FUNDACION MARIE CURIE
Córdoba - Argentina

Congreso sobre Avances Integrados en Oncología, Radiocirugía y Física Médica: Innovación y Precisión en el tratamiento del cáncer

Indicaciones y formas de RT según el tipo molecular:

Luminal B ensayo Neo-Checkray

Philip Poortmans, MD, PhD

Iridium Netwerk & Antwerp University, Antwerpen (B)

Former President

Conflict of interest

Affidea – medical advisor

MSD - consultant

And I worry about the future…


STOP
THE
WARS

Radiation therapy & immune therapy – Neo-CheckRay

- Introduction
- Breast cancer immunogenicity
- Immunotherapy in BC: where are we?
- Luminal-B BC: Neo-CheckRay
- Discussion
- Conclusions

MBN2023
Oncoplastic Breast Meeting
Masters & Promises

https://images.app.goo.gl/e86xRFQpFaKhhViU7

Radiation Therapy & Immune Therapy:
The next paradigm?

Philip Poortmans, MD, PhD

Iridium Netwerk & Antwerp University, Antwerpen (B)

Former President

Alice Zamagni, MD

Radiation Oncology Unit, Azienda USL-IRCCS di Reggio Emilia (I)

Department of Medical and Surgical Sciences, University of Bologna (I)

RT & immune therapy: *Introduction*

Recommendations on integration of radiation therapy with targeted treatments for breast cancer consensus meeting

Florence (IT), 16-17th June 2023

Grand Hotel Mediterraneo, Lungarno del Tempio, 44

Endorsed by

ESTRO

Carlotta Becherini	Florence, Italy
Saverio Caini	Florence, Italy
Charlotte Coles	Cambridge, UK
Javier Cortes	Barcelona, Spain
Clare Isacke	London, UK
Orit Kaidar-Person	Sheba Tel Hashomer, Israel
Matteo Lambertini	Genoa, Italy
Lorenzo Livi	Florence, Italy
Elisabetta Marangoni	Paris, France
Icro Meattini	**Florence, Italy**
Andrea Morandi	Florence, Italy
Birgitte Offersen	Aarhus, Denmark
Philip Poortmans	Antwerp, Belgium
Hope Rugo	San Francisco, USA
Viola Salvestrini	Florence, Italy
Luca Visani	Florence, Italy

Sara Alkner	Lund, Sweden
Liesbeth Boersma	Maastricht, The Netherlands
Maurizio Callari	Milan, Italy
Saverio Cinieri	Brindisi, Italy
Robert Clarke	Manchester, UK
Giuseppe Curigliano	Milan, Italy
Lucia Del Mastro	Genoa, Italy
Maria Ekholm	Jönköping, Sweden
Alessandra Gennari	Novara, Italy
Stephanie Kroeze	Zurich, Switzerland
Marcos Malumbres	Madrid, Spain
Ingvil Mjaaland	Stavanger, Norway
Gustavo Nader Marta	São Paulo, Brazil
Gil Morgan	Lund, Sweden
Shani Paluch-Shimon	Jerusalem, Israel
Barbara Pistilli	Paris, France
Sofia Rivera	Paris, France
Sven Rottenberg	Bern, Switzerland
Asal Shoushtari Rahimi	Dallas, USA
Cristina Saura	Barcelona, Spain
Tanja Skyttä	Tampere, Finland
Tanja Spanic	Ljubljana, Slovenia
Frank Vicini	Royal Oak, USA

RT & immune therapy: *Introduction*

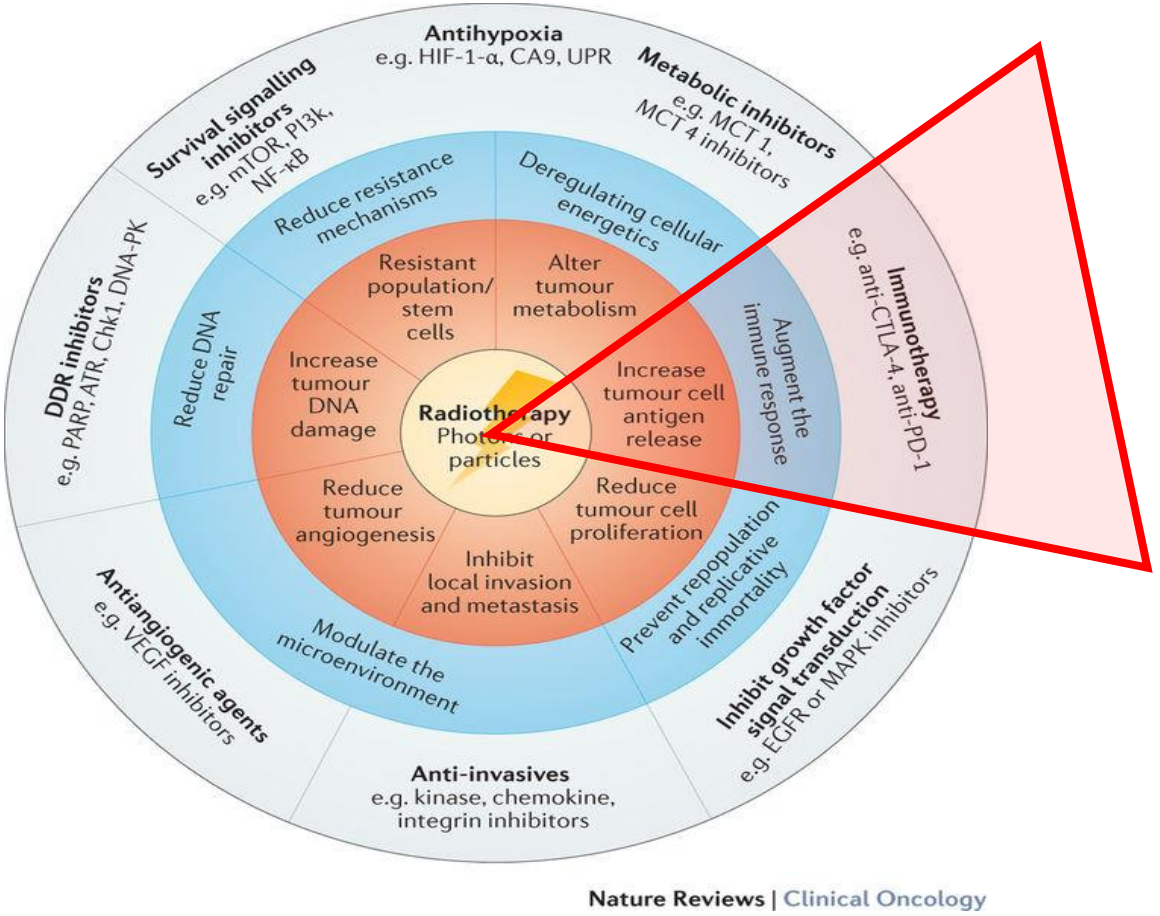
Policy Review

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†*

Meattini I, et al. Lancet Oncol 2024;25:e73–83.

RT & immune therapy: *Introduction*



Sharma RA, et al. Reviews Clinical Oncology 2016

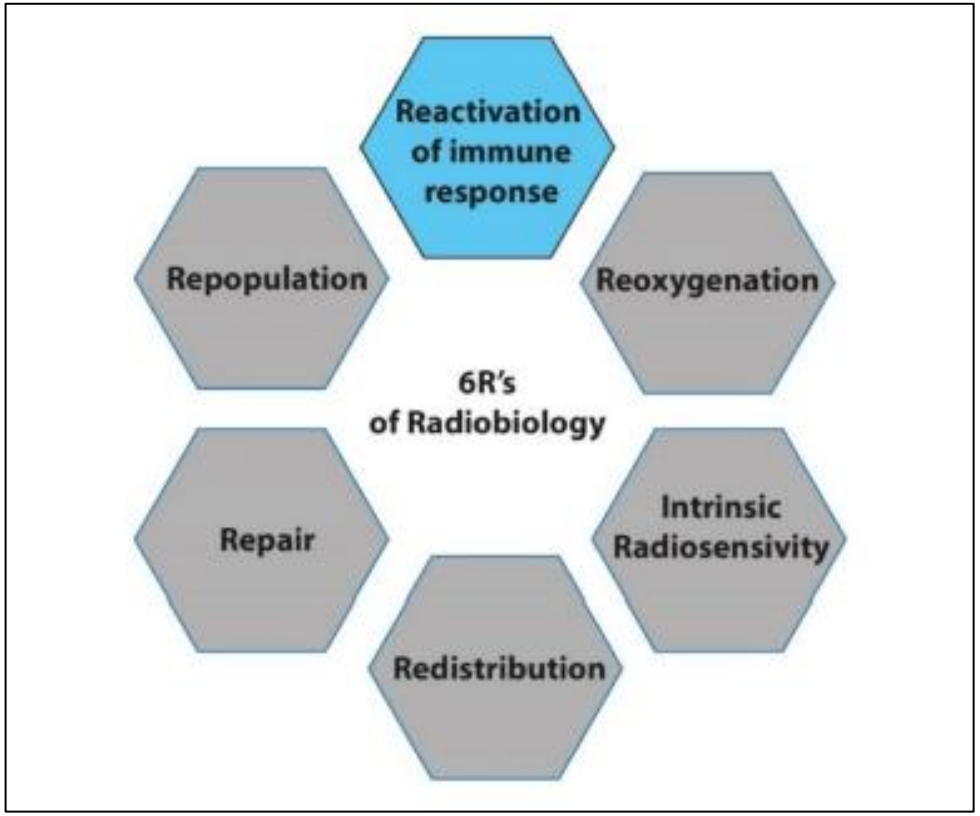
RT & immune therapy: *Introduction*

cancers

Review

The 6th R of Radiobiology: Reactivation of Anti-Tumor Immune Response

Jihane Boustani [1,†], Mathieu Grapin [1,†], Pierre-Antoine Laurent [1], Lionel Apetoh [2] and Céline Mirjolet [1,2,*]



Mind:
Predatory journal!

Boustani J, et al. Cancers (Basel). 2019;11:860.

RT & immune therapy: *Introduction*

cancers

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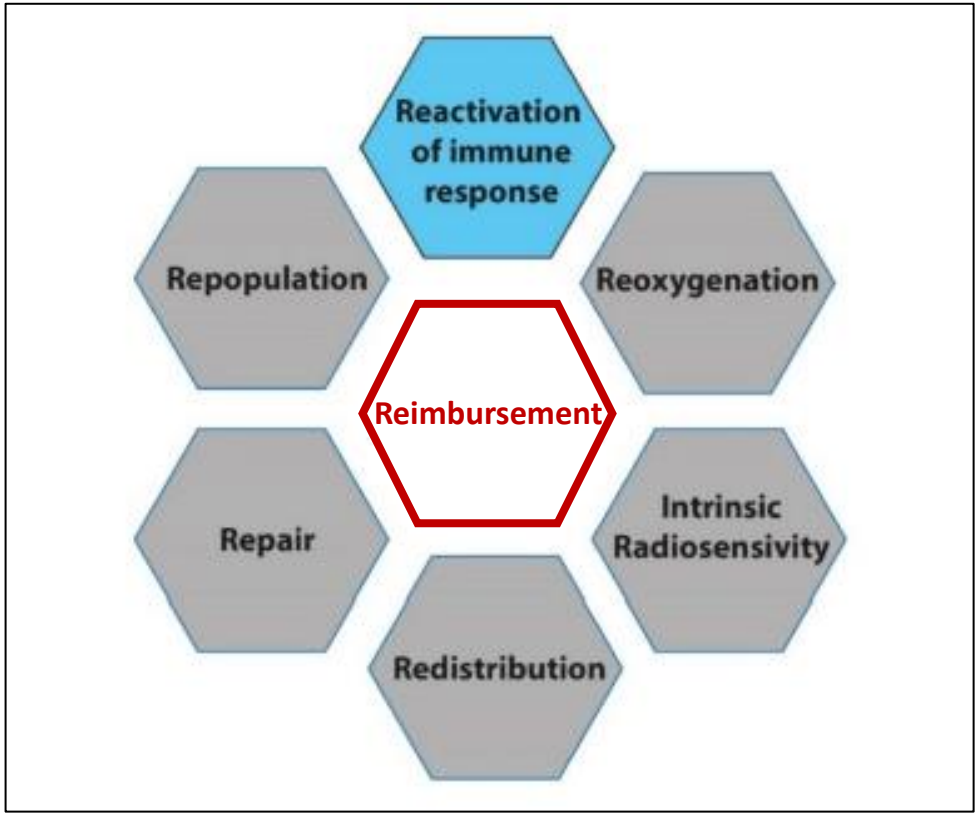

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RT & immune therapy: *Introduction*

BJC British Journal of Cancer

www.nature.com/bjc

REVIEW ARTICLE

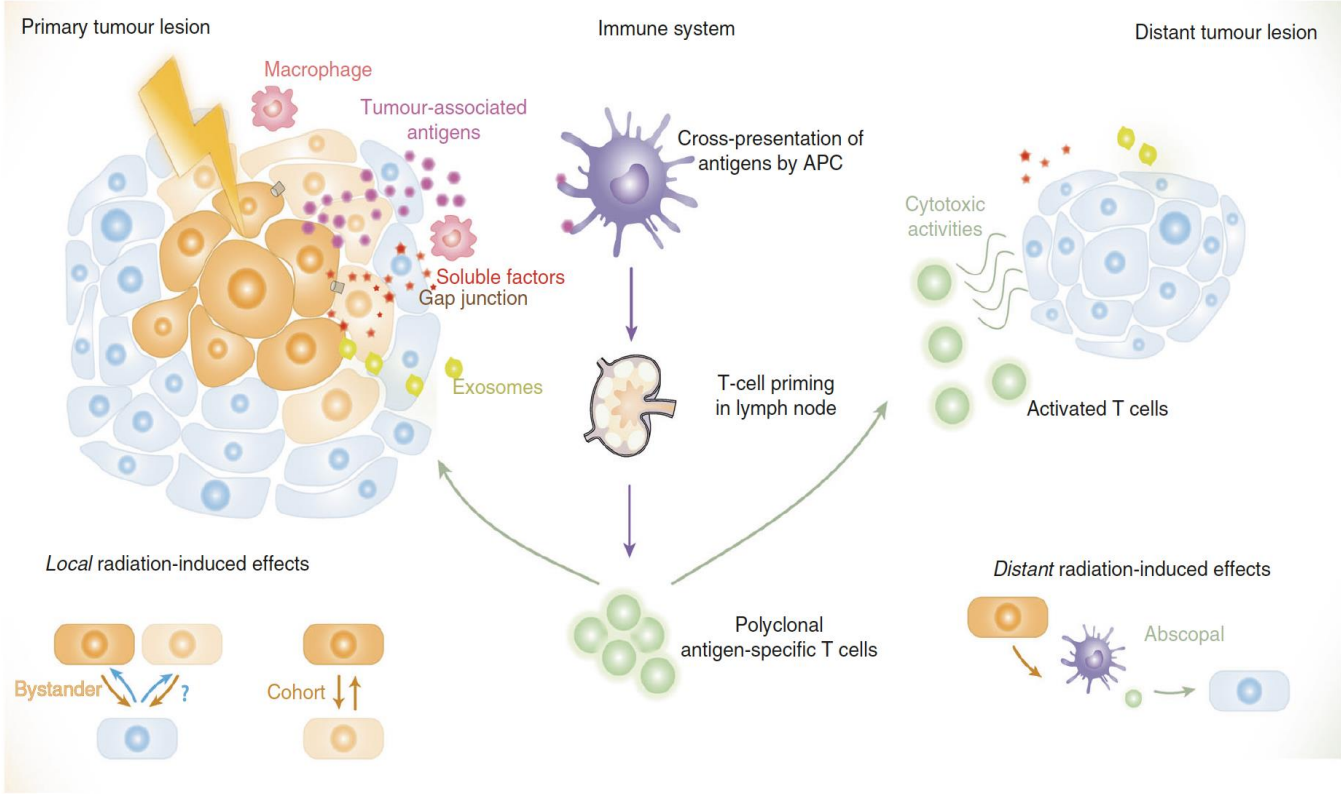
Radiation-induced bystander and abscopal effects: important lessons from preclinical models

Elisabeth Daguenet[1,2,3], Safa Louati[1,3], Anne-Sophie Wozny[3,4], Nicolas Vial[1], Mathilde Gras[1,2], Jean-Baptiste Guy[1,3], Alexis Vallard[1,3], Claire Rodriguez-Lafrasse[3,4] and Nicolas Magné[1,2,3]

Daguenet E, et al. British Journal of Cancer. 2020;123:339–348.

