Antibody Drug Conjugates as Neoadjuvant Therapy in Breast Cancer

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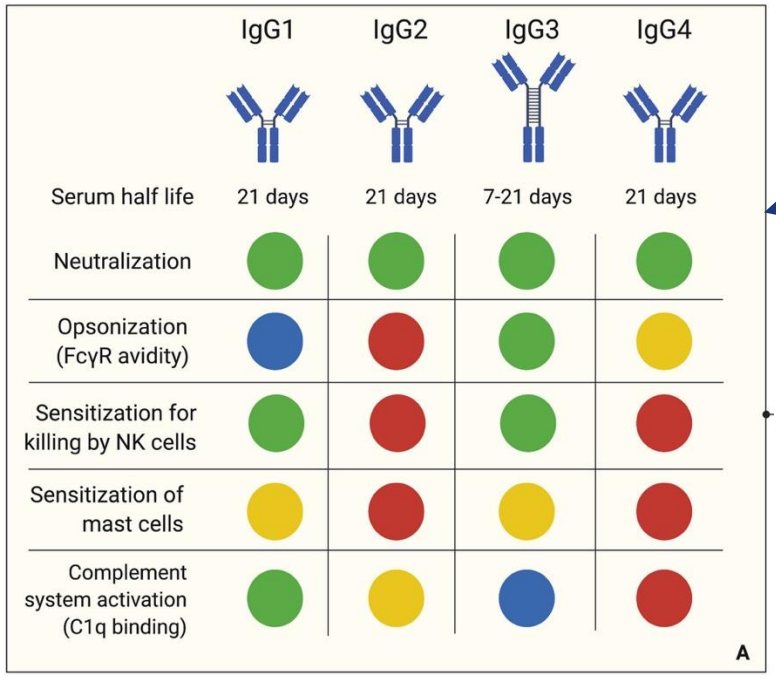
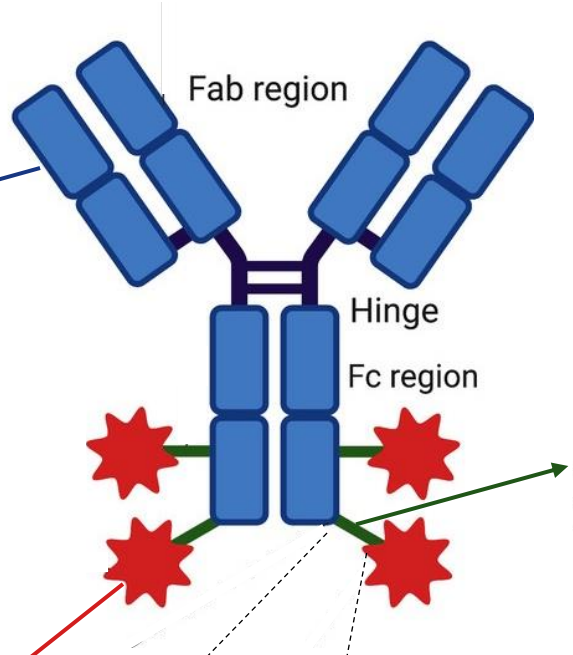
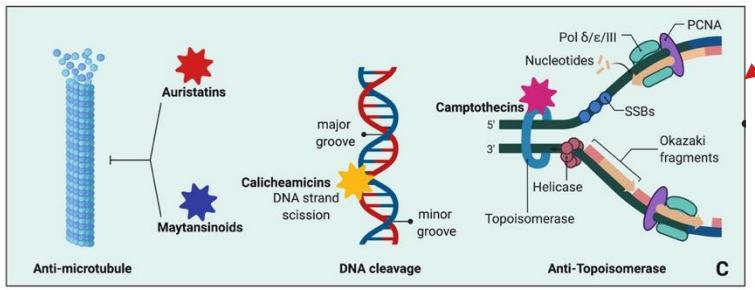
Structure of an ADC and Properties of Its Components

High-complexity engineering constructs

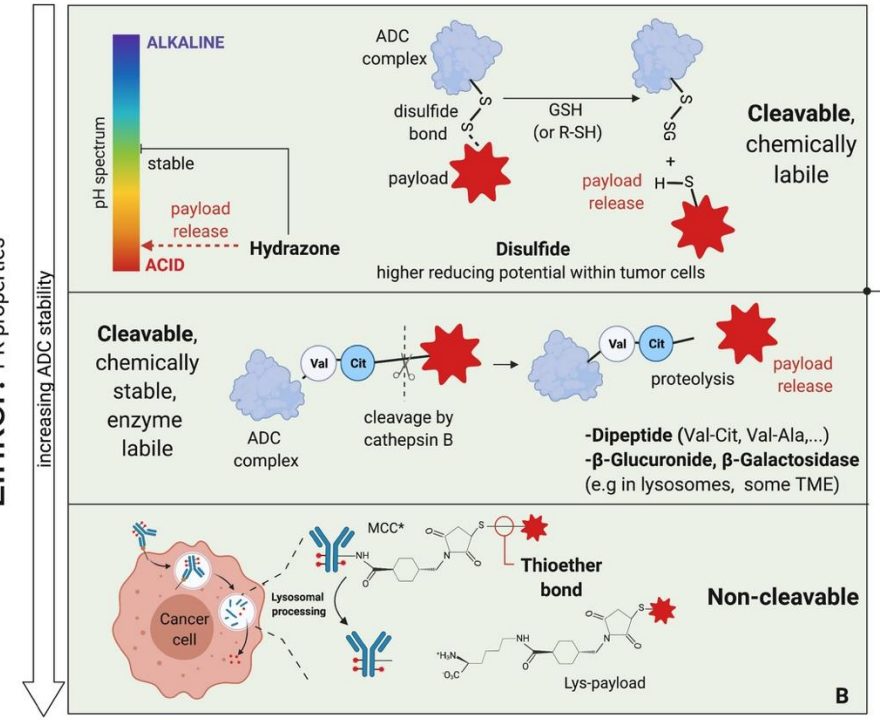






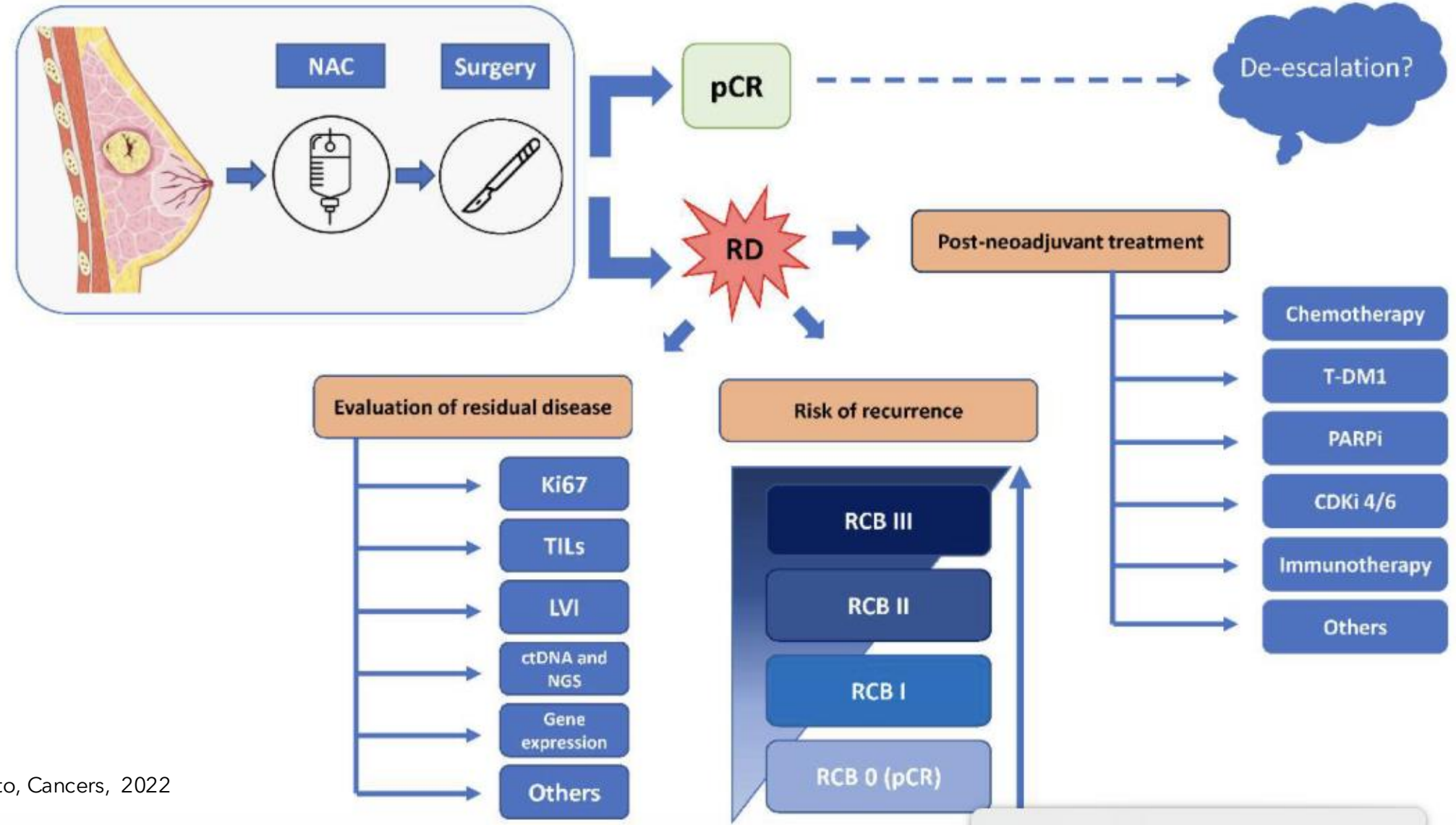
Ab-Linker attachment:
-controlled by conjugation methods;
-defines DAR;
-impact ADC stability and PK properties.

