Follow-up of Persons with Breast Cancer

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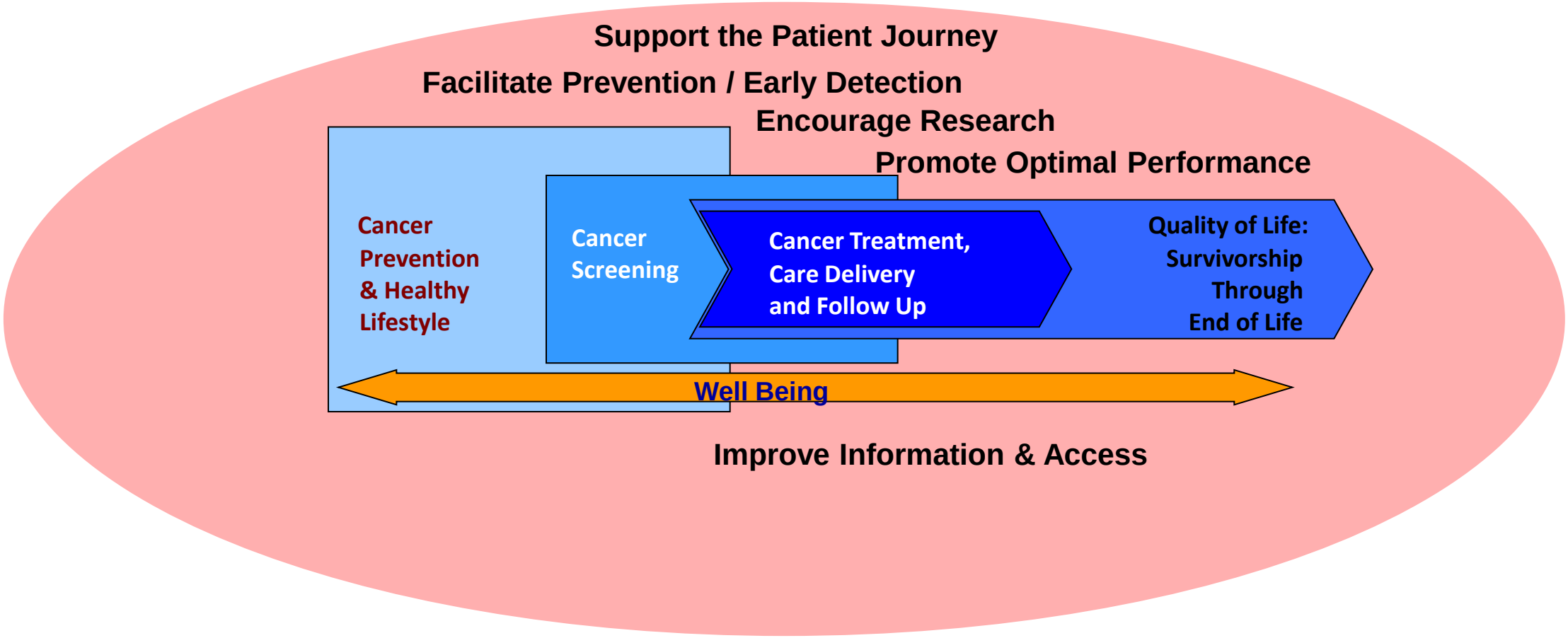
COI

- Advisory Boards
  - Pfizer, Novartis, Astra Zeneca, Lilly, Merck, Gilead,
- Research Funding
  - Pfizer, AstraZeneca
- Other
  - CBCN board, RETHINK breast cancer board

Spectrum of Treatment for the Patient



What are the Goals of Follow-up for Early Breast Cancer

- Provide care for both physical and psychological symptoms that are the result of cancer care
- Diagnose curable disease early so it can be treated for cure
- Diagnose advanced disease early to avoid symptoms/maintain QoL
- ? Diagnose advanced disease early to cure????
- Enhance adherence/compliance with adjuvant medications
- Promote prevention and health including bone, sexual, psychological, cardiac health, neurological health

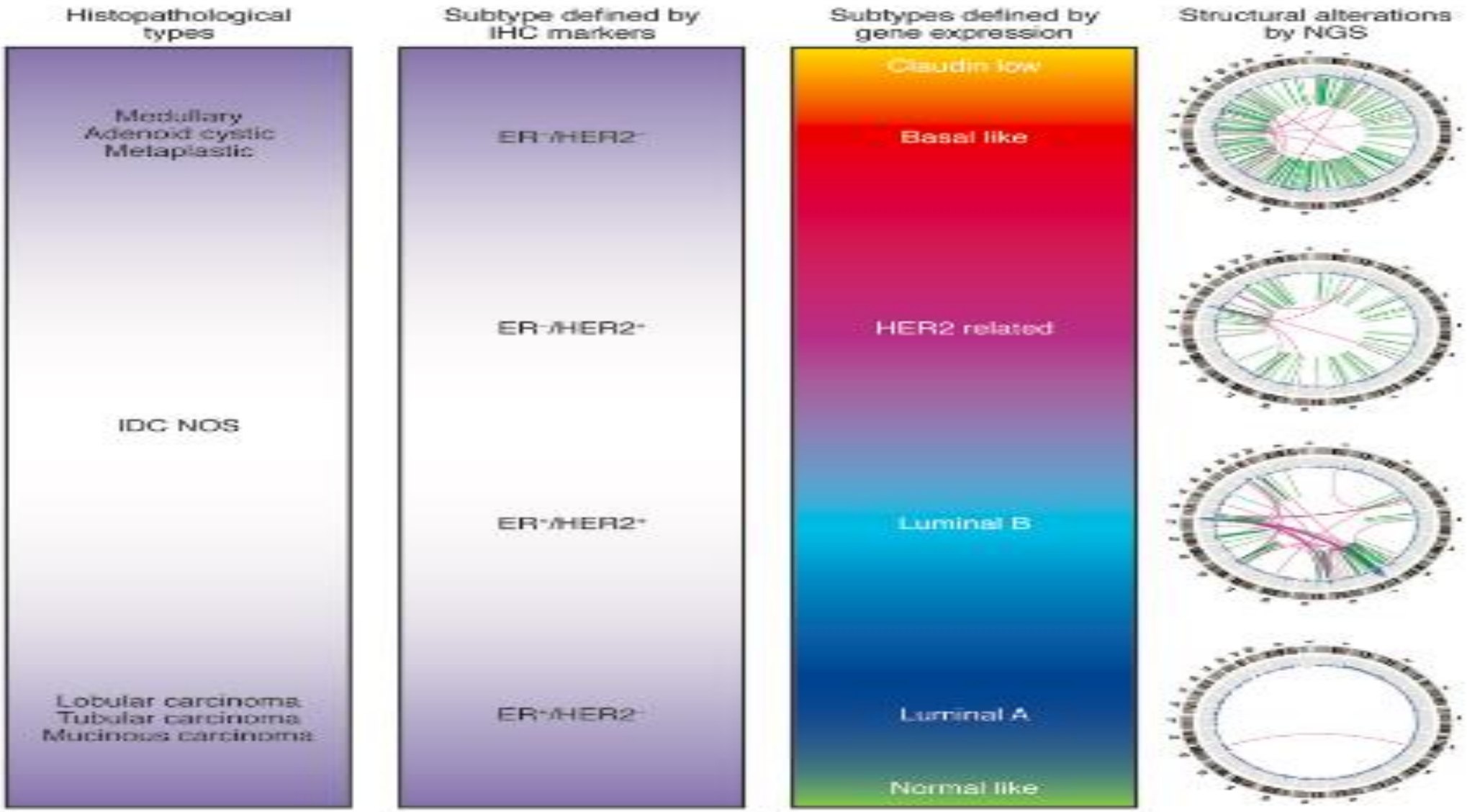
Risk of Breast Cancer Recurrence

- A. Breast cancer can recur locally or diffusely but only in the first 5 years after diagnosis
- B. Breast cancer recurs locally only in the first 5 years and can recur anywhere in the body at any time
- C. The timing and risk of breast cancer recurrence is related to the type of breast cancer that the person had
- D. All breast cancer recurrences are incurable
- E. A and D
- F. None of these are correct

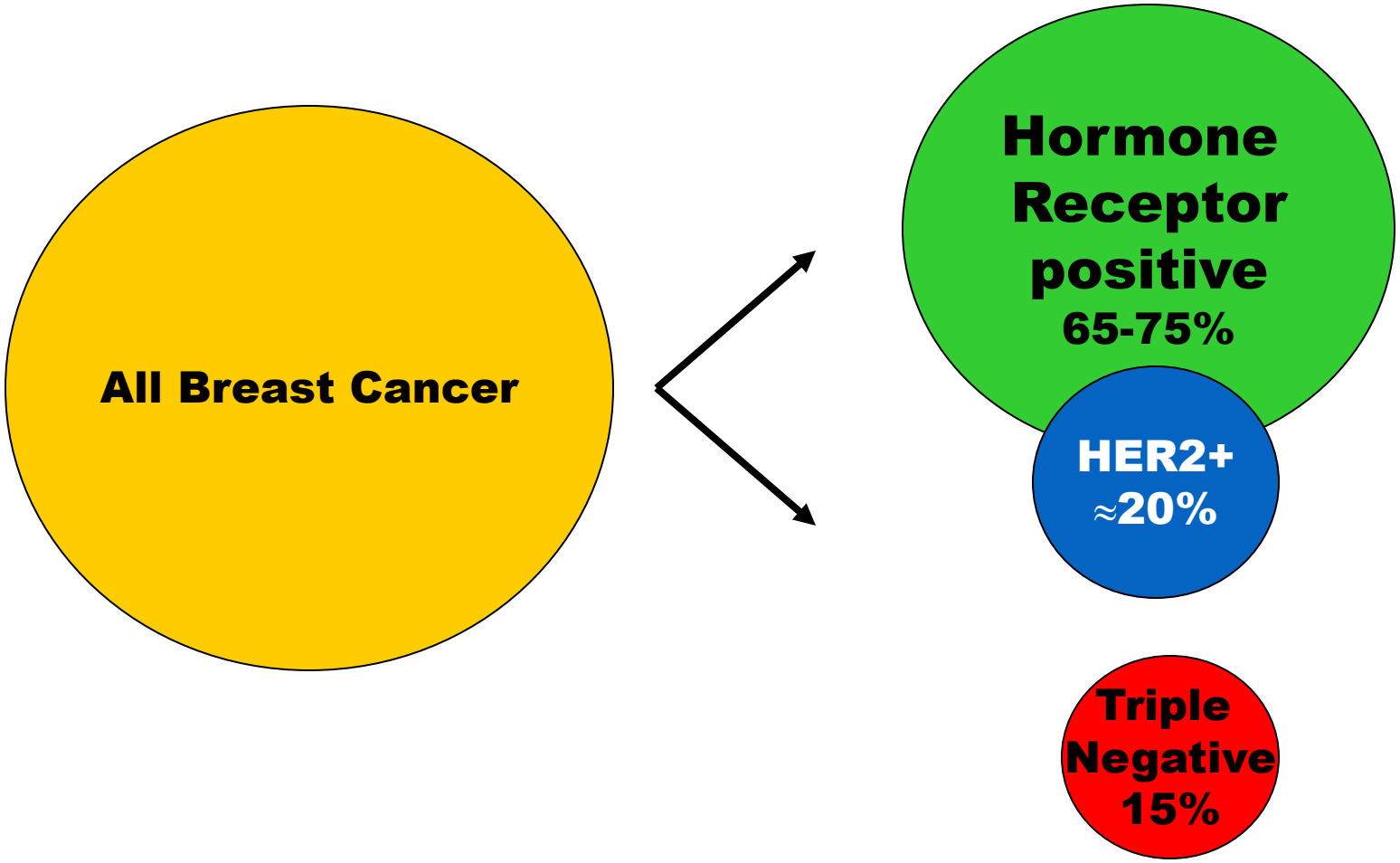
Cancer Properties

- Cancers grow
- Cancers can travel (metastasize) through the blood and/or lymphatic system
- Cancers have both prognostic and predictive features
  - Prognostic – features that predict behaviour
  - Predictive – features that predict response

Breast Cancer Classification



Russnes et al. JCI 2011


All Breast Cancer
Hormone Receptor positive
65-75%
HER2+
≈20%
Triple Negative
15%

Treatment of Early Breast Cancer is Estimating the Risk of Relapse and Response to Treatment

Prognostic Features

What is the risk of relapse?. DFS/OS?
How to Decrease relapse to improve survival
HOW aggressive =**BIOLOGY**
HOW much cancer = **ARCHITECTURE**
(size and nodes)

Predictive Factors

Will the tumour respond?

