IS THERE STILL A ROLE FOR ANTHRACYCLINES IN EARLY STAGE BREAST CANCER?

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CURRENT GUIDELINES

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NCCN Guidelines Version 3.2024
Invasive Breast Cancer

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PREOPERATIVE/ADJUVANT THERAPY REGIMENS[a]

The regimens listed in the table for HER2-negative disease are all category 1 (except where indicated) when used in the adjuvant setting.

HER2-Negative	
Preferred Regimens: • Dose-dense AC (doxorubicin/cyclophosphamide) followed or preceded by paclitaxel every 2 weeks[b] • Dose-dense AC (doxorubicin/cyclophosphamide) followed or preceded by weekly paclitaxel[b] • TC (docetaxel and cyclophosphamide) • Olaparib, if germline *BRCA1/2* mutations[c,d] • High-risk[e] TNBC: Preoperative pembrolizumab + carboplatin + paclitaxel, followed by preoperative pembrolizumab + cyclophosphamide + doxorubicin or epirubicin, followed by adjuvant pembrolizumab • TNBC and residual disease after preoperative therapy with taxane-, alkylator-, and anthracycline-based chemotherapy[d]: Capecitabine	
Useful in Certain Circumstances: • Dose-dense AC (doxorubicin/cyclophosphamide) • AC (doxorubicin/cyclophosphamide) every 3 weeks (category 2B) • CMF (cyclophosphamide/methotrexate/fluorouracil) • AC followed by weekly paclitaxel[b] • Capecitabine (maintenance therapy for TNBC after adjuvant chemotherapy)	**Other Recommended Regimens:** • AC followed by docetaxel every 3 weeks[b] • EC (epirubicin/cyclophosphamide) • TAC (docetaxel/doxorubicin/cyclophosphamide) • For TNBC: ▸ Paclitaxel + carboplatin (various schedules) (category 2A) ▸ Docetaxel + carboplatin (category 2A)

Additional Considerations for Those Receiving Preoperative/Adjuvant Therapy (BINV-L, 3)

HER2 Negative: Preferred

HER2 Positive: Useful in Certain Circumstances

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PREOPERATIVE/ADJUVANT THERAPY REGIMENS[a]

HER2-Positive	
Preferred Regimens: • Paclitaxel + trastuzumab[f] • TCH (docetaxel/carboplatin/trastuzumab) • TCHP (docetaxel/carboplatin/trastuzumab/pertuzumab) • If no residual disease after preoperative therapy or no preoperative therapy: Complete up to one year of HER2-targeted therapy with trastuzumab[i] (category 1) ± pertuzumab. • If residual disease after preoperative therapy: Ado-trastuzumab emtansine (category 1) alone. If ado-trastuzumab emtansine discontinued for toxicity, then trastuzumab (category 1) ± pertuzumab to complete one year of therapy.[g,h] If node positive at initial staging, trastuzumab + pertuzumab (category 1)[i]	
Useful in Certain Circumstances: • Docetaxel + cyclophosphamide + trastuzumab • AC followed by T[b] + trastuzumab[h] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab, various schedules) • AC followed by T[b] + trastuzumab + pertuzumab[h] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab plus pertuzumab, various schedules) • Neratinib[g] (adjuvant setting only) • Paclitaxel + trastuzumab + pertuzumab[h] • Ado-trastuzumab emtansine (TDM-1) (adjuvant setting only)	**Other Recommended Regimens:** • AC followed by docetaxel[b] + trastuzumab[h] (doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab) • AC followed by docetaxel[b] + trastuzumab + pertuzumab[h] (doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab + pertuzumab) • Paclitaxel/carboplatin + trastuzumab + pertuzumab

Additional Considerations for Those Receiving Preoperative/Adjuvant Therapy (BINV-L, 3)

PRO-ANTHRACYCLINE

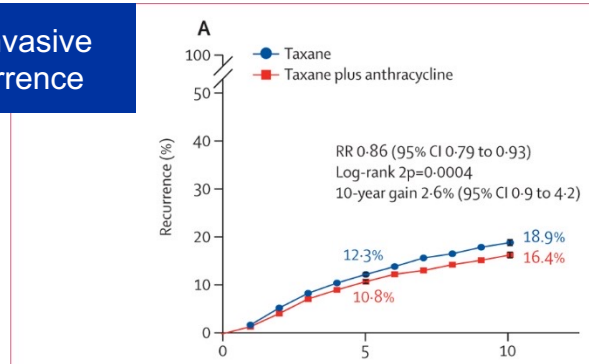
1. Widely available, affordable, & effective drugs against breast cancer on a global level
2. HER2 Negative: Trials designed to demonstrate noninferiority of non-anthracycline regimens have failed in HER2 negative
3. HER2 Positive: No trials designed or statistically powered to show non-inferiority of non-anthracycline regimens
3. Reduce breast cancer recurrence and death
4. Improved management and monitoring of cardiotoxicity

EBCTCG [EARLY BREAST CANCER TRIALISTS' COLLABORATIVE GROUP] META-ANALYSIS

Cardiotoxicity	Leukemia
-Non-breast cancer deaths not increased including CV causes between anthracycline vs non-anthracycline *Pts with elevated cardio risk often excluded and median f/u ~5 yrs	-Trials with data: 12/6768 (0.18%) AML after anthracycline vs 2/6783 (0.03%) who did not receive anthracycline (p=0·013) -Equating to ~1 additional case AML per 700 women treated

10 year cumulative risk of outcomes with Taxane plus Anthracycline vs Taxane without Anthracycline

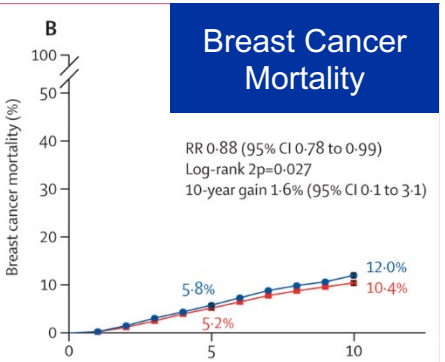
Any Invasive Recurrence



Recurrence rates per year (% [events per woman-years]) and log-rank analyses

Allocation	Years 0–4	Years 5–9	Years ≥10
Taxane plus anthracycline	2·34% (900/38 514)	1·37% (158/11 575)	0·95% (4/420)
Taxane	2·63% (1008/38 389)	1·65% (188/11 388)	0·76% (3/396)
RR (95% CI)	0·87 (0·79–0·95)	0·80 (0·64–0·99)	1·83 (0·36–9·22)
(O–E) / V	−63·8/443·9	−19·1/83·3	0·9 / 1·5

Breast Cancer Mortality



Death rates per year (% [95% CI]: total rate–rate in participants without recurrence) and log-rank analyses

Allocation	Years 0–4	Years 5–9	Years ≥10
Taxane plus anthracycline	1·05% (0·95–1·15)	1·24% (1·04–1·44)	1·10% (0·14–2·06)
Taxane	1·15% (1·04–1·25)	1·42% (1·21–1·63)	1·38% (0·28–2·48)
RR (95% CI)	0·89 (0·78–1·02)	0·85 (0·68–1·06)	0·88 (0·26–2·92)
(O–E) / V	−24·4/208·8	−13·0/79·0	−0·4/2·7

Demographics [N=18,103]	
Median Age	53 yrs (IQR 46-60)
LN involvement	9,731 (53%)
ER+	12,244 (67%)
HER2+	2,577 (14%)

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Anthracycline-containing and taxane-containing chemotherapy for early-stage operable breast cancer: a patient-level meta-analysis of 100 000 women from 86 randomised trials. Lancet. 2023 Apr 15;401(10384):1277-1292. doi: 10.1016/S0140-6736(23)00285-4. PMID: 37061269; PMCID: PMC11023015.

