KBCSG 013/NCT01589367

Phase II randomized study of neoadjuvant 'METformin plus letrozole' versus 'placebo plus letrozole' for ERpositive pOstmenopausal bReast cancer

[METEOR Study]

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Neoadjuvant Endocrine therapy

- **Neoadjuvant endocrine therapy** results in a comparable response but lower toxicity compared with neoadjuvant chemotherapy in women with ER-positive breast cancer upto 74%
- Postmenopausal women, aromatase inhibitors shown higher response rates than tamoxifen
- **Metformin**, commonly used anti-diabetic medicine with minimal side effect
  - Directly activate adenosine monophosphate kinase (AMPK), resulting in the downstream **inhibition of mTOR signaling**
  - Decreases in circulating insulin and insulin-like growth factor (IGF) **reduce the activation of the IGF-receptor signaling axis**, resulting in decreases in growth promotion

Semiglazov et al. Cancer 2007
Elermann et al. Ann Oncol 2001
Milneritsch et al. Breast Ca Res Treat 2008
Ellis et al. J Clin Oncol 2008

Anti-tumor effect of Metformin

- Phase II clinical trial of neoadjuvant letrozole with everolimus, an mTOR inhibitor, plus resulted in a better response rate than letrozole alone
- Neoadjuvant metformin shown to lower Ki67 level

Response by Evaluation Type	Treatment Arm: Everolimus + Letrozole (n = 138) No.	Everolimus + Letrozole (n = 138) %	Placebo + Letrozole (n = 132) No.	Placebo + Letrozole (n = 132) %
Clinical palpation				
Complete response	18	13.0	12	9.1
Partial response	76	55.1	66	50.0
No change	34	24.6	39	29.5
Progressive disease	6	4.3	13	9.8
Not available/not assessable	4	2.9	2	1.5
Overall response*	94	68.1	78	59.1
95% CI		60.3 to 75.9		50.7 to 67.5
χ^2 test P		.0616		

Baselga et al. J Clin Oncol 2011

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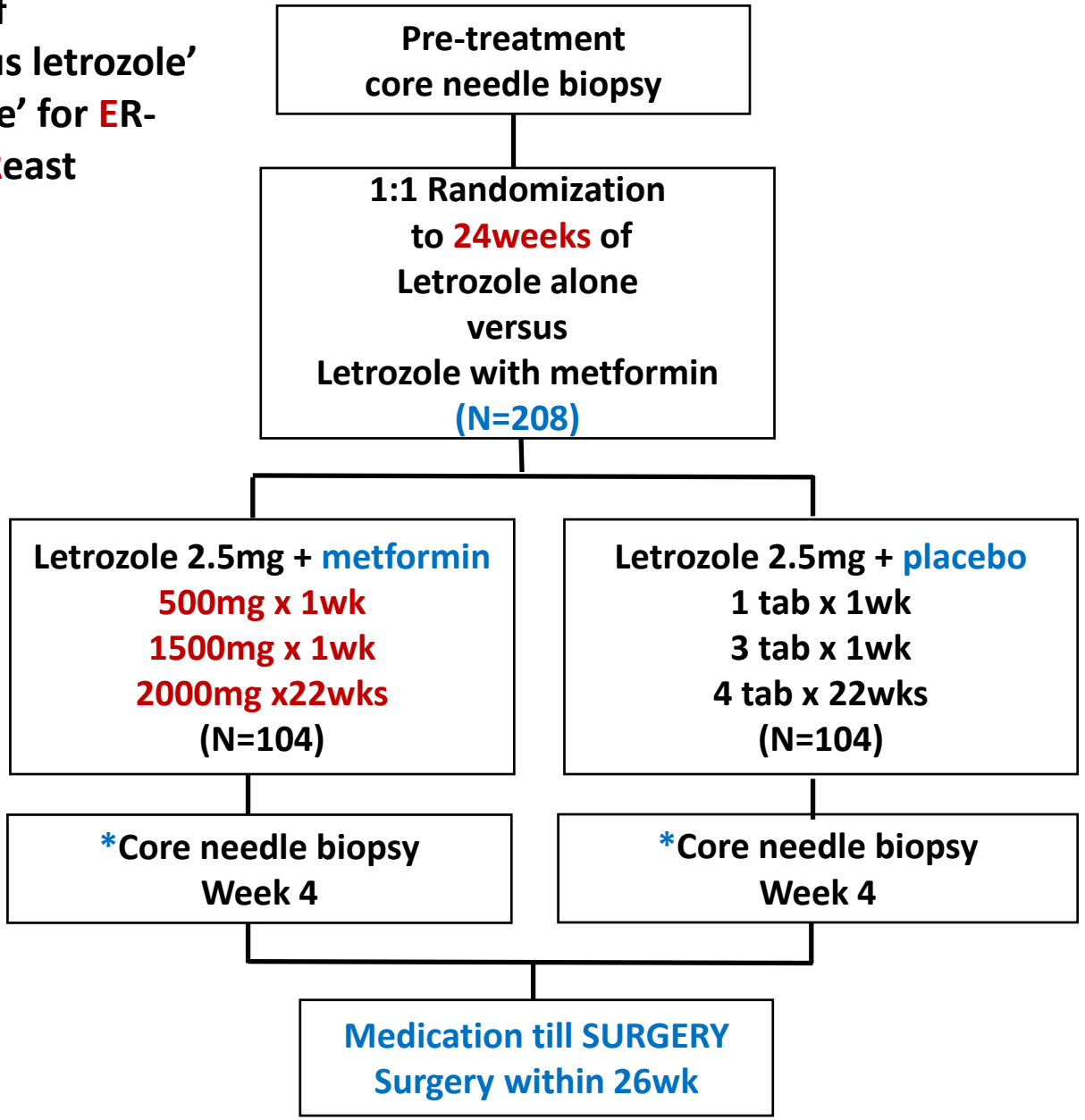

