nbcg NORSK BRYST CANCER GRUPPE

Nytt fra NBCG

etter styringsgruppemøte 13.06.19

Bjørn Naume
Leder NBCG

Hva skal vi gjennom

- Endringer/justeringer i anbefalingene
- Kreftforskningsprisen
- Litt om studier
- Litt om status nye metoder

Arvelig kreft

Endring i anbefaling Øvre aldersgrense for MR bryst ved BRCA mutasjonsbærer-tilstand

- Det finnes ikke vitenskapelig grunnlag for å avgjøre når MR kontroller skal opphøre (524).
  - Øvre aldersgrense for MR kontroller varierer mellom ulike land. Eksempelvis er øvre aldersgrense ca. 55 år i Sverige (525) og 60 år i Nederland (360), mens det i USA ikke er noen øvre aldergrense (526).
- Ved økende alder avtar tettheten i brystvevet og sensitiviteten ved mammografi øker. I en metaanalyse fra 2015 konkluderes det imidlertid med at MR + mammografi gir økt sensitivitet for påvisning av brystkreft også etter fylte 50 år (527).
- Etter en samlet vurdering, basert på retningslinjer i flere andre land og tidligere norsk praksis, vil følgende øvre aldersgrense for MR bryst legges inn i Handlingsprogrammet:
  - **70 år for kvinner med mammografisk tetthet ACR C og D**
  - **60 år for kvinner med mammografisk tetthet ACR A og B.**

- Oversikt som viser aldersgrenser for MR screening i ulike land: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5508745/

Arvelig kreft

- BRCA mutasjonsbærere og prevensjonsmidler som inneholder østrogen
  - dette frarådes ikke

Patologi-diagnostikk

- Nye retningslinjer:
  - HER2 status: justert etter siste ASCO/CAP anbefaling
  - Presisering for Ki67: - inkluderer undersøkelse av Ki67 på biopsi ved neoadjuvant behandling; innlemmes i nytt Handlingsprogram
  - Undersøkelse av operasjonspreparat etter neoadjuvant terapi

Patologigruppens forslag til undersøkelse av operasjonspreparater etter neoadjuvant terapi (januar 2019)

Gradering av behandlingsrespons (Royal College of Pathologists):

- **Tumorstørrelse etter neoadjuvant behandling**
- **Tumorrespons:**
  - Komplett patologisk respons (pCR): intet invasivt karsinom (ev kun DCIS) tilstede.
  - Partiell patologisk respons (pPR), enten:
    - Liten tumorrest (< 10%)
    - Moderat tumorrest (10-50%)
    - Stor tumorrest (> 50%)
  - Ingen tegn til respons (pNR)
- **Lymfeknuterespons:**
  - Ingen tegn til metastase eller behandlet metastase
  - Metastase ikke påvist, men tegn på behandlingsrespons (fibrose)
  - Vital metastase påvist, men også fibrose (behandlingsrespons)
  - Vital metastase påvist uten tegn på behandlingsrespons
- **Rapportering av prognostiske og prediktive markører:**
  - Rutinemessig rapportering av ER, PR, HER-2 og Ki67 (eller mitoser) i operasjonspreparat etter neoadjuvant behandling er ikke anbefalt som rutine.

Rekonstruktiv kirurgi

- Liten endring i retningslinjen knyttet til forsinket primær rekonstruksjon med eget vev

Kirurgi/onkologi

Justering i kriterium for neoadjuvant behandling.

- I dagens retningslinje:
  - cT2 HER2 positive og TNBC kan vurderes eller anbefales for neoadjuvant behandling.
- Konsensus fra St Gallen 2017 og 2019 anbefaler stadium 2 (cT2cN0 eller cT1-2cN0)
- Anbefalingen endres til å gjelde pasienter med stadium 2 (utvider indikasjon til tumores <2 cm dersom det er positiv lymfeknytestatus i axille)

Kirurgi

- Axillediagnostikk/kirurgi etter neoadjuvant behandling av pasienter med lymfeknutepositiv axillestatus
  - SN diagnostikk «bommer» på klinisk (pre-neoadjuvant) positiv lymfeknute i cirka 40% av tilfellene: positiv lymfeknute bør merkes

Stråleterapi (1)

- Nye retningslinjer for inntegning av CTV etter rekonstruksjon

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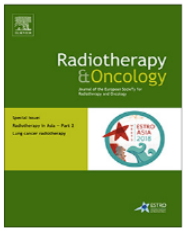

Original Article

ESTRO consensus guideline for target volume delineation in the setting of postmastectomy radiation therapy after implant-based immediate reconstruction for early stage breast cancer

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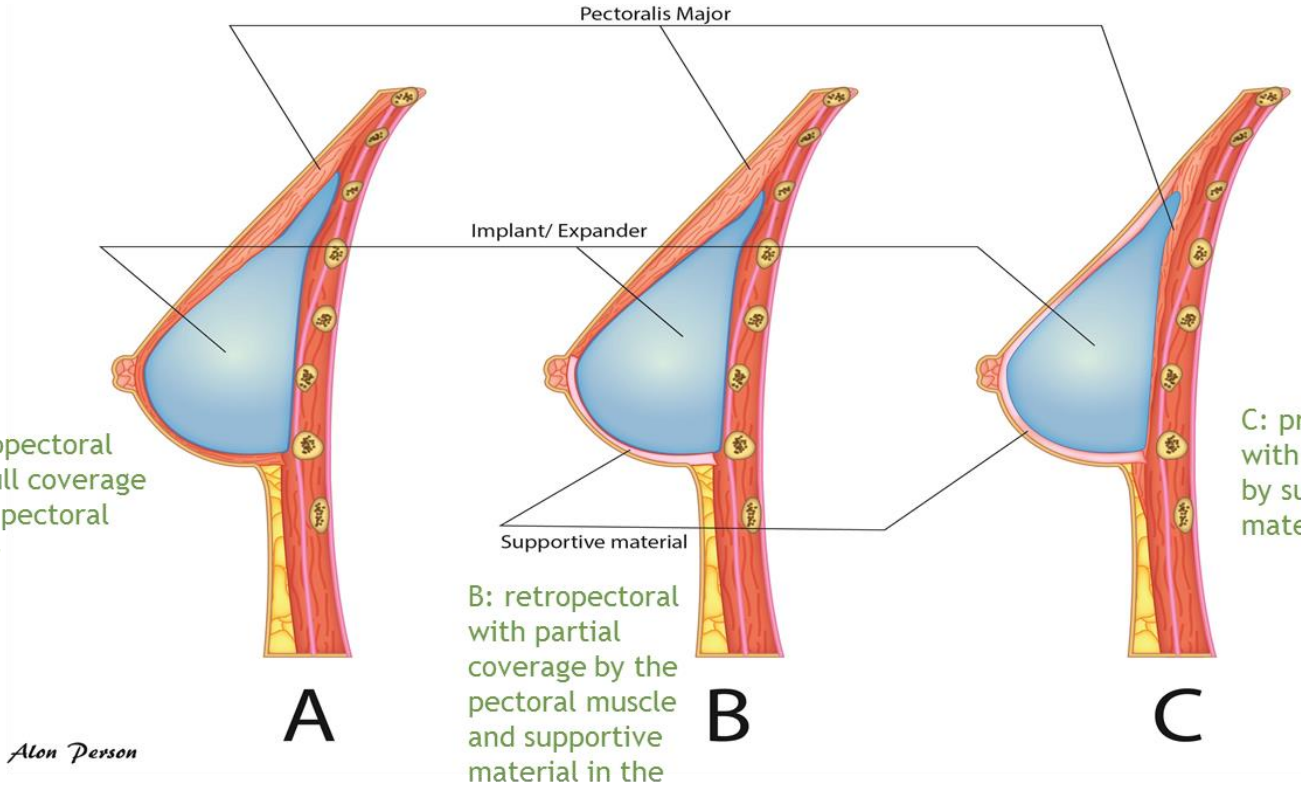


A:retropectoral with full coverage by the pectoral muscle

B: retropectoral with partial coverage by the pectoral muscle and supportive material in the lower part

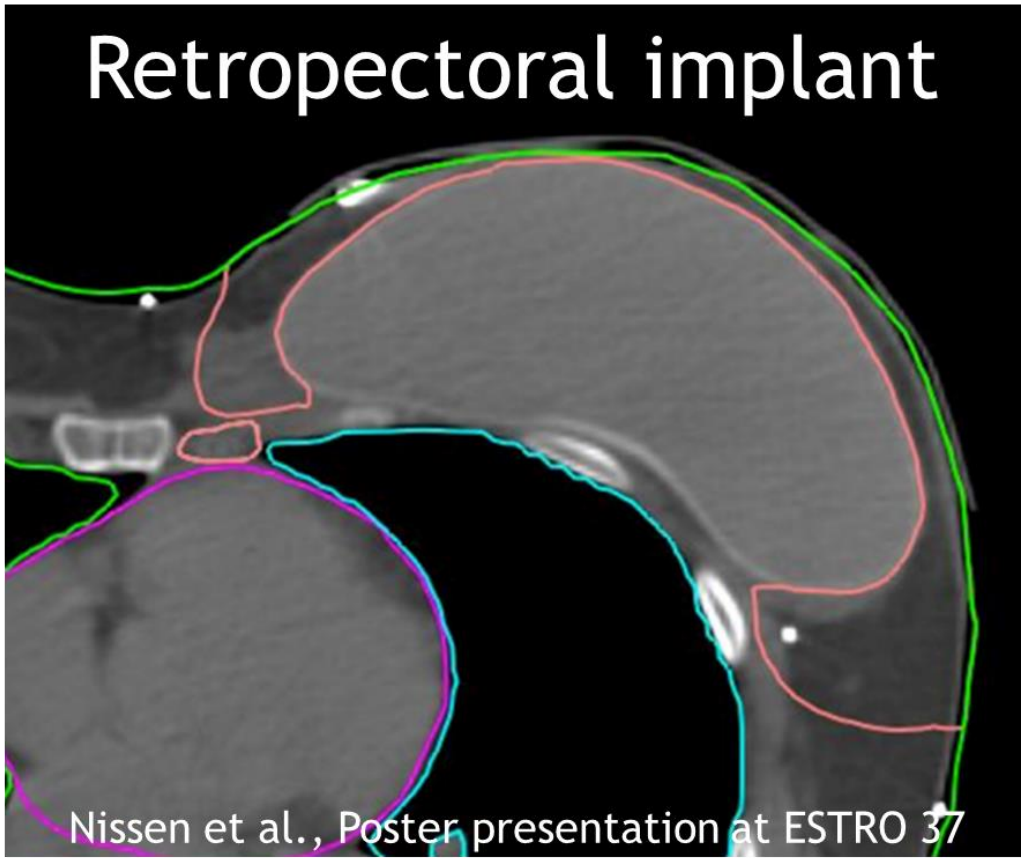
C: prepectoral with full coverage by supportive material

Kaidar-Person & Offersen et al, Radiother & Oncol, 2019

Agreement

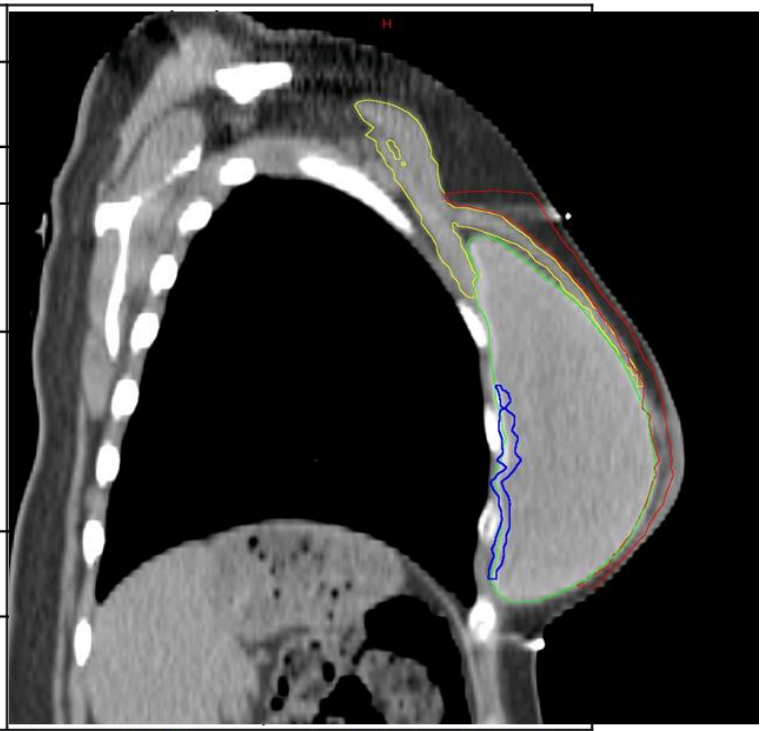
Most patients:
➔ CTVp_chestwall is ventral to the implant

Selected patients (e.g. if locally advanced breast cancer):
➔ CTVp_chestwall includes ventral & dorsal to implant to include both the subcutaneous lymphatics and the prepectoral lymphatics



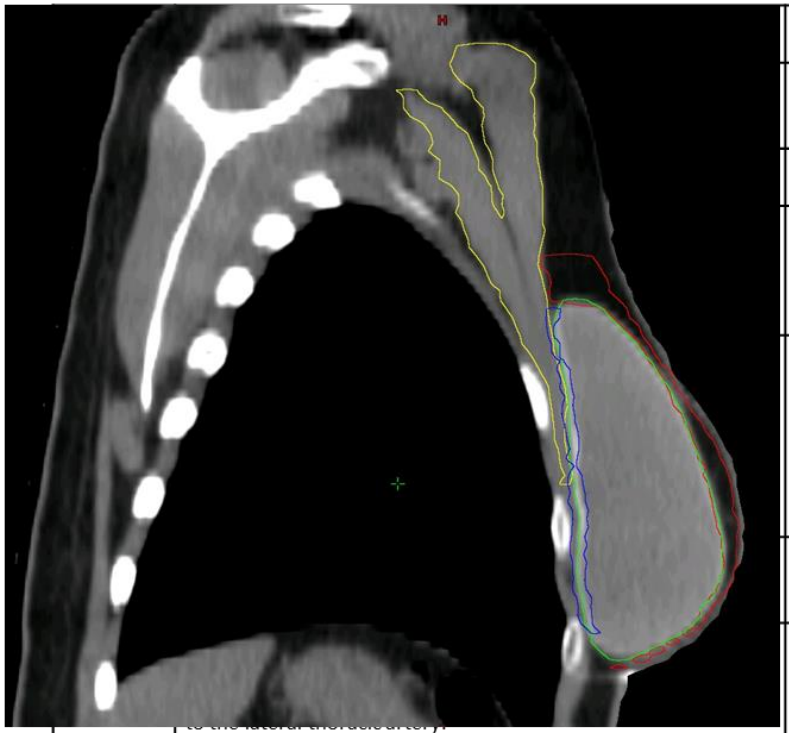
ESTRO consensus on target volume determination in early breast cancer operated with mastectomy and immediate implant reconstruction

Border per region	CTV Retro-pectoral implant:
Cranial	Guided by palpable/visible signs, planning CT; if appropriate guided by the contralateral breast; maximally up to the caudal edge of the sterno-clavicular joint
Caudal	Guided by palpable/visible signs; if appropriate guided by the contralateral breast
Ventral	1. Ventral part: if possible, up to 3-5 mm under the skin surface; 2. Dorsal part caudal from original insertion of pectoral muscle: the dorsal side of the implant.
Dorsal	1. Ventral part: major pectoral muscle or implant where no muscle; 2. Dorsal part caudal from original insertion of pectoral muscle: ribs and intercostal muscles. ** consider including the superficial part of the pectoral muscle if it is thin or in case of local invasion.
Medial	Guided by palpable/visible signs; if appropriate guided by the contralateral breast. Lateral to the medial perforating mammary vessels.
Lateral	Guided by palpable/visible signs; if appropriate guided by the contralateral breast. Usually ventral to the mid-axillary line (important, location of most residual glandular tissue). Ventral to the lateral thoracic artery.



