Royal Free London
NHS Foundation Trust

Systemic Treatment for Breast Cancer: Addressing The Management of Early Breast Cancer

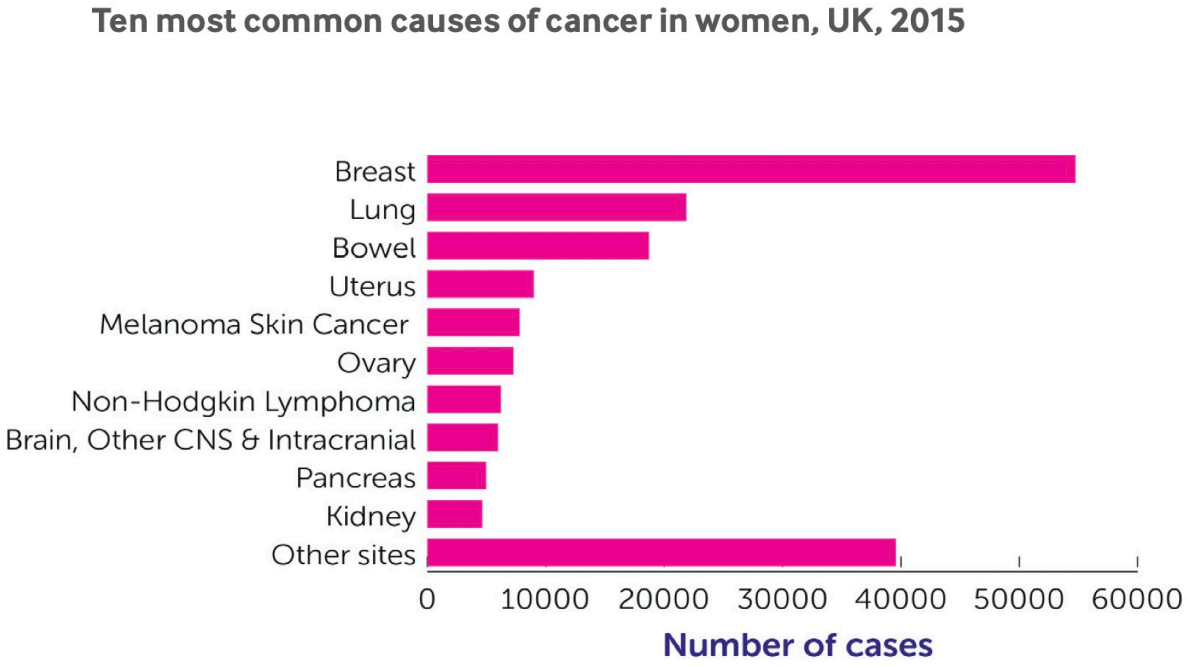
Dr Neha Chopra

Consultant Medical Oncologist

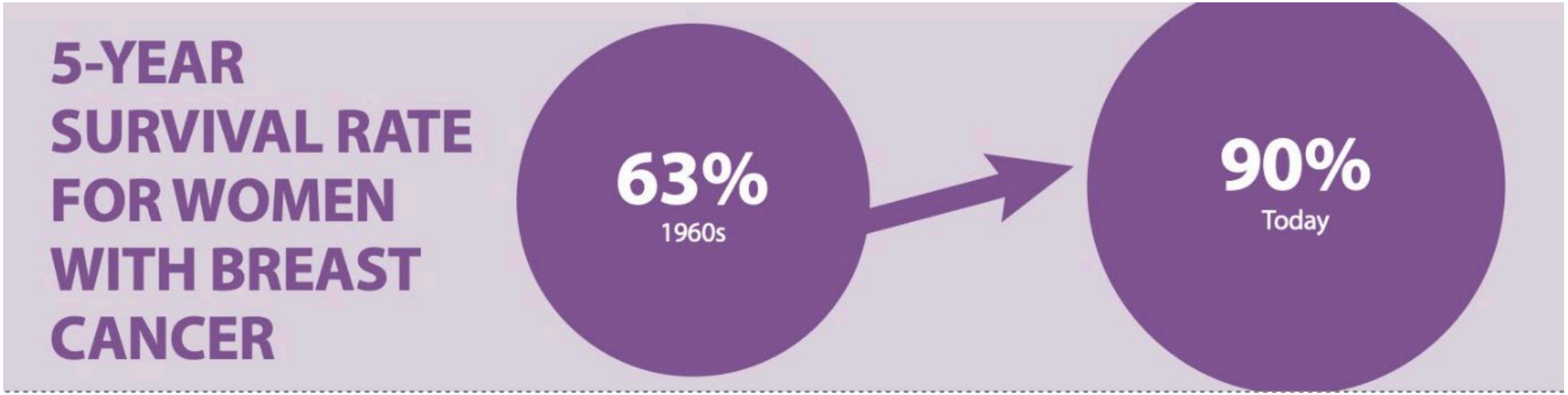
neha.chopra@nhs.net

WHY IS BREAST CANCER SO IMPORTANT?

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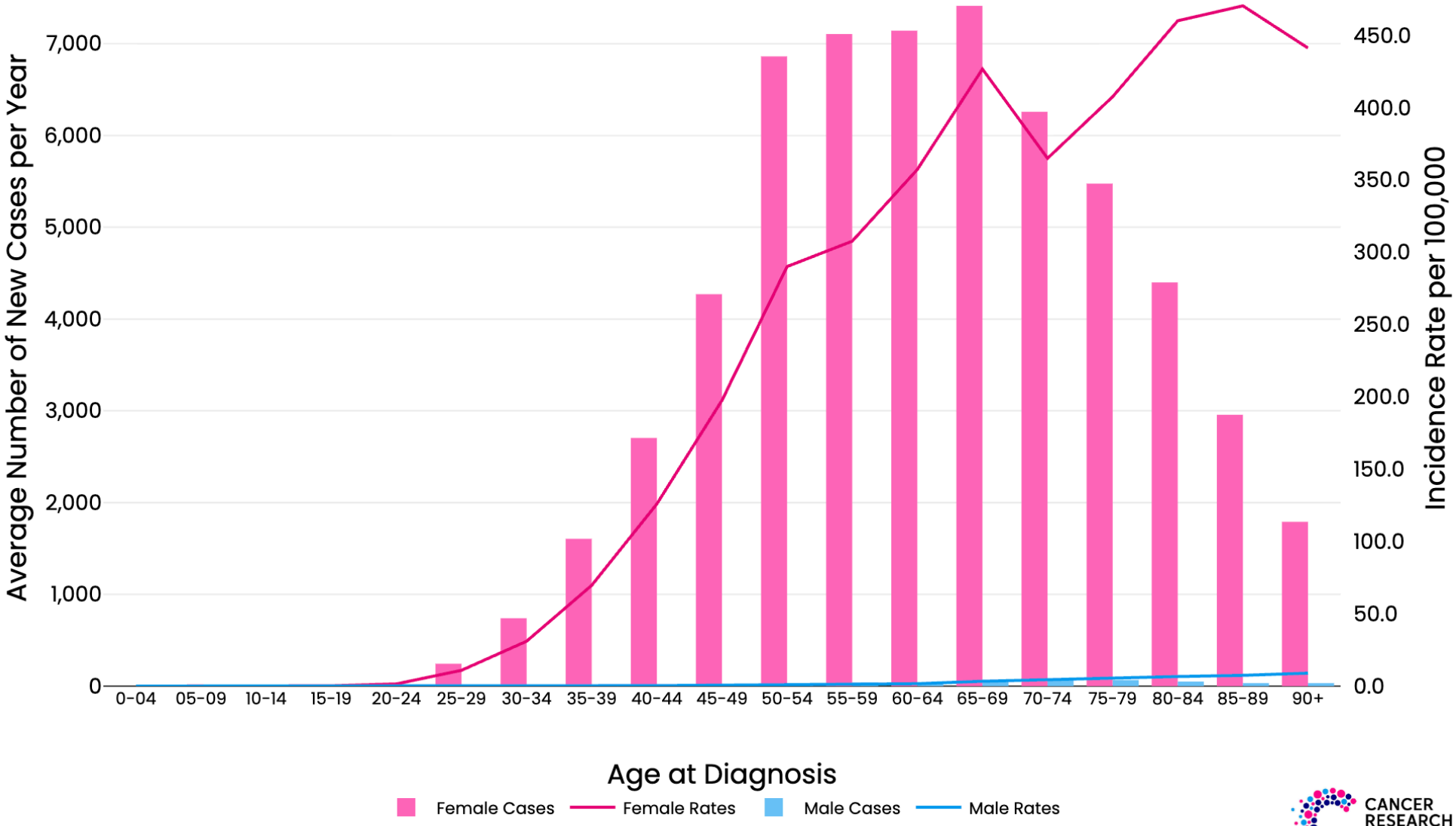






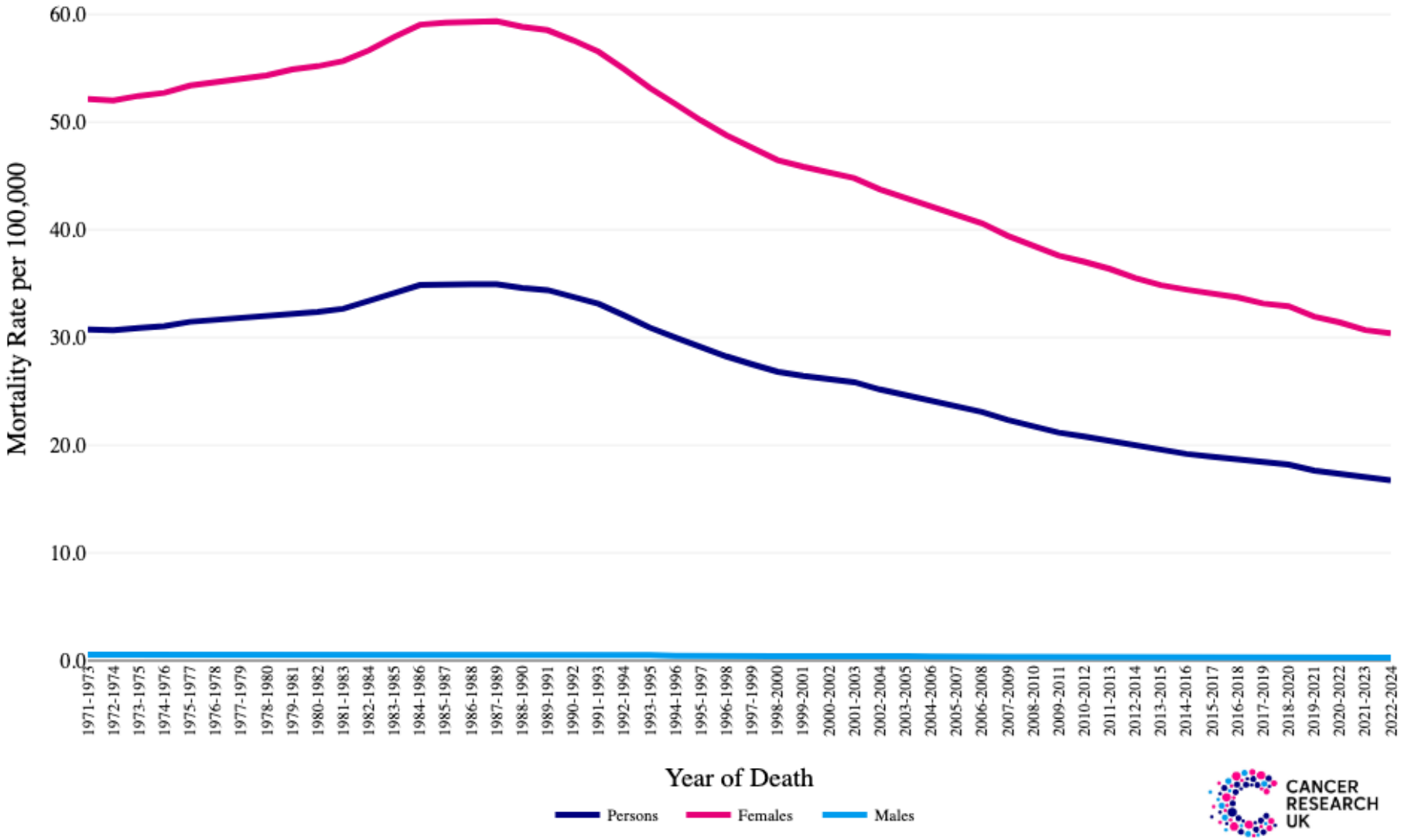
https://www.bma.org.uk/media/2112/bma-womens-health-cancer-in-women-aug-2018.pdf

Breast Cancer (C50) Average Number of New Cases per Year and Age-Specific Incidence Rates per 100,000 Females and Males, UK, 2019, 2021-2022



CANCER RESEARCH UK

Breast Cancer (C50), European Age-Standardised Mortality Rates per 100,000 Persons, UK, 1971-2024



CANCER RESEARCH UK

WHO GETS BREAST CANCER....?

Men get it too
<1%

Can happen in younger women

RISK FACTORS



AGE

Most invasive breast cancers are found in women ages

55 or older.

GENDER

Breast cancer is

100 times

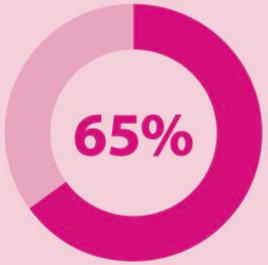
more common in women than men. About 287,850 new cases of invasive breast cancer will be diagnosed in 2022.

FAMILY HISTORY

Women with an **immediate blood relative**, such as a mother or sister, who has had breast cancer are

twice as likely

to develop the disease.



GENETICS

Women with a mutated BRCA1 gene have about a

55-72 percent

lifetime risk of developing breast cancer. **The average woman's lifetime risk is 12%.**

BRCA 1/2

HIGH BREAST DENSITY

Women with less fatty tissue and more glandular and fibrous tissue may be at **higher risk for developing breast cancer.**

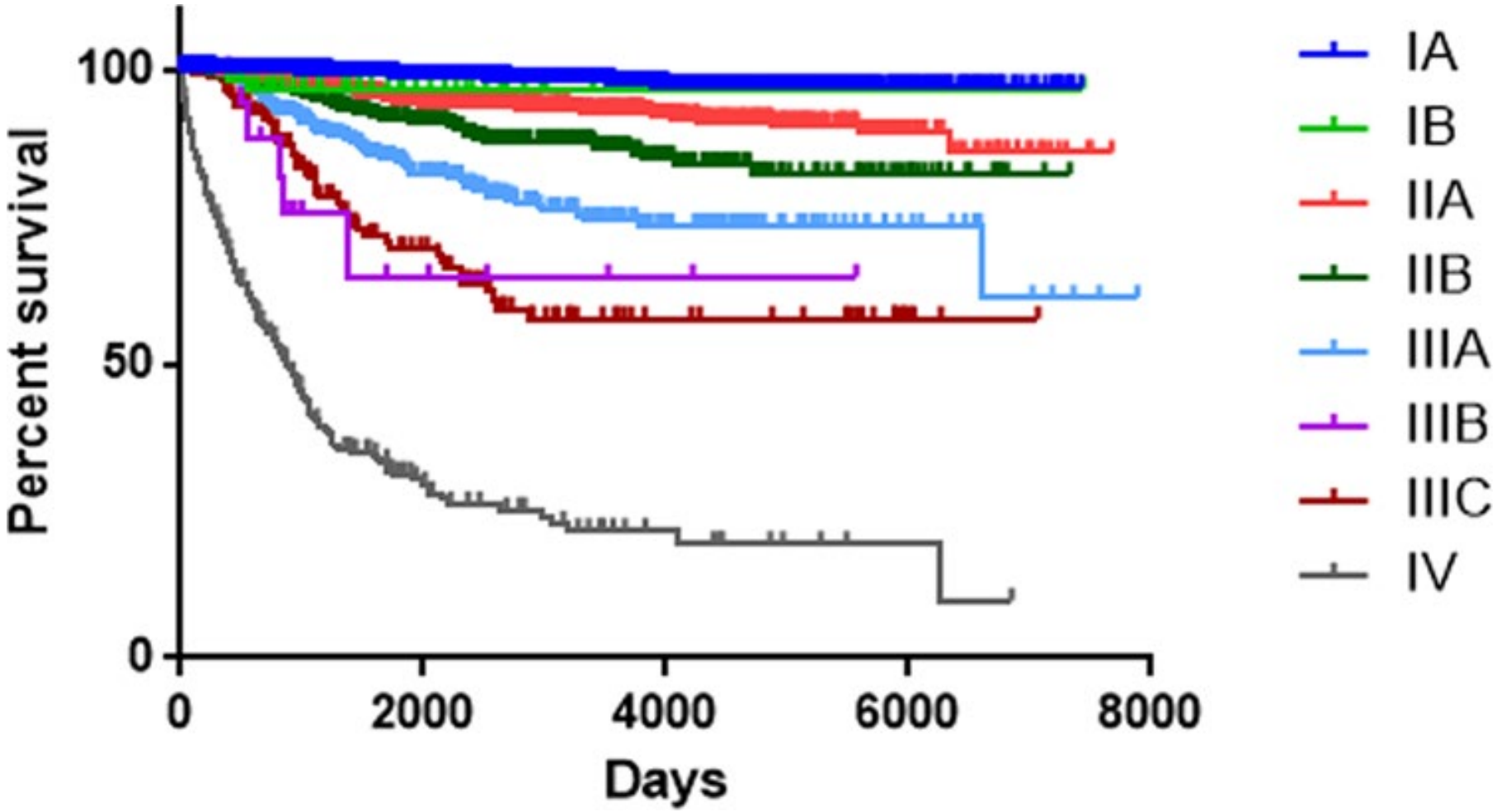
OBESITY

Fat tissue may contribute to increases in estrogen levels, and high levels of estrogen may increase the risk of breast cancer.

