NAT; neoadjuvererende terapi

- hvilke regimer bør vi bruge?
- bør den være subtype specifik?

Bent Ejlertsen

DBCG internat 4.&5. november 2019

UNIVERSITY OF COPENHAGEN

Neoadjuvant Systemic Chemotherapy Clinical Benefit

	Oxford LoE	Oxford GR	AGO
▪ Survival is similar after neoadjuvant (preoperative, primary) and adjuvant systemic therapy (with same regimen and cycle number)	1a	A	
▪ Pathological complete response is associated with improved survival	1b	A	
▪ Can achieve operability in primary inoperable tumors	1b	A	
▪ Improved options for breast conserving surgery	1b	A	
▪ Decreases rate of axillary lymph node dissection	3b	C	
▪ Allows individualization of therapy according to mid-course treatment effect	1b	B	
▪ Allows individualization of post-neoadjuvant treatment*	1b	B	

* Study participation recommended

Neoadjuvant Systemic Chemotherapy Clinical Benefit

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✓ Pathological complete response is associated with improved survival		Cortazar et al. Lancet 2014;384:164
▪ Can achieve operability in primary inoperable tumors	1b	A
▪ Improved options for breast conserving surgery	1b	A
▪ Decreases rate of axillary lymph node dissection	3b	C
▪ Allows individualization of therapy according to mid-course treatment effect	1b	B
▪ Allows individualization of post-neoadjuvant treatment*	1b	B

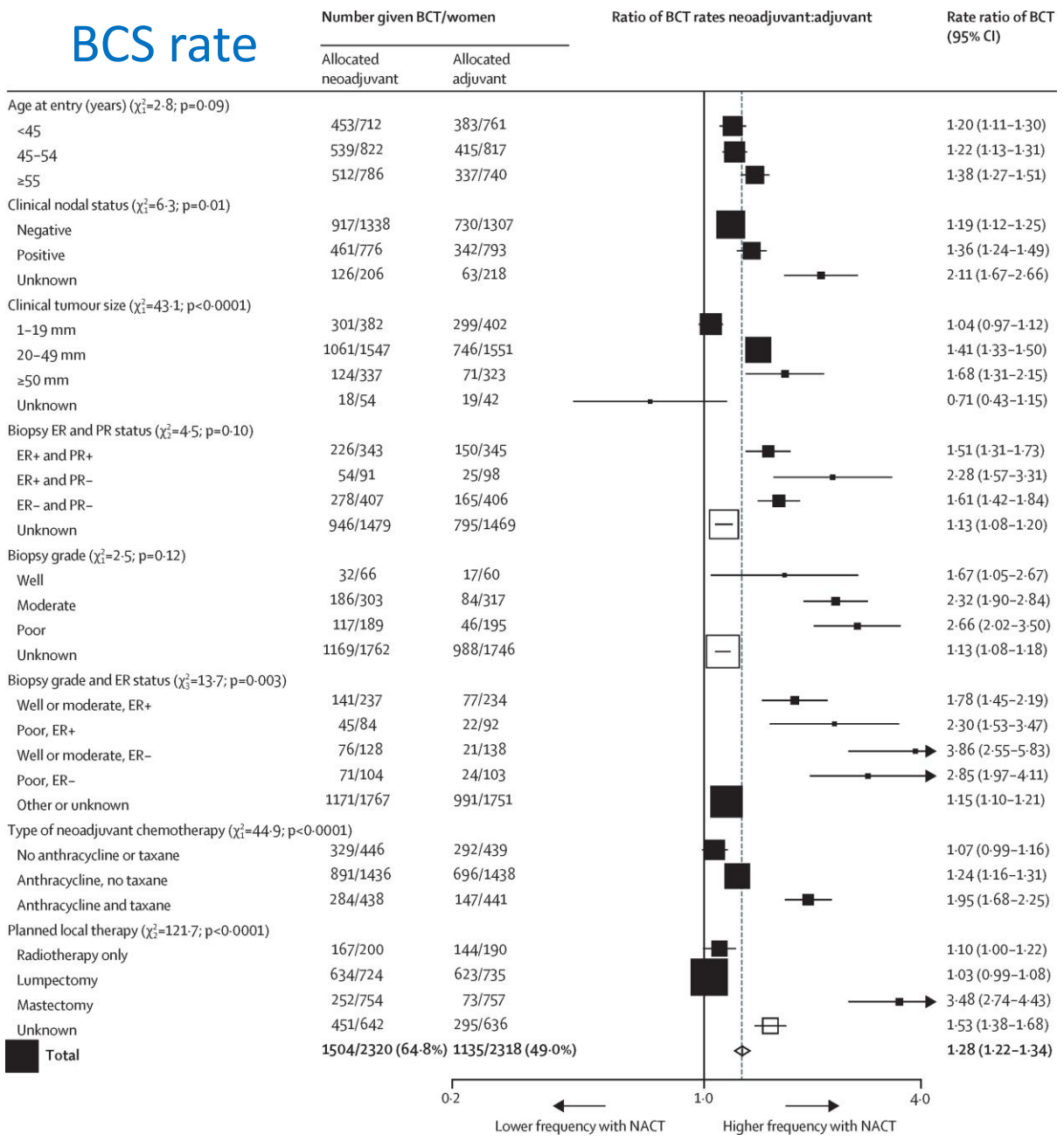
* Study participation recommended

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) corresponding to 60% vs. 50 %.

