



**2024 Breast Cancer Congress**

with Updates from the 2023 SABCS

**Friday, February 2, 2024**

12:10 PM – 12:35 PM CST

# Surgical Management of Invasive Breast Cancer with SABCS Updates

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## NCCN Guidelines Version 1.2024 Invasive Breast Cancer

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### DIAGNOSIS (CLINICAL)

**Localized breast cancer:**  
Invasive,  
non-inflammatory,  
non-metastatic (M0)

### WORKUP<sup>a</sup>

- History and physical exam
- Imaging:
  - ▶ Diagnostic bilateral mammogram
  - ▶ Ultrasound as necessary
  - ▶ Breast MRI<sup>b</sup> (optional), with special consideration for mammographically occult tumors
- Pathology review<sup>c</sup>
- Determination of tumor estrogen/progesterone receptor (ER/PR) status and HER2 status<sup>d</sup>
- Genetic counseling and testing if patient is at risk<sup>e</sup> for hereditary breast cancer (TNBC) (at any age), or is a candidate for adjuvant olaparib
- Address fertility and sexual health concerns as appropriate<sup>f</sup>
- Pregnancy test in all patients of childbearing potential<sup>g</sup> (If pregnant, see [PREG-1](#))
- Assess for distress<sup>g</sup>
- Consider additional imaging studies only in the presence of signs and symptoms of metastatic disease and for patients who are clinically high risk ([BINV-18](#))<sup>h</sup>

### CLINICAL STAGE

cT0,cN+,M0



See [NCCN Guidelines for Occult Primary](#)

cT1–T4,  
≥cN0,M0

Criteria for  
preoperative  
systemic  
therapy  
([BINV-M](#))

Not  
considering  
preoperative  
systemic  
therapy

Considering  
preoperative  
systemic  
therapy

Locoregional treatment<sup>i</sup>  
• BCS Followed by RT  
([BINV-2](#))  
or  
• Mastectomy Followed  
by RT ([BINV-3](#))

Additional Workup  
Prior to Preoperative  
Systemic Therapy  
([BINV-12](#))

Inflammatory breast cancer (IBC)



Workup for IBC ([IBC-1](#))

Metastatic (M1) invasive breast cancer



Stage IV (M1) or  
Recurrent disease

Workup for Recurrent or  
Stage IV (M1) Disease ([BINV-18](#))

<sup>a</sup> For tools to aid optimal assessment and management of older adults, see [NCCN Guidelines for Older Adult Oncology](#).

<sup>b</sup> Breast MRI may be useful for characterizing axillary and/or internal mammary nodal disease. See [Principles of Dedicated Breast MRI Testing \(BINV-B\)](#).

<sup>c</sup> The panel endorses the College of American Pathologists Protocol for pathology reporting for all invasive and noninvasive carcinomas of the breast. <http://www.cap.org>.

<sup>d</sup> [Principles of Biomarker Testing \(BINV-A\)](#).

<sup>e</sup> For risk criteria, see [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic](#).

<sup>f</sup> For Fertility and Birth Control, see [BINV-C](#). The general considerations for fertility and sexual health/function outlined for specific populations in [NCCN Guidelines for Adolescent and Young Adult \(AYA\) Oncology](#) and [NCCN Guidelines for Survivorship](#) are applicable to all patients diagnosed with breast cancer.

<sup>g</sup> See [NCCN Guidelines for Distress Management](#).

<sup>h</sup> Routine systemic staging is not indicated for non-metastatic (M0) cancer in the absence of systemic symptoms. If metastatic disease is suspected, see Workup on [BINV-18](#).

<sup>i</sup> Patients with a known genetic predisposition to breast cancer may have an increased risk of contralateral or ipsilateral breast cancers after breast-conservation therapy. Risk reduction strategies including prophylactic mastectomies should be discussed. See [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic](#).

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

## LANDMARK TRIALS

- NSABP B-06
- EBCTCG
- NSABP B-17
- NSABP B-24
- CALGB 9343

## NEW LANDMARK TRIALS

- ACOSOG 11102

# NSABP B-06

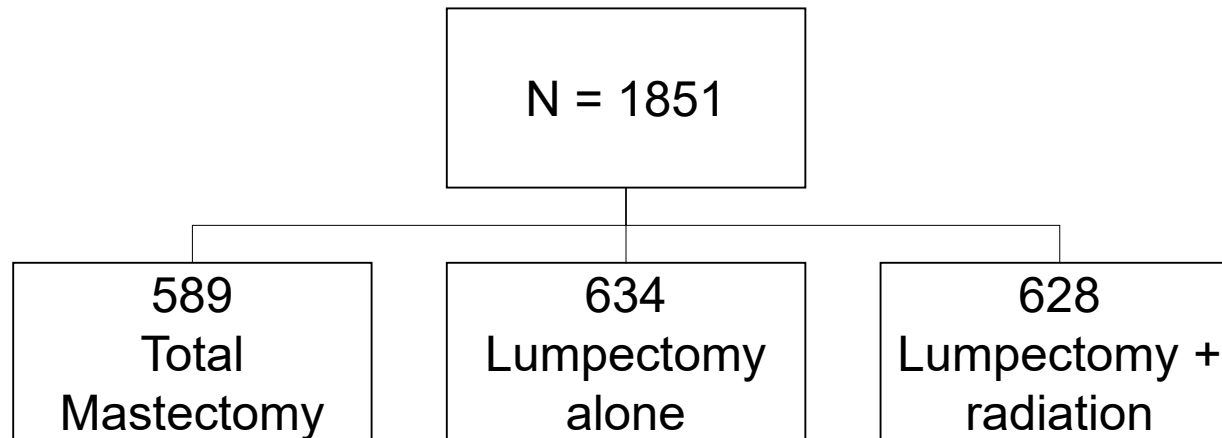
## Total Mastectomy vs. Lumpectomy (BCS)

- **Why a mastectomy at all?**
- **Aim of the Study:**
  - Determine if lumpectomy, with or without XRT was as effective as mastectomy
- **Trial Enrollment:** 1976 – 1984
- **N = 2163**
  - 1851 had follow-up data
- 20-year follow up
- **Eligibility:**
  - Tumors < 4cm
  - Stage I or II (could be cN+)
  - All patients received ALND
  - Patients with positive nodes received chemotherapy (melphalan & fluorouracil)
- **Lumpectomy:**
  - Tumor free surgical margins – *no ink on tumor*
  - Patients with positive margins underwent total mastectomy

Fisher, B. NEJM. 2002; 347:1233-41. 4

# NSABP B-06

## Total Mastectomy vs. Lumpectomy (BCS)

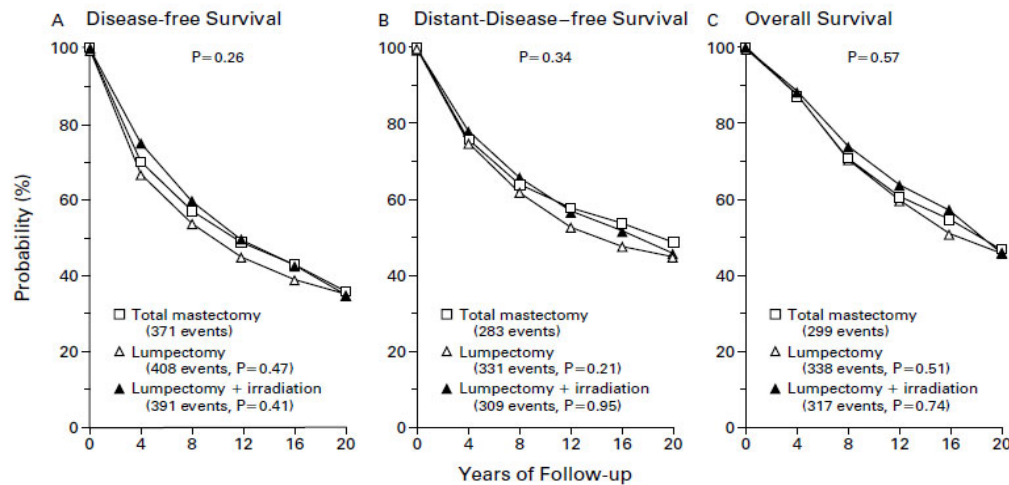


Fisher, B. NEJM. 2002; 347:1233-41.

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# NSABP B-06

## Total Mastectomy vs. Lumpectomy (BCS)



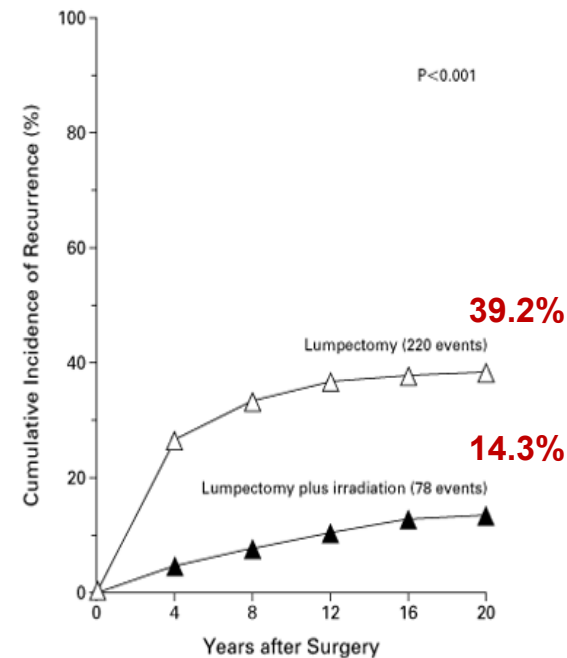
- DFS & Distant DFS & OS: **No significant difference** among 3 groups
- *Lumpectomy followed by XRT is appropriate therapy for women, provided the margins of resected specimens are free of tumor and an acceptable cosmetic result can be obtained.*

Fisher, B. NEJM. 2002; 347:1233-41. 6

# NSABP B-06

## Total Mastectomy vs. Lumpectomy (BCS)

- Significantly fewer LR w/ RT
- Overall LR: (@20 yrs follow-up)
  - BCS alone: **39.2%**
  - BCS + XRT: **14.3%**
- *Independent* of nodal status
  - Node *negative*
    - BCS alone: **36.2%**
    - BCS + XRT: **17.0%**
  - Node *positive*
    - BCS alone: **44.2%**
    - BCS + XRT: **8.8%**
- Majority (73%) of LR after BCS alone occurred in first 5-yrs, LR more evenly distributed if XRT



Fisher, B. NEJM. 2002; 347:1233-41.

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# EBCTCG\* Recurrence & Breast Cancer Death: Meta-Analysis

- Effect of Radiotherapy after Breast-Conserving Surgery on 10-year Recurrence and 15-year Breast Cancer Death: **Meta-Analysis of Individual Patient Data** for **10,801 Women** in **17 Randomized Trials**.

