DANISH BREAST CANCER GROUP

Status for nationale forsøg

Medicinsk Udvalg

A Knop

Status for (inter)nationale forsøg

(Neo)adjuverende

MASTER. A randomized, multicenter, double-blind phase III, placebo-controlled comparison of standard (neo)adjuvant therapy plus placebo versus standard (neo)adjuvant therapy plus atorvastatin in patients with early breast cancer.

Nordic Trip Trial (NTT) . A Translational Randomized Phase III Study Exploring the Effect of the Addition of Capecitabine to Carboplatine Based Chemotherapy in Early "Triple Negative" Breast Cancer

CryoPAC . Et åbent randomiseret fase 2 forsøg med kølehandske og sokker overfor ingen forebyggelse i forbindelse med adjuverende paclitaxel.

Astefania. (adj TDM1 +/- atezolizumab til HER2 pos. ptt med non-PCR efter neoadjuverende behandling.

Destiny 05. Post-neoadjuvant trastuzumab deruxtecan (T-DXd) versus T-DM1 in patients with residual invasive disease following neoadjuvant therapy. Et randomiseret fase lll forsøg hos patienter med HER2 positiv brystkræft.

CheckMate 7FL. El. NeoNivo Neoadjuverende nivolumab versus placebo . Et randomiseret fase lll forsøg hos patienter med ER postiv og HER2 negativ brystkræft.

ALEXANDRA . A randomized fase lll study comparing atezolizumab (Anti PD-L1 Antibody) in combination with adjuvant anthracycline/taxane-based chemotherapy versus chemotherapy alone in patients with operable triple-negative breast cancer

Metastaserende

Destiny-06. A study of Trastuzumab Deruxtecan (T-DXd) vs Investigator's Choice Chemotherapy in HER2-low, Hormone Receptor Positive, Metastatic Breast Cancer.

Destiny-09 . Trastuzumab Deruxtecan (T-DXd) With or Without Pertuzumab Versus Taxane, Trastuzumab and Pertuzumab in HER2-positive Metastatic Breast Cancer.

BO41843/Giredestrant (oral SERD) (A Phase III, randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of GDC-9545 combined with palbociclib compared with letrozole combined with palbociclib in patients with ER-positive, HER2-negative locally advanced (recurrent or progressed) or metastatic breast cancer.)

INAVO 120/Inavolisib . Phase III study evaluating the efficacy and safety of Inavolisib + Palbociclib + Fulvestrant vs Placebo + Palbociclib + Fulvestrant in patients with PIK3CA-mutant, HR+ HER2-Negative, Locally Advanced or Metastatic Breast Cancer.

PostMONARCH . Phase III study of fulvestrant +/- abemaciclib following progression om a CDK4/6i + endocrine therapy.

ImmunoBreast - A Phase Ib Study Phase Ib, open-label, single-arm, clinical study to determine the safety, tolerability and trends of efficacy of ALECSAT as an add-on therapy to standard treatment with carboplatin and gemcitabine in female patients with locally advanced inoperable or metastatic TNBC, which has received no more than two prior systemic therapies for mTNBC, max 2 prior lines for mBC (Investigator initeret)

CAPItello-292 : A Phase Ib/III Randomised Study of Capivasertib plus Palbociclib and Fulvestrant versus Placebo plus Palbociclib and Fulvestrant in Hormone Receptor-Positive and Human Epidermal Growth Factor Receptor 2-Negative Locally Advanced, Unresectable or Metastatic Breast Cancer (CAPItello-292).

Adjuverende
To nationale - et nordisk

MASTER. A randomized, multicenter, double-blind phase III, placebo-controlled comparison of standard (neo)adjuvant therapy plus placebo versus standard (neo)adjuvant therapy plus atorvastatin in patients with early breast cancer.

Nordic Trip Trial (NTT) . A Translational Randomized Phase III Study Exploring the Effect of the Addition of Capecitabine to Carboplatine Based Chemotherapy in Early "Triple Negative" Breast Cancer

CryoPAC . Et åbent randomiseret fase 2 forsøg med kølehandske og sokker overfor ingen forebyggelse i forbindelse med adjuverende paclitaxel.

Early breast cancer statin trial
the master trial

A randomized, multicenter, double-blind, placebo-controlled comparison of standard (neo)adjuvant therapy plus placebo versus standard (neo)adjuvant therapy plus atorvastatin in patients with early breast cancer

MAmmary cancer **ST**atin **ER** positive trial

Novo Nordisk Foundation

Breast Cancer and Statins, in general

EPIDEMIOLOGY:

Observational studies have demonstrated lower breast cancer recurrence and breast cancer- specific mortality among statin users[1-3]

***IN VITRO* :**

In breast cancer cell lines, statins inhibit proliferation and induce apoptosis[4-5]

IN VIVO :

In mouse models, statins inhibit cancer growth[6]

IN HUMANS:

In breast cancer patients, statins decrease proliferation

and increase apoptosis/cell death in tumors[7-8]

1) Nielsen et al., NEJM 2012 2) Murtola et al., PLOS ONE 2014 3) Ahern et al., Lancet Oncol 2014 4) Spampanato et al., Int J Oncol 2012 5) Koyuturk et al., Cancer Letter 2007 6) Campbell et al., Cancer Res 2006 7) Garwood et al., Breast Cancer Res Treat 20108) Wang et al., Oncotarget 2015

STATINS and BC-prognosis

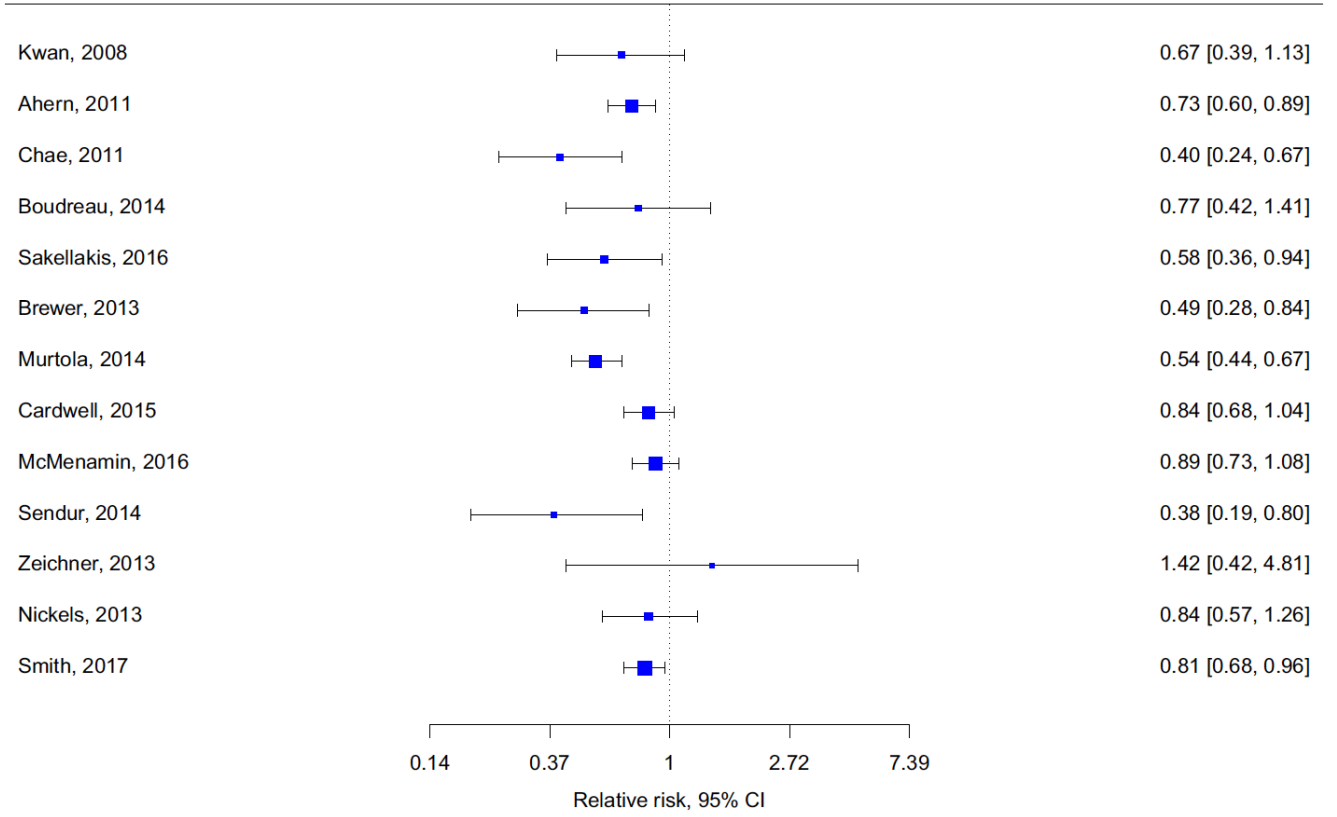
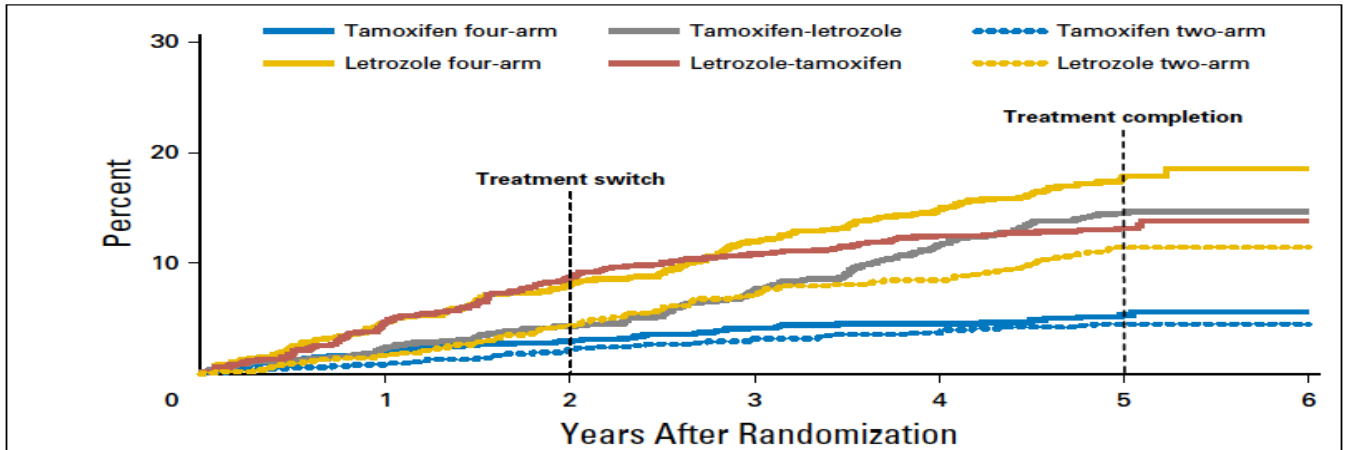