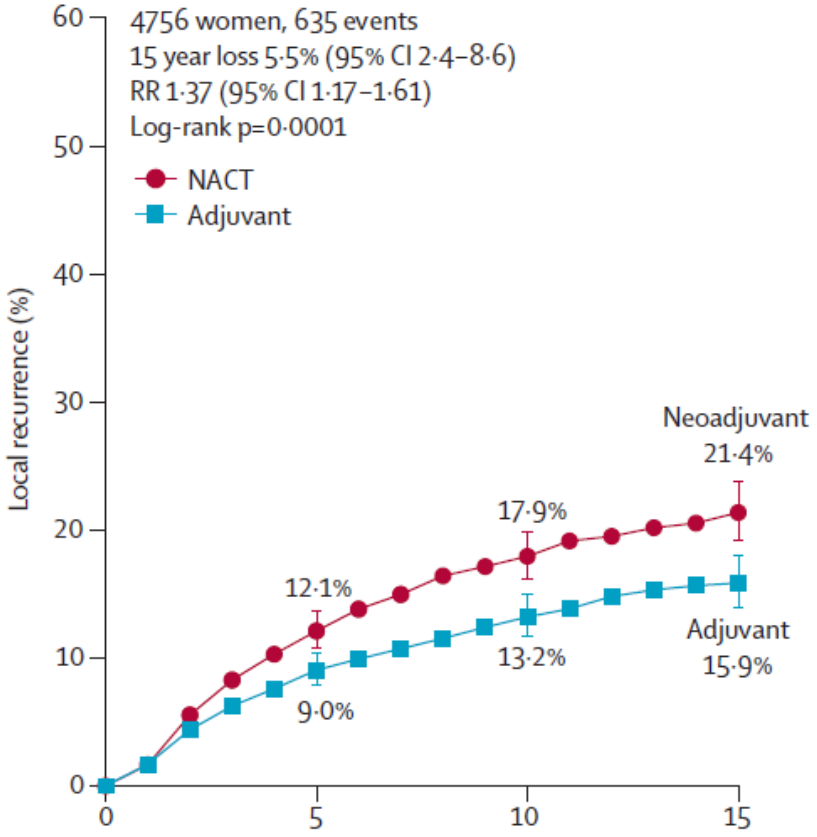
BCS rate



EBCTCG. Lancet Oncol 2018;19:27-39

EBCTCG meta-analysis of neoadjuvant vs adjuvant chemotherapy

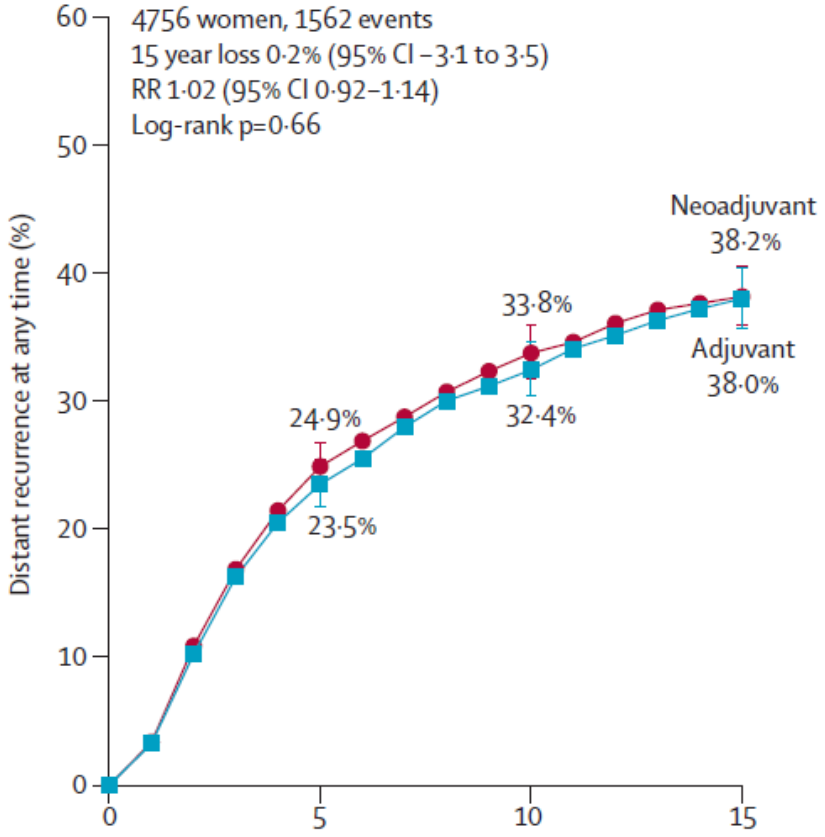
Local recurrence



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

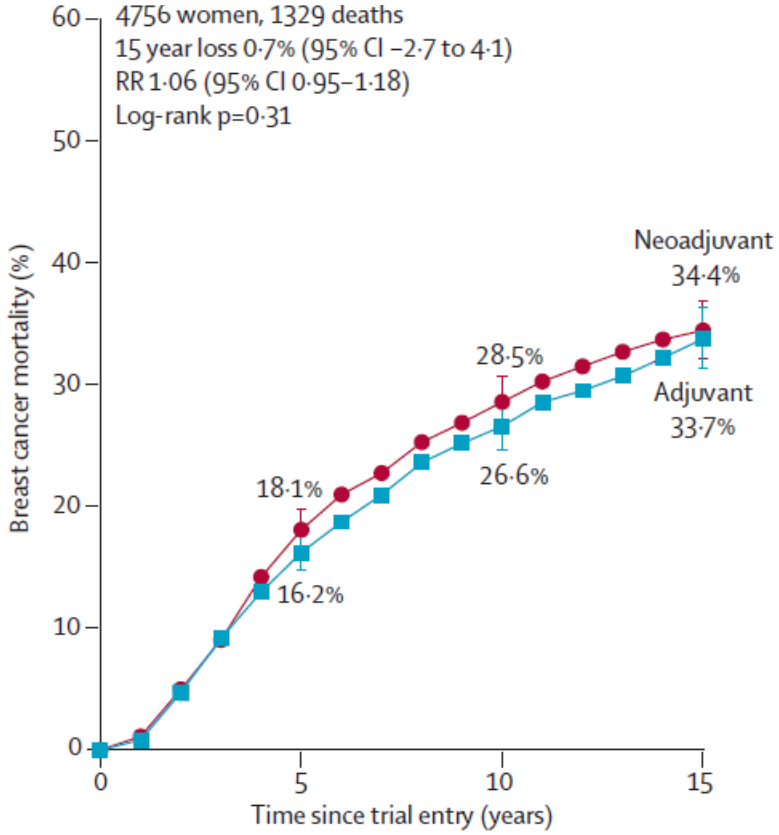


Distant recurrence at any time crude rates (events per woman-years) and log-rank analyses

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

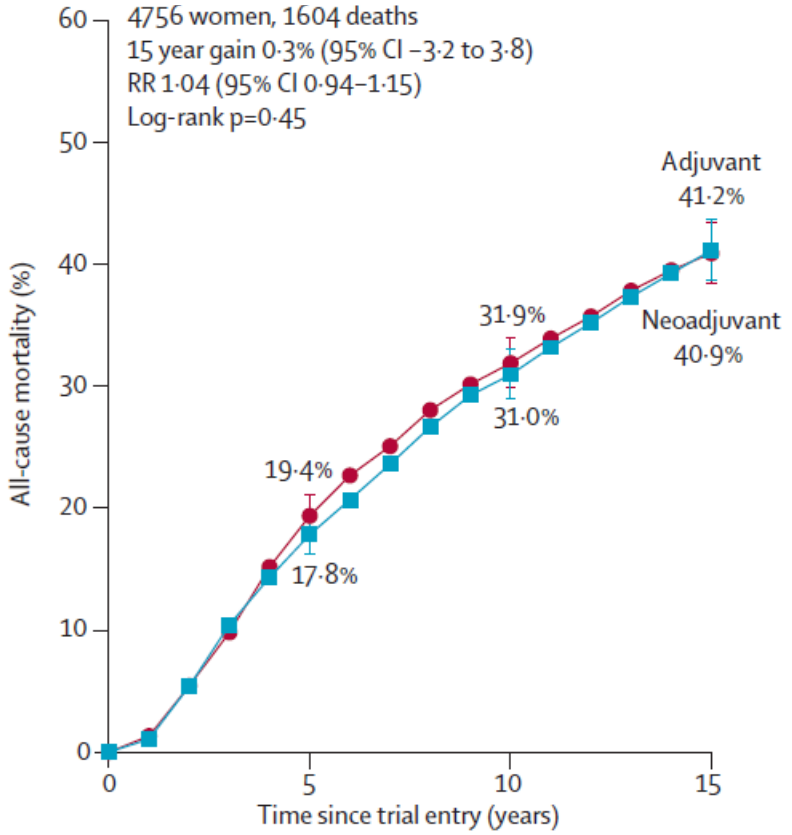
Breast cancer mortality



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



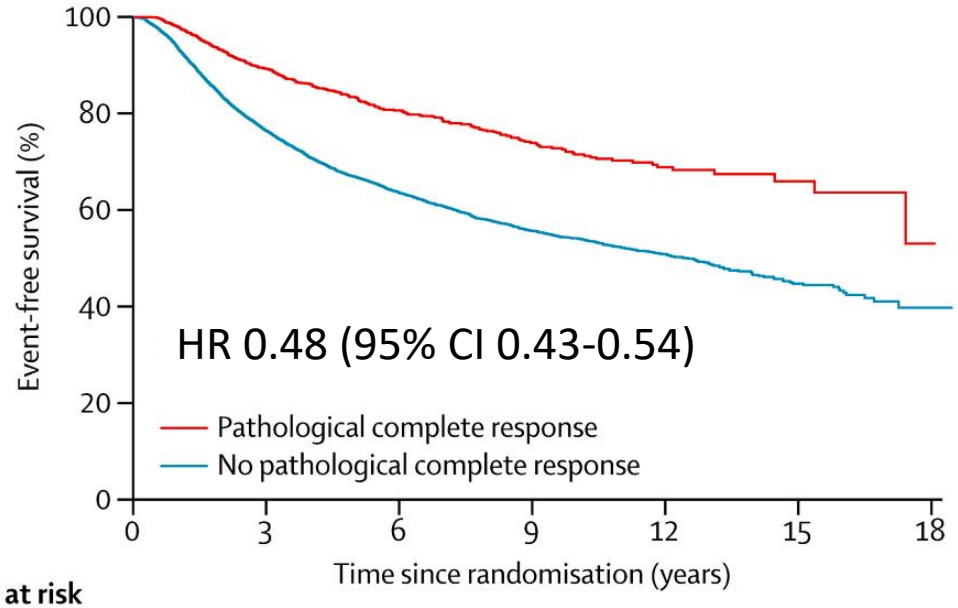
Any death crude rates (events per woman-years) and log-rank analyses

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

CTNeoBC pooled analysis
Prognostic value of pCR

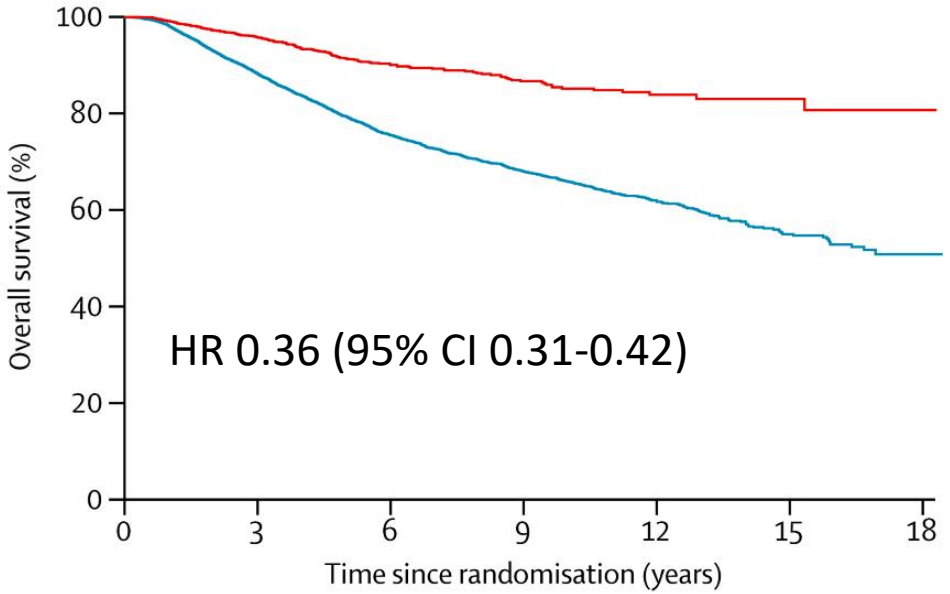
FDA established the Collaborative Trials in neoadjuvant Breast Cancer (CTNeoBC) with international investigators of neoadjuvant trials with available long-term data.

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



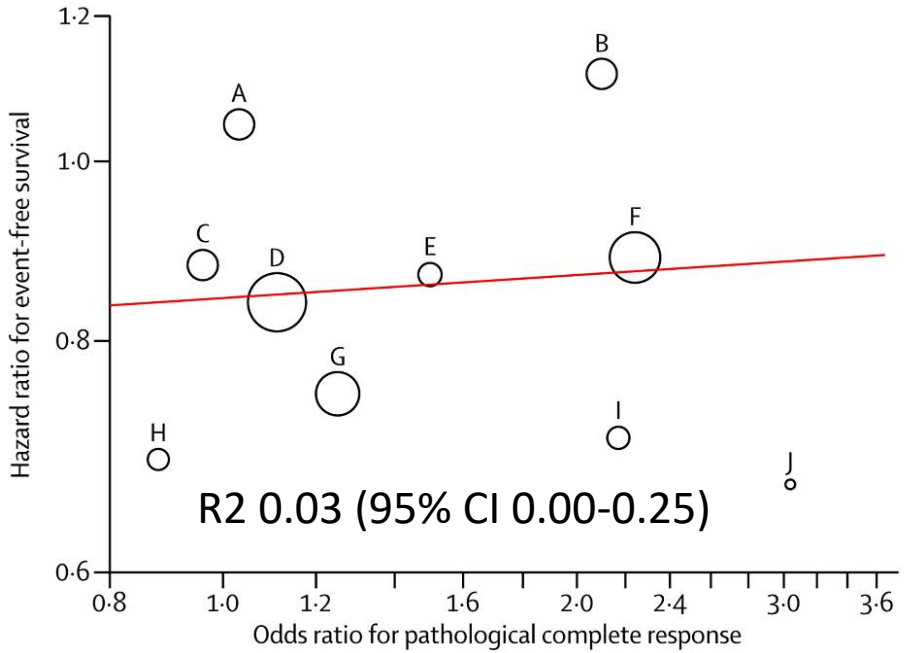
	2131	1618	640	383	145	43	3
	9824	7119	3173	1859	659	209	3

