Radiation therapy can be safely avoided in women age 50 or older with stage I non TNBC

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The Royal
Melbourne Hospital

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2024
Invasive Breast Cancer

NCCN Guidelines Index
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Discussion

LOCOREGIONAL TREATMENT OF cT1–3, cN0 or cN+, M0 DISEASE[a]: BREAST-CONSERVING SURGERY (BCS) FOLLOWED BY RT

WBRT ± boost[p] to tumor bed, and consider comprehensive regional nodal irradiation (RNI) in patients with central/medial tumors, pT3 tumors, or pT2 tumors and one of the following high-risk features: grade 3, extensive lymphovascular invasion (LVI), or hormone-receptor (HR)-negative.[s]

Negative axillary nodes →

WBRT ± boost[p] to tumor bed, and consider comprehensive regional nodal irradiation (RNI) in patients with central/medial tumors, pT3 tumors, or pT2 tumors and one of the following high-risk features: grade 3, extensive lymphovascular invasion (LVI), or hormone-receptor (HR)-negative.[s]
or
Consider APBI/PBI in selected patients who are low risk (category 1)[p,q]
or
Consider omitting breast irradiation if adjuvant endocrine therapy is planned and following criteria are met (category 1):
1) ≥70 y, HR+, HER2-negative, cN0, pT1[r,s]
2) ≥65 y, HR+, HER2-negative, pN0, pT ≤3 cm[s]

• WBRT planned

consider compreher
any portion of the u

≥4 positive[o] axillary nodes →

WBRT ± boost[p] to tumor bed (category 1) + com
including any portion of the undissected axilla a

“Safely avoided”

1. without harm or injury:
2. without risk or danger:
3. in a way that protects from loss, damage, or harm:
4. without likelihood of being wrong;


DANGER
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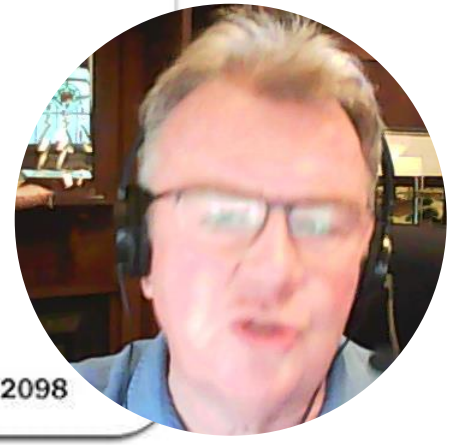


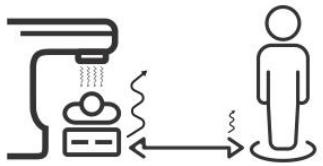
Presumably Radiation is safe...

RADIATION SAFETY:
What is ALARA?
As Low as Reasonably Achievable

1 Time

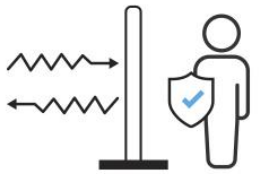
Minimize the time spent near a radiation source to only what it takes to get the job done

2 Distance



Maximize your distance from a radiation source as much as you can. The greater the distance, the lower the dose

3 Shielding



Put something between you and the radiation source.

Balancing risks

Risks of RT

Risks of no RT

Complications of radiation therapy:

Acute toxicity:

- Burned skin
- Moist desquamation
- Pain
- Dry swallow
- Tickly cough
- Fatigue
- Disruption to daily life

More Complications:

Acute toxicity:

- Burned skin
- Moist desquamation
- Pain
- Dry swallow
- Tickly cough
- Fatigue
- Disruption to daily life

Medium term toxicity:

- Fibrosis
- Fat necrosis
- Shape distortions
- Chronic pain
- Psychological impact
- Reduced upper limb mob
- Financial and social toxi

Even More Complications:

Acute toxicity:

- Burned skin
- Moist desquamation
- Pain
- Dry swallow
- Tickly cough
- Fatigue
- Disruption to daily life

Medium term toxicity:

- Fibrosis
- Fat necrosis
- Shape distortions
- Chronic pain
- Psychological impact
- Reduced upper limb mobility
- Financial and social toxicity

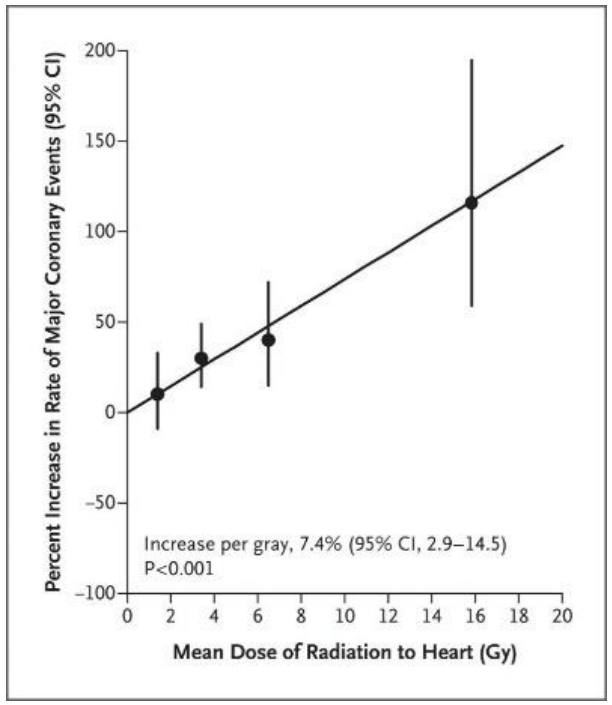
Second cancers:

- Lung
- Esophagus
- Angiosarcoma

Longer term effects:

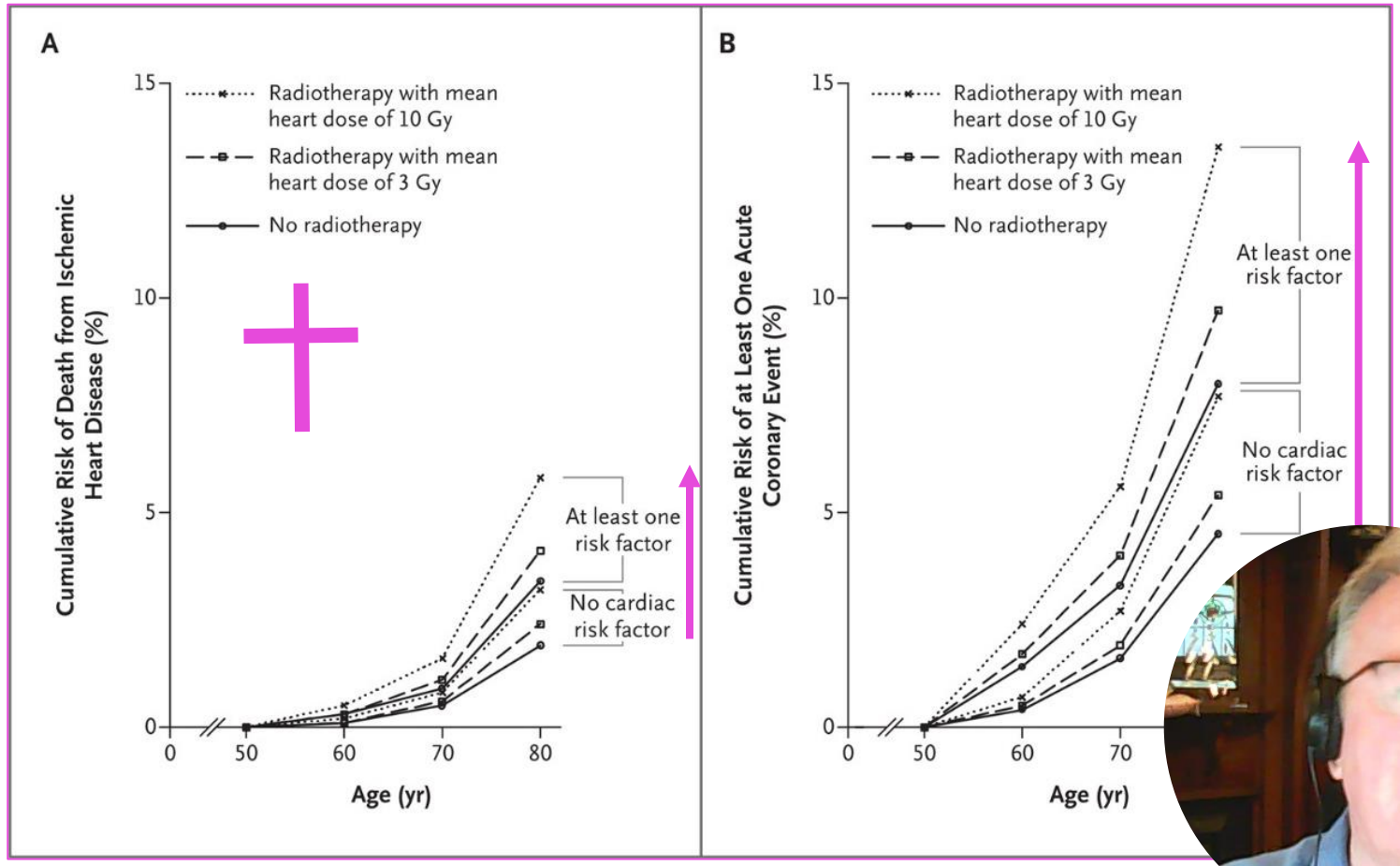
- Skin changes
- Telangiectasia
- Fibrosis
- Chronic pain
- Worry of re
- Less limb
- Brachial pl

And it does not stop there:



No "safe dose" of radiotherapy to the heart

Cardiac events and mortality increase with age and co-morbidities



Darby SC et al NEJM 2

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 randomised trials

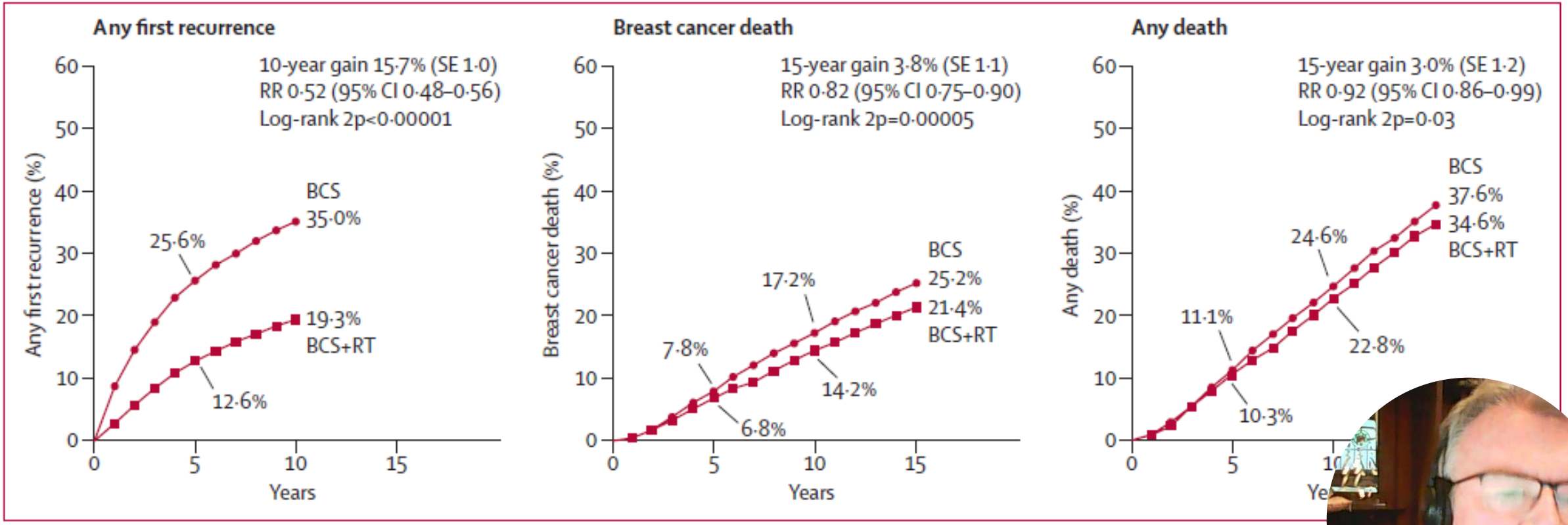
*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

Summary

Background After breast-conserving surgery, radiotherapy reduces recurrence and breast cancer death, but it may do so more for some groups of women than for others. We describe the absolute magnitude of these reductions according to various prognostic and other patient characteristics, and relate the absolute reduction in 15-year risk of breast cancer death to the absolute reduction in 10-year recurrence risk.

Lancet 2011;

Lancet 201


Any first recurrence
10-year gain 15·7% (SE 1·0)
RR 0·52 (95% CI 0·48–0·56)
Log-rank 2p<0·00001
Any first recurrence (%)
60
50
40
30
20
10
0
0
5
10
15
Years
BCS
35·0%
25·6%
19·3%
BCS+RT
12·6%
Breast cancer death
15-year gain 3·8% (SE 1·1)
RR 0·82 (95% CI 0·75–0·90)
Log-rank 2p=0·00005
Breast cancer death (%)
17·2%
BCS
25·2%
21·4%
BCS+RT
7·8%
14·2%
6·8%
Any death
15-year gain 3·0% (SE 1·2)
RR 0·92 (95% CI 0·86–0·99)
Log-rank 2p=0·03
Any death (%)
BCS
37·6%
34·6%
BCS+RT
24·6%
11·1%
22·8%
10·3%

Lancet 201

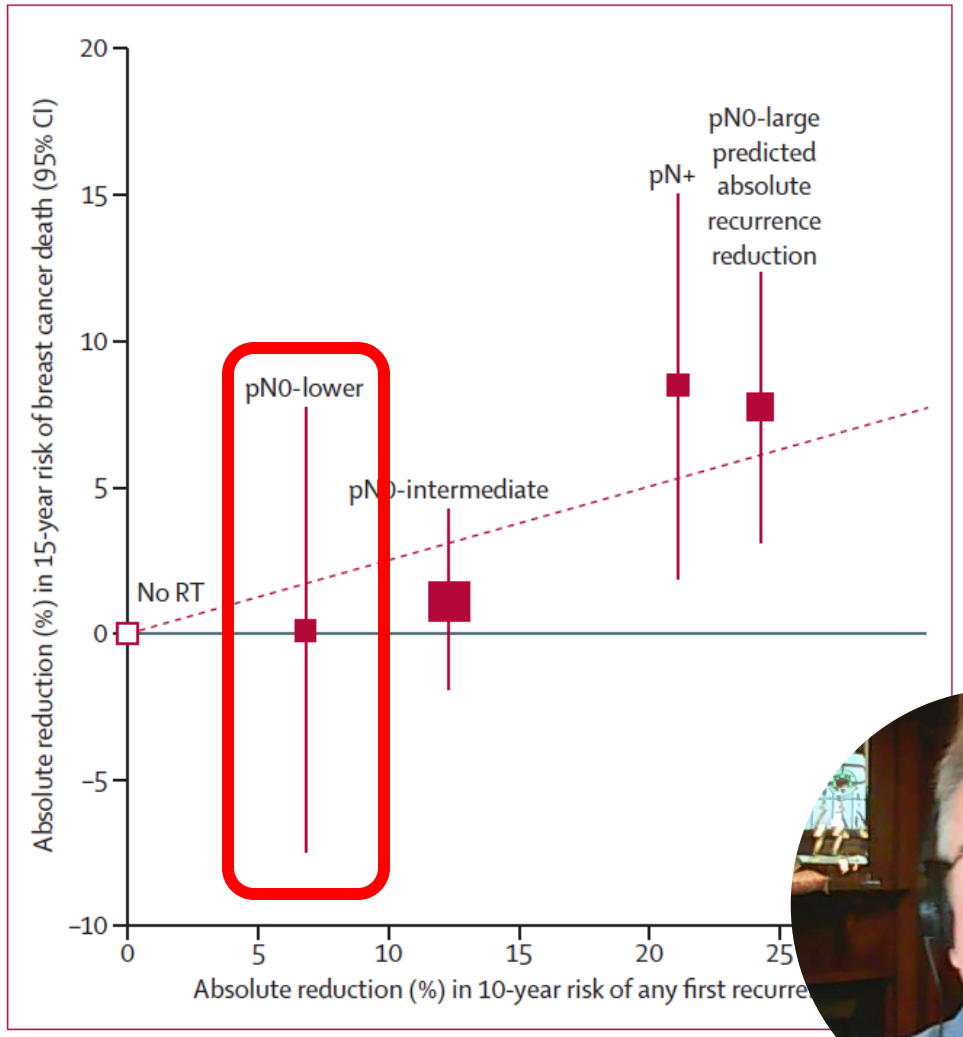
	Events per woman-year during years 0–9		Ratio of annual event rates BCS+RT vs BCS (CI)*
	Allocated BCS+RT	Allocated BCS	
(a) Entry age (trend χ^2_1=0·0; 2p=0·9)			
<40 years	5·9%	11·5%	0·49 (0·32–0·76)
40–49 years	2·7%	6·1%	0·44 (0·33–0·58)
50–59 years	1·9%	4·0%	0·47 (0·36–0·61)
60–69 years	1·6%	3·6%	0·45 (0·35–0·59)
70+ years	1·0%	2·1%	0·45 (0·28–0·72)
(b) Tumour grade (trend χ^2_1=0·0; 2p=0·9)			
Low	1·0%	2·5%	0·43 (0·29–0·65)
Intermediate	2·2%	4·4%	0·47 (0·35–0·63)
High	4·1%	9·8%	0·43 (0·32–0·58)
Grade unknown	1·8%	3·6%	0·48 (0·39–0·59)
(c) Tumour size (trend χ^2_1=1·7; 2p=0·2)			
T1 (1–20 mm)	1·5%	3·5%	0·42 (0·36–0·50)
T2 (21–50 mm)	4·5%	8·9%	0·50 (0·37–0·66)
Various/unknown	2·9%	4·2%	0·74 (0·43–1·27)
(d) Surgery, ER status, and trial policy of tamoxifen use† (heterogeneity χ^2_3=11·4; 2p=0·01)			
Lumpectomy, ER-positive no tamoxifen	3·3%	8·0%	0·41 (0·33–0·52)
Lumpectomy, ER-poor	5·2%	8·5%	0·65 (0·46–0·94)
>Lumpectomy, ER-positive no tamoxifen/ER-poor	1·6%	3·2%	0·51 (0·39–0·67)
Lumpectomy, ER-positive with tamoxifen	0·9%	2·4%	0·38 (0·29–0·51)

Lancet 201

- pN0 divided into groups according to predicted absolute reduction in LR risk
  - Lower – 12.0 vs 18.9%
  - Inter – 12.4% vs 18.9%
  - Large – 26.0% vs 50.3%

- Differences in 15yr breast cancer mortality
  - Lower – 0.1% (-7.5 to 7.7)
  - Inter – 1.1% (-2.0 to 4.2)
  - Large – 7.8% (3.1 to 12.5)

- **A 6.9% reduction in LR at 10 years has no impact in breast cancer mortality**

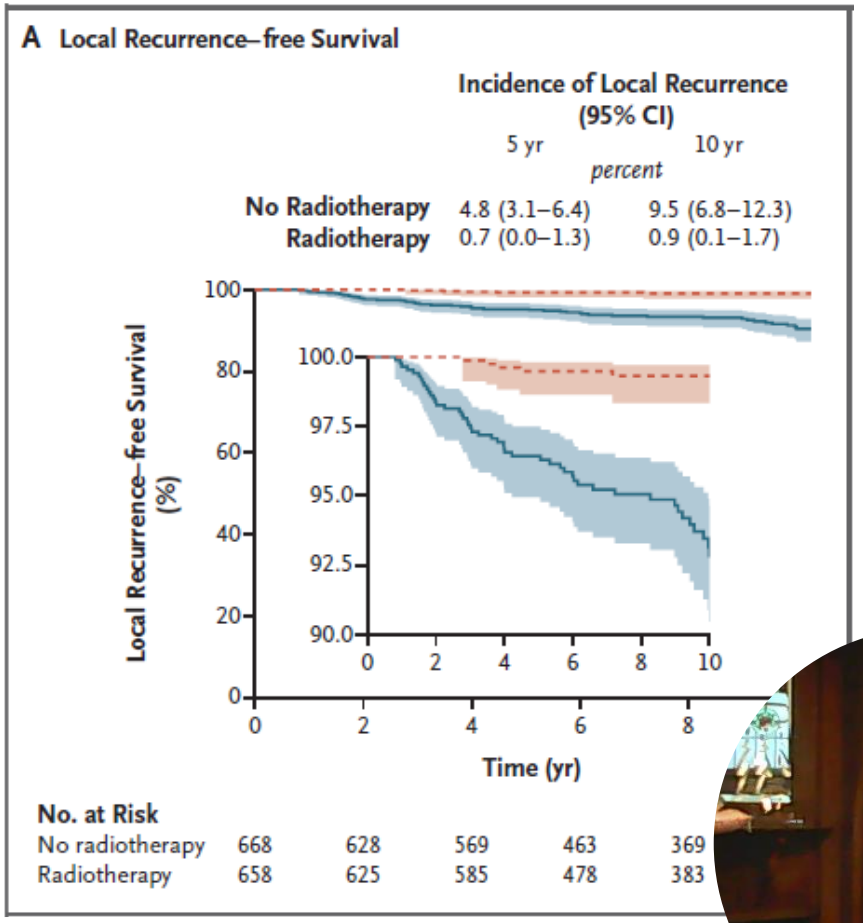


Lancet 201

PRIME 2 – RCT of RT omission

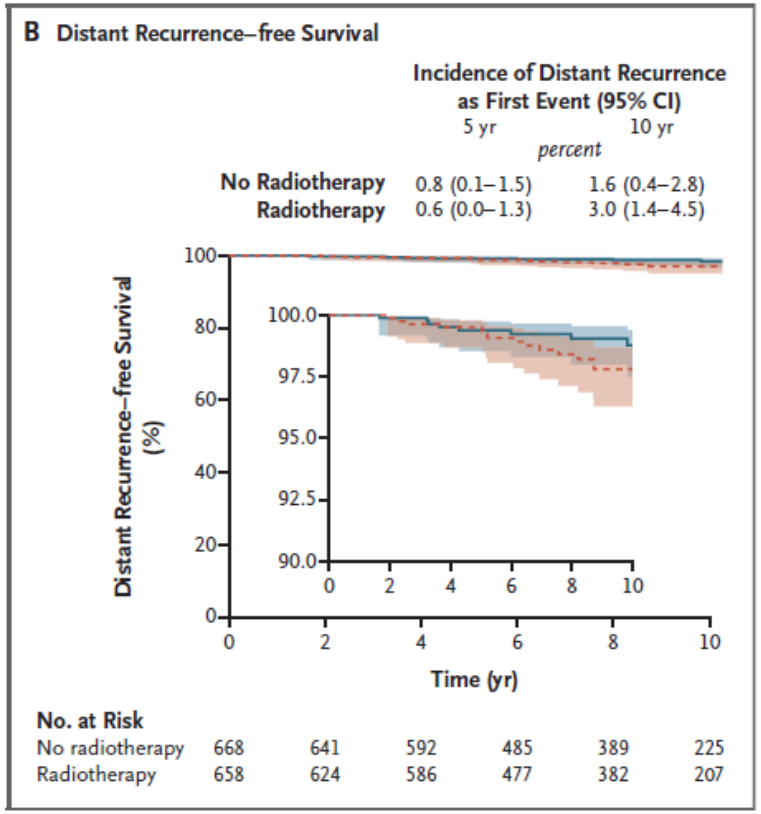
- 65 or over
- Tumour size <30mm
- Node negative
- ER or PR positive – i.e. not TNBC
- Not Grade 3 and LVI positive

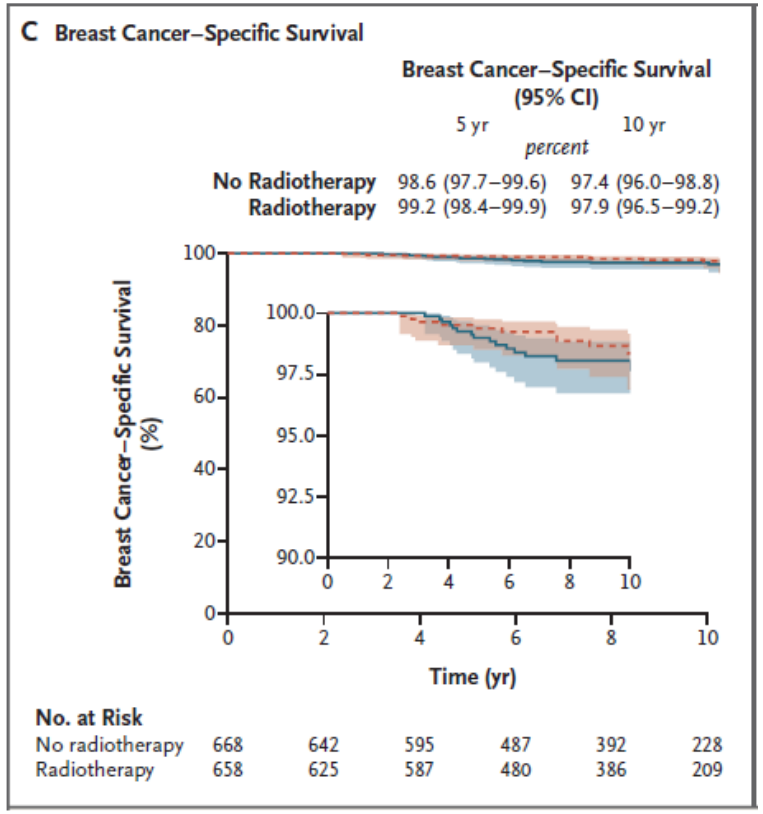
- Her2 status not measured
  - No anti-HER2 therapy

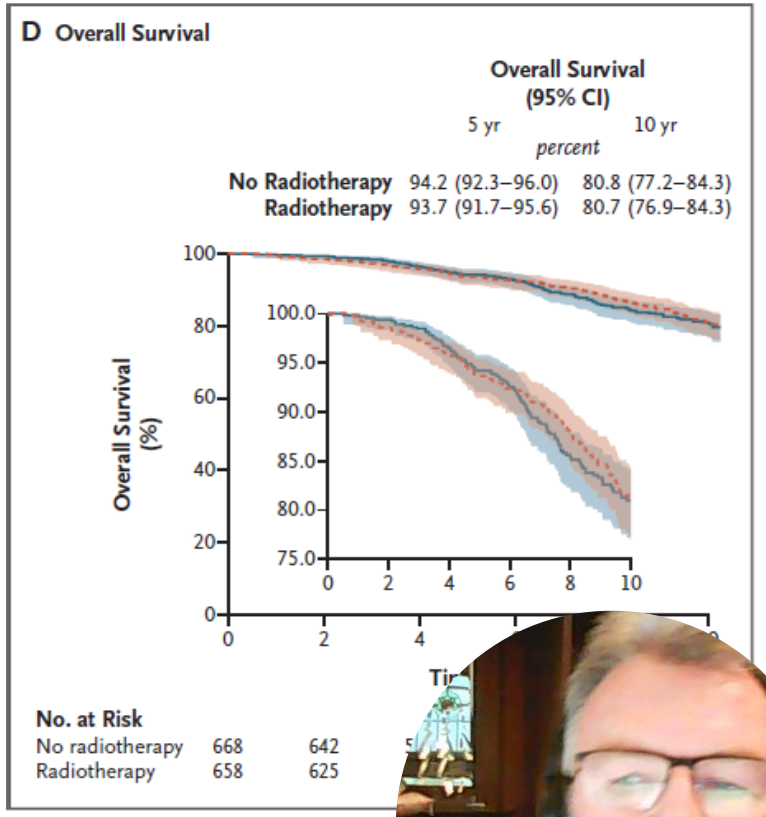


Kunkler et al;

PRIME 2







Kunkler et al;

What about patients 50-65yo?