Kaidar-Person & Offersen et al, Radiother & Oncol, 2019

ESTRO consensus on target volume determination in early breast cancer operated with mastectomy and immediate implant reconstruction

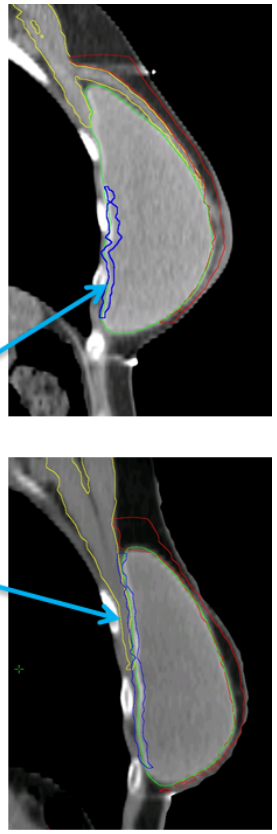


CTV Pre-pectoral implant
Guided by palpable/visible signs, planning CT; if appropriate guided by the contralateral breast; maximally up to the caudal edge of the sterno-clavicular joint
Guided by palpable/visible signs; if appropriate guided by the contralateral breast
1) Ventral part: if possible up to 3-5 mm under the skin surface; 2) Dorsal part: the dorsal side of the implant.
1) Ventral part: ventral side of the implant. 2) Dorsal part: ventral side of the pectoral muscles or ribs and intercostal muscles where no muscle is present. ** consider including the superficial part of the pectoral muscle in case of local invasion
Guided by palpable/visible signs; if appropriate guided by the contralateral breast. Lateral to the medial perforating mammary vessels.
Guided by palpable/visible signs; if appropriate guided by the contralateral breast. Usually ventral to the mid-axillary line (important, location of most residual glandular tissue). Ventral to the lateral thoracic artery.

Kaidar-Person & Offersen et al, Radiother & Oncol, 2019 *in press*

Indications for including a volume dorsal to the implant in the CTVp_chestwall:

- Partial inclusion in post-pectoral implant positioning: in case of the presence of adverse factors and/or if the tumour was localised in areas within the breast close to the dorsal fascia that was not covered by the initial position of the major pectoral muscle: separate volume (blue volume)
- Complete inclusion in pre-pectoral implant positioning: in case of the presence of adverse factors and/or if the tumour was localised in areas within the breast close to the dorsal fascia (blue volume)
- **Adverse prognostic tumour characteristics** include:
- Large primary breast cancer (pT3) treated by mastectomy and IBR-i
- Locally advanced breast cancer (LABC) with non-pathological complete response to primary systemic therapy
- Invasion of the major pectoral muscle and/or the chest wall



Kaidar-Person & Offersen et al, Radiother & Oncol, 2019

Stråleterapi (2)

- Protonbestråling: Følgende tekst innlemmes i Handlingsprogrammet:
  «Ut over bestråling av spesielt vanskelig beliggende metastaser, nær kritiske strukturer eller nært opptil tidligere bestrålt område hvor overlapp ikke er ønskelig, i sammenheng med at foton/elektronbestrålningsopplegg ikke vil gi et tilfredsstillende resultat, bør protonterapi kun benyttes i kliniske studier.»

Stråleterapi (3)

- **Strålebehandling og onkoplastikk.**
- ***I Handlingsprogrammet står følgende tekst: Boost-bestråling (for pasientert <40(50)år) etter Onkoplastisk brystkonserverende behandling (OBCS)***
- *Indikasjon for strålebehandling med boost er den samme som ved BCT. Bruk av boost ved stråleterapi er vist å redusere lokale tilbakefall etter BCT og i særlig grad hos pasienter <40 (50) år, men har ikke vist overlevelsesgevinst. OBCS kan vanskeliggjøre boost- bestråling pga usikker lokalisering av primær tumorseng. Remodellering av brystet kan gjøre det umulig å gjenfinne opprinnelig tumorområde dersom sårhulen ikke merkes med klips som er plassert like etter tumorreseksjonen og før den onkoplastiske rekonstruksjonen. Klips gir bedre definering av området som bør bestråles med boost. Det forutsettes også en grundig operasjonsbeskrivelse og et nært samarbeid mellom kirurg og onkolog. På denne måten sikres at adekvat område får tiltenkt boost og at vev utenfor målområdet spares for unødvendig strålebelastning da dette kan medføre et dårligere kosmetisk resultat med mer fibrose.*

Stråleterapi (3 - forts)

- I tilfeller hvor boostvolumet forventes å bli/blir stort. Det er enighet om følgende:
  - Det bør vurderes grundig om pasienten er kandidat eller ikke for OBCS i forbindelse med planlegging av det kirurgiske inngrep (MDT vurdering), det bør gis informasjon til pasient om at stort boostvolum gir økt risiko for fibroseutvikling
  - Dersom boostvolumet blir spesielt stort, kan en vurdere å gi redusert boostdosering (2 Gy x 5) eller ingen boost (risiko/nytteforholdet taler for lite nytte av boostbestråling).
  - Det legges inn en veiledende informasjon om størrelse på strålevolum som bør gjøre at volumet begrenses: max 40% av non-boost volum (CTV-bryst-CTV-boost) kan få 95% av boost dosen.

Stråleterapi (4) – lokoregional rebestråling

- **Ved lokoregionale residiv kan rebestråling vurderes individuelt etter grundig gjennomgang av alle behandlingsalternativer i multidisiplinært team inkludert onkolog med stråleterapierfaring.** Det må tas hensyn til særlig to momenter. Først, muligheten for **stråleresistens** i tumor hvis det er kort tid mellom primær stråleterapi og et residiv som er lokalisert i et område hvor det tidligere er gitt adekvat stråledose. I tillegg må **summert stråledose til omkringliggende normalvev vurderes akseptabel** ved doseplanlegging. **Forventet klinisk nytteverdi av rebestråling må være større enn potensielle bivirkninger** [2].

- Selv om pasienter med lokoregionale residiv har høy risiko for samtidige eller senere metastaser vil mange pasienter ha lang sykdomsfri overlevelse eller kurasjon etter residivbehandling [2]. Også ved utbredt sykdom kan lokalbehandling gi god palliasjon. Det må utvises forsiktighet med tanke på å unngå høye doser i overlappsoner, pleuxus brachialis, beinvev og lymfeåresystemet. Ved ipsilaterale residiv i brystet etter tidligere standard behandling med brystbevarende operasjon og stråleterapi gir standard behandling mastectomi under 10% risiko for senere sekundært residiv [3, 4].

- **Hos pasienter med lokaliserte sene residiv i brystet (>48 mnd) etter BCT og helbrystbestråling som ikke ønsker mastectomi kan brystbevarende behandling etterfulgt av rebestråling i enkelttilfeller vurderes etter nøye gjennomgang av risiko/nytte i følgende tilfeller**: lav-risiko sykdom (østrogen-reseptor positiv, HER2 reseptor negativ sykdom), lav histologisk grad, lite (<2 cm) fritt fjernet ikke-lobulært carsinom og fravær av uttalt DICS, forventet godt kosmetisk resultat basert på ratio mellom tumorstørrelse og størrelse på brystet, begrensede bivirkninger fra primær stråleterapi og multidisiplinært team med bred stråleterapikompetanse. **I slike tilfeller vil partiell brystbestråling være å anbefale fremfor helbrystbestråling** som vil innebære større risiko for skade på friskt vev. De største studiene på dette området har vært gjort med kateterbasert interstitiell brachyterapi (5), men partiell strålebehandling gitt med standard ekstern strålebehandlingsteknikk vil også være et godt alternativ og undersøkes i en større RTOG studie.

Adjuvant medikamentell behandling

- Dosedens/doseintens kjemoterapi
- Postneoadjuvant behandling
- Antracyklinfri alternativ adjuvant kjemoterapi
- Neoadjuvant behandling ved BRCA mutasjonsbærertilstand
- Endokrin neoadjuvant behandling

Dose-intens kjemoterapi

Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

Summary

Background Increasing the dose intensity of cytotoxic therapy by shortening the intervals between cycles, or by giving individual drugs sequentially at full dose rather than in lower-dose concurrent treatment schedules, might enhance efficacy.

Methods To clarify the relative benefits and risks of dose-intense and standard-schedule chemotherapy in early breast cancer, we did an individual patient-level meta-analysis of trials comparing 2-weekly versus standard 3-weekly schedules, and of trials comparing sequential versus concurrent administration of anthracycline and taxane chemotherapy. The primary outcomes were recurrence and breast cancer mortality. Standard intention-to-treat log-rank analyses, stratified by age, nodal status, and trial, yielded dose-intense versus standard-schedule first-event rate ratios (RRs).

Findings Individual patient data were provided for 26 of 33 relevant trials identified, comprising 37 298 (93%) of 40 070 women randomised. Most women were aged younger than 70 years and had node-positive disease. Total cytotoxic drug usage was broadly comparable in the two treatment arms; colony-stimulating factor was generally used in the more dose-intense arm. Combining data from all 26 trials, fewer breast cancer recurrences were seen with dose-intense than with standard-schedule chemotherapy (10-year recurrence risk 28·0% *vs* 31·4%; RR 0·86, 95% CI 0·82–0·89; p<0·0001). 10-year breast cancer mortality was similarly reduced (18·9% *vs* 21·3%; RR 0·87, 95% CI 0·83–0·92; p<0·0001), as was all-cause mortality (22·1% *vs* 24·8%; RR 0·87, 95% CI 0·83–0·91; p<0·0001). Death without recurrence was, if anything, lower with dose-intense than with standard-schedule chemotherapy (10-year risk 4·1% *vs* 4·6%; RR 0·88, 95% CI 0·78–0·99; p=0·034). Recurrence reductions were similar in the seven trials (n=10 004) that compared 2-weekly chemotherapy with the same chemotherapy given 3-weekly (10-year risk 24·0% *vs* 28·3%; RR 0·83, 95% CI 0·76–0·91; p<0·0001), in the six trials (n=11 028) of sequential versus concurrent anthracycline plus taxane chemotherapy (28·1% *vs* 31·3%; RR 0·87, 95% CI 0·80–0·94; p=0·0006), and in the six trials (n=6532) testing both shorter intervals and sequential administration (30·4% *vs* 35·0%; RR 0·82, 95% CI 0·74–0·90; p<0·0001). The proportional reductions in recurrence with dose-intense chemotherapy were similar and highly significant (p<0·0001) in oestrogen receptor (ER)-positive and ER-negative disease and did not differ significantly by other patient or tumour characteristics.