RT & immune therapy: *Introduction*

Schematic overview of local and distant effects triggered by ***tumour irradiation***



Bystander effects between high-dose-targeted cells (dark orange) or low-dose-targeted cells (light orange) and non-irradiated cells (blue)

Cohort effects occur between high-dose-targeted cells and low-dose-targeted cells.

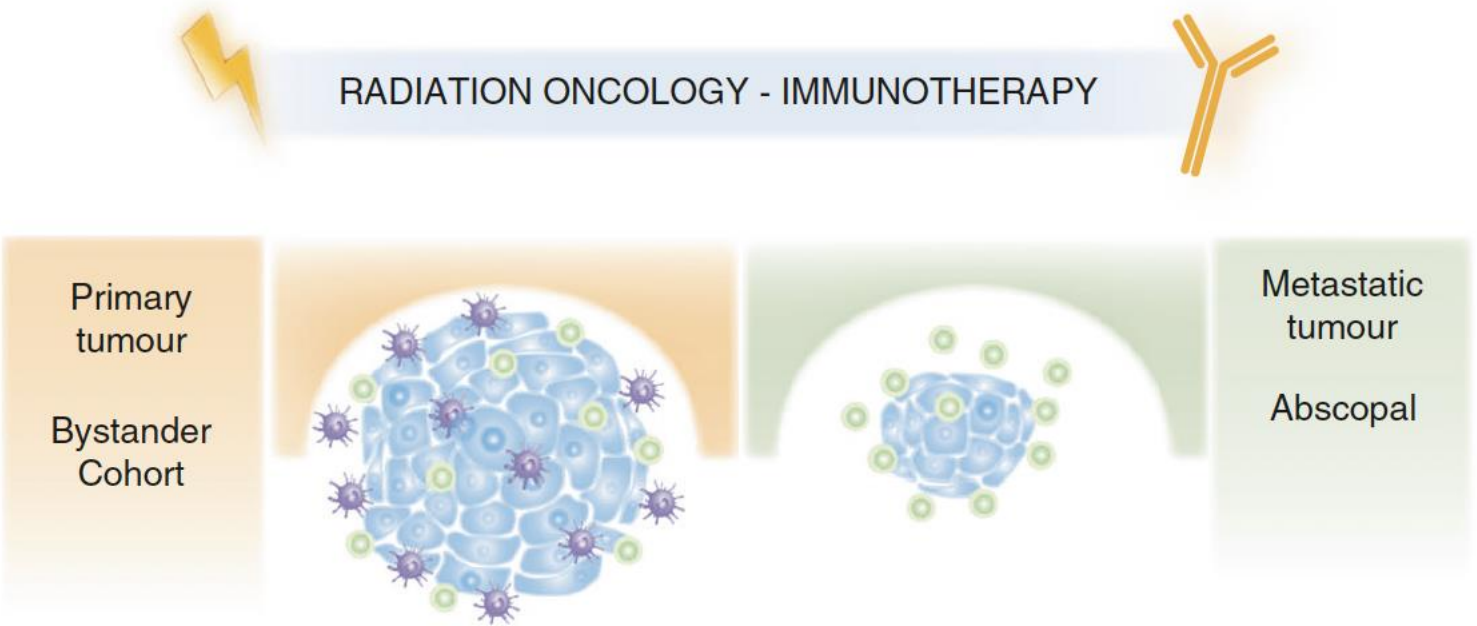
Irradiation induces immunogenic cell death in cancer cells ➔ release of tumour-associated antigens (TAAs) (pink dots) ➔ activating immune system

Abscopal effect ➔ distant sites

Daguenet E, et al. British Journal of Cancer. 2020;123:339–348.

RT & immune therapy: *Introduction*

Preclinical experimental strategies for efficient radio-immunotherapy combinations in clinical routine



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RT & immune therapy: *Introduction*

- ✓ Numerous clinical studies investigating radiotherapy as a combination partner for immunotherapies, particularly immune-checkpoint inhibitors, failed to reveal a therapeutic benefit over either treatment modality alone.

- ✓ In this context, radiotherapy has often been applied according to conventional regimens and/or target volumes, with limited consideration for potential radiotherapy-driven immunomodulation.

- ✓ Conventional radiation doses and fractionation schedules might result in robust immunosuppression in the tumour microenvironment, at least in part reflecting the repeated killing of circulating immune effector cells.

- ✓ Conventional radiotherapy target volumes are also expected to exacerbate local and systemic immunosuppression given that they often include tumour-draining lymph nodes (which are key sites for the initiation of anticancer immunity) and circulating immune cells.

- ✓ Multiple cellular alterations elicited by radiotherapy are temporally dynamic, suggesting that the treatment schedule (relative timing and sequencing) is a major determinant of the efficacy of radiotherapy–immunotherapy combinations.

- ✓ We surmise that improved radiotherapy regimens and target volumes might enable the development of radiotherapy–immunotherapy combinations with superior clinical activity, at least in some patient populations.

Galluzzi L, et al. Nat Rev Clin Oncol. 2023;20:543-557.

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Radiation therapy & immune therapy – Neo-CheckRay

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- Immunotherapy in BC: where are we?
- Luminal-B BC: Neo-CheckRay
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RT & immune therapy: *BC immunogenicity*

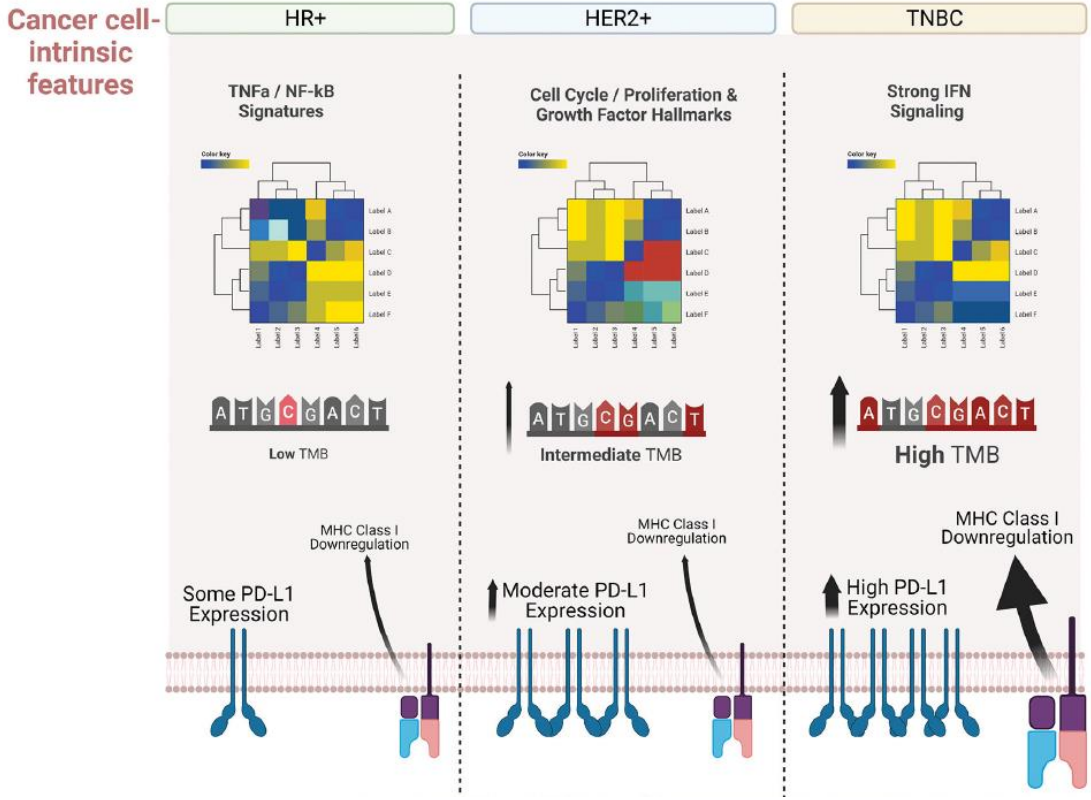
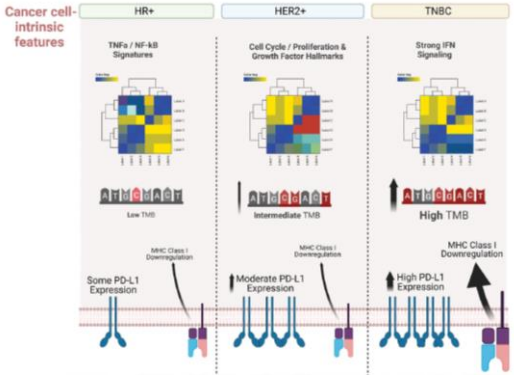


FIGURE 2:
(A) Comparison of unique tumor-intrinsic features of the breast cancer subtypes. Key differences in intrinsic genomically-upregulated pathways, tumor mutational burden (TMB), tumor PD-L1 expression, and MHC Class I downregulation can all contribute to different TIMEs for each breast cancer subtype. **(B) Comparison of unique cancer cell-extrinsic, immune cell-related features across the main breast cancer subtypes.** In HR+ breast cancer, there are generally increased proportions of tumor-associated macrophages (TAMs) that tend to be immunosuppressive along with decreased T cell infiltration and the presence

Onkar SS, et al. Cancer Discov. 2023; Jan 9;13(1):23-40

RT & immune therapy: *BC immunogenicity*



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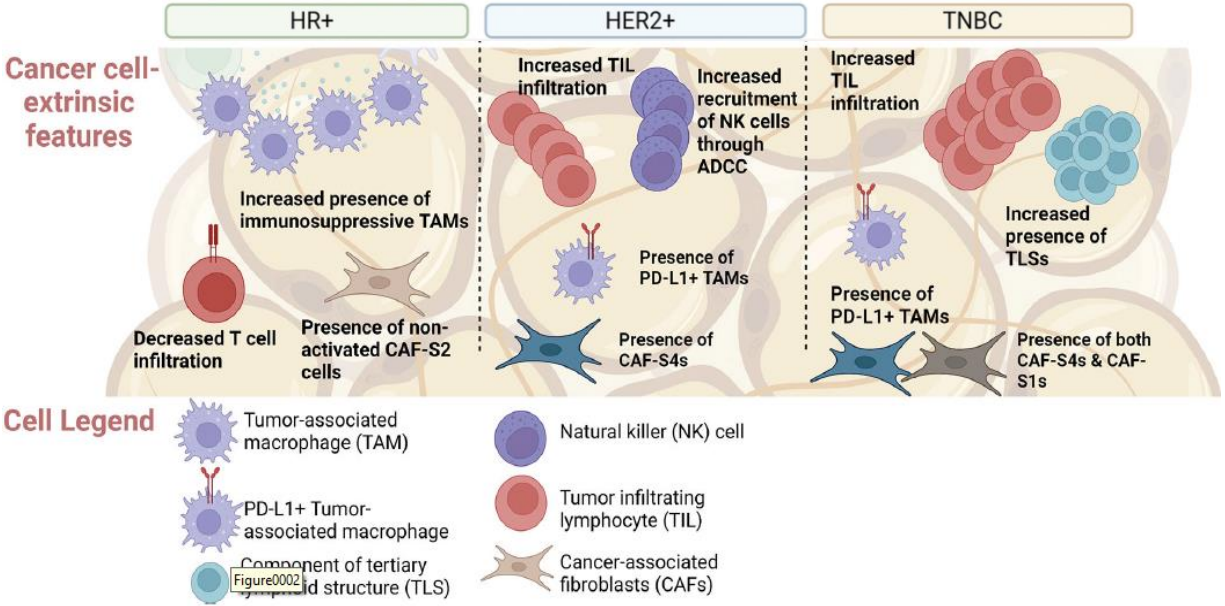

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RT & immune therapy: *Evidence in BC - postoperative*

Study	Lead Institution	Phase/N	Tumor type	Intervention
SWOG S1418/NRG BR006: Pembrolizumab as adjuvant therapy for TNBC (NCT02954874)	SWOG Cancer Research Network	III/1155	TNBC no pCR	RT (SoC) ± Pembrolizumab
BreastImmune03: Evaluate the clinical benefit of a post-op treatment with RT+nivolumab+ipilimumab VS RT+capecitabine for TNBC pts with residual disease (NCT03818685)	Centre Leon Berard	II/114	TNBC no pCR	RT (SoC)+nivolumab+ipilimumab vs RT (SoC)+capecitabine
Pembrolizumab in Combination With Hormonal Therapy During or After Radiation in Patients With HR+ Inflammatory Breast Cancer who Did Not Achieve a pCR to Neoadjuvant Chemotherapy (NCT02971748)	MD Anderson Cancer Center	II/37	HR+ IBC	Hormonal therapy + Pembrolizumab + RT (SoC)

