DBCG

Neo-adjuverende medicinsk behandling

Bent Ejlertsen

1977
40
2017
DBCG

16th ACTA ONCOLOGICA SYMPOSIUM

Baggrund; neoadjuverende behandling

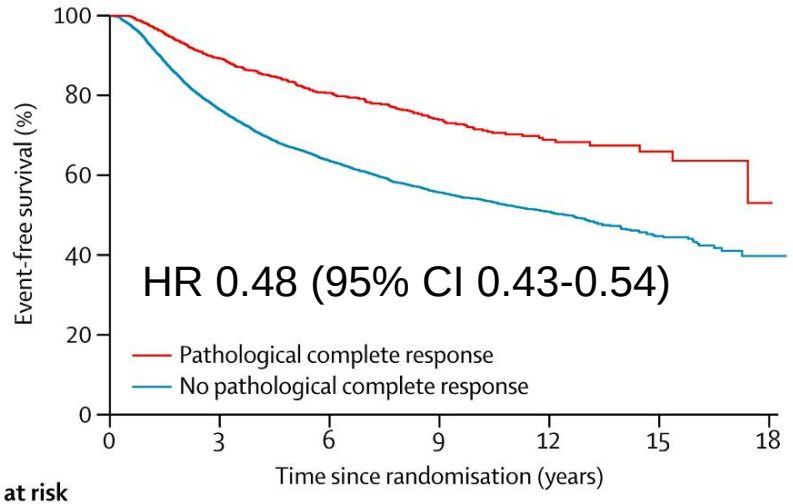
- Eneste mulighed hos patienter med inoperabel brystkræft.
- Af Bonadonna udvidet hvis mastektomi er eneste mulighed mhp. BCS.
- Erfaringerne med neoadjuverende endokrin terapi er begrænsede.
- Effekten afhænger subtype:
  - Luminal brystkræft
  - ER og HER2 negativ
  - HER2 positive

CTNeoBC pooled analysis

Prognostic value of pCR

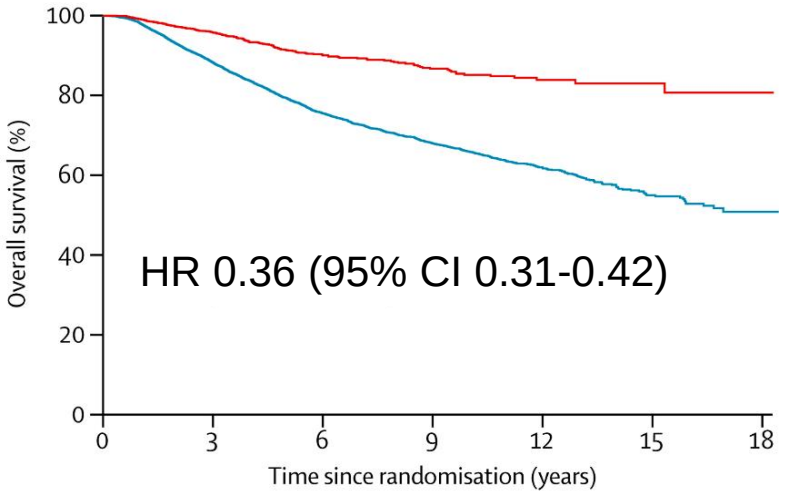
FDA established the Collaborative Trials in neoadjuvant Breast Cancer (CTNeoBC) with international investigators of neoadjuvant trials with available long-term data.

Event-free survival



Number at risk							
Pathological complete response	2131	1513	583	337	124	35	2
No pathological complete response	9824	6169	2674	1523	525	165	1

