Clinical Study Report

Study Title	An open-label, multi-center, sINGlE arm clinical study to evaluate treatment efficacy and quality of life in women with hormone-receptor-positive, HER2-negative loco-regionally recurrent or metastatic Breast cancer receiving palbociclib (PD 0332991) in combination with an aromatase inhibitor, or fulvestrant after prior endocrine therapy
Document status	Final
Version number	Version 1.0 dated 19 December 2023
Date of final version of the study report	
Protocol-No.	IOM-04318
EudraCT-No.	2015-001603-32
Sponsor	iOMEDICO AG Ellen-Gottlieb-Straße 19 D-79106 Freiburg im Breisgau
Authors of report	[redacted]

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.

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1. Title Page

Study title	An open-label, multi-center, sINGlE arm clinical study to evaluate treatment efficacy and quality of life in women with hormone-receptor-positive, HER2-negative loco-regionally recurrent or metastatic Breast cancer receiving palbociclib (PD 0332991) in combination with an aromatase inhibitor, or fulvestrant after prior endocrine therapy
Short title	INGE-B
Protocol number	IOM-04318
EudraCT No.	2015-001603-32
Investigational product	Palbociclib (PD 0332991, Ibrance®) in combination with an aromatase inhibitor or fulvestrant
Comparator	Not applicable
Indication	Hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced breast cancer (ABC)
Design	Prospective, open-label, single arm multicenter interventional study
Development phase	Phase II
Sponsor	iOMEDICO AG Ellen-Gottlieb-Straße 19 D-79106 Freiburg im Breisgau
Coordinating investigator	Dr. Manfred Welslau Klinikum Aschaffenburg Aschaffenburg, Germany
Study initiation date	06-Sept-2016
Study termination date	15-Feb-2023
Authors of report	[redacted]
Version and date of report	Final version 1.0 dated 19 December 2023

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.

2. Synopsis

e.g. (see E3 Annex I):

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Name of Active Ingredient: Palbociclib		

Title of study:
An open-label, multi-center, sINGlE arm clinical study to evaluate treatment efficacy and quality of life in women with hormone-receptor-positive, HER2-negative loco-regionally recurrent or metastatic Breast cancer receiving palbociclib (PD 0332991) in combination with an aromatase inhibitor, or fulvestrant after prior endocrine therapy (INGE B)

Short title: INGE-B

Coordinating Investigator:
Dr. med. Manfred Welslau, Klinikum Aschaffenburg, Aschaffenburg, Germany

Study centers:
In total, 79 study centers in Germany were initiated, of these, 64 centers enrolled patients (refer to section 2.2).

Publication (reference):
None.

Study period: 06-Sept-2016 – 28-Dec-2022; DBL 15-Feb-2023 • First-patient-in (date of first enrollment): 06-Sep-2016 • Last-patient-in (date of last enrollment): 28-Dec-2018 • Last-patient-out (end of treatment): 28-Dec-2022 • Last-patient-last-visit (end of safety follow-up): 28-Dec-2022	**Phase of development:** Phase II

Objectives:

Primary objective

- To determine efficacy in terms of Clinical Benefit Rate (CBR) according to RECIST v1.1 at 24 weeks after start of treatment

Secondary objectives

- To assess efficacy with respect to the following outcomes:
  - progression-free survival (PFS)
  - overall survival (OS)
  - overall response rate (ORR)
  - clinical benefit rate (CBR)
  - disease control rate (DCR)
  - 1-year PFS rate and 2-year PFS rate
  - 1-year OS rate and 2-year OS rate
- To determine safety and tolerability in terms of (serious) adverse events ((S)AEs), routine safety laboratory, and frequency and duration of hospitalization
- To evaluate patient reported health-related quality of life (QoL) using the questionnaires FACT-B, BFI and HADS-D in patients treated with palbociclib plus aromatase inhibitor (AI)/fulvestrant
- To compare QoL with real-life patients receiving first-line chemotherapy in the non-interventional MaLife study*:
  - in terms of FACT-B, fatigue (BFI) and depression and anxiety (HADS-D) scores
  - Physician's assessment of patient's overall health status and change in health status compared to previous visit, assessed with a 2 item questionnaire
  - Exploration whether organ-specific symptoms can serve as indicators for progressive disease

Tertiary objectives

- To establish a decentral, virtual biobank for future collection and central analysis of predictive biomarkers of the CDK4/6 pathway**

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*Off note: Since approval of palbociclib the CDKi + AI combination therapy was rapidly implemented in routine care in Germany and therefore, a comparison of quality of life between patients receiving CDKi + AI vs chemotherapy is no longer of medical interest and hasn't been analyzed.

** Off note: This objective was not considered in the CSR, since no tumor samples had been collected upon CSR finalization.

