Are We Winning The War On Cancer?

Douglas Yee, MD
Director, Masonic Cancer Center

Masonic Cancer Center
University of Minnesota

Comprehensive Cancer Center designated by the National Cancer Institute

What Have We Learned In The Last 50 Years About Breast Cancer?

Masonic Cancer Center
University of Minnesota

Comprehensive Cancer Center designated by the National Cancer Institute

Mr. Nixon:

You can cure cancer.

If prayers are heard in Heaven, this prayer is heard the most:

"Dear God, please. Not cancer."

Still, more than 318,000 Americans died of cancer last year.

This year, Mr. President, you have it in your power to begin to end this curse.

As you agonize over the Budget, we beg you to remember the agony of those 318,000 Americans. And their families.

We urge you to remember also that we spend more each day on military matters than each year on cancer research. And, last year, more than 21 times as much on space research as on cancer research.

We ask a better perspective, a better way to allocate our money to save hundreds of thousands of lives each year.

America can do this. There is not a doubt in the minds of our top cancer researchers that the final answer to cancer can be found.

Already, 4 out of about 200 types of cancer can be cured with drugs. And 37 other drugs will cause temporary remission in 17 other types of cancer.

Dr. Sidney Farber, Past President of the American Cancer Society, believes: "We are so close to a cure for cancer. We lack only the will and the kind of money and comprehensive planning that went into putting a man on the moon."

Why don't we try to conquer cancer by America's 200th birthday?

What a holiday that would be! Cancer could be then where smallpox, diphtheria and polio are today—almost nonexistent.

If you fail us, Mr. President, this will happen:

One in six Americans now alive, 34,000,000 people, will die of cancer unless new cures are found.

One in four Americans now alive, 51,000,000 people, will have cancer in the future.

We simply cannot afford this.

Our nation has the money on one hand and the skills on the other. We must, under your leadership, put our hands together and get this thing done.

Surely, the war against cancer has the support of 100% of the people. It is a war in which we lost 21 times more lives last year than we lost in Viet Nam last year. A war we can win and put the entire human race in our debt.

To the public, cancer patients, their friends and relatives:

Write or wire the President, urging him to put more funds behind cancer research. Or, please use this coupon.

Dear Mr. Nixon:
Cancer research needs more funds. Please provide them in your 1971 budget. *Please.*

NAME_____

ADDRESS_____

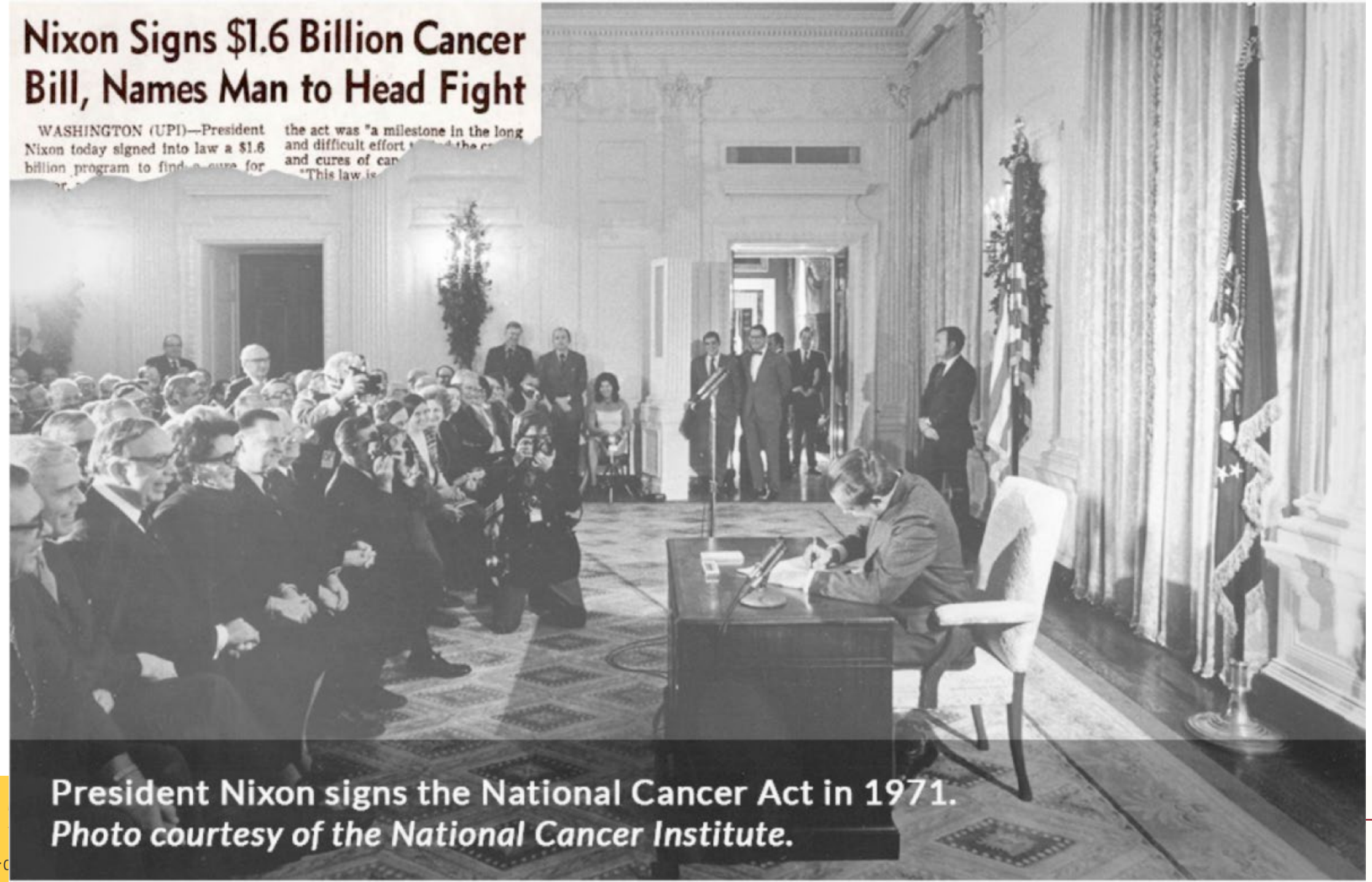
CITY_____ STATE_____ ZIP_____

Mail this coupon to: The President
The White House
Washington, D.C.

