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 |
| PROTOCOL NUMBER: | ML27765 v3.0 (Roche Pharma AG); P0229 (iOMEDICO AG); NCT01697488 (ClinicalTrials.gov Identifier) |
| VERSION NUMBER: | Final V 1.0 |
| STUDIED MEDICINAL PRODUCT: | Bevacizumab (Avastin®) |
| COUNTRY OF STUDY POPULATION: | Germany |
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| DATE FINAL: | See electronic date stamp below |

Date and Time(UTC) | Reason for Signing | Name
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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

NIS Data Science Responsible: Ann-Katrin Sommer
Roche Pharma AG
Grenzach-Wyhlen, Germany

Date of the abstract: 18 May 2020

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*

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Patients &lt;70 years</th>
<th>Patients ≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients enrolled</td>
<td>1,090 (100.0)</td>
<td>583 (100.0)</td>
<td>507 (100.0)</td>
</tr>
<tr>
<td>Number of patients treated with bevacizumab (Avastin®)</td>
<td>1,041 (95.5)</td>
<td>560 (96.1)</td>
<td>481 (94.9)</td>
</tr>
<tr>
<td>Number of patients in CAP (n, %)</td>
<td>824 (75.6)</td>
<td>453 (77.7)</td>
<td>371 (73.2)</td>
</tr>
<tr>
<td>Number of patients excluded from CAP (n, %)</td>
<td>266 (24.4)</td>
<td>130 (22.3)</td>
<td>136 (26.8)</td>
</tr>
</tbody>
</table>
## 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)).

### Reasons for exclusion from CAP (n, %)

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

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

1Reasons 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 – 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

<table>
<thead>
<tr>
<th>Age subgroup</th>
<th>CAP</th>
<th>Patients &lt;70 years</th>
<th>Patients ≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, N</td>
<td>824</td>
<td>453</td>
<td>371</td>
</tr>
</tbody>
</table>

Treatment duration

<table>
<thead>
<tr>
<th></th>
<th>Events, n (%)</th>
<th>25% quantile [95% CI]</th>
<th>Median [95% CI]</th>
<th>75% quantile [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients &lt;70 years</td>
<td>453 (55.0%)</td>
<td>6.7 [ 5.7, 7.8]</td>
<td>13.8 [12.7, 14.5]</td>
<td>NA [17.5, NA]</td>
</tr>
<tr>
<td>Patients ≥70 years</td>
<td>227 (50.1%)</td>
<td>7.9 [ 6.4, 9.1]</td>
<td>14.6 [13.9, 15.2]</td>
<td>NA [18.0, NA]</td>
</tr>
<tr>
<td>Total number of applications</td>
<td>12,431</td>
<td>18.0</td>
<td>25.0</td>
<td>17.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.0</td>
<td>25.0</td>
<td>17.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>max</td>
<td>24.0</td>
<td>17.5</td>
</tr>
<tr>
<td>Total (cumulative) dose (mg/kg)</td>
<td>267.1</td>
<td>14.7</td>
<td>381.5</td>
<td>239.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>min</td>
<td>381.5</td>
<td>14.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>max</td>
<td>374.9</td>
<td>381.5</td>
</tr>
<tr>
<td>Dose intensity (mg/kg per week)</td>
<td>5.1</td>
<td>2.3</td>
<td>108.1</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>min</td>
<td>108.1</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>max</td>
<td>106.8</td>
<td>108.1</td>
</tr>
<tr>
<td>Any treatment modification</td>
<td>653 (79.2%)</td>
<td>361 (79.7%)</td>
<td>292 (78.7%)</td>
<td></td>
</tr>
</tbody>
</table>
## Age subgroup

<table>
<thead>
<tr>
<th>Kind of treatment modification</th>
<th>CAP (Patients &lt;70 years)</th>
<th>Patients ≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose increase</td>
<td>50 (6.1%)</td>
<td>32 (7.1%)</td>
</tr>
<tr>
<td>Dose reduction</td>
<td>57 (6.9%)</td>
<td>22 (4.9%)</td>
</tr>
<tr>
<td>Therapy delay</td>
<td>227 (27.5%)</td>
<td>122 (26.9%)</td>
</tr>
<tr>
<td>Therapy interruption</td>
<td>556 (67.5%)</td>
<td>303 (66.9%)</td>
</tr>
<tr>
<td>Reason for treatment modification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient’s wish</td>
<td>148 (18.0%)</td>
<td>81 (17.9%)</td>
</tr>
<tr>
<td>Physician decision</td>
<td>590 (71.6%)</td>
<td>328 (72.4%)</td>
</tr>
<tr>
<td>Toxicity</td>
<td>110 (13.3%)</td>
<td>55 (12.1%)</td>
</tr>
</tbody>
</table>

## Carboptatin and Paclitaxel therapy

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

CAP = Core analysis population; CI = Confidence interval; Max = Maximum; Min = Minimum; N/n = Number; NA = Not reached.

$^1$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

<table>
<thead>
<tr>
<th>Age subgroup</th>
<th>CAP</th>
<th>Patients &lt;70 years</th>
<th>Patients ≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, N</td>
<td>824</td>
<td>453</td>
<td>371</td>
</tr>
<tr>
<td>Progression-free survival(^1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events, n [%]</td>
<td>368 (44.7%)</td>
<td>200 (44.2%)</td>
<td>168 (45.3%)</td>
</tr>
<tr>
<td>Median [95% CI]</td>
<td>19.4 [18.7, 20.3]</td>
<td>20.0 [18.7, 21.2]</td>
<td>19.3 [17.6, 20.2]</td>
</tr>
<tr>
<td>75% quantile [95% CI]</td>
<td>23.6 [22.4, 24.8]</td>
<td>23.9 [22.4, 26.3]</td>
<td>23.3 [21.5, 24.6]</td>
</tr>
<tr>
<td>6-month rate [95%-CI]</td>
<td>95.2% [93.4, 96.5]</td>
<td>97.2% [95.1, 98.4]</td>
<td>92.6% [89.3, 95.0]</td>
</tr>
<tr>
<td>12-month rate [95%-CI]</td>
<td>79.5% [76.4, 82.3]</td>
<td>80.2% [75.9, 83.9]</td>
<td>78.7% [73.7, 82.8]</td>
</tr>
<tr>
<td>18-month rate [95%-CI]</td>
<td>57.5% [52.9, 61.8]</td>
<td>60.1% [54.0, 65.7]</td>
<td>54.2% [47.2, 60.6]</td>
</tr>
<tr>
<td>Overall survival(^1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events, n [%]</td>
<td>181 (22.0%)</td>
<td>86 (19.0%)</td>
<td>95 (25.6%)</td>
</tr>
<tr>
<td>25% quantile [95% CI]</td>
<td>19.3 [17.8, 20.4]</td>
<td>20.3 [18.2, 22.5]</td>
<td>18.6 [16.7, 20.0]</td>
</tr>
<tr>
<td>Median [95% CI]</td>
<td>24.6 [23.7, 26.3]</td>
<td>26.7 [23.9, 29.8]</td>
<td>22.9 [21.7, 25.5]</td>
</tr>
<tr>
<td>75% quantile [95% CI]</td>
<td>31.5 [27.8, 47.0]</td>
<td>39.8 [28.9, 54.1]</td>
<td>27.1 [25.6, 35.2]</td>
</tr>
<tr>
<td>12-month rate [95%-CI]</td>
<td>91.1% [88.7, 93.0]</td>
<td>92.3% [89.1, 94.5]</td>
<td>89.6% [85.6, 92.5]</td>
</tr>
<tr>
<td>18-month rate [95%-CI]</td>
<td>78.5% [74.4, 82.1]</td>
<td>81.0% [75.4, 85.4]</td>
<td>75.5% [68.8, 80.9]</td>
</tr>
<tr>
<td>24-month rate [95%-CI]</td>
<td>53.3% [46.1, 59.8]</td>
<td>59.5% [49.7, 68.1]</td>
<td>45.5% [35.2, 55.3]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Best response</th>
<th>CAP</th>
<th>Patients &lt;70 years</th>
<th>Patients ≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (non-missing)</td>
<td>707</td>
<td>392</td>
<td>315</td>
</tr>
<tr>
<td>CR</td>
<td>307 (43.4%)</td>
<td>195 (49.7%)</td>
<td>112 (35.6%)</td>
</tr>
<tr>
<td>PR</td>
<td>203 (28.7%)</td>
<td>106 (27.0%)</td>
<td>97 (30.8%)</td>
</tr>
<tr>
<td>ORR</td>
<td>510 (72.1%)</td>
<td>301 (76.8%)</td>
<td>209 (66.3%)</td>
</tr>
<tr>
<td>SD</td>
<td>153 (21.6%)</td>
<td>66 (16.8%)</td>
<td>87 (27.6%)</td>
</tr>
<tr>
<td>PD</td>
<td>27 (3.8%)</td>
<td>16 (4.1%)</td>
<td>11 (3.5%)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>17 (2.4%)</td>
<td>9 (2.3%)</td>
<td>8 (2.5%)</td>
</tr>
<tr>
<td>Missing</td>
<td>117</td>
<td>61</td>
<td>56</td>
</tr>
</tbody>
</table>

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)**
**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

---

**Patients reported with respective TEAE, n (%), n (cases)**

<table>
<thead>
<tr>
<th>TEAE Description</th>
<th>Total¹</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE (N=824)</td>
<td>616</td>
<td>3,645</td>
</tr>
<tr>
<td>Any serious TEAE</td>
<td>222</td>
<td>438</td>
</tr>
<tr>
<td>Any TEAE with CTCAE severity grade ≥ grade 3</td>
<td>317</td>
<td>583</td>
</tr>
<tr>
<td>Any causally related TEAE²</td>
<td>330</td>
<td>1,036</td>
</tr>
<tr>
<td>Any causally related serious TEAE²</td>
<td>72</td>
<td>96</td>
</tr>
<tr>
<td>Any TEAE leading to discontinuation of bevacizumab (Avastin®)</td>
<td>145</td>
<td>206</td>
</tr>
</tbody>
</table>

¹Patients can occur in more than one category of the table. ²Causally related TEAEs were defined as those with a possible, probable or definite relationship to bevacizumab (Avastin®). ³TEAE 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.

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CTCAE = Common Terminology Criteria for Adverse Events; N/n = Number; TEAE = Treatment-emergent adverse event.
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**

<table>
<thead>
<tr>
<th>Patients reported with respective (serious) causally related TEAE, n (%), n (cases)</th>
<th>Total(^1) (N = 824)</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>616 (74.8%)</td>
<td>3,645</td>
</tr>
<tr>
<td>Any causally related TEAE(^2)</td>
<td>330 (40.0%)</td>
<td>1,036</td>
</tr>
<tr>
<td>Any causally related serious TEAE(^2)</td>
<td>72 (8.7%)</td>
<td>96</td>
</tr>
<tr>
<td>Any causally related fatal TEAE(^2)</td>
<td>5 (0.6%)</td>
<td>6</td>
</tr>
</tbody>
</table>

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**

<table>
<thead>
<tr>
<th>Total CAP (N=824)</th>
<th>Patients(^1) (N %)</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of deaths, n, %</td>
<td>181 (22.0%)</td>
<td></td>
</tr>
<tr>
<td>Patients reported with fatal TEAE, n, %, n (cases)</td>
<td>Any TEAE</td>
<td>616 (74.8%)</td>
</tr>
<tr>
<td>All fatal TEAE(^2)</td>
<td>30 (3.6%)</td>
<td>43</td>
</tr>
<tr>
<td>Fatal causally related TEAE(^3)</td>
<td>5 (0.6%)</td>
<td>6</td>
</tr>
<tr>
<td>Fatal non-related TEAE(^3)</td>
<td>24 (2.9%)</td>
<td>29</td>
</tr>
<tr>
<td>Fatal TEAE – causality unknown(^3)</td>
<td>5 (0.6%)</td>
<td>8</td>
</tr>
</tbody>
</table>

CAP = Core analysis population; N/n = Number; TEAE = Treatment-emergent adverse event.
Patients can occur in more than one category of the table. 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. 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.
## LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADR</td>
<td>Adverse drug reaction</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>AMG</td>
<td>German Medicinal Products Act (deutsches Arzneimittelgesetz)</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CAP</td>
<td>Core analysis population</td>
</tr>
<tr>
<td>CA-125</td>
<td>Cancer antigen 125</td>
</tr>
<tr>
<td>CDB</td>
<td>Clinical database CRO</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CR</td>
<td>Complete response</td>
</tr>
<tr>
<td>CRO</td>
<td>Contract research organization</td>
</tr>
<tr>
<td>CTCAE</td>
<td>Common Terminology Criteria for Adverse Events</td>
</tr>
<tr>
<td>DBL</td>
<td>Database lock</td>
</tr>
<tr>
<td>DMP</td>
<td>Data management plan</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case Report Form</td>
</tr>
<tr>
<td>EDC</td>
<td>Electronic data capture</td>
</tr>
<tr>
<td>EOC</td>
<td>Epithelial ovarian cancer</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organisation for Research and Treatment of Cancer</td>
</tr>
<tr>
<td>EOT</td>
<td>End of treatment</td>
</tr>
<tr>
<td>FIGO</td>
<td>Fédération Internationale de Gynécologie et d’Obstétrique</td>
</tr>
<tr>
<td>FL</td>
<td>First-line</td>
</tr>
<tr>
<td>FPI</td>
<td>First-patient-in</td>
</tr>
<tr>
<td>FTC</td>
<td>Fallopian tube cancer</td>
</tr>
<tr>
<td>FU</td>
<td>Follow-Up</td>
</tr>
<tr>
<td>GCIG</td>
<td>Gynaecologic cancer intergroup</td>
</tr>
<tr>
<td>G-CSF</td>
<td>Granulocyte-colony stimulating factor</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed consent form</td>
</tr>
<tr>
<td>IMP</td>
<td>Investigational medicinal product</td>
</tr>
<tr>
<td>IRC</td>
<td>Independent review of radiologic and clinical data</td>
</tr>
<tr>
<td>LoE</td>
<td>Lack of Efficacy</td>
</tr>
<tr>
<td>LPI</td>
<td>Last-patient-in</td>
</tr>
<tr>
<td>LVEF</td>
<td>Left Ventricular Ejection Fraction</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>MAH</td>
<td>Marketing authorization holder</td>
</tr>
<tr>
<td>Max</td>
<td>Maximum</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>Min</td>
<td>Minimum</td>
</tr>
<tr>
<td>NA</td>
<td>Not applicable / Not reached</td>
</tr>
<tr>
<td>NCI</td>
<td>National Cancer Institute</td>
</tr>
<tr>
<td>NIO</td>
<td>Niedergelassener internistischer Onkologe / Office-based medical oncologist</td>
</tr>
<tr>
<td>NIS</td>
<td>Non-interventional study</td>
</tr>
<tr>
<td>ORR</td>
<td>Overall response rate</td>
</tr>
<tr>
<td>OS</td>
<td>Overall survival</td>
</tr>
<tr>
<td>PD</td>
<td>Progressive disease</td>
</tr>
<tr>
<td>PFS</td>
<td>Progression-free survival</td>
</tr>
<tr>
<td>PPC</td>
<td>Primary peritoneal carcinoma</td>
</tr>
<tr>
<td>PR</td>
<td>Partial response</td>
</tr>
<tr>
<td>PT</td>
<td>Preferred term</td>
</tr>
<tr>
<td>QLQ</td>
<td>Quality of life questionnaire</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>Q1</td>
<td>First quartile</td>
</tr>
<tr>
<td>Q3</td>
<td>Third quartile</td>
</tr>
<tr>
<td>RECIST</td>
<td>Response Evaluation Criteria In Solid Tumors</td>
</tr>
<tr>
<td>SADR</td>
<td>Serious adverse drug reaction</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>(S)AE</td>
<td>(Serious) Adverse event</td>
</tr>
<tr>
<td>SAERT</td>
<td>Serious Adverse Event Reconciliation Tool</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical analysis plan</td>
</tr>
<tr>
<td>SD</td>
<td>Stable disease</td>
</tr>
<tr>
<td>SD / Std</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SDB</td>
<td>Safety database Roche</td>
</tr>
<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>SOC</td>
<td>System organ class</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard operating procedure</td>
</tr>
<tr>
<td>STIAMP</td>
<td>Suspected Transmission of Infectious Agent by Medicinal Product</td>
</tr>
<tr>
<td>TEAE</td>
<td>Treatment-emergent adverse event</td>
</tr>
<tr>
<td>TFL</td>
<td>Tables, Figures, Listings</td>
</tr>
<tr>
<td>TMF</td>
<td>Trial master file</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular endothelial growth factor</td>
</tr>
</tbody>
</table>
### 3. MILESTONES

**Table 3-1 Study milestones**

<table>
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<th>Milestone</th>
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<tr>
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09 January 2017

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01 February 2017

Study status report 60 / study progress report 18
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Study status report 61 / study progress report 19
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Study status report 62 / study progress report 20
02 May 2017

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01 June 2017

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03 July 2017

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Study status report 66 / study progress report 24
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02 November 2017

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01 December 2017

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02 January 2018

Study status report 71 / study progress report 29
01 February 2018

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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
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

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Protocol ML27765 / P0229
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**
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

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<th>At the end of intensive documentation or at premature termination</th>
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<tr>
<td>Patient informed consent</td>
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<tr>
<td>Demographic data*</td>
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<td>Previous disease</td>
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<td>Comorbidities</td>
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<tr>
<td>Tumor anamnensis*</td>
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<td>Pretreatment</td>
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<tr>
<td>Selected hematologic and clinical chemistry laboratory parameters (optional)</td>
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<td>Tumor marker CA-125</td>
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<td>Anamnesis and treatment of hypertension, if present</td>
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<tr>
<td>Information on physician’s choice of treatment</td>
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<td>Tumor evaluation</td>
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<td>Existing supportive therapy</td>
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<td>(S)AEs*</td>
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<td>Situations requiring expedited reporting*</td>
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<td>AEs of special interest*</td>
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<td>Information on bevacizumab (Avastin®)</td>
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<td>Data on concomitant palliative radiotherapy, if applicable</td>
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<td>Evaluation of treatment from physician’s point of view</td>
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<td>End of treatment</td>
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<tr>
<td>Reason for premature termination</td>
<td>x</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Provided by patient**

<table>
<thead>
<tr>
<th>Questionnaires</th>
<th>Baseline documentation</th>
<th>15-months intensive documentation period (documentation each cycle)</th>
<th>At the end of intensive documentation or at premature termination</th>
</tr>
</thead>
<tbody>
<tr>
<td>QoL: EORTC QLQ-C30 and QLQ-OV28*</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

*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.*
Demographic and anamnestic data of the patient including year of birth, baseline questionnaire number and information on patient status (weight, size, Performance Status); \(^1\) information on patient status only (weight and performance status); \(^2\) at initial diagnosis and at treatment start; \(^3\) including correct staging, histology, grading and postoperative tumor residual; \(^4\) (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). \(^5\) persisting (S)AEs; \(^6\) including quality deficiencies, counterfeits (or suspicion), and occupational exposure. These were to be reported even in the absence of an AE. \(^7\) see Table 1 Annex 1. List of stand-alone documents; \(^8\) 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-threatening 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>
<thead>
<tr>
<th>Categories</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of open queries</td>
<td>678</td>
<td>100</td>
</tr>
<tr>
<td>Arterial hypertension – Anamnesis</td>
<td>5</td>
<td>0.7</td>
</tr>
<tr>
<td>Concomitant medication</td>
<td>13</td>
<td>1.9</td>
</tr>
<tr>
<td>End of treatment documentation</td>
<td>40</td>
<td>5.9</td>
</tr>
<tr>
<td>Laboratory parameters</td>
<td>8</td>
<td>1.2</td>
</tr>
<tr>
<td>Patient status</td>
<td>32</td>
<td>4.7</td>
</tr>
<tr>
<td>Physician’s assessment of treatment</td>
<td>11</td>
<td>1.6</td>
</tr>
<tr>
<td>Previous and concomitant diseases</td>
<td>19</td>
<td>2.8</td>
</tr>
<tr>
<td>Previous therapies</td>
<td>12</td>
<td>1.8</td>
</tr>
<tr>
<td>Progress documentation – General</td>
<td>24</td>
<td>3.5</td>
</tr>
<tr>
<td>Progress documentation – Antineoplastic therapy</td>
<td>10</td>
<td>1.5</td>
</tr>
<tr>
<td>Registration</td>
<td>9</td>
<td>1.3</td>
</tr>
<tr>
<td>(Serious) adverse event</td>
<td>140</td>
<td>20.6</td>
</tr>
<tr>
<td>Supportive therapy / palliative radiotherapy</td>
<td>8</td>
<td>1.2</td>
</tr>
<tr>
<td>Tumor anamnesis</td>
<td>18</td>
<td>2.7</td>
</tr>
<tr>
<td>Tumor assessment</td>
<td>20</td>
<td>2.9</td>
</tr>
</tbody>
</table>
Number of open queries at the time of database lock¹

<table>
<thead>
<tr>
<th>Category</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor marker CA 125</td>
<td>5</td>
<td>0.7</td>
</tr>
<tr>
<td>Tumor therapy</td>
<td>202</td>
<td>29.8</td>
</tr>
<tr>
<td>Queries not allocated to any category</td>
<td>102</td>
<td>15.0</td>
</tr>
<tr>
<td>Query processing status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Queries with answer of the site</td>
<td>69</td>
<td>10.2</td>
</tr>
<tr>
<td>Queries without answer of the site</td>
<td>609</td>
<td>89.8</td>
</tr>
<tr>
<td>Queries without answer of the site</td>
<td>609</td>
<td>89.8</td>
</tr>
<tr>
<td>Query with safety-tag</td>
<td>43</td>
<td>7.1</td>
</tr>
<tr>
<td>Queries in the category (serious) adverse event</td>
<td>111</td>
<td>18.2</td>
</tr>
</tbody>
</table>

¹Database 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, istudy 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:

\[
OS \text{ [months]} = (\text{date of death} - \text{date of first administration of bevacizumab (Avastin®)} + 1)/30.4375
\]

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) 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
Figure 8-1  CONSORT flow diagram

**Enrollment**

Patients enrolled (n= 1090)

Excluded (n= 49)
- No Avastin administered

**Treatment**

Patients treated with Avastin (n= 1041)

Excluded (n= 217)
- Wrong dosing (dose or frequency of application) (n= 163)
- Missing or wrong combination partner (n= 134)
- Wrong FIGO stage (n= 14)
- Wrong indication (n= 5)
- Prior therapies not according to SmPC (n= 10)
- Retrospective enrollment (n= 4)

**Analysis**

Patients in CAP (n= 624)
- Patients <70 years (n= 453)
- Patients ≥70 years (n= 371)

**End of treatment**

Reasons for end of treatment (CAP/ <70/ ≥70)
- Adverse event (n= 139/ 64/ 75)
- Death (n= 25/ 7/ 18)
- End of documentation after 15 months (n= 426/ 250/ 176)
- Lost-to-Follow-Up (n= 24/ 16/ 8)
- Patient’s wish (n= 94/ 38/ 56)
- Tumor progression (n= 254/ 139/ 115)
- Tumor remission (n= 18/ 11/ 7)
- No end of treatment documentation (n= 34/ 9/ 25)
- Other reason (n= 76/ 49/ 27)

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 subgroup¹

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Patients &lt;70 years</th>
<th>Patients ≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients enrolled</td>
<td>1,090 (100.0)</td>
<td>583 (100.0)</td>
<td>507 (100.0)</td>
</tr>
<tr>
<td>Number of patients treated with bevacizumab (Avastin®)</td>
<td>1,041 (95.5)</td>
<td>560 (96.1)</td>
<td>481 (94.9)</td>
</tr>
<tr>
<td>Number of patients in CAP (n, %)</td>
<td>824 (75.6)</td>
<td>453 (77.7)</td>
<td>371 (73.2)</td>
</tr>
<tr>
<td>Number of patients excluded from CAP (n, %)²</td>
<td>266 (24.4)</td>
<td>130 (22.3)</td>
<td>136 (26.8)</td>
</tr>
</tbody>
</table>

[Source: OTILIA_Tables_Final_4_20200420: Table 14.1.1].
CAP = Core analysis population; N/n = Number.
¹Definition of CAP and subgroups is provided in chapter 7.8.2 Statistical Considerations and Planned Sample Size;
²Reasons 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 – subgroups³ (CAP)

<table>
<thead>
<tr>
<th></th>
<th>CAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients, N</td>
<td>824</td>
</tr>
<tr>
<td>Number of patients in respective subgroup, N</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Patients &lt;70 years</td>
<td>453</td>
</tr>
<tr>
<td>Patients ≥70 years</td>
<td>371</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>Patients without primary surgery</td>
<td>45</td>
</tr>
<tr>
<td>Patients with primary surgery</td>
<td>779</td>
</tr>
</tbody>
</table>

[Source: OTILIA_Tables_Final_4_20200420: Table 14.1.1 and Table 14.2.1].
CAP = Core analysis population; N/n = Number.
³Definition 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

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

Reasons for end of treatment documentation (n, %)

<table>
<thead>
<tr>
<th>Reasons for end of treatment documentation (n, %)</th>
<th>Total</th>
<th>Patients &lt;70 years</th>
<th>Patients ≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients in CAP</td>
<td>824 (100.0)</td>
<td>453 (100.0)</td>
<td>371 (100.0)</td>
</tr>
<tr>
<td>AE not related to therapy</td>
<td>25 (3.0)</td>
<td>8 (1.8)</td>
<td>17 (4.6)</td>
</tr>
<tr>
<td>AE related to therapy</td>
<td>40 (4.9)</td>
<td>11 (2.4)</td>
<td>29 (7.8)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>44 (5.3)</td>
<td>30 (6.6)</td>
<td>14 (3.8)</td>
</tr>
<tr>
<td>Death</td>
<td>16 (1.9)</td>
<td>5 (1.1)</td>
<td>11 (3.0)</td>
</tr>
<tr>
<td>End of documentation after 15 months</td>
<td>349 (42.4)</td>
<td>213 (47.0)</td>
<td>136 (36.7)</td>
</tr>
<tr>
<td>Lost-to-Follow-up</td>
<td>15 (1.8)</td>
<td>10 (2.2)</td>
<td>5 (1.3)</td>
</tr>
<tr>
<td>Other reason (specification)</td>
<td>48 (5.8)</td>
<td>31 (6.8)</td>
<td>17 (4.6)</td>
</tr>
<tr>
<td>Patient’s wish</td>
<td>7 (0.8)</td>
<td>3 (0.7)</td>
<td>4 (1.1)</td>
</tr>
<tr>
<td>Patient’s wish (no toxicity)</td>
<td>53 (6.4)</td>
<td>24 (5.3)</td>
<td>29 (7.8)</td>
</tr>
<tr>
<td>Tumor progression</td>
<td>196 (23.8)</td>
<td>105 (23.2)</td>
<td>91 (24.5)</td>
</tr>
<tr>
<td>Tumor remission</td>
<td>13 (1.6)</td>
<td>7 (1.5)</td>
<td>6 (1.6)</td>
</tr>
<tr>
<td>No EOT documentation</td>
<td>18 (2.2)</td>
<td>6 (1.3)</td>
<td>12 (3.2)</td>
</tr>
</tbody>
</table>

Source: OTILIA_Tables_Final_4_20200429: 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.