- NRG-BR007 - The DEBRA Trial: De-escalating Breast Radiation After Lumpectomy for Low Risk, Estrogen Receptor Positive, Breast Cancer
  - Age ≥50 years, pT1N0, RS≤18

- NRG-BR008 – HERO: A Phase III Randomized Trial of Radiotherapy Optimization for Low-Risk HER2-Positive Breast Cancer
  - Age ≥40 years, HER2+, pT1N0

BREAST CANCER TRIALS

Formerly known as the
Australia & New Zealand Breast Cancer Trials Group

ANZ 1002: PROSPECT

Post-operative Radiotherapy Omission in Selected Patients with Early breast Cancer Trial

A Two-Arm Cohort study using MRI to assess post-operative radiotherapy omission in selected patients with early breast cancer

GB Mann, AR Skandarajah, N Zdenkowski, J Hughes, A Park, D Petrie, K Saxby, SM Grimmond, A Murugasu, AJ Spillane, BH Chua, H Badger, H Braggett, V Gebski, A Mou, JP Collins , AK Rose

Trials Save Lives
breastcancertrials.org.au

PROSPECT Schema

PATIENT POPULATION

- Female, aged ≥ 50
- Unifocal, breast cancer cT1N0
- Not TNBC, no LVI, no EIC
- Pre-op MRI (all BIRADS 3+ lesions biopsied)

Eligibility

ALLOCATION

- BPE low
- pT1N0, no LVI, no EIC
- 2mm radial margins
- No occult malignancy

Management with no radiotherapy "Group 1"

N = 201

- BPE high
- Ineligible pathology
- Occult malignancy

Standard Management "Group 2"

N = 242

Systemic therapy mandated

FOLLOW-UP

10 years follow up:
- MG at 6 months then annually
- MRI at 18 months
- Patient contact at 5 & 10 years

10 years follow up:
- MG annually
- Patient contact at 5 & 10 years

Sample collection for:
- Translational research

Parallel studies:
- Fear of Cancer Recurren
- HRQoL

Mann et al The

Events in entire cohort at time of primary analysis

Group 1 patients (201/201)	Events
Ipsilateral invasive LR	2
Ipsilateral regional recurrence	1
Ipsi regional and Distant recurrence	1
Contralateral cancer	2
Group 2 patients (228/242)	
Ipsilateral recurrence	3
Contralateral cancer	3

Events at 5 years

- 1% Ipsilateral LR
- 1% isolated regional recurrence
- 1% distant recurrence
- 2% contralateral primary

Mann et al The

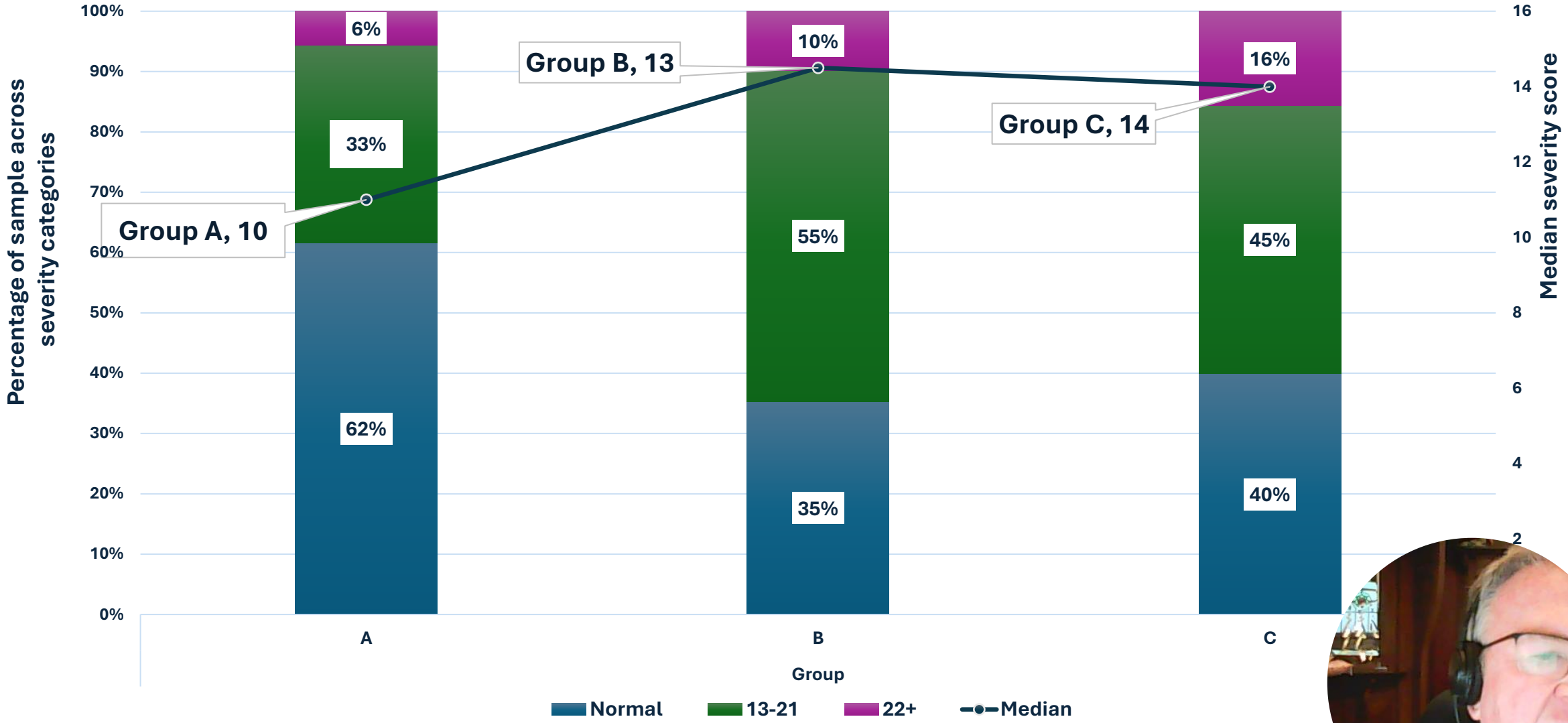
PROSPECT Quality of Life study

- Three groups of women:
  - enrolled in PROSPECT (had MRI, omitted RT) → Group A
  - screened out of PROSPECT (had MRI, had RT) → Group B
  - clinically matched to those who had PROSPECT MRI (no MRI, had RT)→ Group C

- Fear of Cancer Recurrence Inventory (FCRI) – severity subscale
  - Cut-offs ≥13/36 (need further assessment) and ≥22/36 (clinically severe FCR)

Stafford et al; B

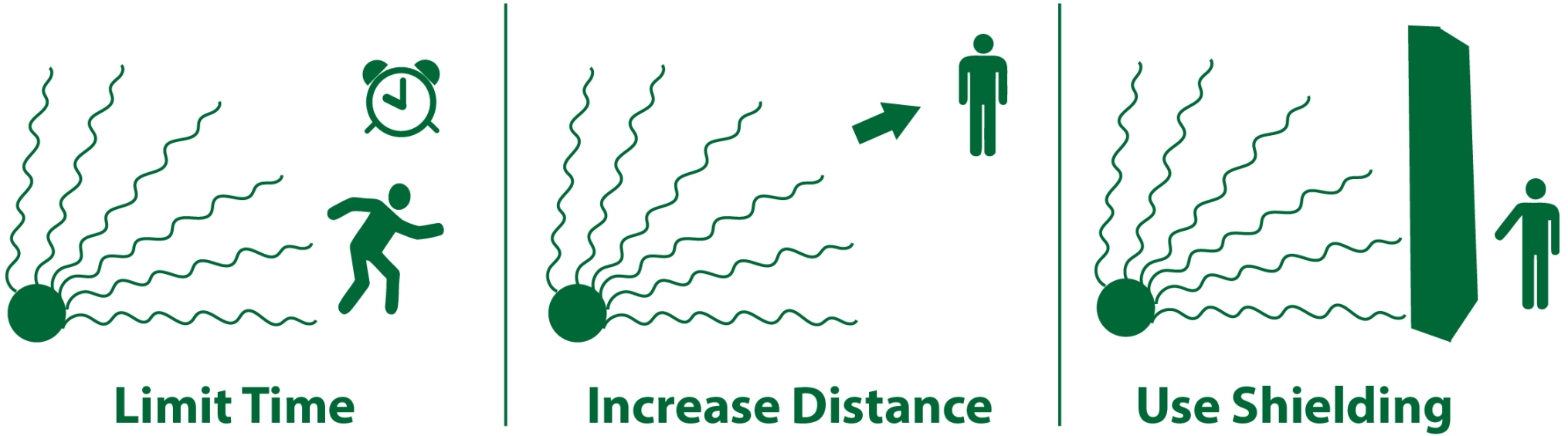
FCR across groups by severity and median



Stafford et al; B

Making radiation less dangerous

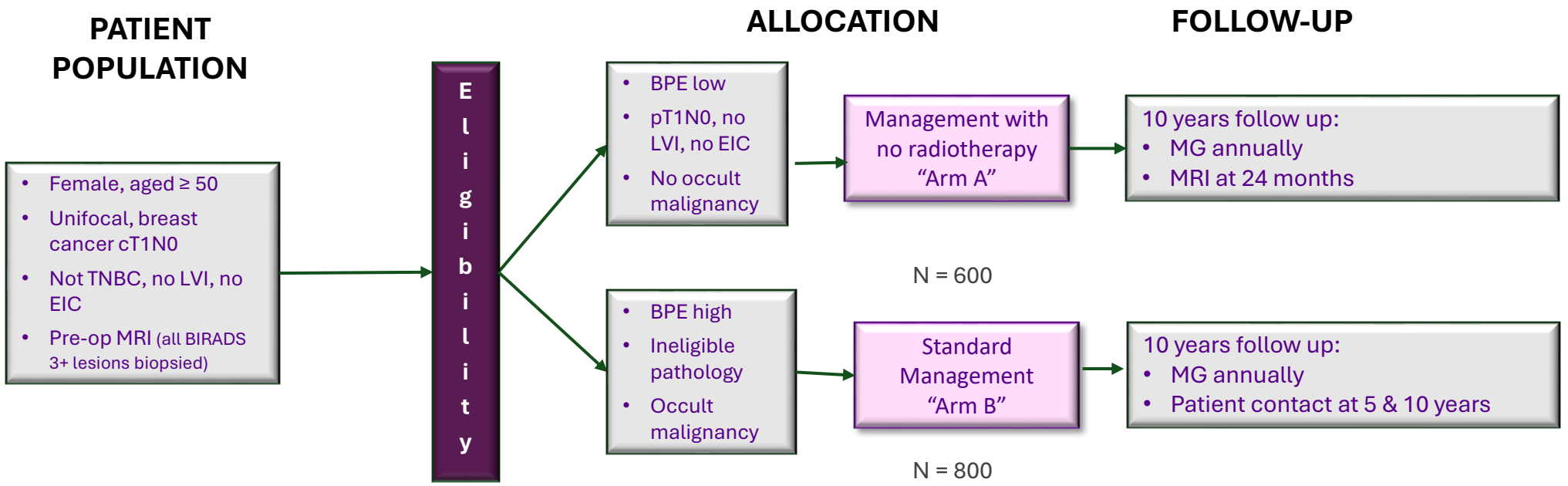
To reduce radiation exposure:



Omit it altogether.....

PROSPECTIVE Schema

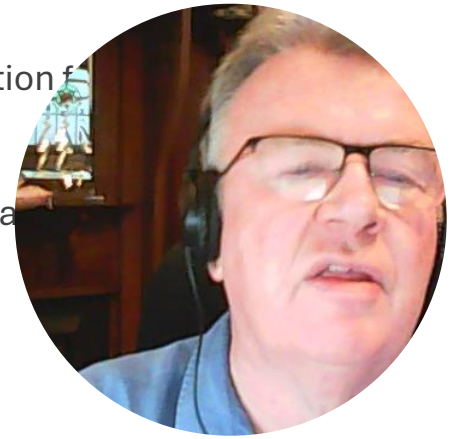
PROSPECT International **V**alidation **E**xperience (Phase III, two-arm, non-randomised),



Omission of radiation in women over 50 with Stage 1 non-TNBC

Endocrine therapy not mandated for lower risk

Data/sample collection f
- ET compliance
- QoL
- Translational resea



Treatment Aims

- To reduce the impact of the disease
- We tend to :
  - over-estimate the benefit of our treatments
  - under-estimate the risks and side effects
  - not consider the costs
- We should recommend treatments that reduce the risk of death
  - We should discuss the risks and benefits of other treatments

De-escalation

- Theoretically most people agree with the aim
  - Practically it is very difficult.

- Over-treatment is hidden (and feels good to us)
  - Happy patients who have no recurrence
  - Believe they have been cured by all the treatment

- Under-treatment is obvious
  - Unhappy patients
  - May blame the doctors

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LOCOREGIONAL TREATMENT OF cT1–3, cN0 or cN+, M0 DISEASE[a]: BREAST-CONSERVING SURGERY (BCS) FOLLOWED BY RT

BCS[j] with surgical axillary staging (category 1)[i,k,l,m] ± oncoplastic reconstruction[n]

→ See BINV-4 to determine whether adjuvant systemic therapy is indicated

Negative axillary nodes →
WBRT ± boost[p] to tumor bed, and consider comprehensive regional nodal irradiation (RNI) in patients with central/medial tumors, pT3 tumors, or pT2 tumors and one of the following high-risk features: grade 3, extensive lymphovascular invasion (LVI), or hormone-receptor (HR)-negative.[s]
or
Consider APBI/PBI in selected patients who are low risk (category 1)[p,q]
or
Consider omitting breast irradiation if adjuvant endocrine therapy is planned and following criteria are met (category 1):
1) ≥70 y, HR+, HER2-negative, cN0, pT1[r,s]
2) ≥65 y, HR+, HER2-negative, pN0, pT ≤3 cm[s]

1–3 positive axillary nodes →
Meets ALL of the following criteria:
- cT1–T2, cN0
- No preoperative chemotherapy
- 1–2 positive sentinel lymph nodes (SLNs)
- WBRT planned

→ Yes to all → WBRT ± boost (use of comprehensive RNI with or without intentional inclusion of axilla at the discretion of the radiation oncologist) (category 1)

→ No → WBRT with inclusion of the undissected axilla to tumor bed (catego… consider compreh… any portion of the u…

≥4 positive[o] axillary nodes → WBRT ± boost[p] to tumor bed (category 1) + com… including any portion of the undissected axilla at…

Radiation therapy **can** be safely avoided in women age 50 or older with stage I non TNBC

The data is not the barrier

"Who should I examine first,
you or your lawyer?"

UCSF School of Medicine

Five days, not five years

Radiotherapy for favorable early-stage breast cancer

Nicolas D. Prionas, MD PhD
Department of Radiation Oncology
University of California, San Francisco
November 1, 2024

Disclosure Information

Nicolas D. Prionas, MD PhD

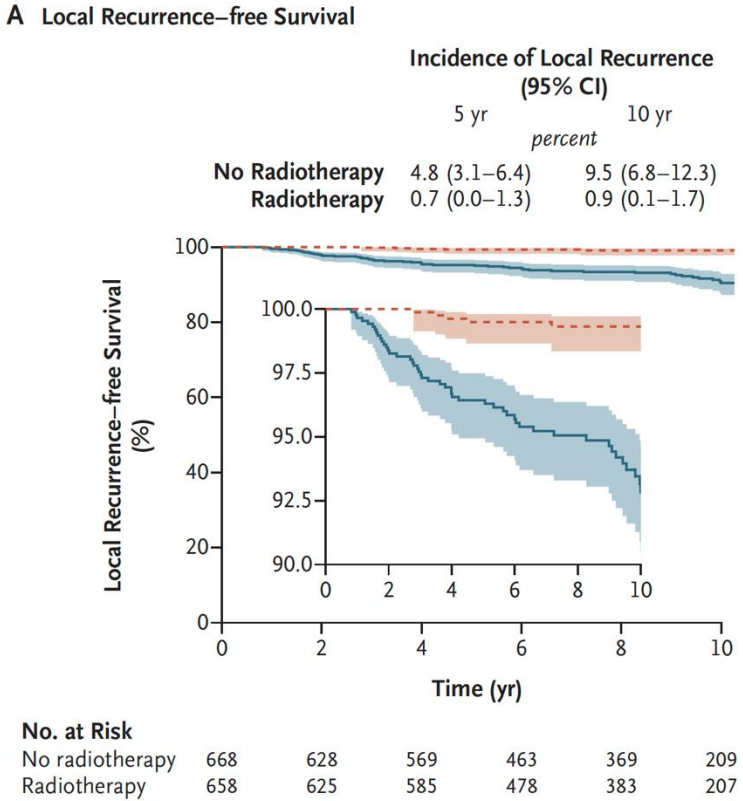
I have no financial relationships to disclose.

Claim:

Radiation therapy can be safely avoided in:

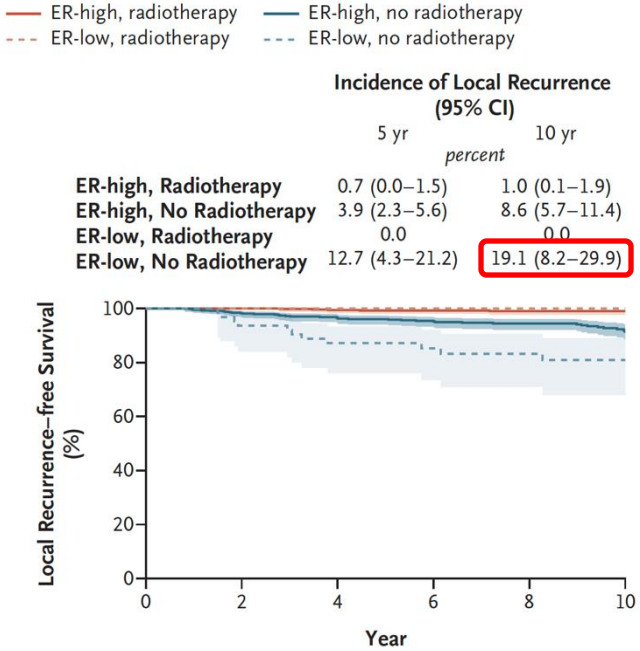
- *women age 50 or older*
- *with stage I*
- *non-TNBC*

PRIME II – 10-year outcomes



Kunkler et al. Breast-Conserving Surgery with or without Irradiation in Early Breast Cancer. NEJM. 2023.

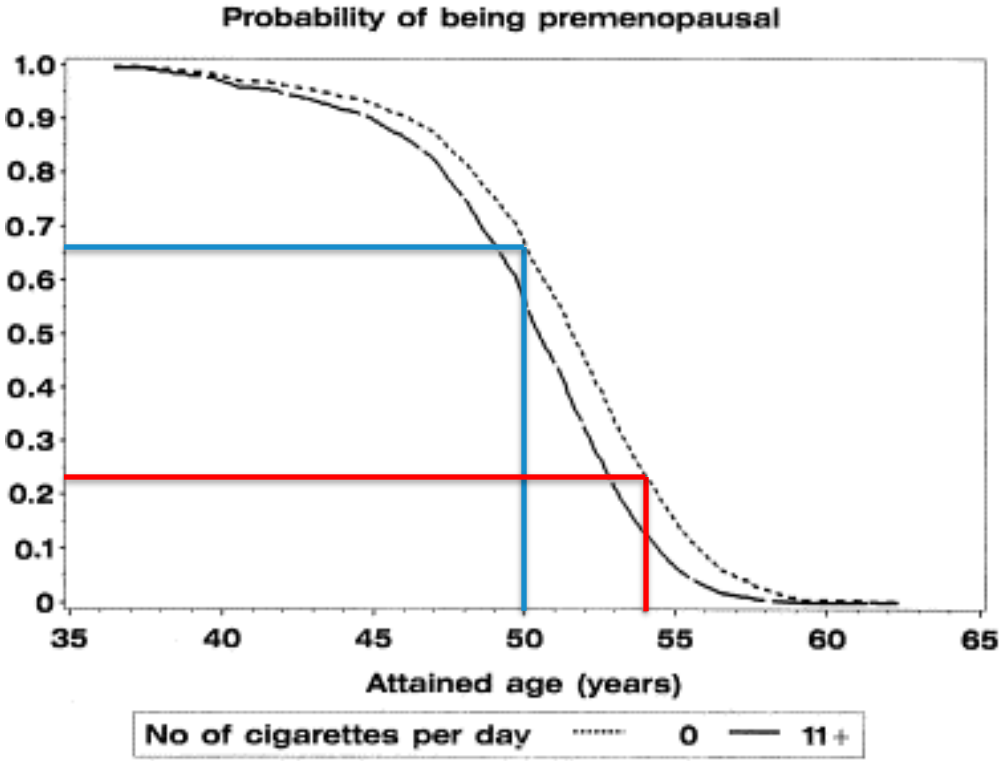
PRIME II - ER-low



ER-low:
- Allred < 7
- ER < 20 fmol/mg
- ER < 50%
- IHC < “+++”

Kunkler et al. Breast-Conserving Surgery with or without Irradiation in Early Breast Cancer. NEJM. 2023.

Why 50 years of age?

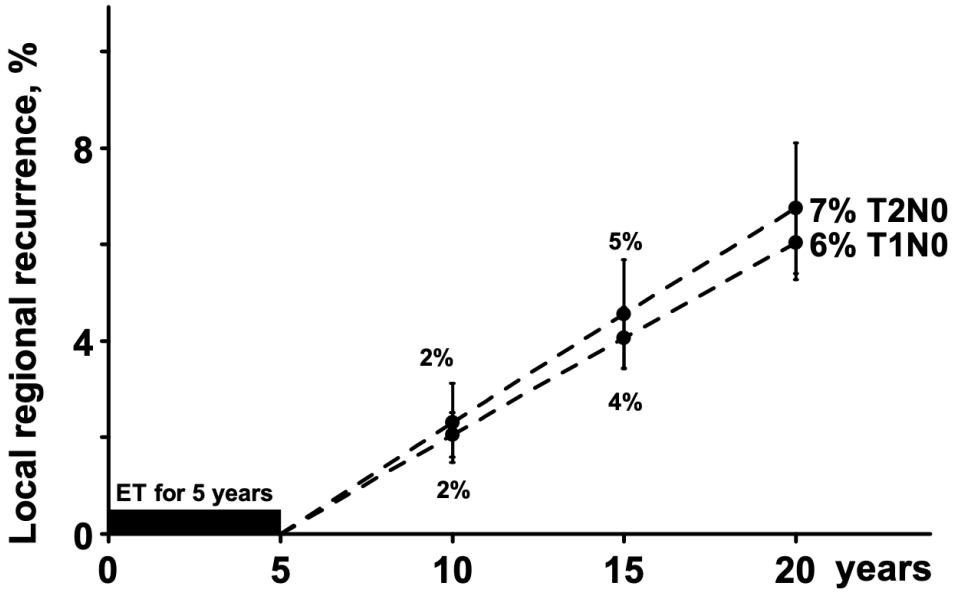


PROSPECT
- 16% of patients 50-54 yo
- Only 78 patients <60 yo

Kato et al. Prospective Study of Factors Influencing the Onset of Natural Menopause. J of Clin Epidemiology. 1998. 51 (12).

UCSF

Recurrence risk increases linearly with time



No. at risk (and, in each 5-year period, no. of events and annual rate)

T2N0	4225	(70, 0.5%)	1549	(17, 0.4%)	401	(3, 0.3%)	91
T1N0	11424	(159, 0.4%)	4655	(60, 0.5%)	1268	(9, 0.3%)	226

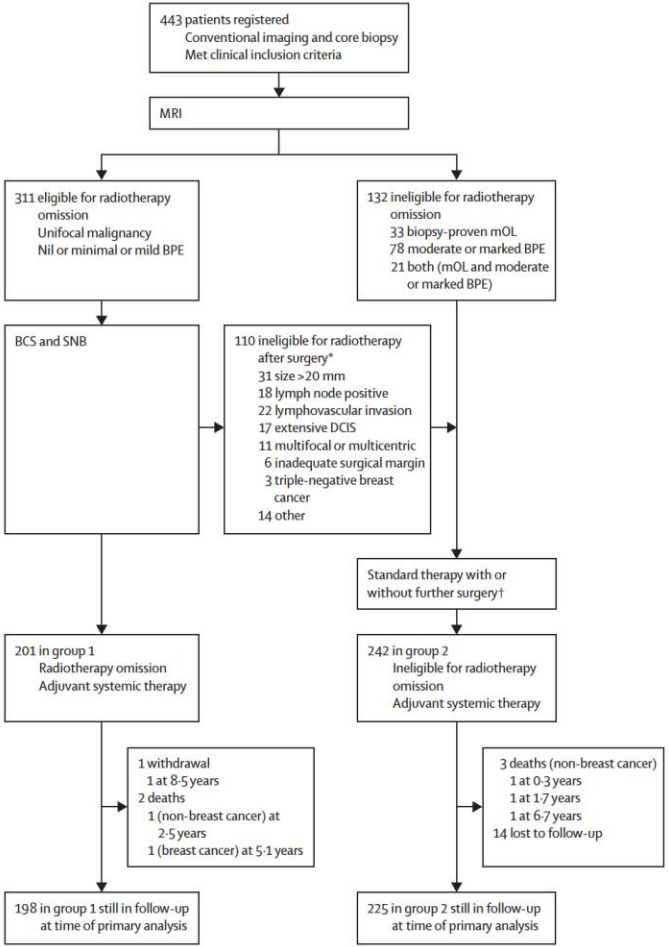
Pan et al. 20-Year Risks of Breast-Cancer Recurrence after stopping Endocrine Therapy at 5 Years. NEJM. 2017

UCSF

PROSPECT Trial

- 311 eligible for XRT
  - 22 LVSI+ (7%)
  - 17 EIC+ (5.5%)
  - 6 Margins (2%)
  - 14 “Other” clinical decision (4.5%)

19% of T1N0 XRT-eligible patients excluded from omission



Mann et al. Postoperative radiotherapy omission in selected patients with early breast cancer following preoperative breast MRI (PROSPECT): primary results of a prospective two-arm study. Lancet. 2024.

UCSF

Other adverse features

	PRIME II	PROSPECT
Grade 3	3.4%	5%
LVSI	4.8%	0%
ER-low	9.7%	---
Lobular	---	12%
Ki67	---	---
Genomic assay	---	---

Not all breast MRI is equal

- MD Anderson MRI review
  - 88 cases referred from around the US

TABLE 5. Most Common Technical Deficiencies

Type of Deficiency	No. (%) of Patients	No. (%) of Patients for Whom Repeat MRI was Recommended
Artifact	65 (74)	29 (33)
T2-weighted or equivalent sequence deficiency	33 (38)	14 (16)
Delayed-phase last postcontrast T1-weighted sequence deficiency	24 (27)	9 (10)
Early-phase first postcontrast T1-weighted sequence deficiency	20 (23)	8 (9)

TABLE 6. Distribution of Recommendations to Repeat Breast MRI

Number of Technical Deficiencies	Number of Outside MRIs	Recommendation to Repeat MRI
0	28	13 (46%)
1	19	11 (58%)
2–4	26	11 (42%)
>4	15	6 (40%)

Ruiz-Flores et al. Variation in Technical Quality of Breast MRI. Academic Radiology. 2020.

UCSF

Cost of recurrence

- Quality of life
  - Recurrence impairs physical, functional, and emotional well-being of patients and their family members.
- Financial
  - Repeat work-up (H&P, fertility?, imaging, pathology) and treatment (surgery, adjuvant therapies)
- Physical
  - Cosmesis of repeat breast conservation vs Mastectomy

Accelerated Partial Breast Irradiation

- APBI has less acute and late toxicity

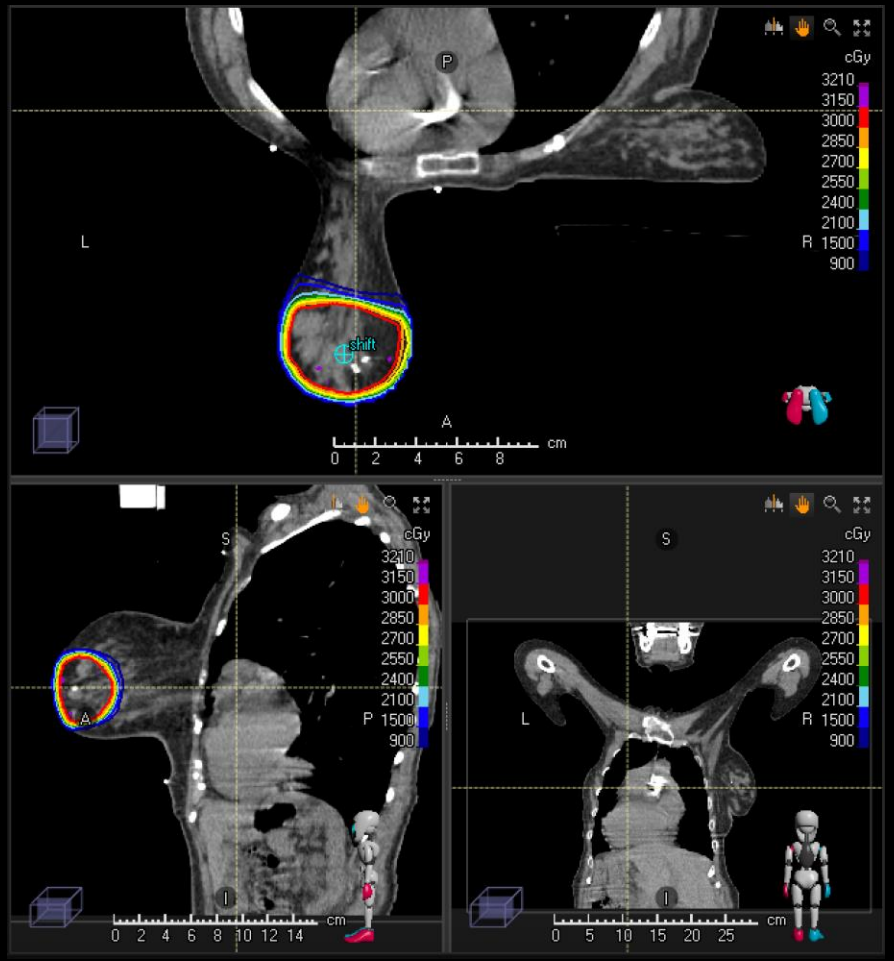
- APBI has better cosmesis (patient and MD rated)

Toxicity	APBI	WBRT
Acute	G1: 19.1% **G2+: 2.0%**	G1: 28.8% G2+: 37.7%
Late	G1: 4.5% **G2+: 0%**	G1: 27.3% G2+: 2.7%

Meattini et al. Accelerated Partial-Breast Irradiation Compared with Whole-Breast Irradiation for Early Breast Cancer: Long-Term Results of the Randomized Phase III APBI-IMRT-FLORENCE Trial. JCO. 2021.

