IMPlementing geriatric assessment for dose Optimization of CDK 4/6-inhibitors in older bReasT cAncer patieNTs – a pragmatic randomized-controlled trial (IMPORTANT trial)

Sponsor:	Region Örebro County
Supported by:	Project: 101104589 — IMPORTANT HORIZON-MISS-2022-CANCER-01
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Study Design:	Phase III & IV integrated, Multicenter, open-label, prospective, randomized, controlled, non-inferiority trial with a pragmatic approach (Low Interventional).
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3. Sponsor's Protocol Signature Page

Protocol Version 4.0_18nov2024

I herewith certify study's design

Sponsor's responsible for the study name: Antonis Valachis

Signature: 

Date: 18 Nov 2024

4. Principal Investigator's Protocol Signature Page:

Signature of the principal investigator at the study site

The signatory agrees to the content if the final clinical study protocol as presented

Protocol Version 4.0_18nov2024

Principal Investigator Name:

Site number:

Signature:

Date:

5. Glossary

AB	Advisory Board
AEs	Adverse events
ALCOA+	Attributable, Legible, Contemporaneous, Original, Accurate, and Complete, Consistent, Enduring, and Available
CA	Competent authority
CC	Clinical Coordinator
CDK	Cyclin-dependent kinase
CGA	Comprehensive geriatric assessment
CI	Confidence Intervals
CONSORT	Consolidated Standards of Reporting Trials
CRO	Contract Research Organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DATECAN	Definition for the Assessment of Time-to-event Endpoints in CANcer trials
DMP	Data management plan
EC	European commission
eCRF	electronic case report form
ECs	Ethics committees
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ET	Endocrine therapy
EU	European Union
FDA	Food and Drug Administration
GCP	Good clinical practice
HER2	Human epidermal growth factor receptor 2
HR	Hormone receptor
HRQoL	Health related quality of life
HTA	Health technology assessment
IADL	Instrumental activities of daily living
ICER	incremental cost effectiveness ratio
ICF	Informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committees
iMCQ	iMTA Medical Consumption Questionnaire
iMTA	Institute for Medical Technology Assessment
IRBs	Institutional Review Boards
ITT	Intention-to-treat
MHI	Mental Health Inventory
MOS	Medical Outcomes Study
OARS	Older Americans Resources and Services
OS	Overall survival
OTU	Overall treatment utility
PCC	Project Coordination Committee
PEC	Privacy & Ethics Committee
PFS	Progression-free survival
PROMs	Patient-reported outcome measures
PTC	Project Technical Committee

QoL	Quality of life
RCTs	Randomised clinical trials
RWE	Real-world evidence
SAE	Serious adverse event
SAR	Serious Adverse Reaction
SIOG	International Society of Geriatric Oncology
SmPC	Summary of product characteristics
SOPs	Standard Operational Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
TP	Treated population
TTF	Time to treatment failure
WHO	World Health Organisation

6. Trial summary

Sponsor Region Örebro län	**Grant Agreement Nr. (Funded by European Union)** 101104589
EUCT Number 2023-506620-87-00	

Short Title	**IMPORTANT Trial**
Full Title	**IMP**lementing geriatric assessment for dose **O**ptimization of CDK 4/6-inhibitors in older b**R**eas**T** c**A**ncer patie**NT**s – a pragmatic randomized-controlled trial
Chief Investigator	Assoc. Prof. Antonis Valachis
Population	Older breast cancer patients (≥ 70 years old) with advanced HR-positive/HER2-negative breast cancer, not amenable for curative treatment and without prior therapy for advanced disease, who are suitable to receive CDK 4/6-inhibitors plus endocrine therapy.
Trial Design	Phase III & IV Integrated, Multicenter, open-label, prospective, randomized, controlled, non-inferiority trial with a pragmatic approach (Low Intervention Trial).
Study Rationale	• In patients with advanced hormone-receptor (HR-) positive breast cancer, the combination of endocrine therapy with CDK 4/6-inhibitors is the standard of care as initial treatment approach. • Older cancer patients are underrepresented in clinical trials (including pivotal trials on CDK 4/6-inhibitors). • Real-world evidence studies have showed that older patients are at increased risk for adverse events when treated with CDK 4/6-inhibitors; lower initial dose is common in clinical practice, though without evidence. • Comprehensive geriatric assessment (CGA) seems to be a reliable tool for optimization of treatment strategy in older cancer patients.
Aims	• To investigate the time to treatment failure (TTF) in vulnerable or frail older breast cancer patients treated with lower initial dose of CDK 4/6-inhibitors plus endocrine therapy compared to the recommended full dose of CDK 4/6-inhibitors. • To compare the two treatment arms (lower initial dose of CDK 4/6-inhibitor vs. full dose) in terms of overall survival (OS), investigator-assessed progression-free survival (PFS), time to chemotherapy initiation, overall treatment utility (OTU; composite endpoint which integrates efficacy, tolerability, QoL and patient acceptability), treatment tolerability, patients' quality of life (QoL), and cost-effectiveness.
Research Questions	1. Does a CGA-based initial dose modification scheme for CDK 4/6-inhibitors for vulnerable/frail older patients with advanced breast cancer result in a similar time to treatment failure compared to full dose CDK 4/6-inhibitors? 2. Does lower initial dose of CDK 4/6-inhibitors impact OS, PFS and time to chemotherapy initiation? 3. Does lower initial dose CDK 4/6-inhibitors offer advantages in terms of OTU? 4. Does lower initial dose of CDK 4/6-inhibitors provide advantages in terms of patient-reported outcomes? 5. Does lower initial dose of CDK 4/6-inhibitors provide advantages in terms of cost-effectiveness?

Endpoints	**Primary endpoint** • Time to treatment failure **Secondary endpoints** • Overall Treatment Utility • Overall survival • Progression free survival • Time to chemotherapy initiation • Toxicity • QoL • Time to QoL deterioration • Cost-effectiveness
Sample Size	36-month accrual period with 495 patients to be included. Aim to recruit 149 patients for the fit cohort to be treated and followed, and 346 patients for the vulnerable / frail cohort to be randomized during this recruitment period.
Inclusion Criteria	The following inclusion criteria will be applied: 1.Patients male or female aged at least 70 years old at the time of informed consent. Male patients should use adequate contraceptive methods (e.g., double-barrier contraception) during therapy and for at least 14 weeks after completing therapy. 2.Histologically or cytologically confirmed diagnosis of HR-positive (defined as estrogen-receptor ≥ 1%), HER2-negative breast cancer according to analysis of the most recent tumor specimen by local laboratory. 3.Advanced (locoregionally recurrent or metastatic) breast cancer not amenable to curative treatment. 4.No prior systemic treatment for advanced disease (recurrence during neo-/adjuvant endocrine therapy is allowed). A prior period of treatment with aromatase inhibitors or fulvestrant for up to 56 days from the CDK 4/6-inhibitor initiation is allowed as long as there is no disease progression during this time period. 5.Adjuvant treatment with CDK4/6-inhibitors is allowed provided a disease-free interval from treatment end >12 months. 7.Written informed consent prior to any study-specific procedures. 8.Adequate organ function as defined in the summary of product characteristics (SmPC) for the CDK 4/6-inhibitors that is planned to be used including ECG for assessment of QT interval before treatment with ribociclib. Specifically, the following thresholds should be used to define adequate organ function: absolute neutrophil counts of ≥ 1,000/mm3, platelet counts of ≥ 100,000/mm3; ALT and/or AST ≤ 3 x upper limit normal (ULN), total bilirubin ≤ 2 x ULN; eGFR ≥ 30 mL/min. 9.Able to swallow capsules. 10.Able to understand and consent in English language or in native language for each participating country.
Main exclusion criteria	Eligible patients will be excluded if they have one of the following criteria: 1.Patients considered from treating physician as non-suitable for treatment with CDK 4/6-inhibitors. 2. Patients with cognitive impairment (as assessed by treating physician) that preclude the ability to fill out the self-reported CGA. 3.Contraindications according to SmPC for the CDK 4/6-inhibitors that is planned to be used. Specifically, any hypersensitivity to the active substance or to any of the excipients or to peanut, soya (for ribociclib) or use of preparations containing St. John's Wort (for palbociclib) are contraindications. 4.Presence of visceral crisis, lymphangitis carcinomatosis, or leptomeningeal carcinomatosis. 5.History of any other cancer (except of non-melanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission for a minimum of 3 years. 6.Participating in other interventional trial.
Follow-up	**Treatment phase:** Follow-up for efficacy outcome and OTU take place every three (+/- 28 days) months post randomization. Follow-up for questionnaire assessments take place at 3, 6, 9, 12, 15, 18, 21, and 24 months post randomization depending on the questionnaire. Follow-up for toxicity is before each cycle and up

	to 28 days after the end of CDK 4/6-inhibitors. This phase continues until disease progression, participant/clinician decision to stop or up to 24 months. **Post-treatment phase** (survival follow-up): It will continue after the treatment phase and will collect information until death, lost to follow up, consent withdrawal by the patient, or up to 5 years from treatment initiation for each patient.
Trial Management	The Department of Oncology, Örebro University Hospital Contact: Assoc. Prof. Antonis Valachis Email: important@oru.se, antonios.valachis@oru.se

7. Study rationale

The addition of CDK 4/6-inhibitors to endocrine therapy has been shown to improve both progression-free (PFS) and overall survival (OS) in patients with hormone-receptor positive (HR+) advanced breast cancer in 1st or 2nd line setting[1]. The efficacy of CDK 4/6-inhibitors seems to be present in all patient subgroups, including older patients who were included in the pivotal randomized trials (1). However, older cancer patients are underrepresented in clinical trials and their baseline characteristics may differ from older cancer patients in real-world setting, thus making the generalizability of the results from randomized trials problematic[2].

Current evidence from both randomized trials (RCTs) and real-world evidence (RWE) studies suggests that older breast cancer patients derive clinical benefit from the addition of CDK 4/6-inhibitors to endocrine therapy but with higher risk for adverse events and treatment discontinuation compared to younger patients[3]. The recommended starting dose for CDK 4/6-inhibitors is, however, the same irrespective of patient characteristics. Considering the higher risk for adverse events in older patients, it might be reasonable to initiate CDK 4/6-inhibitors at a lower dose. In fact, this clinical approach seems to be a relatively common practice according to RWE studies[4,$]. In a randomized trial of full vs. lower dose of ribociclib in a study cohort of patients with median age 58 years, no statistically significant differences in terms of responses or progression-free survival were observed whereas lower risk for toxicity was evident in lower dose[5]. However, no randomized evidence specifically for older patients does exist on initiating with a lower dose of CDK 4/6-inhibitors, so this practice is merely based on clinical observation than existing evidence.

There is growing evidence on the multidimensional role of comprehensive geriatric assessment (CGA) in older cancer patients. CGA refers to the implementation of a validated framework for the evaluation of ageing-related domains in older cancer patients that might impact cancer treatment decisions[6]. Through CGA, older cancer patients can be categorized as fit, vulnerable, or frail. Based on this categorization, CGA-guided interventions can be applied to potentially improve patients' health status. The implementation of CGA and CGA-guided interventions in older cancer patients seem to reduce treatment-related toxicities according to recently published RCTs[7,§].Nevertheless, few RCTs dedicated to older cancer patients have used geriatric assessment as a baseline tool to optimize cancer treatment strategy.

In MRC-FOCUS2 trial, frail older patients with metastatic colorectal cancer were randomized to four different chemotherapy regimens (FOLFOX vs. FLV vs. Capecitabine vs. CAPOX; all in reduced dose of 80%). The results indicated that chemotherapy in combination was preferable than monotherapy in

[1] Li J, Huo X, Zhao F, Ren D, Ahmad R, Yuan X, Du F, Zhao J. Association of Cyclin-Dependent Kinases 4 and 6 Inhibitors With Survival in Patients With Hormone Receptor-Positive Metastatic Breast Cancer: A Systematic Review and Meta-analysis. JAMA Netw Open. 2020;3:e2020312

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[6] Mohile SG, Dale W, Somerfield MR, et al.. Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. J Clin Oncol. 2018;36:2326-2347

[7] Li D, Sun CL, Kim H, Soto-Perez-de-Celis E, et al. Geriatric Assessment-Driven Intervention (GAIN) on Chemotherapy-Related Toxic Effects in Older Adults With Cancer: A Randomized Clinical Trial. JAMA Oncol. 2021;7:e214158

[§] Mohile SG, Mohamed MR, Xu H, Culakova E, et al. Evaluation of geriatric assessment and management on the toxic effects of cancer treatment (GAP70+): a cluster-randomised study. Lancet. 2021 Nov 20;398(10314):1894-1904.

this older patient group[8]. In ESOGIA-GFPC-GECP 08-02 trial, treatment allocation based on CGA (platinum-based in fit patients; monotherapy in vulnerable; best supportive care in frail) failed to improve the outcome of older patients with non-small-cell lung cancer compared to treatment allocation based on clinical decision[9]. In GO2 trial, lower initial chemotherapy dose of CAPOX in frail (as assessed by clinical decision and geriatric assessment) patients with advanced gastroesophageal cancer was non-inferior compared to full dose with less toxicity and better patient experience[10].