1Reasons for exclusion from CAP are explained in more detail in the minutes of the data review meeting. Multiple reasons for exclusion from CAP possible. 2In 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.
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>
<thead>
<tr>
<th>Table 8-4</th>
<th>Comparison of the analysis population in third interim analysis and final analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Third interim analysis</td>
</tr>
<tr>
<td>Total number of enrolled patients</td>
<td>1,085 (100.0)</td>
</tr>
<tr>
<td>Number of excluded patients</td>
<td>277 (25.4)</td>
</tr>
<tr>
<td>Number of patients in Per Protocol Population</td>
<td>808 (74.1)</td>
</tr>
<tr>
<td>Patients &lt;70 years</td>
<td>426 (39.1)</td>
</tr>
<tr>
<td>Patients ≥70 years</td>
<td>382 (35.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reasons for exclusion</th>
<th>Third interim analysis</th>
<th>N (%)</th>
<th>Final analysis</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cycle with bevacizumab (Avastin®)</td>
<td>95 (8.7)</td>
<td>Missing or wrong combination partner</td>
<td>134 (12.3)</td>
<td></td>
</tr>
<tr>
<td>+ carboplatin + paclitaxel</td>
<td></td>
<td>Wrong dosing (dose or frequency of application)</td>
<td>163 (15.0)</td>
<td></td>
</tr>
<tr>
<td>Bevacizumab (Avastin®) dose to low/high/not determinable</td>
<td>87 (8.0)</td>
<td>Retrospective enrollment</td>
<td>4 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Retrospective inclusion</td>
<td>69 (6.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Received prior therapy</td>
<td>36 (3.3)</td>
<td>Prior therapies not according to SmPC</td>
<td>10 (0.9)</td>
<td></td>
</tr>
<tr>
<td>FIGO stage not appropriate/unknown</td>
<td>34 (3.1)</td>
<td>Wrong FIGO stage</td>
<td>14 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Third interim analysis</td>
<td>N (%)</td>
<td>Final analysis</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------------------</td>
<td>-------</td>
<td>----------------------------------------------------</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td>No treatment visit</td>
<td>29 (2.7)</td>
<td>No bevacizumab (Avastin® administered</td>
<td>49 (4.5)</td>
<td></td>
</tr>
<tr>
<td>Off-label substance at the beginning of the therapy</td>
<td>16 (1.5)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Tumor subtype unknown</td>
<td>15 (1.4)</td>
<td>Wrong indication</td>
<td>5 (0.5)</td>
<td></td>
</tr>
</tbody>
</table>

[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

<table>
<thead>
<tr>
<th>Reasons for removal of patients from the EDC</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All deleted patients, N</strong></td>
<td>72</td>
</tr>
<tr>
<td>Reasons, n (%)</td>
<td></td>
</tr>
<tr>
<td>Screening failure</td>
<td>54 (75.0%)</td>
</tr>
<tr>
<td>Patient was mistakenly registered in eCRF</td>
<td>16 (22.2%)</td>
</tr>
<tr>
<td>Duplicate registration entry</td>
<td>2 (2.8%)</td>
</tr>
</tbody>
</table>

[Source: ML27765_Otilia_Geloeschte_Patienten_20171018; Table 1, Annex 1. List of stand-alone documents].
eCRF = electronic case report form; 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, years¹ | N       |         |        |
| Mean                            | 65.4    | 57.6    | 74.9    |
| Std                             | 10.85   | 8.43    | 3.16    |
| Median                          | 68.0    | 58.4    | 74.6    |

Clinical Study Report Number 1100702, Final Version 1.0
Protocol ML27765 / P0229
<table>
<thead>
<tr>
<th>Parameter</th>
<th>CAP</th>
<th>Patients &lt;70 years</th>
<th>Patients ≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>25% quantile</td>
<td>57.3</td>
<td>52.3</td>
<td>72.2</td>
</tr>
<tr>
<td>75% quantile</td>
<td>74.2</td>
<td>64.5</td>
<td>76.9</td>
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<tr>
<td>Min</td>
<td>25.9</td>
<td>25.9</td>
<td>70.1</td>
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<tr>
<td>Max</td>
<td>83.4</td>
<td>70.2</td>
<td>83.4</td>
</tr>
<tr>
<td>Age at start of therapy in decades, n, (%)³</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 years</td>
<td>90 (10.9)</td>
<td>90 (19.9)</td>
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</tr>
<tr>
<td>50 - &lt;60 years</td>
<td>163 (19.8)</td>
<td>163 (36.0)</td>
<td>0 (0)</td>
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<tr>
<td>60 - &lt;70 years</td>
<td>198 (24.0)</td>
<td>198 (43.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>70 - &lt;80 years</td>
<td>347 (42.1)</td>
<td>2 (0.4)</td>
<td>345 (93.0)</td>
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<tr>
<td>≥80 years</td>
<td>26 (3.2)</td>
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<td>26 (7.0)</td>
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<td>Weight, kg</td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>802</td>
<td>444</td>
<td>358</td>
</tr>
<tr>
<td>Median</td>
<td>65.0</td>
<td>64.0</td>
<td>65.0</td>
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<tr>
<td>Min</td>
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<td>41.0</td>
<td>41.0</td>
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<td>120.0</td>
<td>107.0</td>
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<td>BMI, kg/m²</td>
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<tr>
<td>N</td>
<td>802</td>
<td>444</td>
<td>358</td>
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<tr>
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<td>23.9</td>
<td>24.6</td>
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<tr>
<td>Min</td>
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<td>16.2</td>
<td>15.6</td>
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<tr>
<td>Max</td>
<td>43.5</td>
<td>43.5</td>
<td>42.3</td>
</tr>
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<td>BMI category, n (%)</td>
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<td>≤ 20 kg/m²</td>
<td>126 (15.3)</td>
<td>80 (17.7)</td>
<td>46 (12.4)</td>
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<tr>
<td>&gt; 20 - ≤ 25 kg/m²</td>
<td>343 (41.6)</td>
<td>180 (39.7)</td>
<td>163 (43.9)</td>
</tr>
<tr>
<td>&gt; 25 - ≤ 30 kg/m²</td>
<td>242 (29.4)</td>
<td>133 (29.4)</td>
<td>109 (29.4)</td>
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<tr>
<td>&gt; 30 kg/m²</td>
<td>113 (13.7)</td>
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<td>53 (14.3)</td>
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<td>ECOG performance status, n, (%)</td>
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<td>343</td>
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<tr>
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<td>297 (38.2)</td>
<td>199 (45.7)</td>
<td>98 (28.6)</td>
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<tr>
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<td>195 (56.9)</td>
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<td>77 (9.9)</td>
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<td>9 (2.6)</td>
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<td>18</td>
<td>28</td>
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<tr>
<td>Medical conditions with stop date prior to first bevacizumab (Avastin®) administration, n (%)</td>
<td>92 (11.2)</td>
<td>49 (10.8)</td>
<td>43 (11.6)</td>
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<td>Medical conditions ongoing at first bevacizumab (Avastin®) administration, n (%)</td>
<td>365 (44.3)</td>
<td>142 (31.3)</td>
<td>223 (60.1)</td>
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<td>Persistent arterial hypertension, n (%)</td>
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<td>339 (41.1)</td>
<td>132 (29.1)</td>
<td>207 (55.8)</td>
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<tr>
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<td>485 (58.9)</td>
<td>321 (70.9)</td>
<td>164 (44.2)</td>
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<td>117 (88.6)</td>
<td>195 (94.2)</td>
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<td>15 (11.4)</td>
<td>12 (5.8)</td>
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<td>Time from primary diagnosis to start of front-line treatment, months</td>
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<td>3.3</td>
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<td>Parameter</td>
<td>CAP</td>
<td>Patients &lt;70 years</td>
<td>Patients ≥70 years</td>
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<td>-----</td>
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<td>-------------------</td>
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<tr>
<td></td>
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<tr>
<td>STD</td>
<td>11.47</td>
<td>13.33</td>
<td>8.63</td>
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<td>1.4</td>
<td>1.4</td>
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<td>75% quantile</td>
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<td>2.6</td>
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<td>0.3</td>
</tr>
<tr>
<td>Max</td>
<td>115.6</td>
<td>115.6</td>
<td>91.3</td>
</tr>
</tbody>
</table>

Time from primary surgery to start of front-line treatment, months

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>N</td>
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<td>439</td>
<td>338</td>
</tr>
<tr>
<td>Mean</td>
<td>3.8</td>
<td>4.4</td>
<td>3.0</td>
</tr>
<tr>
<td>STD</td>
<td>10.94</td>
<td>12.75</td>
<td>7.94</td>
</tr>
<tr>
<td>Median</td>
<td>1.7</td>
<td>1.7</td>
<td>1.8</td>
</tr>
<tr>
<td>25% quantile</td>
<td>1.3</td>
<td>1.3</td>
<td>1.4</td>
</tr>
<tr>
<td>75% quantile</td>
<td>2.3</td>
<td>2.3</td>
<td>2.2</td>
</tr>
<tr>
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<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Max</td>
<td>115.3</td>
<td>115.3</td>
<td>91.3</td>
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</table>

Localization of surgery

<table>
<thead>
<tr>
<th>Localization of surgery</th>
<th>CAP</th>
<th>Patients &lt;70 years</th>
<th>Patients ≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adnexa</td>
<td>624 (75.7%)</td>
<td>352 (77.7%)</td>
<td>272 (73.3%)</td>
</tr>
<tr>
<td>Appendix</td>
<td>144 (17.5%)</td>
<td>85 (18.8%)</td>
<td>59 (15.9%)</td>
</tr>
<tr>
<td>Diaphragm peritoneum</td>
<td>118 (14.3%)</td>
<td>65 (14.3%)</td>
<td>53 (14.3%)</td>
</tr>
<tr>
<td>Liver</td>
<td>42 (5.1%)</td>
<td>27 (6.0%)</td>
<td>15 (4.0%)</td>
</tr>
<tr>
<td>Lung</td>
<td>5 (0.6%)</td>
<td>2 (0.4%)</td>
<td>3 (0.8%)</td>
</tr>
<tr>
<td>Lymph node para-aortal</td>
<td>291 (35.3%)</td>
<td>185 (40.8%)</td>
<td>106 (28.6%)</td>
</tr>
<tr>
<td>Lymph node pelvin</td>
<td>300 (36.4%)</td>
<td>193 (42.6%)</td>
<td>107 (28.8%)</td>
</tr>
<tr>
<td>Omentum</td>
<td>550 (66.7%)</td>
<td>315 (69.5%)</td>
<td>235 (63.3%)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>527 (64.0%)</td>
<td>312 (68.9%)</td>
<td>215 (58.0%)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>12 (1.5%)</td>
<td>10 (2.2%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>438 (53.2%)</td>
<td>252 (55.6%)</td>
<td>186 (50.1%)</td>
</tr>
<tr>
<td>Small and large intestine</td>
<td>280 (34.0%)</td>
<td>161 (35.5%)</td>
<td>119 (32.1%)</td>
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<tr>
<td>Spleen</td>
<td>30 (3.6%)</td>
<td>20 (4.4%)</td>
<td>10 (2.7%)</td>
</tr>
<tr>
<td>Uterus</td>
<td>412 (50.0%)</td>
<td>253 (55.8%)</td>
<td>159 (42.9%)</td>
</tr>
<tr>
<td>Other</td>
<td>169 (20.5%)</td>
<td>100 (22.1%)</td>
<td>69 (18.6%)</td>
</tr>
<tr>
<td>No surgery</td>
<td>45 (5.5%)</td>
<td>13 (2.9%)</td>
<td>32 (8.6%)</td>
</tr>
</tbody>
</table>

Type of tumor, n (%)

<table>
<thead>
<tr>
<th>Type of tumor</th>
<th>CAP</th>
<th>Patients &lt;70 years</th>
<th>Patients ≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelial ovarian carcinoma</td>
<td>662 (80.3%)</td>
<td>367 (81.0%)</td>
<td>295 (79.5%)</td>
</tr>
<tr>
<td>Fallopian tube carcinoma</td>
<td>58 (7.0%)</td>
<td>27 (6.0%)</td>
<td>31 (8.4%)</td>
</tr>
<tr>
<td>Peritoneal carcinoma</td>
<td>104 (12.6%)</td>
<td>59 (13.0%)</td>
<td>45 (12.1%)</td>
</tr>
</tbody>
</table>

FIGO stage, n (%)

<table>
<thead>
<tr>
<th>FIGO stage</th>
<th>CAP</th>
<th>Patients &lt;70 years</th>
<th>Patients ≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIB</td>
<td>116 (14.1%)</td>
<td>65 (14.3%)</td>
<td>51 (13.7%)</td>
</tr>
<tr>
<td>IIIC</td>
<td>472 (57.3%)</td>
<td>265 (58.5%)</td>
<td>207 (55.8%)</td>
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<tr>
<td>IV</td>
<td>236 (28.6%)</td>
<td>123 (27.2%)</td>
<td>113 (30.5%)</td>
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Grading, n (%)

<table>
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<th>CAP</th>
<th>Patients &lt;70 years</th>
<th>Patients ≥70 years</th>
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</thead>
<tbody>
<tr>
<td>G1 – well differentiated (low grade)</td>
<td>22 (2.7%)</td>
<td>13 (2.9%)</td>
<td>9 (2.4%)</td>
</tr>
<tr>
<td>G2 – moderately differentiated (intermediate grade)</td>
<td>153 (18.6%)</td>
<td>99 (21.9%)</td>
<td>54 (14.6%)</td>
</tr>
<tr>
<td>G3 – poorly differentiated (high grade)</td>
<td>565 (68.6%)</td>
<td>312 (68.9%)</td>
<td>253 (68.2%)</td>
</tr>
<tr>
<td>G4 – undifferentiated (high grade)</td>
<td>12 (1.5%)</td>
<td>2 (0.4%)</td>
<td>10 (2.7%)</td>
</tr>
<tr>
<td>GX – grade cannot be assessed</td>
<td>72 (8.7%)</td>
<td>27 (6.0%)</td>
<td>45 (12.1%)</td>
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</table>

Histological type, n (%)
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<thead>
<tr>
<th>Parameter</th>
<th>CAP</th>
<th>Patients &lt;70 years</th>
<th>Patients ≥70 years</th>
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<tbody>
<tr>
<td>N</td>
<td>779</td>
<td>440</td>
<td>339</td>
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<tr>
<td>Clear cell</td>
<td>13</td>
<td>(1.7%)</td>
<td>9 (2.0%)</td>
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<tr>
<td>Endometroid</td>
<td>22</td>
<td>(2.8%)</td>
<td>14 (3.2%)</td>
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<td>Mucinous</td>
<td>19</td>
<td>(2.4%)</td>
<td>13 (3.0%)</td>
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<tr>
<td>Serous</td>
<td>606</td>
<td>(77.8%)</td>
<td>333 (75.7%)</td>
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<td>(3.1%)</td>
<td>13 (3.0%)</td>
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<tr>
<td>Other</td>
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<td>58 (13.2%)</td>
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### Ascites, n (%)

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<th>Patients ≥70 years</th>
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<td>N</td>
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<td>406</td>
<td>304</td>
</tr>
<tr>
<td>0 mL</td>
<td>6</td>
<td>(0.8%)</td>
<td>3 (0.7%)</td>
</tr>
<tr>
<td>&gt;0-500 mL</td>
<td>12</td>
<td>(1.7%)</td>
<td>6 (1.5%)</td>
</tr>
<tr>
<td>&gt;500 mL</td>
<td>100</td>
<td>(14.1%)</td>
<td>58 (14.3%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>592</td>
<td>(83.4%)</td>
<td>339 (83.5%)</td>
</tr>
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<td>47</td>
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### Residual disease, n (%)

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<tbody>
<tr>
<td>R0 – no residual tumor</td>
<td>229</td>
<td>(29.4%)</td>
<td>139 (31.6%)</td>
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<tr>
<td>R1 – microscopic residual tumor (≤1 cm)</td>
<td>175</td>
<td>(22.5%)</td>
<td>106 (24.1%)</td>
</tr>
<tr>
<td>R2 – macroscopic residual tumor (&gt;1 cm)</td>
<td>192</td>
<td>(24.6%)</td>
<td>99 (22.5%)</td>
</tr>
<tr>
<td>RX – the presence of residual tumor cannot be assessed</td>
<td>183</td>
<td>(23.5%)</td>
<td>96 (21.8%)</td>
</tr>
<tr>
<td>Missing</td>
<td>45</td>
<td></td>
<td>13</td>
</tr>
</tbody>
</table>

### Baseline CA125, U/ml

<table>
<thead>
<tr>
<th></th>
<th>CAP</th>
<th>Patients &lt;70 years</th>
<th>Patients ≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>736</td>
<td>421</td>
<td>315</td>
</tr>
<tr>
<td>Median</td>
<td>174</td>
<td>164</td>
<td>189</td>
</tr>
<tr>
<td>25% quantile</td>
<td>50.3</td>
<td>44.0</td>
<td>60.3</td>
</tr>
<tr>
<td>75% quantile</td>
<td>532.9</td>
<td>496.0</td>
<td>581.3</td>
</tr>
</tbody>
</table>

### Charlson Comorbidity Index

<table>
<thead>
<tr>
<th>Value</th>
<th>CAP</th>
<th>Patients &lt;70 years</th>
<th>Patients ≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>644</td>
<td>(78.2%)</td>
<td>364 (80.4%)</td>
</tr>
<tr>
<td>1</td>
<td>31</td>
<td>(3.8%)</td>
<td>14 (3.1%)</td>
</tr>
<tr>
<td>2</td>
<td>123</td>
<td>(14.9%)</td>
<td>62 (13.7%)</td>
</tr>
<tr>
<td>≥3</td>
<td>26</td>
<td>(3.2%)</td>
<td>13 (2.9%)</td>
</tr>
</tbody>
</table>

### Blood pressure at baseline

<table>
<thead>
<tr>
<th></th>
<th>CAP</th>
<th>Patients &lt;70 years</th>
<th>Patients ≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (non-missing)</td>
<td>599</td>
<td>347</td>
<td>252</td>
</tr>
<tr>
<td>Normal blood pressure</td>
<td>215</td>
<td>(35.9%)</td>
<td>131 (37.8%)</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>183</td>
<td>(30.6%)</td>
<td>109 (31.4%)</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>201</td>
<td>(33.6%)</td>
<td>107 (30.8%)</td>
</tr>
<tr>
<td>Missing</td>
<td>225</td>
<td>106</td>
<td>119</td>
</tr>
</tbody>
</table>

### Electrocardiogram at baseline

<table>
<thead>
<tr>
<th></th>
<th>CAP</th>
<th>Patients &lt;70 years</th>
<th>Patients ≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (non-missing)</td>
<td>339</td>
<td>132</td>
<td>207</td>
</tr>
<tr>
<td>Normal</td>
<td>163</td>
<td>(48.1%)</td>
<td>71 (53.8%)</td>
</tr>
<tr>
<td>Minor dysrhythmia or ST changes</td>
<td>13</td>
<td>(3.8%)</td>
<td>3 (2.3%)</td>
</tr>
<tr>
<td>Therapy-requiring dysrhythmia or ST changes</td>
<td>6</td>
<td>(1.8%)</td>
<td>2 (1.5%)</td>
</tr>
<tr>
<td>Not done</td>
<td>157</td>
<td>(46.3%)</td>
<td>56 (42.4%)</td>
</tr>
<tr>
<td>Missing</td>
<td>485</td>
<td>321</td>
<td>164</td>
</tr>
</tbody>
</table>

### Echocardiography at baseline

<table>
<thead>
<tr>
<th></th>
<th>CAP</th>
<th>Patients &lt;70 years</th>
<th>Patients ≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (non-missing)</td>
<td>339</td>
<td>132</td>
<td>207</td>
</tr>
<tr>
<td>Normal</td>
<td>95</td>
<td>(28.0%)</td>
<td>35 (26.5%)</td>
</tr>
<tr>
<td>Pathological</td>
<td>22</td>
<td>(6.5%)</td>
<td>3 (2.3%)</td>
</tr>
</tbody>
</table>
### Parameter

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CAP</th>
<th>Patients &lt;70 years</th>
<th>Patients ≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not done</td>
<td>222 (65.5%)</td>
<td>94 (71.2%)</td>
<td>128 (61.8%)</td>
</tr>
<tr>
<td>Missing</td>
<td>485</td>
<td>321</td>
<td>164</td>
</tr>
</tbody>
</table>

Doppler sonography of extracardiac vessels at baseline

<table>
<thead>
<tr>
<th>N (non-missing)</th>
<th>339</th>
<th>132</th>
<th>207</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>12 (3.5%)</td>
<td>4 (3.0%)</td>
<td>8 (3.9%)</td>
</tr>
<tr>
<td>Mild stenoses</td>
<td>2 (0.6%)</td>
<td>1 (0.8%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Not done</td>
<td>325 (95.9%)</td>
<td>127 (96.2%)</td>
<td>198 (95.7%)</td>
</tr>
<tr>
<td>Missing</td>
<td>485</td>
<td>321</td>
<td>164</td>
</tr>
</tbody>
</table>

[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)

<table>
<thead>
<tr>
<th>Weight, kg</th>
<th>CAP</th>
<th>Patients &lt;70 years</th>
<th>Patients ≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>At Baseline</td>
<td>Last documented</td>
</tr>
<tr>
<td>CAP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>802</td>
<td>824</td>
<td>824</td>
</tr>
<tr>
<td>Median</td>
<td>65.0</td>
<td>65.9</td>
<td>62.0</td>
</tr>
<tr>
<td>25% quantile</td>
<td>58.0</td>
<td>59.0</td>
<td>55.0</td>
</tr>
<tr>
<td>75% quantile</td>
<td>75.0</td>
<td>75.0</td>
<td>70.4</td>
</tr>
<tr>
<td>Patients &lt;70 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>444</td>
<td>453</td>
<td>453</td>
</tr>
<tr>
<td>Median</td>
<td>64.0</td>
<td>66.3</td>
<td>62.0</td>
</tr>
<tr>
<td>25% quantile</td>
<td>57.0</td>
<td>59.0</td>
<td>55.0</td>
</tr>
<tr>
<td>75% quantile</td>
<td>76.0</td>
<td>77.0</td>
<td>72.0</td>
</tr>
<tr>
<td>Patients ≥70 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>358</td>
<td>371</td>
<td>371</td>
</tr>
<tr>
<td>Median</td>
<td>65.0</td>
<td>65.0</td>
<td>62.0</td>
</tr>
<tr>
<td>25% quantile</td>
<td>58.9</td>
<td>58.0</td>
<td>55.0</td>
</tr>
</tbody>
</table>
In the CAP the median BMI at baseline was 24.2 kg/m² and the median of the last documented BMI was 24.8 kg/m². The median of the lowest documented BMI in the CAP was 23.3 kg/m² (Table 8-8). In the subgroup of patients <70 years the median BMI at baseline was 23.9 kg/m² and the median of the last documented BMI was 25.1 kg/m². The median of the lowest documented BMI in the subgroup of patients <70 years was 23.3 kg/m² (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/m². The median of the lowest documented BMI in the subgroup of patients ≥70 years was 23.3 kg/m² (Table 8-8).