Anti PD-1: Pembrolizumab, Nivolumab
Anti CTLA-4: Ipilimumab

Santa-Maria CA, et al. Semin Radiat Oncol. 2022 Jul;32(3):291-297; Jungles KM, et al. Front Oncol. 2022;12:1022542

RT & immune therapy: *Evidence in BC - preoperative*

Study	Lead Institution	Phase/N	Tumor type	Intervention
Neo-CheckRay: neo-adjuvant CT combined with SBRT ± durvalumab and oleclumab in Luminal B BC (NCT03875573)	Jules Bordet Institute	II/147	HR+/Her2- high risk	SBRT (24 Gy in 3 fr) ± durvalumab and oleclumab
CBCV: converting HR+ BC into an individualized vaccine (NCT03804944)	Weill Medical College of Cornell University	II/100	HR+/Her2-	HT + RT (24 Gy in 3 fr) ± FLT-3, pembrolizumab or both
BC study of pre-op pembrolizumab+radiation (NCT03366844)	Cedars Sinai Medical Center	I/60	HR+/Her2- TNBC	Pembrolizumab + RT (24 Gy in 3 fr)
Effects of Pembrolizumab on the TME in TNBC ± IORT (NCT02977468)	Columbia University	I/15	TNBC	Pembrolizumab + IORT
P-RAD: pre-op Pembro + RT in BC (NCT04443348)	Massachussetts General Hospital	II/120	HR+/Her2- high risk TNBC	Pembrolizumab + NAC ± RT (9 or 24 Gy in 3 fr), includes non-randomized arm with proton therapy
BreastVAX: Preoperative RT Boost to Enhance Effectiveness of ICI in Operable Breast Cancer (NCT04454528)	Perelman Center for Advanced Medicine (Pennsylvania)	Ib-II/27	TNBC HR+/Her2- (cN+) Her2+ (cT1)	Pembrolizumab + RT (single fr 7 Gy)

Anti PD-1: Pembrolizumab; Anti PD-L1: Durvalumab; Anti CD73: Oleclumab; FLT3: FMS-like tyrosine kinase 3

Jungles KM, et al. Front Oncol. 2022;12:1022542; Santa-Maria CA, et al. Semin Radiat Oncol. 2022 Jul;32(3):291-297

RT & immune therapy: *Evidence in BC*

- Limited efficacy in BC as monotherapy
- Most robust responses in TNBC, PD-L1 positive, first-line palliative setting
- Uncertainties about what to do after the progression
- Not neglectable toxicities ≥ G3

Nguyen AT, et al. Clin Breast Cancer. 2021;21(2):143-152

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BARCELONA 2024 ESMO congress

NEO-CHECKRAY primary endpoint results

A randomized phase 2 trial evaluating Stereotactic Body Radiation Therapy (SBRT) to the Primary Breast Cancer +/- Durvalumab +/- Oleclumab combined with Neoadjuvant Chemotherapy for Early-Stage High Risk ER+/HER2-

Alex De Caluwé, Isabelle Desmoulins, Kim Cao, Vincent Remouchamps, Adinda Baten, Eleonore Longton, Karine Peignaux, Guilherme Nader Marta, Luca Arecco, Elisa Agostinetto, Paulus Kristanto, Xavier Catteau, Denis Larsimont, Roberto Salgado, Philip Poortmans, Christos Sotiriou, Martine Piccart, Michail Ignatiadis, Emanuela Romano, Laurence Buisseret

An investigator-initiated trial sponsored by the JULES BORDET Institute
Brussels, Belgium

Background

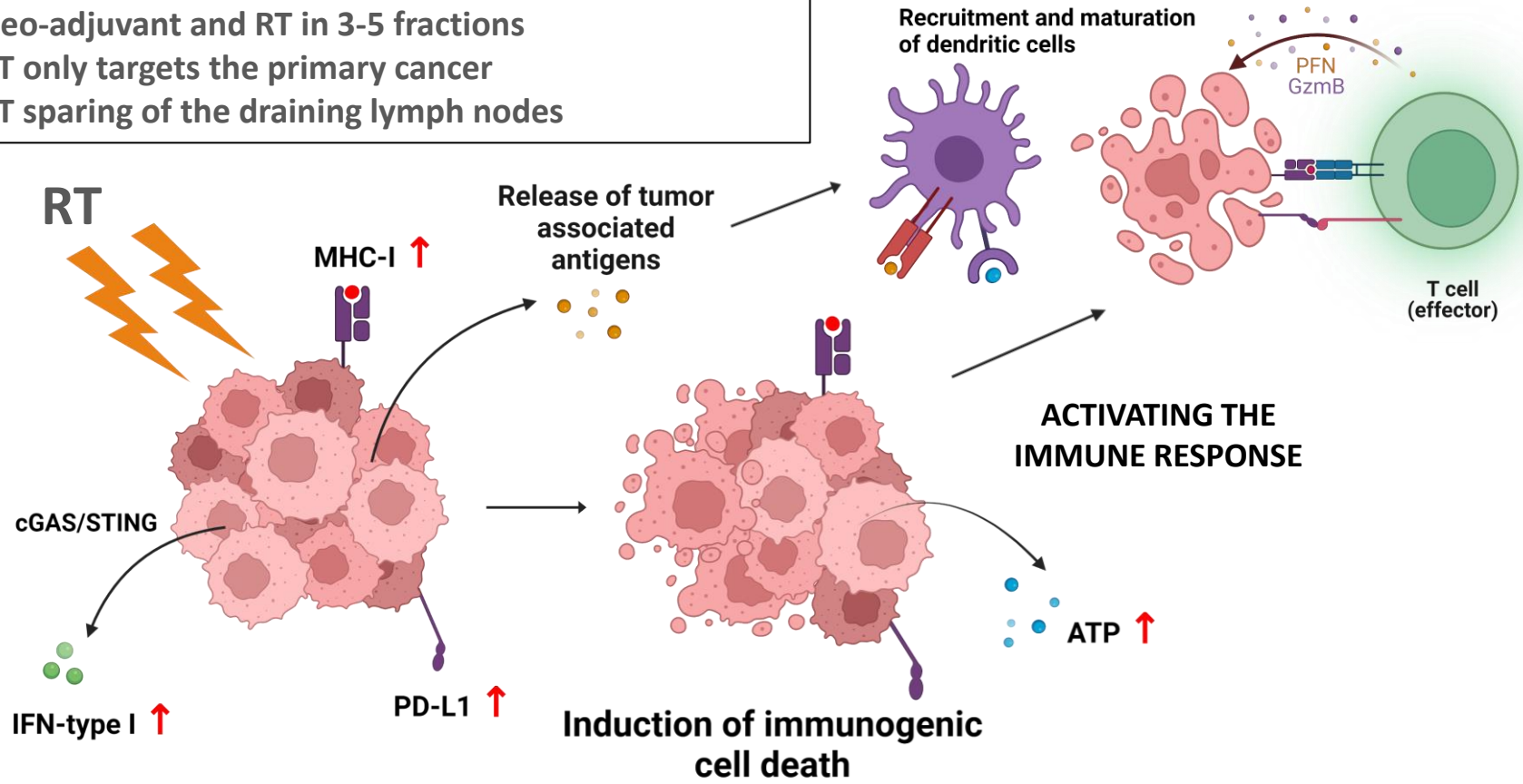
Early-Stage Luminal B Breast Cancer (highly proliferative ER+/HER2-)

- **High risk luminal B breast cancer (BC):**
  - Defined by higher stage, younger age, high-risk genomic assays, and low ER
  - Benefits from (neo) adjuvant chemotherapy
  - Pathological complete response (pCR) rates after neo-adjuvant chemotherapy (NACT): 15%
- Luminal B BC is an **immune "cold" tumor** (unlike TNBC):
  - ↓TILs (tumor invading lymphocytes)
  - ↓PD-L1 expression
- **PD-1/PD-L1 immune checkpoint inhibitors added to NACT increase pCR rate:** [1,2]
  - Overall absolute ↑ pCR Δ **9%** (15% → 24%) [1,2]
  - PD-L1 negative subgroup ↑ pCR Δ **4%** (3% → 7% [1] & 10% → 14% [2])
- Could **new immunotherapy combination strategies** further increase pCR% and provide long term benefit in luminal B BC?

[1] Cardoso F, Keynote-756, Ann. Oncol, 2023; [2] Loi S, Checkmate 7-FL, Ann. Oncol, 2023.

Background: can radiation therapy stimulate the immune response?

Optimal RT+ICB combination:
- Neo-adjuvant and RT in 3-5 fractions
- RT only targets the primary cancer
- RT sparing of the draining lymph nodes



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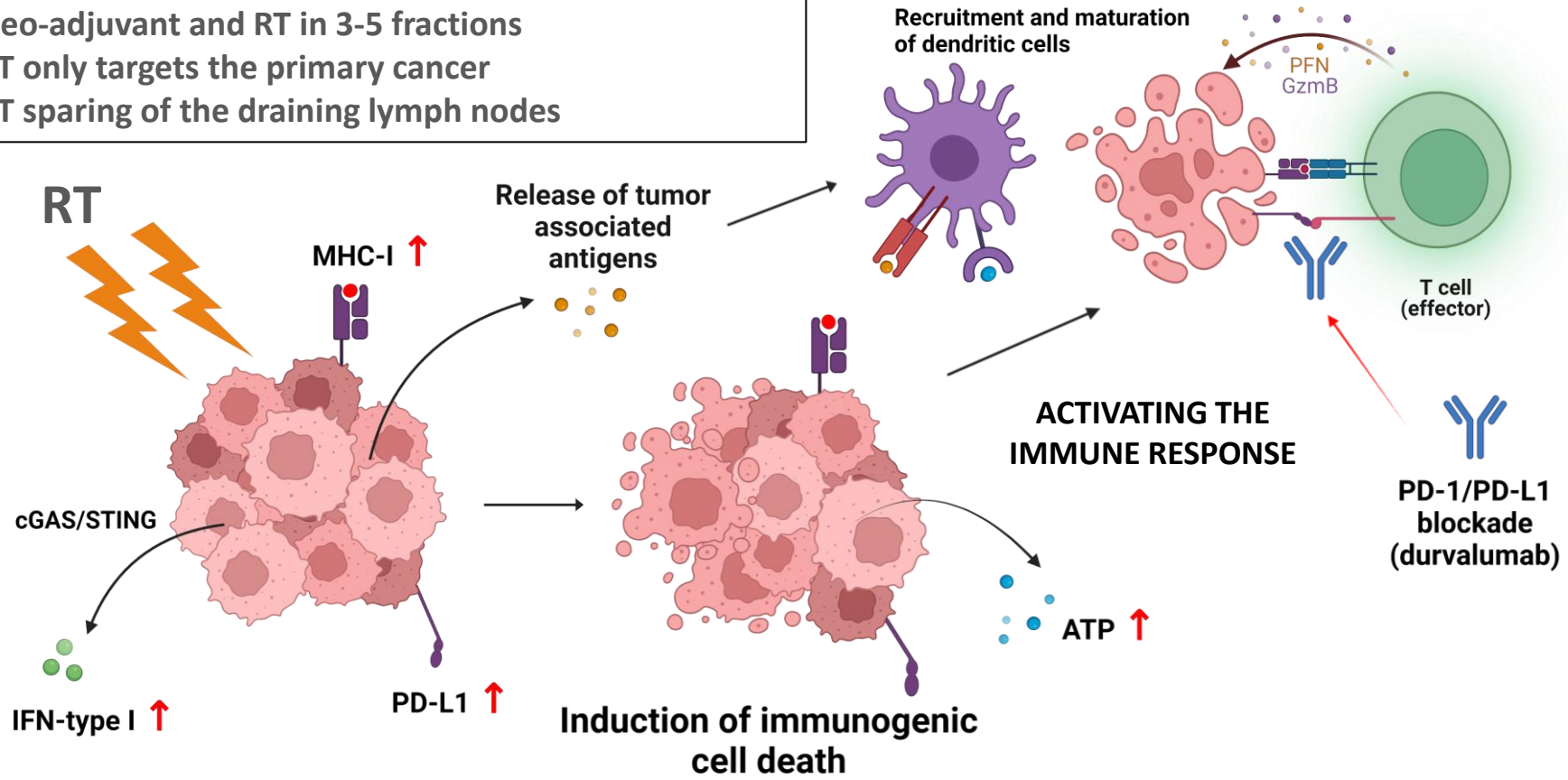

Nenclares et al, JCO, 2022

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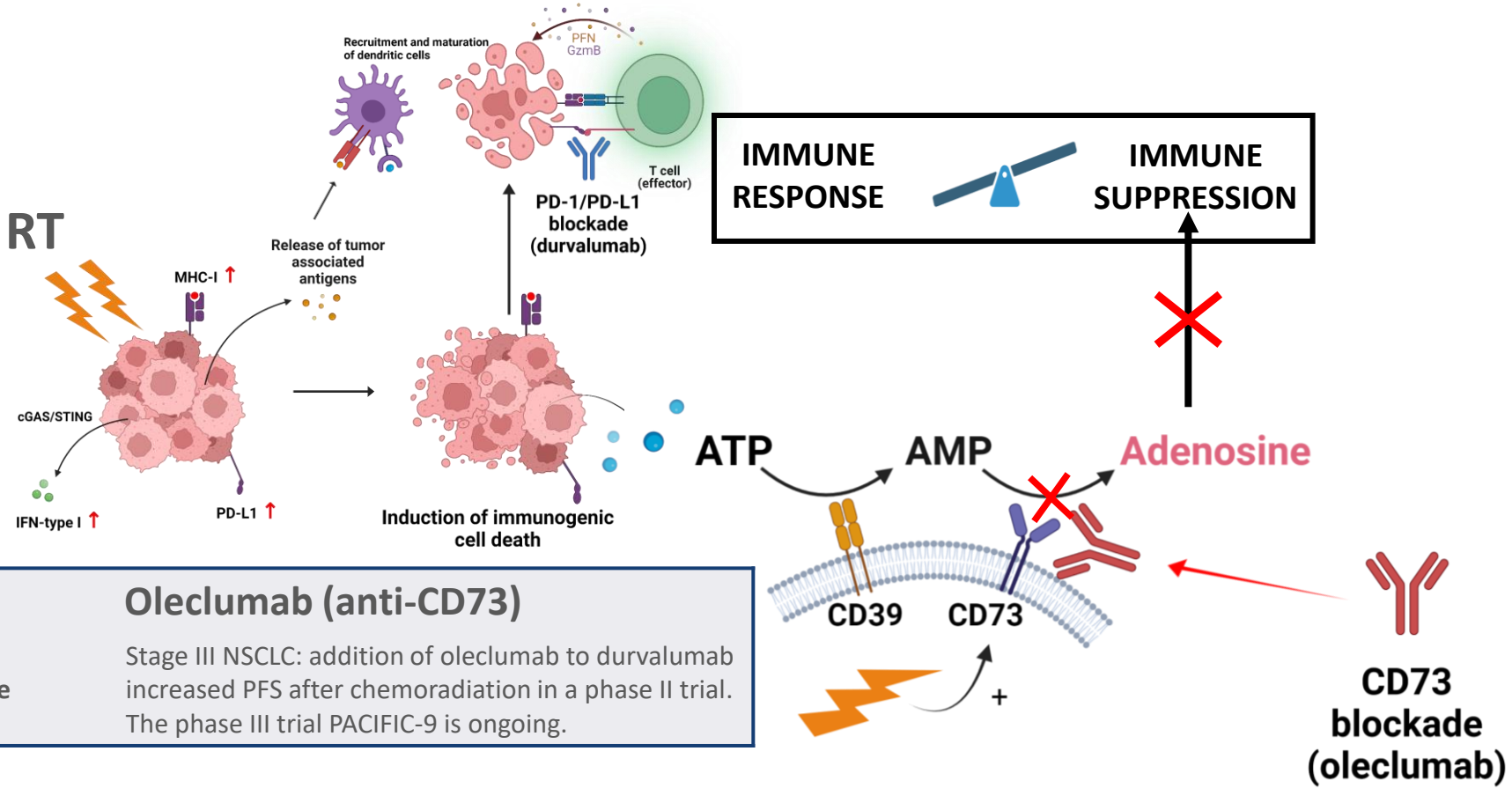
Background: immunosuppression through the adenosine pathway



Oleclumab (anti-CD73)

Clinical evidence

Stage III NSCLC: addition of oleclumab to durvalumab increased PFS after chemoradiation in a phase II trial. The phase III trial PACIFIC-9 is ongoing.

