SABCS 2022:
Radiation Oncology Highlights

Bethany Anderson, MD
Associate Professor, Radiation Oncology
University of WI

Objectives

- Discuss two abstracts studying hypofractionation (one 2D, one protons) & place these into clinical context.
- Discuss one abstract studying a novel gene signature to identify candidates for radiotherapy omission & place this into clinical context.

GS5-12 Hypofractionated Radiotherapy in patients with Breast Cancer (HRBC): Acute toxicity data of a phase III randomized study

Phase III trial of adjuvant radiotherapy:

- 3 weeks (40 Gy in 15 fractions to breast; 35 Gy in 15 fractions to chest wall)
- 2 weeks (34 Gy in 10 fractions)
- Boost of 8 Gy in 2 fractions allowed in both arms
- 2D treatment planning, cobalt therapy in ~45%.

1,121 patients with pT1-4 pN0-3 after lumpectomy (~20%) or mastectomy without implant reconstruction (~80%). SCV treated in ~85%, IM nodes treated in ~40%.

Dr. Budhi Singh Yadav
& colleagues

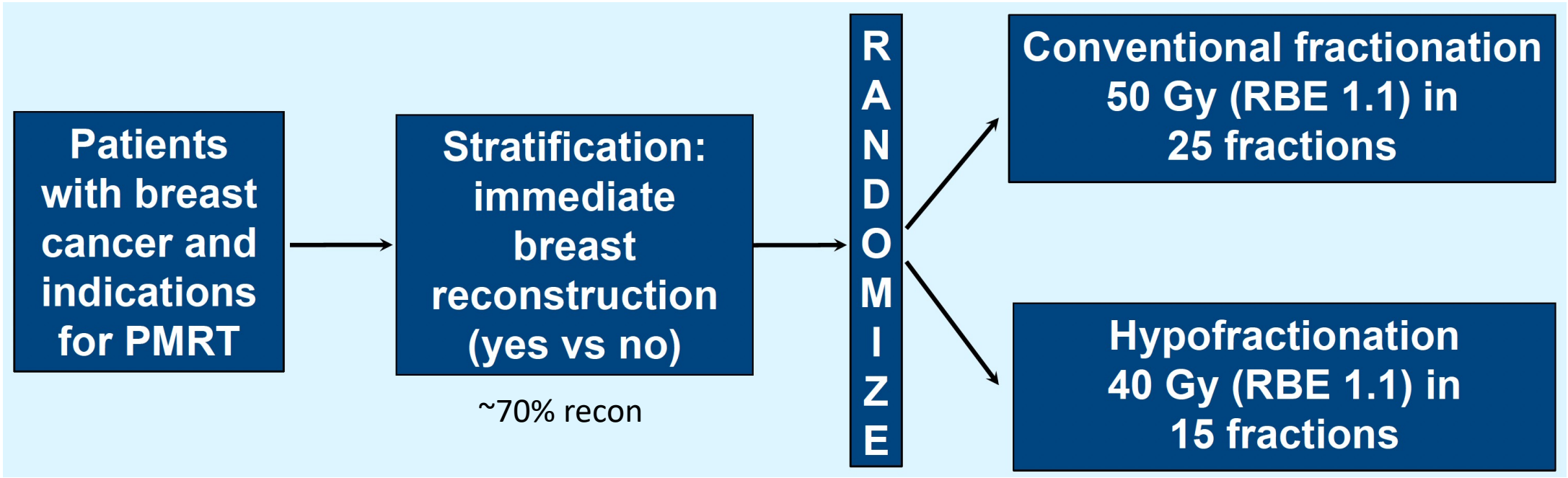
GS5-12 Hypofractionated Radiotherapy in patients with Breast Cancer (HRBC): Acute toxicity data of a phase III randomized study

Acute toxicity as per RTOG scale at 1 month			
RTOG grade Skin	3 weeks (N = 562) n (%)	2 weeks (N = 549) n (%)	Fisher's Exact Test p-value
0	237 (42)	266 (48)	0.15
1	211 (38)	191 (35)	
2	98 (17)	82 (15)	
3	16 (3)	10 (2)	

As per Harvard/NSABP/RTOG scale at last follow up			
Cosmesis	3 weeks (N = 557) n (%)	2 weeks (N = 543) n (%)	Fisher's Exact Test p-value
Excellent/Good	499 (90)	509 (94)	0.016
Fair/Poor	58 (10)	34 (6)	

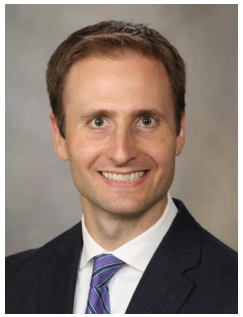
(?)

GS4-05 Phase II randomized trial of conventional versus hypofractionated post-mastectomy proton radiotherapy



Primary objective: determine whether the 24-month complication rate of 15 fraction proton PMRT is acceptable relative to 25 fractions

Dr. Rob Mutter
& colleagues



GS4-05 Phase II randomized trial of conventional versus hypofractionated post-mastectomy proton radiotherapy

24-month complication	25 fraction N = 41	15 fraction N = 41	Estimated difference (95% one-sided CI)	P-value
Yes	6 (14.6%)	8 (19.5%)	4.8% [, 18.5%]	0.26
No	35 (85.4%)	33 (80.5%)		

Because the upper bound of the 95% CI for the absolute difference exceeded 10%, non-inferiority could not be claimed. Therefore, a test for superiority was not performed.

