An open label, randomized controlled prospective multicenter two arm phase IV trial to determine patient preference for everolimus in combination with exemestane or capecitabine in combination with bevacizumab for advanced (inoperable or metastatic) HER2-negative hormone receptor positive breast cancer

CLINICAL STUDY REPORT

Document Status	Final Version 1.0
Protocol No.	iOM-12293 / CRAD001JDE58T (version 5.0 dated 30-June-2017)
EudraCT No.	2013-005329-22
Sponsor	iOMEDICO AG, Freiburg, Germany
Medical Director at iOMEDICO AG	[redacted]
Team Leader at iOMEDICO AG	[redacted]
Project Leader at iOMEDICO AG	[redacted]
Date of Final Version of the Study Report	15-June-2018

This study was performed in compliance with the ICH (International Conference of Harmonization) GCP (Good Clinical Practices) guidelines. Essential documents will be retained in accordance with the ICH-GCP guidelines.

1. Title Page

Study Title	An open label, randomized controlled prospective multicenter two arm phase IV trial to determine patient preference for everolimus in combination with exemestane or capecitabine in combination with bevacizumab for advanced (inoperable or metastatic) HER2-negative hormone receptor positive breast cancer
Short Title	IMPROVE
Protocol No.	iOM-12293 / CRAD001JDE58T (version 5.0 dated 30-June-2017)
EudraCT No	2013-005329-22
Investigational Products	Capecitabine + Bevacizumab / Everolimus + Exemestane (Arm A)
Comparator	Everolimus + Exemestane / Capecitabine + Bevacizumab (Arm B)
Indication	Postmenopausal patients with advanced (inoperable or metastatic) HER2/neu (human epidermal growth factor receptor 2)-negative hormone receptor-positive breast cancer without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor and no prior palliative chemotherapy.
Design	Open label, randomized, controlled, prospective, multicenter, two arm clinical trial with a crossover design.
Development Phase	Phase IV
Sponsor	iOMEDICO AG Hanferstr. 28 79108 Freiburg, Germany
Coordinating Investigator	[redacted]
Study Initiation Date	17-Oct-2014
End of Recruitment Date	24-Apr-2017
Study Termination Date	30-Sep-2017
Date of Data Base Lock	25-Jan-2018
Author of Report	[redacted], iOMEDICO AG
Version and Date of Report	Final Version 1.0, 15-June-2018

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2. Synopsis

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Name of Finished Product: NA (not applicable)		
Name of Active Ingredients: Capecitabine (Xeloda®) Bevacizumab (Avastin®) Everolimus (Afinitor®) Exemestane (Aromasin®)		

Title of Study:
An open label, randomized controlled prospective multicenter two arm phase IV trial to determine patient preference for everolimus in combination with exemestane or capecitabine in combination with bevacizumab for advanced (inoperable or metastatic) HER2-negative hormone receptor positive breast cancer

Short Title: IMPROVE

Coordinating Investigator:
[redacted]

Study Centers:
Twenty-six study centers in Germany enrolled patients in this study out of the total 40 initiated sites (Table 2 ; section 2.2).

Publication (reference):
NA

Study Period:	**Phase of Development:**
First-patient-in; date of first enrolment: 17-Oct-2014 Last-patient-in; date of last enrolment: 24-Apr-2017 Study termination date: 30-Sep-2017	Phase IV

Objectives:

Primary Objective

- To compare patients' preferences for either of the two treatment combinations Eve (everolimus) plus Exe (exemestane) or Cap (capecitabine) in combination with Bev (bevacizumab) after failure of standard anti-hormonal therapy in patients with advanced (inoperable or metastatic) HER2/neu (human epidermal growth factor receptor 2)-negative hormone receptor positive breast cancer.

Secondary Objectives

- To evaluate the reasons for the preference as assessed by the patient's preference questionnaire.
- To compare patient-reported treatment satisfaction as assessed by the treatment satisfaction questionnaire in first- and second-line treatment.
- To investigate differences in QoL (quality of life) by the EORTC (European Organisation for Research and Treatment of Cancer) QLQ (quality of life questionnaire)-C30 (30-item core module) and EORTC QLQ-FA13 (13-item module on fatigue) questionnaires.
- To assess PFS (progression-free survival) rates after 12 weeks of therapy in first- (PFS rate 1) and second-line (PFS rate 2) treatment.
- To assess clinical benefit by determining the ORR (overall response rate) and DCR (disease control rate) based on tumor assessment by investigator as per RECIST version 1.1 (Response Evaluation

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Criteria In Solid Tumors).

- To evaluate safety and tolerability throughout the study including assessments of clinical laboratory tests, TEAEs (treatment-emergent adverse events) and study drug withdrawal due to a TEAE.
- To determine physicians' treatment preference as assessed by the physician's preference questionnaire.
- To explore PFS and OS (overall survival) across respective treatment arm and per treatment line.

