Decennale di
HIGHLIGHTS in
RADIOTERAPIA

Update degli Studi Practice Changing 2024

Undicesima Edizione

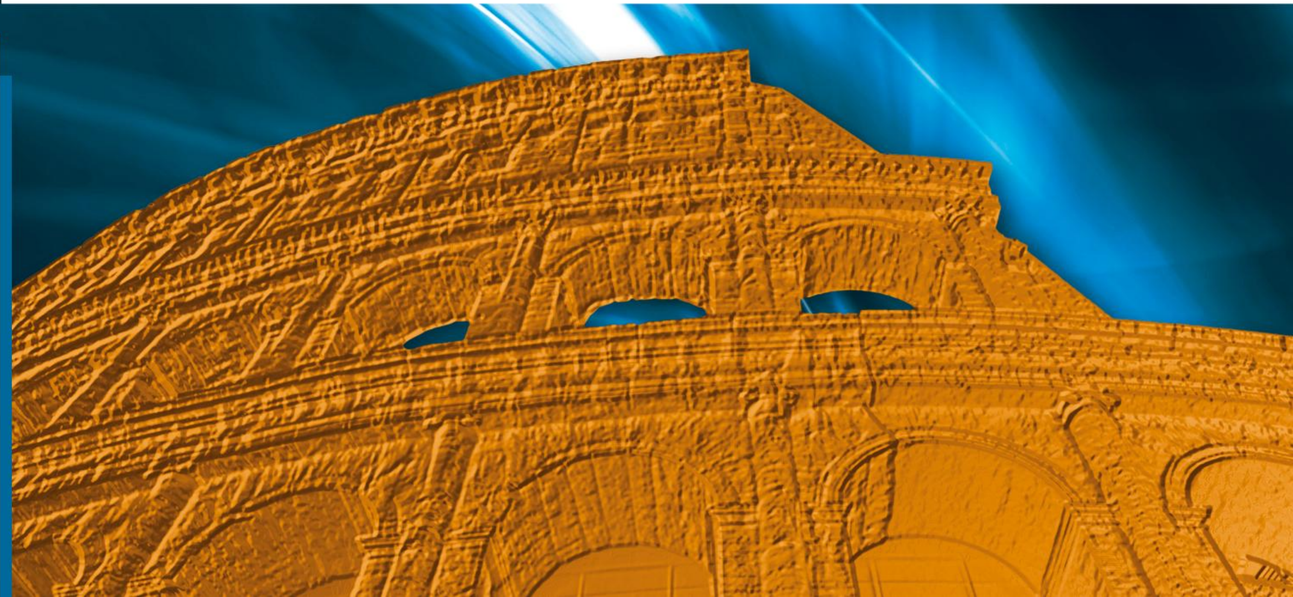
In memoria di Renzo Corvò

ROMA
30-31 gennaio 2025
Starhotels Metropole

New evidence and practice changing treatments in breast tumors

Maria Carmen De Santis, MD
mariacarmen.desantis@istitutotumori.mi.it; twitter @MariaCarmenDeS1

Fondazione I.R.C.C.S Istituto Nazionale Tumori di Milano



No Conflict of interest to declare

» **Treatment Escalation**

- DBCG IMN2
- SUPREMO
- NATALEE
- KEYNOTE 522

» **Treatment Descalation**

- SENOMAC
- INSEMA
- OPBC-05/ICARO
- IDEA
- EUROPA (Prof. Livi)
- IRMA
- COMET
- RTCHARM

Radiotherapy to regional nodes in early breast cancer: an individual patient data meta-analysis of 14 324 women in 16 trials

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

Findings

Newer Trials (1989–2008, 12,167 patients):

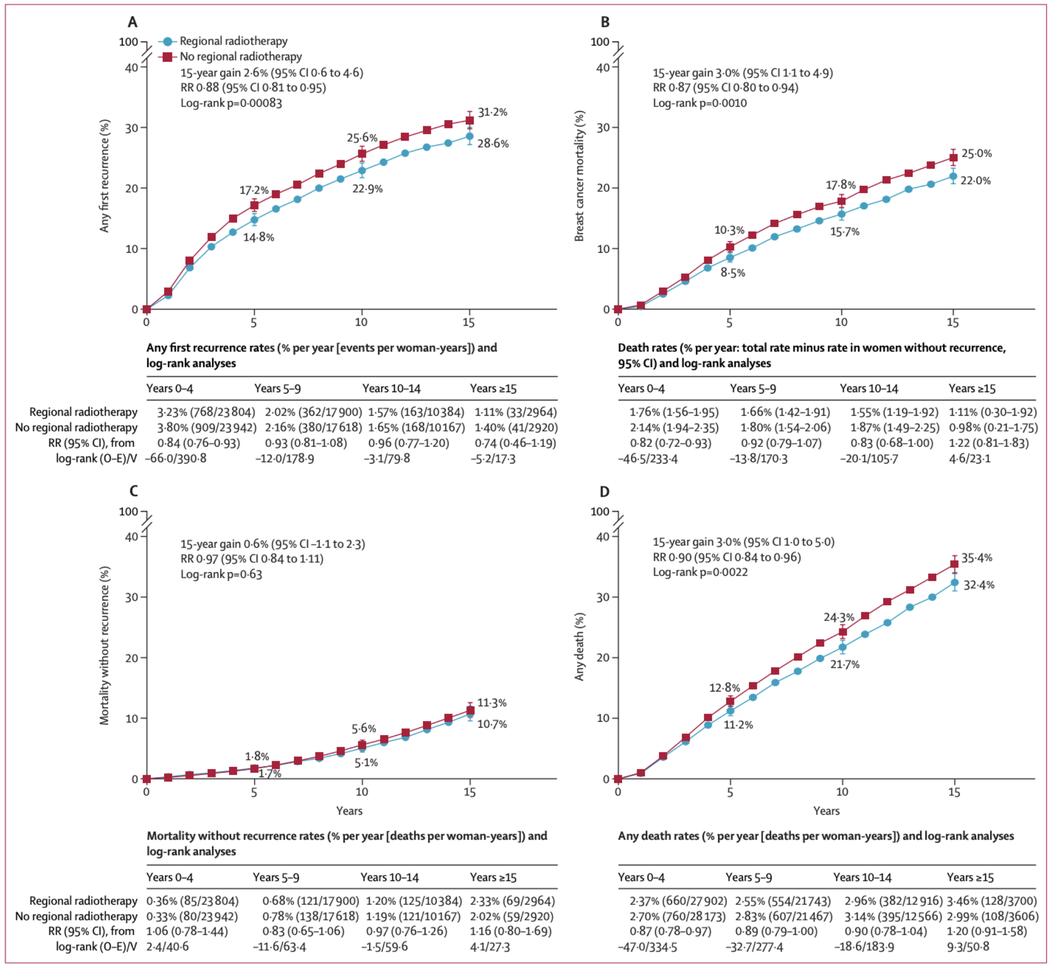
- Reduced recurrence (RR 0.88; p=0.0008)
- Reduced breast cancer mortality (RR 0.87; p=0.0010)
- No significant effect on non-breast-cancer mortality
- Reduced all-cause mortality (RR 0.90; p=0.0022)

15-year breast cancer mortality reductions:

- 1.6%: No positive axillary nodes
- 2.7%: 1–3 positive axillary nodes
- 4.5%: 4+ positive axillary nodes

Older Trials (1961–1978, 2,157 patients):

- No reduction in breast cancer mortality (RR 1.04; p=0.55)
- Increased non-breast-cancer mortality (RR 1.42; p=0.00023), primarily after 20 years
- Increased all-cause mortality (RR 1.17; p=0.0067)



Any first recurrence rates (% per year [events per woman-years]) and log-rank analyses

	Years 0–4	Years 5–9	Years 10–14	Years ≥15
Regional radiotherapy	3·23% (768/23 804)	2·02% (362/17 900)	1·57% (163/10 384)	1·11% (33/2964)
No regional radiotherapy	3·80% (909/23 942)	2·16% (380/17 618)	1·65% (168/10 167)	1·40% (41/2920)
RR (95% CI), from	0·84 (0·76–0·93)	0·93 (0·81–1·08)	0·96 (0·77–1·20)	0·74 (0·46–1·19)
log-rank (O–E)/V	−66·0/390·8	−12·0/178·9	−3·1/79·8	−5·2/17·3

Death rates (% per year: total rate minus rate in women without recurrence, 95% CI) and log-rank analyses

	Years 0–4	Years 5–9	Years 10–14	Years ≥15
	1·76% (1·56–1·95)	1·66% (1·42–1·91)	1·55% (1·19–1·92)	1·11% (0·30–1·92)
	2·14% (1·94–2·35)	1·80% (1·54–2·06)	1·87% (1·49–2·25)	0·98% (0·21–1·75)
	0·82 (0·72–0·93)	0·92 (0·79–1·07)	0·83 (0·68–1·00)	1·22 (0·81–1·83)
	−46·5/233·4	−13·8/170·3	−20·1/105·7	4·6/23·1

Mortality without recurrence rates (% per year [deaths per woman-years]) and log-rank analyses

	Years 0–4	Years 5–9	Years 10–14	Years ≥15
Regional radiotherapy	0·36% (85/23 804)	0·68% (121/17 900)	1·20% (125/10 384)	2·33% (69/2964)
No regional radiotherapy	0·33% (80/23 942)	0·78% (138/17 618)	1·19% (121/10 167)	2·02% (59/2920)
RR (95% CI), from	1·06 (0·78–1·44)	0·83 (0·65–1·06)	0·97 (0·76–1·26)	1·16 (0·80–1·69)
log-rank (O–E)/V	2·4/40·6	−11·6/63·4	−1·5/59·6	4·1/27·3

Any death rates (% per year [deaths per woman-years]) and log-rank analyses

	Years 0–4	Years 5–9	Years 10–14	Years ≥15
	2·37% (660/27 902)	2·55% (554/21 743)	2·96% (382/12 916)	3·46% (128/3700)
	2·70% (760/28 173)	2·83% (607/21 467)	3·14% (395/12 566)	2·99% (108/3606)
	0·87 (0·78–0·97)	0·89 (0·79–1·00)	0·90 (0·78–1·04)	1·20 (0·91–1·58)
	−47·0/334·5	−32·7/277·4	−18·6/183·9	9·3/50·8

Figure 2: **Effect of regional node radiotherapy in the eight newer trials on (A) any recurrence, (B) breast cancer mortality, (C) non-breast-cancer mortality, and (D) any death**
One newer trial of 1334 women that reported only all-cause mortality is included only in graph D. RR=rate ratio.

EBCTCG. Lancet. 2023

Radiotherapy to regional nodes in early breast cancer: an individual patient data meta-analysis of 14 324 women in 16 trials

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

Interpretation

- Post-1980s trials show significant reductions in breast cancer and all-cause mortality, reflecting advancements in radiotherapy techniques
- Pre-1980s trials highlight increased non-breast-cancer mortality, likely due to outdated RT methods

	Regional radiotherapy	No regional radiotherapy	Gain from regional radiotherapy
Any recurrence			
pN0	19·0%	21·3%	2·3%
pN1–3	25·6%	28·5%	2·9%
pN4+	46·8%	51·1%	4·3%
Breast cancer mortality			
pN0	10·9%	12·5%	1·6%
pN1–3	20·3%	23·0%	2·7%
pN4+	40·5%	45·0%	4·5%

Data are 15-year cumulative risks. The overall rate ratios (RRs) for any recurrence (RR=0·88; figure 3) and breast cancer mortality (0·87; figure 3) were applied to annual rates of any recurrence and breast cancer mortality in the trials, averaged over treatment groups (there was no significant heterogeneity in the proportional reductions [RRs] for any recurrence and breast cancer mortality). pN0=pathologically node negative. pN1–3=one to three involved axillary lymph nodes. pN4+=four or more involved axillary lymph nodes.

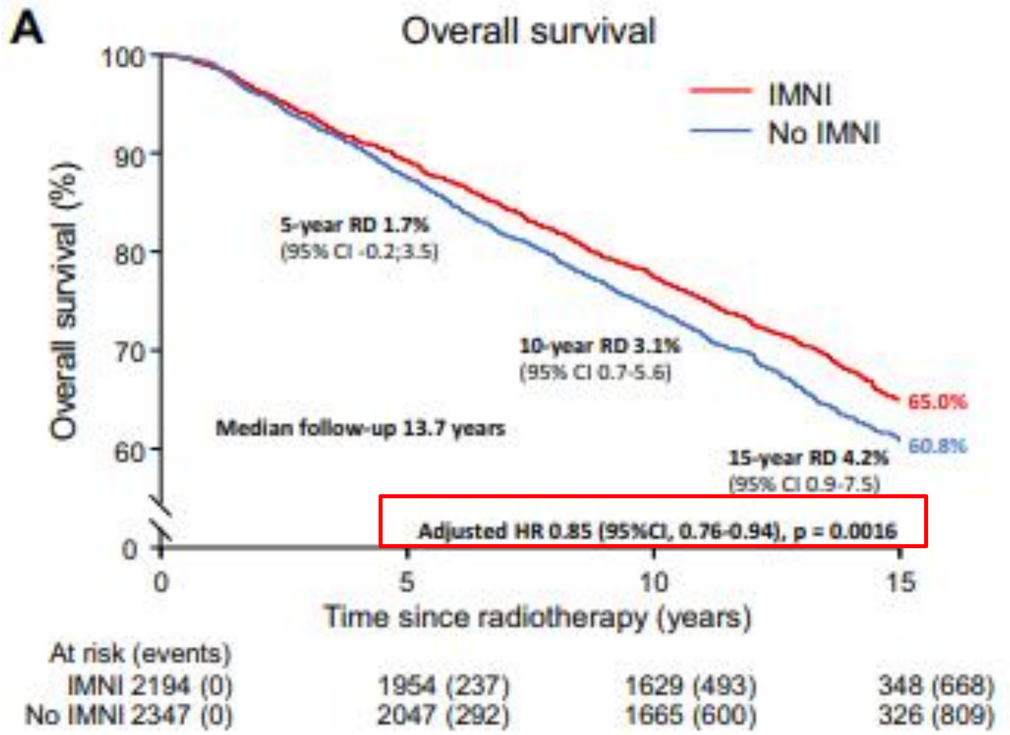
Table 2: **Absolute effect of regional node radiotherapy on 15-year risk of any recurrence and breast cancer mortality by nodal status in 10 833 women in the seven newer trials with data on recurrence**

EBCTCG. Lancet. 2023

Internal mammary node irradiation in 4541 node-positive breast cancer patients treated with newer systemic therapies and 3D-based radiotherapy (DBCG IMN2): a prospective, nationwide, population-based cohort study

Anders W. Mølby Nielsen,[a,b,*] Lise B. J. Thorsen,[a,b,c] Demet Özcan,[a,d] Louise W. Matthiessen,[e] Else Maae,[f] Marie L. H. Milo,[g] Mette H. Nielsen,[h] Trine Tramm,[a,d] Jens Overgaard,[a,b] and Birgitte V. Offersen,[a,b,c,i] on behalf of the DBCG RT Committee

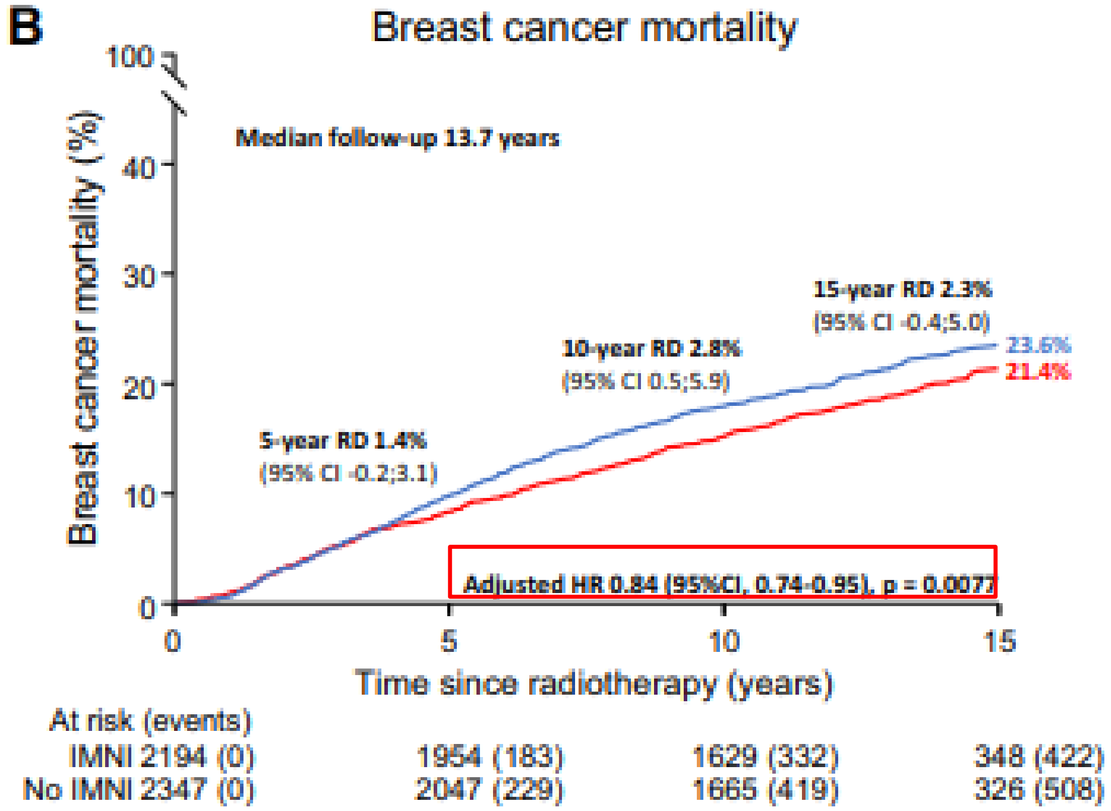
- 4541 patients were included in the period January 2007–May 2014
- Median age was 59 years
- Among patients receiving chemotherapy, 99.8% were given cyclophosphamide, 90.4% epirubicin, 96.2% taxanes
- The median follow-up was 13.7 years
- Primary endpoint was OS

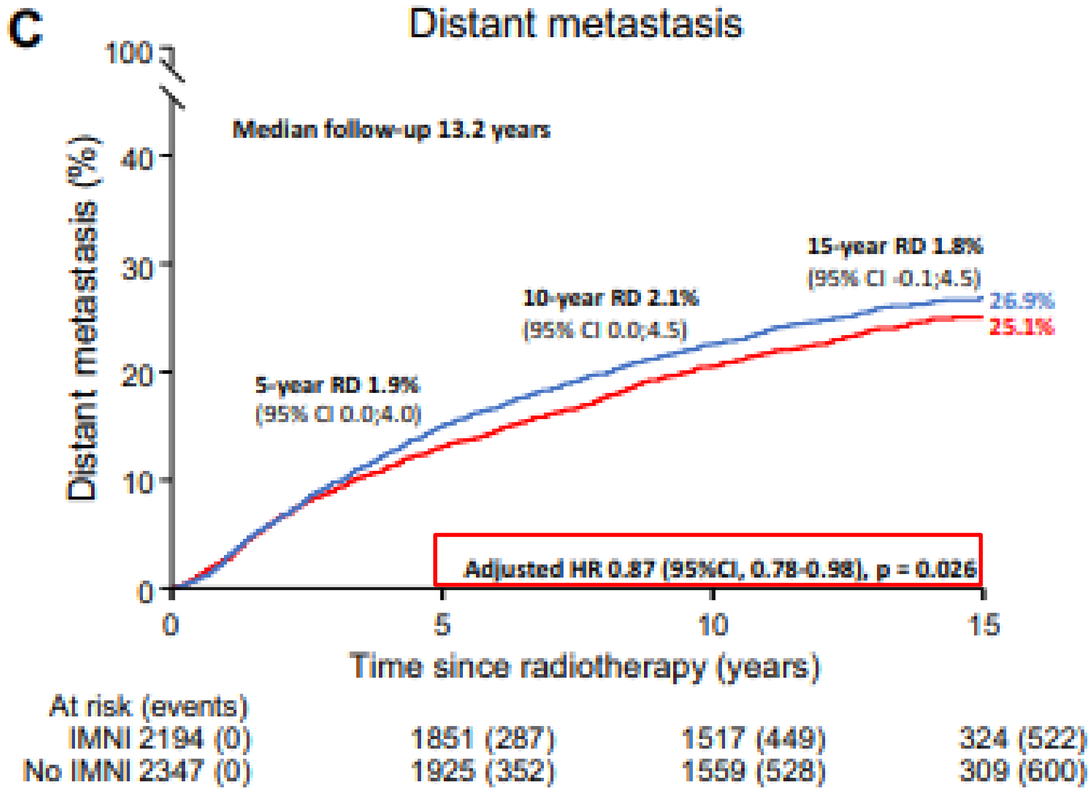


Nielsen A et al. The Lancet Regional Health – Europe 2025

Internal mammary node irradiation in 4541 node-positive breast cancer patients treated with newer systemic therapies and 3D-based radiotherapy (DBCG IMN2): a prospective, nationwide, population-based cohort study

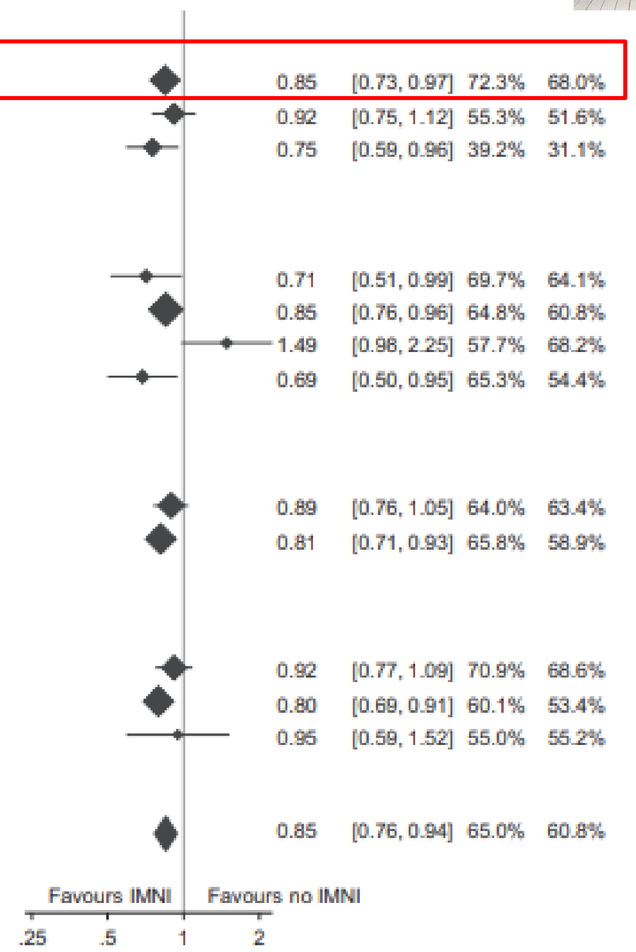
Anders W. Mølby Nielsen,[a,b,*] Lise B. J. Thorsen,[a,b,c] Demet Özcan,[a,d] Louise W. Matthiessen,[e] Else Maae,[f] Marie L. H. Milo,[g] Mette H. Nielsen,[h] Trine Tramm,[a,d] Jens Overgaard,[a,b] and Birgitte V. Offersen,[a,b,c,i] on behalf of the DBCG RT Committee