These randomized data suggest that CGA could potentially be used at baseline to optimize cancer treatment strategy. However, this approach has only been tested in older cancer patients treated with chemotherapy and not in patients who are eligible for targeted therapies. In case of targeted therapies, the ”one-size-fits-all” approach in starting dose is the current standard, although clinical experience suggests that lower initial doses can be beneficial in some patient subgroups[4,$].

The aim of the present randomized trial is to investigate whether a CGA-based initial dose modification scheme for CDK 4/6-inhibitors for vulnerable/frail older patients with advanced breast cancer would result in a similar time to treatment failure, better patient experience (in terms of toxicity and quality of life) without compromising treatment efficacy.

7.1 Extent and evaluation of current knowledge

Reducing the initial dose of CDK 4/6-inhibitors in older breast cancer patients to reduce the risk of adverse events seems to be a relatively common clinical practice according to real-world evidence[4]. However, this treatment approach has not been evaluated in a prospective clinical study in older cancer patients that would produce results contributing to higher level of evidence.

The implementation of CGA in decision making process for older cancer patients candidated to chemotherapy, has been investigated in some randomized trials[7-9]. These studies have shown that chemotherapy dose optimization based on CGA, might be of value in terms of reducing adverse events. However, no randomized trial has implemented CGA-based decision making in situations where targeted therapies such as kinase inhibitors are the treatment of choice. Although kinase inhibitors have a larger therapeutic window than chemotherapy, their dosing strategy is based in a one-size-fits-all approach where all patients are recommended the same initial dose with adjustment in case of toxicity. However, recent pharmacological data suggest that kinase inhibitors’ large therapeutic window enables the potential use of lower doses for improving the tolerability without jeopardizing the efficacy[11].

Taken together, implementing CGA-based approach in decision making for dose optimization of CDK 4/6-inhibitors in an older patient population with well-documented higher risk for toxicity and discontinuation due to toxicity, is an appealing strategy.

7.2 Clinical evidence on lower dose of CDK 4/6-inhibitors in patients with metastatic breast cancer

There are no prospective studies investigating dose optimization strategies regarding CDK 4/6-inhibitors in older breast cancer patients. Available evidence evidence for older patients is based on real-world retrospective studies where a lower starting dose strategy seems to be a relatively common practice based on clinical experience alone[4,$]. In a prospective randomized trial including both pre- and

[8] Seymour MT, Thompson LC, Wasan HS, et al; FOCUS2 Investigators; National Cancer Research Institute Colorectal Cancer Clinical Studies Group. Chemotherapy options in elderly and frail patients with metastatic colorectal cancer (MRC FOCUS2): an open-label, randomised factorial trial. Lancet. 2011;377:1749-59

[9] Corre R, Greillier L, Le Caër H, et al. Use of a Comprehensive Geriatric Assessment for the Management of Elderly Patients With Advanced Non-Small-Cell Lung Cancer: The Phase III Randomized ESOGIA-GFPC-GECP 08-02 Study. J Clin Oncol. 2016;34:1476-83

[10] Hall PS, Swinson D, Cairns Daet al; GO2 Trial Investigators. Efficacy of Reduced-Intensity Chemotherapy With Oxaliplatin and Capecitabine on Quality of Life and Cancer Control Among Older and Frail Patients With Advanced Gastroesophageal Cancer: The GO2 Phase 3 Randomized Clinical Trial. JAMA Oncol. 2021;7:869-877

[11] Goldstein MJ, Peters M, Weber BL, Davis CB. Optimizing the Therapeutic Window of Targeted Drugs in Oncology: Potency-Guided First-in-Human Studies. Clin Transl Sci. 2021;14:536-543

postmenopausal women with breast cancer, lower initial dose of CDK 4/6-inhibitor ribociclib did not result in statistically significant worse response rates (41.5% for lower dose vs. 45.3% in full dose) or progression-free survival (24.9 months for lower dose vs. 25.1 months in full dose)5. In addition, fewer dose-dependent adverse events of grade ≥ 3 and fewer dose reductions were observed in the lower initial dose arm. Although the trial did not demonstrate noninferiority (in terms of response rate that was the primary endpoint), the differences between the two treatment arms were only numerical and suggest that a better patient selection with higher risk for adverse events (as older vulnerable patients) would be benefitted from a lower initial dose without compromising the expected efficacy.

The ongoing RIBOB trial is a prospective observational study where older breast cancer patients treated with the CDK 4/6-inhibitor ribociclib, and endocrine therapy as 1st line treatment will be prospectively followed regarding efficacy of the combination, safety, quality of life and age-related metrics[12]. The study does not use CGA-based strategy as a part of treatment decision making and does not include any interventional arm for dose optimization. The FACILE trial evaluates the feasibility of delivering full dose ribociclib and letrozole in metastatic breast cancer patients aged 70 years and older. Patients are evaluated at baseline by the means of a CGA, but initial dose modification based on the result of the assessment is not allowed [**]. As a result, our study is the only prospective study that implements CGA-based strategy for decision making regarding a targeted therapy in older cancer patients and investigates a dose optimization intervention.

7.3 Clinical evidence on implementing CGA in cancer care

Level I evidence supports the implementation of CGA in older cancer patients, to reduce treatment-related toxicity and improve quality of life[§].

CDK 4/6-inhibitors plus endocrine therapy is the preferred treatment approach for patients with advanced HR-positive/HER2-negative breast cancer based on level I evidence derived from several pivotal randomized trials[1]. Moreover, this combination is the preferred treatment option for this patient subgroup according to international guidelines[13]. The SIOG guidelines dedicated to older breast cancer patients, recognize the combination of CDK 4/6-inhibitors and endocrine therapy as a suitable treatment in older patients but highlights the potential need of frequent dose adjustments[14].

Starting dose reduction of CDK 4/6-inhibitors is a relatively common clinical practice in older breast cancer patients but with limited evidence. The study implements two approaches with high level of evidence, namely the use of CGA-approach in treatment decision making and the use of CDK 4/6-inhibitors as the initial treatment of choice, to investigate whether a common clinical practice (starting dose reduction of CDK 4/6-inhibitors in older patients) with evidence of low certainty can be standardized using a more individualized-based approach.

8. Objective(s) of the clinical study

The primary objective of the IMPORTANT study is to investigate the time to treatment failure (TTF) in vulnerable or frail older breast cancer patients treated with lower initial dose of CDK 4/6-inhibitors plus endocrine therapy compared to the recommended full dose of CDK 4/6-inhibitors. TTF is a composite endpoint allowing the integration of toxicity in addition to efficacy into the definition of

[12] Available at: https://clinicaltrials.gov/ct2/show/NCT03956654 (Accessed 6th September 2022)

** Available at: https://clinicaltrials.gov/ct2/show/NCT03944434 (Accessed 1st March 2023)

[13] Cardoso F, Paluch-Shimon S, Senkus Eet al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020;31:1623-1649.

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treatment benefit and is considered a suitable endpoint for clinical trials dedicated to older cancer patients[15].

The secondary objectives are to compare the two treatment arms (lower initial dose of CDK 4/6-inhibitor vs. full dose) in terms of overall survival (OS), investigator-assessed progression-free survival (PFS), time to chemotherapy initiation, overall treatment utility (OTU; composite endpoint which integrates efficacy, tolerability, QoL and patient acceptability), treatment tolerability, patients' quality of life (QoL) and cost-effectiveness.

Implementation of CGA is essential for the study design and will be performed in all eligible patients at baseline. Based on the CGA, two patient cohorts will be defined, fit older patients and vulnerable/frail older patients. The randomization to lower initial vs. full dose of CDK 4/6-inhibitors will be applied to patients in the vulnerable/frail cohort. Fit older patients will receive full dose of CDK 4/6-inhibitors according to current clinical practice and will serve as a control group. Their results will be analyzed in a descriptive manner including all the primary and secondary endpoints that are described for the vulnerable/frail cohort.

9. Characteristics of the study population

Eligible patients for the IMPORTANT study are older breast cancer patients (≥ 70 years old) with advanced HR-positive/HER2-negative breast cancer, not amenable for curative treatment and without prior therapy for advanced disease. The age limit was set at 70 years old considering the international guidelines suggesting this threshold to define older patients where specific recommendations are applied[16].

9.1 Inclusion criteria

The following inclusion criteria will be applied:

1. Patients male or female aged at least 70 years old at the time of informed consent. Male patients should use adequate contraceptive methods (e.g., double-barrier contraception) during therapy and for at least 14 weeks after completing therapy.
2. Histologically or cytologically confirmed diagnosis of HR-positive (defined as estrogen-receptor ≥ 1%), HER2-negative breast cancer according to analysis of the most recent tumor specimen by local laboratory.
3. Advanced (locoregionally recurrent or metastatic) breast cancer not amenable to curative treatment.
4. No prior systemic treatment for advanced disease (recurrence during neo-/adjuvant endocrine therapy is allowed). A prior period of treatment with aromatase inhibitors or fulvestrant for up to 56 days from the CDK 4/6-inhibitor initiation is allowed as long as there is no disease progression during this time period.
5. Adjuvant treatment with CDK4/6-inhibitors is allowed provided a disease-free interval from treatment end >12 months.
6. Written informed consent prior to any study-specific procedures.
7. Adequate organ function as defined in the summary of product characteristics (SmPC) for the CDK 4/6-inhibitors that is planned to be used. including ECG for assessment of QT interval before treatment with ribociclib. Specifically, the following thresholds should be used to define adequate organ function: absolute neutrophil counts of ≥ 1,000/mm^3, platelet counts of ≥ 100,000/mm^3; ALT and/or AST ≤ 3 x upper limit normal (ULN), total bilirubin ≤ 2 x ULN; eGFR ≥ 30 mL/min.

[15] Wildiers H, Mauer M, Pallis A, et al. End points and trial design in geriatric oncology research: a joint European organisation for research and treatment of cancer--Alliance for Clinical Trials in Oncology--International Society Of Geriatric Oncology position article. J Clin Oncol. 2013;31:3711-8

[16] Biganzoli L, et al. Updated recommendations regarding the management of older patients with breast cancer: a joint paper from the European Society of Breast Cancer Specialists (EUSOMA) and the International Society of Geriatric Oncology (SIOG). Lancet Oncol. 2021;22:e327-e340.

8. Able to swallow capsules.

9. Able to understand and consent in English language or in native language for each participating country.

9.2 Exclusion criteria

Eligible patients will be excluded if they have one of the following criteria:

1. Patients considered from treating physician as non-suitable for treatment with CDK 4/6-inhibitors.
2. Patients with cognitive impairment (as assessed by treating physician) that preclude the ability to fill out the self-reported CGA.
3. Contraindications according to SmPC for the CDK 4/6-inhibitors that is planned to be used. Specifically, any hypersensitivity to the active substance or to any of the excipients or to peanut, soya (for ribociclib) or use of preparations containing St. John's Wort (for palbociclib) are contraindications.
4. Presence of visceral crisis, lymphangitis carcinomatosis, or leptomeningeal carcinomatosis.
5. History of any other cancer (except of non-melanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission for a minimum of 3 years.
6. Participating in other interventional trial.

9.3 Gender aspects

Breast cancer is predominantly a cancer type that affects female patients. The lifetime risk of developing breast cancer for men in the general population is 0.1%, and <1% of all breast cancer diagnoses occur in men[17]. As a result, male breast cancer is a rare disease. The treatment strategies in male breast cancer are mainly based on extrapolation of studies performed in female breast cancer[18]. Considering CDK 4/6-inhibitors in male breast cancer, men were excluded from pivotal randomized trials and current data supporting use of CDK4/6 inhibitors in men are limited to retrospective cohort studies where effectiveness and safety of CDK 4/6-inhibitors in men seem to be similar to women[19]. As a result, ASCO recommends that "*CDK 4/6 inhibitors can be used in men as they are used in women*"[20]. . Our study will address the role of tailoring the starting dose of CDK4/6 inhibitors according to the level of patients' fitness also in vulnerable/frail men.

10. Design of the clinical study

The study is a multicenter, open-label randomized-controlled trial with a pragmatic approach. The randomized-controlled design will enable the comparison of the two treatment strategies (lower initial dose vs. full initial dose) by minimizing potential confounders.

Randomization is performed by an authorized member of staff at the site, and can only occur after (a) eligibility has been confirmed, (b) written informed consent has been obtained, and (c) the baseline CGA assessment has been completed (see below).

Randomization is performed centrally using the electronic data capture system SMART-TRIAL. The following information will be required at randomization:

- Stratification factor details (see below)
- Confirmation of eligibility
- Confirmation of written informed consent and date

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[18] Hassett MJ, Somerfield MR, Baker ER, Cardoso F, Kansal KJ, Kwait DC, Plichta JK, Ricker C, Roshal A, Ruddy KJ, Safer JD, Van Poznak C, Yung RL, Giordano SH. Management of Male Breast Cancer: ASCO Guideline. J Clin Oncol. 2020;38:1849-1863
[19] Yildirim HC, et al. Clinical outcomes of cyclin-dependent kinase 4-6 (CDK 4-6) inhibitors in patients with male breast cancer: A multicenter study. Breast. 2022;66:85-88
[20] Hassett MJ, et al. Management of Male Breast Cancer: ASCO Guideline. J Clin Oncol. 2020;38:1849-1863

- Confirmation that the baseline CGA has been completed.