Conventional
- 5 patients had unplanned surgical intervention for contracture
- 1 patient had infectious complication that did not require surgical intervention

Hypofractionation
- 8 patients had infectious complications, of whom 7 required surgical intervention

Univariate analysis – only immediate breast reconstruction was significantly associated with complications (p=0.018)

GS4-05 Phase II randomized trial of conventional versus hypofractionated post-mastectomy proton radiotherapy

Adverse Events Grade ≥ 2 (CTCAE v. 4.0)		25 fraction (N = 41)	15 fraction (N = 41)	P-value
Acute AE*, n (%)	Breast Infection	1 (2.4)	3 (7.3)	0.615
	Esophagitis	0 (0.0)	2 (4.9)	0.493
	Skin Hyperpigmentation	3 (7.3)	2 (4.9)	0.999
	Arm lymphedema	0 (0.0)	1 (2.4)	0.999
	Dermatitis Radiation	18 (43.9)	6 (14.6)	0.006
Late AE**, n (%)	Breast Infection	0 (0.0)	5 (12.2)	0.054
	Breast Edema	0 (0.0)	1 (2.4)	0.999
	Skin Hyperpigmentation	0 (0.0)	3 (7.3)	0.240
	Arm Lymphedema	0 (0.0)	1 (2.4)	0.999
	Telangiectasia***	3 (7.3)	4 (9.8)	0.999

GS5-12 Hypofractionated Radiotherapy in patients with Breast Cancer (HRBC): Acute toxicity data of a phase III randomized study

GS4-05 Phase II randomized trial of conventional versus hypofractionated post-mastectomy proton radiotherapy

What does this mean for clinical practice?

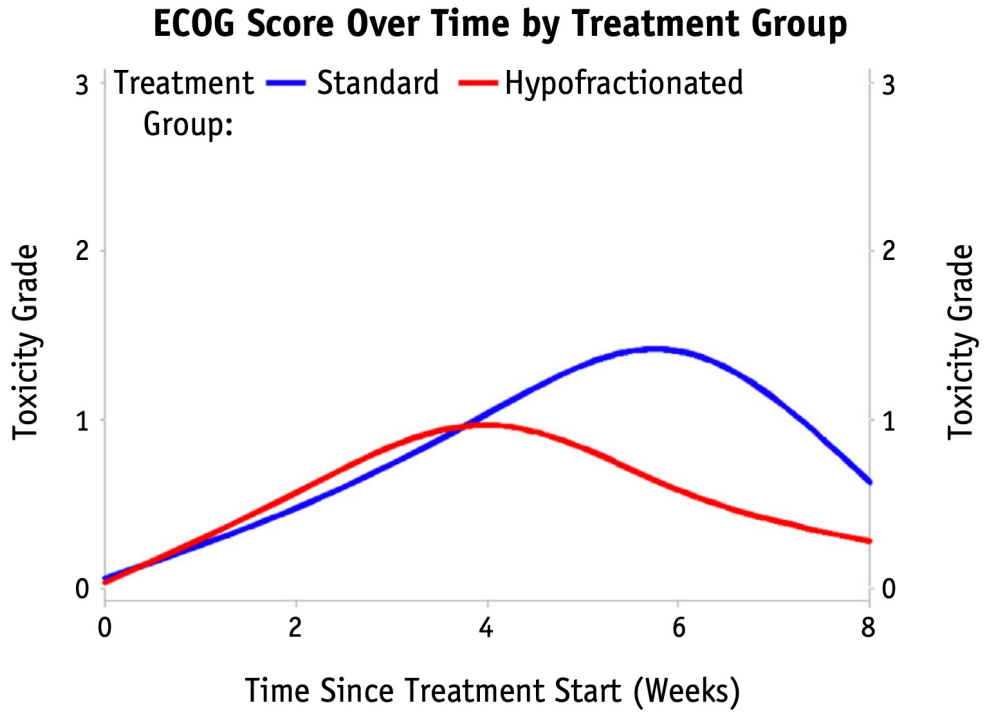
- Role of hypofractionation for postmastectomy/regional nodal irradiation
- Role of hypofractionated PMRT with breast reconstruction
- Role of protons in postmastectomy/regional nodal irradiation
- Role of ultrahypofractionation (<3-week treatment schedules) in regional nodal irradiation

Role of hypofractionation for postmastectomy & regional nodal irradiation

Multiple randomized trials of hypofractionation (~3 weeks) vs “conventional” fractionation (~5 weeks) after breast conserving surgery have shown equal local control & equal/better toxicity outcomes.

Ontario Clinical Oncology Group

**Total dose matters more than fraction size*



Arsenault J et al. *Int J Radiat Oncol Biol Phys.* 2020;107(5):943-948.

Role of hypofractionation for postmastectomy & regional nodal irradiation

Multiple randomized trials of hypofractionation (~3 weeks) vs “conventional” fractionation (~5 weeks) after breast conserving surgery have shown equal local control & equal/better toxicity outcomes.

Hypofractionation to regional nodes (SCV, level III axilla, IM) ***not*** currently included in ASTRO or NCCN guidelines.