Linker-Drug attachment:
-controlled by cleavable/ non-cleavable technology;
-defines nature of active payload species, payload release rate;
-contributes to on-/off-target toxicity;
-affects ADC solubility, stability and potency.



Adapted from Tarantino P et al. CA Cancer J Clin. 2022 Mar;72(2):165-182

Why is Neoadjuvant Tx for Aggressive Breast Cancer Better?

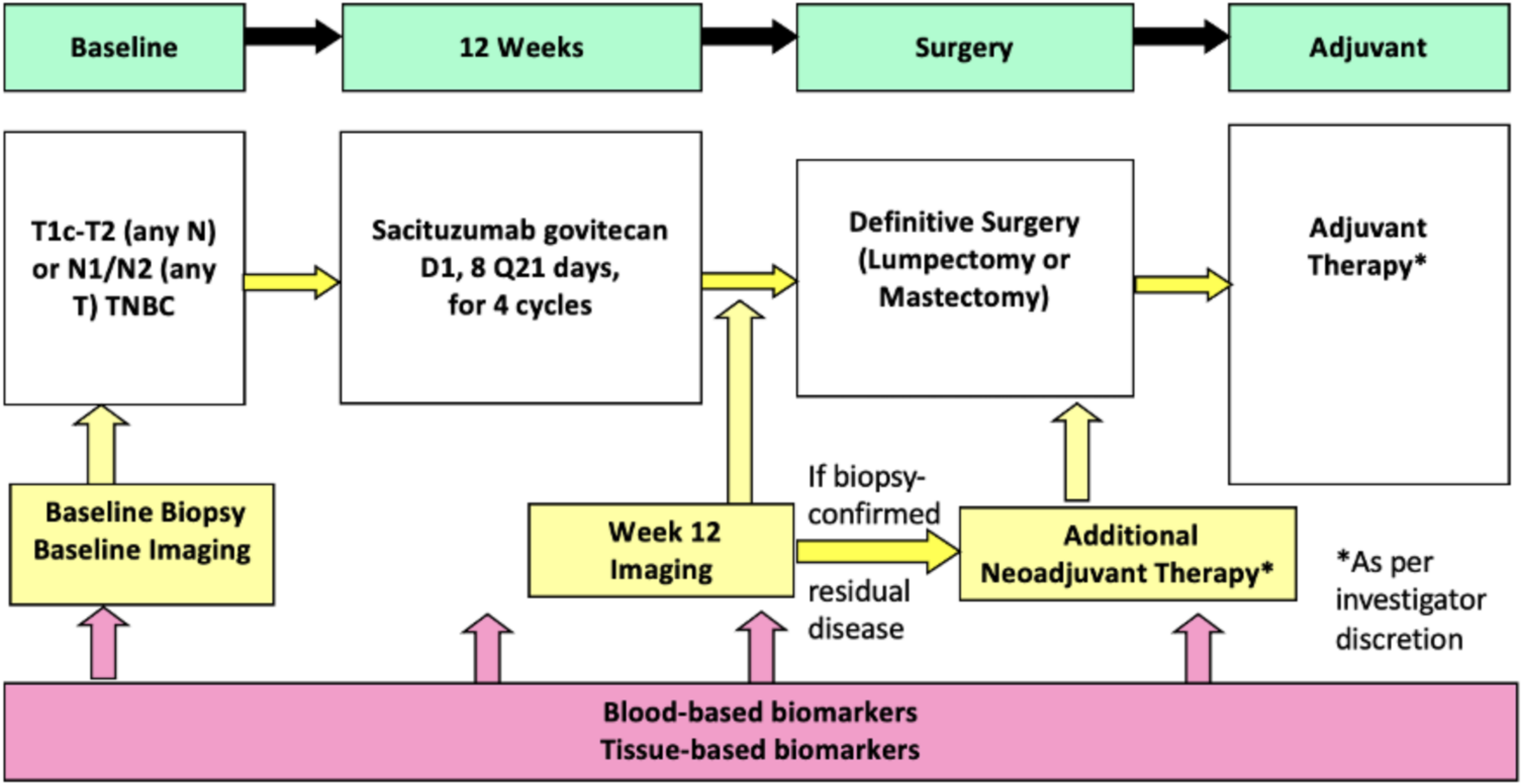


Agostinetto, Cancers, 2022

Neoadjuvant vs. MBC Trial Success

- **Bar is higher** – no room for error when you're going for cure
- **Goal is pCR!!!! – Beat Keynote 522**
- **Less tolerance of toxicity**
- Specific toxicities that are INTOLERABLE
  - Secondary Malignancy
  - Eye tox – especially long term
  - Neuropathy
  - ILD
  - Cardiotoxicity
  - Tox that limits ability to get further therapy if needed
- Tox that IS tolerable
  - Neutropenia – as long as responsive to GCSF
  - Alopecia as long as not permanent (though holy grail is to avoid this!!!)

NeoSTAR: Sacituzumab govitecan


Baseline
12 Weeks
Surgery
Adjuvant
T1c-T2 (any N) or N1/N2 (any T) TNBC
Sacituzumab govitecan D1, 8 Q21 days, for 4 cycles
Definitive Surgery (Lumpectomy or Mastectomy)
Adjuvant Therapy*
Baseline Biopsy
Baseline Imaging
Week 12 Imaging
If biopsy-confirmed residual disease
Additional Neoadjuvant Therapy*
*As per investigator discretion
Blood-based biomarkers
Tissue-based biomarkers