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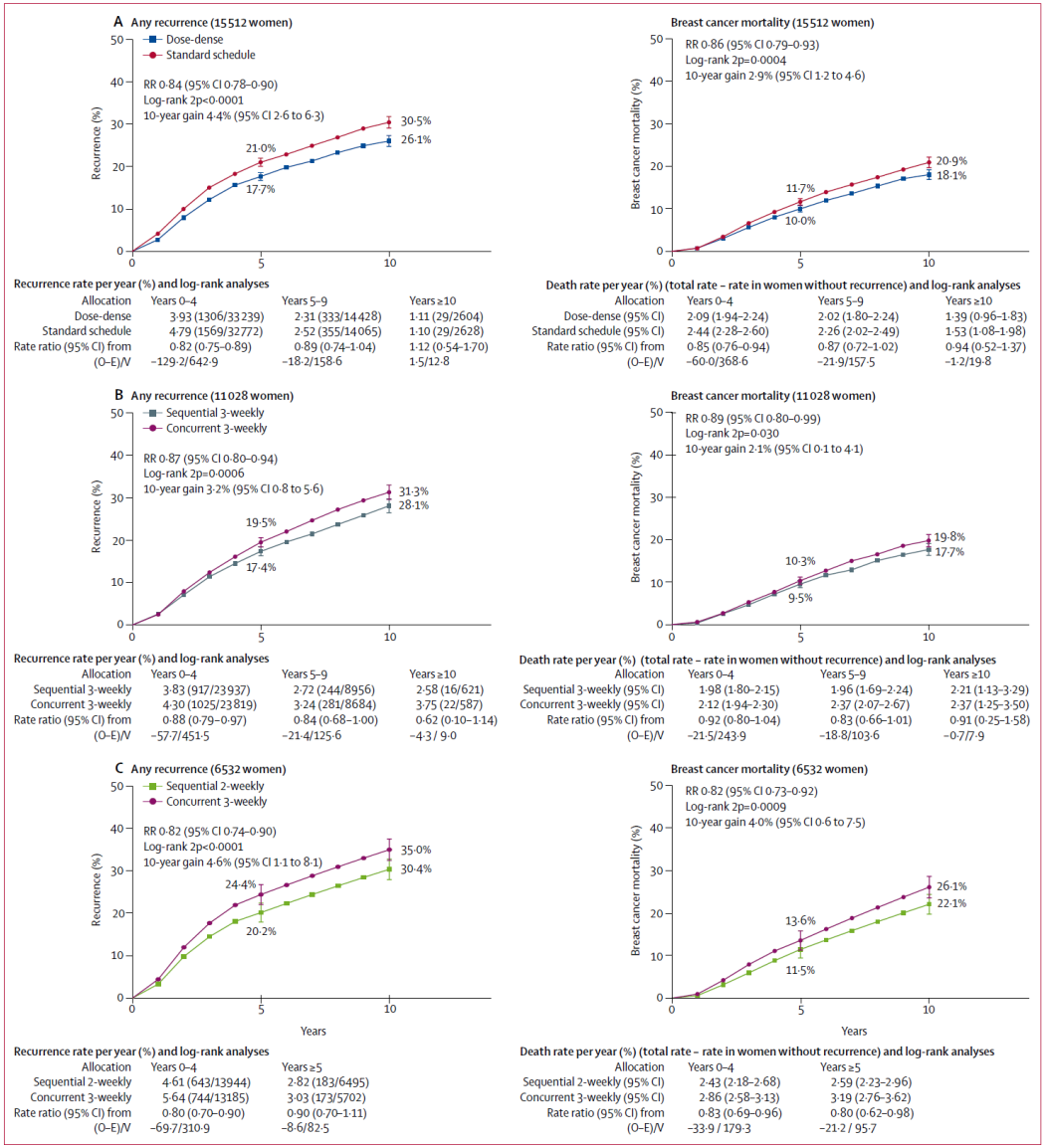
Dosedens og sekvensiell gir begge bedret RFS og BCS



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

Allocation	Years 0–4	Years 5–9	Years ≥10
Dose-dense	3·93 (1306/33 239)	2·31 (333/14 428)	1·11 (29/2604)
Standard schedule	4·79 (1569/32 772)	2·52 (355/14 065)	1·10 (29/2628)
Rate ratio (95% CI) from	0·82 (0·75–0·89)	0·89 (0·74–1·04)	1·12 (0·54–1·70)
(O–E)/V	−129·2/642·9	−18·2/158·6	1·5/12·8

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-dense (95% CI)	2·09 (1·94–2·24)	2·02 (1·80–2·24)	1·39 (0·96–1·83)
Standard schedule (95% CI)	2·44 (2·28–2·60)	2·26 (2·02–2·49)	1·53 (1·08–1·98)
Rate ratio (95% CI) from	0·85 (0·76–0·94)	0·87 (0·72–1·02)	0·94 (0·52–1·37)
(O–E)/V	−60·0/368·6	−21·9/157·5	−1·2/19·8

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

Allocation	Years 0–4	Years 5–9	Years ≥10
Sequential 3-weekly	3·83 (917/23 937)	2·72 (244/8956)	2·58 (16/621)
Concurrent 3-weekly	4·30 (1025/23 819)	3·24 (281/8684)	3·75 (22/587)
Rate ratio (95% CI) from	0·88 (0·79–0·97)	0·84 (0·68–1·00)	0·62 (0·10–1·14)
(O–E)/V	−57·7/451·5	−21·4/125·6	−4·3 / 9·0

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

Allocation	Years 0–4	Years 5–9	Years ≥10
Sequential 3-weekly (95% CI)	1·98 (1·80–2·15)	1·96 (1·69–2·24)	2·21 (1·13–3·29)
Concurrent 3-weekly (95% CI)	2·12 (1·94–2·30)	2·37 (2·07–2·67)	2·37 (1·25–3·50)
Rate ratio (95% CI) from	0·92 (0·80–1·04)	0·83 (0·66–1·01)	0·91 (0·25–1·58)
(O–E)/V	−21·5/243·9	−18·8/103·6	−0·7/7·9

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

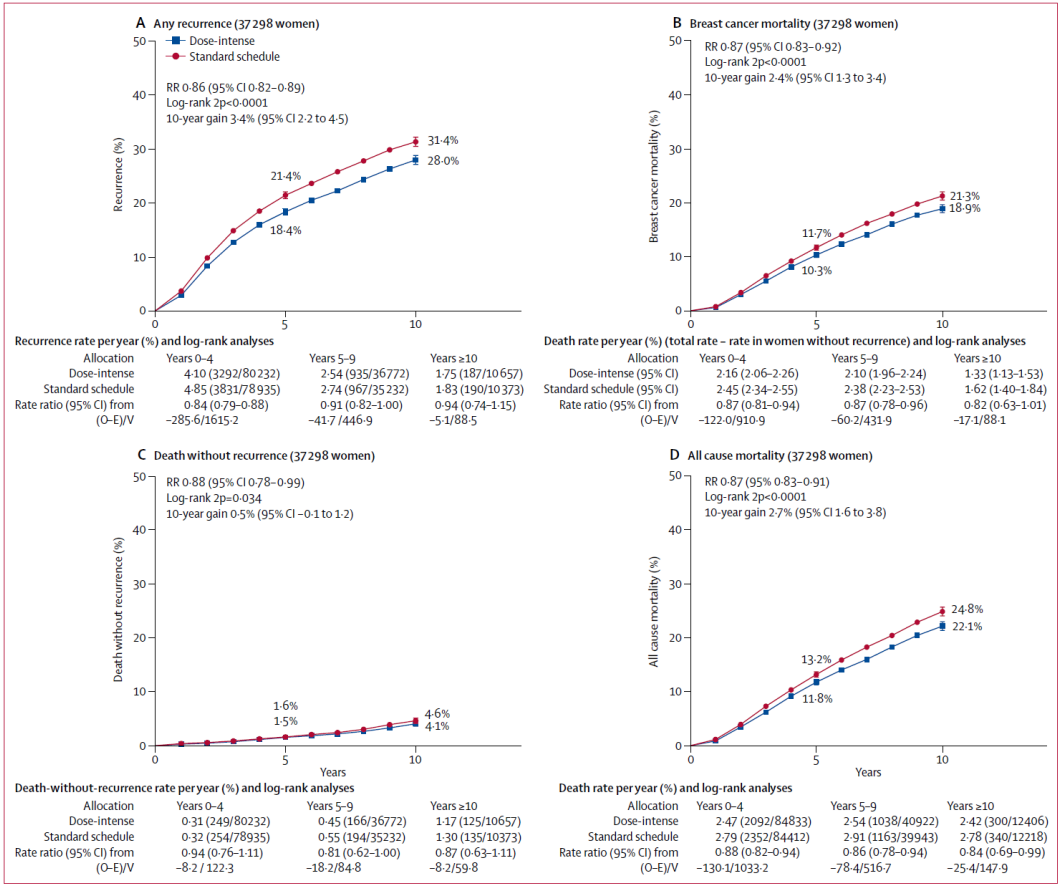
Allocation	Years 0–4	Years ≥5
Sequential 2-weekly	4·61 (643/13 944)	2·82 (183/6495)
Concurrent 3-weekly	5·64 (744/13 185)	3·03 (173/5702)
Rate ratio (95% CI) from	0·80 (0·70–0·90)	0·90 (0·70–1·11)
(O–E)/V	−69·7/310·9	−8·6/82·5

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

Allocation	Years 0–4	Years ≥5
Sequential 2-weekly (95% CI)	2·43 (2·18–2·68)	2·59 (2·23–2·96)
Concurrent 3-weekly (95% CI)	2·86 (2·58–3·13)	3·19 (2·76–3·62)
Rate ratio (95% CI) from	0·83 (0·69–0·96)	0·80 (0·62–0·98)
(O–E)/V	−33·9 / 179·3	−21·2 / 95·7

Figure 3: **10-year risk of any recurrence (left) and breast cancer death (right) for all trials (confounded and unconfounded)**
(A) Dose-dense (2-weekly) versus standard schedule (3-weekly) chemotherapy. Of the 15 512 women, 65% are N+. (B) Sequential versus concurrent chemotherapy (both 3-weekly). Of the 11 028 women, 91% are N+. (C) Sequential (2-weekly) versus concurrent (3-weekly) therapy. Of the 6532 women, 90% are N+.

Pooled analysis of all dose-intensification trials



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

Allocation	Years 0–4	Years 5–9	Years ≥10
Dose-intense	4·10 (3292/80 232)	2·54 (935/36 772)	1·75 (187/10 657)
Standard schedule	4·85 (3831/78 935)	2·74 (967/35 232)	1·83 (190/10 373)
Rate ratio (95% CI) from	0·84 (0·79–0·88)	0·91 (0·82–1·00)	0·94 (0·74–1·15)
(O–E)/V	−285·6/1615·2	−41·7 /446·9	−5·1/88·5

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)	2·16 (2·06–2·26)	2·10 (1·96–2·24)	1·33 (1·13–1·53)
Standard schedule (95% CI)	2·45 (2·34–2·55)	2·38 (2·23–2·53)	1·62 (1·40–1·84)
Rate ratio (95% CI) from	0·87 (0·81–0·94)	0·87 (0·78–0·96)	0·82 (0·63–1·01)
(O–E)/V	−122·0/910·9	−60·2/431·9	−17·1/88·1

Death-without-recurrence rate per year (%) and log-rank analyses

Allocation	Years 0–4	Years 5–9	Years ≥10
Dose-intense	0·31 (249/80 232)	0·45 (166/36 772)	1·17 (125/10 657)
Standard schedule	0·32 (254/78 935)	0·55 (194/35 232)	1·30 (135/10 373)
Rate ratio (95% CI) from	0·94 (0·76–1·11)	0·81 (0·62–1·00)	0·87 (0·63–1·11)
(O–E)/V	−8·2 / 122·3	−18·2/84·8	−8·2/59·8

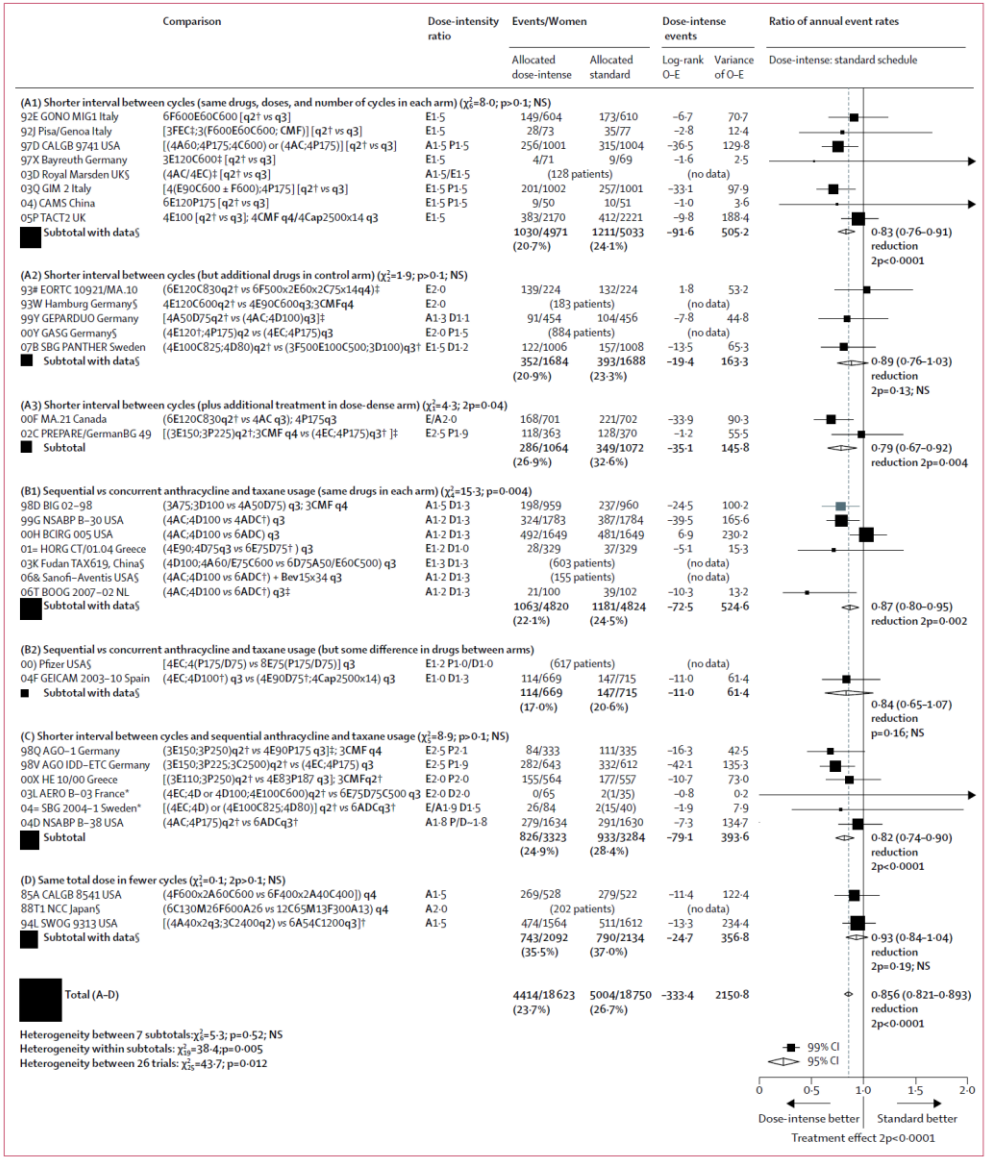
Death rate per year (%) and log-rank analyses

Allocation	Years 0–4	Years 5–9	Years ≥10
Dose-intense	2·47 (2092/84 833)	2·54 (1038/40 922)	2·42 (300/12 406)
Standard schedule	2·79 (2352/84 412)	2·91 (1163/39 943)	2·78 (340/12 218)
Rate ratio (95% CI) from	0·88 (0·82–0·94)	0·86 (0·78–0·94)	0·84 (0·69–0·99)
(O–E)/V	−130·1/1033·2	−78·4/516·7	−25·4/147·9

Figure 4: Pooled analysis of all dose-intensification trials

10-year cumulative risk of any recurrence (A), breast cancer mortality (B), death without recurrence (C), all-cause mortality (D), for dose-intense versus standard schedule arm. Of the 37 298 women, 77% are N+. RR=rate ratio.

