

The logo for the Atlanta Breast Cancer Conference. It features the word "Atlanta" in a simple sans-serif font, followed by "Breast" in a large, bold, black script font, and "Cancer" in a smaller sans-serif font below it. The word "CONFERENCE" is written in white, uppercase, sans-serif letters inside a red rounded rectangle.

Atlanta Breast Cancer CONFERENCE

Future Directions in
Multi-disciplinary Breast Cancer Care – The Radiation Oncologist's Perspective

September 27, 2025



Future Directions in Multi-disciplinary Breast Cancer Care – The Radiation Oncologist's Perspective

Mylin A. Torres MD
James W. Keller Distinguished Professor in Radiation Oncology
Department of Radiation Oncology
Co-Leader, Cancer Prevention and Control Program
Winship Cancer Institute
Emory University



Disclosures

- Pfizer
- Varian
- There will be no discussion of off-label drug or device use or references to proprietary technology

Outline

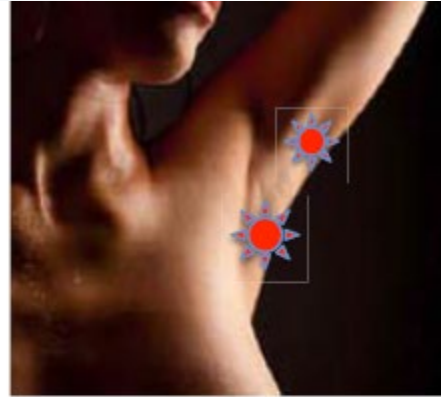
1. Radiation in the context of axillary surgery de-escalation
2. Sequencing radiation with new systemic agents

De-Escalation of Axillary Surgery with Up Front Breast Surgery

Morbidity of Axillary Surgery



**Lymphedema
(10-15%)**

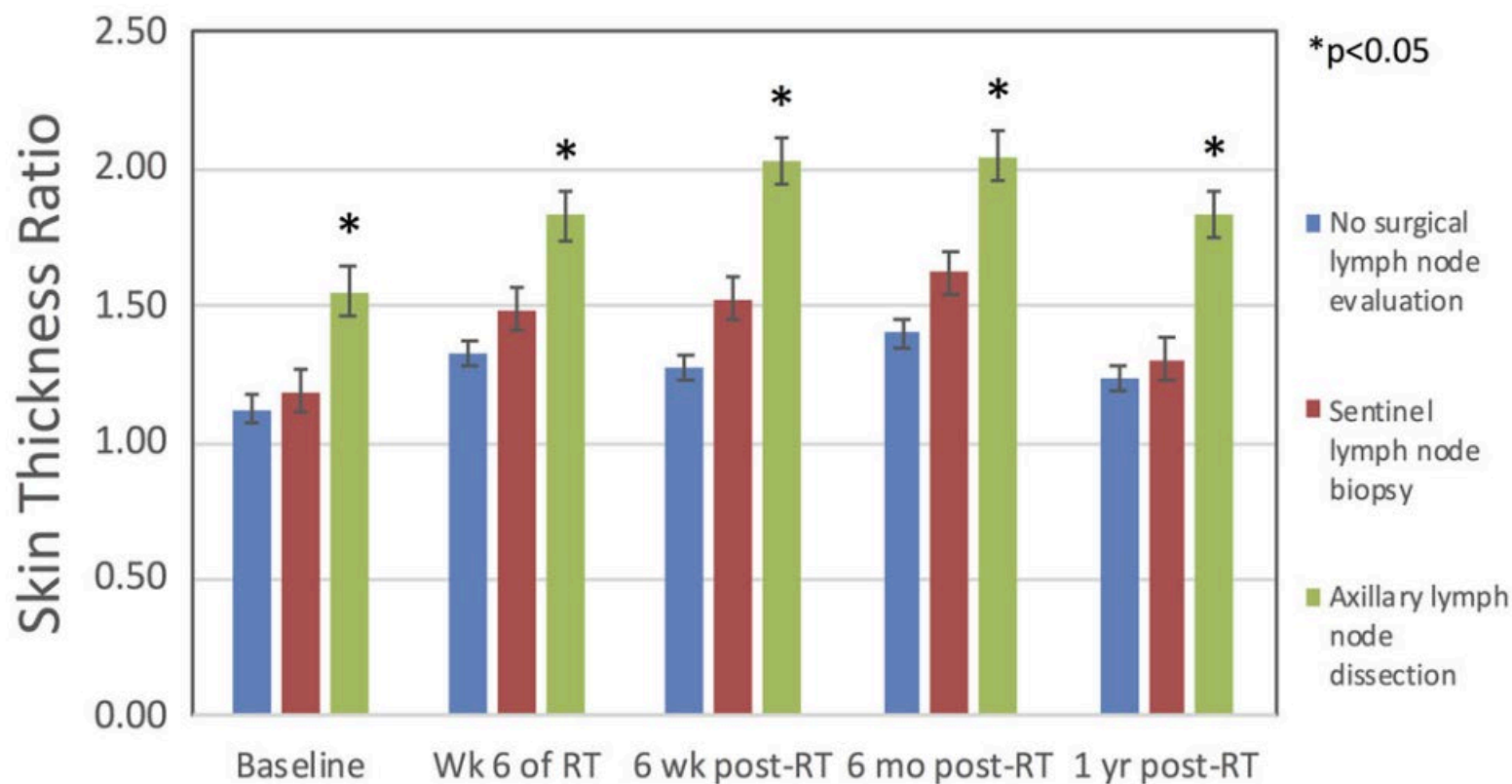


**Chronic Pain
(5-10%)**



**Axillary Web Syndrome
(30-50%)**

Breast Skin Thickening Worsened by Lymph Node Dissection



Baseline STRA also predicted for worse breast skin thickening at 1 year, $p<0.001$
ALND predicted for worse baseline breast skin thickening, $p=0.03$

Cosmetic Outcome after Radiation

Baseline

Week 6 of XRT

6 weeks post XRT

1 year post XRT

Excellent



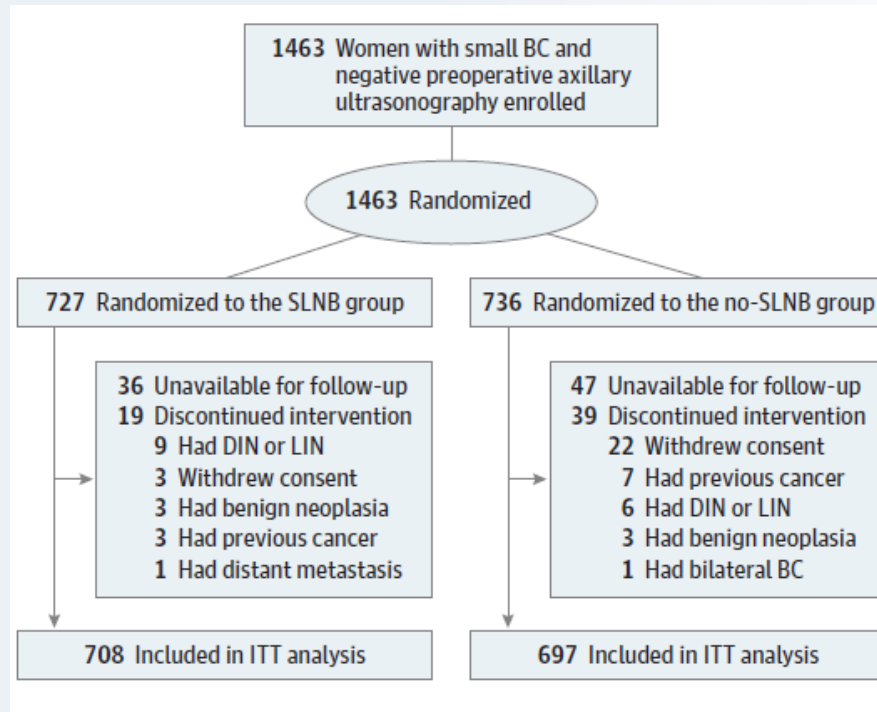
Poor



Can we OMIT sentinel node biopsy (AVOID any axillary surgery) in patients with clinically node negative disease?

SOUND and INSEMA Trials

SOUND



BC indicates breast cancer; DIN, ductal intraepithelial neoplasia; ITT, intention to treat; LIN, lobular intraepithelial neoplasia; and SLNB, sentinel lymph node biopsy.

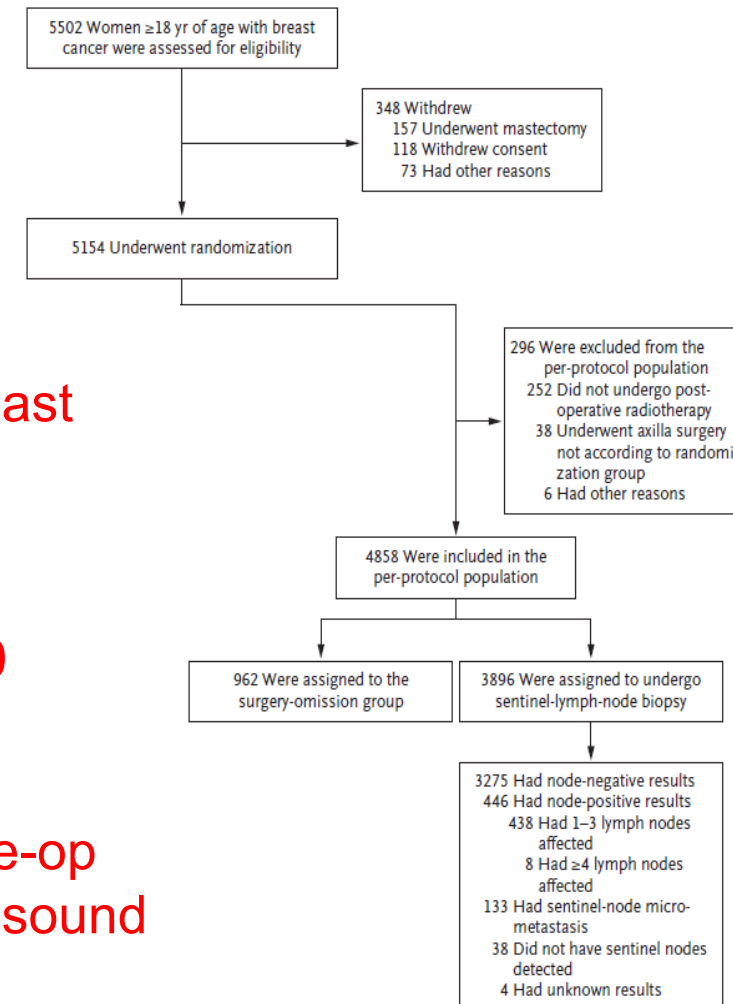
Gentilini et al., JAMA Oncology, 2023

INSEMA

- 90% cT1N0 invasive breast cancer ($\leq 2.0\text{cm}$)

- 10% cT2N0 (2-5cm)

★ Negative pre-op axillary ultrasound



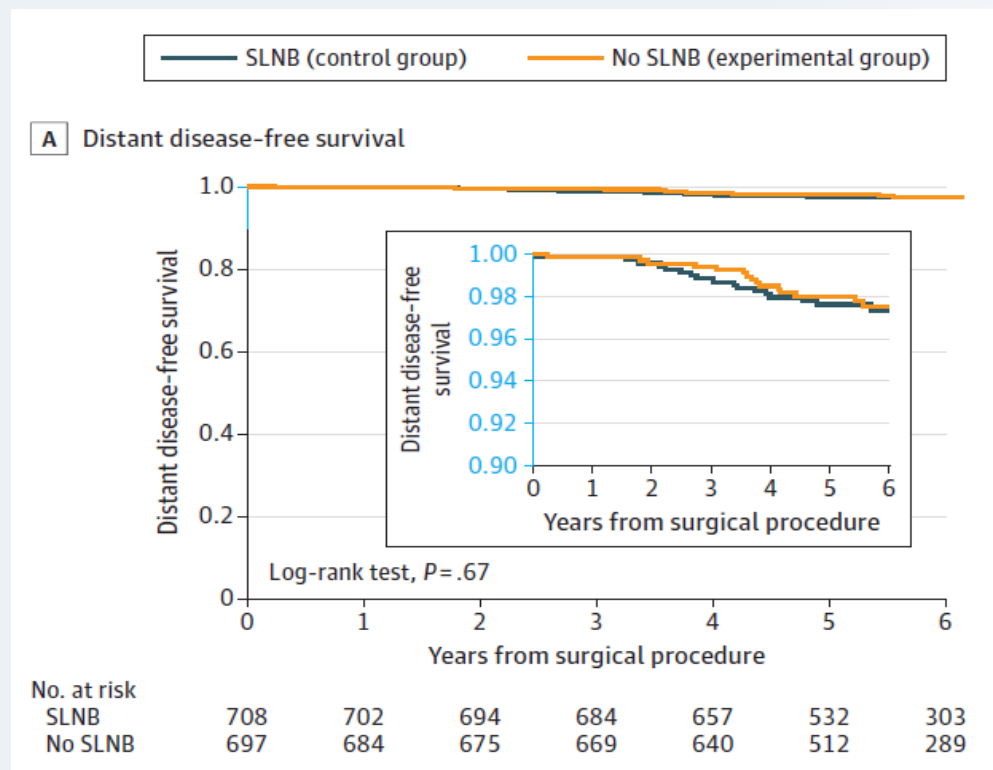
Reimer et al., NEJM, 2024

SOUND and INSEMA Patient, Tumor, and Treatment Characteristics

- $\geq 80\%$ age 50 years or older
- $\geq 75\%$ postmenopausal
- $\geq 80\%$ pT1
- 85% pN0
- $\geq 80\%$ Gr1 or 2
- $\geq 87\%$ HR+, Her2-
- 13-20% received chemotherapy
- $\geq 90\%$ received endocrine tx
- $\geq 98\%$ received radiation
(almost all whole breast irradiation, ~10% received PBI on SOUND)

