

Post-SABCS 2023: Surgery

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Belgium



DECEMBER 5-9, 2023 | @SABCSSanAntonio



COI - Disclosure

- 100% employee UZ and KU-Leuven.
- My institution received financial compensation on my behalf for advisory boards, lecture fees and/or consultancy fees from Pfizer, Novartis, Eli Lilly, Astra Zeneca, Menarini, Roche and Gilead.
- I did ever receive travel support from Novartis, Astra Zeneca, Pfizer, Roche and Eli Lilly.



My presentation overview

Mainly SABCS 2023

I. Controversies in Breast Surgery

II. Evolution of axillary surgery: Is less safe?

I. Controversies in Breast Surgery

- A. *mBRCA1* & Unilateral EBC : Is CL (prophylactic) mastectomy better? [GS02-04](#)
- B. DCIS: wide local excision with ≥ 2 mm margin? [PS01-06 & 01--10](#)
- C. EBC: yearly FU mammogram: Is “less frequent” worse than “annual”? [GS03-02](#)
- D. Local therapy in stage IV disease? [BCRT 2024 Belgian Data](#)

EBC= Early Breast Cancer

DCIS= Ductal Carcinoma In Situ

FU= Follow-Up

A. Contra-lateral prophylactic mastectomy in *mBRCA1* with unilateral EBC: Impact on survival

GS02-04 Kelly A. Metcalfe et al.



CPM in *mBRCA1*: 13th EBCC Manifesto

CBC risk = 3-4x *mBRCA* ½ & *mBRCA1* > *mBRCA2*

CPM “may” improve BCSS and OS (HR 0.37-0.52)

Considered “reasonable option” despite better (neo)adj. Rx (TNBC)?

CBC: contra-lateral breast cancer

CPM: contra-lateral prophylactic mastectomy

1. Evans DG et al. BCRT 2013; 140: 135-42
2. Metcalfe K et al. BMJ 2014; 348; g226
3. Heemskerk-Gerritsen BA et al. IJC 2015; 136: 668-77
4. Schmidt MK et al. Eur J Cancer 2023

Study Objective

“Impact of bilat. ME vs unilat. Sx on BCM?”

Risk of CBC and BCM by Sx

2482 *mBRCA1* Unilat EBC; [43 yrs] ‘95-’21; 11 countries/ 26 centres)

Initial surgery

- BCT (n=852)
- Unilat. mastectomy (n=1141)

- Bilat. mastectomy (n=489)



Bilat. Sx during FU allowed
n=529

Methods

Questionnaires to pts for demographics

Medical files for clinical data

FU: 8.9 yrs (Date of last FU or Death)

CBC = Contra-Lateral Breast Cancer

BCM= Breast Cancer Mortality

EBC= Early Breast Cancer

BCT = Breast Conservative Therapy

Sx = Surgery

A very heterogeneous population:

75% Grade 3

75% ER-neg

Unilateral mastectomy:

- Larger tumors and more with LN+ BC

Bilateral mastectomy:

- Younger 41.3 yr

- More recent 2014

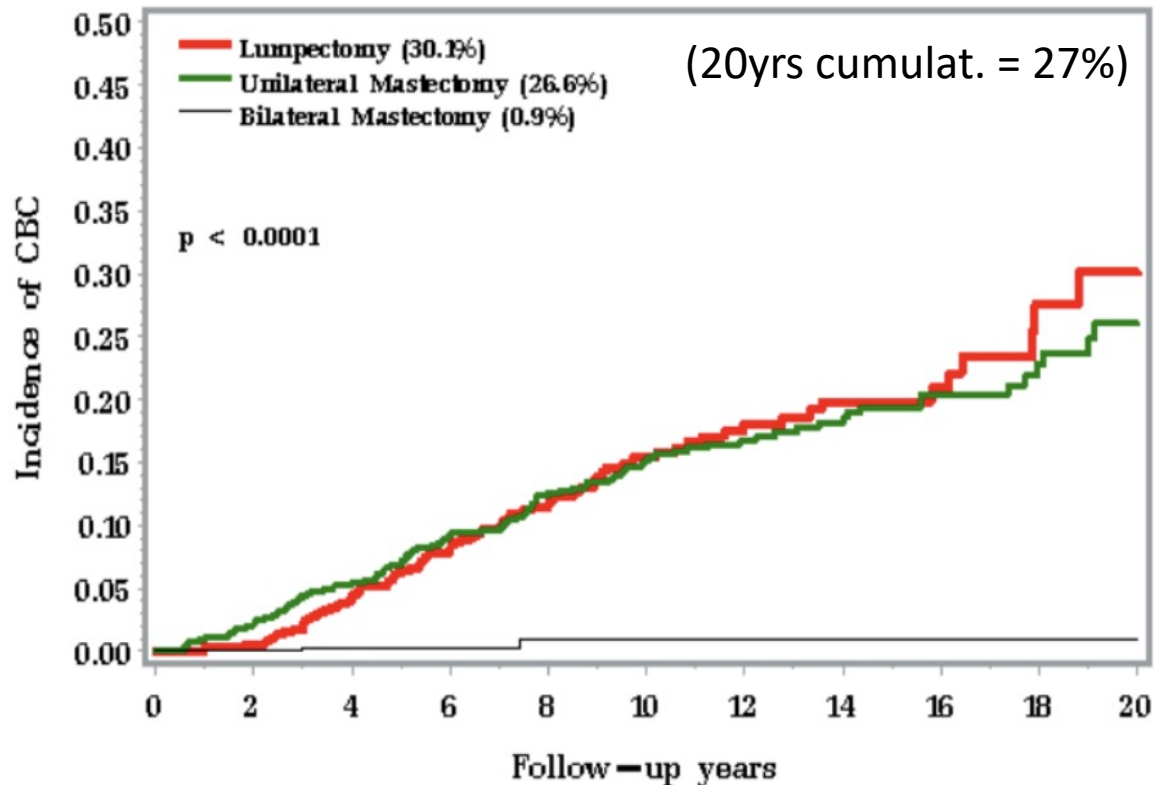
- Shorter FU 6.5 yr

***adjusted by**

- age at dx (<=40, 30-50, 50+)
- ER (Neg/Pos)
- size
- lymph node (Neg/Pos)
- bilat. oophorectomy (time dependent)
- adj. tam (No/Yes)
- adj. chemo (No/Yes)
- bilat Sx if 1st Sx unilat. (time dependent)

Outcome

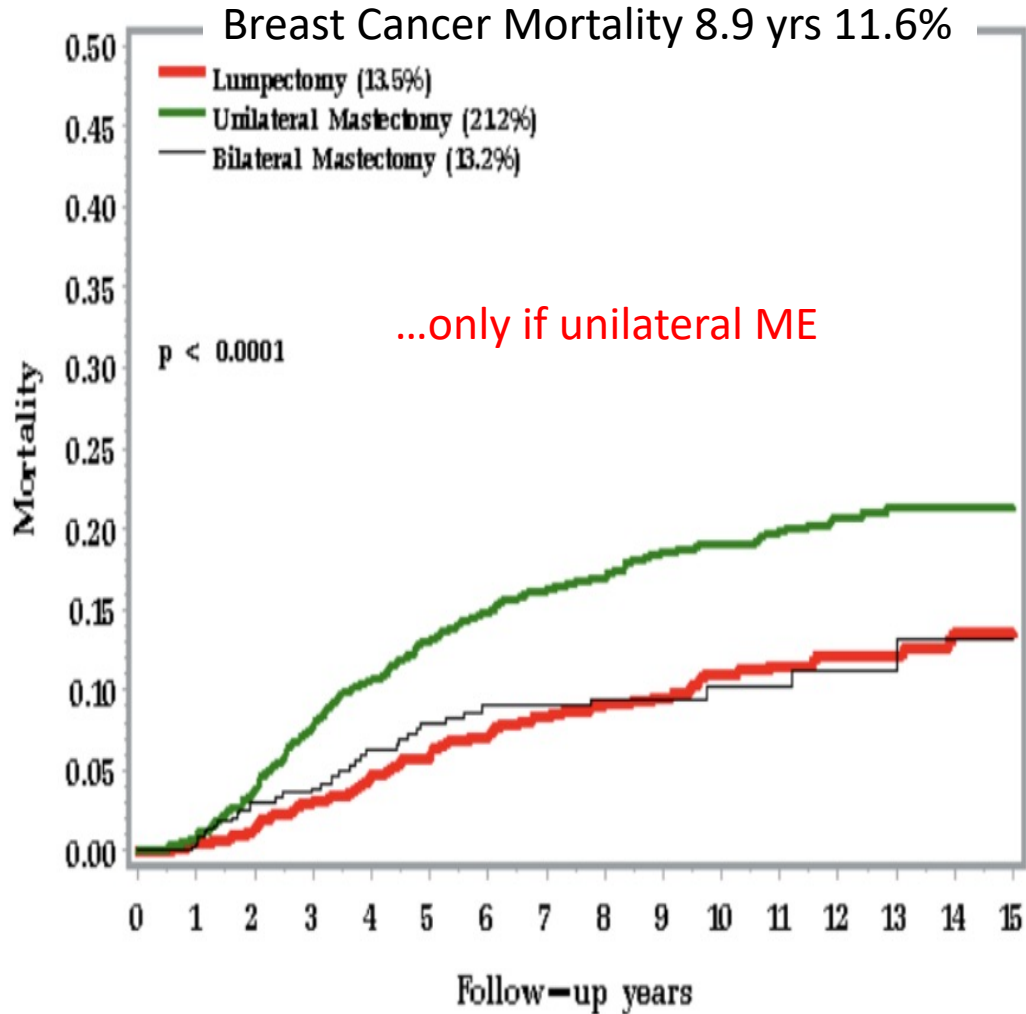
- CBC 8.9yrs= 11.5% &
- predicts BCM factor 2.22... **but**



