SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Modena
Policlinico

VII SESSIONE

Controversie cliniche

Radioterapia dopo terapia neoadiuvante

Bruno Meduri

Azienda Ospedaliero-Universitaria di Modena (IT)

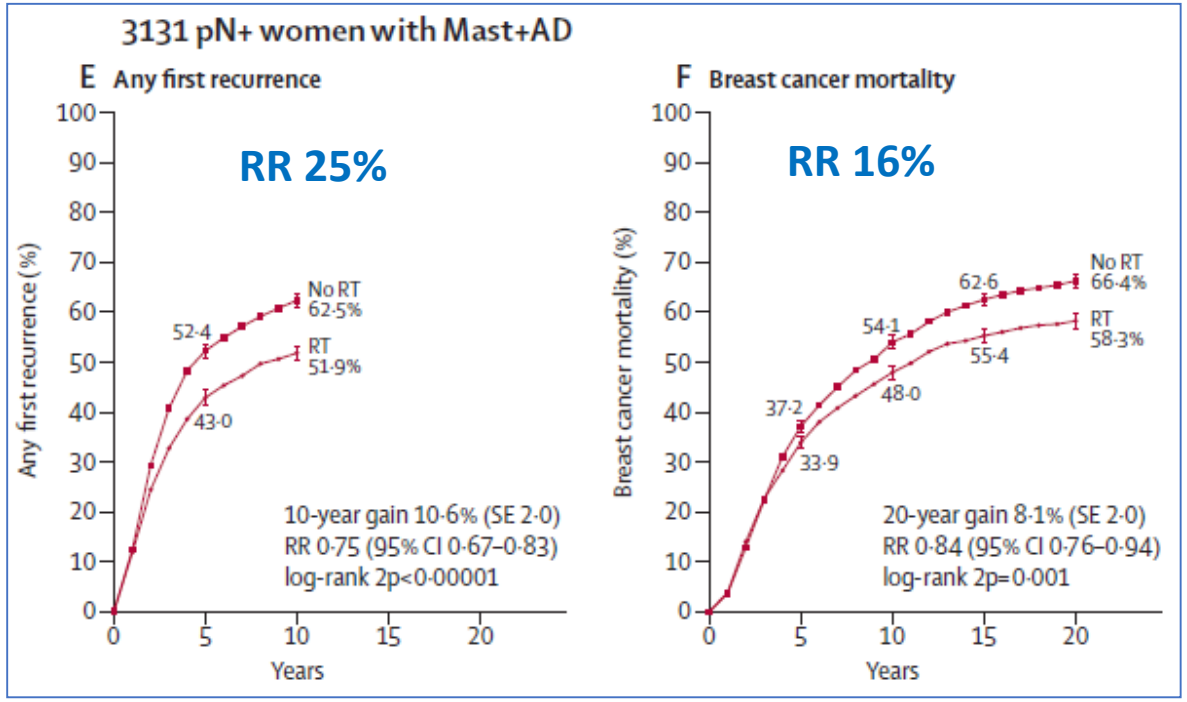
@brunomeduri

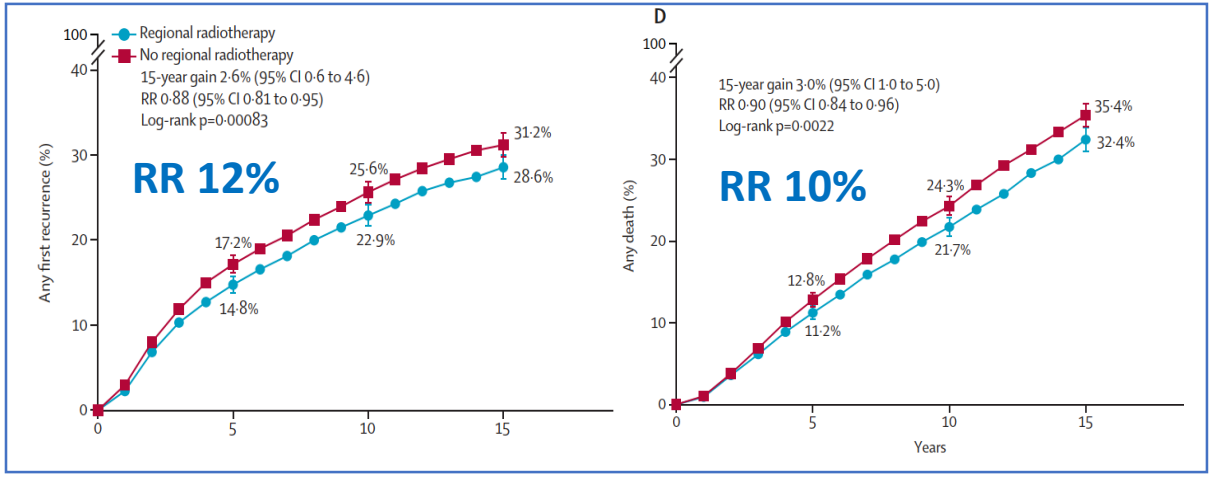
Adjuvant RT without NACT

Post Mastectomy RT reduced in pN+ the

10-year risk of a recurrence of any type by 10,6%

20-year risk of death from breast cancer by 8,1%





RNI after conservative surgery:

reduction distant metastasis (in all patients)
and mortality (especially in pN4+ patients)

EBCTCG, *Lancet* **2014**; 383: 2127-35

EBCTCG, *Lancet* **2023**

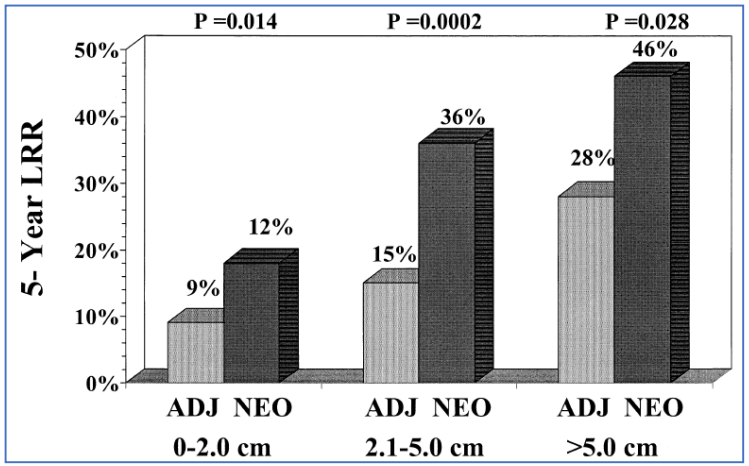
Agenda

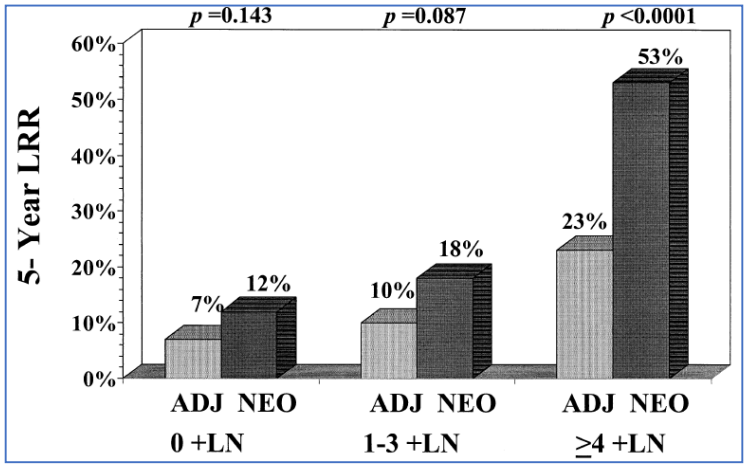
- Response to neoadjuvant chemotherapy and adjuvant RT
- Integration of RT with systemic treatments

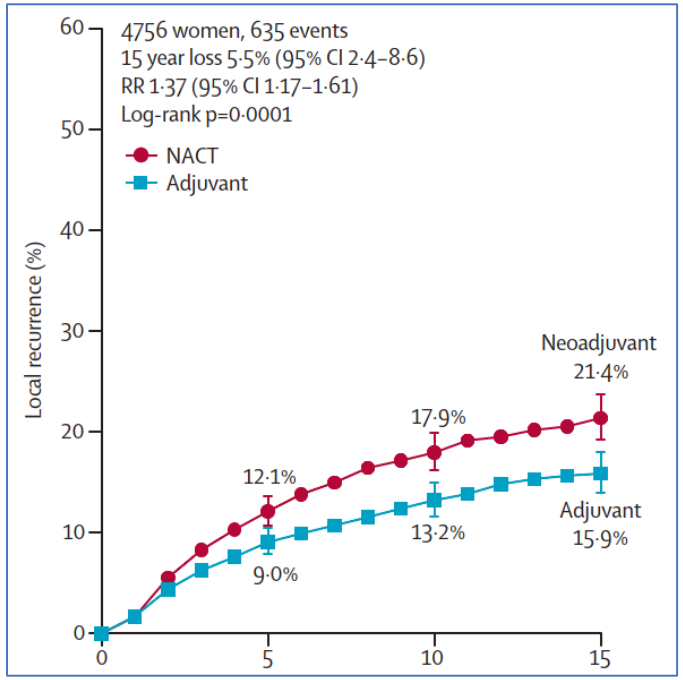
NACT and pathological response

Rischio di LRR in funzione del solo stadio patologico è differente per pazienti trattate con CT NAD rispetto alle pazienti sottoposte a CHT adiuvante

