Neoadjuverende protokoller på vej

NACT

ER+/HER2÷
ER÷/HER÷(TNBC)
HER2+

Kemoterapi	Taxan & EC or ddEC?
Endokrin terapi	How long?
	Immunoterapi?
Post-neoadjv. terapi	AI / OFS+AI?

Kemoterapi	Taxan – nabpaclitaxel? & EC or ddEC?
	Carbo?
	Immunoterapi? If – how long?
Post-neoadjv. terapi	Cis/carbo?

Kemoterapi	wPac-docetaxel? EC or ddEC? Platin?
HER2 targeteret terapi	Double HER2 blocade?
Post-neoadjv. Terapi	T-DM1

Protokoller

ER+/HER2÷(High Risk ERpos)

Nivo-Neo Trial

ER÷/HER÷ (TNBC)

NordicTrip Trial

HER2+

NordicHER2 Trial

Christina Bjerre, RH National Coordinator

ER+, HER2- Nivo-Neo Trial

Nivo-Neo Trial
ER+, HER2-, High Risk

- 1400 participants will be screened to treat 1200 eligible participants with
- nivolumab (Arm A; n = 600) or
- nivolumab placebo (Arm B; n = 600)
- in combination with neoadjuvant chemotherapy and adjuvant ET

Page: 1

Protocol Number: CA2097FL
IND Number: 136,843
EX-US Non-IND
EUDRACT Number: 2019-002469-37
Date: 01-Jul-2019

CLINICAL PROTOCOL CA2097FL

A Randomized, Multicenter, Double-blind, Placebo-controlled Phase 3 Study of Nivolumab Versus Placebo in Combination With Neoadjuvant Chemotherapy and Adjuvant Endocrine Therapy in Patients With High-risk, Estrogen Receptor-Positive (ER+), Human Epidermal Growth Factor Receptor 2-Negative (HER2-) Primary Breast Cancer

(CheckMate 7FL: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 7FL)

Short Title:

Nivolumab or Placebo with Neoadjuvant Chemotherapy and Adjuvant Endocrine Therapy in ER+/HER2- Breast Cancer

Studiedesign

ER+, HER2- (konfimeret)
Grad III **eller** grad II med ER 1-9%
Inflammatorisk sygdom kan indgå

Væv tilrådighed
PS: 0-1

PDL-1 ≥ 1% el. < 1%
Grade II el III
N+/-
Dose-dense or not

R

O

Nivolumab +
12 x P q1 + 4 x AC q2

Nivolumab 7 mdr.
Endokrin behandling

Placebo +
12 x P q1 + 4 x AC q2

Placebo 7 mdr.
Endokrin behandling

Under studiet - livskvalitet

EORTC QLQ-C30

EORTC QLQ-BR23

EQ-5D-5L

FACIT GP5

Under studiet - PK

12 “ekstra blodprøver”

Table 9.5-1: Pharmacokinetic and Anti-drug Antibody Sampling Schedule for All Participants (CA2097FL)

Study Day of Sample Collection	Event	Time (Relative To Nivolumab/Placebo Dose) Hour:Min	Nivolumab PK Sample	Nivolumab IMG Sample
Neoadjuvant (Pre-surgery) PTX Treatment (Cycles 1-4, 1 cycle = 3 weeks)				
C1D1	Predose[a]	0:00	X	X
	EOI[b]	0:30	X	
C2D1	Predose[a]	0:00	X	X
C3D1	Predose[a]	0:00	X	X
Neoadjuvant (Pre-surgery) AC Treatment (Cycles 1-4, 1 cycle = 2 or 3 weeks)				
C1D1	Predose[a]	0:00	X	X
C2D1	Predose[a]	0:00	X	X
C3D1	Predose[a]	0:00	X	X
Adjuvant (Post-surgery)Treatment (Cycles 1-7, 1 cycle = 4 weeks)				
C1D1	Predose[a]	0:00	X	X
	EOI[b]	0:30	X	
C2D1	Predose[a]	0:00	X	X
C3D1	Predose[a]	0:00	X	X
C7D1	Predose[a]	0:00	X	X

Abbreviations: AC = anthracycline + cyclophosphamide; C = cycle; D = day; EOI = end of infusion; IMG = immunogenicity; PK = pharmacokinetic; PTX = paclitaxel.

Under studiet - evaluering

- Images will also be submitted to a central imaging vendor and may undergo blinded independent central review (BICR) at any time during the study

Biomarkører

- PD-L1(confirmed), PD-1,GEP, CD8 density, and TIL subsets in the tumor. CD3, CD8, major histocompatibility complex class I/II, and CD163. Analyses of messenger RNA (mRNA; and/or micro RNA [miRNA]) will be completed using RNA isolated from tumor tissue.
- Secondly, pharmacodynamics biomarkers reflective of overall intratumoral inflammation status may be assessed using pre- and post-treatment tumor samples to understand potential synergistic effects of combination therapy.
- Peripheral pharmacodynamics biomarkers may be assessed via immuno-phenotyping and cytokine immunoassays using blood specimens.
- Potential utility of circulating tumor DNA (ctDNA) and/or other circulating biomarkers in monitoring microscopic residualdisease burden and detecting recurrence will also be evaluated.

Biopsi & Biomarkører

- a: Biomarker sampling may be obtained
- b: Whole blood for DNA sample may be taken on C1D1 or any other visit.
- **D: Tumor tissue submission prior to randomization is mandatory. A fresh biopsy is required if a recent tumor specimen (collected 60 days) is not available.**
- E: Optional tumor biopsy at this timepoint (▫2 days, if clinically feasible).
- F:Blood draw at this timepoint may occur ▫2 days of the day of surgery.
- G: Surgical resection tumor sample collection at the time of surgery is required for biomarker analysis.
- H: If biopsy or surgical resection is performed at time of disease recurrence and/or progression, a tumor sample (within 40 days) should be submitted to the central laboratory.
- i: ctDNA plasma collection at 1 year from start of adjuvant treatment, and then annually until the end of study

Table 9.8-1: Biomarker Sampling Schedule for All Participants (CA2097FL)

Study Day of Sample Collection	Event	Serum for Soluble Factor[a]	Whole Blood for Immunophenotyping[a]	Whole Blood for PBMC[a]	Whole Blood for DNA[b]	Whole Blood for RNA[a]	Plasma for ctDNA[a]	Stool Microbiome[c]	Tumor Biopsy
Screening									X[d]
Neoadjuvant (Pre-surgery) PTX Treatment (Cycles 1-4, 1 cycle = 3 weeks)									
C1D1	Predose	X	X	X	X	X	X	X	
C2D1	Predose	X	X	X		X	X		X[e]
Neoadjuvant (Pre-surgery) AC Treatment (Cycles 1-4, 1 cycle = 2 or 3 weeks)									
C1D1	Predose	X	X	X		X	X		
C3D1	Predose	X	X	X		X	X		
Surgery		X[f]	X[f]	X[f]		X[f]	X[f]		X[g]
Adjuvant (Post-surgery) Treatment (1 cycle = 4 weeks)									
C2D1	Predose	X	X	X		X	X		
C3D1	Predose	X	X	X		X	X		
C7D1	Predose	X	X	X		X	X		
End of Adjuvant Therapy							X		
Disease Recurrence and/or Progression		X	X	X		X	X		X[h]
Follow up Period									
Follow ups (annually until the end of study)[i]							X		

Patologi efter OP: RCB

- The primary tumor bed area in its 2 dimensions. For multifocal tumors (defined as the presence of 2 or more foci of cancer within the same breast quadrant), the largest lesion must be ≥ 2 cm and designated as the “target” lesion for the RCB determination.
- The overall cancer cellularity (percentage of area).
- The proportion of in situ disease (percentage of area).
- The number of positive lymph nodes.
- The diameter of the largest lymph node metastasis.

Timelines

I DK forventes første pt randomiseret i feb 2020

BMS indsender til Etisk Komite og LMS i november

4 sites i DK - RH, Herlev, Næstved og Århus, 5 pt hvert sted.