Fig. 2 *The prognostic value of statin treatment in the adjuvant breast cancer setting illustrated by a forest plot of the currently reported studies.*

Endocrine treatment
Different effects on cholesterol levels – and initiation of cholesterol lowering medication

RESULT:

Letrozol treated patients more often initiated cholesterol lowering medication - compared to tamoxifen treated patients



	No. of Patients	Events	Cumulative Incidence %, Years 1-5				
			1	2	3	4	5
Tamoxifen four-arm	1,417	70	1.9	3.0	4.2	4.5	5.3
Letrozole four-arm	1,380	229	4.7	8.0	12.0	14.8	17.9
Tamoxifen-letrozole four-arm	1,411	190	2.7	4.8	8.3	12.4	15.2
Letrozole-tamoxifen four-arm	1,380	179	5.4	9.6	11.8	13.4	14.0
Tamoxifen two-arm	868	37	0.1	2.2	3.2	3.7	4.5
Letrozole two-arm	870	93	1.7	4.4	7.1	8.5	11.4

Cholesterol, Cholesterol-Lowering Medication Use, and Breast Cancer Outcome in the BIG 1-98 Study
S Borgquist et al. J Clin Oncol . 2017 Apr 10;35(11):1179-1188.

Cholesterol, cholesterol lowering medication, and breast cancer outcome

Table 4. Marginal Structural Modeling Results of Initiation of CLM During Endocrine Treatment and Outcome Among All Treatment Arms

Variable	No.	HR	95% CI	*P*
No. of patients	5,944			
No. of DFS events	1,432			
No. of patients reporting CLM initiation during protocol therapy	697			
DFS model results				
Univariable weighted*		0.81	0.67 to 0.97	.02
Multivariable weighted†		0.79	0.66 to 0.95	.01
No. of BCFI events	940			
No. of patients reporting CLM initiation during protocol therapy	697			
BCFI model results				
Univariable weighted*		0.77	0.61 to 0.97	.03
Multivariable weighted†		0.76	0.60 to 0.97	.02
No. of DRFI events	729			
No. of patients reporting CLM initiation during protocol therapy	697			
DRFI model results				
Univariable weighted*		0.75	0.57 to 0.98	.04
Multivariable weighted†		0.74	0.56 to 0.97	.03

RESULT:

Patients initiating CLM had a significant improved prognosis compared to those without CLM

Cholesterol, Cholesterol-Lowering Medication Use, and Breast Cancer Outcome in the BIG 1-98 Study
S Borgquist et al. J Clin Oncol . 2017 Apr 10;35(11):1179-1188.

Cholesterol, Cholesterol Lowering Medication Use, and Breast Cancer Outcomes in the BIG 1-98 Study

IBCSG

IN CONCLUSION

- Serum cholesterol levels decreased during therapy with tamoxifen
- The incidence of CLM treatment was greatest during therapy with letrozole
- Cholesterol-lowering medication during endocrine treatment appears to have a favorable impact on DFS, BCFI and DRFI

MASTER trial, OBjectives

- **PRIMARY OBJECTIVE:**
- To compare invasive disease-free survival (IDFS) in patients randomized to standard (neo)adjuvant therapy plus placebo or standard (neo)adjuvant therapy plus atorvastatin

- **SECONDARY OBJECTIVES:**
- - To compare overall survival (OS), recurrence-free interval (RFI), distant recurrence-free interval (DRFI) including associations with first site of recurrence, cardiac death-free interval, and overall safety in the two treatment arms.
- - To investigate morbidity endpoints
- - To address translational endpoints

MASTER trial design obs: OBSERVATIONAL COHORT

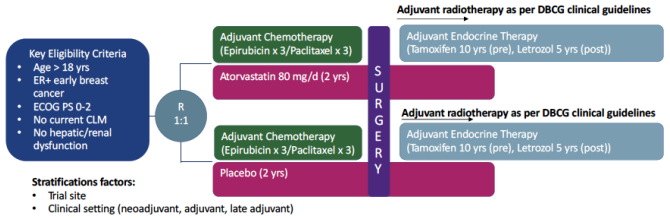
Non-randomized patient cohort on any cholesterol-lowering medication at diagnosis

Patients eligible for MASTER – any clinical setting:

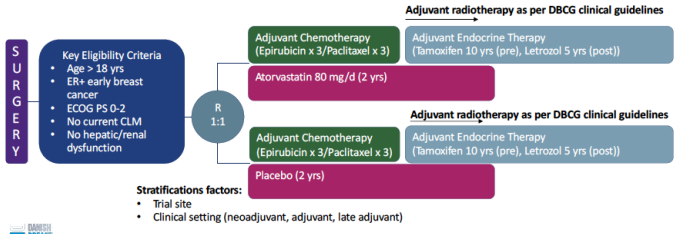
Participation in observational cohort:

1. CRF
2. PRO
3. Blood samples

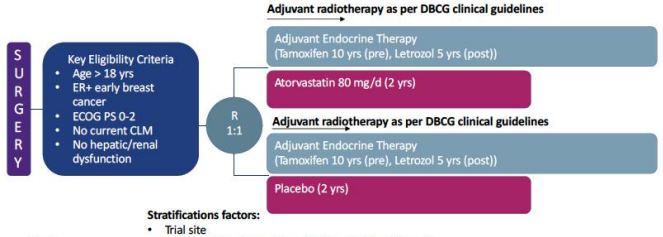
MASTER TRIAL DESIGN, NEOADJUVANT



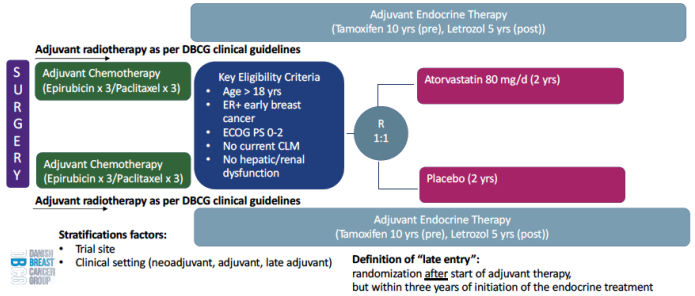
MASTER TRIAL DESIGN, EARLY ADJUVANT



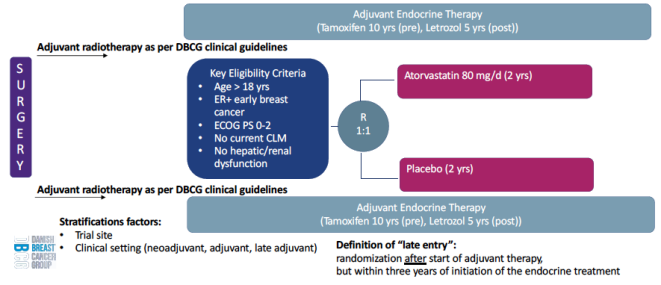
MASTER TRIAL DESIGN, EARLY ADJUVANT, ET ONLY