HER2 NEGATIVE:
ABC [ANTHRACYCLINES IN EARLY BREAST CANCER] TRIALS

- 3 sequential adjuvant trials
  - LN+ or high risk LN-; HER2-
  - Randomized to TC6 or TaxAC (docetaxel or paclitaxel)
- AIM: TC x 6 cycles noninferior to TaxAC
  - HR for IDFS >1.18 for TC6 vs TaxAC defined as prespecified margin of inferiority for TCx6
- N=4181

TABLE 1. Patient and Tumor Characteristics by Parent ABC Protocol Data as of September 30, 2020

Patient or Tumor Characteristic	USOR 06-090 (n = 1,287)	B-46-I/07132 (n = 1,051)	B-49 (n = 1,843)	Total (N = 4,181)	P[a]
Follow-up, years, median	9.4	6.5	6.7	6.9	NA
Age, years, %					
≤49	37	38	32	35	
50-59	38	35	35	36	<.0001
≥60	26	27	34	30	
Race, %					
White	88	83	84	85	
Black or African American	10	12	11	11	
Asian	2	2	2	2	<.0001
Other/unknown	1	3	3	2	
Ethnicity, %					
Hispanic or Latino	11	11	8	10	
Not Hispanic or Latino	89	85	90	88	<.0001
Unknown	0	4	2	2	
Hormonal receptor status, %					
ER- or PgR-positive	71	67	69	69	
ER- and PgR-negative	29	33	31	31	.15
No. of positive nodes, %					
0	35	38	46	40	
1-3	51	43	40	44	
4-9	11	14	11	11	<.0001
≥10	3	5	4	4	
Histologic grade, %					
Low	12	10	9	10	
Intermediate	38	37	36	37	
High	45	52	55	51	<.0001
Unknown	5	1	<0.5	2	

Charles E. Geyer et al. Long-Term Follow-Up of the Anthracyclines in Early Breast Cancer Trials (USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49 [NRG Oncology]). *JCO* **42**, 1344-1349(2024).DOI:10.1200/JCO.23.01428

- **2017:** Median f/u 3.3 yrs demonstrated HR 1.23 – TCx6 inferior to TaxAC b/c >1.18
- **April 2024:** Median f/u 6.9 yrs; 4243 enrolled and 4181 analyzed

Cardiotoxicity	Leukemia
-TaxAC vs TC6 increased non-breast cancer deaths (62 vs 34; p=0.003) -Deaths numerically higher for cardiac (8 vs 3; p=0.13) in TaxAC	-TaxAC vs TC6 increased leukemias (7 vs 1; p=0.03);

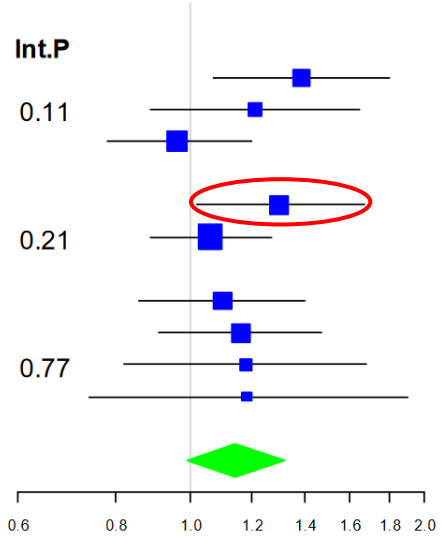
Confidence interval includes the upper boundary of the prespecified inferiority threshold of 1.18

Noninferiority of TC6 not demonstrated in ITT population

Additional 332 events in this analysis

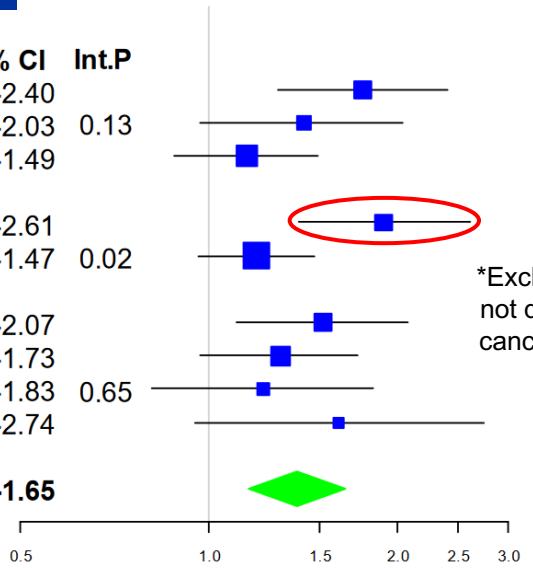
IDFS

Protocol	Evnts (TaxAC)	Evnts (TC)	HR	95% CI	Int.P
USOR06090	97	140	1.39	1.07-1.80	
B-46/07132	75	88	1.21	0.89-1.65	0.11
B-49	170	161	0.96	0.78-1.20	
Hormone					
Neg	114	139	1.30	1.02-1.67	
Pos	228	250	1.06	0.89-1.27	0.21
Nodes+					
0	120	141	1.10	0.86-1.40	
1-3	130	145	1.16	0.91-1.47	
4-9	57	67	1.18	0.82-1.68	0.77
10+	35	36	1.18	0.74-1.90	
Overall	**342**	**389**	**1.14**	**0.99-1.32**	



RFI

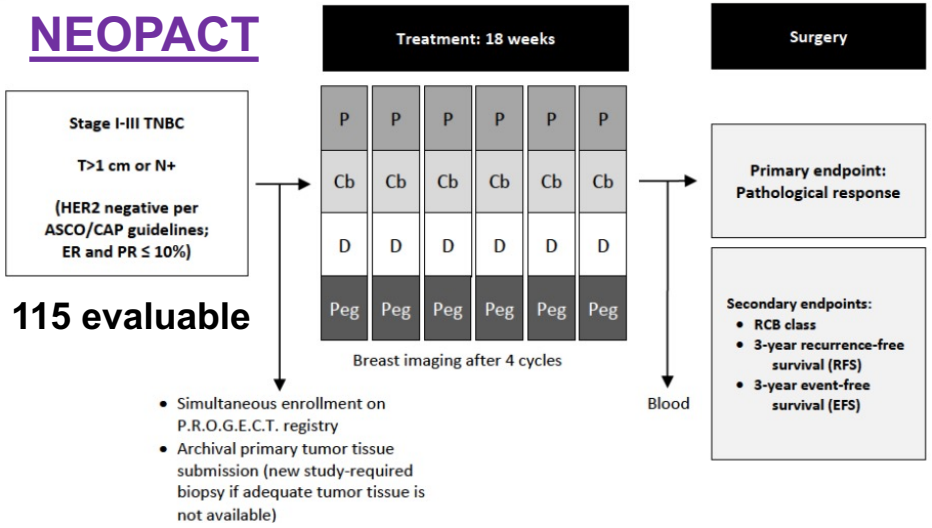
Protocol	Evnts (TaxAC)	Evnts (TC)	HR	95% CI	Int.P
USOR06090	61	111	1.76	1.29-2.40	
B-46/07132	50	68	1.40	0.97-2.03	0.13
B-49	105	116	1.15	0.88-1.49	
Hormone					
Neg	62	107	1.90	1.39-2.61	
Pos	154	188	1.19	0.96-1.47	0.02
Nodes+					
0	64	104	1.52	1.11-2.07	
1-3	84	105	1.30	0.97-1.73	
4-9	43	53	1.22	0.81-1.83	0.65
10+	25	33	1.61	0.95-2.74	
Overall	**216**	**295**	**1.38**	**1.16-1.65**	



*Excluded deaths not due to breast cancer as events

HER2 NEGATIVE:

NEOPACT



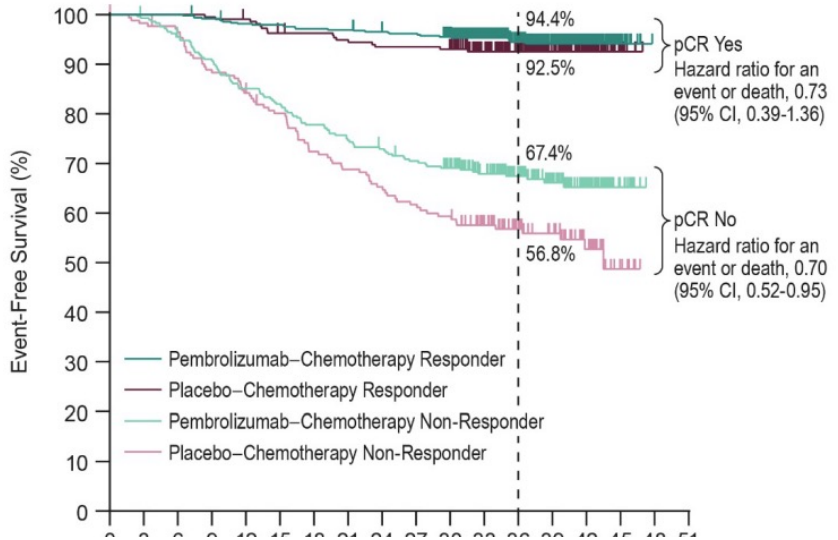
115 evaluable

14% Stage I
Sensitivity analysis after excluding Stage I - pCR 56%

81% with residual disease received adjuvant chemo; majority anthracycline-based regimens