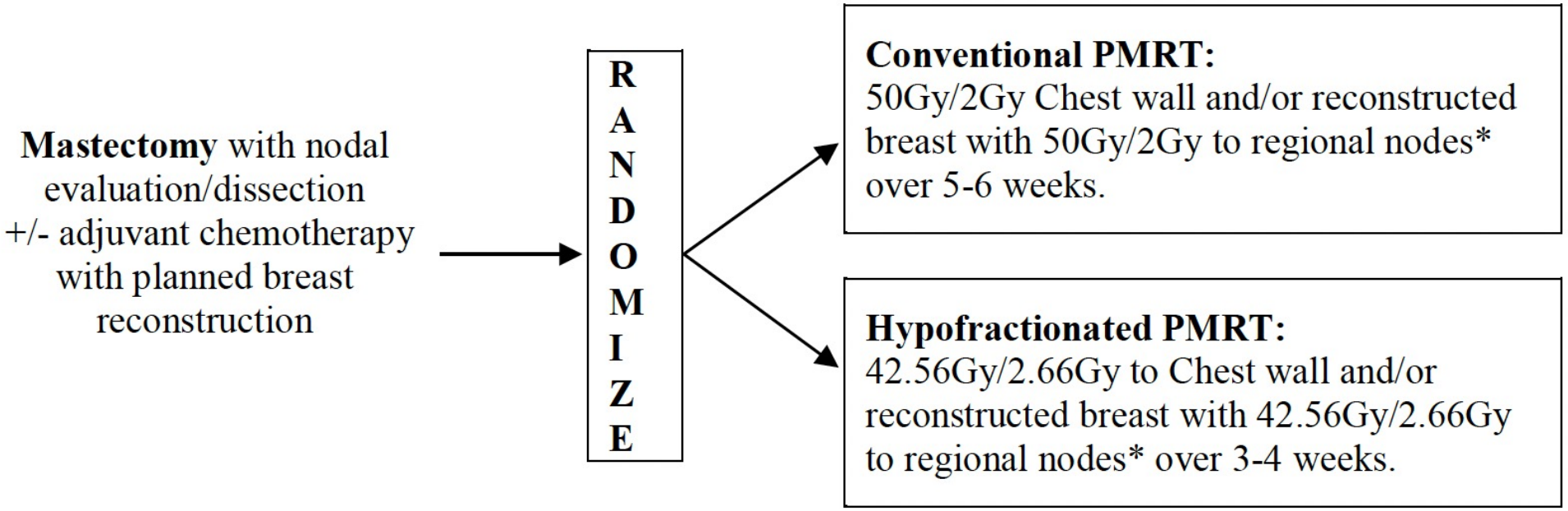
- START trials allowed PMRT/RNI (START A ~15% & START B ~8%)
- Chinese PMRT phase III trial – Wang SL et al. *Lancet Oncol.* 2019;20(3):353-360
- Growing number of smaller studies published
- Allowed on certain cooperative group trials (i.e., MA.39 “TAILOR-RT”)
- Recommended by Royal College of Radiology consensus statement – www.rcr.ac.uk

Role of hypofractionated PMRT in women undergoing breast reconstruction

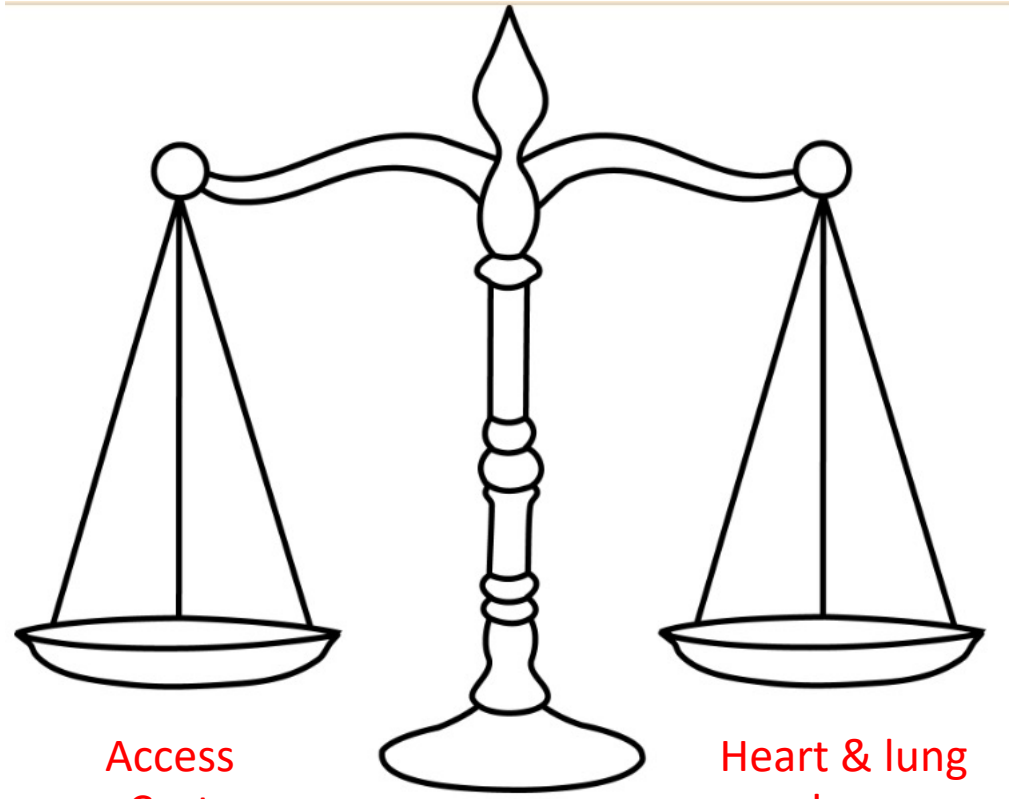
Chinese PMRT phase III trial—breast reconstruction not allowed

Wang SL et al. *Lancet Oncol.* 2019;20(3):353-360

Alliance A221505 “RT CHARM”