Overall survival



	2131	1618	640	383	145	43	3
	9824	7119	3173	1859	659	209	3

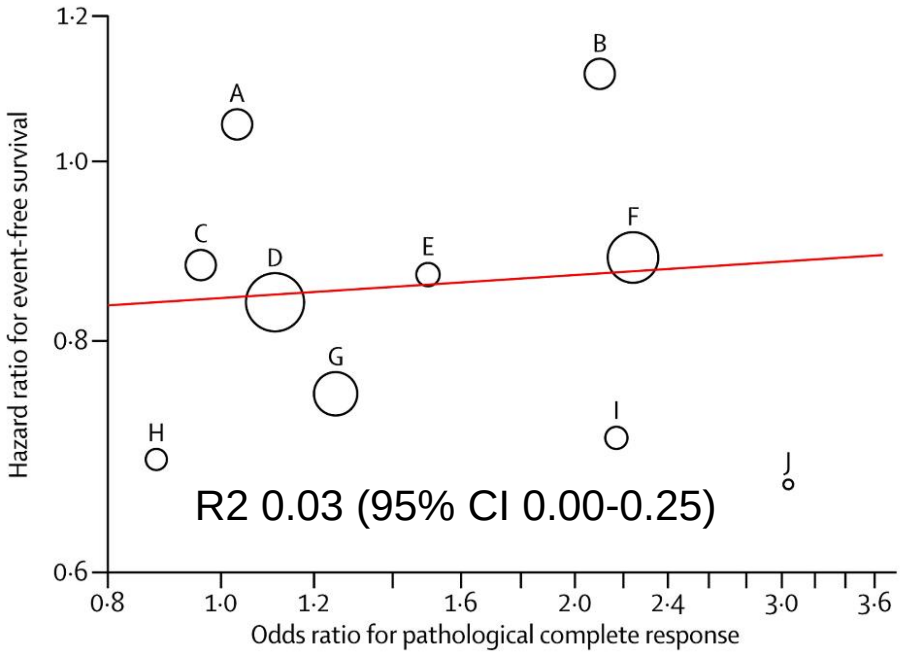
Cortazar et al. Lancet 2014;384:164-72

CTNeoBC pooled analysis

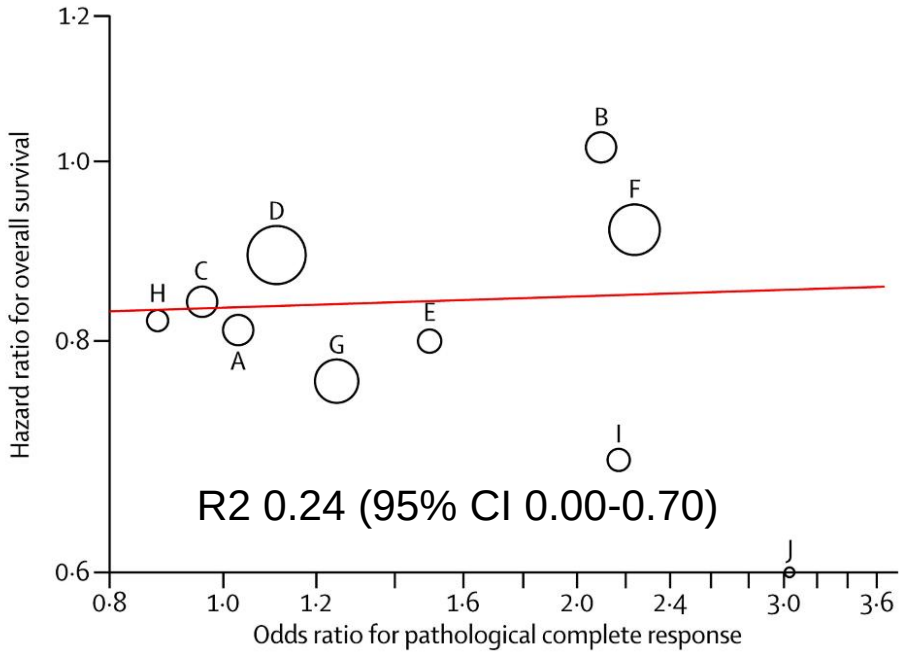
Value of pCR as intermediate endpoint

At trial level, little association between increase in pCR and effect on EFS or OS

Event-free survival



Overall survival



Cortazar et al. Lancet 2014;384:164-72

CTNeoBC pooled analysis

pCR according to tumor characteristics

Histology and grade

Characteristics	pCR %	95% CI
Type		
Lobular	7.8	6.3-9.4
Ductal	15.5	14.7-16.3
Mixed	22.7	19.0-26.8
Malignancy		
Grade 1	7.8	5.4-10.7
Grade 2	12.3	12.3-13.3
Grade 3	25.8	24.3-27.4

Molecular subtype

Characteristics	pCR %	95% CI
HR+, HER2-, G1-2	7.5	6.3-8.7
HR+, HER2-, G3	16.2	13.4-19.3
HER2+, HR+, +T	30.9	26.3-35.8
HER2+, HR+, ÷T	18.3	15.5-21.3
HER2+, HR-, +T	50.3	45.0-55.5
HER2+, HR-, ÷T	30.2	26.0-34.5
Triple negative	33.6	30.9-36.4

G: grade; HR: hormone-receptor; T: trastuzumab

Cortazar et al. Lancet 2014;384:164-72

Key neoadjuvant trials in HER2+ BC

Study	Regimens	N	pCR, all	pCR, HR+	pCR, HR÷
NeoALTTO	CT+lapatinib	455	24.7	16.1	33.7
Baselga 2012	CT+trastuzumab		29.5	22.7	36.5
	CT+L+T		51.3	41.6	61.3
NSABP B-41	CT+lapatinib	519	53.2	48.0	60.6
Robidoux 2013	CT+trastuzumab		52.5	46.7	65.5
	CT+L+T		62.0	55.6	73.0
NSABP FB-7	CT+neratinib	126	33.3	27.6	46.2
Jacobs 2015	CT+trastuzumab		38.1	29.6	57.1
	CT+N+T		50.0	30.4	73.7
NeoSphere	CT+trastuzumab	417	29.0	20.0	38.8
Gianni 2012	CT+P+T		45.8	26.0	63.2
	P+T		16.8	5.9	27.3
	CT+pertuzumab		24.0	17.4	30.0

pCR: pathological complete response ; HR: hormone receptor; CT: chemotherapy; L:lapatinib; T:trastuzumab; N:neratinib; P:pertuzumab.

TNBC; er der noget nyt?

Genomisk klassifikation

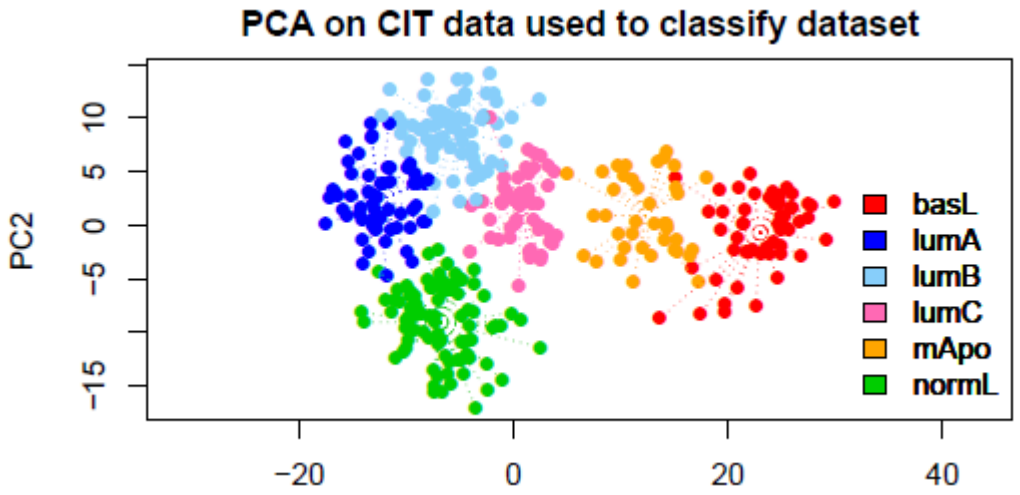
- Vanderbilt, Lehmann 2011
- Baylor, Burstein 2015
- Unicancer, Jézéquel 2015

