



Making Breast Cancer History

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Disclosures

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Steering Committee (no honoraria): Gilead, Greenwich Life Sciences

Advisory Boards:

no honoraria- Merck, BMS, Pfizer, Lily, Daiichi/Astrazeneca;
honoraria accepted- Seattle Genetics, CALIBR/SCRIPPs,
Immunomic Therapeutics

Breast Cancer ABC's

Breast Cancer: Epidemiology

Expected new BC cases (2024 estimate)



Breast	310,720	32%
Lung & bronchus	118,270	12%
Colon & rectum	71,270	7%
Uterine corpus	67,880	7%
Melanoma of the skin	41,470	4%
Non-Hodgkin lymphoma	36,030	4%
Pancreas	31,910	3%
Thyroid	31,520	3%
Kidney & renal pelvis	29,230	3%
Leukemia	26,320	3%
All sites	972,060	

1 in 8 lifetime risk in the US for women of average risk

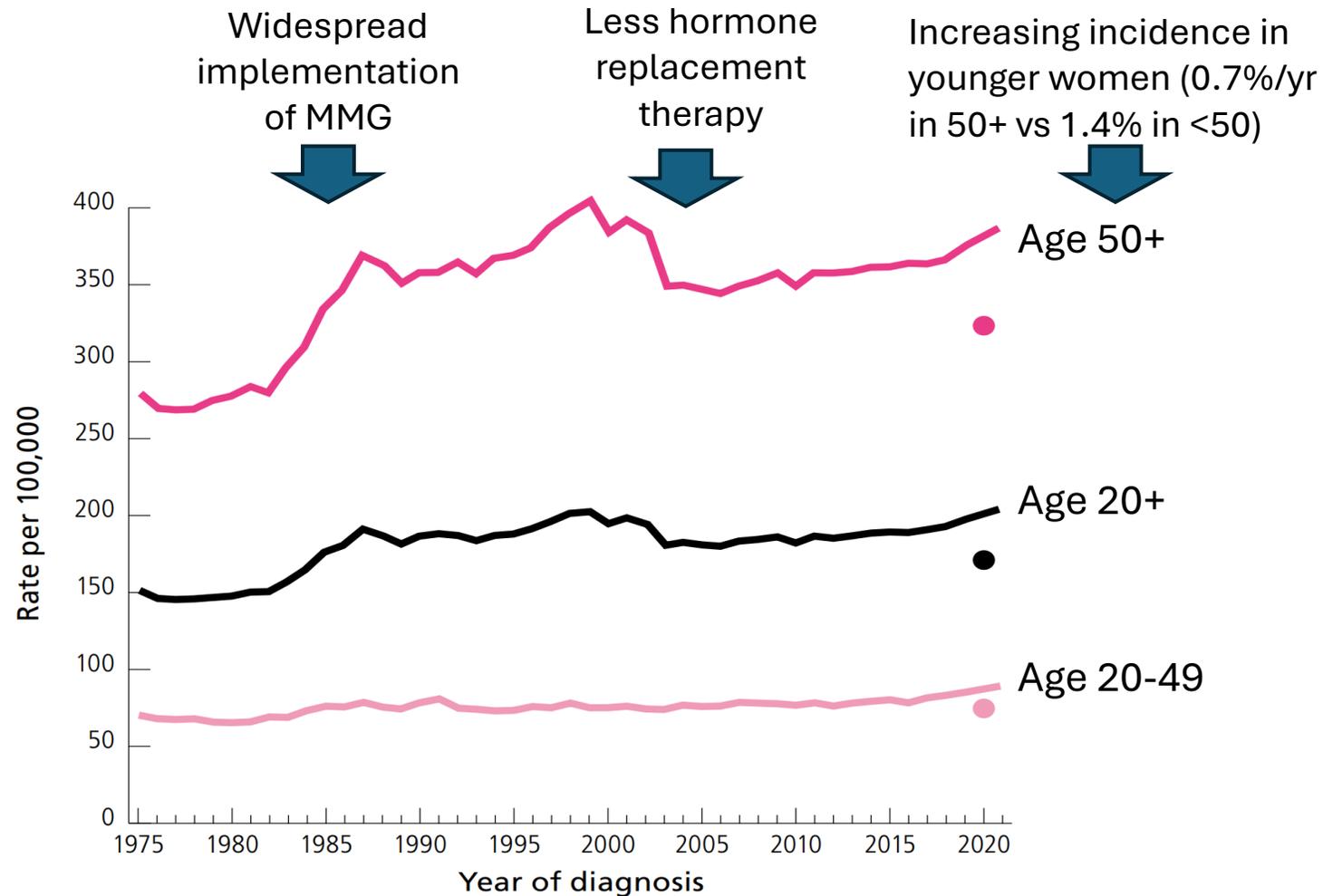
Expected deaths (2024 estimate)



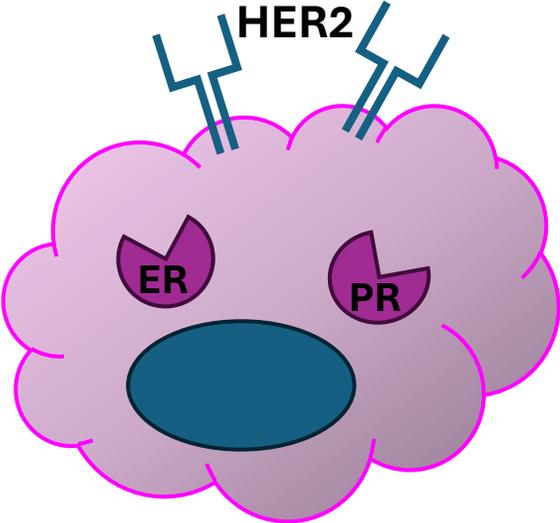
Lung & bronchus	59,280	21%
Breast	42,250	15%
Pancreas	24,480	8%
Colon & rectum	24,310	8%
Uterine corpus	13,250	5%
Ovary	12,740	4%
Liver & intrahepatic bile duct	10,720	4%
Leukemia	10,030	3%
Non-Hodgkin lymphoma	8,360	3%
Brain & other nervous system	8,070	3%
All sites	288,920	

In 2022, 2.3 million women diagnosed with breast cancer and 670 000 deaths globally

Breast Cancer Incidence Over Time



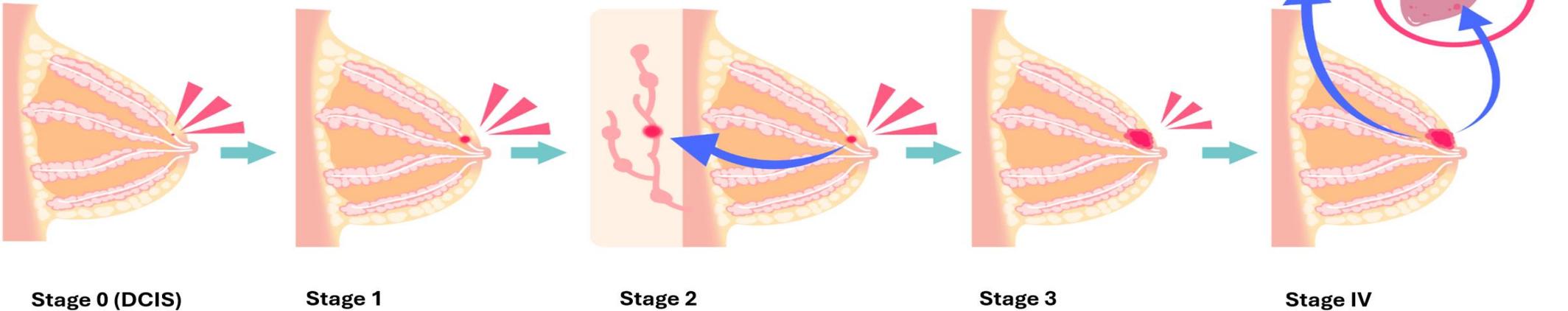
Diagnosing breast cancer: subtype + stage



