Bestro Autumn Meeting

Combined Treatment Strategies

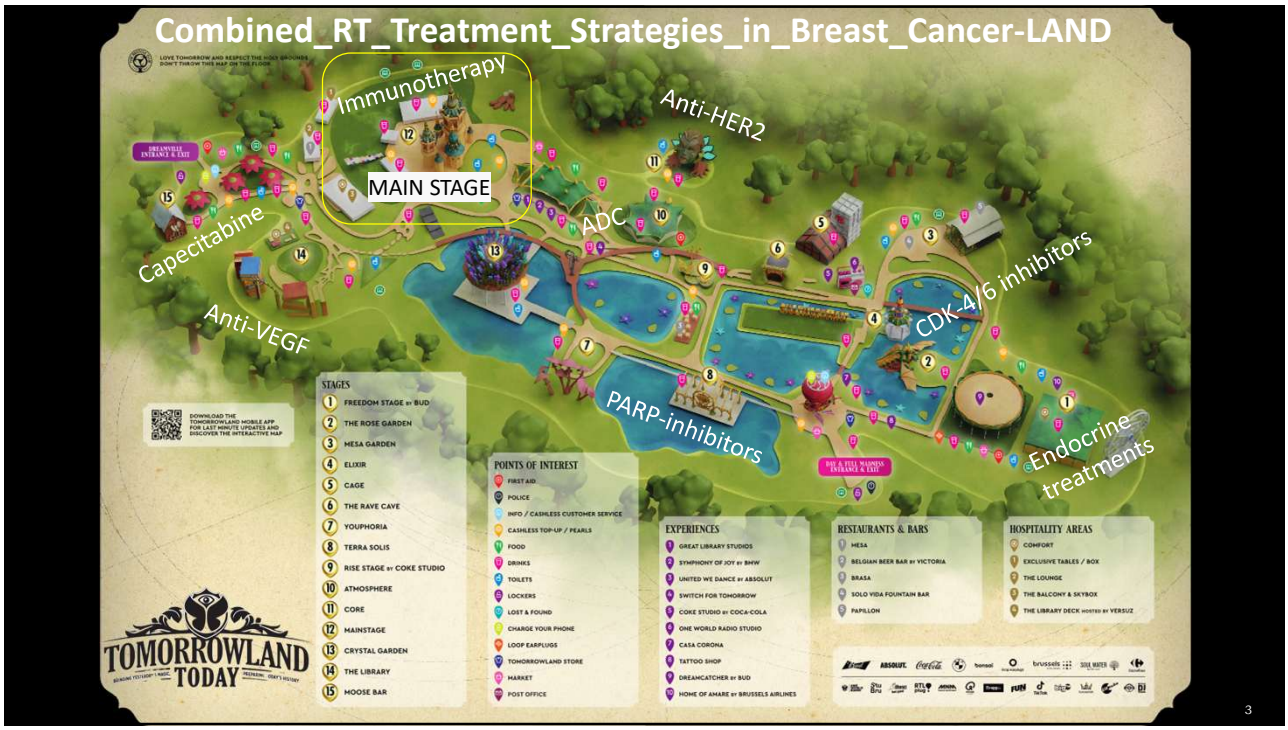
** Breast Cancer **

Alex De Caluwé
Institut Jules Bordet & AZ St Maarten

DECLARATION OF INTERESTS

Alex De Caluwé

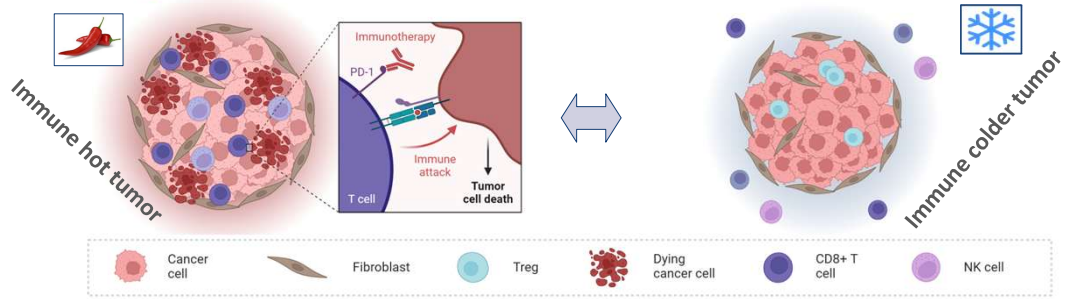
- Research funding to my institution (Institut Jules Bordet) from AstraZeneca
- Non-financial interests:
  - Member / scientific committee member of
    - EORTC Breast Cancer Group
    - ESMO Early Breast Cancer Track



Neo-adjuvant immunotherapy in breast cancer

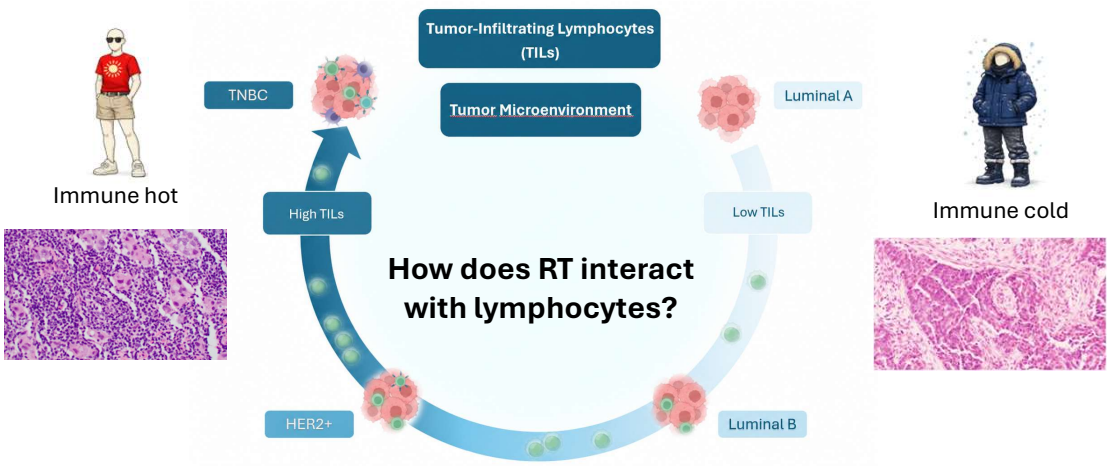
Effect of adding anti-PD(L)1 to chemotherapy

Triple negative BC (ER- HER2-)	Luminal B BC (ER+ HER2-)
Keynote-522	Keynote-756
pCR ↑ 13,6%	pCR ↑ 8,5% (less gain in PD-L1 neg)
EFS ↑ 7,7%	EFS/OS: not mature yet
OS ↑ 4,9%	
→ neo-adj immuno-chemo is standard of care	→ neo-adj immuno-chemo is NOT standard of care



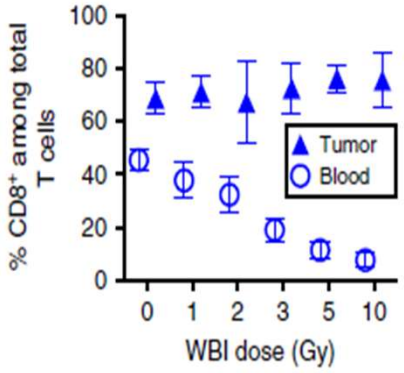
Breast Cancer and the Immune Response

Different breast cancer subtypes → different interactions with the immune system

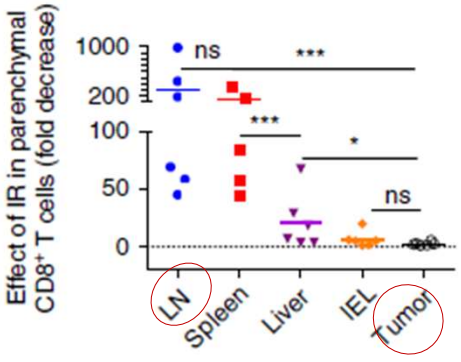


Is RT an evil destructor of lymphocytes?

Radiation destroys lymphocytes in <u>blood</u>, *but not in the tumor*



Radiation destroys lymphocytes in <u>LN</u>, *but not in the tumor*



→ **Should we avoid giving RT to blood and lymph nodes** if we want to preserve immunotherapy effect?

Arina et al, Nat Com, 2019

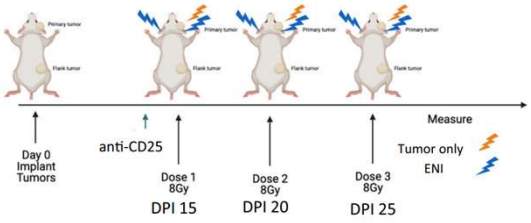
Elective nodal irradiation mitigates systemic immunity

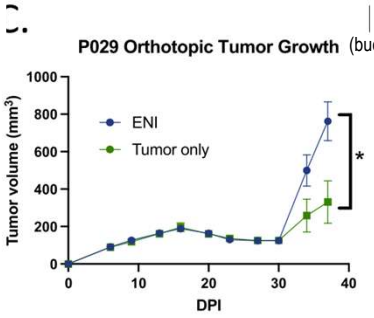
nature communications

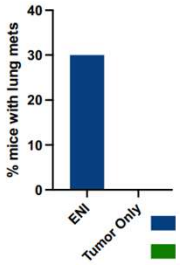
Article

https://doi.org/10.1038/s41467-022-34676-w

Elective nodal irradiation mitigates local and systemic immunity generated by combination radiation and immunotherapy in head and neck tumors