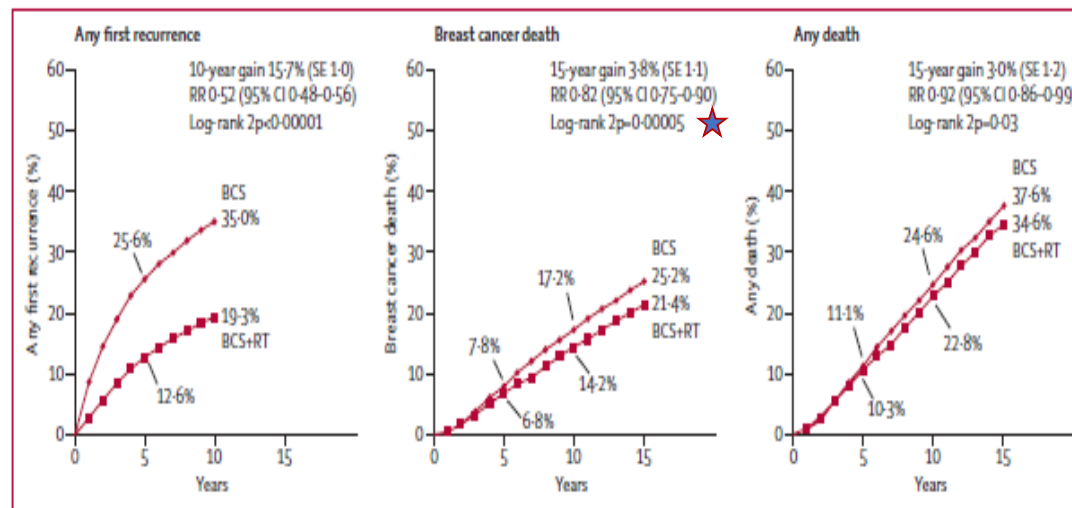


Figure 1: Effect of radiotherapy (RT) after breast-conserving surgery (BCS) on 10-year risk of any (locoregional or distant) first recurrence and on 15-year risks of breast cancer death and death from any cause in 10 801 women (67% with pathologically node-negative disease) in 17 trials

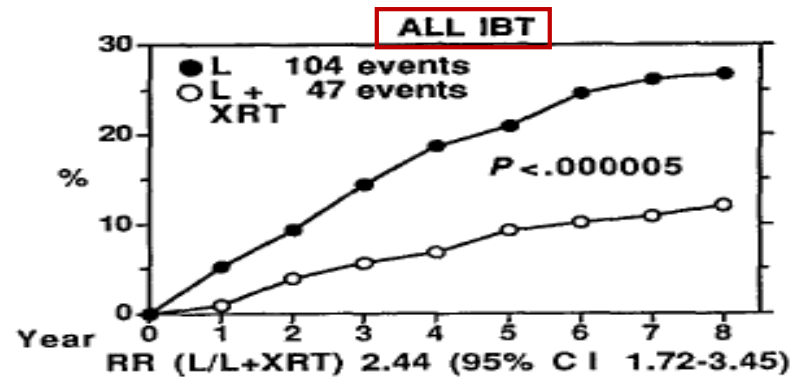
\*EBCTCG: Early Breast Cancer Trialists' Collaborative Group

EBCTCG. Lancet. 2011; 378: 1707-16. 8

# NSABP B-17

## BCS vs. BCS+XRT (DCIS)

- **B-06 → Same results for DCIS?**
- **Aim of the Study:** Determine if lumpectomy w/ XRT was more effective than lumpectomy alone
- **Trial Enrollment:** 1985 - 1990
- **N = 818**
  - 405 lumpectomy
  - 413 lumpectomy + XRT (50 Gy)
  - Tumor free surgical margins – *no ink on tumor*
- **7.5-year follow up**



- 8-year IBTR – In Breast Tumor Recurrence
  - Lumpectomy Alone: **26.8%**
    - 13.4% as *DCIS*, 13.4% as *invasive*
  - Lumpectomy + XRT: **12.1%**
    - 8.2% as *DCIS*, 3.9% as *invasive*

Fisher, B. JCO. 1998; 16: 441-52. 10



# NSABP B-24

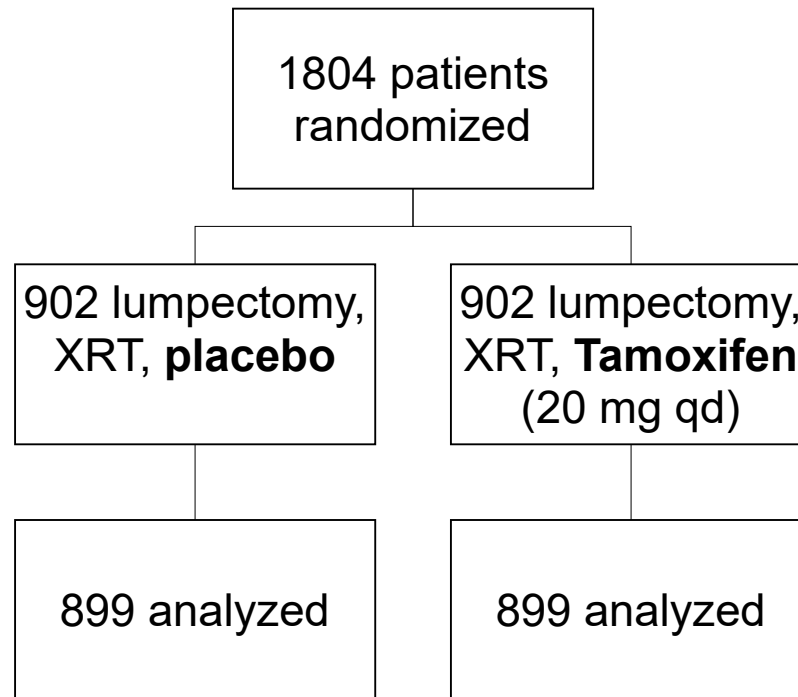
## BCS+XRT vs. BCS+XRT +Tamoxifen

- **Does adding tamoxifen provide even more benefit? (DCIS trial)**
- **Aim of the study:** determine if tamoxifen was more beneficial than lumpectomy & XRT alone.
- **Trial Enrollment:** 1991-1994
- Double-blind, randomized trial
- **N = 1804** patients with DCIS
  - Lump & XRT +/- Tamoxifen x 5 yrs
- 6 years follow up
- **Primary endpoints:**
  - Occurrence of invasive or non-invasive tumors in ipsilateral & contralateral breasts
- **Positive margins**
  - 16.1% in placebo group
  - 15.5% in Tam group

Fisher, B. Lancet. 1999; 353: 1993-2000. 12

# NSABP B-24

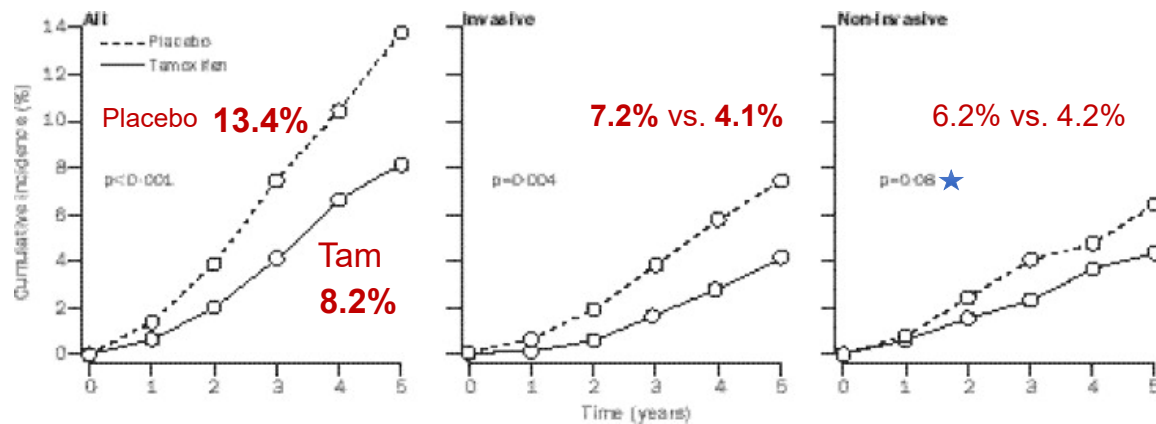
## BCS+XRT vs. BCS+XRT +Tamoxifen



Fisher, B. Lancet. 1999; 353: 1993-2000. 13

# NSABP B-24

## BCS+XRT vs. BCS+XRT +Tamoxifen



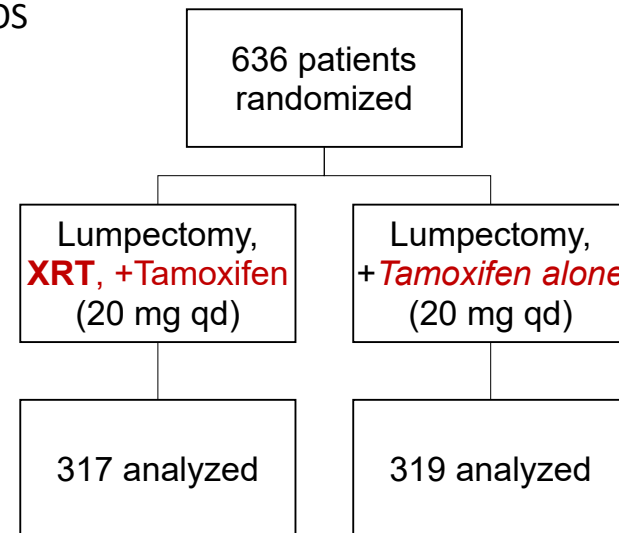
- **All** breast events (ipsilateral & contralateral) reduced from **13.4%** to **8.2%**
- **37% fewer events** in the tamoxifen group
  - 43% fewer invasive breast cancer events (**7.2% vs. 4.1%**)
  - 31% fewer noninvasive breast cancer events (**6.2% vs. 4.2%**)★
- **The addition of tamoxifen was effective in prevention of all breast cancer events and ipsilateral invasive breast cancer events**

Fisher, B. Lancet. 1999; 353: 1993-2000. 14

# CALGB 9343

- **AIM:** to determine if BCS+Tam is as effective as BCS+RT+Tam in *women >70* with early breast cancer – **do we need RT in older women?**
- **Enrollment:** 1994 - 1999
- **N** = 650, Follow up: 12.6 years
- **Eligibility:**
  - **≥70, clinical stage I breast cancer**
  - All cN0 – ALND allowed, but discouraged
  - Initially, cT1-2 (<4cm) any ER status, broadened to include cT1, ER positive
- **Procedure:**
  - All: BCS to neg. margin (no tumor on ink)
  - RT group: 45-Gy whole breast and low axilla + 14-Gy tumor bed boost

- **Primary endpoints:** LRR, frequency of mastectomy, breast-cancer specific survival, OS



\*CALGB: Cancer and Leukemia Group B

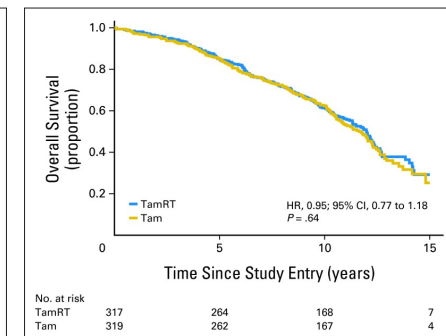
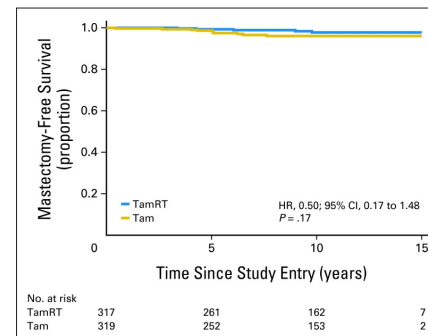
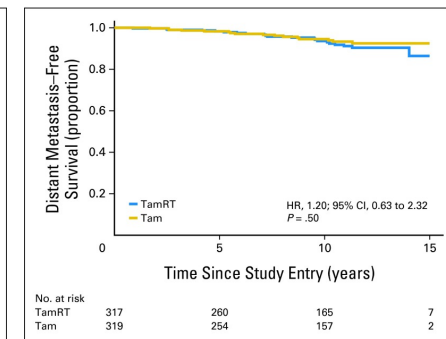
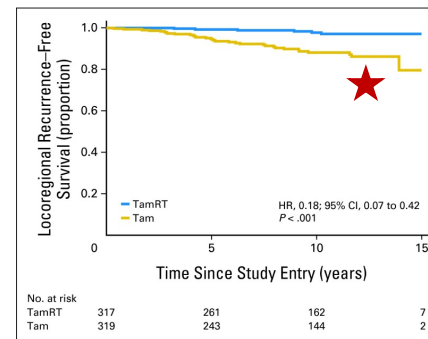
Hughes, KS. NEJM, 2004; 351: 971-977.  
Hughes, KS. JCO, 2013; 31: 2382-2387.

