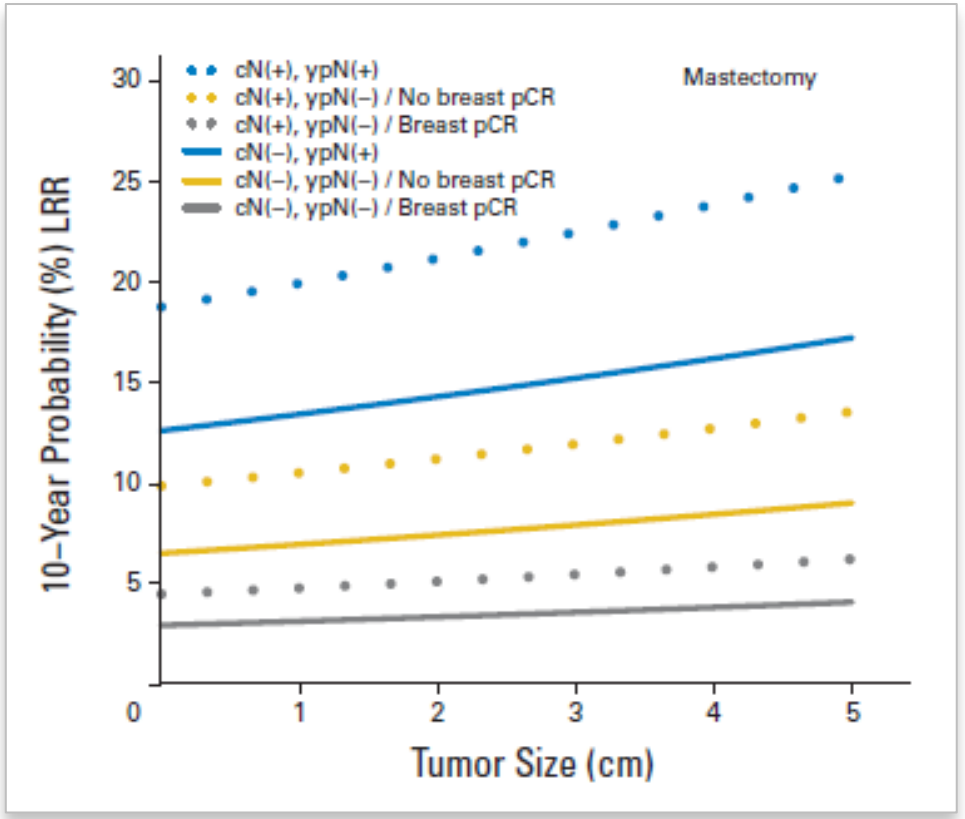
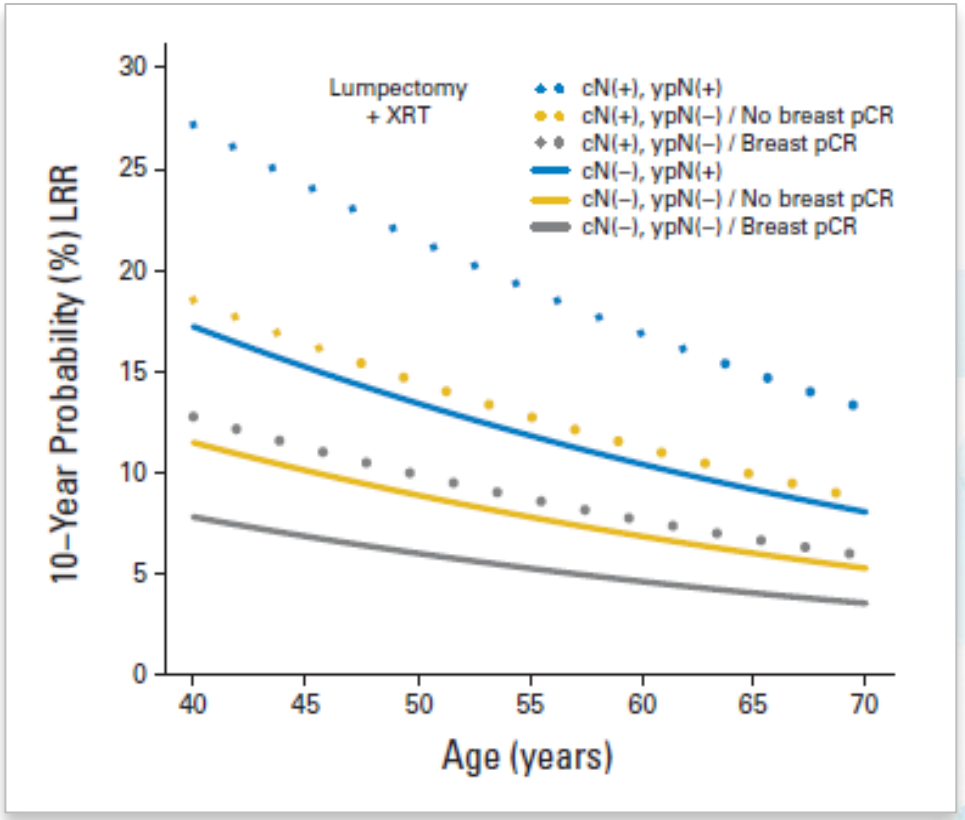
Radiation in the setting of pCR has to be based on pre-treatment (vs post treatment) assessment

YES

Who is at risk of LRR after PST?

stage and response to PST

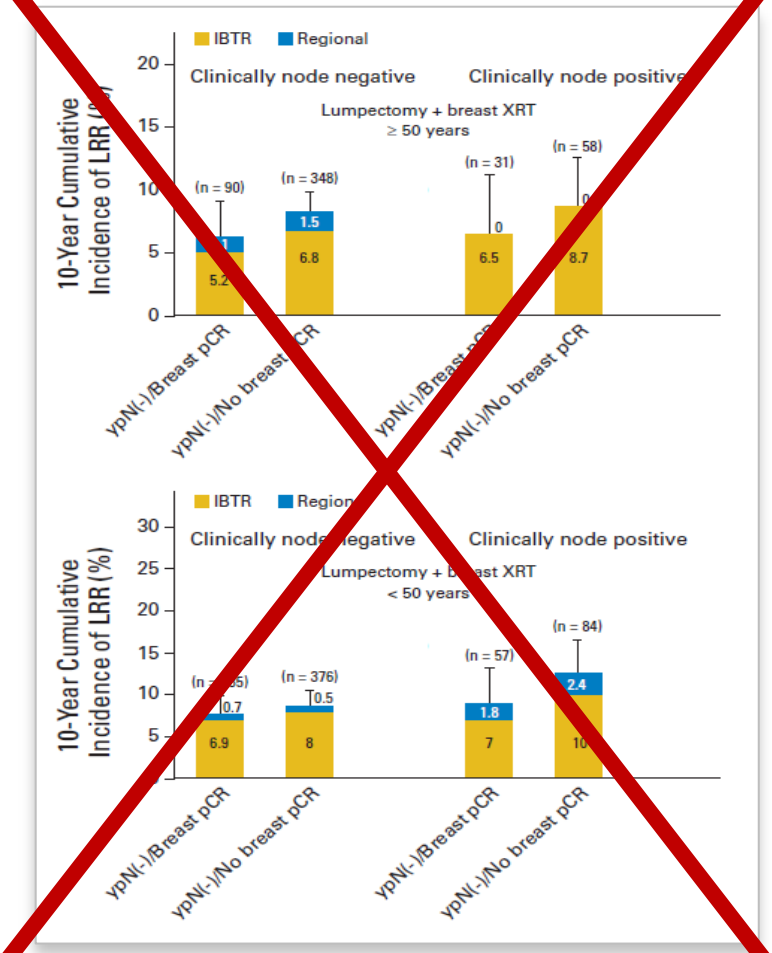




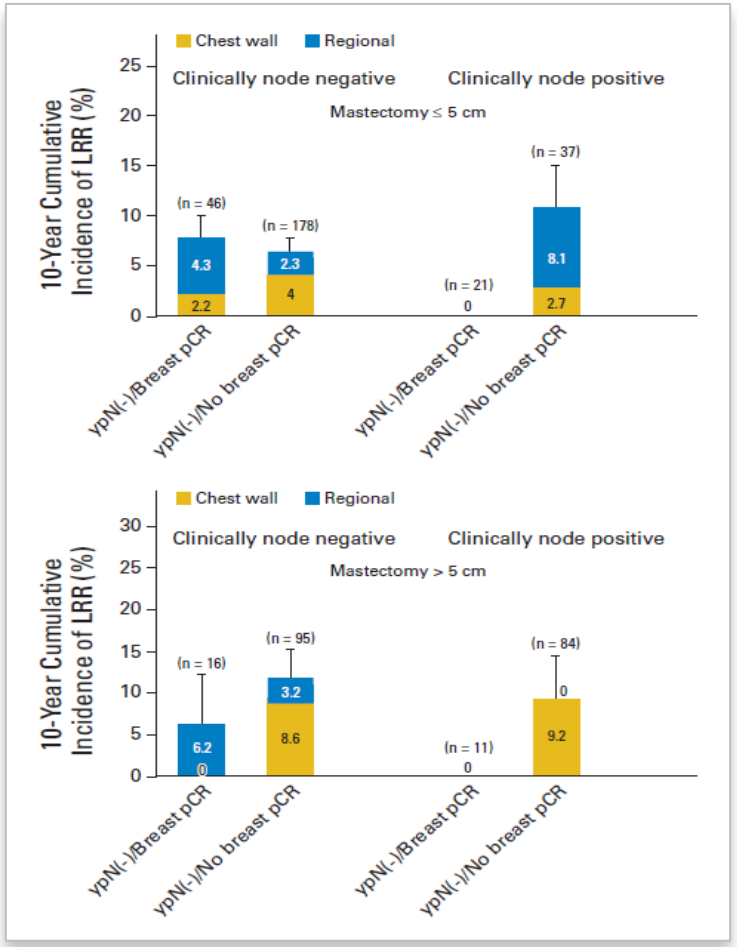
pooled analysis of NSABP B-18 and NSABP B-27
no RNI allowed

Mamounas, JCO 2012

Nodal recurrences in ypN0 pts



BCT patients



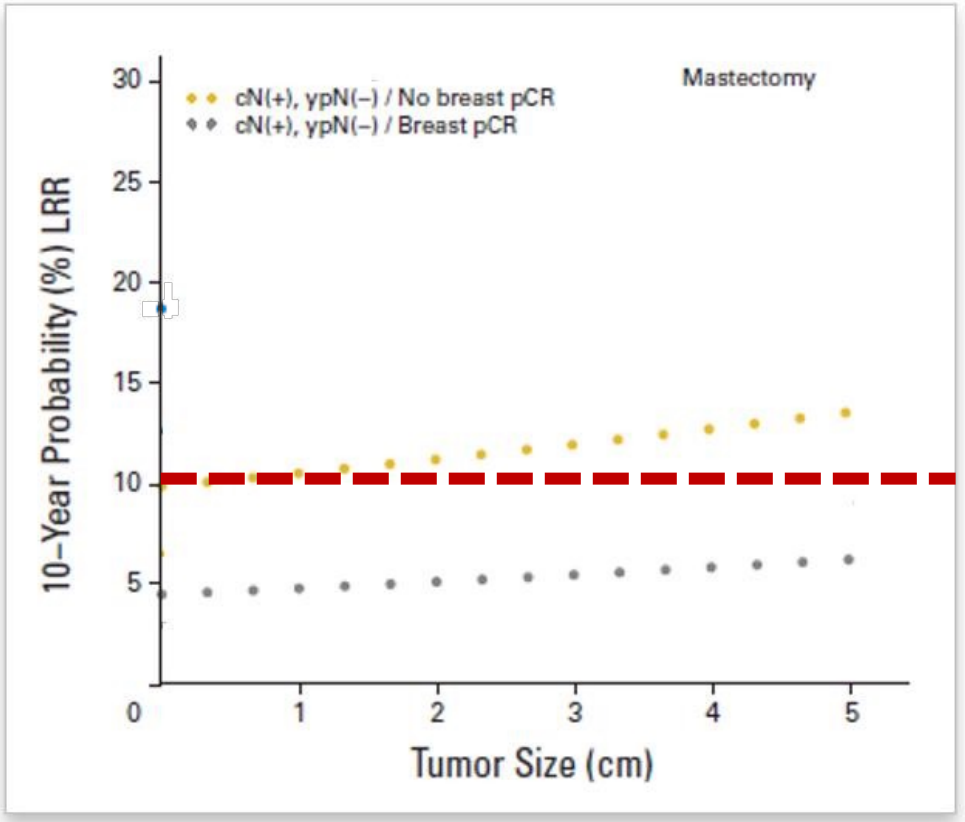
mastectomy patients

pooled analysis of NSABP B-18 and NSABP B-27

Mamounas, JCO 2012

Who is at risk of LRR after PST?