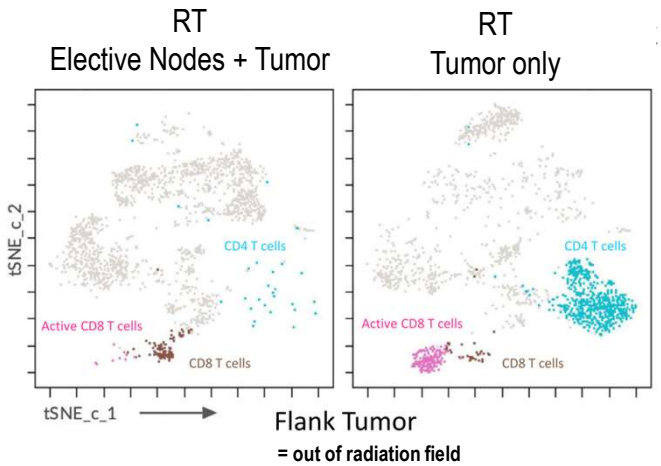




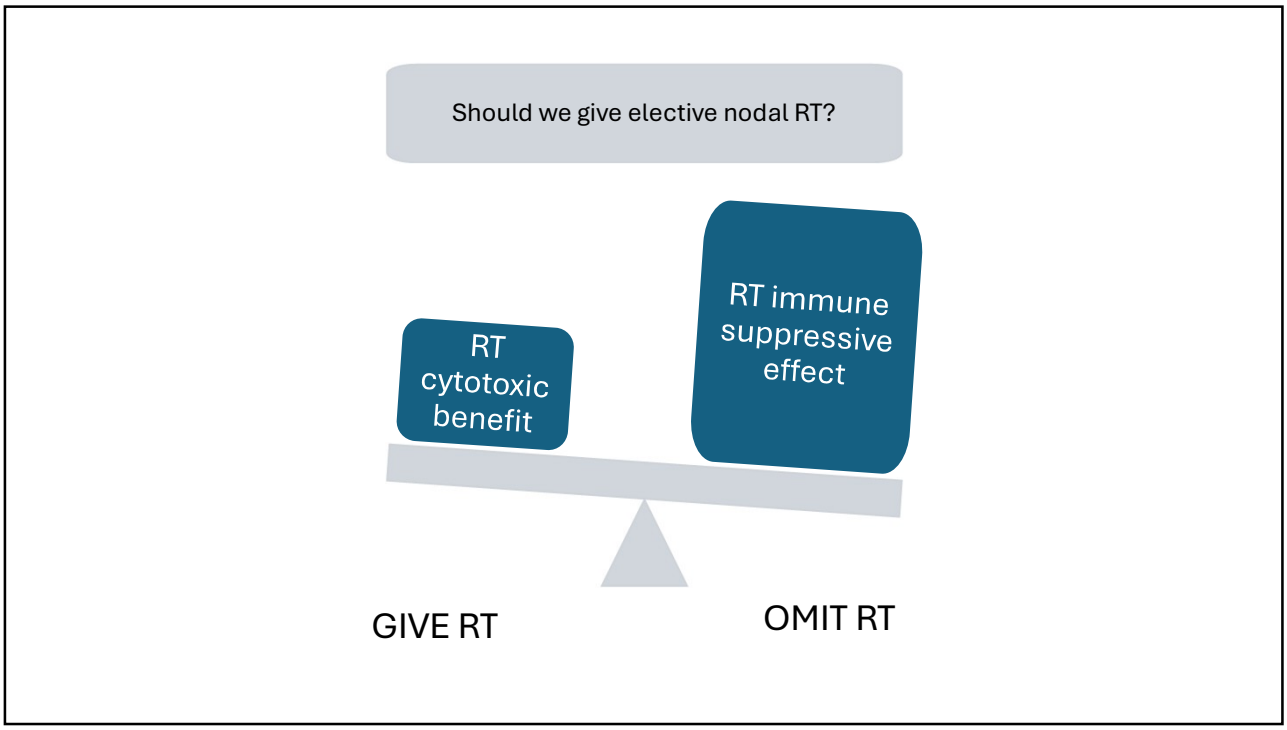
ENI = elective nodal irradiation

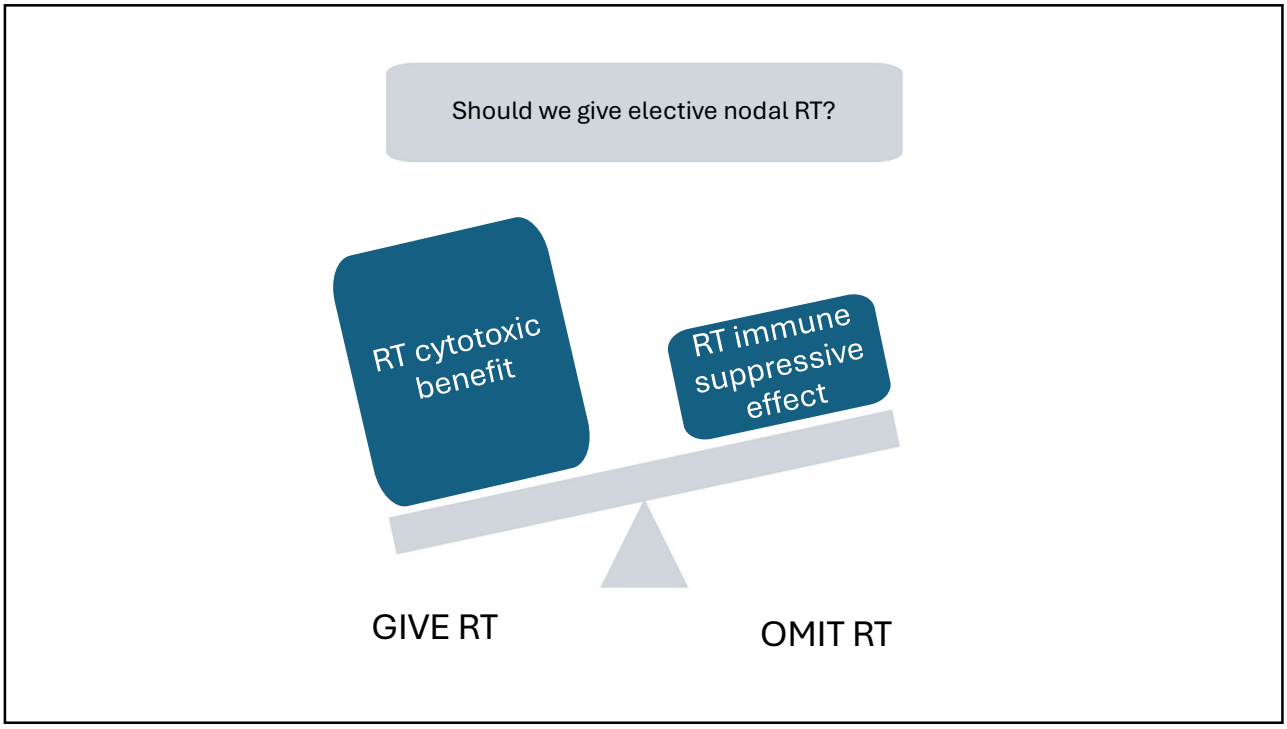
Darragh et al, Nat Com, 2022

Elective nodal irradiation mitigates systemic immunity



Darragh et al, Nat Com, 2022


Should we give elective nodal RT?
RT cytotoxic benefit
RT immune suppressive effect
GIVE RT
OMIT RT


Should we give elective nodal RT?
RT cytotoxic benefit
RT immune suppressive effect
GIVE RT
OMIT RT



De-escalation of regional nodal irradiation after pCR in breast cancer

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Omitting Regional Nodal Irradiation after Response to Neoadjuvant Chemotherapy

E.P. Mamounas,[1] H. Bandos,[2,3] J.R. White,[4] T.B. Julian,[5] A.J. Khan,[6] S.F. Shaitelman,[7]

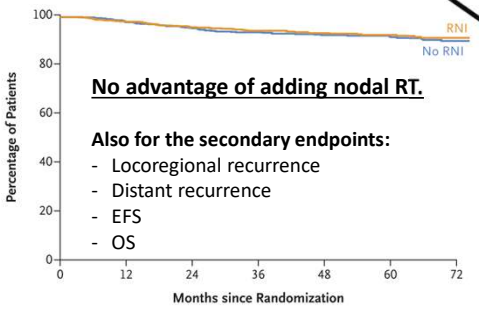
NSABP-51/RTOG 1304

Primary endpoint:
Invasive breast cancer free survival
Superiority design

N = 1556

Invasive Breast Cancer Recurrence-free Survival

SELECTED FOR PCR



No advantage of adding nodal RT.

Also for the secondary endpoints:
- Locoregional recurrence
- Distant recurrence
- EFS
- OS

	No. of Events	5-Year Estimate (percent)
RNI	50	92.7
No RNI	59	91.8

Hazard ratio for invasive breast cancer recurrence or death from breast cancer 0.88 (95% CI, 0.60–1.28)
P=0.51

No. at Risk							
RNI	772	717	644	544	427	294	172
No RNI	784	744	663	557	437	309	192

Figure 1. Effect of Regional Nodal Irradiation on the Invasive Breast Cancer Recurrence–free Interval.
Shown is the 5-year estimate of survival free from invasive breast cancer recurrence or death from breast cancer. RNI denotes regional nodal irradiation.

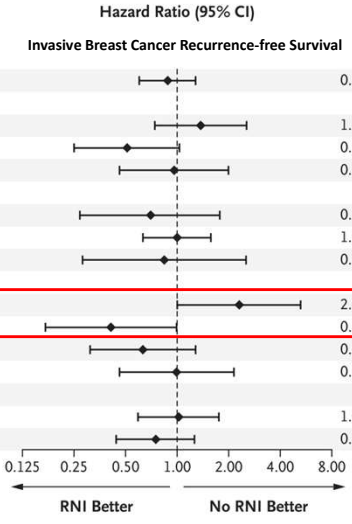
Maimounas et al, NEJM, 2025



De-escalation of regional nodal irradiation after pCR

B Exploratory Analysis

Subgroup	RNI (no. of events/total)	No RNI (no. of patients)	5-Year Estimate RNI (percent)	5-Year Estimate No RNI (percent)	Hazard Ratio (95% CI)
All patients	50/772	59/784	92.7	91.8	0.88 (0.60–1.28)
Age					
≤49 yr	24/312	18/311	92.0	92.8	1.37 (0.74–2.54)
50–59 yr	12/254	25/257	94.4	90.4	0.51 (0.25–1.03)
≥60 yr	14/206	16/216	91.7	92.4	0.96 (0.46–1.99)
Race					
Black	8/140	11/135	93.4	92.6	0.70 (0.27–1.77)
White	36/533	40/543	92.1	91.6	1.00 (0.63–1.57)
Other	6/99	8/106	95.3	91.8	0.84 (0.28–2.52)
Tumor subtype					
Triple negative	19/188	8/169	88.4	95.0	2.30 (1.00–5.25)
HR+, HER2–	7/155	17/173	94.0	90.5	0.41 (0.17–0.99)
HR–, HER2+	12/183	20/198	92.4	88.8	0.63 (0.31–1.28)
HR+, HER2+	12/246	14/244	95.7	93.3	0.99 (0.46–2.14)
Axillary surgery					
ALND with or without SLNB	25/338	27/357	91.8	92.0	1.02 (0.59–1.75)
SLNB alone	25/434	32/427	93.5	91.5	0.75 (0.44–1.26)



Deleterious effect of RT in TNBC?

Maimounas et al, NEJM, 2025

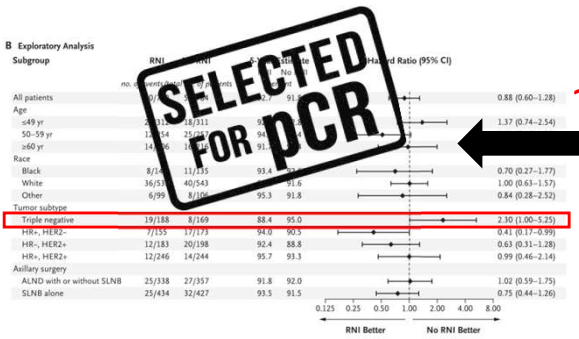


De-escalation of regional nodal irradiation after pCR

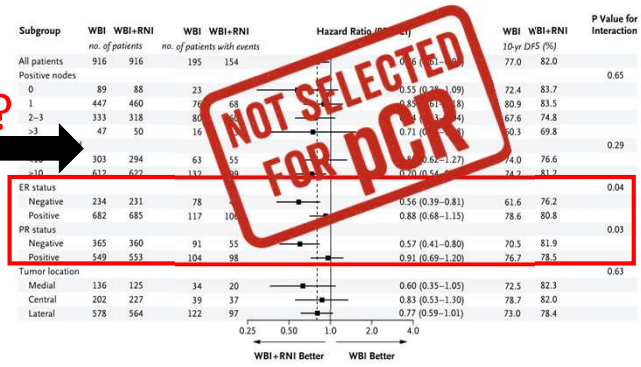
Whole breast RT +/- RNI

NSABP-51/RTOG 1304: + RNI worse for TNBC

MA20 trial: + RNI better for TNBC



?