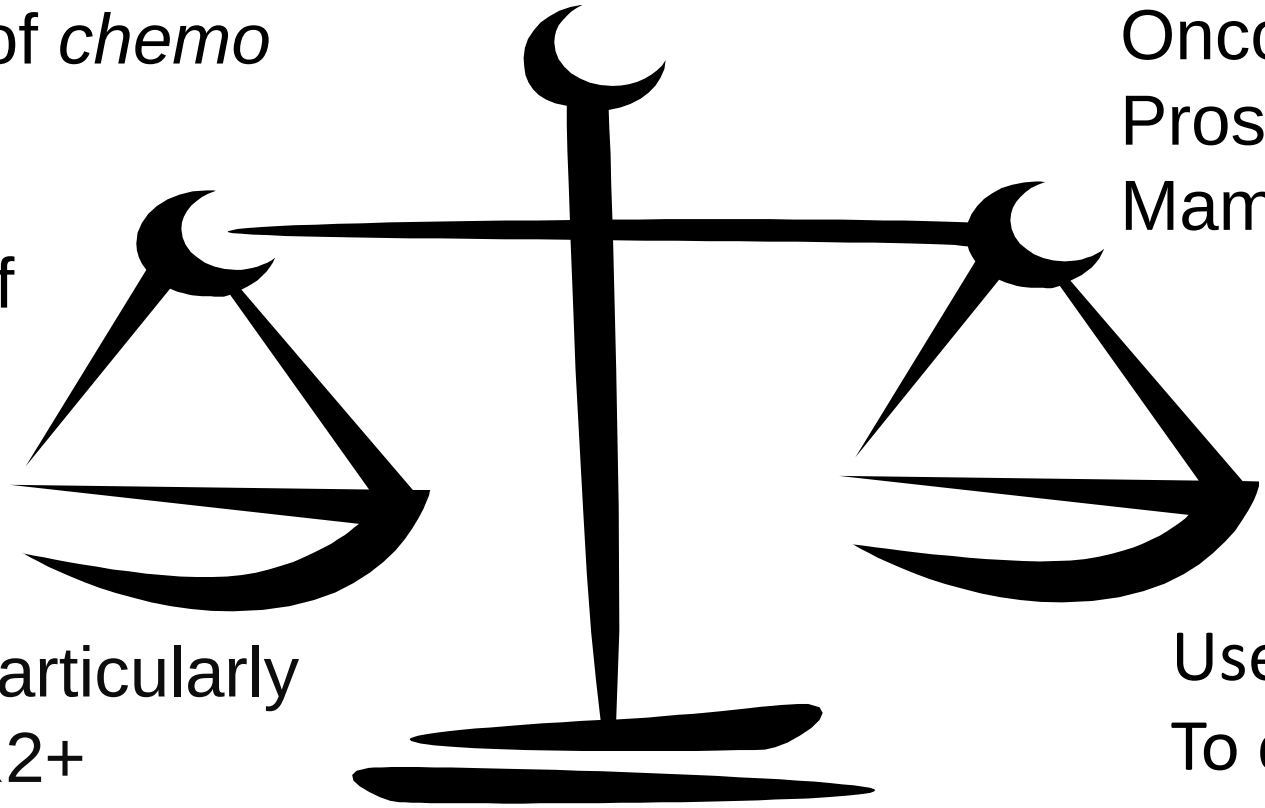
- Endocrine Rx?
- Chemotherapy
- Anti HER Rx
- ? IO
- PARPi
- Other treatments?

In Early Breast Cancer the Risk of Cancer Recurrence and Responsiveness Must Be Balanced with Toxicity

Use of *genomic tests*
OncotypeRS
Prosigna,
Mammoprint

Decreasing use of *chemo*
in ER+

Decreasing use of
anthracyclines



Increasing use of
*Neoadjuvan*t Rx particularly
in TNBC and HER2+

Use of Germline Testing
To determine therapy

Post neoadjuvant therapy
in ER- and HER2 +

Increase in *supportive*
care such as exercise trials

Current Summary of Adjuvant Treatment of EBC

Triple Negative
ER, PR, HER2 negative

↓

Chemo
+/- ?IO
+/ PARPi

HER2 positive
ER negative or positive

↓

Chemo plus anti-HER2 therapy + endocrine (ET) if ER+

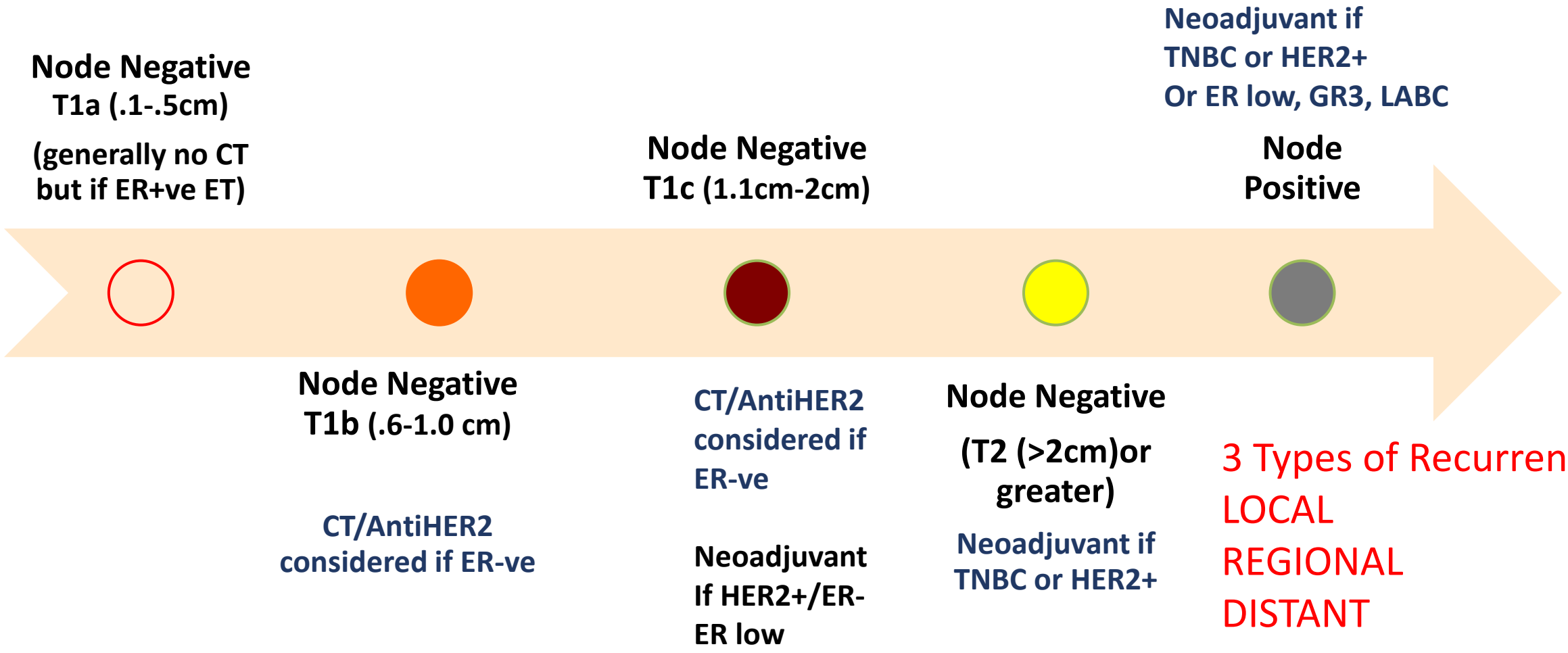
+/- Bone modifying agents

ER positive and HER2 negative

↓

ET +/- Chemo
based on prognostic/ genomic factors
+/ PARPi

The Risk Spectrum
Who To Treat with Neoadjuvant or Adjuvant



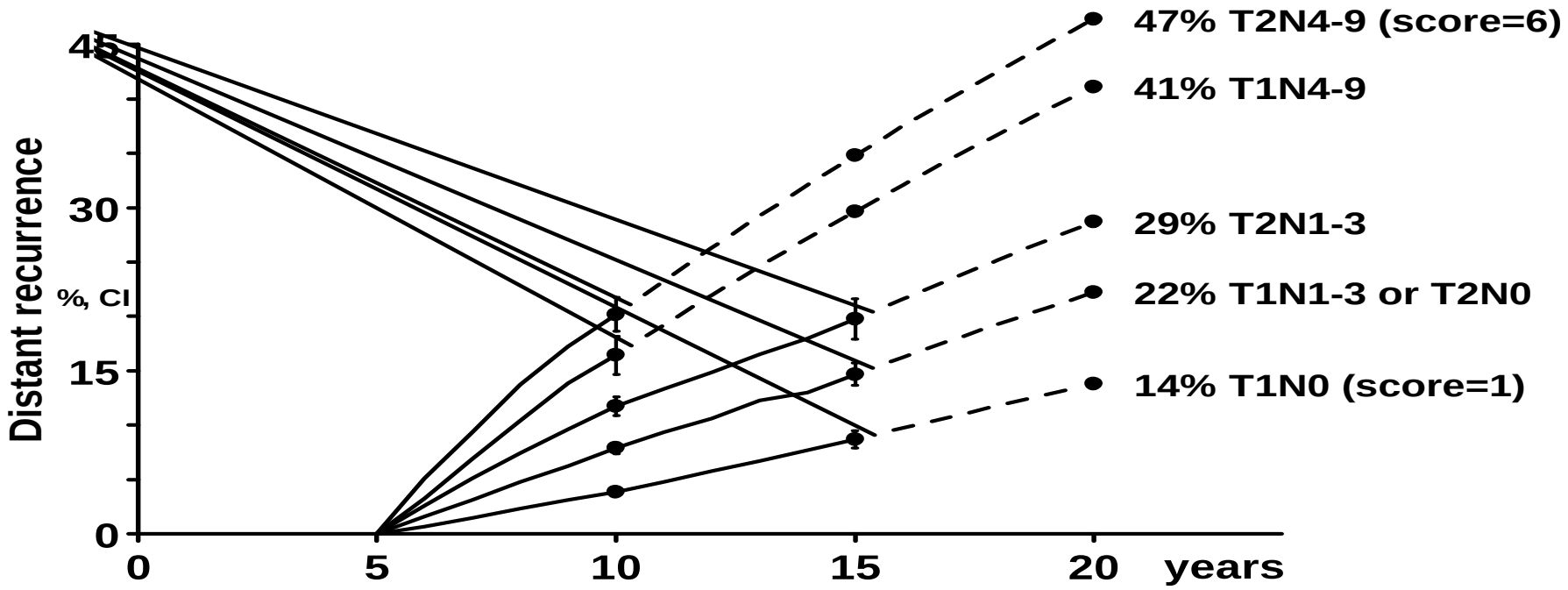
Stage distribution at presentation

Stage	Definition	% Patients
I	T1N0	50
IIA	T0N1 T1N1 T2N0	30
IIB	T2N1 T3N0	
IIIA	T0N2 T1N2 T2N2	15
IIIB	T4Nany	
IIIC	TanyN3	
IV	TanyNanyM1	5

HR+ Breast Cancer Relapse Risk Remains for YEARS!

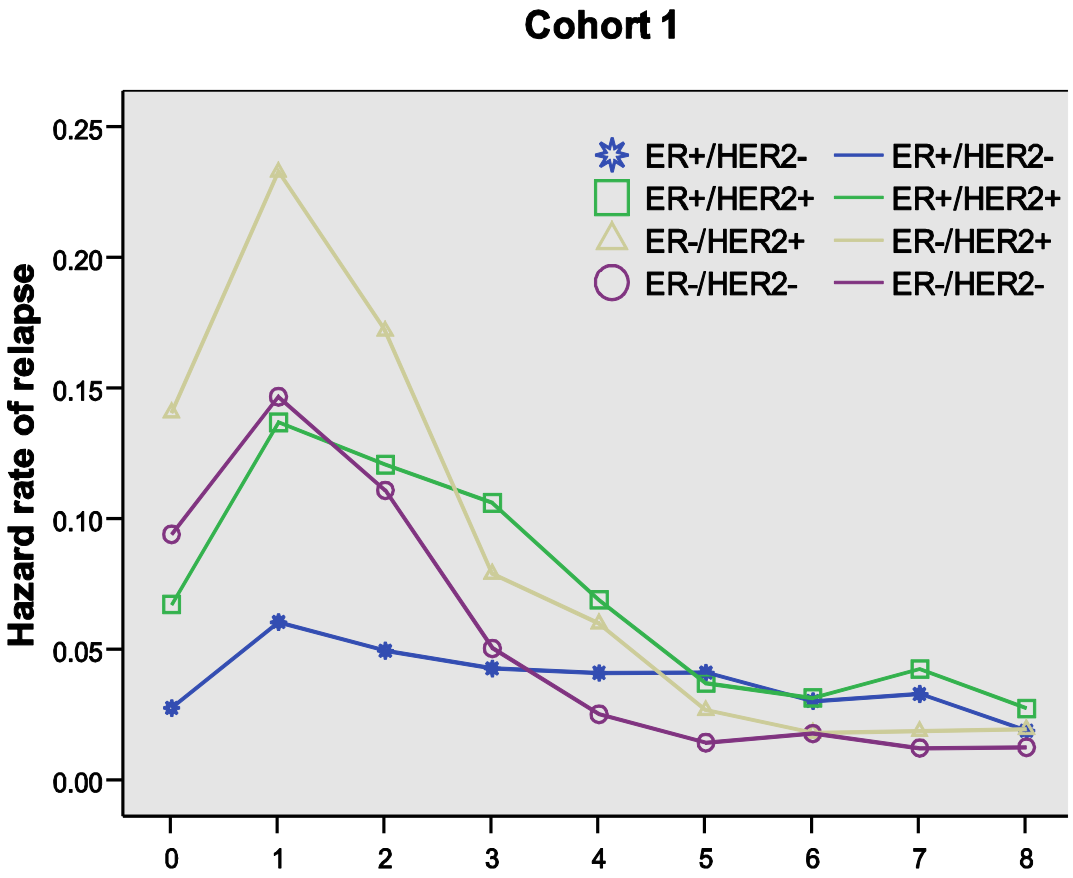
Effect of additive "T+N score" (range 1-6)