Explorative Objective

- To explore the relationship between QoL scores and patients' preference.

Please note that the explorative analyses were not performed due to small number of available observations.

Methodology:
This was an open label, randomized, controlled, prospective, multicenter, two arm clinical trial with a crossover design. The clinical trial protocol and its amendments are displayed in Table 1 (section 2.1).

Number of Patients (planned and analyzed):	**Planned:** N=192 **Screened:** N=86 Due to low recruitment rate and emergence of new treatment options, the recruitment was stopped after 77 patients had been randomized as per decision by the sponsor.	**Randomized:** Total N=77 Cap + Bev / Eve + Exe (arm A): N=39 Eve + Exe / Cap + Bev (arm B): N=38 **End of Study:** Started follow-up: Total: N=44 Arm A: N=22 Arm B: N=22 Completed follow-up: Total: N=21 Arm A: N=9 Arm B: N=12	**Analyzed:** <u>Efficacy</u> ITT (intent-to-treat): Arm A: N=39 Arm B: N=38 mITT (modified ITT): Arm A: N=5 Arm B: N=8 <u>Safety:</u> SAF (safety set): Arm A: N=37 Arm B: N=37

Diagnosis and *Main* Criteria for Inclusion:
Patients were included in the study if they aged ≥18 years, were diagnosed with HER2/neu-negative, ER (estrogen receptor)/PR (progesterone receptor)-positive inoperable or metastatic adenocarcinoma of the breast, had confirmed postmenopausal status, had failed ≥1 non-steroidal aromatase inhibitor therapy, had ECOG (Eastern Cooperative Oncology Group) performance status score of ≤2, and had no evidence of uncontrolled CNS (central nervous system) metastases or symptomatic visceral metastases. Patients were ineligible if they had received prior palliative cytotoxic chemotherapy or had been treated previously with mTOR (mammalian target of rapamycin)-inhibitors (prior treatment with Exe was allowed). All inclusion and exclusion criteria are detailed in section 9.3 .

Test Product, Dose and Mode of Administration:
Arm A: Cap + Bev / Eve + Exe

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Patients allocated to Arm A first received Cap in combination with Bev (*first treatment phase; first-line therapy*) and were treated until progression or intolerable toxicity or other reason for treatment end. After a washout phase of 7-28 days patients crossed over to the planned *second treatment phase / second-line therapy* (Eve + Exe) and were treated until progression or intolerable toxicity or any other reason for end of treatment.

Dose and Mode of Administration:
Capecitabine: 1000 mg/m^2 per os twice daily as combined 150 mg and 500 mg tablets on days 1 to 14 of each 21-day cycle, followed by a seven-day rest period (i.e. off-treatment)

Bevacizumab: 15 mg/kg intravenously once every three weeks (i.e. 5 mg/kg/week dose equivalent)

Everolimus: 10 mg per os once daily

Exemestane: 25 mg per os once daily

Duration of Treatment:
Patients received both treatment combinations in a consecutive manner; therefore the treatment duration for each patient lasted from first study drug application in the first treatment phase until last study drug application in the second treatment phase including a washout phase of 7-28 days prior to crossover. For patients, who did not crossover to the second treatment phase, treatment duration lasted from first study drug application until last study drug application in the first treatment phase. Patients were treated until progression or intolerable toxicity or other reason for end of treatment in respective treatment phase.

Reference Therapy, Dose and Mode of Administration:
Arm B: Eve + Exe (experimental therapy) / Cap + Bev (reference therapy)
Patients allocated to Arm B first received Eve in combination with Exe (*first treatment phase; first-line therapy*) and were treated until progression or intolerable toxicity or other reason for treatment end. After a washout phase of 7-28 days patients crossed over to the planned *second treatment phase / second-line therapy* (Cap + Bev) and were treated until progression or intolerable toxicity or any other reason for end of treatment.

Dose and Mode of Administration:

Everolimus: 10 mg per os once daily

Exemestane: 25 mg per os once daily

Capecitabine: 1000 mg/m^2 per os twice daily as combined 150 mg and 500 mg tablets on days 1 to 14 of each 21-day cycle, followed by a seven day rest period (i.e. off-treatment)

Bevacizumab: 15 mg/kg intravenously once every three weeks (i.e. 5 mg/kg/week dose equivalent)

Criteria for evaluation:

Efficacy

Primary Endpoint
Patient's preference for either of the following treatment combinations after failure of ≥1 standard anti-hormonal therapy:

- Eve + Exe

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OR

- Cap + Bev

The preference was ascertained by using a patient preference questionnaire as assessed after 12 weeks of therapy in the second treatment phase.
In case of an early (<12 weeks) treatment discontinuation in the second treatment phase, the patient preference questionnaire was to be completed within two weeks after discontinuation for any other reason than PD (progressive disease). The preference questionnaire asked patients to select between either first regimen, second regimen or no preference.