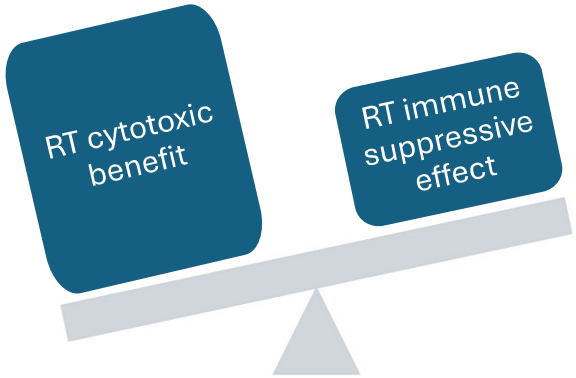


Maimounas et al, NEJM, 2025

Whelan et al, NEJM, 2015

No pCR
(or no neo-adjuvant systemic therapy)

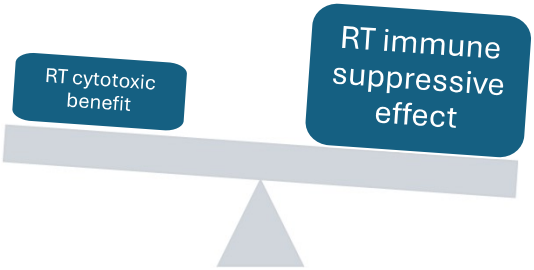
pCR = documented response
to neo-adjuvant systemic therapy



GIVE RT!!

No pCR
(or no neo-adjuvant systemic therapy)

pCR = documented response
to neo-adjuvant systemic therapy



OMIT RT??



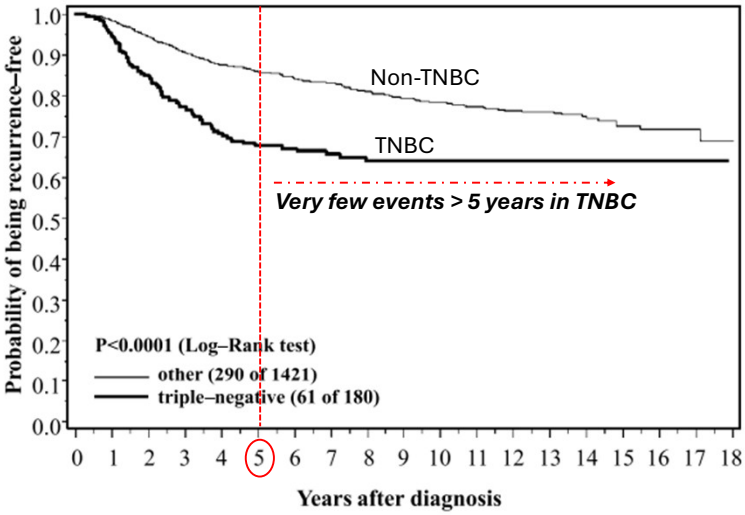
De-escalation of regional nodal irradiation

Is nodal irradiation deleterious in TNBC that are in pCR?

Counter-arguments:

- **Other trials have shown a benefit using nodal RT in TNBC.**
  → ***You can only compare with trials that selected for pCR!***
- **This data only has 5 years follow-up, we need to wait for longer follow-up.**

De-escalation of regional nodal irradiation



In ER+, 2/3 of events occur > 5 years

In TNBC, > 90% of events occur < 5 years

Dent R et al, Clin Ca Res, 2007

De-escalation of regional nodal irradiation

Tailoring radiotherapy in cT1–2N1 breast cancer to nodal response on primary chemotherapy (RAPCHEM: BOOG 2010–03): 10-year follow-up results of a Dutch, prospective, registry study

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

Mauritz et al, Lancet Oncolog, 2026



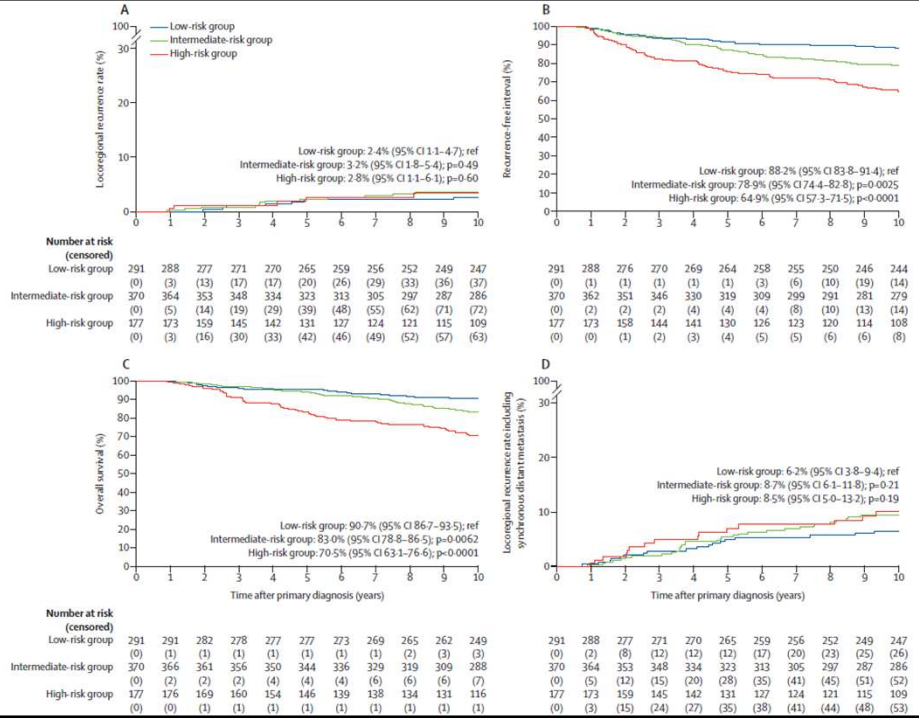
De-escalation of regional nodal irradiation

	Radiotherapy strategy after lumpectomy	Radiotherapy strategy after mastectomy
Low-risk group ypN0 or ypN0(sn)		
ypN0 (ALND)	Whole breast radiotherapy	No radiotherapy
If SLNB before primary systemic treatment and no ALND: cN1mi (SLNB) and no risk factor; or if SNLB after primary systemic treatment and no ALND: ypN0 (SLNB and/or MARI)	Whole breast radiotherapy	No radiotherapy
	NO NODAL RT	
Intermediate-risk group		
ypN1 (ALND)	Whole breast radiotherapy	Chest-wall radiotherapy
If SLNB before primary systemic treatment and no ALND: cN1mi (SLNB) and ≥1 risk factor or ≤2 macrometastasis in SLNB and no risk factor; or if SNLB after primary systemic treatment and no ALND: ypN1mi (SLNB and/or MARI) and no risk factors	Whole breast radiotherapy; axilla radiotherapy levels I–II	Chest-wall radiotherapy; axilla radiotherapy levels I–II
High-risk group		
ypN2+ (ALND)	Whole breast radiotherapy; axilla radiotherapy levels III–IV	Chest-wall radiotherapy; axilla radiotherapy levels III–IV
If SLNB before primary systemic treatment and no ALND: ≤2 macrometastasis in SLNB and ≥1 risk factor or ≥3 metastasis in SLNB; or if SNLB after primary systemic treatment and no ALND: ypN1mi (SLNB and/or MARI) and ≥1 risk factor or ypN1 (SLNB and/or MARI)	Whole breast radiotherapy; axilla radiotherapy levels I–IV	Chest-wall radiotherapy; axilla radiotherapy levels I–IV

ALND=axillary lymph node dissection. SLNB=sentinel lymph node biopsy. MARI=marking of the axilla with radioactive iodine. Risk factors were grade 3 tumour, age ≤40 years, tumour size >3 cm, and lymphovascular invasion. Levels of radiotherapy were defined according to the Danish Breast Cancer Cooperative Group atlas.[53]

Table 1: Risk group definition and corresponding radiotherapy strategy

Mauritz et al, Lancet Oncolog, 2026



cT1-2N1 → ypN0(sn)