Created with BioRender.com

Allard B *et* al. Nat Rev Clin Onc, 2020 ; Wennerberg et al. Cancer Immunol Res 2020; Herbst R. et al. JCO 2022

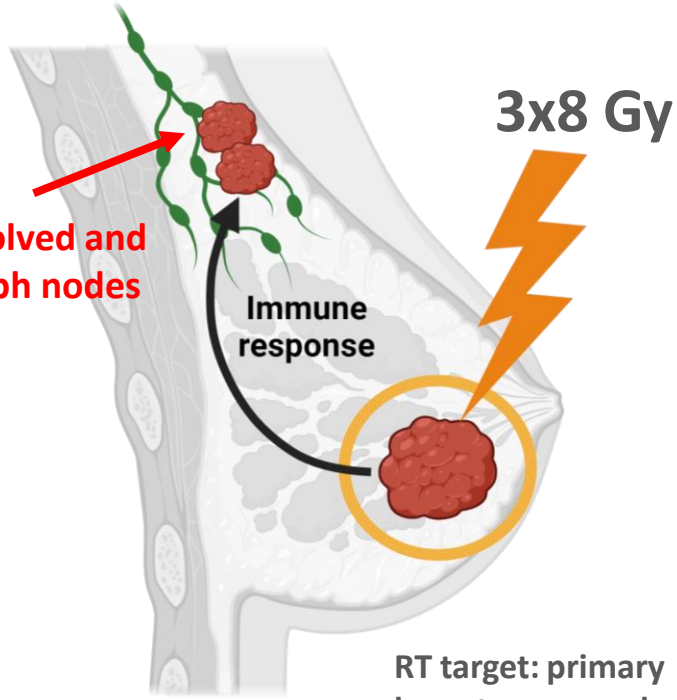
High risk early luminal B BC

Hypothesis:

Radiation therapy works synergistically with durvalumab and oleclumab to enhance the immune response.

How to add radiation therapy in the neo-adjuvant setting?

Chemo-(immunotherapy) → Surgery → Whole breast RT / Chest Wall RT / Nodal RT → Tumorbed boost → RT on tumor



No RT to involved and draining lymph nodes

RT target: primary breast cancer only

What radiation dose?

Immune modulating SBRT = iSBRT	
RT Intent	**Immunomodulation** Non-ablative intent of RT
RT dose	3 daily fraction of 8 Gy
When?	Shortly before the second cycle of durvalumab

Neo-CheckRay Study Design

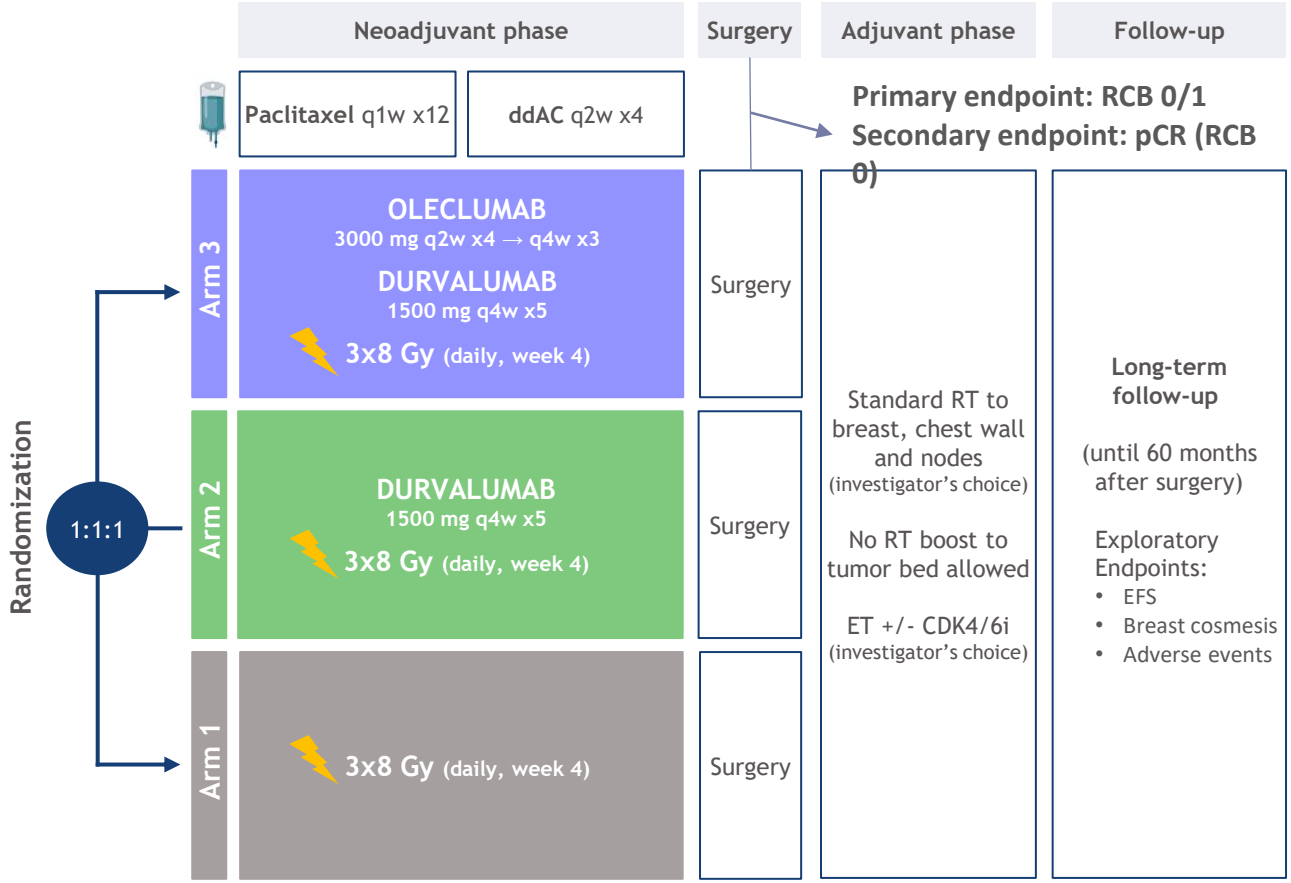
Screening

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.

Study endpoints and primary endpoint power calculation

Objective

Investigate NACT + iSBRT +/- DURVA +/- OLE to increase treatment response in early, MammaPrint High Risk, luminal B BC.

Primary endpoint

RCB 0-1 rate in ITT population

Secondary endpoints

pCR in ITT population (ypT0/TisypN0)
Safety and tolerability; % breast conserving surgery
Event Free Survival (EFS)

Exploratory endpoints

Fertility
Breast Cosmesis
Translational endpoints

Primary endpoint power calculation	
Accrual durantion, months	32
Sample size	132 (44 per arm)
Randomization	3 arms, 1:1:1
Hypothesized rates: control arm vs the 2 experimental arms	**15% vs 45%** **RCB 0/1**
Alpha	0.05
Power	80%

Final analysis in ITT population	
N screened patients	200
N randomized patients	147
N MammaPrint low risk after randomisation (excluded from ITT)	10
N non-evaluable in ITT	2*
N evaluable patients in ITT population	**135**
Data cut off date	03/09/2024

* 1 patient withdrew consent to participate in the trial before the surgery timepoint.

RT & immune therapy: *Neo-CheckRay*

De Caluwé *et al. BMC Cancer* (2021) 21:899
https://doi.org/10.1186/s12885-021-08601-1

BMC Cancer

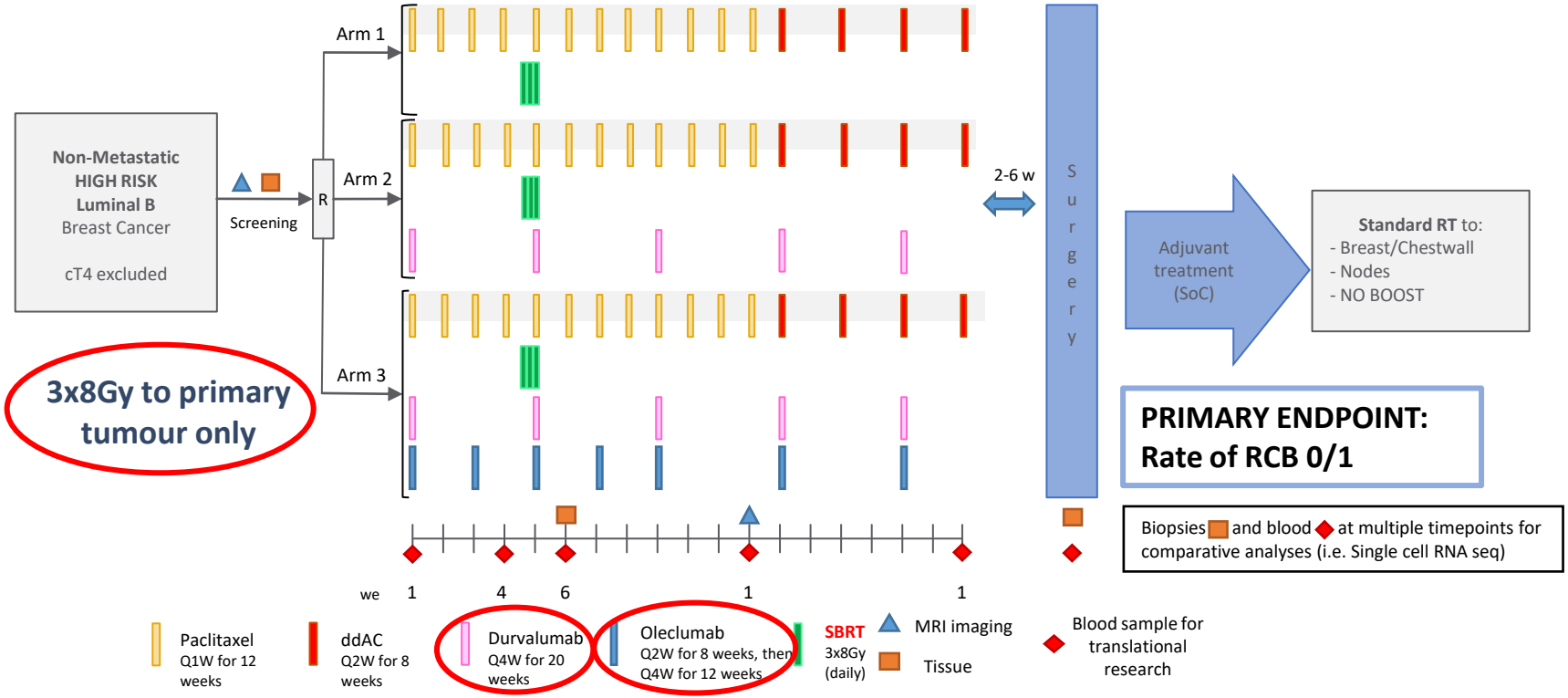
STUDY PROTOCOL Open Access

Neo-CheckRay: radiation therapy and adenosine pathway blockade to increase benefit of immuno-chemotherapy in early stage luminal B breast cancer, a randomized phase II trial

Alex De Caluwé[1*], Laurence Buisseret[1], Philip Poortmans[2], Dirk Van Gestel[1], Roberto Salgado[3], Christos Sotiriou[1], Denis Larsimont[1], Marianne Paesmans[1], Ligia Craciun[1], Drisis Stylianos[1], Christophe Vandekerckhove[1], Fabien Reyal[4], Veys Isabelle[1], Daniel Eiger[1], Martine Piccart[1], Emanuela Romano[4†] and Michail Ignatiadis[1†]

De Caluwé A, et al. BMC Cancer. 2021;21:899.

RT & immune therapy: *Neo-CheckRay*



De Caluwé A, et al. BMC Cancer. 2021;21:899.