HEAVY DRINKING

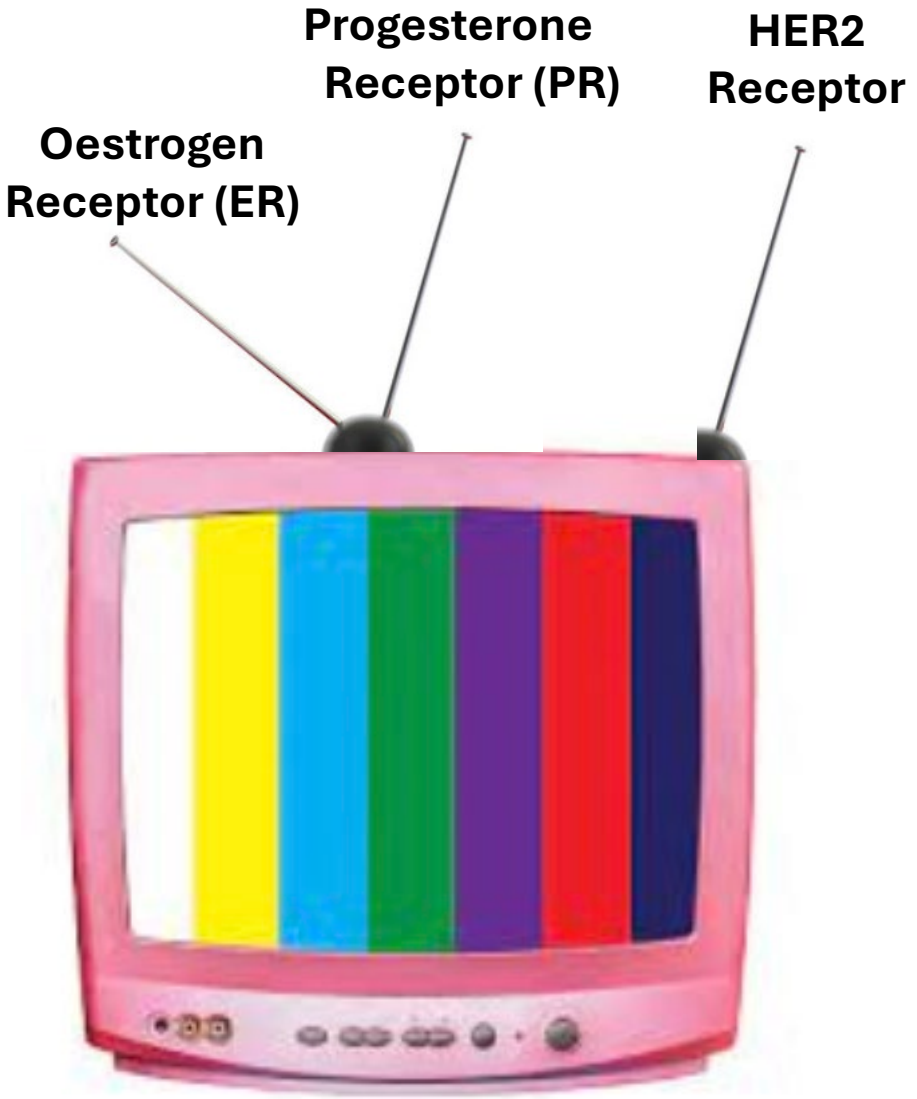
Alcohol use is linked to an increased risk of developing breast cancer. The risk increases with the amount of alcohol consumed.

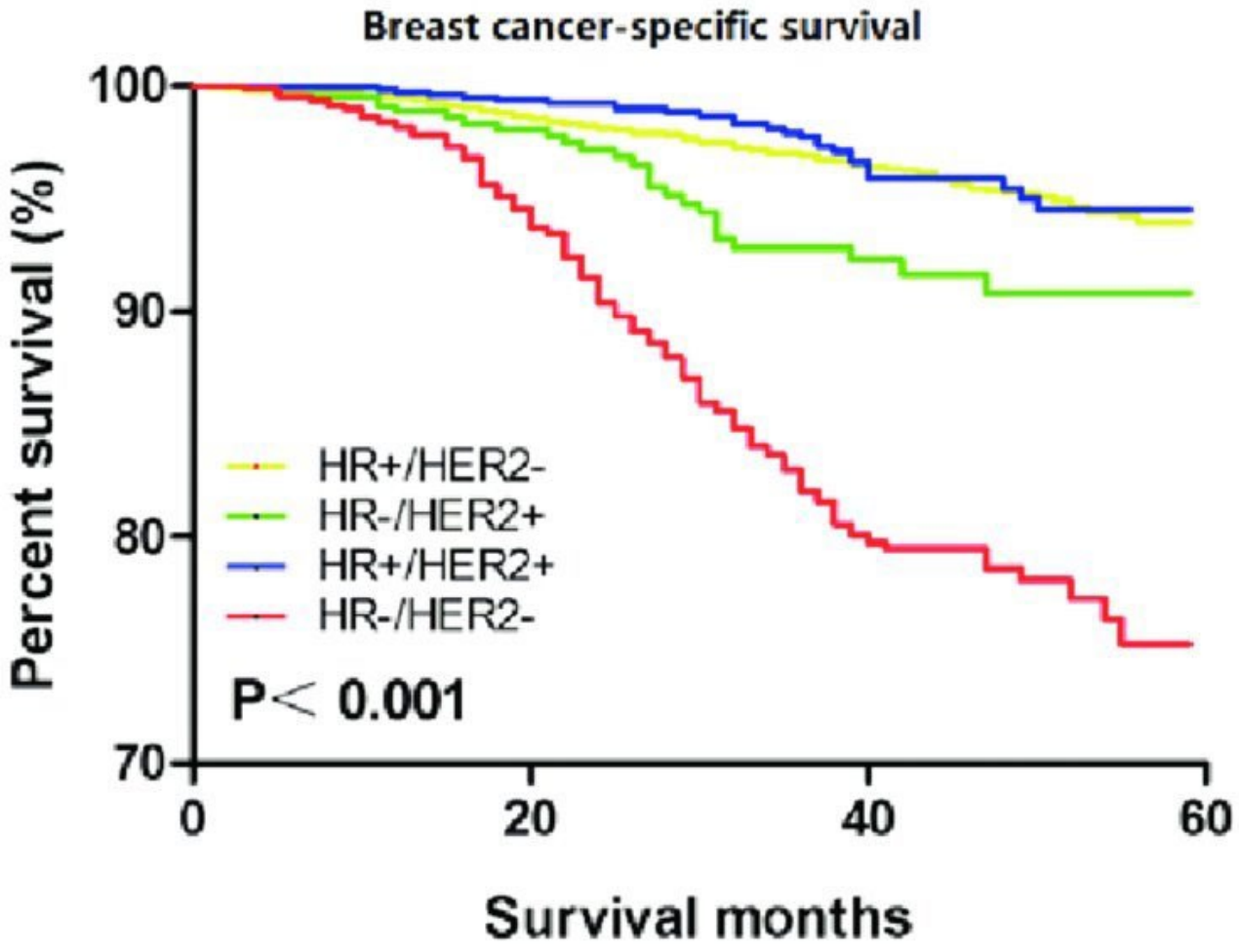
Breast cancer survival by staging



https://doi.org/10.1038/s41379-020-00650-4

What are receptors……and are they important?





Molecular Subtyes of Breast Cancer



- **Luminal A [40%]**
  ER+/PR+, HER2-
- **Normal-like [2-8%]**
  ER+/PR+, HER2-
- **Luminal B [20%]**
  ER+/PR+, HER2+/-
- **HER2-enriched [10-15%]**
  ER-/PR-, HER2+
- **Basal-like/Triple Negative [15-20%]**
  ER-/PR-, HER2-

Good

Prognosis

Poor

Clinical history

What is important to ask in a breast cancer history:

Age:

- Breast cancer is postmenopausal women
- Can happen in younger – more aggressive

Family history

- Breast/ ovarian prostate cancer
- Degree of relative
- BRCA1/2, PALB2 mutation

Reproductive factors:

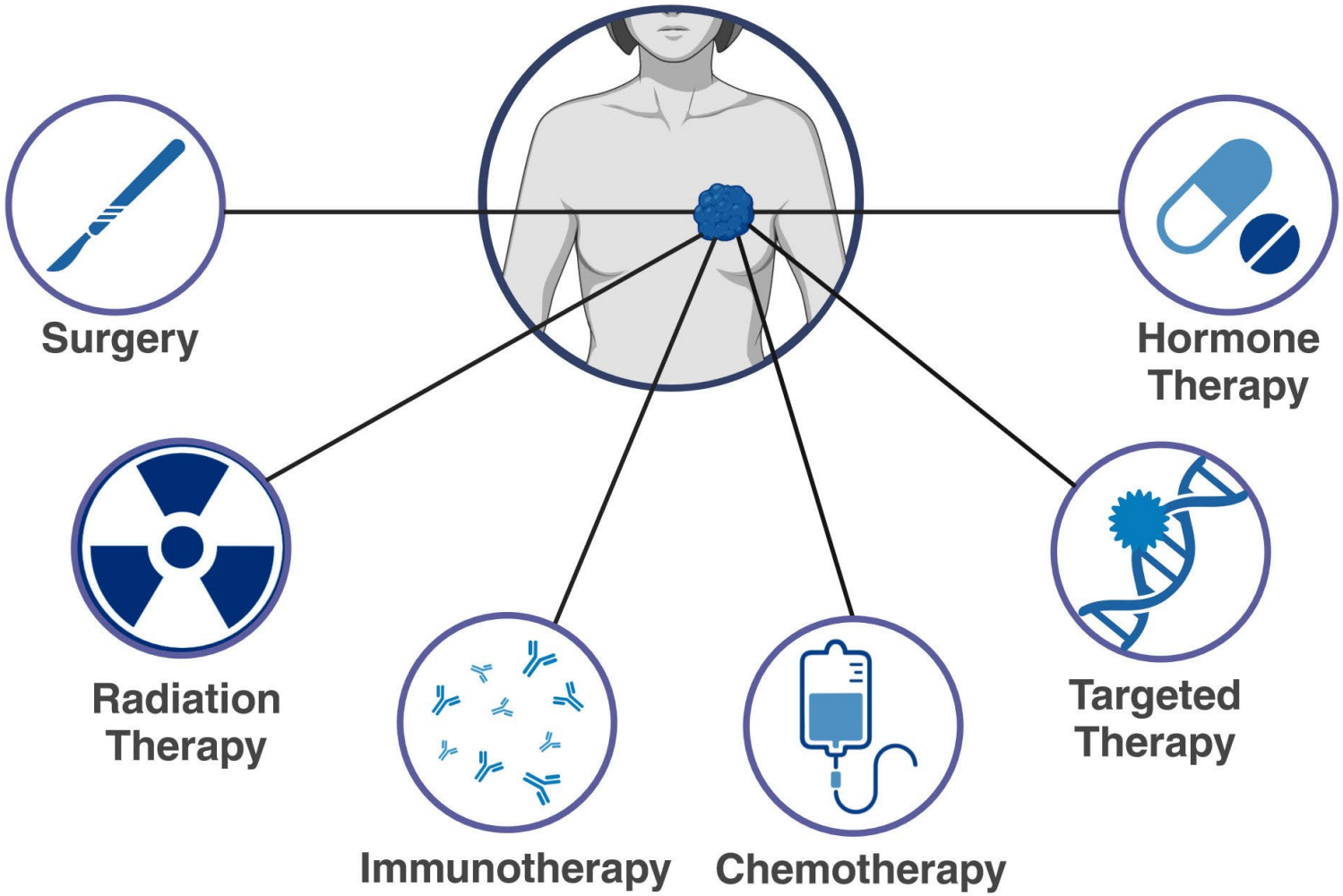
- Menstruation start/ stop
- Age of 1st child
- Number of children
- Breastfeed
- OCP use
- HRT use

Lifestyle:

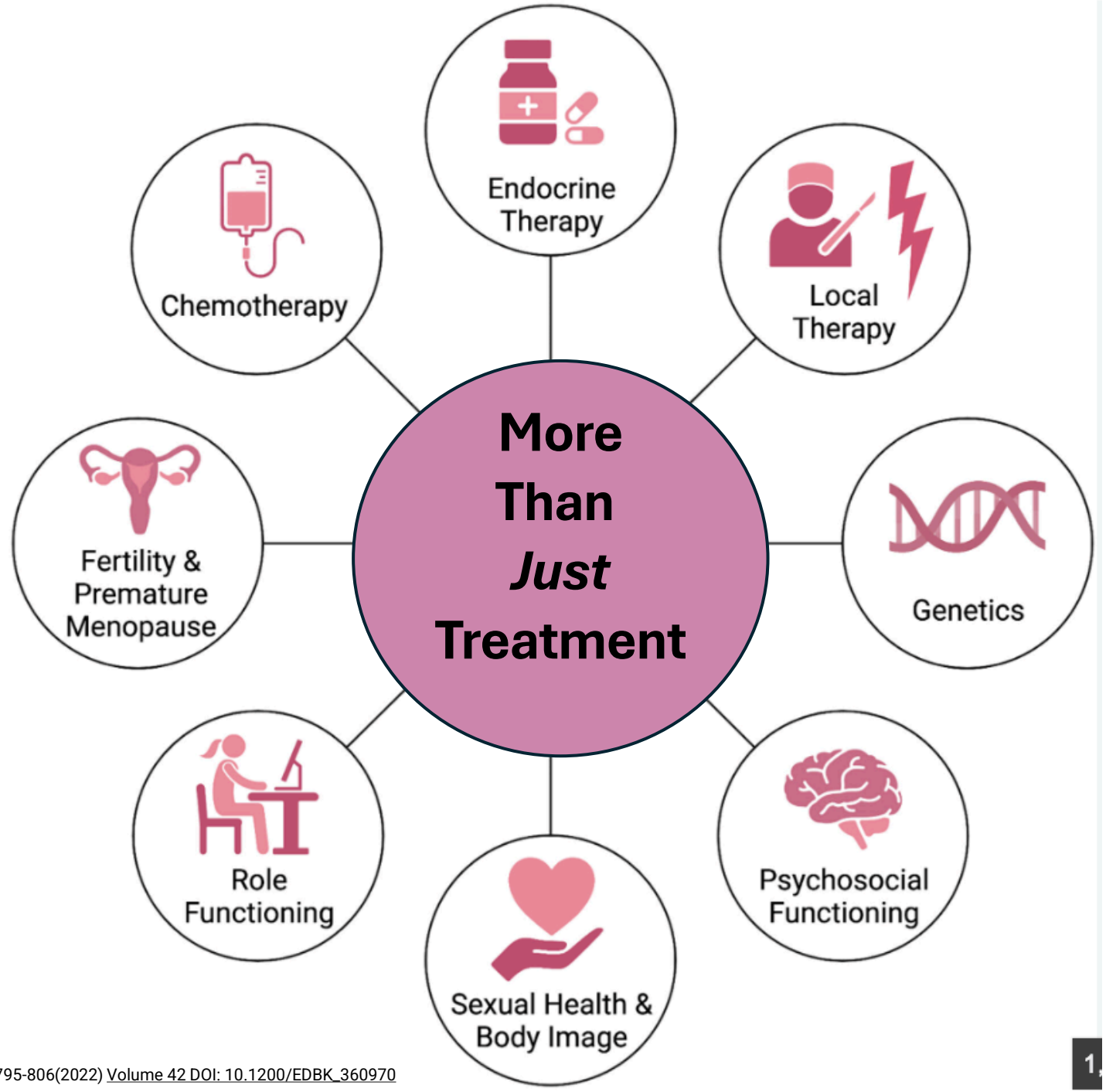
- Smoking (pack years)
- Alcohol
- Weight (BMI?)