UCSF

Prone APBI


P
L
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3210
3150
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2850
2700
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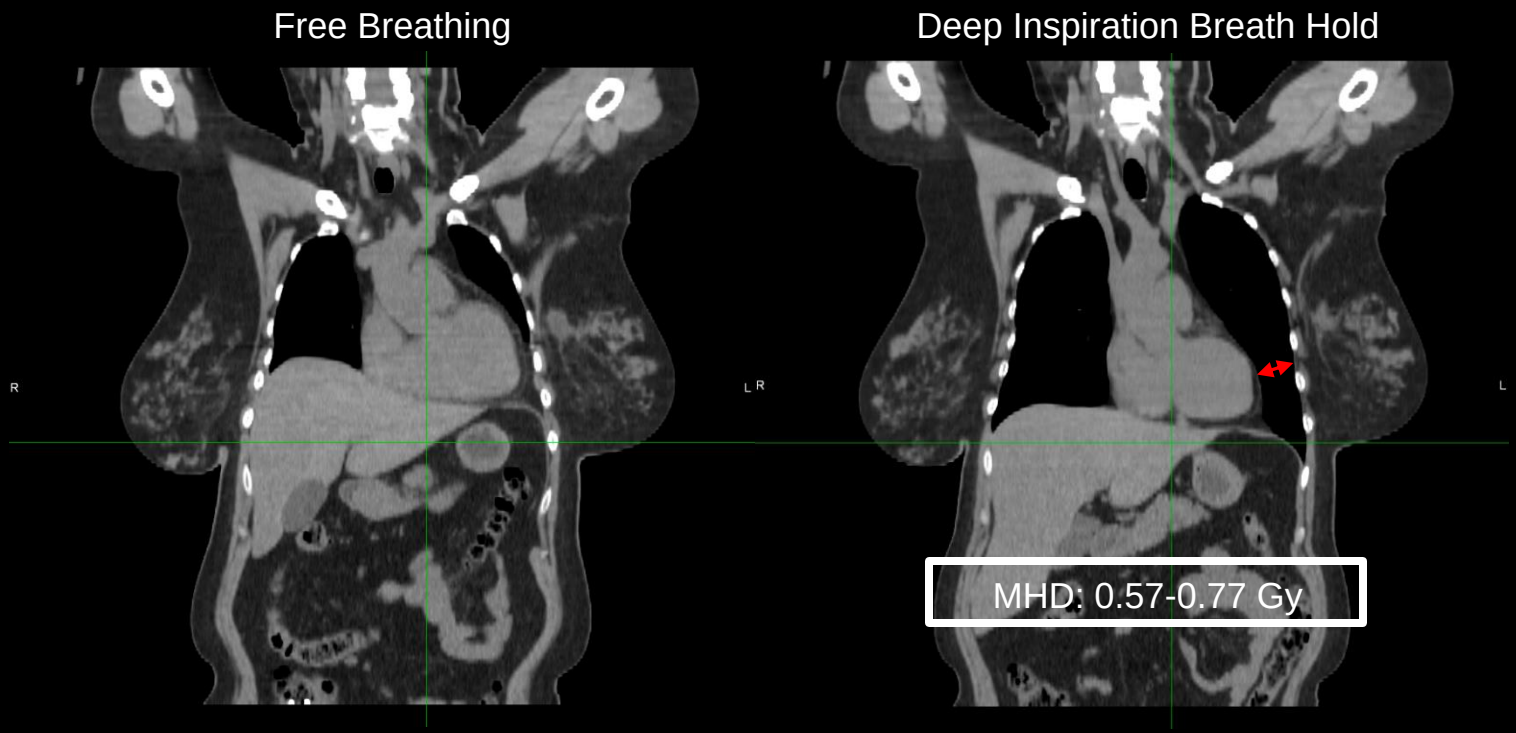
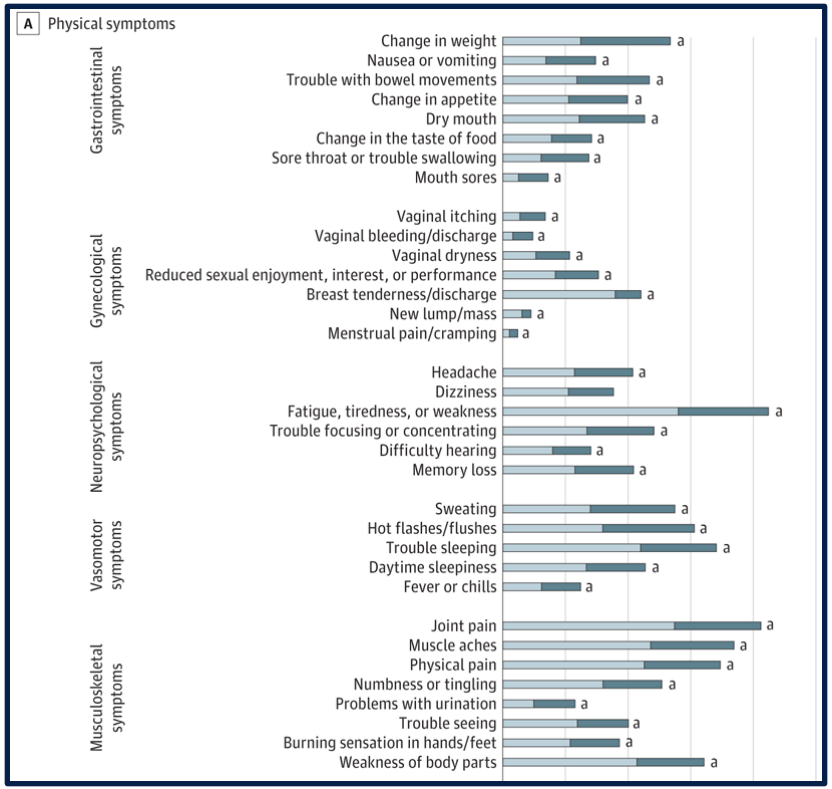
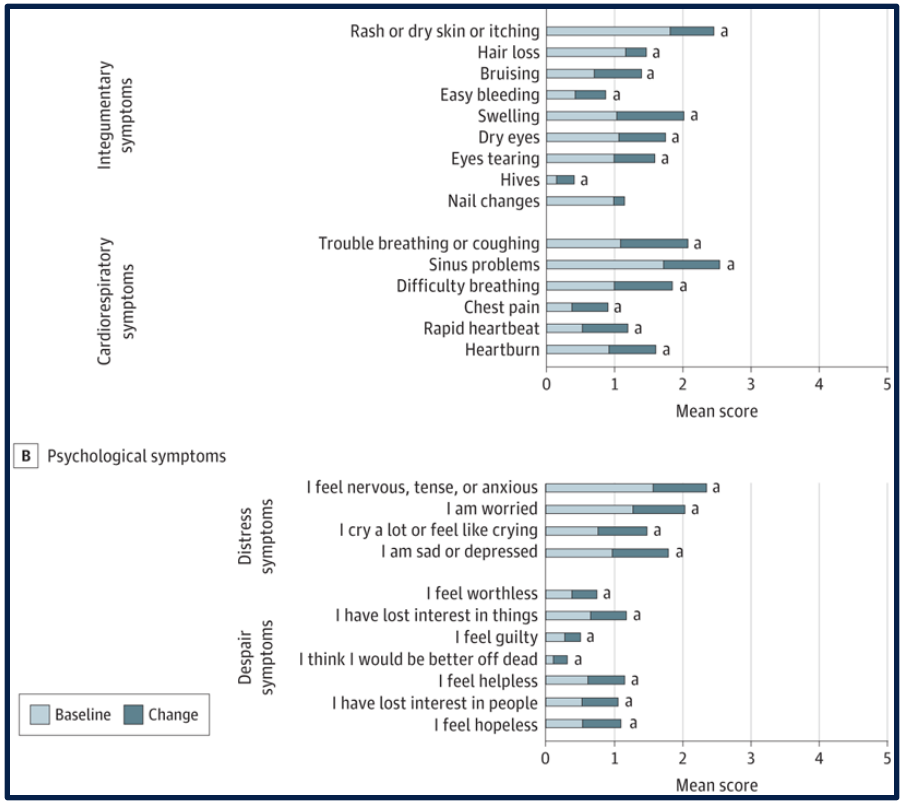
Cardiac avoidance - DIBH



Shah et al. Initial outcomes with image-guided partial breast irradiation delivered with intensity-modulated radiation therapy. *Breast J*. 2020.

Endocrine therapy is toxic





Hu et al. Racial Differences in Patient-Reported Symptoms and Adherence to Adjuvant Endocrine Therapy Among Women With Early-Stage, Hormone Receptor–Positive Breast Cancer. *JAMA Netw Open.* 2022.

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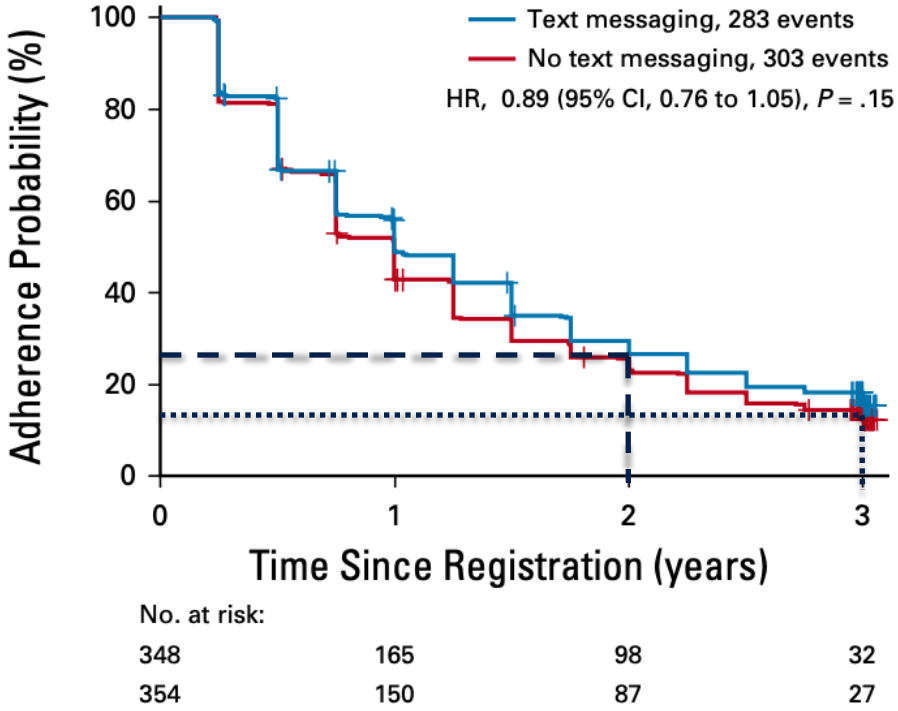
Low adherence to endocrine therapy

- SWOG S1105



PROSPECT Trial Endocrine Therapy

- 87% completed 5 years of endocrine therapy

	Index cancer pathology	Radiotherapy given for index cancer	Timing of event	Subsequent event location	Subsequent event management	5-year IIRR (upper 95% CI, two-sided)*
Group 1 (n=201)—primary outcome						
Event 1	12 mm; grade 2; ER-positive, HER2-negative	No	4·5 years	Ipsilateral invasive	BCS, radiotherapy, systemic therapy	1·0% (5·4%)
Group 1 (n=201)—secondary outcomes						
Event 2	18 mm; grade 1; ER-positive, HER2-negative	No	7·5 years	Ipsilateral invasive	Total mastectomy and SNB, systemic therapy	NA

Mann et al. Postoperative radiotherapy omission in selected patients with early breast cancer following preoperative breast MRI (PROSPECT): primary results of a prospective two-arm study. Lancet. 2024.

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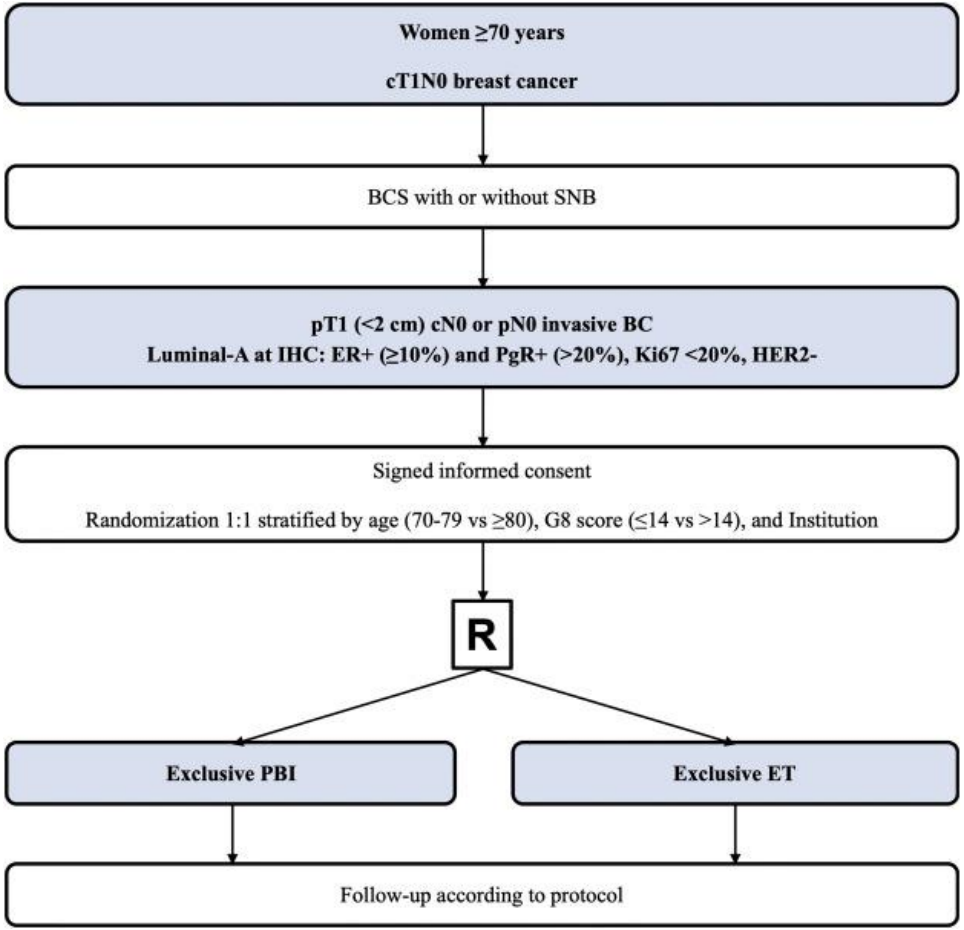
EUROPA Trial

- Primary Endpoints
  - PROMs
  - IBTR
- Secondary Endpoints
  - LRR, DM, BCSS, OS
  - AEs
  - Cosmesis



Claim:

Radiation therapy can be safely avoided in:

- *women age 50 or older*
- *with stage I*
- *non-TNBC*

Truth:

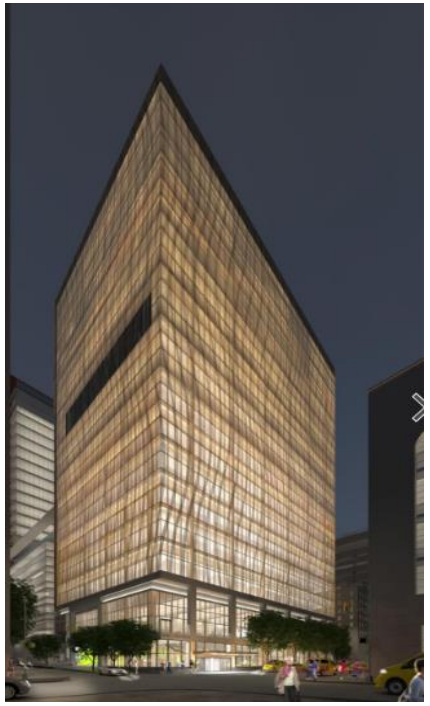
Radiation therapy can be safely ~~avoided~~ administered in:

- *women age 50 or older*
- *with stage I*
- *non-TNBC*

University of California
San Francisco

Department of Radiation Oncology

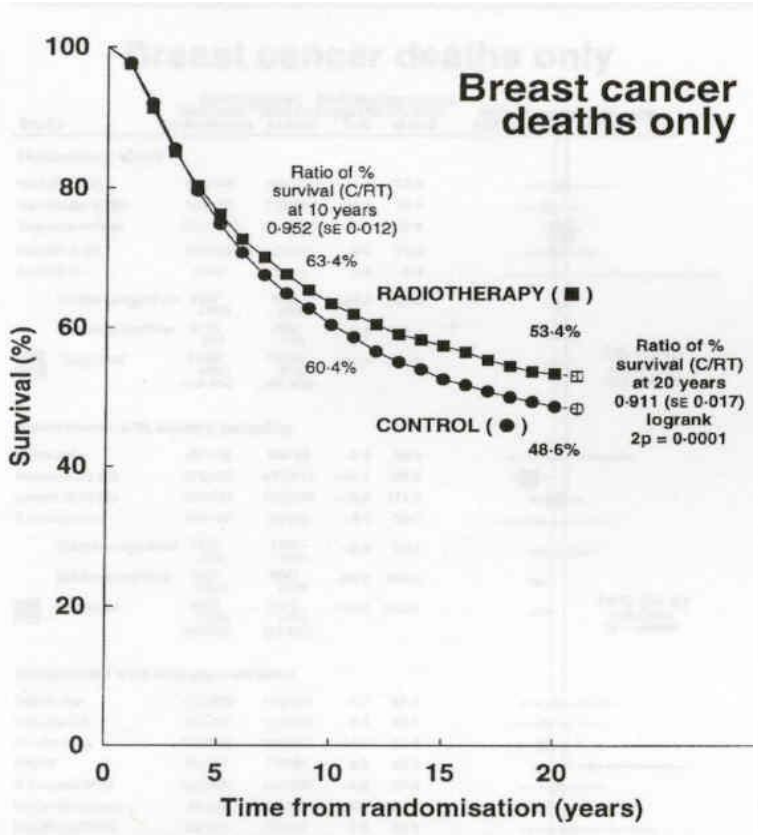
Weill Cornell Medicine

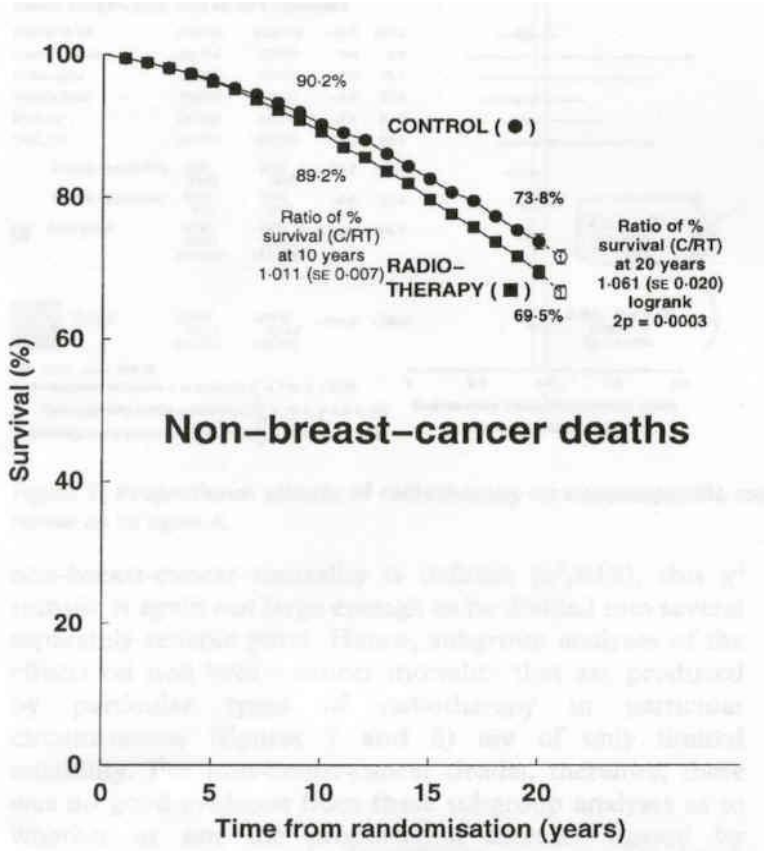


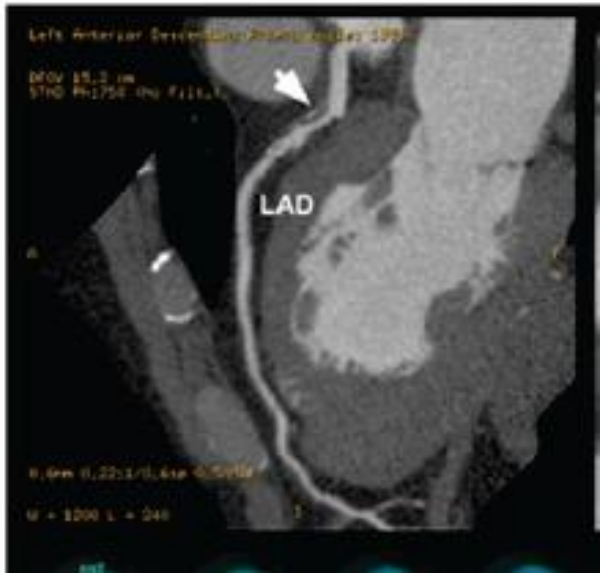
Heart and Left Anterior Descending Coronary Artery (LAD) exposure from hypo-fractionated whole breast radiotherapy with a prone set up.

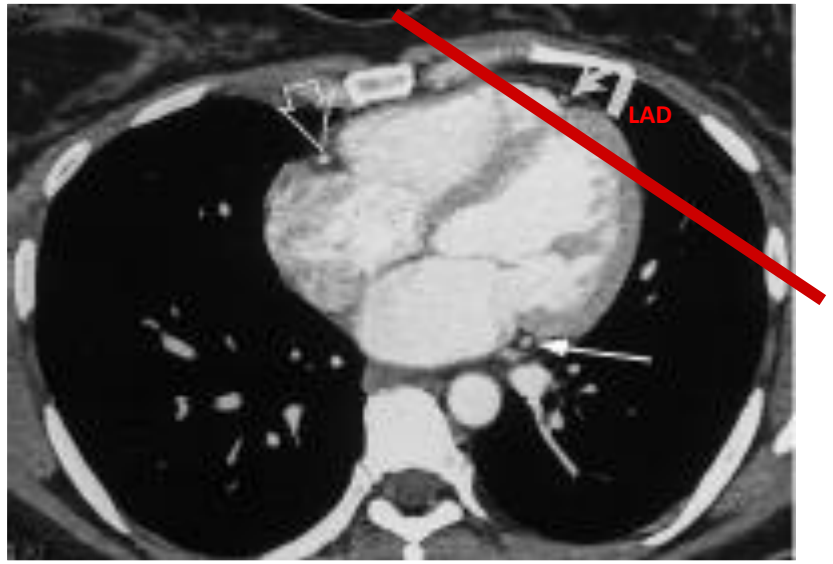
Fabiana Gregucci, MD, Elisabetta Bonzano, MD, John Ng, MD, Sharanya Chandrasekhar, MS, Lhaden Tshering BS, Xi Kathy Zhou, PhD, Maria Fenton-Kerimian, NP, Ryan Pennell, PhD, Silvia C Formenti, MD.

Historical Meta-analysis of 20,000 breast cancer patients in 40 randomized trials 20 y









↑ RT related vascular mortality: RR 1.3 p = 0.0007

Good idea to spare the heart…

The Lancet 2000 May 20;355(9217):1757-70

Heart and Left Anterior Descending Coronary Artery (LAD) exposure from hypo-fractionated whole breast radiotherapy with a prone set up: the NYU-Cornell experience

Weill Cornell Medicine

VOLUME 25 · NUMBER 16 · JUNE 1 2007

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase I-II Trial of Prone Accelerated Intensity Modulated Radiation Therapy to the Breast to Optimally Spare Normal Tissue

Silvia C. Formenti, Daniela Gidea-Addeo, Judith D. Goldberg, Daniel F. Roses, Amber Guth, Barry S. Rosenstein, and Keith J. DeWyngaert

A B S T R A C T

Clinical Investigation

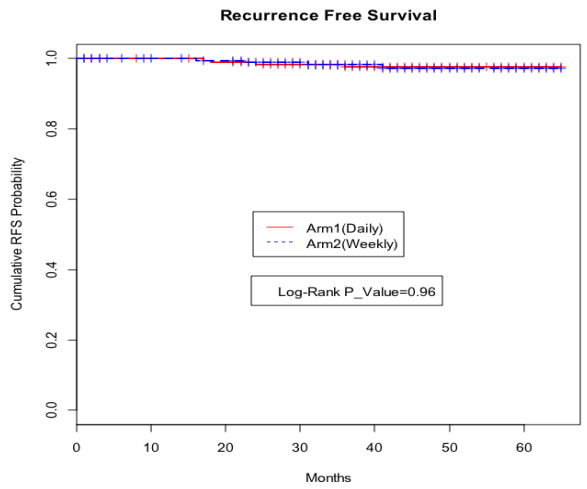
International Journal of Radiation Oncology biology • physics

www.redjournal.org

Prone Breast Intensity Modulated Radiation Therapy: 5-Year Results

Etin-Osa O. Osa, MD,* Keith DeWyngaert, PhD,* Daniel Roses, MD,† James Speyer, MD,‡ Amber Guth, MD,† Deborah Axelrod, MD,† Maria Fenton Kerimian, NP,* Judith D. Goldberg, ScD,§ and Silvia C. Formenti, MD*

*Departments of *Radiation Oncology, †Surgery, ‡Medical Oncology, and §Population Health, New York University School of Medicine, New York, New York*



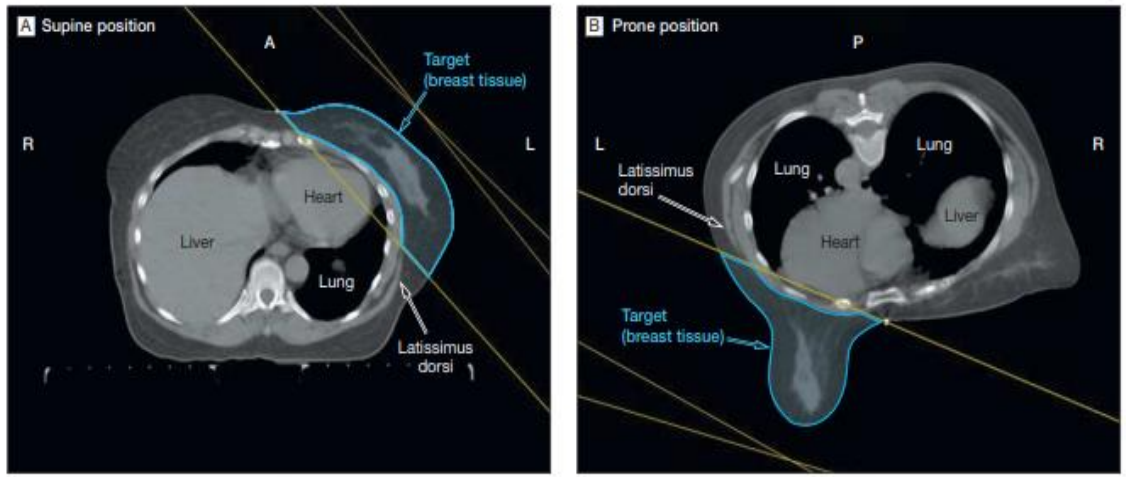
RESEARCH LETTER

JAMA Network

Prone vs Supine Positioning for Breast Cancer Radiotherapy

Silvia C. Formenti, MD
J. Keith DeWyngaert, PhD
Gabor Jozsef, PhD
Judith D. Goldberg, ScD

Figure. Example of a Patient With Better Exclusion of the Heart and Lung When Prone



Placing the posterior edge of the fields on a plane connecting the midline to the anterior extent of the latissimus dorsi muscle ensures comparable breast coverage.

Prone setup consistently superior at sparing heart and lung

Heart and Left Anterior Descending Coronary Artery (LAD) exposure from hypo-fractionated whole breast radiotherapy with a prone set up: the NYU-Cornell experience

Weill Cornell Medicine

Scientific Article

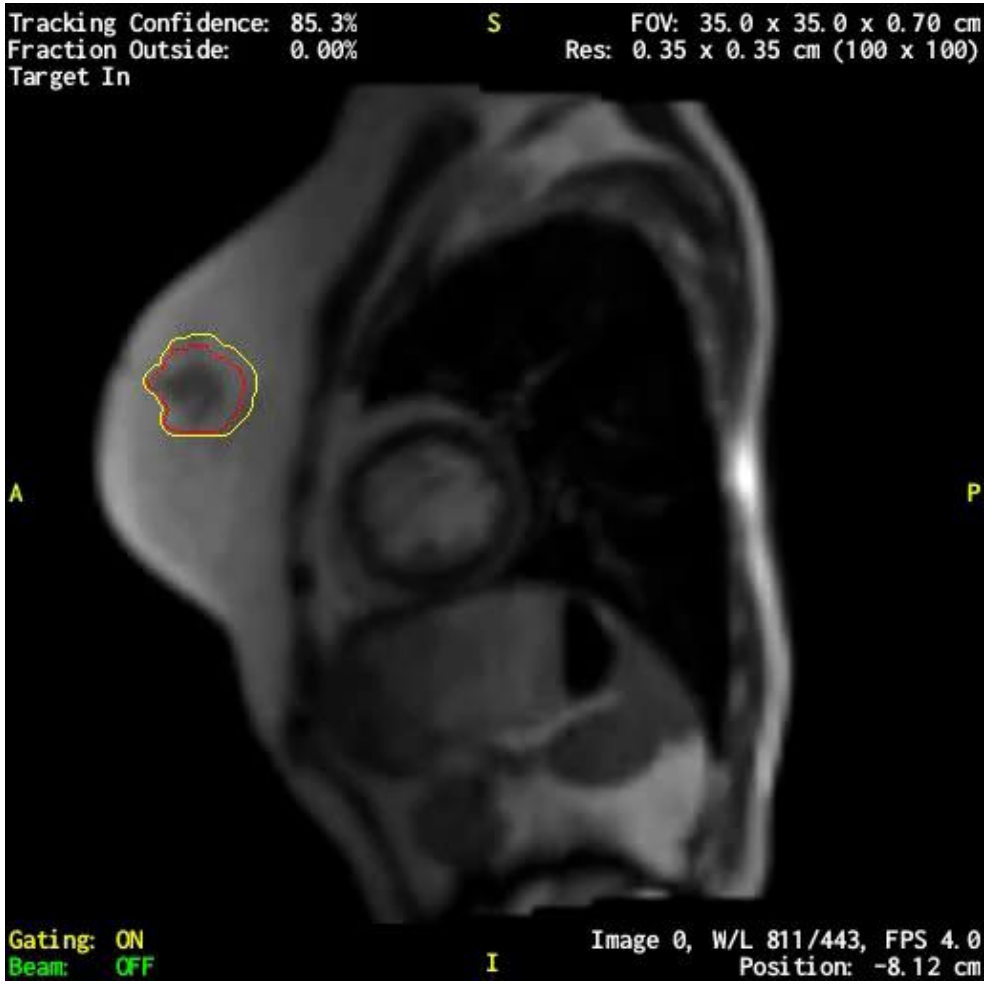
Preplanning prediction of the left anterior descending artery maximum dose based on patient, dosimetric, and treatment planning parameters

Benjamin T. Cooper MD [a], Xiaochun Li PhD [b], Samuel M. Shin MD [a], Aram S. Modrek BS [a], Howard C. Hsu MD [a], J.K. DeWyngaert PhD [a], Gabor Jozsef PhD [a], Stella C. Lymberis MD [a], Judith D. Goldberg ScD [b], Silvia C. Formenti MD [a,*]

International Journal of Radiation Oncology biology • physics
www.redjournal.org

deep tangent edge at least 3 mm from closest contoured LAD point assures LAD Dmax < 10 Gy and LAD Dmean < 3.3Gy

Intra-fraction immobilization



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Aims.