CITIZENS COMMITTEE FOR THE CONQUEST OF CANCER
866 United Nations Plaza, New York, N.Y., Solomon Garb, M.D., Emerson Foote, Co-chairmen

Advertisement
December 9, 1969

Mary Lasker
1900-1994



President Nixon signs the National Cancer Act in 1971.
Photo courtesy of the National Cancer Institute.

Special Article

CANCER UNDEFEATED

JOHN C. BAILAR III, M.D., PH.D., AND HEATHER L. GORNIK, M.H.S.

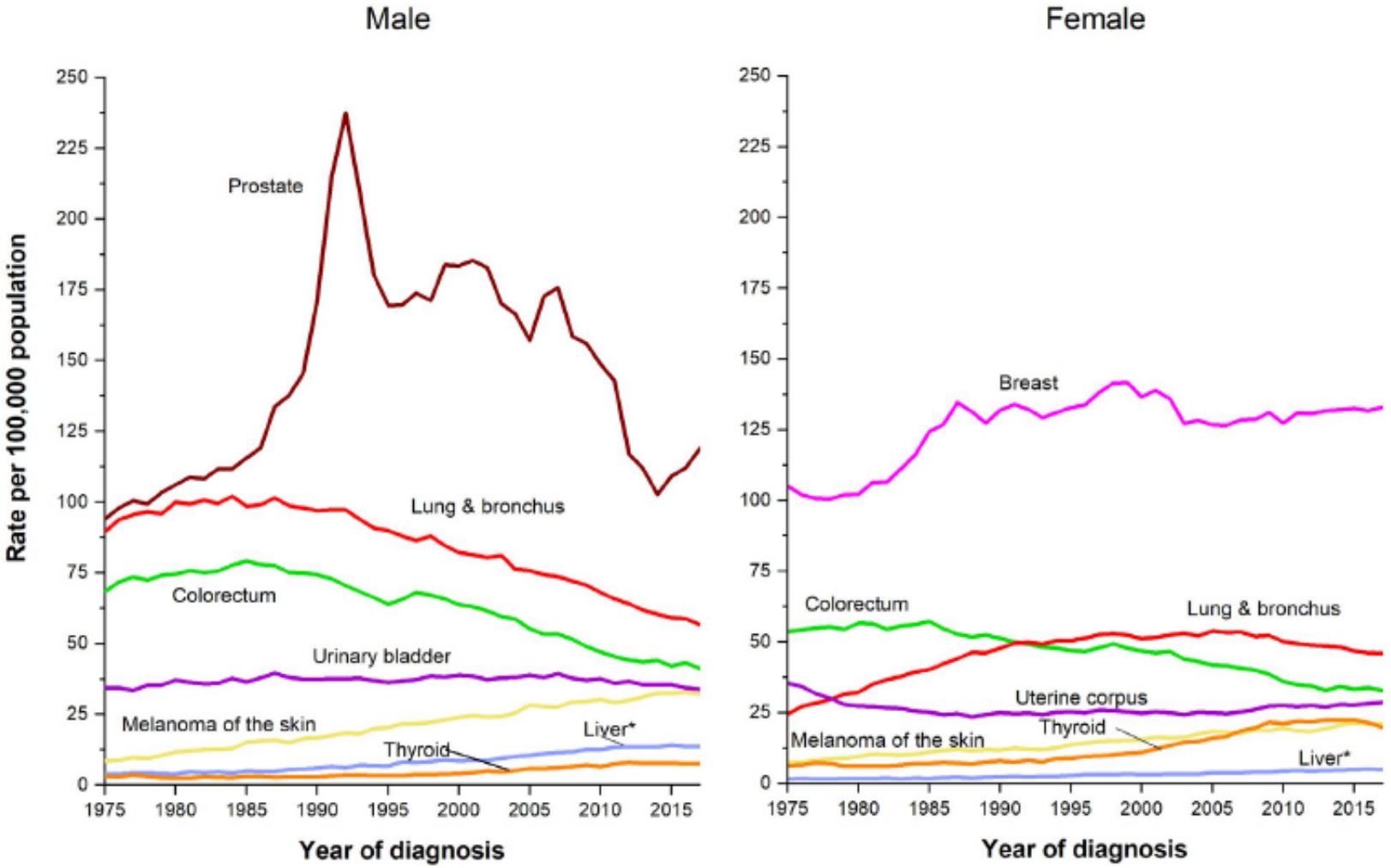
Conclusions The war against cancer is far from over. Observed changes in mortality due to cancer primarily reflect changing incidence or early detection. The effect of new treatments for cancer on mortality has been largely disappointing. The most promising approach to the control of cancer is a national commitment to prevention, with a concomitant rebalancing of the focus and funding of research. (N Engl J Med 1997;336:1569-74.)

What Does A “Win” Look Like For Breast Cancer?

