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Ribociclib–Letrozole Combination as an Alternative for Neoadjuvant Chemotherapy in Selected Postmenopausal Patients with Luminal Breast Cancer (BOOG 2017-01)

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ABSTRACT

Purpose: In hormone receptor–positive, HER2-negative, early-stage breast cancer, cyclin-dependent kinase 4 and 6 inhibition combined with endocrine therapy could represent a less toxic alternative to neoadjuvant chemotherapy (CT). The NEOLBC trial studied whether neoadjuvant ribociclib plus letrozole (RL) results in a doubling of complete cell-cycle arrest (CCCA; Ki67 <1% on IHC) compared with CT in the surgical specimen in luminal breast cancer.

Patients and Methods: This randomized phase II trial tailored neoadjuvant therapy in postmenopausal patients with early, luminal, HER2-negative, stage II/III breast cancer based on the percentage of Ki67-positive cancer cells after 2 weeks of letrozole. Patients with a Ki67 ≥1% were randomized between RL and standard CT. Secondary endpoints included pathologic response and toxicity.

Results: Of 161 registered patients, 70 were randomized, and 66 started the allocated treatment. The CCCA in the surgical specimen was similar for both groups: 35.3% in the RL group and 31.3% in the CT group ($P = 0.73$). The response according to Miller and Payne was not significantly different between the two groups, nor was the pathologic complete response rate. Overall toxicity was observed more often in the CT group. In the RL group, eight patients discontinued treatment due to toxicity, and in the CT group, 10 patients discontinued treatment.

Conclusions: Although the primary endpoint was not met, the NEOLBC trial (NCT03283384) showed a similar CCCA and pathologic response for RL and CT with less toxicity. Therefore, RL as an alternative to neoadjuvant CT merits further investigation.

Introduction

Breast cancer is the most common cancer in women worldwide; with around 70% of all invasive breast carcinomas being hormone receptor (HR)–positive, HER2-negative (HR+/HER2−), this subtype accounts for most breast cancer–related deaths (1–3).

Neoadjuvant systemic therapy is frequently used in patients with HR+/HER2− stage II/III breast cancer although it is still not known precisely for which patients chemotherapy (CT) can be omitted and other (endocrine-based) therapies will suffice as substantial heterogeneity exists in patients' therapy response (4–7). Although CT is currently the first choice for the majority of patients with HR+/HER2− breast cancer receiving neoadjuvant treatment, it rarely results in a pathologic complete response (pCR), especially in tumors expressing a low percentage of the proliferation marker Ki67-positive cells (8–11). Alternatively, endocrine therapy is less toxic and leads to the same number of objective responses and breast-conserving surgeries as compared with CT in postmenopausal women with HR+ breast cancer (12). Currently, guidelines support the use of endocrine therapy as a reasonable option for older, fragile patients and for postmenopausal patients with strong estrogen receptor (ER)–positive tumors to increase treatment options (13–16). Cyclin-dependent kinase 4 and 6 inhibition (CDK4/6i) in combination with endocrine therapy is an interesting alternative to CT in HR+/HER2− early-stage breast cancer as numerous studies have shown CDK4/6i in combination with endocrine therapy to be superior to endocrine therapy alone in both early and advanced breast cancer (17–21).

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Translational Relevance

For patients with hormone receptor–positive, HER2-negative, stage II/III breast cancer, it is unknown for which patients chemotherapy (CT) can be omitted and replaced by endocrine-based therapies. Our phase II NEOLBC (tailoring neoadjuvant therapy in hormone receptor–positive, HER2-negative, luminal breast cancer) study demonstrated a similar complete cell-cycle arrest (defined as Ki67 <1% on IHC) and pathologic response at surgery in postmenopausal patients with luminal breast cancer using neoadjuvant ribociclib–letrozole (RL) combination compared with neoadjuvant CT. In addition, less toxicity was observed in the RL group. These data support the use of the RL combination as an interesting alternative to CT in selected patients with early luminal breast cancer. Phase III investigation is warranted.