*recommendation

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Enrollment criteria

- **Inclusion criteria**
  - **Estrogen receptor positive** breast cancer
    - **ER-positive ≥10%** nuclear staining by IHC , **Allred score≥3**
  - **Clinically measurable**
  - 20≤ Age <80yr
  - **Postmeno**pausal women
    - Age≥60yr
    - Bilateral oopherectomy
    - **FSH>30 mIU/mL with LMP>1yr**
  - ECOG 0-2
  - Adequate bone marrow/ renal/ liver function

- **Exclusion criteria**
  - **Diabetes**
    - **HbA1c≥6.5 or FBS≥126mg/dL**
  - **Bilateral breast cancer**
  - **Clinically T4 or N3**
  - **Diffuse microcalcification**
  - Male breast cancer
  - Chemotherapy or anti-estrogen therapy within 2yr
  - Contraindication to metformin

Study endpoints

- **Primary endpoint**
  - **Clinical response rate: CR and PR** by ***caliper***

- **Secondary endpoint**
  - pCR (absence of *invasive* carcinoma both breast and axillary LN) rate
  - Breast Conserving Rate
  - Core needle biopsy_ week 4 (recommendation)
    - Ki-67, Biomarker study
  - Percent mammographic density change (mmg, MRI)
  - Toxicity Profile_ neoadjuvant letrozole, metformin

Randomization

- 1:1 randomization with block (2:4) randomization method (SAS 9.2) by CRO
- Double blinded
- Stratification factor _ 12 Centers in Korea

- Target enroll= **208** (104 each group)
  - Response rate difference (ε=p2-p1)=15%
    - Estimated RR of Control(p1)=55%, Metformin(p2)=70%
  - Equal sample size, α=01, power 80%
  - Estimated drop out 10%

Response to Endocrine therapy

Clinical response: CR+PR rate
Only breast tumor mass
d/t difficulty in measurement of ALN by caliper