39 mdrs enrollment

Standardbehandling til high risk, ER+, HER2-

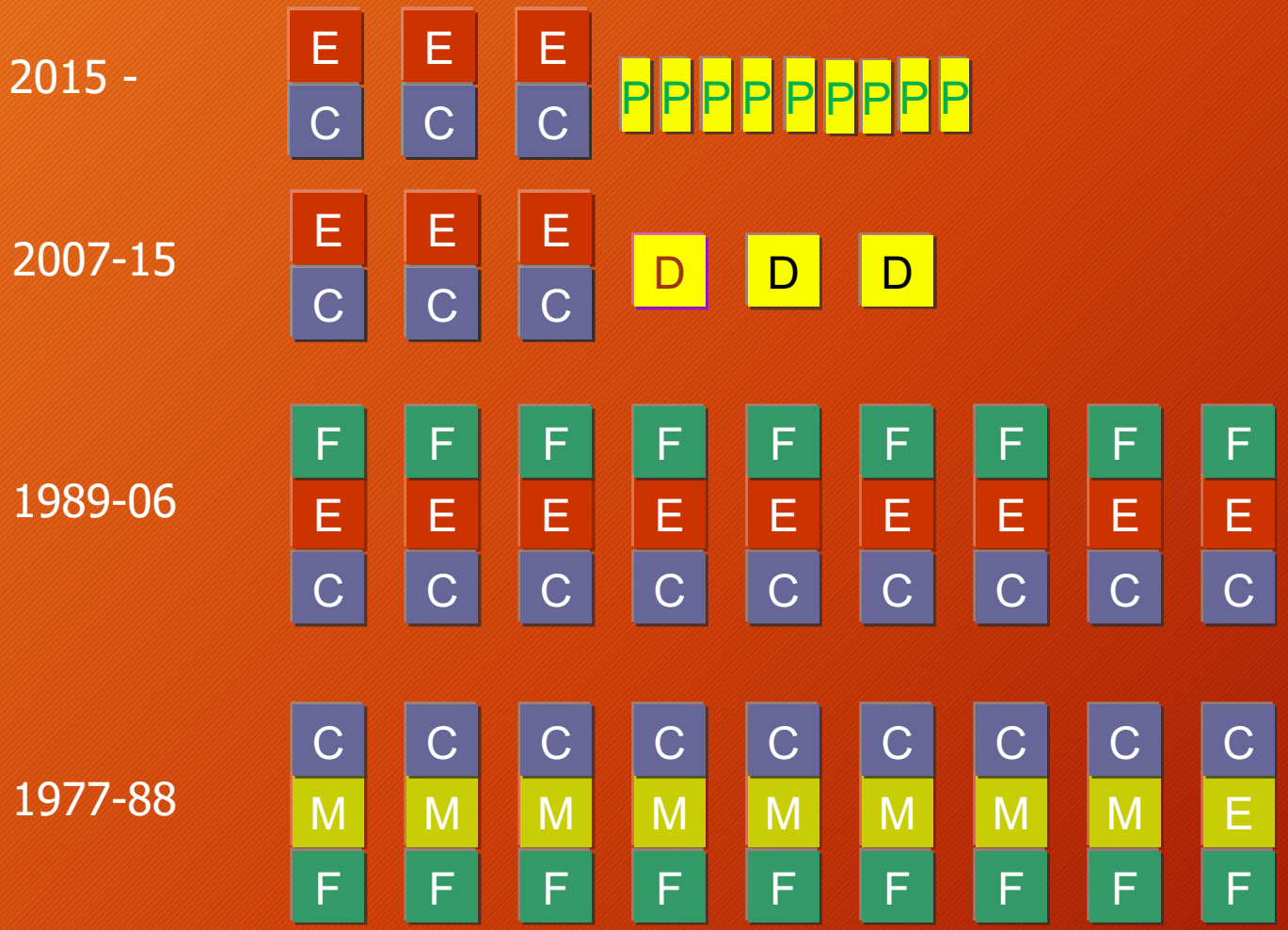
12 x P q1 + 4 x AC q2 → Endokrin behandling

Bent Ejlertsen, RH National Coordinator

ER-, HER2- NordicTrip Trial

Først lidt baggrund….

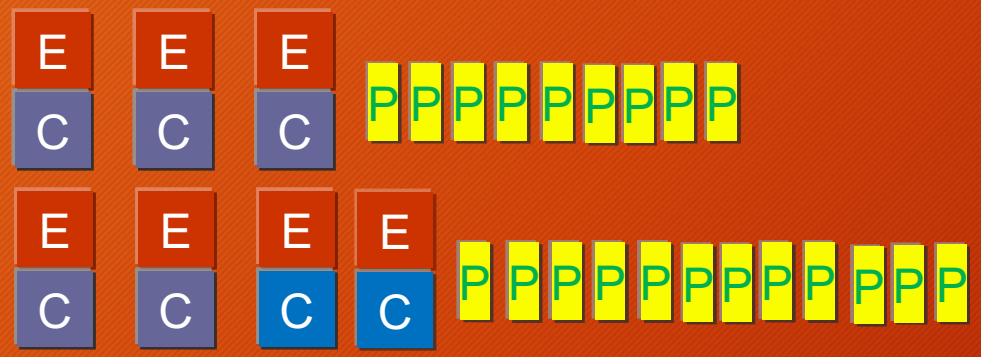
Kemoterapi i DBCG



Standard behandling til eTNC 2019

(neo)Adjuverende

Downstaging



Hvis ikke pCR + 6 mdr's Capecitabine

Nye spillere på TNBC banen

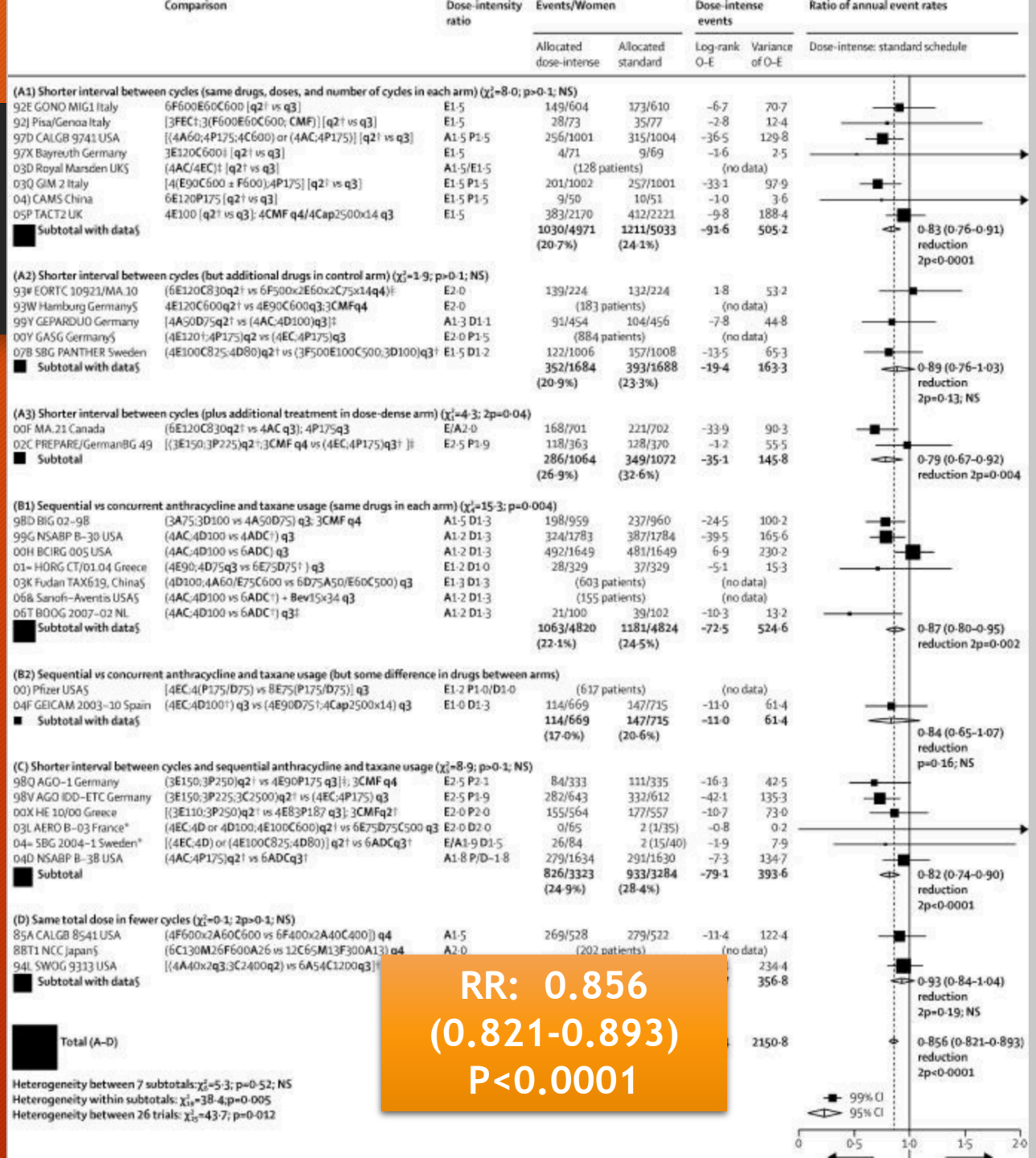
- Dose-dense kemoterapi
- Capecitabine
- Immunterapi
- Carboplatin
- PARPi

Dose-Dense

Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37298 women with early breast cancer in 26 randomised trials

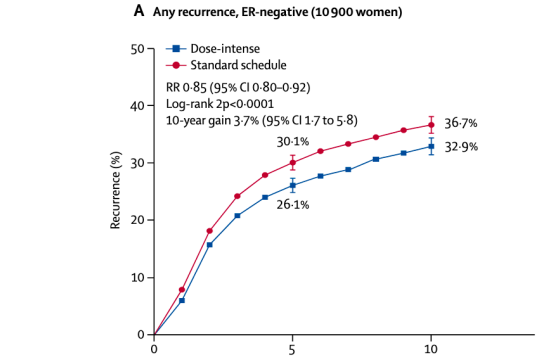
- Reduktionen er nok moderat, men
- Standard kemoterapi vs. ingen reducerer risikoen for brystkræftdød med 1/3.
- Dose-dense kemoterapi vs. ingen - med antracyclin og taxan – nedsætter risikoen for brystkræftdød med ca 40% de første 10 år efter diagnose.