Methodology:
INGE-B was a prospective, open-label, single-arm, multicenter phase II study. Amendments of the clinical trial protocol are displayed in Table 1 (section 2.1)

Number of patients: Planned: N= 360 Enrolled: N= 388	planned: N = 360 screened: N = 388	treated: N = 351 completed: N = 350	analyzed efficacy: (FAS) N = 350 analyzed efficacy: (mPP) N = 107 analyzed safety: (SAF) N = 351

Diagnosis and main criteria for inclusion:
Eligible patients were aged ≥18 years, female (any menopausal state), diagnosed with advanced, defined as locally advanced inoperable or metastatic, HR-positive, HER2-negative adenocarcinoma of the breast, measurable disease as per RECIST v1.1 or bone-only disease, had ECOG performance status 0-2, and were eligible for palliative treatment with palbociclib + AI / fulvestrant according to the respective summary of product characteristics (SmPCs). All inclusion and exclusion criteria are detailed in sections 9.3.1 and 9.3.2.

Test product, dose and mode of administration, batch number:
Palbociclib (PD 0332991, Ibrance®; 125 mg/day orally on days 1 to 21 of a 28-day cycle) + AI (once a day orally on a continuous daily schedule – days 1 to 28 of a 28-day cycle; letrozole (2.5 mg/day) or anastrozole (1 mg/day) or exemestane (25 mg/day)) or fulvestrant (intramuscular administration; 500 mg/application on days 1, 15 and 29 in cycle 1 and thereafter once per a 28-day cycle).

The selection of endocrine combination partner was at the discretion of respective treating physician.

Batch number: Refer to appendix 16.1.6; following the marketing approval of the combination of palbociclib and an AI / fulvestrant in the European Union (November 2016), all study medication used was prescribed medication (i.e., commercially available).

Duration of treatment:
Patients were treated until progressive disease (PD), intolerable toxicity, withdrawal of informed consent, or death. Treatment could be continued beyond Response Evaluation Criteria in Solid Tumors (RECIST)-defined PD in case of negligible or clinically irrelevant disease progression according to the local investigator's discretion until clinically relevant disease progression or symptomatic deterioration.

Palbociclib was administered in combination with an endocrine partner (AI or fulvestrant). In case of permanent discontinuation of AI / fulvestrant, palbociclib treatment had to be withdrawn. Endocrine treatment with AI or fulvestrant could be continued after discontinuation of palbociclib. In pre- or perimenopausal women, endocrine treatment must be combined with a luteinizing hormone-releasing hormone (LHRH) agonist. If treatment with the LHRH agonist was discontinued, palbociclib and AI / fulvestrant treatment had to be withdrawn. Discontinuation of palbociclib and AI / fulvestrant treatment (or AI / fulvestrant if palbociclib had been discontinued earlier) was defined as end of treatment (EOT).

Reference therapy, dose and mode of administration, batch number:
Not applicable.

Criteria for evaluation:

Efficacy

- The primary efficacy endpoint of this study was CBR defined as the proportion of patients with complete response (CR), partial response (PR), or stable disease (SD) ≥ 24 weeks on study according to RECIST v1.1.
- Secondary efficacy endpoints included:
  - PFS
  - OS
  - ORR
  - CBR (CR, PR, or stable disease lasting for 24 weeks or longer)
  - DCR (PR or SD lasting for 48 weeks or longer)
  - 1-year PFS rate and 2-year PFS rate
  - 1-year OS rate and 2-year OS rate
  -

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Safety and tolerability

- (S)AEs until 30 days after EOT: frequency, severity according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03, coding according to Medical Dictionary for Regulatory Activities (MedDRA)
- Routine safety laboratory until EOT (+ safety follow-up)
- Frequency and duration of hospitalization until PD or start of next antineoplastic therapy

Patient-reported outcome (PRO): health-related QoL, fatigue, anxiety and depression

- QoL over time and change from baseline assessed with the FACT-B (Functional Assessment of Cancer Therapy-Breast) questionnaire every 12 weeks until PD (or start of next antineoplastic therapy, whatever came first)
- Fatigue at all questionnaire time points, assessed with the Brief Fatigue Inventory (BFI) questionnaire
- Depression and anxiety at all questionnaire time points, assessed with the Hospital Anxiety and Depression Scale (HADS-D) questionnaire
- Comparison of QoL with real-life patients who received first-line chemotherapy in the non-interventional MaLife study (please, refer to section “objectives”)
    - QoL (FACT-G, fatigue (BFI) and depression and anxiety (HADS-D) after 12 and 24 weeks of treatment
- Physician’s assessment of patient’s overall health status and change in health status compared to previous visit
    - assessed with 2 item questionnaire each cycle/ at scheduled patient visit until PD or start of next antineoplastic therapy, whatever came first
- Exploration whether organ-specific symptoms can serve as indicators for progressive disease
    - the following organ-specific symptoms were assessed: lung: cough, dyspnea; bones: pain: Additionally, as a general symptom, fatigue was assessed as indicator for PD.

Statistical methods:

The statistical analyses performed are detailed in the statistical analysis plan v2.1 (dated 19-Dec-2022) provided in Appendix 16.1.9 (refer to section 16). In general, summaries are presented by treatment group and subgroup. No formal comparisons were performed.

Determination of sample size

Due to the exploratory nature of the study, no formal sample size estimation was performed.

Analysis populations

Full Analysis Set (FAS)

- The FAS comprised all patients who received at least one dose of palbociclib and the respective endocrine partner and was the relevant population for all analyses but safety analyses.