The randomization will be stratified by country, type of CDK 4/6-inhibitor used (palbociclib vs. ribociclib vs. abemaciclib), type of endocrine therapy (aromatase inhibitors vs. fulvestrant), and level of vulnerability (vulnerable vs. frail). These stratification factors will enable balancing the study results in terms of potential differences related to treatment traditions or socio-economic status (stratification by academic site), pharmacological properties (different CDK 4/6-inhibitors), the biology of disease in terms of endocrine resistance (different endocrine therapies), or health status (vulnerable or frail).

The study has a pragmatic design in several aspects:

- The inclusion criteria are broad, and the target cohort is expected to be more representative of patients seen in clinical practice compared to pivotal randomized trials on CDK 4/6-inhibitors.
- The study arms include treatment strategies that are standard-of-care according to all international treatment guidelines. The study will address the dose optimization of standard-of-care treatment in older breast cancer patients.
- The study incorporates CGA as a part of treatment decision making for this patient group which is recommended by international guidelines as an essential tool in older cancer patients.
- The follow-up strategy resembles the current follow-up strategy in clinical practice without additional blood tests or radiological examinations. Patients will be required to fill out self-questionnaires about QoL and CGA during the follow-up, but these are the only study-related actions beyond clinical practice.

11. Type of intervention

All eligible patients will be evaluated using a CGA before randomization that will be an essential part of decision-making process. CGA is self-reported and can be answered electronically or in paper. Study personnel will double-check with the patient the replies to ensure that the all replies are relevant and in accordance with what the patient wanted to reply. The CGA will be based on the geriatric assessment tool from Cancer and Aging Research Group[21] which is self-administered questions (Appendix A). The replies to questions will be assessed by the investigators for classification to fit, vulnerable or frail but the questionnaires are self-administered given the advantages of this approach compared to clinician-driven questionnaires in terms of consumed time and flexibility without compromising the validity of information retrieved .

Seven main domains will be evaluated through CGA: functional status; comorbidity; cognition; psychological; social functioning; social support; nutrition. Patients will be classified as fit, vulnerable, or frail based on the assessment of all seven domains (0 domains impaired for fit; 1-3 domains impaired for vulnerable; > 3 domains impaired for frail). For vulnerable and frail patients, suitable interventions (according to the impaired domains) will be offered according to each clinical site's clinical practice. The definition of impaired status in each domain as well as a description of suggested interventions that could be offered to the patients after CGA are summarized in Appendix Table B. The proposed interventions for any vulnerable/frail patient will be captured during the study period, but they are not dictated by the study protocol to enable a more pragmatic approach on the implementation of CGA-results in clinical practice.

After applying the CGA process, the treatment strategy in terms of CDK 4/6-inhibitor dose optimization will be as follows:

[21] Available at: https://www.mycarg.org/ (Accessed on 6th September 2022)

1. Fit cohort: full dose (Palbociclib 125 mg x 1 for 21 days – 7 days off; Ribociclib 600 mg x 1 for 21 days – 7 days off; Abemaciclib 150 mg x 2 daily) added to physician's choice endocrine therapy.
2. Vulnerable/frail cohort: randomization to full dose added to endocrine therapy (according to fit cohort) or -1 level dose reduction (Palbociclib 100 mg x 1 for 21 days – 7 days off; Ribociclib 400 mg x 1 for 21 days – 7 days off; Abemaciclib 100 mg x 2 daily) added to endocrine therapy.

A dose escalation from -1 level dose reduction to full dose is allowed at the discretion of investigator in the vulnerable/frail cohort randomized to lower initial dose. In cacse of dose reductions due to toxicity, no dose escalation is permitted. Changes between different CDK 4/6-inhibitors due to toxicity are allowed with the obligation to use the same dose level as the previous CDK 4/6-inhibitor. Any dose change will be collected to be used in the final analysis. A schematic overview of the IMPORTANT trial is shown in Figure 1 below.

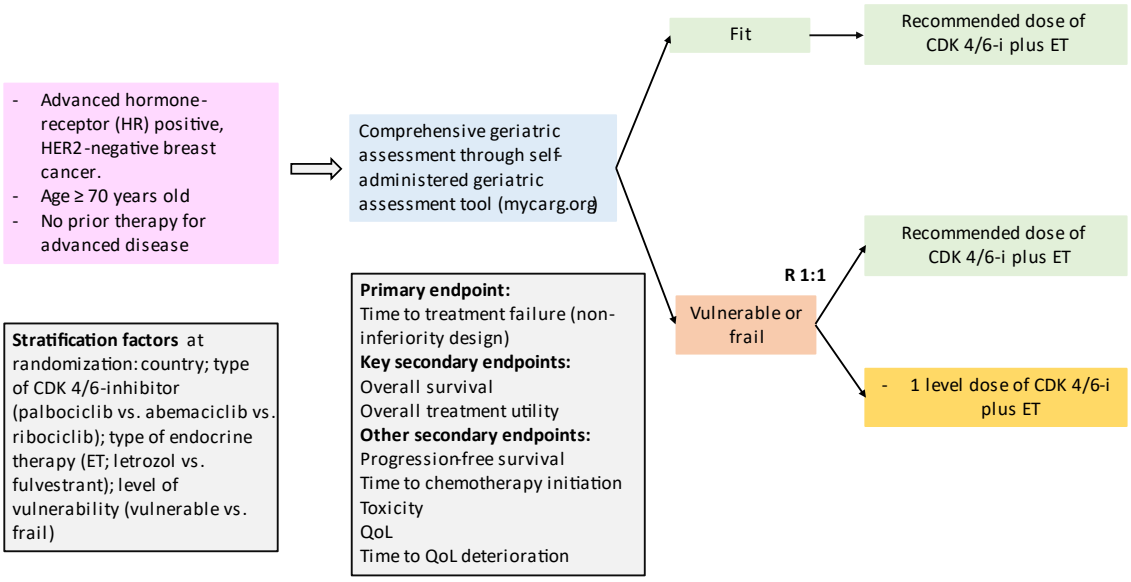


Figure 1: IMPORTANT trial overview

12. Description and timing of study procedures

To determine the generalizability of the trial results, sites are required to maintain a Screening Form logging all patients with older breast cancer patients (≥ 70 years old) with advanced HR-positive/HER2-negative breast cancer. This records the age, gender and whether the patient enters the IMPORTANT trial. For patients who were not eligible, the reason for ineligibility is recorded; for patients who were eligible but not included in the trial, the reason for the patient not entering the trial is recorded.

Eligible patients will be informed about the study by the treating physician. After informed consent, CGA will be performed at baseline. Patients categorized as fit according to the CGA will receive treatment with CDK 4/6-inhibitors in full dose plus endocrine therapy whereas patients categorized as vulnerable/frail will be randomized to either full dose or lower initial dose of CDK 4/6-inhibitors. The treatment with CDK 4/6-inhibitors should start within 14 days after randomization. Endocrine therapy is recommended to start at the same time as CDK 4/6-inhibitors initiation but a period of up to 28 days prior treatment with endocrine therapy is allowed (see inclusion criteria).

The treatment will continue until cancer progression, unacceptable toxicity, or participant / physician decision to stop. In case of treatment interruption due to toxicity, the participant will still be followed in accordance with treatment phase follow-up scheme until disease progression or up to 24 months. A re-initiation of CDK 4/6-inhibitors during this period will not be considered as a new treatment line whenever it occurs as long as there is no disease progression before re-initiation. After the 24-month

period, the patients without disease progression or unacceptable toxicity will continue the treatment with CDK 4/6-inhibitors and endocrine therapy according to local clinical practices but the patient follow-up within the IMPORTANT trial will be simplified to survival follow-up (as stated below).

The follow-up strategy in terms of treatment efficacy and toxicity resembles the current follow-up strategy in clinical practice without additional blood tests or radiological examinations. The follow-up will include toxicity evaluation before each treatment cycle as well as clinical and radiological evaluation of treatment efficacy every three months. Patient-reported outcomes will be captured through self-questionnaires during the study period.

The different study outcomes will be captured as follows:

- Follow-up for efficacy outcome: objective assessment at baseline and at every three (+/- 28 days) months until disease progression, participant / physician decision to stop, or death, whichever occurs first. The objective assessment includes clinical evaluation, evaluation through tumor markers, and/or imaging evaluation according to local practices and treating physician's decision. The overall objective assessment of treating physician will be considered. The date of clinical progression is defined as the date of the clinical assessment at which progression is identified.
- Follow-up for patient value/acceptability: at the first treatment evaluation, which will be performed three (+/- 28 days) months after treatment initiation.
- Follow-up for toxicity: assessment by physician or nurse according to clinical practice at baseline and before each treatment cycle during study period and up to 28 days after treatment discontinuation due to any cause. After 24 months with the patient still on treatment, the toxicity follow-up scheme will be decided by the treating physician as the patient will be followed according to survival follow-up within the trial (see below).
- Follow-up for QoL: self-assessment through QoL questionnaires at baseline and then every 3 months during the first 12 months and every 6 months thereafter until disease progression, participant / physician decision to stop, death, or up to 24 months from treatment initiation whichever occurs first.
- Age-related metrics: CGA will be performed at baseline and then every 6 months until disease progression, participant / physician decision to stop, death, or up to 24 months until treatment initiation whichever occurs first.
- Medical Consumption Questionnaire (for cost-effectiveness analysis): self-assessment every 3 months during the first 12 months and every 6 months thereafter until disease progression, participant / physician decision to stop, death, or up to 24 months from treatment initiation whichever occurs first.
- Survival follow-up: All patients will be followed for survival from the end of treatment phase and for up to 5 years from treatment initiation. Survival follow-up will be done every 12 - 16 weeks or earlier if a survival update is required to meet safety or regulatory needs. Survival information can be obtained by clinical visits or telephone calls until death, the patient is lost to follow up, or the patient withdraws consent for survival follow-up. During the survival follow-up period, the date of disease progression to CDK 4/6-inhibitors (for patients continuing this treatment after the trial treatment phase) and any subsequent treatment strategy will be captured.

A flowchart of study procedures is presented in Table 1 below.

Table 1. IMPORTANT trial study procedures.

Procedure	Screening phase		Treatment phase within trial (Follow up)								Post-treatment phase (Survival follow-up)
	Screening	Randomization									
Months since randomization			3	6	9	12	15	18	21	24	Every 3-4 months until death, lost to follow up, or the patient withdraws consent for survival follow-up, or up to 5 years for each patient (60 months)
Time window (days)	Up to -28 days	Up to -7 days	+/- 28	+/- 28	+/- 28	+/- 28	+/- 28	+/- 28	+/- 28	+/- 28	
Inclusion/exclusion criteria	X	X									
Informed consent	X										
Demography and medical history	X										
Physical examination*	X		As indicated								
Comprehensive Geriatric Assessment[i]	X			X		X		X		X	
Quality of Life assessment[i]	X		X	X	X	X		X		X	
Medical Consumption Questionnaire[i]			X	X	X	X		X		X	
Randomization		X									
Treatment with CDK 4/6-inhibitors and endocrine therapy [ii,iii]			◄	—	—	—	—	—	—	►	To be continued according to treating physician
Efficacy evaluation[i]	Baseline objective measurement		X	X	X	X	X	X	X	X	
Overall Treatment Utility			X								
Toxicity	Baseline measurement** (clinical, blood analyses)		Before each cycle and up to 28 days after the end of CDK 4/6-inhibitors								
Survival follow-up information											Date of disease progression to CDK 4/6-inhibitors (for patients continuing this treatment after the trial treatment phase); any subsequent treatment strategy; date and reason of death.

[i]until disease progression, participant / physician decision to stop, or death
[ii]the treatment with CDK 4/6-inhibitors should start within 14 days after randomization
[iii]endocrine therapy is recommended to start at the same time as CDK 4/6-inhibitors initiation but a period of up to 28 days prior treatment with endocrine therapy is allowed
*Physical examination includes assessment of performance status and clinical assessment of any clinically detected metastatic lesion
**Blood analyses include full blood count, liver function tests, and renal function. Any additional analyses are based on patient's health status and are on the discretion of the investigator. Blood analysed during treatment phase is only performed according to the clinical practice.

13. Recruitment process

Patients will be recruited directly from the clinical centers participating in the study or will be referred to them from nearby Hospitals.
Seven clinical sites and one research network with 5 Hospitals will contribute to the recruitment of the study population, from six different countries, Sweden, Finland, Norway, Italy, Spain, and Greece. Specifically, the following Academic Hospitals will participate in the study:

- Department of Oncology, Örebro University Hospital, Sweden. *
- Department of Oncology, Akademiska University Hospital, Uppsala, Sweden
- Department of Oncology, Helsinki University Hospital, Helsinki, Finland
- Department of Oncology, Akerhus University Hospital, Oslo, Norway
- 'Sandro Pitigliani' Department of Medical Oncology, Hospital of Prato, Prato, Italy
- Oncology Department, Azienda Ospedaliero Universitaria Careggi, Florence, Italy.
- Department of Medical Oncology, Hospital Clinic of Barcelona, Barcelona, Spain
- In addition, the Hellenic Cooperative Oncology Group (HeCOG), a research network, will participate with 6 Hospitals (Department of Medical Oncology, St Luke's Clinic in Thessaloniki, Medical Oncology Unit, S. Andrew Hospital in Patras, Fourth Oncology Department & Comprehensive Clinical Trials Center, Metropolitan Hospital in Athens, Second Department of Medical Oncology, Hygeia Hospital in Athens, Division of Oncology, Department of Medicine, University Hospital, University of Patras Medical School in Patras, 2nd Propaedeutic Clinic of Internal Medicine, Oncology Unit, “Attikon” University General Hospital, Athens).

