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A Cancer Center Designated by the National Cancer Institute

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DDHO Debate:

Should Patients with Stage I Triple Negative Breast Cancer Receive Neoadjuvant Therapy?

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Pros vs Cons

Biology trumps stage

Prognostic

Micrometastatic control

Platform for drug development

Tailor adjuvant strategy

Survival

Operability

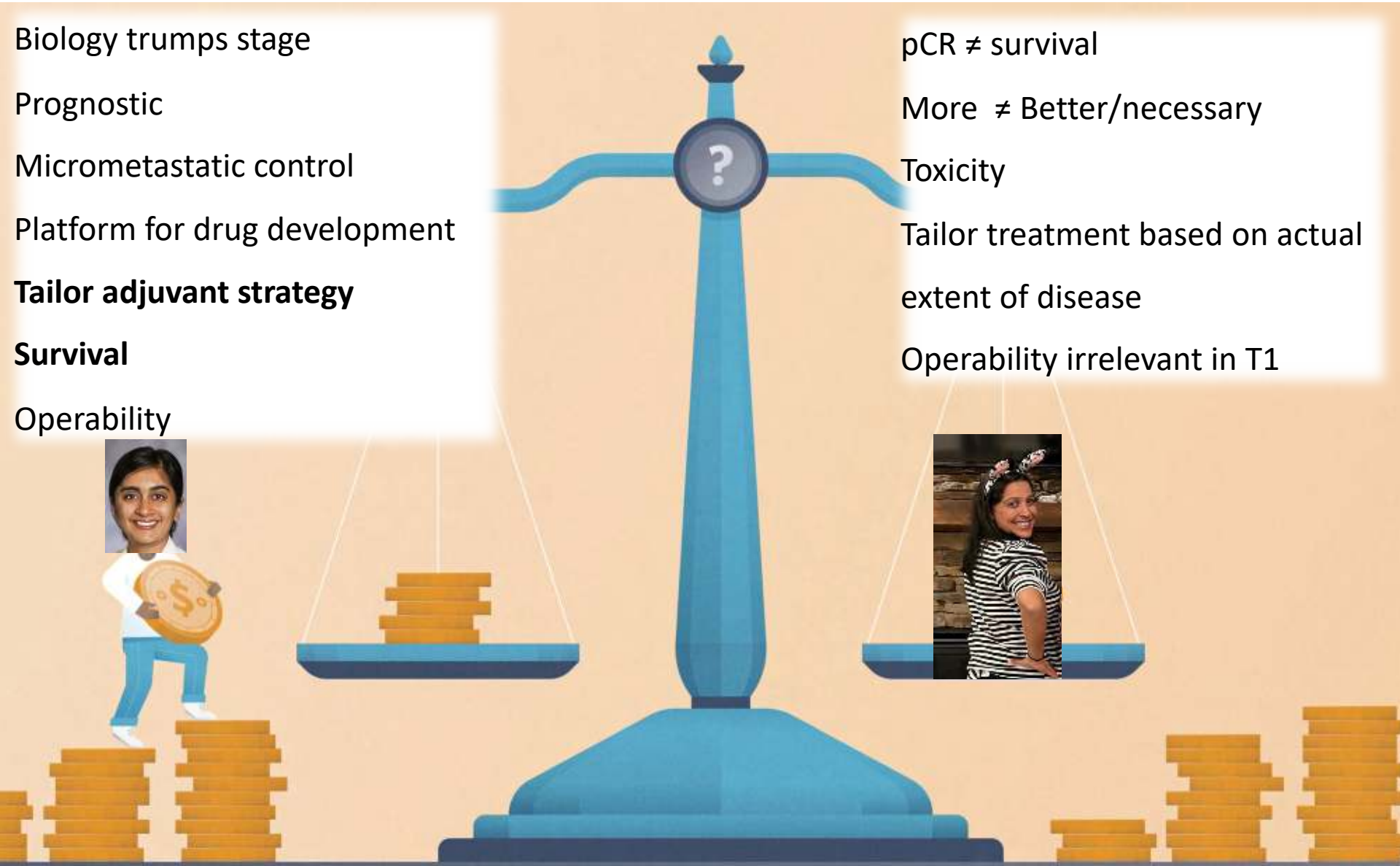
pCR ≠ survival

More ≠ Better/necessary

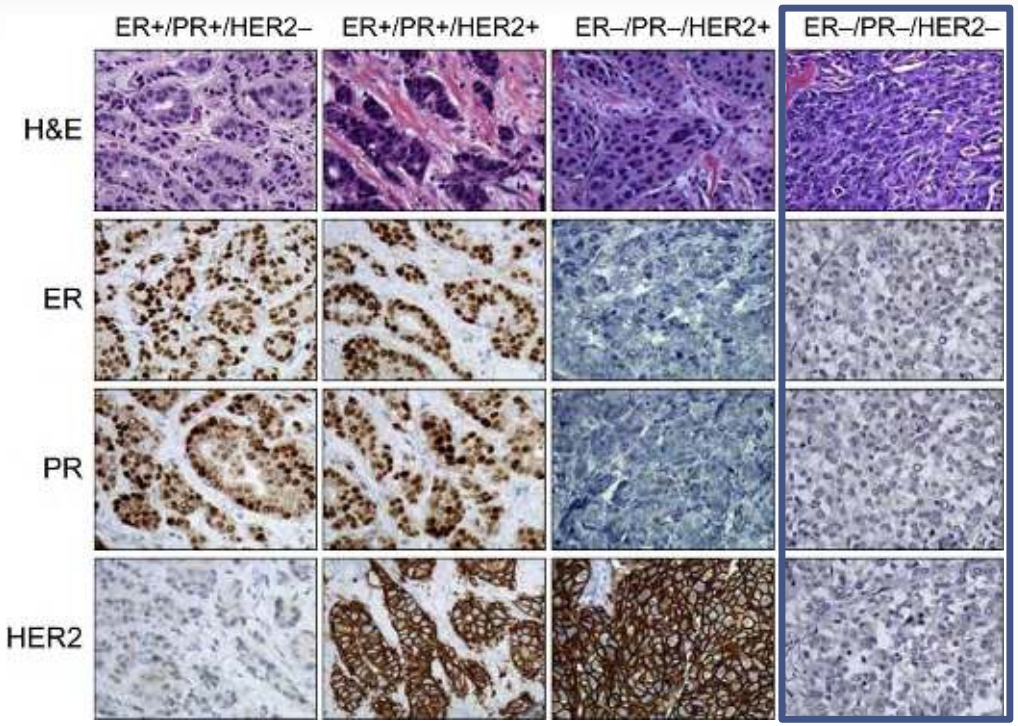
Toxicity

Tailor treatment based on actual extent of disease

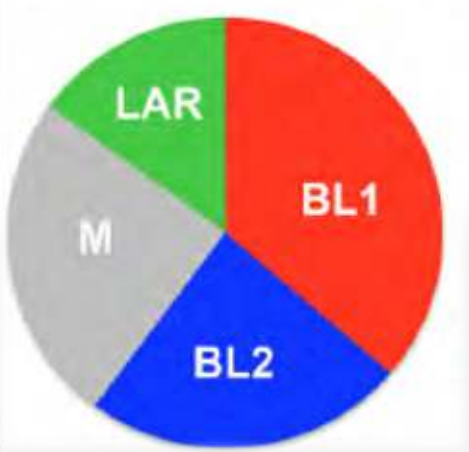
Operability irrelevant in T1



Triple Negative Breast Cancer



- Absence of ER, PR, Her2 IHC biomarkers
- 4 molecular subtypes
- Higher grade and more **advanced stage** at presentation
- 10-15%, but > common in women who are younger, Black, Latinx, or have a mutated BRCA1 gene



