Jahrestagung der Deutschen, Österreichischen und Schweizerischen Gesellschaften für Hämatologie und Medizinische Onkologie

Update frühes Mammakarzinom

HER2-positiv: Im Spannungsfeld von Eskalation und Deeskalation

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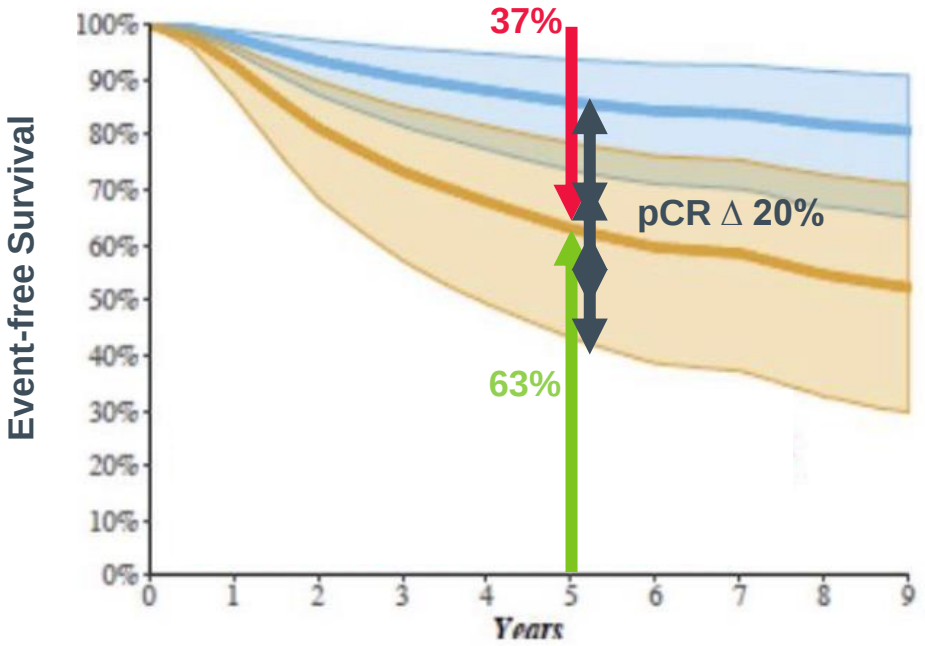
CCCIT Center for Clinical Cancer and Immunology Trials
LIMCR Laboratory for Immunological and Molecular Cancer Research

UNIVERSITÄTSKLINIK FÜR INNERE MEDIZIN III
MIT HÄMATOLOGIE, INTERNISTISCHER ONKOLOGIE, HÄMOSTASEOLOGIE, INFEKTIOLOGIE, RHEUMATOLOGIE UND ONKOLOGISCHES ZENTRUM

Disclosures

Employment: none
Leadership: none
Stock and Other Ownership Interests: none
Honoraria: Amgen, Daiichi Sankyo, Eli Lilly, Gilead, MSD, Novartis, Pfizer, Roche, Seagen
Consulting or Advisory Role: Amgen, AstraZeneca, Daiichi Sankyo, Eli Lilly, Gilead, Merk, MSD, Novartis, Pfizer, Pierre Fabre, Roche, Stemline
Speakers' Bureau: none
Research Funding: none
Patents, Royalties, Other Intellectual Property: none
Expert Testimony: none
Travel, Accommodations, Expenses: Amgen, Daiichi Sankyo, Eli Lilly, Gilead, Merk, Pfizer, Roche
Other Relationship: none

Korrelation pCR und Langzeitüberleben bei HER2+ Patientinnen



Blue: pCR group
Orange: Residual disease (RD) group

5-year EFS
pCR vs residual disease:
86% vs 63%

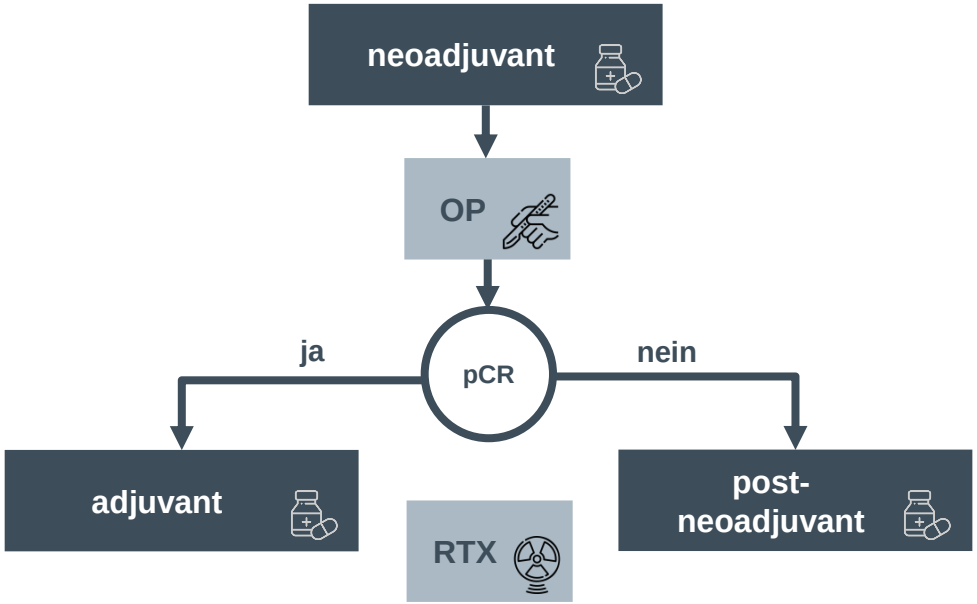
Patient-level analyis of over overall
27,000 patients

