Post-ASCO 2018
Brystkreft

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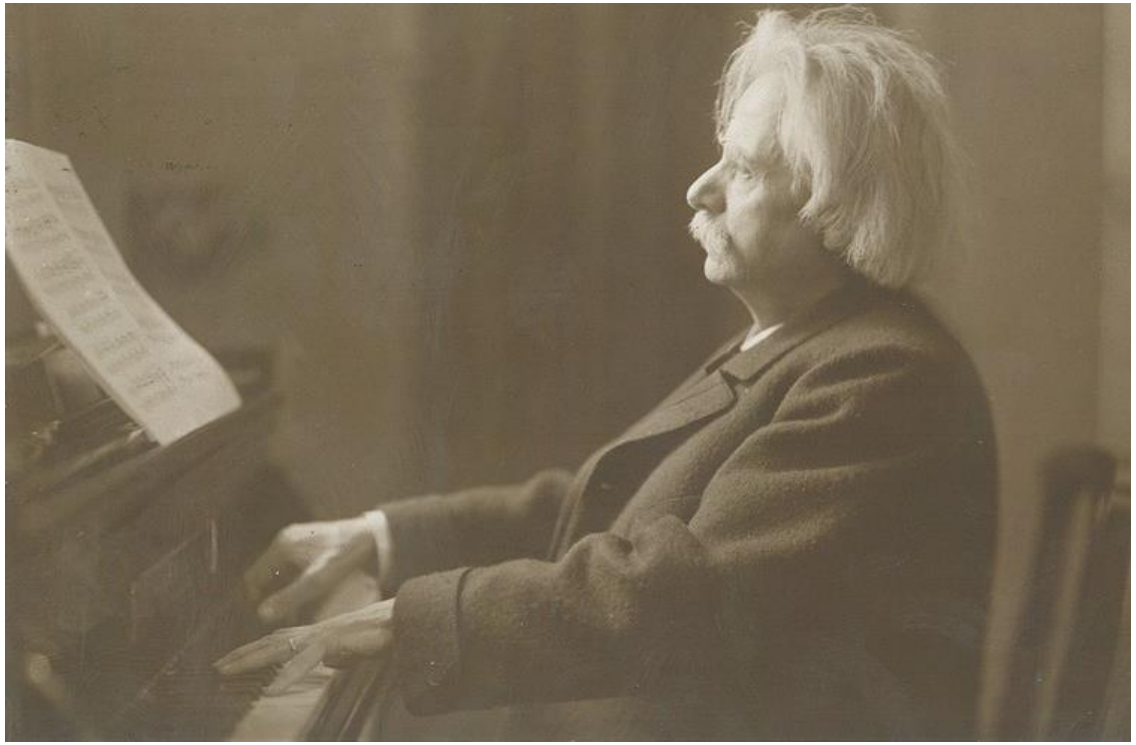
1. amanuensis, Klinisk inst. 2, UIB
K.G. Jebsen senter for genom-rettet kreftterapi

175 årsdagen til Edvard Grieg

- ”Lukten på Tyskebryggen likefrem begeistrer meg. Ja, jeg tror sant for dyden at det er både torsk og pale i min musikk!”

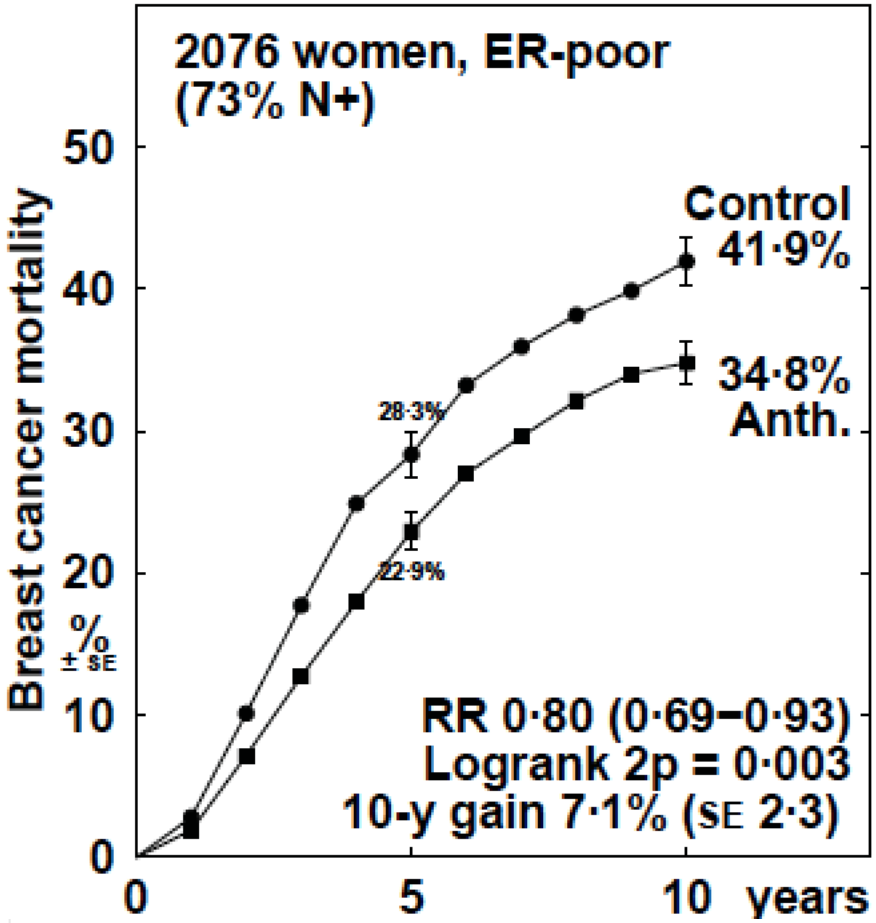


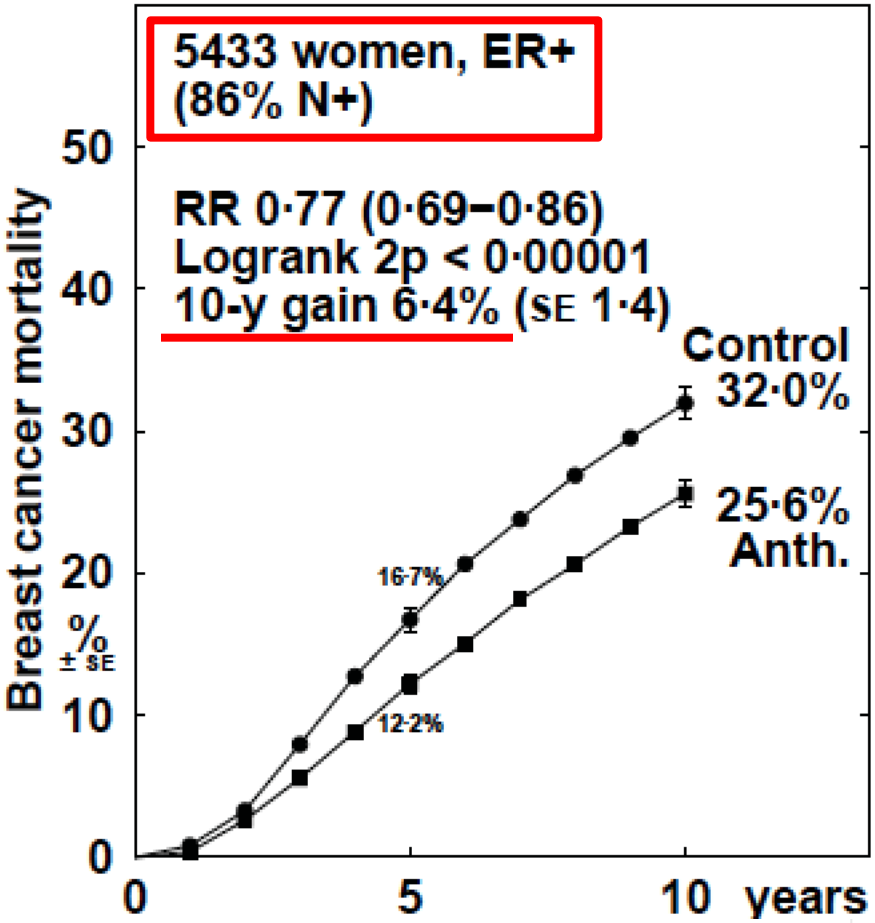
Sentrale tema ASCO 2018: Brystkreft

- persontilpasset behandling
  - genpanel for å styre adjuvant behandling
- de-eskalering av adjuvant behandling
  - utelate cellegift, kun endokrin behandling
  - PARP hemmer i stedet for cellegift neoadjuvant
- CDK4/6 hemmer sammen med fulvestrant 1. linje
  - MONALEESA-3
- immunterapi
  - forsiktig optimisme