The neoadjuvant setting is ideal to use as a window of opportunity to better select the most suitable therapy for each individual patient. Ki67 response to short-term preoperative endocrine therapy is known to be an important biomarker for sensitivity to endocrine therapy (6, 7, 22–24). NEOLBC (NCT03283384) is a randomized phase II trial that tailored neoadjuvant therapy in postmenopausal patients with early, luminal [ER >50%, progesterone receptor (PR) any], HER2-negative, stage II/III breast cancer based on the percentage of Ki67-positive cancer cells after 2 weeks of letrozole. Patients with a Ki67 <1% after 2 weeks were advised to continue treatment with letrozole alone outside the study. Patients with a Ki67 ≥1% after 2 weeks were randomized between ribociclib plus letrozole (RL) and CT [dose-dense AC-T regimen (doxorubicin and cyclophosphamide followed by paclitaxel or docetaxel)]. The primary aim was to improve the number of patients with a complete cell-cycle arrest (CCCA; Ki67 <1% on IHC) in the surgical specimen, aiming for a doubling in the RL group (70% of patients) compared with the CT group (35% of patients). Secondary endpoints included pathologic response and toxicity (25).

Patients and Methods

Study population

In this randomized controlled study, postmenopausal patients with histologically proven HR-positive (ER ≥ 50%, PR any), HER2-negative, stage II/III early-stage breast cancer, amenable to receive neoadjuvant dose-dense AC-T (doxorubicin plus cyclophosphamide followed by paclitaxel or docetaxel) CT, were included. Furthermore, patients had to have measurable disease, a World Health Organization performance status of 0 to 2, and adequate bone marrow, liver, and renal function. Patients had to give written informed consent. The study (NCT03283384) was conducted in accordance with the Declaration of Helsinki and approved by the Medical Ethical Committee of the Leiden University Medical Center (LUMC). This study was conducted in adherence to the CONSORT guidelines.

Study design and drugs

Patients started with 2 weeks of letrozole, followed by an additional tumor biopsy. These biopsies were processed locally into a formalin-fixed, paraffin-embedded sample, after which the sample was sent to the Department of Pathology of the LUMC for central determination of the Ki67 percentage on IHC. Patients with a Ki67 <1% were advised to continue neoadjuvant letrozole, whereas patients with a Ki67 ≥1% were randomized between neoadjuvant dose-dense AC-T CT (four cycles doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 2 weeks plus G-CSF, followed by four cycles docetaxel 100 mg/m^2 every 3 weeks or 12 cycles paclitaxel 80 mg/m^2 weekly) or neoadjuvant letrozole (2.5 mg daily) plus ribociclib (600 mg/day on days 1–21 of a 4-week cycle) for 20 weeks (five cycles). Until definitive neoadjuvant treatment started, patients continued letrozole (for a maximum of 6 weeks). Patients receiving CT were scheduled to undergo surgery within 6 weeks after completion of CT. Surgery for patients receiving RL was planned directly following treatment (medication was continued until 1–7 days before surgery; **Fig. 1**). If the period between the last ribociclib dose of the fifth cycle and planned surgery was more than 7 days, patients started a new cycle, and surgery could take place at any point in this cycle. Postoperative treatment decisions were not part of the trial and were left to the discretion of the patient and the treating physician.

Randomization

Patients were randomized centrally at the Clinical Research Center of the Department of Surgery of the LUMC by block randomization with various block sizes, stratified by age (<65 vs. ≥65 years) and clinical disease stage (stage II vs. stage III), using the ProMISe system (https://www.msbi.nl/promise/ProMISe.aspx).

Primary and secondary endpoints

The primary endpoint was the difference in CCCA (defined as <1% of tumor cells expressing Ki67 on IHC) in the surgical specimen between patients treated with neoadjuvant RL and CT.