The selection of the different clinical sites was performed based on the different geographical location and health care systems to increase the generalizability of the study results. All selected clinical sites have previously successfully collaborated in multicenter clinical trials.

Competitive recruitment between the clinical sites will be accepted. The accrual period is 36 months and within this period there might be institution-specific circumstances that can impact the accrual rates in corresponding clinical sites. Allowing competitive recruitment increases the possibility for a successful accrual at the end of the accrual period. The IMPORTANT trial steering committee will follow the accrual rates for each clinical site and discuss, along with the principal investigator from the corresponding clinical site, potential mitigation strategies as referral from other Hospitals nearby.

* In Sweden, a research network with non-academic Hospitals (General Hospital of Gävle, General Hospital of Sörmland, General Hospital of Västerås, General Hospital of Karlstad, General Hospital of Falun) within the same healthcare region (Mid-Sweden) as the participating academic Hospitals (Uppsala and Örebro) will also be able to include patients to the study according to the following procedure:
-Eligible patients will be identified through treating oncologist at the local Hospital
-Patients will be referred to one of the participating academic Hospitals (Uppsala or Örebro)
-Patients will be informed about the study by investigators and upon informed consent, they will be included and randomized.
-Information about randomization will be shared with the local oncologist
-The local oncologist will treat and follow up the patient in accordance to the clinical practice.
-The patient will receive questionnaires electronically through eCRF
-All study-related information will be collected from academic Hospitals through patient journal with help with the National Patient Overview (a national electronic platform that connects the electronic patient records from different Hospitals in Sweden).

14. Decentralized approach

The trial enables a hybrid decentralized approach where the initial patient visit should be in-person whereas the visits for efficacy and toxicity evaluation can be performed digitally according to local practices.

The study protocol suggests that the following patient visits can be performed digitally: efficacy evaluation during treatment phase after agreement between the treating physician and the patient; toxicity evaluation before each cycle.

All PROMs will primarily be collected electronically through the eCRF system supporting the decentralized approach of the trial. The eCRF system will collect all PROMs but the calculations and interpretations of scores from each questionnaire will be performed by the investigators. If patients do not have access to electronical means, questionnaires will be sent to the patients per post thus allowing data collection without the need for the patient to be at the Hospital in person.

The digital patient visits for efficacy and/or toxicity assessment will be performed using the digital solution that is locally approved.

15. Interim analysis and design adaptations

A toxicity-driven interim analysis will be performed when 100 patients will be included to the study to evaluate the toxicity rates and assess the need for adaptations in terms of initial dose adjustment strategies for vulnerable/frail patient cohort.

The Independent Data Monitoring Committee (IDMC), consisting of three independent clinical experts in oncology and geriatrics, is responsible for providing external oversight of patient safety in IMPORTANT trial independently of the Clinical Trial Committee. After reviewing the aggregated toxicity data, IDMC may recommend the trial continue without modifications, continue with specific modifications, or be stopped for safety concerns. There will be no prespecified rules for stopping the trial due to safety concerns. The recommendations of the IDMC will be communicated to the Clinical Trial Committee.

No efficacy interim analysis is planned considering the data from the prospective AMALEE trial where no statistically significant differences in terms of efficacy were observed in an unselected cohort of patients with breast cancer.

The IMPORTANT Clinical Trial Committee is also responsible for potential adaptations in study design based on potential new clinical evidence of significance. In fact, the use of pragmatic stratification factors as type of CDK 4/6-inhibitors or type of endocrine therapy used will facilitate the study design to be adapted if a new CDK 4/6-inhibitor becomes available (by adding the new CDK 4/6-inhibitors in the stratification without the need for re- sampling) or if CDK4/6-inhibitor proves to be more favourable with a specific endocrine therapy (a re-sampling will be performed using the stratification factor as guide and using only the more favourable combination in the eligible patients).

16. Definition of end of trial

The trial has two phases during the treatment and follow-up period. Regarding the treatment phase, where follow-up using questionnaires for CGA, QoL, and medical consumption use will be applied, the end is defined by the presence of disease progression, participant / physician decision to stop, death, or up to 24 months from treatment initiation. The post-treatment phase (survival follow-up) will continue after the treatment phase and will collect information until death, lost to follow up, consent withdrawal by the patient, or up to 5 years from treatment initiation for each patient. As a result, the end of trial in terms of collecting relevant questionnaires is up to 24 months for patients without disease progression, participant / physician decision to stop, or death and up to 60 months for survival follow-up for each patient.

17. Early study termination

The study can be terminated at any time for any reason by the sponsor. Should this be necessary, the patient should be seen as soon as possible for information about early termination. Given the fact that treatment with CDK 4/6-inhibitors is the current standard-of-care, patients will continue their treatment as planned. The treating physician is responsible to decide upon the dose level of CDK 4/6-inhibitors. The sponsor will be responsible for informing IRBs and/or ECs of the early termination of the trial.

18. Dose modification strategies

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. These changes must be recorded on the eCRF (electronic Case Report Form).

For aromatase inhibitors, the established clinical dose of letrozole (2.5 mg/day) or anastrozole (1 mg/day) or exemestane (25 mg/day) will be used in each arm and no dose modification is planned in this study. Similarly, the established clinical dose of 500 mg (2 x 250 mg intramuscularly) every 28 days with an additional dose at Cycle 1, Day 15 will be used for fulvestrant without dose modifications.

Management of severe or intolerable adverse reactions requires temporary dose reduction and/or interruption of palbociclib, ribociclib, or abemaciclib therapy. The strategies for dose reduction, interruption, or discontinuation of CDK 4/6-inhibitors that are included in each medication's SmPCs are recommended for the trial. Interruption of CDK 4/6-inhibitors without disease progression is allowed irrespective of the duration. The trial treatment will be discontinued if there is disease progression during the CDK 4/6-inhibitors interruption period. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

All dose modification strategies will be captured to the eCRF.

19. Drug supply and storage

All three CDK 4/6-inhibitors (palbociclib, ribociclib, abemaciclib), which are a part of treatment strategy in both experimental and standard arm, have been approved by the European Medicine Agency in the same treatment setting as the eligible patients[22]. Following the EMA approval, the CDK 4/6-inhibitors are reimbursed in Europe as the standard treatment approach in patients with advanced HR+/HER2-negative breast cancer. The reimbursement strategy for CDK 4/6-inhibitors in Europe ensures the availability of medication during the study execution.

20. Treatment compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit during treatment phase and information provided by the patient and/or caregiver. This information must be captured in the source document at each patient visit.

21. Concomitant medications

Appropriate documentation of all forms of supportive care and concomitant medications must be captured at baseline visit in the eCRF. With the exceptions listed in the sections below, therapies for cancer will not be permitted while patients are on study treatment.

- The recommendations from SmPC for each CDK 4/6-inhibitor regarding concomitant medications that should be avoided or used carefully during the treatment phase should be followed. **Surgery and/or radiotherapy for locoregionally recurrent disease or inoperable**

[22] Duranti S, Fabi A, Filetti M, et al. Breast Cancer Drug Approvals Issued by EMA: A Review of Clinical Trials. Cancers (Basel). 2021;13:5198

primary breast cancer: A patient with locoregionally recurrent breast cancer may receive surgery and/or radiotherapy if study treatment renders the tumor operable. However, such a patient should not receive CDK 4/6-inhibitor for the period beginning at least 7 days prior to surgery and continuing until at least 14 days after completion of surgery to allow for tissue healing and recovery. There is no restriction on the duration of this period without study treatment and, after this period ends, study treatment may resume. Considering treatment interruption before, during, and after radiotherapy, the same principles as described in the Palliative radiotherapy section are applied.

- **Palliative radiotherapy**: The treatment is allowed during the treatment phase if clinically indicated. If fractionated radiotherapy is planned, a treatment interruption of CDK 4/6-inhibitors for 5 days before radiotherapy, during radiotherapy, and 5 days after radiotherapy is recommended. If single-fraction radiotherapy is planned, there is no need for treatment interruption. No treatment interruption for endocrine therapy is necessary irrespectively the number of fractions planned.
- **Bisphosphonates and RANK-L targeted agents:** Patients with bone metastases present on imaging should be appropriately treated with bisphosphonates or RANK-L targeted agents (for example, denosumab), per respective approved labels. Initiation of treatment with bone-modifying agents can begin whenever during treatment or post-treatment study phase. Patients receiving bisphosphonates or RANK-L targeted agents can switch treatments (for example, replace a bisphosphonate with denosumab) while on study treatment as judged by their treating physicians. Use of bone-modifying agents and potential switching strategies should be reported on the eCRFs.
- **Growth factors**: Growth factors may be administered in accordance with national and international guidelines. Use of growth factors should be reported on the eCRFs.
- **Supportive care**: Patients should receive full supportive care as judged by their treating physician. If it is unclear whether a therapy should be regarded as supportive care, the investigator should consult the study sponsor. Use of any supportive care therapy should be reported on the eCRFs.

22. Efficacy measures

Primary outcome is **time to treatment failure** defined as the time from randomization to treatment discontinuation because of any reason including disease progression (see definition for PFS regarding this event), treatment toxicity, or death due to any cause.

Secondary outcomes include two key endpoints (OTU, OS) and other endpoints as PFS, time to chemotherapy initiation, toxicity assessment, QoL assessment, and time to QoL deterioration.

Overall treatment utility (OTU) is a composite endpoint that will be assessed at the first efficacy evaluation. OTU incorporates objective and participant-reported outcome measures of anticancer efficacy, tolerability and acceptability of treatment providing a simple "good, intermediate or poor" categorization of outcome. Acceptability will be assessed through a single question "*How worthwhile do you think your treatment has been?*" with the following response alternatives: very much – quite a bit – a little – not at all.

The following criteria will be applied to score OTU 3 months + / - 28 days after randomization:

- Is the treatment considered to have helped?
  - Scored as "YES" if there is no evidence of objective disease progression.
  - Scored as "NO" if there is evidence of objective disease progression.
- Is the treatment tolerable?
  - Scored as "YES" if both of the following apply: no SAR or SUSAR attributed to treatment; no deterioration of global QoL according to EORTC QLQ-C30 with > 10

points which is considered minimally important difference for patients with advanced breast cancer[23]
    - Scored as “NO” if any of the following applies: any SAR or SUSAR attributed to treatment; deterioration of global QoL according to EORTC QLQ-C30 with > 10 points.
- Is the treatment acceptable?
    - Scored as “YES” if the patient’s response to question "How worthwhile do you think your treatment has been?" is not "Not at all".
    - Scored as “NO” if the patient’s response to the question "How worthwhile do you think your treatment has been?" is "Not at all".

The final scoring of OTU is categorized as good (patient is alive and scores are “YES” for all three questions), intermediate (patient is alive and scores “NO” to one of three questions), or poor (patient scores NO to at least two of three questions, or patient has died).

Overall survival is defined as the time from randomization to death from any cause. Participants who are not known to have died will be censored at the last date they were known to be alive. Deaths will be reported by sites up to 5 years for each participant.

P**rogression-free survival** is defined as the time from randomization to first documented evidence of disease progression or death from any cause. The objective assessment for disease progression includes clinical evaluation, evaluation through tumor markers, and/or imaging evaluation according to local practices and treating physician’s decision. The overall objective assessment of treating physician will be considered. The date of clinical progression is defined as the date of the clinical assessment at which progression is identified. Participants who do not progress will be censored at the last date they were known to be alive and progression free.

Time to chemotherapy initiation is defined as the time from randomization until the initiation of chemotherapy at any treatment line after CDK 4/6-inhibitors.

Toxicity will be assessed based on adverse events, as graded by CTCAE v 5.0 before each cycle and up to 28 days after the end of CDK 4/6-inhibitors.

QoL will be assessed using three validated questionnaires, EORTC QLQ-C30 (Appendix C), ELD-14 (Appendix D), and EQ-5D-5L (Appendix E). The assessment will be performed every 3 months during the first 12 months and every 6 months thereafter until disease progression, participant / physician decision to stop, death, or up to 24 months from treatment initiation. Through questionnaires, **time to QoL deterioration,** defined as the time from randomization until any clinically meaningful worsening (using minimal important differences as cut-off) of any QoL aspect measured by the questionnaires will be assessed. CGA is also based on self—reporting (study personnel will double-check with the patient the replies to ensure that the all replies are relevant and in accordance with what the patient wanted to reply) and will be performed at baseline (before randomization) and every 6 months until disease progression, participant / physician decision to stop, death, or up to 24 months from treatment initiation.

All questionnaires will be administered in the patient’s local language at the beginning of the study visit prior to any interaction with the study investigator including any tests, treatments, or receipt of results from any tests to avoid biasing the patient’s perspective. The questionnaires will be sent electronically through eCRF but the possibility of paper CRF will be available. In case of paper CRF, patients should be given sufficient space and time to complete all study questionnaires and all administered questionnaires should be reviewed for completeness. If missing responses are noted, patients should be encouraged to complete any missing responses.