↓

No nodal RT

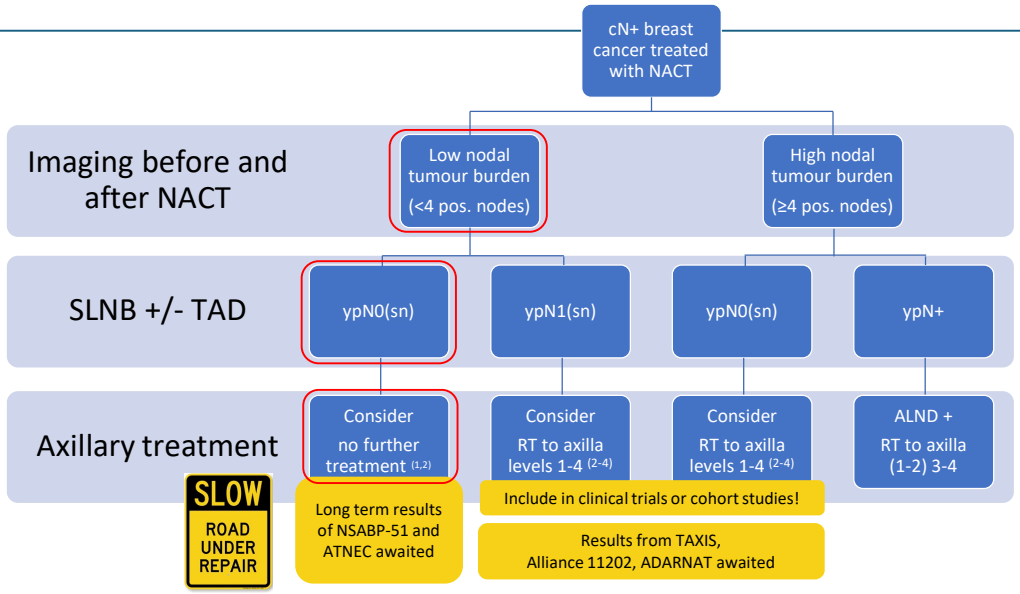
↓

Excellent 10-year locoregional control & OS data

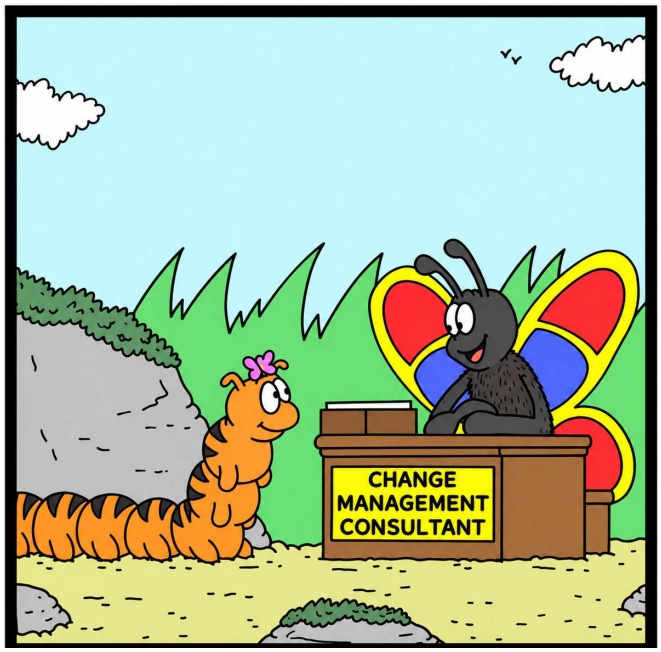
Mauritz et al, Lancet Oncolog, 2026



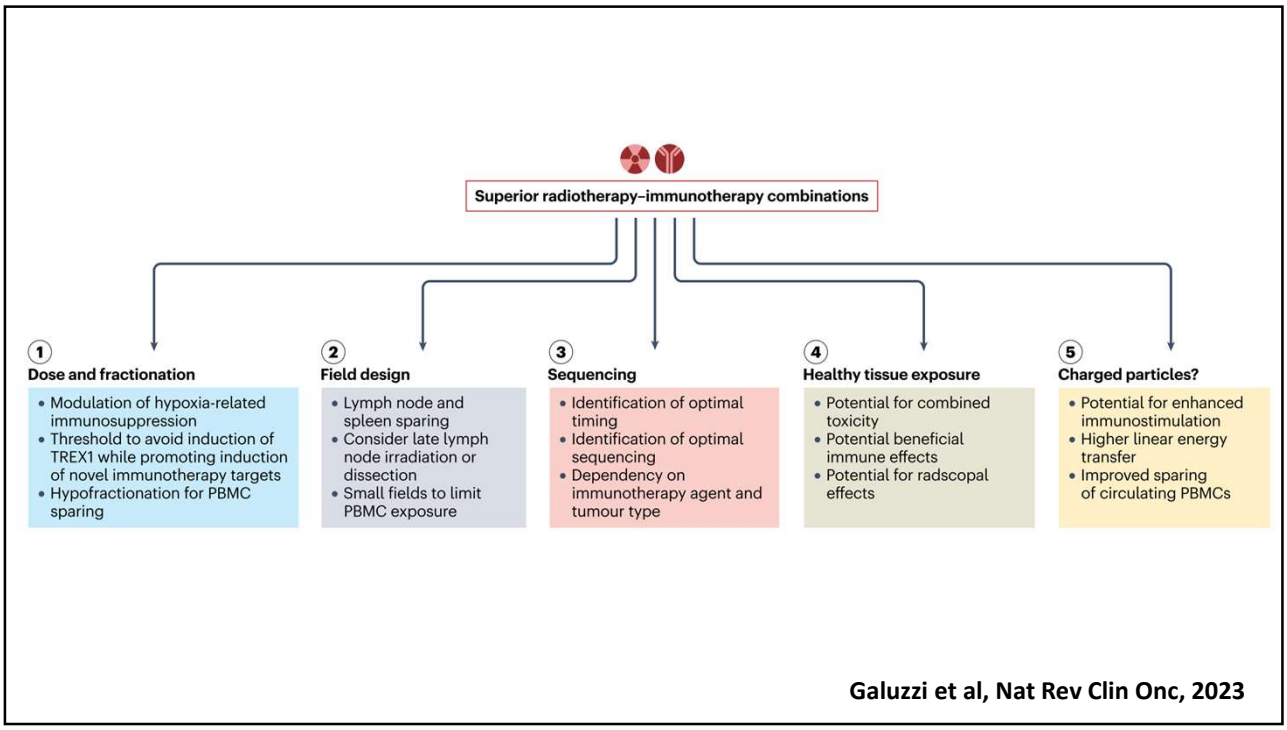
De-escalation of regional nodal irradiation
How to implement in clinical practice?



1) **Maimounas, NEJM, 2025**. 2) **Mauritz, Lancet Oncolog, 2026**. 3) Muslumanoglu, Cancer, 2024. 4) Boersma, The Breast, 2023.



alex.decaluwe@hubruxelles.be



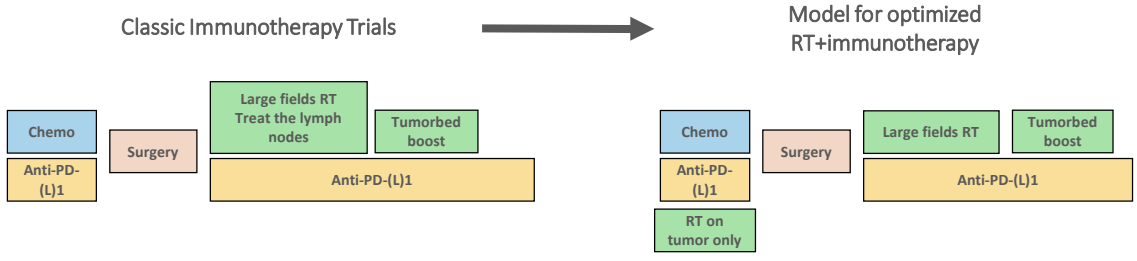
Galuzzi et al, Nat Rev Clin Onc, 2023

How to optimally combine RT and anti-PD-(L)1 in early breast cancer?

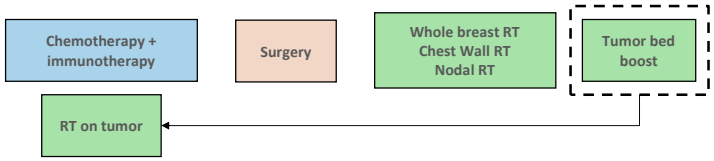
PRE-CLINICAL & EMERGING CLINICAL INSIGHTS ON HOW TO COMBINE RT + ICI:

- Neo-adjuvant > adjuvant > metastatic
- Use few fractions
- Deliver RT to primary tumor only and use small fields to avoid immunodepletion
- Avoid to give radiation to tumor draining lymph nodes

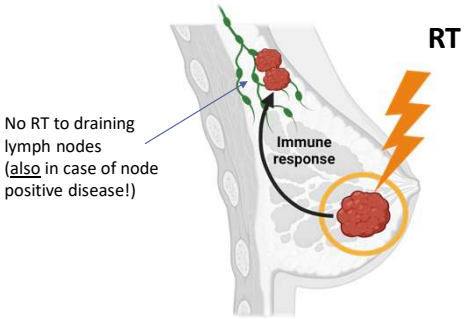
→ Should we rethink the way we deliver RT when it is combined with immunotherapy?



From Emerging Clinical Insights → Phase 2 trials → Is it time for validation in phase 3 trials?



Concept tested in phase II trials:
- **Neo-CheckRay** in **ER+** breast cancer
- **P-RAD** in **TNBC**/ER+