1. To measure the mean heart dose (MHD) and LAD mean and maximum doses (Dmean and Dmax) in **524 consecutive patients with left-side breast cancer** who have undergone hypo-fractionated whole breast radiotherapy (WBRT) with a concomitant boost to the post-operative cavity in prone position

2. To compare the dosimetry results to those reported in the literature for other techniques

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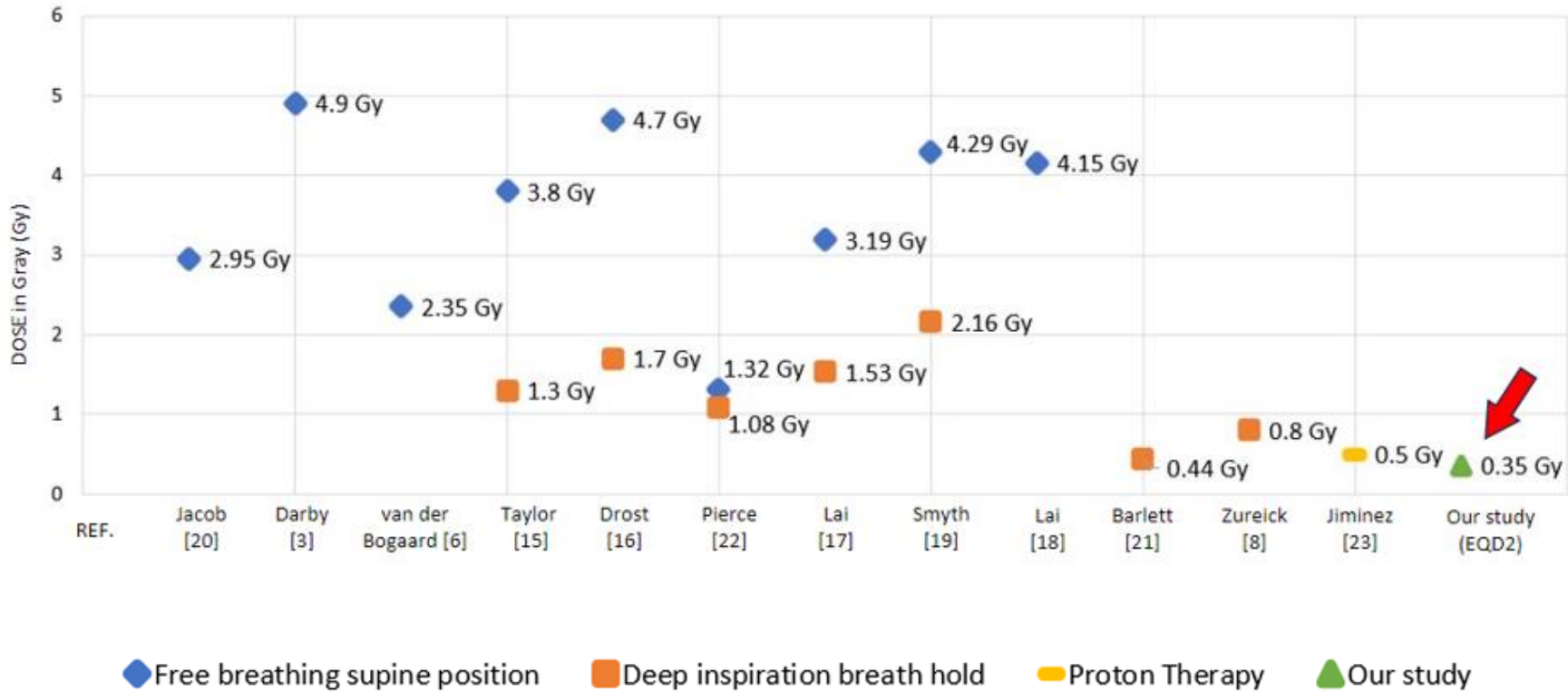
MEAN HEART DOSE



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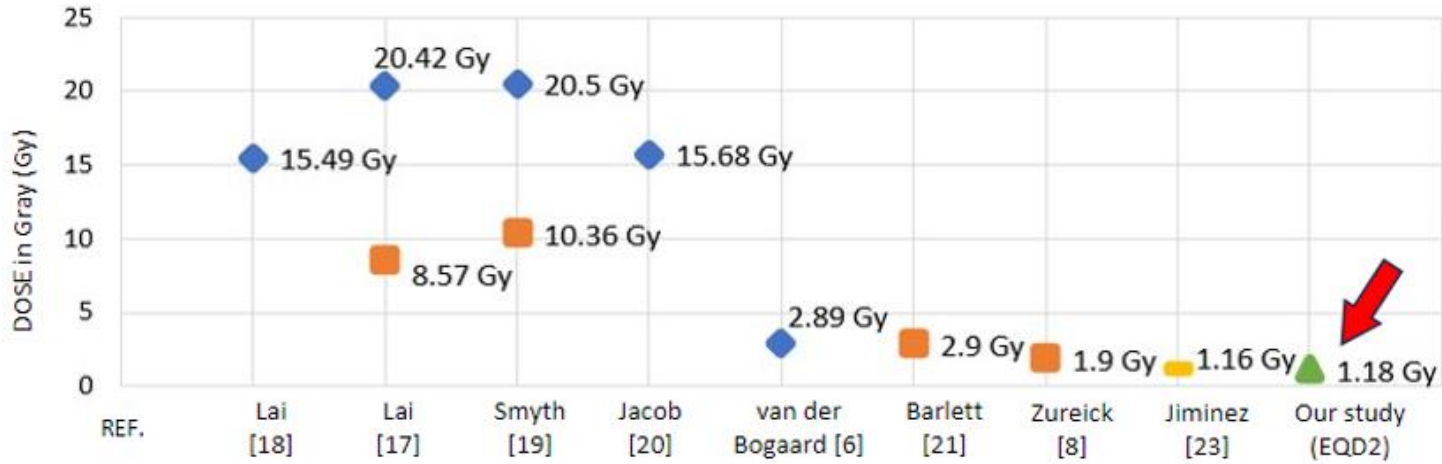
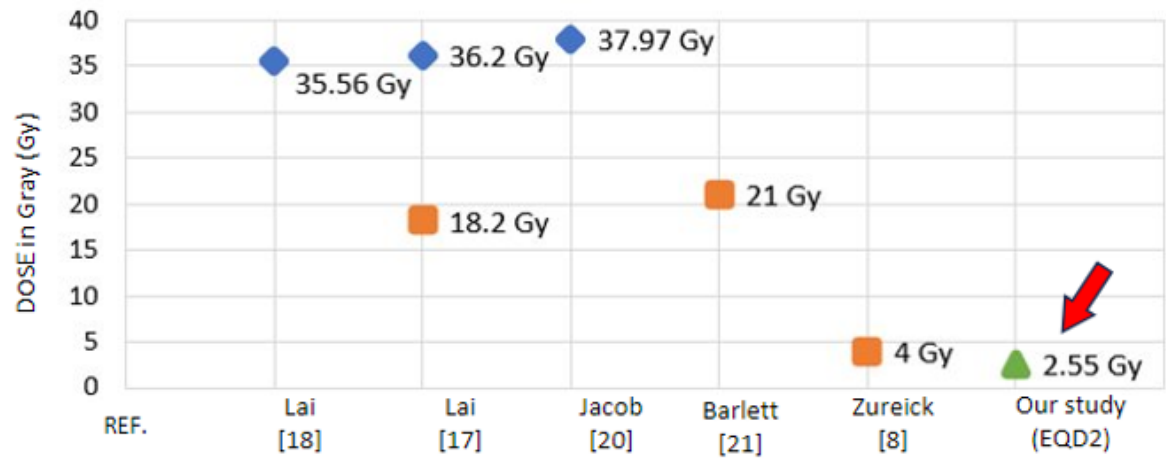


LAD DMean

LAD DMax



Free breathing supine position Deep inspiration breath hold Proton Therapy Our study

Heart and Left Anterior Descending Coronary Artery (LAD) exposure from hypo-fractionated whole breast radiotherapy with a prone set up: the NYU-Cornell experience

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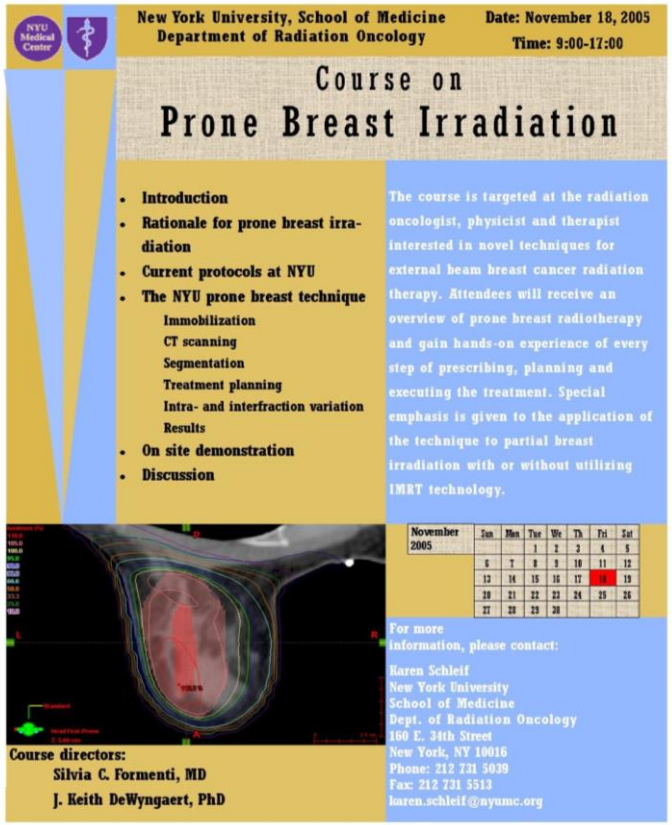
New York University, School of Medicine
Department of Radiation Oncology

Date: November 18, 2005
Time: 9:00-17:00

Course on
Prone Breast Irradiation

- Introduction
- Rationale for prone breast irradiation
- Current protocols at NYU
- The NYU prone breast technique
  - Immobilization
  - CT scanning
  - Segmentation
  - Treatment planning
  - Intra- and interfraction variation
  - Results
- On site demonstration
- Discussion

The course is targeted at the radiation oncologist, physicist and therapist interested in novel techniques for external beam breast cancer radiation therapy. Attendees will receive an overview of prone breast radiotherapy and gain hands-on experience of every step of prescribing, planning and executing the treatment. Special emphasis is given to the application of the technique to partial breast irradiation with or without utilizing IMRT technology.

November 2005

Sun	Mon	Tue	We	Th	Fri	Sat
		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30			

For more information, please contact:

Karen Schleif
New York University
School of Medicine
Dept. of Radiation Oncology
160 E. 34th Street
New York, NY 10016
Phone: 212 731 5039
Fax: 212 731 5513
karen.schleif@nyumc.org

Course directors:
Silvia C. Formenti, MD
J. Keith DeWyngaert, PhD

Easy technique to learn and easy to design prone board!

US Patent No 7.763.864 B2

- CT simulator
- Linear accelerator


frontiers in ONCOLOGY

METHODS ARTICLE
published: 11 October 2011
doi: 10.3389/fonc.2011.00031

The role of a prone setup in breast radiation therapy

*Nelly Huppert, Gabor Jozsef, Keith DeWyngaert and Silvia Chiara Formenti**

Department of Radiation Oncology, New York University School of Medicine, New York University Langone Medical Center, New York, NY, USA

Heart and Left Anterior Descending Coronary Artery (LAD) exposure from hypo-fractionated whole breast radiotherapy with a prone set up: the NYU-Cornell experience

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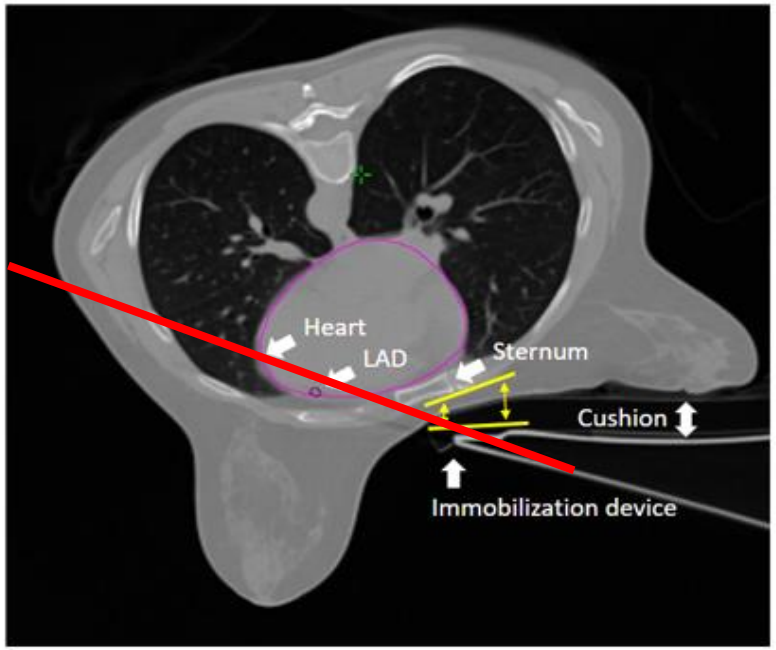
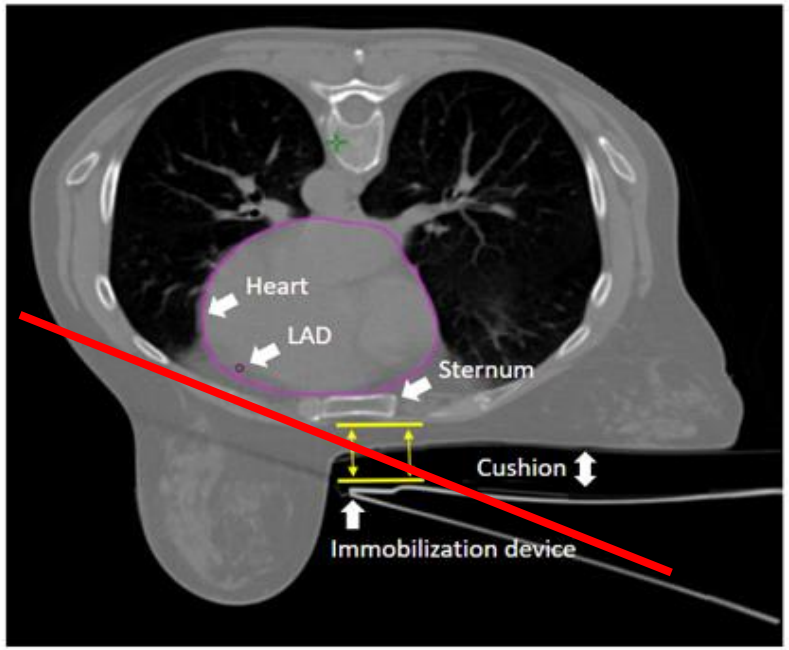
Common error: prone axial rotation/sinking



(A)



(B)

Key steps include:

1) accurately contouring the heart surface and LAD

1) Sternum **horizontally positioned** on immobilization device, to prevent sinking or axial rotation

2) placing the medial edge of the tangents at least 2.46 mm from the contoured LAD

Conclusions

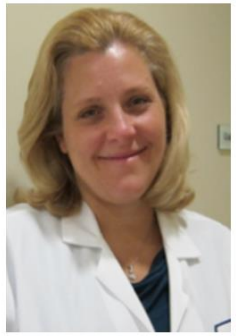
- In patients with left-side breast cancer, prone hypo-fractionated WBRT with a concomitant boost to the post-operative cavity results in optimal dose-sparing of the heart and LAD, regardless of individual body conformation and treatment volumes, without compromising target coverage.
- **Heart and LAD exposures were consistently lower than any other techniques reported in the literature**
- This approach can be easily adopted at any RT-based facility with the potential for globally offering a safe and sustainable care path for breast cancer treatment.

Cornell team


S. Formenti M.D.


J.K. DeWyngaert


O. Balogun M.D.

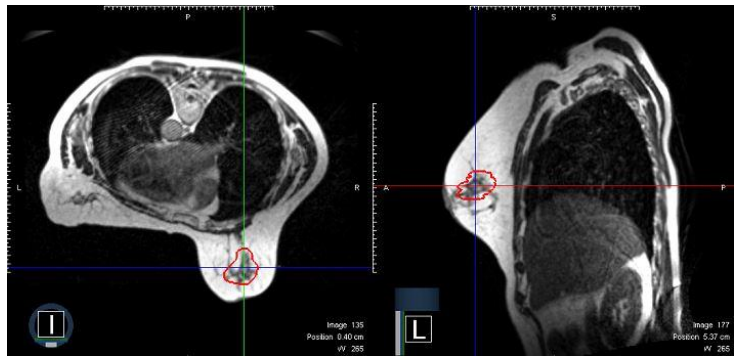

M. Kerimian, N.P.

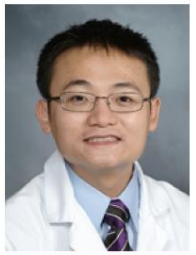
Residents, now in academia

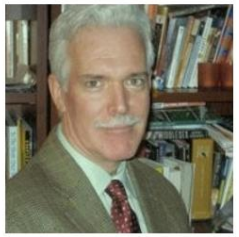
Nelly Huppert
Stella Lymberis
Shannon McDonalds
Min Tam Truong
Ariel Hirsh
Christine Min
Jim Mitchell
Michelle Alonso Basanta
Matthew Hardee
Oniynye Balogun
Sam Shin
Raini Sethi
Etin Osa Osa
Ben Cooper

Physicists, Dosimetrists and RTT

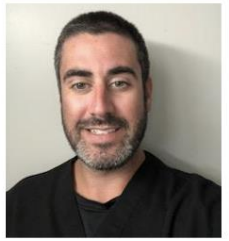
3/2/2021 first MR-guided prone treatment











Our patients!

EQUALS
Elaine ESR1 & Quality of Life Survey

EQUALS: Vaginal/Sexual Health (VSH) in Patients with ER+/HER2- Metastatic Breast Cancer (mBC)

Sarah L. Sammons,[1*] Jane L. Meisel,[2*] Kelly Shanahan,[3*] Timothy J. Pluard,[4*] David J. Portman,[5] Elizabeth Attias[5]

[1]Duke University, Duke Cancer Institute, Durham, NC; [2]Emory Winship Cancer Institute, Atlanta, GA; [3]Metavivor Research and Support, Inc, Annapolis, MD; [4]Saint Luke's Cancer Institute, Kansas City, MO; [5]Sermonix Pharmaceuticals, Columbus, OH

*Members of the EQUALS Steering Committee

Sermonix Pharmaceuticals

Disclosure

EQUALS
Elaine ESR1 & Quality of Life Survey

- Sermonix Pharmaceuticals—CEO, founder and stockholder
- Practicing gynecologist and women's health researcher for 20 years
- Co-Chair—Menopause Society and International Society for the Study of Women's Sexual Health 2013 Consensus Conference on Terminology associated with genitourinary symptoms associated with menopause

Introduction and Objectives

EQUALS
Elaine ESR1 & Quality of Life Survey

- Vaginal and sexual health (VSH) issues are commonly reported, in more than two-thirds, of women with breast cancer (BC)[1,2]
- However, these concerns are often under-recognized and understudied in women with BC being treated with endocrine therapy (ET)
- Studies on the prevalence, impact, and management of vaginal and sexual side effects are limited in women with metastatic BC (mBC)
- The overall objectives of EQUALS (ESR1 QUAlity of Life Survey) were to explore quality of life (QoL) and symptoms, biomarkers, treatment side effects, and patient-medical team communication of women with ER+/HER2- mBC[3-5]
- Among these surveys, we found that VSH issues were a primary QoL concern among women with mBC[3-5]
- Here, we summarize the common VSH thread in ER+/HER2- mBC patients from three EQUALS studies[3-5]

Sermonix Pharmaceuticals

1. Huynh V, et al. *Ann Surg Oncol* 2022;29(10):6238-6251. 2. Gambardella A, et al. *Endocrine* 2018;60(3):510-515. 3. Sammons SL, et al. *Cancer Res*. 2023;83(5 Suppl): P6-09-01. 4. Shanahan K, et al. *Menopause*. 2023;30:P-89. 5. Sammons S, et al. *Cancer Res*. 2024;84(9 Suppl): PO5-12-06.

Methods: EQUALS

EQUALS
Elaine ESR1 & Quality of Life Survey

EQUALS 1[1]
- Jun 2022
- 42 questions

EQUALS 2[2]
- Mar/Apr 2023
- 50 questions

EQUALS 3[3]
- Jun/Sep 2023
- 55 questions

Sent or posted online

ER+/HER2-
mBC patients

- Cure Media Group
- Facebook and Twitter groups
- Authors' contacts
- Breast cancer clinic patients
- METAvivor
- FORCE (Facing Hereditary Cancer EMPOWERED)
- The Chrysalis Initiative

- Questions on QoL varied between surveys (EQUALS 2 focused mostly on VSH)
- Survey answers were summarized descriptively and reported according to questions asked in each survey
- Patients received a $10 gift card at survey completion

Sermonix Pharmaceuticals

1. Sammons SL, et al. *Cancer Res*. 2023;83(5 Suppl): P6-09-01. 2. Shanahan K, et al. *Menopause*. 2023;30:P-89. 3. Sammons S, et al. *Cancer Res*. 2024;84(9 Suppl): PO5-12-06.

Responder Characteristics[1-3]

EQUALS
Elaine ESR1 & Quality of Life Survey

- Women (n=887) were a wide range of ages
- One-third and one-half were non-white in EQUALS 1 and 3, respectively; most were white in EQUALS 2
- Half (EQUALS 2 and 3) to almost three-quarters (EQUALS 1) lived in an urban and/or suburban setting
- About three-quarters had completed some higher education
- Most household incomes ranged from $25,000 to $100,000
- Women had received 1-4 lines of mBC treatment, including endocrine therapies, targeted therapies, antibody-drug conjugates, chemotherapy, and others

		EQUALS 1 (n=474)	EQUALS 2 (n=200)	EQUALS 3 (n=213)
Age, years	Distribution (varied by study)	<40 189 (40) 40-49 99 (21) 50-59 95 (20) 60-69 73 (15) ≥70 18 (4)	<47 43 (22) 47-55 52 (26) 56-60 47 (24) >60 58 (29)	<40 19 (9) 40-49 74 (34) 50-59 72 (34) 60-69 26 (12) ≥70 23 (11)
Race/ Ethnicity, n (%)	White Hispanic/Latino Black/African American American Indian/Alaskan Native Asian Declined to answer	319 (67) 112 (24) 32 (7) 12 (3) 7 (1) 1 (0)	170 (85) 15 (8) 13 (7) 1 (1) 1 (1) 1 (1)	94 (44) 103 (48) 9 (4) 4 (2) 0 3 (1)
Living setting, n (%)	Rural Suburban Urban	144 (30) 162 (34) 168 (35)	101 (51) 73 (37) 26 (13)	109 (51) 58 (27) 46 (22)
Highest education, n (%)	Some high school High school Bachelor's degree Master's degree Doctoral degree (JD/MD/PhD)	7 (1) 125 (28) 244 (51) 79 (17) 19 (4)	18 (9) 36 (18) 110 (55) 26 (13) 10 (5)	5 (2) 57 (27) 118 (55) 25 (12) 8 (4)
Average household income, n (%)	<$25,000 $25,000 to <$50,000 $50,000 to <$75,000 $75,000 to <$100,000 $100,000 to <$150,000 ≥$150,000 Declined to answer	14 (3) 116 (25) 104 (22) 83 (18) 87 (18) 46 (10) 24 (5)	3 (2) 18 (9) 76 (38) 36 (18) 28 (14) 23 (12) 16 (8)	11 (5) 45 (21) 87 (41) 29 (14) 15 (7) 9 (4) 17 (8)

1. Sammons SL, et al. *Cancer Res*. 2023;83(5 Suppl): P6-09-01. 2. Shanahan K, et al. *Menopause*. 2023;30:P-89. 3. Sammons S, et al. *Cancer Res*. 2024;84(9 Suppl): PO5-12-06.

Sermonix Pharmaceuticals

Vaginal Symptom Prevalence

EQUALS
Elaine ESR1 & Quality of Life Survey

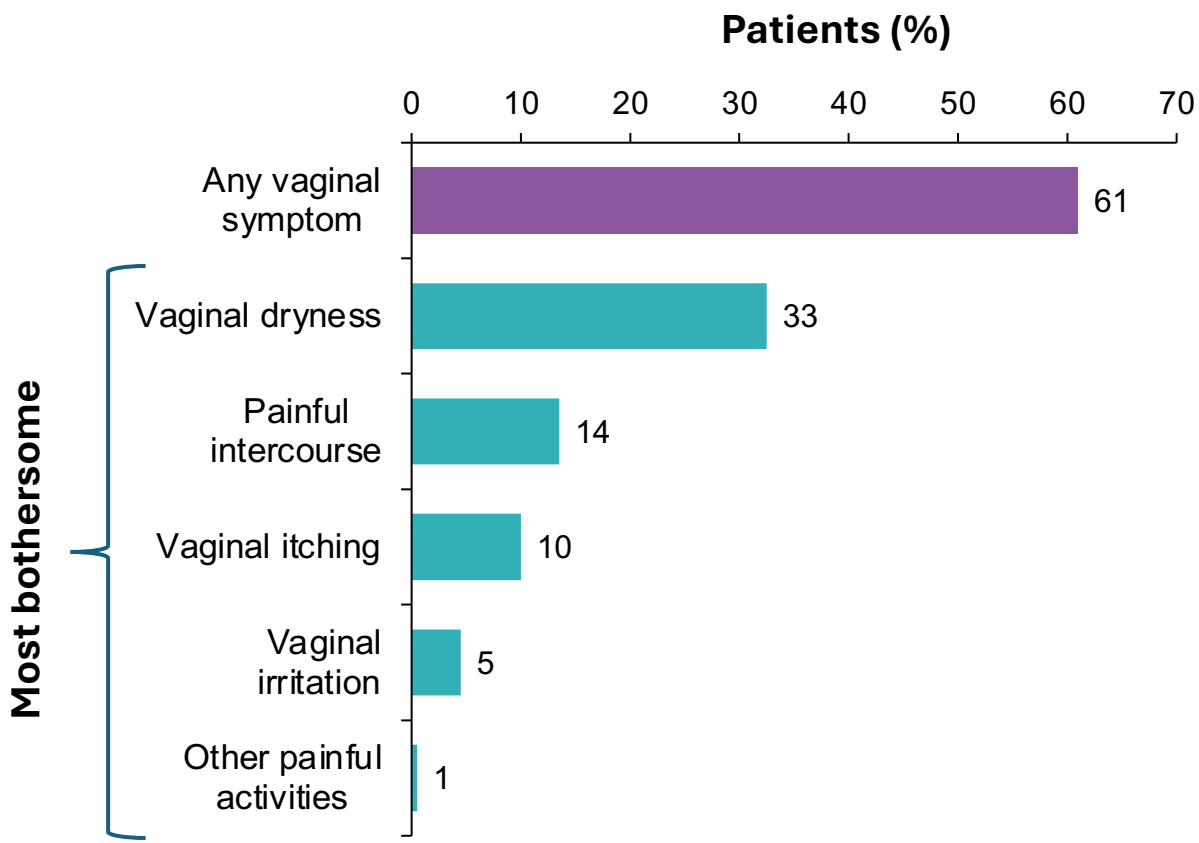
EQUALS 1 and 3[1,2]

- Common side effects impacting QoL were vaginal atrophy/dryness in EQUALS 1 and 3, and sexual dysfunction in EQUALS 3

EQUALS 2[3]

- Vaginal symptoms were
  - Experienced by 61% of patients (**Figure**)
  - Associated with BC treatment for a mean of 4.8 years
- Most bothersome symptoms were vaginal dryness, painful intercourse, vaginal itching, and vaginal irritation (**Figure**)

EQUALS 2[3]



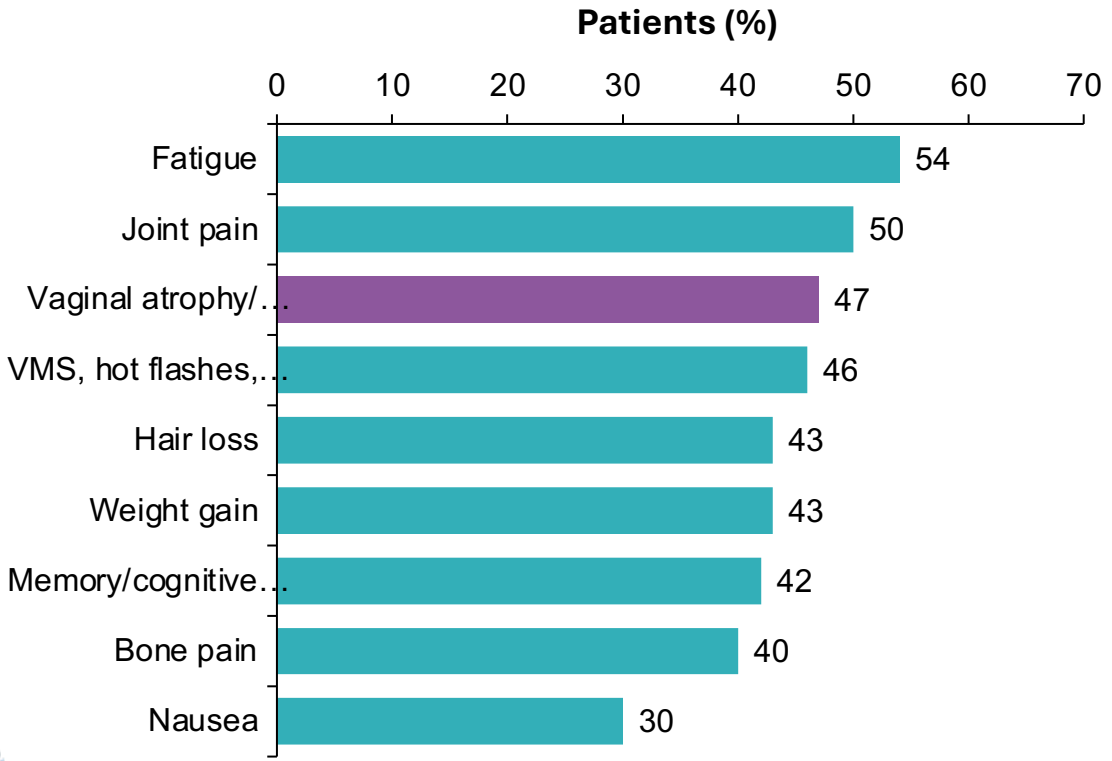
1. Sammons SL, et al. *Cancer Res*. 2023;83(5 Suppl): P6-09-01. 2. Sammons S, et al. *Cancer Res*. 2024;84(9 Suppl): PO5-12-06. 3. Shanahan K, et al. *Menopause*. 2023;30:P-89.

