Mammary Fold Webinar

(February 2026)

San Antonio Breast Cancer Symposium

(December 9 – 12, 2025, San Antonio, Texas)

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Introduction

- 48th Annual San Antonio Breast Cancer Symposium

- **10,000** clinicians and scientists from **80** countries
- Range of presentations and keynote talks covering:
  - breast cancer screening and prevention
  - loco-regional and systemic therapies
  - basic science/translational medicine
  - educational sessions interspersed

SAN ANTONIO BREAST CANCER SYMPOSIUM®

UT Medicine CTRC Health Science Center San Antonio | AACR American Association for Cancer Research | Baylor College of Medicine

- **2,249** abstracts accepted for poster presentations (c.f. **1,887** for 2023)

Introduction

- **Educational sessions** → fully integrated into main program with parallel sessions

- Provide *foundational* knowledge as well as *updates* on cutting edge translational research (potentially practice changing)

- Programme Committee **broad representation** from:
  - senior clinicians
  - scientists
  - patient advocates with emphasis on quality of life

- Facilitates comprehensive approach with focus on standards of clinical care and survivorship issues → *patient-centric* philosophy

William L. McGuire Award Lecture – The Bumpy Road to Progress: Changes in the Management of the Axilla

[Armando Giuliano, CEDARS SINAI MEDICAL CENTER, LOS ANGELES]

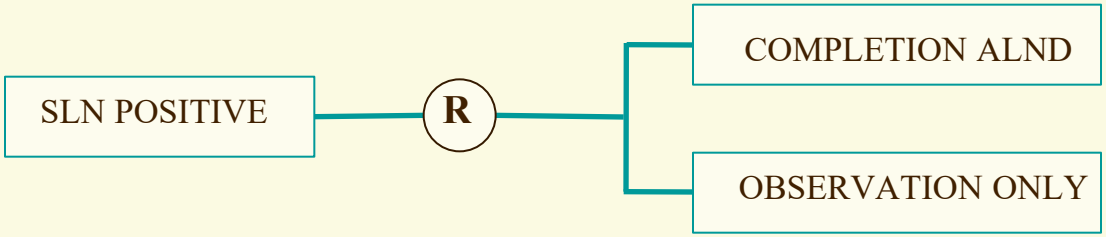
- **Pioneer** in transforming surgical management of the axilla in early-stage breast cancer patients:
  1) Introduction of sentinel lymph node biopsy techniques for clinically node negative patients
  2) Conception and execution of seminal ACOSOG Z0011 trial

- **Surgical resection** of malignant nodal tissue → basic *tenet* breast cancer surgery for 100 years since Halsted's **radical mastectomy**

- **Z0011** trial → proposed *omission* axillary lymph node dissection in **biopsy-proven** node positive disease in context of primary surgery (based on failure of NSABP-B04 trial to show survival advantage for ALND)

Omission of axillary dissection

- **ACOSOG Z0011** trial randomized ~**900** SLN biopsy positive patients (macro-/micrometastases [**1-2**]) to completion ALND or observation only [www.acosog.org/studies/organ]



- All patients underwent BCS and received whole breast irradiation and systemic therapy (hormonal therapy [46%] or chemotherapy [57%] of physicians choice)

- No difference in either loco-regional recurrence or overall survival between 2 arms (incomplete accrual and f/u only 6yrs) [GUILIANO A et al. 2011]

William L. McGuire Award Lecture – The Bumpy Road to Progress: Changes in the Management of the Axilla [Armando Giuliano, CEDARS SINAI MEDICAL CENTER, LOS ANGELES]

- **Z0011** trial considered almost **heretical** and even **unethical** by professional colleagues, patients and advocates:
  - generated strong **opinions/emotions** amongst clinicians (surgeons and medical oncologists)
  - reluctance to **participate** in trial and provide patients (recruitment challenges/poor accrual)
  - trial was **'hated'** by many
  - **personal** impact of vehement opposition (mental well-being)

- **Steadfast** in belief that *omission* of completion ALND → would *not* compromise overall survival of patients
  - permit **less extensive** surgery and better quality of life
  - emphasized that NSABP B-04 trial included **node positive** patients
  - Z0011 recruited pathologically node positive patients – confirmed with SLNB

William L. McGuire Award Lecture – The Bumpy Road to Progress: Changes in the Management of the Axilla [Armando Giuliano, CEDARS SINAI MEDICAL CENTER, LOS ANGELES]

- **Z0011** came close to being abandoned by Guiliano as the *'hated'* trial*
- Initial results confirmed statistical **non-inferiority** for omission of completion ALND
- Trial continued but failed to reach accrual target (approximately **50%**)
- Results of trial published in *New York Times*

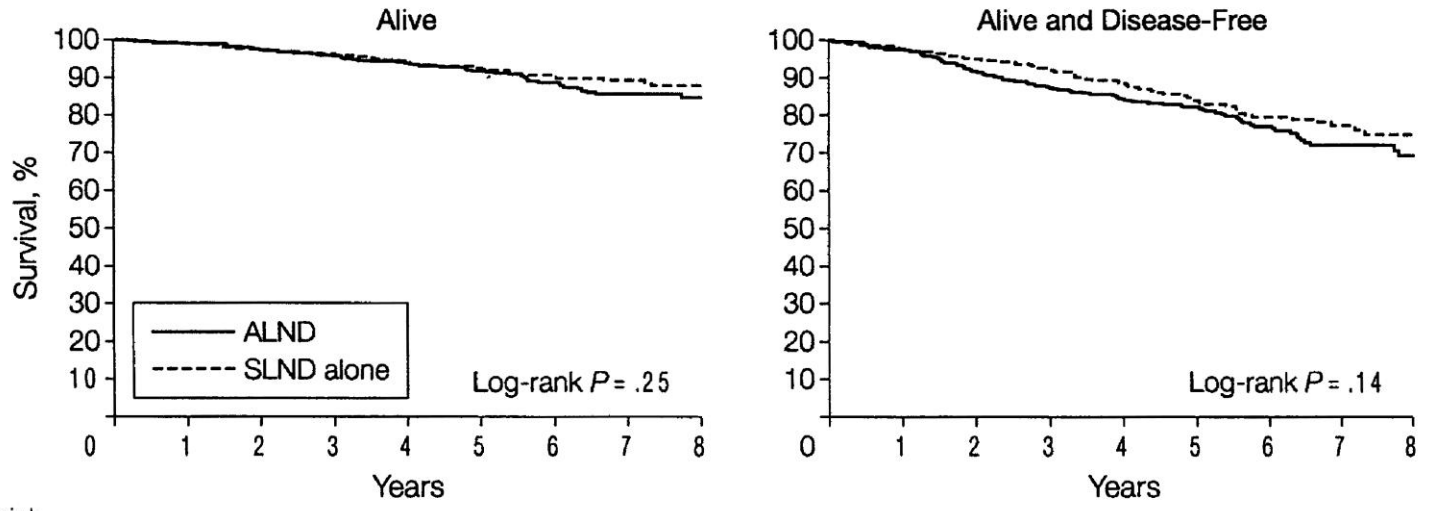

The New York Times

- Physicians need **data** to change practice – preferably ***randomized***!

* Surgeons conditioned by experience to minimize risk – innately averse to change

William L. McGuire Award Lecture – The Bumpy Road to Progress: Changes in the Management of the Axilla [Armando Giuliano, CEDARS SINAI MEDICAL CENTER, LOS ANGELES]

Figure 2. Survival of the ALND Group Compared With SLND-Alone Group



ALND indicates axillary lymph node dissection; SLND, sentinel lymph node dissection.

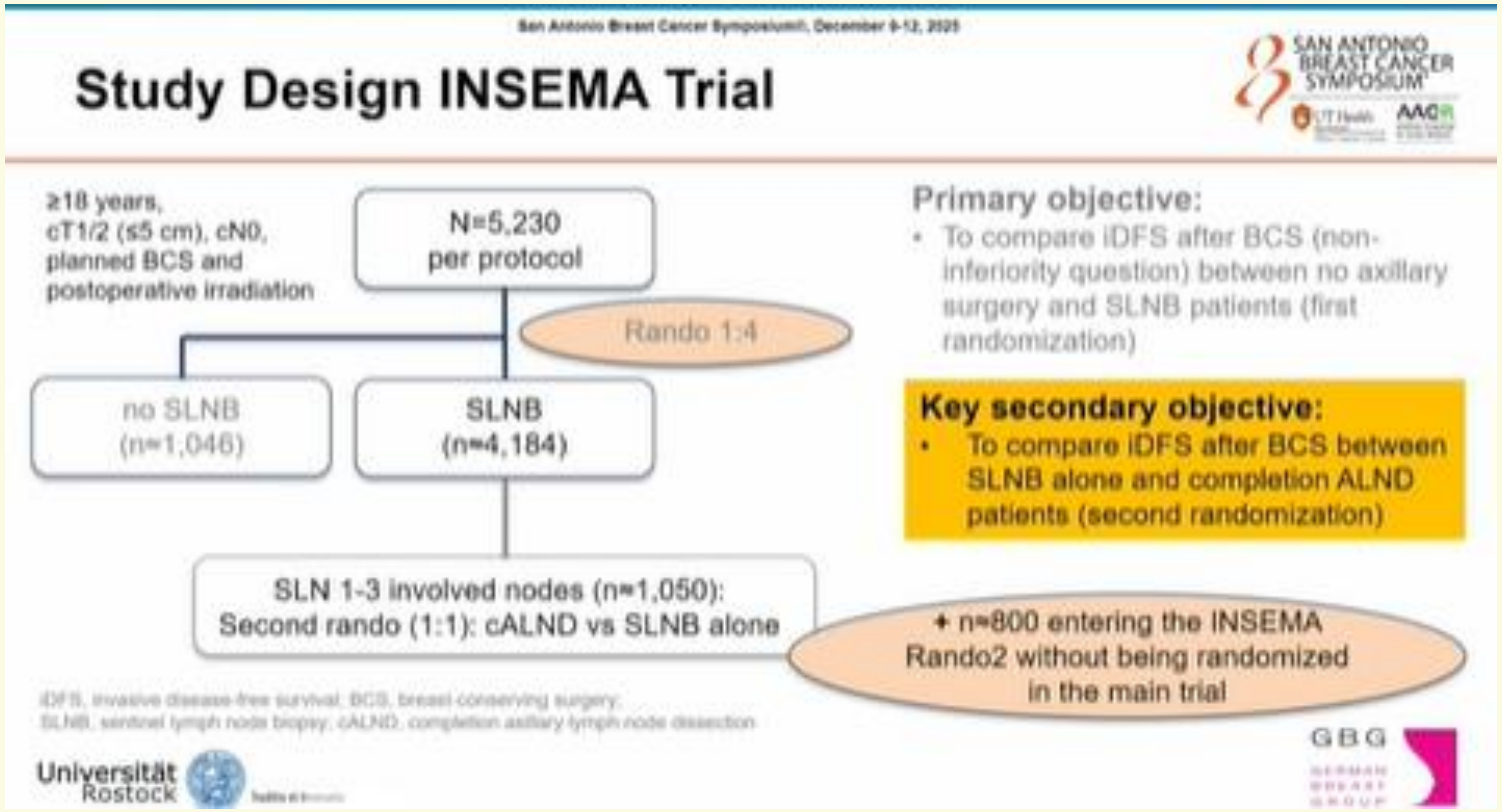
GS2-02 – Axillary surgery in breast cancer patients with one to three sentinel node macrometastases and breast conserving surgery [Toralf Reimer, UNIVERSITY OF ROSTOCK, GERMANY]

- **INSEMA** - randomized trial → investigating omission of *SLN biopsy* in clinically node negative patients (**T1-2** (≤5cm), **N0**) with outcome and quality-of-life data (n=**5502**)

- Multi-center **non-inferiority** trial with → primary objective of comparing invasive DFS after BCS between *SLN biopsy* and *no SLN biopsy* (1:4) [Reimer T et al. Geburtsh Frauenheillk 2017; 77: 149 - 157]

- Secondary randomization for *SLN biopsy* positive patients (n=**485**):
  - *SLN biopsy alone* versus *SLN biopsy + ALND* → (1:1allocation)
  - secondary objective invasive DFS for *SLN biopsy* alone versus with *ALND*

GS2-02 – Axillary surgery in breast cancer patients with one to three sentinel node macrometastases and breast conserving surgery [Toralf Reimer, UNIVERSITY OF ROSTOCK, GERMANY]



GS2-02 – Axillary surgery in breast cancer patients with one to three sentinel node macrometastases and breast conserving surgery [Toralf Reimer, UNIVERSITY OF ROSTOCK, GERMANY]

- Results of primary randomization ⟶ presented at **San Antonio Breast Cancer Symposium** (2024) at median follow up **73.6** months [Reimer T et al. NEJM 2024; doi:10.1056/NEJM/oa2412063]

- Estimated 5 year **invasive DFS** similar for SLN biopsy (**91.7%**) and no SLN biopsy (**91.9%**) groups [HR 0.91*; 95% CI 0.73 – 1.14]

  Omission of SLN biopsy declared ***non-inferior*** to SLN biopsy and concordant with results of **SOUND** trial [Gentilini O et al. JAMA Oncol 2023]

- Lower incidence of **arm symptoms** including lymphedema (**1.8%** v **5.7%**), upper limb morbidity (**2.0%** v **3.5%**), and pain (**2.0%** v **4.2%**)

- *Hazard ratio below pre-specified non-inferiority margin

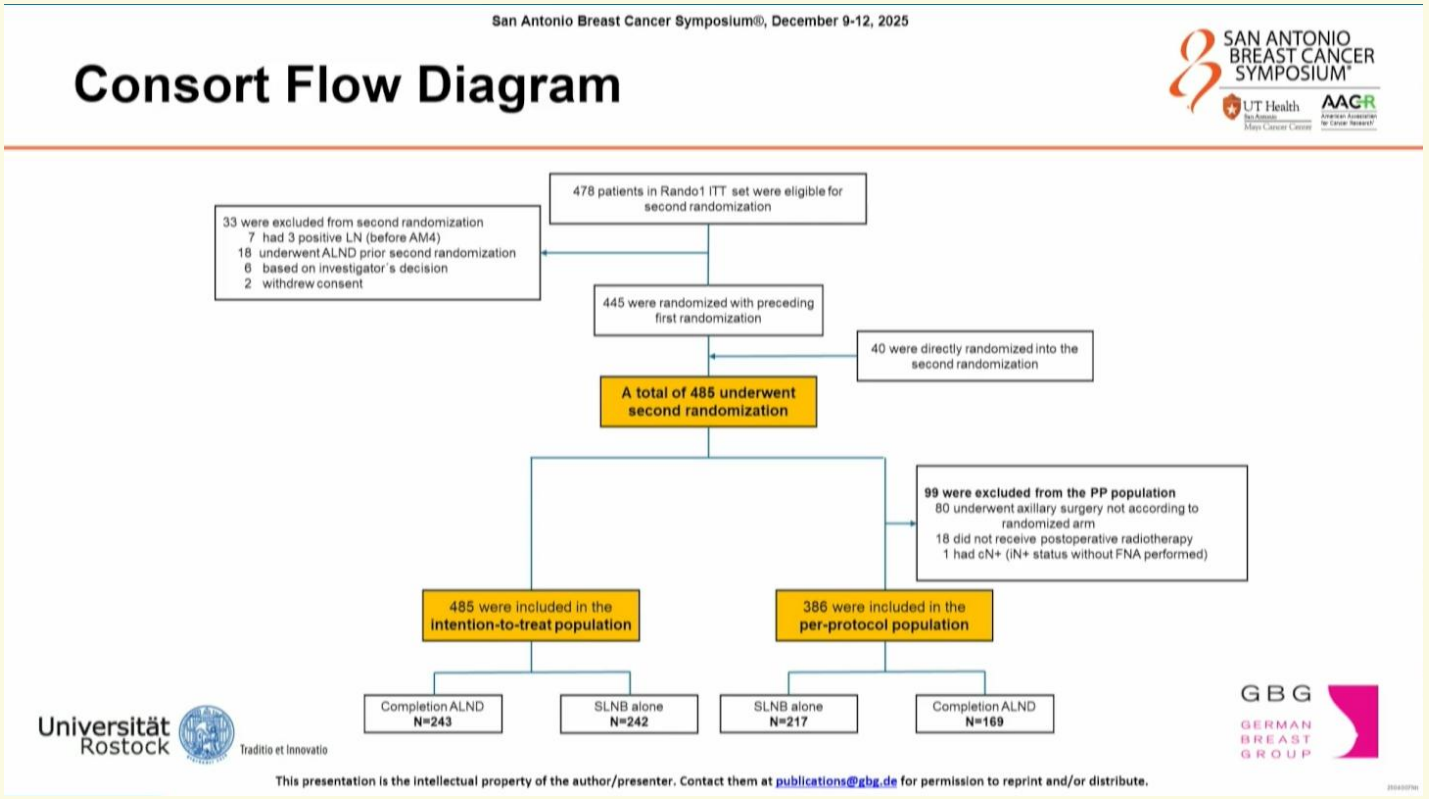
GS2-02 – Axillary surgery in breast cancer patients with one to three sentinel node macrometastases and breast conserving surgery [Toralf Reimer, UNIVERSITY OF ROSTOCK, GERMANY]

- Several validation trials post-**Z0011** → confirmed omission of completion ALND is safe for **BCS** patients with *macrometastases* in 1 or 2 sentinel nodes after primary surgery:

  - **SINODAR-ONE** trial >> included **22%** mastectomy patients (T1,T2)
  - **SENOMAC** trial >> included few T3 tumors, **34%** mastectomy patients, **~90%** patients received nodal irradiation both arms of trial
  - results of **POSNOC** trial awaited (closed to recruitment; data being analyzed)

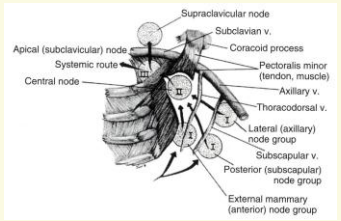
- **INSEMA Rando2** analysis → aimed to provide further data confirming non-inferiority of SLN biopsy alone to completion ALND (limited node positive disease (pN1a)

GS2-02 – Axillary surgery in breast cancer patients with one to three sentinel node macrometastases and breast conserving surgery [Toralf Reimer, UNIVERSITY OF ROSTOCK, GERMANY]



GS2-02 – Axillary surgery in breast cancer patients with one to three sentinel node macrometastases and breast conserving surgery [Toralf Reimer, UNIVERSITY OF ROSTOCK, GERMANY]

- Separate analyses performed of intention-to-treat (ITT) (n=**485**) and per protocol (PP) populations (n=**386**)
- Only **445/485** patients ITT population → primary randomization
- Patient and tumor characteristics PP set (well-matched SLN only/cALND):
  - median age 59 years (52 – 68) (small number age <50 years = **16.6%**)
  - median pre-operative tumor size = <2cm (**80.2%** versus **82%**)
  - majority luminal subtype (HR+/HER2-) = **93.4%**
  - majority with low Ki-67 (≤20%) (**84.6%** versus **76.6%**)



- Mean number of SLNs removed = **2.4** (median 2) and **13.2** (median 13) for completion ALND

GS2-02 – Axillary surgery in breast cancer patients with one to three sentinel node macrometastases and breast conserving surgery [Toralf Reimer, UNIVERSITY OF ROSTOCK, GERMANY]

- Notably higher rates of adjuvant therapies administered → for completion ALND group (amongst PP population):

	completionALND	SLN biopsy alone
CHEMOTHERAPY	**39.8%**	**33.6%** [p=0.239]
WBI (conventional fractionation)	**87.0%**	**75.1%** [p=0.004]
TUMOR BED BOOST	**88.8%**	**80.6%** [p=0.035]
REGIONAL NODAL IRRADIATION	**36.0%**	**20.6%** [p=0.019]