Secondary Endpoints

- Reasons for preference as assessed by the patient's preference questionnaire.
- Patient-reported treatment satisfaction as assessed by the treatment satisfaction questionnaire used both in the first treatment phase and in the second treatment phase.
- QoL as assessed by the EORTC QLQ-C30 and EORTC-QLQ-FA13 questionnaires.
- PFS defined as the time from start of study treatment to the first documented tumor progression (investigators' assessment as per RECIST version 1.1) or death due to any cause, whichever occurred first as assessed in the first and second treatment phase, respectively. PFS was estimated by using the Kaplan-Meier method.
- ORR and disease control as per RECIST version 1.1.
- OS defined as the time from start of treatment until date of death due to any cause. OS was estimated by using the Kaplan-Meier method.
- Physician's treatment preference as assessed by the physician's preference questionnaire.

Safety

- As a *secondary endpoint*, safety and tolerability were assessed by evaluation of clinical laboratory tests, urinalysis, vital signs, TEAEs and study drug withdrawal due to a TEAE. The AEs were graded based on NCI (National Cancer Institute)-CTCAE (Common Terminology Criteria for Adverse Events) version 4.03.

Statistical Analysis:
The statistical analyses performed are detailed in the SAP (Statistical Analysis Plan) version 1.0 dated 16-Nov-2015 (Appendix 16.1.9).

Determination of Sample Size
Sample size was calculated using a Chi-square test to account for differences in the patient-reported preference for Eve + Exe or Cap + Bev. The assumptions for the null hypotheses were chosen according to the PISCES trial (1).

- Null hypothesis: There is no difference in patients' preference for either therapy (assuming that 80% of patients do have a preference, whereas 20% cannot decide).
- Alternative hypothesis: There is a true difference in patient's preference, whereby 52.5% of patients prefer regimen Eve + Exe, 27.5% of patients prefer regimen Cap + Bev, and 20% are indifferent.

For α=0.05 and 80% power the required patient number in the IMPROVE trial was n=124 (62 per treatment arm). To test the hypothesis using Chi-square test at least 124 patients who have completed the treatment

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preference questionnaire were needed. Accounting for the expected drop out rate of 35%, a total of 192 patients had to enter the study.

Due to low recruitment rate and emergence of new treatment options, the recruitment was stopped after 77 patients had been randomized.

Statistical Methods

Analytical Populations
The statistical analysis comprised the following analytical populations:

Efficacy

- Intent-to-treat population: The ITT population comprised all patients to whom study treatment had been assigned by randomization. According to the intent to treat principle, patients were analyzed according to the study arm they had been assigned to during the randomization procedure.
  The ITT population was the relevant population for the efficacy evaluation including demographic and other baseline characteristics as well as study treatment evaluations. It served as an additional analytical population for all patient-reported outcomes.

- Modified ITT population: The mITT population comprised all patients who qualified for analysis of the primary endpoint, i.e. all patients who met the following criteria:
  - had received at least 12 weeks of first-line treatment or less for other reasons than PD
  - had crossed over to second-line treatment within 12 weeks after termination of first-line treatment
  - had received at least 12 weeks of second-line treatment or less for other reasons than PD
  - had answered the preference question on patients' preference questionnaire

The mITT population was the relevant population for the analysis of the primary endpoint and all patient-reported outcomes. All secondary efficacy endpoints as well as the description of baseline characteristics were repeated with the mITT population.

- Subgroups (ITT) [stratification parameters]
  - Visceral metastases versus non-visceral only metastases
  - Prior (neo)adjuvant treatment (anthracyclines and/or taxanes [YES versus NO])
  - Prior palliative anti-hormonal therapies (0-1 versus >1)
  - DFI (disease free interval) ≤2 years versus >2 years

Safety

- Safety Set: The SAF included all patients who had received at least one dose of study medication. Patients were analyzed according to the study treatment they had actually received.

Summary Statistics
Summary statistics included the following types of variables:

- Nominal variables including frequencies and percentages.
- Ordinal variables including frequencies, percentages, mean, median, minimum and maximum.
- Continuous variables including number (N) of observations, mean, standard deviation, 25th percentile, median, 75th percentile, minimum and maximum.

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- Corresponding 95% CIs (confidence intervals) where applicable

Efficacy Evaluations – Primary Endpoint

Patient Preference Questionnaire
The patient (treatment) preference questionnaire was to be filled out after 12 weeks of treatment in the second treatment phase or within two weeks after early (<12 weeks) treatment discontinuation in the second treatment phase for any other reason than PD. The preference questionnaire asked patients to select between either first regimen, second regimen or no preference. A Chi-square test was used to test the hypothesis on a 5% α-level. The CI was calculated using the Clopper-Pearson formula.