Mainstream genetics
Breast cancer <40
Bilateral breast cancer <50 years
TNBC <60 years
Male (any age)
History of ovarian cancer
Breast cancer <45 years & a 1st degree relative with breast cancer aged <45 years
Manchester score ≥ 15 (or BOADICEA ≥ 10%)
Ashkenazi Jewish

Breast Cancer Treatments



https://www.cancer.gov/types/breast/treatment/by-stage



Adapted from - Am Soc Clin Oncol Educ Book 42, 795-806(2022) Volume 42 DOI: 10.1200/EDBK_360970



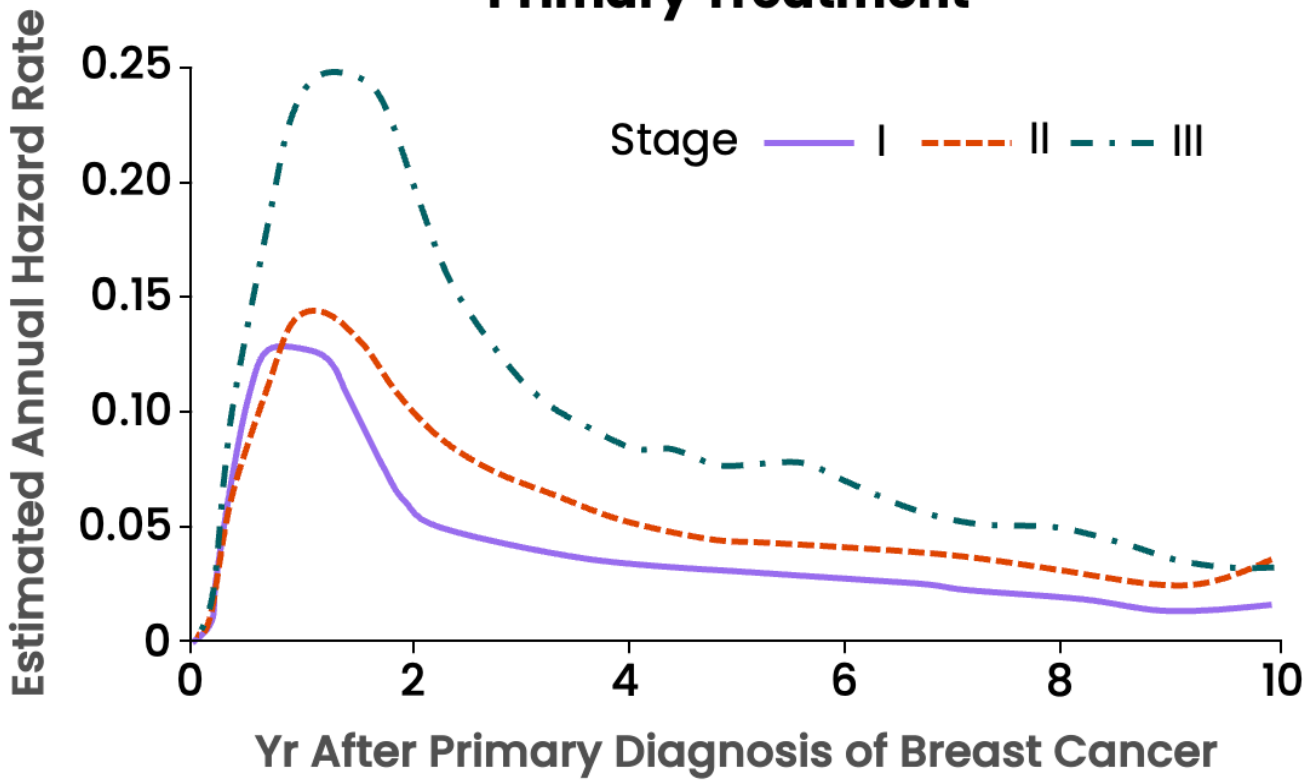
Non specific treatment for cancer and non cancer cells

Inhibits activity of specific genes, proteins or antibodies that are helping the cancer to grow



It is all about RISK.....What is the RISK.....Then decide What is the best Treatment

Risk of First Recurrence After Primary Treatment[1]



Recurrence Risk Increases With[2-5]

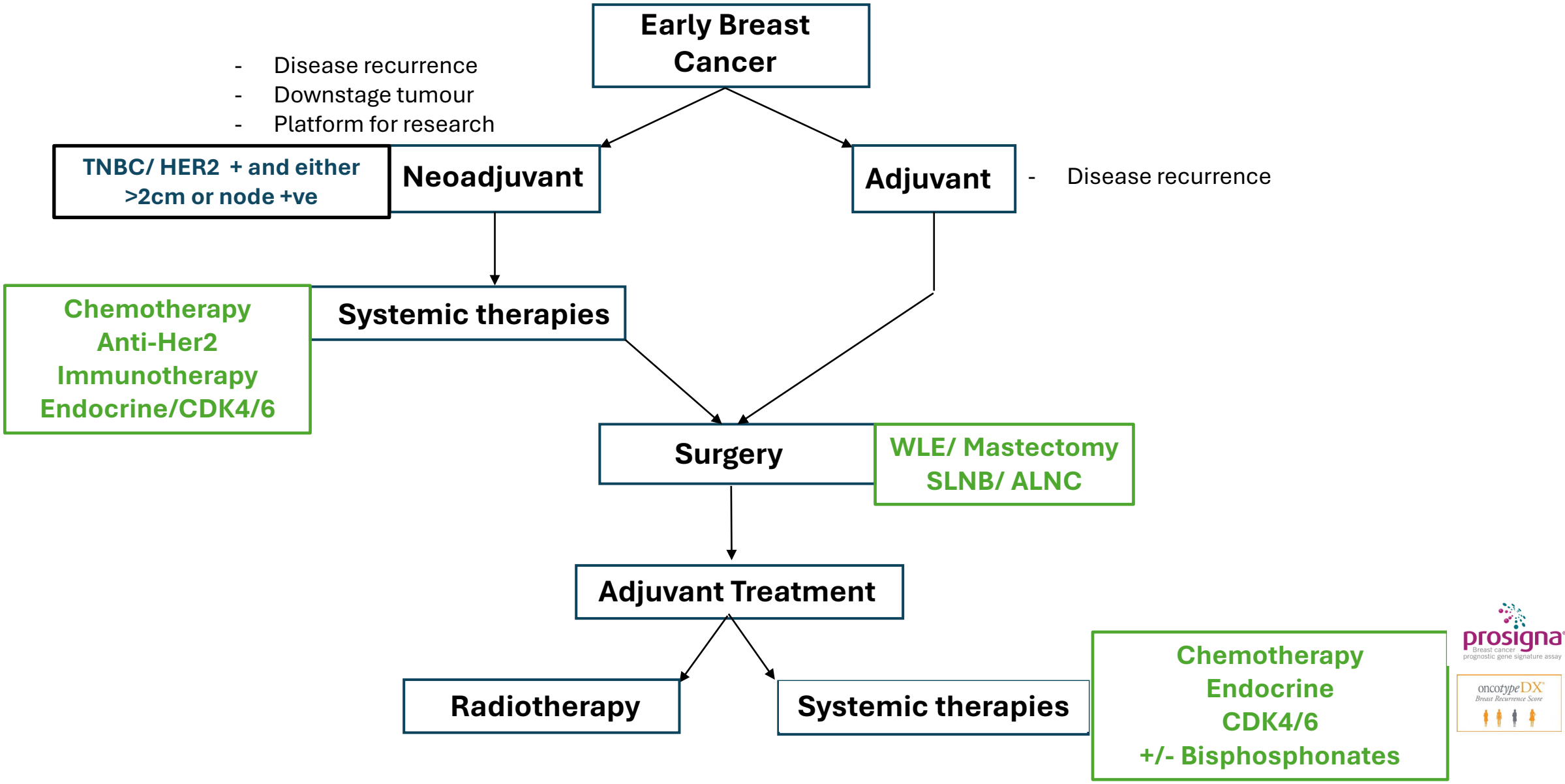
- ET resistance
- Larger tumor size
- Node positivity
- Higher grade
- Higher proliferation rate (ie, Ki-67 index)
- Lower ER and/or PgR levels
- Luminal B, HER2-enriched, and basal-like molecular subtypes

1. Cheng. Cancer Epidemiol Biomarkers Prev. 2012;21:800. 2. Fan. Future Med Chem. 2015;7:1511.
3. Garutti. Cancers. 2022;14:1898. 4. Pan. NEJM. 2017;377:1836. 5. Pan. SABCS 2019. Abstr GS2-04.

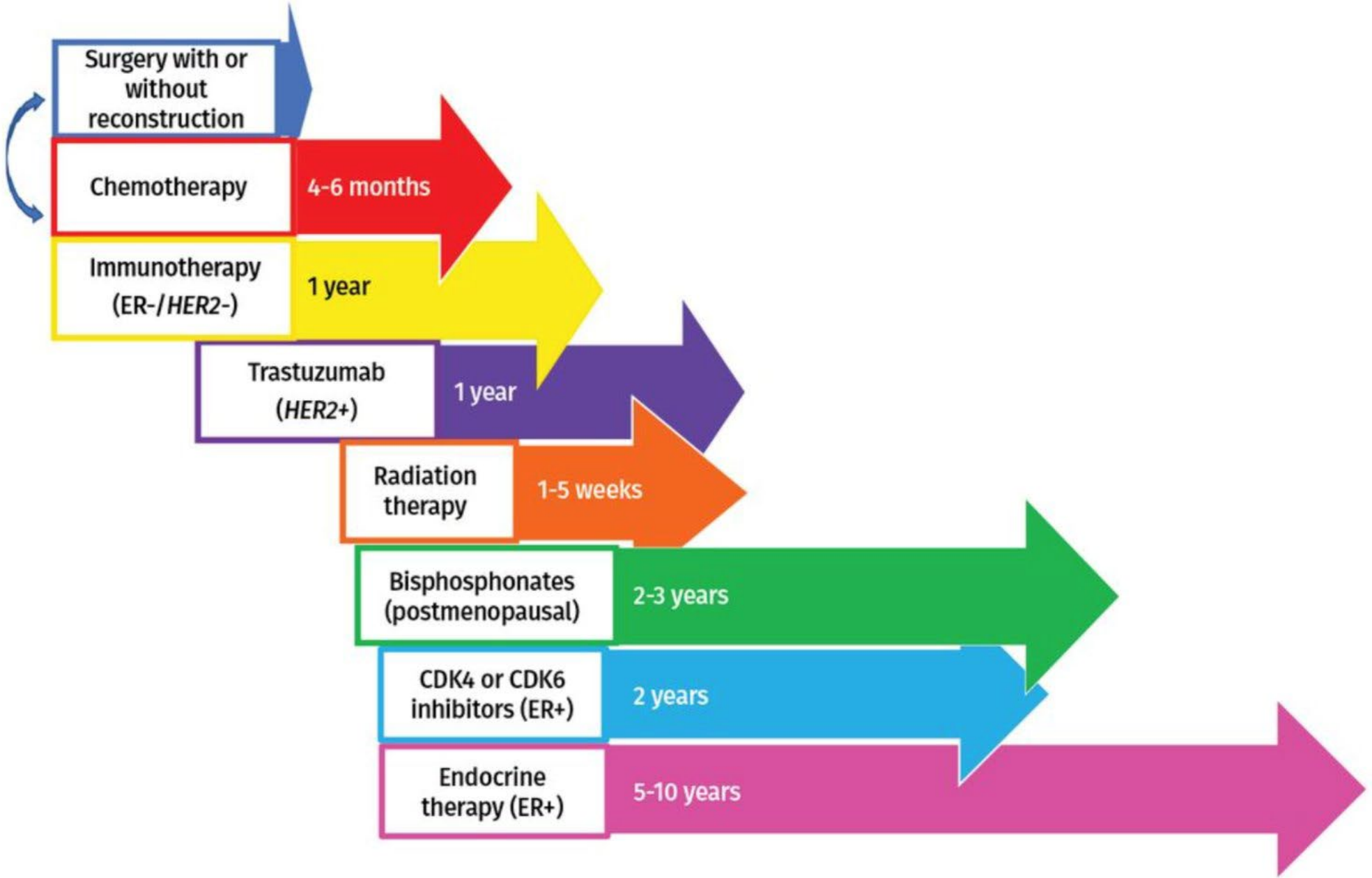
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Early breast cancer - CURABLE

Need to know RECEPTORS to decide treatment



Early Breast Cancer



Why choose neoadjuvant therapy?

2005

Neoadjuvant therapy was primarily used to:

- Downstage tumors
- Improve surgical outcomes
- Increase breast conservation

2026

Neoadjuvant therapy now allows us to:

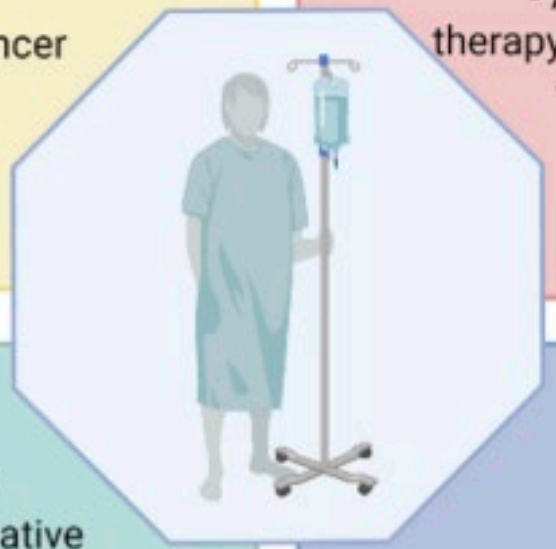
- Inform prognosis
- Tailor postoperative therapy
- Explore treatment de-escalation
- Evaluate novel agents rapidly

Neoadjuvant therapy has evolved from a surgical strategy into a platform for treatment personalization and therapeutic innovation in HER2-positive breast cancer

Neoadjuvant Treatment

Neoadjuvant chemotherapy indications :
- Triple negative breast cancer >1cm
- HER2 positive breast cancer >3cm or node positive
- High risk luminal breast cancer
- Inflammatory breast cancer

Neoadjuvant regimens :
- Combination of anthracyclines and taxanes
- Addition of HER2-targeted therapy in HER2 positive subtype
- Addition of platinum and immunotherapy in triple negative subtype



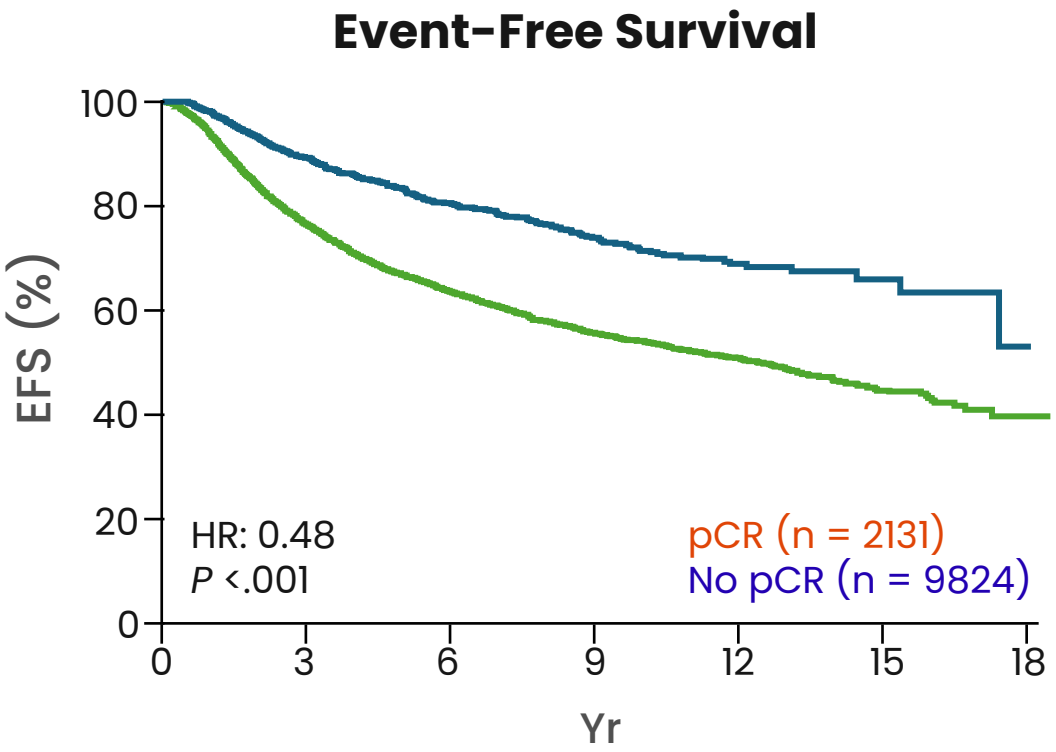
Advantages :
- Evaluation of sensitivity
- Enabling breast conservative surgery
- Downstaging of lymph node status
- Micro-metastasis eradication
- Tailoring of adjuvant therapy

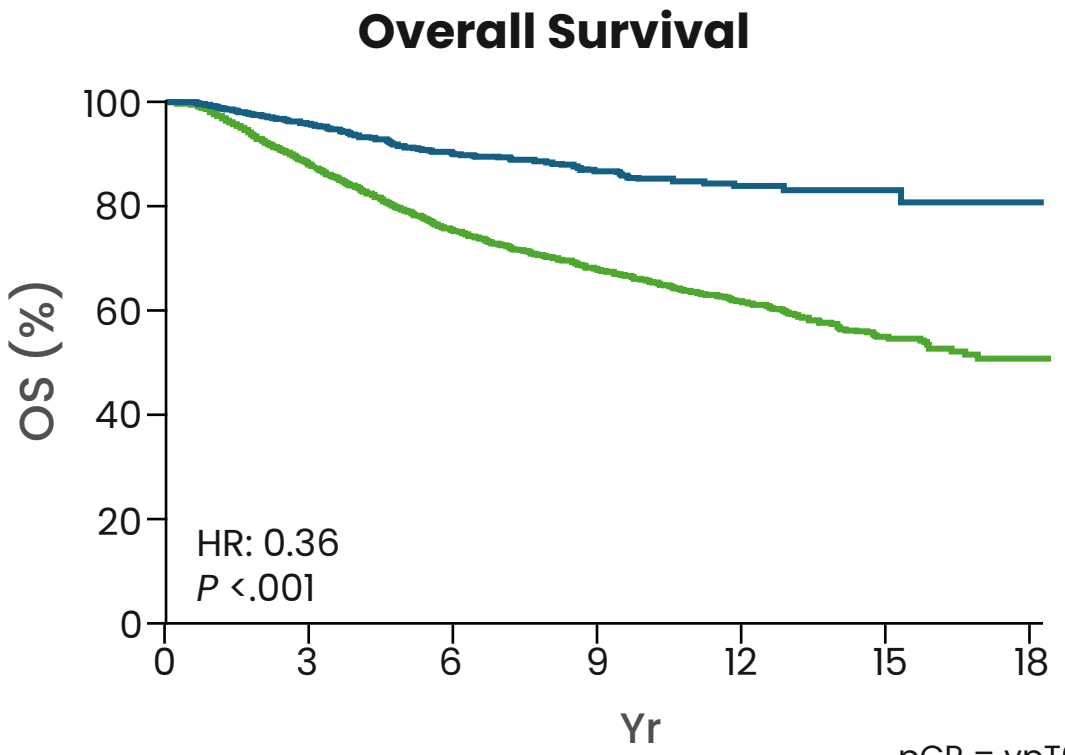
Disadvantages :
-Adverse events of NAC (*e.g.* cardiotoxicity, neuropathy)
-May delay surgery
- Healing difficulties after surgery
- Progression can occur during NAC

Main goal of neoadjuvant chemotherapy : achieving pathological complete response

Pathological complete response associated with better OS

Central Role of pCR in Neoadjuvant Therapy: Association of pCR With EFS and OS





pCR = ypT0/is ypN0

Patients who attain a pCR have more favorable long-term outcomes

Cortazar. Lancet. 2014;384:164.