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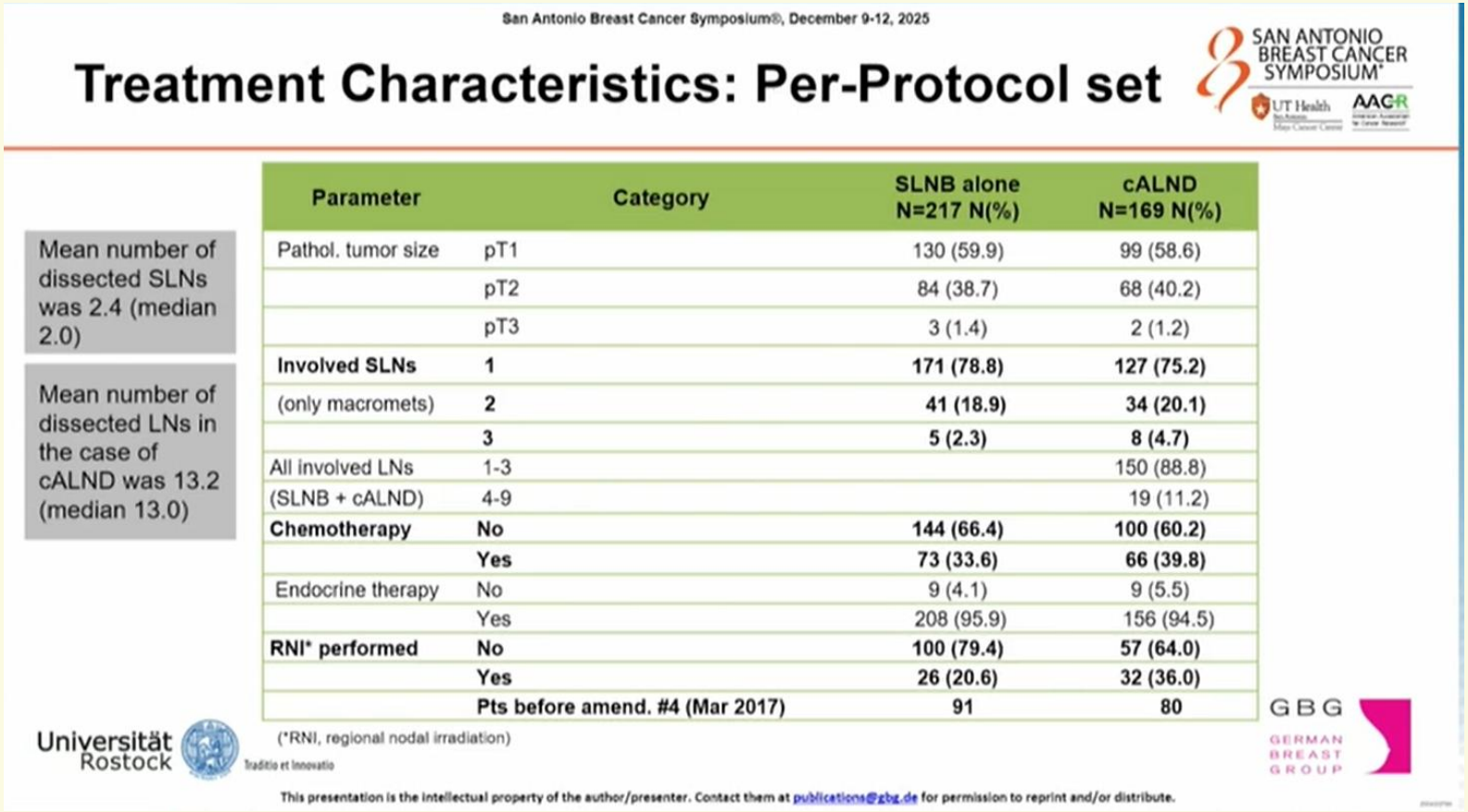


Parameter	Category	SLNB alone N=217 N(%)	cALND N=169 N(%)
Pathol. tumor size	pT1	130 (59.9)	99 (58.6)
	pT2	84 (38.7)	68 (40.2)
	pT3	3 (1.4)	2 (1.2)
Involved SLNs	**1**	**171 (78.8)**	**127 (75.2)**
(only macromets)	**2**	**41 (18.9)**	**34 (20.1)**
	3	**5 (2.3)**	**8 (4.7)**
All involved LNs	1-3		150 (88.8)
(SLNB + cALND)	4-9		19 (11.2)
Chemotherapy	**No**	**144 (66.4)**	**100 (60.2)**
	Yes	**73 (33.6)**	**66 (39.8)**
Endocrine therapy	No	9 (4.1)	9 (5.5)
	Yes	208 (95.9)	156 (94.5)
RNI* performed	**No**	**100 (79.4)**	**57 (64.0)**
	Yes	**26 (20.6)**	**32 (36.0)**
	Pts before amend. #4 (Mar 2017)	**91**	**80**

GS2-02 – Axillary surgery in breast cancer patients with one to three sentinel node macrometastases and breast conserving surgery [Toralf Reimer, UNIVERSITY OF ROSTOCK, GERMANY]

RESULTS

- Initial **co-primary endpoint** = **iDFS** for second randomisation

- **Target accrual** for **Rando-2** trial not achieved (n=**1,968**) ⟶ actual rate of SLN positivity (1 – 2 nodes macro) *lower* than expected*

- **iDFS** down-graded from co-primary endpoint to **secondary outcome**

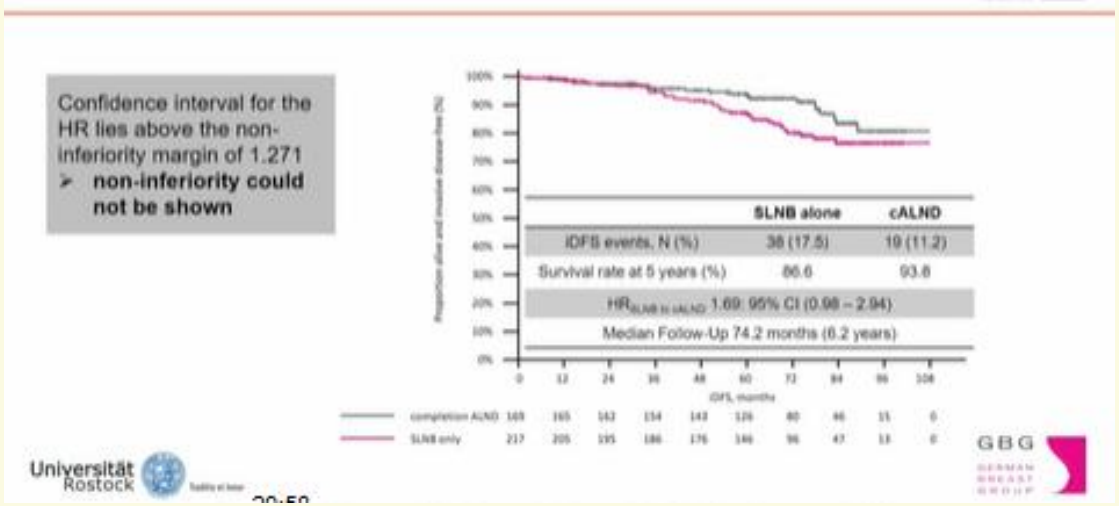
- **Non-inferiority** defined as 5-year iDFS **>76.5%** for SLN biopsy alone [HR <1.271] compared with expected value of **81%** for cALND

* 11.3% versus 25.0% (and post-Z0011 *changes* standard practice)

GS2-02 – Axillary surgery in breast cancer patients with one to three sentinel node macrometastases and breast conserving surgery [Toralf Reimer, UNIVERSITY OF ROSTOCK, GERMANY]

RESULTS

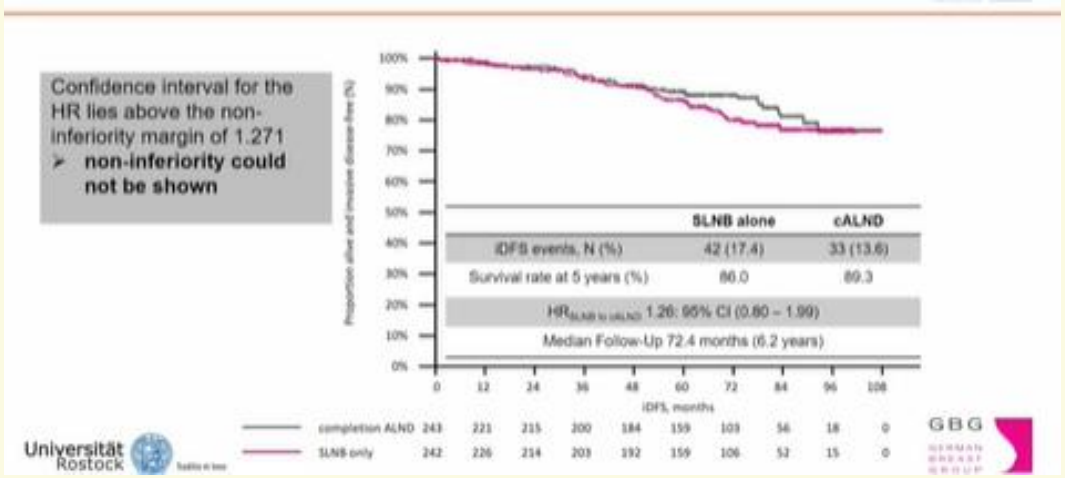
- Median follow up **74.2** months (PP and ITT analyses for **non- inferiority**)
- Non-inferiority not shown for PP analysis ⟶ despite no difference estimated 5-year **iDFS** rates for SLN biopsy alone (**86.6%**) compared with cALND (**93.8%**) [HR 1.69; 95% CI 0.98 – 2.94; p=0.058] (upper CI >**1.271**)



GS2-02 – Axillary surgery in breast cancer patients with one to three sentinel node macrometastases and breast conserving surgery [Toralf Reimer, UNIVERSITY OF ROSTOCK, GERMANY]

RESULTS

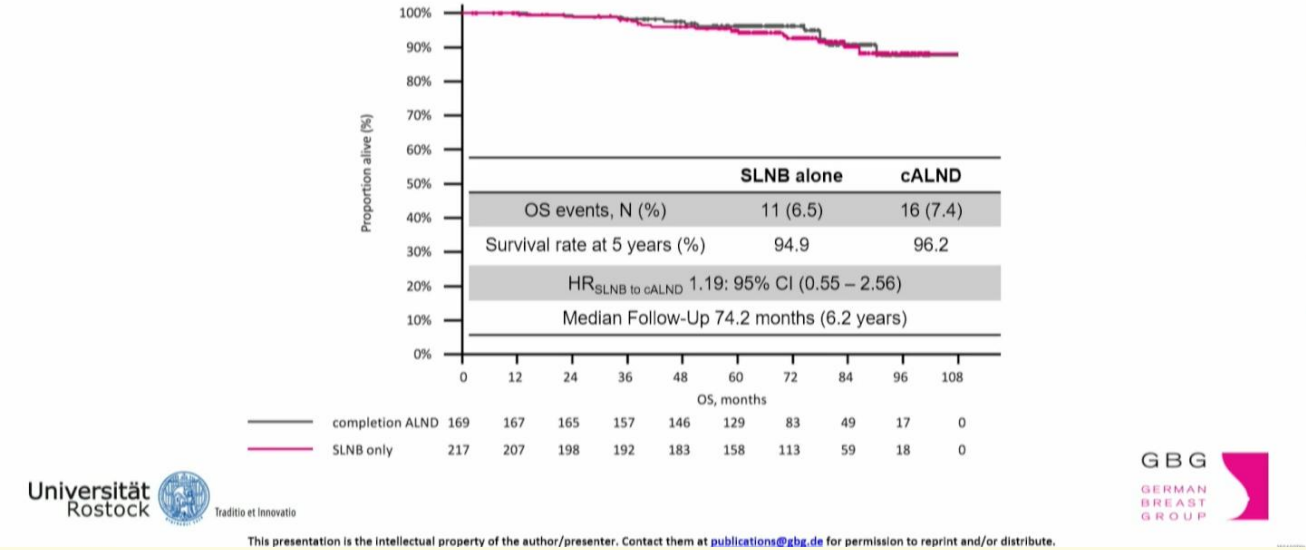
- For ITT analysis ⟶ no significant difference in 5-year iDFS for SLN biopsy alone (**86.0%**) compared with cALND (89.3%) [HR 1.26; 95% CI 0.80 – 1.99; p=0.314]
- Non-inferiority *not* upheld as upper confidence level (**1.99**) lies above non-inferiority margin of **1.271**



GS2-02 – Axillary surgery in breast cancer patients with one to three sentinel node macrometastases and breast conserving surgery [Toralf Reimer, UNIVERSITY OF ROSTOCK, GERMANY]

RESULTS

- Similar 5-year rates of overall survival for → standard (**94.9%**) and intervention (**96.2%**) groups [HR 1.19; 95% CI 0.55 – 12.56; p=0.663]



GS2-02 – Axillary surgery in breast cancer patients with one to three sentinel node macrometastases and breast conserving surgery [Toralf Reimer, UNIVERSITY OF ROSTOCK, GERMANY]

RESULTS

- Low rates of **loco-regional** recurrence → 5-year cumulative incidence rates of 1.1% for SLN biopsy alone and 0% for cALND
- Despite *range* of **radiotherapy** schedules within trial → no differences in volumes and dosages of radiation to the axilla (levels I – III)

Parameter	Category	SLNB alone N=217 N (%)	cALND N=169 N (%)	p-value
RT-technique	- 3D-CRT (tangential fields)	120 (56.1)	96 (56.8)	0.996
	- IMRT / VMAT	49 (22.8)	40 (23.6)	
	- Simultaneous integrated boost	25 (11.7)	18 (10.7)	
	- Deep inspiration breathhold	6 (2.8)	4 (2.4)	
	- Other	14 (6.5)	11 (6.5)	
Fractionation	- conventional	**157 (75.1)**	**147 (87.0)**	**0.004**
	- hypofractionation	**52 (24.9)**	**22 (13.0)**	
Boost	- yes	**175 (80.6)**	**150 (88.8)**	**0.035**
	- no	**42 (19.4)**	**19 (11.2)**	
Boost technique	- External beam (3D-CRT)	87 (50.6)	75 (50.7)	0.762
	- External beam (IMRT/VMAT)	37 (21.5)	32 (21.6)	
	- External beam (Electrons)	8 (4.7)	3 (2.0)	
	- Intraoperative (Electrons)	7 (4.1)	11 (7.4)	
	- Intraoperative (Photons)	3 (1.7)	2 (1.4)	
	- Interstitial brachytherapy	4 (2.3)	4 (2.7)	
	- Other	26 (15.1)	21 (14.2)	

No differences in axillary radiotherapy dose (levels I-III) were detected between study arms.

GS2-02 – Axillary surgery in breast cancer patients with one to three sentinel node macrometastases and breast conserving surgery [Toralf Reimer, UNIVERSITY OF ROSTOCK, GERMANY]

Discussion

- Secondary analysis of **INSEMA** trial ⟶ provides further data supporting omission of cALND in SLN biopsy positive patients:
  - **98%** patients with 1 – 2 nodes containing macrometastases (c.f **Z0011**)
  - relatively long duration of follow (**6.2** years)
  - incorporated prospective assessment of *incidental* axillary irradiation

- Significant differences between study groups ⟶ RT *fractionation* schedules, application of *boost* and RNI (*not axilla*)

- Confounding of 5-year **iDFS** data ⟶ from cross-over between PP and ITT groups

GS2-02 – Axillary surgery in breast cancer patients with one to three sentinel node macrometastases and breast conserving surgery [Toralf Reimer, UNIVERSITY OF ROSTOCK, GERMANY]

Discussion

- ***No*** statistically significant differences ⟶ between *SLN biopsy alone* and *completion ALND* observed in subset analysis (**ITT** or **PP**) for outcomes:
  - invasive disease-free survival (**iDFS**)
  - overall survival (**OS**)
  - loco-regional recurrence

- Non-inferiority *not* demonstrated either subset ⟶ alluding to possible **oncological detriment** from omission of cALND

- Final 10-year follow up data *anticipated* in **2029**

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GS2-03 – Insights of applied radiotherapy among patients undergoing breast conserving surgery with or without axillary sentinel lymph node biopsy [Guido Hildebrandt, UNIVERSITY MEDICINE ROSTOCK, GERMANY]

- **INSEMA** trial → patients with documented *dose* distribution to:
  - ipsilateral axillary nodes levels **I-III**
  - details of regional nodal irradiation (**RNI**)
  - RNI if **≥4** nodes involved

- All patients received **whole breast irradiation** (+/- boost)

- Note **50%** patients in INSEMA → received potentially *therapeutic* dose to level I nodes (**>85%** prescribed breast dose)

- Incidental axillary dose to higher level nodes (**II** + **III**) + use of **RNI**:
  - more frequent in SLN biopsy arm versus no SLN biopsy
  - RNI ◣ SLN biopsy (**4.0%**) versus no SLN biopsy (**0.6%**)

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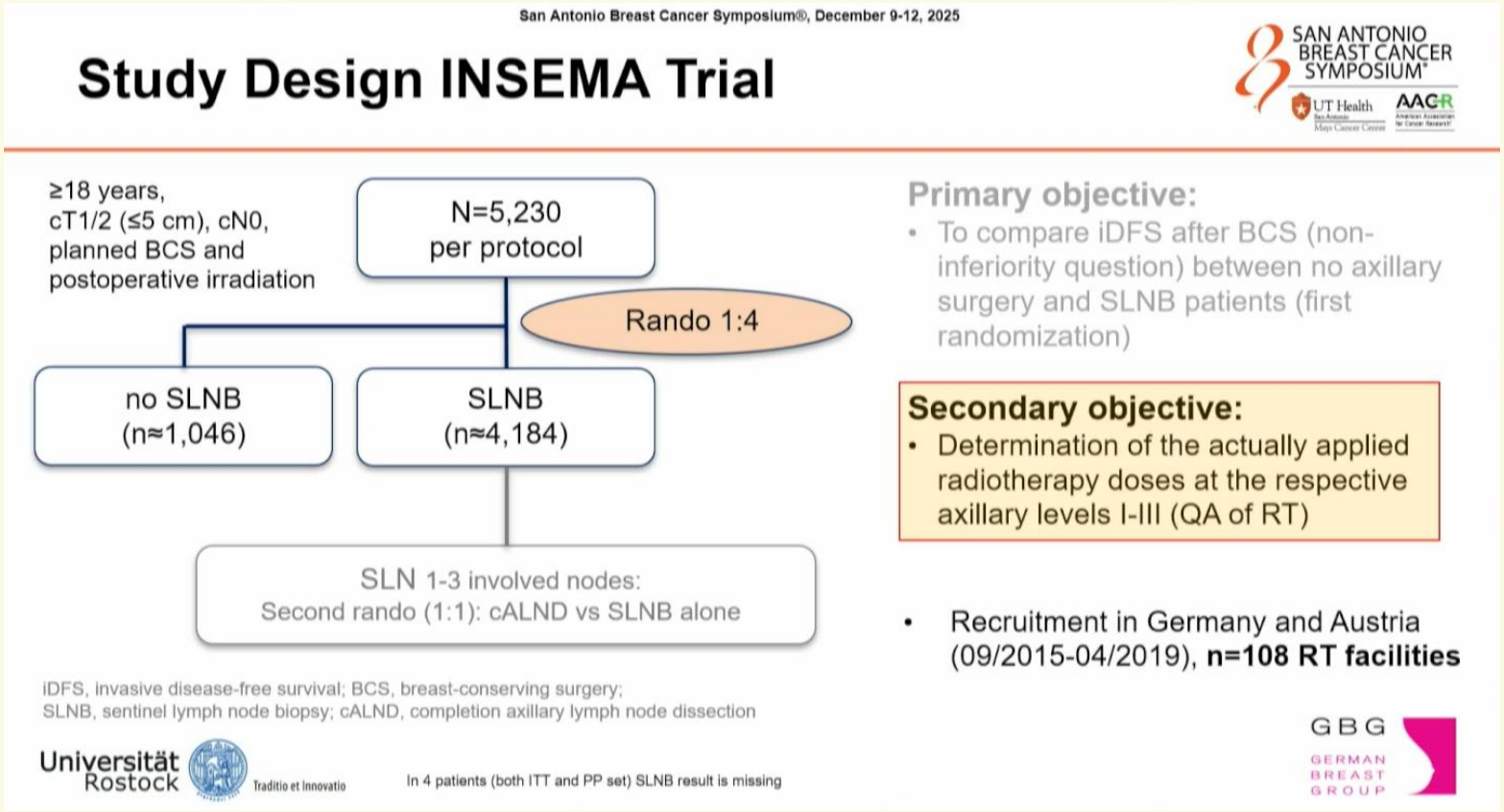