Laura M Sprint et al. SABCS 2018 #GS2-03

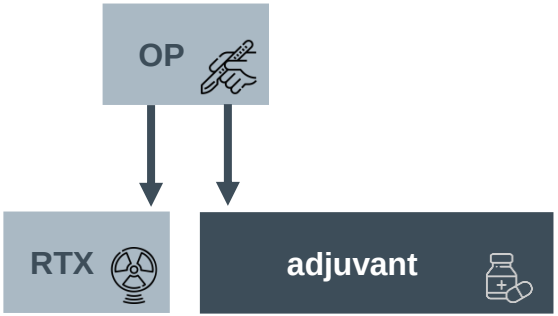
Konzepte der Systemtherapie

Konzepte der Systemtherapie bei frühen HER+ Mammakarzinomen

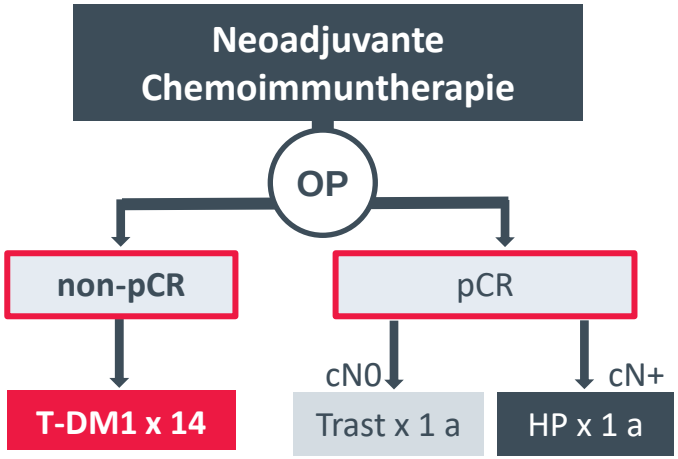
Neoadjuvante Therapie



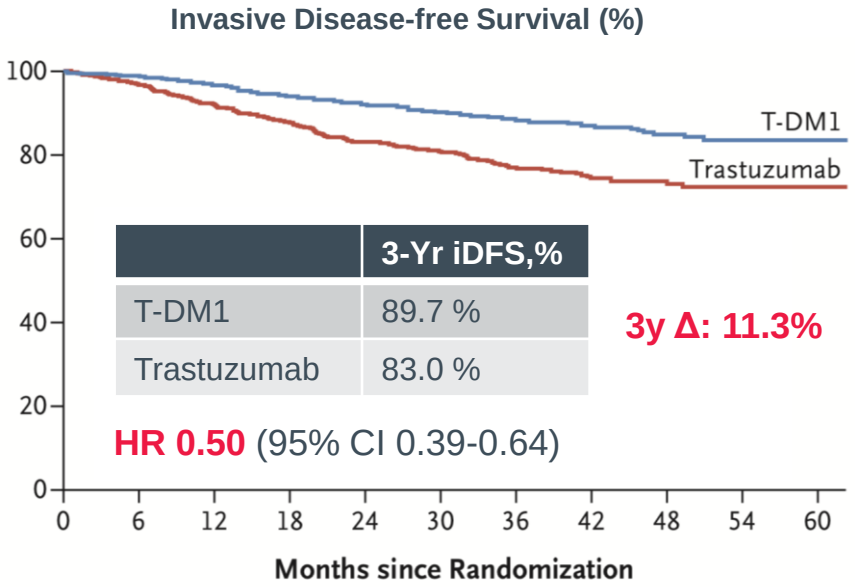
Primäre Operation



Response Adaptierte Therapie – HER2+



KATHERINE Studie:
adjuvant T-DM1 vs Trastuzumab bei non-pCR



	3-Yr iDFS,%
T-DM1	89.7 %
Trastuzumab	83.0 %

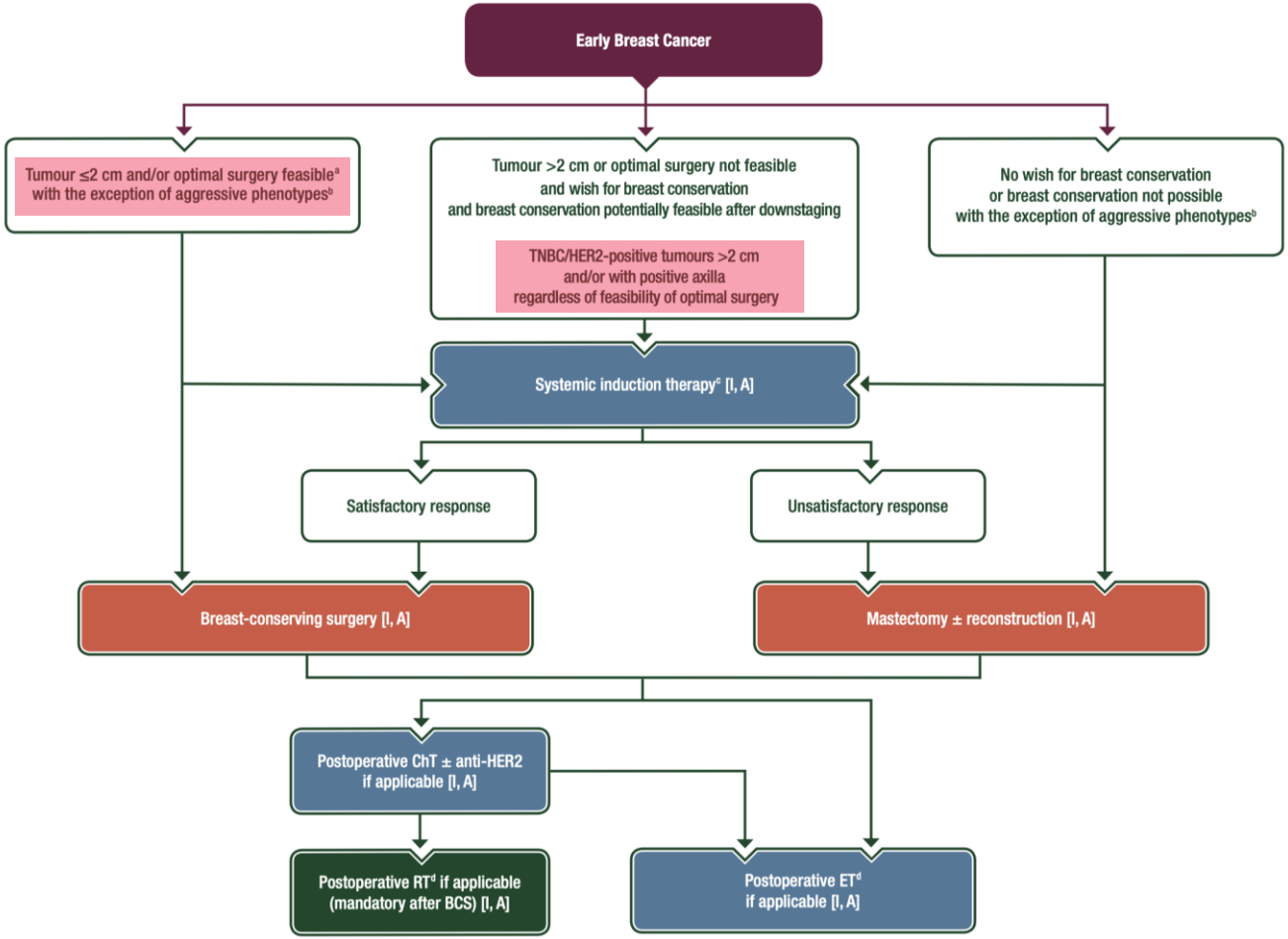
3y Δ: 11.3%

HR 0.50 (95% CI 0.39-0.64)

G. von Minckwitz et al. NEJM 2019 (PMID: 30516102)

ESMO – Early breast cancer treatment algorithm

HER2-positive cancers should be treated **with ChT plus antiHER2 therapy, with the possible exception of selected cases with very low risk, such as T1aN0 tumours** [I, A].



F. Cardoso et al.
Ann Oncol 2019 (PMID: 31161190)

ASCO Guideline - Neoadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast Cancer

Recommendation 5.1

- Patients with node-positive or high-risk node-negative, HER2-positive disease should be offered neoadjuvant therapy with an anthracycline and taxane or non-anthracycline-based regimen in combination with trastuzumab. Pertuzumab may be used with trastuzumab in the neoadjuvant setting.

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
High	Strong

Recommendation 5.2

- Patients with T1a N0 and T1b N0, HER2-positive disease should not be routinely offered neoadjuvant chemotherapy or anti-HER2 agents outside of a clinical trial.

Informal consensus	
Evidence Quality	**Strength of Recommendation**
Intermediate	Moderate

L. A. Korde et al. J Clin Oncol 2021 (PMID: 33507815)

Neoadjuvante zielgerichtete Therapie bei HER2-positiven Tumoren

Guidelines Breast
Version 2023.1D

	Oxford LoE	Oxford GR	AGO
▪ Pertuzumab + Trastuzumab in Kombination mit Chemotherapie (high-risk bei cT2-4 und / oder cN+)	2b	B	++
▪ Trastuzumab in Kombination mit Standard-Kombinations-Chemotherapie (low-risk)*	1b	A	+
▪ HER2 gerichtete Substanzen ohne Chemotherapie	2b	B	+/-

* Trastuzumab + Monochemotherapie bevorzugt in der adjuvanten Therapie einzusetzen

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

AGO Empfehlung **Neoadjuvante (Primaere) systemische Therapie,** Stand: 15.04.2023,
https://www.ago-online.de/leitlinien-empfehlungen/leitlinien-empfehlungen/kommission-mamma

Standardtherapien (?)

Welches neoadjuvante Chemotherapieprotokoll in Kombination mit Trastuzumab und Pertuzumab?

Neoadjuvante Chemotherapiestudien mit Pertuzumab

Trial name	Primary Endpoint	Treatment	pCR rate (ypT0/is, ypN0)	Comments
KRISTINE randomized phase 3	pCR	TCH+P×6	**55.7%** (N= 123/221)	Clinical state IIA–IIIA: 83%, HR+ 62.4%
TRYPHAENA randomized phase 2	Cardiac safety	Arm A: FEC + H + P ×3 → D+H+P×3	**56.2%** (N=41/73)	HR+ 53.4%, N+: 71.3%
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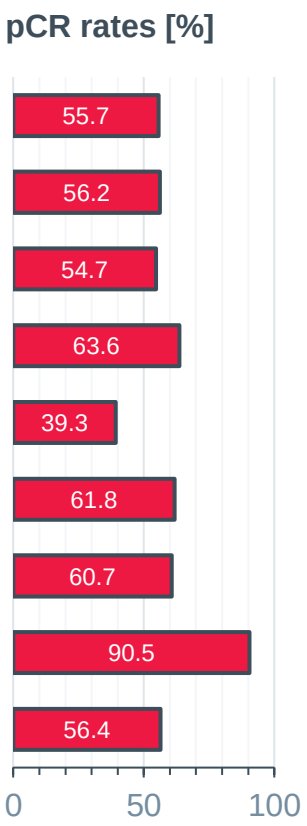

Hurvitz SA et al, Lancet Oncol 2018;19(1):115–26. Schneeweiss A et al, Ann Oncol 2013;24(9):2278–84. Gianni L et al, Lancet Oncol 2012;13(1):25–32. Swain et al, Ann Oncol 2018; 29(3):646-53. Nitz UA et al, Ann Oncol 2017;28(11):2768-72; O. Gluz et al. JAMA Oncol 2023 (PMID: 37166817)

Anthrazyklin oder Anthrazyklin-frei?