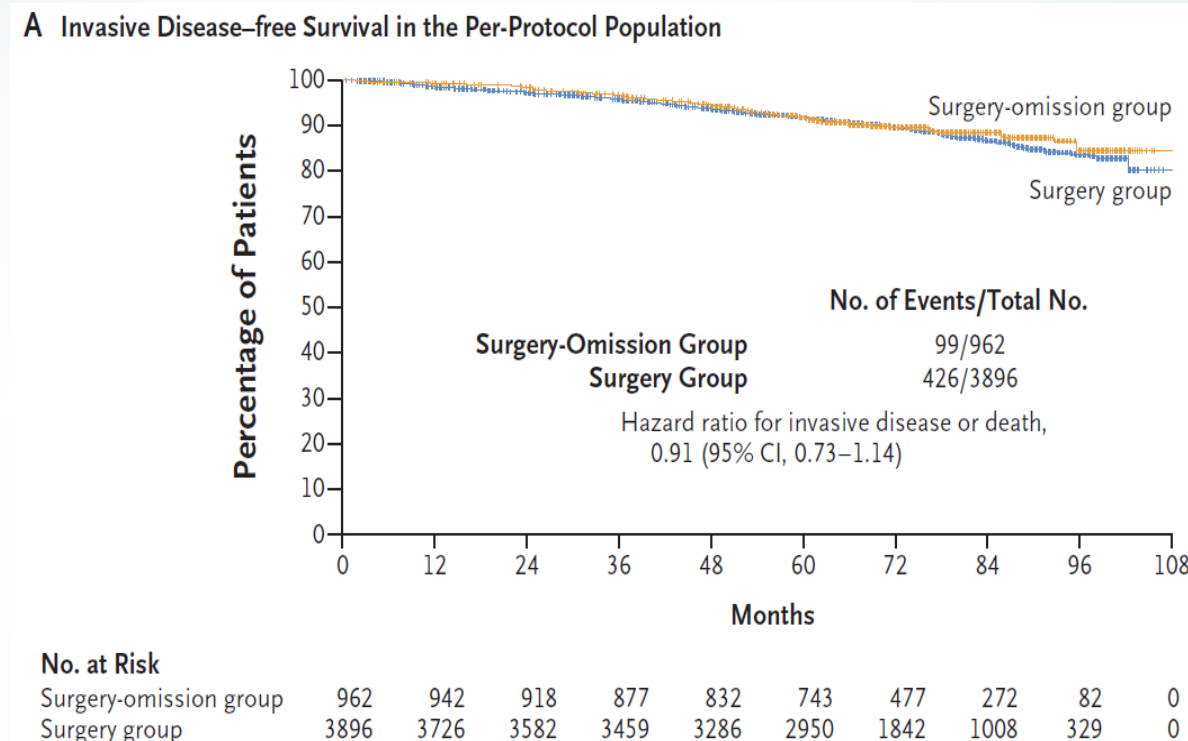
Primary Endpoints

SOUND



No differences in DFS or OS
No difference in axillary recurrence rates (~0.4% vs. 0.7%)

INSEMA



No differences in OS

2025 ASCO Guideline Update: Sentinel Lymph Node Biopsy in Early-Stage Breast Cancer

Findings from multi-institutional trials in academic and community practice settings indicate that patients with low-risk breast cancer and negative nodal status (confirmed by pre-operative ultrasound) may avoid SLNbx:

- Post-menopausal &
- Age >50 &
- pT1 &
- ER+/PR+/Her2- &
- Gr 1 or 2 disease &
- Receive radiation treatment &
- Receive hormone therapy

Under-represented:

- Lobular
- TNBC
- HER2+
- Gr 3
- T2 tumors
- Mastectomy
- PBI

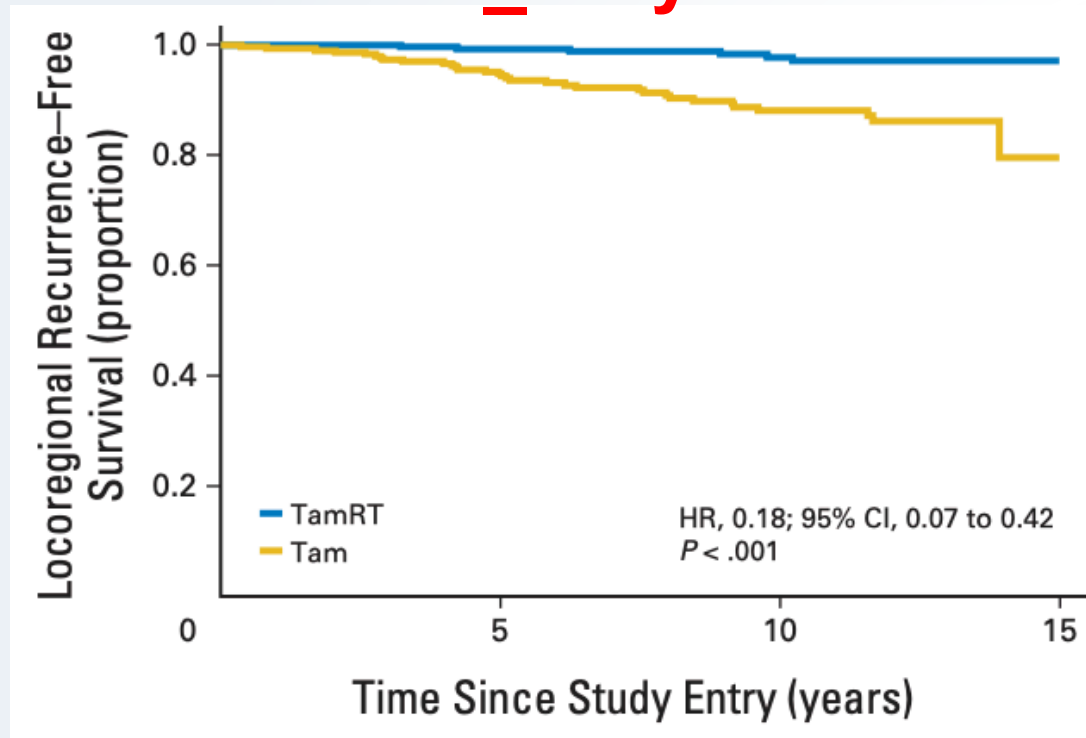
Systemic Therapy and Radiation Recommendations

- **85%** of all SOUND and INSEMA patients with a negative axillary ultrasound have tumors that are pN0
- Omission of SLNbx should not alter adjuvant systemic therapy or radiation recommendations in the appropriate patients who can safely forego SLNbx:
 - Post-menopausal &
 - Age >50 &
 - pT1 &
 - ER+/PR+/Her2- &
 - Gr 1 or 2 disease &
 - Receive radiation treatment &
 - Receive hormone therapy

Is radiation always necessary when the axilla is not staged surgically?

Radiation Benefit in Low-Risk Patients (pT1N0, HR+)

≥ 70 years

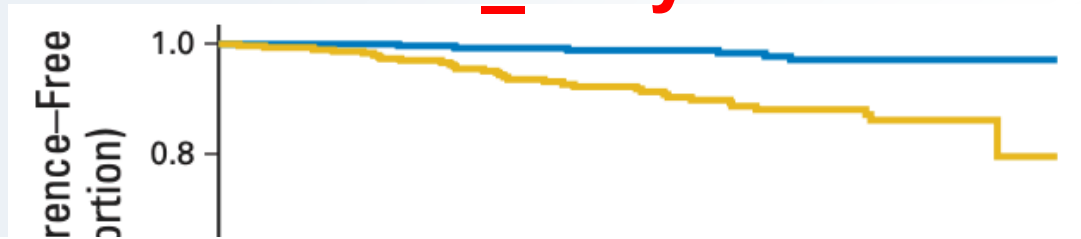


10-year LRR:
10% Tam vs. 2% RT-Tam

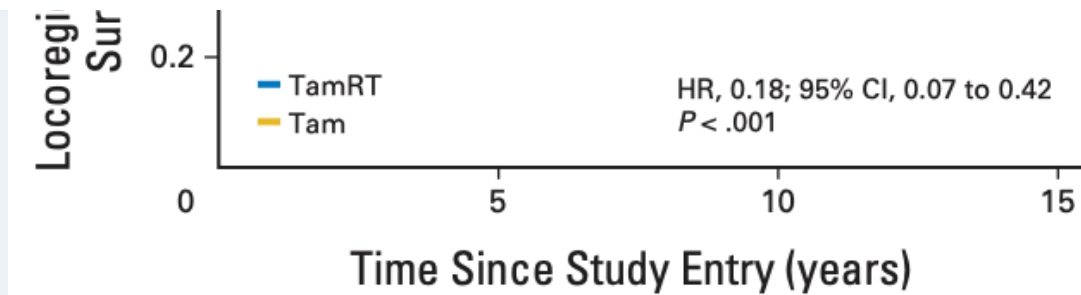
CALGB 9343

Radiation Benefit in Low-Risk Patients (pT1N0, HR+)

≥ 70 years



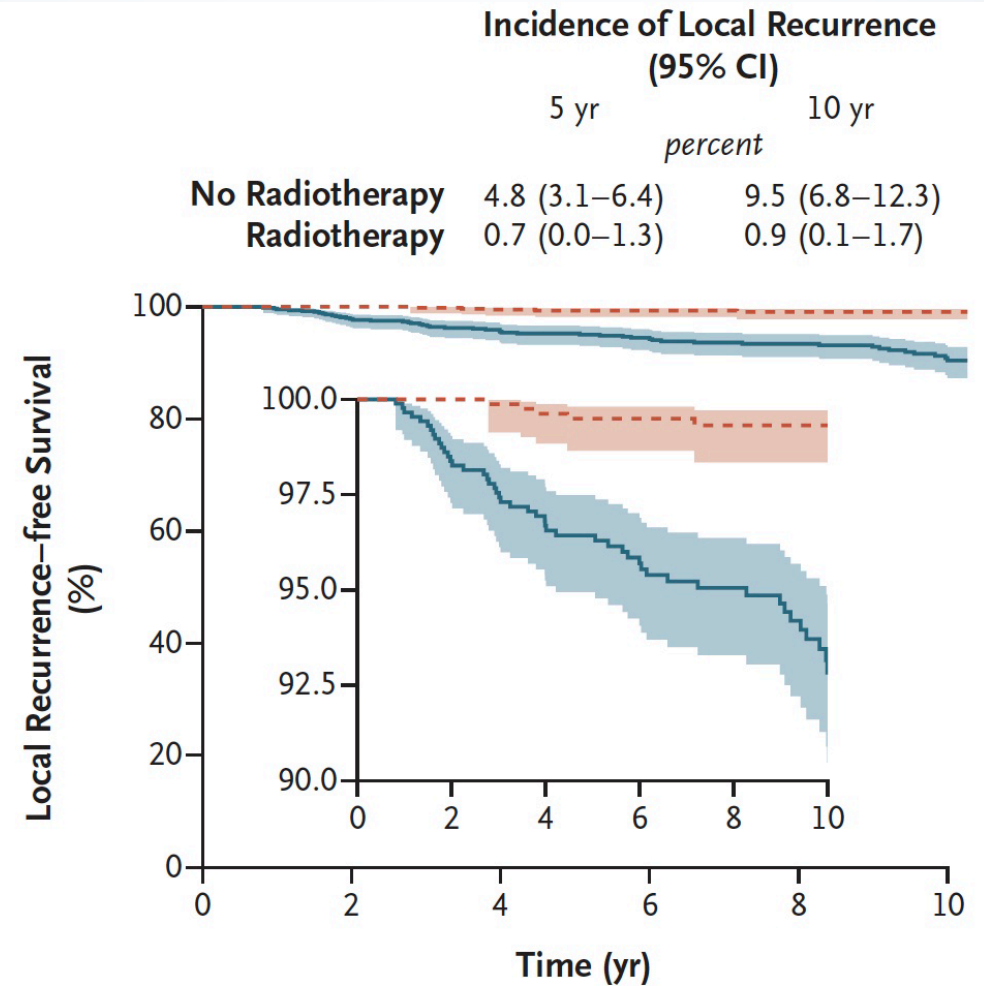
~2/3 of patients did not have sentinel node biopsy or axillary lymph node dissection



CALGB 9343

PRIME II 10-year Results

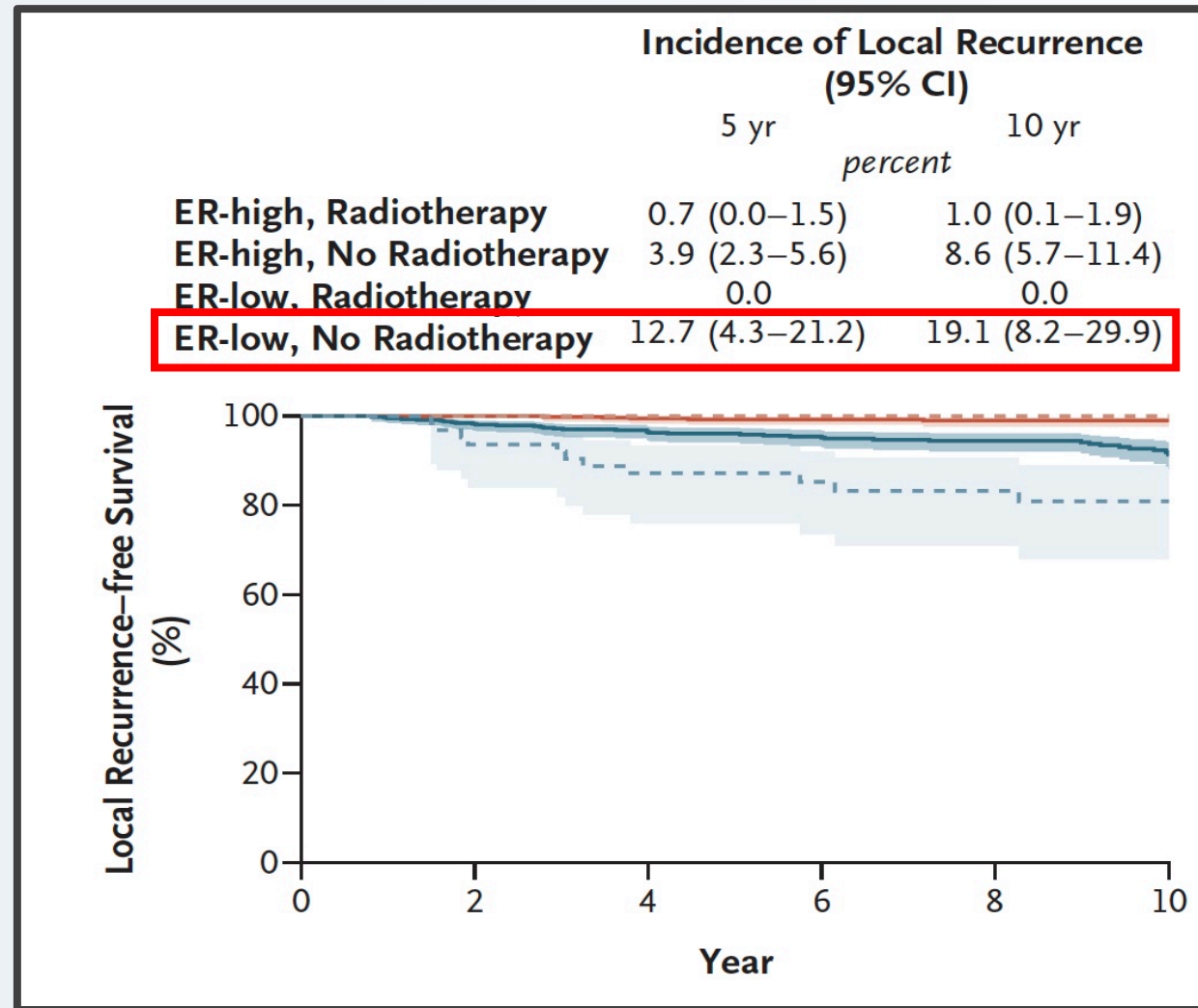
- Inclusion: Age ≥ 65 , ≤ 3 cm, node negative, HR+
- **Surgical axillary staging was required**
- $<5\%$ of tumors were Grade 3 or had LVSI
- 12% of tumors were T2
- 10-year LRFS:
 - ✓ 9.5% HT vs. 0.9% HT-RT



Kunkler et al. NEJM 2023;388 (7):585-594.