Role of protons in postmastectomy radiotherapy & regional nodal irradiation

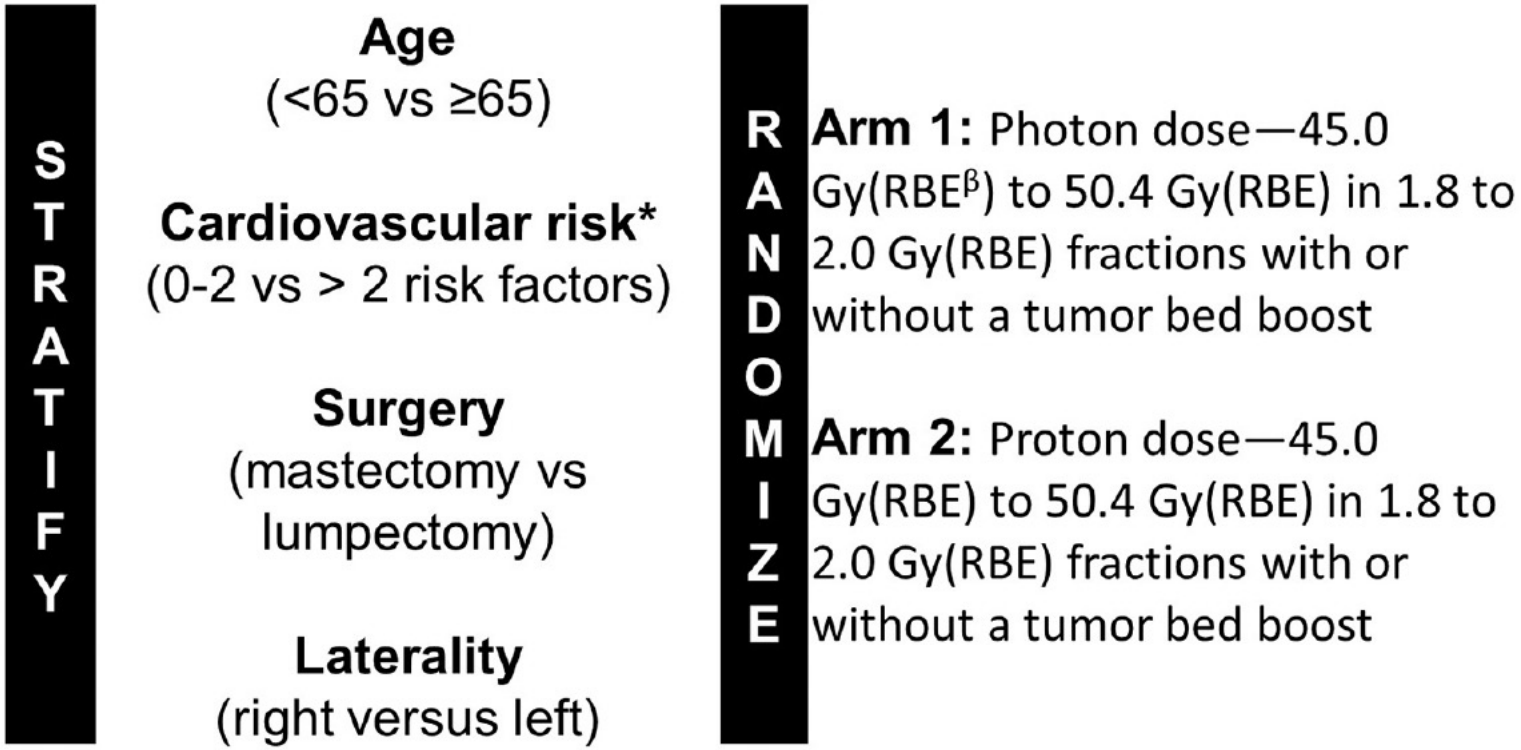


Access
Cost
Skin toxicity?

Heart & lung dose

Role of protons in postmastectomy radiotherapy & regional nodal irradiation

Pragmatic Randomized Trial of Proton vs. Photon Therapy for Patients With Non-Metastatic Breast Cancer: A Radiotherapy Comparative Effectiveness (RADCOMP) Consortium Trial



1,278 patients to be enrolled

Role of protons in postmastectomy radiotherapy & regional nodal irradiation

Pragmatic Randomized Trial of Proton vs. Photon Therapy for Patients With Non-Metastatic Breast Cancer: A Radiotherapy Comparative Effectiveness (RADCOMP) Consortium Trial

Primary Objective:

- Compare the effectiveness of proton vs. photon therapy in reducing **major cardiovascular events**

Secondary Objectives:

- Breast cancer control rates, overall survival
- Patient-reported QOL outcomes
- Develop predictive models to examine the association of radiation dose distribution (to heart and other normal tissues) and major cardiovascular events and quality of life outcomes.

Role of ultrahypofractionation in postmastectomy radiotherapy & regional nodal irradiation