[23] Musoro JZ, Coens C, Fiteni F, et al. JNCI Cancer Spectrum (2019) 3(3): pkz037

23. Cost-effectiveness analysis

Resource use, length of life and quality of life data will be collected during the trial for the purpose of conducting an economic evaluation.

Effects: Length of life will be based on the mortality data from the trial. Health related QoL will be measured using the EuroQol EQ-5D-5L questionnaire. The EQ-5D-5L is a generic QoL instrument, consisting of five questions (each with five levels) and a visual analogue scale. Utility values will be calculated from the collected EQ-5D-5L data using relevant national tariffs to reflect international differences in health preferences, and to enable the estimation of quality-adjusted life years (QALYs) in both arms of the trial.

Healthcare costs: To estimate costs for medication, the prescription data (product, dosage, frequency) will be collected in the eCRF. Data on the utilization of concomitant medication will also be collected. Local medication list prices will be obtained with the help of consortium partners to complete the computation of medication costs. Hospital resource use will be collected in the eCRF. This includes the number of outpatient visits, admission and discharge dates of hospitalization, costs for disease monitoring (e.g., blood count, liver function, electrocardiogram), laboratory and imaging costs (e.g., CT, bone scan), and any treatment initiated to address adverse events (e.g., neutropenia). Data on non-hospital medical resource use will be reported by patients using a shorted version of the iMTA Medical Consumption Questionnaire (iMCQ; Appendix F). Healthcare resource use will be valued using reference prices where available, or prices in previously published literature when reference prices are not available.

Societal costs: To allow for an economic evaluation taking a societal perspective, relevant societal costs will be collected. Informal care utilization will be measured using a limited number of questions on volume and type of informal care used. The valuation of informal care will be done using local tariffs. Given the age of the target population of the trial, it is expected that the majority of patients are not performing paid labor. Therefore, productivity costs will not be measured.

Measurements: All questionnaires collecting patient reported data for the economic evaluation (i.e., the EQ-5D-5L, and the abbreviated iMCQ for non-hospital healthcare costs including questions on informal care use) will be completed every 3 months during the first 12 months and every 6 months thereafter until disease progression, participant / physician decision to stop, death, or up to 24 months whichever occurs first. In addition, the EQ-5D-5L will be completed at baseline.

Analysis: A complete description of the analysis of the data collected for the cost-effectiveness analysis will be provided in the statistical analysis plan. By default, a trial based economic evaluation with a time horizon equal to the trial duration will be conducted. However, if not all relevant differences in costs and health outcomes between treatment arms are observed during the trial period, a model-based analysis may be considered. Mean total and incremental costs and mean and incremental health effects per patient will be calculated. The outcomes of the study will be represented in an incremental cost effectiveness ratio (ICER). Different scenario analyses will be conducted to address structural uncertainty. Uncertainty in the results will be explored with appropriate methods, such as deterministic and probabilistic sensitivity analysis.

24. Safety monitoring and reporting

Definition of Adverse Events: An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events eCRF. Conditions that were already present at the time of informed consent should be recorded on the

Medical History page of the patient's CRF. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each contact for efficacy or toxicity evaluation during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (start and end dates)
3. Its relationship to the study treatment
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)
7. Whether it is serious, where a serious adverse event (SAE) is defined later.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event eCRF. Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Laboratory AEs: Laboratory abnormalities that constitute an AE (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment), should be recorded on the Adverse Events eCRF. Whenever possible, a diagnosis, rather than a symptom, should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal, or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE version 5 does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion.

Serious AEs:
Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening.
- Results in persistent or significant disability/incapacity.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Jeopardized the participant or required intervention to prevent one of the above.
- Is otherwise considered medically significant by the investigator.

Medical and scientific judgement must be exercised in deciding whether an event is serious in other situations. These characteristics / consequences must be considered at the time of the event and do not refer to an event which hypothetically may have caused one of the above.

Note that hospitalizations for the following reasons should not be reported as serious adverse events:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (i.e. to perform study-related assessments).
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent.
- Social reasons and respite care in the absence of any deterioration in the patient's general condition.

Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event.

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 28 days after the patient has stopped study treatment must be reported to the sponsor via eCRF within 24 hours of learning of its occurrence.

Any SAEs experienced after this 28 day-period should only be reported to the sponsor if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the eCRF; all applicable sections of the eCRF must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the eCRF SAE page and submit/send electronically the completed e-CRF page to Sponsor for assessmentwithin 24 hours . A copy of the eCRF SAE page must be kept at the study site as a SAE completed form.

Follow-up information is submitted/sent electronically in the same way as the original SAE Report was submitted/sent, updating the e-CRF, stating/chosing by the e-CRF options, that this is a follow-up to the previously reported SAE or the final recorded SAE report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the SmPC for each medication where a causal relation is suspected, the sponsor is responsible to report to Health Authorities as well as all the investigators.

Suspected Unexpected Serious Adverse Reactions (SUSARs), namely a serious adverse drug reaction that is deemed to have been related to one of the trial investigational drugs but the nature or severity of which, is not consistent with the known toxicity profile, will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries. Sponsor is also responsible for reporting SUSARs to the Eudravigilance database.

The active monitoring period for toxicity occurs from the time of randomization until 28 days after CDK 4/6-inhibitor is permanently ceased. During this period, all SAEs and SUSARs occurring must be recorded and faxed to the Department of Oncology, Örebro University Hospital within 24 hours of the research staff becoming aware of the event. For patients entering the survival follow-up phase and

continue with CDK 4/6-inhibitors (namely 24 months after treatment initiation without disease progression), only SAEs or SUSARs where the investigator suspects a causal relationship to the trial treatment should be reported to the sponsor.

25. Statistical considerations

General considerations: A full statistical analysis plan will be written before any analyses are undertaken. Any changes to the finalized analysis plan, and reasons for changes, will be documented. It is planned that the data from all centers participating in the trial will be combined, so that an adequate number of patients are available for analysis. Statistical analysis of this study will be the responsibility of study sponsor.

Efficacy analyses will be based on the intention-to-treat (ITT) analysis set. This population is defined as all patients randomized to study treatment. Patients in the fit cohort will be analyzed separately as a control group. Safety analyses will be based on the treated population (TP), defined as all patients receiving at least 1 dose of CDK 4/6-inhibitor.

Sensitivity analyses may be performed for relevant endpoints, for example to consider differing assumptions about missing data if there is a significant number of missing data and will be detailed in the full statistical analysis plan.

For time-to-event variables, Kaplan-Meier method will be used to visualize curved based on treatment groups whereas median estimates with corresponding 95% Confidence Intervals (CI) will be presented by treatment groups. For time to chemotherapy initiation and time to QoL deterioration, death due to any cause will be considered as competing event and the cumulative incidence function will be used for visualization. Cox's Proportional Hazards model, if appropriate, adjusting for the covariates of interest, will also be used to compare time-to-event variables between the treatment groups. Treatment and covariate estimates, hazards ratios, and 95% CIs will be presented for all variables incorporated in the models.

For OTU, treatment groups will be compared using ordered logistic regression to adjust for covariates of interest. Treatment and covariate estimates, odds ratios, and 95% CIs will be presented for all variables incorporated in the model.

For toxicity, the maximum grade per participant for each toxicity and rates of toxicities overall and per cycle will be summarized descriptively for each treatment group.

QoL aspects will be summarized for each treatment arm at each post-randomization time-point, using adjusted for baseline mean scores and 95% CIs. These summaries and differences between treatment arms will be obtained and compared using a multi-level repeated measures model accounting for data at all post-baseline time points. Data will also be summarized descriptively using bar charts, box plots and summary tables.

Pre-defined subgroup analyses for each study endpoint will be performed based on stratification factors whereas exploratory subgroup analyses might be performed for variables of potential interest.

Sample size calculation

Vulnerable/frail cohort: a non-inferiority study design is applied. We assume TTF of 18 months for the experimental arm and 16 months for the standard arm (small benefit of the experimental arm due to the anticipated lower rate of discontinuation due to toxicity). Considering a 1-sided 5% significance and 80% power, a non-inferiority hazard ratio margin of 1.19 (translating into an absolute margin of 2.5 months in TTF) and a dropout rate of 10%, 346 patients should be randomized to prove non-inferiority of treatment strategy with lower initial dose compared to full dose in terms of TTF.

Fit cohort: no formal statistical considerations are applied but the cohort will be analyzed with descriptive statistics.

Considering a distribution of 30 % fit and 70%[24] vulnerable/frail patients, the study would need to screen 495 patients.

Fit cohort: **149** patients to be treated and followed.

Vulnerable/frail cohort: **346** patients to be randomized.

26. Data collection and management

Patient-related data from medical records will be collected through the eCRF system SMART-TRIAL. The use of eCRF system offers improved data quality, online discrepancy management, multicenter management, faster database lock etc. Main objectives behind eCRF development are preserving and maintaining quality and integrity of data.

The data of interest has been defined by the IMPORTANT trial steering committee in accordance with the study protocol compliance, regulatory requirements enabling Sponsor to test the hypothesis or answer the trial related questions. The collected data will be pseudonymized with the key file to be kept secured to each clinical site according to each site's Standard Operational Procedures (SOPs).

The following data will be collected:

- Baseline
  - Demographics (age, sex, socioeconomic status)
  - Prior medical history (co-morbidities, concomitant medications)
  - Tumor-related characteristics
    - Anatomical and biological characteristics of primary and metastatic disease
    - Number and site of metastatic lesions
  - Treatment-related characteristics
    - Prior surgical procedures for breast cancer
    - Type, duration (including dates for initiation and end, reason for discontinuation) of prior oncological therapy
  - Physical examination (weight, height, WHO performance status, tumor status if feasible)
  - Patient-reported outcomes (CGA, QoL)
  - Toxicity
- Treatment phase
  - Tumor assessment
  - Dose modifications
  - Patient-reported outcomes (CGA, QoL)
  - Toxicity
  - Patient-reported outcomes
  - Supportive treatment of interest
  - Survival status
- Post-treatment phase
  - Subsequent treatment
  - Survival status

Patient-reported outcomes will be collected through the same eCRF system.

[24] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3196774/

Moreover, the Consortium shall adhere to a detailed data management plan which shall be updated at least once during the project.

27. Monitoring

Monitoring is defined as the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, applicable SOPs and the Principles of GCP.

The sponsor in collaboration with the CRO will develop a systematic, prioritized, risk-based approach to monitoring of this clinical trial.
The risks to clinical trial processes & clinical trial data will be evaluated at both the system level (e.g., SOPs, computerized systems, personnel) and clinical trial level (e.g., trial design, data collection, informed consent process) against existing risk controls by considering:

(a) The likelihood of errors occurring.
(b) The extent to which such errors would be detectable.
(c) The impact of such errors on human subject protection and reliability of trial results.

The sponsor will document the rationale for the resulting monitoring strategy in applicable manuals (e.g., in the Monitoring Manual)".

28. Regulatory and ethical considerations

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Guideline for GCP, relevant effective SOPs, the Clinical Trial Regulation EU No536/2014, the General Data Protection Regulation (GDPR), the principles of Good Clinical Practice and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP, or applicable regulations will be treated as "protocol deviation".

The investigator will inform the sponsor/CRO immediately of any urgent safety measures taken to protect the trial participants against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

This trial will be initiated only after

A) all required documentation has been reviewed and approved by the respective IRB/IEC and CA according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

B) The Clinical Trial Agreements are fully executed in each participating site.

C) All relevant documentation has been reviewed by the sponsor/CRO and found in accordance with ICH-GCP standards, Regulatory requirements , SOP pre-requisite.s

The investigator will be responsible for the following:

- Providing annual & end of study written summaries of the status of the study to the IRB/IEC in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by each IRB/IEC procedures.
- Notifying the sponsor/CRO immediately (within 24 hours of learning of its occurrence) for any GCP Serious Breach (or suspected GCP Serious Breach) so the sponsor can comply with the requirements for reporting to Authorities. Any breach of the following aspects is serious and should be notified:

a) The Regulation (EU) No 536/2014.

b) The clinical trial protocol version applicable at the time of the breach which is likely to affect to a significant degree:

• the safety of a trial participant and/or

• the rights of a trial participant and/or

• the reliability and robustness of the data generated in the clinical trial.

29. Informed consent process

Prior to participation in the trial, written informed consent must be obtained from each participant) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent form must be retained by the investigator as part of the trial records. A signed copy of the informed consent must be given to each participant. The participant must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the participant's own free will with the informed consent form after confirming that the participant understands the contents. The investigator or delegate must sign (or place a seal on) and date the informed consent form. Re-consenting may become necessary when new relevant information becomes available that could influence the decision for participating in the study and should be conducted according to the sponsor's/CRO's instructions and timelines. The consent and re-consenting process should be properly documented in the source documentation.

30. Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial participant.

Source data as well as reported data should follow the "ALCOA+ principles" and be Attributable, Legible, Contemporaneous, Original, Accurate, and also be Complete, Consistent, Enduring, and Available. Changes to the data should be traceable (audit trail).

Data reported on the CRF must be consistent with the source data or the discrepancies must be clearly documented and justifiable.

The medical records of the participant-available at the site- may not be sufficient to confirm eligibility for the trial and the investigator may need to request earlier medical history records and evidence of any diagnostic tests and therapeutic regiments.