Efficacy Evaluations – Secondary Endpoints

Reasons for Preference
The reasons (frequency tables) for the treatment preference were captured in the patient preference questionnaire if a clear preference was stated. Patients were able to select reasons for their choice of the preferred therapy out of a 16-item list of possible reasons with the opportunity to address self-reported reasons. Patients were finally asked to identify one main reason for choice of preference.

Progression Free Survival and Overall Survival
PFS and OS were estimated using the Kaplan-Meier method. PFS was analyzed for the first treatment phase and second treatment phase separately. First-line PFS was defined as the time from start of first-line therapy to progression or death due to any cause before start of a new therapy. Patients without progression or death were censored at the date of last tumor evaluation in the first-line. Second-line PFS was defined as the time from start of second-line therapy to progression or death due to any cause before start of a new therapy. Patients without progression or death were censored at the date of last tumor evaluation. OS was defined as the time from start of therapy in the first treatment phase to death of any cause. Patients without documented date of death at the end of study were censored with the last date known to be alive. Patients who did not receive any study treatment were censored with the date of randomization.
Tables of PFS and OS by treatment arm are provided together with median and quartiles including the 95% CI as well as frequencies of censored patients. Corresponding survival plots are presented.
Log-Rank test (p-value) was performed to assess whether the estimated PFS / OS was significantly different between treatment arms.

Progression Free Survival Rate
PFS rates after 12 weeks of therapy were analyzed for each treatment phase using the Kaplan-Meier method including 95% CI.

Response Rates
Response rates were evaluated on the basis of the best documented tumor response for each patient as assessed by the investigator. Included in the analyses were both patients with measurable lesion and those with non-measurable lesions.
The ORR (CR [complete remission] + PR [partial remission]) and the DCR (CR+PR+SD [stable disease]) were both calculated per treatment phase. Rates are reported with a 95% CI as calculated using the Clopper-Pearson formula.

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Treatment Satisfaction
A satisfaction-with-therapy questionnaire was administered 12 weeks after Day 1 of the first cycle in the first treatment phase and 12 weeks after Day 1 of first cycle in the second treatment phase (or 2 weeks after early discontinuation in each phase) and assessed by arm and therapy line. The module consists of 9 items that are scored on 4-point Likert scales, ranging from 1 ("I strongly agree") to 4 ("I strongly disagree").

Differences in overall treatment satisfaction (item A09 of the questionnaire) were analyzed by arm and treatment line using an asymptotic chi-square test for the dichotomized item (satisfied versus not satisfied):

- "Satisfied" is the sum of the levels "I strongly agree" and "I agree".
- "Not satisfied" is the sum of the levels "I disagree" and "I strongly disagree".

EORTC QLQ-C30 Questionnaire
The EORTC QLQ-C30 questionnaire provides five functional scales, three symptom scales, two global items (collectively providing the global health status score) and several single items. Descriptive statistics were performed for each single item, each subscale and the global health status score by treatment combination. As for single items, frequency tables of these were generated. Differences in the global health status score between the treatment arms were tested for first treatment phase and the second treatment phase using a t-test. This t-test was performed both for baseline and week 12 questionnaires.

EORTC QLQ-FA13 Questionnaire
The EORTC QLQ-FA13 questionnaire consists of 13 items providing three subscales plus two global single items. Descriptive statistics were performed for each single item and each subscale by treatment combination. As for single items, frequency tables of these were generated.

Physicians' Treatment Preference
Physicians' treatment preference for therapy combination Eve + Exe or Cap + Bev or no preference was assessed using the same questions as used in the patients' treatment preference questionnaire. Physicians were asked to evaluate their preference of treatment combination as first-line therapy. Physicians could select between either first regimen, second regimen or no preference. Furthermore, physicians were able to select reasons for their choice of the preferred therapy out of a 15-item list of possible reasons with the opportunity to address self-reported reasons. Physicians were finally asked to identify one main reason for choice of preference. Additionally, physicians had the opportunity to say "I treat the patient for a short time and have no preference" in case they had not attended the whole study with the patient. Rates and corresponding 95% CIs are presented. Frequency tables are displayed including the reasons for the preference.