Breast cancer subtype	Proportion
ER+ (HER2-)	70%
HER2+ (ER-any)	15%
Triple negative	15%

Early-stage breast cancer (curable)

Metastatic breast cancer (not curable)

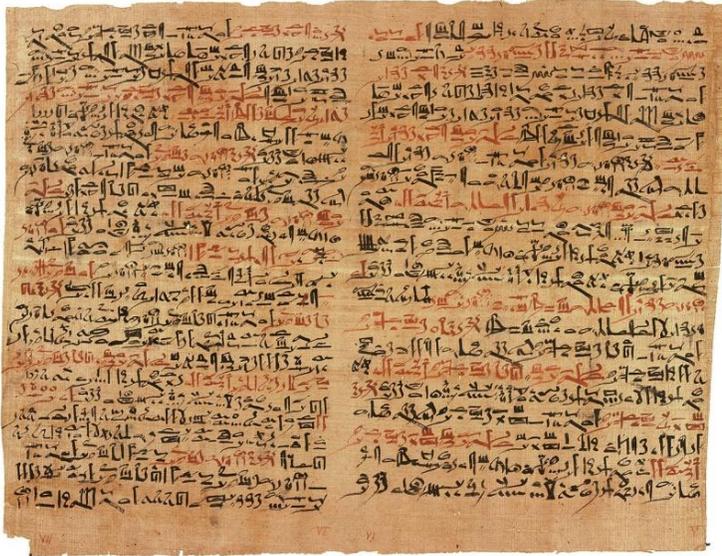


Breast Cancer History

Breast cancer has been a problem for a long-time ...

The Edwin Papyrus: Imhotep (Egyptian physician-architect)

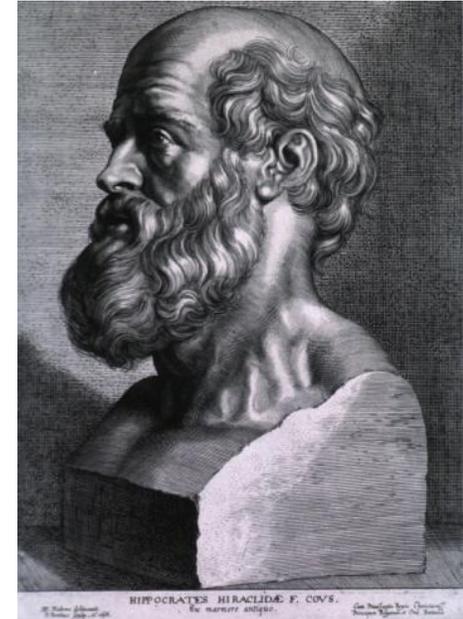
- Oldest record of breast cancer (ca 3000-2500 BC)
- When described as “cool to touch, budging, and spread all over the breast”; treatments “none”



The Edwin Smith Papyrus



Sculpture of Imhotep
(ca.2650-2600 BC)

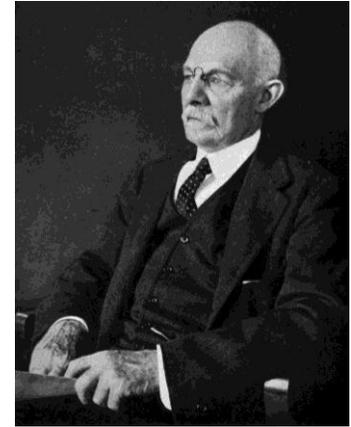


Hippocrates (ca. 400 BC) described tumors as karkinoma, due “crab like tentacles” → an imbalance of humors (blood, phlegm, yellow and black bile)

Taking a “stab” at breast cancer: more not always better

The “Halstead” Radical Mastectomy

- Removing the breast, NAC, pectoralis major/minor, ALND → very morbid, but could cure some patients
- Standard of care 1895 until mid-1970’s



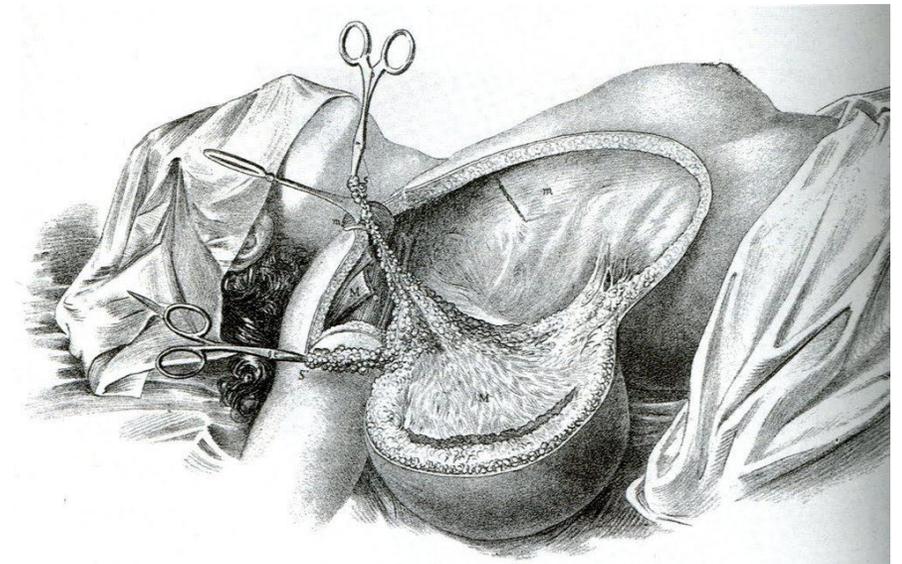
William Halsted
(1852-1922)



Bernard Fisher
(1918-2019)

The Lumpectomy (partial mastectomy)

- Along with radiation, similar outcomes to mastectomy

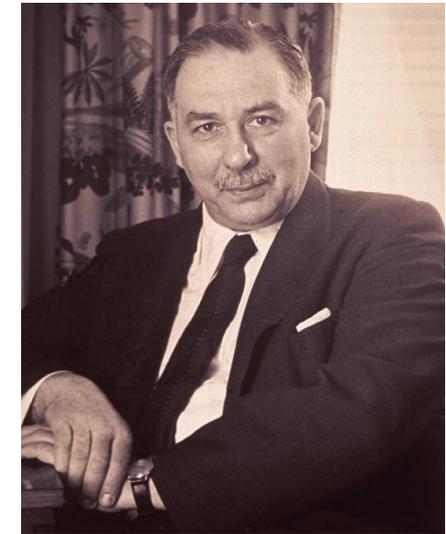
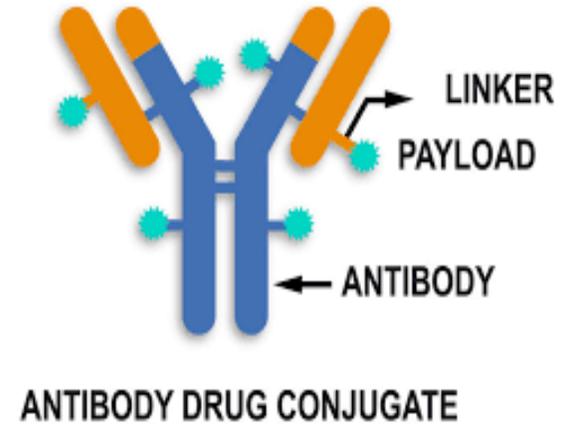