HER2+ve EBC

- **WHO to ESCALATE/give NACT**
- T2+**N0**: accel EC, taxol HP/ TCHP then **12m herceptin if pCR**
- T2+**N1**: accel EC taxol HP then **12m HP if pCR** (APHINITY[1])
- **ALL**: if ***non pCR give adjuvant TDM1***

  (12m anti her2 therapy total) rather than H or HP (KATHERINE[2])

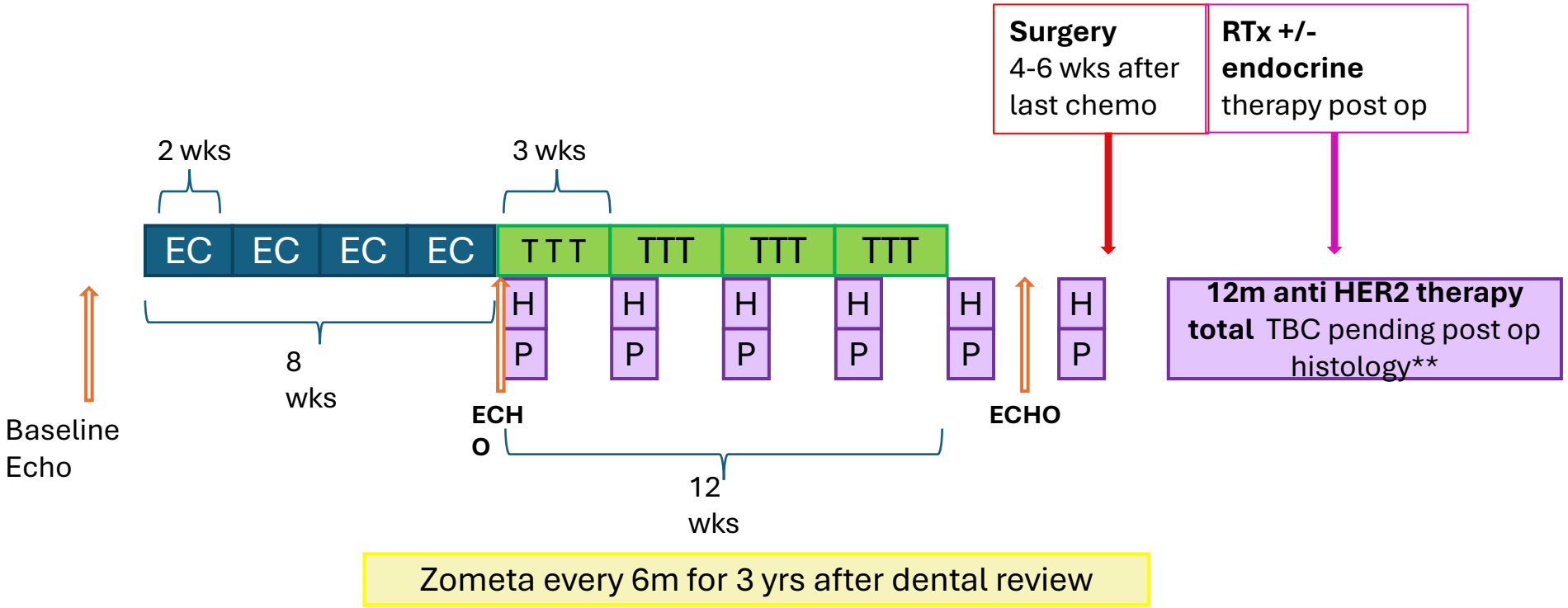
  OR CLINICAL TRIAL

- **De escalate in**
- <2cm N0
  - especially if G2 or ER+
- APT regime: 12 weeks taxol plus 12m herceptin[3]
- Or consider 6m herceptin instead of 12m (PERSEPHONE trial[4])
- Consider THP in neoadjuvant setting
  - T1c
  - Node negative
  - CompassHER-pCR
  - neoCARP

NEW DATA:
Destiny-Breast 05
Destiny- Breast11

1. Von Minckwitz et al N Engl J Med 2017; 377:122-131
2. Von Minckwitz et al N Engl J Med 2019; 380:617-628
3. S Tolaney et al JCO, no. 22 (August 01, 2019) 1868-1875
4. H Earl Lancet 2019 DOI:https://doi.org/10.1016/S0140-6736(19)30650-6

NACT HER2+ve: ACCELERATED EC TAXOL HP

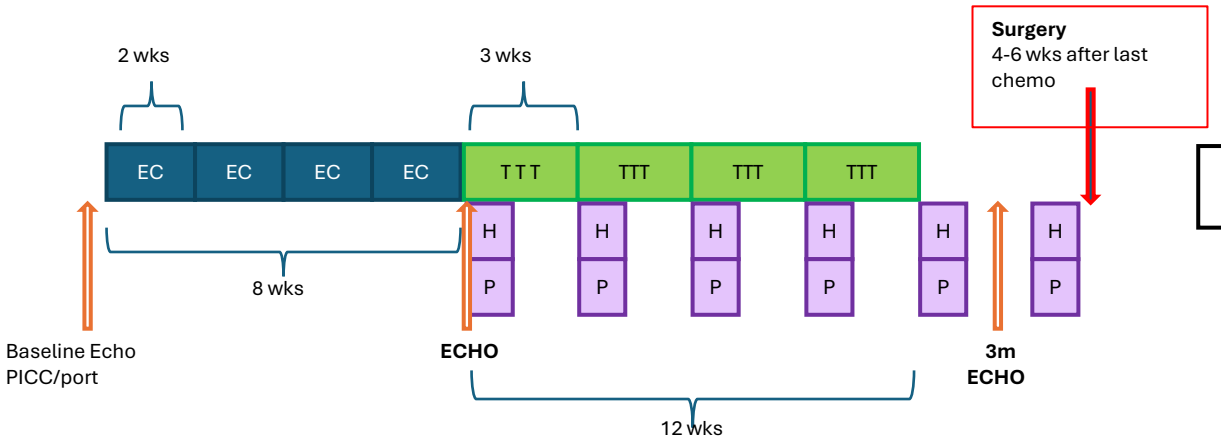


Summary

- Accelerated EC x4 every 2 wks
- Weekly taxol for 12 wks with HP every 3 wks
- HP continues until post op review
- 12m anti HER2 therapy – confirmed at post op review**
- Baseline Echo, repeat after 4 EC, then every 3 months
- Radiotherapy/endocrine therapy after surgery
- 6 monthly zometa for post menopausal pts after dental review

NACT HER2+ve

***12m anti HER2 therapy in TOTAL: to be decided at MDT on review of post op histology ?pCR achieved*



Zometa every 6m for 3 yrs after dental review

MDT

Complete pCR

If NODE –ve at outset and NO FIRBROSIS in SLNB:

- **STOP PERTUZUMAB**
- **switch to SUBCUT TRASTUZUMAB**

Complete 12m anti her2 therapy in total.
4m Echo

If NODE +VE at outset OR evidence of FIBROSIS IN NODES:

- **Continue HP 12m total**
- **3m Echo. CDF form**

No/ incomplete pCR

ALL non pCR:

- **Stop HP**
- **switch to TDM1/ Trial**
- **3m Echo. CDF form**

Complete 12m anti her2 therapy in total

TNBC EBC

- **NACT/escalate**
  - High risk e.g. N+, >2cm
  - Genetic testing
- Carbo/taxol →EC +pembro (Keynote-522)
- Pembro cont in adj setting 6 weeks – 12 months total
- BRCA Mutation – adjuvant Olaparib (OlympiA study)

- **De escalate** if elderly/comorbidities:
- give adjuvant chemo
- Give weekly taxol (+/- zometa)

ER+ve EBC

- **Escalate if clinical RF**

  (G3, node+, high risk Oncotype/ Prosigna)

- Accelerate EC and taxol (give 2 weekly)

- **De escalate in lower risk patients**:

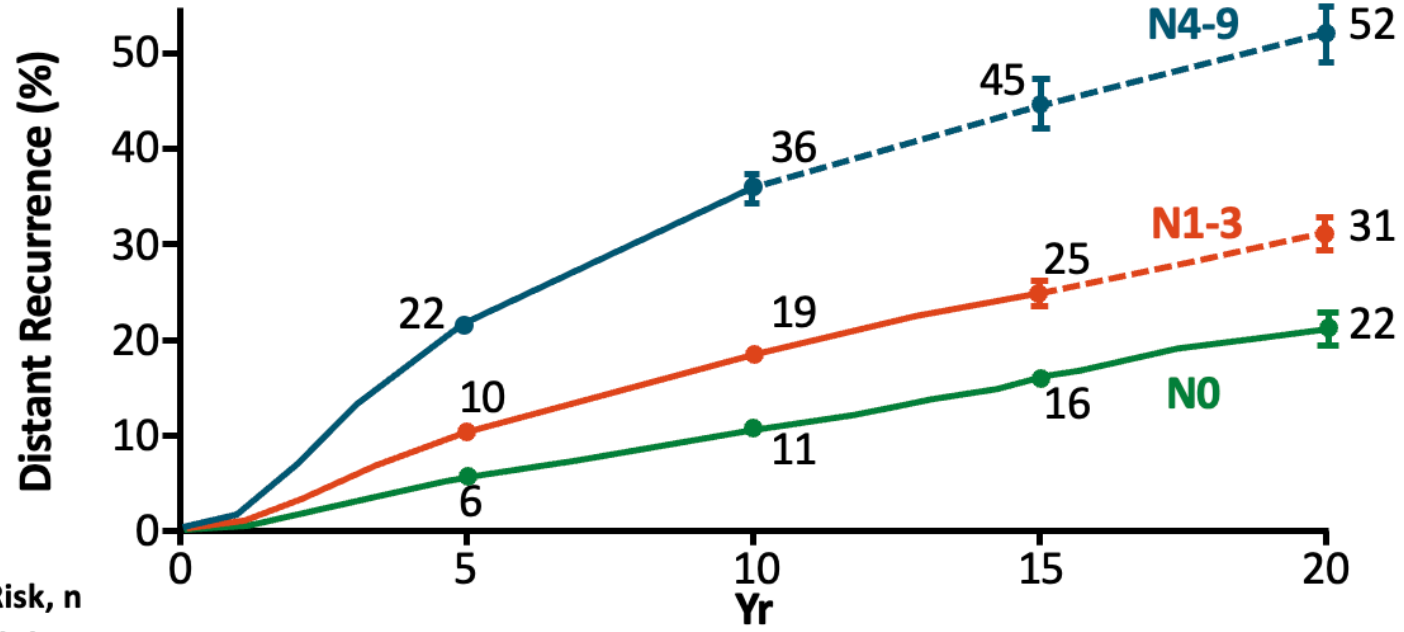
- Oncotype/ Prosigna in ER+HER2-ve **node –ve (or micromets)**

- No chemo for low risk
- Consider EC x4 for intermediate risk

Adjuvant Treatment – Risk Assessed

Risk of Distant Recurrence After 5 Yr of Endocrine Therapy

- Meta-analysis of patients with ER+ BC diagnosed in 1976-2011 who received 5 yr of ET and were disease free at 5 yr (N = 71,194)[1]



Patients at Risk, n Nodal Status					
N4-9	12,333		2165	259	52
N1-3	**31,936**		**7250**	**949**	**183**
N0	29,925	24,081	8571	1982	414

Dashed line indicates event rate for 5-yr period, not individual yr.

In updated analysis, 20-yr risk of DR was 1/3 lower for N0 ER+ EBC diagnosed after vs before 2000[2]

20-Yr Risk of DR, %	N0 ER+ EBC	
	T1N0	T2N0
Diagnosed before 2000	13	19
Diagnosed after 2000*	8	14

*Projected.

1. Pan. NEJM. 2017;377:1836. 2. Pan. SABCS 2019. Abstr GS2-04.

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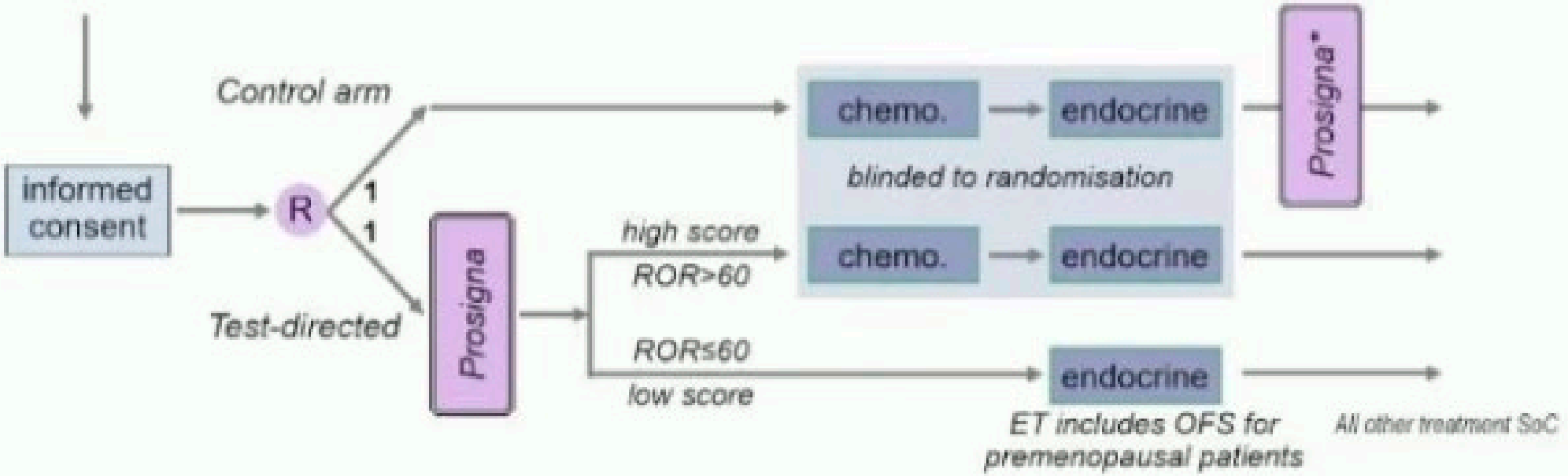
Need to Know What is LOW vs HIGH Risk

LOW RISK	HIGH RISK
Post Menopausal	Pre Menopausal
< 2cm	>2 cm
No Lymph Nodes	Lymph Node Involvement
Low Recurrent Score (Oncotype/ Prosigna)	High Recurrent Score (Oncotype/ Prosigna)
Ki67 <20%	Ki67 >20%

OPTIMA design

Main eligibility criteria

- Women & men age ≥40 with excised breast cancer
- ER-pos (IHC>10%) & HER2-neg
- Nodes: ▸0-9N+,
  ▸minimum T-size requirement if N0/ N1mi
- Neoadjuvant chemotherapy prohibited



*Control arm Prosigna testing used for analysis only. UK control arm testing performed following recruitment completion

Presentation: Prof. Robert C. Stein

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OPTIMA: Baseline Characteristics

Characteristic	Control Arm (n = 2059)	Test-Directed Arm (n = 2094)	Total (N = 4153)
Median age, yr (range)	55 (40-84)	56 (40-82)	56 (40-84)
Menopausal status, n (%)			
• Premenopausal	776 (38)	775 (37)	1551 (37)
• Postmenopausal	1265 (61)	1302 (62)	`2567 (62)
• Men	18 (1)	17 (1)	35 (1)
Grade, n (%)			
• 1/2	1417 (69)	1465 (70)	2862 (69)
• 3	642 (31)	629 (30)	1271 (31)
Tumor size, n (%)			
• <30 mm	1104 (54)	1128 (54)	2232 (54)
• ≥30 mm	955 (46)	966 (46)	3050 (46)
Nodes involved, n (%)			
• 0/micromets	160 (8)	167 (8)	327 (8)
• 1-3*	1515 (74)	1534 (73)	3049 (73)
• 4-9	384 (18)	393 (19)	777 (19)
Median ROR score (IQR)	50 (34-65)	49 (34-65)	--
• ROR ≤60, %	66.0	67.8	--

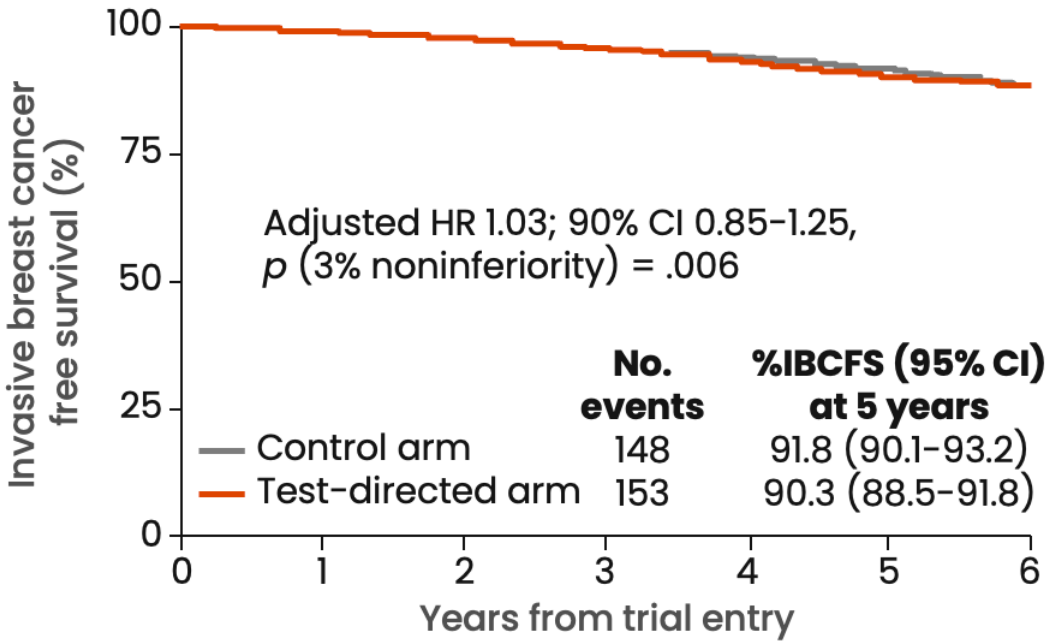
*39% of pN1 tumors had sentinel node biopsy only.

Stein. ASCO 2026. Abstr 500.

