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CLINICAL TRIAL PROTOCOL

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Implementing geriatric assessment for dose optimization of CDK4/6 inhibitors in older breast cancer patients

Antonis Valachis[*,a], Laura Biganzoli[b], Athina Christopoulou[c], Kamilla Fjermeros[d], Elena Fountzila[e], Jürgen Geisler[f], Raquel Gomez-Bravo[g], Peeter Karihtala[h], Paris Kosmidis[i], Angelos Koutras[j], Helena Linardou[k], Henrik Lindman[l], Iván Martínez-Ballestero[m], Anna Belén Rodríguez[g], Icro Meattini[n], Montserrat Munoz-Mateu[g], Mukhrizah Othman[a], Amanda Psyrri[o], Emanuela Risi[b], Aglaia Schiza[l], Nikolaos Spathas[k], Meri Utriainen[h], Luca Visani[p], Soledad Ballesteros[q], Ioannis Basdekis[r], Susanne Dieroff Hay[s], Theo Fotis[t], Samuel Fricker[u], Gimon de Graaf[v], Marit Jenset[s], Tim Kanters[v], Kostas Lampropoulos[w], Christiana Markou[x], Kalliopi Mastoraki[r], Christina Nanou[y], José Manuel Reales Aviles[q], Marianne Santaholma[u] and Thanos Kosmidis[z]

[a]Department of Oncology, Faculty of Medicine & Health, Örebro University, Sweden; [b]Department of Oncology, Hospital of Prato, Azienda USL Toscana Centro, Florence, Italy; [c]Department of Medical Oncology, St Andrews General Hospital of Patras, Patras, Greece; [d]Department of Oncology, Akershus University Hospital, Lørenskog, Norway; [e]Department of Medical Oncology, St Luke's Clinic, Thessaloniki, Greece, European University Cyprus, Nicosia, Cyprus; [f]Department of Oncology, Akershus University Hospital, Lørenskog, Norway & Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway; [g]Medical Oncology Department Hospital Clinic & Translational Genomics & Targeted Therapies in Solid Tumors, IDIBAPS, Barcelona, Spain; [h]Department of Oncology, Helsinki University Hospital Comprehensive Cancer Center & University of Helsinki, Helsinki, Finland; [i]Second Medical Oncology Department, Hygeia Hospital, Athens, Greece; [j]Division of Oncology, Department of Medicine, University Hospital of Patras, Patras, Greece; [k]Fourth Oncology Dept & Comprehensive Clinical Trials Center, Metropolitan Hospital, Athens, Greece; [l]Department of Oncology, Uppsala University Hospital & Department of Immunology, Genetics & Pathology Uppsala University, Uppsala, Sweden; [m]Fundació Clínic per a la Recerca Biomèdica, Barcelona, Spain; [n]Department of Experimental & Clinical Biomedical Sciences "M. Serio", University of Florence, Florence, Italy & Radiation Oncology Unit, Breast Unit, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy; [o]Section of Medical Oncology, Department of Internal Medicine, Faculty of Medicine, National & Kapodistrian University of Athens, Attikon University Hospital, Athens, Greece; [p]Radiation Oncology Unit, Breast Unit, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy; [q]Studies of Aging & Neurodegenerative Diseases Research Group, Universidad Nacional de Educación a Distancia, Madrid, Spain; [r]Circular Economy Foundation, Brussels, Belgium; [s]The Swedish Breast Cancer Association, Stockholm, Sweden; [t]Security Labs Consulting Ltd, Dublin, Ireland; [u]Institute for Interactive Technologies, University of Applied Sciences Northwestern Switzerland, Windisch, Switzerland; [v]Institute for Medical Technology Assessment, Erasmus University Rotterdam, Rotterdam, The Netherlands; [w]Department of Electrical & Computer Engineering, University of Patras, Patras, Greece; [x]School of Law, European University Cyprus, Nicosia, Cyprus & Eunomia Ltd, Dublin, Ireland; [y]Eunomia Ltd, Dublin, Ireland; [z]CareAcross Ltd, London, UK

ABSTRACT

Current evidence from both randomized trials and real-world studies suggests that older patients with advanced hormone receptor-positive/HER2-negative (HR+/HER2) breast cancer derive clinical benefit from the addition of CDK4/6 inhibitors to endocrine therapy. However, a higher risk for adverse events due to CDK4/6 inhibitors among older patients is evident, leading to a trend of initiating CDK4/6 inhibitors at lower dose in clinical practice, though without evidence. The aim of the IMPORTANT-trial, a pragmatic, multinational, open-label, partly decentralized randomized trial is to investigate whether lower starting dose of CDK4/6 inhibitors combined with endocrine therapy is comparable to full dose in older (≥70 years old) patients with advanced HR+/HER2- breast cancer who are assessed as vulnerable or frail based on comprehensive geriatric assessment.