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Central RT-QA – contouring & planning

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Axillary dose parameters in INSEMA patients treated with postop. WBI after BCS[1]

Parameter	SLNB (N = 184)	No SLNB (N = 45)
Axillary level I dose median (percentage of breast dose)		
Mean	72.8	68.6
SD	31.4	30.6
Median	85.9	82.7
Range	1.3-110.5	0.8-99.0
Q1-Q3	54.8-96.6	42.5-95.1
Missing		
Axillary level II dose median (percentage of breast dose)		
Mean	39.9	29.7
SD	38.2	30.8
Median	20.8	13.2
Range	0.4-114.5	0.4-95.8
Q1-Q3	4.5-85.1	4.9-50.0
Missing		
Axillary level III dose median (percentage of breast dose)		
Mean	16.4	12.0
SD	27.1	21.5
Median	3.8	4.0
Range	0.1-105.8	1.1-87.1
Q1-Q3	2.1-12.1	2.4-6.0
Missing		

- analysis of first 3 RT-plans of all study centres (n=276)
  - contouring according to protocol 85 %
  - 3D-CRT 76 %
  - conv. fractionation 83.8 %
  - Boost 88.1 %
- Incidental RT-exposure axillary level I *(SLNB and no SLNB)*
  - ≥ 95% prescribed dose: 25 %
  - ≥ 85% prescribed dose: 50 %

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1 Hildebrandt et al. Int J Radiat Oncol Biol Phys 2020

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GS2-03 – Insights of applied radiotherapy among patients undergoing breast conserving surgery with or without axillary sentinel lymph node biopsy [Guido Hildebrandt, UNIVERSITY MEDICINE ROSTOCK, GERMANY]

- Patients (n= **252**) not receiving post-operative irradiation → similar **invasive disease-free survival** for SLN biopsy versus no SLN biopsy group [HR1.47; 95% CI 0.75 - 2.85 (p=0.26)]

- No **incidental** irradiation to level I nodes *without* breast radiotherapy

- **Omission** of SLN biopsy when BCS undertaken → does not justify compensatory *escalation* of axillary radiotherapy

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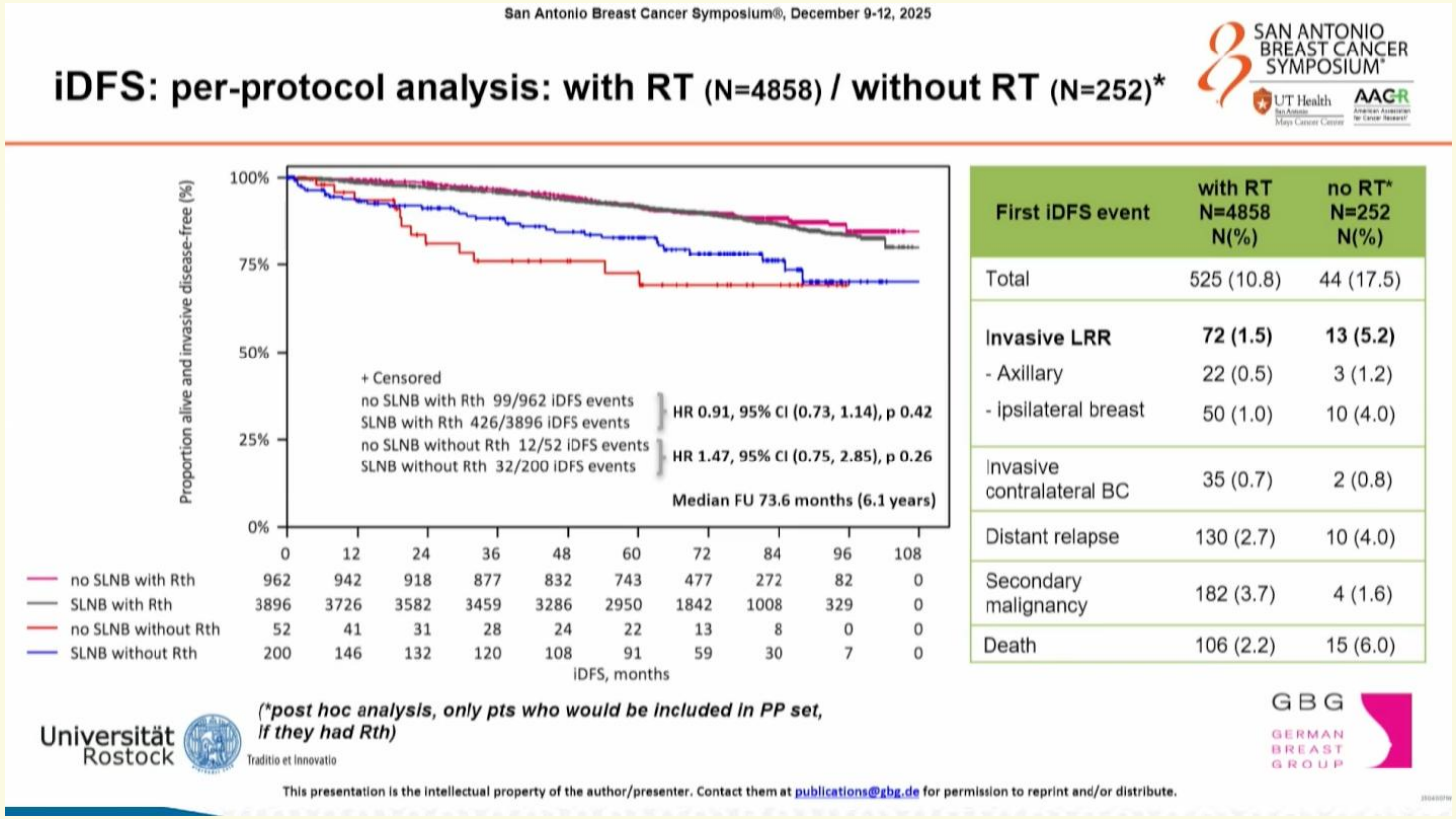

First iDFS event	with RT N=4858 N(%)	no RT* N=252 N(%)
Total	525 (10.8)	44 (17.5)
Invasive LRR	**72 (1.5)**	**13 (5.2)**
- Axillary	22 (0.5)	3 (1.2)
- ipsilateral breast	50 (1.0)	10 (4.0)
Invasive contralateral BC	35 (0.7)	2 (0.8)
Distant relapse	130 (2.7)	10 (4.0)
Secondary malignancy	182 (3.7)	4 (1.6)
Death	106 (2.2)	15 (6.0)

GS2-01 – More versus less axillary surgical staging procedures in breast cancer patients converting from a clinically node positive to negative through NACT - primary endpoint analysis of AXSANA/EUBREAST 3R study

[Thorsten Kuhn, UNIVERSITY OF ULM, GERMANY]

- **AXSANA/EUBREAST** → international prospective registry study examining different axillary **surgical staging** procedures in clinically node positive patients (**cN1-3a**) converting to ycN0 after NACT:
  - **ALND**, **SLN biopsy**, **TAD** or **TLND**
  - choice of surgical staging at discretion of surgeon
  - systemic and LR treatments → institutional/national guidelines

- Co-primary endpoints → evaluating clinical *outcomes* and *morbidity*:
  - **Axillary recurrence-free survival**
  - **Invasive breast cancer-specific disease-free survival**
  - **Quality-of-life** and **arm morbidity**

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[Thorsten Kuhn, UNIVERSITY OF ULM, GERMANY]

- **Principle** aim ⟶ determine whether 3-year **axillary RFS** for less invasive procedures (SLN biopsy, TAD, TLND) *non-inferior* to ALND*

- **Secondary** aim ⟶ compare SLN biopsy with TAD (axillary RFS)

- Results of interim analysis presented at **SABCS2025**:
  - **local** recurrence-free survival
  - **regional** recurrence-free survival
  - **breast cancer-specific** survival
  - **overall** survival

* Above 97% (lower boundary one-sided 95% CI)




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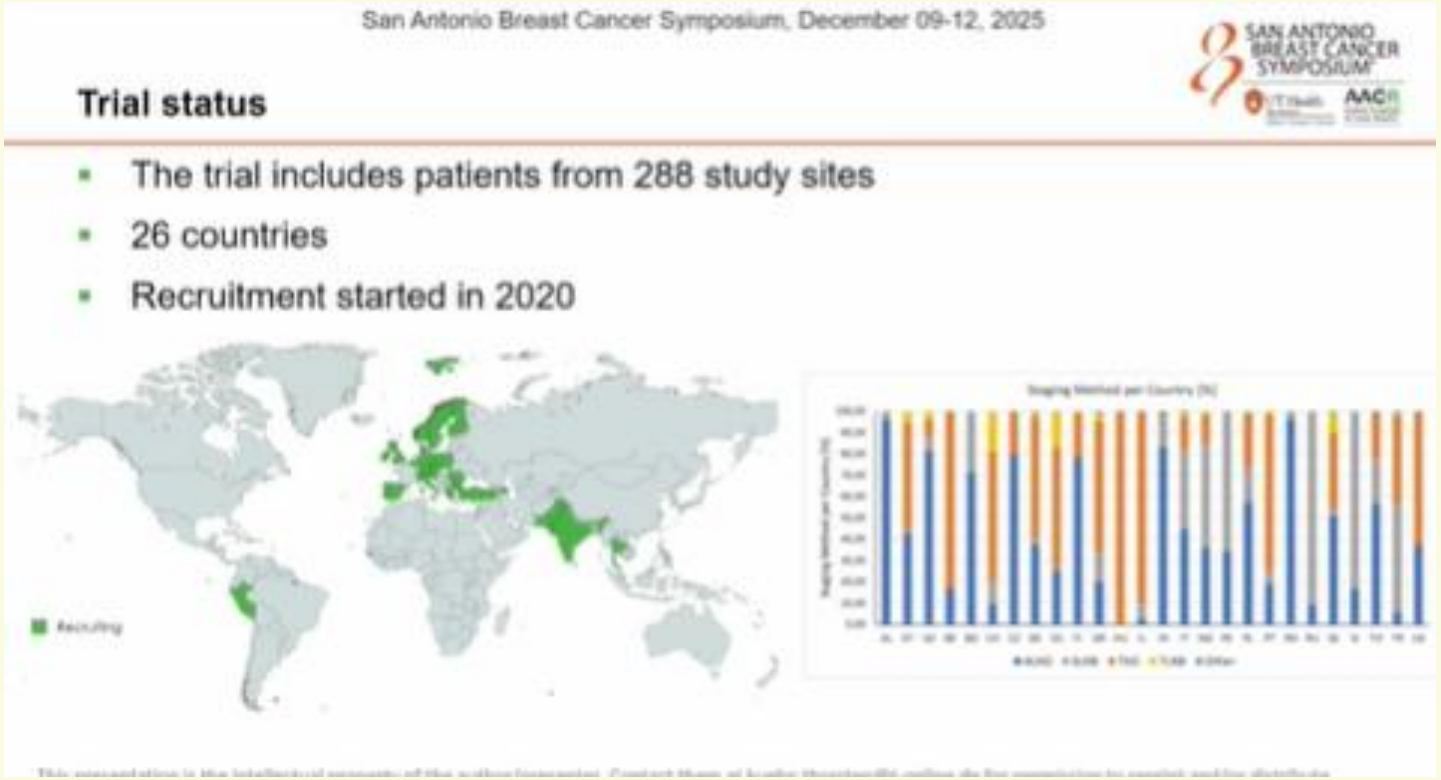


GS2-01 – More versus less axillary surgical staging procedures in breast cancer patients converting from a clinically node positive to negative through NACT - primary endpoint analysis of AXSANA/EUBREAST 3R study

[Thorsten Kuhn, UNIVERSITY OF ULM, GERMANY]

- Median follow up = **2** years (IQR: 1.07 - 2.83) → (**17%** patients with with ≥**3** years follow up [maximum **4.45** years])
- Inclusion of **pathologically** node negative and positive (**ypN0** and **ypN+**)
- Nodal pCR rate = **51.1%**

GS2-01 – More versus less axillary surgical staging procedures in breast cancer patients converting from a clinically node positive to negative through NACT - primary endpoint analysis of AXSANA/EUBREAST 3R study

[Thorsten Kuhn, UNIVERSITY OF ULM, GERMANY]

- Patient characteristics for ALND and lesser surgery (SLN biopsy, TAD, TLND) ⟶ well matched with no significant differences for:
  - median **age**
  - tumor **subtype**, **type** and **grade**
  - breast **pCR**
  - NACT, radiotherapy and adjuvant systemic therapy

- Regional treatment characteristics:

ypN-Stage	Regional Treatment	ALND (%)	Regional Treatment	SLNB/TAD/TLNB (%)
ypN0 (n = 1522)	aRT	232 (47.2)	aRT	548 (53.2)
	No aRT	260 (52.8)	No aRT	482 (46.8)
ypN+ (n = 953)	aRT	171 (63.8)	cALND + aRT	287 (41.9)
	no aRT	97 (36.2)	cALND, no aRT	179 (26.1)
	-	-	No cALND + aRT	160 (23.4)
	-	-	No cALND, no aRT	59 (8.6)

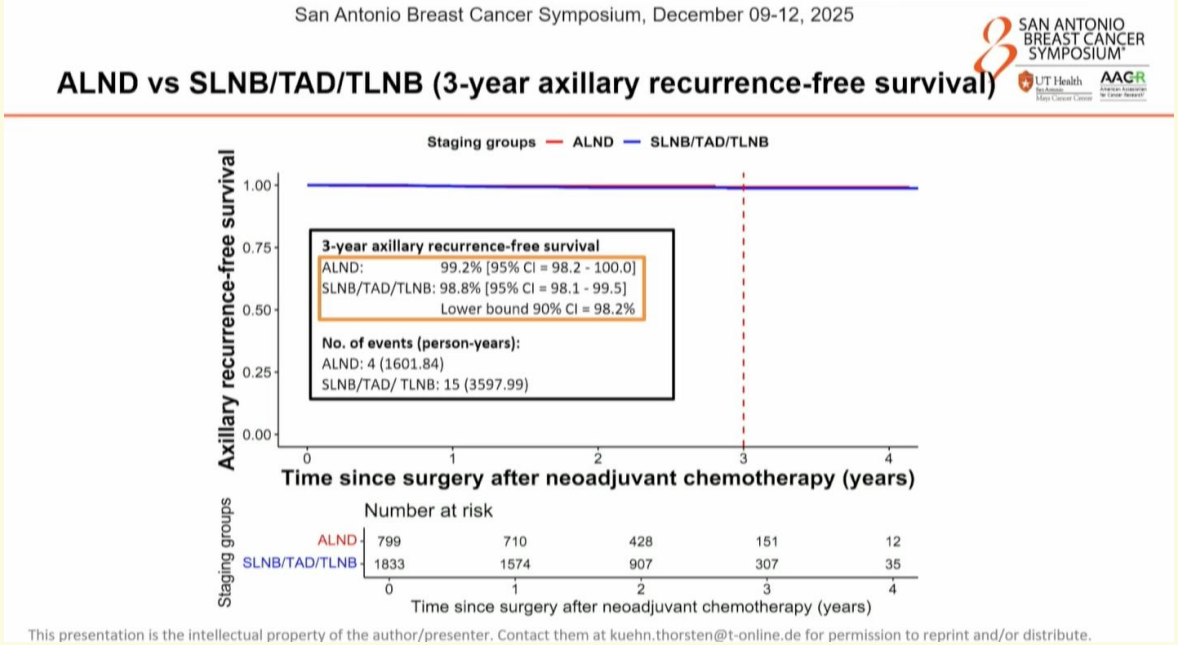
RT = Radiotherapy
aRT = axillary RT: Level I and II included in target volume

GS2-01 – More versus less axillary surgical staging procedures in breast cancer patients converting from a clinically node positive to negative through NACT - primary endpoint analysis of AXSANA/EUBREAST 3R study

[Thorsten Kuhn, UNIVERSITY OF ULM, GERMANY]

RESULTS

- No difference in 3-year axillary RFS between less axillary surgery (**98.8%**) [95% CI 98.1 – 99.5] and ALND groups (**99.2%**) [95% CI 98.2– 1.00] (number of events **15** and **4** for SLN biopsy/TAD/TLND and ALND respectively)

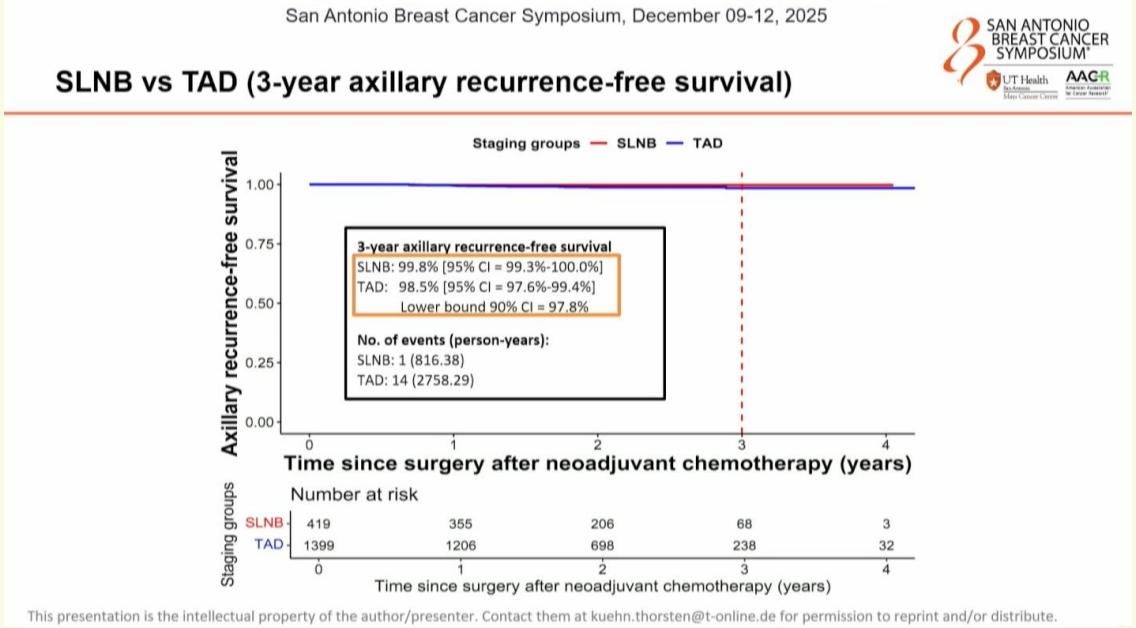


GS2-01 – More versus less axillary surgical staging procedures in breast cancer patients converting from a clinically node positive to negative through NACT - primary endpoint analysis of AXSANA/EUBREAST 3R study

[Thorsten Kuhn, UNIVERSITY OF ULM, GERMANY]

RESULTS

- No difference in 3-year axillary RFS between SLN biopsy (**99.8%**) [95% CI 99.3 – 100.0] and TAD groups (**98.5%**) [95% CI 97.6–99.4] (number of events **1** and **14** for SLN biopsy and TAD respectively)



GS2-01 – More versus less axillary surgical staging procedures in breast cancer patients converting from a clinically node positive to negative through NACT - primary endpoint analysis of AXSANA/EUBREAST 3R study

[Thorsten Kuhn, UNIVERSITY OF ULM, GERMANY]

DISCUSSION

- **AXSANA** provides real-world but *quality-assured* data confirming **non-inferiority** of *lesser* surgical procedures (SLN biopsy, TAD, TLND) for axillary staging in NACT patients converting from **cN1 -3a** to **ycN0**

- Targeting of *clipped* biopsy-confirmed node does not improve 3-year **axillary RFS** compared with *standard* SLN biopsy (details of techniques used?)

