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SENOMAC

Peer Christiansen

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Omitting Axillary Dissection in Breast Cancer with Sentinel-Node Metastases

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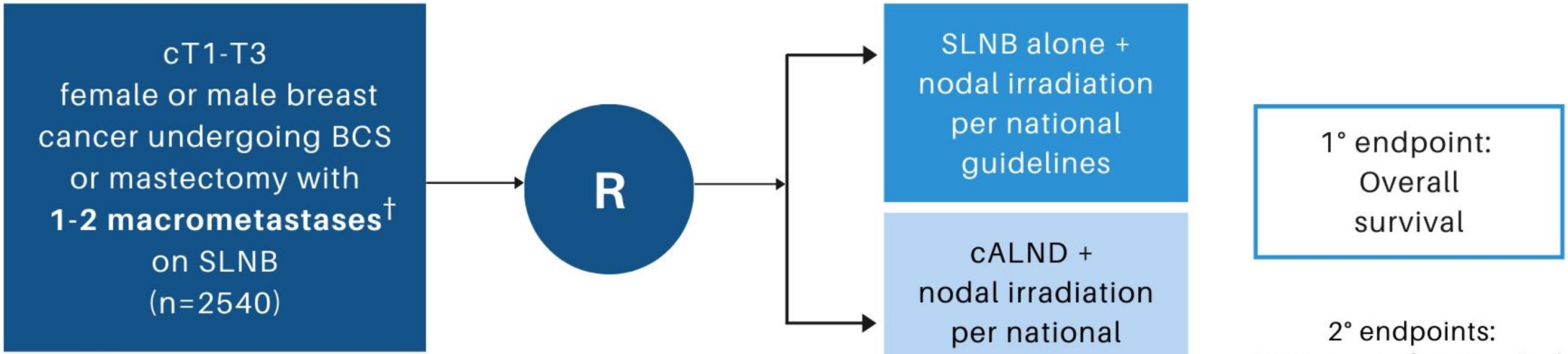
SENOMAC

2015-2021



Preoperative axillary US required

†Additional micrometastases eligible; SLN extracapsular extension eligible

Included patients

Per-Protocol Population

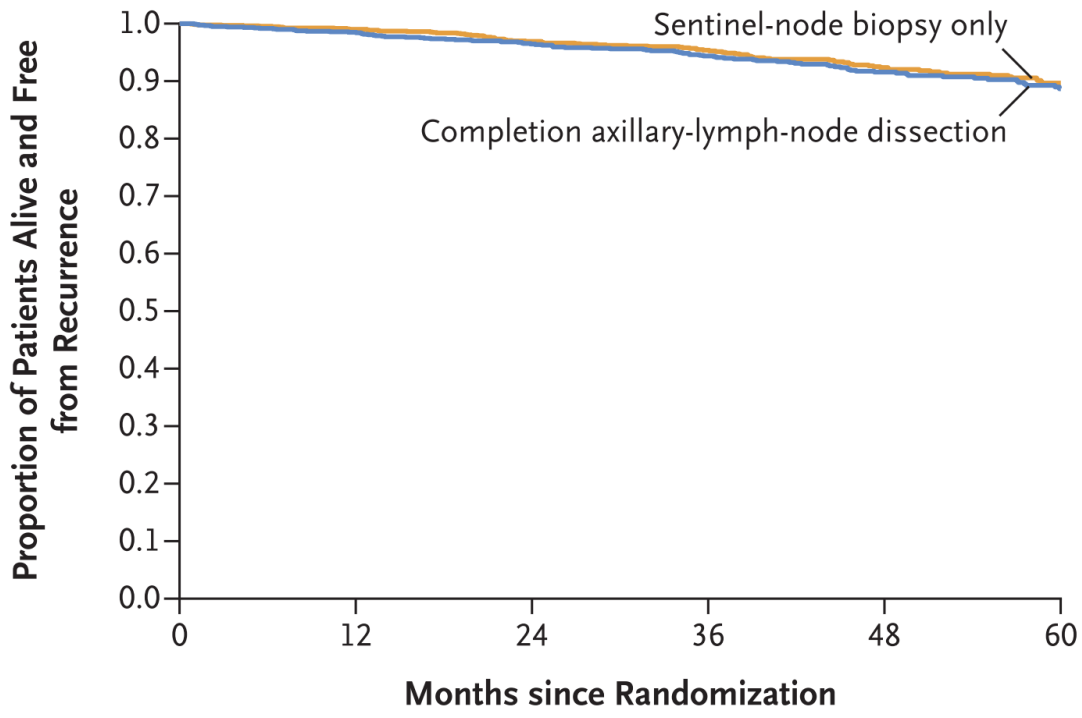
- Sweeden 1553 (61.1%),
- Denmark 803 (31.6%)
- Germany 86 (3.4%)
- Greece 52 (2.0%)
- Italy 46 (1.8%)