TAILORx STUDIEN
- GENTEST FOR Å UNNGÅ CELLEGIFT

Gevinst av cellegift ved høyrisk, HR+ brystkreft





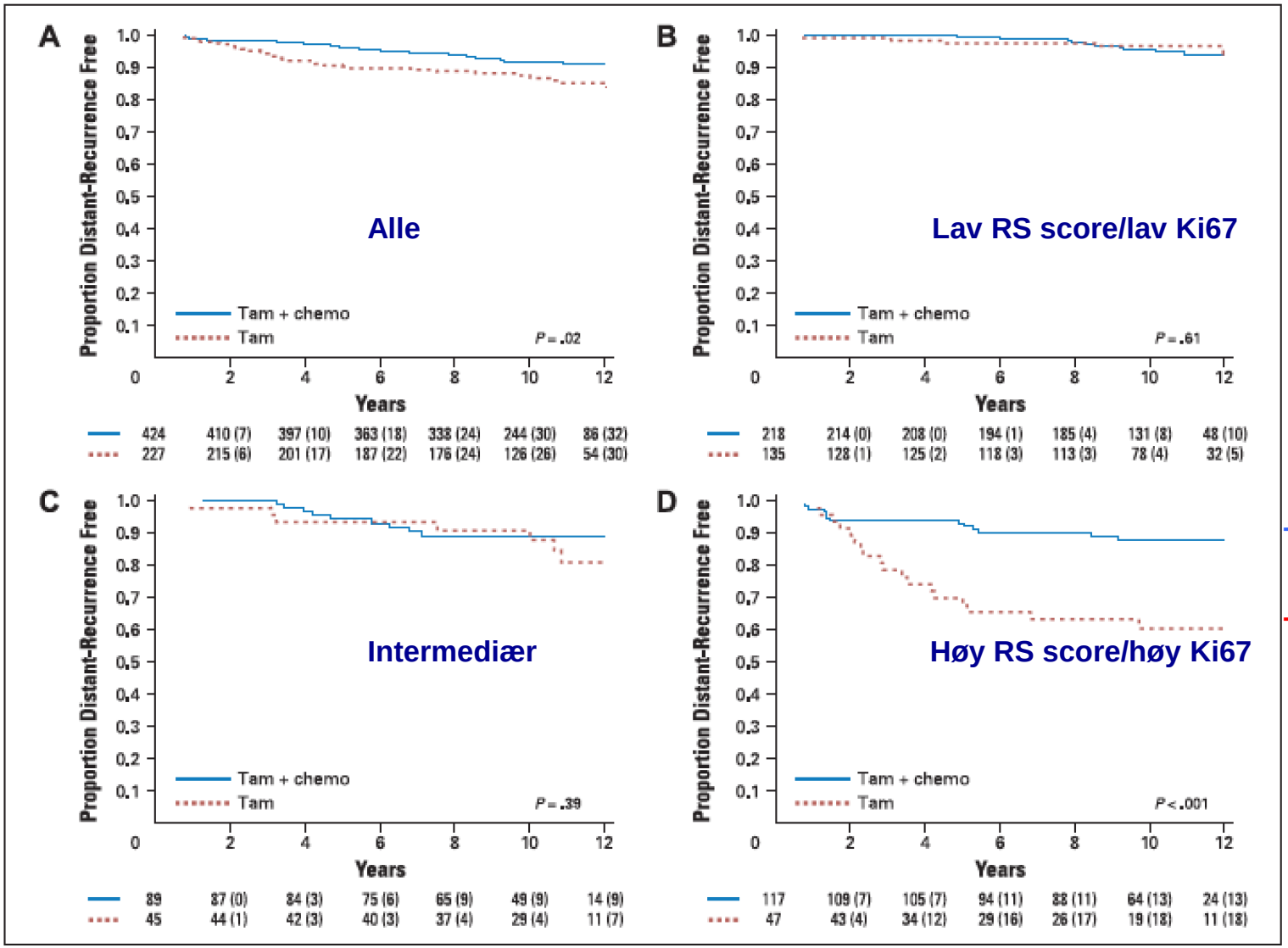
EBCTCG, Lancet, 2012

Anthracyklin-basert cellegift vs. ingen cellegift

HR+ brystkreft er ikke én sykdom

Tamoxifen +/- CMF cellegift ved HR+ brystkreft (N-) – NSABP B20 studien

- overlevelsesgevinst av kjemoterapi kun ved høy celledeling



Tamoxifen + cellegift

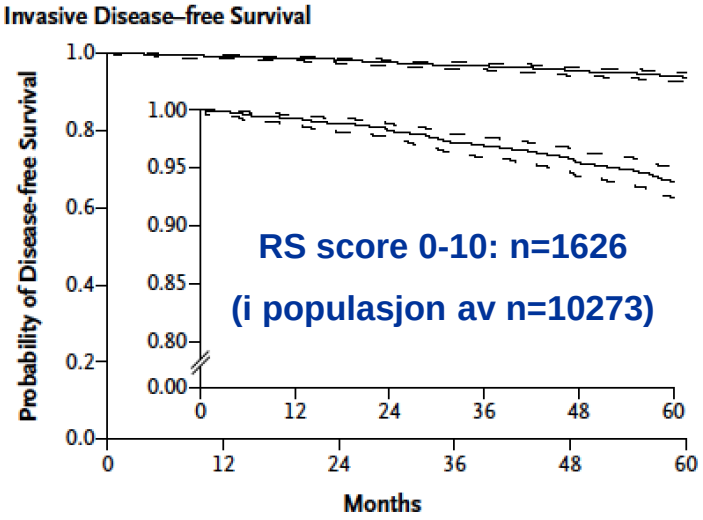
Tamoxifen

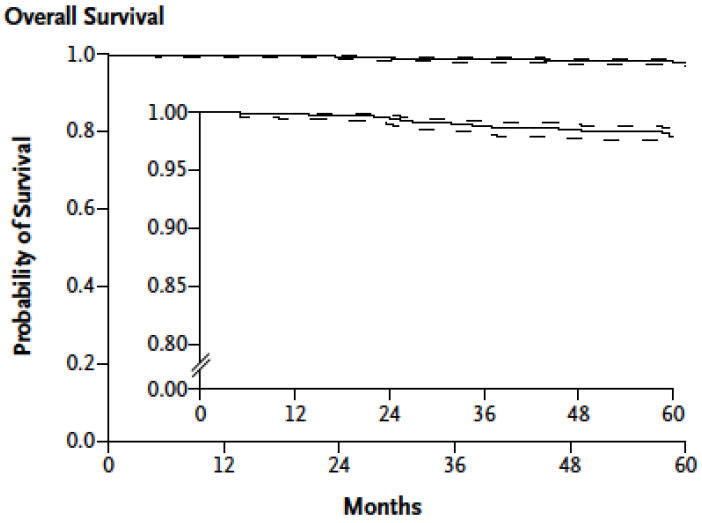
Paik, JCO, 2006

TAILORx

- mål:
  - teste om Oncotype Dx genekspresjonsarray kan brukes prospektivt til å identifisere dem som ikke trenger adjuvant cellegift
- HR+, HER2-, T: 1,1 - 5 cm eller T≤1 cm & grad 2-3, N-
  - *"klinisk-patologisk risikovurdering tilsier cellegift"*

TAILORx:
Utelate kjemoterapi v/HR+ brystkreft og lav genomisk risk





TAILORx studien

Sparano, NEJM, 2015

TAILORx; update ASCO 2018 Sparano et al.

- 10273 pasienter inkludert
  - 1626 m/recurrence (RS) score 0-10 (lav risiko)
    - 5 års follow-up (Sparano, NEJM, 2015)
    - RFS: 99% og OS: 98%
  - 6711 m/RS score 11-25 (intermediær risiko)
  - 1730 m/RS score >25 (høy risiko)

80% av pasientene

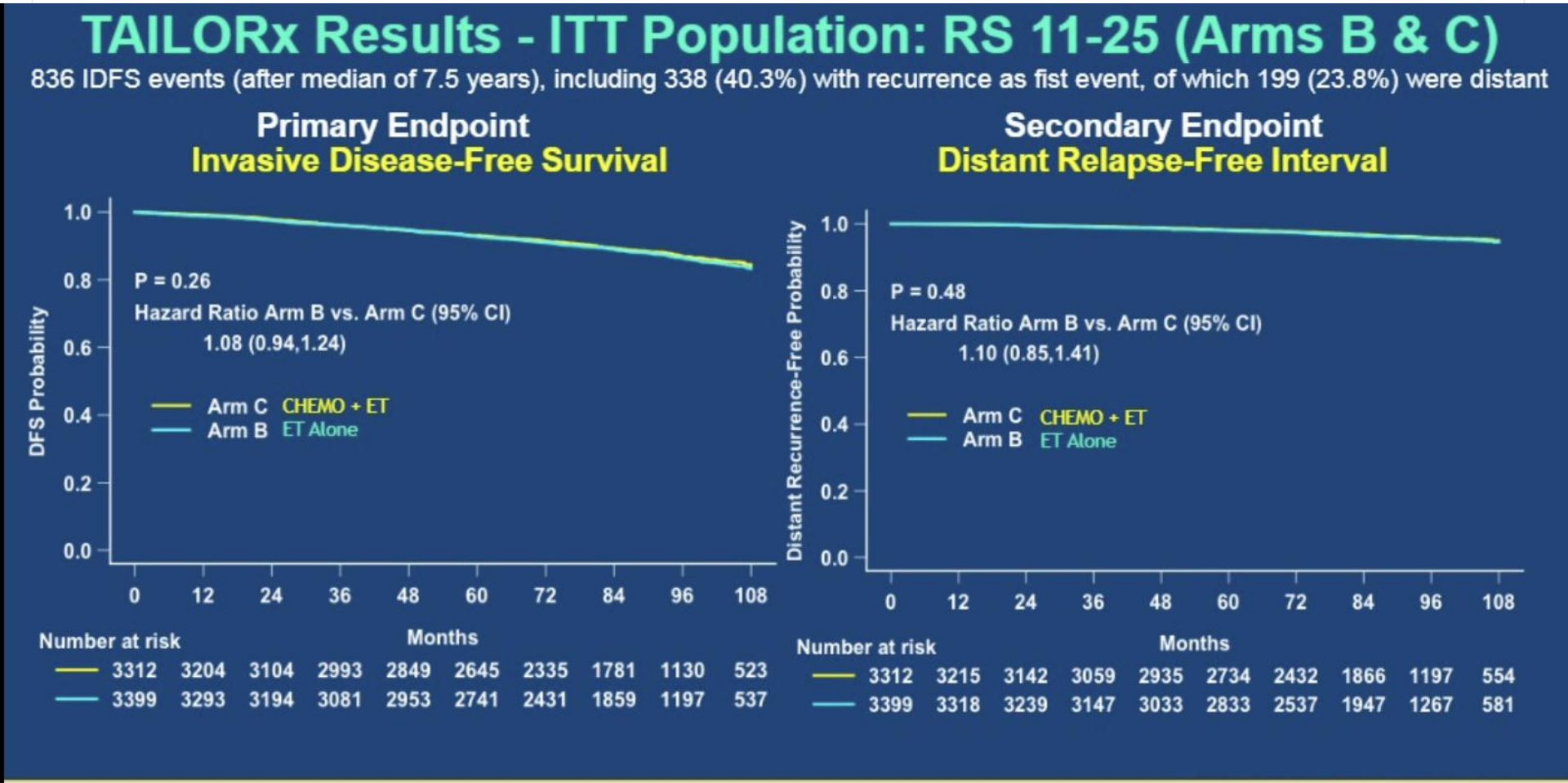
ORIGINAL ARTICLE

Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer

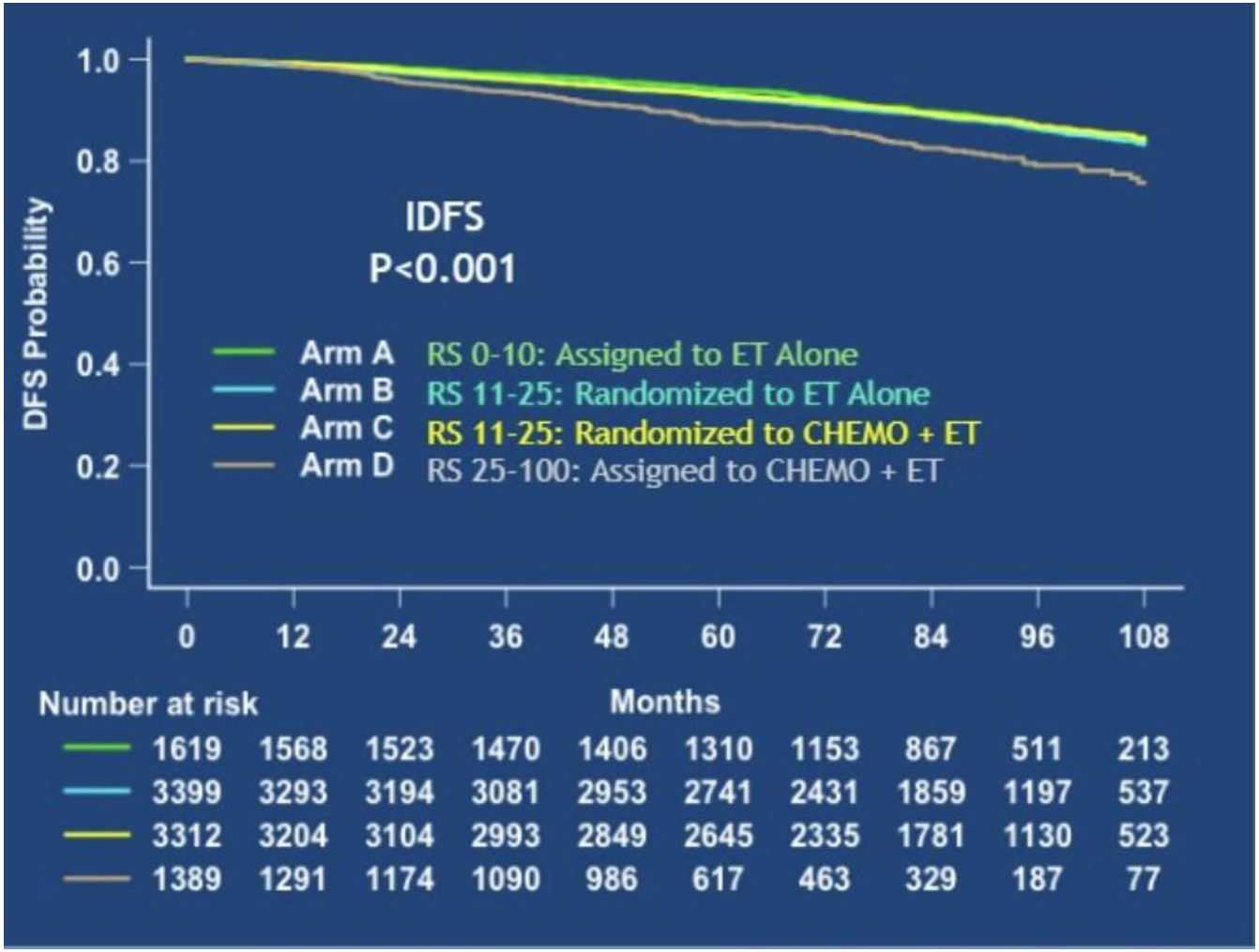
J.A. Sparano, R.J. Gray, D.F. Makower, K.I. Pritchard, K.S. Albain, D.F. Hayes, C.E. Geyer, Jr., E.C. Dees, M.P. Goetz, J.A. Olson, Jr., T. Lively, S.S. Badve, T.J. Saphner, L.I. Wagner, T.J. Whelan, M.J. Ellis, S. Paik, W.C. Wood, P.M. Ravdin, M.M. Keane, H.L. Gomez Moreno, P.S. Reddy, T.F. Goggins, I.A. Mayer, A.M. Brufsky, D.L. Toppmeyer, V.G. Kaklamani, J.L. Berenberg, J. Abrams, and G.W. Sledge, Jr.*