Safety set (SAF)

- The SAF included all patients who received at least one dose of palbociclib and had at least one post-baseline assessment after first study drug administration. The SAF was the relevant population for safety analyses.

Modified Per-Protocol Set (mPP)

- The mPP comprised all patients who received palbociclib plus anastrozole or palbociclib plus exemestane as first-line treatment in the palliative setting. The rationale for this set was the inclusion of patients into treatment groups 5 and 6 who received palbociclib plus AI in later-line treatment instead of first-line treatment according to study protocol. Selected analyses of the FAS were performed additionally with the mPP set.

Patients were analyzed as one of the following treatment groups according to their treatment:
TG1 (LET1): Palbociclib/letrozole (1st -line therapy)
TG2 (LET2+): Palbociclib/letrozole (2nd -or later-line therapy)
TG3 (FUL1): Palbociclib/fulvestrant (1st-line therapy after prior endocrine therapy (adjuvant))
TG4 (FUL2+): Palbociclib/fulvestrant (2nd-or later-line therapy after prior endocrine therapy (adjuvant and/or palliative)
TG5 (ANA1): Palbociclib/anastrozole (1st-line therapy)
TG6 (EXE1): Palbociclib/exemestane (1st-line therapy)

Main statistical methods

Summary Statistics

Summary statistics included the following types of variables:

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Nominal and ordinal variables: frequencies and percentages; continuous variables: Number of valid observations, mean, standard deviation (StD), 25th percentile, median, 75th percentile, minimum, and maximum; Corresponding 95% CI, where applicable.

Efficacy Evaluations – Primary Endpoint
Efficacy analysis was performed for all patients with measurable disease (FAS, N=258) and mPP (N=74) and per treatment group. Response rates were evaluated based on the best overall response (BOR) documented as assessed by the local investigator according to RECIST v1.1. CBR was defined as proportion of patients with BOR (CR, PR, or stable disease lasting for 24 weeks or longer) from day of first study drug administration relative to all patients in the respective population.

Efficacy Evaluations – Secondary Endpoints
All secondary efficacy analysis was performed for patients with measurable disease (FAS, N = 258), all patients with measurable and non-measurable disease (FAS, N=350), mPP (N=107) and per treatment group. Secondary efficacy analyses based on response evaluation by investigator assessment. Time-to-event endpoints (PFS, OS) were estimated by using the Kaplan-Meier (KM) method. PFS was defined as the time interval measured from the day of first study drug administration to first progression or death. OS was defined as the time interval measured from the day of first study drug administration to time of death from any cause. The ORR was defined as proportion of patients with best overall response (CR or PR) relative to all patients in the respective population. The DCR was defined as proportion of patients with BOR (CR or PR or SD) relative to all patients in the respective population.
Rates are reported with exact binomial 95% CI according to the Clopper-Pearson method.

Patient reported Outcome (PRO):
All scales of the FACT-B, HADS-D and BFI questionnaires were calculated according to the respective manual. The remaining efficacy and safety variables were evaluated using descriptive statistics and frequency distributions.

Physician's assessment of patient's global health status:
Physician's assessment of patient's health status was documented using a two-question questionnaire ascertains the patient's overall physical health status, and the global change of the patient's health status. The physician questionnaire was required every cycle at each regularly scheduled patient visit and at the EOT visit. For patients who have not progressed at EOT, the physician questionnaire was continued every 12 weeks until PD or start of next anti-cancer therapy.

Safety Evaluations:
Adverse Events and toxicity were graded according to the CTCAE version 4.03. An AE was classified as a treatment-emergent AE (TEAE) if it had emerged or worsened in the on-treatment period (defined as day of first dose of study medication to 30 days after last dose of study medication). Seriousness of an AE and causal relationship to study treatment (Palbociclib) were assessed by the local investigator. 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).

Summary - Conclusions:
The prospective, multicenter phase 2 INGE-B trial was designed to generate efficacy and safety data on the combination of palbociclib with letrozole (LET1) or fulvestrant (FUL1, FUL2+) in accordance with the PALOMA trials and to generate so far lacking trial data on the combination of palbociclib with anastrozole (ANA1), exemestane (EXE1) or letrozole (LET2+).
After about 6 years of study conduct the clinical part of the study ended on 28-Dec-2022. During this time, 388 patients were enrolled (64 study sites), of whom 350 eligible patients were enrolled to 6 treatment groups.
The following number of patients were included in each treatment group: LET1: n=62; LET2+: n=60; FUL1: n=50; FUL2+: n=61; ANA1: n=60; EXE1: n=57. Median age of all patients included in the final analysis was 65.4 years with a median observation time of 52.9 months for all patients.

Efficacy Results

Primary Endpoint: Clinical Benefit Rate (CBR)
The CBR [95% CI] according to RECIST in patients with measurable disease (FAS) was 71.4% [56.7, 83.4] in LET1, 65.1% [49.1, 79.0] in EXE1, 58.8% [40.7, 75.4] in FUL1, and 56.8% [39.5, 72.9] in ANA1. For treatment groups LET2+ and FUL2+ (second – or later line therapy) the CBR [95% CI] was lower with 45.1% [31.1, 59.7] in LET2, and 40.9% [26.3, 56.8] in FUL2+.