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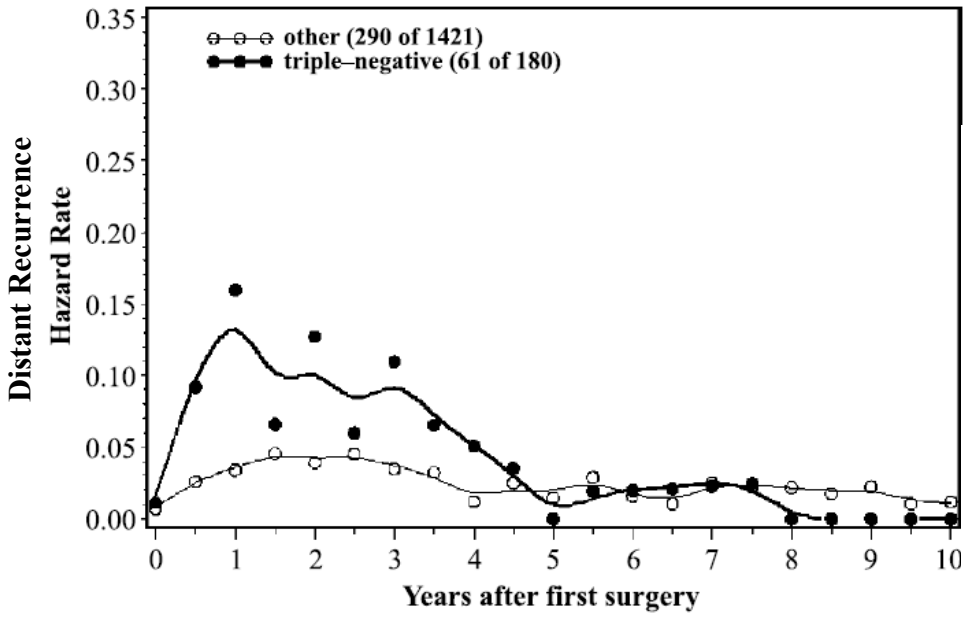
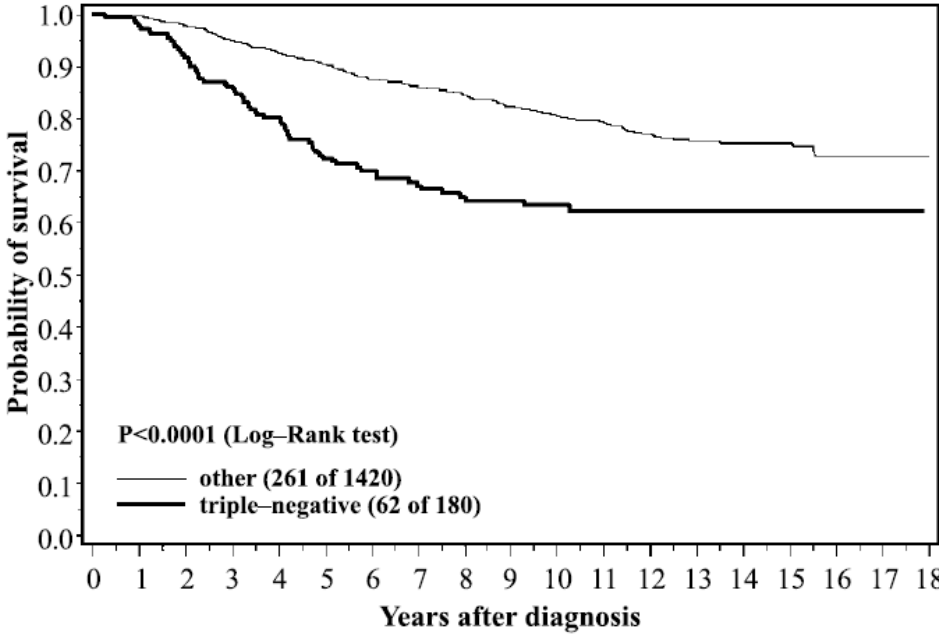
Rivenbark et al. Am J Pathol. 2013.
Lehmann et al. PloS ONE. 2016.

TNBC: Early Recurrence & Higher Mortality





Nearly a quarter will die within 5 years.

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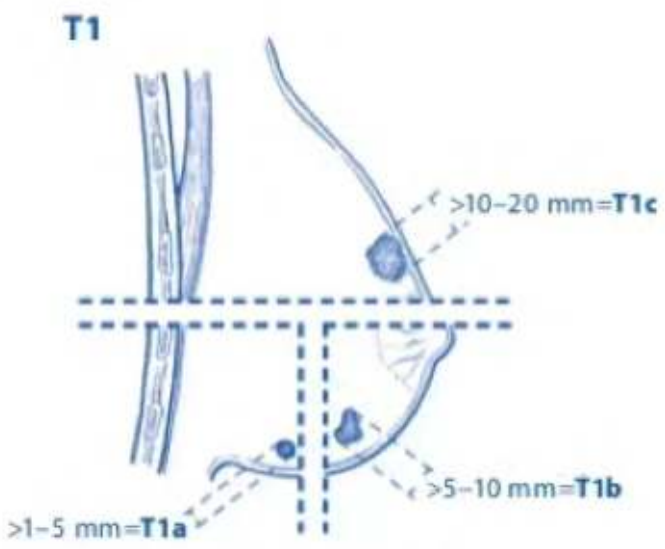
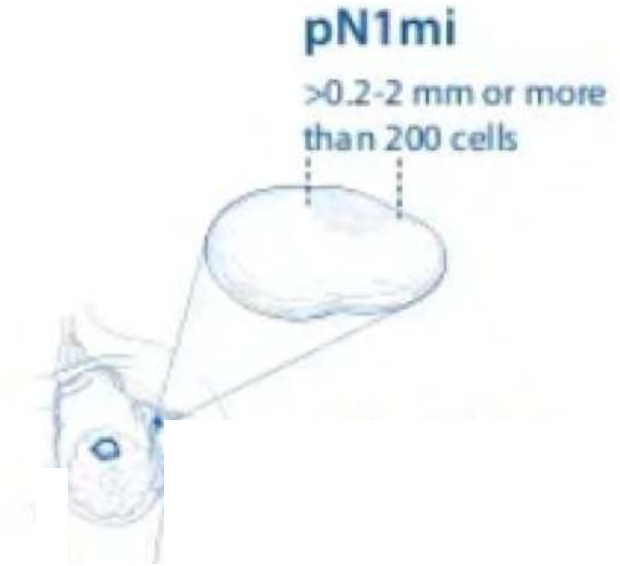
Dent et al. Clin Cancer Res. 2007.
Desantis et al. CA Cancer J Clin. 2019.

Stage I Breast Cancer





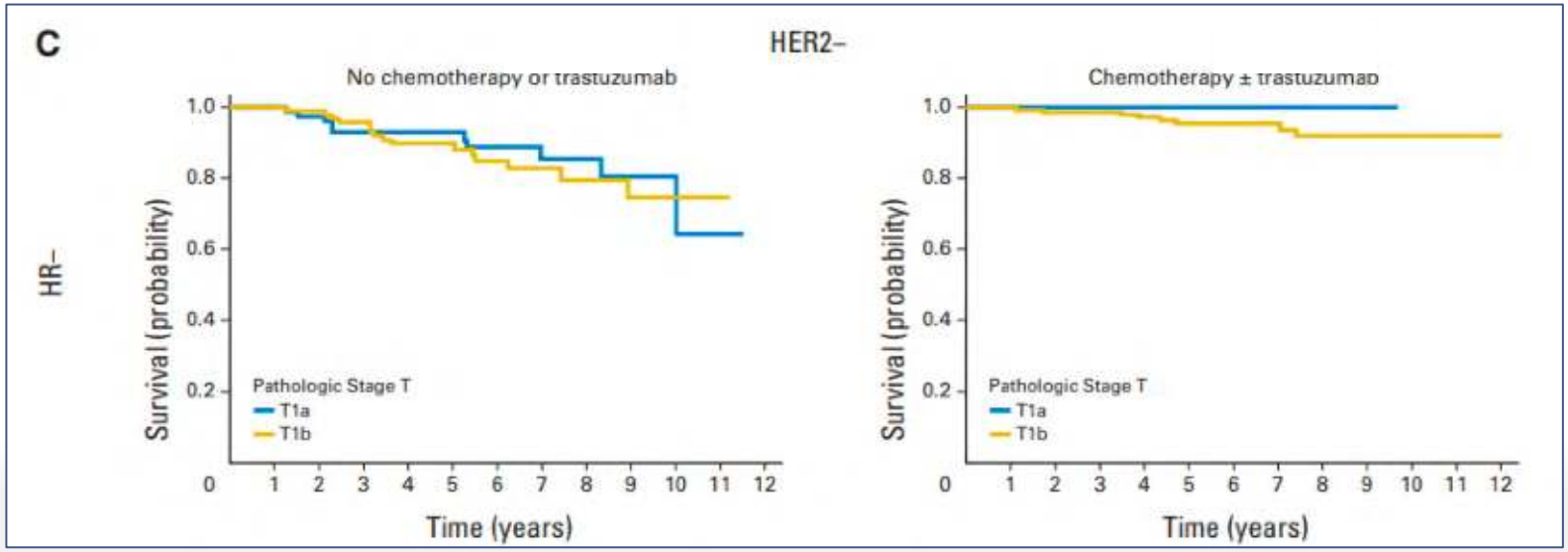
T1: ≤ 2cm

N0-N1mi: node negative or micrometastatic

Image Credit: AJCC
Howlader et al. Cancer Epidemiol Biomarkers Prev. 2018.