KEYNOTE-522

Overall:
pCR 64.8% (95% CI 59.9-69.5%)
EFS 84.5%



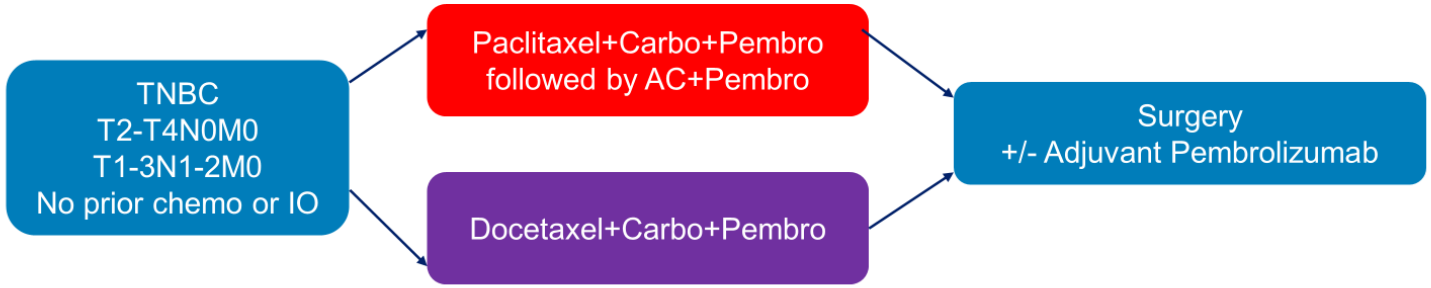
SCARLET [ONGOING]

Shorter Chemo-Immunotherapy Without Anthracycline Drugs for Early-Stage Triple Negative Breast Cancer

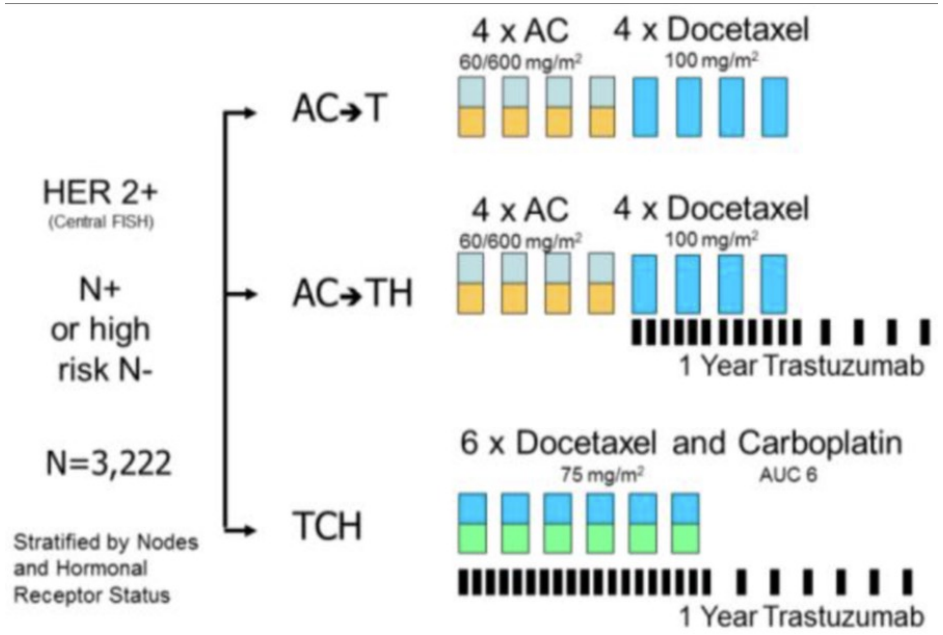
ClinicalTrials.gov ID NCT05929768
Sponsor SWOG Cancer Research Network
Information provided by SWOG Cancer Research Network (Responsible Party)
Last Update Posted 2023-10-25

Planned Enrollment: 2400

Primary Endpoint: Breast Cancer EFS
Secondary Endpoint: pCR, OS, etc.



HER2 POSITIVE:
BCIRG006 [BREAST CANCER INTERNATIONAL RESEARCH GROUP 006]



	AC-T (n=1073)	AC-TH (n=1074)	TCH (n=1075)
10 yr DFS	67.9%	74.6% HR 0.72 (0.61-0.85; p<0.001)	73% HR 0.77 (0.65-0.90; p-0.0011)
10 yr OS	78.7%	85.9% HR 0.63 (0.51-0.79; p<0.0001)	83.3% HR 0.76 (0.62-0.93; p=0.0075)
10 yr DFS in N+	62.2%	69.6% HR 0.72 (0.61-0.87; p<0.001)	68.4% HR 0.75 (0.63-0.90; p=0.0018)

- AC-TH vs TCH: 1-2% difference in 10 yr DFS and 2-3% difference in 10 yr OS
- Suggests minimal benefit of anthracyclines
- TRIAL NOT POWERED for a formal comparison

Table 1: BCIRG-006: Therapeutic Index, Final Analysis at 10 Years

	AC-TH	TCH
Disease-free survival events	269	279
Grade 3/4 congestive heart failure	21 (2%)	4 (0.4%)
Total disease-free survival events	290	283
Treatment-related leukemia	7	0
Sustained LVEF loss > 10%	200	97

AC-TH = doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab; TCH = docetaxel, carboplatin, and trastuzumab; LVEF = left ventricular ejection fraction.

Ishikawa, Takashi et al. "The role of HER-2 in Breast Cancer." Journal of surgery and science 2 1 (2014): 4-9.

Slamon DJ, Eiermann W, Robert NJ, et al. 2015 San Antonio Breast Cancer Symposium. Abstract S5-04. Presented December 11, 2015.

HER2 POSITIVE

- Adjuvant trials: APHINITY and KATHERINE
  - ~77% of patients in both trials received anthracycline-based chemotherapy
  - Similar benefit if anthracyclines were omitted?
- TRAIN-2 and TRYPHAENA
  - Investigate whether omission of anthracycline from neoadjuvant dual HER2 blockade could provide a more favorable risk/benefit ratio
  - Does not impact likelihood of pCR
  - Not statistically powered to establish non-inferiority of omitting anthracycline

Trial	Cardiotoxicity	Leukemia
APHINITY	-CHF or significant LVEF decline: Highest in Anthracycline+HP (0.8%) compared to other groups (0.2-0.4%) -Cardiac death: Only occurred in Anthracycline group [Anthracycline+HP 2 (0.1%) vs Anthracycline+H 2 (0.1%)]	-Not reported
KATHERINE	-No separation anthracycline vs non-anthracycline -Cardiac events (death or CHF): Trastuzumab 4 (0.6%) vs T-DM1 1 (0.1%)	-Not reported
TRAIN-2	-LVEF decline ≥10% from baseline and LVEF <50% reported more in anthracycline (17 of 220 [7.7%]) vs non-anthracycline group (7 of 218 [3.2%]; *P* = .04)	-2 pts anthracyclines vs 0 pts non-anthracycline
TRYPHAENA	-Neoadjuvant HP given concurrently or sequentially with anthracycline-based or concurrent with carboplatin-based result in low incidence of overall LVSD	-Not reported