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# CALGB 9343

- Significant improvement in LRR w/ XRT ★

- *No difference* in:
  - (1) time to mastectomy
  - (2) time to distant metastases
  - (3) breast-cancer specific survival
  - (4) overall survival



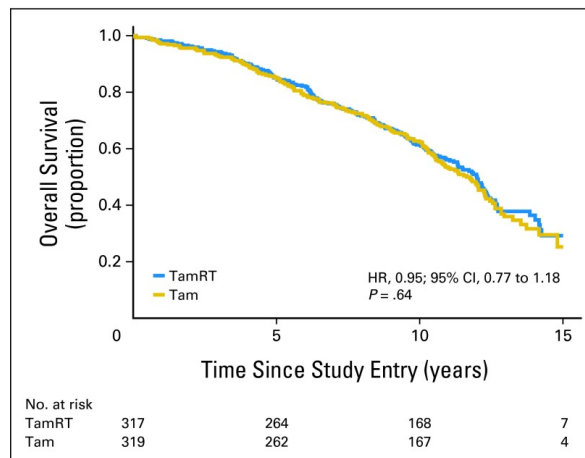
Hughes, KS. NEJM, 2004; 351: 971-977.  
Hughes, KS. JCO, 2013; 31: 2382-2387.

# CALGB 9343

10 year data:

At 12 years follow up:

- **3%** died of breast cancer
- **49%** died of *other* causes



TAM	TAM + XRT
<b>10%</b> recurrence	<b>2%</b> recurrence
20 IBTR	6 IBTR
6 IBTR + mets	0
5 axillary recur only	0
1 IBTR + axillary	0

- Age  $\geq 70$ , w/ cT1N0, ER+ breast cancer, s/p BCS and Tamoxifen, XRT adds **no significant benefit** in OS, DFS, or breast preservation.
- **NOTABLE:** In the group w/ *omission* of RT (Tam only), and *omission* of axillary staging, just **3%** (N=7) had an axillary recurrence
- **Choosing Wisely® campaign** omission of SLNB in patients  $>70$  years with cT1N0 HR+ breast cancer, planned endocrine therapy

# What's NEW in the breast??

# **Impact of *Endocrine Therapy Adherence* on Outcomes in Elderly Women w/ Early-Stage Breast Cancer undergoing *Lumpectomy without Radiation***

*\*Real world data*

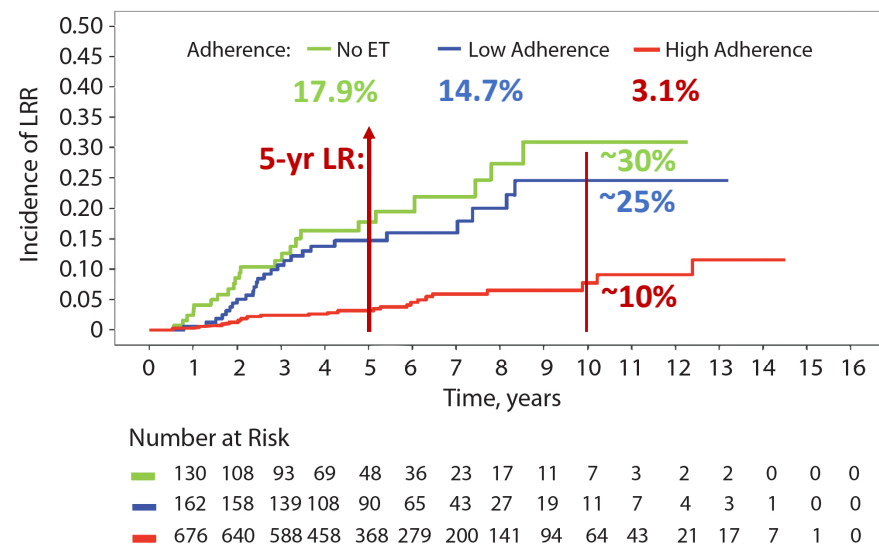
Matar, R. Ann Surg Oncol. **2022**; 29: 4753-4760. 20



## Impact of *Endocrine Therapy Adherence* on Outcomes in Elderly Women w/ Early-Stage Breast Cancer undergoing *Lumpectomy without Radiation*

- **AIM:** evaluate the rate of endocrine adherence and the association with LR
- **Data source:** prospectively maintained institutional database
- **N** = 968 patients
- **Inclusion:** 2004 – 2019
  - **Women  $\geq 70$ , cN0, pT1-2, ER+, BCS w/out RT**
- **Stratified adherence to Endocrine as:**
  - High:  $\geq 80\%$  compliance (70%, N=676)
  - Low:  $< 80\%$  compliance (17%, N=162)
  - No ET: no prescription (13%, N=130)
- **Follow up:** 53 months

- **Median age:** 77 years (younger age & AI use, more compliant)



*No difference in OS, but significant difference in LRR.*

*Need to identify patients unlikely to have high adherence, consider RT*

Matar, R. Ann Surg Oncol. 2022; 29: 4753-4760. 21

# ACOSG Z11102

## Local Recurrence after Breast-Conserving Therapy in Patients with Multiple Ipsilateral Breast Cancer

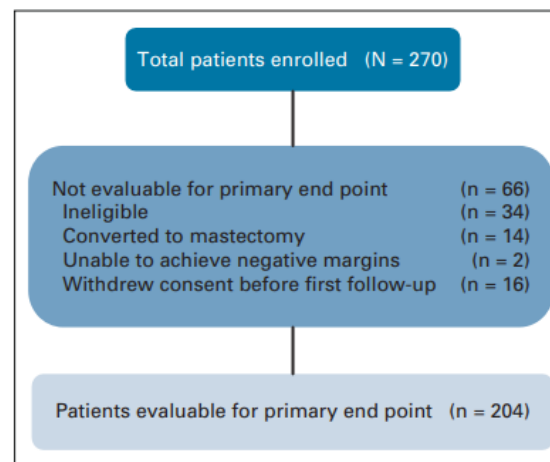
**ACOSOG:** American College of Surgeons Oncology Group

Boughey, JC. J Clin Oncol. 2023; 41:3184-3193. 22

# ACOSG Z11102

## BCS for Multiple Ipsilateral Primaries

- **AIM:** Determine oncological safety and LR of BCS for *multiple ipsilateral breast cancer*
  - *Can we offer BCS with multiple tumors?*
- **Design:** prospective, single-arm
- **Enrollment:** 2012-2016
- **Eligibility:**
  - >40 years, cN0-1, w/ 2-3 foci of biopsy proven breast cancer (at least 1 invasive)
  - Largest <5cm, MRI not required (90% had)
  - At least 2cm normal between sites
  - BCS w/ negative margins (SSO-ASTRO)
  - WBRT w/ boost to each lumpectomy site
  - *Excluded neoadjuvant* patients
- **Endpoint:** cumulative incidence of **LR @5 years w/ a priori rate of acceptability at <8%** (based on unifocal LRR of 10% at 12 years, target N=200)

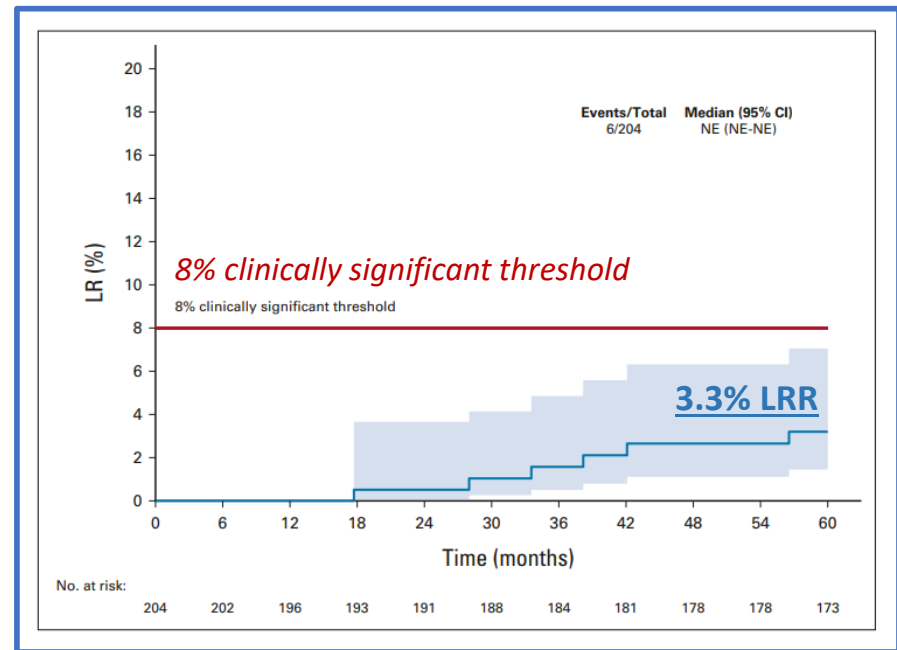


Boughey, JC. J Clin Oncol. 2023; 41:3184-3193. 23

# ACOSG Z11102

## BCS for Multiple Ipsilateral Primaries

- Age: median 61 (range 40-87)
- **70%** had *two* lumpectomy sites
- **Margin re-excision rate: 23%**
- 83% = ER+, 12% = Her2+
- **96% (195/204) completed RT**
- Median FU = 66 months
- **LRR: N=6 pts, 3.3%**
- \*LRR w/ MRI **1.7%**, w/out MRI **22%**



Boughey, JC. J Clin Oncol. 2023; 41:3184-3193. 24

# ACOSG Z11102

## BCS for Multiple Ipsilateral Primaries

LR **did not** differ by most factors:

- Patient Age
- Number of sites of cancer (2 vs.3)
- Tumor Biology
- Pathologic pT stage
- Margin status (neg. vs. close)
- Tumor histology
- Number of lumpectomies
- Adjuvant chemotherapy

LR **DID** differ by:

- MRI performed pre-op,  $p=0.002$ 
  - Yes (N=189): LR: 1.7% (0.6-5.2)
  - No (N=7): **LR: 22.6%** (7.9-55.1)
- Adjuvant endocrine in HR+,  $p=0.025$ 
  - Yes (N=175): LR: 1.9% (0.6-5.6)
  - No (N=20): **LR: 12.5%** (3.3-41.5)

***BCS may be considered for: multi-centric breast cancer, cTis-cT2, with at least 1 site invasive, after MRI evaluation, w/ adjuvant RT & boosts, w/ planned endocrine therapy***

# Now onto the AXILLA ...



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## NCCN Guidelines Version 1.2024 Invasive Breast Cancer

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### CONSIDERATIONS FOR SURGICAL AXILLARY STAGING

cN0 or  
Low  
volume  
disease

No palpable lymph node at diagnosis and limited axillary lymph node involvement on imaging confirmed by needle biopsy ± marker placement<sup>a</sup> in the most suspicious node

SLN mapping and excision<sup>b,c</sup>

**Surgery 1<sup>st</sup>**

SLN not identified

ALND level I/II<sup>f</sup>

SLN negative<sup>c</sup>

No further axillary surgery (category 1) **NSABP B-32**

SLN positive<sup>c</sup>

Breast-conserving surgery

Mastectomy<sup>e</sup>

Meets ALL of the following criteria<sup>g</sup>:

• cT1–T2, cN0

• No preoperative chemotherapy

• 1–2 positive SLNs

• WBRT planned

**ACOSOG Z0011**

Micrometastases seen in SLN<sup>h</sup>

No

Yes to all

ALND level I/II<sup>f</sup>

No further axillary surgery

Meets ALL of the following criteria<sup>i</sup>:

• cT1–T2, cN0

• No preoperative chemotherapy

• 1–2 positive SLNs

• Adjuvant RT planned with intentional inclusion of undissected axilla at risk

**EORTC AMAROS**

No

Yes to all

ALND level I/II<sup>f</sup>

Consider no further axillary surgery<sup>k</sup>

cN+ or  
High  
volume  
disease

Clinically suspicious (palpable) lymph nodes or Significant axillary lymph node disease burden on imaging or Preoperative systemic therapy being considered and suspicious lymph nodes at diagnosis on exam or imaging

US-guided FNA or core biopsy + marker placement recommended<sup>a</sup> in the most suspicious node

FNA or core biopsy negative<sup>d</sup>

**NAC**

FNA or core biopsy positive

Consider preoperative chemotherapy

Yes, preoperative chemotherapy

cN+ remains clinically positive

cN+ converts to clinically node negative

ALND level I/II<sup>f</sup>

SLNB (category 2B)<sup>j</sup>

<sup>a</sup> If a positive lymph node is clipped or tattooed during biopsy, every effort should be made to remove the clipped or tattooed node at the time of surgery. Only the most suspicious node should be marked and retrieved along with SLNs to reduce the false negative rate.