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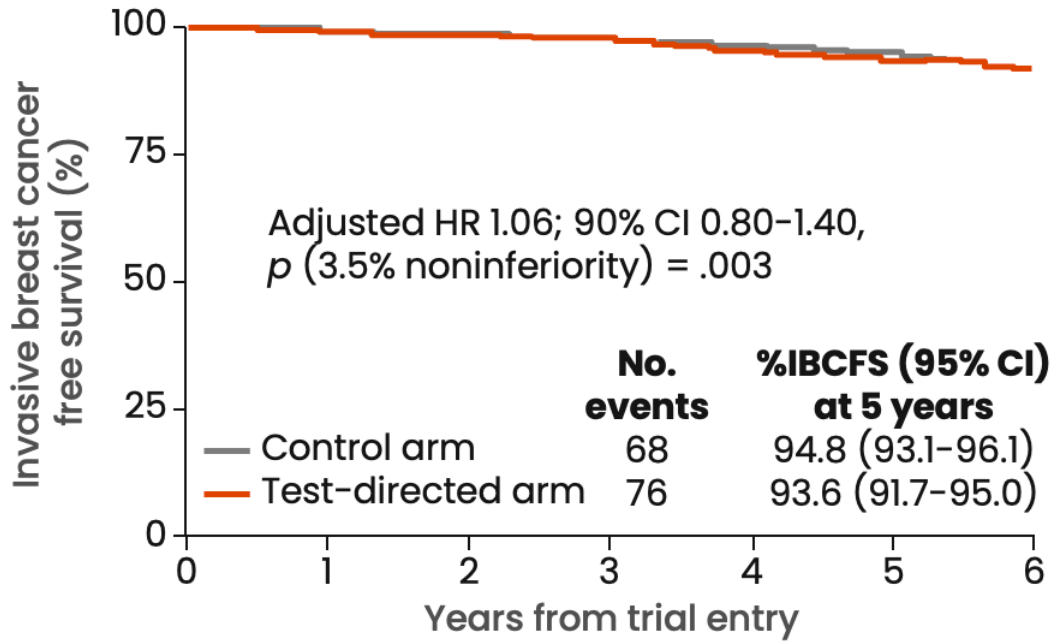
OPTIMA: Invasive Breast Cancer–Free Survival

Complete Per Protocol population



No. at Risk:							
Control arm	2059	1818	1563	1283	999	741	485
Test-directed	2094	1857	1591	1303	989	724	481

ROR ≤60 subpopulation



No. at Risk:							
Control arm	1358	1207	1043	862	672	504	337
Test-directed	1421	1257	1086	905	694	503	342

DECERA CLINICAL Education

Stein. ASCO 2026. Abstr 500. Reproduced with permission.

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OPTIMA: Investigators' Conclusions

- Phase III OPTIMA trial found that pretreatment 50-gene Prosigna testing in patients with high-risk ER+/HER2- EBC and ROR scores ≤60 effectively identifies patients with little/no benefit from chemotherapy
    - This approach allows selected patients to avoid chemotherapy-related toxicities
    - For every 100 patients, ≤2 recurrences will be prevented with chemotherapy
- Investigators conclude that gene expression testing can be used to safely avoid chemotherapy in postmenopausal women and premenopausal women aged ≥40 yr receiving ovarian function suppression, patients with 4-9 involved lymph nodes, and patients with stage IIIA tumors

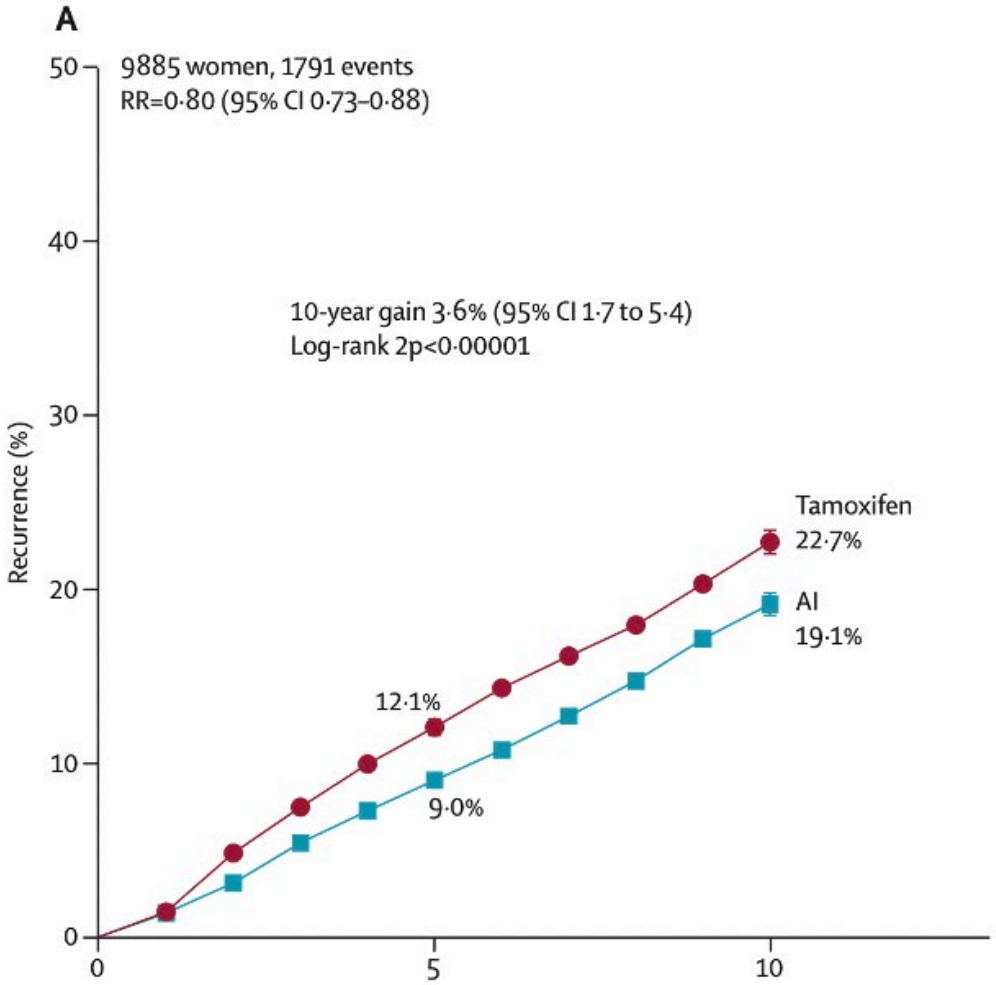
Adjuvant ER+

THEN	2 years Ago	NOW

Tam 5 yrs
AI 5 yrs
	Premenopausal
	•Extended Tam 10 yrs (ATLAS and ATTOM)
	•Zoladex plus AI (TEXT and SOFT)
	
	Perimenopausal
	Tam – AI sequence
	
	Postmenopausal
	Tamoxifen or AI 5 or 10
	
	<u>Offer extended adjuvant if either N+ve or >2cm</u>
	• if well tolerated and bone health stable
		HIGH RISK ER+ HER2-:
		Adjuvant abemaciclib (MonarchE)
		• 1-3 nodes AND >5cm/ grade 3
		• >4 nodes
		• 2 years treatment
		• Alongside endocrine
		
		Adjuvant Ribociclib (NATALEE)
		• **N1, N2**
		• **N0:**
		  ○ Grade 3
		  ○ Grade 2 + high risk:
		  ▪ Ki-67 ≥20%
		  ▪ Oncotype ≥26 or
		  ▪ High risk via genomic risk profiling

NB: the best endocrine therapy is the tablet that the patient will actually take.
Only 60% compliance in clinical trials. Extended adjuvant has not yet been shown to improve survival – especially it patients are elderly. So if patients are struggling with AI consider switch to tamoxifen

Which endocrine in early breast cancer?



Recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–1	Years 2–4	Years 5–9	Year 10+
AI	1·62 (157/9691)	2·14 (285/13336)	2·33 (365/15648)	3·23 (20/619)
Tamoxifen	2·41 (230/9542)	2·62 (338/12906)	2·48 (372/14985)	4·54 (24/529)
Rate ratio (95% CI)	0·64 (0·52–0·78)	0·80 (0·68–0·93)	0·92 (0·79–1·06)	0·72 (0·39–1·30)
from (O-E)/V	−41·1/92·8	−34·1/149·0	−15·5/177·2	−3·6/10·7

Aromatase inhibitors are used in post menopausal women

Tamoxifen in premenopausal women

(Can use tamoxifen in post menopausal if does not tolerate AI)

Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. The Lancet, 2015; 386, 1341-1352

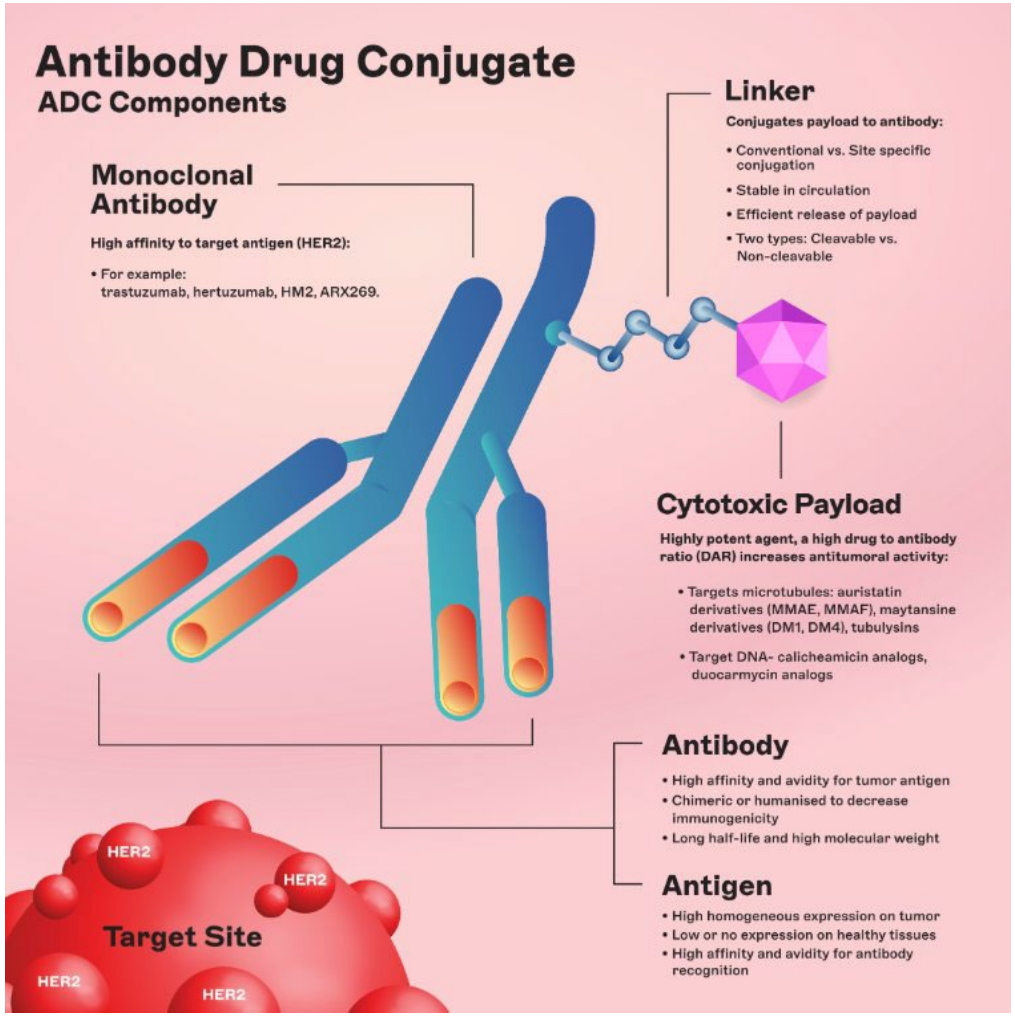
Endocrine - toxicities

Drug	How administered	Mechanism of action	Toxicities
Tamoxifen	Orally once a day, 5mg	Estrogen receptor blocker	GI (N&V, diarrhoea), hot flushes, depression, **VTE,** lethargy, vaginal bleeding, weight gain
Aromatase Inhibitors	Orally once a day Letrozole – 2.5mg Anastrazole – 1mg Exemestane – 25mg	Aromatase inhibitor	N&V, diarrhoea, reduced bone density, **hot flushes, arthralgia** depression, weight gain, **vaginal dryness** lethargy, increased lipids
GnRH Analogues	Injection once a month Goserelin, Leuprolein	Inhibition of estrogen and androgen synthesis	**Hot flushes, amenorrhoea**
Fulvestrant	Once a month injection – 500mg (first month 2 weekly)	Estrogen degrader	GI (N&V, diarrhoea), **joint disorders injection site reactions,** hot flushes

NB: the best endocrine therapy is the tablet that the patient will actually take. Only 60% compliance in clinical trials. Extended adjuvant has not yet been shown to improve survival – especially it patients are elderly. So if patients are struggling with AI consider switch to tamoxifen

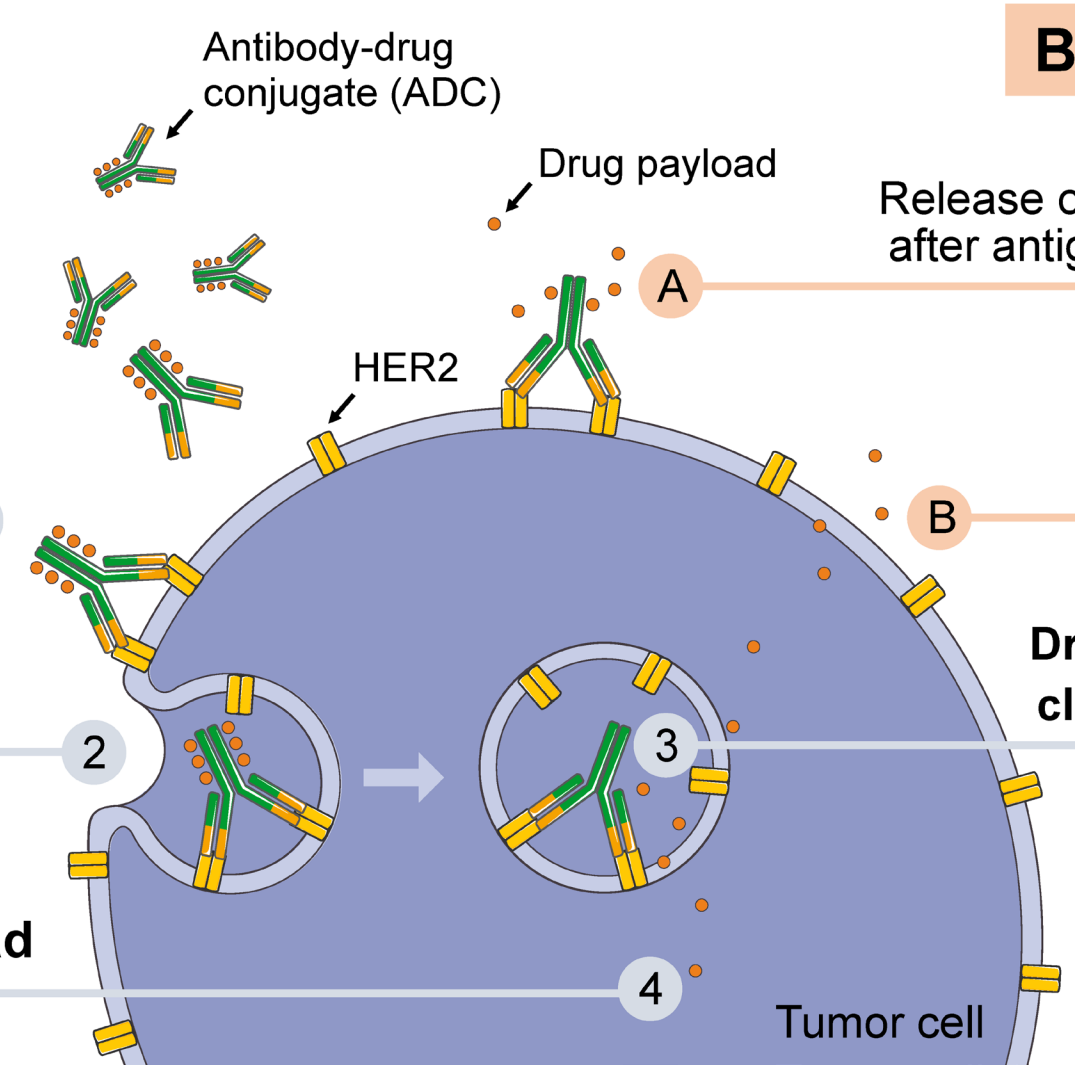
EC taxol backbone	ESCALATE	DE-ESCALATE
ER+ve	Clinically high risk: accelerate EC/T - grade 3/node +ve - high risk Oncotype	N0: Oncotype (other genomic) Low risk – no chemo Intermed risk – consider 4 EC
HER2+ve	>T2N0 NACT Accel EC, then weekly taxol HP If pCR then continue H 12m total	<T2N0 12 weeks taxol plus 12m herceptin (APT regime) Alternative: 6m herceptin rather than 12 (Persephone)
	>T2N+ NACT Accel EC then weekly taxol HP If pCR then continue HP 12m total	
	>T2Nx NACT If non pCR at surgery switch to adjuvant TDM1 alone (complete 12m anti HER2 therapy in total	
TNBC	NACT Carbo/taxol→EC + pembro followed by adjuvant pembro	Adjuvant EC taxol (accelerate if fit) Weekly taxol 12wks (if comorbid)
BRCA 1/2 Mutation	Adjuvant olaparib if residual disease post NACT OR high risk disease (OlympiA trial)	
Zometa	For postmenopausal women on chemo after dental review (risk ONJ): every 6m for 3 yrs. Start early during NACT if having	

The New Kids on the Block.....