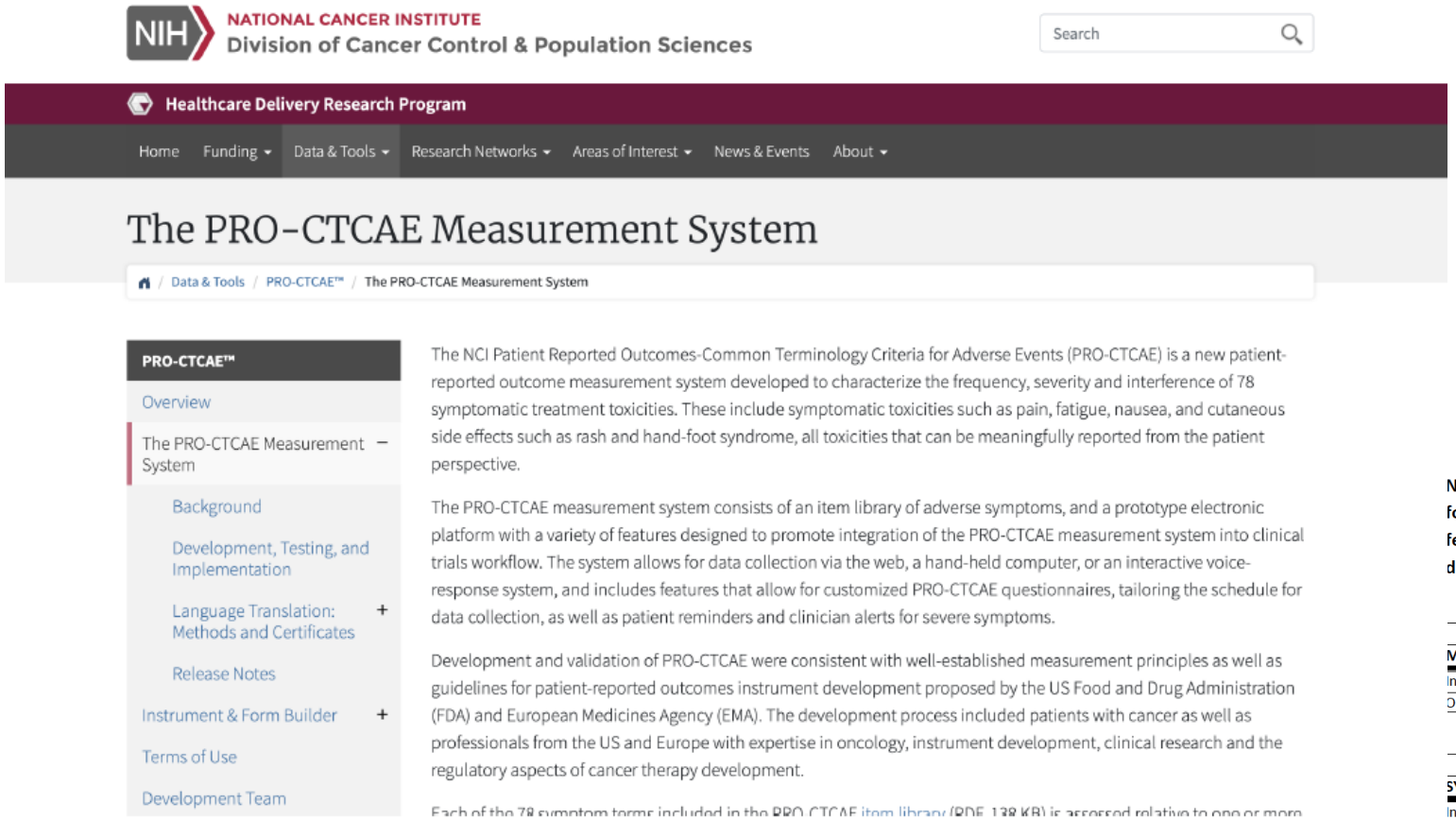
MASTER TRIAL DESIGN, LATE ADJUVANT

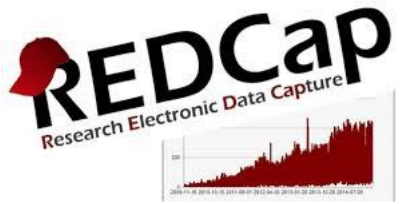


MASTER TRIAL DESIGN, LATE ADJUVANT, ET ONLY



MASTER trial, PRO-CTCAE





NCI- PRO-CTCAE™ ITEMS

Item Library Version 1.0

Når man er i behandling for sin kræftsygdom, oplever man sommetider forskellige symptomer og bivirkninger. For hvert spørgsmål, venligst marker det felt eller sæt et (X) i den boks, som bedst beskriver dine oplevelser i de seneste 7 dage.

1. **PRO-CTCAE™ Symptom Term:** Dry mouth				
MUNDTØRHED				
Inden for de seneste 7 dage, hvad var SVÆRHEDSGRADEN af MUNDTØRHED da det var VÆRST?				
O Ingen	O Mild	O Moderat	O Kraftig	O Meget kraftig

2. **PRO-CTCAE™ Symptom Term:** Difficulty swallowing				
SYNKEBESVÆR				
Inden for de seneste 7 dage, hvad var SVÆRHEDSGRADEN af SYNKEBESVÆR da det var VÆRST?				
O Ingen	O Mild	O Moderat	O Kraftig	O Meget kraftig

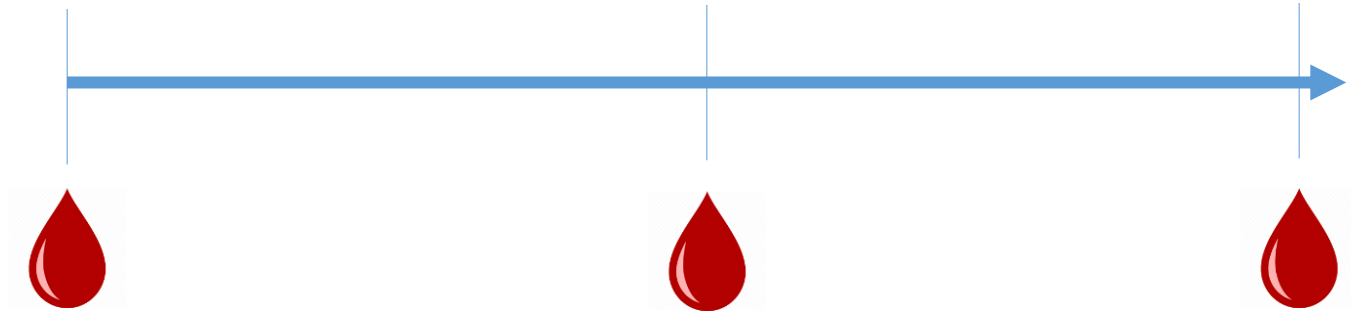
3. **PRO-CTCAE™ Symptom Term:** Mouth/throat sores
SÅR ELLER LÆSIONER I SUMMINDEN I MUND ELLER SVÆLG

MASTER trial, Translational blood

Serum, plasma and whole-blood collected at baseline and during follow-up (year 1, year 2)

Analyzed for prognostic and predictive markers,

i.e. LDL, HDL, cholesterol, triglycerides, Apo-A, and Apo-B, HMGCR SNP´s, circulating antibodies and circulating tumor-DNA.



Første patientinklusion d. 14. januar 2021 (- 3352 to go ☺)

MASTER, Status pr. 01.01.2022

		2021												I alt	Strata		
		Jan	Feb	Mar	Apr	Maj	Jun	Jul	Aug	Sep	Okt	Nov	Dec		1: Neo	2: Adj Early	3: Adj Late
	RAND																
Rigshospitalet		-	-	-	-	-	-	-	-	-	-	-	1	1	0	1	0
Sønderborg		-	-	-	-	-	5	4	3	7	9	12	10	50	1	10	39
Esbjerg		-	-	-	-	-	-	-	-	-	-	5	2	7	0	2	5
Vejle		-	-	-	-	1	2	1	2	2	0	1	1	10	1	4	5
Herning		-	-	-	-	-	4	8	7	2	6	7	6	40	3	20	17
Aarhus		3	4	12	8	12	20	12	10	12	8	7	3	111	7	41	63
I alt		3	4	12	8	13	31	25	22	23	23	32	**23**	**219**	**12**	**78**	**129**
	SELV																
Sønderborg		-	-	-	-	-	4	3	2	2	1	3	2	17			
Vejle		-	-	-	-	-	-	-	1	1	0	0	0	2			
Aarhus		0	2	1	4	4	4	3	1	4	4	5	0	32			
I alt		0	2	1	4	4	8	6	4	7	5	8	**2**	**51**			

