Neoadjuvant and metastatic breast cancer 2024:

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Pennington
Cancer Institute

Disclosures

- Advisor/Consultant: AstraZeneca, Daiichi Sankyo, Novartis, Spectrum, Napo, Genentech, Foundation Medicine, Coherus, GSK
- Speaker Bureau: AstraZeneca, Merck, Daiichi Sankyo, Novartis

Breast Cancer Incidence 2024

Estimated New Cases

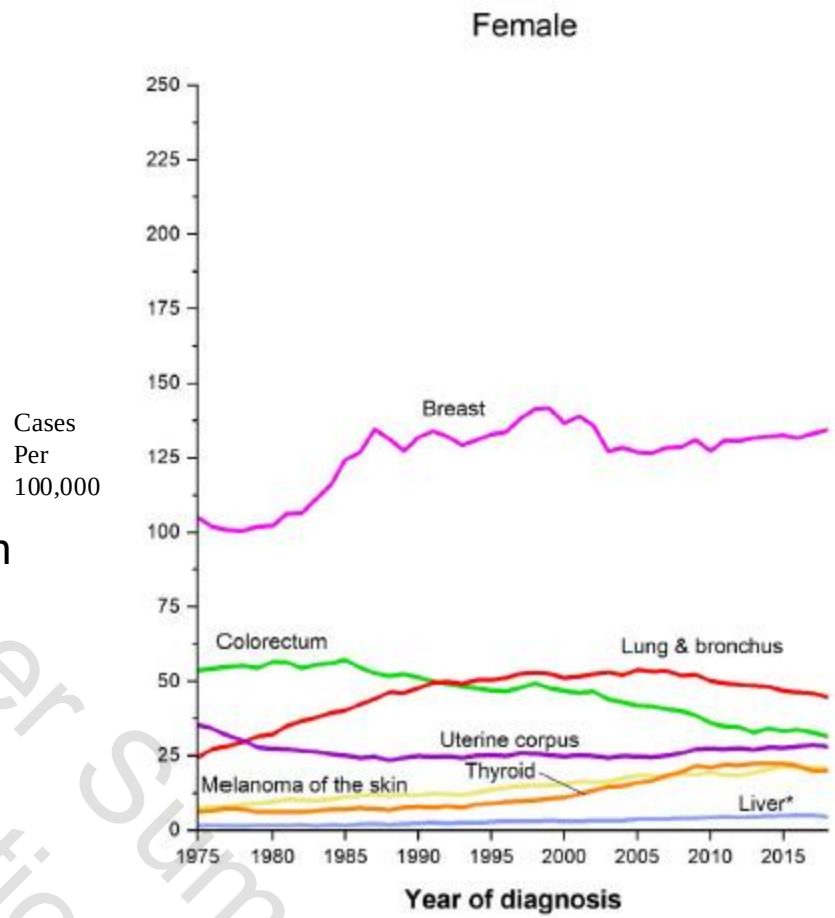
	Males			Females	
Prostate	288,300	29%		Breast	297,790	31%
Lung & bronchus	117,550	12%		Lung & bronchus	120,790	13%
Colon & rectum	81,860	8%		Colon & rectum	71,160	8%
Urinary bladder	62,420	6%		Uterine corpus	66,200	7%
Melanoma of the skin	58,120	6%		Melanoma of the skin	39,490	4%
Kidney & renal pelvis	52,360	5%		Non-Hodgkin lymphoma	35,670	4%
Non-Hodgkin lymphoma	44,880	4%		Thyroid	31,180	3%
Oral cavity & pharynx	39,290	4%		Pancreas	30,920	3%
Leukemia	35,670	4%		Kidney & renal pelvis	29,440	3%
Pancreas	33,130	3%		Leukemia	23,940	3%
All Sites	**1,010,310**	**100%**		**All Sites**	**948,000**	**100%**

Estimated Deaths

	Males			Females	
Lung & bronchus	67,160	21%		Lung & bronchus	59,910	21%
Prostate	34,700	11%		Breast	43,170	15%
Colon & rectum	28,470	9%		Colon & rectum	24,080	8%
Pancreas	26,620	8%		Pancreas	23,930	8%
Liver & intrahepatic bile duct	19,000	6%		Ovary	13,270	5%
Leukemia	13,900	4%		Uterine corpus	13,030	5%
Esophagus	12,920	4%		Liver & intrahepatic bile duct	10,380	4%
Urinary bladder	12,160	4%		Leukemia	9,810	3%
Non-Hodgkin lymphoma	11,780	4%		Non-Hodgkin lymphoma	8,400	3%
Brain & other nervous system	11,020	3%		Brain & other nervous system	7,970	3%
All Sites	**322,080**	**100%**		**All Sites**	**287,740**	**100%**

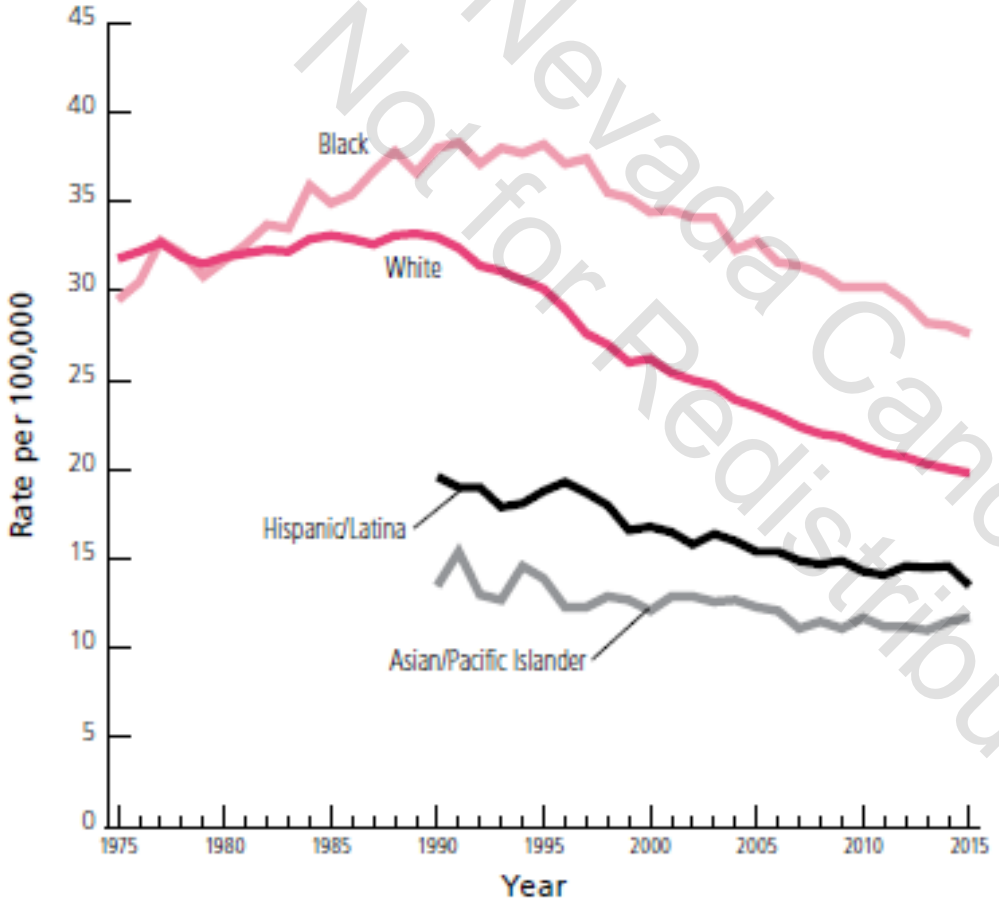
#1 Cancer Dx

#2 Cancer Death



- In situ cancer: 63,000
- Invasive Cancer: 297,000
- Deaths from breast cancer: 43,000
- Lifetime risk 12.6% (one in 8 women)

Figure 6b. Trends in Female Breast Cancer Death Rates by Race/Ethnicity, 1975-2015, US



Overall 40% reduction in breast cancer mortality from 1990

Disparity gap between Black and White remains

1991:
50 year old woman with palpable breast mass and axillary LN
Imaging: 4 cm mass in Left breast, enlarged LN
Biopsy: Invasive cancer, NOS, poorly differentiated
ER+ PR+ by LBA; HER2 N/A; Ki-67 N/A

Total Mastectomy and axillary lymph node dissection:

Path: 4.2 x 4 cm IDC, 2/18 lymph nodes positive

Doxorubicin based adjuvant chemotherapy

Radiation x 5 weeks including all LNs + 1 week boost to chest wall/scar

Tamoxifen for 5 years

1991 Outcome

EFFICACY

- 30-40% chance of distant recurrence at 10 yrs

TOXICITY

- 35-40% chance of clinical lymphedema
- 10-20% chance of chronic chest wall pain/fibrosis
- 1-5% chance of cardiac disease

Treatment changes over past 30 years

1991

- Mastectomy for large tumors
- Radiation to chest wall and TNI if node +
- Multiagent adjuvant chemotherapy
- Tamoxifen for ER+
- Limited understanding of subtypes

2024

- Treat breast cancer by subtype
- Improved imaging and clip placement preoperatively
- Neoadjuvant chemotherapy for many
- Reduce surgery (partial mast) and radiation based on chemotherapy response
- Biologic and Immunologic therapies for many
- Improved endocrine therapy (AIs, OFS)

2024:
50 year old woman with palpable breast mass and LN
Imaging: Mammo +US: 3 cm mass in Left breast, enlarged LN,
MRI: 4 cm mass, 2.5 cm solitary LN
US Biopsy: Invasive ductal ca, grade 3, ER+ 80% PR+ 10%;
HER2 3+; Ki-67 30%;
LN +
Clips placed in breast and LN

Neoadjuvant TCHP; Clinical complete response by exam and imaging

Partial Mastectomy + Targeted axillary dissection

Path: pCR in breast and lymph nodes

Anti-HER2 Ab adjuvant therapy

Radiation to breast/No additional radiation to LNs

Aromatase inhibitor x 5 years

Outcome change over 30+ years

1991

EFFICACY

- 30-40% chance of distant recurrence at 10 yrs

TOXICITY

- 35-40% chance of clinical lymphedema
- 10-20% chance of chronic chest wall pain/fibrosis
- 1-5% chance of cardiac disease

2024

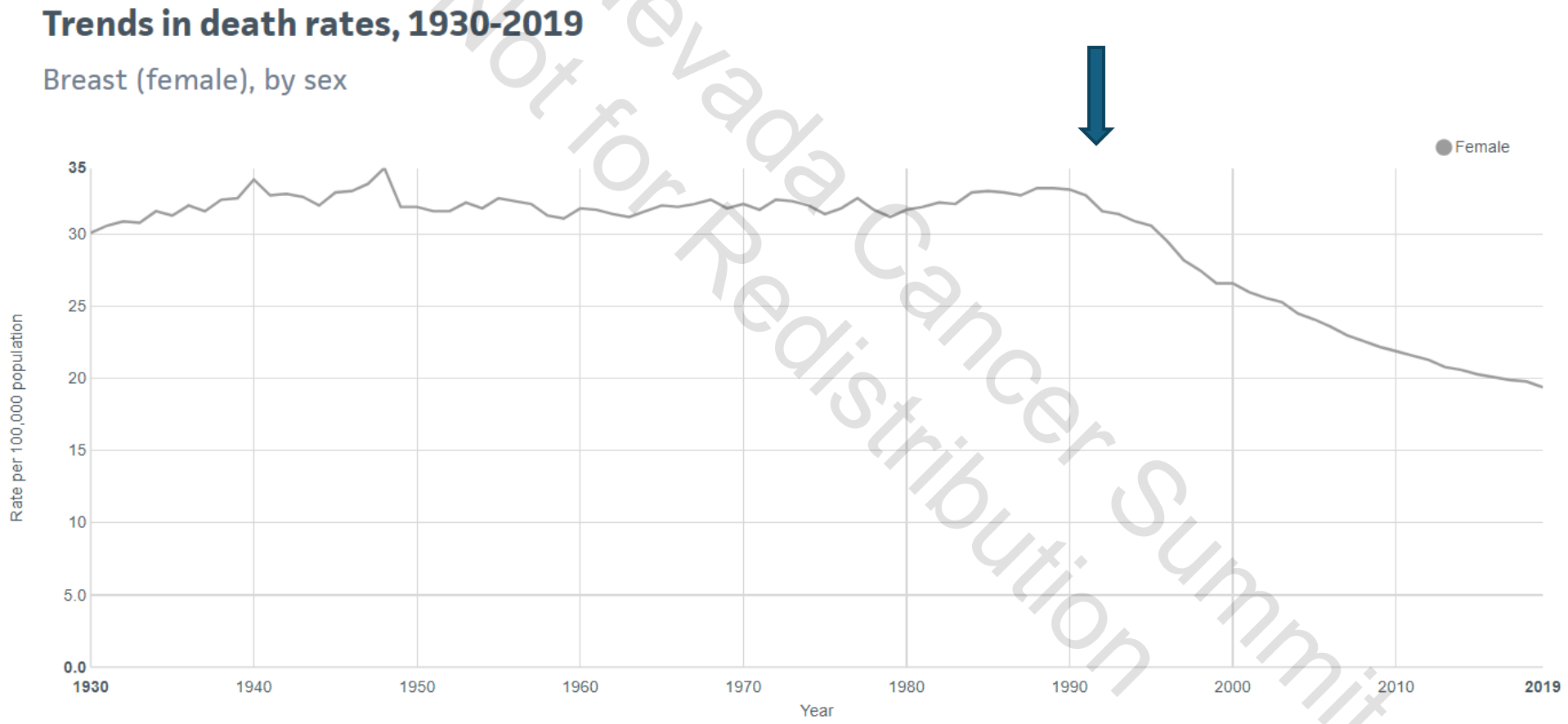
EFFICACY

- 5-10% chance of distant recurrence at 10 yrs

TOXICITY

- 5-10% chance of clinical lymphedema
- 3-5% chance of chronic chest wall pain/fibrosis
- 1-3% chance of cardiac disease

Breast cancer death rates have decreased 40% in past 30 years…
while interventions have reduced toxicity and side effects