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

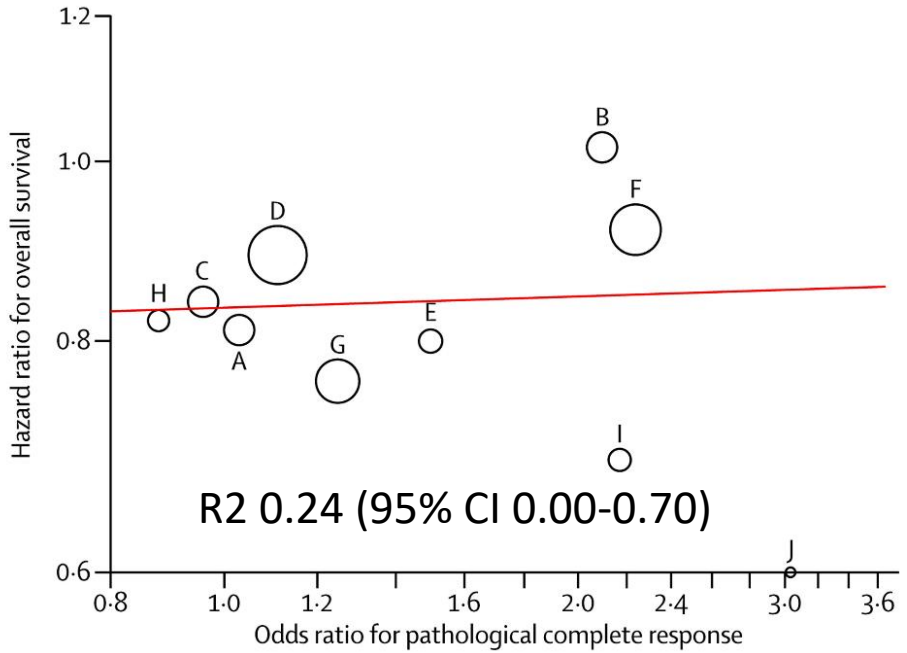
CTNeoBC pooled analysis
Value of pCR as intermediate endpoint

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

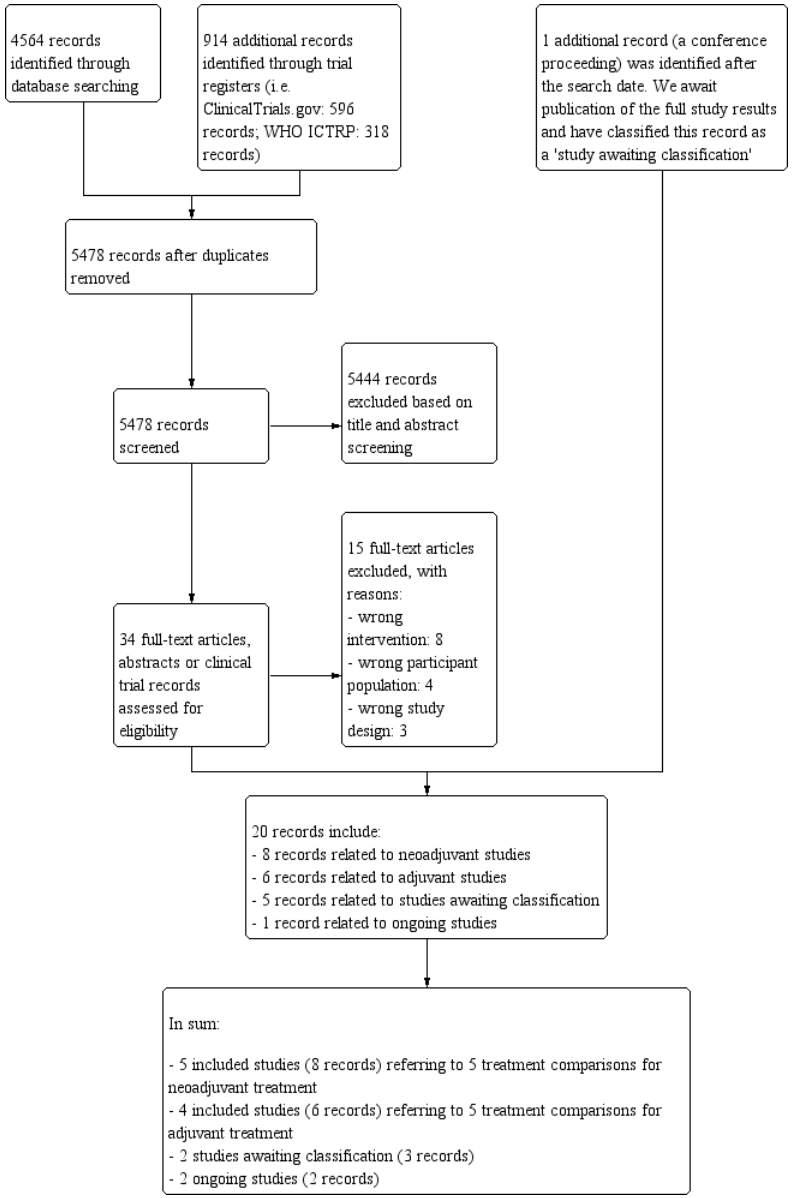
Subtype

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	18.3	15.5-21.3
HER2+, HR+, +T	30.9	26.3-35.8
HER2+, HR-, ÷T	30.2	26.0-34.5
HER2+, HR-, +T	50.3	45.0-55.5
Triple negative	33.6	30.9-36.4

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

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

Sequencing of neoadjuvant anthracyclines and taxenes



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2. Alamgeer M, Ganju V, Kumar B, Fox J, Hart S, White M, et al. Changes in aldehyde dehydrogenase-1 expression during neoadjuvant chemotherapy predict outcome in locally advanced breast cancer. *Breast Cancer Research* 2014;16:R44

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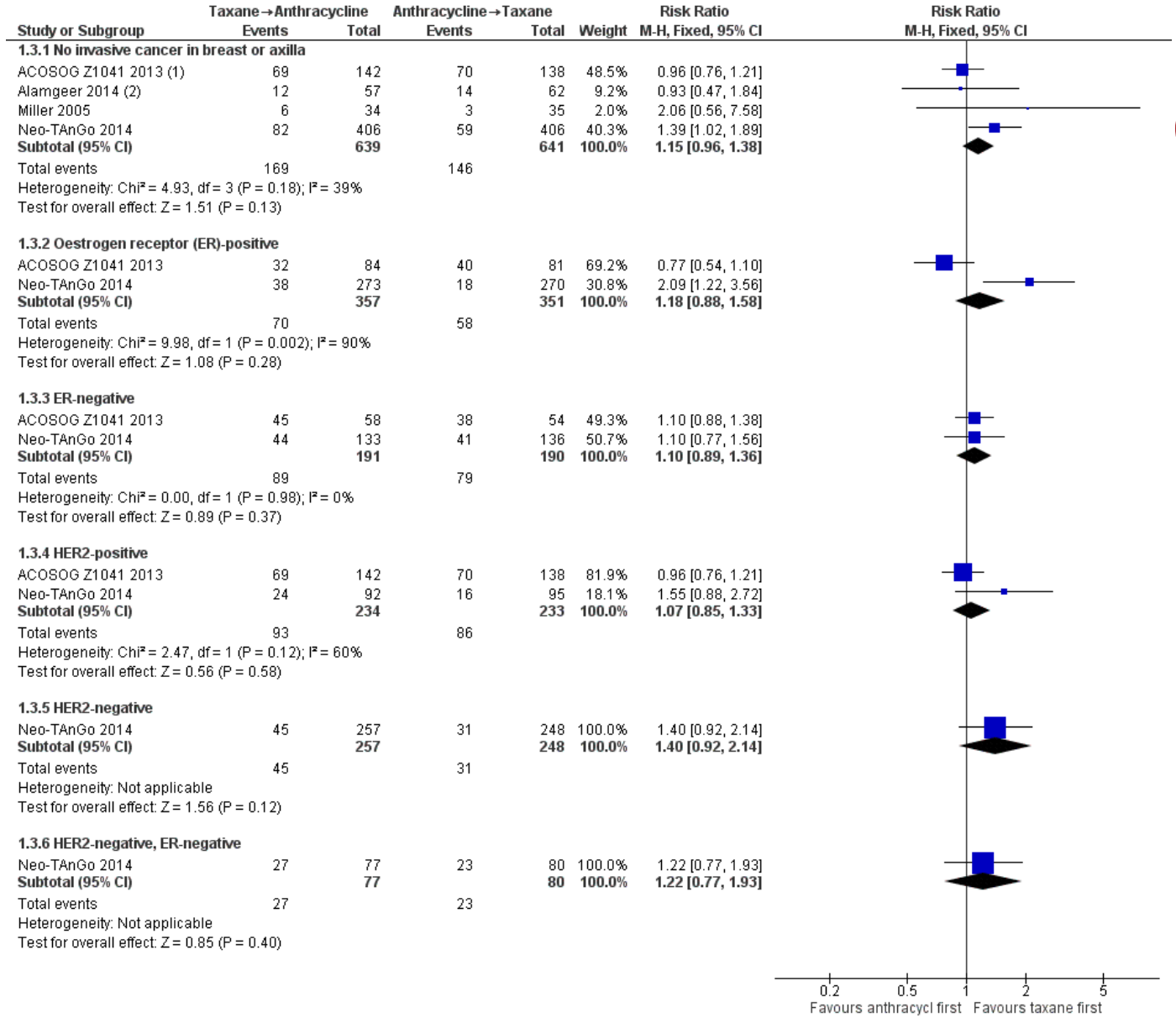
5. Stearns V, Singh B, Tsangaris T, Crawford JG, Novielli A, Ellis MJ, et al. A prospective randomized pilot study to evaluate predictors of response in serial core biopsies to single agent neoadjuvant doxorubicin or paclitaxel for patients with locally advanced breast cancer. *Clin Cancer Res* 2003;9:124-33.