Secondary endpoints included toxicity (all grades and grade III/IV) and the difference in pathologic response [pCR and response according to Miller and Payne (MP)] between the randomized study arms. Although currently the residual cancer burden (RCB) scoring system is often used in the Netherlands, during the NEOLBC trial, the MP scoring system was used frequently. The RCB scoring system might be better in triple-negative breast cancer but is thought to be comparable with the MP scoring system as a prognostic biomarker in HR+ breast cancer (26). Toxicity was recorded by the oncologist or research nurse and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. pCR was defined as the absence of residual invasive cancer within the breast and lymph nodes, excluding isolated tumor cells in the lymph nodes. Histopathology (Ki67 percentage and response according to MP in the breast) was centrally revised by one blinded pathologist (D. Cohen).

Exploratively, the difference in Ki67 percentage from baseline to surgery was determined between the randomized study arms.

Ki67 IHC and quantification

Ki67 staining was performed centrally at the Department of Pathology of the LUMC using the anti-Ki67 antibody (Agilent Technologies, GA626, RRID:AB_2687921) on the automated IHC platform Dako Omnis (GI100) and scored using pathologist-guided imaging analysis (27).

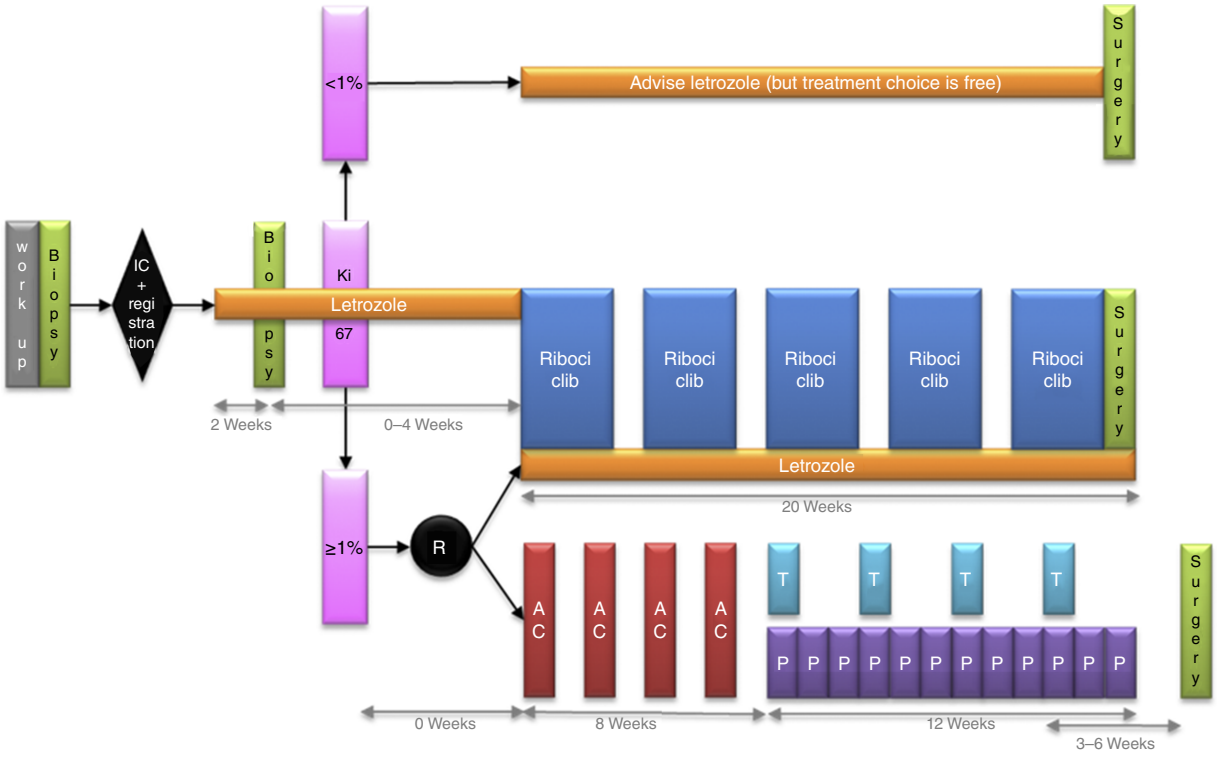

Figure 1.
Study scheme of the NEOLBC study. AC, doxorubicin and cyclophosphamide; IC, informed consent; R, randomization; T, paclitaxel or docetaxel.