Nielsen A et al. The Lancet Regional Health – Europe 2025

Study	IMNI n	IMNI Events	No IMNI n	No IMNI Events	HR	95% CI	IMNI 15y OS	No IMNI 15y OS
Age								
< 35 years	37	7	42	9	0.63	[0.23, 1.71]	80.7%	78.4%
35-49 years	486	73	499	122	0.57	[0.43, 0.77]	83.2%	72.1%
50-59 years	605	151	692	173	0.95	[0.77, 1.19]	72.0%	72.3%
60-69 years	784	279	762	288	0.90	[0.76, 1.06]	59.5%	58.2%
≥ 70 years	282	165	352	224	0.86	[0.69, 1.06]	34.6%	27.0%
Test for interaction, p = 0.063								
Histological type								
IDC	1875	575	2018	698	0.84	[0.75, 0.94]	65.1%	61.0%
ILC	216	81	232	92	0.93	[0.69, 1.26]	58.6%	55.8%
Other	103	19	97	26	0.68	[0.37, 1.25]	77.7%	69.2%
Test for interaction, p = 0.65								
Malignancy grade								
Grade 1	514	140	551	140	0.99	[0.78, 1.26]	67.5%	70.8%
Grade 2	949	300	1010	377	0.83	[0.71, 0.97]	63.9%	57.1%
Grade 3	623	216	680	272	0.81	[0.68, 0.97]	62.7%	56.2%
Missing	108	19	106	27	0.66	[0.36, 1.21]	78.9%	71.2%
Test for interaction, p = 0.48								
Menopausal status								
Premenopausal	648	104	381	160	0.64	[0.50, 0.82]	81.8%	73.5%
Postmenopausal	1546	571	1666	656	0.90	[0.80, 1.01]	58.6%	55.9%
Test for interaction, p = 0.014								
Number of positive LN								
1-3	1490	361	1610	451	0.85	[0.73, 0.97]	72.3%	68.0%
4-9	469	185	512	220	0.92	[0.75, 1.12]	55.3%	51.6%
≥ 10	235	129	225	145	0.75	[0.59, 0.96]	39.2%	31.1%
Test for interaction, p = 0.52								
Number of positive LN								
1-3	1490	361	1610	451	0.85	[0.73, 0.97]	72.3%	68.0%
4-9	469	185	512	220	0.92	[0.75, 1.12]	55.3%	51.6%
≥ 10	235	129	225	145	0.75	[0.59, 0.96]	39.2%	31.1%
Test for interaction, p = 0.52								
IHC Subtype								
ER+/HER2+	256	64	268	87	0.71	[0.51, 0.99]	69.7%	64.1%
ER+/HER2-	1596	485	1680	579	0.85	[0.76, 0.96]	64.8%	60.8%
ER-/HER2+	118	47	152	43	1.49	[0.98, 2.25]	57.7%	68.2%
ER-/HER2-	197	66	213	89	0.69	[0.50, 0.95]	65.3%	54.4%
Test for interaction, p = 0.021								
Tumour Location								
Medial or central	921	286	1011	344	0.89	[0.76, 1.05]	64.0%	63.4%
Lateral	1273	389	1335	471	0.81	[0.71, 0.93]	65.8%	58.9%
Test for interaction, p = 0.37								
Tumour size								
0-20 mm	1035	253	1133	297	0.92	[0.77, 1.09]	70.9%	68.6%
21-50 mm	1075	389	1120	478	0.80	[0.69, 0.91]	60.1%	53.4%
> 50 mm	84	33	94	41	0.95	[0.59, 1.52]	55.0%	55.2%
Test for interaction, p = 0.40								
Overall					0.85	[0.76, 0.94]	65.0%	60.8%



Nielsen A et al. The Lancet Regional Health – Europe 2025

SAN ANTONIO BREAST CANCER SYMPOSIUM®
UT Health San Antonio Mays Cancer Center
AACR American Association for Cancer Research

DECEMBER 10–13, 2024
HENRY B. GONZALEZ CONVENTION CENTER • SAN ANTONIO, TX

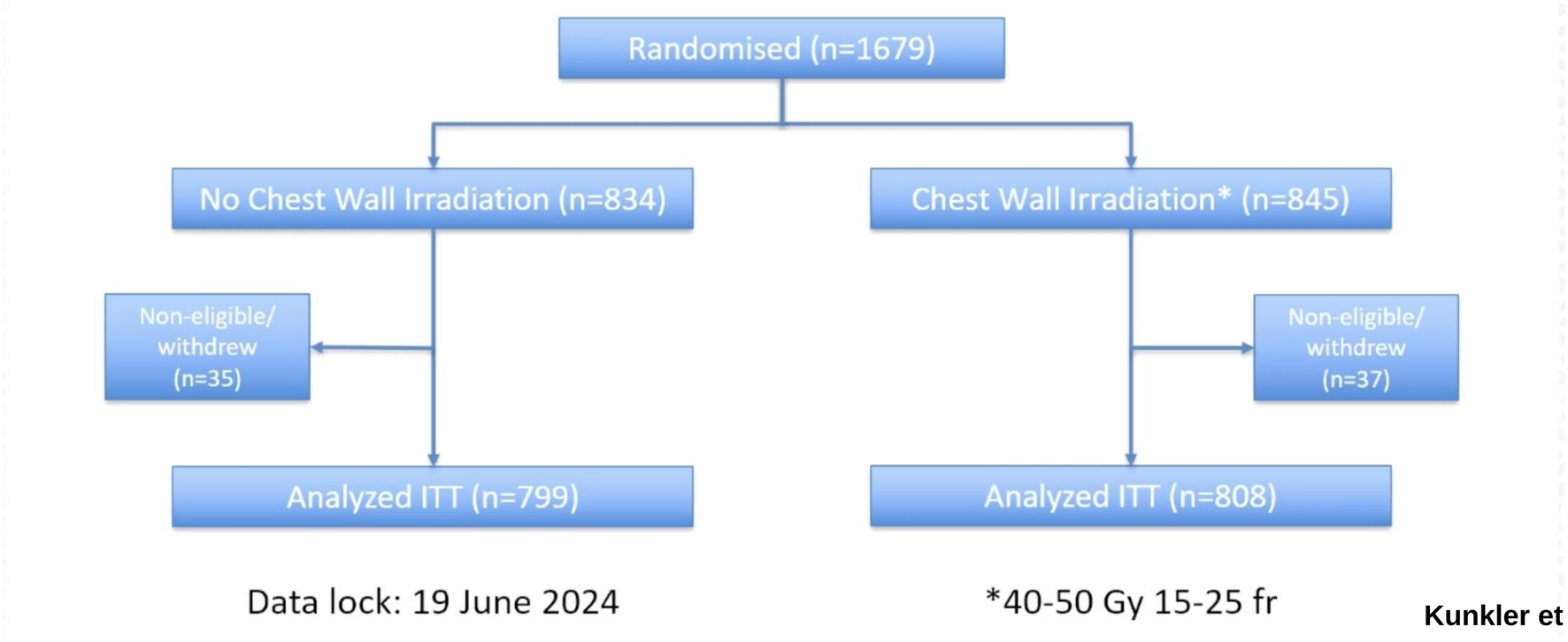
Does postmastectomy radiotherapy in 'intermediate-risk' breast cancer impact overall survival? 10 year results of the BIG 2-04 MRC randomized trial on behalf of the SUPREMO trial investigators

Ian Kunkler, FRCR
Institute of Genetics and Cancer
University of Edinburgh

MRC Medical Research Council

Consort diagram (recruitment 2006-2013)

- pT1N1M0;pT2N1M0 or pT3N0M0 histologically confirmed invasive breast cancer.
- pT2N0M0 if grade 3 and/or lymphovascular invasion
- Undergone simple mastectomy (with minimum of 1mm clear margin) and an axillary staging procedure



Kunkler et al, Abs # GS2-03

SUPREMO – Study population

- Included high risk N0 – **pT2,N0,M0 if grade 3 +/ LVI**
  (also pT3,N0,M0 – but only 11 patients)
- 65% of patients were either node negative or had only 1 involved LN

Number of Nodes	Number of Patients
0	25%
1	40%
2	23%
3	12%

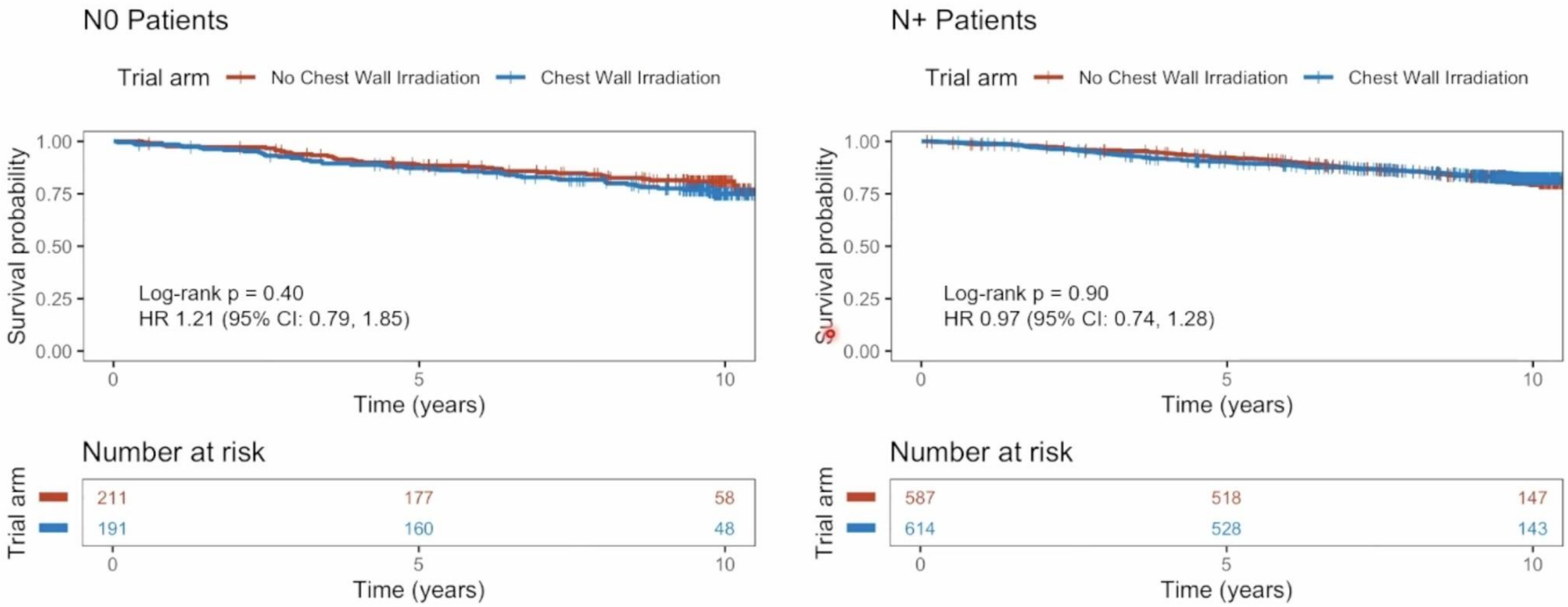
- If node positive had an axillary node clearance (minimum of 8 nodes removed) – ***current treatment would be to offer axillary irradiation rather than axillary node clearance for some of these patients.***

Kunkler et al, Abs # GS2-03

RESULTS: Overall Survival

SAN ANTONIO BREAST CANCER SYMPOSIUM®
UT Health San Antonio Mays Cancer Center
AACR American Association for Cancer Research

Overall Survival by Randomized Treatment and N0 or N+ Status

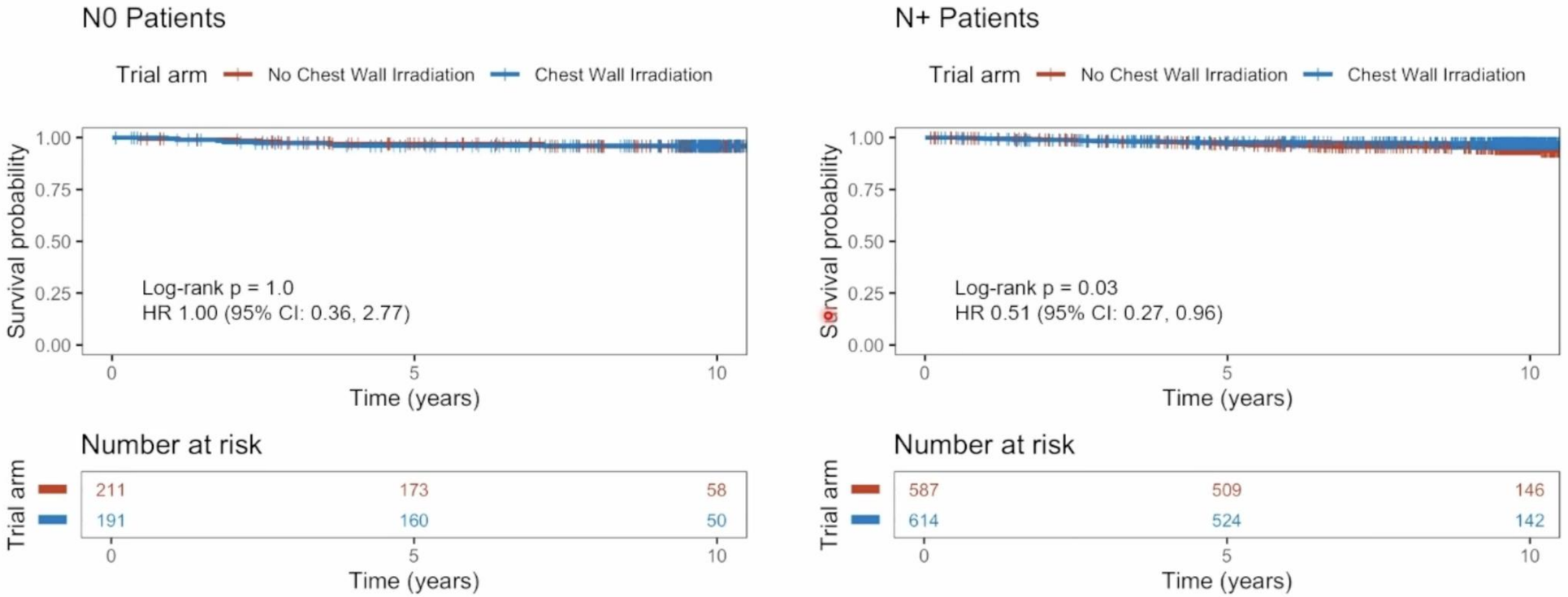


Kunkler et al, Abs # GS2-03

RESULTS: Regional Recurrence

SAN ANTONIO BREAST CANCER SYMPOSIUM®
UT Health San Antonio Mays Cancer Center
AACR American Association for Cancer Research

Regional Recurrence by Randomized Treatment and N0 or N+ Status

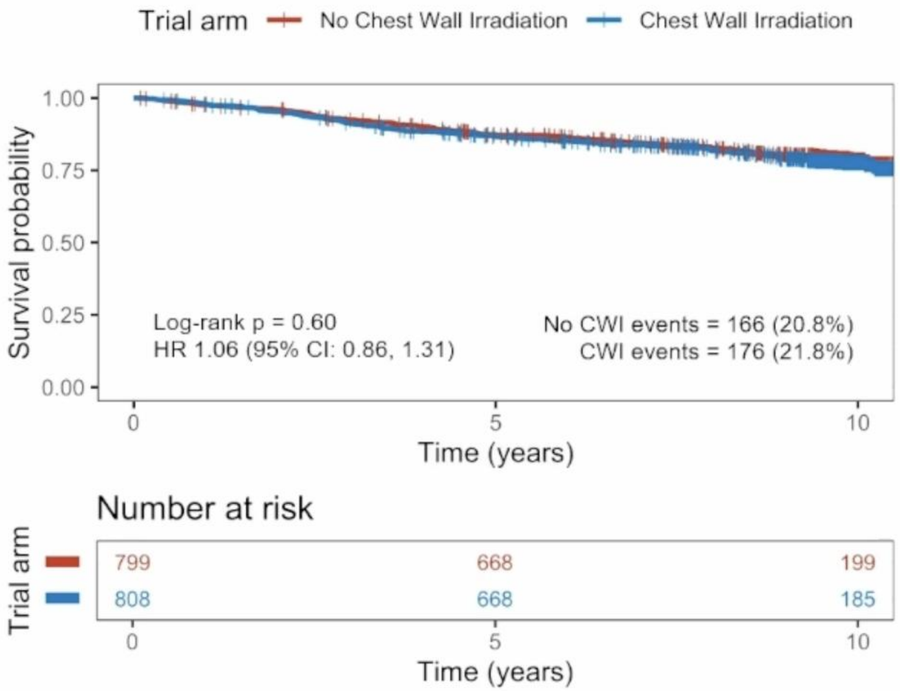


Kunkler et al, Abs # GS2-03

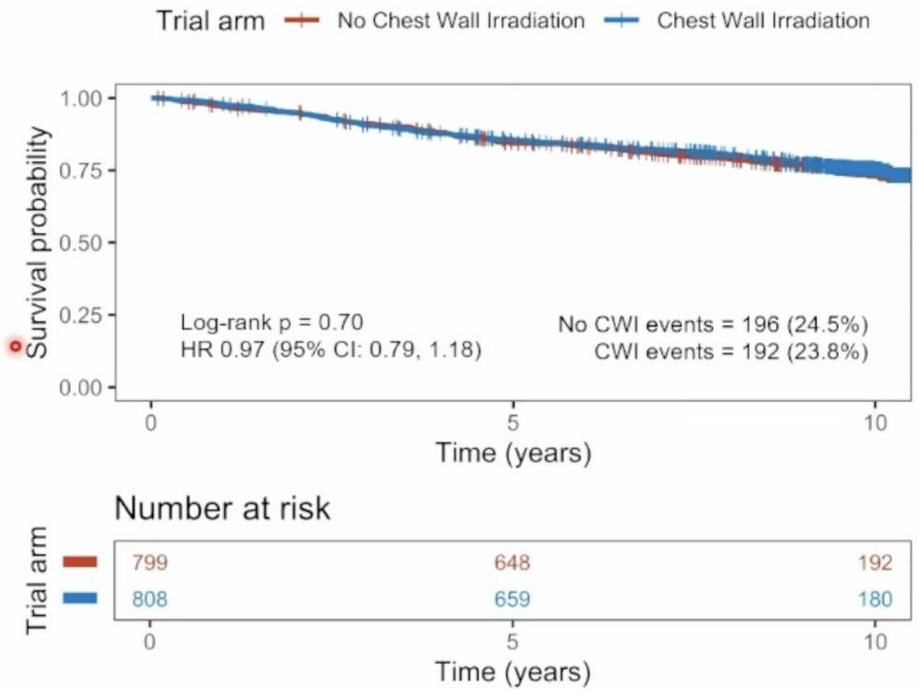
SAN ANTONIO BREAST CANCER SYMPOSIUM®
UT Health San Antonio Mays Cancer Center | AACR American Association for Cancer Research
December 10-13, 2024

RESULTS: Metastasis-free & Disease-free Survival

Kaplan-Meier Curves for ITT Population: Metastasis-free Survival by Randomized Treatment



Kaplan-Meier Curves for ITT Population: Disease-free Survival by Randomized Treatment



Kunkler et al, Abs # GS2-03

SUPREMO - Summary

- No evidence for PMRT in **pT2,N0,M0 if grade 3 +/ LVI**
- *Has not answered the question regarding need for PMRT in pT3,N0,M0*
- Benefit from PMRT in women in the node positive group very small
  but this cannot be generalised to all patients with 1-3 positive node[illegible]
  only 12% had 3 positive nodes.

For pN1 patients in SUPREMO trial Overall Survival HR was 0.82 (0.63-1.05) in favor of CWI.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ribociclib plus Endocrine Therapy in Early Breast Cancer

D. Slamon, O. Lipatov, Z. Nowecki, N. McAndrew, B. Kukielka-Budny, D. Stroyakovskiy, D.A. Yardley, C.-S. Huang, P.A. Fasching, J. Crown, A. Bardia, S. Chia, S.-A. Im, M. Ruiz-Borrego, S. Loi, B. Xu, S. Hurvitz, C. Barrios, M. Untch, R. Moroose, F. Visco, K. Afenjar, R. Fresco, I. Severin, Y. Ji, F. Ghaznawi, Z. Li, J.P. Zarate, A. Chakravartty, T. Taran, and G. Hortobagyi

Slamon D. et al. NEJM. 2024

NATALEE study design

- Adult patients with HR+/HER2− EBC
- Prior ET allowed up to 12 months
- **Anatomic stage IIA**[a]
  - **N0** with:
    - Grade 2 and evidence of high risk:
      - Ki-67 ≥20%
      - Oncotype DX Breast Recurrence Score ≥26 *or*
      - High risk via genomic risk profiling
    - Grade 3
  - **N1**
- **Anatomic stage IIB**[a]
  - N0 or N1
- **Anatomic stage III**
  - N0, N1, N2, or N3

N = 5101[b]

R 1:1[c]

Ribociclib
400 mg/day
3 weeks on/1 week off
for 3 years

NSAI
Letrozole or anastrozole[d] for ≥5 years
+ goserelin in men and premenopausal women

NSAI
Letrozole or anastrozole[d] for ≥5 years
+ goserelin in men and premenopausal women

Randomization stratification
Anatomic stage: II vs III
Menopausal status: men and premenopausal women vs postmenopausal women
Prior (neo)adjuvant chemotherapy: yes vs no
Geographic location: North America/Western Europe/Oceania vs rest of world

Primary end point
- iDFS using STEEP criteria

Secondary end points
- Recurrence-free survival
- Distant disease–free survival
- OS
- HRQoL
- Safety and tolerability
- PK

Exploratory end points
- Locoregional recurrence–free survival
- Gene expression and alterations in tumor ctDNA/ctRNA samples

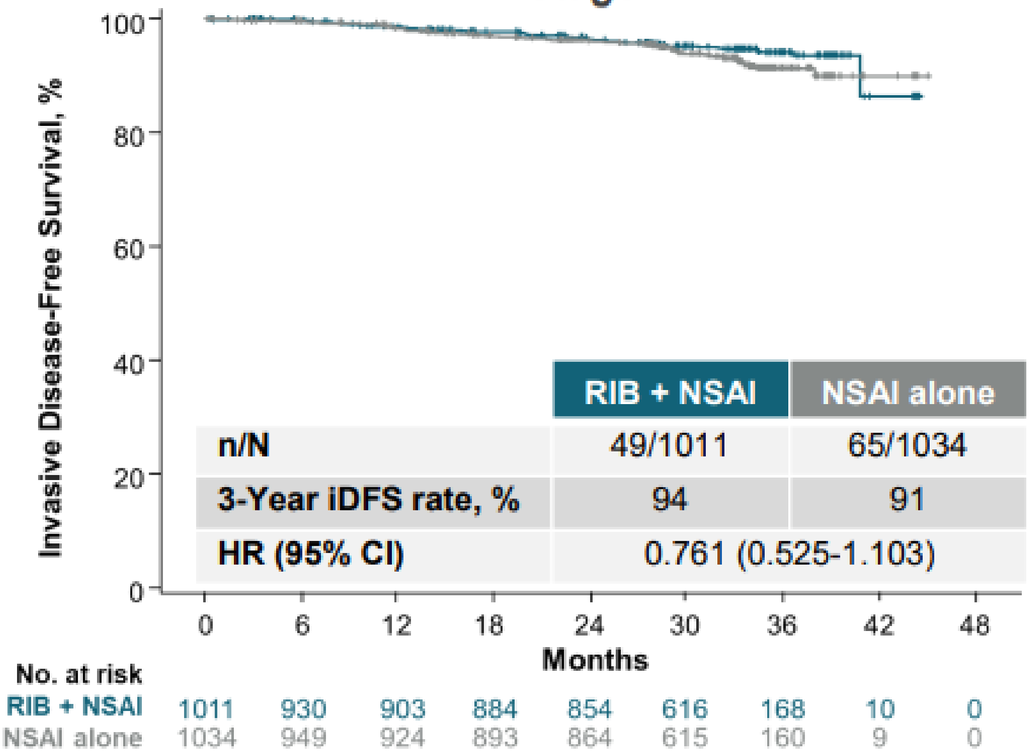
ctDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; HRQoL, health-related quality of life; iDFS, invasive disease-free survival; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PK, pharmacokinetics; R, randomized; STEEP, Standardized Definitions for Efficacy End Points in adjuvant breast cancer trials.
[a] Enrollment of patients with stage II disease was capped at 40%. [b] 5101 patients were randomized from January 10, 2019, to April 20, 2021. [c] Open-label design. [d] Per investigator choice.
1. Slamon D, et al. ASCO 2023. Oral; abstract LBA500. 2. Slamon DJ, et al. *J Clin Oncol*. 2019;37(15 suppl). Abstract TPS597.