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Secondary Endpoints: CBR, ORR, DCR, mPFS, mOS, 1 + 2-year PFS rate, 1 + 2-year OS rate
All secondary efficacy endpoints for all patients are listed for each treatment group in Table 1.

Table 1. Secondary Endpoints (FAS)

	FAS (N=350)					
	LET1 N=62	**LET2+** N=60	**FUL1** N=50	**FUL2+** N=61	**ANA1** N=60	**EXE1** N=57
CBR (%) [95% CI]	71.0 [58.1, 81.8]	48.3 [35.2, 61.6]	64.0 [49.2, 77.1]	50.8 [37.7, 63.9]	76.7 [64.0, 86.6]	73.7 [60.3, 84.5]
ORR (%) [95% CI]	43.5 [31.0, 56.7]	16.7 [8.3, 28.5]	30.0 [17.9, 44.6]	24.6 [14.5, 37.3]	36.7 [24.6, 50.1]	45.6 [32.4, 59.3]
DCR (%) [95% CI]	80.6 68.6, 89.6]	58.3 [44.9, 70.9]	72.0 [57.5, 83.8]	68.9 [55.7, 80.1]	86.7 [75.4, 94.1]	82.5 [70.1, 91.3]
median PFS (months) [95% CI]	18.0 [11.2, 24.3]	8.7 [4.1, 19.4]	13.7 [8.0, 30.4]	8.2 [5.6, 10.9]	23.3 [13.2, 32.1]	22.5 [15.8, 26.9]
median OS (months) [95% CI]	40.0 [32.9, 58.8]	34.7 [20.7, 41.7]	49.2 [31.5, NA]	26.9 [15.6, 37.2]	53.8 [32.1, NA]	34.0 [26.9, 41.0]
1-year PFS rate (%) [95% CI]	60.0 [46.1, 71.4]	42.0 [28.7, 54.6]	52.2 [37.3, 65.1]	35.6 [23.5, 47.9]	67.3 [53.2, 78.0]	66.9 [52.7, 77.7]
2-year PFS rate (%) [95% CI]	39.1 [26.2, 51.7]	25.3 [14.4, 37.8]	45.9 [31.5, 59.2]	22.6 [12.7, 34.3]	44.5 [31.0, 57.2]	45.4 [31.6, 58.2]
1-year OS rate (%) [95% CI]	91.0 [79.6, 96.2]	76.0 [62.2, 85.3]	80.1 [65.2, 89.1]	79.3 [66.4, 87.7]	91.3 [80.4, 96.3]	87.2 [75.0, 93.7]
2-year OS rate (%) [95% CI]	80.2 [66.2, 88.9]	61.2 [46.4, 73.1]	72.7 [56.9, 83.6]	52.6 [38.5, 64.9]	72.1 [58.0, 82.2]	69.9 [55.6, 80.4]

CI = Confidence Interval; FAS = Full Analysis Set; Note that in ANA1 (PAL + ANA 1L) 7 patients, and in EXE1 (PAL + EXE 1L) 3 patients were identified as no first-line patients and were therefore excluded from the mPP population.

Patient-Reported Outcome (FACT-B, BFI, HADS-D)
QoL was assessed by FACT-B, anxiety and depression by HADS-D, and cancer-related fatigue by BFI. The analysis of the FACT-B questionnaire (including physical, functional, emotional, and social/family well-being, breast cancer sub score, FACT-B trial outcome index, FACT-G total score and FACT-B total score) revealed only subtle changes over time for all parameters from baseline to EOT. The assessment of the fatigue (BFI) and depression and anxiety (HADS-D) questionnaires revealed similar results. As the number of returned/evaluable questionnaires decreased over time, not all timepoints could be considered for evaluation of PROs, limiting the interpretation of the data.

Physician's assessment of patient's global health status:
During the first 10 cycles of palbociclib + AI treatment, the patients with a "very good" or "rather good" overall health status increased from 58.8% at baseline to 72.2% at cycle 10.

TEAEs as indicators for PD (Cough or Dyspnea, Bone Pain, and Fatigue):
For patients presenting with CTCAE Grade 1/2 cough or dyspnea (N=90), 13 (14.4%) patients experienced PD within 6 weeks after onset. For patients presenting with CTCAE Grade 1/2 bone pain (N=42), or fatigue (N=144), only 1 (2.4%) patient and 7 (4.9%) patients, respectively, experienced PD within the same time frame.

Safety results:

Extent of Exposure
The median [min-max] relative dose intensity of palbociclib was 93.0% [49.8-102.7] in LET1, 96.4% [62.8-100.5] in LET2+, 99.1% [55.6-106.3] in FUL1, 96.2% [48.1-106.7] in FUL2+, 95.5% [43.2-100.4] in ANA1, and 95.5% [47.6-103.7] in EXE1. The median [min-max] treatment duration was 50 weeks [4.0-312] in LET1, 27.6 weeks [8.3-308] in LET2+, 45.6 weeks [1.3-285] in FUL1, 33.0 weeks [0.7-273.4] in FUL2+, 67.1 weeks [4.0-279.0] in ANA1, and 71.6 weeks [2.7-268.0] in EXE1.
Treatment-Emergent Adverse Events

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Almost every patient experienced a treatment-emergent AE (TEAE) during the study (Table 2).
Serious TEAEs related to study medication were reported in 17 (4.8%) patients, whereas related TEAEs leading to discontinuation of study medication were reported in 21 (6.0%) patients.
In total 21 fatal TEAEs were reported, with one related fatal event (preferred term: urosepsis) in treatment group ANA1, assessed as related to study medication.