Definition of pretreatment luminal A–like and luminal B–like

Pretreatment luminal A–like was defined as Ki67 <15% and PR >20%; all other patients were considered luminal B–like (28).

Statistical analysis

For the primary endpoint, we hypothesized that the use of RL would result in at least a 100% improvement in CCCA at surgery compared with CT (CCCA 70% in the RL arm vs. 35% in the CT arm; ref. 29), and we also hypothesized that under normal circumstances, the number of CCCA in patients receiving CT should be equal to the number of CCCA in patients treated with letrozole only (10). The power calculation (with an 82% power and alpha of 0.05) showed that 31 patients were needed per treatment arm. Therefore, we planned to randomize 35 patients per arm. With the expectation that after 2 weeks of letrozole monotherapy, 50% to 65% of the patients would have a Ki67 of <1% and 35% to 50% would have a Ki67 of ≥1% (29), we planned to include 150 to 200 patients in total.

The intention-to-treat (ITT) analyses included randomized patients who actually started the designated treatment.

Analyses were done using IBM SPSS Statistics for Windows (version 23.0; IBM Corp., RRID:SCR_002865) and R software (version 3.6.3; R Foundation), using χ^2 and Fisher's exact tests and linear-by-linear association.

The study protocol is added as Supplementary Appendix S1.

Data availability

The data generated in this study are not publicly available due to confidentiality (i.e., publicly sharing the data compromises patient consent) but are available from the corresponding author upon reasonable request.

Results

Patient characteristics

From June 2018 to March 2021, 161 patients were registered and screened. Of these 161 patients, 91 were not randomized: 79 due to a Ki67 <1% in the biopsy taken after 2 weeks of letrozole and 12 due to other reasons (**Fig. 2**). The remaining 70 patients were randomized between CT (n = 35) and RL (n = 35). Of these randomized patients, 32 started CT [three refused CT; the median duration of letrozole use until the start of CT was 4.3 weeks (range 2–7.4 weeks)], and 34 started RL (one patient was ineligible due to premenopausal status). The median treatment duration (from registration to surgery) was 28 weeks (range 18–42 weeks) for the CT group and 25 weeks (range 14–32 weeks) for the RL group. Patient characteristics from the randomized patients who actually started treatment were equally distributed between the two groups, except for the PR status (23.5% negative in the RL group vs. 50.0% negative in the CT group; **Table 1**). The representativeness of study participants is shown in Supplementary Table S1.

Efficacy analysis

In the ITT patients, the CCCA in the surgical specimen was similar for both groups: 35.3% in the RL versus 31.3% in the CT group (P = 0.73). The pathologic response according to MP (MP 5 vs. MP 1/2/3/4) was not significantly different between the two groups (11.8% vs. 3.1% reaching MP 5, P = 0.36; ref. 30), as was the

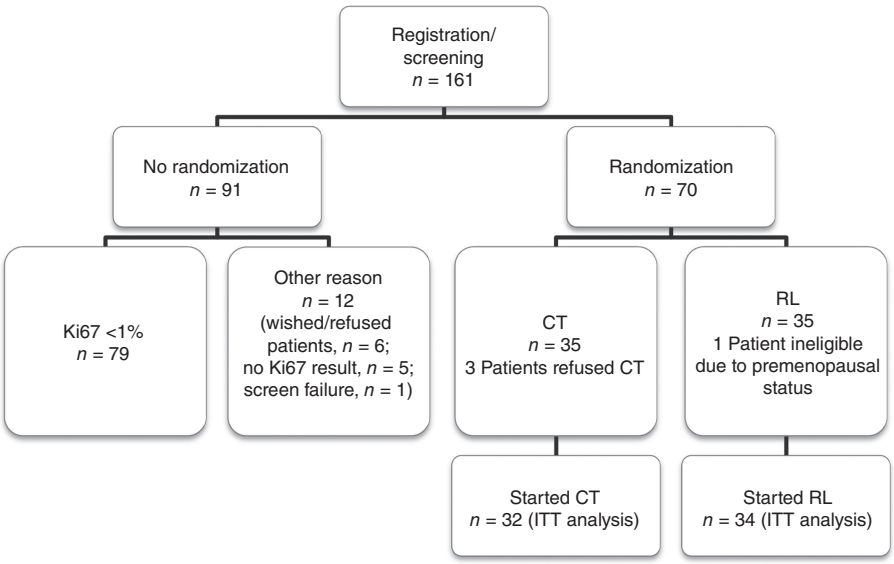

Figure 2.
CONSORT diagram of the NEOLBC study, showing reasons for no randomization, not starting randomized treatment, and the number of patients included in the ITT analysis. IC, informed consent.