Safety Evaluation – Secondary Endpoints

The overall observational period was divided into three mutually exclusive segments:

1. Pre-treatment period: from day of patient's informed consent to the day before first dose of study medication (first treatment phase)
2. On-treatment period: from day of first dose of study medication to 30 days (minimum washout) after last dose of study medication (second treatment phase) or first dose of second phase treatment after crossover
3. Post-treatment period: starting at day 31 after last dose of study medication (second treatment phase)

Adverse Events
AEs and toxicity were graded according to the CTCAE version 4.03. Summary tables for AEs include only AEs

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that started or worsened during the *on-treatment period*, that is TEAEs assessed as temporally related to the study medication. The number of patients with TEAEs (new or worsening from baseline) are summarized with MedDRA (Medical Dictionary for Regulatory Activities) classified SOC (system organ class) and PT (preferred term) by severity (based on CTCAE grades) for each treatment sequence in each treatment phase. For the aggregated statistical analyses, a TEAE was classified as study drug-related if the relationship was classified as "related" by the investigator.

Clinical Laboratory Evaluations
Laboratory parameters were solely analyzed based on the quantitatively documented parameter values. Laboratory data did not constitute AEs and were included in the safety evaluation only if they were symptoms of an AE. In this case, they were assigned to a diagnosis and a severity grade.

Summary - Overall conclusion:

The IMPROVE study was pre-maturely terminated (initially planned to have 192 eligible patients randomized in total to Arm A or Arm B). The recruitment was stopped after 77 patients had been randomized to either Arm A (N=39) or Arm B (N=38) [ITT population]. The primary endpoint was patients' preference for either of the two regimens Cap + Bev or Eve + Exe 12 weeks after crossover to second-line regimen. However, the primary endpoint was not reached when considering the small analytical population (mITT) (due to low number of evaluable patients and premature termination of study) used for evaluation of the primary endpoint. There was a very low number of patients' preference questionnaires available as a high number of patients did not cross over to second-line therapy, and, consequently, this resulted in a small number of available observations for the mITT population (Arm A: n=5; Arm B: n=8). Due to the small mITT population, it was only included when presenting the outcome of the primary endpoint as was the relevant population in this analysis (primary objective). Furthermore, exploratory analyses were not performed due to the small number of available observations (hence, descriptive statistics only). For the secondary endpoints, only the ITT population was used; Arm A: first-line N=39; second-line N=17; Arm B: first-line N=38; second-line N=19.

Efficacy Results

Patients' Treatment Preference (mITT population)
Overall, 8 (61.5%; 95% CI: 31.6-86.1) patients reported Cap + Bev as their preferred regimen as compared to Eve + Exe (n=2; 15.4%; 95% CI: 1.9-45.4) [p=0.1653]. Three (23.1%; 95% CI: 5.0-53.8) patients could not decide for either regimen. When looking at the two treatment arms separately, 40 % (n=2; 95% CI: 5.3-85.3) and 75% (n=6; 95% CI: 34.9-96.8) of the patients reported Cap + Bev as their preferred therapy in Arm A and Arm B, respectively, as compared to Eve + Exe (Arm A: 20.0% [n=1; 95% CI: 0.5-71.6]; Arm B: 12.5% [n=1; 95% CI: 0.3-52.7]). Forty percent (n=2; 95% CI: 5.3-85.3) of the patients in Arm A and 12.5% (n=1; 95% CI: 0.3-52.7) in Arm B were indecisive.

Physician's Treatment Preference
In total, there were 36 patients who had received both first-line therapy and second-line therapy for whom the respective treating physicians had provided their preferred treatment regimen (for their respective patient(s); n=36 cases).
Overall for the ITT population, in 26.0% (n=20; 95% CI: 16.6-37.2) and 13.0% (n=10; 95% CI: 6.4-22.6) of the cases the preferred regimen was Cap + Bev and Eve + Exe, respectively. In 6 (7.8%; 95% CI: 2.9-16.2) cases no preferred regimen was reported. When looking at the arms separately, in 25.6% (n=10; 95% CI: 13.0-42.1) of the cases in Arm A the preferred regimen was Cap + Bev as compared to Eve + Exe (n=5; 12.8% [95% CI: 4.3-27.4]). As for Arm B, in 26.3% (n=10; 95% CI: 13.4-43.1) of the cases Cap + Bev was the preferred regimen while in 13.2% (n=5; 95% CI: 4.4-28.1) of the cases the preferred regimen was Eve + Exe.

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First-Line and Second-Line Progression-Free Survival
The Kaplan-Meier-estimated first-line PFS was longer (p=0.0008) in Arm A (median 11.1 months [95% CI: 7.8 – 18.0]) as compared to Arm B (median 3.5 months [95% CI: 2.7 – 5.5]). The estimated 3-months first-line PFS rate was 79.3% (95% CI: 61.4 – 89.6) in Arm A and 51.4% (95% CI: 34.4 – 65.9) in Arm B. There was no major difference (p=0.8345) in the estimated second-line PFS between Arm A (median 3.7 months [95% CI: 2.4 – 7.8]) and Arm B (median 3.6 months [95% CI: 2.3 – 5.5]). The estimated 3-months second-line PFS rate was 62.5% (95% CI: 34.9 – 81.1) in Arm A and 63.2% (95% CI: 37.9 – 80.4) in Arm B.