- Fewer cancer diagnoses
  - Identify cancer causes – not clear preventable causes
  - Employ appropriate individualized screening strategies - WISDOM
  - Develop prevention (lifestyle changes, drugs, etc) for people at high risk – tamoxifen, raloxifene
- Fewer cancer deaths
  - Individualized approaches to cancer therapy – HER2 and Estrogen Receptor
  - Develop new treatment strategies for refractory cancers – New drug strategies
- Improve quality of life for cancer survivors
  - Minimized toxic therapy when not necessary – OncotypeDx™
  - “Target” cancer therapies to only the tumor – New drugs
- Address health care disparities
  - Cancer outcomes directly linked to socioeconomic status and ancestry/ethnic groups – new risk modeling for Black women*

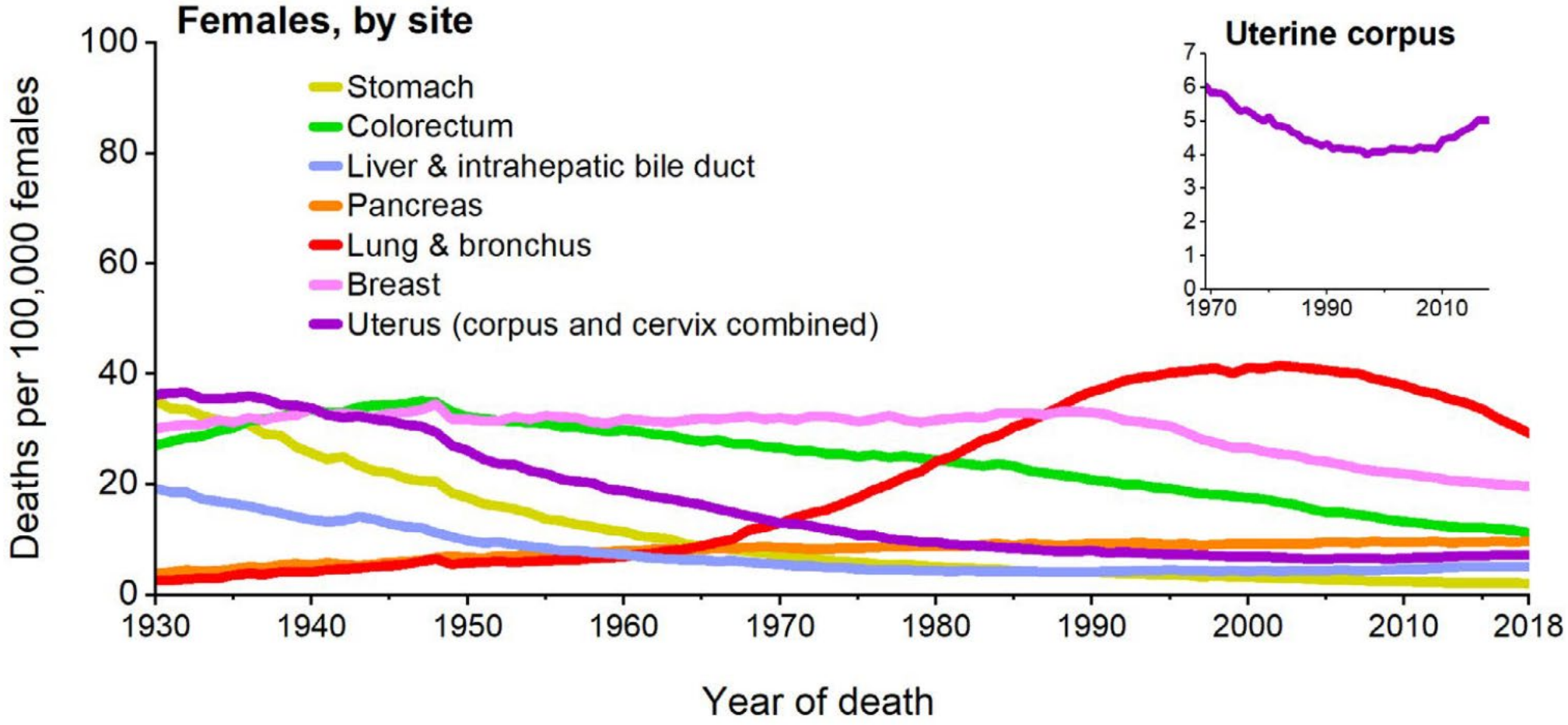
* Palmer JR, et al. A validated risk prediction model for breast cancer in US Black women. J Clin Oncol 39:3866-3877 2021.