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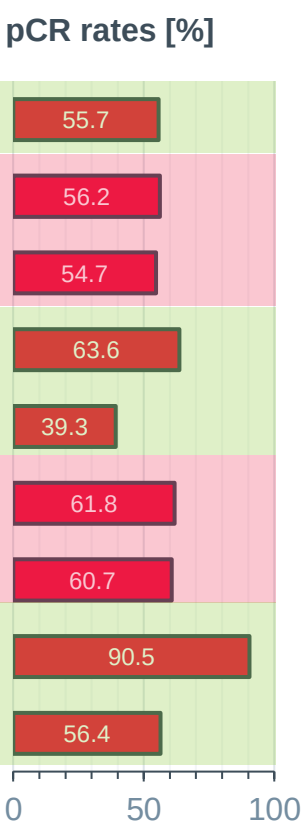
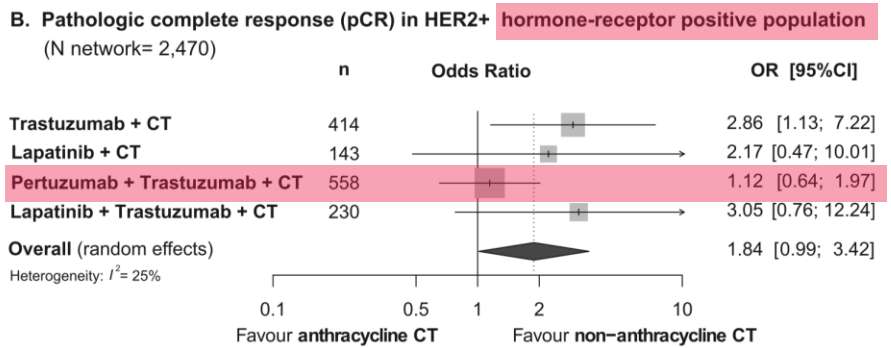
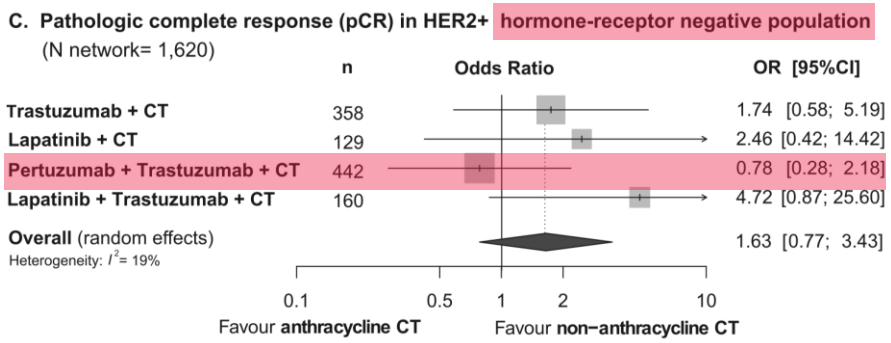
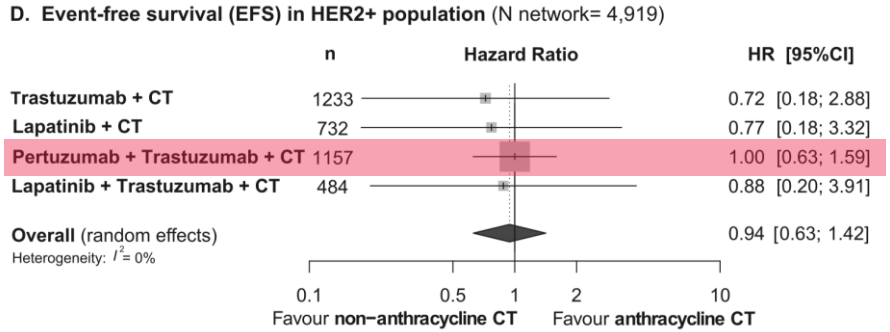


Hurvitz SA et al, Lancet Oncol 2018;19(1):115–26. Schneeweiss A et al, Ann Oncol 2013;24(9):2278–84. Gianni L et al, Lancet Oncol 2012;13(1):25–32. Swain et al, Ann Oncol 2018; 29(3):646-53. Nitz UA et al, Ann Oncol 2017;28(11):2768-72; O. Gluz et al. JAMA Oncol 2023 (PMID: 37166817)

Welche neoadjuvante Therapie – Anthrazyklin notwendig? Network Metanalysis



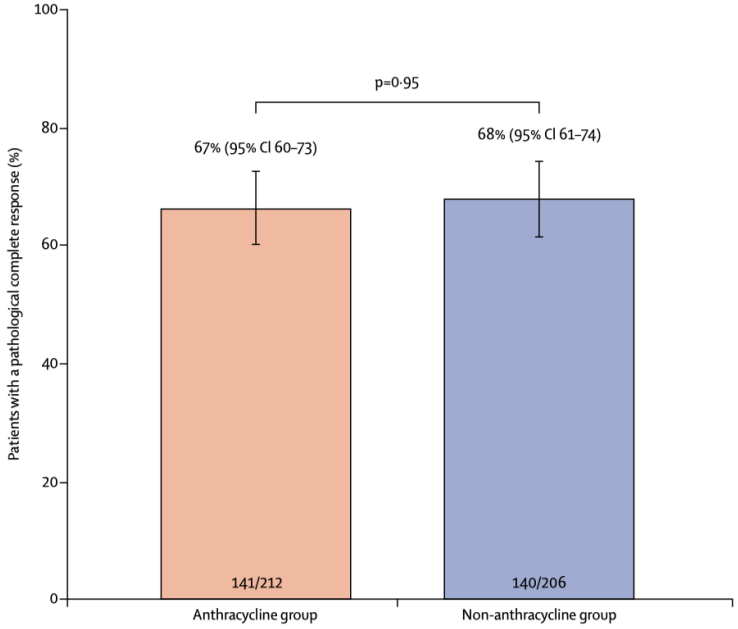


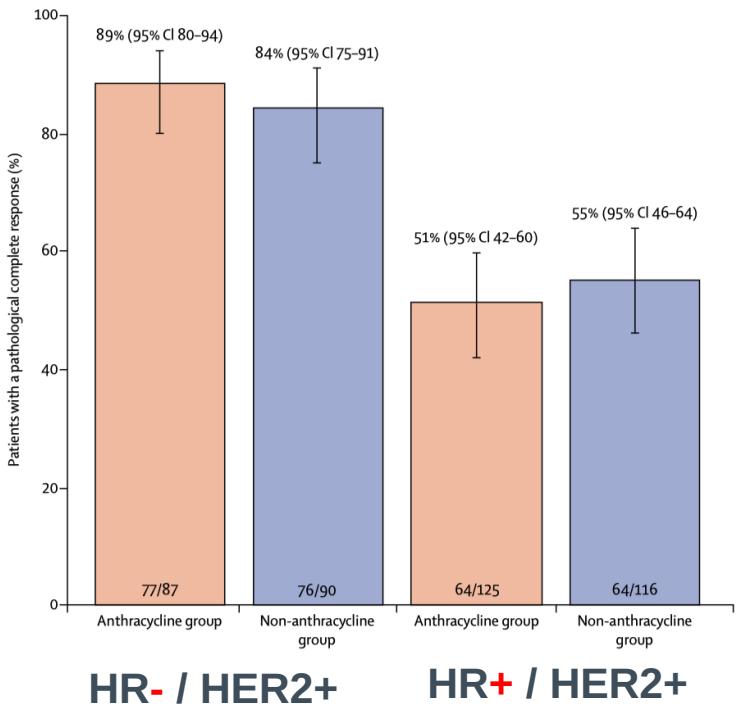


G. Villacampa et al. Eur J Cancer 2023 (PMID: 37142539)

TRAIN-2 – randomisierte Phase 3 Studie Anthrazyklin vs Anthrazyklin frei

9 Zyklen Schema: FEC ×3 → TCb + HP (x6) vs TCb + HP (x9)





M. S. van Ramshorst et al. Lancet Oncol 2018 (PMID: 30413379)

Anthrazyklin plus 5FU oder 5FU-frei?

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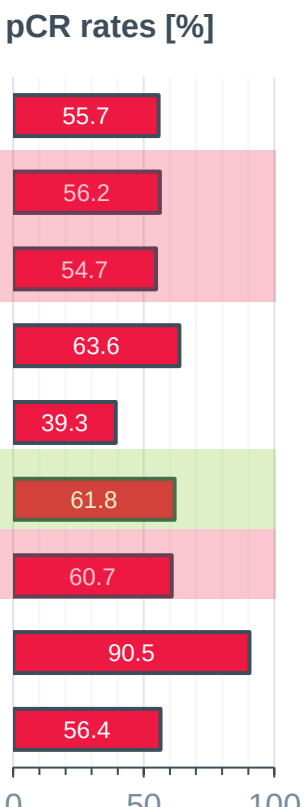

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Neoadjuant 6 oder 8 Zyklen?

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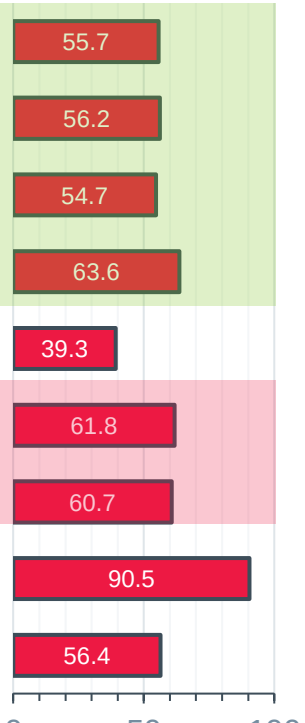

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Deeskalierte neoadjuvante Therapien

Deeskalierte Chemoimmuntherapien: Taxan + HP

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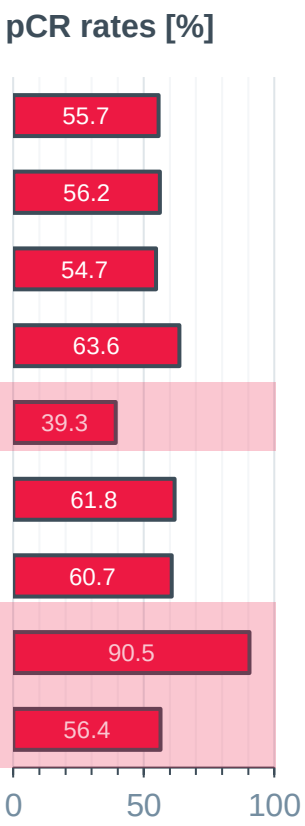

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Histopathologische prädiktive Biomarker für pCR