PRIME II: Benefit of Radiation in ER-low Tumors

ER-Low tumors:
e.g., <50% of cells
positive for ER



Kunkler et al. NEJM 2023;388 (7):585-594.

Omission of Radiation Candidates

- ≥ 65 years of age
- T1 tumors, node negative (**pre-operative axillary ultrasound based on the SOUND TRIAL**)
- Grade 1 or 2
- High ER+
- Patient likely to be adherent to HT
- No LVSI
- Low genomic risk score

Systemic Therapy and Radiation Recommendations

- **In patients with axillary ultrasound that is negative, 13-14.9% pN1 and 0.2-0.6% pN2**
 - Systemic therapy decisions dependent upon genomic assay score (e.g., 21-Gene Recurrence Score) of primary tumor, except in premenopausal patient or those with pN2 disease
 - cdk4/6 inhibitors, PARPi recommended in all patients with pN2 disease
 - Ribociclib recommended in patients with pT2, Gr3, node negative disease
 - PBI not administered in N+ breast cancer
 - RNI administered in N2 and some N1 breast cancers

Is radiation necessary when patients with pN1 disease are treated with sentinel lymph node biopsy only?

Overview of axillary management in early breast cancer

Presenter: Gurdeep S. Mannu D.Phil FRCS

University of Oxford

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

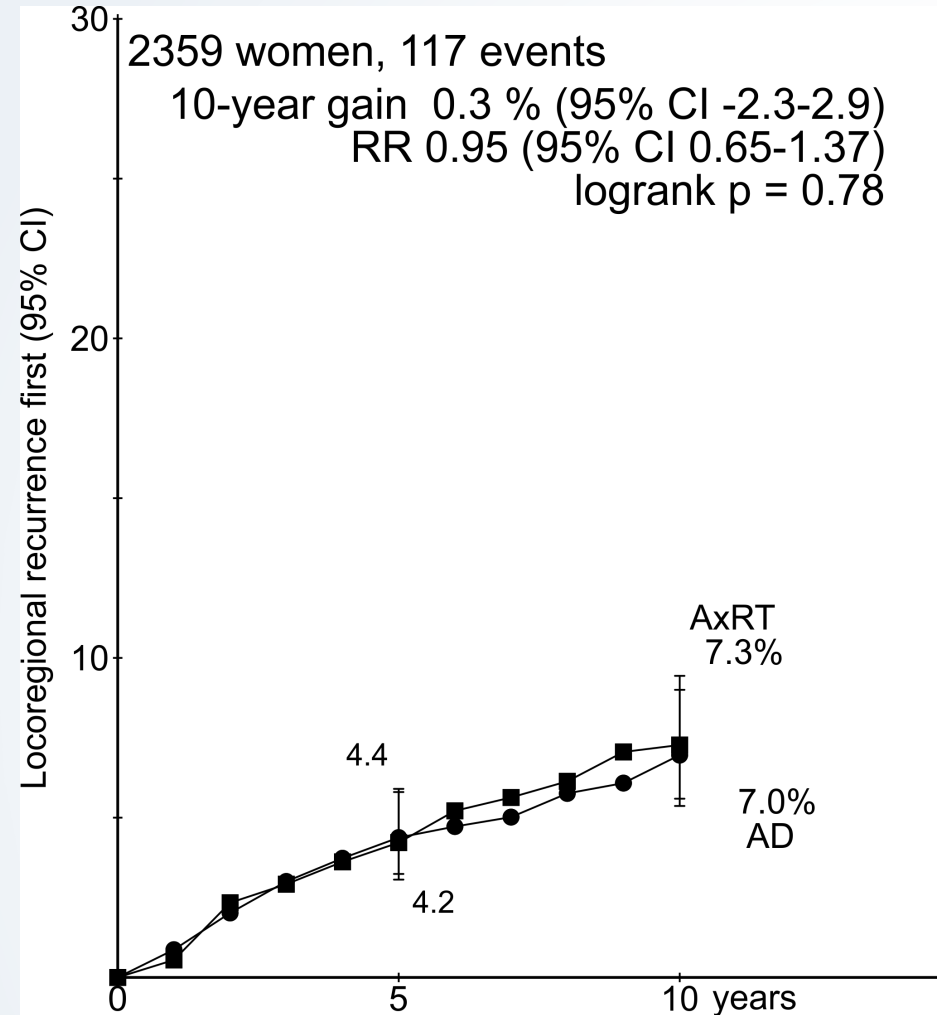
Writing Committee: Gurdeep Mannu , Graham Beake, Richard Berry, David Dodwell, Robert Hills, Paul McGale, Stewart Anderson, Ian Campbell, Armando Giuliano, Reshma Jagsi, Thorsten Kuhn, Rebecca Llewelyn-Bennet, Terry Mamounas, Robert Mansel, Pascal Roy, Emiel Rutgers, Nisha Sharma, Sandra Swain*, Jonas Bergh*
(*joint senior co-authors)

Axillary dissection vs Axillary radiotherapy in cN0 who have pN+ (<3 nodes)

Trial	Recruitment	Women
<u>Pre-SLNB era</u>		
WSSA Glasgow	1972-1977	212
Edinburgh	1980-1983	167
Scottish	1987-1995	81
<u>SLNB era</u>		
AMAROS	2001-2010	1425
OTOASOR	2002-2009	474

Axillary dissection vs Axillary radiotherapy

Locoregional recurrence



Axillary dissection vs Axillary radiotherapy

Summary of outcomes



No oncologic benefit with ALND in SLNbx positive patients and lymphedema significantly worse in patients treated with axillary dissection

Conclusions

- Axillary recurrences are rare (~1%)
- More axillary surgery at least doubles lymphedema (~20%) and increases lymphedema **risk** significantly when compared with axillary radiation

Take Home

- Axillary radiation may replace full axillary lymph node dissections in cN0 patients with positive sentinel lymph nodes (<3 nodes) and is associated with less risk for lymphedema
- Is radiation following SLNbx adequate treatment of the axilla in cN1 or pN2 disease or higher?
- Unclear whether patients with 3 or more positive sentinel lymph nodes may forego full ALND

Summary of Radiation Recommendations

Clinical Scenario	Radiation?
≥ 65 year-old with pT1N0, Gr 1 or 2, ER+,PR+,Her2- status post BCS and No Axillary Surgery (i.e., No SLN bx)	Option to Omit
< 65 year-old with invasive breast cancer of any subtype status post BCS with or without omission of SLNBx	Y – WBI or PBI (for select, favorable risk patients)
≥ pN1 status post BCS with ALND or SLNBx alone	Y – WBI +/- RNI
≥ pN1 status post mastectomy with SLNBx alone	Y – if 3 or more nodes, young/premenopausal, T3/T4 <u>or</u> TNBC <u>or</u> Her2+ dz, then PMRT + RNI
≥ T4 or pN2 or pN3 status post BCS or mastectomy	Y – WBI XRT/PMRT + RNI

De-Escalation of Axillary Surgery after Neoadjuvant Chemotherapy (NACT)

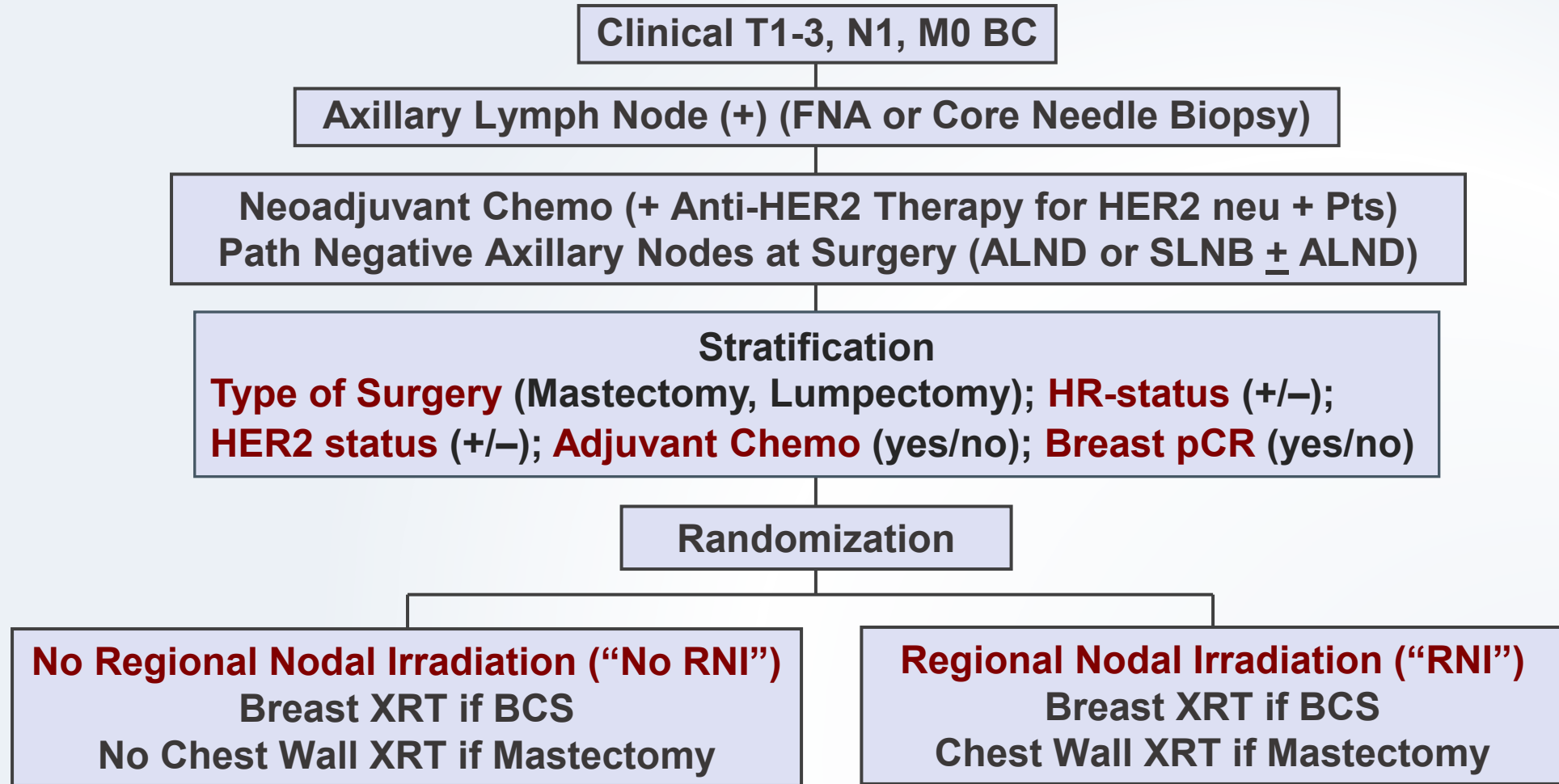
Is regional nodal radiation necessary when cN1 becomes ypN0 disease?

Loco-regional Irradiation in Patients with Biopsy-proven Axillary Node Involvement at Presentation Who Become Pathologically Node-negative After Neoadjuvant Chemotherapy: Primary Outcomes of NRG Oncology/NSABP B-51/RTOG 1304

Eleftherios P. Mamounas^{1*}, Hanna Bandos², Julia R. White^{3*}, Thomas B. Julian⁴, Atif J. Khan⁵, Simona F. Shaitelman⁶, Mylin A. Torres⁷, Frank A. Vicini⁸, Patricia A. Ganz⁹, Susan A. McCloskey¹⁰, Peter C. Lucas^{11,12}, Nilendu Gupta³, X. Allen Li¹³, Beryl McCormick⁵, Saumil Gandhi⁶, Rahul D. Tendulkar¹⁴, Vivek S. Kavadi¹⁵, Masahiko Okamoto¹⁶, Samantha Andrews Seaward¹⁷, William J. Irvin, Jr.¹⁸, Jolinta Lin⁷, Robert Mutter¹⁹, Thierry M. Muanza²⁰, Andrew A. Muskovitz²¹, Reshma Jagsi²², Anna C. Weiss^{23,24}, Walter J. Curran, Jr.⁷, and Norman Wolmark¹²

*These authors contributed equally.

