

Best of SABCS 2022



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COUNTRY
DATE

Innovations in Radiation Therapy

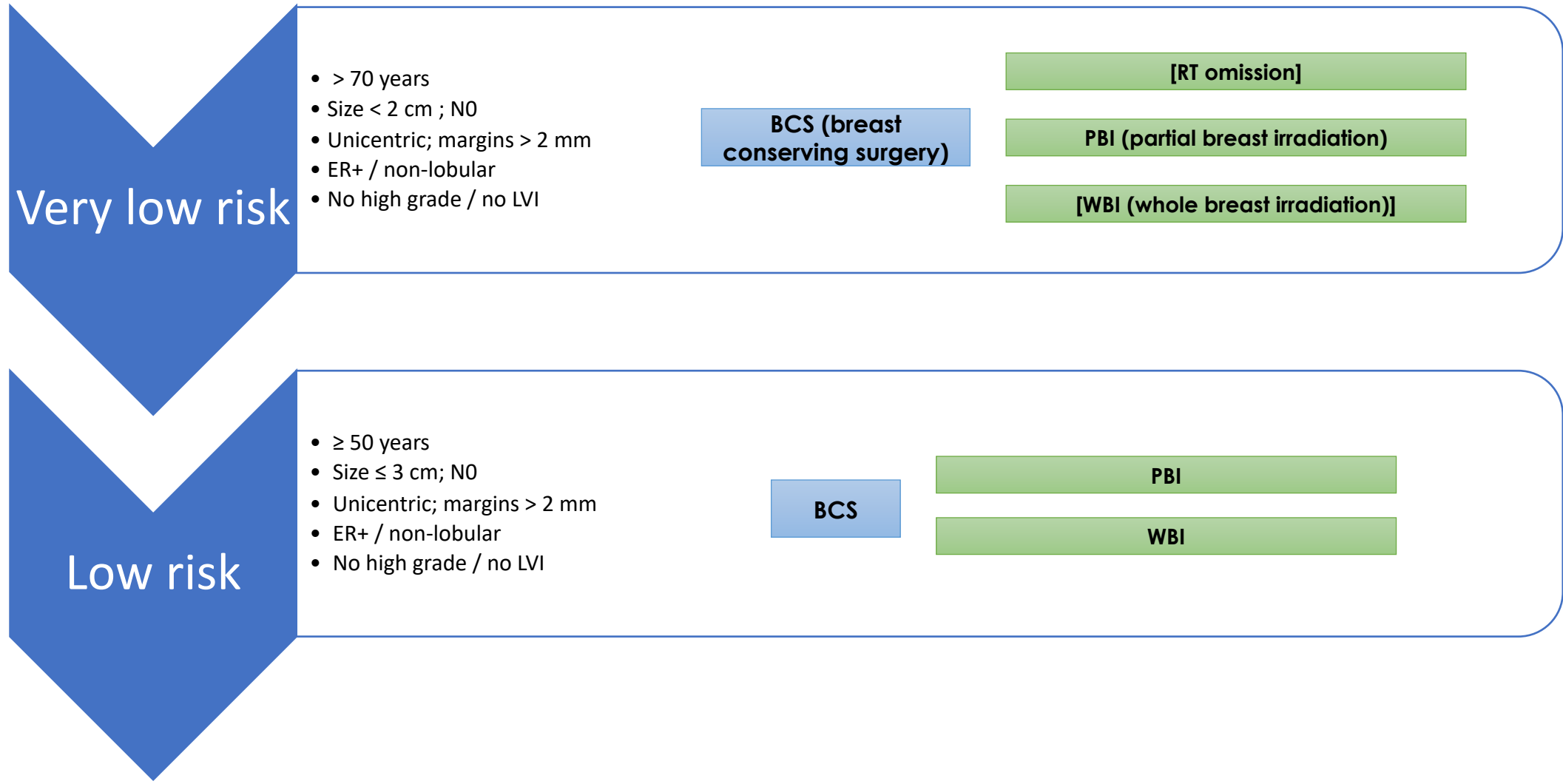
Dr. Alex De Caluwé

Jules Bordet Institute – Brussels
AZ St Maarten - Mechelen

Disclosures

- AstraZeneca (institutional grant to Institut Jules Bordet)

What's new for low risk breast cancer?



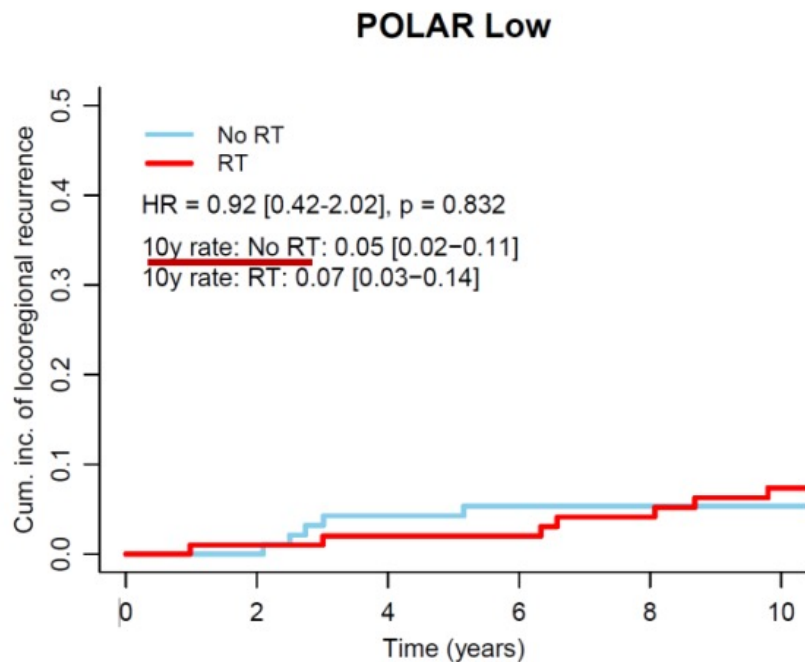
Genomic profile to guide RT omission in low risk?

Included patients: **very low to low risk**

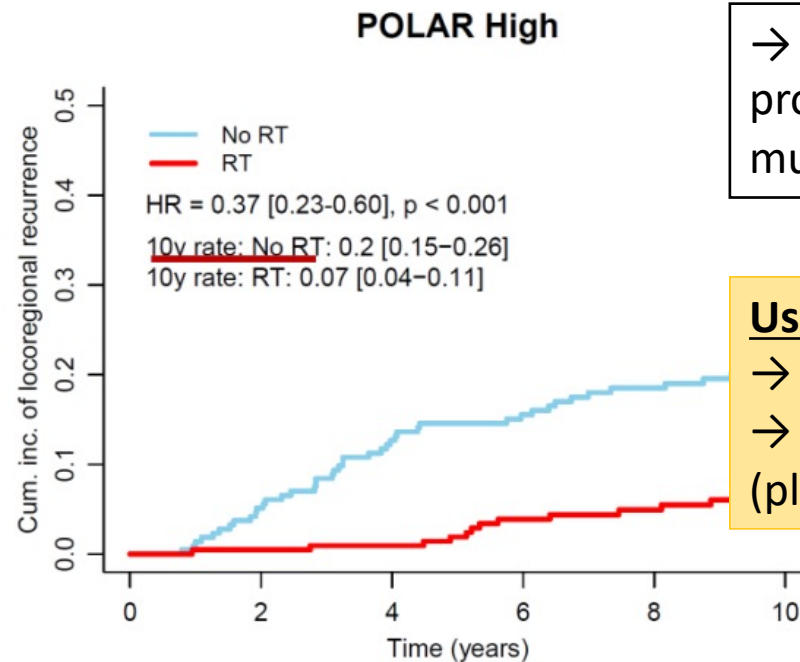
→ ER+/HER2- ; stage I-II; cN0; breast conserving surgery; no indication for systemic treatment

'POLAR' gene signature - 'profile for the omission of local adjuvant radiation'; 16-gene signature

RETROSPECTIVE validation in 3 cohorts (Sweden; Canada; Scotland)



	0	2	4	6	8	10
No RT	94	83	64			
RT	100	91	73			



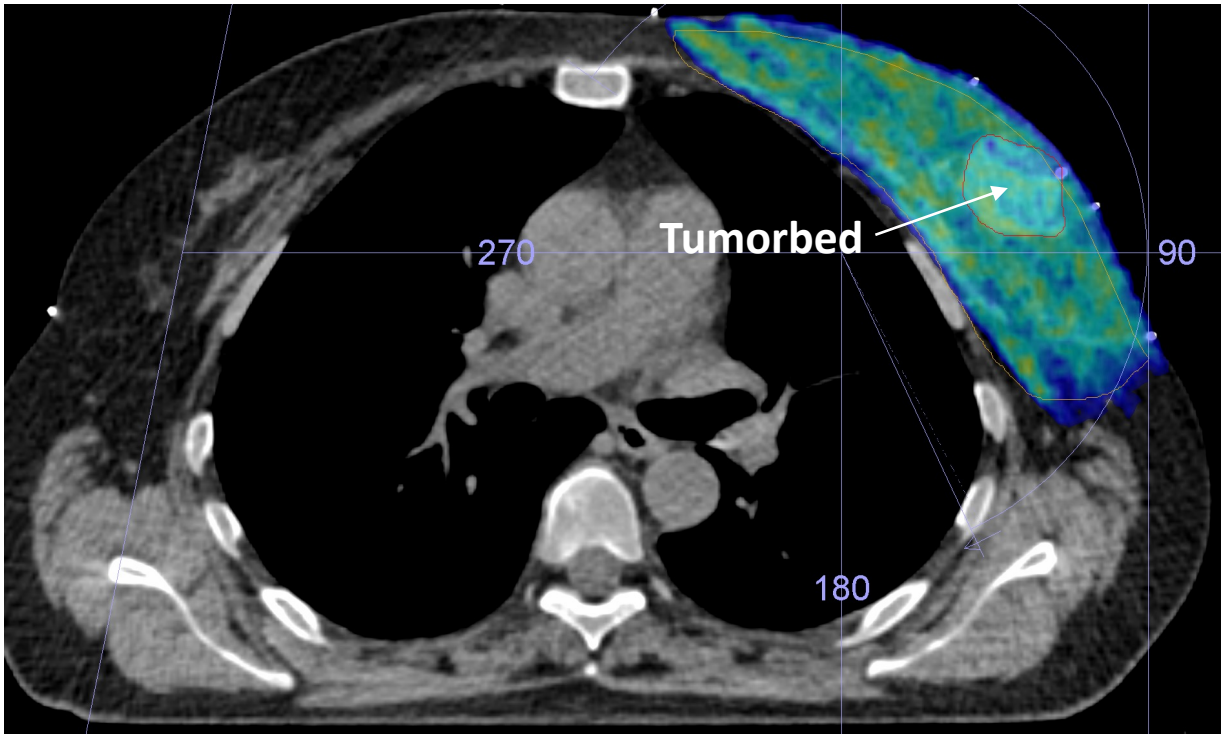
	0	2	4	6	8	10
No RT	215	164	120			
RT	214	177	119			