WSG-TP-II Studie: pCR in Abhängigkeit der HER2 Expression

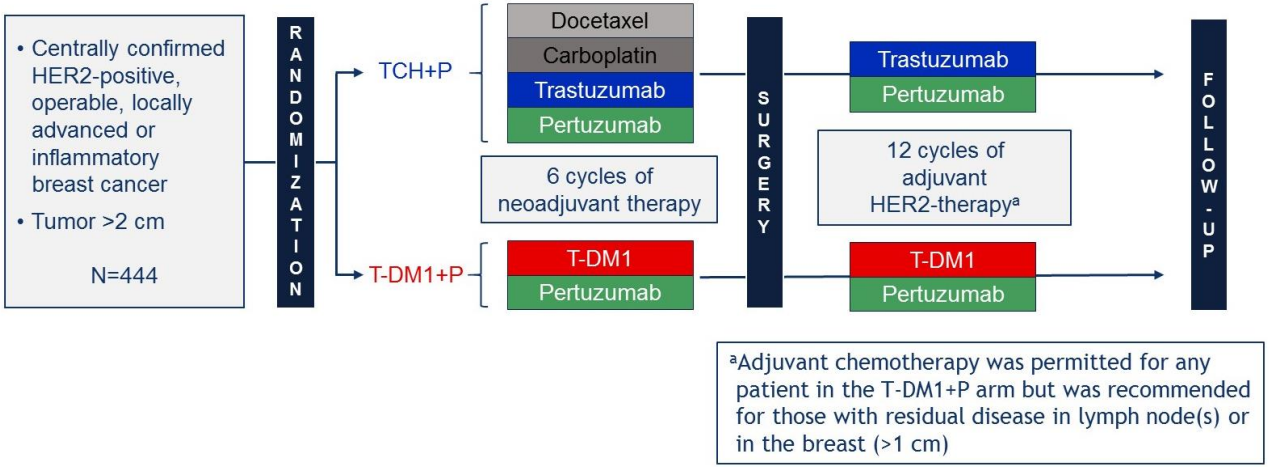
Table 2. Pathological Complete Response Rate by Local and Central *ERBB2* Status in Both Trial Arms

Pathological complete response	% (95% CI)	
	Endocrine therapy plus trastuzumab and pertuzumab (n = 100)	Paclitaxel plus trastuzumab and pertuzumab (n = 107)
Local *ERBB2* immunohistochemistry		
0-2	0.0 (0.0-33.6)	28.6 (8.4-58.1)
≥3	26.1 (17.3-36.6)	60.9 (49.9-71.2)
Central *ERBB2* immunohistochemistry		
0-2	0.0 (0.0-52.2)	12.5 (0.3-52.7)
≥3	25.0 (16.6-35.1)	59.8 (49.0-69.9)

O. Gluz et al. JAMA Oncol 2023 (PMID: 37166817)

KRISTINE Studie - Neoadjuvante Therapie mit T-DM1

Studiendesign – Phase III



Stratification: local HR status, geographic location, clinical stage at presentation
Primary Endpoint: pCR by local assessment (ypT0/is, ypN0)
Secondary Endpoints: EFS, iDFS, OS, safety, PRO

Primäres Ergebnis:

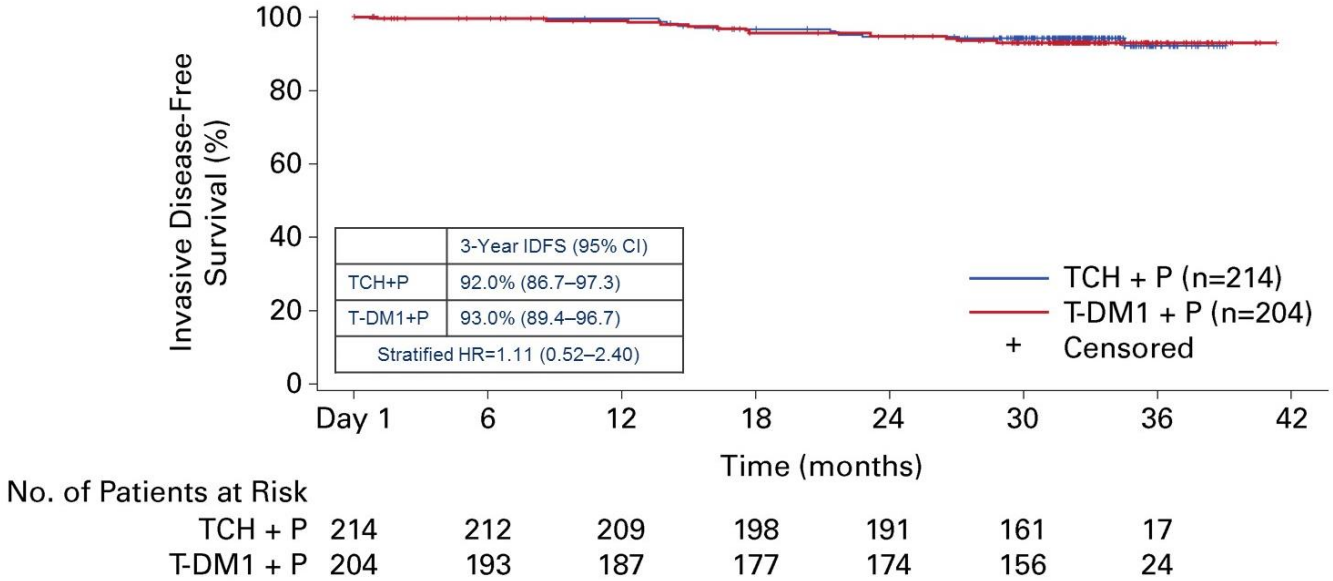
- Neadjuvante Therapie mit TCH+P hatte höhere pCR Raten im Vergleich zu T-DM1 + P:
  - pCR 56% vs 44%,
  - P = 0.0155

Adjuvante Chemotherapie (T-DM1 Arm): non-pCR: 33.1% vs pCR: 9.1%

S Hurvitz et al. ASCO 2019 #500; S. Hurvitz et al. Lancet Oncology 2018

KRISTINE Studie - Neoadjuvant Therapie mit T-DM1

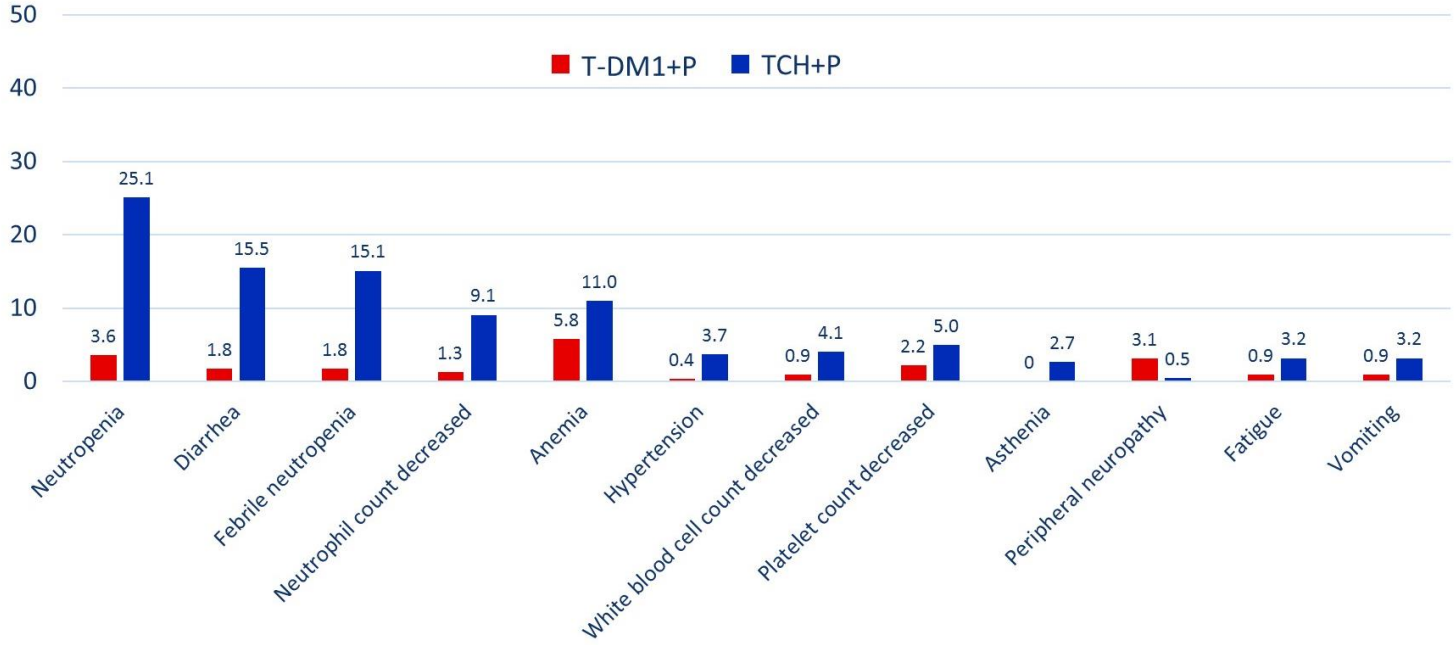
Invasives Krankheits-freies Überleben (iDFS)