Overall Survival
There was no major difference (p=0.2088) in the Kaplan-Meier-estimated OS between Arm A (median 28.8 months; 95% CI: 19.7-NA) and Arm B (median 24.7 months; 95% CI: 13.9-28.8).

First-Line and Second-Line Overall Response Rate
The first-line ORR was higher in Arm A (23.1% [95% CI: 11.1 – 39.3]; n=9 [CR=3; PR=6]) as compared to Arm B (10.5% [95% CI: 2.9 – 24.8]; n=4 [CR=1; PR=3]). No patients in Arm A were documented with a CR or PR while on second-line therapy (ORR=0%), whereas 3 (7.9%) patients in Arm B were reported with a PR and none with a CR (ORR=7.9% [95% CI: 1.7 – 21.4]).

Treatment Satisfaction
The majority of the patients in the ITT population in both arms were satisfied both with first-line therapy (Arm A: n=30 [76.9%]; Arm B: n=24 [63.2%]) and second-line therapy (Arm A: n=10 [58.8%]; Arm B: n=11 [57.9%]). There was no major difference between arms neither in first-line therapy (p=0.3832) nor in second-line therapy (p=0.6243)..

Quality of Life
There was no major difference in mean global health scores between arms in either treatment phase (General QoL – EORTC-QLQ-C30). There was a considerable variation in the reported scores both across arms and treatment phases.

Safety Results

Evaluation of extent of exposure was performed on the ITT population both for first-line (Arm A: N=39; Arm B: N=38) and second-line therapy (Arm A: N=17; Arm B: N=19). Evaluation of safety (AEs) was performed on the SAF population both for first-line (Arm A: N=37; Arm B: N=37) and second-line therapy (Arm A: N=17; Arm B: N=19) comprising all patients who received at least one dose of study medication.

Duration of First-Line and Second-Line Therapy
The median duration [min – max] of first-line therapy was longer in Arm A (6.4 months [0.0 – 29.2]) than in Arm B (3.4 months [0.1 – 26.1]). As for the second-line, the median duration of therapy was 2.7 months [0.4 – 20.0] in Arm A and slightly longer in Arm B (4.0 months [0.2 – 29.2]).

12-Weeks Relative Dose Intensity
The overall median 12-week-relative dose intensity for respective study was slightly higher in Arm B as compared to Arm A. The median 12-week-relative dose intensity for respective study drug in Arm A during first-line and second-line therapy was 98.5% (Bev) and 92.0% (Cap) [first-line] and 90.5% (Eve) and 100.0% (Exe) [second-line]. As for Arm B, the median 12-week-relative dose intensity for respective study drug during first-line and second-line treatment was 100.0% (Eve) and 100.0% (Exe) [first-line] and 99.1% (Bev) and 101.1% (Cap) [second-line].

First-Line and Second-Line Therapy Dose Modifications and Interruptions
Patients in both arms were subjected to first-line therapy dose modifications and interruptions. In Arm A, 23 (59.0%) patients were reported with ≥1 dose modifications with Cap and 6 (15.4%) patients were documented

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with Bev dose modification(s). Five (12.8%) patients were reported with ≥1 interruptions of Cap therapy within a cycle. In Arm B, as for dose modifications, 1 (2.6%) patient was reported with ≥1 dose modifications with Exe and 15 (39.5%) patients were documented with Eve dose modification(s). Five (13.2%) patients were documented with ≥1 interruptions of Exe therapy within a cycle, whereas 14 (36.8%) patients were reported with interruption(s) of Eve therapy within a cycle.
Patients in both arms were subjected to second-line therapy dose modifications and interruptions. In Arm A, 6 (35.3%) patients were subjected to ≥1 dose modifications with Eve (and 1 (5.9%) patient was documented with Exe dose modification(s). Six (35.3%) patients were reported with ≥1 interruptions of Eve therapy within a cycle and 3 (17.6%) patients were documented with interruption(s) of therapy with Exe within a cycle. In Arm B, 9 (47.4%) patients were reported with ≥1 dose modifications with Cap (and 3 (15.8%) patients were documented with Bev dose modification(s). Three (15.8%) patients were documented with ≥1 interruption(s) of Cap therapy within a cycle.

