

# Post Neoadjuvant Chemotherapy and the Axilla

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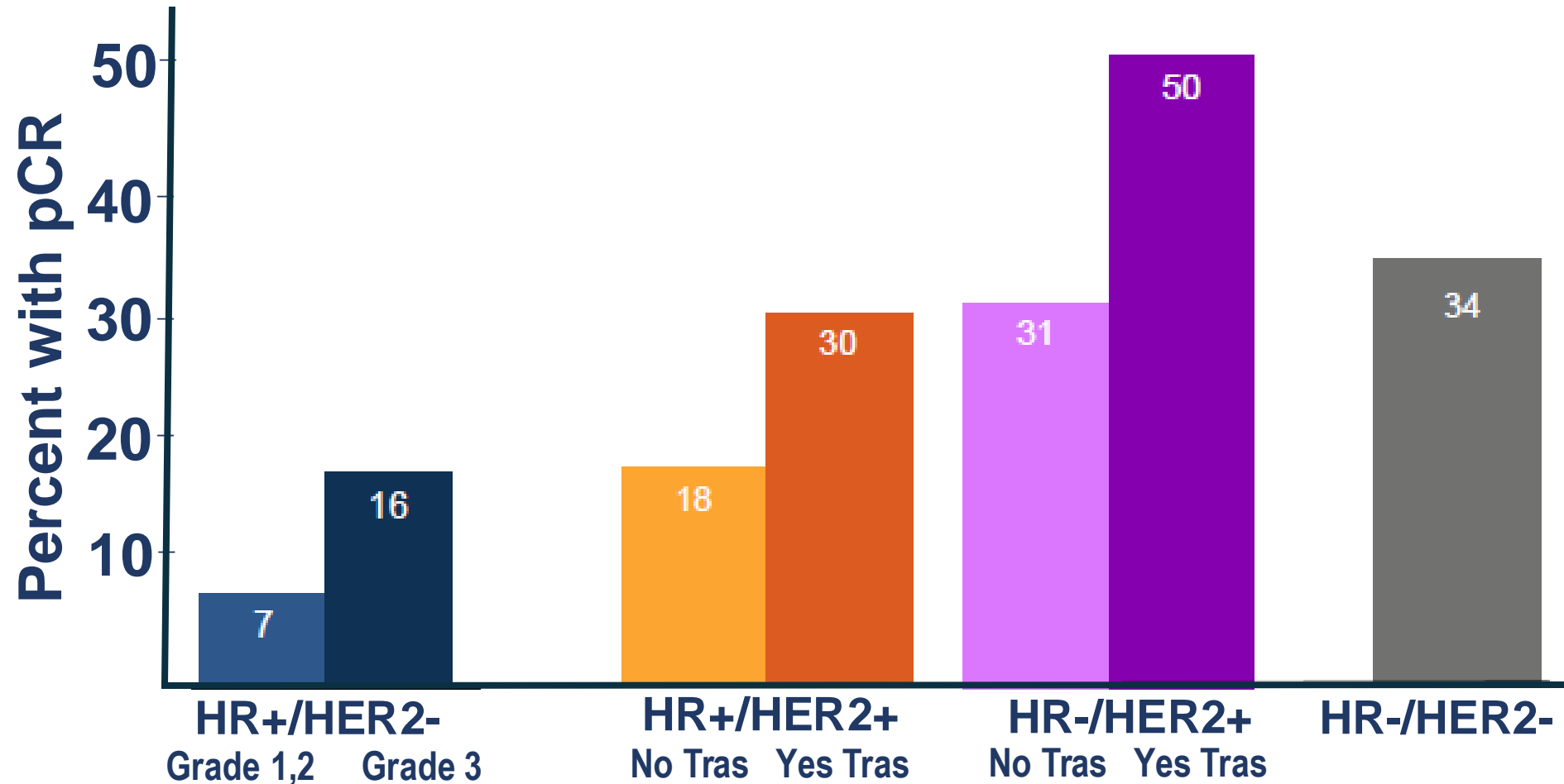
# Evolution in Clinical Rationale for Neoadjuvant Chemotherapy (NAC)

- NAC was originally utilized to convert patients with **inoperable LABC** to **surgical candidates**
- **Similar outcomes** were shown between **NAC** and **adjuvant chemotherapy** in RCTs in patients with **operable or locally advanced BC**
- NAC became a **reasonable alternative** to adjuvant chemotherapy for those with **large operable disease**
- NAC offers **several potential clinical advantages** over adjuvant chemotherapy **in appropriately selected candidates**

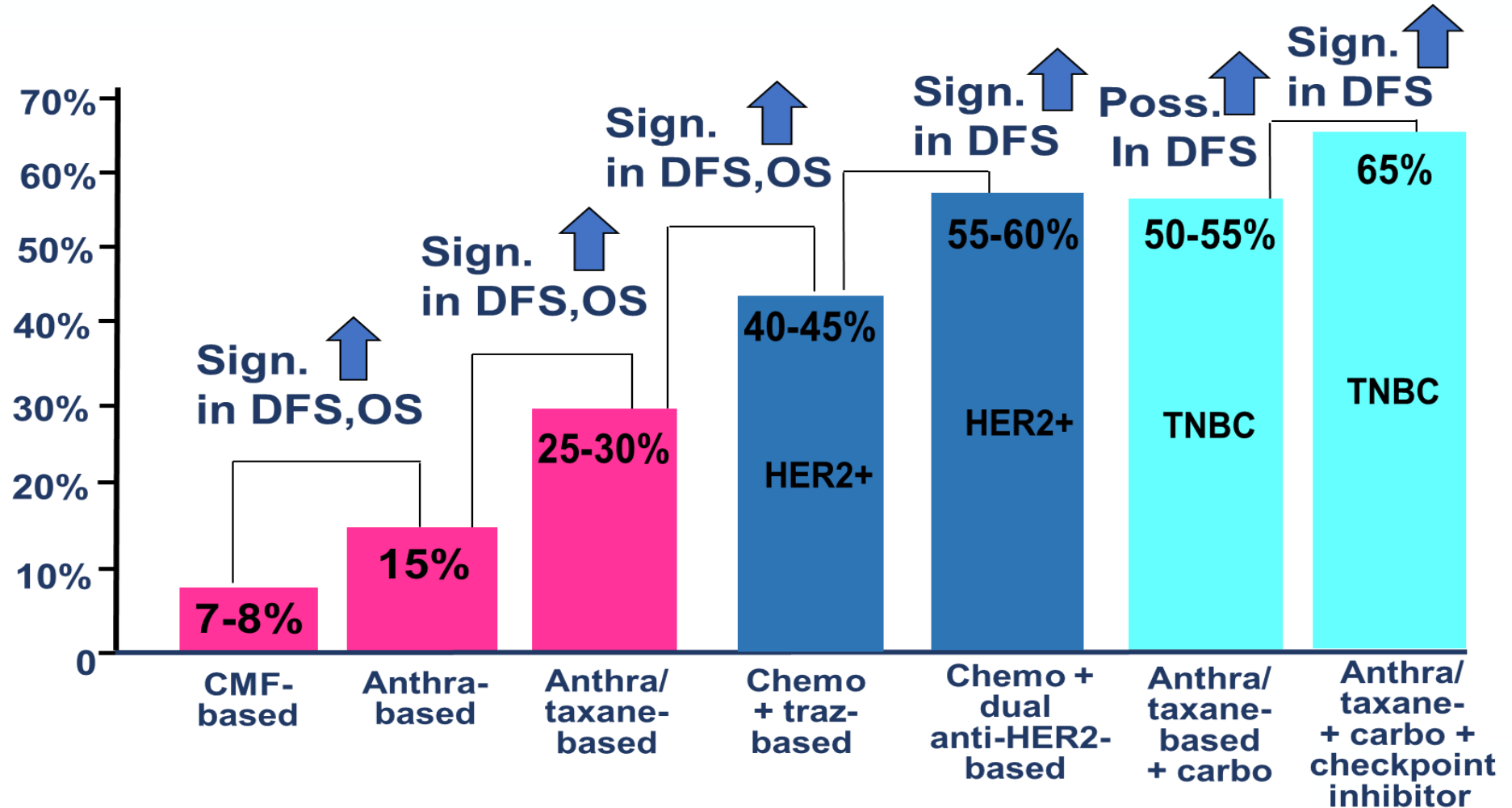
# Pathologic Complete Response (pCR): A Surrogate Endpoint for NAC Efficacy

- Patients who achieve **pCR** following NAC have **significantly better outcomes** than those who do not
- As a result, pCR has become a **surrogate endpoint for NC efficacy**
- pCR can be utilized for **accelerated approval of new agents** for the neoadjuvant treatment of breast cancer

# CTNeoBC Meta Analysis: pCR Rates by Tumor Subtype



# pCR Rates and Adjuvant Chemotherapy Efficacy



# How Can We Maximize the Clinical Impact of NAC in the Era of Precision Medicine?

- Continue to identify better predictors of pCR, so we can use NAC in patients more likely to benefit and avoid it in those less likely to benefit:
  - Use of baseline biomarkers
  - Identify early changes in biomarkers with NAC
- Use pCR and EFS for accelerated **drug approval**
- Use primary tumor response to individualize loco-regional and **systemic therapy**

# Tailoring Loco-Regional Therapy with NAC

## Initial Focus

- Conversion of patients with **inoperable** tumors to **operable** candidates
- Conversion of **mastectomy** candidates to candidates for **breast conserving surgery**
- Improvement in **cosmesis** by **reducing the size of lumpectomy** in breast conserving surgery candidates with large tumors or unfavorable location (proximity to nipple-areola complex, inferior-pole tumors)

