La valutazione della risposta durante e dopo la terapia neoadiuvante

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Disclosures

Potential conflicts of interest*

- Amgen
- Astrazeneca**
- Daichii Sankyo
- Celgene
- Eisai**
- Eli Lilly
- Gilead
- GSK
- Ipsen
- Italfarmaco
- Menarini
- MSD
- Novartis
- Pierre-Fabre
- Pfizer
- Roche**
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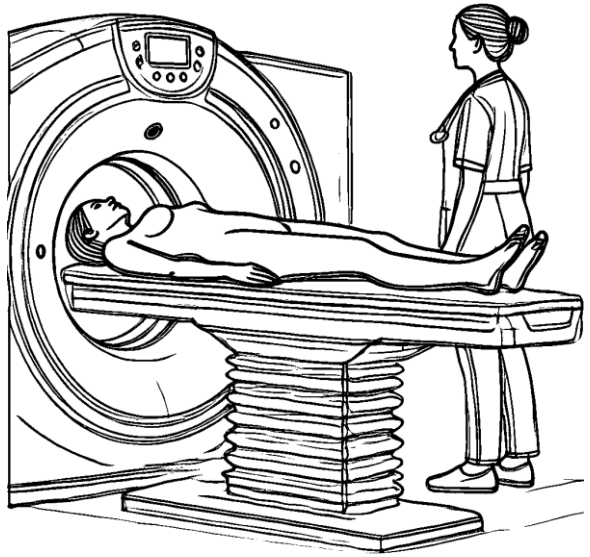
Views are my own, and do not necessarily represent opinions or positions of University of Udine, or IRCCS National Cancer Institute, Centro di riferimento Oncologico, Aviano.

Radiological and Pathological Response Assessment in Neoadjuvant Breast Cancer Therapy: Why It Matters

Radiological response

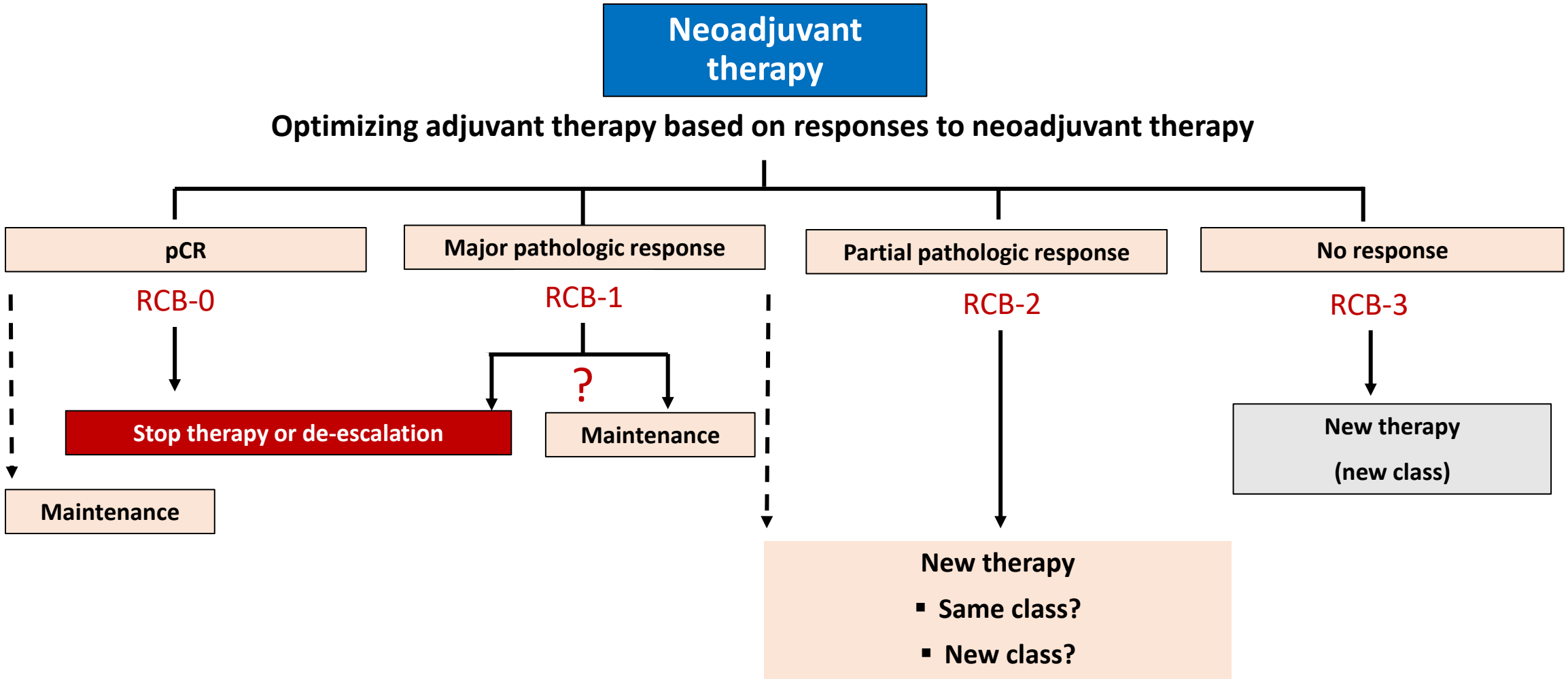
- Guides surgical planning
- Early identification of responders vs non-responders
  - potential treatment adaptation