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

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

[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

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

[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>
<thead>
<tr>
<th>Table 8-10</th>
<th>Most common concomitant diseases (&gt;1.0%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td><strong>CAP</strong></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (without end organ damage)</td>
<td>824</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>75</td>
</tr>
<tr>
<td>9.1%</td>
<td></td>
</tr>
<tr>
<td>Depression / psychological disorder</td>
<td>54</td>
</tr>
<tr>
<td>6.6%</td>
<td></td>
</tr>
<tr>
<td>Other tumor</td>
<td>48</td>
</tr>
<tr>
<td>5.8%</td>
<td></td>
</tr>
<tr>
<td>Chronic gastrointestinal disease</td>
<td>40</td>
</tr>
<tr>
<td>4.9%</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>24</td>
</tr>
<tr>
<td>2.9%</td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>22</td>
</tr>
<tr>
<td>2.7%</td>
<td></td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>22</td>
</tr>
<tr>
<td>2.7%</td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>12</td>
</tr>
<tr>
<td>1.9%</td>
<td></td>
</tr>
<tr>
<td>Mild liver disease</td>
<td>17</td>
</tr>
<tr>
<td>1.5%</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>17</td>
</tr>
<tr>
<td>1.5%</td>
<td></td>
</tr>
<tr>
<td>Other tumor</td>
<td>18</td>
</tr>
<tr>
<td>4.9%</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>17</td>
</tr>
<tr>
<td>4.9%</td>
<td></td>
</tr>
<tr>
<td>Chronic gastrointestinal disease</td>
<td>17</td>
</tr>
<tr>
<td>3.5%</td>
<td></td>
</tr>
<tr>
<td>Depression / psychological disorder</td>
<td>17</td>
</tr>
<tr>
<td>3.5%</td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>13</td>
</tr>
<tr>
<td>3.5%</td>
<td></td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>11</td>
</tr>
<tr>
<td>3.5%</td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>10</td>
</tr>
<tr>
<td>1.2%</td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>10</td>
</tr>
<tr>
<td>1.2%</td>
<td></td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>10</td>
</tr>
<tr>
<td>1.2%</td>
<td></td>
</tr>
<tr>
<td><strong>Patients &lt;70 years</strong></td>
<td></td>
</tr>
<tr>
<td>Depression / psychological disorder</td>
<td>31</td>
</tr>
<tr>
<td>6.8%</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (without end organ damage)</td>
<td>29</td>
</tr>
<tr>
<td>6.4%</td>
<td></td>
</tr>
<tr>
<td>Other tumor</td>
<td>22</td>
</tr>
<tr>
<td>4.9%</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>13</td>
</tr>
<tr>
<td>2.9%</td>
<td></td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>11</td>
</tr>
<tr>
<td>2.4%</td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>9</td>
</tr>
<tr>
<td>2.0%</td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>9</td>
</tr>
<tr>
<td>2.0%</td>
<td></td>
</tr>
<tr>
<td>Chronic gastrointestinal disease</td>
<td>9</td>
</tr>
<tr>
<td>1.5%</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>6</td>
</tr>
<tr>
<td>1.3%</td>
<td></td>
</tr>
<tr>
<td>Mild liver disease</td>
<td>5</td>
</tr>
<tr>
<td>1.1%</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>5</td>
</tr>
<tr>
<td>1.1%</td>
<td></td>
</tr>
<tr>
<td>Other tumor</td>
<td>5</td>
</tr>
<tr>
<td>1.1%</td>
<td></td>
</tr>
<tr>
<td><strong>Patients ≥70 years</strong></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (without end organ damage)</td>
<td>46</td>
</tr>
<tr>
<td>12.4%</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>41</td>
</tr>
<tr>
<td>11.1%</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>18</td>
</tr>
<tr>
<td>4.9%</td>
<td></td>
</tr>
<tr>
<td>Other tumor</td>
<td>18</td>
</tr>
<tr>
<td>4.9%</td>
<td></td>
</tr>
<tr>
<td>Chronic gastrointestinal disease</td>
<td>17</td>
</tr>
<tr>
<td>4.6%</td>
<td></td>
</tr>
<tr>
<td>Depression / psychological disorder</td>
<td>17</td>
</tr>
<tr>
<td>4.6%</td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>13</td>
</tr>
<tr>
<td>3.5%</td>
<td></td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>11</td>
</tr>
<tr>
<td>3.0%</td>
<td></td>
</tr>
<tr>
<td>Hearing loss</td>
<td>9</td>
</tr>
<tr>
<td>2.4%</td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>7</td>
</tr>
<tr>
<td>1.9%</td>
<td></td>
</tr>
<tr>
<td>Mild liver disease</td>
<td>7</td>
</tr>
<tr>
<td>1.9%</td>
<td></td>
</tr>
<tr>
<td>Moderate to severe renal disease</td>
<td>7</td>
</tr>
<tr>
<td>1.9%</td>
<td></td>
</tr>
<tr>
<td>Polyneuropathy</td>
<td>7</td>
</tr>
<tr>
<td>1.9%</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>5</td>
</tr>
<tr>
<td>1.3%</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus with end organ damage</td>
<td>5</td>
</tr>
<tr>
<td>1.3%</td>
<td></td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th></th>
<th>Age subgroup</th>
<th>Surgery subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAP</td>
<td>Patients &lt;70 years</td>
</tr>
<tr>
<td>Patients, N</td>
<td>824</td>
<td>453</td>
</tr>
<tr>
<td>Events, n [%](^2)</td>
<td>368 (44.7%)</td>
<td>200 (44.2%)</td>
</tr>
<tr>
<td>75% quantile [95% CI]</td>
<td>23.6 [22.4, 24.8]</td>
<td>23.9 [22.4, 26.3]</td>
</tr>
<tr>
<td>6-month rate [95% CI]</td>
<td>95.2% [93.4, 96.5]</td>
<td>97.2% [95.1, 98.4]</td>
</tr>
<tr>
<td>12-month rate [95% CI]</td>
<td>79.5% [76.4, 82.3]</td>
<td>80.2% [75.9, 83.9]</td>
</tr>
<tr>
<td>18-month rate [95% CI]</td>
<td>57.5% [52.9, 61.8]</td>
<td>60.1% [54.0, 65.7]</td>
</tr>
</tbody>
</table>

\[\text{Source: OTILIA_Tables_Final_4_20200420: Table 14.2.1}\].

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.
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.
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.
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.

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

<table>
<thead>
<tr>
<th>ECOG performance status group</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1 vs. 0-1</td>
<td>1.05</td>
<td>[0.75, 1.49]</td>
<td>0.763</td>
</tr>
<tr>
<td>Unknown vs. 0-1</td>
<td>1.10</td>
<td>[0.69, 1.75]</td>
<td>0.700</td>
</tr>
</tbody>
</table>

**Body mass index group**

| ≤ 20 vs. > 20-25                    | 1.06         | [0.76, 1.49] | 0.718   |
### Hazard ratio

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

[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

<table>
<thead>
<tr>
<th></th>
<th>Age subgroup</th>
<th>Surgery subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAP</td>
<td>Patients &lt;70 years</td>
</tr>
<tr>
<td>Patients, N</td>
<td>824</td>
<td>453</td>
</tr>
<tr>
<td>Best response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (non-missing)</td>
<td>707</td>
<td>392</td>
</tr>
<tr>
<td>CR</td>
<td>307 (43.4%)</td>
<td>195 (49.7%)</td>
</tr>
<tr>
<td>PR</td>
<td>203 (28.7%)</td>
<td>106 (27.0%)</td>
</tr>
<tr>
<td>ORR</td>
<td>510 (72.1%)</td>
<td>301 (76.8%)</td>
</tr>
<tr>
<td>SD</td>
<td>153 (21.6%)</td>
<td>66 (16.8%)</td>
</tr>
<tr>
<td>PD</td>
<td>27 (3.8%)</td>
<td>16 (4.1%)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>17 (2.4%)</td>
<td>9 (2.3%)</td>
</tr>
<tr>
<td>Missing</td>
<td>117</td>
<td>61</td>
</tr>
</tbody>
</table>

[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)

<table>
<thead>
<tr>
<th>Age subgroup</th>
<th>Surgery subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP</td>
<td>Patients &lt;70 years</td>
</tr>
<tr>
<td>Patients, N</td>
<td>824</td>
</tr>
<tr>
<td>Events, n (%)</td>
<td>181 (22.0%)</td>
</tr>
<tr>
<td>75% quantile [95% CI]</td>
<td>31.5 [27.8, 47.0]</td>
</tr>
<tr>
<td>12-month rate [95%-CI]</td>
<td>91.1% [88.7, 93.0]</td>
</tr>
<tr>
<td>18-month rate [95%-CI]</td>
<td>78.5% [74.4, 82.1]</td>
</tr>
<tr>
<td>24-month rate [95%-CI]</td>
<td>53.3% [46.1, 59.8]</td>
</tr>
</tbody>
</table>

[Source: OTILIA_Tables_Final_4_20200420; Table 14.2].

CAP = Core analysis population; CI = Confidence interval; N/n = Number; NA = Not reached.

Overall survival was estimated using the Kaplan-Meier method. Due to the low number of events the present OS data are no reliable estimators.
Overall survival was estimated using the Kaplan-Meier method. Due to the low number of events the present OS data are no reliable estimators.
Overall survival was estimated using the Kaplan-Meier method. Due to the low number of events the present OS data are no reliable estimators.

[Source: OTILIA_Figures_Final_3_20200127: Figure 2.2.2].
CI = Confidence interval; N/n = Number; OS = Overall survival.
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

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

[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**

<table>
<thead>
<tr>
<th>Therapy Decision – Institution, n (%)</th>
<th>CAP (N=824)</th>
<th>Patients &lt;70 years (N=453)</th>
<th>Patients ≥70 years (N=371)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic physician</td>
<td>52 (6.3%)</td>
<td>27 (6.0%)</td>
<td>25 (6.7%)</td>
</tr>
<tr>
<td>Gynecologist</td>
<td>76 (9.2%)</td>
<td>42 (9.3%)</td>
<td>34 (9.2%)</td>
</tr>
<tr>
<td>NIO</td>
<td>80 (9.7%)</td>
<td>48 (10.6%)</td>
<td>32 (8.6%)</td>
</tr>
<tr>
<td>Oncologic consultation</td>
<td>49 (5.9%)</td>
<td>28 (6.2%)</td>
<td>21 (5.7%)</td>
</tr>
<tr>
<td>Tumor board</td>
<td>561 (68.1%)</td>
<td>305 (67.3%)</td>
<td>256 (69.0%)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (0.7%)</td>
<td>3 (0.7%)</td>
<td>3 (0.8%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Therapy Decision - Decisive factors, n (%)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of patient</td>
<td>214 (26.0%)</td>
<td>120 (26.5%)</td>
<td>94 (25.3%)</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>52 (6.3%)</td>
<td>24 (5.3%)</td>
<td>28 (7.5%)</td>
</tr>
<tr>
<td>Concomitant medication</td>
<td>18 (2.2%)</td>
<td>6 (1.3%)</td>
<td>12 (3.2%)</td>
</tr>
<tr>
<td>Distance clinic to home</td>
<td>21 (2.5%)</td>
<td>9 (2.0%)</td>
<td>12 (3.2%)</td>
</tr>
<tr>
<td>Efficacy of therapy</td>
<td>571 (69.3%)</td>
<td>320 (70.6%)</td>
<td>251 (67.7%)</td>
</tr>
<tr>
<td>General condition of patient</td>
<td>246 (29.9%)</td>
<td>133 (29.4%)</td>
<td>113 (30.5%)</td>
</tr>
<tr>
<td>Guideline</td>
<td>695 (84.3%)</td>
<td>381 (84.1%)</td>
<td>314 (84.6%)</td>
</tr>
<tr>
<td>Patient wish</td>
<td>86 (10.4%)</td>
<td>41 (9.1%)</td>
<td>45 (12.1%)</td>
</tr>
<tr>
<td>Study results</td>
<td>404 (49.0%)</td>
<td>236 (52.1%)</td>
<td>168 (45.3%)</td>
</tr>
<tr>
<td>Tolerability of therapy</td>
<td>265 (32.2%)</td>
<td>130 (28.7%)</td>
<td>135 (36.4%)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (0.7%)</td>
<td>1 (0.2%)</td>
<td>5 (1.3%)</td>
</tr>
</tbody>
</table>

[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

<table>
<thead>
<tr>
<th></th>
<th>Age subgroup</th>
<th>Surgery subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAP</td>
<td>Patients &lt;70 years</td>
</tr>
<tr>
<td><strong>Patients, N</strong></td>
<td>824</td>
<td>453</td>
</tr>
<tr>
<td><strong>Events, n (%)</strong></td>
<td>453 (55.0%)</td>
<td>227 (50.1%)</td>
</tr>
<tr>
<td>25% quantile [95% CI]</td>
<td>6.7 [5.7, 7.8]</td>
<td>7.9 [6.4, 9.1]</td>
</tr>
</tbody>
</table>

[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>
<thead>
<tr>
<th></th>
<th>CAP</th>
<th>Patients &lt;70 years</th>
<th>Patients ≥70 years</th>
<th>No prior surgery</th>
<th>Prior surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, N</td>
<td>824</td>
<td>453</td>
<td>371</td>
<td>45</td>
<td>779</td>
</tr>
<tr>
<td>Mean</td>
<td>3.4</td>
<td>3.4</td>
<td>3.4</td>
<td>3.2</td>
<td>3.4</td>
</tr>
<tr>
<td>StD</td>
<td>1.47</td>
<td>1.32</td>
<td>1.64</td>
<td>0.99</td>
<td>1.50</td>
</tr>
<tr>
<td>Median</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>25% quantile</td>
<td>3.0</td>
<td>3.4</td>
<td>2.9</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>75% quantile</td>
<td>3.7</td>
<td>3.7</td>
<td>3.7</td>
<td>3.7</td>
<td>3.7</td>
</tr>
<tr>
<td>Min</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Max</td>
<td>17.7</td>
<td>15.5</td>
<td>17.7</td>
<td>4.9</td>
<td>17.7</td>
</tr>
</tbody>
</table>

[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)

<table>
<thead>
<tr>
<th></th>
<th>Age subgroup</th>
<th>Surgery subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAP</td>
<td>Patients &lt;70 years</td>
</tr>
<tr>
<td>Patients, N</td>
<td>824</td>
<td>453</td>
</tr>
<tr>
<td>Mean</td>
<td>3.2</td>
<td>3.3</td>
</tr>
<tr>
<td>StD</td>
<td>1.08</td>
<td>1.01</td>
</tr>
<tr>
<td>Median</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>25% quantile</td>
<td>2.8</td>
<td>3.0</td>
</tr>
<tr>
<td>75% quantile</td>
<td>3.6</td>
<td>3.7</td>
</tr>
<tr>
<td>Min</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Max</td>
<td>14.1</td>
<td>12.7</td>
</tr>
</tbody>
</table>

[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>
<thead>
<tr>
<th>Age subgroup</th>
<th>Surgery subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP</td>
<td>Patients &lt;70 years</td>
</tr>
<tr>
<td>Patients, N</td>
<td>824</td>
</tr>
<tr>
<td>Events, n (%)</td>
<td>453 (55.0%)</td>
</tr>
<tr>
<td>25% quantile [95% CI]</td>
<td>7.5 [ 6.2, 8.3]</td>
</tr>
</tbody>
</table>

[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>
<thead>
<tr>
<th></th>
<th>Age subgroup</th>
<th>Surgery subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAP</td>
<td>Patients &lt;70 years</td>
</tr>
<tr>
<td>Patients, N</td>
<td>824</td>
<td>453</td>
</tr>
<tr>
<td>n applications</td>
<td>12,431</td>
<td>7,153</td>
</tr>
<tr>
<td>Mean</td>
<td>15.1</td>
<td>15.8</td>
</tr>
<tr>
<td>Std</td>
<td>6.96</td>
<td>6.67</td>
</tr>
<tr>
<td>Median</td>
<td>18.0</td>
<td>19.0</td>
</tr>
<tr>
<td>25% quantile</td>
<td>9.0</td>
<td>11.0</td>
</tr>
<tr>
<td>75% quantile</td>
<td>21.0</td>
<td>21.0</td>
</tr>
<tr>
<td>Min</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Max</td>
<td>25.0</td>
<td>25.0</td>
</tr>
</tbody>
</table>

[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>
<thead>
<tr>
<th></th>
<th>Age subgroup</th>
<th>Surgery subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAP</td>
<td>Patients &lt;70 years</td>
</tr>
<tr>
<td>Patients, N</td>
<td>824</td>
<td>453</td>
</tr>
<tr>
<td>n applications</td>
<td>12,431</td>
<td>7,153</td>
</tr>
<tr>
<td>Mean</td>
<td>224.0</td>
<td>235.1</td>
</tr>
<tr>
<td>Std</td>
<td>103.52</td>
<td>99.48</td>
</tr>
<tr>
<td>Median</td>
<td>267.1</td>
<td>284.7</td>
</tr>
<tr>
<td>25% quantile</td>
<td>135.9</td>
<td>157.8</td>
</tr>
<tr>
<td>75% quantile</td>
<td>314.0</td>
<td>314.7</td>
</tr>
<tr>
<td>Min</td>
<td>14.7</td>
<td>14.8</td>
</tr>
<tr>
<td>Max</td>
<td>381.5</td>
<td>381.5</td>
</tr>
</tbody>
</table>

[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)

<table>
<thead>
<tr>
<th></th>
<th>Age subgroup</th>
<th>Surgery subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAP</td>
<td>Patients &lt;70 years</td>
</tr>
<tr>
<td>Patients, N</td>
<td>824</td>
<td>453</td>
</tr>
<tr>
<td>n applications</td>
<td>4,656</td>
<td>2,552</td>
</tr>
<tr>
<td>Mean</td>
<td>38.3</td>
<td>46.4</td>
</tr>
<tr>
<td>STD</td>
<td>155.13</td>
<td>207.15</td>
</tr>
<tr>
<td>Median</td>
<td>30.0</td>
<td>30.0</td>
</tr>
<tr>
<td>25% quantile</td>
<td>25.0</td>
<td>25.0</td>
</tr>
<tr>
<td>75% quantile</td>
<td>30.0</td>
<td>30.0</td>
</tr>
<tr>
<td>Min</td>
<td>4.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Max</td>
<td>2,893.0</td>
<td>2,893.0</td>
</tr>
</tbody>
</table>

[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/m² (120.0 – 1,575.0 mg/m²) (Table 8-24).

In both age subgroups of patients <70 and ≥70 years the median total dose of paclitaxel was 1,050.0 mg/m² (122.0 – 1,575.0 mg/m² and 120.0 – 1,440.0 mg/m²) (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/m² (175.0 – 1,200.0 mg/m² and 120.0 – 1,575.0 mg/m²) (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>
<thead>
<tr>
<th></th>
<th>Age subgroup</th>
<th>Surgery subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAP</td>
<td>Patients &lt;70 years</td>
</tr>
<tr>
<td>Patients, N</td>
<td>824</td>
<td>453</td>
</tr>
<tr>
<td>n applications</td>
<td>4,546</td>
<td>2,550</td>
</tr>
<tr>
<td>Mean</td>
<td>919.4</td>
<td>955.3</td>
</tr>
<tr>
<td>Std</td>
<td>231.21</td>
<td>209.18</td>
</tr>
<tr>
<td>Median</td>
<td>1,050.0</td>
<td>1,050.0</td>
</tr>
<tr>
<td>25% quantile</td>
<td>875.0</td>
<td>875.0</td>
</tr>
<tr>
<td>75% quantile</td>
<td>1,050.0</td>
<td>1,050.0</td>
</tr>
<tr>
<td>Min</td>
<td>120.0</td>
<td>122.0</td>
</tr>
<tr>
<td>Max</td>
<td>1,575.0</td>
<td>1,575.0</td>
</tr>
</tbody>
</table>

[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)

<table>
<thead>
<tr>
<th></th>
<th>CAP</th>
<th>Patients &lt;70 years</th>
<th>Patients ≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>824</td>
<td>453</td>
<td>371</td>
</tr>
<tr>
<td>n applications</td>
<td>12,431</td>
<td>7,153</td>
<td>5,278</td>
</tr>
<tr>
<td>Mean</td>
<td>8.4</td>
<td>7.8</td>
<td>9.2</td>
</tr>
<tr>
<td>StdD</td>
<td>17.80</td>
<td>16.12</td>
<td>19.65</td>
</tr>
<tr>
<td>Median</td>
<td>5.1</td>
<td>5.1</td>
<td>5.1</td>
</tr>
<tr>
<td>25% quantile</td>
<td>4.8</td>
<td>4.8</td>
<td>4.7</td>
</tr>
<tr>
<td>75% quantile</td>
<td>5.4</td>
<td>5.3</td>
<td>5.5</td>
</tr>
<tr>
<td>Min</td>
<td>2.3</td>
<td>2.3</td>
<td>2.4</td>
</tr>
<tr>
<td>Max¹</td>
<td>108.1</td>
<td>108.1</td>
<td>106.8</td>
</tr>
</tbody>
</table>

[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.
¹Maximum 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

<table>
<thead>
<tr>
<th>Any treatment modification</th>
<th>CAP (N=824)</th>
<th>Patients &lt;70 years (N=453)</th>
<th>Patients ≥70 years (N=371)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any treatment modification bevacizumab (Avastin®)</td>
<td>653 (79.2%)</td>
<td>361 (79.7%)</td>
<td>292 (78.7%)</td>
</tr>
<tr>
<td>Any treatment modification carboplatin</td>
<td>354 (43.0%)</td>
<td>186 (41.1%)</td>
<td>168 (45.3%)</td>
</tr>
<tr>
<td>Any treatment modification paclitaxel</td>
<td>387 (47.0%)</td>
<td>192 (42.4%)</td>
<td>195 (52.6%)</td>
</tr>
</tbody>
</table>

[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®)\(^1\)

<table>
<thead>
<tr>
<th>Kind of treatment modification</th>
<th>CAP (N=824)</th>
<th>Patients &lt;70 years (N=453)</th>
<th>Patients ≥70 years (N=371)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose increase</td>
<td>50 (6.1%)</td>
<td>32 (7.1%)</td>
<td>18 (4.9%)</td>
</tr>
<tr>
<td>Dose reduction</td>
<td>57 (6.9%)</td>
<td>22 (4.9%)</td>
<td>35 (9.4%)</td>
</tr>
<tr>
<td>Therapy delay(^2)</td>
<td>227 (27.5%)</td>
<td>122 (26.9%)</td>
<td>105 (28.3%)</td>
</tr>
<tr>
<td>Therapy interruption(^2)</td>
<td>556 (67.5%)</td>
<td>303 (66.9%)</td>
<td>253 (68.2%)</td>
</tr>
</tbody>
</table>

[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®)

<table>
<thead>
<tr>
<th>Reason for Treatment Modification</th>
<th>CAP (N=824)</th>
<th>Patients &lt;70 years (N=453)</th>
<th>Patients ≥70 years (N=371)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient’s wish</td>
<td>148 (18.0%)</td>
<td>81 (17.9%)</td>
<td>67 (18.1%)</td>
</tr>
<tr>
<td>Physician decision</td>
<td>590 (71.6%)</td>
<td>328 (72.4%)</td>
<td>262 (70.6%)</td>
</tr>
<tr>
<td>Toxicity</td>
<td>110 (13.3%)</td>
<td>55 (12.1%)</td>
<td>55 (14.8%)</td>
</tr>
<tr>
<td>Visit created by mistake</td>
<td>21 (2.5%)</td>
<td>8 (1.8%)</td>
<td>13 (3.5%)</td>
</tr>
</tbody>
</table>