Rischio di LRR: correlato anche allo stadio clinico pre-CHT NAD







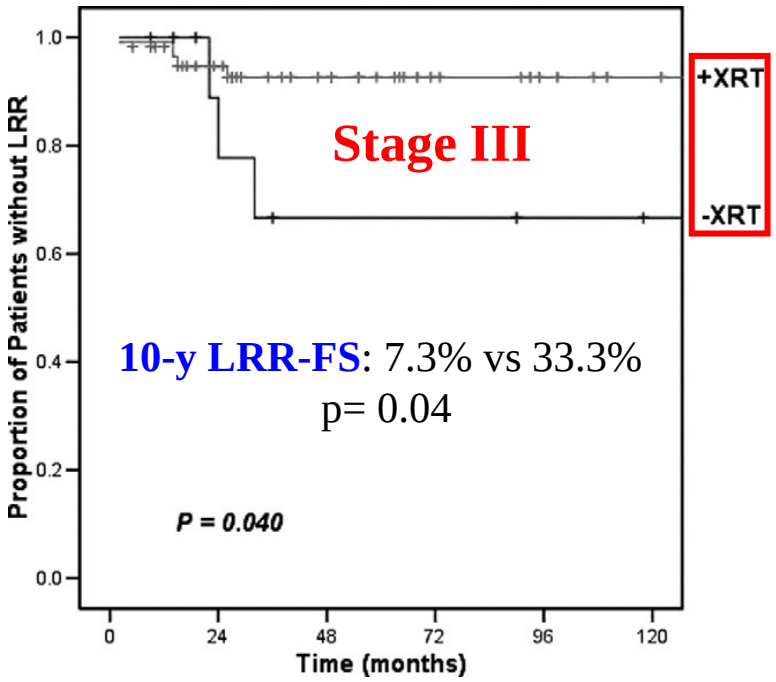
Essenziale corretta stadiazione clinica pre-CHT NAD

Early Breast Cancer Trialists' Collaborative G., *Lancet Oncol* **2018;** 19: 27-39 - Buchholz T. A., *IJROBP* 53:880-888, 2002

NACT and pathological response

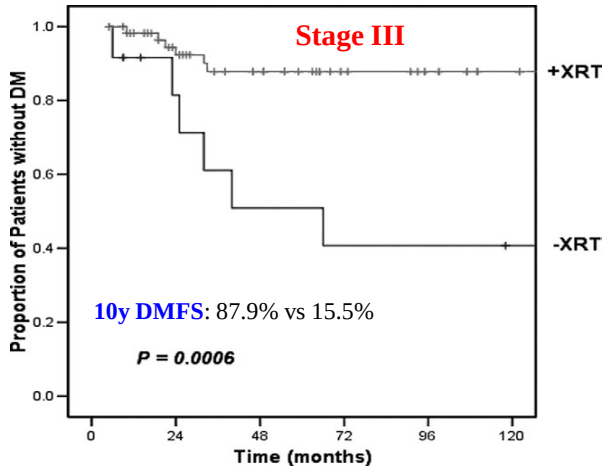
Stadio clinico III (N2; T3N1; T4)

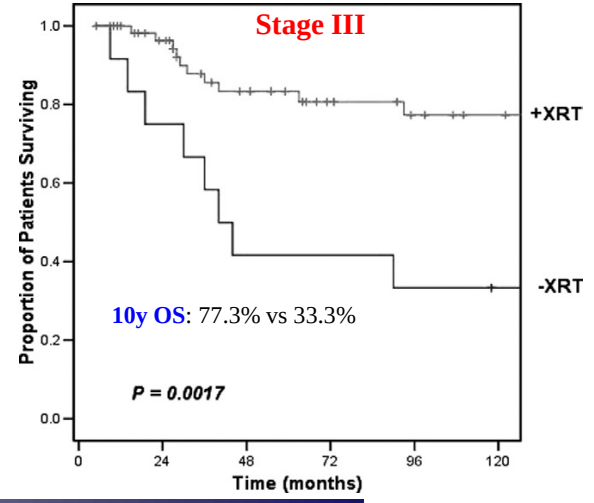
106 pts (74 stage III) with ***pathologic complete response*** after NAD CHT and mastectomy



«…the risk of LRR appears to be high…»

"…PMRT treating the chest wall and *undissected draining nodal basins* to pts with clinical Stage III and pCR at the time of mastectomy…"

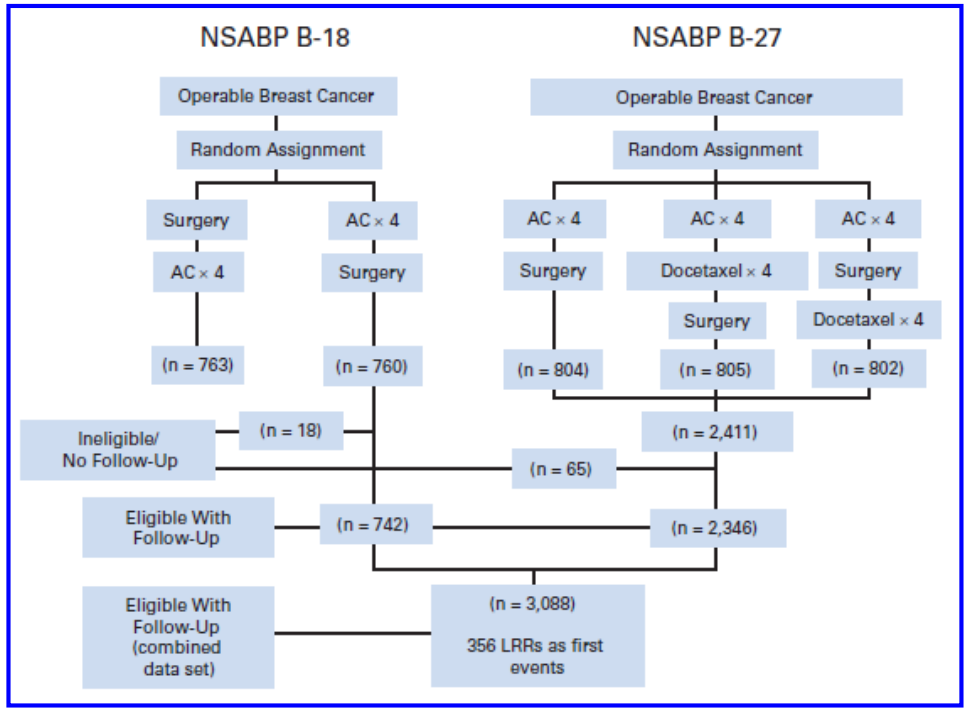




McGuire S.E., I*JROBP 68:*1004–1009, 2007

RNI after NACT

Clinical stage II (T1/T2 N1; T2/T3 N0)



3008 pts, 356 LR (nodal LR: 3.6% in mastectomy e 2.2% in lumpectomy)

Combined clinical stage at random assignment		
cT1-2N0	65	51
cT1-2N1	22	20
cT3N0	8	19
cT3N1	5	10

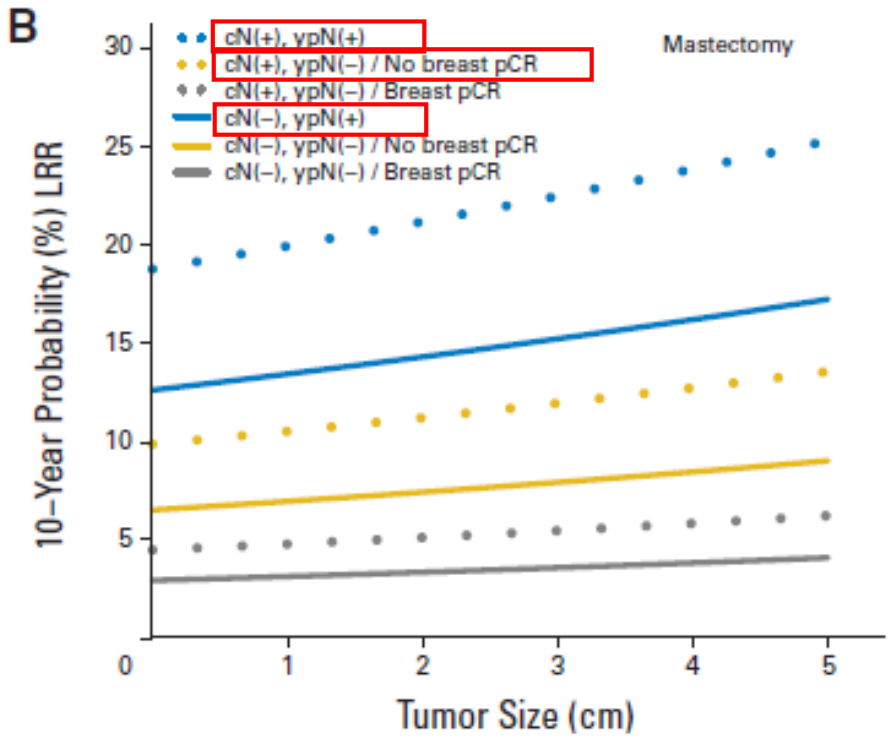
Significant ***independent predictors of LRR*** in multivariate analysis:

- age at random assignment (< 50 years)
- clinical tumor size before NAD CHT (>5 cm)
- clinical nodal status before NAD CHT (cN+)
- pathologic nodal status/pathologic breast tumor response (ypN negative/no breast pCR and ypN +)

Mamounas E.P., *JCO* 30:3960-3966, 2012

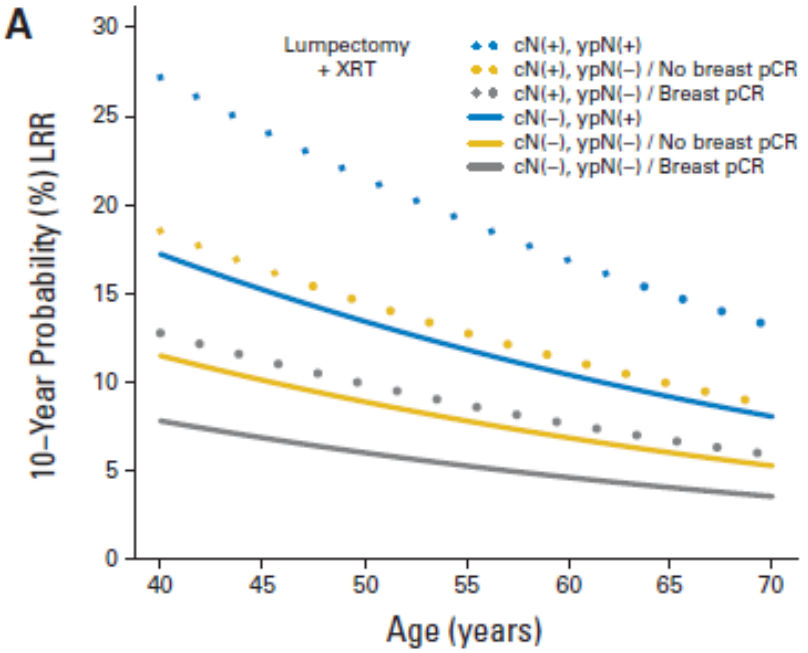
RNI after NACT

Clinical stage II
(T1/T2 N1; T2/T3 N0)



?! Competitive endpoint ?!