- Much **heterogeneity** in regional radiotherapy but findings *independent* tumor characteristics on multivariate analysis (Cox proportional hazards; $p<0.05$)

- Very *limited* duration of follow up → need to assess long-term impact of differences in axillary staging on **BCSS** and **OS**

GS2-11 –Omission of sentinel lymph node biopsy in clinically T1-2 node negative breast cancer patients treated with breast-conserving therapy: results of the Dutch BOOG 2013-08randomised controlled trial after a median follow-up of 5 years [M.L. Smidt, MAASTRICHT UNIVERSITY MEDICAL CENTER, NETHERLANDS]

BACKGROUND

- Discussion of omission of axillary surgical staging ⟶ based on results of **SOUND** and **INSEMA** trials [JAMA Oncol 2023; NEJM 2025]

- Few advantages of SLN biopsy for ***older*** patients with smaller clinically node negative HR positive, HER2 negative tumors

- Information from SLN biopsy ⟶ does not usually influence systemic therapies and **≤3%** of these patients have ≥4 positive nodes*

•*minimal risk of under-treatment from failure to receive CDK 4/6 inhibitor

GS2-11 –Omission of sentinel lymph node biopsy in clinically T1-2 node negative breast cancer patients treated with breast-conserving therapy: results of the Dutch BOOG 2013-08randomised controlled trial after a median follow-up of 5 years [M.L. Smidt, MAASTRICHT UNIVERSITY MEDICAL CENTER, NETHERLANDS]

Omission of SLNB in Patients Age < 70 Years: Ongoing Trials

Trial	Country	# Patients	Inclusion	Randomization Arms	Endpoints
SOUND (2012-2021) Reported	Italy	1560	BCS+XRT, cT1N0	Observation SLNB	DDFS
INSEMA (2015-2024) Active, not recruiting	Germany	5505	BCS+XRT, cT1-2N0	Observation SLNB ↓ 1-3 SLN macromet ALND vs. no ALND	IDFS (5 years)
BOOG 2013-08 (2015-2027) Active, recruiting	Netherlands	1644	BCS+XRT, cT1-2N0	Observation SLNB	Regional recurrence (up to 10 years)
NAUTILUS (2020-2027) Active, recruiting	Korea	1734	BCS+XRT, cT1-2N0	Observation SLNB	IDFS (5 years)
SOAPET (2019-2027)	China	1528	cT1-2N0	PET Stage 1 – assess NPV Stage 2 – SLNB omitted	Stage 1 – NPV Stage 2 – RFS/DDFS (5 years)

GS2-11 –Omission of sentinel lymph node biopsy in clinically T1-2 node negative breast cancer patients treated with breast-conserving therapy: results of the Dutch BOOG 2013-08randomised controlled trial after a median follow-up of 5 years [M.L. Smidt, MAASTRICHT UNIVERSITY MEDICAL CENTER, NETHERLANDS]

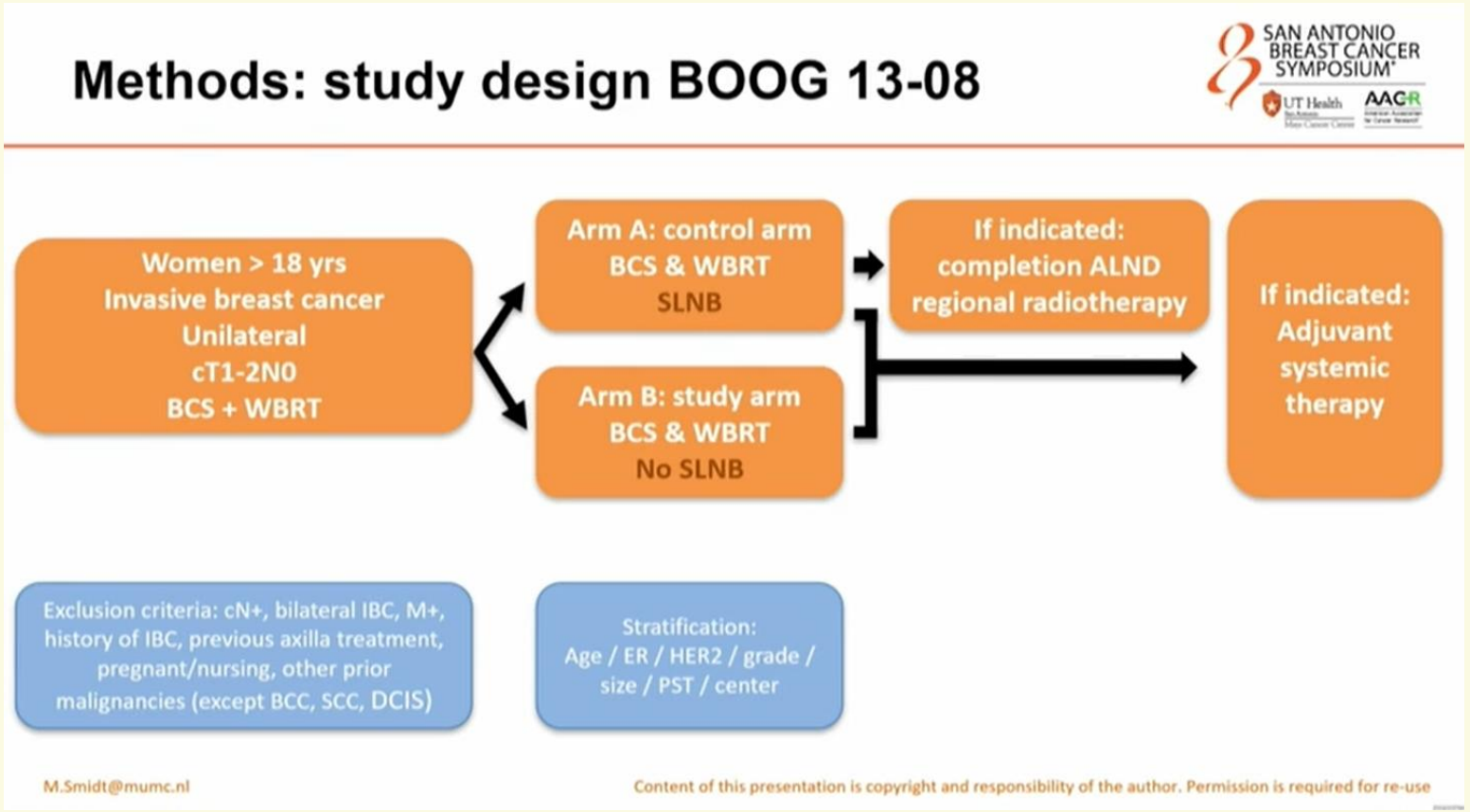
- **BOOG 2013-08** randomized **non-inferiority** trial → examined omission SLN biopsy in early stage breast cancer patients treated with breast conservation surgery and whole breast RT:

  - total of **1,574** patients (median age = 61.5 years)
  - T1 (**83%**) and T2 (**17%**) tumors
  - HR positive; HER2 negative (**86.8%**)
  - grade III = **17.2%** (similar to **SOUND**)

- Primary endpoint = **regional recurrence-free survival** (5-year)*
- Non-inferiority margin = **5%** (no more than 5% in favor of SLN biopsy)
- Median follow up = **5 years** (all patients at least 3 years follow up)

* secondary endpoints = local recurrence, distant disease-free survival, death events

GS2-11 –Omission of sentinel lymph node biopsy in clinically T1-2 node negative breast cancer patients treated with breast-conserving therapy: results of the Dutch BOOG 2013-08randomised controlled trial after a median follow-up of 5 years [M.L. Smidt, MAASTRICHT UNIVERSITY MEDICAL CENTER, NETHERLANDS]



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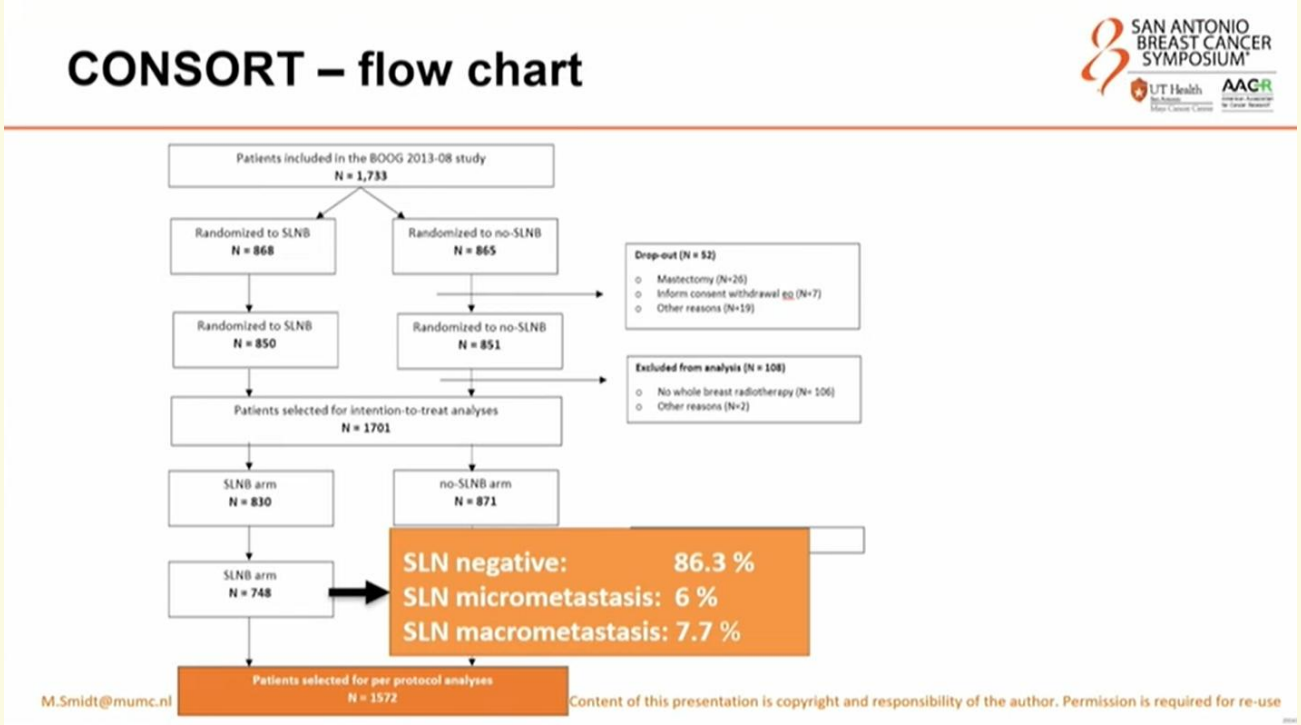
- Majority of patients pathologically node negative ⟶ with macrometastases in **7.7%** and micrometastases in **6%** (~**SOUND/INSEMA**)



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- Of note, only half of these *low-risk* patients ⟶ received any type **systemic therapy** (despite omission of SLN biopsy in experimental arm):
  - SLN biopsy group = **51.3%**
  - non-SLN biopsy group = **52.6%**

- Similar proportion of patients in standard and intervention group received **hormonal therapy** or **chemotherapy** (+/- targeted therapy)

	HER2+	50 (6.2)	57 (7.7)	
Adjuvant systemic therapy	None	432 (52.6)	383 (51.3)	.649
	Chemotherapy	93 (11.3)	97 (13.0)	.592
	Targeted therapy	36 (4.4)	44 (5.9)	.394
	Endocrine therapy	354 (43.1)	334 (44.8)	.777

GS2-11 –Omission of sentinel lymph node biopsy in clinically T1-2 node negative breast cancer patients treated with breast-conserving therapy: results of the Dutch BOOG 2013-08randomised controlled trial after a median follow-up of 5 years [M.L. Smidt, MAASTRICHT UNIVERSITY MEDICAL CENTER, NETHERLANDS]

RESULTS

- High rates of 5-year **regional recurrence-free survival** for SLN biopsy (**96.6%**) and no SLN biopsy (**94.2%**) groups **:**

absolute difference = **2.35%**

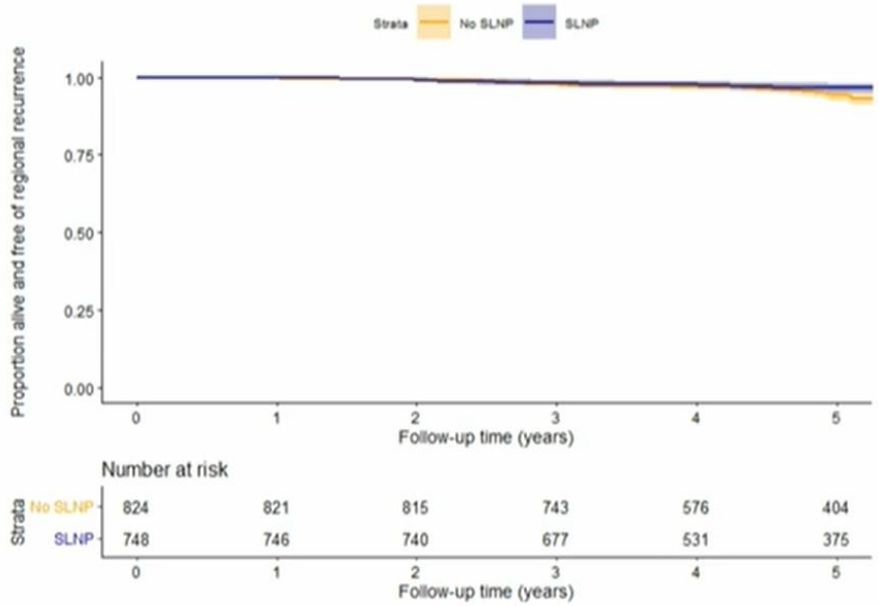
- Low rates of 5-year **regional recurrence** for SLN biopsy (**0.6%**) and no SLN biopsy groups (**1.2%**):

absolute difference = **0.7%**

- **Non-inferiority** upheld as well below *a priori* margin of **5%**

GS2-11 –Omission of sentinel lymph node biopsy in clinically T1-2 node negative breast cancer patients treated with breast-conserving therapy: results of the Dutch BOOG 2013-08randomised controlled trial after a median follow-up of 5 years [M.L. Smidt, MAASTRICHT UNIVERSITY MEDICAL CENTER, NETHERLANDS]

Results - RRFS



Median 5-year (IQR 3.23-5.17)

SLNB: 96.6% (95% CI 95.2-98.0)

No SLNB: 94.2% (95% CI 92.4-96.0)

Absolute difference of 2.35%

(95% CI 0.06-4.72)

5% non-inferiority margin is not exceeded

ITT analysis same output

M.Smidt@mumc.nl

GS2-11 –Omission of sentinel lymph node biopsy in clinically T1-2 node negative breast cancer patients treated with breast-conserving therapy: results of the Dutch BOOG 2013-08randomised controlled trial after a median follow-up of 5 years [M.L. Smidt, MAASTRICHT UNIVERSITY MEDICAL CENTER, NETHERLANDS]

DISCUSSION

- Findings *accord* with results of **SOUND** and **INSEMA** trial and confirm safety of omitting SLN biopsy in selected low risk patients
- Recommend omission of SLN biopsy in patients **>50** years with **T1** grade **I** or **II**, hormone receptor **positive**, HER2 **negative** tumors
- Endocrine therapy *not* **pre-requisite** for oncologic safety of SLN biopsy omission and lack of confirmation of **pathological** node negativity
- Additional follow up necessary for evaluation of **T2** tumors

Debate – Do All Early-stage Breast Cancer Patients Need Axillary Staging? [Chaired by Melissa Pilewskie, WEISER FAMILY CENTER FOR BREAST CARE, UNIVERSITY OF MICHIGAN, USA]

DISCUSSION

- Agreement that ⟶ universal **axillary staging** can *no longer* be recommended as SOC for *clinically* node negative early breast cancer
- Many centers in United States and Europe ⟶ not changed practice based on **SOUND** and **INSEMA** trials (*dichotomy* of opinion) :
  - '*Choosing Wisely* ' recommendation for women **>70** years (2016)
  - majority older women (**70%**) ⟶ continue to undergo routine SLN biopsy
- No oncological disadvantage (**L-R recurrence /survival**) from selective *omission* of SLN biopsy [post-M, T1 N0 grade I/II, HR+ve,HER2 -ve (**ASCO 2025**)]




Debate – Do All Early-stage Breast Cancer Patients Need Axillary Staging? [Chaired by Melissa Pilewskie, WEISER FAMILY CENTER FOR BREAST CARE, UNIVERSITY OF MICHIGAN, USA]

DISCUSSION

- **Nodal pathology** ⟶ may influence decisions for radiotherapy and adjuvant systemic therapy (**CDK 4/6** inhibitor) (+ duration endocrine therapy)
- Declaration of *pathologically* negative nodes necessary for trials of **partial** breast irradiation and **omission** breast RT
- Many patients and providers ⟶ not *comfortable* with omission of SLN biopsy despite recent trial data and potential surgical risks
- De-escalation of treatment must be **inter-disciplinary** with input from surgeons, radiotherapists and medical oncologists




GS2-09 The single-arm confirmatory trial of tamoxifen alone without surgery for low-risk DCIS of the breast (ER positive HER2 negative) (LORETTA trial:JCOG1505) [Hiroji Iwata, NAGOYA CITY UNIVERSITY GRADUATE MEDICAL SCHOOL OF MEDICAL SCIENCES]

- Current surgical treatment of DCIS non-evidence based and not evolved with increasing knowledge of natural history of DCIS
- Surgical options often based on surgeon preference and '*doing something must be better than waiting for something to happen*'
- Women should be **fully informed** about potential hazards of **over-diagnosis** and risk/benefit ratio for treatment in context of DCIS

Trials of low-risk DCIS (active surveillance)

	LORIS	LORD	COMET	LORETTA
Study	AS	AS	AS+ET (choice)	AS+ET
Screening	MMG	MMG	MMG	MMG,US, MRI**
Nuclear grade	1 or 2	1	1 or 2	1 or 2
Comedo necrosis	No	No	Eligible	No
ER	N/S	N/S	Positive	Positive
HER2	N/S	N/S	Negative***	Negative
Size	N/S	Any size	Any size	≤ 2.5 cm
Target	932	1240	1200	340

AS: Active surveillance, ET: Endocrine therapy, N/S: Not stipulated in study protocol, *: single arm confirmatory trial, **: breast US and MRI, ***: if tested.