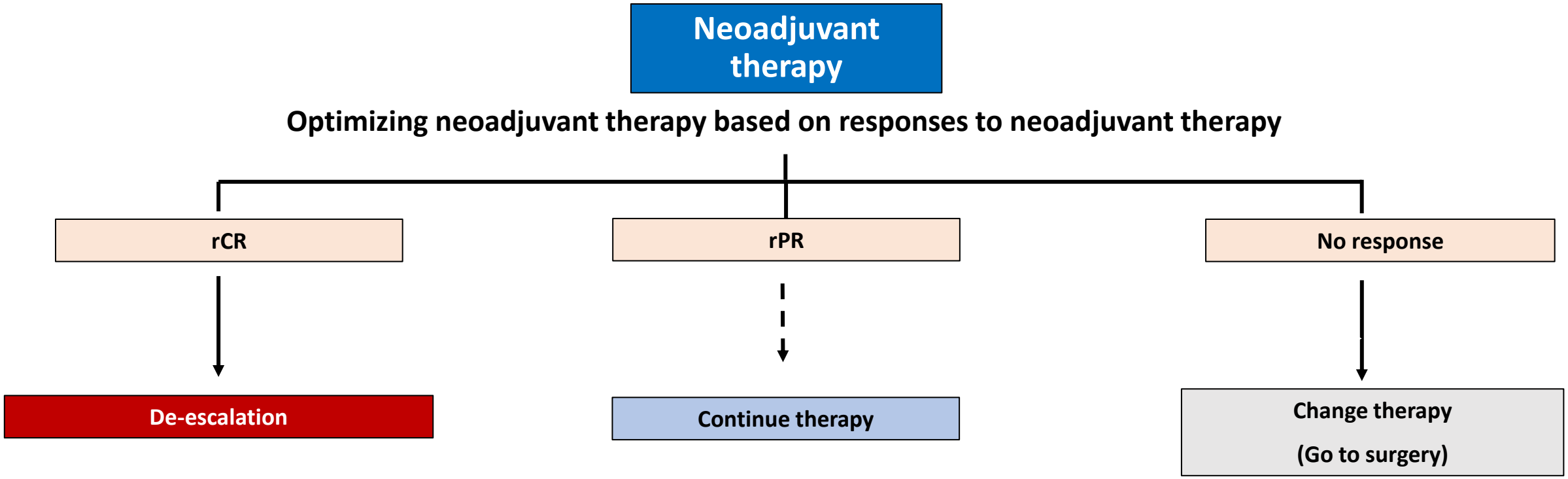
Pathological response

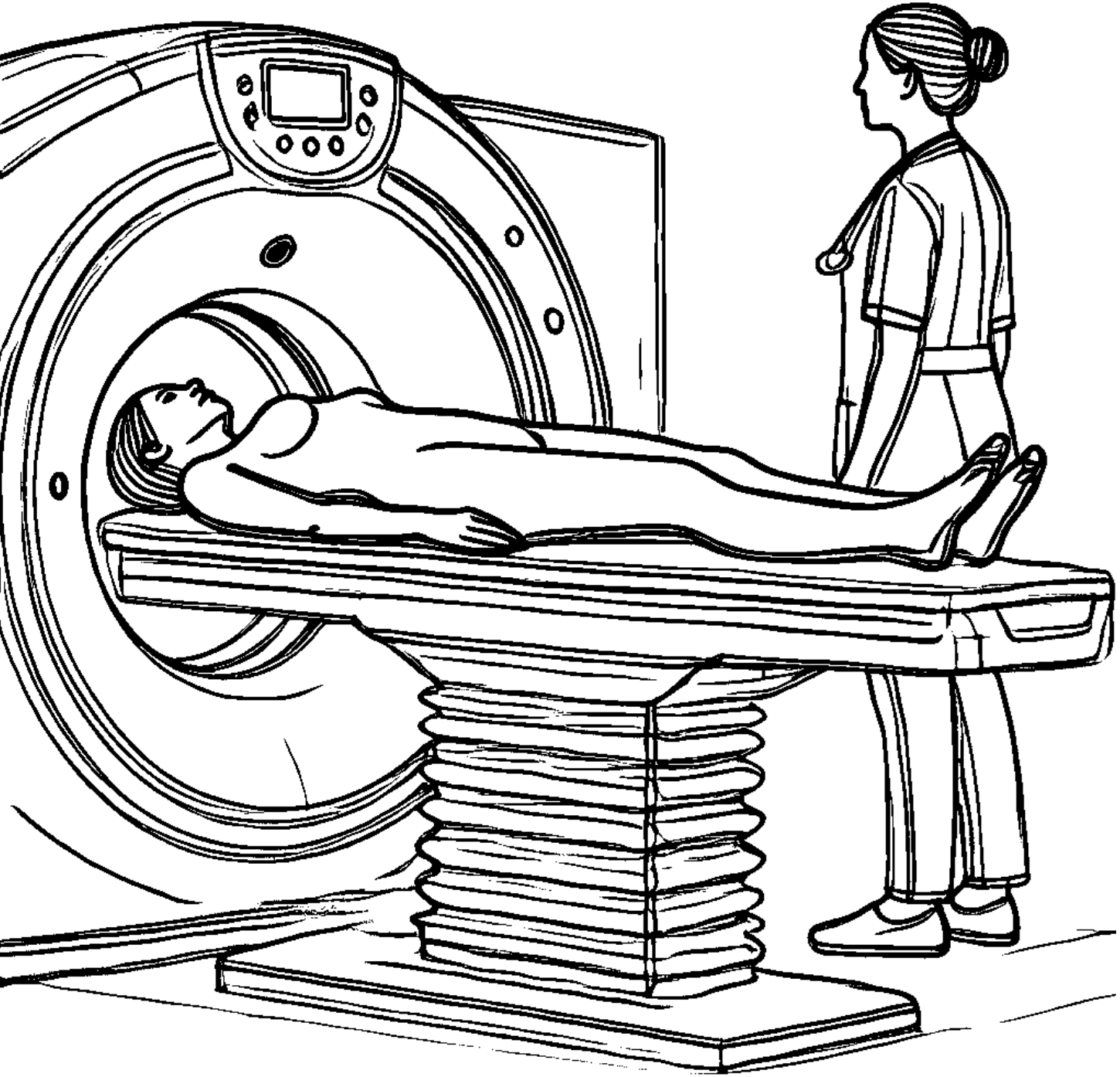
- Predicts long-term outcomes
- Informs adjuvant treatment decisions
  - Escalation
  - De-escalation

Optimizing Therapeutic Decisions Based on Response to Neoadjuvant Therapy



Optimizing Therapeutic Decisions Based on Response to Neoadjuvant Therapy





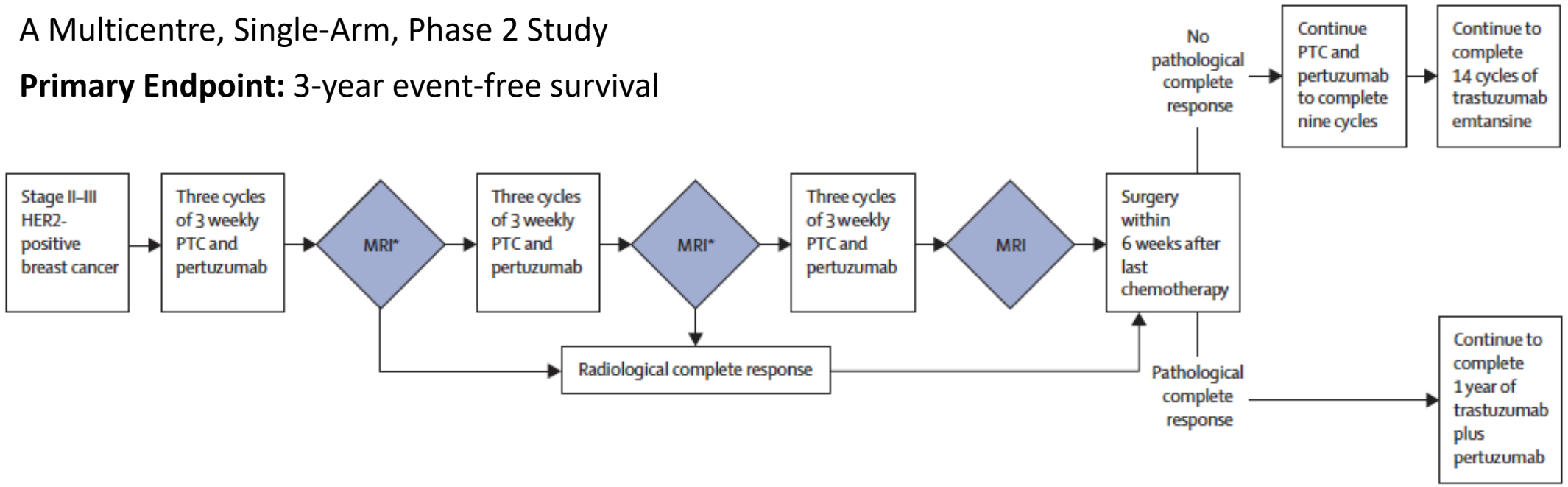
Imaging-guided strategies

The HER2-Positive Disease Example

TRAIN-3: MRI-guided optimisation of neoadjuvant chemotherapy duration in stage II-III HER2-pos BC

A Multicentre, Single-Arm, Phase 2 Study

Primary Endpoint: 3-year event-free survival



Treatment Regimen: paclitaxel 80 mg/m² on days 1 and 8 of each 21-day cycle and carboplatin AUC 6 on day 1 of each 21-day cycle. Maximum number of cycles: nine. Trastuzumab and Pertuzumab at standard doses.

van der Voort A, et al. Lancet Oncol 2024;25(5):603-613.