Searching for Magic Bullets

- Paul Ehrlich, the “father of chemotherapy”
 - Conceptualized delivering a toxin with an agent of selectivity: a *zauberkuugel* (magic bullet) → the ADC!
- During WWI nitrogen mustards found to have toxic effects on white blood cells → found to have activity in lymphoma
- Sidney Farber found that anti-folates could result in remissions to childhood leukemias in 1947, after initial studies that folates could accelerate disease



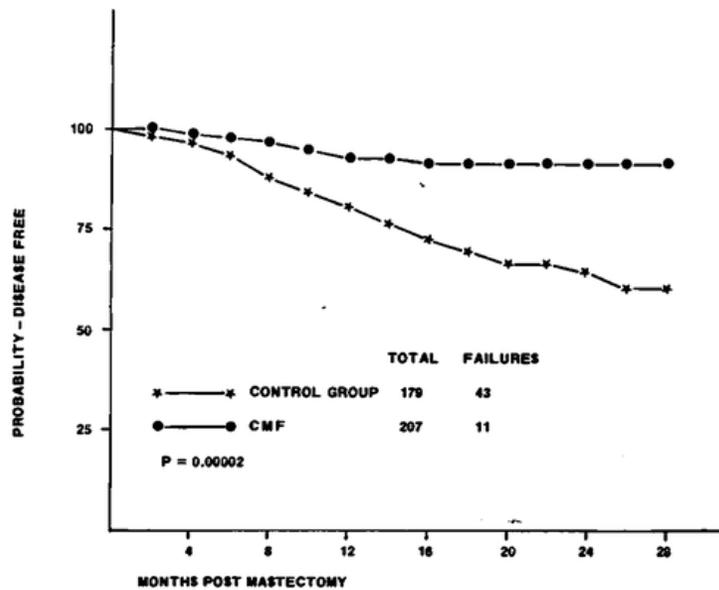
Paul Ehrlich
(1854-1915)



Sidney Farber
(1903-1973)

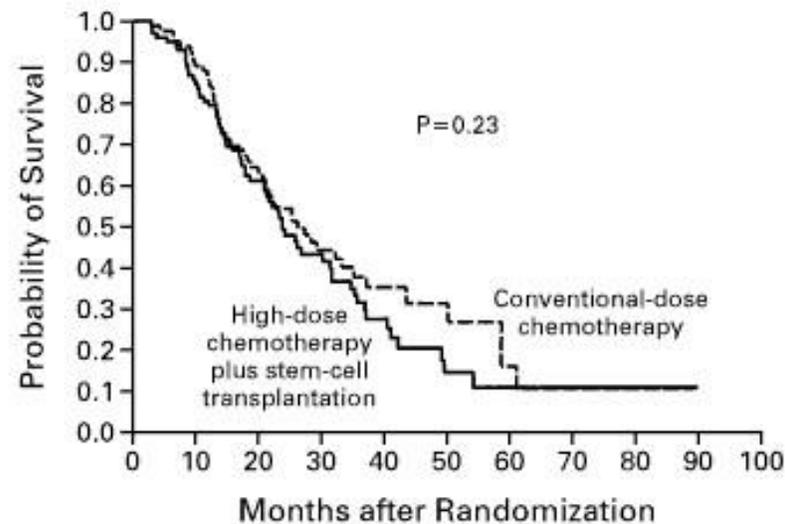
Lessons learned in developing chemotherapy

Adjuvant chemotherapy can eliminate micrometastatic disease and ↓ recurrence

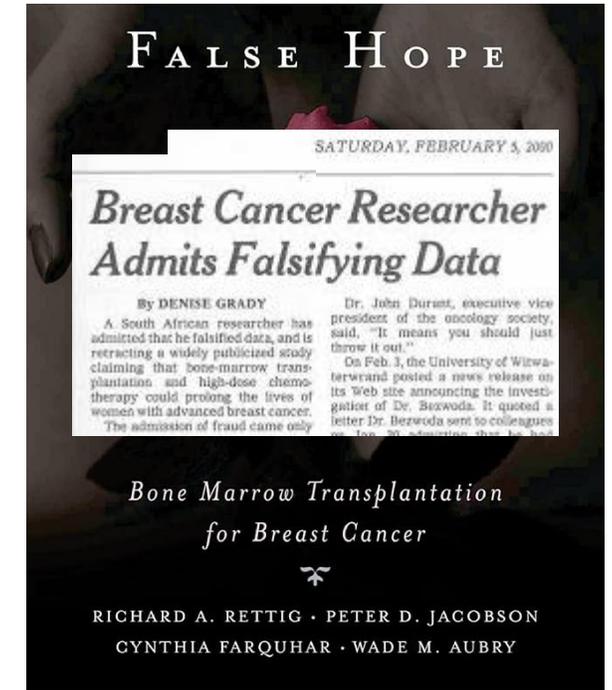


Bonadonna NEJM 1976

In childhood leukemias more chemotherapy resulted in better outcomes— could it do the same in breast cancer? No!



Stadmauer NEJM 2002



HOWEVER

Pressure to allow pts to get BMTs based on promising (*but falsified!*) data → BMTs offered at many centers until ultimately benefits disproven

Learning from biology: receptor targeting in breast cancer

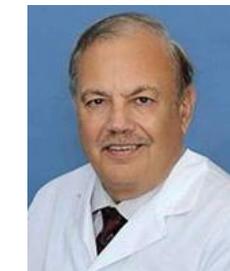
- Targeting the estrogen receptor
 - 1895: George Beatson discovered oophorectomy could shrink breast tumors
 - 1958: Elwood Jensen discovered the estrogen receptor
 - In 1962: Dora Richardson synthesized tamoxifen
- Targeting HER2
 - 1970's: HER2 gene discovered
 - 1980's: cloned by Axel Ullrich
 - Academic/industry partnership between Dennis Slamon and Genentech → first monoclonal antibody against HER2, trastuzumab, in phase 1 by 1992, first approval in 1998