Treatment Discontinuation Due to Treatment-Emergent Adverse Event
During the course of the study, 12 (32.4%) patients and 2 (11.8%) patients in Arm A were reported with TEAEs that led to study drug withdrawal during first-line and second-line therapy, respectively. As for Arm B, 2 (5.4%) patients were reported with TEAEs leading to discontinuation of study drug during first-line therapy (none in second-line). In Arm A, one patient (improve.1170.3) experienced a serious TEAE, gastric perforation of CTCAE grade 3 during first-line therapy attributable to Bev. Both Bev and Cap were withdrawn and the AE resolved subsequently. Another patient (improve.1829.7) was reported with serious TEAE paralysis (of recurrent glossopharyngeal nerve) of CTCAE grade 2 during first-line therapy attributable to Cap. Both Cap and Bev were discontinued and the AE resolved subsequently. As for Arm B, there was one case of serious TEAE attributable to study drug leading to study drug withdrawal reported. This patient (improve.245.1) had experienced vertigo of CTCAE grade 3 during first-line therapy attributable to both Eve and Exe. Both study drugs were withdrawn and the AE resolved subsequently.

Treatment-Emergent Adverse Events
The percentage of patients with TEAEs in first-line and second-line treatment phases were similar between arms (Arm A: first-line: 97.3%; second-line: 88.2%; Arm B: first-line: 97.3%; second-line: 84.2%). The (first-line; median treatment duration: 6.4 months) Bev-related (51.4%) and Cap-related (89.2%) TEAEs in Arm A were observed at lower percentages in (second-line therapy; median treatment duration: 4.0 months) Arm B (Bev: 42.1%; Cap: 63.2%), which might be attributable to differences in treatment duration. A similar intriguing pattern was observed with Eve and Exe: first-line therapy (median treatment duration: 3.4 months) in Arm B with 83.8% Eve-related and 51.4% Exe-related TEAE versus second-line therapy (median treatment duration: 2.7 months) in Arm A with 58.8% Eve-related and 17.6% Exe-related TEAEs.

Serious Treatment-Emergent Adverse Events
The percentage of patients with serious TEAEs were observed at lower percentage in first-line therapy in Arm A (35.1%) as compared to Arm B (45.9%). Looking at second-line therapy, the pattern was the opposite (Arm A: 52.9%; Arm B: 42.1%). Bev-related serious TEAE was observed at lowest percentage in Arm A (5.4%) as compared to Arm B (15.8%). Cap-related serious TEAE was only reported in Arm A (10.8%). As for Eve-related serious TEAE, this was observed at higher percentage in second-line therapy (Arm A: 23.5%) compared to first-line therapy (Arm B: 13.5%). Exe-related serious TEAE was only reported in Arm B (5.4%).

Most Frequent Treatment-Emergent Adverse Events (PT)
In Arm A, the most frequent (≥10% of patients) TEAEs during first-line therapy were palmar-plantar erythrodysaesthesia syndrome (56.8%), nausea (40.5%), fatigue (35.1%), diarrhea (32.4%), hypertension (29.7%), stomatitis (24.3%), decreased appetite (16.2%), dyspnea (16.2%), headache (16.2%), peripheral sensory neuropathy (16.2%), viral upper respiratory tract infection (16.2%), arthralgia (13.5%), cough (13.5%), vomiting (13.5%), abdominal pain (10.8%), back pain (10.8%), mucosal inflammation (10.8%), urinary tract infection (10.8%), and weight decreased (10.8%). As for the second-line therapy, the most common TEAEs were anemia (23.5%), cough (17.6%), dyspnea (17.6%), fatigue (17.6%), diarrhea (11.8%), epistaxis (11.8%),

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infection (11.8%), mucosal inflammation (11.8%), pain (11.8%), pelvic pain (11.8%), and pneumonia (11.8%). In Arm B, the most frequent TEAEs during first-line therapy were diarrhea (29.7%), nausea (24.3%), mucosal inflammation (18.9%), bone pain (16.2%), cough (16.2%), fatigue (16.2%), headache (16.2%), oedema peripheral (16.2%), anemia (13.5%), decreased appetite (13.5%), oropharyngeal pain (13.5%), rash (13.5%), stomatitis (13.5%), vomiting (13.5%), weight decreased (13.5%), abdominal pain upper (10.8%), aphthous ulcer (10.8%), arthralgia (10.8%), C-reactive protein increased (10.8%), dry mouth (10.8%), dysgeusia (10.8%), dyspnea (10.8%), epistaxis (10.8%), and musculoskeletal pain (10.8%). As for the second-line therapy, the most common TEAEs were palmar-plantar erythrodysaesthesia syndrome (31.6%), diarrhea (26.3%), nausea (26.3%), dyspnea (21.1%), hypertension (15.8%), pleural effusion (15.8%), cough (10.5%), C-reactive protein increased (10.5%), fatigue (10.5%), oedema peripheral (10.5%), and peripheral sensory neuropathy (10.5%).