# Tailoring Loco-Regional Therapy with NAC

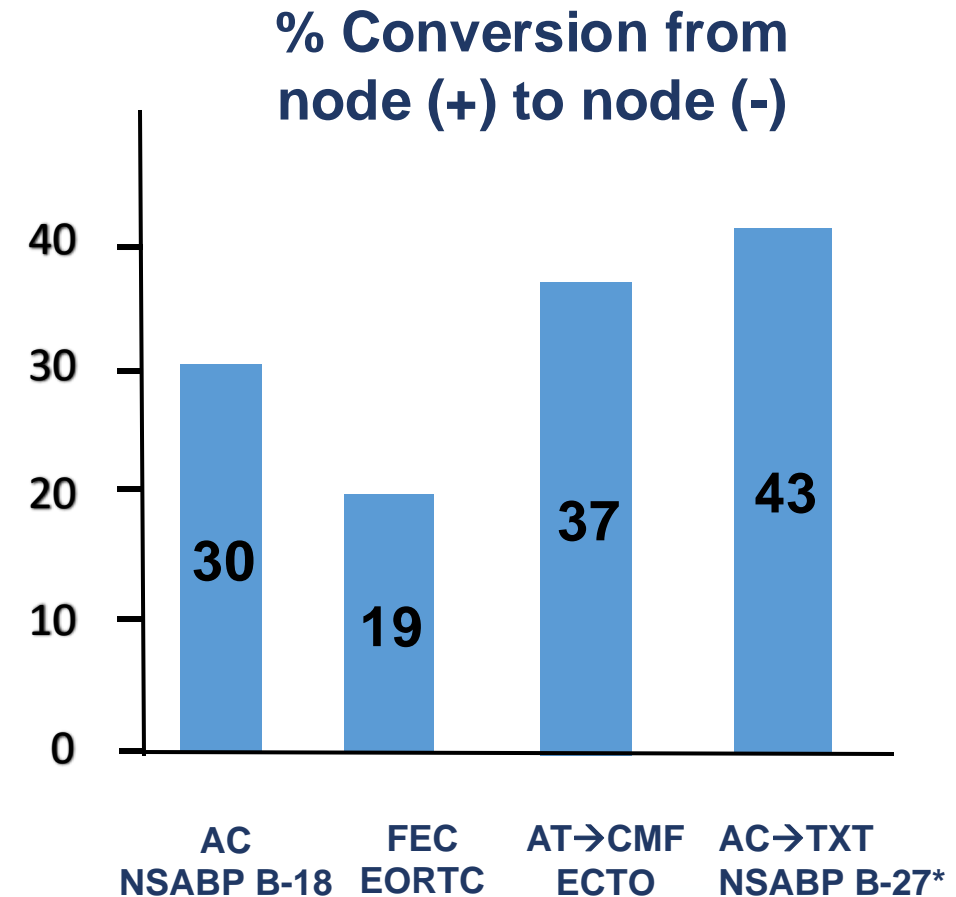
## Recent Developments and Trends

- Reduction in the **extent of axillary surgery** by down-staging involved axillary nodes (SLNB)
- Reduction in the **extent of loco-regional XRT** by down-staging primary tumors and axillary nodes
- Potential for **eliminating a loco-regional therapy altogether (surgery or XRT)** with use of more active regimens and/or appropriate patient selection (imaging/biomarkers)



# Effect of NAC on Axillary Nodal Metastases

- In early RCTs comparing NAC to surgery first, NAC down-staged axillary nodes in 30%-40% of the patients
- **50%-75% axillary down-staging** expected in **triple-negative** and **HER2+** patients
- Potential for decreasing the extent of axillary surgery with **sentinel node biopsy (SLNB)**



\*Assuming 30% nodal down-staging with neoadjuvant AC

# Decreasing the Extent of Axillary Surgery With NAC

- This concept is currently mostly applicable to patients with **operable breast cancer** ( $cT_{1-3}$   $N_0$ - $cN_1$ )
- **Feasibility and accuracy of SLNB after NAC is questionable in patients with LABC** ( $T_4$ ,  $cN_2$ , IBC)

# Management of Pts With cN0 Axilla Before NAC

- **SLNB alone after NAC** has become the **arguable standard** if the **SLN is negative**
- This approach capitalizes on the **down staging effect of NAC** in sub-clinically involved axillary nodes
- **No differences in SLN Identification Rate or False Negative Rate** when compared to upfront SLNB:
  - **Meta-analysis: SLNB after NAC → ALND (16 studies, 1,456 pts)**
  - **Pooled IR for SLNB: 96%**      **Pooled FNR: 6%**

# SLNB After NAC in Pts With Documented cN+: Four Prospective Trials

	Z1071	SENTINA	SN FNAC	GANEA-2
N	649	592(cN+)*	153	307
Mapping	Dual Tracer Recommended:79%	Technetium required	Technetium required, IHC	Dual Tracer Recommended
Pre-op Bx?	Yes	Yes (25%)	Yes	Yes
Nodal pCR	41%	52% ypN0	35%	34%
IR	92.7%	80.1%	87.6%	79.5%
<b>FNR (Overall)</b>	<b>12.6%</b>	<b>14.2%</b>	<b>8.4%</b>	<b>11.9%</b>
1 SLN	31.5%	24.3%	18.2%	19.3%
2 SLN	21.1%	18.5%	4.9%	
≥3 SLN	9.1%	7.3%		7.8%

**Z1071: FNR was 6.8% when clip found in SLNs but 19% when clip was found in the ALND**

# Clipped Node Removal +/- SLNB

## MDACC Experience

Clipped node +/- SLN to reflect the status of the nodal basin in all-comers undergoing NAC

	N	Node +	pCR (%)	FNR (%)
Clipped Node	191	120	37%	4.2% (95%CI, 1.4-9.5)
SLN	118	74	37%	10.1% (95%CI, 4.2-19.8)
SLN + Clipped Node	118	74	37%	1.4% (95%CI, 0.03-7.3)

Clipped node was not a SLN in 23% of pts  
 → *“Targeted Axillary Dissection”*

# Radioactive Iodine Seed Placement in the Axilla With SLNB After NAC in Breast Cancer:

## Results of the Prospective Multi-Center RISAS trial

RISAS procedure  
successful  
N=223/227 (98%)

pCR axilla  
35.4%

- **FNR = 5/144 = 3.47%** (CI, 1.38-7.16)
- **NPV = 73/78 = 93.59%** (CI, 87.0-97.4)
- **Non-inferiority inconclusive → upper bound CI > 6.24%**

Axillary pCR  
(N=79, ALND  
performed in 73)

Residual axillary  
disease  
(N=144, ALND  
performed in 135)

**MARI<sup>1</sup>**

**IR: 97%**

**FNR: 7%**

**NPV: 83.3%**

<sup>1</sup>Donker M et al. *Ann Surg.* 2015;261(2):378-382.

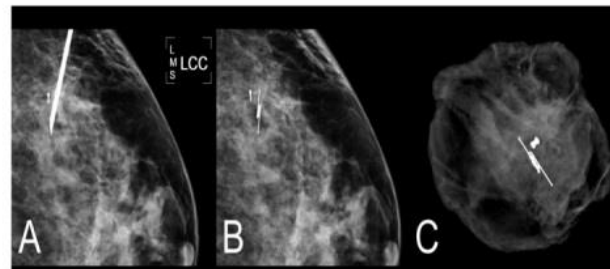
# New Methods of Wireless Lymph Node Localization



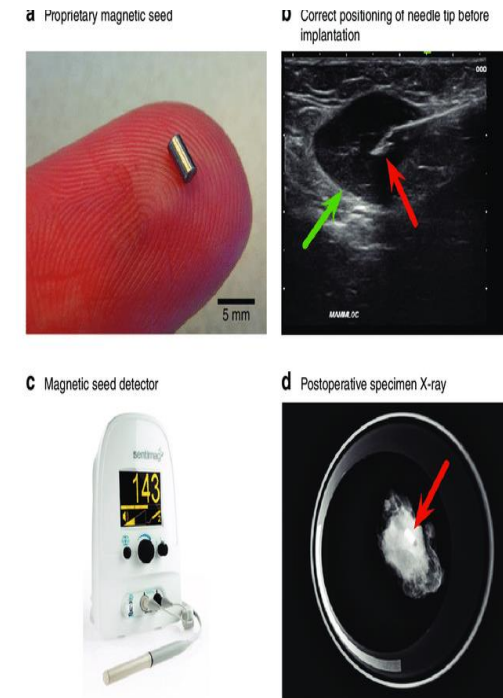
**Radioactive Seeds**



Figure 1. SAVI SCOUT System Components.