DK - Before exclusion

- Copenhagen 288
- Aarhus 141
- Viborg 110
- Aalborg 100
- Aabenraa 80
- Vejle 67
- Odense 53
- Randers 18
- Esbjerg 16

Table 2. Recurrence-free Survival Analyses (Per-Protocol Population).*

Variable	Sentinel-Node Biopsy Only (N = 1335)	Completion Axillary-Lymph-Node Dissection (N = 1205)
Recurrence — no. (%)		
Local	12 (0.9)	10 (0.8)
Regional	6 (0.4)	6 (0.5)
Distant	44 (3.3)	53 (4.4)
Death — no. (%)	62 (4.6)	69 (5.7)
Cause of death — no./total no. (%)		
Breast cancer	24/62 (39)	31/69 (45)
Other cause	30/62 (48)	30/69 (43)
Unknown	8/62 (13)	8/69 (12)
Recurrence or death as first event — no. (%)		
No	1240 (92.9)	1109 (92.0)
Yes	95 (7.1)	96 (8.0)



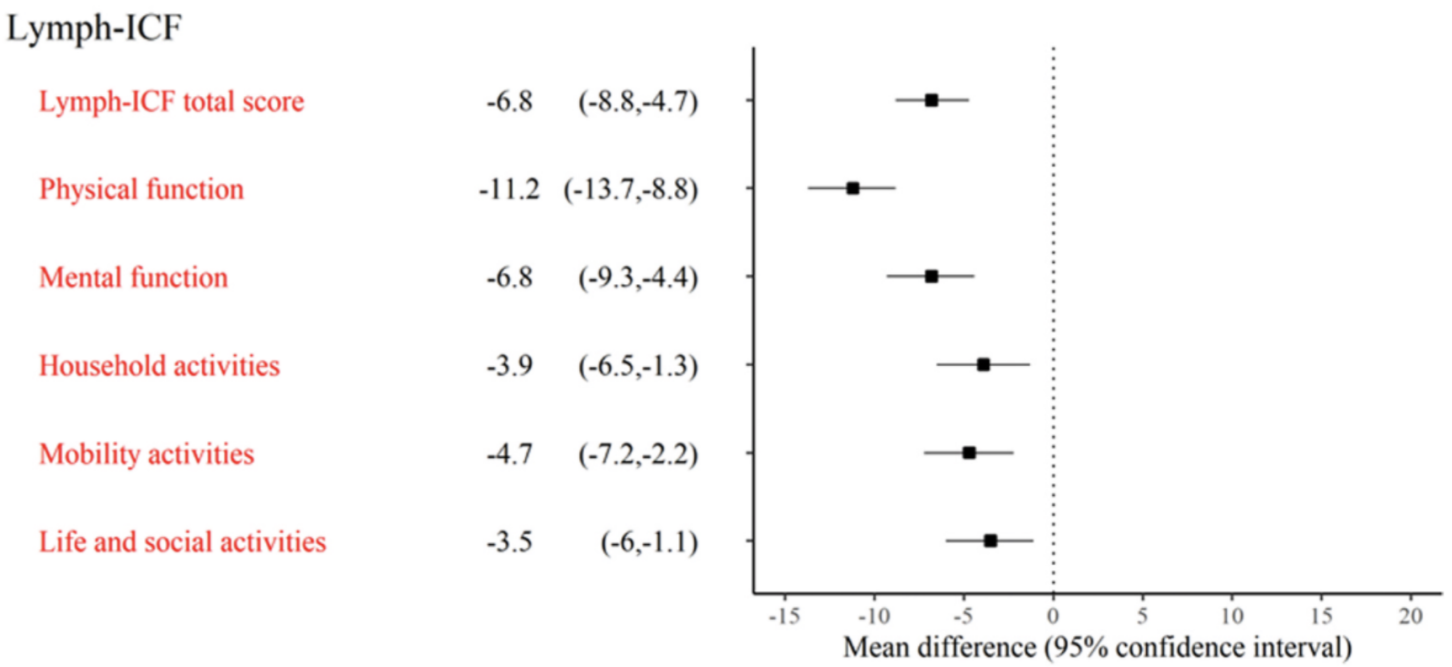
	No. of Events	Recurrence-free Survival (95% CI)
		percent
Sentinel-Node Biopsy Only	89	89.7 (87.5–91.9)
Dissection	91	88.7 (86.3–91.1)