Slamon D. et al. NEJM. 2024

NATALEE iDFS by anatomic stage

Consistent iDFS benefit with ribociclib + NSAI in patients with stage II or III disease

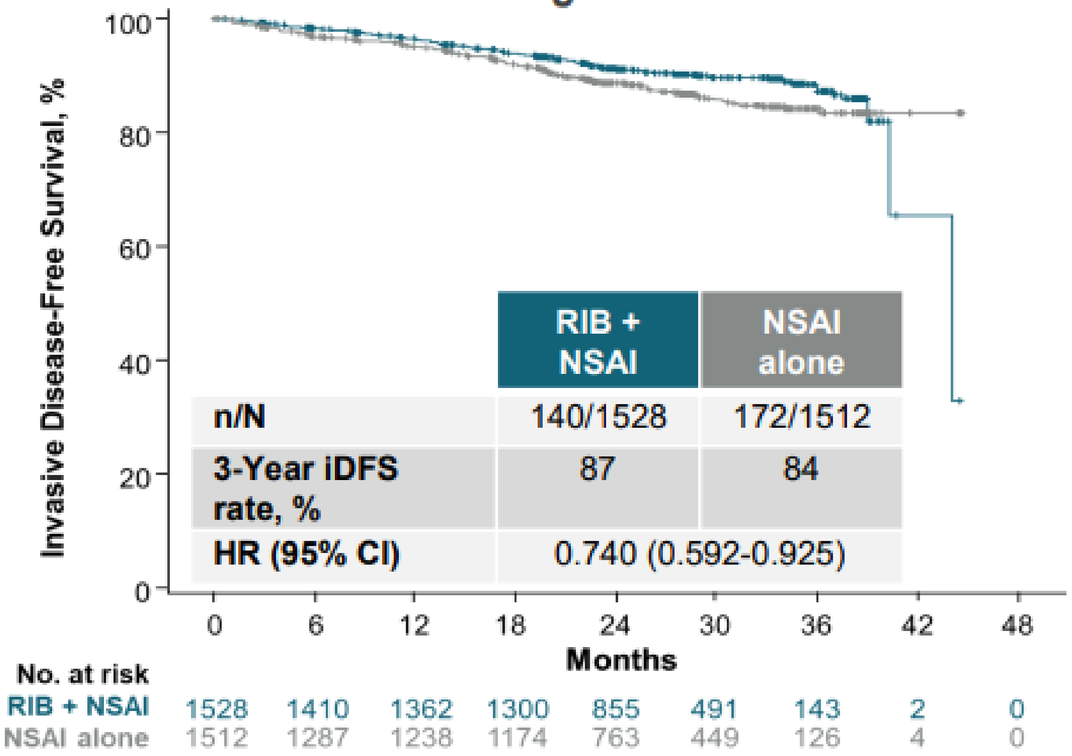
Stage II



	RIB + NSAI	NSAI alone
n/N	49/1011	65/1034
3-Year iDFS rate, %	94	91
HR (95% CI)	0.761 (0.525-1.103)	

No. at risk									
RIB + NSAI	1011	930	903	884	854	616	168	10	0
NSAI alone	1034	949	924	893	864	615	160	9	0

Stage III



	RIB + NSAI	NSAI alone
n/N	140/1528	172/1512
3-Year iDFS rate, %	87	84
HR (95% CI)	0.740 (0.592-0.925)	

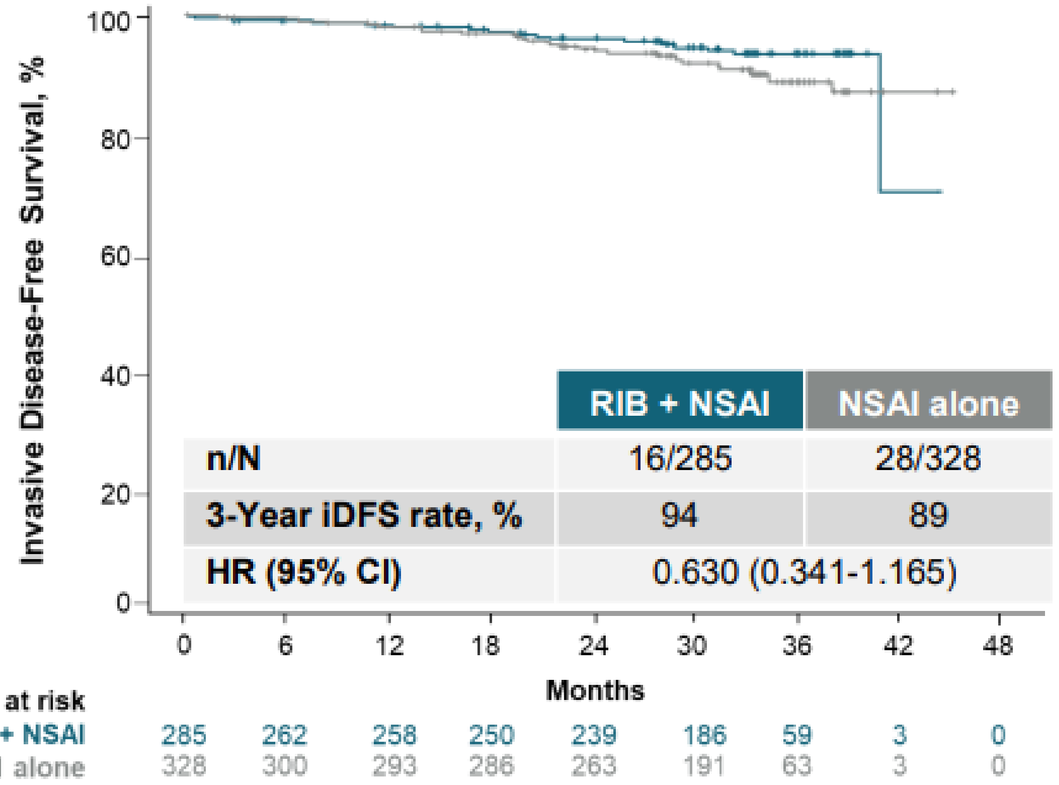
No. at risk									
RIB + NSAI	1528	1410	1362	1300	855	491	143	2	0
NSAI alone	1512	1287	1238	1174	763	449	126	4	0

iDFS, invasive disease-free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

NATALEE iDFS by nodal status

Ribociclib + NSAI prolonged iDFS regardless of nodal status

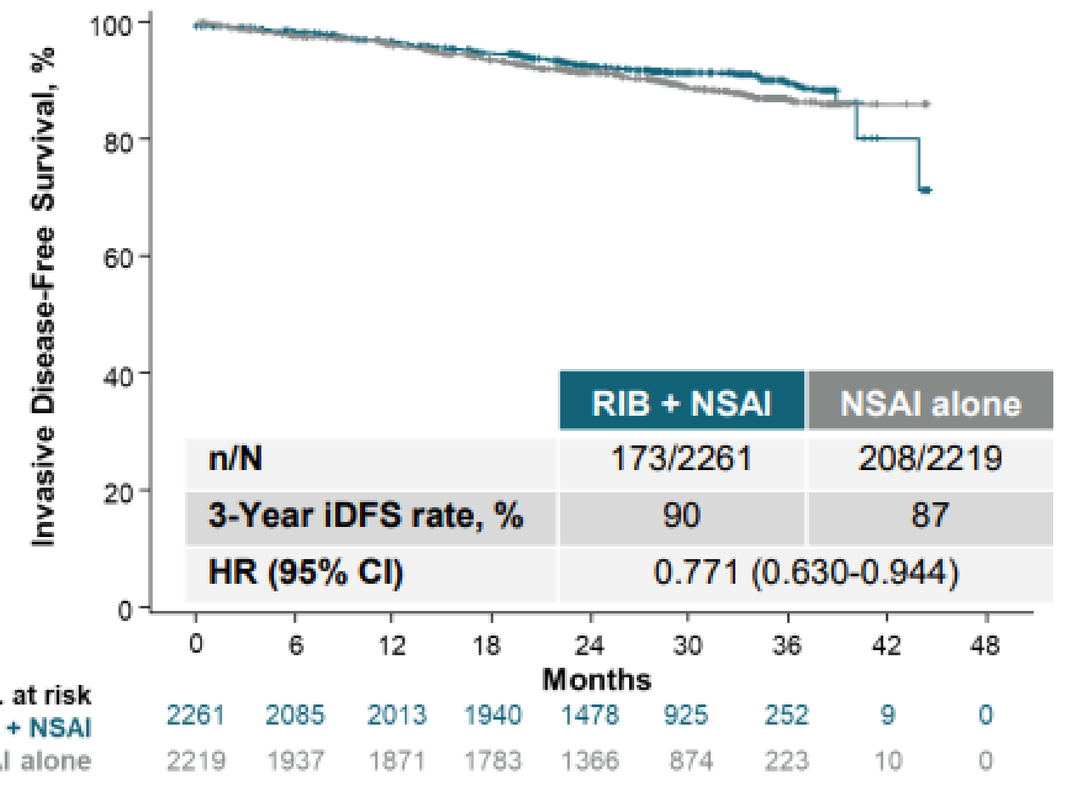
N0



	RIB + NSAI	NSAI alone
n/N	16/285	28/328
3-Year iDFS rate, %	94	89
HR (95% CI)	0.630 (0.341-1.165)	

No. at risk									
RIB + NSAI	285	262	258	250	239	186	59	3	0
NSAI alone	328	300	293	286	263	191	63	3	0

N1-N3



	RIB + NSAI	NSAI alone
n/N	173/2261	208/2219
3-Year iDFS rate, %	90	87
HR (95% CI)	0.771 (0.630-0.944)	

No. at risk									
RIB + NSAI	2261	2085	2013	1940	1478	925	252	9	0
NSAI alone	2219	1937	1871	1783	1366	874	223	10	0

iDFS, invasive disease-free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

Conclusions

- The iDFS benefit with ribociclib + NSAI across clinically relevant patient subgroups was generally consistent with that observed in the ITT population of NATALEE, suggesting that the benefit is not driven by any particular subgroup
- iDFS benefit was observed with ribociclib + NSAI over NSAI alone regardless of disease stage, nodal involvement, menopausal status, age, and Ki-67 score
- The control arm of NATALEE confirms that the patient population is at risk of recurrence, including those with N0 and stage II disease

These data reinforce previously reported results which showed significantly lowered risk of recurrence with ribociclib + NSAI compared with NSAI alone across a broad population of patients with stage II and III HR+/HER2− early breast cancer

iDFS, invasive disease-free survival; ITT, intent-to-treat; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NSAI, nonsteroidal aromatase inhibitor.

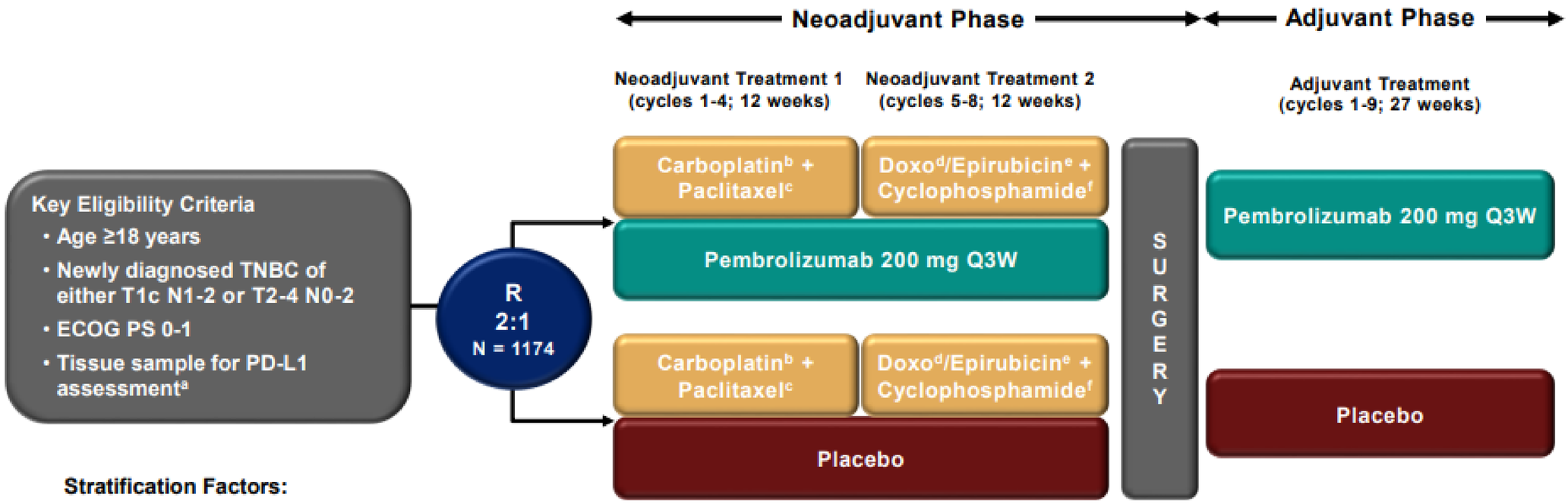
BARCELONA 2024 ESMO congress

Neoadjuvant Pembrolizumab or Placebo + Chemotherapy Followed by Adjuvant Pembrolizumab or Placebo for High-Risk Early-Stage Triple-Negative Breast Cancer: Overall Survival Results from the Phase 3 KEYNOTE-522 Study

Peter Schmid,[1] Javier Cortes,[2] Rebecca Dent,[3] Heather McArthur,[4] Lajos Pusztai,[5] Sherko Kümmel,[6] Carsten Denkert,[7] Yeon Hee Park,[8] Rina Hui,[9] Nadia Harbeck,[10] Masato Takahashi,[11] Seock-Ah Im,[12] Michael Untch,[13] Peter A. Fasching,[14] Fatima Cardoso,[15] Jing Zhao,[16] Xuan Zhou,[16] Konstantinos Tryfonidis,[16] Gursel Aktan,[16] Joyce O'Shaughnessy[17]

[1]Centre for Experimental Cancer Medicine, Barts Cancer Institute, Queen Mary University London, London, UK; [2]International Breast Cancer Center (IBCC), Pangaea Oncology, Quironsalud Group, Barcelona, Spain; Medical Scientia Innovation Research (MedSIR), Barcelona, Spain; Faculty of Biomedical and Health Sciences, Department of Medicine, Universidad Europea de Madrid, Madrid, Spain; [3]National Cancer Centre Singapore, Duke – National University of Singapore Medical School, Singapore; [4]University of Texas Southwestern Medical Center, Dallas, TX, USA; [5]Yale School of Medicine, Yale Cancer Center, New Haven, CT, USA; [6]Breast Unit, Kliniken Essen-Mitte, Essen, Germany and Charité – Universitätsmedizin Berlin, Department of Gynecology with Breast Center, Berlin, Germany; [7]Institute of Pathology, Philipps-University Marburg and University Hospital Marburg, Marburg, Germany; [8]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [9]Westmead Breast Cancer Institute, Westmead Hospital and the University of Sydney, Sydney, NSW, Australia and Centre of Cancer Medicine, School of Clinical Medicine, University of Hong Kong, Hong Kong; [10]Breast Center, Dept. OB&GYN, LMU University Hospital, Munich, Germany; [11]Hokkaido University Hospital, Sapporo, Japan; [12]Seoul National University Hospital, Cancer Research Institute, Seoul National University, Seoul, Republic of Korea; [13]Breast Cancer Center, Helios Klinikum Berlin-Buch, Berlin, Germany; [14]University Hospital Erlangen, Comprehensive Cancer Center Erlangen-EMN, Erlangen, Germany; [15]Breast Unit, Champalimaud Clinical Center/ Champalimaud Foundation, Lisbon, Portugal; [16]Oncology, Merck & Co., Inc., Rahway, NJ, USA; [17]Baylor University Medical Center, Texas Oncology, Sarah Cannon Research Institute, Dallas, TX, USA

KEYNOTE-522 Study Design (NCT03036488)



Stratification Factors:
- Nodal status (+ vs -)
- Tumor size (T1/T2 vs T3/T4)
- Carboplatin schedule (QW vs Q3W)

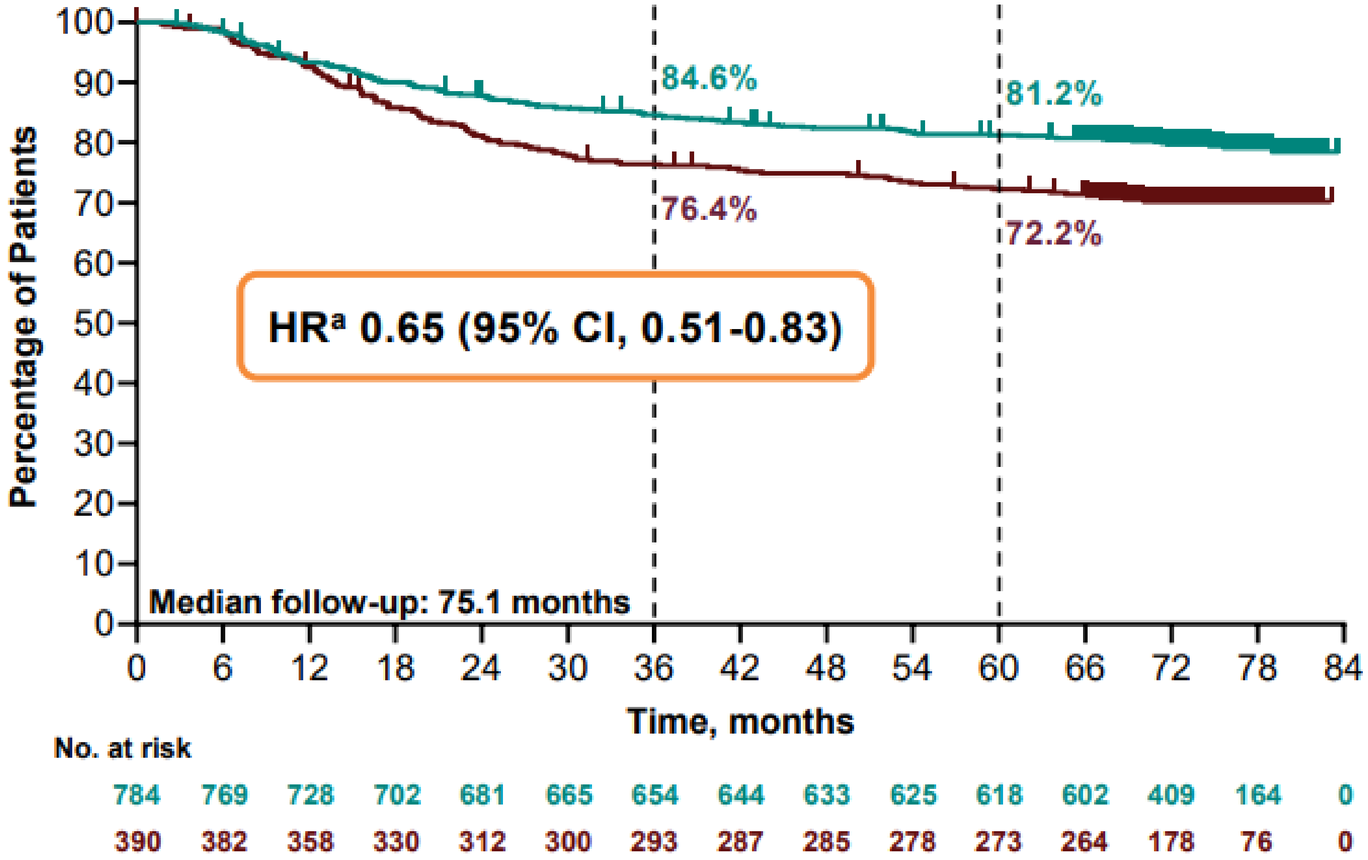
Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post-treatment included)

Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post-treatment included)

[a]Must consist of at least 2 separate tumor cores from the primary tumor. [b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW. [c]Paclitaxel dose was 80 mg/m² QW. [d]Doxorubicin dose was 60 mg/m² Q3W. [e]Epirubicin dose was 90 mg/m² Q3W. [f]Cyclophosphamide dose was 600 mg/m² Q3W.

Schmid P. et al. NEJM. 2020

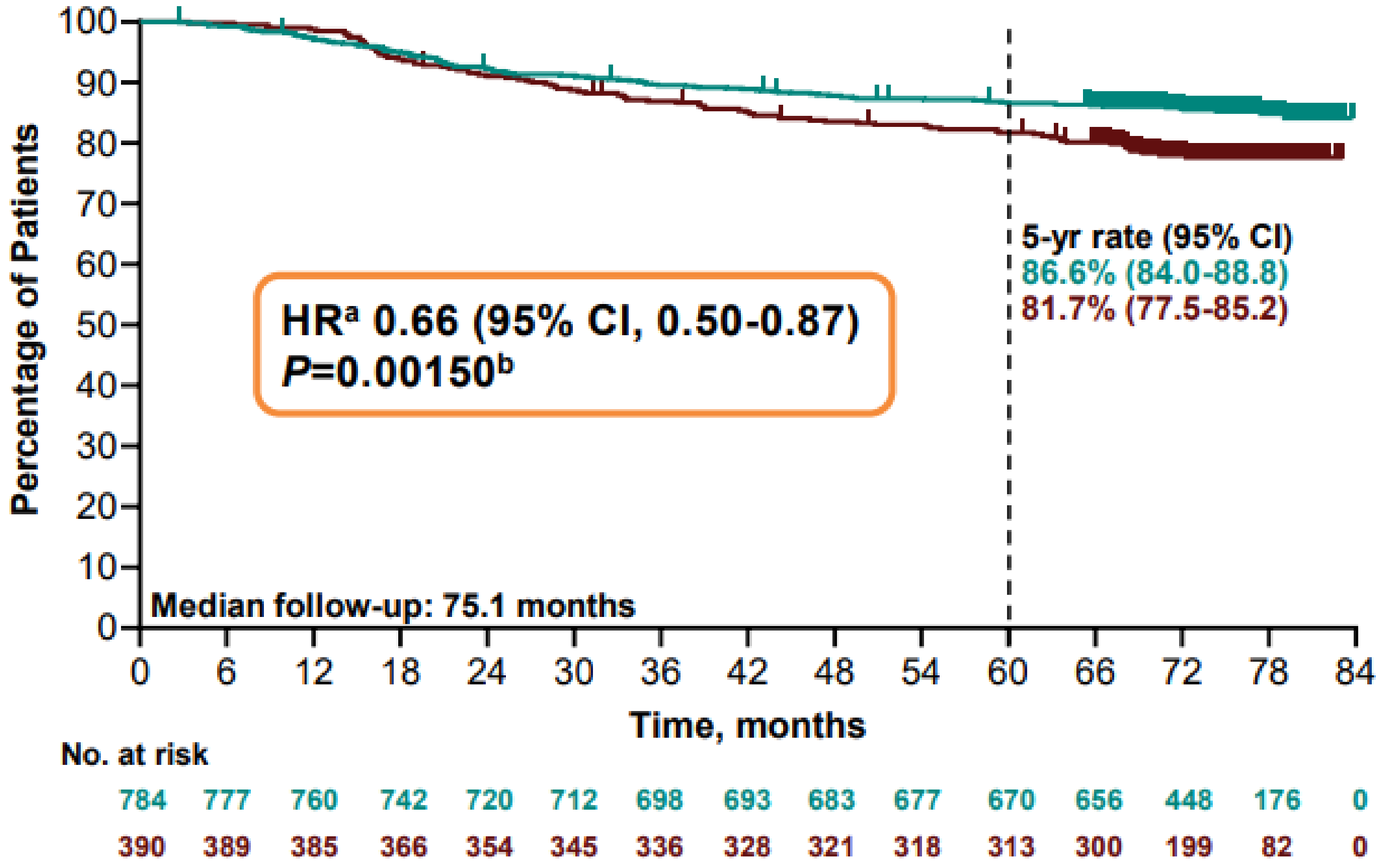
Updated Event-Free Survival



	Pts w/ Event
Pembro + Chemo/Pembro	20.3%
Placebo + Chemo/Placebo	29.2%

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff date: March 22, 2024.

