Clinical Epidemiology

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STUDY PROTOCOL

Statin Therapy in Early Breast Cancer: The MASTER Trial; A Randomized Phase III, Placebo-Controlled Comparison of Standard (Neo)Adjuvant Therapy Plus Atorvastatin versus Standard (Neo)Adjuvant Therapy Plus Placebo

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Purpose: Statin use has been consistently associated with improved clinical outcomes (especially recurrence) in breast cancer in multiple observational studies backed by compelling preclinical evidence. The strength of this evidence warrants a clinical trial to test the efficacy of statin exposure on breast cancer recurrence.

Patients and Methods: The double-blind, phase III, randomized, placebo-controlled MASTER (MAmmary cancer STatins in ER positive breast cancer) trial includes women diagnosed with early-stage, estrogen receptor-positive (ER+) breast cancer who are candidates for systemic (neo)adjuvant therapy. Enrolled patients are given standard (neo)adjuvant therapy and additionally randomized to either atorvastatin (80 mg/day) or placebo for two years. The trial's primary outcome is invasive disease-free survival (IDFS), with a target accrual of 3360 patients in total to achieve 80% power (two-sided alpha=0.05) to detect a 25% reduction in the risk of an IDFS event comparing the statin and placebo arms. At 3-, 6-, 12-, and 24-month follow-up time points, patients will have blood drawn for biomarker studies, answer patient-reported outcome (PRO) questionnaires, and control for adverse events. Subsequently, patients will receive annual PRO-criteria for Adverse Events (CTCAE) questionnaires until the completion of their 10 years of follow-up. Secondary endpoints include additional clinical endpoints; pathological response (neo-adjuvant treated patients), recurrence-free survival, distant-recurrence-free interval, overall survival and cardiac death-free interval, co-morbidity, and health-related quality-of-life measured by PRO-CTCAE questionnaires during and beyond study medication. Translational endpoints are evaluated in collected blood- and tumor samples.

Discussion: If a protective effect of statins on breast cancer recurrence is supported by evidence from the MASTER trial, then the indications for a safe, well-tolerated, and inexpensive treatment can be expanded towards improved clinical outcomes for breast cancer patients.

Keywords: statin, breast cancer, recurrence, cholesterol, endocrine therapy, randomized trial

Received: 3 December 2024
Accepted: 6 April 2025
Published: 17 April 2025

Introduction

Cholesterol-lowering statins may have cancer-inhibiting properties. Studies examining whether statins reduce cancer incidence and/or mortality have shown inconsistent results. A recent meta-analysis by Chen et al investigated the influence of statin therapy on cancer incidence and mortality by summarizing evidence from randomized controlled trials; they found no reduction in cancer incidence with statins compared with placebo and no decrease in cancer mortality.[1] It has however been suggested that the cancer-inhibiting properties of statins are post-diagnostic regarding cancer recurrence, progression, and mortality in breast cancer patients. A systematic review and meta-analysis by Manthravadi et al showed that the use of statins (lipophilic statins) was associated with improved recurrence-free survival,[2] and a recent review and meta-analysis by Jaiswal et al support these findings by also showing an association between statin use and reduced recurrence compared to non-statin users.[3]

Clinical and Epidemiological Evidence

Several retrospective studies have shown an association between statins and reduced recurrence or cancer-specific mortality in women with breast cancer.[4–7] In 2017, we conducted a study nested in the Breast International Group 1–98 trial (BIG 1–98), in which the Danish Breast Cancer Group (DBCG) was a key partner and important trial contributor. Initiation of cholesterol-lowering medication during endocrine therapy was associated with improved breast-cancer-free interval (HR_{adj}=0.76, 95% CI: 0.60–0.97) and distant-recurrence-free interval (HR_{adj}=0.74, 95% CI: 0.56–0.97).[8] The study was the first to support the beneficial effect of statins on breast cancer outcomes nested within a large, international, randomized clinical trial of contemporary adjuvant endocrine therapy. Given the evidence supporting a protective effect of statins on breast cancer recurrence in observational studies, prominent studies have called for clinical trials testing the effects of statins independently of cholesterol levels.[9]