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1. Introduction

1.1. Background & rationale

The addition of CDK4/6 inhibitors to endocrine therapy has been shown to improve both progression-free survival (PFS) and overall survival (OS) in patients with hormone-receptor positive (HR+) advanced breast cancer in first- or second-line setting [1]. The efficacy of CDK4/6 inhibitors is present in all patient subgroups, including older patients who were included in the pivotal

CONTACT Antonis Valachis Tel.: 0046735617691; Antonios.valachis@oru.se

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randomized trials [1]. However, older cancer patients are under-represented in clinical trials and their baseline characteristics may differ from older cancer patients in real-world setting, thus making challenging the generalizability of the results from randomized clinical trials (RCTs) [2].

Current evidence from both RCTs and real-world evidence studies suggests that older breast cancer patients derive clinical benefit from the addition of CDK4/6 inhibitors to endocrine therapy; however, they face higher risk for adverse events and treatment discontinuation compared with younger patients [3]. The recommended starting dose for CDK4/6 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 CDK4/6 inhibitors at a lower dose. In fact, this clinical approach seems to be a relatively common practice according to real-world evidence studies [4,5]. In a prospective randomized trial including both pre- and postmenopausal women affected by breast cancer (median age 58 years), lower initial dose of CDK4/6 inhibitor ribociclib did not result in statistically significant worse response rates (41.5% for lower vs 45.3% in full dose) or PFS (24.9 months for lower vs 25.1 months in full dose) [6]. In addition, fewer dose-dependent adverse events of grade $\geq$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 end point), the differences between the two treatment arms were only numerical and suggest that patients at higher risk for adverse events (as older vulnerable patients) could benefit from a lower initial dose without compromising the expected efficacy [6]. However, no randomized evidence specifically for older patients does exist on initiating with a lower dose of CDK4/6 inhibitors. In other words, this practice is merely based on clinical observation and experience rather 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 aging-related domains in older cancer patients that might impact cancer treatment decisions [7]. 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 seems to reduce treatment-related toxicities according to recently published RCTs [8,9]. 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 this older patient group [10]. 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 with treatment allocation based on clinical decision [11]. 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 with a full dose with less toxicity and better patient experience [12].

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 the 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 [4,5]. Besides, 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 [13].

As a result, the aim of the present randomized trial is to investigate whether a CGA-based initial dose reduction of CDK4/6 inhibitors in vulnerable/frail older patients with advanced breast cancer would result in a similar time-to-treatment-failure (TTF) and better patient experience (in terms of toxicity and quality of life [QoL]) without compromising treatment efficacy.

1.2. Objectives

The primary objective of the IMPORTANT trial is to investigate the TTF in vulnerable or frail older breast cancer patients treated with lower initial dose of CDK4/6 inhibitors plus endocrine therapy compared with the recommended full dose of CDK4/6 inhibitors. The secondary objectives are to compare the two treatment arms (lower initial dose of CDK4/6 inhibitor vs full dose) in terms of OS, investigator-assessed PFS, time to chemotherapy initiation, overall treatment utility (OTU), toxicity, patients' health-related QoL and cost-effectiveness.

1.3. Trial design

IMPORTANT is a pragmatic, multinational, open-label, partly decentralized, randomized controlled clinical trial with a noninferiority approach dedicated to older patients (≥70 years old) with advanced HR+/human epidermal growth factor receptor 2-negative (HR+/HER2-) breast cancer suitable for first line therapy with CDK4/6 inhibitors given in concert with endocrine treatment.

2. Materials & methods

2.1. Study settings

Seven clinical sites in Sweden, Finland, Norway, Italy, and Spain as well as one research network, the Hellenic Cooperative Oncology Group (HeCOG) with six hospitals in Greece, will recruit patients to IMPORTANT trial (Table 1).