Natural History of T1a/T1b TNBC

5 yr Survival Outcomes of Patients with T1a and T1b TNBC				
Outcome	T1a No CTX (n=74)	T1a CTX (n=25)	T1b No CTX (n=94)	T1b CTX (n=170)
OS	94	100	91	96
BCSS	95	100	95	98
IDFS	86	91	81	88
DRFS	93	100	90	96



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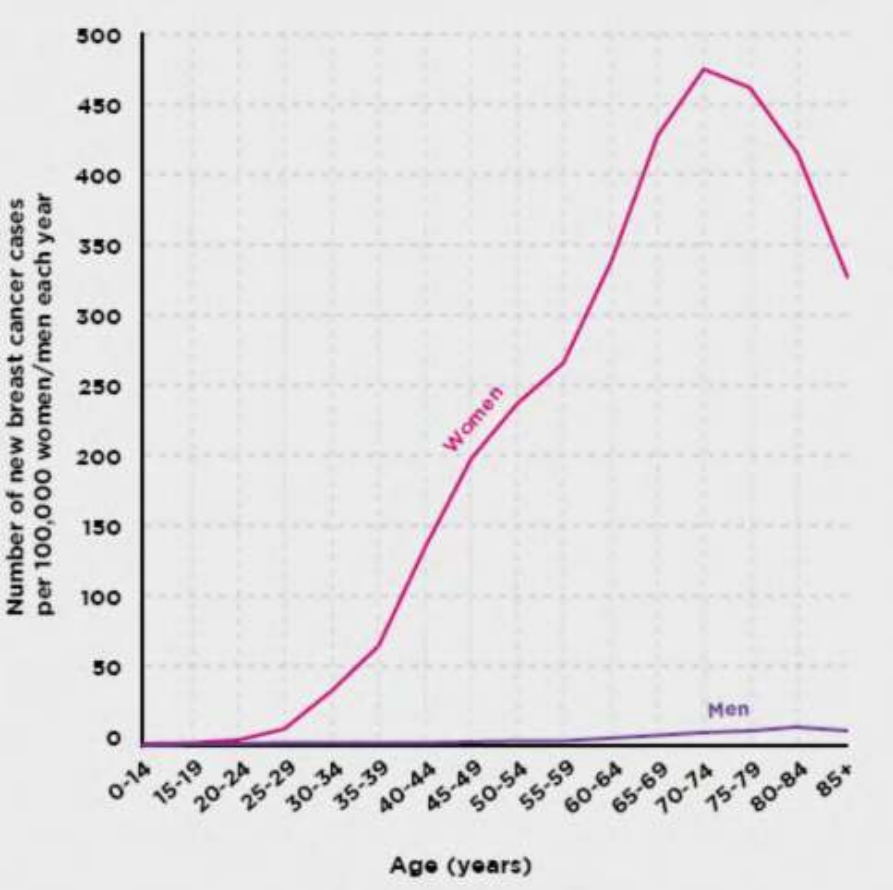
Vaz-Luis et al. JCO. 2014

Curative Regimens

- Docetaxel-Cyclophosphamide (TC)
- DD Doxorubicin-Cyclophosphamide f/b Paclitaxel
- DD Doxorubicin-Cyclophosphamide f/b Paclitaxel-Carboplatin*
- Pembrolizumab-Paclitaxel-Carboplatin f/b Pembrolizumab-Anthracycline-Cyclophosphamide f/b adjuvant Pembrolizumab (KEYNOTE 522)

Pivotal Trials That Led to Use of These Regimens Did Not Include Stage I Patients

OS in T1c (1cm-2cm) TNBC



Age-specific BC Rates in the US

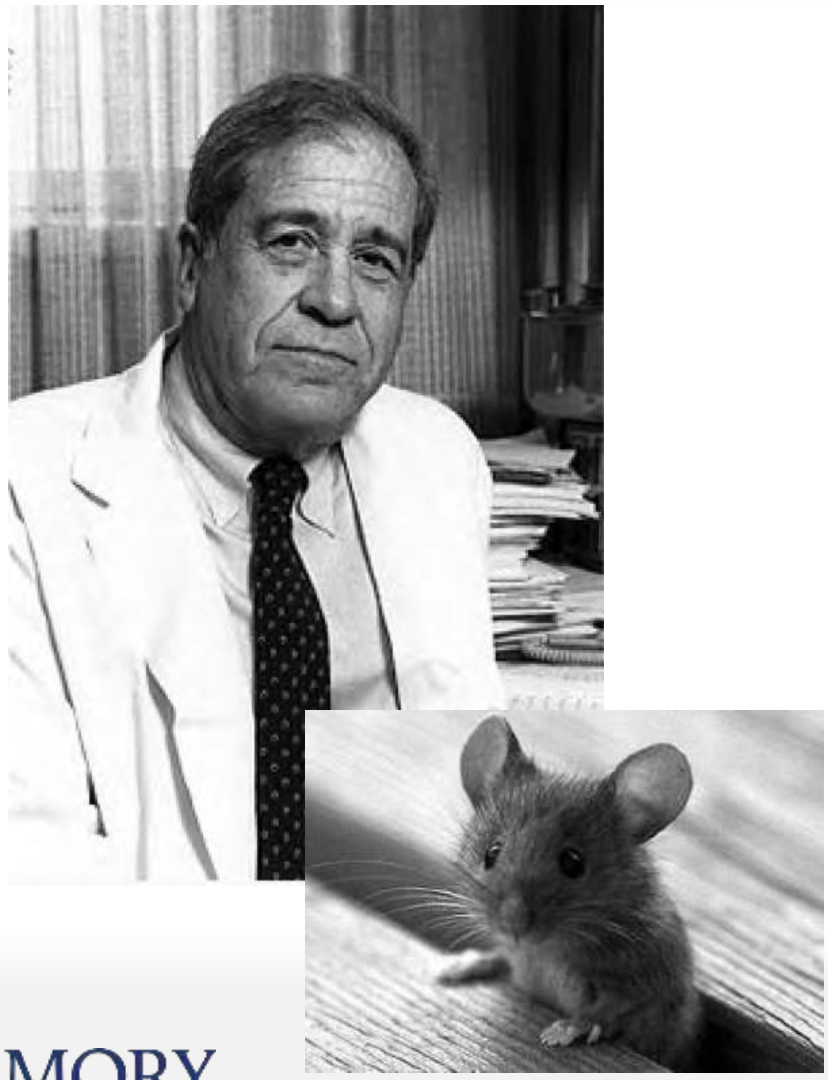
predict breast cancer

NHS

3rd Generation Adjuvant Chemotherapy Outcomes		
Clinical Variable	5y OS	10y OS
1cm		
Age 40	92	88
Age 50	90	85
Age 62	88	79
2cm		
Age 40	89	85
Age 50	88	82
Age 62	85	75

Data Sources: UK Predict; Susan G. Komen (SEER 2015-2019)