Table 2. Summary of TEAEs (SAF)

Type of AE **n (%) [cases]**	**LET1** **(N=62)**	**LET2+** **(N=60)**	**FUL1** **(N=50)**	**FUL2+** **(N=61)**	**ANA1** **(N=60)**	**EXE1** **(N=57)**
All TEAE	61 (98.4%) [879]	58 (96.7%) [608]	49 (98.0%) [564]	57 (93.4%) [581]	58 (96.7%) [855]	55 (96.5%) [693]
Serious TEAE	24 (38.7%) [54]	13 (21.7%) [22]	16 (32.0%) [25]	25 (41.0%) [42]	14 (23.3%) [23]	20 (35.1%) [34]
Related serious TEAE	4 (6.5%) [6]	3 (5.0%) [4]	1 (2.0%) [1]	4 (6.6%) [4]	4 (6.7%) [4]	1 (1.8%) [1]
Grade 3/4 TEAE	47 (75.8%) [178]	41 (68.3%) [98]	29 (58.0%) [94]	37 (60.7%) [157]	37 (61.7%) [165]	39 (68.4%) [165]
Related grade 3/4 TEAE	36 (58.1%) [116]	29 (48.3%) [64]	21 (42.0%) [66]	26 (42.6%) [113]	29 (48.3%) [135]	28 (49.1%) [96]
TEAE leading to discontinuation of treatment	10 (16.1%) [13]	5 (8.3%) [9]	3 (6.0%) [3]	12 (19.7%) [18]	12 (20.0%) [22]	12 (21.1%) [18]
Related TEAE leading to discontinuation of treatment	2 (3.2%) [2]	-	2 (4.0%) [2]	6 (9.8%) [7]	5 (8.3%) [15]	5 (8.8%) [5]
Fatal TEAE	5 (8.1%) [7]	4 (6.7%) [4]	1 (2.0%) [2]	6 (9.8%) [6]	2 (3.3%) [2]	3 (5.3%) [3]
Related fatal TEAE	-	-	-	-	1 (1.7%) [1]	-

TEAE = Treatment-Emergent Adverse Event; CTCAE = Common Terminology Criteria for Adverse Events; N/n = Number; SAF = Safety Set. Displayed are TEAEs defined as AEs having emerged or worsened in the *on-treatment period*. An AE was classified as related to study medication palbociclib if the causal relationship had been classified as "suspected relationship" by the investigator or if the description of the relationship was missing. Percentages correspond to the number of patients with at least one documented AE of the respective toxicity grade or in the SAF (Total). n (%) represents the number and proportion of patients with respective (type of) AE, [] contain the number of cases.

Most frequent TEAEs ≥20% (CTCAE Grade 3, 4, all Grades) reported in the safety set, are among those events expected in terms of the known safety profiles of palbociclib (Table 3). The frequencies reported are slightly lower than expected from the safety profile of palbociclib. The most frequent reported event is neutropenia as expected from the safety profile of palbociclib.

Table 3. Most frequent TEAEs ≥20% (CTCAE Grade 3, 4, all Grades) (SAF)

Preferred Term (PT) **n (%) [cases]**	**SAF (N=351)**		
	Grade 3	**Grade 4**	**All Grades**
Neutropenia	108 (30.8%) [348]	25 (7.1%) [28]	155 (44.2%) [538]
Fatigue	8 (2.3%) [8]	-	123 (35.0%) [152]
Nausea	1 (0.3%) [1]	-	91 (25.9%) [137]
Leukopenia	38 (10.8%) [54]	3 (0.9%) [4]	80 (22.8%) [153]
Alopecia	-	-	78 (22.2%) [86]
Diarrhoea	4 (1.1%) [4]	-	72 (20.5%) [111]
System Organ Class (SOC)			
Infections and infestations	27 (7.7%) [32]	-	172 (49.0%) [378]

CTCAE = Common Terminology Criteria for Adverse Events; N/n = Number; SAF = Safety Set.
Percentages correspond to the number of patients with at least one documented AE of the respective toxicity grade or in the SAF (Total). n (%) represents the number and proportion of patients with respective (type of) AE, [] contain the number of cases.

In total 85 patients (24.2%) out of the safety set were hospitalized during the study and median duration of hospitalization was 7 days for all patients.

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Conclusion:
The results of the open label, single arm phase II study INGE-B confirm the findings of the pivotal trials evaluating efficacy, health related QoL and safety of palbociclib + letrozole or fulvestrant in first or later line treatment of HR+ HER2- advanced or metastatic breast cancer (PALOMA-1, -2 and -3).
Complementary to the well-established endocrine combination partners letrozole and fulvestrant, the two aromatase inhibitors anastrozole and exemestane were shown to be effective and safe in combination with palbociclib in first line treatment and extend endocrine based therapy options in palliative treatment of HR+ Her2- metastatic breast cancer.
No new safety signals were observed.