[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

<table>
<thead>
<tr>
<th>Kind of Treatment Modification</th>
<th>CAP (N=824)</th>
<th>Patients &lt;70 years (N=453)</th>
<th>Patients ≥70 years (N=371)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose increase</td>
<td>31 (3.8%)</td>
<td>22 (4.9%)</td>
<td>9 (2.4%)</td>
</tr>
<tr>
<td>Dose reduction</td>
<td>98 (11.9%)</td>
<td>45 (9.9%)</td>
<td>53 (14.3%)</td>
</tr>
<tr>
<td>Therapy delay²</td>
<td>124 (15.0%)</td>
<td>66 (14.6%)</td>
<td>58 (15.6%)</td>
</tr>
<tr>
<td>Therapy interruption²</td>
<td>198 (24.0%)</td>
<td>109 (24.1%)</td>
<td>89 (24.0%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[Source: OTILIA_Tables_Final_3_20200122: Table 14.2.20a; Table 14.2.20b].
CAP = Core analysis population; N/n = Number.
²Multiple observations provided. ²There 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>
<thead>
<tr>
<th>Reason for treatment modification of carboplatin</th>
<th>CAP (N=824)</th>
<th>Patients &lt;70 years (N=453)</th>
<th>Patients ≥70 years (N=371)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient’s wish</td>
<td>46 (5.6%)</td>
<td>22 (4.9%)</td>
<td>24 (6.5%)</td>
</tr>
<tr>
<td>Physician decision</td>
<td>253 (30.7%)</td>
<td>141 (31.1%)</td>
<td>112 (30.2%)</td>
</tr>
<tr>
<td>Toxicity</td>
<td>100 (12.1%)</td>
<td>50 (11.0%)</td>
<td>50 (13.5%)</td>
</tr>
<tr>
<td>Visit created by mistake</td>
<td>9 (1.1%)</td>
<td>2 (0.4%)</td>
<td>7 (1.9%)</td>
</tr>
</tbody>
</table>

[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>
<thead>
<tr>
<th>Kind of treatment modification of paclitaxel1</th>
<th>CAP (N=824)</th>
<th>Patients &lt;70 years (N=453)</th>
<th>Patients ≥70 years (N=371)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose increase</td>
<td>12 (1.5%)</td>
<td>7 (1.5%)</td>
<td>5 (1.3%)</td>
</tr>
<tr>
<td>Dose reduction</td>
<td>110 (13.3%)</td>
<td>43 (9.5%)</td>
<td>67 (18.1%)</td>
</tr>
<tr>
<td>Therapy delay2</td>
<td>112 (13.6%)</td>
<td>62 (13.7%)</td>
<td>50 (13.5%)</td>
</tr>
<tr>
<td>Therapy interruption2</td>
<td>246 (29.9%)</td>
<td>122 (26.9%)</td>
<td>124 (33.4%)</td>
</tr>
</tbody>
</table>

[Source: OTILIA_Tables_Final_4_20200420: Table 14.2.21a; Table 14.2.21b].
CAP = Core analysis population; N/n = Number.
1Multiple observations provided. 2There 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

<table>
<thead>
<tr>
<th>Reason for Treatment Modification</th>
<th>CAP (N=824)</th>
<th>Patients &lt;70 years (N=453)</th>
<th>Patients ≥70 years (N=371)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient’s wish</td>
<td>44 (5.3%)</td>
<td>21 (4.6%)</td>
<td>23 (6.2%)</td>
</tr>
<tr>
<td>Physician decision</td>
<td>258 (31.3%)</td>
<td>138 (30.5%)</td>
<td>120 (32.3%)</td>
</tr>
<tr>
<td>Toxicity</td>
<td>141 (17.1%)</td>
<td>59 (13.0%)</td>
<td>82 (22.1%)</td>
</tr>
<tr>
<td>Visit created by mistake</td>
<td>8 (1.0%)</td>
<td>2 (0.4%)</td>
<td>6 (1.6%)</td>
</tr>
</tbody>
</table>

[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

<table>
<thead>
<tr>
<th>Reasons for end of treatment documentation (n, %)</th>
<th>Total (N=824)</th>
<th>Patients &lt;70 years (N=453)</th>
<th>Patients ≥70 years (N=371)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>824</td>
<td>453</td>
<td>371</td>
</tr>
<tr>
<td>AE not related to therapy¹</td>
<td>25 (3.0)</td>
<td>8 (1.8)</td>
<td>17 (4.6)</td>
</tr>
<tr>
<td>AE related to therapy¹</td>
<td>40 (4.9)</td>
<td>11 (2.4)</td>
<td>29 (7.8)</td>
</tr>
<tr>
<td>Adverse event¹</td>
<td>44 (5.3)</td>
<td>30 (6.6)</td>
<td>14 (3.8)</td>
</tr>
<tr>
<td>Death</td>
<td>16 (1.9)</td>
<td>5 (1.1)</td>
<td>11 (3.0)</td>
</tr>
<tr>
<td>End of documentation after 15 months</td>
<td>349 (42.4)</td>
<td>213 (47.0)</td>
<td>136 (36.7)</td>
</tr>
<tr>
<td>Lost-to-Follow-up</td>
<td>15 (1.8)</td>
<td>10 (2.2)</td>
<td>5 (1.3)</td>
</tr>
</tbody>
</table>
Clinical Study Report Number 1100702, Final Version 1.0
Protocol ML27765 / P0229

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

[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

<table>
<thead>
<tr>
<th></th>
<th>CAP (N=824)</th>
<th>Patients &lt;70 years (N=453)</th>
<th>Patients ≥70 years (N=371)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (non-missing)</td>
<td>822</td>
<td>451</td>
<td>371</td>
</tr>
<tr>
<td>Yes</td>
<td>7 (0.9%)</td>
<td>5 (1.1%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>No</td>
<td>802 (97.6%)</td>
<td>441 (97.8%)</td>
<td>361 (97.3%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>13 (1.6%)</td>
<td>5 (1.1%)</td>
<td>8 (2.2%)</td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

[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

<table>
<thead>
<tr>
<th></th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP</td>
<td>493</td>
</tr>
<tr>
<td>Patients &lt;70 years</td>
<td>360</td>
</tr>
<tr>
<td>Patients ≥70 years</td>
<td>133</td>
</tr>
</tbody>
</table>

[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

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 weeks</th>
<th>24 weeks</th>
<th>39 weeks</th>
<th>66 weeks</th>
<th>Early discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP (N=493)</td>
<td>405</td>
<td>394</td>
<td>365</td>
<td>327</td>
<td>258</td>
<td>35</td>
</tr>
<tr>
<td>Patients &lt;70 years (N=360)</td>
<td>(64.6%)</td>
<td>(62.8%)</td>
<td>(58.2%)</td>
<td>(52.2%)</td>
<td>(41.1%)</td>
<td>(5.6%)</td>
</tr>
<tr>
<td>Patients ≥70 years (N=133)</td>
<td>308</td>
<td>301</td>
<td>283</td>
<td>249</td>
<td>199</td>
<td>26</td>
</tr>
<tr>
<td>Patients ≥70 years (N=133)</td>
<td>(58.3%)</td>
<td>(66.7%)</td>
<td>(62.7%)</td>
<td>(55.2%)</td>
<td>(44.1%)</td>
<td>(5.8%)</td>
</tr>
<tr>
<td>Patients &lt;70 years (N=360)</td>
<td>97</td>
<td>93</td>
<td>82</td>
<td>78</td>
<td>59</td>
<td>9</td>
</tr>
<tr>
<td>Patients ≥70 years (N=133)</td>
<td>(55.1%)</td>
<td>(52.8%)</td>
<td>(46.6%)</td>
<td>(44.3%)</td>
<td>(33.5%)</td>
<td>(5.1%)</td>
</tr>
</tbody>
</table>

[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.
EORTC QLQ-C30: Change from baseline in Global health status (mean) - Age subgroups

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

<table>
<thead>
<tr>
<th></th>
<th>12 weeks</th>
<th>24 weeks</th>
<th>39 weeks</th>
<th>66 weeks</th>
<th>Early discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP (N=493)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>353</td>
<td>327</td>
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<td>231</td>
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<tr>
<td>Mean</td>
<td>1.4</td>
<td>10.3</td>
<td>11.8</td>
<td>11.0</td>
<td>5.9</td>
</tr>
<tr>
<td>Std</td>
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<td>24.68</td>
<td>25.41</td>
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<tr>
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<td>8.3</td>
<td>8.3</td>
<td>8.3</td>
</tr>
<tr>
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<td>0.0</td>
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<tr>
<td>75% quantile</td>
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</tr>
<tr>
<td>Min</td>
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<tr>
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<td>83.3</td>
<td>83.3</td>
<td>66.7</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>271</td>
<td>257</td>
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<td>178</td>
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<td>Mean</td>
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<td>5.8</td>
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<tr>
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<tr>
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<td>83.3</td>
<td>83.3</td>
<td>83.3</td>
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</table>
Patients ≥70 years (N=133)  

<table>
<thead>
<tr>
<th></th>
<th>12 weeks</th>
<th>24 weeks</th>
<th>39 weeks</th>
<th>66 weeks</th>
<th>Early discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
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<tr>
<td>75% quantile</td>
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<td>37.5</td>
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<tr>
<td>Min</td>
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<tr>
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<td>66.7</td>
<td>83.3</td>
<td>66.7</td>
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[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 score 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**

![Graph showing change in nausea and vomiting](image)

[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 score 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**

<table>
<thead>
<tr>
<th></th>
<th>12 weeks</th>
<th>24 weeks</th>
<th>39 weeks</th>
<th>66 weeks</th>
<th>Early discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CAP (N=493)</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>N</td>
<td>355</td>
<td>329</td>
<td>291</td>
<td>232</td>
<td>31</td>
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<td>Mean</td>
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</tr>
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<td>25% quantile</td>
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<td>-16.7</td>
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<td>0.0</td>
<td>0.0</td>
<td>16.7</td>
</tr>
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<td>Min</td>
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<td>-100.0</td>
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<td>-83.3</td>
</tr>
<tr>
<td>Max</td>
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<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>50.0</td>
</tr>
<tr>
<td><strong>Patients &lt;70 years (N=360)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>274</td>
<td>258</td>
<td>225</td>
<td>180</td>
<td>23</td>
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<tr>
<td>Mean</td>
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<td>2.9</td>
</tr>
<tr>
<td>Std</td>
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</tr>
<tr>
<td>25% quantile</td>
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<td>-16.7</td>
<td>-16.7</td>
<td>-16.7</td>
</tr>
<tr>
<td></td>
<td>12 weeks</td>
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<td>39 weeks</td>
<td>66 weeks</td>
<td>Early discontinuation</td>
</tr>
<tr>
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<tr>
<td>75% quantile</td>
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<td>16.7</td>
</tr>
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<td>-33.3</td>
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<tr>
<td>Max</td>
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<td>100.0</td>
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<td>100.0</td>
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</tr>
</tbody>
</table>

Patients ≥70 years (N=133)

<p>| | | | | | |</p>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>81</td>
<td>71</td>
<td>66</td>
<td>52</td>
<td>8</td>
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<td>-16.9</td>
<td>-15.9</td>
<td>-21.5</td>
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</tr>
<tr>
<td>StD</td>
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<td>28.10</td>
<td>33.26</td>
<td>25.21</td>
<td>40.27</td>
</tr>
<tr>
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<td>0.0</td>
<td>0.0</td>
<td>-16.7</td>
<td>8.3</td>
</tr>
<tr>
<td>25% quantile</td>
<td>-16.7</td>
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<tr>
<td>75% quantile</td>
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<td>25.0</td>
</tr>
<tr>
<td>Min</td>
<td>-100.0</td>
<td>-100.0</td>
<td>-100.0</td>
<td>-83.3</td>
<td>-83.3</td>
</tr>
<tr>
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<td>33.3</td>
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<td>16.7</td>
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</tbody>
</table>

[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 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

![Figure 8-12](image)

[Source: OTILIA_Figures_Final_3_20200127: Figure 14.2.5].
CAP = Core analysis population; EORTC = European Organisation for Research and Treatment of Cancer; QLQ = Quality of life questionnaire.
A high score 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

![Figure 8-13](image)

[Source: OTILIA_Figures_Final_3_20200127: Figure 14.2.5a].
EORTC = European Organisation for Research and Treatment of Cancer; QLQ = Quality of life questionnaire.
A high score for a symptom scale/item represents a high level of symptomatology/problems.
### Table 8-39  EORTC QLQ-C30: Change from baseline in Appetite loss

<table>
<thead>
<tr>
<th></th>
<th>12 weeks</th>
<th>24 weeks</th>
<th>39 weeks</th>
<th>66 weeks</th>
<th>Early discontinuation</th>
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<tr>
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<td></td>
<td></td>
</tr>
<tr>
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<td>355</td>
<td>328</td>
<td>290</td>
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<td>Mean</td>
<td>-5.6</td>
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<tr>
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[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 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

![Graph showing change in constipation from baseline.](image)

*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 score 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

![Graph showing change in constipation from baseline for age subgroups.](image)

*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 score for a symptom scale/item represents a high level of symptomatology/problems.
Table 8-40  EORTC QLQ-C30: Change from baseline in constipation

<table>
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<tr>
<th></th>
<th>12 weeks</th>
<th>24 weeks</th>
<th>39 weeks</th>
<th>66 weeks</th>
<th>Early discontinuation</th>
</tr>
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<tbody>
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<td></td>
<td></td>
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[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 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

![Graph showing change from baseline in Peripheral neuropathy (mean) for CAP](image)

[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 score 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

![Graph showing change from baseline in Peripheral neuropathy (mean) for age subgroups](image)

[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 score for a symptom scale/item represents a high level of symptomatology/problems.
Table 8-41   EORTC QLQ-OV28: Change from baseline in peripheral neuropathy

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<th>66 weeks</th>
<th>Early discontinuation</th>
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<td></td>
<td></td>
</tr>
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<td>30</td>
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<td>32.5</td>
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<td>66.7</td>
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</tr>
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<td></td>
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<td>33.3</td>
<td>16.7</td>
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[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 score 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

A high score 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

A high score 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 14.2.6].
CAP = Core analysis population; EORTC = European Organisation for Research and Treatment of Cancer; QLQ = Quality of life questionnaire.
A high score 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 14.2.8a].
EORTC = European Organisation for Research and Treatment of Cancer; QLQ = Quality of life questionnaire.
A high score 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**

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<th>66 weeks</th>
<th>Early discontinuation</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>350</td>
<td>324</td>
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<td>230</td>
<td>28</td>
</tr>
<tr>
<td>Mean</td>
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<td>-8.1</td>
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<td>Std</td>
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<th>12 weeks</th>
<th>24 weeks</th>
<th>39 weeks</th>
<th>66 weeks</th>
<th>Early discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>78</td>
<td>68</td>
<td>63</td>
<td>50</td>
<td>6</td>
</tr>
<tr>
<td>Mean</td>
<td>23.5</td>
<td>-3.9</td>
<td>-10.6</td>
<td>-6.0</td>
<td>-22.2</td>
</tr>
<tr>
<td>Std</td>
<td>40.60</td>
<td>41.74</td>
<td>42.68</td>
<td>48.88</td>
<td>45.54</td>
</tr>
<tr>
<td>Median</td>
<td>16.7</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>-33.3</td>
</tr>
<tr>
<td>25% quantile</td>
<td>0.0</td>
<td>-33.3</td>
<td>-33.3</td>
<td>-33.3</td>
<td>-66.7</td>
</tr>
<tr>
<td>75% quantile</td>
<td>33.3</td>
<td>33.3</td>
<td>0.0</td>
<td>33.3</td>
<td>33.3</td>
</tr>
<tr>
<td>Min</td>
<td>-66.7</td>
<td>-100.0</td>
<td>-100.0</td>
<td>-100.0</td>
<td>-66.7</td>
</tr>
<tr>
<td>Max</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>33.3</td>
</tr>
</tbody>
</table>

[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 score 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...

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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

<table>
<thead>
<tr>
<th>Therapy satisfaction</th>
<th>CAP</th>
<th>Patients &lt;70 years</th>
<th>Patients ≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (non-missing)</td>
<td>792</td>
<td>440</td>
<td>352</td>
</tr>
<tr>
<td>Excellent</td>
<td>32</td>
<td>(4.0%)</td>
<td>19 (4.3%)</td>
</tr>
<tr>
<td>Very good</td>
<td>201</td>
<td>(25.4%)</td>
<td>117 (26.6%)</td>
</tr>
<tr>
<td>Good</td>
<td>390</td>
<td>(49.2%)</td>
<td>217 (49.3%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>145</td>
<td>(18.3%)</td>
<td>73 (16.6%)</td>
</tr>
<tr>
<td>Poor</td>
<td>24</td>
<td>(3.0%)</td>
<td>14 (3.2%)</td>
</tr>
<tr>
<td>Missing</td>
<td>32</td>
<td>13</td>
<td>19</td>
</tr>
</tbody>
</table>

**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                 |
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

<table>
<thead>
<tr>
<th>Medication</th>
<th>CAP</th>
<th>Patients &lt;70 years</th>
<th>Patients ≥70 years</th>
<th>No prior surgery</th>
<th>Prior surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab (Avastin®)</td>
<td>67</td>
<td>(8.1%)</td>
<td>45 (9.9%)</td>
<td>22 (5.9%)</td>
<td>3 (6.7%)</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>153</td>
<td>(18.6%)</td>
<td>86 (19.0%)</td>
<td>67 (18.1%)</td>
<td>10 (22.2%)</td>
</tr>
<tr>
<td>Carboplatin/Docetaxel/Trastuzumab</td>
<td>1</td>
<td>(0.1%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Carboplatin/Doxorubicin</td>
<td>5</td>
<td>(0.6%)</td>
<td>1 (0.2%)</td>
<td>4 (1.1%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Carboplatin/Gemcitabine</td>
<td>14</td>
<td>(1.7%)</td>
<td>10 (2.2%)</td>
<td>4 (1.1%)</td>
<td>3 (6.7%)</td>
</tr>
<tr>
<td>Carboplatin/Paclitaxel</td>
<td>7</td>
<td>(0.8%)</td>
<td>5 (1.1%)</td>
<td>2 (0.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>9</td>
<td>(1.1%)</td>
<td>8 (1.8%)</td>
<td>1 (0.3%)</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Cisplatin/Gemcitabine</td>
<td>1</td>
<td>(0.1%)</td>
<td>1 (0.2%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Cyclophosphamidide</td>
<td>3</td>
<td>(0.4%)</td>
<td>3 (0.7%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>1</td>
<td>(0.1%)</td>
<td>1 (0.2%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>4</td>
<td>(0.5%)</td>
<td>2 (0.4%)</td>
<td>2 (0.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>121</td>
<td>(14.7%)</td>
<td>69 (15.2%)</td>
<td>52 (14.0%)</td>
<td>10 (22.2%)</td>
</tr>
<tr>
<td>Etoposide</td>
<td>1</td>
<td>(0.1%)</td>
<td>1 (0.2%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Extern, Substanz Unbekannt</td>
<td>1</td>
<td>(0.1%)</td>
<td>0 (0.0%)</td>
<td>1 (0.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Farletuzumab</td>
<td>1</td>
<td>(0.1%)</td>
<td>1 (0.2%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>(0.1%)</td>
<td>1 (0.2%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>93</td>
<td>(11.3%)</td>
<td>59 (13.0%)</td>
<td>34 (9.2%)</td>
<td>6 (13.3%)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>1</td>
<td>(0.1%)</td>
<td>1 (0.2%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Niraparib</td>
<td>1</td>
<td>(0.1%)</td>
<td>0 (0.0%)</td>
<td>1 (0.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Olaparib</td>
<td>5</td>
<td>(0.6%)</td>
<td>4 (0.9%)</td>
<td>1 (0.3%)</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Olaparib/Placebo</td>
<td>1</td>
<td>(0.1%)</td>
<td>0 (0.0%)</td>
<td>1 (0.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>42</td>
<td>(5.1%)</td>
<td>29 (6.4%)</td>
<td>13 (3.5%)</td>
<td>4 (8.9%)</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>2</td>
<td>(0.2%)</td>
<td>2 (0.4%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Ramucirumab</td>
<td>1</td>
<td>(0.1%)</td>
<td>1 (0.2%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Drug</td>
<td>CAP</td>
<td>Patients &lt;70 years</td>
<td>Patients ≥70 years</td>
<td>No prior surgery</td>
<td>Prior surgery</td>
</tr>
<tr>
<td>--------------</td>
<td>---------</td>
<td>--------------------</td>
<td>--------------------</td>
<td>------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>5 (0.6%)</td>
<td>4 (0.9%)</td>
<td>1 (0.3%)</td>
<td>0 (0.0%)</td>
<td>5 (0.6%)</td>
</tr>
<tr>
<td>Topotecan</td>
<td>42 (5.1%)</td>
<td>25 (5.5%)</td>
<td>17 (4.6%)</td>
<td>3 (6.7%)</td>
<td>39 (5.0%)</td>
</tr>
<tr>
<td>Trabectedin</td>
<td>25 (3.0%)</td>
<td>18 (4.0%)</td>
<td>7 (1.9%)</td>
<td>2 (4.4%)</td>
<td>23 (3.0%)</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>1 (0.1%)</td>
<td>1 (0.2%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Treosulfan</td>
<td>24 (2.9%)</td>
<td>12 (2.6%)</td>
<td>12 (3.2%)</td>
<td>1 (2.2%)</td>
<td>23 (3.0%)</td>
</tr>
<tr>
<td>Trofosfamide</td>
<td>2 (0.2%)</td>
<td>0 (0.0%)</td>
<td>2 (0.5%)</td>
<td>0 (0.0%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Unbekannt</td>
<td>2 (0.2%)</td>
<td>2 (0.4%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>1 (0.1%)</td>
<td>0 (0.0%)</td>
<td>1 (0.3%)</td>
<td>0 (0.0%)</td>
<td>1 (0.1%)</td>
</tr>
</tbody>
</table>

[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

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

[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

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

[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

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

[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

<table>
<thead>
<tr>
<th>End of treatment</th>
<th>0 (23.9%)</th>
<th>1 (17.1%)</th>
<th>2 (2.0%)</th>
<th>3 (0.2%)</th>
<th>4 (0.0%)</th>
<th>Non-Missing (43.2%)</th>
<th>Missing (17.1%)</th>
<th>Total (43.2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>119</td>
<td>85</td>
<td>10</td>
<td>1</td>
<td>0</td>
<td>215</td>
<td>12</td>
<td>227</td>
</tr>
<tr>
<td>1</td>
<td>59 (11.8%)</td>
<td>132 (26.5%)</td>
<td>20 (4.0%)</td>
<td>4 (0.8%)</td>
<td>0 (0.0%)</td>
<td>215</td>
<td>9</td>
<td>224</td>
</tr>
<tr>
<td>2</td>
<td>10 (2.0%)</td>
<td>23 (4.6%)</td>
<td>13 (2.6%)</td>
<td>3 (0.6%)</td>
<td>0 (0.0%)</td>
<td>49 (9.8%)</td>
<td>3</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>1 (0.2%)</td>
<td>10 (2.0%)</td>
<td>7 (1.4%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>18 (3.6%)</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>0 (0.0%)</td>
<td>1 (0.2%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (0.2%)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Non-missing</td>
<td>189 (38.0%)</td>
<td>251 (50.4%)</td>
<td>50 (10.0%)</td>
<td>8 (1.6%)</td>
<td>0 (0.0%)</td>
<td>498 (100.0%)</td>
<td>24</td>
<td>522</td>
</tr>
<tr>
<td>Missing</td>
<td>108</td>
<td>138</td>
<td>27</td>
<td>7</td>
<td>0</td>
<td>280</td>
<td>22</td>
<td>302</td>
</tr>
</tbody>
</table>
| 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

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

[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

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

[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

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

[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

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

[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

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

[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)

<table>
<thead>
<tr>
<th>Patients reported with respective TEAE, n (%), n (cases)</th>
<th>Total¹ (N = 824)</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>616 (74.8%)</td>
<td>3,645</td>
</tr>
<tr>
<td>Any serious TEAE</td>
<td>222 (26.9%)</td>
<td>438</td>
</tr>
<tr>
<td>Any TEAE with CTCAE severity grade ≥ grade 3</td>
<td>317 (38.5%)</td>
<td>583</td>
</tr>
<tr>
<td>Any causally related TEAE²</td>
<td>330 (40.0%)</td>
<td>1,036</td>
</tr>
<tr>
<td>Any causally related serious TEAE²</td>
<td>72 (8.7%)</td>
<td>96</td>
</tr>
<tr>
<td>Any TEAE leading to discontinuation of bevacizumab (Avastin®)</td>
<td>145 (17.6%)</td>
<td>206</td>
</tr>
<tr>
<td>Any causally related fatal TEAE³</td>
<td>5 (0.6%)</td>
<td>6</td>
</tr>
</tbody>
</table>