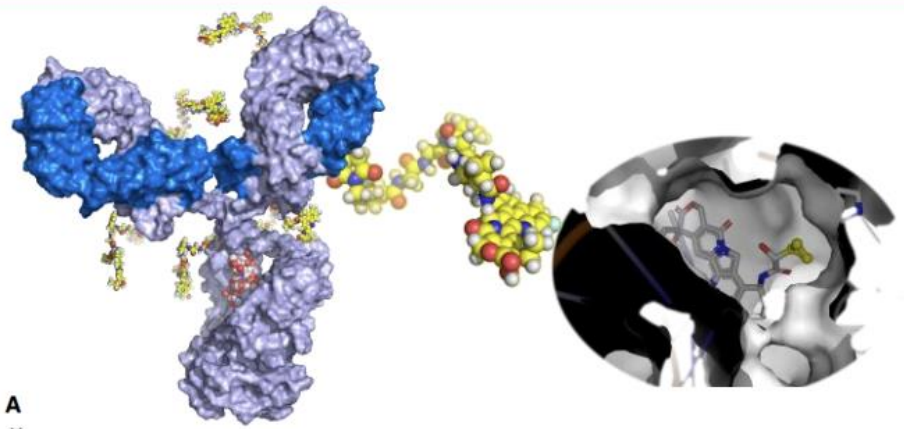
NeoSTAR Demographics and Efficacy

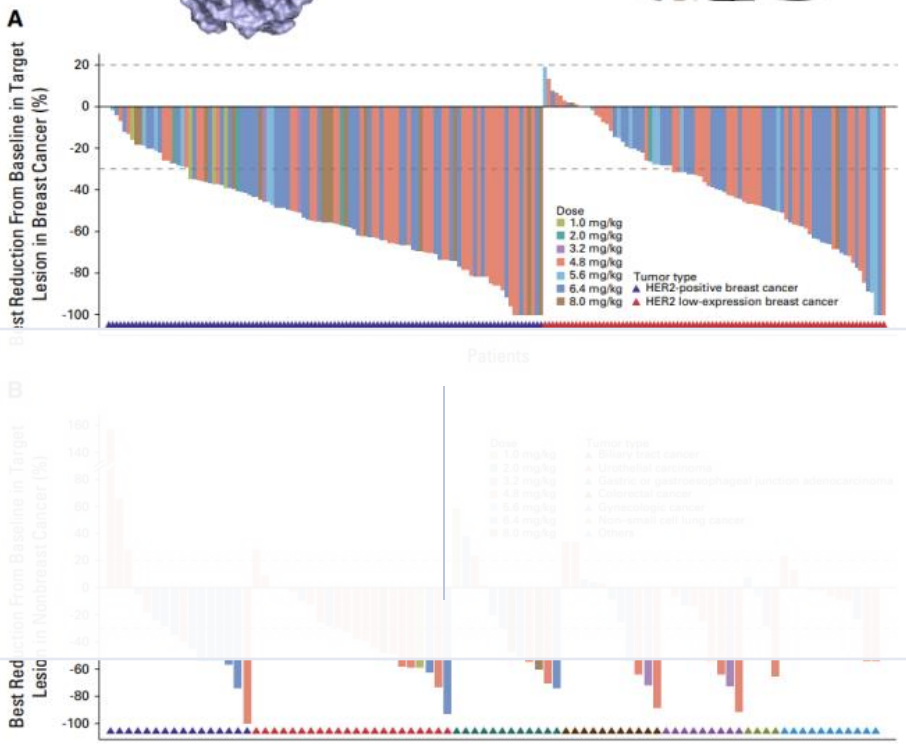
- Lower risk population given exclusion of T3, T4 and N3
- 50 patients treated
  - Median age 48
  - 52% Stage 2
- Overall pcR rate 30%
- 21 patients received additional chemotherapy
  - Of those 7 patients (33%) achieved pCR
- 2 year EFS was 100% from those who received SG alone

HER2 ADCs : FASCINATE-N +T’Dxd

Background: SHR-A1811

- **SHR-A1811** is a novel HER2-targeted new-generation ADC composed of trastuzumab, a cleavable linker, and the topoisomerase I inhibitor payload SHR169265:[1]
  - Payload **SHR169265**: high membrane permeability and potent cell-killing effect;
  - **Protease-cleavable GGFG linker**: high stability;
  - Moderate **drug-antibody ratio of 6** and minimal amount of early-released toxin contribute to a favorable safety profile.
- **A global phase 1 study of SHR-A1811** in heavily pretreated HER2-expressing or mutated advanced solid tumors:[2]
  - **Promising antitumor activity**: ORR was **59.9%** for all tumors; **76.3%** for HER2+ BC and **60.4%** for HER2 low-expressing BC;
  - **Manageable safety**: **interstitial lung disease** occurred in only **2.6%** of patients;
  - **Recommended dose**: 4.8 or 6.4 mg/kg.

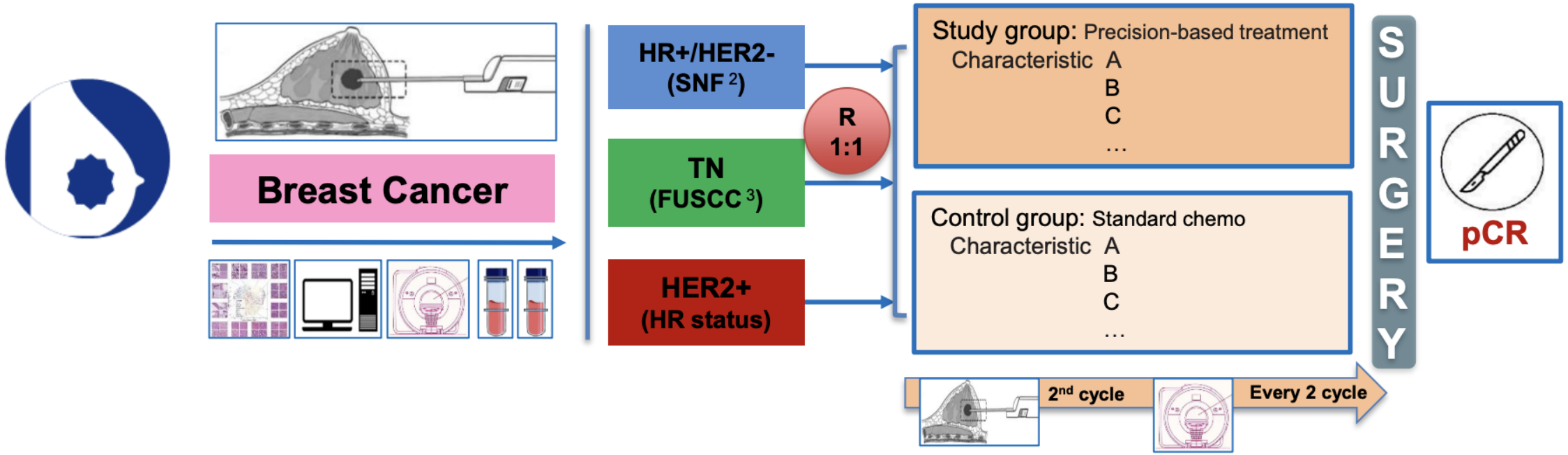




References: 1. 2023 AACR LB031. 2. J Clin Oncol. 2024;42(29):3453-65.