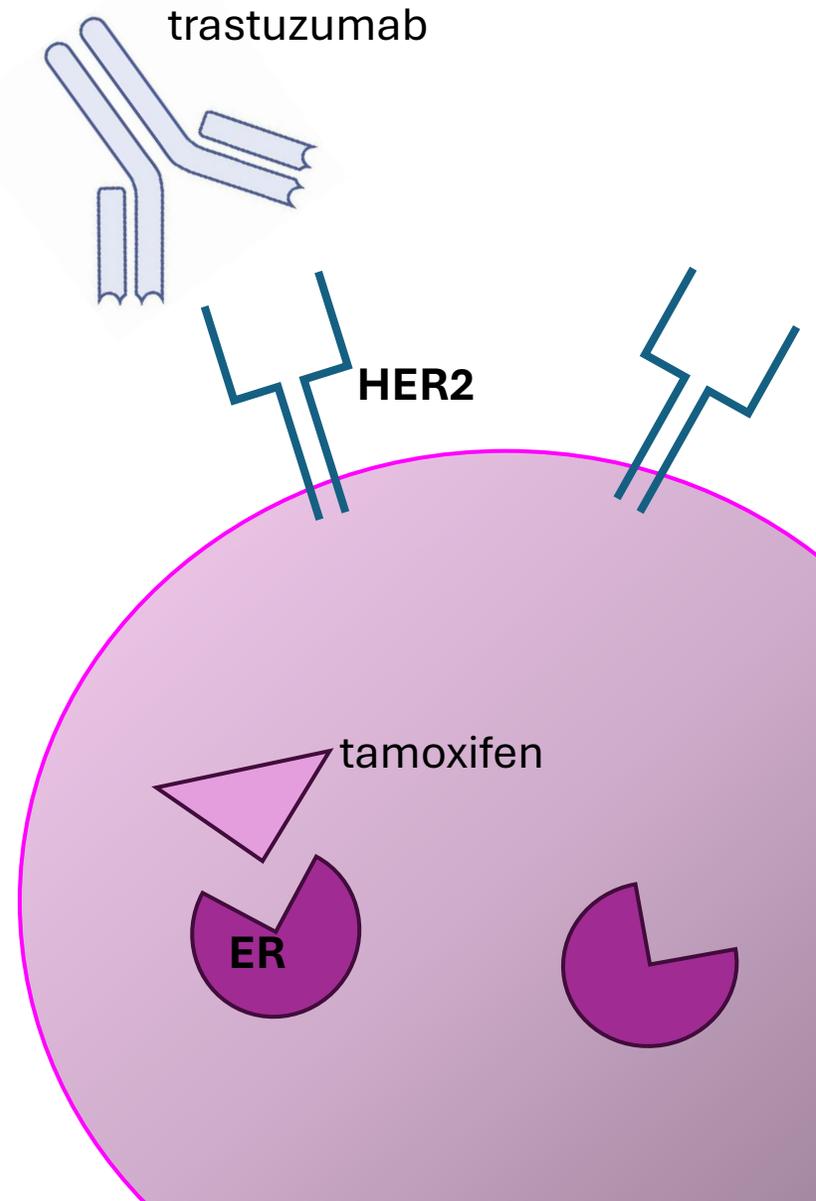
George Beatson
(1848-1933)



Dora Richardson
(1919-1998)



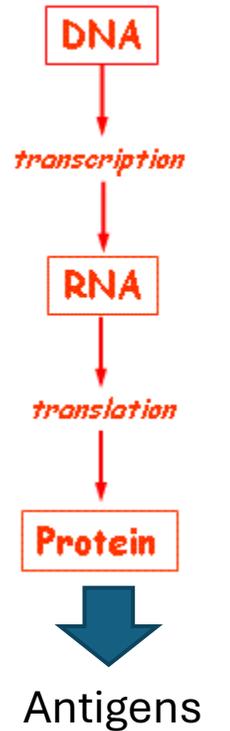
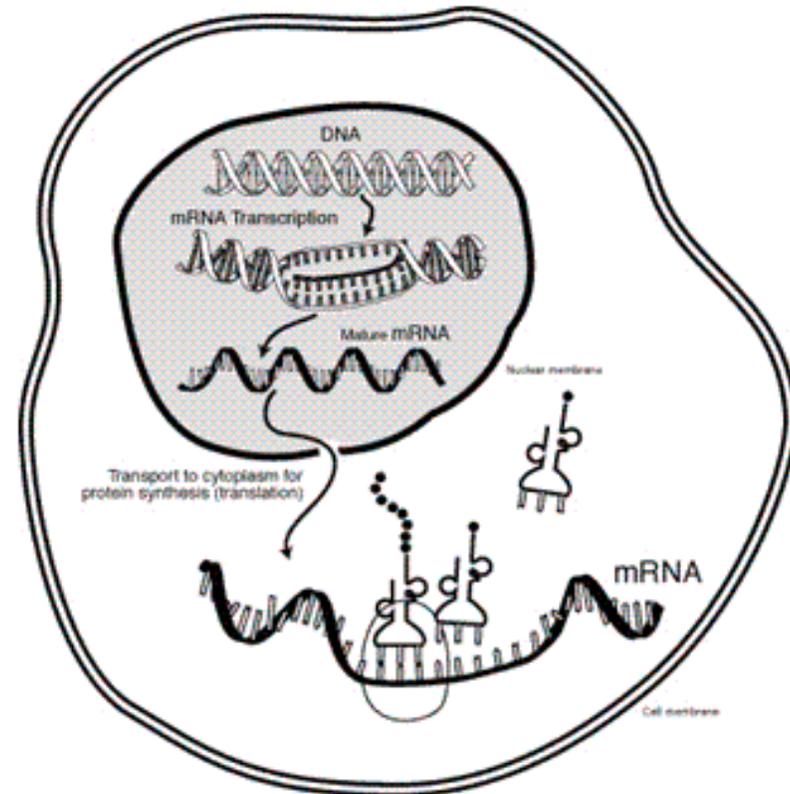
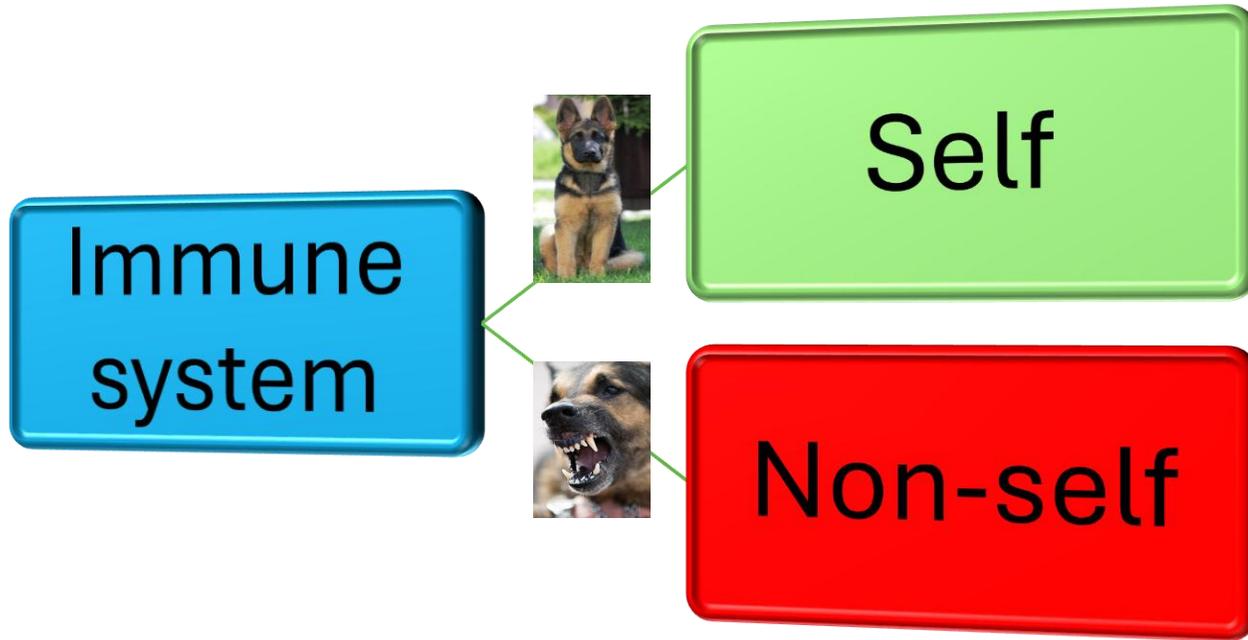
Dennis Slamon