International Research Collaboration

UK – **LORIS** Netherlands – **LORD** USA – **COMET** JAPAN –**LORETTA**

GS2-09 The single-arm confirmatory trial of tamoxifen alone without surgery for low-risk DCIS of the breast (ER positive HER2 negative) (LORETTA trial:JCOG1505)

[Hiroji Iwata, NAGOYA CITY UNIVERSITY GRADUATE MEDICAL SCHOOL OF MEDICAL SCIENCES]

- LORETTA trial → single arm confirmatory study evaluating endocrine therapy alone without surgery for low-risk DCIS:
  - age **≥40** years (newly diagnosed unilateral DCIS)
  - nuclear grade **I** and **II** (no comedo necrosis)
  - ER strongly positive **(≥10%)**
  - size on imaging **≤2.5cm** (MMG, US, MRI)

- Acquisition *sufficient* amount of material → with **percutaneous needle biopsy** techniques:
  - stereotactic-guided VAB for calcification (**8** - **12**-gauge; **≥6** passes)
  - ultrasound-guided biopsy if detected by US (**14**-gauge; **≥3** passes;16-gauge; **≥5** passes)

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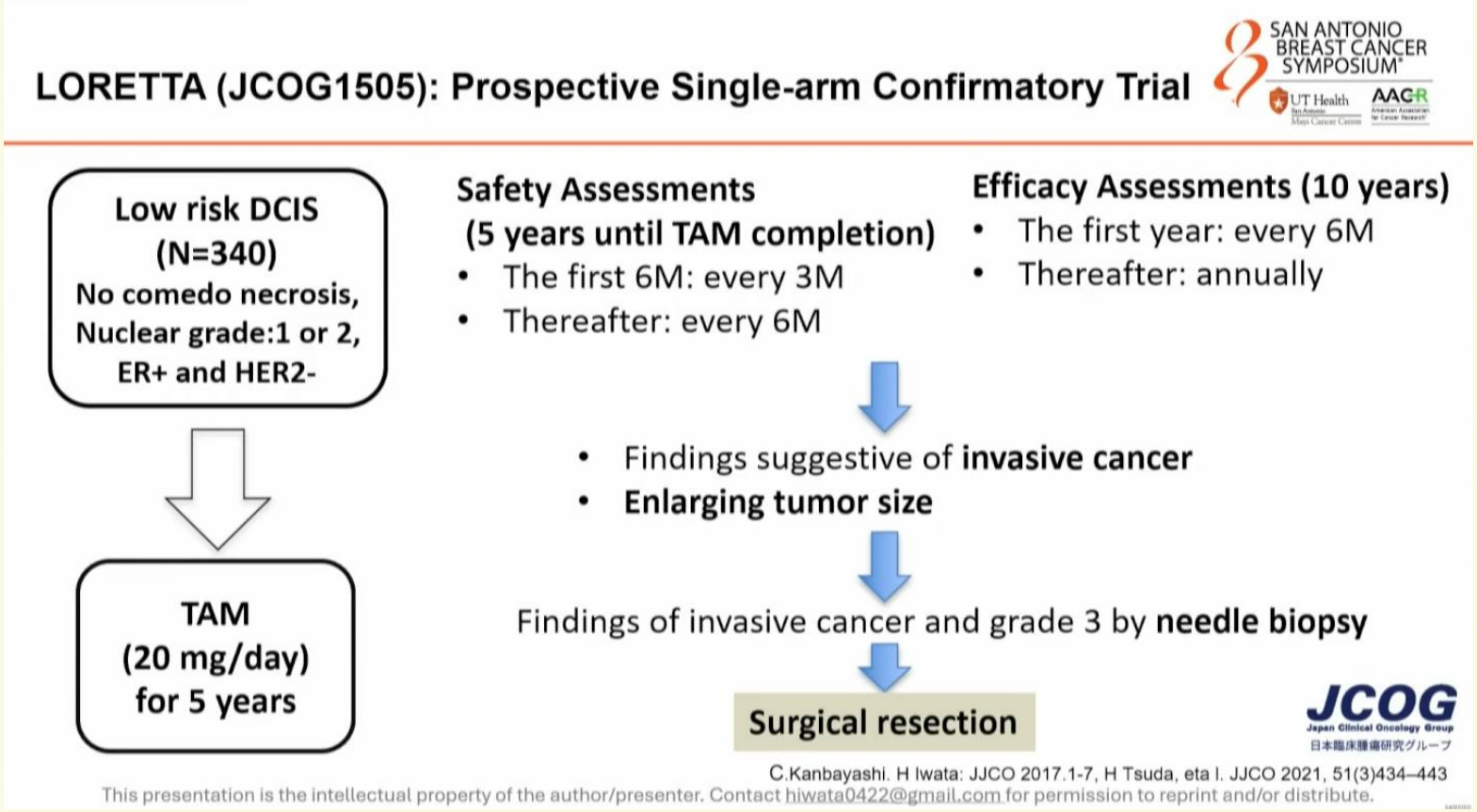

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- **PRIMARY ENDPOINT** = 5-year cumulative incidence proportion ipsilateral invasive cancer (**CIPIC**)

- **SECONDARY ENDPOINTS** included:
  - ipsilateral breast cancer-free survival
  - contralateral breast cancer-free survival
  - overall survival
  - surgical proportion/timing
  - safety

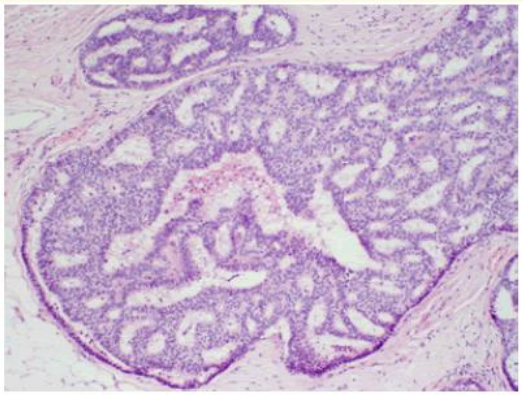

Figure 2: Low grade DCIS lesion.




GS2-09 The single-arm confirmatory trial of tamoxifen alone without surgery for low-risk DCIS of the breast (ER positive HER2 negative) (LORETTA trial:JCOG1505)

[Hiroji Iwata, NAGOYA CITY UNIVERSITY GRADUATE MEDICAL SCHOOL OF MEDICAL SCIENCES]

RESULTS

- Pre-specified threshold of **7%** for 5-year cumulative incidence proportion ipsilateral invasive cancer (**CIPIC**)*
- 5-year **CIPIC** for patients receiving tamoxifen alone without surgery *exceeded* pre-specified threshold at median follow up of **36** months
- Nonetheless, **CIPIC** relatively low = **9.8%** (less than10%)
- Trial *failed* to meet primary endpoint for **CIPIC**

*[one-sided alpha 2.5%; 95% power]

GS2-09 The single-arm confirmatory trial of tamoxifen alone without surgery for low-risk DCIS of the breast (ER positive HER2 negative) (LORETTA trial:JCOG1505) [Hiroji Iwata, NAGOYA CITY UNIVERSITY GRADUATE MEDICAL SCHOOL OF MEDICAL SCIENCES]

Primary Endpoint: 5-year IPIC

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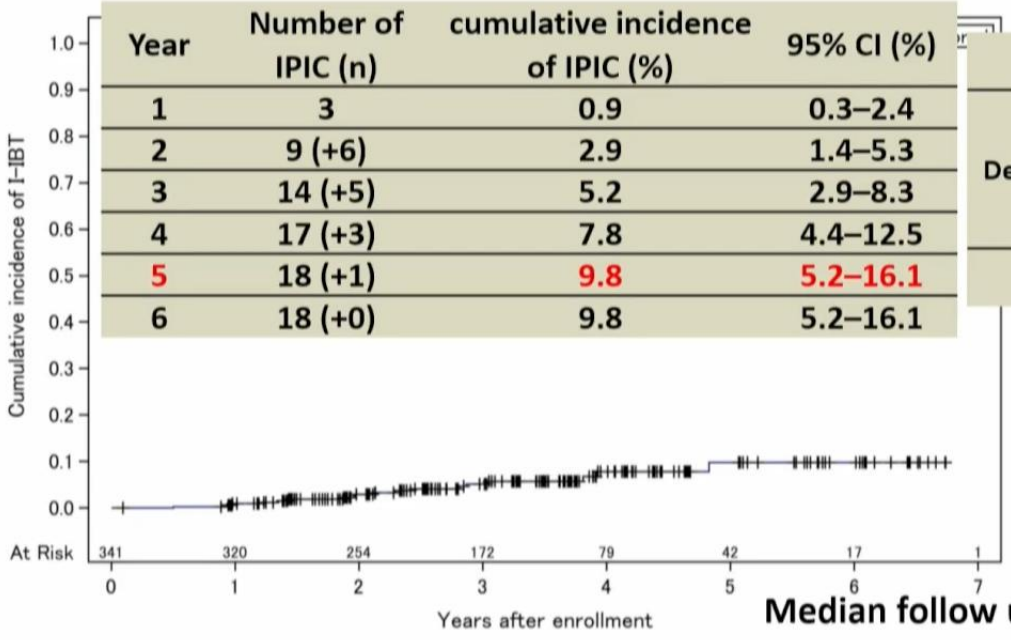
Year	Number of IPIC (n)	cumulative incidence of IPIC (%)	95% CI (%)
1	3	0.9	0.3–2.4
2	9 (+6)	2.9	1.4–5.3
3	14 (+5)	5.2	2.9–8.3
4	17 (+3)	7.8	4.4–12.5
5	18 (+1)	9.8	5.2–16.1
6	18 (+0)	9.8	5.2–16.1



Competitive risk (N=16)	
Death (unrelated)	Ipsilateral mastectomy (without invasive cancer)
1	15

Primary endpoint: Not met
(The upper limit of the confidence interval exceeded 7.0%)

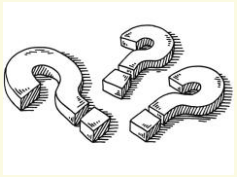
Median follow up: 36.0 mo (0.0-80.4 mo)

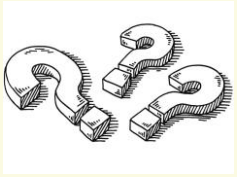
GS2-09 The single-arm confirmatory trial of tamoxifen alone without surgery for low-risk DCIS of the breast (ER positive HER2 negative) (LORETTA trial:JCOG1505)

[Hiroji Iwata, NAGOYA CITY UNIVERSITY GRADUATE MEDICAL SCHOOL OF MEDICAL SCIENCES]

DISCUSSION

- 5-year cumulative incidence of invasive cancer was **9.8%** for tamoxifen alone without surgery for low-risk DCIS
- Continuing development of invasive cancer ⟶ up to 5 years with size **>2cm** ⟶ being risk factor for invasive cancer
- **Longer term** follow up essential





- Acceptability of CIPIC ⟶ matter of **clinical judgment** with most panelists feeling *uncomfortable* at recommending endocrine therapy alone (accords with impact of **COMET** trial data presented SABCS 2024)

GS2-09 The single-arm confirmatory trial of tamoxifen alone without surgery for low-risk DCIS of the breast (ER positive HER2 negative) (LORETTA trial:JCOG1505)

[Hiroji Iwata, NAGOYA CITY UNIVERSITY GRADUATE MEDICAL SCHOOL OF MEDICAL SCIENCES]

DISCUSSION

- Shared decision-making essential → in context of **de-escalation** policies for low-risk DCIS
- Encourage patient engagement and education → facilitate better *adherence* to hormonal therapy
- Manageable side-effects of endocrine therapy in **LORETTA** trial and no major *hepatic* dysfunction from tamoxifen therapy

GS2-07 Effect of Preoperative Breast MRI Staging on Local Regional Recurrence (LRR) in Early Stage Breast Cancer: Alliance A)11104/ACRIN6694

[Isobelle Bedrosian, UNIVERSITY of TEXAS MD ANDERSON CANCER]

BACKGROUND

- Routine **pre-operative** MRI → controversial with *widespread* usage USA but more *selective* approach Europe
  - more accurately determines local disease **extent** than MMG/US
  - assumption detection/treatment disease based on MRI → improves **outcomes**

- Disadvantages of breast MRI with known **harms**:
  - further evaluation with second look US +/-**additional** biopsies*
  - increased rates of **mastectomy**
  - **delays** to surgery

- Most studies reveal *no* reduction in **re-operation** rates (including randomized **COMICE** trial [nor loco-regional recurrence **BREAST-MRI** trial])

* US or MRI-guided

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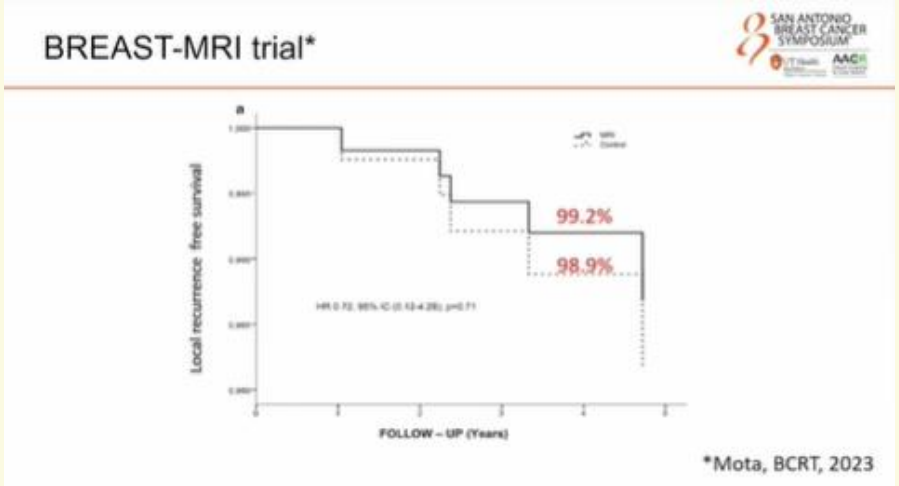


	MRI group (N=255)	Control Group (N=267)
HR+	206 (81.1%)	211 (79.6%)
HER2	6 (2.4%)	7 (2.6%)
HER2/HR+	24 (9.4%)	25 (9.4%)
Triple negative	18 (7.1%)	22 (8.3%)
Missing	1	2

*Mota, BCRT, 2023

mainly HR *positive* cases

GS2-07 Effect of Preoperative Breast MRI Staging on Local Regional Recurrence (LRR) in Early Stage Breast Cancer: Alliance A)11104/ACRIN6694

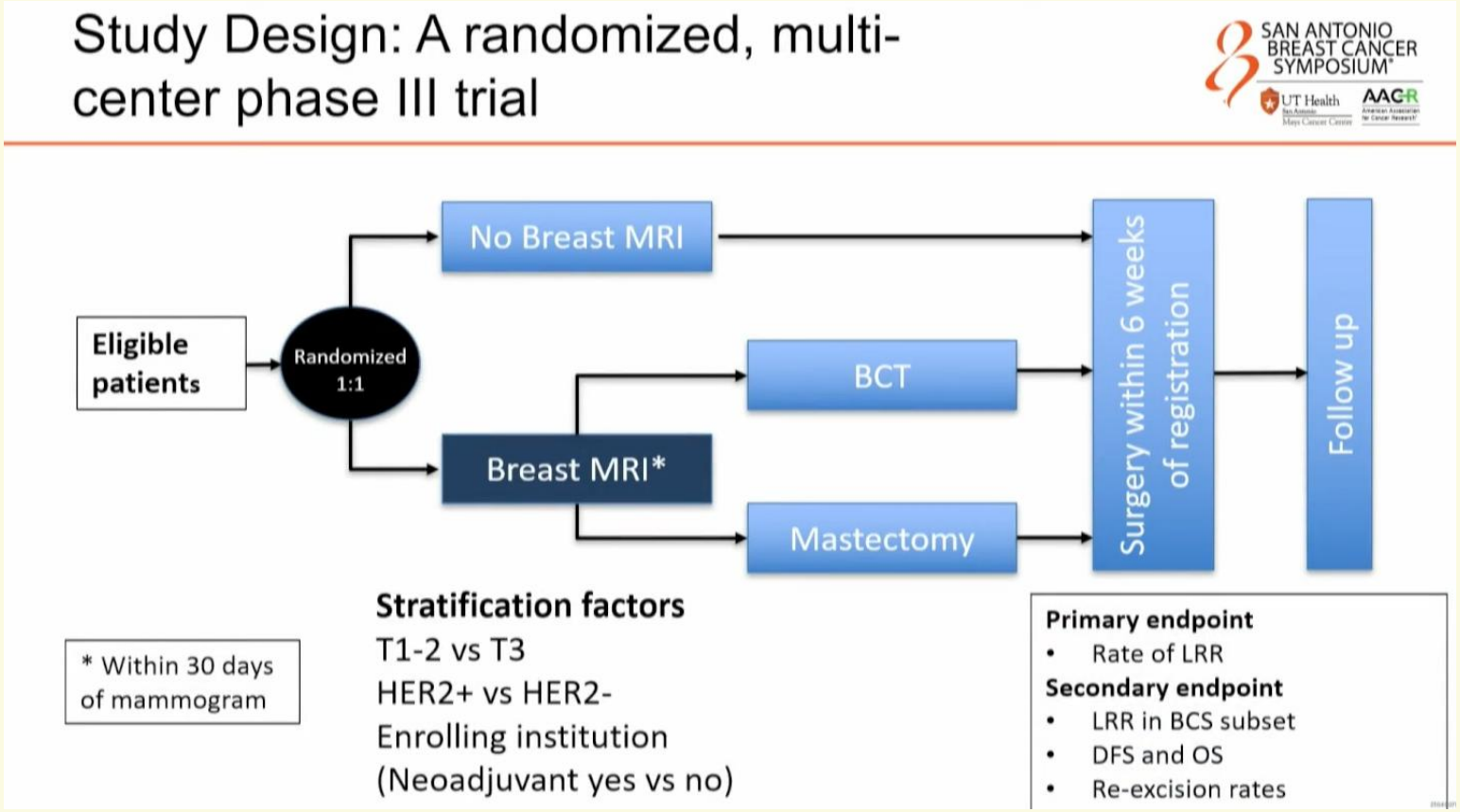
[Isobelle Bedrosian, UNIVERSITY of TEXAS MD ANDERSON CANCER]

- Phase 3 **ALLIANCE A011104** aimed to determine whether pre-operative **MRI** imaging ⟶ *improved* rates of loco-regional recurrence in early-stage hormone-receptor **negative** breast cancer
  - 319 patients (median age 58.9 years)
  - stage I or II (T1 = 72.1%; node negativc= 93.4%)
  - all hormone receptor negative (TNBC or ER/PR-ve/HER2+ve)
  - chemotherapy in 85% (17.6% neoadjuvant)

- Patients **randomly** assigned to undergo breast MRI (n=**161**) or not (n=**158**) f*ollowing* MMG

- In **NACT** patients, **pCR** rates of **39.3%** versus **52%** and adjuvant **RT** rates of **85%** versus **85.4%** in MRI and no-MRI groups respectively

GS2-07 Effect of Preoperative Breast MRI Staging on Local Regional Recurrence (LRR) in Early-Stage Breast Cancer: Alliance A)11104/ACRIN6694 [Isobelle Bedrosian, UNIVERSITY of TEXAS MD ANDERSON CANCER]



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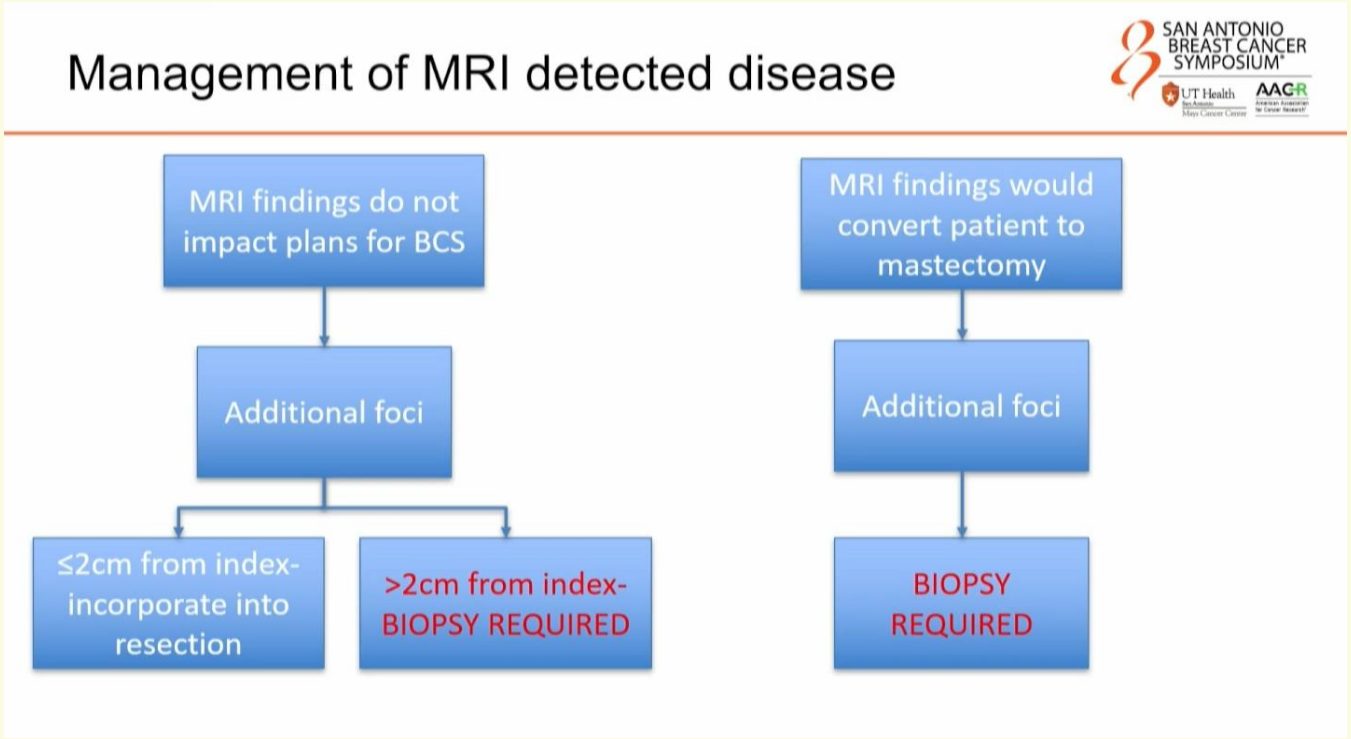