Vaginal/Sexual Symptoms Impact QoL

EQUALS
Elaine ESR1 & Quality of Life Survey

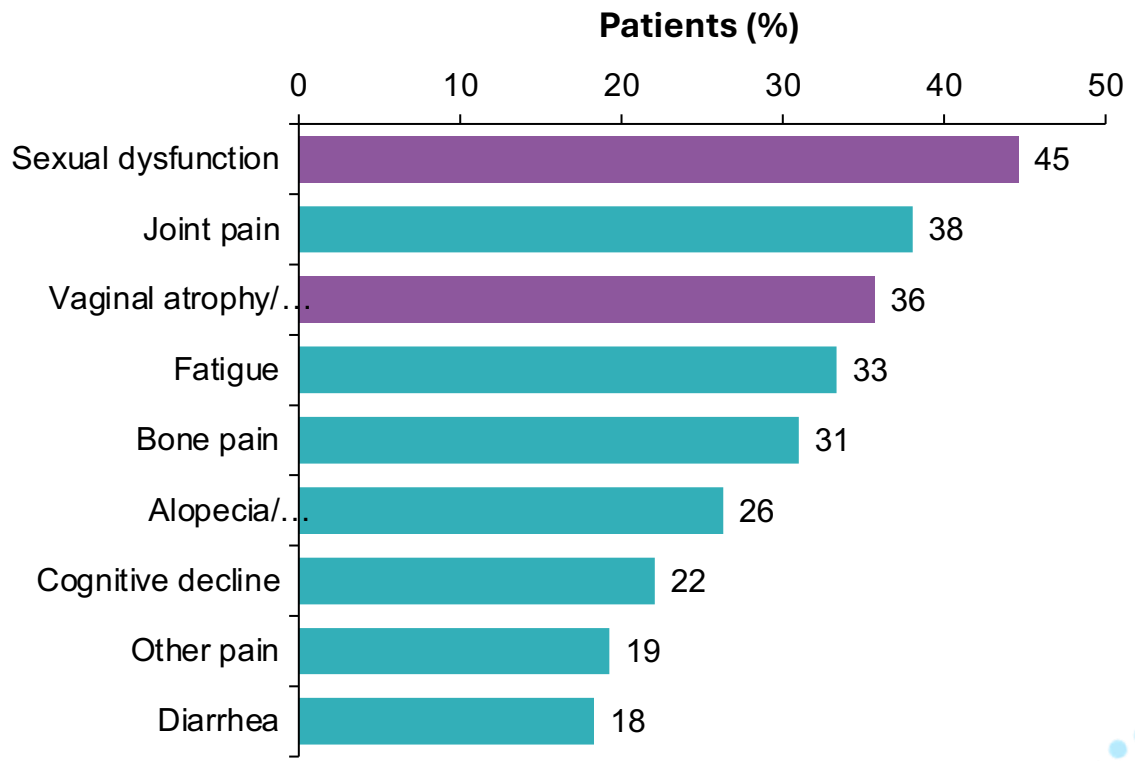
EQUALS 1[1]

Vaginal atrophy/dryness impacted QoL the most or moderately in almost half (47%) of patients



EQUALS 3[2]

Sexual dysfunction and vaginal atrophy/dryness were the first and third side effects impacting QoL the most



Sermonix Pharmaceuticals

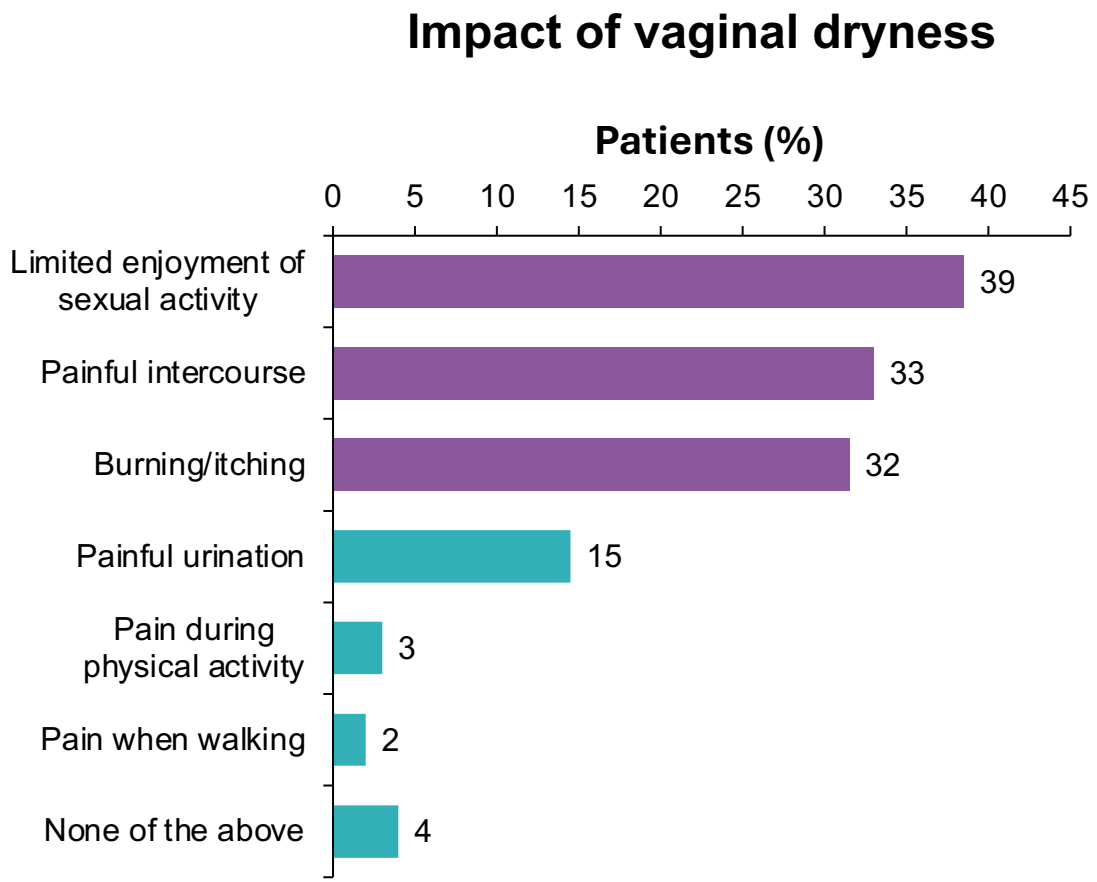
1. Sammons SL, et al. *Cancer Res*. 2023;83(5 Suppl): P6-09-01. 2. Sammons S, et al. *Cancer Res*. 2024;84(9 Suppl): PO5-12-06.

Impact of Vaginal/Sexual Side Effects

EQUALS
Elaine ESR1 & Quality of Life Survey

EQUALS 2

- Vaginal/sexual side effects
  - Negatively impacted frequency of sexual intercourse (61%) and self-esteem (64%)
  - Made 51% feel isolated
- Most commonly reported effects of vaginal dryness were limited enjoyment of sexual activity, pain with intercourse, and vaginal itching/burning (**Figure**)
- More than half (54%) reported that they never/almost never felt sexual desire/interest in the past month
  - This was especially true when prior ET had negatively impacted sexual health (61%)
- Low sexual desire bothered 56% of patients



Sermonix Pharmaceuticals

Shanahan K, et al. *Menopause*. 2023;30:P-89.

Vaginal/Sexual Side Effects Were Concerning

EQUALS
Elaine ESR1 & Quality of Life Survey

EQUALS 1[1]

62% of patients worried about sexual intimacy

EQUALS 2[2]

80% of patients were concerned about the vaginal and sexual side effects of BC treatment

EQUALS 3[3]

In 27% of patients, sexual dysfunction was reported as extremely/moderately concerning

1. Sammons SL, et al. *Cancer Res*. 2023;83(5 Suppl): P6-09-01. 2. Shanahan K, et al. *Menopause*. 2023;30:P-89. 3. Sammons S, et al. *Cancer Res*. 2024;84(9 Suppl): PO5-12-06.

Discussing Vaginal/Sexual Side Effects

EQUALS
Elaine ESR1 & Quality of Life Survey

Women were uncomfortable talking about vaginal and sexual side effects, and felt poorly informed about them and poorly equipped by their medical team to manage them

EQUALS 1 and 2[1,2]

- 31% to 61% of women were uncomfortable discussing sexual side effects with their medical team
- Twice as likely to discuss with their gynecologist than oncologist
- Oncologist gender influenced women's comfort discussing vaginal/sexual side effects
  - 41% to 60% of women with female oncologists felt uncomfortable
  - 56% to 64% of women with male oncologists felt uncomfortable

EQUALS 2[2]

- Approximately one-third of women felt
  - Poorly informed about these side effects by their medical team (38%)
  - Poorly equipped to improve these side effects (33%)

Looking forward

93% of patients in EQUALS 2 expressed interest in an FDA-approved, well-tolerated, BC treatment that also improved vaginal and sexual health

Sermonix Pharmaceuticals

1. Sammons SL, et al. *Cancer Res*. 2023;83(5 Suppl): P6-09-01. 2. Shanahan K, et al. *Menopause*. 2023;30:P-89.

Conclusions

EQUALS
Elaine ESR1 & Quality of Life Survey

- Our review of three EQUALS confirms that
  - Women being treated for ER+/HER2- mBC experienced and were concerned about their vaginal/sexual side effects
  - Such side effects negatively impacted many women's frequency of intercourse, self-esteem, and feelings of isolation
- Many women were uncomfortable discussing these symptoms with their medical team and felt poorly informed and equipped to manage them
- While mBC patients were surveyed, early-stage BC patients also encounter such treatment side effects, highlighting the need for
  - Therapies that improve vaginal/sexual outcomes and side effects
  - Better communication between patients and their medical team about managing these side effects

No Longer a “Necessary Evil”

Managing Genitourinary Syndrome of Menopause in Cancer Survivors

Catherine Lu Dugan B.A., Alisha Othieno M.D., Mindy Goldman M.D.

11/01/2024

Why does GSM happen in cancer survivors?

- **Estrogens**: A group of hormones that play an important role in many different parts of the body
- Hormone-receptor positive (HR+) tumors use estrogen to grow
- Genitourinary Syndrome of Menopause (**GSM**): A collection of symptoms such as vaginal dryness, painful intercourse, and recurrent urinary tract infections

Topical Estrogen Can Be Safe for Survivors

ACOG
The American College of Obstetricians and Gynecologists

NCCN National Comprehensive Cancer Network®

The Menopause Society™
Leading the Conversation

1. Non-hormonal treatment is first line treatment
2. Hormonal-based treatments are an option for many breast cancer survivors

Let's talk about GSM

↑ Systemic Estrogen = ↑ HR+ Tumor

↓ Systemic Estrogen = ↑ GSM

↑ Local Estrogen ≠ ↑ Systemic Estrogen

References

Dugan CL, Othieno AA, Goldman ME. Genitourinary Syndrome of Menopause in Cancer Survivors. Clinical Obstetrics Gynecology 2024 Mar 1;67(1):89-100. doi: 10.1097/GRF.0000000000000848. Epub 2023 Dec 18. PMID: 38108399.

AT THE FOREFRONT
UChicago Medicine

Is pCR Enough to Limit Systemic Therapy: Pro

Rita Nanda, M.D.
Director, Breast Oncology Program
Associate Professor of Medicine

RISE UP for Breast Cancer
November 1, 2024
San Francisco, CA

Disclosures

Advisory Board: AstraZeneca, Daiichi Sankyo, Exact Sciences, GE, Gilead, Guardant Health, Merck, Moderna, Novartis, OBI, Pfizer, Sanofi, Seagen, Stemline, Summit Therapeutics

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CME Speaker: SITC/Medscape, Research to Practice, Prime Education, OncLive, Clinical Care Options, Creative Education Concepts

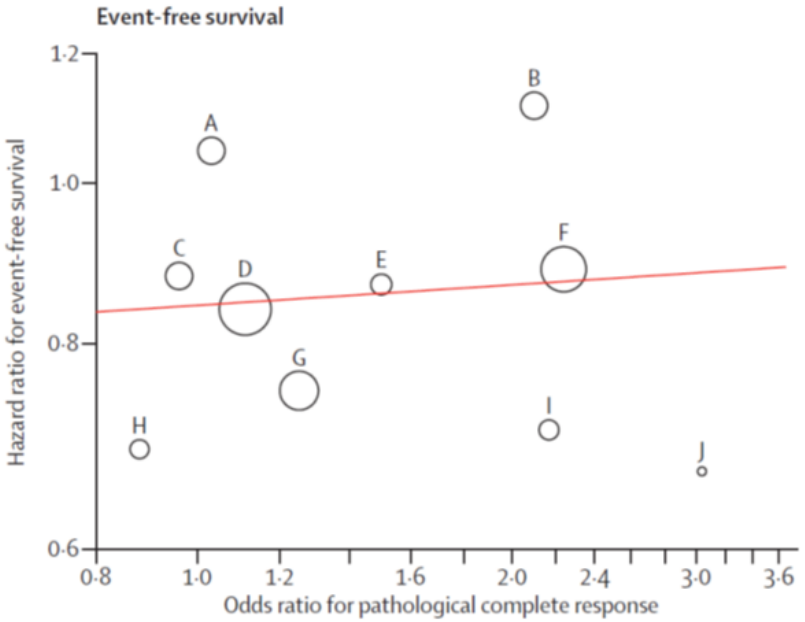
Role of pCR in Breast Cancer

- pCR is defined as the absence of invasive cancer in the breast and axilla after neoadjuvant therapy (ypT0/Tis ypN0)
- pCR has been investigated at the trial level
  - Correlates with EFS/DFS/OS
  - Surrogate endpoint for FDA accelerated approval of novel agents
- pCR has been investigated at the patient level
  - Prognostic-correlates with improvement in longterm outcomes
  - Tailor therapy—is pCR enough to limit systemic therapy?

Inconsistent Correlation Between pCR and EFS in EBC

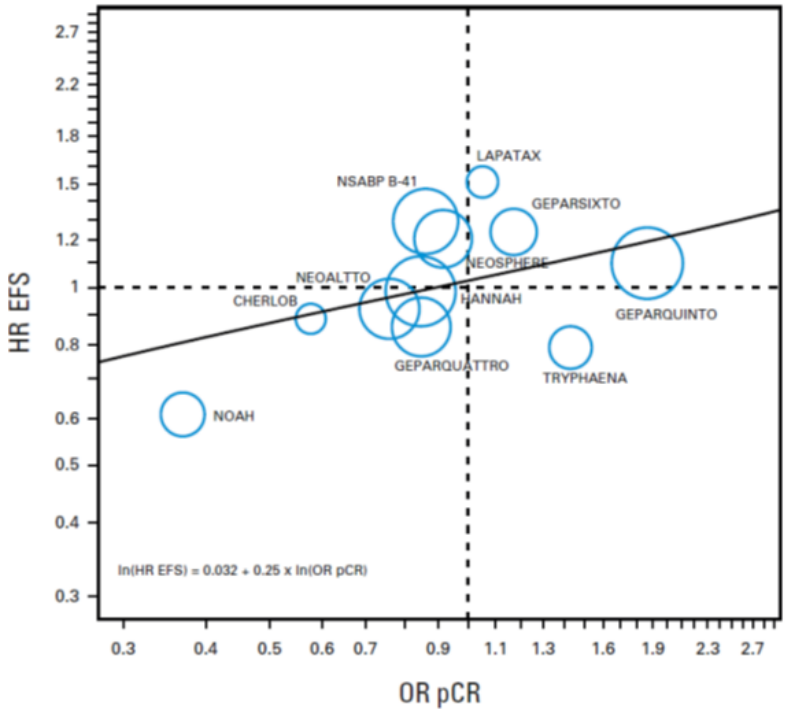
- Trial level meta-analysis of small underpowered studies show weak correlation between two statistical metrics, Odds Ratio for pCR and Hazard rate for EFS
- Meta-analysis of individually underpowered trials does not increase the level of evidence

CTNeoBC pooled analysis



Cortazar P, et al. The Lancet, 384:164-172, 2014

Pooled analysis of HER2+ trials

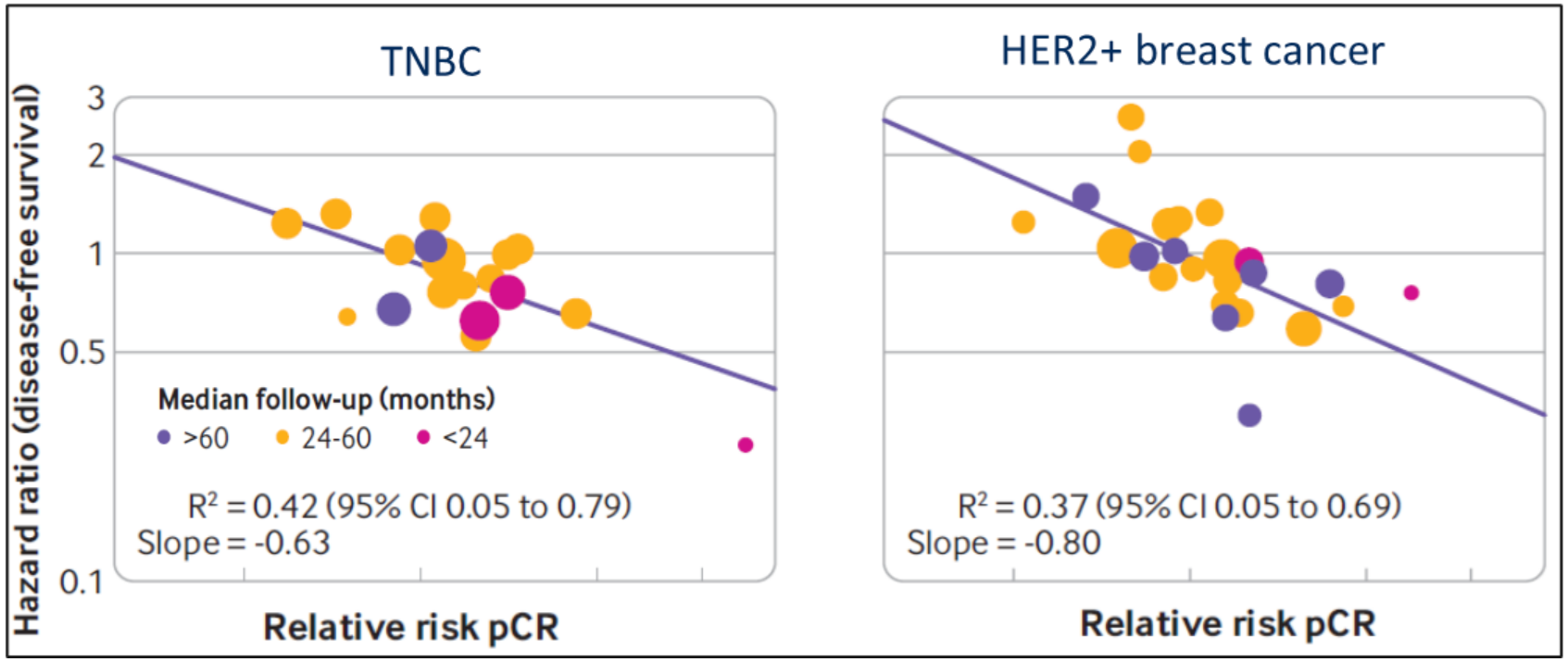


Squifflet P, et al. J Clin Oncol, 41:2988-1997, 2023

Limitations of Neoadjuvant Trials

- Goal of neoadjuvant studies is to rapidly identify promising systemic therapies using pCR as an endpoint-as such most are underpowered for longterm outcomes
- Despite being underpowered, some trials/meta-analyses do demonstrate an improvement in DFS

Correlation between pCR and DFS in TNBC and HER2+ breast cancer



Conforti F. et al. Br Med J 2021 Dec 21;375

Impact of pCR on EFS in Neoadjuvant Trial in TNBC

BrighTNess[17]	III	PTX → AC PTX+Cb → AC PTX+Cb+Vel → AC	pCR	31 vs 58 vs 53 *P*=.0001 (PTX+Cb +Vel vs PTX)	4-y EFS, 68.5% vs 79.3% vs 78.2% HR, 0.63 (PTX+Cb+Vel vs PTX) HR, 1.12 (PTX+Cb+Vel vs PTX+Cb HR, 0.57 (PTX+Cb vs PTX)	Showed the translation of platinum-related pCR Improvement into long-term clinically meaningful benefit
CALGB 40603[11]	II	PTX → AC PTX+Bev → AC+Bev PTX+Cb → AC PTX+Cb+Bev → AC+Bev	pCR	39 vs 43 vs 49 vs 60 *P*=.0029 (with Cb vs without Cb) *P*=.057 (with Bev vs without Bev)	5-y EFS: HR, 0.99 (95% CI, 0.70–1.40) (with Cb vs without Cb) HR, 0.91 (95% CI, 0.64–1.29) (with Bev vs without Bev)	Showed platinum agents improve pCR rate, did not demonstrate improvement in EFS with platinum
GeparSixto[13,100]	II	PTX+npLD+Bev → EC PTX+npLD+Bev+Cb → EC	pCR	36.9 vs 53.2 *P*=.005	3-y DFS, 76.8% vs 86.1% HR, 0.56 (95% CI, 0.34–0.93)	Showed platinum agents improve pCR rate and demonstrated improvement in EFS with platinum
NeoSTOP[40]	II	PTX+Cb → AC DXP+Cb	pCR	54 vs 54		Showed clinically meaningful pCR results with anthracycline-free regimen for TN patients
KEYNOTE-522[12,30]	III	PTX+Cb+Pla → AC/EC+Pla PTX+Cb+Pembro → AC/EC+Pembro * Adjuvant Pembro/Pla	pCR and EFS	55.6 vs 63	3-y EFS, 76.8% vs 84.5% HR, 0.63 (95% CI, 0.48–0.82)	Established the role of immunotherapy in the neoadjuvant/adjuvant treatment paradigm of TN patients Innovative coprimary endpoints design
IMpassion031[27]	III	nab-PTX +Pla → AC+Pla nab-PTX+Atezo → AC+Aetzo * Adjuvant Atezo/Pla	pCR in ITT and pCR in PD-L1+	41 vs 58 *P*=.004	EFS, HR, 0.76 (95% CI, 0.4–1.44)	Demonstrated pCR improvement with the addition of immunotherapy to NACT
GeparNuevo[28,101]	II	nab-PTX+Pla → AC+Pla nab-PTX+Durva → AC+Durva	pCR	44.2 vs 53.4 *P*=.29	3-y IDFS, 76.9% vs 84.9% HR, 0.48 (95% CI, 0.24–0.97)	Evaluated the role of immune-system priming with a 'window' phase Demonstrated long-term benefit from neoadjuvant ICI without the administration of postsurgery immunotherapy

Spring et al, JNCCN 2022

Improvement in pCR associated with trial level improvement in EFS when trials powered appropriately

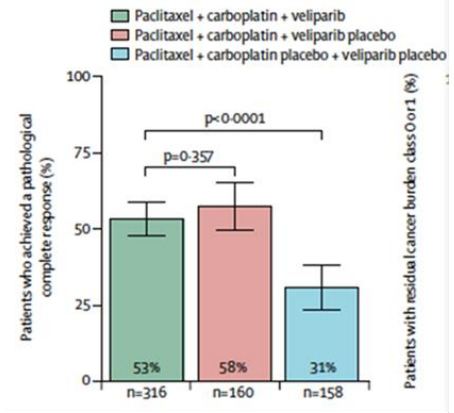
- T->AC: pCR ~30-40%
- T+carbo->AC: pCR ~50-55%
- T+carbo+pembro->AC+pembro: pCR ~64%

The Addition of Carboplatin to Paclitaxel Followed by AC Improves pCR and EFS in TNBC

BrighTNess trial results

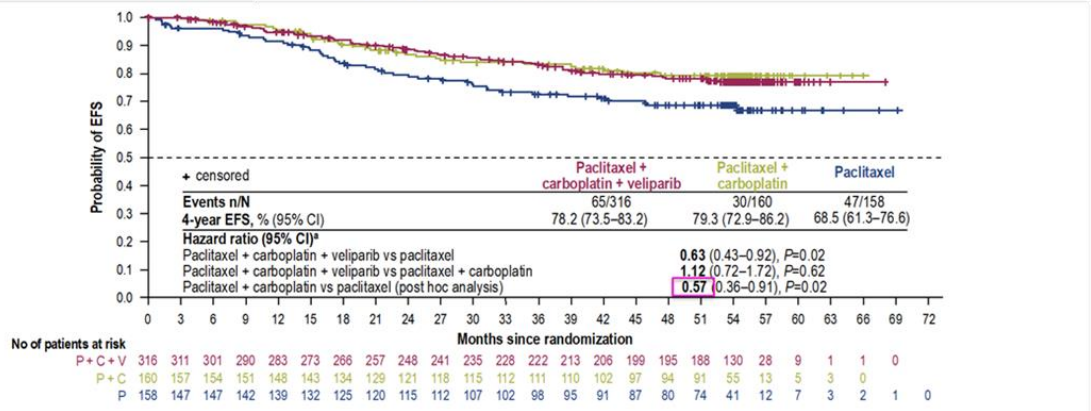
pCR rate 53-58%

Valiparib (PARPi) provided no benefit



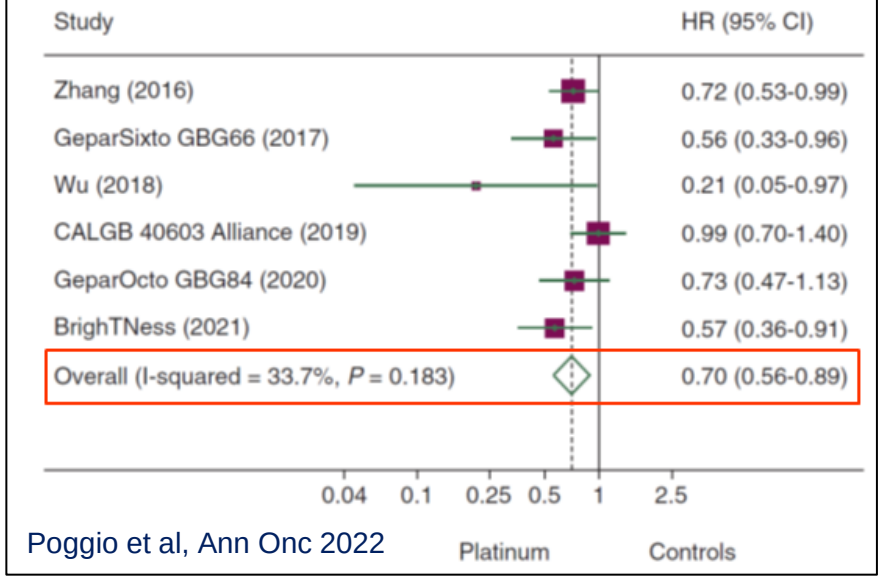
Loibl S et al. Lancet Oncol 19:497-509, 2018

4.5-year Event Free Survival



Geyer CE et al. Annals Onc 33:384-94, 2022

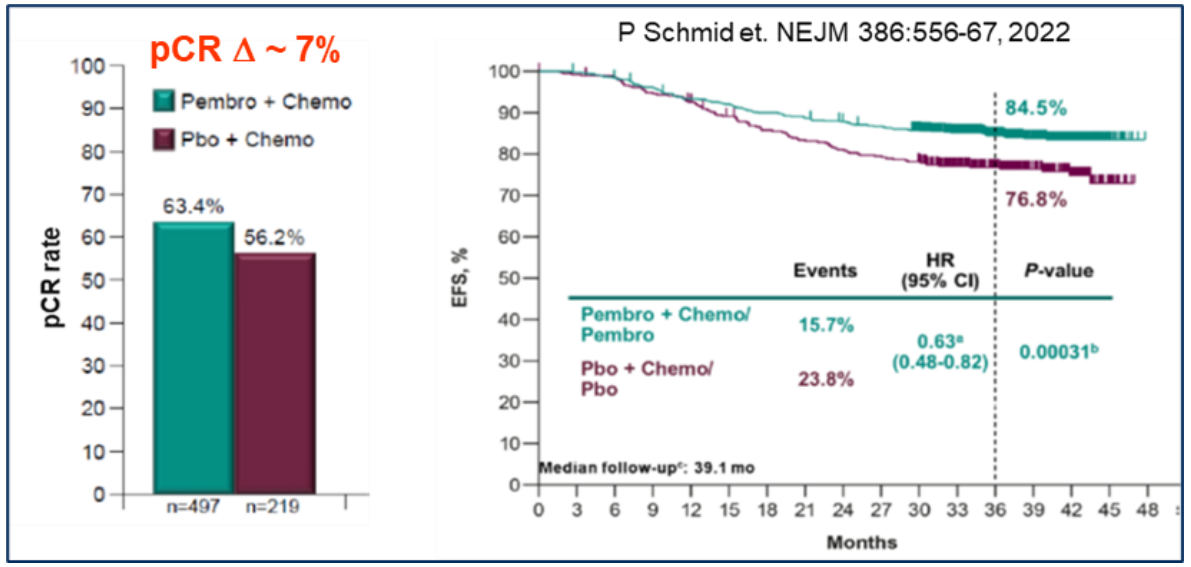
Meta-analysis of EFS in 6 randomized trials