RT & immune therapy: *Neo-CheckRay*

Open access Original research

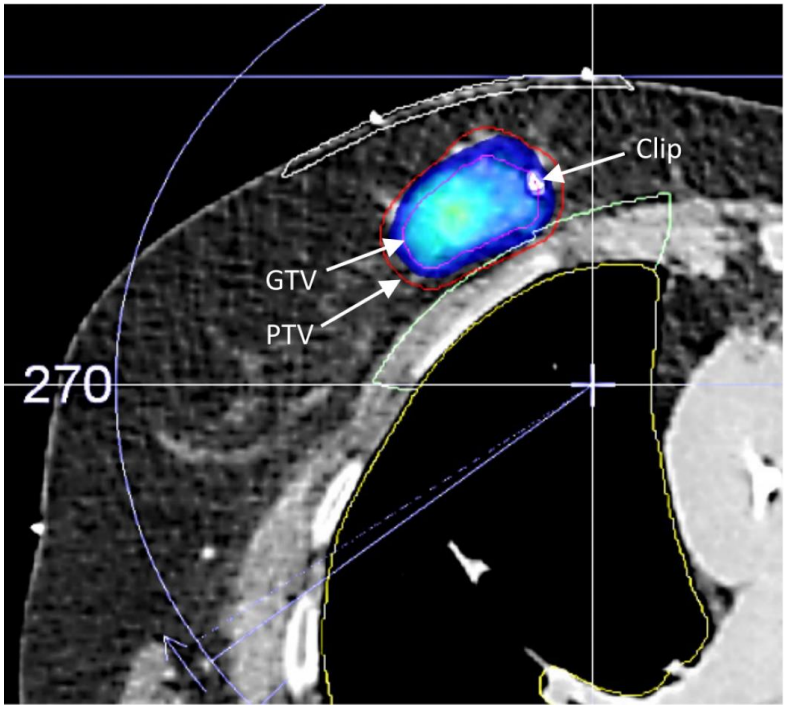
Journal for ImmunoTherapy of Cancer

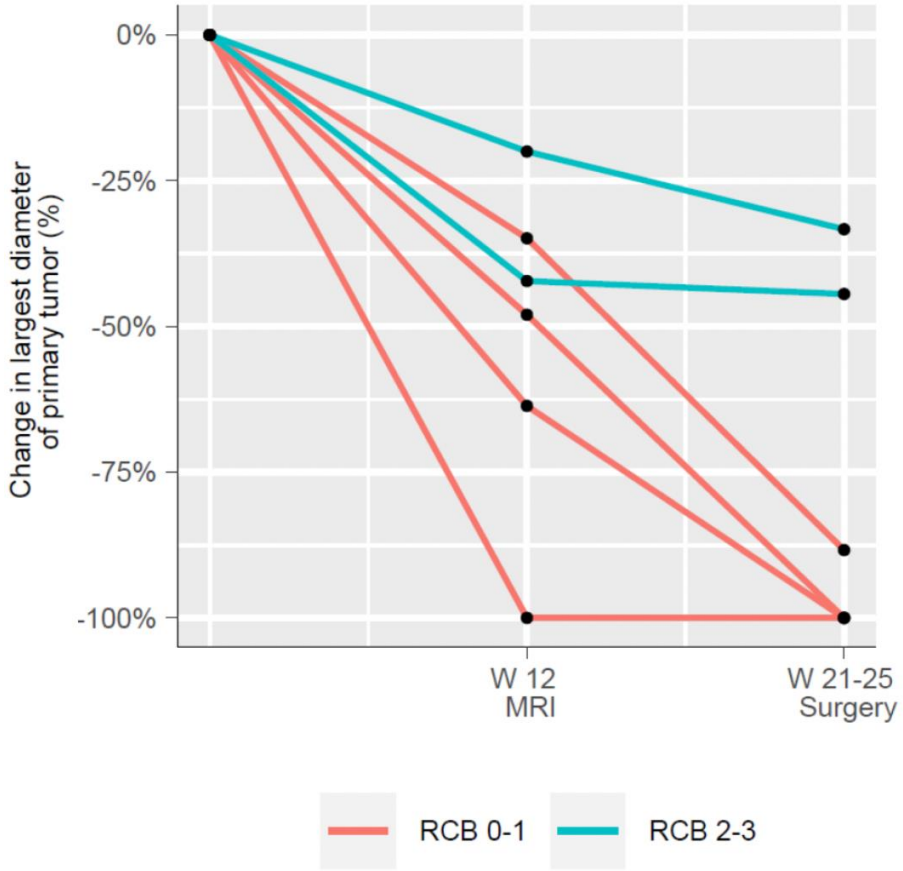
First-in-human study of SBRT and adenosine pathway blockade to potentiate the benefit of immunochemotherapy in early-stage luminal B breast cancer: results of the safety run-in phase of the Neo-CheckRay trial

Alex De Caluwe [1], Emanuela Romano,[2] Philip Poortmans,[3] Andrea Gombos,[4] Elisa Agostinetto,[5] Guilherme Nader Marta,[5] Zoe Denis,[6] Stylianos Drisis,[7] Christophe Vandekerkhove,[8] Antoine Desmet,[1] Catherine Philippson,[1] Ligia Craciun,[9] Isabelle Veys,[10] Denis Larsimont,[9] Marianne Paesmans,[5] Dirk Van Gestel,[1] Roberto Salgado,[11] Christos Sotiriou,[4] Martine Piccart-Gebhart,[4] Michail Ignatiadis,[4] Laurence Buisseret [4]

De Caluwe A, et al. J Immunother Cancer 2023;11:e007279.

RT & immune therapy: *Neo-CheckRay*





De Caluwe A, et al. J Immunother Cancer 2023;11:e007279.

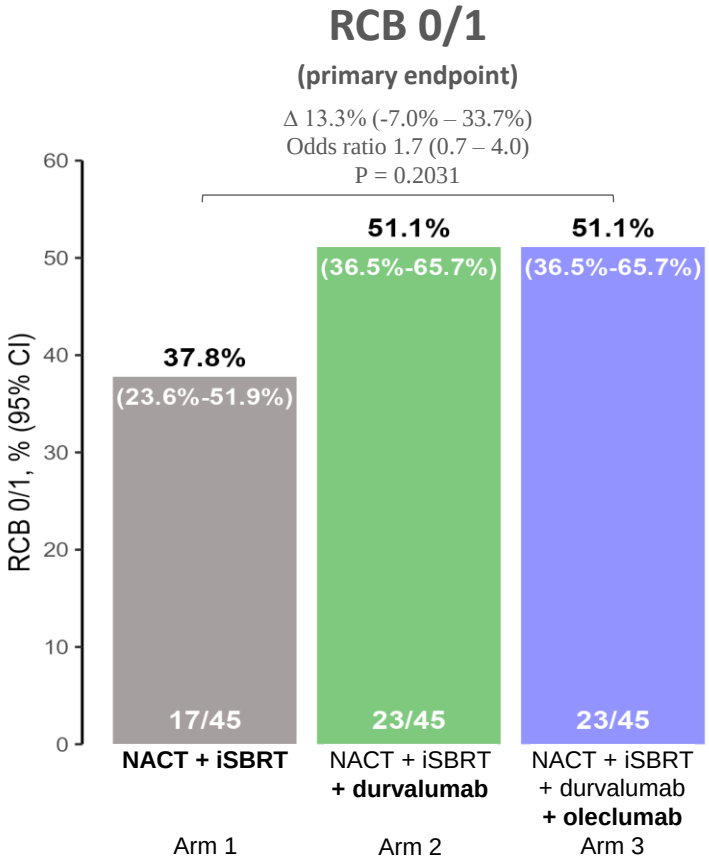
RT & immune therapy: *Neo-CheckRay*

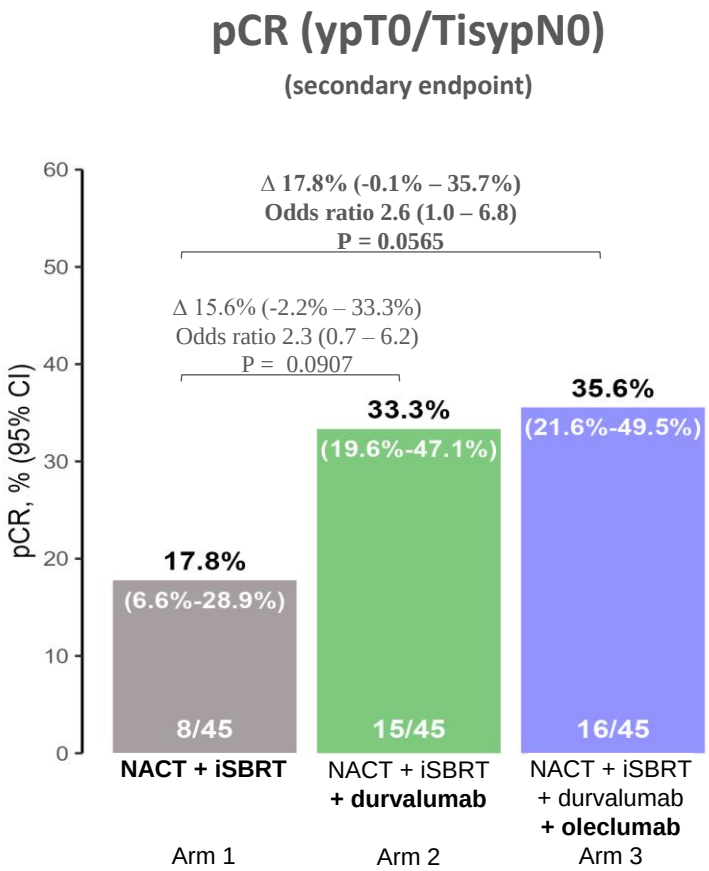
*In conclusion, the Neo-CheckRay first-in-human safety run-in demonstrates that the combination of NACT, ICB, oleclumab and SBRT 3*8 Gy to the primary tumor is feasible with encouraging results at surgery and with a manageable toxicity profile in early luminal B BC.*

This novel combination is under further investigation in an ongoing phase II trial to evaluate its efficacy.

De Caluwe A, et al. J Immunother Cancer 2023;11:e007279.

RCB 0/1 and pCR in ITT population (n=135)

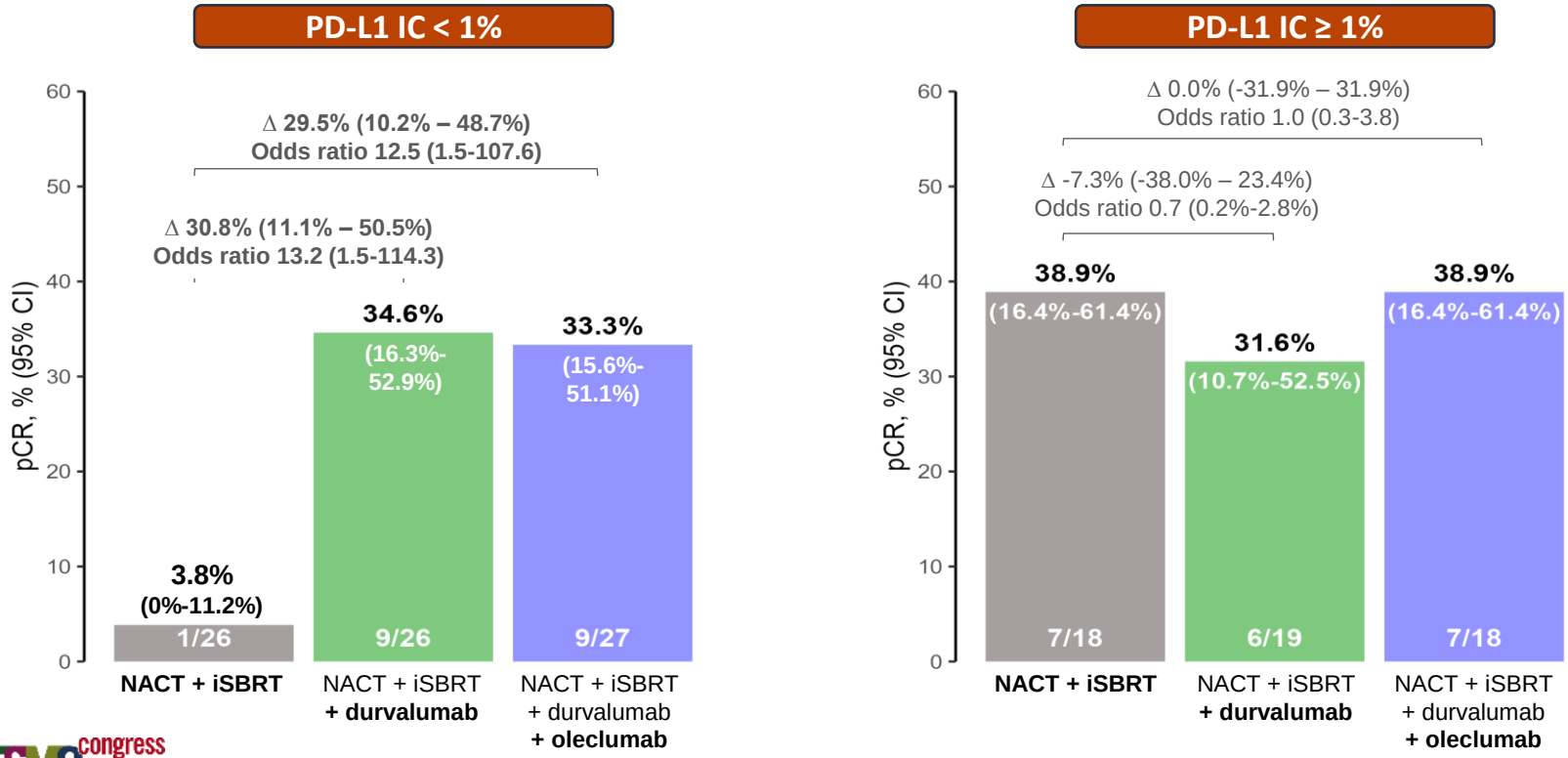




Trial powered to detect 15% → 45% RCB 0/1

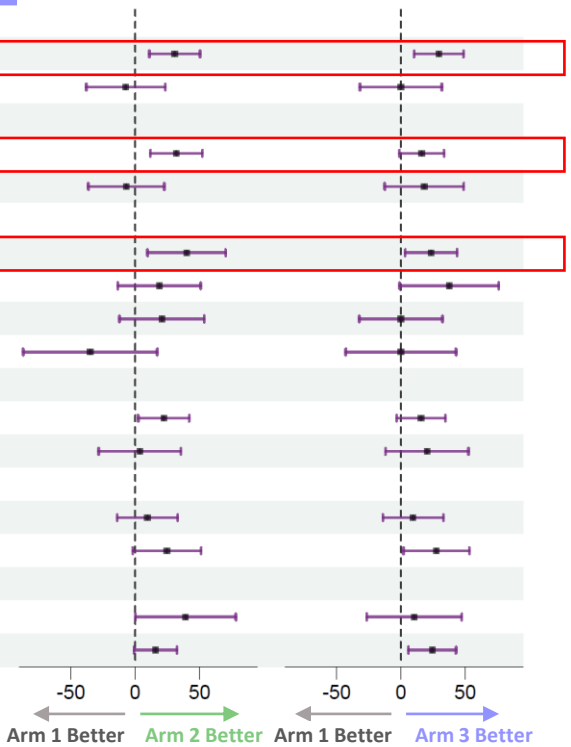
Exploratory subgroup analysis in ITT according factor PD-L1 (stratification factor)

pCR (ypT0/TisypN0)