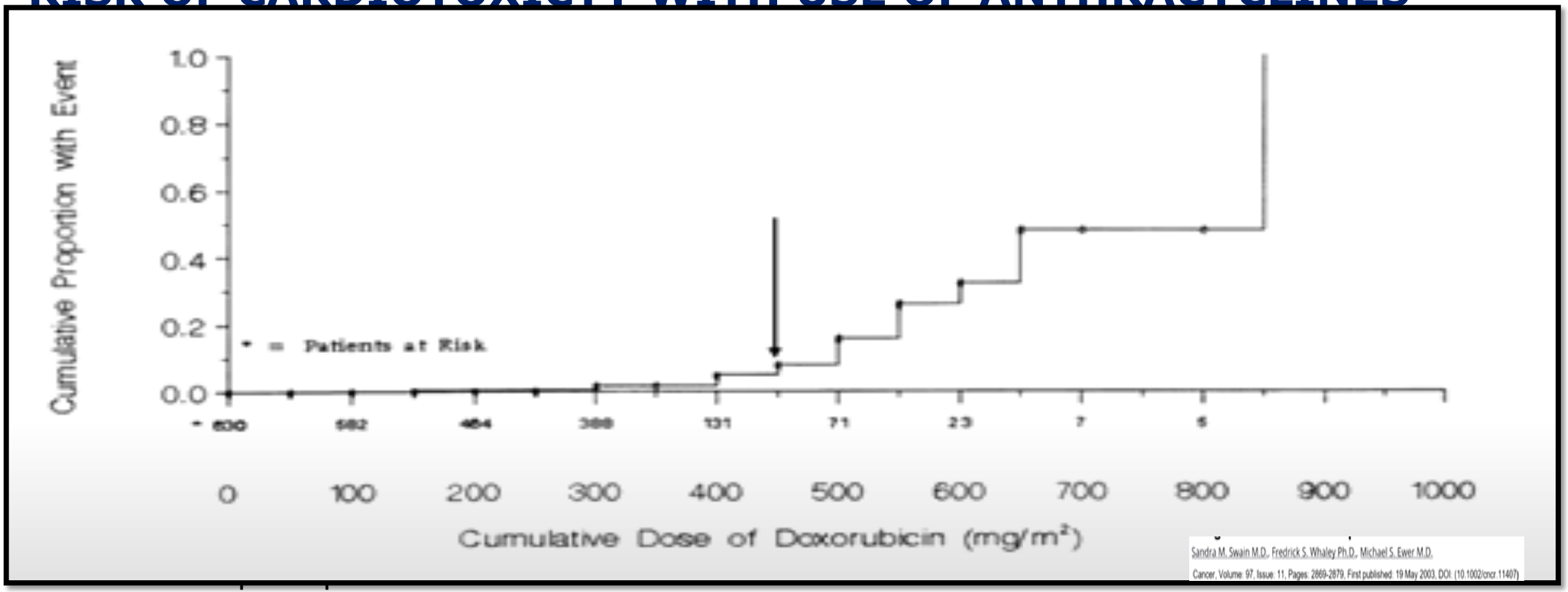
von Minckwitz G, et al. N Engl J Med. 2017. PMID: 28581356
von Minckwitz G, et al.. *N Engl J Med*. 2019;380(7):617-628. doi:10.1056/NEJMoa1814017
Schneeweiss A, et al. *Ann Oncol*. 2013;24(9):2278-2284. doi:10.1093/annonc/mdt182

van der Voort A, et al. Three-Year Follow-up of Neoadjuvant Chemotherapy With or Without Anthracyclines in the Presence of Dual ERBB2 Blockade in Patients With ERBB2-Positive Breast Cancer: A Secondary Analysis of the TRAIN-2 Randomized, Phase 3 Trial. JAMA Oncol. 2021 Jul 1;7(7):978-984. doi: 10.1001/jamaoncol.2021.1371. PMID: 34014249; PMCID: PMC8138752.

CONS OF USING ANTHRACYCLINES IN EARLY STAGE BREAST CANCER

- RISK OF CARDIOTOXICITY
- RISK OF SECONDARY CANCER /LEUKEMIA
- HIGH RISK OF TOXICITY (PATIENT NICKNAME “RED DEVIL”) WITH SMALL CLINICAL BENEFIT IN CERTAIN POPULATIONS
  - INFERTILITY
  - COGNITIVE DYSFUNCTION
  - FATIGUE
  - DO NOT LEAD TO CURE IN ALL BREAST CANCERS

RISK OF CARDIOTOXICTY WITH USE OF ANTHRACYCLINES



- **Cardiac Toxicity Occurs During Exposure and Evolves Over Time**
  - Dose dependent and can be irreversible
  - Most patients present 2-4 years after anthracycline exposure. Rarely patients can develop symptoms acutely within weeks to months of exposure

Risk of Cardiovascular Disease in Women With and Without Breast Cancer: The Pathways Heart Study

Heather Greenlee, ND, PhD[1,2,3]; Carlos Iribarren, MD, MPH, PhD[4]; Jamal S. Rana, MD, PhD[4,5]; Richard Cheng, MD, MSc[2,3]; Mai Nguyen-Huynh, MD, MAS[4,6]; Eileen Rillamas-Sun, PhD[1]; Zaixing Shi, PhD[1,7]; Cecile A. Laurent, MS[4]; Valerie S. Lee, MHS[4]; Janise M. Roh, MSW, MPH[4]; Margarita Santiago-Torres, PhD[1]; Hanjie Shen, MS[1]; Dawn L. Hershman, MD, MS[8]; Lawrence H. Kushi, ScD[4]; Romain Neugebauer, PhD[4]; and Marilyn L. Kwan, PhD[4]

- **POPULATION** : A total of 13,642 women with Breast Cancer were matched to 68,202 controls without Breast Cancer

- **RESULTS:**

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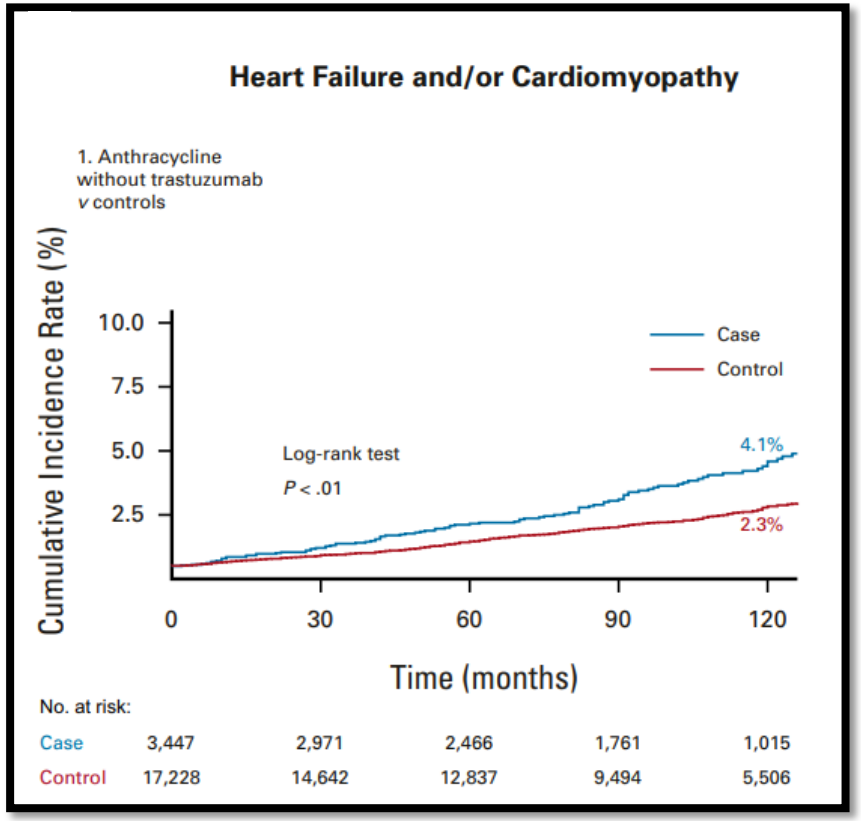

Adjusted HR for Heart Failure : 1.84 (1.21 to 2.80)

Adjusted HR for Cardiac Related Death: 2.91 (1.96 to 4.33)

Risk of Cardiovascular Disease in Women With and Without Breast Cancer: The Pathways Heart Study