DeSantis, CE et al; CA-A Cancer Journal for Clinicians 2019

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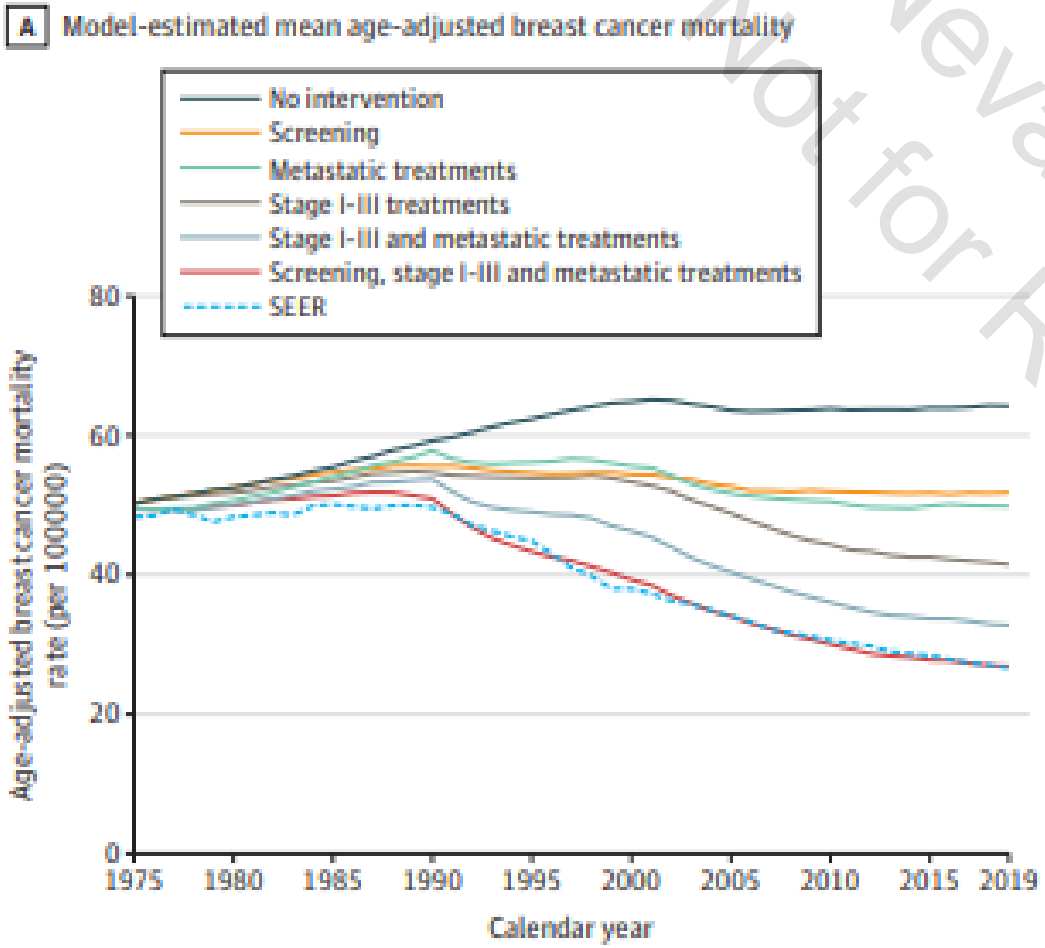
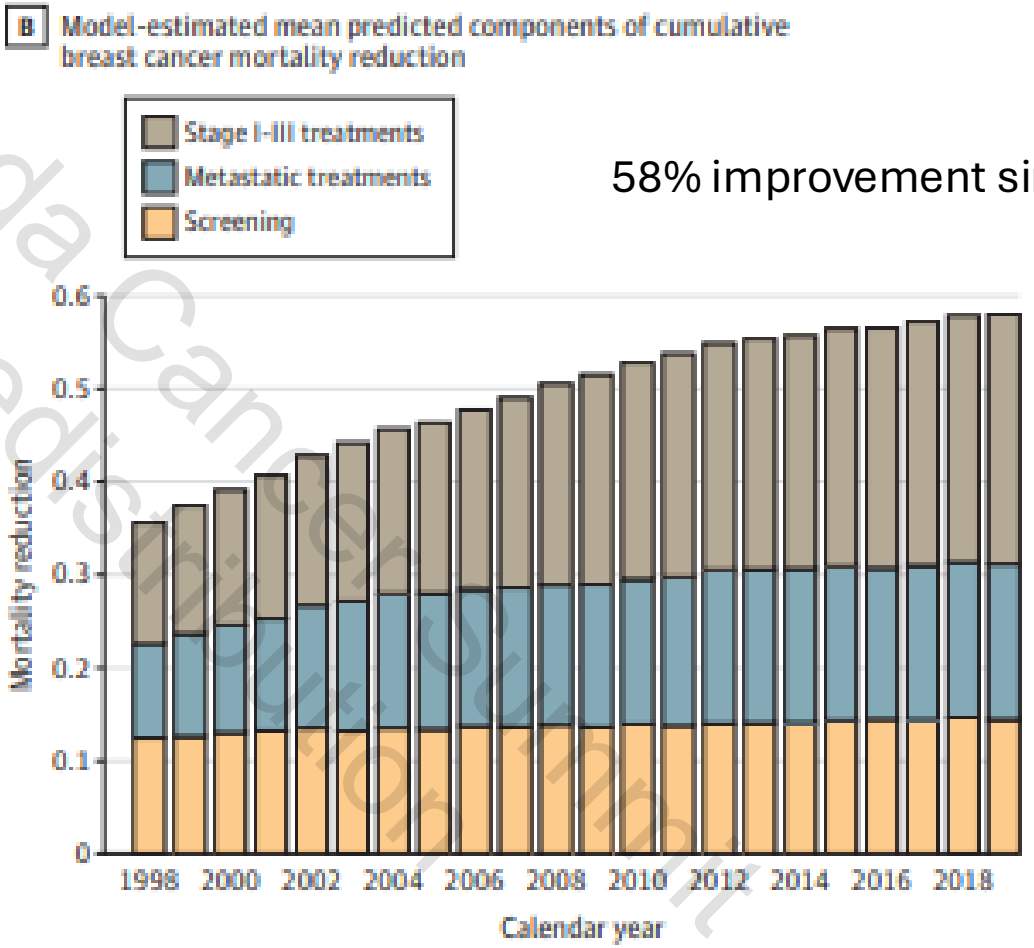
Improvements in Breast Cancer Mortality are due to: Improvements in adjuvant therapy, metastatic therapy, and screening





58% improvement since 1975

Adjuvant: 47%

Metastatic: 29%

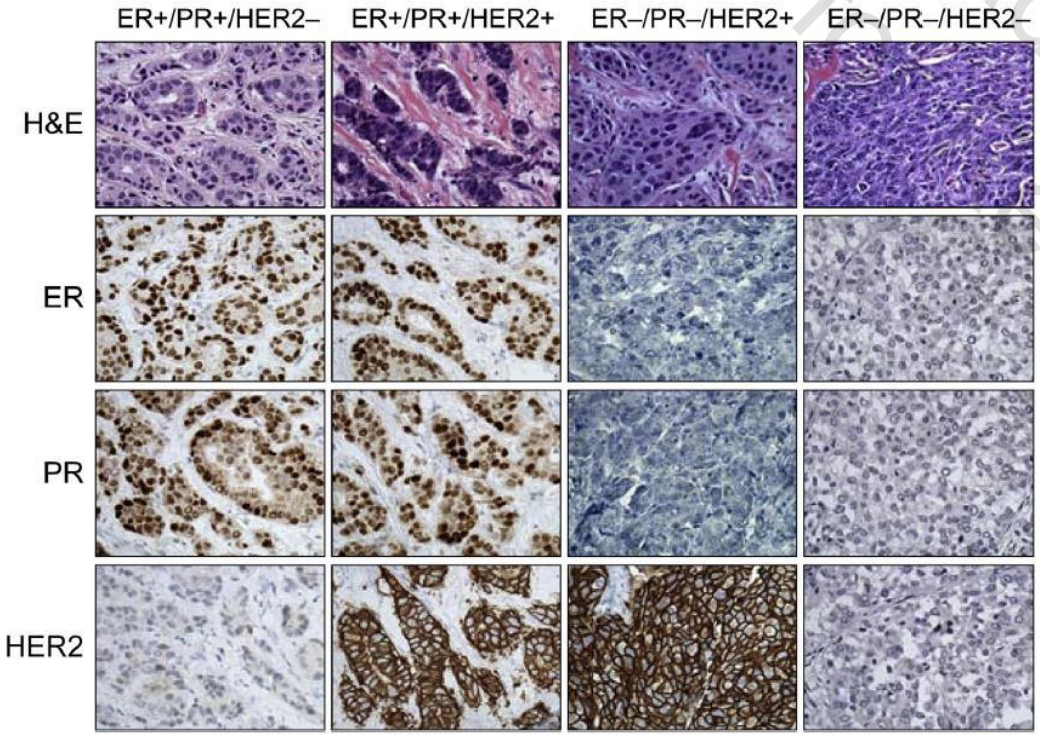
Screening: 25%

JAMA 2024

2019-2024: Incremental improvement in adjuvant and metastatic treatment

Invasive breast is composed of 3 major subtypes

	HR+HER2-	HER2+	TNBC
%	65	10	10	15



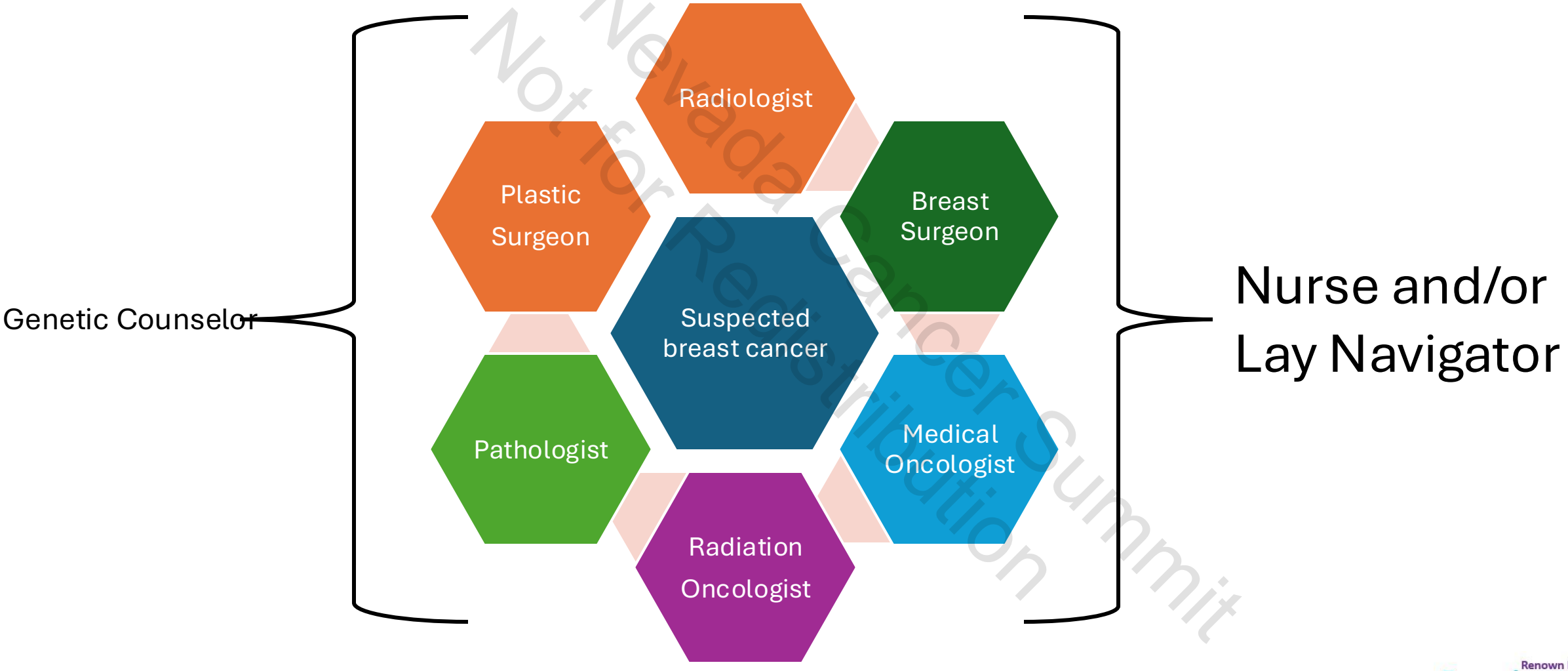
Immunohistochemistry Standard

- Estrogen receptor (ER)
- Progesterone receptor (PR)
- Human Epidermal growth factor Receptor-2 (HER2)
- Ki-67

Definition of ER/PR status:

- ER-negative: < 1% positive tumor cells
- ER-positive> 10% positive tumor cells
- ER-low: 1-10% positive tumor cells

The multidisciplinary team for early breast cancer

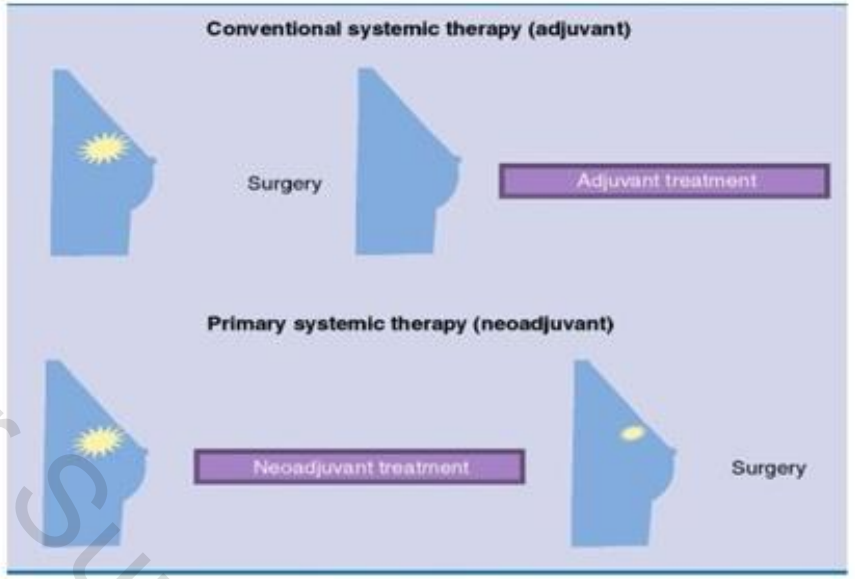


Increasing the cure rate for breast cancer: Lessons learned

- Early stage have higher cure rate
  - Screening
  - Early detection
- All invasive breast cancers have the potential for distant micromets at diagnosis
  - Adjuvant therapy can cure micrometastatic disease
    - Perioperatively
    - Postoperatively
    - Preoperatively
- Metastatic disease (macrometastatic disease) can be controlled by better therapy
  - Treat by subtype
  - Develop targeted therapy

Why use Neoadjuvant Systemic Therapy?

- Traditional
  - Downstage disease, improve resectability and breast conservation
  - Reduce extent of axillary surgery
- Contemporary
  - Risk stratification to guide adjuvant therapy
  - Provide long-term prognostic information
  - Early assessment of novel agents/combinations
- Growing
  - Response/resistance biomarkers to optimize patient selection for available therapies
  - Pathological response-guided escalation and de-escalation clinical trials



Which EBC patients Should Be Considered for Preoperative Systemic Therapy for EBC?

Patients with HER2+ EBC who have a tumor ≥ 2 cm (T2) diameter or who have node-positive disease regardless of hormone receptor status should receive neoadjuvant chemotherapy with the addition of trastuzumab/pertuzumab

Patients with TNBC who have a tumor ≥ 2 cm (T2) diameter or who have node-positive disease should receive neoadjuvant chemotherapy with the addition of pembrolizumab

Patients with HR+HER2- EBC who are high-risk by age, tumor size, nodal status, and grade should consider neoadjuvant chemotherapy

Critical Need:
Coordination between the surgeon, medical oncologist and radiologist during neoadjuvant therapy

Modern Principles of Neoadjuvant Chemotherapy

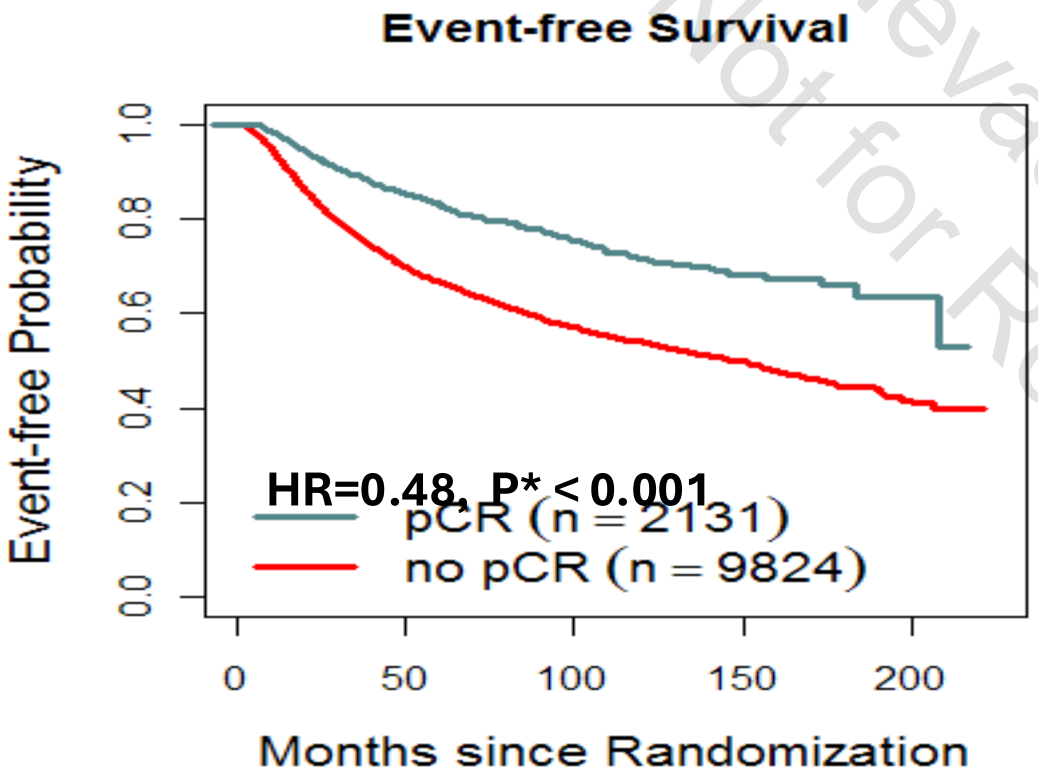
- Use the same chemotherapy before as would be used after
- Follow clinical response by examination and imaging
- Stop chemotherapy and proceed to surgery only if progression while on chemotherapy (<5%)
- Response guided chemotherapy for some?
- pCR is a surrogate for better long-term outcome on an individual patient basis