Hazard ratio for recurrence or death, 0.89 (95% CI, 0.66–1.19)
P<0.001 for noninferiority

No. at Risk						
Sentinel-node biopsy only	1335	1276	1069	832	577	307
Dissection	1205	1159	1009	772	544	274

Figure 2. Recurrence-free Survival (Per-Protocol Population).

Shown are Kaplan–Meier curves for the secondary end point of recurrence-free survival.



Appelgren et al. The Breast 2022 doi.10.1016/j.breast.2022.02.013

Articles

Axillary clearance and chemotherapy rates in ER+HER2– breast cancer: secondary analysis of the SENOMAC trial

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Aim

- To investigate whether the choice of axillary staging affected the proportion of patients receiving adjuvant chemotherapy, and the recurrence-free survival. In addition, the nodal stage of patients with and without AC was compared.

Methods

- Primary endpoint: the proportion of patients receiving adjuvant chemotherapy in each randomization arm
- Secondary endpoints:
  - the mean number of positive lymph nodes
  - the proportion of patients identified as having pN2-3 disease per randomization arm
  - 5-year recurrence free survival (RFS) was compared between randomization arms for Danish postmenopausal patients

Table 1: Patient, tumour, and treatment characteristics among patients with ER+ HER2- breast cancer included in the SENOMAC trial according to randomized assignment				
	Completion AC	SLNB only	Total	p-value
Total number of patients, N	1010	1158	2168	
Total number of lymph nodes removed Mean (SD) Median [min-max]	 15.45(7.08) 14.00[1.00-51.00]	 2.31(1.51) 2.00[1.00-15.00]	 8.43(8.22) 4.00[1.00-51.00]	<0.001
Number of positive lymph nodes Mean (SD) Median [min-max]	 2.34(3.09) 1.00[1.00-42.00]	 1.29(0.54) 1.00[1.00-5.00]	 1.78(2.21) 1.00[1.00-42.00]	<0.001
Nodal stage, N (%) pN1 pN2 pN3	 872(86.3) 108(10.7) 30(3.0)	 1151(99.4) 7(0.6) 0(0.0)	 2023(93.3) 115(5.3) 30(1.4)	<0.001
Breast surgery performed, N (%) Breast-conserving surgery Mastectomy	 665 (65.8) 345 (34.2)	 745 (64.3) 413 (35.7)	 1410 (65.0) 758 (35.0)	0.491

	Premenopausal patients (N = 615)			Postmenopausal patients (N = 1492)		
	Completion AC	SLNB only	p-value	Completion AC	SLNB only	p-value
Total number of patients, N	278	337		713	779	
Total number of lymph nodes removed			<0.001			<0.001
Mean (SD)	14.94 (6.97)	2.55 (1.75)		15.59 (7.06)	2.21 (1.37)	
Median [Min-Max]	14.00 [1.00–51.00]	2.00 [1.00–15.00]		14.00 [1.00–50.00]	2.00 [1.00–12.00]	
Number of positive lymph nodes			<0.001			<0.001
Mean (SD)	2.45 (3.51)	1.29 (0.53)		2.30 (2.92)	1.29 (0.54)	
Median [Min-Max]	2.00 [1.00–37.00]	1.00 [1.00–4.00]		1.00 [1.00–42.00]	1.00 [1.00–5.00]	
Adjuvant chemotherapy, N (%)			0.248			0.0923
Yes	238 (85.6)	276 (81.9)		337 (52.9)	378 (48.5)	
No	39 (14.0)	60 (17.8%)		334 (46.8)	401 (51.5)	
Missing	1 (0.4)	1 (0.3%)		2 (0.3%)	0 (0)	
Duration of chemotherapy[a] (weeks)			0.885			0.642
Mean (SD)	16.62 (3.78)	16.67 (3.50)		16.20 (4.13)	16.27 (4.01)	
Median [Min-Max]	17.37 [0.00–26.06]	17.37 [0.00–30.40]		17.37 [0.00–30.40]	17.37 [0.00–52.11]	
Missing, N (%)	12 (5.0)	10 (3.6)		11 (2.9)	14 (3.7)	

Abbreviations: ER: estrogen receptor, AC: axillary clearance, SLNB: sentinel lymph node biopsy. [a]In patients treated with chemotherapy.