Studiene og kjemoregimene



Kjerneresultatet og tolkningen

- Sekvensiell behandling med antracyklin etterfulgt av taxan er bedre enn konkomitant behandling. Dette er samsvarende med det adjuvante behandlingsopplegg i Norge gjennom flere år, hvor det har vært indikasjon for å benytte taxan.
- Dose dense dosering q2w av EC/AC og paclitaxel/docetaxel er bedre enn q3w. Metaanalysen inkluderer ikke sammenlignende studier av dose dens behandling med 4 EC90 q3w etterfulgt av 12 paclitaxel ukentlig.

Anbefaling

- NBCGs gjeldende anbefaling om sekvensiell behandling med antracyklin (EC90) etterfulgt av taxan (docetaxel 3qw eller paklitaxel 1qw) tar høyde for de viktigste resultatene i metaanalysen

  Men for lokalavanserte høyrisikopasienter med rasktutviklende klinikk kan det på individuelt grunnlag vurderes å kombinere både dose dens og sekvensiell behandling i form av 4 EC90 q2w etterfulgt av 4 docetaxel 75 mg/m2 q2w eller 12 paklitaxel qW.
  Obs toksisitet, G-CSF støtte

Postneoadjuvant behandling

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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, K. Aogi, H. Iwata, J. Jeong,

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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, N. Wolmark, P. Rastogi, A. Schneeweiss, A. Redondo, H.H. Fischer, W. Jacot, A.K. Conlin, C. Arce-Salinas, I.L. Wapnir, C. Jackisch, M.P. DiGiovanna, P.A. Fasching, J.P. Crown, P. Wülfing, Z. Shao, E. Rota Caremoli, H. Wu, L.H. Lam, D. Tesarowski, M. Smitt, H. Douthwaite, S.M. Singel, and C.E. Geyer, Jr., for the KATHERINE Investigators*

CREATE-X

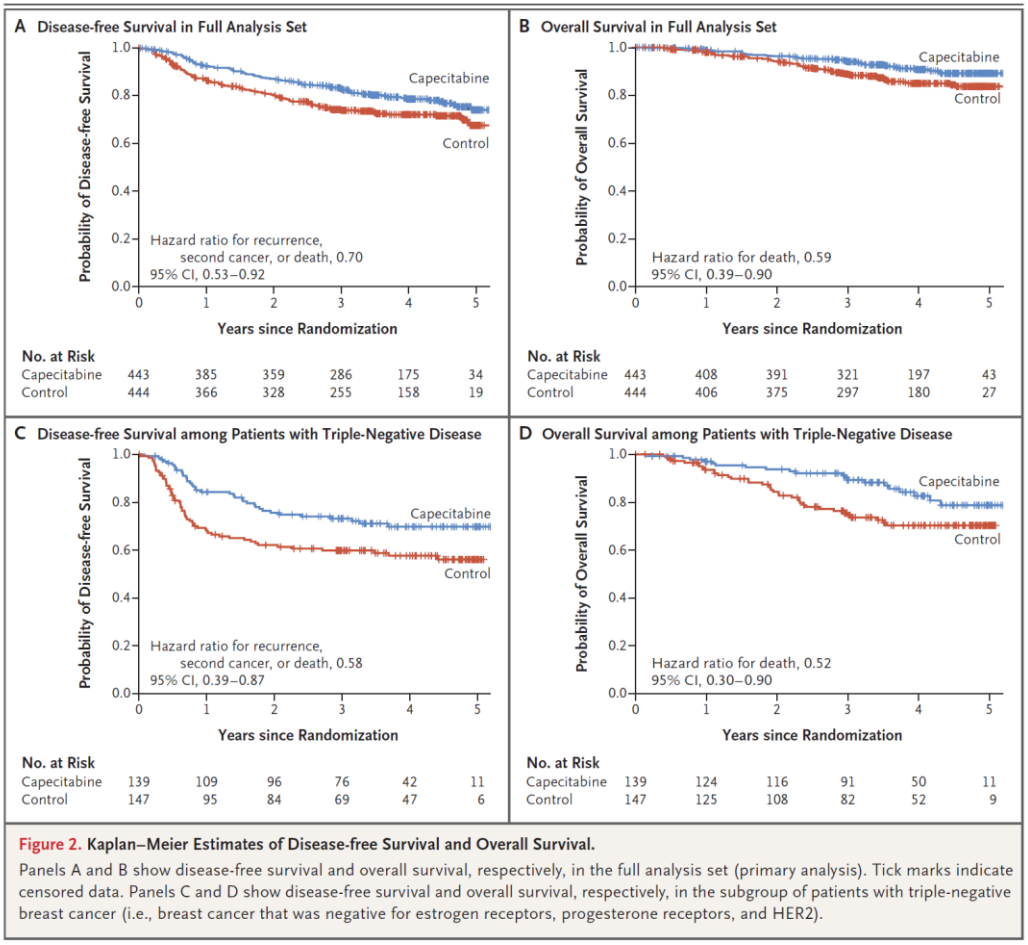


Figure 2. Kaplan–Meier Estimates of Disease-free Survival and Overall Survival.
Panels A and B show disease-free survival and overall survival, respectively, in the full analysis set (primary analysis). Tick marks indicate censored data. Panels C and D show disease-free survival and overall survival, respectively, in the subgroup of patients with triple-negative breast cancer (i.e., breast cancer that was negative for estrogen receptors, progesterone receptors, and HER2).

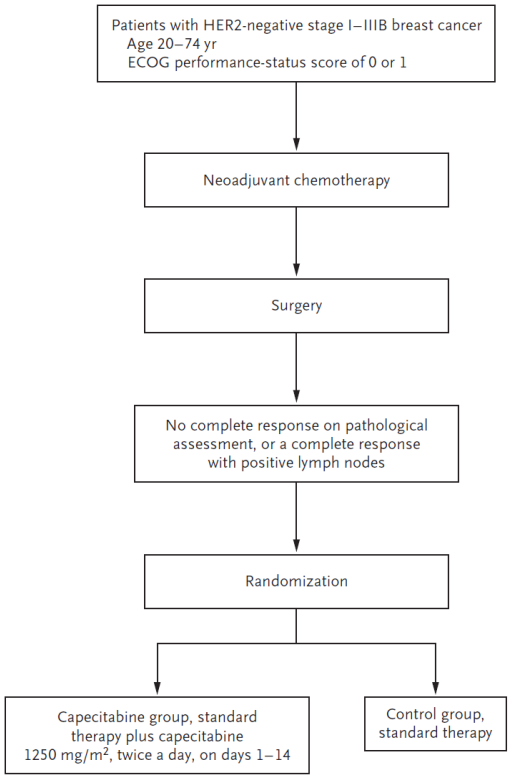


Figure 1. Trial Design.
Neoadjuvant chemotherapy involved at least four cycles of an anthracycline. However, if the anthracycline was administered for less than four cycles, one of the following four regimens could be used: fluorouracil and epirubicin (at a dose of ≥100 mg per square meter of body-surface area) and cyclophosphamide (FEC) for three cycles, followed by docetaxel at a dose of 75 mg per square meter for three cycles; FEC for three cycles, followed by docetaxel at a dose of 75 mg per square meter and cyclophosphamide at a dose of 600 mg per square meter (TC) for three cycles; TC for three cycles, followed by FEC for three cycles; or TC only for four cycles. Patients who had serious adverse events or disease progression were included if they completed at least two cycles of chemotherapy. If patients had positive lymph nodes, combined chemotherapy with an anthracycline and taxane (docetaxel or paclitaxel, as chosen by the physician) was recommended. The Eastern Cooperative Oncology Group (ECOG) performance status is scored on a scale of 0 to 5, with 0 indicating no symptoms and higher scores indicating greater disability related to tumor. Standard therapy included 5 years of endocrine therapy for hormone-receptor–positive cancer, no further systemic treatment for hormone-receptor–negative cancer, and radiotherapy if indicated. HER2 denotes human epidermal growth factor receptor 2.

Subgruppeanalyser

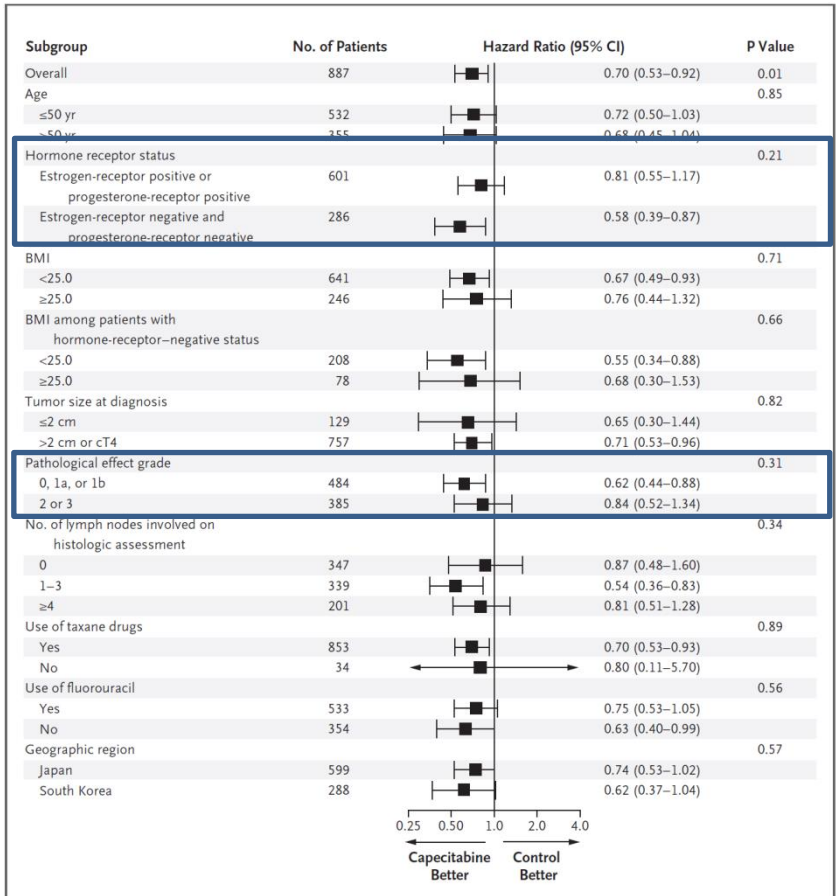


Figure 3. Subgroup Analysis of Disease-free Survival in the Full Analysis Set.

On the basis of the Cox model, prespecified subgroup analyses for background or prognostic factors were conducted to estimate hazard ratios with 95% confidence intervals and to test for interaction among subgroups with the use of two-sided P values. Post hoc subgroup analyses were conducted regarding body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) in all patients and BMI in patients with hormone-receptor–negative disease. A tumor size of cT4 indicates a tumor of any size with direct extension to the chest wall or skin. Data on tumor size were missing for one patient in the capecitabine group. The pathological effect of neoadjuvant chemotherapy was graded from 0 to 3 according to the response criteria of the Japanese Breast Cancer Society[16]: grade 0 indicates no response, grade 1a a mild response, grade 1b a moderate response, grade 2 a marked response, and grade 3 a complete response. Data on pathological effect were missing for nine patients in each group. Arrows indicate that the limits of the confidence interval are not shown.

Katherine studien

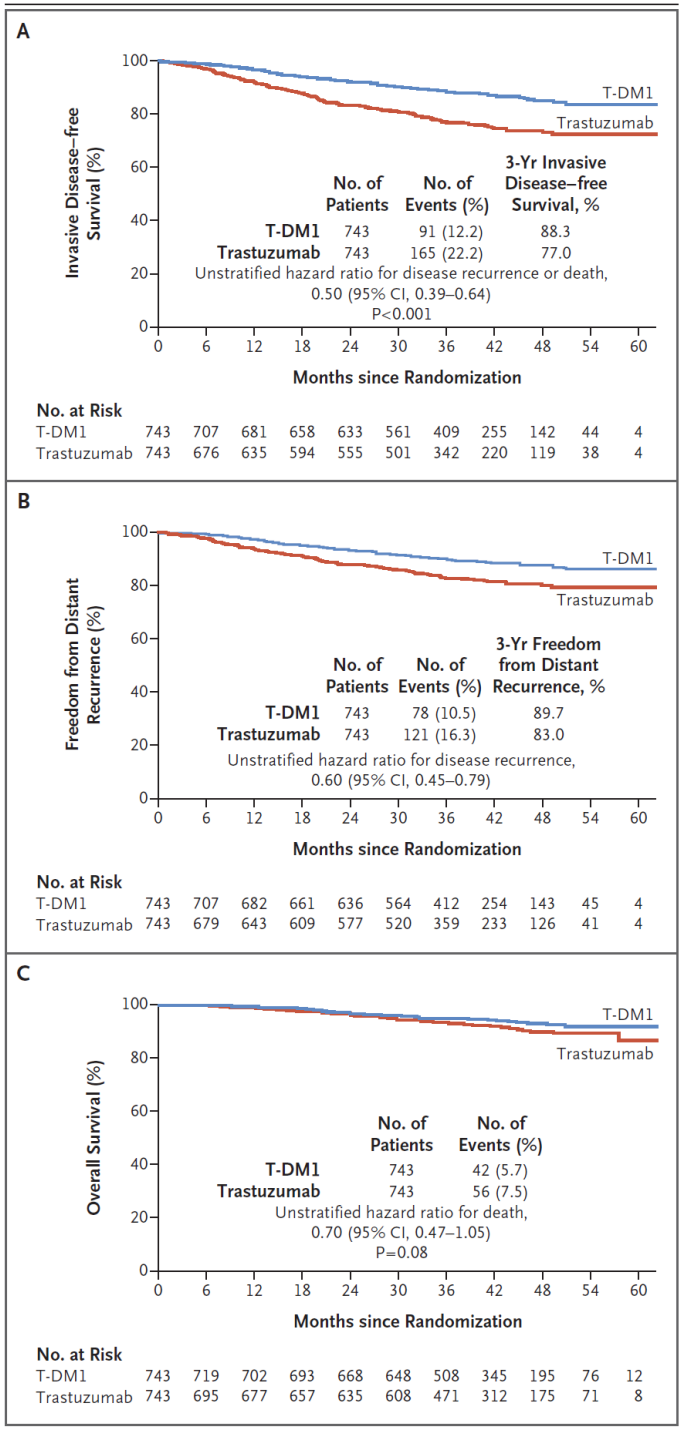


Figure 1. Kaplan–Meier Estimates of Survival in the Interim Analysis.