Heather Greenlee, ND, PhD[1,2,3]; Carlos Iribarren, MD, MPH, PhD[4]; Jamal S. Rana, MD, PhD[4,5]; Richard Cheng, MD, MSc[2,3]; Mai Nguyen-Huynh, MD, MAS[4,6]; Eileen Rillamas-Sun, PhD[1]; Zaixing Shi, PhD[1,7]; Cecile A. Laurent, MS[4]; Valerie S. Lee, MHS[4]; Janise M. Roh, MSW, MPH[4]; Margarita Santiago-Torres, PhD[1]; Hanjie Shen, MS[1]; Dawn L. Hershman, MD, MS[8]; Lawrence H. Kushi, ScD[4]; Romain Neugebauer, PhD[4]; and Marilyn L. Kwan, PhD[4]

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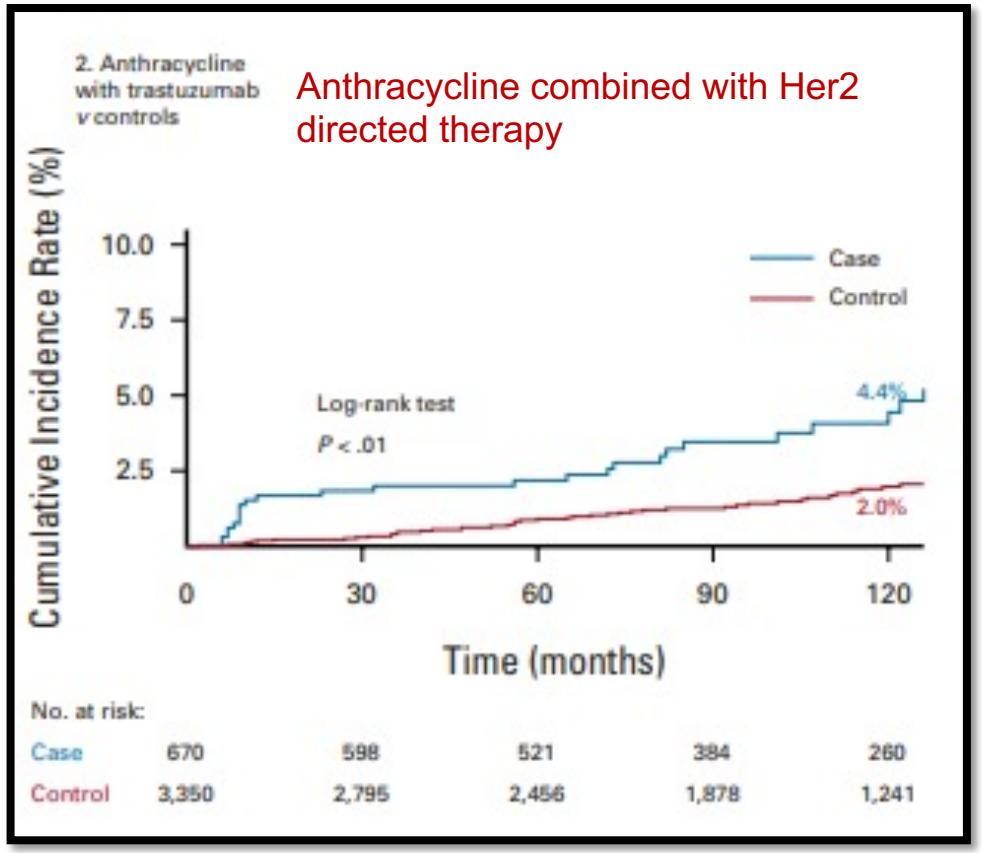
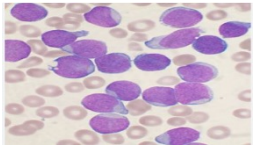
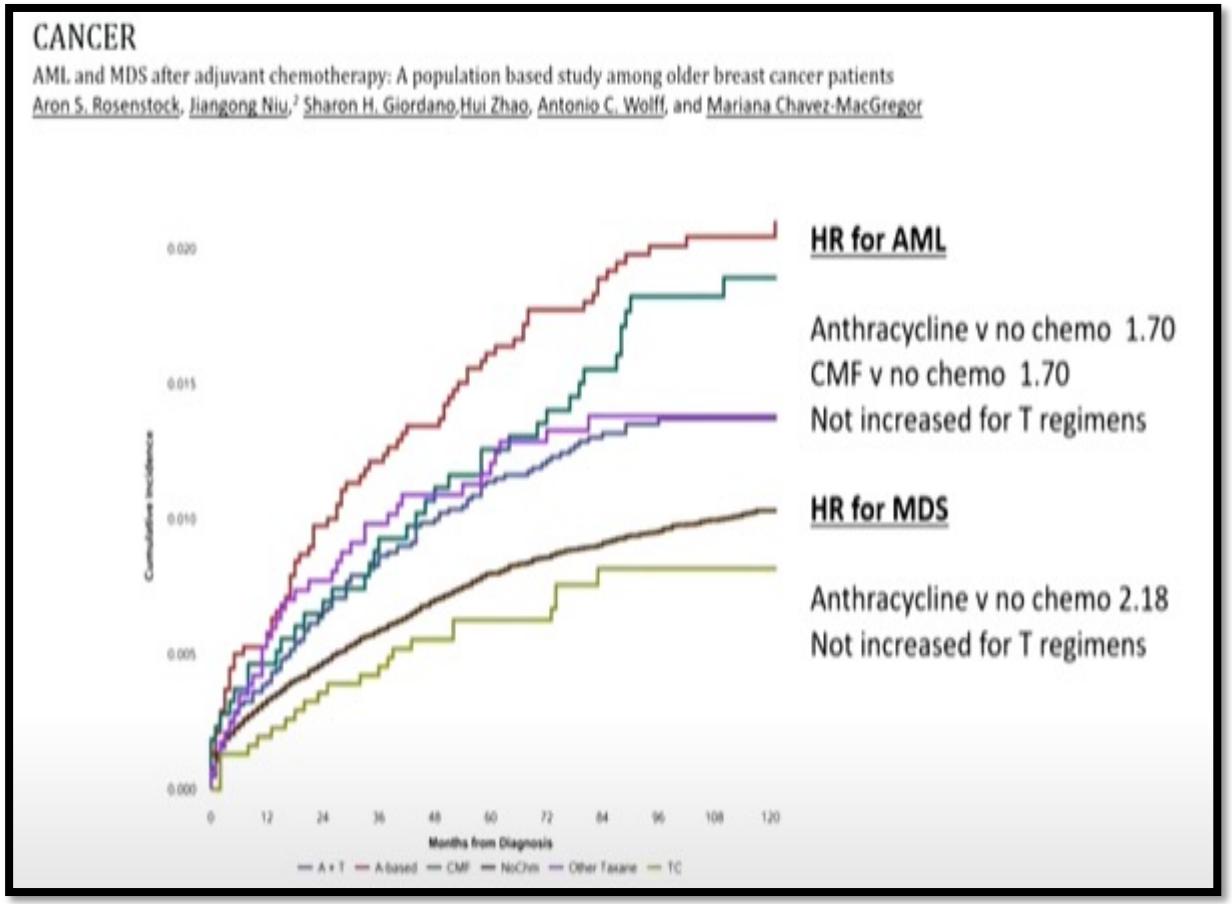


Adjusted HR: 3.68 (1.79 to 7.59)



RISK OF LEUKEMIA WITH USE OF ANTHRACYCLINES

- Dose dependent
- Increase risk when combined with alkylating agents (ie cyclophosphamide)
- Most commonly associated with Acute Myeloid Leukemia and Myelodysplastic Syndrome and tend to be more aggressive in nature then leukemias not associated with exposure to anthracycline
- Often occur 5-10 years after exposure to drug