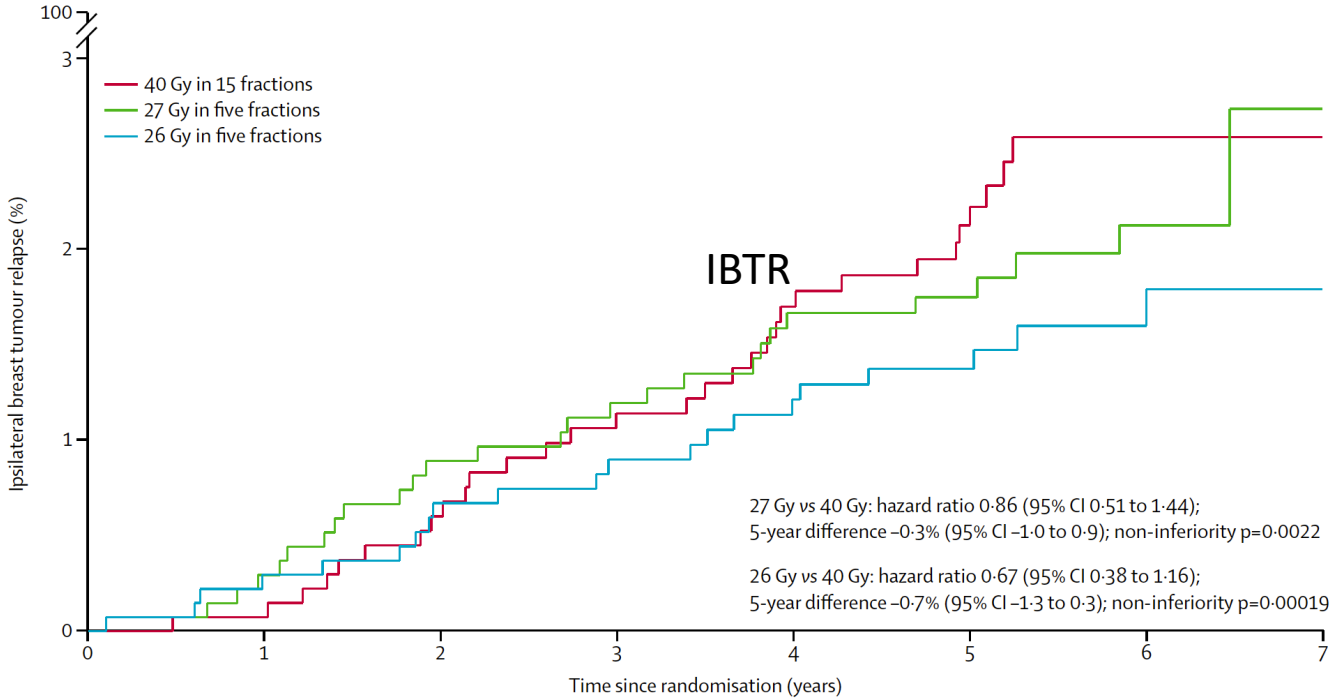
UK Fast Forward

2011-2014: 4,096 patients age ≥18 with pT1-T3 pN0-1 cancer receiving WBI ***without regional nodal irradiation***; lumpectomy boost at 2 Gy/F permitted:

- 40 Gy at 2.67 Gy/F once daily
- 26 Gy at 5.2 Gy/F once daily
- 27 Gy at 5.4 Gy/F once daily

5-year results:

- **26 Gy at 5.2 Gy/F once daily has noninferior local control & similar normal tissue effects.**
- **27 Gy at 5.4 Gy/F once daily was worse.**



Brunt AM et al. *Lancet.* 2020;395(10237):1613-1626.

Role of ultrahypofractionation in postmastectomy radiotherapy & regional nodal irradiation

Ultrahypofractionation (26 Gy at 5.2 Gy/F) being studied in FAST-Forward nodal substudy

Abstract Title: First results of FAST-Forward phase 3 RCT nodal substudy: 3-year normal tissue effects

Authors: Duncan Wheatley[1], Joanne Haviland[2], Jaymini Patel[2], Mark Sydenham[2], Abdulla Alhasso[3], Charlie Chan[4], Susan Cleator[5], Charlotte Coles[6], Ellen Donovan[7], Anna Kirby[8], Cliona Kirwan[9], Zohal Nabi[10], Elinor Sawyer[11], Navita Somaiah[8], Isabel Syndikus[12], Karen Venables[13], John Yarnold[14], A Murray Brunt[15], Judith Bliss[2]

Results

467 patients were randomised 04/2016-10/2018 from 50 UK centres (181 40Gy, 182 26Gy, 104 27Gy). Median age was 60yrs; 7%, 53% & 40% were tumour grade 1, 2 & 3 respectively; 26% received a boost (of which 13% 16Gy/8Fr, 58% 10Gy/5Fr, 29% other). Data returns/expected (excluding deaths & withdrawals) were 89% (367/414) 2-year patient questionnaires and 89% (375/420) 3-year clinical follow-up. Patients reported 2-year moderate/marked arm/hand swelling in 13/127 (10%) for 40Gy, 10/134 (7%) for 26Gy and 12/89 (13%) for 27Gy; estimated absolute differences: -2.8% (90%CI -8.6, 3.0) for 26Gy and 5.1% (90%CI -2.9, 13.2) for 27Gy vs 40Gy. 2-year prevalence of other patient-reported NTE were comparable for 26Gy and 40Gy (table). Clinicians reported arm lymphoedema at 3 years in 11/130 (8%) for 40Gy, 15/123 (12%) for 26Gy, 9/85 (11%) for 27Gy.

Conclusion

At 2-3 years' follow-up there is no early indication that outcomes relating to arm or shoulder adverse effects are different for 26Gy/5Fr compared with the standard 15Fr regimen but definitive assessment of non-inferiority will await the formal primary analysis at 5 years.

Wheatley D et al. ESTRO 2022. Abstract OC-0101.

Role of ultrahypofractionation in postmastectomy radiotherapy & regional nodal irradiation

Dr. Yadav & colleagues are currently accruing to a phase III trial of the same 1-week schedule (26 Gy at 5.2 Gy/F) vs their 2-week schedule (34 Gy at 3.4 Gy/F).

Varied techniques: 2D, 3D, DIBH

SABCS Hypofractionation Abstract Conclusions

- Mutter *et al*: Small phase IIR trial (n = 82) shows promising results of modern proton PMRT, including hypofractionation, in a heterogeneous patient population including many receiving reconstruction.
  - RT-CHARM to further clarify the role of hypofractionated PMRT (photons) with breast reconstruction.
  - RADCOMP to further clarify the role of protons (conventionally fractionated) in women receiving PMRT/regional nodal irradiation.
  - My opinion: Reasonable to use hypofractionation (esp. photons) for PMRT, esp when no TE/implant is present.
- Yadav *et al*: Large phase III trial (n = 1,121) shows promising early toxicity results of a 2D planned 2-week hypofractionation schedule.
  - My opinion: Longer-term follow-up from this & esp. Fast Forward Nodal Substudy required prior to using these fractionation regimens for PMRT/RNI.