Preclinical Evidence and Mechanisms

The molecular target for statins, the hydroxymethylglutaryl-coenzyme A-reductase (HMGCR), is a transmembrane glycoprotein that regulates the mevalonate pathway, which produces cholesterol, steroid-based hormones, and non-sterol isoprenoids.[9,10] If hepatic HMGCR activity is inhibited, reduced intracellular cholesterol levels in hepatocytes will trigger up-regulation of low-density lipoprotein cholesterol (LDL-C) receptors to scavenge cholesterol from the serum to maintain intracellular cholesterol levels, thereby reducing circulating cholesterol.[10] The molecular basis for statin use as a breast cancer therapeutic agent is that cancer cells depend on cholesterol for continued growth and survival.[9,11] Therefore, attenuating cholesterol biosynthesis could be a promising anti-cancer strategy since rapidly proliferating cancer cells have an increased cholesterol demand to enable cell membrane synthesis.[11,12] By lowering plasma levels of LDL-cholesterol and 27-hydroxycholesterol (27HC), their availability for use by cancer cells is reduced.[13] Additionally, direct inhibition of HMGCR by statins depletes intratumoral reserves of isoprenoids, which are key regulators of cancer cell proliferation and metastasis.[14,15]

A decade of accumulating molecular and clinical evidence supporting the beneficial effects of statins on breast cancer progression motivated the development of this large-scale, clinical, Phase III trial aiming to investigate the impact of statin therapy on breast cancer recurrence among patients with early-stage ER+ breast cancer. We hypothesize that the addition of statin treatment to the current standard breast cancer treatment will reduce the risk of recurrence in patients with early breast cancer. The MASTER (MAmmary cancer, STatins, ER positive) trial attempts to answer this question (ClinicalTrials.gov #NCT04601116).

Aim

The overall aim is to investigate whether adding atorvastatin to standard therapy is associated with improved recurrence-free survival in ER+ breast cancer patients.

Materials and Methods

Study Setting

The study is conducted in Denmark at 10 subsites in close collaboration with the Danish Breast Cancer Group (DBCG). The DBCG holds a strong history in the initiation and conduction of academic clinical trials and houses a comprehensive

clinical database of all Danish breast cancer patients in which all departments of pathology, surgery, and oncology report clinical data on diagnostics, treatment, and follow-up.

Trial Design

The MASTER trial is a prospective, multicenter, double-blind, placebo-controlled, phase III trial 1:1 randomizing early breast cancer patients with ER+ disease to receive either atorvastatin 80 mg daily (arm A) or placebo (arm B) for two years in addition to standard (neo)adjuvant therapy (Figure 1). The trial is conducted according to Good Clinical Practice (GCP) guidelines. Patients receiving cholesterol-lowering medication at the time of eligibility assessment can be included in the observation cohort to evaluate the prognosis of continued statin use on breast cancer diagnosis. The participating subsites are responsible for the inclusion of patients and their follow-up.

Inclusion and Exclusion

Pre- or postmenopausal women with primary, ER+ breast cancer, stage I–III, who are candidates for (neo)adjuvant systemic therapy or are ≤3 years into their adjuvant endocrine therapy are eligible for inclusion. Inclusion and exclusion criteria are shown in Figure 2.

Randomization

Random 1:1 assignment using permuted blocks stratified by institution is performed centrally using the DBCG's Clinical Data Management System. Randomization is based on stratification for the trial site and clinical setting (neoadjuvant/adjuvant early entry/adjuvant late entry – the latter enabling enrolment during the last two years of endocrine treatment). The randomization code is stored at the DBCG data center. In an acute situation for a participating patient, where demasking of the randomization code is required, this is facilitated through the trial sponsor site, Aarhus University Hospital, upon requirement from one of the principal investigators.

Early versus Late Trial Entry

Patients can be included at several stages during their (neo)adjuvant treatment. Patients that receive neoadjuvant treatment can be included in an *early neoadjuvant* cohort (during the first half of neoadjuvant treatment), *early adjuvant* cohort (from the second part of neoadjuvant treatment until three months into endocrine treatment), or in a late adjuvant cohort (after three months until three years) (Figure 1). Patients receiving adjuvant chemotherapy can be included in the early adjuvant cohort (during the first part of adjuvant chemotherapy), and in the late adjuvant cohort (during the second part of chemotherapy until three years of endocrine therapy) (Figure 1). Patients not allocated to chemotherapy, but adjuvant endocrine therapy alone, are eligible in the early adjuvant cohort (during the initial three months of endocrine treatment) or in the late adjuvant cohort (after three months until three years of endocrine treatment) (Figure 1).

