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The use of ribociclib/letrozole combination as an alternative for neoadjuvant chemotherapy in selected patients with early luminal breast cancer

Introduction

In hormone receptor-positive, HER2-negative early-stage breast cancer (BC), cyclin-dependent kinases 4 and 6 inhibition (CDK4/6i) in combination with endocrine therapy (ET) could represent an alternative to neoadjuvant chemotherapy (NAC).

Materials and methods

NEOLBC is a randomized phase II trial that tailored neoadjuvant therapy in postmenopausal patients with early, luminal (ER >50%, PR any), HER2-negative, stage II/III BC based on the percentage of Ki67 positive cancer cells after a window of opportunity of two weeks letrozole. Patients with a Ki67 ≥1% after two weeks were randomized between ribociclib plus letrozole (RL) and chemotherapy (CT; dose dense doxorubicin and cyclophosphamide 4x followed by 12x weekly paclitaxel or 4x 3-weekly docetaxel (AC-T regimen)). The primary objective was to determine if RL gives a doubling in complete cell cycle arrest (CCCA; Ki67 <1% on IHC) as compared to CT in the surgical specimen (70% vs. 35% of patients, respectively). Secondary endpoints included pathological response, toxicity and ER pathway activity (measured by the OncoSIGNal qPCR test).

Acknowledgments

We are greatly indebted to the patients participating in the NEOLBC trial.

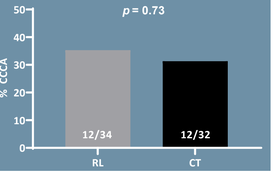
Results

Out of 161 registered patients, 70 patients were randomized and 66 patients started treatment; 34 RL and 32 CT. Patient characteristics were equally distributed between the two groups, except for the PR status (RL 23.5% negative vs. 50.0% negative in the CT group).

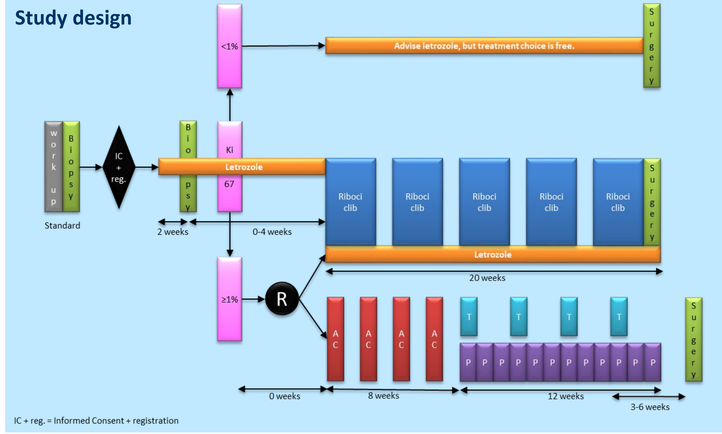
In the intention to treat analysis, the CCCA in the surgical specimen was similar for both groups: 35.3% in the RL vs. 31.3% in the CT group (p = 0.73). The pathological complete response (pCR) in the breast was not significantly different between the two groups (11.8% vs. 3.1%, p = 0.36), nor was the pCR rate in breast plus lymph nodes (8.8% vs. 3.1%, p = 0.61) for the RL vs. CT group, respectively. Although in the RL group more neutropenia was observed (grade III/IV toxicity), no patients with febrile neutropenia were seen in this group compared to two (6.3%) patients in the CT group. In the RL group eight patients (23.5%) discontinued treatment early due to toxicity (two SAE's were observed) vs. 10 patients (31.3%) discontinuing treatment in the CT group (one SAE).

For the ER pathway activity analyses, 30 extra patients on letrozole monotherapy were included. ER pathway activity decreased after two weeks letrozole in all groups and continued to decrease in the letrozole monotherapy group, remained stable in RL group but increased in the CT group at surgery.

An explorative analysis on the difference in Ki67% (decline, no change, increase) from baseline to surgery showed a decline in 73.5% vs. 50.0%, no change in 17.6% vs. 31.3% and an increase in 8.8% vs. 18.8% of patients (p = 0.06) for the RL vs. CT group, respectively.



Study design



IC + reg. = Informed Consent + registration

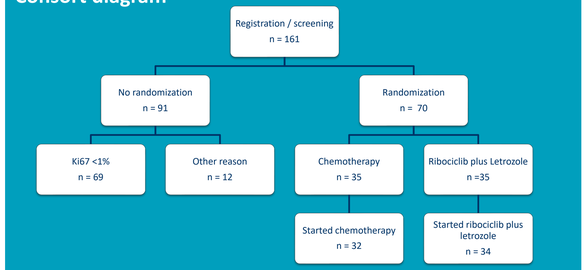
Patient characteristics

	RL (n = 34)	CT (n = 32)
Age (median, range)	64 (47-76)	62.5 (47-76)
WHO status		
0	30	25
1	4	7
T-classification		
T1	5	2
T2	21	22
T3	7	7
T4	1	1
N-classification		
N0	16	13
N1	15	13
N2	2	5
N3	1	1
Stage		
II	27	22
III	7	10
HR status		
ER+/PR-	8	16
ER+/PR+	26	16
Luminal		
A-like	20	13
B-like	14	19
Biopsy grade		
I	3	4
II	21	19
III	9	7
Not done	1	2
Biopsy Ki67%		
<10%	22	22
≥10%	12	10

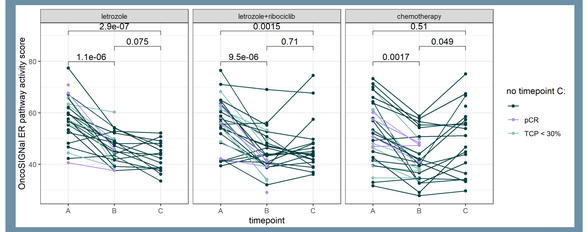
Grade III/IV toxicity

	RL		CT	
	N	%	N	%
Neutrophil count decrease	16	47.1	4	12.5
Hypertension	9	26.5	11	34.4
Alanine aminotransferase increase	4	11.8	0	0.0
White blood cell decrease	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
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

Consort diagram



ER pathway activity



Conclusions

Although the primary endpoint was not met, the NEOLBC trial (NCT03283384) showed a similar (numerically even better) CCCA and pathological response at surgery for RL vs. CT. Therefore, RL as an alternative for NAC merits further investigation.

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