Fire subtyper

- Basal-like
- Mesenchymal
- Immune-enriched
- LAR or AR-positive

Højere pCR i ventetiden

- Platiner (GeparSixto, CALGB 40603)
- Nab-paclitaxel (GeparSepto)



The 2017 EBCTCG meta-analysis

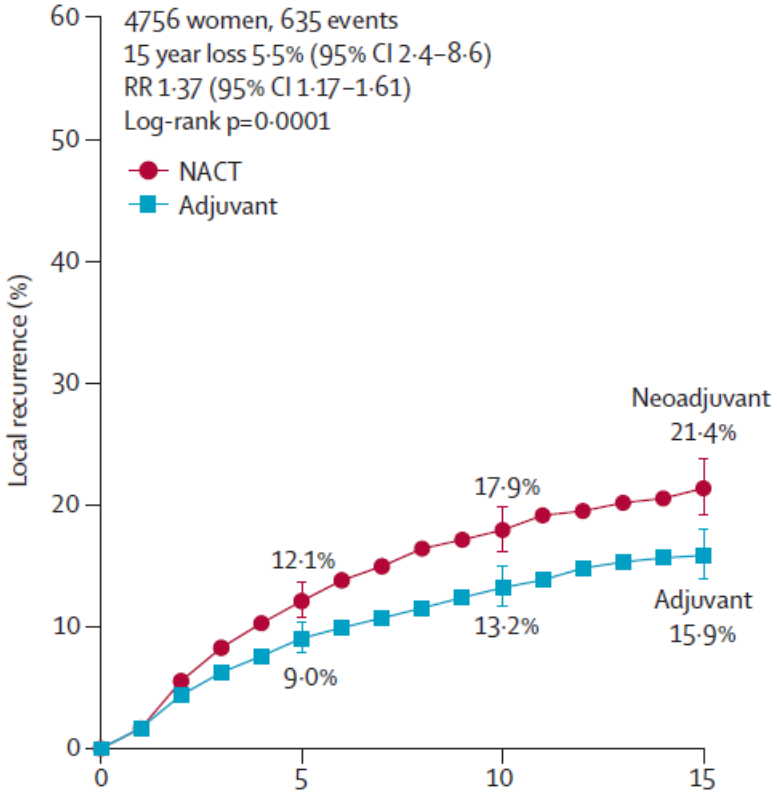
Neoadjuvant versus adjuvant chemotherapy

- Individual data available from 10 of 16 eligible trials and from the 4756 (91%) women.
- Trial entry was 1983 to 2002 and median follow-up was 9 years.
- One gave both taxane and anthracycline, 4 an anthracycline and 4 neither.
- Resultet in higher rates of BCS (rate ratio 1.28 95% CI 1.22-1.34).