Sample Size

Sample size calculations were based on a 10-year IDFS of 80% (annual hazard rate of 0.0223). A sufficient number of patients is sought to provide 80% power (alpha=0.05) to detect a 25% reduction in the hazard of an IDFS event (HR=0.75). A total of 379 events during follow-up are required. With an estimated 5% drop-out at five years (annual hazard rate 0.0103), this is estimated to be achieved by a total recruitment of 3360 participants over three years and an additional five years of follow-up (median follow-up of 6.5 years). The latest status from 01.11.2024 showed that 1293 patients have been included in the MASTER trial: 999 patients in the randomized cohort and 294 patients in the observational cohort.

Objectives and Endpoints

The primary objective is to compare invasive disease-free survival (IDFS) rates in patients randomized to standard (neo)adjuvant therapy plus atorvastatin with the rates in patients randomized to standard (neo)adjuvant therapy plus placebo for the following events: Ipsilateral invasive breast tumor recurrence (invasive breast cancer involving the same breast parenchyma as the original primary); Regional invasive breast cancer recurrence (invasive breast cancer in the axilla, regional lymph nodes, chest wall, and

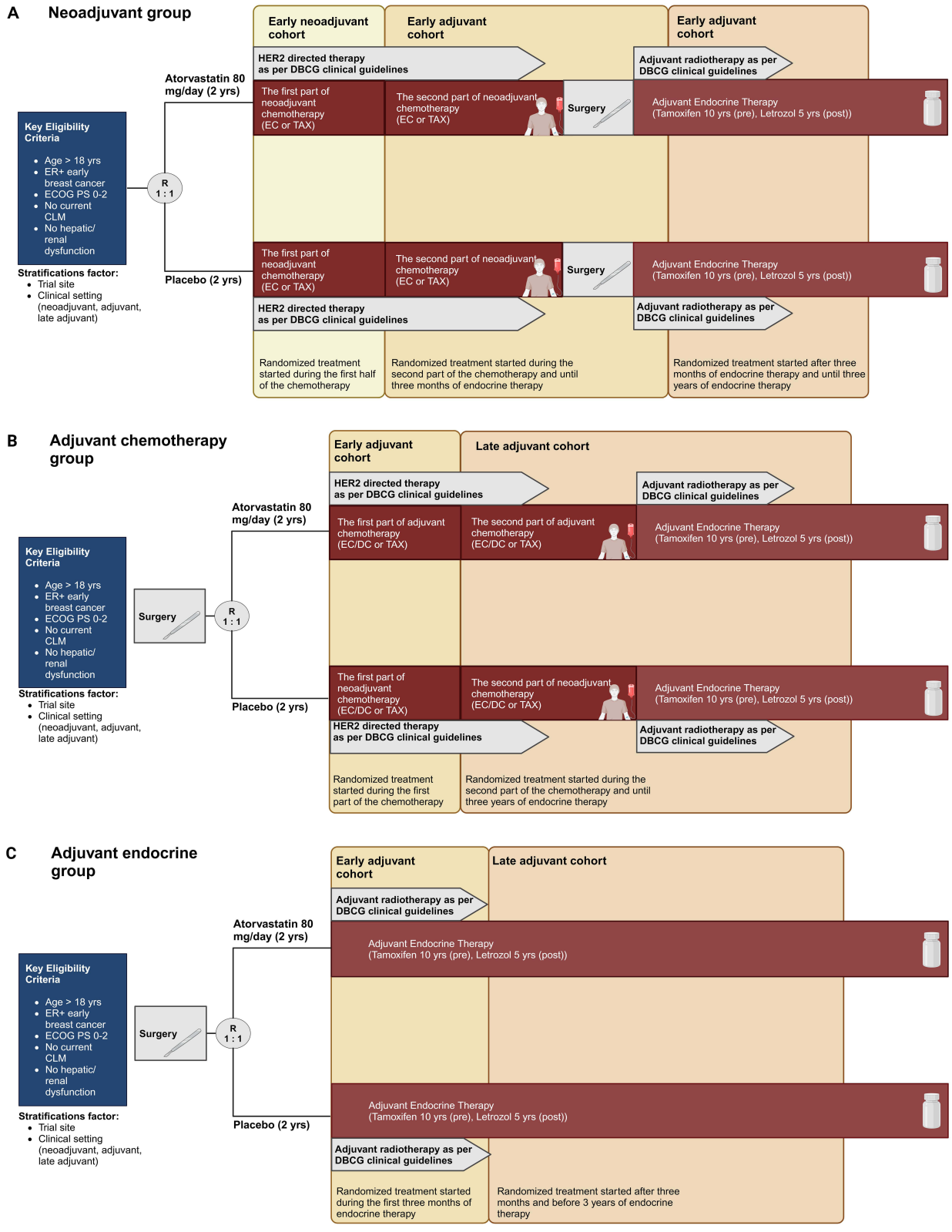

Figure 1 Study design. The figure illustrates the study design with randomization in either early or late cohorts regarding the treatment group the participant belongs to (**A**) neoadjuvant, (**B**) adjuvant with chemotherapy, and (**C**) adjuvant with only endocrine therapy). The observation group follows the same standard treatment as the groups mentioned above and continues their statin treatment as before the cancer diagnosis.
Abbreviations: EC, Epirubicin and cyclophosphamide, TAX, Taxol, DC, Docetaxel and cyclophosphamide.