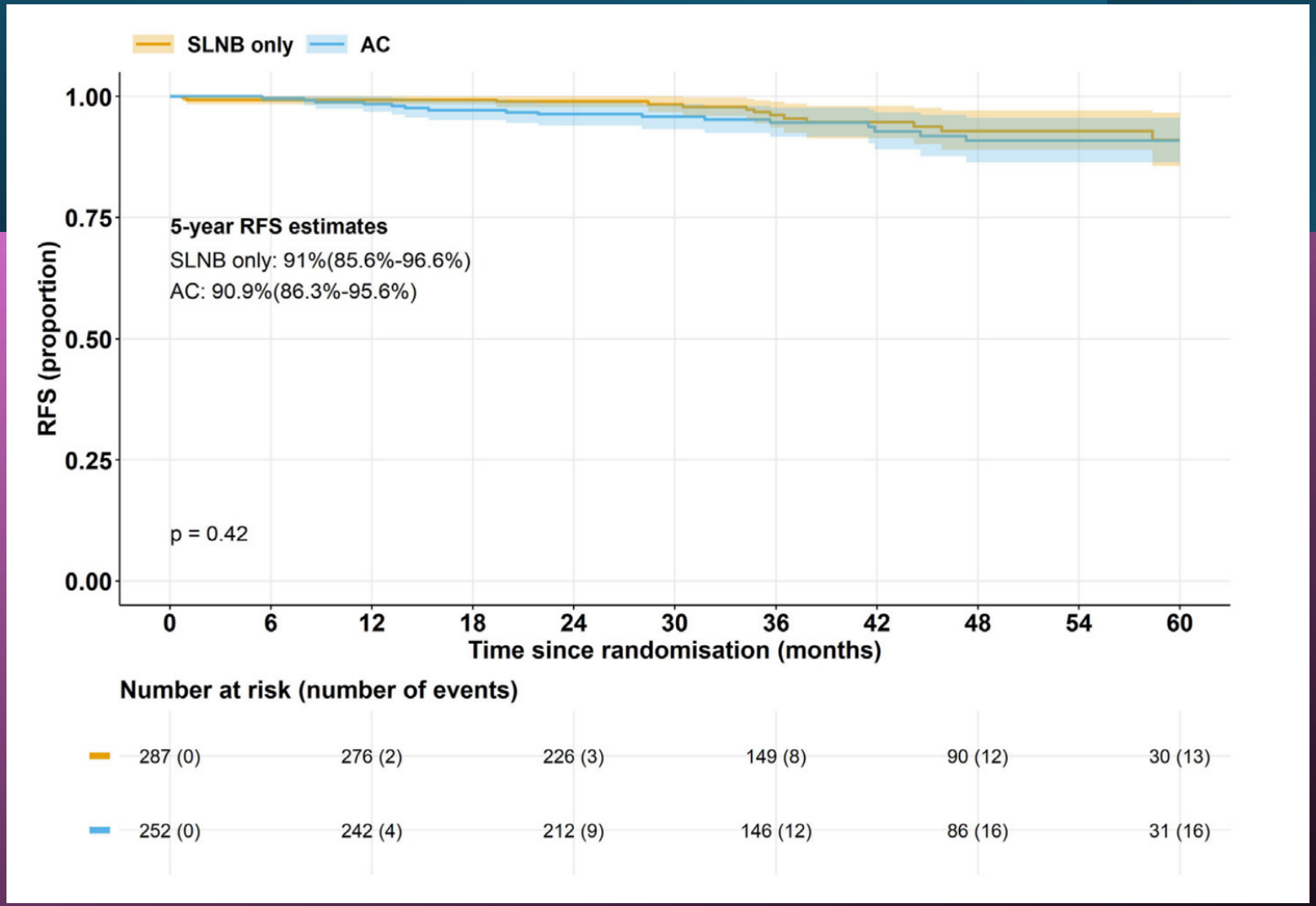
Table 2: **Nodal status and proportion receiving chemotherapy among patients with ER+HER2– breast cancer included in the SENOMAC trial according to randomized assignment and menopausal status according to type of endocrine treatment.**