2.2. Eligibility criteria

Eligible patients for the IMPORTANT trial are older female or male 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 considering the international guidelines suggesting this threshold to define older patients where specific recommendations are applied [14]. Table 2 shows the detailed inclusion and exclusion criteria.

2.3. Interventions

All eligible patients will be evaluated using a CGA before randomization. The results of CGA will be an essential part of decision-making process. The CGA will be based on the geriatric assessment tool from Cancer and Aging Research Group [15] which includes self-administered questions. The corresponding answers will be assessed by the investigators for classification to fit, vulnerable or frail. However, the questionnaires are self-administered providing advantages of this approach compared with clinician-driven questionnaires in terms of time consumption and flexibility without compromising the validity of information retrieved.

Seven main domains will be evaluated through CGA: functional status, comorbidity, number of falls, psychological, social functioning, social support and 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 Supplementary Table S1. Although CGA-guided interventions are mandatory, they are not dictated by the study protocol, but they can follow local practices to enable a more pragmatic approach on the implementation of CGA-results in clinical practice. All CGA-guided interventions that are applied will be captured.

After applying the CGA process, the treatment strategy in terms of CDK4/6 inhibitor dose optimization will be as follows:

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

Changes between different CDK4/6 inhibitors due to toxicity are allowed with the obligation to use the same dose level as the previous CDK4/6 inhibitor. The possibility of dose escalation to full dose for patients randomized to lower initial dose is allowed at the discretion of investigator A schematic overview of the IMPORTANT trial is shown in Figure 1.

2.4. Outcomes

2.4.1. Primary end point

The primary end point of the IMPORTANT study is to investigate the TTF (defined as the time from randomization to treatment discontinuation because of any reason including disease progression, treatment toxicity, or death due to any cause) in vulnerable/ frail older breast cancer patients treated with lower initial dose of CDK4/6 inhibitors plus endocrine therapy compared with fit patients treated with the recommended full dose of CDK4/6 inhibitors. TTF is a composite end point allowing the integration of toxicity in addition to efficacy into the definition of treatment benefit and is considered a suitable end point for clinical trials dedicated to older cancer patients [16].

2.4.2. Secondary end points

The secondary end points are to compare the two treatment arms (lower initial dose of CDK4/6 inhibitor vs full dose) in terms of OTU, investigator-assessed PFS, time to chemotherapy initiation, OS, toxicity, QoL, time to QoL deterioration and cost-effectiveness.

Table 1. Participating clinical sites.

Clinical sites	Location
Department of Oncology, Örebro University Hospital, Örebro	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
Section of Medical Oncology, Department of Internal Medicine, Faculty of Medicine, National and Kapodistrian University of Athens, Attikon University Hospital	Greece
Fourth Oncology Department & Comprehensive Clinical Trials Center, Metropolitan Hospital, Athens	Greece
Department of Medical Oncology, St Luke's Clinic, Thessaloniki	Greece
Division of Oncology, Department of Medicine, University Hospital, University of Patras Medical School, Patras	Greece
Medical Oncology Unit, S. Andrew Hospital, Patras	Greece
2nd Medical Oncology Department, Hygeia Hospital, Athens	Greece

Table 2. Inclusion and exclusion criteria of IMPORTANT trial.

Inclusion criteria	Exclusion criteria
• 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. • Histologically or cytologically confirmed diagnosis of HR-positive (defined as estrogen-receptor $\geq$ 1%), HER2-negative breast cancer according to analysis of the most recent tumor specimen by local laboratory. • Advanced (locoregionally recurrent or metastatic) breast cancer not amenable to curative treatment. • 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 28 days from the CDK 4/6-inhibitor initiation is allowed. • Adjuvant treatment with CDK4/6-inhibitors is allowed provided a disease-free interval from treatment end >12 months. • Either measurable disease or non-measurable bone only disease, but evaluable according to RECIST criteria 1.1. • Written informed consent prior to any study-specific procedures. • Adequate organ function as defined in the summary of product characteristics (SmPC) for the CDK4/6 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 $\geq$ 1000/mm3, platelet counts of $\geq$ 100,000/mm3; ALT and/or AST $\leq 3 \times$ upper limit normal (ULN), total bilirubin $\leq 2 \times$ ULN; eGFR $\geq$ 30 ml/min. • Able to swallow capsules. • Able to understand and consent in English language or in native language for each participating country.	• Patients considered from treating physician as non-suitable for treatment with CDK4/6 inhibitors. • Patients with cognitive impairment (as assessed by treating physician) that preclude the ability to fill out the self-reported comprehensive geriatric assessment. • Contraindications according to SmPC for the CDK4/6 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. • Presence of visceral crisis, lymphangitis carcinomatosis, or leptomeningeal carcinomatosis. • History of any other cancer (except of non-melanoma skin cancer or carcinoma *in situ* of the cervix), unless in complete remission with no therapy for a minimum of 3 years. • Participating in other interventional trial.