Date of report: Final v1.0, 19-December-2023

2.1. List of Protocol Amendments

Table 2-1 List of Protocol Amendments

Protocol-Amendment	***Type of Amendment***	***Changes implemented***	***Protocol Version (Date)***	***Favorable opinion of the central ethics committee[1] (Date)***	***Approval by the competent authority[1] (Date)***
Initial Study Protocol	*NA*	*NA*	*V3.0 (29 Apr 2016)*	14 Jun 2016	17 May 2016
AM 1	Substantial	Amendment to the study protocol: The IMP *palbociclib* obtained marketing authorization in November 2016 *Therefore, Palbociclib was commercially available and prescribed by the investigators since* March 2017. The patient population was extended to 360 pre- and perimenopausal patients in 85 sites, scheduled for palliative treatment with the combination of Palbociclib and Letrozole for first- and later-line and the combination partners Anastrozole for first line, Exemestane for first-line or fulvestrant for first- and later-line after prior endocrine therapy. The recruitment period was extended from 12 to 28 months until December 2018. *The ICF was amended (v5.0 dated 06 Feb 2017) due to changes in the SmPC Ibrance® (11/2016).*	v 6.0 (01 Feb 2017)	23 Feb.2017	23 Feb 2017
AM 2	Substantial	Amendment to the study protocol*:* *Implementation of an interim analysis (fulvestrant treatment groups); implementation of a modified per protocol analysis population (mPP); submission of SmPC Ibrance® (07/2018).*	v 7.0 (17 Dec 2018)	10 Jan 2019	16 Jan 2019
AM 3	Substantial	Amendment to the *informed consent form (ICF):* *Implementation of an additional patient leaflet / informed consent form no. 1 (v2.0 dated 15 Apr 2020) due to safety changes in the SmPC Ibrance® (11/2019);*	NA	20 Apr 2020	16 Mar 2020

AM 4	Substantial	Amendment to the study protocol*:* *Implementation of an addendum to the study protocol (Addendum v1.0 dated 10 Sep 2020).* *Implementation of an additional patient leaflet / informed consent form no.2 (v1.0 dated 10 Sep 2020) due to the change of the formulation of Ibrance® from capsule to film coated (SmPC (06/2020)).*	v 7.0 (17 Dec 2018) Protocol Addendum v1.0 (10 Sep 2020)	17 Sep 2021	Implicit approval
AM 5	Substantial	Amendment to *the informed consent form (ICF):* *Implementation of an additional patient leaflet / informed consent form (no. 3 (v2.0 dated 09 May 2022) due to safety changes in the SmPC Ibrance® (07/2021).*	*NA*	28 Apr 2022	22 Apr 2022

IMP = Investigational Medicinal Product; NA = Not Applicable; SmPC = Summary of Product Characteristics

[1]The initial clinical study protocol and all its amendments were reviewed and approved by the ethical committees (ECs) and relevant competent authority as required. All favorable opinions of the leading EC and approvals by the relevant competent authority are available in the Trial Master File.

2.2. List of Study Sites

Table 2-2 List of Study Sites

No.	Title	First name	Surname	Center (Name); Department	Street / House No.	ZIP code	City	Country
1	Dr.	Zaher	Alwafai	Universitätsmedizin Greifswald; Frauenheilkunde und Geburtshilfe	Ferdinand-Sauerbruch-Straße	17489	Greifswald	Germany
2		Sandra	Ammon	Klinikum Nürnberg Nord; Frauenheilkunde, Schwerpunkt Gynäkologie	Prof.-Ernst-Nathan-Str. 1	90419	Nürnberg	Germany
3	Dr. med.	Dirk-Toralf	Baerens	Gynäko-Onkologische Praxis	Eichstr. 5	31241	Ilsede	Germany
4	Dr. med.	Michael	Berghorn	Allgemeines Krankenhaus Celle/Klinik für Gynäkologie	Siemensplatz 4	29223	Celle	Germany
5	Prof. Dr. med.	Cosima	Brucker	Klinikum Nürnberg Nord; Frauenheilkunde, Schwerpunkt Gynäkologie	Prof.-Ernst-Nathan-Str. 1	90419	Nürnberg	Germany
6	Dr. med.	Dieter	Bürkle	Zentrum Ambulante Onkologie	Schlichtener Str. 105	73614	Schorndorf	Germany
7	Dr. med.	Steffi	Busch	MVZ GmbH; Gynäkologisch-onkologische Schwerpunktpraxis	Bei der Marienkirche 6	99974	Mühlhausen	Germany
8	PD Dr. med.	Jolanta	Dengler	Onkologische Schwerpunktpraxis	Allee 40	74072	Heilbronn	Germany
9	Dr. med.	Reinhard	Depenbusch	Onkologische Schwerpunktpraxis	Brunnenstr. 14	33332	Gütersloh	Germany
10	Dr. med.	Mustafa	Deryal	Caritasklinikum Saarbrücken; Frauenklinik	Rheinstr. 2	66113	Saarbrücken	Germany
11	Dr. med.	Sven	Detken	MVZ Onkologie Barmbek GmbH	Rübenkamp 220	22307	Hamburg	Germany
12	Dipl.-Med.	Steffen	Dörfel	Onkozentrum Dresden/Freiberg	Leipziger Str. 118	01127	Dresden	Germany
13	Dr. med.	Thomas	Fietz	Schwerpunktpraxis für Hämatologie und Internistische Onkologie, Gastroenterologie	Virchowstr. 10c	78224	Singen (Hohentwiel)	Germany
14		Jens	Gerber	Städtisches Klinikum Dessau; Frauenheilkunde und Geburtshilfe	Auenweg 38	06847	Dessau-Roßlau	Germany
15		Tobias	Graefe	Hämatologisch Onkologischer Schwerpunkt	Süntelstr. 11a	22457	Hamburg	Germany
16	Prof. Dr. med.	Frank	Griesinger	Pius-Hospital Oldenburg; Hämatologie, Onkologie	Georgstr. 12	26121	Oldenburg	Germany
17	Prof. Dr. med.	Martin	Griesshammer	Johannes Wesling Klinikum Minden; Innere Medizin, Hämatologie, Onkologie	Hans-Nolte-Str. 1	32429	Minden	Germany
18		Matthias	Groschek	Hämatologie - Onkologie - Stolberg	Steinfeldstr. 7	52222	Stolberg	Germany
19	Dr. med.	Volker	Hagen	St.-Johannes-Hospital; Innere Medizin II	Johannesstr. 9-17	44137	Dortmund	Germany
20	Dr. med.	Antje	Hahn	Klinikum Mittelbaden; Frauenheilkunde und Geburtshilfe	Balger Str. 50	76532	Baden-Baden	Germany