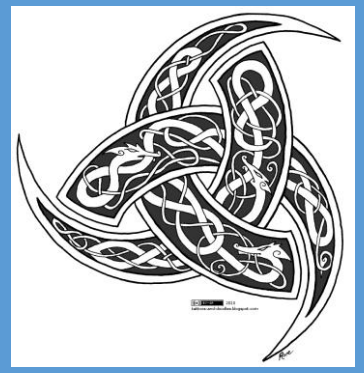
MASTER
D B C G

Nordic Trip Trial

- Sverige; 18 sites
- Danmark; Aalborg, Aarhus, Vejle (Esbjerg), Sønderborg, OUH, Næstved, RH (BOH), Herlev og Hillerød
- Finland; 1 site
- Island; 1 site

DANISH BREAST CANCER GROUP

NTT

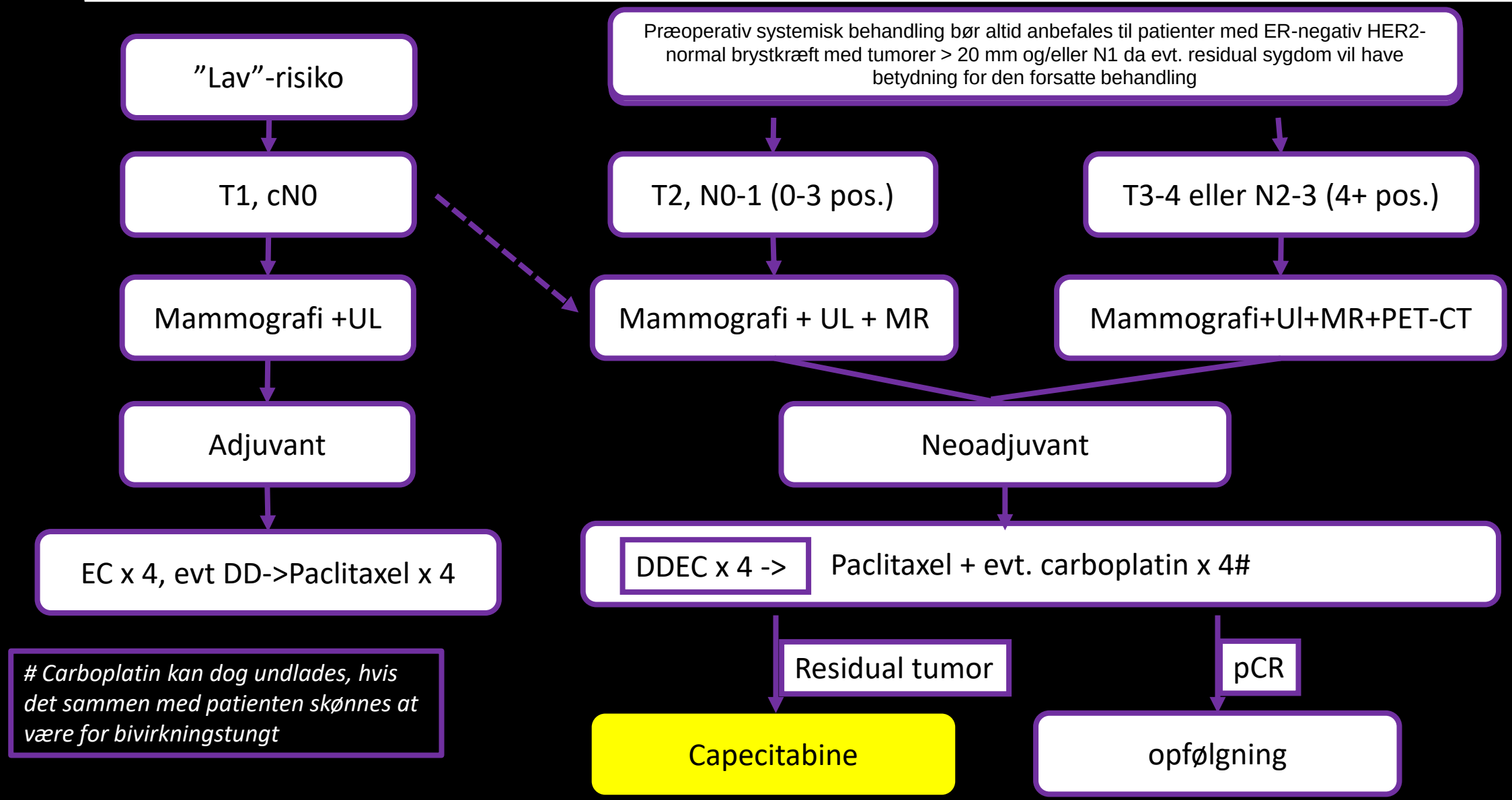


Nordic Trip/NBG-19-01, a translational randomized phase III study exploring the effect of the addition of capecitabine to carboplatinum based chemotherapy in early “triple negative” breast cancer.

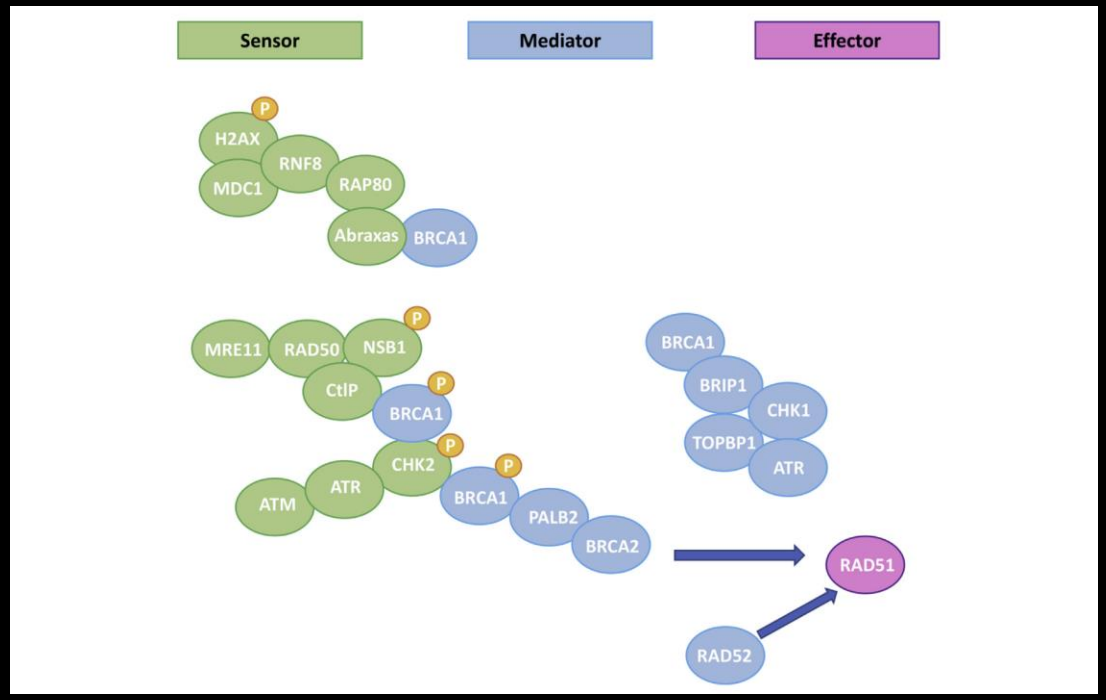
NACT til patienter med tripple-negativ brystkræft

- Heterogen gruppe, udgør 9-12% af brystkræfttilfælde
- Direkte korrelation mellem pCR og prognose:
  - Metaanalyse: Bedre event-free survival og OS, hvis CR på NACT
- Oftest ret kemo-sensitiv - pCR 30-40 % på standard antracycklin og taxan – ca. 60% med tillæg af carboplatin
- NACT er standardbehandling til patienter med tumorer større end 2 cm og/eller N+
- Og