https://doi.org/10.2147/CLEP.S509873

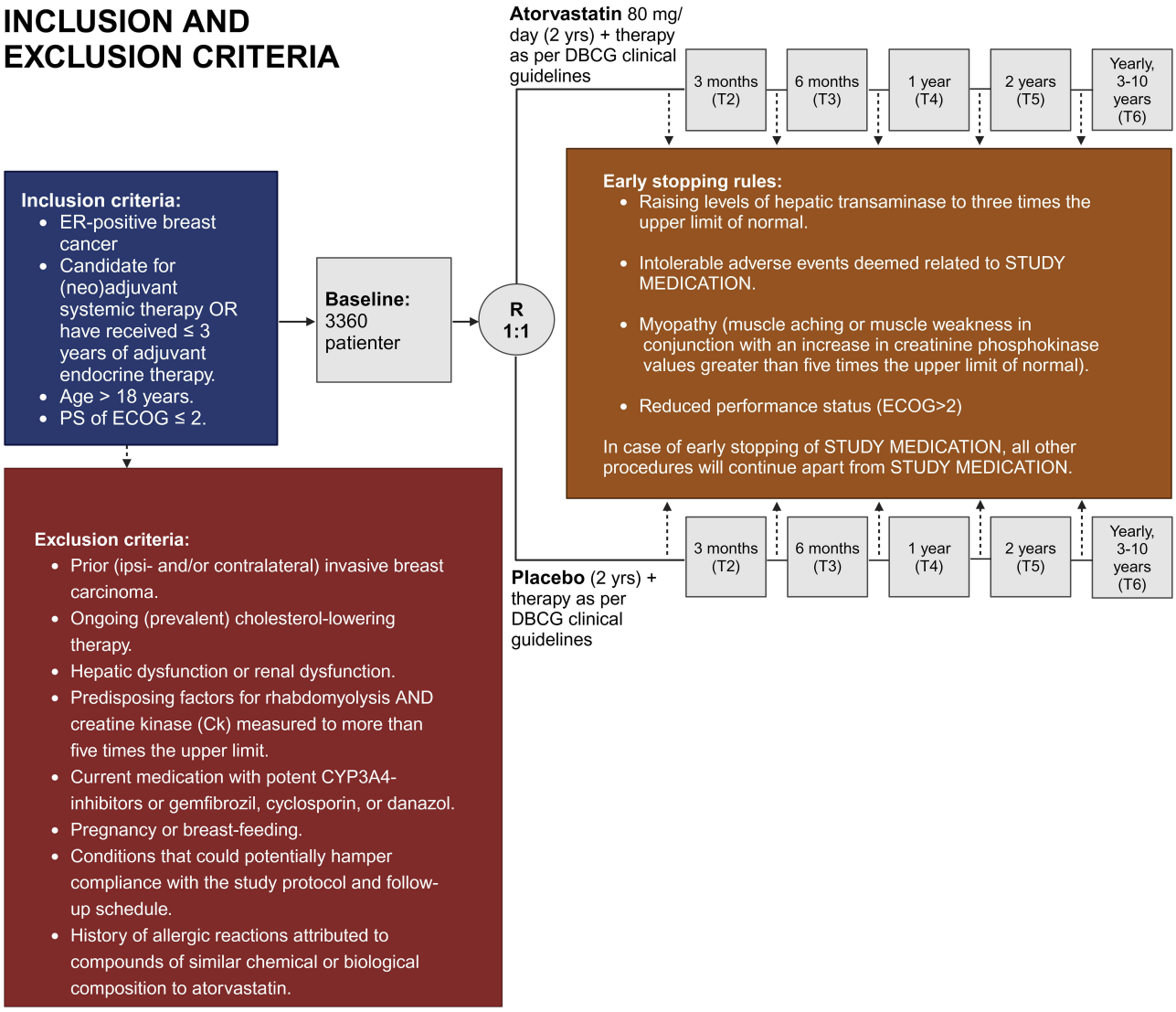

Figure 2 Inclusion and exclusion criteria and stopping rules.
Abbreviation: T, Time of follow-up.

skin of the ipsilateral breast); Distant recurrence (metastatic disease-breast cancer that has either been biopsy confirmed or clinically diagnosed as recurrent invasive breast cancer); Death attributable to any cause (including breast cancer, non-breast cancer, or unknown cause); Contralateral invasive breast cancer; Second primary non-invasive cancer. Endpoints are defined by the STEEP system.[16]

The translational objectives include molecular biological predictors of (neo)adjuvant atorvastatin in breast cancer patients based on tumor tissue and circulating markers of response to atorvastatin correlated with the clinical response.

Eligible patients who are already taking cholesterol-lowering medication (ie, prevalent statin users) are offered participation in an observational non-randomized cohort among which prospective data and biological samples are collected similarly to the randomized cohort. The objective of the observational cohort is to evaluate breast cancer prognosis among prevalent statin users who continue treatment after breast cancer diagnosis, to better emulate the anticipated real-world scenario surrounding statin use as a breast cancer adjuvant therapy.

Study Medication

All randomized patients receive study medication (atorvastatin 80 mg daily or placebo) for two years. Among the available statins on the market, atorvastatin was selected given its superior bioavailability, strong affinity to HMGCR, and safety profile

https://doi.org/10.2147/CLEP.S509873

even at high dosages with the 80 mg dosing being standard dosing, ie, as cardio protection following a myocardial infarction due to atherosclerosis. Study medication is discontinued if 1) there are any safety concerns, 2) cholesterol-lowering therapy becomes clinically indicated, 3) discontinuation is requested by the participant and/or her treating physician, and 4) in case of an incident