*adjust by age at dx (≤ 40 , 30-50, 50+), size (5), nodes (Neg/Pos), surgery, oophorect.(time dependent), tam (yes/no), ER (+/-), CT

BCM	Multivariate * HR(95%CI)P
All subjects Contralateral BC No Yes (time dependent)	1 2.22(1.49-3.32) <0.0001
Age ≤ 40 years Contralateral BC No Yes (time dependent)	1 2.71(1.40-5.24)0.003
Age >40 years Contralateral BC No Yes (time dependent)	1 1.99(1.19-3.31)0.008

Breast Cancer Mortality by Surgery Type



BCM against BCT	Multivariate * HR(95%CI)P
All subjects	
BCT	1
Unilateral Mastectomy	1.22(0.92-1.62)0.17
Bilateral Mastectomy	0.88(0.58-1.13)0.19
Age ≤40 years	
BCT	1
Unilateral Mastectomy	1.28(0.81-2.04)0.29
Bilateral Mastectomy	0.94(0.51-1.72)0.84
Age >40 years	
BCT	1
Unilateral Mastectomy	1.15(0.80-1.65)0.44
Bilateral Mastectomy	0.83(0.46-1.48)0.52

Bilateral ME versus unilateral Sx Adjusted HR for BCM: 0.78 (95% CI 0.55-1.13; p = 0.19)

Conclusions

If unilateral surgery for EBC

- CBC is more likely and a risk factor for breast cancer death
- Driven by unilateral mastectomy (larger T, more LN-pos) and not by BCT;

BCM after bilateral mastectomy not different from BCT

- Breast conservation is a reasonable option in women with unilateral unifocal brca

...Critical Note

- Population recruited 26yrs period (variation systemic protocols)
- Newer therapies (IO; PARP)
- Other HBOC genes like PALB2

B. DCIS: wide local excision with $\geq 2\text{mm}$ margin?

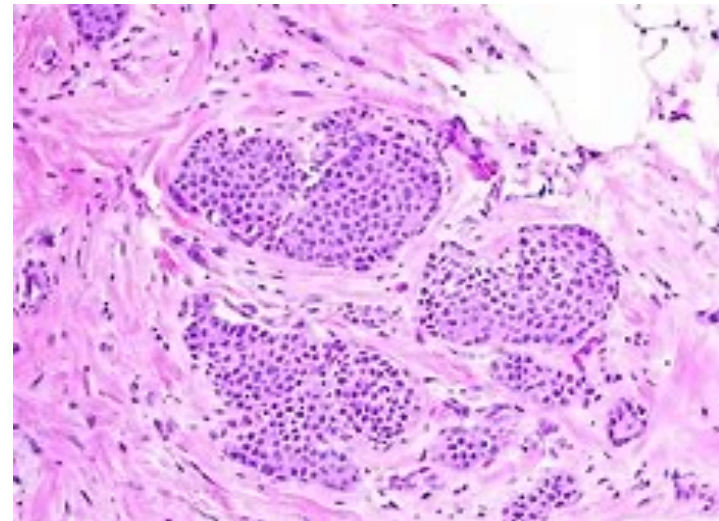
Breast Conservative Surgery for DCIS

PS01-06: The relationship between margin status $< 2\text{mm}$ and local recurrence in DCIS

S. Alsafi; Republic of Korea

PS01-10: Surgical margins & outcome are associated with increased recurrence and OS

JF Robertson; Nottingham and M Sibbering UH-Derby & Burton



Surgical margins for DCIS

2016 SSO-ASTRO-ASCO Consensus Guideline – 2mm margin

- Meta-analysis of 20 studies with 7883 pts: 2mm vs smaller significant less IBTR

The St. Gallen Consensus Conference on EBC

- 2017: 2 mm margins
- 2023: < 2mm & no ink on tumor + comedonecrosis = *BOOST (not if low risk DCIS)

2018 UK The National Institute for Health and Care Excellence (NICE)

- Not enough evidence to define optimal margin width between 0 and 2mm

2019 UK Association of Breast Surgery consensus statement:

- 1mm margin

*Chua et al Lancet 2022: BIG3-07/TROG07.01 RCT of WBI +/- boost in high-risk DCIS (4.4% benefit local relapse)

Morrow et al. Ann Surg Oncol 2016
NICE guideline.nice.org.uk/guidance/ng101.2018
Curigliano et al. Ann Oncol 2017; 2023

PS01-06: The relationship between margin status of <2mm and local recurrence in DCIS patients

Alsafi S, Lee SB, Kim J, et al.

PS01-10: Surgical margins in breast conserving surgery (BCS) for ductal carcinoma in-situ (DCIS) and clinical outcomes: significant associations with increased recurrence and overall survival

Robertston J, Sibbering DM, Ndebele-Mahati SG, et al.

	Alsafi et al.	Robertson et al.
Years	2000-2018	2003-2014
Number of patients	1,866	17,260 Info margins 13,867
0 < 2mm margin	824 (44%)	2784 (20%)
Radiation therapy	95%	59% (a lot 'unknown')

Median follow-up time was 8.2 yrs

Is 2mm the appropriate margin for DCIS?

- Alsafi et al.: local recurrence-free survival was not associated with margin width ($< 2\text{mm}$ vs $\geq 2\text{mm}$) if postop radiotherapy

If no RT, 10yr LR, margins $< 2\text{mm}$ = 16.4%; $\geq 2\text{mm}$ 5.5% (HR, 5.7; 95% CI, 1.106-29.46, $p=0.038$)

- Robertson et al.: shorter time to recurrence for any margin width $< 2\text{mm}$ compared to $\geq 2\text{mm}$
 - Improved overall survival with $\geq 2\text{mm}$ margin
 - Increased recurrence with more episodes of breast conserving surgery (>1 BCS in 19%)

Is 2mm the appropriate margin for DCIS?

Data support continued use of 2mm margins:

Importance of adjuvant therapies (ET + RT)

UZ Leuven:

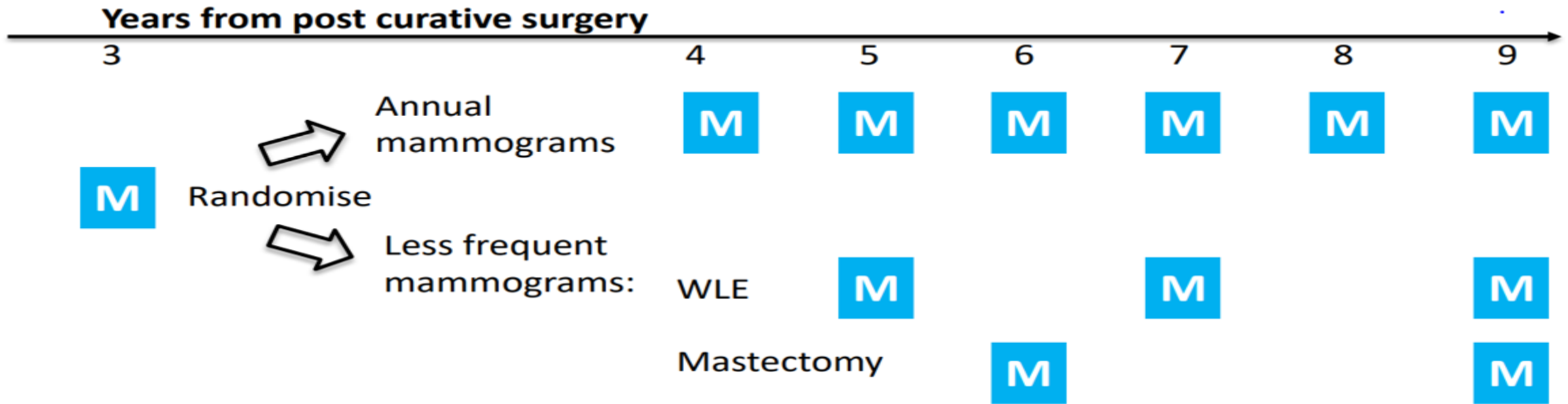
- no ink on DCIS (St. Gallen 2023)
- If limited pos margin extra boost or re-excision (MOC/COM decision)

GS03-02

Mammo-50

C. Mammographic surveillance in *EBC. Annual vs less frequent mammography: a non-inferiority trial in >50yrs with 3yrs DFS