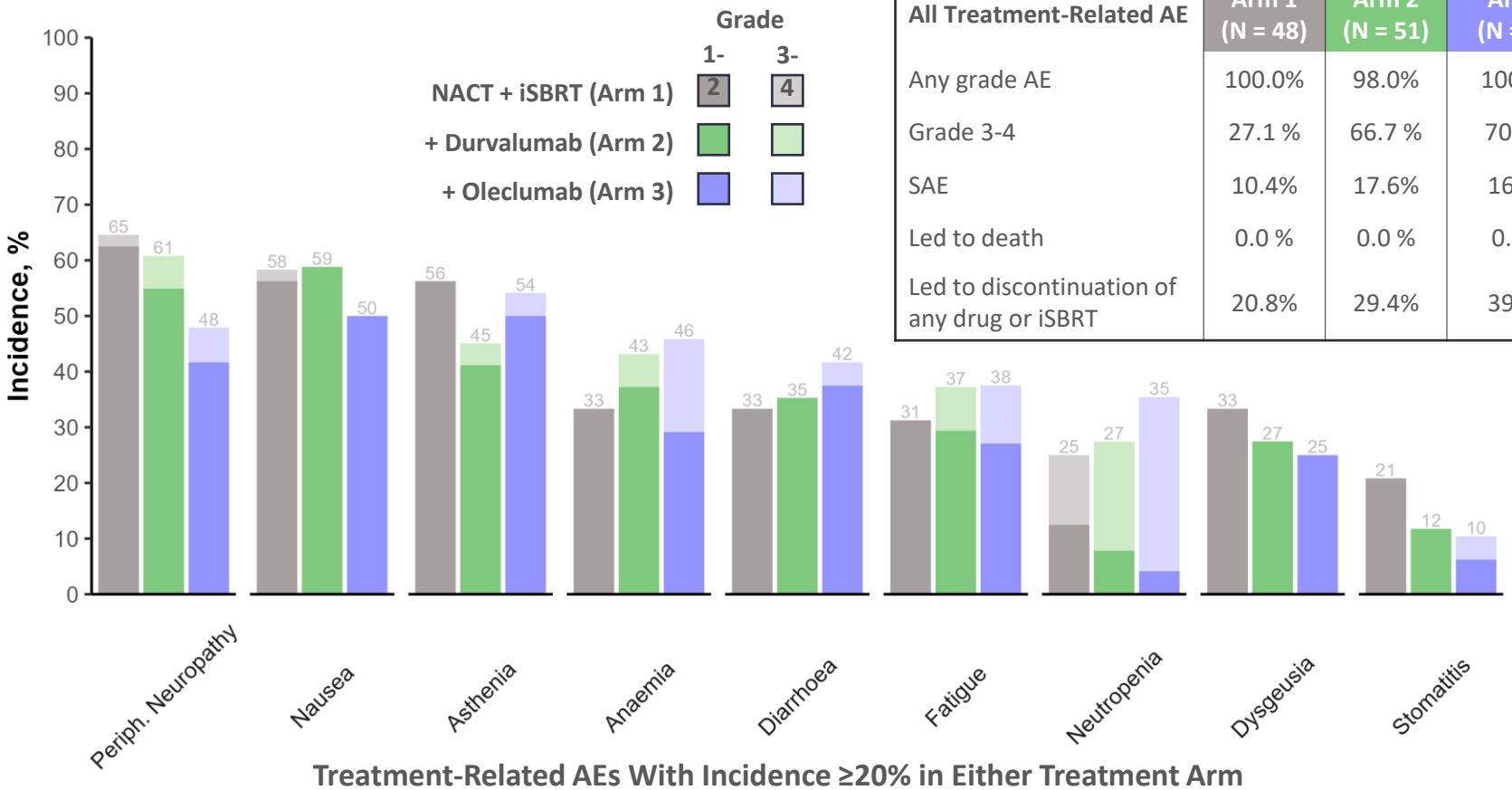


pCR in subgroups (n=135)

		N A1	N A2	N A3	Arm 1 NACT + iSBRT pCR (95% CI)	Arm 2 NACT + iSBRT + DURVA pCR (95% CI)	Arm 3 NACT + iSBRT + DURVA + OLE pCR (95% CI)
Stratified	PD-L1 (IC-score)						
	<1%	26	26	27	3.8 (-3.5-11.2)	34.6 (16.3-52.9)	33.3 (15.6-51.1)
	≥1%	18	19	18	38.9 (16.4-61.4)	31.6 (10.7-52.5)	38.9 (16.4-61.4)
	Nodal Status						
	cN+	26	25	25	3.8 (-3.5-11.2)	36.0 (17.2-54.8)	20.0 (4.3-35.7)
	cN0	19	20	20	36.8 (15.2-58.5)	30.0 (9.9-50.1)	55.0 (33.2-76.8)
	Combination						
	PD-L1 <1% (IC) – cN+	18	10	17	0.0 (0.0-0.0)	40.0 (9.6-70.4)	23.5 (3.4-43.7)
	PD-L1 <1% (IC) – cN0	8	16	10	12.5 (-10.4-35.4)	31.2 (8.5-54.0)	50.0 (19.0-81.0)
	PD-L1 ≥1% (IC) - cN+	8	15	8	12.5 (-10.4-35.4)	33.3 (9.5-57.2)	12.5 (-10.4-35.4)
	PD-L1 ≥1% (IC) - cN0	10	4	10	60.0 (29.6-90.4)	25.0 (-17.4-67.4)	60.0 (29.6-90.4)
	PD-L1 (CPS)						
	<1	27	27	26	7.4 (-2.5-17.3)	29.6 (12.4-46.9)	23.1 (6.9-39.3)
	≥1	17	18	18	35.3 (12.6-58.0)	38.9 (16.4-61.4)	55.6 (32.6-78.5)
	Stromal TILs						
	<1%	21	21	21	14.3 (-0.7-29.3)	23.8 (5.6-42.0)	23.8 (5.6-42.0)
	≥1%	22	21	24	18.2 (2.1-34.3)	42.9 (21.7-64.0)	45.8 (25.9-65.8)
	MammaPrint						
	Ultra High	14	8	13	35.7 (10.6-60.8)	75.0 (45.0-105.0)	46.2 (19.1-73.3)
	High	29	35	32	6.9 (-2.3-16.1)	22.9 (8.9-36.8)	31.2 (15.2-47.3)



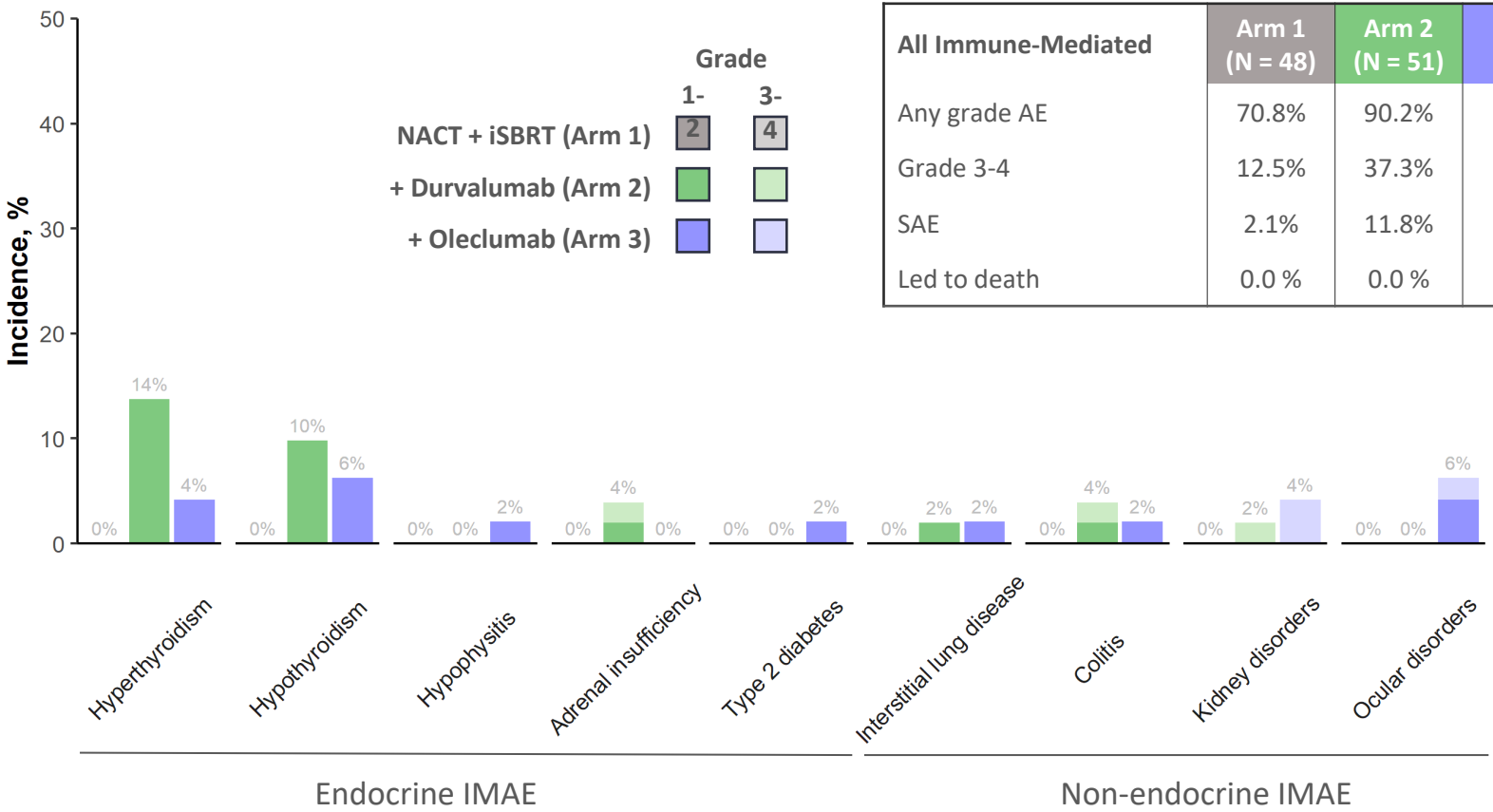
Treatment-Related AEs in Neoadjuvant Phase (n=147)



Treatment-Related AEs With Incidence ≥20% in Either Treatment Arm

All Treatment-Related AE	Arm 1 (N = 48)	Arm 2 (N = 51)	Arm 3 (N = 48)
Any grade AE	100.0%	98.0%	100.0%
Grade 3-4	27.1 %	66.7 %	70.8 %
SAE	10.4%	17.6%	16.7%
Led to death	0.0 %	0.0 %	0.0 %
Led to discontinuation of any drug or iSBRT	20.8%	29.4%	39.5%

Immune-Mediated AEs in Neoadjuvant Phase (n=147)



All Immune-Mediated	Arm 1 (N = 48)	Arm 2 (N = 51)	Arm 3 (N = 48)
Any grade AE	70.8%	90.2%	91.7%
Grade 3-4	12.5%	37.3%	31.3%
SAE	2.1%	11.8%	6.3%
Led to death	0.0 %	0.0 %	0.0 %

Immune-Mediated AEs were pre-listed, regardless of treatment or immune relatedness by the investigator.

iSBRT and surgery (n=147)

iSBRT 3x8 Gy

	Arm 1 (N = 48)	Arm 2 (N = 51)	Arm 3 (N = 48)
Any grade AE	12.5%	15.7%	18.8%
Grade 3-4 AE	0%	0%	0%
Grade 1-2 AE	12.5%	15.7%	18.8%
Radiodermatitis	0%	0%	6.3%
Radiation pneumonitis	0%	0%	0%
Breast oedema	0%	0%	0%
Breast pain	4.2%	2.0%	0%

Surgery

	Arm 1 (N = 48)	Arm 2 (N = 51)	Arm 3 (N = 48)
Type of surgery			
Breast-conserving	66.7%	74.5%	68.1%
Mastectomy	33.3%	25.5%	31.9%
Surgery delayed (> 6 weeks after last systemic treatment)	6.3%	2.0%	8.5%
Any grade AE	14.6%	17.6%	14.6%
Grade 3-4 AE	2.1%	0.0%	2.1%
Grade 1-2 AE	12.5%	17.6%	12.5%
Infection after surgery	4.2%	5.9%	4.2%
Hematoma/Erythema	2.1%	5.9%	0%
Wound complication	0%	0%	4.2%

AE related to iSBRT and surgery up to 30 days after surgery.

Summary and conclusions

NEO-CHECKRAY trial in early luminal B BC:

- **First phase II trial** investigating the addition to **immuno-chemo** of:
  - **iSBRT 3x8Gy** to the primary tumor *to induce an immune response*
  - **Anti-CD73** (oleclumab) *to decrease the production of immunosuppressive adenosine*
- The trial demonstrated **promising activity at surgery** of the novel treatment combination which will need to be further validated in larger trials
- The benefit iSBRT and immunotherapy combination is **more pronounced in patients with PD-L1<1%**
- The novel treatment combinations were **safe and feasible**.
- Extensive ongoing **translational research**, including on-treatment biopsies one week after iSBRT, aims to better understand mechanisms of response and the contribution of oleclumab.