Basal-like/ER÷,HER2÷



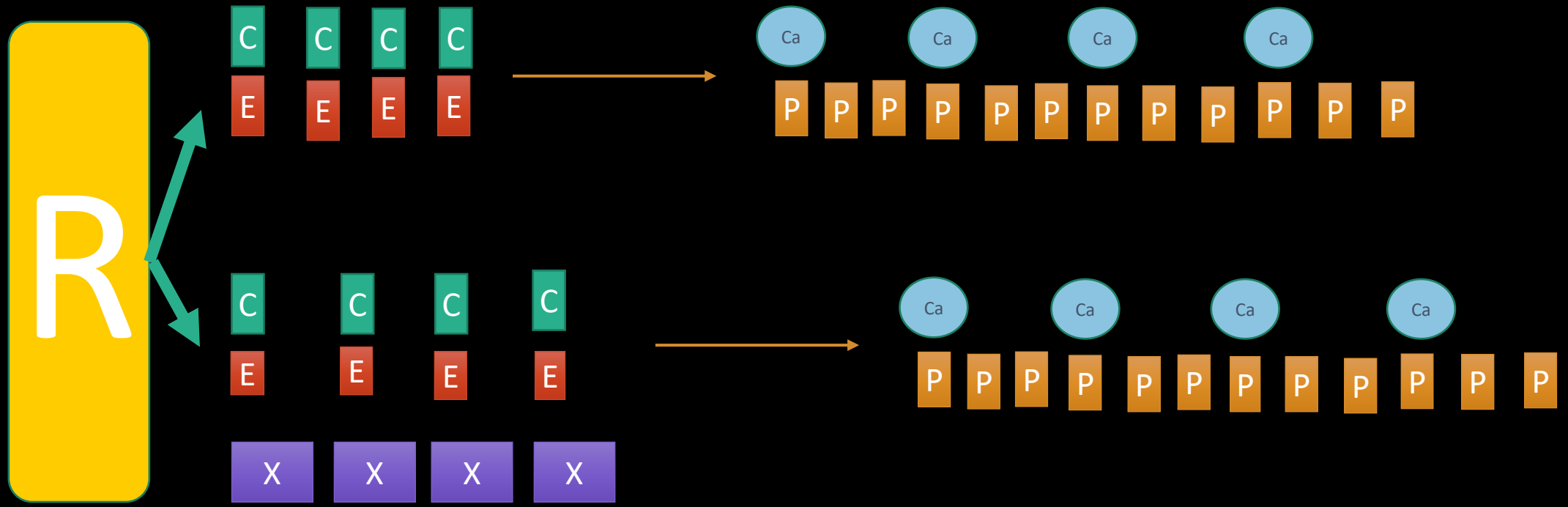
Homologous Repair Deficiency - HRD



Yderlige translationelle endpoints, bl.a.:
Sammenligne pCR-rate i 2 behandlingsarme i forskellige TNBC subtyper:
BRCA deficiency
Germline vs somatisk vs epigenetisk tab af BRCA funktion

- 50-75% har defekt DNA-repair.
- Har patienter med HRD bedre effekt af kemoterapi og bedre IDFS – mål for kemosensitivitet?
- Kan tillæg af capecitabine til carboplatin-baseret præoperativ kemoterapi øge pCR-raten?
  - IDFS (Invasive Disease Free Survival)
  - BCSS (Breast Cancer Specific Survival)
  - DRFS (Distant Recurrence Free Survival)
  - OS (overall Survival)

Design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Pragmatisk studie

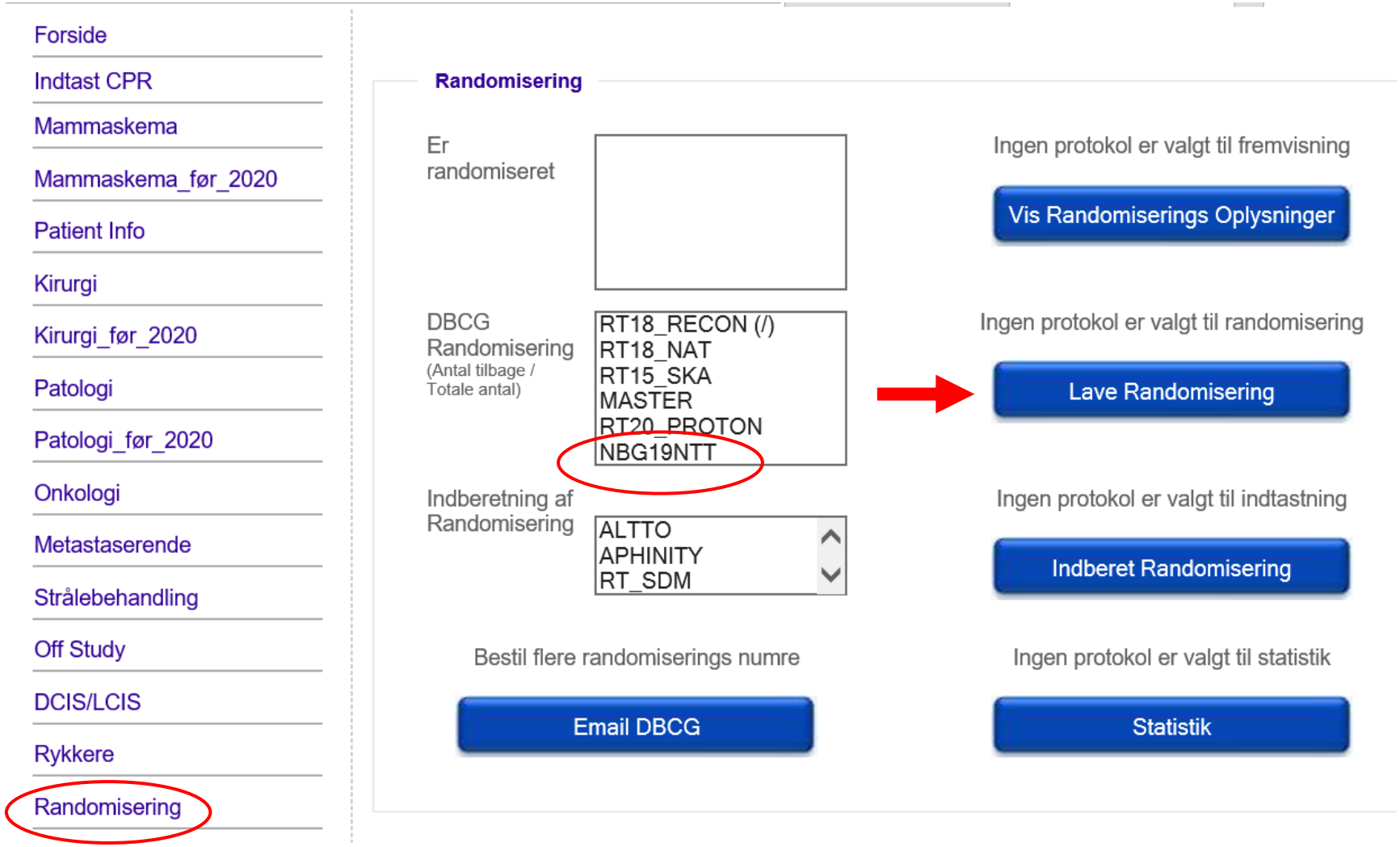
Udredning og behandling stort set ”som vi plejer”:

- Mammografi
- MR-Mammae før start, efter 2 serier og præoperativt
- PET-CT hvis node-pos
- Iodkorn mv iht alm praksis biopsi som vi plejer + biopsi til projekt
- Genetisk udredning
- Ct DNA - Genomisk Medicin på RH ansvarlig i DK

Randomisering

- Randomisering vil ske i forholdet 1:1 mellem de to behandlingsarme A og B, stratificeret for land, N-status and T-status.

DBCG-modul



The trip team

Bidrag fra DBCG

Randomisering & database
- Maj-Britt Jensen og Michael Jespersen
- DBCG er vært for databasen
- Kirurgi-, patologi-, og onkologidata overføres

Monitoring
- Ann Raaberg, DBCG

Vævsbiobank
- Anne-Vibeke Lænkholm
- Roskilde er forsøgets centrale patologiafd.

Genomisk Medicin på RH varetager
forsøgsblodprøver på danske patienter

Study team i Lund
- Niklas Loman, PI og sponsor
- Åke Borg, genomisk lab., Lund
- Heidi Grill Magnusson
- Lina Zander

Laboratoriet I Göteborg
- Barbro Linderholm
- ctDNA lab. i Göteborg

Patientantal og studieforløb

- Total 820 patienter hvoraf 250 fra Danmark
- **Per dec.21 – 81 patienter randomiseret – 6 fra RH**

- Første patient blev inkluderet januar 2020
- Rekruttering forventes komplet efter 3 år
- Forventet dato for sidste patient afsluttet (behandling): 30. juni 2023
- **Behandlingsvarighed:** 20-23 uger
- **Follow-up:** 10 år

CryoPac

Effects of Cryotherapy on Objective and Subjective Symptoms of Paclitaxel-Induced Neuropathy in Patients with Early Breast Cancer.

A Randomized Prospective Controlled Trial.

Der er nu aktiv inklusion på alle 4 sites

- Nationalt har vi inkluderet 142 patienter.

	NOH	RH	AUH	SØNDERBORG
Åbnede for inklusion	uge 2, 2021.	uge 2, 2021.	uge 19, 2021.	Uge 22, 2021.
Antal patienter inkluderet:	**32**	**67**	**41**	**2**

The incidence of CIPN with paclitaxel and docetaxel is dose dependent and occurs with higher cumulative dose and higher dose per cycle.
The incidence of taxane-associated chemotherapy-induced peripheral neuropathy ranges from **11% to 64% for docetaxel** and **57% to 83% for paclitaxel**, which in 2–33% is severe. A patient-reported outcome study found that **CIPN numbness persisted in 67%–80%** of patients for one year following the completion of paclitaxel therapy .

Der er ændringer på vej….

- Inklusionskriterierne udvides til at omfatte patienter planlagt til 3 og 4 serier paclitaxel, samt 6 serier Docetaxel-Cyclofosfamid.
- Target sample size udvides til 300 patienter.
- Der arbejdes på at udvide med Herlev som endnu et site.
- VEK-tillægsgodkendelse forventes til feb. 2022.