<sup>b</sup> SLN mapping injections may be peritumoral, subareolar, or subdermal.

<sup>c</sup> Sentinel node involvement is defined by multilevel node sectioning with hematoxylin and eosin (H&E) staining. Cytokeratin IHC may be used for equivocal cases on H&E. Routine cytokeratin IHC to define node involvement is not recommended in clinical decision-making.

<sup>d</sup> If clinically negative axilla before chemotherapy and then have a positive sentinel node after chemotherapy, consider completion axillary lymph node dissection or multidisciplinary tumor board discussion on appropriateness of radiation of axilla without further surgery.

<sup>e</sup> Limited data exist for patients with mastectomy.

<sup>f</sup> Axillary Lymph Node Staging (BINV-E).

<sup>g</sup> ACOSOG Z0011: Giuliano AE, et al. JAMA 2017;318:918-926.

<sup>h</sup> Galimberti V, et al. Lancet Oncol 2013;14:297-305.

<sup>i</sup> EORTC AMAROS: Donker M, et al. Lancet Oncol 2014;15:1303-1310; Rutters E, et al. Cancer Res 2019;79-GS4-01-GS04-01.

<sup>j</sup> Limited data exist for ≥3 positive SLNs.

<sup>k</sup> In the mastectomy setting, in patients who were initially cN0, who have positive nodes on SLNB, and have no axillary dissection, RT to the chest wall should include undissected axilla at risk ± RNI.

<sup>l</sup> Among patients shown to be N+ prior to preoperative systemic therapy, SLNB has a >10% false-negative rate when performed after preoperative systemic therapy, which can be improved by marking and removing the most suspicious biopsied node, using dual tracers, and by obtaining ≥3 sentinel nodes (targeted axillary lymph node dissection). (Caudle AS, et al. J Clin Oncol 2016;34:1072-1078.)

<sup>m</sup> Note: All recommendations are category 2A unless otherwise indicated.

<sup>n</sup> Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

## LANDMARK TRIALS

### Surgery 1<sup>st</sup>

- NSABP B-32
- ACOSOG Z0011
- EORTC AMAROS

### Following NAC

- SENTINA
- ACOSOG Z1071
- MDACC TAD

# NSABP B-32

## SLNB vs. SLNB+ALND in cN0 patients

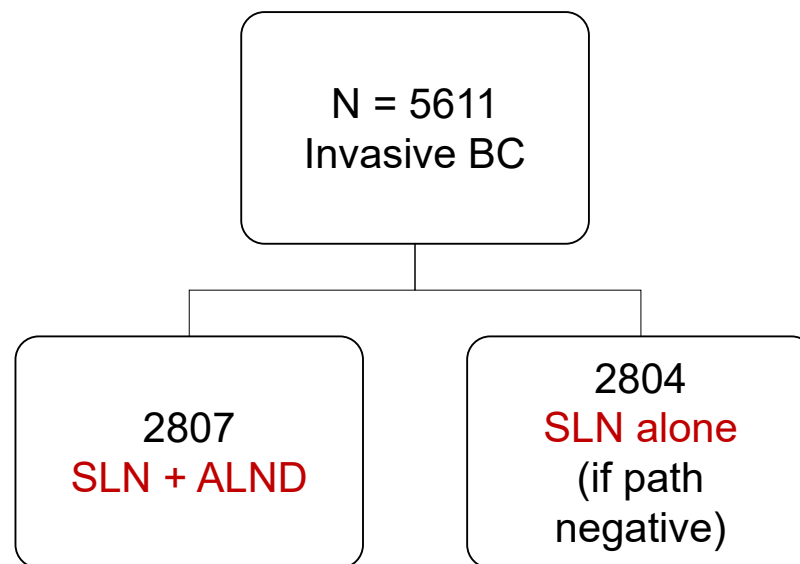
- Is SLNB a reasonable way to stage the axilla in **pN0 pts**?
- **AIM:** determine *whether SLNB achieves the same survival & regional control as ALND*, with fewer side-effects
- **Trial Enrollment:** 1999 - 2004
- **Enrolled:** N = **5611** (!)
- **Sites:** 80 centers (US/Canada)
- **Follow-up:** 8-years
- **SLNB:** Tc<sup>99</sup> radiotracer & isosulfan blue
- Outcome analyses performed on women with pN0
- Primary endpoint: OS
- Designed to detect a OS difference of 2% between sentinel node-negative patients in the two groups at 5 years.
- Morbidity also evaluated

Lancet Oncol. 2010; 11:927-933. 29



# NSABP B-32

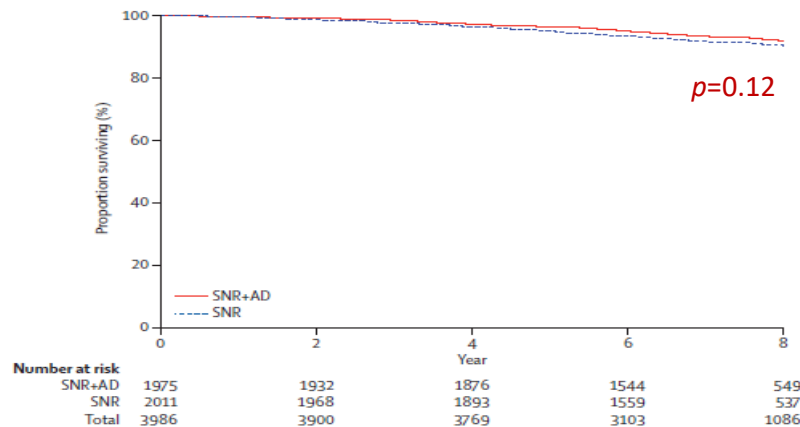
## SLNB vs. SLNB+ALND in cN0 patients



Lancet Oncol. 2010; 11:927-933. 30

# NSABP B-32

## SLNB vs. SLNB+ALND in cN0 patients



	SLNB + ALND (N = 1975)	SLNB (N = 2011)
Local recurrence	54 (2.7%)	49 (2.4%)
Regional recurrence	8 ( <b>0.4%</b> )	14 ( <b>0.7%</b> )
Distant metastasis	55 (2.8%)	64 (3.2%)



- N = 3989 pN0 sentinel nodes
- **No difference** in Overall Survival  
8-year K-M estimates:
  - **91.8%** (SLNB+ALND)
  - **90.3%** (SLND)

- **<1% regional node recurrences** after SLNB
- 3-year *lymphedema rates* ( $\geq 10\%$  arm volume diff): **14%** (SLNB+ALND) vs **8%** (SLNB)

Lancet Oncol. 2010; 11:927-933. 31

# NSABP B-32

## SLNB vs. SLNB+ALND in cN0 patients

- SLNB detection in Group 1 (w/ALND):
  - 2544 / 2619 = **97.1%**
- **False-negative rate: 9.8%** 
  - Related to number of nodes removed
- **Overall study: False-negative rate (FNR) = 9.8%\***
  - Women with **1** detected SLN: **FNR = 17.7%**
  - Women with **2** detected SLN: **FNR = 10.0%**
  - Women with **3** detected SLN: **FNR = 7%** 

When the SLN is negative, SLN surgery *alone* with no further ALND is appropriate, safe and effective therapy

Lancet Oncol. 2010; 11:927-933. 32

# ACOSOG Z0011

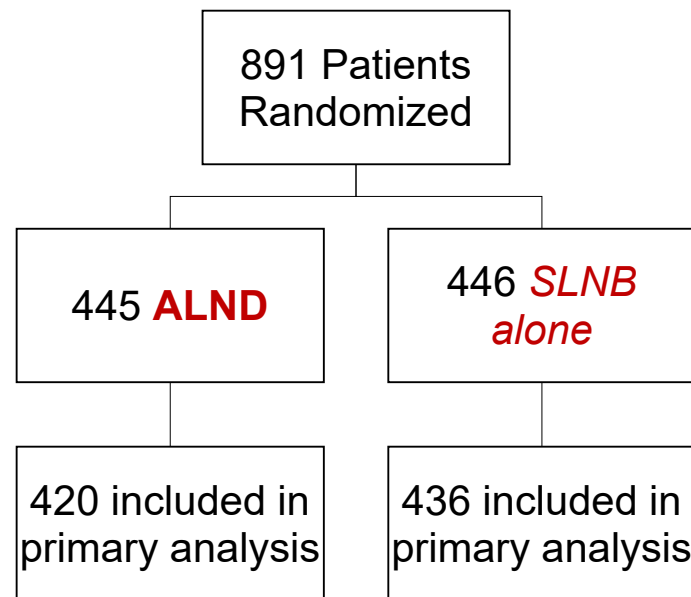
## ALND vs. No ALND in cN0, pN+ (1-2)

- **AIM:** To determine *if SLNB alone* would provide *similar loco-regional control & OS as ALND* for women with *pN+*, SLN that was H&E *positive*
- **Trial Enrollment:** 1999-2004
- **Enrolled:** **N = 891**
  - Target: 1900, 115 sites
  - Closed early – poor accrual, few events
- **\*Possible omission of ALND in pN+** was considered radical & harmful
  - *Limited potential participation*
- **Eligibility:**
  - Surgery first
  - cT1 – T2 invasive tumors
  - cN0 = “no palpable adenopathy”
  - **1 or 2 positive SLN** on frozen section, touch prep, or H&E permanent section
  - All underwent lumpectomy and tangential whole breast radiation
  - **Randomized: ALND vs. no add’l surgery**
  - Any systemic therapy

JAMA. 2011; 305: 569-575. 34

# ACOSOG Z0011

## ALND vs. No ALND in cN0, pN+ (1-2)



JAMA. 2011; 305: 569-575. 35

# ACOSOG Z0011

## ALND vs. No ALND in cN0, pN+ (1-2)

Characteristic	ALND (n = 420)	SLND only (n = 436)
Age, median	56	54
Tumor size, Median pT2	1.7cm 32.1%	1.6cm 29.4%
LVI, present	129 (40.6%)	113 (35.2%)
Receptor status		
ER+	82.8%	82.7%
ER-	17.2%	17.3%

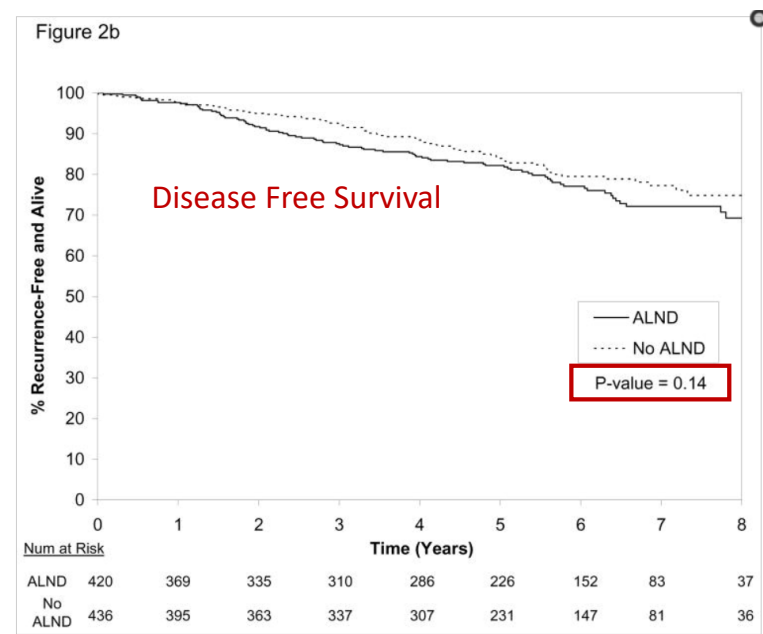
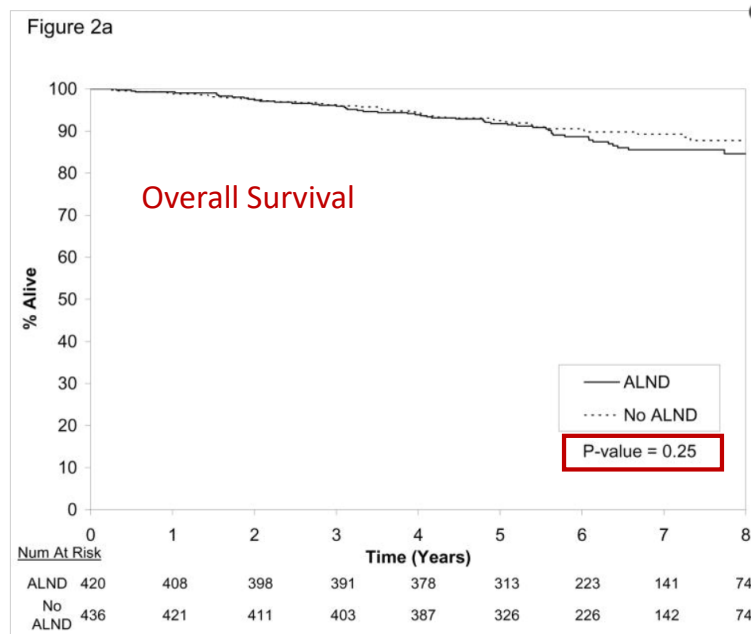
Similar groups except: **Median Nodes = 17 (ALND), 2 (SLNB)**

JAMA. 2011; 305: 569-575.