Invasive disease–free survival (Panel A) was defined as the time from randomization until the date of the first occurrence of one of the following: recurrence of ipsilateral invasive breast tumor, recurrence of ipsilateral locoregional invasive breast cancer, contralateral invasive breast cancer, a distant disease recurrence, or death from any cause. Distant recurrence (Panel B) was defined as evidence of breast cancer in any anatomical site — other than ipsilateral invasive breast tumor or recurrence of locoregional invasive breast cancer — that was either histologically confirmed or clinically diagnosed as recurrent invasive breast cancer. No statistical adjustments were made for multiple comparisons. For overall survival (Panel C), the P value for the boundary for significance in this prespecified interim analysis was less than 0.000032, corresponding to a hazard ratio of less than 0.43. CI denotes confidence interval.

Subgruppeanalyser

Subgroup	T-DM1	Trastuzumab	Hazard Ratio for Invasive-Disease Event (95% CI)	3-Yr Invasive Disease–free Survival Rate	
	no. of patients with an invasive-disease event/total no.			T-DM1	Trastuzumab
				%	
All patients	91/743	165/743	0.50 (0.39–0.64)	88.3	77.0
Age group					
<40 yr	20/143	37/153	0.50 (0.29–0.86)	86.5	74.9
40–64 yr	64/542	113/522	0.49 (0.36–0.67)	88.8	77.1
≥65 yr	7/58	15/68	0.55 (0.22–1.34)	87.4	81.1
Clinical stage at presentation					
Inoperable breast cancer	42/185	70/190	0.54 (0.37–0.80)	76.0	60.2
Operable breast cancer	49/558	95/553	0.47 (0.33–0.66)	92.3	82.8
Hormone-receptor status					
Negative (ER-negative and progesterone-receptor–negative or unknown)	38/209	61/203	0.50 (0.33–0.74)	82.1	66.6
Positive (ER-positive, progesterone-receptor–positive, or both)	53/534	104/540	0.48 (0.35–0.67)	90.7	80.7
Preoperative HER2-directed therapy					
Trastuzumab alone	78/600	141/596	0.49 (0.37–0.65)	87.7	75.9
Trastuzumab plus additional HER2-directed agent or agents	13/143	24/147	0.54 (0.27–1.06)	90.9	81.8
Pathological nodal status after preoperative therapy					
Node-positive	62/343	103/346	0.52 (0.38–0.71)	83.0	67.7
Node-negative or NE	29/400	62/397	0.44 (0.28–0.68)	92.8	84.6
Primary tumor stage at definitive surgery					
ypT0, ypT1a, ypT1b, ypT1mic, ypTis	40/331	52/306	0.66 (0.44–1.00)	88.3	83.6
ypT1, ypT1c	14/175	42/184	0.34 (0.19–0.62)	91.9	75.9
ypT2	25/174	44/185	0.50 (0.31–0.82)	88.3	74.3
ypT3	9/51	21/57	0.40 (0.18–0.88)	79.8	61.1
ypT4	3/12	6/11	0.29 (0.07–1.17)	70.0	30.0
Regional lymph-node stage at definitive surgery					
ypN0	28/344	56/335	0.46 (0.30–0.73)	91.9	83.9
ypN1	29/220	50/213	0.49 (0.31–0.78)	88.9	75.8
ypN2	16/86	38/103	0.43 (0.24–0.77)	81.1	58.2
ypN3	17/37	15/30	0.71 (0.35–1.42)	52.0	40.6
ypNX	1/56	6/62	0.17 (0.02–1.38)	98.1	88.7

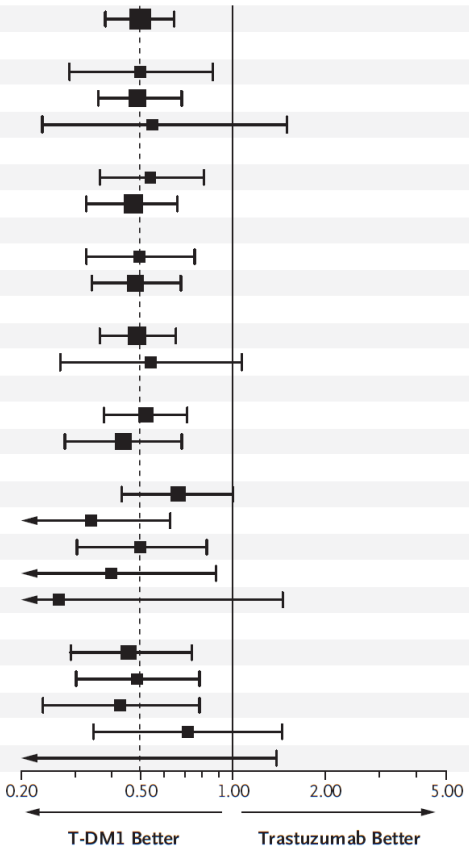


Figure 2. Subgroup Analysis of Invasive Disease–free Survival.

Five patients with a ypT1 tumor stage had ypT1 disease without further subspecification. The ypT4 category includes all patients with ypT4 and one patient with ypTX. The size of the black squares corresponds to the number of patients. ER denotes estrogen receptor, and HER2 human epidermal growth factor receptor 2.

Anbefaling post-neoadjuvant TNBC

- **Vi konkluderer med at pasienter med trippel negativ brystkreft og betydelig gjenværende cancer (ypN+ eller ≥ypT1c) ved operasjon bør vurderes for adjuvant capecitabine.** Dette betyr pasienter som ved operasjon har enten har positiv lymfeknutestatus eller >1 cm residual tumor i brystet.
- Anbefalt dosering av capecitabine er 8 sykluser, med 1000 mg/m2 x 2 i 14 av 21 dager. Dosen er lavere enn startdosen i CREATE-X, men de fleste i den studien måtte dosereduseres, og vår anbefalte dose er erfaringsmessig den høyeste akseptable dose i metastatisk setting.

Anbefaling postneoadjuvant HER2+ BC

- Vi konkluderer med at adjuvant trastuzumab-emtansine 14 sykluser anbefales for pasienter med residual tumor (ypT1c eller større) etter neoadjuvant behandling for HER2 positiv brystkreft.

Antracyklinfri alternativ adjuvant kjemoterapi

original report

West German Study PlanB Trial: Adjuvant Four Cycles of Epirubicin and Cyclophosphamide Plus Docetaxel Versus Six Cycles of Docetaxel and Cyclophosphamide in HER2-Negative Early Breast Cancer

Ulrike Nitz, MD[1,2]; Oleg Gluz, MD[1,2,3]; Michael Clemens, MD[4]; Wolfram Malter, MD[3]; Toralf Reimer, PhD, MD[5]; Benno Nuding, MD[6]; Bahriye Aktas, MD[7,8]; Andrea Stefek, DrMed[9]; Anke Pollmanns, MD[10]; Fatemeh Lorenz-Salehi, DrMed[11]; Christoph Uleer, MD[12]; Petra Krabisch, MD[13]; Sherko Kuemmel, MD, PhD[14]; Cornelia Liedtke, MD, PhD[1,15]; Steven Shak, MD[16]; Rachel Wuerstlein, MD[1,17]; Matthias Christgen, PhD[18]; Ronald E. Kates, PhD[1]; Hans H. Kreipe, MD, PhD[18]; and Nadia Harbeck, MD, PhD[1,17]
on behalf of the West German Study Group PlanB Investigators

abstract

PURPOSE The West German Study Group PlanB trial evaluated an anthracycline-free chemotherapy standard (six cycles of docetaxel and cyclophosphamide [TC]) in the routine treatment of human epidermal growth factor receptor 2–negative early breast cancer (EBC).

PATIENTS AND METHODS Patients with pT1 to pT4c, all pN+, and pN0/high-risk EBC were eligible. High-risk pN0 was defined by one or more of the following: pT greater than 2, grade 2 to 3, high urokinase-type plasminogen activator/plasminogen activator inhibitor-1, hormone receptor (HR) negativity, and less than 35 years of age. After an early amendment, all HR-positive tumors underwent recurrence score (RS) testing, with chemotherapy omission recommended in RS less than or equal to 11 pN0 to pN1 disease. Patients were randomly assigned to four cycles of epirubicin $(E)_{90}$/cyclophoshamide $(C)_{600}$ followed by four cycles of docetaxel $(T)_{100}$ or six cycles of $T_{75}C_{600}$ (administered once every 3 weeks). The primary end point was disease-free survival (DFS); secondary end points were overall survival (OS) and safety. The protocol specified $P = .05$ for a noninferiority margin of 4.4% for all patients combined.

RESULTS Of the 3,198 registered patients, 348 (RS ≤ 11) omitted chemotherapy, and 401 were not randomly assigned. The intention-to-treat population included 2,449 patients (1,227 EC-T *v* 1,222 TC: postmenopausal, 62.2% *v* 60.8%; pN0, 58.2% *v* 59.5%; pT1, 57.6% *v* 52.3%; HR positive, 81.4% *v* 82.2%; RS greater than 25 [in HR-positive patients], 26.2% *v* 27.5%). Within the safety population (1,167 *v* 1,178 patients), 87.5% *v* 93.0% completed therapy. After a 60-month median follow-up, 5-year outcomes were similar in the EC-T and TC arms (DFS, 89.6% [95% CI, 87.9% to 91.5%] *v* 89.9% [95% CI, 88.1% to 91.8%]; OS, 94.5% [95% CI, 93.1% to 95.9%] *v* 94.7% [95% CI, 93.3% to 96.1%]). The DFS difference was within the noninferiority margin of the original trial design. Five treatment-related deaths were reported for TC (one for EC-T), despite a trend toward more-severe adverse events in the latter. Interaction analysis revealed no predictive trends with respect to key factors, including triple-negative, luminal A/B-like, pN, age, and RS status.

CONCLUSION In the West German Study Group PlanB trial, 5-year outcomes for TC and EC-T were equally excellent. Six cycles of TC is an effective/safe option in human epidermal growth factor receptor 2–negative EBC with pN0 high genomic risk or pN1 EBC with genomically intermediate- to high-risk disease.

J Clin Oncol 37:799-808.

Resultat

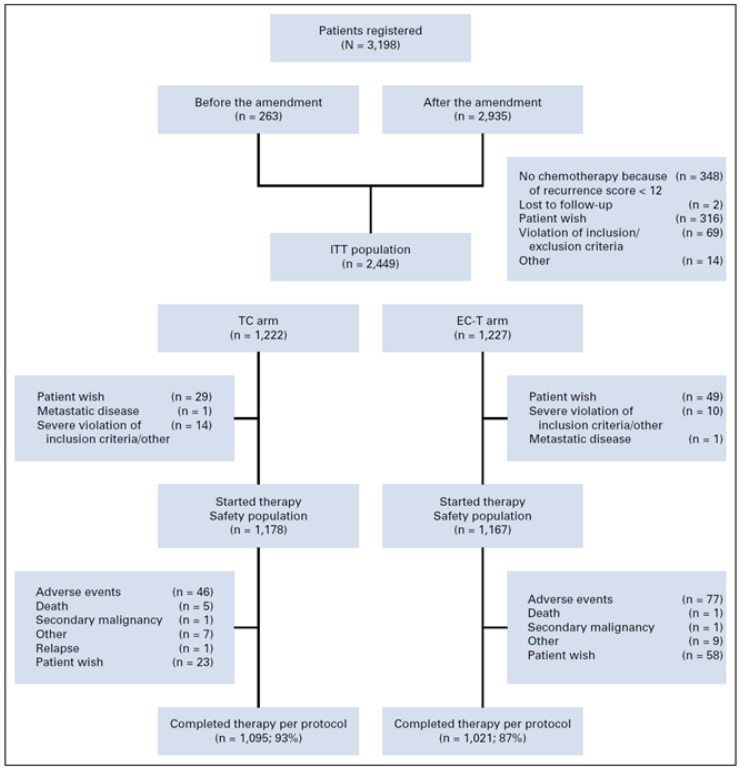


FIG 1. West German Study Group PlanB trial CONSORT diagram. EC-T, epirubicin and cyclophosphamide followed by docetaxel; ITT, intention to treat; TC, docetaxel and cyclophosphamide.