Zaheed et al. Cochrane Reviews 2019, issue 2



Footnotes
(1) Data derived from 2013 ASCO abstract; full-text article did not provide data
(2) pCR defined as no invasive or in situ carcinoma in the breast or axillary lymph nodes

Conclusion

Administration of taxes first probably resulted in little to no difference in:

- Overall survival (HR 0.80, 95% CI 0.60 to 1.08)
- Disease-free survival (HR 0.84, 95% CI 0.65 to 1.09)
- Pathological complete response (RR 1.15, 95% CI 0.96 to 1.38)
- Conlusion: high-to-low-certainty evidende of equvivalent outcomes

Neoadjuvant Systemic Chemotherapy Recommended Regimens and Schedules

	Oxford LoE	Oxford GR	AGO
▪ Standard protocols used in the adjuvant setting with a duration of at least 18 weeks*	1a	A	++
▪ Taxane followed by anthracycline	1a	A	+
▪ Platinum in TNBC (irrespective of BRCA status)	2b	B	+
▪ Nab-Paclitaxel weekly instead of Paclitaxel weekly	1b	B	+

* See chapter Adjuvant Chemotherapy

Neoadjuvant Systemic Chemotherapy Recommended Regimens and Schedules

Guidelines Breast
Version 2019.1

	Oxford LoE	GR	AGO
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▪ Taxane followed by anthracycline	1a	A	+
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Different kind of evidence

* See chapter Adjuvant Chemotherapy


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Cancer Australia


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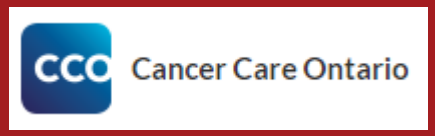
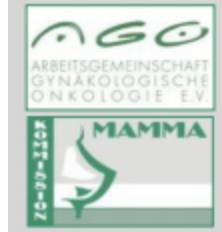

CCO
Cancer Care Ontario


NCCN
National Comprehensive
Cancer Network®


NICE National Institute for
Health and Care Excellence



Guidelines Breast
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Subtype-specific Strategies for Systemic Treatment

	AGO
If chemotherapy is indicated systemic treatment before surgery (neoadjuvant) should be preferred	
HR+/HER2- and „low risk"	
▪ Endocrine therapy without chemotherapy	++
HR+/HER2- and „high risk"	
▪ Conventionally dosed AT- based chemotherapy (q3w)	+
▪ Dose dense chemotherapy (including weekly schedule)	++
▪ Followed by endocrine therapy	++
HER2+	
▪ Trastuzumab (plus Pertuzumab neoadjuvant at high risk)	++
▪ Sequential A/T-based regimen with concurrent T + anti Her 2 therapy	++
▪ Anthracycline-free, platinum-containing regimen	+
▪ Anthracycline-free, taxane-containing regimen	+
Triple-negativ (TNBC)	
▪ Conventionally dosed AT-based chemotherapy	+
▪ Dose dense chemotherapy (AT - based including weekly schedule)	++
▪ Neoadjuvant platinum-containing chemotherapy	+

Biomarker specific strategy for NAT

Does sequential EC-paclitaxel still fit all!

ER÷/HER2÷ (TNBC)

- Kemoterapi
  - Platin - cis/carbo?
  - Taxan – nabpaclitaxel?
  - EC or ddEC
- Immunoterapi
- PARPi
- Post-neoadjv. terapi
  - Capecitabine
- NordicTrip Trial

HER2+

- Kemoterapi
  - Platin
  - wPac -docetaxel
  - EC or ddEC
- HER2 targeteret terapi
  - Double HER2
- Post-neoadjv. terapi
  - T-DM1
- NordicHER2 Trial

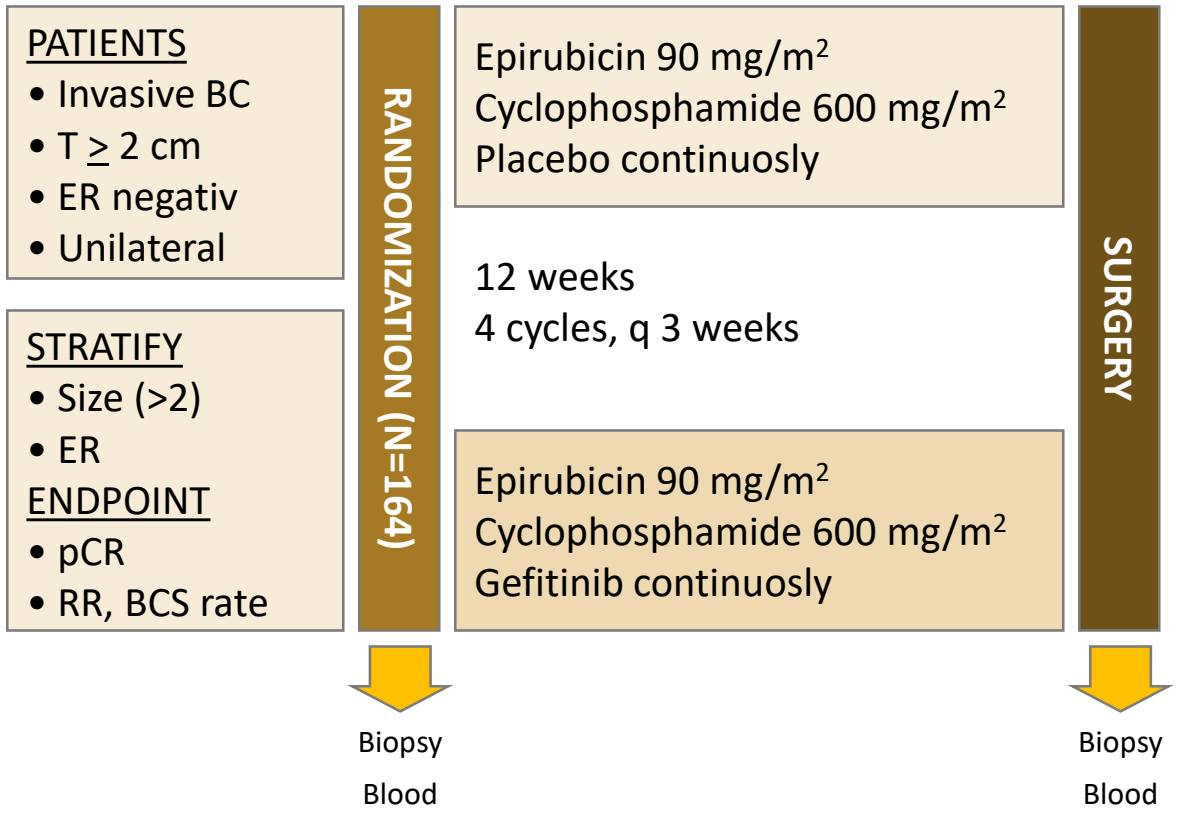
ER+/HER2÷

- Kemoterapi
  - Taxan
  - EC or ddEC
- Endokrin terapi
- Immunoterapi
- Post-neoadjv. terapi
  - AI / OFS+AI
- Nivo-Neo Trial

Effect of adding gefitenib to neoadjuvant chemotherapy in estrogen receptor negativ breast cancer; a randomized phase II trial

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

Neoadjuvant **I**ressa, **C**yclophosphamide, and **E**pirubicin
a randomized phase 2 trial



Kort om NICE forsøget

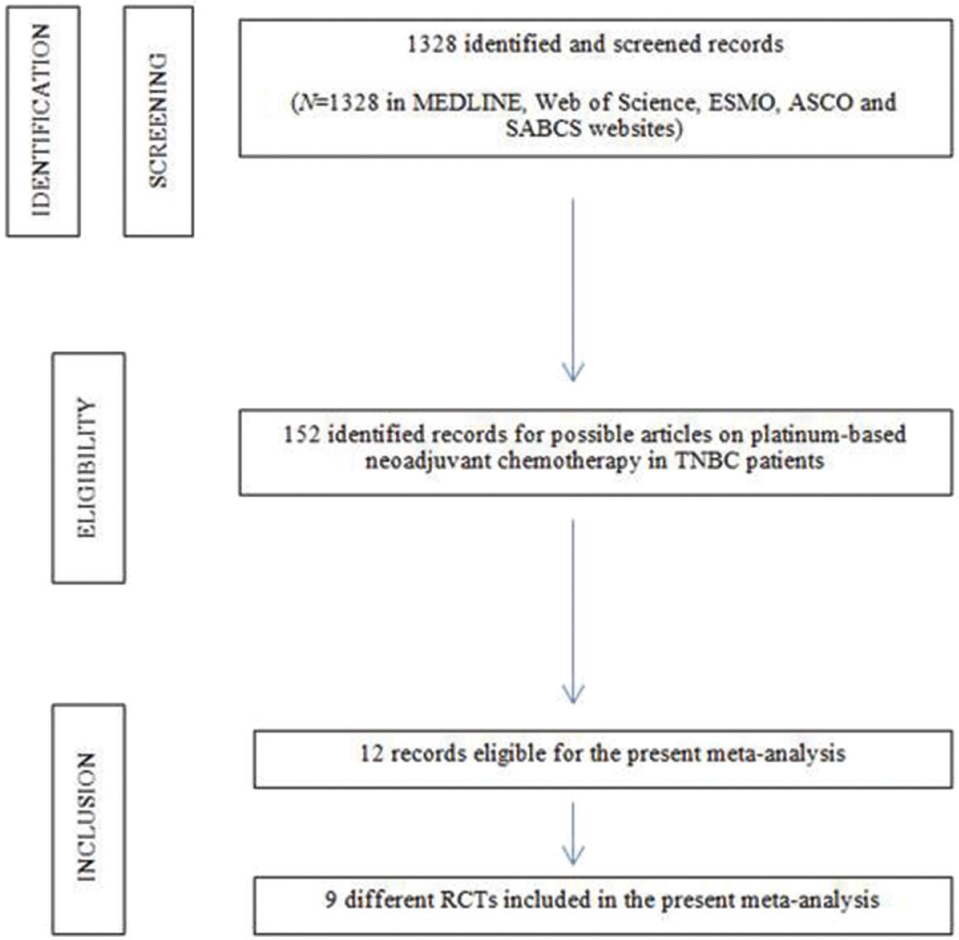
- Investigator initieret og industri sponsoreret
  - Fuld finansiering fra sponsor
  - Sponsor stod for godkendelser og monitorering
- Central indsamling af væv og blod
  - FFPE til Herlev
  - Frosset væv til KB og Lund (FedEx)
  - Blodprøverne til sponsor
- Afsluttet april 2007 (sidste EC)
- Resultater
  - pCR rate på 12% og ingen significant effekt af gefitinib
- Publikation
  - SABCS 2007 abstrakt blev trukket pga. fejl
  - Centralt review af pCR, RR og toksicitet
  - Fejlene skyldtes sponsors datamanagement
  - BCRT i 2011 som led i ph.d.