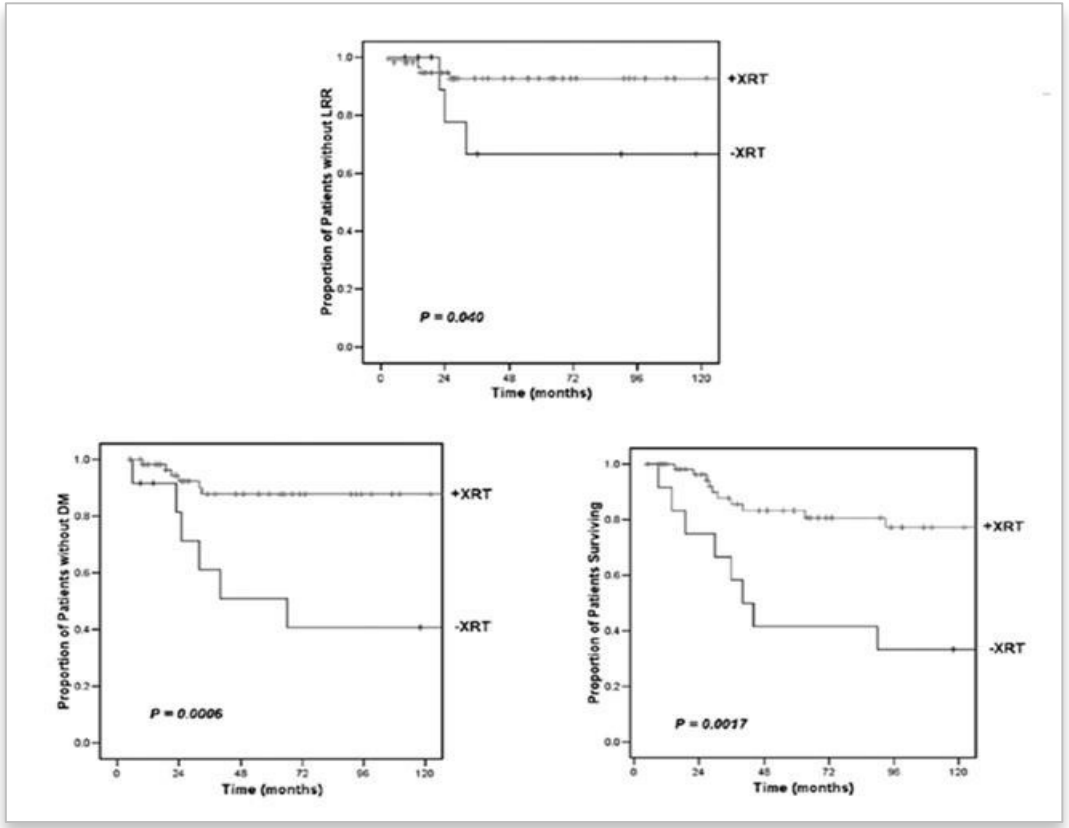
stage and response to PST



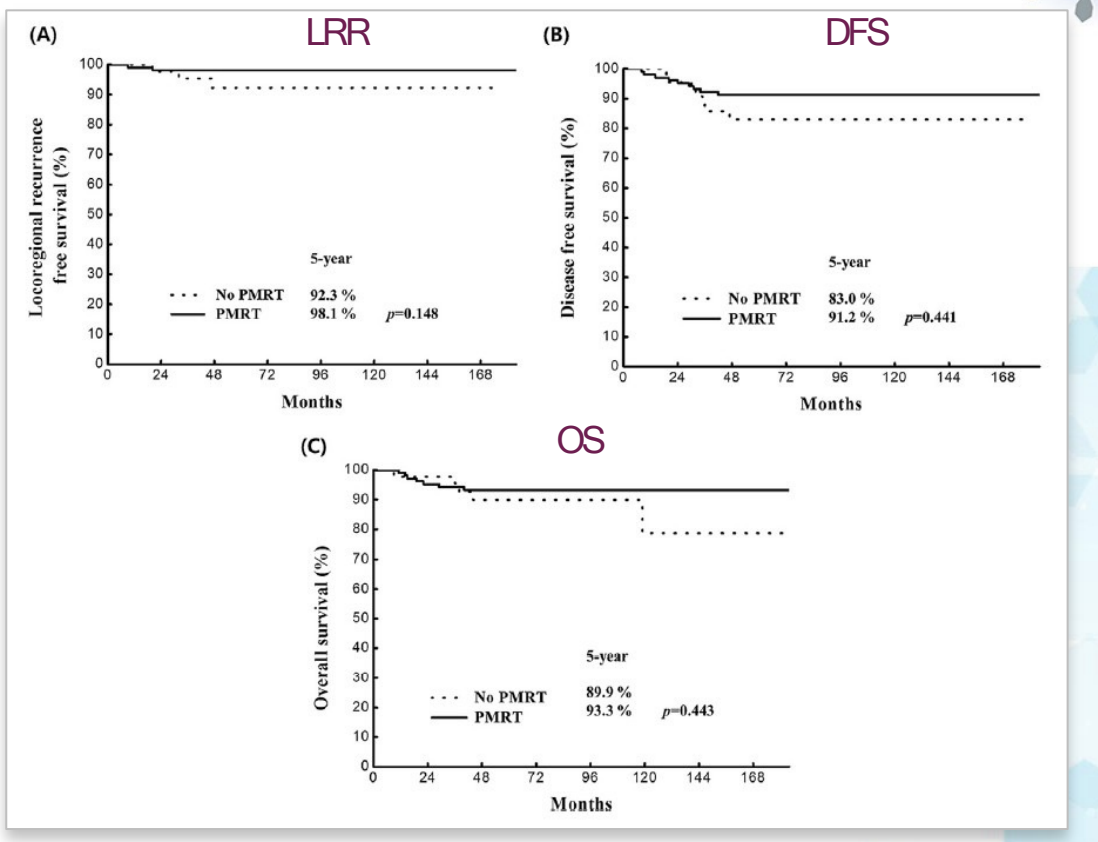
pooled analysis of NSABP B-18 and NSABP B-27
no RNI allowed

Mamounas, JCO 2012

Post-PST PMRT improves outcomes - in high-risk patients/maybe???



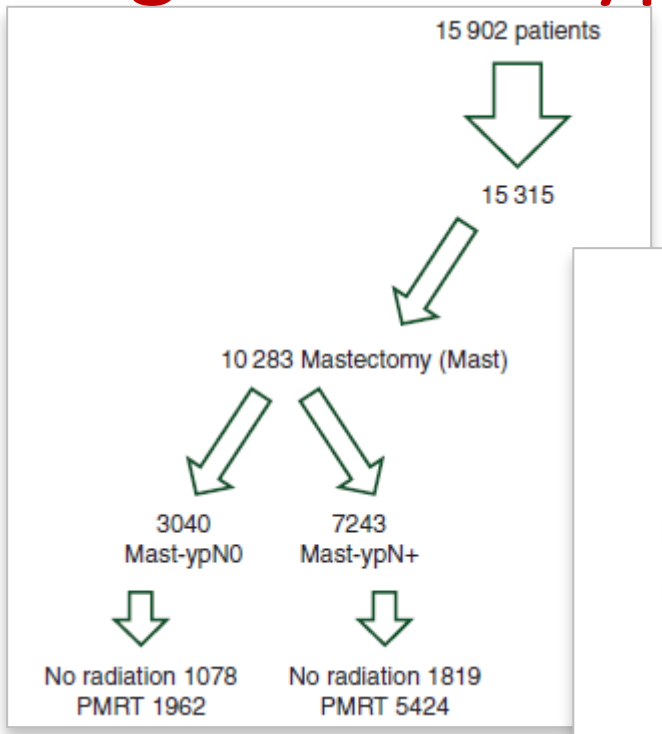
74 st. III ypT_0N_0 pts
M.D. Anderson

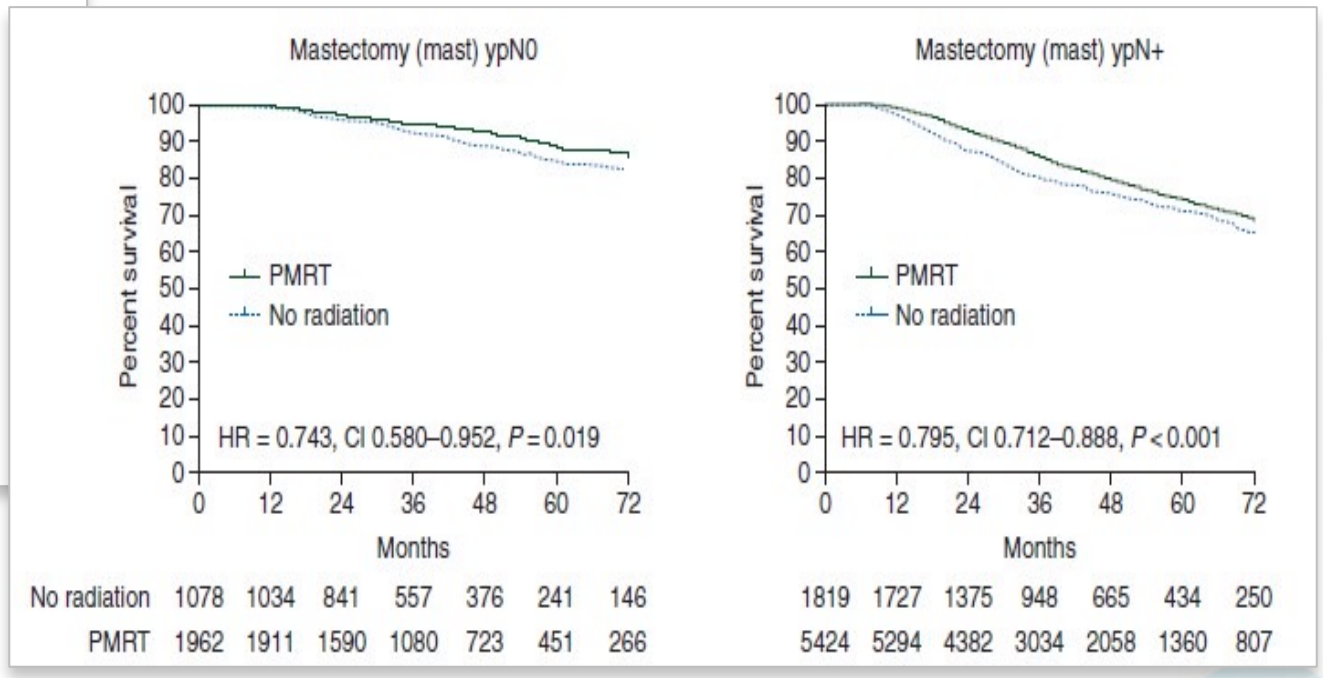


KROG 12-05
151 st. II-III ypN_0 pts

, IJROBP 2007, Shim, IJROBP 2014

Post-PST PMRT improves outcomes - regardless of ypN stage?