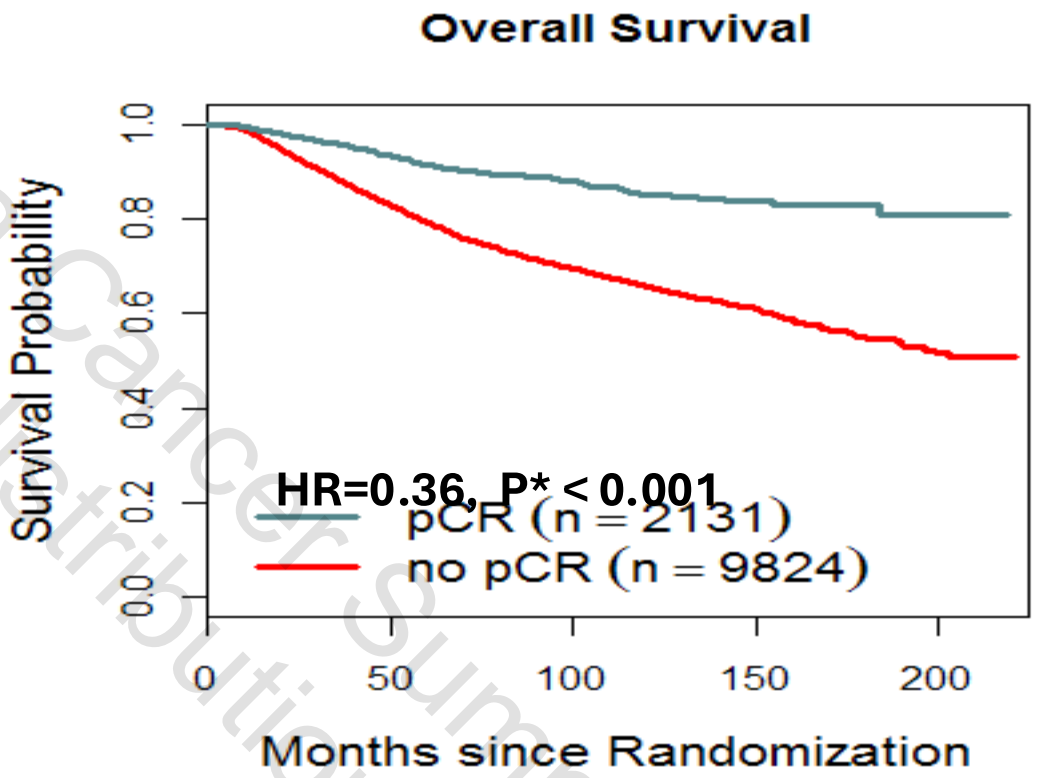
Pathologic Complete Response (pCR)
Primary goal of NACT in TNBC and HER2+ BC

- Definition: No invasive cancer in the breast or axillary lymph nodes (ypT0,ypN0)
  - Residual DCIS does not influence the definition
  - Caution: Multiple other definitions used in earlier studies

- Prognostic for long term outcome at the individual patient level

Association of pCR on EFS and OS





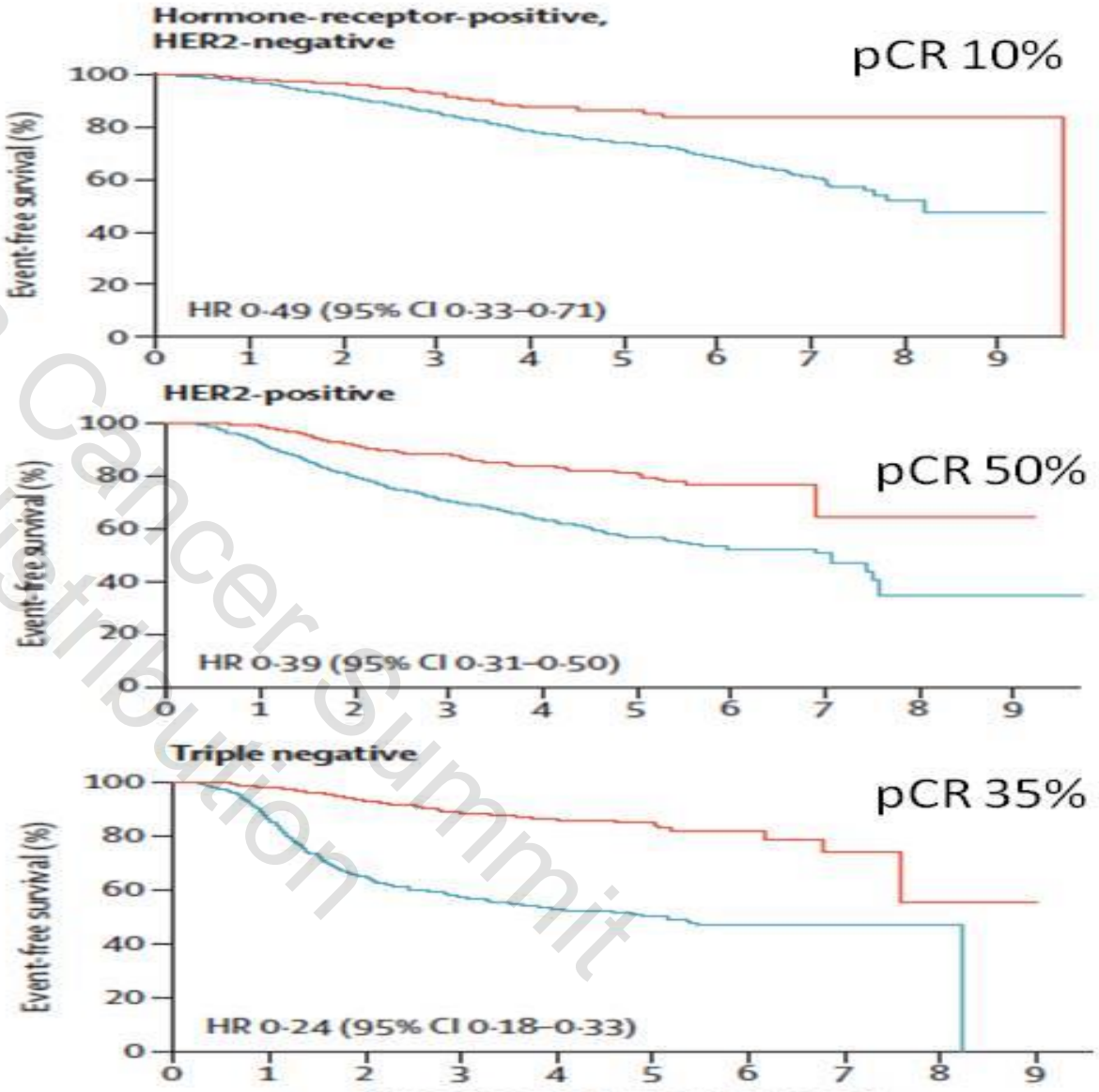
pCR=ypT0/is ypN0

* Nominal p-value

Cortazar et al, Lancet 2014; 384: 164-72

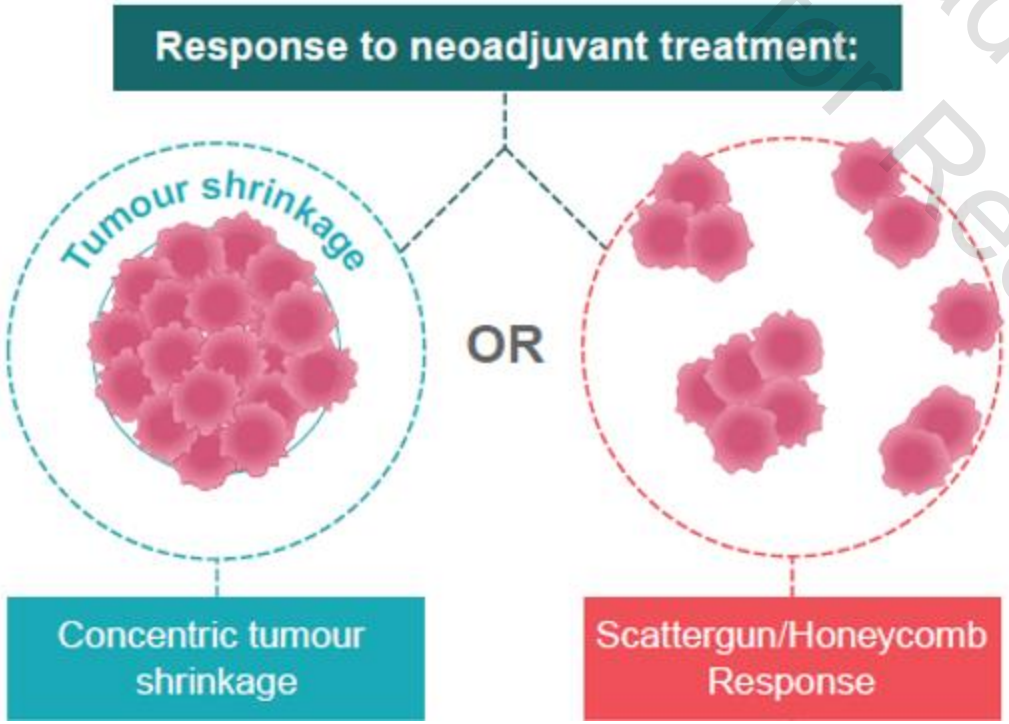
What the CTNeoBC meta-analysis tells us about pCR

- **pCR is a reliable prognostic marker**
  - Individual patients with pCR have superior outcomes
- **Definition matters: Eradication of invasive cancer from breast + nodes sufficient**
  - Residual DCIS not prognostically important
- **Subtype matters: Magnitude of difference in outcome between pCR+ and no pCR differs between subgroups**



Cortazar et al, Lancet 2014; 384: 164-72

Response to NACT is heterogeneous

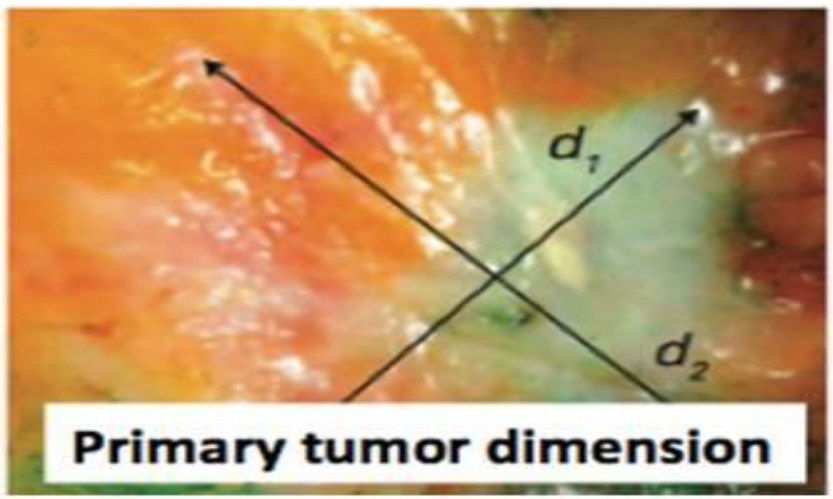


Traditional staging by TNM after NACT
(yp T, yp N)
doesn't represent prognosis well

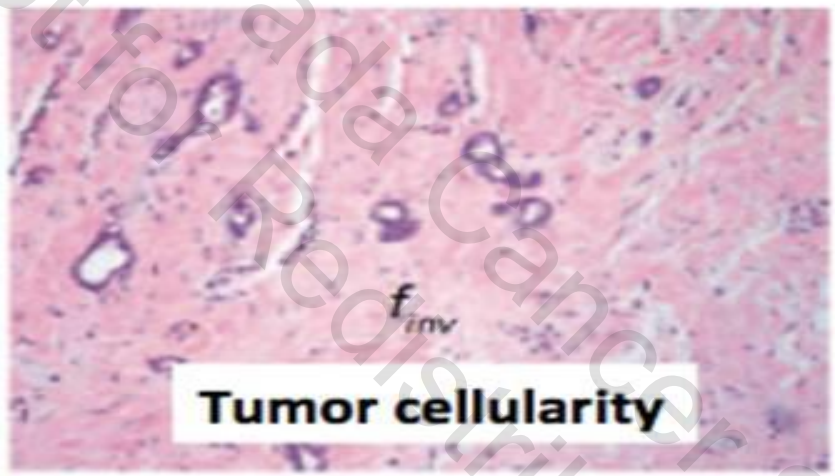
Can we do better to sort patients who need additional therapy?

Residual Cancer Burden (RCB) as an alternative neoadjuvant biomarker

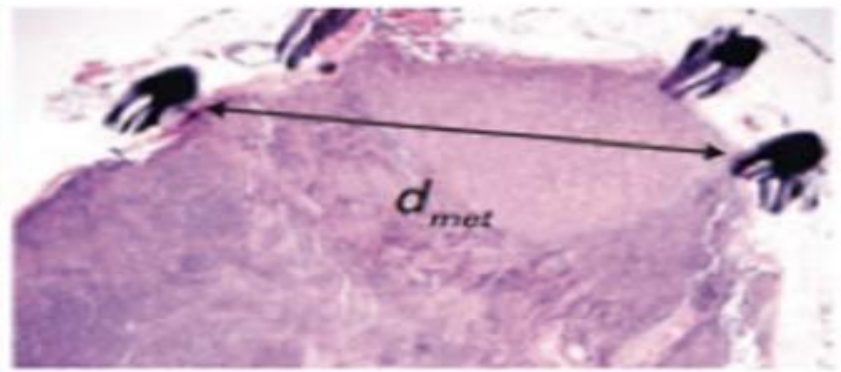
Method to quantify residual disease ranging from pathological complete response to extensive residual disease.



Primary tumor dimension



Tumor cellularity



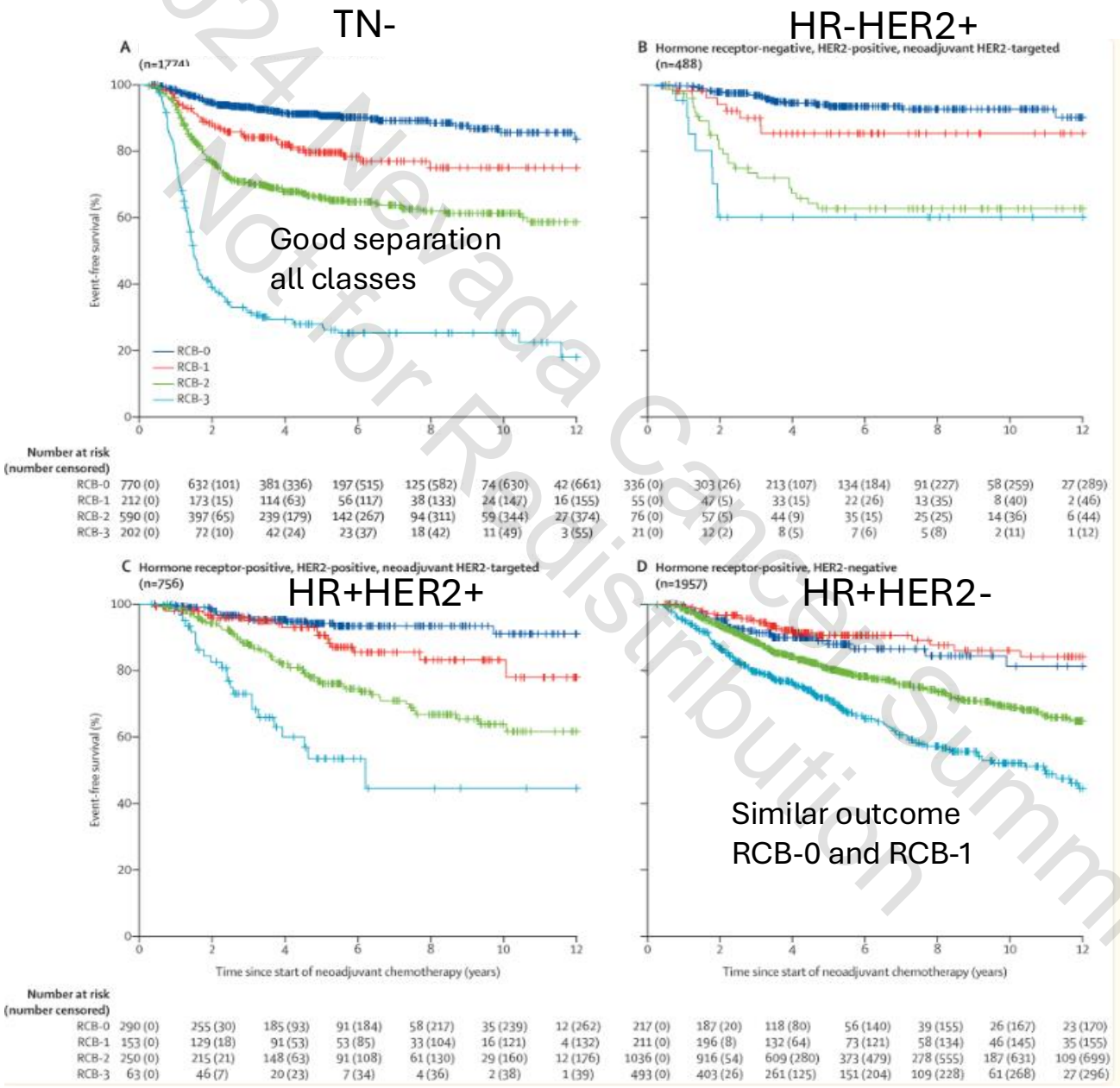
Size/number involved nodes

Highly reproducible:

- Concordance correlation coefficient = 0.931 (0.908–0.949).
- Overall accuracy = 0.989.
- Kappa coefficient for overall agreement = 0.583 (0.539–0.626).