Janet A. Dunn, University of Warwick, UK



Primary outcomes: **BCSS** & cost effectiveness

Secondary outcomes: **RFI** & OS

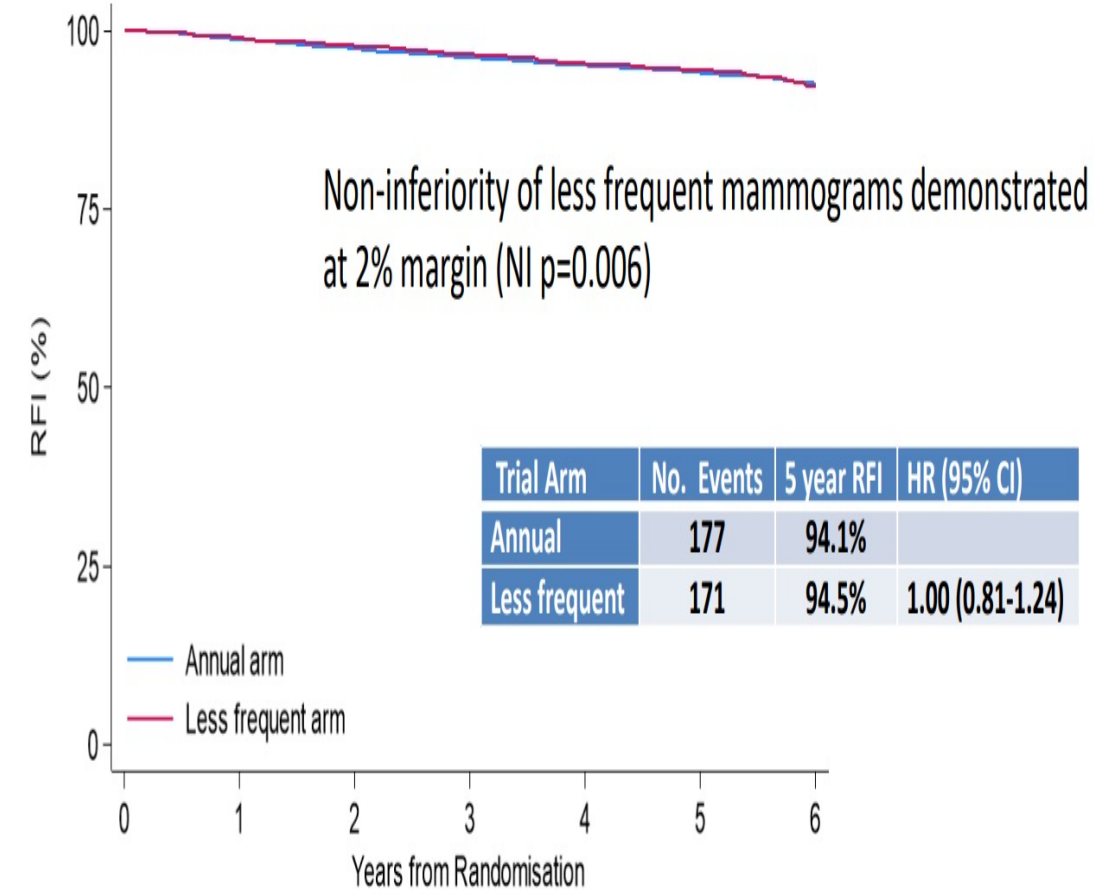
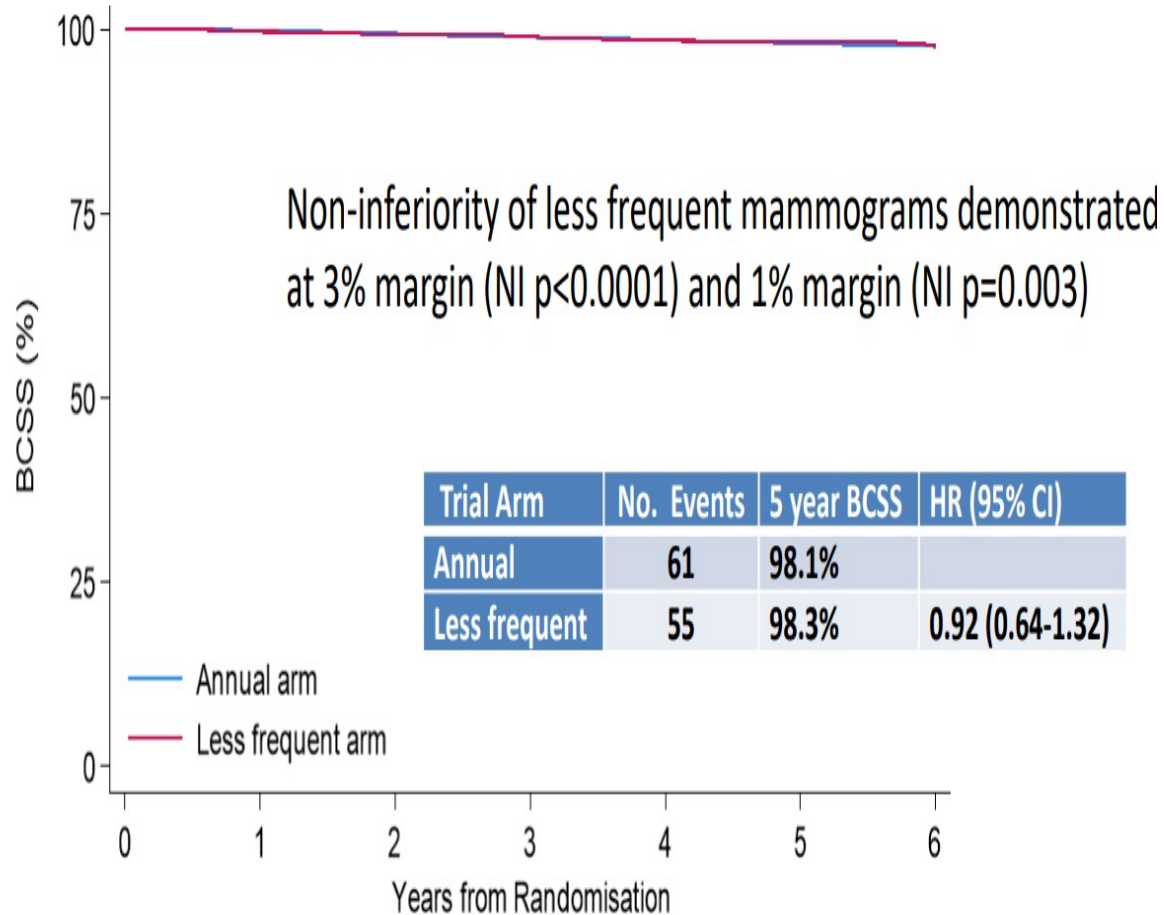
* Includes non-invasive disease

5000 women to detect:
3% absolute non-inferiority margin for BCSS
2% absolute non-inferiority margin for RFS
Median FU = 5.7 yrs

Median follow-up for alive patients 5.7 years (IQR 5.0-6.0 yrs);

Breast Cancer Specific Survival (BCSS)

Recurrence free interval (RFI)



Number at risk

	0	1	2	3	4	5	6
Annual arm	2618	2591	2554	2500	2426	1906	538
Less frequent arm	2617	2514	2456	2398	2307	1837	471

Number at risk

	0	1	2	3	4	5	6
Annual arm	2618	2563	2502	2439	2346	1835	515
Less frequent arm	2617	2494	2425	2353	2244	1779	442

Conclusions:

3yr post therapy in >50yrs, less frequent mammo is non inferior

Persistent moderate to high levels of stress in ¼

Need for ongoing survivorship support

These findings support change in clinical practice, ...

...there were many unanswered questions

UZ Leuven policies 'FU' adapted prior to SABCS 2023





Surgery of the primary tumor in patients with *de novo* metastatic breast cancer: a nationwide population-based retrospective cohort study in Belgium

Mariana Brandao et al.

2010-2014: 1985 pts, 534 (26.9%) in the “Surgery” and 1451 (73.1%) in the “No Surgery” group (alive at 9m).

Brussels 49%; Flanders 20%; Wallonia 34%

mOS Surgery vs No Surgery (adj HR 0.56; 0.49–0.64); **50% died within 5 yrs “Surgery”**

Propensity score matching (477 pts in each arm) = same findings (No Surgery/ Upfront = Late Surgery)

UZL 2014-2018 KCE cohort

173 / 2551 St IV (6.7%)

152 excluding wrong affiliation, wrong stage, prior diagnosis of breast or other cancer

- 21 **surgery** (13,8%; 1 BCS; most ‘oligo’); 6 died <5 yrs of diagnosis (**28.5%**)

-131 **no surgery** (86,2%)

-116 alive 9m after diagnosis;

-67/116 died <5 yrs (57.7%) **58/116 (50%) in ‘no surgery’ DOBC**

II. Evolution of axillary surgery: Is less safe?

Better screening, reduced LN burden, better systemic therapy, breast RT covers most of low axilla

1960-1980s

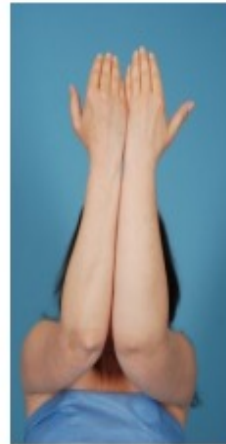
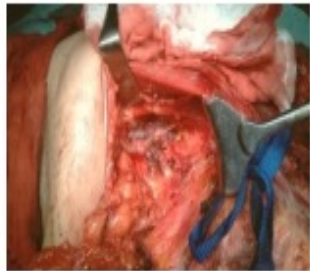
1990s

2000s

ALND

SLNB for
cN0

SLNB ± RT
for pN+



cT1-2N0 & pN1(sn)

[1-2 pos SLN]

Safe to omit ALND

Despite *13-35% pos LN left behind
10 yr FU: Axillary recurrence +/- 1%

(*)

ACOSOG Z0011 : 2010

IBCSG 23-01: 2013

EORTC AMAROS: 2014

SINODAR-ONE: 2022

Adapted
T. King & M. Morrow ,

4 new studies
SABCS 2023



II. Evolution of axillary surgery: Is less safe?

- **cN0 → pN1(sn)**

ALND to decide on syst Rx (nodal burden)

SINODAR-ONE PS01-04

- **cN0-1 → pN1(sn)**

Is SLN safe in more aggressive brca?