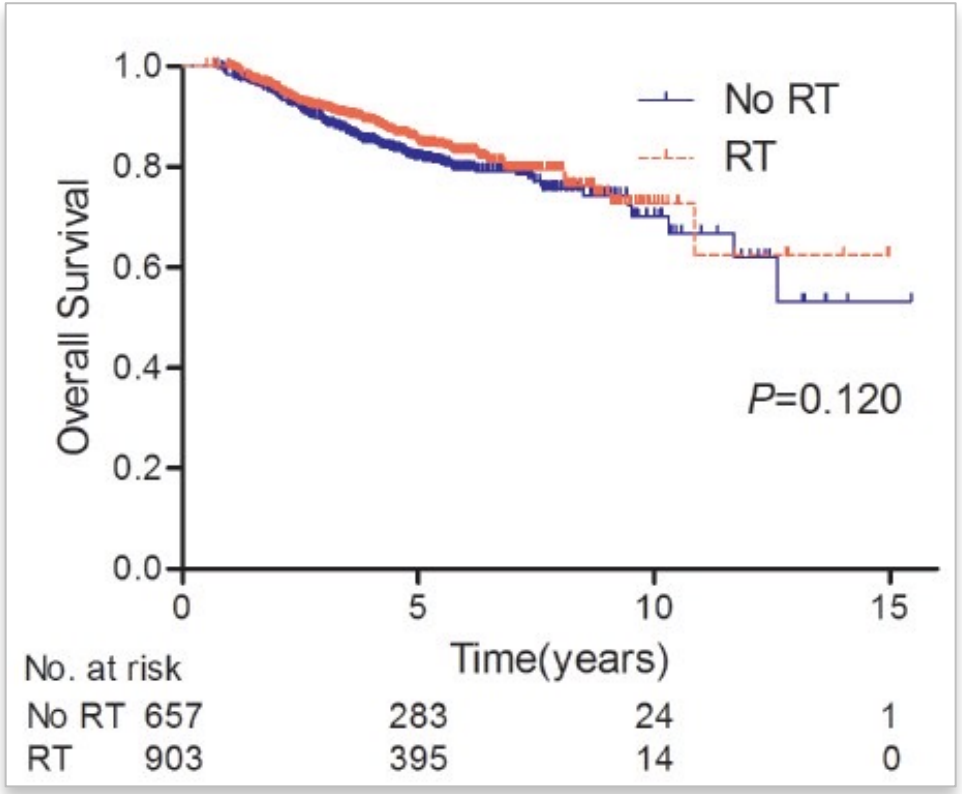
10283 cT1-3N1 postmastectomy pts
National Cancer Database

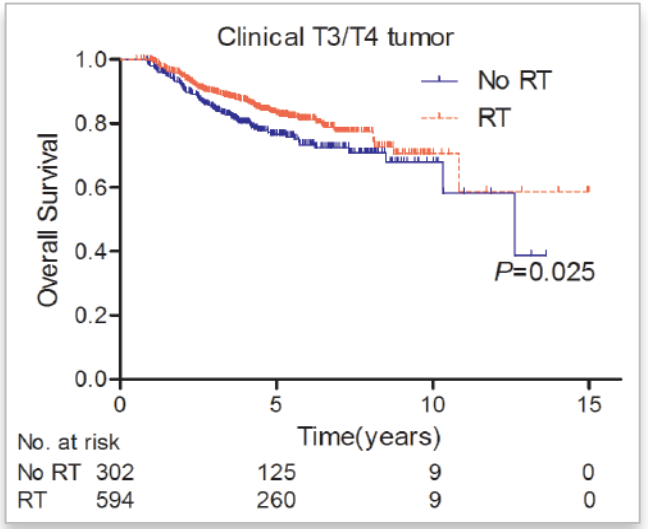
Rusthoven, Ann Oncol 2016

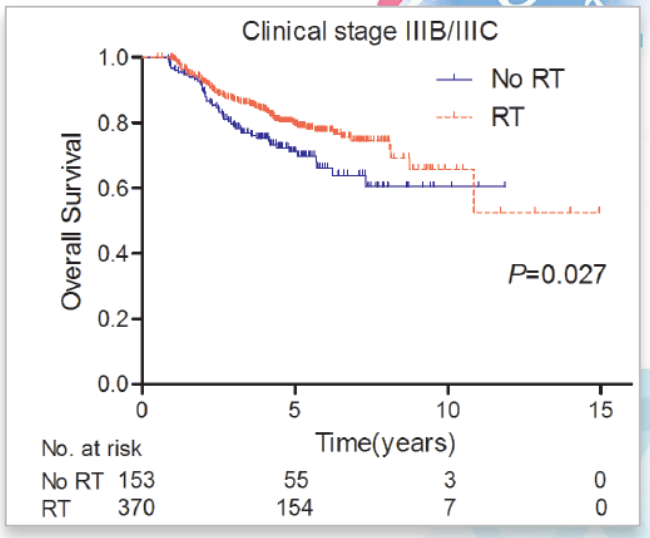
- **The role of postmastectomy radiotherapy in clinically node positive, stage II-III breast cancer patients with pathological negative nodes after neoadjuvant chemotherapy: an analysis from the NCDB**

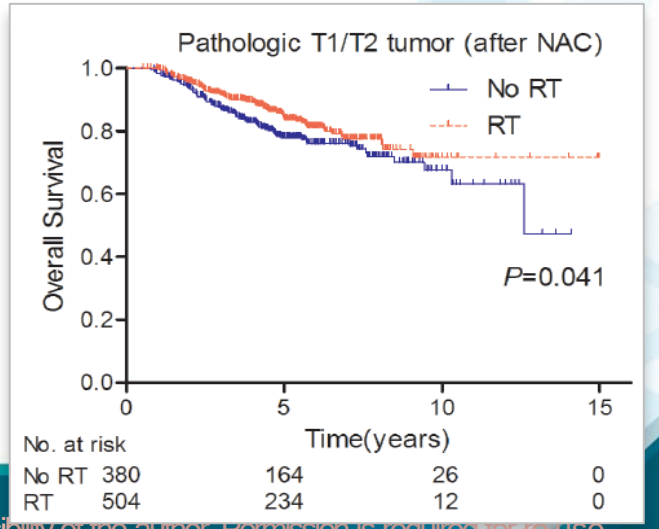
1560 st. st. II(N+)-III ypN_0 pts
National Cancer Database

Post-PST PMRT improves outcomes - in high-risk patients only?





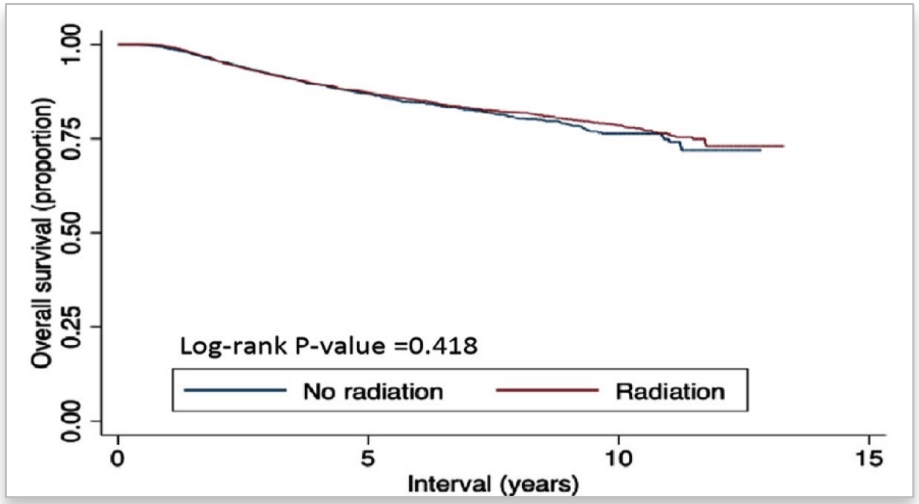




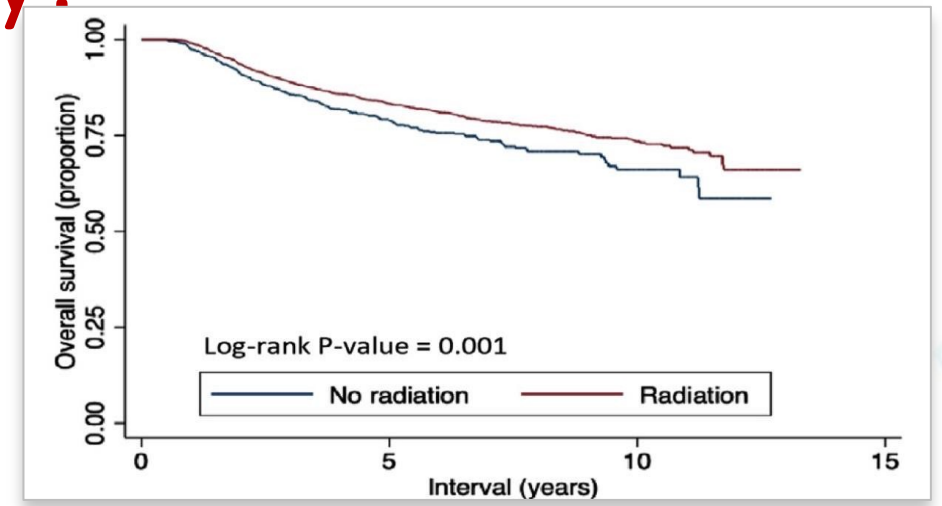
1560 st. st. II(N+)-III ypN_0 pts
National Cancer Database

Liu, Oncotarget 2016

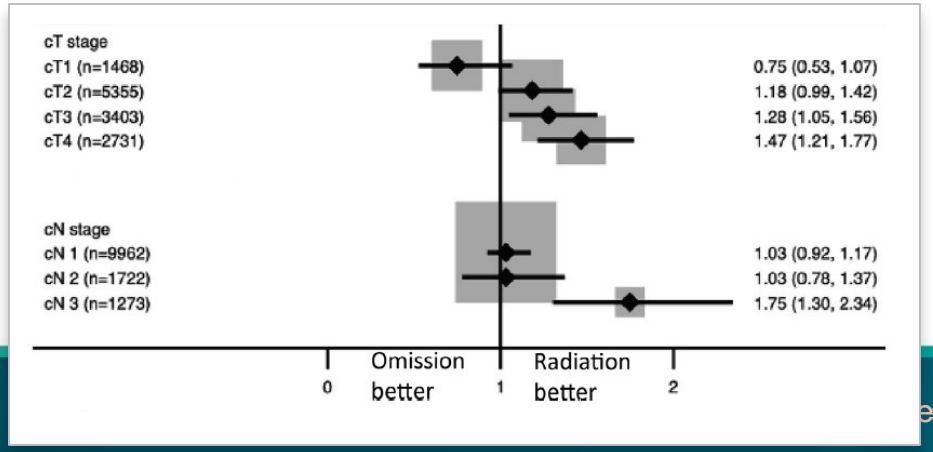
Post-PST PMRT improves outcomes - in high-risk patients only?