Chemotherapy to postmenopausal patients

Sweeden	60.0%
Denmark	36.0%
Greece	64.3%
Germany	43.9%
Italy	60.0%

Denmark

- ALND 41.3%
- SN 31.4%


SLNB only
AC
1.00
0.75
0.50
0.25
0.00
RFS (proportion)
5-year RFS estimates
SLNB only: 91%(85.6%-96.6%)
AC: 90.9%(86.3%-95.6%)
p = 0.42
0
6
12
18
24
30
36
42
48
54
60
Time since randomisation (months)
Number at risk (number of events)
287 (0)
276 (2)
226 (3)
149 (8)
90 (12)
30 (13)
252 (0)
242 (4)
212 (9)
146 (12)
86 (16)
31 (16)

Fravalg af aksilrømning

- Når aksilrømning udelades hos patienter med 1 eller 2 positive sentinel nodes (SN), så kan disse patienter ikke med sikkerhed stadieinddeles.
- Fra SENOMAC-studiet ved vi at 30 % af patienter med 1 positiv SN (makrometastase) og 50% af patienter med 2 positive SN (makrometastase) har flere lymfeknudemetastaser, og vi ved at 10 % af patienter med 1 positiv SN og 34% af patienter med 2 positive SN har 4 eller flere lymfeknudemetastaser (pN2 - pN3).
- Påvisning af pN2-3 medfører udredning for fjernmetastaser, fx PET-CT, og har betydning for hvilken adjuverende systemisk behandling der anbefales.

Fravalg af aksilrømning

Ad udredning for fjernmetastaser

Udredning med **PET-CT**, eller tilsvarende, tilbydes alle patienter med lymfeknudemetastaser og ukendt pN stadie.

Ad allokering til systemisk behandling

Anbefaling af adjuverende systemisk behandling afhænger af menopausestatus:

- Præmenopausale patienter med lymfeknudespredning, men ukendt pN stadie anbefales **8 serier kemoterap**i (ved ER positiv og HER2 lav sygdom ddEC efterfulgt af paclitaxel - eller omvendt rækkefølge).
- Postmenopausale patienter ER positiv og HER2 lav IHC profil og 1-2 positive SN, men ukendt pN stadie, behandles i henhold til PSI idet ukendt pN stadie som minimum klassificeres som **PSI 2**. For patienter med PSI 2 kan PAM50 bruges vejledende for tilvalg af kemoterapi. Patienter med PSI 3-4 anbefales 8 serier kemoterapi (ddEC efterfulgt af paclitaxel – eller omvendt rækkefølge). Til patienter med PSI 2 og non-luminal A subtype, anbefales 6 serier kemoterapi (DC el EC/pac).

Articles

Completion axillary lymph node dissection for the identification of pN2–3 status as an indication for adjuvant CDK4/6 inhibitor treatment: a post-hoc analysis of the randomised, phase 3 SENOMAC trial

*Jana de Boniface, Matilda Appelgren, Robert Szulkin, Sara Alkner, Yvette Andersson, Leif Bergkvist, Jan Frisell, Oreste Davide Gentilini, Michalis Kontos, Thorsten Kühn, Dan Lundstedt, Birgitte Vrou Offersen, Roger Olofsson Bagge, Toralf Reimer, Malin Sund, Peer Christiansen, Lisa Rydén, Tove Filtenborg Tvedskov, on behalf of the SENOMAC Trialists' Group**

Numbers needed to treat

- 8 patients needed to undergo a cALND to identify one candidate for adjuvant abemaciclib in accordance with monarchE criteria
- CT + ET vs. ET alone an absolute risk reduction of 7,9%
- 13 patients need to be treated with abemaciclib to avoid one invasive disease-free survival event at 5 years
- **104 (8 multiplied by 13) patients would need to undergo a cALND to avoid one invasive disease-free survival event at 5 years**
  - **8 clinical signs of lymphoedema**
  - **6 treatment of lymphoedema**

Research

JAMA Surgery | Original Investigation

Prediction of High Nodal Burden in Patients With Sentinel Node–Positive Luminal *ERBB2*-Negative Breast Cancer

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Figure 2. Nomogram for Predicting the Probability of High Nodal Burden