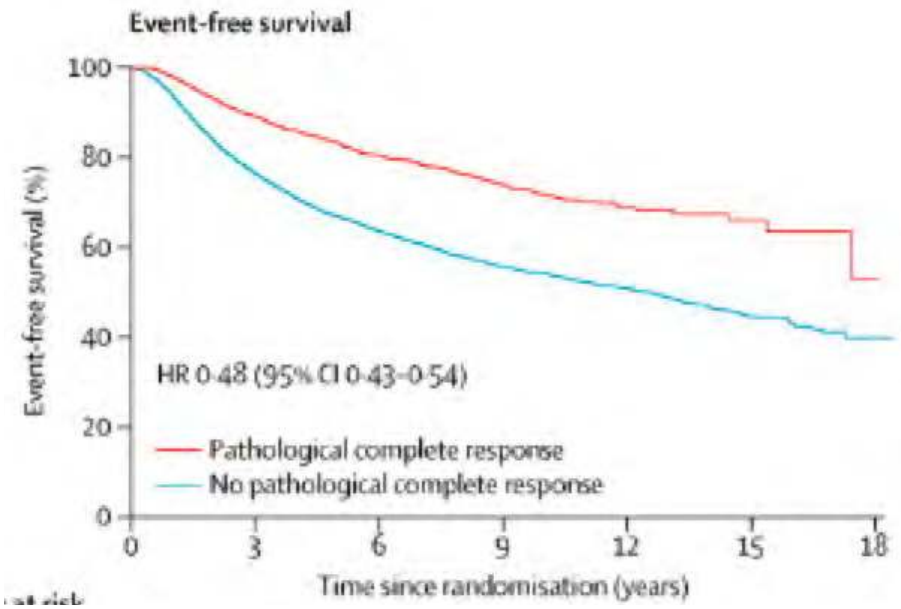
Micrometastatic Control

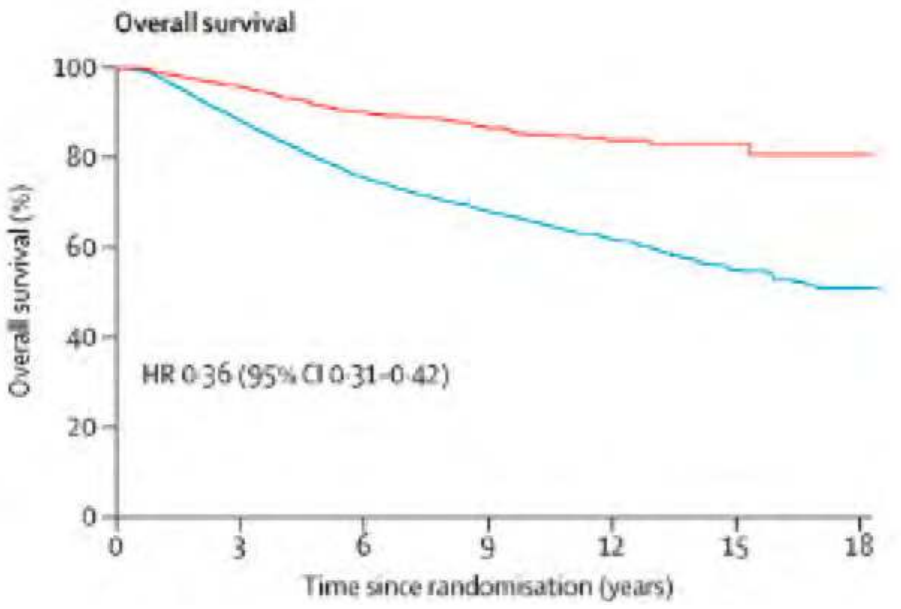


- Early mouse models suggested removal of a primary tumor impacted the kinetics of cells in a metastasis
- Presence of “growth-stimulating factor” following resection
- Preoperative therapy prevented increase in cell proliferation following surgery and reduced mets

Fisher et al. Cancer Res. 1989

pCR, Recurrence & Survival in TNBC





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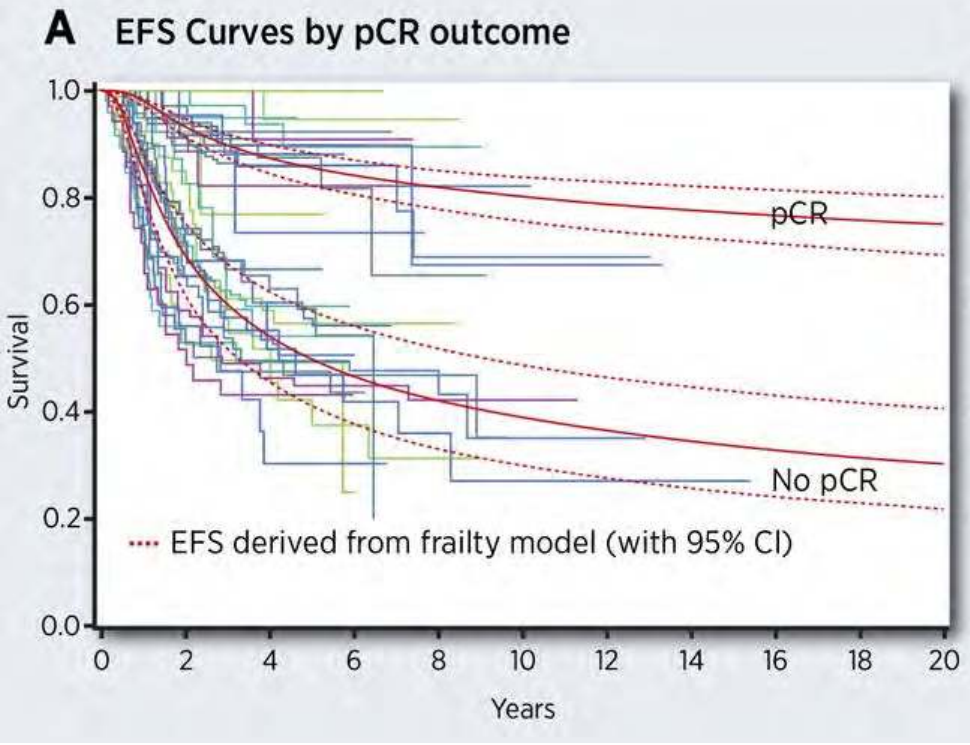
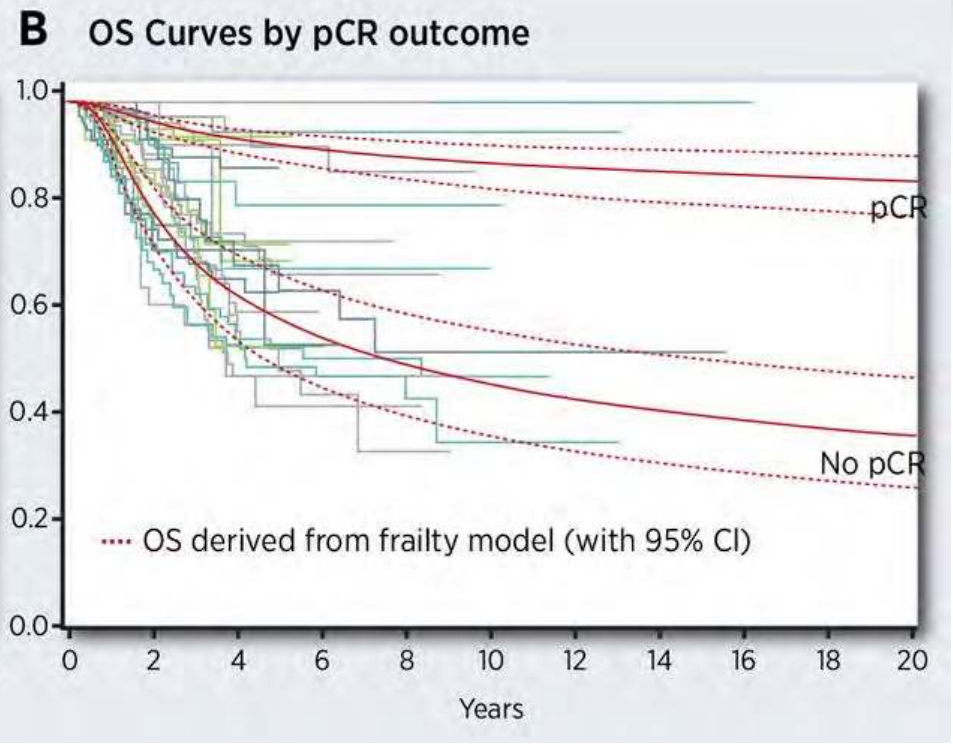
Cortazar et al. Lancet. 2014.
EBCTG. Lancet Oncology. 2018.





EFS 86% vs 50%
HR 0.24 (95% CI 0.2- 0.29)

OS 92% vs 58%
HR 0.19 (95% CI 0.15- 0.24)

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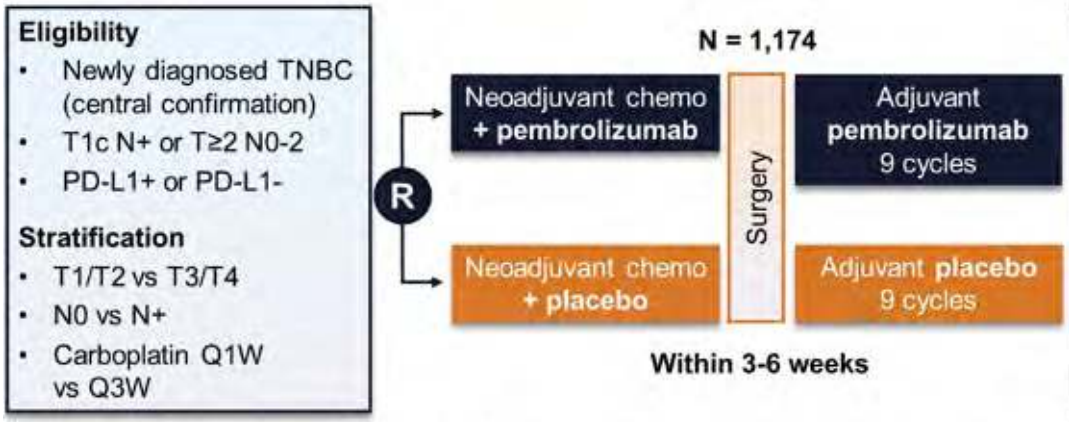
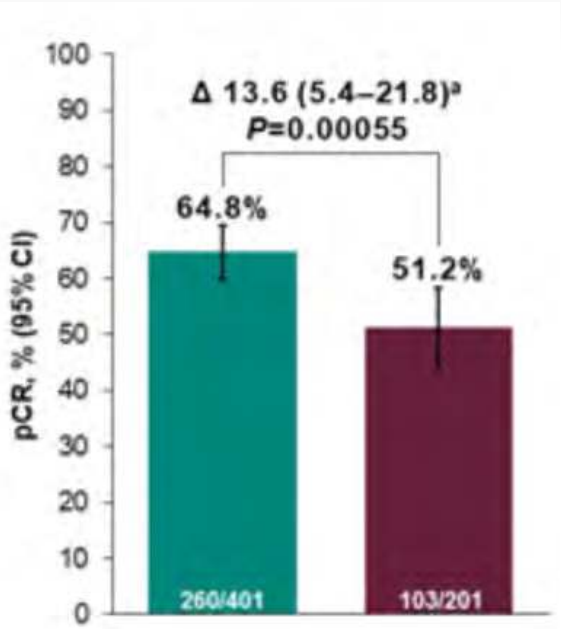
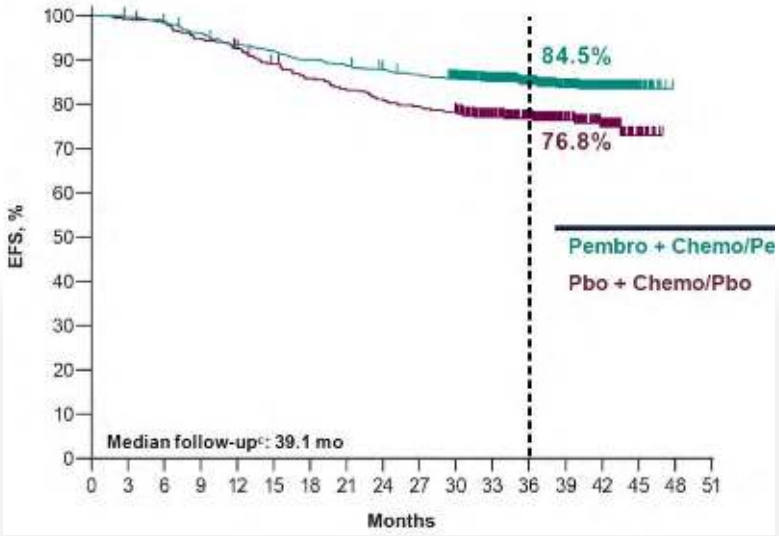
Huang et al. Cancer Res. 2020.