all patients



non-"NSABP B-51-like" patients



14690 st. $cT_{1\text{-}4}N_{1\text{-}3}$ ypN_0 pts
National Cancer Database

Haque, R&O 2021

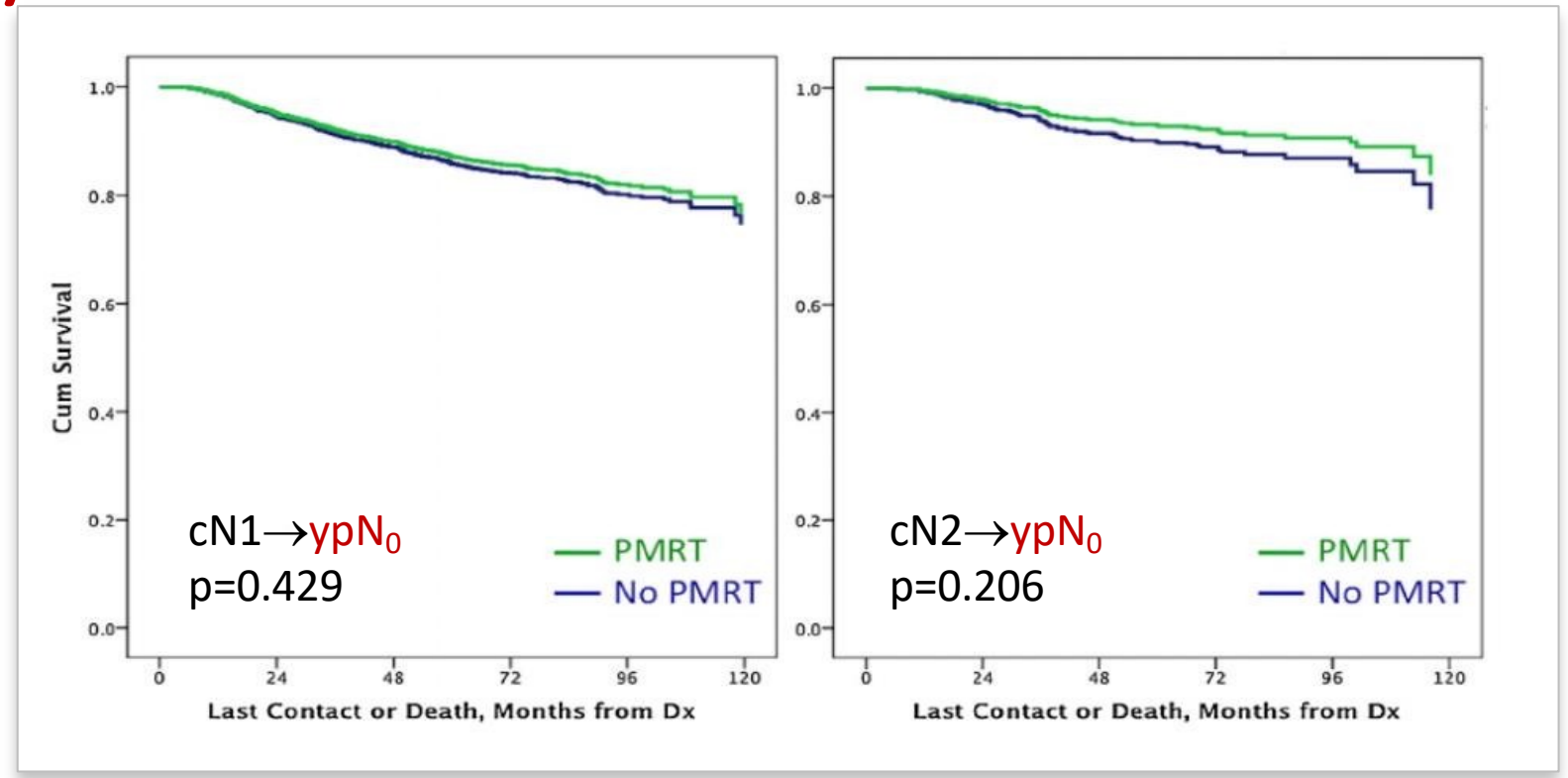
Post-PST PMRT improves outcomes –maybe?

- Post-mastectomy radiation therapy and overall survival after neoadjuvant chemotherapy

8321 cN+ pts (2004-2008)
- 6140 cN1
- 2181 cN2

National Cancer Database

Post-PST PMRT improves outcomes –maybe?



8321 cN+ pts (2004-2008)
- 6140 cN1
- 2181 cN2

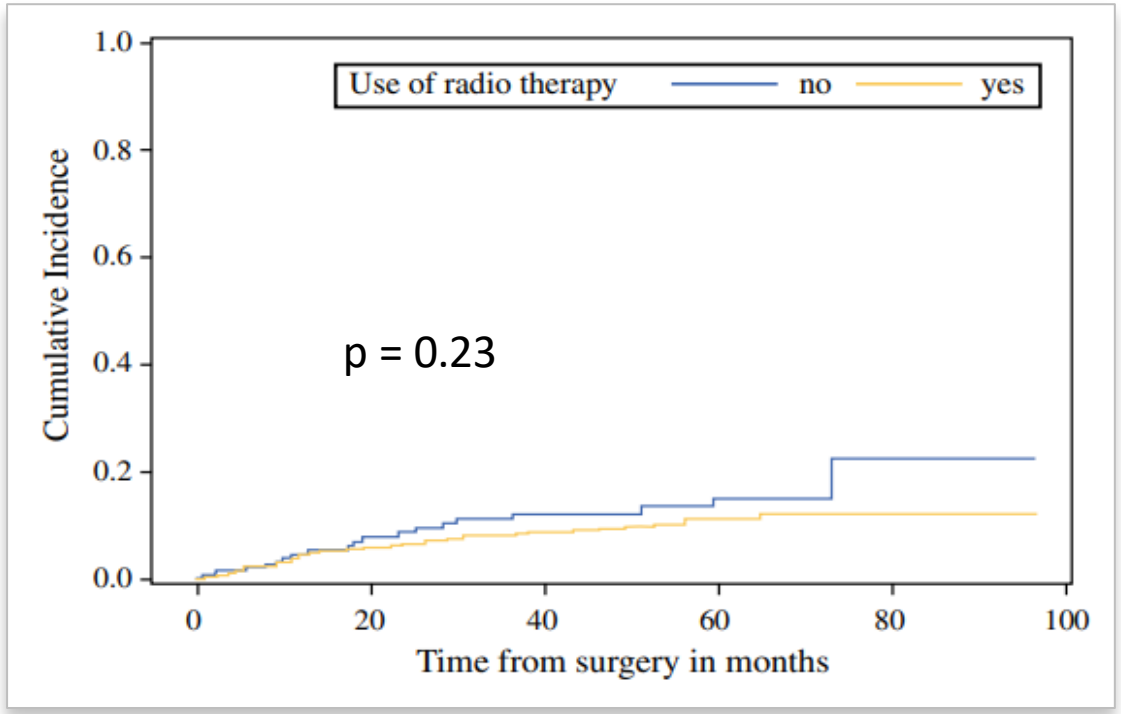
National Cancer Database

Kantor, J Surg Oncol 2017

- Post-Mastectomy Radiotherapy After Neoadjuvant Chemotherapy in Breast Cancer: A Pooled Retrospective Analysis of Three Prospective Randomized Trials

817 post-PST, postmastectomy pts
non-inflammatory BC
GeparTrio, GeparQuattro, GeparQuinto-trials

Post-PST PMRT improves outcomes
- in some patients?



LRR

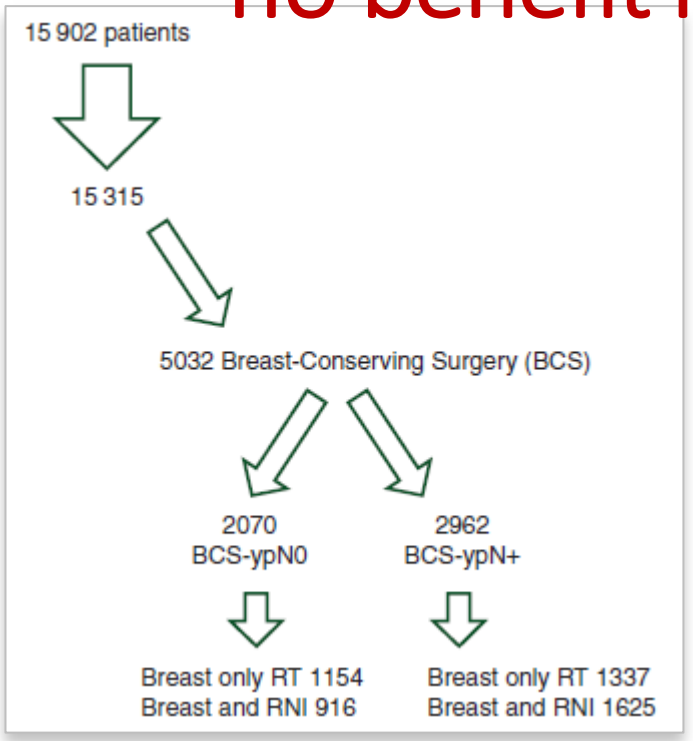
multivariate analysis

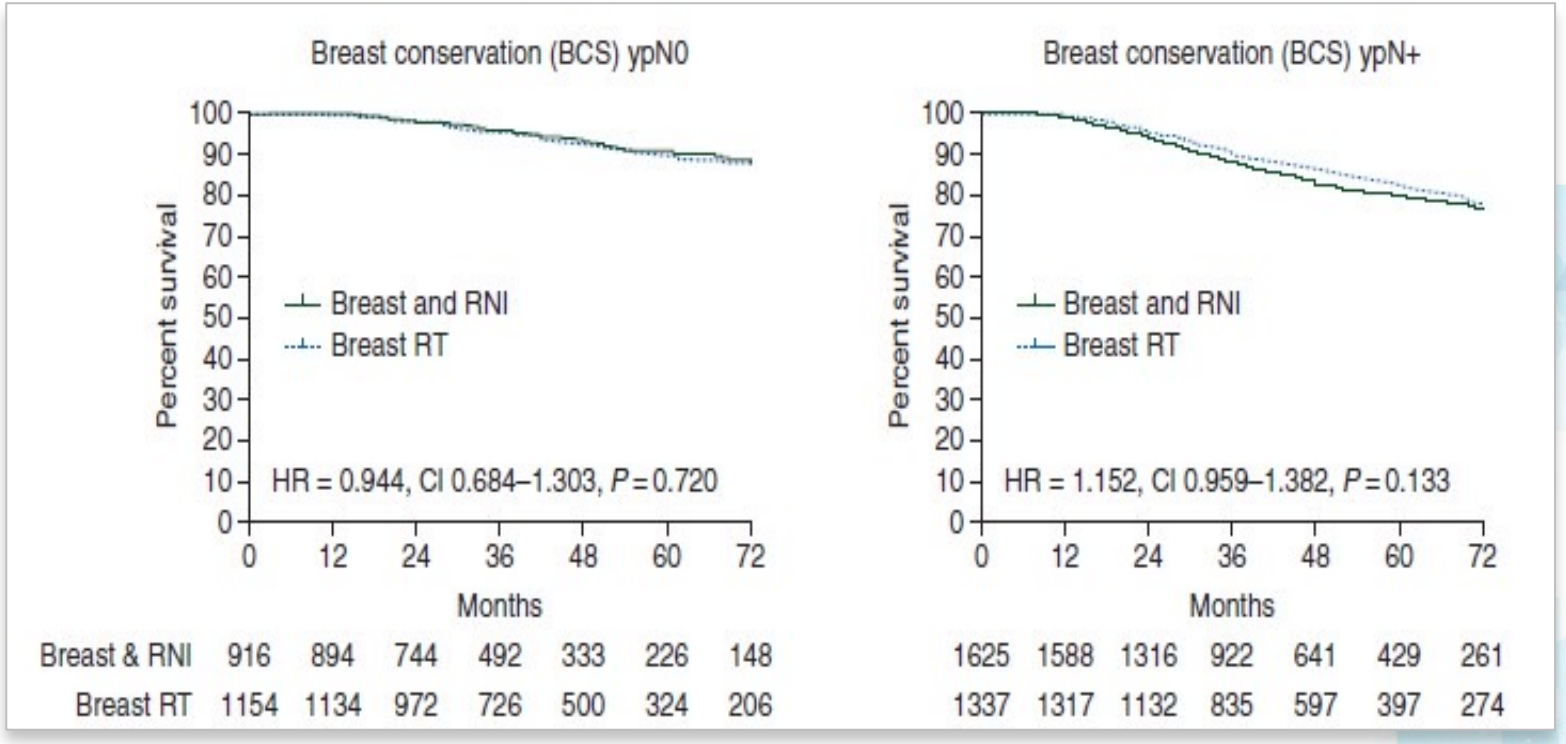
Parameter	LRR [HR (95% CI)]	LRR *p* value
Age (years)		0.34
≥ 50	1.0 (Ref)	
40–49	0.7 (0.4–1.21)	0.2
< 40	1.08 (0.54–2.15)	0.82
Histology		0.31
Ductal invasive	1.0 (Ref)	
Lobular invasive	0.64 (0.28–1.43)	0.28
Other	0.42 (0.09–1.88)	0.26
Grading		0.51
G1	1.0 (Ref)	
G2	0.93 (0.23–3.79)	0.91
G3	1.25 (0.3–5.17)	0.76
ER-negative	4.5 (2.42–8.37)	< 0.01
PR-negative	0.52 (0.29–0.96)	0.04
HER2/neu-positive	0.58 (0.32–1.06)	0.08
cT		0.71
cT1	1.0 (Ref)	
cT2	1.59 (0.39–6.57)	0.52
cT3	1.45 (0.35–6.04)	0.61
cT4a–c	2.13 (0.45–10.11)	0.34
cN+	2.14 (1.19–3.87)	0.01
Study number		0.53
GeparQuinto	1.0 (Ref)	
GeparTrio	0.78 (0.43–1.41)	0.41
GeparQuattro	0.7 (0.36–1.36)	0.29
pCR [ypT0 ypN0]	0.38 (0.11–1.29)	0.12
Radiotherapy	0.51 (0.27–1.0)	0.05