Study Schema



FNA: Fine Needle Aspiration; ALND: Axillary Lymph Node Dissection; SLNB: Sentinel Lymph Node Biopsy; XRT: Radiation; BCS: Breast Conserving Surgery

Baseline Characteristics

Characteristic		No RNI (%) n=821	RNI (%) n=820
Age	Median	52 years	52 years
	≤ 49 yrs	40	41
	50-59 yrs	32	33
	≥ 60 yrs	28	26
Race	Asian	8	6
	Black/African American	17	18
	White	69	69
	Unknown/Other	6	6
Ethnicity	Hispanic or Latino	14	14
	Not Hispanic or Latino	83	82
	Unknown	3	3
Clinical Tumor Size	T1	21	21
	T2	59	61
	T3	20	18

<40 yrs 15%

Baseline Characteristics

Characteristic		No RNI (%) n=821	RNI (%) n=820
Tumor Subtype	Triple-negative	21	23
	ER+ and/or PR+/HER2-	22	20
	ER- and PR-/HER2+	25	24
	ER+ and/or PR+/HER2+	31	33
Breast Surgery	Lumpectomy	58	58
	→ Mastectomy	42	42
Axillary Surgery	→ SLNB	55	56
	ALND (+/-SLNB)	45	44
pCR in Breast	No	22	21
	Yes	78	79
Adjuvant Chemotherapy	No	100	99
	Yes	<1	1

56% Her2+
22% TNBC

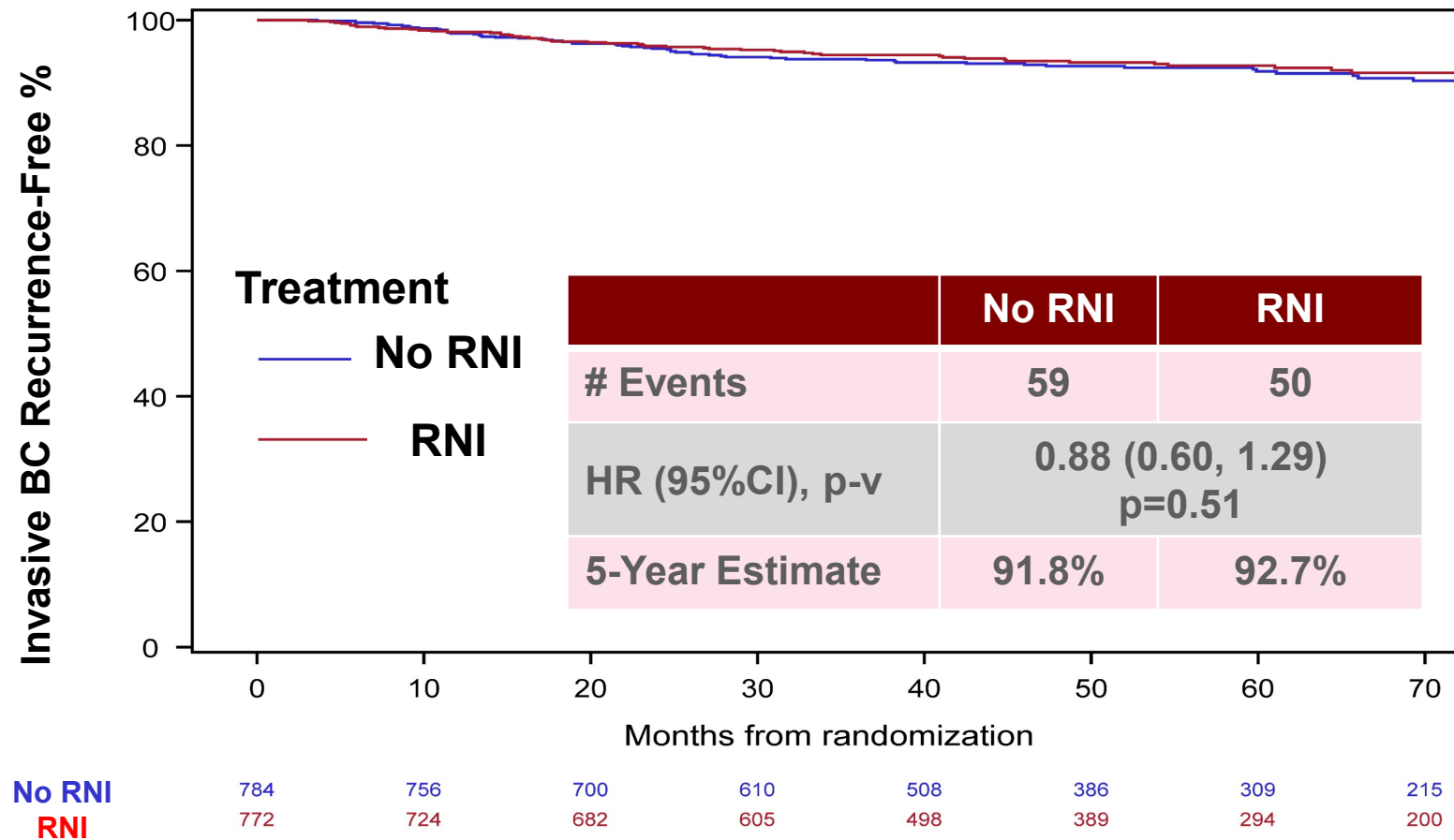
Baseline Characteristics

Characteristic		No RNI (%) n=821	RNI (%) n=820
Tumor Subtype	Triple-negative	21	23
	ER+ and/or PR+/HER2-	22	20
	ER- and PR-/HER2+	25	24
	ER+ and/or PR+/HER2+	31	33
Breast Surgery	Lumpectomy	58	58
	Mastectomy	42	42
Axillary Surgery	SLNB	55	56
	ALND (+/-SLNB)	45	44
pCR in Breast	No	22	21
	Yes	78	79
Adjuvant Chemotherapy	No	100	99
	Yes	<1	1

56% Her2+
22% TNBC

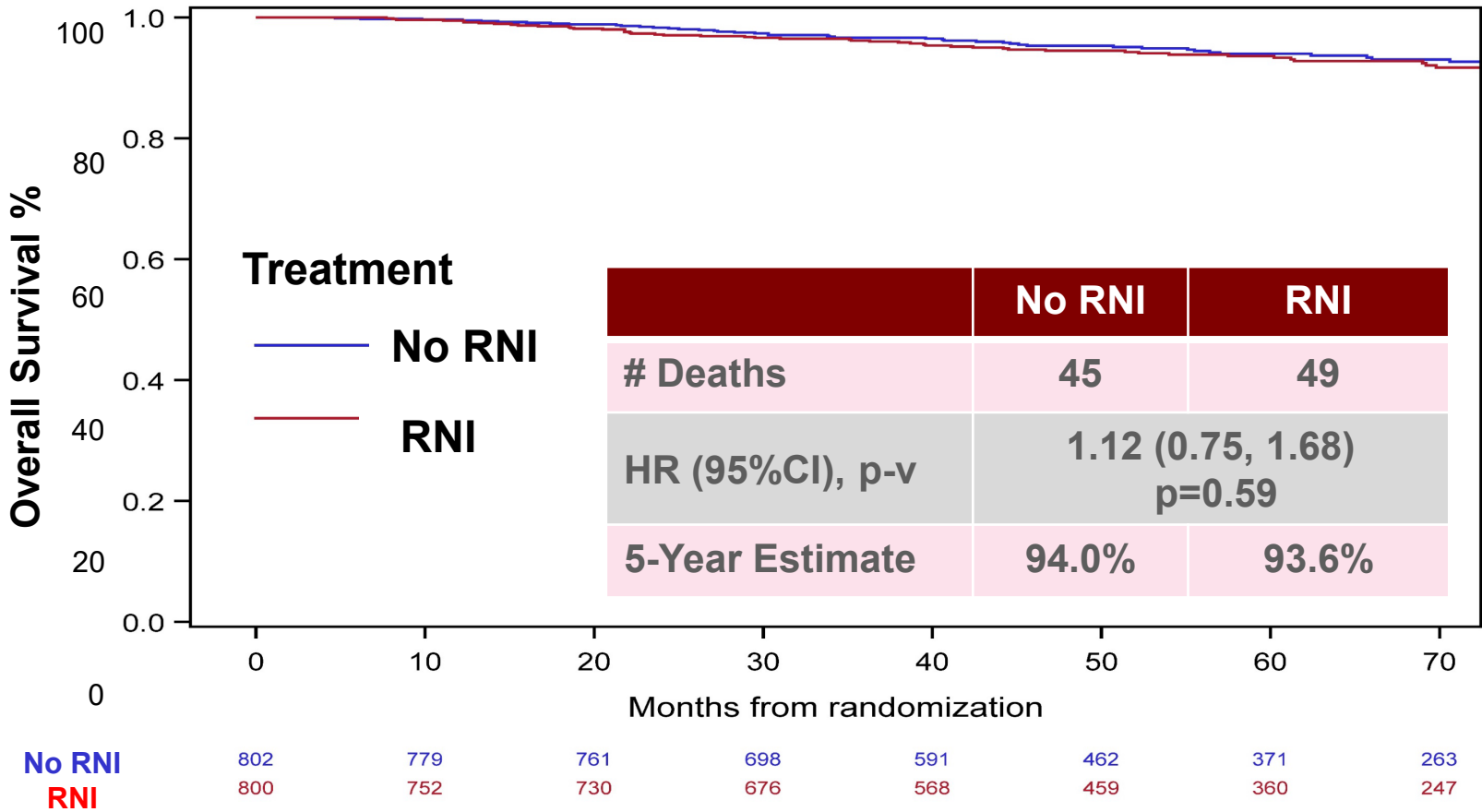
Primary Endpoint

Invasive Breast Cancer Recurrence-free Interval (IBCRFI)

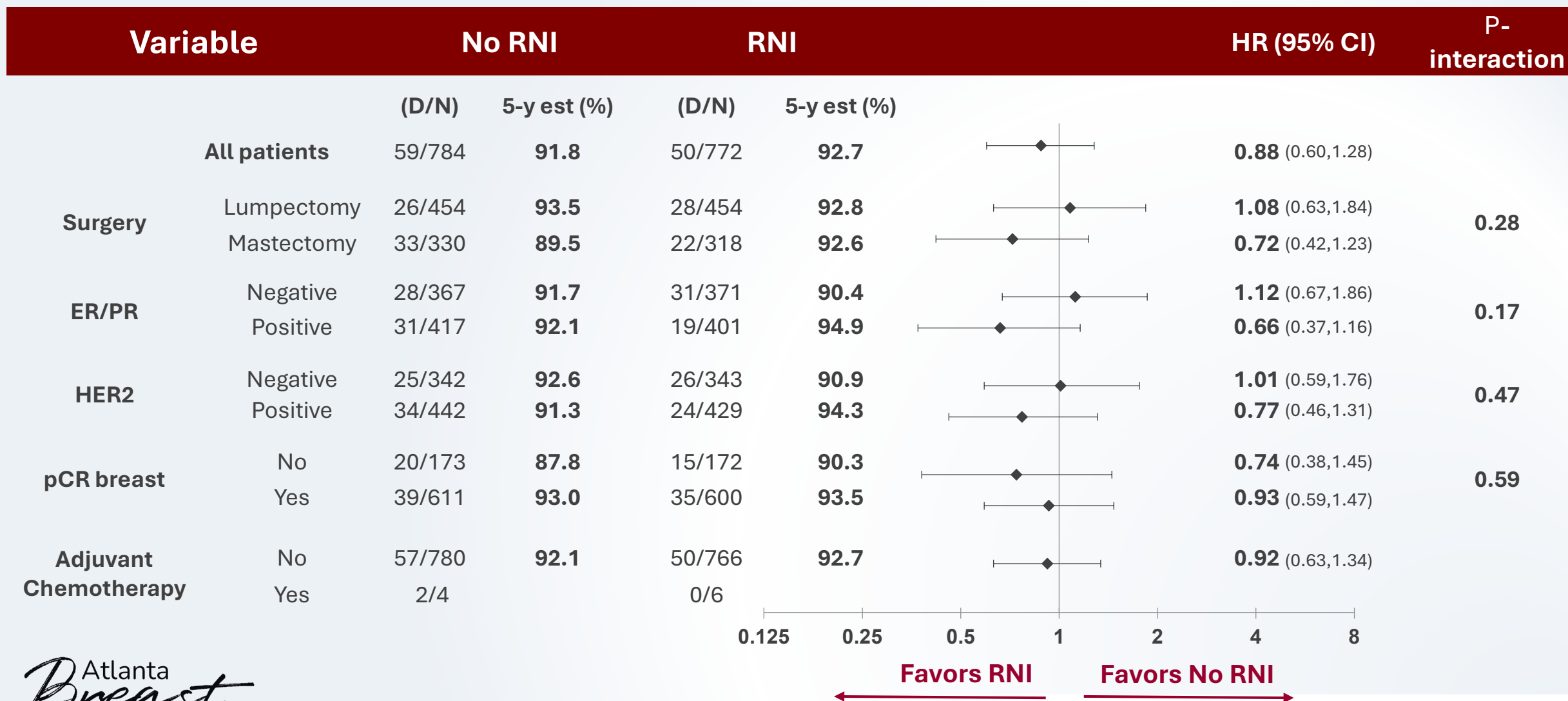


Secondary Endpoint

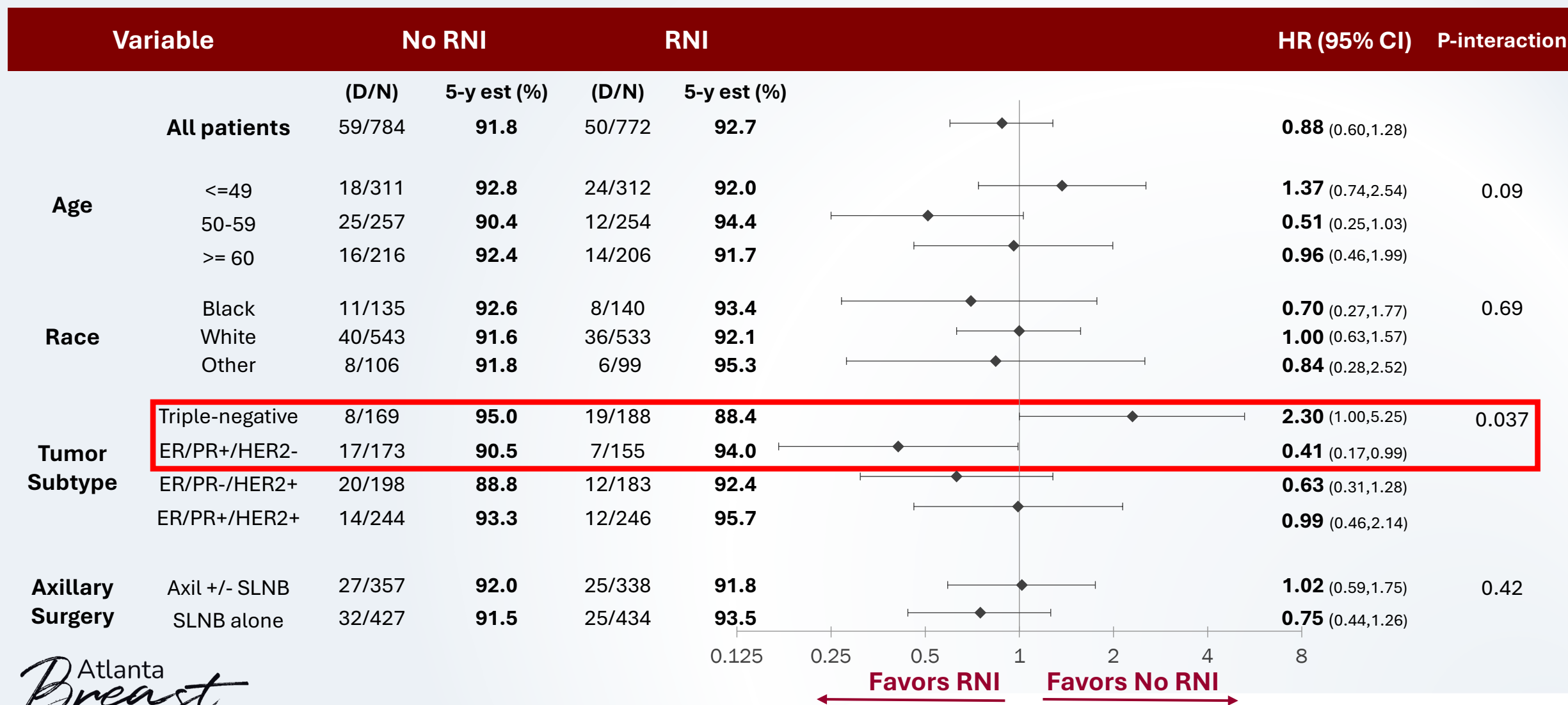
Overall Survival (OS)