**Savi Scout**



**Magnetic Seeds**

# Axillary Recurrence Rate With (-) SLNB Alone After NAC

Author	# Pts	Pre-NAC Stage	Median F/U	# Axillary Recurrence	% Axillary Recurrence
<b>Classe</b>	419	cN0	36 mos	1	<b>0.2%</b>
<b>Kahler-Ribeiro-Fontana</b>	305	cN0	92 mos	7	<b>2.3%</b>
	123	cN1-2	92 mos	2	<b>1.6%</b>
<b>Martelli</b>	95	cN0	108 mos	0	<b>0%</b>
	81	cN1	108 mos	0	<b>0%</b>
<b>Piltin</b>	159	cN1-3	34 mos	1	<b>0.6%</b>
<b>Wong</b>	101	cN0	36 mos	1	<b>1%</b>
	58	cN1,2	36 mos	0	<b>0%</b>



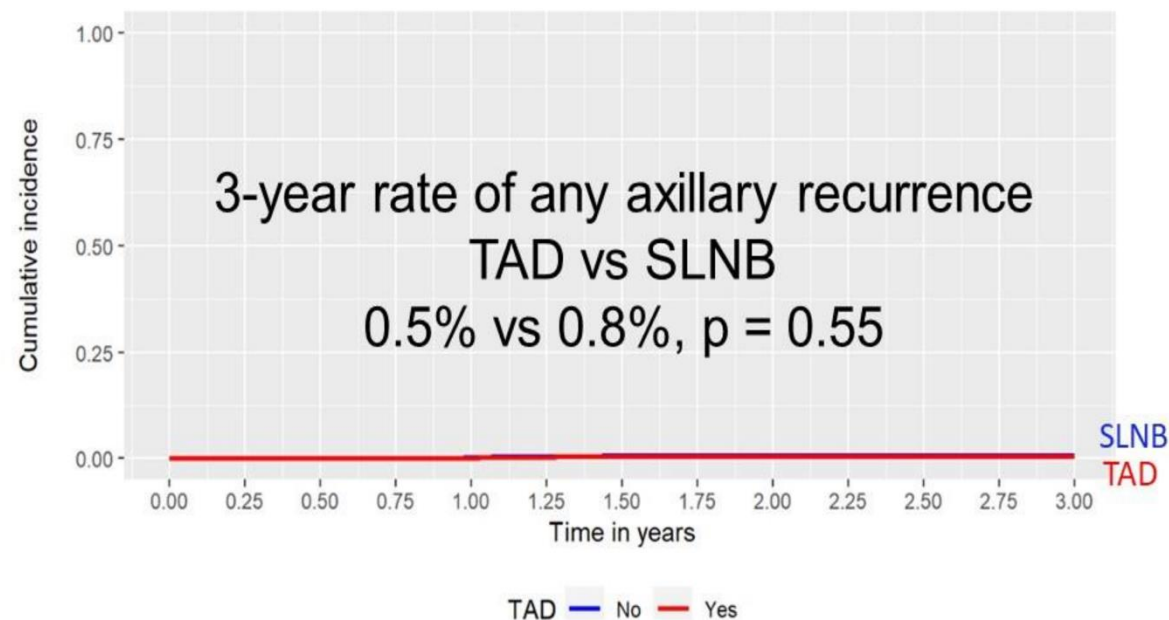
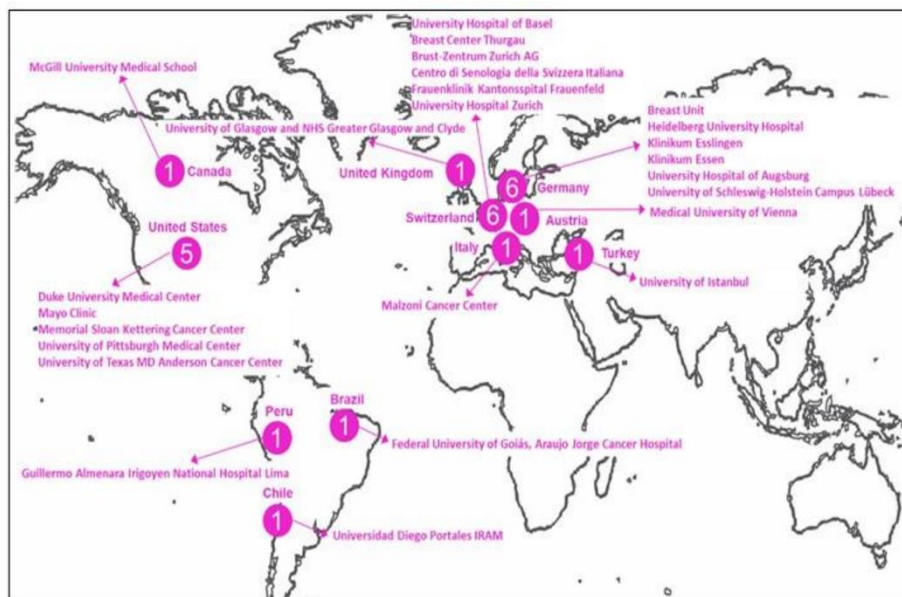
# Axillary Recurrence Rate With (-) SLNB Alone After NAC

Author	# Pts	Axillary Surgery	Median F/U Years	Nodal Irradiation	Axillary Recurrence
<b>Milan</b>	70	SLNB Single Tracer	5.1	0%	<b>0%</b>
<b>MSKCC</b>	234	SLNB Dual Tracer	3.3	70%	<b>0.4%</b>
<b>NEOSENTI</b>	211	SLNB Single Tracer (65%)	3.0	100%	<b>0%</b>
<b>MARI</b>	99	MARI	3.0	43%	<b>1.0%</b>
<b>Asan Center</b>	314	SLNB Single Tracer	5.4	87%	<b>3.2%</b>
<b>Fudan Univ.</b>	75	TAD	3.1	65%	<b>0%</b>

# TAD vs. SLNB

## Axillary Recurrence

- OMA: Retrospective real-world study<sup>1,2</sup>
- 2013-2020: 478 TAD versus 666 SLNB



<sup>1</sup>Montagna G, Morrow M, Weber WP, et al. JAMA Oncol. 2024 Apr 25: Online ahead of print.

<sup>2</sup>Presented at San Antonio Breast Cancer Symposium® 2022

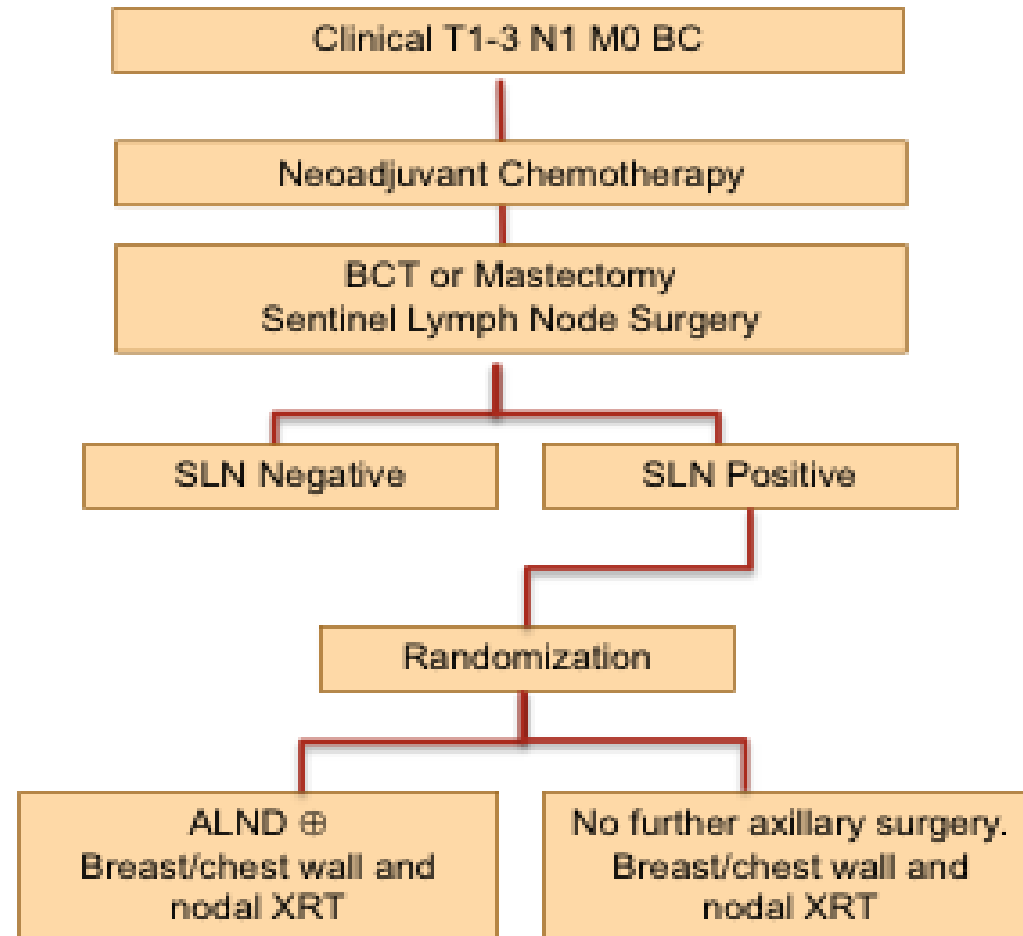
# What to Do if the SLNs Are Still Positive After NAC?