pCR rate (8.8% vs. 3.1%, $P = 0.61$) for the RL versus CT group, respectively (**Fig. 3**). Details on pathologic outcome (Ki67 percentage and MP) are shown in Supplementary Table S2.

The analysis of the difference in Ki67% (decline, no change, increase) from baseline to surgery showed a decline in 73.5% versus 50.0%, no change in 17.6% versus 31.3%, and an increase in 8.8% versus 18.8% of patients ($P = 0.06$) for the RL versus CT group, respectively (**Fig. 4**).

Toxicity

The most common grade III/IV adverse event (AE) in the RL group was neutropenia [16 (47.1%) of 34 patients]. The most common grade III/IV AEs in the CT group were hypertension [6 (18.8%) of 32 patients], leukopenia [5 (15.6%)], neutropenia [4 (12.5%)], and febrile neutropenia [2 (6.3%)]. Febrile neutropenia was only observed in the CT group (6.3%) versus no patients (0%) in the RL group (**Table 2**). No grade V toxicity was reported.

Overall toxicity (all grades) was observed more often in the CT group (Supplementary Table S3). The most common AEs in the RL group were neutropenia [32 (94.1%) of 34 patients], fatigue [20 (58.8%)], leukopenia [19 (55.9%)], and creatinine increase [17 (50.0%)]. The most common AEs in the CT group were peripheral sensory neuropathy [28 (87.5%) of 32 patients], anemia [27 (84.4%)], fatigue [23 (71.9%)], alkaline phosphatase increase [22 (68.8%)], leukopenia [21 (65.6%)], reported alopecia [19 (59.4%)], and nausea [17 (53.1%)]. In the RL group, neutropenia was observed in almost all patients [32 (94.1%)], whereas in the CT group, neutropenia was observed in 13 (40.6%) of patients. As expected, no febrile neutropenia was seen in the RL group compared with two (6.3%) patients in the CT group.

In the RL group, 15 out of 34 (44%) patients had a dose reduction during treatment, compared with 22 out of 32 (69%) patients in the CT group. In the RL group, eight patients (23.5%) discontinued treatment early due to toxicity, and in the CT group, 10 patients (31.3%) discontinued treatment. In the RL group, liver toxicity led to a dose reduction in three (8.8%) patients and a delay in the start of a new cycle in three (8.8%) patients.

Discussion

In the NEOLBC trial, we studied whether neoadjuvant CT could be replaced by the potentially less toxic and more effective RL combination in patients with HR+ stage II/III breast cancer. Neoadjuvant therapy was tailored based on the percentage of Ki67-positive cells following a two-week window of letrozole treatment. Although the primary endpoint (a doubling of the number of CCCAs in the RL group vs. the CT group) was not met, we showed a comparable number of CCCAs and pathologic responses at surgery in patients using RL compared with CT in the ITT analysis. Additionally, less toxicity was observed in the RL group. Finally, the change in Ki67 percentage from baseline to surgery showed that a greater proportion of patients in the RL group experienced a decrease, whereas fewer patients exhibited an increase in Ki67 percentage compared with the CT group.