Maria Lendorf, afdelingslæge, PhD

4 TDX forsøg. Neoadjuverende + metastaserende

Destiny-05. Post-neoadjuvant trastuzumab deruxtecan (T-DXd) versus T-DM1 in patients with **residual invasive disease following neoadjuvant therapy**. Et randomiseret fase lll forsøg hos patienter med HER2 positiv brystkræft.

Destiny-06. A study of Trastuzumab Deruxtecan (T-DXd) vs Investigator's Choice Chemotherapy in **HER2-low, Hormone Receptor Positive**, Metastatic Breast Cancer.

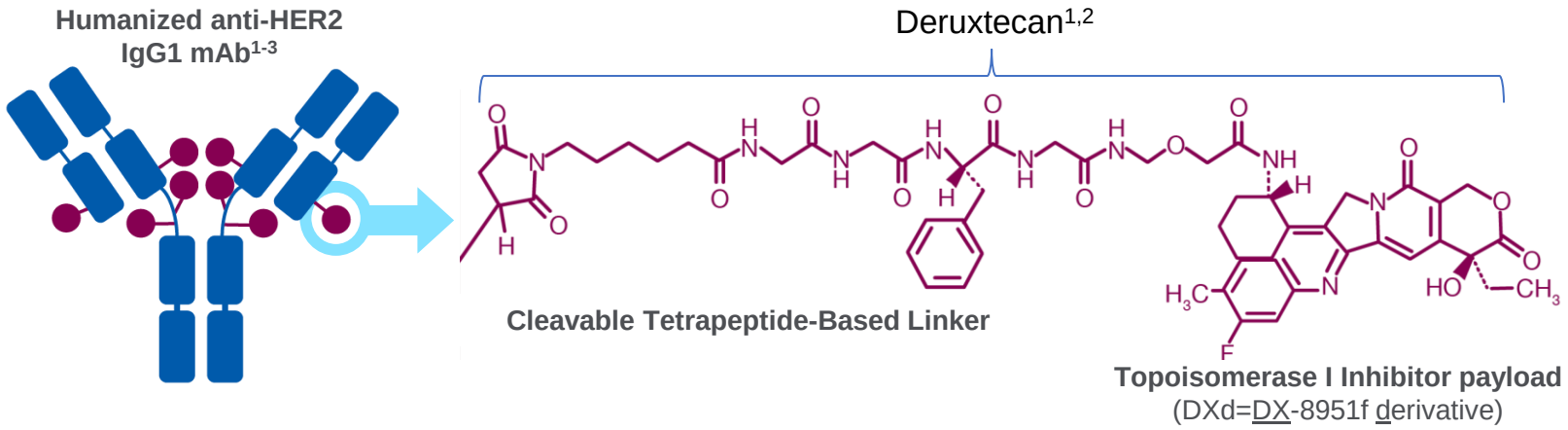
Destiny-09. Trastuzumab Deruxtecan (T-DXd) With or Without Pertuzumab Versus Taxane, Trastuzumab and Pertuzumab in HER2-positive Metastatic Breast Cancer.

Destiny-12. an open label phase **3b/4 multicenter**, multinational 2 cohort study for patients with or without brain metastasis in **pretreated HER2-positive metastatic breast cancer** who received no more than 2 lines/regimens of therapy in the metastatic setting (excluding tucatinib).

T-DXd Was Designed With 7 Key Attributes

T-DXd is an ADC composed of 3 components[1,2]:

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as **trastuzumab**, covalently linked to:
- A topoisomerase I inhibitor payload, an **exatecan** derivative, via
- A tetrapeptide-based cleavable **linker**

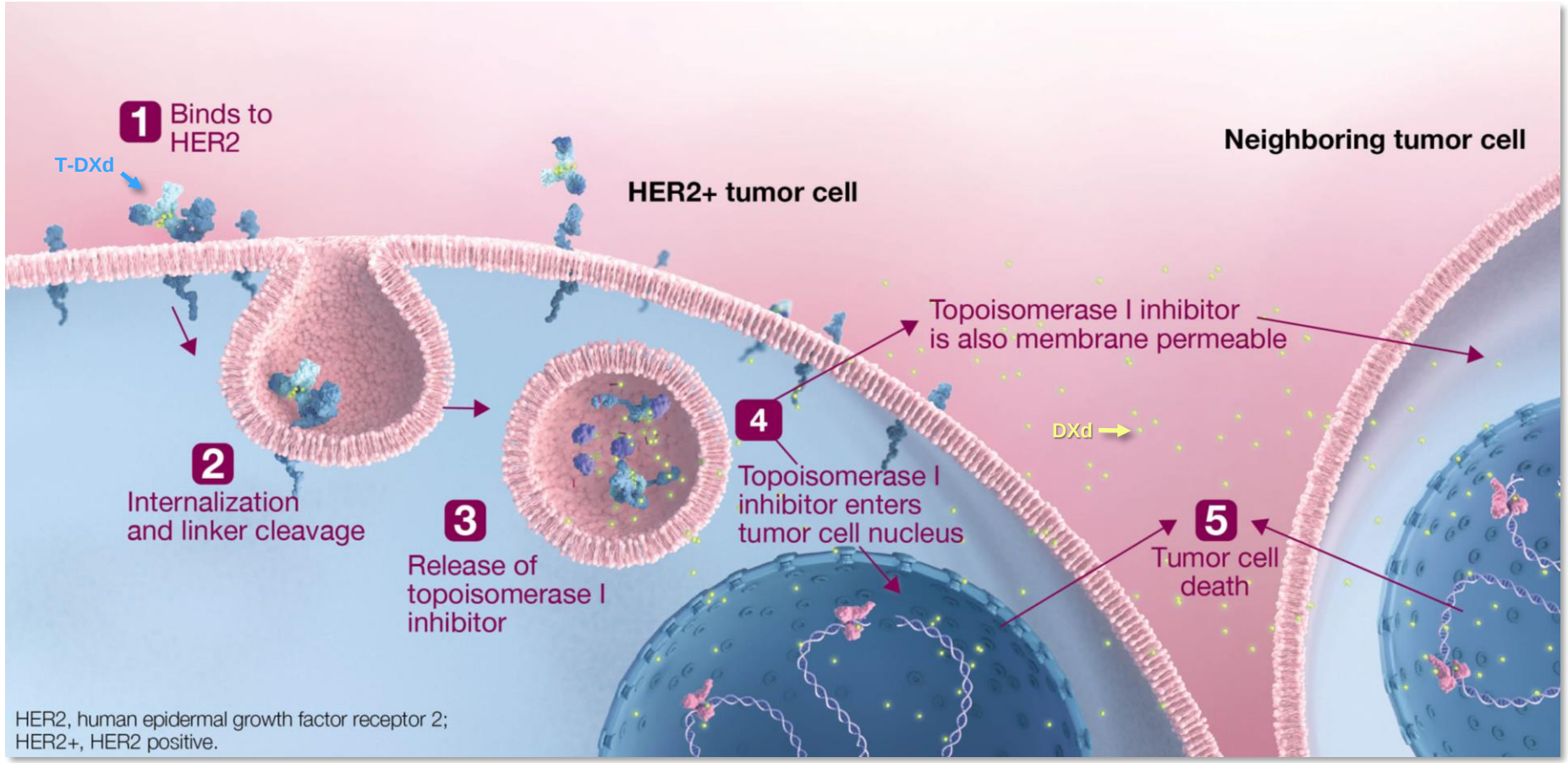


- Payload mechanism of action: topoisomerase I inhibitor [a,1,2]
- High potency of payload [a,1,2]
- High drug to antibody ratio ≈ 8 [a,1,2]
- Payload with short systemic half-life [a,1,2]
- Stable linker-payload [a,1,2]
- Tumor-selective cleavable linker [a,1,2,]
- Bystander antitumor effect [a,1,4]

[a]The clinical relevance of these features is under investigation.