Regional nodal recurrence:
Higher in no pCR after NAD CHT



… pathologic ***response in the breast*** and ***pathologic axillary nodal status*** have a major impact on the rates and patterns of LRR …

Mamounas E.P., *JCO* 30:3960-3966, 2012

RT after NACT

cStage II-III with pCR

CLINICAL INVESTIGATION Breast

POSTMASTECTOMY RADIATION IMPROVES THE OUTCOME OF PATIENTS WITH LOCALLY ADVANCED BREAST CANCER WHO ACHIEVE A PATHOLOGIC COMPLETE RESPONSE TO NEOADJUVANT CHEMOTHERAPY

Sean E. McGuire, M.D., Ph.D.,* Ana M. Gonzalez-Angulo, M.D.,† Eugene H. Huang, M.D.,*

106 patients with clinical stage II-III; median follow-up was 62 months

PMRT: chest wall, supraclavicular fossa/axillary apex and internal mammary chain

Characteristic	Nonirradiated (n = 34) No. of patients	%	Irradiated (n = 72) No. of patients	%
Clinical stage				
IB	2	(6)	0	(0)
IIA	13	(38)	1	(1)
IIB	7	(21)	9	(17)
IIIA	5	(15)	29	(37)
IIIB	6	(17)	21	(29)
IIIC	1	(3)	12	(15)

Stage II: 32 pts

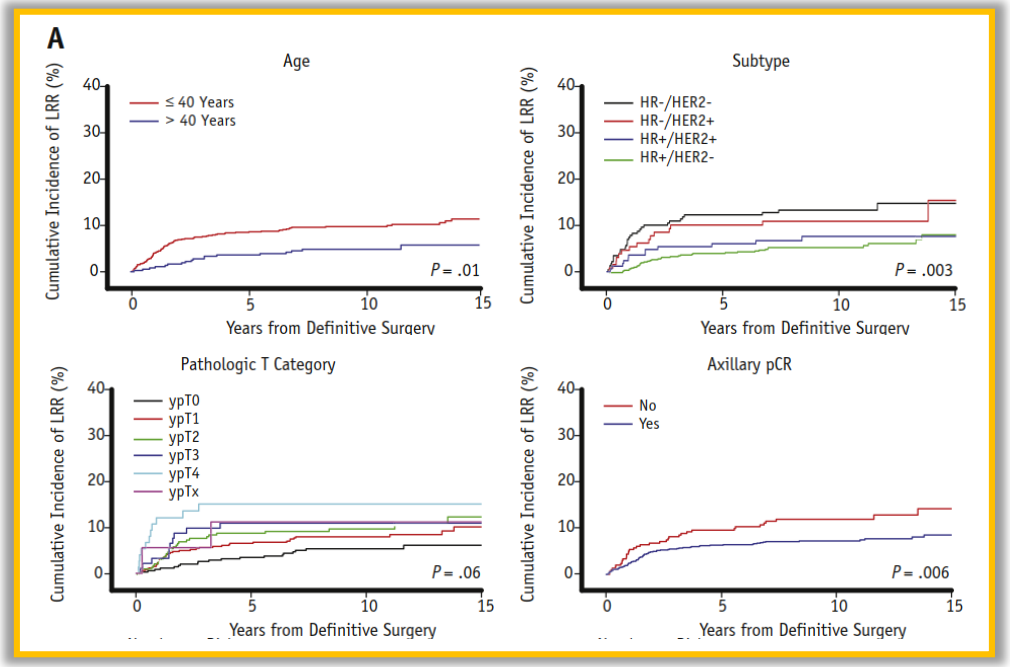
10-year LRR rates : 0% for both the patients treated with RT and those not receiving RT

McGuire S.E., I*JROBP 68:*1004–1009, 2007

RT after NACT

Long-Term Impact of Regional Nodal Irradiation in Patients With Node-Positive Breast Cancer Treated With Neoadjuvant Systemic Therapy

Median FUP: 10.2 y
162 (12.6%) LRR of the 1289 pts



RNI significantly reduced the risk:

LRR (HR: 0.497; P=0.02) and DR (HR: 0.731; P=0.04)

strong reduction in HER2+ (HR: 0.237; P=0.0003)

Factors associated with 10-year risk of LRR

Younger age (12.0% age 40 y vs 7.3% >40 y; P=.01)

Lack of axillary pCR (9.7% for no pCR vs 4.8% for pCR; P=.006)

High nuclear grade (10.3% grade III vs 4.5% grade I-II; P=.001)

Lymph nodes removed (17.6% for <10 vs 7.6% for 10; P=.001)

High clinical N category (9.3% for N3 vs 13.7% for N2 vs 7.4% for N1; P=.051)

High ypT category (15.0% for ypT4, 10.9% for ypT3, 10.1% for ypT2, 7.9% for ypT1, 5.3% for ypT0; P=.06)

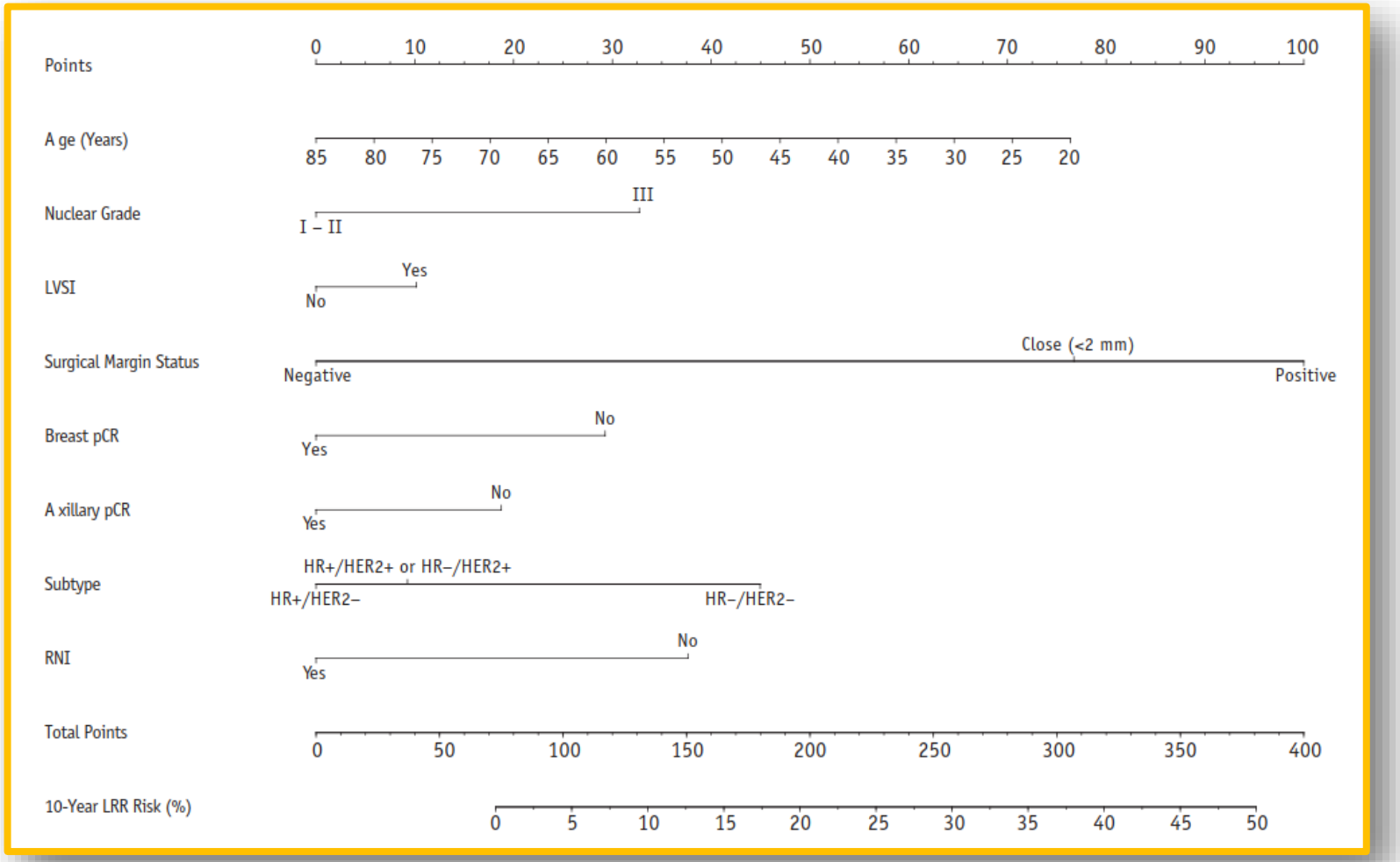
Lobular or unfavorable histologic subtype (22.0% for other unfavorable, 15.8% for lobular, 8.5% for ductal; P=.04)

TN subtype or HER2+ (13.3% for TN vs 10.9% for HR-/HER2+ vs 7.6% for HR+/HER2+ vs 5.7% for HR+/HER2-; P=.003)

Stecklein S. R., et al., *Int J Radiat Oncol Biol Phys* **2018;** 102: 568-77

RT after NACT

Nomogram to Predict 10-Year Risk of LRR in Patients with Clinical Stage II or III Breast Cancer with ***Cytologically-Confirmed Axillary Lymph Node*** Metastases Treated with Neoadjuvant Systemic Therapy and Surgery