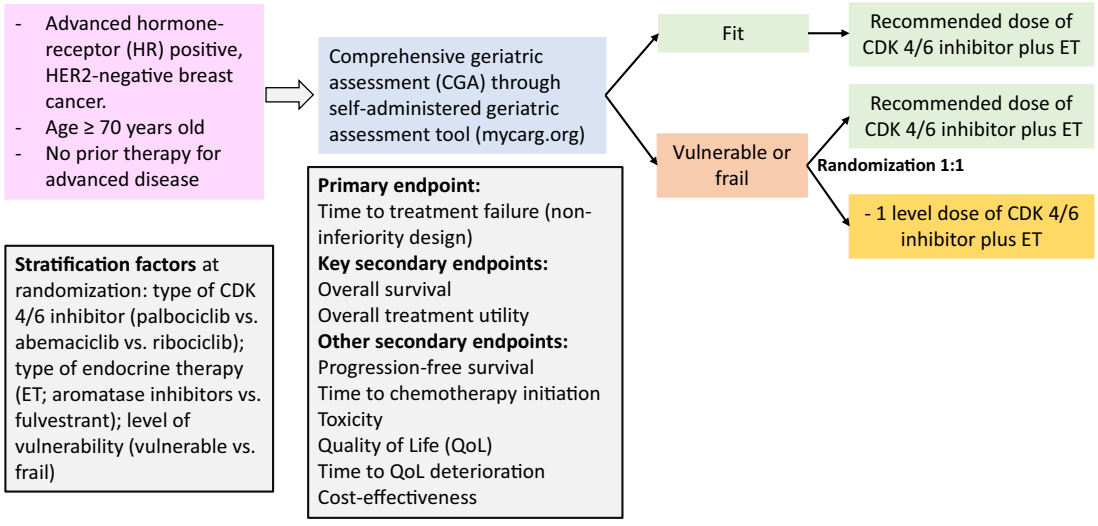

Figure 1. IMPORTANT trial overview.

OTU is a composite end point 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 time from randomization to first documented evidence of disease progression or death from any cause defines PFS. 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 as performed by the 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 CDK4/6 inhibitors.

The time from randomization to death from any cause defines OS. 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.

Toxicity will be assessed based on adverse events, as graded by CTCAE version 5.0 before each cycle and up to 28 days after the end of CDK4/6 inhibitors.

Health-related QoL will be assessed using three validated questionnaires, EORTC QLQ-C30, ELD-14, and EQ-5D-5L. 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 [17]) of any QoL aspect measured by the questionnaires will be assessed.

Cost-effectiveness analyses will be performed by using healthcare resource utilization, length of life and QoL data captured during the trial. This data will be complemented with self-reported non hospital healthcare and informal care utilization through a questionnaire combining elements of the iMTA Medical Consumption Questionnaire [18] and the iMTA Valuation of Informal Care Questionnaire [19], which will be assessed 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.

2.5. Participant timelines

Eligible patients will be informed about the study by the treating physician. After informed consent, CGA will be performed at baseline. Based on the CGA, two patient cohorts will be defined as outlined above. The treatment with CDK4/6 inhibitors should start within 14 days after randomization. Endocrine therapy is recommended to start at the same time as CDK4/6 inhibitors initiation but a period of up to 28 days prior treatment with endocrine therapy is allowed.

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 CDK4/6 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 CDK4/6 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.

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 CDK4/6 inhibitors (for patients continuing this treatment after the trial treatment phase) and any subsequent treatment strategy will be captured.

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 3 months. Patient-reported outcomes will be captured through self-questionnaires during the study period. A detailed description of study schedule is shown in Table 3.