1. Nakada T, et al. *Chem Pharm Bull (Tokyo).* 2019;67(3):173-185. **2.** Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. **3.** Trail PA, et al. *Pharmacol Ther.* 2018;181:126-142. **4.** Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

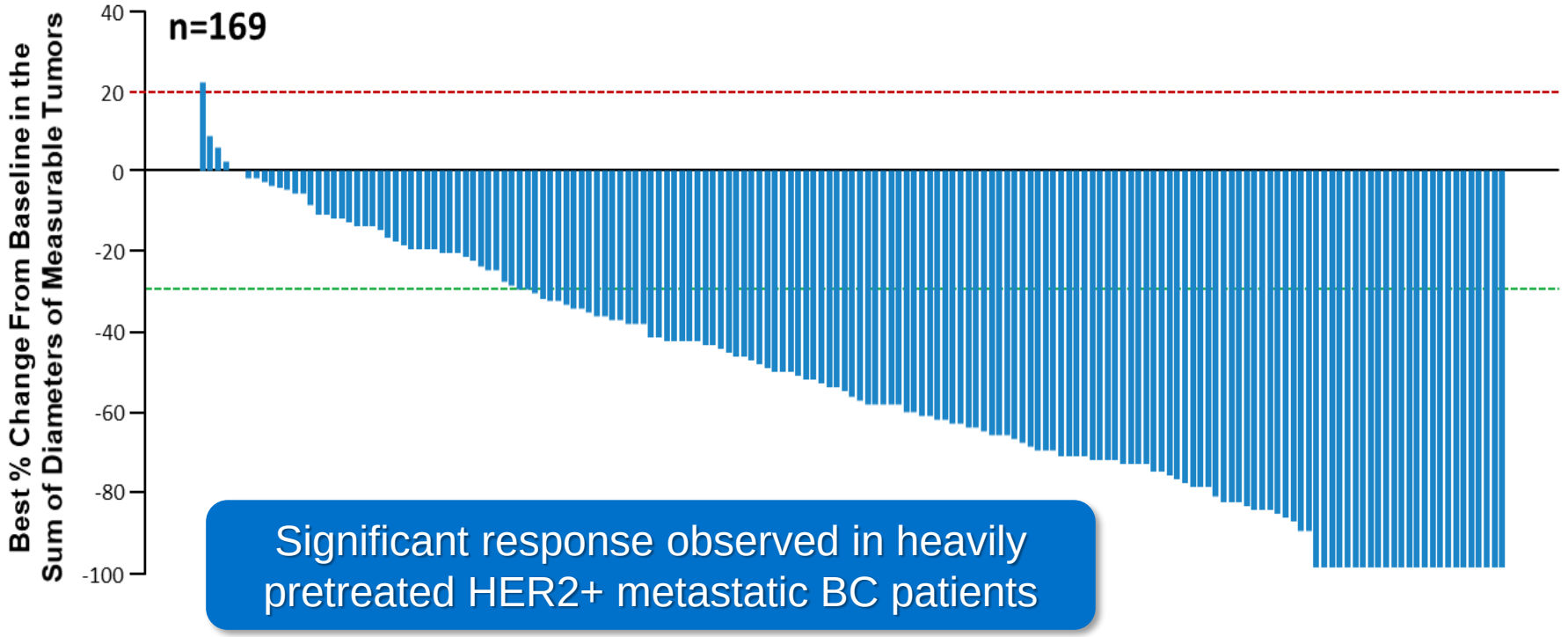
Trastuzumab deruxtecan (T-DXd) allows for efficient delivery and release of the topoisomerase I inhibitor payload at the tumor site[1-4]



1. The mAb component of T-DXd selectively binds to HER2 expressed on the tumor cell surface
2. T-DXd is internalized by the cell and intracellular lysosomal enzymes upregulated in tumor cells cleave the peptide linker
3. The topoisomerase I inhibitor payload is released into the cytoplasm of the cell
4. The released payload enters the cell nucleus and causes damage to the tumor cell's DNA. The payload also has high-cell membrane permeability that enables elimination of both target tumor cells and the surrounding tumor cells
5. Damage to tumor cell DNA results in tumor cell death

1. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108.
2. Ogitani Y, et al. *Cancer Sci.* 2016;107:1039-1046.
3. Supplement to: Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.
4. Nakada T, et al. *Chem Pharm Bull (Tokyo).* 2019;67(3):173-185.

Results from DESTINY-Breast01: T-DXd in HER2+ metastatic BC patients previously treated with T-DM1 in the advanced/metastatic setting[1]



Significant response observed in heavily pretreated HER2+ metastatic BC patients

Median # of prior cancer regimens (range): 6 (2-27)
% previously treated with trastuzumab and T-DM1: 100

EFFICACY

- **Confirmed[2] ORR: 61.4%[a]** (95% CI, 54.0%-68.5%); 12 CRs
- **DCR: 97.3%** (95% CI, 93.8%-99.1%)
- **Median DOR: 20.9 months** (95% CI, 13.8-16.9)
- **Median PFS: 19.4 months** (95% CI, 14.1-NE)
- **Median OS: 24.6 months** (95% CI, 23.1-NE)

Data Cutoff: 8-Jun-2020

1. Modi S, et al. SABCS 2020; 2. By independent central review.

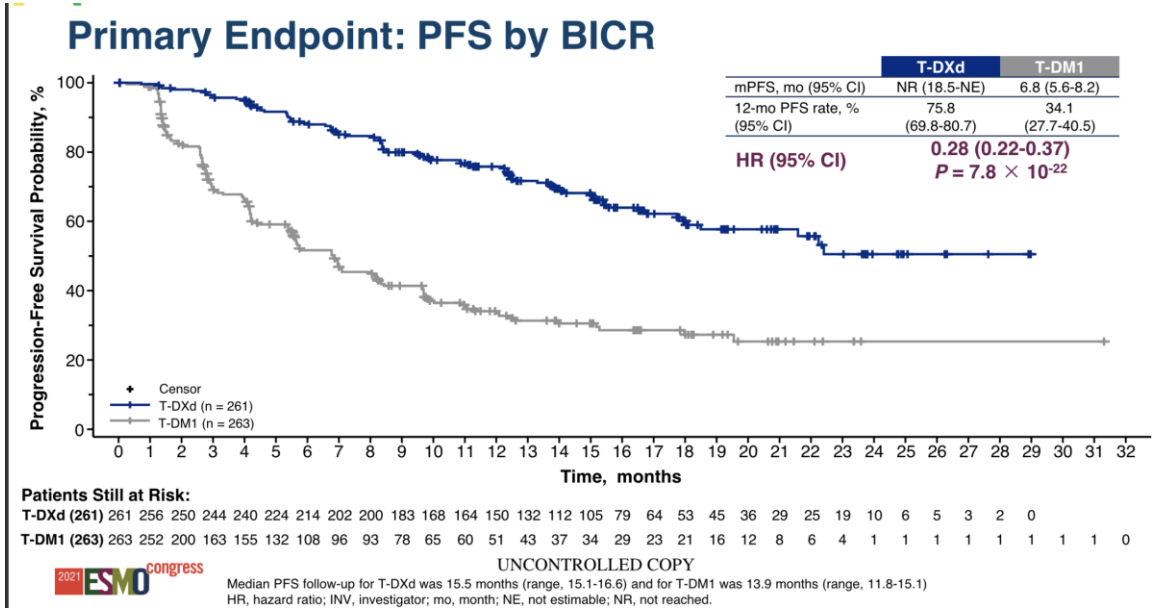
The line at 20% indicates progressive disease; the line at −30% indicates partial response.

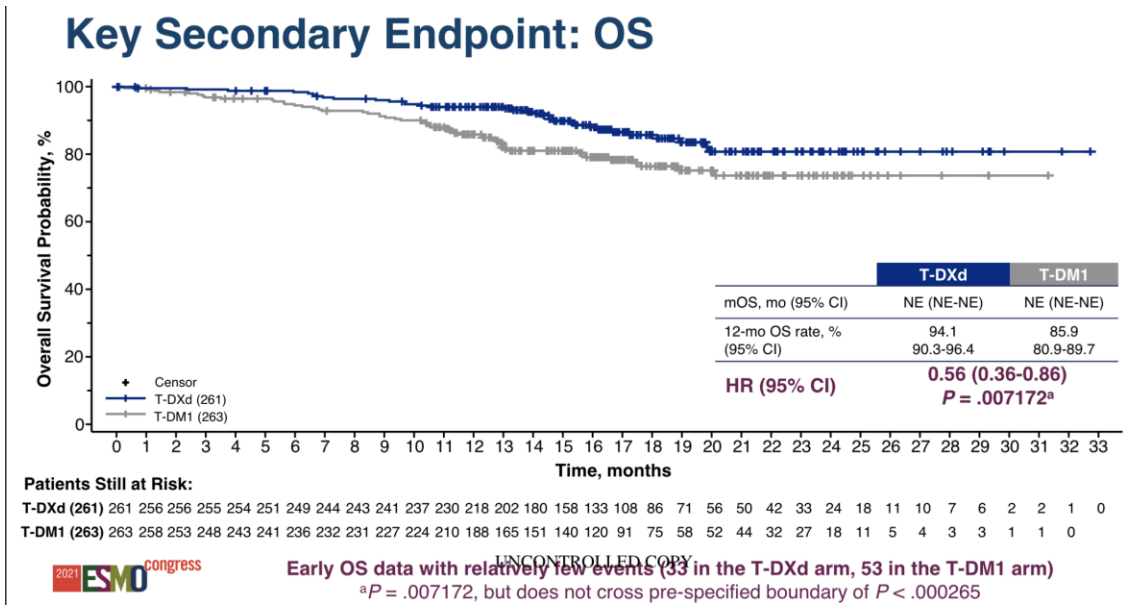
a Includes all patients who received T-DXd 5.4 mg/kg (intent-to-treat analysis; N=184). One subject had a PR prior to the 08 Jun 2020 cutoff date which was confirmed after the cut-off date. The subject had a confirmed BOR of PR on the first PR date in the central data but was not included in the analysis of DoR.