NEJM, 4/6-18

TAILORx:
Ingen gevinst av kjemoterapi v/HR+ brystkreft og intermediær genomisk risk



TAILORx: alle risikogrupper



TAILORx: subgruppeanalyser (exploratory)

- **Other observations**
  - **Age – RS – Chemo treatment interaction:**
    - Some chemo benefit in women 50 or younger with a RS 15-25
    - Greatest impact on distant recurrence with RS 21-25

Oversikt NBCGs retningslinjer for adjuvant systemisk behandling. *Gjelder fra 01.02.18.*

Hoved-gruppe	Subgruppering ved undersøkelser av tumor	Ytterligere subgruppering	Generell terapi-anbefaling	Grunnlag for annet terapi-valg
HR+ HER2-	**Lum A-liknende*** ***Følgende karakteristika: Lav proliferasjon, G1-2, HR>50%, og HER2-**	**pT1a-b pN0**	Ingen behandling	
		pT1c pN0 grad 1	Ingen behandling	
		pT1c grad 2 pN0 **pT2pN0** **pT1-2pN1**	Endokrin behandling Zoledronsyre ved postmenopausal status	Tumorstørrelse og omfang av lymfeknutemetastaser kan gi grunnlag for kjemoterapi (EC90 x 4)
		pN2-3	EC90 x 4 etterfulgt av endokrin behandling Zoledronsyre ved postmenopausal status	Spesielt omfattende lymfeknutemetastasering sykdom kan gi grunnlag for å gi EC90 x 4 → taxan
	LumB-liknende* ***Følgende karakteristika: høy proliferasjon og G2-3** **eller** **HR<50%**	**pT1a-b pN0**	Endokrin behandling Zoledronsyre ved postmenopausal status	Lav HR positivitet eller høyere proliferasjongrad kan gi grunnlag for kjemoterapi (EC90 x 4) Individuell vurdering av grunnlag for systembehandling kan gjøres ved små pT1apN0 tumores
		pT1c-pT2 pN0 **pT1-2pN1-3**	EC90 x 4 etterfulgt av endokrin behandling Zoledronsyre ved postmenopausal status	Høyere proliferasjongrad og/eller mange lymfeknutemetastaser kan gi grunnlag for å gi EC90 x 4 → taxan
HR+ HER2+		**pT1pN0**	Taxan/trastuzumab etterfulgt av trastuzumab og endokrin behandling Zoledronsyre ved postmenopausal status	Individuell vurdering av grunnlag for systembehandling kan gjøres ved små pT1apN0 tumores Spesielt høy risikoprofil kan gi grunnlag for EC90 x 4 → taxan/trastuzumab
		Alle andre	EC90 x 4 → taxan/trastuzumab etterfulgt av trastuzumab og endokrin behandling Zoledronsyre ved postmenopausal status	
HR- HER2+		**pT1pN0**	Taxan/trastuzumab etterfulgt av trastuzumab Zoledronsyre ved postmenopausal status	Individuell vurdering av grunnlag for systembehandling kan gjøres ved små pT1apN0 tumores Spesielt høy risikoprofil kan gi grunnlag for EC90 x 4 → taxan/trastuzumab
		Alle andre	EC90 x 4 → taxan/trastuzumab etterfulgt av trastuzumab Zoledronsyre ved postmenopausal status	
HR- HER2-			EC90 x 4 → taxan Zoledronsyre ved postmenopausal status	Lav proliferasjongrad og histologisk grad kan gi grunnlag for å utelate taxaner Individuell vurdering av grunnlag for systembehandling kan gjøres ved små pT1apN0 tumores

Konsekvenser av TAILORx i Norge

- Oncotype Dx identifiserer pasienter med HR+, HER2-, N- brystkreft uten nytte av cellegift (80%)
- 40000 kr + forsendelse til USA (ingen takst i Norge)
- Oncotype Dx vs. Mammaprint vs. PAM50?
- hvor mange spares for cellegift i Norge?
  - 1200 brystkreftopererte aktuell for slik analyse per år?
    - HR+, HER2-, N-, grad 2/3 : ca. 1200 av 3300 pasienter (36%)...*
  - 80% av 1200 = 960 kvinner/menn
    - men mange av disse får ikke cellegift i Norge i dag (basert på klinisk-patologisk profil)

***NBCR data (inkomplette):**

85% HR+, 85% HER2-, 75% N-, 85% grad 2-3

30% av alle brystkreftopererte mottar cellegift i dag

ASCO 2018; Oppdatert analyse TEXT/SOFT, Regan et al.

Absolute Improvements in Freedom from Distant Recurrence with Adjuvant Endocrine Therapies for Premenopausal Women with HR+ HER2-negative Breast Cancer: Results from TEXT and SOFT

Meredith M. Regan, Prudence A. Francis, Olivia Pagani, Gini F. Fleming, Barbara A. Walley, Giuseppe Viale, Marco Colleoni, István Láng, Henry L. Gómez, Carlo Tondini, Graziella Pinotti, Angelo Di Leo, Alan S. Coates, Aron Goldhirsch, Richard D. Gelber, for the SOFT and TEXT Investigators and International Breast Cancer Study Group

2018 ASCO ANNUAL MEETING
#ASCO18

IBCSG
INTERNATIONAL BREAST CANCER STUDY GROUP
Presented By Meredith Regan

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tailoring Adjuvant Endocrine Therapy for Premenopausal Breast Cancer

P.A. Francis, O. Pagani, G.F. Fleming, B.A. Walley, M. Colleoni, I. Láng, H.L. Gómez, C. Tondini, E. Ciruelos, H.J. Burstein, H.R. Bonnefoi, M. Bellet, S. Martino, C.E. Geyer, Jr., M.P. Goetz, V. Stearns, G. Pinotti, F. Puglisi, S. Spazzapan, M.A. Climent, L. Pavesi, T. Ruhstaller, N.E. Davidson, R. Coleman, M. Debled, S. Buchholz, J.N. Ingle, E.P. Winer, R. Maibach, M. Rabaglio-Poretti, B. Ruepp, A. Di Leo, A.S. Coates, R.D. Gelber, A. Goldhirsch, and M.M. Regan, for the SOFT and TEXT Investigators and the International Breast Cancer Study Group*

Francis et al, NEJM, 4/6-18

SOFT and TEXT Designs

Enrolled: Nov03 - Apr11

- Premenopausal HR+
- ≤12 wks after surgery
- Planned OFS
- No planned chemo (40%)
  OR planned chemo (60%)

RANDOMIZE

TEXT (n=2672)

→ **Tamoxifen+OFS x 5y**

→ **Exemestane+OFS x 5y**

Current Follow-up

Median follow-up 9 years

- Premenopausal HR+
- ≤12 wks after surgery
- No chemo (47%)

OR

- Remain premenopausal ≤ 8 mos after chemo (53%)

RANDOMIZE

SOFT (n=3066)

→ **Tamoxifen x 5y**

→ **Tamoxifen+OFS x 5y**

→ **Exemestane+OFS x 5y**

Median follow-up 8 years

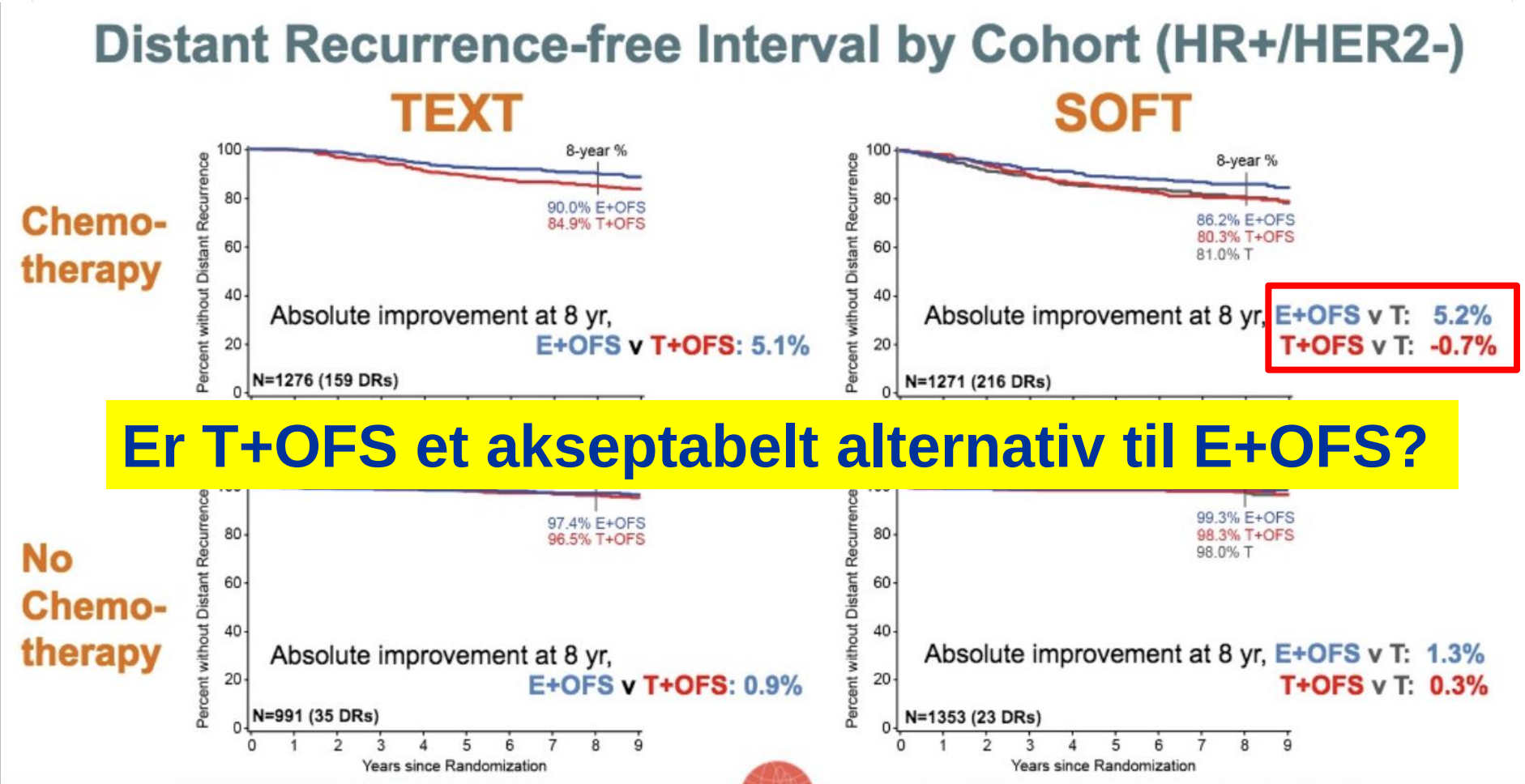
OFS=ovarian function suppression

Characteristics by Cohort (HR+/HER2-)

		TEXT		SOFT	
Chemo-therapy	N=1276	Age<40	30%	N=1271	Age<40	49%
		LN+	69%		LN+	58%
		T-size>2cm	52%		T-size>2cm	46%
		PgR<50%	23%		PgR<50%	38%
		Grade 3	30%		Grade 3	28%
		Ki-67≥20%	42%		Ki-67≥20%	35%
No Chemo-therapy	N=991	Age<40	16%	N=1353	Age<40	9%
		LN+	21%		LN+	9%
		T-size>2cm	20%		T-size>2cm	13%
		PgR<50%	13%		PgR<50%	9%
		Grade 3	15%		Grade 3	9%
		Ki-67≥20%	27%		Ki-67≥20%	19%