EBCTCG: Early Breast Cancer Trialists' Collaborative Group
Lancet 2019; 393: 1440–52



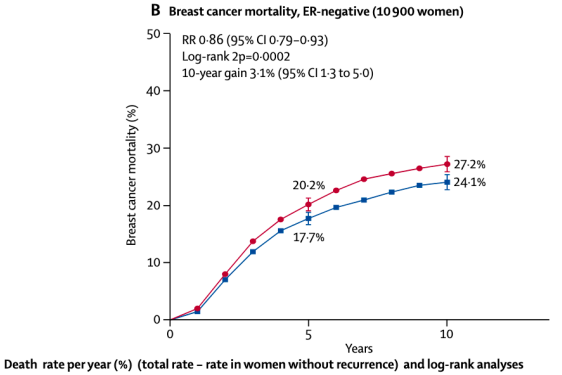
EBCTCG: Early Breast Cancer Trialists' Collaborative Group

Lancet 2019; 393: 1440–52



Recurrence rate per year (%) and log-rank analyses

Allocation	Years 0–4	Years 5–9	Years ≥10
Dose-intense	6·32 (1374/21 741)	1·99 (213/10 697)	1·50 (64/4266)
Standard schedule	7·45 (1593/21 390)	2·10 (217/10 342)	1·50 (66/4387)
Rate ratio (95% CI) from	0·84 (0·77–0·91)	0·94 (0·75–1·12)	0·98 (0·63–1·33)
(O–E)/V	−119·8/671·3	−6·6/103·5	−0·7/31·7



Death rate per year (%) (total rate – rate in women without recurrence) and log-rank analyses

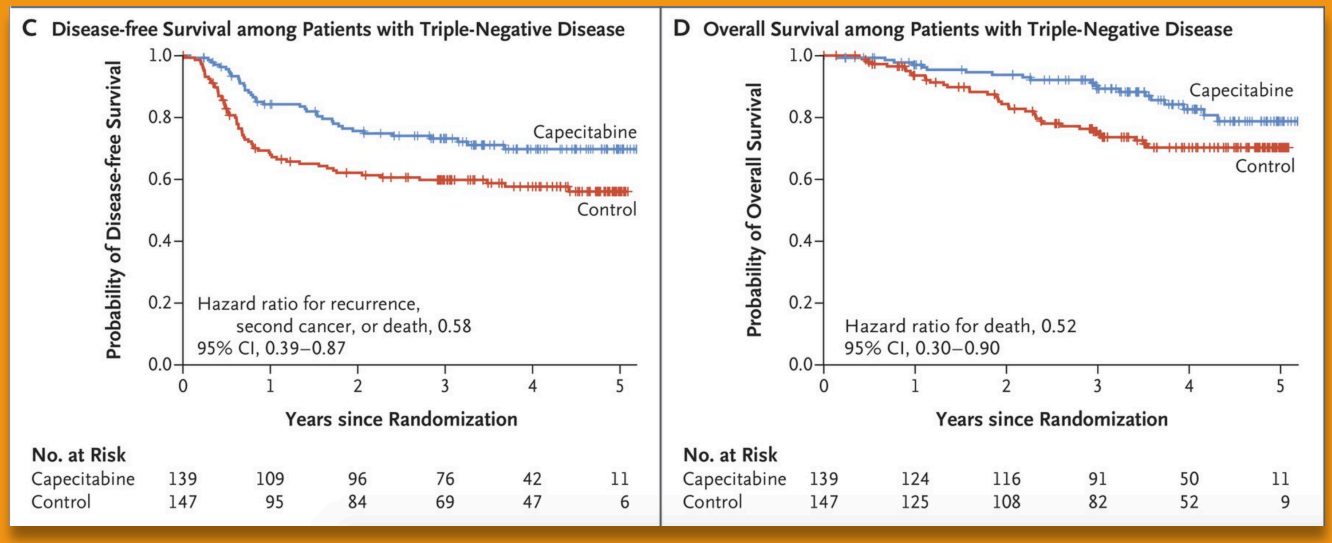
Allocation	Years 0–4	Years 5–9	Years ≥10
Dose-intense (95% CI)	3·92 (3·67–4·18)	1·76 (1·52–1·99)	0·77 (0·55–1·00)
Standard schedule (95% CI)	4·47 (4·20–4·74)	2·07 (1·82–2·33)	0·82 (0·59–1·04)
Rate ratio (95% CI) from	0·86 (0·78–0·95)	0·83 (0·66–1·00)	0·94 (0·54–1·34)
(O–E)/V	−68·3/463·1	−20·9/111·7	−1·4/22·5

Figure 6: **10-year recurrence (A) and breast cancer mortality (B) by oestrogen receptor status**

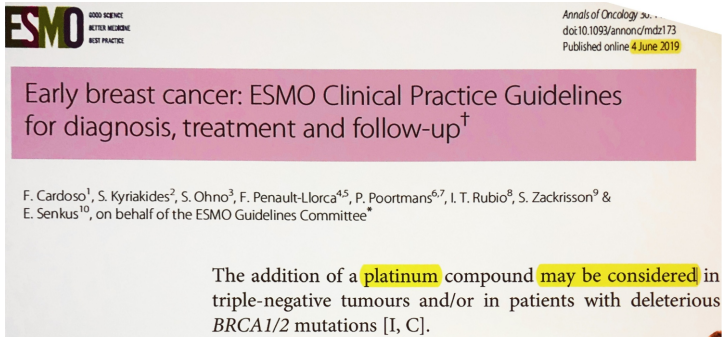
Post-adjuverende Xeloda

Post-neoadjuverende capecitabine

June 1, 2017
N Engl J Med 2017; 376:2147-2159
DOI: 10.1056/NEJMoa1612645



Carboplatin til eTNBC



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 3…
doi:10.1093/annonc/mdz173
Published online 4 June 2019

Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

F. Cardoso[1], S. Kyriakides[2], S. Ohno[3], F. Penault-Llorca[4,5], P. Poortmans[6,7], I. T. Rubio[8], S. Zackrisson[9] & E. Senkus[10], on behalf of the ESMO Guidelines Committee*

The addition of a platinum compound may be considered in triple-negative tumours and/or in patients with deleterious *BRCA1/2* mutations [I, C].

ESO-ESMO 3rd international consensus guidelines for breast cancer in young women (BCY3)

Shani Paluch-Shimon [a,1], Olivia Pagani [b,1], Ann H. Partridge [c], Omalkhair Abulkhair [d], Maria-João Cardoso [e], Rebecca Alexandra Dent [f], Karen Gelmon [g], Oreste Gentilini [h], Nadia Harbeck [i], Anita Margulies [j], Dror Meirow [a], Giancarlo Pruneri [l], Elzbieta Senkus [m], Tanja Spanic [n], Medha Sutliff [o], Luzia Travado [e], Fedro Peccatori [k,2], Fatima Cardoso [e,*,2]

- The incorporation of platinum agents in TNBC or *BRCA*-associated tumors in the neo-adjuvant setting to improve pathological complete response rates (pCR) ***may be considered, however, remains controversial***.
- The use of platinum agents can further adversely impact fertility and increased toxicity may compromise standard duration and dosing of systemic treatment, and this needs to be clearly communicated to patients.

NCCN Guidelines v3. 2019

- Even though the results of randomized trials show improvement in pCR rates when carboplatin is added to anthracycline- and taxane-based chemotherapy, the long-term outcomes such as OS or DFS associated with the incorporation of carboplatin are not yet known. Therefore, at this time, the NCCN Panel ***does not*** recommend addition of carboplatin to neoadjuvant standard chemotherapy for patients with TNBC outside a clinical trial setting,

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2019
Invasive Breast Cancer

Neoadjuverende Carboplatin til TNBC?

Et vedvarende tilbagevendende spørgsmål

Neoadjuverende Carboplatin til TNBC?

Traditionelle brystkræft studier har fokuseret på ”ad on” behandli reducerer tilba

Neoadjuverende kemoterapi har nogle e:

vurdering af om det er den kemoterapi – surrogat rer

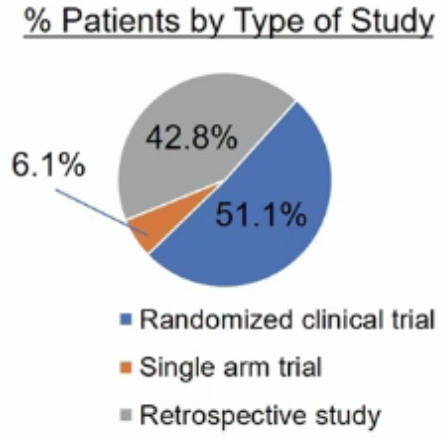
operationsreslutat

Carboplatin – vs. pCR – vs. Overlevelse?????

Metaanalyse SABCC 2018 Spring L

Results: Select Study Characteristics

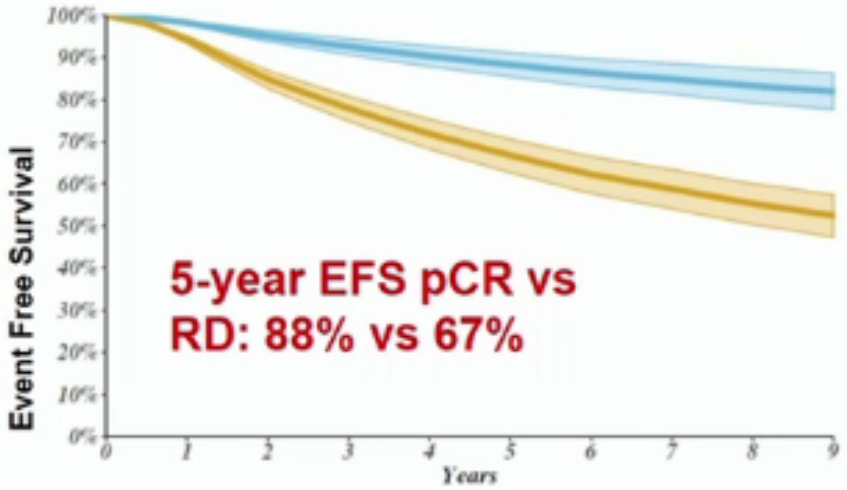
- Publication dates (range): 1999-2016
- Broad global patient population, including United States, Mexico, Europe, Kuwait, Saudi Arabia, China, Japan, and Korea
- Median follow-up for recurrence (range): 48 months (21.3-107)
- Median follow-up for survival (range): 49.9 months (31.2-118)