S Hurvitz et al. ASCO 2019 #500

KRISTINE Studie - Neoadjuvant Therapie mit T-DM1

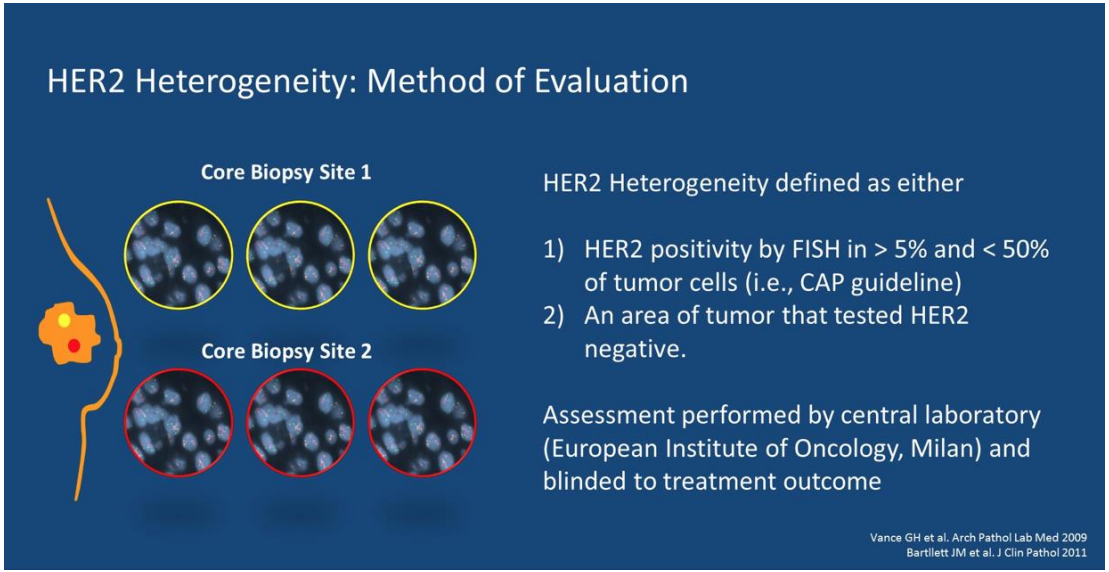
Therapienebenwirkungen: ≥ Grad 3 AEs mit > 2% Differenz zw. den Therapiegruppen

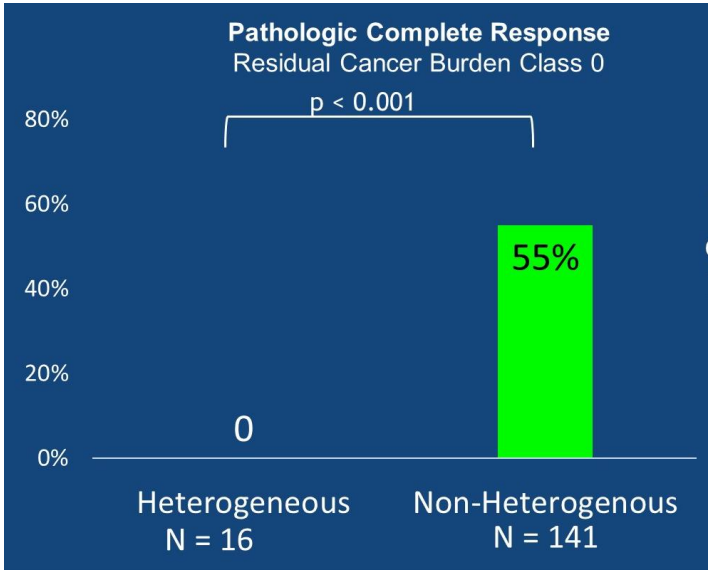


S Hurvitz et al. ASCO 2019 #500

Histopathologische prädiktive Biomarker für pCR

Phase II Studie zur Evaluierung der HER2 Heterogenität als Prädiktor für einen Response auf eine neoadjuvante Therapie mit T-DM1 und Pertuzumab

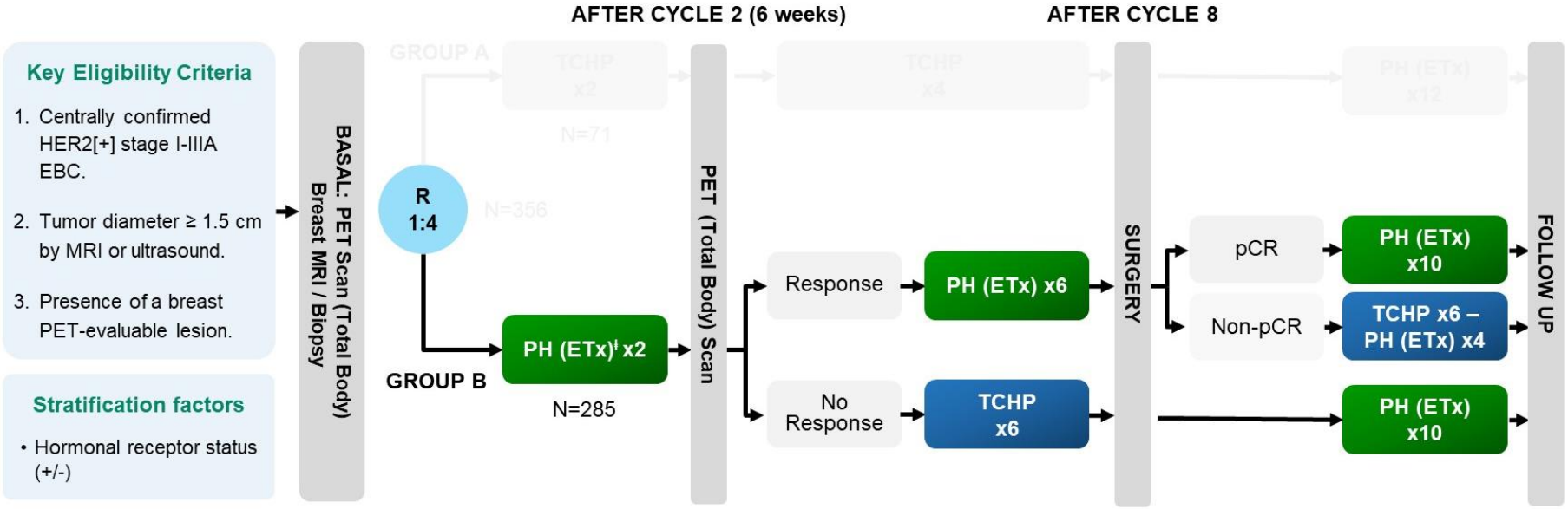




0. Metzger Filho et al. ASCO 2019 #502

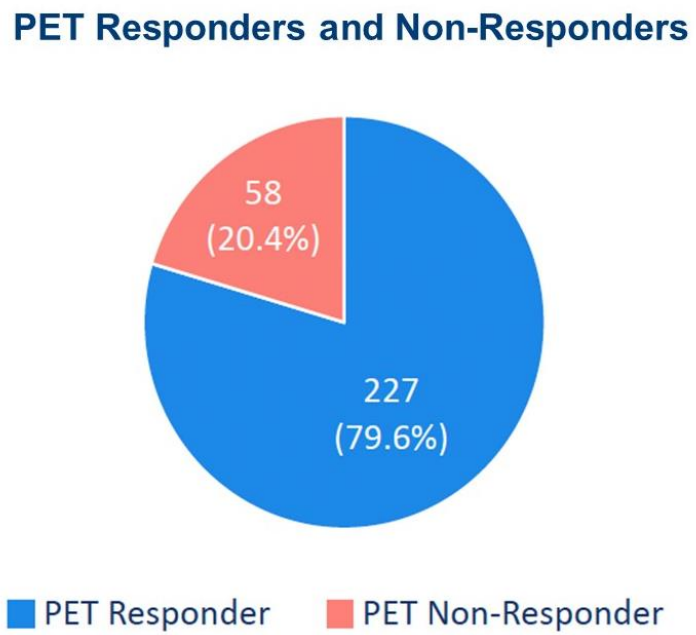
Dynamische Biomarker für pCR

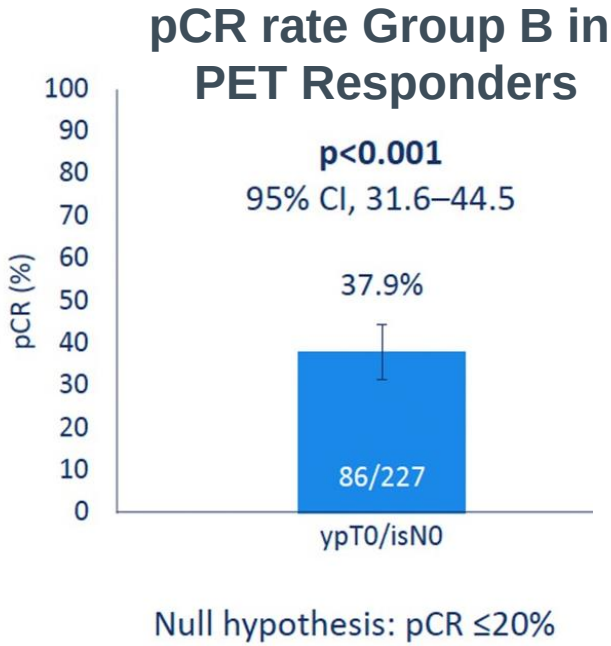
PHERGAIN Studie – PET/CT Response gesteuerte Deeskalation (HER2+)