ASCO 2018: 8 års observasjonstid TEXT/SOFT

- T-OS like mange fjernrecidiv som T alene

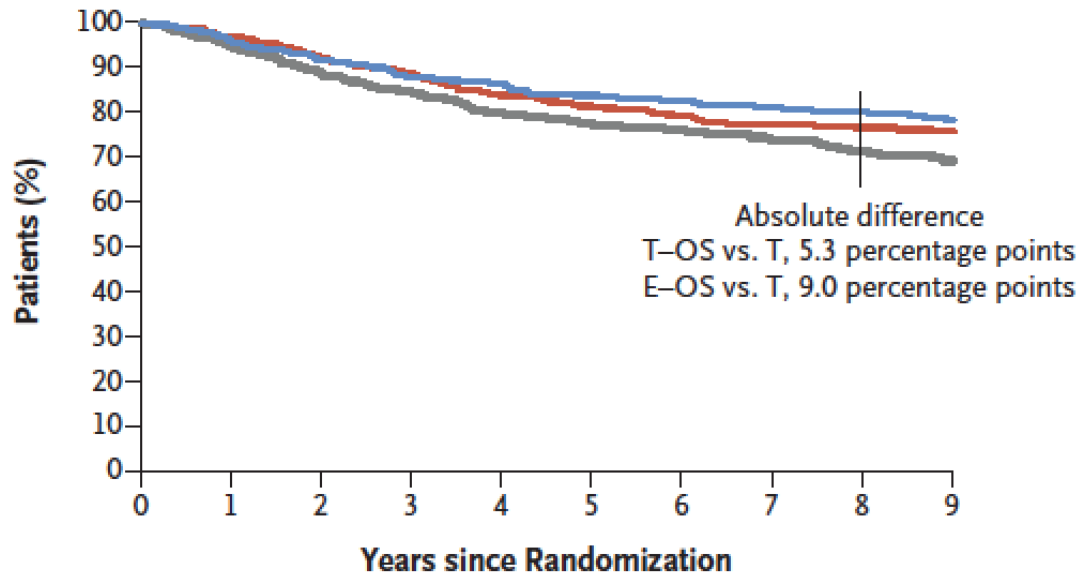


Er T+OFS et akseptabelt alternativ til E+OFS?

TEXT/SOFT:

- E-OS og T-OS bedre sykdomsfri overlevelse enn T alene

Disease-free Survival in Patients with Previous Chemotherapy



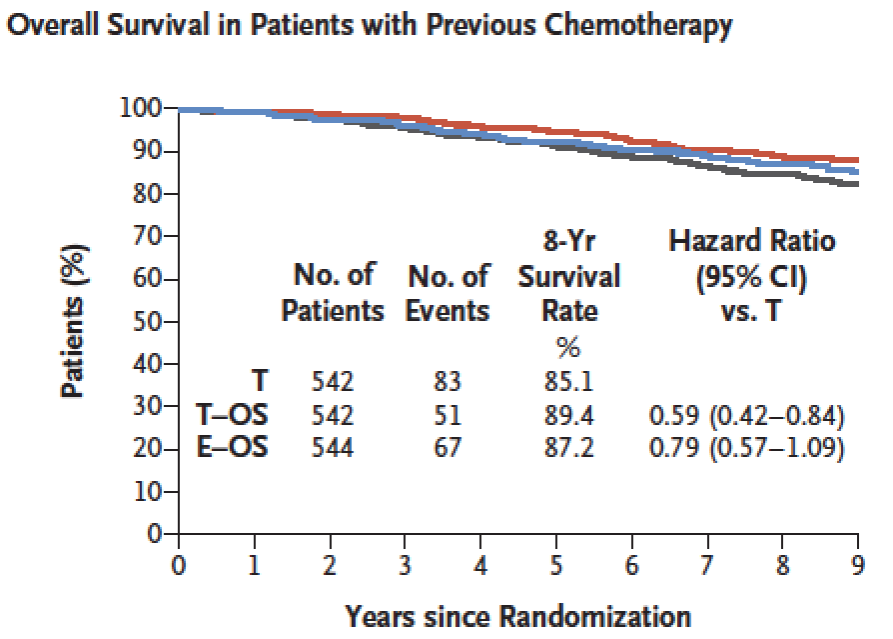
	No. of Patients	No. of Events	8-Yr Disease-free Survival Rate %	Hazard Ratio (95% CI) vs. T
T	542	148	71.4	
T–OS	542	120	76.7	0.76 (0.60–0.97)
E–OS	544	108	80.4	0.68 (0.53–0.88)

No. at Risk

T	496	427	373	249	102
T–OS	515	456	396	282	129
E–OS	513	456	414	291	115

Francis, NEJM, 2018

TEXT/SOFT:
E-OS og T-OS bedre totaloverlevelse enn T alene



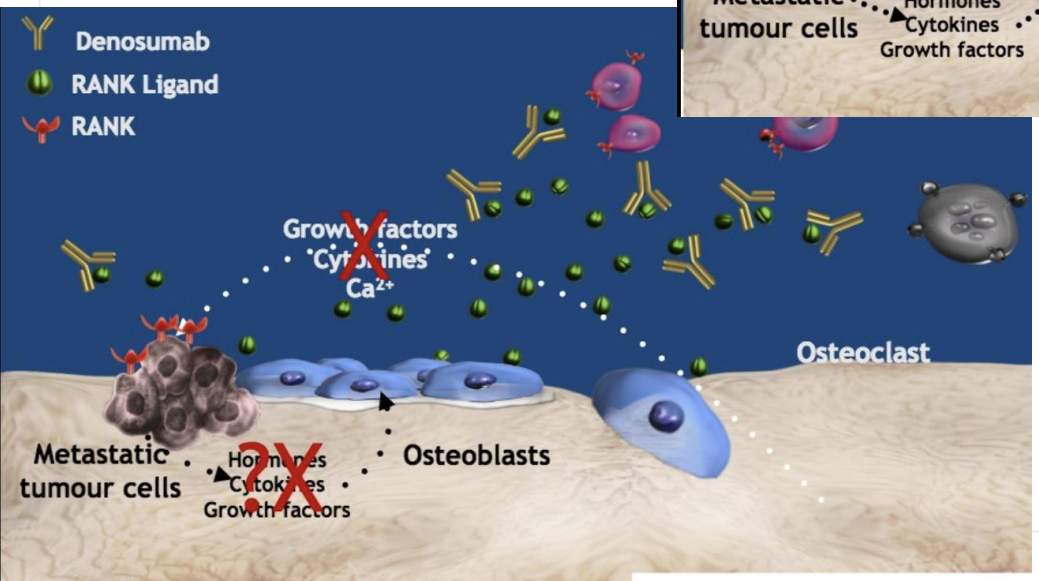
No. at Risk					
T	534	497	461	310	139
T–OS	532	513	477	335	153
E–OS	535	506	465	331	137

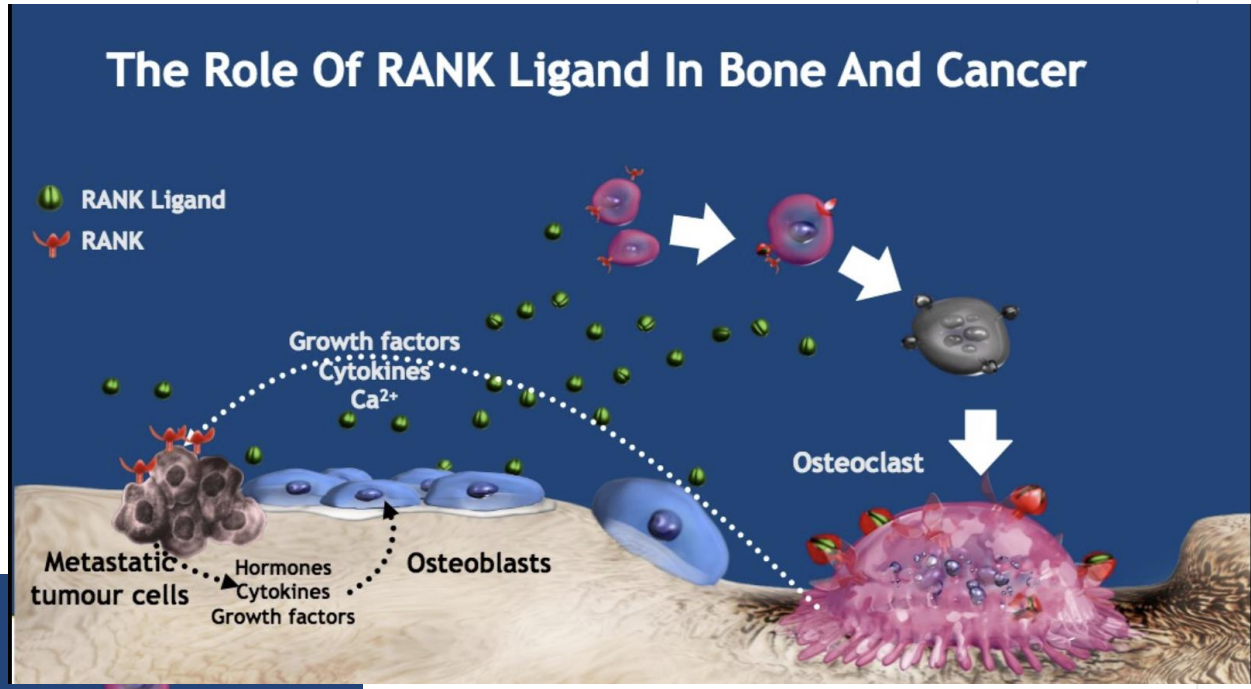
Francis, NEJM, 2018

ADJUVANT DENOSUMAB

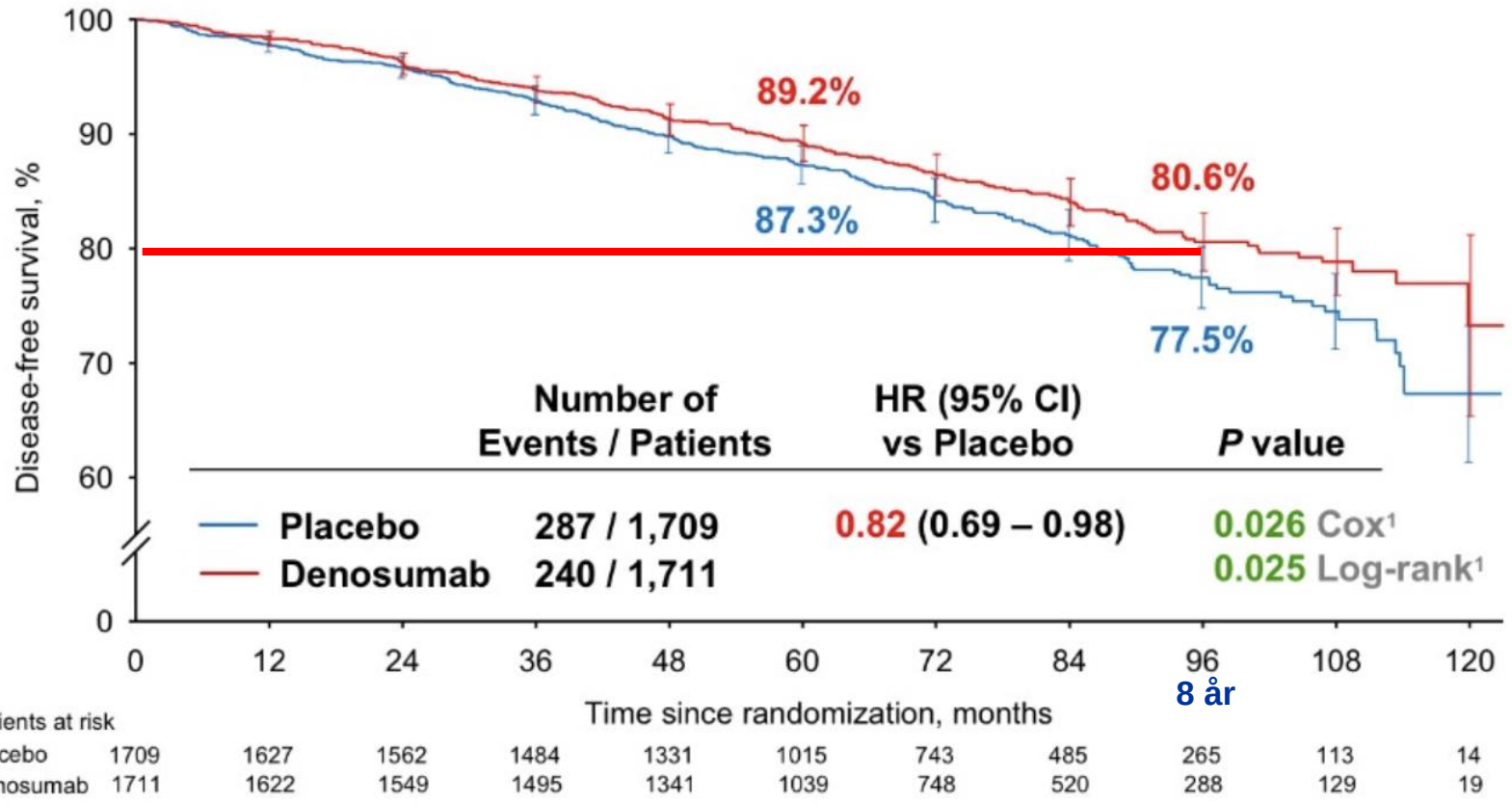
- BEDRE ENN ZOLEDRONSYRE ADJUVANT?