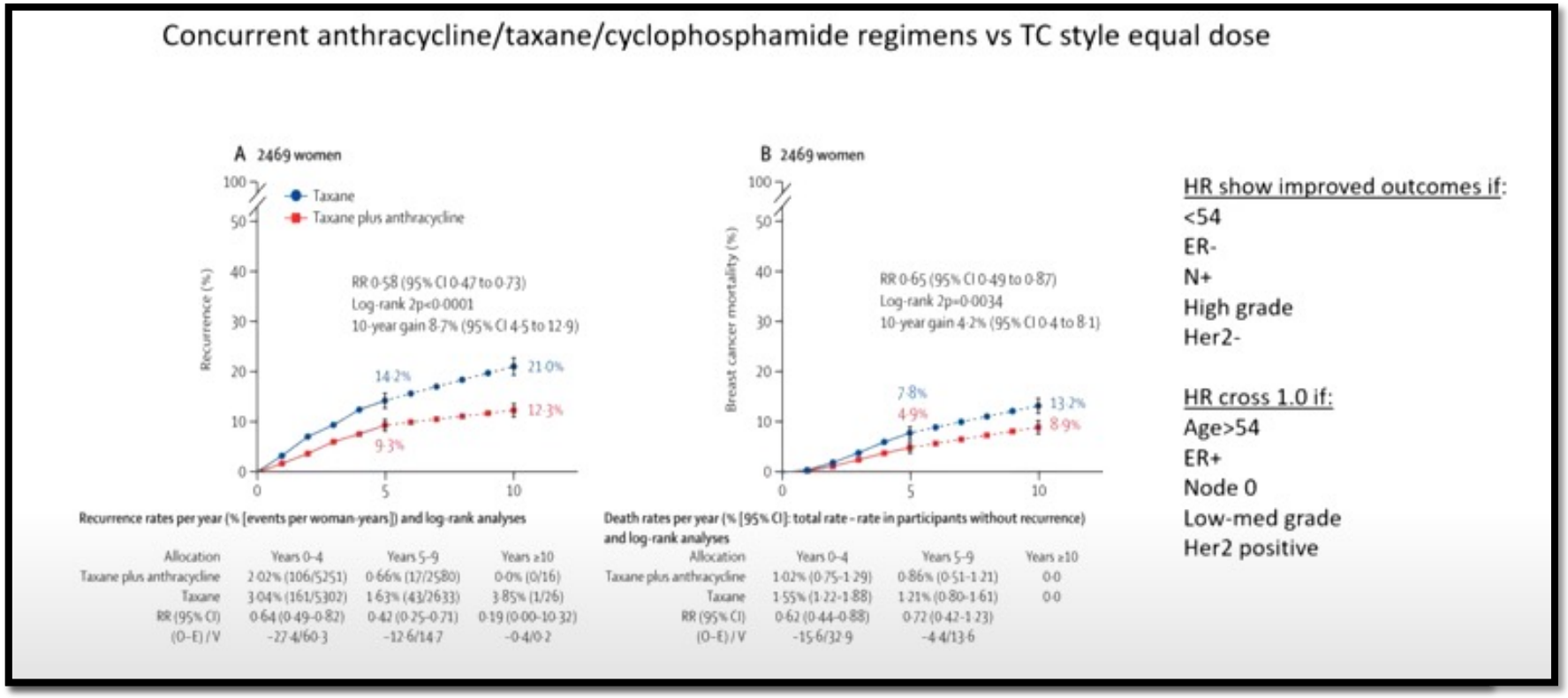


DOES THE BENEFIT OUTWEIGH THE RISK

Anthracycline-containing and taxane-containing chemotherapy for early-stage operable breast cancer: a patient-level meta-analysis of 100 000 women from 86 randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

Concurrent anthracycline/taxane/cyclophosphamide regimens vs TC style equal dose



Recurrence rates per year (% [events per woman-years]) and log-rank analyses

Allocation	Years 0–4	Years 5–9	Years ≥10
Taxane plus anthracycline	2·02% (106/5251)	0·66% (17/2580)	0·0% (0/16)
Taxane	3·04% (161/5302)	1·63% (43/2633)	3·85% (1/26)
RR (95% CI)	0·64 (0·49–0·82)	0·42 (0·25–0·71)	0·19 (0·00–10·32)
(O–E) / V	−27·4/60·3	−12·6/14·7	−0·4/0·2

Death rates per year (% [95% CI]: total rate - rate in participants without recurrence) and log-rank analyses

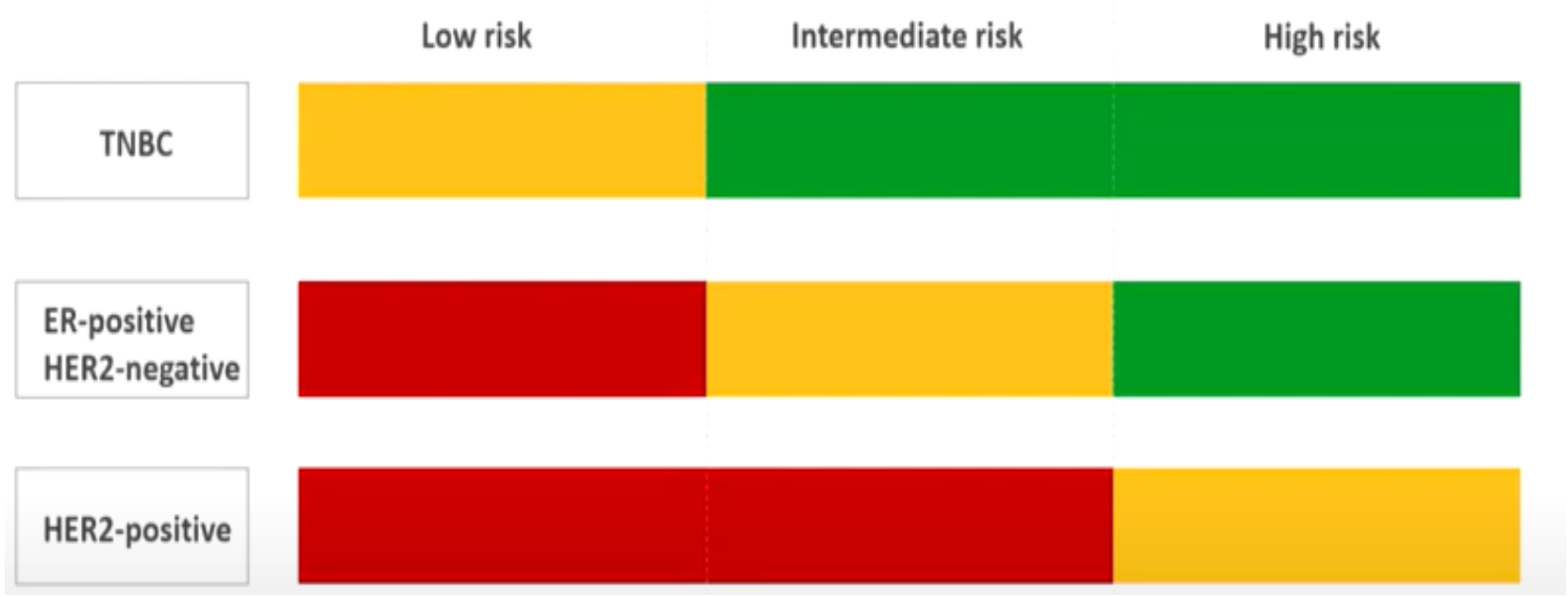
Allocation	Years 0–4	Years 5–9	Years ≥10
Taxane plus anthracycline	1·02% (0·75–1·29)	0·86% (0·51–1·21)	0·0
Taxane	1·55% (1·22–1·88)	1·21% (0·80–1·61)	0·0
RR (95% CI)	0·62 (0·44–0·88)	0·72 (0·42–1·23)	
(O–E) / V	−15·6/32·9	−4·4/13·6	

HR show improved outcomes if:
- <54
- ER-
- N+
- High grade
- Her2-

HR cross 1.0 if:
- Age>54
- ER+
- Node 0
- Low-med grade
- Her2 positive

Lancet. 2023 Apr doi: 10.1016/S0140-6736(23)00285-4.