→ POLAR continuous score was prognostic and predictive in multivariate analysis for RT benefit

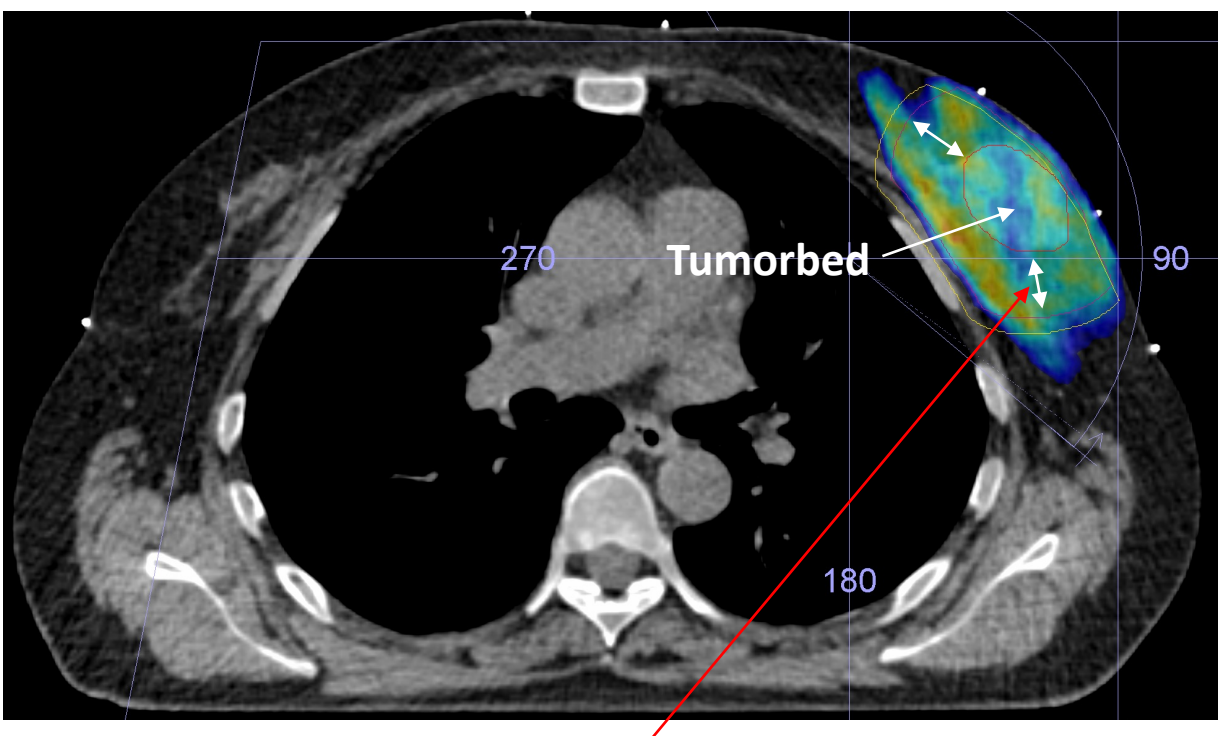
Usable in clinical practice?
→ NOT YET
→ **Prospective** validation necessary (planned)

What's new for PBI (partial breast irradiation)?

WBI (whole breast irradiation)



PBI (partial breast irradiation)



Margin to account for
microscopic disease
(CTV margin)

B-39 / RAPID / IMPORT-LOW / FLORENCE

DCIS / Invasive
T < 4.0 cm
Neg Margins
0-3 + LNs

DCIS / Invasive
T < 3.0 cm
Neg Margins
NO

Invasive
T < 4.0 cm
Neg Margins
0-3 + LNs

DCIS / Invasive
T < 2.5 cm
5mm Margins
0-3 + LNs

RANDOMIZED

Whole Breast Irradiation

50 Gy/50.4 Gy (25-28 fx) optional boost
42.5 Gy (16 fx) optional boost
40 Gy (15 fx) no boost
50 Gy (25 fx) + 10Gy boost

Partial Breast Irradiation

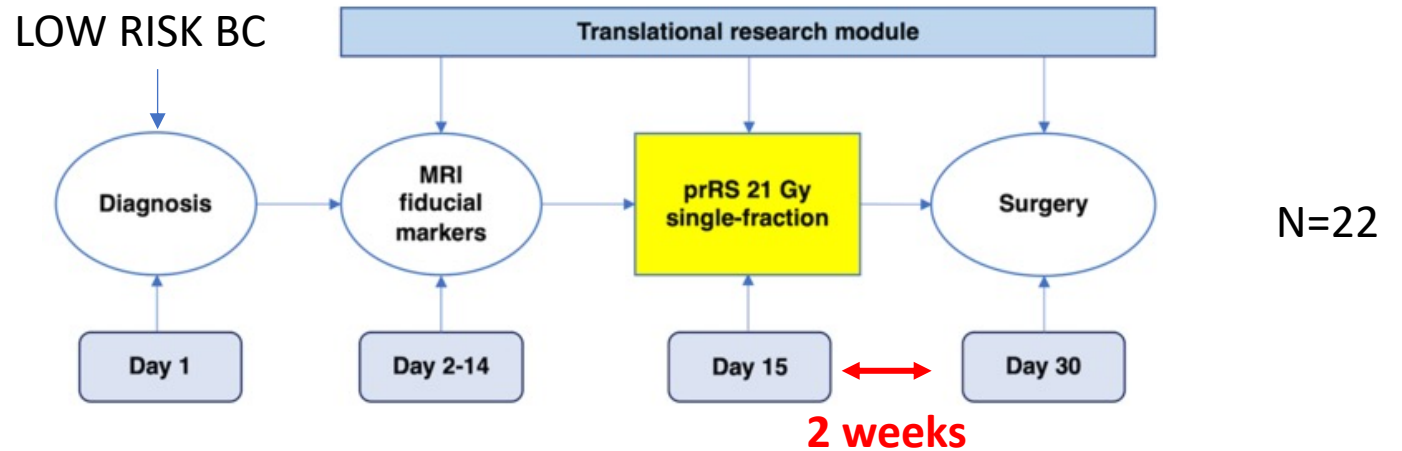
34 Gy (10 BID) brachy / 38.5 Gy (10 BID) ExB
38.5 Gy (10 BID)
40 Gy (15 fx)
30 Gy (5 fx QOD)

Results: 1) non-inferiority of partial breast on local control
2) equivalent or improved late normal-tissue effects

Novel PBI approaches presented at SABCS 2022



ROCK phase II trial



Technique:

- CyberKnife
- Fiducials (3-5)

Toxicity:

- Acute:
 - 1 G2 (breast edema)
 - **No G3 or G4**
- Late
 - 1 G2 (induration)
 - **14% poor cosmesis**
 - **No G3 or G4**

Local control:

- 22 patients treated
- **2/22 pCR (9%)**
- **3/22 positive axillary nodes at surgery**
- **3/22 positive resection margins**
- **2/22 patients received post-operative WBRT**

Conclusion/limitation:

- Feasible technique with overall favorable safety profile
- Limited follow-up
- Low number of patients
- More details needed on target/margin delineation

Longer time between SBRT and surgery = more pathologic complete response

Trial – Dose	Time between RT and surgery	Pathological complete response rate (%)
ROCK 1x21Gy	< 14 days	9%
ABLATIVE 1x20Gy	6 months	33%
ABLATIVE 1x20Gy	8 months	48%

Novel PBI approaches presented at SABCS 2022

Unresectable or inoperable patients

PBI
(partial breast irradiation)

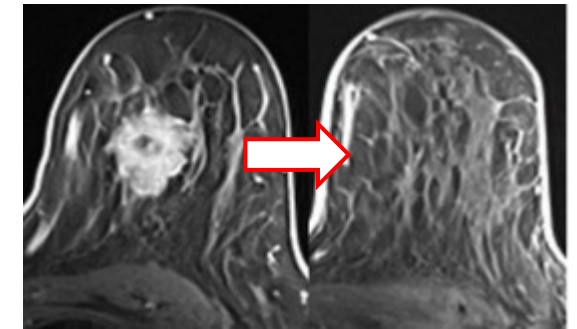
~~Surgery~~



Unresectable or medical inoperable patients



SBRT
5x7 Gy / 5x8 Gy



Palhares, SABCS, 2022

Characteristics per treatment course	N = 61
Reasons for not undergoing surgery	
Unresectable tumour	10%
Patient refusal	18%
Medically inoperability	34%
Metastatic disease	38%

Conclusion

- **2-year local control 88.6%**
- 16% G3+ acute AE; 4% G4 (skin)
- Less toxicity with VMAT/IMRT in comparison to 3D
- Good option for non-surgical candidates

Limitation:

- Retrospective design (phase I underway)
- Heterogeneous dose (between 35Gy/5x and 40Gy/5x)
- More details needed on target/margin delineation

PBI: what to do in clinical practice today?

European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice consensus recommendations on patient selection and dose and fractionation for external beam radiotherapy in early breast cancer



Icro Meattini, Carlotta Becherini, Liesbeth Boersma, Orit Kaidar-Person, Gustavo Nader Marta, Angel Montero, Birgitte Vrou Offeresen, Marianne C Aznar, Claus Belka, Adrian Murray Brunt, Samantha Dicunzio, Pierfrancesco Franco, Mechthild Krause, Mairead MacKenzie, Tanja Marinko, Livia Marrazzo, Ivica Ratoso, Astrid Scholten, Elżbieta Senkus, Hilary Stobart, Philip Poortmans, Charlotte E Coles**

Meatinni, Lancet Oncolog, 2022

PBI dose guidelines:

- 40 Gy /15x
- 26-30 Gy /5x
- **Do not offer twice a day schemes similar to RAPID**

→ 26 Gy in 5 fractions

Moderate risk

- < 50 years
- Size > 3 cm; N0
- High grade tumors / LVI
- Close or positive margins



Surgery



WBI

Sequential tumorbed boost

SIB (simultaneous integrated boost)