817 post-PST, postmastectomy pts
non-inflammatory BC
GeparTrio, GeparQuattro, GeparQuinto-trials

Krug, Ann Surg Oncol 2019

RNI in post-PST BCT pts
- no benefit regardless of ypN stage

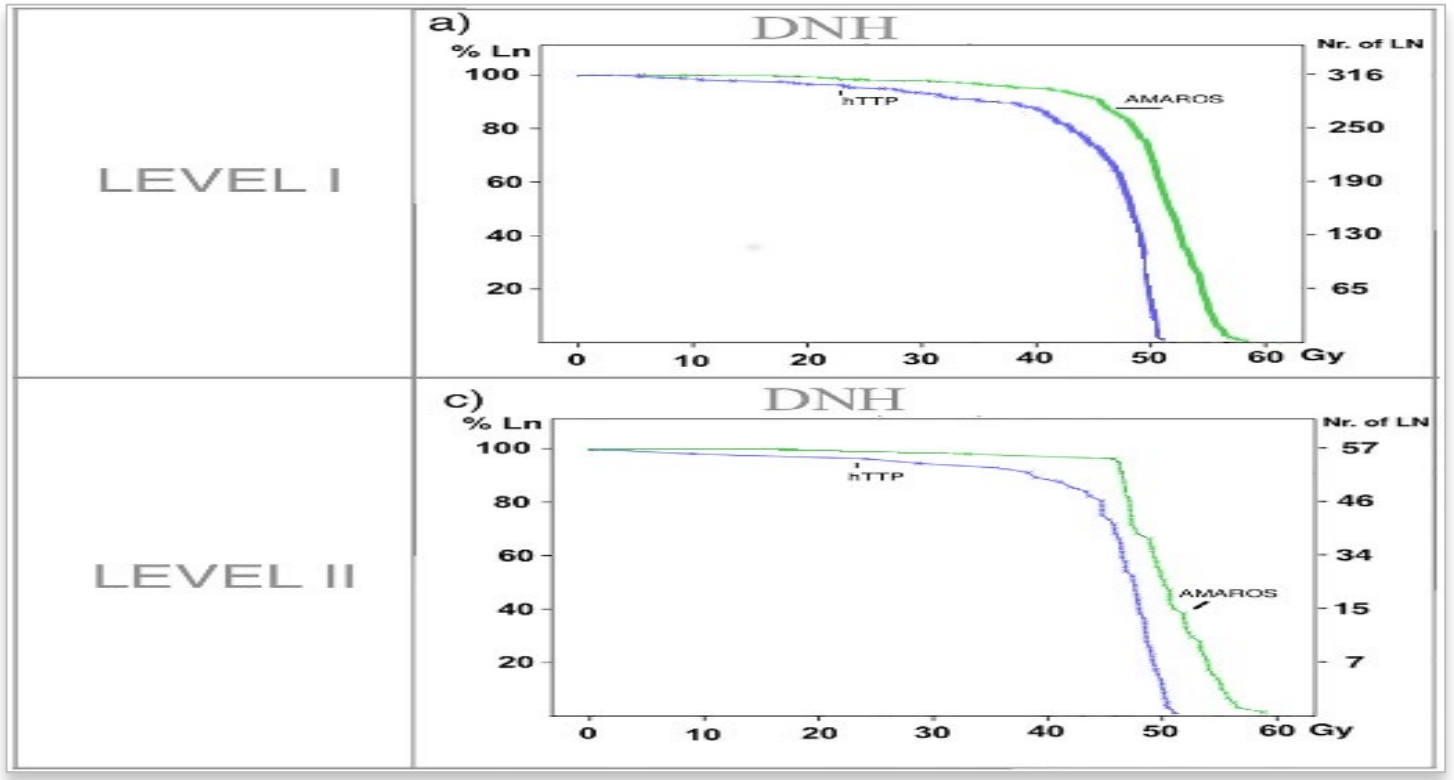




5032 cT1-3N1 BCT pts
National Cancer Database

Rusthoven, Ann Oncol 2016

Post-BCS RT - axilla coverage



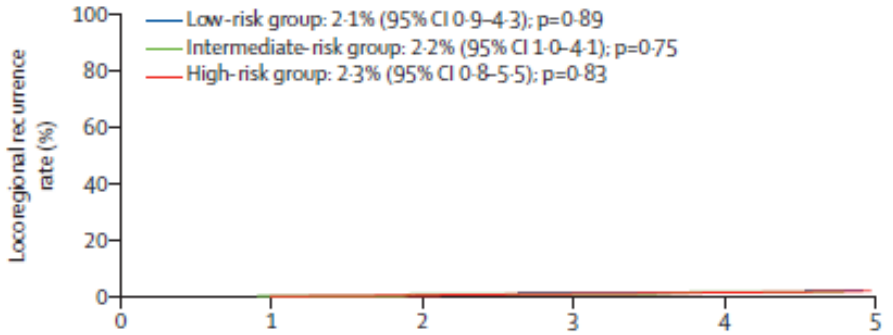
ACOSOG Z0011 – „high tangents"

Borm, R&O 2020

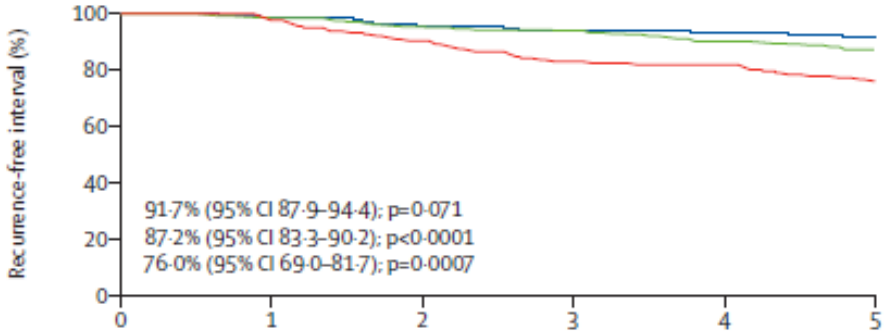
De-escalation of radiotherapy after primary chemotherapy in cT1–2N1 breast cancer (RAPCHEM; BOOG 2010–03): 5-year follow-up results of a Dutch, prospective, registry study

Sabine R de Wild, Linda de Munck, Janine M Simons, Janneke Verloop, Thijs van Dalen, Paula H M Elkhuizen, Ruud M A Houben, A Elise van Leeuwen, Sabine C Linn, Ruud M Pijnappel, Philip M P Poortmans, Luc J A Strobbe, Jelle Wesseling, Adri C Voogd, Liesbeth J Boersma

	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	



LRR



RFI

de Wild, Lancet Oncol 2022, Boersma, R&O 2020

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

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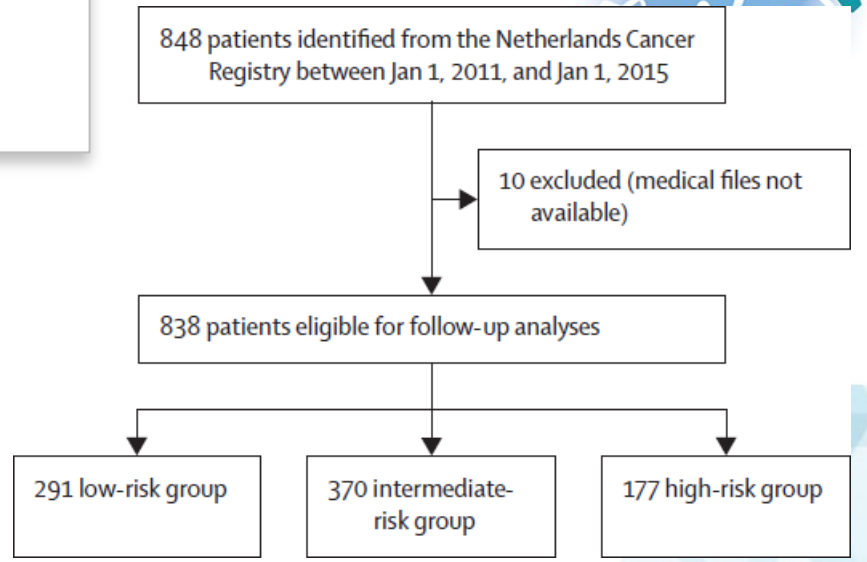

post-BCS (WBRT) – 14 pts

post-mastectomy (no RT) – 6 pts

no RNI – 20 pts

	Low-risk group (n=291)
Axillary surgery	..
ALND	234 (80%)
SLNB before primary chemotherapy, no ALND	16 (5%)
SLNB or MARI after primary chemotherapy, no ALND	41 (14%)

Wild, Lancet Oncol 2022, Boersma, R&O 2020


supremo
MRC
EORTC
BIG
TROG
MRC SUPREMO
(BIG 2-04)
Selective Use of Postoperative
Radiotherapy aftEr MastectOmy
Phase III randomised trial of chest wall RT
in intermediate- risk breast cancer
Kunkler I, Canney P, Price A, Anderson N, Dixon J, Sainsbury
R, Aird E, Thomas G, Bowman A, Thomas J, Bartlett J, Devine
I, Denvir M, McDonagh T, Russell N, Cairns J, Boon Chua,
Karlsson P, Northridge D, Scullion R, van Tienhoven G,
Velikova G, Walker A

awaited!!!

Do ALL N1 patients require RT???

any recurrence

Nodal status					
pN0	194/1093	228/1095	−18·3	101·9	0·84 (0·69–1·01)
pN1–3	603/2812	682/2910	−31·6	311·0	0·90 (0·81–1·01)
pN4+	502/1219	553/1232	−32·4	239·5	0·87 (0·77–0·99)

breast cancer mortality

Nodal status					
pN0	126/1093	162/1095	−16·4	68·6	0·79 (0·62–1·00)
pN1–3	481/2812	543/2910	−23·7	247·3	0·91 (0·80–1·03)
pN4+	437/1219	483/1232	−32·3	210·5	0·86 (0·75–0·98)

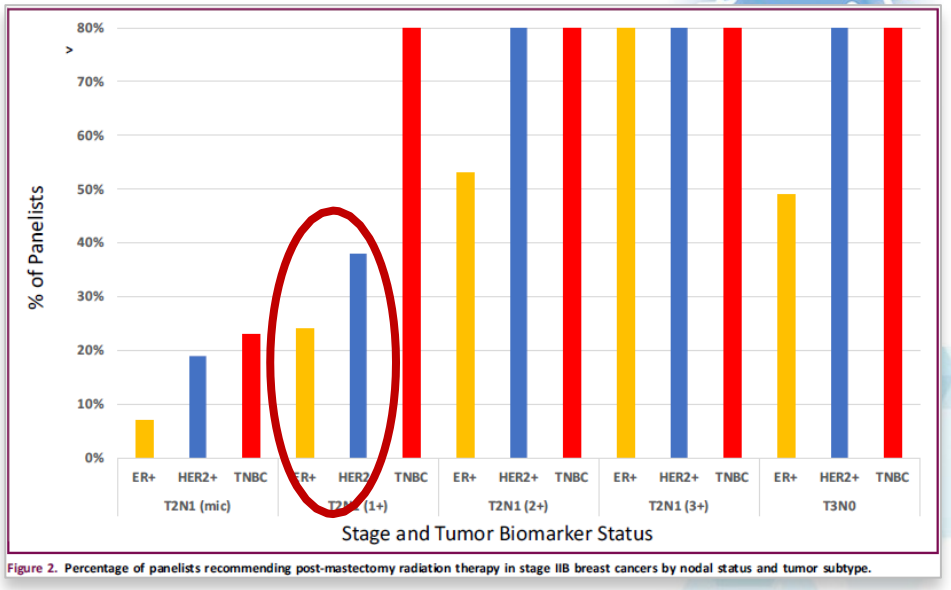

Figure 2. Percentage of panelists recommending post-mastectomy radiation therapy in stage IIB breast cancers by nodal status and tumor subtype.