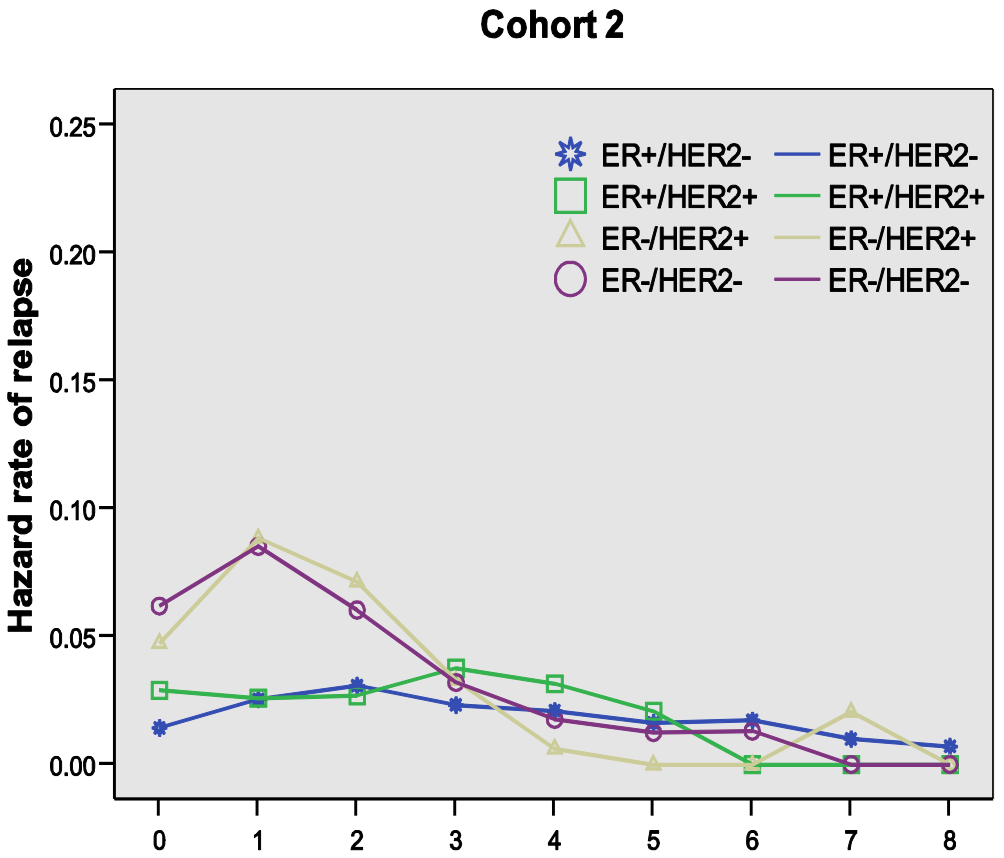
Score: 1/ 2 for T1/ T2, plus 0/ 1/ 4 for N0/ N1-3/ N4-9



Pan et al EBCTCG NEJM 2017

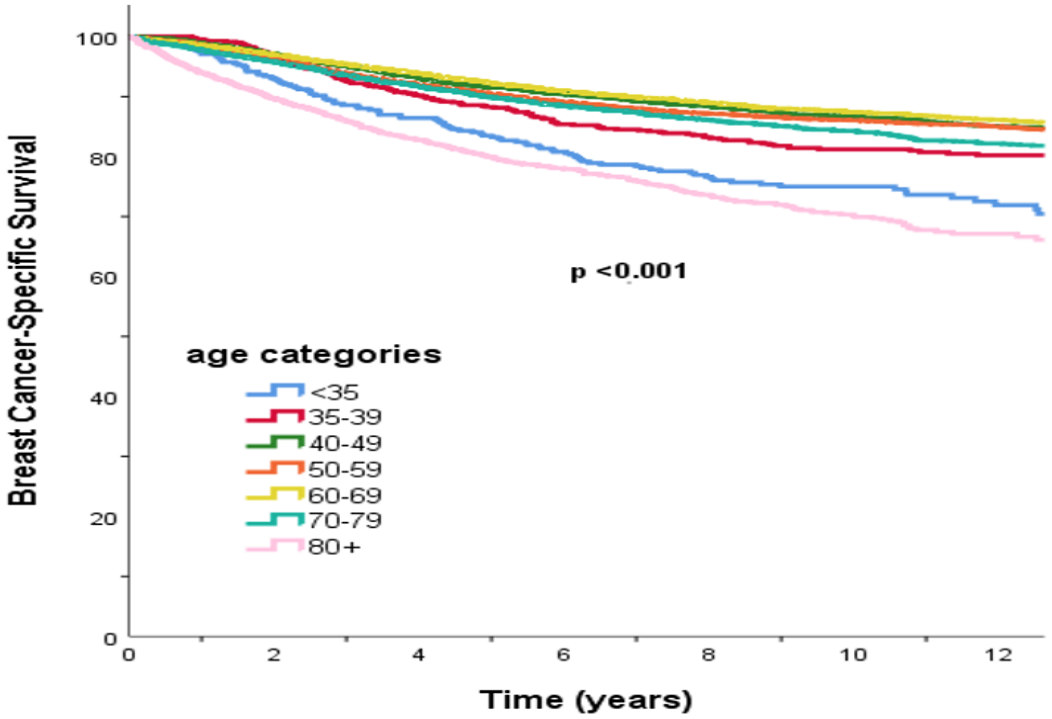
Patterns Of Breast Cancer Recurrence Determined by Subtype of Primary





Cossetti et al, JCO 2015

Does Age Affect Outcomes with Breast Cancer?



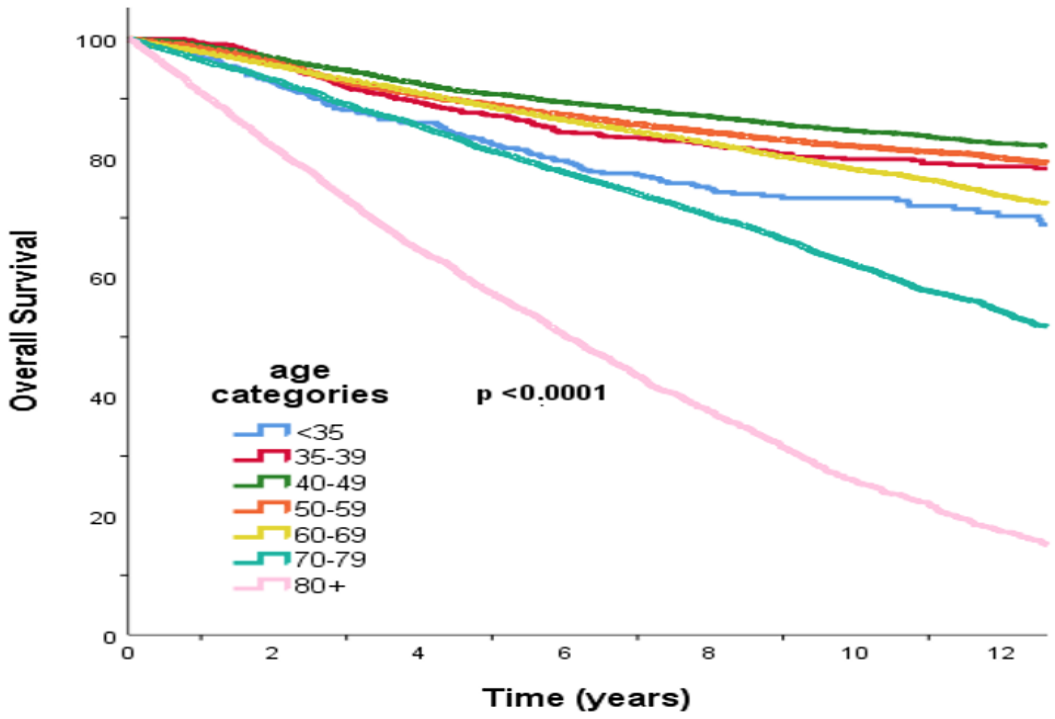


Figure 1. Kaplan Meir curves of BCSS and OS by age category.

Jackson et al Breast 2023

What are the Goals of Follow-up for Early Breast Cancer

- Provide care for both physical and psychological symptoms that are the result of cancer care
- **Diagnose curable disease early so it can be treated for cure**
- **Diagnose advanced disease early to avoid symptoms**
- **? Diagnose advanced disease early to cure????**
- Enhance adherence/compliance with adjuvant medications
- Promote prevention and health including bone, sexual, psychological, cardiac health

Types of Recurrence - Local and Local Regional

IMPORTANT to DIAGNOSE EARLY when POTENTIALLY CURABLE

- **Local Recurrence**
  - In breast
  - Diagnosis with mammograms, physical examination, ultrasound, MRI if necessary and ultimately biopsy
  - USUALLY curable
  - If prior radiation usually requires a mastectomy
  - If while on endocrine therapy and still HR+ may need a switch to another endocrine agent
- **Local /Regional Recurrence**
  - Involves breast and /or nodes
  - May be surgically curable
  - May need radiation to nodal areas if not treated previously

Mammograms should be done for women with a prior diagnosis of early breast cancer

A. Every 2 years until age 79
B. Starting 6 – 12 months after treatment and continuing every year indefinitely
C. Can be either diagnostic or screening mammograms
D. Should be diagnostic mammograms
E. A and C
F. B and D
G. None of these answers

Imaging of Breasts for Persons with Breast Tissue (1)

1. Persons with residual breast tissue should have annual diagnostic mammograms starting 6 – 12 months after treatment.

- If asymptomatic no other breast imaging is required
- If dense breasts, ultrasounds may be indicated
- If worrisome undiagnosed findings, MRI may be indicated.

2. A new primary malignancy in the contralateral breast occurs at a rate of approximately 0.5% to 1% per year.

- The average 50 year old woman who has had breast cancer once carries approximately a 10-15% risk of a second contralateral breast cancer (invasive or DCIS) over the next 25 years.
- Adjuvant hormone therapy will reduce this risk
- Contralateral imaging should be done annually

Imaging of Breasts for Persons with Breast Tissue (2)

3. Persons who have confirmed g*BRCA2* and g*BRCA1* mutations and a prior breast cancer carry approximately 35% and 45% risk of a second breast cancer over 25 years respectively.

- Guidelines recommend mammograms and MRIs done on an annual basis usually alternating at 6 months intervals.
- MRIs can be stopped when older and/or density decreases.

4. Persons who have had breast reconstruction and bilateral mastectomies do not need breast imaging unless there is a clinical concern.

- If there is a change in the contour an ultrasound and sometimes MRI are helpful
- If there is a lump mammograms, ultrasound and biopsy under ultrasound
- Most mastectomies do not remove ALL the breast tissue so rarely a local recurrence can happen

Types of Recurrence – Distant

- Distant suggests lymphatic or hematological spread
- May be oligometastatic (fewer than 5 lesions) or Diffuse
- STILL breast cancer regardless of where it is
- Should be biopsied to confirm it is breast cancer and also to get markers – is it ER+/PR+/HER2+/PI3K+?
- Usually not curable but this may be changing and diagnosis at a time when the person is still in a fit shape promotes longer/better survival
- Usual sites
  - Bone, liver, lung, nodes, brain, etc etc
  - Sites vary with type of breast cancer to some degrees
  - BONE is most common in ER+ and in TNBC
  - Lobular cancer often goes diffusely to stomach, peritoneum, pleura without liver mets,

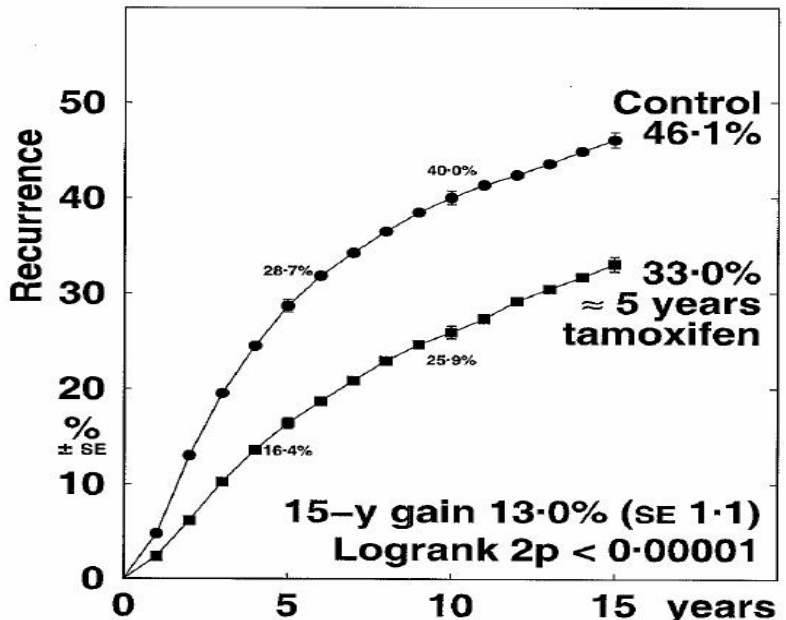
Follow up of a person with a prior diagnosis of early breast cancer should include:

- A. Annual mammograms but no other regular imaging tests
- B. Annual blood work including tumour markers
- C. Physical examination every 6 months for the first 2 years and then annually after that until year 5
- D. Physical examination ever 6 months for the first 5 years and then annually after that indefinitely
- E. Should be done by an oncologist or a surgeon
- F. A and D
- G. A, B, and D

Follow- up of Breast Cancer Patients for Systemic Recurrence

- History and Physical Examination every 6 months for 5 years and then annually
- If asymptomatic no imaging other than mammograms
- If asymptomatic no routine blood work other than usual for age
- BMD if early menopause, on endocrine therapy, other risk factors
- IF any symptoms that are persistent, image!!
- IF any physical findings that are concerning, image and biopsy!!
- IF concerns call /email the prior oncologist to see