KEYNOTE-522







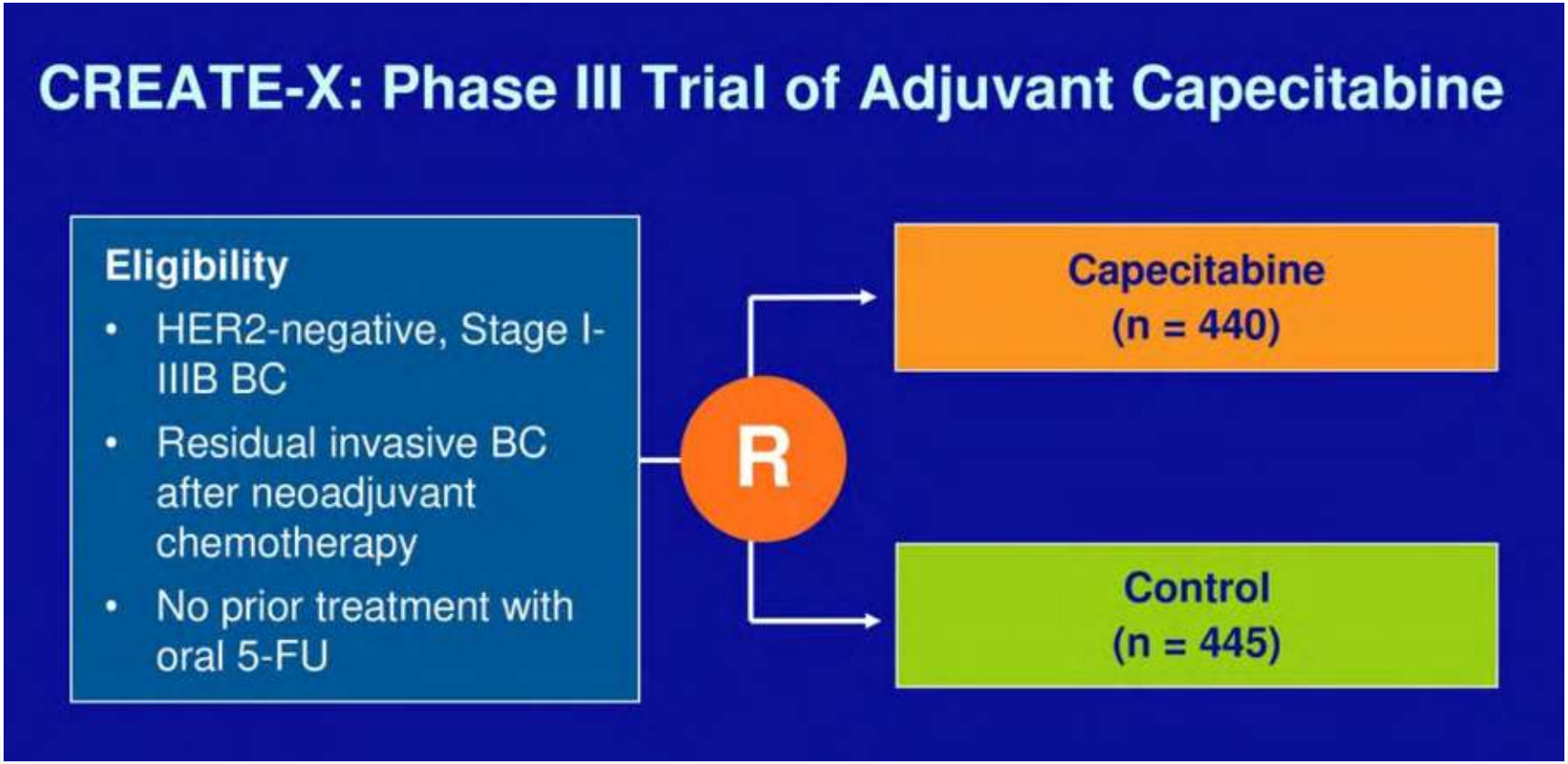
Chemoimmunotherapy arm:
pCR 65%; 3y EFS 84.5%
no pCR 35%; 3y EFS 67%

Schmid et al. NEJM. 2021.

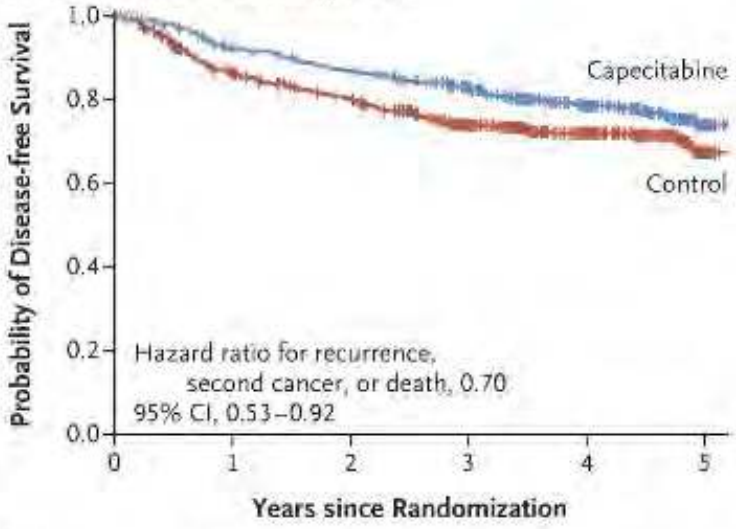
Adjuvant Strategies: High risk early stage TNBC

Trial	Eligibility	Strategy	Status
KN522	Stage II/III TNBC	Preop chemo i/o f/b 9 cycles adjuvant Pembroluzimab *	Approved
CREATE-X	Stage I- IIIB no pCR **TNBC** or ER+	Capecitabine 1250mg/m2 x 6-8 cycles	SOC for TNBC w/o pCR
OlympiA	BRCA+ **TNBC:** either ≥cT1c, ≥N1 or no pCR ER+: N1 or CPS+EG ≥3	Olaparib x 1y	Approved
EA1131	TNBC Stage II/III preop ≥ypT1c	Obs vs Cisplatin x4 vs Carboplatin x4 vs Cape 1000mg/m2 x 6	Adjuvant platinum not superior to Capecitabine