PMRT is recommended for high-risk disease (including involved resection margins, ≥4 involved ALNs and T3-T4 tumours) independent of the nodal status. It should also be considered in patients with intermediate-risk features (e.g. lymphovascular invasion, age), including those with 1-3 positive ALNs.[31]

EBCTCG, Lancet 2023; Curigliano, Ann Oncol 2023; Loibl, Ann Oncol 2024

so let's have a look on B-51…

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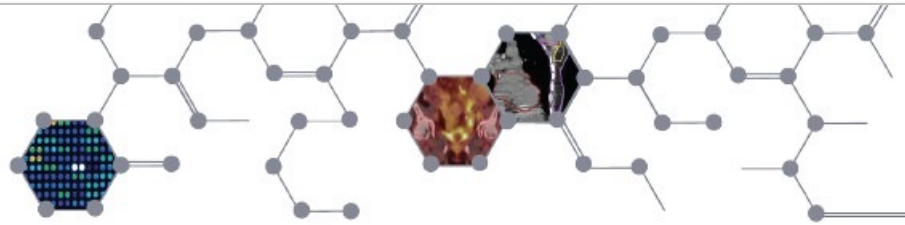
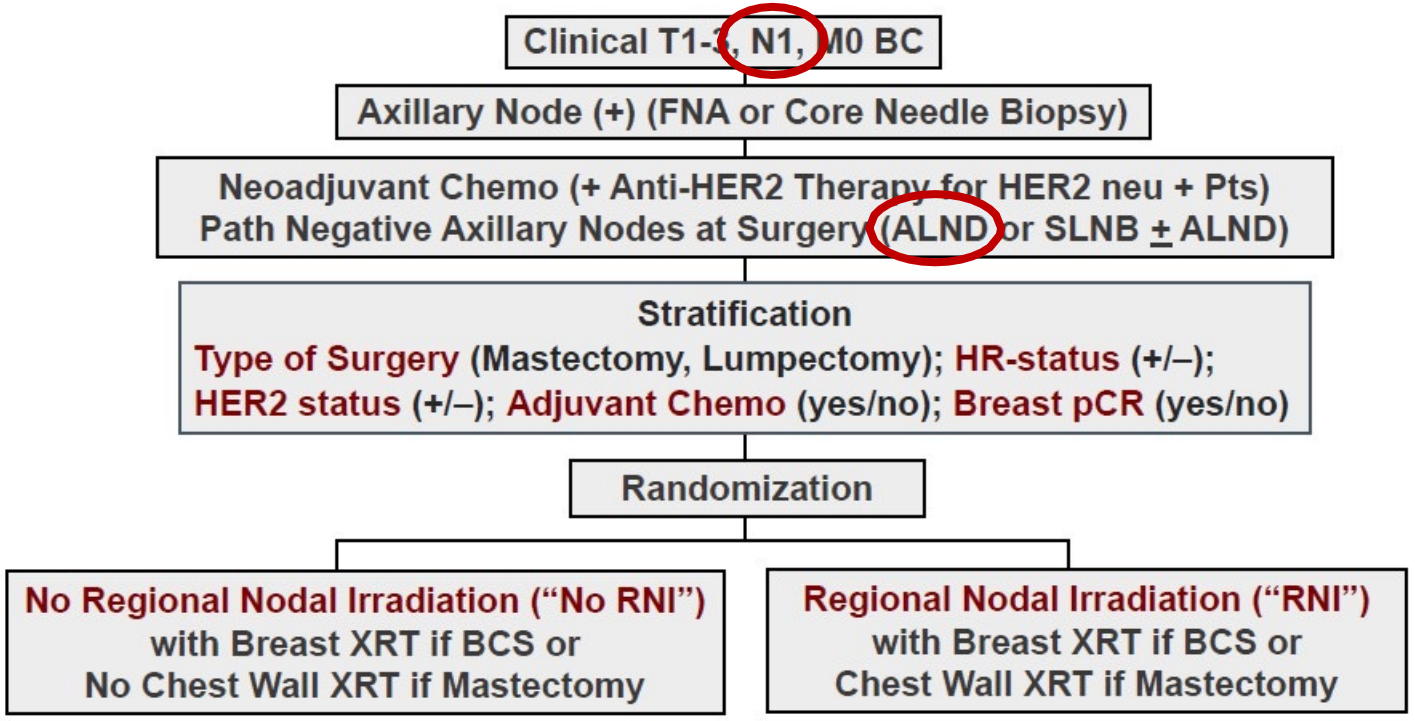


DEC 5-9, 2023
SAN ANTONIO BREAST CANCER SYMPOSIUM

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 Bandos[2], Julia R. White[3*], Thomas B. Julian[4], Atif J. Khan[5], Simona F. Shaitelman[6], Mylin A. Torres[7], Frank A. Vicini[8], Patricia A. Ganz[9], Susan A. McCloskey[10], Peter C. Lucas[11,12], Nilendu Gupta[3], X. Allen Li[13], Beryl McCormick[5], Saumil Gandhi[6], Rahul D. Tendulkar[14], Vivek S. Kavadi,[15], Masahiko Okamoto[16], Samantha Andrews Seaward[17], William J. Irvin, Jr.[18], Jolinta Lin [7], Robert Mutter[19], Thierry M. Muanza[20], Andrew A. Muskovitz[21], Reshma Jagsi[22], Anna C. Weiss[23,24], Walter J. Curran, Jr.[7], and Norman Wolmark[12]

Study Schema



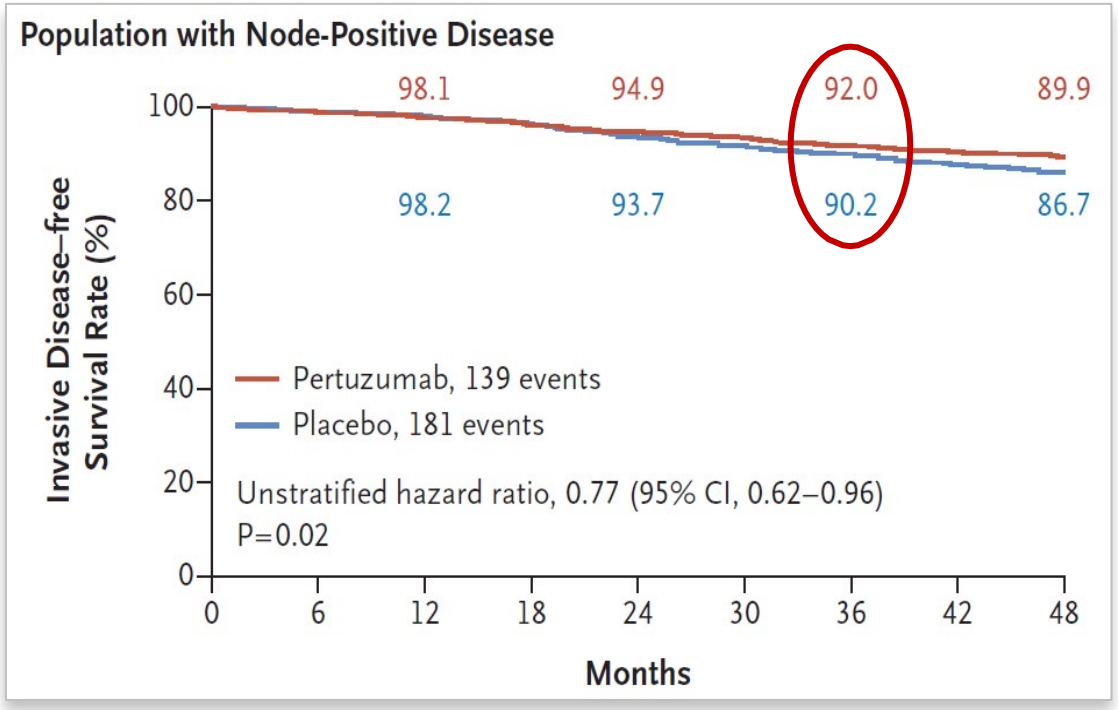
FNA: Fine Needle Aspiration; ALND: Axillary Lymph Node Dissection; SLNB: Sentinel Lymph Node Biopsy; XRT: Radiation

Statistical Considerations

- Primary endpoint – invasive BC recurrence-free interval (IBCRFI)
- Study was designed to have 80% power to detect 35% reduction in annual IBCRFI rate (4.6% abs. risk reduction in 5-yr cumulative rate)
- Per protocol, final analysis was to occur after 172 events or 10 years after study initiation.
- Here we report the time-driven analysis, prespecified in the protocol
- Definitive analysis was based on the intent-to-treat principle
- Patients were analyzed as randomized, regardless of eligibility or protocol compliance
- Patients with no follow-up or not at risk for recurrence were excluded

How much is needed to approve a new drug???

APHINITY



FDA Approves Genentech's Perjeta (Pertuzumab) for Adjuvant Treatment of Specific Type of Early Breast Cancer

South San Francisco, CA -- December 20, 2017 -- Genentech, a member of the Roche Group (SIX: RO, ROG; OTCQX: RHHBY), today announced the U.S. Food and Drug Administration (FDA) has approved Perjeta ® (pertuzumab), in combination with Herceptin® (trastuzumab) and chemotherapy (the Perjeta-based regimen), for adjuvant (after surgery) treatment of HER2-positive early breast cancer (EBC) at high risk of recurrence.

von Minckwitz, NEJM 2017

Patient Population

- From Sep 2013 to Dec 2020, 1,641 patients were randomized
  - 39 patients excluded: 37 no follow-up; 2 not at risk for the primary endpoint
- 1602 patients were analyzed for overall survival
  - 46 patients excluded due to no clinical follow-up
- 1556 patients (No RNI: 784; RNI: 772) were analyzed for disease-related endpoints
- **Median Follow-up Time: 59.5 months (IQR 40.7-74.1)**

Baseline Characteristics (1)

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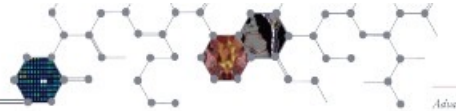
Characteristic		No RNI (%) n=821	RNI (%) n=820
Age	**Median**	52 years	52 years
	≤ 49 yrs	40	41
	50-59 yrs	32	33
	≥ 60 yrs	28	26
Race	Asian	8	6
	Black/African American	17	18
	White	69	69
	Unknown/Other	6	6
Ethnicity	Hispanic or Latino	14	14
	Not Hispanic or Latino	83	82
	Unknown	3	3
Clinical Tumor Size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

Baseline Characteristics (2)



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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

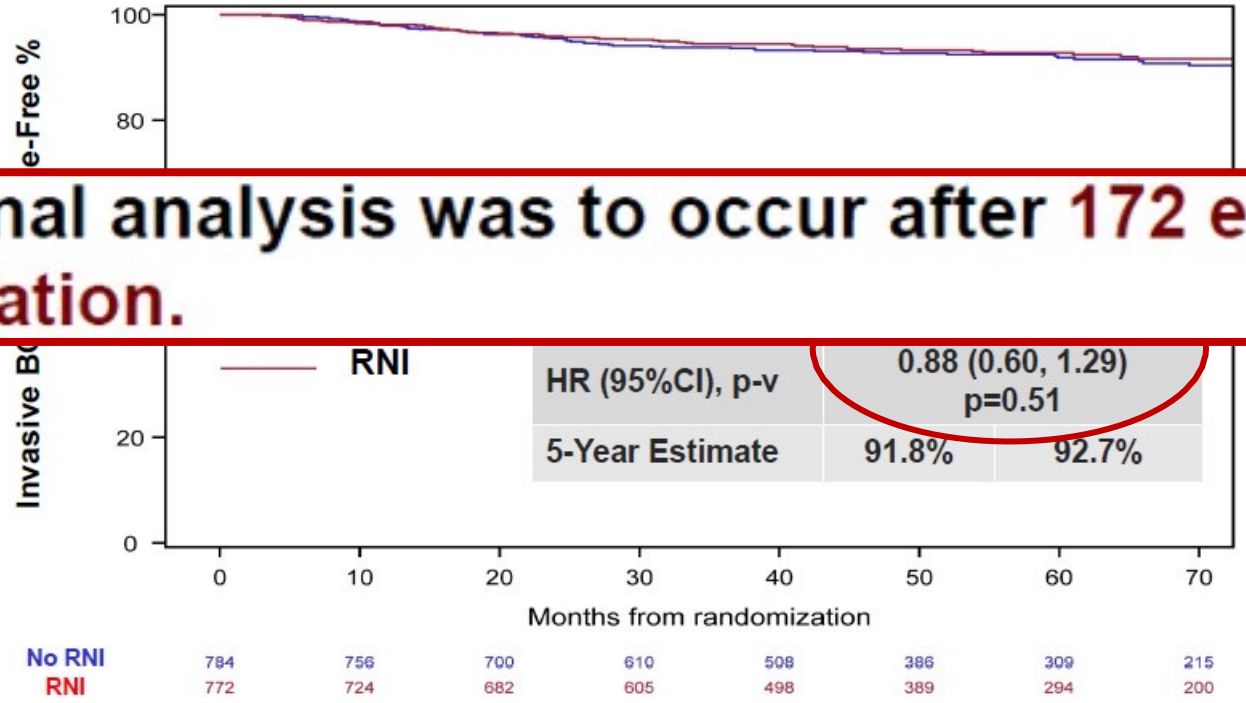
Baseline Characteristics (2)