Immunotherapy in Breast Cancer

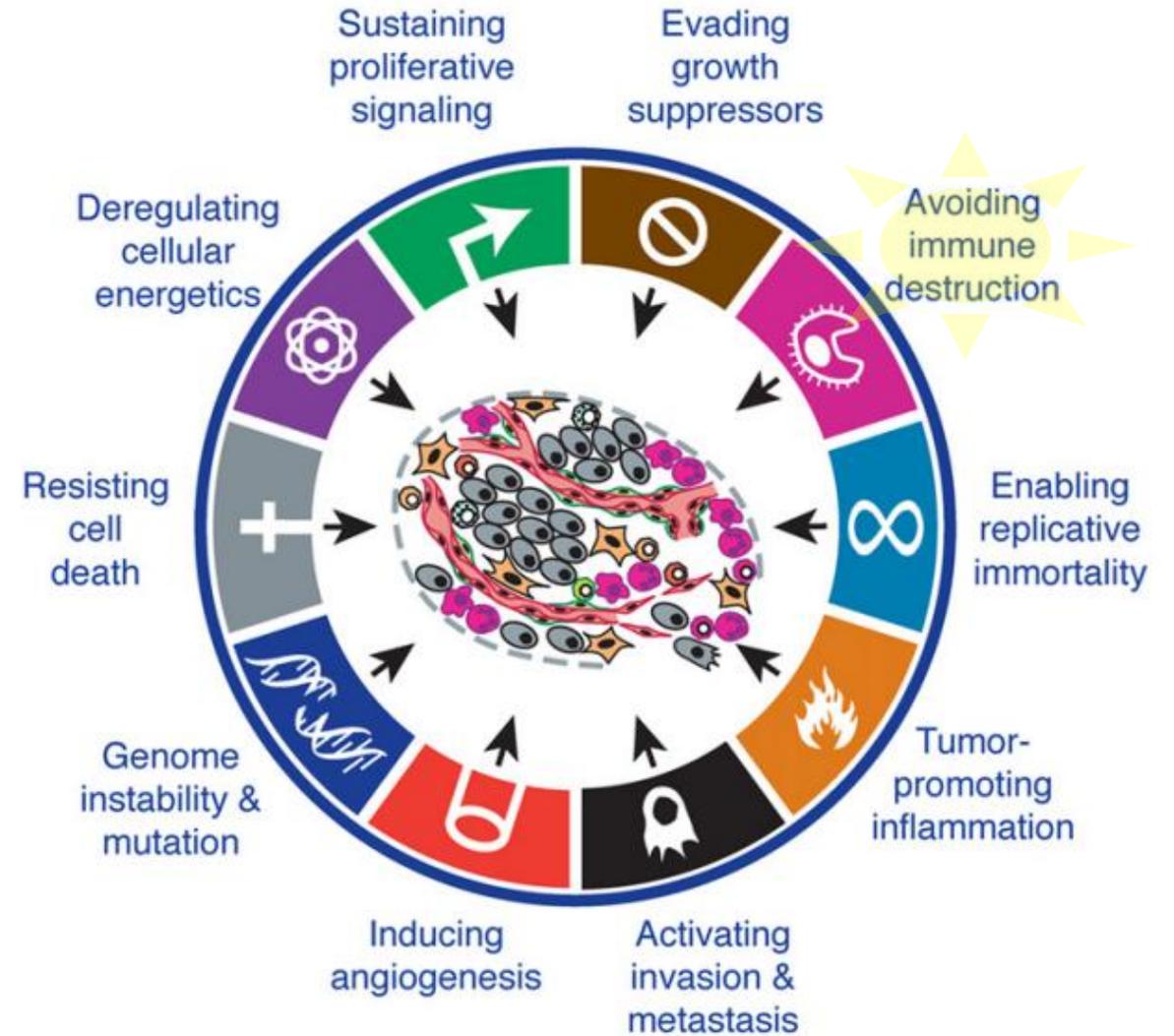
What is your immune system?

Your defense system to protect against diseases (ie infections, cancer)