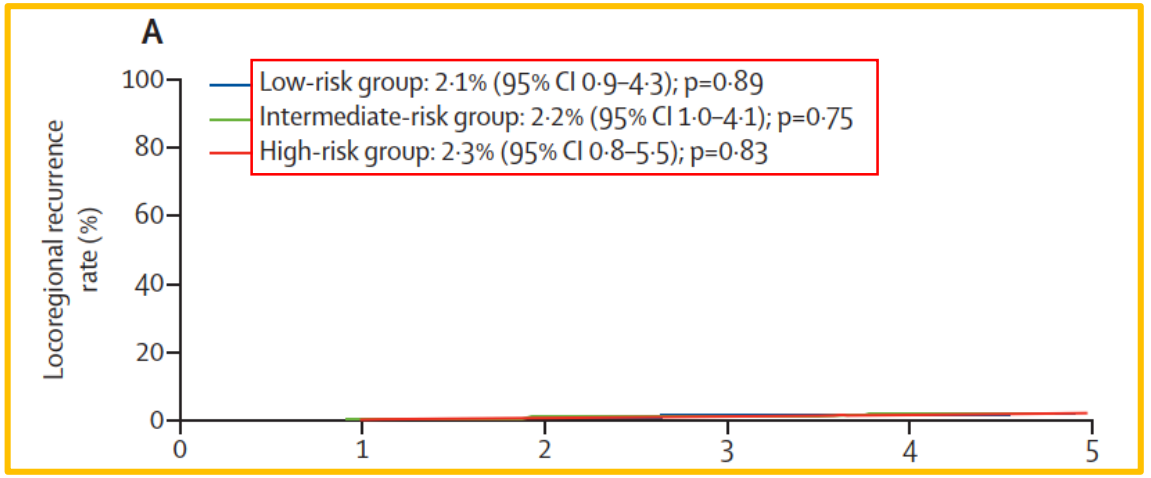
Stecklein S. R., et al., *Int J Radiat Oncol Biol Phys* **2018;** 102: 568-77

NACT and pathological response

De-escalation of radiotherapy after primary chemotherapy in cT1–2N1 breast cancer (RAPCHEM; BOOG 2010–03): 5-year follow-up results of a Dutch, prospective, registry study

Hypothesis: **5-year locoregional recurrence rate less than 4%** if the study guideline was followed

	Radiotherapy after breast conserving therapy	Radiotherapy after mastectomy
Low-risk group		
ypN0 (ALND)	Whole breast radiotherapy	..
If SLNB before primary chemotherapy and no ALND: cN1mi (SLNB), no risk factor*; or if SLNB after primary chemotherapy and no ALND: ypN0 (SLNB)	Whole breast radiotherapy	..
Intermediate-risk group		
ypN1 (ALND)	Whole breast radiotherapy	Chest wall radiotherapy
If SLNB before primary chemotherapy and no ALND†: cN1mi (SLNB), ≥1 risk factor*, or cN1 (SLNB), ≤2 macrometastases, no risk factor*; or if SLNB after primary chemotherapy and no ALND†: ypN1mi (SLNB), no risk factor*	Whole breast radiotherapy; in addition axilla level I and II†	Chest wall radiotherapy; in addition axilla level I and II†
High-risk group		
ypN2–3 (ALND)	Whole breast radiotherapy; axilla level III and IV	Chest wall radiotherapy; axilla level III and IV
If SLNB before primary chemotherapy and no ALND†: cN1 (SLNB), with ≤2 macrometastases and ≥1 risk factor*, or ≥3 macrometastases; or if SLNB after primary chemotherapy and no ALND†: ypN1mi (SLNB), ≥1 risk factor*, or ypN1 (SLNB)	Whole breast radiotherapy; axilla level III and IV; in addition axilla level I and II†	Chest wall radiotherapy; axilla level III and IV; in addition axilla level I and II†



cT1–2N1 patients treated with NACT, it seems oncologically safe to deescalate locoregional radiotherapy based on ypN status following ALND

de Wild S. R., et al., *Lancet Oncol* **2022;** 23: 1201-10

Adjuvant RT after NAD chemotherapy

Session: General Session 2

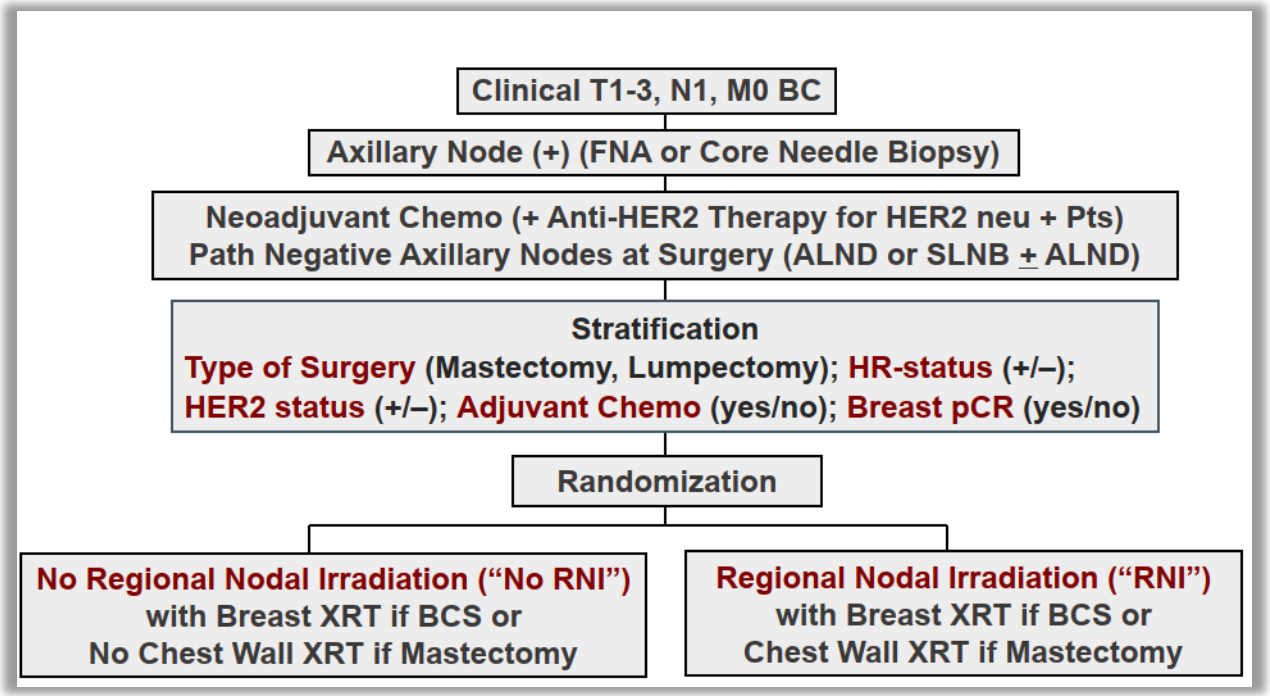
(GS02-07) Loco-Regional Irradiation in Patients with Biopsy-proven Axillary Node Involvement at Presentation Who Become Pathologically Node-negative After Neoadjuvant Chemotherapy: Primary Outcomes of NRG Oncology/NSABP B-51/RTOG 1304

Thursday, December 7, 2023 9:45 AM – 10:00 AM CT Location: Hall 1

CME/CNE 0.25 AMA PRE Credit Hours

Eleftherios Mamounas (1) **Hanna Bandos** (2) **Julia White** (3) **Thomas Julian** (4) **Atif Khan** (5) **Simona Shaitelman** (6)

Adjuvant RT after NAD chemotherapy



NSABP B-51/RTOG 1304

Primary Objective: to evaluate if adjuvant CWI+RNI significantly improves *Invasive Breast Cancer Recurrence-free Interval* in cN+ pts found to be ypN0 after NAC

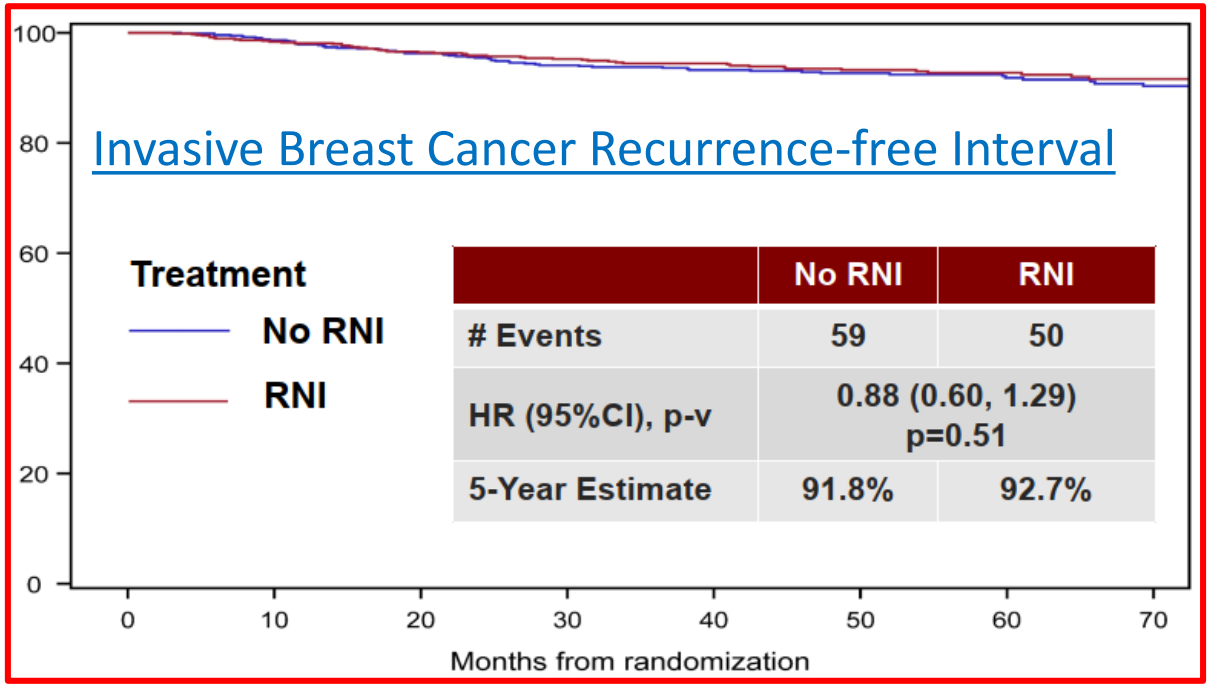
Statistics: designed to have 80% power to detect 35% reduction in annual IBCRFI rate (4.6% abs. risk reduction in 5-yr cumulative rate)
Final analysis after 172 events or 10 years after study initiation