TRAIN-3: patient characteristics

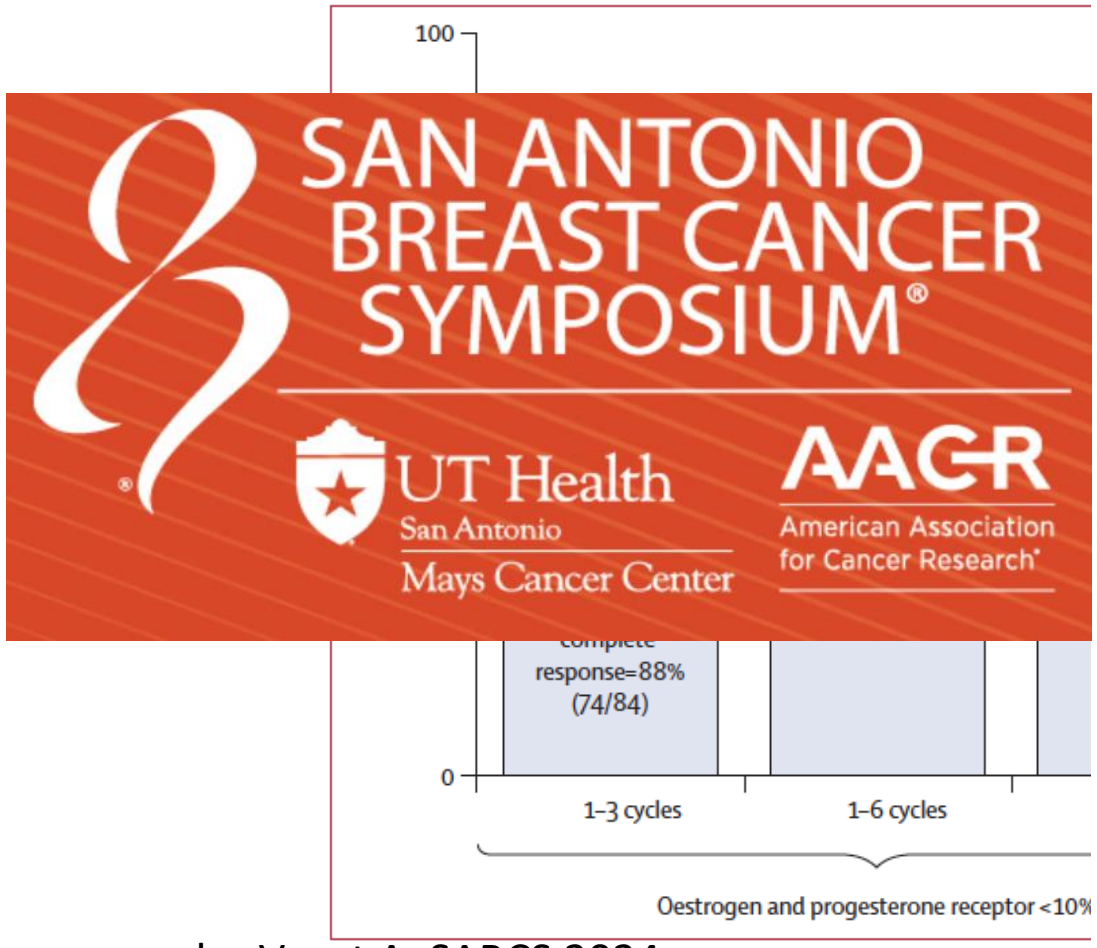
Sample size: 467 (235 HR-negative, 232 HR-positive)
Median Age: 51 years (IQR 43–59)
Tumour Stages

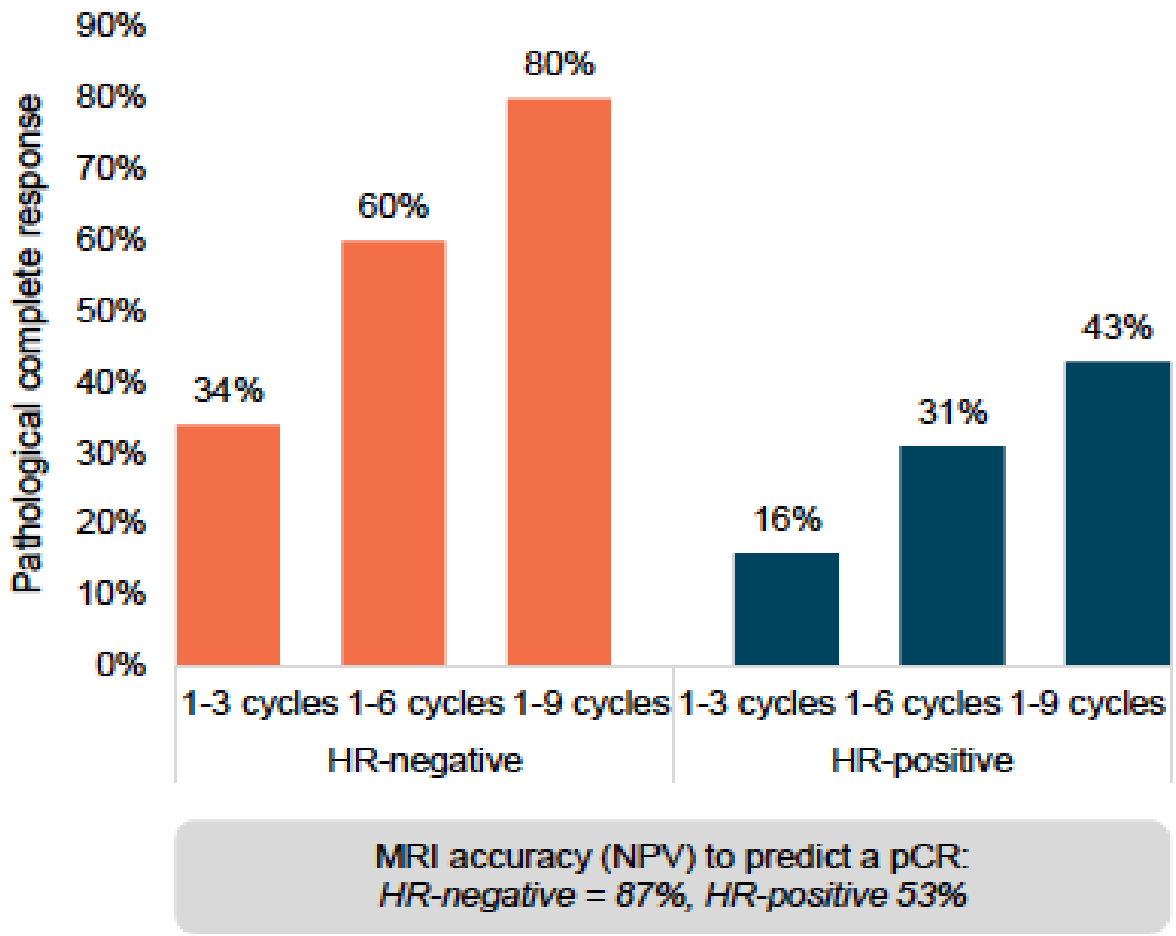
- Stage II: 69%, Stage III: 31%
- HER2 IHC 3+: 82%

Lymph Node Involvement: 60%
Menopausal Status: 45% postmenopausal

van der Voort A, et al. Lancet Oncol 2024;25(5):603-613.