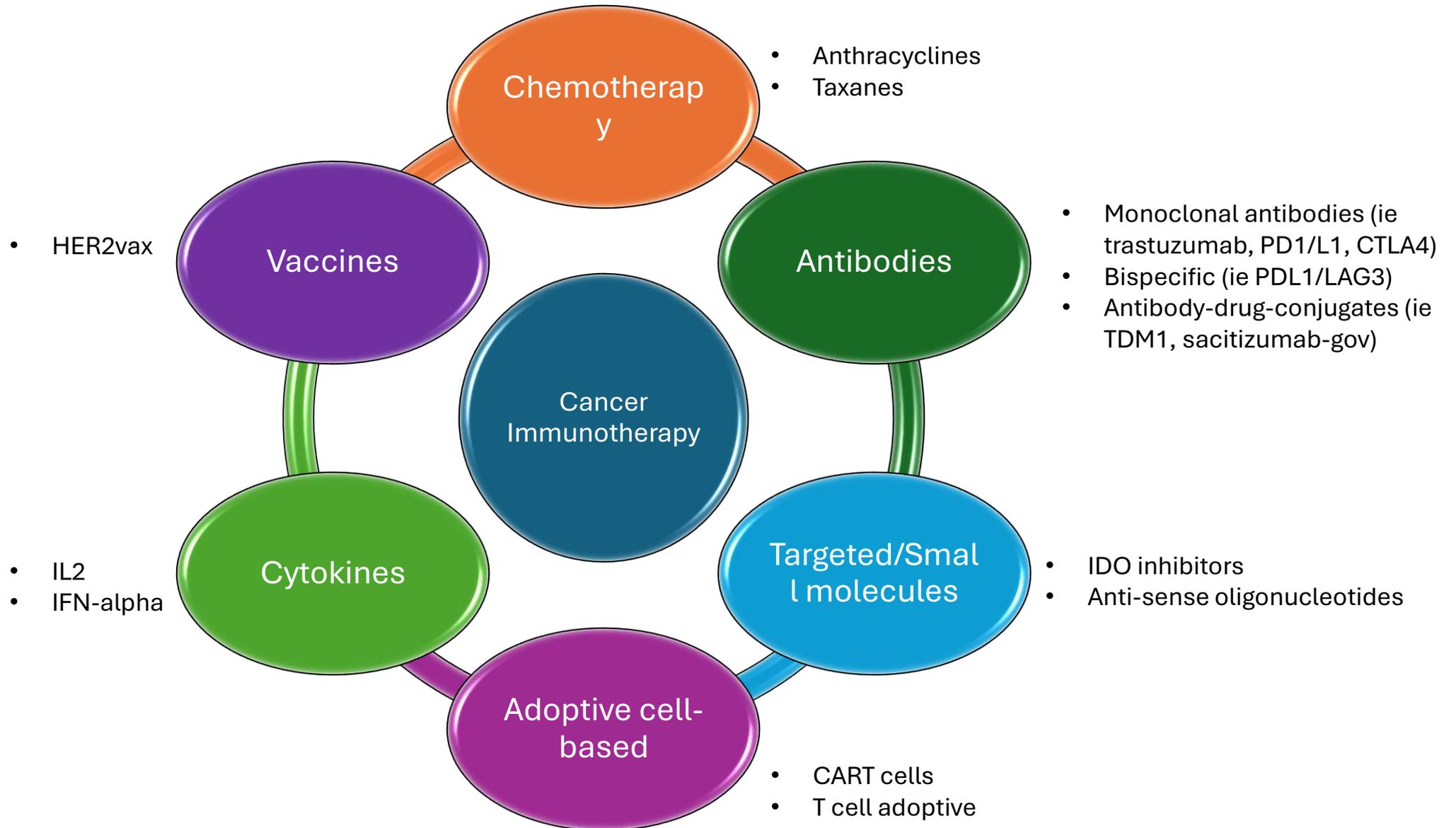


Cancer immunology

- Hallmark of cancer is to avoid immune system
- Mechanisms of immune escape
 - Low immunogenicity
 - Tumor-induced immunosuppression
 - Antigenic modulation

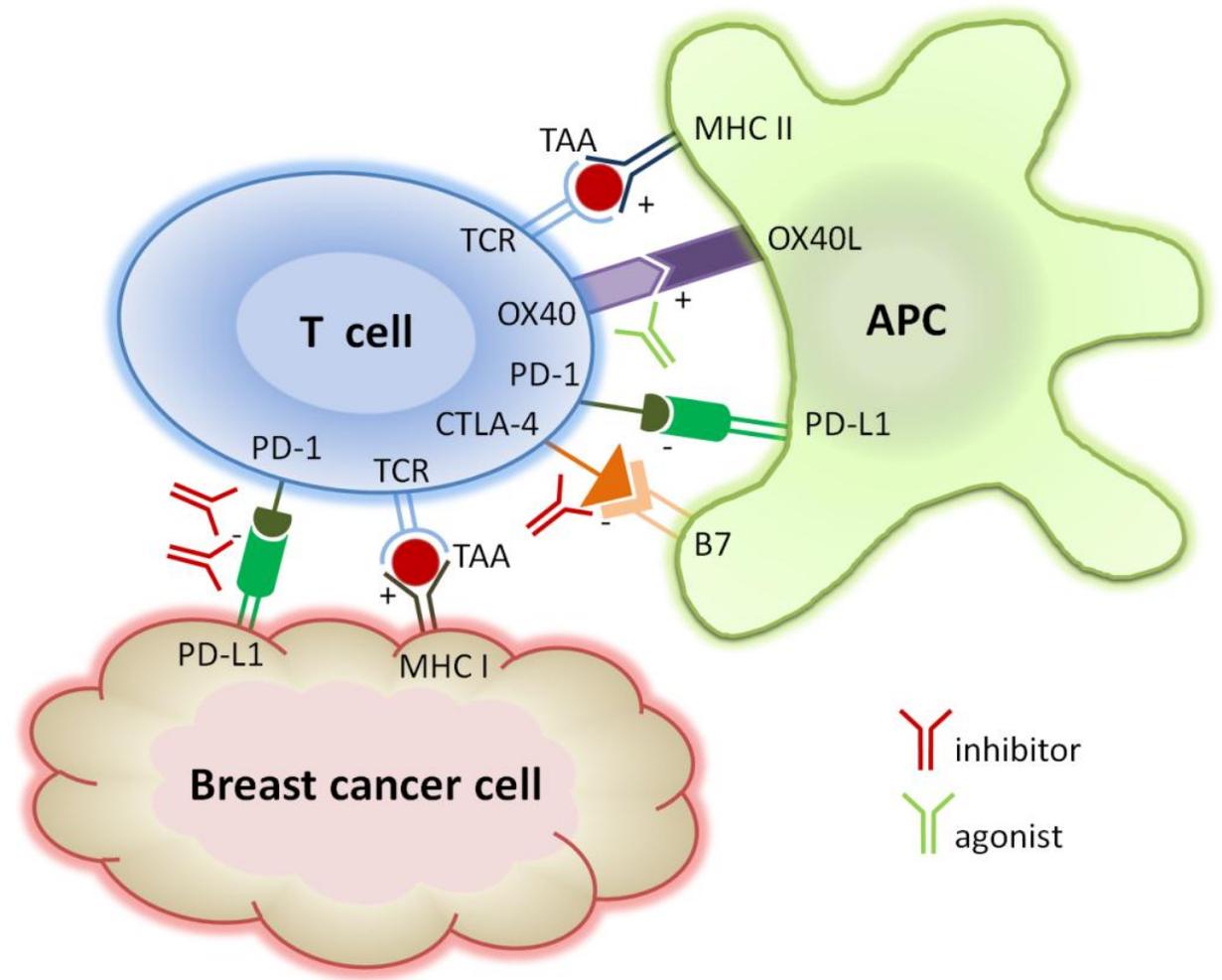


Cancer Immunotherapy



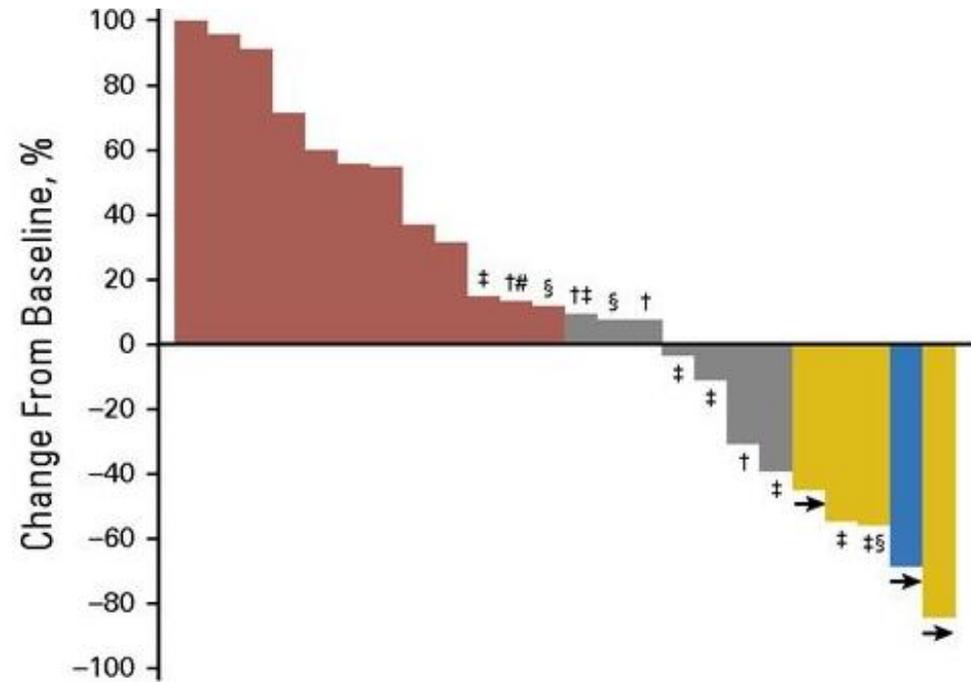
Immune checkpoints in cancer

- Immune checkpoints control T cell activation through various mechanisms
- PD1/PDL1 blockade active in many cancers