Table 3. 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 from treatment initiation 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[d]	X					As indicated					
Comprehensive geriatric assessment[a]	X			X		X		X		X	
Quality of life assessment[a]	X		X	X	X	X		X		X	
Medical consumption questionnaire[a]			X	X	X	X		X		X	
Randomization		X									
Treatment with CDK4/6 inhibitors and endocrine therapy[a,b,c]			◄	———	———	———	———	►			To be continued according to treating physician
Efficacy evaluation[a]	Baseline objective measurement		X	X	X	X	X	X	X	X	
Overall treatment utility			X								
Toxicity	Baseline measurement[e] (clinical, blood analyses)		Before each cycle and up to 28 days after the end of CDK4/6 inhibitors								
Survival follow-up information											Date of disease progression to CDK4/6 inhibitors (for patients continuing this treatment after the trial treatment phase); any subsequent treatment strategy; date and reason of death.

X indicates procedure that is applicable to the corresponding study phases i.e., screening phase; treatment phase and post-treatment phase.
[a]Until disease progression, participant/physician decision to stop or death.
[b]The treatment with CDK4/6 inhibitors should start within 14 days after randomization.
[c]Endocrine therapy is recommended to start at the same time as CDK4/6 inhibitors initiation but a period of up to 28 days prior treatment with endocrine therapy is allowed.
[d]Physical examination includes assessment of performance status and clinical assessment of any clinically detected metastatic lesion.
[e]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.

2.6. Sample size

In this study, a noninferiority study design is applied to vulnerable/frail cohort. TTF of 18 months is assumed for the experimental arm and 16 months for the standard arm with a small benefit of the experimental arm due to the anticipated lower rate of discontinuation due to toxicity. Considering a one-sided 5% significance and 80% power, a noninferiority 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 noninferiority of treatment strategy with lower initial dose compared with full dose in terms of TTF.

There will be no formal statistical considerations applied to the fit cohort, but the cohort will be analyzed with descriptive statistics. Considering a distribution of 30% fit and 70% vulnerable/frail patients, the study would need to screen 495 patients. Therefore, 149 patients in the fit cohort will be treated and followed, and 346 patients in the vulnerable/frail cohort will be randomized.

2.7. Recruitment

Patients will be recruited directly from the clinical sites participating in the trial (Table 1) or will be referred to them from nearby hospitals. Competitive recruitment between the clinical sites will be accepted. The accrual period is 30 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.

3. Methods: randomization

Randomization is performed centrally using the electronic data capture system (eCRF) Greenlight Guru Clinical. The following information will be required at randomization: stratification factor details; confirmation of eligibility; confirmation of written informed consent and date and confirmation of completed baseline CGA.

The randomization will be stratified by type of CDK4/6 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 pharmacological properties (different CDK4/6 inhibitors), the biology of disease in terms of endocrine resistance (different endocrine therapies) or health status (vulnerable or frail).

4. Methods: data collection, management & analysis

4.1. Data collection methods & management

Data protection and data security measures are implemented for the collection, storage, and processing of participant data in accordance with EU regulation 2016/679 General Data Protection Regulation. Patient-related data from medical records will be collected through the eCRF system clinical. 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. All patient-reported outcome measures will primarily be collected electronically through the eCRF system supporting the decentralized approach of the trial. If patients do not have access to electronical means, questionnaires will be sent to the patients by post thus allowing data collection without the need for the patient to be at the hospital in person.

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).

4.2. Statistical methods

Efficacy analyses will be based on the intention-to-treat 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, defined as all patients receiving at least one dose of CDK4/6 inhibitor. Sensitivity analyses may be performed for relevant end points, 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 curves 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 a 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, hazard 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 multilevel 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 end point will be performed based on stratification factors whereas exploratory subgroup analyses might be performed for variables of potential interest.

5. Methods: monitoring

5.1. Data monitoring

The sponsor in collaboration with the contract research organization (CRO) has developed a systematic, prioritized, risk-based approach to monitoring of this clinical trial. The risks to clinical trial processes and clinical trial data will be evaluated at both the system level (SOPs, computerized systems, personnel) and clinical trial level (trial design, data collection, informed consent process) against existing risk controls by considering: the likelihood of errors occurring; the extent to which such errors would be detectable and the impact of such errors on human subject protection and reliability of trial results.

5.2. Harms

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. 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 CDK4/6 inhibitors in breast cancer patients who are older than 70 years old. Regarding potential cons, a slightly lower effectiveness of a lower starting dose compared with a full dose cannot be entirely excluded, although a lower starting dose of CDK4/6 inhibitors has so far not been shown to be less effective compared with a 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 a full dose for patients randomized to a lower initial dose is allowed at the discretion of the 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 (CDK4/6 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 the treating physician as suitable for treatment with CDK4/6 inhibitors. As a result, no additional medications will be given within the trial.