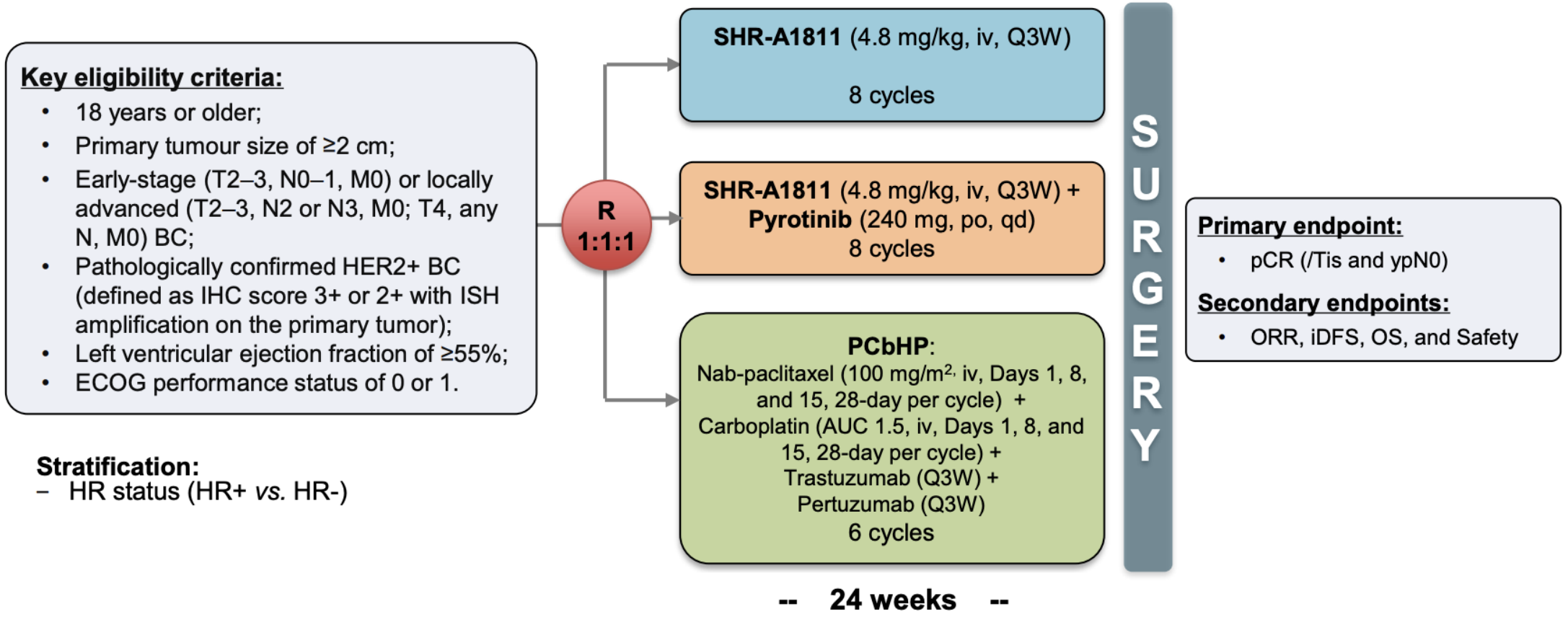
Study Design: FASCINATE-N

Fudan University Shanghai Cancer Center Breast Cancer Precision Platform Series study-Neoadjuvant therapy (NCT05582499) [1]



- Randomized, open-label, single-center, phase 2 umbrella trial.
- **Using multiomic characteristics to classify in different subtypes: Luminal SNF,[2] TN FUSCC classification,[3] and HER2+ HR status.**
- To test the efficacy of subtyping-based treatment and to evaluate the efficacy of targeted therapies through Bayesian monitoring method.

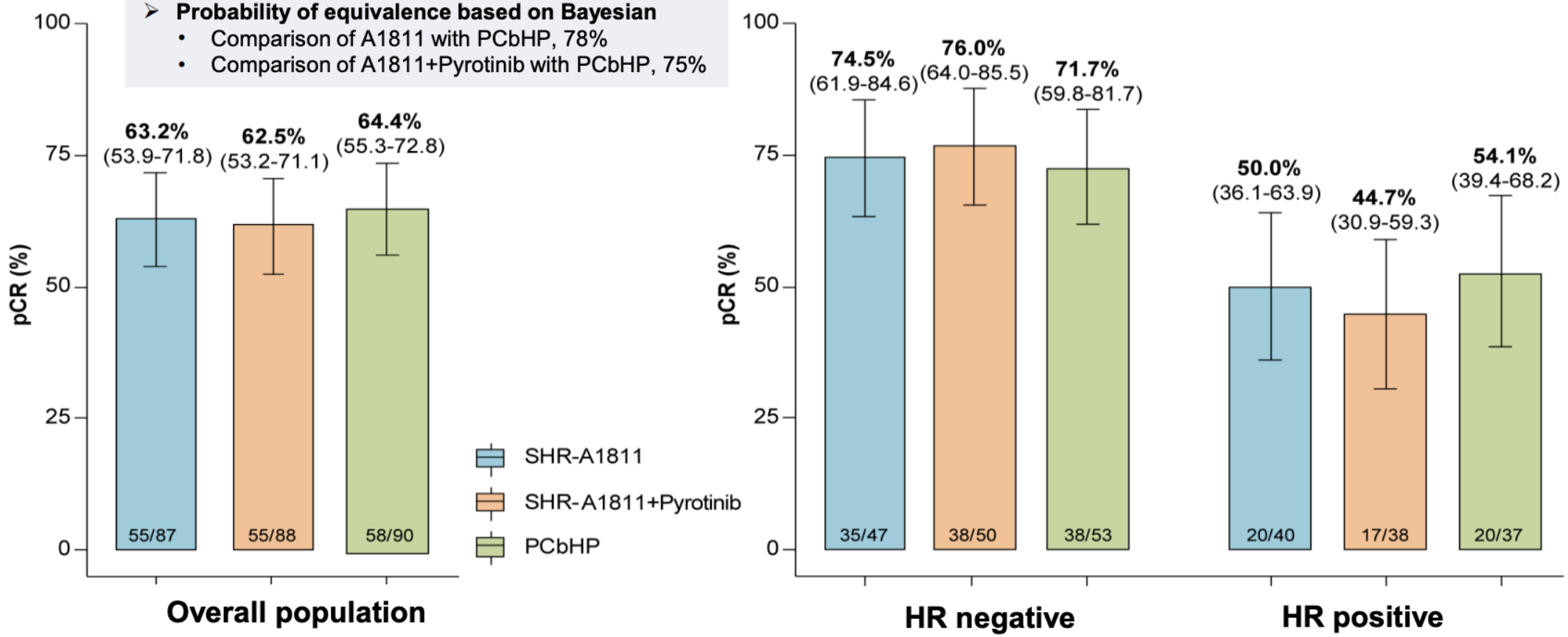
HER2+ Subtype Study Design



Tumor assessments, including CT or MRI scans, were conducted by investigators at baseline and every two cycles thereafter until disease progression, patient withdrawal, initiation of new therapy, or death, in accordance with RECIST (version 1.1) guidelines.

Efficacy Analysis: pCR

- **Probability of equivalence based on Bayesian**
  - Comparison of A1811 with PCbHP, 78%
  - Comparison of A1811+Pyrotinib with PCbHP, 75%



Data are % (90% CI).

There was no significant difference in pCR rate among the SHR-A1811, SHR-A1811 plus pyrotinib, and PCbHP groups