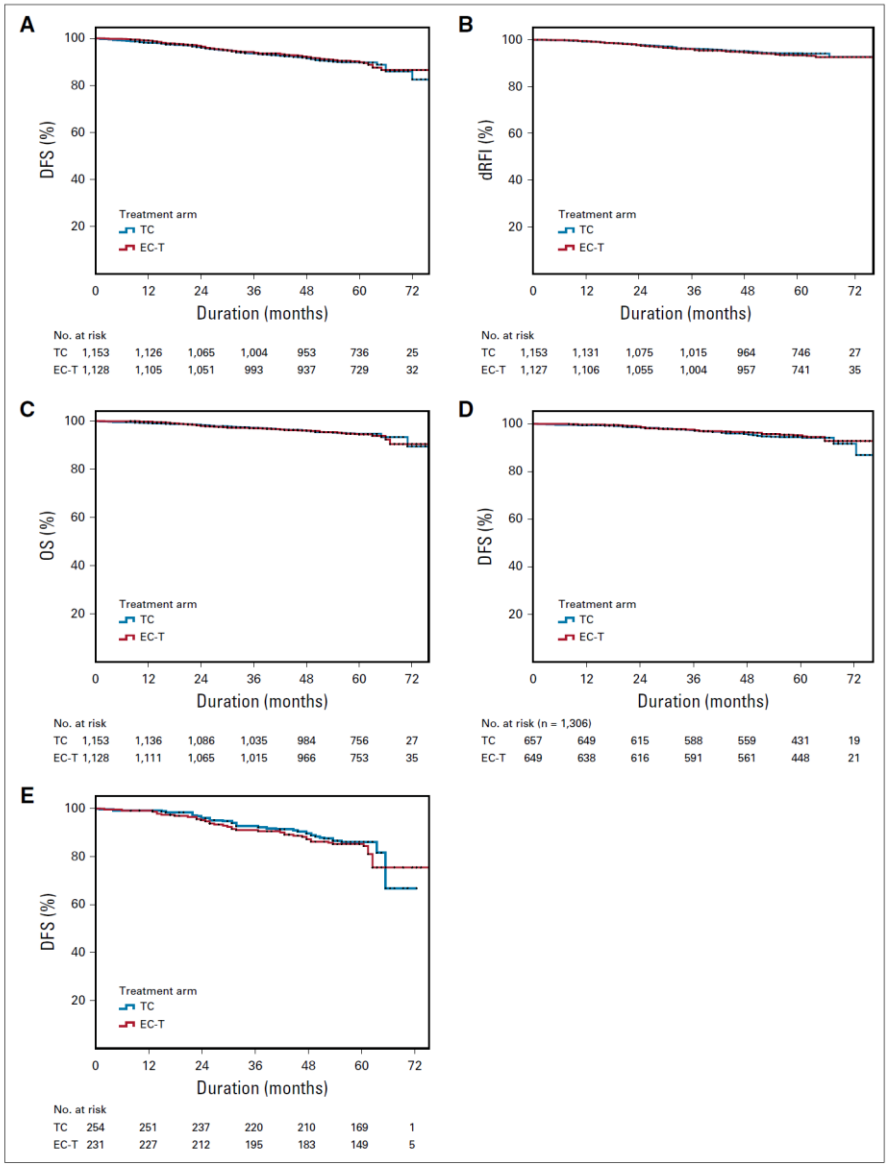


FIG 2. (A) Disease-free survival (DFS), (B) distant recurrence-free interval (dRFI), and (C) overall survival (OS) by treatment arm. (D) DFS by treatment arm and recurrence score (RS) of 25 or less and (E) DFS by treatment arm and RS greater than 25; the intention-to-treat population includes patients with RS measured (after early amendment). For the docetaxel and cyclophosphamide (TC) versus epirubicin and cyclophosphamide followed by docetaxel (EC-T) arms, respectively, numbers at risk were as follows: DFS and OS, n = 1,153 *v* 1,128; dRFI, n = 1,153 *v* 1,127; DFS/RS of 25 or less, n = 657 *v* 649; and DFS/RS greater than 25, n = 254 *v* 231. Patients in the intention-to-treat population with missing follow-up data (n = 69 *v* 99 for TC *v* EC-T, respectively) are omitted (one extra missing for dRFI).

Subgruppeanalyser

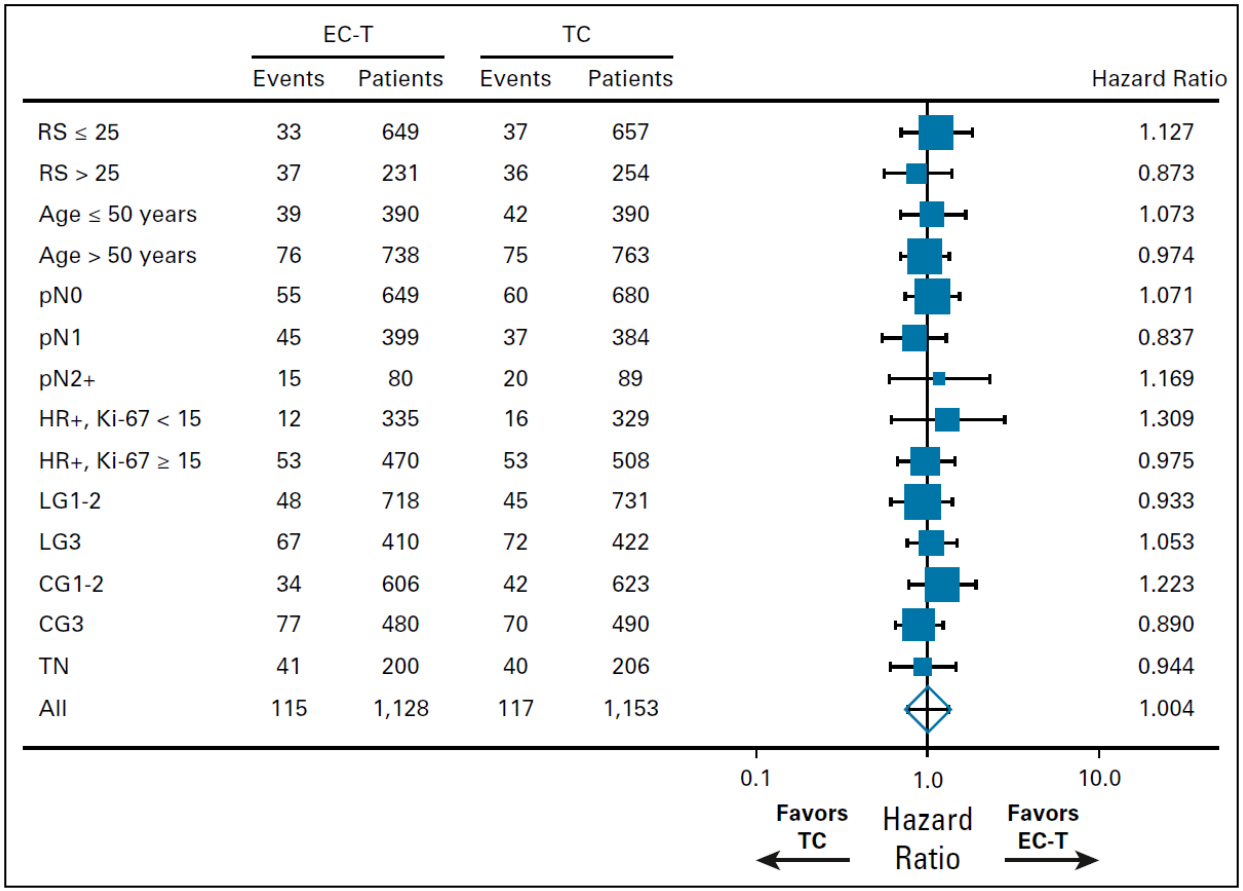


FIG 3. Forest plot of disease-free survival chemotherapy arm hazard ratios in subgroups (95% CIs, no corrections for multiple testing). CG, central grade; EC-T, epirubicin and cyclophosphamide followed by docetaxel; HR+, hormone receptor positive; Ki-67, protein encoded by the *MKI67* gene; LG, local grade; RS, recurrence score; TC, docetaxel and cyclophosphamide; TN, triple negative.

Oversikt over studier (med vs uten antracyklin)

TABLE 3. Summary of Large Trials in HER2-Negative EBC That Evaluated an Anthracycline-Free Regimen (TC) Versus a Conventional Anthracycline-Taxane Regimen

Trial	No. of Patients	Median Follow-Up	Experimental Regimen	Control Regimen	Inclusion Criteria	DFS	OS
USOR 9735[12]	1,016	7 years	4 × $T_{75}C_{600}$ once every 3 weeks	4 × $A_{60}C_{600}$	Stage I-III HER2 negative BC	7 year: 81% (TC) *v* 75%; *P* = .033	7 year: 87% (TC) *v* 82%; *P* = .032
ABC pooled analysis[6]	4,242	40 months	6 × $T_{75}C_{600}$ once every 3 weeks	USOR 06-090/NSABP B-46: 6 × $T_{75}A_{50}C_{500}$ once every 3 weeks NSABP B-49: 4 × $A_{60}C_{600}$ once every 3 weeks → 12 × Pac_{80} once every week 4 × $A_{60}C_{600}$ once every 2 weeks → 12 × Pac_{80} once every week 4 × $A_{60}C_{600}$ every 2 weeks → 4 × Pac_{175} once every 2 weeks	HER2 negative: pN+ or pN0 with one or more of the following criteria: HR negative, grade 3, RS ≥ 25 (NSABP B-46/B-49), or RS ≥ 31 (USOR 06-090)	4-year invasive DFS: 88.2% (TC) *v* 90.7%, *P* = .04	4 year: 94.7% (TC) *v* 95.0%; *P* = .6
DBCG 07-READ[7]	2,012	65 months	6 × $T_{75}C_{600}$ once every 3 weeks	3 × FE_{90}/C_{600} once every 3 weeks → 3 × T_{100} once every 3 weeks	Topoisomerase II-normal: pN+ and pN0 high-risk (< 39 years, tumor size > 2 cm, grade 2/3, ER negative, or HER2 positive)	5 year: 88.3% (TC) *v* 87.9%; *P* = 1	5 year: 93.3% *v* 94.8%; *P* = .41
WSG PlanB	2,449	61 months	6 × $T_{75}C_{600}$ once every 3 weeks	4 × $E_{90}C_{600}$ once every 3 weeks → 4 × T_{100} every 3 weeks	HER2 negative, pN+, or pN0 with one or more of the following risk factors: ≥ pT2, grade 2/3, high uPA/PAI-1, < 35 years, or ER/PR negative)	5 year: 89.9% (TC) *v* 89.6%	5 year: 95.9% (TC) *v* 94.5%

NOTE. Subscripts indicate dose in mg per square meter.

Abbreviations: ABC, Anthracyclines in Early Breast Cancer; AC, doxorubicin and cyclophosphamide; DBCG, Danish Breast Cancer Group; DFS, disease-free survival; EBC, early breast cancer; EC-T, epirubicin and cyclophosphamide followed by docetaxel; ER, estrogen receptor; FEC, fluorouracil, epirubicin, and cyclophosphamide; HER2, human epidermal growth factor receptor 2; NSABP, National Surgical Adjuvant Breast and Bowel Project; OS, overall survival; Pac, paclitaxel; PR, progesterone receptor; TAC, docetaxel with doxorubicin and cyclophosphamide; TC, docetaxel and cyclophosphamide; uPA/PAI-1, urokinase-type plasminogen activator/plasminogen activator inhibitor-1; USOR, US Oncology Research; WSG, West German Study Group.

4TC = 4AC

6TC ≈ 4AC→4T

Anbefaling

- TC x4 er ekvipotent med EC90 x4 for midlere risikogruppe.
- I denne forbindelse oppfattes docetaxel 75 mg/m2 + cyclophosphamide 600 mg/m2 q3w som ekvipotent med paclitaxel 80 mg/m2 qW + cyclophosphamide 600 mg/m2 q3w.

…forts

- **6 TC er sannsynligvis like bra som 4 EC90 etterfulgt av 4 docetaxel, basert på PlanB studien og DBCG-07 READ studien (kun topoisomerase 2-normale), men muligens inferior for høy N+ status basert på ABC meta-analysen og NSABP-30 studien**. Der er færre høyrisiko-pasienter i PlanB enn i NSABP-30 studien som viser at AC + taxan (4+4 kurer) er bedre enn ACT 4 kurer eller AT 4 kurer (13) – men her fikk altså pasienter med AT (=TC) 4 og ikke 6 kurer. I NSABP-30 hadde alle pasientene N+ sykdom, 42% var pT1, og 25% HR negative. I PlanB hadde 58% N0 sykdom, 57% pT1, 18% HR negative. NSABP-30 studien ligger som del av grunnlaget for bruk av EC-T hos pasienter med N+ sykdom i norske guidelines per idag. **Således kan vi ikke si med sikkerhet at 6 TC er like bra som EC-T (4+4) for dem med høyest risikoprofil.** Likevel, i PlanB studien var der ingen subgrupper, inkl. dem med N+ sykdom, som kom dårligere ut med TC enn EC-T.

Anbefaling

- TC regimet (6 TC) oppfattes som et akseptabelt alternativ til EC-Docetaxel (4+4) eller EC-paklitaxel ukentlig (4 EC + 12 uker paclitaxel), især for dem med mindre omfattende lymfeknutemetastaser og med cardiale risikofaktorer som gjør at man vil unngå anthracycliner.

Neoadjuvant behandling ved BRCA mutasjonsbærertilstand

- Den sannsynlig mest effektive behandlingen for denne typen brystkreft neoadjuvant oppfattes å være platinum cellegift sammen med taxan. Videre vil pasientens almentilstand og beinmargsfunksjon være bedre ved start av behandling enn senere, når flere cellegiftkurer er gitt. **Det anbefales derfor at man starter med det mest potente regimet, dvs. carboplatin/paclitaxel ved kimcelle BRCA mutasjon.**

Endokrin neoadjuvant behandling

- **Vi anbefaler at neoadjuvant endokrin terapi implementeres for luminal A-liknende lokalavanserte svulster.** Ved manglende fall i Ki67 eller manglende tumorskrumpning skal man skifte til kjemo. Klinisk evaluering anbefales hver 3.-4. uke av onkolog med erfaring i slik behandling, idet man må monitorere slike pasienter nøye og skifte behandling raskt ved vedvarende stabil sykdom (>2 mnd) eller progress. Det anbefales at man måler PAM50 og/eller Ki67 på biopsi tatt før behandlingsstart; og der luminal A svulster kjennetegnes av lav PAM50 score, evt. lav Ki67 og grad 1-2 differensiering.