Anti-RANK ligand: denosumab





ASCO 2018; Denosumab 60 mg q6m ABCSG-18 studien, Gnant et al.



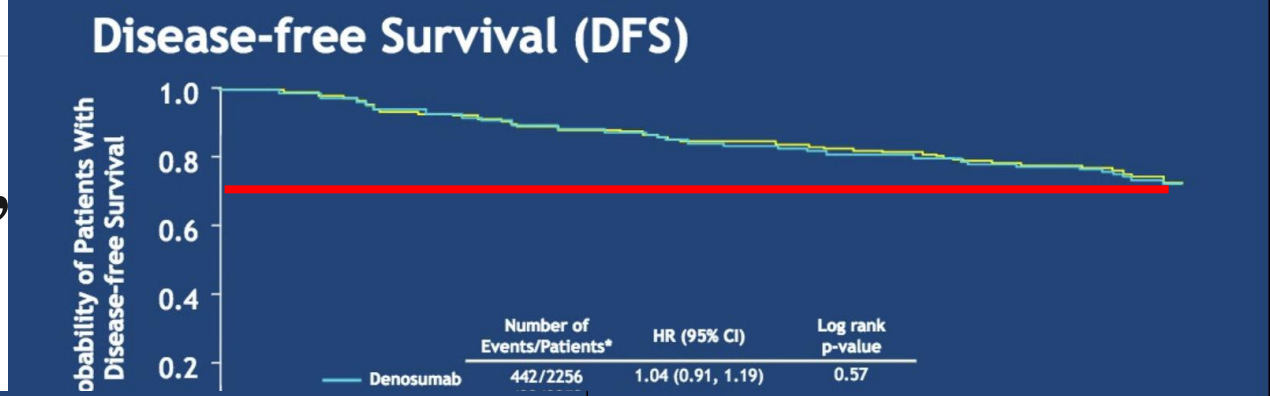
3% absolutt risikoreduksjon

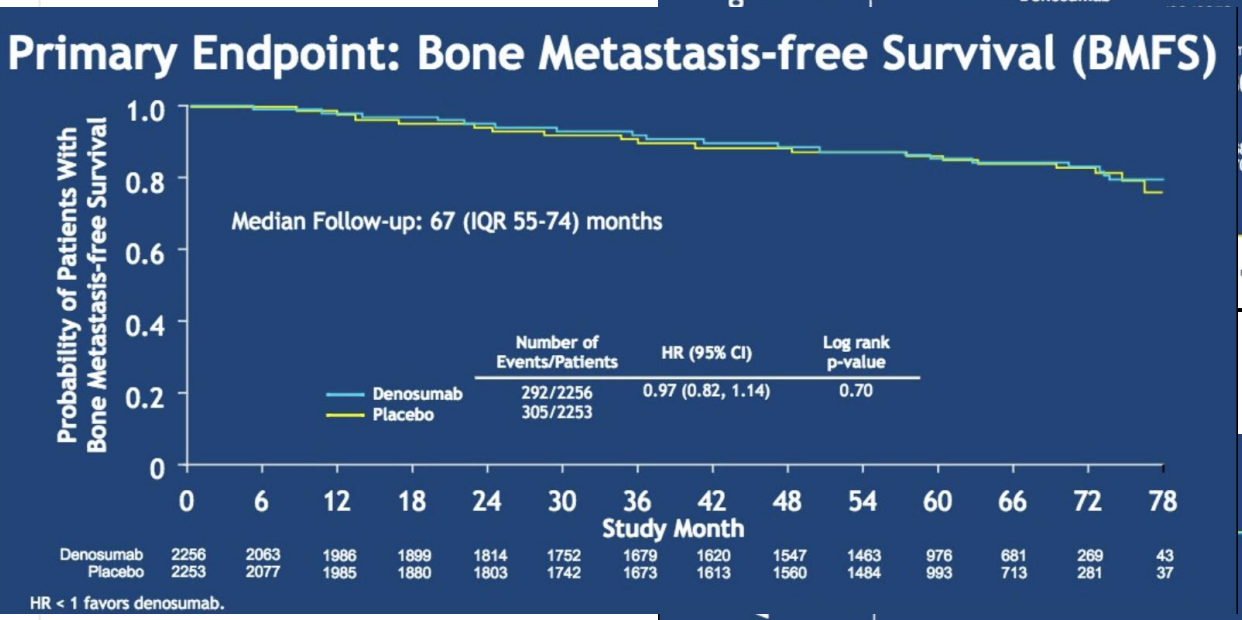
28% relativ risikoreduksjon for recidiv vs. placebo – ikke vs. zoledronsyre...

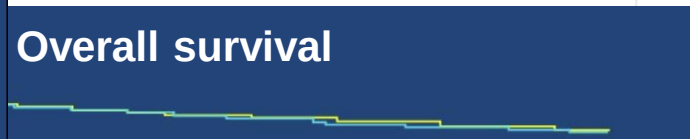
ASCO 2018;
D-CARE studien,

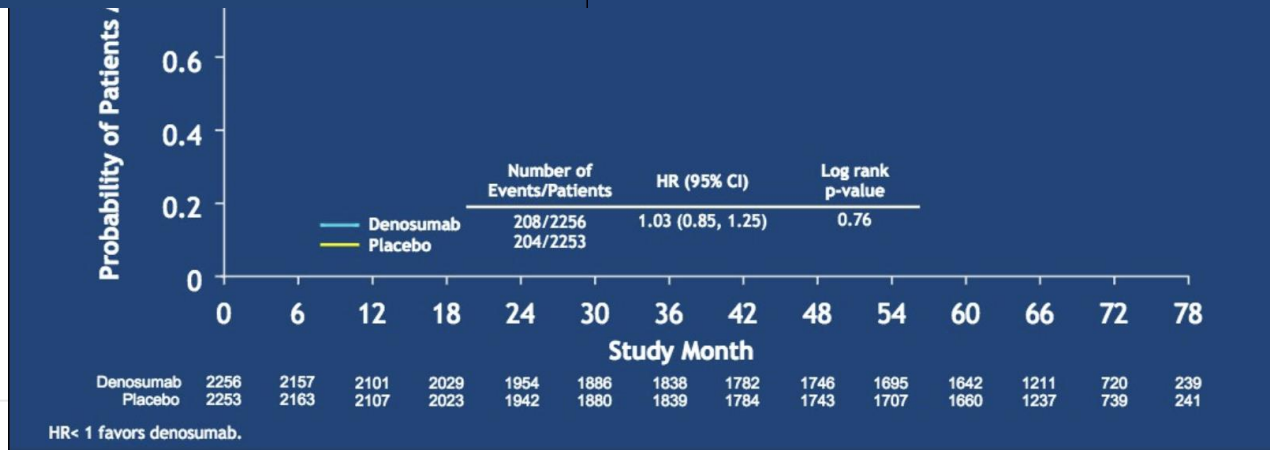
Coleman et al.

Denosumab 120 mg q3-4w



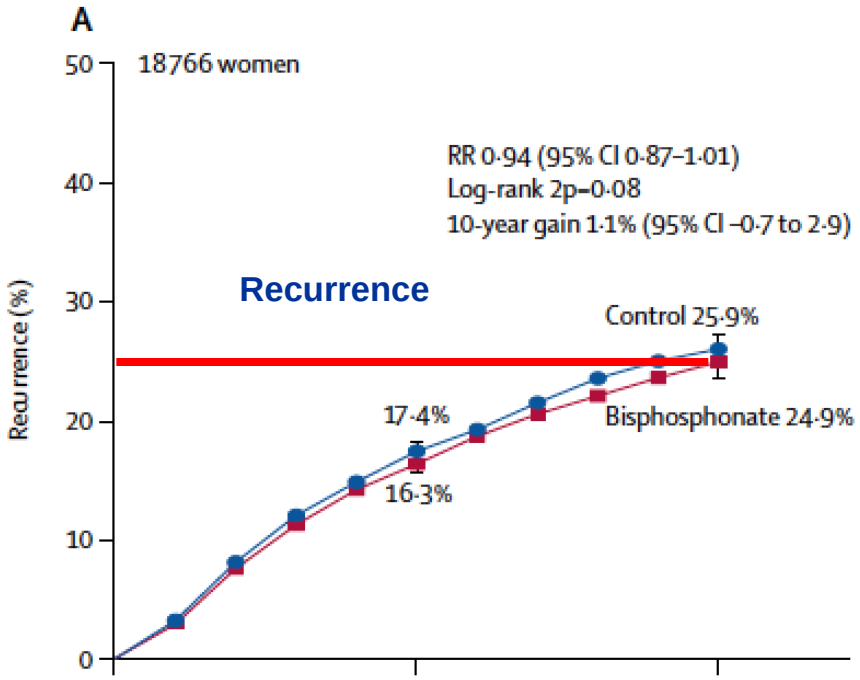


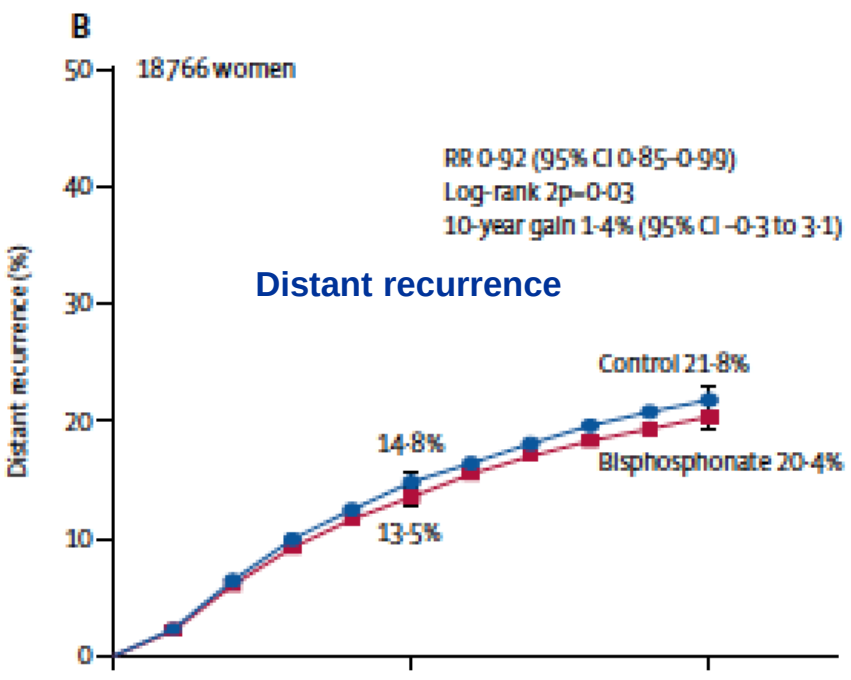




Haukeland University Hospital

Adjuvant bisfosfonat





Recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–4	Years 5–9	Years ≥10
Bisphosphonate	3·63 (1415/38 979)	2·34 (308/13 171)	0·87 (15/1724)
Control	3·85 (1384/35 984)	2·36 (314/13 322)	0·95 (17/1790)
Rate ratio (95% CI)	0·93 (0·85–1·01)	0·98 (0·81–1·14)	0·72 (CI 0·01–1·43)
from (O–E)/V	−41·9/593·7	−3·1/139·4	−1·8/5·5