≈ 5 years tamoxifen vs. Not
RECURRENCE
ER+



Recurrence rates (% / year) and logrank analyses

Allocation	Years 0 – 4	Years 5 – 9	Years 10 – 14	Year 15+
Tamoxifen	3·75 (869 / 23183)	2·63 (442 / 16838)	2·06 (213 / 10353)	1·79 (88 / 4928)
Control	6·68 (1420 / 21247)	3·44 (483 / 14027)	2·11 (177 / 8406)	1·77 (70 / 3962)
Rate ratio, from	0·53 SE 0·03	0·69 SE 0·06	0·96 SE 0·10	0·90 SE 0·16
(O–E) / V	–332·7 / 520·2	–78·3 / 212·1	–3·3 / 91·1	–3·8 / 35·2

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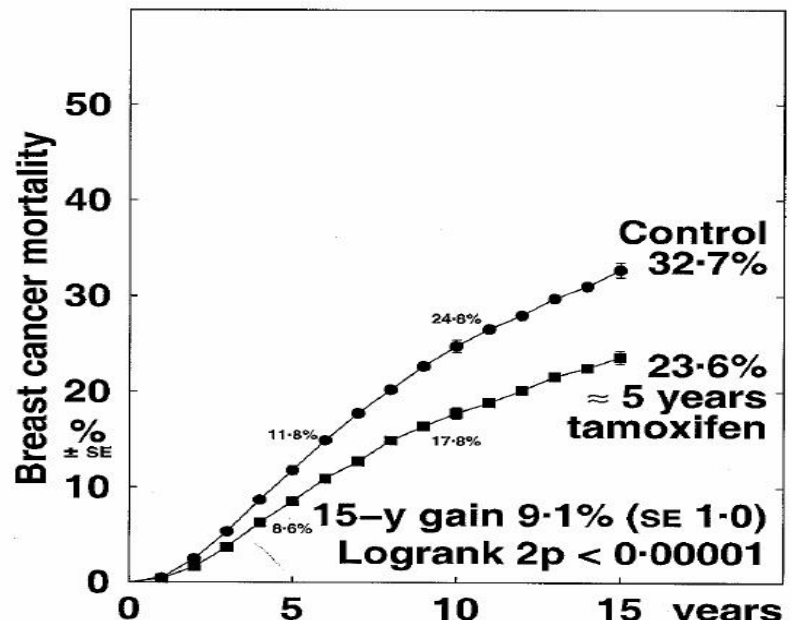
Not for publication or citation

≈ 5 years tamoxifen vs. Not
BREAST CANCER MORTALITY
ER+



Death rates (% / year: total rate – rate in women without recurrence) & logrank analyses

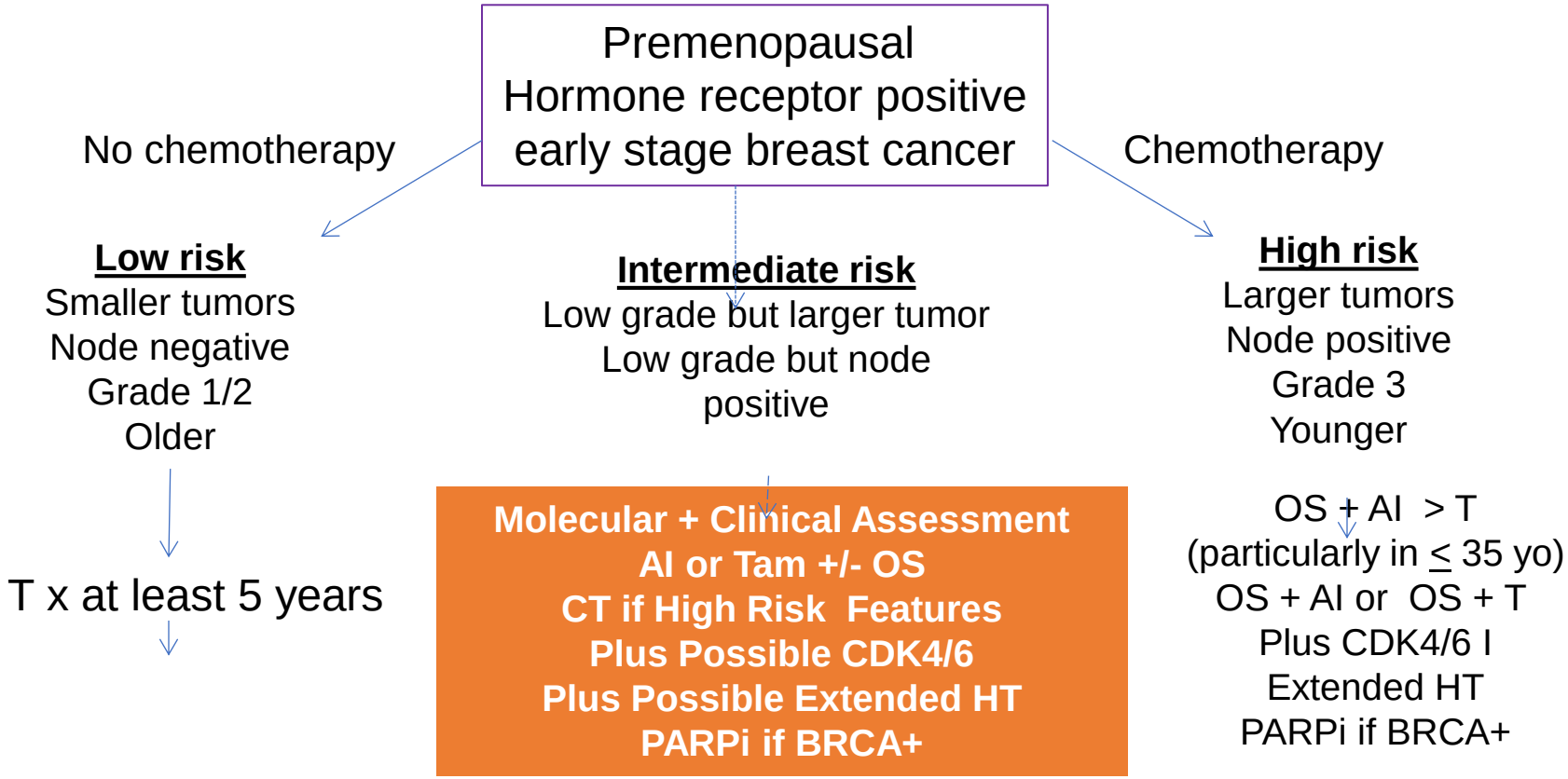
Allocation	Years 0 – 4	Years 5 – 9	Years 10 – 14	Year 15+
Tamoxifen	1·79 SE 0·09	2·24 SE 0·11	1·49 SE 0·11	1·49 SE 0·16
Control	2·44 SE 0·10	3·16 SE 0·13	2·26 SE 0·15	1·86 SE 0·19
Rate ratio, from	0·71 SE 0·05	0·67 SE 0·06	0·66 SE 0·08	0·87 SE 0·14
(O–E) / V	–81·6 / 237·5	–88·6 / 225·1	–39·5 / 95·9	–6·0 / 41·7

13:02:26 15 September 2010
Fig 6. Not for publication or cita

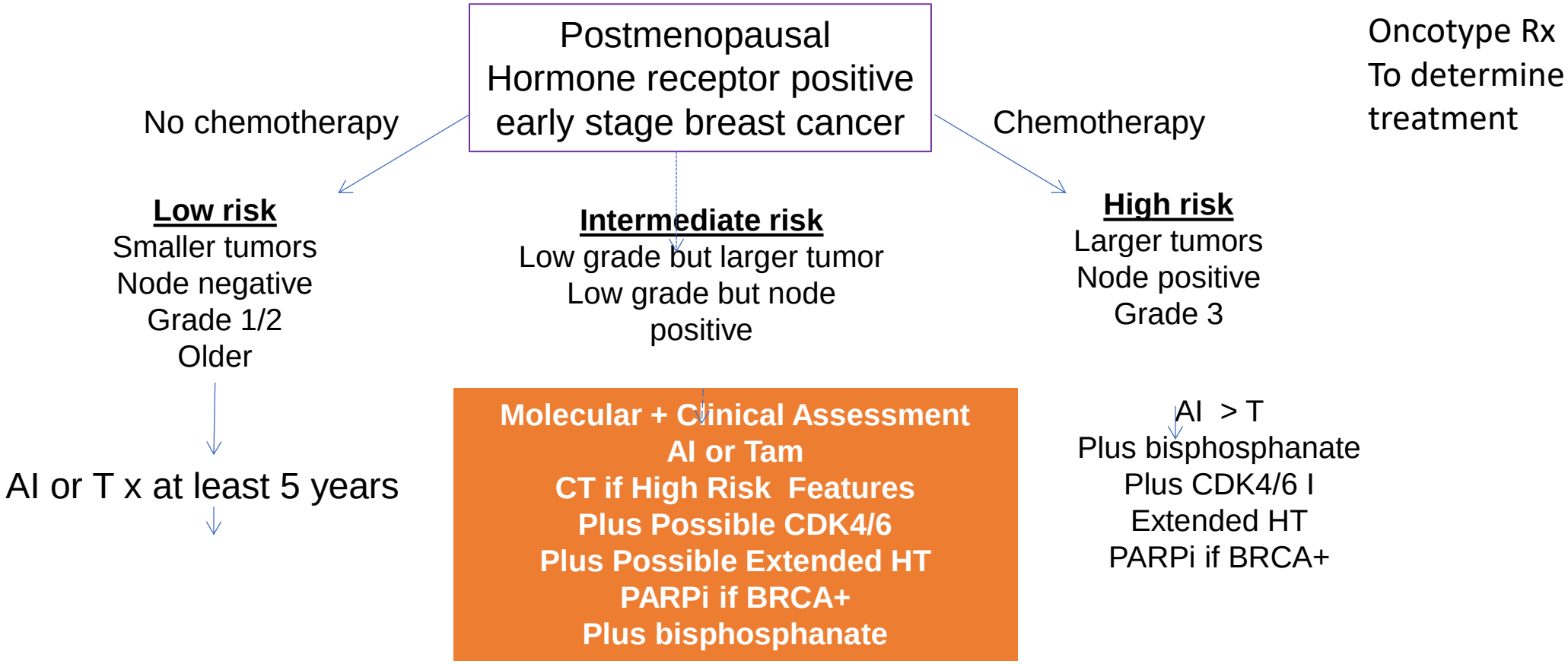
Defining Premenopausal and Young Women

- Older studies used < 50 or even <55 as the cutoff regardless of menopausal status
- Studies have also looked at < 40 or < 35 as cohorts with a worse outcome
- Defining menopausal status is not just one simple blood test or from history but is over time
- Treatment induced menopause may be transient or permanent and this affects definition

Algorithm for Premenopausal Hormone Receptor Positive Disease



Algorithm for Postmenopausal Hormone Receptor Positive Disease

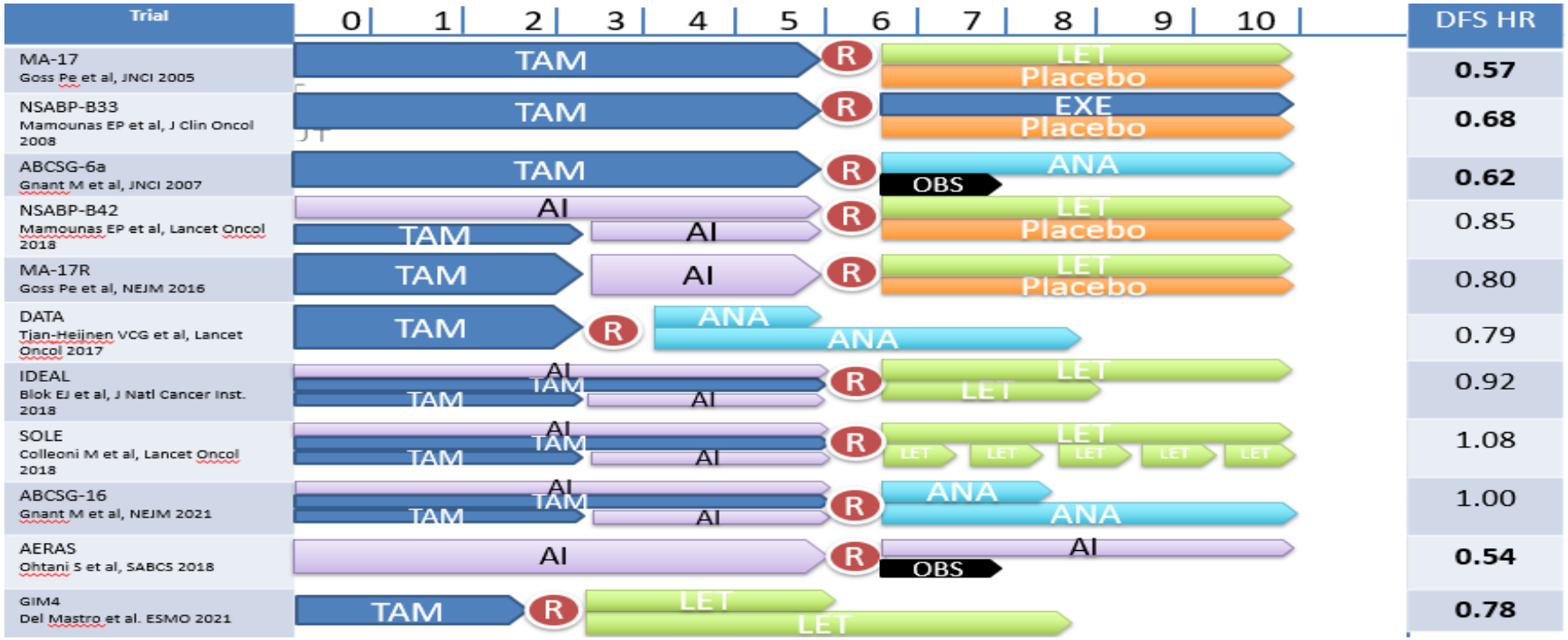


Extended Adjuvant? More than 5 years of Endocrine Therapy

- Effect on Distant AND on Contralateral cancers
- Each patient needs to be assessed in terms of risk and benefit
- For high risk patients extended adjuvant therapy may provide a benefit in terms of distant, localregional and contralateral disease
- For lower risk patients the risk of toxicity may outweigh the benefits

Trials of Extended Adjuvant Hormone Therapy

Which Agent? Which Patient Group? How Long?