DESTINY Breast11: Neoadjuvant HER2+ BC

NCT05113251

Population

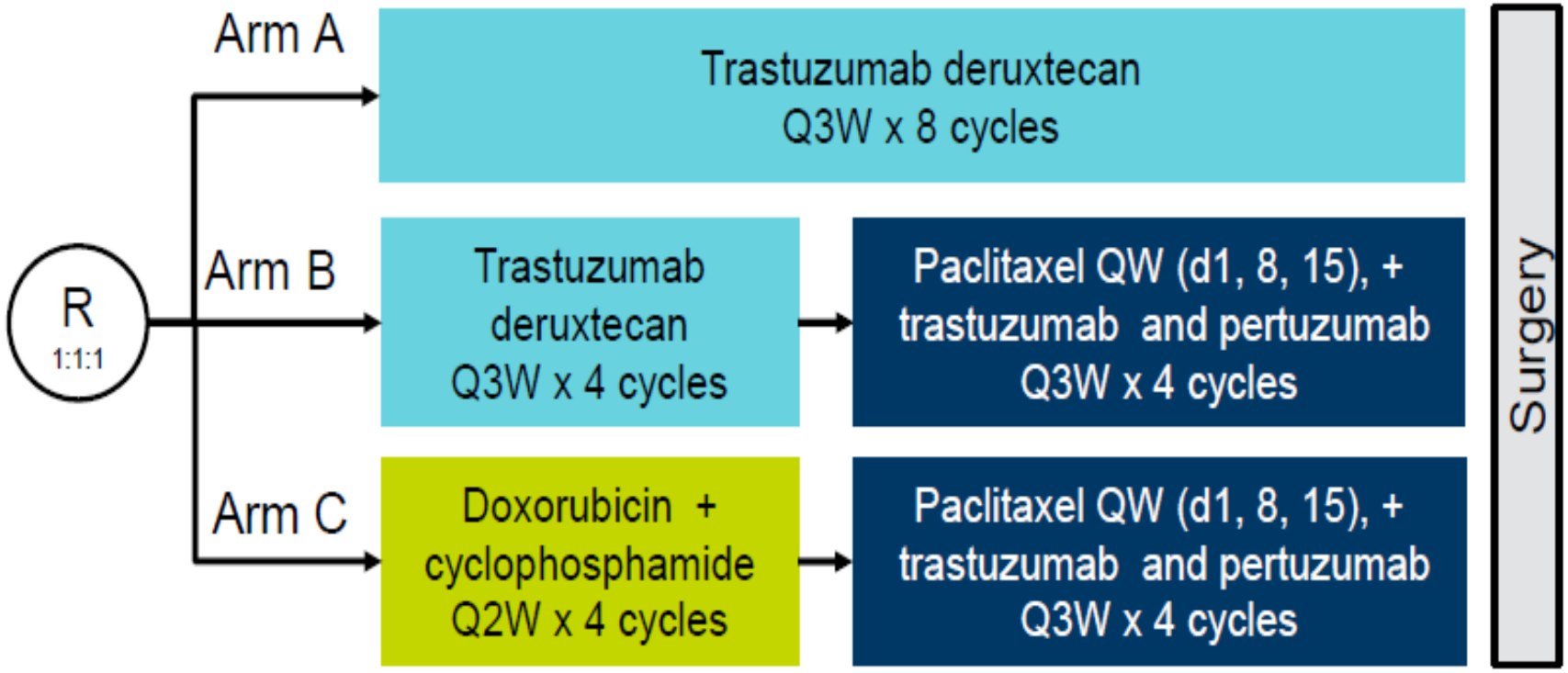
HER2+ EBC

HR+ or HR-

High-risk defined as one of the following:

- $T_xN_{1-3}M_0$
- $T_{3-4}N_xM_0$
- Inflammatory BC

Study Design

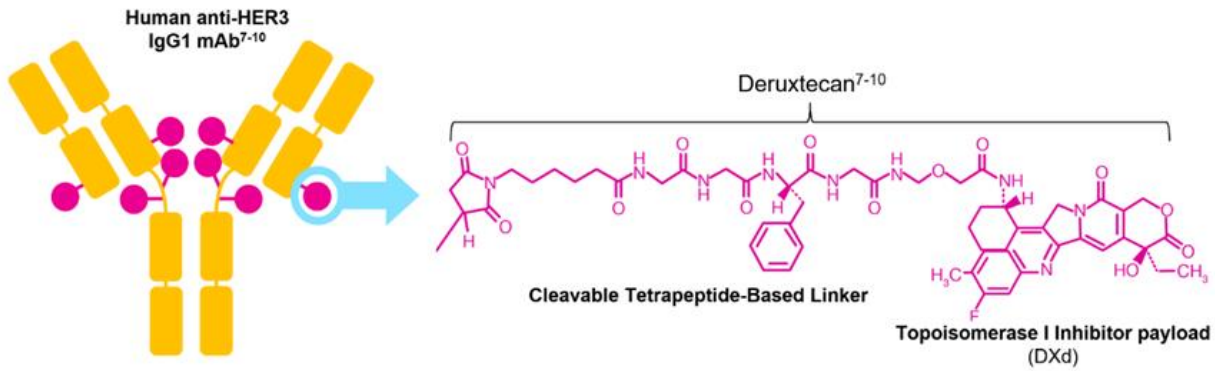


HER3 D’xd : Solti-Valentine

Background

- HER3 is overexpressed in MBC and has been associated with poor clinical outcomes[1-5]
- Patritumab deruxtecan (HER3-DXd; U3-1402) is a novel investigational ADC directed against HER3 that has 3 components:
  - a fully human anti-HER3 IgG1 monoclonal antibody (patritumab)
  - a topoisomerase I inhibitor payload, an exatecan derivative,
  - a tetrapeptide-based cleavable linker
- Safety and preliminary antitumor activity of DXd were previously reported in this ongoing, phase 1/2 clinical trial (NCT02980341/JapicCTI-163401)[6]
  - Initial results from the dose-escalation and dose-finding cohorts demonstrated antitumor activity in heavily pretreated patients with HER3-expressing MBC

Structure of HER3-DXd (Antibody-Drug Conjugate)

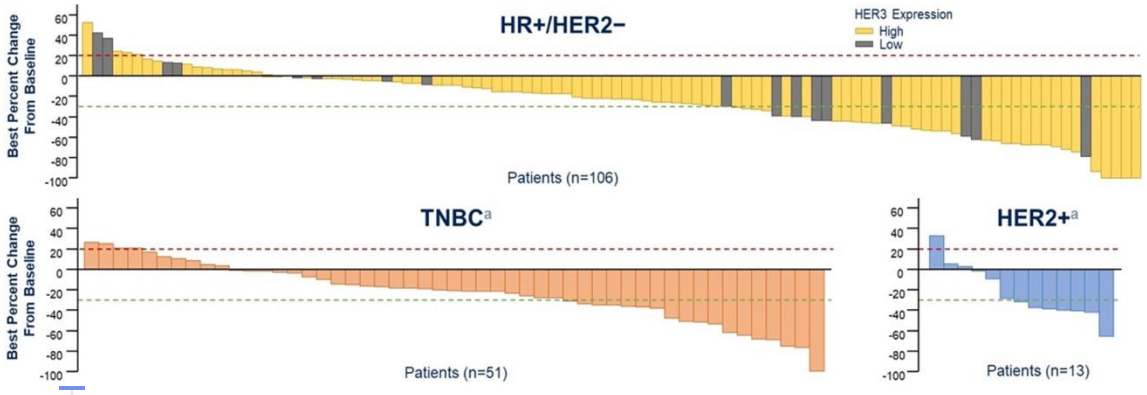


1. Mishra R, et al. Oncol Rev. 2018;12(1):355; 2. Gala K, et al. Clin Cancer Res. 2014;20(6):1410-1416; 3. Mota JM, et al. Oncotarget. 2017;8(51):89284-89306; 4. Mujoo K, et al. Oncotarget. 2014;5(21):10222-10236.
5. Fontanini G, et al. Clin Cancer Res. 1998;4(1):241-249; 6. Masuda N, et al. SABCS 2018. Poster PD1-03.

