causally related TEAEs, one patient was reported with 2 fatal events (urosepsis and acute kidney injury).

Conclusion on the overall safety assessment from this NIS corroborate the known safety profile of the product bevacizumab (Avastin®) (29).

9.4 GENERALIZABILITY

Generalizability of data collected within a NIS is subject to limitations as outlined above.

However, the patients included in this study consisted of an unselected population recruited in 240 study sites across Germany (routine clinical practice), reflecting the “real-world” setting of the study.

The number of enrolled patients (1,090) and the maximum of a 27-month observational period per patient sufficed to meet the primary objective of the study.

The EDC system (*iostudy office edc*) used in this study is a password-protected, validated and secure system, operating as per guidelines of FDA 21 CFR Part 11; hence, providing a reliable source of data. In addition, review and cleaning of the eCRF data was performed as well as reconciliation of safety data.

This NIS was designed to evaluate the effectiveness and safety of bevacizumab (Avastin®) in patients with newly diagnosed advanced EOC, FTC or PPC treated with bevacizumab (Avastin®) in combination with carboplatin/paclitaxel as first-line therapy in routine clinical practice. The data obtained in this study provides an important and valuable estimate of how clinical efficacy documented in controlled, randomized trials translates into effectiveness in routine clinical practice in Germany.

10. OTHER INFORMATION

Not applicable.

11. CONCLUSION

The data obtained in the non-interventional study OTILIA (NCT01697488) provide a valuable and important estimate of how clinical efficacy documented in controlled, randomized clinical trials translates into effectiveness in routine clinical practice in Germany.

While OTILIA demonstrates that first-line bevacizumab (Avastin®) therapy in combination with carboplatin/paclitaxel in patients with newly diagnosed FIGO stage IIIB-IV EOC, FTC and PPC is effective in routine clinical practice, a direct comparison with the results obtained in the pivotal trials is subject to limitations due to differences in patient characteristics and study settings including clear cut inclusion and exclusion criteria, assessment schemes and assessment specifications.

The safety information reported in this study is consistent with the known safety profile of bevacizumab (Avastin®). No new safety signals emerged.

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APPENDICES

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Table 1 List of stand-alone documents

Number	Document Reference Number	Date	Title
1	A_1_2_00	22 September 2011	AVASTIN_NIS_Ovar_Beobachtungsplan_FINAL V 1.6
2	A_1_2_01	06 February 2014	OTILIA_Beobachtungsplan_V2.0_inkl_Anhang
3	A_1_2_02	25 July 2014	ML27765_Otilia_BoP_Amendm2_fv3.0_20140725_inclAttachm_sign
4	A_1_2_00	22 September 2011	Avastin_NIS_Ovar_Anlage2 1.0_SAE Reporting Form 010911
5	A_1_2_00	22 September 2011	AVASTIN_NIS_Ovar_Anlage3_Pregnancy Reporting Form_gcp_for000023_v5_0
6	A_1_3_1_00	12 September 2011	OTILIA_Pat Einwilligungserklaerung_1.1_20111212
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8	A_1_3_1_02	28 July 2014	Otilia_Patienteninformation_und_-einwilligungserklärung_V3_20140728
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10	A_1_5_1	14 August 2017	V12_OTILIA_ecrf_screens_20170814
11	A_1_8	26 July 2012	OTILIA ML27765_Note to file_off label use_260712
12	A_1_9	06 October 2011	OTILIA_NIS_FB_QLQC30_QLQ OV28_20111006
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14	G_1_1_1	06 February 2014	OTILIA_AE_Report_Form_BoP2.0
15	G_1_1_1	17 February 2017	ML27765_SAE and AESI_gcp_for003221v10_new 2017
16	G_1_1_1	06 February 2014	OTILIA_Pregnancy_Report_Form_BoP2.0
17	G_1_1_1	17 February 2017	ML27765_Pregnancy Report Form_new 2017 v. 4.0
18	G_7	17 December 2019	ML27765_Otilia_Safety_Diskrepancies_final
19	L	18 October 2017	ML27765_Otilia_Geloeschte_Patienten_20171018
20	M	18 December 2019	OTILIA_offene_Queries_zu_DB_Lock
21	N_1	02 October 2014	ML27765_Otilia_SAP_Interim1_v1.0_final
22	N_1	08 February 2016	ML27765_Otilia_SAP_Interim2_v1.0

23	N_1	01 December 2016	OTILIA SAP zur Zusatzanalyse 2.IA_signiert_20161222
24	N_1	24 January 2017	20170203 OTILIA SAP 3.IA signiert
25	N_1	28 February 2017	OTILIA_Statistischer Analyseplan_20170320_signiert
26	N_1	08 May 2017	ML27765_Otilia_SAP_Interim3_Version3.1_ 20170508
27	N_1	20 December 2018	OTILIA_SAP_v1_clean
28	N_1	12 September 2019	OTILIA_SAP_v2_clean
29	N_2_1	01 December 2014[1]	Otilia_Interimsanalyse_V1.2_20141201
30	N_2_1	16 March 2016[1]	Otilia_Interimsanalyse2_Listings_Version1.1
31	N_2_1	15 April 2016[1]	Otilia_Interimsanalyse2_Figures_Version1.2
32	N_2_1	27 April 2016[1]	Otilia_Interimsanalyse2_Tables_Version1.3
33	N_2_1	28 March 2017[1]	Otilia_Interimsanalyse3_Listings_v1.0
34	N_2_1	05 April 2017[1]	Otilia_Interimsanalyse3_Figures_v1.1_2017 0405
35	N_2_1	08 May 2017[1]	Otilia_Interimsanalyse3_Tables_Part_I_v1.2 _20170508
36	N_2_1	05 April 2017[1]	Otilia_Interimsanalyse3_Tables_Part_II_v1.1 _20170405
37	N_2_3	02 August 2019	OTILIA_Zentrenliste_2019082
38	N_2_3	17 June 2019	OTILIA_DRM_minutes_20190617_final
39	N_2_3	06 December 2019[1]	OTILIA_Listings_Final_2_20191206
40	N_2_3	27 January 2020[1]	OTILIA_Figures_Final_3_20200127
41	N_2_3	20 April 2020[1]	OTILIA_Tables_Final_4_20200420
42	N_2_3	18 May 2020	Signature page of Scientific Responsible

[1]THE DATE OF RESPECTIVE INTERIM REPORT REFLECTS THE TIME POINT OF REPORT GENERATION.

ANNEX 2. DIFFERENCE BETWEEN THE CLINICAL DATABASE AND THE SAFETY DABASE

The complete list of discrepancies between the clinical database and the safety database is available as a separate electronic file due to its size (Table 1; Annex 1. List of stand-alone documents).

ANNEX 3. ADDITIONAL INFORMATION

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