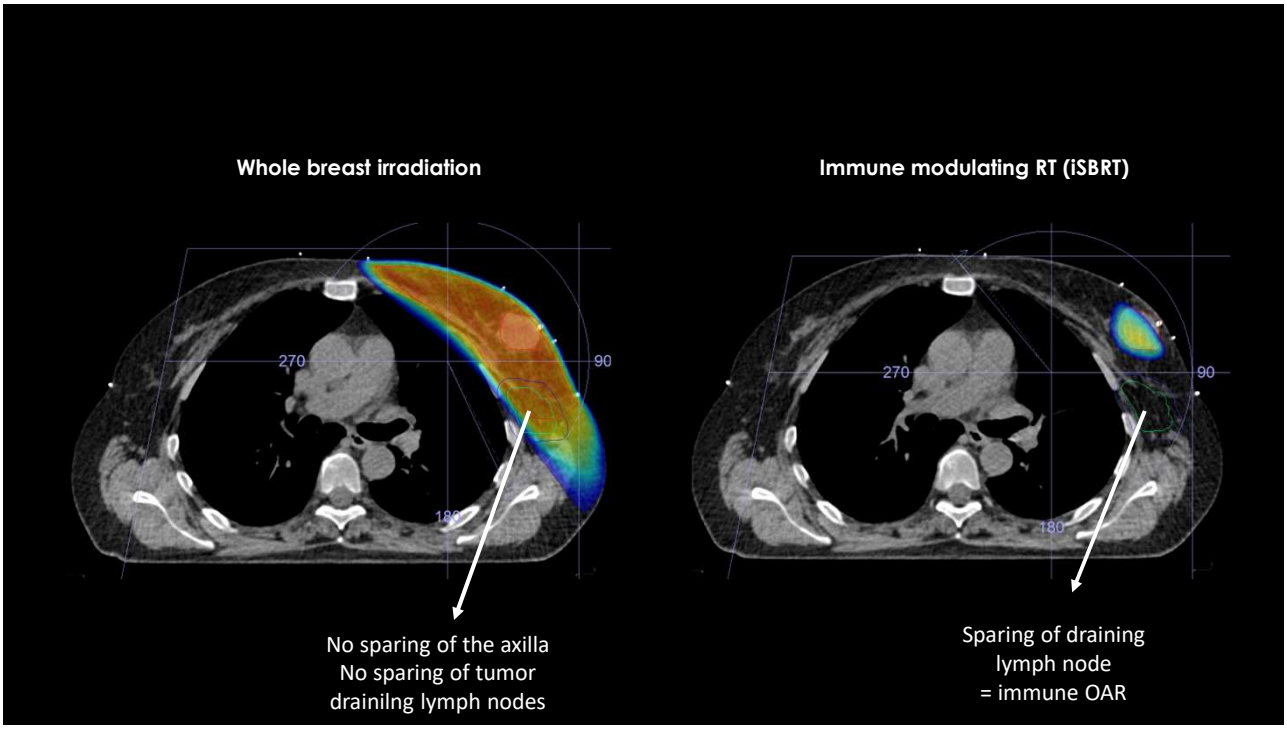


RT target: primary breast cancer only

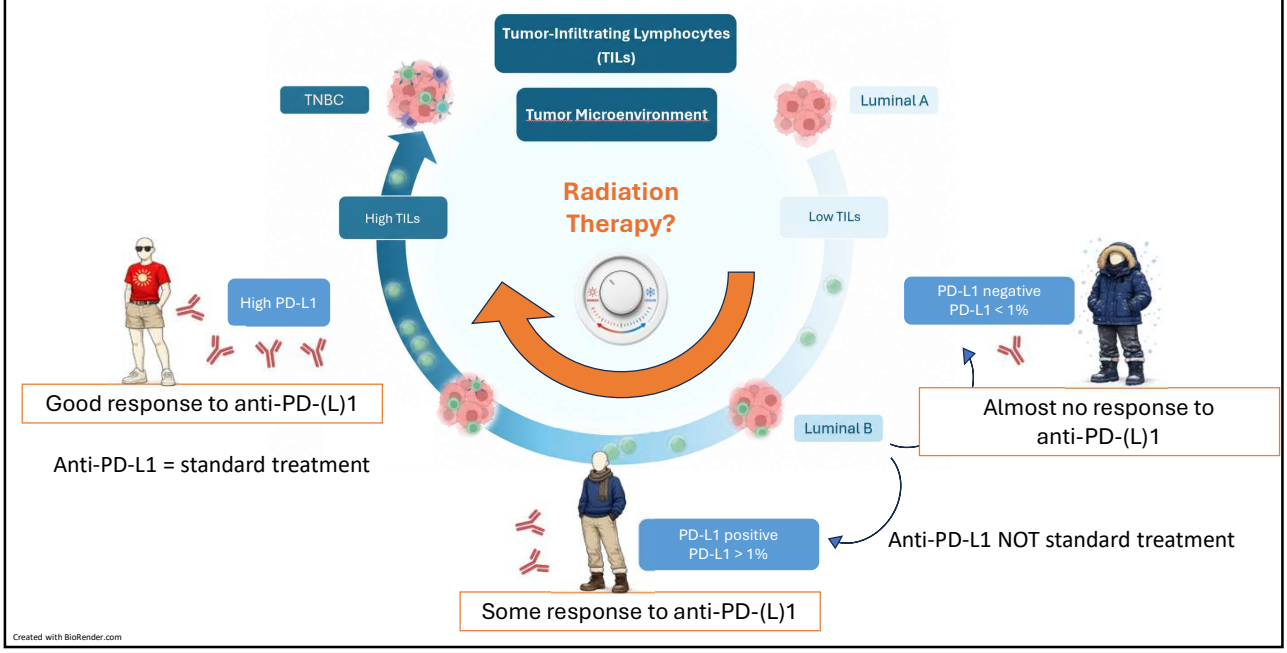
What radiation dose?

Immune modulating RT = iRT

RT Intent	**Immunomodulation** Non-ablative intent of RT
RT dose	3 daily fractions of ***3-8 Gy***



In what breast cancer subtypes investigate this strategy?



Good response to anti-PD-(L)1

Anti-PD-L1 = standard treatment

Almost no response to anti-PD-(L)1

Anti-PD-L1 NOT standard treatment

Some response to anti-PD-(L)1

Neo-CheckRay Phase II Randomized Trial

nature medicine

Article https://doi.org/10.1038/s41591-026-04453-z

Neoadjuvant stereotactic body radiation therapy with durvalumab and oleclumab in ER$^+$HER2$^-$ breast cancer: a randomized phase 2 trial

Alex De Caluwé[1], Isabelle Desmoulins[2], Kim Cao[3], Vincent Remouchamps[4], Adinda Baten[5], Eleonore Longton[6], Karine Peignaux[2], Andrea Joaquin Garcia[1], David Venet[1], Luca Arecco[1], Elisa Agostinetto[1], Guilherme Nader-Marta[1], Zoë Denis[1], Jennifer Dhont[1], Paulus Kristanto[1], Xavier Catteau[1], Denis Larsimont[1], Roberto Salgado[7,8], Philip Poortmans[9,10], John Stagg[11], Christos Sotiriou[1], Martine Piccart[1], Michail Ignatiadis[1], Emanuela Romano[3] & Laurence Buisseret[1]

[1]Institut Jules Bordet, Hôpitaux Universitaires de Bruxelles (H.U.B), Université Libre de Bruxelles (ULB), Brussels, Belgium. [2]Centre Georges-François Leclerc, Université Bourgogne Europe, Dijon, France. [3]Institut Curie, Paris, France. [4]CHU St Elisabeth, Namur, Belgium. [5]Universitaire Ziekenhuizen Leuven, Leuven, Belgium. [6]Hôpital Universitaire St Luc, Brussels, Belgium. [7]ZAS Hospitals, Antwerp, Belgium. [8]Peter Mac Callum Cancer Centre, Melbourne, Victoria, Australia. [9]Iridium Netwerk, Antwerp, Belgium. [10]University of Antwerp, Antwerp, Belgium. [11]Goodman Cancer Institute, McGill University, Montreal, Quebec, Canada. e-mail: alex.decaluwe@bordet.be

Nature Medicine | Volume 32 | July 2026 | 2461–2472





7 participating sites in Belgium and France

Investigator-initiated, academic trial,

n = 147 patients randomized
ER+, MammaPrint High-Risk

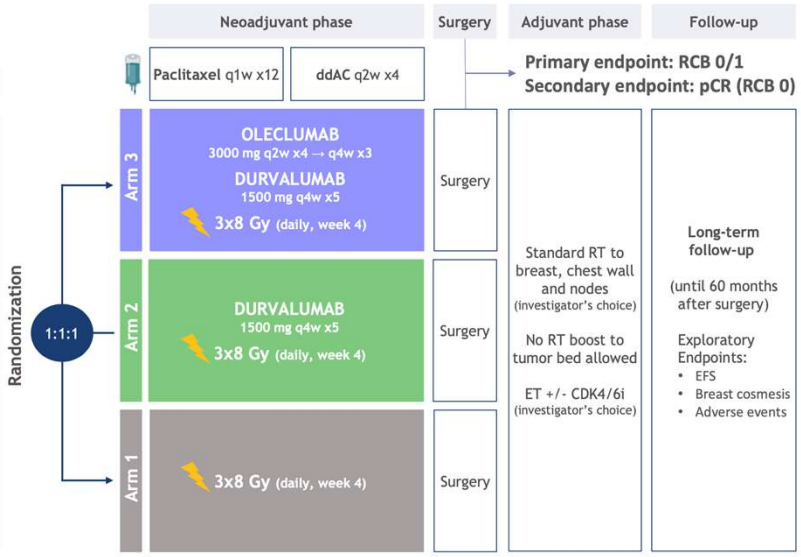
Screening

Key inclusion criteria

- Newly diagnosed early ER+ HER2– breast cancer
- Grade 3 or grade 2 with Ki67≥15%
- **MammaPrint® high risk**
- cT1c-3 (≥ 2 cm) cN0 *or* cT1c-3 (≥ 1.5 cm) cN1-3
- ECOG PS 0-1
- Adequate organ function
- Tissue available for PD-L1 assessment (central lab)

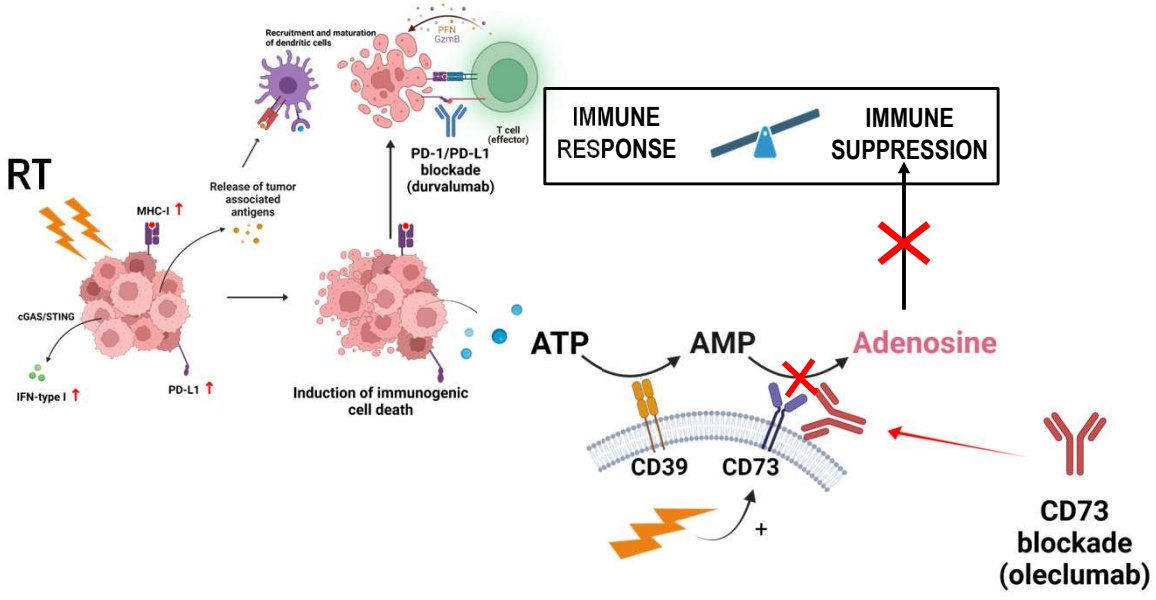
Stratification factors

- PD-L1 IC (≥ 1% or < 1%) by SP263
- Nodal status (positive or negative)
- cT1/cT2 or cT3

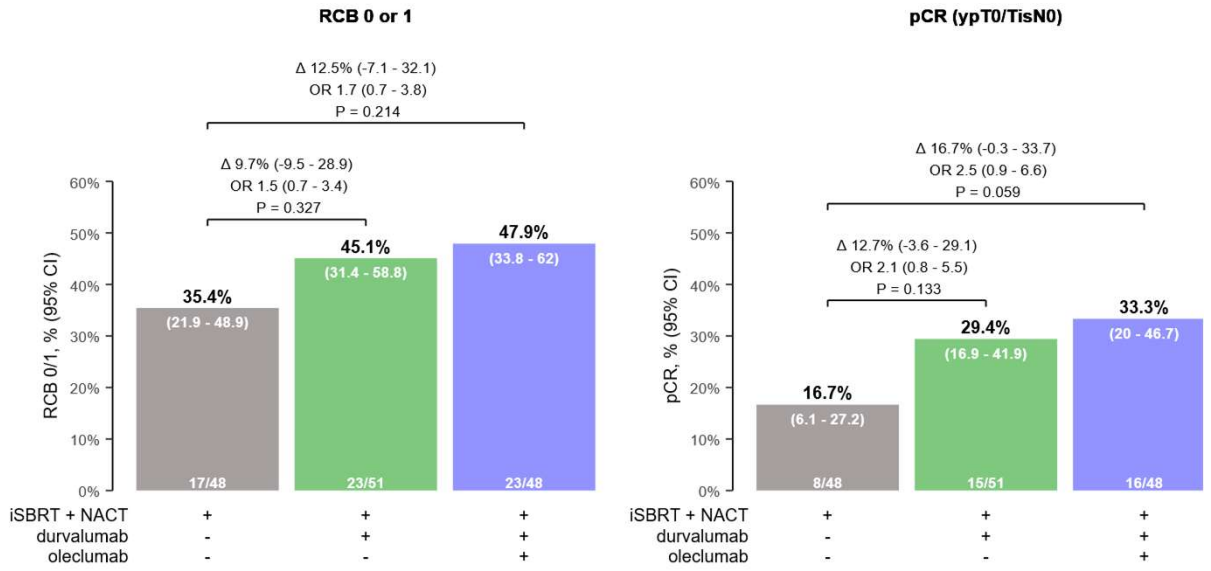


The Immune Cell score (IC score) is defined as the % of tumor area occupied by PD-L1 stained immune cells. RCB, residual cancer burden; RCB-0: no residual disease; RCB-1: minimal residual disease.