As a part of risk/benefit assessment during IMPORTANT trial conduction, a toxicity-driven interim analysis will be performed when 100 patients have been 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. An 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 IMPORTANT Trial Steering 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 IMPORTANT Trial Steering Committee.

5.3. Auditing

The investigator/institution will allow site trial-related monitoring, audits, Institutional Review Board/Independent Ethics Committees 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., European Medicines Agency and US FDA). The accuracy of the data will be verified by direct comparison with the source documents. The sponsor and CRO will also monitor compliance with the protocol and good clinical practice (GCP). The investigator should notify the sponsor and CRO immediately of any such inspection. Audits and inspections may occur at any time during or after the completion of the study.

6. Ethics & dissemination

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 International Council for Harmonisation (ICH) Harmonised Guideline for GCP, relevant effective SOPs, the Clinical Trial Regulation (EU) No 536/2014, the General Data Protection Regulation, 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 and 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.

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 or the participant's legally accepted representative.

In terms of dissemination strategy, IMPORTANT trial adopts open access practices that improve the openness, integrity and reproducibility of its outcomes. Scientific publications that will occur in the trial lifecycle, both in conferences and journals, will focus on the relevant to the scope of IMPORTANT trial. Moreover, scientific publication of the trial will be offered in the open access principle.

7. Conclusion

Level I evidence supports the implementation of CGA in older cancer patients, to reduce treatment-related toxicity and improve QoL [8–12]. CDK4/6 inhibitors plus endocrine therapy is the preferred treatment approach for patients with advanced HR+/HER2- 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 [14]. The EUSOMA and SIOG guidelines dedicated to older breast cancer patients, recognize the combination of CDK4/6 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 CDK4/6 inhibitors is a relatively common clinical practice in older breast cancer patients supported by limited evidence [4,5]. Taken together, implementing CGA-based approach in decision making for dose optimization of CDK4/6 inhibitors in an older patient population with well-documented higher risk for toxicity and treatment discontinuation due to toxicity, represents an appealing strategy.

The IMPORTANT trial implements two approaches with high level of evidence, namely the use of CGA-approach in treatment decision making of older patients with cancer and the use of CDK4/6 inhibitors as the initial treatment of choice, to investigate whether a common clinical practice (starting dose reduction of CDK4/6 inhibitors in older patients) with evidence of low certainty can be standardized using a more individualized-based approach.

The IMPORTANT trial is the first randomized controlled trial that implements a CGA-based strategy for decision making regarding dose optimization of a targeted therapy in older cancer patients and offers a framework on how to design and plan similar trials investigating dose optimization interventions in older patients.

Article highlights

Breast cancer treatment overview in older patients

- In patients with advanced hormone receptor- (HR-) positive/HER2-negative breast cancer, the combination of endocrine therapy with CDK4/6 inhibitors is the standard of care as initial treatment approach.
- Older cancer patients are underrepresented in clinical trials, including pivotal trials on CDK4/6 inhibitors.
- Real-world evidence studies have showed that older patients are at increased risk for adverse events when treated with implementation of CDK4/6 inhibitors; lower initial dose is common in clinical practice, though without evidence.
- Comprehensive geriatric assessment (CGA) seems to be a reliable tool for the optimization of treatment strategy in older cancer patients.

IMPORTANT trial design

- IMPORTANT is pragmatic, multi-national, open-label, partly de-centralized randomized trial investigating whether a lower initial dose of CDK4/6 inhibitors combined with endocrine therapy is comparable to a full dose in older (≥70 years old) patients with advanced HR+/HER2- breast cancer that are assessed as vulnerable or frail based on CGA.
- Eligible patients are older female or male 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 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 3 months. Patient-reported outcomes will be captured through self-questionnaires during the study period.
- A total of 495 patients are to be enrolled with 30-month accrual period with 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.

Categorization & randomization in IMPORTANT trial
- Patients will be categorized based on self-reported CGA to fit or vulnerable/frail depending on domains of age metrics that are impaired.
- Patients categorized as vulnerable/frail will be randomized (1:1) to -1 level lower initial dose or full dose of CDK 4/6 inhibitors combined with endocrine therapy. Stratification factors during randomization are the type of CDK4/6 inhibitor used (palbociclib vs ribociclib vs abemaciclib), the type of endocrine therapy (aromatase inhibitors vs fulvestrant) and the level of vulnerability based on CGA (vulnerable vs frail).