IBCRFI – Subgroup Analysis by Stratification Factors



IBCRFI – Subgroup Analysis by Stratification Factors

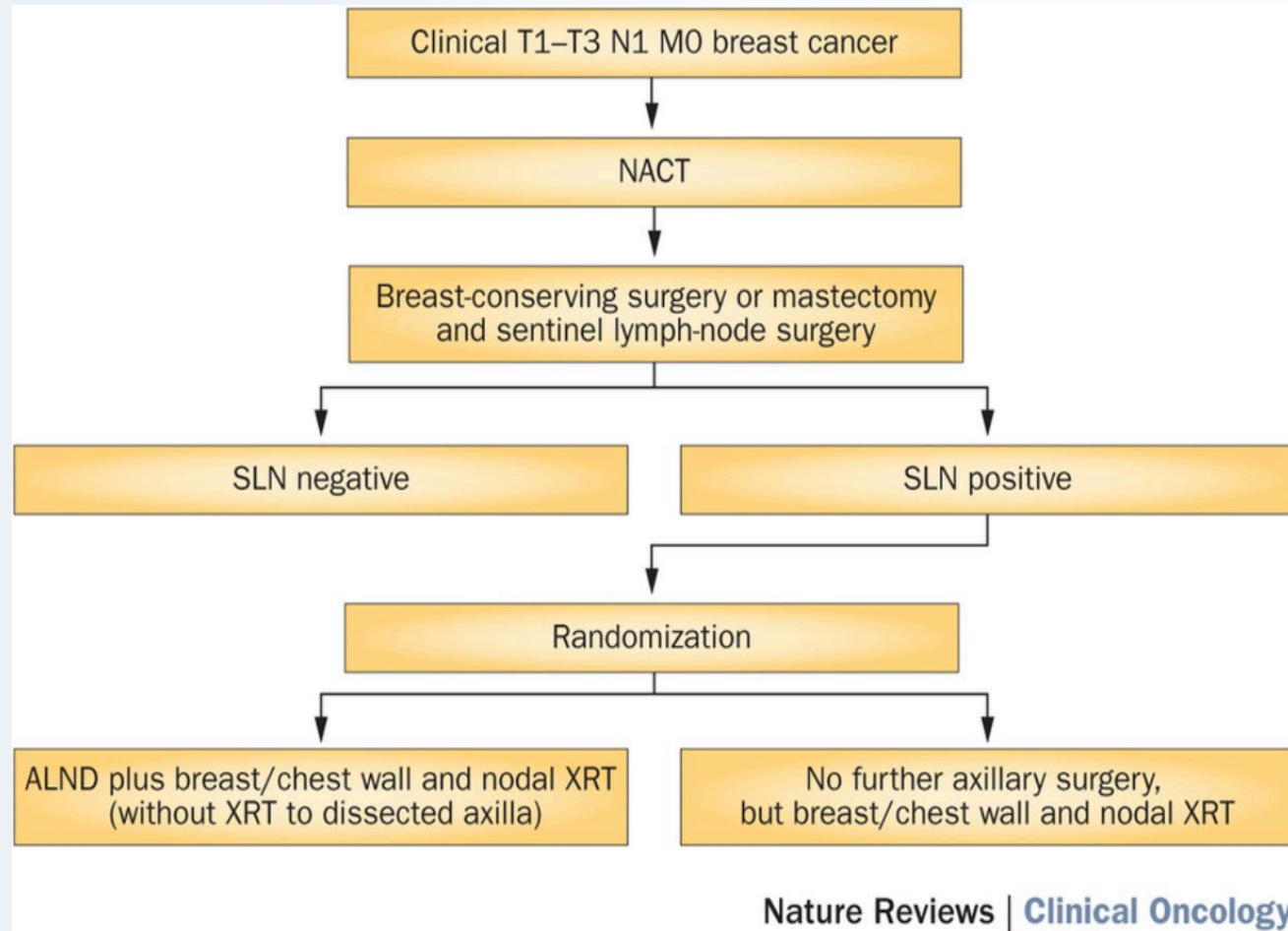


Conclusions

1. At a median follow-up of 5 years, regional nodal irradiation does not appear to benefit the following patients with ypN0 disease:
 - Her2+ &
 - Breast pCR &
 - Patients $\geq$ age 50
2. Consider regional nodal irradiation in other patients with ypN0 disease (e.g., premenopausal patients with TNBC)

Can radiation replace a full axillary lymph node dissection in patients with positive sentinel nodes after neoadjuvant chemotherapy?

ALLIANCE A11202



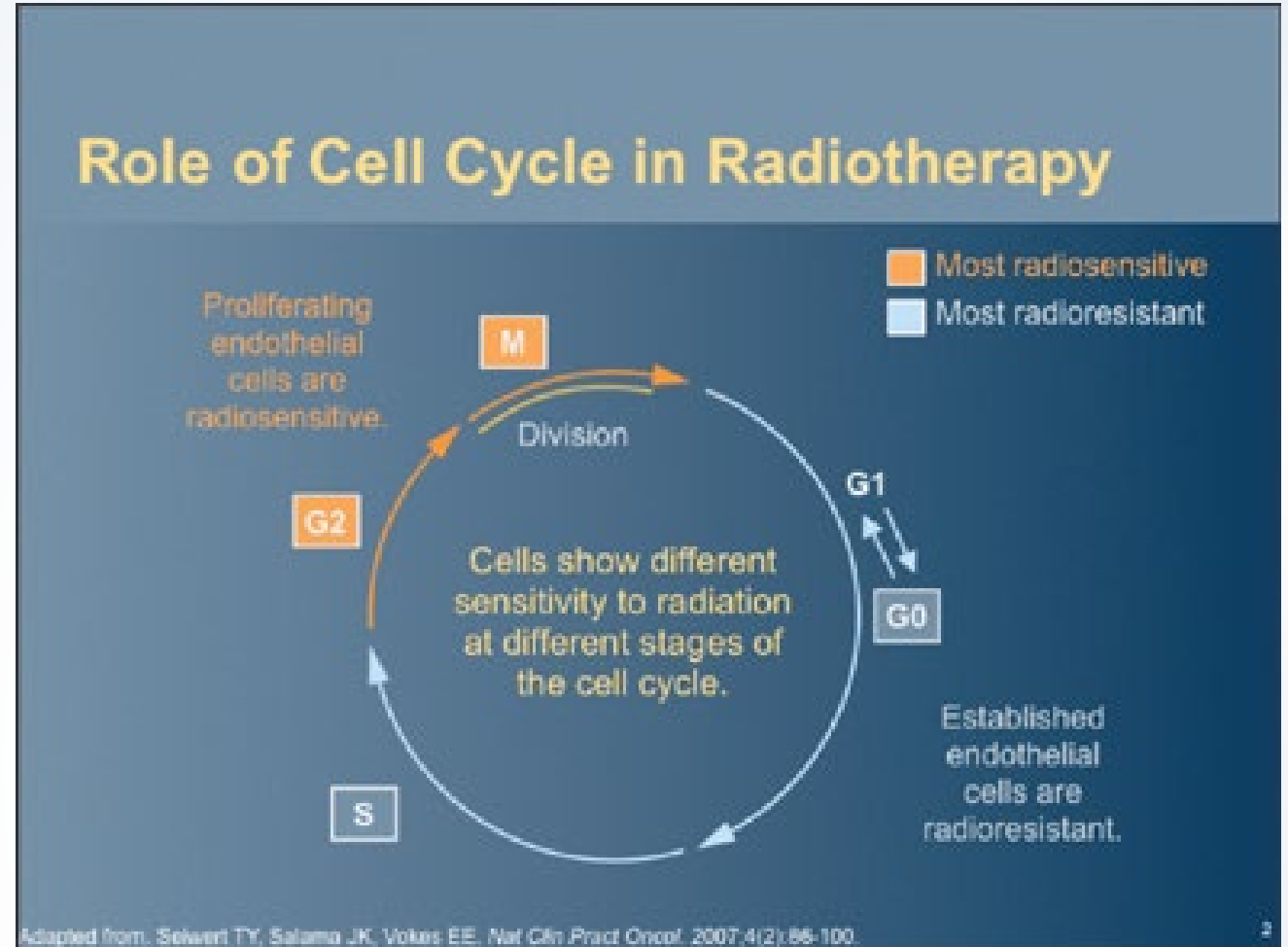
Summary of Radiation Recommendations in cN+ patients treated with NACT

Clinical Scenario	Radiation?
Postmenopausal, HER2+, with cN1 <u>and</u> pCR in breast and pCR in nodes following NACT	Omit
Pre- or postmenopausal, ER+, <u>or</u> TNBC with cN1 <u>or</u> no pCR in breast following NACT regardless of nodal response	Y – WBI or PMRT + RNI
≥ ypN1mi status post BCS or mastectomy with ALND or SLNBx alone	Y – WBI or PMRT + RNI
cT3/4 or cN2 or cN3 status post BCS or mastectomy following NACT regardless of response	Y – WBI or PMRT + RNI

Sequencing Radiation with New Systemic Agents

How does radiation work?

- High energy x-rays which cause DNA double strand breaks and cell death
- Preferentially kills rapidly proliferating cancer cells due to their poor repair mechanism
- Most radiosensitive phases of the cell cycle are G2/M
- Most radioresistant phases are G1, G0, and S



Concurrent versus sequential radiation and systemic therapy treatment

- Is concurrent treatment better than with either agent alone?
- Are recurrence rates higher when treatments are combined than when treatments are given sequentially?
- Are toxicities of one treatment exacerbated by the other if administered concurrently?
- What is more convenient and practical?

What is concurrent?

One widely adopted definition considers XRT concurrent when given within 5 drug half-lives of systemic therapy

Drug	Median Half-life	5 half-lives
Olaparib	15 hours	75 hours ($\approx$ 3 days)
Lapatinib	24 hours	120 hours ($\approx$ 5 days)
Abemaciclib	24.8 hours	124 hours ($\approx$ 5 days)
Palbociclib	28.8 hours	144 hours ($\approx$ 6 days)
Everolimus	30 hours	150 hours ($\approx$ 6 days)
Ribociclib	29.7 – 54.7 hours	148.5 – 273.5 hours ($\approx$ 6 - 11 days)
Talazoparib	90 hours	450 hours ($\approx$ 19 days)
Trastuzumab-emtansine	96 hours	480 hours ($\approx$ 20 days)
Trastuzumab-deruxtecan	168 hours	840 hours ($\approx$ 35 days)
Trastuzumab	456 hours	2280 hours ($\approx$ 95 days)
Bevacizumab	480 hours	2400 hours ($\approx$ 100 days)
Nivolumab	578 hours	2890 hours ($\approx$ 121 days)
Atezolizumab	648 hours	3240 hours ($\approx$ 135 days)

Most clinical trials leading to approval of systemic treatments do not collect comprehensive radiation details or information regarding radiation-related toxicities

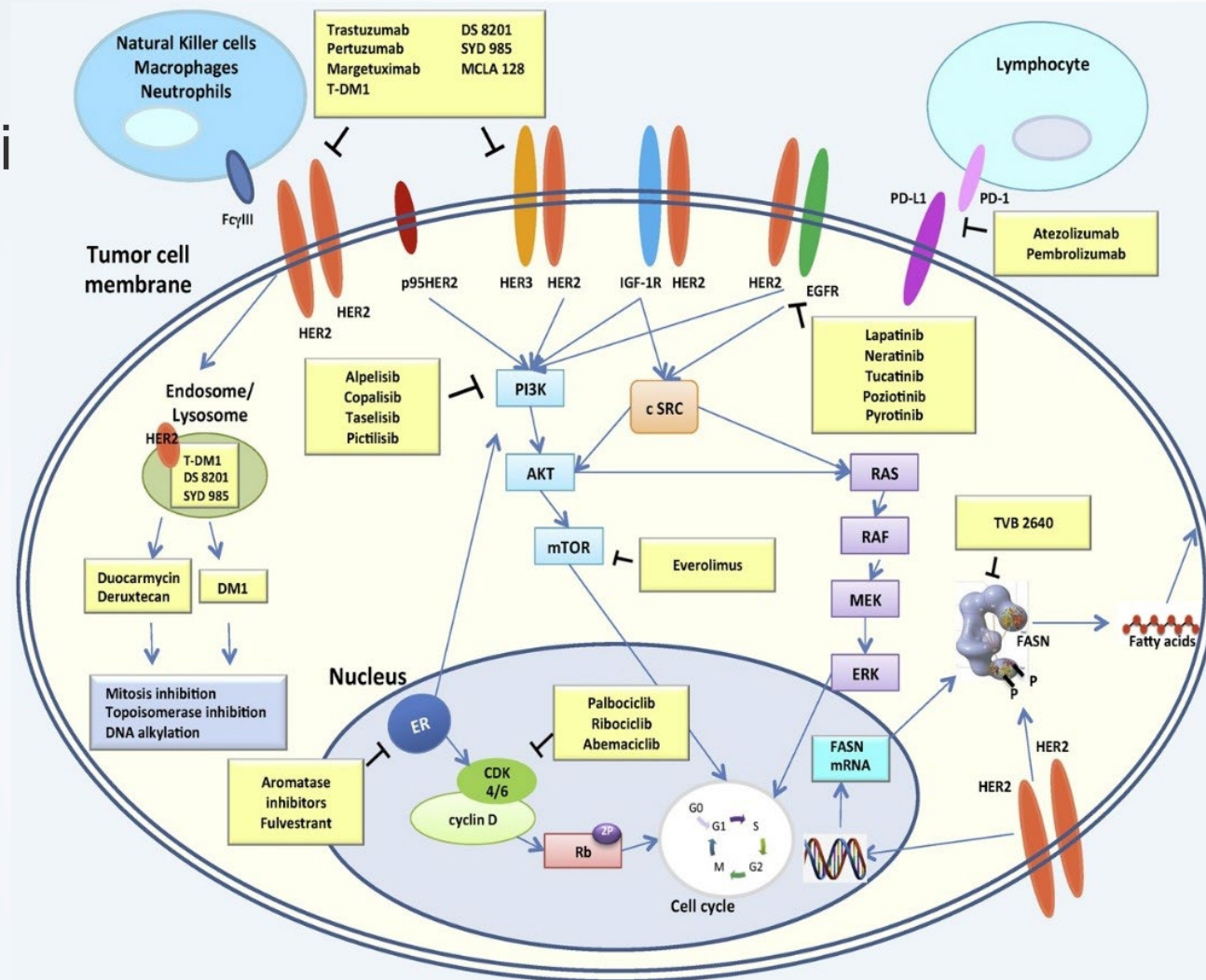
**How do we sequence radiation with
systemic treatments?
What are the appropriate radiation
dose and volumes?**