Reported adherence rate from 59.9% in IDEAL to 80% in ATLAS, MA17, ABCSG 16

Do I offer Extended Adjuvant Therapy?

- 45 year old with a T2, N2, ER+, PR-, HER2- lobular cancer.
- Treated with partial mastectomy, ddACT, radiation
- BMD normal
- ? 5 years of Tamoxifen
  ? 10 years of tamoxifen
- ? 5 years of tamoxifen and then switch to AI?
- ? Early or late switch strategy ?

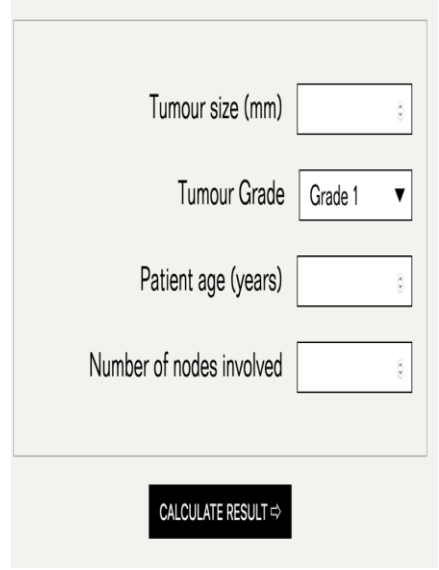
Do I offer Extended Adjuvant Therapy?

- 57 year old with a T2, N2, ER 7/8, PR-2/8, HER2- lobular cancer.
- Treated with partial mastectomy, ddACT, radiation, tamoxifen x 2 and anastrazole x 3 years
- BMD osteopenia

- 57 year old with a T2, N0, ER8/8, PR8/8, HER2 negative cancer with diffuse DCIS.
- Treated with bilateral mastectomies, Anastrazole x 5 years
- BMD osteopenia

Extended Adjuvant

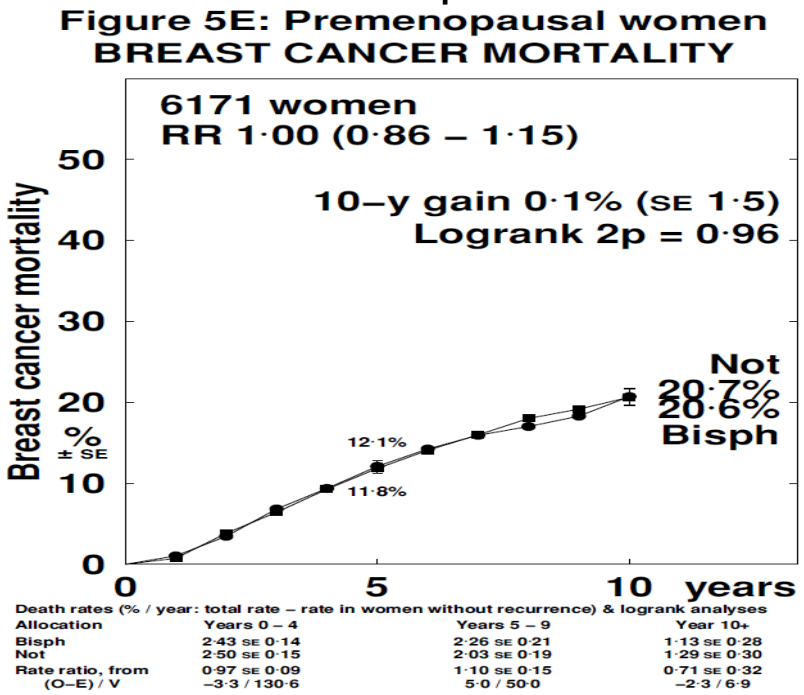
- MA17R and B43 – benefit
- CTS5 tool
  - for calculating estimate of benefit
  - https://www.cts5-calculator.com/
- ASCO guidelines
- Discussion on an individual basis
- AI unless intolerant of AI or premenopausal



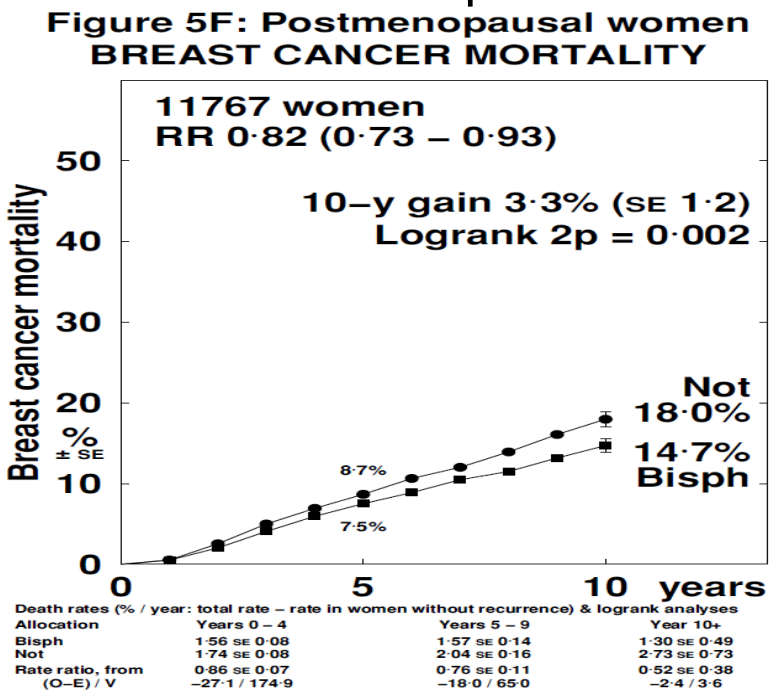
Richman et al,
Validation, ASCO 2019

Effect of adjuvant bisphosphonates
Breast Cancer Mortality By Menopausal Status

Premenopausal‡



Postmenopausal



‡ includes women aged < 45 if unknown

EBCTCG, Lancet 2015

HER2 in Breast Cancer

- A *prognostic* factor
- A *predictive* factor for choosing therapy
- Herceptin, pertuzumab, TDM1,TDX-d, tucatinib etc are targeted therapies against HER2
- Herceptin improves survival in early and recurrent breast cancer
- Dual therapy has been shown to be effective dependent on the combination

Risk of Relapse with HER2 positive cancers

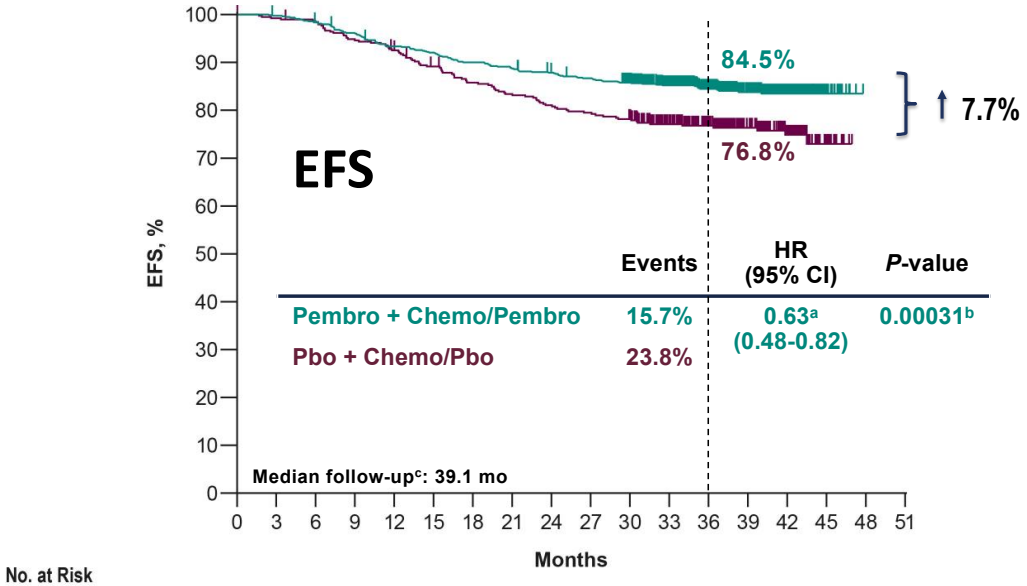
- Higher risk if no adjuvant anti HER2 therapy but now with anti HER2 therapy risk is generally low
- ER+/HER2 positive can relapse any time after diagnosis
- ER-/HER2 positive tend to relapse in the first 5 years after diagnosis

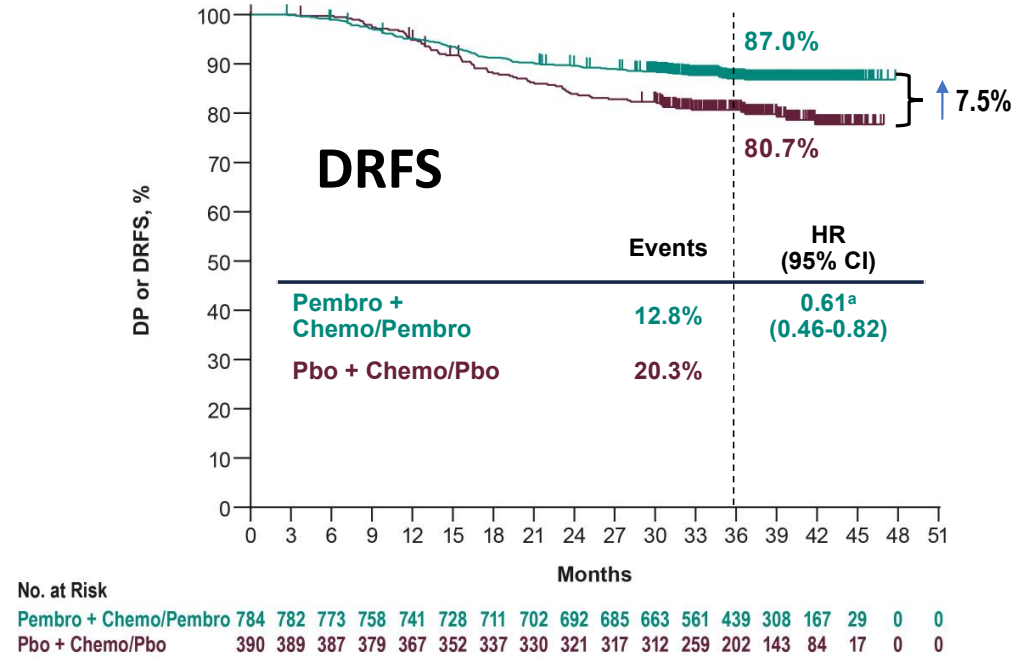
- BRAIN mets are a common site of relapse!!! In some series up to 50% of persons with metastatic HER2 positive cancer get brain mets at some point
- Bone, liver, lung, nodes