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

patients, who had NO axillary treatment:

Primary Endpoint

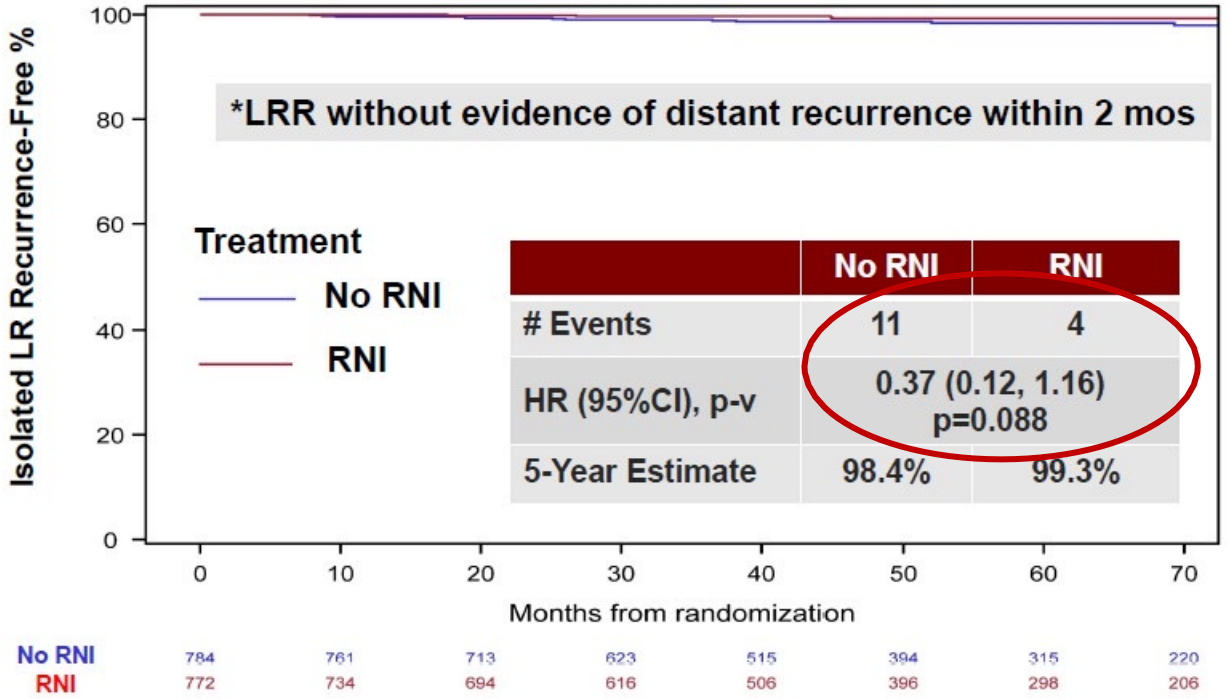
Invasive Breast Cancer Recurrence-free Interval (IBCRFI)



Per protocol, final analysis was to occur after 172 events or 10 years after study initiation.

Secondary Endpoints

Isolated Loco-Regional Recurrence-free Interval (ILRRFI)*



	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%

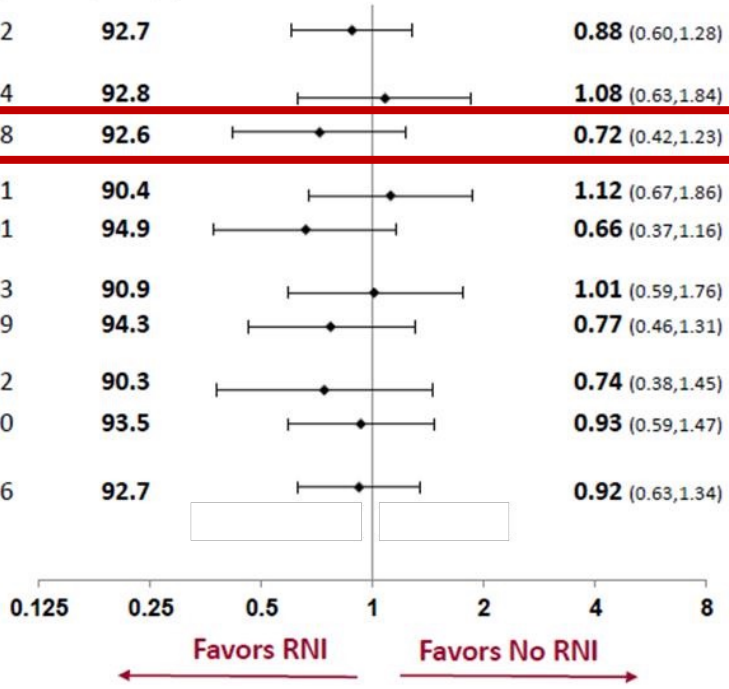
Secondary Endpoints

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

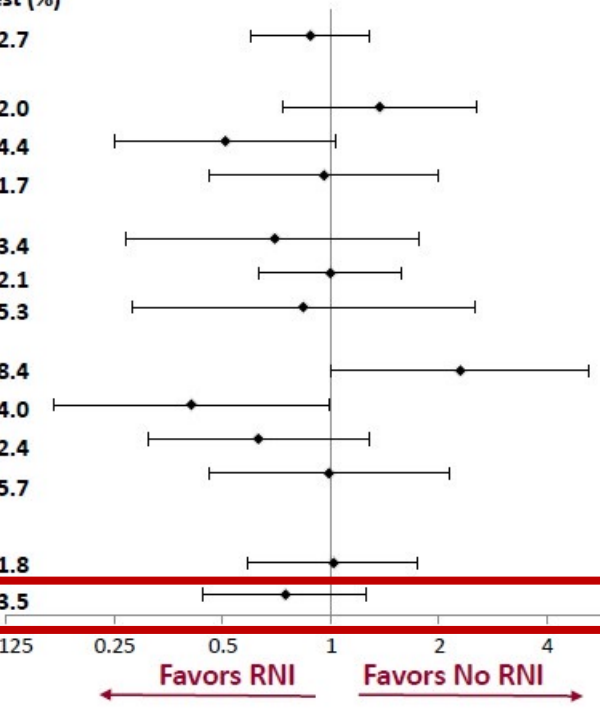
IBCRFI – Subgroup Analysis by Stratification Factors

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)	
Surgery	Lumpectomy	26/454	**93.5**	28/454	**92.8**	**1.08** (0.63,1.84)	**0.28**
	Mastectomy	33/330	**89.5**	22/318	**92.6**	**0.72** (0.42,1.23)	
ER/PR	Negative	28/367	**91.7**	31/371	**90.4**	**1.12** (0.67,1.86)	**0.17**
	Positive	31/417	**92.1**	19/401	**94.9**	**0.66** (0.37,1.16)	
HER2	Negative	25/342	**92.6**	26/343	**90.9**	**1.01** (0.59,1.76)	**0.47**
	Positive	34/442	**91.3**	24/429	**94.3**	**0.77** (0.46,1.31)	
pCR breast	No	20/173	**87.8**	15/172	**90.3**	**0.74** (0.38,1.45)	**0.59**
	Yes	39/611	**93.0**	35/600	**93.5**	**0.93** (0.59,1.47)	
Adjuvant Chemotherapy	No	57/780	**92.1**	50/766	**92.7**	**0.92** (0.63,1.34)	
	Yes	2/4		0/6			



IBCRFI – Exploratory Subgroup Analysis

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)	



Dec 5-9, 2023

HR $_{\text{mastectomy}}$ 0.72

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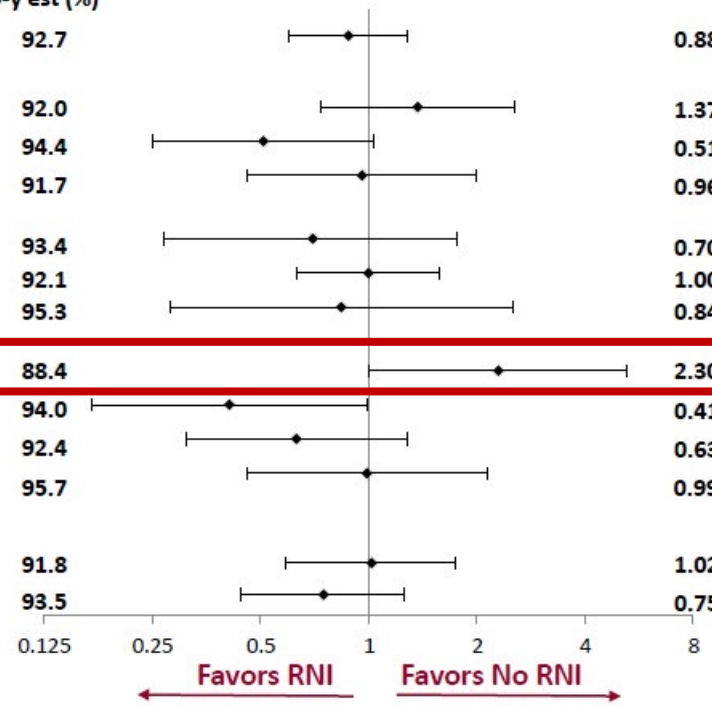
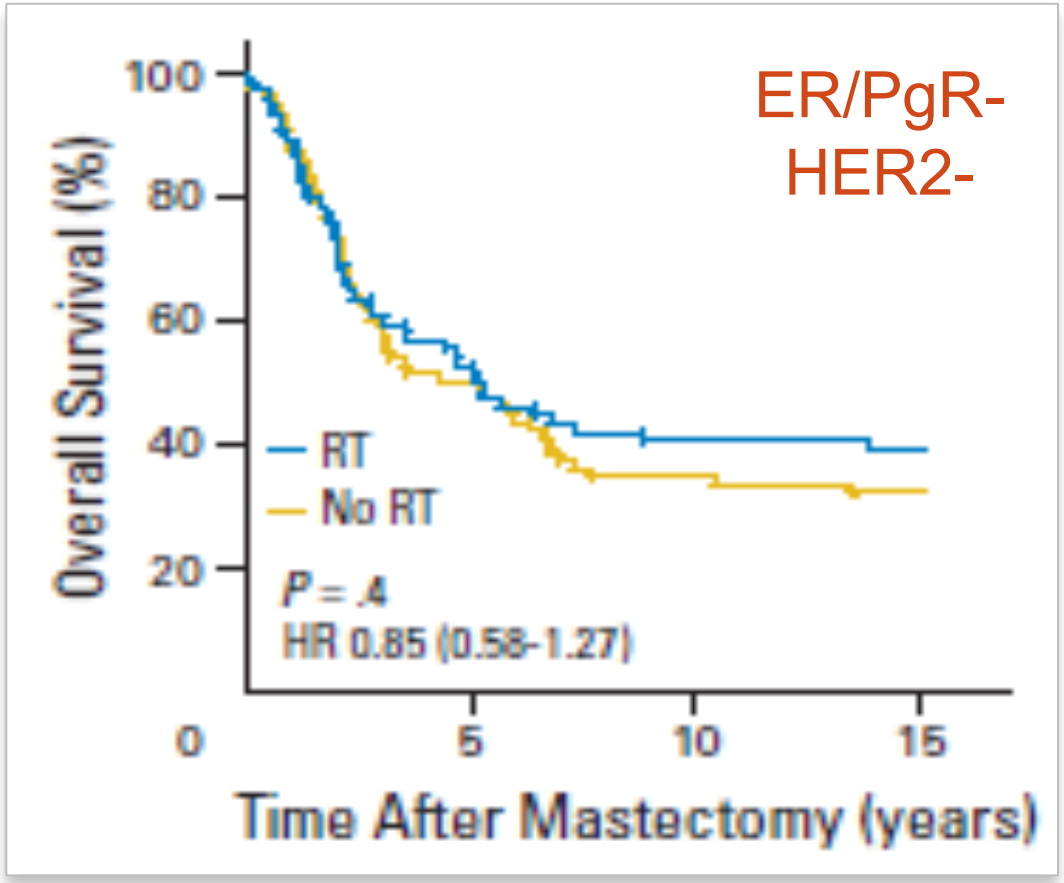