High risk

- N+



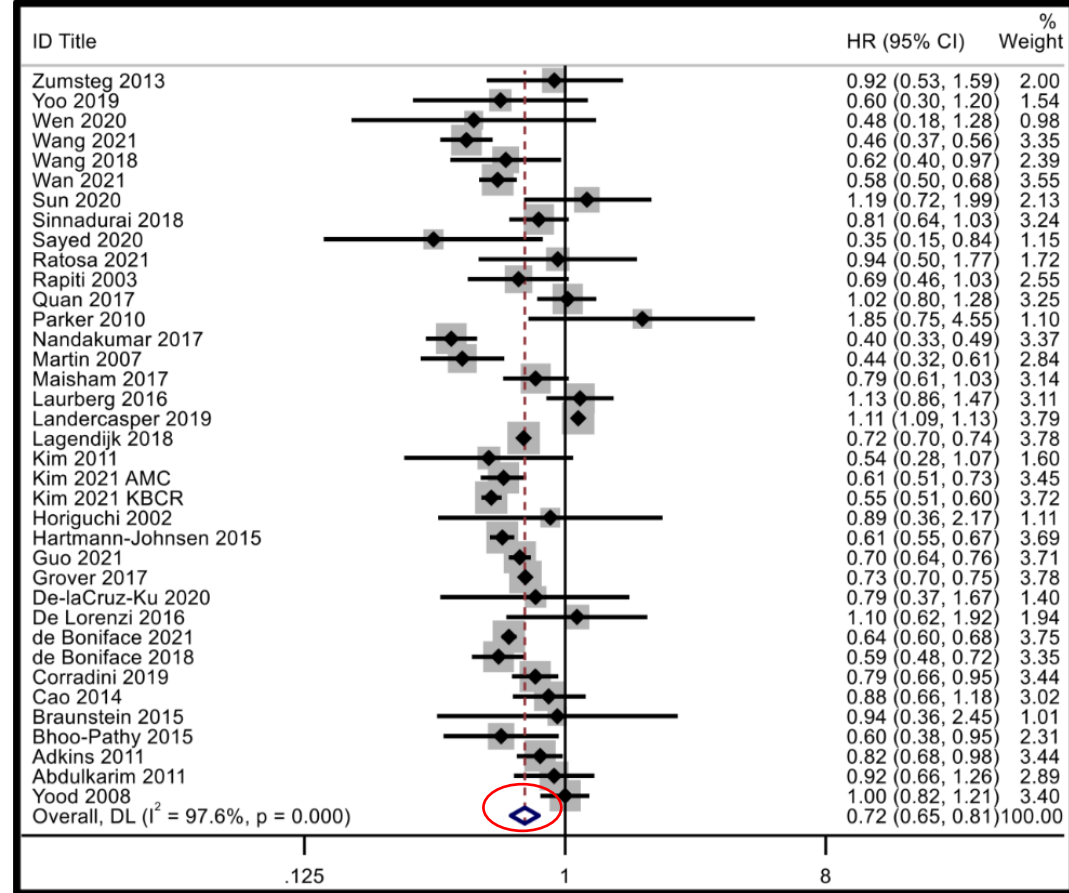
Surgery



**WBI + SIB + locoregional RT levels 1-4
+/- internal mammary nodes**

Is mastectomy equivalent to BCS + RT?

Meta-analysis of contemporary trials Overall Survival

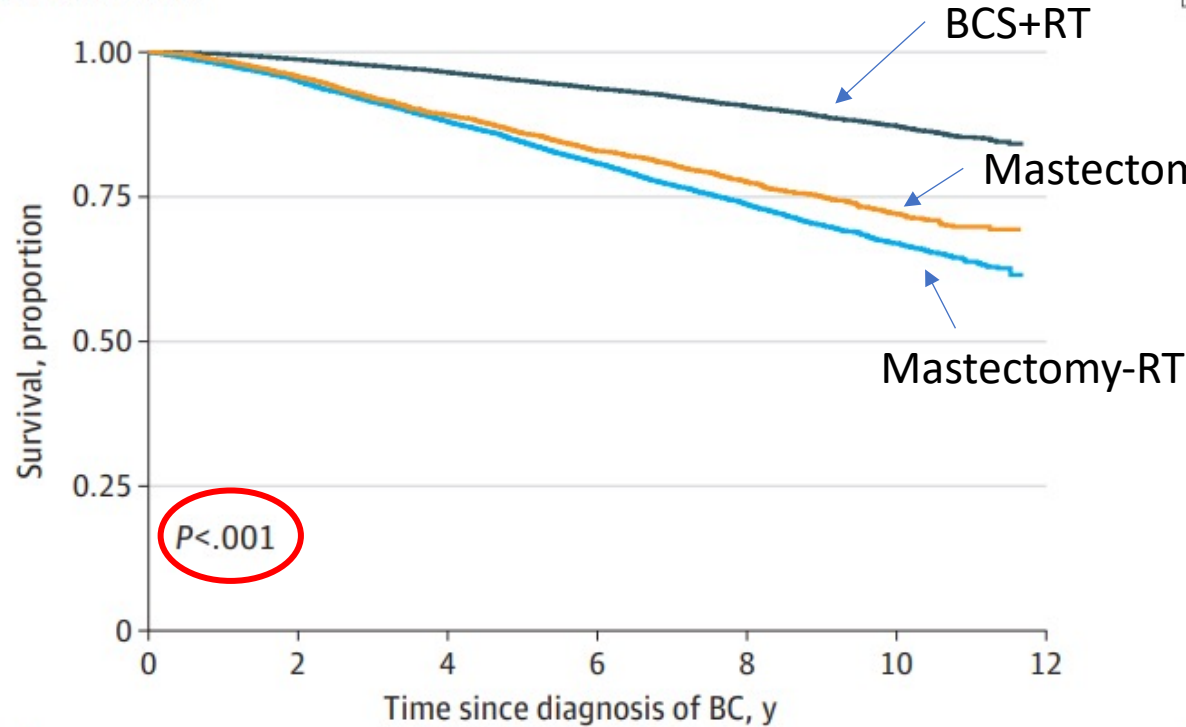


Favors BCS + RT ← → Favors mastectomy

Is mastectomy equivalent to BCS + RT?

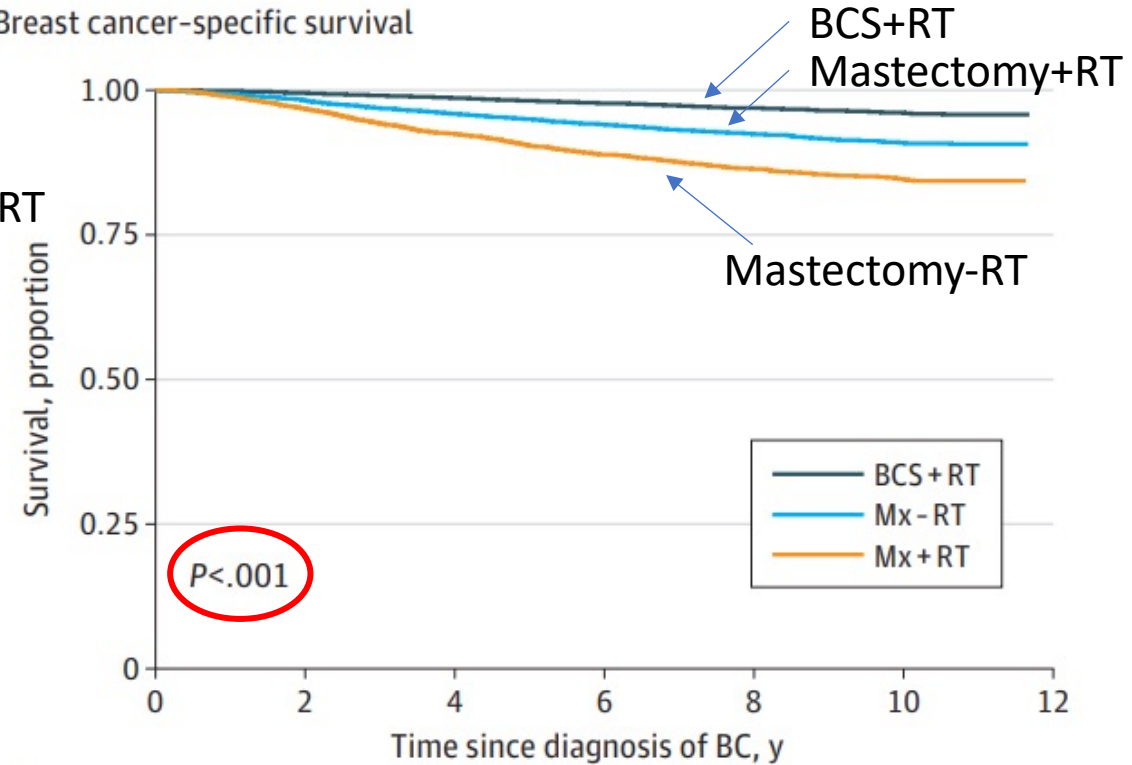
Swedish Cohort of 48.986 patients

A Overall survival



No. at risk	0	2	4	6	8	10	12
BCS+RT	29367	19449	14449	10449	7449	5449	3695
Mx-RT	12413	7982	5982	4481	3481	2481	1528
Mx+RT	7206	4481	3481	2481	1481	981	811