From Pre-Clinical Insights → Clinical Trial Design **Immunosuppression through the Adenosine Pathway**

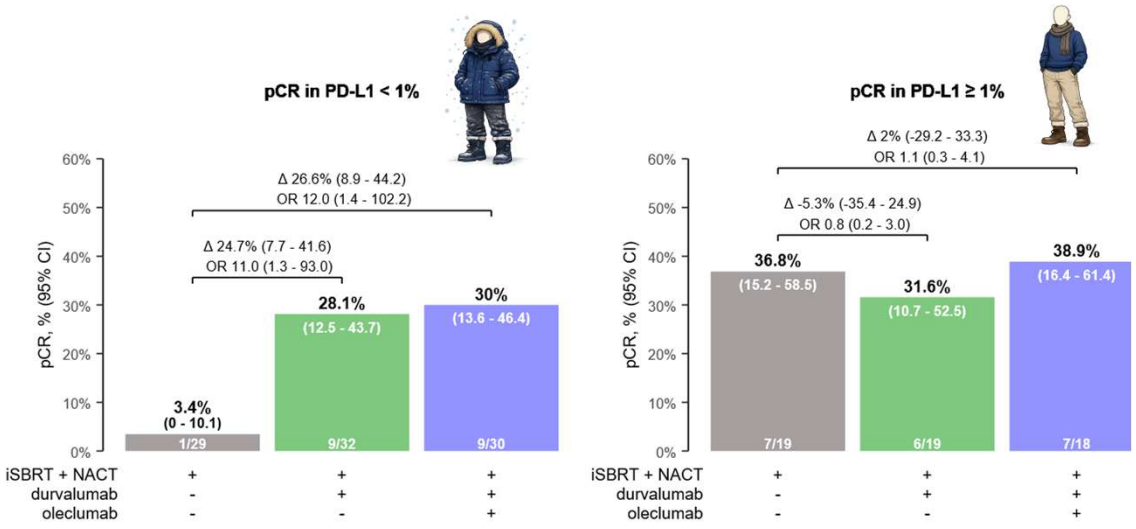


Neo-CheckRay Phase II trial – Primary Endpoint



De Caluwé *et al*. Nature Medecine 2026

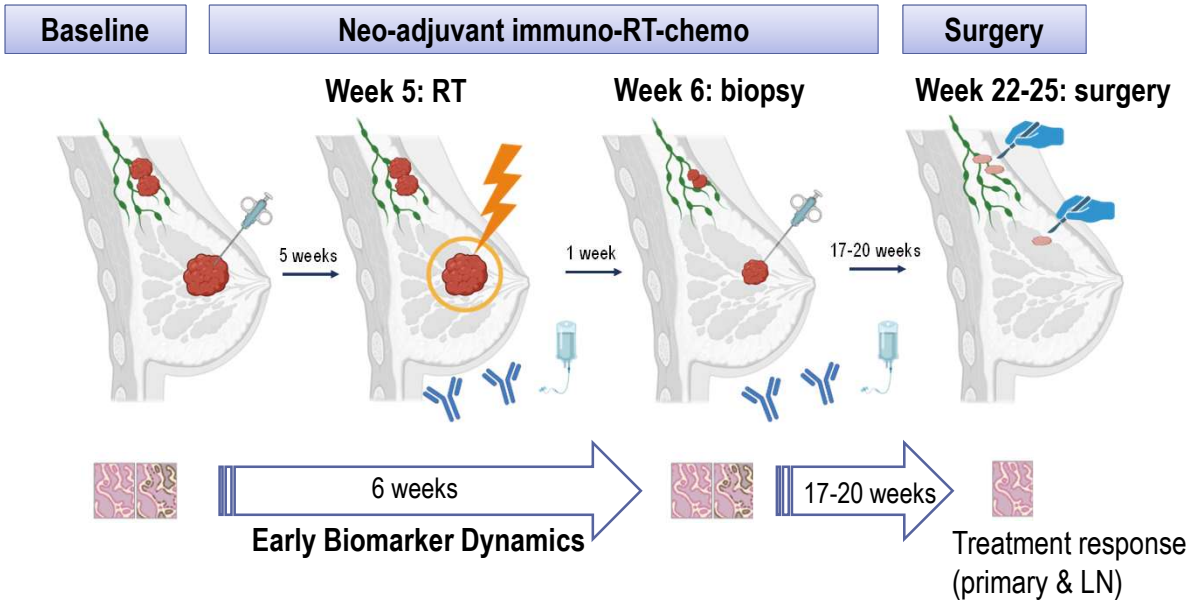
Neo-CheckRay Phase II trial – pCR according to PD-L1 (stratification factor – centrally assessed)



Results suggest 3x8 Gy converts PD-L1 negative responses to PD-L1 positive responses

De Caluwé *et al*. Nature Medecine 2026

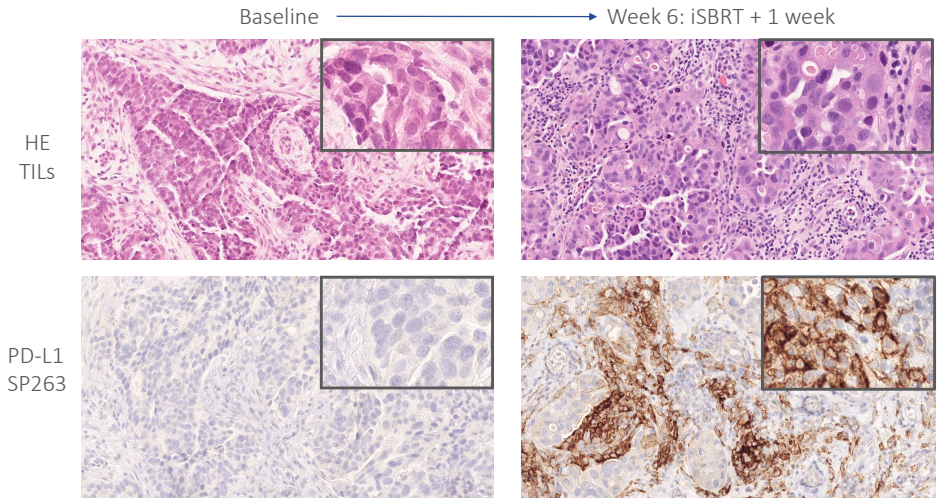
Early Biomarker Dynamics: Comparing Baseline to 1 week after iSBRT



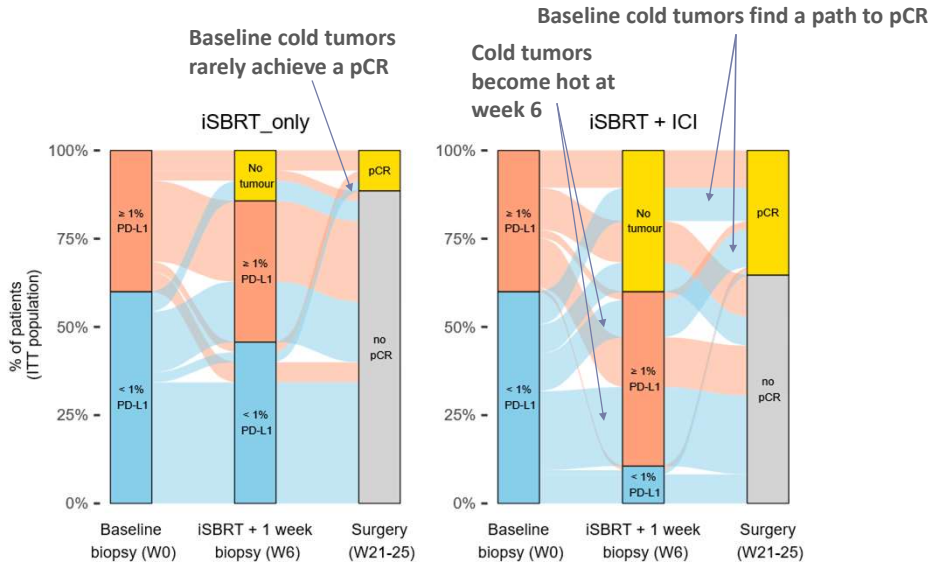
NEO-CHECKRAY TRIAL

Priming the immune response with iSBRT

Exploratory biomarker analyses



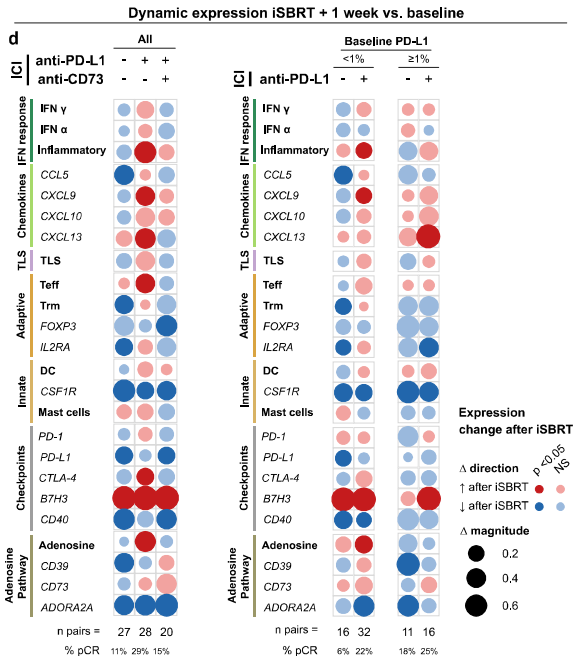
Early Biomarker Dynamics: Comparing Baseline to 1 week after iSBRT (n=147)