For the CRF, data must be derived from source documents, for example:

- Participant identification: gender, year of birth (in accordance with local laws and regulations)
- Medical history, Medication history, Concomitant therapy
- AEs and SAEs (onset date [mandatory] and end date [if available])
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation.

31. Audit and inspection

The investigator/institution will allow site trial-related monitoring, audits, IRB/IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must always be available

for review by the monitor, auditor and regulatory inspector (e.g. EMA, FDA). The accuracy of the data will be verified by direct comparison with the source documents described above. The sponsor/CROwill also monitor compliance with the protocol and GCP. The investigator should notify the sponsor/CRO immediately of any such inspection. Audits and inspections may occur at any time during or after completion of the study.

32. Storage period of records

The Trial Master File, which includes records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion in accordance with Article 58 of the Clinical Trial Regulation, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor/CRO. No records may be transferred to another location or party without written notification to the sponsor/CRO. However, the participants' medical records at the trial site shall be archived in accordance with national law with which the sponsor is responsible to familiarise itself with.

33. Data protection

Data protection and data security measures are implemented for the collection, storage, and processing of participant data in accordance with EU regulation 2016/679 GDPR.

To ensure confidentiality of records and personal data, only pseudonymized data will be transferred to the sponsor by using a participant identification number instead of the participant's name. The code is only available at the site and must not be forwarded to the sponsor/CRO. In case participants' records are forwarded, e.g. for SAE processing, personal data that can identify the participant will be redacted by the site prior to forwarding. Access to the participant files and clinical data is strictly limited; personalized treatment data may be given to the participant's personal physician or to other appropriate medical personnel responsible for the participant's welfare. Data generated at the site because of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB/IEC, and the regulatory authorities.

A potential data security breach will be assessed regarding the implications for the rights and privacy of the affected person(s). Immediate actions as well as corrective and preventive actions will be implemented. Respective regulatory authorities, IRBs/IECs, and participants will be notified as appropriate under Articles 33 and 34 of the GDPR.

Moreover, all information required to be given to data subjects in accordance with Article 13 of the GDPR shall be provided through the Informed Consent Form (ICF).

34. Risk-benefit evaluation

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial participant protection and reliability of the results as well as identification and assessment of associated risks. A Quality and Risk Management Plan or alternative plan, in line with the guidance provided by ICH Q9 and ICH-GCP E6, documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.

In terms of risk-benefit evaluation of trial-specific strategies, patient information includes a detailed description on potential pros and cons of study inclusion. Specifically, the implementation of CGA as a part of the decision-making process can help clinicians to get a better understanding of patients' health status. In addition, study participation will help the investigators to get more insight into the use of CDK

4/6-inhibitors in breast cancer patients who are older than 70 years old. Regarding potential cons, a slightly lower effectiveness of lower starting dose compared to full dose cannot be entirely excluded, although a lower starting dose of CDK 4/6-inhibitors has so far not been shown to be less effective compared to full dose in patients older than 70 years old. To mitigate this risk, suitable follow-up strategies will be performed to investigate how effective the treatment is and inform the investigators on how to continue with the treatment. Moreover, the possibility of dose escalation to full dose for patients randomized to lower initial dose is allowed at the discretion of investigator. An additional con when participating in the study is the extra time needed for filling out the questionnaires related to the trial. No additional diagnostic or monitoring strategies will be applied to the trial participants.

An age-specific risk for older patients is the risk of polypharmacy. Trial participants will receive additional medications (CDK 4/6-inhibitors and endocrine therapy) but this treatment strategy will be the same for the patients even outside of the trial considering that eligible patients are those considered from treating physician as suitable for treatment with CDK 4/6-inhibitors. As a result, no additional medications will be given within the trial.

35. Development of the clinical study protocol

35.1 Scientific advice from regulatory and health technology assessment bodies

The consortium for the IMPORTANT trial includes a partner with expertise on regulatory and health technology assessment (HTA), to ensure access to regulatory intelligence in all study phases. Specifically, the Institute for Medical Technology Assessment (iMTA) has been a core part of the consortium during the study design to ensure that all relevant outcomes for a cost-effectiveness analysis will be captured. Besides, iMTA will be responsible for the HTA that will be performed based on the study results as a part of the study outcomes.

35.2 Clinical efficacy, safety, and methodological guidelines

In terms of efficacy outcomes, the study utilized the DATECAN initiative to define the time-to-event endpoints[25]. Besides, the EORTC-SIOG proposal for endpoints in geriatric oncology research was considered to select relevant composite endpoints as the TTF and the OTU[14].

In terms of toxicity, the reporting requirements according to the Clinical Trials Directive from EU will be applied throughout the study process[26].

The study will be conducted and reported in accordance with the CONSORT statement[27].

35.3 Involvement of citizens / patients, carers in drawing up the clinical study protocol

A Patient / caregiver advisory panel will be constructed with the help of Europa Donna and the Swedish Breast Cancer Patient Association during the first months of the project. The Advisory panel will actively participate in the discussions of the IMPORTANT steering committee to finalize the study protocol before study initiation. The aspects of special interest for the Advisory panel are the relevance of study endpoints from a patient and caregiver perspective, the informed consent content and process, and the convenience of the study procedure for the patients and the caregivers.

Apart from the advisory panel, all clinical partners will engage targeted groups of citizens and relevant civil societies when study results are available to collect additional input during project setup. This

[25] Gourgou-Bourgade S, Cameron D, Poortmans P, et al. Guidelines for time-to-event end point definitions in breast cancer trials: results of the DATECAN initiative (Definition for the Assessment of Time-to-event Endpoints in CANcer trials)†. Ann Oncol. 2015;26:873-879

[26] Available at: https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A02001L0020-20090807 (Accessed: 6th September 2022)

[27] Moher D, Schulz KF, Altman D; CONSORT Group (Consolidated Standards of Reporting Trials). The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA. 2001;285:1987-91

continuous feedback will help the consortium to gain a broader perspective on the potential impact of IMPORTANT trial.

36. Study Organizational Structure

The scientific and operational governance of the clinical study will be ensured through the collaboration of several governing bodies with distinct roles including the Clinical Coordinator, the IMPORTANT trial steering committee, the Project Coordination committee, the Technical Committee, the Privacy & Ethics Committee, the Advisory board, and the Independent Data Monitoring Committee. A description of their roles is presented in Table 2 below.

Table 2. Description of IMPORTANT committees

Committee	Members	Roles
IMPORTANT trial steering committee	Chair: Clinical lead Members: • Clinical partners; ORB, RUL, AHUS, LHUTC, UNIFI, HUS, HCB / FCRB, HECOG • Technical partners; UPAT, CARE, SLC • Partners with legal, ethics or other expertise of interest; IMTA, CEF, EUNL, BRO (patient representatives), UNED, FHNW	• Agreement of final protocol • Monitor and supervise the progress of the study towards its interim and overall objectives • Review at regular intervals relevant information from other sources that might impact study design • Decide about necessary changes to the protocol • Consider the recommendations of the Independent Data Monitoring Committee • Follow-up of recruitment and dropouts; suggestion for mitigating strategies when needed
Project Coordination committee	Chair: Project Coordinator Members: • Clinical lead • One representative from clinical partners • One representative from technical partners (technical coordinator) • PHAZE as CRO • EUNL	• Resources management and distribution • Project monitoring • Ensure proper communication with EC • Administrative and support activities • Setting up an appropriate communication and collaborative environment for the consortium members (e.g., mailing lists, project repository, internal wikis, and reporting tools)
Technical committee	Chair: SLC Members:	• Ensuring the quality and soundness of the scientific

	• One representative from each technical partner; UPAT, CARE • Project coordinator • One representative from clinical partners • PHAZE as CRO • Partners with ethics expertise or other expertise of interest; EUNL	and technical work performed in the project • Driving the technical activity • Coordinating technical discussion among partners • Ensuring consistency and complementarity of technical development and settling technical conflicts • Supporting the project coordinator in reporting within all technical issues providing continuous identification and mitigation of technical risks • Compliance to the Data Management Plan
Privacy & Ethics committee	Chair: EUNL Members: • Clinical lead • Clinical partners; ORB, RUL, AHUS, LHUTC, UNIFI, HUS, HCB / FCRB, HECOG • Technical partners; UPAT, CARE, SLC • Partners with ethics expertise or other expertise of interest; EUNL, BRO, PHAZE	• Monitor the whole project activities for compliance with the security, privacy and ethical requirements • Ensuring that all legal and privacy guidelines are aligned with relevant regulations and also pushed and followed in implementation level • Development and implementation of Data Management Plan (DMP)
Advisory Board	Chair: clinical lead Members: • Patient and caregiver representatives; BRO, Europa Donna (external) • Clinical partners; ORB, RUL, AHUS, LHUTC, UNIFI, HUS, HCB / FCRB, HECOG • Technical partner with experience in patient-reported experience; CARE	• Provide feedback during study design • Provide insight on study-related information and educational material • Provide insight on final study results, potential implications and dissemination channels
Independent Data Monitoring Committee	Members: • Three external experts in geriatric oncology and/or breast cancer	• Assess the results of the interim analysis • Assess the safety data • Assess the risk-benefit balance of the study • Make recommendation to the Trial Steering Committee

36.1 Study sponsor

Since the trial is an investigator-initiated clinical trial, the clinical coordinator is the sponsor. Assoc Prof Antonis Valachis from the Department of Oncology at Örebro University Hospital will serve as sponsor and Clinical Coordinator whereas his department is the Coordinating Center. The Department of Oncology at Örebro University Hospital is an Academic department with a broad spectrum of clinical activities including medical oncology (chemotherapy, targeted therapies, immunotherapy) and radiotherapy (both external and brachytherapy) for all types of malignant diseases as well as several research programs. The Department offers high-quality cancer care for cancer patients of any cancer type and stage, and it is a leading partner of the Mid-Sweden network for breast cancer research and the Swedish Breast Cancer Group.

36.2 Composition, role and functioning of the planned boards

Clinical Coordinator (CC): the CC will be responsible for the clinical aspects of the project, and the coordination of the clinical partners and the IMPORTANT trial. The CC of the project will be Assoc Prof Antonis Valachis from the Department of Oncology, Örebro University Hospital, Sweden.
IMPORTANT trial steering committee: will be consisted of the CC, the principal investigators of the clinical sites, representatives from the technical partners and from partners with legal or ethics expertise. The trial steering committee will oversee the execution and progress of the study according to the study protocol and in accordance to Good Clinical Practice.

Project Coordination Committee (PCC): PCC is an intermediary between European Commission (EC) and the consortium, is in charge of general public project representation, and is responsible for project controlling including: delivery of the project results, reporting, handling the payments and accounts, and correct application of HORIZON program rules. The PCCM will oversee the overall coordination of the project activities. IMPORTANT's PCC will be coordinated by the administrative Office of the Region Örebro county responsible for clinical research.

Project Technical Committee (PTC): PTC is responsible for making and overseeing all technical decisions in the project. It is responsible for putting into place mechanisms for the WPs to ensure the quality of work, produced deliverables, and any technical papers produced at the WP level. The PTC will ensure development and supply of all necessary technical solutions that will be used in the IMPORTANT trial to clinical sites.

Privacy & Ethics Committee (PEC): PEC is responsible for all privacy regulatory obligations and contractual obligations related to ethical issues deriving from the usage of clinical data in the project.

Advisory Board (AB): the AB will consist of patient and caregiver representatives from the Swedish Breast Cancer patient association and Europa Donna as well as healthcare professionals dedicated to cancer care from the IMPORTANT clinical sites. AB's role is to provide feedback during study design, provide insight on study-related information, educational material and on final study results.

Independent Data Monitoring Committee (IDMB): IDMB will consist of three experts in the field of breast cancer and geriatric oncology. Its role will be to review accumulating trial data by treatment group in order toto monitor patient safety and efficacy, ensure the validity and integrity of the trial, and make a benefit-risk assessment. The IDMB will also assess the safety data from the toxicity-driven interim analysis that will be performed in the vulnerable/frail patient cohort.

37. Publication policy

The success of the trial depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributorship.

Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based on substantial contribution according to the International Committee of Medical Journal Editors (ICMJE) Guidelines:

- conception and design, or acquisition of data, or analysis and interpretation of data,
- drafting the article or revising it critically for important intellectual content,
- and final approval of the version to be published.

Considering this, all primary investigators at each study site will be named as authors in any publication. In addition, sub-investigators will also be listed as co-authors if they fulfil the above criteria. To keep the transparency of the process, authorship and contributorship will be discussed and agreed upon IMPORTANT Trial Steering Committee.

To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the analysis of the primary endpoint, either for trial publication or oral presentation purposes, without the permission of the Trial Steering Committee. In addition, individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the trial until the first publication of the analysis of the primary endpoint.