ADC - Mode of Action

Classical ADC mode of action



ADC binding to HER2 receptor

Internalization by endocytosis

Cytotoxic effect induced by drug payload

Bystander killing effect

A — Release of drug payload from the antibody after antigen binding before internalization

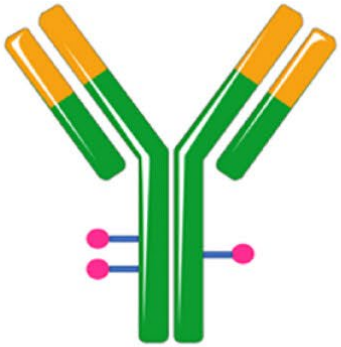
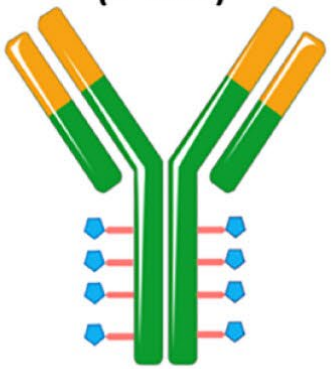
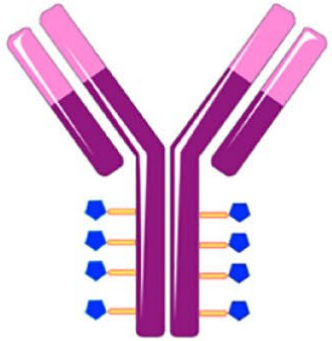
B — Release of drug payload into the intercellular space due to a high drug membrane permeability

Drug payload release after linker cleavage by lysosomal enzymes

A high drug-to-antibody ratio increases antitumoral efficacy despite a low HER2 antigen density on tumor cells

Image from Rinnerthaler. Int J Mol Sci. 2019;20:1115. HER2 directed antibody-drug-conjugates beyond T-DM1 in breast cancer.

ADCs in breast cancer

	Trastuzumab emtansine (T- DM1)	Trastuzumab deruxtecan (T- DXd)	Sacituzumab govitecan
			
Monoclonal antibody	Trastuzumab	Trastuzumab	Sacituzumab, hRS7
Type of monoclonal antibody	Humanized IgG1	Humanized IgG1	Humanized IgG1
Target antigen	HER2	HER2	Trop-2
Payload	Emtansine	Deruxtecan	SN-38
Payload class	Maytansinoid - Microtubule inhibitor	Camptothecin - Topoisomerase-I inhibitor	Camptothecin - Topoisomerase-I inhibitor
Payload membrane permeability	Low	High	High
Bystander effect	No	Yes	Yes
Linker subtype	Non-cleavable	Cleavable	Cleavable
Linker structure	Thioether linker (SMCC)	Tetrapeptide-based	Hydrolysable (CL2A)
Linker cleavage trigger	Lysosomal degradation	Lysosomal cathepsins	Low pH
Drug-to-antibody ratio	≈ 3.5:1 (mean)	≈ 8:1	≈ 7.6:1 (mean)
Conjugation	Stochastic Random Lysine	Site-specific Cysteine residues	Maleimide moiety
Endocytosis mechanism	Caveolae-endocytic pathway	Caveolae-endocytic pathway	Clatherin-mediated endocytosis
Half-life	≈ 4 days	≈ 7 days	≈ 15 hours (mean)
Excretion	Biliary	Biliary	Biliary (enterohepatic circulation)

Nader-Marta Therapeutic Advances in Medical Oncology. 2023;15

Common AEs Associated With ADCs

T-DXd	%	T-DM1	%	Sacituzumab Govitecan	%	Dato-DXd	%
• Nausea	61-79	• Nausea	40	• Nausea	57-69		
• **Fatigue**	32-59	• Fatigue	36	• **Neutropenia**	64	• Nausea	56
• Increased AST/ALT	42-48	• Constipation	27	• **Fatigue**	51-58	• **Stomatitis/ mucositis**	54
• Alopecia	21-46	• **Thrombocytopenia**	31	• Alopecia	38-49		
• Thrombocytopenia	24-28	• **Diarrhoea**	24	• Constipation	34-37	• Alopecia	32
• **ILD/pneumonitis**	10-12	• Increased AST/ALT	29	• Vomiting	23-49	• **Ocular events**	19
				• **Diarrhoea**	64		

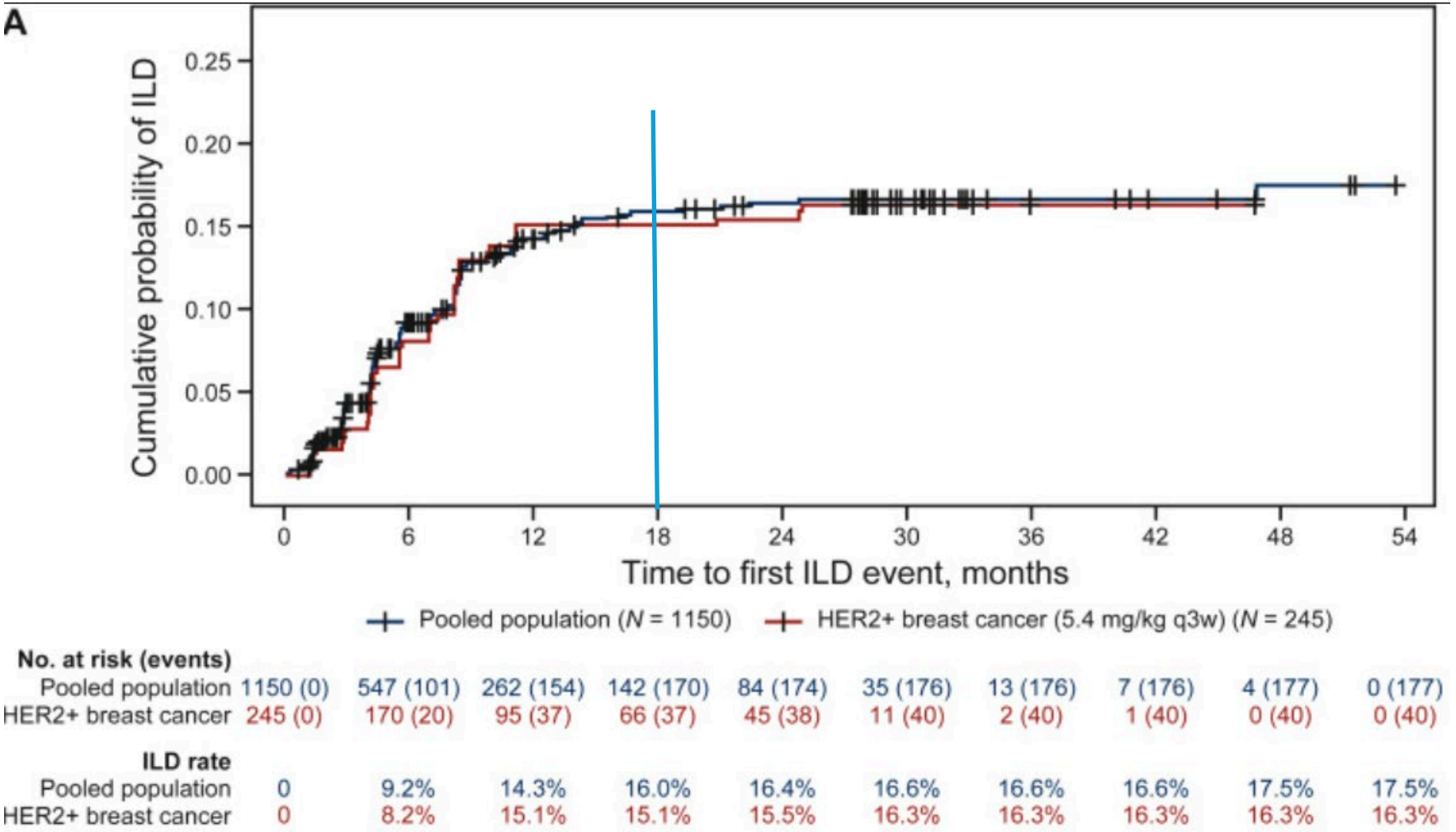
Slide credit: clinicaleducationalliance.com:
cea clinical education alliance

Pneumonitis

Incidence of ILD/pneumonitis with T-DXd:

45 patients (12.1%)

- **13 (3.5%) grade 1**
- **24 (6.5%) grade 2**
- **5 (1.3%) grade 3**
- **3 (0.8%) grade 5 events**



No. at risk (events)										
Pooled population	1150 (0)	547 (101)	262 (154)	142 (170)	84 (174)	35 (176)	13 (176)	7 (176)	4 (177)	0 (177)
HER2+ breast cancer	245 (0)	170 (20)	95 (37)	66 (37)	45 (38)	11 (40)	2 (40)	1 (40)	0 (40)	0 (40)
ILD rate										
Pooled population	0	9.2%	14.3%	16.0%	16.4%	16.6%	16.6%	16.6%	17.5%	17.5%
HER2+ breast cancer	0	8.2%	15.1%	15.1%	15.5%	16.3%	16.3%	16.3%	16.3%	16.3%

https://doi.org/10.1016/j.esmoop.2022.100554

Management of ILD/Pneumonitis by Severity

Grade of ILD/Pneumonitis	Management
Grade 1 (asymptomatic)	Hold until resolved to grade 0, then:
	▪ Start corticosteroids (eg, ≥0.5 mg/kg/day prednisolone or equivalent)
	▪ If resolved ≤28 days from onset, maintain dose
	▪ If resolved >28 days after onset, reduce dose by 1 level
Grades 2-4 (symptomatic)	▪ Permanently discontinue with confirmed grade 2 or higher
	▪ Promptly initiate systemic corticosteroids (eg, ≥1 mg/kg/day prednisolone or equivalent for ≥14 days, followed by gradual taper for ≥4 wk)

https://ukbcg.org/media/31696/ukbcg-approved-version-ild-management-guidance_v12.pdf

Tarantino. JAMA Oncol. 2021;7:1873.

Metastatic disease - Basic Principles

- **DeNovo vs Relapse**

- **If relapse**
  - Time interval
  - Previous treatments
  - Current treatment

- **Need confirmation of MBC - biopsy**
  - ER+ vs HER2+ vs TNBC
  - PDL1
  - PIK3CA
  - ESR1
  - Genetics

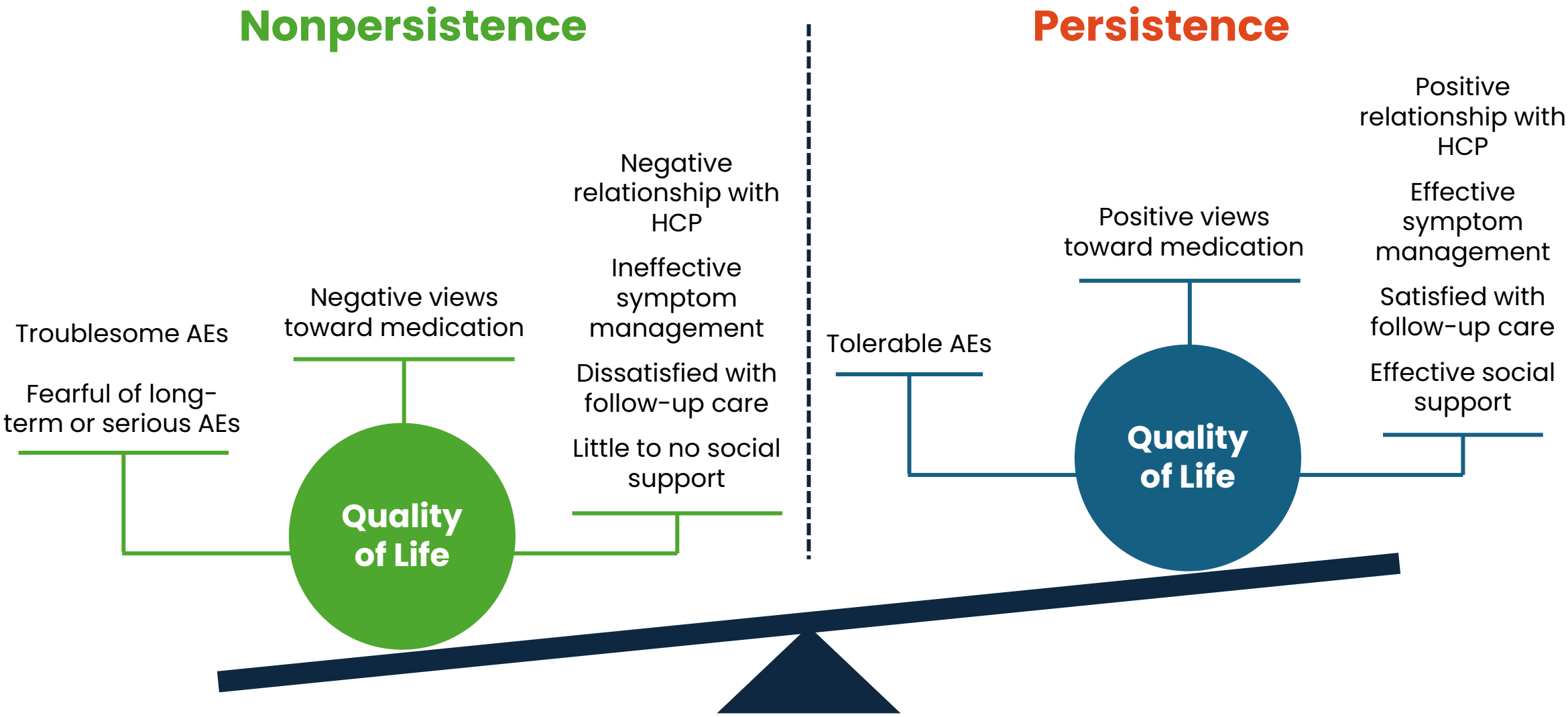
- **Complete staging**
  - CT CAP and Bone scan
  - Brain – if symptomatic
  - PET if clinically indicated

Treatment options…?

- Least toxic AND Most effective
- Check receptor status
- Target the Target
- Patient fitness (WHO PS)
- Clinical Trial options
- Optimisation of health and quality of life
- Monotherapy preferred to limit toxicity
- RT to manage local symptoms

PATIENT CONSIDERATIONS

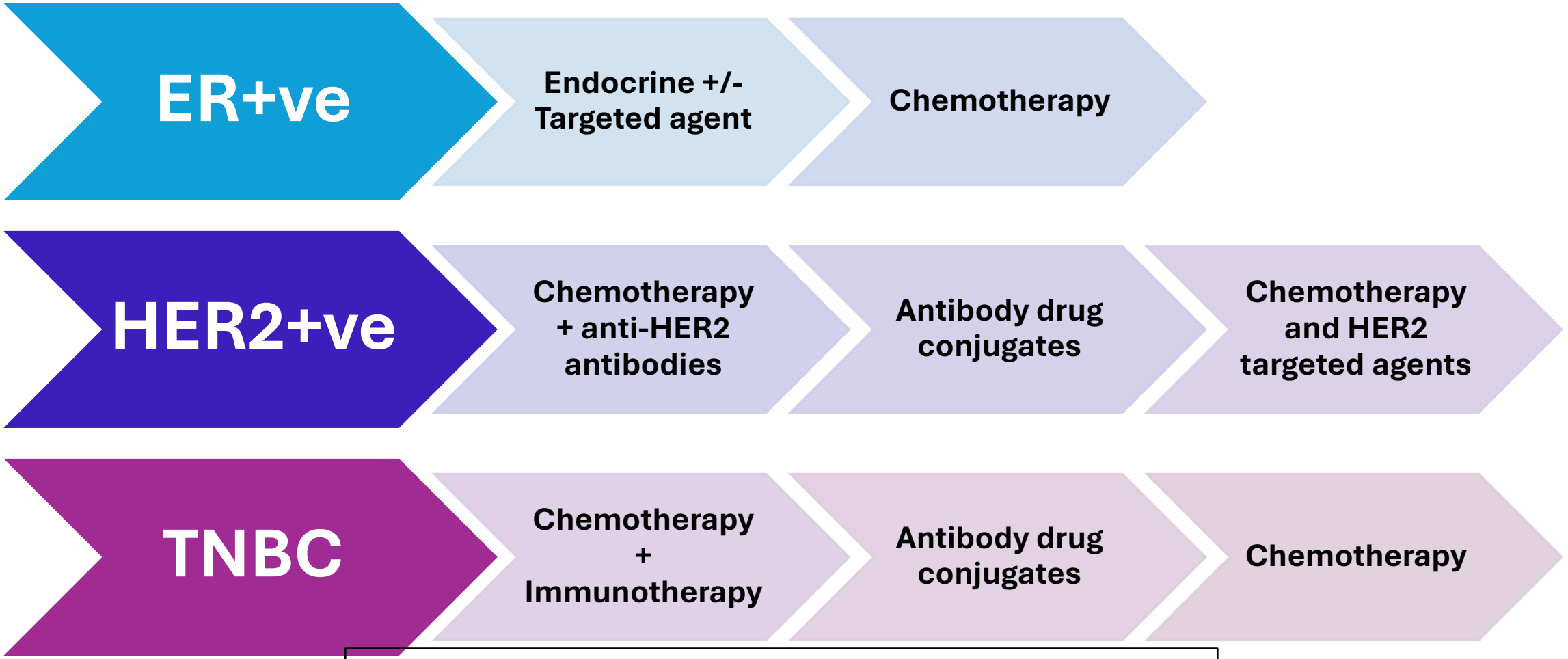
Balancing Quantity and Quality of Life



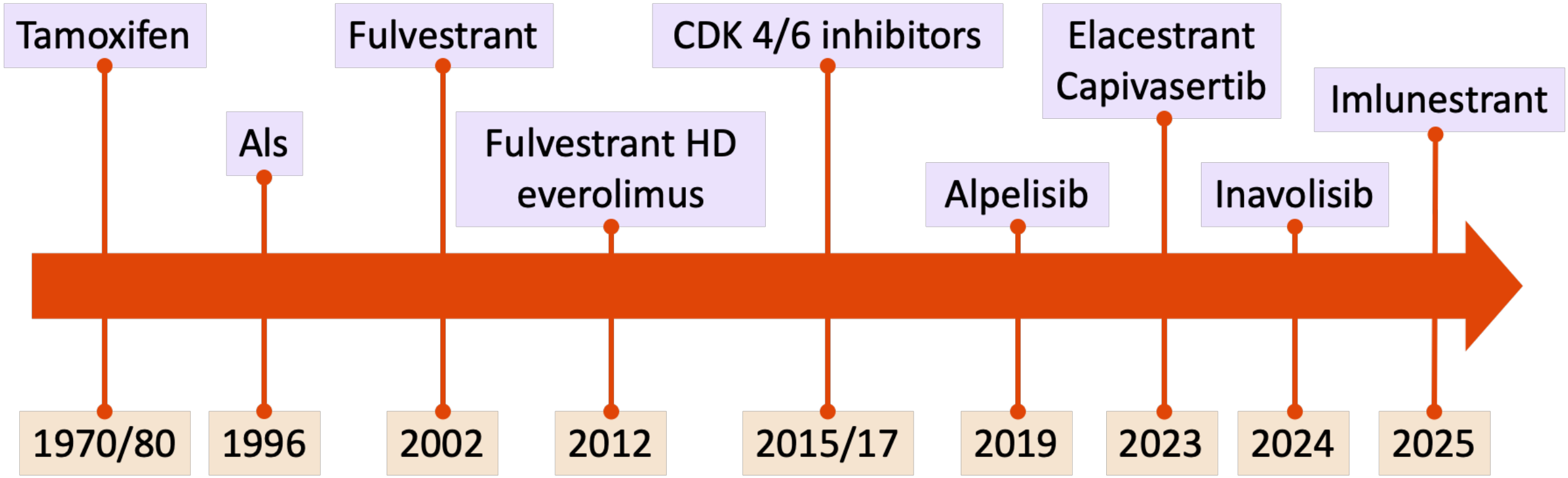
Adapted from Lambert. BMC Cancer. 2018;18:732.