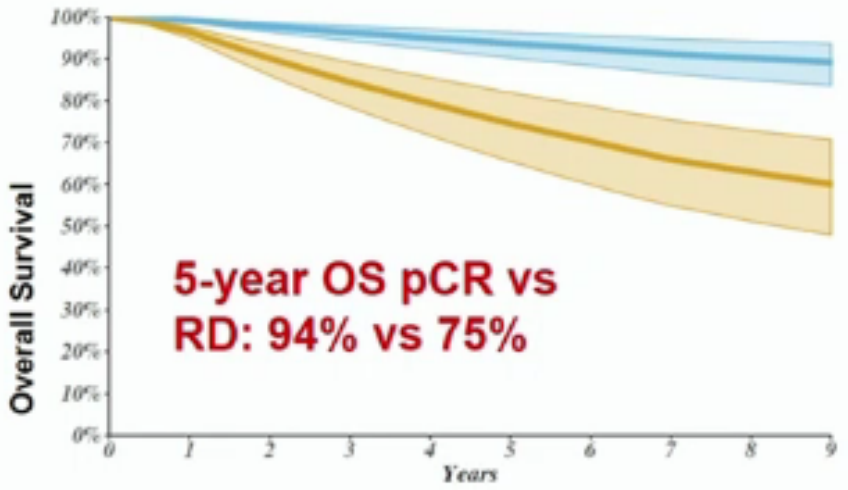


Knapt 30.000 pt

pCR and EFS _ OS

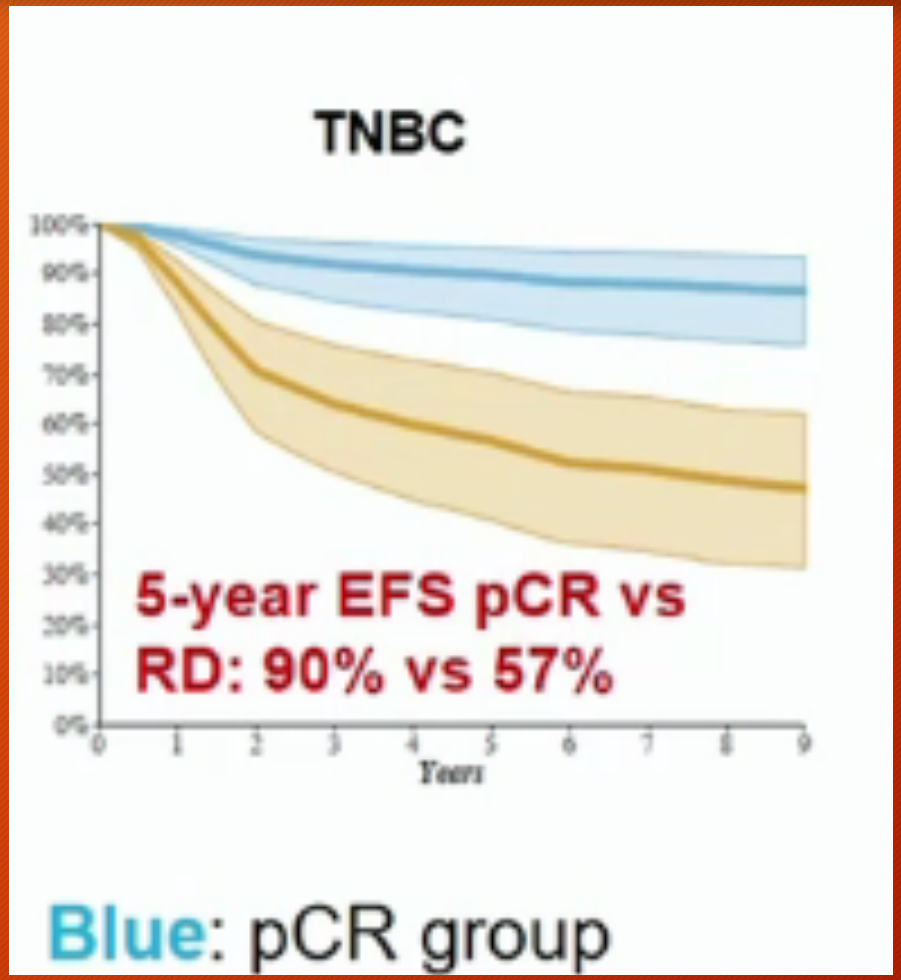
Results: EFS and OS in Overall Population



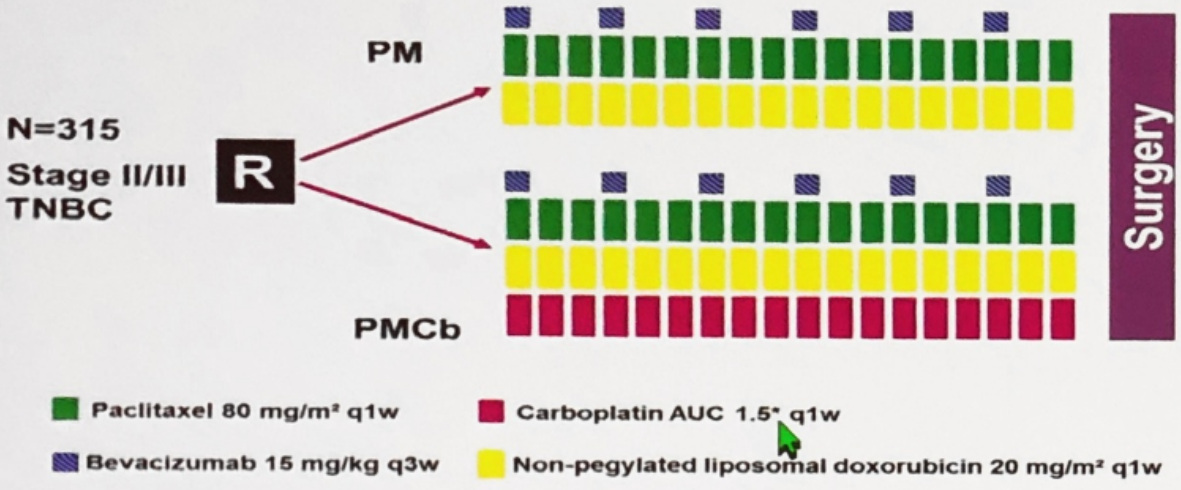


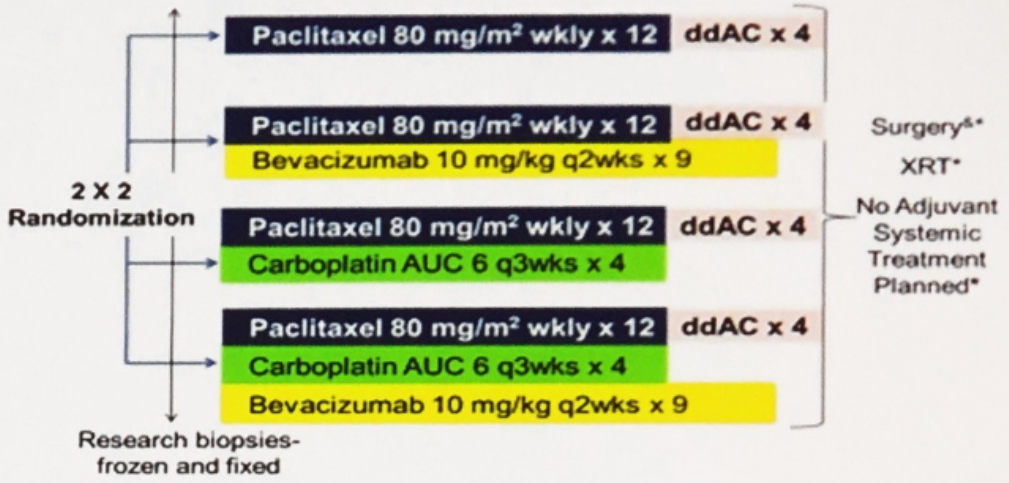
Blue: pCR group
Orange: Residual disease (RD) group

pCR og OS og subtype



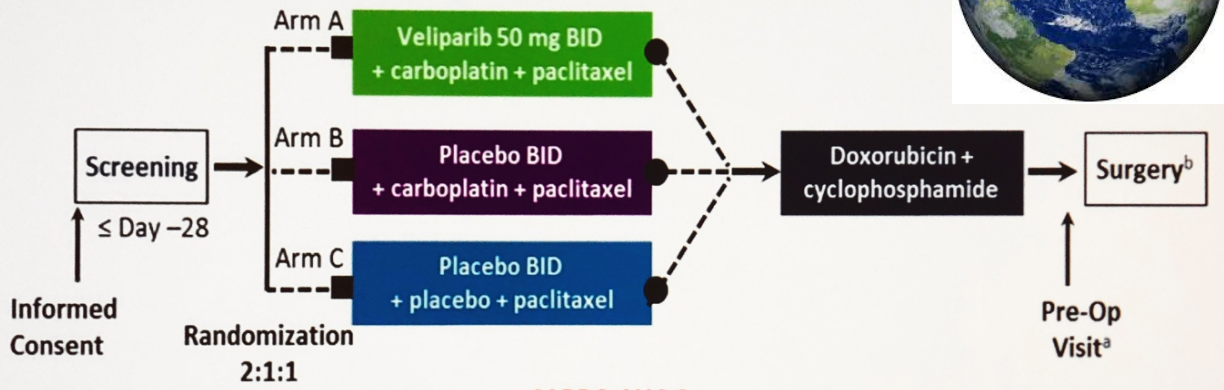
GeparSixto and CALGB 40603:



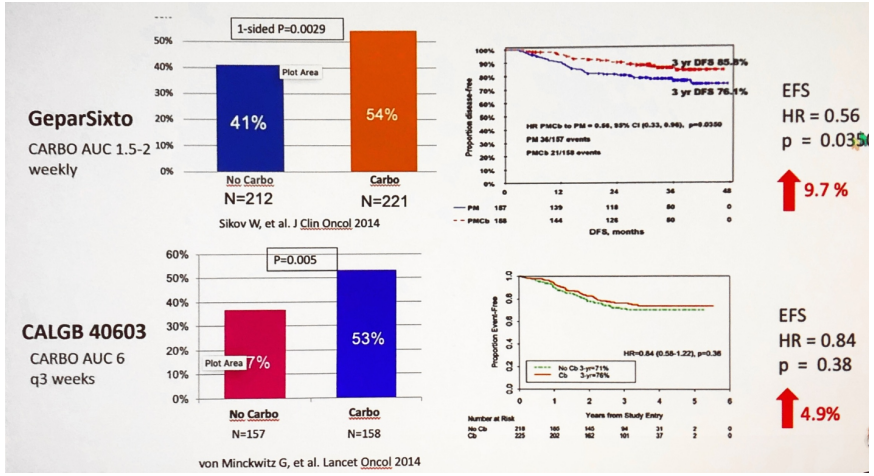


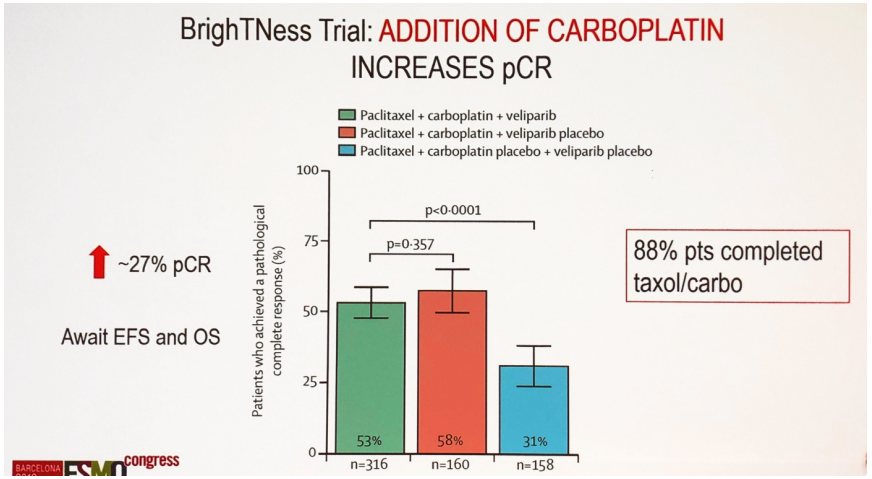
BrighTNesS TRIAL

145 sites in 15 countries



Carboplatin gav øget pCR





Loibl S Lancet Oncol 2018

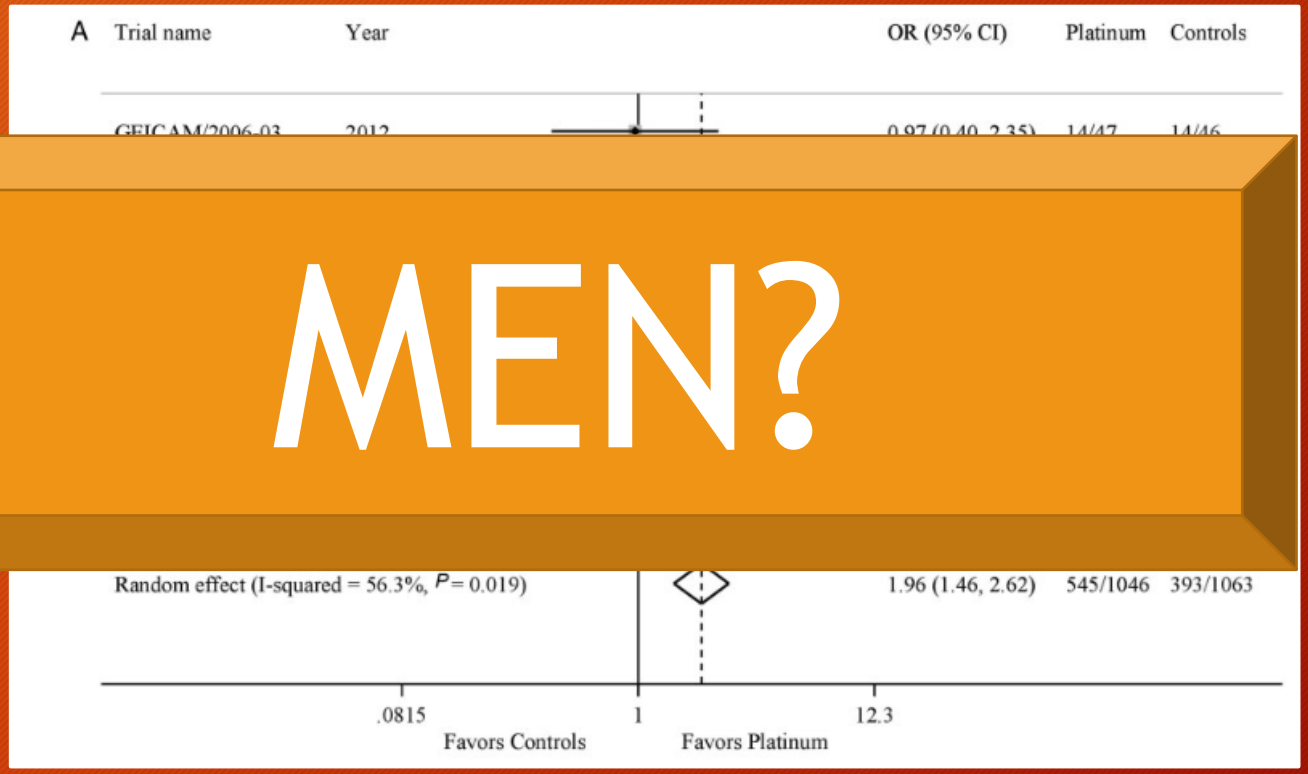
Neoadjuverende carboplatin

Studier har N til at finde pC

ikke langtidsoverlevelse….

Platin-baseret NACT øger p

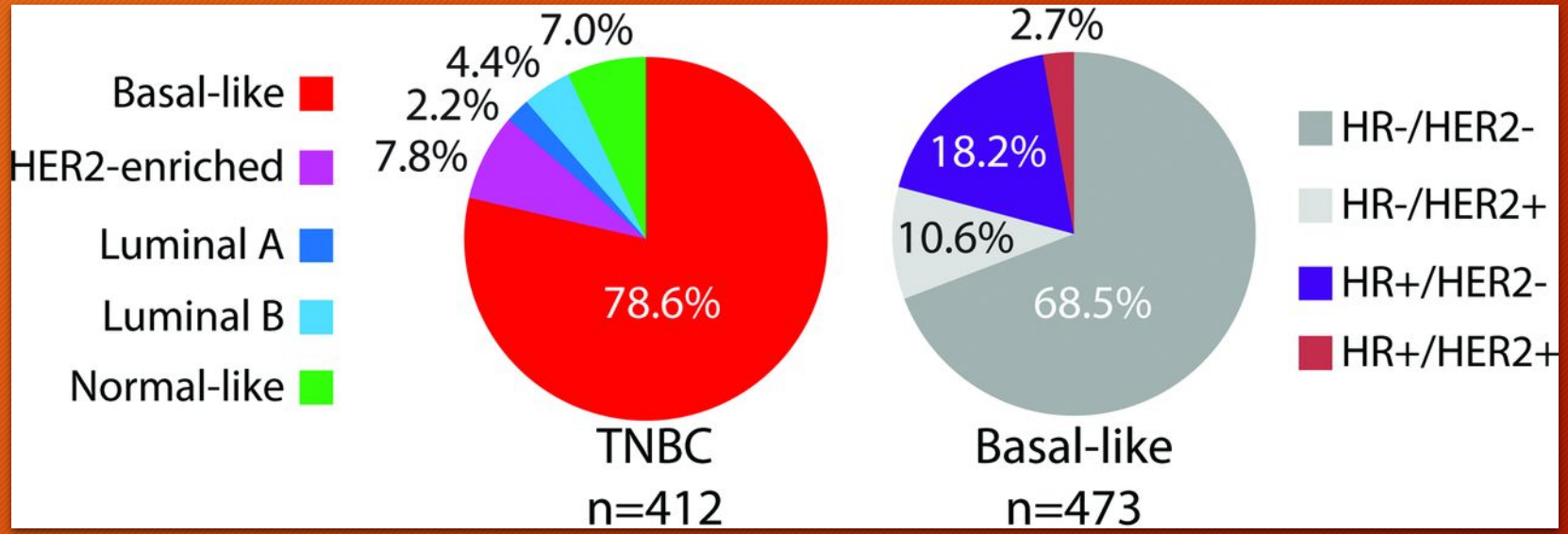
fra 37,0% - 52,1%, p< 0.001



MEN?