breast cancer event (any new invasive breast cancer, including local/regional, contralateral or distant recurrence). Atorvastatin is a well-documented drug prescribed for continuous use over several years, and the appearance of other incident illnesses aside from the aforementioned breast cancer events does not indicate discontinuation of atorvastatin.

Patient Reported Outcomes

Quality of life captured through patient-reported outcomes (PRO) is collected through a REDCap questionnaire based on PRO-Common Terminology Criteria for Adverse Events (CTCAE), version 1.0, (Danish), for which a separate link is sent via Email to the patient at each of the time points stated in Table 1. Patient replies are gathered in a REDCap database hosted at Aarhus University, Denmark. Patients are informed that the PRO data are collected for evaluation upon completion of study enrolment, which implies that the reported outcomes are not evaluated during the trial. Thus, all potential adverse events are to be reported to their treating physician, who will decide on potential further action.

Table 1 Follow-Up During the Trial

Required Investigations	Baseline (T1)	3 Months (± 14 days) (T2)	6 Months (± 14 days) (T3)	1 Year (± 14 days) (T4)	2 Years (± 14 days) (T5)	Yearly (± 28 days) 3–10 (T6)
Inclusion – exclusion criteria (DBCG)	X					
Informed consent	X					
Randomization (DBCG)	X					
CRF MASTER flow (DBCG)	X	X[c]	X[c,d]	X[c,d]	X[c,d]	X[d]
CRF MASTER AE (DBCG)	X	X[c,d]	X[c]	X[c,d]	X[c]	
Study medication Start/ Adherence (DBCG) *(Randomized group only)*	X	X	X	X	X	
Patient Reported Outcome (RedCap)	X	X	X	X	X	X
Pathological response *(Neoadjuvant group only)*			X			
HCG[e] (serum or urine) *(Randomized group only)*	X					
Hepatic (ALAT) function *(Only at baseline for the observational cohort)*	X[b]	X		X	X	
Renal (creatinine) function	X[b]					
Creatinine kinase[a] *(Randomized group only)*	(X)					
Translational blood samples	X		(X *neoadjuvant cohort patients*)	X	X	
Translational tumor tissue samples from existing tissue	X		(X *neoadjuvant cohort patients*)			