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# ACOSOG Z0011

## ALND vs. No ALND in cN0, pN+ (1-2)



# ACOSOG Z0011

## ALND vs. No ALND in cN0, pN+ (1-2)

- **Notable:** In the completion ALND group, **27.3% (N=97/355)** had additional metastases in LN removed by ALND
- A quarter of patients who *DID NOT* have ALND, also likely harbored positive nodes
- Z0011 documents the high rate of *locoregional control* achieved with modern multimodality therapy, without ALND – *advances in systemic therapy*
  - 100% of Z0011 pts were pN+, 90% survival at 5-years
  - **With NO add'l axillary surgery → 0.9% regional failure (@ 8 years) with 27% residual positive nodes**

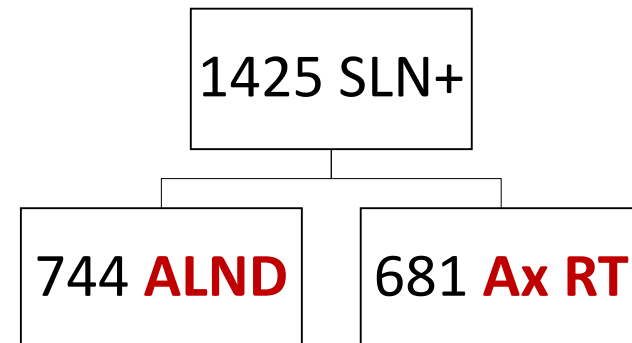
Recurrence	ALND (n = 420)	SLNB (n = 436)
Local	15 (3.6%)	8 (1.8%)
Regional	2 ( <b>0.5%</b> )	4 ( <b>0.9%</b> )
Total Locoregional	17 (4.1%)	12 (2.8%)
Survival	91.8%	92.5%



# EORTC AMAROS

## ALND vs. Axillary RT in cN0, pN+

- **AIM:** to determine whether axillary XRT provided similar axillary local control as ALND in patients with a positive SLN.
- **Trial Enrollment:** 2001 – 2010
- **Enrolled:** **N = 4823**, 34 centers in Europe, N = 1425 with SLN+
- **Eligibility:** cT1-2, cN0 → pN+
- ALND group → **33%** had additional positive nodes
  - Z0011 (27%)
- Allowed mastectomy: **18%**

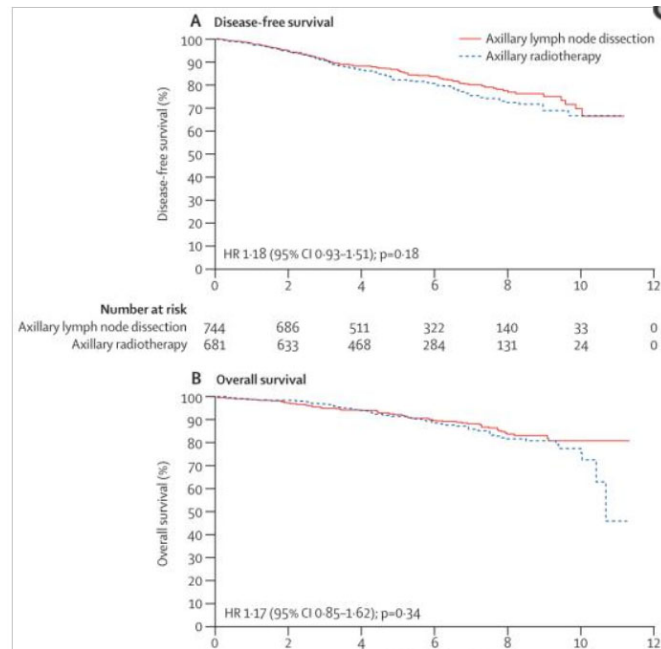


Lancet Oncol. 2014; 15: 1303-1310. 40

# EORTC AMAROS

## ALND vs. Axillary RT in cN0, pN+

- **No difference** in DFS or OS



- **5-year axillary recurrence:**
  - **0.4%** (95% CI 0.00–0.92) in the **ALND**
  - **1.2%** (95% CI 0.31–2.08) in the **Ax XRT**
- *ALND and Ax XRT after a positive SLNB provide excellent and comparable axillary control for patients with cT1–2 breast cancer and cN0*
  - *Allowed the inclusion of mastectomy*

Lancet Oncol. 2014; 15: 1303-1310. 41

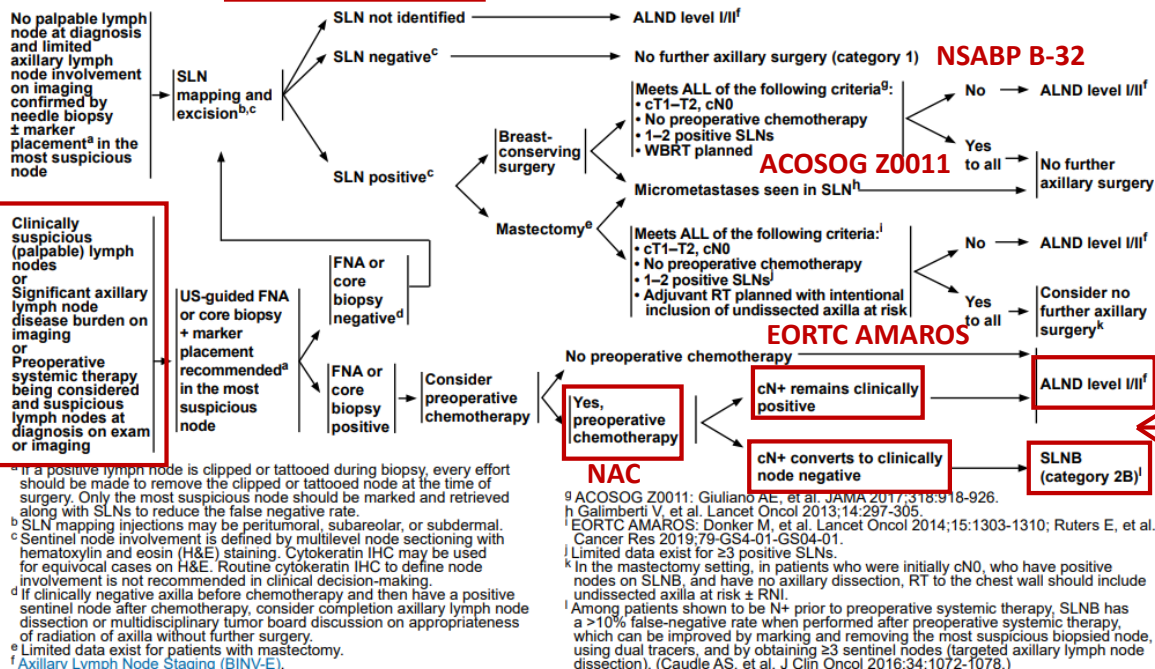


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## NCCN Guidelines Version 1.2024 Invasive Breast Cancer

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### CONSIDERATIONS FOR SURGICAL AXILLARY STAGING



Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

## LANDMARK TRIALS

### Surgery 1<sup>st</sup>

- NSABP B-32
- ACOSOG Z0011
- EORTC AMAROS

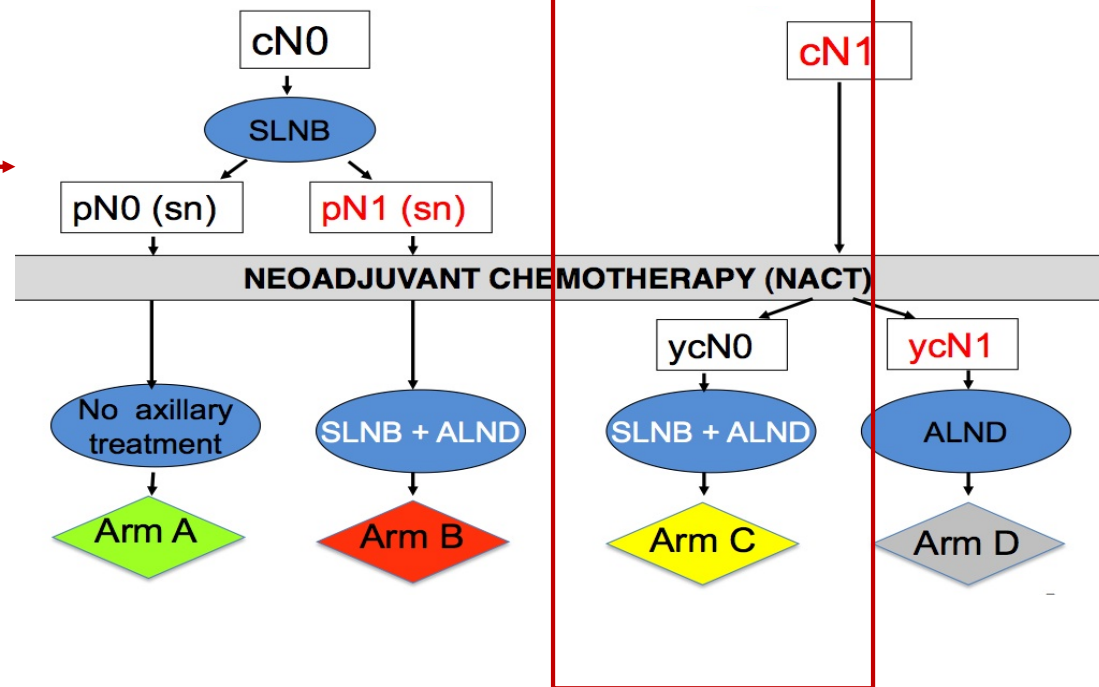
### Following NAC

- SENTINA
- ACOSOG Z1071
- MDACC TAD

# SENTINA (SENTinel NeoAdjuvant)

## Can we do SLNB after NAC?

- **AIM:** determine accuracy of SLNB in cN+, after NAC and ycN0
- **Design:** 4-arm, randomized study, 100+ institutions
- **Eligibility:**
  - NAC, 6 cycles, w/ anthracycline
- **ARM C: N=590**
  - cN1, NAC, ycN0
  - ycN0 = no longer palpable, normal by US, or if morphologically normal structure of hilum & cortex



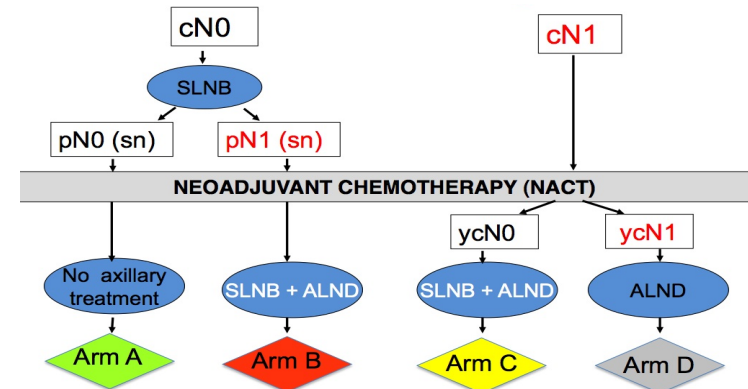
Lancet Oncol. 2013, 14: 609-618.