GS2-07- Effect of Preoperative Breast MRI Staging on Local Regional Recurrence (LRR) in Early Stage Breast Cancer: Alliance A)11104/ACRIN6694 [Isobelle Bedrosian, UNIVERSITY of TEXAS MD ANDERSON CANCER]

Local Regional Treatment

SAN ANTONIO BREAST CANCER SYMPOSIUM

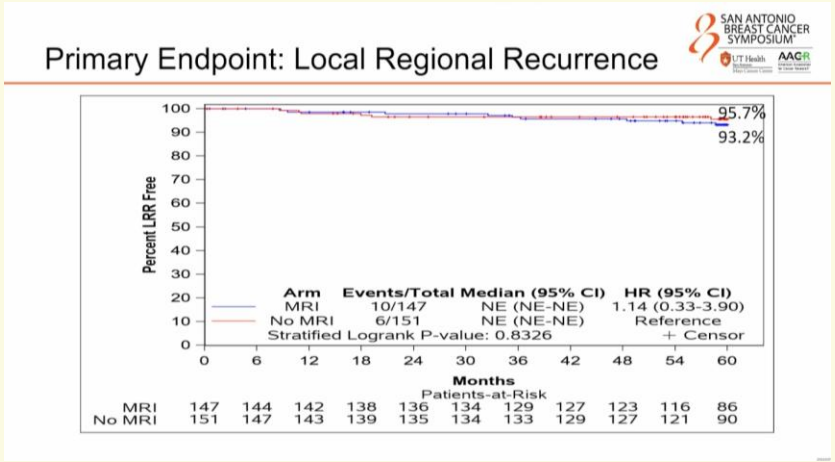
	Arm		
	No MRI (N=158)	MRI (N=161)	P-value
Initial Breast Surgery			0.67
Initial BCS	140 (92.7%)	134 (91.2%)	
Initial bilateral mastectomy	5 (3.3%)	4 (2.7%)	
Initial mastectomy	6 (4.0%)	9 (6.1%)	
Patient did not have surgery	7	14	
Axillary Surgery			0.1
ALND only	3 (2.0%)	6 (4.1%)	
Both	4 (2.6%)	10 (6.8%)	
Neither	1 (0.7%)	4 (2.7%)	
SLN biopsy only	143 (94.7%)	127 (86.4%)	
Patient did not have surgery	7	14	
Final Margin Status			1
< 2mm	37 (24.5%)	36 (24.5%)	
>= 2mm	104 (68.9%)	101 (68.7%)	
Positive (tumor at surgical margin)	10 (6.6%)	10 (6.8%)	
Patient did not have surgery	7	14	
Adjuvant Radiation			0.92
No	22 (14.6%)	22 (15.0%)	
Yes	129 (85.4%)	125 (85.0%)	

GS2-07 Effect of Preoperative Breast MRI Staging on Local Regional Recurrence (LRR) in Early Stage Breast Cancer: Alliance A)11104/ACRIN6694 [Isobelle Bedrosian, UNIVERSITY of TEXAS MD ANDERSON CANCER]

RESULTS

- At a median follow up of **61.1** months ⟶ no significant difference in rates of loco-regional recurrence between the groups

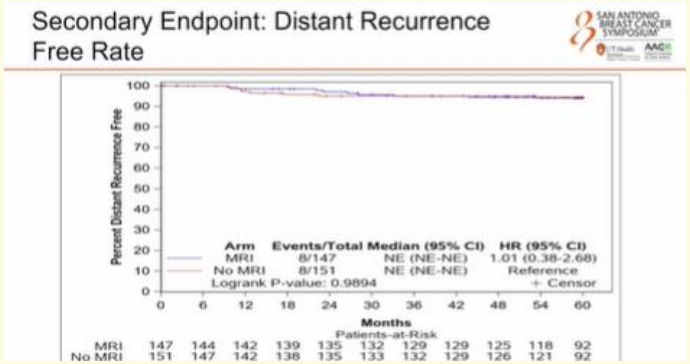
- No difference in 5-year rates of **loco-regional control** between MRI (**93.2%**) or no-MRI groups (**95.7%**) [HR 1.1; 95% CI 0.3 – 3.9]

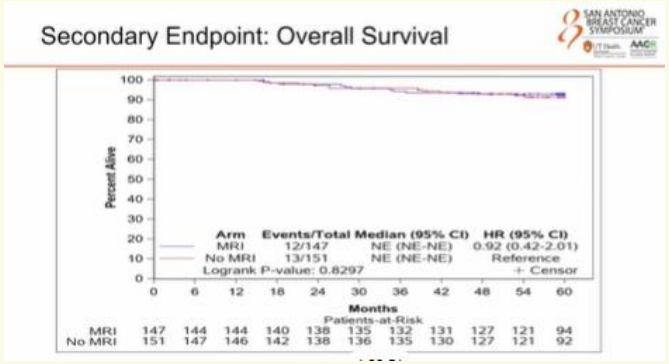


GS2-07 Effect of Preoperative Breast MRI Staging on Local Regional Recurrence (LRR) in Early Stage Breast Cancer: Alliance A)11104/ACRIN6694 [Isobelle Bedrosian, UNIVERSITY of TEXAS MD ANDERSON CANCER]

RESULTS

- No difference in 5-year **distant recurrence-free** rates (**93.2%**) or overall survival (**92.2%**) ⟶ between MRI and no-MRI groups





GS2-07 Effect of Preoperative Breast MRI Staging on Local Regional Recurrence (LRR) in Early Stage Breast Cancer: Alliance A)11104/ACRIN6694

[Isobelle Bedrosian, UNIVERSITY of TEXAS MD ANDERSON CANCER]

DISCUSSION

- Explored use of routine pre-operative MRI to improve local staging in patients with more aggressive tumor biology (**TNBC** or **HR-ve/HER2+ve**)
- No impact on clinical outcomes - **LRR**, **DRFS**, **OS** median f/u 5 years
- 5-year rates of LRR → very low for more *aggressive* tumor types
- **Adjuvant therapies** may *ablate* any ***additional foci*** of disease detected by MRI (therefore MRI unnecessary)
- Harms appear to *outweigh* benefits of **routine pre-operative** MRI in newly diagnosed early stage breast cancer patients

GS3-01 Menopausal Hormone Therapy and the Risk of Breast Cancer in Women with a Pathogenic Variant in BRCA1 or BRCA2

[Joanne Kotsopoulos, WOMEN'S COLLEGE HOSPITAL RESEARCH AND INNOVATION INSTITUTE, UNIVERSITY of TOTONTO]

BACKGROUND

- Women with mutations in BRCA1 and BRCA2 tumor suppressor genes → high risk for breast, ovarian or fallopian tube tumors

- Pathogenic gene mutation carrier → justifies recommendation for risk-reducing surgery (bilateral salpingo-oophorectomy):
  - **BRCA1** mutation → RRS before age **40** years
  - **BRCA2** mutation → RRS before age **45** years

- '*Profound effect*' of BSO on **overall mortality** but side effects from induction of early menopause
  [Kotsopoulos J, et al JAMA Oncol 2024; 10(4): 484 - 492]

GS3-01 Menopausal Hormone Therapy and the Risk of Breast Cancer in Women with a Pathogenic Variant in BRCA1 or BRCA2

[Joanne Kotsopoulos, WOMEN'S COLLEGE HOSPITAL RESEARCH AND INNOVATION INSTITUTE, UNIVERSITY of TOTONTO]

BACKGROUND

- **PROSE** study revealed marked impact of **BSO** with *halving* of breast cancer risk (**21%** versus **42%**) [HR0.47; 95%CI 0.29 – 0.77]

- Several studies report *similar* magnitude of effect for **BSO** on breast cancer risk

- **BSO** before 40 years → *lower* cumulative risk breast cancer by age 70 years for BRCA1/2 **pathogenic** mutation carriers

GS3-01 Menopausal Hormone Therapy and the Risk of Breast Cancer in Women with a Pathogenic Variant in BRCA1 or BRCA2

[Joanne Kotsopoulos, WOMEN'S COLLEGE HOSPITAL RESEARCH AND INNOVATION INSTITUTE, UNIVERSITY of TORONTO]

BACKGROUND

- Reluctance to prescribe hormone replacement therapy (HRT) due to concerns → oncological safety (**Women's Health Initiative** (2002)) :
  - estrogen + progestin ► nominally *increased* risk breast cancer
  - higher risk cardiovascular disease, stroke and pulmonary embolism
  - FDA to change warning labels on HRT preparations (November 2025)

- Limited data on use of HRT by women with BRCA1/2 mutations

- Need to optimise management of **menopausal symptoms** in women with early surgical menopause (avoid **chronic** symptoms of estrogen depletion)

GS3-01 Menopausal Hormone Therapy and the Risk of Breast Cancer in Women with a Pathogenic Variant in BRCA1 or BRCA2

[Joanne Kotsopoulos, WOMEN'S COLLEGE HOSPITAL RESEARCH AND INNOVATION INSTITUTE, UNIVERSITY of TORONTO]

- Does **HRT** use after menopause *increase* risk of breast cancer in BRCA carriers? (risk levels in relation to type of **mutation** and **formulation***)

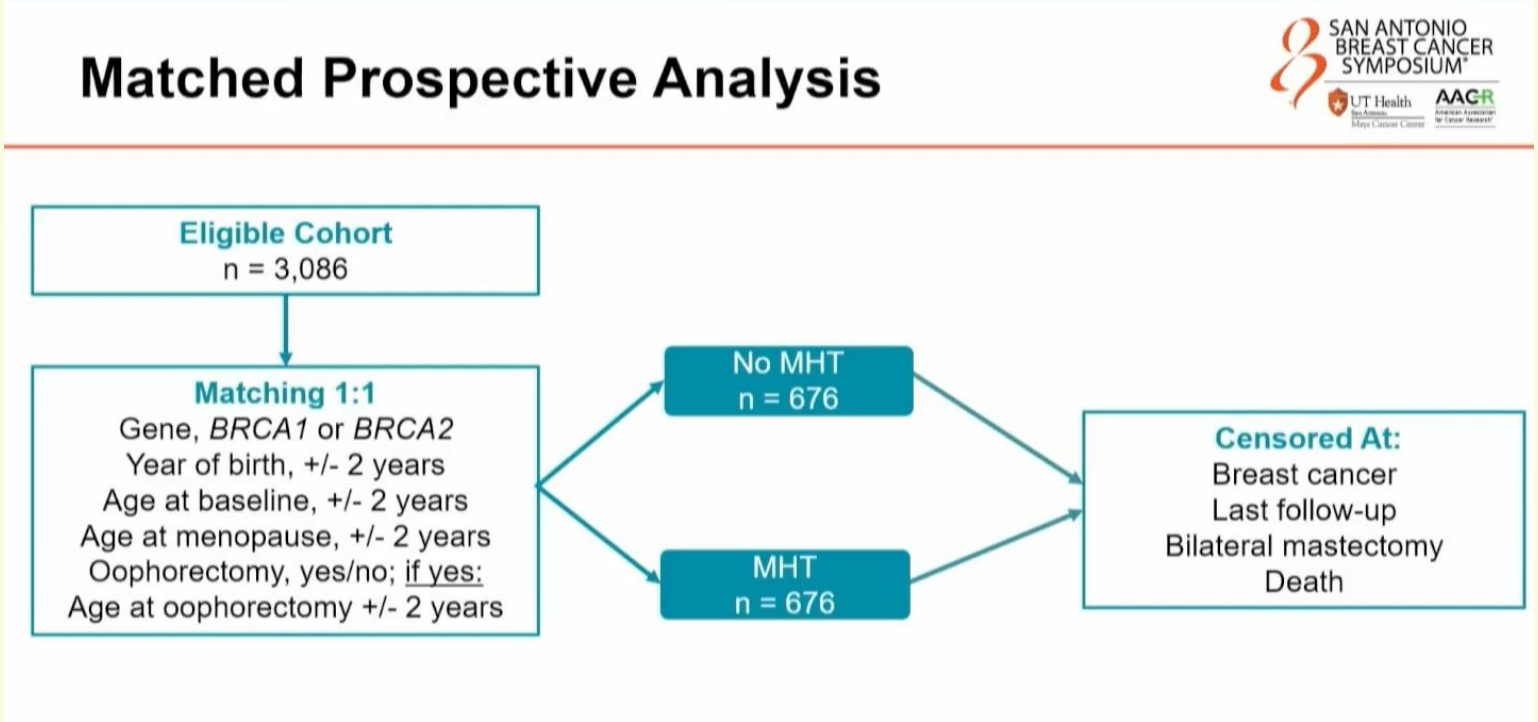
- **Matched prospective** analysis → based on data from large global study of HRT use *after* menopause (surgical or natural):
  - health-related questionnaires every **2** years
  - data on **exposure** to HRT, **screening** practice and **outcomes**

- Total of **676** matched pairs of women → use of **HRT** or not after menopause:
  - mean age **43.8** years (22 - 76)
  - birth year, age at baseline, BRCA1/2 mutation, BSO (+age)

* tibolone, progesterone alone, estrogen alone or E+P, conjugated E + basedoxifene (**SERM**)

GS3-01 Menopausal Hormone Therapy and the Risk of Breast Cancer in Women with a Pathogenic Variant in BRCA1 or BRCA2

[Joanne Kotsopoulos, WOMEN'S COLLEGE HOSPITAL RESEARCH AND INNOVATION INSTITUTE, UNIVERSITY of TORONTO]



GS3-01 - Menopausal Hormone Therapy and the Risk of Breast Cancer in Women with a Pathogenic Variant in BRCA1 or BRCA2

[Joanne Kotsopoulos, WOMEN'S COLLEGE HOSPITAL RESEARCH AND INNOVATION INSTITUTE, UNIVERSITY of TORONTO]

Characteristics of *BRCA* carriers who did vs. did not initiate MHT after menopause

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Variables, mean (range) or n (%)	No MHT (n = 676)	MHT (n = 676)	*P*	
Year of birth	1962.3 (25-85)	1961.7 (25-83)	0.30	
Age at baseline	43.8 (22-76)	43.8 (22-76)	0.97	
Years of follow-up	4.6 (0.1-15)	6.6 (0.1-15)	<0.0001	
Gene				
BRCA1	548 (81.1)	548 (81.1)		
BRCA2	128 (18.9)	128 (18.9)	matched	
Parity				
No	78 (11.8)	100 (15.5)		
Yes	562 (88.2)	554 (84.5)	0.11	
Preventive mastectomy				
No	482 (71.3)	550 (81.4)		
Yes	194 (28.7)	126 (18.6)	<0.0001	
Bilateral oophorectomy				
No	35 (5.2)	35 (5.2)	matched	
Yes	641 (94.8)	641 (94.8)		
Age at oophorectomy	44.4 (28-68)	44.3 (28-67)	0.84	
MHT				
Age at first use	43.6 for the 62 users*	43.2		
Duration of use, years	4.6 (0.25-15)*	5.7 (0.25-35)	0.56	

*

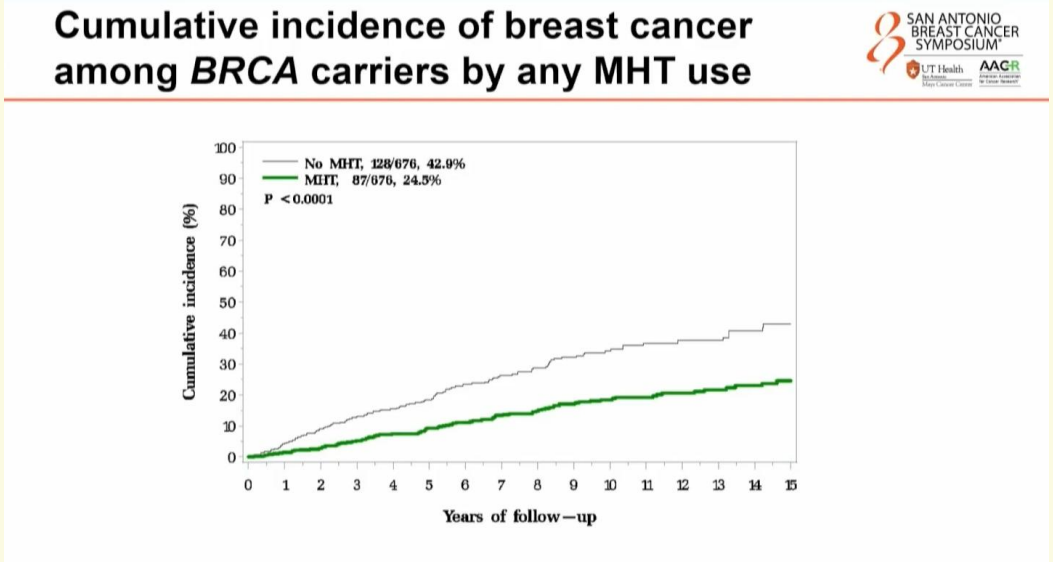
*

GS3-01 Menopausal Hormone Therapy and the Risk of Breast Cancer in Women with a Pathogenic Variant in BRCA1 or BRCA2

[Joanne Kotsopoulos, WOMEN'S COLLEGE HOSPITAL RESEARCH AND INNOVATION INSTITUTE, UNIVERSITY of TORONTO]

RESULTS

- Use of **HRT** associated with significantly *lower* risk for development breast cancer (**12.9%** versus **18.9%**; p=0.002) [HR **0.48** 95% CI 0.36-0.63]
  - risk reduction with separate analysis **BRCA1** [HR **0.5**;95% CI 0.37 - 0.66]
  - risk reduction with separate analysis **BRCA2** [HR **0.35**;95% CI 0.15 - 0.82]



GS3-01 Menopausal Hormone Therapy and the Risk of Breast Cancer in Women with a Pathogenic Variant in BRCA1 or BRCA2

[Joanne Kotsopoulos, WOMEN'S COLLEGE HOSPITAL RESEARCH AND INNOVATION INSTITUTE, UNIVERSITY of TORONTO]

RESULTS

- Use of estrogen only **HRT** ⟶ associated with dramatically *lower* risk for development breast cancer (**63%**) [HR **0.37** 95% CI 0.24-0.57]
- Use of estrogen + progesterone **HRT** ⟶ no impact on risk for development breast cancer [HR **0.94** 95% CI 0.54-1.63]