Trends In Cancer Incidence From 1975



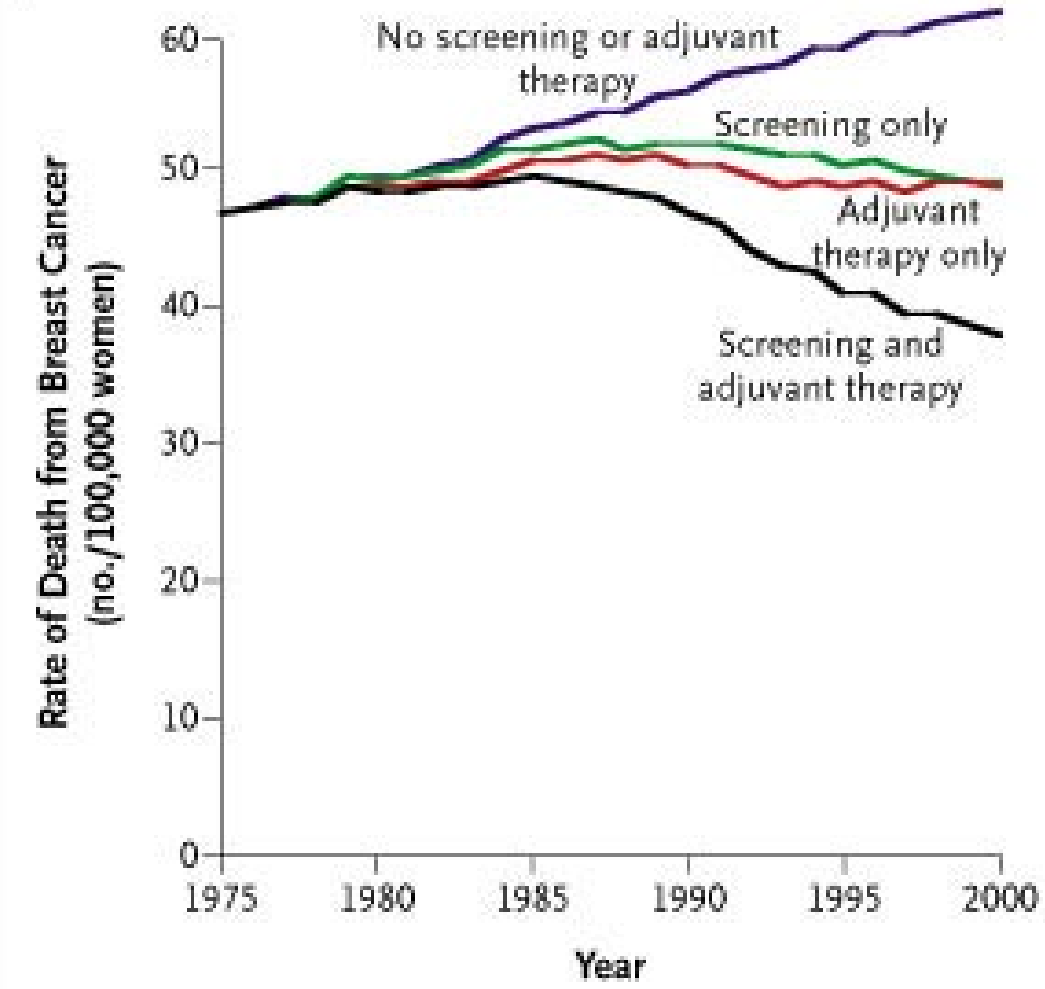
Siegel, et al. CA Cancer J Clin 71:7 2021 PMID: 33433946