Symmans et al. J Clin Oncol. 2007; Peintinger, Modern Pathology, 2015

RCB in 5161 patients: Prognosis varies by subtype



Yau, C et al. Lancet Onc 2022

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Neoadjuvant Chemotherapy for TNBC

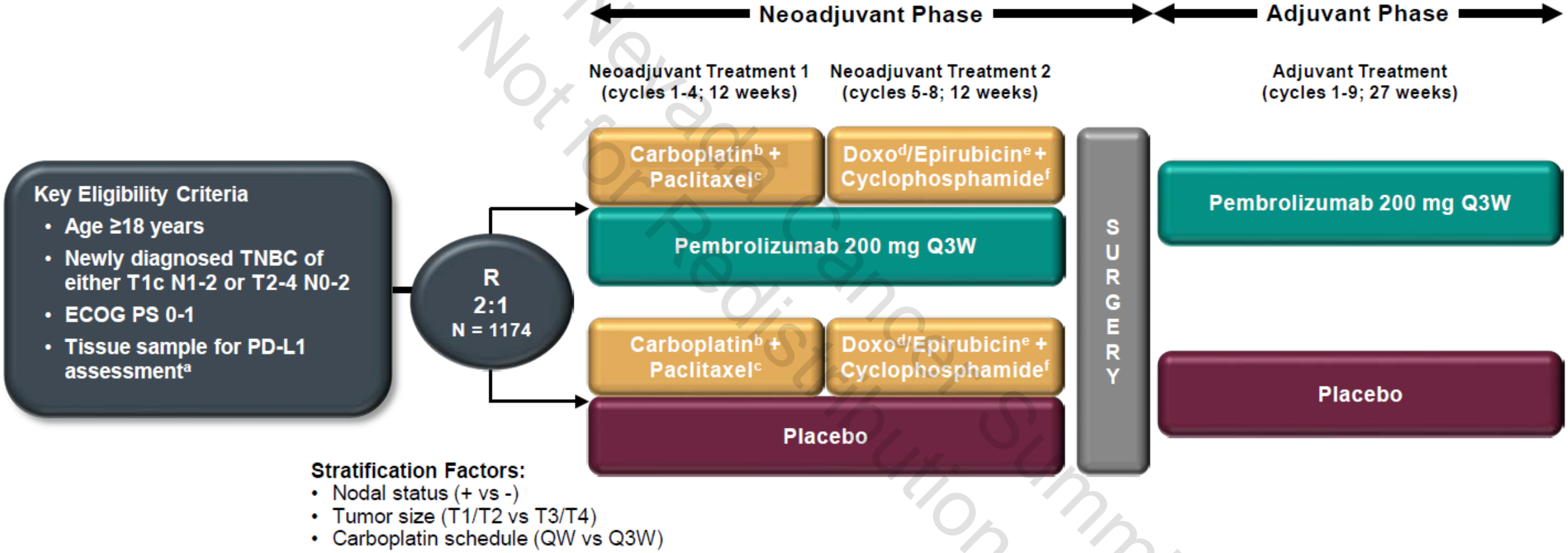
<u>No targeted therapies available</u>

- Anthracycline and Taxanes give best response
- Dose density
- Addition of carboplatin improves pCR and EFS

Recent advances

- TNBC is more immune-activated (increased TILs); implications for Immune therapy

KEYNOTE-522 Study Design (NCT03036488)



Stratification Factors:
- Nodal status (+ vs -)
- Tumor size (T1/T2 vs T3/T4)
- Carboplatin schedule (QW vs Q3W)

Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

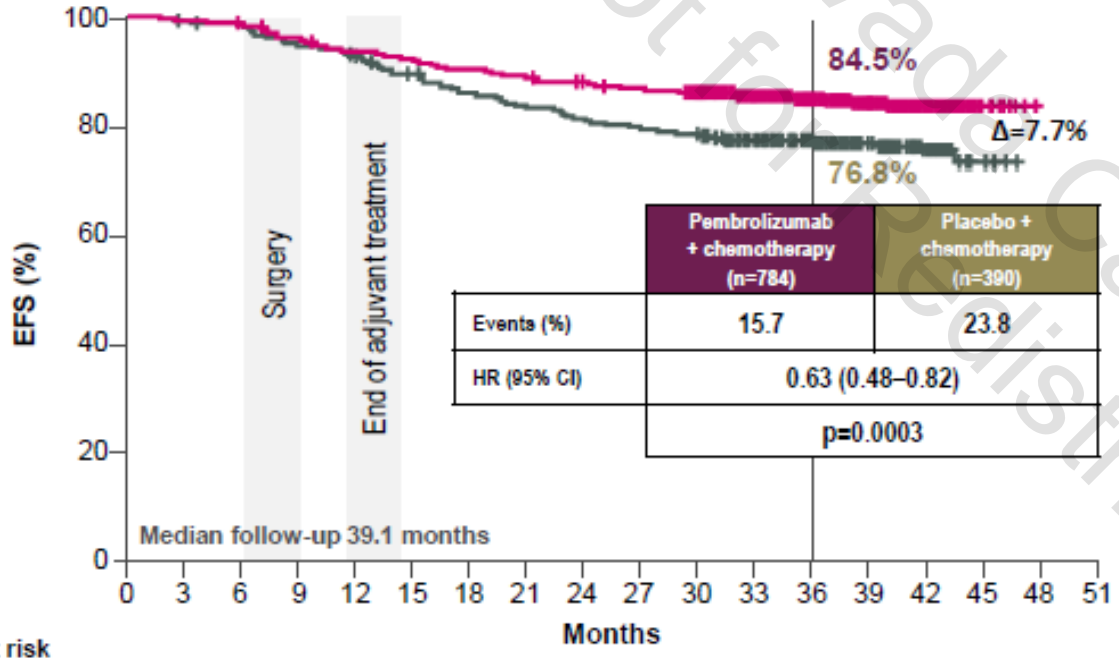
Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

Schmid P, ESMO Virtual Plenary 2021

KEYNOTE-522: EFS at IA4

KEYNOYTE-522[1] (IA4)
Pembrolizumab + CT vs placebo + CT in early TNBC

EFS in KEYNOTE-522 (IA4)[1]

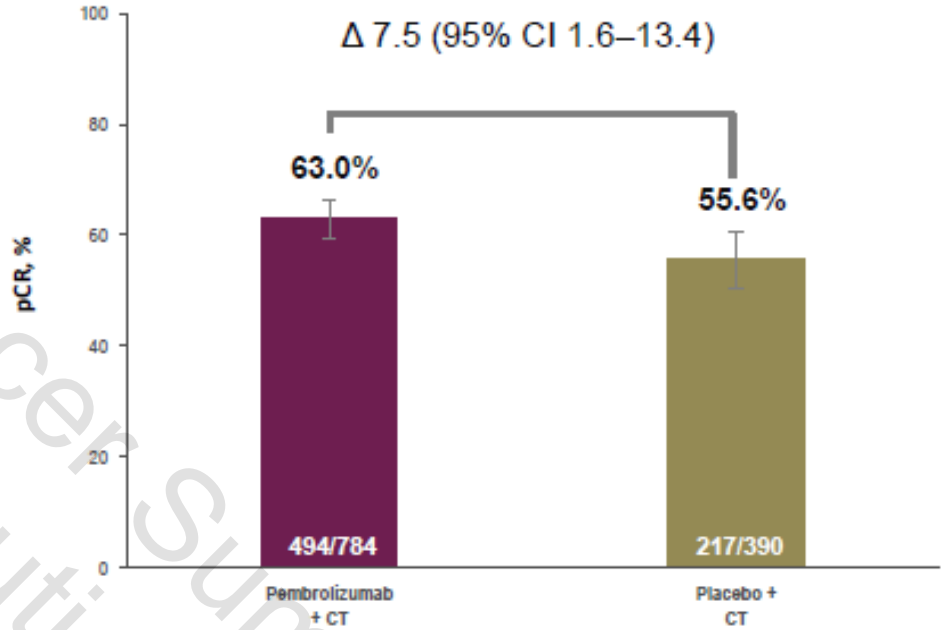


No. at risk

Pembrolizumab + CT	784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
Placebo + CT	390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

KEYNOYTE-522 (IA3)*[2]
Pembrolizumab + CT vs placebo + CT in early TNBC

pCR in KEYNOTE-522 (IA3)[2]

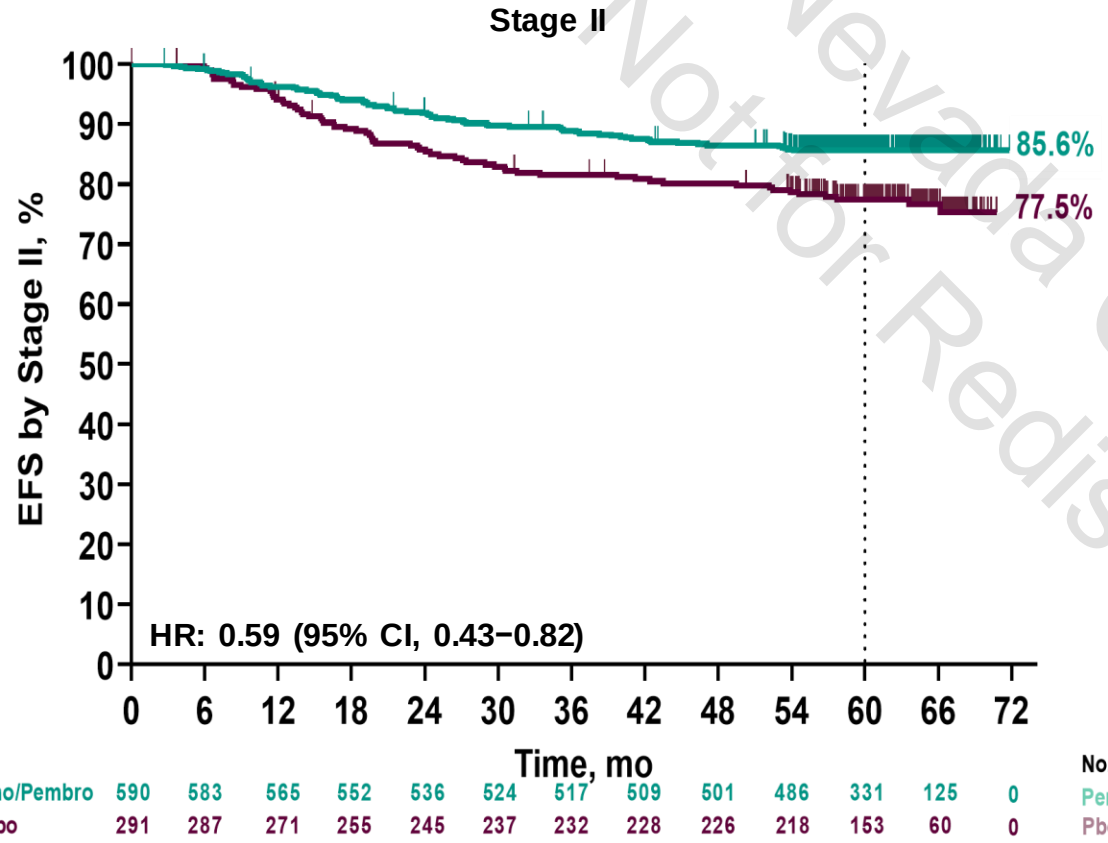


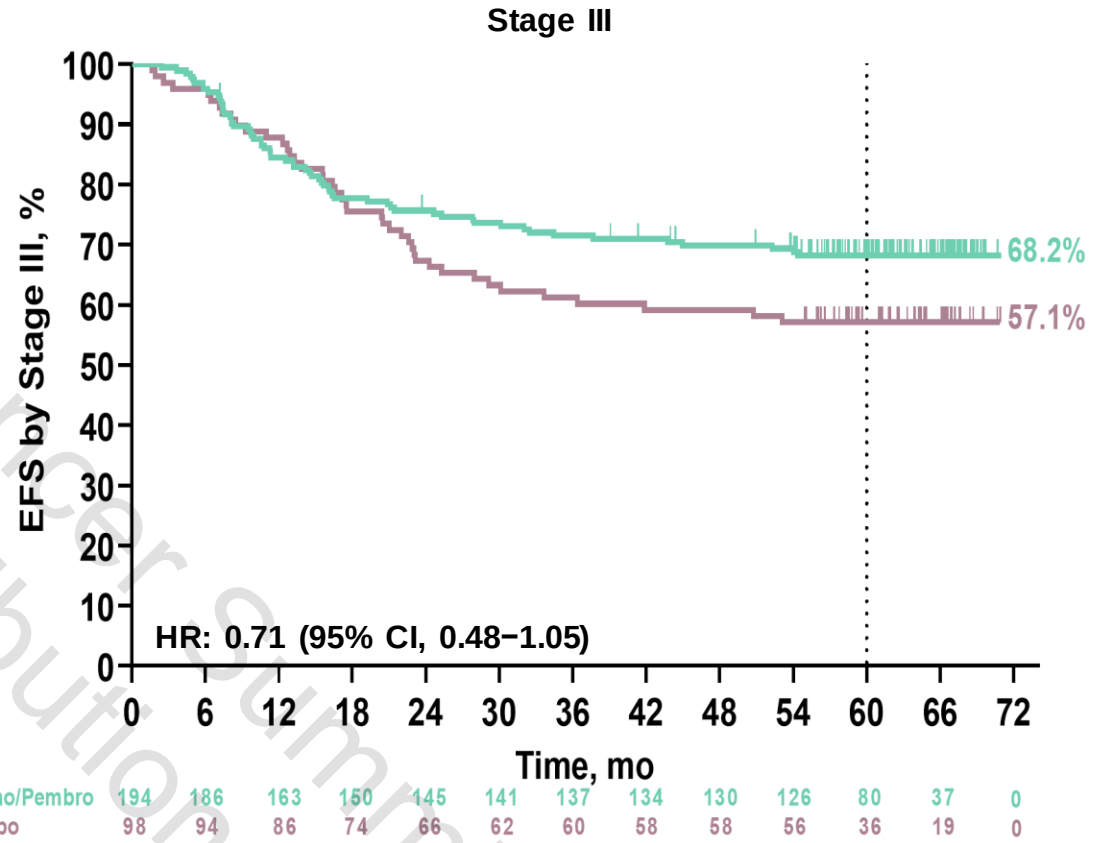
All 1174 participants in ITT
(Data cut-off date 23 March 2020, median follow-up 26 months)

1. Schmid P, et al. Presented at ESMO Virtual Plenaries; 15–16 July 2021. Abstract VP7-2021. 2. Schmid P et al. New Engl J Med 2022 3. Pembrolizumab ODAC Briefing Document For Public Release. BLA 125514 Supplement-089. February 2021.

LONG TERM FOLLOWUP OF KN-522

EFS at IA6 by Disease Stage

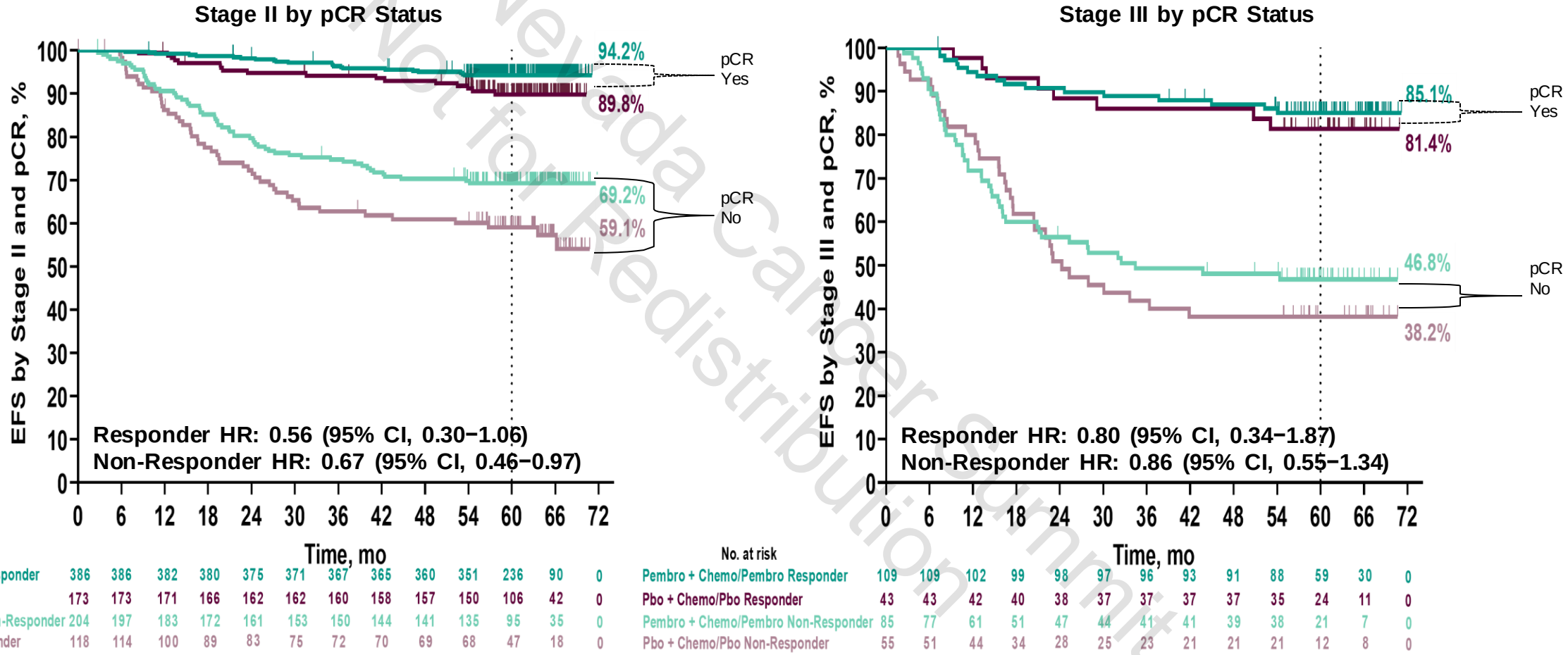




Data cutoff date of March 23, 2023.