CREATE-X

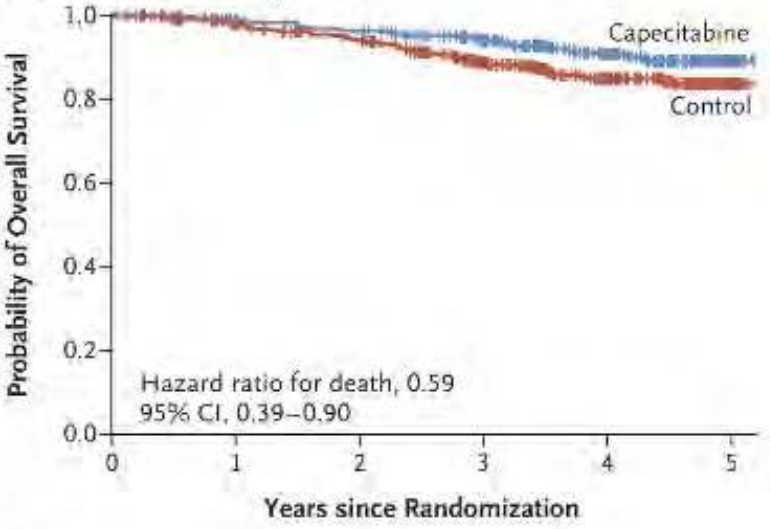

CREATE-X: Phase III Trial of Adjuvant Capecitabine
Eligibility
• HER2-negative, Stage I-IIIB BC
• Residual invasive BC after neoadjuvant chemotherapy
• No prior treatment with oral 5-FU
R
Capecitabine (n = 440)
Control (n = 445)

A Disease-free Survival in Full Analysis Set



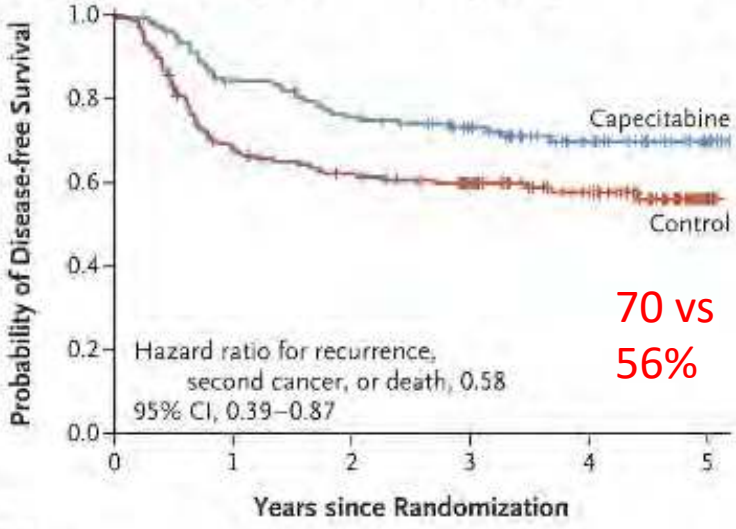
No. at Risk						
Capecitabine	443	385	359	286	175	34
Control	444	366	328	255	158	19

B Overall Survival in Full Analysis Set



No. at Risk						
Capecitabine	443	408	391	321	197	43
Control	444	406	375	297	180	27

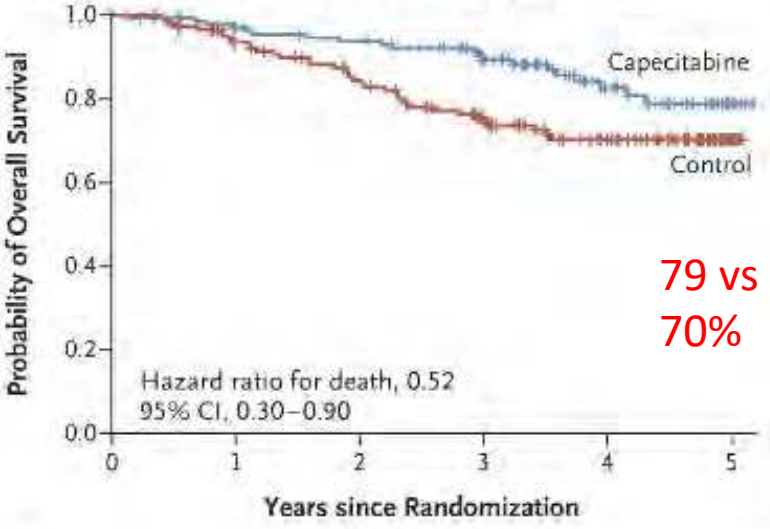
C Disease-free Survival among Patients with Triple-Negative Disease



70 vs 56%

No. at Risk						
Capecitabine	139	109	96	76	42	11
Control	147	95	84	69	47	6

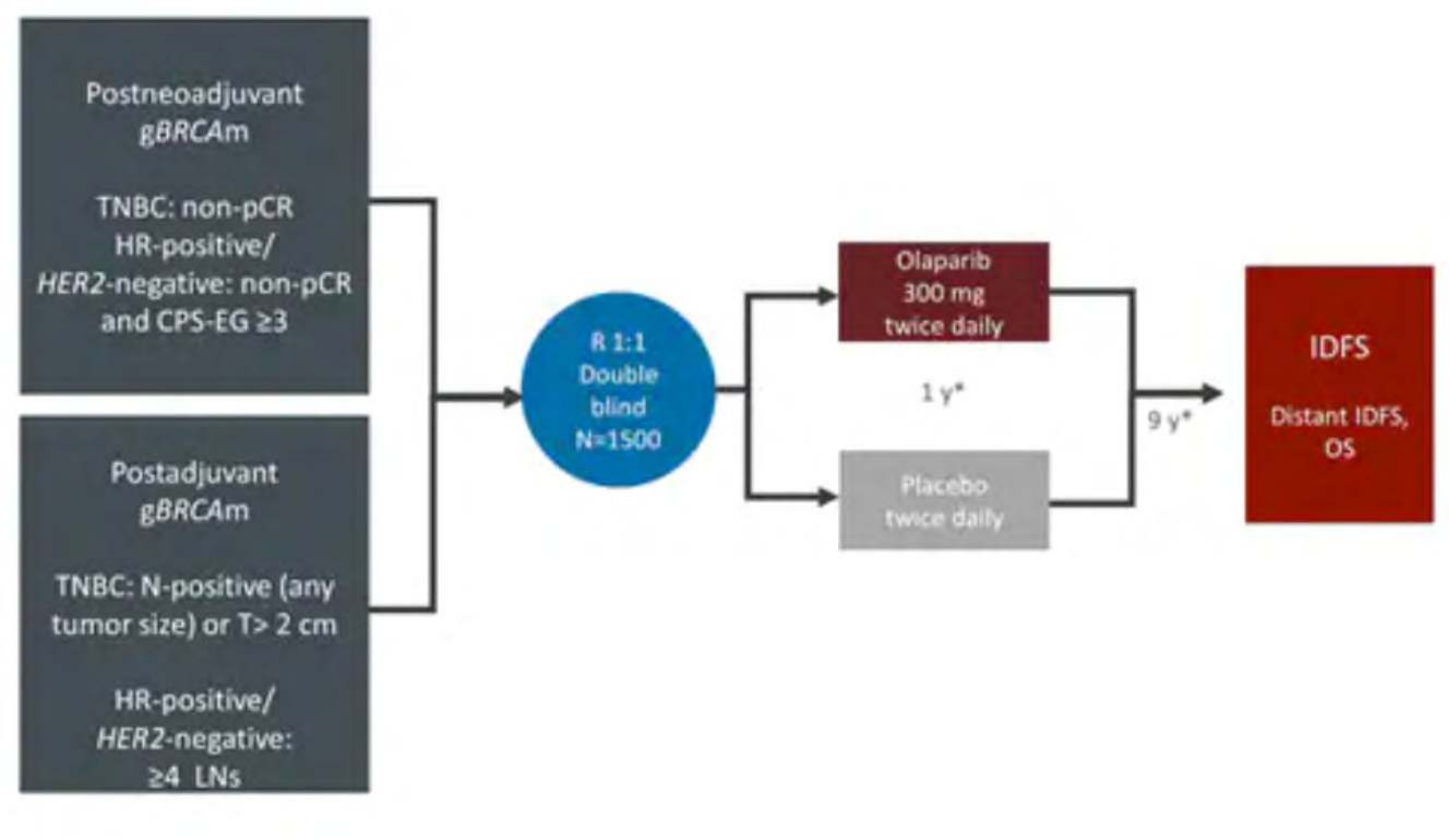
D Overall Survival among Patients with Triple-Negative Disease