Poggio et al, Ann Onc 2022

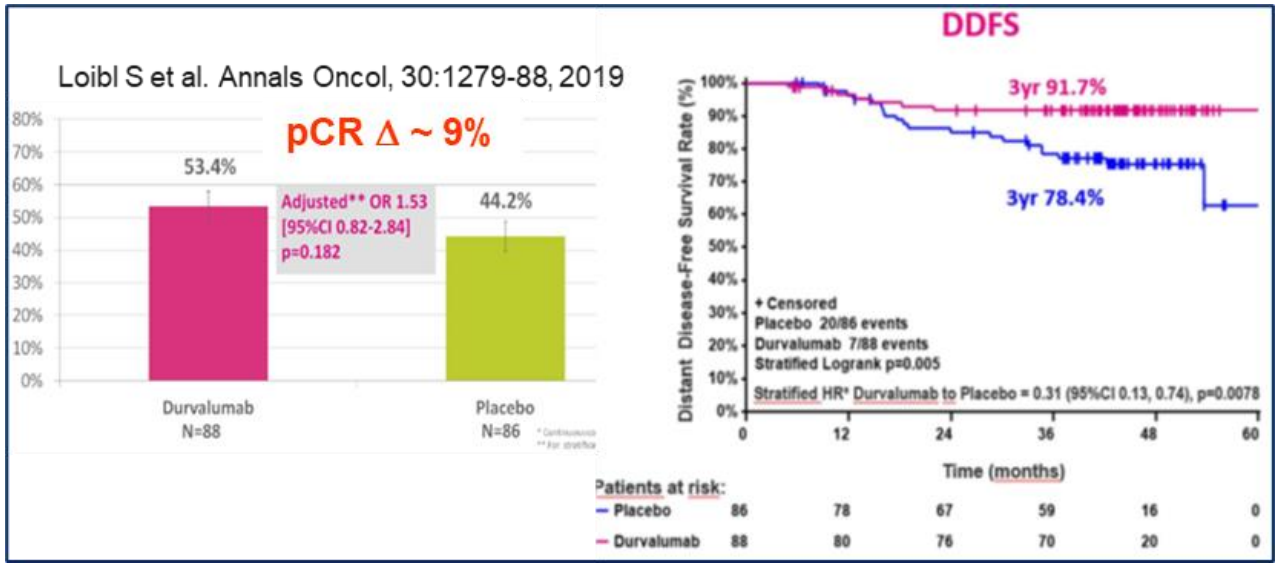
Addition of Immunotherapy to NACT Improves pCR and Long-term Outcomes in KN-522 and GeparNuevo

KEYNOTE-522



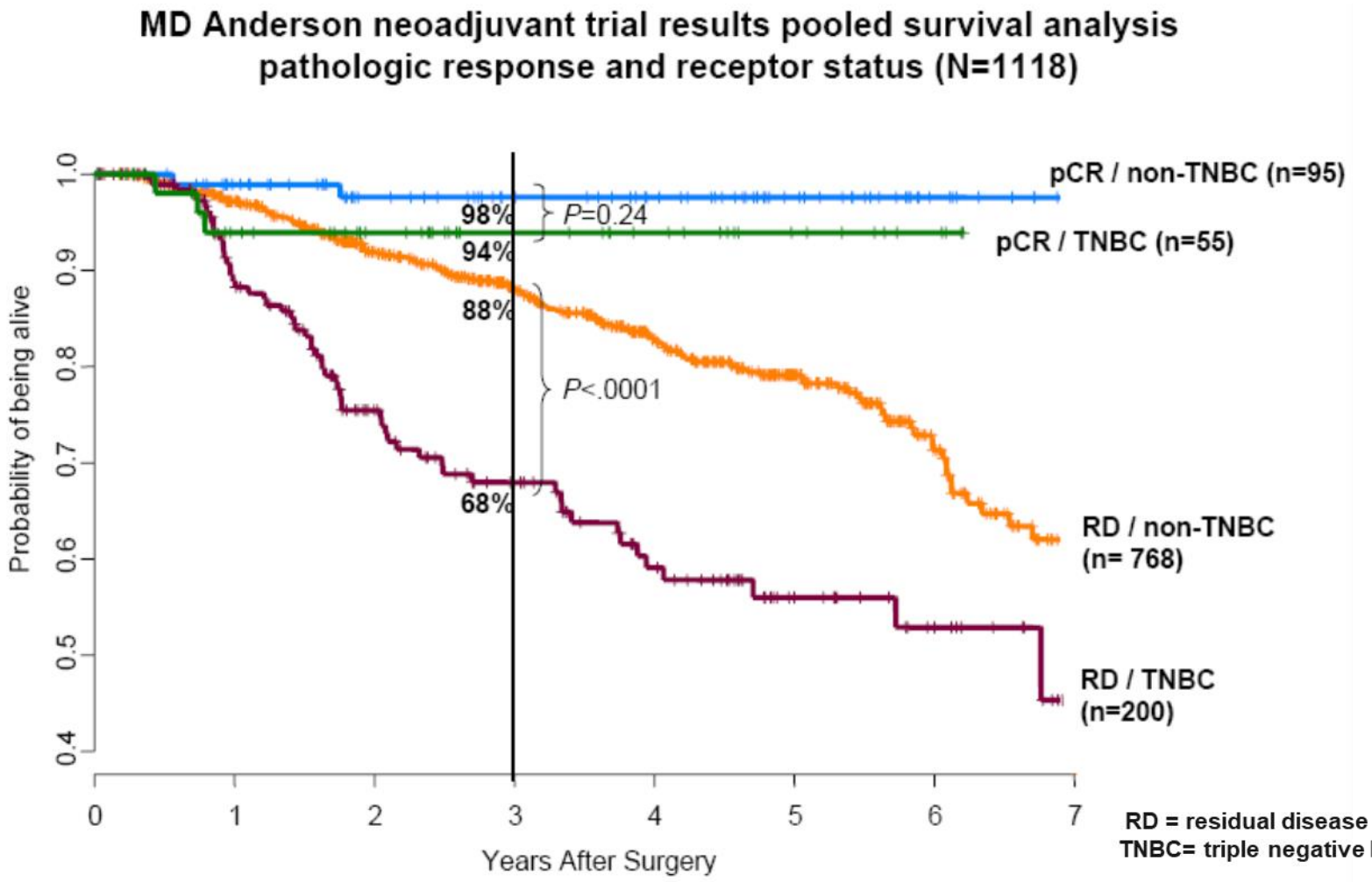
Significant improvement in pCR, EFS, and OS

GeparNuevo



Significant improvement in pCR and EFS without adjuvant IO

pCR is a Predictor of Long-term Survival in EBC



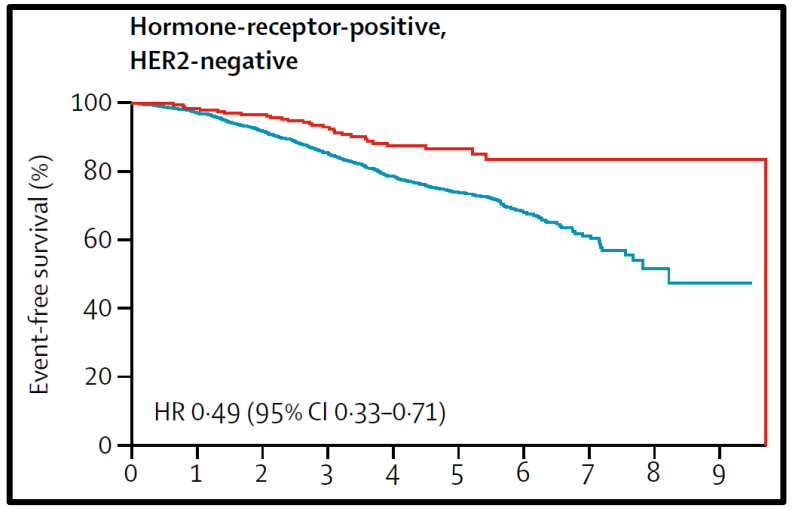
RD = residual disease
TNBC= triple negative breast cancer

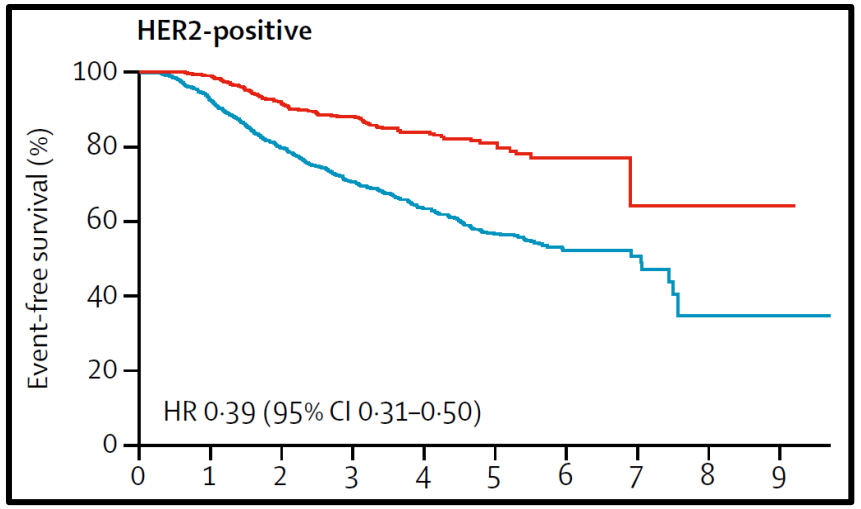
Multiple studies investigating pCR and EFS/DFS/OS in EBC at the patinent level had similar findings

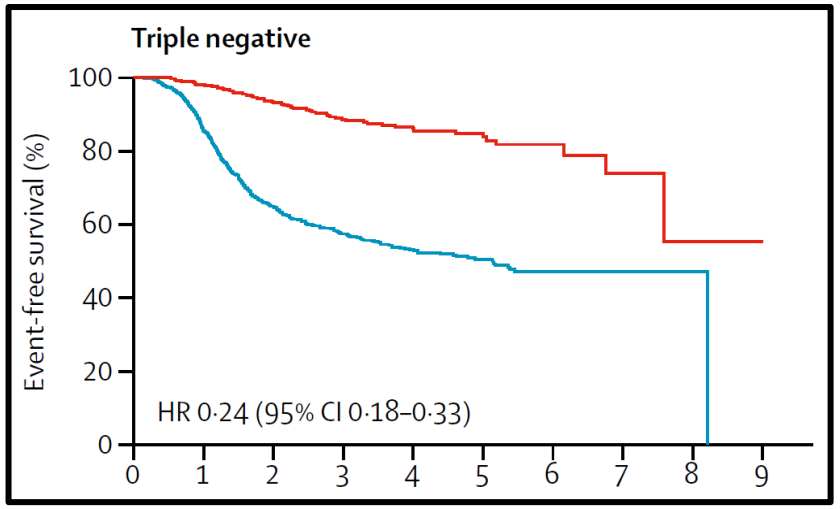
Liedtke et al, JCO 2008

Association Between pCR and EFS by Breast Cancer Subtype

- 12 international neoadjuvant trials (>200 pts/trial)
- 11,955 patients total
- Regardless of subtype, strong correlation between pCR and EFS-strongest in TNBC and HER2+







Cortazar et al, Lancet 2014

Summary

- Robust patient-level data demonstrating that pCR associated with improved long-term outcomes
- Appropriately powered trials have also demonstrated significant correlation b/w pCR and EFS/DDFS (even OS!) at the trial level
- Lack of pCR is not necessarily associated with poor long-term outcome
  - Adjuvant therapy affects outcome: T-DM1, capecitabine, ?immunotherapy
  - ctDNA clearance, reduction in RCB
- Is pCR enough to limit systemic therapy? **YES**

AT THE FOREFRONT
UChicago Medicine

Thank You!

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Special thank you to Lajos Pusztai, M.D., D.Phil

Is pCR enough to limit systemic therapy: NO

Cesar A. Santa-Maria, MD MSCI

Associate Professor of Oncology

Breast and Gynecological Malignancies Group

Sidney Kimmel Comprehensive Cancer Center

Johns Hopkins Medicine

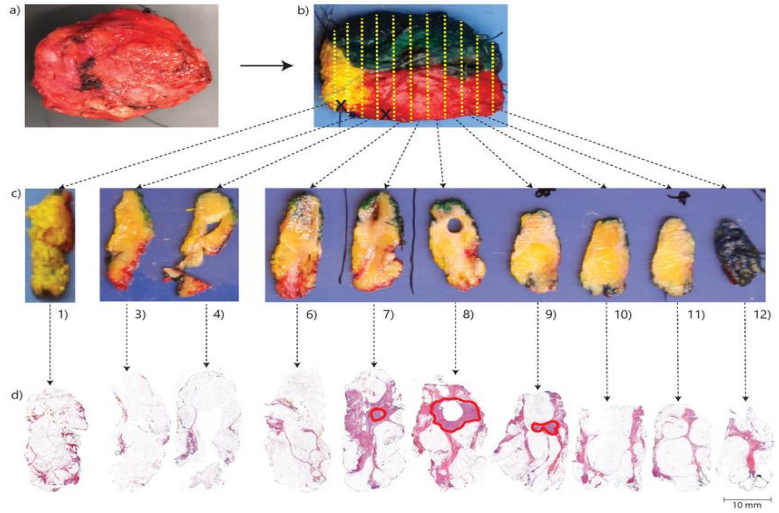
Argument overview

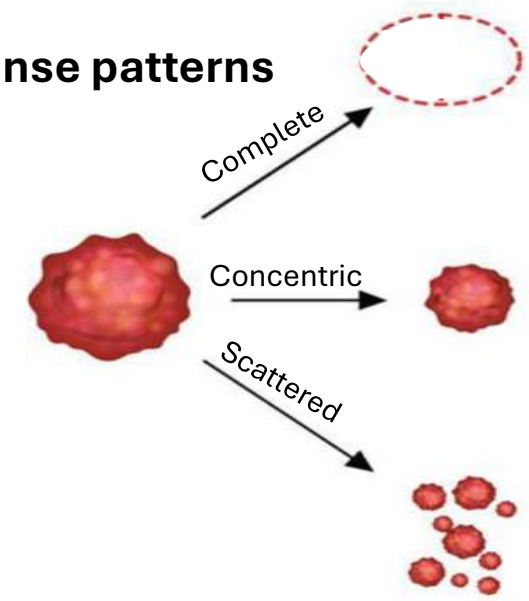
For pCR to limit systemic therapy it must:

- Be robust and reproducible
- Reliably predict patient outcomes
- Predict lack of benefit to adjuvant systemic therapy

Technical limitations in pCR assessment

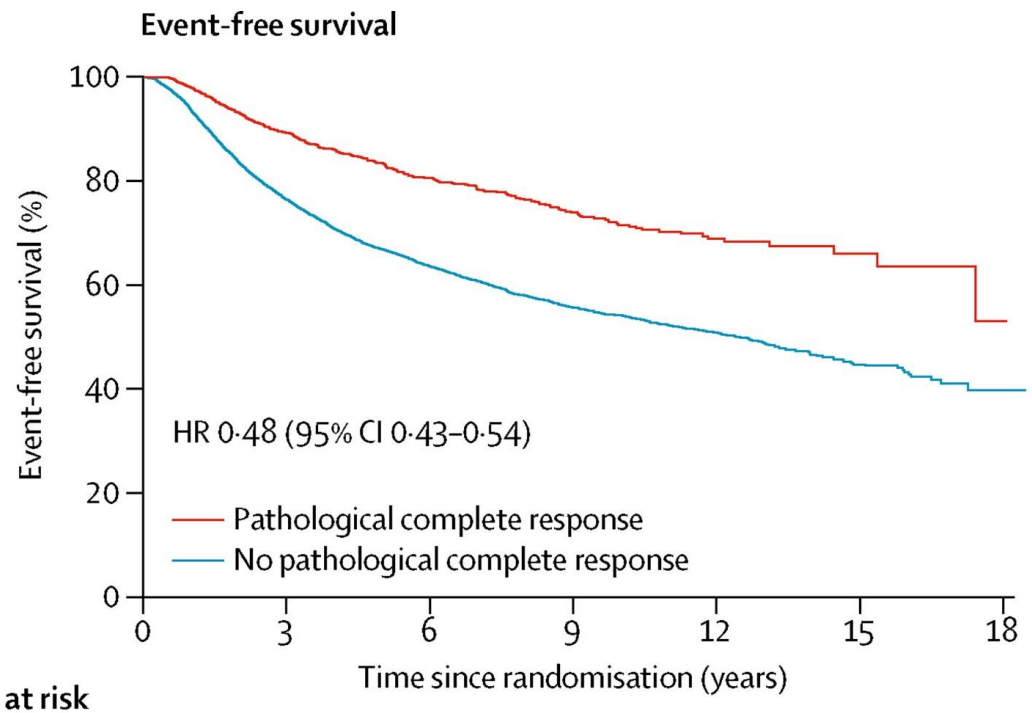
- pCR is the gold standard in assessing response to neoadjuvant therapy
- Technical/path factors:
  - Processing lacks standardization (ie routine grossing procedures, tumor bed sectioning/sampling)
  - Sectioning may miss a small focus of invasive disease
    - Particularly a potential issue in larger tumors
    - Response pattern after neoadjuvant therapy can vary
  - Centralized assessment can result in some discordance

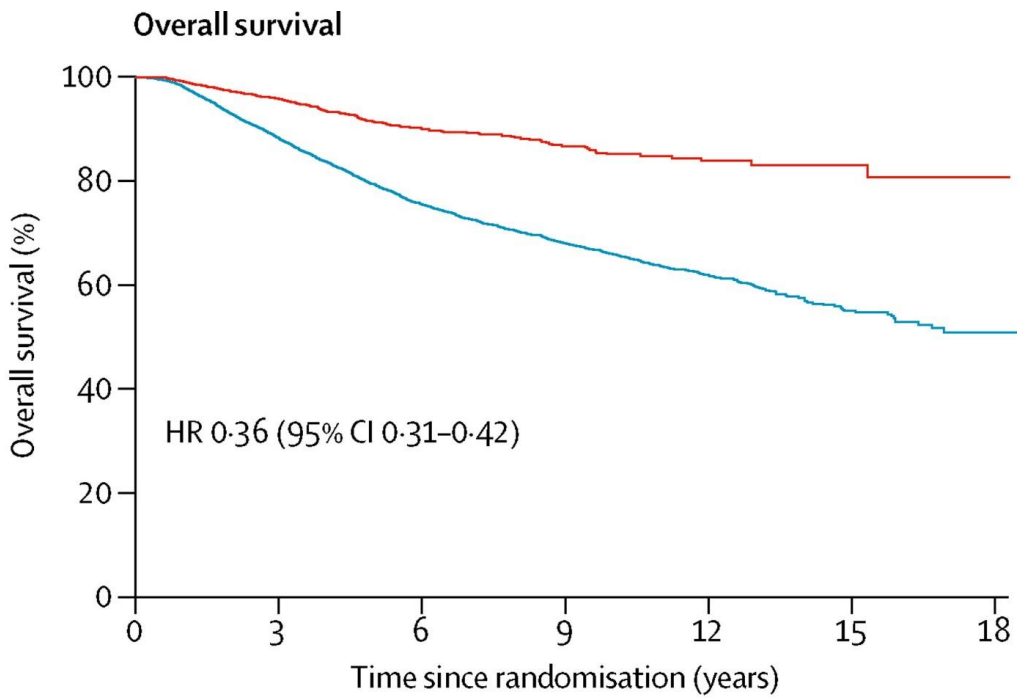




Han et al Arch Pathol Lab Med 2020; Huang et al Front Bioeng Biotechnol 2021

Patients achieving pCR have a better prognosis than those who do not: but not a perfect relationship



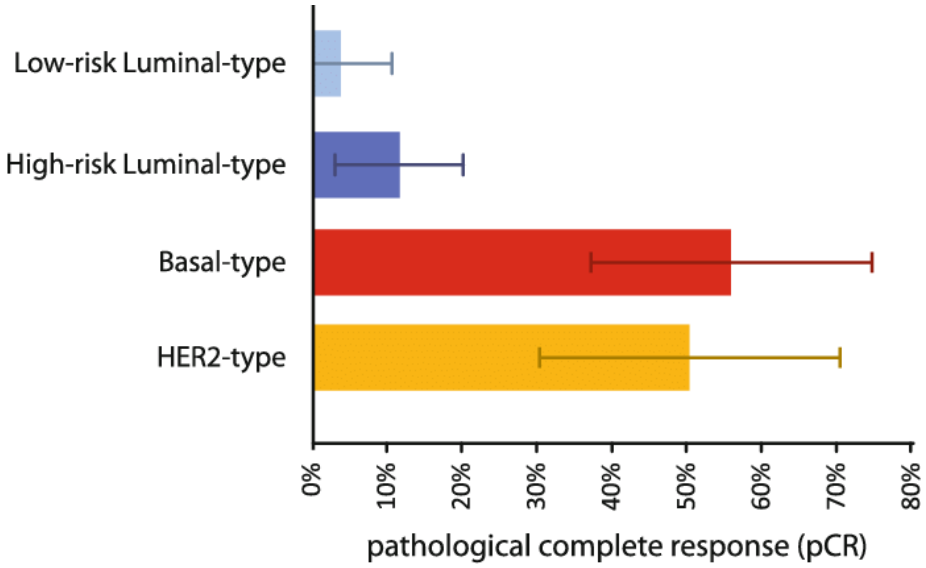


Number at risk							
Pathological complete response	2131	1513	583	337	124	35	2
No pathological complete response	9824	6169	2674	1523	525	165	1

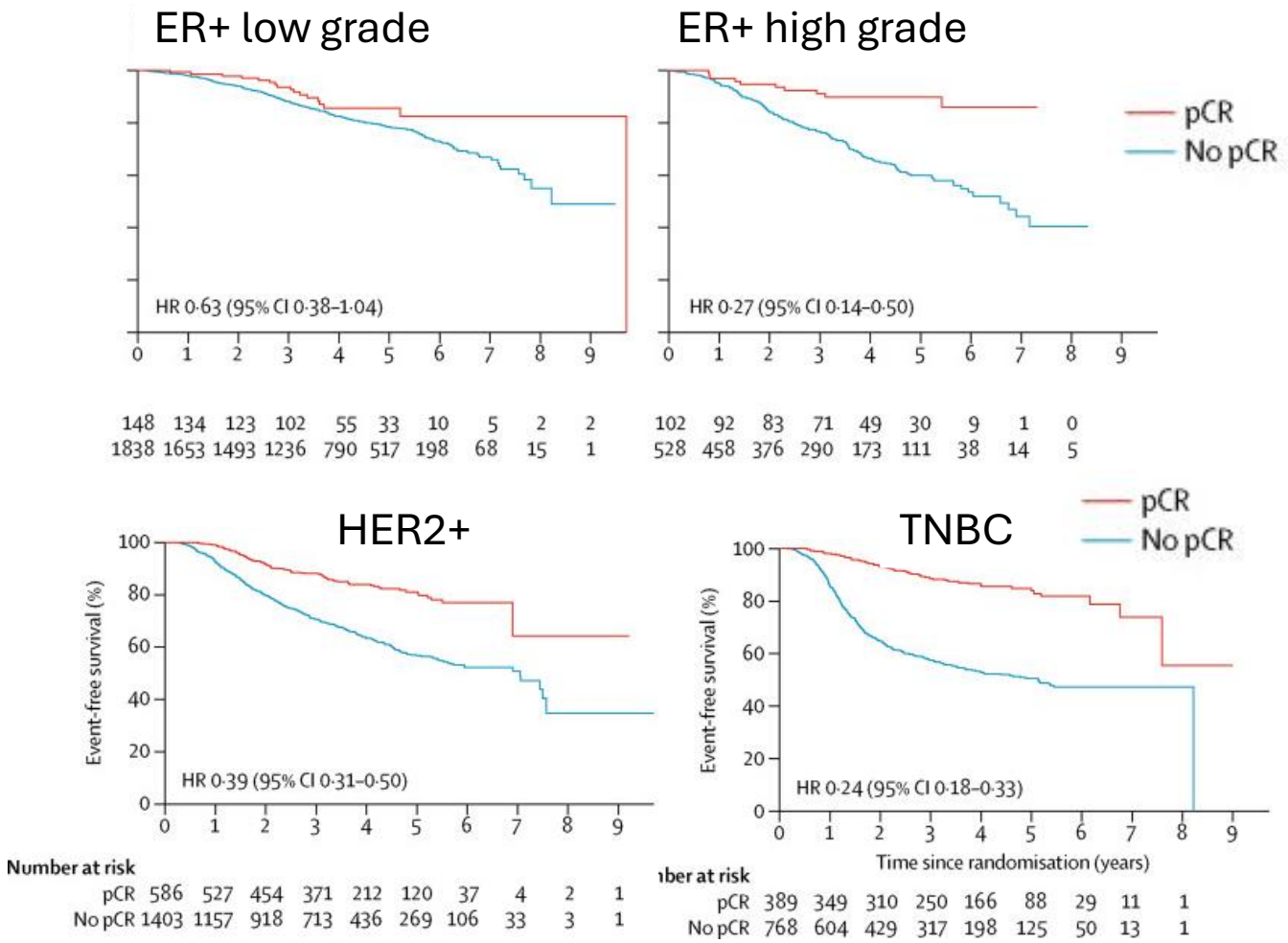
	2131	1618	640	383	145	43	3
	9824	7119	3173	1859	659	209	3

Cortazar et al Lancet 2014

pCR rate to chemotherapy varies by subtype, pCR relationship with survival does as well

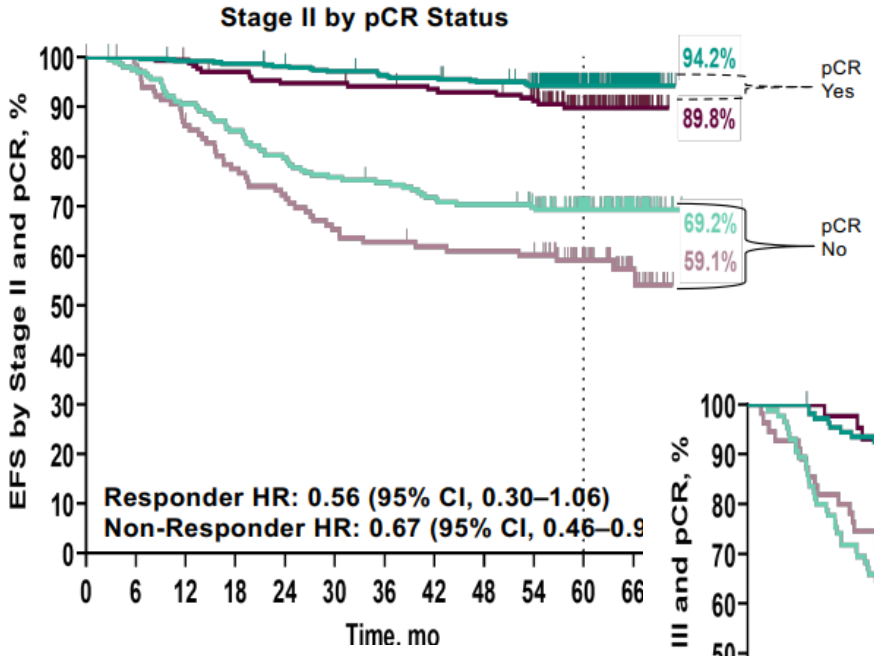


Krijgsman et al BCRT 2012

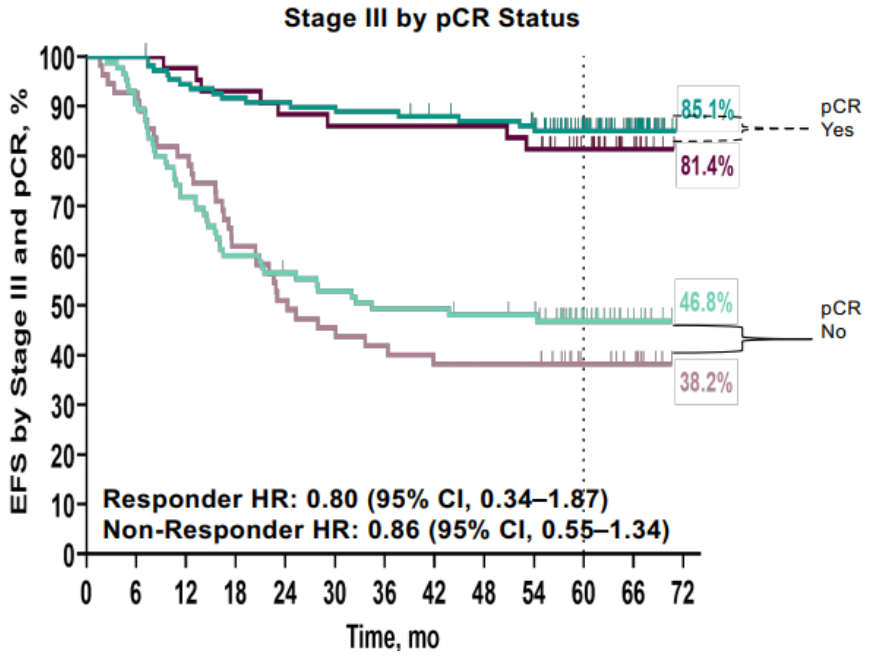


Cortazar et al Lancet 2014

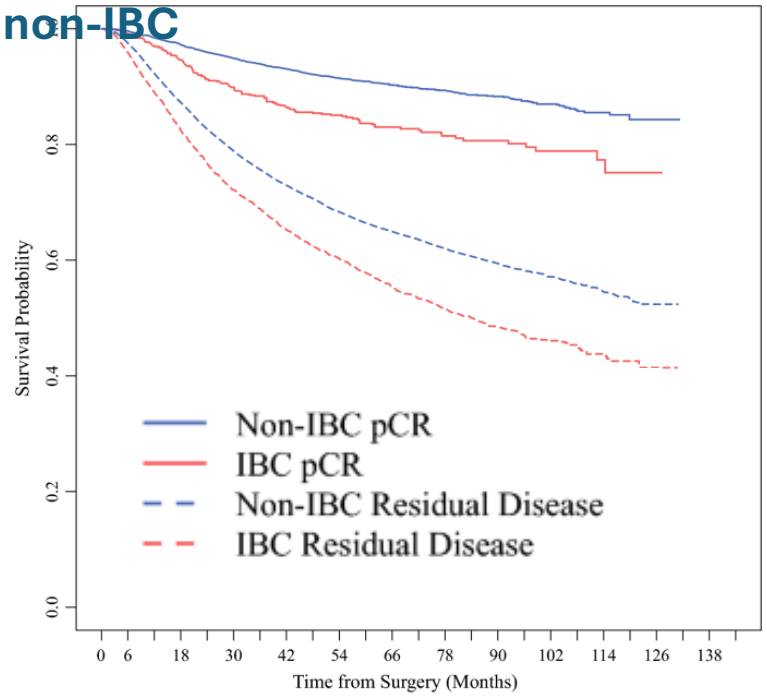
Baseline clinical stage matters, pts with higher stage have higher rates of recurrence post-pCR