APPROACH TO USE OF ANTHRACYLINES

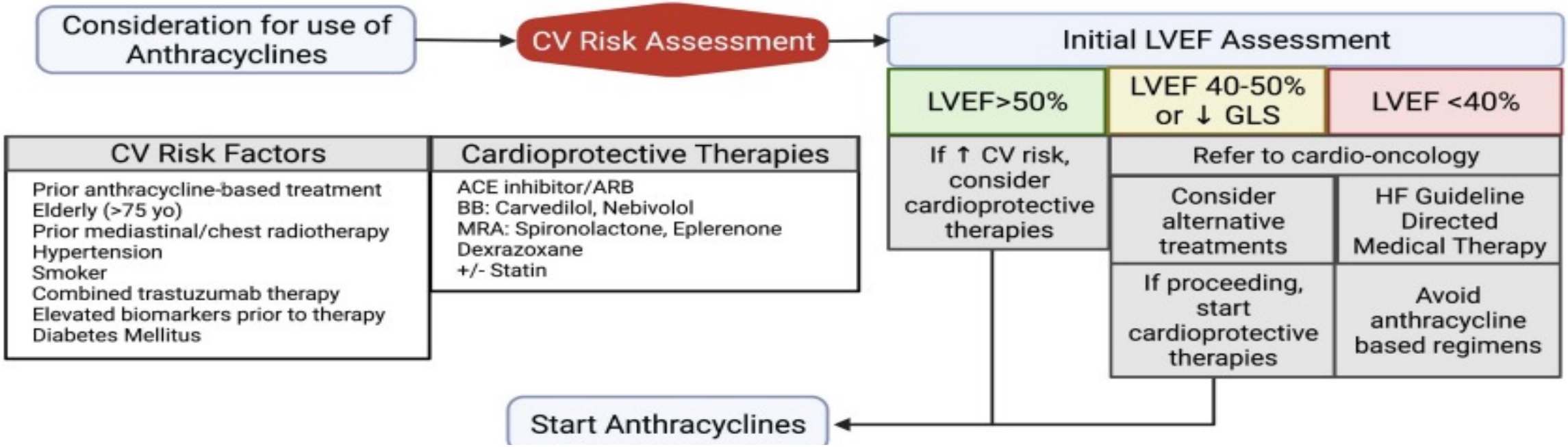


ANTHRACYCLINES

- Not recommended
- Consider
- Recommended

Figure 1: Presentation from Dr Martine Piccart SABCS 2023: Anthracyclines…to give or not to give? "For" argument.
Figure 2: Front. Cardiovasc. Med., 21 April 2022 Sec. Cardio-Oncology. Volume 9 - 2022 | https://doi.org/10.3389/fcvm.2022.863314

CARDIAC CONSIDERATIONS WITH ANTHRACYCLINE USE

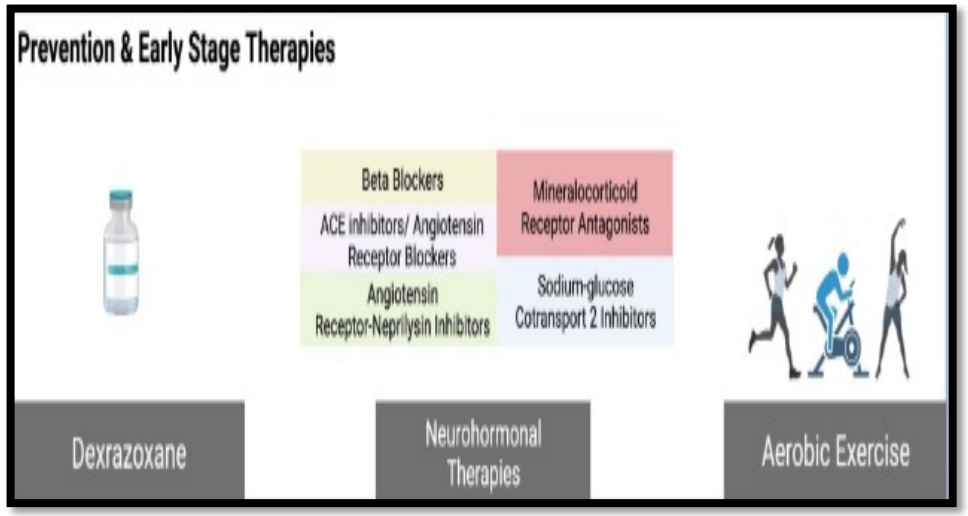


Minimize risk by focusing on patient selection, cardiac monitoring, and preventative measures

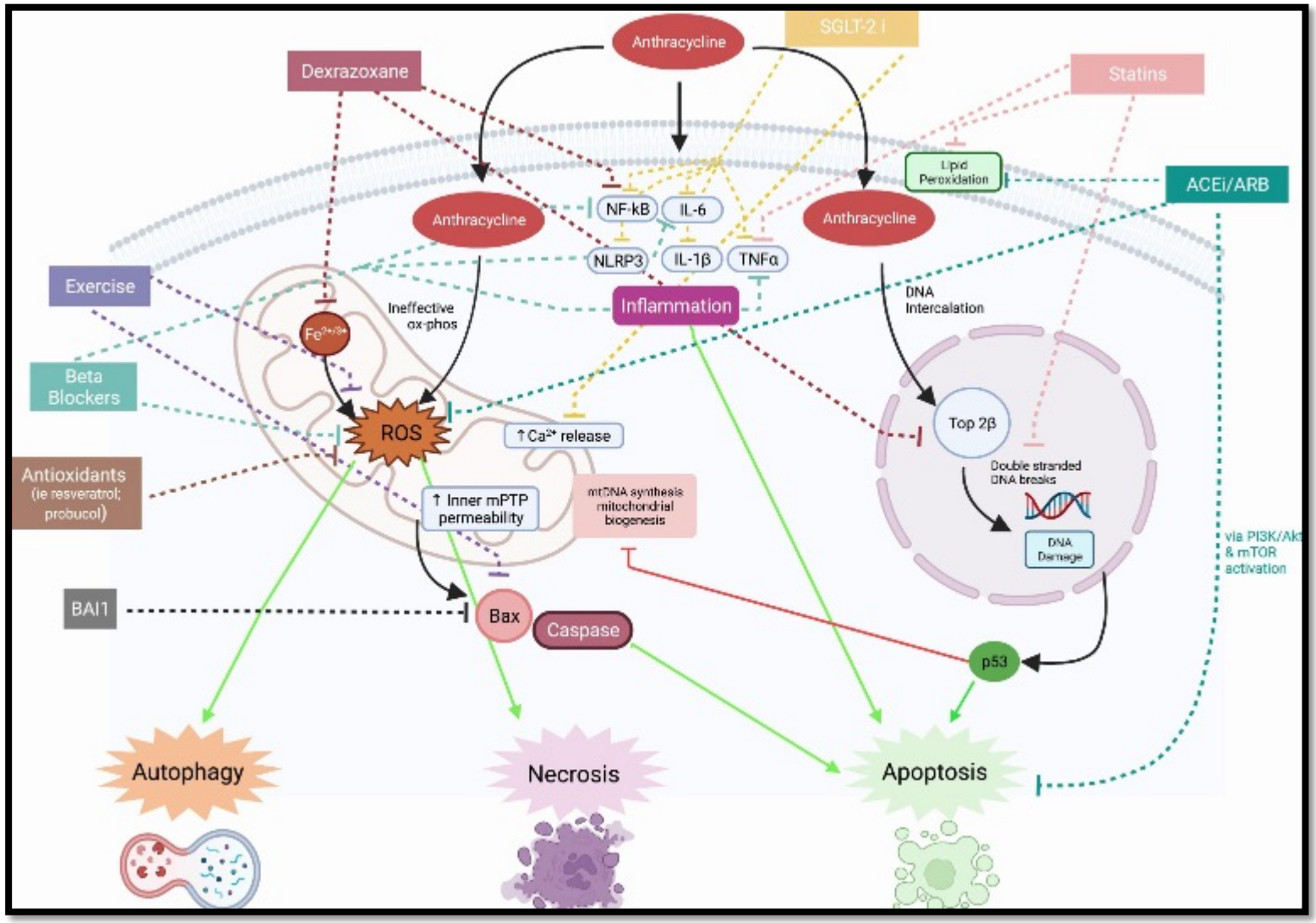
- ❑ Screen for cardiac risk factors (age >60, DM, HTN, HLD, Smoking, Obesity, etc.)
- ❑ Echocardiogram (LVEF, GLS, etc.)
- ❑ Collaborate with cardio-oncologists
- ❑ Consider cardioprotective agents: ACE inhibitors and/or Beta Blockers

Front. Cardiovasc. Med., 21 April 2022 Sec. Cardio-Oncology. Volume 9 - 2022 | https://doi.org/10.3389/fcvm.2022.863314