Notes: [a]Predisposing factors for rhabdomyolysis, including hypothyroidism, reduced renal function, any muscle- or liver disease, or excessive alcohol consumption above 14 drinks/week AND creatine kinase (CK) measured to more than five times the upper limit (CK only measured in case of predisposing factors). [b]Blood samples are allowed to be taken up to 28 days before T1. [c]Either done by phone interview or attendance at the clinic. [d]Data collected from the patient file. [e]Only fertile women.

Translational Studies

Translational research is performed in cooperation with the clinical-laboratory units at participating trial sites. Blood samples of 30mL are drawn at three time points: at baseline, one and two years after inclusion (Table 1). Frozen blood samples are stored in a designated research biobank at the Bio and Genome Bank Denmark (https://www.regioner.dk/rbgben). Serum, plasma, and whole blood collected at baseline and during follow-up will be analyzed for statin-associated prognostic and treatment-predictive markers (*eg*, LDL, HDL, cholesterol, triglycerides, Apo-A, Apo-B, 27HC, inflammatory markers, and various germline SNPs related to statin disposition). Tumor samples are stored according to clinical routines at the Departments of Pathology affiliated with the trial sites, and upon completion of trial enrollment, triplet sample cores of 1 mm in diameter are arranged in a tissue microarray and stored in a research biobank at the DBCG for future research (RH-2015-122, I-Suite nr: 03903). Tumor tissue sampled at baseline (for neoadjuvant patients both at diagnosis and surgery) will be analyzed for biomarkers of prognosis and treatment prediction, ie, HMGCR, LDL-R expression along with HMGCR down-stream products in the mevalonate pathway (eg, FPP, GGPP, and phosphorylated-ERK, the latter indicating an activated Ras pathway).

Data Management

All data are registered using an electronic Case Report Form (eCRF). Monitoring of data is performed according to Good Clinical Practice (GCP) guidelines. In the eCRF, data on age, completed surgery, tumor- and lymph node characteristics, as well as neoadjuvant and adjuvant therapy and potential side effects to study medication are collected. Further registration of clinical status (potential recurrence, vital status) is performed by the treating physician at follow-up. Data is managed by the DBCG central office at Rigshospitalet, Copenhagen, Denmark (https://www.dbcg.dk/about-dbcg/).

Data on comorbidity, cardiac-death-free interval, and overall survival by any cause will be collected through the Danish Civil Registration System and the Death Registry.

Safety

Renal function (plasma creatinine) and hepatic function (alanine-aminotransferase; ALAT) are measured at baseline. Hepatic function is also analyzed before the first clinical visit at three months after initiation of study medication and is also measured again after 12 and 24 months. In case of renal or hepatic dysfunction above the described limits measured in blood samples during the monitoring period, extended monitoring will be initiated and continued, enabling sufficient information for potential treatment adjustments. Adverse events are recorded in the MASTER trial eCRF in the DBCG database and monitored continuously during active treatment. Their frequencies are reported to the sponsor equal to the coordinating national trial site, Department of Oncology, Aarhus University Hospital, Denmark (https://www.en.auh.dk/). Toxic effects are categorized using a modified version of the NCI CTCAE, Version 5.0.

Follow-Up and Statistical Methods

The patients will receive two years of treatment with study medication and will be followed for 10 years from the randomization date (Table 1). The data are expected to be ready for primary analysis five years after inclusion (with a median follow-up of 6.5 years). Patients will be followed in the clinic according to the current clinical guidelines in Denmark. The data will be stored for 25 years after the termination of the study, that is, the inclusion period and 10 years of follow-up. A recurrence will be defined as any invasive breast cancer recurrence irrespective of localization.

The primary analysis will be an unadjusted intention-to-treat – analysis, using the stratification parameters included in the randomization. Missing data will be updated from clinical records if the data are available, and otherwise from relevant registries.