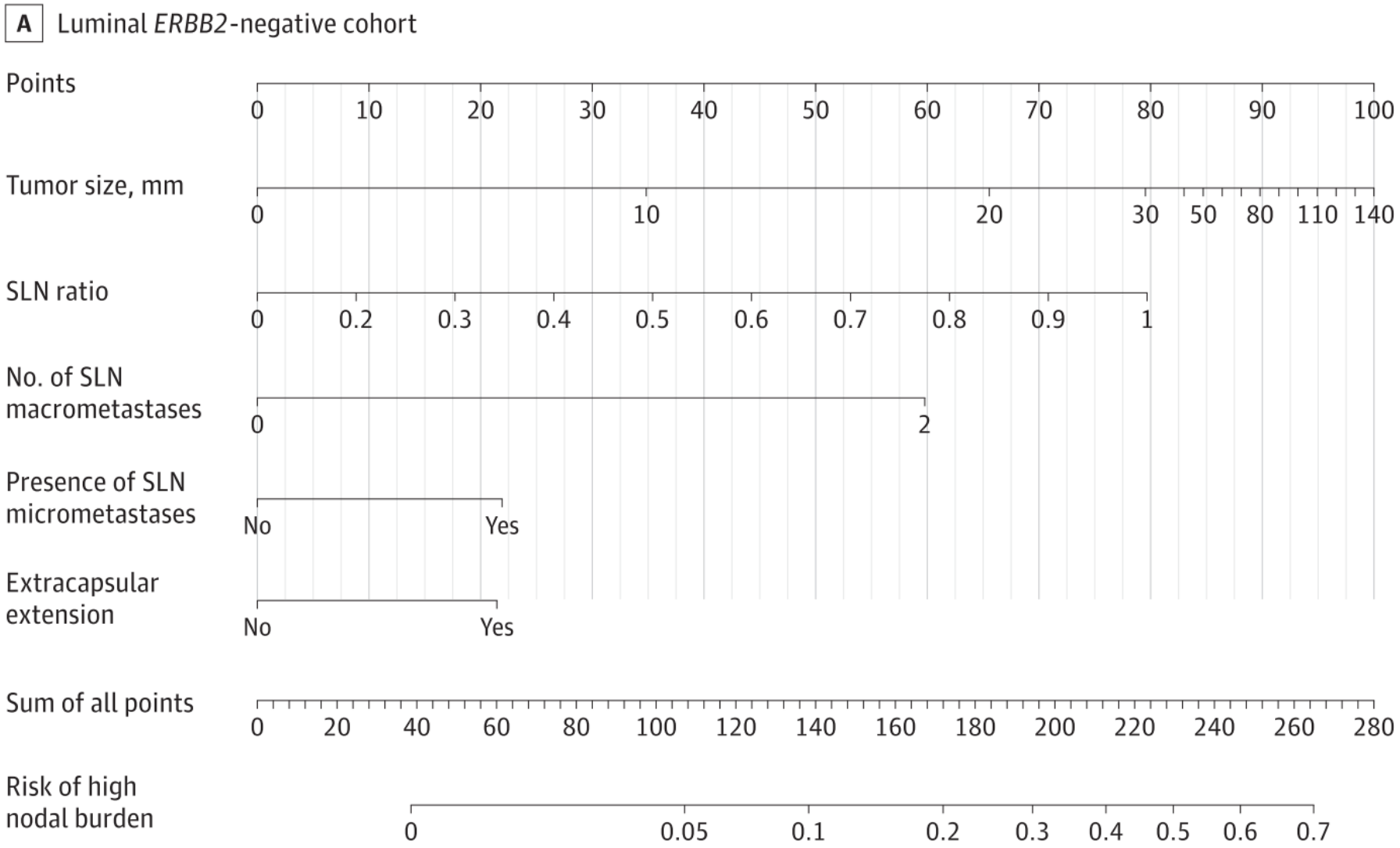
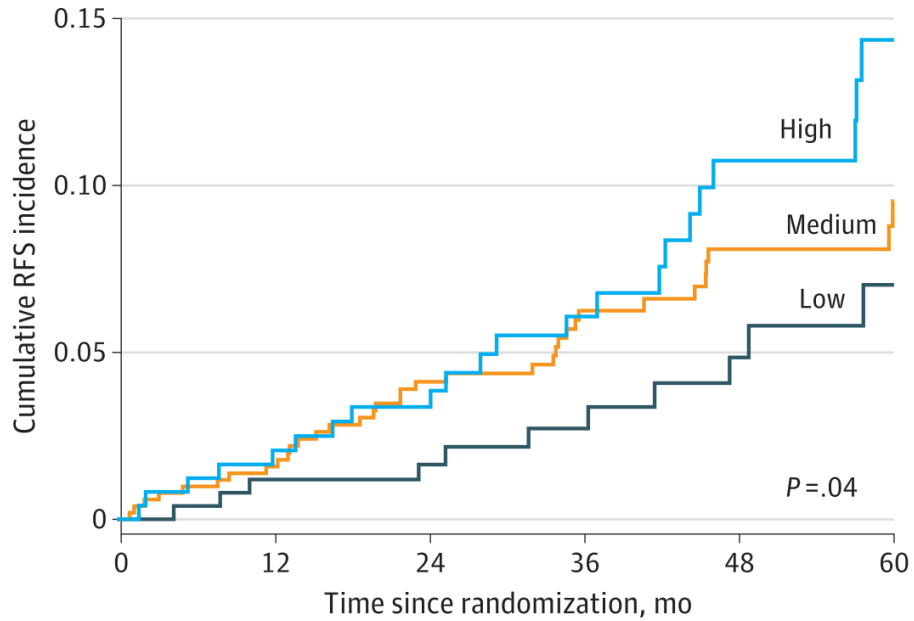