Study	n	Non-SLN positivity
Jeruss	104	71%
Galimberti	396	71.5%
Moo	171	61%

**High rates of Non-SLN positivity after NAC across all studies**

# ALLIANCE A11202 Trial

## ALND vs. Not in cN1 Patients With + SLNB after NAC

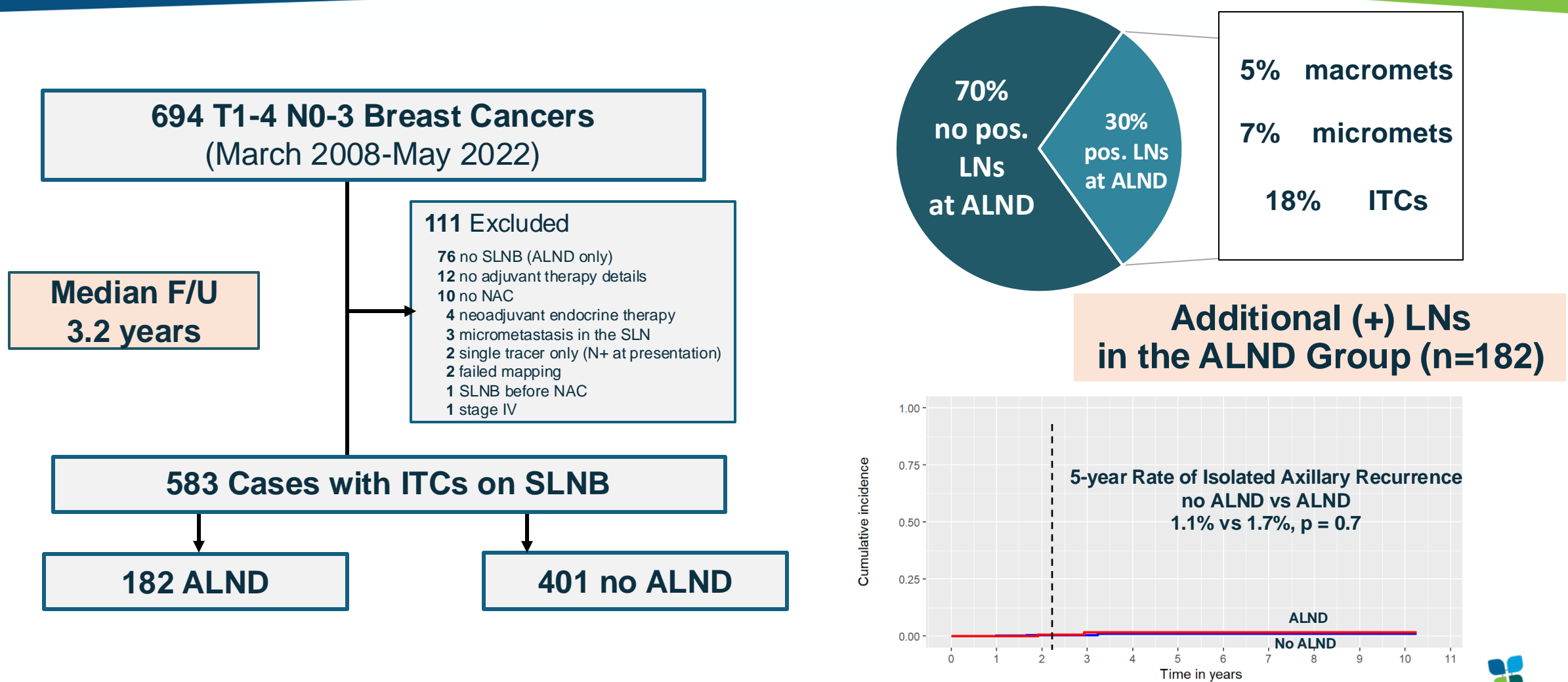


# Rates of Non-SLN Positivity with + SLNs After NAC According to Size of SLN Metastases

	ACOSOG Z1071	SN FNAC	MSKCC
<b>Micromets</b>	164/273 (60.1%)	3/8 (37%)	34/61 (56%)
<b>Macromets</b>		28/44 (64%)	75/121 (62%)

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

# Are Nodal Isolated Tumor Cells (ITCs) After NAC an Indication for Axillary Lymph Node Dissection?



# Importance of Minimizing SLNB False-Negative Rate After NAC

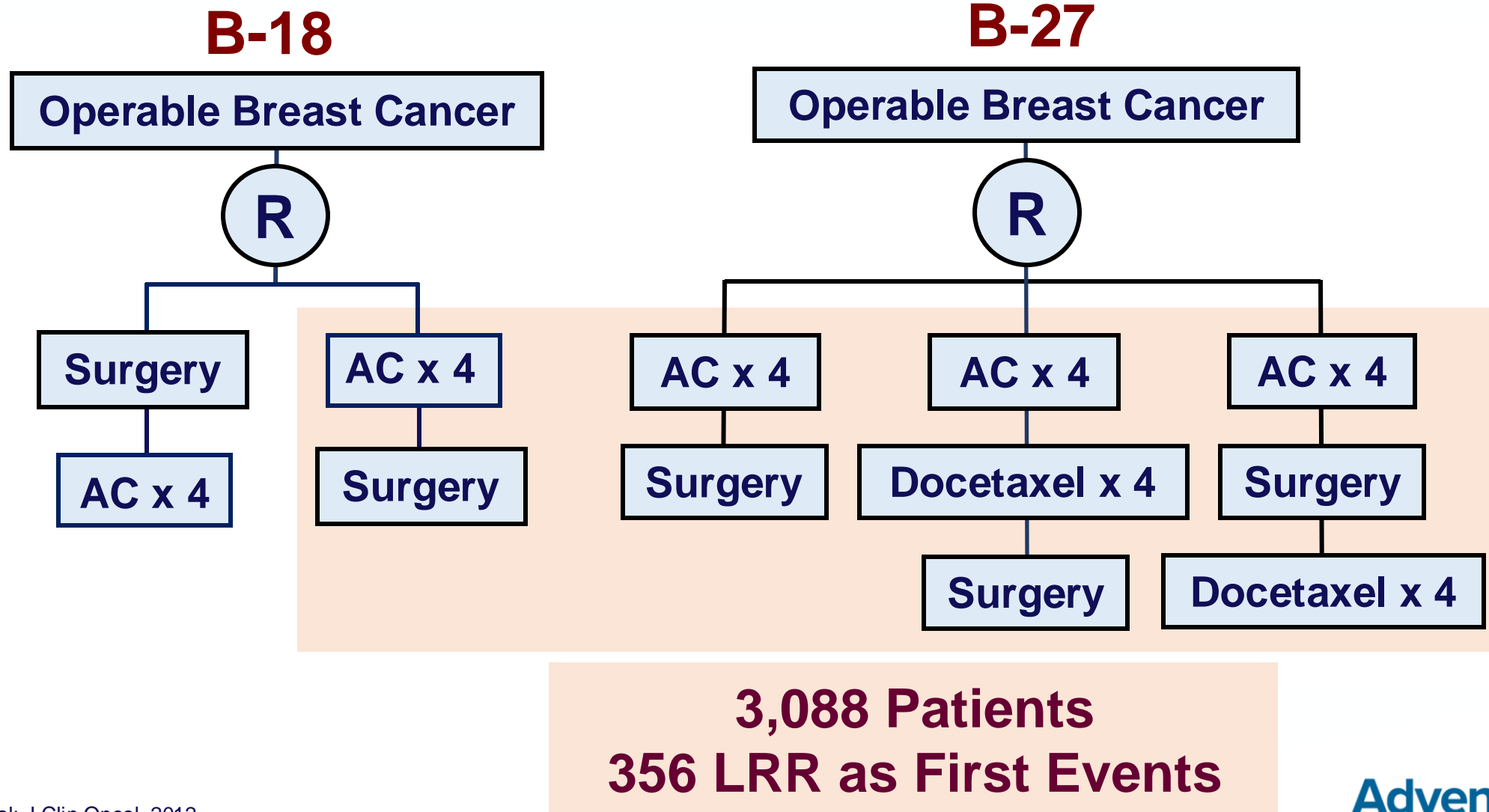
- Accurately identifying residual disease in the axilla after NAC could **dictate appropriate radiotherapy use and appropriate post-NAC systemic Rx:**
  - Capecitabine in TNBC
  - T-DM1 in HER2+
  - Abemaciclib in ER+/HER2-
  - Olaparib in *BRCA*+ patients
- Additionally, several clinical trials are currently evaluating adjuvant therapy **escalation or de-escalation strategies based on path response in the breast and lymph nodes**

# Can We Tailor Use of Regional Nodal Irradiation in cN+ Patients Who Convert to ypN0 With NAC?

- For patients who undergo **upfront surgery** and have **+ axillary lymph nodes**, the **benefit of adjuvant RNI** including the chest wall after mastectomy or when added to whole breast irradiation after lumpectomy is **well established**.
- **Patients who present with cN+ and become ypN0** after NAC have **lower LRR rates** compared to those who remain ypN+
- **Do such patients benefit from RNI?**