Key Secondary Endpoint: Overall Survival

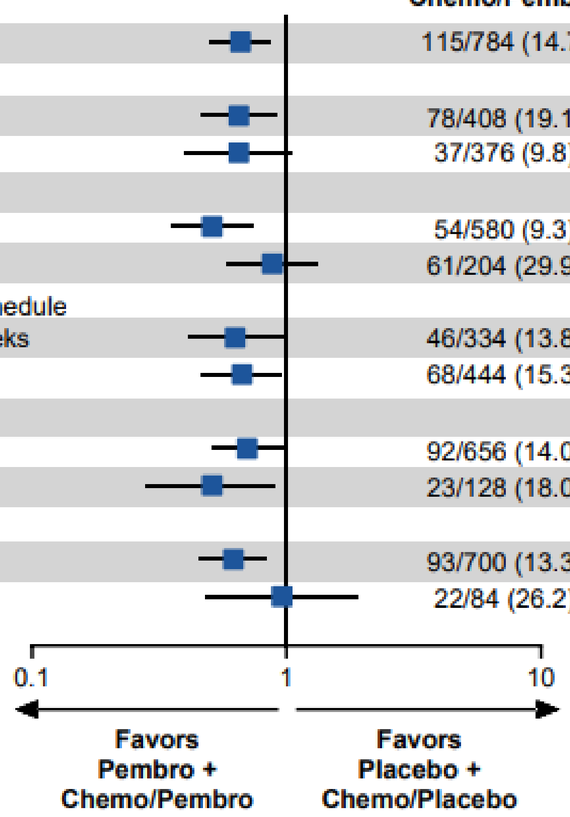


	Pts w/ Event
Pembro + Chemo/Pembro	14.7%
Placebo + Chemo/Placebo	21.8%

[a]The unstratified piecewise HR was 0.87 (95% CI, 0.57-1.32) before the 2-year follow-up and 0.51 (95% CI, 0.35-0.75) afterwards. The weighted average HR with weights of number of events before and after 2-year follow-up was 0.66. 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. Data cutoff date: March 22, 2024.

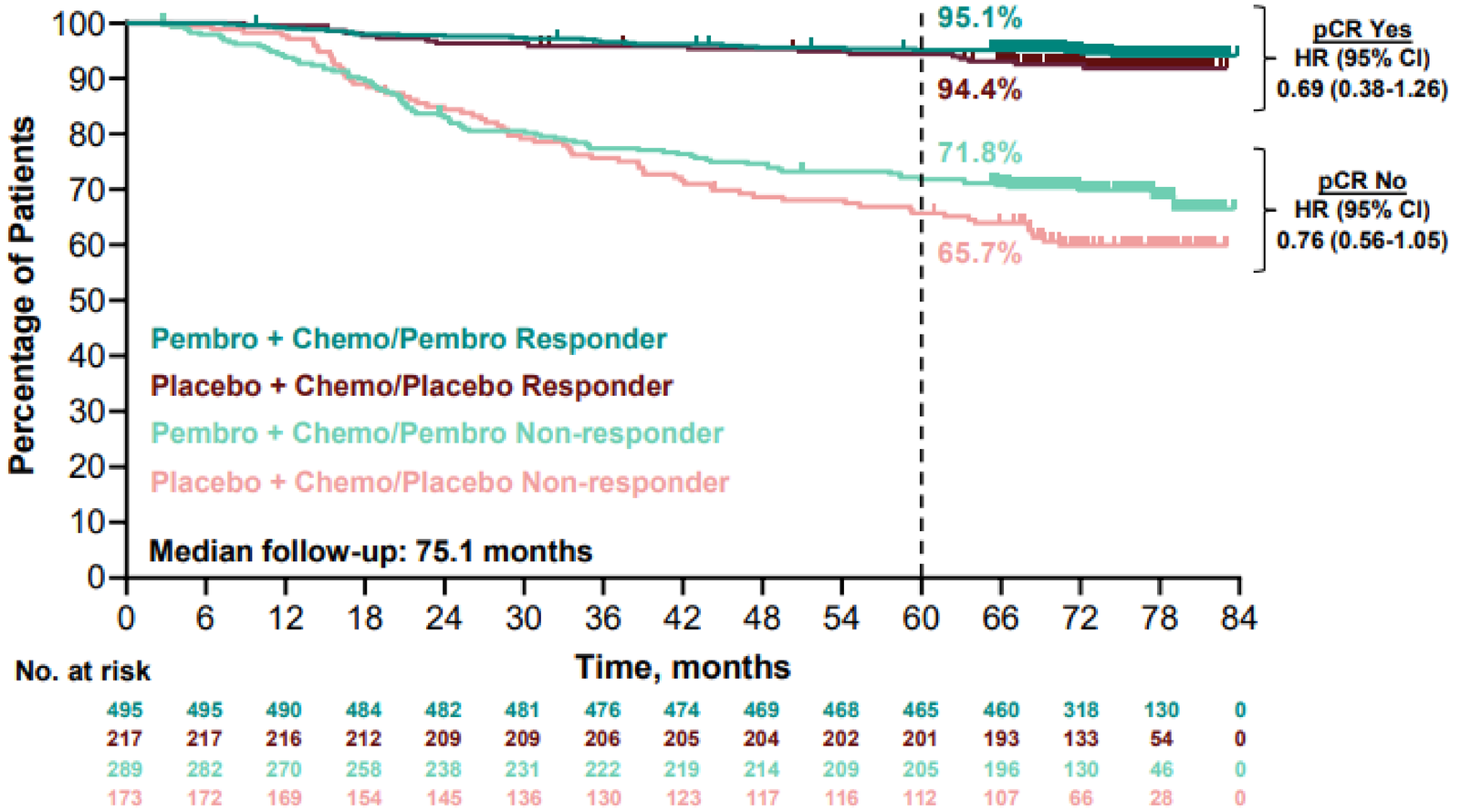
Overall Survival in Patient Subgroups

Subgroup	No. Events/No. Patients (%) Pembro + Chemo/Pembro	Placebo + Chemo/Placebo	Hazard Ratio (95% CI)
Overall	115/784 (14.7)	85/390 (21.8)	0.66 (0.50 to 0.87)
Nodal status			
Positive	78/408 (19.1)	56/196 (28.6)	0.65 (0.46 to 0.91)
Negative	37/376 (9.8)	29/194 (14.9)	0.65 (0.40 to 1.05)
Tumor size			
T1/T2	54/580 (9.3)	51/290 (17.6)	0.51 (0.35 to 0.75)
T3/T4	61/204 (29.9)	34/100 (34.0)	0.88 (0.58 to 1.34)
Carboplatin schedule			
Every 3 weeks	46/334 (13.8)	36/167 (21.6)	0.63 (0.41 to 0.97)
Weekly	68/444 (15.3)	49/220 (22.3)	0.67 (0.46 to 0.96)
PD-L1 status			
CPS ≥1	92/656 (14.0)	62/317 (19.6)	0.70 (0.51 to 0.97)
CPS <1	23/128 (18.0)	23/69 (33.3)	0.51 (0.28 to 0.91)
Age category			
<65 years	93/700 (13.3)	72/342 (21.1)	0.62 (0.45 to 0.84)
≥65 years[a]	22/84 (26.2)	13/48 (27.1)	0.96 (0.48 to 1.91)



For overall population and PD-L1 subgroups, analyses based on Cox regression model with Efron's method of tie handling with treatment as a covariate and stratified by nodal status (positive vs negative), tumor size (T1/T2 vs T3/T4), and frequency of carboplatin (once weekly vs once every 3 weeks); for other subgroups, analysis based on unstratified Cox model. [a]Based on the small sample size and few events, results should be interpreted with caution. Data cutoff date: March 22, 2024.

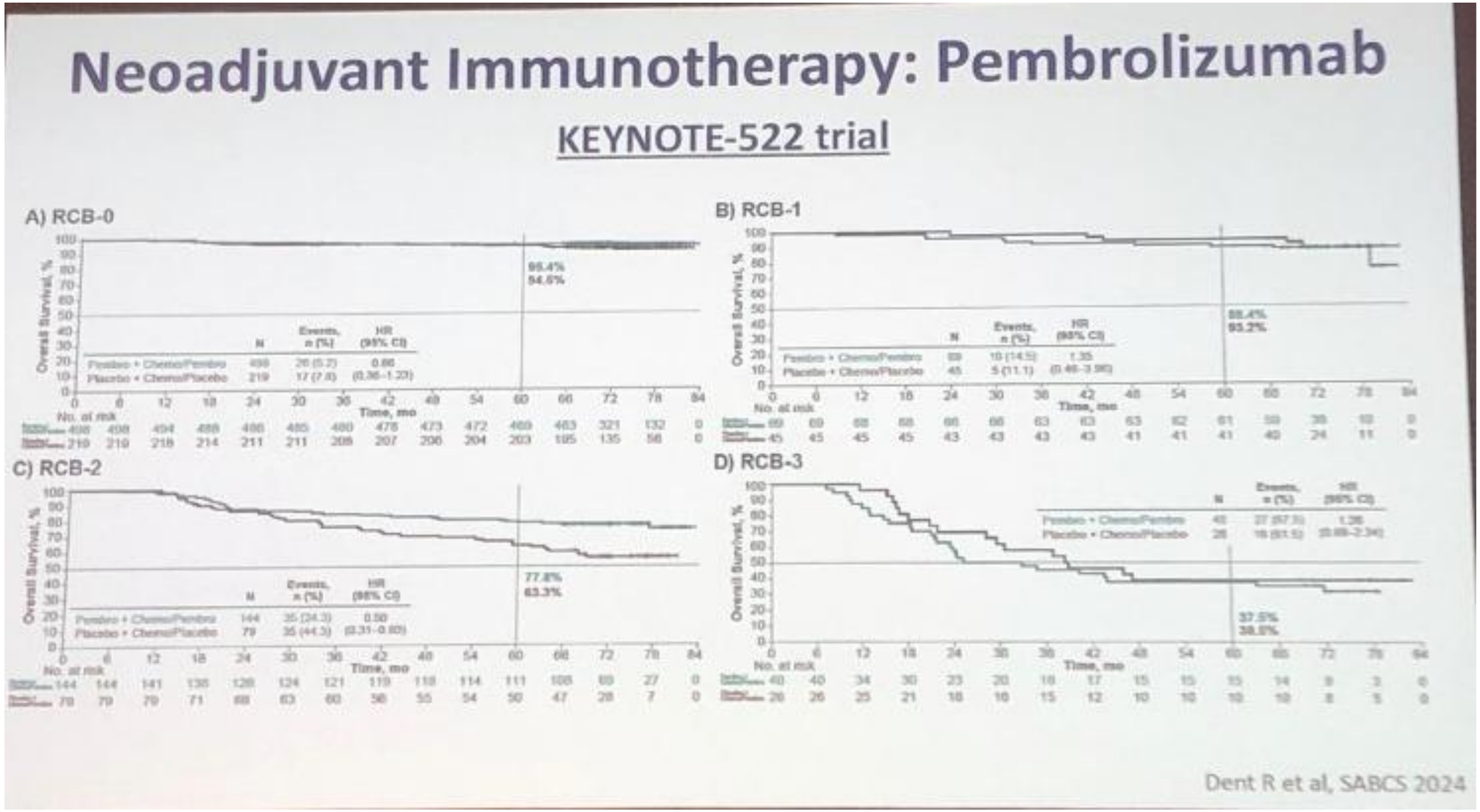
Overall Survival by Pathologic Complete Response (yp T0/Tis ypN0)



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.

Neoadjuvant Immunotherapy: Pembrolizumab

KEYNOTE-522 trial



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 4, 2024 VOL. 390 NO. 13

Omitting Axillary Dissection in Breast Cancer with Sentinel-Node Metastases

J. de Boniface, T. Filtenborg Tvedskov, L. Rydén, R. Szulkin, T. Reimer, T. Kühn, M. Kontos, O.D. Gentilini, R. Olofsson Bagge, M. Sund, D. Lundstedt, M. Appelgren, J. Ahlgren, S. Norenstedt, F. Celebioglu, H. Sackey, I. Scheel Andersen, U. Hoyer, P.F. Nyman, E. Vikhe Patil, E. Wieslander, H. Dahl Nissen, S. Alkner, Y. Andersson, B.V. Offersen, L. Bergkvist, J. Frisell, and P. Christiansen, for the SENOMAC Trialists' Group*

- Between January 2015 and December 2021, a total of 2766 were randomized with one or two sentinel-node macrometastases.
- Adjuvant treatment and radiation therapy were used in accordance with national guidelines.
- The primary endpoint was OS
- The median follow-up was 46.8 months
- Postoperative radiation therapy targeting regional lymphnodes was done in 89.9% in the sentinel-node biopsy–only group.
- One third of the patients had extracapsular extension in the sentinel-node biopsy sample.

Table 1. Characteristics of the Patients and Tumors (Per-Protocol Population).*

Characteristic	Sentinel-Node Biopsy Only (N=1335)	Completion Axillary-Lymph-Node Dissection (N=1205)
Age		
Mean — yr	61.0±12.0	60.9±11.7
Median (range) — yr	61 (20–94)	61 (34–90)
Distribution — no. (%)		
<40 yr	37 (2.8)	32 (2.7)
40–49 yr	220 (16.5)	194 (16.1)
50–64 yr	549 (41.1)	483 (40.1)
65–74 yr	334 (25.0)	342 (28.4)
≥75 yr	195 (14.6)	154 (12.8)
Tumor size — mm†		
Mean	24.4±15.5	24.2±16.9
Median (range)	20 (0.2–155)	20 (1–155)
Tumor stage — no. (%)‡		
T1	710 (53.2)	651 (54.0)
T2	552 (41.3)	480 (39.8)
T3	73 (5.5)	74 (6.1)
No. of removed sentinel lymph nodes — no. (%)		
1 or 2	934 (70.0)	856 (71.0)
3 or 4	349 (26.1)	303 (25.1)
>4	52 (3.9)	46 (3.8)
Mean	2.1±1.2	2.1±1.2
Median (range)	2 (1–11)	2 (1–9)
No. of sentinel lymph-node macrometastases — no. (%)		
1	1143 (85.6)	1008 (83.7)
2	192 (14.4)	197 (16.3)
No. of axillary metastases		
Mean	1.3±0.5	2.3±3.0
Median (range)	1 (1–5)	1 (1–42)
Type of breast surgery — no. (%)		
Breast-conserving surgery	845 (63.3)	775 (64.3)
Mastectomy	490 (36.7)	430 (35.7)
Tumor histologic type — no. (%)		
Invasive carcinoma, no special type	997 (74.7)	939 (77.9)
Lobular carcinoma	278 (20.8)	226 (18.8)
Other	60 (4.5)	40 (3.3)
Nottingham histologic grade — no. (%)§		
Grade 1	243 (18.2)	211 (17.5)
Grade 2	786 (58.9)	717 (59.5)
Grade 3	298 (22.3)	263 (21.8)
Missing data	8 (0.6)	14 (1.2)

Table 1. (Continued.)

Characteristic	Sentinel-Node Biopsy Only (N=1335)	Completion Axillary-Lymph-Node Dissection (N=1205)
Tumor subtype — no. (%)¶		
ER-positive, HER2-negative	1166 (87.3)	1034 (85.8)
ER-positive, HER2-positive	84 (6.3)	88 (7.3)
ER-negative, HER2-positive	23 (1.7)	34 (2.8)
ER-negative, HER2-negative	57 (4.3)	46 (3.8)
Missing data	5 (0.4)	3 (0.2)
Ki-67 proliferation index		
Mean — %	24.6±17.2	24.8±17.7
Median (range) — %	20 (1–98)	20 (1–98)
Missing data — no. (%)	13 (1.0)	18 (1.5)

De Boniface J et al. NEJM 2024

Omitting Axillary Dissection in Breast Cancer – SENOMAC Trial Results

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 APRIL 4, 2024 VOL. 390 NO. 13

Omitting Axillary Dissection in Breast Cancer with Sentinel-Node Metastases

Findings

Population Analysis:

- SNB-only group: 1,335 patients
- Dissection group: 1,205 patients

Recurrence-Free Survival (5 years):

- SNB-only group: 89.7% (95% CI: 87.5–91.9)
- Dissection group: 88.7% (95% CI: 86.3–91.1)
- Hazard ratio: 0.89 (95% CI: 0.66–1.19), below the noninferiority margin (P<0.001)

Radiation Therapy Use:

- SNB-only group: 89.9% received nodal radiation
- Dissection group: 88.4% received nodal radiation

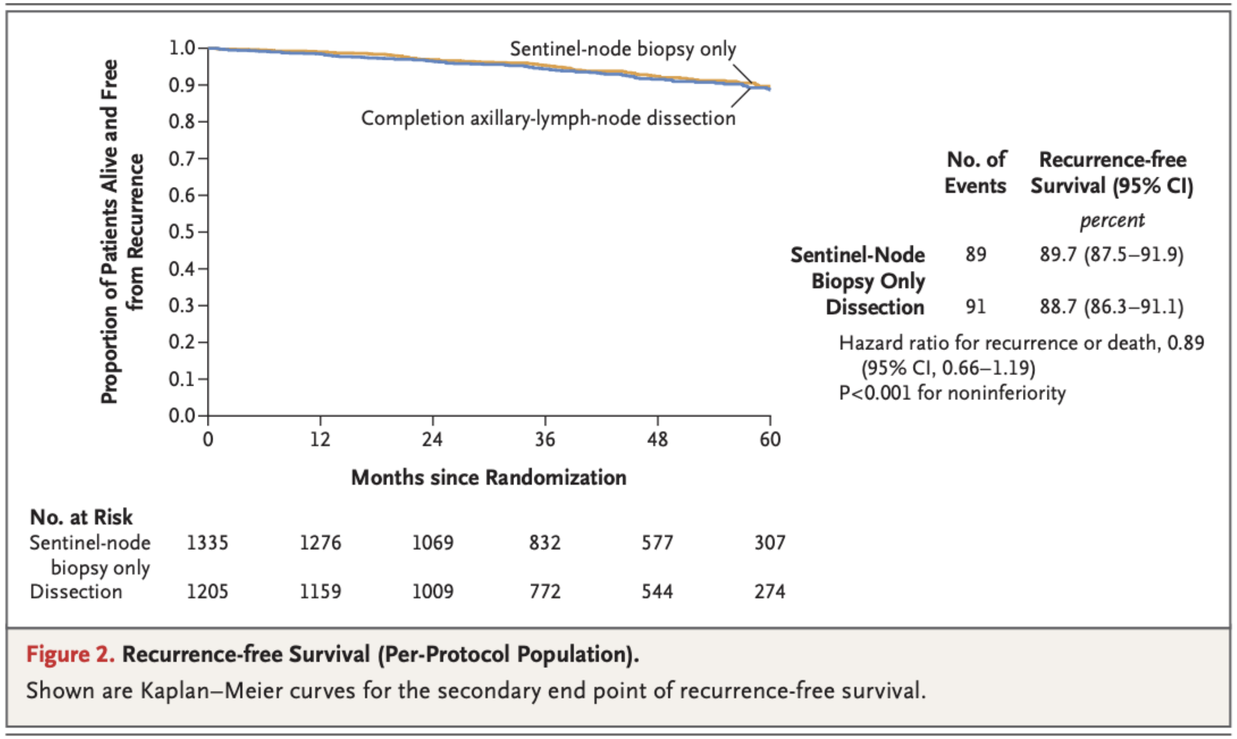


Figure 2. Recurrence-free Survival (Per-Protocol Population).
Shown are Kaplan–Meier curves for the secondary end point of recurrence-free survival.

De Boniface J et al. NEJM 2024

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 APRIL 4, 2024 VOL. 390 NO. 13

Omitting Axillary Dissection in Breast Cancer with Sentinel-Node Metastases

Conclusions

- Omission of cALND is noninferior to dissection in recurrence-free survival for patients with sentinel-node macrometastases, most of whom received nodal radiation therapy

- Results suggest that SNB alone, combined with appropriate adjuvant therapy, may be a safe standard of care for select patients

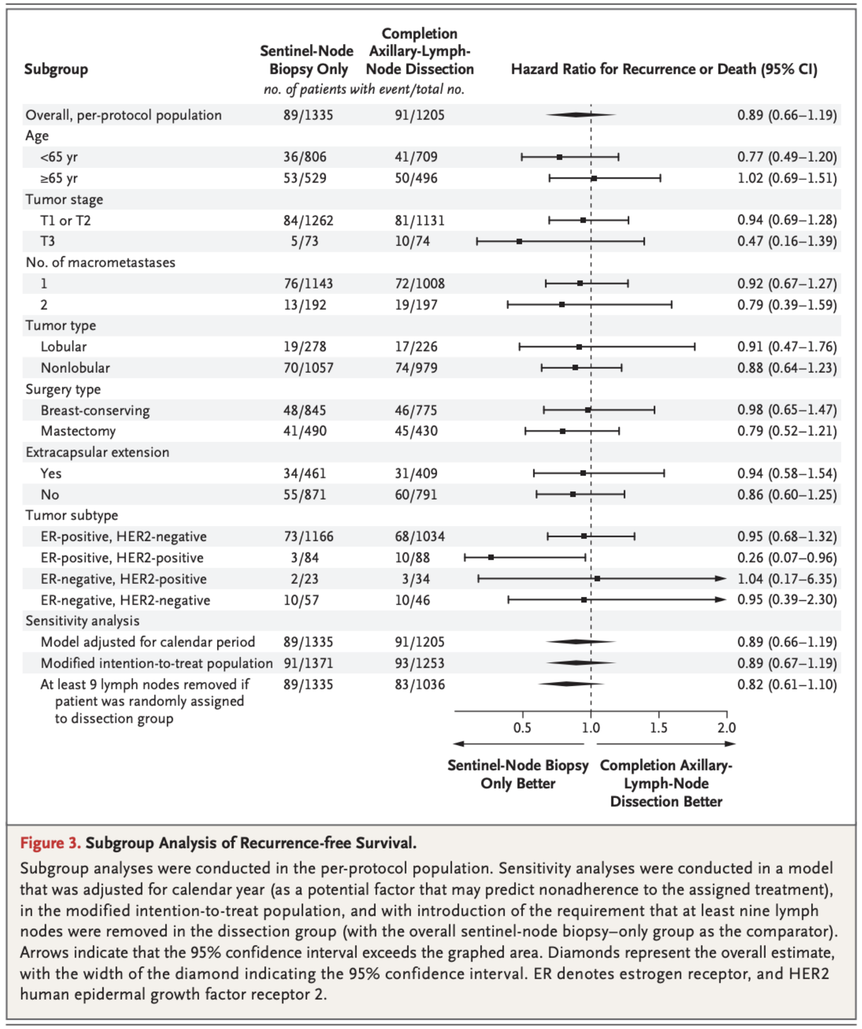


Figure 3. Subgroup Analysis of Recurrence-free Survival.
Subgroup analyses were conducted in the per-protocol population. Sensitivity analyses were conducted in a model that was adjusted for calendar year (as a potential factor that may predict nonadherence to the assigned treatment), in the modified intention-to-treat population, and with introduction of the requirement that at least nine lymph nodes were removed in the dissection group (with the overall sentinel-node biopsy–only group as the comparator). Arrows indicate that the 95% confidence interval exceeds the graphed area. Diamonds represent the overall estimate, with the width of the diamond indicating the 95% confidence interval. ER denotes estrogen receptor, and HER2 human epidermal growth factor receptor 2.