Bernsdorf et al. BCRT 2011; 126: 463
Bernsdorf et al. BCRT 2011; 128: 165

Platinum-based neo-adjuvant chemotherapy in TNBC

A systemic review and meta-analysis

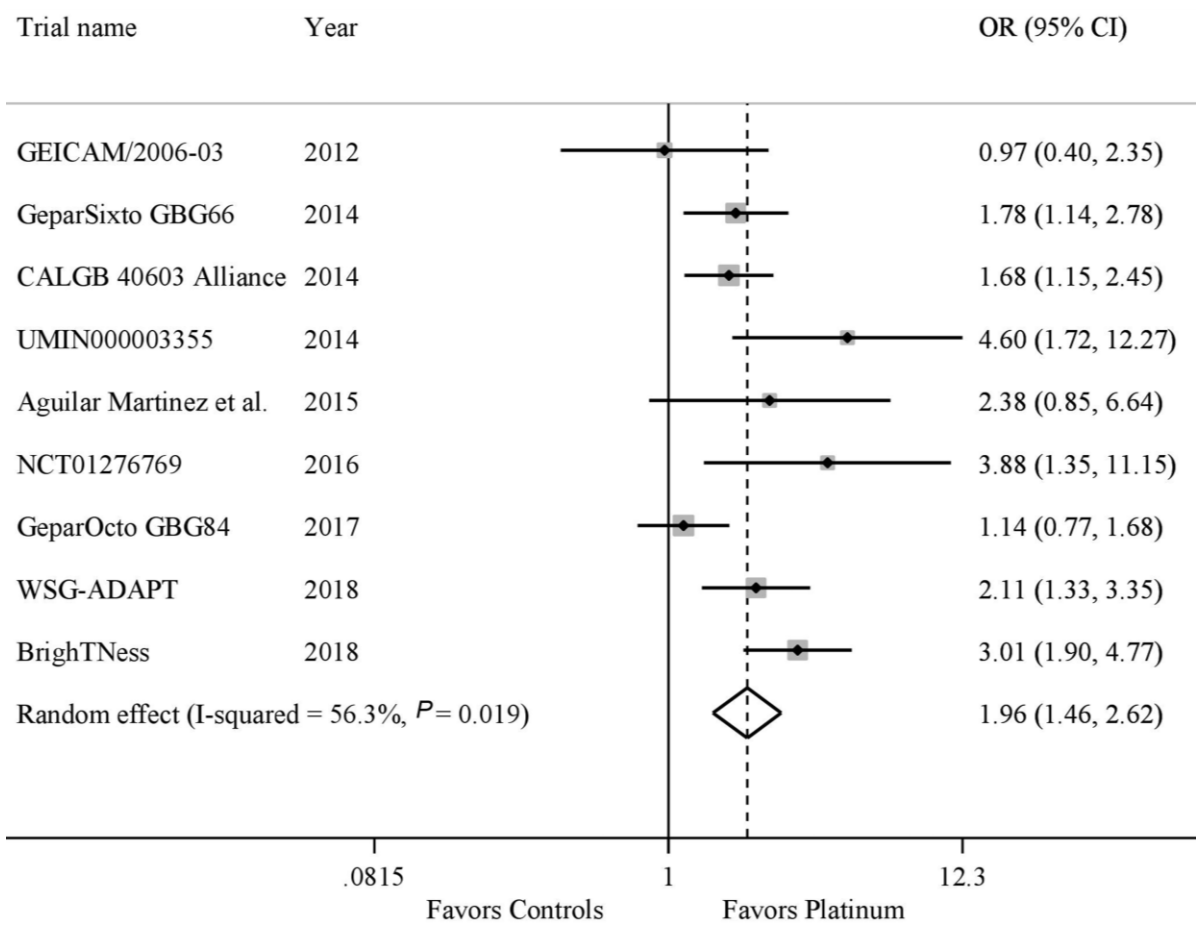
ANNALS OF ONCOLOGY



Study	Design	1. end point	2nd end points	Treatment arms	N
GEICAM/2006-03 Alba et al. 2012	Phase II	ypT0/is	ypT0/is pN0, clinical response rate, safety,	EC—DCb EC—D	47 46
GeparSixto GBG66 Loibl et al. 2018	Phase II	ypT0 pN0	ypT0/is pN0, clinical response rate, safety	P+Dox+Bev+Cb P+Dox+Bev	158 157
Alliance 40603 Sikov et al. 2016	Phase II	ypT0/is	ypT0/is pN0, safety, RFS and OS	P+Cb±Bev → ddAC P±Bev → ddAC	221 212
UMIN000003355 Ando et al. 2014	Phase II	ypT0/is pN0	Clinical response rate, safety, DFS	PCb → CEF P → CEF	37 38
Aguilar Martinez et al. 2015	Phase II	ypT0/is pN0	Clinical response rate, safety	Cis+P → Cis+Dox P → FAC	30 31
NCT01276769 Zhang et al. 2016	Phase II	ypT0/is pN0	ORR, safety, RFS, OS	PCb EP	44 43
GeparOcto GBG84 Schneeweiss 2017	Phase III	ypT0/is pN0	Toxicity, DFS, OS	PDoxCb DdEPC	203 200
WSG-ADAPT Gluz et al. 2017	Phase II	ypT0/is pN0	Toxicity, EFS, OS	Nab-P+Cb Nab-P+Gem	146 178
BrighTNess Loibl et al. 2018	Phase III	ypT0/is pN0	Clinical response rate, toxicity, EFS, OS	P+Cb → AC P → AC	160 158

Poggio et al. Ann Oncol 2018;29:1497-1508

Odds ration for pCR

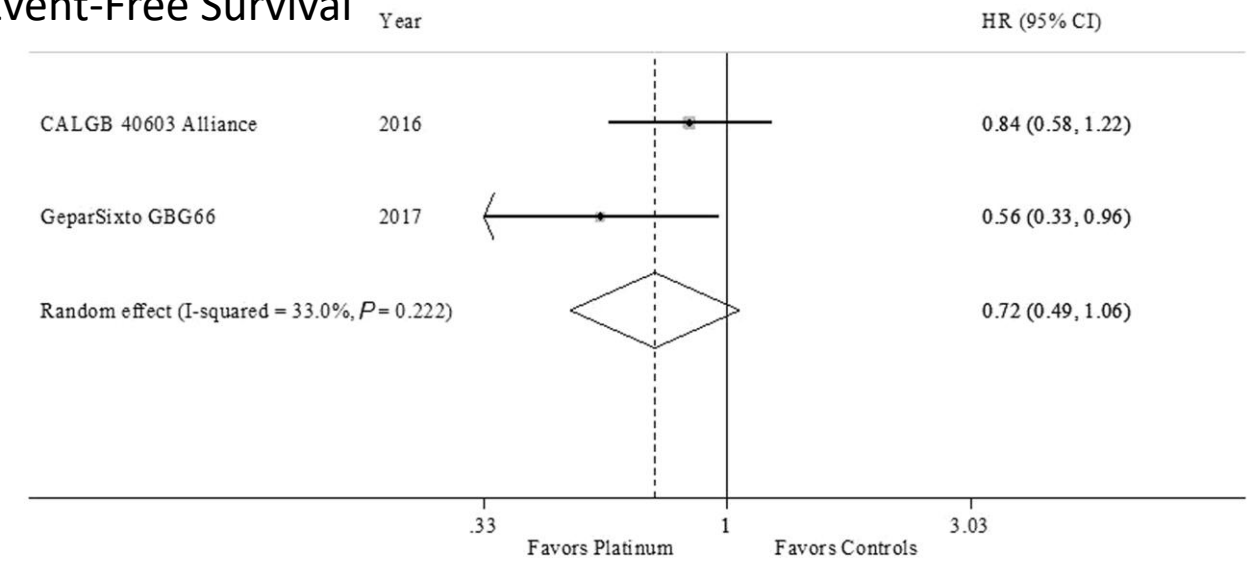


Platinum is associated with increased pCR but only two studies reported OS:

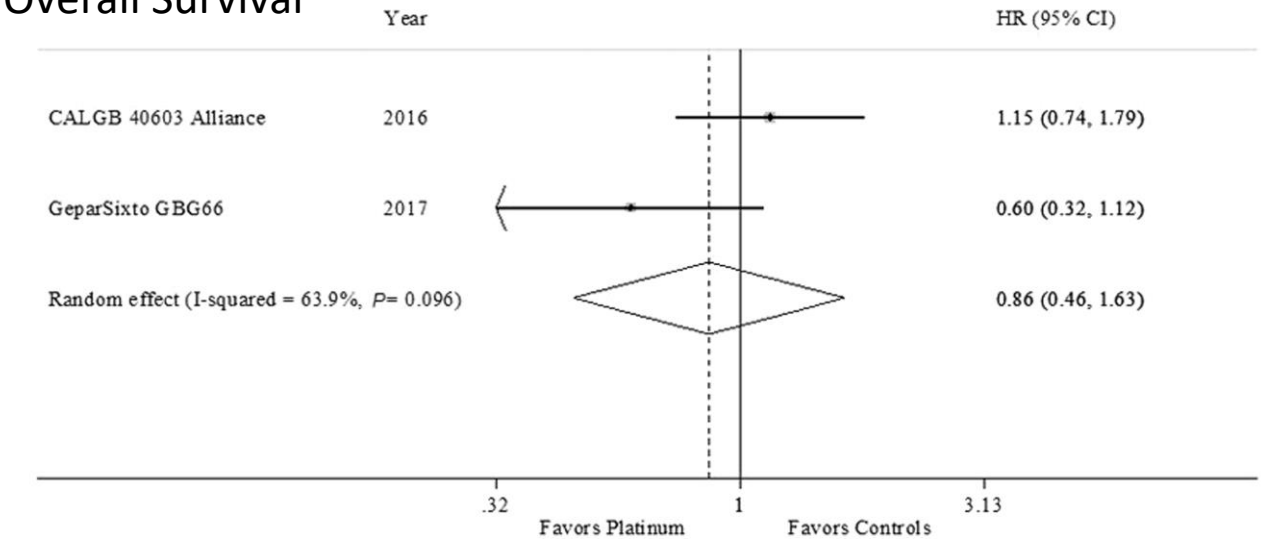
- Overall survival (HR 0.86, 95% CI 0.46 to 1.63)
- Disease-free survival (HR 0.72, 95% CI 0.49 to 1.06)
- Pathological complete response (RR 1.96, 95% CI 1.46 to 2.62)
- Conclusion: pCR improved by platinum in TNBC

Poggio et al. Ann Oncol 2018;29:1497-1508

Event-Free Survival



Overall Survival



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Sikov WM, Berry DA, Perou CM, et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). J Clin Oncol. 2015;33(1):13-21.