Early Breast Cancer Trialists' Collaborative Group. Lancet Oncol 2018;19:27-39

EBCTCG meta-analysis of neoadjuvant vs adjuvant chemotherapy

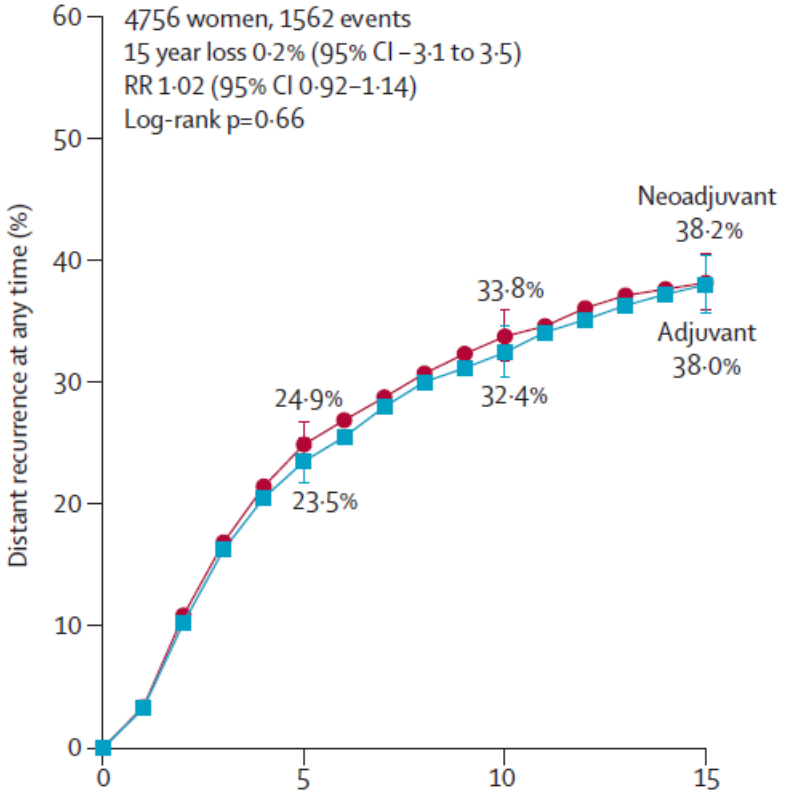
Local recurrence



Local recurrence crude rates (events per woman-years) and log-rank analyses

	Years 0–4	Years 5–9	Years 10–14	Years ≥15
Neoadjuvant	2·58 (245/9493)	1·43 (79/5528)	0·93 (26/2784)	2·16 (16/740)
Adjuvant	1·95 (185/9477)	0·96 (54/5618)	0·69 (19/2769)	1·42 (11/772)
Rate ratio	1·35 (1·11–1·64)	1·53 (1·08–2·17)	1·29 (0·70–2·38)	1·11 (0·48–2·57)
(95% CI) from (O–E)/V	30·4/102·0	13·6/31·8	2·7/10·3	0·6/5·4

Distant recurrence

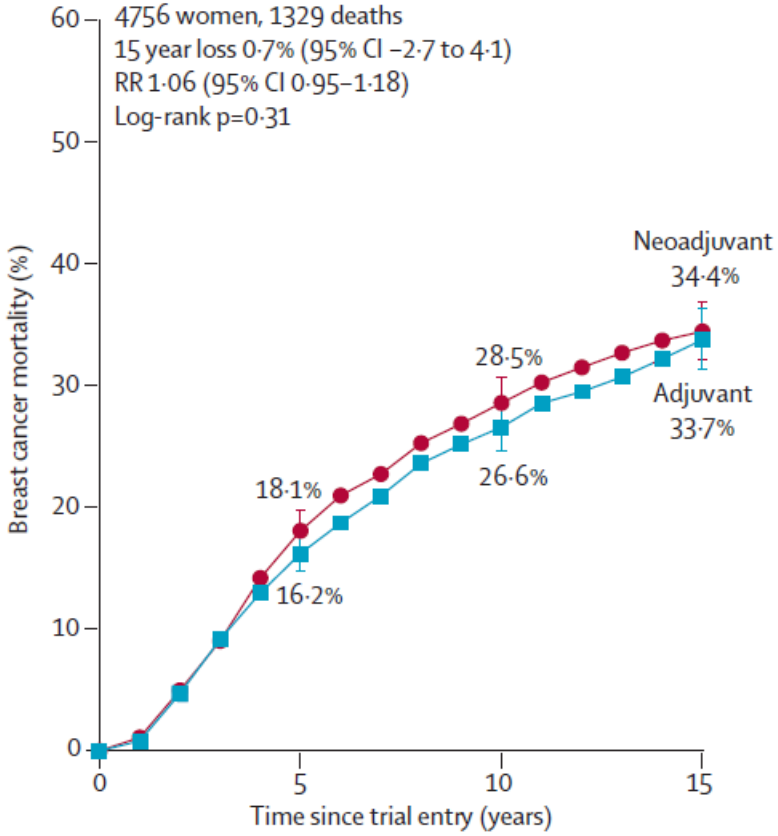


Distant recurrence at any time crude rates (events per woman-years) and log-rank analyses

Years 0–4	Years 5–9	Years 10–14	Years ≥15
5·69 (568/9983)	2·58 (162/6291)	1·49 (50/3351)	1·44 (14/974)
5·44 (535/9840)	2·54 (157/6187)	1·84 (60/3270)	1·74 (16/919)
1·07 (0·94–1·21)	0·99 (0·79–1·24)	0·80 (0·55–1·18)	0·75 (0·35–1·61)
16·5/251·5	−0·6/75·5	−5·7/25·8	−1·9/6·7

EBCTCG meta-analysis of neoadjuvant vs adjuvant chemotherapy

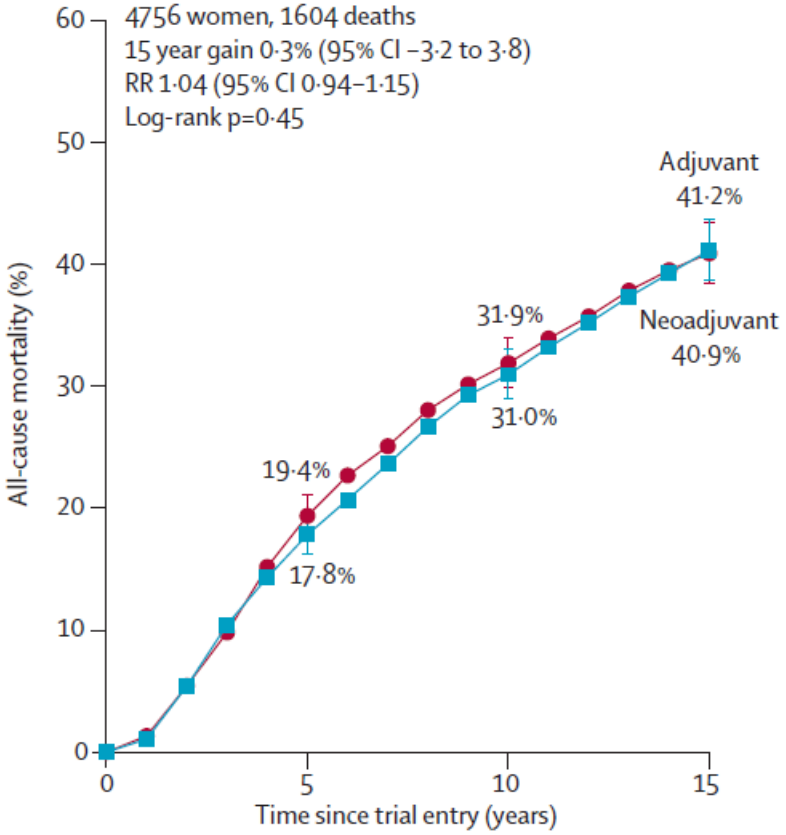
Breast cancer mortality



Breast cancer mortality crude rates (events per woman-years) and log-rank analyses