Retningslinjer for behandling av residiv/metastaser

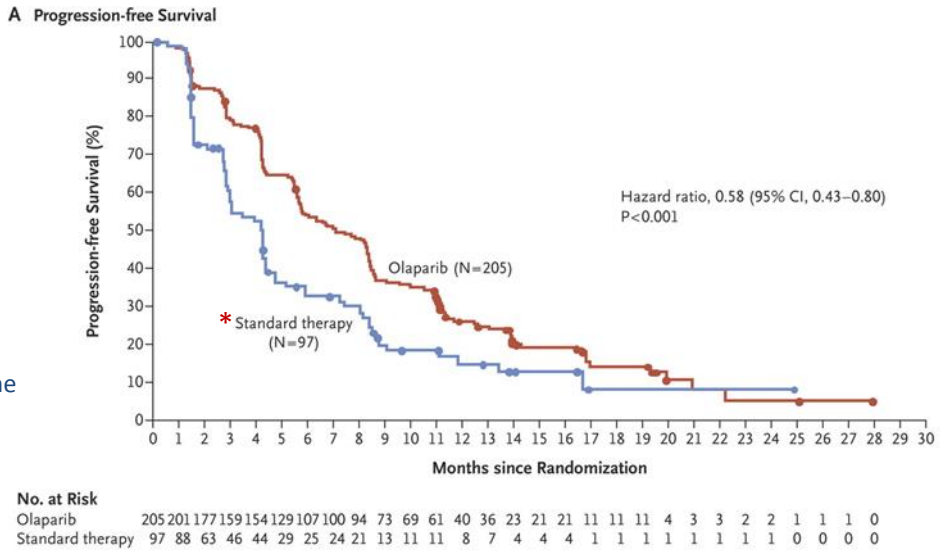
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Olaparib for Metastatic Breast Cancer in Patients with a Germline *BRCA* Mutation

Mark Robson, M.D., Seock-Ah Im, M.D., Ph.D., Elżbieta Senkus, M.D., Ph.D., Binghe Xu, M.D., Ph.D., Susan M. Domchek, M.D., Norikazu Masuda, M.D., Ph.D., Suzette Delaloge, M.D., Wei Li, M.D., Nadine Tung, M.D., Anne Armstrong, M.D., Ph.D., Wenting Wu, Ph.D., Carsten Goessl, M.D., Sarah Runswick, Ph.D., and Pierfranco Conte, M.D.

N Engl J Med 2017;377:523-33.



*Capecitabine,eribulin, vinorelbine

Reduserte bivirkninger sammenlignet med cellegift

PARP hemmere

- OlympiAD studien (n=302) viste en forlengelse i progresjonsfri overlevelse på 7 vs. 4.2 mndr, men ingen forskjell i totaloverlevelse (19.3 vs. 17.1 mndr.) etter median FU 25 mndr, for **olaparib** vs. cellegift (20, 21).
- Tilsvarende har EMBRACA studien vist en forlengelse i progresjonsfri overlevelse på 8.6 vs. 5.6 mndr, men ingen forskjell i totaloverlevelse på 22.3 vs. 18.1 mndr. etter median F-U 12 mndr, for **talazoparib** vs. Cellegift.

Olaparib ved BRCA mutasjonsbærertilstand

Olaparib for pasienter med kimcelle BRCA1/2 mutasjon og metastatisk brystkreft:

- Olaparib er nå i 2019 (FDA/EMA) godkjent for bruk til denne pasientgruppen i metastatisk setting. Pasientene skal ha fått tidligere anthracyklin og taxanbehandling, og dessuten endokrin terapi dersom de er hormonreseptorpositive, HER2 negative. Videre er det viktig at brystkreftsykdommen fremdeles er enten platinum-naïve eller fremdeles platinum-sensitiv iht. hvordan studiene har vært gjennomført. Dvs. at **pasientene skal enten ha respondert på platinum cellegift, og skiftes over til olaparib mens sykdommen enda er platinum sensitiv, eller platinum kan ikke gis til den aktuelle pasient pga. kontraindikasjoner**.
- **Olaparib oppfattes som godt alternativ til standard kjemoterapi.** Det samme gjelder talazoparib, men denne er foreløpig ikke godkjent for bruk i Norge.
- Alternativene til pasienter i denne situasjonen vil være cellegiftbehandling med eribulin, capecitabine m.v. og disse regimene gir generelt mer bivirkninger enn olaparib. **Det er viktig å merke seg at PARP hemmerbehandling ikke er aktuelt etter progress på platinum kjemoterapi, pga. sannsynlig kryssresistens.**

Kombinasjon av fulvestrant og aromatasehemmer (1. linje metastatisk)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Overall Survival with Fulvestrant plus Anastrozole in Metastatic Breast Cancer

Rita S. Mehta, M.D., William E. Barlow, Ph.D., Kathy S. Albain, M.D.,
Ted A. Vandenberg, M.D., Shaker R. Dakhil, M.D., Nagendra R. Tirumali, M.D.,
Danika L. Lew, M.A., Daniel F. Hayes, M.D., Julie R. Gralow, M.D.,
Hannah H. Linden, M.D., Robert B. Livingston, M.D.,*
and Gabriel N. Hortobagyi, M.D.

Resultat

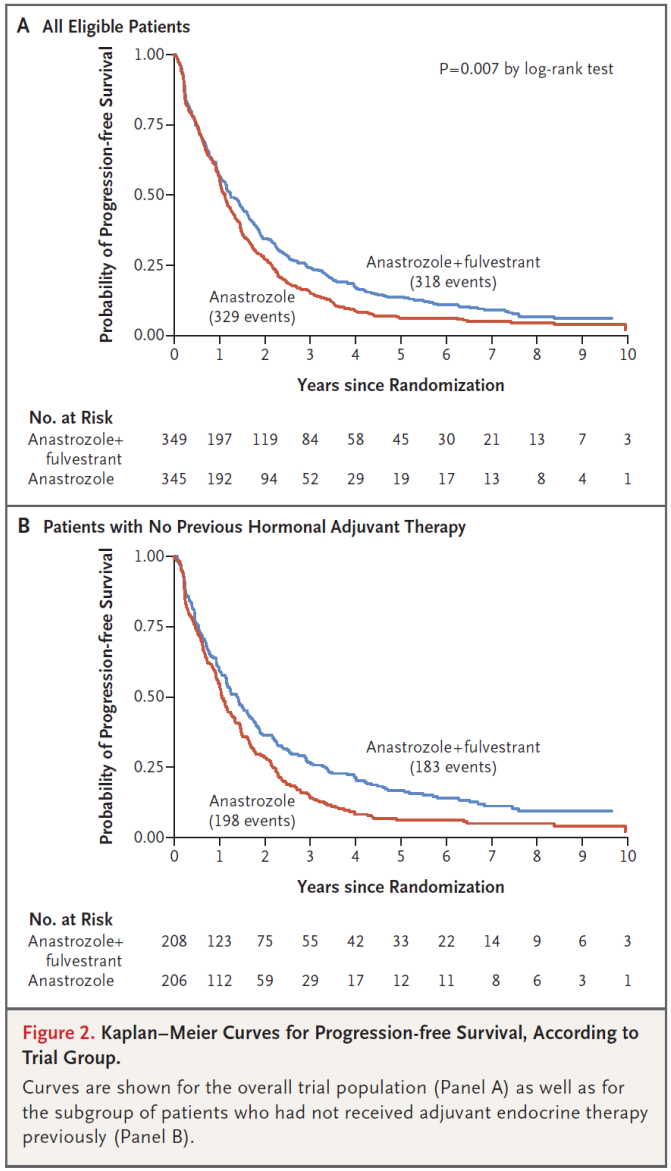


Figure 2. Kaplan–Meier Curves for Progression-free Survival, According to Trial Group.

Curves are shown for the overall trial population (Panel A) as well as for the subgroup of patients who had not received adjuvant endocrine therapy previously (Panel B).

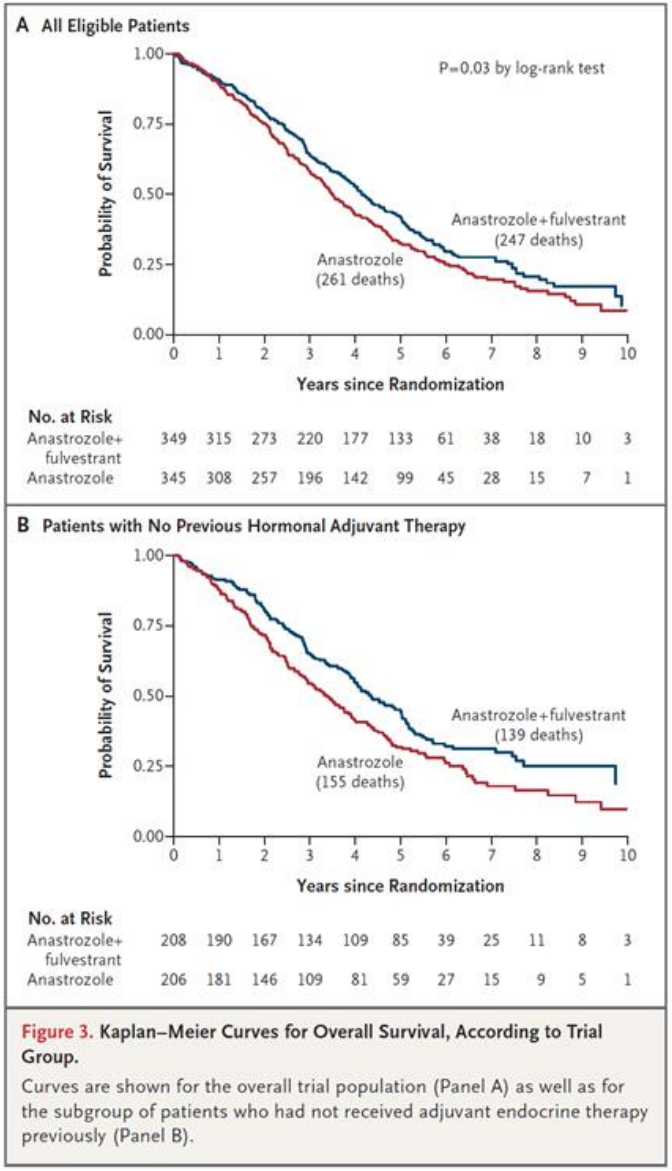


Figure 3. Kaplan–Meier Curves for Overall Survival, According to Trial Group.

Curves are shown for the overall trial population (Panel A) as well as for the subgroup of patients who had not received adjuvant endocrine therapy previously (Panel B).

Subgruppeanalyser

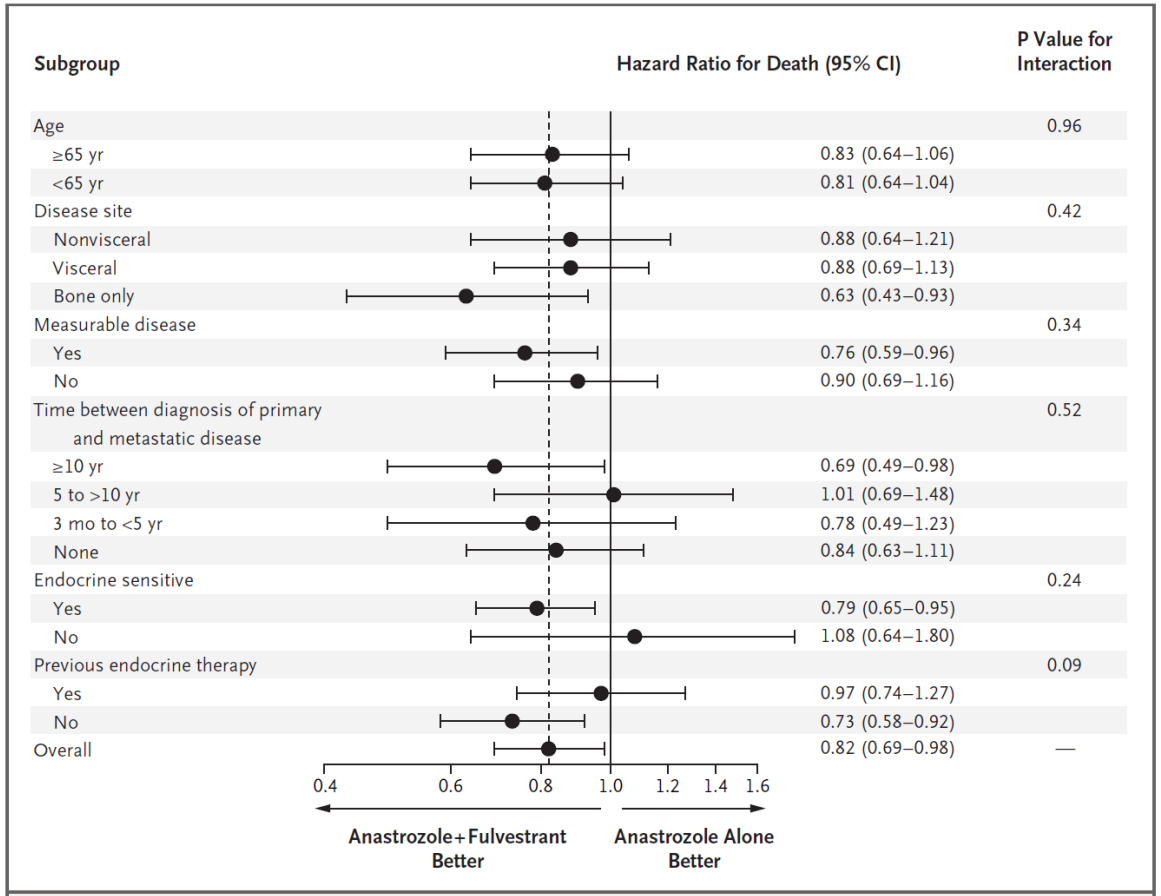


Figure 4. Subgroup Analysis of Overall Survival.

Shown are the results of subgroup analyses of the treatment effect on overall survival. Hazard ratios for death in the group that received combination therapy with fulvestrant plus anastrozole, as compared with the group that received anastrozole alone, are shown along with 95% confidence intervals.

Table 1. Overall Survival with Anastrozole plus Fulvestrant, as Compared with Anastrozole Alone.*

Variable	No. of Patients	No. of Deaths	Hazard Ratio for Death (95% CI)	P Value	Median Overall Survival	Patients Alive at 5 Yr (95% CI)
					mo	%
Total trial population	694		0.82 (0.69–0.98)	0.03		
Anastrozole	345	261			42.0	33 (28–38)
Anastrozole plus fulvestrant	349	247			49.8	42 (37–47)
Previous endocrine therapy†						
Yes	280		0.97 (0.74–1.27)	—		
Anastrozole	139	106			43.5	34 (26–42)
Anastrozole plus fulvestrant	141	108			48.2	38 (30–46)
No	414		0.73 (0.58–0.92)	—		
Anastrozole	206	155			40.3	32 (25–38)
Anastrozole plus fulvestrant	208	139			52.2	45 (38–51)

Anbefaling

- Resultatene fra denne studien endrer ikke på NBCG sine retningslinjer som anbefaler aromatasehemmer (AI) + CDK4/6 hemmer (for de fleste) i første linje ved HR+ HER2- MBC.
- Kombinasjonen av AI + fulvestrant (250 mg i.m.) kan vurderes der CDK4/6 hemmer ikke er aktuelt hos pasienter som er behandlingsnaïve m.t.p. endokrin terapi.