Worse EFS in stage 3 vs 2 in pts achieving a pCR in KEYNOTE-522

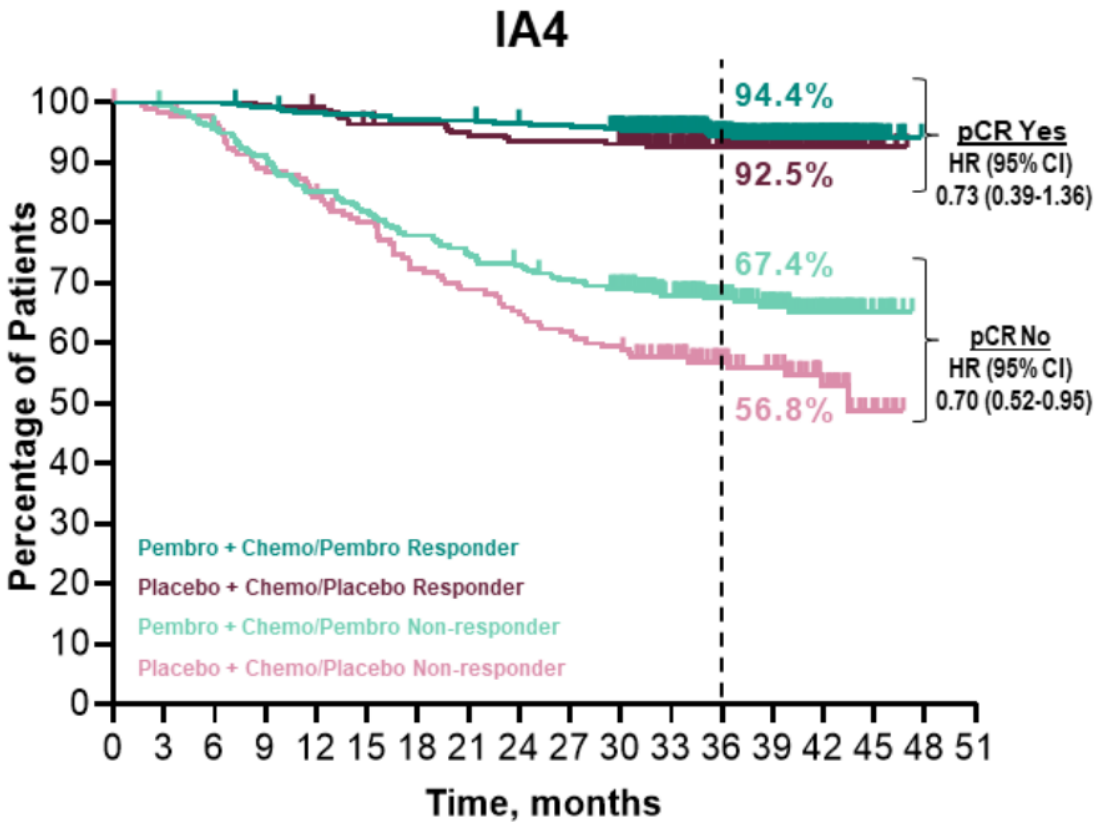


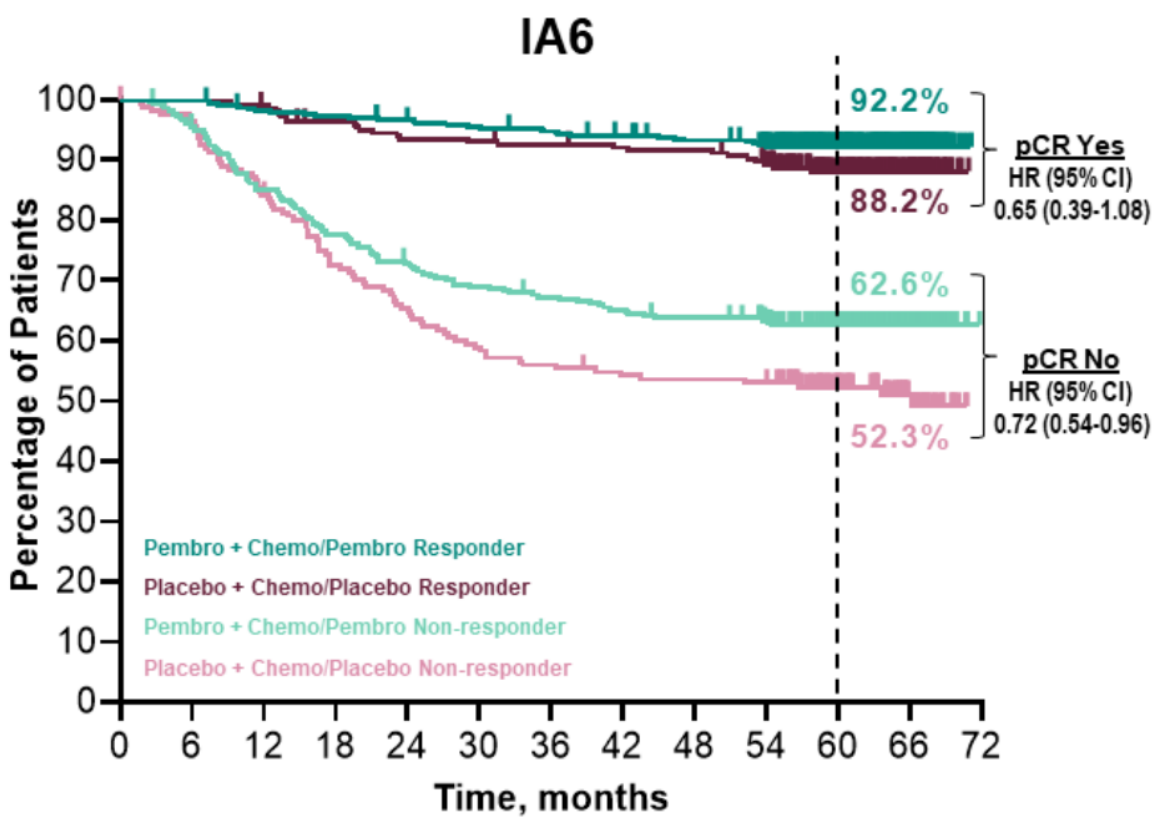
NCDB study finding pCR in pts with IBC associated with lower DFS than non-IBC



Schmid et al SABCS 2023, Parrish et al Breast Oncology 2024, Huober et al npj breast cancer 2023

Does the path to pCR matter?

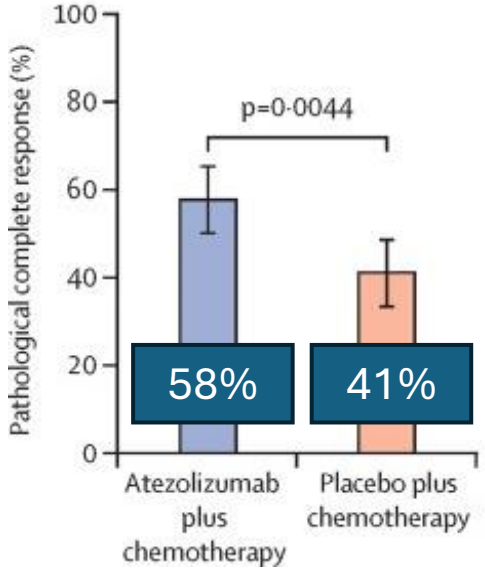


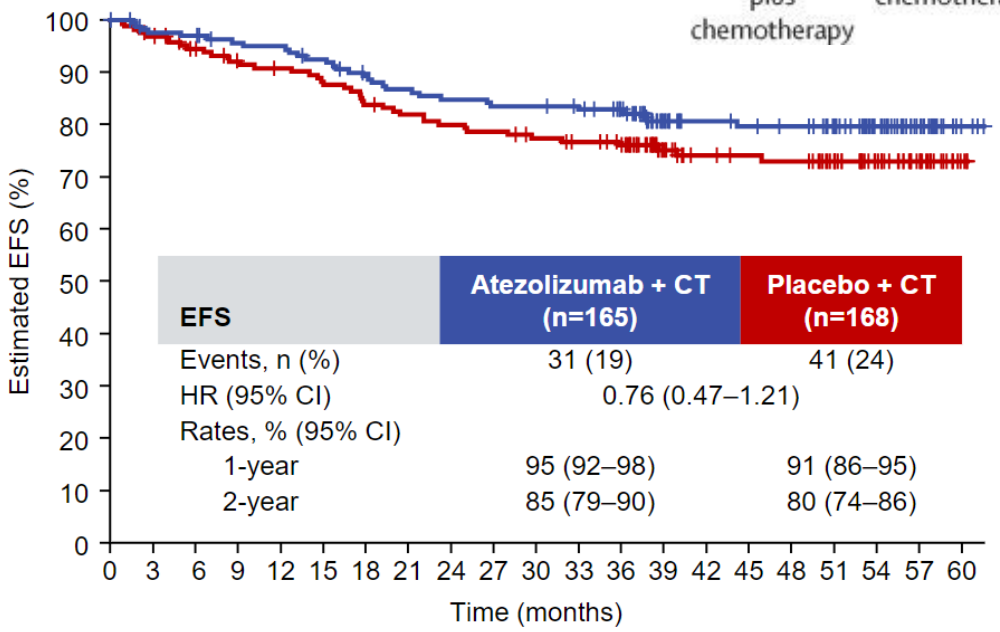


Schmid et al ESMO 2023

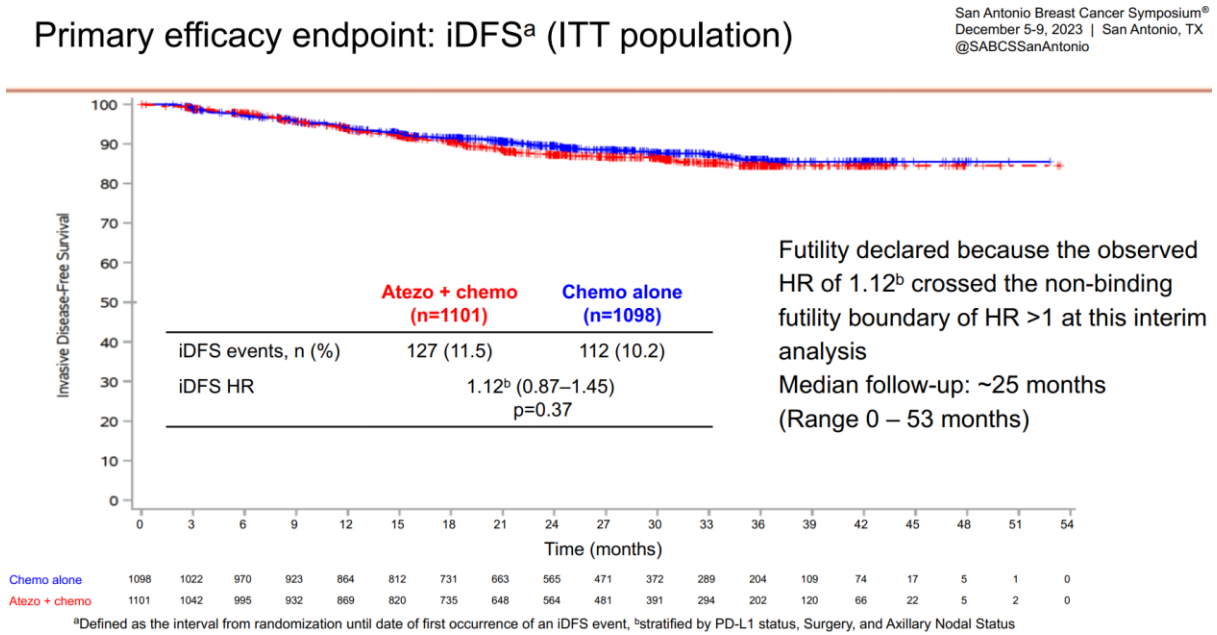
Does neoadjuvant administration matter?

IMpassion031:
neoadjuvant atezolizumab ↑pCR but ?modest ↑EFS (not powered for EFS)





IMpassion030: adjuvant atezolizumab does not improve iDFS



Mittendorf et al Lancet 2020; Barrios et al ESMO 2023; Ignatiadis et al SABCS 2023

Can we use pCR to limit systemic therapy?

Maybe, but still a research question! Not ready for routine practice!

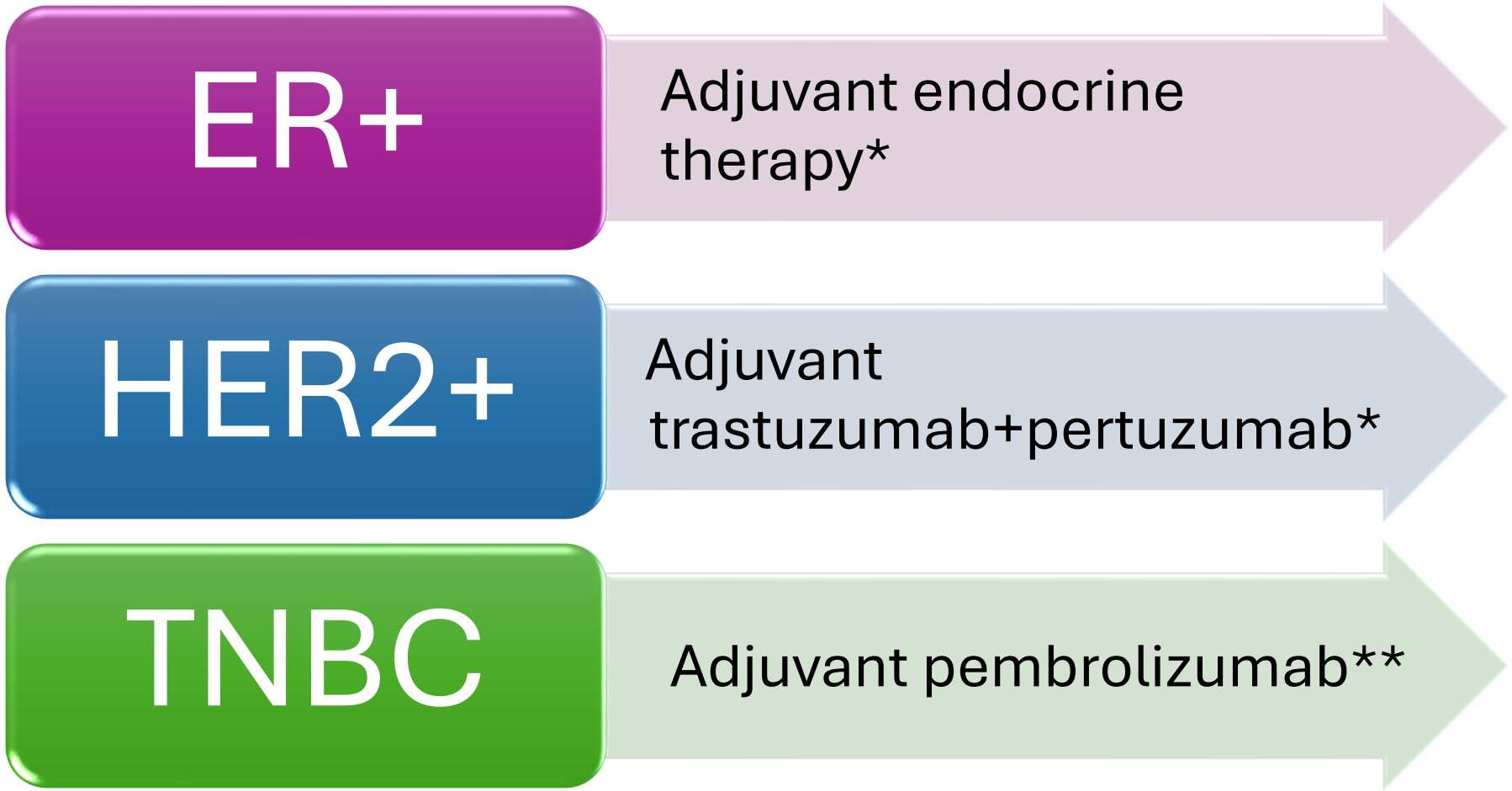
TNBC

- **SWOG 2212 (SCARLET)**
  - KN522 vs Doce/carbo/pembro x6 → if pCR no further chemo (but pembro still given)
- **OPTIMICE-pCR**
  - Post-pCR pembrolizumab vs obs

HER2-positive

- **PHERGAIN**
  - Modular adapted therapy using early PET changes, allowing patients achieving pCR on HP to continue without chemo (95% 3yr iDFS)
- **COMPASS-pCR**
  - THP x4 → no further chemo if pCR (but HP continued)

Standard of care adjuvant therapy post-pCR



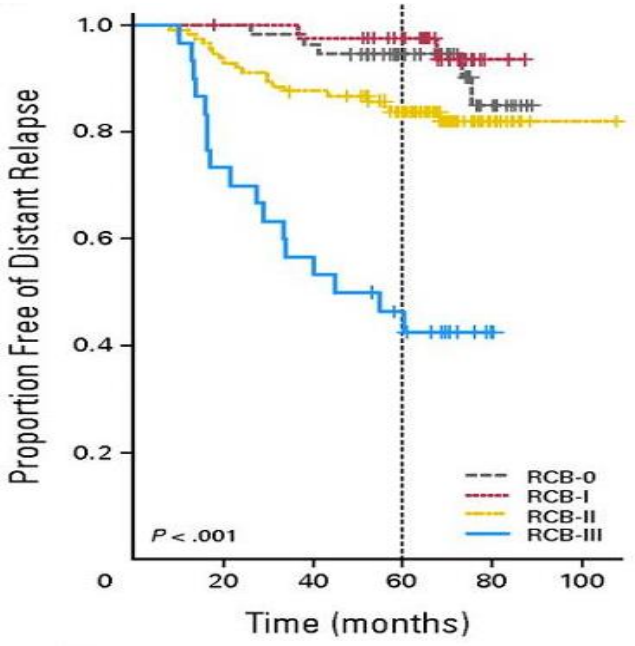
NCCN Breast Cancer v5.2024

* category 1
**category 2A

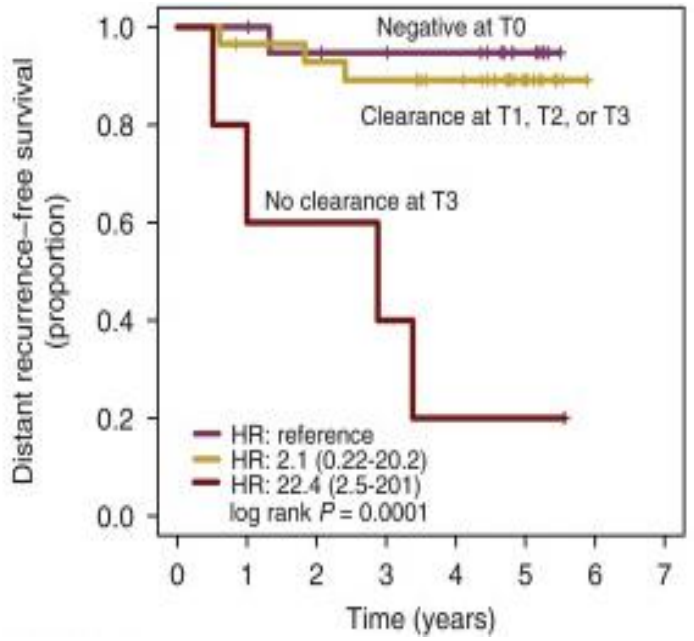
Refining associations between pathological response and outcomes

- pCR is binary, extent of residual disease can affect outcomes → ie RCB index can further quantify
- Early PET changes associated with pCR (lack of SUV has high NPV for pCR and RFS)
- Lack of ctDNA clearance associated with RD and lower DRFS

RCB and recurrence



ctDNA dynamics and DRFS



Fraser et al JCO 2007; Thomas et al Mod Pathol 2017; Connolly et al JCO 2019; Magbanua et al Ann of Oncol 2021

Conclusions

1. **Is pCR assessment robust and reproducible?** Its our gold standard, but has technical limitations
2. **Does pCR reliably predict patient outcomes?** pCR is prognostic in proliferative breast cancers, but associations with survival are not perfect
3. **Does pCR predict lack of benefit to adjuvant systemic therapy?** We do not know yet, current guidelines still recommend adjuvant therapy post-pCR

Should pCR limit adjuvant systemic therapy? NO! At this time, pCR should not be used routinely to limit systemic therapy outside of a clinical trial

pCR is not a final endpoint of therapy, rather an important prognostic marker, not yet predictive of benefit to adjuvant therapy

Thank you!

1889

2024

UCSF Helen Diller Family Comprehensive Cancer Center

Is pCR Enough?

Hope S. Rugo, MD
Professor of Medicine and Winterhof Family Distinguished Professor of Breast Oncology
Director, Breast Oncology and Clinical Trials Education
University of California San Francisco Comprehensive Cancer Center

For pCR to be enough…..

- Trials prior to IO studies were not powered to look at EFS
  - Current standards include powering neoadjuvant trials for EFS (~300 pts vs 1200-1500)
- Does pCR need to preduct benefit from post neoadjuvant therapy
  - Not always: for HR+ disease the benefit includes primary prevention, reducing local recurrence
- Based on KN522
  - The path to pCR did not impact survival
    - This suggests that post neoadjuvant therapy can indeed be moderated by response at surgery
- Is it a robust enough marker
  - Yes when following careful pathology guidelines
  - Use of RCB improves the robustness of pCR as a marker
- Additional biomarkers
  - ctDNA in patients with pCR

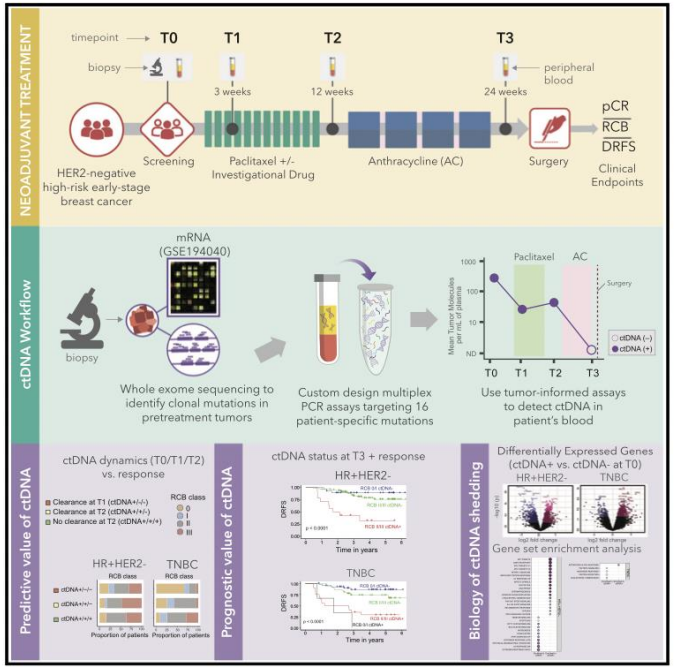
ctDNA (early) clearance *during* NAC predicts response
ctDNA non-clearance *after* NAC predicts early recurrence Exploratory Biomarker – ctDNA in plasma

Article

Cancer Cell

Clinical significance and biology of circulating tumor DNA in high-risk early-stage HER2-negative breast cancer receiving neoadjuvant chemotherapy

Graphical abstract



Authors

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Correspondence

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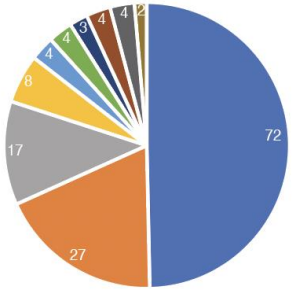
In brief

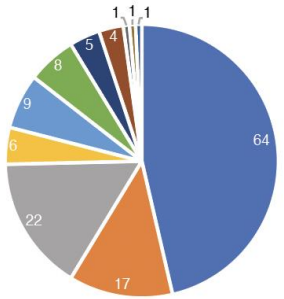
Magbanua et al. examine the dynamics of ctDNA in plasma of high-risk early-stage breast cancer patients receiving neoadjuvant chemotherapy. Understanding the predictive and prognostic value of ctDNA and biology of ctDNA shedding in different breast cancer subtypes can inform the use of ctDNA for treatment selection to improve patient outcomes.

Circulating Tumor DNA (exploratory biomarker):
Personalized 16 tumor mutated specific fragments
Serial liquid biopsies: 283 pts various treatment arms

HR+HER2- n=145



TNBC n=138



Compiled Series by Subtype

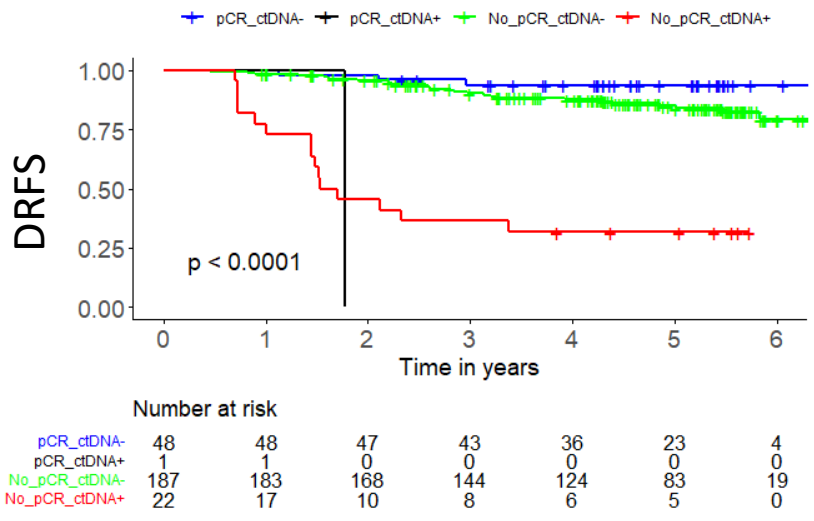
- Paclitaxel
- Paclitaxel + Pembrolizumab
- Paclitaxel + MK-2206
- Paclitaxel + Ganitumab
- Irinotecan + Talazoparib
- Paclitaxel + Ganetespib
- Paclitaxel + AMG 386
- Paclitaxel + Pembrolizumab 8-Cycle
- Paclitaxel + ABT 888 + Carboplatin
- Paclitaxel + Neratinib
- SGN-LIV1A

Mark Magbanua

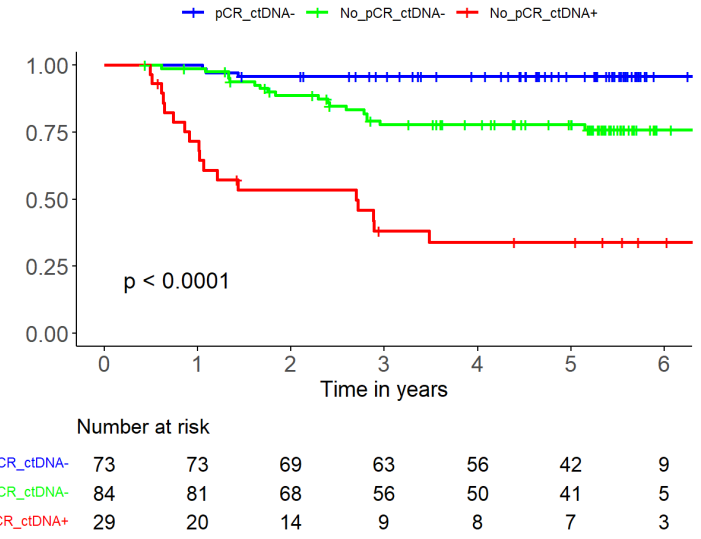
Magbanua et al, Cancer Cell, 2023
https://doi.org/10.1016/j.ccell.2023.04.008