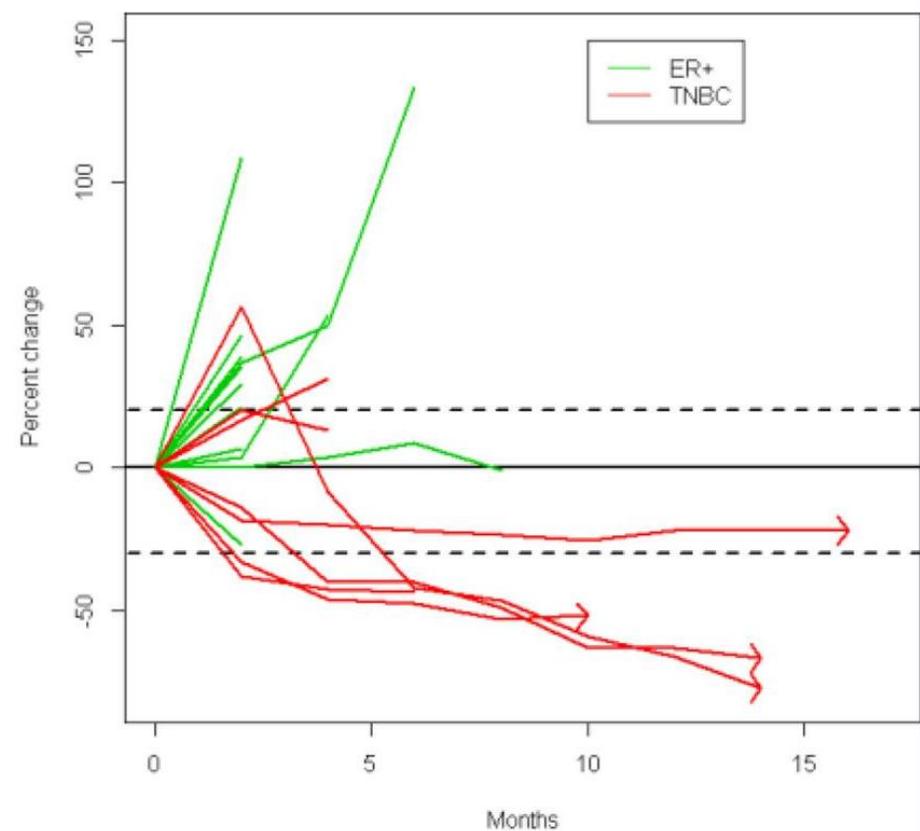
First reports of ICIs in metastatic breast cancer

First report of pembrolizumab in mTNBC: KEYNOTE-012



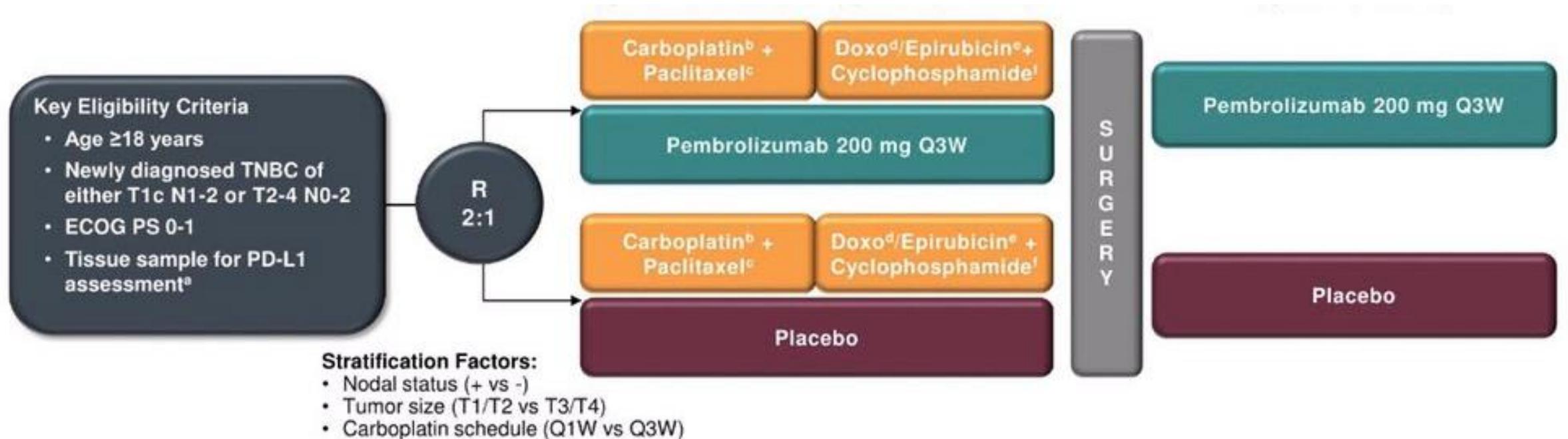
Nanda et al JCO 2016

First dual ICI report in breast cancer: durvalumab/tremelimumab in metastatic ER+ and TNBC



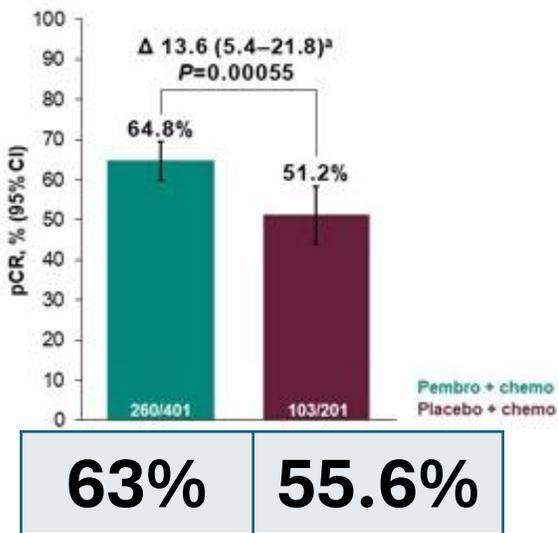
Santa-Maria et al. Oncotarget 2018

KEYNOTE-522: adding pembrolizumab to neoadjuvant chemotherapy in TNBC



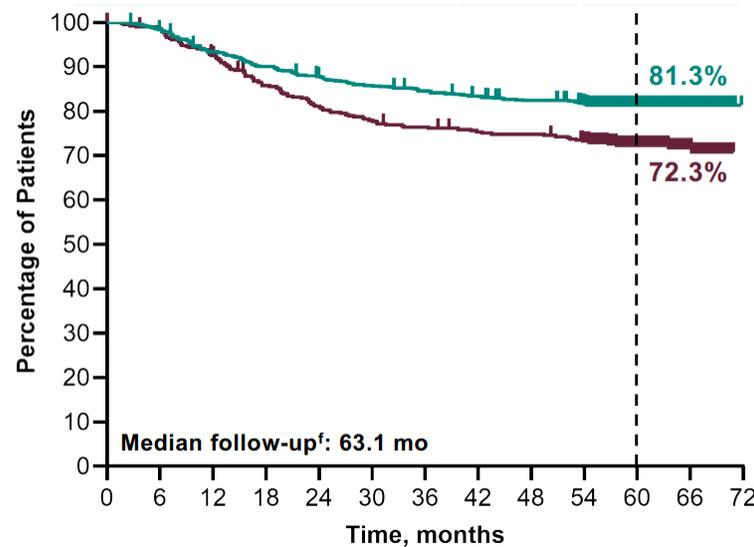
Adding immunotherapy to neoadjuvant chemotherapy ↑ efficacy, but ↑ toxicity too