These results are in line with earlier phase II trials with CDK4/6i plus endocrine therapy combination versus CT although these studies had different patient selection and primary endpoints (4, 5, 31). In two studies, patients with clinically high-risk, HR+/HER2− disease were selected using the Prosigna Breast Cancer Prognostic Gene Signature Assay (PAM50 test) and then randomized between CDK4/6i plus letrozole and CT (4, 5). The study endpoints were RCB 0–I rate [NeoPAL study with palbociclib (5)] and low risk of relapse disease according to the PAM50 test [CORALLEEN study with ribociclib (4)]. In both studies, the CDK4/6i plus endocrine therapy arm seemed to have similar efficacy outcomes with less toxicity compared with the CT arm. The final results of the RIGHT Choice trial in pre- and perimenopausal women with locoregionally recurrent or metastatic, clinically aggressive HR+/HER2− disease, not amenable to curative therapy, also support our findings, showing a benefit in progression-free survival and better tolerability for first-line RL versus combination CT (31). Combining these data with the findings from the current trial, a phase III analysis of neoadjuvant CDK4/6i versus CT is recommended for selected patients with luminal breast cancer.

The Ki67 percentage following 2 weeks of endocrine therapy was chosen as a biomarker based on its prediction of residual risk and

Table 1. Baseline patient characteristics of randomized patients who started treatment.

	RL (*n* = 34)	CT (*n* = 32)
Age at registration (median, range)	64 (47–76)	62.5 (47–76)
World Health Organization status		
0	30 (88.2%)	25 (78.1%)
1	4 (11.8%)	7 (21.9%)
cT classification		
cT1	5 (14.7%)	2 (6.3%)
cT2	21 (61.8%)	22 (68.8%)
cT3	7 (20.6%)	7 (21.9%)
cT4	1 (2.9%)	1 (3.1%)
cN classification		
cN0	16 (47.1%)	13 (40.6%)
cN1	15 (44.1%)	13 (40.6%)
cN2	2 (5.9%)	5 (15.6%)
cN3	1 (2.9%)	1 (3.1%)
cStage		
cII	27 (79.4%)	22 (68.8%)
cIII	7 (20.6%)	10 (31.3%)
HR status		
ER+/PR−	8 (23.5%)	16 (50.0%)
ER+/PR+	26 (76.5%)	16 (50.0%)
Tumor type		
Ductal	18 (52.9%)	18 (56.2%)
Lobular	9 (26.5%)	10 (31.3%)
NST	7 (20.6%)	4 (12.5%)
Luminal		
A–like	20 (58.8%)	13 (40.6%)
B–like	14 (41.2%)	19 (59.4%)
Grade (BR)		
I	3 (8.8%)	4 (12.5%)
II	21 (61.8%)	19 (59.4%)
III	9 (26.5%)	7 (21.9%)
Not done	1 (2.9%)	2 (6.3%)
Ki67%		
>1%–10%	22 (64.7%)	22 (68.8%)
≥10%	12 (35.3%)	10 (31.3%)

Luminal A–like is defined as Ki67 <15% and PR >20% [28].
Abbreviations: BR, Bloom–Richardson; NST, no special type.

long-term outcomes in the IMPACT and POETIC trials (22–24, 32–34), besides being inexpensive and easily available. Moreover, a CCCA based on Ki67 ≤2.7% as the primary endpoint in the NeoPalAna trial showed that CDK4/6i (palbociclib), in addition to anastrozole, significantly increased the CCCA rate compared with anastrozole monotherapy in both luminal A and luminal B type breast cancer (29).

Ki67 percentage determination on IHC is subject to debate. Both intra- and interobserver variability exists, among other factors, due to the heterogeneous character of (luminal) breast cancer tissue (27). In this study, we aimed to overcome this by having a single experienced pathologist (D. Cohen) centrally determine the Ki67 percentage in the diagnostic biopsy, as well as in the 2-week biopsy and the surgical specimen. In other trials, Ki67 cutoff points such as 2.7% and 10% have been used (22, 29). The cutoff point for randomization and CCCA in this study was chosen to be <1% to minimize interobserver variation (expert pathologist opinion) and to avoid undertreatment. As a rebound of the Ki67 percentage is known to occur upon washout of the CDK4/6 inhibitor (29), surgery for patients treated with RL was planned directly following neoadjuvant treatment.