J. Cortes et al. ASCO 2023 #LBA506

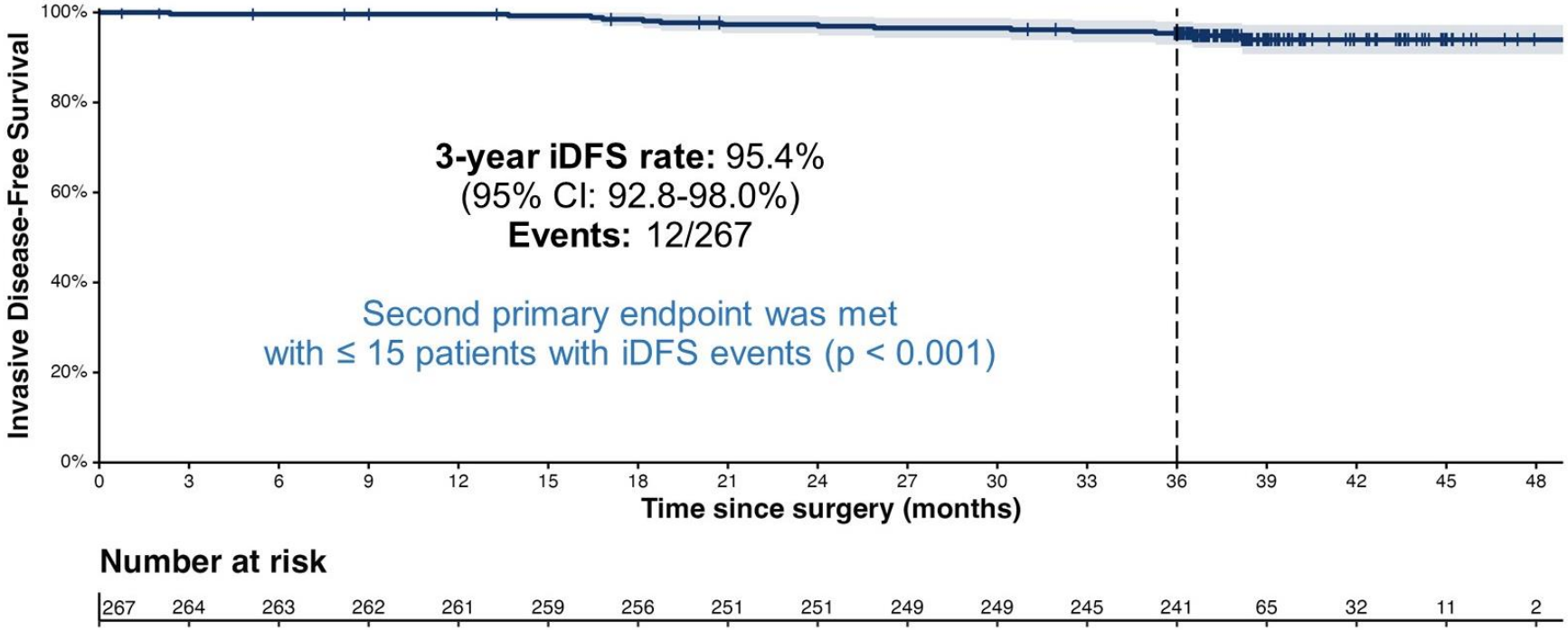
PHERGAIN Studie – PET/CT Response gesteuerte Deeskalation (HER2+)





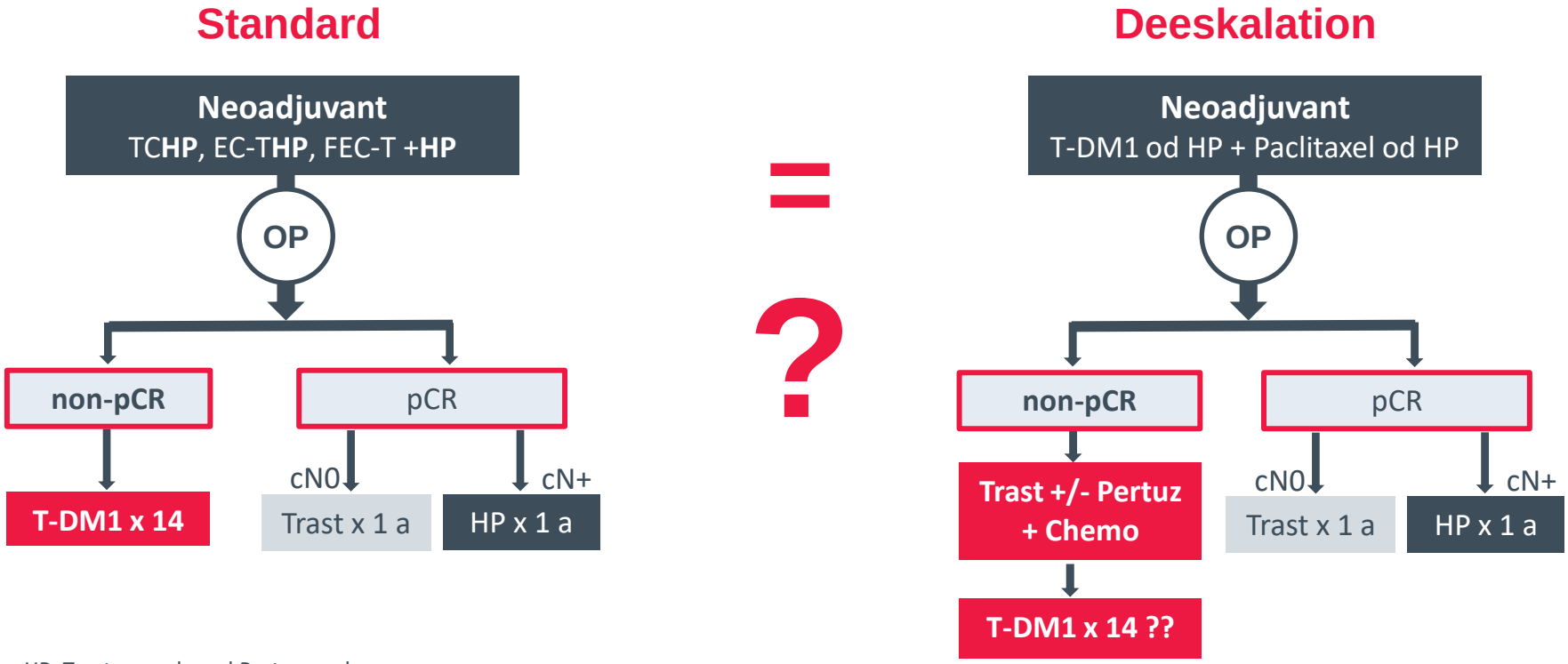
J. Cortes et al. ASCO 2023 #LBA506

PHERGAIN Studie – 3-Jahres iDFS in Gruppe B



J. Cortes et al. ASCO 2023 #LBA506

Deeskalation neoadjuvant – Response-adaptiert adjuvant ?



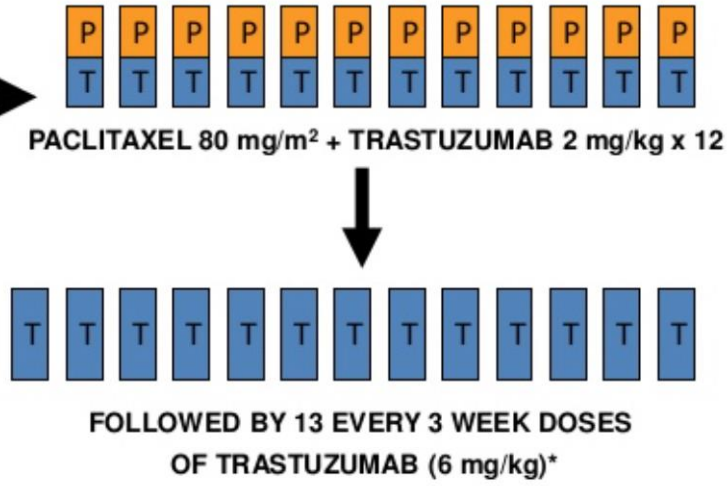
HP: Trastuzumab und Pertuzumab

Deeskalierte adjuvante Therapie?

Deeskalierte adjuvante Therapie – APT Studie

- **HER2 + early BC**
- ER/PR + or –
- Node negative
- ≤ 3m

N=406



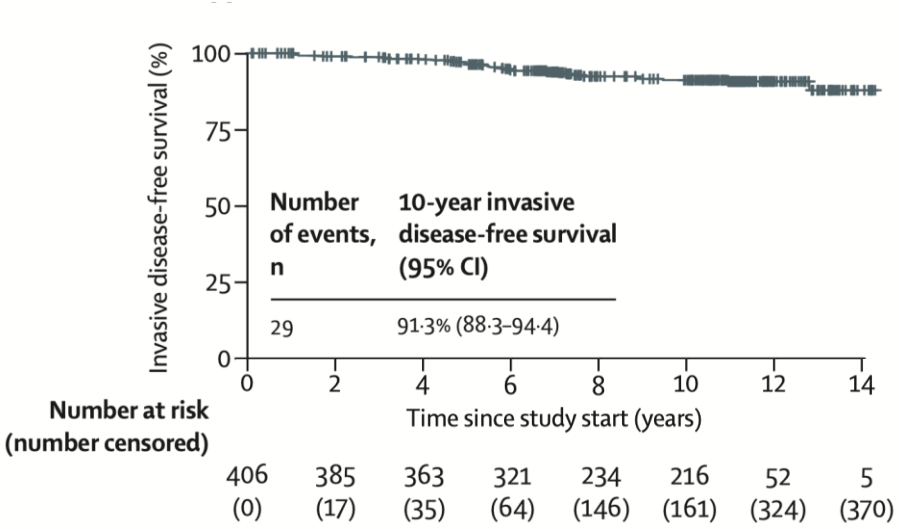
Baseline Characteristics

Tumor size	no. (%)
T1mic: ≤0.1 cm	9 (2.2)
T1a: >0.1 to ≤0.5 cm	68 (16.7)
T1b: >0.5 to ≤1.0 cm	124 (30.5)
T1c: >1.0 to ≤2.0 cm	169 (41.6)
T2: >2.0 to ≤3.0	36 **(8.9)**