Poggio F Ann Oncol 2018

TNBC er en heterogen sygdom – usandsynligt at mere kemo (eller platin) er nødvendig til alle

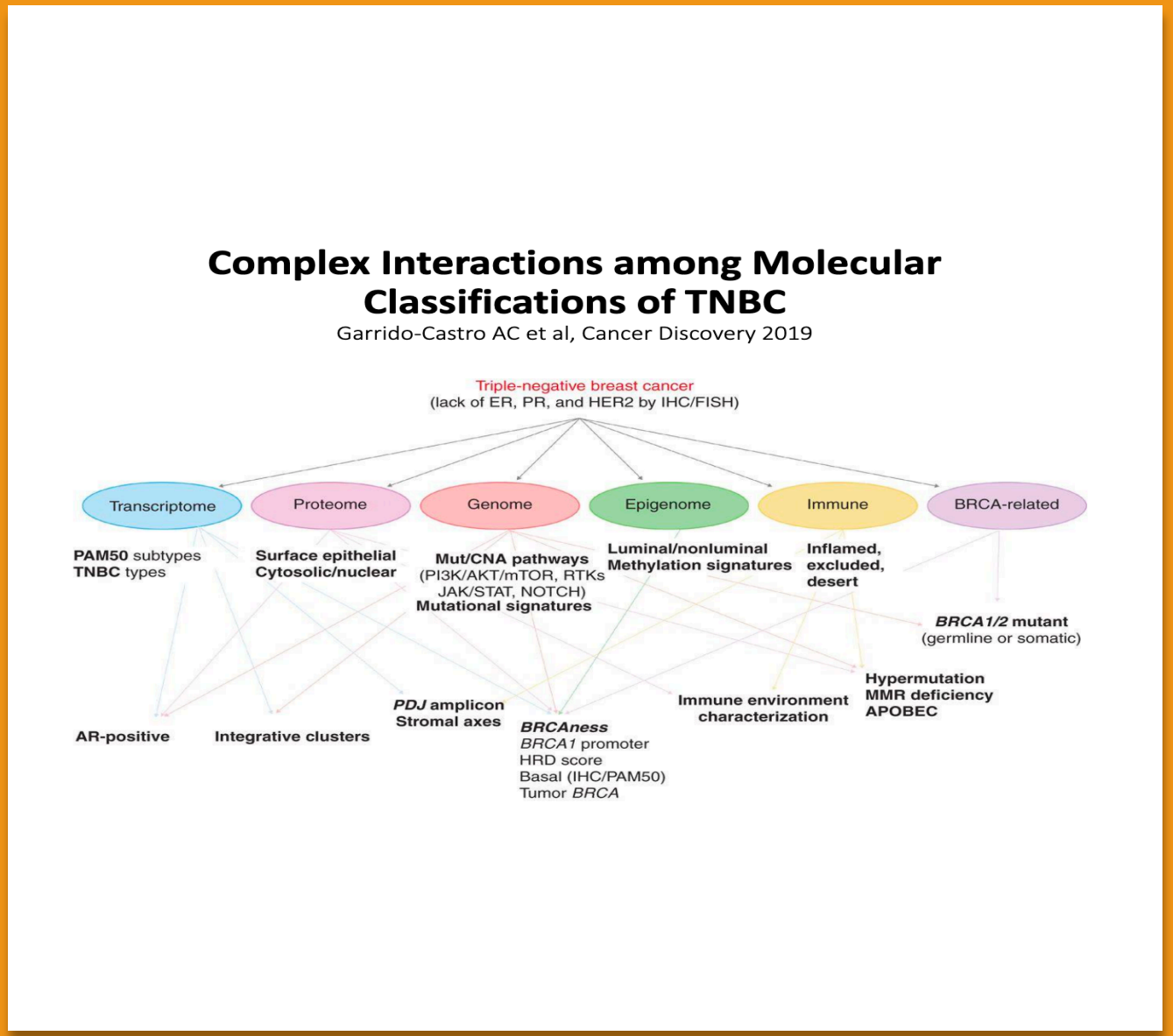


Distribution of the intrinsic molecular and pathology-based subtypes within triple-negative and basal-like tumors.
Abbreviations: HR, hormone receptor; TNBC, triple-negative breast cancer.

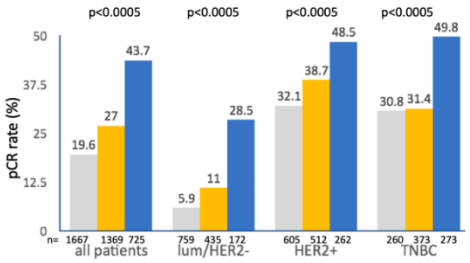
Aleix Prat et al. The Oncologist 2013;18:123-133

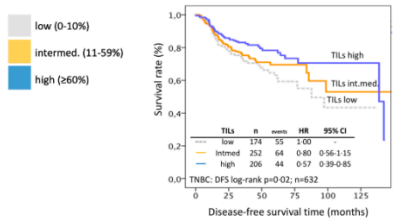
The Oncologist

TNBC er en heterogen sygdom – usandsynligt at mere kemo (eller platin) er nødvendig til alle



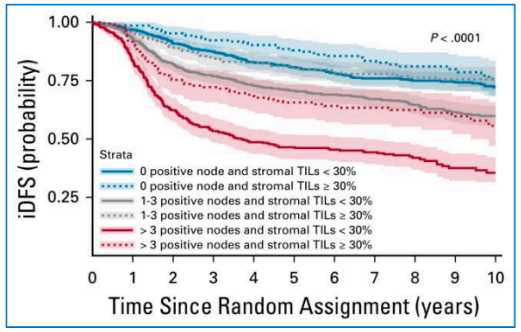
Neoadjuvant
(n=3771, GBG trials)





Denkert et al, Lancet Oncol, 2018

Adjuvant
(n=2148, TNBC)



Loi et al, J Clin Oncol. 2019, Mar 1

Current guidelines

St. Gallen consensus 2019
„...the panel recommended that tumor infiltrating lymphocytes (TILs) be routinely characterized in triple negative breast cancer (TNBC) because of their prognostic value."

New WHO classification of breast tumors (in preparation)
TILs are a new standard biomarker in TNBC

Ann Oncol. 2019 Aug 2. pii: mdz235. doi: 10.1093/annonc/mdz235. [Epub ahead of print]

Estimating the Benefits of Therapy for Early Stage Breast Cancer The St Gallen International Consensus Guidelines for the Primary Therapy of Early Breast Cancer 2019.

Burstein HJ[1], Curigliano G[2], Loibl S[3], Dubsky P[4], Gnant M[5], Poortmans P[6], Colleoni M[2], Denkert C[7], Piccart-Gebhart M[8], Regan M[9], Senn HJ[10], Winer EP[1], Thurlimann B[10].

BARCELONA 2019 ESMO congress

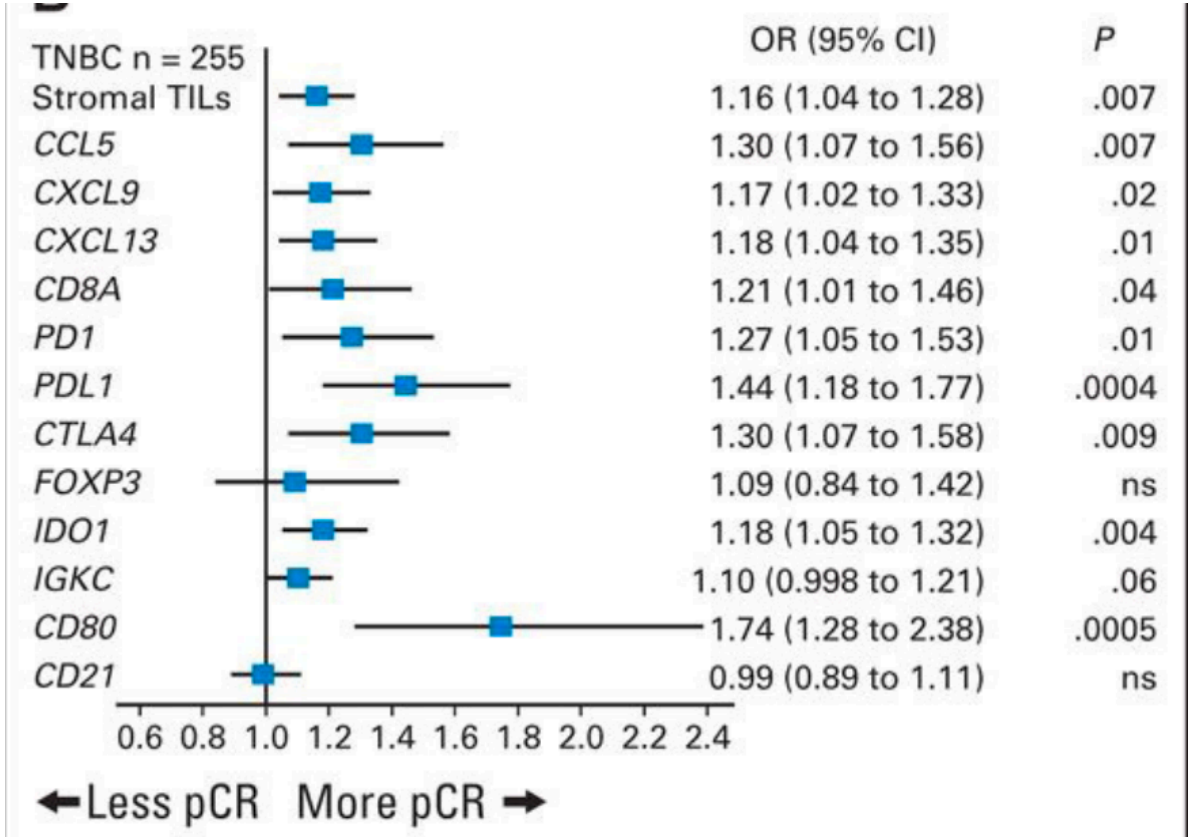
Philipps Universität Marburg

GBG GERMAN BREAST GROUP

TILs & prognosis and prediction

Stromal TILs & Carboplatin

DOI: 10.1200/JCO.2014.58.1967
Journal of Clinical Oncology 33, no. 9 (March 20, 2015) 983-991.