The exploratory subgroup analysis will be an adjusted per-protocol analysis, with the investigation of a heterogeneous effect according to a) neoadjuvant vs early vs late entry cohorts, b) endocrine treatment alone vs chemotherapy (± anti-epidermal growth factor receptor 2; anti-HER2) + endocrine treatment, c) pre- vs postmenopausal status.

To include the observational cohort, a multivariable analysis will be conducted so it can be compared with the randomized cohort. We will look at the cumulative incidence to assess competing risk factors for the defined endpoints.

Overall Safety

Overall safety will be examined and reported as a Serious Adverse Event (SAE) and unexpected serious and suspected adverse reactions (SUSARs). Both SAE and SUSARs are reported and analyzed continuously. All SAEs are reported from the start of the study medication until 30 days after termination of the study medication. SAEs are reported by the investigators from the subsites to the sponsor site (The Department of Oncology, Aarhus University Hospital) within 24 hours after the investigator becomes aware of the event.

SUSARs are reported by the sponsor to the authorities, the Medical Products Agency, and the ethics committee following the relevant legal requirements and ICH's guidelines for GCP. SUSARs that are deadly or life-threatening are to be reported as fast as possible and no later than 7 days after the sponsor becomes aware of the event. All other SUSARs must be reported within 15 days to the Medical Product Agency.

Discussion

Drug repurposing – that is, identifying and proving new applications for already approved drugs – is on the horizon given the challenges of bringing novel drugs to the market.[17] The advantages of repurposing drugs are both financial, timewise, and in terms of patient safety. Statins are drugs developed for and currently used in the cardio-vascular setting, although now being tested for their repurposing capacity in oncology. Consistent evidence from retrospectively analyzed data shows a potential beneficial role of statins in early breast cancer,[2,18,19] although this has yet to be proven in a randomized trial setting. Multiple clinical trials listed at ClinicalTrials.gov (N=52, date 22.11.2023) are investigating the associations between statins and breast cancer. However, the MASTER trial is the only listed phase III, randomized trial, thus potentially being able to prove a novel clinical indication for statin use. The biological rationale for cholesterol-lowering statins, as cancer drugs, is evident through actions on several molecular pathways, ie, the mevalonate pathway associated with isoprenoids such as GGPP and FPP[20] and the Hippo signaling pathway for which YAP/TAZ are effectors.[21,22] Further, the deprivation of tumors by lowering cholesterol is another tentative mechanism of action given the need for cholesterol for membrane formation in highly proliferative cancer cells.[23] These are essential biological factors for cancer growth irrespective of cancer type. However, statins have additional mechanisms of action specifically for ER+ breast cancer. Cholesterol is fundamental for producing steroid hormones, such as estradiol, which is important for the growth of ER+ breast cancer.[23] In alignment with LDL-C, the cholesterol metabolite 27HC is lowered by statins,[13] and the stimulation of the ER in breast cancer is consequently hampered (shown in mice).[24] These additional biological modes of action in ER+ breast cancer and the supporting clinical evidence for ER+ disease[8] prompted us to design the MASTER trial, particularly for ER+ breast cancer.

Breast cancer is the most frequently diagnosed cancer among women in countries with a high development index.[25] As such, a proven impact of statins on breast cancer outcomes would have important public health and clinical implications. Based on the aforementioned results from the BIG 1–98 trial, the addition of statins in the adjuvant setting would reduce the breast cancer recurrence hazard for ER+ patients by about 24%, at least during the first eight years after completion of adjuvant therapy.[8] Further, the MASTER trial will determine which patients are susceptible to treatment-associated comorbidities, which is valuable knowledge that can be incorporated into a risk stratification model and ultimately into clinical guidelines. In addition to the expected clinical achievements, the translational studies associated with the MASTER trial will provide important knowledge to the field of endocrine treatment, lipid metabolism, and breast cancer. Taken together, the MASTER trial research activities will be instrumental in understanding the interplay between statin therapy and breast cancer progression and consequently impact future clinical guidelines for improved clinical outcomes among breast cancer patients.