US Women's Cancer Mortality – 1930-2018



Siegel, et al. CA Cancer J Clin 71:7 2021 PMID: 33433946

Better Outcomes Due To More Screening and More Adjuvant Therapy



Berry, et al. N Engl J Med 353:1784 2005 PMID: 16251534

Women Informed to Screen Depending On Measures of risk – WISDOM Screening Trial

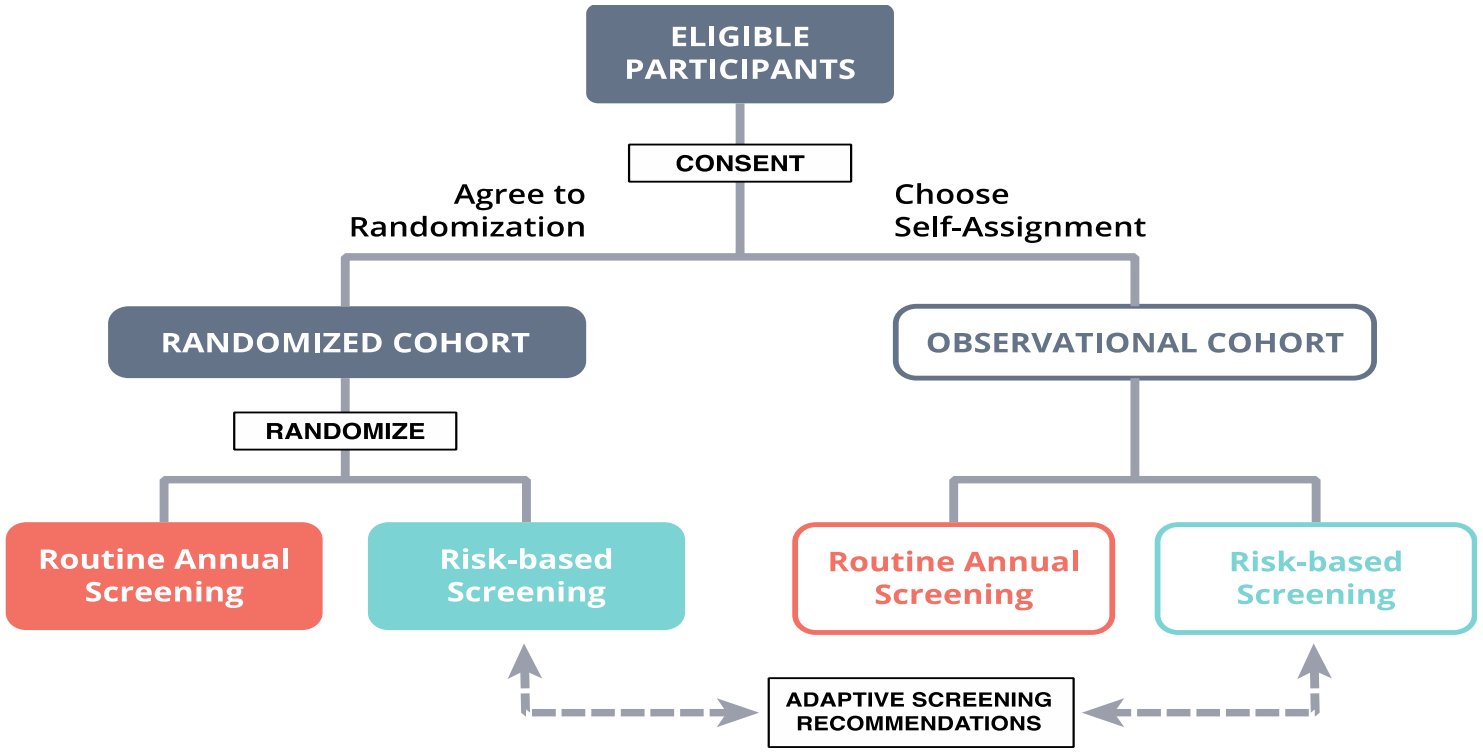


Table 1: Risk-based screening recommendations currently employed in WISDOM

Highest Risk	Elevated Risk	Average Risk	Lowest Risk
BRCA1/2, TP53, PTEN, STK11, CDH1 mutation carrier OR ATM, PALB2 or CHEK2 mutation carrier with positive family history of breast cancer OR Women with a ≥6% 5-year risk (risk of an average BRCA carrier) OR Women with a history of mantle radiation between ages 10-30 years	Women aged 40-49 with extremely dense breasts OR Women at a ≥1% 5-year risk of developing ER- breast cancer based on susceptibility SNPs OR Women in top 2.5th percentile of risk by 1-year age category OR ATM, PALB2 or CHEK2 mutation carrier without a positive family history** of breast cancer	Women aged 50-74 OR Women aged 40-49 with a ≥1.3% 5-year risk (risk of an average 50 year-old woman)	Women aged 40-49 with a <1.3% 5-year risk of developing breast cancer
Annual mammogram+ MRI	Annual mammogram*	Biennial mammogram†	No screening until age 50

* If individual does not meet criteria for annual mammogram + MRI
† If individual does not meet criteria for annual mammogram or annual mammogram + MRI
** Family history is defined as a first degree relative with breast cancer, two second-degree relatives with breast cancer, or one second-degree relative diagnosed prior to age 45.

PI: Laura Esserman, UCSF NCT02620852

A Decade of New Drug Approvals in Breast Cancer

- Hormone Receptor +
  - ER
    - Fulvestrant
  - CDK 4/6 inhibitors
    - Palbociclib
    - Ribociclib
    - Abemaciclib
  - PI3K-mTOR
    - Alpelisib
    - Everolimus
- HER2 positive
  - moAb
    - Pertuzumab
    - Margetuximab
  - TK inhibitors
    - Lapatinib
    - Neratinib
    - Tucatinib
  - ADCs
    - TDM1
    - T-DXd
- TNBC
  - PD-L1/PD-1
    - Atezolizumab (withdrawn)
    - Pembrolizumab
  - ADCs
    - Sacituzumab govitecan
  - PARPi
    - Olaparib
    - Talazoparib
  - Chemotherapy
    - Eribulin