Systemic Treatments and Radiation Sequencing

Systemic Therapy	Concurrent or Sequential XRT?
Tamoxifen, AIs, Fulvestrant	Both
Trastuzumab, Pertuzumab	Both
Bisphosphonates, RANK Ligand Inhibitors	Both

New Systemic Agents in Breast Cancer in Routine Practice

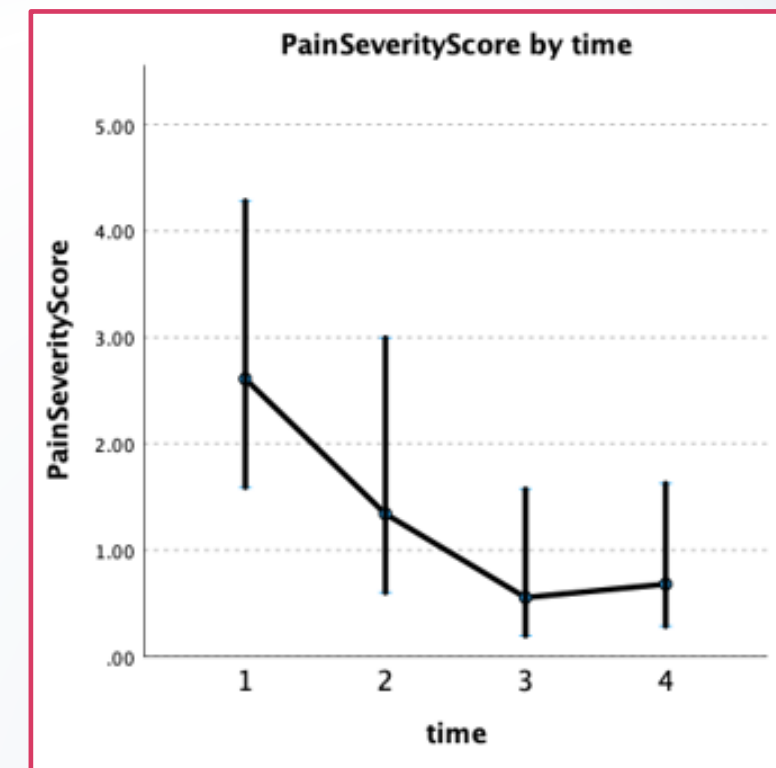
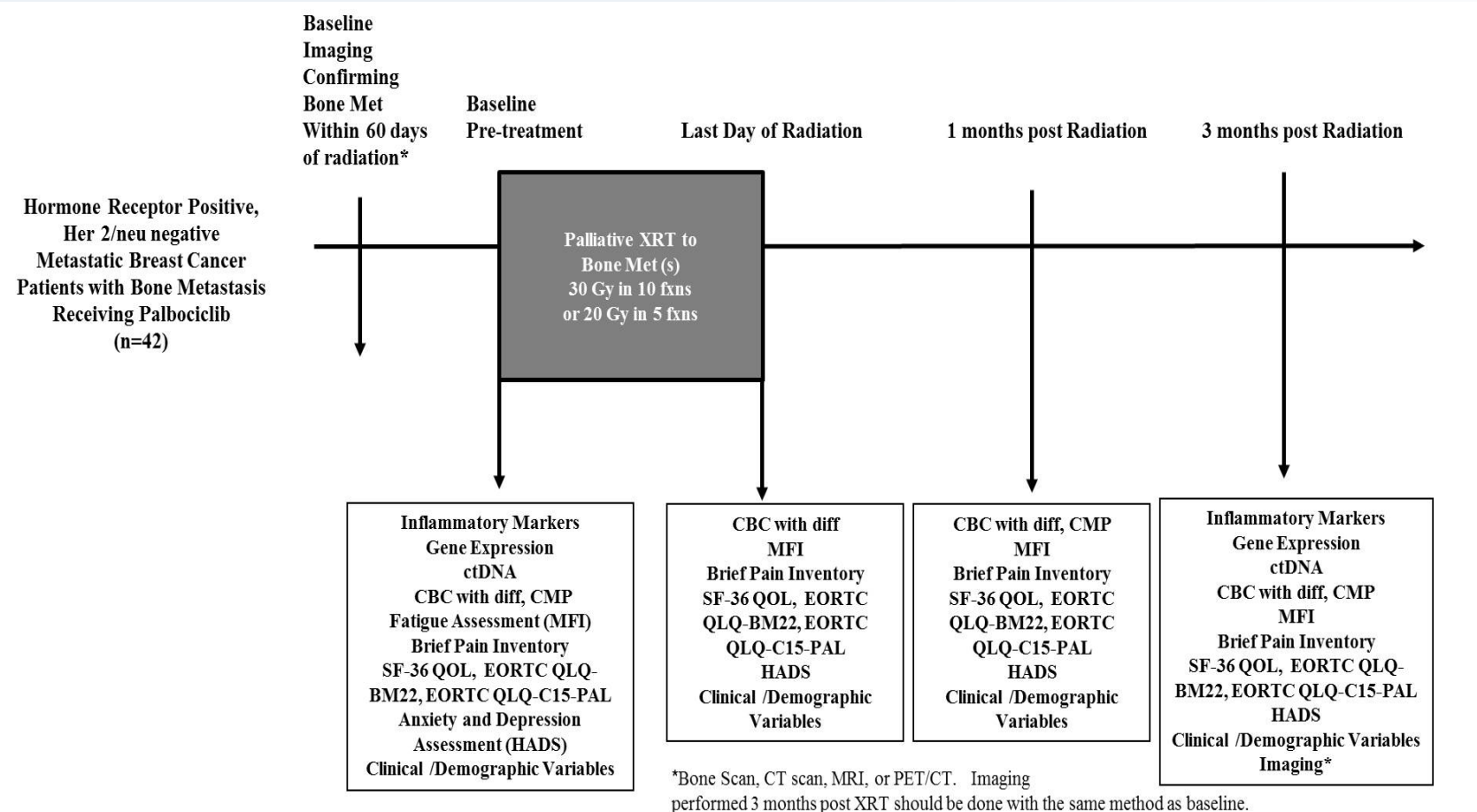
ADCs: T-DM1, TDXD, Saci
Capecitabine
CDK4/6 inhibitors
Pembrolizumab
PARP inhibitors



Systemic Treatments and Radiation Sequencing

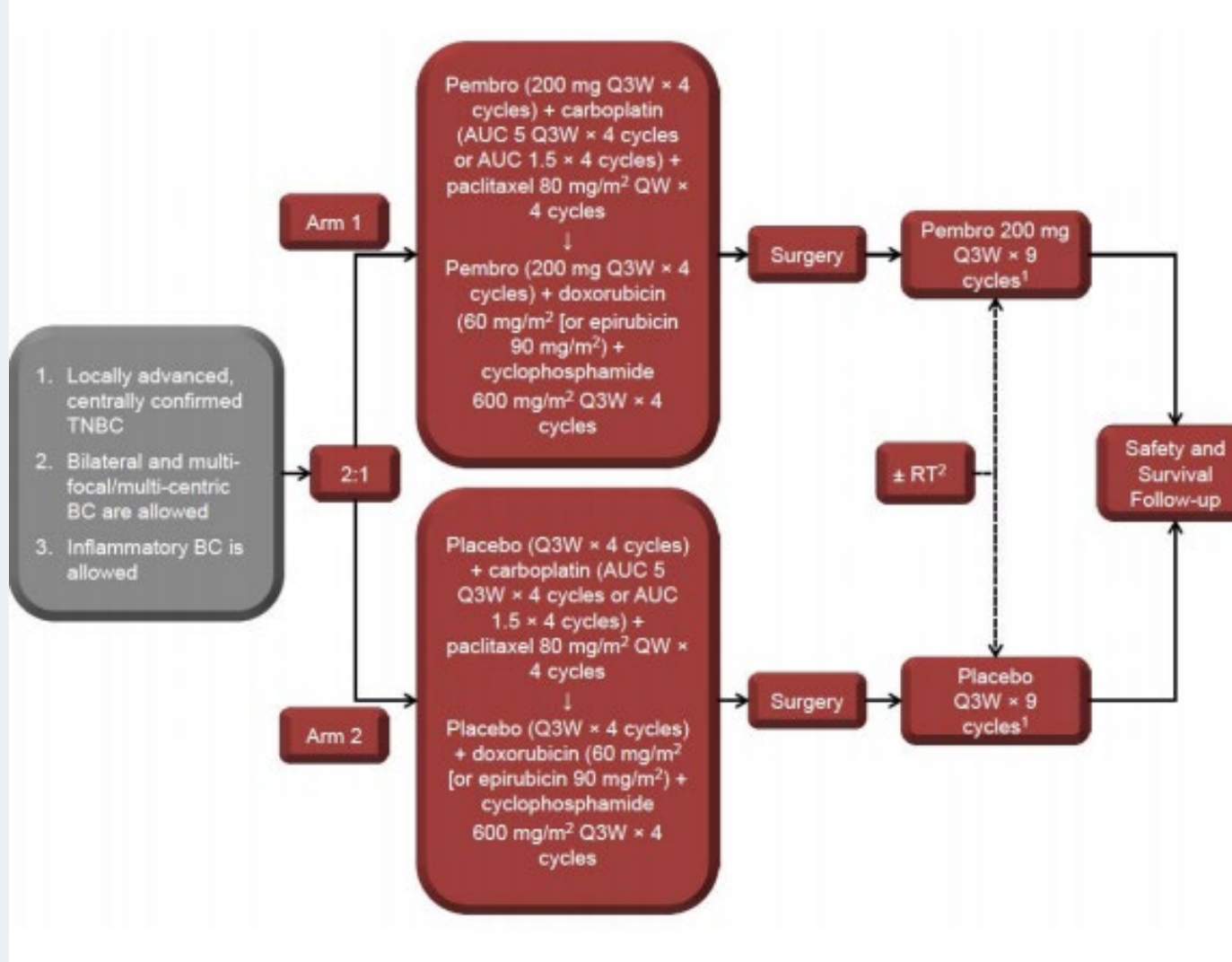
Systemic Therapy	Concurrent or Sequential XRT?
Abemaciclib, ribociclib	Sequential, XRT first in Stage I-III ? Concurrent in Stage IV
Capecitabine	Sequential, XRT first in Stage I-III ? Concurrent in Stage IV
Pembrolizumab	Both in Stage I-IV; if sequential, typically Pembro first
Olaparib	Sequential, XRT first in Stage I-III ? Concurrent in Stage IV
ADCs (T-DM1, TDXD, Saci)	Concurrent if breast only XRT ? Sequential with RNI first ? Sequential with CNS XRT

Emory Phase II ASPIRE Trial Concurrent Palbociclib and XRT for Bone Mets



No Grade 4 or higher neutropenia
Acceptable rates of toxicity

KEYNOTE-522



- Original Protocol - pembrolizumab restarted at least 2 weeks post-XRT and not concurrently
- Protocol amended to allow concurrent administration as evidence indicates both can have synergistic effects without increased toxicity

Post-Hoc Analysis of KEYNOTE-522 (N=1174 total, 715 treated with XRT)

Chemo +	Concurrent Radiation	Sequential Radiation	No Radiation
Pembrolizumab	Gr 3-5 AEs 4.9%	Gr 3-5 AEs 6.8%	Gr 3-5 AEs 7.5%
	Immune AEs 9.7%	Immune AEs 11.8%	Immune AEs 9.0%
Placebo	Gr 3-5 AEs 2.2%	Gr 3-5 AEs 3.1%	Gr 3-5 AEs 2.9%
	Immune AEs 4.4%	Immune AEs 5.7%	Immune AEs 10.0%

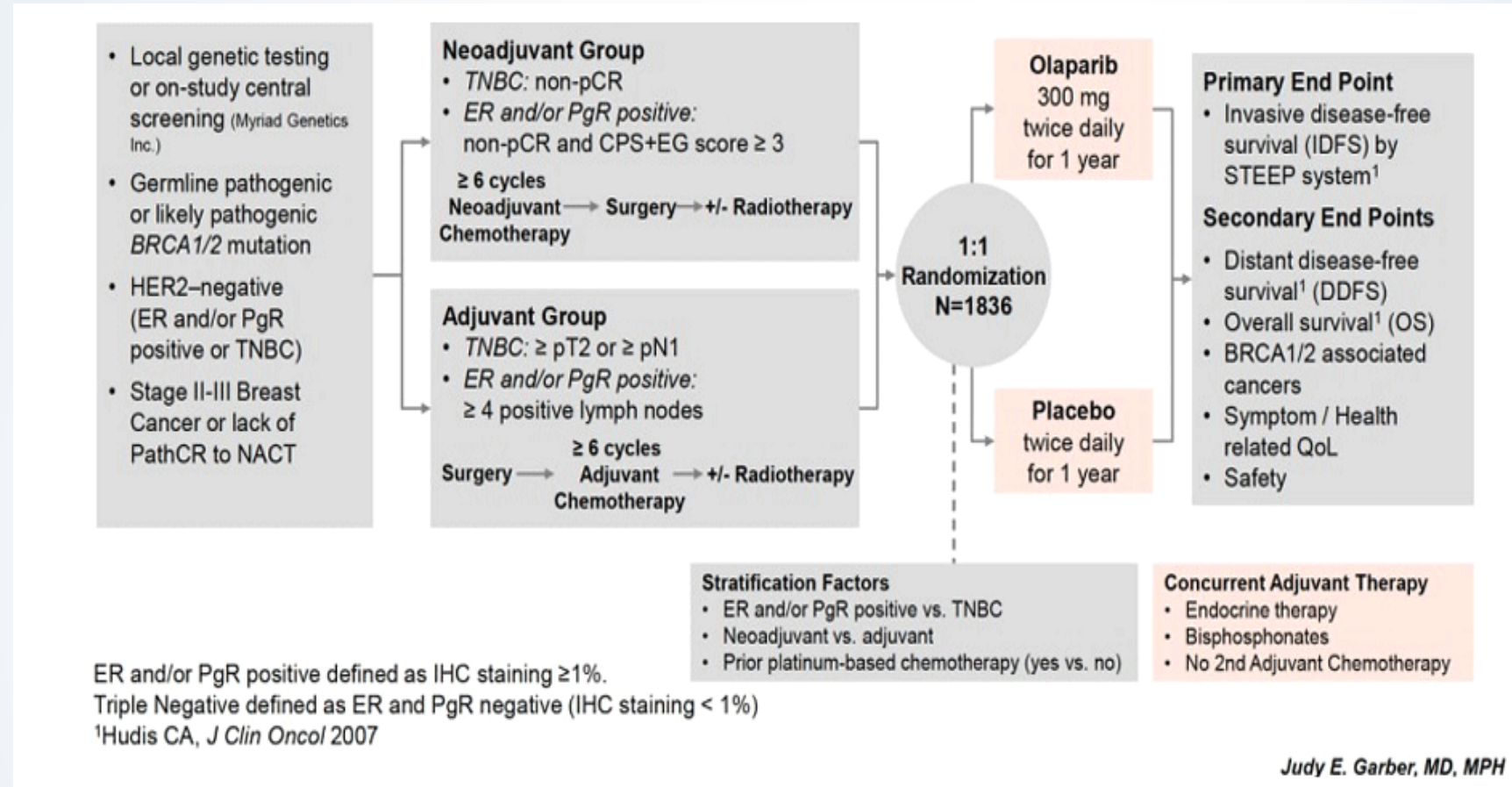
*2 (0.4%) treatment related AE deaths, both in patients who received pembro and XRT