44

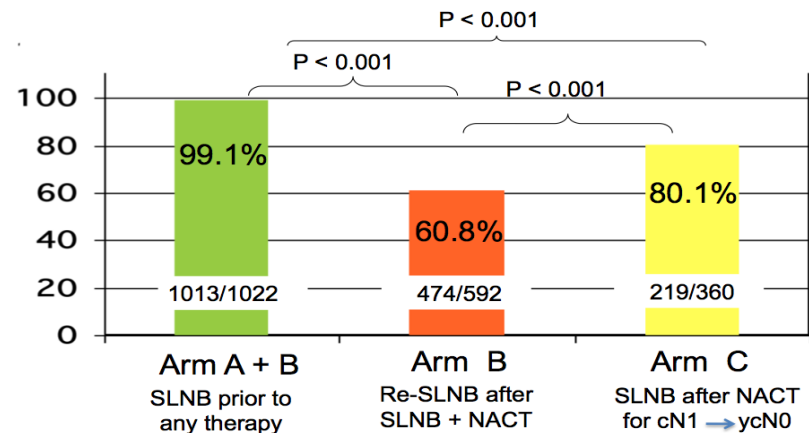
# SENTINA

## (SENTinel NeoAdjuvant)

- **Arms A & B: N=1022 (1<sup>st</sup> SLNB):**
  - Detection rate 99.1%
- **Arm B: N=592 (2<sup>nd</sup> SLNB):**
  - Detection rate 60.8%
  - False negative rate: **51.6%**
  - **Do not repeat SLNBx after NAC**
- **Arm C: N=360 (SLNB after NACT):**
  - Detection rate **80.1%**
  - False negative rate: **14.2%**



### Sentinel Lymph Nodes Detected and Removed



# SENTINA

## (SENTinel NeoAdjuvant)

- Detection of SLNs, Arm C:
- Overall detection rate w/  
radiocolloid *alone*:
  - **77.4%**
  - (302/389; 72.9-81.4)

- Overall detection rate w/  
radiocolloid & blue dye:
  - **87.8%**
  - 144/164; 81.8-92.4)

\*Significantly increased **detection rate** with **dual agent** in MV analysis

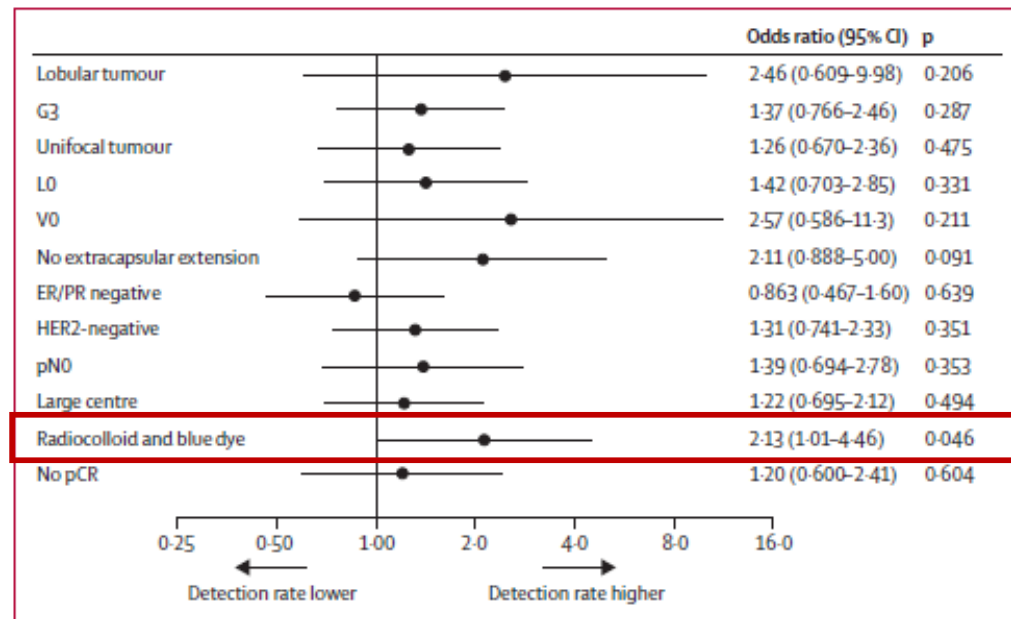


Figure 3: Multivariate regression analysis for detection rate (arm C)

G3=grade 3. L0=no lymphovascular invasion. V0=no vascular invasion. ER/PR=oestrogen receptor/progesterone receptor. pN0=pathologically node-negative. pCR=pathological complete response.

# SENTINA

## (SENTinel NeoAdjuvant)

- **False Negative Rate of SLNs, Arm C:**
- Overall: **14.2%**
- FNRs inversely proportional to number of SLN retrieved
- Accuracy if particularly unfavorable if only 1 or 2 SLN are removed (recall NSABP B-32)
  - **7.3%** if 3 nodes
- Dual agent tracer improves FNRs
  - **8.6%** if dual agent

	Arm B (n=64)	Arm C (n=226)
Overall false-negative rate (n/N; 95% CI)	51.6% (33/64; 38.7–64.2)	14.2% (32/226; 9.9–19.4)
False-negative rate, according to number of sentinel nodes removed		
1	66.7% (16/24)	24.3% (17/70)
2	53.8% (7/13)	18.5% (10/54)
3	50.0% (5/10)	7.3% (3/41)
4	50.0% (3/6)	0.0% (0/28)
5	18.2% (2/11)	6.1% (2/33)
False-negative rate, according to detection technique		
Radiocolloid alone	46.2% (18/39)	16.0% (23/144)
Radiocolloid and blue dye	60.9% (14/25)	8.6% (6/70)

Data are rate (number of patients), unless otherwise stated.

**Table 4: False-negative rate of sentinel-lymph-node resection in patients with positive nodes, according to selected factors**

**Overall detection rate and accuracy of SLNB are inferior for patients who convert during chemotherapy to node negative disease**

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# ACOSOG Z1071

## SLNB after NAC in cN+ → ycN0

- **Trial Enrollment: 2009 - 2011**
- **Enrolled:** N=756, 126 sites
- **Eligibility:**
  - cT0-4, cN1-2, M0 → NAC
  - SLNB and ALND (**all** pts had ALND)
  - (SENTINA “Arm C”)
- SLN = hot, blue, palpably abnormal
- Dual agent *recommended*
- Protocol required at least 2 SLN identified
- H&E stained, positive defined as metastases of 0.2mm or larger (no ITCs)

- 80% used dual agent

### Identified:

- 12% identified 1 SLN
- 24% identified 2 SLN
- **23% identified 3 SLN**
- **14% identified 4 SLN**
- **21% identified 5 or more**

*58% identified ≥3 SLN\**

JAMA. 2013, 310: 1455-1461.

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# ACOSOG Z1071

## SLNB after NAC in cN+ → ycN0

- Overall trial FNR = **12.6%**
  - Single agent: FNR = **20.3%**
  - Dual agent: FNR = **10.8%**
  - 2 SLN identified: FNR = **21.1%**
  - 3 SLN identified: FNR = **9.1%**
- *Conclusion: the **12.6%** was higher than pre-specified threshold of 10%*

Table 3. Factors Affecting the Likelihood of a False-Negative Sentinel Lymph Node Finding in the 310 Women With cN1 Disease at Presentation, 2 or More SLNs Examined, and Residual Nodal Disease After Neoadjuvant Chemotherapy

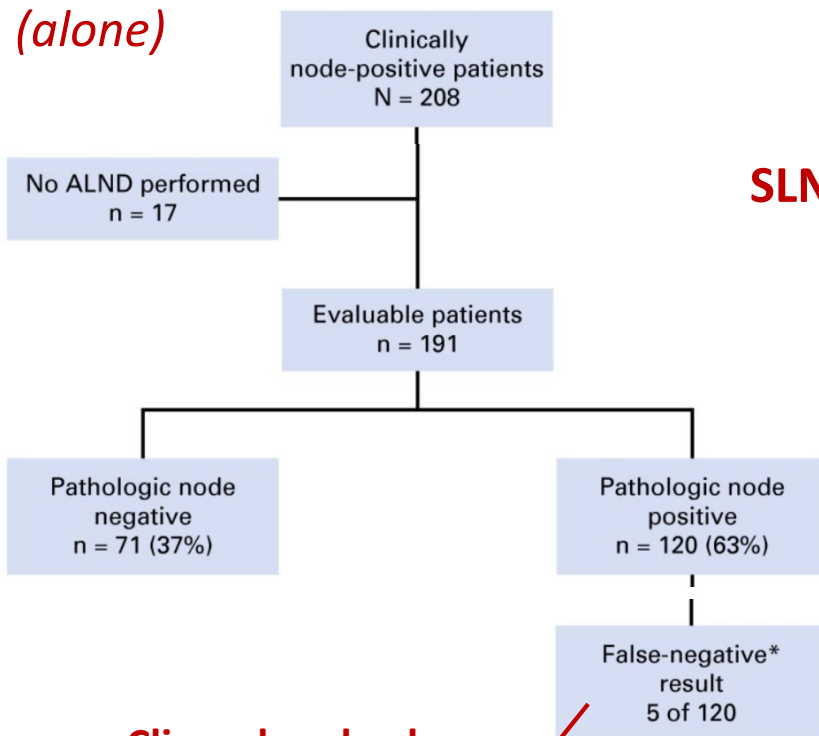
	False-Negative SLN Findings, No. (Total)	FNR (95% CI), %	Fisher Exact Test, P Value
Age, y			
18.0-49.9	20 (150)	13.3 (8.3-19.8)	.73
≥50.0	19 (160)	11.9 (7.3-17.9)	
BMI			
≥25.0	25 (227)	11.0 (7.3-15.8)	.18
<25.0	14 (83)	16.9 (9.5-26.7)	
Palpable, fixed, or matted nodes after chemotherapy <sup>a</sup>			
Yes	10 (52)	19.2 (9.6-32.5)	.17
No	28 (247)	11.3 (7.7-16.0)	
Mapping agents used			
Single	12 (59)	20.3 (11.0-32.8)	.05
Dual	27 (251)	10.8 (7.2-15.3)	
Multiple injection sites <sup>b</sup>			
Yes	5 (70)	7.1 (2.4-15.9)	.21
No	30 (225)	13.3 (9.2-18.5)	
No. of SLNs examined			
2	19 (90)	21.1 (13.2-31.0)	.007
≥3	20 (220)	9.1 (5.6-13.7)	

# Targeted Axillary Dissection (TAD)

## Evaluation of clipped nodes after NAC

- **AIM:** to determine:
  - If pathologic changes in a *clipped node* reflects the *status* of the nodal basin
  - If TAD (clipped node + SLNB) improves the FNR
- **Design:** prospective registry, single site
- **Trial Enrollment:** 2011 – 2015
- **Enrolled:** **N = 208** (191 completed ALND)
- **Eligibility:**
  - Axillary US for all patients
  - Biopsy-proven nodal metastases
  - Clipped placed at biopsy
  - NAC
  - SLNB: Tc-<sup>99</sup>, blue dye, or both
  - **All** I<sup>125</sup> seed for localization