Krop et al, SABCS '20

Patritumab Deruxtecan Across HER3 Expression Levels

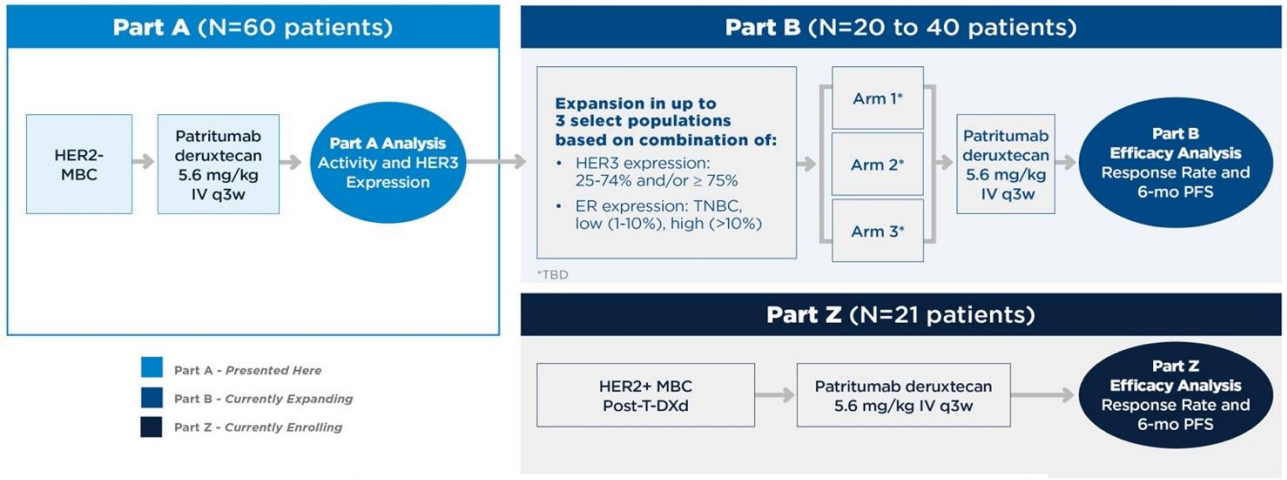
Ph I/II U3-1402-J101

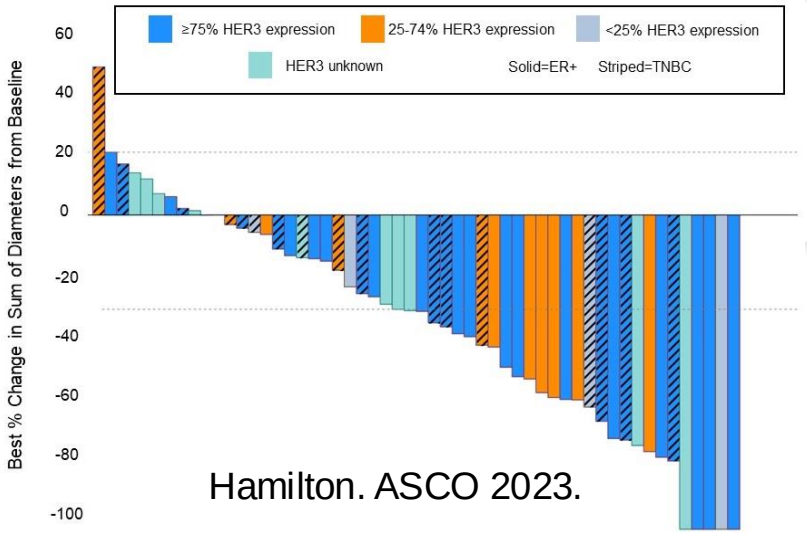


	HR+/HER2- N=113	TNBC N=53	HER2+ N=14
HER3 status	High or Low	High	High
Prior Lines of Therapy	6 (2-13)	2 (1-13)	5.5 (2-11)
Confirmed ORR, %	30.1	22.6	42.9
Median PFS, mo	7.4	5.5	11.0

Krop. ASCO 2022.

BRE-354

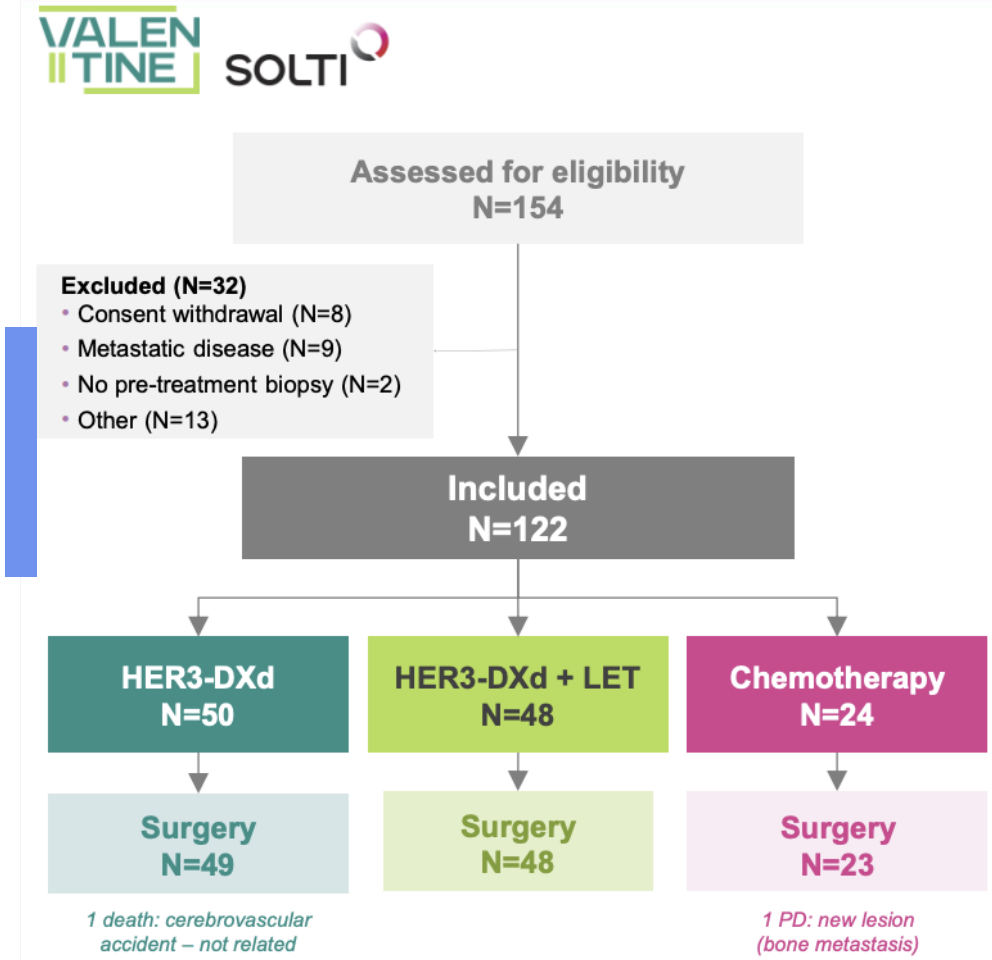




Hamilton. ASCO 2023.

Baseline Characteristics

BREAST CANCER SYMPOSIUM®
UT Health San Antonio Mays Cancer Center
AACR American Association for Cancer Research
December 10-13, 2024



Recruitment period: November 2022 to September 2023
Data cut-off: April 22nd, 2024

IHC: Immunohistochemistry; ISH: *In situ* hybridization; LET: letrozole

	HER3-DXd N=50	HER3-DXd + LET N=48	Chemotherapy N=24	Overall N=122
Age, median (range)	51 (29-77)	49 (32-82)	52 (31-73)	51 (29-82)
Female	50 (100.0%)	48 (100.0%)	23 (95.8%)	121 (99.2%)
Pre/Perimenopausal	24 (48.0%)	28 (58.3%)	12 (52.2%)[a]	64 (52.9%)
cT stage				
T1-T2	29 (58.0%)	29 (60.4%)	17 (70.8%)	75 (61.5%)
T3-T4	21 (42.0%)	19 (39.6%)	7 (29.2%)	47 (38.5%)
Lymph node positive	38 (76.0%)	37 (77.1%)	18 (75.0%)	93 (76.2%)
Stage				
II	32 (64%)	29 (60.4%)	17 (70.8%)	78 (64.0%)
III	18 (36.0%)	19 (39.6%)	7 (29.2%)	44 (36.0%)
Histological Grade				
G1-G2	38 (82.6%)	35 (79.5%)	14 (66.7%)	87 (78.4%)
Not available	4	4	3	11
HER2 IHC[b]				
0	20 (40.0%)	16 (33.3%)	9 (37.5%)	45 (36.9%)
1+	18 (36.0%)	21 (43.8%)	6 (25.0%)	45 (36.9%)
2+	12 (24.0%)	11 (22.9%)	8 (33.3%)	31 (25.4%)
Local Ki67 median (range)	35 (20-85)	37 (18-80)	35 (20-90)	35 (18-90)
HER3 IHC[c]				
High	29 (80.6%)	31 (83.8%)	15 (88.2%)	75 (83.3%)
Low	5 (13.9%)	4 (10.8%)	2 (11.8%)	11 (12.2%)
Negative	2 (5.6%)	2 (5.4%)	0	4 (4.4%)
Not available	14	11	7	32
Intrinsic subtype (PAM50)				
Basal-Like	0	1 (2.1%)	0	1 (0.8%)
HER2-Enriched	1 (2.0%)	2 (4.2%)	1 (4.3%)	4 (3.3%)
Luminal A	21 (42.0%)	14 (29.2%)	10 (43.5%)	45 (37.2%)
Luminal B	27 (54.0%)	29 (60.4%)	11 (47.8%)	67 (55.4%)
Normal-Like	1 (2.0%)	2 (4.2%)	1 (4.3%)	4 (3.3%)
Not available	0	0	1	1

[a]One male; [b]One sample with HER2 IHC NA/ISH negative in chemotherapy arm (4.2%); [c]HER3 measured by membrane protein expression (%) using anti-HER3 recombinant rabbit mAb clone SP438 (Ventana Medical Systems), 10X: High:≥75%, Low: <75% and ≥25%, Negative: <25%.