	Years 0–4	Years 5–9	Years 10–14	Years ≥15
Neoadjuvant	3·90 (412/10567)	2·82 (191/6785)	1·93 (69/3570)	1·24 (13/1050)
Adjuvant	3·49 (364/10432)	2·81 (190/6771)	2·19 (78/3559)	1·18 (12/1014)
Rate ratio	1·12 (0·97–1·30)	1·03 (0·84–1·27)	0·88 (0·63–1·21)	0·90 (0·41–1·97)
(95% CI) from (O–E)/V	20·5/179·6	2·8/91·6	−4·8/36·6	−0·7/6·2

Death form any cause

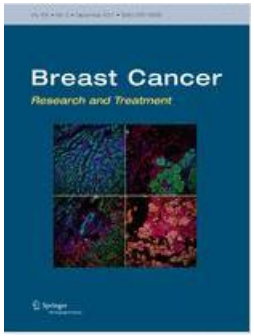


Any death crude rates (events per woman-years) and log-rank analyses

Years 0–4	Years 5–9	Years 10–14	Years ≥15
4·22 (446/10567)	3·51 (238/6785)	2·91 (104/3570)	3·52 (37/1050)
3·86 (403/10432)	3·56 (241/6771)	3·20 (114/3559)	2·07 (21/1014)
1·09 (0·95–1·25)	0·98 (0·81–1·17)	0·90 (0·68–1·18)	1·69 (0·95–2·99)
16·7/196·6	−2·7/112·2	−5·6/51·3	6·1/11·7

Breast Cancer Res Treat (2011) 126:463–470
DOI 10.1007/s10549-011-1352-2

CLINICAL TRIAL



Effect of adding gefitinib to neoadjuvant chemotherapy in estrogen receptor negative early breast cancer in a randomized phase II trial

Mogens Bernsdorf, Christian Ingvar, Leif Jörgensen, Malgorzata K. Tuxen, Erik H. Jakobsen, Anna Saetersdal, Marie Louise Kimper-Karl, Niels Kroman, Eva Balslev, Bent Ejlertsen

Abstract Gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor, has shown both anti-proliferative and anti-tumoral activity in breast cancer. This study was designed to determine the effect of adding gefitinib to neoadjuvant epirubicin and cyclophosphamide (EC) on tumor response rates. Women with unilateral, primary operable, estrogen receptor negative invasive breast cancer $\geq$ 2 cm were eligible for inclusion. Randomized patients were to receive four cycles of neoadjuvant EC plus 12 weeks of either gefitinib (250 mg daily) or placebo. Primary endpoint was pathologic complete response (pCR), and secondary endpoints were complete response (CR) and overall objective response (OR). 181 patients were randomized. A pCR was observed in 17% (12/71) of patients treated with gefitinib and in 12% (9/73) of patients treated with placebo (4.57% difference, 95% CI −7.19 to 6.33; $P = 0.44$). CR was observed in 10% of patients in both the gefitinib (7/71) and the placebo group (7/73) (0.27% difference, 95% CI −9.6 to 10.2; $P = 0.96$). There was no significant difference in OR (5.96%; 95% CI −9.9 to 21.9; $P = 0.45$) between the two groups. Post hoc subgroup analysis showed a significant difference in pCR between triple negative breast cancer (TNBC) and non-TNBC tumors ($P = 0.03$). More patients in the gefitinib arm had hematological toxicity ($P = 0.15$) and discontinued treatment (9/94 vs. 2/86) because of adverse events (AE). Tumor response rates were similar in the two groups. A significantly higher pCR rate was observed post hoc in TNBC versus non-TNBC independent of treatment. More patients in the gefitinib group discontinued treatment because of AE.

Keywords Breast cancer · Neoadjuvant treatment · Gefitinib · Triple negative

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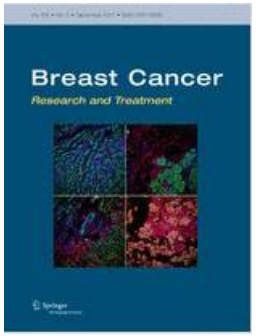


PATIENTS
- Invasive BC
- T ≥ 2 cm
- ER neg.
- Unilateral

STRATIFY
- Size (>2)
- ER

ENDPOINT
- pCR
- RR, BCS rate

RANDOMIZATION (N=164)

Epirubicin 90 mg/m²
Cyclophosphamide 600 mg/m²
Placebo continuosly

4 cycles, q 3 weeks

Epirubicin 90 mg/m²
Cyclophosphamide 600 mg/m²
Gefitinib continuosly

SURGERY (pCR)

Epirubicin 90 mg/m²
Cyclophosphamide 600 mg/m²

OR

Docetaxel 100 mg/m²

Tumor biopsy
Blood sample

Tumor biopsy
Blood sample

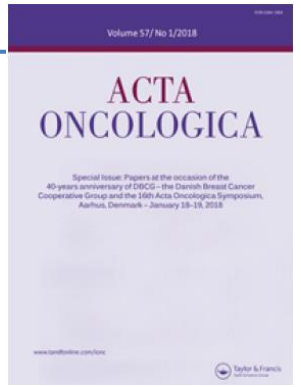
Table 4 Clinical and pathologic tumor response, PP