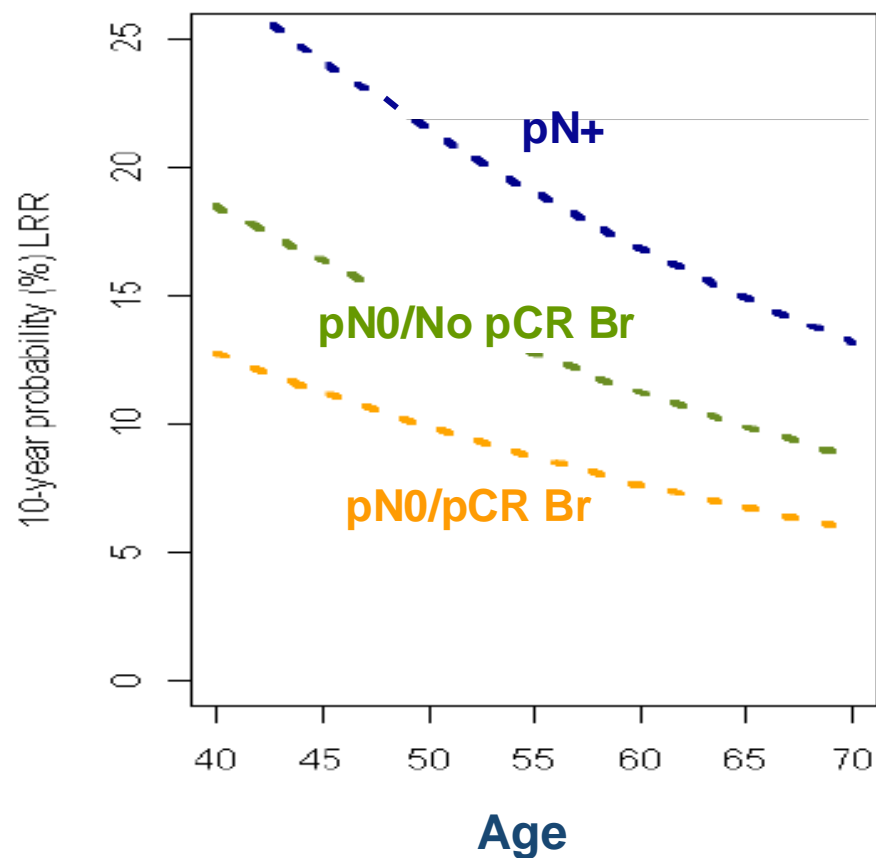


# NSABP B-18/B-27: Combined Analysis

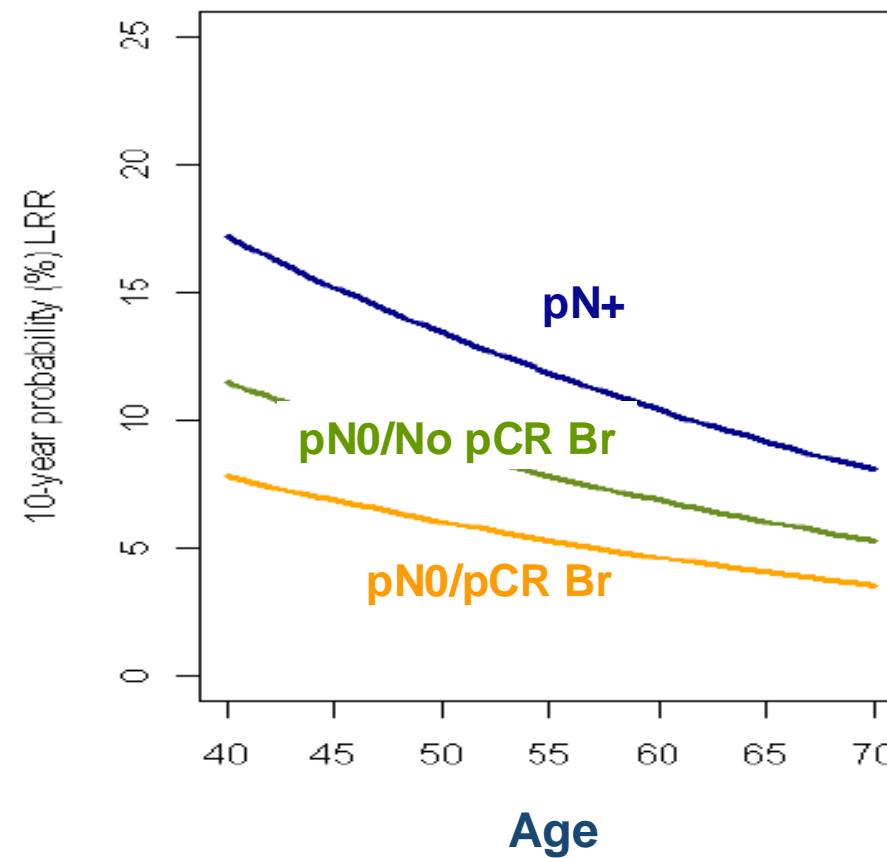


# Nomogram for Prediction of 10-Year Rate of LRR After NC: Lumpectomy + XRT

## Clin N (+)

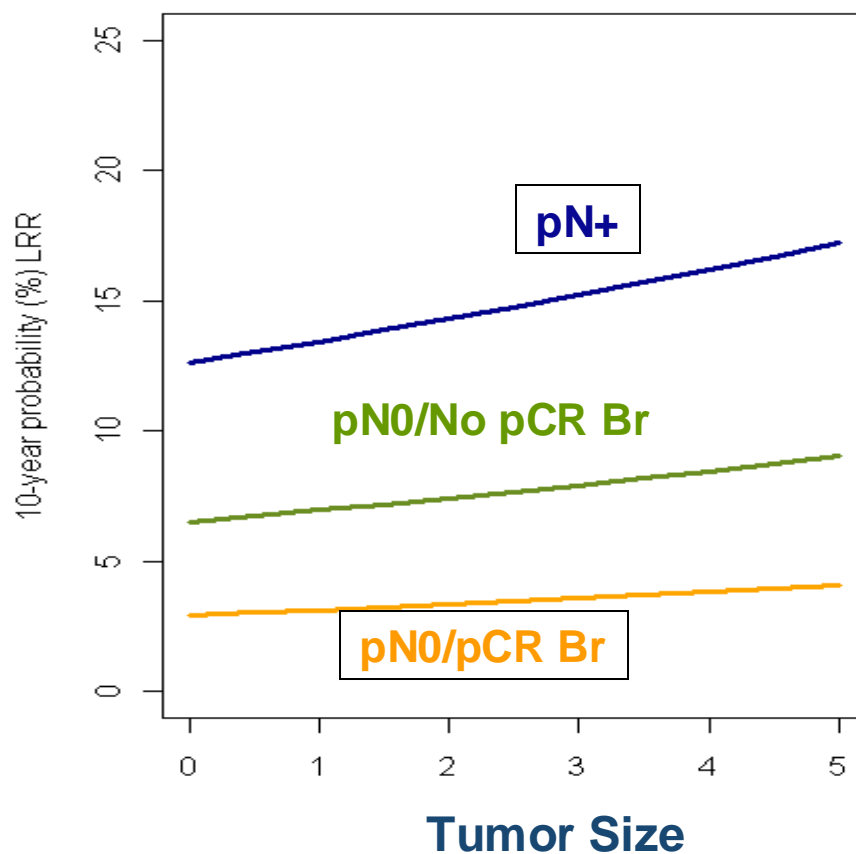


## Clin N (-)

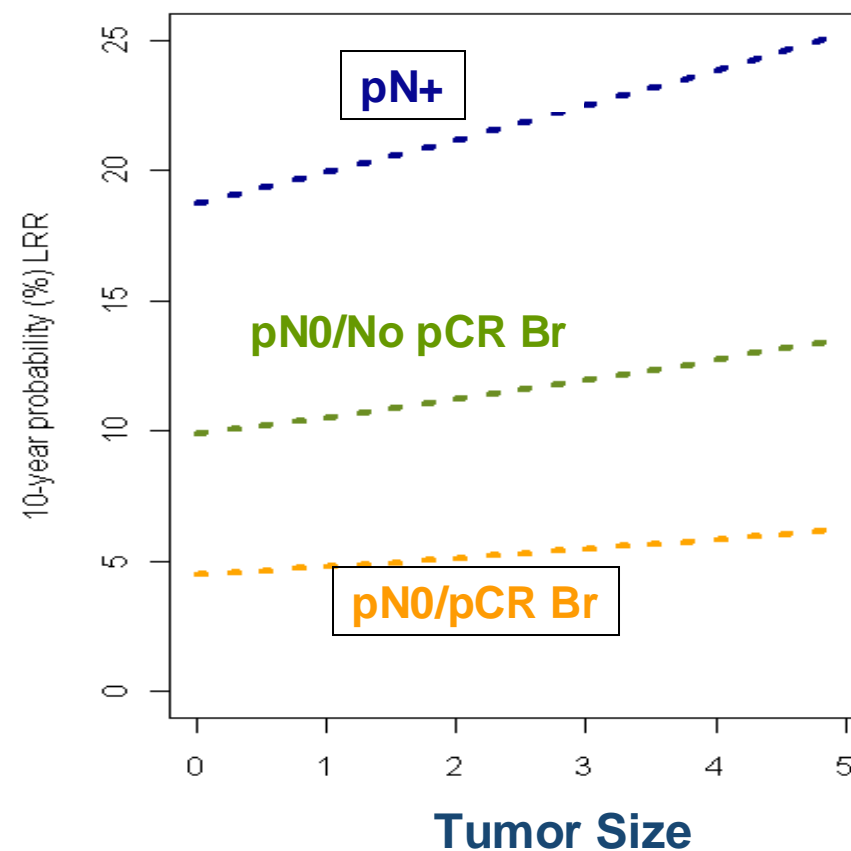


# Nomogram for Prediction of 10-Year Rate of LRR After NC: Mastectomy

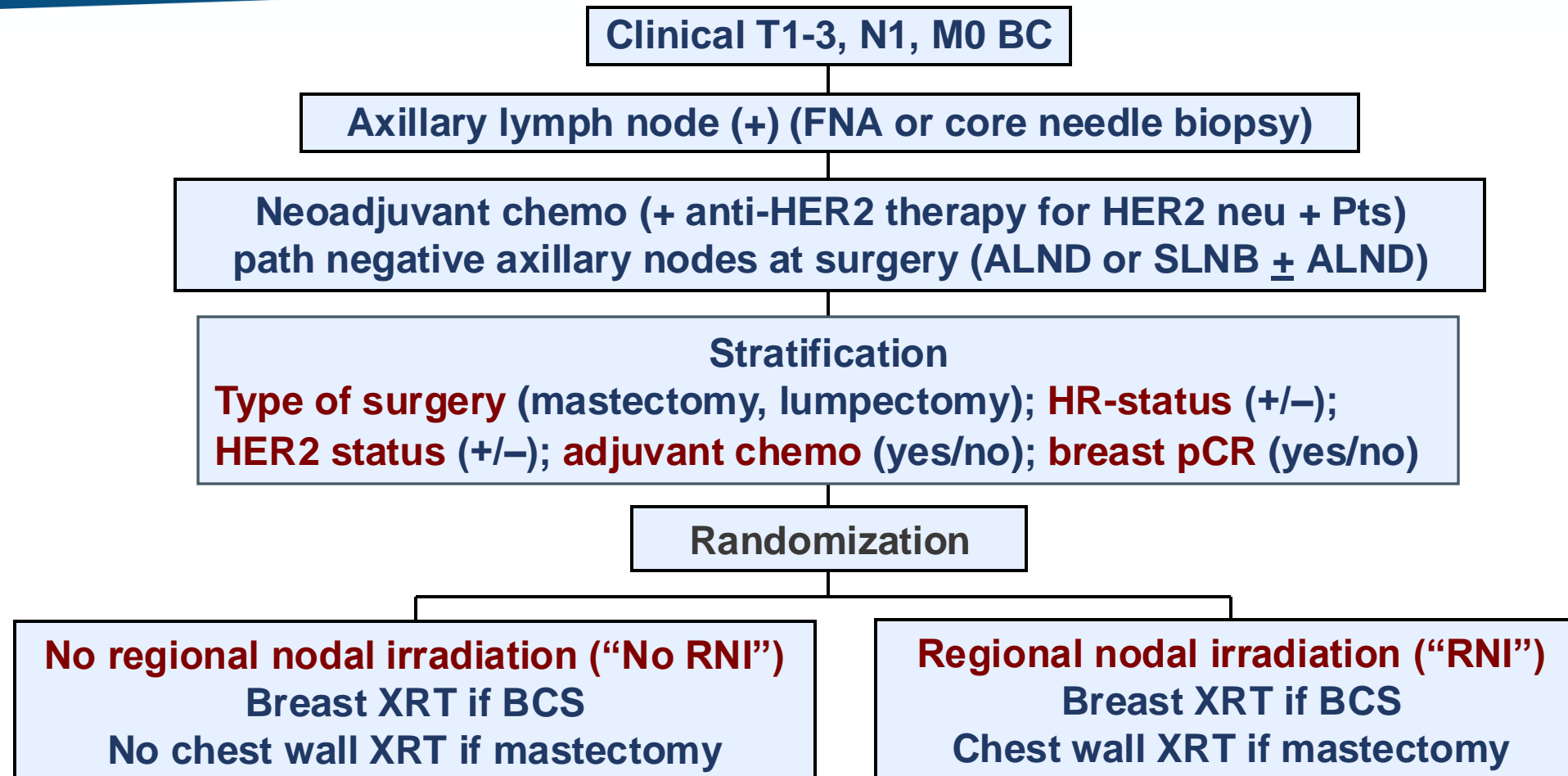
## Clin N (-)



## Clin N (+)

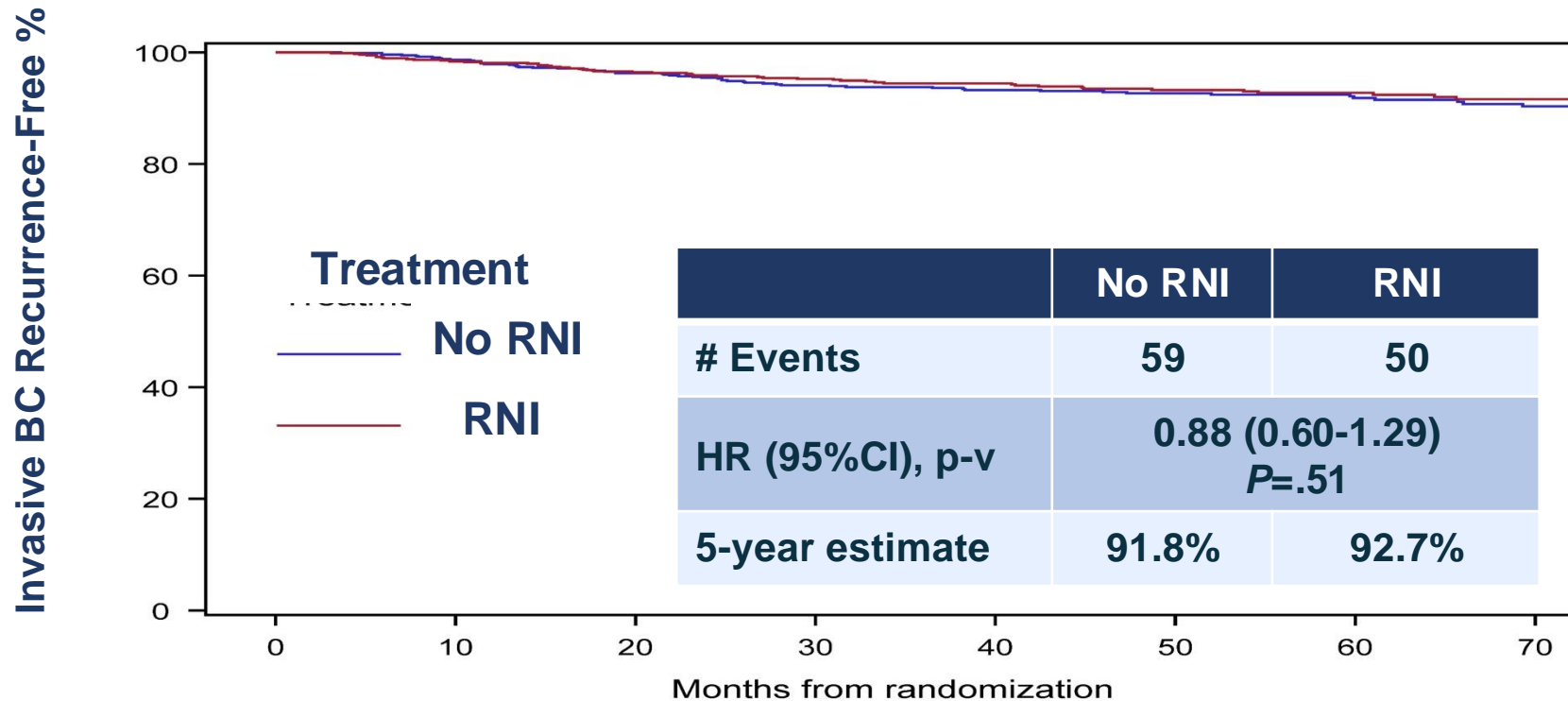