Arora, et al. Clin Cancer Res 2021 PMID: 34711632

Discovery of Immune Checkpoints

The Nobel Prize in Physiology or Medicine 2018

© Nobel Media AB. Photo: A. Mahmoud

James P. Allison

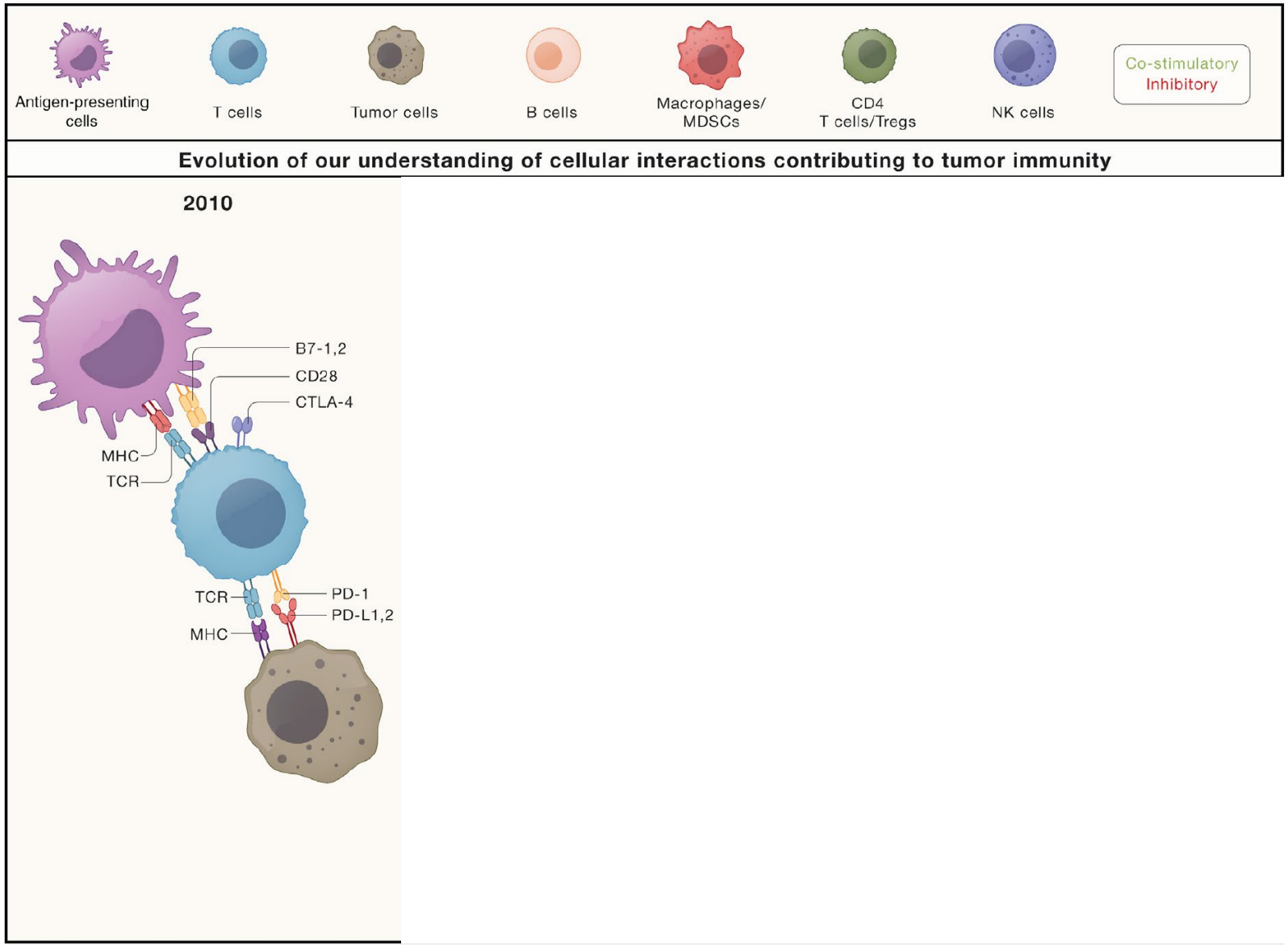
Prize share: 1/2

© Nobel Media AB. Photo: A. Mahmoud

Tasuku Honjo

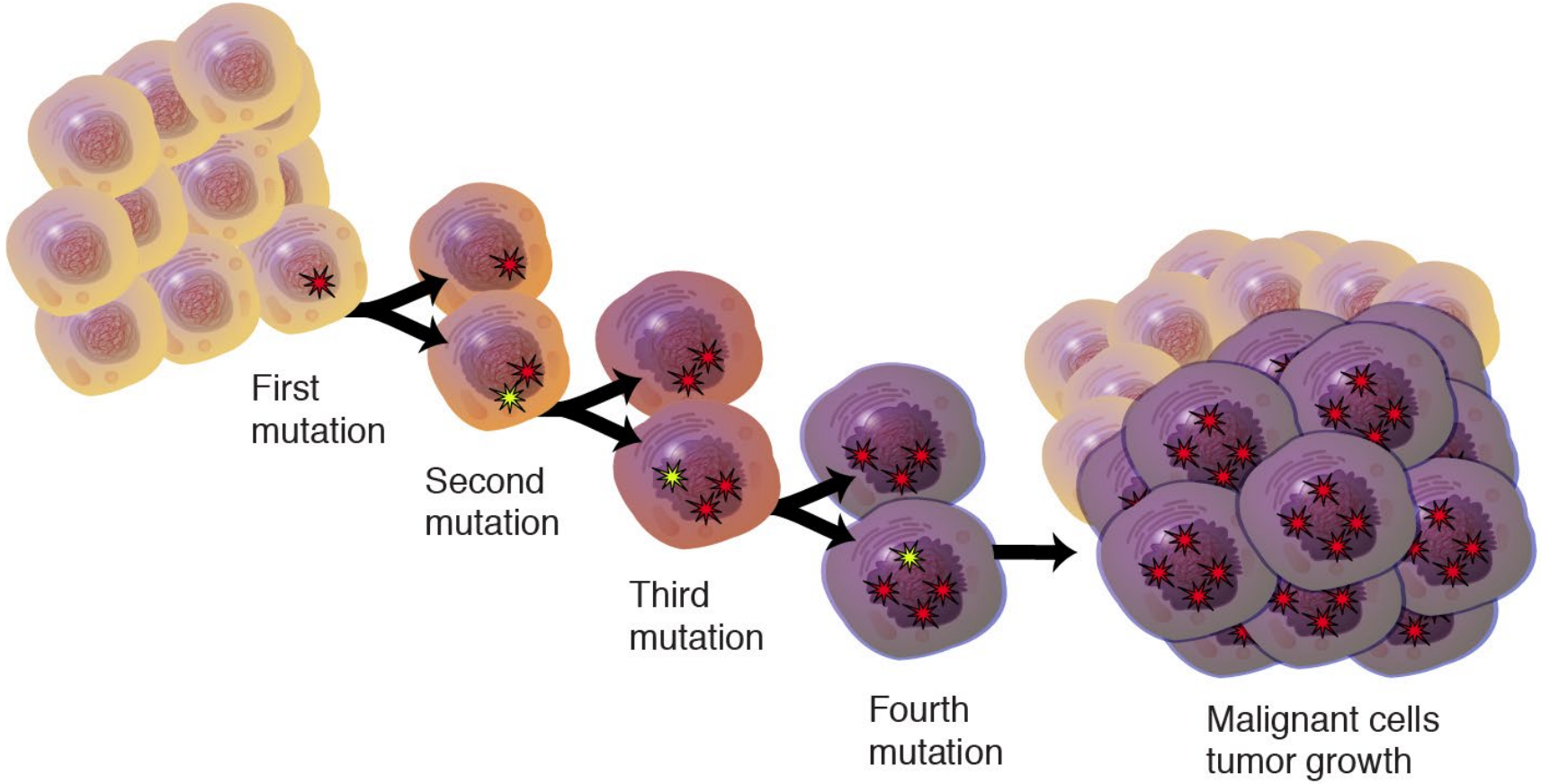
Prize share: 1/2

The Nobel Prize in Physiology or Medicine 2018 was awarded jointly to James P. Allison and Tasuku Honjo "for their discovery of cancer therapy by inhibition of negative immune regulation."