Adjuvant RT after NAD chemotherapy

Patients: From Sep 2013 to Dec 2020, **1556 pts** (No RNI: 784; RNI: 772) analyzed for disease-related endpoints

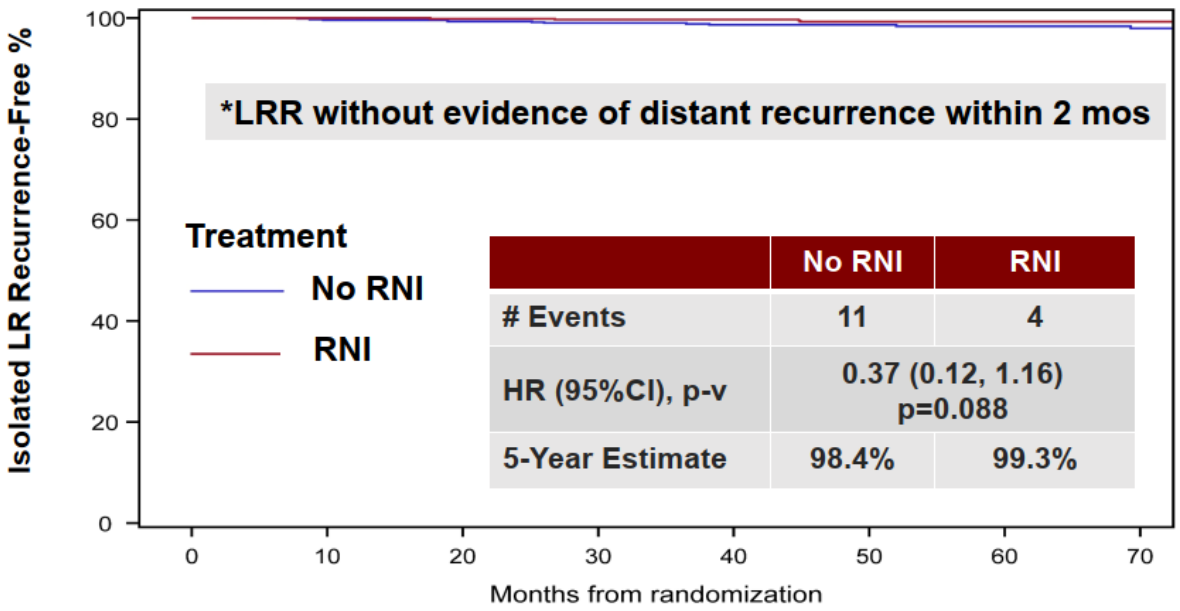
Median Follow-up Time: 59.5 months

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



	No RNI	RNI
# Events	59	50
HR (95%CI), p-v	0.88 (0.60, 1.29) p=0.51	
5-Year Estimate	91.8%	92.7%

Adjuvant RT after NAD chemotherapy

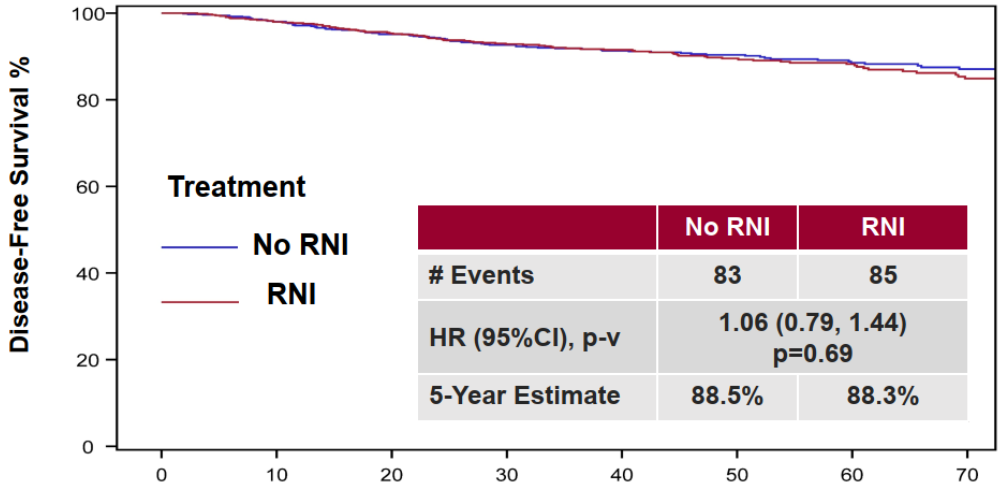


	No RNI	RNI
# Events	11	4
HR (95%CI), p-v	0.37 (0.12, 1.16) p=0.088	
5-Year Estimate	98.4%	99.3%

Location of Isolated LRR

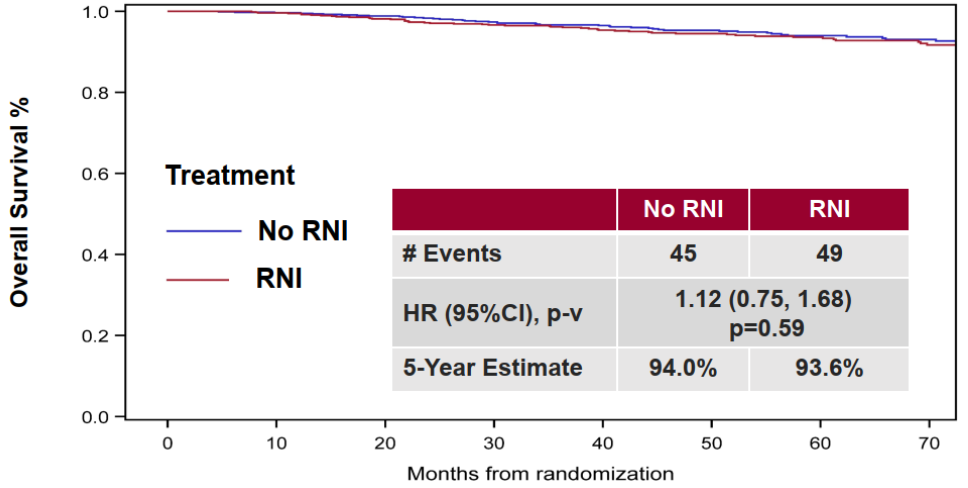
Location	No RNI #	RNI #	Total #
Local	2	4	6
Regional	8	0	8
Loco-regional	1	0	1
Total	11	4	15

Disease-free Survival (DFS)



	No RNI	RNI
# Events	83	85
HR (95%CI), p-v	1.06 (0.79, 1.44) p=0.69	
5-Year Estimate	88.5%	88.3%

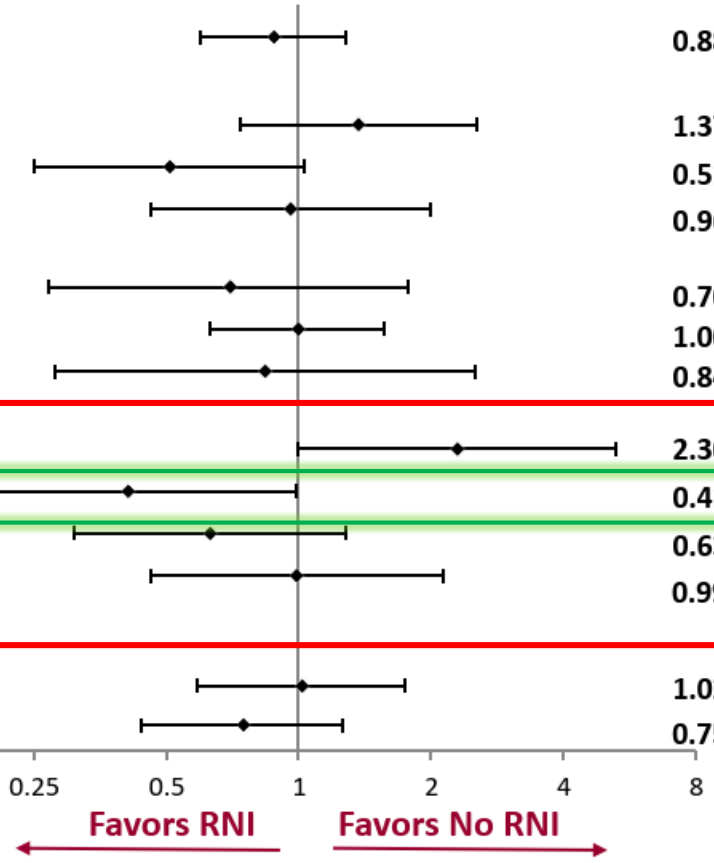
Overall Survival (OS)



	No RNI	RNI
# Events	45	49
HR (95%CI), p-v	1.12 (0.75, 1.68) p=0.59	
5-Year Estimate	94.0%	93.6%

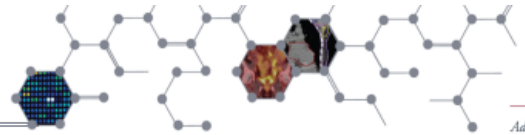
Adjuvant RT after NAD chemotherapy

Variable		No RNI (D/N)	No RNI 5-y est (%)	RNI (D/N)	RNI 5-y est (%)	HR (95% CI)	P-interaction
	All patients	59/784	**91.8**	50/772	**92.7**	**0.88** (0.60,1.28)	
Age	<=49	18/311	**92.8**	24/312	**92.0**	**1.37** (0.74,2.54)	0.09
	50-59	25/257	**90.4**	12/254	**94.4**	**0.51** (0.25,1.03)	
	>= 60	16/216	**92.4**	14/206	**91.7**	**0.96** (0.46,1.99)	
Race	Black	11/135	**92.6**	8/140	**93.4**	**0.70** (0.27,1.77)	0.69
	White	40/543	**91.6**	36/533	**92.1**	**1.00** (0.63,1.57)	
	Other	8/106	**91.8**	6/99	**95.3**	**0.84** (0.28,2.52)	
Tumor Subtype	Triple-negative	8/169	**95.0**	19/188	**88.4**	**2.30** (1.00,5.25)	0.037
	ER/PR+/HER2-	17/173	**90.5**	7/155	**94.0**	**0.41** (0.17,0.99)	
	ER/PR-/HER2+	20/198	**88.8**	12/183	**92.4**	**0.63** (0.31,1.28)	
	ER/PR+/HER2+	14/244	**93.3**	12/246	**95.7**	**0.99** (0.46,2.14)	
Axillary Surgery	Axil +/- SLNB	27/357	**92.0**	25/338	**91.8**	**1.02** (0.59,1.75)	0.42
	SLNB alone	32/427	**91.5**	25/434	**93.5**	**0.75** (0.44,1.26)	