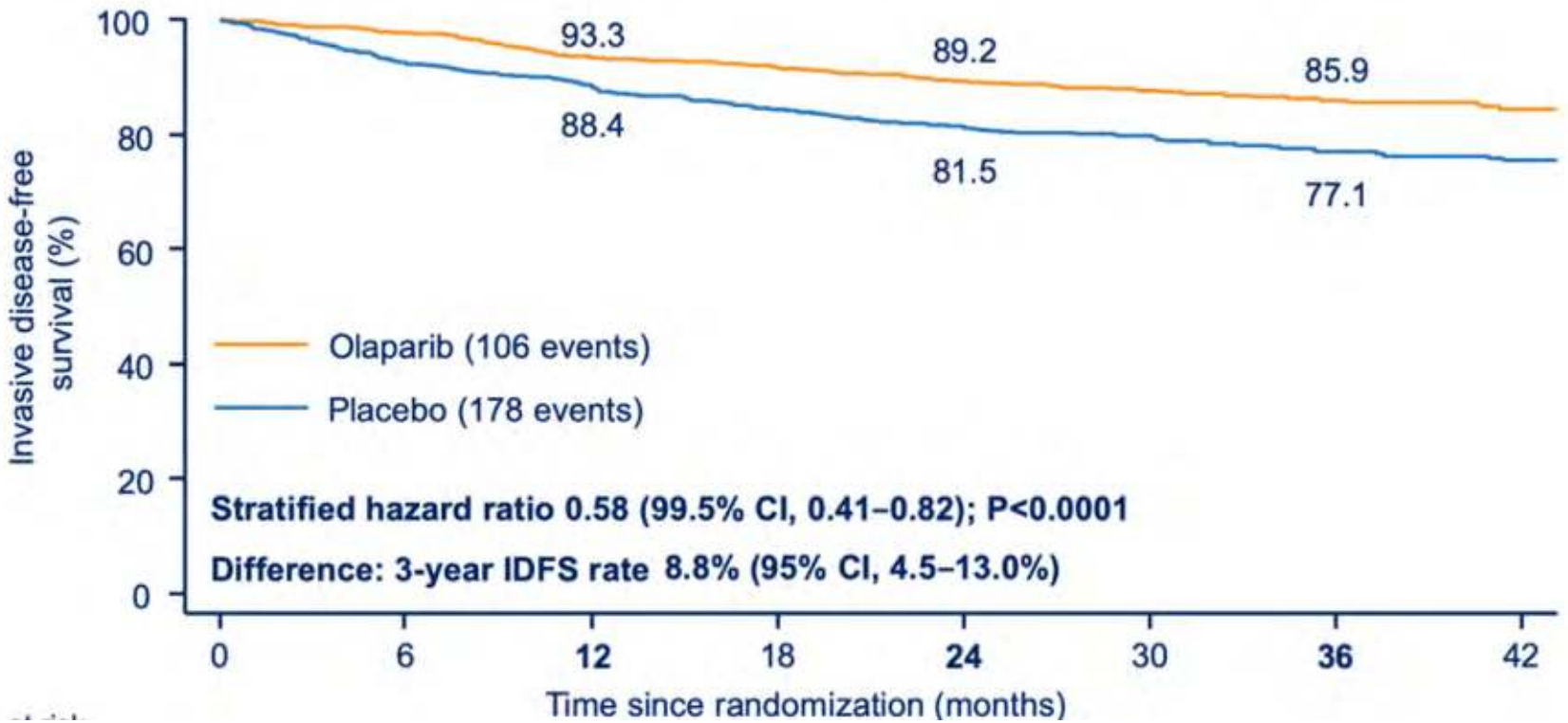
79 vs 70%

No. at Risk						
Capecitabine	139	124	116	91	50	11
Control	147	125	108	82	52	9

OlympiA


Postneoadjuvant
gBRCAm
TNBC: non-pCR
HR-positive/
HER2-negative: non-pCR
and CPS-EG ≥3
Postadjuvant
gBRCAm
TNBC: N-positive (any
tumor size) or T> 2 cm
HR-positive/
HER2-negative:
≥4 LNs
R 1:1
Double
blind
N=1500
Olaparib
300 mg
twice daily
1 y*
Placebo
twice daily
9 y*
IDFS
Distant IDFS,
OS

OlympiA



TNBC Patients:
Events: 11.6% vs 20.2%
HR 0.56 (95% CI 0.43, 0.73)

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EA1131

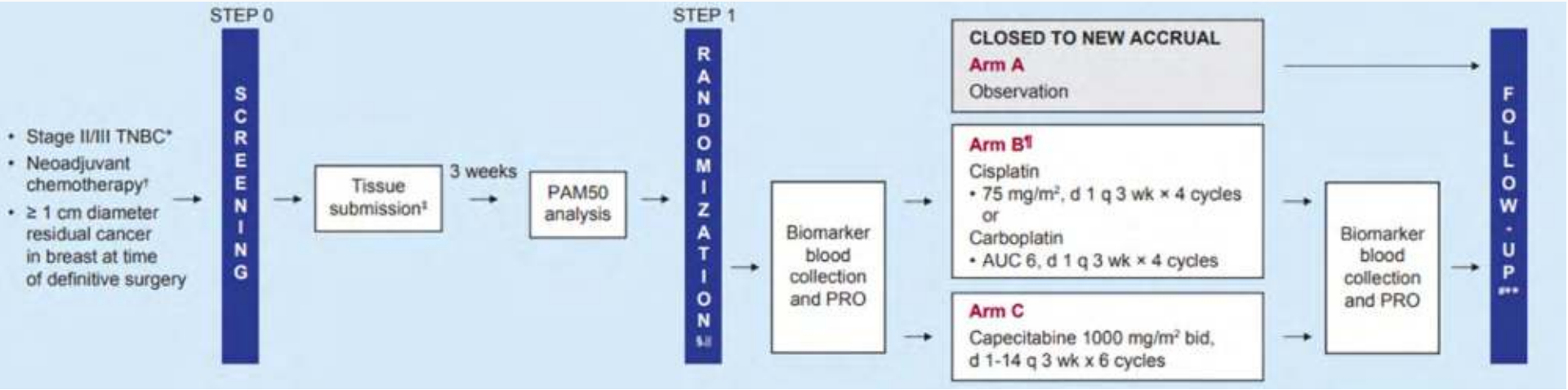


TABLE 1: 3-Year Invasive Disease–Free Survival From EA1131 Trial

Intrinsic Subtype	Capecitabine	Platinum	Hazard Ratio (95% Confidence Interval)
Basal subtype	49%	42%	1.06 (0.62–1.81)
Nonbasal subtype	69%	46%	1.94 (0.69–5.45)

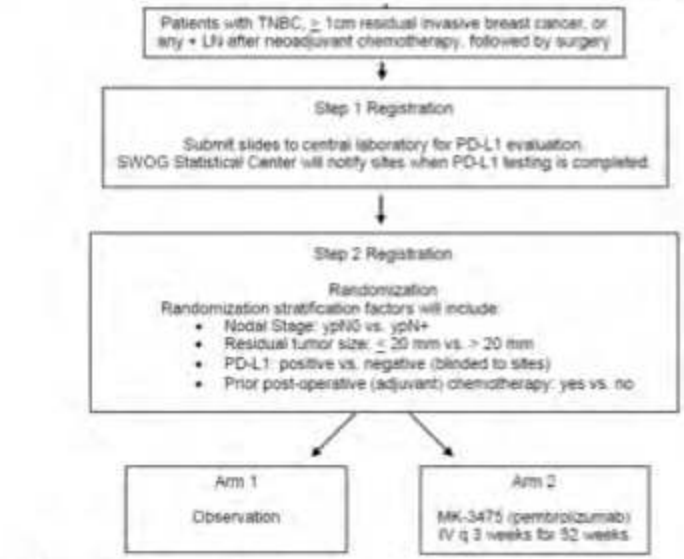
Adjuvant Strategies for Residual Disease: Ongoing Trials

Trial	Eligibility	Strategy	Status
S1418	TNBC ≥ypT1c or ≥N1	Obs* vs Adjuvant Pembroluzimab x 1y	Results pending; will stratify by PD-L1 status and use of adjuvant tx
PERSEVERE	TNBC: Stage I-III at dx ≥ypT1c or ≥ypN1 or RCB 2/3	ctDNA enriched, genomically directed post-neoadjuvant trial	Enrolling
ASPRIA	TNBC no pCR If ypT0m then LN+	Adjuvant sacituzumab govitecan-hziy and atezolizumab x 6	SOC for TNBC w/o pCR

S1418/NRG BR006

SWOG S1418 / NRG BR006

A Randomized, Phase III Trial to Evaluate the Efficacy and Safety of MK-3475 as Adjuvant Therapy for Triple Receptor-Negative Breast Cancer with ≥ 1 cm Residual Invasive Cancer or Positive Lymph Nodes (ypN1mi, ypN1-3) After Neoadjuvant Chemotherapy



NOTE: Radiation therapy may be given concurrently on Arm 1 or Arm 2.

Primary Objective:
Compare invasive disease-free survival (IDFS) between patients randomized to receive 1 year of pembrolizumab adjuvant therapy to no pembrolizumab) in both the entire study population and also in the PD-L1 positive subset.