PREVENTION OF CARDIOTOXICTY FROM USE OF ANTHRACYCLINES



Frontiers Cardiovascular Med
Novel Therapeutics for Anthracycline Induced Cardiotoxicity
Jacqueline T. Vuong,Ashley F. Stein-Merlob, Richard K. Cheng, Eric H. Yang
Volume 9 - 2022 | https://doi.org/10.3389/fcvm.2022.863314

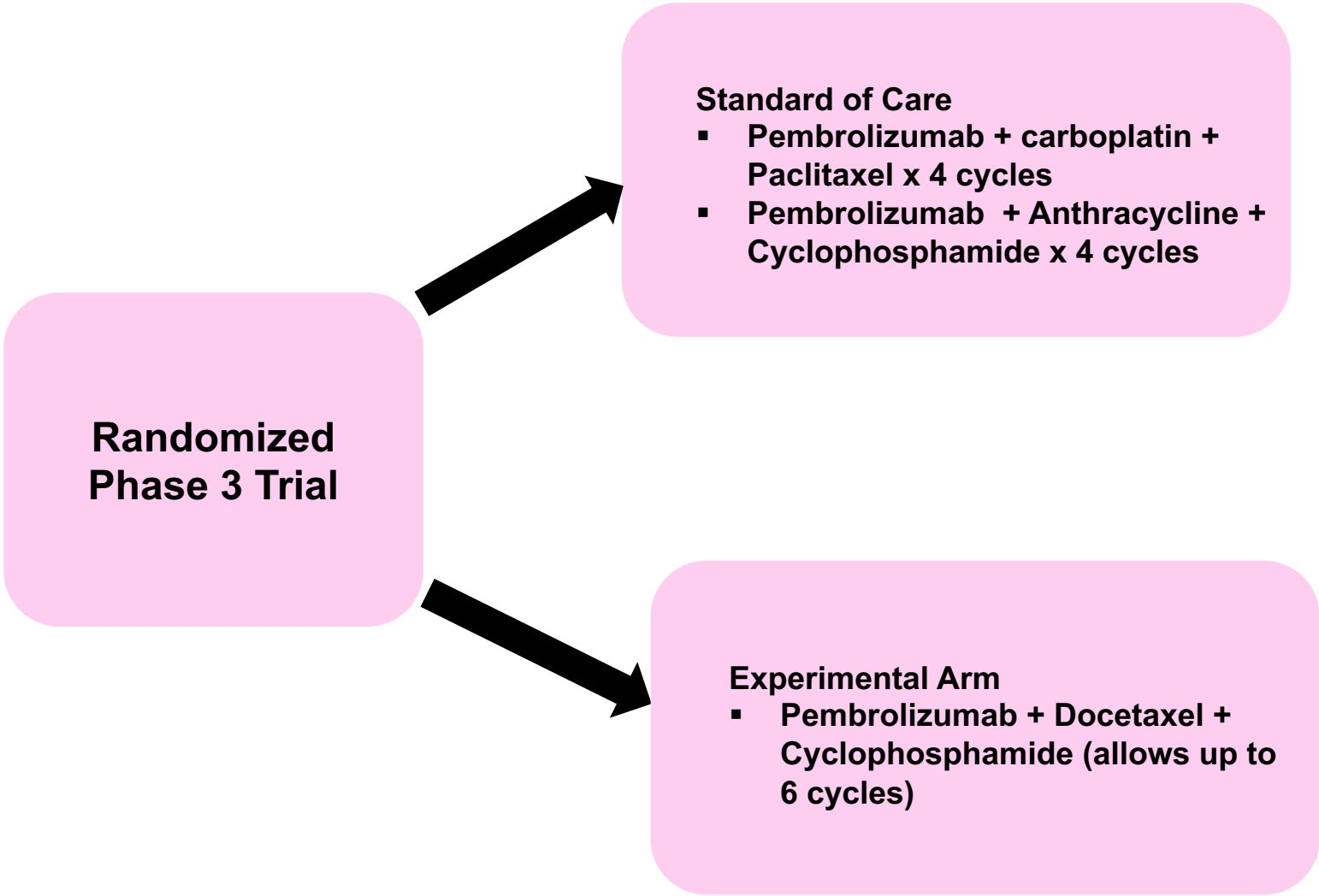


CAN ANTHRACYLINES BE ELIMINATED FROM USE IN EARLY STAGE BREAST CANCER IN THE FUTURE

- **Tailored Decision Making**
  - Factoring in response to therapy
  - Factoring unique targets
    - PARP inhibitors for BRCA gene driven cancers
  - Factoring tumor types
    - CDK 4/6 inhibitors for luminal cancers
    - Immunotherapy in triple negative breast cancers

- **Incorporation of Novel Drugs**
  - Novel ER blockers for luminal cancers
  - Vaccines
  - Antibody Drug Conjugates
    - Sacituzumab–govitecan (TROP2)
    - Datopotamab-Deruxtecan (TROP2)
    - Trastuzumab-Deruxtecan (HER2 low)

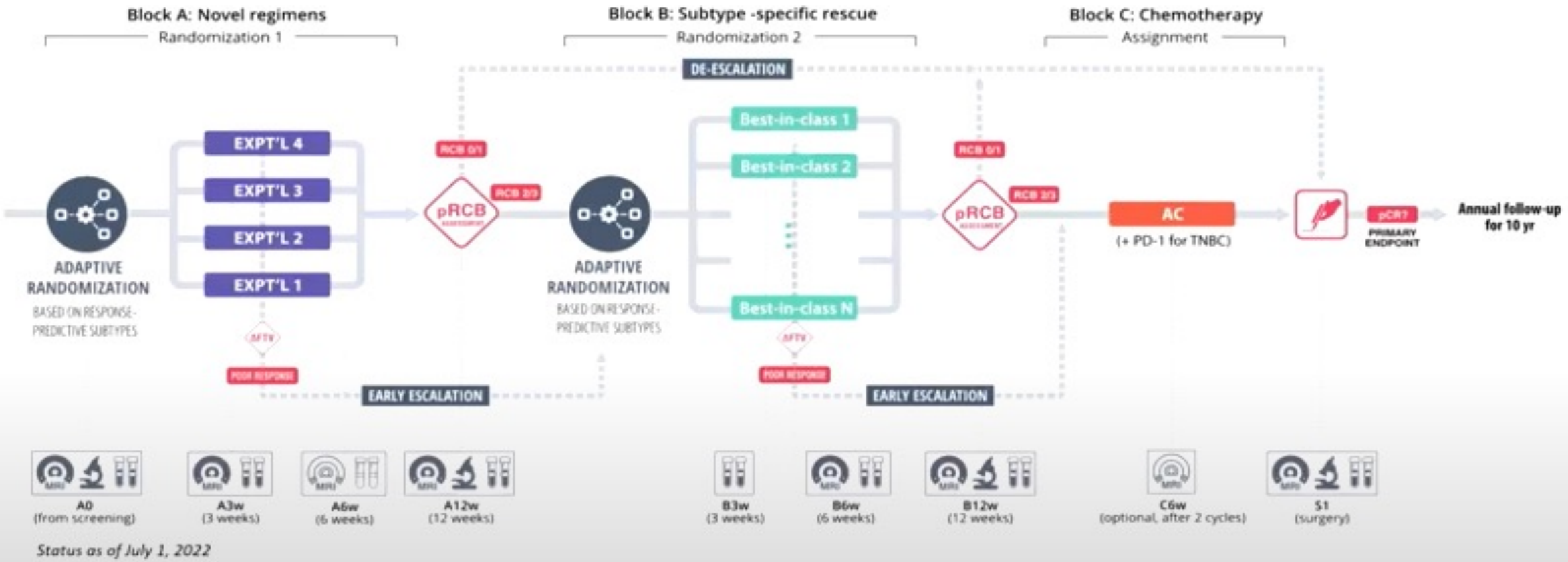
SWOG SCARLET TRIAL: TESTING SHORTER CHEMO-IMMUNOTHERAPY WITHOUT ANTHRACYCLINE DRUGS FOR EARLY-STAGE TRIPLE NEGATIVE BREAST CANCER



INCLUSION CRITERIA

- Triple negative breast cancer (also include patients with ER and/or PR 1-4%)
- T2-T4, N0, M0
- T1-T3, N1-2, M0

I SPY 2.2 Schema



Status as of July 1, 2022

QUESTIONS