[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)

<table>
<thead>
<tr>
<th>Patients reported with respective TEAE, n (%), n (cases)</th>
<th>&lt;70 years Total</th>
<th>≥70 years Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 453) Cases</td>
<td>(N = 371) Cases</td>
</tr>
<tr>
<td>Any TEAE</td>
<td>328 (72.4%)</td>
<td>288 (77.6%)</td>
</tr>
<tr>
<td>Any serious TEAE</td>
<td>100 (22.1%)</td>
<td>122 (32.9%)</td>
</tr>
<tr>
<td>Any TEAE with CTCAE severity grade ≥ grade 3</td>
<td>150 (33.1%)</td>
<td>167 (45.0%)</td>
</tr>
<tr>
<td>Any causally related TEAE²</td>
<td>192 (42.4%)</td>
<td>138 (37.2%)</td>
</tr>
<tr>
<td>Any causally related serious TEAE²</td>
<td>37 (8.2%)</td>
<td>35 (9.4%)</td>
</tr>
<tr>
<td>Any TEAE leading to discontinuation of bevacizumab (Avastin®) treatment³</td>
<td>66 (14.6%)</td>
<td>79 (21.3%)</td>
</tr>
<tr>
<td>Any TEAE leading to death</td>
<td>12 (2.6%)</td>
<td>18 (4.9%)</td>
</tr>
</tbody>
</table>

[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)

<table>
<thead>
<tr>
<th>Patients reported with respective TEAE, n (%), n (cases)</th>
<th>No prior surgery</th>
<th>Prior surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (N = 45)</td>
<td>Total (N = 779)</td>
</tr>
<tr>
<td>Any TEAE</td>
<td>29 (64.4%)</td>
<td>587 (75.4%)</td>
</tr>
<tr>
<td>Any serious TEAE</td>
<td>14 (31.1%)</td>
<td>208 (26.7%)</td>
</tr>
<tr>
<td>Any TEAE with CTCAE severity grade ≥ grade 3</td>
<td>19 (42.2%)</td>
<td>298 (38.3%)</td>
</tr>
<tr>
<td>Any causally related TEAE2</td>
<td>10 (22.2%)</td>
<td>320 (41.1%)</td>
</tr>
<tr>
<td>Any causally related serious TEAE2</td>
<td>3 (6.7%)</td>
<td>69 (8.9%)</td>
</tr>
<tr>
<td>Any TEAE leading to discontinuation of bevacizumab (Avastin®) treatment3</td>
<td>6 (13.3%)</td>
<td>139 (17.8%)</td>
</tr>
<tr>
<td>Any TEAE leading to death</td>
<td>3 (6.7%)</td>
<td>27 (3.5%)</td>
</tr>
</tbody>
</table>

[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>
<thead>
<tr>
<th>MedDRA SOC</th>
<th>MedDRA PT</th>
<th>Total Patients N=824</th>
<th>&lt;70 years Patients N=453</th>
<th>≥70 years Patients N=371</th>
<th>No prior surgery Patients N=45</th>
<th>Prior surgery Patients N=779</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Any event</td>
<td>315 (38.2%)</td>
<td>604</td>
<td>179 (39.5%)</td>
<td>355</td>
<td>136 (36.7%)</td>
<td>249</td>
</tr>
<tr>
<td>Nausea</td>
<td>112 (13.6%)</td>
<td>112</td>
<td>66 (14.6%)</td>
<td>66</td>
<td>46 (12.4%)</td>
<td>46</td>
<td>7 (15.6%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>92 (11.2%)</td>
<td>92</td>
<td>55 (12.1%)</td>
<td>55</td>
<td>37 (10.0%)</td>
<td>37</td>
<td>3 (6.7%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>82 (10.0%)</td>
<td>82</td>
<td>49 (10.8%)</td>
<td>49</td>
<td>33 (8.9%)</td>
<td>33</td>
<td>3 (6.7%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>66 (8.0%)</td>
<td>66</td>
<td>37 (8.2%)</td>
<td>37</td>
<td>29 (7.8%)</td>
<td>29</td>
<td>5 (11.1%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>44 (5.3%)</td>
<td>44</td>
<td>20 (4.4%)</td>
<td>20</td>
<td>24 (6.5%)</td>
<td>24</td>
<td>2 (4.4%)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>32 (3.9%)</td>
<td>32</td>
<td>25 (5.5%)</td>
<td>25</td>
<td>7 (1.9%)</td>
<td>7</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>29 (3.5%)</td>
<td>29</td>
<td>21 (4.6%)</td>
<td>21</td>
<td>8 (2.2%)</td>
<td>8</td>
<td>29 (3.7%)</td>
</tr>
<tr>
<td>Ascites</td>
<td>14 (1.7%)</td>
<td>14</td>
<td>7 (1.5%)</td>
<td>7</td>
<td>7 (1.9%)</td>
<td>7</td>
<td>14 (1.8%)</td>
</tr>
<tr>
<td>Ileus</td>
<td>14 (1.7%)</td>
<td>14</td>
<td>10 (2.2%)</td>
<td>10</td>
<td>4 (1.1%)</td>
<td>4</td>
<td>3 (6.7%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>10 (1.2%)</td>
<td>10</td>
<td>7 (1.5%)</td>
<td>7</td>
<td>3 (0.8%)</td>
<td>3</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Subileus</td>
<td>9 (1.1%)</td>
<td>9</td>
<td>4 (0.9%)</td>
<td>4</td>
<td>5 (1.3%)</td>
<td>5</td>
<td>9 (1.2%)</td>
</tr>
<tr>
<td>Large intestine perforation</td>
<td>6 (0.7%)</td>
<td>6</td>
<td>4 (0.9%)</td>
<td>4</td>
<td>2 (0.5%)</td>
<td>2</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>4 (0.5%)</td>
<td>4</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>3 (0.8%)</td>
<td>3</td>
<td>4 (0.5%)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>4 (0.5%)</td>
<td>4</td>
<td>3 (0.7%)</td>
<td>3</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>4 (0.5%)</td>
</tr>
<tr>
<td>Gingival bleeding</td>
<td>4 (0.5%)</td>
<td>4</td>
<td>2 (0.4%)</td>
<td>2</td>
<td>2 (0.5%)</td>
<td>2</td>
<td>4 (0.5%)</td>
</tr>
<tr>
<td>Toothache</td>
<td>4 (0.5%)</td>
<td>4</td>
<td>2 (0.4%)</td>
<td>2</td>
<td>2 (0.5%)</td>
<td>2</td>
<td>4 (0.5%)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>3 (0.4%)</td>
<td>3</td>
<td>2 (0.4%)</td>
<td>2</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>3 (0.4%)</td>
</tr>
<tr>
<td>Abdominal hernia</td>
<td>3 (0.4%)</td>
<td>3</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>2 (0.5%)</td>
<td>2</td>
<td>3 (0.4%)</td>
</tr>
<tr>
<td>Abdominal pain lower</td>
<td>3 (0.4%)</td>
<td>3</td>
<td>3 (0.7%)</td>
<td>3</td>
<td>1 (2.2%)</td>
<td>1</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>MedDRA SOC</td>
<td>MedDRA PT</td>
<td>Total Patients N=824</td>
<td>&lt;70 years Patients N=453</td>
<td>≥70 years Patients N=371</td>
<td>No prior surgery Patients N=45</td>
<td>Prior surgery Patients N=779</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>-----------</td>
<td>----------------------</td>
<td>--------------------------</td>
<td>--------------------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
<td></td>
</tr>
<tr>
<td>Aphthous ulcer</td>
<td>3 (0.4%)</td>
<td>3 (0.7%)</td>
<td>3</td>
<td></td>
<td>3 (0.4%)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>3 (0.4%)</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>2 (0.5%)</td>
<td>2</td>
<td>3 (0.4%)</td>
<td>3</td>
</tr>
<tr>
<td>Faecaloma</td>
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<td>&lt;70 years Patients N=453</td>
<td>≥70 years Patients N=371</td>
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<td>Prior surgery Patients N=779</td>
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<td>&lt;70 years Patients N=453</td>
<td>≥70 years Patients N=371</td>
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<td>Prior surgery Patients N=779</td>
<td>Cases</td>
</tr>
<tr>
<td>-----------------------------</td>
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<tr>
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<tr>
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<td>MedDRA PT</td>
<td>Vena cava thrombosis</td>
<td>Blood and lymphatic system disorders</td>
<td>Anaemia</td>
<td>Leukopenia</td>
<td>Thrombocytopenia</td>
<td>Neutropenia</td>
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<tr>
<td>Total Patients N=824</td>
<td>Cases</td>
<td>Total Patients N=453</td>
<td>Cases</td>
<td>≥70 years Patients N=371</td>
<td>Cases</td>
<td>No prior surgery Patients N=45</td>
<td>Cases</td>
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<td>1 (0.2%)</td>
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Clinical Study Report Number 1100702, Final Version 1.0
Protocol ML27765 / P0229
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</tr>
<tr>
<td>Musculoskeletal discomfort</td>
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<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
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<tr>
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<td>8</td>
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<tr>
<td>MedDRA SOC</td>
<td>MedDRA PT</td>
<td>Total Patients N=824</td>
<td>N=453</td>
<td>≥70 years Patients N=371</td>
<td>N=45</td>
<td>≥70 years Patients N=779</td>
<td>N=779</td>
</tr>
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<td>Erythema</td>
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<td>6 (0.8%)</td>
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<tr>
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<td>3 (0.4%)</td>
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<tr>
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<tr>
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<td>2 (0.5%)</td>
<td>2 (0.3%)</td>
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<tr>
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<tr>
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<td>2 (0.3%)</td>
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<tr>
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<tr>
<td>Decubitus ulcer</td>
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<tr>
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<td>1 (0.2%)</td>
<td>1 (0.3%)</td>
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<tr>
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</tr>
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<tr>
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<td>1 (0.1%)</td>
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</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Any event</td>
<td>119 (14.4%)</td>
<td>148 (11.0%)</td>
<td>66 (18.6%)</td>
<td>82 (8.9%)</td>
<td>115 (14.8%)</td>
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</tr>
<tr>
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<td>MedDRA PT</td>
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<td>&lt;70 years Patients N=453</td>
<td>≥70 years Patients N=371</td>
<td>No prior surgery Patients N=45</td>
<td>Prior surgery Patients N=779</td>
<td>Cases</td>
</tr>
<tr>
<td>------------------------------------</td>
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<td>--------------------------</td>
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</tr>
<tr>
<td>Dyspnoea</td>
<td></td>
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<td>25 (5.5%)</td>
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<td>1 (2.2%)</td>
<td>53 (6.8%)</td>
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<tr>
<td>Epistaxis</td>
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<tr>
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<td>8 (2.2%)</td>
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<td>2 (4.4%)</td>
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<tr>
<td>Cough</td>
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<td>8</td>
<td>11 (1.4%)</td>
<td>11</td>
</tr>
<tr>
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<td></td>
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<td>3 (0.7%)</td>
<td>6 (1.6%)</td>
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<td>9 (1.2%)</td>
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<tr>
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<td>4 (0.9%)</td>
<td>5 (1.3%)</td>
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<tr>
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<tr>
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<tr>
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<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
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<tr>
<td>Aspiration</td>
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<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
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</tr>
<tr>
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<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
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<tr>
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<tr>
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<td>1 (0.2%)</td>
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<tr>
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<td>1 (0.2%)</td>
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<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
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<tr>
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<td>1 (0.3%)</td>
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<tr>
<td>Productive cough</td>
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<td>1 (0.2%)</td>
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<tr>
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<td>1 (0.2%)</td>
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<td>1 (0.3%)</td>
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<tr>
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<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1 (0.1%)</td>
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</tr>
<tr>
<td>MedDRA SOC</td>
<td>MedDRA PT</td>
<td>Total Patients N=824</td>
<td>&lt;70 years Patients N=453</td>
<td>≥70 years Patients N=371</td>
<td>No prior surgery Patients N=45</td>
<td>Prior surgery Patients N=779</td>
<td>Cases</td>
</tr>
<tr>
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<td>-------------------------</td>
<td>-------------------------</td>
<td>-------------------------------</td>
<td>-------------------------------</td>
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</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Any event</td>
<td>62 (7.5%)</td>
<td>30 (6.6%)</td>
<td>32 (8.6%)</td>
<td>1 (2.2%)</td>
<td>61 (7.8%)</td>
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<td></td>
<td>Proteinuria</td>
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<td>19 (4.2%)</td>
<td>16 (4.3%)</td>
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<td>35 (4.5%)</td>
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<td>Hydronephrosis</td>
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<td>5 (0.6%)</td>
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</tr>
<tr>
<td></td>
<td>Haematuria</td>
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<td>4 (1.1%)</td>
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<td>4 (0.5%)</td>
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</tr>
<tr>
<td></td>
<td>Acute kidney injury</td>
<td>3 (0.4%)</td>
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<td>1 (0.3%)</td>
<td>1</td>
<td>3 (0.4%)</td>
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<tr>
<td></td>
<td>Urinary incontinence</td>
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<td>1 (0.3%)</td>
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<td>1 (2.2%)</td>
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<tr>
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<td>1 (0.2%)</td>
<td>1 (0.3%)</td>
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<td>2 (0.3%)</td>
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<tr>
<td></td>
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<td>1 (0.2%)</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>2 (0.3%)</td>
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</tr>
<tr>
<td></td>
<td>Prerenal failure</td>
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<td>1 (0.2%)</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>2 (0.3%)</td>
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<tr>
<td></td>
<td>Urinary tract obstruction</td>
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<td>1 (0.2%)</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>2 (0.3%)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Bladder discomfort</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>1 (0.1%)</td>
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</tr>
<tr>
<td></td>
<td>Bladder irritation</td>
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<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>1 (0.1%)</td>
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</tr>
<tr>
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<td>Cystitis haemorrhagic</td>
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<tr>
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<td>Incontinence</td>
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<tr>
<td></td>
<td>Nephrotic syndrome</td>
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<td>Pollakiuria</td>
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<td>Renal failure</td>
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<tr>
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<td>Stress urinary incontinence</td>
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<td>Urinary tract disorder</td>
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<td>MedDRA PT</td>
<td>Total Patients N=824</td>
<td>N=453</td>
<td>N=371</td>
<td>N=45</td>
<td>N=779</td>
<td>Cases</td>
</tr>
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<td></td>
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<td>58 (7.0%)</td>
<td>30 (6.6%)</td>
<td>39</td>
<td>28 (7.5%)</td>
<td>43</td>
<td>3 (6.7%)</td>
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<td>Any event</td>
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<td>Blood creatinine increased</td>
<td>11 (1.3%)</td>
<td>6 (1.3%)</td>
<td>6</td>
<td>5 (1.3%)</td>
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<td>1 (2.2%)</td>
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<tr>
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<td>Weight decreased</td>
<td>7 (0.8%)</td>
<td>3 (0.7%)</td>
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<td>4 (1.1%)</td>
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<td>1 (2.2%)</td>
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<td>Alanine aminotransferase increased</td>
<td>5 (0.6%)</td>
<td>3 (0.7%)</td>
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<td>2 (0.5%)</td>
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<td>5 (0.6%)</td>
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<tr>
<td></td>
<td>Gamma-glutamyltransferase increased</td>
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<td>Blood alkaline phosphatase increased</td>
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<td>Blood pressure increased</td>
<td>4 (0.5%)</td>
<td>2 (0.4%)</td>
<td>2</td>
<td>2 (0.5%)</td>
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<td>4 (0.5%)</td>
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<tr>
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<td>C-reactive protein increased</td>
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<td>Haemoglobin decreased</td>
<td>4 (0.5%)</td>
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<td>White blood cell count decreased</td>
<td>4 (0.5%)</td>
<td>1 (0.2%)</td>
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<td>3 (0.8%)</td>
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<td>4 (0.5%)</td>
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<tr>
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<td>Aspartate aminotransferase increased</td>
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<td>Neutrophil count decreased</td>
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<td>Blood creatine abnormal</td>
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<tr>
<td>MedDRA SOC</td>
<td>MedDRA PT</td>
<td>Total Patients N=824</td>
<td>&lt;70 years Patients N=453</td>
<td>≥70 years Patients N=371</td>
<td>No prior surgeryPatients N=45</td>
<td>Prior surgery Patients N=779</td>
<td>Cases</td>
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<tr>
<td>Liver function test increased</td>
<td>2 (0.2%)</td>
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<td>1 (0.3%)</td>
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<tr>
<td>Platelet count decreased</td>
<td>2 (0.2%)</td>
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<td>2 (0.4%)</td>
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<td>2 (0.3%)</td>
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<tr>
<td>Protein urine present</td>
<td>2 (0.2%)</td>
<td>2</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>2</td>
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<tr>
<td>Biopsy bone marrow</td>
<td>1 (0.1%)</td>
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<td>1 (0.2%)</td>
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<td>1 (0.3%)</td>
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<tr>
<td>Blood alkaline phosphatase increased</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>1 (0.1%)</td>
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<tr>
<td>Blood lactate dehydrogenase increased</td>
<td>1 (0.1%)</td>
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<td>1 (0.3%)</td>
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<td>1 (0.1%)</td>
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<tr>
<td>Blood potassium decreased</td>
<td>1 (0.1%)</td>
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<td>1 (0.3%)</td>
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<td>1 (0.1%)</td>
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<tr>
<td>Blood sodium decreased</td>
<td>1 (0.1%)</td>
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<td>1 (0.3%)</td>
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<td>1 (0.1%)</td>
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<tr>
<td>Blood urine present</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>1 (0.1%)</td>
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</tr>
<tr>
<td>Body temperature increased</td>
<td>1 (0.1%)</td>
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<td>1 (0.3%)</td>
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<td>1 (0.1%)</td>
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<td>General physical condition</td>
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<td>1 (0.1%)</td>
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<tr>
<td>Hepatic enzyme increased</td>
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<td>1 (0.2%)</td>
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<tr>
<td>Lymphocyte count decreased</td>
<td>1 (0.1%)</td>
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<td>1 (0.3%)</td>
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<td>1 (0.1%)</td>
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</tr>
<tr>
<td>Nitrite urine present</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>1 (0.1%)</td>
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</tr>
<tr>
<td>Nutritional condition abnormal</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>1 (0.1%)</td>
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</tr>
<tr>
<td>Protein total decreased</td>
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<td>1 (0.3%)</td>
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<td>1 (0.1%)</td>
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</tr>
<tr>
<td>Red blood cells urine</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.3%)</td>
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<td>1 (0.1%)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>MedDRA SOC</td>
<td>MedDRA PT</td>
<td>Total Patients N=824</td>
<td>&lt;70 years Patients N=453</td>
<td>≥70 years Patients N=371</td>
<td>Patients N=779</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Sensory level abnormal</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.2%)</td>
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<td>1 (0.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumour marker increased</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1 (0.1%)</td>
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</tr>
<tr>
<td>Urological examination</td>
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<td>1 (0.2%)</td>
<td>1</td>
<td>1 (0.1%)</td>
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</tr>
<tr>
<td>Vitamin B12 decreased</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>1 (0.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Any event</td>
<td>55 (6.7%)</td>
<td>68</td>
<td>32 (7.1%)</td>
<td>42</td>
<td>23 (6.2%)</td>
<td>26</td>
</tr>
<tr>
<td>Insomnia</td>
<td>18 (2.2%)</td>
<td>18</td>
<td>12 (2.6%)</td>
<td>12</td>
<td>6 (1.6%)</td>
<td>6</td>
<td>18 (2.3%)</td>
</tr>
<tr>
<td>Depression</td>
<td>15 (1.8%)</td>
<td>15</td>
<td>12 (2.6%)</td>
<td>12</td>
<td>3 (0.8%)</td>
<td>3</td>
<td>15 (1.9%)</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>14 (1.7%)</td>
<td>14</td>
<td>6 (1.3%)</td>
<td>6</td>
<td>8 (2.2%)</td>
<td>8</td>
<td>14 (1.8%)</td>
</tr>
<tr>
<td>Restlessness</td>
<td>4 (0.5%)</td>
<td>4</td>
<td>2 (0.4%)</td>
<td>2</td>
<td>2 (0.5%)</td>
<td>2</td>
<td>4 (0.5%)</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>3 (0.4%)</td>
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<td>2 (0.4%)</td>
<td>2</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>3 (0.4%)</td>
</tr>
<tr>
<td>Nervousness</td>
<td>2 (0.2%)</td>
<td>2</td>
<td>2 (0.4%)</td>
<td>2</td>
<td>2 (0.3%)</td>
<td>2</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Stress</td>
<td>2 (0.2%)</td>
<td>2</td>
<td>2 (0.4%)</td>
<td>2</td>
<td>2 (0.3%)</td>
<td>2</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1 (0.1%)</td>
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<td>1 (0.1%)</td>
</tr>
<tr>
<td>Confusional state</td>
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<td>1 (0.3%)</td>
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<td>1 (0.1%)</td>
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<td>1 (0.1%)</td>
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<tr>
<td>Disorientation</td>
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<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>1 (0.1%)</td>
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<td>1 (0.1%)</td>
</tr>
<tr>
<td>Emotional distress</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Hallucination, auditory</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Hallucination, visual</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Irritability</td>
<td>1 (0.1%)</td>
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<td>1 (0.3%)</td>
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<td>1 (0.1%)</td>
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<td>1 (0.1%)</td>
</tr>
<tr>
<td>Listless</td>
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<td>1 (0.2%)</td>
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<td>1 (0.1%)</td>
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<td>Psychiatric decompensation</td>
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<td>1 (0.3%)</td>
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<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>MedDRA SOC</td>
<td>MedDRA PT</td>
<td>Total Patients N=824</td>
<td>&lt;70 years Patients N=453</td>
<td>≥70 years Patients N=371</td>
<td>No prior surgery Patients N=45</td>
<td>Prior surgery Patients N=779</td>
<td>Cases</td>
</tr>
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</tr>
<tr>
<td>Psychotic disorder</td>
<td>Any event</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
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<tr>
<td>Decreased appetite</td>
<td>23 (2.8%)</td>
<td>23</td>
<td>9 (2.0%)</td>
<td>9</td>
<td>14 (3.8%)</td>
<td>14</td>
<td>36</td>
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<tr>
<td>Dehydration</td>
<td>9 (1.1%)</td>
<td>9</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>8 (2.2%)</td>
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<td>2</td>
</tr>
<tr>
<td>Hyperkalaemia</td>
<td>6 (0.7%)</td>
<td>6</td>
<td>4 (0.9%)</td>
<td>4</td>
<td>2 (0.5%)</td>
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<tr>
<td>Vitamin D deficiency</td>
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<td>1 (0.2%)</td>
<td>1</td>
<td>3 (0.8%)</td>
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<td>2</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>3 (0.4%)</td>
<td>3</td>
<td>1 (0.2%)</td>
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<td>2 (0.5%)</td>
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<tr>
<td>Hyponatraemia</td>
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<td>3</td>
<td>1 (0.2%)</td>
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<td>2 (0.5%)</td>
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<tr>
<td>Hypercholesterolaemia</td>
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<td>1 (0.3%)</td>
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<td>Type 2 diabetes mellitus</td>
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<td>2 (0.5%)</td>
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</tr>
<tr>
<td>Abnormal loss of weight</td>
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<td>1</td>
<td></td>
<td></td>
<td>1 (0.3%)</td>
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</tr>
<tr>
<td>Fluid retention</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1 (0.2%)</td>
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<td>1</td>
</tr>
<tr>
<td>Hypocalcaemia</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.2%)</td>
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<td>1 (0.2%)</td>
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<tr>
<td>Hypovolaemia</td>
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<td>1 (0.2%)</td>
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<td>1 (0.2%)</td>
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<td>Iron deficiency</td>
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Clinical Study Report Number 1100702, Final Version 1.0
Protocol ML27765 / P0229