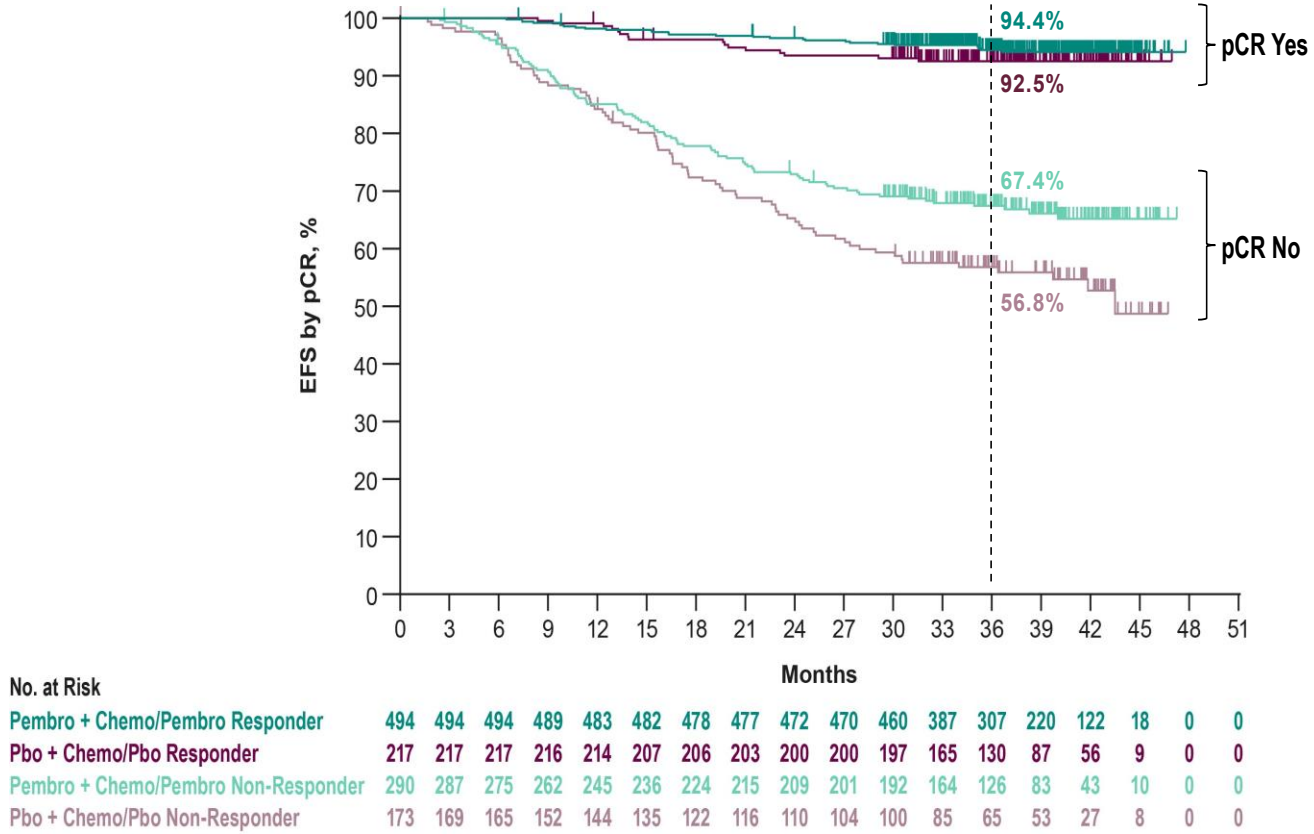
Triple Negative Breast Cancers

- Comprise approximately 15% of all invasive cancers
- More common in:
  - Younger patients
  - BRCA1 mutation carriers (up to 80%)
- Associated with:
  - high grade / high Ki67
  - p53 mutations
  - increased expression of EGFR
  - CK5/6
  - Vimentin, cKIT, SRC
  - ?BRCA like mutations which confer resistance

Pembrolizumab + CT Improves EFS and DRFS



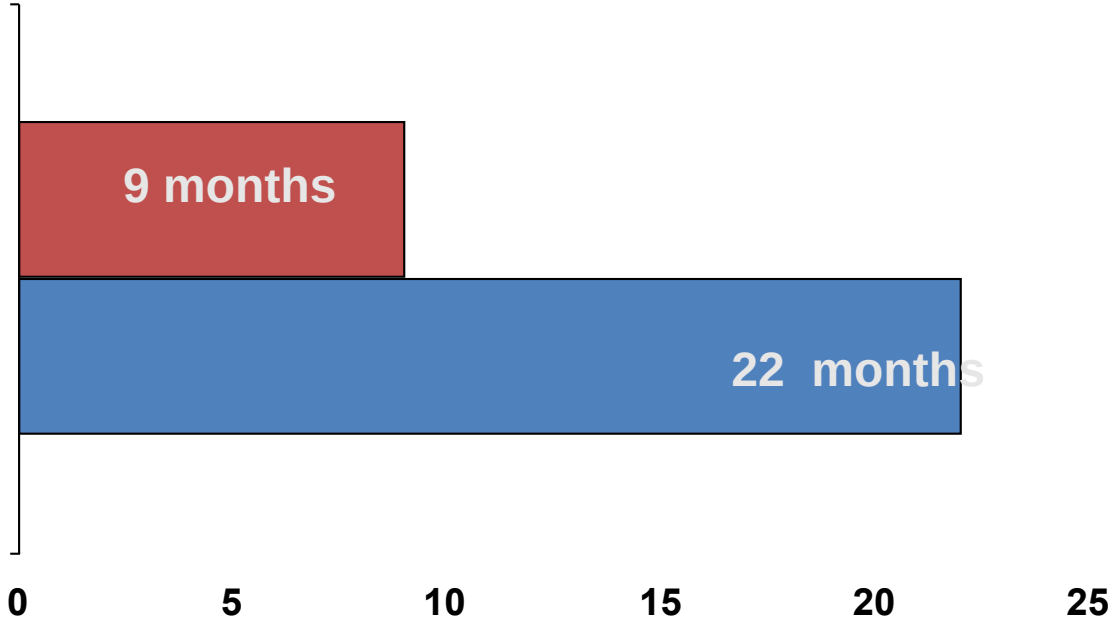




Schmid et al, NEJM 2022

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [b]**Prespecified *P*-value boundary of 0.00517 reached at this analysis.**
[c]Defined as the time from randomization to the data cutoff date of March 23, 2021.

But if TNBC relapse the Median Time from Distant Relapse to Death is often short
This is historical data and new data is better but there is still a discrepancy between survival of Stage IV for TNBC vs other subtypes



Dent R, Trudeau M, Pritchard K, Hana W, Narod S. et al. Clinical Cancer Res 2007

Toxicity of our Adjuvant Therapies
May be Acute OR Chronic and NEED ATTENTION

- Chemotherapy
  - Neutropenia, alopecia, GI, neuropathy, fatigue
- Immunotherapy
  - Pneumonitis, colitis, thyroid dysfunction, hypopit, hypersensitivity
- AntiHER2 therapy
  - cardiac toxicity, diarrhea, fatigue
- Hormonal therapy
  - Hot flushes, arthralgias, myalgias, sexual issues, hair thinning
- CDK4/6 inhibitors
  - Neutropenia, mucositis, fatigue
- PARP inhibitors
  - Anemia, GI

Dealing with the Side Effects of Treatment

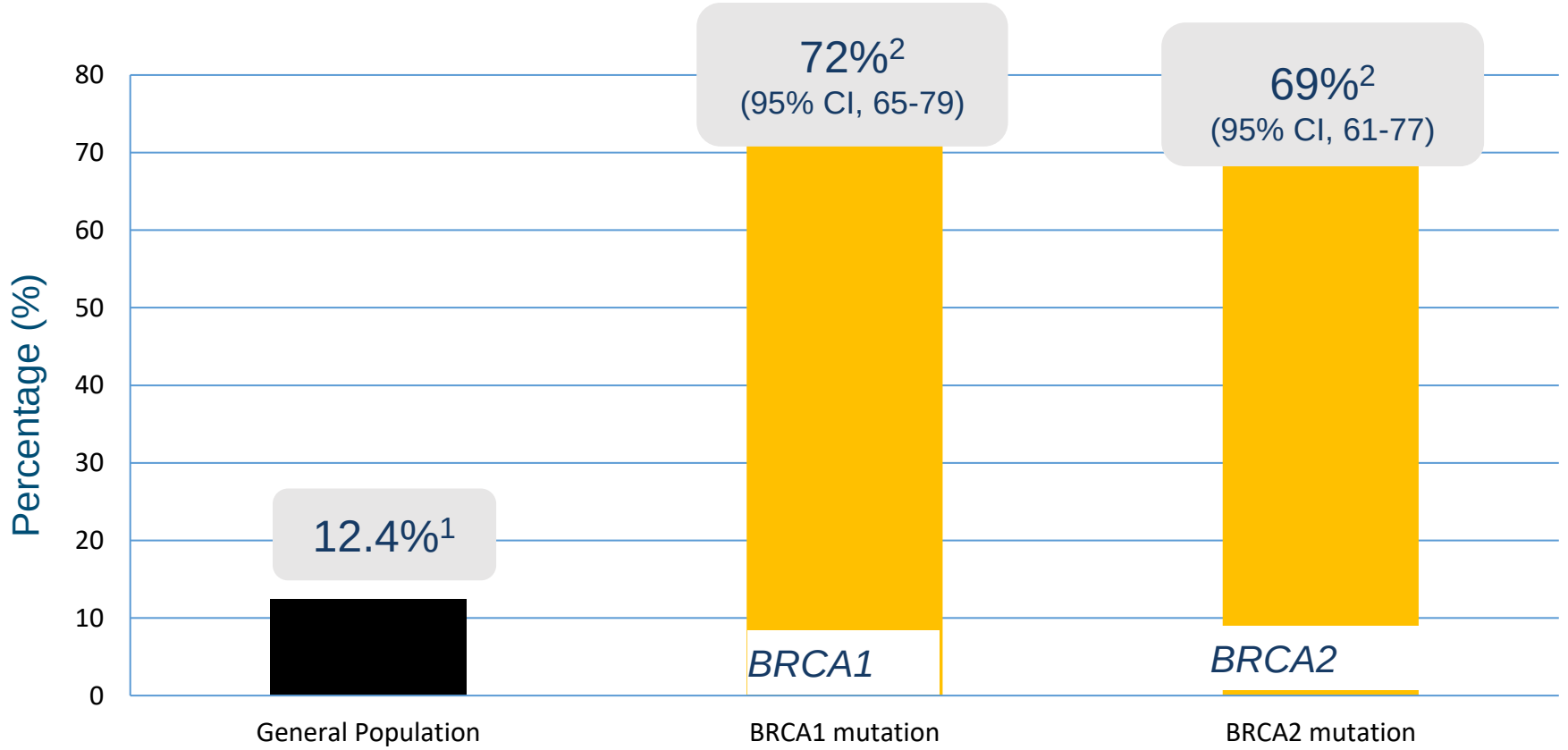
- Listen to patients
  - Are these toxicities of treatment
  - Are they affecting compliance and adherence to current meds
  - Are these related to treatment or other disease?
- Support
  - Are they somatic complaints? Societal? Psychological?
  - All of the above
- Educate patients
  - What to expect
  - When to expect onset, peak, resolution
  - When and who to call
  - Support groups – they are not alone

Survivorship Issues - Life After a Diagnosis

- Neurological
  - Chemo brain, peripheral neuropathy
- Cardiac
  - Cardiotoxic treatment with chemo and RT
- Bone health
  - Early menopause, toxicity of drugs both chemo and endocrine
- Fertility
  - Reproductive issues
  - Pregnancy after a diagnosis of breast cancer
- Sexual and Menopausal issues
  - Sudden onset, early onset, issues of HRT
  - Reproductive issues, sexuality
- Psychological issues
  - Losses, Issues of Uncertainty, Family/support group

BRCA MUTATIONS AND BREAST CANCER RISK

Risk for Developing Breast Cancer



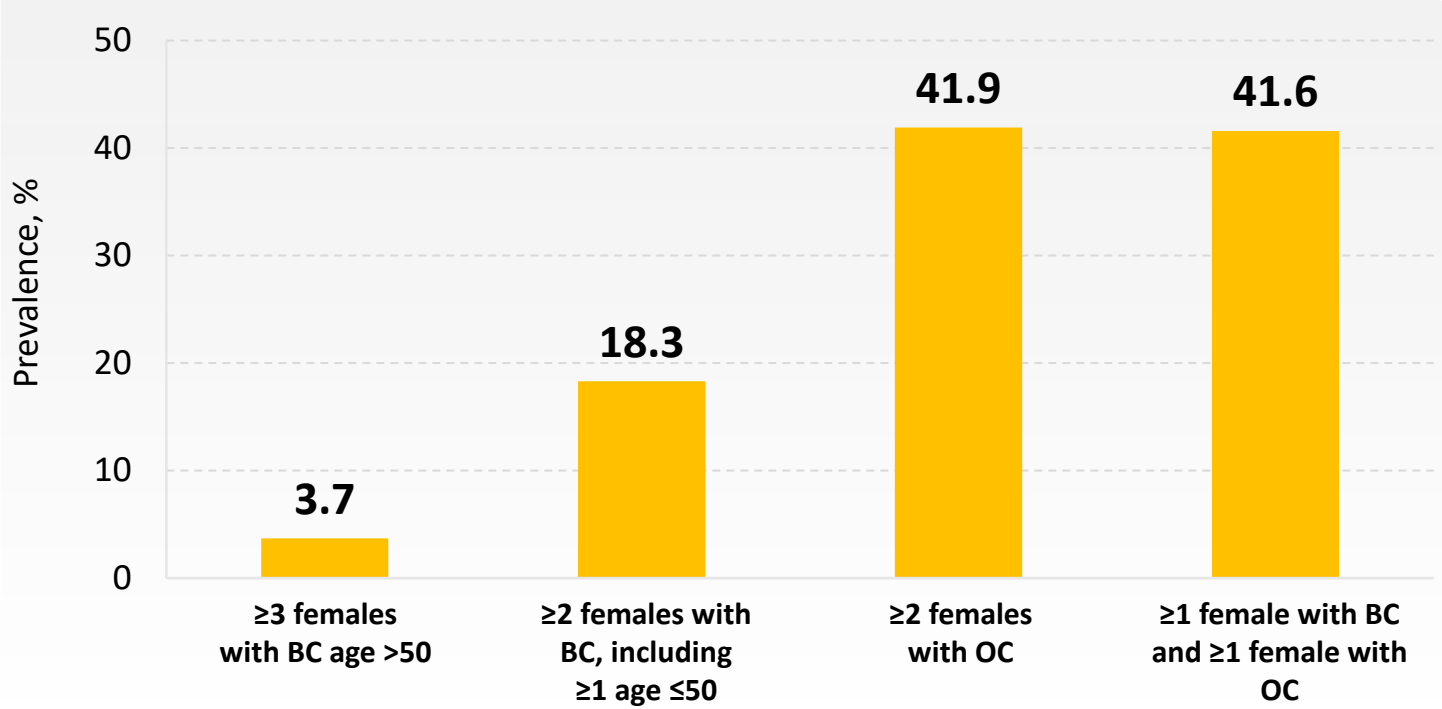
SEER data are expressed as lifetime risk[1]; *BRCA* cohort data (N = 3886) are expressed as cumulative risk to age 80 years[2].
BRCA = BReast CAncer susceptibility gene; SEER = Surveillance, Epidemiology, and End Results.