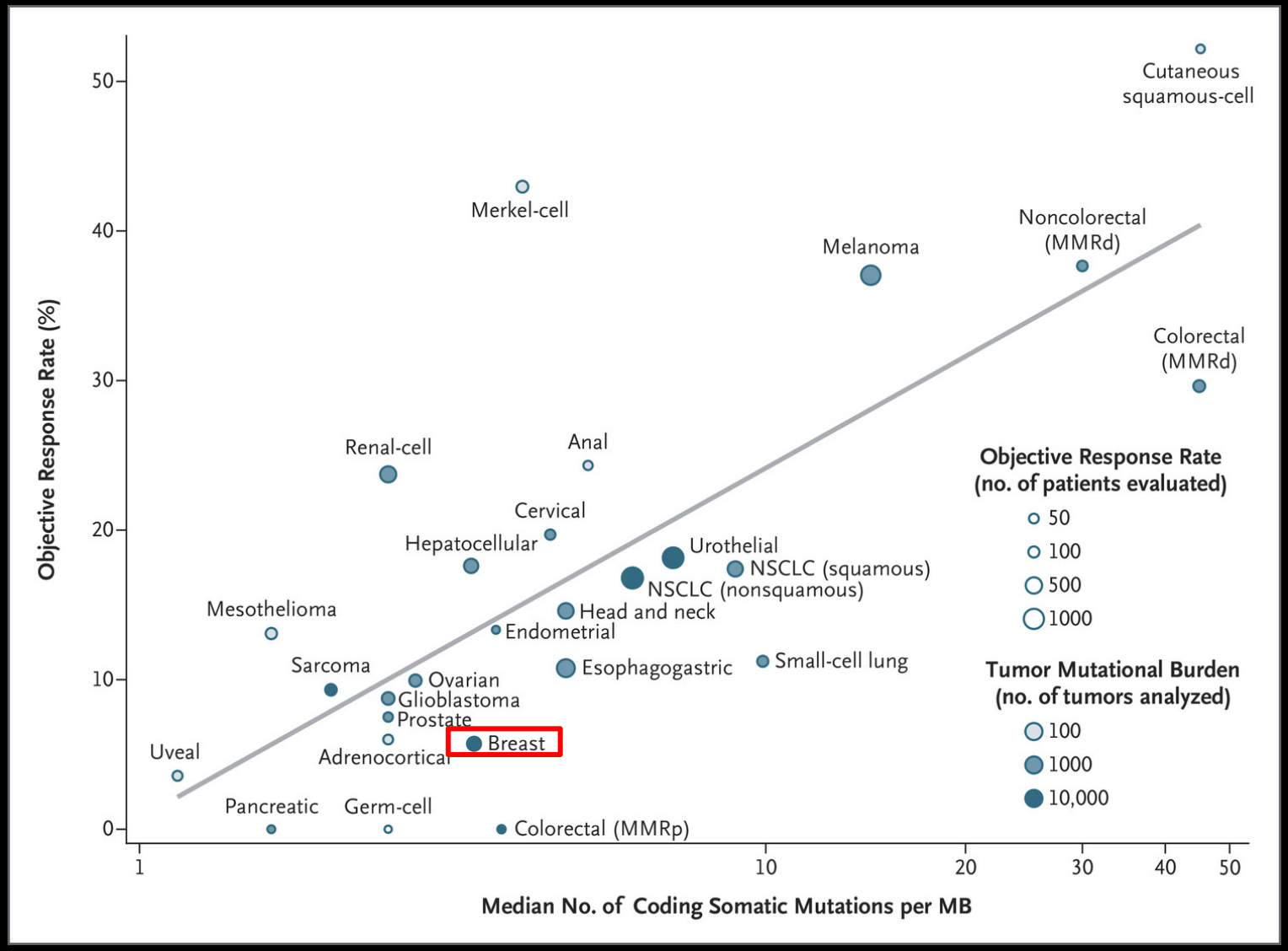
Morad, et al. Cell 184:5309 2021 PMID: 34624224

DNA Mutation As A Cause Of Cancer And A Target For Immunotherapy



Cancer (genome.gov)

Correlation between Tumor Mutational Burden and Objective Response Rate with Anti–PD-1 or Anti–PD-L1 Therapy in 27 Tumor Types.



Yarchoan M et al. N Engl J Med 2017;377:2500-2501.