169
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<th>&lt;70 years Patients N=453</th>
<th>≥70 years Patients N=371</th>
<th>No prior surgery Patients N=45</th>
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<td>MedDRA SOC</td>
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<td>2 (0.4%)</td>
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<td>Hospice care</td>
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<tr>
<td>MedDRA SOC</td>
<td>MedDRA PT</td>
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<td>≥70 years Patients N=371</td>
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<td>Prior surgery Patients N=779</td>
<td>Cases</td>
</tr>
<tr>
<td>------------</td>
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<td>--------------------------</td>
<td>------------------------</td>
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<td>-------</td>
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<td>Tinnitus</td>
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<td>2 (0.3%)</td>
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<tr>
<td>Ear disorder</td>
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<td>1 (0.3%)</td>
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<td>1 (0.3%)</td>
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<td>11 (3.0%)</td>
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<td>3 (0.8%)</td>
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<td>3</td>
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<td>Visual acuity reduced</td>
<td>3 (0.4%)</td>
<td>3</td>
<td>2 (0.4%)</td>
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<td>1 (0.2%)</td>
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<tr>
<td>Cataract</td>
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<td>1 (0.3%)</td>
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<td>1 (0.3%)</td>
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<tr>
<td>Entropion</td>
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<td>1 (0.3%)</td>
<td>1</td>
<td>1 (0.3%)</td>
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<tr>
<td>Eye haemorrhage</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.3%)</td>
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<td>1 (0.3%)</td>
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Clinical Study Report Number 1100702, Final Version 1.0
Protocol ML27765 / P0229
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<tr>
<th>MedDRA SOC</th>
<th>MedDRA PT</th>
<th>Total Patients N=824</th>
<th>&lt;70 years Patients N=453</th>
<th>≥70 years Patients N=371</th>
<th>No prior surgery Patients N=45</th>
<th>Prior surgery Patients N=779</th>
<th>Cases</th>
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<tbody>
<tr>
<td>Eye inflammation</td>
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<td>1</td>
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<td>Retinal detachment</td>
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<td>Any event</td>
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<td>2</td>
</tr>
<tr>
<td>Vaginal disorder</td>
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<td>1 (0.2%)</td>
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<td>1</td>
<td>2</td>
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<td>Vaginal fistula</td>
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<tr>
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<td>1</td>
<td>1 (0.2%)</td>
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<tr>
<td>Nipple exudate bloody</td>
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<td>1</td>
<td>1 (0.2%)</td>
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<tr>
<td>Vaginal discharge</td>
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<td>1</td>
<td>1 (0.2%)</td>
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</tr>
<tr>
<td>Vaginal haemorrhage</td>
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<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Any event</td>
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<td>6 (0.7%)</td>
<td>6</td>
<td>3 (0.7%)</td>
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<td>Autoimmune hepatitis</td>
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<td>1</td>
<td>1 (0.2%)</td>
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<tr>
<td>Bile duct stone</td>
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<tr>
<td>Cholecystitis</td>
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<tr>
<td>Cholelithiasis</td>
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<tr>
<td>Hepatotoxicity</td>
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<td>1 (0.1%)</td>
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<td>1 (0.2%)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Portal vein thrombosis</td>
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<td>1 (0.1%)</td>
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<tr>
<td>MedDRA SOC</td>
<td>MedDRA PT</td>
<td>Total Patients N=824 Cases</td>
<td>&lt;70 years Patients N=453 Cases</td>
<td>≥70 years Patients N=371 Cases</td>
<td>No prior surgery Patients N=45 Cases</td>
<td>Prior surgery Patients N=779 Cases</td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
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<td>---------------------------</td>
<td>-------------------------------</td>
<td>-------------------------------</td>
<td>---------------------------------------</td>
<td>----------------------------------</td>
<td></td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>Any event</td>
<td>4 (0.5%) 4</td>
<td>3 (0.7%) 3</td>
<td>1 (0.3%) 1</td>
<td>4 (0.5%) 4</td>
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<td></td>
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<tr>
<td>Hypothyroidism</td>
<td>Any event</td>
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<td>3 (0.7%) 3</td>
<td>1 (0.3%) 1</td>
<td>4 (0.5%) 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product issues</td>
<td>Any event</td>
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<td>1 (0.2%) 1</td>
<td>1 (0.3%) 1</td>
<td>2 (0.3%) 2</td>
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<tr>
<td>Device dislocation</td>
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<td>1 (0.2%) 1</td>
<td>1 (0.3%) 1</td>
<td>1 (0.1%) 1</td>
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<td></td>
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<tr>
<td>Device malfunction</td>
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<td></td>
<td>1 (0.1%) 1</td>
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<td></td>
</tr>
</tbody>
</table>

[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)

<table>
<thead>
<tr>
<th>MedDRA SOC</th>
<th>MedDRA PT</th>
<th>Total Patients N=824</th>
<th>&lt;70 years Patients N=453</th>
<th>≥70 years Patients N=371</th>
<th>No prior surgery Patients N=45</th>
<th>Prior surgery Patients N=779</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular disorders</td>
<td>Any event</td>
<td>317 (38.5%)</td>
<td>529 (33.1%)</td>
<td>150 (45.0%)</td>
<td>238 (42.2%)</td>
<td>291 (42.2%)</td>
<td>298 (491)</td>
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<td>Hypertension</td>
<td>94 (11.4%)</td>
<td>101 (8.8%)</td>
<td>40 (9.4%)</td>
<td>29 (8.3%)</td>
<td>43 (9.5%)</td>
<td>3 (6.7%)</td>
<td>6 (11.4%)</td>
</tr>
<tr>
<td>Hypertensive crisis</td>
<td>12 (1.5%)</td>
<td>12 (3.3%)</td>
<td>3 (0.7%)</td>
<td>3 (0.8%)</td>
<td>9 (2.4%)</td>
<td>2 (4.4%)</td>
<td>2 (1.3%)</td>
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<tr>
<td>Lymphocele</td>
<td>5 (0.6%)</td>
<td>5 (0.7%)</td>
<td>4 (0.9%)</td>
<td>4 (0.9%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>5 (0.6%)</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>2 (0.2%)</td>
<td>2 (0.6%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Angiopathy</td>
<td>1 (0.1%)</td>
<td>1 (0.2%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Circulatory collapse</td>
<td>1 (0.1%)</td>
<td>1 (0.1%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Embolism arterial</td>
<td>1 (0.1%)</td>
<td>1 (0.1%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
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<td>≥70 years Patients N=371</td>
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### MedDRA SOC: Respiratory, thoracic and mediastinal disorders

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<th>Total Patients N=824 Cases</th>
<th>&lt;70 years Patients N=453 Cases</th>
<th>≥70 years Patients N=371 Cases</th>
<th>No prior surgery Patients N=45 Cases</th>
<th>Prior surgery Patients N=779 Cases</th>
<th>Cases</th>
</tr>
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<td>Status epilepticus</td>
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<tr>
<td><strong>Any event</strong></td>
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<td><strong>21</strong></td>
<td><strong>9 (2.0%)</strong></td>
<td><strong>9 (2.4%)</strong></td>
<td><strong>12</strong></td>
<td><strong>18 (2.3%)</strong></td>
<td><strong>21</strong></td>
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<tr>
<td>Dyspnoea</td>
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<td><strong>3</strong></td>
<td><strong>13 (3.5%)</strong></td>
<td><strong>13</strong></td>
<td><strong>15 (1.9%)</strong></td>
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### MedDRA SOC: Injury, poisoning and procedural complications

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<th>Total Patients N=824 Cases</th>
<th>&lt;70 years Patients N=453 Cases</th>
<th>≥70 years Patients N=371 Cases</th>
<th>No prior surgery Patients N=45 Cases</th>
<th>Prior surgery Patients N=779 Cases</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall</td>
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<tr>
<td>Rib fracture</td>
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Clinical Study Report Number 1100702, Final Version 1.0
Protocol ML27765 / P0229
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<td>N=371</td>
<td>N=45</td>
<td>N=779</td>
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<td>Cases</td>
<td>Cases</td>
<td>Cases</td>
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<td>1 (0.2%)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic enzyme increased</td>
<td>1 (0.1%)</td>
<td>1 (0.2%)</td>
<td>1</td>
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<td></td>
</tr>
<tr>
<td>Liver function test increased</td>
<td>1 (0.1%)</td>
<td>1 (0.3%)</td>
<td>1</td>
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</tr>
<tr>
<td>Platelet count decreased</td>
<td>1 (0.1%)</td>
<td>1 (0.2%)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein urine present</td>
<td>1 (0.1%)</td>
<td>1 (0.2%)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urological examination</td>
<td>1 (0.1%)</td>
<td>1 (0.2%)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>1 (0.1%)</td>
<td>1 (0.3%)</td>
<td>1</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>White blood cell count decreased</td>
<td>1 (0.1%)</td>
<td>1 (0.2%)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>14 (1.7%)</td>
<td>15 (0.7%)</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any event</td>
<td>7 (0.8%)</td>
<td>7 (0.2%)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dehydration</td>
<td>2 (0.2%)</td>
<td>2 (0.5%)</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>2 (0.2%)</td>
<td>2 (0.5%)</td>
<td>2</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hyponatraemia</td>
<td>1 (0.1%)</td>
<td>1 (0.2%)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>1 (0.1%)</td>
<td>1 (0.2%)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MedDRA SOC</td>
<td>MedDRA PT</td>
<td>Total Patients N=824</td>
<td>Cases</td>
<td>&lt;70 years Patients N=453</td>
<td>Cases</td>
<td>≥70 years Patients N=371</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------------------------------------------</td>
<td>----------------------</td>
<td>-------</td>
<td>--------------------------</td>
<td>-------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Hypovolaemia</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td><strong>Any event</strong></td>
<td>14 (1.7%)</td>
<td>14</td>
<td>11 (2.4%)</td>
<td>11</td>
<td>3 (0.8%)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>4 (0.5%)</td>
<td>4</td>
<td>3</td>
<td>3 (0.7%)</td>
<td>3</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>3 (0.4%)</td>
<td>3</td>
<td>2</td>
<td>2 (0.4%)</td>
<td>2</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Hydronephrosis</td>
<td>3 (0.4%)</td>
<td>3</td>
<td>3</td>
<td>3 (0.7%)</td>
<td>3</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Cystitis noninfective</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Prerenal failure</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Urinary bladder haemorrhage</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td><strong>Any event</strong></td>
<td>6 (0.7%)</td>
<td>6</td>
<td>2 (0.4%)</td>
<td>2</td>
<td>4 (1.1%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Atrial flutter</td>
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<td>1 (0.3%)</td>
<td>1</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>1 (2.2%)</td>
</tr>
<tr>
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<td>1</td>
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<td>1</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Left ventricular dysfunction</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Right ventricular extrasystoles</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td><strong>Any event</strong></td>
<td>6 (0.7%)</td>
<td>6</td>
<td>4 (0.9%)</td>
<td>4</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Bone pain</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Fistula</td>
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<td>1</td>
<td>1</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>MedDRA SOC</td>
<td>MedDRA PT</td>
<td>Total Patients N=824</td>
<td>&lt;70 years Patients N=453</td>
<td>≥70 years Patients N=371</td>
<td>No prior surgery Patients N=45</td>
<td>Prior surgery Patients N=779</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------------------</td>
<td>----------------------</td>
<td>--------------------------</td>
<td>--------------------------</td>
<td>-------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td></td>
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<td>1 (0.1%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
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<td>1</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
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</tr>
<tr>
<td>Spinal pain</td>
<td></td>
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<td>1 (0.2%)</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Any event</td>
<td></td>
<td>4 (0.5%)</td>
<td>2 (0.4%)</td>
<td>2 (0.5%)</td>
<td>4 (0.5%)</td>
<td>4 (0.5%)</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholecystitis</td>
<td></td>
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<td>1 (0.2%)</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
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</tr>
<tr>
<td>Cholelithiasis</td>
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</tr>
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<td>Hepatotoxicity</td>
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<td>1 (0.3%)</td>
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</tr>
<tr>
<td>Portal vein thrombosis</td>
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<td>1</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
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</tr>
<tr>
<td>Any event</td>
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<td>4 (0.5%)</td>
<td>2 (0.4%)</td>
<td>2 (0.5%)</td>
<td>4 (0.5%)</td>
<td>4 (0.5%)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td></td>
<td>2 (0.2%)</td>
<td>1 (0.2%)</td>
<td>1 (0.3%)</td>
<td>2 (0.3%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Confusional state</td>
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<td>1</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Depression</td>
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<td>1 (0.2%)</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Any event</td>
<td></td>
<td>4 (0.5%)</td>
<td>1 (0.2%)</td>
<td>3 (0.8%)</td>
<td>3 (0.4%)</td>
<td>3 (0.4%)</td>
</tr>
<tr>
<td>Surgical and medical procedures</td>
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<td></td>
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<td></td>
</tr>
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<td>Gastrectomy</td>
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<td>1 (0.2%)</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Ileostomy</td>
<td></td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Incisional hernia repair</td>
<td></td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Liver ablation</td>
<td></td>
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<td>1</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Any event</td>
<td></td>
<td>3 (0.4%)</td>
<td>2 (0.4%)</td>
<td>1 (0.3%)</td>
<td>3 (0.4%)</td>
<td>3 (0.4%)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td></td>
<td>1 (0.1%)</td>
<td>1 (0.2%)</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Dry skin</td>
<td></td>
<td>1 (0.1%)</td>
<td>1 (0.2%)</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Skin ulcer</td>
<td></td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td>2 (0.2%)</td>
<td>2 (0.5%)</td>
<td>2 (0.3%)</td>
<td>2 (0.3%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Cataract</td>
<td></td>
<td>1 (0.1%)</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
<td>1 (0.1%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>MedDRA SOC</td>
<td>MedDRA PT</td>
<td>Total Patients N=824</td>
<td>&lt;70 years Patients N=453</td>
<td>≥70 years Patients N=371</td>
<td>No prior surgery Patients N=45</td>
<td>Prior surgery Patients N=779</td>
</tr>
<tr>
<td>------------</td>
<td>--------------------------</td>
<td>----------------------</td>
<td>--------------------------</td>
<td>--------------------------</td>
<td>-------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Entropion</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td></td>
<td>Any event</td>
<td>2 (0.2%)</td>
<td>2</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td></td>
<td>Anaphylactic reaction</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td></td>
<td>Contrast media allergy</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Any event</td>
<td>2 (0.2%)</td>
<td>2</td>
<td>2 (0.5%)</td>
<td>2</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Product issues</td>
<td>Vaginal fistula</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td></td>
<td>Vaginal haemorrhage</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td></td>
<td>Any event</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td></td>
<td>Device malfunction</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>1 (0.1%)</td>
</tr>
</tbody>
</table>

[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)

<table>
<thead>
<tr>
<th>MedDRA SOC</th>
<th>MedDRA PT</th>
<th>Total Patients N=824</th>
<th>&lt;70 years Patients N=453</th>
<th>≥70 years Patients N=371</th>
<th>No prior surgery Patients N=45</th>
<th>Prior surgery Patients N=779</th>
<th>Cases</th>
</tr>
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<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Any event</td>
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<tr>
<td></td>
<td></td>
<td>222 (26.9%)</td>
<td>413</td>
<td>100 (22.1%)</td>
<td>173</td>
<td>122 (32.9%)</td>
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<td></td>
<td>Abdominal pain ileus</td>
<td>72 (8.7%)</td>
<td>86</td>
<td>34 (7.5%)</td>
<td>42</td>
<td>38 (10.2%)</td>
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<td></td>
<td>Vomiting</td>
<td>13 (1.6%)</td>
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<td>9 (2.0%)</td>
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<td>4 (1.1%)</td>
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<td></td>
<td>Ascites</td>
<td>7 (0.8%)</td>
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<td>4 (1.1%)</td>
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<td></td>
<td>Large intestine perforation</td>
<td>6 (0.7%)</td>
<td>6</td>
<td>2 (0.4%)</td>
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<td>4 (1.1%)</td>
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<td></td>
<td>Subileus</td>
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<td>2 (0.4%)</td>
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<td>4 (1.1%)</td>
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<tr>
<td></td>
<td>Nausea</td>
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<td>1 (0.2%)</td>
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<td>3 (0.8%)</td>
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<tr>
<td></td>
<td>Diarrhoea</td>
<td>3 (0.4%)</td>
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<td>1 (0.2%)</td>
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<td>2 (0.5%)</td>
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<td></td>
<td>Intestinal perforation</td>
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<td>1 (0.2%)</td>
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<td>2 (0.5%)</td>
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<tr>
<td></td>
<td>Abdominal pain upper</td>
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<td>2</td>
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<td>2</td>
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<td>1 (0.1%)</td>
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<td>1 (0.1%)</td>
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<td>1</td>
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<td>1 (0.1%)</td>
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<td>MedDRA PT</td>
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<td>≥70 years Patients N=371</td>
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<td>Prior surgery Patients N=779</td>
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<td>≥70 years Patients</td>
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<td>Prior surgery Patients</td>
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<td>N=371</td>
<td>N=45</td>
<td>N=779</td>
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<td></td>
<td></td>
<td>Cases</td>
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<td>Cases</td>
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<td>Peritonitis</td>
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<td>1 (0.3%)</td>
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<td>1 (0.1%)</td>
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</tr>
<tr>
<td>Abdominal abscess</td>
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<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
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<td>1 (0.1%)</td>
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<tr>
<td>Anal abscess</td>
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<td>1 (0.2%)</td>
<td>1 (0.3%)</td>
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<td>1 (0.3%)</td>
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<td>1 (0.1%)</td>
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<td>1 (0.1%)</td>
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<tr>
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<td>1 (0.1%)</td>
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<td>1 (0.1%)</td>
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<td>1 (0.1%)</td>
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<td>9 (2.4%)</td>
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<td>1 (1.8%)</td>
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<td>MedDRA SOC</td>
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<td>&lt;70 years Patients N=453</td>
<td>≥70 years Patients N=371</td>
<td>No prior surgery Patients N=45</td>
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</tr>
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</tr>
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<td>General physical health deterioration</td>
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<td>11 (3.0%)</td>
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<td>2 (0.4%)</td>
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<td>4 (0.5%)</td>
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<td>2 (0.4%)</td>
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<td>1 (0.3%)</td>
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<td>3 (0.4%)</td>
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<td>2 (0.3%)</td>
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<td>2 (0.3%)</td>
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<td>Multiple organ dysfunction syndrome</td>
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<td>2 (0.3%)</td>
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<td>1 (0.2%)</td>
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<td>1 (0.3%)</td>
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<td>1 (0.3%)</td>
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<td>1 (0.3%)</td>
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<td>1 (0.3%)</td>
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<td>2 (4.4%)</td>
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<tr>
<td>Vascular disorders</td>
<td>34 (4.4%)</td>
<td>35</td>
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<tr>
<td>Hypertension</td>
<td>11 (1.3%)</td>
<td>11</td>
<td>3 (0.7%)</td>
<td>3</td>
<td>8 (2.2%)</td>
<td>8</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Hypertensive crisis</td>
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<td>3 (0.7%)</td>
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<td>4 (1.1%)</td>
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<td>7 (0.9%)</td>
</tr>
<tr>
<td>Thrombosis</td>
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<td>2 (0.4%)</td>
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<td>3 (0.8%)</td>
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<td>5 (0.6%)</td>
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<tr>
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</tr>
<tr>
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<td>1 (0.3%)</td>
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<td>3 (0.4%)</td>
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<td>Hypotension</td>
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<td>1 (0.3%)</td>
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<td>1 (0.1%)</td>
</tr>
<tr>
<td>MedDRA SOC</td>
<td>MedDRA PT</td>
<td>Total Patients</td>
<td>&lt;70 years Patients</td>
<td>≥70 years Patients</td>
<td>No prior surgery Patients</td>
<td>Prior surgery Patients</td>
<td>Cases</td>
</tr>
<tr>
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</tr>
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<td>34 (7.1%)</td>
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<td>19 (5.1%)</td>
<td>25</td>
<td>1 (2.2%)</td>
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<tr>
<td>Nervous system disorders</td>
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<td>3 (0.4%)</td>
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<tr>
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<tr>
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<td>2 (0.5%)</td>
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<td>2 (0.3%)</td>
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<td>1 (0.3%)</td>
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<td>1 (0.1%)</td>
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<tr>
<td>Cerebral infarction</td>
<td>1 (0.1%)</td>
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<td>1 (0.3%)</td>
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<td>1 (0.1%)</td>
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</tr>
<tr>
<td>Disturbance in attention</td>
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<td>1 (0.3%)</td>
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</tr>
<tr>
<td>Dysaesthesia</td>
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<td>1 (0.3%)</td>
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<tr>
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<td>1 (0.3%)</td>
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<td>Generalised tonic-clonic seizure</td>
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<td>1 (0.3%)</td>
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<td>1 (0.1%)</td>
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</tr>
<tr>
<td>Headache</td>
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<td>1 (0.3%)</td>
<td>1</td>
<td>1 (0.1%)</td>
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</tr>
<tr>
<td>Hypoesthesia</td>
<td>1 (0.1%)</td>
<td>1 (0.3%)</td>
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<td>1 (0.3%)</td>
<td>1</td>
<td>1 (0.1%)</td>
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</tr>
<tr>
<td>IVth nerve paresis</td>
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<td>1 (0.3%)</td>
<td>1</td>
<td>1 (0.1%)</td>
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</tr>
<tr>
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<td>1 (0.3%)</td>
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<td>1 (0.3%)</td>
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<td>1 (0.1%)</td>
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</tr>
<tr>
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<td>1 (0.3%)</td>
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<td>1 (0.3%)</td>
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<td>1 (0.1%)</td>
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</tr>
<tr>
<td>MedDRA SOC</td>
<td>MedDRA PT</td>
<td>Total Patients N=824</td>
<td>&lt;70 years Patients N=453</td>
<td>≥70 years Patients N=371</td>
<td>No prior surgery Patients N=45</td>
<td>Prior surgery Patients N=779</td>
<td>Cases</td>
</tr>
<tr>
<td>------------</td>
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<td>-------------------------</td>
<td>--------------------------</td>
<td>-----------------------------</td>
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</tr>
<tr>
<td>Noninfective encephalitis</td>
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<tr>
<td>Partial seizures</td>
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<tr>
<td>Peripheral paralysis</td>
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<tr>
<td>Status epilepticus</td>
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<td>1 (0.3%)</td>
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<td>1 (0.1%)</td>
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</tr>
<tr>
<td>Any event</td>
<td>21 (2.5%)</td>
<td>24</td>
<td>13 (2.9%)</td>
<td>15</td>
<td>8 (2.2%)</td>
<td>9</td>
<td>20 (2.6%)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>8 (1.0%)</td>
<td>8</td>
<td>6 (1.3%)</td>
<td>6</td>
<td>2 (0.5%)</td>
<td>2</td>
<td>7 (0.9%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>5 (0.6%)</td>
<td>5</td>
<td>3 (0.7%)</td>
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<td>2 (0.5%)</td>
<td>2</td>
<td>5 (0.6%)</td>
</tr>
<tr>
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<td>1 (0.2%)</td>
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<td>5 (0.6%)</td>
</tr>
<tr>
<td>Pancytopenia</td>
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<td>2 (0.4%)</td>
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<td>1 (0.3%)</td>
<td>1</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
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<td>2 (0.4%)</td>
<td>2</td>
<td>1 (0.3%)</td>
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<td>2 (0.3%)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
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<td>1 (0.2%)</td>
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<td>1 (0.1%)</td>
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<td></td>
</tr>
<tr>
<td>Bone marrow failure</td>
<td>18 (2.2%)</td>
<td>20</td>
<td>8 (1.8%)</td>
<td>9</td>
<td>10 (2.7%)</td>
<td>11</td>
<td>17 (2.2%)</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>7 (0.8%)</td>
<td>7</td>
<td>3 (0.7%)</td>
<td>3</td>
<td>4 (1.1%)</td>
<td>4</td>
<td>7 (0.9%)</td>
</tr>
<tr>
<td>Malignant neoplasm progression</td>
<td>2 (0.2%)</td>
<td>2</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Metastases to meninges</td>
<td>2 (0.2%)</td>
<td>2</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>MedDRA SOC</td>
<td>MedDRA PT</td>
<td>Total Patients N=824</td>
<td>Cases</td>
<td>&lt;70 years Patients N=453</td>
<td>Cases</td>
<td>≥70 years Patients N=371</td>
<td>Cases</td>
</tr>
<tr>
<td>------------</td>
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<td>-------</td>
<td>--------------------------</td>
<td>-------</td>
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</tr>
<tr>
<td>Abdominal wall neoplasm benign</td>
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<td>Cancer pain</td>
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<tr>
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<td>1 (0.3%)</td>
</tr>
<tr>
<td>Malignant pleural effusion</td>
<td>1 (0.1%)</td>
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<td>1 (0.2%)</td>
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<td></td>
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<td>1 (0.3%)</td>
</tr>
<tr>
<td>Metastases to central nervous system</td>
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</tr>
<tr>
<td>Metastases to liver</td>
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<td>1 (0.3%)</td>
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</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
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<td>6 (1.3%)</td>
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<td>11 (3.0%)</td>
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<tr>
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<td>2 (0.4%)</td>
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<td>6 (1.6%)</td>
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<td>1 (0.3%)</td>
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<tr>
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<tr>
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<td>MedDRA PT</td>
<td>Total Patients</td>
<td>&lt;70 years Patients</td>
<td>≥70 years Patients</td>
<td>No prior surgery Patients</td>
<td>Prior surgery Patients</td>
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<tr>
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<td>N=824 Cases</td>
<td>N=453 Cases</td>
<td>N=371 Cases</td>
<td>N=45 Cases</td>
<td>N=779 Cases</td>
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</tr>
<tr>
<td>Pleurisy</td>
<td></td>
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<td>1 (0.2%)</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
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<td>16 (1.9%)</td>
<td>4 (0.9%)</td>
<td>12 (3.2%)</td>
<td>12 (2.2%)</td>
<td>15 (1.9%)</td>
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</tr>
<tr>
<td>Injury, poisoning and</td>
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<td>1 (0.3%)</td>
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</tr>
<tr>
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Clinical Study Report Number 1100702, Final Version 1.0
Protocol ML27765 / P0229
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<td></td>
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<td>Cases</td>
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</tbody>
</table>