No.	Title	First name	Surname	Center (Name); Department	Street / House No.	ZIP code	City	Country
21	Dr. med.	Ludger	Heflik	Praxis und Tagesklinik für Onkologie und Hämatologie	Am Stadion 9	45659	Recklinghausen	Germany
22	Prof. Dr. med.	Jens	Huober	Universitätsklinikum Ulm; Frauenheilkunde, Geburtshilfe	Prittwitzstr. 43	89075	Ulm	Germany
23	Dr. med.	Gabriele	Kaltenecker	Städtisches Klinikum Karlsruhe; Frauenklinik	Moltkestr. 90	76133	Karlsruhe	Germany
24	Dr. med.	Markus	Keller	Schwarzwald-Baar Klinikum; Klinik für Frauenheilkunde	Klinikstr. 11	78052	Villingen-Schwenningen	Germany
25		Sandra	Ketzler-Henkel	Gemeinschaftspraxis für Hämatologie und Onkologie am Knappschaftskrankenhaus	Am Knappschafts-krankenhaus 1	44309	Dortmund	Germany
26	Dr. med.	Jan	Knoblich	Onkologische Schwerpunktpraxis	Röntgenstr. 10	79539	Lörrach	Germany
27	Dr. med.	Andreas	Köhler	Gemeinschaftspraxis für Hämatologie und Onkologie	Röntgenstr. 6-8	63225	Langen	Germany
28	PD Dr. med.	Hans-Christian	Kolberg	Marienhospital Bottrop; Gynäkologie und Geburtshilfe	Josef-Albers-Str. 70	46236	Bottrop	Germany
29	Dr. med.	Thomas W.	Kubin	Kliniken Südostbayern Klinikum Traunstein; Hämatologie/Onkologie/Palliativmedizin	Cuno-Niggl-Str. 3	83278	Traunstein	Germany
30	Dr. med.	Thomas	Kuhn	Gynäkologisch-onkologische Schwerpunkpraxis	Rosenbergstr. 21	70176	Stuttgart	Germany
31	Prof. Dr. med.	Thorsten	Kühn	Klinikum Esslingen; Frauenheilkunde und Geburtshilfe	Hirschlandstr. 97	73730	Esslingen	Germany
32	PD Dr. med.	Christian Martin	Kurbacher	Gynäkologisches Zentrum Bonn	Friedensplatz 16	53111	Bonn	Germany
33	PD Dr. med.	Rüdiger	Liersch	GEHO - Dres. Lerchenmüller, Kratz-Albers,Timmer, Bieker & Liersch	Düesbergweg 128	48153	Münster	Germany
34	Dr. med.	Hartmut	Linde	MVZ für Blut- und Krebserkrankungen	Kurfürstenstr. 20	14467	Potsdam	Germany
35	Prof. Dr. med.	Diana	Lüftner	Immanuel Klinik Märkische Schweiz	Lindenstr. 68-70	15377	Buckow	Germany
36	Dr. med.	Johannes	Meiler	Klinik Dr. Hancken; Hämatologie und Onkologie	Harsefelder Str. 8	21680	Stade	Germany
37	Dr. med.	Lothar	Müller	Onkologie UnterEms	Annenstr. 11	26789	Leer	Germany
38	Prof. Dr. med.	Holger	Nückel	Hämatologisch-onkologische Schwerpunktpraxis	Kurt-Schumacher-Platz 4	44787	Bochum	Germany
39	Dr. med.	Marika Henriette	Princk	Universitätsklinikum Schleswig-Holstein - Campus Lübeck; Frauenheilkunde und Geburtshilfe	Ratzeburger Allee 160	23538	Lübeck	Germany