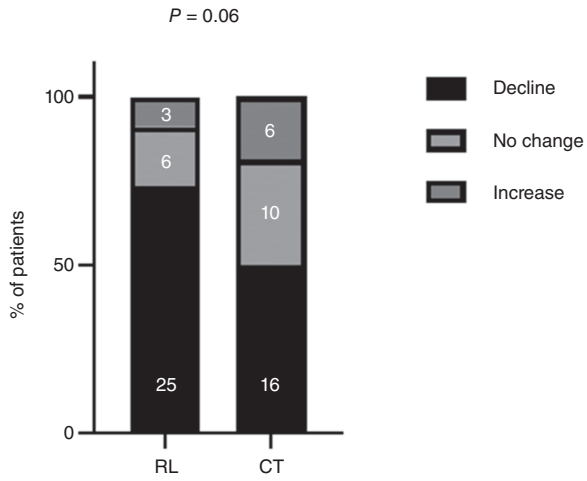

Figure 4.
Difference in Ki67 percentage from baseline to surgery, showing the number (in white) and percentage of patients with a decline, no change, or an increase in Ki67 percentage from baseline to surgery in the two randomized treatment arms.

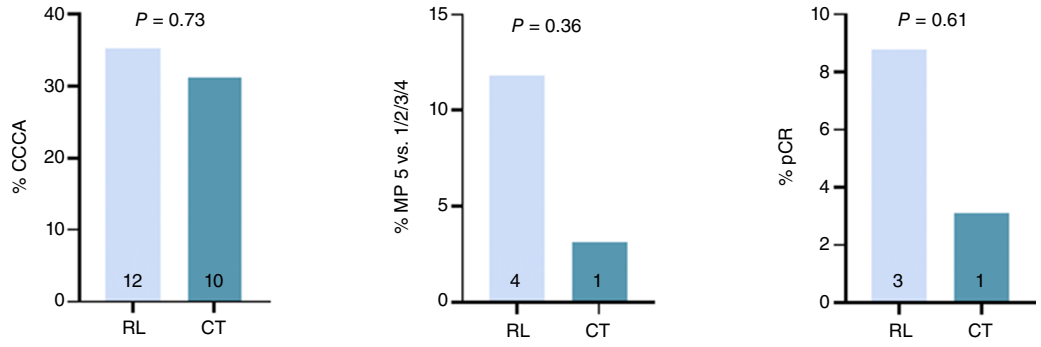

Figure 3.
Pathologic response (CCCA, MP, and pCR) to either neoadjuvant RL or CT.

Table 2. Grade III/IV toxicity.

	RL		CT	
Grade III/IV toxicity	***n***	**%**	***n***	**%**
Neutropenia	16	47.1	4	12.5
Hypertension	6	17.6	6	18.8
Alanine aminotransferase increase	4	11.8	0	0.0
Aspartate aminotransferase increase	2	5.9	0	0.0
Leukopenia	1	2.9	5	15.6
Diarrhea	1	2.9	0	0.0
Hyperglycemia	1	2.9	0	0.0
Other skin disorder	1	2.9	0	0.0
Sinusitis	1	2.9	0	0.0
Urinary tract infection	1	2.9	0	0.0
Febrile neutropenia	0	0.0	2	6.3
Anemia	0	0.0	1	3.1
Hypotension	0	0.0	1	3.1
Platelet count decrease	0	0.0	1	3.1
Tooth infection	0	0.0	1	3.1
Upper respiratory infection	0	0.0	1	3.1
Vascular disorders, other	0	0.0	1	3.1

Grade III/IV side effects were scored according to the Common Terminology Criteria for Adverse Events version 4.03. Each side effect was scored a maximum of once per patient.

The optimal duration of neoadjuvant RL is currently unknown. From trials with neoadjuvant endocrine therapy, we know that 6 months of endocrine therapy gives better pCR rates than 3 months of endocrine therapy (35). In the current trial, the duration was specifically chosen to be similar to the neoadjuvant CT to allow comparison of results. Within our study, eight patients in the RL group received adjuvant CT. However, the benefit of postoperative CT following neoadjuvant RL treatment in cases with, for example, pathologically positive lymph nodes is yet unknown, and additional research is required. Data from the POETIC and ADAPT trials showed that particularly patients with a high Ki67 percentage after endocrine induction therapy had an unfavorable prognosis and may derive benefit from CT or alternative (neo)adjuvant treatment strategies beyond endocrine therapy (7, 22), as studied in the NEOLBC study.