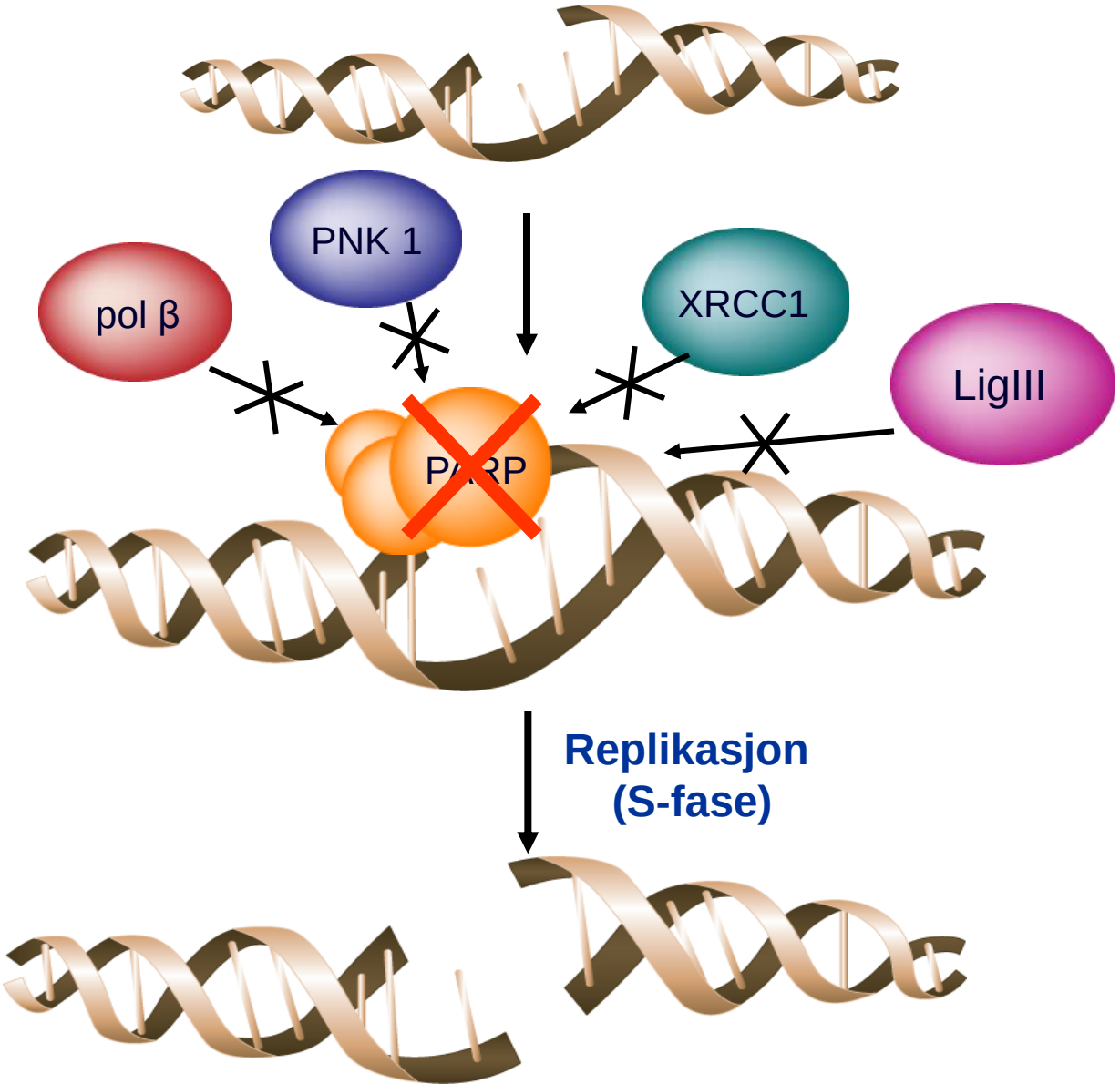
Distant recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–4	Years 5–9	Years ≥10
Bisphosphonate	2·97 (1173/39 559)	1·84 (253/13 746)	0·67 (13/1932)
Control	3·20 (1170/36 571)	1·82 (253/13 931)	1·08 (21/1941)
Rate ratio (95% CI)	0·91 (0·83–0·99)	0·99 (0·81–1·18)	0·47 (0·21–1·03)
from (O–E)/V	−47·5/499·9	−0·7/114·3	−4·5/5·9

EBCTCG, Lancet, 2015

NEOADJUVANT TALAZOPARIB VED BRCA MUTERT BRYSTKREFT

PARP hemmere ved g*BRCA* brystkreft



DNA SSB

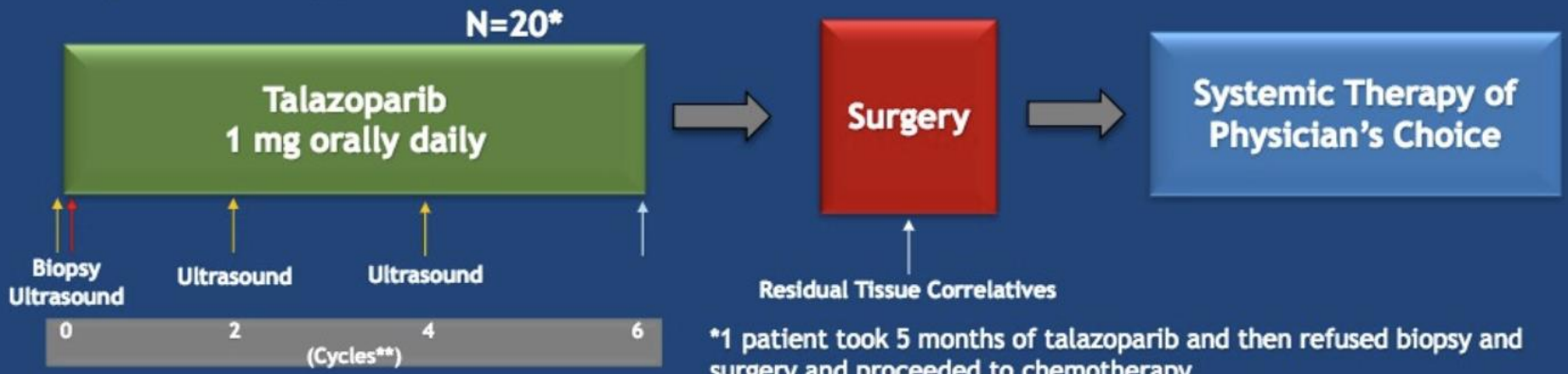
PARP hemmere forhindrer reparasjon av DNA enkelttrådbrudd

Replikasjon (S-fase)

DNA DSB

ASCO 2018;
Neoadjuvant talazoparib, Litton et al.

Study Design



*1 patient took 5 months of talazoparib and then refused biopsy and surgery and proceeded to chemotherapy
** 1 cycle=28 days

Eligibility

- Tumors > 1 cm
- Clinical Stage I-III
- BRCA mutation
- No previous therapy for invasive breast cancer

Exclusion

- HER2 positive

Primary Objectives

- pCR (ypT0/is ypN0)
- RCB-0 + RCB-I

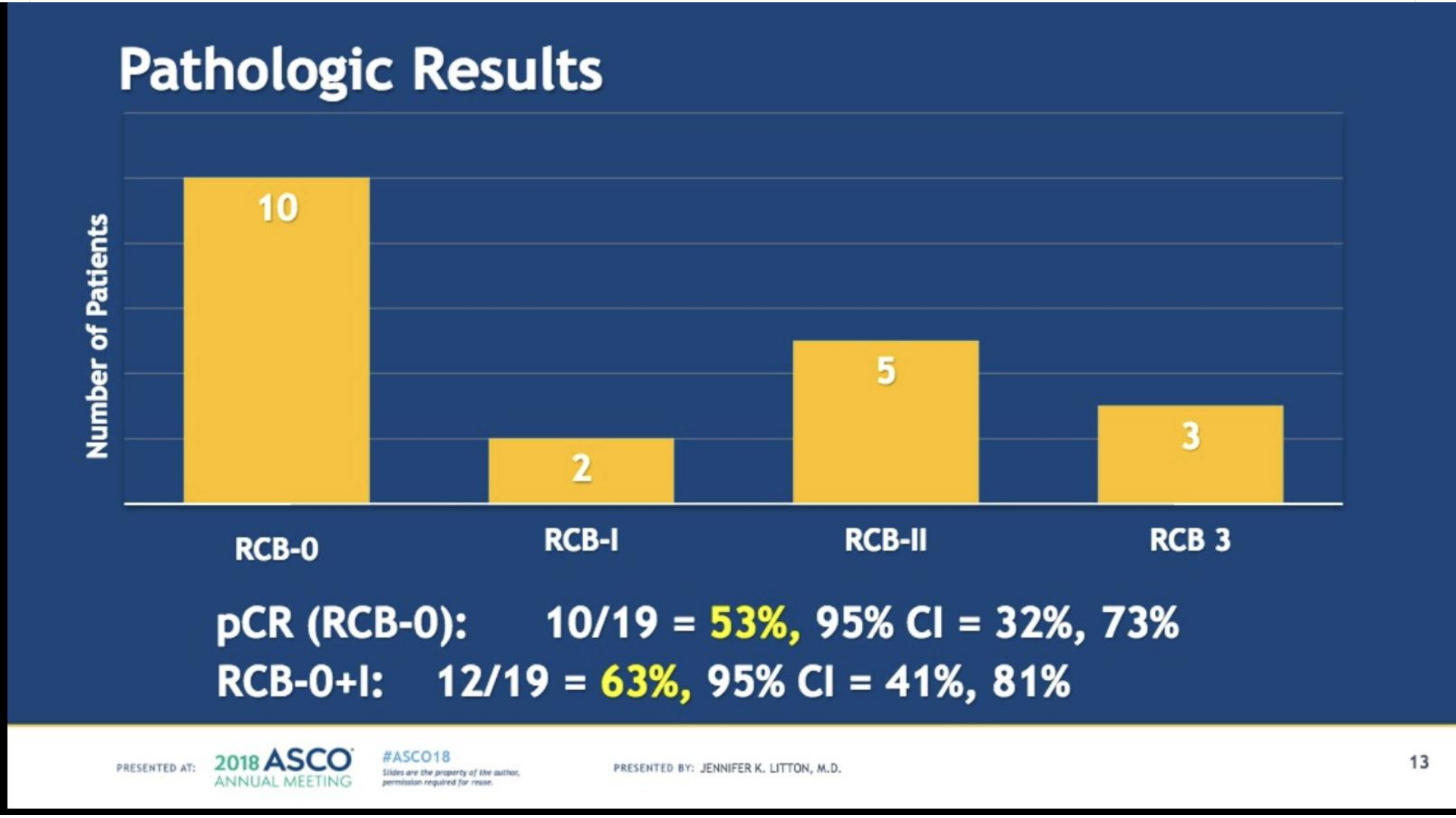
Secondary Objective

- Evaluate toxicity

Baseline Characteristics N = 20

Characteristics		Number of Patients
Age	Median=38 (Range 23-58)	
Race	White	7
	Black	5
	Hispanic	5
	Asian	3
Clinical Stage	I	5
	II	12
	III	3
Histology	Ductal	18
	Lobular	1
	Metaplastic-chondrosarcomatous	1
BRCA mutation	1	17
	2	3
Tissue Receptor Subtype	TNBC (<10% ER or PR)	15
	Hormone Receptor positive (≥10%)	5

ASCO 2018;
Neoadjuvant talazoparib, Litton et al.



Future Neoadjuvant trials in BRCA mutation carriers

Talazo + **Platinum based therapy** > **Talazo alone** ?

Additive rather than truly synergistic combinational effects (1,2)

Talazo + **Immune checkpoint blockade** > **Talazo alone** ?

Strong rationale :
- **Elevated NeoAg load** (3)
- **PDL1 upregulated by PARP inh** (4)

Talazo + **Other DDR* inh Ex ATR inhibitor** > **Talazo alone** ?