SENOMAC-trial GS02-06

- **cN1 → ycN0**

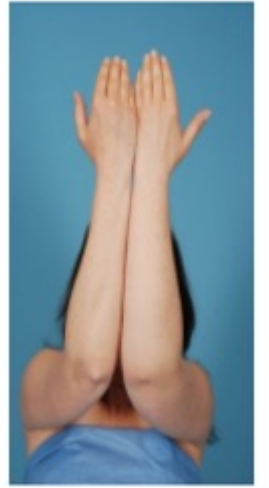
TAD versus SLN

NEOSENTITURK PS01-01

- **cN(0-)1 → ypN(i+)**

ALND is SOC; de-escalate?

OPBC05/EUBREAST-ICARO GS02-02



cN0, pN1(sn) : Total Nodal Burden: To dissect (ALND) or not to dissect?

PS01-04

The surgeon's perspective on the prediction of ≥ 4 LN metas in cT1-2N0 pts:

A comparative analysis of the per-protocol population of the **SINODAR-ONE** clinical trial

Damiano Gentile, Milan, Italy

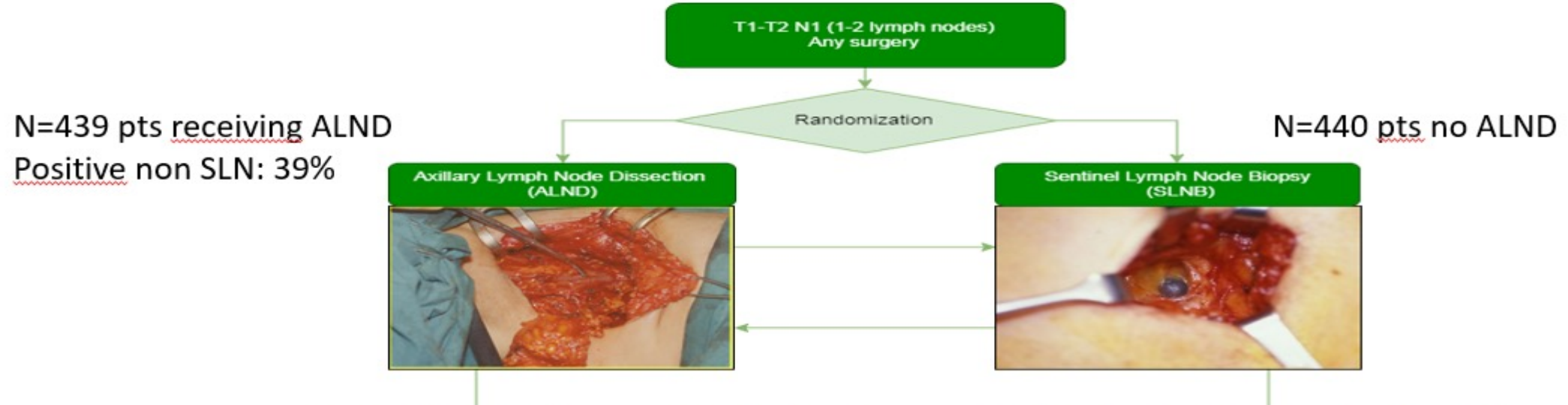


Study design: Multicenter RCT

Age 40-75 yrs
Unilateral inv breast cancer
cN0, <3 pos LN macro met

SINODAR
ONE

TNBC (20%), T2 (33%)
High grade
Mastectomy (20%)

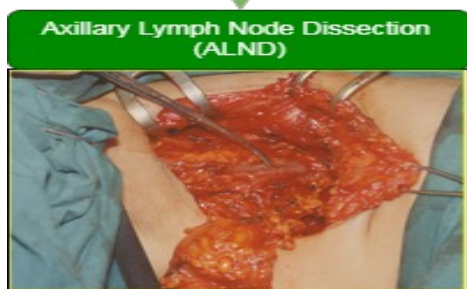


Adj Syst & Radiotherapy ~ institutional regimen: "Mostly standard tangient fields"
At FU (3 yrs) no difference in relapse nor survival

Results

SINODAR
ONE

N=439 pts completion ALND
Positive Non-SLN: 39%



T1-T2 N1 (1-2 lymph nodes)
Any surgery

	SINODAR-ONE Rate of pN2 among node positive patients
pN2	16%
ILC	26%
G3	46%
2+ SLNs	32%

Independent variables	Odds ratio (OR)	95% Confidence Interval (CI95%)	p-value
Lobular Carcinoma	4.185	1.284-1.443	0.041
G3	5.930	2.134-2.289	0.015
pT2	5.260	15.330-16.346	0.022
2 positive SLNs	13.188	1.179-1.280	<0.0001

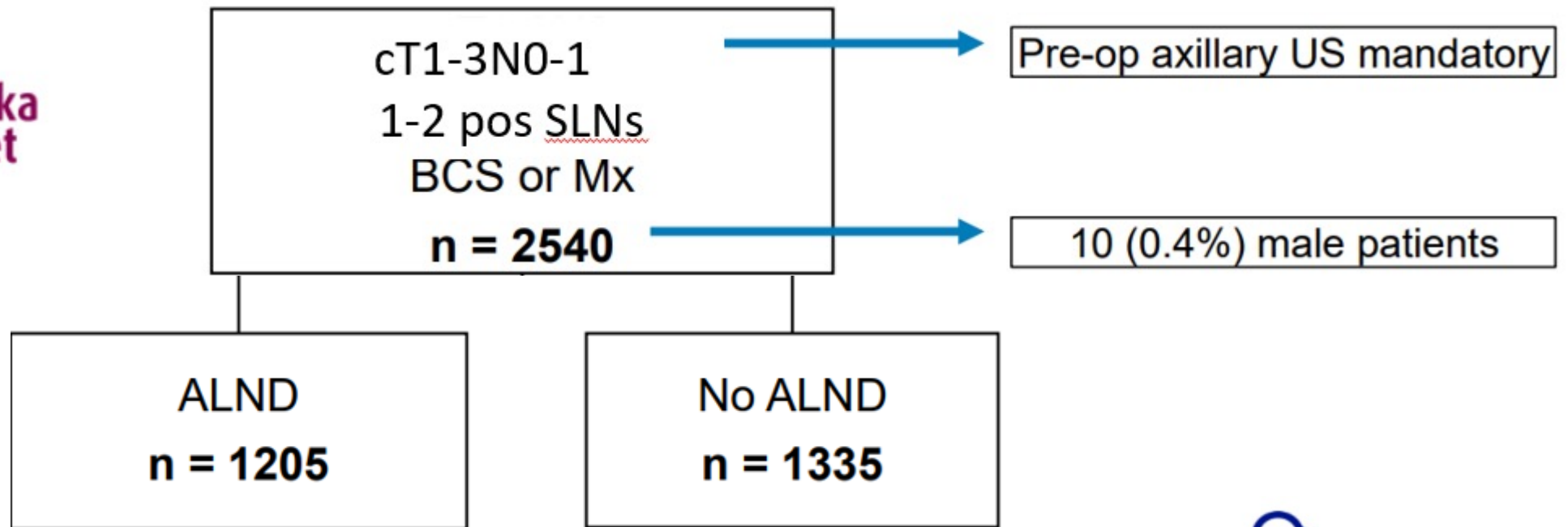
pN2: ACOSOG-Z0011 (13.7%); AMAROS (14%)

UZL: “Routine ALND not indicated for systemic Rx decisions”
cN0 pN1(sn) → Completion ALND: SLN macro + T >5cm or >2 + SLN

Is SLN safe in more aggressive brca? GS02-06

Recurrence free survival following pN1(sn) breast cancer without completion ALND First results of the international randomized SENOMAC non-inferiority clinical trial