GS4-03 Validation of Profile for the Omission of Local Adjuvant Radiotherapy (POLAR) in a meta-analysis of three randomized controlled trials of breast conserving surgery +/- radiotherapy

Background: Profile for the Omission of Local Adjuvant Radiotherapy (POLAR) is a 16-gene molecular signature developed to identify **invasive** breast cancer patients who may be candidates for RT omission after BCS. ***No overlapping genes with Oncotype Dx.***

Methods:

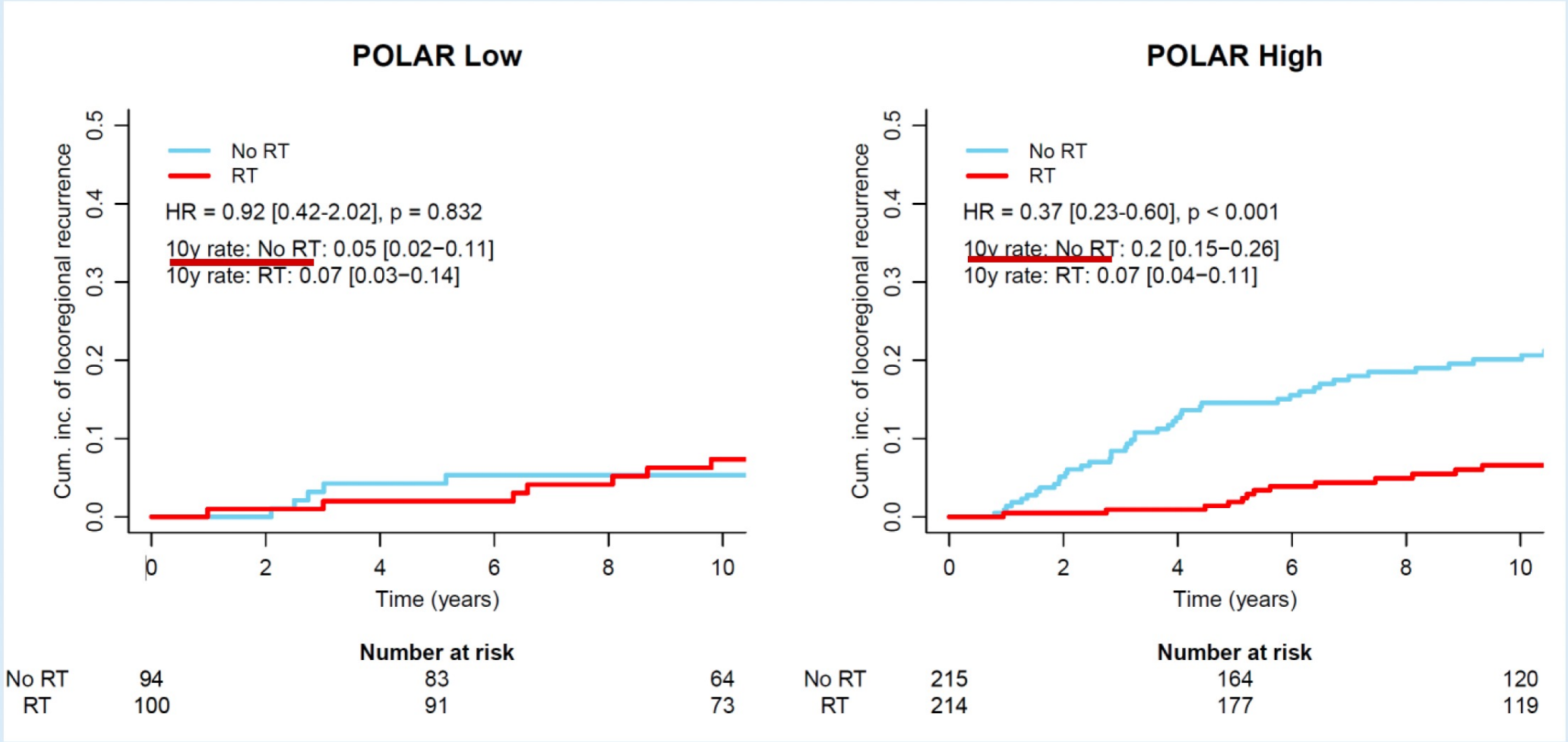
- Patient-level meta-analysis performed in 623 node-negative breast cancer patients with ER+/HER2-negative tumors enrolled in three RCTs of **BCS +/- RT**: SweBCG91RT, Scottish Conservation Trial (SCT) and Princess Margaret Hospital (PMH).
- Systemic therapy: no systemic therapy for SweBCG91RT, chemotherapy or adjuvant endocrine therapy, but not both, in SCT, and tamoxifen but no chemotherapy for PMH.

GS4-03 Validation of Profile for the Omission of Local Adjuvant Radiotherapy (POLAR) in a meta-analysis of three randomized controlled trials of breast conserving surgery +/- radiotherapy

Results: The test for interaction between RT treatment and POLAR was statistically significant (p = 0.022). Patients with a high POLAR score (N=429 [69%]) had a large benefit from RT (10-year cumulative incidence of LRR: **20%** [15%-26%] for those not treated with RT vs **7%** [4%-11%] for those treated with RT; hazard ratio for RT vs no RT: 0.37 [0.23-0.60], p < 0.001), whereas there was **no evidence of benefit from RT for patients with a low POLAR score** (N=194 [31%], 10-year cumulative incidence of LRR: 5% [2%-11%] for those not treated with RT vs 7% [3%-14%] for those treated with RT; hazard ratio for RT vs no RT: 0.92 [0.42-2.02], p = 0.832).

GS4-03 Validation of Profile for the Omission of Local Adjuvant Radiotherapy (POLAR) in a meta-analysis of three randomized controlled trials of breast conserving surgery +/- radiotherapy

Cumulative incidence of LRR in POLAR Low vs High, stratified by treatment arm (N=623)



GS4-03 Validation of Profile for the Omission of Local Adjuvant Radiotherapy (POLAR) in a meta-analysis of three randomized controlled trials of breast conserving surgery +/- radiotherapy

What does this mean for clinical practice?