Biomarker specific strategy for NAT

Does sequential EC-paclitaxel still fit all!

ER÷/HER2÷ (TNBC)

- Kemoterapi
  - Platin - cis/carbo?
  - Taxan – nabpaclitaxel?
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- Immunoterapi
- PARPi
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  - Capecitabine
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HER2+

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  - wPac -docetaxel
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  - T-DM1
- NordicHER2 Trial

ER+/HER2÷

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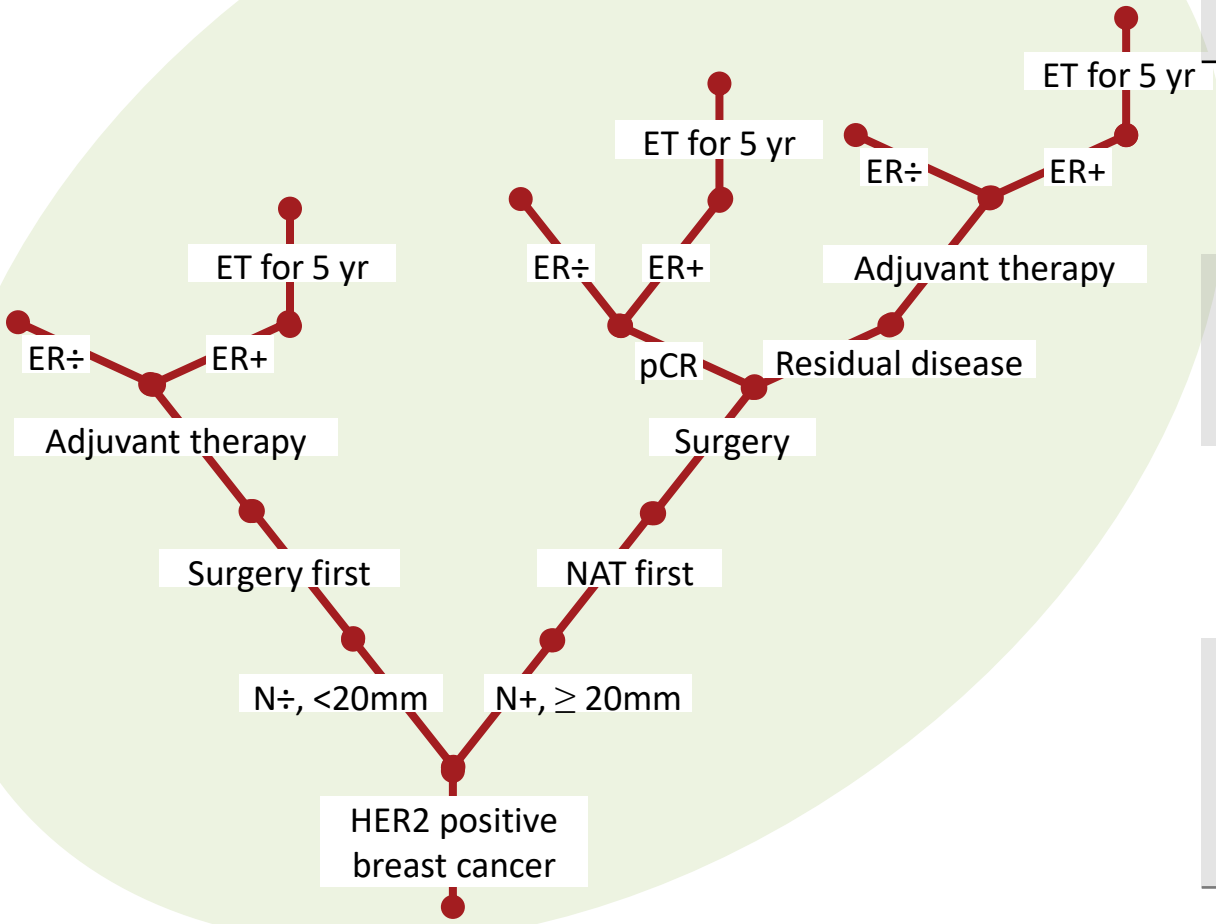
  - Taxan
  - EC or ddEC
- Endokrin terapi
- Immunoterapi
- Post-neoadjv. terapi
  - AI / OFS+AI
- Nivo-Neo Trial

HER2 positive early breast cancer



Double HER2 targeting

Study	Regimen	N	pCR		
			all	HR+	HR÷
NeoALTTO	CT+trastuzumab	455	29.5	22.7	36.5
Baselga 2012	CT+lapatinib		24.7	16.1	33.7
	CT+T+lapatinib		51.3	41.6	61.3
NSABP B-41	CT+trastuzumab	519	52.5	46.7	65.5
Robidoux 2013	CT+lapatinib		53.2	48.0	60.6
	CT+T+lapatinib		62.0	55.6	73.0
NSABP FB-7	CT+trastuzumab	126	38.1	29.6	57.1
Jacobs 2015	CT+neratinib		33.3	27.6	46,2
	CT+T+neratinib		50.0	30.4	73.7
NeoSphere	CT+trastuzumab	417	29.0	20.0	38.8
Gianni 2012	CT+pertuzumab		24.0	17.4	30.0
	CT+T+pertuzumab		45.8	26.0	63.2
	T+pertuzumab		16.8	5.9	27.3

HR: hormone receptor; CT: chemotherapy; T:trastuzumab.

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  - EC or ddEC
- Immunoterapi
- PARPi
- Post-neoadjv. terapi
  - Capecitabine
- NordicTrip Trial

HER2+

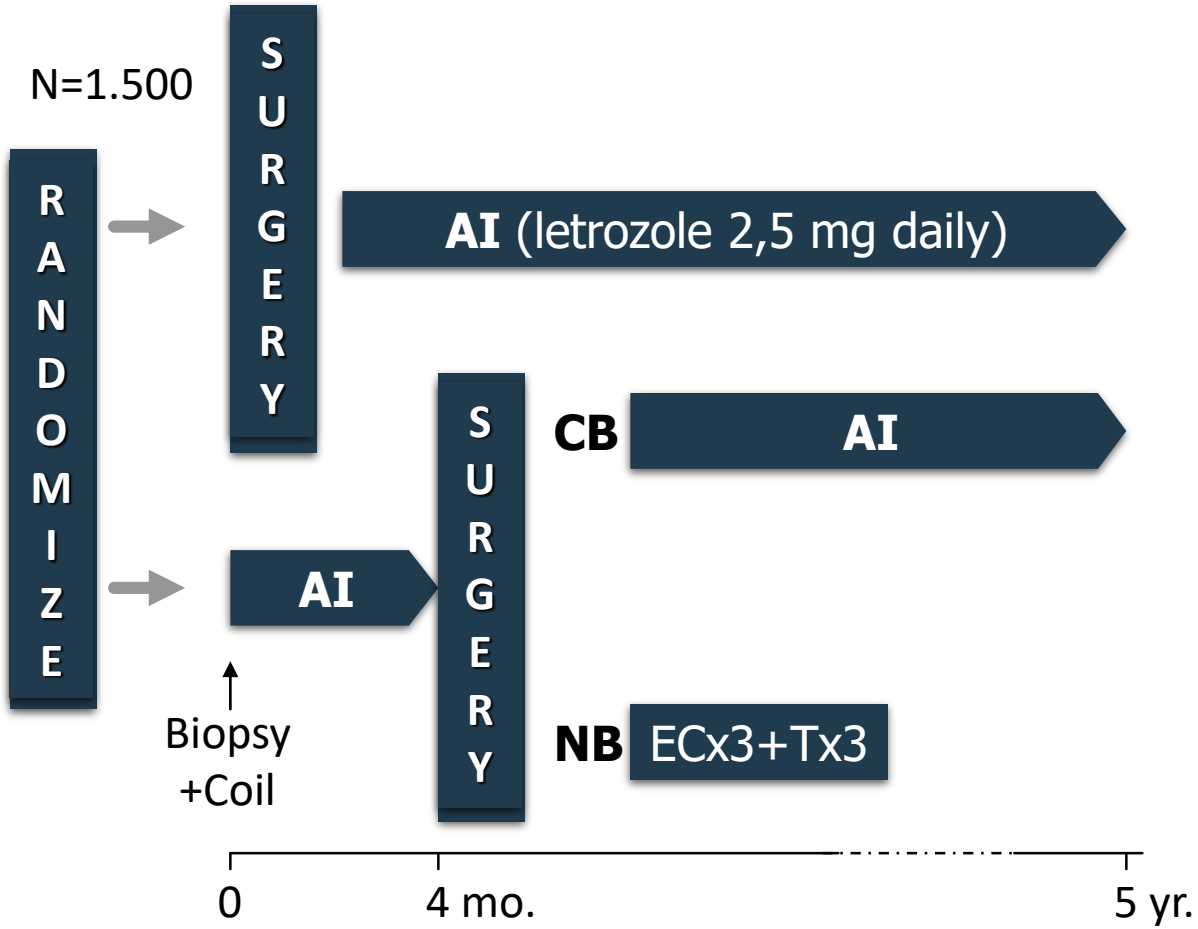
- Kemoterapi
  - Platin
  - wPac -docetaxel
  - EC or ddEC
- HER2 targeteret terapi
  - Double HER2
- Post-neoadjv. terapi
  - T-DM1
- NordicHER2 Trial

ER+/HER2÷

- Kemoterapi
  - Taxan
  - EC or ddEC
- Endokrin terapi
- Immunoterapi
- Post-neoadjv. terapi
  - AI / OFS+AI
- Nivo-Neo Trial

DBCG-07 REAL Trial

- **R**andomised trial of **E**ndocrine **A**gainst **L**ocoregional therapy first
- Eligible were women > 59 with operable ER positive BC and tumor size > 20mm.