Perhaps best explored for sensitizing non BRCAm TNBC to PARP inh ? (5)

*DDR = DNA damage repair

INSTITUT JULES BORDET INSTITUUT

(1) Rugo H et al, N Engl J Med, 2016
(2) Loibl S et al, The Lancet Oncology, 2018
(3) Strickland KC, Oncotarget, 2016
(4) Jiao S et al, Clin Cancer Res, 2017
(5) McCabe N et al, Cancer Res, 2006

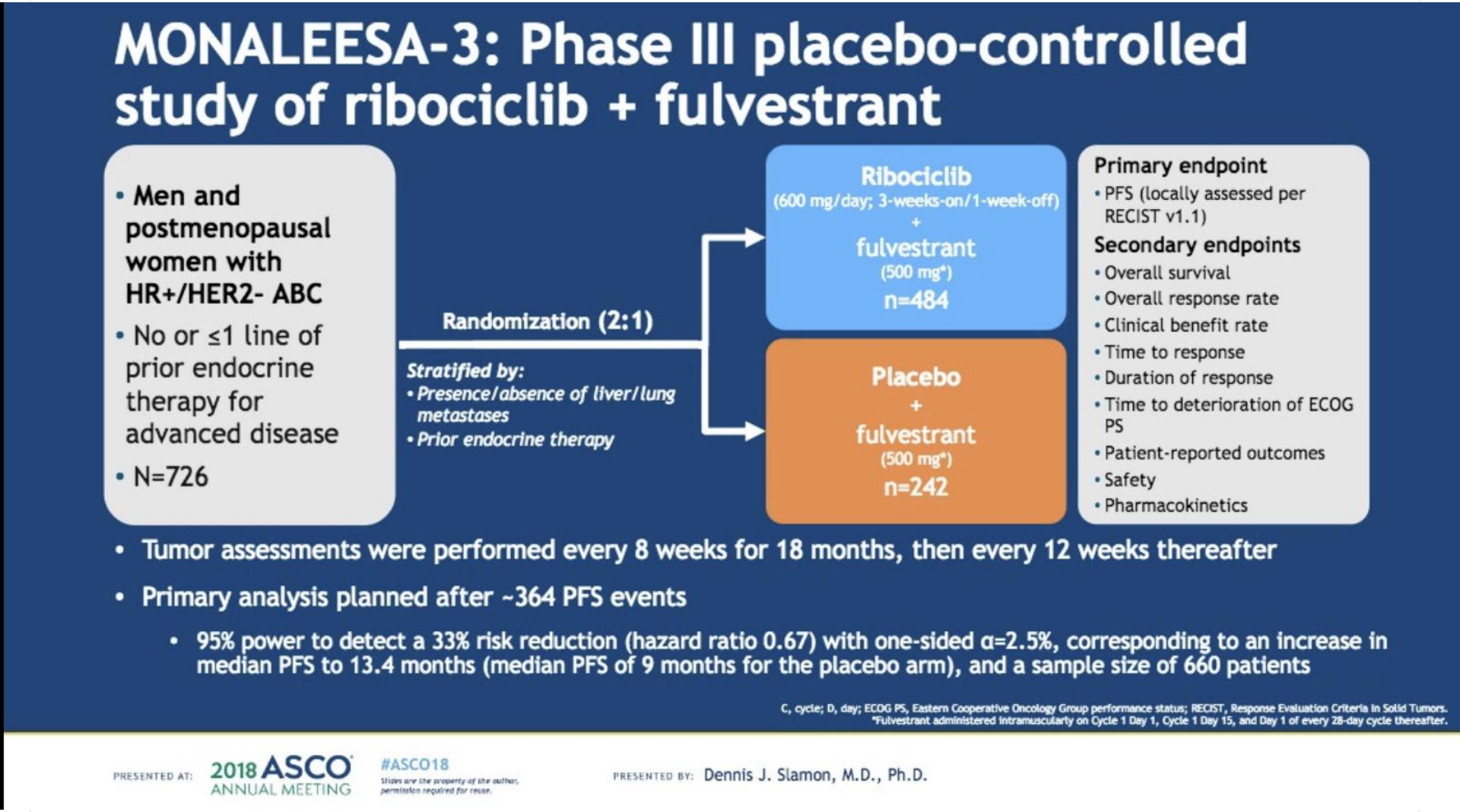
ULB iris

METASTATISK BRYSTKREFT

CDK4/6 HEMMER

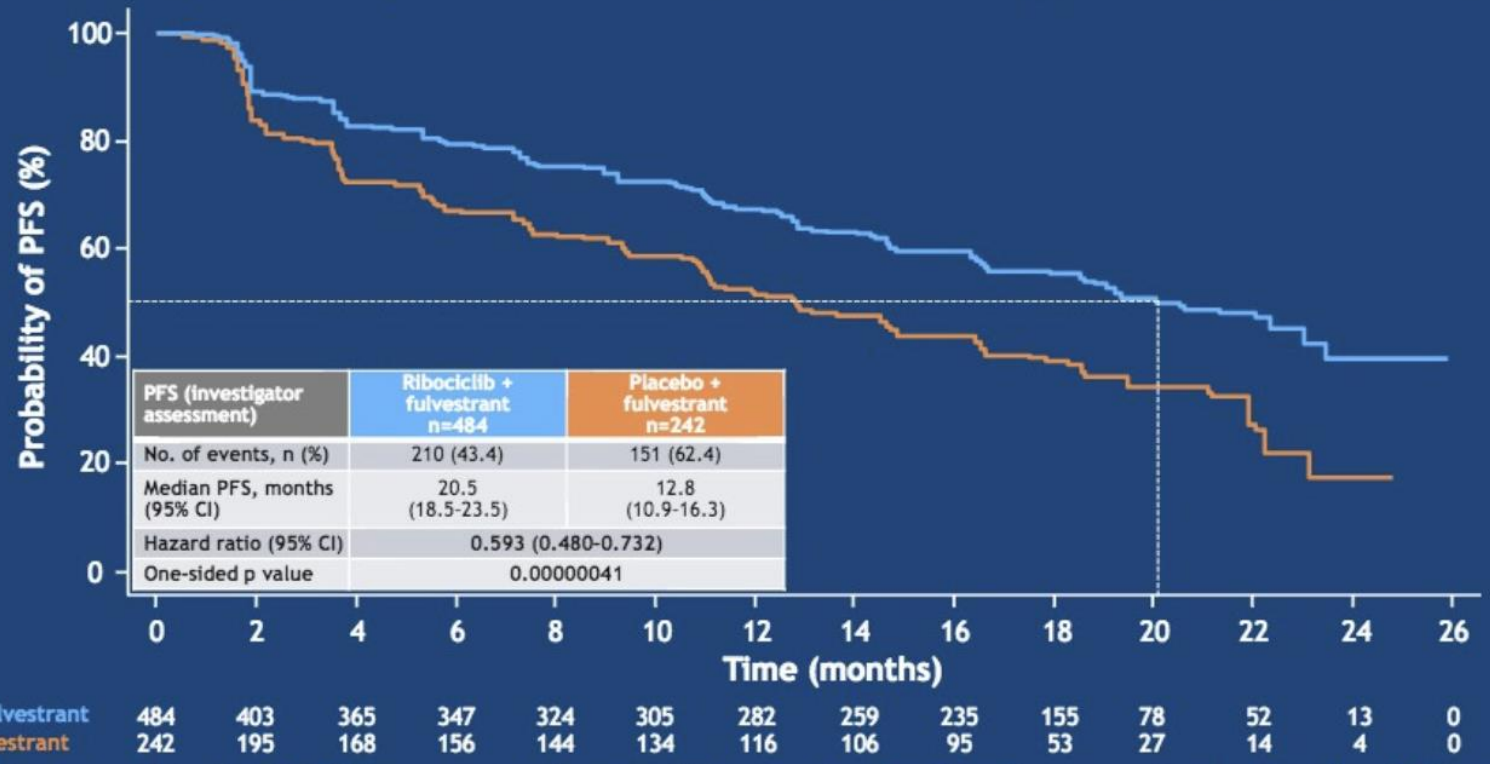
- SAMMEN MED FULVESTRANT I 1. LINJE…

ASCO 2018; MONALEESA-3 studien, Slamon et al.



1. eller 2. linjes behandling; fulvestrant + ribociclib

Primary endpoint: PFS (investigator-assessed)



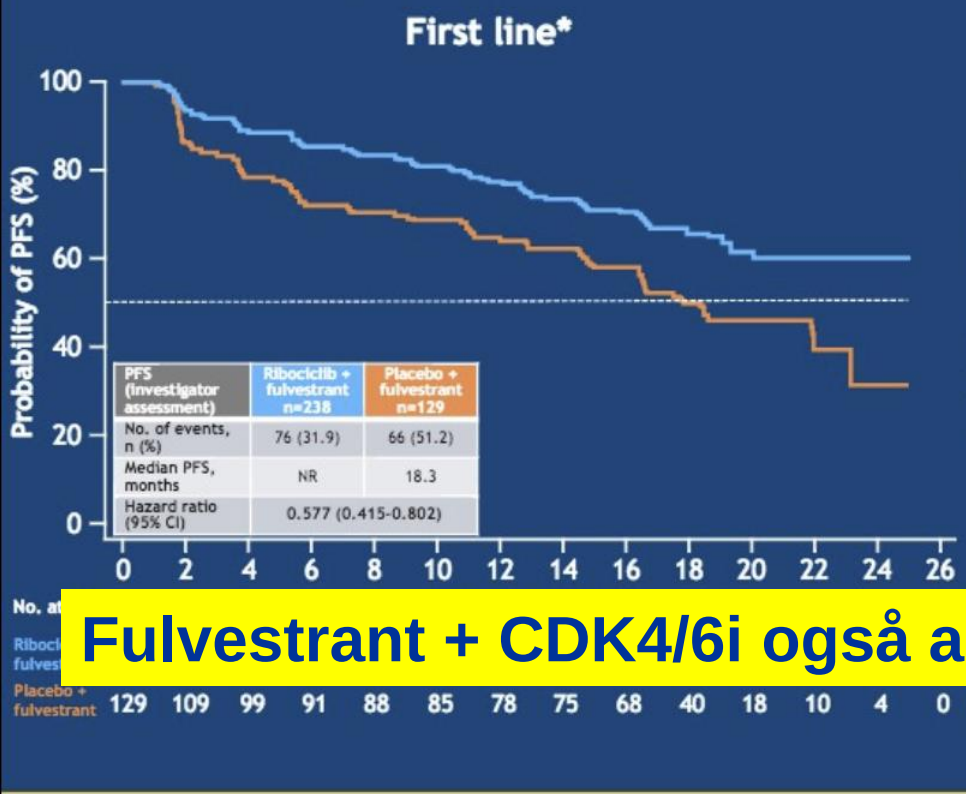
PFS (investigator assessment)	Ribociclib + fulvestrant n=484	Placebo + fulvestrant n=242
No. of events, n (%)	210 (43.4)	151 (62.4)
Median PFS, months (95% CI)	20.5 (18.5-23.5)	12.8 (10.9-16.3)
Hazard ratio (95% CI)	0.593 (0.480-0.732)	
One-sided p value	0.00000041	