TRAIN-3: cumulative response rates according to hormone receptor status

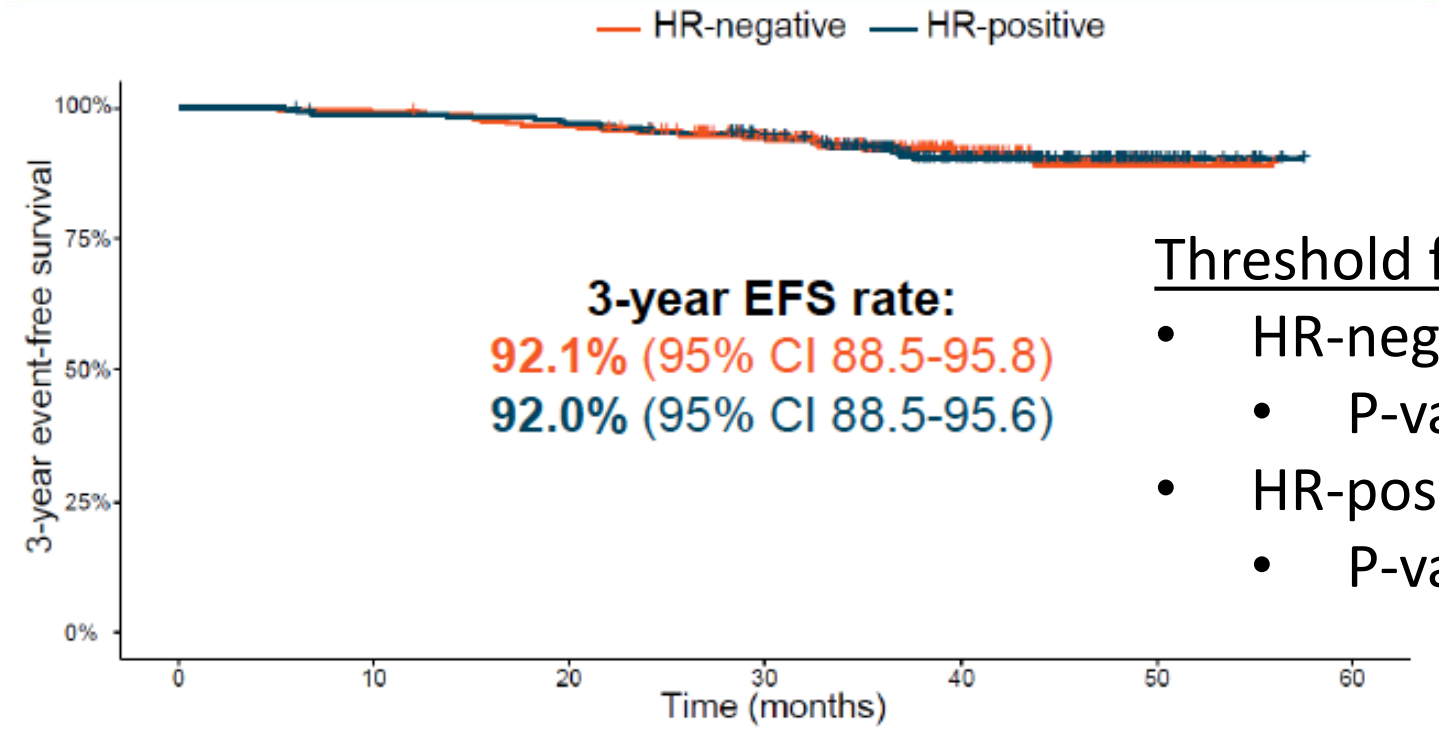




van der Voort A, SABCS 2024.

TRAIN-3 Update from SABCS 2024

Primary Endpoint (3-year event-free survival)



Threshold for success met:

- HR-negative events: 19 (≤38 allowed)
  - P-value=0.001
- HR-positive events: 21 (≤34 allowed)
  - P-value=0.023

van der Voort A, et al. SABCS 2024.

TRAIN-3: THM

- Demonstrated feasibility of MRI-based response monitoring for treatment tailoring.
- Reduced toxicity in early responders with fewer cycles.
- Key Insight: One in three HR-negative patients and one in six HR-positive patients achieved pCR with just 3 cycles

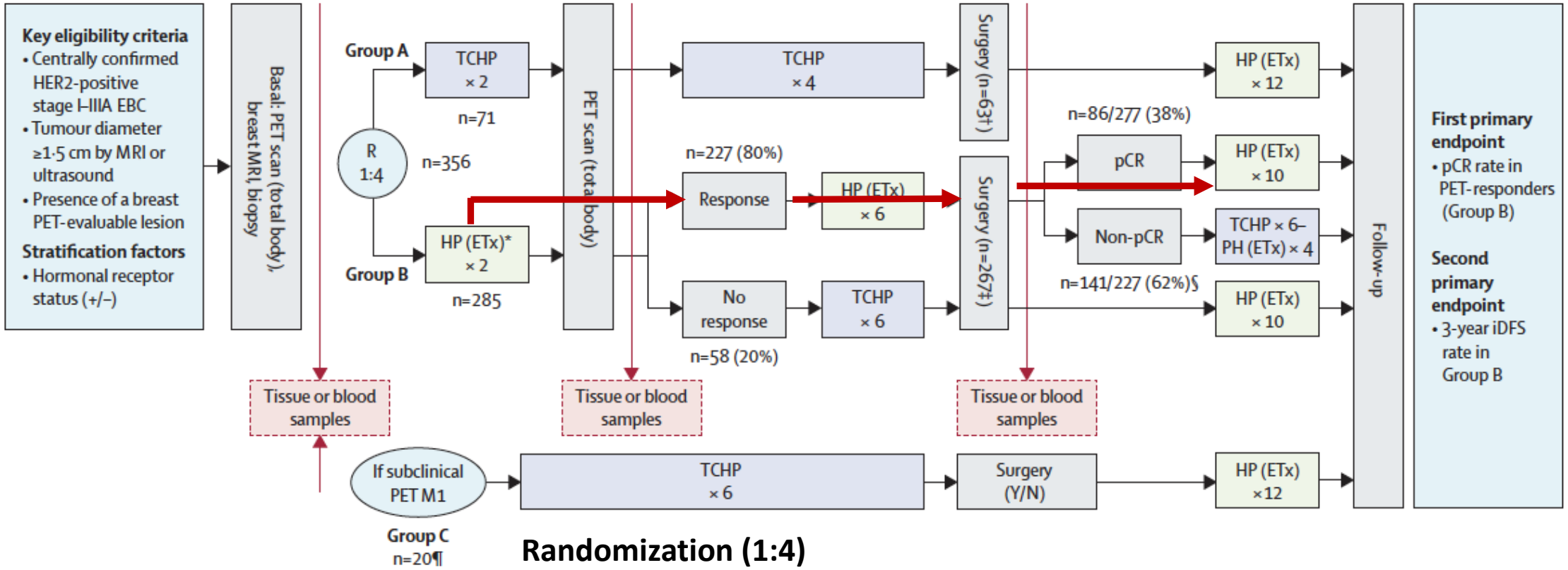
Limitations

- Results not generalizable beyond study population
  - conducted only in Dutch hospitals
- Local radiological/pathological assessments without central review.

van der Voort A, et al. Lancet Oncol 2024;25(5):603-613.

PHERGain: a randomised, open-label, phase II trial

Risk-adapted design based on non-invasive biomarkers (18F-FDG-PET)



Randomization (1:4)

Group A: TCHP (docetaxel + carboplatin + trastuzumab + pertuzumab)

Group B: Dual blockade (trastuzumab + pertuzumab), PET-guided

Pérez-García JM,. Lancet 2024;403(10437):1649-1659.

PHERGain: Key decision points

Post 2 Cycles of Therapy in Group B

- **PET Assessment**
  - Responders: ≥40% reduction in SUVmax.
    - Continue trastuzumab + pertuzumab ± ET
  - Non-Responders: Switch to TCHP (6 cycles).

Post-Surgery Decisions for Group B PET-Responders

- **pCR:** No further chemotherapy.
- **No pCR:** Adjuvant TCHP for 6 cycles.

Pérez-García JM,. Lancet 2024;403(10437):1649-1659.

PHERGain: Primary Endpoints

Pathological Complete Response (pCR)

- **38%** of PET responders in Group B achieved pCR with dual HER2 blockade (trastuzumab + pertuzumab) without chemotherapy.

3-Year Invasive Disease-Free Survival (iDFS)

- Group B: **94.8%** (95% CI 91.4–97.1), meeting the primary endpoint.
- 3-Y i DFS among PET responders who achieved pCR without chemotherapy: **96.4%** (95% CI 92.4–100).

Pérez-García JM,. Lancet 2024;403(10437):1649-1659.