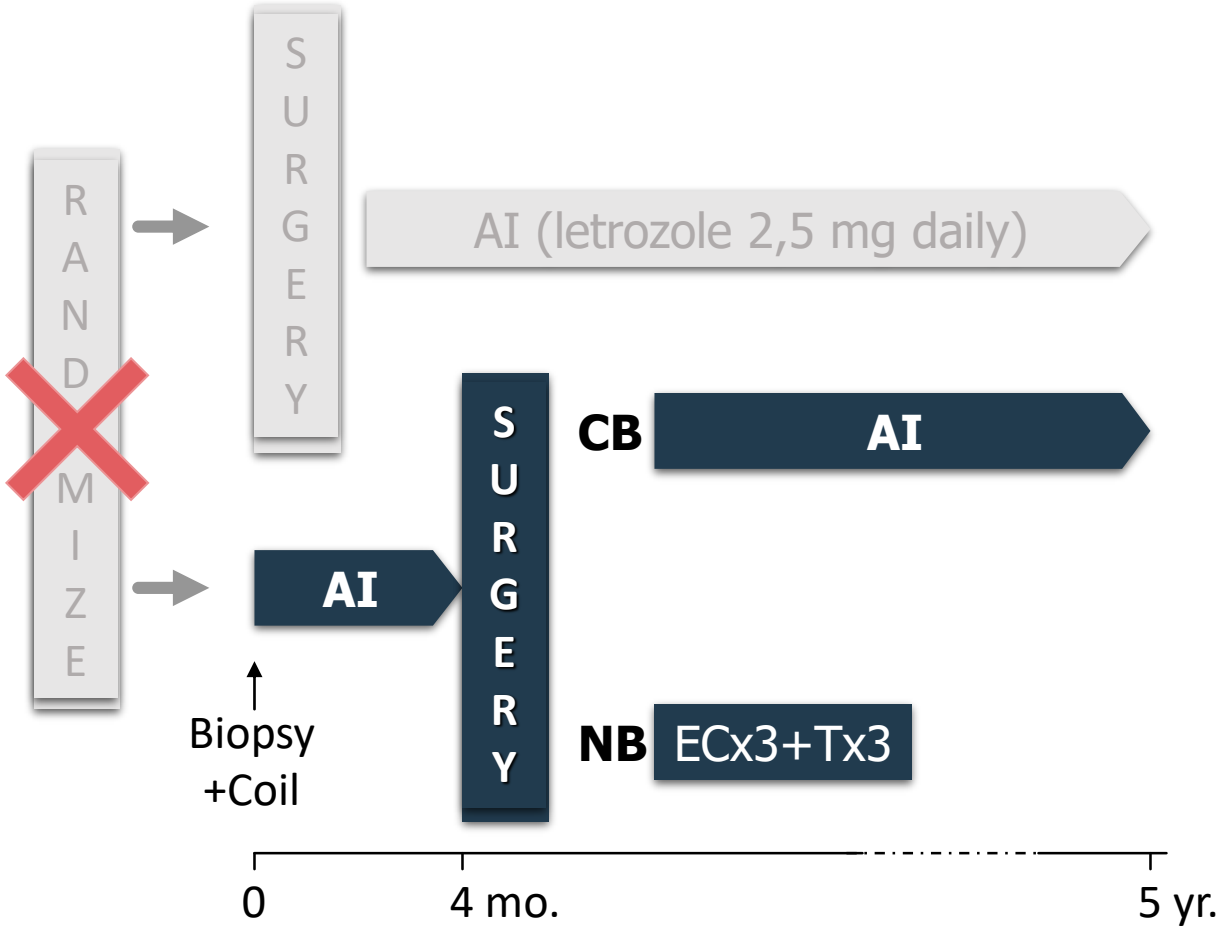
Timeline

November 2006	FU internat	Ideoplæg Protokol, 1. udkast
	Procedurer	Randomisering Datamoduler Monitorering Vævsindsamling
	Finansiering	1 mill. forskningsråd 25 mill. industrien 3 mill. KBVU
	Myndigheder	Etiske komiteer EMEA ClinTrial.gov
Februar 2009	Klar til start	Investigator møder Forsøgssteder initieres
April 2010	Rekruttering	31 deltagere
Juni 2010	REAL lukkes	EMEA og VEK info 25 forsøgssteder lukkes 28 mill. returneres

Skriver et al. Acta Oncol 2018; 57: 31-37

Neoadjuvant letrozole for postmenopausal estrogen receptor-positive, HER2-negative breast cancer patients

Signe K. Skriver, Anne-Vibeke Laenkholm, Birgitte B. Rasmussen BB, Jürgen Handler, Bo Grundtmann, Tove F. Tvedskov, Peer Christiansen, Ann S. Knoop, Maj-Britt Jensen, Bent Ejlertsen



Kort om REAL forsøget

- Investigator initieret og industri sponsoreret
  - Del-finansiering fra sponsor
  - DBCG stod for godkendelser og monitorering
- Central indsamling af væv og blod
  - FFPE til Herlev
  - Frosset væv til OUH (Dansk CancerBiobank)
  - Blodprøverne til RH
- Afsluttet juni 2010 (manglende rekruttering)
- Resultater
  - A total of 112 patients and pathological response evaluated in 109.
  - An overall mean 15% decrease in tumor size ($p<.0001$)
  - One pCR and 55% had a partial pathological response (≥30 tumor cell loss)
- Publikation
  - Acta Oncol i 2018 som led i ph.d.

Skriver et al. Acta Oncol 2018; 57: 31-37

Neoadjuvant Systemic Therapy Procedures in Case of No Early Response

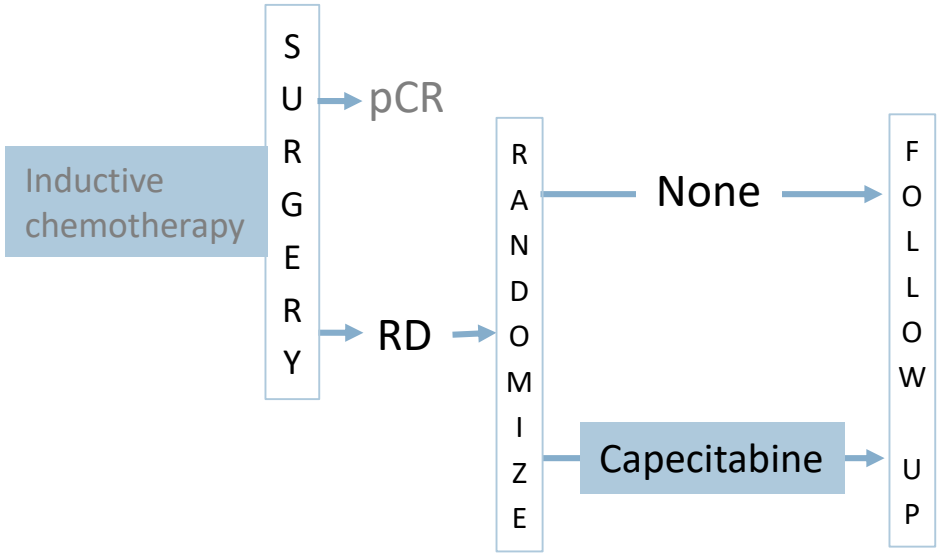
Guidelines Breast
Version 2019.1

	Oxford LoE	GR	AGO
In case of no change:			
▪ Completion of neoadjuvant chemotherapy (NACT) followed by surgery	2b	C	++
▪ Continuation of NACT with non cross-resistant regimen	2b	B	+
▪ AC or EC x 4 → D x 4 or Pw x 12	2b	B	+
▪ DAC x 2 → NX x 4	1b	B	+
In case of progressive disease:			
▪ Stop of NACT and surgery or radiotherapy	4	D	++
▪ Additional adjuvant chemotherapy with non cross-resistant regimen	4	D	+/-

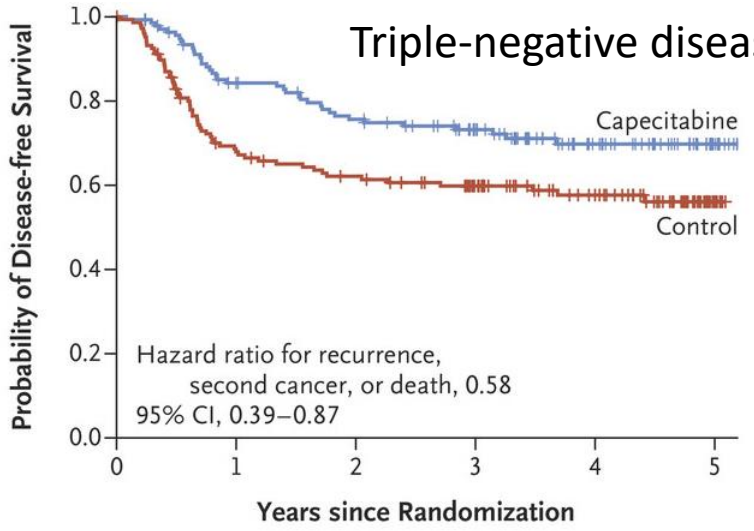
The NEW ENGLAND JOURNAL *of* MEDICINE
ESTABLISHED IN 1812 JUNE 1, 2017 vol. 376 no. 22

Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy

N. Masuda, S.-J. Lee, S. Ohtani, Y.-H. Im, E.-S. Lee, I. Yokota, K. Kuroi, S.-A. Im, B.-W. Park, S.-B. Kim, Y. Yanagita, S. Ohno, S. Takao, et al.