SOLTI VALENTINE: Study Design

BREAST CANCER SYMPOSIUM®
UT Health San Antonio Mays Cancer Center
AACR American Association for Cancer Research
December 10-13, 2024

VALENTINE SOLTI

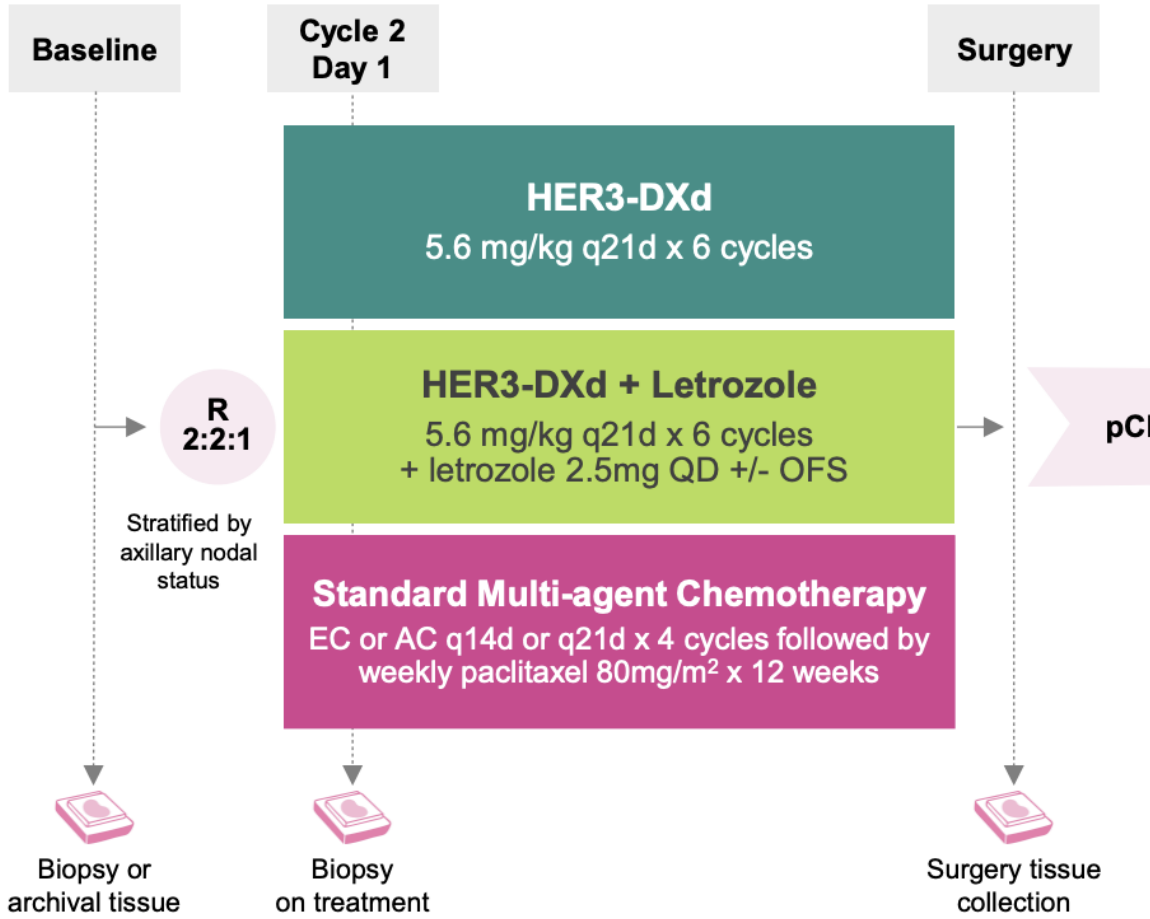
Parallel, randomized, non-comparative, open-label, phase II trial (NCT05569811)

N=120

Key eligibility criteria:

- Pre- and post-menopausal women, or men
- Primary operable breast cancer ≥1 cm by MRI
- HR+/HER2-negative[a]
- Ki67 ≥20%[a] and/or high genomic risk (gene signature)
- No prior treatment for the current breast cancer
- Available pre-treatment FFPE core-needle biopsy

[a]HR, HER2, and Ki67 determined by local assessment.



Primary Endpoint:

- Rate of pCR (ypT0/is ypN0) at surgery

Secondary Endpoints:

- ORR
- CelTIL score change, Ki67 drop, PAM50, ROR
- Safety
- iDFS

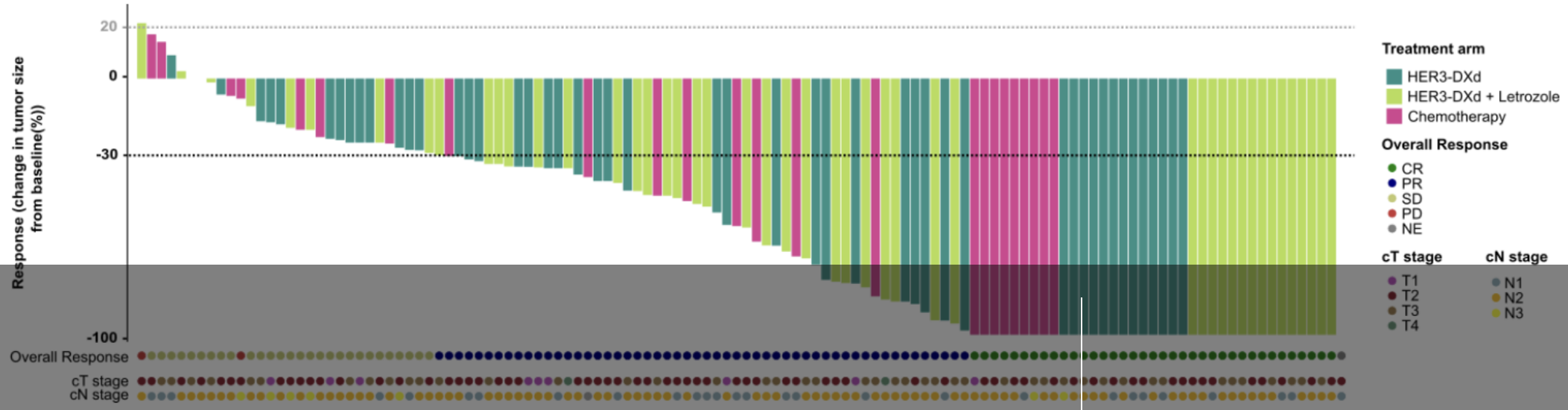
AC: Doxorubicin 60 mg/m² plus cyclophosphamide 600 mg/m²; **EBC:** Early breast cancer; **EC:** Epirubicin 90 mg/m² plus cyclophosphamide 600 mg/m²; **FFPE:** Formalin-fixed paraffin-embedded; **HR:** Hormone receptor; **iDFS:** Invasive disease-free survival; **OFS:** Ovarian function suppression (LHRH analogs); **ORR:** Objective response rate; **QD:** Every day; **pCR:** Pathological complete response; **ROR:** Risk of

HER3-DXd showed pCR and ORR rates similar to standard multi-agent chemotherapy

SAN ANTONIO BREAST CANCER SYMPOSIUM®
UT Health San Antonio Mays Cancer Center
AACR American Association for Cancer Research
December 10-13, 2024

ALEN TINE SOLTI

	HER3-DXd N=50	HER3-DXd + LET N=48	Chemotherapy N=24	Overall N=122
pCR rate				
N	2	1	1	4
% (95%CI[a])	4.0% (0.5-13.7)	2.1% (0.1-11.1)	4.2% (0.1-21.1)	3.3% (0.9-8.2)
ORR				
N	35	39	17	91
% (95%CI[a])	70.0% (55.4-82.1)	81.3% (67.4-91.1)	70.8% (48.9-87.4)	74.6% (65.9-82.0)
PD				
N (%)	0	1 (2.1%)	1 (4.2%)	2 (1.6%)