De Caluwé *et al*. Nature Medicine 2026

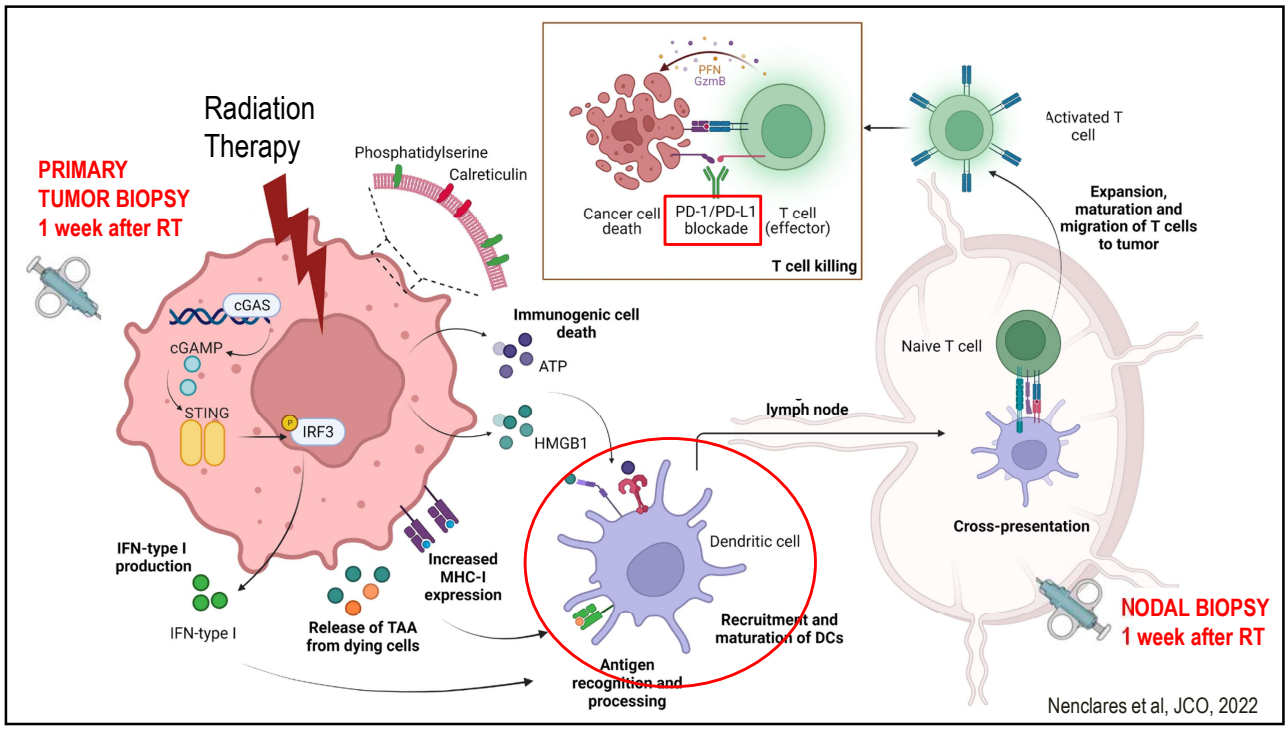
Early Biomarker Dynamics: Comparing Baseline to 1 week after iSBRT (n=147)

Treatment-induced changes in immune gene expression in 75 paired biopsies



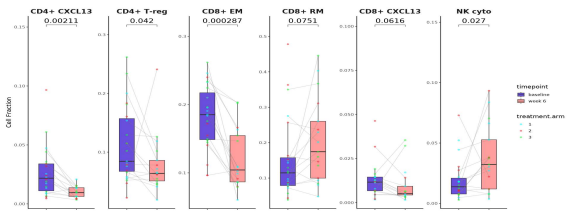
Activation of immune related features when RT is combined with ICI

De Caluwé *et al*. Nat Med 2026



DYNAMIC CHANGES
Baseline → 1 week after 3x8 Gy

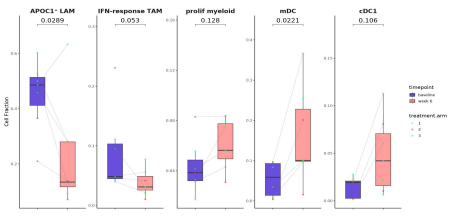
PRIMARY BREAST CANCER



Baseline → RT + 1 week

Contraction of CXCL13/TLS/Tfh programs

LYMPH NODE



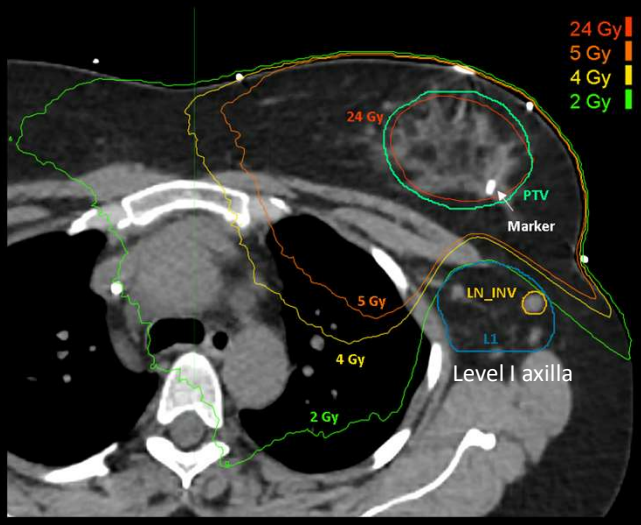
Baseline → RT + 1 week

Enrichment in mDC, cDC1 in LN

Redistribution of dendritic cells from the primary tumor to the lymph nodes
= suggesting a vaccine-like effect

Carausu et al, SABCS, 2025

Is sparing the tumor draining lymph nodes important?



How to consider the tumor draining lymph nodes?

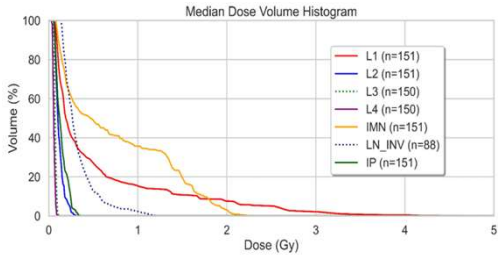
?

A target for RT?

An organ at risk that we should protect?

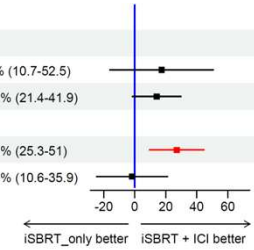
De Caluwé et al, Radiotherapy and Oncology, 2025

Neo-CheckRay Phase II trial: Radiation Therapy to the Tumor Draining Lymph Nodes



57% < 1 Gy to axilla 43% ≥ 1 Gy to axilla

iSBRT doses			
PTV D95%			
< 15 Gy	1/7; 14.3% (-11.6-40.2)	6/19; 31.6% (10.7-52.5)	17.3% (-16-50.6)
≥ 15 Gy	7/40; 17.5% (5.7-29.3)	25/79; 31.6% (21.4-41.9)	14.1% (-1.5-29.8)
Dose to axilla level 1			
< 1 Gy	3/27; 11.1% (-0.7-23)	21/55; 38.2% (25.3-51)	27.1% (9.6-44.5)
≥ 1 Gy	5/20; 25% (6-44)	10/43; 23.3% (10.6-35.9)	-1.7% (-24.5-21.1)



No pCR gain by ICI if > 1 Gy to the axilla

De Caluwé *et al*. Nat Med 2026

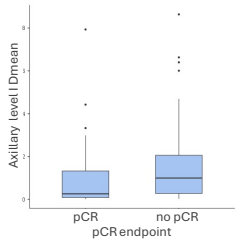
Incidental immune-related organ irradiation and pCR in Neo-CheckRay

Exploratory analysis – ICI-treated patients (n=98)

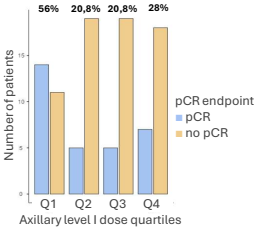
Justin Nguyen, MD
Institut Jules Bordet



AXILLARY LEVEL I



Median dose
0,261 Gy vs 0,998 Gy
p=0,039



Q1 (<0,125Gy): 14/25 pCR = 56.0%
Q2–Q4: 17/73 pCR = 23.3%
p = 0,002

Axillary level I : Overall quartile comparison : **p = 0.022**

Under analysis:
- Thymic dose
- Impact on thymic health

(Submission to ESTRO 2027)

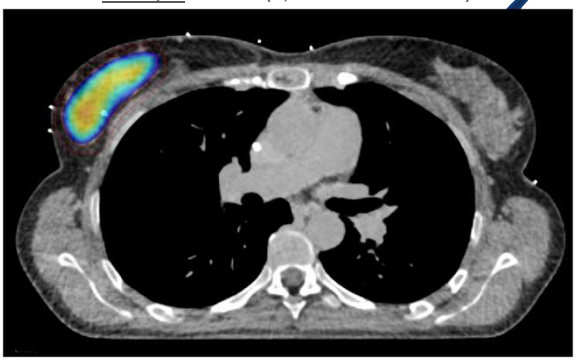
Unpublished data

Breast Cosmesis



Zineb Belbaraka, MD
Institut Jules Bordet

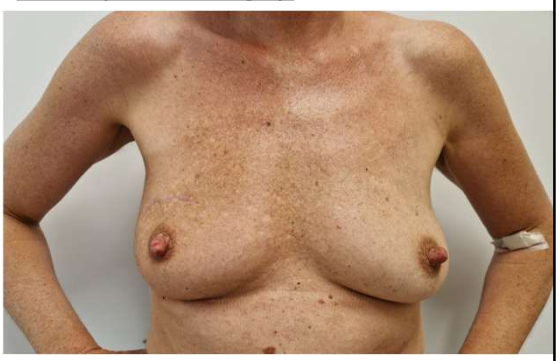
Example: cT3N0 (6,5 cm luminal B BC)



3x8Gy pre-op SBRT + immuno-chemo
(Neo-CheckRay arm 2)

Excellent clinical response
↓
Breast conserving surgery
↓
Pathological complete response

Result 3 years after surgery:



Abstact will be submitted to ESTRO 2027

What about TNBC? ⟶ P-RAD trial

H.U.B Hôpital Universitaire de Bruxelles / Academisch Ziekenhuis Brussel | Clinical Trials Center

2026 ASCO ANNUAL MEETING

Primary Results from the Triple Negative Cohort of TBCRC-053 (P-RAD): A Randomized Trial of No, Low, or High Dose Preoperative RADiation with Pembrolizumab and Chemotherapy in Node-Positive Breast Cancer

A.Y. Ho*, L.M. Spring*, F. Gharibpoor, R.C. Blitzblau, J. P. Leone, Y. Abdou, C. Santa-Maria, J. D. Anampa, A. J. Khan, J. Fox, S. Dent, J. L. Wright, L. E. Warren, E.A. Mittendorf, E.S. Hwang, L.A. Carey, S. Patil, B.C. Calhoun, L. Norton, G.P. Gupta

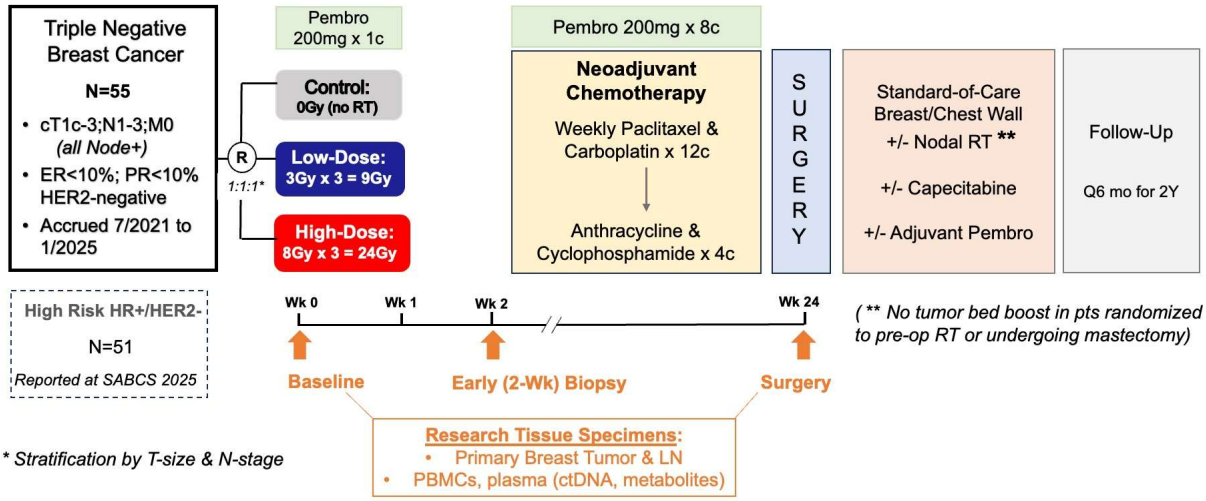
Presenter: Alice Y. Ho, M.D.
Houston Methodist Academic Institute

tbcrc Translational Breast Cancer Research Consortium

BCRF Breast Cancer Research Foundation

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TBCRC-053: P-RAD Multicenter Randomized Phase II Clinical Trial