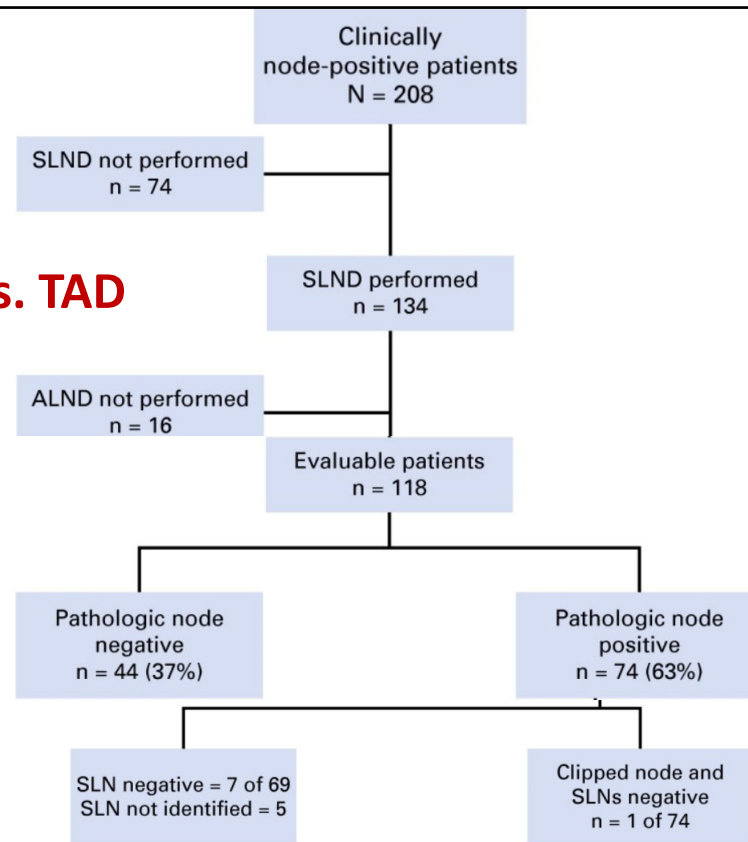
## CLIPPED NODE (alone)



Clipped node alone:  
4.2%

False-negative rate  
4.2%  
(95% CI, 1.4 to 9.5)

## SLNB vs. TAD



Sentinel nodes  
alone: 10.1%

False-negative rate  
SLN alone = 10.1% (95% CI 4.2 to 19.8)  
SLN + evaluation of the clipped node = 1.4% (95% CI, 0.03 to 7.3)  
P = .03

TAD: 1.4%

# Targeted Axillary Dissection (TAD)

## Evaluation of clipped nodes after NAC

- **CONCLUSION**

- *Significant improved accuracy of axillary staging post-NAC by performing TAD, (SLNB + clipped node)*
- FNR for TAD was 2.0% vs 10.1% for SLNB alone
- Although sample size limits statistical comparison of the two approaches, these exploratory data are promising

- **ACOSOG Z1071** - clipped node (N=170 / 663)

- 107 pts (63%) for whom *the clipped node* was retrieved as an SLN, the **FNR was 6.8%** (95% CI, 1.9% to 16.5%)
- Supports clipped node is valuable for FNR

- Clipped node *was not a SLN* (post-NAC) in **23%**
- SLNB w/ *dual tracers* in 65 pts (**55%**)  
*\*This suggests retrieving additional nodes and using dual agent may have identified clipped node as a SLN*

Similar FNR\*: *different (very small numbers)*

- Single-tracer mapping (**10.0%**; 3 of **30**)
- Dual agent mapping (**10.3%**; 4 of **39**)

Similar FNR:

- < 2 SLNs removed (**10.7%**; 6 of 56)
- ≥ 2 SLNs removed (**7.7%**; 1 of 13)

- *What is the FNR w/ dual agent & 3 nodes?*

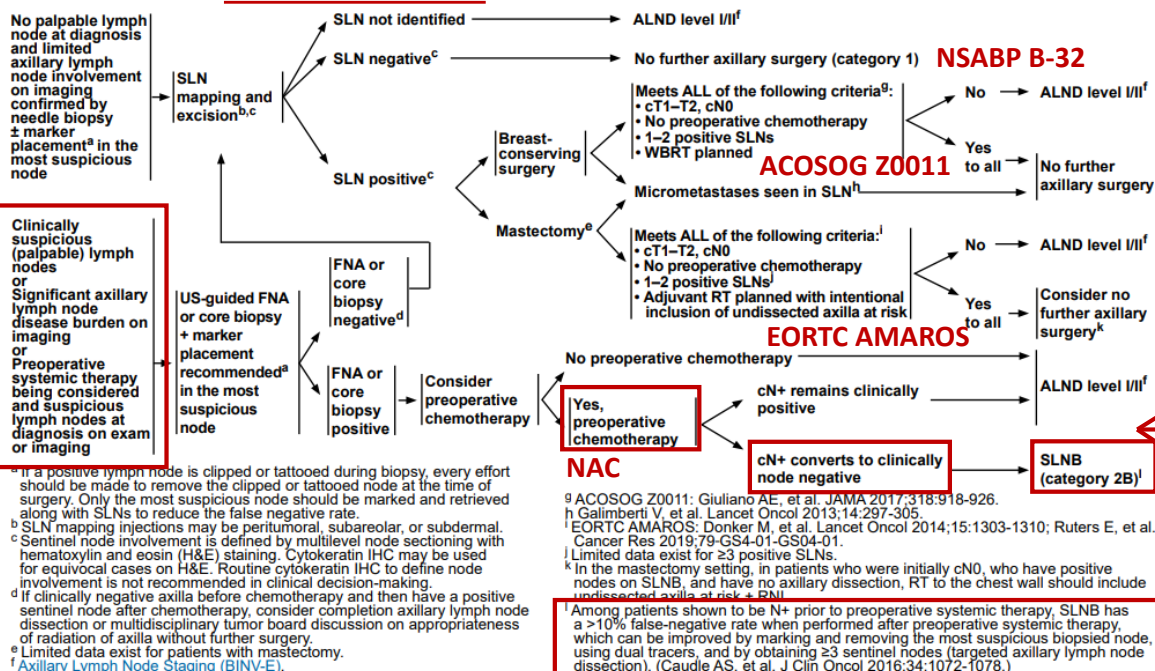


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## NCCN Guidelines Version 1.2024 Invasive Breast Cancer

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### Surgery 1<sup>st</sup>

- NSABP B-32
- ACOSOG Z0011
- EORTC AMAROS

### Following NAC

- SENTINA
- ACOSOG Z1071
- MDACC TAD

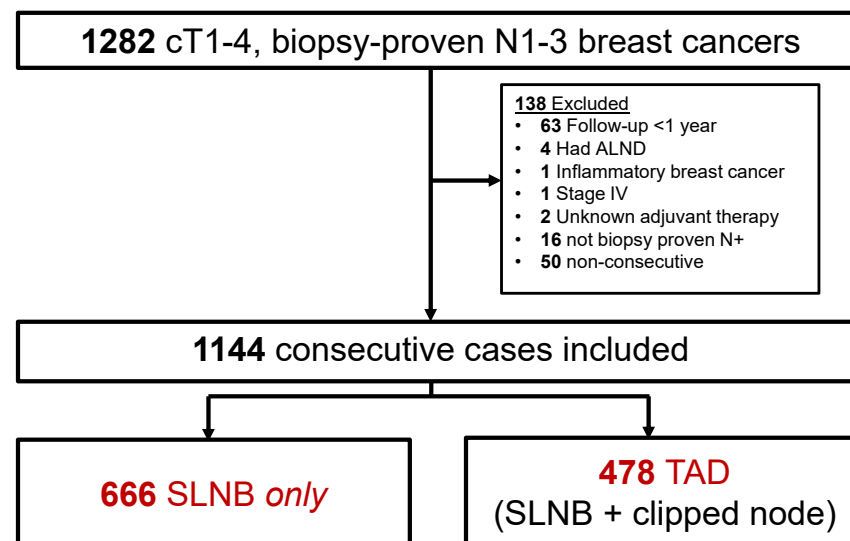


# What's NEW in the axilla??

## OPBC-04/EUBREAST-06/OMA Study

Oncological Outcomes following **SLNB** or **TAD** in Breast Cancer Patients  
downstaging from **cN+** → **ycN0** with NAC

- **AIM:** to determine:
  - whether the reduction in FNR observed w/ **TAD** translates into a reduction in axillary recurrence
  - rates of axillary recurrence after SLNB (w/ dual tracer) vs. TAD
- **Enrollment:**
  - retrospective, international, multi-center (25 centers, 11 countries),
  - Included cases: 2013-2020
- **Enrolled:** N=1282
- **Inclusion:** cT1-4, cN1-3 (biopsy proven), NAC, ycN0, axillary procedure of choice, **ypN0**
- **Excluded:** ALND, inflammatory, stage IV, <1y FU



SABCS, 2022. Montagna, G. JAMA Oncol, *in press*. 56

## OPBC-04/EUBREAST-06/OMA Study

Oncological Outcomes following **SLNB** or **TAD** in Breast Cancer Patients  
downstaging from **cN+** → **ycN0** with NAC

### **SLNB only, N = 666**

- Dual-tracer mapping: 666 (**100%**)
- Clip placement: 150/666 (**23%**)
- Clipped node removed  
(without localization): 129/150 (**86%**)
- Median follow-up: **4.2 years**

### **TAD, N = 478 (SLNB + clipped node)**

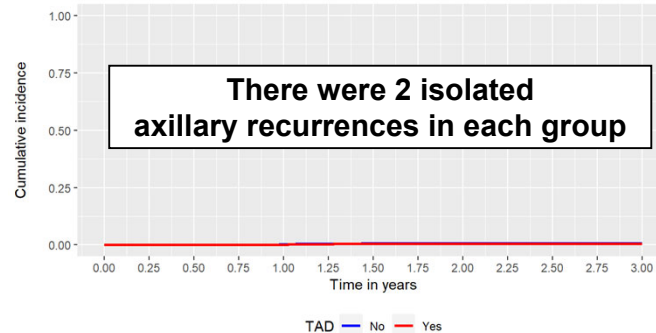
- Dual-tracer mapping: (**78%**)
- Clipped node removed: 466/478 (**99%**)
- Localization technique
  - Radioactive seed: 343/478 (**72%**)
  - Wire: 115/478 (**24%**)
  - Ultrasound: 11/478 (**2.3%**)
  - Other (Magseed, tattoo, wire): 9/478 (**1.9%**)
- Median follow-up: **2.7 years**

SABCS, 2022. Montagna, G. JAMA Oncol, *in press*. 57



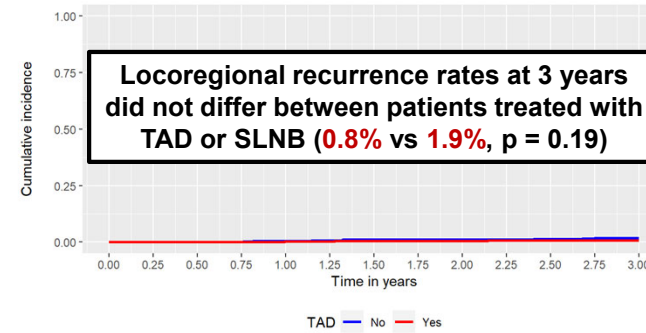
# OPBC-04/EUBREAST-06/OMA Study

3-year rate of **any axillary recurrence** TAD vs SLNB  
(**0.5% vs 0.8%**,  $p = 0.55$ )



**No difference** in isolated axillary recurrences

3-year rate of **locoregional recurrence** TAD vs SLNB  
(**0.8% vs 1.9%**,  $p = 0.19$ )



**No difference** in locoregional recurrences

	Overall n = 1144	SLNB n = 666	TAD n = 478	p value
# of SLNs removed (median, IQR)	3 (3, 5)	4 (3, 5)	3 (2, 4)	< 0.001
# of total LNs removed (mean, SD)	4.2 (2.03)	4.4 (2.04)	3.9 (1.97)	< 0.001