B Breast cancer-specific survival

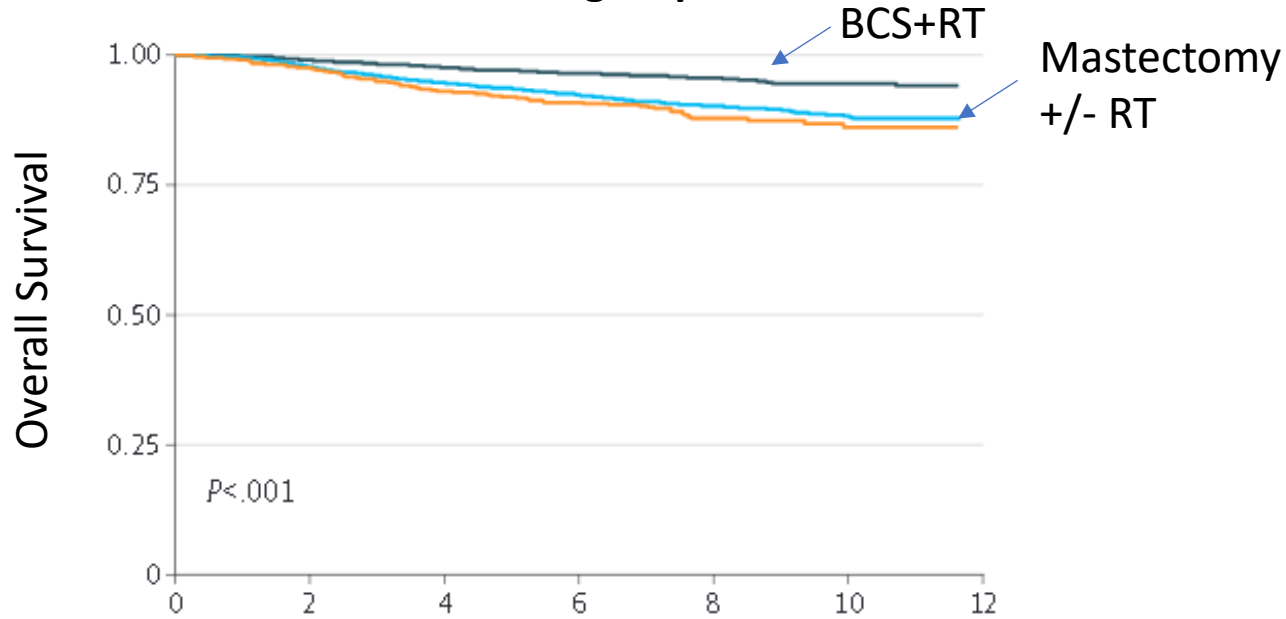


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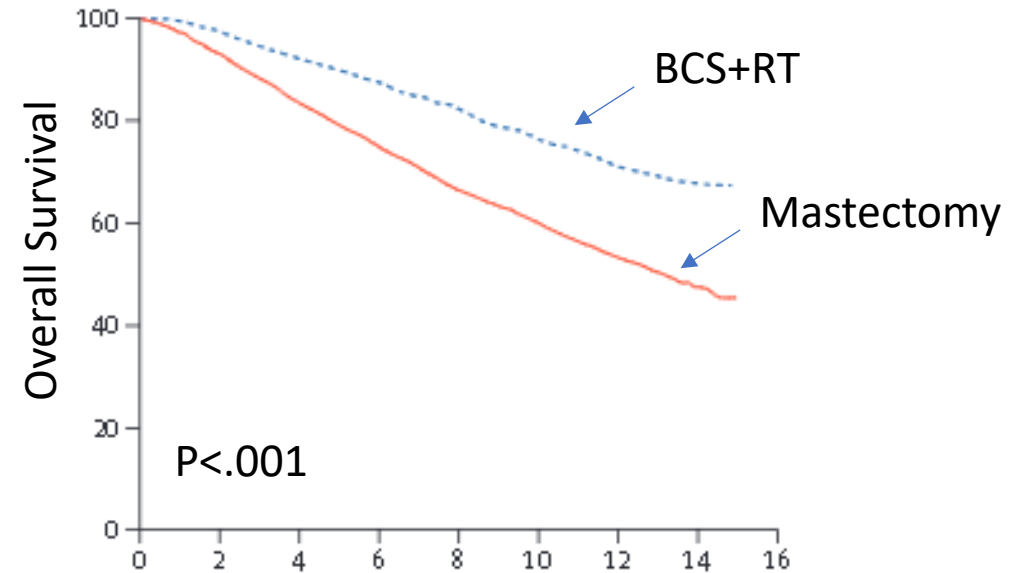
Is mastectomy equivalent to BCS + RT?

T2N0 subgroup

Swedish Cohort of 48.986 patients
T2N0 subgroup



Dutch Cohort of 37.207 patients
T2N0 subgroup



After adjustment for confounders:
(age, stage, comorbidities, socio-economic factors)
OS and BCSS benefit of BCS+RT:
HR = 0,57 (CI 0,52-0,60) and HR = 0,60 (CI 0,52-0,68)

After adjustment for confounders:
(age, stage, comorbidities)
OS and relative survival benefit of BCS+RT at 10 years:
HR = 0,81 (CI 0,78-0,85)

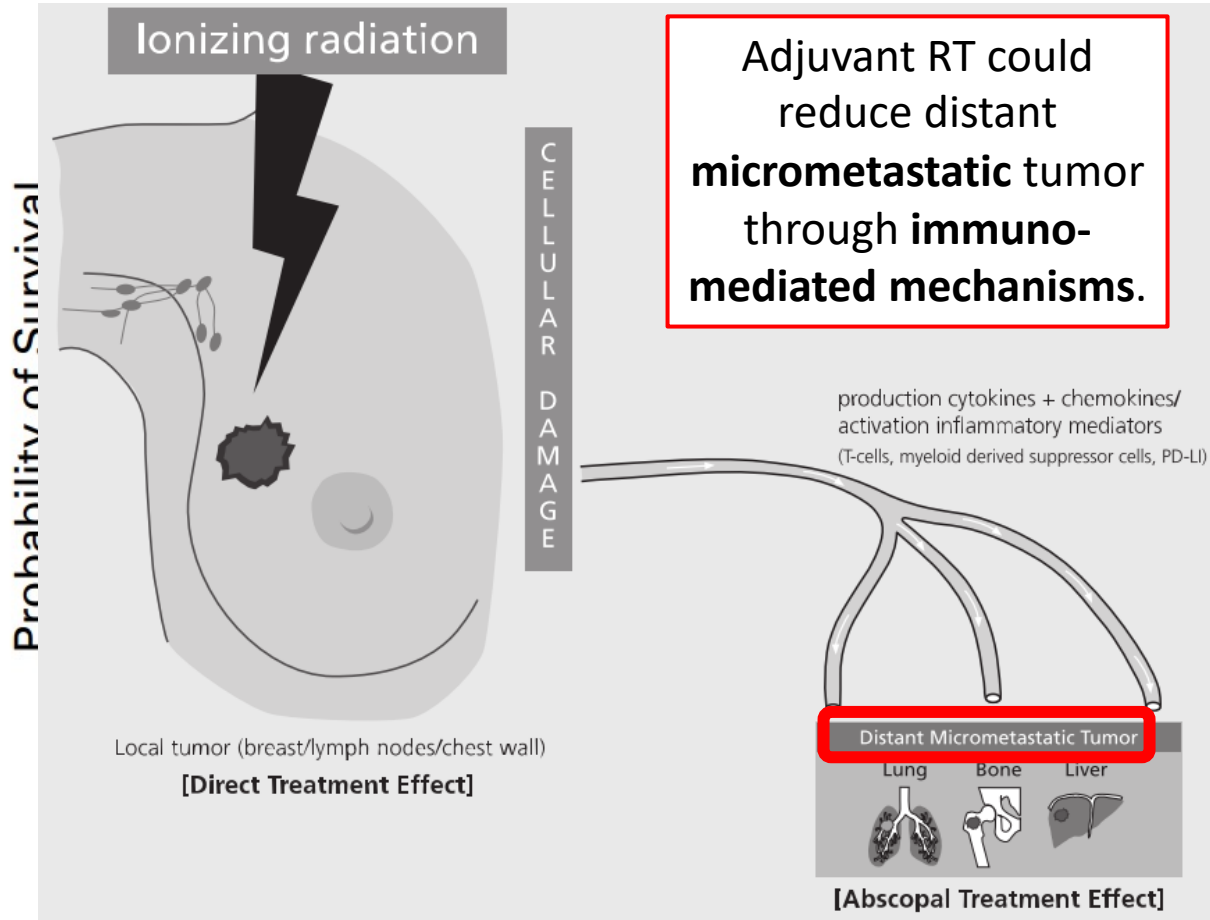
**Contemporary population-based data indicate mastectomy is inferior to
BCS+RT for OS and BCSS**

“We wonder if a paradox exists—patients might pursue mastectomy out of the mistaken belief that they are getting the most aggressive (often confounded with the best) treatment, when in fact the opposite might be true.”

Royce et al, Lancet Oncolog, 2020

BCS+RT is a powerful combination

Contemporary population-based data indicate mastectomy is inferior to BCS+RT for OS and BCSS *WHY IS THIS?*



TODAY = dramatic improvements in :

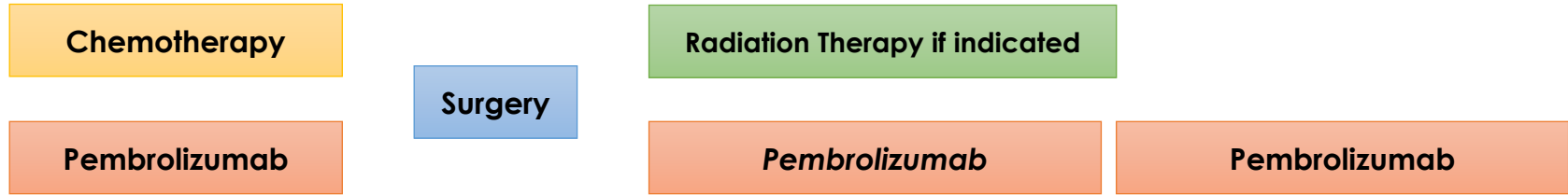
- Imaging (MRI!)
- Pathology
- Breast conserving surgery
- Radiation therapy (cardiac and lung sparing!)
- Systemic treatments

However, also to be considered:

- Immuno-mediated mechanisms of RT
- Underestimated synergy between novel systemic treatments - ET - RT

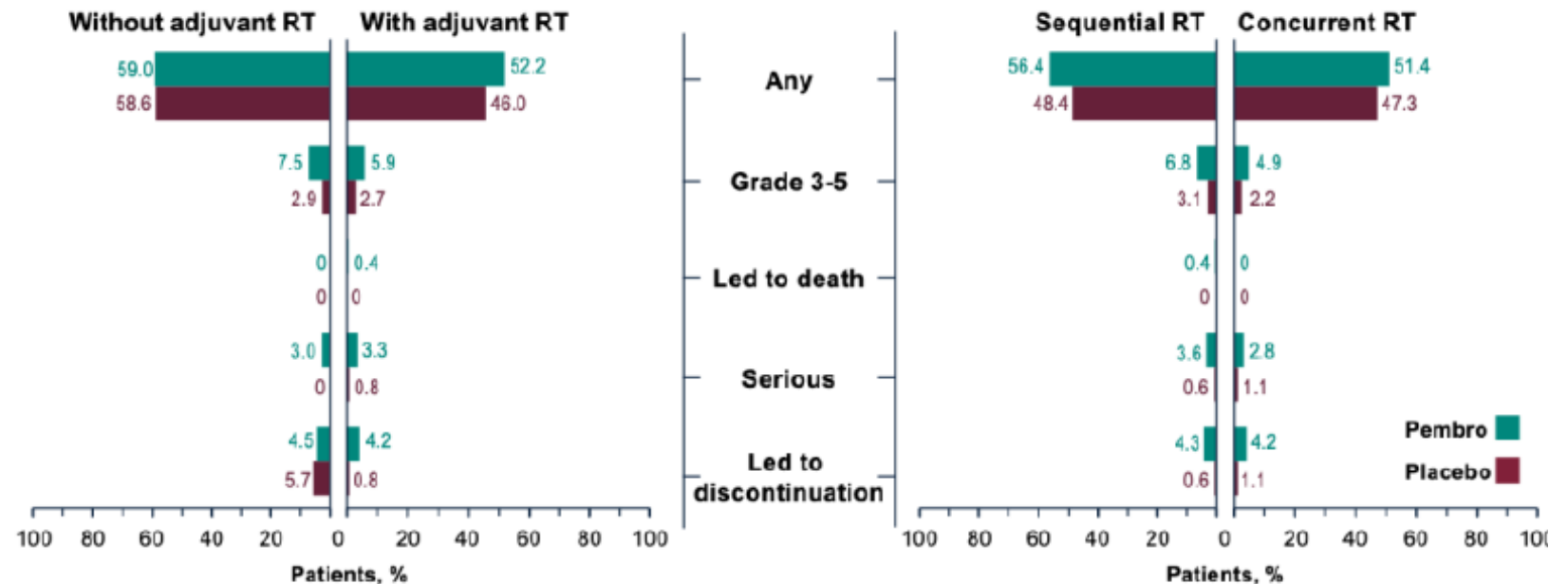
How to optimise the immune-mediated RT effect?