De Boniface J et al. NEJM 2024

Comparison between SENOMAC, Z0011 and AMAROS

Characteristic	SENOMAC	Z0011	AMAROS
Period	2015-2021	1999-2004	2001-2010
Population	2766 patients	891 patients	1425 patients
Surgery	Conservative and mastectomy	Conservative only	Conservative and mastectomy
N Metastases	Macrometastases (micrometastes allowed)	Micro and macrometastases (40% micro)	Micro and macrometastases
Tumors	T1-T3	T1-T2	T1-T2
Extracapsular extension	Allowed	Excluded	Not reported
Mastectomy	>33% of cases	Not allowed	17.4% of cases
Nodal RT	89% of cases	Not standardized	Study arm

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Axillary Surgery in Breast Cancer — Primary Results of the INSEMA Trial

Background

- Axillary surgery has long been a standard part of breast-conserving therapy (BCT)
- The necessity of axillary staging in patients with clinically node-negative, invasive breast cancer has been debated
- The INSEMA trial investigated whether axillary surgery could be omitted without compromising invasive disease-free survival (iDFS)

Methods

- **Trial Type:** Prospective, randomised, noninferiority study
- **Population:** 5,502 patients with clinically node-negative, invasive breast cancer (T1/T2, tumour size ≤5 cm) scheduled for BCT
- **Intervention Groups:**
  - **Surgery-omission group:** No axillary surgery
  - **Surgery group:** Sentinel-lymph-node biopsy (SLNB)
- **Primary Endpoint:** iDFS (per-protocol analysis)
- **Noninferiority Criteria:** 5-year iDFS ≥85%, with an upper hazard ratio (HR) limit <1.271
- **Median Follow-Up:** 73.6 months

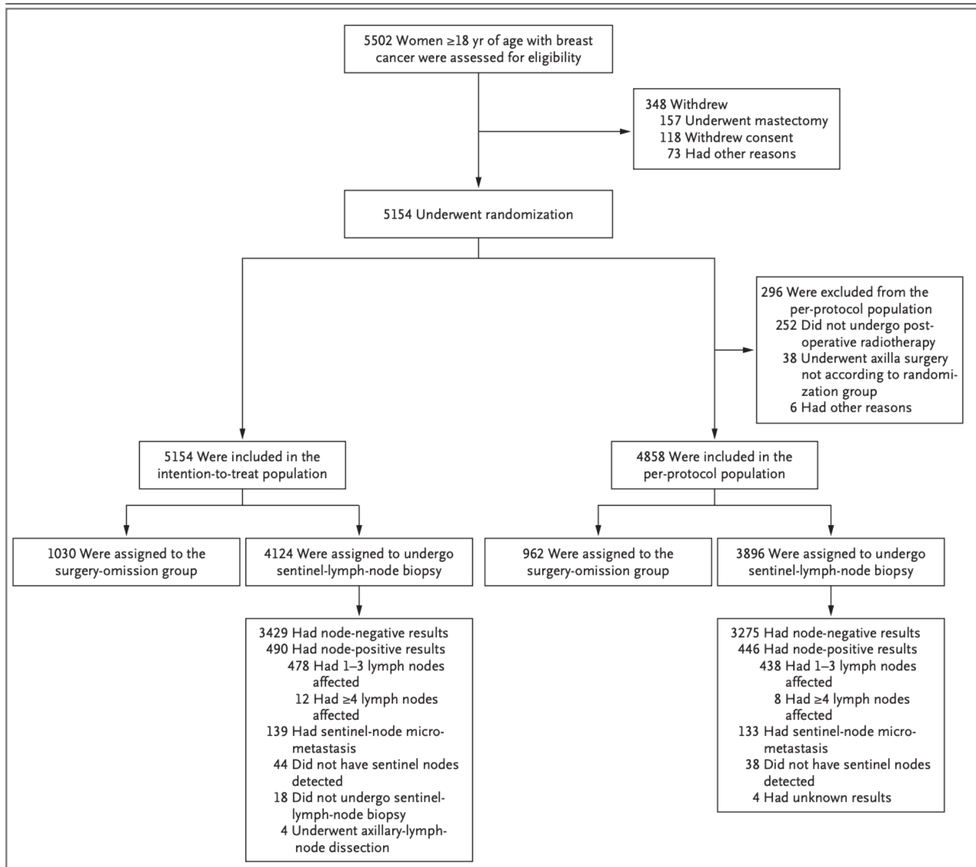


Figure 1. Randomization and Analysis.
Failed sentinel-lymph-node mapping was an indication for axillary-lymph-node dissection according to the trial protocol, based on the guideline released by the American Society of Breast Surgeons in November 2014.

Reimer T, et al. N Engl J Med. 2024

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Axillary Surgery in Breast Cancer — Primary Results of the INSEMA Trial

Findings

Primary Outcome:

5-year iDFS:

- **Surgery-omission group:** 91.9% (95% CI: 89.9–93.5)
- **Surgery group:** 91.7% (95% CI: 90.8–92.6)
- Hazard ratio: 0.91 (95% CI: 0.73–1.14)

Axillary Recurrence:

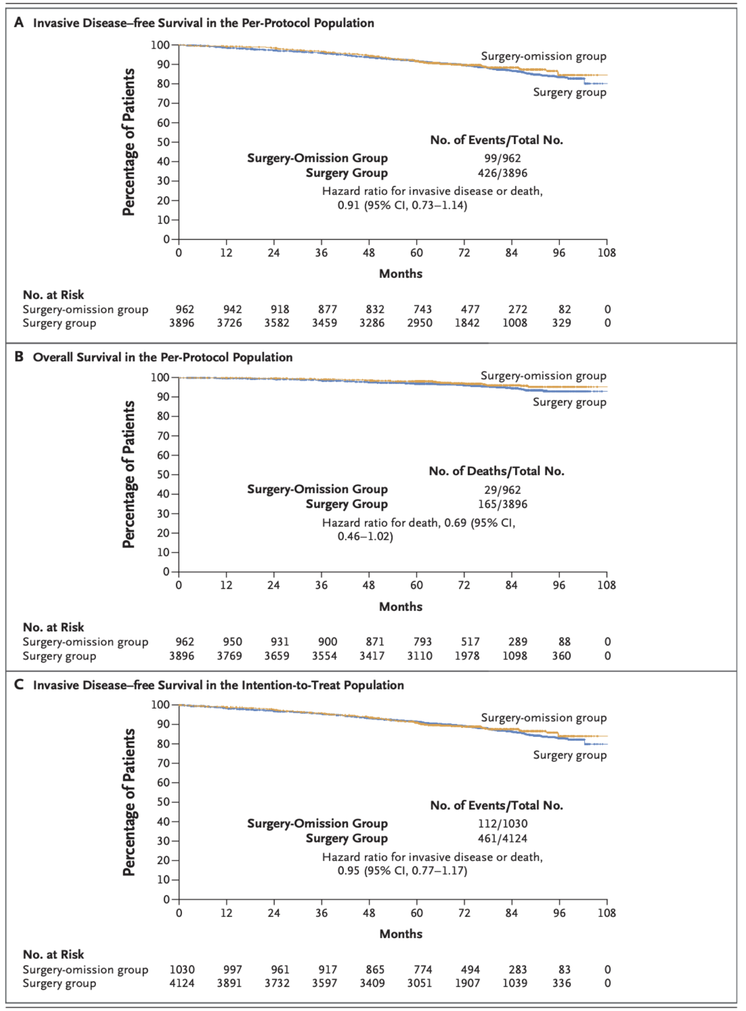
- Surgery-omission: 1.0%
- Surgery group: 0.3%

Mortality Differences:

- Surgery-omission group: 1.4%
- Surgery group: 2.4%

Safety and QoL Outcomes:

- Reduced lymphedema
- Improved arm mobility
- Less pain in arm/shoulder movement



Reimer T, et al. N Engl J Med. 2024

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Axillary Surgery in Breast Cancer — Primary Results of the INSEMA Trial

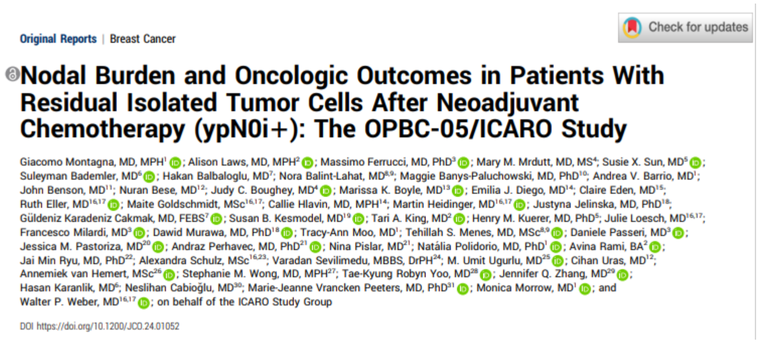
Conclusions

- Omission of surgical axillary staging was noninferior to SLNB in iDFS after 6 years
- Patients in the surgery-omission group experienced fewer adverse effects and better quality of life
- Findings challenge the necessity of routine axillary staging in selected patients, potentially reshaping standards of care

Table 2. Summary of Primary-Outcome Events in the Per-Protocol Population.

Event	No Sentinel-Lymph-Node Biopsy (N=962)	Sentinel-Lymph-Node Biopsy (N=3896)	All Patients (N=4858)
Any primary-outcome event — no. (%)			
No	863 (89.7)	3470 (89.1)	4333 (89.2)
Yes	99 (10.3)	426 (10.9)	525 (10.8)
First primary-outcome event — no. (%)			
Invasive locoregional relapse	18 (1.9)	54 (1.4)	72 (1.5)
Invasive contralateral breast cancer	10 (1.0)	25 (0.6)	35 (0.7)
Distant relapse	26 (2.7)	104 (2.7)	130 (2.7)
Secondary cancer	32 (3.3)	150 (3.9)	182 (3.7)
Death	13 (1.4)	93 (2.4)	106 (2.2)
Locoregional relapse — no. (%)			
Axillary recurrence	10 (1.0)	12 (0.3)	22 (0.5)
Invasive ipsilateral breast recurrence	8 (0.8)	42 (1.1)	50 (1.0)
Death from any cause — no./ total no. (%)			
Breast cancer	0	1/93 (1.1)	1/106 (0.9)
Second, nonbreast cancer	0	3/93 (3.2)	3/106 (2.8)
Other known cause	7/13 (53.8)	43/93 (46.2)	50/106 (47.2)
Unknown cause	6/13 (46.2)	46/93 (49.5)	52/106 (49.1)

Reimer T, et al. N Engl J Med. 2024



Original Reports | Breast Cancer

Check for updates

Nodal Burden and Oncologic Outcomes in Patients With Residual Isolated Tumor Cells After Neoadjuvant Chemotherapy (ypN0i+): The OPBC-05/ICARO Study

Giacomo Montagna, MD, MPH[1]; Alison Laws, MD, MPH[2]; Massimo Ferrucci, MD, PhD[3]; Mary M. Mrdutt, MD, MS[4]; Susie X. Sun, MD[5]; Suleyman Bademler, MD[6]; Hakan Balbaloglu, MD[7]; Nora Balint-Lahat, MD[8,9]; Maggie Banys-Paluchowski, MD, PhD[10]; Andrea V. Barrio, MD[1]; John Benson, MD[11]; Nuran Bese, MD[12]; Judy C. Boughey, MD[4]; Marissa K. Boyle, MD[13]; Emilia J. Diego, MD[14]; Claire Eden, MD[15]; Ruth Eller, MD[16,17]; Maite Goldschmidt, MSc[16,17]; Callie Hlavin, MD, MPH[14]; Martin Heidinger, MD[16,17]; Justyna Jelinska, MD, PhD[18]; Güldeniz Karadeniz Cakmak, MD, FEBS[7]; Susan B. Kesmodel, MD[19]; Tari A. King, MD[2]; Henry M. Kuerer, MD, PhD[5]; Julie Loesch, MD[16,17]; Francesco Milardi, MD[3]; Dawid Murawa, MD, PhD[18]; Tracy-Ann Moo, MD[1]; Tehillah S. Menes, MD, MSc[8,9]; Daniele Passeri, MD[3]; Jessica M. Pastoriza, MD[20]; Andraz Perhavec, MD, PhD[21]; Nina Pislar, MD[21]; Natália Polidorio, MD, PhD[1]; Avina Rami, BA[2]; Jai Min Ryu, MD, PhD[22]; Alexandra Schulz, MSc[16,23]; Varadan Sevilimedu, MBBS, DrPH[24]; M. Umit Ugurlu, MD[25]; Cihan Uras, MD[12]; Annemiek van Hemert, MSc[26]; Stephanie M. Wong, MD, MPH[27]; Tae-Kyung Robyn Yoo, MD[28]; Jennifer Q. Zhang, MD[29]; Hasan Karanlik, MD[6]; Neslihan Cabioğlu, MD[30]; Marie-Jeanne Vrancken Peeters, MD, PhD[31]; Monica Morrow, MD[1]; and Walter P. Weber, MD[16,17]; on behalf of the ICARO Study Group

DOI https://doi.org/10.1200/JCO.24.01052

Background

- To investigate the role of axillary lymph node dissection (ALND) in patients with residual isolated tumor cells (ITCs) in the sentinel lymph nodes (SLNs) after neoadjuvant chemotherapy.

- **Methods**

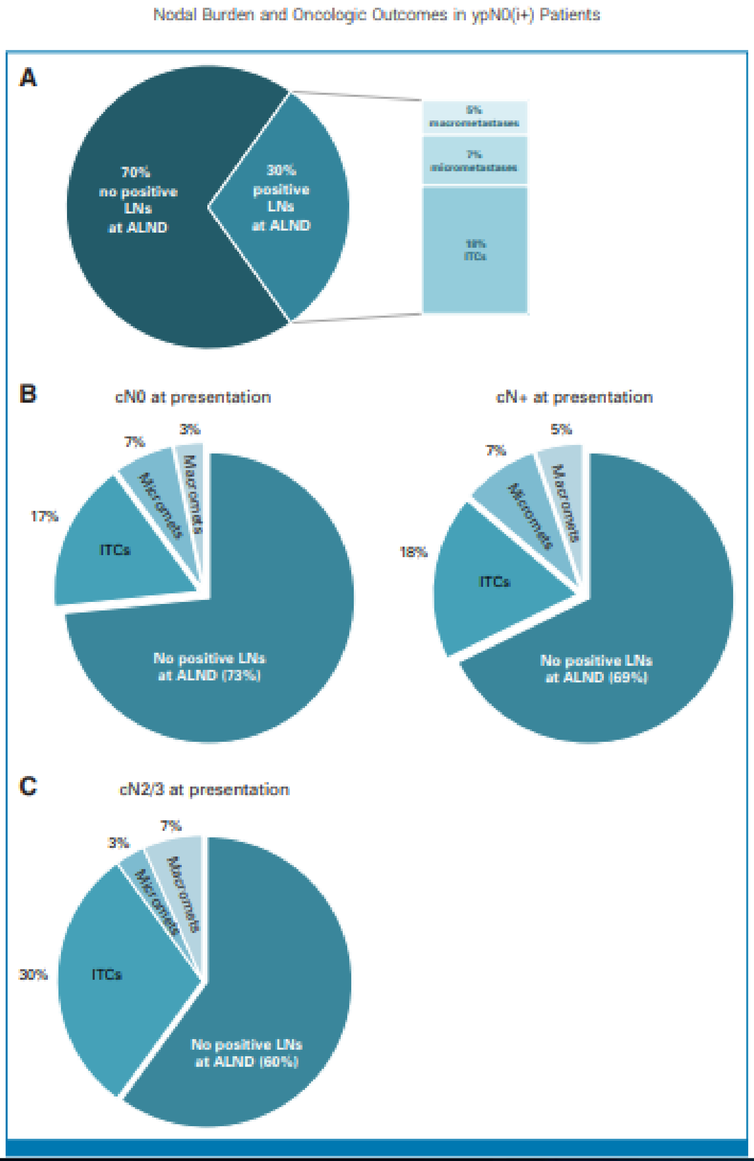
- **Trial Type:** Retrospective. Patients with stage I to III breast cancer with ITCs in SLNs after NAC from 62 centers in 18 countries.

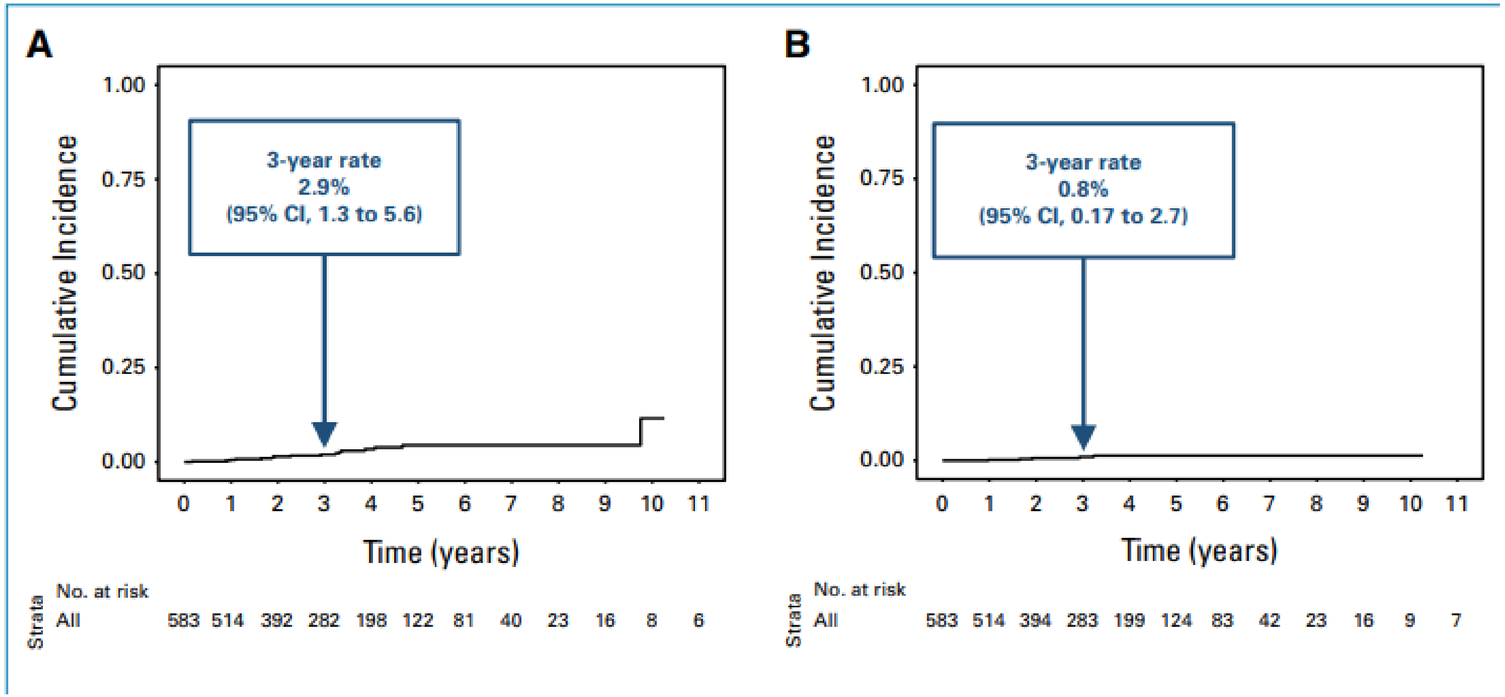
- **Population:** 583 patients were included, of whom 182 (31%) had completion ALND and 401 (69%) did not.

- **Primary Endpoint:** The primary end point was the 3-year rate of any axillary recurrence.