[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 frequently reported 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>
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<th>MedDRA SOC</th>
<th>MedDRA PT</th>
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<th>Cases</th>
<th>&lt;70 years Patients N=453</th>
<th>Cases</th>
<th>≥70 years Patients N=371</th>
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<th>No prior surgery Patients N=45</th>
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<td>192 (42.4%)</td>
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<td>Total Patients N=824 Cases</td>
<td>&lt;70 years Patients N=453 Cases</td>
<td>≥70 years Patients N=371 Cases</td>
<td>No prior surgery Patients N=45 Cases</td>
<td>Prior surgery Patients N=779 Cases</td>
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### Clinical Study Report Number 1100702, Final Version 1.0

**Protocol ML27765 / P0229**

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**Respiratory, thoracic and mediastinal disorders**

<p>| Epistaxis                       | 19 (2.3%)                                     | 19                   | 12 (2.6%)             | 12                    | 7 (1.9%)                      | 7                            | 19 (2.4%) 19 |
| Dympnoea                        | 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   |</p>
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### Renal and urinary disorders

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<th>&lt;70 years Patients N=453</th>
<th>≥70 years Patients N=371</th>
<th>No prior surgery Patients N=45</th>
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<td>Cases</td>
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<td>Fall</td>
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<tr>
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<td>1</td>
<td>1 (0.2%)</td>
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<tr>
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<td></td>
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<td>1</td>
<td>1 (0.2%)</td>
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<tr>
<td>Wrist fracture</td>
<td></td>
<td>1 (0.1%)</td>
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<td><strong>Ear and labyrinth disorders</strong></td>
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<td>5 (0.6%)</td>
<td>2 (0.4%)</td>
<td>3 (0.8%)</td>
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<td>MedDRA SOC</td>
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<td>Total Patients N=824</td>
<td>&lt;70 years N=453</td>
<td>≥70 years N=371</td>
<td>No prior surgery N=45</td>
<td>Prior surgery N=779</td>
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<tr>
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<td></td>
<td>Eye inflammation</td>
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<td>Immune system disorders</td>
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<td>Seasonal allergy</td>
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<td>Reproductive system and breast disorders</td>
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<tr>
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<td>Vaginal disorder</td>
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<tr>
<td></td>
<td>Vaginal fistula</td>
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<tr>
<td>Surgical and medical procedures</td>
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<td>Dental care</td>
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</tr>
</tbody>
</table>

[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.
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.
^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>
<thead>
<tr>
<th>MedDRA SOC</th>
<th>MedDRA PT</th>
<th>Total Patients N=824 Cases</th>
<th>&lt;70 years Patients N=453 Cases</th>
<th>≥70 years Patients N=371 Cases</th>
<th>No prior surgery Patients N=45 Cases</th>
<th>Prior surgery Patients N=779 Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any event, n, %, n (cases)</td>
<td></td>
<td>145 (17.6%)</td>
<td>203 (14.6%)</td>
<td>100 (21.3%)</td>
<td>103 (13.3%)</td>
<td>13 (17.8%)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Any event</td>
<td>33 (4.0%)</td>
<td>33 (3.5%)</td>
<td>16 (4.6%)</td>
<td>17 (3.2%)</td>
<td>33 (4.2%)</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>21 (2.5%)</td>
<td>21 (2.0%)</td>
<td>9 (3.2%)</td>
<td>12 (3.2%)</td>
<td>21 (2.7%)</td>
</tr>
<tr>
<td></td>
<td>Deep vein thrombosis</td>
<td>5 (0.6%)</td>
<td>5 (0.4%)</td>
<td>2 (0.8%)</td>
<td>3 (0.8%)</td>
<td>5 (0.6%)</td>
</tr>
<tr>
<td></td>
<td>Thrombosis</td>
<td>4 (0.5%)</td>
<td>4 (0.7%)</td>
<td>3 (0.8%)</td>
<td>1 (0.3%)</td>
<td>4 (0.5%)</td>
</tr>
<tr>
<td></td>
<td>Embolism arterial</td>
<td>1 (0.1%)</td>
<td>1 (0.1%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
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<tr>
<td></td>
<td>Hypertensive crisis</td>
<td>1 (0.1%)</td>
<td>1 (0.2%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td></td>
<td>Venous thrombosis limb</td>
<td>1 (0.1%)</td>
<td>1 (0.2%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Any event</td>
<td>27 (3.3%)</td>
<td>35 (3.3%)</td>
<td>21 (3.2%)</td>
<td>14 (2.6%)</td>
<td>5 (2.3%)</td>
</tr>
<tr>
<td></td>
<td>Ileus</td>
<td>6 (0.7%)</td>
<td>6 (0.9%)</td>
<td>4 (0.9%)</td>
<td>2 (0.5%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td></td>
<td>Large intestine perforation</td>
<td>5 (0.6%)</td>
<td>5 (0.7%)</td>
<td>3 (0.8%)</td>
<td>2 (0.5%)</td>
<td>1 (2.2%)</td>
</tr>
<tr>
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<td>Abdominal pain</td>
<td>2 (0.2%)</td>
<td>2 (0.2%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>2 (0.3%)</td>
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<tr>
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<td>Ascites</td>
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<td>2 (0.2%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
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<td>Gastric perforation</td>
<td>2 (0.2%)</td>
<td>2 (0.2%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
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<td>Subileus</td>
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<td>2 (0.2%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain upper</td>
<td>1 (0.1%)</td>
<td>1 (0.2%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td></td>
<td>Colitis</td>
<td>1 (0.1%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea</td>
<td>1 (0.1%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
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<tr>
<td></td>
<td>Diverticulum intestinal</td>
<td>1 (0.1%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td></td>
<td>Duodenal obstruction</td>
<td>1 (0.1%)</td>
<td>1 (0.2%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
</tr>
</tbody>
</table>

Table 8-62  Treatment-emergent adverse events leading to discontinuation of bevacizumab (Avastin®) treatment (MedDRA PT by SOC) – total and by subgroup (CAP)
<table>
<thead>
<tr>
<th>MedDRA SOC</th>
<th>MedDRA PT</th>
<th>Total Patients N=824</th>
<th>&lt;70 years Patients N=453</th>
<th>≥70 years Patients N=371</th>
<th>No prior surgery Patients N=45</th>
<th>Prior surgery Patients N=779</th>
<th>Cases</th>
<th>Cases</th>
<th>Cases</th>
<th>Cases</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyschezia</td>
<td>1 (0.1%)</td>
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<td>1</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
<td>1</td>
<td></td>
<td></td>
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<td></td>
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<td>Enterocutaneous fistula</td>
<td>1 (0.1%)</td>
<td>1</td>
<td></td>
<td></td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
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<tr>
<td>Gastric ulcer</td>
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<td>1</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Gastrintestinal wall thickening</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemorrhoids</td>
<td>1 (0.1%)</td>
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<td>1</td>
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<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
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</tr>
<tr>
<td>Impaired gastric emptying</td>
<td>1 (0.1%)</td>
<td>1</td>
<td></td>
<td></td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
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<td></td>
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</tr>
<tr>
<td>Intestinal obstruction</td>
<td>1 (0.1%)</td>
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<td></td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
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</tr>
<tr>
<td>Mechanical ileus</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
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</tr>
<tr>
<td>Nausea</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Short-bowel syndrome</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
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</tr>
<tr>
<td>General disorders and administration site conditions</td>
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</tr>
<tr>
<td>General physical health deterioration</td>
<td>7 (0.8%)</td>
<td>7</td>
<td>2 (0.4%)</td>
<td>2</td>
<td>5 (1.3%)</td>
<td>5</td>
<td>7 (0.9%)</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired healing</td>
<td>3 (0.4%)</td>
<td>3</td>
<td>2 (0.4%)</td>
<td>2</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>3 (0.4%)</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>2 (0.2%)</td>
<td>2</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>2 (0.3%)</td>
<td>2</td>
<td></td>
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</tr>
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<td>Fatigue</td>
<td>2 (0.2%)</td>
<td>2</td>
<td>2 (0.4%)</td>
<td>2</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>2 (0.3%)</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>1 (0.1%)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>1 (0.1%)</td>
<td>1</td>
<td></td>
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</tr>
<tr>
<td>Death</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>1 (0.1%)</td>
<td>1</td>
<td></td>
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</tr>
<tr>
<td>Oedema peripheral</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>1 (0.1%)</td>
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<td></td>
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<td>≥70 years Patients</td>
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<td>≥70 years Patients N=371</td>
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<td>Prior surgery Patients N=779</td>
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<td>Cases</td>
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<td>10 (1.3%)</td>
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<td>Malignant neoplasm progression</td>
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<td></td>
<td>Metastases to central nervous system</td>
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<td>1 (2.2%)</td>
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<td>Metastases to liver</td>
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<td>Respiratory, thoracic and mediastinal disorders</td>
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<td>5 (1.3%)</td>
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<td>≥70 years Patients N=371</td>
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<td>Prior surgery Patients N=779</td>
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<tr>
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<td>7 (0.9%)</td>
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<tr>
<td>Injury, poisoning and procedural complications</td>
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<td>2 (0.4%)</td>
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<tr>
<td>Ankle fracture</td>
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<td>1 (0.3%)</td>
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<tr>
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<tr>
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<tr>
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<td>8</td>
<td>4 (0.9%)</td>
<td>4</td>
<td>3 (0.8%)</td>
<td>4</td>
<td>7 (0.9%)</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3 (0.4%)</td>
<td>3</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>2 (0.5%)</td>
<td>2</td>
<td>3 (0.4%)</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>2 (0.2%)</td>
<td>2</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>2 (0.3%)</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fistula</td>
<td>2 (0.2%)</td>
<td>2</td>
<td>2 (0.4%)</td>
<td>2</td>
<td></td>
<td></td>
<td>2 (0.3%)</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>1 (0.1%)</td>
<td>1</td>
<td></td>
<td></td>
<td>1 (0.3%)</td>
<td>1</td>
<td></td>
<td>1 (0.1%)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any event</td>
<td>5 (0.6%)</td>
<td>5</td>
<td>4 (0.9%)</td>
<td>4</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>5 (0.6%)</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td>2 (0.2%)</td>
<td>2</td>
<td>2 (0.4%)</td>
<td>2</td>
<td></td>
<td></td>
<td>2 (0.3%)</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1 (0.1%)</td>
<td>1</td>
<td></td>
<td></td>
<td>1 (0.3%)</td>
<td>1</td>
<td></td>
<td>1 (0.1%)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic dysfunction</td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.2%)</td>
<td>1</td>
<td></td>
<td></td>
<td>1 (0.1%)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MedDRA SOC</td>
<td>MedDRA PT</td>
<td>Total Patients N=824</td>
<td>&lt;70 years N=453</td>
<td>≥70 years N=371</td>
<td>No prior surgery N=45</td>
<td>Prior surgery N=779</td>
<td>Cases</td>
<td>Patients</td>
<td>Cases</td>
<td>Patients</td>
<td>Cases</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>-------------------</td>
<td>----------------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>----------------------</td>
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<td>-------</td>
<td>----------</td>
<td>-------</td>
<td>----------</td>
<td>-------</td>
</tr>
<tr>
<td>Left ventricular dysfunction</td>
<td>Any event</td>
<td>1 (0.1%)</td>
<td>1 (0.2%)</td>
<td>1 (0.8%)</td>
<td>1</td>
<td>1</td>
<td>0.1%</td>
<td>453</td>
<td>2 (0.4%)</td>
<td>371</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin ulcer</td>
<td></td>
<td>3 (0.4%)</td>
<td>3 (0.8%)</td>
<td>3 (0.8%)</td>
<td>3</td>
<td>3</td>
<td>0.4%</td>
<td>453</td>
<td>1 (0.3%)</td>
<td>371</td>
<td>0.2%</td>
</tr>
<tr>
<td>Hidradenitis</td>
<td></td>
<td>1 (0.1%)</td>
<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1</td>
<td>0.1%</td>
<td>453</td>
<td>0.4%</td>
<td>371</td>
<td>0.2%</td>
</tr>
<tr>
<td>Pruritus generalised</td>
<td></td>
<td>1 (0.1%)</td>
<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1</td>
<td>0.1%</td>
<td>453</td>
<td>0.4%</td>
<td>371</td>
<td>0.2%</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td>3 (0.4%)</td>
<td>5 (0.6%)</td>
<td>4 (0.8%)</td>
<td>1 (0.3%)</td>
<td>1 (2.2%)</td>
<td>0.4%</td>
<td>453</td>
<td>2 (0.4%)</td>
<td>371</td>
<td>0.8%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>Any event</td>
<td>3 (0.4%)</td>
<td>2 (0.4%)</td>
<td>2 (0.4%)</td>
<td>1 (0.3%)</td>
<td>1 (2.2%)</td>
<td>0.4%</td>
<td>453</td>
<td>0.3%</td>
<td>371</td>
<td>0.4%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td>2 (0.2%)</td>
<td>2 (0.4%)</td>
<td>2 (0.4%)</td>
<td>1 (0.3%)</td>
<td>1 (2.2%)</td>
<td>0.2%</td>
<td>453</td>
<td>0.4%</td>
<td>371</td>
<td>0.4%</td>
</tr>
<tr>
<td>Liver function test increased</td>
<td></td>
<td>1 (0.1%)</td>
<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1</td>
<td>0.1%</td>
<td>453</td>
<td>0.2%</td>
<td>371</td>
<td>0.2%</td>
</tr>
<tr>
<td>Protein urine present</td>
<td></td>
<td>1 (0.1%)</td>
<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1</td>
<td>0.1%</td>
<td>453</td>
<td>0.2%</td>
<td>371</td>
<td>0.2%</td>
</tr>
<tr>
<td>Weight decreased</td>
<td></td>
<td>1 (0.1%)</td>
<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1</td>
<td>0.1%</td>
<td>453</td>
<td>0.2%</td>
<td>371</td>
<td>0.2%</td>
</tr>
<tr>
<td>Vaginal fistula</td>
<td>Any event</td>
<td>3 (0.4%)</td>
<td>3 (0.8%)</td>
<td>3 (0.8%)</td>
<td>1</td>
<td>1</td>
<td>0.4%</td>
<td>453</td>
<td>0.4%</td>
<td>371</td>
<td>0.4%</td>
</tr>
<tr>
<td>Vaginal haemorrhage</td>
<td></td>
<td>2 (0.2%)</td>
<td>2 (0.5%)</td>
<td>2 (0.5%)</td>
<td>2</td>
<td>2</td>
<td>0.2%</td>
<td>453</td>
<td>0.4%</td>
<td>371</td>
<td>0.4%</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td>1 (0.1%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>1</td>
<td>0.1%</td>
<td>453</td>
<td>0.3%</td>
<td>371</td>
<td>0.3%</td>
</tr>
<tr>
<td>Dehydration</td>
<td>Any event</td>
<td>1 (0.1%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>1</td>
<td>0.1%</td>
<td>453</td>
<td>0.3%</td>
<td>371</td>
<td>0.3%</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td></td>
<td>1 (0.1%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1</td>
<td>1</td>
<td>0.1%</td>
<td>453</td>
<td>0.3%</td>
<td>371</td>
<td>0.3%</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td>1 (0.1%)</td>
<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1</td>
<td>0.1%</td>
<td>453</td>
<td>0.2%</td>
<td>371</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>MedDRA SOC</th>
<th>MedDRA PT</th>
<th>Total Patients N=824</th>
<th>&lt;70 years Patients N=453</th>
<th>≥70 years Patients N=371</th>
<th>No prior surgery Patients N=45</th>
<th>Prior surgery Patients N=779</th>
<th>Cases</th>
<th>Cases</th>
<th>Cases</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autoimmune hepatitis</strong></td>
<td>Any event</td>
<td>1 (0.1%)</td>
<td>1 (0.2%)</td>
<td>1</td>
<td></td>
<td>1 (0.1%)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
<td>Any event</td>
<td>1 (0.1%)</td>
<td>1 (0.2%)</td>
<td>1</td>
<td></td>
<td>1 (0.1%)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sarcoidosis</strong></td>
<td>Any event</td>
<td>1 (0.1%)</td>
<td>1 (0.2%)</td>
<td>1</td>
<td></td>
<td>1 (0.1%)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Surgical and medical procedures</strong></td>
<td></td>
<td>1 (0.1%)</td>
<td>1 (0.2%)</td>
<td>1</td>
<td></td>
<td>1 (0.1%)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[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)

<table>
<thead>
<tr>
<th></th>
<th>Patients¹</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>Total number of deaths, n, %</td>
<td>181 (22.0%)</td>
<td></td>
</tr>
<tr>
<td>Patients reported with fatal TEAE, n, %, n (cases)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any TEAE</td>
<td>616 (74.8%)</td>
<td>3,645</td>
</tr>
<tr>
<td>All fatal TEAE²</td>
<td>30 (3.6%)</td>
<td>43</td>
</tr>
<tr>
<td>Fatal causally related TEAE³</td>
<td>5 (0.6%)</td>
<td>6</td>
</tr>
<tr>
<td>Fatal non-related TEAE³</td>
<td>24 (2.9%)</td>
<td>29</td>
</tr>
<tr>
<td>Fatal TEAE – causality unknown³</td>
<td>5 (0.6%)</td>
<td>8</td>
</tr>
</tbody>
</table>

¹Patients can occur in more than one category of the table. ²For 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. ³Causally 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)**

<table>
<thead>
<tr>
<th>MedDRA SOC</th>
<th>MedDRA PT</th>
<th>Total Patients N=824</th>
<th>&lt;70 years Patients N=453</th>
<th>≥70 years Patients N=371</th>
<th>No prior surgery Patients N=45</th>
<th>Prior surgery Patients N=779</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Patients with any fatal event, n, %, n (cases)</em></td>
<td>Any event</td>
<td>12 (1.5%)</td>
<td>12 (0.9%)</td>
<td>4 (0.9%)</td>
<td>8 (2.2%)</td>
<td>8 (0.7%)</td>
<td>12 (1.5%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Death</td>
<td>6 (0.7%)</td>
<td>2 (0.4%)</td>
<td>2 (0.4%)</td>
<td>4 (1.1%)</td>
<td>4 (0.8%)</td>
<td>6 (0.8%)</td>
</tr>
<tr>
<td></td>
<td>General physical health deterioration</td>
<td>3 (0.4%)</td>
<td>3 (0.8%)</td>
<td>3 (0.8%)</td>
<td>3 (0.8%)</td>
<td>3 (0.4%)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Multiple organ dysfunction syndrome</td>
<td>2 (0.2%)</td>
<td>2 (0.4%)</td>
<td>2 (0.4%)</td>
<td>2 (0.4%)</td>
<td>2 (0.3%)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Impaired healing</td>
<td>1 (0.1%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal disorders¹</td>
<td>Any event</td>
<td>9 (1.1%)</td>
<td>4 (0.9%)</td>
<td>4 (0.9%)</td>
<td>5 (1.3%)</td>
<td>7 (2.4%)</td>
<td>7 (0.9%)</td>
</tr>
<tr>
<td></td>
<td>Ileus</td>
<td>3 (0.4%)</td>
<td>2 (0.4%)</td>
<td>3 (0.4%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>3 (0.4%)</td>
</tr>
<tr>
<td></td>
<td>Intestinal perforation</td>
<td>3 (0.4%)</td>
<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
<td>2 (0.5%)</td>
<td>2 (0.4%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td></td>
<td>Ascites</td>
<td>1 (0.1%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea</td>
<td>1 (0.1%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td></td>
<td>Duodenal obstruction</td>
<td>1 (0.1%)</td>
<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td></td>
<td>Intestinal ischaemia</td>
<td>1 (0.1%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>1 (0.1%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>Any event</td>
<td>9 (1.1%)</td>
<td>5 (1.1%)</td>
<td>6 (1.1%)</td>
<td>4 (1.1%)</td>
<td>5 (2.2%)</td>
<td>2 (0.4%)</td>
</tr>
<tr>
<td></td>
<td>Malignant neoplasm progression</td>
<td>4 (0.5%)</td>
<td>2 (0.4%)</td>
<td>2 (0.4%)</td>
<td>2 (0.4%)</td>
<td>2 (0.5%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td></td>
<td>Metastases to meninges</td>
<td>2 (0.2%)</td>
<td>2 (0.2%)</td>
<td>1 (0.2%)</td>
<td>1 (0.3%)</td>
<td>1 (2.2%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>MedDRA SOC</td>
<td>MedDRA PT</td>
<td>Total Patients</td>
<td>&lt;70 years Patients</td>
<td>≥70 years Patients</td>
<td>No prior surgery Patients</td>
<td>Prior surgery Patients</td>
<td></td>
</tr>
<tr>
<td>----------------------------</td>
<td>-----------------------------------------------</td>
<td>----------------</td>
<td>--------------------</td>
<td>--------------------</td>
<td>--------------------------</td>
<td>------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=824</td>
<td>Cases</td>
<td>N=453</td>
<td>Cases</td>
<td>N=371</td>
<td>Cases</td>
<td>N=45</td>
</tr>
<tr>
<td>Metastases to peritoneum</td>
<td></td>
<td>2 (0.2%)</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Malignant pleural effusion</td>
<td></td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.2%)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastases to central nervous system</td>
<td></td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.2%)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoplasm progression</td>
<td></td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.2%)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td>2 (0.2%)</td>
<td>1</td>
<td>1 (0.2%)</td>
<td>1</td>
<td>1 (0.3%)</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
<td>1 (0.1%)</td>
<td>1</td>
<td></td>
<td>1 (0.3%)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Urosepsis</td>
<td></td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.2%)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td>1 (0.1%)</td>
<td>2</td>
<td>1 (0.2%)</td>
<td>2</td>
<td>1 (2.2%)</td>
<td>2</td>
</tr>
<tr>
<td>Leukopenia</td>
<td></td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.2%)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.2%)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.2%)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td></td>
<td>1 (0.1%)</td>
<td>1</td>
<td></td>
<td>1 (0.3%)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td>1 (0.1%)</td>
<td>1</td>
<td></td>
<td>1 (0.2%)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td></td>
<td>1 (0.1%)</td>
<td>1</td>
<td></td>
<td>1 (0.3%)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.2%)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td>1 (0.1%)</td>
<td>1</td>
<td>1 (0.2%)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[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.