LONG TERM FOLLOWUP OF KN-522

EFS at IA6 by Disease Stage in Patients With and Without pCR



Data cutoff date of March 23, 2023.

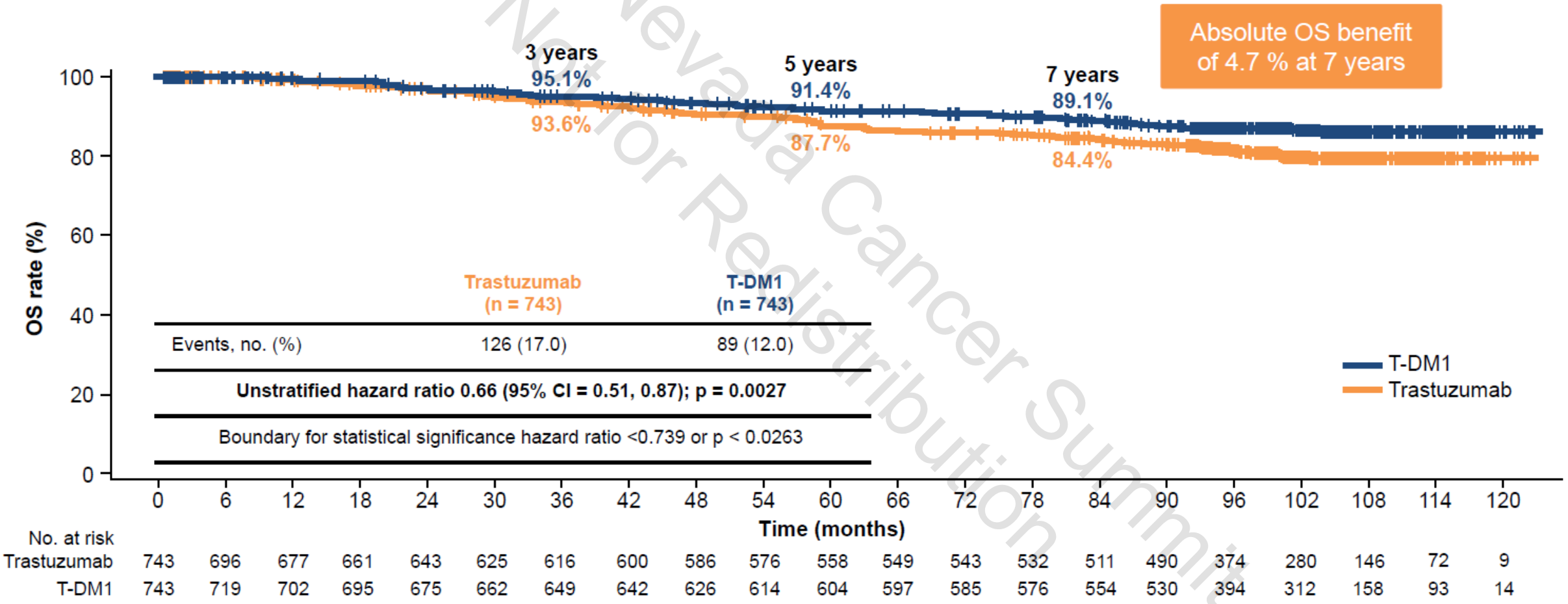
Neoadjuvant Therapy for HER2+ disease

- Anthracycline + taxane based chemotherapy
- Trastuzumab added significantly
- Pertuzumab added benefit (pCR and EFS) to chemo + trastuzumab
- Non-anthracycline regimens give equal results to anthracycline with less cardiac toxicity

Neoadjuvant Non-Anthracycline Taxane/Carbo-Based Regimens with trastuzumab +/- pertuzumab (N=895)

Regimen/ Study	N	tpCR
TCH x 6 **TRIO B07/Hurvitz, et al. Nature Comm 2020**	34	**47%**
TCHP x 6 **TRYPHAENA/Schneeweiss, et al. Ann Oncol 2013**	77	**64%**
TCHP x 6 **KRISTINE-TRIO-021/Hurvitz, et al. Lancet Oncol 2018**	221	**56%**
TCHP x 4 (in HR+ only) **NSABP B52/Rimawi, et al. Cancer Res 2016, SABCS S3-06**	155	***41%*** ***HR+ only***
Paclitaxel/Carbo/Trastuzumab/Pertuzumab x 9 **TRAIN-2/van Ramshorst et al. Lancet Oncol 2018**	206	**68%**
TCH x 6 **neoCARH/Gao, et al. ASCO 2020 Abs 585**	131	**56%**
TCHP x 6 **PHERGAIN/Perez-Garcia, et al. Lancet 2021**	71	**58%**

KATHERINE 2nd OS interim analysis; median follow-up 8.4 years (101 months)



Significant reduction in risk of death by 34% with T-DM1

Neoadjuvant therapy for HR+HER2- disease

- Grade 3
- Young (<40)
- At least T2N1
- Typically dose dense AC-T chemotherapy

- Some patients are candidates for Neoadjuvant endocrine therapy

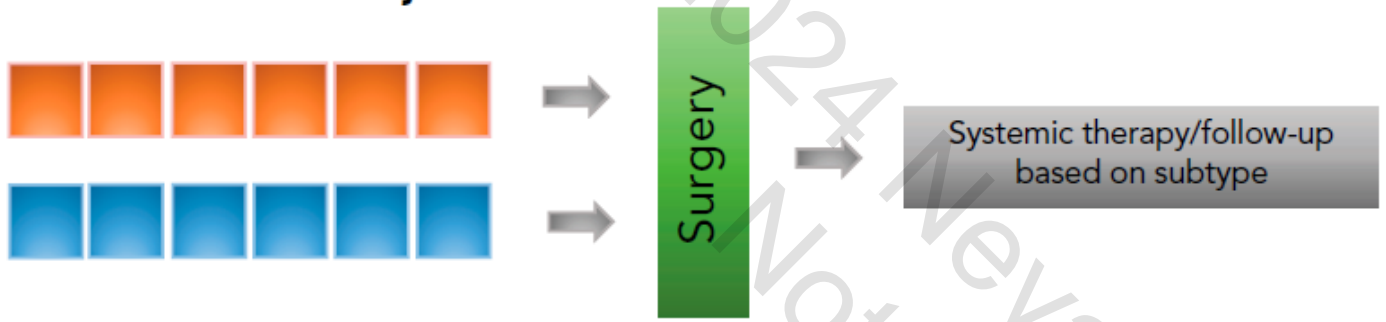
Adjuvant therapy after neoadjuvant therapy:

Varies by response to therapy

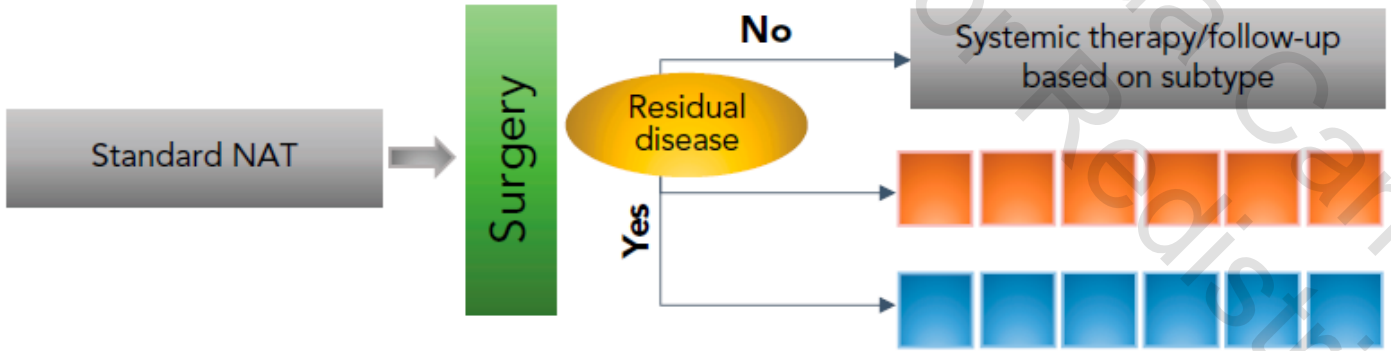
For non-pCR patients:

- HER2+: Additional anti-HER2 therapy (T-DM1)
- TNBC: Continue Pembro if by KN-522 +/-capecitabine
- HR+HER2-: Endocrine therapy + abemaciclib
- BRCA 1/2+: Olaparib

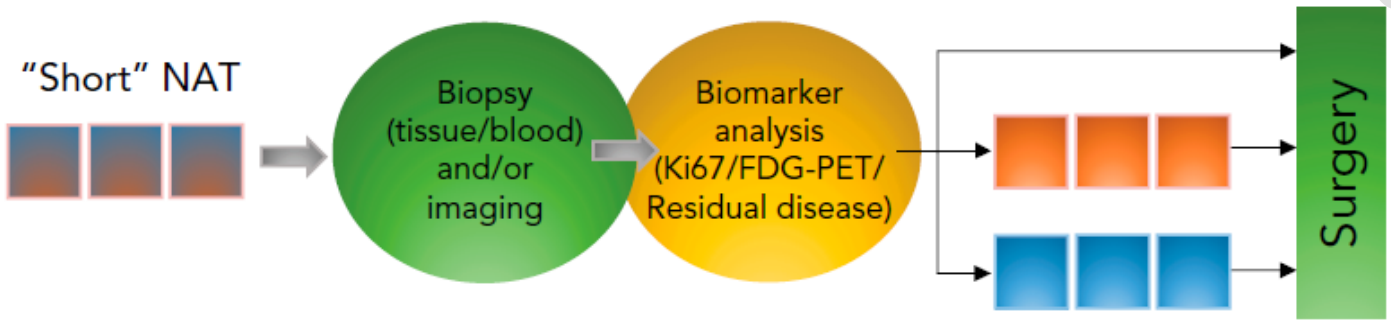
A. Traditional neoadjuvant trials



B. Postneoadjuvant/Residual disease trials (postsurgical adaptation)



C. Adaptive neoadjuvant trials (presurgical adaptation)

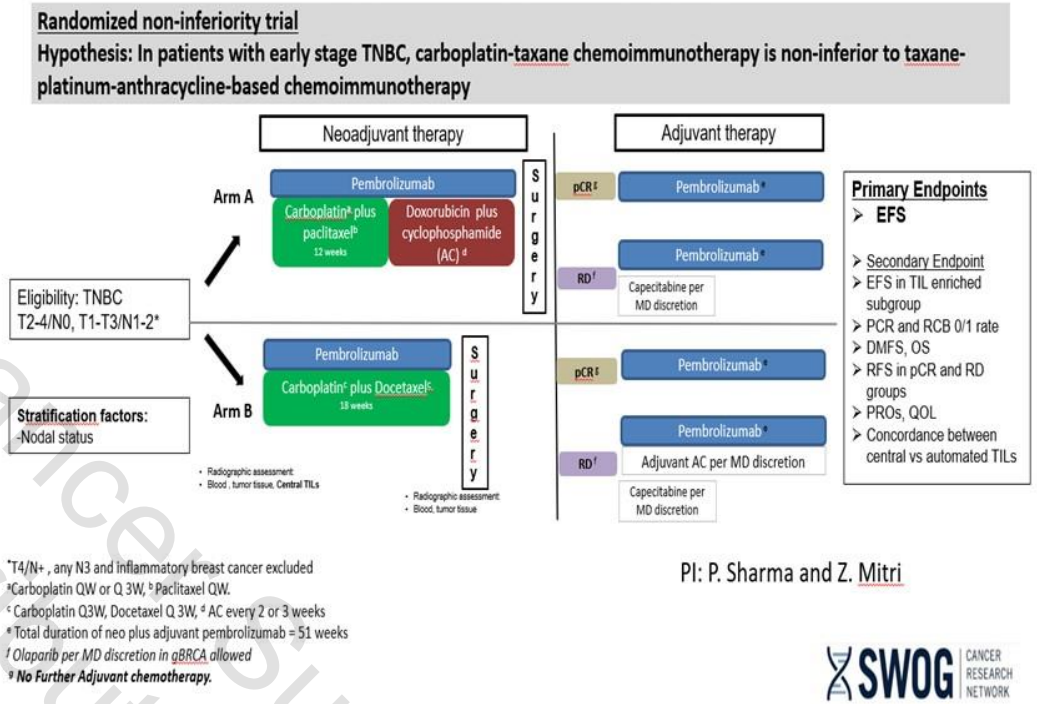


	Potential Benefits	Potential Limitations
A. Traditional neoadjuvant trials	• Downstaging of breast and axilla; reduced extent of surgery • Prognostic information (RCB/pCR)	• One-size-fits-all • Overtreatment (neoadjuvant) • Undertreatment (postneoadjuvant)
B. Postneoadjuvant/Residual disease trials (postsurgical adaptation)	• Improved prognosis for highest-risk patients (treatment escalation)	• One-size-fits-all (neoadjuvant) • Overtreatment (postneoadjuvant) • Increased toxicity and cost
C. Adaptive neoadjuvant trials (presurgical adaptation)	• Reduced toxicity for lower-risk patients (treatment de-escalation) • Predictive information • Biomarker evaluation	• Undertreatment (neoadjuvant) • Increased complexity

Neoadjuvant chemo-immunotherapy for TNBC Treatment optimization

- Treatment de-escalation: Do all patients need 4-drug poly-chemotherapy when immunotherapy is part of neoadjuvant systemic therapy?
  - I-SPY 2.2: Ongoing arms assessing novel agents/combinations to allow early de-escalation
  - Chemotherapy de-escalation: S2212 (SCARLET)
- Treatment escalation: Early identification of patients unlikely to achieve optimal response with standard neoadjuvant treatment
  - Tissue, Imaging +/- Machine learning/AI, Circulating biomarkers (ctDNA)
  - Neoadjuvant testing of novel more effective therapies
- Preferential immunotherapy response biomarkers

Shorter anthracycline-free Chemoimmunotherapy Adapted to pathological Response in Early TNBC (SCARLET)



*T4/N+ , any N3 and inflammatory breast cancer excluded
[a]Carboplatin QW or Q 3W, [b] Paclitaxel QW.
[c] Carboplatin Q3W, Docetaxel Q 3W, [d] AC every 2 or 3 weeks
[e] Total duration of neo plus adjuvant pembrolizumab = 51 weeks
[f] *Olaparib per MD discretion in gBRCA allowed*
[g] ***No Further Adjuvant chemotherapy.***

PI: P. Sharma and Z. Mitri

SWOG CANCER RESEARCH NETWORK

"True optimization is the revolutionary contribution of modern research to decision processes."
George Dantzig

Metastatic Breast Cancer

Incidence of Metastatic Breast Cancer

- 3%-6% of patients have MBC at the initial diagnosis of breast cancer in US

- 20% of patients with stage I to III at diagnosis will develop MBC (without systemic therapy)

Goals of Systemic Therapy in MBC

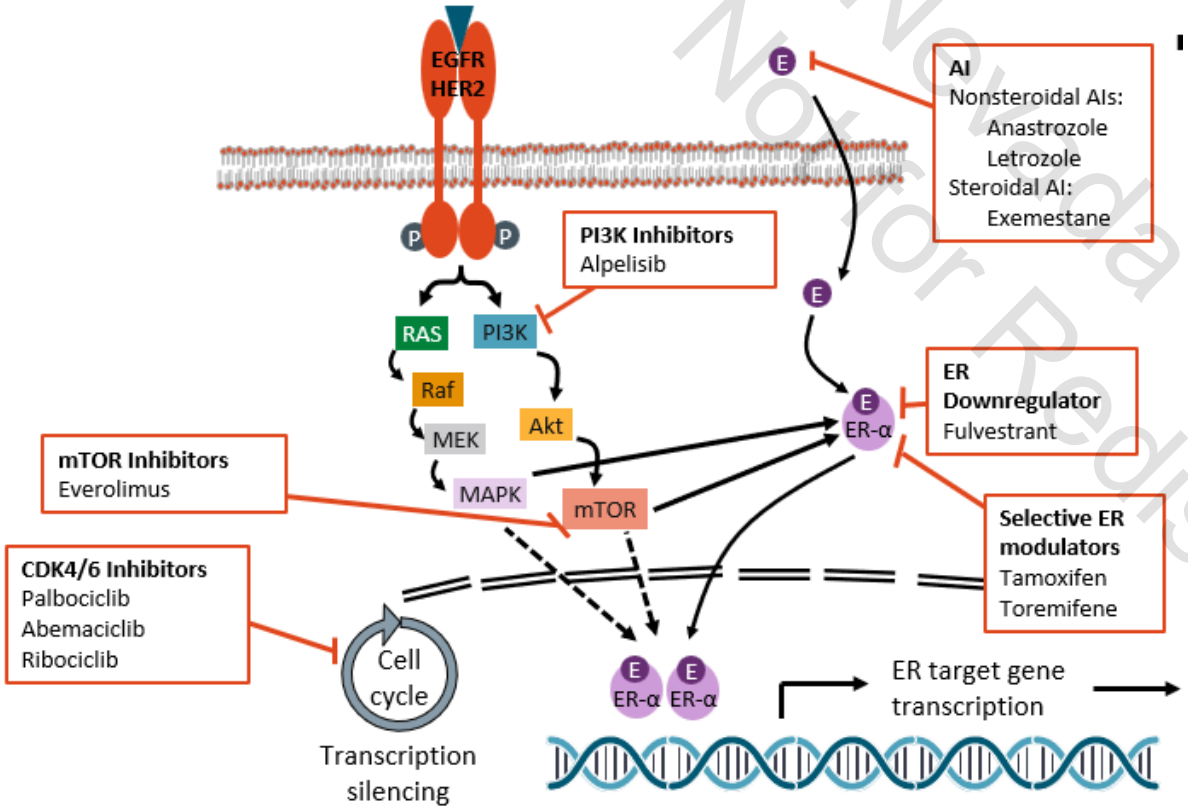
- Improve survival
- Delay time to disease progression
- Palliate symptoms
- Minimize toxicity of therapy

Individualized Management of MBC

Tumor biology (Subtype)	• Hormone receptor status (protein) • HER2 status (protein or gene)
Tumor aggressiveness	• Timing of relapse since primary diagnosis • Location of mets (visceral vs non-visceral) • Extent of metastatic spread (oligo vs polymets)
Prior adjuvant therapy	• Endocrine, biologic or chemotherapy • Combined treatments
Local and systemic approaches	• Oligometastatic disease • Surgery, radiofrequency ablation, stereotactic radiotherapy
Patient	• Preferences – scheduling issues • Symptoms • Co-morbidities

Individualize treatment to patient and tumor biology

What Is the Optimal Therapy for a Patient With Advanced HR+/HER2- Breast Cancer?