38. History of Important Changes

Version	Date	Section of study protocol	Amendment or update	Reason
2	06 November 2023	Inclusion Criteria	Added: *Male patients should use adequate contraceptive methods (e.g., double-barrier contraception) during therapy and for at least 14 weeks after completing therapy.*	Asked from Authorities
2	06 November 2023	Inclusion Criteria	Added: *including ECG for assessment of QT interval before treatment with ribociclib. Specifically, the following thresholds should be used to define adequate organ function: absolute neutrophil counts of ≥ 1,000/mm3, platelet counts of ≥ 100,000/mm3; ALT and/or AST ≤ 3 x upper limit normal (ULN), total bilirubin ≤ 2 x ULN; eGFR ≥ 30 mL/min.*	Asked from Authorities
2	06 November 2023	Exclusion Criteria	Added: *Specifically, any hypersensitivity to the active substance or to any of the excipients or to peanut, soya (for ribociclib) or use of preparations containing St. John's Wort (for palbociclib) are contraindications.*	Asked from Authorities
2	06 November 2023	7. Study Rationale	Added: *In a randomized trial of full vs. lower dose of ribociclib in a study cohort of patients with median age 58 years, no statistically significant differences in terms of responses or progression-free survival were observed whereas lower risk for toxicity was evident in lower dose .*	Asked from Authorities

Version	Date	Section of study protocol	Amendment or update	Reason
2	06 November 2023	7.Study Rationale	Added: *In a prospective randomized trial including both pre- and postmenopausal women with breast cancer, lower initial dose of CDK 4/6-inhibitor ribociclib did not result in statistically significant worse response rates ……. would be benefitted from a lower initial dose without compromising the expected efficacy.*	Asked from Authorities
2	06 November 2023	Type of Intervention	Added: *The replies to questions will be assessed by the investigators for classification to fit, vulnerable or frail but the questionnaires are self-administered given the advantages of this approach compared to clinician-driven questionnaires in terms of consumed time and flexibility without compromising the validity of information retrieved .*	Asked from Authorities
2	06 November 2023	10. Type of Intervention	Added: *A dose escalation from -1 level dose reduction to full dose is allowed at the discretion of investigator in the vulnerable/frail cohort randomized to lower initial dose. In cacse of dose reductions due to toxicity, no dose escalation is permitted.*	Asked from Authorities
2	06 November 2023	14. Decentralized approach	Added: *The eCRF system will collect all PROMs but the calculations and interpretations of scores from each questionnaire will be performed by the investigators.*	Asked from Authorities
2	06 November 2023	15. Interim analysis	Added: *considering the data from the prospective AMALEE trial where no statistically significant differences in terms of efficacy were observed in an unselected cohort of patients with breast cancer.*	Asked from Authorities
2	06 November 2023	34. Risk-benefit evaluation	In terms of risk-benefit evaluation of trial-specific strategies, patient information includes a detailed description on potential pros and cons of study inclusion. …… As a result, no additional medications will be given within the trial.	Asked from Authorities
3	28 November 2023	2. Clinical co-investigators	added: *Prof Amanda Psyrri*	Study design
3	28 November 2023	11. Type of intervention	Added: *CGA is self-reported and can be answered electronically or in paper. Study personnel will double-check with the patient the replies to ensure that the all replies are relevant and in accordance with what the patient wanted to reply.*	Asked from Authorities

Version	Date	Section of study protocol	Amendment or update	Reason
3	28 November 2023	22. Efficacy measures	Added: *(study personnel will double-check with the patient the replies to ensure that the all replies are relevant and in accordance with what the patient wanted to reply)*	Asked from Authorities
3	28 November 2023	29. Informed consent process	Deletion of legal rep and impartial witness	Asked from Authorities
4	18 nov 2024	Inclusion Criteria	4.28 days changed to *56 days from the CDK 4/6-inhibitor initiation is allowed* Added: *as long as there is no disease progression during this time period.*	Some patients that were planned for palliative radiotherapy before initiation of CDK 4/6-inhibitors were excluded due to this restriction of 28 days. From a biological point of view, there is no need to exclude these patients as they are still receiving their 1st line therapy as long as there is no disease progression.
4	18 nov 2024	Inclusion criteria	Deleted: 6.Either measurable disease or non-measurable bone only disease, but evaluable according to RECIST criteria	Considering the pragmatic study design, no RECIST assessment is performed. The assessment can be based to clinical evaluation, laboratory status, and/or radiological assessment as per physician's choice. This is specified in the protocol.

Version	Date	Section of study protocol	Amendment or update	Reason
4	18 nov 2024	Exclusion criteria	Added: *2. Patients with cognitive impairment (as assessed by treating physician) that preclude the ability to fill out the self-reported CGA.*	Patients with cognitive impairment will not be able to adequately reply to questionnaires before randomization. Considering the importance of replies on randomization process, we decided to include an exclusion criterion to clarify this issue.
4	18 nov 2024	Exclusion criteria	5. deleted: *with no therapy*	A complete remission with or without therapy for at least 3 years is enough to include a patient with prior malignancy.
4	18 nov 2024	21. Concomitant medication	Deleted from treatment phase	There is no need according to study's endpoint to collect concomitant medication during treatment phase, only at baseline
4	18 nov 2024	Flowchart	update	Blood analysis is not obligatory, but only performed according to the clinical practice.

Version	Date	Section of study protocol	Amendment or update	Reason
4	18 nov 2024	Appendix G	Deleted	SAE reporting process changed
4	18 nov 2024	+/- one month	Replaced by +- 28 days	In order to be consistent with the flowchart
4	18 nov 2024	24. Safety monitoring and reporting	Information about all SAEs is collected and record[illegible] ~~Report Form (Appendix G)~~eCRF; all applicable sections of the fo[illegible] provide a clinically thorough report. The investigator must asse[illegible] E to each specific study treatment (if there is more than one stu[illegible] age ~~SAE Report Form in English,~~ and submit/send electronically the completed e-CRF page to Sponsor for ~~assessment, signed form by fax~~ within 24 hours ~~to the Department of Oncology, Örebro University Hospital~~. ~~A copy of the The original copy of the~~eCRF SAE ~~Report Form and the fax confirmation sheet~~page must be kept ~~with the case report form documentation~~ at the study site as a SAE completed form. Follow-up information is submitted/sent electronically ~~to the same contact(s) to whom~~in the same way as the original SAE Report ~~Form~~ was submitted/sent, updating the e-CRF, ~~using a new SAE Report Form~~ stating/chosing by the e-CRF options, that this is a follow-up to the previously reported SAE or the final recorded SAE report~~and giving the date of the original report~~. Each re-occurrence, Penelope Anagnostopoulou, 14/11/2024 13:56:00 added: electronically	In order to reflect SAE reporting new process.
4	18 nov 2024	Sample Size	36-month accrual period instead of 30	Study extension
4	18 nov 2024	13. Recruitment process	36-month accrual period instead of 30	Study extension
4	18nov2024	13. Recruitment process	Addition: * In Sweden, a research network with non-academic Hospitals (General Hospital of Gävle, General Hospital of Sörmland, General Hospital of Västerås, General Hospital of Karlstad, General Hospital of Falun) within the same healthcare region (Mid-Sweden) as the participating academic Hospitals (Uppsala and Örebro) will also be able to include patients to the study according to the following procedure: -Eligible patients will be identified through treating oncologist at the local Hospital -Patients will be referred to one of the participating academic Hospitals (Uppsala or Örebro) -Patients will be informed about the study by investigators and upon informed consent, they will be included and randomized. -Information about randomization will be shared with the local oncologist -The local oncologist will treat and follow up the patient in accordance to the clinical practice. -The patient will receive questionnaires electronically through eCRF -All study-related information will be collected from academic Hospitals through patient journal with help with the National Patient Overview (a national electronic platform that connects the electronic patient records from different Hospitals in Sweden).	Addition of satellites in Sweden

Appendix A. MyCARG Comprehensive Geriatric Assessment Questionnaire (English version)

MyCARG Comprehensive Geriatric Assessment Questionnaire

OARS MULTIDIMENSIONAL FUNCTIONAL ASSESSMENT QUESTIONNAIRE – IADL (7 questions)

1. Can you use the telephone ...

   - ☐ 2 without help, including looking up contacts and dialling;
   - ☐ 1 with some help (can answer phone or call an emergency number, but need a special phone or help in getting the number or dialling); or
   - ☐ 0 are you completely unable to use the telephone?

2. Can you get to places out of walking distance ...

   - ☐ 2 without help (drive your own car, or travel alone on buses, or taxis);
   - ☐ 1 with some help (need someone to help you or go with you when traveling); or
   - ☐ 0 are you unable to travel unless emergency arrangements are made for a specialised vehicle like an ambulance?

3. Can you go shopping for groceries or clothes [ASSUMING HAS TRANSPORTATION] ...

   - ☐ 2 without help (taking care of all shopping needs yourself, assuming you had transportation);
   - ☐ 1 with some help (need someone to go with you on all shopping trips); or
   - ☐ 0 are you completely unable to do any shopping?

4. Can you prepare your own meals ...

   - ☐ 2 without help (plan and cook full meals yourself);
   - ☐ 1 with some help (can prepare some things but unable to cook full meals yourself); or
   - ☐ 0 are you completely unable to prepare any meals?

5. Can you do your housework ...

   - ☐ 2 without help (can clean floors, etc.);
   - ☐ 1 with some help (can do light housework but need help with heavy work); or
   - ☐ 0 are you completely unable to do any housework?

6. Can you take your own medicine ...

   - ☐ 2 without help (in the right doses at the right time);
   - ☐ 1 with some help (able to take medicine if someone prepares it for you and/or reminds you to take it); or
   - ☐ 0 are you completely unable to take your medicines?

7. Can you handle your own money ...

   - ☐ 2 without help (write cheques, pay bills, etc.);
   - ☐ 1 with some help (manage day-to-day buying but need help with managing your bank account and paying your bills); or
   - ☐ 0 are you completely unable to handle money?

Physical Activities: Medical Outcomes Study (MOS) Physical Health (10 questions)

INSTRUCTIONS: The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Limited a lot	Limited a little	Not limited at all
1. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	**1**	**2**	**3**
2. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	**1**	**2**	**3**
3. Lifting or carrying groceries	**1**	**2**	**3**
4. Climbing several flights of stairs	**1**	**2**	**3**
5. Climbing one flight of stairs	**1**	**2**	**3**
6. Bending, kneeling, or stooping	**1**	**2**	**3**
7. Walking more than a mile	**1**	**2**	**3**
8. Walking several blocks	**1**	**2**	**3**
9. Walking one block	**1**	**2**	**3**
10. Bathing or dressing yourself	**1**	**2**	**3**

Current Health Rating: Karnofsky Self-Reported Performance Rating Scale (1 question)

1. Which one of the following phrases best describes you at this time?

- ☐ Normal no complaints; no symptoms of disease
- ☐ Able to carry on normal activity; minor symptoms of disease
- ☐ Normal activity with effort; some symptoms of disease
- ☐ Cares for self; unable to carry on normal activity or to do active work
- ☐ Requires occasional assistance, but is able to care for most of own personal needs
- ☐ Requires considerable assistance for personal care
- ☐ Disabled; requires special care and assistance
- ☐ Severely disabled; requires continuous nursing care

Falls (1 question)

1. How many times have you fallen in the last 6 months?
   - ☐ One or more times
   - ☐ None

Medications (1 question => 3 more questions)

1. Are you taking any medications?
   - ☐ Yes (please answer the 3 following questions)

     1. How many prescribed medications are you taking?

     2. How many over-the-counter medications are you taking?

     3. How many herbs and vitamins are you taking?

   - ☐ No

Comorbidity: Physical Health Section OARS (15 questions)

Your Health

INSTRUCTIONS: We would like to ask you a few questions about any health problems you might have. Do you have any of the following illnesses at the present time? Please fill in the appropriate box (**no** or **yes**). If you fill in '**yes**', please tell us how much the illness interferes with your activities: **Not at all, Somewhat, or A great deal**. Fill in the appropriate box.

			If you have the illness, how much does it interfere with your activities?		
	NO	**YES**	**NOT AT ALL**	**SOMEWHAT**	**A GREAT DEAL**
1. Other cancers or leukaemia	☐	☐ ▶	☐	☐	☐
2. Arthritis or rheumatism	☐	☐ ▶	☐	☐	☐
3. Glaucoma	☐	☐ ▶	☐	☐	☐
4. Emphysema or chronic obstructive pulmonary disease	☐	☐ ▶	☐	☐	☐
5. High blood pressure	☐	☐ ▶	☐	☐	☐
6. Heart disease	☐	☐ ▶	☐	☐	☐
7. Circulation trouble in arms or legs	☐	☐ ▶	☐	☐	☐
8. Diabetes	☐	☐ ▶	☐	☐	☐
9. Stomach or intestinal disorder	☐	☐ ▶	☐	☐	☐
10. Osteoporosis	☐	☐ ▶	☐	☐	☐
11. Chronic liver or kidney disease	☐	☐ ▶	☐	☐	☐
12. Stroke	☐	☐ ▶	☐	☐	☐
13. Depression	☐	☐ ▶	☐	☐	☐

14. How is your eyesight (with glasses or contacts)

☐ Excellent ☐ Good ☐ Fair ☐ Poor ☐ Totally blind

If Fair, Poor or Totally blind, how much does it interfere with your activities?

☐ NOT AT ALL ☐ SOMEWHAT ☐ A GREAT DEAL

15. How is your hearing (with a hearing aid, if needed)?

☐ Excellent ☐ Good ☐ Fair ☐ Poor ☐ Totally deaf

If Fair, Poor or Totally deaf, how much does it interfere with your activities?

☐ NOT AT ALL ☐ SOMEWHAT ☐ A GREAT DEAL

Nutritional Status (1 question => 1 question)

1. Have you lost weight involuntarily for the last 6 months?
   - ☐ Yes
   - ☐ No

   If yes, how much?