Radiation therapy & immune therapy – Neo-CheckRay

- Introduction
- Breast cancer immunogenicity
- Immunotherapy in BC: where are we?
- Luminal-B BC: Neo-CheckRay
- Discussion
- Conclusions

https://images.app.goo.gl/eyiH5tKyU8Vq7RYWA

RT & immune therapy: *Evidence in BC*

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

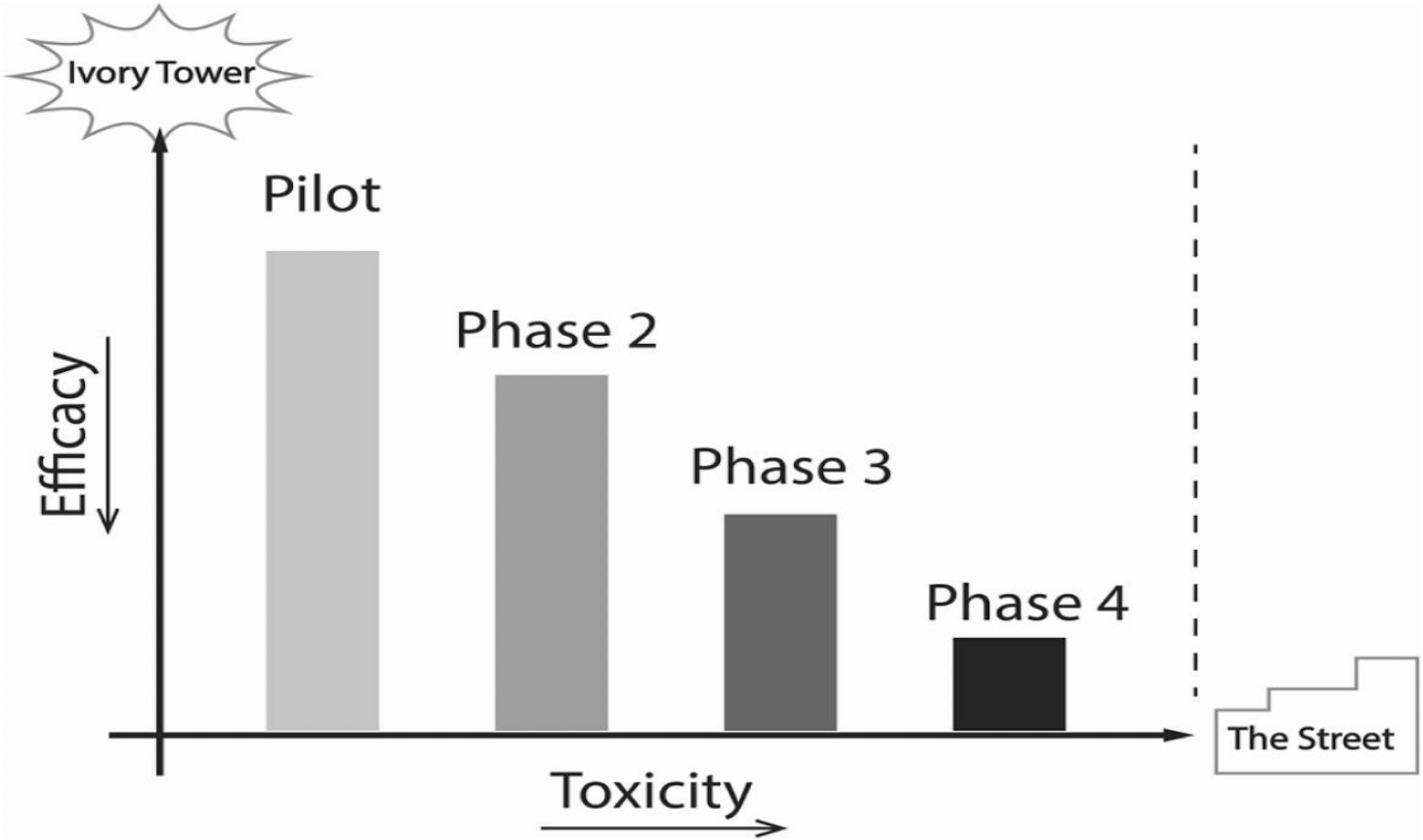
Review Article

Essential requirements for reporting radiation therapy in breast cancer clinical trials: An international multi-disciplinary consensus endorsed by the European Society for Radiotherapy and Oncology (ESTRO)

Orit Kaidar-Person [a,b,c], Icro Meattini [d,e,*], Liesbeth J. Boersma [c], Carlotta Becherini [e], Javier Cortes [f,g], Giuseppe Curigliano [h,i], Evandro de Azambuja [j], Nadia Harbeck [k], Hope S. Rugo [l], Lucia Del Mastro [m,n], Alessandra Gennari [o], Clare M. Isacke [p], Maja Vestmø Maraldo [q], Elisabetta Marangoni [r], Gustavo Nader Marta [s,t], Ingvil Mjaaland [u], Viola Salvestrini [e], Tanja Spanic [v,w], Luca Visani [e], Andrea Morandi [d], Matteo Lambertini [m,n], Lorenzo Livi [d,e], Charlotte E. Coles [x], Philip Poortmans [y,z], Birgitte V. Offersen [aa]

Kaidar-Person O, et al. Radiother Oncol 2024;195:110060.

RT & immune therapy: *Evidence in BC*



Kaidar-Person O, et al. Radiother Oncol 2024;195:110060.

RT & immune therapy: *Evidence in BC*

International multi-disciplinary consensus on the integration of radiation therapy with new systemic treatments for breast cancer: ESTRO endorsed recommendations

Statement	Consensus (%)
Key question 1. Minimal Requirements of Radiation Therapy Features in Clinical Trials Assessing Novel Drugs for Breast Cancer	
1a. Long term safety data is needed for combining new-biological agents with RT for patients with early breast cancer [V, A]	Strong consensus (95)
1b. When combining new agents and RT, reporting of RT details and toxicity should be mandatory when reporting safety data for both the early and advanced settings [V, A]	Unanimous consensus (100)
1c. There is a lack of high-quality clinical data concerning the combination of RT and new drugs for breast cancer: prospective research studies are strongly recommended to strengthen the evidence-base [V, A]	Unanimous consensus (100)
1d. The potential risks, benefits, and uncertainties regarding the combination of RT and new drugs for breast cancer should be fully discussed with the patient [V, A]	Unanimous consensus (100)

Meattini I, et al. Lancet Oncol 2024;25:e73–83.

RT & immune therapy: *Discussion*

Radiotherapy and Oncology 206 (2025) 110836

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Adapting radiation therapy to immunotherapy: Delineation and treatment planning of pre-operative immune-modulating breast iSBRT in 151 patients treated in the randomized phase II Neo-CheckRay trial

A.De Caluwé [a,*], S. Bellal [a], K. Cao [b], K. Peignaux [c], V. Remouchamps [d], A. Baten [e], E. Longton [f], I. Bessieres [c], J. Vu-Bezin [b], Y. Kirova [b], D.Van Gestel [a], I. Desmoulins [c], M. Ignatiadis [a], E. Romano [b], L. Buisseret [a], M. Piccart [a], C. Vandekerkhove [a], A. Gulyban [a], P. Poortmans [g]

De Caluwe A, et al. Radiother Oncol 2025;206:110836.

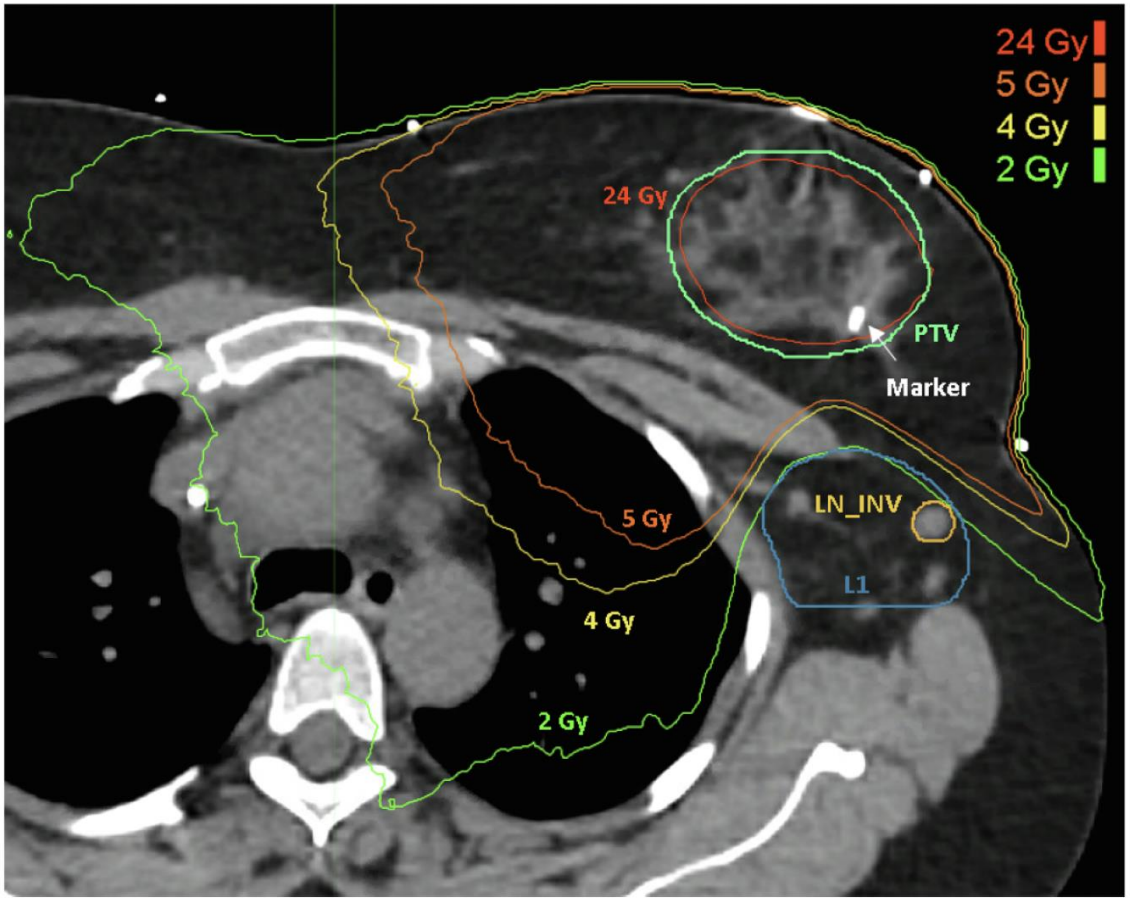
RT & immune therapy: *Discussion*

Radiation therapy protocol and achieved doses in the Neo-CheckRay trial.

Trial protocol			Achieved in the trial (n = 151)		
Volume	Constraint	Planning priority	Median (90 % CI)	Min-max	% of plans that achieved goal
Target doses					
GTV_eval	V22.8 Gy > 95 % (=V95%)	2	97.4 % (26.5–100)	0–100	60.0 %
PTV_eval	V19.2 Gy > 80 % (=V80%)	4	95.5 % (56.1–100)	0–100	79.4 %
Conformality					
Body	D0.1 cc < 36 Gy	/	25 Gy (20.5–27.3)	13.3–19.2	99.3 %
	D2cc < 28.8 Gy	/	25 Gy (20.5–27.3)	13.3–19.2	99.3 %
Body-PTV	D0.1 cc < 31.2 Gy	/	22.5 (17.5–24.7)	12.6–25.5	100 %
	D2cc < 24 Gy	/	22.5 Gy (17.5–24.7)	12.6–25.5	100 %
Body-(PTV + 3 cm)	D0.1 cc < 12 Gy	/	0 Gy (0.0–0.0 Gy)	0.0–0.0	100 %
Organs at risk					
Skin-3	D0.1 cc < 19.2 Gy	1	9.2 Gy (7.5–18.6)	0.1–21.7	98.0 %
Skin-5	D10cc < 15 Gy	1	9.2 (3.4–14.2)	0.0–17.7	98.0 %
Chest wall	D1cc < 15 Gy	3	14.6(4.3–24.4)	0.0–30	55.6 %
	D15cc < 10 Gy	3	7.7(0.1–15.8)	0.0–23.6	79.4 %
Ipsilateral non-target breast *	V24Gy < 30 %	8	0.0(0–0.6)	0.0–0.8	100 %
	V15Gy < 60 %	8	4.6(1.2–14.3)	0.1–22.8	100 %
Contralateral breast	D1cc < 1 Gy	7	1.0(0.4–2.4)	0.1–24.4	49.6 %
Ipsilateral lung	V20Gy < 2 %	6	0.0(0.0–0.0)	0.0–0.1	100 %
	V10Gy < 10 %	6	0.0(0.0–0.8)	0.0–4.6	100 %
	V5Gy < 20 %	6	1.6(0.0–7.9)	0.0–18.4	100 %
Contralateral lung	V20Gy < 1 %	6	0.0 (0.0–0.0)	0.0–0.0	100 %
	V10Gy < 2 %	6	0.0(0.0–0.0)	0.0–0.0	100 %
	V5Gy < 3 %	6	1.6 (0.0–7.9)	0.0–18.4	99.3 %
Lungs	dMean < 5 Gy	6	0.6 (0.2–1.2)	0.1–1.8	100 %
Heart	V20Gy ≤ 1 %	5	0.0 (0.0–0.0)	0.0–0.0	100 %
	V10Gy ≤ 2 %	5	0.0 (0.0–0.0)	0.0–0.3	100 %
	V5Gy ≤ 5 %	5	0.0 (0.0–1.0)	0.0–7.3	99.3 %
	dMean ≤ 2 %	5	0.5 (0.1–1.4)	0.0–2.1	100 %

De Caluwe A, et al. Radiother Oncol 2025;206:110836.