Lack of RT benefit in TNBC patients…

DBCG trials 82bc



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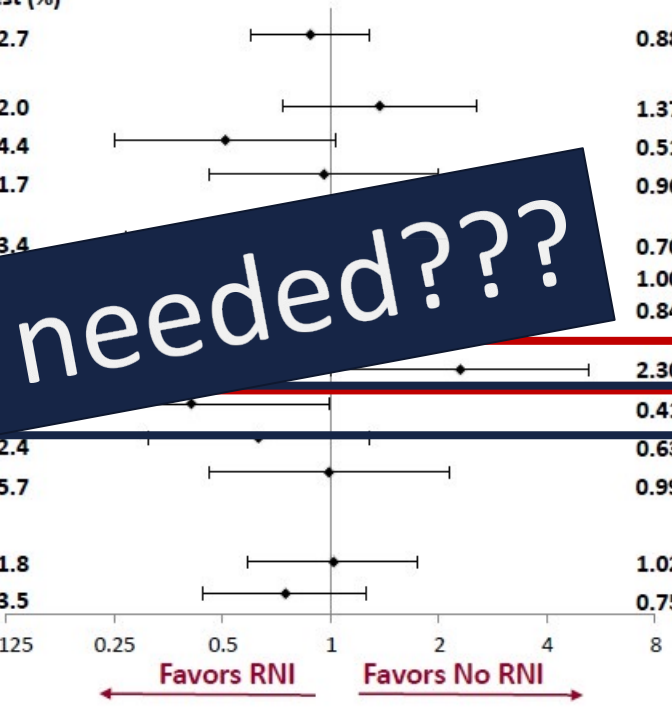
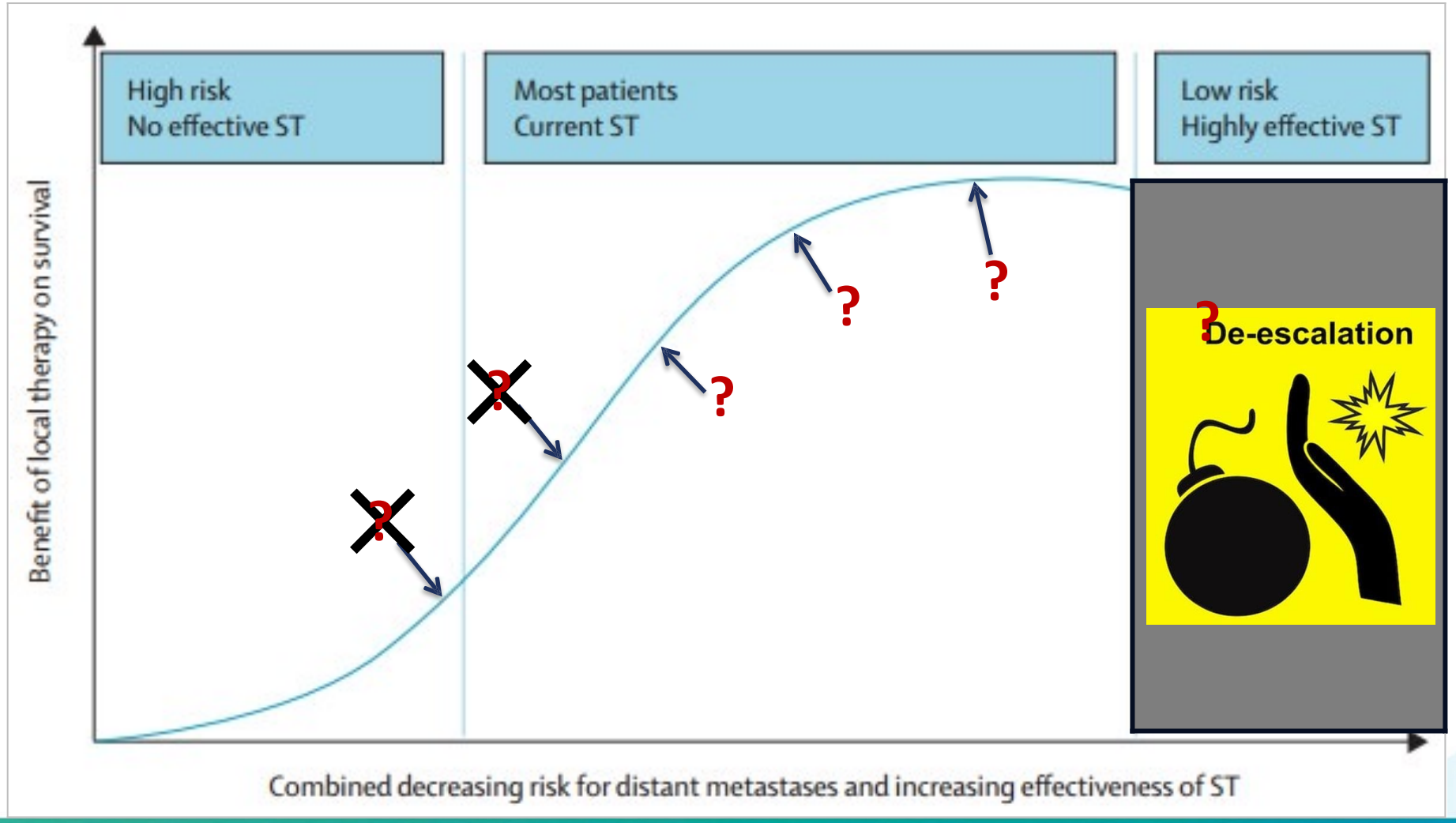


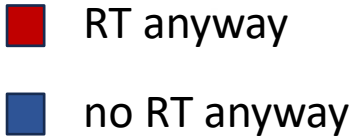
longer f/u needed???

So, where are we?



When should we plan radiation in the setting of pCR based ALSO on pre-treatment assessment?

- „non-NSABP-51-like" patients
  - T_4
  - N_{2-3}
- „NSABP-51-like" patients???
  - post-mastectomy
  - post-SLNB
  - residual disease in the breast (no pCR)
  - younger age
  - less aggressive phenotypes (luminal)
  - 1 involved LN/luminal (HER2+?)



ALND patients – do they need RNI?

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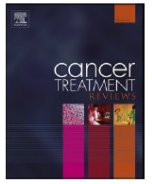


De-escalation of axillary irradiation for early breast cancer – Has the time come?

Elżbieta Senkus [a,*], Maria Joao Cardoso [b,c], Orit Kaidar-Person [d,e,f], Aleksandra Łacko [g,h], Icro Meattini [i,j], Philip Poortmans [k,l]

Recommendations for axillary lymph node dissection and irradiation of axillary nodal volumes in relation to pathological nodal status in cN+ patients converting to ycN0 after primary systemic therapy and sentinel lymph node biopsy /targeted axillary dissection.

	Risk group	ypN0	ypN0(i+), ypN1mi	ypN1 ≤2	ypN1 >3
PST (ChT or ET)	Low	Axillary RT: level I and II; consider RNI omission if WBI or chest wall RT	Axillary RT: level I and II	ALND, if not: axillary RT: level I and II	ALND + axillary RT: non-resected part up to level IV
	High	Axillary RT: level I-IV	Axillary RT: level I-IV	ALND + axillary RT: non-resected part up to level IV	ALND + axillary RT: non-resected part up to level IV

Risk group definition:

- Low Risk: ≤2 cN+ before PST AND complete response in the breast AND age >40
- High Risk: >2 cN+ before PST AND/OR TNBC AND/OR incomplete response in the breast AND/OR age <40.

extent of breast RT – issue for another big discussion…

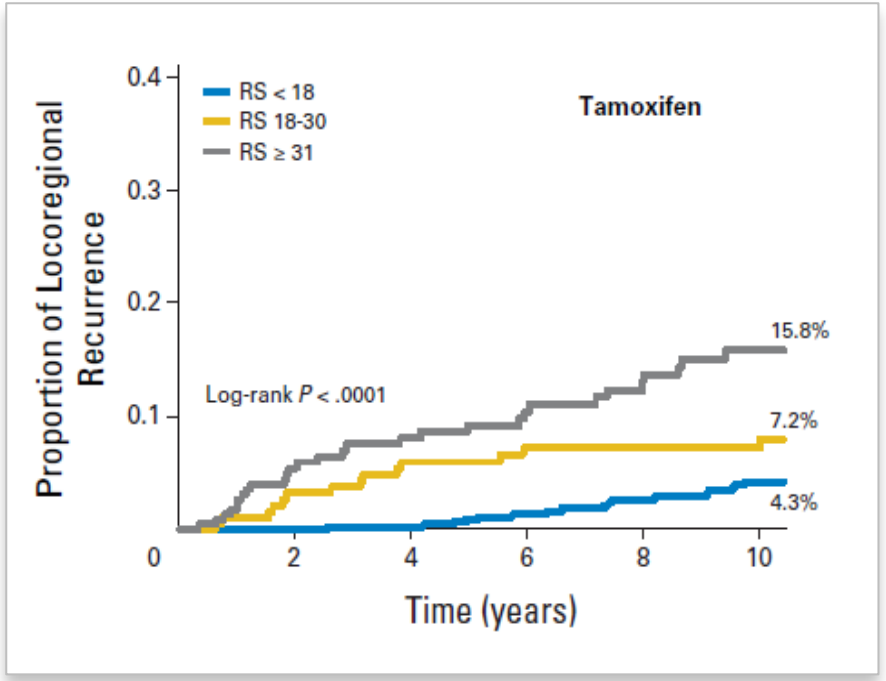
Elżbieta Senkus

Treatment of breast cancer – moving target

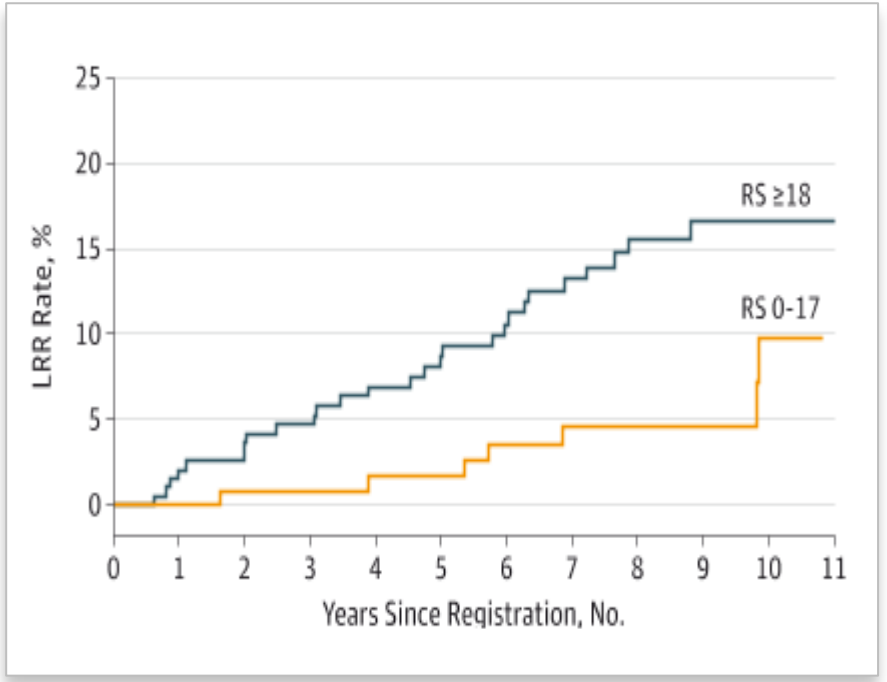
- immunotherapy
- CDK4/6 inhibitors
- new anti-HER2 agents
- …

Elżbieta Senkus

LRR risk is determined by biology



NSABP B-14 and B-20
N0



SWOG S8814
N+

and THAT will determine our decisions in the future!