Jana de Boniface, Stockholm, Sweden



Swedish Research Council



SENOMAC Consort Diagram

Prim Endpoint: OS

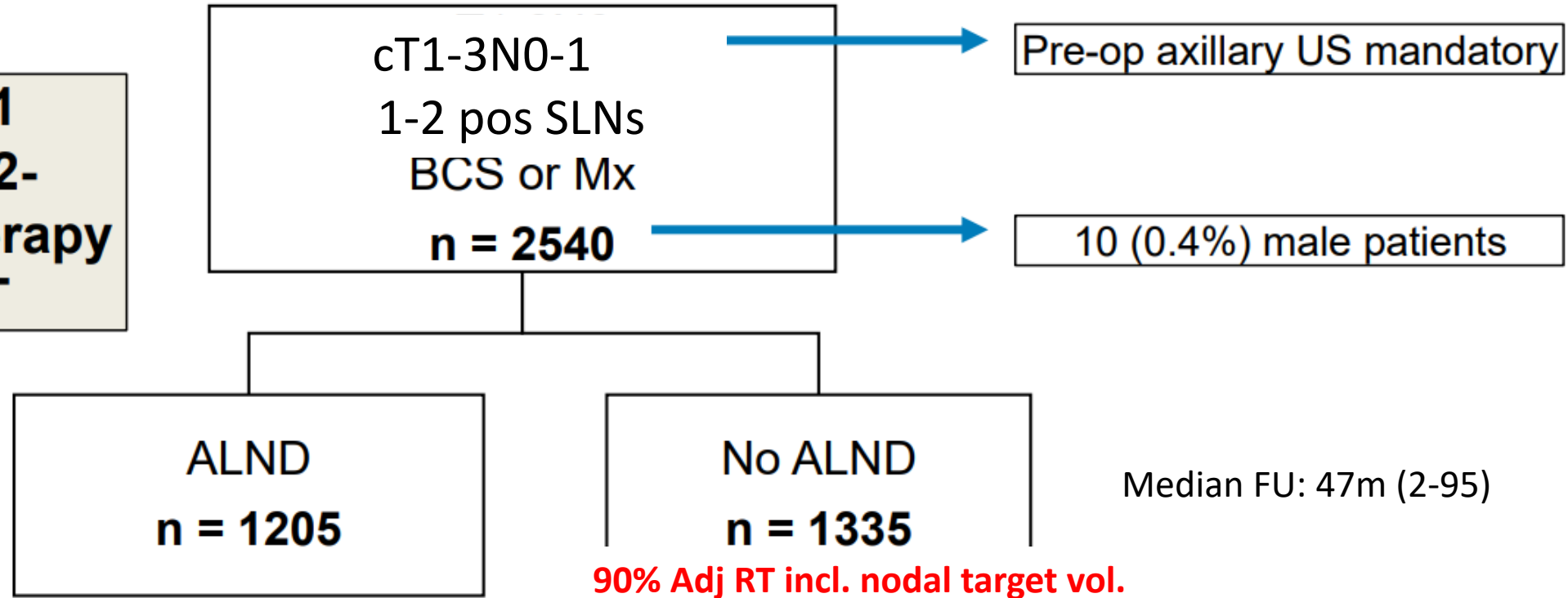
Sec Endpoint: RFS

2.5% non-infer margin

HR 0.90 and CI < 1.44

190 events / 3000pts

Median age 61
87% HR+/HER2-
99% systemic therapy
88% nodal RT



How is SENOMAC different from Z0011 and AMAROS?
Enrolled male patients!, 6% had cT3 tumors, 34% had mECE, 1.4% had positive FNA, and a large number mastectomy patients enrolled (n = 920, 36%)

Results: Axilla

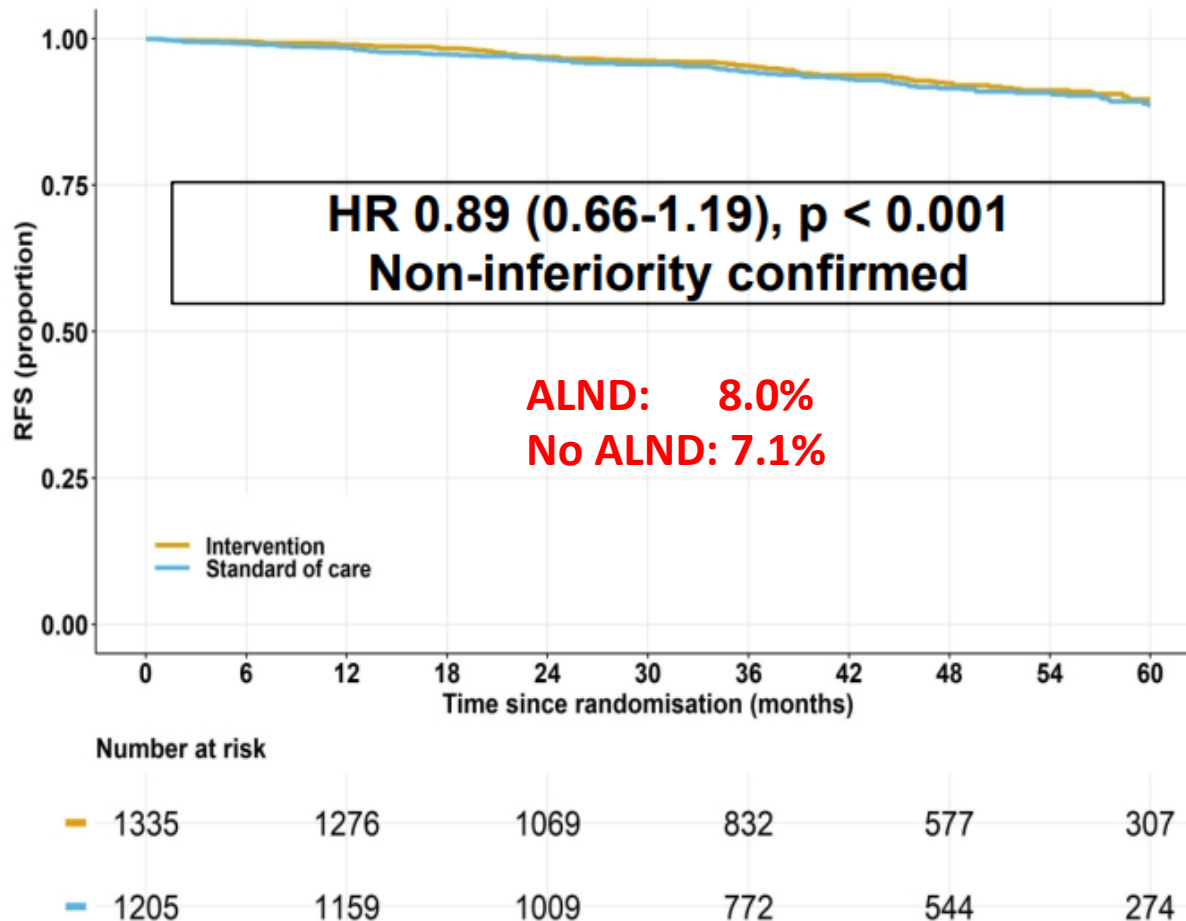
- Non-sentinel lymph node (SLN) metastases on axillary dissection in 403 patients (34.5%)
 - If 1 SLN met: 31.3%
 - If 2 SLN met: 51.3%
- Pathological nodal stage (primary surgery)

	Standard of Care	Intervention
pN1	1016 (84.3%)	1311 (98.2%)
pN2	116 (9.6%)	7 (0.5%)
pN3	35 (2.9%)	0 (0%)

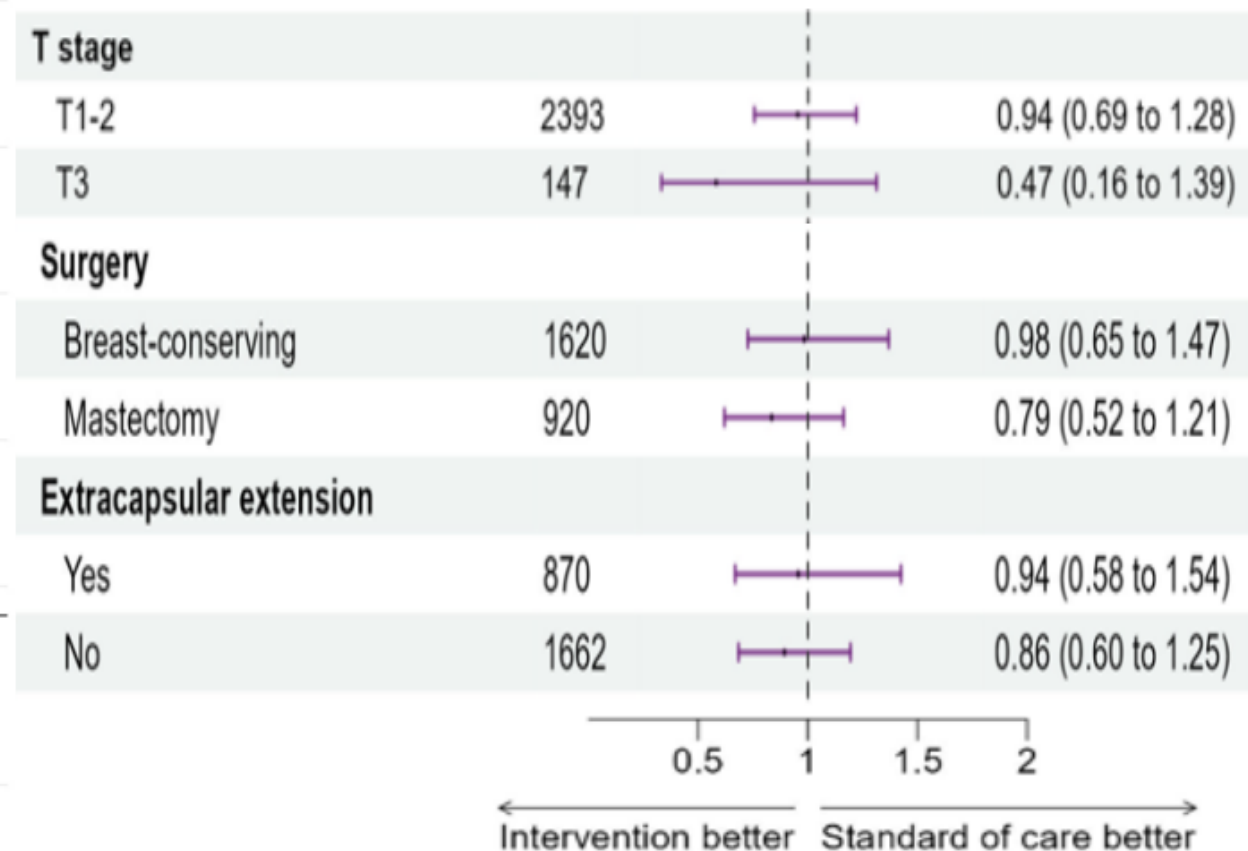
SENOMAC Confirmed Safety of SLNB + RT for Patients with 1-2 Positive SLNs

PRO: The Breast; 63; 2022

Recurrence-Free Survival (events)