Figure 3. Prognostic Value of the High Nodal Burden Prediction Model

A Cox regression model estimates for the association between nomogram points and RFS in the luminal *ERBB2*-negative cohort

	Covariate[a]	HR (95% CI)[b]	*P* value	Proportional hazards *P* value
Luminal cohort: n = 1005	No. of nomogram points	1.07 (1.02-1.13)	.01	0.48

B Kaplan-Meier curves of cumulative incidence of RFS events by nomogram score categories in the luminal *ERBB2*-negative cohort



No. at risk (No. of events)

Low	252 (0)	242 (3)	207 (4)	158 (6)	115 (9)	55 (11)
Medium	509 (0)	487 (8)	419 (20)	323 (28)	229 (33)	114 (35)
High	244 (0)	234 (4)	205 (8)	150 (13)	102 (19)	62 (22)

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Original Article

Quality assessment of radiotherapy in the prospective randomized SENOMAC trial

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Prescribed treatment according to the radiotherapy plan.

	All Swedish patients N = 874	cALND arm SE N = 420	SLN only arm SE N = 454	P-value *	All Danish patients N = 302	cALND arm DK N = 145	SLN only arm DK N = 157	P-value *
Intended RT targets								
Breast/Chest Wall				0.336				
No	1 (0 %)	0 (0 %)	1 (0 %)		0 (0 %)	0 (0 %)	0 (0 %)	
Yes	873 (100 %)	420 (100 %)	453 (100 %)		302 (100 %)	145 (100 %)	157 (100 %)	
Level I***				0.331				<0.001
No	539 (62 %)	266 (63 %)	273 (60 %)		129 (43 %)	125 (86 %)	4 (3 %)	
Yes	335 (38 %)	154 (37 %)	181 (40 %)		173 (57 %)	20 (14 %)	153 (97 %)	
Level II-IV				0.530				
No	35 (4 %)	15 (4 %)	20 (4 %)		0 (0 %)	0 (0 %)	0 (0 %)	
Yes	839 (96 %)	405 (96 %)	434 (96 %)		302 (100 %)	145 (100 %)	157 (100 %)	
IMN				0.576				0.297
No	753 (86 %)	359 (85 %)	394 (87 %)		1 (0 %)	1 (1 %)	0 (0 %)	
Yes	121 (14 %)	61 (15 %)	60 (13 %)		301 (100 %)	144 (99 %)	157 (100 %)	

As expected, there was a systematic difference in inclusion of level I between randomization arms in Danish SENOMAC patients due to national guidelines. However, even when not intentionally included in the target, most of level I received a therapeutic dose.

SENOMAC – main conclusions
Clinical node negative breast cancer with 1-2 SLN macrometastases

- Recurrence free survival: Omission of completion axillary-lymph-node dissection noninferior to ALND
- Arm morbidity is significantly worse affected by ALND than by SLN biopsy only
- Level I received a high dose coverage even when not intentionally included in the target
- Potential under-treatment of postmenopausal patients with ER+HER2– breast cancer
- ALND should be discouraged for the purpose of identify N2-3 disease
- Nomograms may facilitate systemic treatment decisions without exposing patients to the risk of arm morbidity due to completion ALND