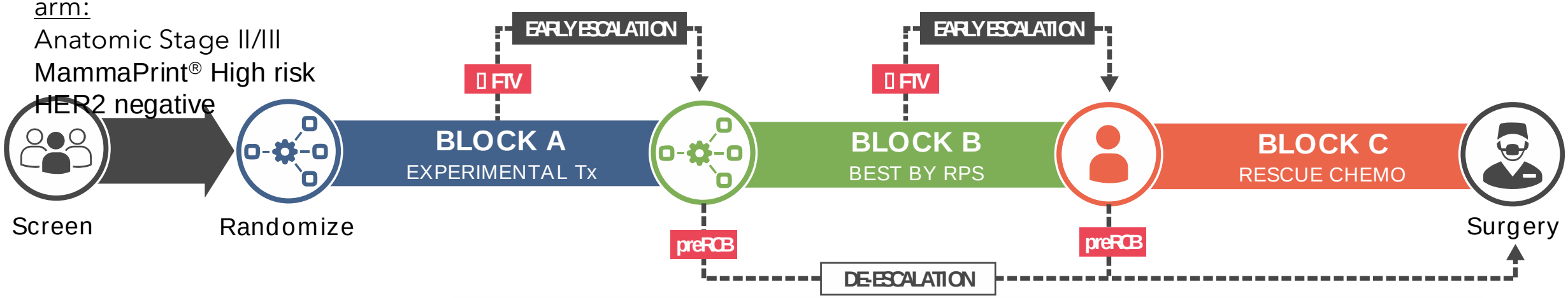
[a] 95% exact binomial confidence interval (by Clopper-Pearson method)

ORR: objective response rate; pCR: pathological complete response; PD: progressive disease.

I-SPY 2: The Perfect Platform for Neoadjuvant ADC Exploration!

I-SPY 2.2 Design Features: Multiple Sequential Regimens

Eligibility for Dato+Durva arm:
Anatomic Stage II/III
MammaPrint® High risk
HER2 negative



Treatment Assignments/Randomization ***based on Response Predictive Subtype (RPS)***

HR+ HER2- Immune- DRD-	Taxol	AC
HR- HER2- Immune- DRD-:	Taxol + Carbo + Pembro	AC + Pembro
HER2- Immune+:	Taxol + Carbo + Pembro	AC + Pembro
HER2- Immune- DRD+:	Taxol + Carbo + Pembro	AC + Pembro
HER2- Immune- DRD+:	Taxol + Carbo	AC + Pembro

Comparator arm: Dynamic control

Specific to each subtype identified from previously tested I-SPY2 agents between March 2010 and April 2022 (e.g. paclitaxel -> AC ; paclitaxel +

New I-SPY 2.2 Design Features: Multiple Sequential Regimens Called Blocks

Block A

- Investigational agents without standard chemo across RPS

Block B

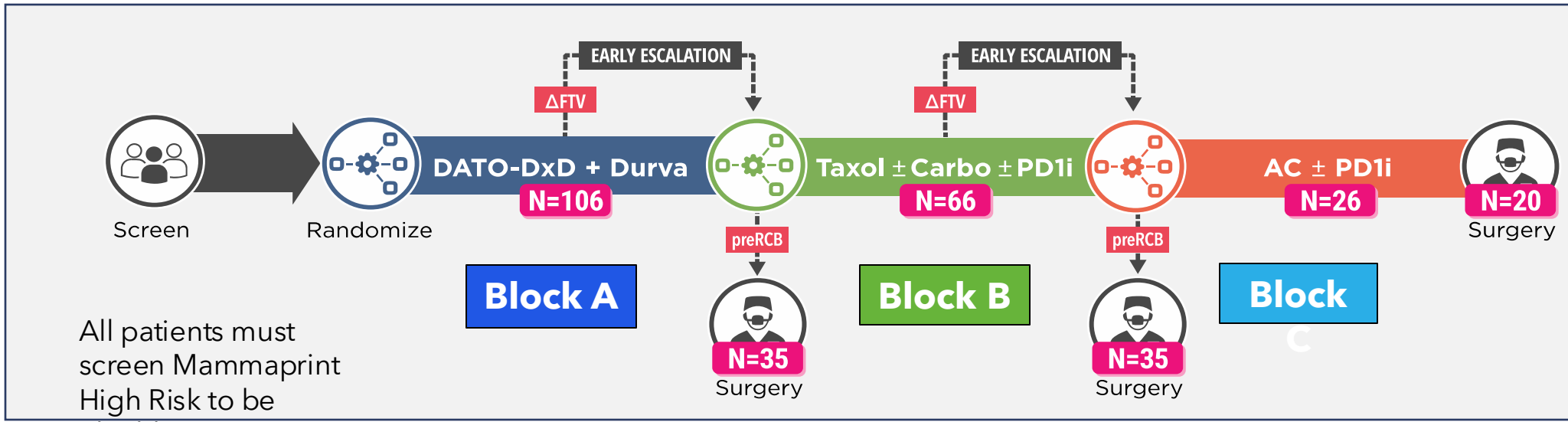
- Optimal regimens based on Response Predictive Subtypes (RPS) and SOC
- Investigational agents to improve response

Block C

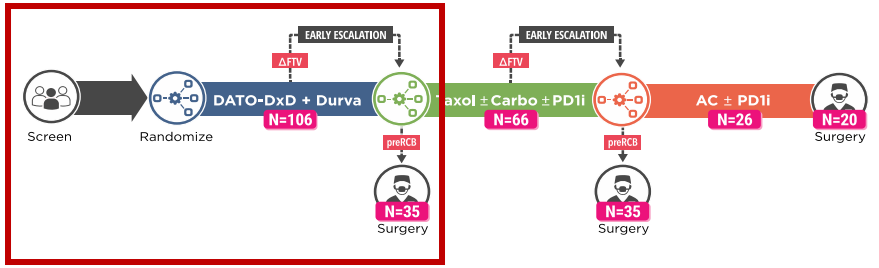
- Adriamycin/Cytoxan
- Adriamycin/Cytoxan + IO per SOC

Surgery

- pCR and RCB endpoints



Efficacy of Block A



- Dato + Durva meets the graduation threshold in the Immune+ subtype

Response Predictive Subtype	N	pCR	non-pCR*	Modeled Rate (95% CI)	Threshold	P(>Thr)
HR+Immune-DRD-	25	0	23	3% (0%-7%)	15%	0.00
HR-Immune-DRD-	23	2	14	13% (3%-23%)	15%	0.33
Immune+	**47**	**20**	**11**	**65% (47%-83%)**	**40%**	**0.99**
Immune-DRD+	11	3	6	24% (4%-44%)	40%	0.06

Receptor Subtypes	N	pCR	non-pCR*	Modeled Rate (95% CI)	Threshold	P(>Thr)
HR+	42	4	29	18% (6%-30%)	15%	0.68
HR-	64	21	25	44% (32%-56%)	40%	0.74

* Includes Patients with Biopsy Positive for Invasive Cancer after Block A or non-pCR or in subsequent blocks

I-SPY ADCs Already Tested!!!

- Trastuzumab emtansine + pertuzumab
- Ladiratuzumab vedotin (LIV1-A)
- Datopotamab deruxtecan +/- durvalumab
- Trastuzumab deruxtecan + rilvegostimig (PD-1/TIGIT bispecific) (ongoing)
- Trastuzumab duocarmazine (SYD-985)
- ARX-788
- Dan 222 + Niraparib (ongoing)

Unanswered questions

- Which ADCs need biomarker testing and biomarkers?
- How do we assess HR+ patient in efficacy analyses since rates of pCR are low and late distant relapse can occur?
- What tox is acceptable and what is not?
- What are the best combinational strategies?

Thank You!!!!