1For 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)]

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Date of first administration</th>
<th>Preferred Term</th>
<th>System Organ Class</th>
<th>Start date of adverse event</th>
<th>End date of adverse event</th>
<th>Causality to Bevacizumab (Avastin®)</th>
<th>Action taken with Bevacizumab (Avastin®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>77007</td>
<td>2013-09-04</td>
<td>Intestinal ischaemia</td>
<td>Gastrointestinal disorders</td>
<td>2013-11-19</td>
<td>2013-11-19</td>
<td>Not related</td>
<td>None</td>
</tr>
<tr>
<td>40002</td>
<td>2012-12-05</td>
<td>Intestinal perforation</td>
<td>Gastrointestinal disorders</td>
<td>2013-09-23</td>
<td>2013-09-29</td>
<td>Not related</td>
<td>None</td>
</tr>
<tr>
<td>215001</td>
<td>2013-03-25</td>
<td>Ileus</td>
<td>Gastrointestinal disorders</td>
<td>2013-06-27</td>
<td>2013-07-16</td>
<td>YES</td>
<td>None</td>
</tr>
<tr>
<td>215001</td>
<td>2013-03-25</td>
<td>Ileus</td>
<td>Gastrointestinal disorders</td>
<td>2013-07-16</td>
<td>2013-07-16</td>
<td>Not related</td>
<td>None</td>
</tr>
<tr>
<td>245009</td>
<td>2014-03-13</td>
<td>Ileus</td>
<td>Gastrointestinal disorders</td>
<td>2014-09-06</td>
<td>2014-09-29</td>
<td>Unknown</td>
<td>Drug Withdrawn</td>
</tr>
<tr>
<td>22006</td>
<td>2013-03-06</td>
<td>Ileus</td>
<td>Gastrointestinal disorders</td>
<td>2014-02-13</td>
<td>2014-02-22</td>
<td>Unknown</td>
<td>Temporary interruption</td>
</tr>
<tr>
<td>22006</td>
<td>2013-03-06</td>
<td>Vomiting</td>
<td>Gastrointestinal disorders</td>
<td>2014-02-13</td>
<td>2014-02-22</td>
<td>Unknown</td>
<td>Temporary interruption</td>
</tr>
<tr>
<td>22006</td>
<td>2013-03-06</td>
<td>Diarrhoea</td>
<td>Gastrointestinal disorders</td>
<td>2014-02-13</td>
<td>2014-02-22</td>
<td>Unknown</td>
<td>Temporary interruption</td>
</tr>
<tr>
<td>76013</td>
<td>2014-10-09</td>
<td>Ascites</td>
<td>Gastrointestinal disorders</td>
<td>2015-09-01</td>
<td>2015-09-12</td>
<td>Not related</td>
<td>None</td>
</tr>
<tr>
<td>Patient ID</td>
<td>Date of first administration</td>
<td>Preferred Term</td>
<td>System Organ Class</td>
<td>Start date of adverse event</td>
<td>End date of adverse event</td>
<td>Causality to Bevacizumab (Avastin®)</td>
<td>Action taken with Bevacizumab (Avastin®)</td>
</tr>
<tr>
<td>-----------</td>
<td>-----------------------------</td>
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<td>---------------------------------------------------------</td>
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<td>----------------------------</td>
<td>--------------------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>242001</td>
<td>2013-06-27</td>
<td>Death</td>
<td>General disorders and administration site conditions</td>
<td>2013-08-20</td>
<td>2013-08-20</td>
<td>Unknown</td>
<td>None</td>
</tr>
<tr>
<td>270004</td>
<td>2016-12-20</td>
<td>Death</td>
<td>General disorders and administration site conditions</td>
<td>2017-05-06</td>
<td>2017-05-06</td>
<td>Not related</td>
<td>None</td>
</tr>
<tr>
<td>38007</td>
<td>2016-08-04</td>
<td>Death</td>
<td>General disorders and administration site conditions</td>
<td>2017-10-08</td>
<td>2017-10-08</td>
<td>Not related</td>
<td>None</td>
</tr>
<tr>
<td>98004</td>
<td>2013-08-28</td>
<td>Multiple organ dysfunction syndrome</td>
<td>General disorders and administration site conditions</td>
<td>2013-09-30</td>
<td>2013-10-08</td>
<td>Not related</td>
<td>None</td>
</tr>
<tr>
<td>185002</td>
<td>2012-10-23</td>
<td>Impaired healing</td>
<td>General disorders and administration site conditions</td>
<td>2012-11-14</td>
<td>2013-01-11</td>
<td>Not related</td>
<td>Temporary interruption</td>
</tr>
<tr>
<td>156005</td>
<td>2014-01-07</td>
<td>Death</td>
<td>General disorders and administration site conditions</td>
<td>2014-10-25</td>
<td>2014-10-25</td>
<td>Possible</td>
<td>Dose reduction followed by permanent discontinuation</td>
</tr>
<tr>
<td>22006</td>
<td>2013-03-06</td>
<td>General physical health deterioration</td>
<td>General disorders and administration site conditions</td>
<td>2014-02-10</td>
<td>2014-02-22</td>
<td>Not related</td>
<td>Temporary interruption</td>
</tr>
<tr>
<td>76020</td>
<td>2016-10-17</td>
<td>Death</td>
<td>General disorders and administration site conditions</td>
<td>2016-10-26</td>
<td>2016-10-26</td>
<td>Not related</td>
<td>None</td>
</tr>
<tr>
<td>125004</td>
<td>2013-11-19</td>
<td>Multiple organ dysfunction syndrome</td>
<td>General disorders and administration site conditions</td>
<td>2014-10-06</td>
<td>2014-10-31</td>
<td>Not related</td>
<td>Temporary interruption</td>
</tr>
<tr>
<td>195001</td>
<td>2013-01-22</td>
<td>Death</td>
<td>General disorders and administration site conditions</td>
<td>2014-06-16</td>
<td>2014-06-16</td>
<td>Unknown</td>
<td>None</td>
</tr>
<tr>
<td>261005</td>
<td>2016-11-22</td>
<td>General physical health deterioration</td>
<td>General disorders and administration site conditions</td>
<td>2017-04-11</td>
<td>2017-05-15</td>
<td>Not related</td>
<td>Drug Withdrawn</td>
</tr>
<tr>
<td>Patient ID</td>
<td>Date of first administration</td>
<td>Preferred Term</td>
<td>System Organ Class</td>
<td>Start date of adverse event</td>
<td>End date of adverse event</td>
<td>Causality to Bevacizumab (Avastin&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Action taken with Bevacizumab (Avastin&lt;sup&gt;®&lt;/sup&gt;)</td>
</tr>
<tr>
<td>------------</td>
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<td>-----------------------------------------------------</td>
<td>--------------------------------------------------------</td>
<td>-----------------------------</td>
<td>----------------------------</td>
<td>-----------------------------------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>261006</td>
<td>2016-11-04</td>
<td>General physical health deterioration</td>
<td>General disorders and administration site conditions</td>
<td>2016-12-21</td>
<td>2016-12-21</td>
<td>Not related</td>
<td>Drug Withdrawn</td>
</tr>
<tr>
<td>143007</td>
<td>2014-02-13</td>
<td>Hepatotoxicity</td>
<td>Hepatobiliary disorders</td>
<td>2014-05-08</td>
<td>2014-08-13</td>
<td>Not related</td>
<td>None</td>
</tr>
<tr>
<td>98004</td>
<td>2013-08-28</td>
<td>Urosepsis</td>
<td>Infections and infestations</td>
<td>2013-09-30</td>
<td>2013-10-08</td>
<td>Probable</td>
<td>Drug Withdrawn</td>
</tr>
<tr>
<td>22011</td>
<td>2015-12-02</td>
<td>Pneumonia</td>
<td>Infections and infestations</td>
<td>2016-04-05</td>
<td>2016-04-05</td>
<td>Not related</td>
<td>Drug Withdrawn</td>
</tr>
<tr>
<td>154004</td>
<td>2013-03-07</td>
<td>Malignant neoplasm progression</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>2013-09-16</td>
<td>2014-01-20</td>
<td>Not related</td>
<td>Drug Withdrawn</td>
</tr>
<tr>
<td>21008</td>
<td>2013-07-24</td>
<td>Metastases to meninges</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>2014-04-03</td>
<td></td>
<td>Not related</td>
<td>None</td>
</tr>
<tr>
<td>6020</td>
<td>2013-12-04</td>
<td>Malignant neoplasm progression</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>2015-03-18</td>
<td>2015-04-30</td>
<td>Not related</td>
<td>None</td>
</tr>
<tr>
<td>121003</td>
<td>2014-12-30</td>
<td>Metastases to peritoneum</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>2016-01-05</td>
<td>2016-04-06</td>
<td>Not related</td>
<td>None</td>
</tr>
<tr>
<td>134001</td>
<td>2012-07-10</td>
<td>Malignant neoplasm progression</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>2012-08-06</td>
<td>2012-09-03</td>
<td>Not related</td>
<td>Drug Withdrawn</td>
</tr>
<tr>
<td>22006</td>
<td>2013-03-06</td>
<td>Malignant neoplasm progression</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>2014-02-10</td>
<td>2014-02-22</td>
<td>Unknown</td>
<td>Drug Withdrawn</td>
</tr>
<tr>
<td>125004</td>
<td>2013-11-19</td>
<td>Metastases to peritoneum</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>2014-10-22</td>
<td>2014-10-31</td>
<td>Not related</td>
<td>Drug Withdrawn</td>
</tr>
<tr>
<td>Patient ID</td>
<td>Date of first administration</td>
<td>Preferred Term</td>
<td>System Organ Class</td>
<td>Start date of adverse event</td>
<td>End date of adverse event</td>
<td>Causality to Bevacizumab (Avastin®)</td>
<td>Action taken with Bevacizumab (Avastin®)</td>
</tr>
<tr>
<td>-----------</td>
<td>-----------------------------</td>
<td>---------------------------------</td>
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<td>---------------------------</td>
<td>-------------------------------------</td>
<td>-----------------------------------------</td>
</tr>
<tr>
<td>120003</td>
<td>2014-03-26</td>
<td>Neoplasm progression</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>2014-12-25</td>
<td>2014-12-25</td>
<td>Not related</td>
<td>None</td>
</tr>
<tr>
<td>77005</td>
<td>2013-05-17</td>
<td>Metastases to central nervous system</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>2013-10-15</td>
<td>2013-12-06</td>
<td>Not related</td>
<td>Drug Withdrawn</td>
</tr>
<tr>
<td>77005</td>
<td>2013-05-17</td>
<td>Metastases to meninges</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>2013-10-15</td>
<td>2013-12-06</td>
<td>Not related</td>
<td>Drug Withdrawn</td>
</tr>
<tr>
<td>98004</td>
<td>2013-08-28</td>
<td>Acute kidney injury</td>
<td>Renal and urinary disorders</td>
<td>2013-10-08</td>
<td>2013-10-08</td>
<td>Probable</td>
<td>Drug Withdrawn</td>
</tr>
<tr>
<td>60001</td>
<td>2013-03-27</td>
<td>Angiopathy</td>
<td>Vascular disorders</td>
<td>2013-12-18</td>
<td>2013-12-18</td>
<td>Unknown</td>
<td>None</td>
</tr>
</tbody>
</table>

[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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CAP</th>
<th>Patients &lt;70 years</th>
<th>Patients ≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients enrolled, N</td>
<td>824</td>
<td>453</td>
<td>371</td>
</tr>
<tr>
<td>Age at start of therapy, years^1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>68.0</td>
<td>58.4</td>
<td>74.6</td>
</tr>
<tr>
<td>Min - Max</td>
<td>25.9-83.4</td>
<td>25.9-70.2</td>
<td>70.1-83.4</td>
</tr>
<tr>
<td>Age at start of therapy &lt;70 / ≥70 years, n, (%)^1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70 years</td>
<td>451 (54.7%)</td>
<td>451 (99.6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>≥70 years</td>
<td>373 (45.3%)</td>
<td>2 (0.4%)</td>
<td>371 (100%)</td>
</tr>
<tr>
<td>ECOG performance status, n, (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>297 (38.2%)</td>
<td>199 (45.7%)</td>
<td>98 (28.6%)</td>
</tr>
<tr>
<td>1</td>
<td>389 (50.0%)</td>
<td>194 (44.6%)</td>
<td>195 (56.9%)</td>
</tr>
<tr>
<td>2</td>
<td>77 (9.9%)</td>
<td>36 (8.3%)</td>
<td>41 (12.0%)</td>
</tr>
<tr>
<td>3</td>
<td>15 (1.9%)</td>
<td>6 (1.4%)</td>
<td>9 (2.6%)</td>
</tr>
<tr>
<td>Missing</td>
<td>46</td>
<td>18</td>
<td>28</td>
</tr>
<tr>
<td>Ongoing comorbidities, n (%)</td>
<td>365 (44.3%)</td>
<td>142 (31.3%)</td>
<td>223 (60.1%)</td>
</tr>
<tr>
<td>Persistent arterial hypertension, n (%)</td>
<td>339 (41.1%)</td>
<td>132 (29.1%)</td>
<td>207 (55.8%)</td>
</tr>
<tr>
<td>Charlson Comorbidity Index^2</td>
<td>0</td>
<td>644 (78.2%)</td>
<td>364 (80.4%)</td>
</tr>
<tr>
<td></td>
<td>≥1</td>
<td>180 (21.8%)</td>
<td>89 (19.6%)</td>
</tr>
<tr>
<td>Type of tumor, n (%)</td>
<td></td>
<td>46</td>
<td>18</td>
</tr>
<tr>
<td>Epithelial ovarian carcinoma</td>
<td>662 (80.3%)</td>
<td>367 (81.0%)</td>
<td>295 (79.5%)</td>
</tr>
<tr>
<td>Fallopian tube carcinoma</td>
<td>58 (7.0%)</td>
<td>27 (6.0%)</td>
<td>31 (8.4%)</td>
</tr>
<tr>
<td>Peritoneal carcinoma</td>
<td>104 (12.6%)</td>
<td>59 (13.0%)</td>
<td>45 (12.1%)</td>
</tr>
<tr>
<td>FIGO stage, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>116 (14.1%)</td>
<td>65 (14.3%)</td>
<td>51 (13.7%)</td>
</tr>
<tr>
<td>IIIC</td>
<td>472 (57.3%)</td>
<td>265 (58.5%)</td>
<td>207 (55.8%)</td>
</tr>
<tr>
<td>IV</td>
<td>236 (28.6%)</td>
<td>123 (27.2%)</td>
<td>113 (30.5%)</td>
</tr>
<tr>
<td>Grading, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>22 (2.7%)</td>
<td>13 (2.9%)</td>
<td>9 (2.4%)</td>
</tr>
<tr>
<td>G2</td>
<td>153 (18.6%)</td>
<td>99 (21.9%)</td>
<td>54 (14.6%)</td>
</tr>
<tr>
<td>G3</td>
<td>565 (68.6%)</td>
<td>312 (68.9%)</td>
<td>253 (68.2%)</td>
</tr>
<tr>
<td>G4</td>
<td>12 (1.5%)</td>
<td>2 (0.4%)</td>
<td>10 (2.7%)</td>
</tr>
<tr>
<td>Grading unknown</td>
<td>72 (8.7%)</td>
<td>27 (6.0%)</td>
<td>45 (12.1%)</td>
</tr>
<tr>
<td>Histological type, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear cell</td>
<td>13 (1.7%)</td>
<td>9 (2.0%)</td>
<td>4 (1.2%)</td>
</tr>
<tr>
<td>Endometroid</td>
<td>22 (2.8%)</td>
<td>14 (3.2%)</td>
<td>8 (2.4%)</td>
</tr>
<tr>
<td>Mucinous</td>
<td>19 (2.4%)</td>
<td>13 (3.0%)</td>
<td>6 (1.8%)</td>
</tr>
<tr>
<td>Serous</td>
<td>606 (77.8%)</td>
<td>333 (75.7%)</td>
<td>273 (70.5%)</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>24 (3.1%)</td>
<td>13 (3.0%)</td>
<td>11 (3.2%)</td>
</tr>
<tr>
<td>Other</td>
<td>95 (12.2%)</td>
<td>58 (13.2%)</td>
<td>37 (10.9%)</td>
</tr>
<tr>
<td>Missing</td>
<td>45</td>
<td>13</td>
<td>32</td>
</tr>
</tbody>
</table>

[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.

^1Age 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. ^2Charlson 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

<table>
<thead>
<tr>
<th>Age subgroup</th>
<th>Surgery subgroup</th>
<th>CAP</th>
<th>Patients</th>
<th>Patients</th>
<th>No prior surgery</th>
<th>Prior surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70 years</td>
<td>Patients</td>
<td>824</td>
<td>453</td>
<td>371</td>
<td>45</td>
<td>779</td>
</tr>
<tr>
<td>≥70 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Progression-free survival\(^1\)

<table>
<thead>
<tr>
<th>Events, n [%](^2)</th>
<th>CAP</th>
<th>Patients</th>
<th>Patients</th>
<th>No prior surgery</th>
<th>Prior surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>368</td>
<td>453</td>
<td>(44.7%)</td>
<td>(44.2%)</td>
<td>(45.3%)</td>
<td>(60.0%)</td>
</tr>
<tr>
<td>200</td>
<td>168</td>
<td>(44.2%)</td>
<td>(45.3%)</td>
<td>(60.0%)</td>
<td>(43.8%)</td>
</tr>
<tr>
<td>19.4</td>
<td>19.3</td>
<td>(44.7%)</td>
<td>(44.2%)</td>
<td>(45.3%)</td>
<td>(60.0%)</td>
</tr>
<tr>
<td>[18.7, 20.3]</td>
<td>[18.7, 21.2]</td>
<td>[17.6, 20.2]</td>
<td>[14.2, 22.2]</td>
<td>[18.7, 20.3]</td>
<td></td>
</tr>
</tbody>
</table>

Overall survival\(^1\)

<table>
<thead>
<tr>
<th>Events, n [%](^3)</th>
<th>CAP</th>
<th>Patients</th>
<th>Patients</th>
<th>No prior surgery</th>
<th>Prior surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>181</td>
<td>86</td>
<td>(22.0%)</td>
<td>(19.0%)</td>
<td>(25.6%)</td>
<td>(28.9%)</td>
</tr>
<tr>
<td>95</td>
<td>13</td>
<td>(25.6%)</td>
<td>(28.9%)</td>
<td>(32.5%)</td>
<td>(36.8%)</td>
</tr>
<tr>
<td>24.6</td>
<td>22.9</td>
<td>[23.9, 26.3]</td>
<td>[21.7, 25.5]</td>
<td>NA</td>
<td>[23.8, 26.3]</td>
</tr>
<tr>
<td>[23.7, 26.3]</td>
<td>[39.8]</td>
<td>[21.7, 25.5]</td>
<td>NA</td>
<td>[23.8, 26.3]</td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>510</td>
<td>301</td>
<td>209</td>
<td>480</td>
<td></td>
</tr>
<tr>
<td>(72.1%)</td>
<td>(76.8%)</td>
<td>(66.3%)</td>
<td>(75.0%)</td>
<td>(72.0%)</td>
<td></td>
</tr>
</tbody>
</table>

[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

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

[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>
<thead>
<tr>
<th>Table 9-4</th>
<th>Details on bevacizumab (Avastin®) therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age subgroup</td>
<td>CAP</td>
</tr>
<tr>
<td>Patients, N</td>
<td>824</td>
</tr>
<tr>
<td>Treatment duration¹</td>
<td>453 (55.0%)</td>
</tr>
<tr>
<td>Total number of administrations</td>
<td></td>
</tr>
<tr>
<td>n applications</td>
<td>12,431</td>
</tr>
<tr>
<td>Median</td>
<td>18.0</td>
</tr>
<tr>
<td>Min-Max</td>
<td>1.0-25.0</td>
</tr>
<tr>
<td>Dose intensity (mg/kg per week)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>5.1</td>
</tr>
<tr>
<td>Min-Max²</td>
<td>2.3-108.1</td>
</tr>
<tr>
<td>Any treatment modification</td>
<td>653 (79.2%)</td>
</tr>
<tr>
<td>Kind of treatment modification³</td>
<td></td>
</tr>
<tr>
<td>Therapy interruption⁴</td>
<td>556 (67.5%)</td>
</tr>
<tr>
<td>Therapy delay⁴</td>
<td>227 (27.5%)</td>
</tr>
<tr>
<td>Dose reduction</td>
<td>57 (6.9%)</td>
</tr>
<tr>
<td>Dose increase</td>
<td>50 (6.1%)</td>
</tr>
<tr>
<td>Reason for treatment modification⁵</td>
<td></td>
</tr>
<tr>
<td>Physician decision</td>
<td>590 (71.6%)</td>
</tr>
<tr>
<td>Patient’s wish</td>
<td>148 (18.0%)</td>
</tr>
<tr>
<td>Toxicity</td>
<td>110 (13.3%)</td>
</tr>
<tr>
<td>Visit created by mistake</td>
<td>21 (2.5%)</td>
</tr>
</tbody>
</table>

¹Treatment duration of bevacizumab (Avastin®) was estimated using the Kaplan-Meier method. ²Maximum dose intensity of bevacizumab (Avastin®) seems to be a mistake in documentation. ³Multiple observations provided. ⁴There 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.

[Source: OTILIA_Tables_Final_4_20200420; Table 14.2.7; Table 14.2.11a; 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.

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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

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

[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. 2Multiple observations provided. 3There 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

<table>
<thead>
<tr>
<th>Age subgroup</th>
<th>CAP</th>
<th>Patients &lt;70 years</th>
<th>Patients ≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, N</td>
<td>824</td>
<td>453</td>
<td>371</td>
</tr>
</tbody>
</table>
| Treatment duration
  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
  Therapy interruption
    | 246 (29.9%) | 122 (26.9%) | 124 (33.4%) |
  Therapy delay    | 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
  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

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

[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%))
### Overview of Treatment-Emergent Adverse Events

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

<table>
<thead>
<tr>
<th>Patients reported with respective TEAE, n (%), n (cases)</th>
<th>CAP (N=824)</th>
<th>Patients ≥70 years (N=371)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients¹</td>
<td>Patients¹</td>
</tr>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td></td>
<td>Cases</td>
<td>Cases</td>
</tr>
<tr>
<td>Any TEAE</td>
<td>616 (74.8%)</td>
<td>288 (77.6%)</td>
</tr>
<tr>
<td>Any serious TEAE</td>
<td>222 (26.9%)</td>
<td>122 (32.9%)</td>
</tr>
<tr>
<td>Any TEAE with CTCAE severity grade ≥ grade 3</td>
<td>317 (38.5%)</td>
<td>167 (45.0%)</td>
</tr>
<tr>
<td>Any causally related TEAE</td>
<td>330 (40.0%)</td>
<td>138 (37.2%)</td>
</tr>
<tr>
<td>Any causally related serious TEAE¹</td>
<td>72 (8.7%)</td>
<td>35 (9.4%)</td>
</tr>
<tr>
<td>Any TEAE leading to discontinuation of bevacizumab (Avastin®) treatment²</td>
<td>145 (17.6%)</td>
<td>79 (21.3%)</td>
</tr>
<tr>
<td>All fatal TEAE</td>
<td>30 (3.6%)</td>
<td>18 (4.9%)</td>
</tr>
<tr>
<td>Fatal causally related TEAE²</td>
<td>5 (0.6%)</td>
<td>6</td>
</tr>
<tr>
<td>Fatal non-related TEAE²</td>
<td>24 (2.9%)</td>
<td>29</td>
</tr>
<tr>
<td>Fatal TEAE – causality unknown²</td>
<td>5 (0.6%)</td>
<td>8</td>
</tr>
</tbody>
</table>

Patients <70 years (N=453)

<table>
<thead>
<tr>
<th>Patients reported with respective TEAE, n (%), n (cases)</th>
<th>Patients¹</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td></td>
<td>Cases</td>
<td></td>
</tr>
<tr>
<td>Any TEAE</td>
<td>328 (72.4%)</td>
<td>1,952</td>
</tr>
<tr>
<td>Any serious TEAE</td>
<td>100 (22.1%)</td>
<td>187</td>
</tr>
<tr>
<td>Any TEAE with CTCAE severity grade ≥ grade 3</td>
<td>150 (33.1%)</td>
<td>267</td>
</tr>
<tr>
<td>Any causally related TEAE</td>
<td>192 (42.4%)</td>
<td>671</td>
</tr>
<tr>
<td>Any causally related serious TEAE¹</td>
<td>37 (8.2%)</td>
<td>53</td>
</tr>
<tr>
<td>Any TEAE leading to discontinuation of bevacizumab (Avastin®) treatment²</td>
<td>66 (14.6%)</td>
<td>102</td>
</tr>
<tr>
<td>All fatal TEAE</td>
<td>12 (2.6%)</td>
<td>20</td>
</tr>
</tbody>
</table>

[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.
¹Patients can occur in more than one category of the table. ²Causally related TEAEs were defined as those with a possible, probable or definite relationship to bevacizumab (Avastin®). ³TEAE 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. ⁴For 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 |
|----------------------------------------|---------------------------------|---------------------------------|---------------------------------|
| **TEAEs (≥10% in CAP or age subgroup)** | **CAP (N=824)** | **Patients <70 years (N=453)** | **Patients ≥70 years (N=371)** |
| 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%)     | 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%)      |
| Pancreatitis                          | 5 (0.6%)       | 1 (0.2%)      | 4 (1.1%)      |
| Subleuic                              | 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

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

[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 IIIIC (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 IIIIC (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.

12. REFERENCES


APPENDICES
## ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Table 1 List of stand-alone documents

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ANNEX 2. DIFFERENCE BETWEEN THE CLINICAL DATABASE AND THE SAFETY DATABASE

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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<td>Emil Barell-Straße 1, D-79639 Grenzach-Wyhlen</td>
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<td>Scientific Leader</td>
<td>Dr. Oliver Tomé</td>
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CRO = Contract research organization