Immunotherapy and XRT in Metastatic Breast Cancer

Study first author	Design	Tumor phenotype (n)	Brain mets	Timing of RT (first fraction) and ICI	N	Primary endpoint	Efficacy	TRAEs
Ahmed ²⁵	Phase 1b nonrandomized single arm	HR+/HER2- (4) HR-/HER2+ (2) TN (6)	≤10 brain mets	ICI 7 d before RT	12	Safety, DLTs	Median ICC - 6.2 mo (95% CI, 3-14); 6- and 12-mo control rates - 55% and 22%. Median TTSP - NR; 6- and 12-mo rates - 63% and 51%.	No DLTs noted. No grade 3 or 4 nonneurologic side effects.
Page ²⁶	Phase 2 nonrandomized	Cohort A - HER2- (20) Cohort B - HER2+ (6)	Brain mets indicated for RT	ICI within 5 d before or 3 d after RT	26	12-wk non-CNS DCR	12-week non-CNS DCR Cohort A - 10% Cohort B - 33%	Any grade - fatigue (46%), nausea (46%), diarrhea (24%), and colitis (24%) Grade 3 - colitis (12%) and diarrhea (8%)
Barroso-Sousa ²⁷	Phase 2 Nonrandomized single arm	HR+ HER2-	Treated brain mets	ICI 2-7 d before RT	8	ORR	ORR- 0% Median PFS - 1.4 mo (95% CI, 0.4-2.1) Median OS - 2.9 mo (95% CI, 0.9-3.6)	Fatigue (50%), increased aspartate aminotransferase (50%), anemia (25%), arthralgia (25%), dyspnea (25%), and nausea (25%). Only 1 grade 3 AE.
Ho ²⁸	Phase 2 Nonrandomized single arm	TNBC	Treated brain mets	ICI 1-3 d before RT	17	ORR at 13 wk	ORR - 17.6% (3 CRs, 1 SD)	Radiation dermatitis (29%), fatigue (18%), skin changes (12%), and nausea (12%)
Voorwerk ²⁹	Phase 2 randomized 5 arm adaptive study	TNBC	Treated brain mets	Not available	12	PFS	ORR - 8.33% (n = 1) No CR 6-month PFS rate - 17%	Not available
Takada ³⁰	Phase 1/2 nonrandomized	Cohort A - luminal-like disease (18), cohort B - luminal-like disease and TNBC (10)	Without brain mets	ICI 24 h after RT	28	ORR of unirradiated lesions	ORR: Cohort A - 11%, cohort B - 0%; DCR: Cohort A - 39%, cohort B - 0%; median PFS (mo): Cohort A - 4.1 (95% CI, 2.1-6.1), cohort B - 2.0 (95% CI, 1.2-3.7)	Cohort A - 56% Cohort B - 36% 1 grade 3 TRAE
Sun ³¹	Phase 2 nonrandomized single arm	TNBC	Treated brain mets	SBRT followed by ICI (exact timing unclear)	28	CBR	CBR - 21.4%, 2 CR, 1 PR, and 3 SD Median OS - 6.6 mo	TRAEs - 78.6%, irAEs - 46.4%, hypothyroidism (21.4%), hyperthyroidism (10.7%); 1 pneumonitis
David ³²	Phase 3 randomized, open label	TNBC	N/A	ICI within 5 d of RT	50	PFS	Median PFS - 3.1 mo ORR - 10%	Not available
Schmid ³³	Phase 3 randomized	TNBC	Treated brain mets	Not available	Pts who received palliative RT: Experimental arm - 32, control arm - 24	PFS OS	Outcomes not available for patients receiving palliative RT	AEs not available for patients receiving palliative RT

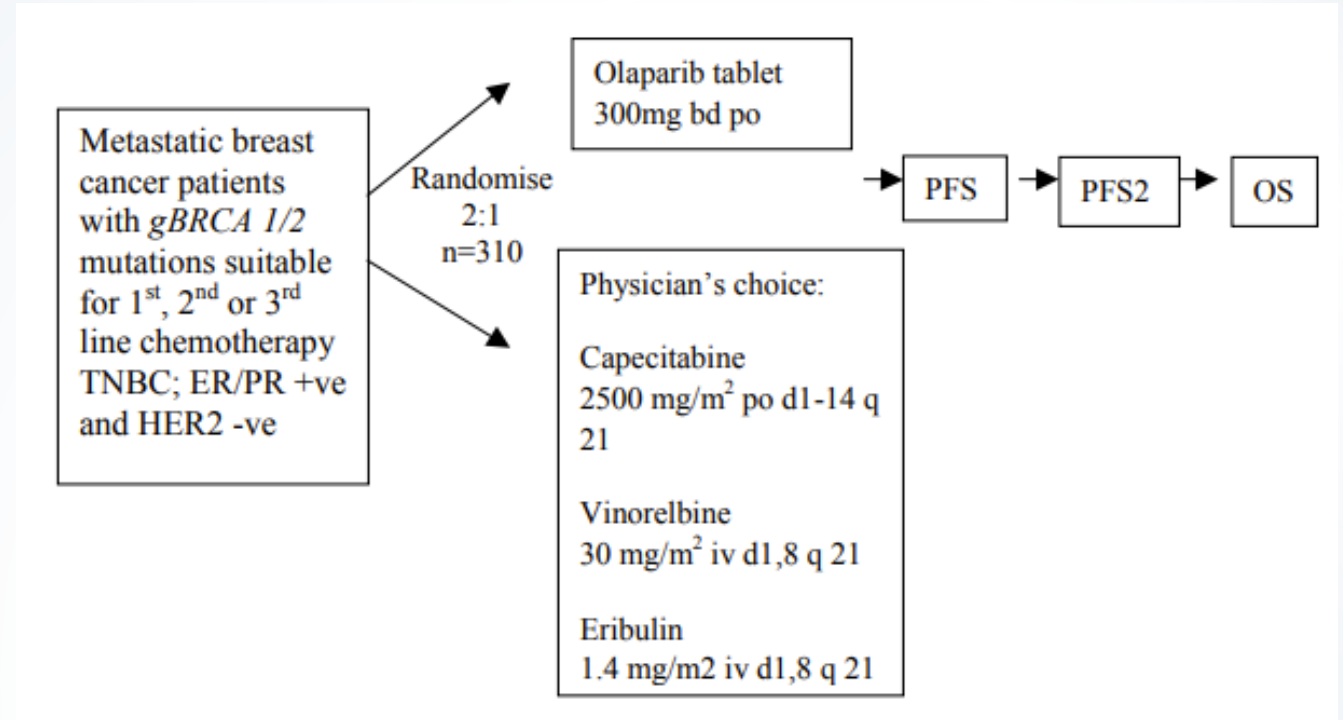
OlympiA: Sequential Olaparib in gBRCA carriers with early-stage breast cancer after XRT completion

- 1836 patients, 70% received XRT
- XRT had to be completed at least 2 but not >12 weeks prior to study entry
- Olaparib group: 7 patients had pneumonitis and 2 had radiation pneumonitis
- Placebo group: 8 patients had pneumonitis and 4 had radiation pneumonitis



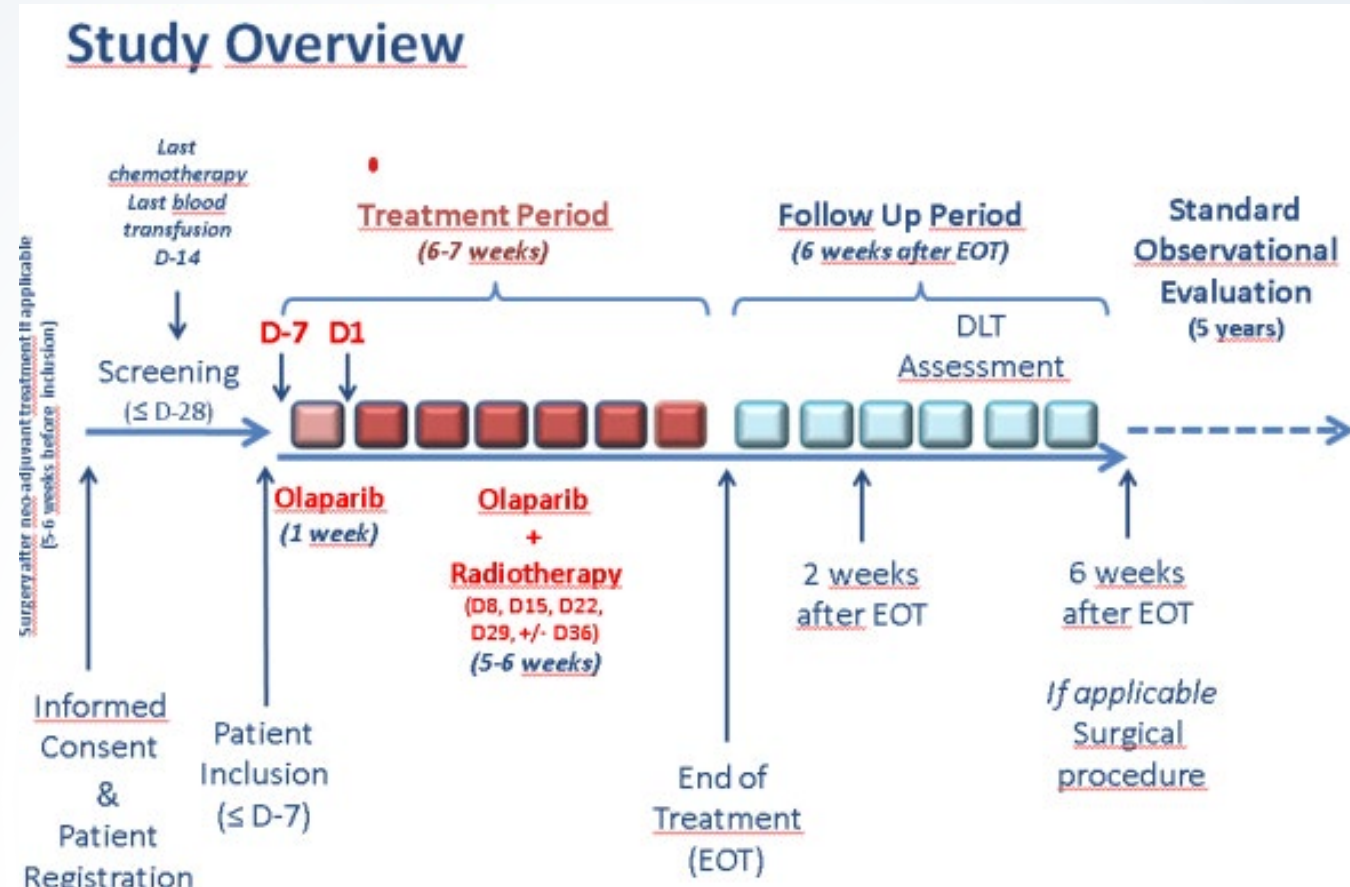
OlympiAD: Sequential XRT in gBRCA Carriers with Metastatic Breast Cancer Treated with Olaparib

- 302 patients
- Olaparib stopped 3 days prior to XRT
- No XRT details
- One patients discontinued standard treatment (not Olaparib) due to XRT skin injury
- No XRT AEs leading to discontinuation in Olaparib arm



RadioPARP: Phase I of Olaparib and XRT

- 24 patients with incomplete path response after NACT or unresectable TNBC despite NACT (including metastatic and inflammatory breast cancer)
- No DLTS with Olaparib dose up to 200mg BID and concurrent breast/chestwall/RNI XRT of 50 Gy at 2 Gy per fxn
- No late Grade 3 AEs at 5 years of follow up
- Among patients with HRD, 5-yr 100% Local regional control
- Among patients without HRD, 5-yr 60% locoregional recurrence-free survival
- Metastasis-free and Overall Survival not impacted by HRD status



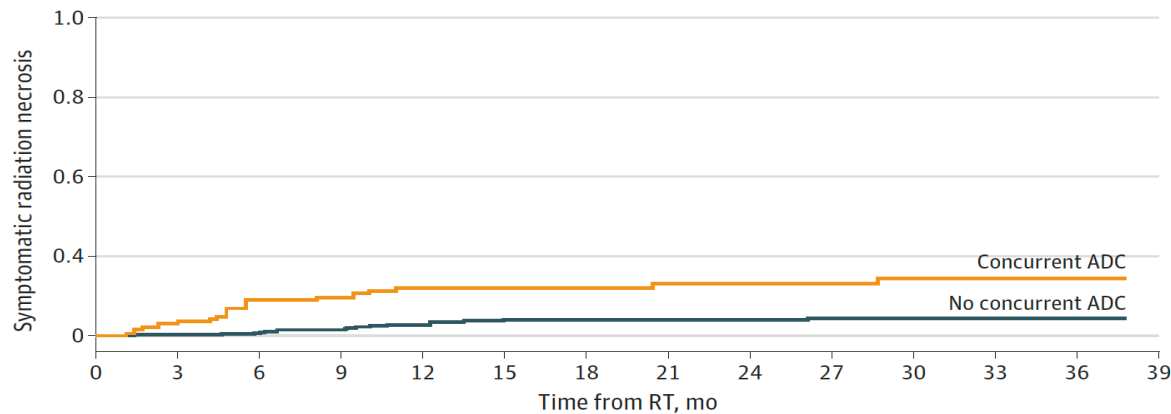
MSKCC Retrospective Study of Concurrent SRS and ADCs