1. SEER Cancer Stat Fact Sheets: Female Breast Cancer. National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/statfacts/html/breast.html.
2. Kuchenbaecker KB, et al. JAMA. 2017 Jun 20;317(23):2402-2416.

Family history alone does not identify all patients with BRCA mutations[1]

>5%
of patients with BC have a BRCAm[1]

BRCAm *prevalence is higher in patients with a family history of breast or ovarian cancers*[2]



62%
of BC patients with a BRCAm were reported to occur without a family history of ovarian or breast cancer[a] (57/92)[3]

[a]Note that the Swedish Breast Cancer Group criteria for recommending *BRCA1/2* testing also includes young age at onset, male breast cancer, and multiple tumours.
BC = breast cancer; BRCAm = BRCA mutation; BRCA = *BRCA1* and/or *BRCA2; BRCA1* = breast cancer gene 1; *BRCA2* = breast cancer gene 2; OC = ovarian cancer.
1. Winter C, et al. *Ann Oncol*. 2016;27:1532–1538. 2. Kast K, et al. *J Med Genet*. 2016;53(7):465-471. 3. Li J, et al. *Int J Cancer*. 2019;144(5):1195-1204.

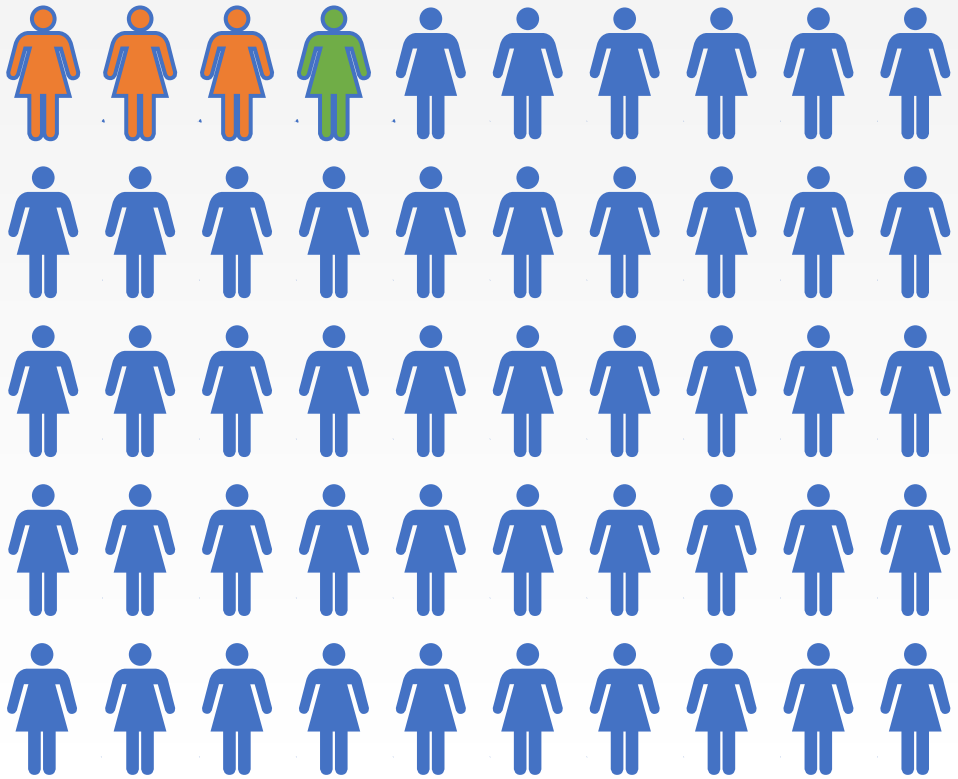
A higher proportion of patients with TNBC have BRCA mutations than those with HR-positive disease

~24%

of **TNBC** patients have BRCA mutations

~9%

of **HR-positive** patients have BRCA mutations



gBRCAm sBRCAm

BRCA = *BRCA1* and/or *BRCA2; BRCA1* = breast cancer gene 1; *BRCA2* = breast cancer gene 2; HR = hormone receptor; TNBC = triple negative breast cancer.
Winter C, et al. *Ann Oncol*. 2016;27:1532–1538: Supplementary Appendix.

However, because of the higher incidence of HR-positive cancer, there are more patients with BRCA mutations in this subtype

Estimated prevalence of BRCAm within unselected BC patients by receptor subtype

BC = breast cancer; BRCA = *BRCA1* and/or *BRCA2; BRCA1* = breast cancer gene 1; *BRCA2* = breast cancer gene 2; BRCAm = BRCA mutation; HER2=human epidermal growth factor receptor 2; HR-positive=hormone receptor-positive; TNBC=triple negative breast cancer.
Winter C, et al. *Ann Oncol*. 2016;27:1532–1538: Supplementary Appendix.

Novel consenting and counselling strategies may act as guide to streamline gBRCAm testing and improve turnaround time Mainstreaming is increasingly used in BC

Consenting through MDT members[2,3]

Trained MDT members directly consent patients for genetic testing (eg, oncologists or nurses)

Group telegenetics[4]

Genetic counsellors consult multiple patients simultaneously

Technology-enabled education[4]

Patients access genetic counselling via video conferencing

Embedding genetic counsellors[5]

Coordinated counselling during oncology visits

Members of the cancer team should undergo training before consenting patients for genetic testing[1,6]

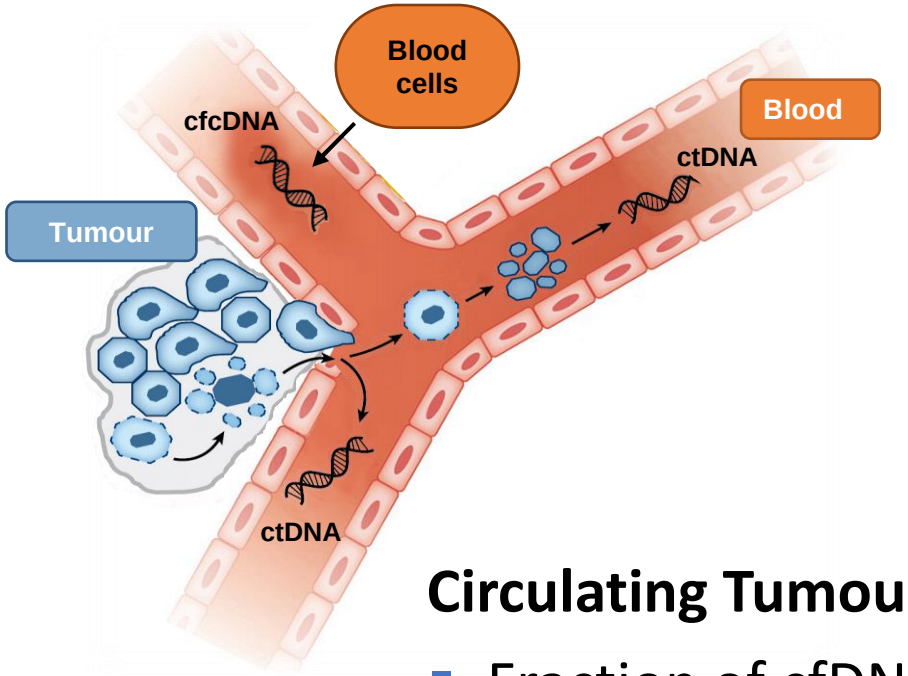
BRCA, *BRCA1* and/or *BRCA2*; gBRCAm, germline *BRCA1* and/or *BRCA2* mutation; MDT, multidisciplinary team.

1. Hoogerbrugge N, et al. *Eur J Hum Genet.* 2016;24(suppl 1):S19-S26. 2. George A, et al. *Sci Rep*. 2016;6:29506. 3. Lopez V. *Asia Pac J Oncol Nurs*. 2018;5(4):391-393. 4. Stoll K, et al. *Am J Med Genet C Semin Med Genet*. 2018;178(1):24-37. 5. McCuaig J, et al. *J Med Genet*. 2018;55(9):571-577. 6. Robson ME, et al. *J Clin Oncol*. 2015;33(31):3660-3667.

Does EARLY Diagnosis of Recurrence Make a Difference in Outcome?

- YES in terms of early diagnosis of local recurrence
- To date NO in terms of diagnosis of metastatic disease using regular scans
- To date NO in terms of diagnosis of metastatic disease using tumour markers such as CA15-3, CEA, CA125 etc
- HOWEVER, diagnosing recurrence at the time of first symptoms may improve tolerance of treatment and provide psychological support
- HOWEVER, New technologies such as circulating tumour DNA – ctDNA may change this paradigm in the future

Liquid Biopsies of cfDNA or ctDNA



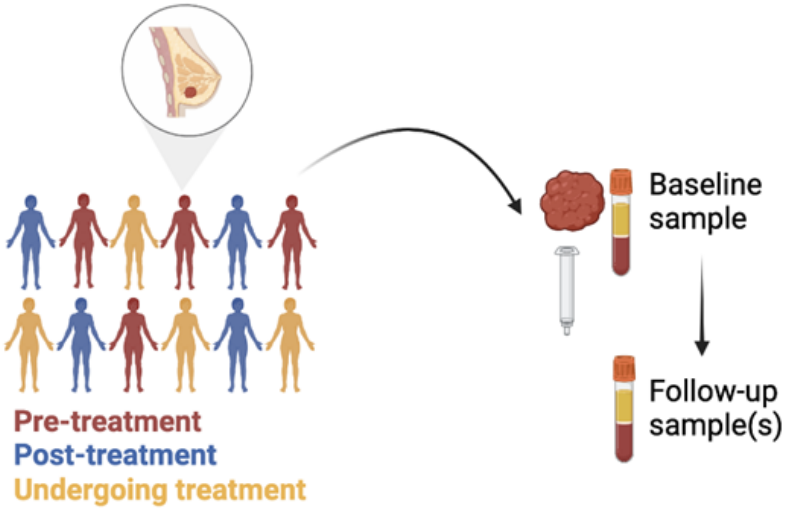
Cell-free circulating DNA

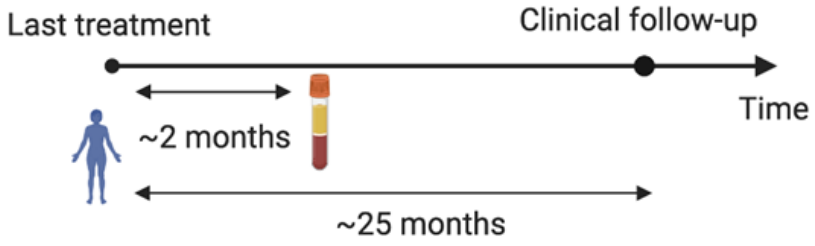
- From apoptotic/necrotic cells
- Fragmented: < 200 bp
- Short half life: < 30 min

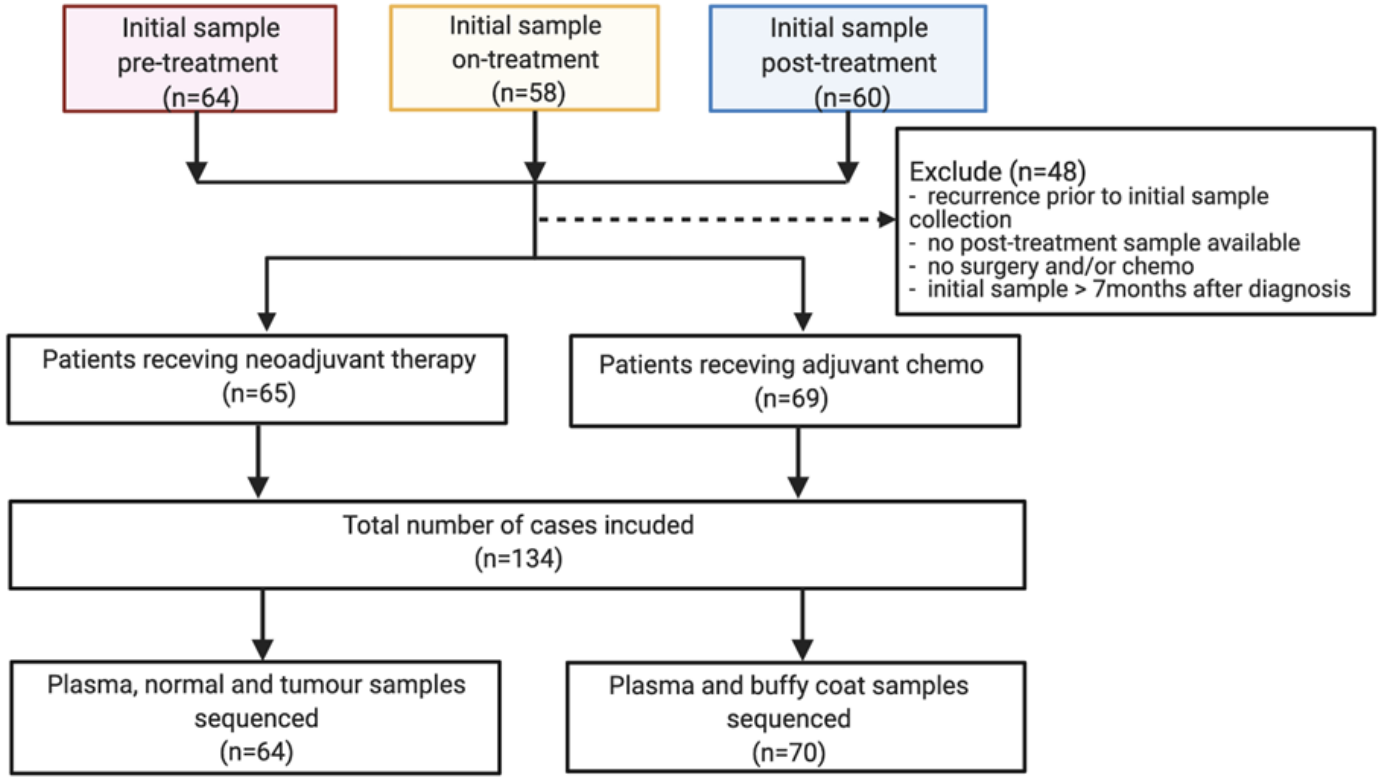
Circulating Tumour DNA

- Fraction of cfDNA
- Contains tumour-related molecular alterations
- Blood contains DNA from all metastatic sites