No.	Title	First name	Surname	Center (Name); Department	Street / House No.	ZIP code	City	Country
40	Dr. med.	Jacqueline	Rauh	GIM - Gemeinschaftspraxis; Innere Medizin	Pferdebachstr. 29	58455	Witten	Germany
41	Dr. med.	Dietmar	Reichert	Gemeinschaftspraxis für Hämatologie und Onkologie	Kuhlenstr. 53 D	26655	Westerstede	Germany
42	Prof. Dr. med.	Toralf	Reimer	Klinikum Südstadt Rostock; Frauenklinik	Südring 81	18059	Rostock	Germany
43	Prof. Dr. med.	Christoph	Salat	Medizinisches Zentrum für Hämatologie und Onkologie	Winthirstr. 7	80639	München	Germany
44	Dr. med.	Reiner	Sandner	MVZ für Hämatologie und Onkologie Passau GmbH	Dr.-Emil-Brichta-Str. 3	94036	Passau	Germany
45	Dr. med.	Lars	Scheuer	Onkologische Schwerpunktpraxis	Hilgardstr. 30	67346	Speyer	Germany
46	Dr. med.	Sebastian	Schlott	Hämato-Onkologisches Zentrum Kassel	Goethestr. 47	34119	Kassel	Germany
47	Dr. med.	Hans-Roland	Schmitt	Gemeinschaftspraxis Dres. Schmitt und Eulenbruch	Kirchstr. 3	70839	Gerlingen	Germany
48	PD Dr. med.	Jan	Schröder	MVZ für Hämatologie und Onkologie	Schulstr. 13	45468	Mülheim a.d.R.	Germany
49	Dr. med.	Heribert	Stauder	Krankenhaus Barmherzige Brüder; Onkologie und Hämatologie	Prüfeninger Str. 86	93049	Regensburg	Germany
50	Prof. Dr. med.	Alexander	Stein	Hämatologisch-Onkologische Praxis Eppendorf (HOPE)	Eppendorfer Landstr. 42	20249	Hamburg	Germany
51	Univ.-Prof. Dr. med.	Elmar	Stickeler	Uniklinik RWTH Aachen; Gynäkologie und Geburtsmedizin	Pauwelsstr. 30	52074	Aachen	Germany
52	Prof. Dr. med.	Marc	Sütterlin	Universitätsklinikum Mannheim; Frauenklinik	Theodor-Kutzer-Ufer 1-3	68167	Mannheim	Germany
53	Dr. med.	Arne	Terjung	Helios Klinikum Krefeld; Klinik für Frauenheilkunde	Lutherplatz 40	47805	Krefeld	Germany
54	Prof. Dr. med.	Marc	Thill	Agaplesion Markus Krankenhaus; Klinik für Gynäkologie und Gynäkologische Onkologie	Wilhelm-Epstein-Str. 4	60431	Frankfurt a.M.	Germany
55	Prof. Dr. med.	Christoph	Thomssen	Universitätsklinikum Halle (UKH); Universitätsklinik und Poliklinik für Gynäkologie	Ernst-Grube-Str. 40	06120	Halle (Saale)	Germany
56	Dr. med.	Oliver	Tomé	St. Vincentius-Kliniken; Gynäkologie und Geburtshilfe	Edgar-von-Gierke-Str. 2	76135	Karlsruhe	Germany
57	PD Dr. med.	Tanja	Trarbach	MVZ des Klinikums Wilhelmshaven	Friedrich-Paffrath-Str. 100	26389	Wilhelmshaven	Germany
58	Prof. Dr. med.	Michael	Untch	Helios Klinikum Berlin-Buch; Gynäkologie	Schwanebecker Chaussee 50	13125	Berlin	Germany
59		Raquel	von Schumann	Brustzentrum Niederrhein im ev. Krankenhaus Bethesda	Ludwig-Weber-Str. 15	41061	Mönchen-gladbach	Germany
60	Dr. med.	Manfred	Welslau	MVZ am Klinikum Aschaffenburg GmbH	Am Hasenkopf 1	63739	Aschaffenburg	Germany

No.	Title	First name	Surname	Center (Name); Department	Street / House No.	ZIP code	City	Country
61	PD Dr. med.	Anja	Welt	Universitätsklinikum Essen; Innere Klinik Tumorforschung	Hufelandstr. 55	45147	Essen	Germany
62	Prof. Dr. med.	Pauline	Wimberger	Universitätsklinikum Carl Gustav Carus Dresden; Frauenheilkunde	Fetscherstr. 74	01307	Dresden	Germany
63	Dr. med.	Mark-Oliver	Zahn	ÜBAG MVZ Onkologische Kooperation Harz	Kösliner Str. 14	38642	Goslar	Germany
64	Dr. med.	Matthias	Zaiss	Praxis für interdisziplinäre Onkologie & Hämatologie	Wirthstr. 11c	79110	Freiburg i.Br.	Germany