IMPORTANT trial end points
- The primary end point is time-to-treatment failure; secondary end points include overall treatment utility, investigator-assessed progression-free survival, overall survival, time to chemotherapy initiation, toxicity, quality-of-life (QoL), time to QoL deterioration and cost-effectiveness.

Author contributions

All authors listed have contributed in all four aspects: substantial contributions to the conception or design of the work; or the acquisition, analysis or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

A Valachis: conceptualization, methodology, resources, writing – original draft, writing – review & editing, project administration, funding acquisition. L Biganzoli: conceptualization, methodology, resources, writing – review & editing. A Christopoulou: conceptualization, methodology, resources, writing – review & editing. K Fjermeros: conceptualization, methodology, resources, writing – review & editing. E Fountzila: conceptualization, methodology, resources, writing – review & editing. J Geisler: conceptualization, methodology, resources, writing – review & editing. R Gomez-Bravo: conceptualization, methodology, writing – review & editing. P Karihtala: conceptualization, methodology, software, resources, writing – original draft, writing – review & editing. P Kosmidis: conceptualization, methodology, resources, writing – review & editing. A Koutras: conceptualization, methodology, resources, writing – review & editing. H Linardou: conceptualization, methodology, resources, writing – review & editing. H Lindman: conceptualization, methodology, resources, writing – review & editing. I Martínez-Ballestero: resources, writing – review & editing. AB Rodríguez: resources, writing – review & editing. I Meattini: conceptualization, methodology, resources, writing – review & editing. M Munoz-Mateu: conceptualization, methodology, resources, writing – review & editing. M Othman: resources, writing – review & editing, project administration. A Psyrri: conceptualization, methodology, resources, writing – review & editing. Emanuela Risi: conceptualization, methodology, resources, writing – review & editing. Aglaia Schiza: conceptualization, methodology, resources, writing – review & editing. Nikolaos Spathas: conceptualization, methodology, resources, writing – review & editing. M Utriainen: conceptualization, methodology, resources, writing – review & editing. L Visani: conceptualization, methodology, resources, writing – review & editing. S Ballesteros: conceptualization, methodology, resources, writing – review & editing. I Basdekis: conceptualization, methodology, software, resources, writing – review & editing. SD Hay: conceptualization, methodology, resources, writing – review & editing. T Fotis: conceptualization, methodology, software, resources, writing – review & editing, project administration. S Fricker: conceptualization, methodology, software, resources, writing – review & editing. G de Graaf: conceptualization, methodology, software, resources, writing – review & editing. M Jenset: conceptualization, methodology, resources, writing – review & editing. T Kanters: conceptualization, methodology, software, resources, writing – review & editing. K Lampropoulos: conceptualization, methodology, software, resources, writing – review & editing, project administration, funding acquisition. C Markou: conceptualization, methodology, resources, writing – review & editing, project administration. K Mastoraki: conceptualization, methodology, software, resources, writing – review & editing, project administration. C Nanou: conceptualization, methodology, resources, writing – review & editing, project administration. JMR Aviles: conceptualization, methodology, resources, writing – review & editing. M Santaholma: conceptualization, methodology, resources, software, writing – review & editing. T Kosmidis: conceptualization, methodology, software, resources, writing – review & editing, project administration, funding acquisition.

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Competing interests disclosure

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Writing disclosure

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate regulatory and ethical approvals from each country and will follow the principles outlined in the Declaration of Helsinki for human experimental investigations. In addition, informed consent will be obtained from the participants involved. The trial protocol has been assessed and approved by the following Ethical Review Authorities: the Norwegian Ethics Committees for Clinical Trials on Medicinal Products and Medical Devices, the Swedish Ethical Review Authorities (reference nr 5.1.2-2024-000465), the Drug Research Ethics Committee of the Hospital Clínic of Barcelona (reference nr: HCB/2023/0872), the Finnish National Committee on Medical Research Ethics (reference nr T/119/2023), and the territorial ethical committee in Liguria.

ORCID

Antonis Valachis https://orcid.org/0000-0001-6059-0194

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Papers of special note have been highlighted as: • of interest; •• of considerable interest

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