Kong Olav Vs kreftforskningspris
kr. 1.000.000,-

NBCG studier

Studie 1-9

Study	NBCG-numbering		Reference/ comment
1	Svenocam1	Weekly Adriamycin versus VAC in dvanced breast cancer. A randomized trial.	1
2	Svenocam2	Weekly Adriamycin vs. 4-epidoxorubicin every second week in dvanced breast cancer. A randomized trial.	2
3	Svenocam3	Megestrol acetate versus aminoglutethimide for metastatic breast cancer.	3
4	NBCG1	Adjuvant tamoxifen for pre- and postmenopausal women with estrogen receptor positive, node positive breast cancer: a randomized study.	4, 8
5	NBCG2	Adjuvant endocrine treatment (goserelin vs tamoxifen) in pre-menopausal patients with operable node positive stage II breast cancer. A prospective randomized national multicenter study.	5, 8
6	NBCG3	Cyclical use of tamoxifen and high-dose medroxyprogesterone acetate in advanced estrogen receptor positive breast cancer.	6-8
7		Droloxifen study 1: Influence of treatment with the anti-oestrogen 3-hydroxytamoxifen (droloxifene) on plasma sex hormone levels in postmenopausal patients with breast cancer	36
8	-	Droloxifen study 2: Influence of droloxifene on metastatic breast cancer as first-line endocrine treatment.	37
9	NBCG4	Protocol for treatment and FU of in situ carcinomas	Premature closure (no results)

Studie 10-17

10	SBG9401	Tailored fluorouracil, epirubicin, and cyclophosphamide compared with marrow-supported high-dose chemotherapy as adjuvant treatment for high-risk breast cancer: a randomised trial.	27-29
11	SBG9404	Docetaxel compared with sequential methotrexate and 5-fluorouracil in patients with advanced breast cancer after anthracycline failure	30
12	NBCG5	Randomized, placebo-controlled trial of clodronate in patients with primary operable breast cancer.	9
13	Exe027	A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer.	32-35
14	NBCG6/ NeoTax	Evaluation of epi-adriamycin versus paclitaxel for primary medical treatment ("neo-adjuvant chemotherapy" in patients with locally advanced (stage III, T3/4 and/or N2) non-inflammatory breast cancer with or without limited distant metastases; phase II study	10-14, analyses ongoing
15	NBCG7/ Exe031	Effects of exemestane administered for 2 years versus placebo on bone mineral density, bone biomarkers, and plasma lipids in patients with surgically resected early breast cancer.	15-16
16	HERA	Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial.	26
	HABITS	Hormone replacement therapy in breast cancer survivors – is it safe.	31
17	NBCG8	Evaluation of clinical effects of and predictive factors to docetaxel and trastuzumab in sequence followed by combination as first line treatment in patients with HER2-positive breast cancers.	Closed before study was started

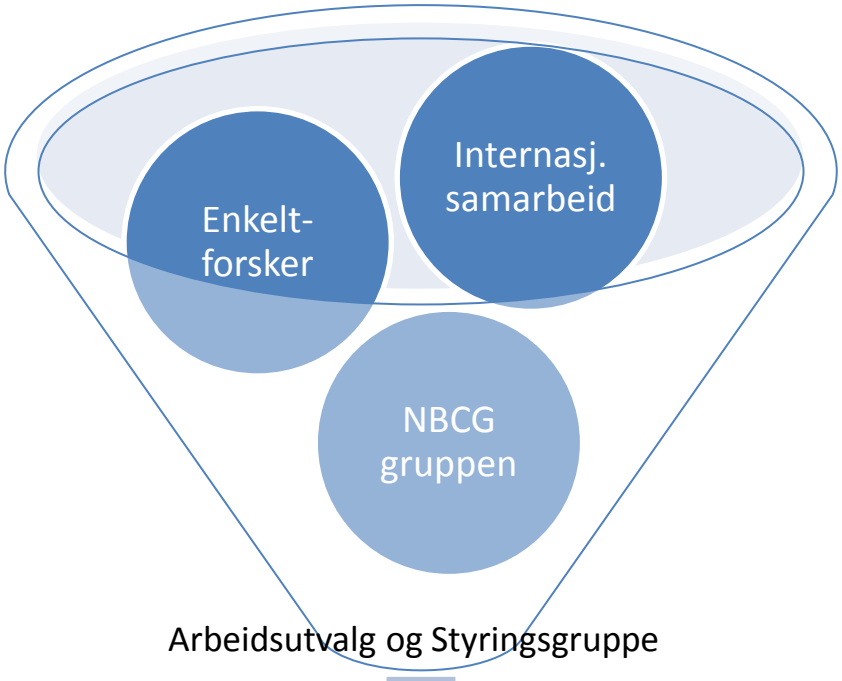
Studie 18-23

18	NBCG9/ SATT	Secondary Adjuvant (rescue) Treatment with docetaxel (Taxotere) and detection of isolated tumor cells in bone marrow as a surrogate marker for effect - in node positive and high risk node negative breast cancer after standard adjuvant epirubicin-containing treatment (SATT)	17-19, analyses ongoing
19	NBCG10	Weekly Paclitaxel plus Capecitabine versus Docetaxel Every 3 Weeks plus Capecitabine in Metastatic Breast Cancer.	20
20	NBCG11/ ABCSG21	A randomized phase II study comparing anastrozole and fulvestrant to anastrozole for adjuvant treatment of postmenopausal patients with early breast cancer and disseminated tumour cells in bone marrow	Premature closure (no results)
21	NBCG12/ ALTTO	Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation study. A randomised, multi-centre, open-label, phase III study of adjuvant lapatinib, trastuzumab, their sequence and their combination in patients	21,22
22	NBCG13/ NeoALTTO	NeoALTTO (Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) study. A randomised, multicentre, open-label, phase III study of neoadjuvant lapatinib, trastuzumab, and their combination plus paclitaxel in women with HER2/ErbB2 positive primary breast cancer	23,24
23	NBCG14/ EBBA2	*Energy Balance and Breast Cancer Aspects (EBBA2)*	25 Closed for inclusion, follow up and analyses ongoing

Studie 24-30

24	NBCG15/ PETREMAC	PErsonalized TREatment of high-risk MAmmary Cancer – the PETREMAC Trial	Ongoing recruitment
25	NBCG16/ IBCSG 48-14	Pregnancy Outcome and Safety of Interrupting Therapy for Women With Endocrine Responsive Breast Cancer	Ongoing recruitment
26	NBCG17/ ALICE	Atezolizumab Combined With Immunogenic Chemotherapy in Patients With Metastatic Triple-negative Breast Cancer	Ongoing recruitment
27	NBCG18/ ICON	A randomized phase IIb study evaluating immunogenic chemotherapy combined with ipilimumab and nivolumab in patients with luminal B breast cancer.	Ongoing recruitment
28	NBCG19/ EMIT1	Establishment of Molecular profiling for Individual clinical routine Treatment decision in Early Breast Cancer	Inclusion starts in September 2018
29	NBCG20/ OPTIMA	Optimal Personalised Treatment of early breast cancer using Multi-parameter Analysis (OPTIMA)/ EMITEBC-2	Inclusion starts in September 2018
30	NBCG21/ PETREMAC2	PErsonalized TREatment of high-risk MAmmary Cancer – the PETREMAC 2 Trial	Inclusion starts early 2019

Initiativ eller forslag til studier - NBCG



Arbeidsutvalg og Styringsgruppe

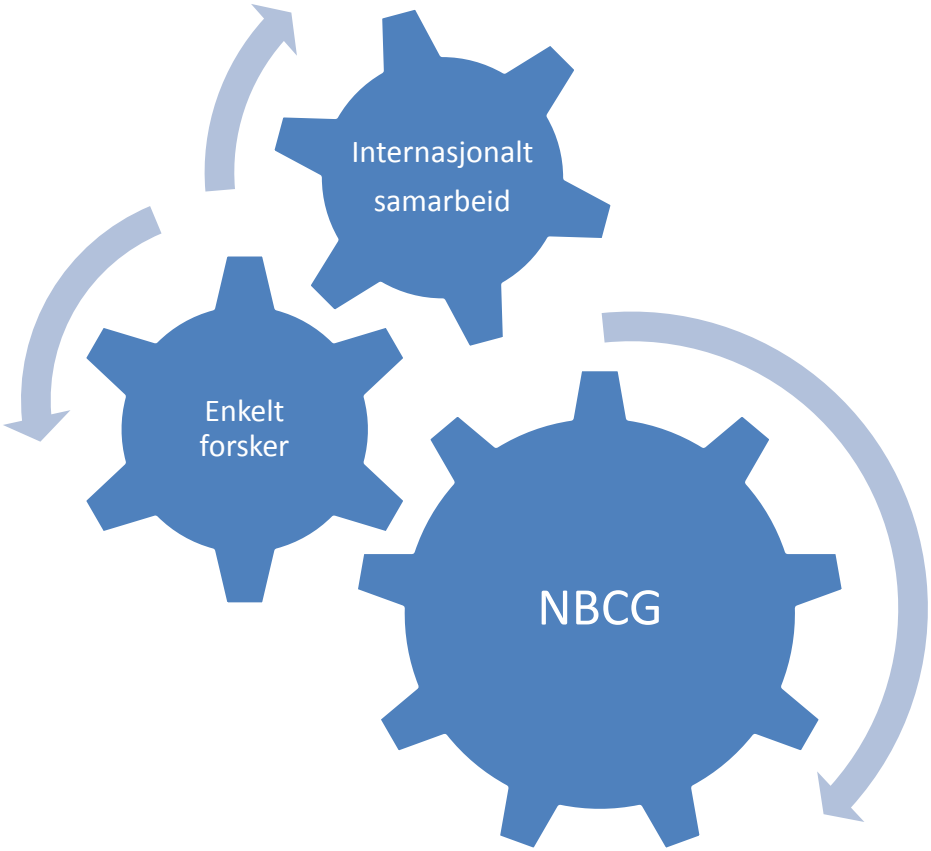
NBCG vurderer relevans, interesse, gjennomførbarhet

Ikke-nbcg studie

NBCG studie

NBCG - forskning

Samarbeid og interaksjon



- Enkeltforskere i NBCG
- Forskningsmiljø utenfor NBCG
- Internasjonalt:
  - Breast International group
  - Scandinavian Breast Group/ Nordic Breast Group
  - Andre grupper

Mål

Landsdekkende tilbud/ deltagelse

Pågående studier

Trial	About what	Testing..	Collaborator/ responsible
POSITIVE trial (NBCG16/ IBCSG 48-14)	Pregnancy after breast cancer	abruption of endocrine adjuvant treatment to allow pregnancy	IBCSG
ALICE (NBCG17)	Check-point inhibitor in triple negative BrCa	immunogenic chemotherapy (liposomal doxorubicin 2qw + oral cyclophosphamide 2/4 weeks) +/- azetolizumab (anti-PD-L1)	Jon Amund Kyte
ICON (NBCG18)	Check-point inhibitors in HR+HER2- BrCa	immunogenic chemotherapy +/- nivolumab (anti-PD1) and low dose ipililumab (anti-CTLA4)	Jon Amund Kyte
Skagen-1	Radiotherapy	hypo-fractionated locoregional treatment and integrated boost in breast cancer	Skagen study group – Birgitte Offersen
EMIT1 (NBCG19)	Gene expression profiling by Prosigna – implementation and decision impact	more precise prognostic classification and adjuvant treatment decisions of HR+HER2- node negative patients by gene expression profiling (Prosigna) ; establishing molecular breast cancer profiling within all Norwegian health regions	Bjørn Naume
OPTIMA (EMIT2/NBCG20)	Prosigna test to decide use of chemotherapy in high risk BrCa	omission of chemotherapy by Prosigna test in high risk HR+HER2- node positive patients compared to use of standard chemotherapy	UK-OPTIMA -Rob Stein NO-OPTIMA - B Naume

I planleggingsfase/oppstartsfase

Trial	About what	Testing..	Collaborator/ responsible
NATURAL	Radiotherapy de-escalation	no irradiation versus partial breast irradiation for low risk HR+ node negative BrCa patients	DBCG – Birgitte Offersen
PETREMAC2	Molecular subgroup neoadjuvant treatment	molecular characterisation to decide neoadjuvant treatment (PErsonalized TREatment of high-risk MAmmary Cancer).	Hans Petter Eikesdal
INDAX	Axillary surgery deescalation	individualized axillary treatment of initially biopsy-proven node-positive breast cancer after neoadjuvant chemotherapy	EUBREAST

Nye studier til diskusjon

- Taormina – studien (svensk initiativ)
  - Systemisk behandling +/- stereotaktisk strålebehandling av oligometastaser
- Breclim-2

NBCGs nettside som hjelpeverktøy for kliniske studier

https://nbcg.no/pagaende-studier-apne-for-inklusjon/

Hva ønsker vi å gjøre med prispengene

- Ansette en person i 20% stilling (4-5 år) med arbeidsområde:
  - Bidra i arbeidet med å få i gang 2-3 nasjonale studier med deltagelse fra hele Norge
  - Gjøre Norge mer attraktive for deltagelse i interessante intervensjonsstudier med god finansiering
  - Bidra til å underbygge/lette logistikken knyttet til å gjennomføre nasjonale kliniske brystkreftstudier

Status for vurderinger av medikamenter og metoder

- **Pertuzumab**
  - Pertuzumab (Perjeta) til behandling av HER2-positive metastatisk og tidlig brystkreft kommer opp i Beslutningsforum 17.juni
- **Abemaciclib (CDK4/6 hemmer)**
- **Prosigna (genekspresjonsprofilering for å bedre prognostisk presisjon og valg av adjuvant behandling)**
  - **«Hurtig» metodevurdering ennå ikke ferdig 2 år etter at Prosigna test ble sendt inn til Nye Metoder**
  - **Det er søkt om unntak på gruppenivå for å benytte testen nasjonalt frem til beslutning foreligger (mai 2019)**

Takk