Detection of residual disease in early breast cancer with clinically actionable PCR hotspot assay



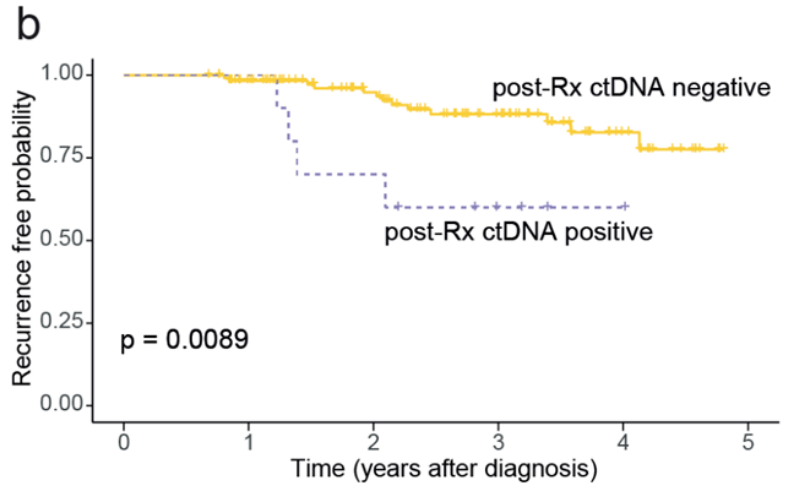


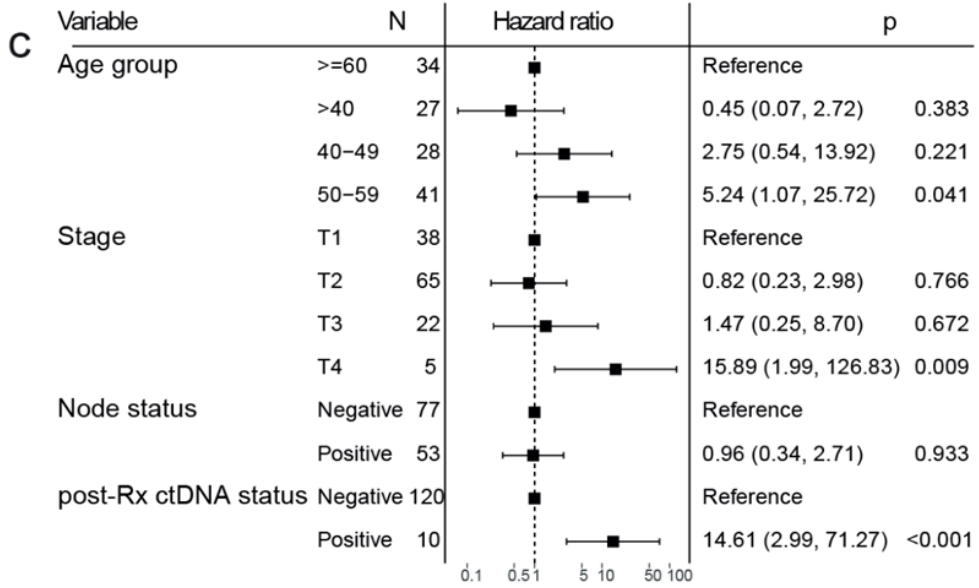


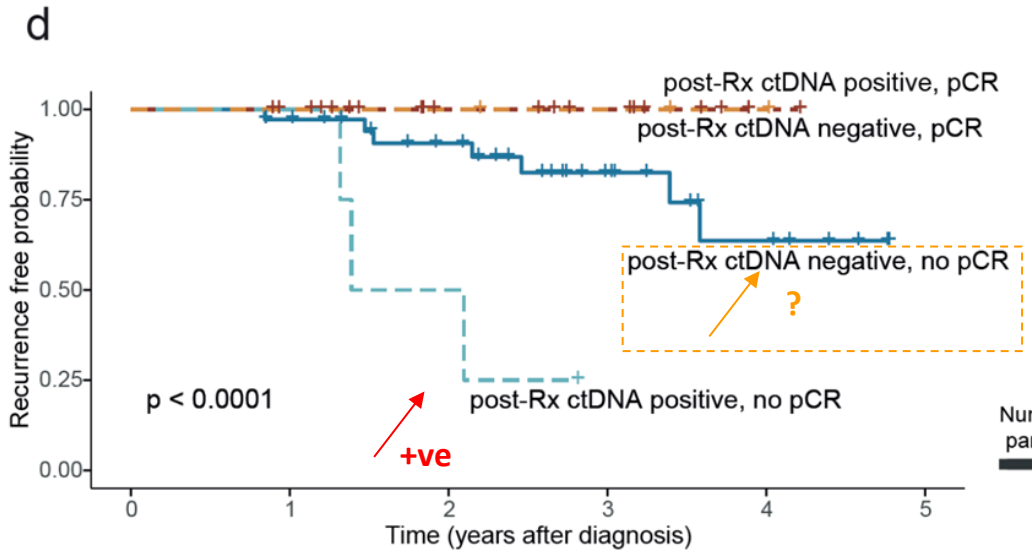
Neoadjuvant treatment - incomplete tissue response (pathCR -ve) at higher risk for relapse

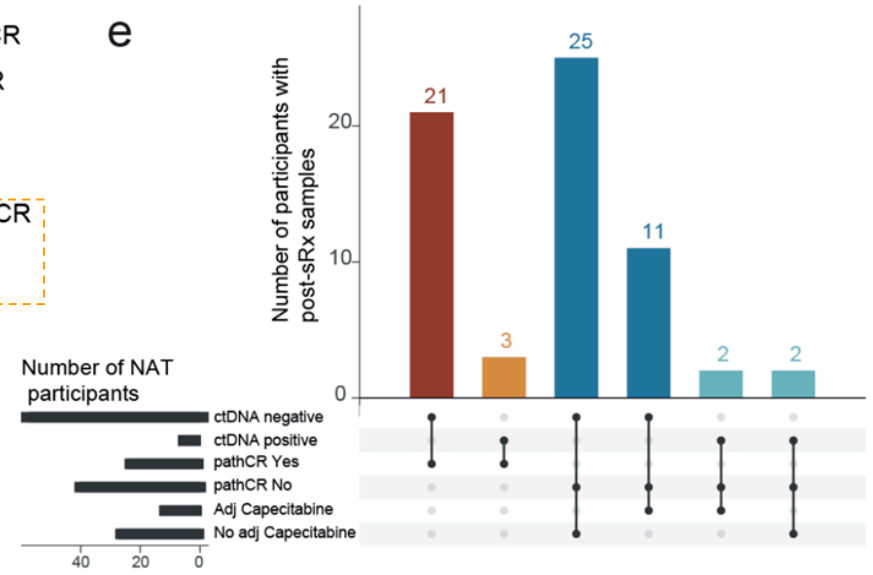
Zaikova et al, Nature Breast Cancer 2024

ctDNA within 6 months of treatment: incomplete pathCR + detectable ctDNA -> very high risk of early relapse









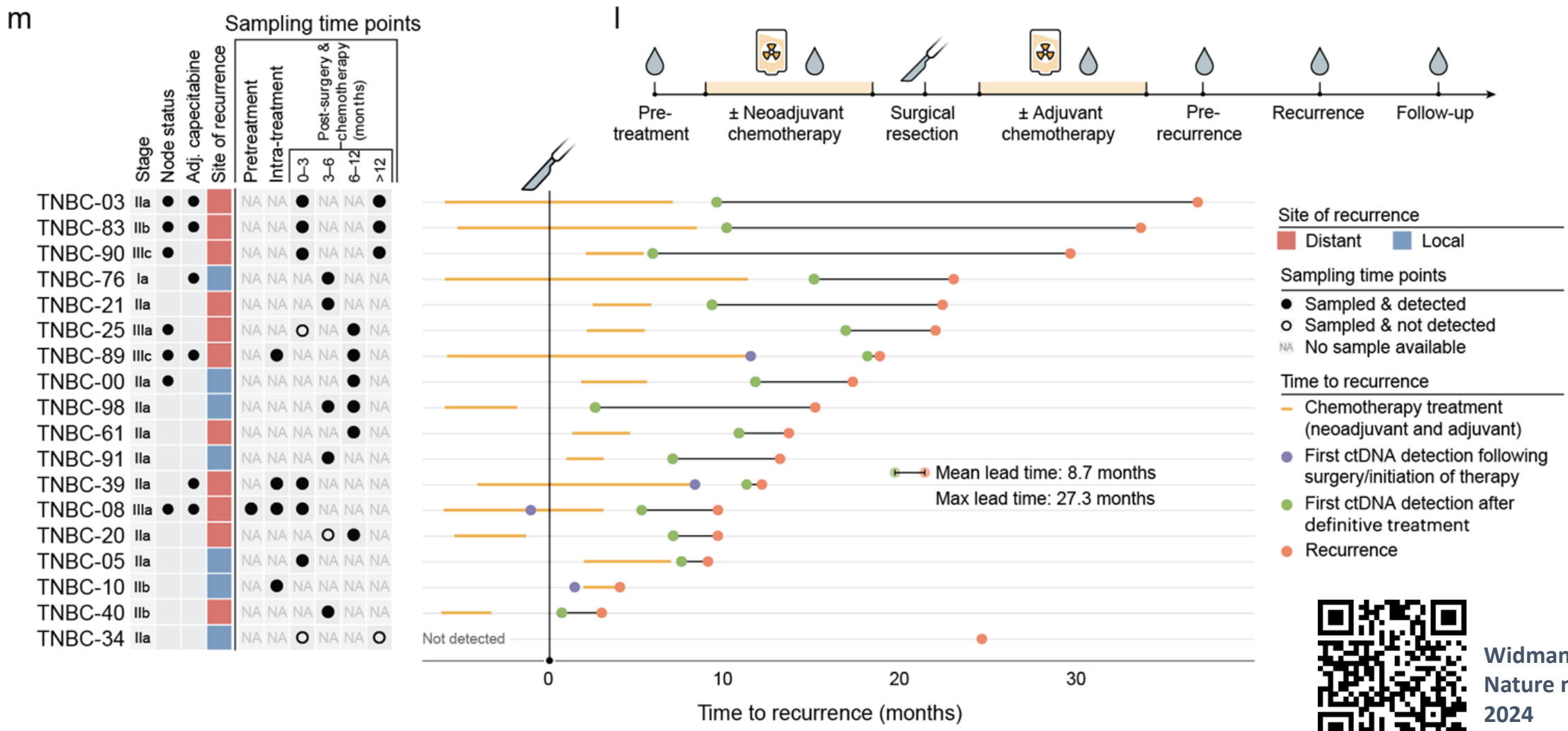
Zaikova et al, Nature Breast Cancer 2024

WGS anticipation of relapse in early TNBC MOHCC cohort

Median lead time 8.7 months, max lead time 27.3 months

MRD-EDGE : perioperative TNBC, n = 18 patients | n = 45 plasma samples

17/18 relapses detected with early plasma sampling



Widman et al, Nature medicine 2024

Role of ctDNA in breast cancer- potential BUT

- Can look for mutations in persons with Stage IV cancers
- May be an early indication that the treatment is NO longer effective in Stage IV cancers
- May be an indication that the risk of recurrence is higher than in those without evidence of ctDNA but specificity not yet known for all subtypes
- May diagnose early relapse at a time when the cancer may be more curable IF we have effective treatments – oligomets
- BUT not yet at a stage where we can use it – needs validation -
- Stay tuned

What are the Goals of Follow-up for Early Breast Cancer

- Provide care for both physical and psychological symptoms that are the result of cancer care
- Diagnose curable disease early so it can be treated for cure
- Diagnose advanced disease early to avoid symptoms
- ? Diagnose advanced disease early to cure????
- Enhance adherence/compliance with adjuvant medications
- Promote prevention and health including bone, sexual, psychological, cardiac health, neurological health

Summary

- Survivorship issues are important as we improve the outcomes of women with breast cancer

- Adherence to endocrine therapy is important if it is going to be successful and if this is an issue, referral back to oncology is important

- Further information on the subclassification of tumours and their heterogeneity is coming and will further advance our goal of personalized medicine with an impact on followup guidelines and hopefully less toxicity

- The future may provide blood tests etc that may provide both more reassurance to persons with a history of breast cancer and earlier diagnosis which may or may not improve outcomes for recurrent cancers


Thank you for your attention!