Limitations of our study were the relatively small sample size and some imbalances in baseline characteristics between the two treatment arms (cT1 14.7% vs. 6.3%, cN2 5.9% vs. 15.6%, ER+/PR+ 76.5% vs. 50.0%, and luminal B–like 41.2% vs. 59.4% in the RL vs. the CT group, respectively).

The positive findings from the adjuvant monarchE and NATALEE studies (36–38) have increased interest in the use of neoadjuvant CDK4/6i to select patients who would benefit from them while sparing CT in those with intermediate- and high-risk HR+ breast cancer (39–41). Validation of our findings in a larger patient group is required, and 5-year survival data will follow.

In conclusion, the data from this trial support the use of RL as an interesting alternative to neoadjuvant CT in selected patients with early luminal breast cancer, and therefore, RL as an alternative to neoadjuvant CT merits further investigation.

Authors' Disclosures

M. Cloos-van Balen reports personal fees from Servier and Nordic Farma outside the submitted work. H.M. Oosterkamp reports personal fees from Roche, AstraZeneca, Eli Lilly, MSD, Gilead, Daiichi Sankyo, Novartis, and Pfizer outside the submitted work. A.E. van Leeuwen-Stok reports grants from Novartis during the conduct of the study. S.C. Linn reports grants and nonfinancial support from Novartis during the conduct of the study as well as grants and nonfinancial support from AstraZeneca and Roche and grants from Eurocept Pharmaceuticals and Gilead Sciences outside the submitted work; in addition, S.C. Linn reports patents for PCT/EP2022/073958 and US2024/0404625A1 pending; unrestricted educational fees to the institution (Endeavour Educational Program) and support for travel, accommodation, and daily living from Daiichi Sankyo; and consultancy fees from Agendia and AstraZeneca paid to the institution. J.R. Kroep reports grants from Novartis and Philips during the conduct of the study. No disclosures were reported by the other authors.

Authors' Contributions

A.F. de Groot: Conceptualization, resources, data curation, formal analysis, validation, investigation, visualization, methodology, writing–original draft, project administration, writing–review and editing. **D. Cohen:** Investigation, writing–review and editing. **J.B. Heijns:** Resources, investigation, writing–review and editing. **C.M.P.W. Mandigers:** Resources, investigation, writing–review and editing. **A.J. van de Wouw:** Resources, investigation, writing–review and editing. **M. Cloos-van Balen:** Resources, investigation, writing–review and editing. **J.A. Ropela:** Resources, investigation, writing–review and editing. **H.M. Oosterkamp:** Resources, investigation, writing–review and editing. **M.L. van Bekkum:** Resources, investigation, writing–review and editing. **D. Houtsma:** Resources, investigation, writing–review and editing. **H. Putter:** Conceptualization, formal analysis, methodology, writing–review and editing. **E. Meershoek-Klein Kranenbarg:** Conceptualization, resources, data curation, software, validation, investigation, methodology, writing–original draft, project administration, writing–review and editing. **M. Duijm-de Carpentier:** Conceptualization, resources, data curation, software, validation, investigation, methodology, project administration, writing–review and editing. **K.L. Dijkstra:** Resources, investigation, writing–review and editing. **A.E. van Leeuwen-Stok:** Conceptualization, supervision, funding acquisition, validation, methodology, project administration, writing–review and editing. **S.H. van der Burg:** Writing–review and editing. **G.-J. Liefers:** Conceptualization, resources, methodology, writing–original draft, writing–review and editing. **S.C. Linn:** Conceptualization, resources, supervision, funding acquisition, validation, investigation, methodology, writing–original draft, project administration, writing–review and editing. **J.R. Kroep:** Conceptualization, resources, supervision, funding acquisition, validation, investigation, visualization, methodology, writing–original draft, project administration, writing–review and editing.

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Note

Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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