Adjuvant RT after NAD chemotherapy

Conclusions



NRG ONCOLOGY
Advancing Research. Improving Lives.™

- 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

RNI after NACT

ClinicalTrials.gov

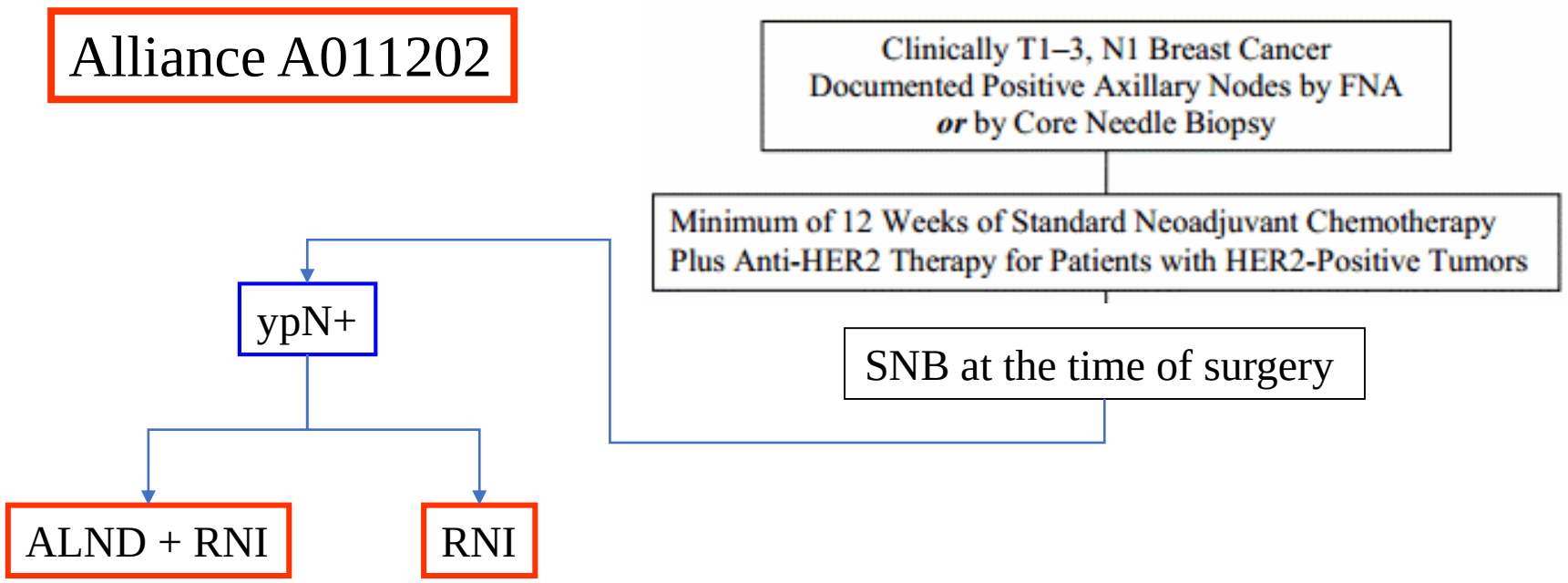
Comparison of Axillary Lymph Node Dissection With Axillary Radiation for Patients With Node-Positive Breast Cancer Treated With Chemotherapy

This study is currently recruiting participants. (see Contacts and Locations)

Verified August 2015 by Alliance for Clinical Trials in Oncology

ClinicalTrials.gov Identifier:
NCT01901094

Alliance A011202



https://clinicaltrials.gov/ct2/show/NCT01901094

Agenda

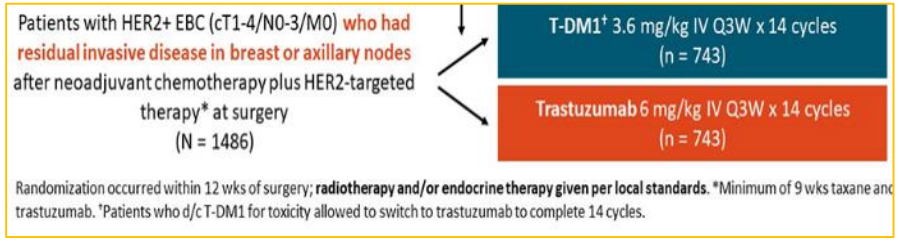
- Response to neoadjuvant chemotherapy and adjuvant RT
- Integration of RT with systemic treatments

RT and Systemic therapy

T-DM1

Anti-HER2

KATHERINE trial



No significant differences
Radiation Dermatitis (27.6% vs 25.4%)
Radiation Pneumonitis (1.5% vs. 0.7%)

Systematic Review

Safety profile of trastuzumab-emtansine (T-DM1) with concurrent radiation therapy: A systematic review and meta-analysis

Radiation Pneumonitis: G2+ and G3+: 1% and < 1% [very low heterogeneity (I^2 0%)]

Radiation Dermatitis: G2+ and G3+: 32% and 1% [very low heterogeneity (I^2 0%)]

T-DM1 and **concomitant adj RT** seems well tolerated

SBRT/SRS Brain

Safety of T-DM1 and concomitant RT for brain M+ is extremely debated

Cases of clinically **symptomatic radiation necrosis** frequently reported, especially in the case of SRS use

(Stumpf PK *Clin Cancer Res* 2019)

Loibl S et al. Ann Oncol. (S2) 2020 - Salvestrini V., et al., *Radiother Oncol* **2023**

von Minckwitz G et al. N Engl J Med 2019

RT and Systemic therapy

CDK4/6 Inhibitors

No information on concomitant treatment from prospective trials

PALOMA trials: recommended to *suspend palbociclib for 7 days* from the day prior to the RT course

MONALEESA trials (NCT01958021, NCT02422615, NCT02278120) : palliative RT *solely for bone pain relief*

MONARCH trials (NCT02107703, NCT02246621): pts requiring RT should have *permanently discontinued therapy*

Table 1. Clinically relevant adverse events observed in the abemaciclib + ET arm regardless of causality

	Abemaciclib + ET (*N* = 2791)				ET alone (*N* = 2800)			
	Any grade	G1	G2	G ≥ 3	Any grade	G1	G2	G ≥ 3
≥10% in the abemaciclib + ET arm								
Patients with ≥1 AE,[a] *n* (%)	2745 (98.4)	165 (5.9)	1192 (42.7)	1388 (49.7)	2486 (88.8)	634 (22.6)	1396 (49.9)	456 (16.3)
Diarrhea	2331 (83.5)	1255 (45.0)	857 (30.7)	219 (7.8)[b]	242 (8.6)	184 (6.6)	52 (1.9)	6 (0.2)
Infections[c]	1429 (51.2)	245 (8.8)	1029 (36.9)	155 (5.6)	1102 (39.4)	229 (8.2)	790 (28.2)	83 (3.0)[d]
Neutropenia	1278 (45.8)	178 (6.4)	554 (19.8)	546 (19.6)	157 (5.6)	66 (2.4)	68 (2.4)	23 (0.8)
Fatigue	1133 (40.6)	632 (22.6)	421 (15.1)	80 (2.9)	499 (17.8)	378 (13.5)	117 (4.2)	4 (0.1)
Nausea	824 (29.5)	623 (22.3)	187 (6.7)	14 (0.5)	252 (9.0)	198 (7.1)	52 (1.9)	2 (0.1)
Anemia	681 (24.4)	383 (13.7)	241 (8.6)	57 (2.0)	104 (3.7)	75 (2.7)	19 (0.7)	10 (0.4)
Headache	546 (19.6)	415 (14.9)	123 (4.4)	8 (0.3)	421 (15.0)	321 (11.5)	95 (3.4)	5 (0.2)
Vomiting	491 (17.6)	375 (13.4)	101 (3.6)	15 (0.5)	130 (4.6)	98 (3.5)	29 (1.0)	3 (0.1)
Stomatitis[e]	385 (13.8)	309 (11.1)	72 (2.6)	4 (0.1)	151 (5.4)	133 (4.8)	18 (0.6)	0 (0.0)
Thrombocytopenia	373 (13.4)	276 (9.9)	61 (2.2)	36 (1.3)	52 (1.9)	40 (1.4)	8 (0.3)	4 (0.1)
Decreased appetite	329 (11.8)	243 (8.7)	70 (2.5)	16 (0.6)	68 (2.4)	53 (1.9)	13 (0.5)	2 (0.1)
Alopecia	313 (11.2)	283 (10.1)	30 (1.1)	N/A	75 (2.7)	68 (2.4)	7 (0.3)	0 (0.0)
Alanine aminotransferase increase (ALT)	343 (12.3)	184 (6.6)	82 (2.9)	77 (2.8)	157 (5.6)	113 (4.0)	25 (0.9)	19 (0.7)
Aspartate aminotransferase increase (AST)	330 (11.8)	220 (7.9)	58 (2.1)	52 (1.9)	137 (4.9)	103 (3.7)	19 (0.7)	15 (0.5)
Rash	312 (11.2)	239 (8.6)	61 (2.2)	11 (0.4)	127 (4.5)	104 (3.7)	23 (0.8)	0 (0.0)
Other AEs of interest—composite terms								
VTE[f]	71 (2.5)	2 (0.1)	31 (1.1)	38 (1.4)[h]	17 (0.6)	0 (0.0)	9 (0.3)	8 (0.3)
PE[g]	28 (1.0)	N/A	N/A	28 (1.0)[i]	4 (0.1)	N/A	N/A	4 (0.1)
ILD[j]	89 (3.2)	44 (1.6)	34 (1.2)	11 (0.4)	37 (1.3)	26 (0.9)	10 (0.4)	1 (0.0)
Pneumonitis	49 (1.8)	21 (0.8)	21 (0.8)	7 (0.3)	10 (0.4)	7 (0.3)	3 (0.1)	0 (0.0)
Radiation pneumonitis	25 (0.9)	13 (0.5)	10 (0.4)	2 (0.1)	15 (0.5)	9 (0.3)	5 (0.2)	1 (0.0)
Increased transaminases[k]	433 (15.5)	241 (8.6)	94 (3.4)	98 (3.5)	209 (7.5)	143 (5.1)	38 (1.4)	28 (1.0)

MonarchE trial

Radiation pneumonitis in patients previously treated with RT were **similar in the two arms**

Half of the ILD events were asymptomatic.