- Not available for clinical use yet.
- Needs to be tested in contemporary clinical trials.
- POLAR is the first genomic classifier that is not only prognostic for LRR but also predictive.

Radiotherapy omission:

Current status

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2022
Invasive Breast Cancer

RT AFTER COMPLETION OF BCS AND AXILLARY STAGING

Negative axillary nodes →

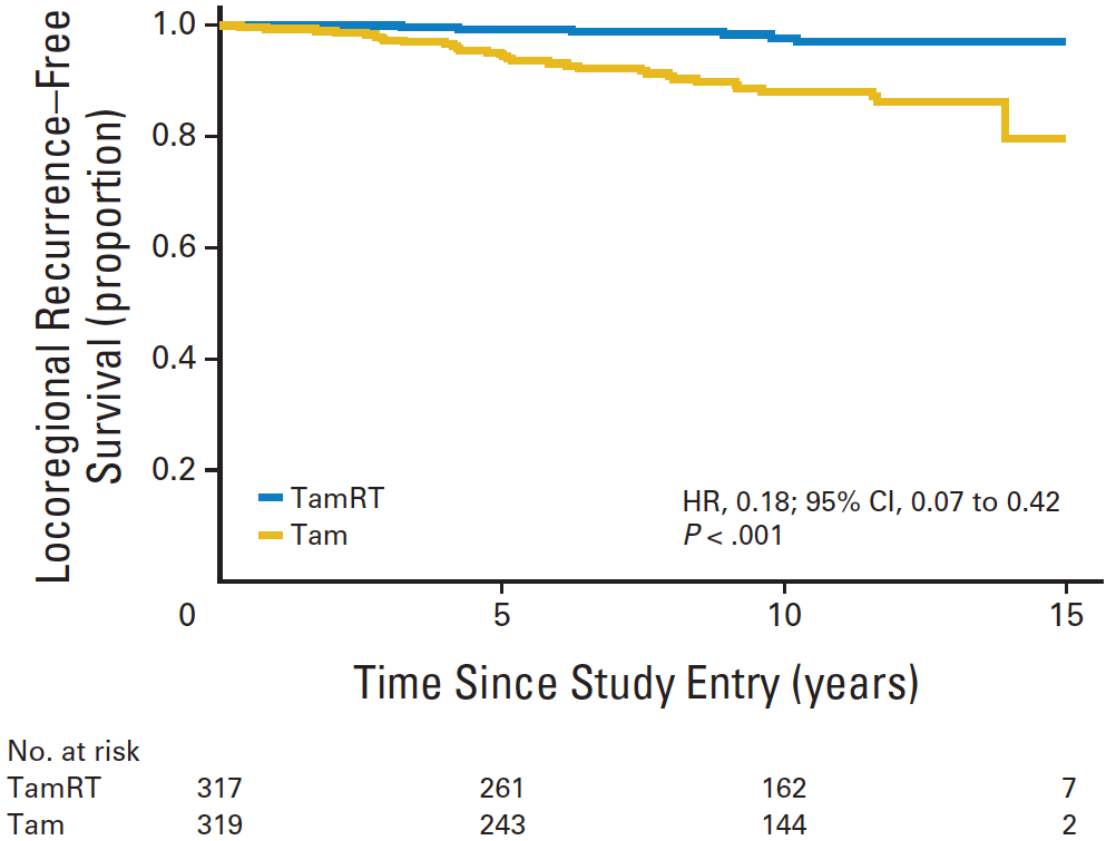
WBRT ± boost[n] to tumor bed, and consider comprehensive regional nodal irradiation (RNI) in patients with central/medial tumors, pT3 tumors, or pT2 tumors with <10 axillary nodes removed and one of the following high-risk features: grade 3, extensive lymphovascular invasion [LVI], or ER-negative.
or
Consideration of APBI in selected low-risk patients.[n,o]
or
Consider omitting breast irradiation in patients ≥70 y of age with ER-positive, cN0, pT1 tumors who receive adjuvant endocrine therapy (category 1)

Radiotherapy omission:

Current status

CALGB 9343:

- 636 women age ≥70 with cT1 cN0 ER+ breast cancer treated with BCS + tamoxifen +/- RT (45 Gy WBI + boost)
- **10Y LRR 10% vs 2%**
- No difference in 10Y OS, BCSS, DM, mastectomy rates



Hughes KS et al. *J Clin Oncol.* 2013;31(9):2382-2387

Radiotherapy omission:
Future directions

- Decreasing minimum age to 65: **PRIME II**
  - pT1-T2 (up to 3 cm) **pN0** ER+ and/or PR+ with **margins ≥1 mm**, **grade 3 or LVSI** permitted (not both; only ~2% grade 3, ~4% +LVSI), Her2 not recorded
  - Tamoxifen +/- WBI +/- boost

SABCS 2020 update:

- 10-year IBTR rate 9.8%, reduced to 0.9% with RT
- 10-year regional recurrence 2.3%, reduced to 0.5% with RT
- No significant difference in OS, DM, BSS or contralateral breast cancer

Kunkler IH et al. SABCS 2020. Abstract GS2-03.