Subgroup Analyses



Narrow CI, significantly below non-inferiority margin, suggests ROBUST data

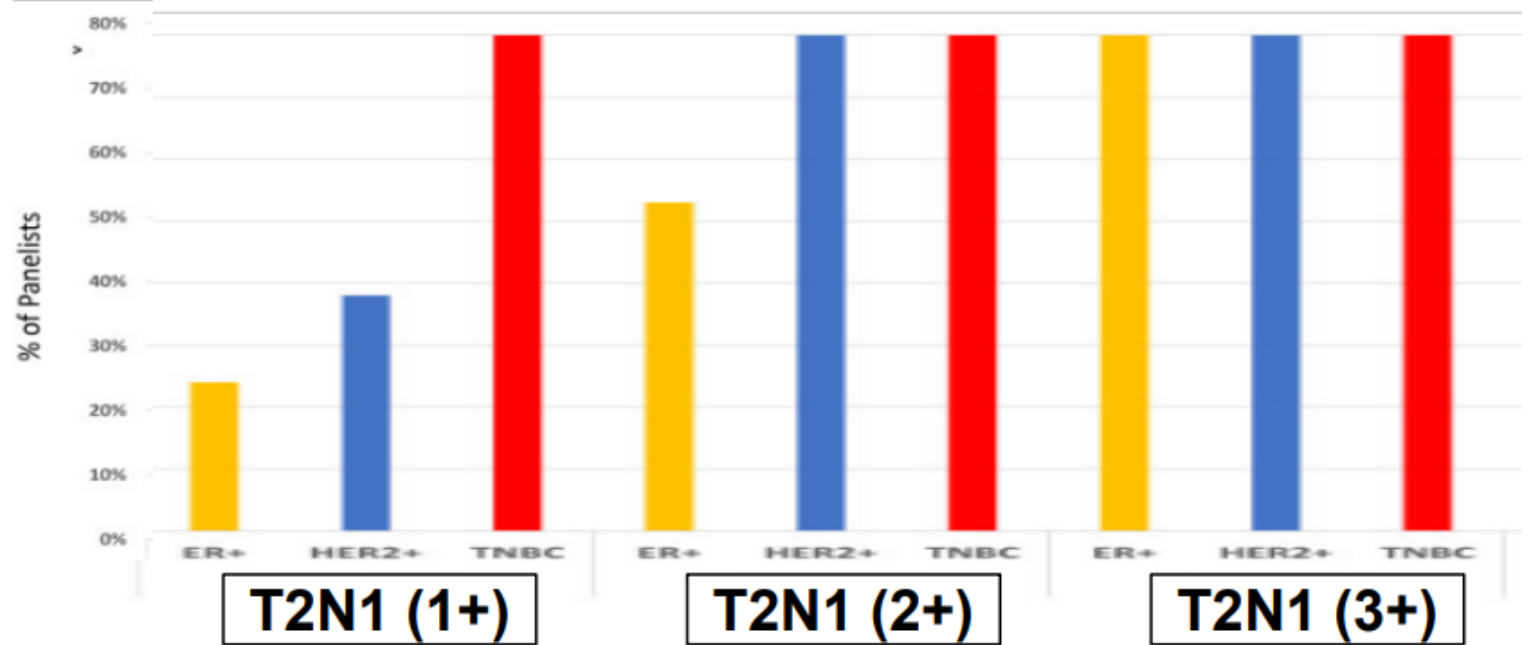
CONCLUSION SENOMAC

Offers solutions for patients not included in ACOZOG; IBCSG; AMAROS; SINEDOR



All patients with pN1 disease are recommended for PMRT +/- Nodal RT

Curigliano G, Ann of Oncol, 2023



St Gallen 2023: Wide variation in recommendations for PMRT in pN1 patients

cN0-1 (FNAC+)
≤2 SLN (macro)

If AxRT, no ALND if ME, pT3, grade 3, mECE
If no PMRT, should we perform ALND or AxRT?

Are There Low-Risk Patient Subsets with 1-2 Positive SLNs Who Can Avoid Axillary Treatment?

TAILOR RT/MA.39
Accrual began Oct 2018

**T3N0 or 1-2 positive SLNs or
1-3 positive nodes [ALND]
ER+/HER2 –
Oncotype ≤ 25**

n = 2140

**BCS: WBI / ME: PMRT
RT to regional nodes**

**BCS: WBI
Mastectomy: no RT**

T-Rex
March 2023-Dec 2028

**T1-2, 1-2 SLN macromets
Unifocal or multifocal
ER+/HER2 –**

n = 1350

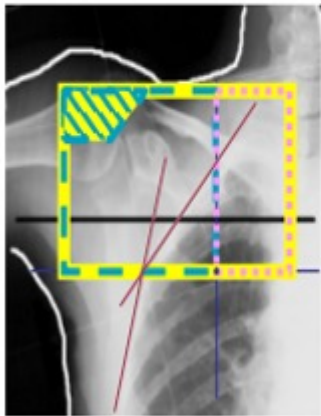
**BCS: WBI / ME: PMRT
RT to regional nodes**

**BCS: WBI
Mastectomy: no RT**

II. Evolution of axillary surgery if cN1 → NACT: Is yp0(sn) safe?

2010s

SLNB for cN1
after NAC



Adapted from T King, MD and M Morrow, MD

cN1 → ycN0 → ypN0(sn)

2013-2019

N=1701

SLN + ALND

ACOSOG Z1071

SENTINA

SN-FNAC

GANEA

FNR SLN >10% (H&E)
+ 2.5- 8.4% (IHC)

If Dual Tracer + ≥ 3SLN
FNR 4.9% - 9.1% (H&E)

If SLN + clipped node (TAD)
6.8% (ACOSOG Z1071)

PS01-01:

*NEOSENTITURK-study

2358 pts; 1179 cN1-3 → ypN0(sn)

28m FU 0.3% Ax Recurrence

Updated SABCS 2023

Prospect, non-RCT, cN+, 'ycN0'
SLN (n=620) vs TAD (n=356)

If ypN0; n° removed LN

**TAD, 4.2±1.9 vs
SLNB 3.9±1.9, p=0.034**

Omission of ALND in cN+ → ypN- : Oncologic Outcomes

Study (Year)	Yrs of Study	cN+→cN0 (n)	Axillary Surgery Technique	pN0 no ALND	Axillary RT	Median f/u	Ax recurrence rate	Distant recurrence rate
MSKCC (2020)	2014-2019	555	SLNB with ≥3 SLN	234	78%	35mo	1 (0.4%)	4-yr distant recurrence rate = 6.1%
Milan (2016)	2000-2010	147	SLNB (0% DT)	70	35%	61mo	0	Absolute distant recurrence rate = 12.8%
Mayo (2020)	2009-2019	315	SLNB	159	78%	34 mo	1 (0.6%)	NR
Montreal (2020)	2013-2018	132	SLNB (100% DT)	60	71%	36mo	0	5-yr distant recurrence rate = 13.7%
EUBREAST-06 (SABCS 2022)	2014-2020	666	SLNB (100% DT)	666	74%	NR	0.8% at 4 yrs	5-yr any invasive recurrence rate = 7.8%
EUBREAST-06 (SABCS 2022)	2014-2020	478	TAD	478	78%	NR	0.5% at 3 yrs	5-yr any invasive recurrence rate = 7.3%
NEOSENTITURK (SABCS 2022)	2018-2020	2358	SLNB or TAD	1179	100%	28mo	0.3% at 3 yrs	NR

NEOSENTITURK was updated during SABCS 2023

2024 SOC cN1 → ycN0 = ypN0 (SN/TAD) = no ALND & excellent short term outcome

Barrio A, et al. JAMA Oncol. 2021;7:1851-1855
 Galimberti V, et al. Eur J Surg Oncol. 2016;42:361-368
 Pittin MA, et al. Ann Surg Oncol. 2020;27:4795-4801
 Wong S, et al. Ann Surg Oncol. 2021;28:2621-2629
 Montagna G, et al SABCS 2022
 Caboglu N et al. SABCS 2022

II. Evolution of axillary surgery if ypN0(i+) → Is no-ALND safe?

- **cN(0-)1 → ypN0(i+)** GS02-02

ALND is SOC; de-escalate?

ALND = currently 'the standard'
ypN1mi: 37-56%
ypN1: 62-64%
ypN0(i+): ? (few cases)

- Residual isolated tumor cells (ITCs) are found in ~ 1.5% of patients undergoing NACT
- Data on the likelihood of finding additional + LN in pts with residual ITCs are scarce, and the benefit of ALND is unclear

	ACOSOG Z1071	SN FNAC	MSKCC	OVERALL
ITCs	4/11	4/7	1/6	9/24 (37.5%)

Are nodal ITC in SLN after NACT (ypN0(i+)) an indication for completion ALND? Results from ICARO, a retrospective multicentre cohort study with ITC on SLN after NACT

Giacomo Montagna, MSKCC, NY, USA

The OPBC05/EUBREAST-14R/ICARO study

- To determine how often additional + LNs are found in patients with residual ITCs in SLN
- To evaluate rates of axillary and any invasive recurrence
- To compare outcomes in patients treated with and without ALND



*EUBREAST Network is a charitable independent no profit organization aimed at promoting international research in the field of breast cancer surgery