	Gefitinib ($n = 71$) (n, %)	Placebo ($n = 73$) (n, %)	Total ($n = 144$) (n, %)
Pathologic response			
pCR	12 (17)	9 (12)	21 (15)
Clinical response			
Complete response (CR)	7 (10)	7 (10)	14 (10)
Partial response (PR)	41 (58)	38 (52)	79 (55)
Stable disease (SD)	17 (24)	26 (36)	43 (30)
Progressive disease (PD)	5 (7)	2 (2.7)	7 (5)
Not evaluable/not assessed	1 (1.4)	0 (0)	1 (1)

PP Per protocol

pCR Pathologic complete response

Acta Oncologica, 2018;57:31-37



Neoadjuvant letrozole for postmenopausal estrogen receptor-positive, HER2-negative breast cancer patients, a study from the Danish Breast Cancer Cooperative Group (DBCG)

Signe Korsgaard Skriver, Anne-Vibeke Laenkholm, Birgitte Bruun Rasmussen, Jürgen Handler, Bo Grundtmann, Tove Filtenborg Tvedskov, Peer Christiansen, Ann S. Knoop, Maj-Britt Jensen & Bent Ejlertsen

ABSTRACT

Introduction: Neoadjuvant endocrine treatment (NET) is a low-toxicity approach to achieve operability in locally advanced breast cancer, and to facilitate breast conservation in early breast cancer, particular in patients with highly estrogen receptor (ER) positive and HER2-negative disease. Here, we report the results obtained by neoadjuvant letrozole in patients with early breast cancer in a phase-II design.

Material and methods: A total of 119 postmenopausal women with ER-positive, HER2-negative operable breast cancer were assigned to four months of neoadjuvant letrozole before definitive surgery. Sentinel node or diagnostic fine needle aspiration cytology procedure was performed prior to treatment and the women were assessed prior, at two months, and before surgery with clinical examination, mammography and ultrasonography. Surgical specimens were examined for pathological response. Primary outcome was pathological and clinical response.

Results: The per protocol population consisted of 112 patients. Clinical response was evaluated in 109 patients and pathological response in 108. Overall a mean decrease in tumor size was 15% ($p \leq .0001$). One patient had complete pathological response and 55% of patients had partial pathological response. ER at 100%, ductal subtype, tumor size below 2 cm and lymph node–negative status was significantly associated with a better response to NET and malignancy grade 3 with a poorer response to NET. One patient progressed during treatment and received neoadjuvant chemotherapy. Eight patients received adjuvant chemotherapy due to lack of response.

Conclusion: Neoadjuvant aromatase inhibitor therapy is an acceptable strategy in selected postmenopausal patients with ER-rich and HER2-negative early breast cancer with ductal histology and should be considered when chemotherapy either isn't indicated or feasible.

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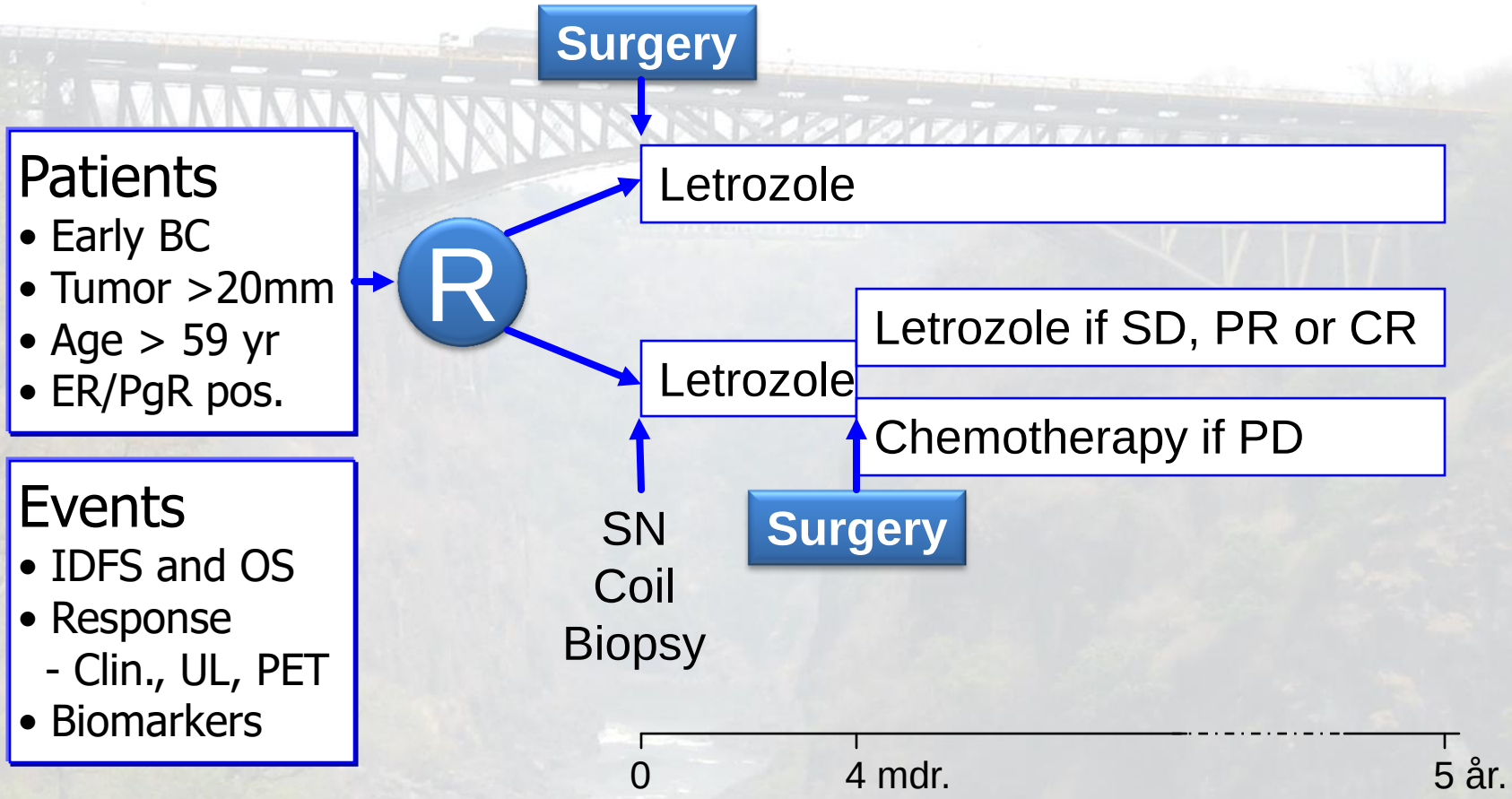
Randomized Trial of Endocrine Therapy Against Locoregional Therapy First