The actual trial status reflects some limitations regarding the inclusion of participants being more challenging than anticipated. Possible explanations point towards logistical constraints may impact the feasibility and scalability of implementing the study: ie, limited time in daily clinical work for trial screening and information. The mitigation strategies to address these challenges are considers generic for clinical trial inclusion, and involves allocated trial personal for screening procedures, regular follow-up with information to trial sites and investigators in terms of actual accrual, in addition to investigator meetings allowing sharing of successful recruitment strategies. Being an academic

trial, the financial trial support is limited to achieved external funding and in-kind support from participating trial sites. Importantly, the financial challenges regarding the production and labeling of the study medication, especially the placebo, are relevant to consider in academic, pharmaceutical trials.

As for patients´ motivation to participate, worries about additional treatment side effects and trial-related procedures can withhold an interest in trial participation. Upon trial inclusion, participant dropouts and non-adherence can potentially influence on the trial's outcomes. We will include a sensitivity analysis that assesses the impact of missing data and have acknowledged these factors as potential sources of bias.

The strength of the study is the performance within a cooperative group such as the DBCG, and the participation of most of the breast cancer treating subsites (10/12) in Denmark. Furthermore, the Danish population is covered by the public health system, which ensures all patients can receive standard cancer treatment. The study therefore reflects the Danish population of women with breast cancer and the treatment provided. In terms of generalizability, we acknowledge that our findings beyond Denmark may require external validation in different populations and healthcare settings.

Conclusion

The MASTER trial is a rigorously designed, randomized, placebo-controlled, phase III study aimed at evaluating the efficacy of atorvastatin in reducing breast cancer recurrence among patients with early-stage, estrogen receptor-positive breast cancer. By leveraging extensive preclinical and observational evidence, this trial has the potential to establish statins as a well-tolerated, cost-effective adjunct to standard (neo)adjuvant therapy. If the trial demonstrates a protective effect of statins on invasive disease-free survival, it could significantly impact clinical practice by expanding treatment options for breast cancer patients. Furthermore, secondary and translational endpoints will provide valuable insights into the broader implications of statin use, including effects on patient-reported outcomes, cardiovascular safety, and biomarker-driven responses. The findings from the MASTER trial may ultimately support the integration of statins into routine oncologic care, offering a widely available and affordable intervention to improve breast cancer outcomes.

Abbreviations

ALAT, Alanine-aminotransferase; Anti-HER2, Anti-epidermal growth factor receptor 2; Apo-A, Apolipoprotein a; Apo-B, Apolipoprotein B; BIG 1-98, Breast International Group 1-98 trial; CTCAE, Criteria for Adverse Events; DBCG, Danish breast cancer Group; DC, Docetaxel and cyclophosphamide; EC, Epirubicin and cyclophosphamide; ER+, Estrogen receptor-positive; FPP, Farnesyl pyrophosphate; GCP, Good Clinical Practice; GGPP, Geranylgeranyl pyrophosphate; 27HC, 27-hydroxycholesterol; HDL, High-density lipoprotein; HMCGR, Hydroxymethylglutaryl-coenzyme A-reductase; IDFS, Invasive disease-free survival; LDL-C, Low-density lipoprotein cholesterol; PRO, Patient-reported outcome; SAE, Serious Adverse Event; SUSARs, Unexpected serious and suspected adverse reactions; TAX, Taxol.

Data Sharing Statement

All clinical data are managed by the Danish Breast Cancer Group, and the data from the PRO-CTCAE questionnaires are registered and stored in the REDCap database. Data access is only granted once the study is terminated and reported. The Trial Committee receives applications by third parties to use data or material collected during this trial and confirms data extraction with the Board of the Danish Breast Cancer Group.

Ethics Approval and Consent to Participate

This trial was approved by the Ethics Committee at Central Region, Denmark, and the Medical Product Agency, Denmark, with registration number EudraCT nr.: 2019-002508-42. Patients are solemnly randomized after written informed consent. The trial complies with the Declaration of Helsinki.

Generative AI and AI-Assisted Technologies

The authors used the free version of Grammarly (v1.2.114.1528) to check the spelling and grammar of this paper.

Acknowledgments

We are greatly thankful to all investigators and research nurses at participating sites within the Danish Breast Cancer Group for their engagement in preparing and initiating the trial.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work is supported by a clinical investigator research grant from the Novo Nordisk Foundation (# NNF18OC0034482).

Disclosure

Dr. Maj-Britt Jensen declares that she has received meeting expenses and personal fees for serving on the Novartis advisory Board. The remaining authors declare that they have no competing interests in this work.

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