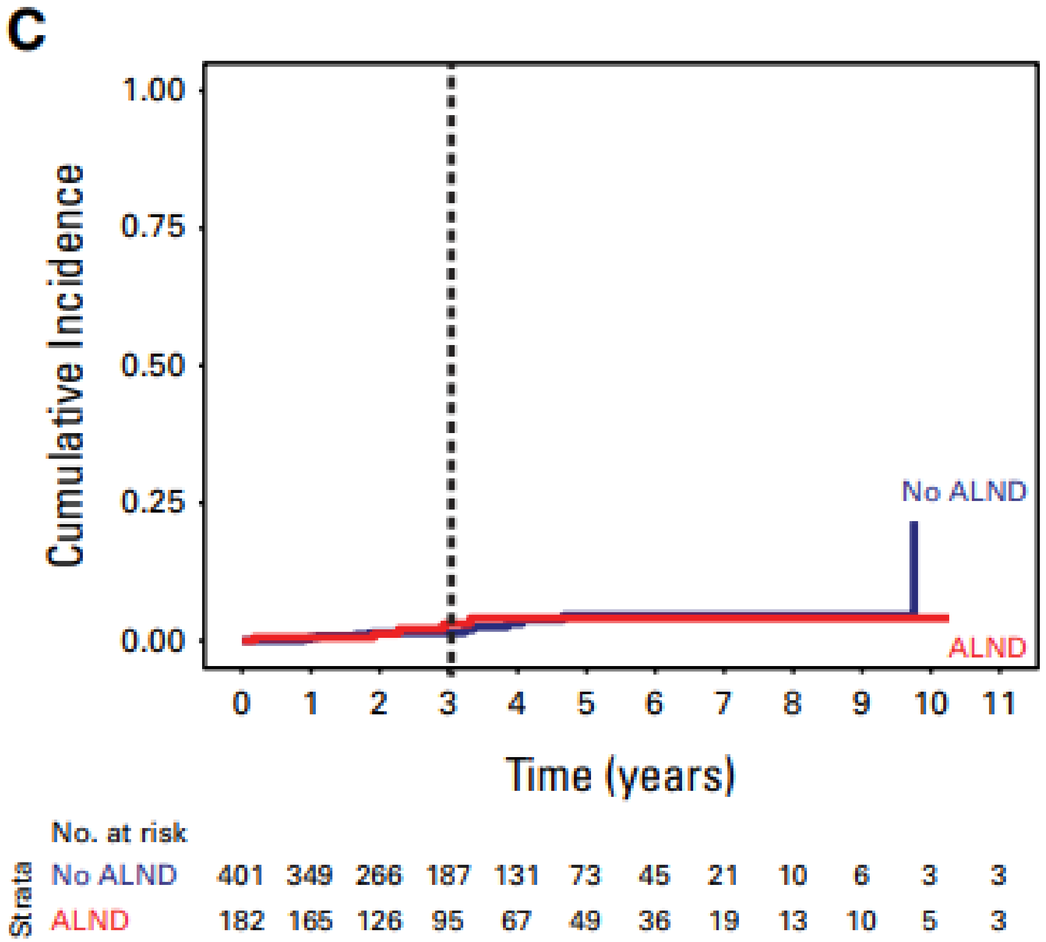
- **Median Follow-Up:** 38 months

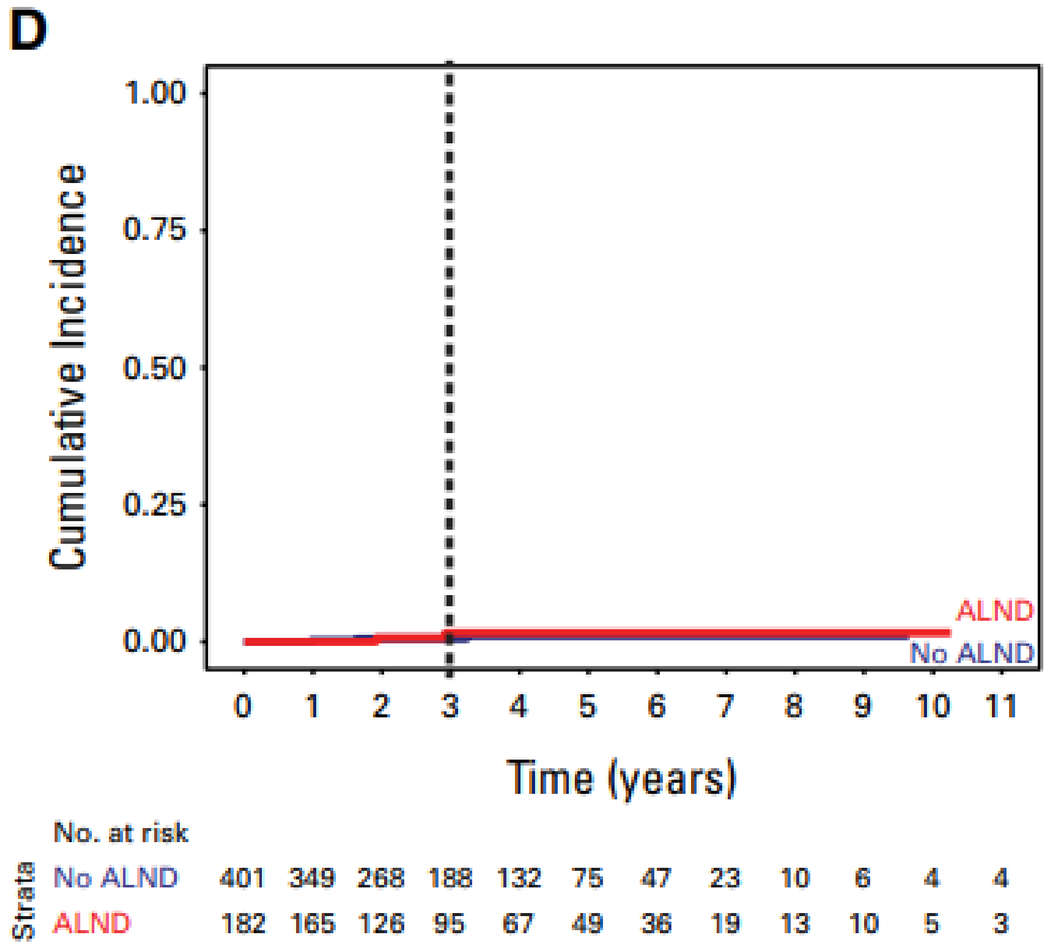
Montagna G, et al. JCO. 2024



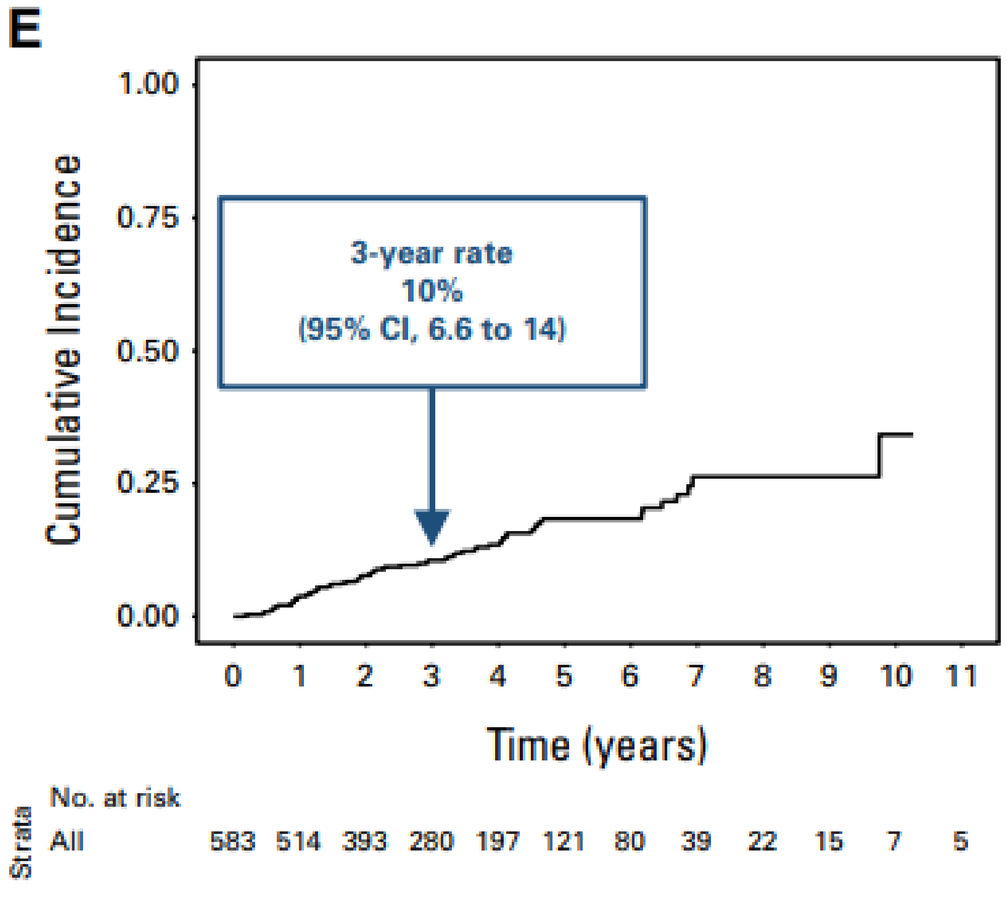


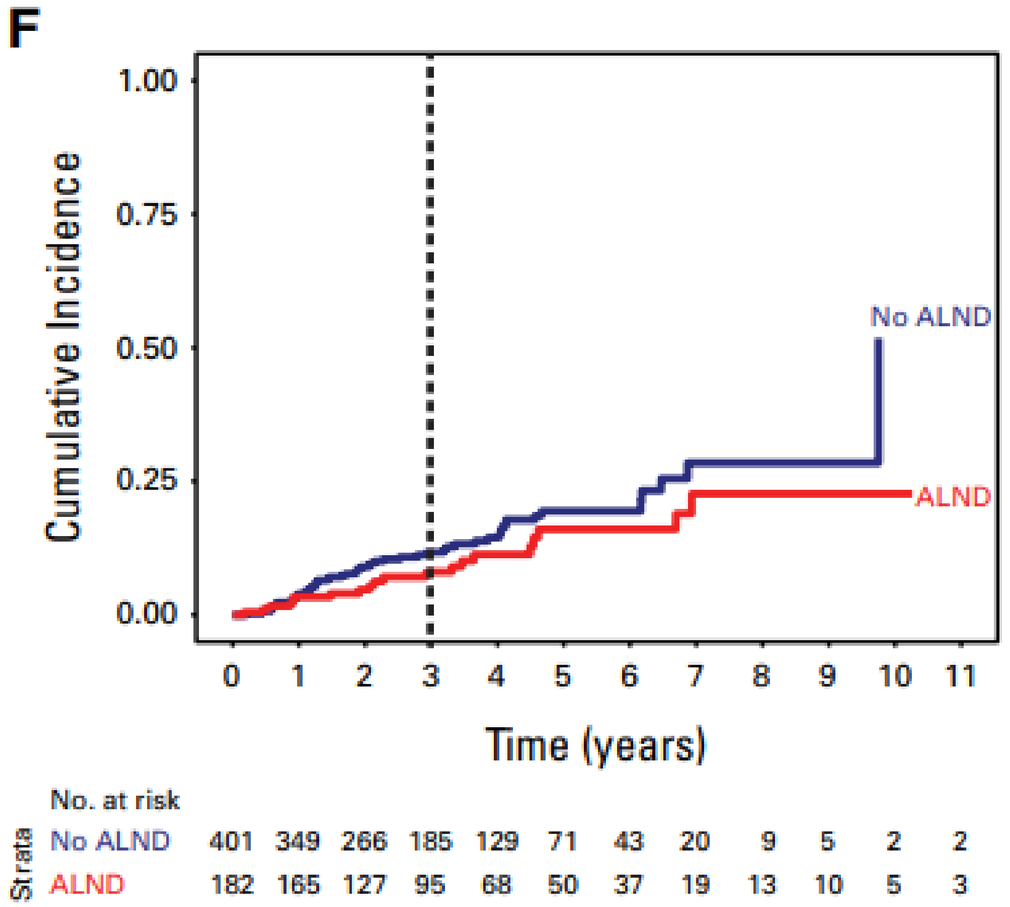
Montagna G, et al. JCO. 2024





Montagna G, et al. JCO. 2024





Montagna G, et al. JCO. 2024

Original Reports | Breast Cancer

Check for updates

Omission of Radiotherapy After Breast-Conserving Surgery for Women With Breast Cancer With Low Clinical and Genomic Risk: 5-Year Outcomes of IDEA

Reshma Jagsi, MD, DPhil[1,2]; Kent A. Griffith, MS[2]; Eleanor E. Harris, MD[3]; Jean L. Wright, MD[4]; Abram Recht, MD[5]; Alphonse G. Taghian, MD, PhD[6]; Lucille Lee, MD[7]; Meena S. Moran, MD[8]; William Small Jr, MD[9]; Candice Johnstone, MD[10]; Asal Rahimi, MD[11]; Gary Freedman, MD[12]; Mahvish Muzaffar, MD[13]; Bruce Haffty, MD[14]; Kathleen Horst, MD[15]; Simon N. Powell, MD, PhD[16]; Jody Sharp, BS[2]; Michael Sabel, MD[2]; Anne Schott, MD[2]; and Mahmoud El-Tamer, MD[16]

DOI https://doi.org/10.1200/JCO.23.02270

- Postmenopausal patients age 50-69 years with pT1N0 unifocal invasive breast cancer with margins ≥2 mm after BCS Luminal A with Oncotype DX 21-gene recurrence score ≤18 were prospectively enrolled in a single-arm trial of radiotherapy omission if they consented to take at least 5 years of ET.
- The primary end point was the rate of locoregional recurrence 5 years after BCS.
- Between June 2015 and October 2018, 200 eligible patients were enrolled.
- The 5-year freedom from any recurrence was 99%.
- Median follow-up time was 5.21 years.

TABLE 1. Characteristics of Patient Sample

Characteristic	Statistics
Year enrolled, No. (%)	
2015	10 (5)
2016	58 (29)
2017	103 (51.5)
2018	29 (14.5)
Age, years	
Mean (SD)	62 (4.9)
Median (IQR)	63 (58-66)
Age group, No. (%)	
50-59	60 (30)
60-69	140 (70)
Zubrod performance status, No. (%)	
0, asymptomatic	175 (87.5)
1, symptomatic, fully ambulatory	25 (12.5)
MRI at the time of diagnosis, No. (%)	
No	134 (67)
Yes	66 (33)
Imaging evidence beyond primary site of tumor, No. (%)	
No	188 (94)
Yes, biopsy-proven nonmalignant	12 (6)
Nodal evaluation procedure, No. (%)	
SLNB only	190 (95)
SLNB, ALND	7 (3.5)
ALND only	3 (1.5)
Histology, No. (%)	
Ductal	169 (84.5)
Lobular	20 (10)
Ductal and lobular	4 (2)
Mucinous	3 (1.5)
Tubular	4 (2)
Oncotype DX 21-gene assay recurrence score	
Mean (SD)	11.2 (4.8)
Median (IQR)	12 (8-15)
Tumor grade, No. (%)	
Well differentiated	85 (42.5)
Moderately differentiated	109 (54.5)
Poorly differentiated	6 (3)
Tumor size, mm	
Mean (SD)	10 (4.6)
Median (IQR)	9 (7-13)
Nodal status, No. (%)	
Node-negative without ITCs	199 (99.5)
ITCs, no cluster >0.2 mm	1 (0.5)
Lymphovascular invasion, No. (%)	
Absent	171 (85.5)
Present	16 (8)
Not reported/unknown	13 (6.5)
Extensive intraductal component, No. (%)	
Absent	90 (45)

(continued in next column)

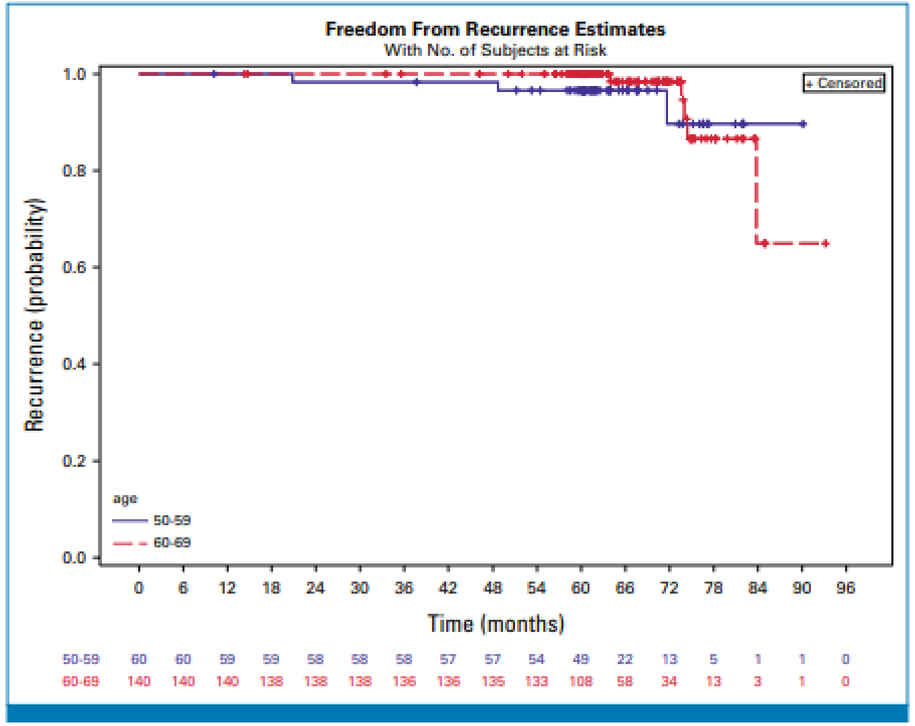


FIG 1. Freedom from recurrence in relation to age cohort.

Jagsi R et al. JCO 2024

ESTRO 2024

To report **5-year results of IRMA trial**

IRMA trial (NCT 01803958)

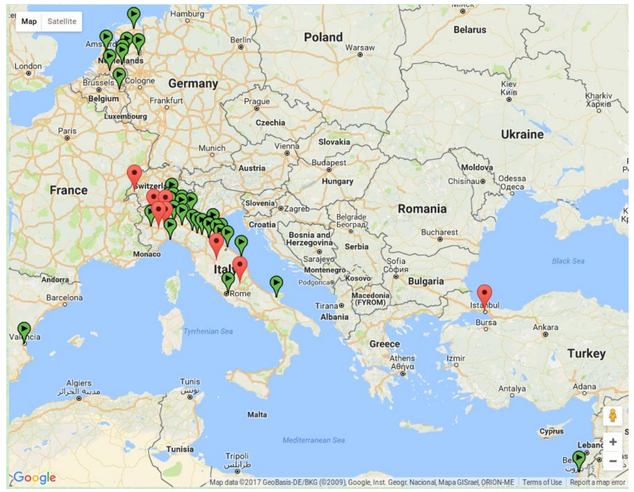
Multicentric randomized trial (Italy, Netherlands, Spain, Switzerland, Israel)

Non inferiority study (APBI vs WBI)

Primary Objective : Local control

(incidence of ipsilateral breast tumour recurrences)

Secondary Objectives: OS, Cosmesis, Toxicity



https://clinicaltrials.gov/ct2/show/NCT01803958 - www.irmatrial.it

ESTRO 2024

Treatment

APBI: 38.5 Gy in 10 fractions b.i.d

WBI: conventional or hypo-fractionated

Adjuvant systemic therapy according to institutional guidelines

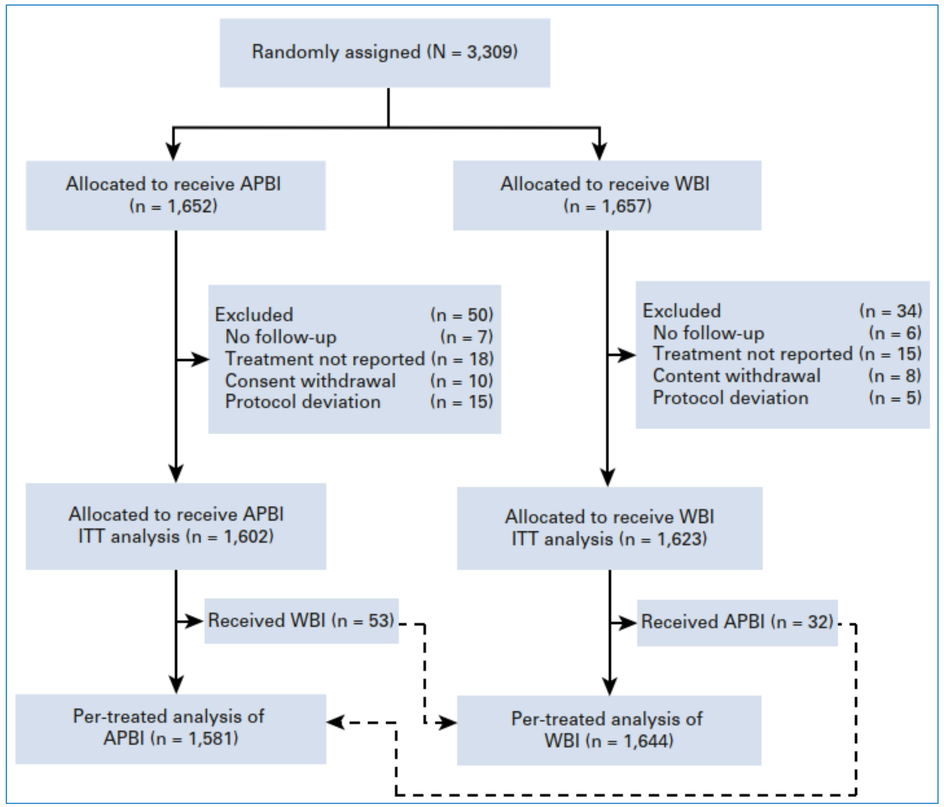
Patients

- Age ≥ 49 years
- Invasive breast cancer (including lobular) < 3 cm, pN0-1, treated with BCS
- Unifocal disease
- Negative resection margins (≥2 mm)

APBI volume and techniques

Technique: 4-5 non-coplanar conformal fields or with intensity modulated RT

CTV: tumour bed [surgical clips (and seroma, if present)] + 1,5 cm, excluding pectoralis major muscle, chest wall, and tissue within 5 mm of the skin --- **PTV**: CTV plus a 1 cm margin



2007 –2019 - **35 European centers**

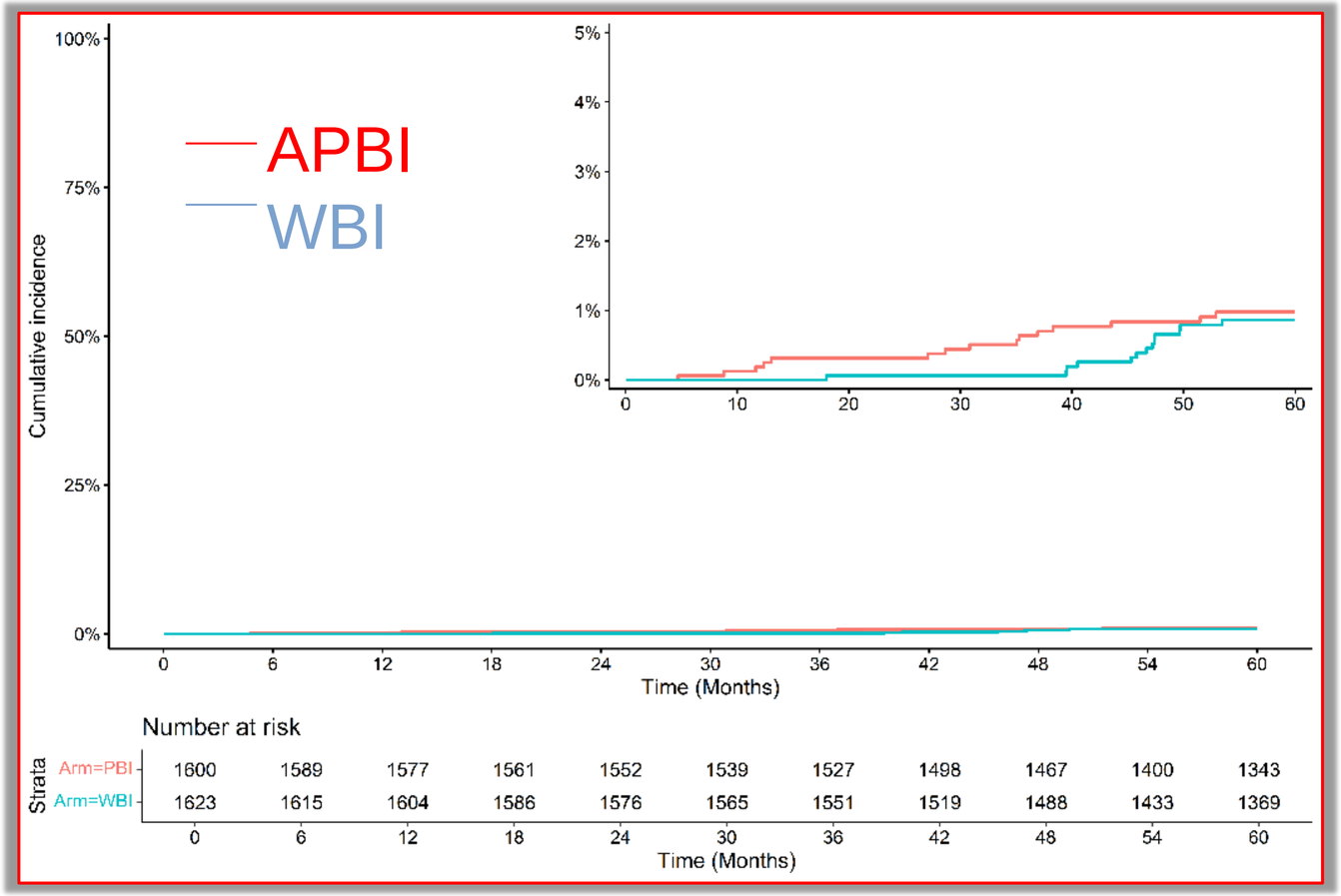
Median FUP: 8 years (IQR 5.6-10.1)

	APBI (N = 1602) n (%)	WBI (N = 1623) n (%)
Age (years)		
Median (IQR)	*65 (58 – 70)*	*65 (58 – 71)*
T stage		
T1	1479 (92.3)	1484 (91.4)
T2	123 (7.7)	138 (8.5)
Unknown	0	1 (0.1)
N stage		
N0	1481 (92.5)	1503 (92.6)
N1	121 (7.5)	119 (7.3)
Unknown	0	1 (0.1)
Tumour grade		
I	453 (28.3)	450 (27.7)
II	896 (55.9)	908 (56.0)
III	224 (14.0)	231 (14.2)
Unknown	29 (1.8)	34 (2.1)
Histology		
Ductal inv	1341 (83.7)	1371 (84.5)
Lobular inv	131 (8.2)	114 (7.0)
Other	123 (7.7)	133 (8.2)
Unknown	7 (0.4)	5 (0.3)

	APBI (N = 1602) n (%)	WBI (N = 1623) n (%)
Hormone Receptor		
ER+/PR+	1366 (85.3)	1383 (85.2)
ER+/PR-	166 (10.3)	161 (9.9)
ER-/PR+	1 (0.1)	5 (0.3)
ER-/PR-	53 (3.3)	66 (4.1)
Unknown	16 (1.0)	8 (0.5)
HER2-neu		
Positive	71 (4.4)	72 (4.4)
Negative	1344 (83.9)	1379 (85.0)
Unknown	187 (11.7)	172 (10.6)
Adjuvant Chemotherapy		
Yes	170 (10.6)	163 (10.0)
No	1432 (89.4)	1457 (89.8)
Unknown	0	3 (0.2)
Hormone Therapy		
Yes	951 (59.4)	949 (58.5)
No	651 (40.6)	671 (41.3)
Unknown	0	3 (0.2)