CDK4/6i and concomitant adjuvant RT should be investigated in clinical trials

Meattini I et al. Cancer Treatment Rev 2022

Rugo HS et al. Ann Oncol 2022

RT and Systemic therapy

PARPi

JAMA Oncology | Original Investigation

Concurrent Olaparib and Radiotherapy in Patients With Triple-Negative Breast Cancer

The Phase 1 Olaparib and Radiation Therapy for Triple-Negative Breast Cancer Trial

Table 2. Treatment-Related Adverse Events Reported During Follow-up

	Toxic effects by olaparib dose and toxic effect grade, No.[a]															
	50 mg Twice daily				100 mg Twice daily				150 mg Twice daily				200 mg Twice daily			
Toxic effect	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
1-y Follow-up (n = 23)																
Pain	0	0	0	0	0	1	0	0	1	0	0	0	2	0	0	0
Fibrosis	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Deformity	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Skin hyperpigmentation	0	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0
Telangiectasia	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Lymphedema	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
2-y Follow-up (n = 20)																
Pain	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0
Fibrosis	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0
Deformity	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Skin hyperpigmentation	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0
Telangiectasia	0	0	0	0	3	0	0	0	0	0	0	0	1	0	0	0
Lymphedema	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0

[a] Toxic effect grades are based on Common Terminology Criteria for Adverse Events, version 4.03.[9]

Olaparib in combination with breast RT in patients with TNBC was well tolerated
Results suggest that olaparib could be safely started earlier in combination with radiotherapy

Available data on this combination are **scarce**.
There is a shortage of long-term safety data and little evidence demonstrating a clinically significant benefit

It remains preferable to not use RT concurrently with PARP inhibitors

Loap P., et al., *JAMA oncology* **2022**

RT and Systemic therapy

Capecitabine

Combining Adjuvant Radiotherapy With Capecitabine in Chemotherapy-resistant Breast Cancer: Feasibility, Safety, and Toxicity

Alexander D. Sherry,[1] Ingrid A. Mayer,[2] Diandra N. Ayala-Peacock,[3] Vandana G. Abramson,[2] Brent N. Rexer,[2] A. Bapsi Chakravarthy[3]

Retrospective on TNBC (stage I-III)

Cape-RT (16 pts) matched 1:3 with **RT alone** (48 pts)

Radiation dermatitis: not significantly different

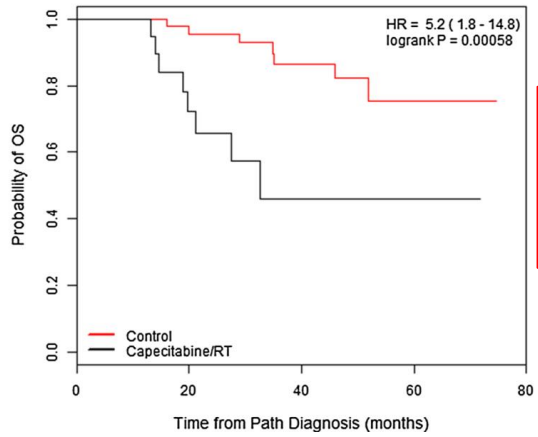
Capecitabine-RT group more **modifications in the RT schedule** (44% vs 17%)

Sherry A et al, Clinical Breast Cancer 2020

Concurrent use of capecitabine with radiation therapy and survival in breast cancer (BC) after neoadjuvant chemotherapy

Matched cohort retrospective study on TNBC

21 pts matched 2:1 with 254 NO capecitabine/RT
All pts received A/T-based NAC and adj RT



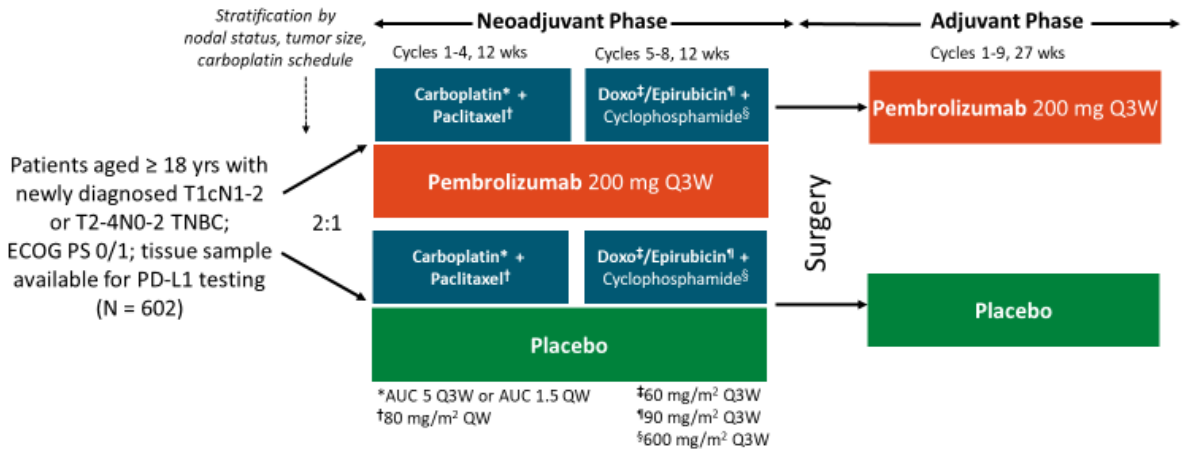
Worse OS
(HR 3.71 95% CI 1.04–13.18, $p = 0.04$)

Liu YL et al. Clin Transl Oncol 2018

RT and Systemic therapy

Immunotherapy

Keynote-522 trial



- Primary endpoints: pCR (ypT0/Tis ypN0) by local review, EFS by local review
- Secondary endpoints: pCR (ypT0 ypN0 and ypT0/Tis), OS, EFS, AE

Several studies of concurrent ICIs and chemoradiation from head and neck and non-small cell lung cancer

Acceptable safety profiles with concurrent use compared with pembrolizumab or chemoradiation alone

After an amendment *concurrent administration RT/Pembro* permitted

Supplementary Materials

Locoregional AEs potentially associated with RT were rare

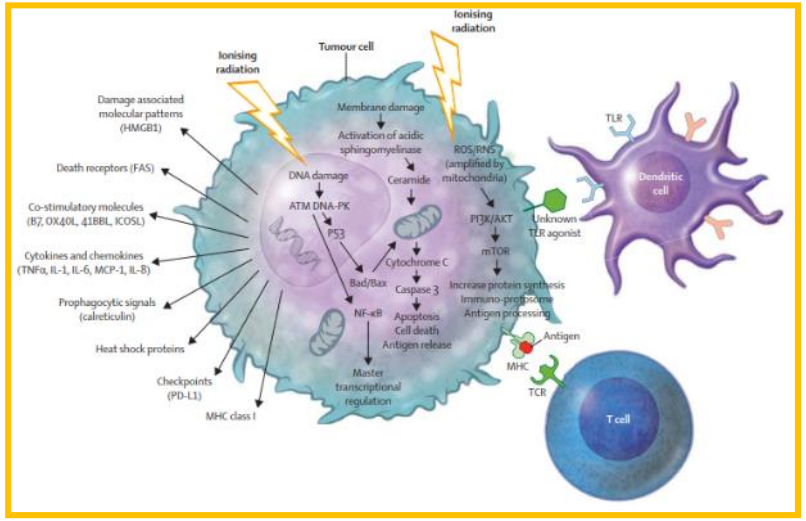
During the adjuvant phase of the study:
Severe skin reaction 1.6% vs 0%
Pneumonitis: 0.9% vs 0.6%
Myocarditis 0.4% vs 0%

Interestingly, LR AEs *during the neoadjuvant phase similar or higher* than during the adjuvant phase

Schmid et al. NEJM 2020

Immunogenic effect of the RT

@brunomeduri



Immunogenic cell death

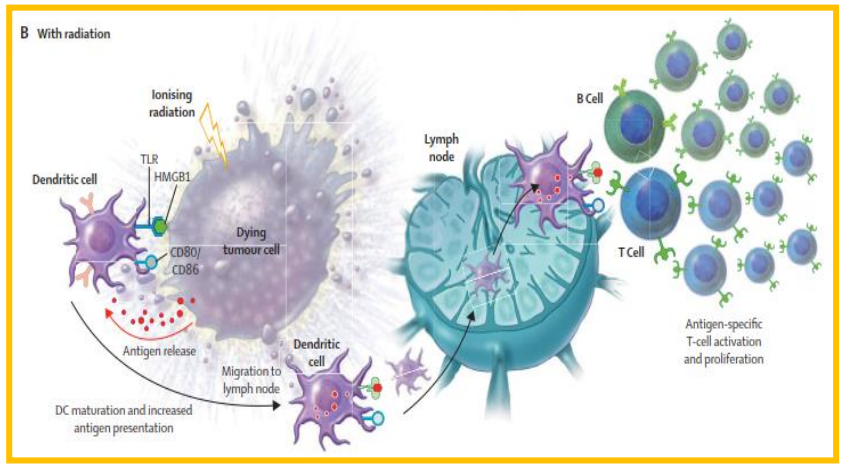
Upregulation of **MHC class I**

(by RT-induced activation of mTOR)

Cell surface translocation of **calreticulina** (DC "eat-me" signal)