- **RECIST criteria v1.1**
  - **CR, Complete response**
    - Absence of primary breast/axillary lesion(<10mm) both clinically and imagings
    - pCR_ Absence of residual breast/axillary lesion except for in situ lesion
    - pINV_ cCR but not pCR
  - **PR, Partial response**
    - Decreased longest LD(long diameter) of breast + Longest SD(short diameter) of axillary LN **≥ 30%**
  - **SD**, Stable disease ***Continue medication***
    - Not PR nor PD
  - **PD** _ Operation
    - Increased Longest LD of breast + Longest SD of axillary LN ≥ **20%**
    - OR Absolute increase **≥ 5mm**
    - OR newly identified lesion

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Breast conserving surgery rate

- **Four categories of surgical method**
  1) Candidate for breast conserving surgery
  2) Marginal for breast conservation
  3) Candidate for mastectomy only

- **Breast conserving rate**
  - Proportions of each 3 categories
    - Initially planned
    - Post-treatment (preOp)
    - **Performed surgery**

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Breast density analysis

- **To evaluate value of breast density change**
  - As a predictive surrogate of response to neoadjuvant endocrine therapy, response to metformin treatment

- **Mammography**
  - Percent mammographic density (%)
  - Contralateral (unaffected) breast, Cranial-caudal view

- **Breast MRI**
  - 3D percent breast density (%)
  - Initial MRI/ week 24 MRI

Toxicity Profile & Study discontinuation

- NCI-CTCAE v 4.0
  - National Cancer Institute, Common Terminology Criteria for Adverse Events
  - Both neoadjuvant Letrozole 2.5mg & metformin 500/ 1500/ 2000mg
  - http://ctep.cancer.gov/reporting/ctc.html

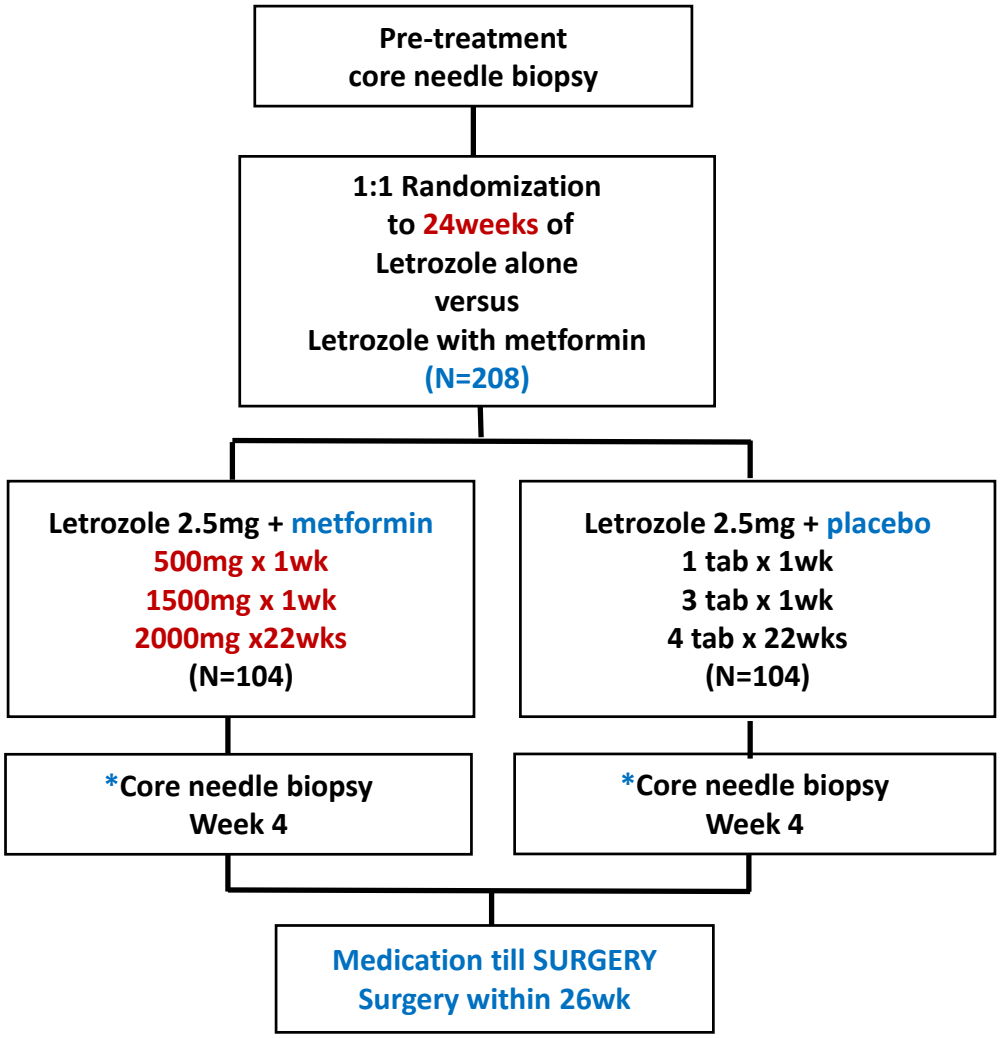
- Study discontinuation
  - **Medication < 252 times(< 18 weeks)**
  - **Disease progression (increase in 20% by caliper)**
  - Life threatening toxicity
  - ECOG 4
  - Major protocol violation
  - **Follow up loss**