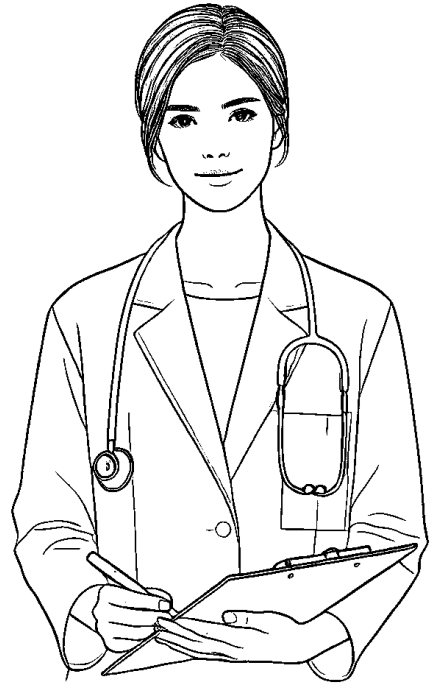
PHERGain uniquely demonstrates the feasibility of a chemo-free strategy in HER2-positive early BC

Chemotherapy Omission

- About **one-third** of patients safely avoided chemotherapy with excellent long-term outcomes.

Reduced Toxicity

- PET-guided strategy significantly lowered adverse events in selected patients.



Pérez-García JM,. Lancet 2024;403(10437):1649-1659.

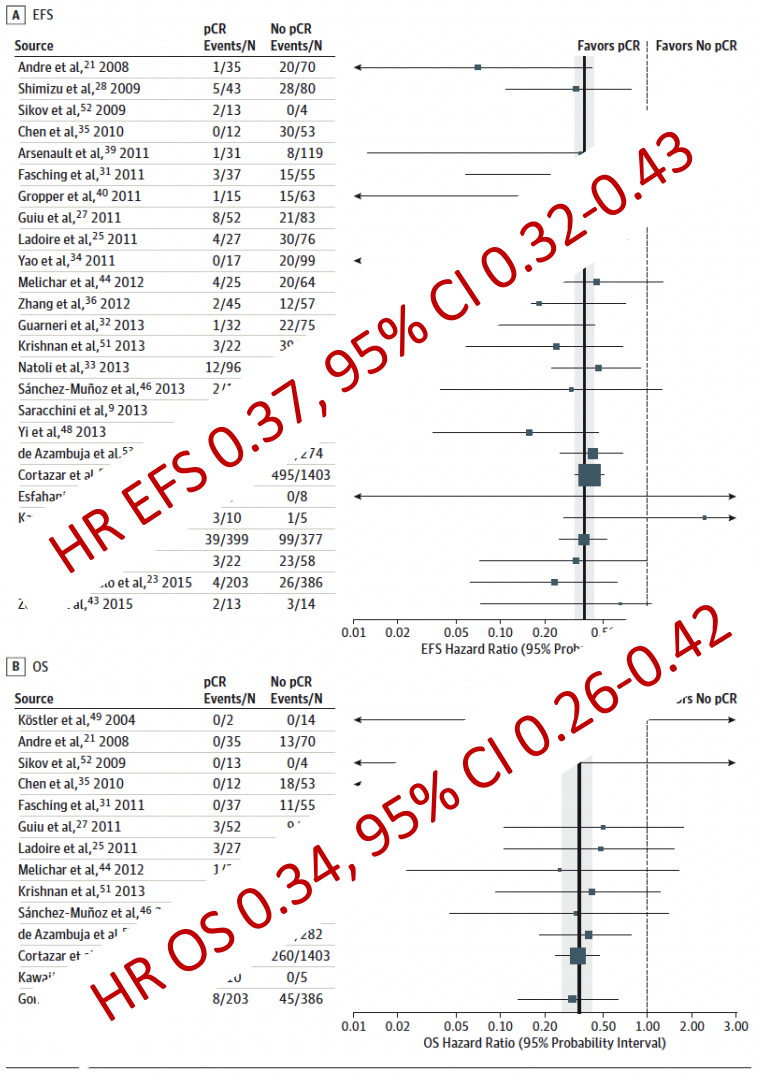
The meaning of pathological response

2016

36 trials

5800 pts

Broglio KR, et al. Association of Pathologic Complete Response to Neoadjuvant Therapy in HER2-Positive Breast Cancer With Long-Term Outcomes: A Meta-Analysis. JAMA Oncol 2016;2(6):751-60.

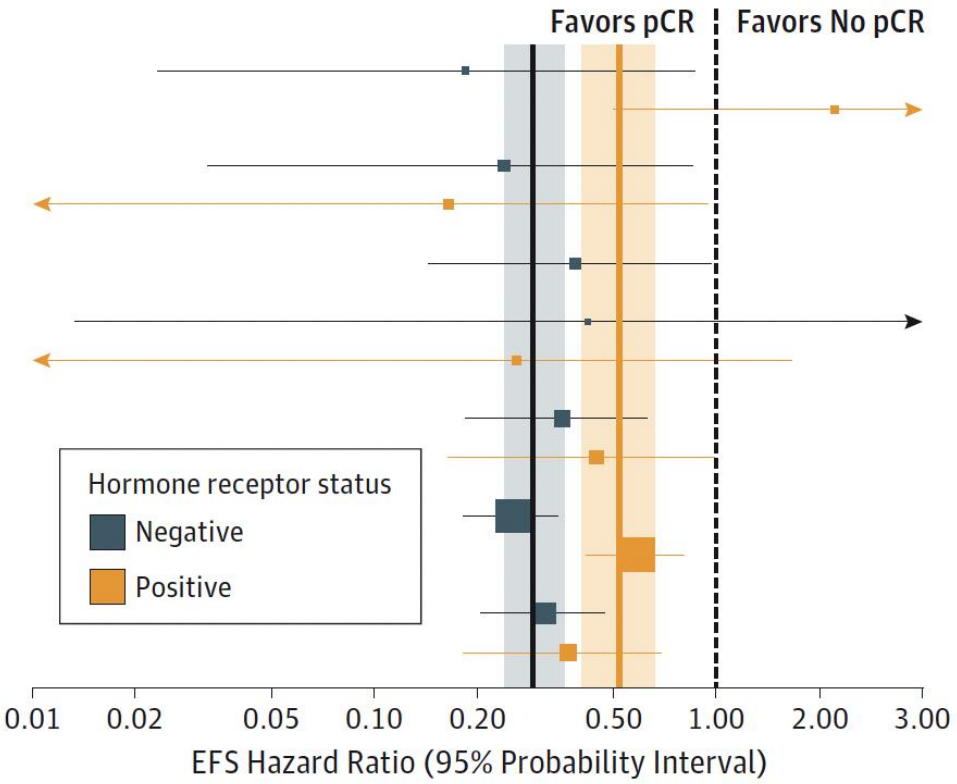


Patients who achieved a pCR (ypT0/is N0) had superior EFS and OS compared with those who did not

Broglio KR, et al. Association of Pathologic Complete Response to Neoadjuvant Therapy in HER2-Positive Breast Cancer With Long-Term Outcomes: A Meta-Analysis. JAMA Oncol 2016;2(6):751-60.

The association was even stronger in the HR-negative subgroup (HR EFS 0.29, 95% CI 0.24-0.36)

Source	pCR Events/N	No pCR Events/N
Esserman et al,[6] 2012	2/19	6/14
	4/11	4/22
Krishnan et al,[51] 2013	2/13	22/42
	1/9	17/38
Natoli et al,[33] 2013	7/44	13/36
Sánchez-Muñoz et al,[46] 2013	1/8	2/8
	1/5	9/17
de Azambuja et al,[53] 2014	14/87	47/124
	6/50	36/150
Cortazar et al,[5] 2014	48/325	223/510
	43/247	243/839
Takada et al,[30] 2014	35/281	62/158
	11/120	54/214



Broglio KR, et al. Association of Pathologic Complete Response to Neoadjuvant Therapy in HER2-Positive Breast Cancer With Long-Term Outcomes: A Meta-Analysis. JAMA Oncol 2016;2(6):751-60.