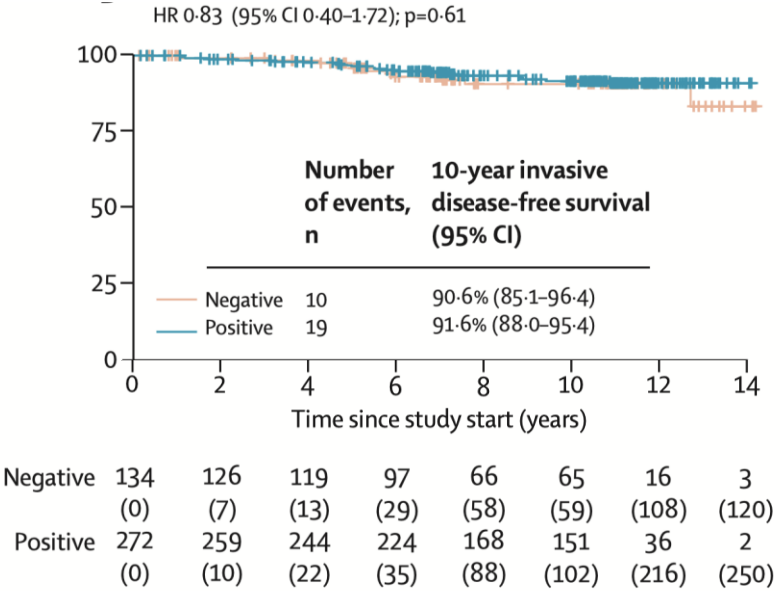
S Tolany et al. SABCS 2013; S Tolany et al. NEJM 2015

Deeskalierte adjuvante Therapie – APT Studie
10 Jahres invasives Krankheits-freies Überleben

iDFS Gesamtpopulation



iDFS nach Hormonrezeptortstatus



S. M. Tolaney et al. Lancet Oncol 2023 (PMID: 36858723)

Verkürzte adjuvant Therapie mit Trastuzumab < 1 Jahr?

Trial	N	Duration of experimental treatment	Predefined margin of non-inferiority	HR DFS (95% CI)	HR OS (95% CI)
Short-Her [1]	627	9 weeks	upper border HR < 1.29 (5y DFS)	**1.06 (0.86-1.31) -** 10y	1.15 (0.85 – 1.56) - 10y
SOLD [5]	2176	9 weeks	HR < 1.385	**1.24 (0.93-1.65)**	1.36 (0.98 – 1.89)
PERSEPHONE [2]	4088	6 months	< 3% (4y DFS)	**1.07 (0.93-1.24)**	1.14 (0.95-1.37)
HORG [3]	241	6 months	HR < 1.53 (3y DFS)	1.57 (0.86 - 2.10)	1.45 (0.57 – 3.67)
PHARE [4]	3380	6 months	HR < 1.15 (DFS)	1.08 (0.93-1.25)	1.13 (0.92-1.39)

1 PF Conte et al. ASCO 2023 #LBA637; 2 HM Earl et al ASCO 2018 #506; HM Earl et al Lancet Oncology 2019; 3 Mavroudis D et al. Ann Oncol 2015;
4 Pivot X et al. SABCS 2018 # GS2-07; 5 H Joensuu et al. SABCS 2017 #GS3-04

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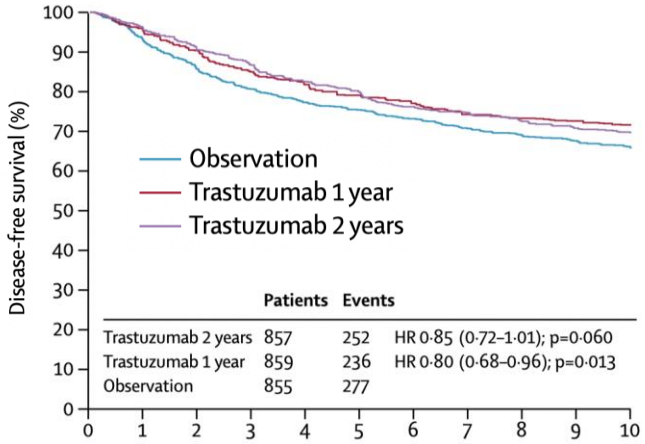
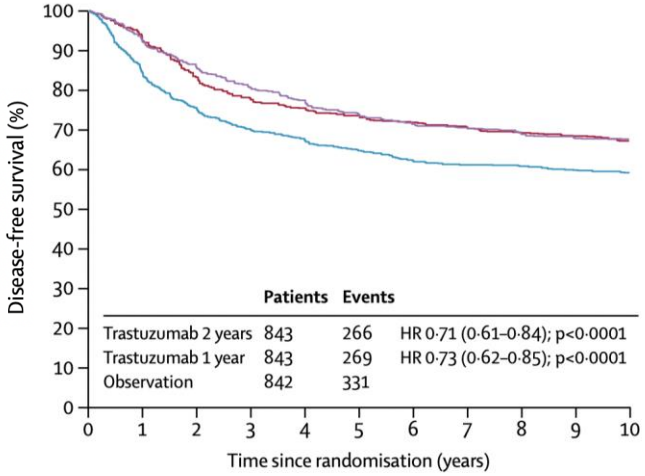
Eskalierte Adjuvante Therapie

Outcome of HER2+ EBC (HERA Trial)

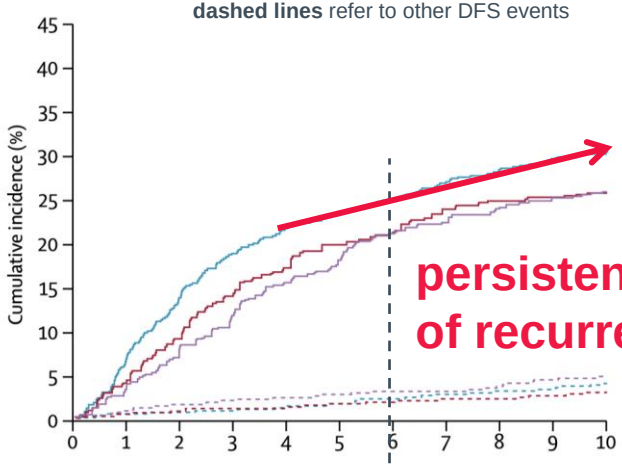
HR+ / HER2+ →

HR- / HER2+ →

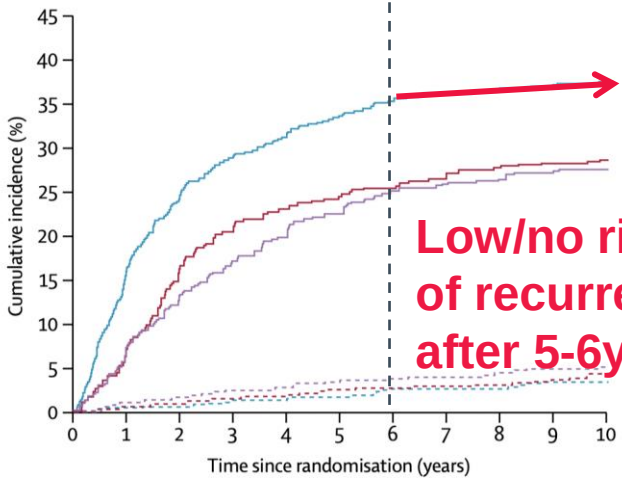




Solid lines refer to **BC events**
dashed lines refer to other DFS events



persistent risk of recurrence

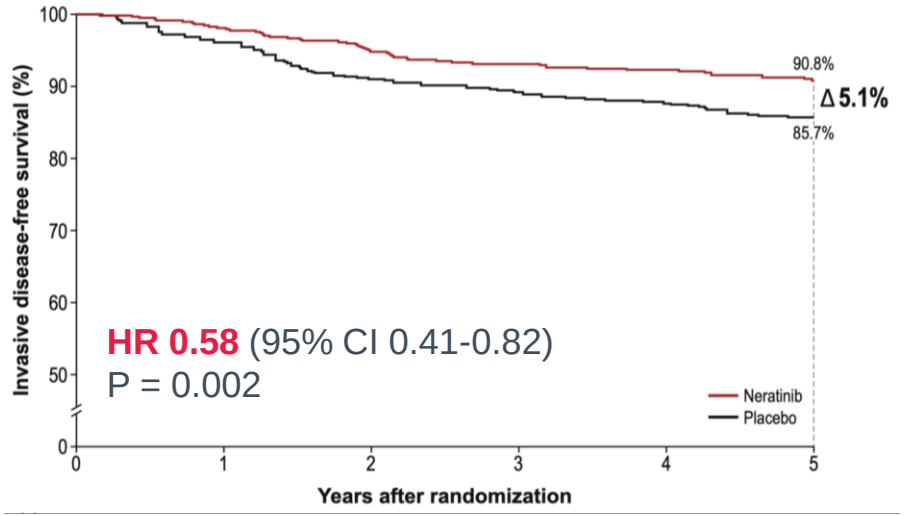


Low/no risk of recurrence after 5-6y

D. Cameron et al.
Lancet 2017 (PMID: 28215665)

ExteNET – Neratinib nach Trastuzumab-basierter adjuvanter Therapie

iDFS HR+/HER2+



- **HER2 + early BC**
- **Prior adjuvant trastuzumab** & chemotherapy
- Stage II–IIIc or residual invasive disease after neadjuvant therapy
- ER/PR + or -