Study Population

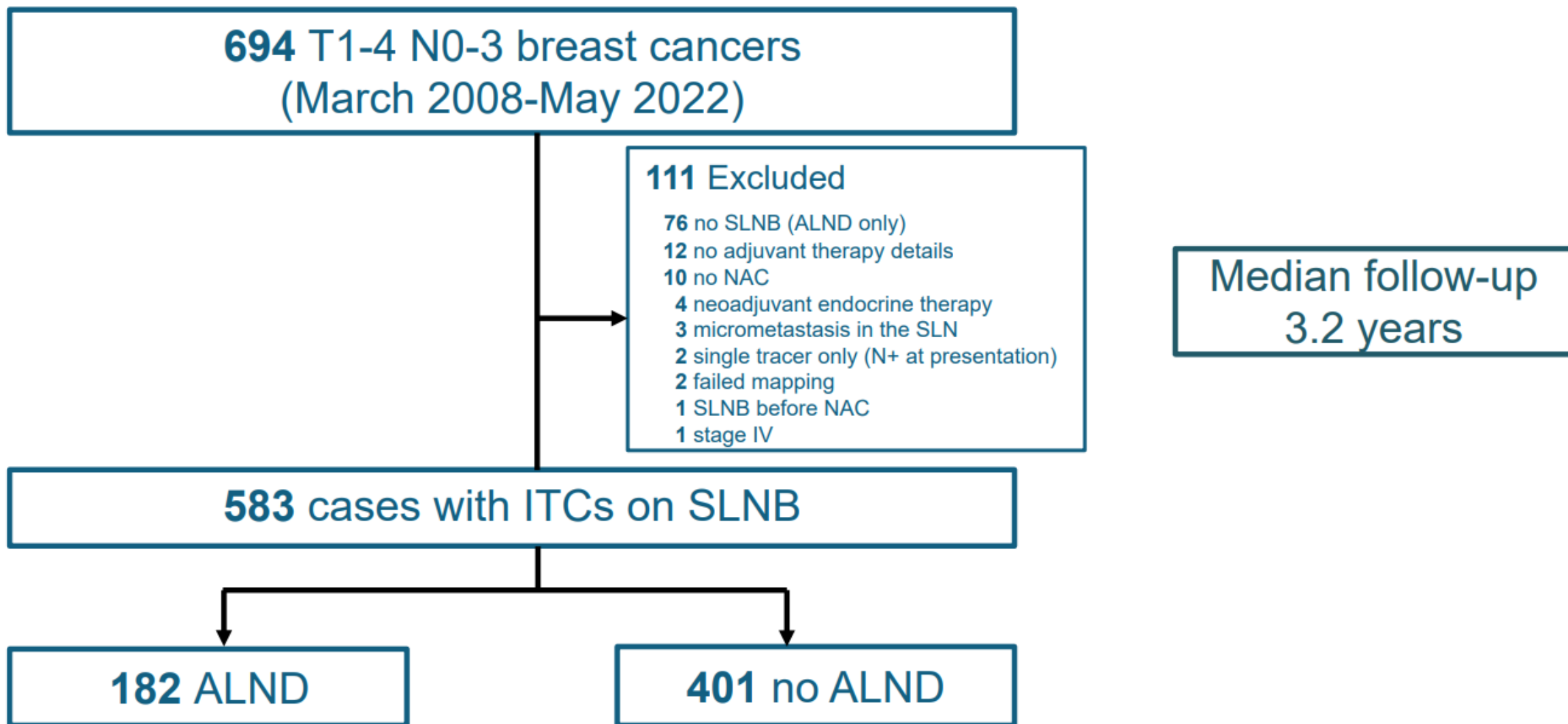
Inclusion criteria

- T1-4 N0-3 BC patients
- Surgery after NAC with detection of ITCs [ypN0(i+)] at frozen section or final pathology
- SLNB performed with dual-tracer mapping or TAD or MARI for N+ and with single tracer for N0
- Detection of ITCs by H&E or IHC

Exclusion criteria

- No SLNB/TAD
- Inflammatory breast cancer
- Stage IV
- NET
- Detection by OSNA (quantitative measurement of target mRNA due to lack of standardized cut-off)

Flow Diagram



Characteristics of 583 pts SLN/TAD(itc): Mean age 48-49yrs; 90% frozen section; CT comparable

No ALND

n= 401

- 93% cN0 (30%) or cN1 (63%)
- 88% ductal
- 32% TNBC or HER2 pos
- 24% LVI pos
- 48% TAD / MARI if cN+
- 3.5 SLN removed
- 8% SLN ITC Frozen section 8%
- 75% Nodal; 78% Chest Wall RT

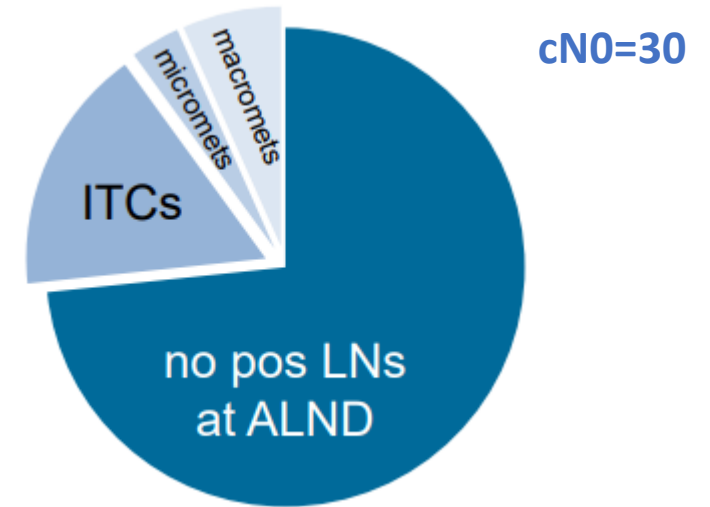
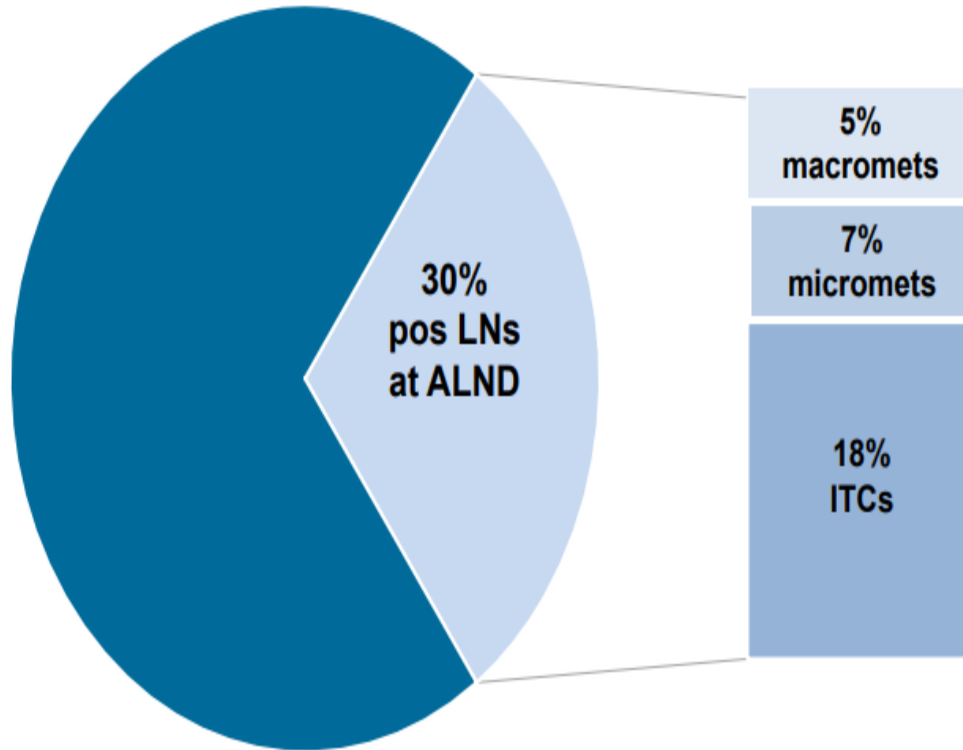
ALND

n= 182

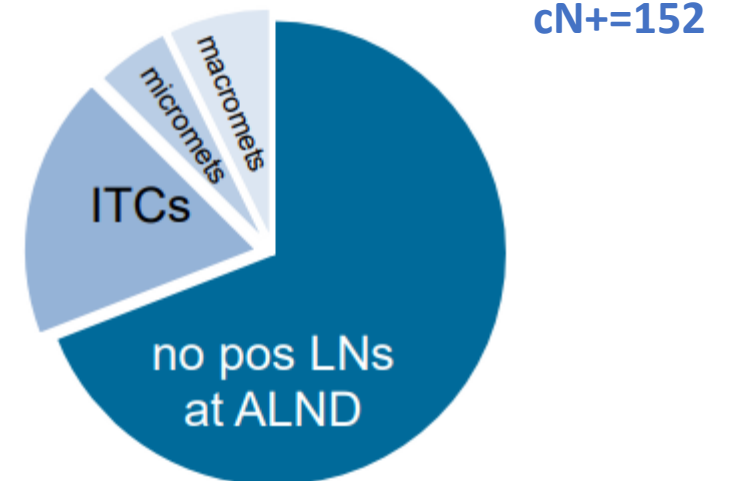
- 83% cN0 (16%) or cN1 (67%)
- 92% ductal
- 28% TNBC or HER2 pos
- 38% LVI pos
- 31% TAD / MARI if cN+
- 2.8% SLN removed
- 62% SLN ITC Frozen section
- 82% Nodal; 89% Chest Wall RT