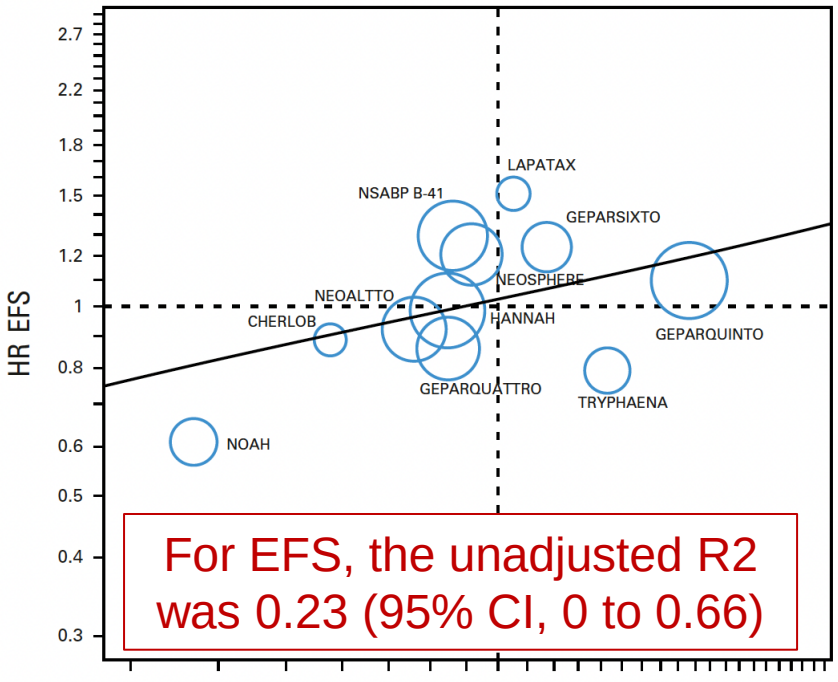
2023

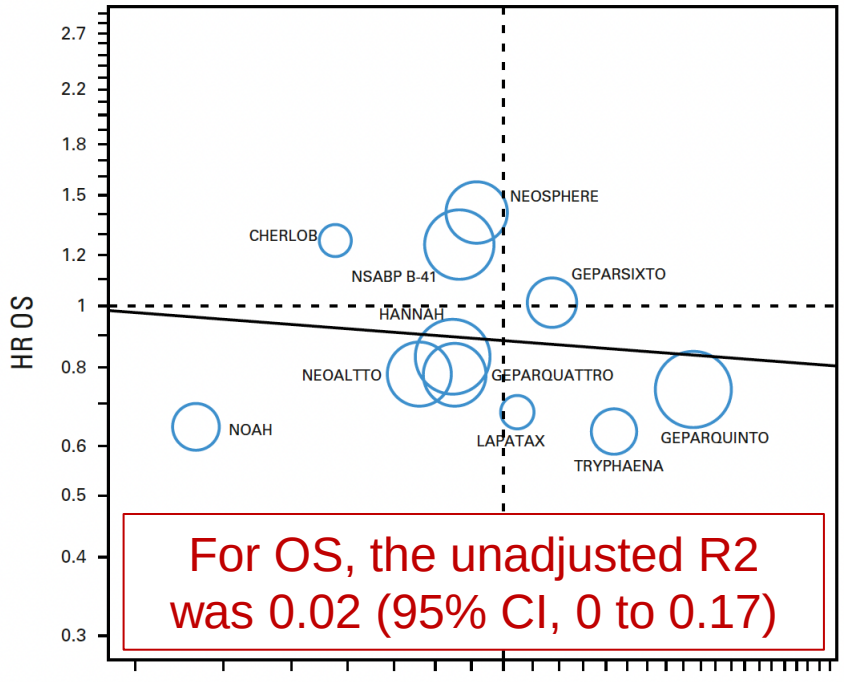
11 trials

3980 pts

Squifflet P, et al. Re-Evaluation of Pathologic Complete Response as a Surrogate for Event-Free and Overall Survival in Human Epidermal Growth Factor Receptor 2-Positive, Early Breast Cancer Treated With Neoadjuvant Therapy Including Anti-Human Epidermal Growth Factor Receptor 2 Therapy. J Clin Oncol 2023;41:2988-2997.

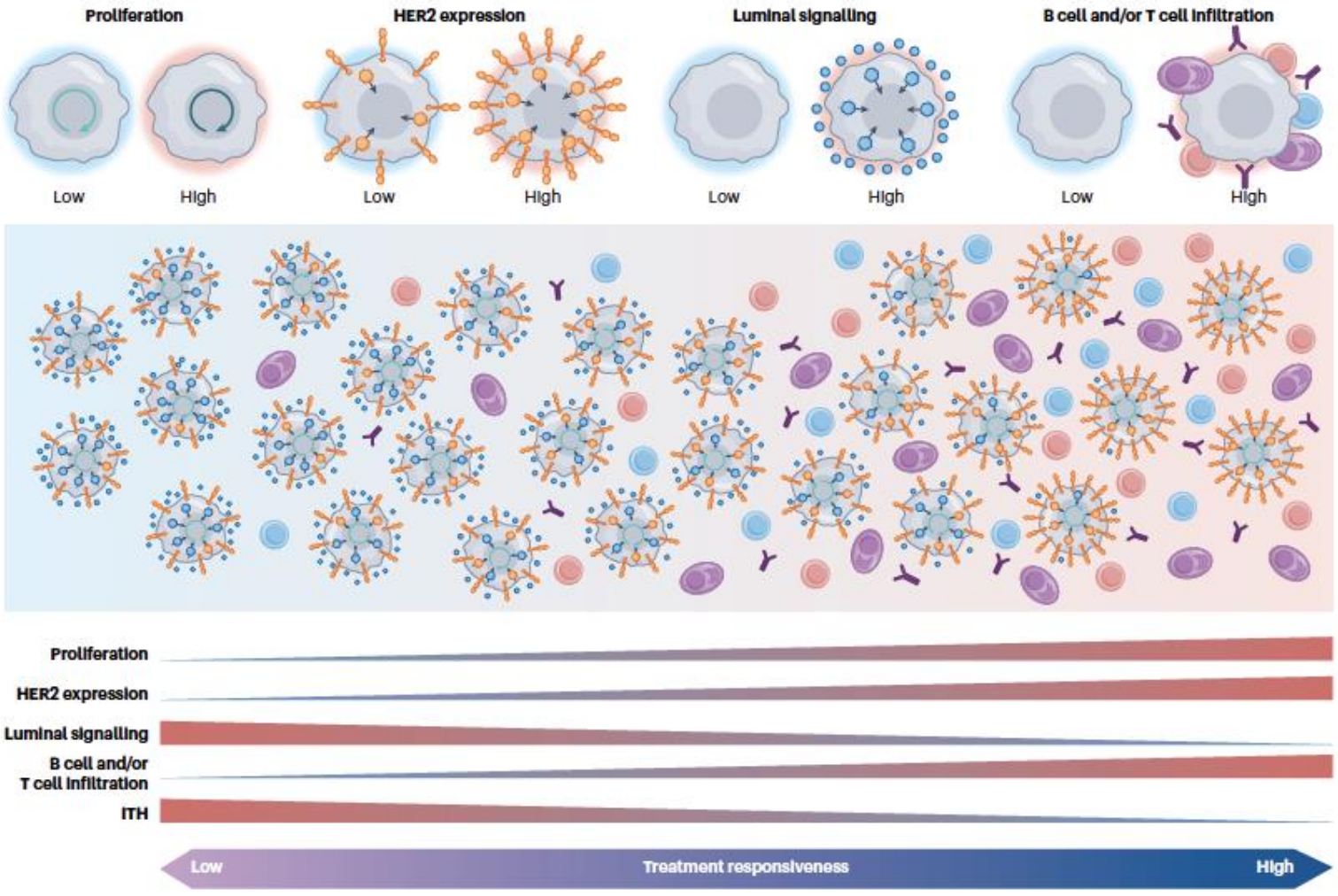
Trial-level associations between the ORs for pCR and the HRs for EFS and OS