Ipsilateral breast tumour recurrence

ESTRO 2024

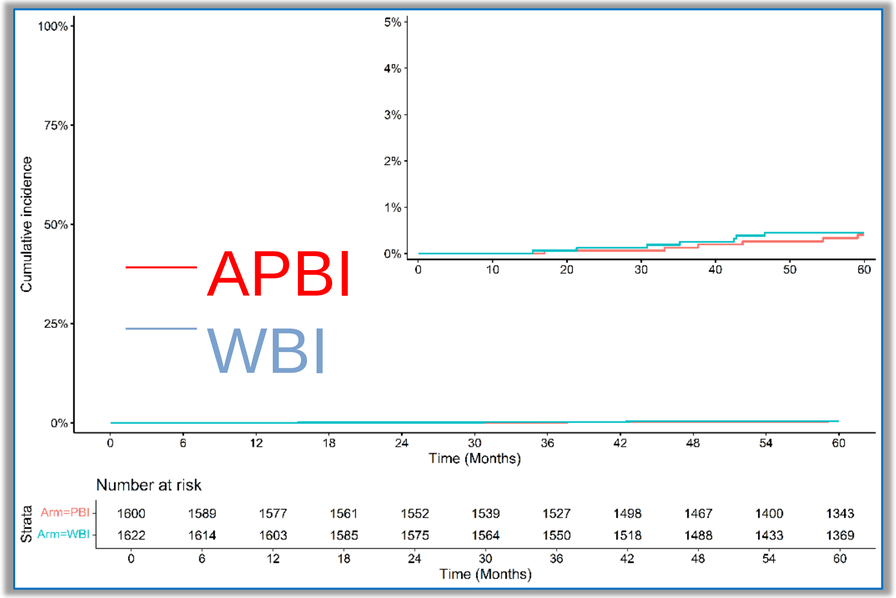


5-year cumulative rate of Ipsilateral breast tumour recurrence

APBI: 1% (95% CI 0.6% - 1.6%)

WBI: 0.8% (95% CI 0.5% - 1.4%)

HR: 1.18 (90% CI 0.63% - 2.2%)



5-year cumulative rate of Regional relapses

APBI: 0.4% (95% CI 0.2% - 0.8%)

WBI: 0.4% (95% CI 0.2% - 0.9%)

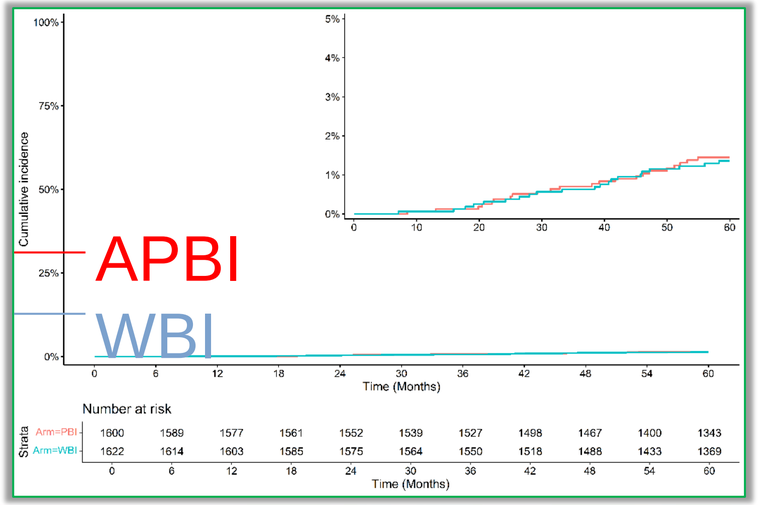
HR: 0.87 (95% CI 0.56% - 2.48%)

5-year cumulative rate of Distant relapses

APBI: 1.4% (95% CI 0.9% - 2.1%)

WBI: 1.3% (95% CI 0.2% - 2%)

HR: 1.07 (95% CI 0.59% - 1.94%)

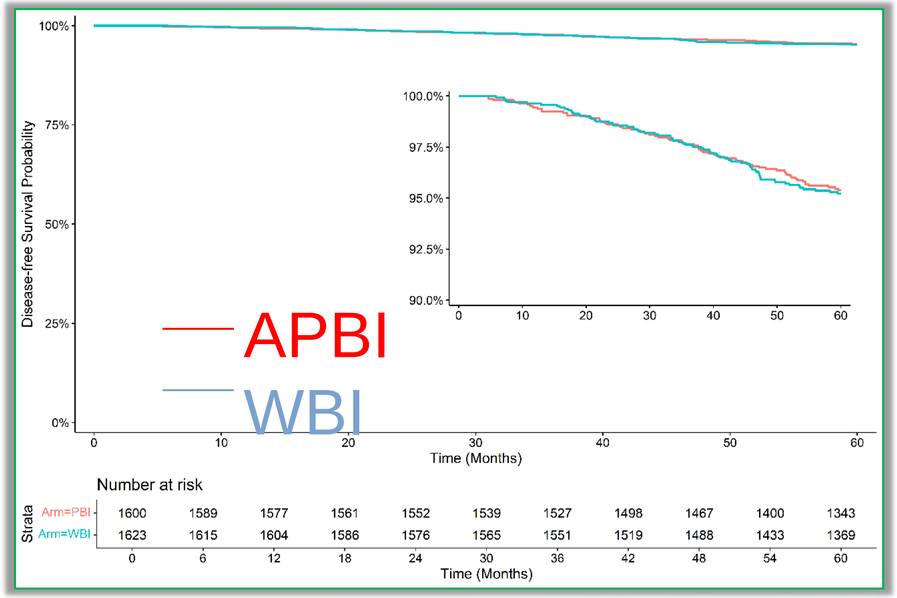


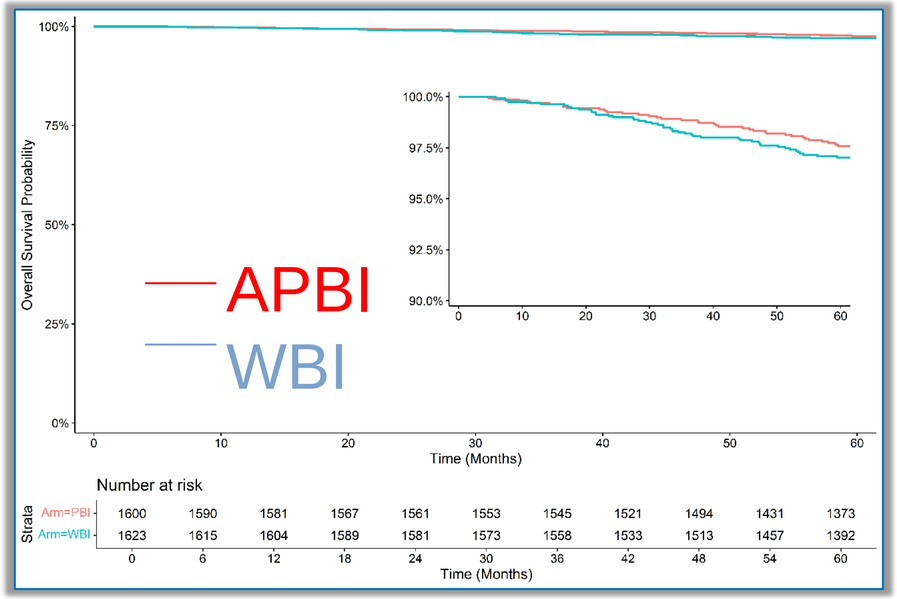
5-year Disease free survival

APBI: 95.4% (95% CI 94.3% - 96.4%)

WBI: 95.2% (95% CI 94.1% - 96.2%)

HR: 0.97 (95% CI 0.69% - 1.33)





5-year Overall survival

APBI: 97.6% (95% CI 96.7% - 98.3%)

WBI: 97% (95% CI 96.1% - 97.8%)

HR: 0.8 (95% CI 0.52% - 1.23%)

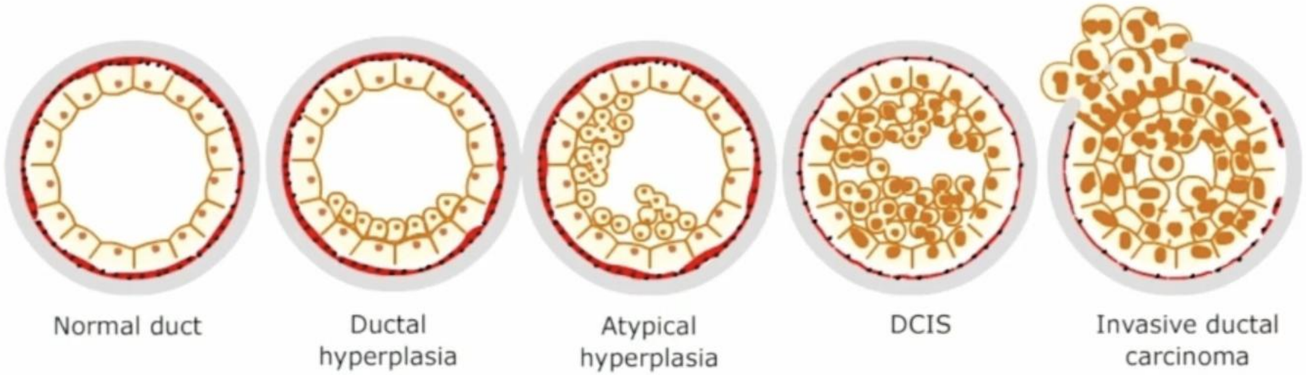
External beam APBI with twice-daily schedule was ***non-inferior*** to whole breast irradiation in preventing IBTR at 5 years

These data significantly strengthen the evidence in favor of external-beam APBI in low risk invasive BC

GS2-05. Primary Outcomes following Active Monitoring or Surgery (+/- Radiation) for Low-risk DCIS: the COMET Study (AFT-25)

E. Shelley Hwang, Terry Hyslop, Thomas Lynch, Marc D Ryser, Anna Weiss, Anna Wolf, Kelsey Norris, Meredith Witten, Lars Grimm, Stuart Schnitt, Sunil Badve, Rachel Factor, Elizabeth Frank, Deborah Collyar, Desiree Basila, Donna Pinto, Mark A Watson, Robert West, Louise Davies, Jenny Donovan, Ayako Shimada, Yutong Li, Yan Li, Antonia V Bennett, Shoshana Rosenberg, Jeff Marks, Eric Winer, Marc Boisvert, Armando Giuliano, Kelsey Larson, Kathleen Yost, Priscilla McAuliffe, Lisa Carey, Alastair Thompson,* Ann H Partridge. *Co-Senior Authors

Background



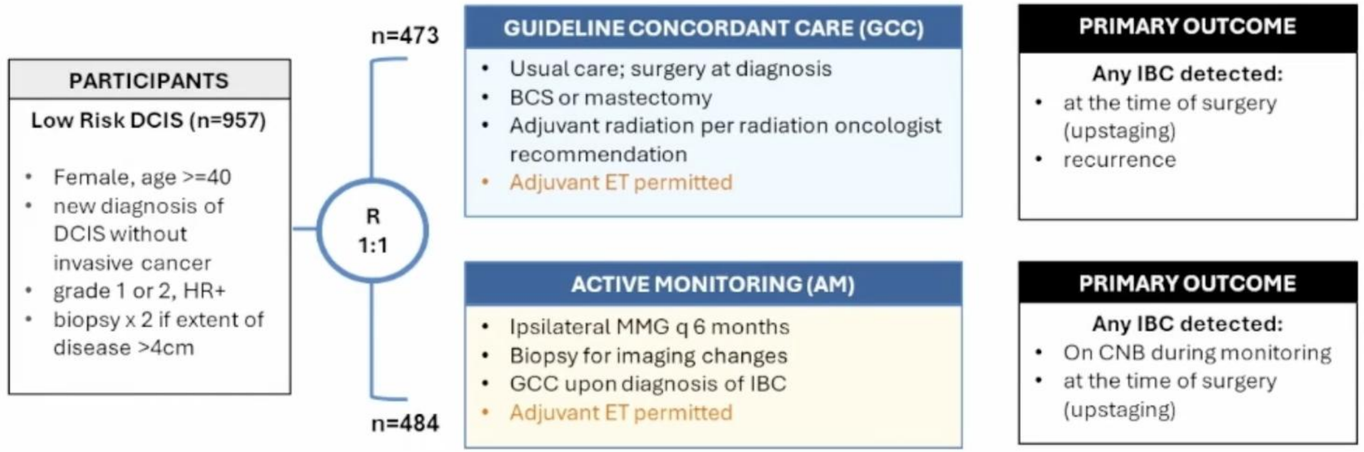
- Ductal carcinoma ***in situ, precancer, preinvasive cancer***
- Estimated incidence of DCIS: over 50,000 new cases annually
- Treatment: surgical excision +/- radiotherapy to prevent progression
- ***DCIS MAY, but DOES NOT ALWAYS progress to invasive cancer; opportunity for active monitoring?***

Ryser M, JNCI 2019
Poelhekken K, Breast 2023
Worni M, JNCI 2015

San Antonio Breast Cancer Symposium® December 10-13, 2024

GS2-05: The COMET Study

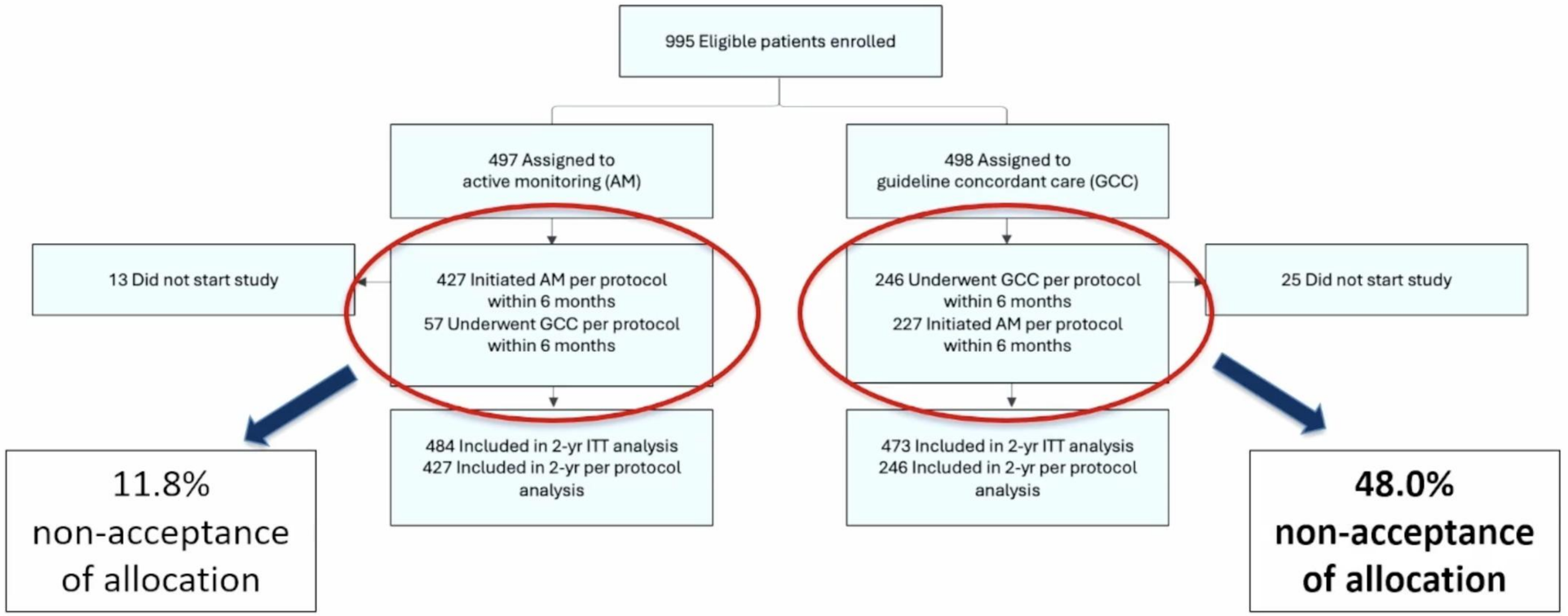
- Randomized, pragmatic non-inferiority trial from 2017–2022
- **Primary objective: 2-year ipsilateral invasive cancer rate**
  - Estimated 10% rate in GCC arm
  - <5% non-inferiority margin



Hwang et al, Abs # GS2-05

San Antonio Breast Cancer Symposium® December 10-13, 2024

GS2-05: The COMET Study



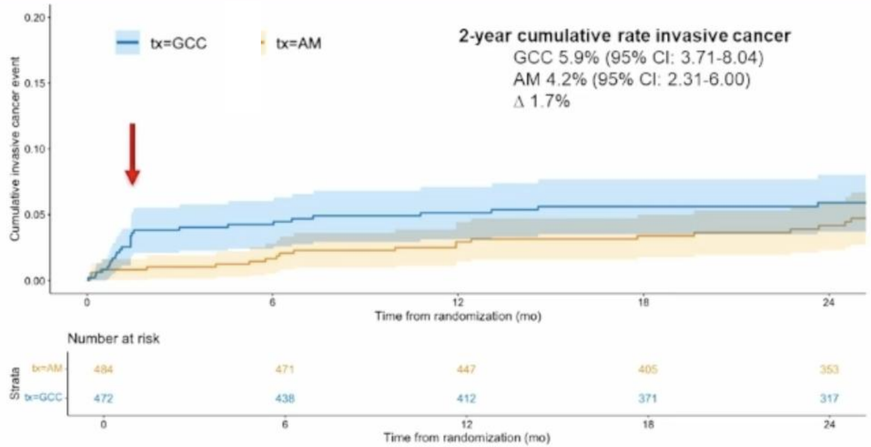
Hwang et al, Abs # GS2-05

San Antonio Breast Cancer Symposium® December 10-13, 2024

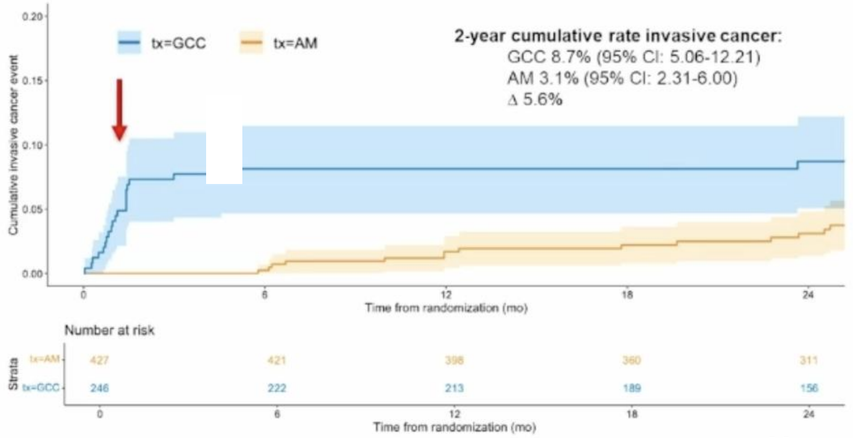
GS2-05: The COMET Study

- Non-inferiority of AM compared to GCC in both analyses
  - Majority of invasive cancers in GCC arm were due to upstage
- 26.6% GCC vs 7.4% AM received RT
- 65.5% GCC vs 71.3% AM received any ET in 2 years
- Majority of invasive cancers small (mean 0.45cm, 0.23−1.1)

ITT



PP



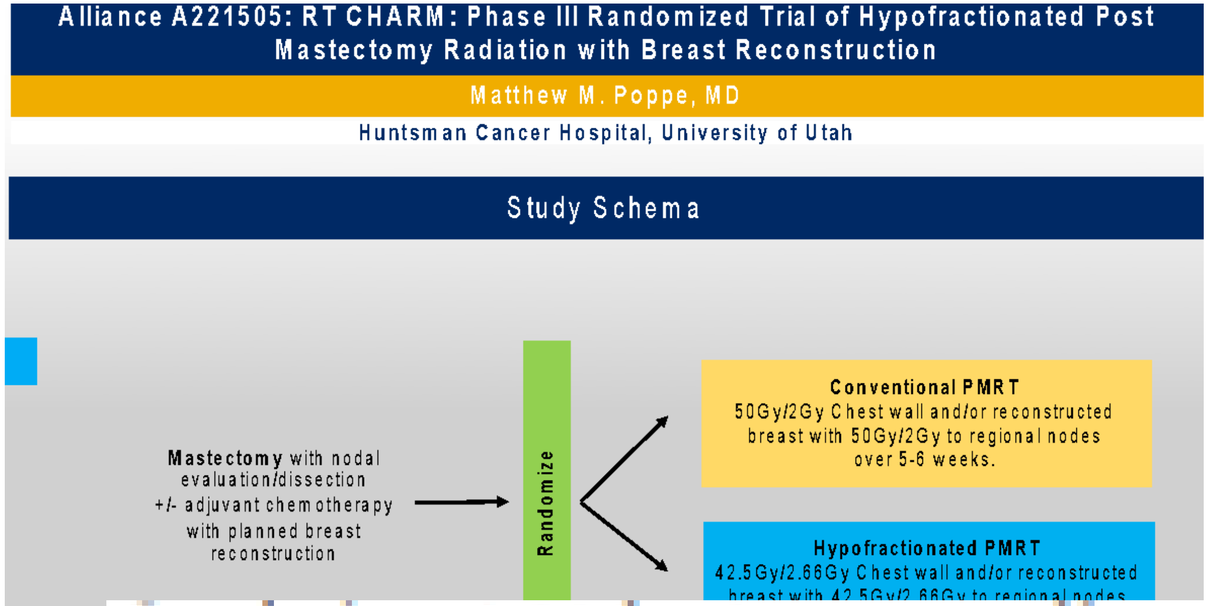
Hwang et al, Abs # GS2-05

San Antonio Breast Cancer Symposium® December 10-13, 2024

Additional considerations for active surveillance of DCIS

- Longer follow up needed – pre-specified analyses at 5 and 7 years
- 48% of patients on GCC did not receive per protocol treatment
  - Indication of significant patient interest in active surveillance of DCIS
- Role of endocrine therapy in AM
- Frequency of additional imaging and biopsies with AM and associated healthcare costs

RT-CHARM



Oral Scientific Sessions

1

A Randomized Trial of Hypofractionated Post-Mastectomy Radiation Therapy (PMRT) in Women with Breast Reconstruction (RT CHARM, Alliance A221505)

M.M. Poppe,[1] J. Le-Rademacher,[2] B.G. Haffty, Jr[3] E.K. Hansen,[4] J. Agarwal,[1] J. Wagner,[5] I. Kong,[6] J. Armer,[7] D.W. Arthur,[8] T.J. Whelan,[9] M.K. Lee,[2] O. Kour,[2] M. Lustberg,[10] A. Partridge,[11] L.A. Carey,[12] K.J. Ruddy,[13] D.K. Gaffney,[1] S.R. Stecklein,[14] M.B. Bernstein,[15] and A.J. Khan[15]; *[1]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, [2]Mayo Clinic, Rochester, MN, [3]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, [4]The Oregon Clinic, Portland, OR, [5]University of Kansas Medical Center, Kansas City, KS, [6]BC Cancer - Vancouver Centre, Vancouver, BC, Canada, [7]University of Missouri, Columbia, MO, [8]Virginia Commonwealth University Health System, Richmond, VA, [9]McMaster University and Juravinski Cancer Centre, Hamilton, ON, Canada, [10]Yale, New Haven, CT, [11]Dana Farber Cancer Institute, Boston, MA, [12]Division of Oncology, University of North Carolina, Chapel Hill, NC, [13]Department of Medical Oncology, Mayo Clinic, Rochester, MN, [14]University of Kansas, [illegible]morial Sloan Ket-*

Conclusion: A 16-fraction course of hypofractionated PMRT appears safe and effective for pts undergoing breast reconstruction and is non-inferior to traditional 25-fraction course of PMRT. (NCT03414970)

Primary endpoint: Non-inferior reconstruction complication rate at 24 months post radiation with hypofractionation

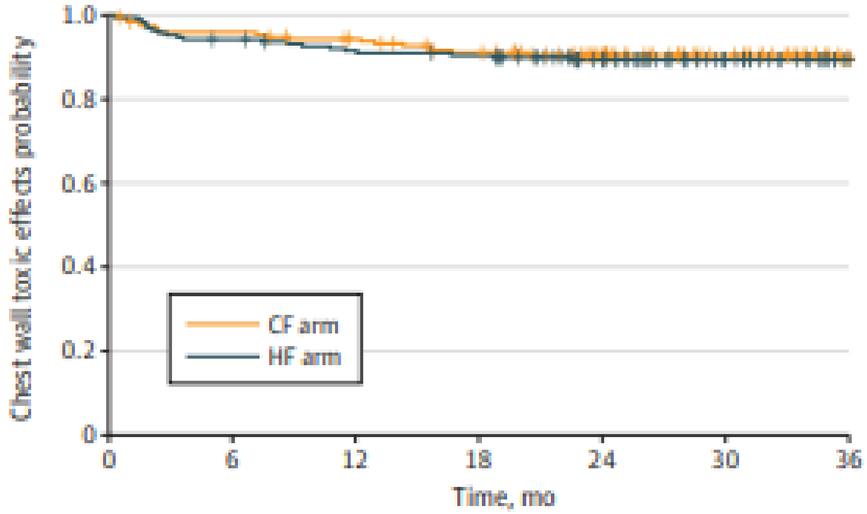
Research

JAMA Oncology | Original Investigation

Hypofractionated vs Conventionally Fractionated Postmastectomy Radiation After Implant-Based Reconstruction
A Randomized Clinical Trial

Julia S. Wong, MD; Hajime Uno, PhD; Angela C. Tramontano, MPH; Lauren Fisher, MPH; Catherine V. Pellegrini, BS; Gregory A. Abel, MD, MPH; Harold J. Burstein, MD, PhD; Yoon S. Chun, MD; Tari A. King, MD; Deborah Schrag, MD, MPH; Eric Winer, MD; Jennifer R. Bellon, MD; Matthew D. Cheney, MD, PhD; Patricia Hardenbergh, MD; Alice Ho, MD, MBA; Kathleen C. Horst, MD; Janice N. Kim, MD; Kara-Lynne Leonard, MD, MS; Meena S. Moran, MD; Catherine C. Park, MD; Abram Recht, MD; Daniel E. Soto, MD, MS; Ron Y. Shiloh, MD; Susan F. Stinson, MD; Kurt M. Snyder, MD; Alphonse G. Taghian, MD, PhD; Laura E. Warren, MD; Jean L. Wright, MD; Rinaa S. Punglia, MD, MPH

Figure 2. Kaplan-Meier Plot for Freedom From Chest Wall Toxic Effects by Treatment Arm



No. at risk							
CF arm	195	185	178	168	147	124	101
HF arm	190	178	171	168	148	121	99

CF indicates conventionally fractionated; HF, hypofractionated.