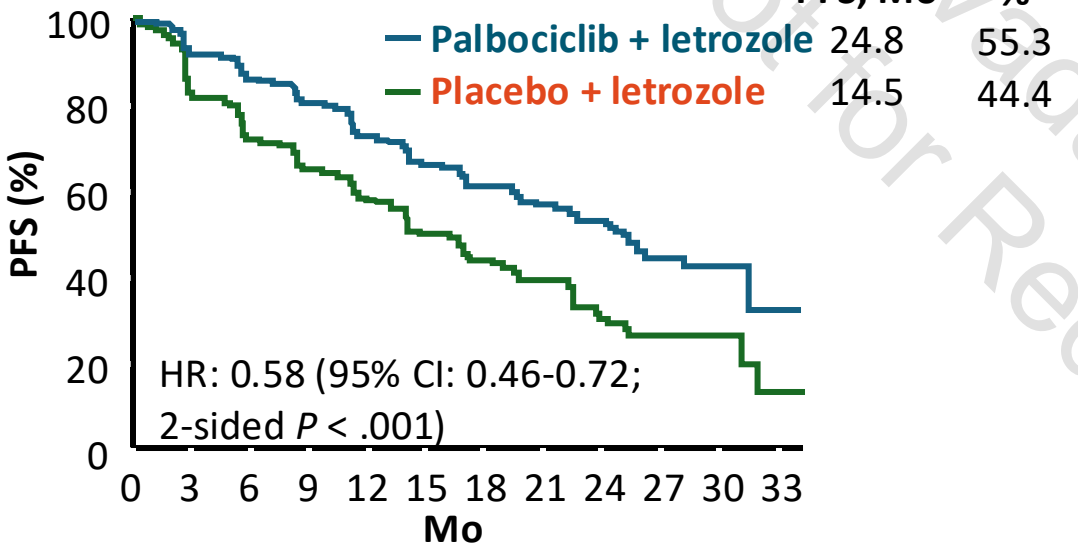


Brufsky. Oncologist. 2018;23:528. AlFakeeh. Curr Oncol. 2018;25:S18. Di Cosimo. Nat Rev Clin Oncol. 2010;7:139.

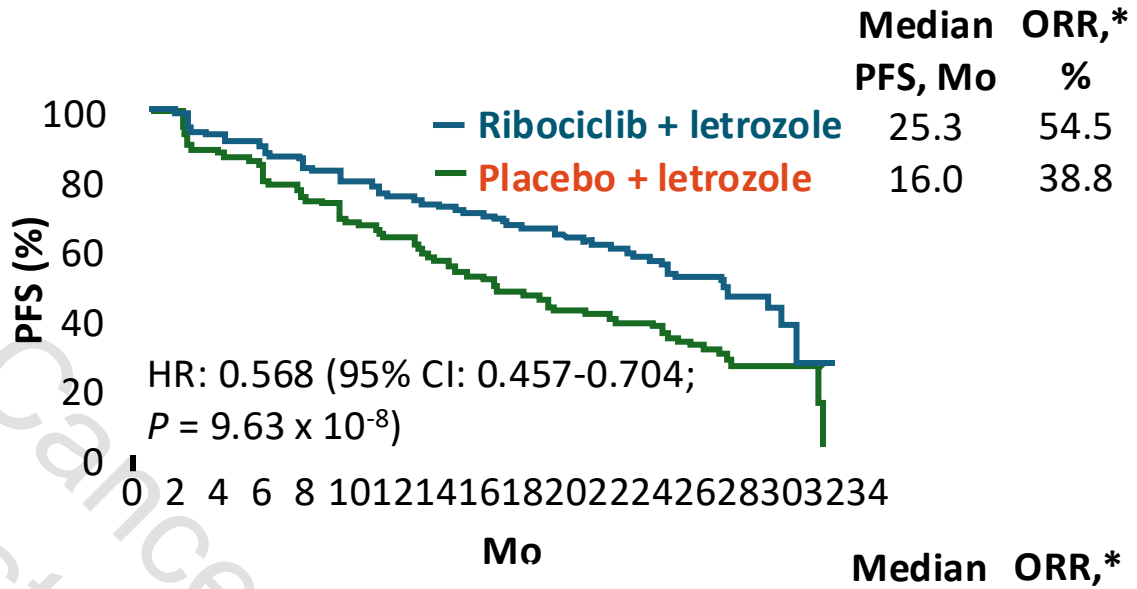
- Endocrine backbone: AIs or SERD (Fulvestrant) + OFS for premenopausal
- First line therapy-Endocrine Based
  - **Combination endocrine and CDK 4/6 inhibitor as first line therapy for most**
  - Premenopausal patients can receive above with OFS
- Second line therapy-Endocrine Based
  - Exemestane + Everolimus
  - Fulvestrant + Everolimus
  - IF PIK3CA mutated, Alpelisib + Fulvestrant
  - If PIK3CA, AKT or PTEN mutated, Capivasertib + Fulvestrant

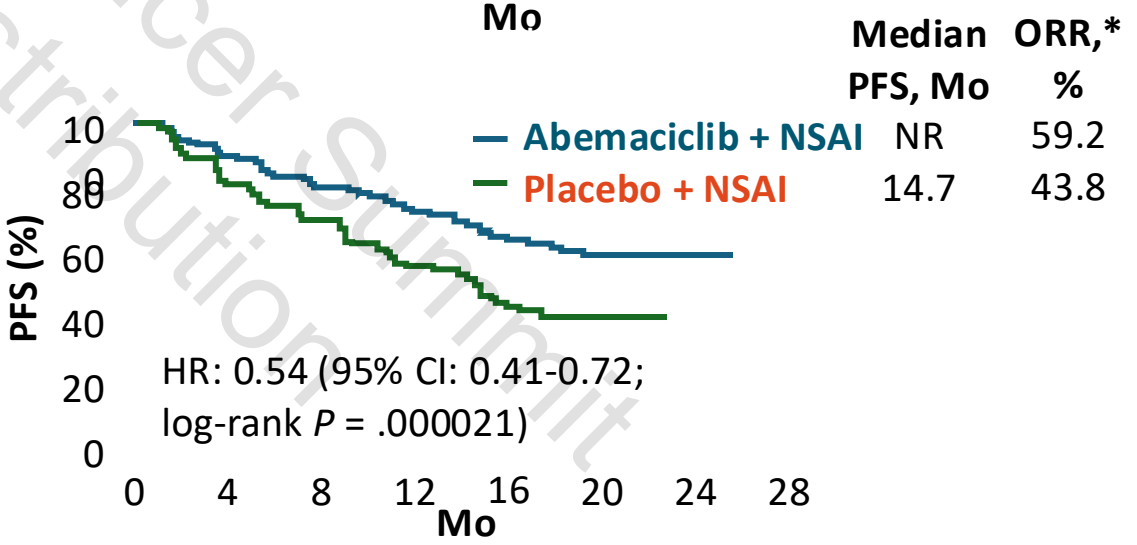
*OFS = ovarian function suppresion.

Trials of Frontline AI ± CDK4/6 Inhibitor in Advanced Postmenopausal Breast Cancer: PFS



Cross-trial comparisons have significant limitations
This information is presented in order to generate discussion, not to make direct comparisons between study results



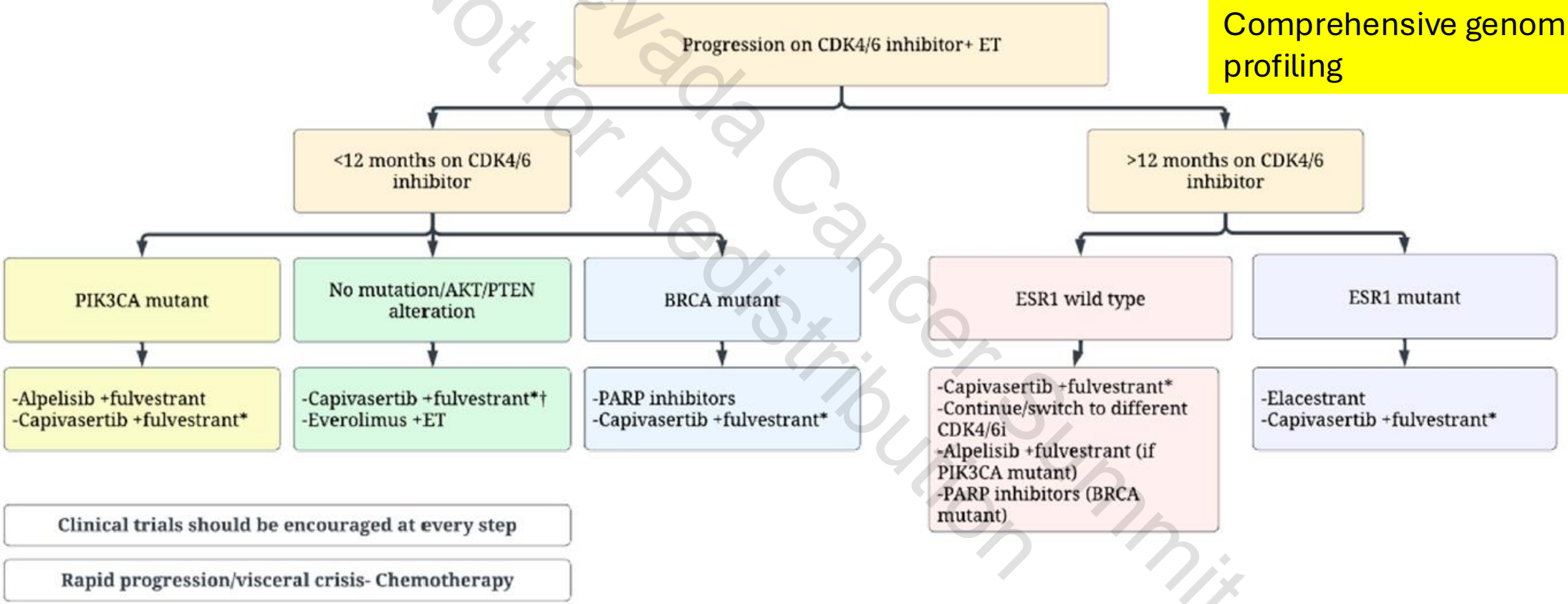


1. Finn. NEJM. 2016;375:1925. 2. Hortobagyi. Ann Oncol. 2018;29:1541.
3. Goetz. JCO. 2017;35:3638.

*ORR for patients with measurable disease.

HR+HER2- MBC: Continue endocrine/targeted therapies until fully resistant

All patients should have Comprehensive genomic profiling



Current NCCN guidelines for HR+HER2- MBC

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

HR-Positive and HER2-Negative with Visceral Crisis[†] or Endocrine Refractory		
Setting	**Subtype/Biomarker**	**Regimen**
First Line	No germline *BRCA1/2* mutation[b]	Systemic chemotherapy BINV-Q (5)
	Germline *BRCA1/2* mutation[b]	PARPi (olaparib, talazoparib)[c] (Category 1, preferred)
Second Line	HER2 IHC 1+ or 2+/ISH negative[d]	Fam-trastuzumab deruxtecan-nxki[e] (Category 1, preferred)
	Not a candidate for fam-trastuzumab deruxtecan-nxki	Sacituzumab govitecan[f] (Category 1, preferred)
		Systemic chemotherapy BINV-Q (5)
Third Line and beyond	Any	Systemic chemotherapy BINV-Q (5)
	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	Targeted agents BINV-Q (6)

[†] According to the 5th ESO-ESMO international consensus guidelines (Cardoso F, et al. Ann Oncol 2020;31:1623-1649) for advanced breast cancer visceral crisis is defined as: "severe organ dysfunction, as assessed by signs and symptoms, laboratory studies and rapid progression of disease. Visceral crisis is not the mere presence of visceral metastases but implies important organ compromise leading to a clinical indication for the most rapidly efficacious therapy."

NCCN Guidelines® Breast Cancer Version 2.2024

Current NCCN guidelines for TN MBC

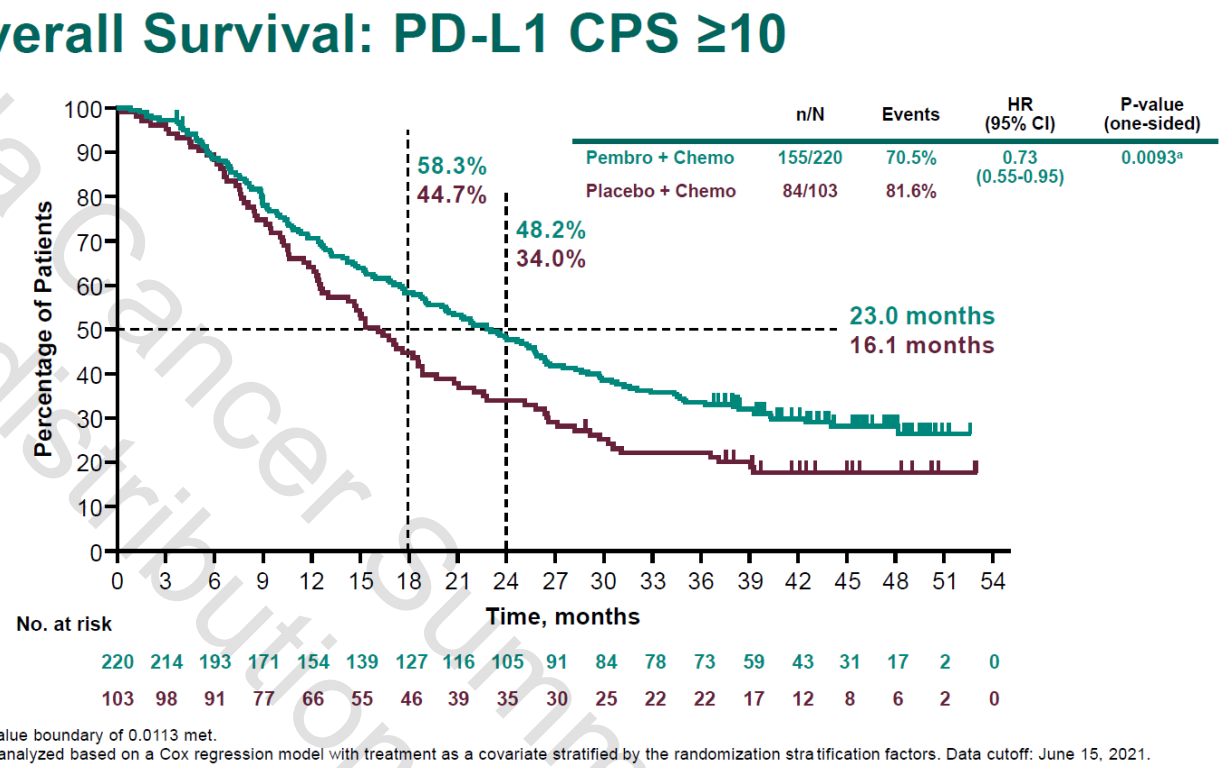
HR-Negative and HER2-Negative (Triple-Negative Breast Cancer; TNBC)		
Setting	**Subtype/Biomarker**	**Regimen**
First Line	PD-L1 CPS ≥10[g] regardless of germline *BRCA* mutation status[b]	Pembrolizumab + chemotherapy (albumin-bound paclitaxel, paclitaxel, or gemcitabine and carboplatin)[h] (Category 1, preferred)
	PD-L1 CPS <10[g] and no germline *BRCA1/2* mutation[b]	Systemic chemotherapy BINV-Q (5)
	PD-L1 CPS <10[g] and germline *BRCA1/2* mutation[b]	• PARPi (olaparib, talazoparib) (Category 1, preferred) • Platinum (cisplatin or carboplatin) (Category 1, preferred)
Second Line	Germline *BRCA1/2* mutation[b]	PARPi (olaparib, talazoparib) (Category 1, preferred)
	Any	Sacituzumab govitecan[i] (Category 1, preferred)
		Systemic chemotherapy BINV-Q (5)
	No germline *BRCA1/2* mutation[b] and HER2 IHC 1+ or 2+/ISH negative[d]	Fam-trastuzumab deruxtecan-nxki[e] (Category 1, preferred)
Third Line and beyond	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	Targeted agents BINV-Q (6)
	Any	Systemic chemotherapy BINV-Q (5)