MHT type	*BRCA1* and *BRCA2* (n = 676 pairs)		
	Cases/Total	HR (95%CI)*	*P*
Any MHT use			
Unexposed	128/676	1.00 (ref)	
Exposed	87/676	0.48 (0.36-0.63)	<0.0001
E alone			
Unexposed	58/291	1.00 (ref)	
Exposed	35/291	0.37 (0.24-0.57)	<0.0001
E+P			
Unexposed	42/244	1.00 (ref)	
Exposed	37/244	0.94 (0.54-1.63)	0.82

*Adjusted for parity and country of residence

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GS3-01 Menopausal Hormone Therapy and the Risk of Breast Cancer in Women with a Pathogenic Variant in BRCA1 or BRCA2

[Joanne Kotsopoulos, WOMEN'S COLLEGE HOSPITAL RESEARCH AND INNOVATION INSTITUTE, UNIVERSITY of TORONTO]

DISCUSSION

- Appears to be *no* adverse effect of **HRT** on breast cancer risk in carriers of either BRCA1 or BRCA2 mutations
- **Lower risk** of breast cancer development for estrogen *alone* preparations (irrespective of route [oral/transdermal] and type of HRT)
- **Concomitant** hysterectomy at time of BSO (permit estrogen only HRT)
- Results not *stratified* by receptor status and *short* follow up (**6** years)
- Unclear whether use of **HRT** after **diagnosis** breast cancer *increases* mortality in BRCA mutation carriers

PD4-07 Younger Age does not Affect Survival among Women with Breast Cancer, BRCA Mutations

[Eva Blondeaux, UNIVERSITY of GENOA, ITALY]

BACKGROUND

- Young age ► risk factor for breast cancer **recurrence** + **mortality**

- Most *apparent* for hormone receptor positive disease
- Unknown whether impact of age at diagnosis *similar* amongst women with **germline pathogenic variants** of BRCA1/2
  - BRCA-associated cancers more likely grade **III**, **TNBC**
  - is young age **additional** adverse prognostic factor within this cohort?
  - important for **risk** assessment, t**reatment** planning and **counseling**




PD4-07 Younger Age does not Affect Survival among Women with Breast Cancer, BRCA Mutations [Eva Blondeaux, UNIVERSITY of GENOA, ITALY]

- Analysed breast cancer outcomes of young women with BRCA1 or BRCA2 germline mutations within **BRCA BCY Collaboration**:
  - total of **5,350** women (109 breast units, 5 continents)
  - aged **≤40** years
  - stage **I - III**
  - diagnosed between Jan 2000 and Dec 2020

- Excluded stage **IV**, **VUS** (BRCA), few details of **RRSO/RRM**

- Aimed to compare oncological outcomes in patients aged ≤30 years with older age groups (31 - 35 years and 36 to 40 years)

PD4-07 Younger Age does not Affect Survival among Women with Breast Cancer, BRCA Mutations [Eva Blondeaux, UNIVERSITY of GENOA, ITALY]

- Primary endpoint = **disease-free survival** (secondary endpoint **OS**)

	PATIENT AGE GROUP		
	≤30	31-35	36-40
BRCA1 mutation	**71.3%**	**62.4%**	**61.1%**
TNBC	**56.3%**	**48.1%**	**46.6%**
HIGH GRADE (III)	**71.3%**	**66.6%**	**65%**
TUMOR SIZE (≤2cm)	**31.7%**	**36.6%**	**39.5%**
CHEMOTHERAPY	**94.4%**	**92.6%**	**89.7%**

PD4-07 Younger Age does not Affect Survival among Women with Breast Cancer, BRCA Mutations [Eva Blondeaux, UNIVERSITY of GENOA, ITALY]

RESULTS

- At a median follow up of **8.2** years → comparable rates of 8-year **DFS** for age groups **≤30** years, **31 - 35** years and **36 - 40** years
- **No** significant association between age at diagnosis and **DFS** for age groups **31 - 35** [aHR 1.03; 95% CI 0.89-1.19] and **36 - 40** [aHR 1.03; 95% CI 0.89-1.19] compared with women aged **≤30** years
- Like wise no differences in **OS** between age groups
- Results described by presenter as "*particularly important and somewhat reassuring*"

PD4-07 Younger Age does not Affect Survival among Women with Breast Cancer, BRCA Mutations [Eva Blondeaux, UNIVERSITY of GENOA, ITALY]

DISCUSSION

- Diagnosis of breast cancer under age 30 years → perception of poorer prognosis with intrinsically more **aggressive** disease:
  - high grade III tumors
  - triple negative profile
  - BRCA1 mutations

- Adverse pathological features → do *not* translate into inferior survival outcomes (**DFS** or **OS**) for younger women (**BRCA** mutations)
- **Age** alone is *not* a poor prognostic factor with appropriate therapies
- "*Individualised treatment strategies*" (**tumor biology + genetic status**)

GS3-04 - Effects of acupuncture vs sham acupuncture and usual care on cancer-related cognitive difficulties among breast cancer survivors: The ENHANCED randomised clinical trial [Jun Mao, MEMORIAL SLOAN KETTERING CANCER CENTER, NEW YORK]

BACKGROUND

- Up to 40% breast cancer survivors ⟶ report significant cognitive impairments following treatment

- Cognitive problems attributed to '**chemo brain**' ⟶ difficulties:
  - attention
  - concentration
  - memory (telephone numbers, assigned tasks)
  - thinking clearly

- Little data on *objective* cognitive impairment (subjective patient reporting)

- **Acupuncture** for insomnia ⟶ "*promising effects'* on subjective cognitive impairment and cognitive function

GS3-04 - Effects of acupuncture vs sham acupuncture and usual care on cancer-related cognitive difficulties among breast cancer survivors: The ENHANCED randomized clinical trial [Jun Mao, MEMORIAL SLOAN KETTERING CANCER CENTER, NEW YORK]

- **ENHANCED** randomised phase 2 trial to → evaluate effect of acupuncture on perceived cognitive impairment + objective cognition:
  - **260** women (mean age 56.6 years, 78.4% white)
  - half had received chemotherapy (**53.5%**)
  - completed treatment (stage 0 - 3 breast cancer)
  - experienced **insomnia**
  - moderate/severe cancer related **cognitive** problems (self-reported)

- Randomly assigned 2:1:1 to receive one of following interventions:

  REAL ACUPUNCTURE (n=**129**)
  SHAM ACUPUNCTURE* (n=**70**)
  USUAL CARE (n=**61**)

* Mimicked real process - no penetration of needles into skin to reach acupuncture points

GS3-04 - Effects of acupuncture vs sham acupuncture and usual care on cancer-related cognitive difficulties among breast cancer survivors: The ENHANCED randomized clinical trial [Jun Mao, MEMORIAL SLOAN KETTERING CANCER CENTER, NEW YORK]

Study Design and Key Eligibility Criteria

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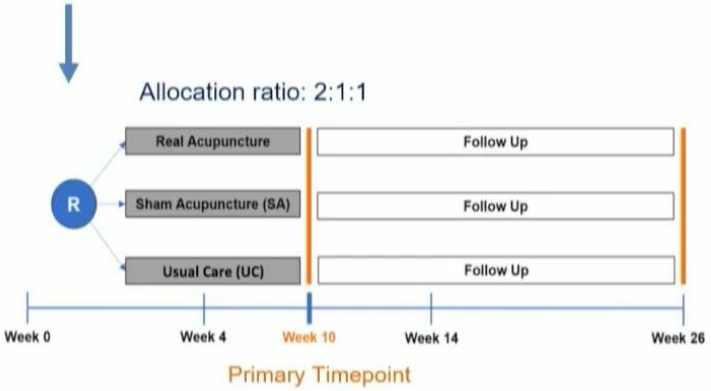
Phase II Randomized Clinical Trial



Key inclusion criteria:

- Stage 0-III breast cancer survivors
- Self-reported moderate or greater CRCD
- Self-reported cognitive functions worsened since diagnosis
- Self-reported insomnia

Key exclusion criteria:

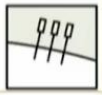
- Cancer diagnosis ≥10 years
- Diagnosis of Alzheimer's or other organic brain disorder
- Primary psychiatric disorder not in remission
- History of stroke or head injury

GS3-04 - Effects of acupuncture vs sham acupuncture and usual care on cancer-related cognitive difficulties among breast cancer survivors: The ENHANCED randomized clinical trial [Jun Mao, MEMORIAL SLOAN KETTERING CANCER CENTER, NEW YORK]

- Treatment sessions ~ **30** minutes duration once weekly (10 weeks)
- **PRIMARY ENDPOINT** = changes in subjective/objective cognition

Real Acupuncture (RA)

- 10 sessions (weekly); 20-30 minutes per session
- Semi-fixed protocol
- Acupoints for cognition and sleep (core), as well as comorbid symptoms (10-26 points in total)
- EA (2 Hz) if clinical indicated



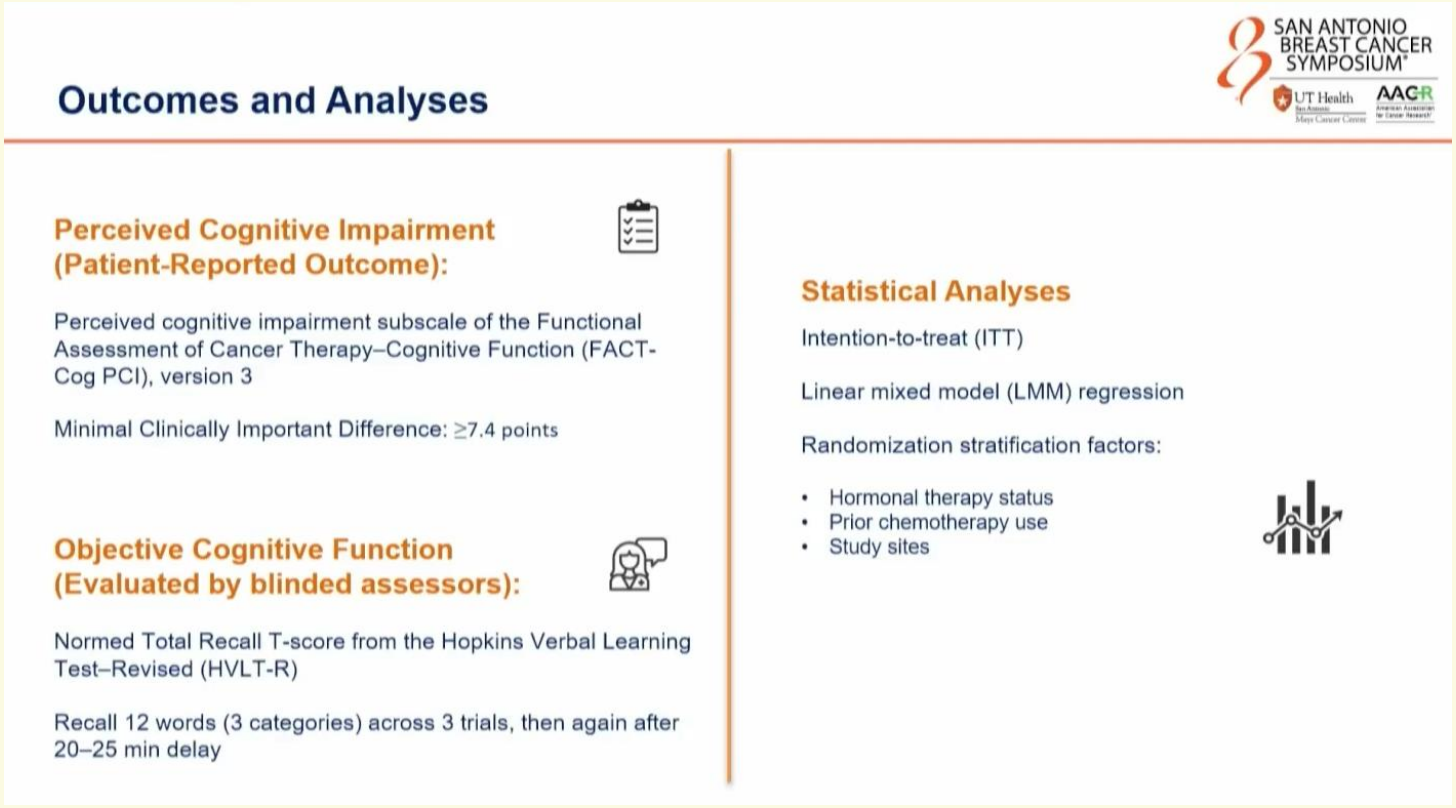
Sham Acupuncture (SA)

- 10 sessions (weekly); 20-30 minutes per session
- Same acupuncturists / care
- Non-acupuncture points
- Needles taped to the skin without penetration
- No EA

Usual Care (UC)

- Received usual medical care as directed by their physicians
- No acupuncture
- Contacted at the same frequency as the acupuncture groups

GS3-04 - Effects of acupuncture vs sham acupuncture and usual care on cancer-related cognitive difficulties among breast cancer survivors: The ENHANCED randomized clinical trial [Jun Mao, MEMORIAL SLOAN KETTERING CANCER CENTER, NEW YORK]



GS3-04 - Effects of acupuncture vs sham acupuncture and usual care on cancer-related cognitive difficulties among breast cancer survivors: The ENHANCED randomised clinical trial [Jun Mao, MEMORIAL SLOAN KETTERING CANCER CENTER, NEW YORK]

RESULTS

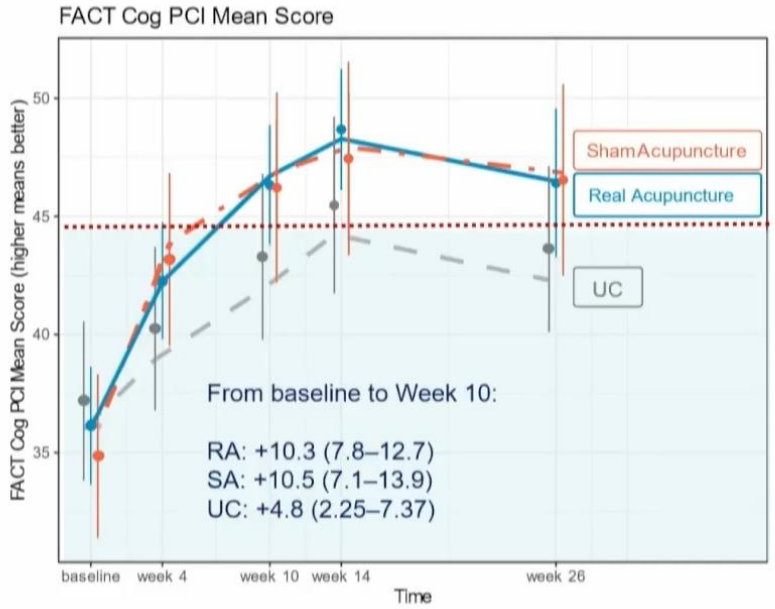
- Clinically meaningful improvements in **subjective** cognitive impairment in both *real* and *sham* acupuncture groups (week 10)

	Point difference from baseline
REAL ACUPUNCTURE	**10.3** [95% CI 7.8 - 12.7]
SHAM ACUPUNCTURE	**10.5** [95% CI 7.1 - 13.9]
USUAL CARE	**4.8** [95% CI 2.25 - 7.37]

- Sensory changes with sham acupuncture → sense of *relaxation*?

GS3-04 - Effects of acupuncture vs sham acupuncture and usual care on cancer-related cognitive difficulties among breast cancer survivors: The ENHANCED randomised clinical trial [Jun Mao, MEMORIAL SLOAN KETTERING CANCER CENTER, NEW YORK]

Subjective: Perceived Cognitive Impairment (FACT-Cog PCI)



Minimal clinically important improvement: 7.4 points

RA was significantly more effective than UC at improving FACT-Cog PCI at

Week 10 (mean difference: 5.5, p=0.003)
Week 26 (mean difference: 5.5, p=0.002)

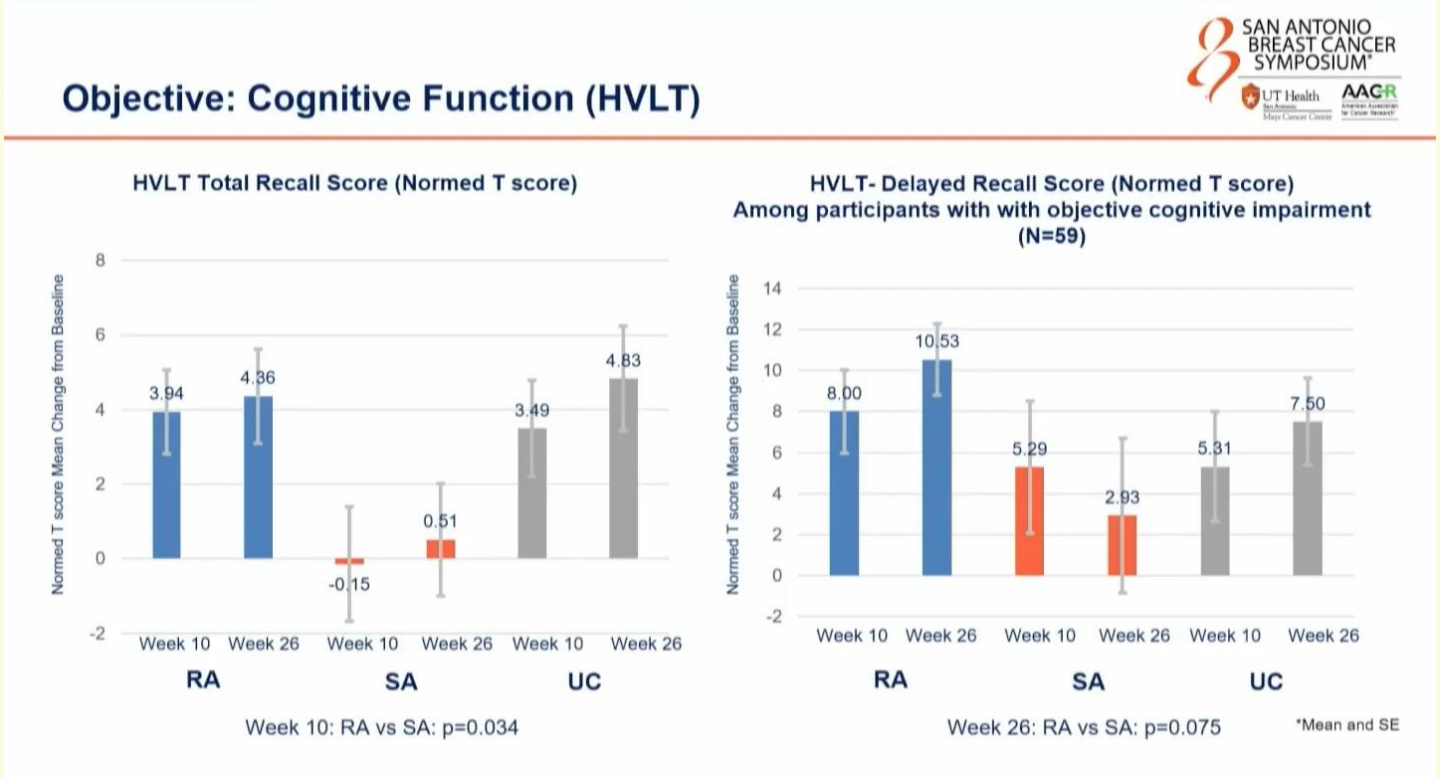
Differences between RA and SA were not statistically significant at either timepoint

GS3-04 - Effects of acupuncture vs sham acupuncture and usual care on cancer-related cognitive difficulties among breast cancer survivors: The ENHANCED randomised clinical trial [Jun Mao, MEMORIAL SLOAN KETTERING CANCER CENTER, NEW YORK]

- Significant improvements in **objective** cognitive function for *real* compared with *sham* acupuncture groups weeks 10 and 26
- Point difference = **4.1** [95% CI 0.32 - 7.87] (p = **0.034**)
- Patients with objective cognitive impairment at **baseline*** derived greater benefit → from *real* acupuncture (versus *sham*/*usual* care)
- " *The specific acupuncture needling may have specific effect on improving objective cognitive function beyond the process of receiving acupuncture*"