Pembrolizumab improves pCR rate



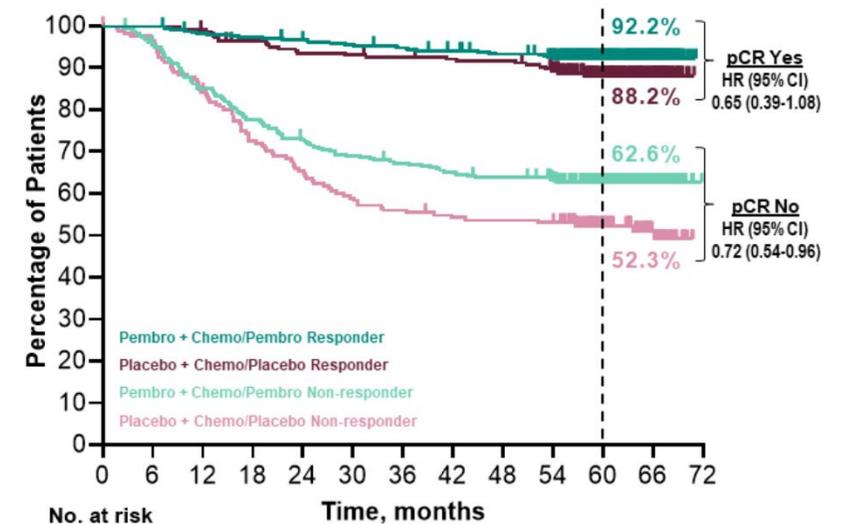
IA3 pCR analysis

Pembrolizumab improves EFS, OS



All Treatment-Related	Pembro + Chemo/Pembro (N = 783)	Pbo + Chemo/Pbo (N = 389)
Any grade	98.9%	99.7%
Grade 3-5	77.1%	73.3%
Led to death	0.5% ^a	0.3% ^b
Led to discontinuation of any drug	27.7%	14.1%

pCR associated with lower risk of recurrence
 → possible **overtreatment**
 RD associated with high risk of recurrence
 → possible **undertreatment**



BUT you won't find out about pCR until you have completed all 6 months of intensive chemo-IO!

NeoADAPT: Pilot PET study in TNBC

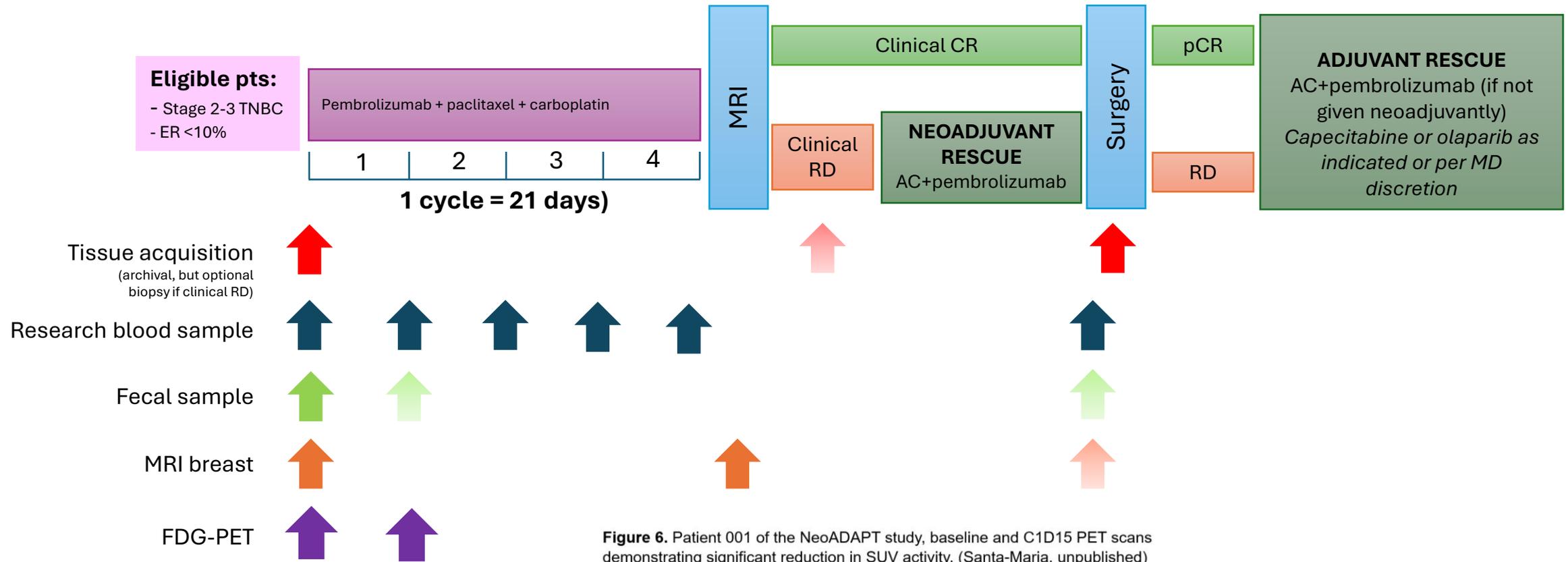
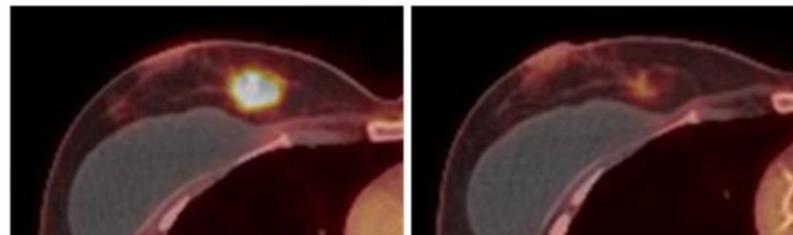


Figure 6. Patient 001 of the NeoADAPT study, baseline and C1D15 PET scans demonstrating significant reduction in SUV activity. (Santa-Maria, unpublished)



Baseline PET

C1D15 PET

- Opened 4/2024
- 20/30 pts enrolled

PI Santa-Maria, co-I Solnes
 (NCT06245889)
 BCRF, SGK, ASCO/CCF ACRA

In conclusion...

- We have come a long way, but still have a long way to go
- Scientific and medical research breakthroughs have dramatically improved outcomes for patients with breast cancer
- The US has been a scientific and medical leader globally by attracting diverse talent from around the world and government funding that has made many of these breakthroughs possible
- Philanthropy plays an increasingly important role in funding research