Grade 3 and Grade 4 Treatment-Emergent Adverse Events (PT)
A higher percentage of patients reported with ≥1 first-line TEAEs of CTCAE grade 3 and 4 were observed in Arm A (73.0%) compared to Arm B (54.1%). Similar percentages of second-line TEAEs of CTCAE grade 3 and 4 were noted between arms (Arm A: 52.9%; Arm B: 52.6%). In Arm A, the most frequently (≥5% of patients) reported CTCAE grade 3 and 4 TEAEs during first-line therapy were palmar-plantar erythrodysaesthesia syndrome (18.9%), hypertension (13.5%), diarrhea (8.1%), diverticulitis (5.4%), and fatigue (5.4%). As for the second-line therapy, the reported CTCAE grade 3 and 4 TEAEs (all >5%) included pain (11.8%), pneumonia (11.8%), anemia (5.9%), ascites (5.9%), atelectasis (5.9%), clostridium difficile colitis (5.9%), diverticulum intestinal haemorrhagic (5.9%), dyspnea (5.9%), fatigue (5.9%), lymphoedema (5.9%) and pelvic pain (5.9%).
In Arm B, the most commonly reported CTCAE grade 3 and 4 TEAEs during first-line therapy were anemia (5.4%), diarrhea (5.4%), erysipelas (5.4%), hypertension (5.4%), ileus (5.4%), nausea (5.4%), and stomatitis (5.4%). As for second-line therapy, the reported CTCAE grade 3 and 4 TEAEs (all >5%) included palmar-plantar erythrodysaesthesia syndrome (10.5%), blood creatinine increased (5.3%), cholecystitis acute (5.3%), cholelithiasis (5.3%), C-reactive protein increased (5.3%), deep vein thrombosis (5.3%), dyspnea (5.3%), hypercalcaemia (5.3%), hypertensive crisis (5.3%), nausea (5.3%), nephrotic syndrome (5.3%), pericardial effusion (5.3%), peripheral sensory neuropathy (5.3%), pleural effusion (5.3%), pulmonary embolism (5.3%), tachyarrhythmia (5.3%), and urinary tract infection (5.3%).

Related Grade 3 and Grade 4 Treatment-Emergent Adverse Events (PT)
In Arm A, the most frequently (≥5% of patients) reported Cap + Bev-related CTCAE grade 3 and 4 TEAEs during first-line therapy were palmar-plantar erythrodysaesthesia syndrome (18.9%), hypertension (10.8%), diarrhea (5.4%), and fatigue (5.4%). As for second-line therapy, the 3 Eve + Exe-related CTCAE grade 3 and 4 TEAEs included 2 cases of pneumonia (11.8%) and one pain case (5.9%).
In Arm B, the most commonly reported Eve + Exe-related CTCAE grade 3 and 4 TEAEs during first-line therapy were diarrhea (5.4%) and stomatitis (5.4%). As for second-line therapy, the 6 Cap + Bev-related CTCAE grade 3 and 4 TEAEs included two cases of palmar-plantar erythrodysaesthesia syndrome (10.5%), and one case each of peripheral sensory neuropathy (5.3%), nephrotic syndrome (5.3%), pulmonary embolism (5.3%), and deep vein thrombosis (5.3%).

Other Safety Observations
One patient (improve.494.5) was reported with “Increase of kidney values” (creatinine) [PT: Blood test abnormal], which was assessed as a SAE Grade 2. A CT of the abdomen revealed Cholecystolithiasis with cholecystitis and hydrops. The study treatment (Bev + Cap) was interrupted; however assessed as not attributable to the event. No concomitant medication was given. Subsequently, the event resolved / improved.

Deaths
A higher percentage of deaths occurred in Arm B (n= 18; 48.6%) as compared to Arm A (n=13; 35.1%). Most deaths in both arms occurred during the FU period (Arm A: n=12; Arm B: n=15) and the reported cause of death was disease progression except for one case where the cause of death was a SAE (tumor progression starting in second-line with date of death in the FU period). Three of the four fatal serious TEAEs occurred in

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Arm B. The cause of death of all four serious TEAEs was PD; none of the fatal cases were assessed as attributable to any study drug.

Overall conclusion

Patients' preference was not significantly different for either therapy. There was a tendency to favor Cap +Bev over Eve + Exe, which was in line with the therapy preference reported by the physicians. Cap + Bev was found to have better efficacy results as compared to Eve + Exe, but at the cost of a higher amount of grade 3/4 AEs bearing in mind the difference in treatment duration between the two regimens. Patient-reported QoL, however, was similar in both arms.

The reported TEAEs during the course of the study were as expected from the study drugs as per current SmPCs. The safety profile appears compatible to the current SmPCs of respective study drug. No new or potentially critical safety issue was identified in this study.

Date and version of report

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