Patient Enrollment

- Enrollment from 2012 to 2017
- 12 institutions

- 218 screened
- 203 randomization
  - 100 metformin, 103 placebo
- 40 dropped

- **163 intention to treat**
- **80 metformin, 83 placebo**



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Characteristics of the patients and tumors

		Total (N=203/163)		Metformin (N=103/80)		Placebo (N=100/83)		
		Number	%	Number	%	Number	%	p value
Age-yr		61.99	SD 7.41	62.2	SD 7.10	61.67	SD 7.71	0.65
cT	cT1	20	12.7%	12	15.2%	8	9.8%	0.568
	cT2	127	78.9%	60	75.9%	67	81.7%	
	cT3	14	8.7%	7	8.9%	7	8.5%	
cN	cN0	92	57.1%	47	59.5%	45	54.9%	0.554
	cN+	69	42.9%	32	40.5%	37	45.1%	
	unknown	2	1.2%	1	1.2%	1	1.2%	
Bx proven LN mets	No	129	79.6%	64	80.0%	65	79.3%	0.908
	Yes	33	20.4%	16	20.0%	17	20.7%	
Histologic type_initial	Ductal	144	88.9%	70	87.5%	74	90.2%	0.613
	Lobular	5	3.1%	2	2.5%	3	3.7%	
	Others	13	8.0%	8	10.0%	5	6.1%	
Tumor grade_initial	1, 2	70	80.5%	34	85.0%	36	76.6%	0.324
	3	17	19.5%	6	15.0%	11	23.4%	
Histologic grade_initial	1,2	84	84.8%	41	87.2%	43	82.7%	0.529
	3	15	15.2%	6	12.8%	9	17.3%	
PR_initial	Negative	35	21.6%	14	17.5%	21	25.6%	0.21
	Positve	127	78.4%	66	82.5%	61	74.4%	
HER2_initial	Negative	152	93.8%	78	97.5%	74	90.2%	0.055
	Positve	10	6.2%	2	2.5%	8	9.8%	
Ki67_Initial	≤10%	85	55.6%	43	56.6%	42	57.5%	0.8
	>10%	68	44.4%	33	43.4%	35	45.5%	
Ki67_4week	≤10%	9	56.3%	6	85.7%	3	33.3%	0.036
	>10%	7	43.8%	1	14.3%	6	66.7%	