RT & immune therapy: *Discussion*



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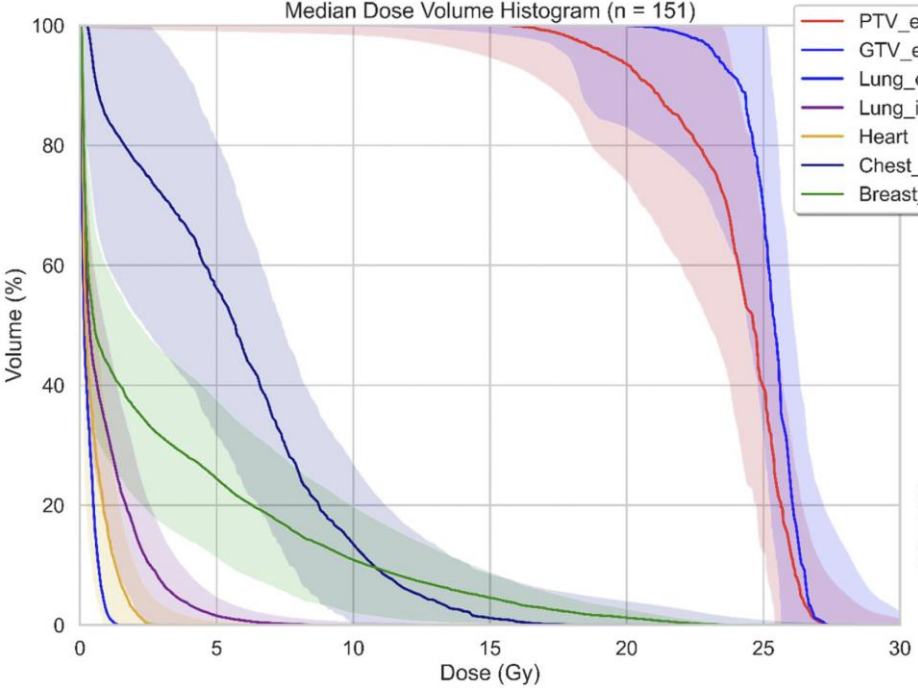
RT & immune therapy: *Discussion*

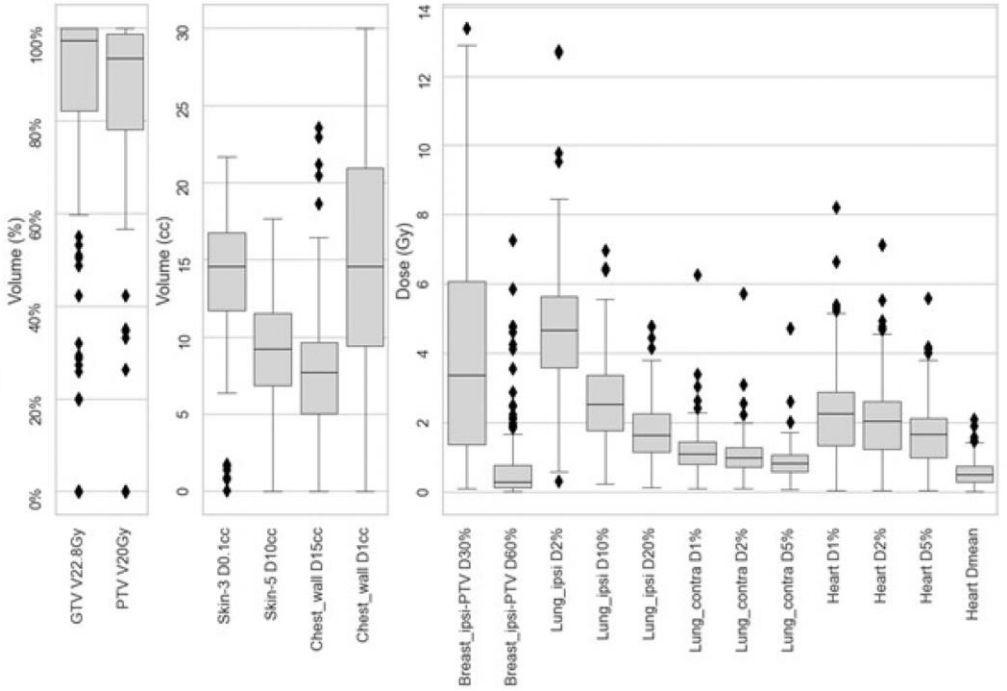
B. Volumes of GTV, PTV and ipsilateral breast.

		N	Median (range)	p
GTV	Overall	151	11.2 cc (0.9–211.3)	
	CT simulation	119	13.6 cc (1.1–203.2)	<0.01
	MRI simulation	32	6.4 cc (0.9–211.3)	
PTV	Overall	151	35.7 cc (4.9–342.4)	
	CT simulation	119	41.4 cc (5.4–334.3)	<0.01
	MRI simulation	32	20.1 cc (4.9–342.4)	
Breast	Ipsilateral breast	151	756 cc (116–2613)	
	% breast involvement by GTV	151	1.5% (0.01–28.2)	

De Caluwe A, et al. Radiother Oncol 2025;206:110836.

RT & immune therapy: *Discussion*





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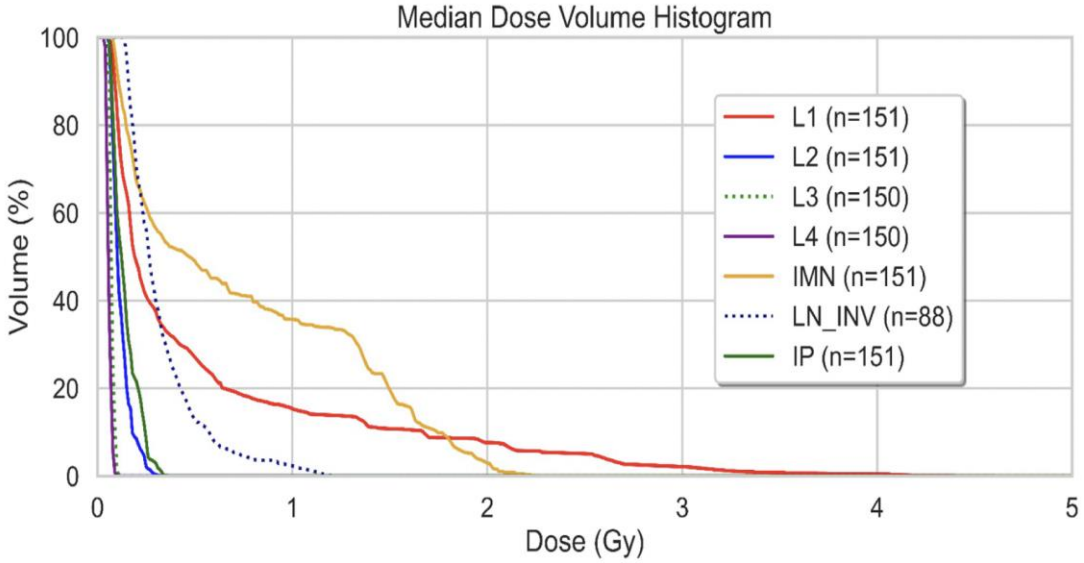
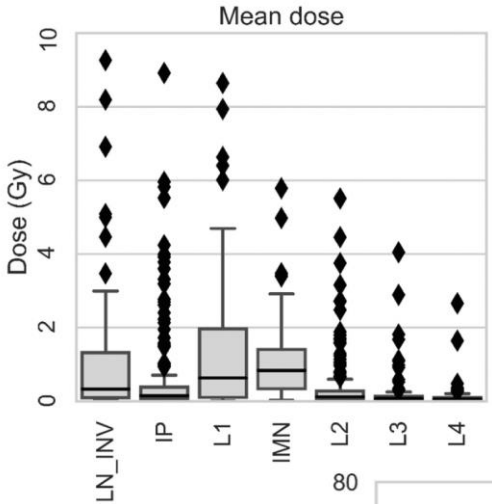
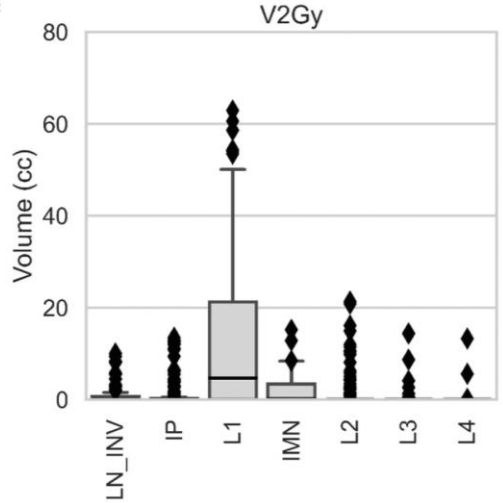
RT & immune therapy: *Discussion*







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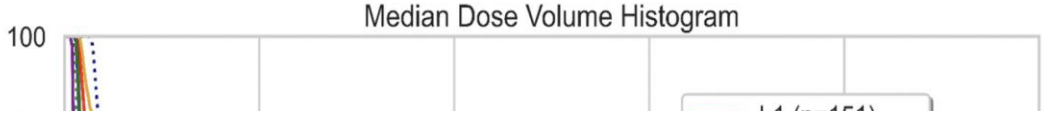
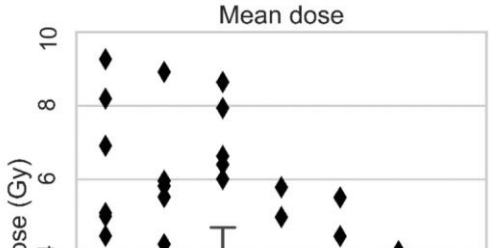
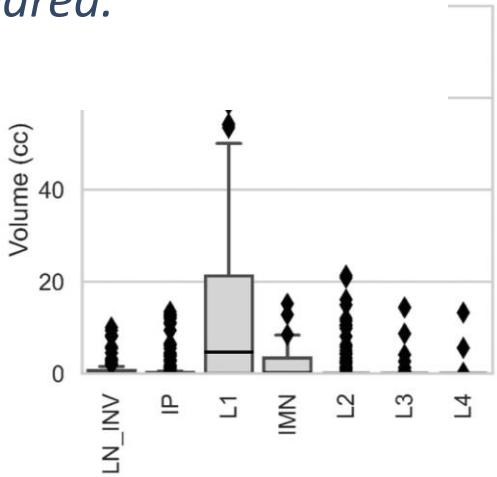
RT & immune therapy: *Discussion*





In the Neo-CheckRay trial, the predefined organs at risk dose constraints were feasible and the TD-LN were adequately spared.



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RT & immune therapy: *Discussion*

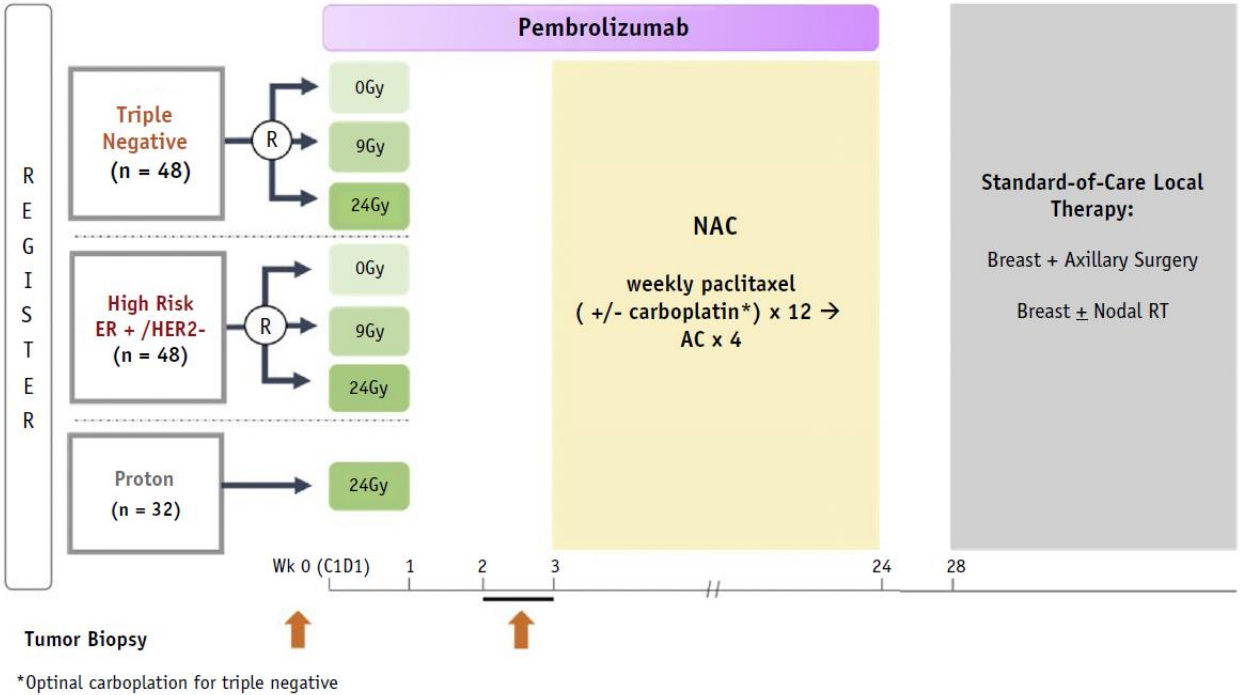

Fig. 4. Trial schema for P-RAD, a randomized study of preoperative chemotherapy, pembrolizumab, and no-, low-, or high-dose radiation in node-positive, HER2− breast cancer. *Abbreviations:* AC = doxorubicin and cyclophosphamide; NAC = neoadjuvant chemotherapy; RT = radiation therapy.

Ho AY, et al. Int J Radiat Oncol Biol Phys. 2020;108(1):227-241

Radiation therapy & immune therapy – Neo-CheckRay

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RT & immune therapy: *Introduction*

Panel 2: **Final consensus statements on key question 2—current evidence regarding the safety profile of a specific new systemic treatment when used in combination with ablative or palliative radiotherapy for intracranial or extracranial sites of disease in the metastatic and locoregional settings**

7) Immunotherapy

7a) Immunotherapy and concomitant radiotherapy could be considered during locoregional radiotherapy for breast cancer [II, B]

- Strong consensus (95%)

7b) Immunotherapy and concomitant radiotherapy including ultra hypofractionated regimens used for stereotactic radiotherapy could be offered for advanced breast cancer [II, B]¶

- Strong consensus (92·5%)

Meattini I, et al. Lancet Oncol 2024;25:e73–83.

RT & immune therapy: *Conclusions*

- There is a strong preclinical rationale to consider radiation therapy as a potential game-changer in combination with immunotherapy, but converting this principle into clinical practice is complicated
- Studies are ongoing, and future results will provide new elements to move further to radioimmunotherapy approaches

RT & immune therapy: *Conclusions*

There remains a lot of work to be done!

- Predictive biomarkers for RT-IO treatments: PD-L1, TILs, TMB, MSI?
- Sequencing: concomitant RT seems to be better - but may optimal timing varies?
- Further associations: PARPi (radiosensitiser!), other immunomodulatory targeted agents?
- Needed to define and/or confirm:
  - Optimal dose: 24 Gy in 3 fractions = derived from preclinical studies;
  - Optimal fractionation: probably better than a single high fraction;
  - Modality: tumour alone vs WBI;
  - Target definition:
    - The smaller the better?
    - Uniform vs heterogeneous irradiation?
    - Primary tumour or surgical bed?
    - Irradiation of lymph nodes?

RT & immune therapy: *Acknowledgements*

Acknowledgments

INSTITUT JULES BORDET INSTITUUT

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Financial support from AstraZeneca and Agendia

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Breast Cancer Radiation Therapy

A Practical Guide for Technical Applications

The book provides, in a comprehensive yet concise way, essential information to improve the knowledge and skills of all healthcare providers involved in the treatment of patients with breast cancer. The content does not focus on general information that is widely available via different sources, but on technical aspects – "hands-on" daily practices and principles of radiation oncology that are not included in other books. Drawing on information taught in courses at e.g. the ESTRO School, as well as the authors' broad clinical experience, the respective contributions reflect and share the expertise of leading experts in breast cancer radiation therapy, supported by sound data and evidence. Each chapter includes a short introduction summarizing the evidence in the literature and "pearls" (a short bullet-point summary), and is enriched by tables, figures and illustrations to provide a concise, easy-to-follow and appealing overview.

The book, containing also useful electronic supplementary material, will be of interest to a wide range of readers, including radiation oncologists, radiation technicians, medical physicists, and others involved in breast cancer care.

ISBN 978-3-030-91169-0

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