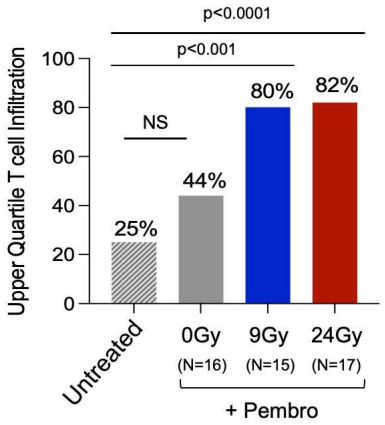
(** *No tumor bed boost in pts randomized to pre-op RT or undergoing mastectomy)*

* *Stratification by T-size & N-stage*

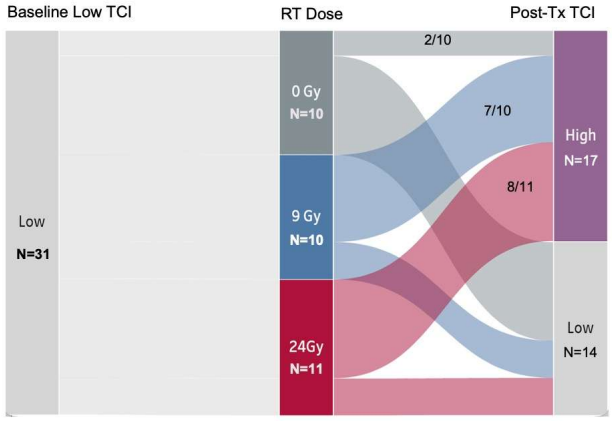
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Pembro + RT (both 9Gy and 24Gy) Significantly Increases TCI

Upper Quartile TCI by RT Dose



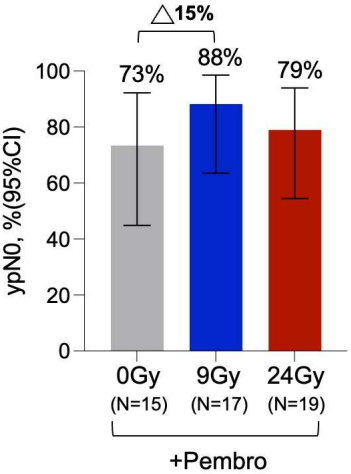
RT converts 71.4% of "Low TCI" tumors to "High TCI"



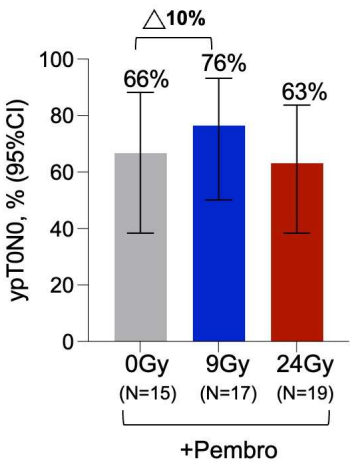
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ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Favorable Surgical Outcomes in RT Arms

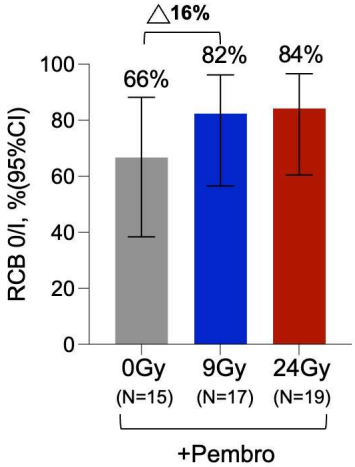
ypN0 (Co-Primary endpoint)



pCR (Secondary endpoint)



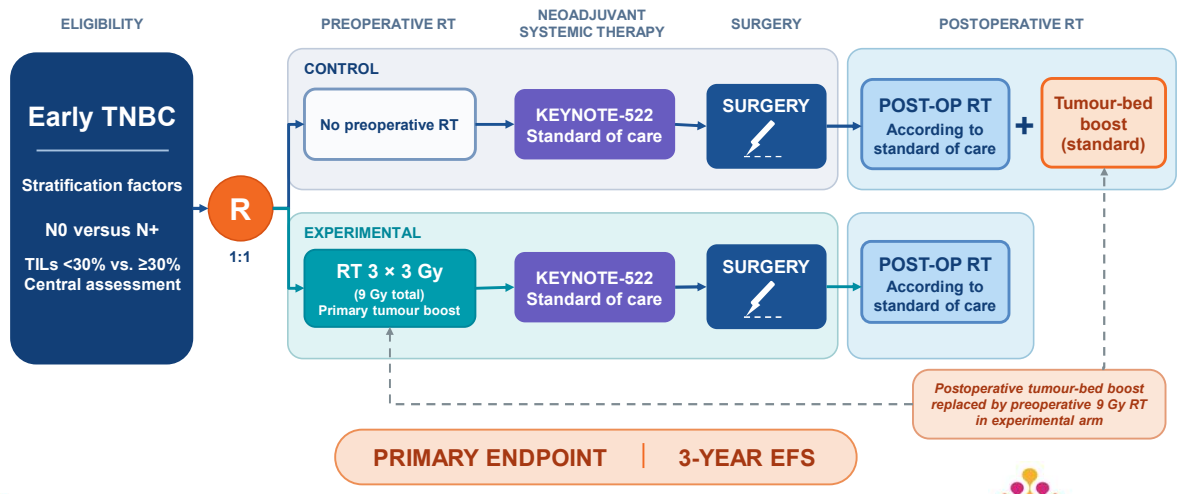
RCB 0/1 (Secondary endpoint)



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SCINTILLA - TNBC - Phase 3 Trial Proposal – Pragmatic & Academic

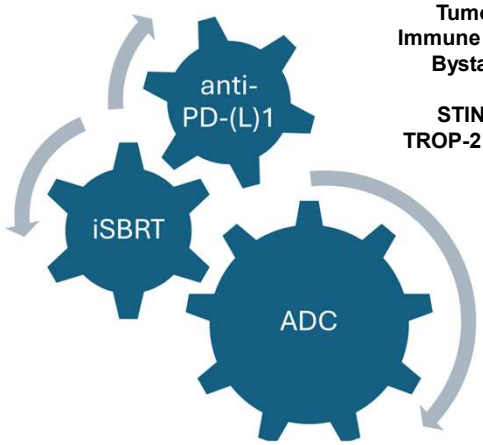
Preoperative immune-modulated RT added to KEYNOTE-522



EORTC
The future of cancer therapy

INSTITUT JULES BORDET INSTITUUT

Combining RT, ADC and anti-PD-(L)1 in early breast cancer, in the neo-adjuvant setting



Tumor antigens ↑
Immune cell infiltration ↑
Bystander effect ↑
PD-L1 ↑
STING pathway ↑
TROP-2 target density ↑



International multidisciplinary consensus on the integration of radiotherapy with new systemic treatments for breast cancer: European Society for Radiotherapy and Oncology (ESTRO)-endorsed recommendations

Icro Meattini, Carlotta Becherini, Saverio Caini, Charlotte E Coles, Javier Cortes, Giuseppe Curigliano, Evandro de Azambuja, Clare M Isacke, Nadia Harbeck, Orit Kaidar-Person, Elisabetta Marangoni, Birgitte V Offersen, Hope S Rugo, Viola Salvestrini, Luca Visani, Andrea Morandi, Matteo Lambertini, Philip Poortmans, Lorenzo Livi*, on behalf of the Consensus Panellist Group†*

Lancet Oncolog, 2024

Practical Overview

Agent	Adjuvant locoregional breast RT	Risk	Other indications	Risk
Anti-HER2 mAbs	Continue; minimize heart/LAD dose		Less data outside breast; adapt for esophagus/H&N/abdomen	
T-DM1 / ADCs	T-DM1 can be considered; newer ADCs in cohorts/trials		Avoid T-DM1 with WBRT/SRS; caution T-DXd lung/ILD	
CDK4/6 inhibitors	Trial/prospective cohort or pause; no robust adjuvant concurrent data		Major adaptation; avoid high-dose thorax, H&N, abdomen/pelvis	
Anti-PD-(L)1	Can be considered; monitor dermatitis/pneumonitis		Can be offered even with ultra-hypofractionation, but watch inflammation	
PARP inhibitors	Prefer sequential/trial; OlympiA used RT before olaparib		Do not offer advanced setting outside trials; low doses radiosensitize	
Capecitabine	Selective use; skin/mucosa and nodal fields drive toxicity		Avoid large mucosal/GI or marrow fields if possible	
Anti-VEGF	Usually avoid concurrent; wound/skin healing concern		Avoid; necrosis/bleeding/fistula risk, especially bowel/CNS/re-RT	

Meattini et al., Lancet Oncol 2024; van Aken et al., Radiother Oncol 2026

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Conclusion - Immunotherapy & RT in Breast Cancer

~~« One size fits all »~~

- Tailor breast radiation therapy to:
  - Breast Cancer Immunologic Subtypes
  - Response to Systemic Therapy + Immunotherapy

- Interaction between RT and IO can enhance systemic effects
  - Combinations of conventional RT and conventional immunotherapy are not always successful
  - Adapting RT approaches to immunotherapy (lymph node sparing, etc) could be a solution, but remains to be valided in phase III trials (?)
  - Outcomes of future clinical trials are likely impacted by the interaction between tumour and non-tumour cells in the TM

Thanks to the teams

Together Everyone Achieves More

INSTITUT JULES BORDET INSTITUUT

Patients & families

NEO-CHECKRAY CTC teams

PI and Collaborators at participating sites

Central Pathology Lab

Statistics team

Radiation Therapy
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Christophe Vandekerkhove
Zineb Belbaraka
Justin Nguyen



The Clinical Trial Support team



The Breast Cancer Translational research Laboratory (BCTL) team

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& co

& X. Catteau, R. Salgado, D. Larsimont, **M. Piccart**

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ULB BRIGHT CORE VUB

Sponsors

Support from AstraZeneca & Agendia for the trials

Fondation contre le cancer

BCRF Breast Cancer Research Foundation

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EORTC The future of cancer therapy

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