Characteristics of the patients and tumors

		Total (N=203/163)		Metformin (N=103/80)		Placebo (N=100/83)		
		Number	%	Number	%	Number	%	p value
Performed surgery	BCS	100	68.0%	48	66.7%	52	69.3%	0.729
	mastectomy	47	32.0%	24	33.3%	23	30.7%	
Tumor size_invasive	≤2cm	48	42.1%	22	37.3%	26	47.3%	0.521
	≤5cm	63	55.3%	35	59.3%	28	50.9%	
	>5cm	3	2.3%	2	3.4%	1	1.8%	
Lymph node status	Negative	77	53.5%	39	53.4%	38	53.5%	0.991
	Positive	67	46.5%	34	46.6%	33	46.5%	
Clinical Response	CR+ PR	97	60.2%	51	63.8%	46	56.8%	0.332
	SD	59	36.6%	28	35.0%	31	38.5%	
	PD	5	3.1%	1	1.3%	4	4.9%	
PEPI_RFS	0	28	21.1%	12	19.0%	16	22.9%	0.706
	1-3	42	31.6%	22	34.9%	20	28.6%	
	≥4	63	47.4%	29	46.0%	34	48.6%	
PEPI_OS	0	28	21.1%	12	19.0%	16	22.9%	0.706
	1-3	42	31.6%	22	34.9%	20	28.6%	
	≥4	63	47.4%	29	46.0%	34	48.6%	

4 week core needle biopsy Ki67 (%)

		Total (N=203/163)		Metformin (N=103/80)		Placebo (N=100/83)		
		Number	%	Number	%	Number	%	p value
Ki67_4week	≤10%	9	56.3%	6	85.7%	3	33.3%	0.036
	>10%	7	43.8%	1	14.3%	6	66.7%	

		Ki67≤10%		Ki67>10%		p
Clinical Response	CR+ PR	8	100.0%	4	44.4%	0.043
	SD	0	0.0%	4	44.4%	
	PD	0	0.0%	1	11.1%	

		Total (N=203/163)		Metformin (N=103/80)		Placebo (N=100/83)		
Ki67_Surgery	≤10%	103	87.3%	50	86.2%	53	88.3%	0.729
	>10%	15	12.7%	8	13.8%	7	11.7%	

		Ki67≤10%		Ki67>10%		p
Clinical Response	CR+ PR	66	64.1%	9	60.0%	0.001
	SD	37	35.9%	4	26.7%	
	PD	0	0.0%	2	13.3%	

Toxicity Profile & Study discontinuation

- **Side effects >Grade 3 in 5 cases**
  - 3cases (thyroid cancer, hypertension) - not related to medication
  - 2cases with GI trouble (vomiting, weight loss)
  - No hypoglycemic event
  - Six cases dropped out because of poor medication intake (<18 weeks)

Summary

- Neoadjuvant endocrine therapy among postmenopausal breast cancer yielded overall clinical response rate of 60.2%
- No significantly higher response rate with additional metformin than letrozole alone, yet numerically higher response observed (63.8% vs 56.8%, p>0.05)
- Five cases had disease progression (metformin arm 1, placebo arm 4)

- No pathological complete response was observed and breast conserving rate was similar in both arms (66.7% vs 69.3%)
- No significant difference in PEPI score between two groups (PEPI 0,, 19.0% vs 22.9%)

- Metformin arm had greater proportion of 4 week Ki67(<10%) than in letrozole alone arm (85.7% vs 33.3%, p=0.036)
- Patients with 4wk-Ki67(<10%) displayed higher clinical response rate than in 4wk-Ki67>10% (100% vs 44.4%, p=0.043)

Thank you very much

Characteristics of the patients and tumors

- 5 연구자 판단 수술 먼저 (caliper SD)
- 7 Enrollment error
- 28 등록 철회 or f/u loss
  - 6 due to medication
  - Wanting to go surgery
  - F/U LOSS

Pathology, biomarker status	RFS		BCSS	
	HR	Points	HR	Points
Pathological tumor size				
T1/2	—	0	—	0
T3/4	2.8	3	4.4	3
Node status				
Negative	—	0	—	0
Positive	3.2	3	3.9	3
Ki67 level				
0%–2.7% (0–1†)	—	0	—	0
>2.7%–7.3% (1–2†)	1.3	1	1.4	1
>7.3%–19.7% (2–3†)	1.7	1	2.0	2
>19.7%–53.1% (3–4†)	2.2	2	2.7	3
>53.1% (>4†)	2.9	3	3.8	3
ER status, Allred score				
0–2	2.8	3	7.0	3
3–8	—	0	—	0