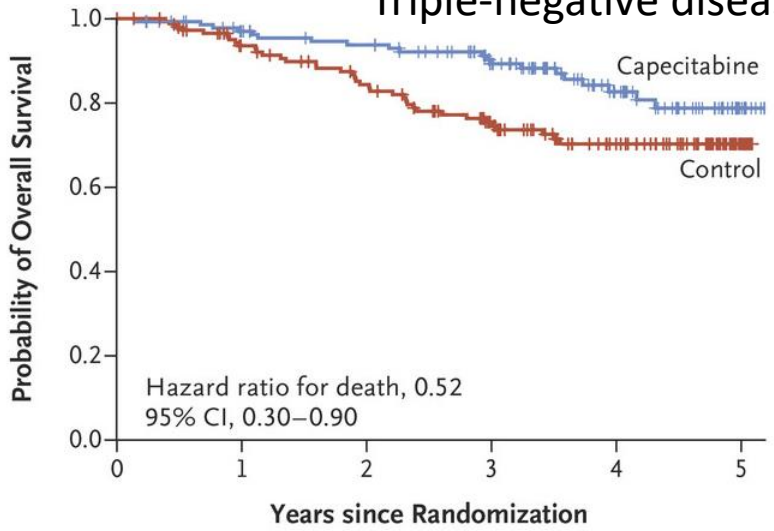
Triple-negative disease



No. at Risk

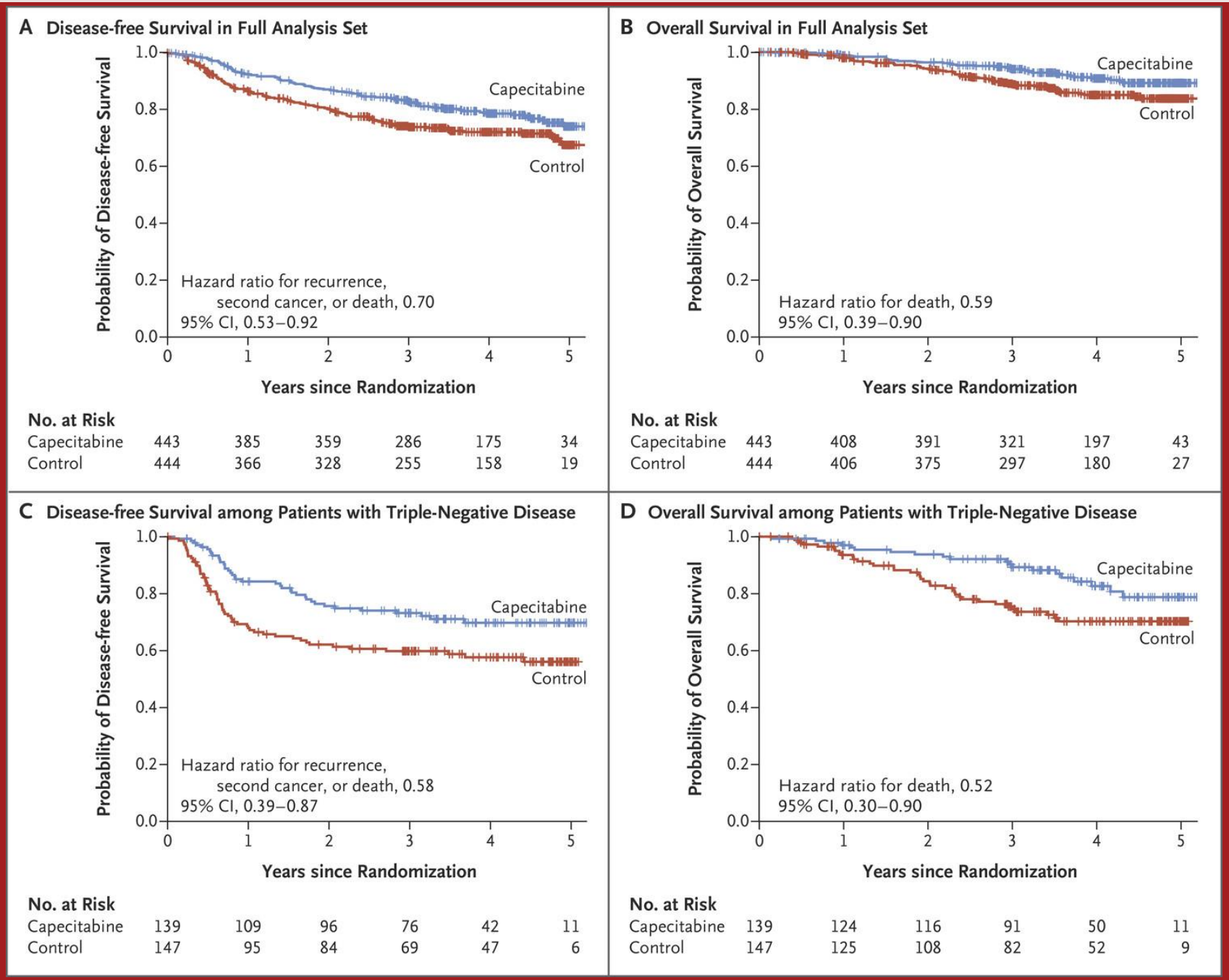
Capecitabine	139	109	96	76	42	11
Control	147	95	84	69	47	6

Triple-negative disease



No. at Risk

Capecitabine	139	124	116	91	50	11
Control	147	125	108	82	52	9



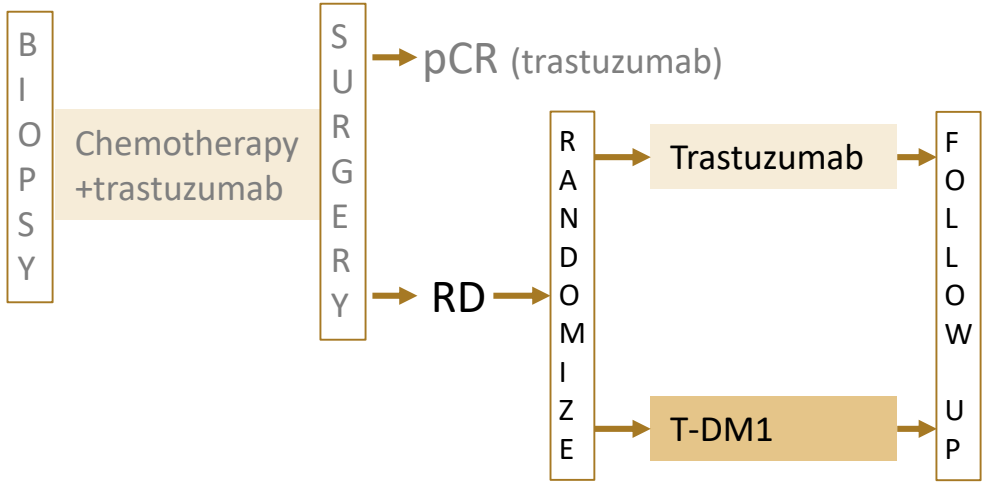
Masuda N et al.
N Engl J Med 2017;376:2147-2159.

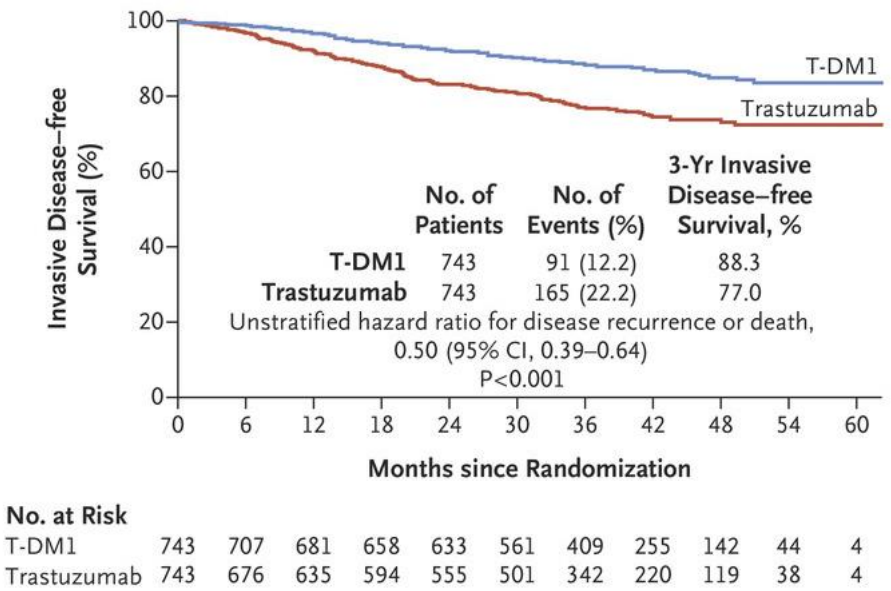
The NEW ENGLAND JOURNAL of MEDICINE

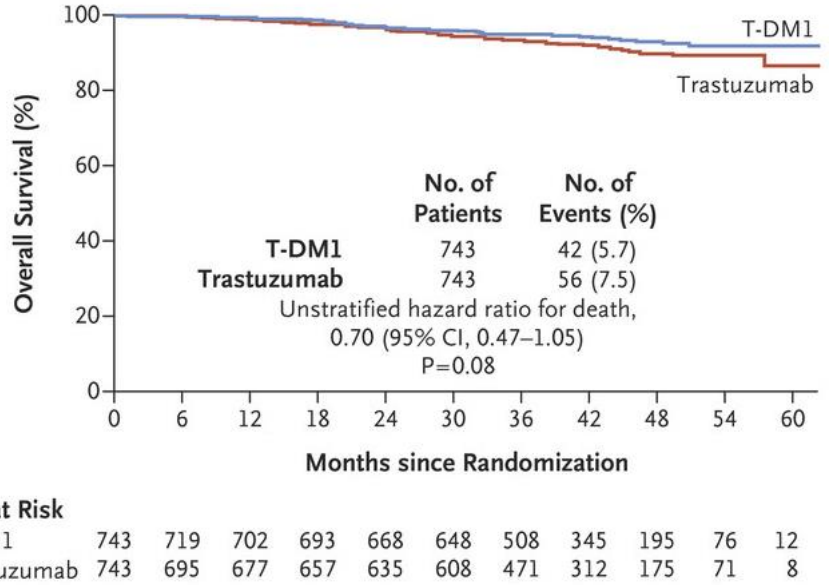
The NEW ENGLAND JOURNAL *of* MEDICINE
ESTABLISHED IN 1812 FEBRUARY 14, 2019 vol. 380 no. 7

Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer

G. von Minckwitz, C.-S. Huang, M.S. Mano, S. Loibl, E.P. Mamounas, M. Untch, et al., for the KATHERINE Investigators







The Katherine Study