NCCN Guidelines® Breast Cancer Version 2.2024

Immunotherapy in MBC: Currently restricted to TNBC with PD-L1 expression

40% of patients have PD-L1 CPS score of >/= 10

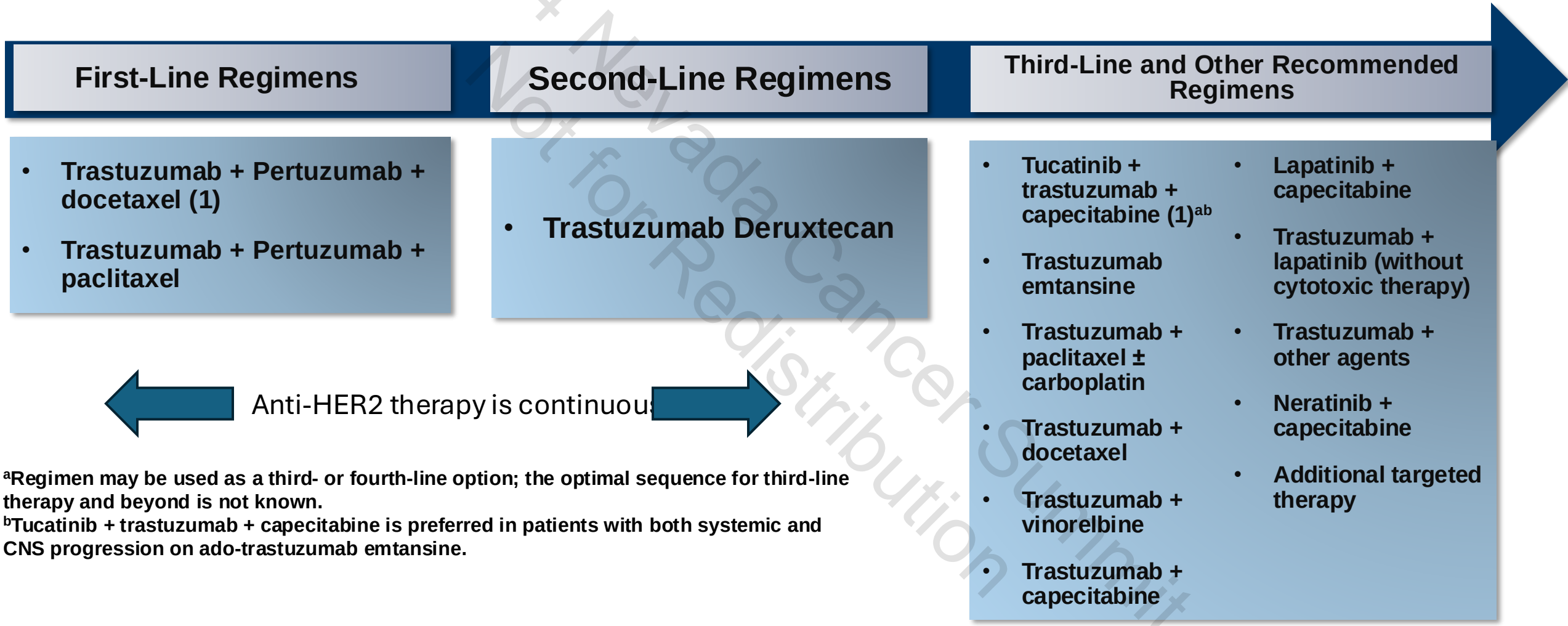
1st line MBC
TNBC (ER-PR-HER2-)
No prior IO
Chemotherapy +/- Pembrolizumab
All PD-L1 levels eligible



aPrespecified *P* value boundary of 0.0113 met.
Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff: June 15, 2021.

PD-L1 negative patients receive chemotherapy and antibody drug conjugates (ADCs)

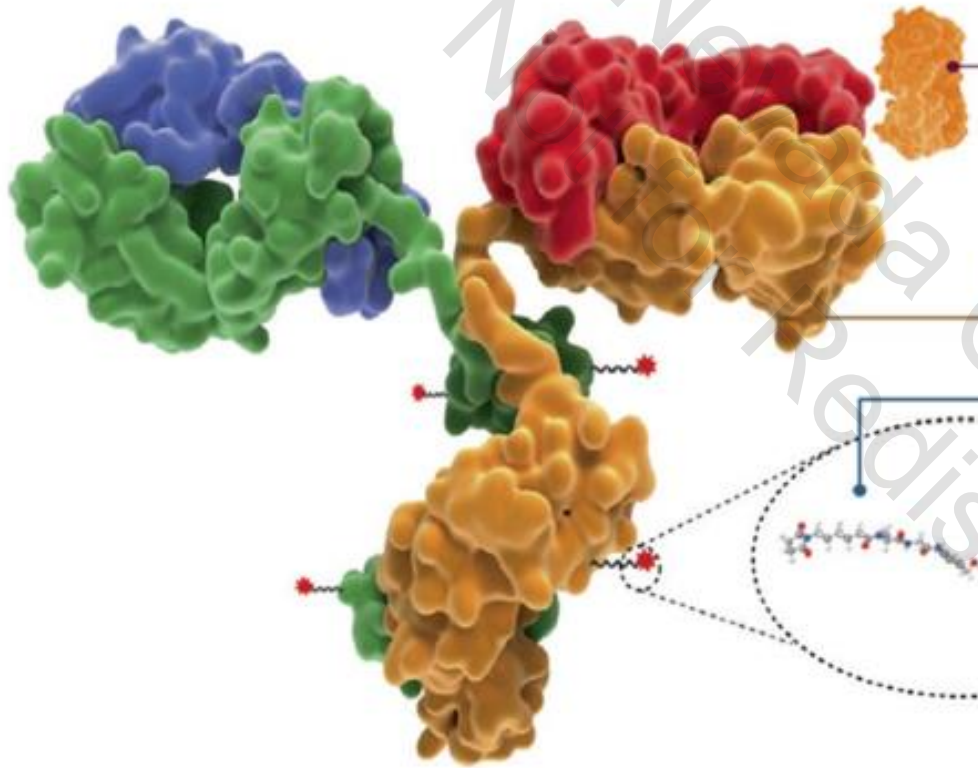
Systemic Therapy Options For HER2+Stage IV Disease NCCN Guidelines



[a]Regimen may be used as a third- or fourth-line option; the optimal sequence for third-line therapy and beyond is not known.
[b]Tucatinib + trastuzumab + capecitabine is preferred in patients with both systemic and CNS progression on ado-trastuzumab emtansine.

NCCN Clinical Practice Guidelines. Breast Cancer. 2022

ADC: Structure and Characteristics



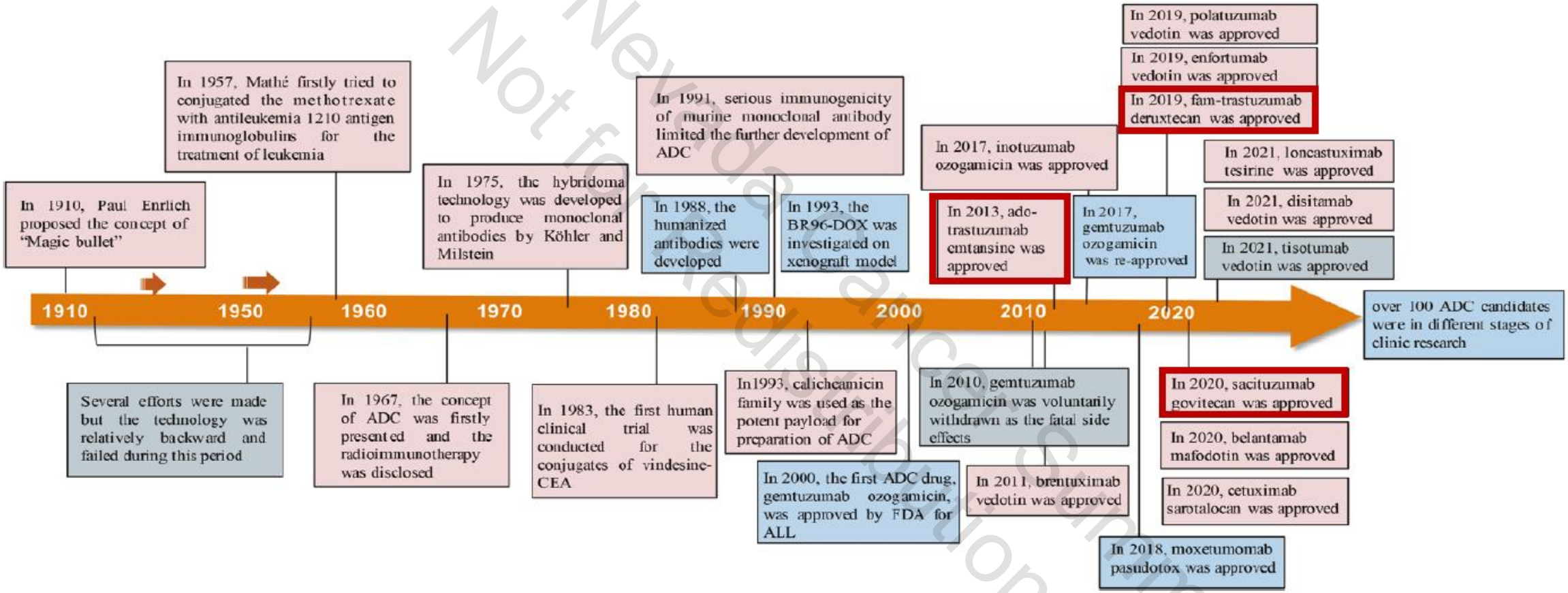
Key functions

Target antigen	Recognition of target cancer cells
Antibody	Guidance system for cytotoxic drugs
Linker	Bridge between antibody and drugs and to control the release of drugs inside cancer cells
Cytotoxic drug	Warhead for destroying cancer cells

Minor changes in ADC components
→ Major Changes in Therapeutic Index

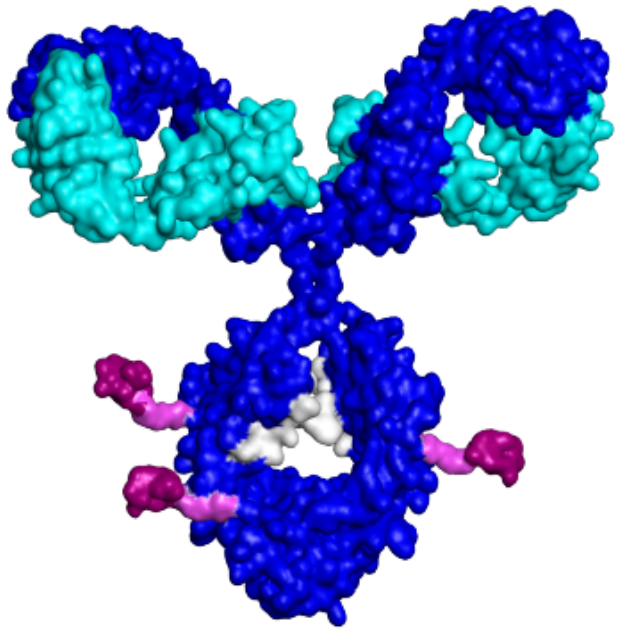
Fu Z et al. Signal transduction and Targeted therapy 2022

ADCs: Development and approval



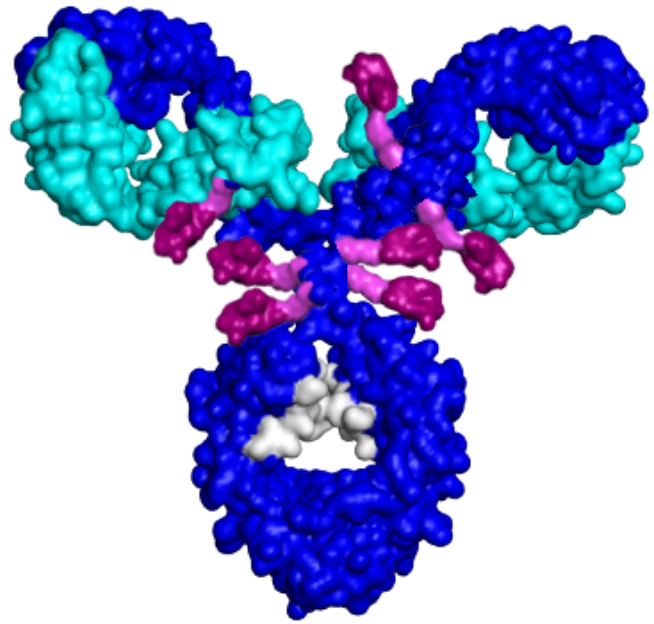
Chau el at. Lancet 2019; 394(10200)
Fu et al. Signal Transduction and Targeted Therapy 2022; 7(93)

T-DM1 versus T-DXd ADC characteristics



Trastuzumab Emtansine

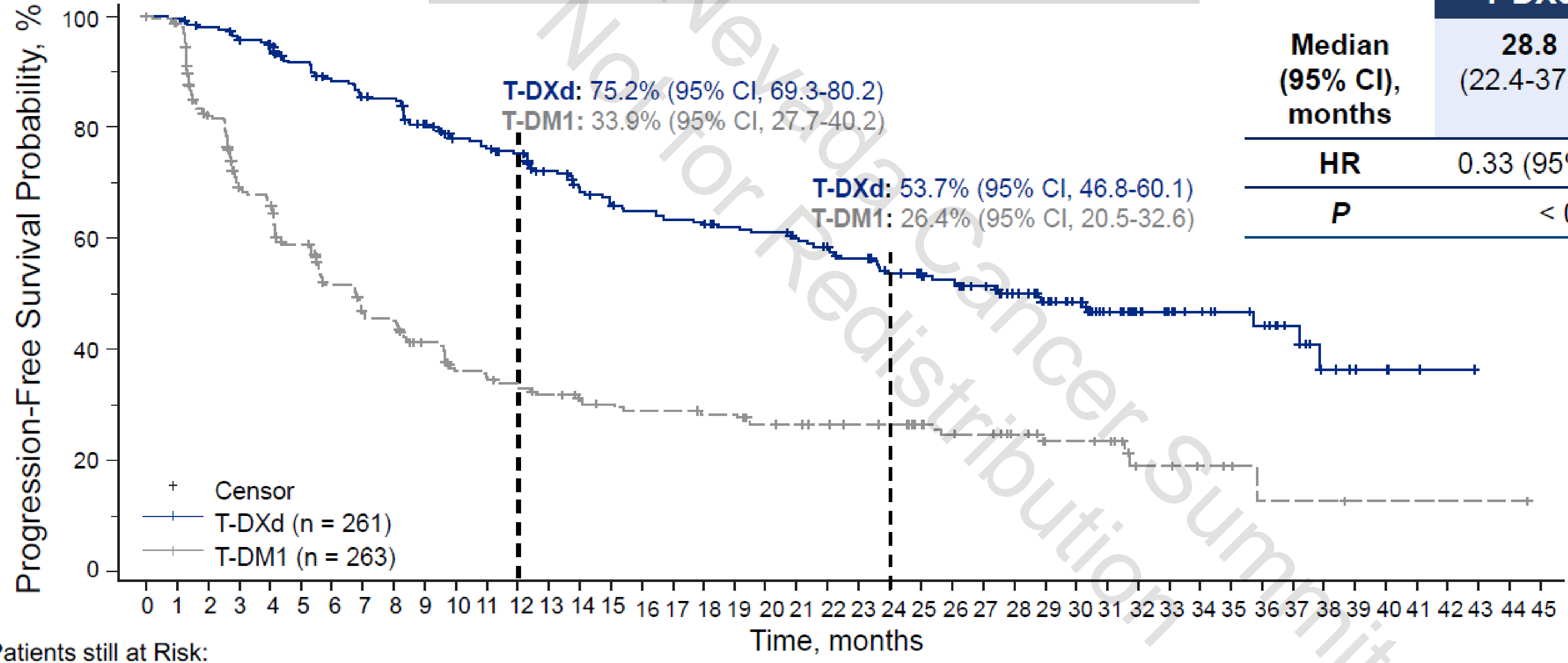
T-DM1[1–3]	ADC Attributes	T-DXd[2–5*]
Trastuzumab	Antibody	Trastuzumab
Emtansine	Payload	Deruxtecan
Anti-microtubule	Payload MoA	Topoisomerase I inhibitor
~3.5:1	Drug-to-antibody ratio	~8:1
No	Tumor-selective cleavable linker?	Yes
No	Evidence of bystander anti-tumor effect?	Yes