Wong JS, et al. JCO. 2024

Fractionation Schemes in Breast Cancer Radiotherapy Systematic Review and Meta-Analysis

Randomised controlled trials on radiation dose fractionation in breast cancer: systematic review and meta-analysis with emphasis on side effects and cosmesis

Shing Fung Lee,[1,2] Samantha K F Kennedy,[3] Saverio Caini,[4] Henry C Y Wong,[5] Pui Lam Yip,[1,2,6] Philip M Poortmans,[7,8] Icro Meattini,[9,10] Orit Kaidar-Person,[11,12,13] Abram Recht,[14] Tarek Hijal,[15] Mylin A Torres,[16] Jeffrey Q Cao,[17] Kimberly S Corbin,[18] J Isabelle Choi,[19] Wee Yao Koh,[1,2] Jennifer Y Y Kwan,[20,21] Irene Karam,[21,22] Adrian W Chan,[21,22] Edward Chow,[21,22] Gustavo N Marta[23,24,25]

Background

Hypofractionation regimens have gained popularity due to shorter treatment times and potential benefits in safety and quality of life

This review comprehensively compares conventional fractionation (CF), moderate hypofractionation (MHF), and ultra-hypofractionation (UHF)

Methods

Study Design: Systematic review and meta-analysis of randomised controlled trials (RCTs)

Data Sources: Ovid MEDLINE, Embase, Cochrane Central, 1986–2023

Population: 20,237 patients across 35 RCTs

Fractionation Regimens:

CF: 50–50.4 Gy over 5–6 weeks

MHF: 39–43 Gy over 3–5 weeks

UHF: 26–30 Gy in 5 fractions over 1–5 weeks

Outcomes: Acute and late side effects, cosmesis, quality of life, recurrence, and survival

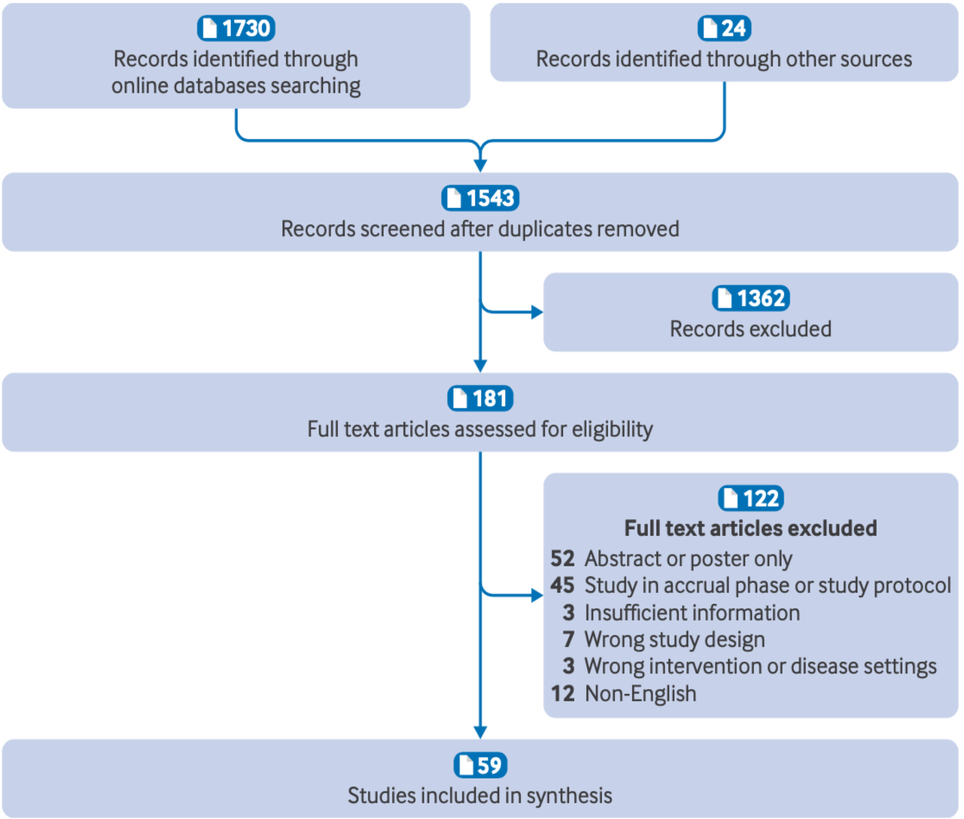


Fig 1 | PRISMA diagram of study selection

Lee SF, et al. BMJ. 2024

Fractionation Schemes in Breast Cancer Radiotherapy
Systematic Review and Meta-Analysis

Randomised controlled trials on radiation dose fractionation in breast cancer: systematic review and meta-analysis with emphasis on side effects and cosmesis

Shing Fung Lee,[1,2] Samantha K F Kennedy,[3] Saverio Caini,[4] Henry C Y Wong,[5] Pui Lam Yip,[1,2,6] Philip M Poortmans,[7,8] Icro Meattini,[9,10] Orit Kaidar-Person,[11,12,13] Abram Recht,[14] Tarek Hijal,[15] Mylin A Torres,[16] Jeffrey Q Cao,[17] Kimberly S Corbin,[18] J Isabelle Choi,[19] Wee Yao Koh,[1,2] Jennifer Y Y Kwan,[20,21] Irene Karam,[21,22] Adrian W Chan,[21,22] Edward Chow,[21,22] Gustavo N Marta[23,24,25]

Findings

Acute Side Effects:

MHF vs. CF: Reduced grade ≥2 radiation dermatitis (RR 0.54; P<0.001)

UHF vs. CF: Further reduction in dermatitis risk (RR 0.27; P<0.001)

Cosmetic Outcomes:

MHF associated with better outcomes compared to CF

UHF showed mixed results; higher doses linked to increased risks of fibrosis and shrinkage

Oncological Outcomes:

Similar survival and recurrence rates across CF, MHF, and UHF

MHF offered disease-free survival benefits in specific regimens (HR 0.86; P=0.03)

Quality of Life:

MHF improved physical well-being and reduced fatigue compared to CF

UHF demonstrated fewer functional declines in short-term follow-up

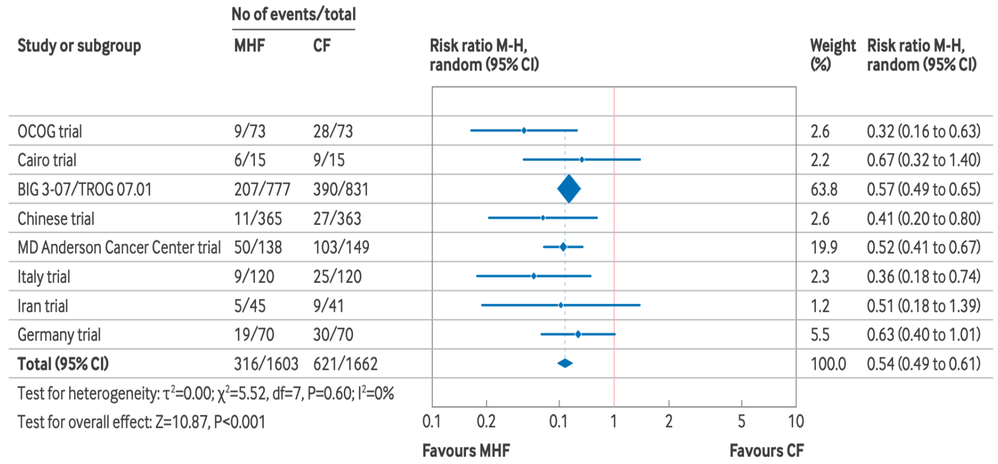


Fig 4 | Forest plot showing risk ratios for grade ≥2 acute radiation dermatitis for moderate versus conventional fractionation in breast conserving treatment trials. Cairo trial used RTOG toxicity criteria for acute radiation dermatitis. CF=conventional fractionation; CI=confidence interval; M-H=Mantel-Haenszel; MHF=moderate hypofractionation

Lee SF, et al. BMJ. 2024

Fractionation Schemes in Breast Cancer Radiotherapy
Systematic Review and Meta-Analysis

Randomised controlled trials on radiation dose fractionation in breast cancer: systematic review and meta-analysis with emphasis on side effects and cosmesis

Shing Fung Lee,[1,2] Samantha K F Kennedy,[3] Saverio Caini,[4] Henry C Y Wong,[5] Pui Lam Yip,[1,2,6] Philip M Poortmans,[7,8] Icro Meattini,[9,10] Orit Kaidar-Person,[11,12,13] Abram Recht,[14] Tarek Hijal,[15] Mylin A Torres,[16] Jeffrey Q Cao,[17] Kimberly S Corbin,[18] J Isabelle Choi,[19] Wee Yao Koh,[1,2] Jennifer Y Y Kwan,[20,21] Irene Karam,[21,22] Adrian W Chan,[21,22] Edward Chow,[21,22] Gustavo N Marta[23,24,25]

Conclusions

MHF is a safer, more convenient alternative to CF, maintaining equivalent oncological outcomes

UHF offers similar efficacy, with the potential for further optimisation and longer follow-up to establish safety

Recommendations support MHF and UHF as preferred regimens in appropriate patient populations

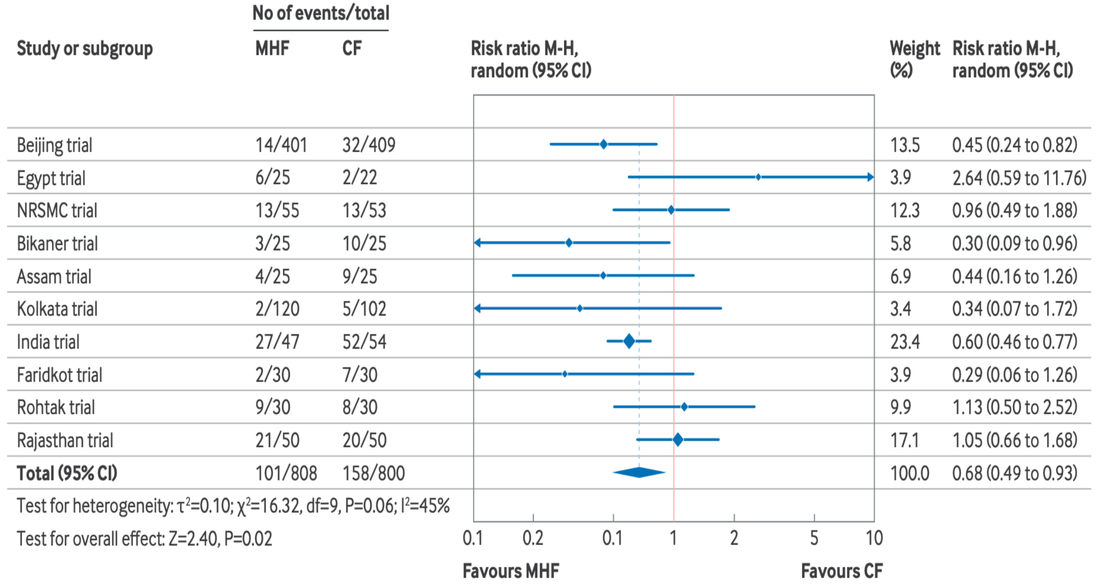


Fig 5 | Forest plot showing risk ratios for grade ≥2 acute radiation dermatitis for moderate versus conventional fractionation in mastectomy trials. Beijing trial reported incidence of acute radiation dermatitis across grade 1–2 and 3; however, only grade 3 data have been included in this forest plot for analysis. Kolkata trial reported incidence of only grade ≥3 acute radiation dermatitis. CF=conventional fractionation; CI=confidence interval; M-H=Mantel-Haenszel; MHF=moderate hypofractionation

Lee SF, et al. BMJ. 2024

Radiotherapy and Oncology 202 (2025) 110591

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Review Article

Dose constraints in breast cancer radiotherapy. A critical review

Fiorenza De Rose [a,1], Maria Carmen De Santis [b,1], Sara Lucidi [a], Riccardo Ray Colciago [c,*], Lorenza Marino [d], Francesca Cucciarelli [e], Eliana La Rocca [f], Francesca Di Pressa [g], Frank Lohr [h,i], Valentina Vanoni [a], Bruno Meduri [g]

[a] Radiation Oncology, APSS, Trento, Italy
[b] Radiation Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy
[c] School of Medicine and Surgery, University of Milan Bicocca, Milan, Italy
[d] Servizio di Radioterapia, Humanitas Istituto Clinico Catanese, Misterbianco, CT, Italy
[e] Radiotherapy Department, Azienda Ospedaliero Universitaria delle Marche, Ancona, Italy
[f] Department of Radiation Oncology, Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy
[g] Department of Radiation Oncology, University Hospital of Modena, Modena, Italy
[h] Proton Therapy Unit, APSS, Trento, Italy
[i] CISMED - Centro Interdipartimentale di Scienze Mediche, University of Trento, Trento, Italy

De Rose F. et al. Radiotherapy and Oncology. 2024

Table 1
Lung dose constraints.

Organ at Risk	Conventional fractionation (2 Gy/fr)		Moderate hypofractionation (2.6–3.2 Gy/fr)		Ultra hypofractionation (5.2 Gy/fr)	
Ipsilateral Lung	*Breast/chest wall* MLD ≤ 8 Gy (range 7.9 3DCRT – 9.4 IMRT) [27]	*Systematic review*	*Breast/chest wall* V_{20Gy} < 10 % ([33,34] – VMAT treatment)	*Phase II Trial*	V_{8Gy} < 15 % [35]	*Phase III Trial*
	V_{10Gy} ≤ 35 % (acceptable < 40 %) [31]	*RTOG 1005*	V_{17Gy} ≤ 25 % [28,29]	*DBCG guidelines and trial protocol (Hypo trial)*		
	V_{5Gy} ≤ 50 % (acceptable < 55 %) [31]	*DBCG guidelines and trial protocol (Hypo trial)*	V_{8Gy} ≤ 35 % (acceptable < 40 %) [31]	*RTOG 1005*		
	V_{20Gy} < 25 % [28,29]	*DBCG guidelines, RTOG 1304, Alliance A221505*	V_{4Gy} ≤ 50 % (acceptable < 55 %) [31]	*Trial protocol (Hypo trial)*		
	Breast/chest wall and RLN	*SKAGEN trial*	MLD < 10–16 Gy ([29,33,34] – VMAT treatment)	*Phase II Trial*		
	V_{20Gy} ≤ 35 % [28,36,38,39]	*Alliance A221505*	*Breast/chest wall and RLN*	*RTOG 1304*		
	V_{10Gy} ≤ 65 % [38]	*DBCG guidelines*	V_{18Gy} ≤ 35 % [36]	*SKAGEN trial*		
	V_{5Gy} ≤ 75 % [38]	*SKAGEN trial*	V_{17Gy} ≤ 35 % [39]			
	MLD ≤ 18 Gy [28,39] (range 14l MRT-20 3DCRT) [27]	*Systematic review*				
Contralateral Lung	*Breast/chest wall* V_{5Gy} ≤ 10 % (acceptable < 15 %) [21,31,36,38]	*QUANTEC, RTOG 1005, RTOG 1304, Alliance A221505*	*Breast/chest wall* V_{4Gy} ≤ 10 % (acceptable < 15 %) [30,31]	*ASTRO guidelines, RTOG 1005*	Not available	
	Breast/chest wall and RLN V_{5Gy} ≤ 15 % [36]	*RTOG 1304*	*Breast/chest wall and RLN* $V_{4.8Gy}$ ≤ 10 % (acceptable < 15 %) [38]	*Alliance A221505*		
Lungs	*Breast/chest wall* MLD ≤ 6 Gy [27]	*Systematic review*	Not available		Not available	

MLD: mean lung dose; 3DCRT: three-dimensional conformal radiotherapy; IMRT: Intensity-modulated radiotherapy; RLN: regional lymph nodes. Doses reported for hypofractionation (moderate or ultra) are not EQD2 if not specified.

De Rose F. et al. Radiotherapy and Oncology. 2024

Table 2
Heart and cardiac substructure dose constraints.

Organ at risk	Conventional fractionation (2 Gy/fr)		Moderate hypofractionation (2.6–3.2 Gy/fr)		Ultra hypofractionation (5.2 Gy/fr)	
Heart	*Breast/chest wall* $V_{20Gy} \leq 5$ % [31,61] $V_{40Gy} \leq 1$ % [61] D_{mean} 2.5 Gy* (optimal) [57,60] $D_{mean} < 4$ Gy [31]	*Original scientific article, trial protocol (RTOG1005)* *Original scientific article, DEGRO guidelines, trial protocol (RTOG1005)*	*Breast/chest wall* $V_{17Gy} \leq 5$ % [61] $V_{35Gy} \leq 1$ % [61] $D_{mean} < 3.2$ Gy [31]	*Original scientific article, trial protocol (RTOG1005)*	$V_{7Gy} < 5$ % (3DCRT) [35] $V_{1.5Gy} < 30$ % (3DCRT) [35] Not available for IMRT and VMAT	*Original scientific article*
	Breast/chest wall and RLN $V_{20Gy} \leq 10$ % [61] $V_{40Gy} \leq 5$ % [61] $D_{mean} < 5$ Gy [36] *With DIBH	*Original scientific article, trial protocol (RTOG 1304)*	*Breast/chest wall and RLN* $V_{17Gy} \leq 10$ % [61] $V_{35Gy} \leq 5$ % [61]	*Original scientific article*		
LADCA	Dmax < 20 Gy [60] Dmax < 45 Gy*[58] Dmean < 10 Gy [29] V30Gy < 2 % [29] V40Gy < 1 % [29] * End-point: cardiac death; as, however, LAD-related and muscle-related toxicity cannot yet reliably be separated, as the dimension of both muscle and LAD is small, and as positioning of the anterior heart is not perfect, it seems prudent to keep maximum dose to the anterior heart – thus also dose to the LAD – in any case ≪ 30 Gy, in line with the published recommendations for anterior heart also reported in this table	*DEGRO guidelines, Original scientific article, Trial protocol (Hypo trial)*	$D_{max} < 17$ Gy [61]	*Original scientific article*		
LV	$D_{mean} < 3$ Gy [56] $D_{mean} < 4.5$ Gy [57] $V_{5Gy} < 17$ % [55] $V_{23Gy} < 5$ % [29]	*Original scientific articles, Trial protocol (Hypo trial)*				

LADCA: Left Anterior Descendent Coronary artery; LV: Left Ventricle; 3DCRT: three-dimensional conformal radiotherapy; IMRT: Intensity-modulated radiotherapy; VMAT: volumetric-modulated arc therapy; Dmax: Maximum dose; Dmean: Mean dose; RT: radiation-therapy. Doses reported for hypofractionation (moderate or ultra) are not EQD2 if not specified.

De Rose F. et al. Radiotherapy and Oncology. 2024

Table 3
Contralateral Breast dose constraints.

Organ at risk	Conventional fractionation (2 Gy/fr)	Moderate hypofractionation (2.6–3.2 Gy/fr)	Ultra hypofractionation (5.2 Gy/fr)
Contralateral Breast	ALARA [30,61,67] $D_{2\%} \leq 1.86$ Gy (RNI −) [31,38] $D_{10\%} \leq 3$ Gy (RNI +) [31,38] $V_{4Gy} < 10$ % [68] $D_{mean} < 4$ Gy [68]	ALARA [30,61,67] $D_{2\%} \leq 1.44$ Gy (RNI −) [31,38] $D_{10\%} \leq 3$ Gy (RNI +) [31,38] $D_{mean} < 3$ Gy [34]	Not available

ALARA: As Low As Reasonably Achievable; D_{mean}: mean dose; D_{max}: Maximum dose; $D_{0.1cc}$: Dose to 0.1 cc of volume; RNI: regional nodes irradiation; Doses reported for hypofractionation (moderate or ultra) are not EQD2 if not specified.

Table 4
Dose constraints for other OARs routinely involved in breast locoregional treatment.

Organ at risk	Conventional fractionation (2Gy/fr)	Moderate hypofractionation (2.6-2.9 Gy/fr)	Ultra hypofractionation (5.2 Gy/fr)
Brachial Plexus	Dmax ≤ 54 Gy [14] $V_{40Gy} < 13.5cm^3$ [85] $V_{50Gy} < 90\%$ [86]	Dmax 46.25 Gy [39]	Not available
Humeral Head	ALARA	ALARA	Not available
Esophagus	Dmean ≤ 11 Gy, $V_{10Gy} \leq 30\%$, $V_{20Gy} \leq 15\%$[87]ˆ ˆ(when contoured along the entire length) Dmean ≤ 31 Gy [88]° °(when contoured from the superior to the inferior border of the supraclavicular PTV)	$V_{25Gy} < 20\%$ and $V_{25Gy} < 0,27$ mL [89]* *(when contoured from the lower border level of the cricoid cartilage to the lower margin of the aortic arch)	Not available
Liver	Dmean ≤ 3 Gy (left breast) [90] Dmean ≤ 4 Gy (right breast) [90]	Dmean ≤ 3 Gy(left breast) , Dmean ≤ 4 Gy (right breast) [90]	Not available
Thyroid	$V_{30Gy} < 50\%$ [91] Dmean < 21 Gy [92]	Dmean < 21 Gy [93]	Not available
Chest Wall	D2cc ≤ 52 Gy [94]	$D_{2cc} \leq 52$ Gy $_{EQD2}$ [94]	Not available
Spinal Cord	Dmax ≤ 45 Gy (optimal) [95] Dmax <50 Gy (mandatory) [95]	Dmax ≤ 37.8 Gy (optimal) [96] Dmax < 42 Gy (mandatory) [96]	Not available

ALARA: As Low As Reasonably Achievable; D_{mean}: mean dose; D_{max}: Maximum dose; Doses reported for hypofractionation (moderate or ultra) are not EQD2 if not specified.

De Rose F. et al. Radiotherapy and Oncology. 2024

Thank you to my colleagues!!!

Thank you for the attention