The pCR is NOT a valuable surrogate endpoint

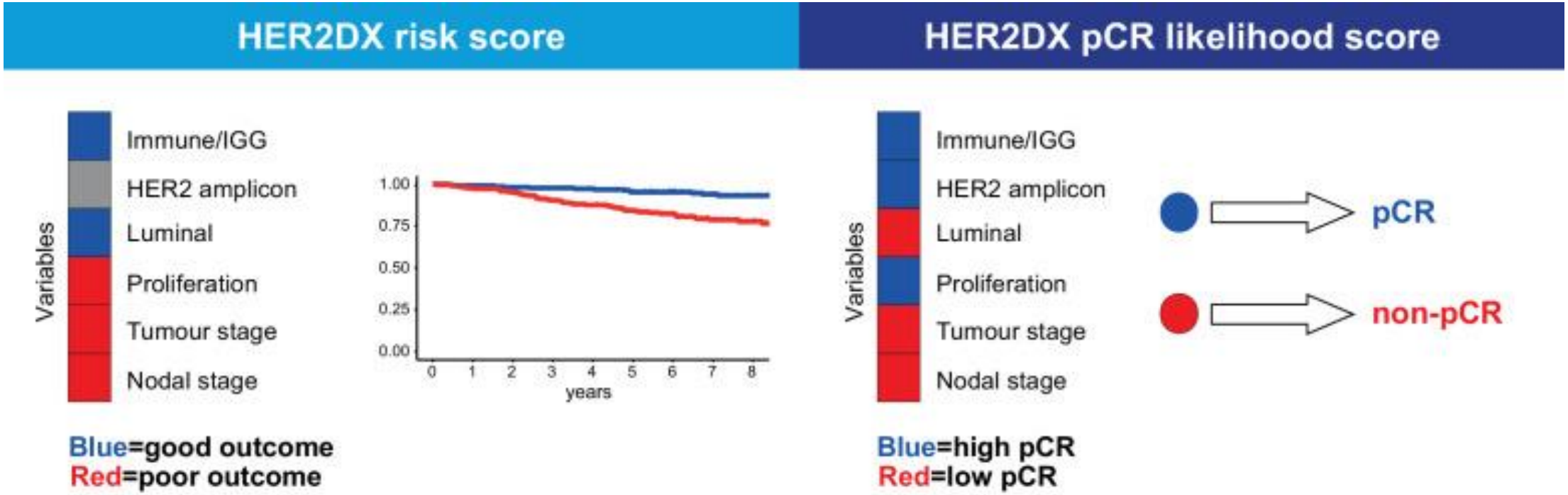
The biological spectrum of treatment responsiveness in HER2+ BC



ITH = intratumoral heterogeneity

Waks AG, et al. Nat Rev Clin Oncol 2024;21(11):818-832.

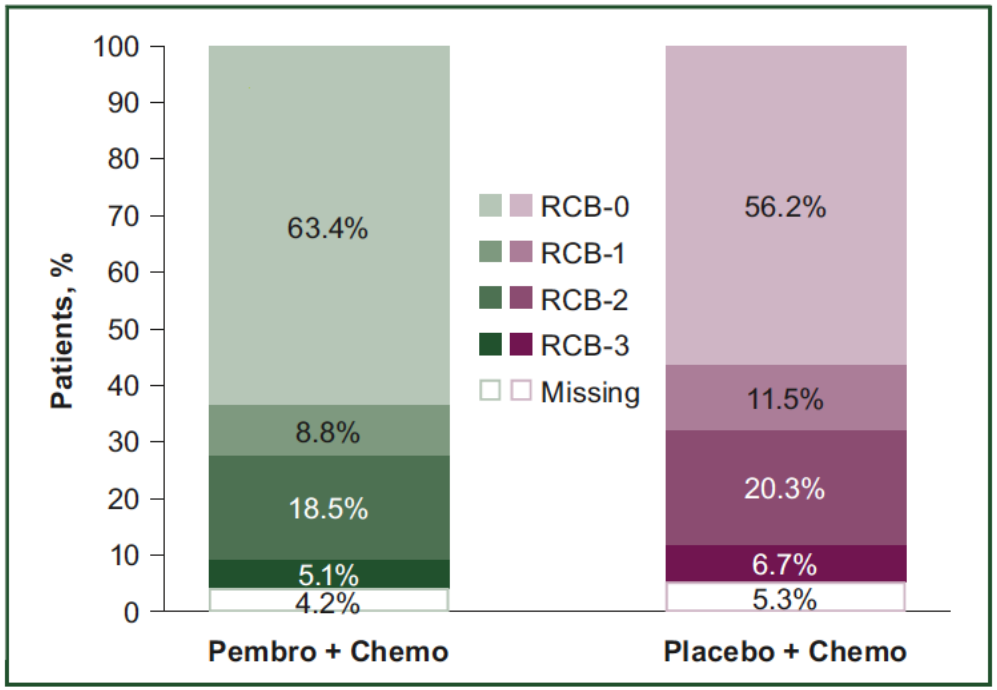
HER2DX



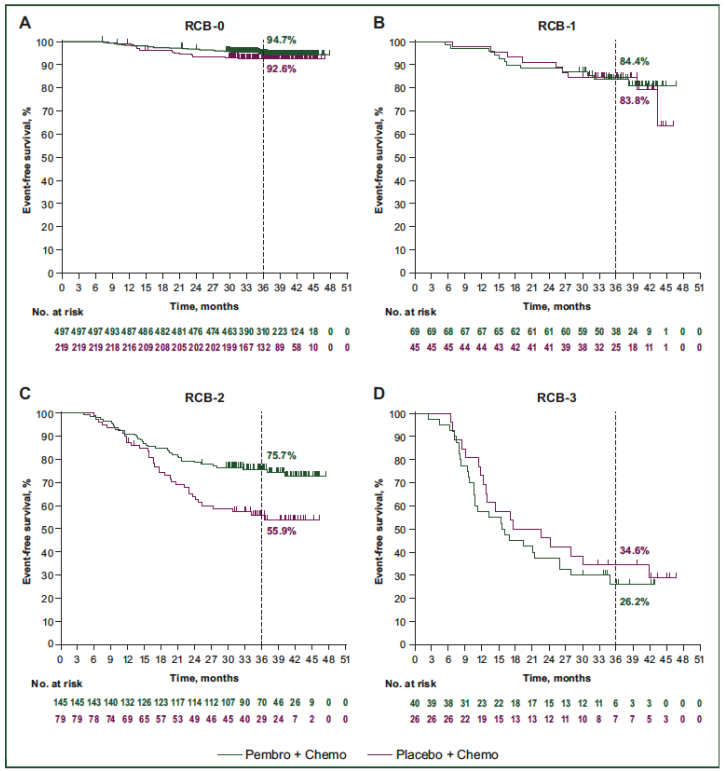
Prat A, et al. EBioMedicine 2022;75:103801. doi: 10.1016/j.ebiom.2021.103801.

The Triple Negative Disease Example

KEYNOTE-522: granular benefits of pembrolizumab across RCB categories



Pembrolizumab shifted RCB categories toward lower burden



Pusztai L, et al. Ann Oncol 2024;35(5):429-436.