# NRG Oncology/NSABP B-51/RTOG 1304



ALND, axillary lymph node dissection; BCS, breast conserving surgery; FNA, fine needle aspiration; SLNB, sentinel lymph node biopsy; XRT, radiation.

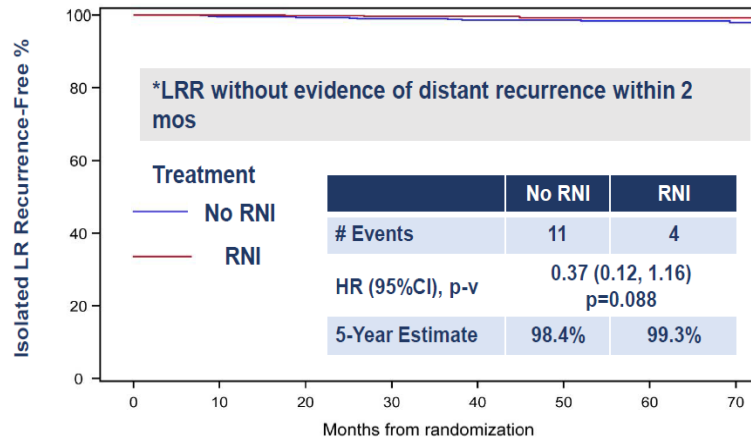
# B-51/1304: Primary Endpoint Invasive Breast Cancer Recurrence-Free Interval



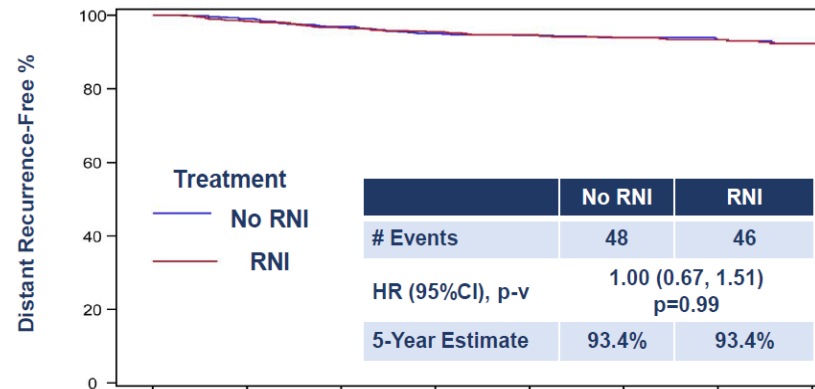
	0	10	20	30	40	50	60	70
<b>No RNI</b>	784	756	700	610	508	386	309	215
<b>RNI</b>	772	724	682	605	498	389	294	200

# B-51/1304: Secondary Endpoints

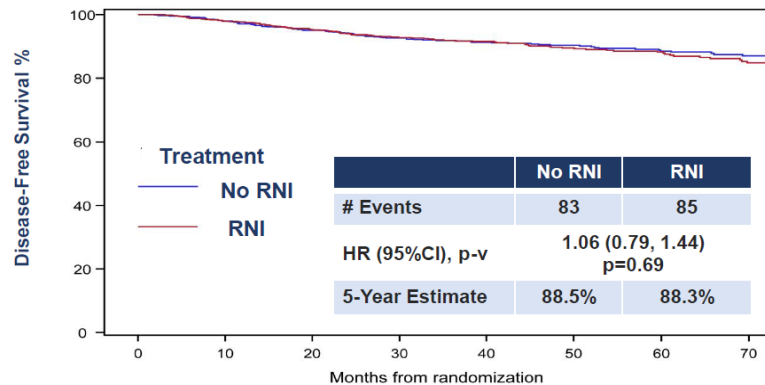
## Isolated Loco-Regional Recurrence-Free Interval\*