Keynote 522
TNBC



KEYNOTE 522 subgroup analysis:

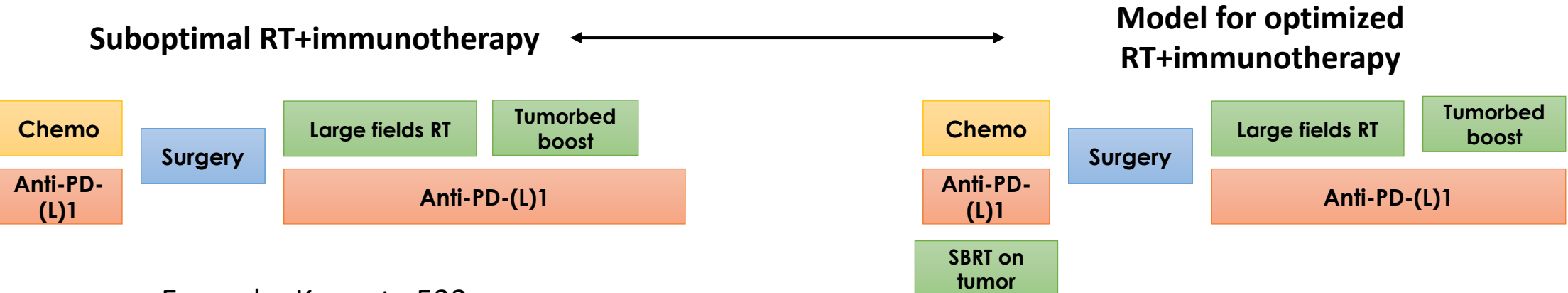
Safe to give adjuvant RT concomitantly with pembro ✓



Is this the best way to combine RT and immunotherapy?

RT – immuno combi: lessons from (pre-)clinical data

- Better RT + immunotherapy combinations:**
- Neo-adjuvant > adjuvant > metastatic
 - Give RT concomitantly (or right before immuno)
 - Use 3-5 fractions
 - Dose per fraction < 9 Gy
 - RT to primary tumor only
 - Avoid to give radiation to lymph nodes



Example: Keynote 522

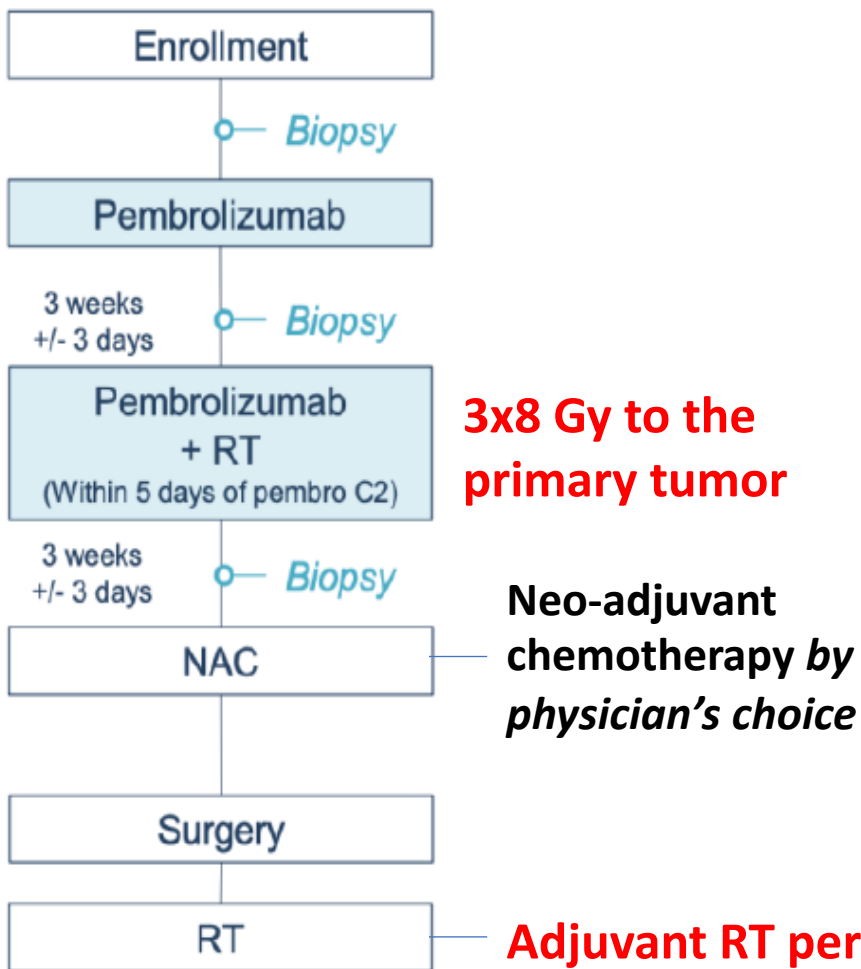
! avoid to treat nodal regions !



The PEARL Trial: Pre-operative PEmbrolizumAb with Radiation Therapy in EarLy Stage Triple Negative Breast Cancer

H.L. McArthur^{1,2}, S. Shiao², S. Karlan², R. Basho², F. Amersi², M. Burnison², A. Mirhadi², A. Chung², C. Chung³, C. Dang², H. Richardson⁴, A. Giuliano², N. Kapoor², B. Larkin², H. Godinez¹, N. Habibi², S. Dunn⁵, S. Knott², C. Martin², P. McAndrew², M. Mita², D. Park², C. Abaya², J. Chen⁵, A. Ly⁵, V. Bossuyt⁵, A.Y. Ho^{2,5}

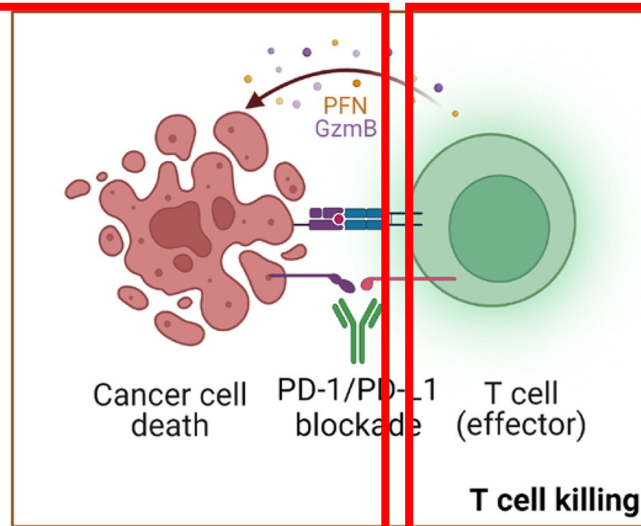
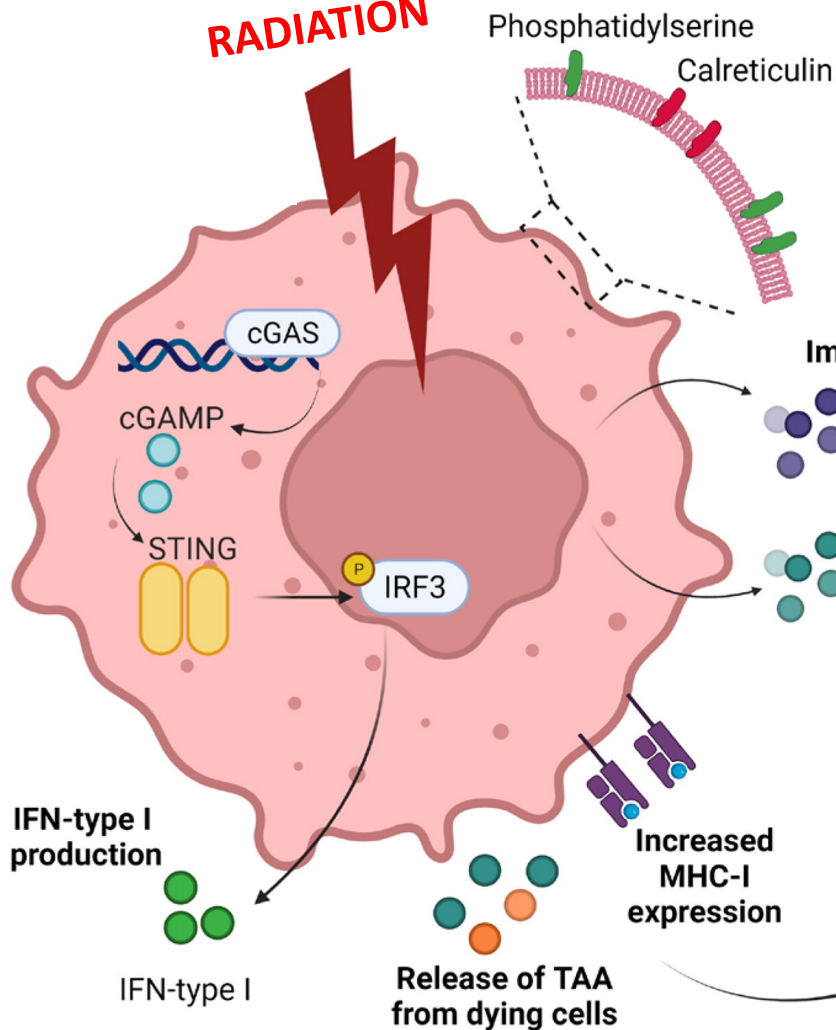
¹UT Southwestern, Dallas, TX. ²Cedars-Sinai Medical Center, Los Angeles, CA. ³The Angeles Clinic, Cedars-Sinai Medical Center, Los Angeles, CA. ⁴Bedford Breast Center, Beverly Hills, CA. ⁵Massachusetts General Hospital, Boston, MA