HMGB1: immune system's *nuclear weapon*

Upregulation of **FAS** (which mediate apoptotic cell death)



Dendritic cell activation driven by calreticulina and HMGB1

RT increases **cross-presentation of tumour-associated epitopes** to CD8 in the draining lymph node (mediated by ***INF-γ***)

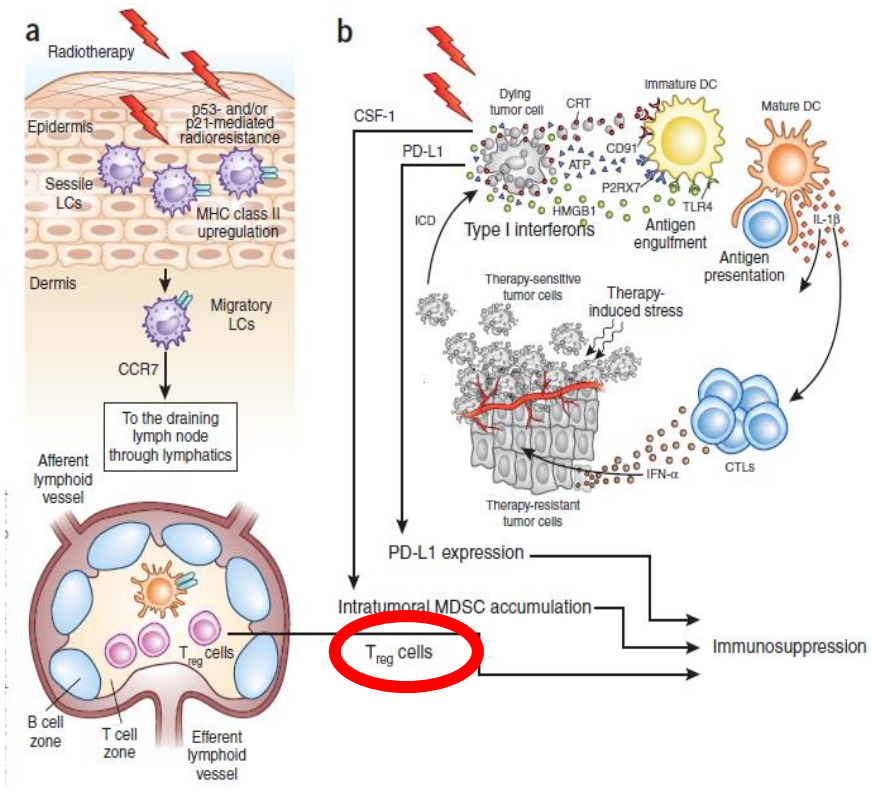
Activation and proliferation of antigen-specific T-cell populations to initiate an immune response

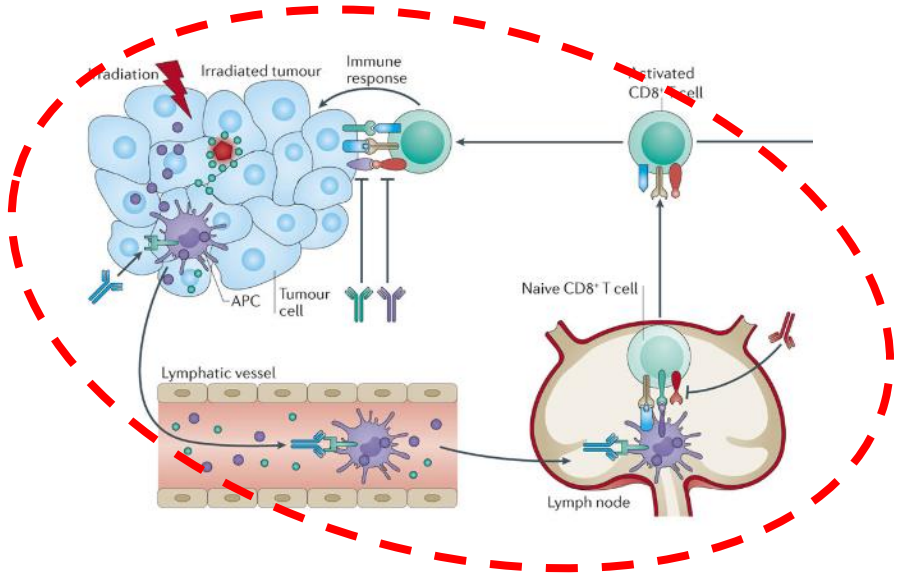
RT increases the density of **tumour-infiltrating lymphocytes (TILs)** with a mechanism probably multifactorial:

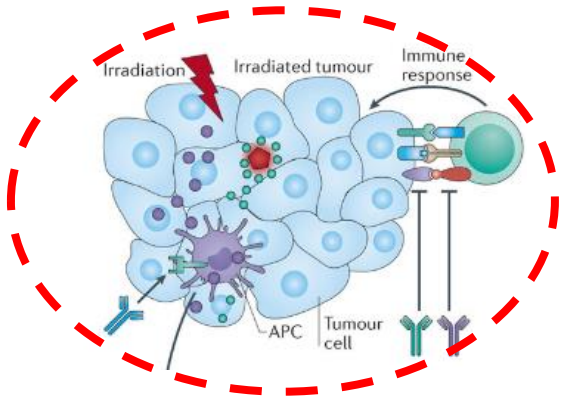
- changes in *vascular endothelium* enhance immune-cell extravasation (E-selectin and ICAM-1)
- increased expression of *chemokine* attractants enhances immune-cell migration and invasion (CXCL16, CXCL21)
- Recruitment and **Repolarization toward M1 phenotype Tumor Associated Macrophages**

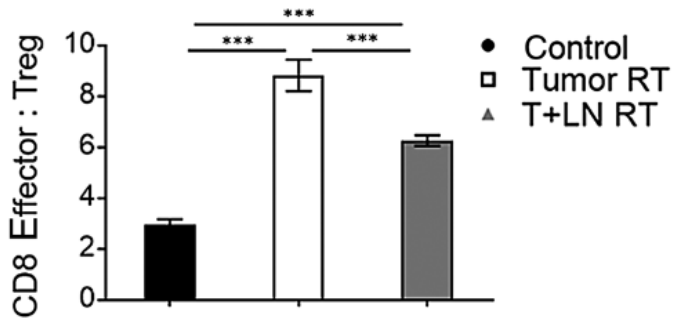
Sharabi A. B., et al., *The Lancet Oncology* **2015**

Immunosuppressive effect









Irradiation induces ***Langerhans cells*** to migrate from the skin to lymph nodes, where they **stimulate regulatory Tcells**

Elective Nodal Irradiation Attenuates the Combinatorial Efficacy of Radiation Therapy and Immunotherapy

Sharabi A. B., et al., *The Lancet Oncology* **2015**

Conclusion

- **Response to neoadjuvant chemotherapy and adjuvant RT**
  - Accurate staging pre-NAD CHT (optimal imaging and better nodal characterization)
  - Possible de-escalation in cT1-2 cN1 with pCR
- **Integration of RT with systemic treatments**
  - RT and concomitant adjuvant systemic therapy in patients without pCR (Cautionary: Capecitabine, PARPi, CDK4/6; Suitable: ICIs, TDM-1)
  - RT-immunotherapy: complex interactions – work in progress

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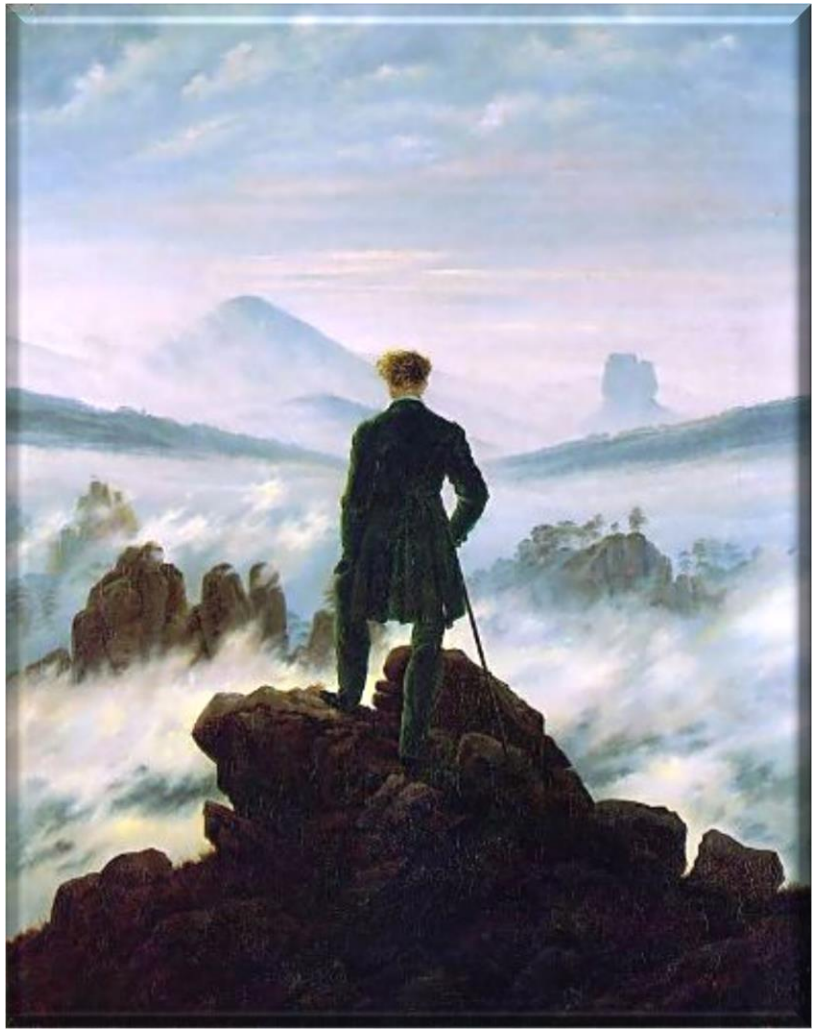

«…Everyone else would climb a peak by looking for a path somewhere on the mountain …someone would climb another mountain altogether and from that distant peak would shine a searchlight back on the first peak…»