SWOG CANCER RESEARCH NETWORK

NCI National Clinical Trials Network — a National Cancer Institute program

NCI Community Oncology Research Program

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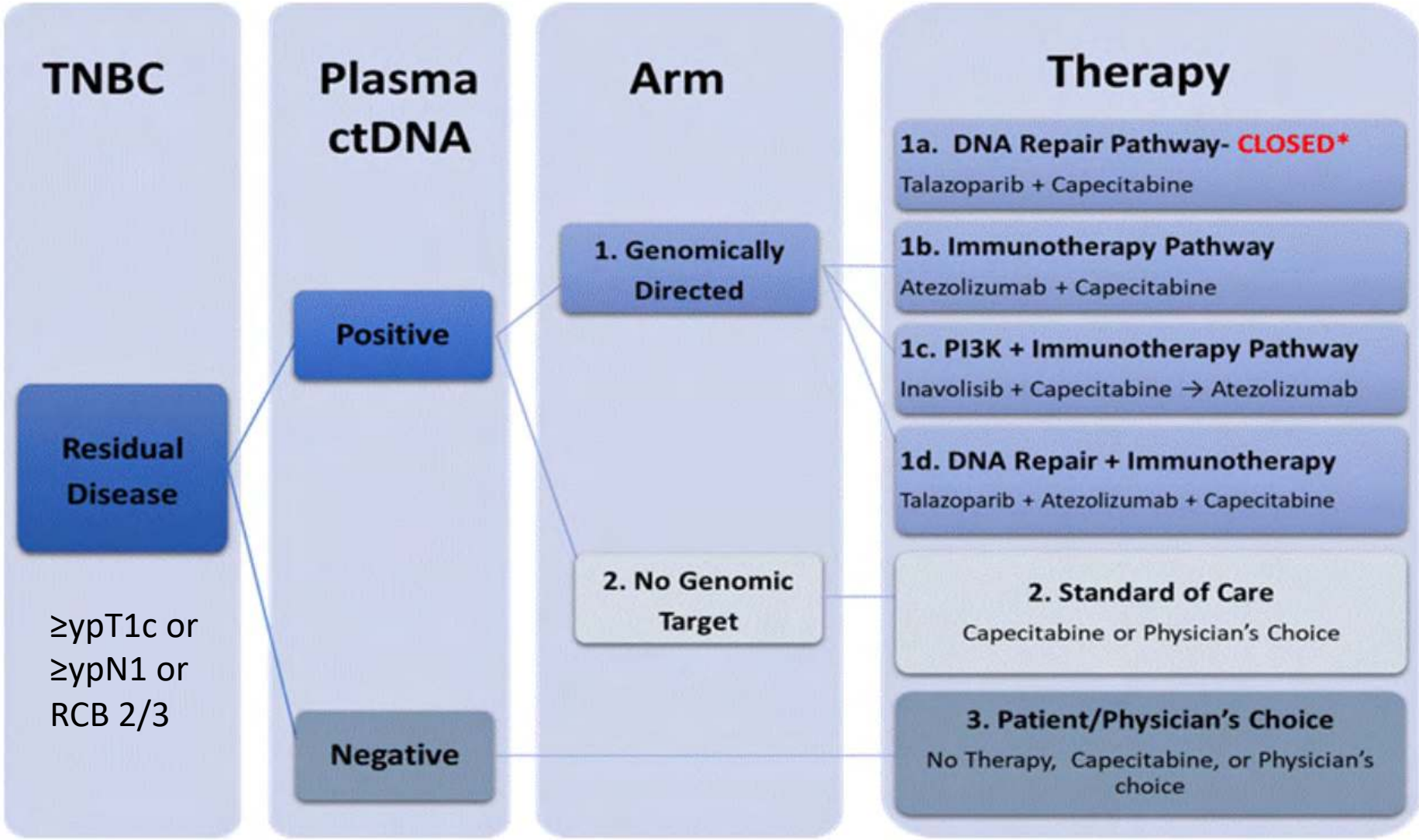
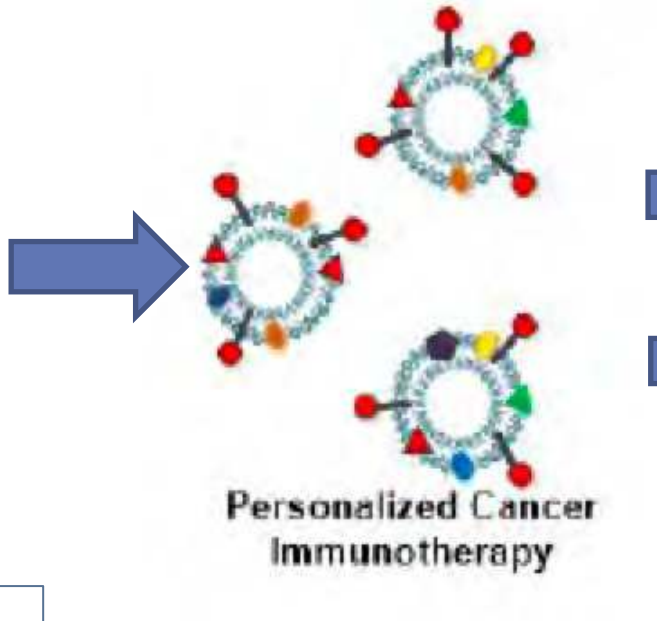
PERSEVERE- Due to open at WCI



Autologous Vaccine Immunotherapy Alone and in Combination with Checkpoint Inhibitor for TNBC

Due to open in late 2022



anti-PD-L1
or
anti-CTLA-4

Resected Prior Tumor
ER/PR≤10%, H2N-
-Residual Disease or after SOC adjuvant chemo

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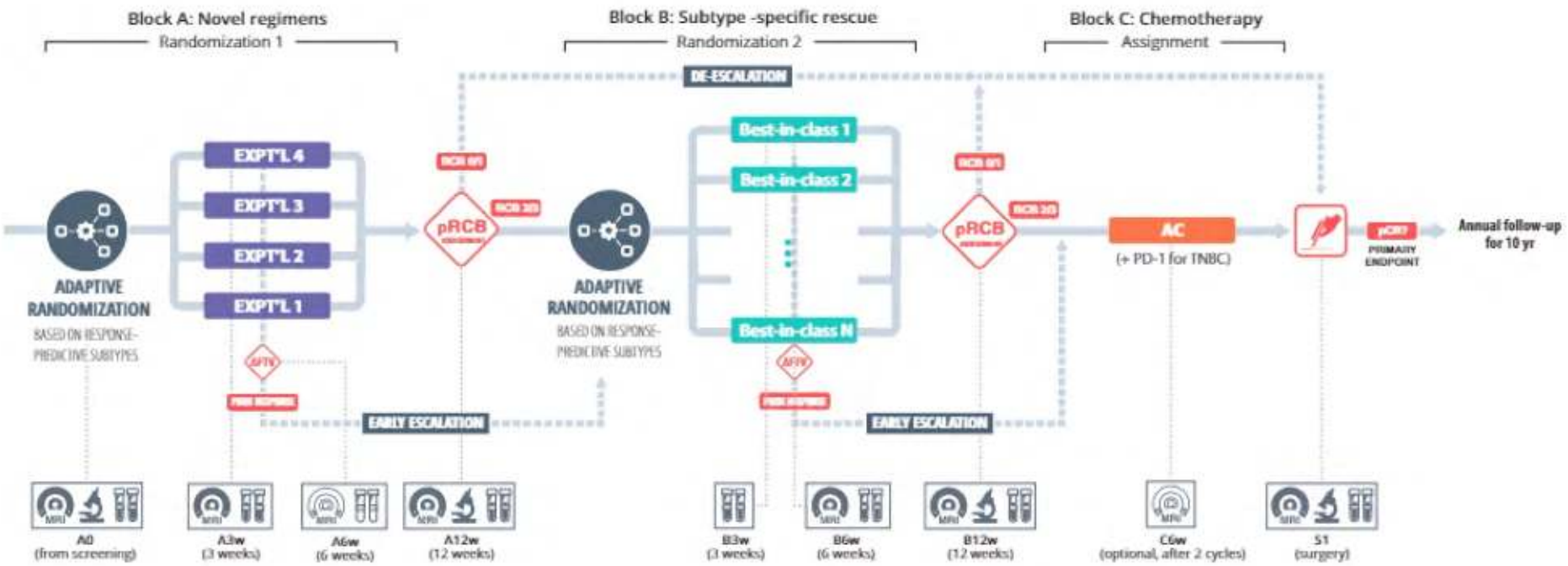
I-SPY 2- Open at WCI

Revised Eligibility Criteria Allow for Smaller Tumors:

LN Negative: ≥2.5cm on exam and ≥2cm on imaging
LN Positive: In breast→≥2cm on exam and ≥1.5cm on imaging



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Should Patients with Stage I Triple Negative Breast Cancer Receive Neoadjuvant Therapy?

- Knowing response to preoperative therapy can alter adjuvant SOC and trial options
- Adjuvant options can reduce relapse and improve survival
- Strongly consider for T1c (>1-2cm)
  - These patients may qualify for preop therapy on I-SPY2
- If you're going to offer chemo for a patient with T1b (<5mm-1cm), then consider delivering it preop if you think the patient could tolerate adaptive adjuvant strategy in the event of residual disease