If ALND: More ITC+ perop (frozen sections) and more nodal/ chest wall RT

Additional Positive Nodes in 182 pts undergoing cALND



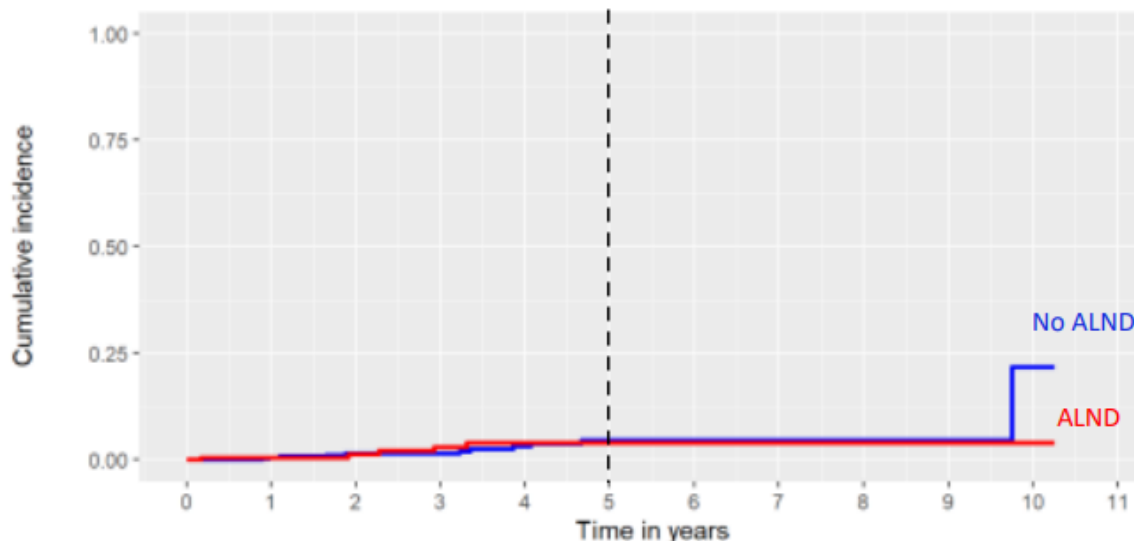
Additional pos LNs at ALND
27% (cN0) vs 31% (cN+), p = 0.6



Axillary Recurrence (No ALND vs ALND)

Isolated or Combined with Local and Distant Recurrence

5-year rate of any axillary recurrence
no ALND vs ALND
4.6% vs 4.1%, p = 0.8

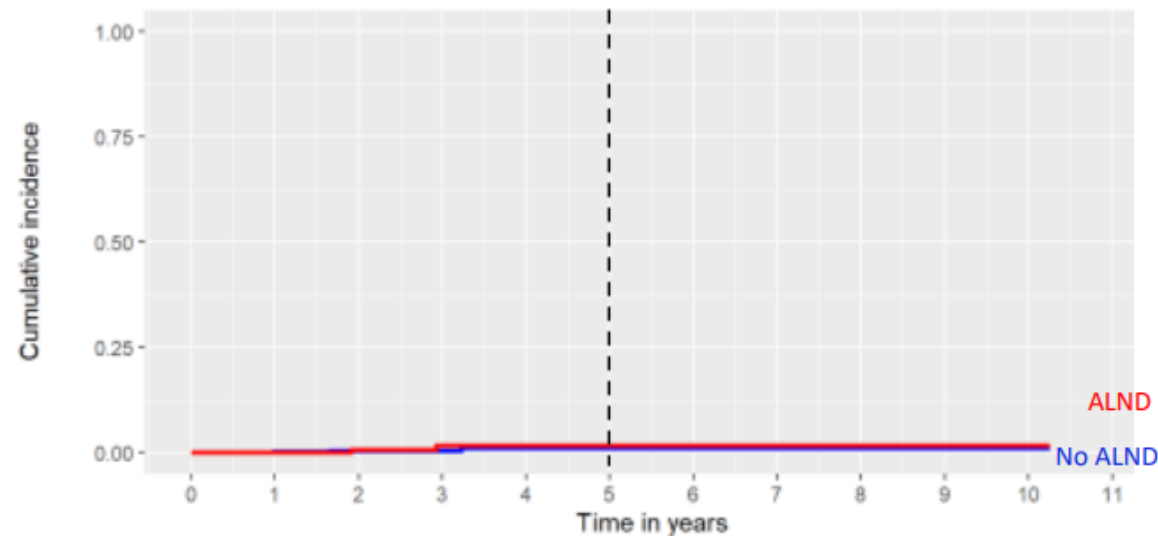


Number at risk

Strata	No ALND	401	349	266	187	131	73	45	21	10	6	3	3
ALND	182	165	126	95	67	49	36	19	13	10	5	3	

Isolated

5-year rate of isolated axillary recurrence
no ALND vs ALND
1.1% vs 1.7%, p = 0.7



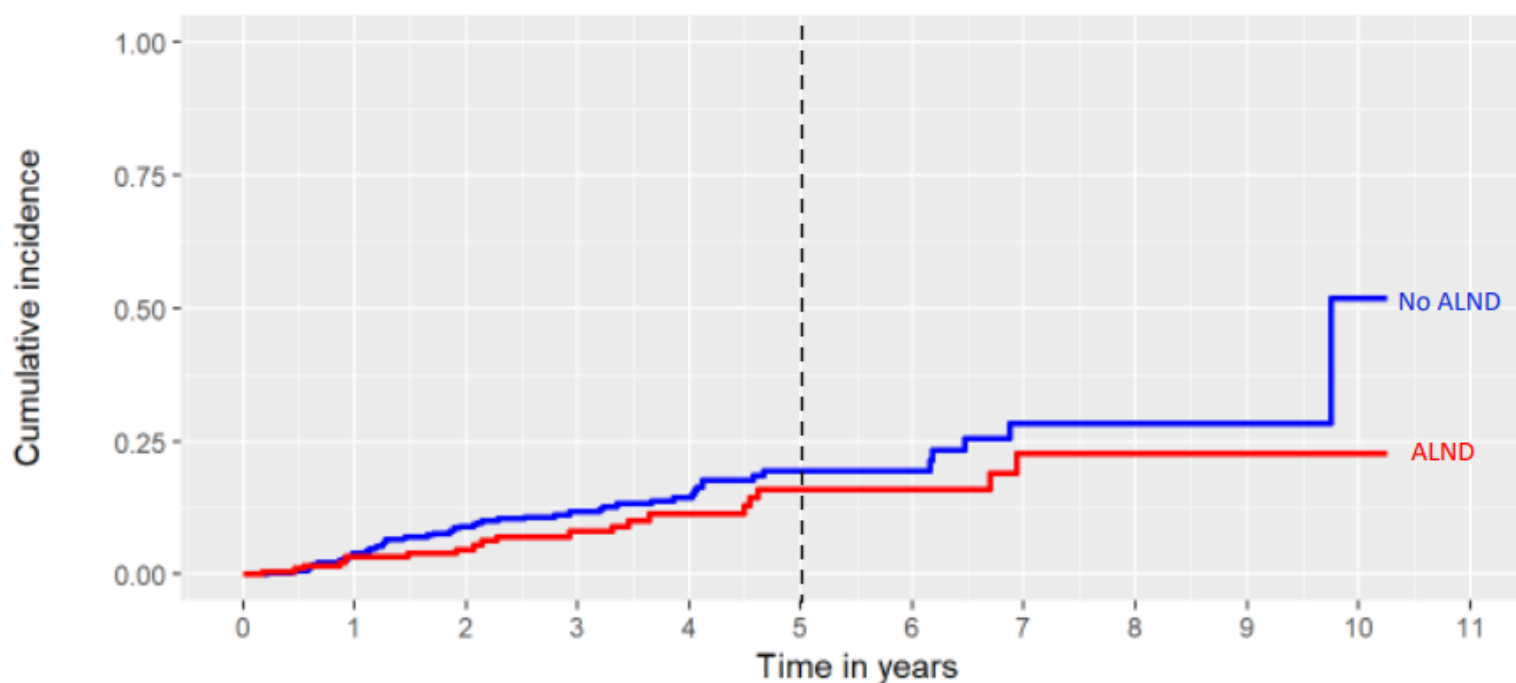
Number at risk

Strata	No ALND	401	349	266	187	131	73	45	21	10	6	3	3
ALND	182	165	126	95	67	49	36	19	13	10	5	3	

Any Invasive Recurrence (No ALND vs ALND)

3.2 yrs of FU

5-year rate of any invasive recurrence no ALND vs ALND
19% vs 16%, p = 0.13



Number at risk

Strata		0	1	2	3	4	5	6	7	8	9	10	11
No ALND		401	349	266	185	129	71	43	20	9	5	2	2
ALND		182	165	127	95	68	50	37	19	13	10	5	3

Strengths and Limitations

Strengths

- First study to compare outcomes in patients with residual ITCs treated with and without ALND
- Large number of patients to examine residual nodal burden in patients with ITCs
- Multicenter
- All settings (public, private, academic, and community hospitals)

Limitations

- Retrospective
- Relatively short median follow-up (3.2 years)
- Pathological assessment was not standardized

The no-ALND arm: Lower risk patients

- Less LN-pos; less LVI

- Less RT

- Less per-op FS

Conclusions

401 ITC in SLN without ALND
“No Longer Rare cases”

- ICARO dataset is the largest to date looking at ITCs in SLN
 - The likelihood of finding additional +LN if ITC's is lower than in pts with residual micro- and macrometastases; 5% in this series
 - No impact of nodal status at presentation
 - Detection ITCs on frozen section was strongly associated with ALND
 - Rates of axillary and invasive recurrence did not differ based on the use of ALND

Real world data

“pragmatic evidence to stop looking for ITC (FS needed post NACT)”