Metastatic - Treatment Overview

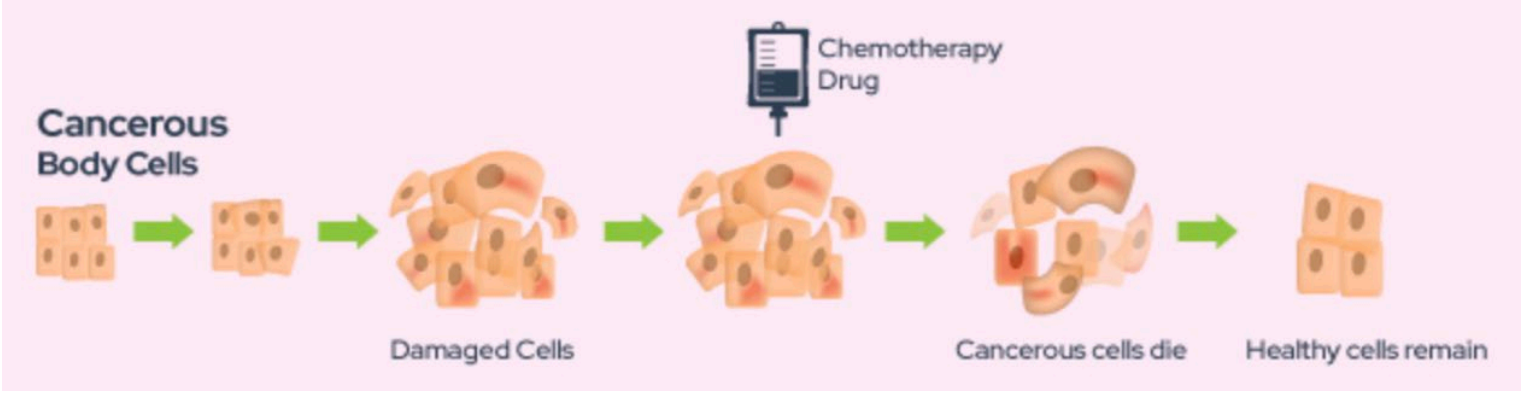
Need to know RECEPTORS to decide treatment



Endocrine Treatment Progression



Chemotherapy



- Chemotherapy works by interfering with cell division
- Side effects result from (predictable) toxicity on dividing cells
- E.g.: Skin, bone marrow, gut, hair, nerves (NB: risk of neutropenic sepsis)
  - **Need to balance the risk v benefit of treatment**
  - **Quality of life issues important for survivorship**

Chemotherapy drugs in breast cancer

Drug	Drug Name	Toxicities
Anthracycline	epirubicin, doxorubicin	Hair loss, nausea & vomiting, neutropenia, LV dysfunction
Alkylating agents	cyclophosphamide	myelosupression, fatigue, abdo pain, constipation, tinitus
Taxane	paclitaxel, docetaxel, nab-paclitaxel	Hair loss, fatigue, neutropenia, peripheral neuropathy, arrythmias – sinus bradycardia, lymphoedema (docetaxel)
Platinum	carboplatin, cisplatin	severe nausea/vomiting, neuropathy, nephrotoxicity, ototoxicity, blood count suppression, electroyte disturbance hair loss, fatigue
Anti metabolite	capecitabine	HFS, diarrhoea, fatigue, abdo discomfort, nausea, mucositis, coronary spasm
Antineoplastics	eribulin	fatigue, alopecia, myelosuppression, peripheral neuropathy, nausea, arthralgia, QTc prolongation
Vinca alkaloids	vinorelbine	myelosupression, fatigue, abdo pain, constipation, peripheral neuropathy

Chemotherapy in Breast Cancer

Early Effects (0-6 months)	Late/ Chronic Effects (6 months – lifetime)
• Cytopenias • Fatigue • Alopecia • Pain • Chemotherapy induced peripheral neuropathy (CIPN) • Neurocognitive dysfunction	• Cardiomyopathy • CIPN • Neurocognitive dysfunction • Psychosocial impact • Secondary cancers • Early menopause • Fertility

Neutropenic Sepsis

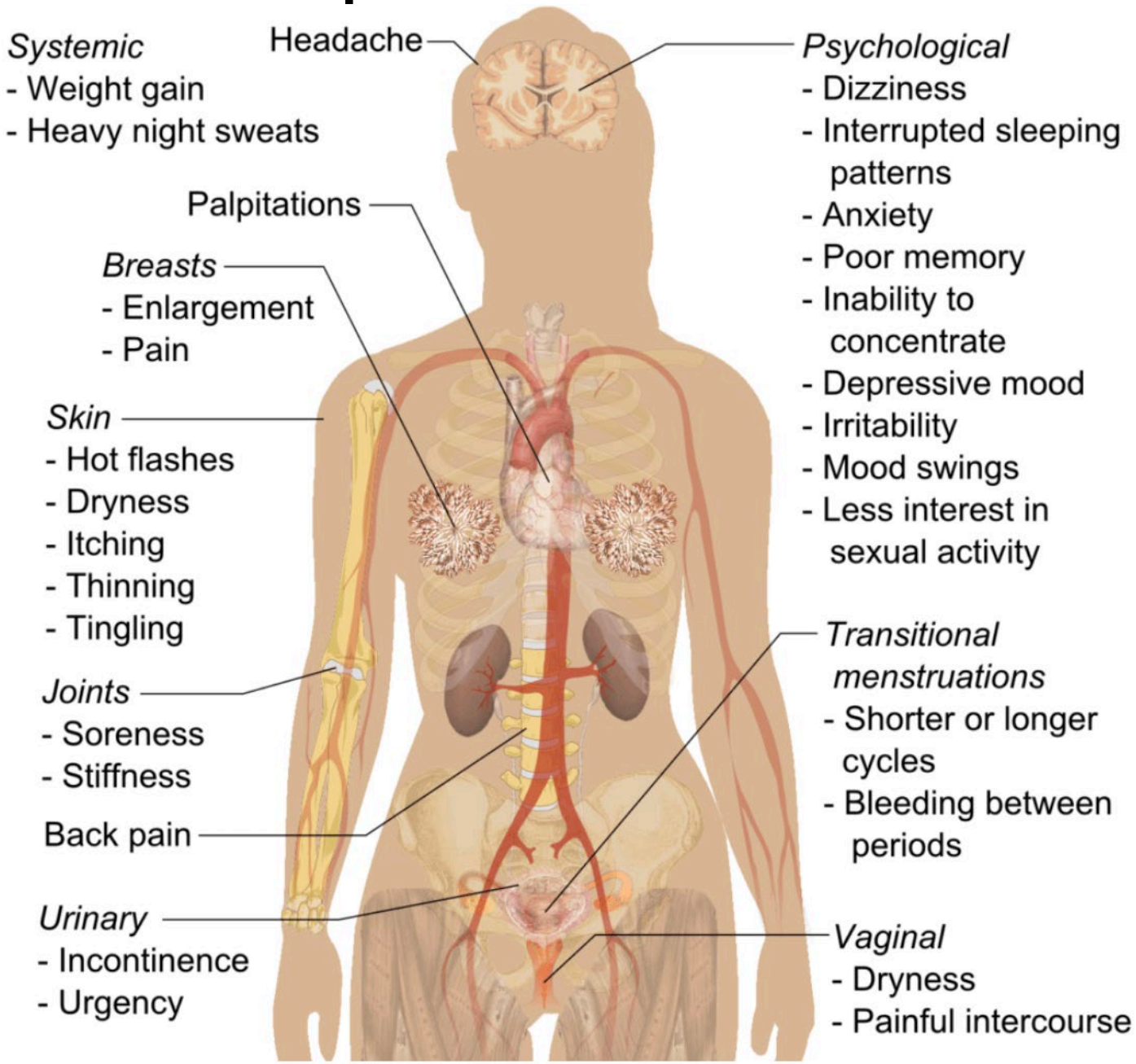
- **Neutropenic sepsis is a potentially life-threatening complication of anticancer and other immunosuppressive drug treatment**

- Defined by NICE as:
  - Absolute neutrophil count of 0.5 x 10^9/L or lower
  - Temperature >38°C or any symptoms and/or signs of sepsis

- Risk of mortality ↑ as ANC ↓

- **Guidelines:**
  - A single body temperature reading of 38°C or two body temperature measurements of 37.5°C
  - Neutrophil count adults: < 0.5 x 10^9/l **OR** <1.0 x 10^9/l and likely to drop further
  - Recent chemotherapy administration (within previous 21 days)

Symptoms of Menopause



What can help?

- Medical treatments:
  - HRT – is it safe?
  - Vaginal estrogens – when appropriate
- Integrated medicine:
  - Acupuncture
  - Homeopathy
  - Other complimentary therapies
- Lifestyle changes:
  - Exercise
  - Yoga/ meditation
  - Balanced diet (soya products)
  - Healthy weight management
  - Stress management
  - Avoiding triggers – hot flushes diary
  - Cognitive behavioral therapy

Non-HRT medication:

- **Antidepressants: Venaflaxine, Citalopram, Duloxetine**

  Reduce core temperature by widening large blood vessels

- **Gabapentinoids- Gabapentin, Pregabalin**

  Effect temperature regulation in the brain (hypothalamus)

- **Oxybutinin**

  Calms nervous system and reduces sweating

- **Clonidine**

  Reduces core temperature by widening small blood vessels

- **Fezolinetant (Veozah) – Neurokinin 3 (NK3) receptor antagonist**

  Effects temperature regulation in the brain (hypothalamus).

  NICE - Fezolinetant is not recommended for those with current breast cancer, other estrogen-dependent cancers, or liver disease.

  Those who have previously had breast cancer or estrogen-dependent cancers and have completed treatment should undergo an individual risk assessment

GMS- Genital (vaginal) and urinary (bladder) symptoms :

Vaginal symptoms:

- Vaginal dryness
- Itching, burning, pain and fragile skin
- Pain/ discomfort during intercourse

• Bladder symptoms:

- Frequent urinary tract infections
- Incontinence
- Pain/ burning on passing urine

These symptoms DO NOT tend to get better with time

Everyday dryness:

- Moisturizers: Hyelofemme, Replense to be used every day
- Increasing blood flow through manual techniques and regular intercourse

Dryness during intercourse:

- Lubricants: Yes, Sylk, to be used before/ during intercourse

Painful intercourse:

- building up slowly, thinking of alternatives

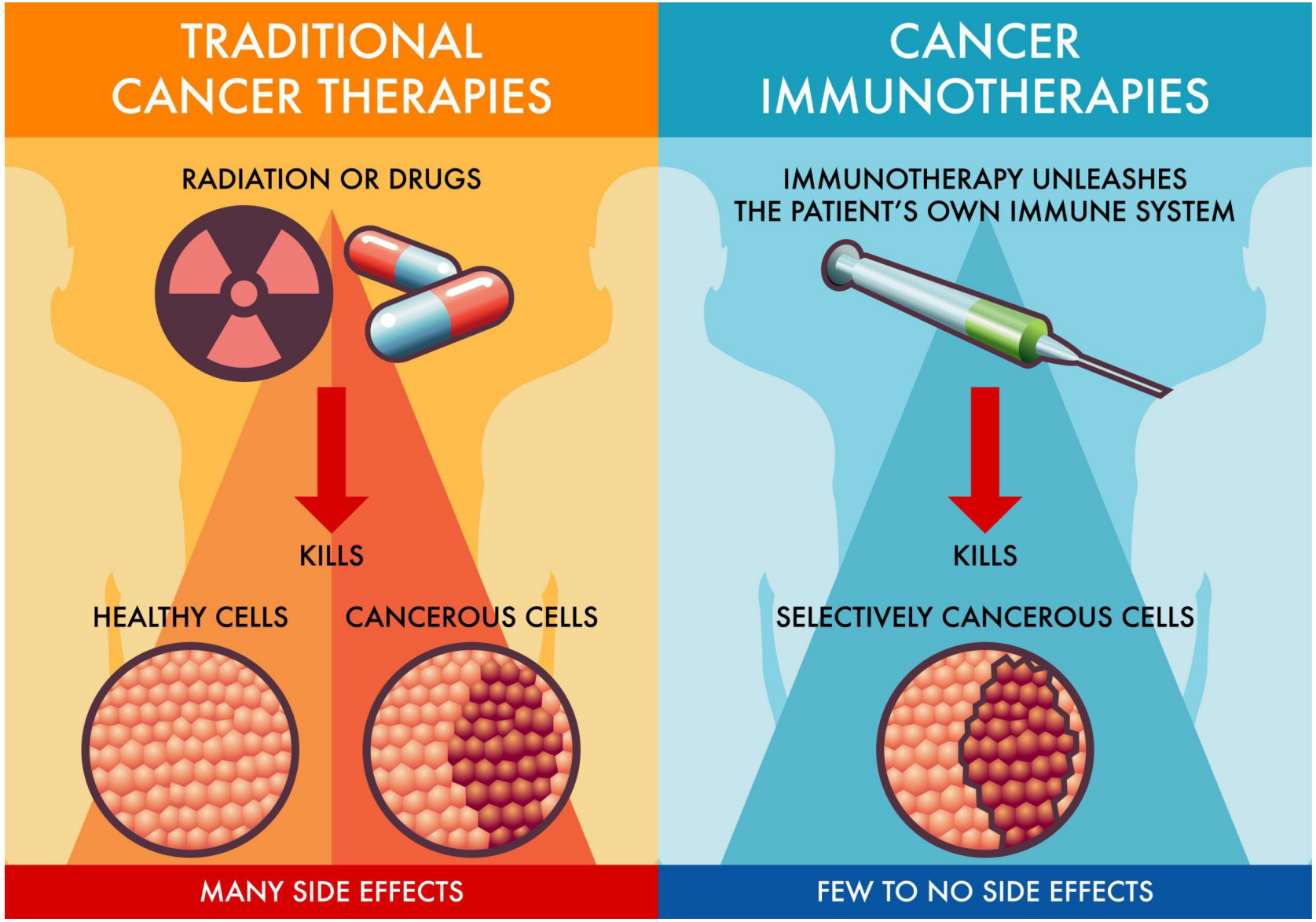
Frequent infections:

- look out for partially cleared infections
- stay hydrated

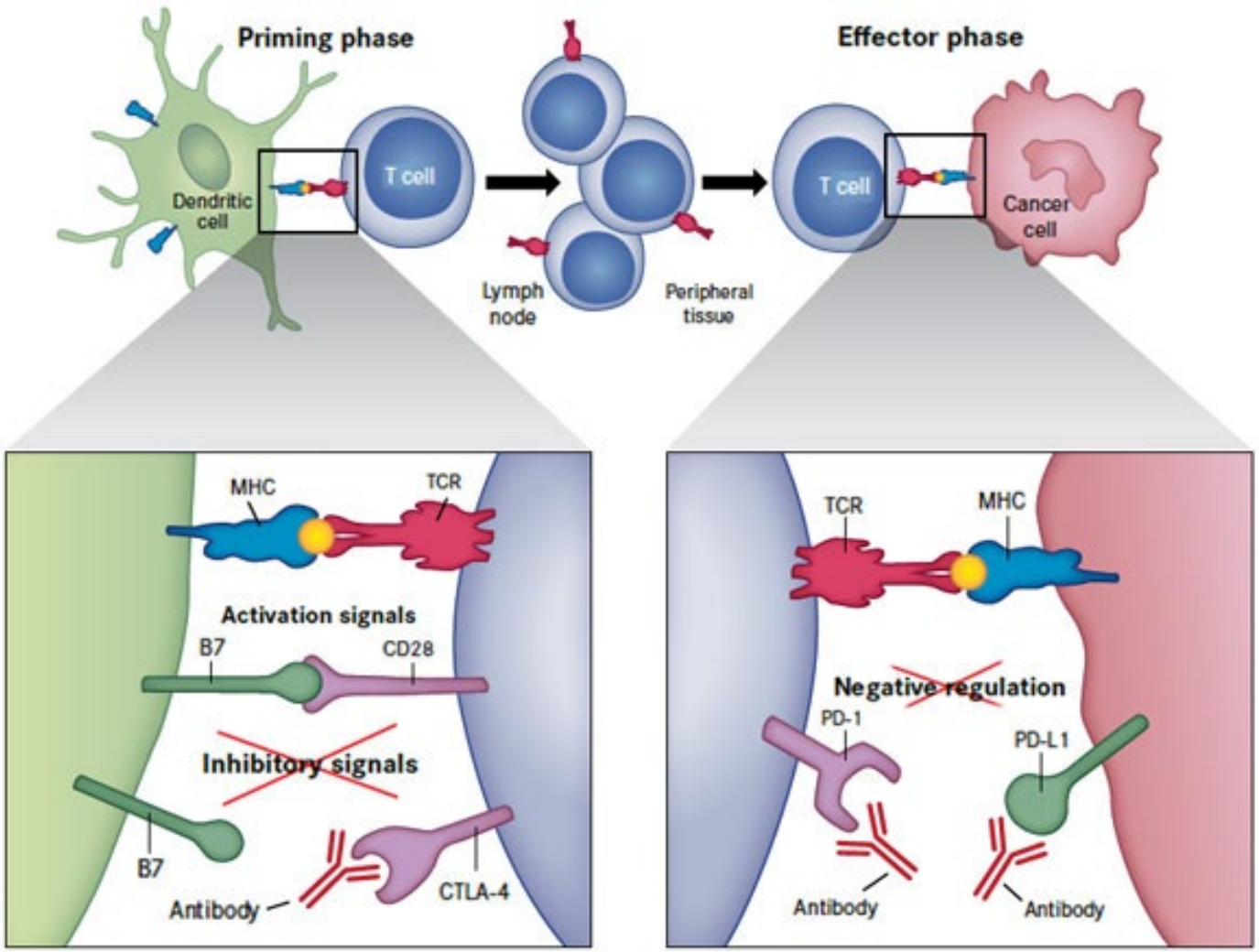
Pelvic Floor exercises and physio

Vaginal Estrogen

How immunotherapy works



Immunotherapy mechanism of action

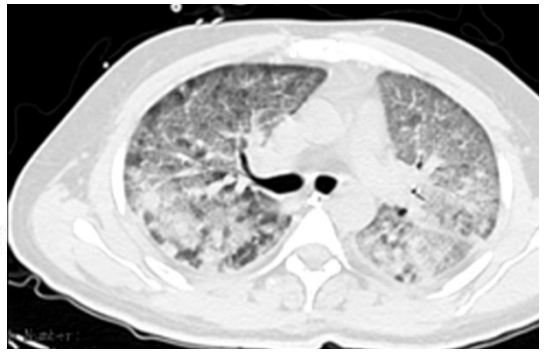


- Atezolizumab: a humanized anti-PD-L1 monoclonal antibody
- Pembrolizumab: a humanized anti-PD-L1 monoclonal antibody
- Approximately 40% met TNBC patients would be eligible for immunotherapy