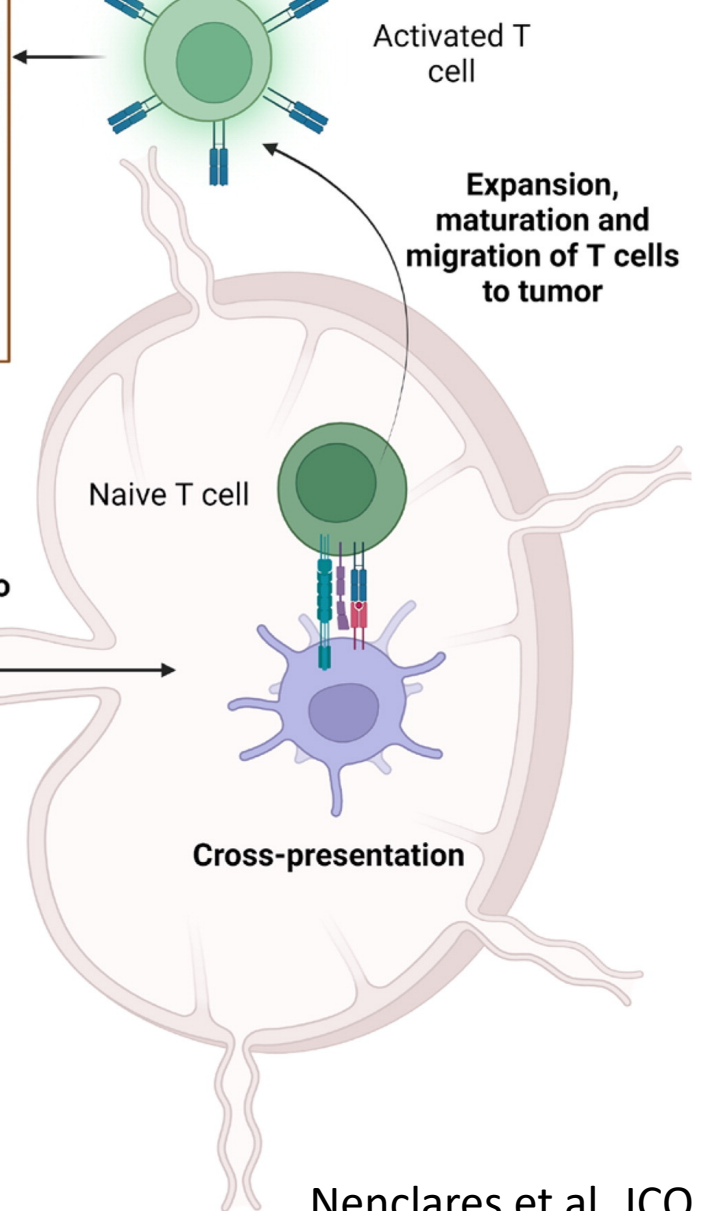
- TNBC only
- Single-institution phase Ib/II
- 50 patients included (34% cN+)
- 33% received AC → T/Carbo
- RESULTS:
 - **Approach is safe and feasible**
 - 74% RCB 0/1
 - 50% BCS; 50% mastectomy

SBRT

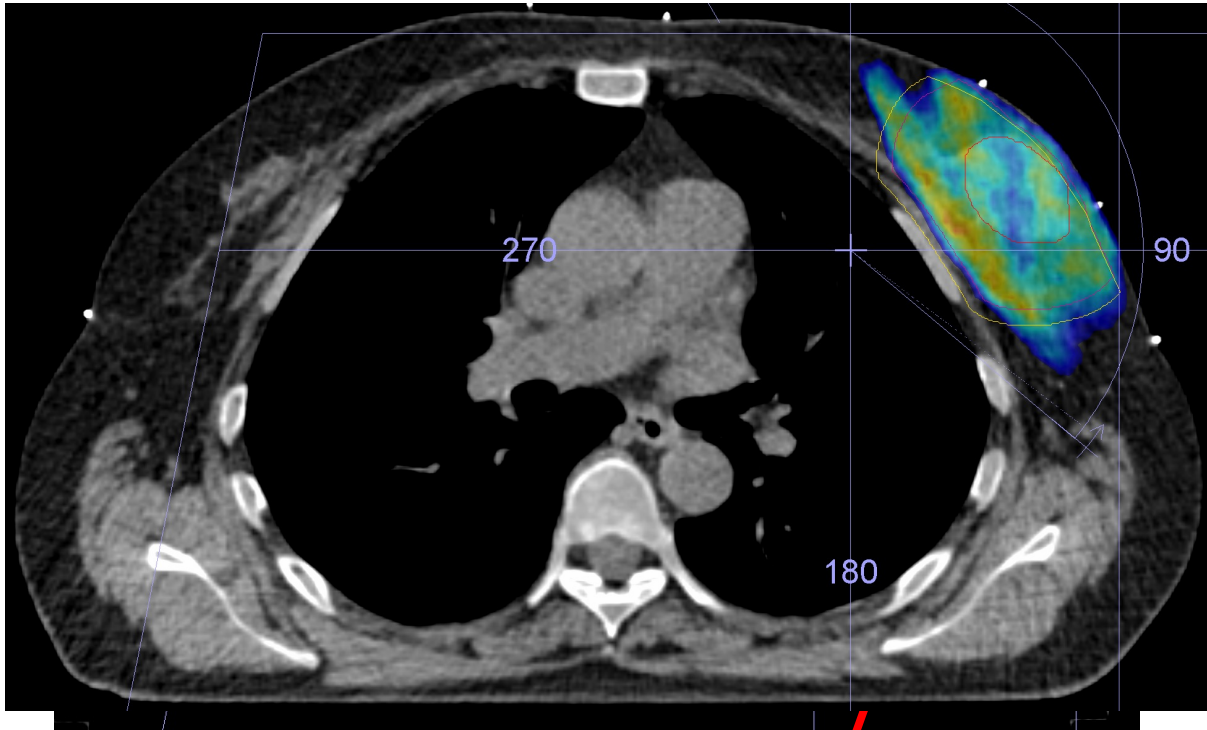
RADIATION



~~**RADIATION**~~

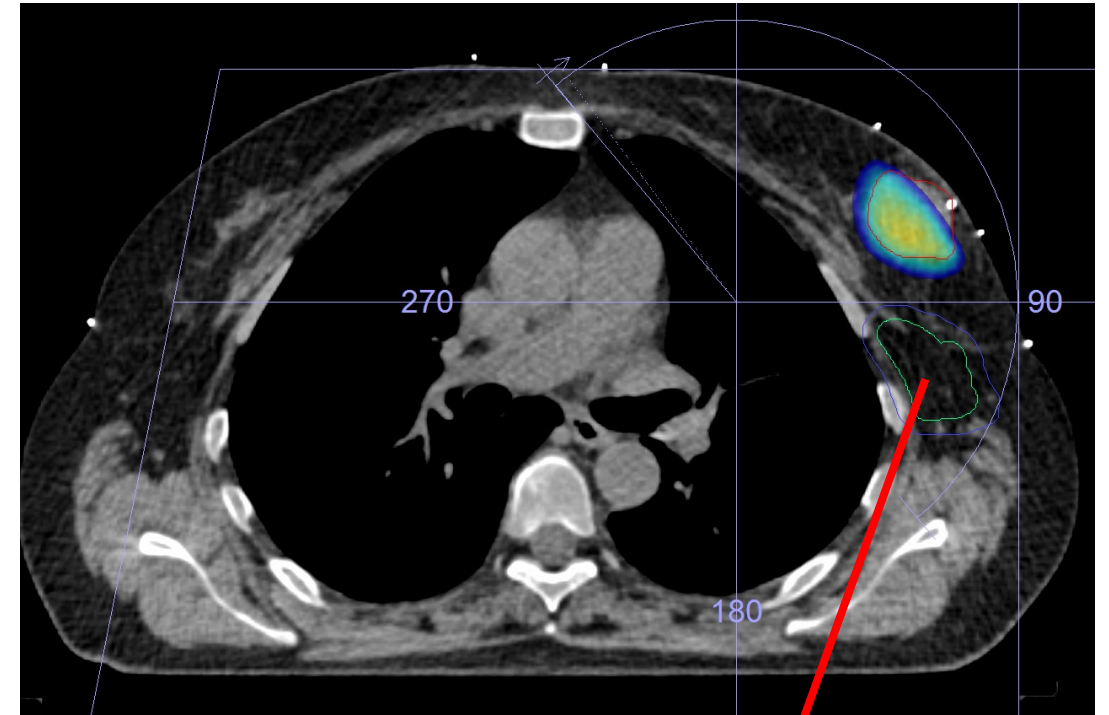


PBI (partial breast irradiation)



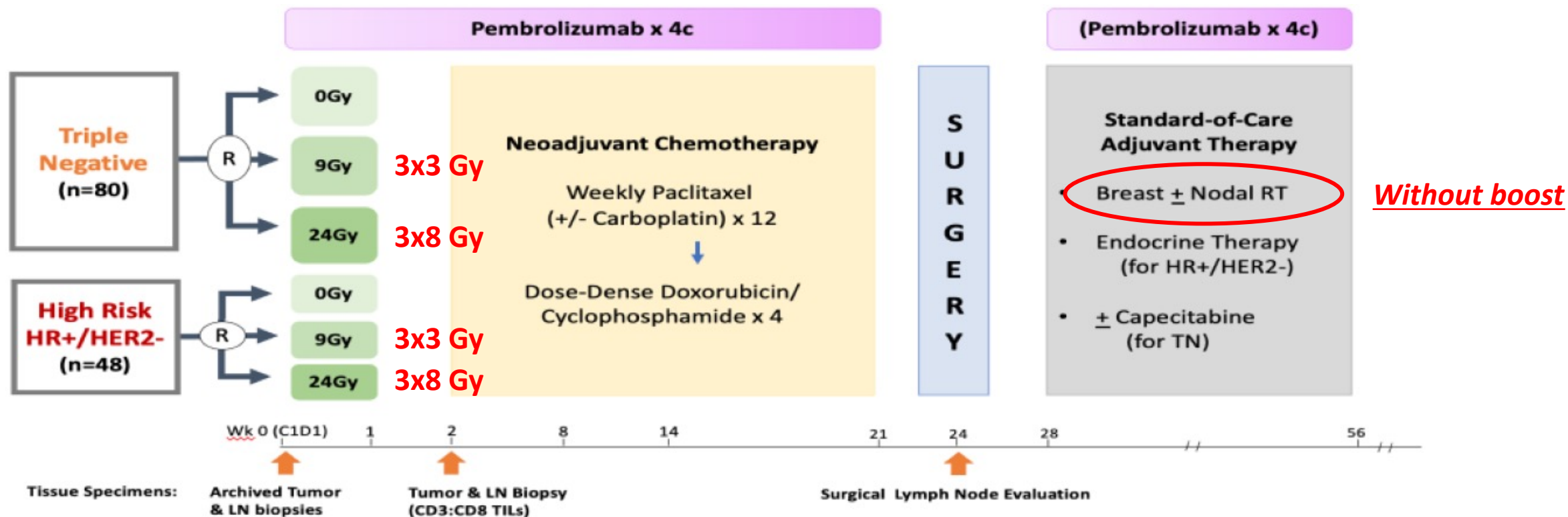
No sparing of the axilla

Pre-operative SBRT to tumor



Dosimetric sparing of
draining lymph nodes

P-RAD: A Randomized Study of Preoperative Chemotherapy, Pembrolizumab and No, Low or High Dose RADIation in Node-Positive, HER2-Negative Breast Cancer