REAL SCIENCE

Patients
- Early BC
- Tumor >20mm
- Age > 59 yr
- ER/PgR pos.

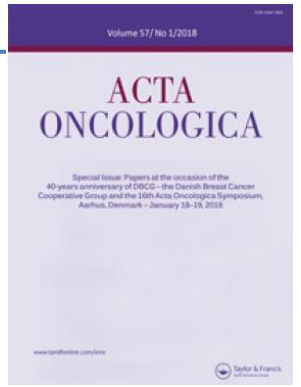
Events
- ~~IDFS and OS~~
- Response
  - Clinical, UL
- Biomarkers

Letrozole **Surgery**

SN
Coil
Biopsy

0 — 4 mdr.

Acta Oncologica, 2018;57:31-37



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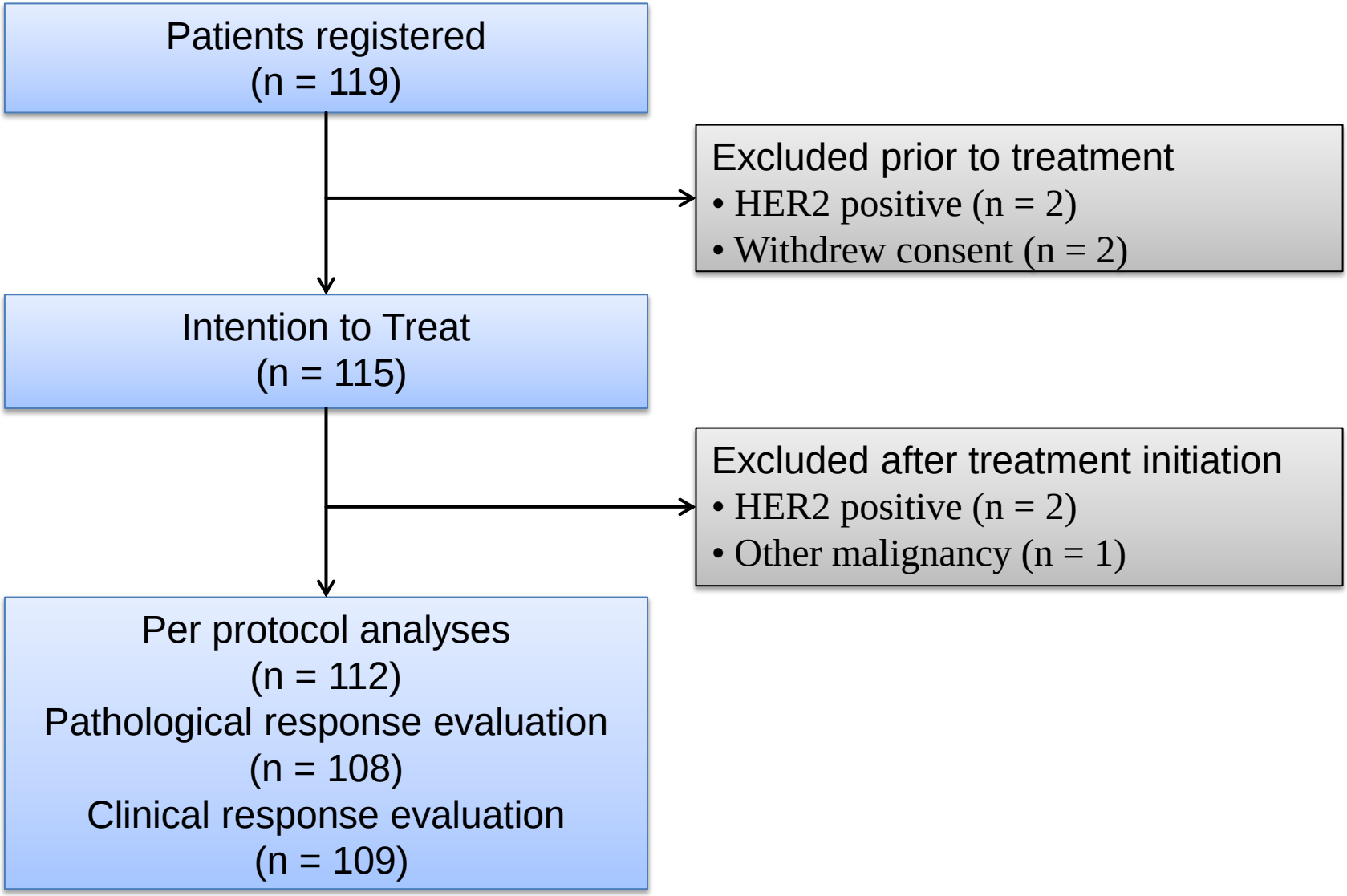
Flow diagram