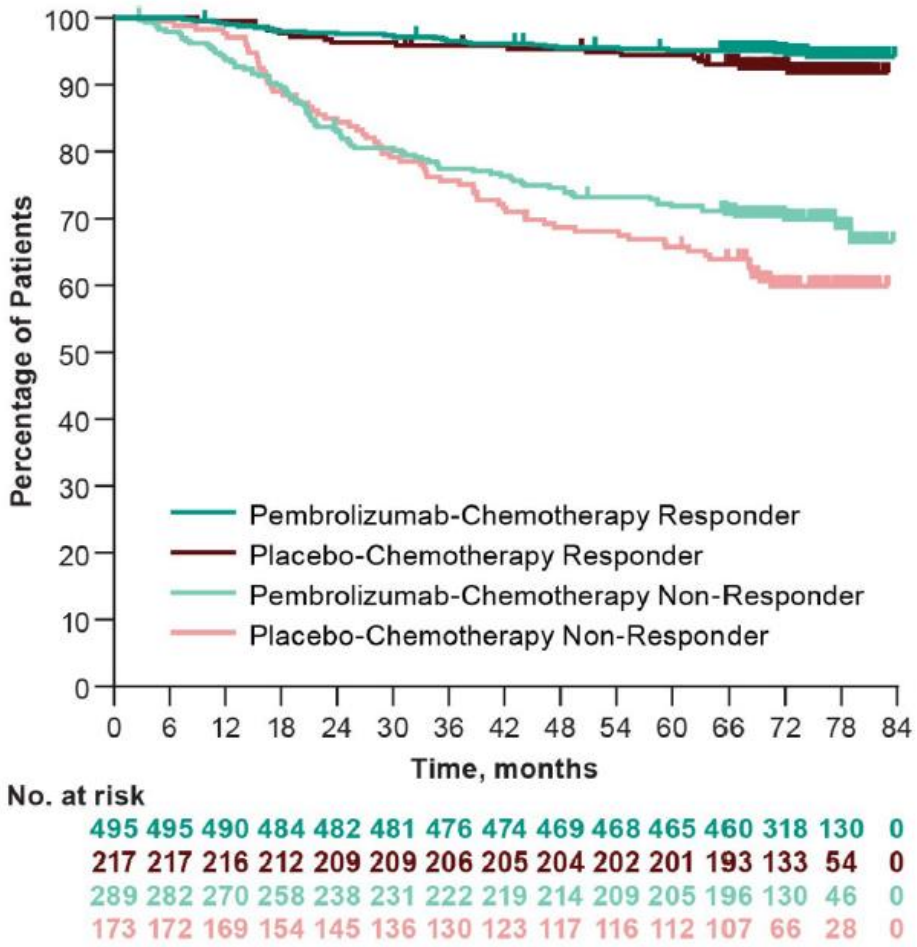
KEYNOTE-522: 36-month distant EFS by RCB categories

RCB Category	Pembrolizumab EFS (%)	Placebo EFS (%)	HR (95% CI)
RCB-0 (pCR)	94.7%	92.6%	0.70 (0.38–1.31)
RCB-1	84.4%	83.9%	0.92 (0.39–2.20)
RCB-2	75.7%	55.9%	0.52 (0.32–0.82)
RCB-3	26.2%	34.6%	1.24 (0.69–2.23)

- Pembrolizumab improved EFS in RCB-0, RCB-1, and RCB-2 categories, with the most pronounced benefit in RCB-2.
- RCB-3 patients had poor outcomes regardless of treatment (HR 1.24, no significant benefit)

Pusztai L, et al. Ann Oncol 2024;35(5):429-436.

Overall survival by pCR (ypT0/Tis ypN0) according to treatment group in the ITT population



Absolute difference in 5-year OS: 0.7%, 95%CI, -2.9 to 4.3%

Absolute difference in 5-year OS: 6.1%, 95%CI, -2.7 to 14.9%

Supplement to: Schmid P, N Engl J Med 2024;391:1981-91.

KEYNOTE-522 OS by RCB categories

- OS at IA7* according to RCB categories
  - RCB-0
  - RCB-1
  - RCB-2
  - RCB-3

SAN ANTONIO BREAST CANCER SYMPOSIUM®

*Median time from randomization to data cutoff (March 22, 2024): 75.1 mo (range: 65.9-84.0).

Dent. SABCS 2024. Abstr PS12-09.

KEYNOTE-522
OS in ITT Population and by RCB Status

SAN ANTONIO BREAST CANCER SYMPOSIUM®

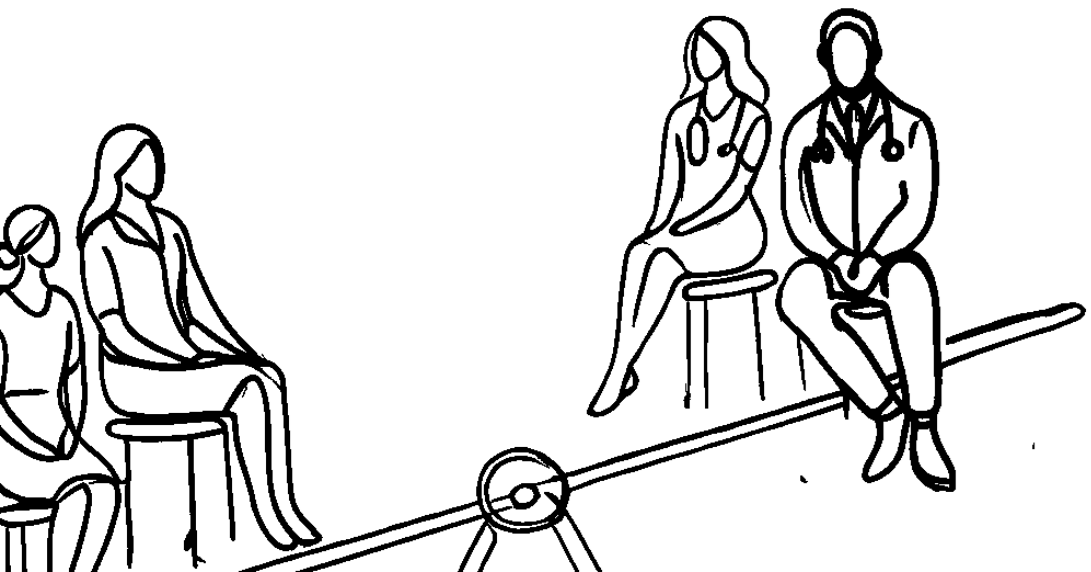
OS	RCB at Surgery, %		Events, n/N (%)		HR (95% CI)	5-Yr Rate, % (95% CI)	
	Pembro + CT	Placebo + CT	Pembro + CT	Placebo + CT		Pembro + CT	Placebo + CT
ITT	--	--	115/784 (14.7)	85/390 (21.8)	0.66 (0.50-0.87; P = .0015)	86.6 (84.0-88.8)	81.7 (77.5-85.2)
RCB category							
▪ RCB-0	63.5	56.2	26/498 (5.2)	17/219 (7.8)	0.66 (0.36-1.23)	95.4	94.5
▪ RCB-1	8.8	11.5	10/69 (14.5)	5/45 (11.1)	1.35 (0.46-3.96)	88.4	93.2
▪ RCB-2	18.4	20.3	35/144 (24.3)	35/79 (44.3)	0.50 (0.31-0.80)	77.8	63.3
▪ RCB-3	5.1	6.7	27/40 (67.5)	16/26 (61.5)	1.26 (0.68-2.34)	37.5	38.5

Dent. SABCS 2024. Abstr PS12-09.

Granular Analysis of Pathological Response in KN-522

Pembrolizumab benefits extends beyond pCR to patients with residual disease (especially RCB-2).

Despite overall EFS benefits, high-risk RCB-3 patients remain a clinical challenge, requiring novel therapeutic approaches.



Limitations

- Exploratory nature of the analysis: No alpha control, findings are descriptive.
- Small RCB-3 subset: Increased variability and possible random fluctuations.
- RCB assessment by local pathologists: Potential interobserver variability, although RCB is a validated prognostic tool.

Imaging-guided strategies

- Imaging (MRI/PET) has the potential to enhance treatment paradigms, supporting more tailored and adaptive therapeutic strategies

Pathological Response

- pCR is associated with improved long-term outcomes (EFS, OS)
- However, pCR has not proven to be a reliable surrogate endpoint for EFS or OS.
- Residual Cancer Burden (RCB) provides a more granular and prognostic classification than the dichotomous pCR/non-pCR.