   ☐

Psychological Status: Mental Health Inventory (MHI)-17 (17 questions)

INSTRUCTIONS: These questions are about how you have been feeling within the past month. Please select an answer that best reflects your situation.

How much of the time during the past month:

	All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time
1. has your daily life been full of things that were interesting to you?	**1**	**2**	**3**	**4**	**5**	**6**
2. did you feel depressed?	**1**	**2**	**3**	**4**	**5**	**6**
3. have you felt loved and wanted?	**1**	**2**	**3**	**4**	**5**	**6**
4. have you been a very nervous person?	**1**	**2**	**3**	**4**	**5**	**6**
5. have you been in firm control of your behaviour, thoughts, emotions, feelings?	**1**	**2**	**3**	**4**	**5**	**6**
6. have you felt tense or high-strung?	**1**	**2**	**3**	**4**	**5**	**6**
7. have you felt calm and peaceful?	**1**	**2**	**3**	**4**	**5**	**6**
8. have you felt emotionally stable?	**1**	**2**	**3**	**4**	**5**	**6**
9. have you felt downhearted and blue?	**1**	**2**	**3**	**4**	**5**	**6**
10. have you felt restless, fidgety, or impatient?	**1**	**2**	**3**	**4**	**5**	**6**
11. have you been moody, or brooded about things?	**1**	**2**	**3**	**4**	**5**	**6**
12. have you felt cheerful, light-hearted?	**1**	**2**	**3**	**4**	**5**	**6**
13. have you been in low or very low spirits?	**1**	**2**	**3**	**4**	**5**	**6**
14. were you a happy person?	**1**	**2**	**3**	**4**	**5**	**6**
15. did you feel you had nothing to look forward to?	**1**	**2**	**3**	**4**	**5**	**6**
16. have you felt so down in the dumps that nothing could cheer you up?	**1**	**2**	**3**	**4**	**5**	**6**
17. have you been anxious or worried?	**1**	**2**	**3**	**4**	**5**	**6**

Social Functioning: MOS Social Activity Limitations Measure (3 questions)

1. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

   - ☐ All of the time
   - ☐ Most of the time
   - ☐ Some of the time
   - ☐ A little of the time
   - ☐ None of the time

2. Compared to your usual level of social activity, has your social activity during the past 6 months decreased, stayed the same, or increased because of a change in your physical or emotional condition?

   - ☐ Much less socially active than before
   - ☐ Somewhat less socially active than before
   - ☐ About as socially active as before
   - ☐ Somewhat more socially active than before
   - ☐ Much more socially active than before

3. Compared to others your age, are your social activities more or less limited because of your physical health or emotional problems?

   - ☐ Much more limited than others
   - ☐ Somewhat more limited than others
   - ☐ About the same as others
   - ☐ Somewhat less limited than others
   - ☐ Much less limited than others

Social Support: MOS Social Support Survey (12 questions)

Social Support

INSTRUCTIONS: People sometimes look to others for companionship, assistance or other types of support. How often is each of the following kinds of support available to you if you need it? (Select an answer that best reflects your situation.)

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
1. to help you if you are confined to bed?	**1**	**2**	**3**	**4**	**5**
2. to listen to you when you need to talk?	**1**	**2**	**3**	**4**	**5**
3. to give you good advice about a crisis?	**1**	**2**	**3**	**4**	**5**
4. to take you to the doctor if you need to go?	**1**	**2**	**3**	**4**	**5**
5. to give you information to help you understand a situation?	**1**	**2**	**3**	**4**	**5**
6. to confide in or talk to about yourself or your problems?	**1**	**2**	**3**	**4**	**5**
7. to prepare your meals if you are unable to do it yourself?	**1**	**2**	**3**	**4**	**5**
8. whose advice you really want?	**1**	**2**	**3**	**4**	**5**
9. to help with daily chores?	**1**	**2**	**3**	**4**	**5**
10. to share your private worries and fears with?	**1**	**2**	**3**	**4**	**5**
11. to turn to for suggestions about how to deal with a personal problem?	**1**	**2**	**3**	**4**	**5**
12. to understand your problems?	**1**	**2**	**3**	**4**	**5**

Appendix Table B. Defining frailty through comprehensive geriatric assessment and suggested interventions

Questionnaire	Description	Score for vulnerable/frail	Suggested intervention strategies
OARS IADL	Consists of 7 questions with the scores ranging from 0 to 14 A higher score indicates less need for assistance.	< 14	Home Safety Evaluation Home Health Aid Referral Personal Emergency Response System if alone
Medical Outcomes Study (MOS) Physical Health Scale	Consists of 10 questions with the scores ranging from 0-100 Higher scores represent better health status	< 60	
Karnofsky Self-Reported Performance Status Scale	1 question	< 70%	
Falls	1 question (Y/N)	>1	Home Health Aid Referral Personal Emergency Response System if Alone
Medications	1 question (number)	>5 medication or any high-risk medication (opioid or CNS-active medication)	Medication review - minimize high risk medications
Comorbidity: Physical Health Section OARS	The number of comorbid conditions are summed. Hearing and eyesight are also rated by the patient.	>3	Referral to specialist (depending on the response) and/or to primary care setting for optimization
Nutritional status	During the last 6 months	≥ 10% during the last 6 months	Referral to nutritionist
Psychological Status: Mental Health Inventory (MHI)-17	The measure yields 3 global scores of psychological distress, psychological well-being, and a total score on a scale of 0-100	<60	Social Work Involvement Consider referral to psychologist Support group information
Social Functioning: MOS Social Activity Limitations Measure	Consists of 3 questions with scores ranging from 0-100	<60	Social Work Involvement Support group information
Social Support: MOS Social Support Survey	12 items used to measure the patient's perception of their social support ranging on a scale of 0-100	< 80	Social Work Involvement Support group information

Appendix C. EORTC QLQC30 questionnaire (English version)

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix D. EORTC ELD14 questionnaire (English version)

ENGLISH

EORTC QLQ-ELD14

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Have you had difficulty with steps or stairs?	1	2	3	4
32. Have you had trouble with your joints (e.g. stiffness, pain)?	1	2	3	4
33. Did you feel unsteady on your feet?	1	2	3	4
34. Did you need help with household chores such as cleaning or shopping?	1	2	3	4
35. Have you felt able to talk to your family about your illness?	1	2	3	4
36. Have you worried about your family coping with your illness and treatment?	1	2	3	4
37. Have you worried about the future of people who are important to you?	1	2	3	4
38. Were you worried about your future health?	1	2	3	4
39. Did you feel uncertain about the future?	1	2	3	4
40. Have you worried about what might happen towards the end of your life?	1	2	3	4
41. Have you had a positive outlook on life in the last week?	1	2	3	4
42. Have you felt motivated to continue with your normal hobbies and activities?	1	2	3	4
43. How much has your illness been a burden to you?	1	2	3	4
44. How much has your treatment been a burden to you?	1	2	3	4

Appendix E. EQ-5D-5L questionnaire (English version)

Health Questionnaire (EQ-5D-5L)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- ☐ 1 I have no problems in walking about
- ☐ 2 I have slight problems in walking about
- ☐ 3 I have moderate problems in walking about
- ☐ 4 I have severe problems in walking about
- ☐ 5 I am unable to walk about

SELF-CARE

- ☐ 1 I have no problems washing or dressing myself
- ☐ 2 I have slight problems washing or dressing myself
- ☐ 3 I have moderate problems washing or dressing myself
- ☐ 4 I have severe problems washing or dressing myself
- ☐ 5 I am unable to wash or dress myself

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- ☐ 1 I have no problems doing my usual activities
- ☐ 2 I have slight problems doing my usual activities
- ☐ 3 I have moderate problems doing my usual activities
- ☐ 4 I have severe problems doing my usual activities
- ☐ 5 I am unable to do my usual activities

PAIN / DISCOMFORT

- ☐ 1 I have no pain or discomfort
- ☐ 2 I have slight pain or discomfort
- ☐ 3 I have moderate pain or discomfort
- ☐ 4 I have severe pain or discomfort
- ☐ 5 I have extreme pain or discomfort

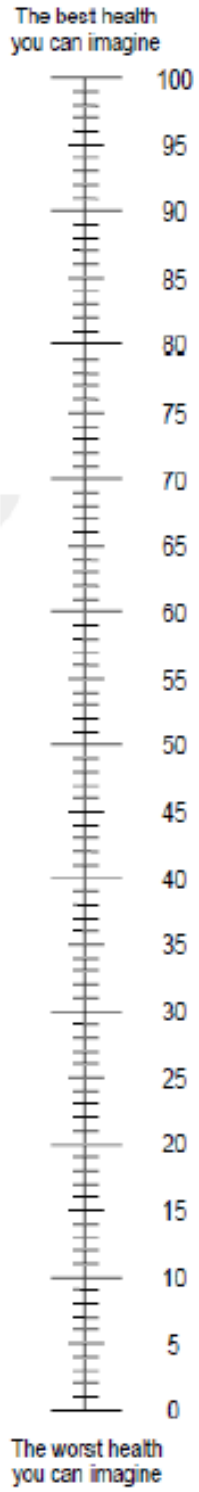
ANXIETY / DEPRESSION

- ☐ 1 I am not anxious or depressed
- ☐ 2 I am slightly anxious or depressed
- ☐ 3 I am moderately anxious or depressed
- ☐ 4 I am severely anxious or depressed
- ☐ 5 I am extremely anxious or depressed

Health Questionnaire (EQ-5D-5L)

- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is **TODAY**
- Now, please write the number you marked on the scale in the below.

YOUR HEALTH TODAY = ☐



Appendix F. Shortened version of the iMTA Medical Consumption Questionnaire

Questionnaire about your use of care

Researchers call this questionnaire the iMTA Medical Consumption Questionnaire (iMCQ).

July 2018 version, amended for IMPORTANT study

General questions

Question A1. On what date did you fill in this questionnaire?

Day		Month		Year			

Questions about healthcare use

Comment
We would like to know which doctors you have consulted in the past 3 months. It is about consultations for yourself. Other healthcare providers also count. For example, the physiotherapist.

Which consultations count?

- Control visits
- Appointments because you had a physical or psychological complaint
- Appointments where the doctor came to your home
- Telephone appointments
- Phone calls with the recipe line

Which consultations do not count?

- Appointments for another person, for example for your husband or wife
- Telephone calls to make an appointment

Are you unsure about the exact number of consultations? Please fill in how many consultations you have had approximately.

Question 1. Have you consulted a general practitioner in the past 3 months?

☐ No
☐ ..... appointments

Question 2. How many appointments did you have with a social worker in the past 3 months?

☐ No appointment
☐ …… appointments

Question 3. How many appointments did you have with a physiotherapist in the past 3 months? Add up all appointments with these therapists.

☐ No appointment
☐ …… appointments

Question 4. How many appointments did you have with a psychologist, a psychotherapist or psychiatrist in the past 3 months? Add up all appointments with these healthcare providers.

☐ No appointment
☐ …… appointments

Question 5a. Have you received home care in the past 3 months?

☐ No
☐ Yes

Have you ticked "Yes"? Then answer questions 5b through 5d.
Otherwise, continue with question 6.

Question 5b. What kind home care have you had in the past 3 months?
You can tick more than 1 box.

☐ Housekeeping and domestic help
example: vacuuming, making bed, going for daily groceries

☐ Personal care
example: help with bathing or dressing

☐ Nursing
example: putting on a bandage, administering medication, measuring blood pressure

Question 5c. How many weeks did you have this home care? Count up all weeks in the past 3 months. *Note: a period of 3 months counts 13 weeks*.

Domestic help: ..... weeks in the past 3 months

Personal care: ..... weeks in the past 3 months

Nursing: ..... weeks in the past 3 months

Question 5d. How many hours of home care did you receive on average in these weeks?

Domestic help: on average ..... hours a week

Personal care: on average ..... hours a week

Nursing: on average ..... hours a week

Question 6a. Have you received help from a family member or acquaintance due to your physical or psychological problems in the past 3 months?

☐ No
☐ Yes

Have you ticked "Yes"? Then answer questions 7b through 7d.
Otherwise, go to question 8.

Question 6b. What kind of help from family members or acquaintances have you had in the past 3 months? You can tick more than 1 box.

☐ Domestic help
example: vacuuming, making bed, shopping, preparing food and drinks, taking care of children

☐ Personal care
example: help with showering or dressing, help with eating and drinking or giving medicines

☐ Practical help
example: support with walking, making trips or visits to acquaintances, visits to the general practitioner or the hospital, arranging help or arranging financial affairs

Question 6c. How many weeks did you have this home care? Count up all the weeks in the past 3 months. *Note: a period of 3 months counts as 13 weeks*.

Domestic help: ... ... weeks in the past 3 months

Personal care: ... ... weeks in the past 3 months

Practical help: ... ... weeks in the past 3 months

Question 6d. How many hours of home care did you receive on average in these weeks?

Domestic help: on average ..... hours a week

Personal care: on average ..... hours a week

Practical help: on average ..... hours a week

Question 7. Have you been admitted to a residential care centre or nursing home in the past 3 months? Have you been admitted more than 1 time in the past 3 months? Then add all the days together.

☐ No
☐ Yes, for ..... days in the past 3 months

That was the last question.