Estrogen receptor positive patients (N=112) treated with neoadjuvant letrozole in 2009-2012

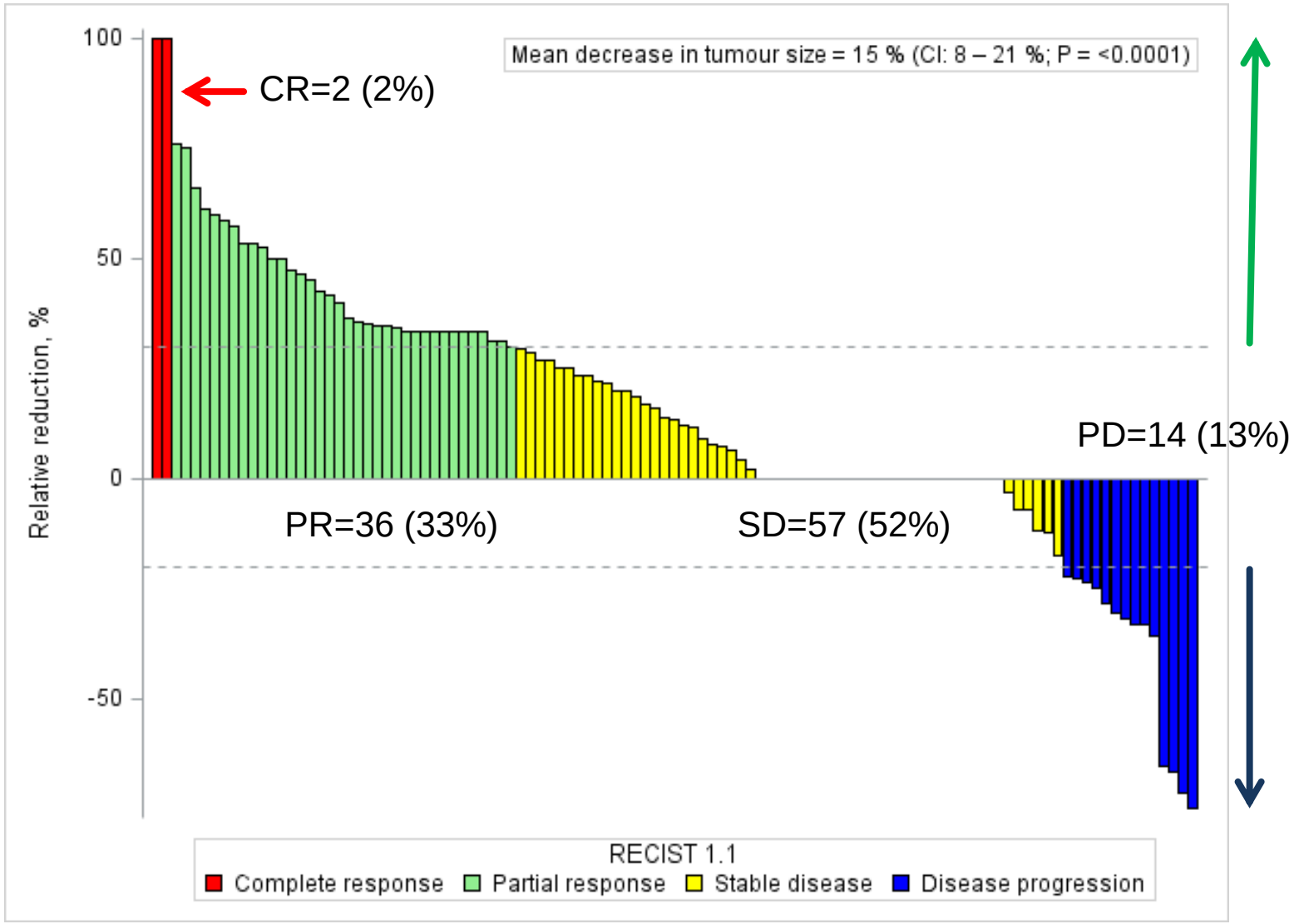
Characteristics	n	%
Age (years)		
60-69	66	59
70-89	46	41
Tumor size (mm)		
<20	50	45
≥20	62	55
Histological type		
Ductal	82	73
Other	30	27
Malignancy grade		
1	42	45
2 or 3	53	55
Nodal status		
Negative	60	54

Treatment duration

- One patient discontinued letrozol after two months due progression.
- A total of 111 patients completed four months of neoadjuvant letrozole.

Pathological response		
Complete response	1	1%
Minimal residual disease	7	6%
Moderate residual disease	52	48%
No response	48	44%

Det kliniske respons



Konklusioner

- Den prognostiske værdi af pCR er velbelyst, men pCR er ikke tæt koblet til DFS eller OS.
- Ved neoadjuverende kemoterpi er risikoen for loko-regional recidiv højere, men ikke risikoen for fjernrecidiv eller død.
- Tumorkarakteristika har betydning for respons på både kemo- og endokrin terapi.

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