Radiotherapy omission:
Future directions

	Patient Age	Biological Selection Criteria	Treatment
NRG BR007 (DEBRA)	50-69 years	Oncotype ≤18	**Phase III:** Endocrine tx +/- RT (APBI or WBI)
IDEA	50-69 years	Oncotype ≤18	Endocrine tx
EXPERT	≥50 years	PAM50 ROR ≤60	**Phase III:** Endocrine tx +/- RT
PRECISION	50-75 years	PAM50	Low risk—endocrine tx only Int/high-risk—endocrine tx + WBI
PRIMETIME	≥60 years	IHC4+clinical *ER, PR, Her2, Ki67*	IHC4+C very low—endocrine tx All others—endocrine tx + WBI
LUMINA	≥55 years	ICH4+clinical	Endocrine tx

Radiotherapy omission:

LUMINA A

- 501 pts age ≥55, T1N0, Gr 1-2, ER/PR+ Her2-, Ki67 ≤13.25%, margins ≥1mm treated with endocrine therapy only.
- Median follow-up 5 years:

Outcome	Events at 5 years	% 5-year Rate (90% CI)
LR	10	2.3 (1.3, 3.8)
Contralateral BC	8	1.9 (1.1, 3.2)
RFS	12	97.3 (95.9, 98.4)
DFS	47 (23 second non-BCs)	89.9 (87.5, 92.2)
OS	13 (1 BC death)	97.2 (95.9, 98.4)

- *ELIOT trial: In a "very low risk" group defined by tumor size <1cm, Grade 1, luminal A, and Ki-67 <14%, the 15-year rate of IBR was 8.1% with IORT and 3.1% with WBI*

Whelan *et al*, ASCO 2022: LBA501

Radiotherapy omission:

Future directions

NRG-BR008 ("HERO"): A Phase III Randomized Trial Seeking to Optimize Use of Radiotherapy in Patients with Early-Stage, Low Risk, HER2-Positive Breast Cancer

NRG ONCOLOGY

Advancing Research. Improving Lives.™

Radiotherapy omission summary

- Karlsson *et al* performed a patient-level meta-analysis of three "classic" +/-RT trials and found POLAR to be both ***prognostic & predictive*** of radiotherapy benefit.
  - Not available for clinical use yet & needs to be prospectively tested.
- Current consensus guidelines: women age ≥70 with T1N0 ER+ cancers taking endocrine therapy.
  - Small benefit to RT does exist in this patient population & modern radiotherapy options are much less burdensome.
- Multiple phase II-III trials recently completed or currently accruing, including NRG BR007
- NRG BR008 to open soon for Her2+ patients getting trastuzumab
- ***Endocrine therapy*** omission research underway (i.e. EUROPA).

thank you

anderson@humonc.wisc.edu

GS4-01 Impact of Breast Conservation Therapy on Local Recurrence in Patients with Multiple Ipsilateral Breast Cancer – Results from ACOSOG Z11102 (Alliance)

- Clinically multifocal or multicentric breast cancer (2-3 lesions, none >5 cm, at least 2 cm apart) treated with BCS → RT
- 270 pts enrolled; 204 evaluable for primary endpoint (LR)
  - 5Y cumulative incidence of LR = 3.1% (95% CI: 1.3-6.4)
  - Equal number of contralateral breast cancers
- Mastectomy rate: 7% (+margins)
- 2Y cosmetic outcome good/excellent in 70%
  - Increasing radiation boost volume associated with acute dermatitis but not worse cosmesis

PD3-01 Neoadjuvant pembrolizumab + chemotherapy vs placebo + chemotherapy followed by adjuvant pembrolizumab vs placebo for early TNBC: Post hoc analysis of adjuvant radiation therapy in the phase 3 KEYNOTE-522 study

Methods: 1174 patients with stage T1c/N1-2 or T2-4/N0-2 TNBC treated with pembro or placebo + carbo/Taxol x 4 → AC x 4 → definitive surgery → pembro/placebo x 9 cycles.

Results: 61% received adjuvant RT (n = 454 pembro, n = 261 placebo); median follow-up ~38 months.

Table. EFS by Adjuvant RT in KEYNOTE-522

Population	Pembro No. events/No. patients (%)	Placebo No. events/No. patients (%)	HR (95% CI)*
With Adjuvant RT†	55/454 (12.1)	52/261 (19.9)	0.58 (0.40 – 0.85)
Concurrent‡	16/144 (11.1)	14/91 (15.4)	0.70 (0.34 – 1.44)
Sequential§	28/280 (10.0)	35/159 (22.0)	0.42 (0.26 – 0.69)
Without Adjuvant RT	68/330 (20.6)	41/129 (31.8)	0.60 (0.41 – 0.89)

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Methods: 1174 patients with stage T1c/N1-2 or T2-4/N0-2 TNBC treated with pembro or placebo + carbo/Taxol x 4 → AC x 4 → definitive surgery → pembro/placebo x 9 cycles.

Results: 61% received adjuvant RT (n = 454 pembro, n = 261 placebo); median follow-up ~38 months.

- Grade 3-5 treatment-related AE rates for pembro vs placebo:
  - 7.5% vs 2.9% without RT
  - 5.9% vs 2.7% with RT
    - 4.9% vs 2.2% with concurrent RT
    - 6.8% vs 3.1% with sequential RT
- Treatment-related AEs led to death in 2 patients (0.4%); both occurred in the pembro arm in patients who received adjuvant RT.
- Immune-mediated AE rates for pembro vs placebo:
  - 9.0% vs 10.0% without RT
  - 10.6% vs 5.0% with RT
    - 9.7% vs 4.4% with concurrent RT
    - 11.8% vs 5.7% with sequential RT

PD3-01 Neoadjuvant pembrolizumab + chemotherapy vs placebo + chemotherapy followed by adjuvant pembrolizumab vs placebo for early TNBC: Post hoc analysis of adjuvant radiation therapy in the phase 3 KEYNOTE-522 study

Conclusion:

- The addition of pembro to neoadjuvant chemo followed by adjuvant pembro provided a clinically meaningful EFS benefit, independent of adjuvant RT administration.
- An EFS benefit was observed in patients who received pembro with either concurrent or sequential adjuvant RT.
- The addition of pembro to adjuvant RT was generally well tolerated. Similar rates of treatment-related AEs and immune-mediated AEs were seen in patients who received adjuvant RT and pembro either concurrently or sequentially, although the sample sizes are modest.