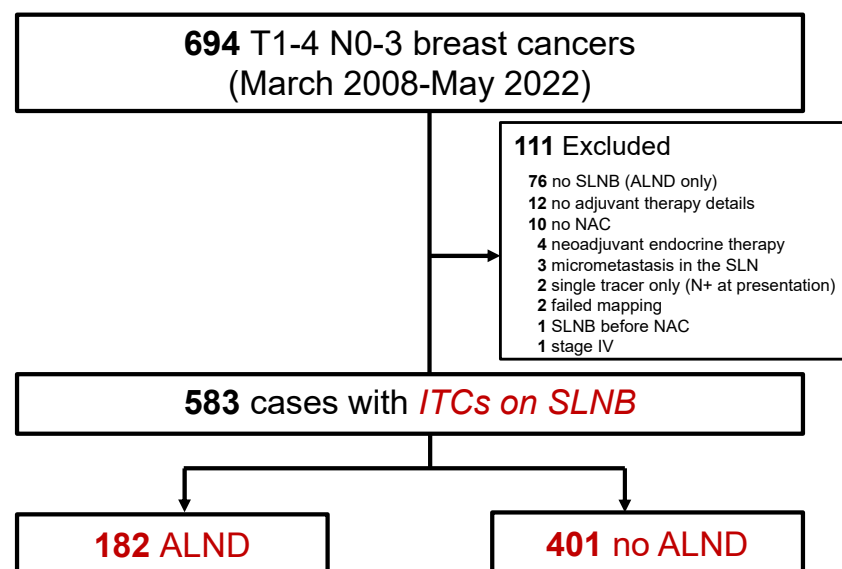
- **Early axillary recurrence is a rare event**
- **Safe to omit ALND in ypN0**
- **Axillary recurrence was not significantly lower in TAD than SLNB**

SABCS, 2022. Montagna, G. JAMA Oncol, *in press*. 58

## OPBC-05 / EUBREAST-14R / ICARO Study

Are **isolated tumor cells (ITCs)** an indication for **ALND** in Breast Cancer Patients  
downstaging from **cN+** → **ycN0** with NAC

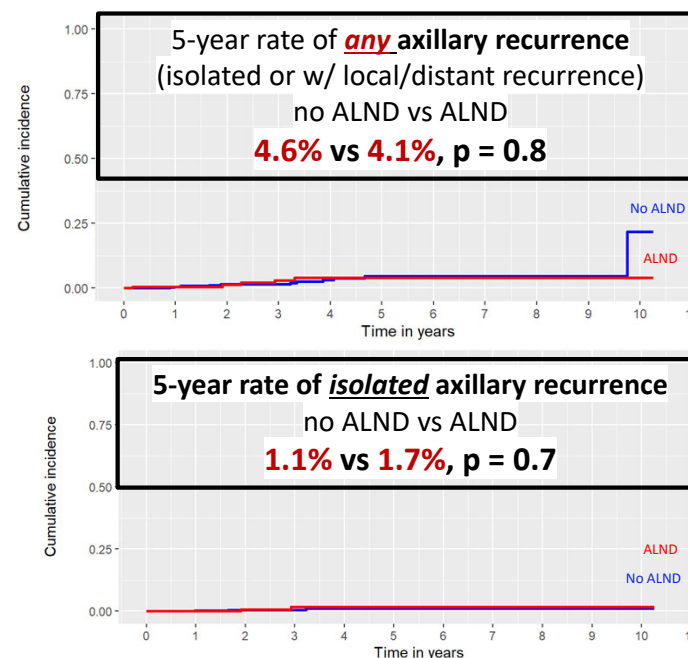
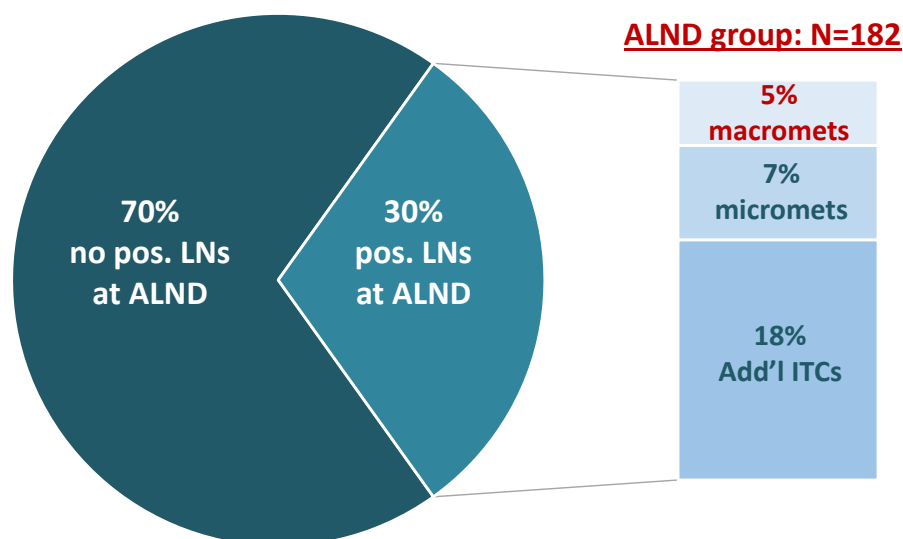
- **Background:** residual *micromets* in SLNs after NAC have high % of additional positive nodes in ALND, and ALND is considered standard of care
- **AIM:** to determine
  - How often add'l positive LNs are identified in patients w/ residual **ITCs only**
  - Evaluate rates of recurrence and outcomes between those w/ and w/out **ALND**
- **Enrollment:**
  - retrospective, international, multi-center (62 centers, 18 countries),
  - Included cases: 2008-2022
- **Enrolled:** **N=694**
- **Inclusion:** cT1-4, cN0-3 (biopsy proven), NAC, ycN0(i+), axillary procedure of choice, **ypN0**
- **Excluded:** directly to ALND, IBC/Stg IV, <1y FU
- **Median follow-up:** 3.2 years



Data presented @ **SABCS, 2023**. Montagna, G, et al. 59

## OPBC-05 / EUBREAST-14R / ICARO Study

Are **isolated tumor cells (ITCs)** an indication for **ALND** in Breast Cancer Patients  
downstaging from **cN+** → **ycN0** with NAC



Data presented @ **SABCS, 2023**. Montagna, G, et al.

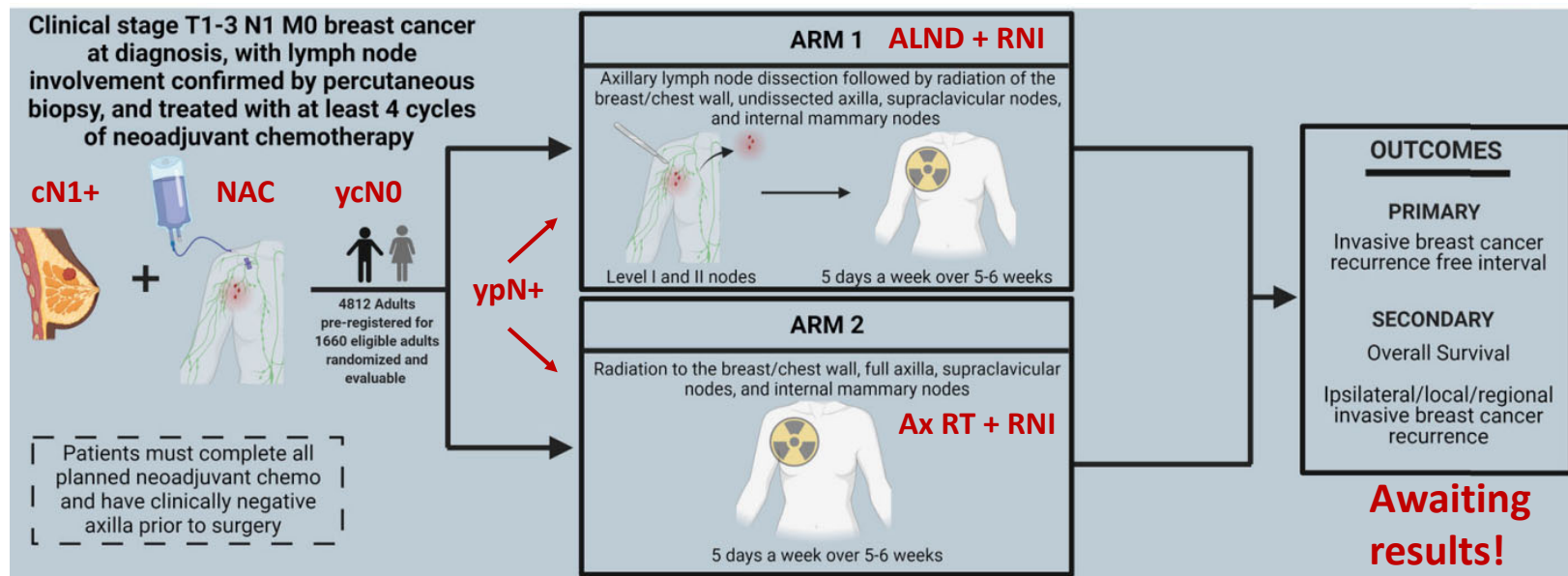
**\*not standard of care at this time!**

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# Comparison of ALND vs. Axillary XRT for patients w/ SLNB-Positive Breast Cancer after Treatment w/ NAC

## Alliance 11202

**AIM:** Can axillary radiation be used in lieu of ALND in patients with residual disease after NAC?



PI: Judy C. Boughey, MD – Mayo Clinic  
NCT: 01901094 – Phase III, randomized, multi-institutional

Ann Surg Oncol. 2022; 29:1526-1527.

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## NCCN Member Institutions

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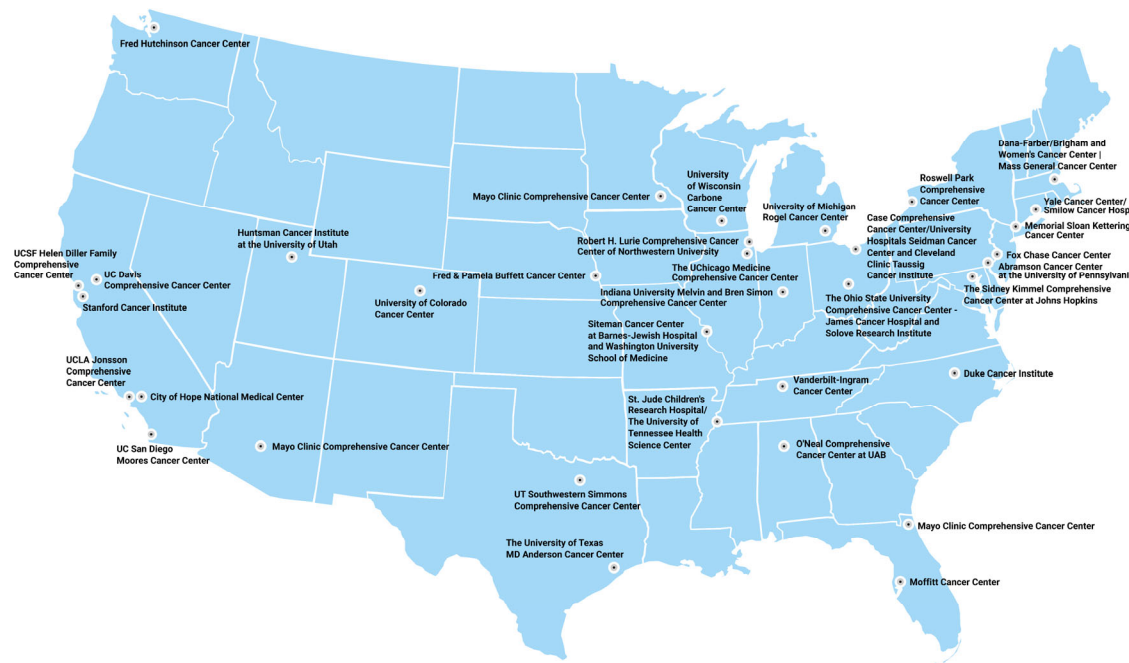
An alliance of leading cancer centers devoted to patient care, research, and education

### Our Mission

To improve and facilitate quality, effective, equitable, and accessible cancer care so all patients can live better lives

### Our Vision

To define and advance high-quality, high-value, patient-centered cancer care globally



**NCCN.org** – For Clinicians | **NCCN.org/patients** – For Patients | **Education.nccn.org** – CE Portal