* 20% participants

GS3-04 - Effects of acupuncture vs sham acupuncture and usual care on cancer-related cognitive difficulties among breast cancer survivors: The ENHANCED randomised clinical trial [Jun Mao, MEMORIAL SLOAN KETTERING CANCER CENTER, NEW YORK]



GS3-04 - Effects of acupuncture vs sham acupuncture and usual care on cancer-related cognitive difficulties among breast cancer survivors: The ENHANCED randomised clinical trial [Jun Mao, MEMORIAL SLOAN KETTERING CANCER CENTER, NEW YORK]

DISCUSSION

- Emphasis on limitations of study in broader context:
  - impact of COVID-I9 (patients with college-level education
  - only 30% evaluated for objective cognitive function at baseline

- Improvements in ⟶ perceived cognitive impairment with *both* real and sham acupuncture
- Real acupuncture ⟶ **superior** for objective cognitive function
- Benefits from needling effects for *perceived* cognitive impairment but **specific effect** of acupuncture per se on *objective* cognitive function

GS2-05 - Primary results from HR+/HER2- cohort of TBCRC-053: A randomised trial of no, low or high dose pre-operative radiation with pembrolizumab and chemotherapy in node positive, HER2 negative breast cancer

[Gaorav Gupta, UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL]]

BACKGROUND

- Confirmed benefits from immune checkpoint inhibitors (ICI) in TNBC [**KEYNOTE 522** trial [Schmid P, et al NEJM 2020; 382:])
- Evidence from **Checkmate 7FL*** and **KEYNOTE-756**** for benefit ICI in *HR positive*, *HER2 negative* tumors (increased pCR rates)
- Benefit confined to tumors with *high* baseline levels of **stromal T-cell infiltration** and **PD-L1**

* Loi S, et al Nat Med 2025; 31: 433 - 441

** Cardoso F, et al Nat Med 2025 31: 442 - 448

GS2-05 - Primary results from HR+/HER2- cohort of TBCRC-053: A randomised trial of no, low or high dose pre-operative radiation with pembrolizumab and chemotherapy in node positive, HER2 negative breast cancer [Gaorav Gupta, UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL]]

Immune checkpoint inhibitors (ICI) in HR+HER2- early-stage breast cancer

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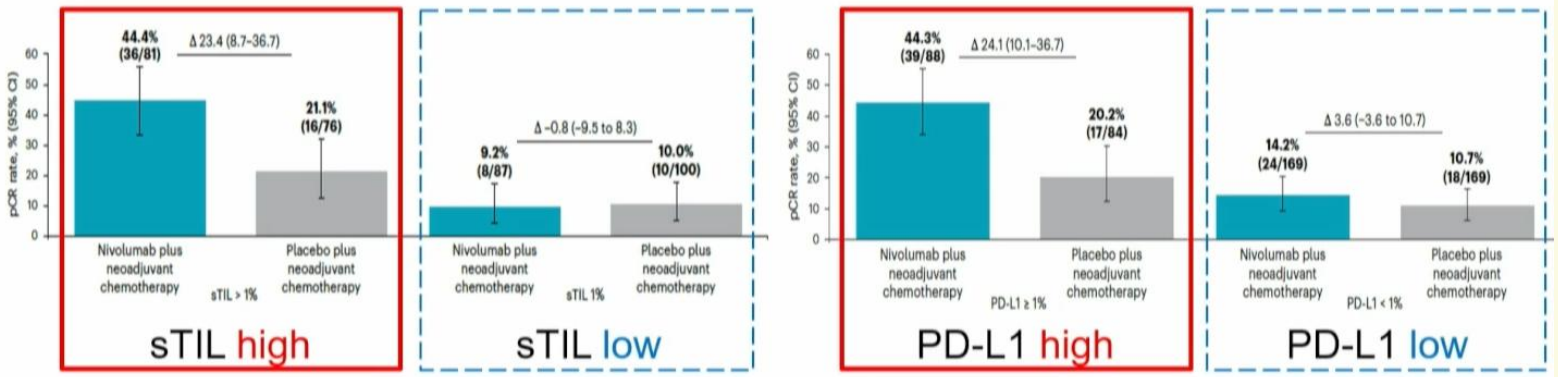
- Checkmate 7FL[1] and KEYNOTE-756[2]: ↑pCR with ICI added to NAC



- ICI benefit only in tumors with high baseline TIL and PD-L1[1]

[1]Loi, et al. *Nat. Med.* 2025 31:433-441. PMID: 39838118 [2]Cardoso, et al. *Nat. Med.* 2025 31:442-448. PMID: 39838117

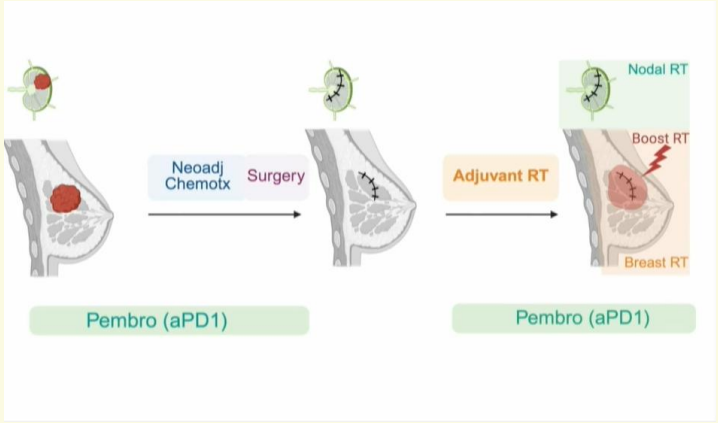
GS2-05 - Primary results from HR+/HER2- cohort of TBCRC-053: A randomised trial of no, low or high dose pre-operative radiation with pembrolizumab and chemotherapy in node positive, HER2 negative breast cancer

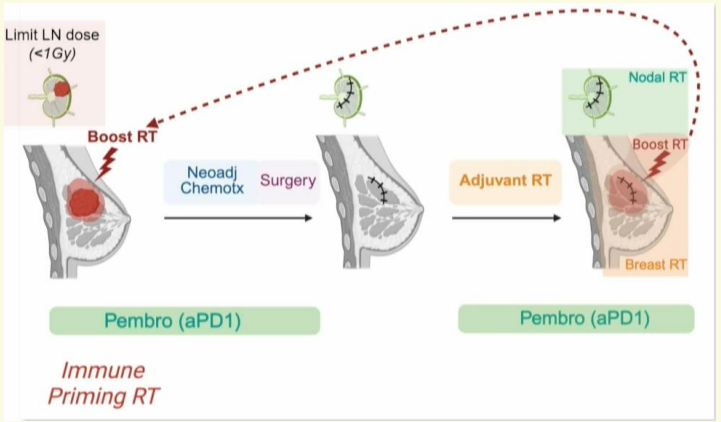
[Gaorav Gupta, UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL]]

QUESTION

- Can response of HR positive/HER2-negative tumors → be increased by enhancing immune infiltration (sTIL/PD-L1) *before* commencing neoadjuvant chemoimmunotherapy?

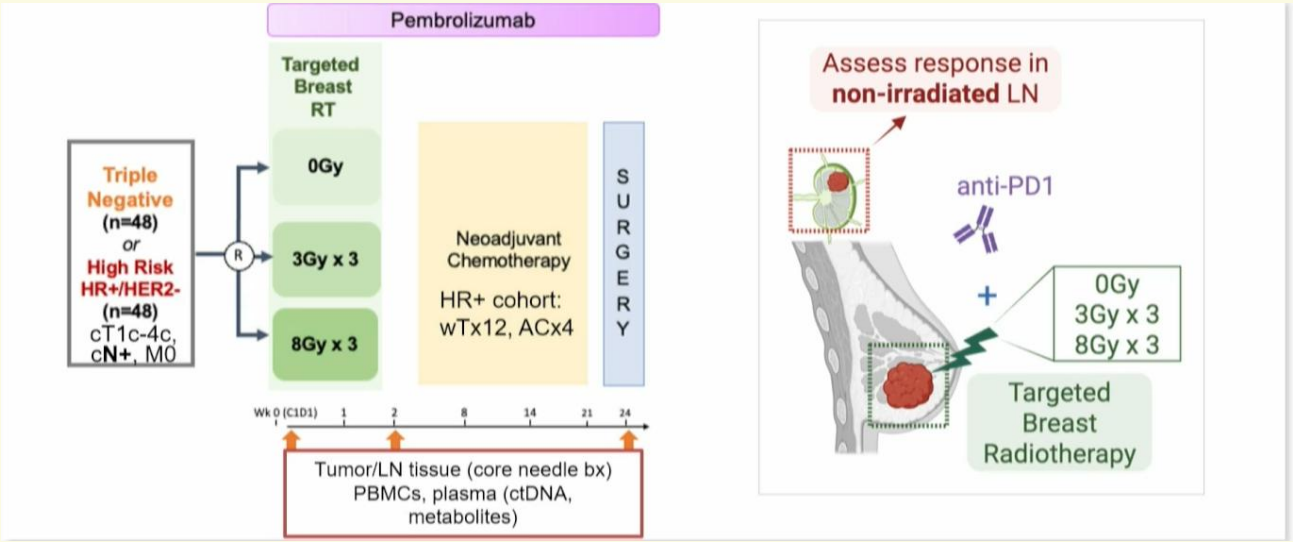
- Re-purpose **radiation therapy** to stimulate immune infiltration?





GS2-05 - Primary results from HR+/HER2- cohort of TBCRC-053: A randomised trial of no, low or high dose pre-operative radiation with pembrolizumab and chemotherapy in node positive, HER2 negative breast cancer [Gaorav Gupta, UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL]]

- **CanTBCRC-053(p-RAD)** randomised trial → evaluating low or high dose pre-operative radiotherapy in HR+, HER2 negative cancers:
  - 49 patients (median age 49.5 years)
  - regional nodal involvement
  - randomised 1:1:1 to none, low dose, high dose radiation (over **3** days)



GS2-05 - Primary results from HR+/HER2- cohort of TBCRC-053: A randomised trial of no, low or high dose pre-operative radiation with pembrolizumab and chemotherapy in node positive, HER2 negative breast cancer

[Gaorav Gupta, UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL]]

- **Primary endpoint** = breast tumor T-cell infiltration (2-week biopsy)*
- **Co-primary endpoint** = complete nodal response rate (ypN0)
- **Secondary endpoints** = composite pCR/RCB + PD-L1 expression
- **Exploratory endpoints** = transcriptional signatures of response

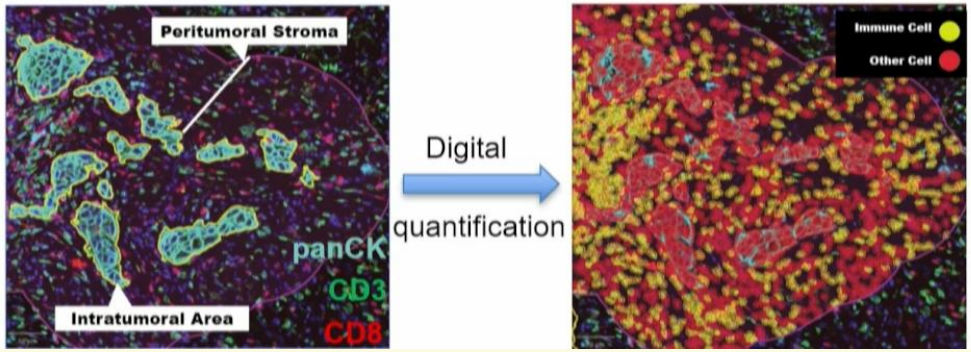



* reference cohort of untreated tumors

GS2-05 - Primary results from HR+/HER2- cohort of TBCRC-053: A randomised trial of no, low or high dose pre-operative radiation with pembrolizumab and chemotherapy in node positive, HER2 negative breast cancer [Gaorav Gupta, UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL]]

Primary Endpoint: T Cell Infiltration (TCI) at 2 wks

- TCI was evaluated by a pre-defined **"Breast Immunoscore"**:
  - Percentile rank of peritumoral (i.e., stromal) and intratumoral CD3/CD8 T cell to tumor ratio relative to an untreated cohort, using multiplexed panCK/CD3/CD8 immunofluorescence
- Upper quartile (≥0.75) TCI is considered a T cell responder



GS2-05 - Primary results from HR+/HER2- cohort of TBCRC-053: A randomised trial of no, low or high dose pre-operative radiation with pembrolizumab and chemotherapy in node positive, HER2 negative breast cancer

[Gaorav Gupta, UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL]]

RESULTS

- Increase in proportion of tumors with *highest* quartile of **T-cell infiltration** with pre-operative radiotherapy:

Radiation dose	level of T-cell infiltration
NO RADIATION	**31%**
RADIATION (9Gy)	**40%**
RADIATION (24Gy)	**53%**

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- **Primary endpoint** analysis ⟶ only *high* radiation dose (**24Gy**) associated with significant increase T-cell infiltration of primary tumor
- High levels of **T-cell infiltration** linked to higher levels of **PD-L1** expression
- Pre-operative radiation treatment at dosage of **24Gy**:
  - increases *both* T-cell infiltration and PD-L1
  - *improved* response rates compared with NACT + immunotherapy

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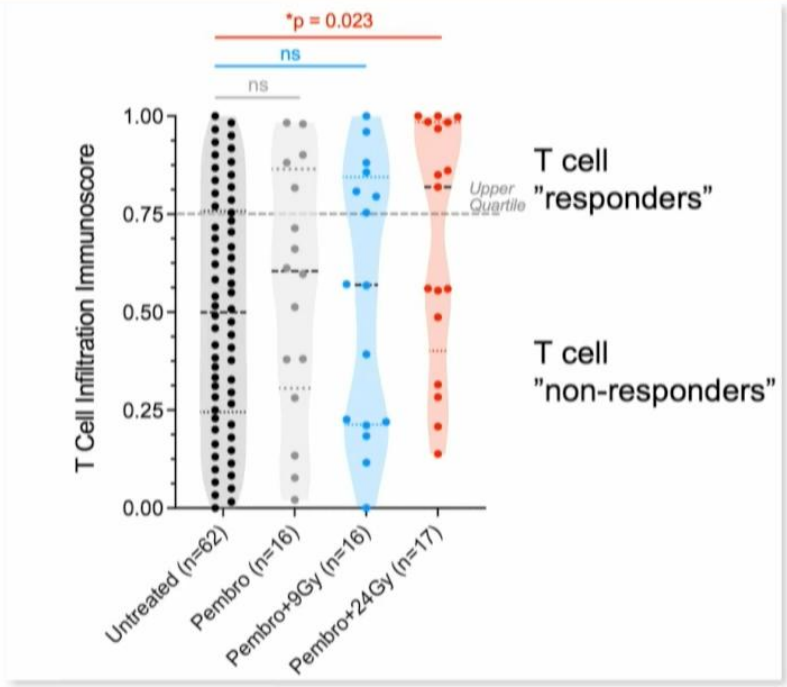
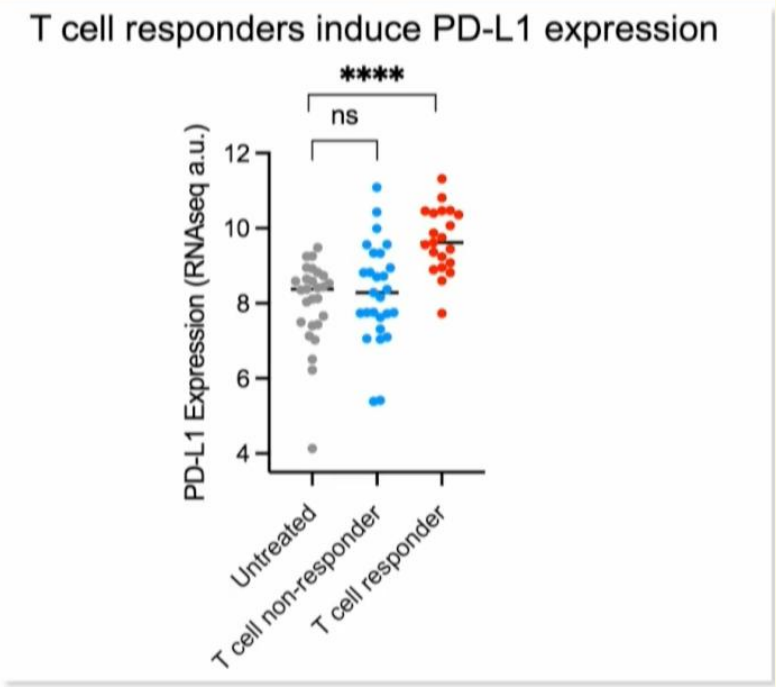
Primary Endpoint: Pembro + 24Gy Significantly Increases TCI





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- Dose dependent **nodal** response → increased rates **ypN0** in surgically excised axillary nodes*:

Radiation dose	Rate of ypN0
NO RADIATION	**24%**
RADIATION (9Gy)	**29%**
RADIATION (24Gy)	**33%**

* Also increased rates overall pCR (**18%**) and lower residual cancer burden (**27%**)

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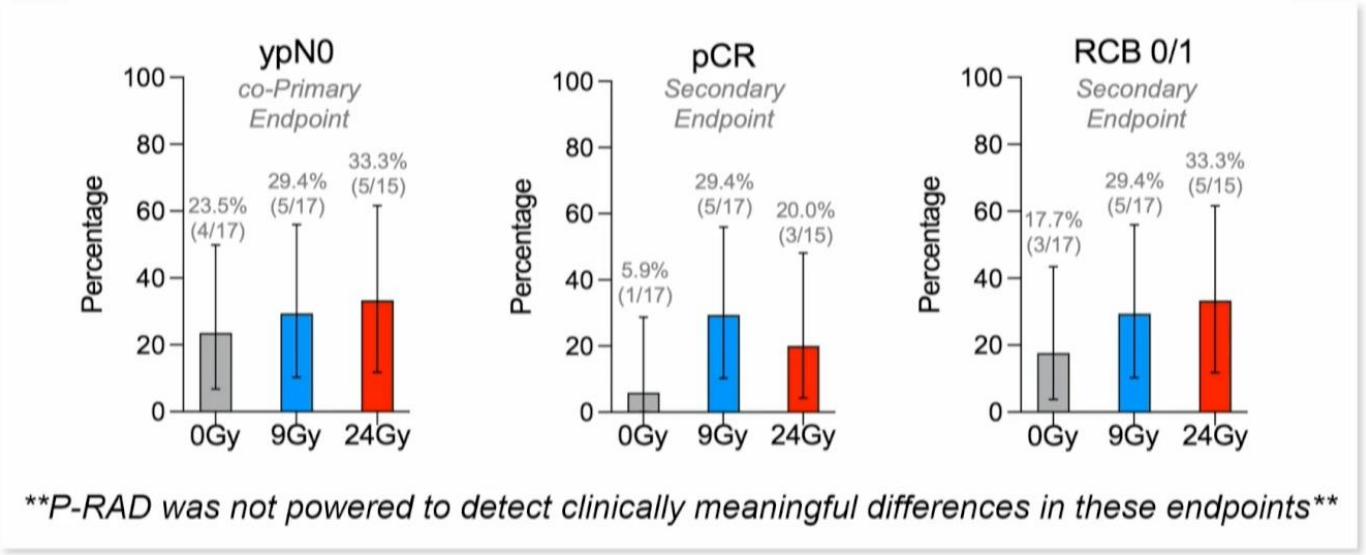
- None of the differences in **surgical outcomes** statistically significant

Surgical Outcomes



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DISCUSSION

- Increase in **T-cell infiltration** with pre-operative RT at dosage **24Gy** combined with pembrolizumab (ICI)
- Impressive rates of response *pathologically* in nodes despite **50%** patients with N2-N3 tumors
- Exploratory analyses → suggest *greatest* benefit in **non-luminal type-A tumors** with i*nduction* of PD-L1 at 2-week biopsy time point
- Small number of patients → further trials to confirm findings and clarify clinical benefits in terms of disease control

THANK YOU