ctDNA non-clearance at surgery predicts recurrence

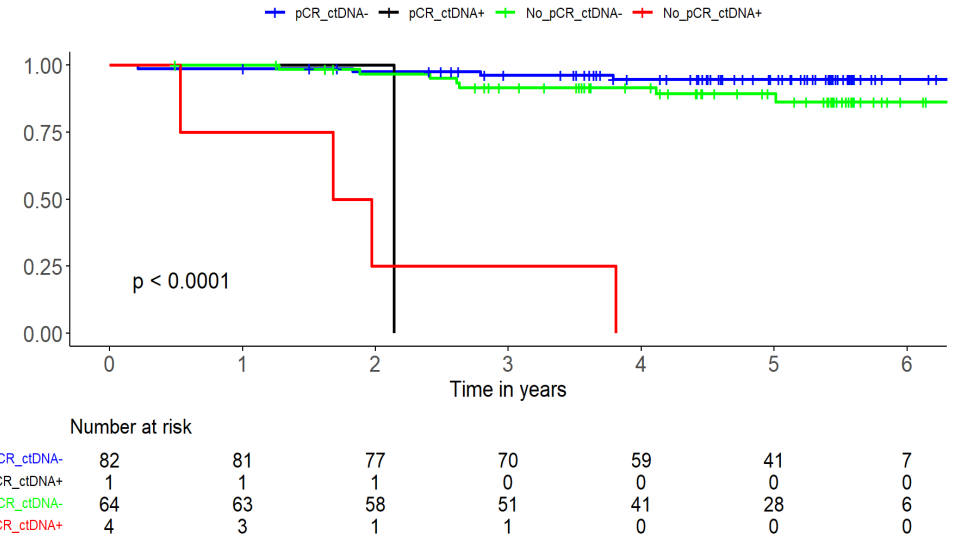
HR+HER2-



TNBC

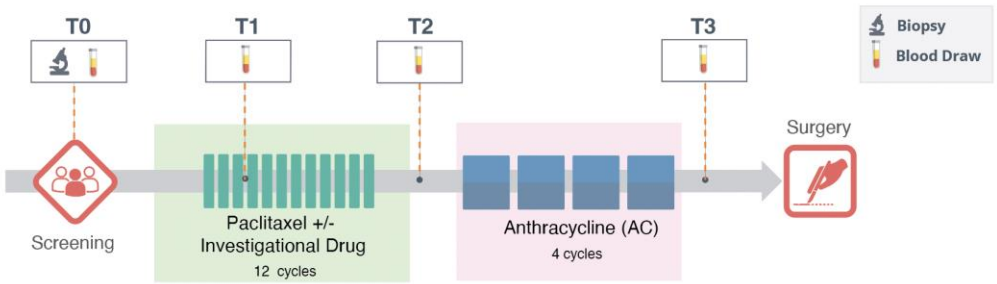


HER2+



pCR ctDNA-
pCR ctDNA+
No pCR ctDNA-
No pCR ctDNA+

T3 = post-neoadjuvant treatment/pre-surgery

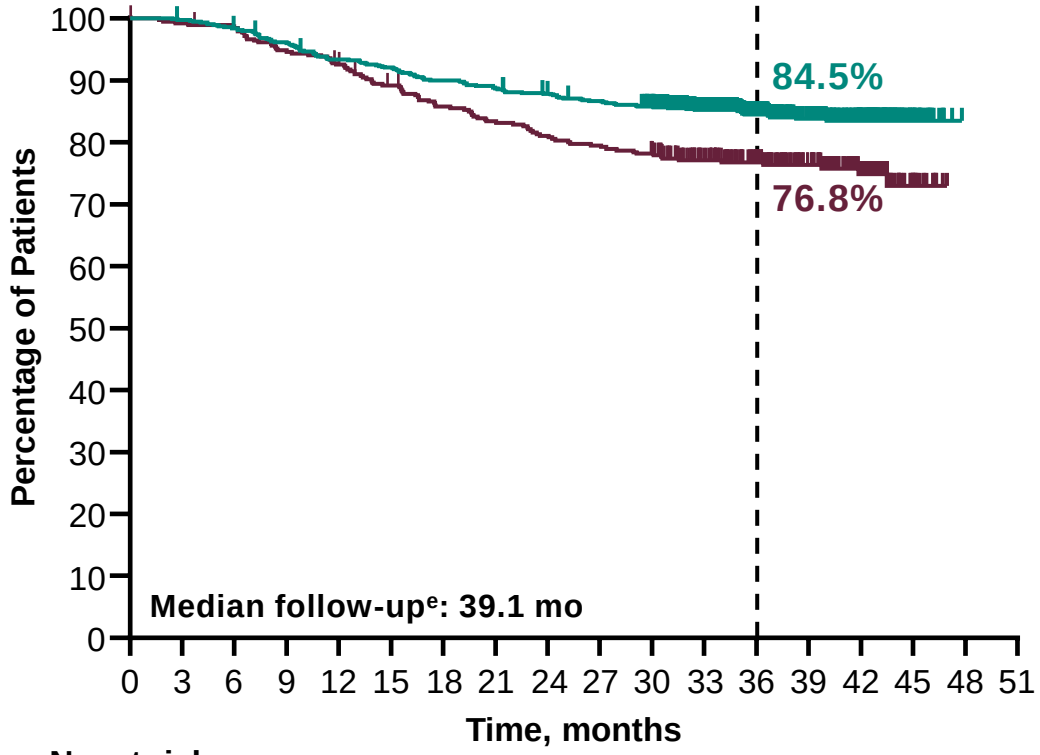


Implications for Adjuvant Therapy

Magbanua et al, Cancer Cell, 2023
https://doi.org/10.1016/j.ccell.2023.04.008

KN522: EFS at IA4 and IA6: median FU 63.1 mo

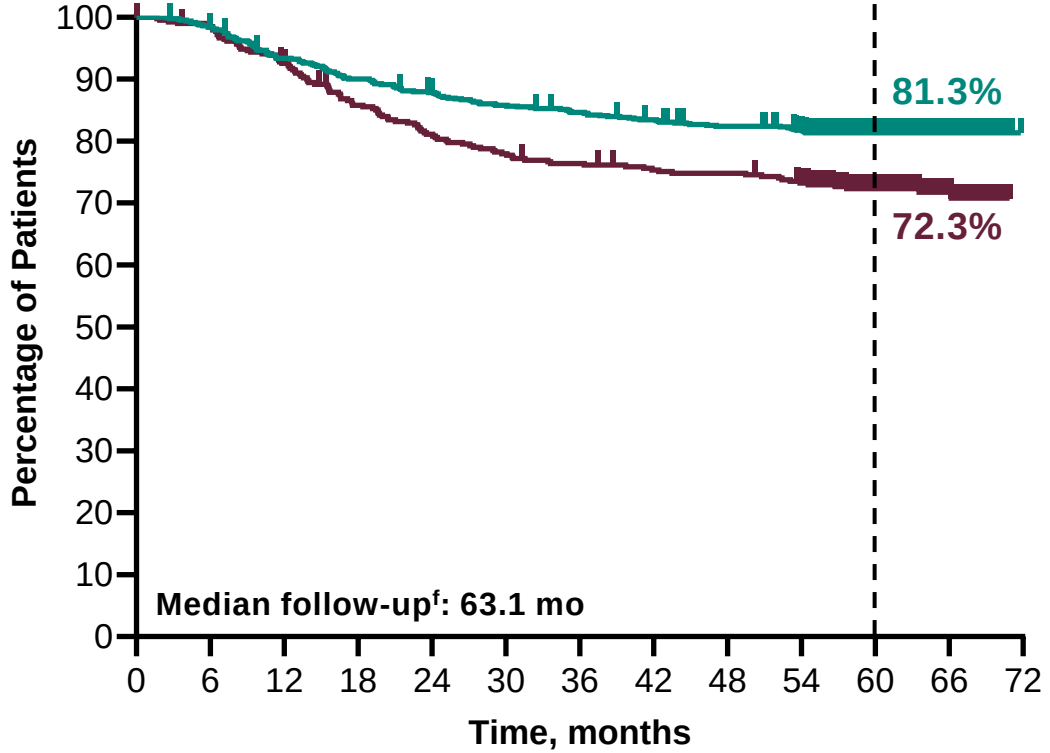
IA4[a]	Events	HR (95% CI)	*P* value
Pembro + Chemo/Pembro	15.7%	0.63[c] (0.48–0.82)	0.00031[d]
Placebo + Chemo/Placebo	23.8%		



No. at risk

784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

IA6[b]	Events	HR (95% CI)
Pembro + Chemo/Pembro	18.5%	0.63[c] (0.49–0.81)
Placebo + Chemo/Placebo	27.7%	



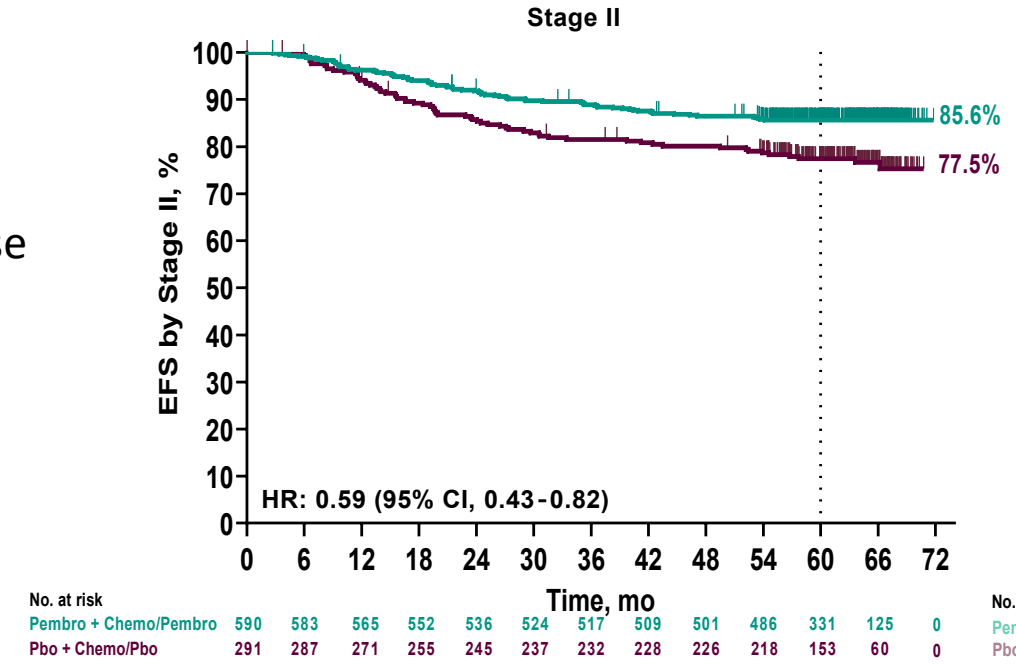
No. at risk

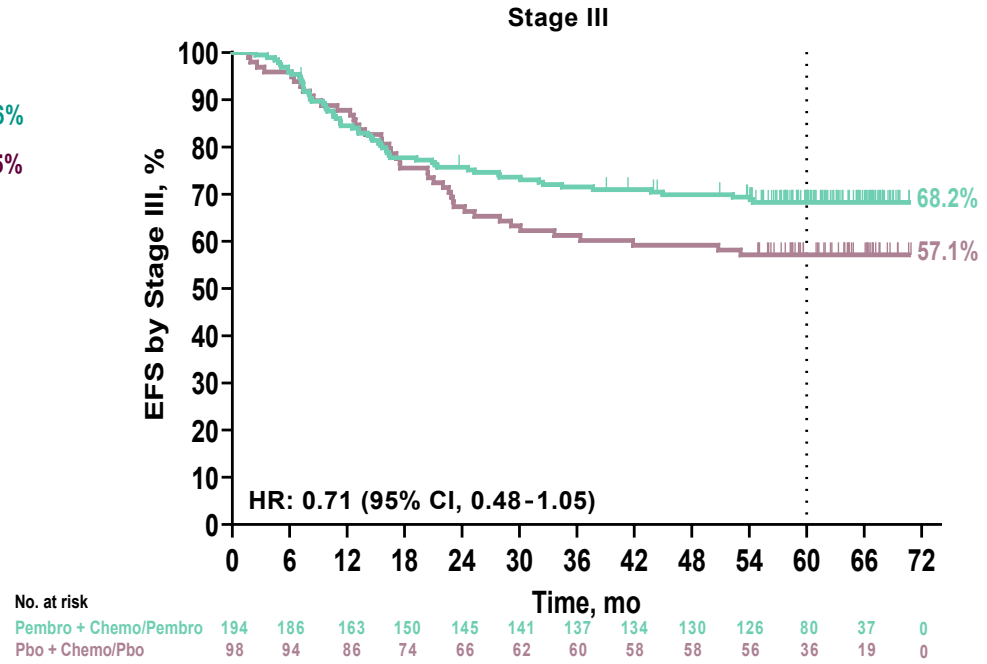
784	769	728	702	681	665	654	643	631	612	411	162	0
390	382	358	329	311	299	292	286	284	274	189	79	0

[a]The 4th prespecified interim analysis of EFS was calendar-driven planned to occur ~48 months after the first participant was randomized. [b]The 6th prespecified interim analysis of EFS was calendar-driven planned to occur ~72 months after the first participant was randomized. [c]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [d]Prespecified *P*-value boundary of 0.00517 was crossed. [e]Defined as the time from randomization to the data cutoff date of March 23, 2021. [f]Defined as the time from randomization to the data cutoff date of March 23, 2023.

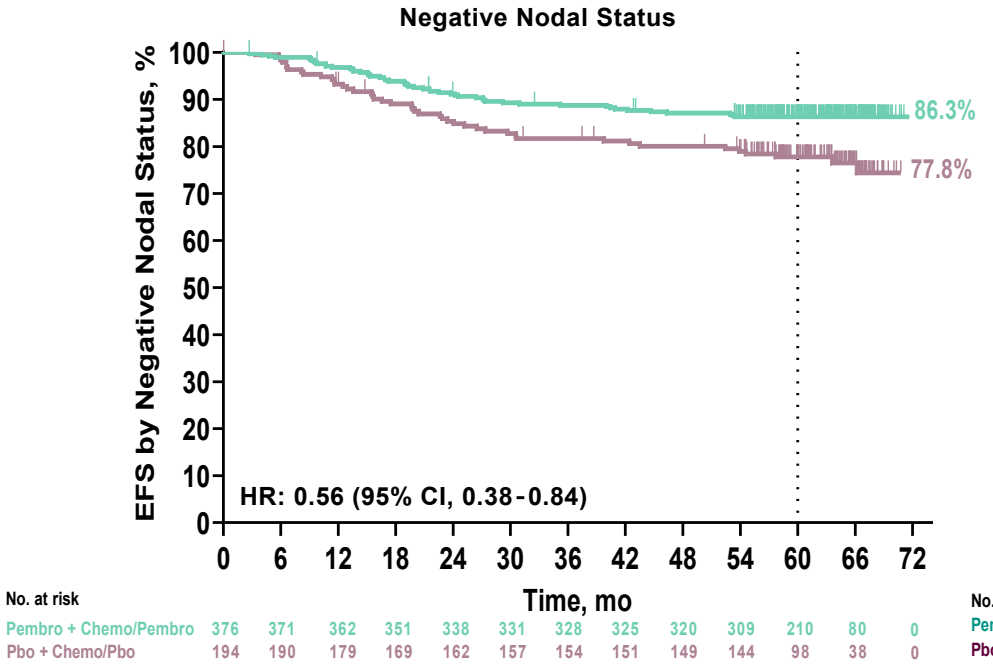
Schmid et al, SABCS 2023

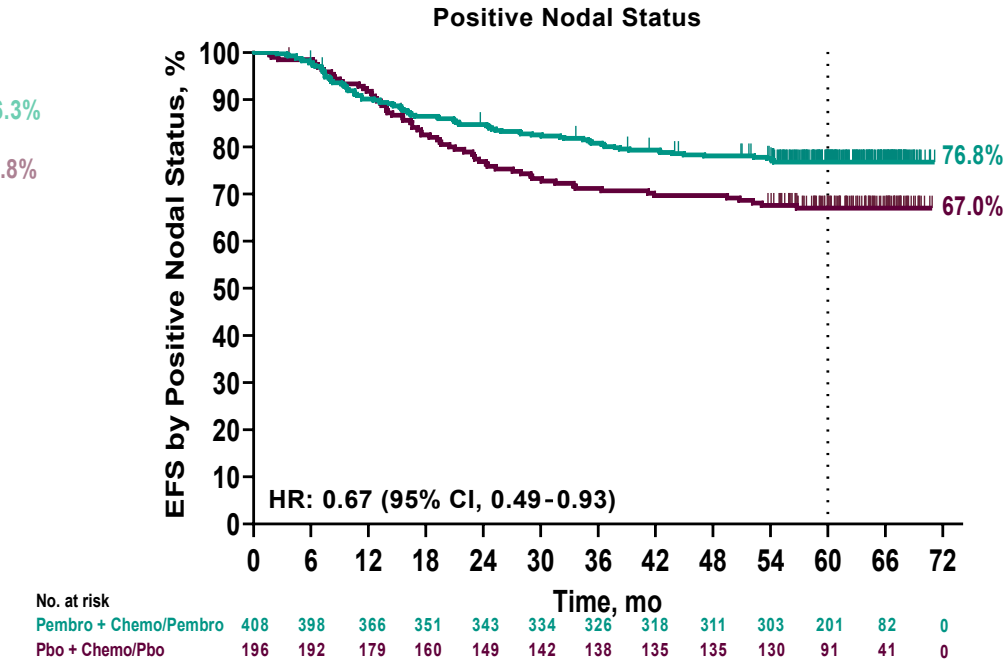
EFS at IA6 by Disease Stage



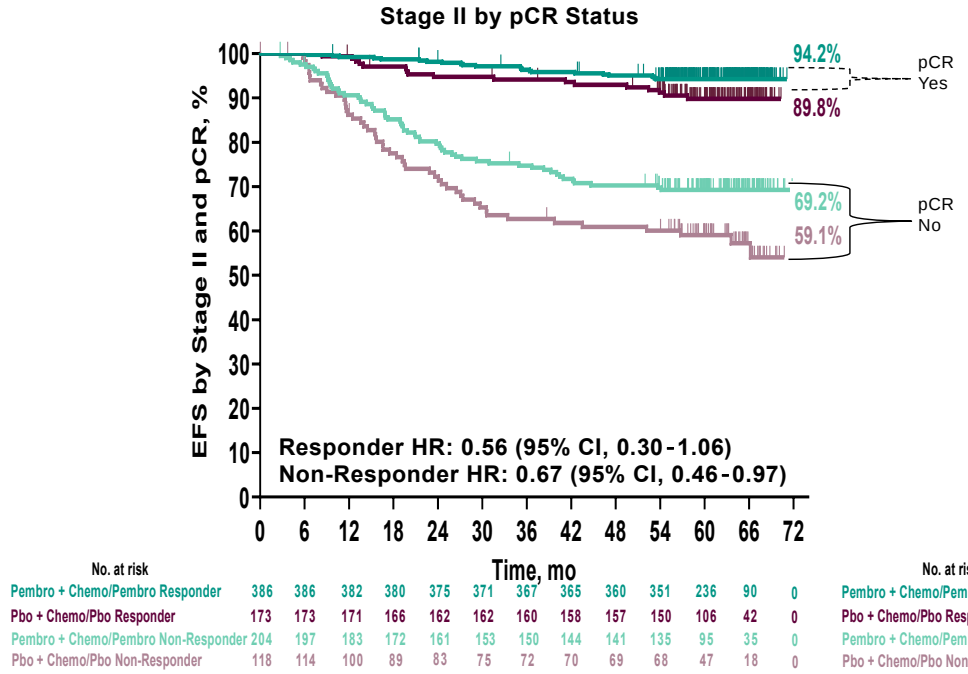


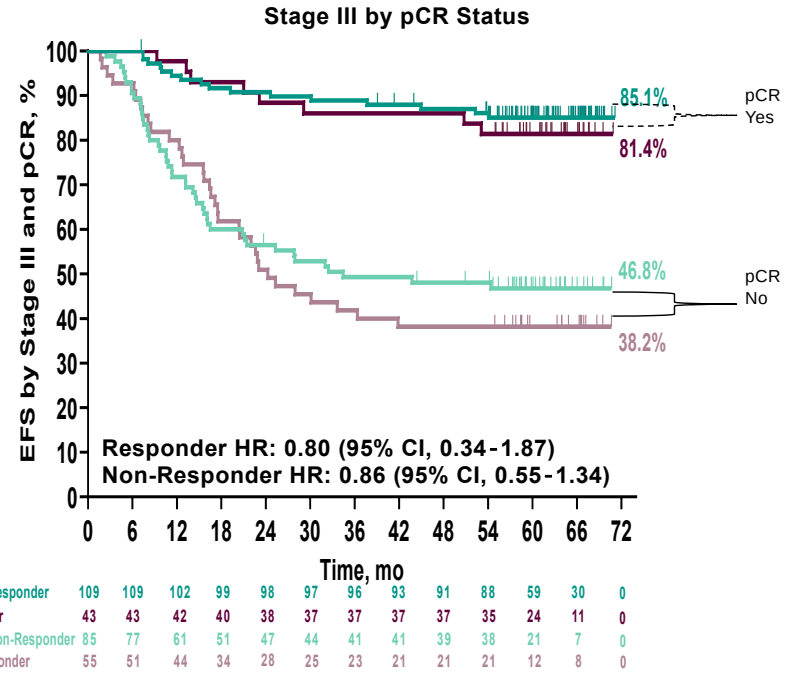
EFS at IA6 by Nodal Status



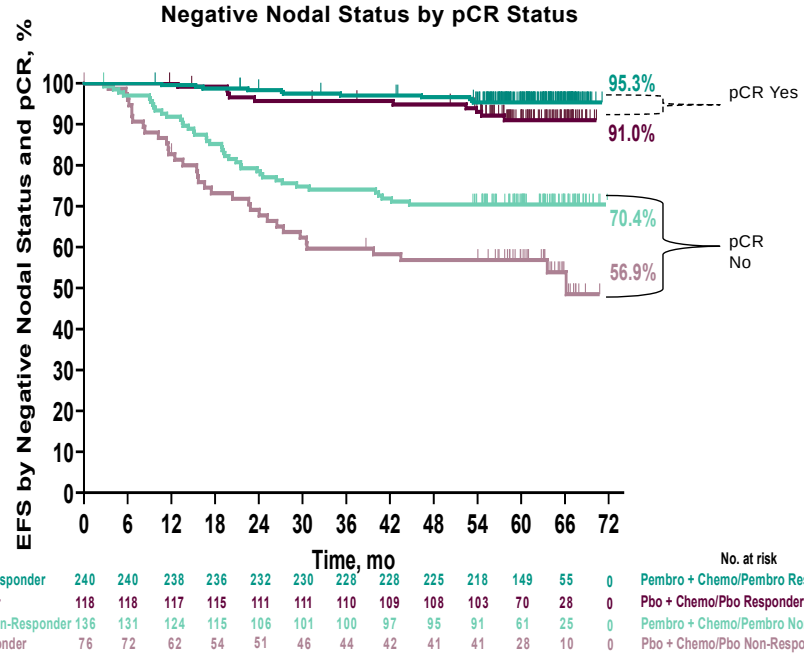


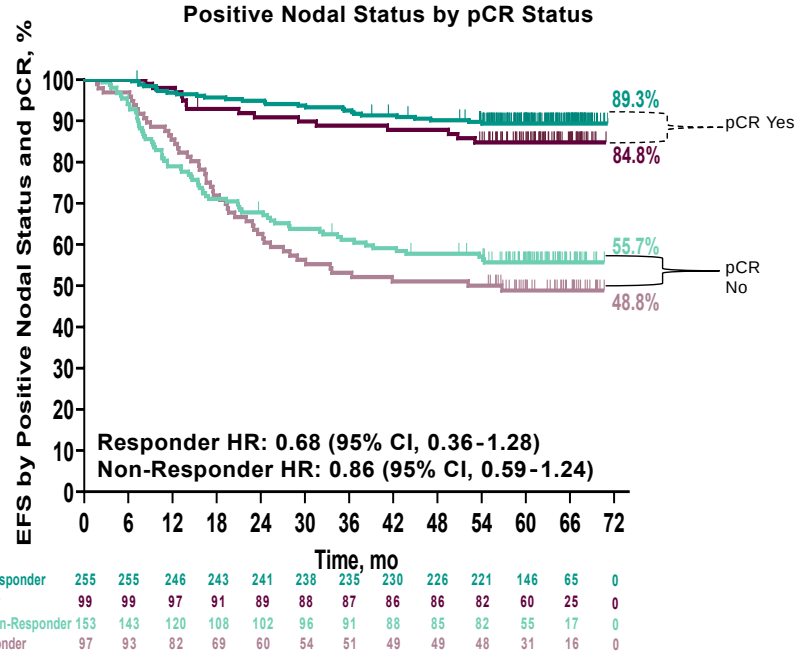
EFS at IA6 by Disease Stage in Patients With and Without pCR



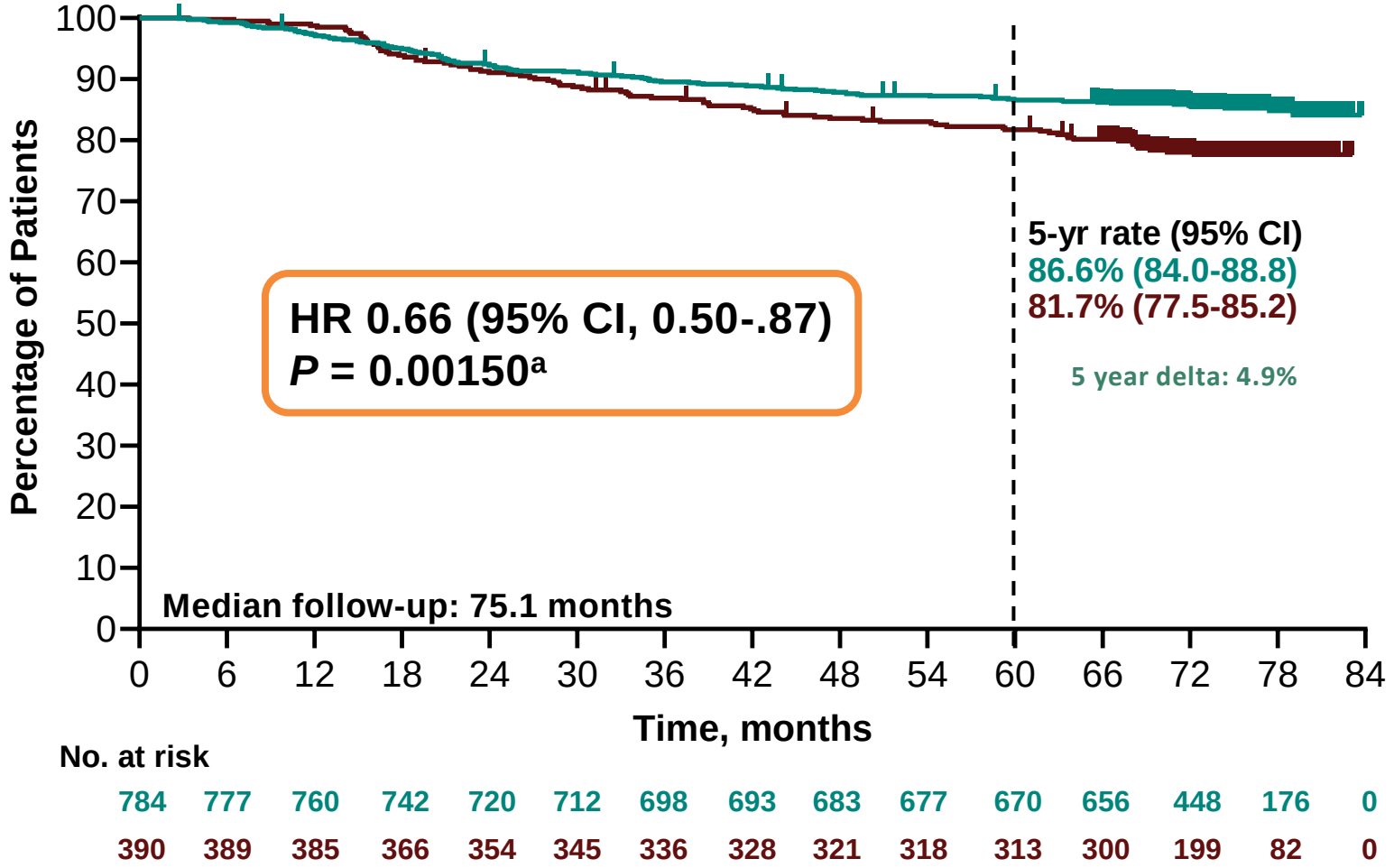


EFS at IA6 by Nodal Status in Patients With and Without pCR





Key Secondary Endpoint: Overall Survival



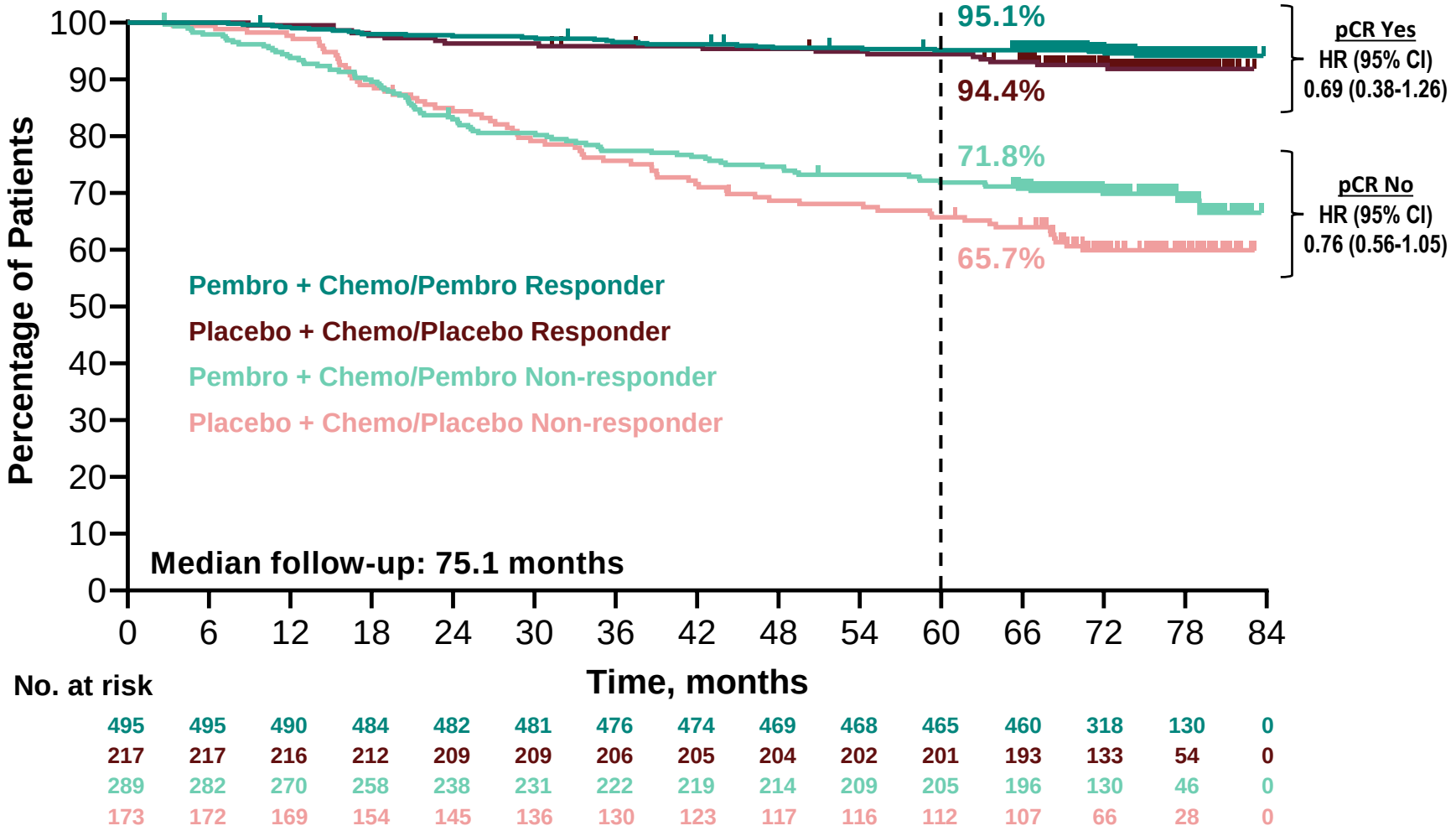
	Pts w/ Event
Pembro + Chemo/Pembro	14.7%
Placebo + Chemo/Placebo	21.8%

67.3% information fraction[a]

[a]With 200 events (67.3% information fraction), the observed *P*-value crossed the prespecified nominal boundary of 0.00503 (1-sided) at this interim analysis. Overall, 86/115 (74.8%) deaths in the pembro group and 62/85 (72.9%) deaths in the placebo group were due to disease progression or recurrence. The unstratified piecewise HR was 0.87 before the 2-year follow-up and 0.51 afterwards. The weighted average HR with weights of number of events before and after 2-year follow-up was 0.66. Data cutoff date: March 22, 2024.

Schmid et al, ESMO 2024

Overall Survival by Pathologic Complete Response (yp T0/Tis ypN0)



This is a non-randomized subgroup analysis based on the post-treatment outcome of pCR and HRs should therefore be interpreted with caution. Data cutoff date: March 22, 2024.

Schmid et al, ESMO 2024

So….is pCR enough?

- Yes
  - For the individual patient
  - In well powered trials
  - For chemotherapy sensitive disease


Thank you!