Characteristic	Patient group ^a		All (N = 98)
	Concurrent ADC	No concurrent ADC	
Patients			
Age, median (range), y ^b	54 (27-77)	55 (34-77)	55 (27-77)
Sex			
Women	33/42 (78.6)	66/74 (89.2)	82/98 (83.7)
Men	9/42 (21.4)	8/74 (10.8)	16/98 (16.3)
Primary cancer diagnosis			
Breast	30/42 (71.4)	55/74 (74.3)	71/98 (72.4)
Non-small cell lung cancer, <i>ERBB2</i> variant	4/42 (9.5)	11/74 (14.9)	13/98 (13.3)
Esophageal and/or gastric cancer, <i>ERBB2</i> amplified	2/42 (4.8)	4/74 (5.4)	6/98 (6.1)
Salivary, <i>ERBB2</i> amplified	3/42 (7.1)	2/74 (2.7)	4/98 (4.1)
Other ^c	3/42 (7.1)	2/74 (2.7)	4/98 (4.1)
ADC received ^d			
Trastuzumab emtansine	21/42 (50.0)	43/74 (58.1)	52/98 (53.1)
Trastuzumab deruxtecan	14/42 (33.3)	42/74 (56.8)	50/98 (51.0)
Sacituzumab govitecan	7/42 (16.7)	23/74 (31.1)	26/98 (26.5)

SRS was 7 days before or up to 21 days after ADC

MSKCC: Symptomatic Radiation Necrosis with SRS and ADCs

A Cumulative incidence of SRN

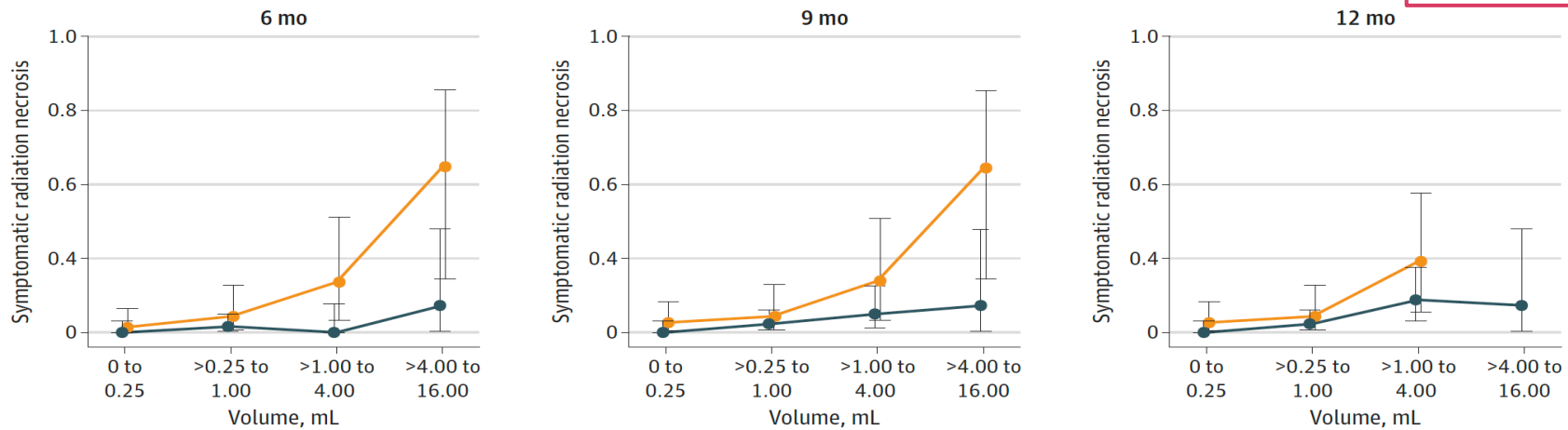


No. at risk													
No concurrent ADC	408	352	301	251	205	172	138	100	75	60	54	48	43
Concurrent ADC	156	136	92	85	53	36	34	32	31	27	25	21	18

SRN rates significantly higher with concurrent ADC irrespective of ADC type

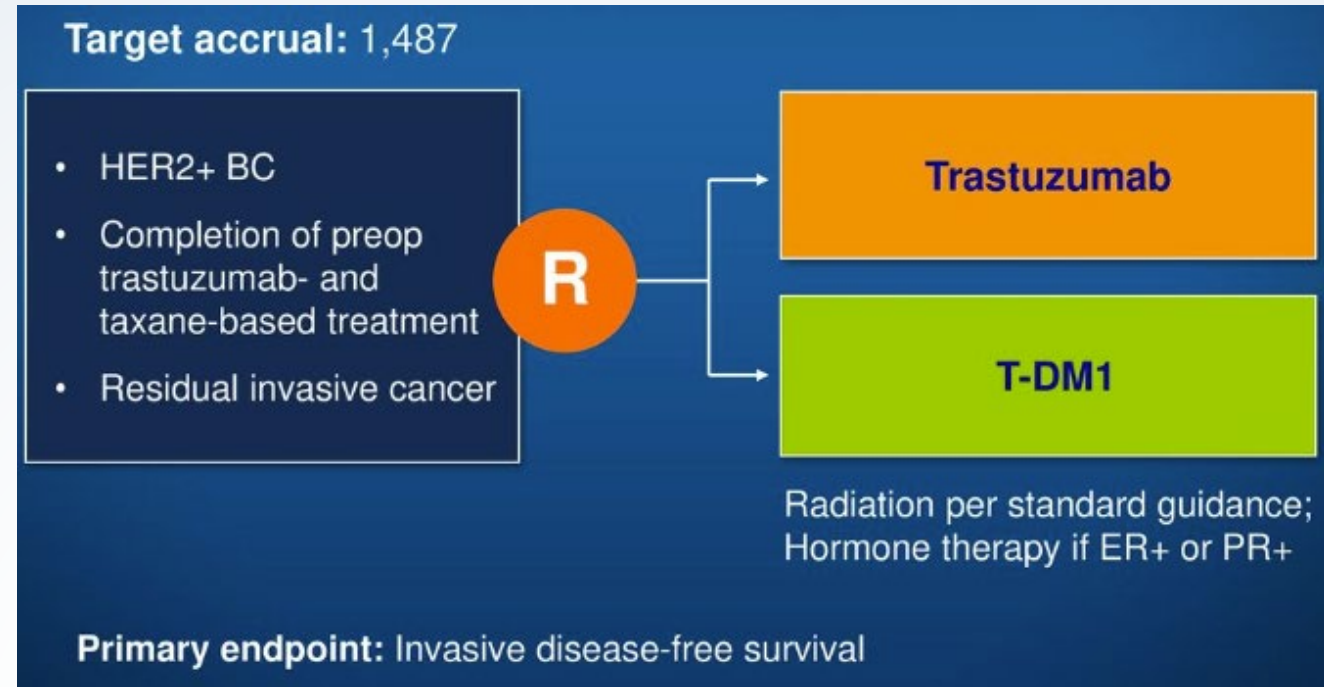
For previously irradiated lesions, 24 mos rate of SRN: 42% with vs. 9.4% without concurrent ADCs

B Point estimates of cumulative incidence of SRN

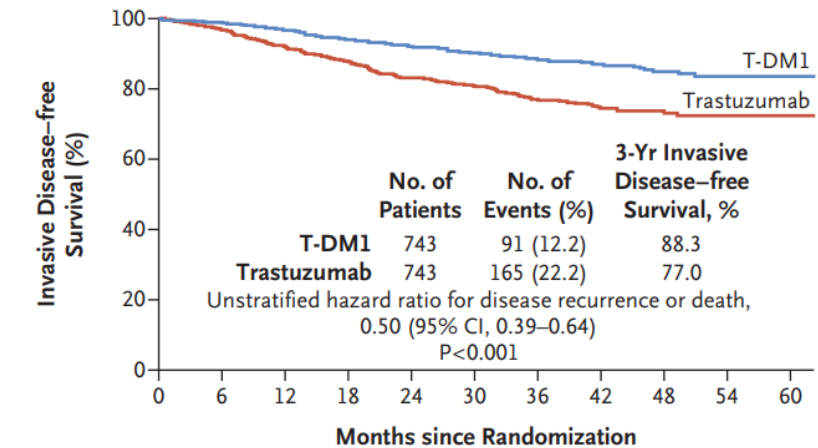


KATHERINE Trial

- Recommended radiation start within 60 days of surgery and given concurrently with trastuzumab or T-DM1
- XRT pneumonitis in 1.5% T-DM1 vs 0.7% trastuzumab pts



Adverse Event	Trastuzumab (n=720)				T-DM1 (n=740)			
	no. of patients (%)							
	Any Grade	Grade 1	Grade 2	Grade 3†	Any Grade	Grade 1	Grade 2	Grade 3†
Fatigue	243 (33.8)	189 (26.3)	53 (7.4)	1 (0.1)	366 (49.5)	247 (33.4)	111 (15.0)	8 (1.1)
Radiation skin injury	199 (27.6)	121 (16.8)	71 (9.9)	7 (1.0)	188 (25.4)	98 (13.2)	80 (10.8)	10 (1.4)

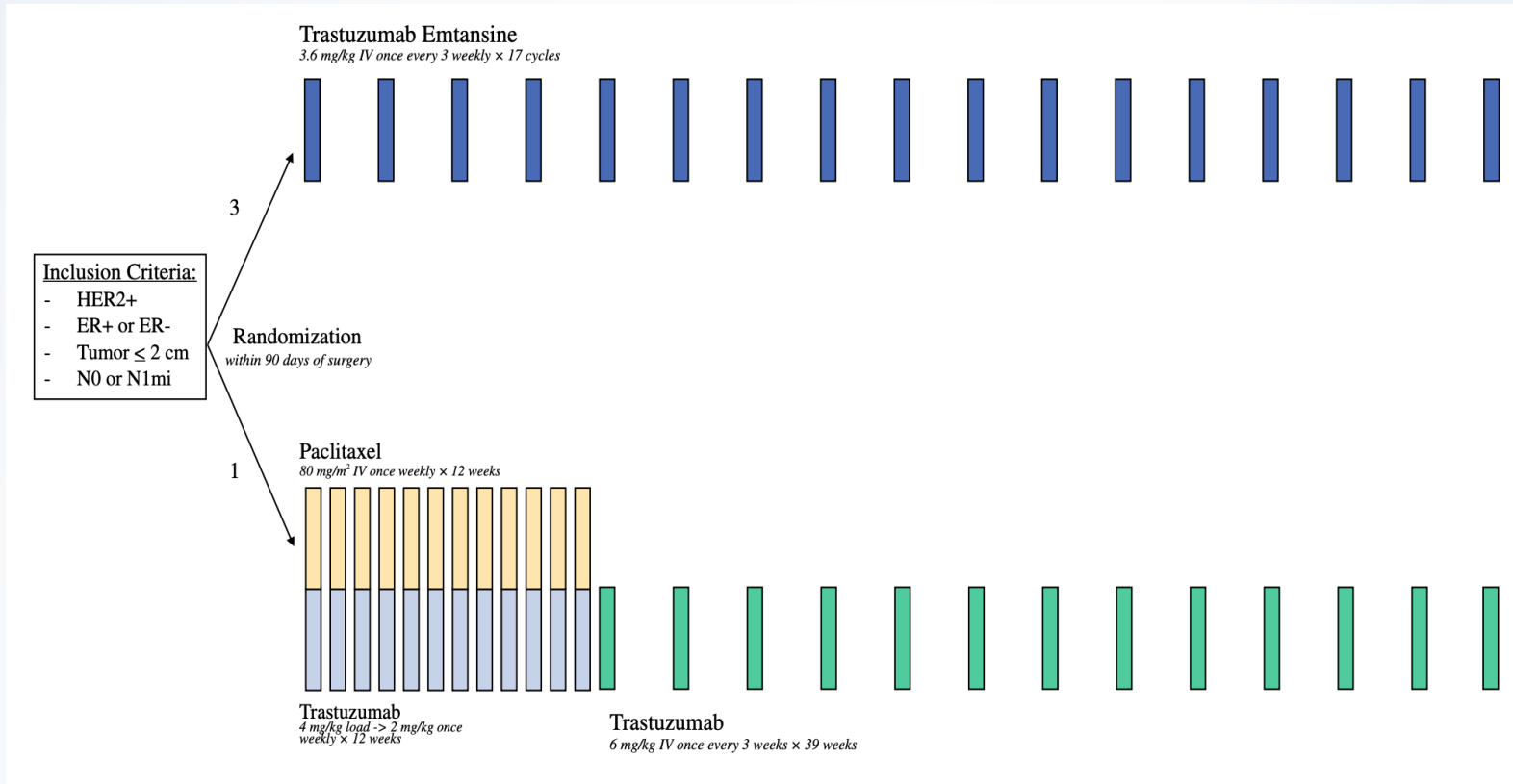


No. at Risk

T-DM1	743	707	681	658	633	561	409	255	142	44	4
Trastuzumab	743	676	635	594	555	501	342	220	119	38	4

ATEMPT Trial (TBCRC 033): Phase II

- 497 patients with Stage I Her2+ breast cancer, concurrent XRT with T-DM1 vs. TH
- <4% received regional nodal XRT
- Skin toxicity (grade ≥ 2) in 33.9% in T-DM1 arm vs. 23.2% in the TH arm ($P = .11$)
- In TD-M1 cohort, Grade ≥ 2 skin toxicity in 49.2% conventionally fractionated vs. 18.9% hypofractionation ($P < .001$)
- Five patients experienced pneumonitis after RT (T-DM1: $n = 4$, 1.0%; TH: $n = 1$, 0.9%)



Knowledge Gaps, Controversial Issues, and Questions

- Lack of Phase III data of concurrent XRT in patients treated with novel agents:
 - ADCs
 - CDK4/6i
 - Immunotherapy
 - PARPi
- Should treatments be sequenced differently for non-metastatic versus metastatic breast cancer?
- What is the best timing for sequential systemic and XRT treatments (days, weeks, months)?
- How does radiation volume (RNI, whole breast vs. APBI, whole brain vs. SRS) and dose contribute to outcomes in the context of systemic therapy?

Questions?