HDR status (homologous repair deficiency) & platin?

Table 2

Efficacy of platinums or DNA-damaging chemotherapy according to HRD status in breast cancer

Clinical trial	Drug	Study population	HRD role
PrECOG 0105 Cisplatin-1 trial Cisplatin-2 trial[51]	Platinum salts	Neoadjuvant TNBC	Patients who were HRD-positive had higher comp onse
Gepar-Sixto trial[6]	Carboplatin	Neoadjuvant TNBC	Patients who were HRD-positive had a better prognosis compared with HRD-negative. No r st conclusions regarding the predictive role of HRD for addition o
SWOG S9313 trial[27]	Doxorubicin and cyclophosphamide	Adjuvant TNBC	Patients who were HRD-positive had a better DFS, even bey *gBRCA1/2* status
TBCRC009 trial[28]	Platinum salts	Advanced, first or second line TNBC	Higher HRD scores were reported in responding patients, independent of *BRCA1/2* mutational status.
TNT trial[29]	Carboplatin	Advanced, first line TNBC	ORR did not correlate with HRD-score of the primary tumours.

- HRD, homologous recombination repair deficiency; ORR, overall response rate; TNBC, triple negative breast cancers.

http://dx.doi.org/10.1136/esmoopen-2018-000480

Neo-adjuverende carboplatin?

Carboplatin medfører højre pCR

Tillæg af carboplatin virker i en undergruppe af patienter, men vi har ingen sikre biomarkører (HDR? TILs?), det kan udpege hvilke pt det gavner

Ingen klare forbedring af DFS og OS

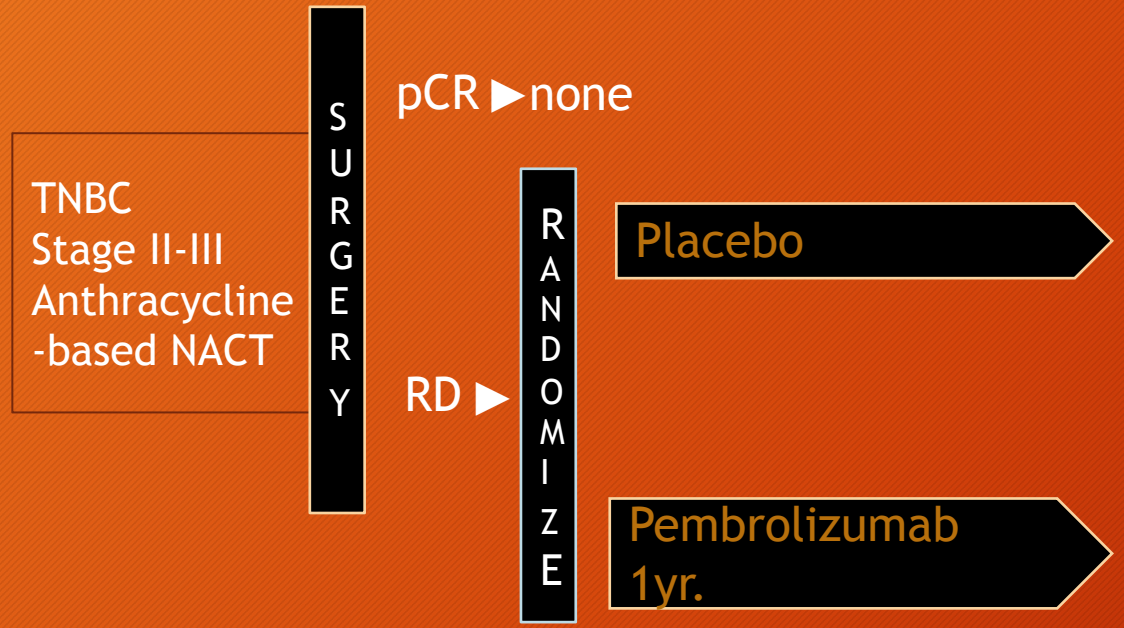
Carboplatin har en håndterbar bivirkningsprofil

Medfører Carboplatin's toxicitet mindre taxan/antracyclin?!

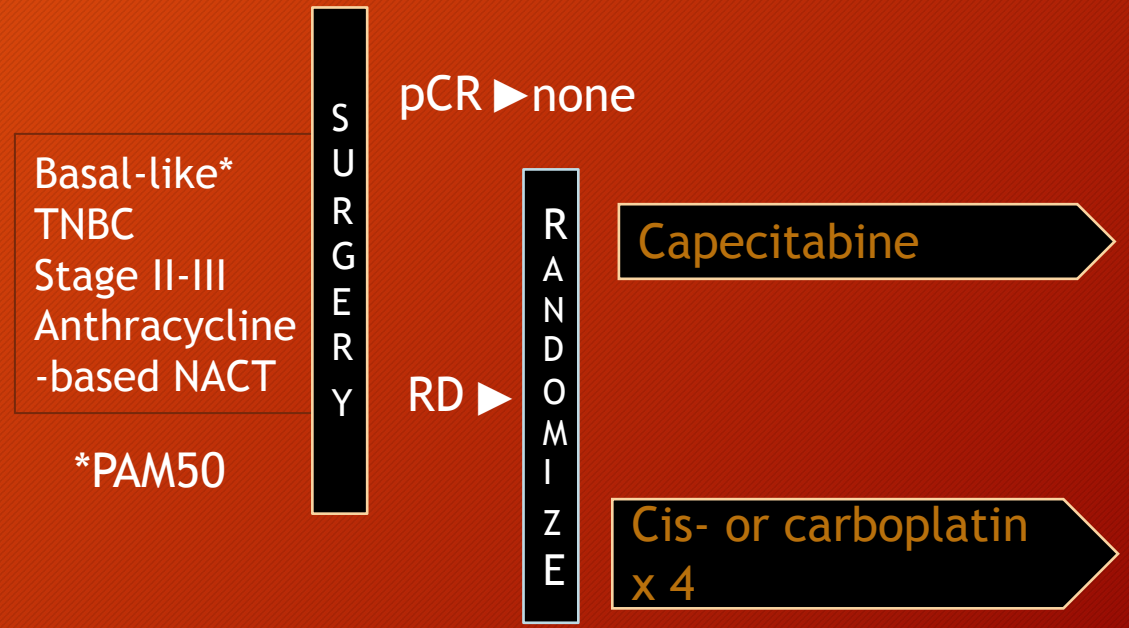
Det er billigt

Post-neoadjuvant therapy in TNBC

- SWOG 1418: immunotherapy



- ECOG-ACRIN 1131; capecitabine



Nordic Trip
ER-, HER2- (TNBC)

- 820 participants will be eligible participants

NORDIC TRIP/NBG-19-01; SWEBCG 19-01
A TRANSLATIONAL RANDOMIZED PHASE III STUDY EXPLORING THE EFFECT OF THE ADDITION OF CAPECITABINE TO CARBOPLATINUM BASED CHEMOTHERAPY IN EARLY "TRIPLE NEGATIVE" BREAST CANCER

Protocol Identification Number: NordicTrip / NBG-19-01

EudraCT Number: 2018-002080-25

Sponsor: Department of Hematology, Oncology and Radiation Physics, Skåne Univerisity Hospital

Involved Organisations:

National organisations:

Swedish Breast Cancer Group (SweBCG) and Swedish Association of Breast Oncologists (SABO)

Danish Breast cancer Group (DBCG)

Finnish Breast Cancer Group (FBCG)

Icelandic Breast Cancer Group (IBCG)

Inklusions kriterier

Node positive disease (N1-3) or if clinically N0 Tumor size >20 mm

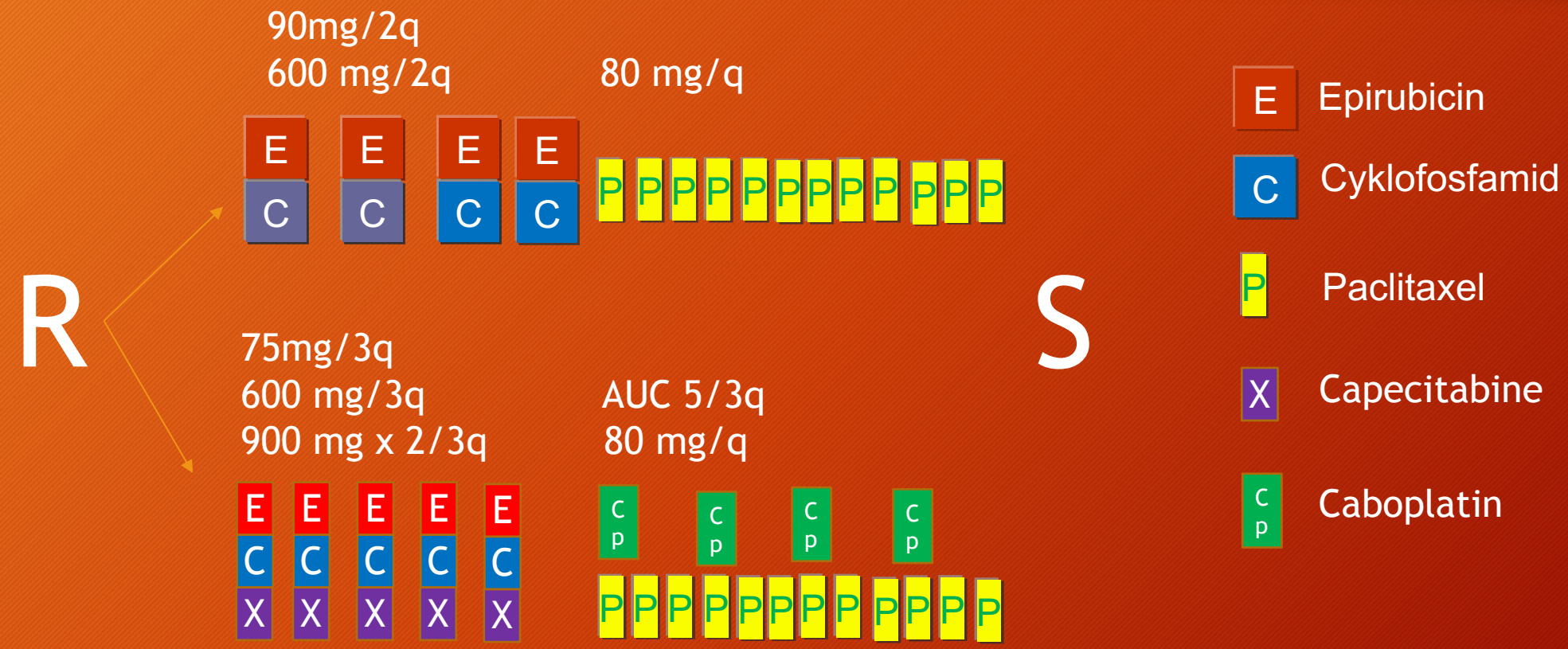
ER negative tumor defined by at least one the following:

a.ER < 1% cells positive by IHC

b.ER <10% cells positive by IHC and PgR <10% cells positive by IHC

Consent for germline mutation screening for BRCA1, BRCA2 and other inherited breast cancer associated genes

Nordic Trip


R
90mg/2q
600 mg/2q
E E E E
C C C C
80 mg/q
P P P P P P P P P P P P
75mg/3q
600 mg/3q
900 mg x 2/3q
E E E E E
C C C C C
X X X X X
AUC 5/3q
80 mg/q
C P C P C P C P
P P P P P P P P P P P P
S
E Epirubicin
C Cyklofosfamid
P Paclitaxel
X Capecitabine
C P Caboplatin

Primære formål:

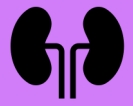
- To compare the effect on pCR rate (ypTis, ypN0) of adding capecitabine to carboplatin-based preoperative chemotherapy in early ER-negative and HER2-negative breast cancer
- Evaluate HRD-status as a potential biomarker for response to the addition of capecitabine to carboplatin-based preoperative chemotherapy

Billede-diagnostik

CT or MRI scan of thorax/abdomen asscreening for metastatic disease in cases with clinically node positive disease (N+by sentinel node biopsy only excluded) or clinically T3-4 tumors).·

Breast imaging (mammography and ultrasoundand/or MRI) before and after two treatment cycles and according to local routines during follow-up.

In case of uncertain response, a second on treatment evaluation can be added after four treatment cycles.·



Clinical assessment of the locoregional tumor extent will be recorded at baseline, after two treatment cycles and preoperatively after the end of preoperative chemotherapy.

Translation

To determine the pCR rates in different treatment arms stratified for (HRD) positive vs. HRD-negative/HRD-intermediate

To characterize different subsets of TNBC in terms of morphology, epigenetic alterations as well as somatic and inherited genetic alterations.

To determine the pCRrate and long-term outcome in subsets of TNBC with defined molecular genetic alterations including BRCA1, BRCA2 and PALB2 germline mutationsand others, BRCA1, BRCA2 and PALB2 somatic mutationsand others and BRCA1 or RAD51 promoter metylation.

Homologous Repair Deficiency = HDR

Translation cont.

To determine the pCR rate and long-term outcome in different histological subtypes of TNBC

To determine the pCR rateand long-term outcomein subsets defined based on markers of immune response, eg tumor infiltrating lymphocytes and PDL1-expression

Analysis of circulating tumor DNA and circulating immune-markers as a marker of treatment response and long-term prognosis

Timelines

Study Period: Estimated date of first patient enrolled: ”fesability” 1 September 2019

15 sites in Sweden, 8 sites in Denmark, 1 site in Finland, 1 site in Iceland

Anticipated recruitment period: 3 years

Estimated date of last patient completed (treatment phase): 31 March 2023

Treatment Duration:18-21weeks

Follow-up:10 years

NordicHER2 Trial

Baggrund

- Ved neoadjuverende behandling anbefales kemoterapi og dobbelt blokade med trastuzumab og pertuzumab til HER2 positiv BC
- Betydningen af valg af kemoterapi på DFS samt OS, er kun sparsomt belyst
- I NeoSphere blev dobbelt blokade givet med docetaxel og efterfulgt af post neoadjuverende anthracyclinholdig kemoterapi (FEC)

TRAIN-2 studiet

- 438 patienter ligeligt randomiseret til FEC (3 serier) efterfulgt af paclitaxel (dag 1 og 8) og carboplatin (6 serier) ELLER 9 serier paclitaxel og carboplatin som i anthracycline gruppen + trastuzumab og pertuzumab i begge grupper.
- Primære end-point var andel ptt med pCR i bryst og aksil
- I anthracyclin gruppen sås pCR hos 141 (67%, 95% CI 60–73) I non-anthracyclin gruppen var tallene 140 (68%, 61–74).
- I USA anbefales paclitaxel, carboplatin og dobbelt blokade

- Hvorvidt tillæg af carboplatin til paclitaxel indebærer en fordel er uafklaret ved HER2 positiv brystkræft

Katherine studiet

- Katherine studiet inkluderede 1486 HER2 positive patienter som ikke havde opnået komplet respons på neoadjuverende behandling
- Randomisering til 14 ugers behandling med TDM-1 eller tradtuzumab
- DFS signifikant bedre blandt pt behandlet med T-DM1 (HR=0,50, CI 0,39-0,64)
- Flere bivirkninger som førte til behandlings stop i T-DM1 gruppen (18% vs. 2%)
- På baggrund af Katherine studiet har FDA godkendt TDM-1 som postoperativ behandling til patienter som ikke opnår komplet respons efter neoadjuverende behandling

Formål

- Under forudsætning af, at T-DM1 godkendes til post-neoadjuverende behandling i DK er det vigtigt at afklare om pt uden komplet respons har gavn af anthracyclin-holdig behandling

NordicHER2 Trial
A Nordic collaboration

Key eligibility

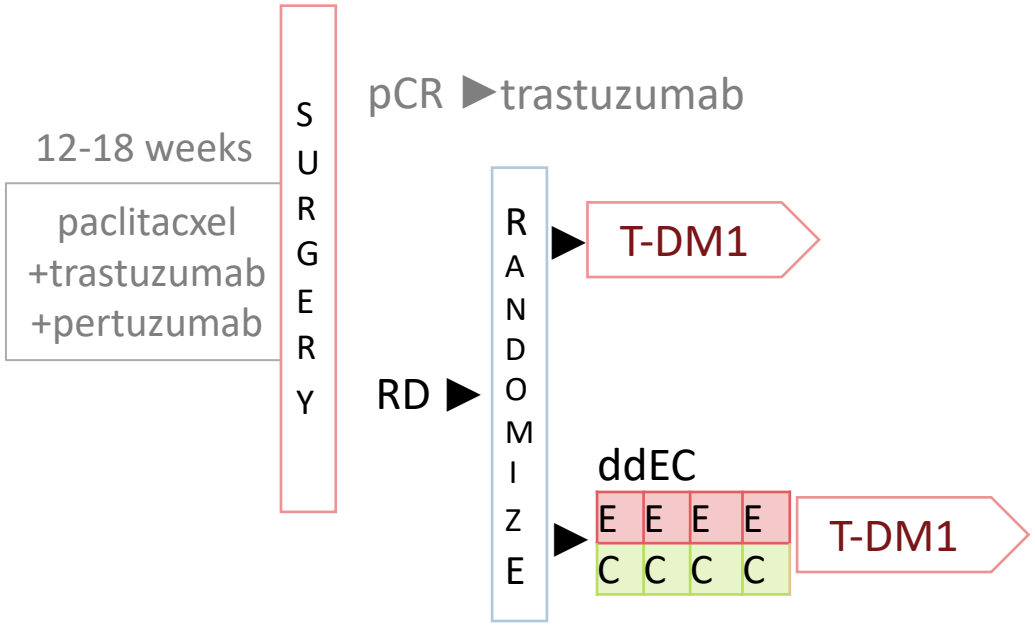
1. HER2 positive breast cancer and residual disease after taxane, trastuzumab plus pertuzumab based neoadjuvant therapy.

Objectives

1. To compare efficacy and toxicity of ddEC followed trastuzumab emtansine (T-DM1) against T-DM1 alone.
2. To evaluate response according to PAM50

Endpoints

1. Invasive disease-free survival.
2. BCSS, DRFS and OS.
3. Her2-enriched vs not



Will involve centers in Denmark and ?.

- Med sample size på 2*516=1032 svarende til inklusion af cirka 350 patienter pr år i 3 år, og yderligere 3 års opfølgning, kan der med 80% sandsynlighed findes en signifikant forskel, såfremt den sande HR=1,60 svarende til DFS 3 år 92,3%
- I DK er der de seneste år registreret ca. 450 HER2 positive patienter med tumor > 1 cm årligt, som er indgået i protokol, enten neoadjuverende, eller med up-front kirurgi. Med det ovennævnte patient-antal, vil det betyde, at protokollen bør sættes op i et nordisk samarbejde.