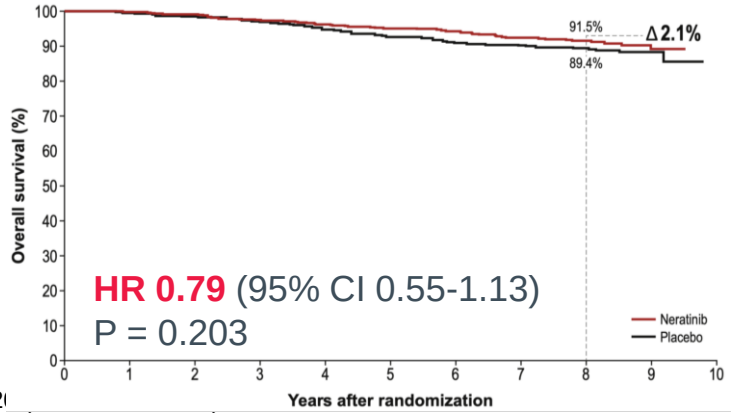
R → 1:1

Neratinib x 1 year 240mg/d

N=2840

Placebo x 1 year

OS HR+/HER2+



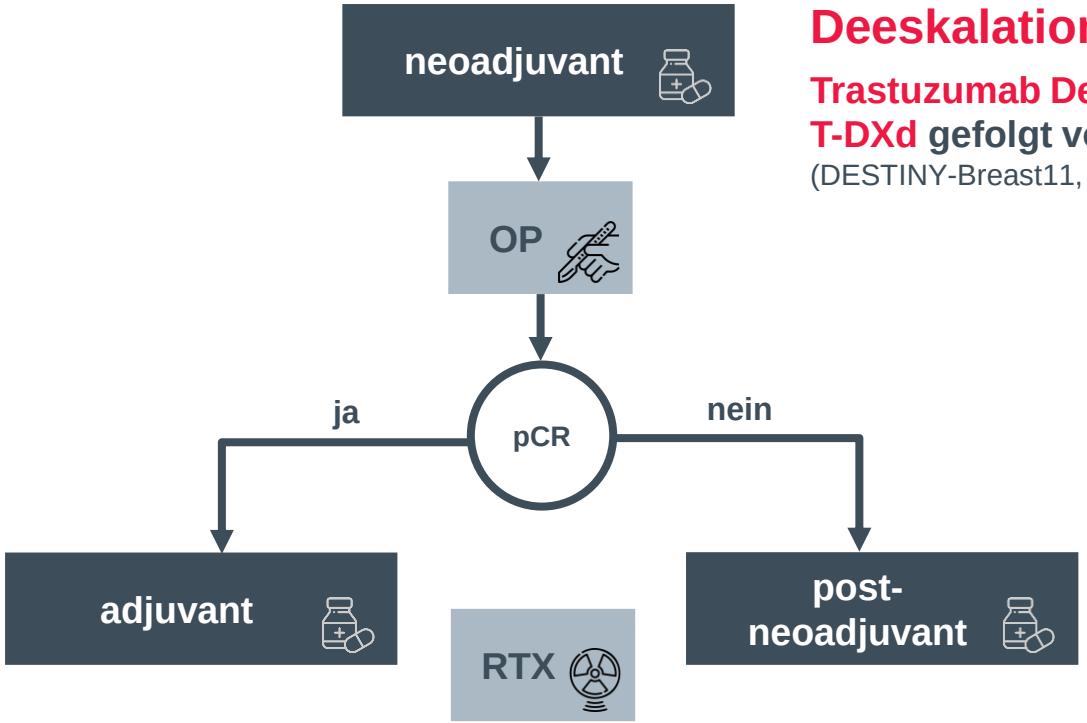
Grad 3/4 Diarrhö: 41%* vs 2%

Kann durch Loperamid auf 31% reduziert werden*

A. Chan et al. Clin Breast Cancer 2021 (PMID: 33183970); * C. H. Barcenas et al. Ann Oncol 202

Laufende Phase 3 Studie bei frühen HER2+ Mammakarzinomen

(mit Indikation zur neoadjuvanten Behandlung)



Deeskalation:

Trastuzumab Deruxtecan (T-DXd) mono vs. T-DXd gefolgt von THP vs. ddAC-THP

(DESTINY-Breast11, Clinicaltrials.gov NCT05113251)

Eskalation:

Trastuzumab-Deruxtecan vs T-DM1

(DESTINY-Breast05, Clinicaltrials.gov NCT04622319)

T-DM1 + Tucatinib vs T-DM1

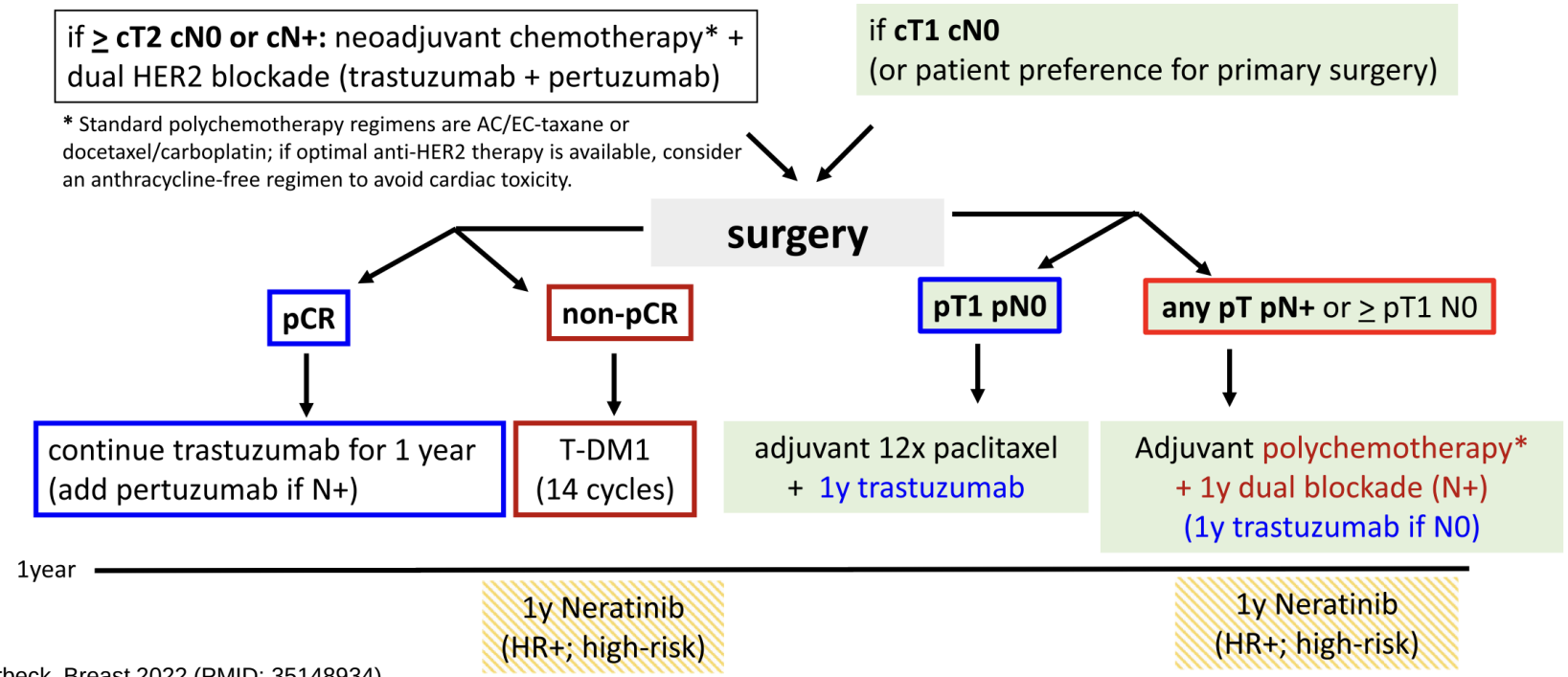
(CompassHER2 RD, Clinicaltrials.gov NCT04457596)

Im Spannungsfeld von Eskalation und Deeskalation
Zusammenfassung

- **Deeksalation**
  - **Vielversprechende Konzepte** (T-DM1, Trastuzumab + Pertuzumab und Paclitaxel, Trastuzumab + Pertuzumab) in klinischen Studien getestet.
  - **Patientinnenselektionen** für solche Strategien **noch nicht ausreichend definiert**
  - **Außerhalb klinischer Studien** derzeit **nur für stark selektionierte Patientinnen** (zB elderly und slow-go)

- **Eskalation**
  - **Postneoadjuvante Therapie mit T-DM1** bei non-pCR **Standard**
  - **Neratinib** bei **Hochrisikopatientinnen** mit HR+/HER2+ einen Optionen
  - **Laufende Studien** mit Integration der *big player* (**Trastuzumab-Deruxtecan und Tucatinib**)

HER2+ Mammakarzinome - (neo-)adjuvante Therapiestrategie 2023



N. Harbeck. Breast 2022 (PMID: 35148934)

Danke für Ihre Aufmerksamkeit