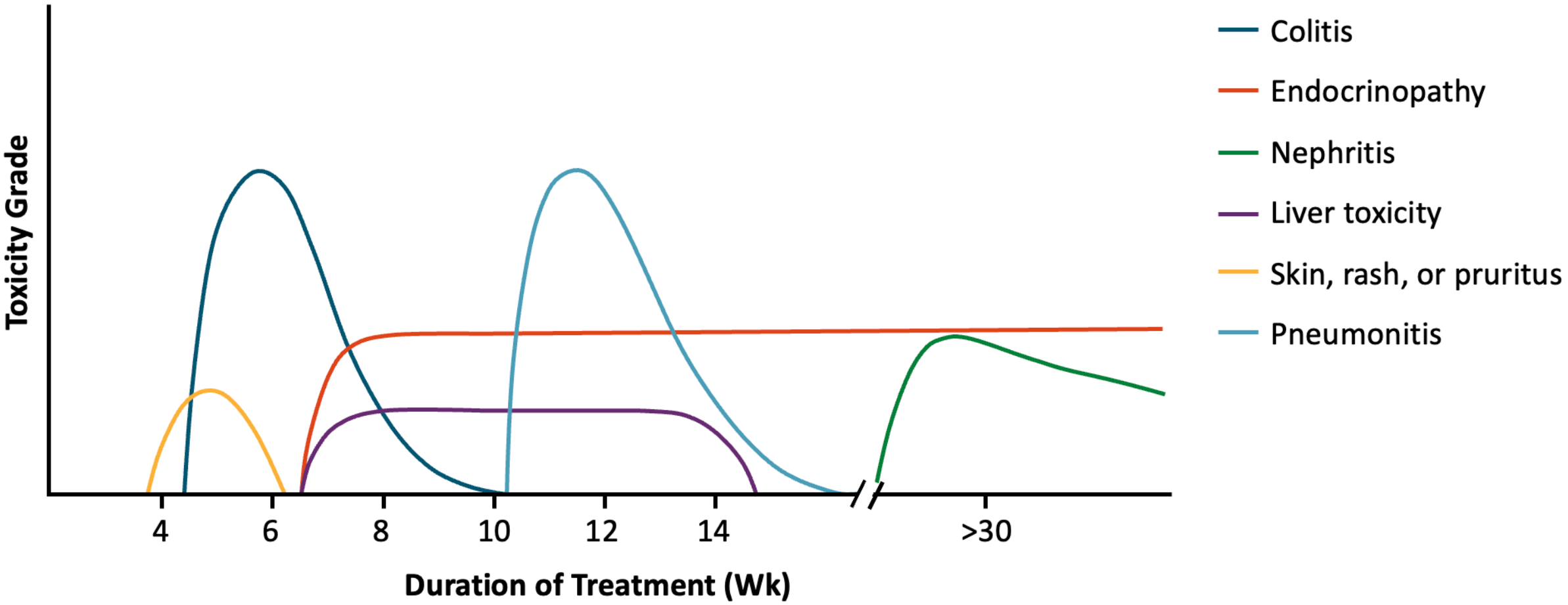
Mittendorf EA, et al. Cancer Immunol Res. 2014;2:361-370; Ghebeh H, et al. Neoplasia. 2006;8:190-198; Liu SV, et al. ASCO 2015. Abstract 8030.

Autoimmune toxicity





Time of Onset and Toxicity Grade of irAEs in Patients Receiving PD-1/PD-L1 Antibodies



Martins. Nat Rev Clin Oncol. 2019:16;563.

Management

- **THINK** IO toxicity
- **GRADE** suspected IO toxicity
- **GIVE** the steroids

Any time from 1st treatment to up to 18 months post-completion

General Guidelines for Management of irAEs

- **Consult promptly with relevant specialists for affected organ systems (eg, GI, dermatology)**
- **Immunotherapy MDT**

Grade 1: Asymptomatic to Mild Symptoms

Observation
Supportive care
Continue ICI

Grade 2: Moderate Symptoms

Consider holding ICI; consider redoes if AE resolves to grade ≤1
Consider low-dose steroids (prednisone 0.5-1 mg/kg/day)

Grade 3: Medically Significant but Not Immediately Life-threatening

Hold ICI; consider redose with caution if AE resolves to grade ≤1
Start high-dose steroids (prednisone 1-2 mg/kg/day)
Slow steroid taper over 4-6 wk once grade ≤1
→ if not improving in 1-3 days, increase immunosuppression

Grade 4: Life-threatening Consequences

Urgent intervention
Permanently discontinue ICI (except for endocrinopathies)

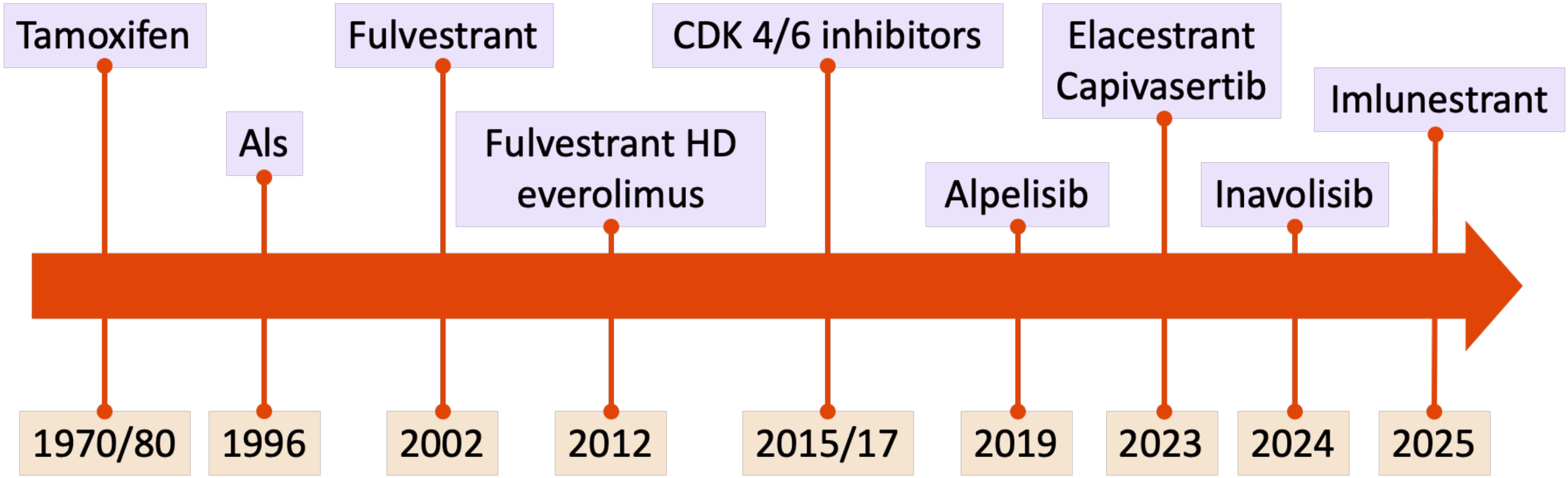
For steroid-refractory AEs, consider adding infliximab, mycophenolate mofetil, etc

Diarrhea → Consider adding infliximab or vedolizumab; consider fecal transplantation if still refractory

Hepatitis → Consider adding mycophenolate mofetil

Schneider. JCO. 2021;39:4073. NCCN. Management of immunotherapy-related toxicities. v.1.2024. nccn.org.

What targeted drugs do we use in breast cancer?



What targeted drugs do we use in breast cancer?

	Early Breast Cancer	Metastatic Breast Cancer
ER positive HER2 -ve	Abemaciclib Ribociclib	Abemaciclib Ribociclib Palbociclib Elacestrant Capivasertib Alpelisib
HER2 +ve	None (yet!)	Tucatinib
BRCA1/2	Olaparib	Olaparib Talazoparib

Oral Targeted Therapy Adherence Considerations

- Pill Burden
- Dosing Schedule and Modifications
- Administration Instructions
- Drug–Drug/ Drug–Food Interactions
- AEs/ Supportive Care
- Frequent Monitoring

Factors Influencing Adherence

According to the WHO, adherence is a multidimensional phenomenon that is influenced by various factors[1-3]



Patient-Related

- Perceptions of necessity, benefit, and quality of life
- Forgetting and self-efficacy
- Preference for alternative
- Routinization
- Depression or anxiety



Therapy-Related

- Side effects
- Modifications and complexity of regimen
- Duration and variations of therapy
- Pill burden



Disease-Related

- Comorbidities
- Unknown tumor size
- Node-positive disease



Healthcare System

- Shorter duration of follow-up visits
- Prescribing errors
- Different physicians responsible for follow-up
- Relationship with HCPs
- Lack of patient involvement in decision-making



Social and Economic

- Younger or older age
- Higher out-of-pocket cost
- Lower income and education level
- Unmarried

Patients and physicians report similar determinants of noncompliance and nonpersistence to oral ET[3]

1. https://www.who.int. 2 Verbrugghe. Cancer Treat Rev. 2013;39:610. 3. Paranjpe. Breast Cancer Res Treat. 2019;174:297.

Slide credit: clinicaleducationalliance.com:
cea clinical education alliance

CDK4/6 Inhibitors

	Abemaciclib	Palbociclib	Ribociclib
Dosage	With ET: 150 mg (1 tablet) Monotherapy: 200 mg (1 tablet)	125 mg (1 tablet or capsule)	600 mg (3 tablets)
Dosing schedule	Twice daily x 28 d; 28-d cycle	Once daily x 21 d; 28-d cycle	Once daily x 21 d; 28-d cycle
Food considerations	With or without food	Capsule: with food Tablet: with or without food	With or without food
Indication	Adjuvant Metastatic	Metastatic	Adjuvant Metastatic

Key AEs With CDK4/6 Inhibitors: Monitoring and Prevention

Diarrhea	Hepatobiliary Toxicity	Neutropenia	VTE	ILD/ Pneumonitis	QT Prolongation
Abemaciclib **Ribociclib**	**Abemaciclib** **Ribociclib** **Palbociclib**	**Abemaciclib** **Ribociclib** **Palbociclib**	**Abemaciclib**	**Abemaciclib** **Ribociclib** **Palbociclib**	**Ribociclib**
Antidiarrheal therapy Increase oral hydration Notify healthcare professional Dietary modification	LFTs before starting treatment Every 2 weeks for 1st 2 cycles	FBC before starting treatment Every 2 weeks for 1st2 cycles	Monitor for signs and symptoms of thrombosis or pulmonary embolism	Monitor for pulmonary symptoms indicative of ILD or pneumonitis (eg, hypoxia, cough, dyspnea)	Monitor for signs and symptoms of QT prolongation

Oral SERD - elacestrant

Most Common AEs ≥10% in Overall Population, %	Elacestrant (n = 237)		SoC (n = 230)	
	Any	Grade ≥3	Any	Grade ≥3
Nausea	35	2.5	19	0.9
Fatigue	26	2	27	1
Vomiting	19	0.8	9	0
Decreased appetite	15	0.8	10	0.4
Diarrhea	13	0	10	1
Musculoskeletal pain	41	7	39	1
Headache	12	2	12	0
Constipation	12	0	6	0
Abdominal pain	11	1	10	0.9
Hot flush	11	0	8	0
Dyspepsia	10	0	2.6	0

- Elacestrant is associated with hypercholesterolemia (30%) and hypertriglyceridemia (27%)
- Incidence of grade 3 and 4 hypercholesterolemia and hypertriglyceridemia: 0.9% and 2.2%, respectively
- Patients should receive lipid profile monitoring prior to starting and periodically while taking this therapy

PARP Inhibitors

Approved PARP Inhibitors in *BRCA*-Mutated Breast Cancer

Olaparib

For adjuvant treatment of adult patients with deleterious g*BRCA*m, HER2- high risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy

Talazoparib

For treatment of deleterious or suspected deleterious g*BRCA*m, HER2- metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting

Adverse Event, %	**Olaparib (OlympiAD)[1]**	**Talazoparib (EMBRACA)[2]**
Grade ≥3 AEs	38 (vs 50 with TPC)	69.6 (vs 64.3 with TPC)
▪ Anemia	16.1	40.2
▪ Neutropenia	9.3	NR
▪ Thrombocytopenia	2.4	NR
MDS/AML	0	1
Nausea (all grades)	58.0	49.7
Alopecia (all grades)	3.4	27.3

HER2-Targeted TKI - Tucatinib

- With trastuzumab and capecitabine
- For adults with advanced unresectable or metastatic HER2+ breast cancer, including brain metastases, and those who received ≥1 prior anti–HER2-based regimen in the metastatic setting
- 300 mg orally twice daily with or without food

Tucatinib

Reversible, highly selective TKI inhibitor for HER2

Common adverse effects:

- Diarrhea
- Nausea
- Fatigue

Managing the most common TKI adverse effects:

- Rule out other possible causes of diarrhea
- Antidiarrheals scheduled or PRN with loperamide

PI3K/AKT/mTOR Inhibitors for HR+ MBC

Everolimus	▪ 10 mg orally once daily ▪ (PI3K/AKT/mTOR inhibitor; no test needed)
Alpelisib	▪ 300 mg orally once daily with food ▪ (*PIK3CA* mutation; confirmed NGS, PCR mutation)
Capivasertib	▪ 400 mg (200 mg oral tablets x2) orally twice daily with or without food for 4 consecutive days followed by 3 days off ▪ (*PIK3CA/AKT1/PTEN* mutation; confirmed NGS, PCR mutation)
Inavolisib	▪ 9 mg orally once daily with or without food ▪ (*PIK3CA* mutation; confirmed NGS, PCR mutation) **Likely to be approved 2026**

Everolimus PI. Alpelisib PI. Capivasertib PI. Inavolisib PI.

Key AEs With PI3K/AKT/mTOR Inhibitors: Monitoring and Prevention to Maximize Adherence

Diarrhea	Stomatitis	Hyperglycemia	Rash	ILD/ Pneumonitis
Alpelisib	Alpelisib	Alpelisib	Alpelisib	Alpelisib
Capivasertib	Capivasertib	Capivasertib	Capivasertib	
Inavolisib	Inavolisib	Inavolisib		
Antidiarrheal therapy Increase oral hydration Notify healthcare professional Dietary modification	Monitor for stomatitis symptoms Consider mouthwash with corticosteroid for management or prophylaxis	Fasting glucose HbA1C Optimise blood glucose before starting treatment	Monitor for signs and symptoms of cutaneous adverse reactions Consider consult with dermatology	Monitor for pulmonary symptoms indicative of ILD or pneumonitis (eg, hypoxia, cough, dyspnea) Hold therapy and evaluate Discontinue if confirmed

Mucocitis

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
No change				
	Soreness/ erythema	Erythema, ulcers; can eat solid food	Ulcers; requires liquid diet only	Alimentation (nourishment) not possible

Treatment of Mucositis

- **Oral Hygiene**

- **Salt water mouthwash** is recommended for all patients in the prevention and management of mucositis. For patients at home, 1 teaspoon of salt may be added to a pint of cooled boiled water.

- Little evidence for using **Chlorhexidine 0.2% mouthwash** to prevent mucositis however it may still be used to treat patients with gingivitis

- **Benzydamine 0.15% (Difflam®) mouthwash**, 10mls rinsed around mouth and expelled four times daily, can help prevent oral mucositis.
  - For treatment use, the dose can increase to 15ml every 1 ½ - 3 hours as necessary.

- **Caphasol mouthwash** can be used in both the treatment and prevention. A dose of 30ml (1 clear ampoule mixed with 1 blue ampoule) rinsed around the mouth for 1 minute, half the solution expelled, and then to be repeated with the remainder of the solution.

- **Gelclair** may be used as a mucosal protectant, 1 sachet to be mixed with 40ml of water, rinsed and gargled then spat out, to be used 3 times daily or as necessary.

- **Steroid mouthwash** may be beneficial in the treatment of mucositis. Using betamethasone soluble tablets, dissolve 500 micrograms in 20ml water and rinse around the mouth 4 times a day.