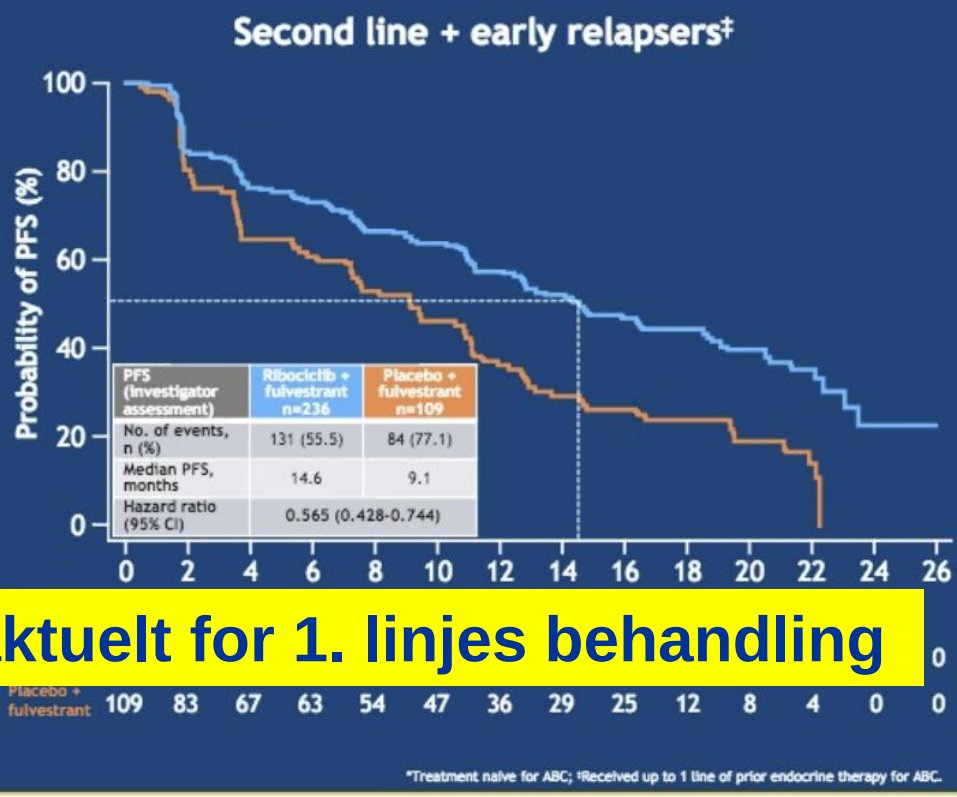
No. at risk

Ribociclib + fulvestrant	484	403	365	347	324	305	282	259	235	155	78	52	13	0
Placebo + fulvestrant	242	195	168	156	144	134	116	106	95	53	27	14	4	0

- The hazard ratio of 0.593 corresponds to a 41% reduction in risk of progression in the ribociclib vs placebo arm

PFS by prior endocrine therapy status





Fulvestrant + CDK4/6i også aktuelt for 1. linjes behandling

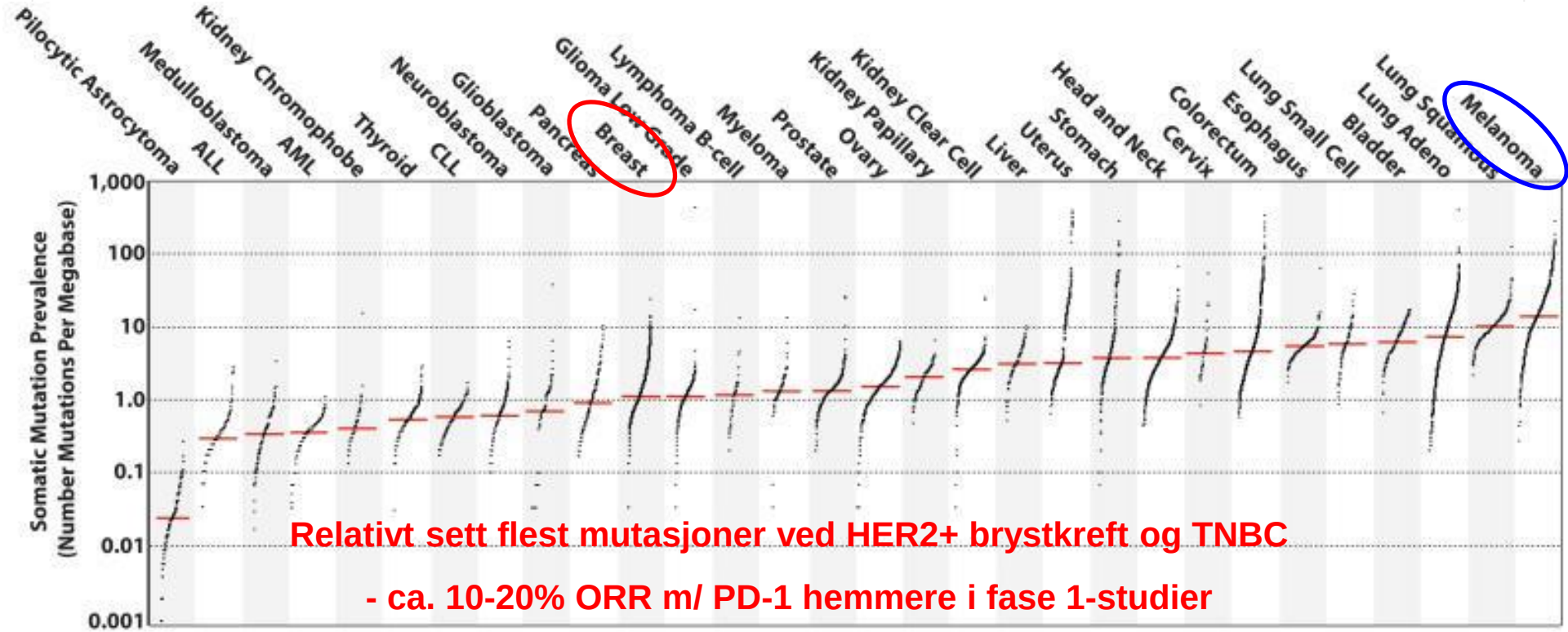
*Treatment naive for ABC; ‡Received up to 1 line of prior endocrine therapy for ABC.

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: Dennis J. Slamon, M.D., Ph.D.

IMMUNTERAPI VED METASTATISK TRIPPEL NEGATIV BRYSTKREFT

Immunterapi ved brystkreft?



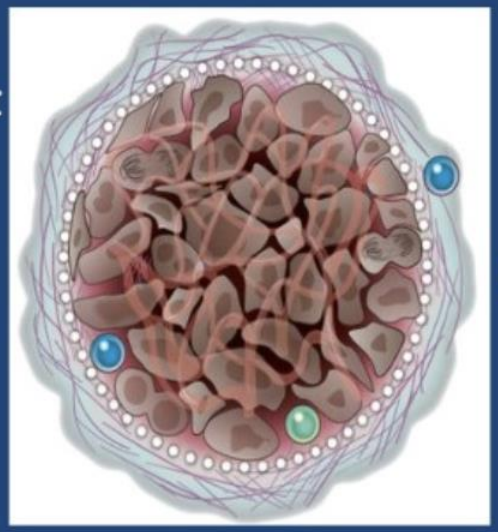
Relativt sett flest mutasjoner ved HER2+ brystkreft og TNBC

- ca. 10-20% ORR m/ PD-1 hemmere i fase 1-studier

Alexandrov *et al. Nature* (2013)

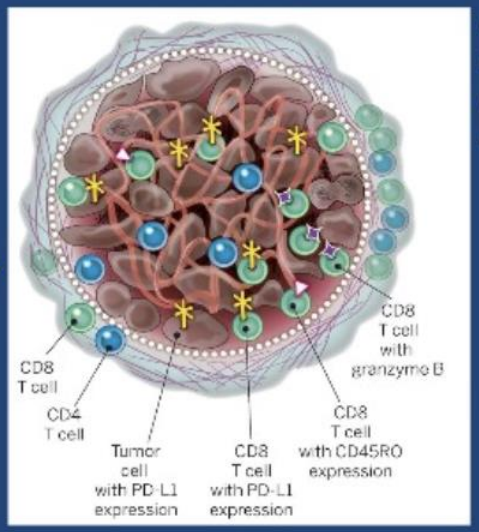
Turning ‘cold’ into ‘hot’ tumor

- few T cells
- non-clonal T cells
- immunosuppressive TME
- low no. of antigens



non-inflamed tumor

?



inflamed tumor

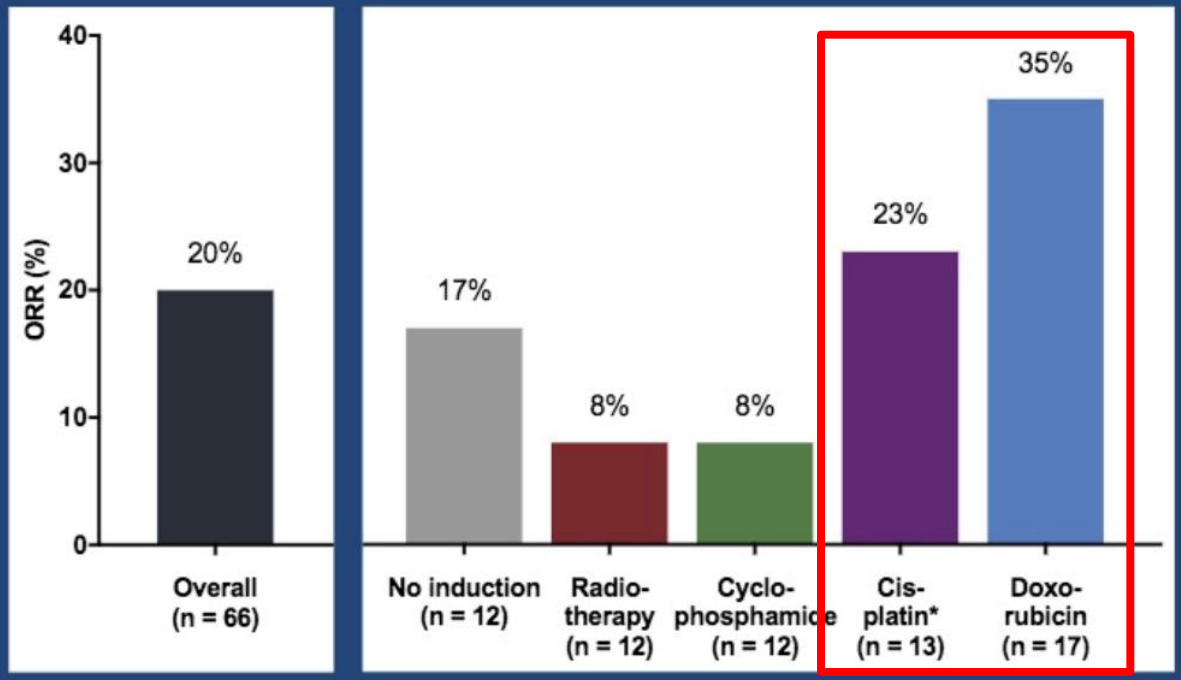
- many T cells
- clonal T cells
- no immunosuppression
- foreign tumor

Adapted from: Sharma & Allison. Science 2015

PRESENTED BY: Marleen Kok, MD, PhD
Netherlands Cancer Institute, Amsterdam, the Netherlands

ASCO 2018; TONIC studien, Kok et al.

Efficacy induction+nivolumab - per cohort -



The non-comparative design of this adaptive trial does not allow statistical comparison between cohorts
According to a 'pick the winner' concept the most promising cohort will be expanded in stage II

1 MSI tumor. M.Kok et al J Clin Oncol Precision Oncology 2017

PRESENTED BY: Marleen Kok, MD, PhD
Netherlands Cancer Institute, Amsterdam, the Netherlands

ASCO 2018; PARPi + pembrolizumab TOPACIO studien, Vinayak et al.

Best Overall Response and Objective Response Rate (ORR)

Response	Response Rate, n (%) Efficacy Evaluable (N=46)*
Complete Response (CR)	3 (7%)
Partial Response (PR)**	10 (22%)
Stable Disease (SD)	10 (22%)
Progressive Disease (PD)	23 (50%)
ORR (CR+PR)	13 (28%)
DCR (CR+PR+SD)	23 (50%)

9 Patients still on treatment
- 2 CR
- 6 PR
- 1 SD

*9 pts did not have evaluable post-baseline tumor assessments and were not included in the evaluable population (6 pts discontinued due to AE; 1 due to clinical progression and 2 for other reasons).

**Responses include both confirmed and unconfirmed; DCR: Disease Control Rate; Data as of April 02, 2018

ASCO 2018; TOPACIO studien, Vinayak et al.

Biomarker-Selected Populations

Efficacy Evaluable Patients	ORR (CR+PR)	DCR (CR+PR+SD)
t*BRCA*mut patients (n=15)	9 (60%)	12 (80%)
HRRmut + t*BRCA*mut (n=20)	11 (55%)	16 (80%)
PD-L1 positive patients (n=25)	9 (36%)	13 (52%)

- Overall Response Rate in all evaluable (biomarker-unselected) patients (N=46): ORR 28%, DCR=50%

Gårsdagen

- billig diagnostikk
- dyr behandling fordi alle skal prøve den

Idag

- dyrere diagnostikk/kreftgenomikk
- billigere behandling fordi personntilpasset