1/ Compare T-cell infiltration between baseline and week 2 biopsy (multiplex CD3+/CD8+)

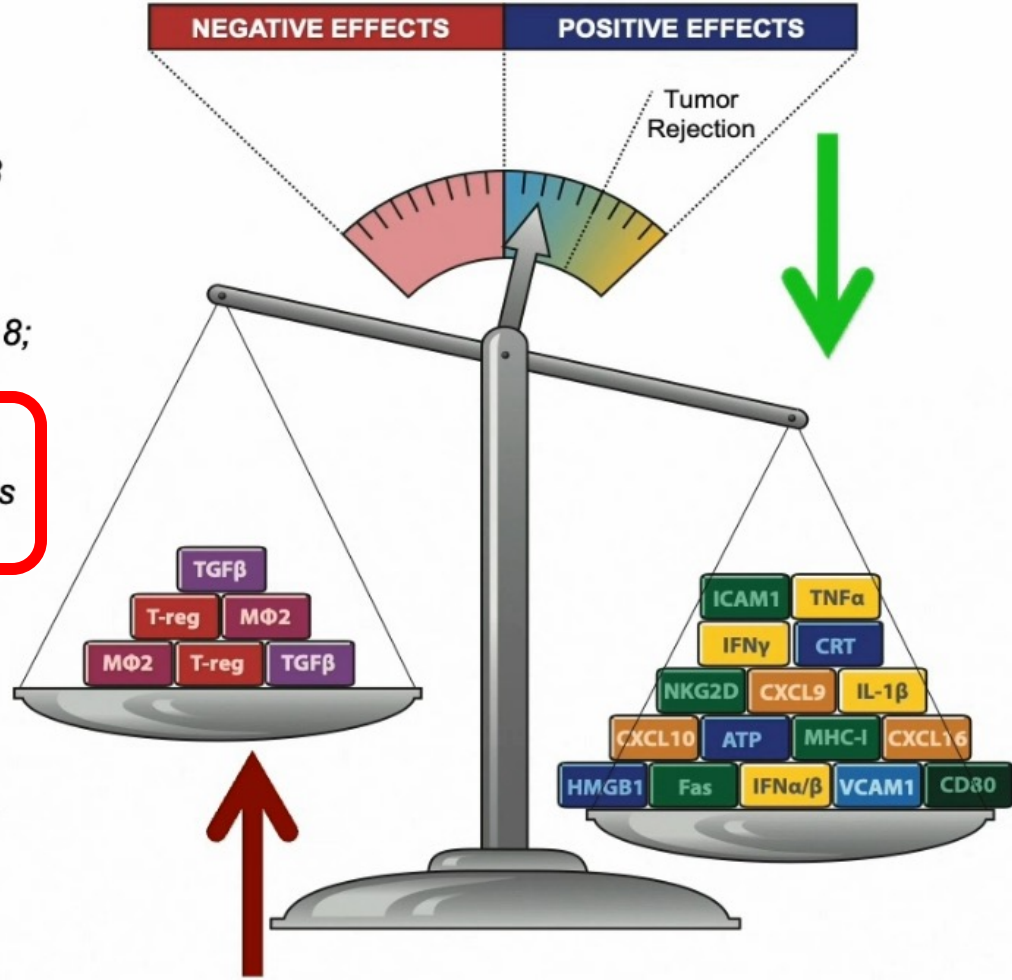
Primary endpoints

2/ Rate of nodal pCR at time of surgery (nodal = untreated by RT)

Trial led by: Alice Ho, Radiation Oncology, Duke University Medical Center

Trial conducted in: Massachusetts GH; Dana-Farber; Memorial Sloan Kettering; John Hopkins; Yale; Duke

Shifting the balance from immunosuppressive to pro-immunogenic signals of radiation



CTLA-4 blockade

Formenti SC et al *Nature Medicine* 2018
Dec;24(12):1845-1851

TGFb blockade

Formenti SC, et al: *Clin Cancer Res* 2018;
June 1:24(11):2493-2504.

CD73 blockade

Rudqvist NP, et al *Cancer Immunol Res*
2018; Feb;6(2):139-150.

VISTA blockade

Pilonas KA et al, *Oncoimmunology* 2020;
(in press)

Activin blockade

De Martino M, et al : *Cancer Immunol Res*
2020; (in press)

TLR agonists

Dewan MZ et al, *Clin Cancer Res*. 2012
Dec 15;18(24):6668-78

DC growth factors (Flt3L, GM-CSF)

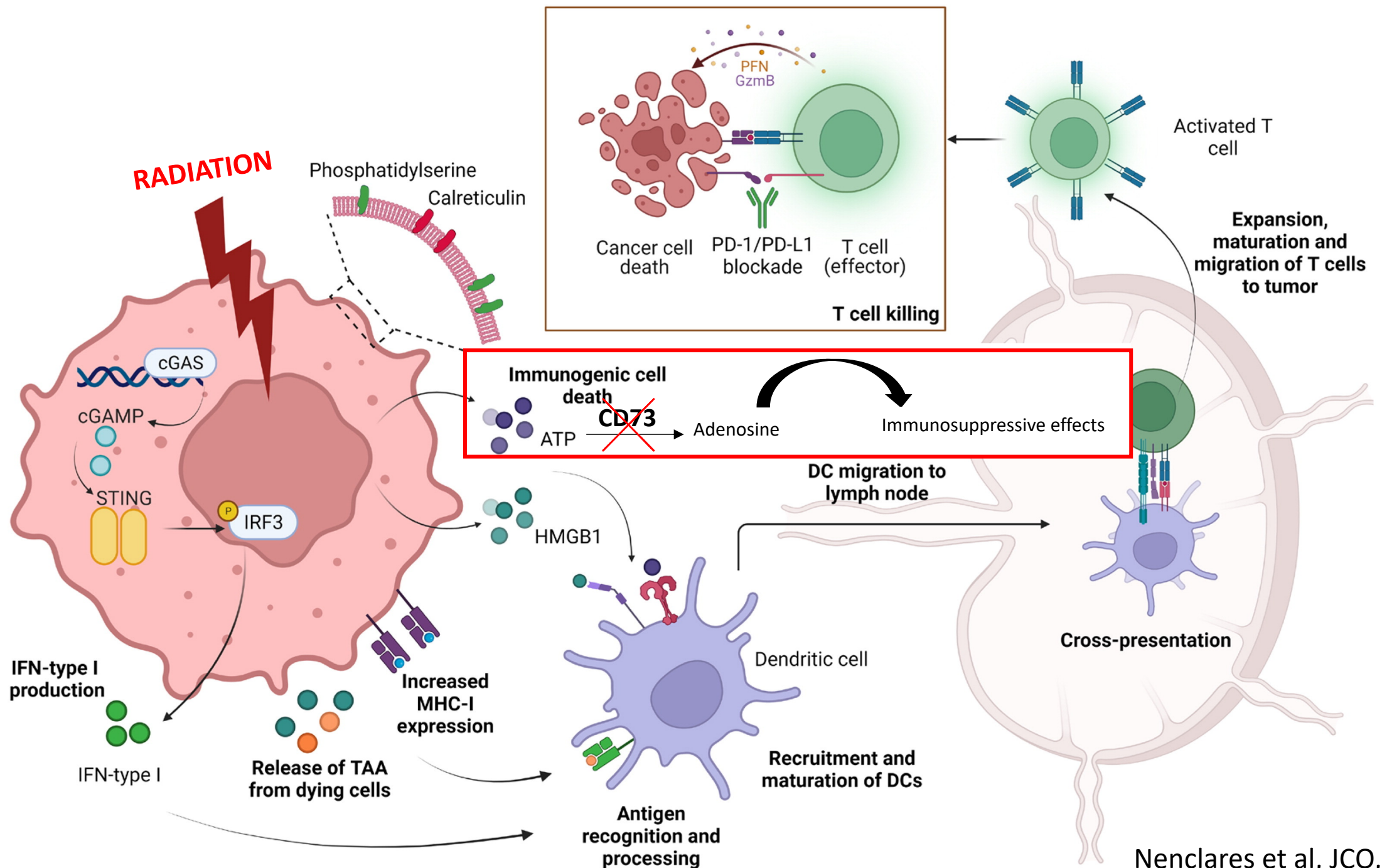
Demaria S, et al. *Int J Radiat Oncol Biol Phys*. 2004; 58(3): 862-870. Golden EB et al. *Lancet Oncol*. 2015 Jul;16(7):795-803

IFN inducers

Vanpouille-Box C, et al *Nat Commun*
2017;Jun 9;8:15618. Formenti SC et al
Nature Medicine 2018 Dec;24(12):1845-1851.

IL-15

Pilonas KA et al *Cancer Immunol Res*. 2020
Aug;8(8):1054-1063



Neo-CheckRay – PHASE II- multicentric- N = 132

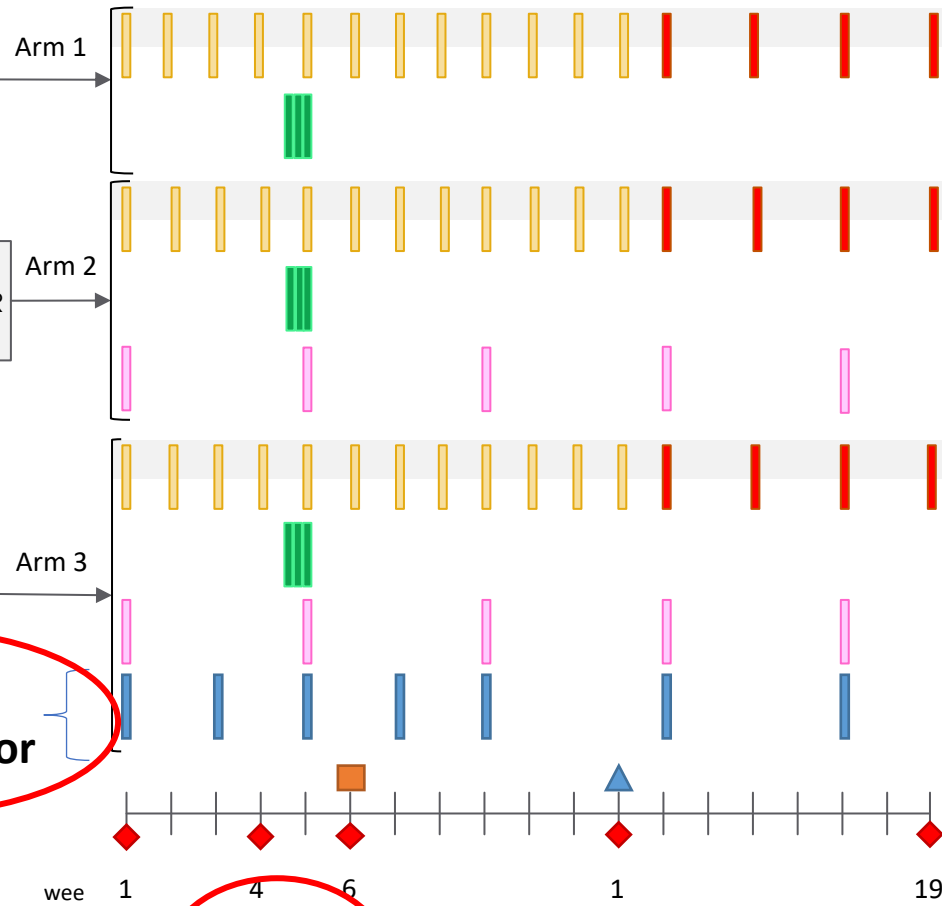


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LUMINAL ONLY
MammaPrint high risk