Trastuzumab Deruxtecan

DESTINY-B03: Updated Primary Endpoint –PFS by BICR

mPFS was ~4X longer for T-DXd compared with T-DM1



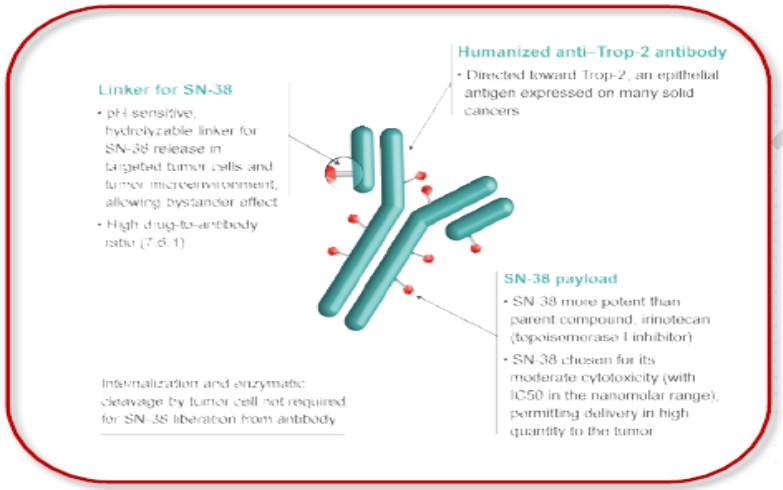
	T-DXd	T-DM1
Median (95% CI), months	**28.8** (22.4-37.9)	**6.8** (5.6-8.2)
HR	0.33 (95% CI, 0.26-0.43)	
P	< 0.000001[a,b]	

Patients still at Risk:

Time, months	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45
T-DXd	261	256	250	244	240	225	216	207	205	191	176	173	167	154	146	140	134	131	130	125	123	117	113	107	99	96	90	82	73	64	55	41	32	28	23	20	18	13	7	5	4	2	1	0		
T-DM1	263	253	201	164	156	134	111	99	96	81	69	67	63	58	54	51	49	49	47	47	42	41	39	37	36	32	28	27	22	19	15	14	8	7	6	4	2	2	2	1	1	1	1	1	1	0

Hurvitz S, et al SABCS 2022

ASCENT: A Phase 3 Study of Sacituzumab Govitecan in mTNBC



NCT02574455

Metastatic TNBC (per ASCO/CAP)

≥2 chemotherapies for advanced disease

[no upper limit; 1 of the required prior regimens could be from progression that occurred within a 12-month period after completion of (neo)adjuvant therapy)]

N=529

R 1:1

Sacituzumab Govitecan (SG)
10 mg/kg IV
days 1 & 8, every 21-day cycle
(n=267)

Treatment of Physician's Choice (TPC)*
(n=262)

Continue treatment until progression or unacceptable toxicity

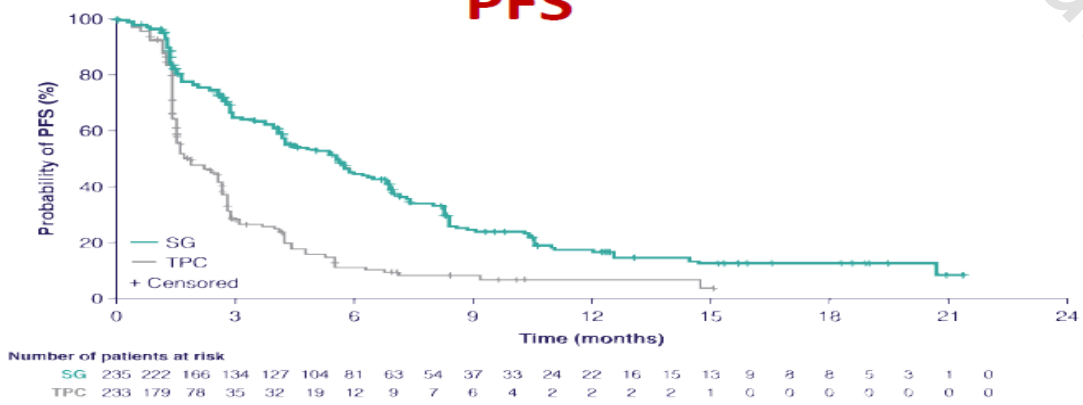
Endpoints

Primary
- PFS†

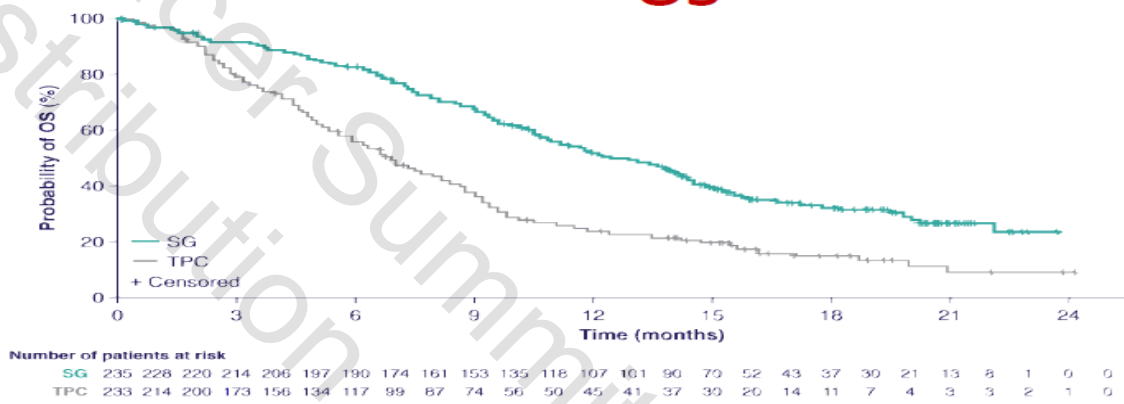
Secondary
- PFS for the full population‡
- OS, ORR, DOR, TTR, safety

Stratification factors
- Number of prior chemotherapies (2-3 vs >3)
- Geographic region (North America vs Europe)
- Presence/absence of known brain metastases (yes/no)

PFS



OS

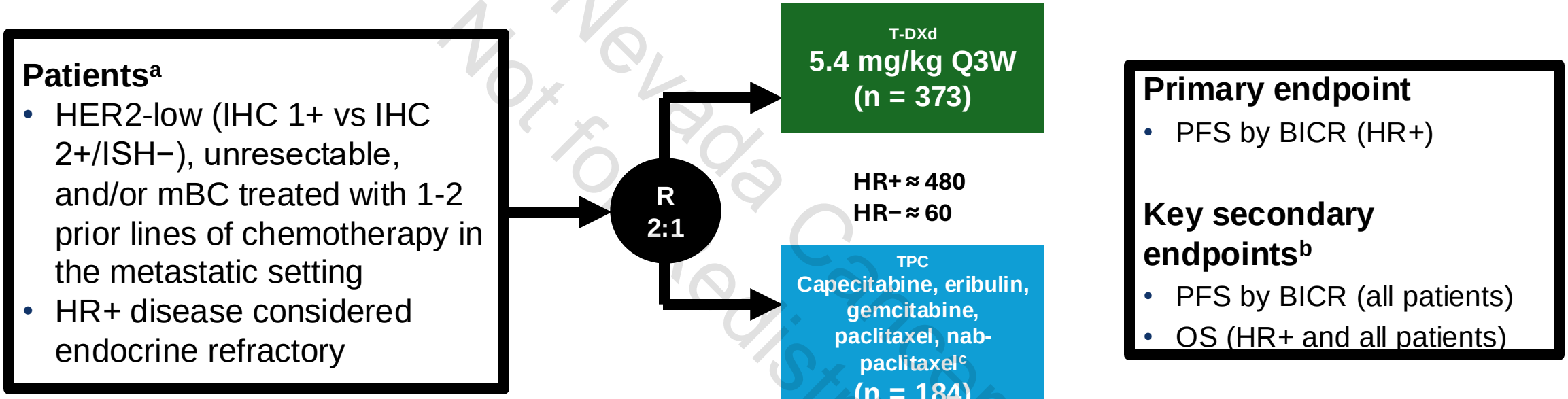


BICR Analysis	SG (n=235)	TPC (n=233)
No. of events	166	150
Median PFS—mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P*-value	**0.41** (0.32-0.52), ***P*<0.0001**	

	SG (n=235)	TPC (n=233)
No. of events	155	185
Median OS—mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P*-value	**0.48** (0.38-0.59), ***P*<0.0001**	

DESTINY-Breast04: First Randomized Phase 3 Study of T-DXd for HER2-low mBC

An open-label, multicenter study (NCT03734029)

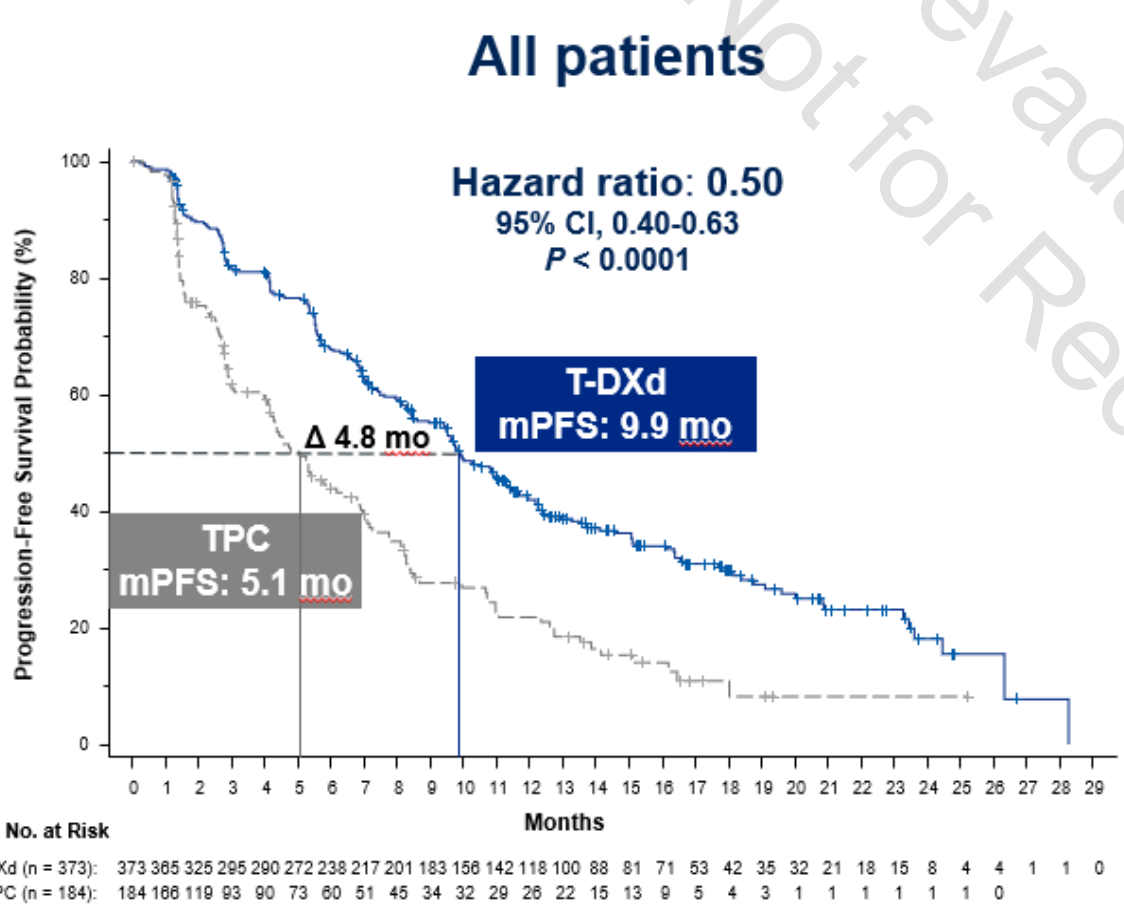


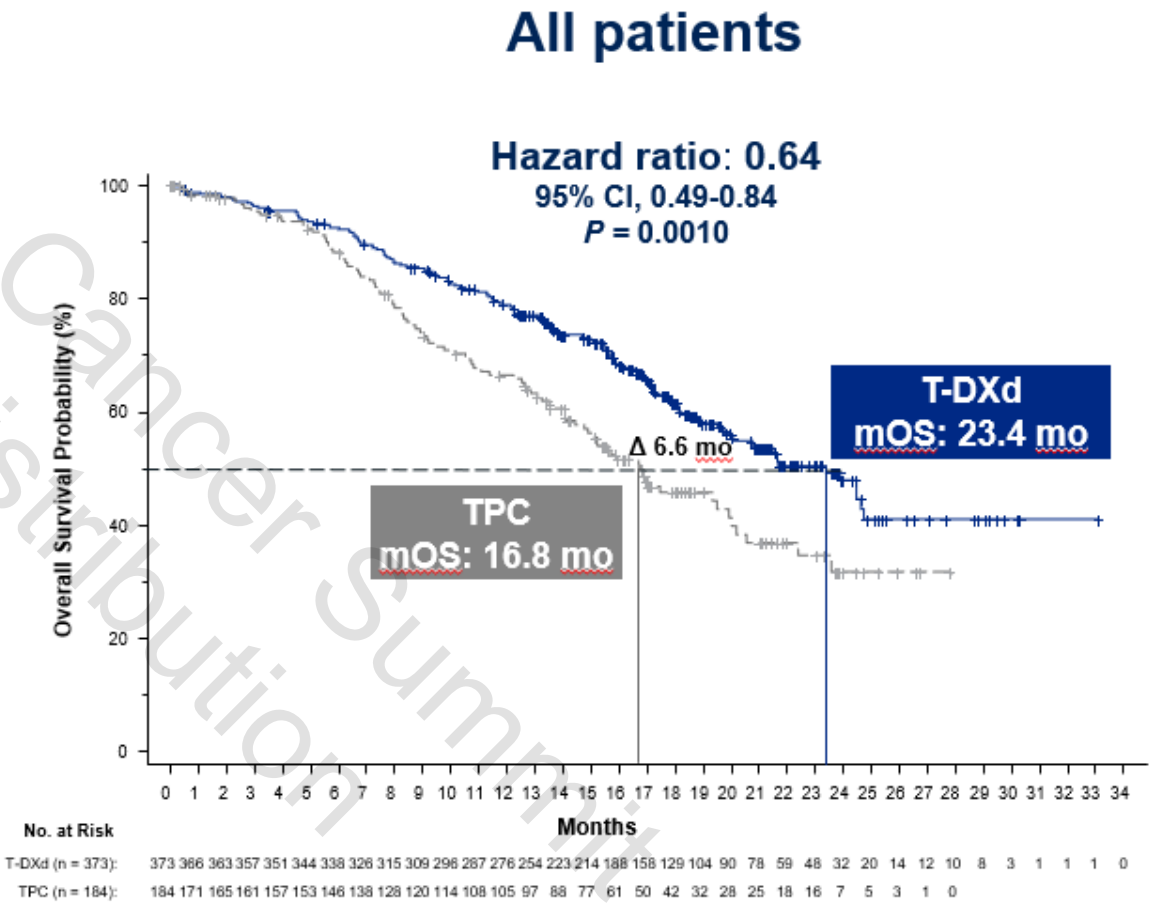
Stratification factors

- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK, cyclin-dependent kinase; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; efficacy in the HR− cohort was an exploratory endpoint. [c]TPC was administered accordingly to the label. [d]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only [IUO] Assay system.

T-DXd vs. chemo after 1st line HER2-low





ADCs have transformed chemotherapy delivery for MBC- and will continue to:

- Moving into first line
- Multiple new agents and payloads
- Bispecifics

Multimodality Therapy of MBC

- Bone targeted agents
  - Adjunct to cancer directed therapy
  - Reduce skeletal related events (fractures, need for radiation and surgery, pain)
  - Bisphosphonates (zoledronic acid) or RANK-ligand inhibitor (denosumab)
  - Typically initiated monthly
- Radiation
    - To painful/symptomatic lesions
- Surgery
  - Do not do mastectomy in de novo stage IV patients
  - Selected use in other circumstances

Outcomes for MBC by subtype: 2024

- HER2+ Disease: Median OS >7 years
- HR+/HER2- Disease: Median OS >6 years
- TNBC: Median OS 2-2.5 years

MBC is now a chronic disease: Ongoing efforts to prolong survival while reducing toxicity so patients can enjoy as normal a life as possible

Thank You!