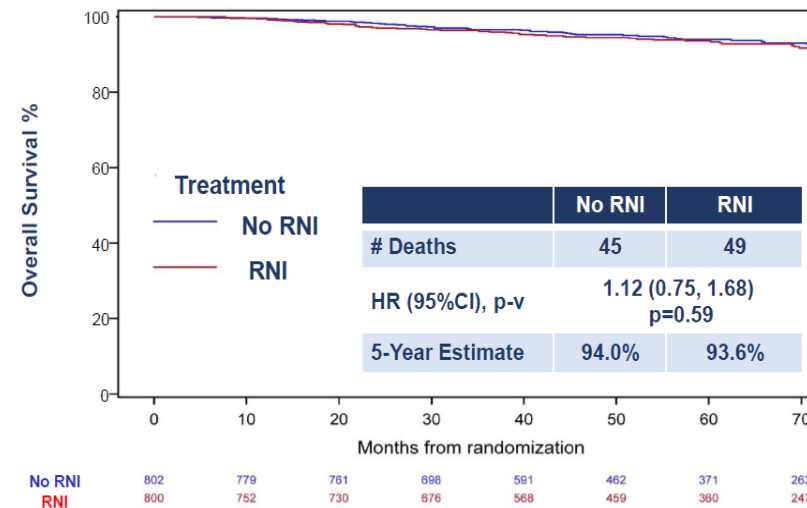
## Distant Recurrence-Free Interval



## Disease-Free Survival



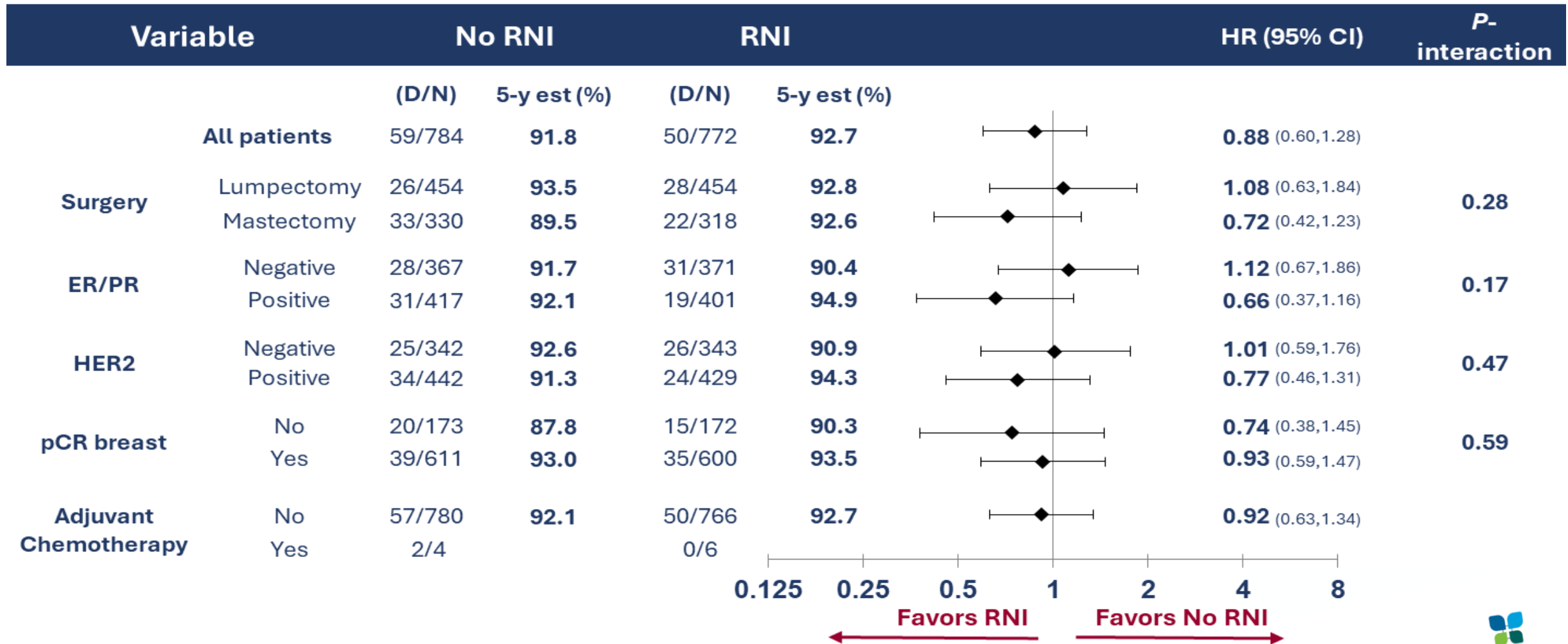
## Overall Survival



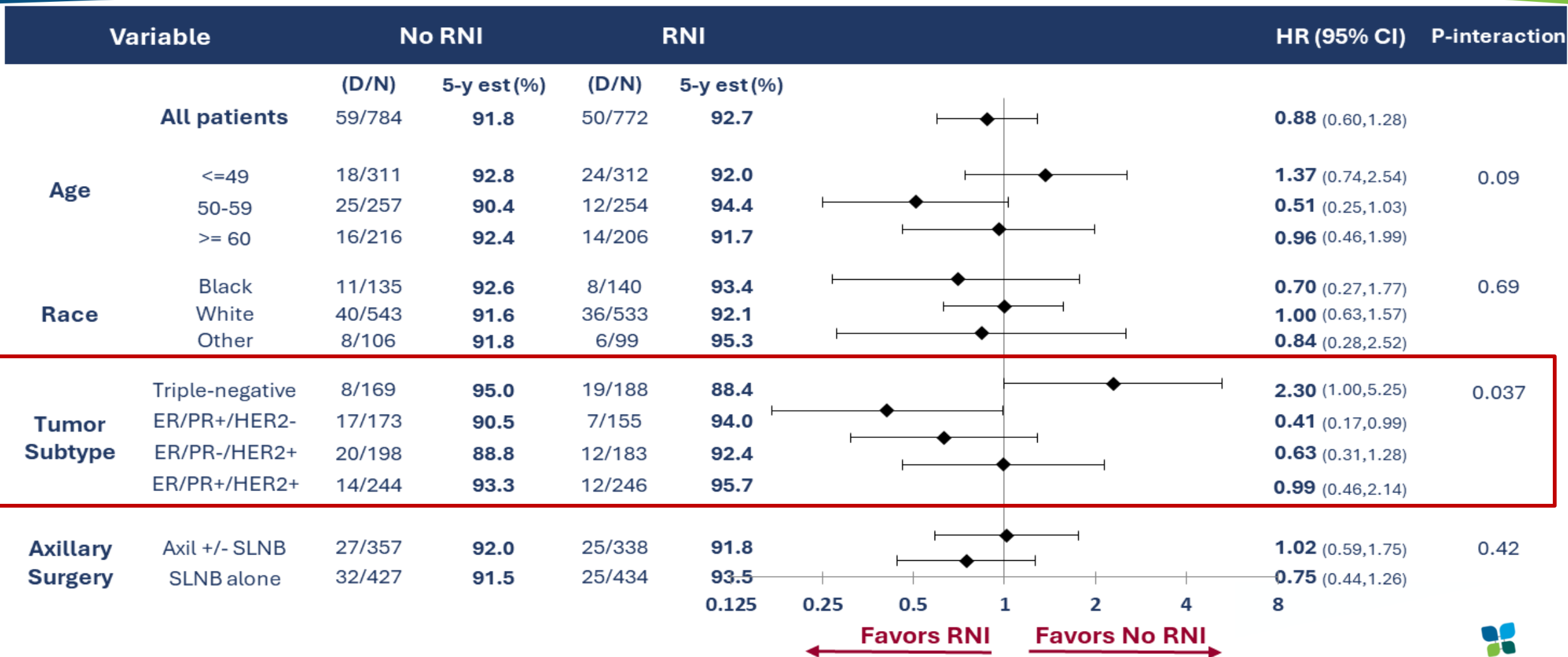
	0	10	20	30	40	50	60	70
No RNI	784	752	693	602	500	380	303	210
RNI	772	722	677	595	488	380	287	193

	0	10	20	30	40	50	60	70
No RNI	802	779	761	698	591	462	371	263
RNI	800	752	730	676	568	459	360	247

# IBCRFI – Subgroup Analysis by Stratification Factors



# IBCRFI – Exploratory Subgroup Analysis





# B-51/1304: Conclusions

- In patients who present with biopsy-proven axillary node involvement (cN+) and convert their axillary nodes to ypN0 after NAC, CWI+RNI after mastectomy, or WBI+RNI after lumpectomy, did not improve the 5-year IBCRFI, LRRFI, DRFI, DFS, or OS
- These findings suggest that downstaging involved axillary nodes with neoadjuvant chemotherapy can optimize adjuvant radiotherapy use without adversely affecting oncologic outcomes
- Follow-up of patients for long-term outcomes continues

# Surgery Omission After NAC

## How to Identify Appropriate Candidates?

- We need a **reliable and reproducible approach** to identify **patients with pCR preoperatively**
- **Clinical examination** has historically shown **low sensitivity** in predicting pCR
- **Mammography and breast ultrasound** have also **limited accuracy** in predicting pCR
- **Accuracy improves with addition of breast MRI**
  - Meta-analysis of 44 studies, 2050 patients
  - **Overall Accuracy : 88%**