Non-Metastatic Luminal B Breast Cancer
cT4 excluded

Screening
R



3x8Gy to primary tumor only

Oleclumab = CD73 inhibitor

Durvalumab Q4W for 20 weeks

2-6 w

S u r g e r y



Standard RT to

- Breast / chest wall
- Nodes
- NO BOOST

PRIMARY ENDPOINT:
Rate of RCB 0/1

- Paclitaxel Q1W for 12 weeks
- ddAC Q2W for 8 weeks
- Durvalumab Q4W for 20 weeks
- Oleclumab Q2W for 8 weeks, then Q4W for 12 weeks
- SBRT 3x8Gy (daily)
- MRI imaging
- Tissue
- Blood sample for translational research

* As per local guidelines
♦ An additional blood sample will be collected at the End of Treatment Visit, Progression, and First Immune Related Toxicity

Study designed & conducted at Institut Jules Bordet

Currently recruiting in Belgian and French centers

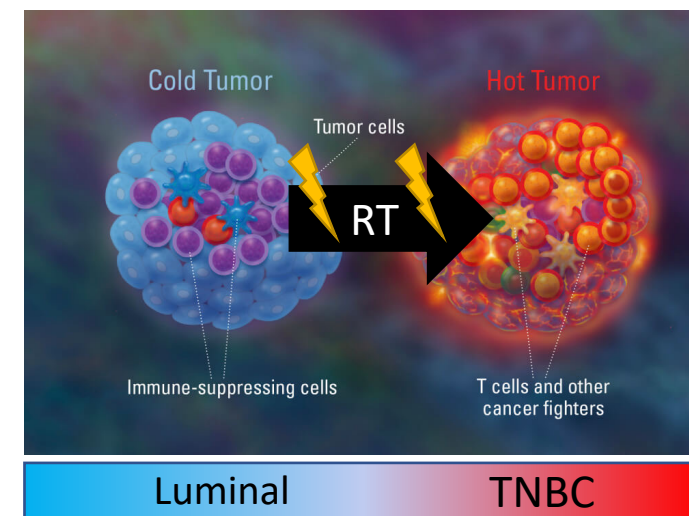
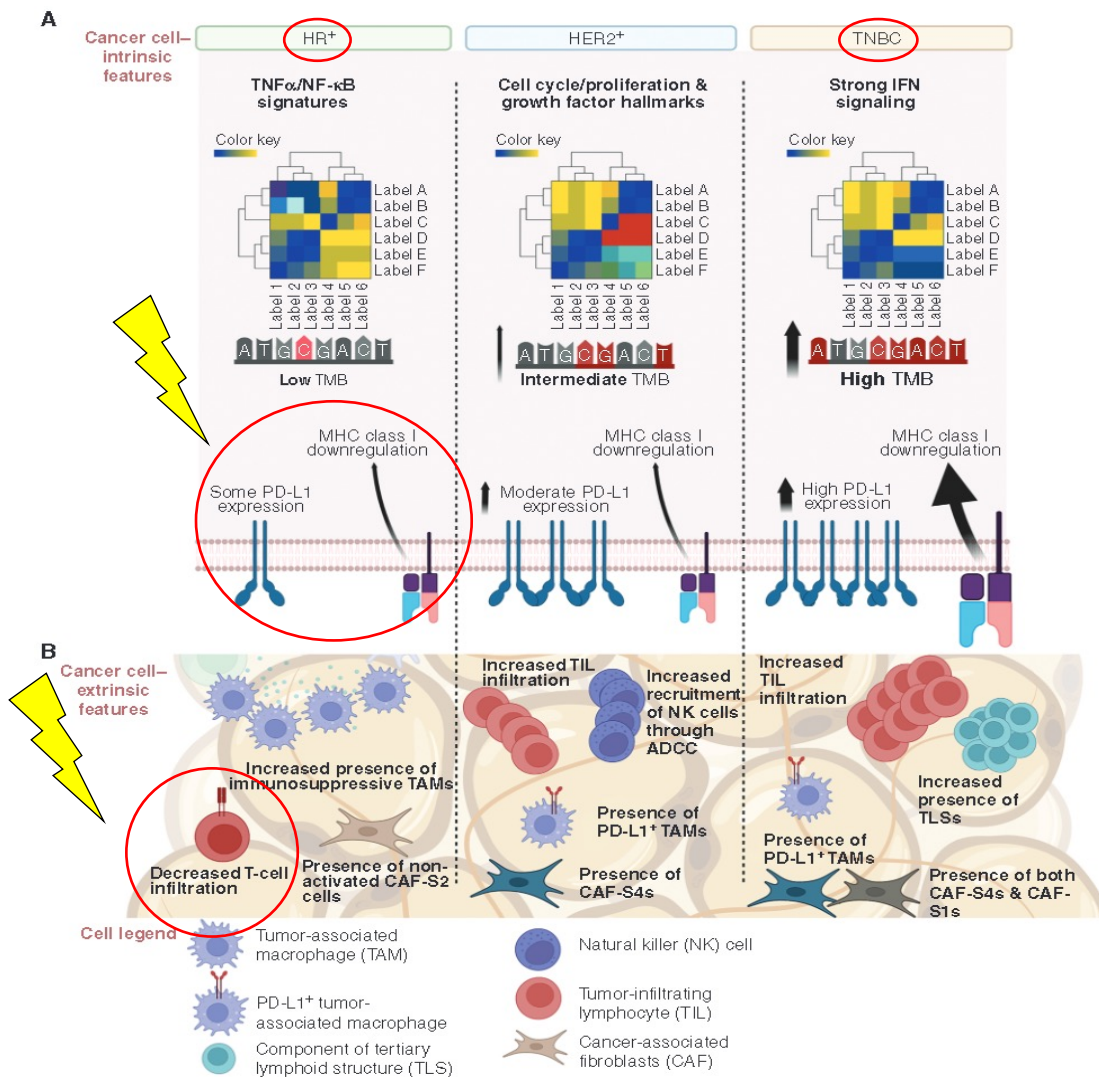
Institut Jules Bordet – UZ Leuven – Namur – Antwerp – Institut Curie – Dijon

Neo-adjuvant combinations of immunotherapy + RT in breast cancer: focus on luminal BC?

Table 1 Active Neoadjuvant, Adjuvant, and Metastatic Clinical Trials Combining ICI/RT in Breast Cancer

Study	Lead institution	Phase/N	Treatment		
Neoadjuvant Clinical Trials					
<u>Neo-CheckRay: Neo-adjuvant Chemotherapy Combined With Stereotactic Body Radiotherapy to the Primary Tumour +/- Durvalumab, +/- Oleclumab in Luminal B Breast Cancer (NCT03875573)</u>	Jules Bordet Institute	II/147	SBRT ± Durvalumab & Oleclumab	3x8Gy	LUMINAL
<u>CBCV: Converting HR+ Breast Cancer Into an Individualized Vaccine (NCT03804944)</u>	Weill Medical College of Cornell University	II/100	ET+RT ± FLT-3, Pembrolizumab or both	3x8Gy	LUMINAL
<u>Breast Cancer Study of Preoperative Pembrolizumab + Radiation (NCT03366844)</u>	Cedars Sinai Medical Center	I/60	Pembrolizumab + RT	3x8Gy	LUMINAL
<u>Effects of MK-3475 (Pembrolizumab) on the Breast Tumor Microenvironment in Triple Negative Breast Cancer With and Without Intra-operative RT: a Window of Opportunity Study (NCT02977468)</u>	Columbia University Irving Medical Center	I/15	Pembrolizumab + IORT	(IORT)	
<u>P-RAD: Pre-op Pembro + Radiation Therapy in Breast Cancer (NCT04443348)</u>	Massachusetts General Hospital	II/120	Pembrolizumab, NAC, & 0 Gy, 9 Gy or 24 Gy RT	3x8Gy; 3x3Gy	LUMINAL & TNBC

Neo-adjuvant combinations of immunotherapy + RT in breast cancer: focus on luminal BC?



Conclusion

**Innovation in Radiation Therapy
= tailor every treatment to individual patient risk**

~~« One size fits all »~~

Reduce toxicity

- Precision ↑
- Irradiated volumes ↓
- Optimise dose to patient

Increase efficacy

- Investigate synergy with novel systemic treatments

Avoid unnecessary mastectomies!

Thank you for your attention!

Acknowledgements

Neo-CheckRay Team



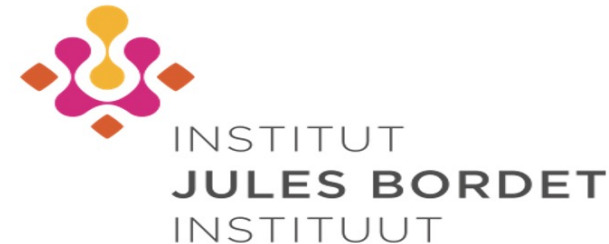
- **L. Buisseret, M. Ignatiadis, M. Piccart**
- **C. Sotiriou, P. Poortmans, E. Romano**

- CTSU Bordet & medical fellows (E. Agostinetto, G. Nader Marta)
- Participating centers Neo-CheckRay trial:
V. Remouchamps, A. Baeten, I. Desmoulins

- Breast Medical oncologists: P. Aftimos, E. De Azambuja, D. De Valeriola, A. Gombos, D. t'Kint
- Breast Surgeons: I. Veys, F. De Neubourg, JM Nogaret, F. Pop, M. Roman, P. Simon, J. Haut
- Breast RT: A. Desmet, C. Philippson, D. Van Kampen, D. Van Gestel
- Pathology: D. Larsimont, L. Craciun, R. Salgado
- Radiology: S. Picchia
- BCTL Bordet

Patients and their families

My colleagues at Jules Bordet Institute



My colleagues at AZ St Maarten