BC=breast cancer; CR=complete response; DCR=disease control rate (CR + PR + SD); ORR=objective response rate (CR + PR); NE=not evaluable; PR=partial response; SD=stable disease.

Dansk RWS ESMO 21: Median PFS was 5.5 months (95% CI, 4.8-6.5) and median OS was 18.5 months (95% CI, 16.2-21.3)

TDM1 vs. TDX. 2 linje HER2+ brystkræft





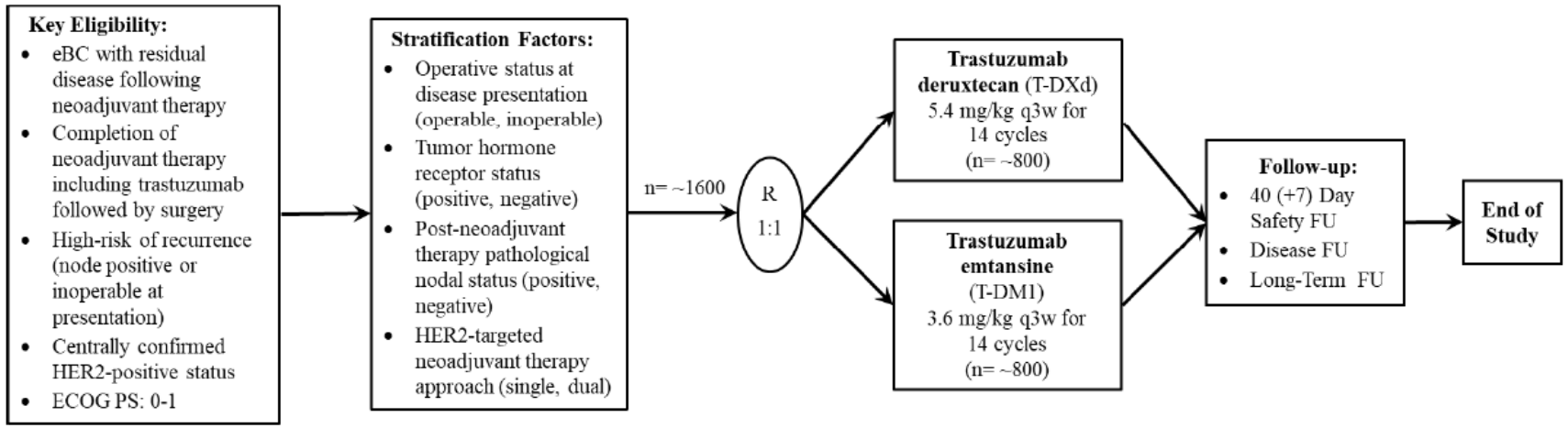
Så på et center nær jer

Et eller flere af forsøgene – pt kan henvises.

Destiny-05 – post neoadjuverende

1.2. Study Schema

Figure 1.1: Study Level Flow Diagram



eBC=early breast cancer (defined as Stages T1–4, N0–3, M0); ECOG PS=Eastern Cooperative Oncology Group performance status; FU=Follow-up; HER2=Human epidermal growth factor receptor 2; R=randomization; q3w=every 3 weeks; T-DXd=trastuzumab deruxtecan (investigational agent); T-DM1=trastuzumab emtansine (control)
Operative status at presentation (prior to neoadjuvant therapy): Operable = clinical stages T1-3,N0-1,M0; Inoperable = clinical stages T4,N0-3,M0 or T1-3,N2-3,M0

Destiny-06 – HER2low

POPULATION

- Advanced/metastatic HR+ breast cancer
- HER2 IHC >0 or 1+ or 2+ (determined based on central IHC assessment of archival tissue collected at time of diagnosis of first metastatic disease or later)

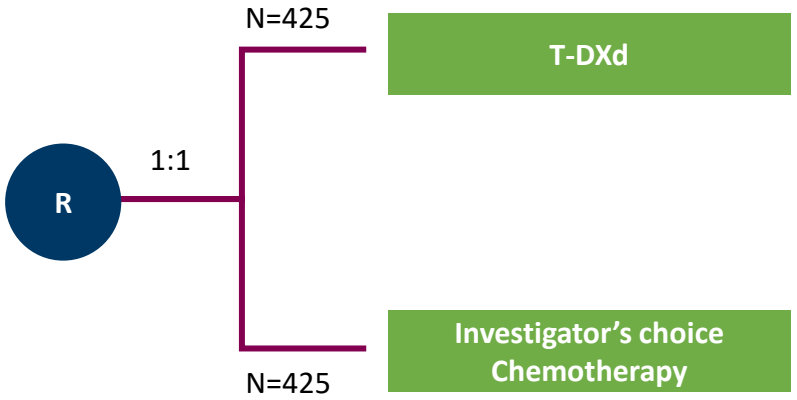
Prior lines of therapy in MBC:

Progression after 2 prior ET+/- targeted therapy, **or** within 6 months of 1st line ET+CDK4/6i

Stratification factors:

- Prior CDK4/6 inhibitor
- HER2 IHC 2+ v. 1+ v. >0<1+
- Prior taxane in non-metastatic setting

TREATMENT



- Chemotherapy options: capecitabine, paclitaxel, nAb-paclitaxel
- Treatment continues until progressive disease or toxicity
- HER2 IHC>0<1+ defined by any IHC staining up to 10% of tumor cells
- Futility analysis in HER2 IHC >0<1+ cohort will be done

ENDPOINTS

Primary:

- PFS (BICR) in HER2-low population

Key Secondary:

- OS in HER2-low population
- PFS in ITT population
- OS in ITT population

Secondary:

- PFS (investigator assessed) in HER2-low population
- ORR and DOR of HER2-low and ITT populations
- Safety and tolerability
- Symptoms, functioning and HRQoL

Exploratory:

- Protein Expression
- ctDNA
- Patient Reported Outcomes

Figure 1 Study Design

Destiny-Breast 09

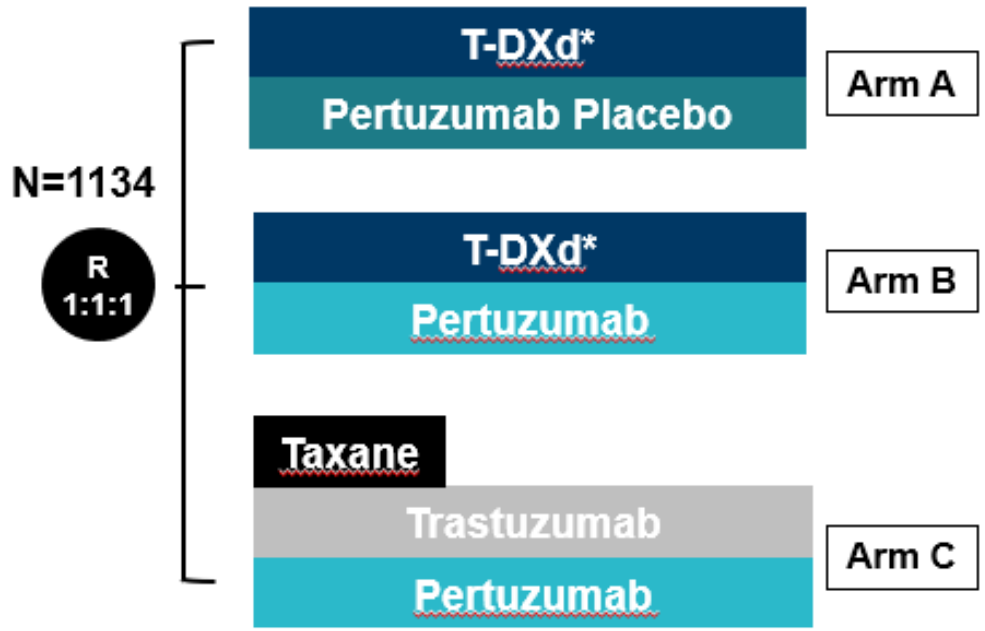
POPULATION

- HER2-positive mBC
- DFI >6 months from last chemotherapy or HER2-targeted therapy in neoadjuvant/adjuvant setting
- No prior systemic treatment for mBC except for endocrine therapy

Stratification factors:

- *De novo* vs recurrent (cap at 50% *de novo*)
- HR-positive vs negative
- *PIK3CA*m (detected vs not detected)

STUDY DESIGN



- *Participants can continue with trastuzumab if T-DXd is discontinued due to toxicity.
- Use of endocrine therapy is allowed for HR-positive participants after discontinuation of taxane or after 6 cycles of T-DXd.
- Taxane can be paclitaxel or docetaxel.
- Pertuzumab-blinded in the T-DXd arms.

ENDPOINTS

Primary:

- PFS (BICR)

Secondary:

- OS
- PFS (Inv. assessed)
- ORR, DoR
- PFS2
- PRO/HRQoL
- PK/ADA
- Safety and tolerability

Exploratory:

- TTF, TFST, TSST
- BMFS, CNS-PFS
- Patient-reported tolerability
- Exploratory biomarkers

Figure 1 Study Design

Destiny-Breast 12