# Image-Guided Biopsy for Improving Prediction of pCR After NAC

- Recently, **image-guided biopsy** of the **tumor bed** has been utilized to **enhance the accuracy** of **predicting pCR** in patients with **clinically complete** and **radiologically complete/near-complete** response to NAC
- This approach has the **potential to further improve the selection of optimal candidates** for **surgery omission**
- **Note:** pCR in this setting typically **does not include presence of residual DCIS**

# Accuracy of Image-Guided Bx for Residual After NAC?

## Prospective Studies

Study	# Pts	FNR %	NPV %
Seoul National University Hospital	40	31	87
RESPONDER Multicenter Study	398	18	81
Dutch MICRA Trial	167	37	75
NRG BR005	98	50	78
MSKCC Trial	20	25	86

Lee HB, et al: BCRT 2020

Vrancken Peeters M, SABCS 2019 and van Hemert AKE: Ann Surg Oncol, 2023

Basik M, SABCS 2019

Sutton EJ, et al: JAMA Network Open 2021

# What About the Axilla?

## Can Imaging Accurately Identify Nodal Mets After NAC?

### SN FNAC Trial

Modality	False Negative Rate	Accuracy
Clinical Exam	82%	45%
Axillary US	47%	62%
SLN Biopsy	8%	95%

# Importance of Identifying Residual Disease Histologically After NAC

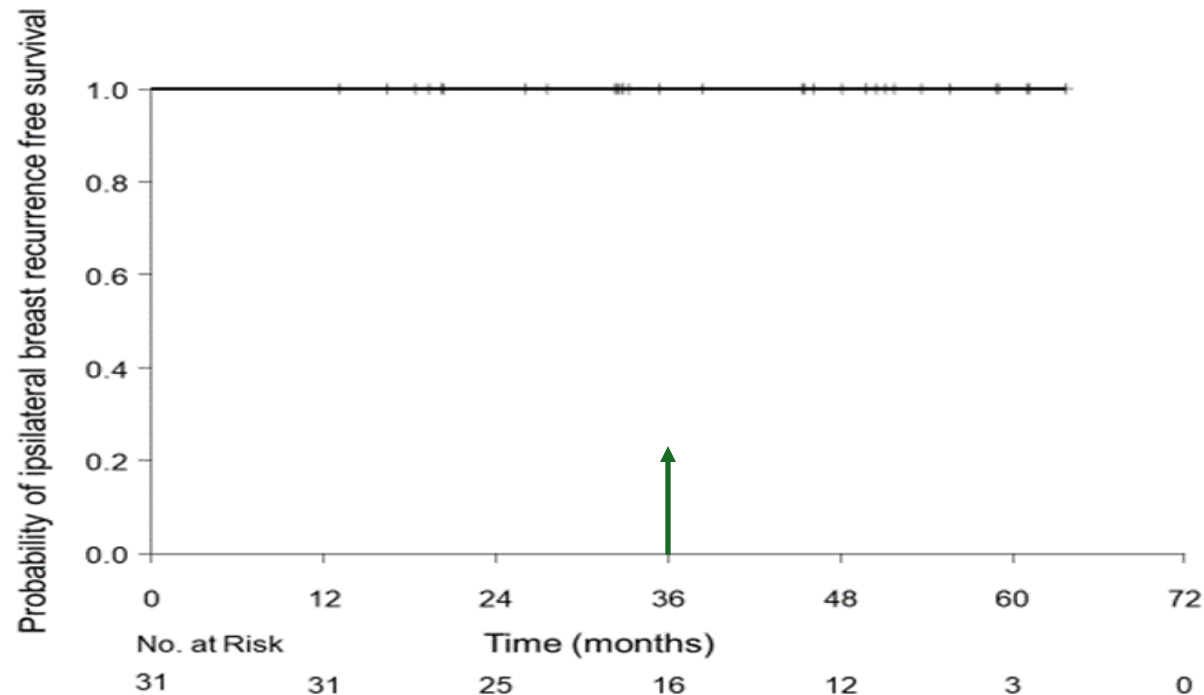
- **pCR provides important prognostic information both in terms of distant recurrence as well as loco-regional recurrence**
- **Local control may be affected if breast XRT is applied without surgery in the presence of residual disease**
- **Missing residual disease in the breast or axilla can affect the use of effective adjuvant systemic therapy**
- **Missing residual disease in the axillary lymph nodes can also affect the use of PMRT and RNI**

# Additional Downsides in the Quest for Surgery Omission After NAC

- **Imaging and multiple needle biopsies to try and establish pCR in the breast**
- **No accurate imaging to identify axillary nodal disease**
- **Omission of surgery will likely result in more intensive follow up imaging and likely more biopsies**
- **Potential for increased patient anxiety**
- **No expectation that surgery omission will improve survival**
- **It can only decrease what is already minimal morbidity**

# MD Anderson Trial: IBTR-free Survival Among Patients Who Did Not Undergo BCS: 3-year Planned Analysis

**N=31**



**100% IBTRFS**

**Secondary  
100% OS/DFS**

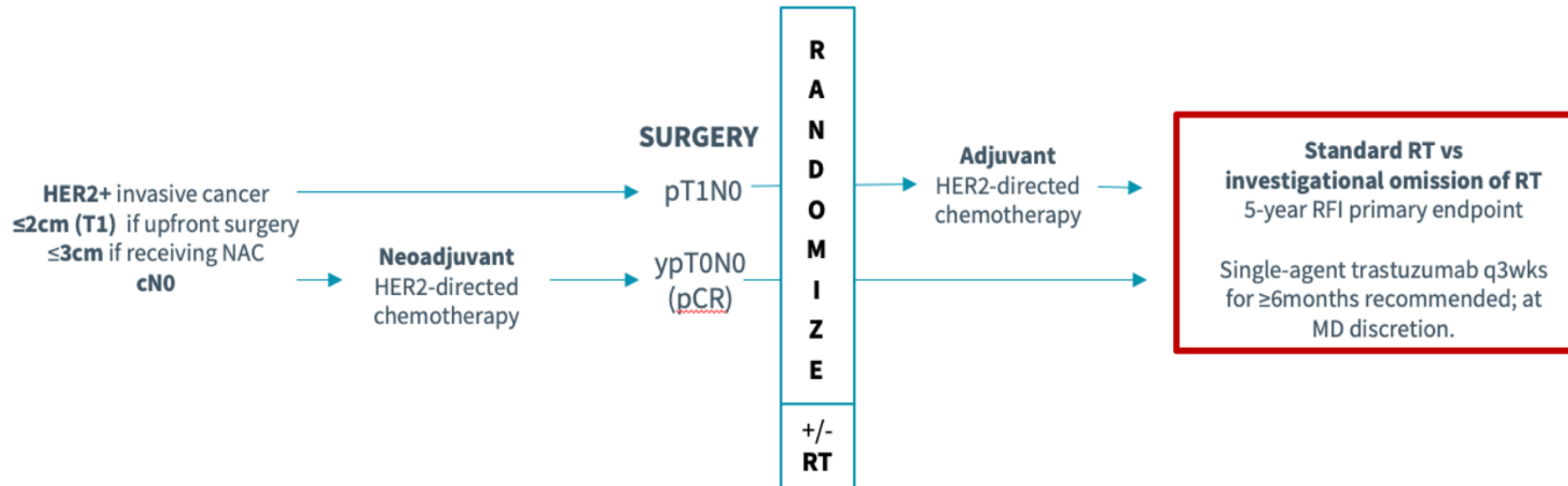
**Median follow-up 38.4 months (IQR 27.6–51.8)**



# Surgery Omission from the Patient's Viewpoint

- **Is undergoing multiple vacuum-assisted biopsies while fully awake a better option than surgery under general anesthesia?**
- **In the era when women increasingly chose bilateral mastectomy for small unilateral cancers for peace of mind, how many would choose surgery omission after NAC?**
- **Is surgery the treatment patients would most want to avoid?**
- **Identifying those who could avoid breast XRT would save patient time, adverse effects, and decrease health care costs**

# NRG-BR008 (HERO): A Phase III RCT Trial Evaluating Omission of Breast XRT for Low-Risk HER-2 Positive BC



## Randomization stratified by:

- Age ( $<60$ ;  $\geq 60$ )
- Primary tumor size ( $\leq 1\text{cm}$ ;  $> 1\text{cm}$ )
- Estrogen receptor status (positive; negative)
- Systemic therapy sequencing (adjuvant; neoadjuvant)

# Summary

- **NAC has allowed de-escalation of surgical therapy in the breast and axilla**
- **This de-escalation has occurred to a greater degree in TNBC and HER2+ BC but also in select ER+/HER- BC patients**
- **De-escalation of regional nodal radiotherapy based on response of axillary lymph nodes to NAC is oncologically safe**
- **For patients with TNBC and HER2 + BC, by individualizing post-neoadjuvant systemic therapy based on pCR, patient outcomes can be improved over the traditional adjuvant approach**

# Summary

- Increasing efficacy of NAC in select breast cancer subtypes and improvements in breast imaging have increased the number of patients with pCR **questioning the need for surgical resection**
- The **accuracy of imaging or imaging + minimally invasive core needle biopsies** in identifying residual disease after NAC **has not been convincingly demonstrated**
- **Omission of surgery after NAC should be limited to clinical research studies** addressing oncologic safety, need of additional imaging studies and the effects of this approach to patient anxiety, inconvenience and QOL

**Thank You!**