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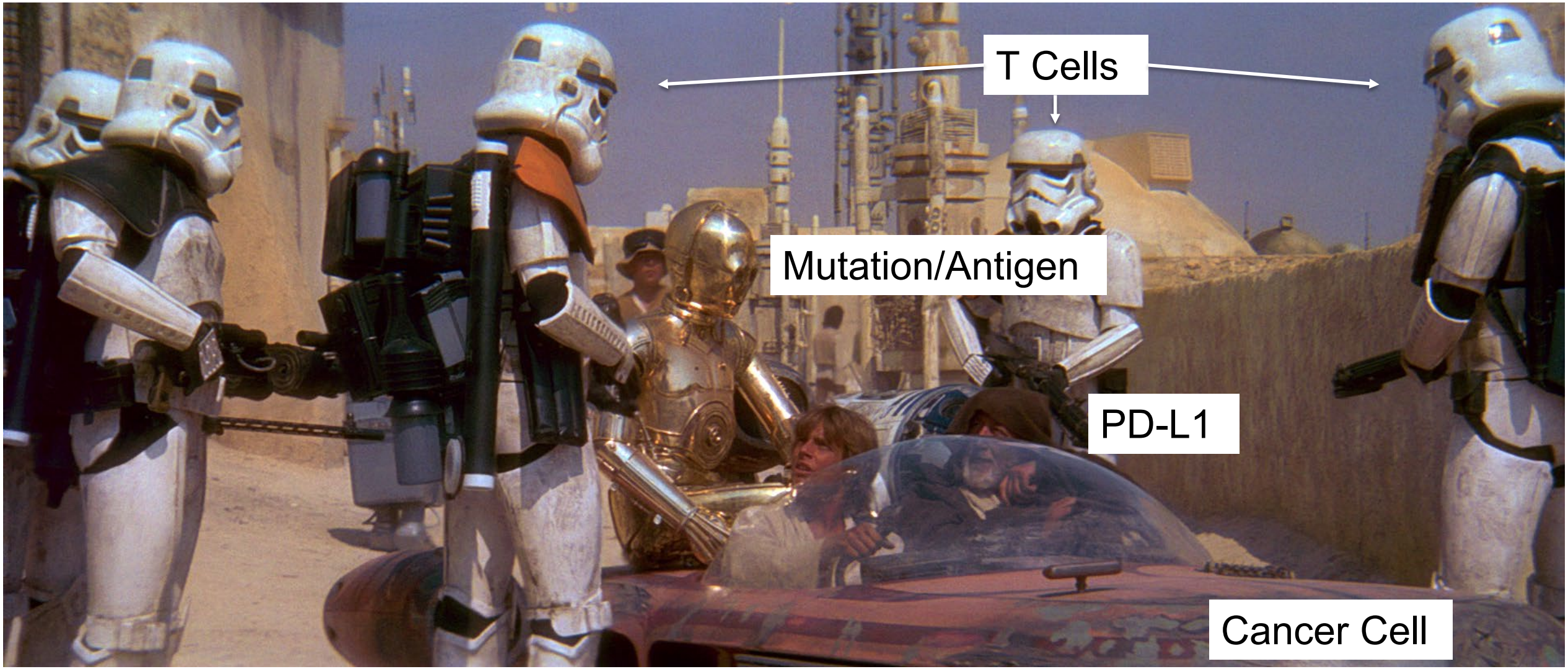
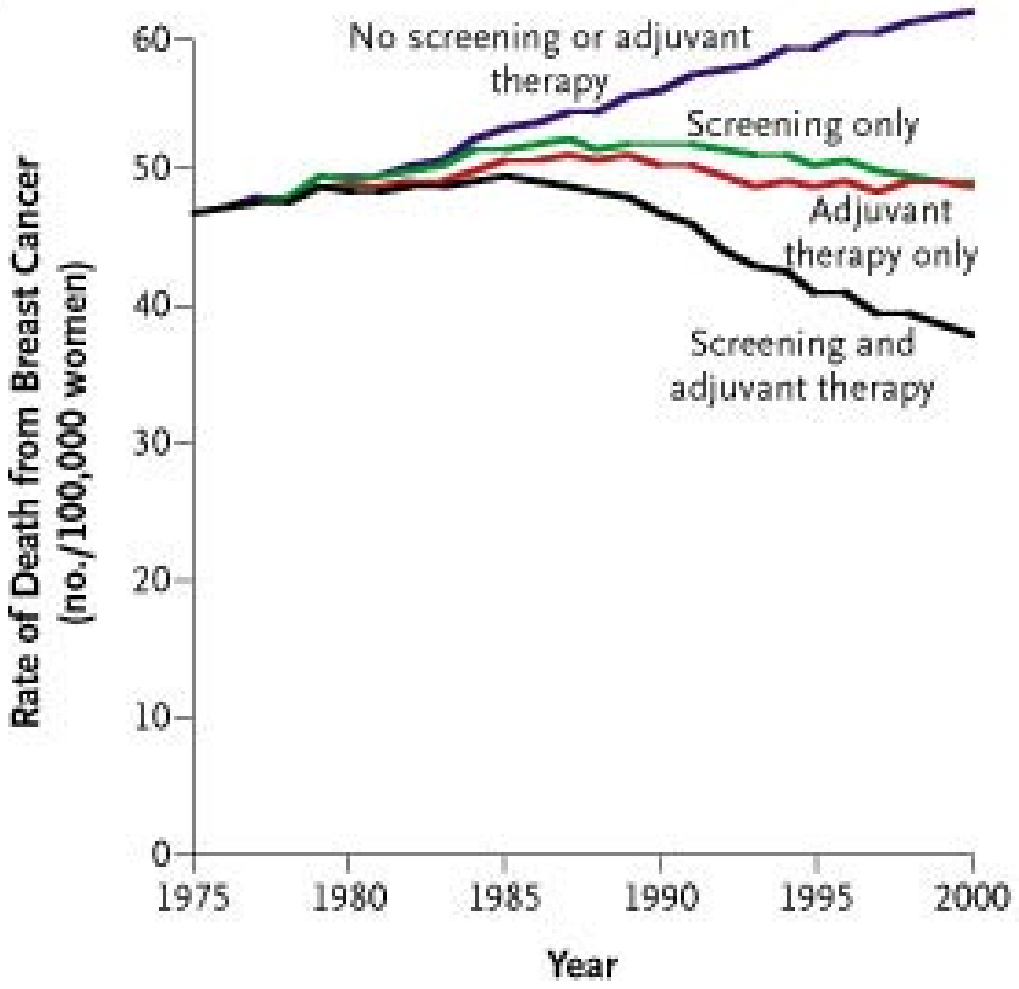
PD-L1 – A Jedi Mind Trick
These Are Not The Cells You're Looking For

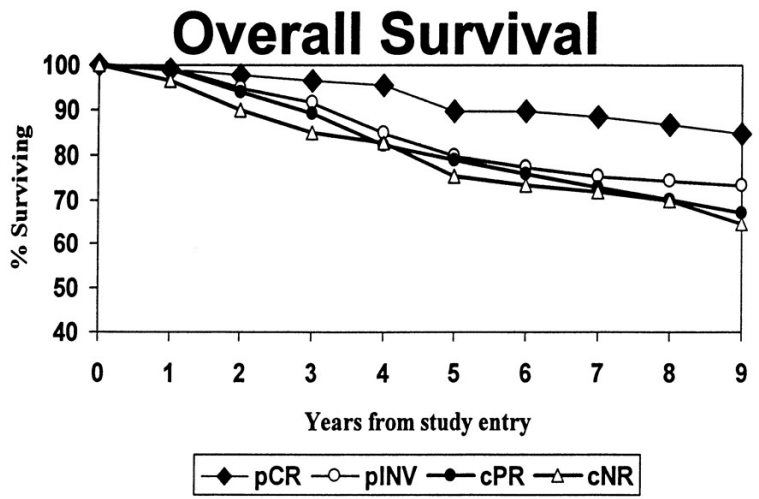


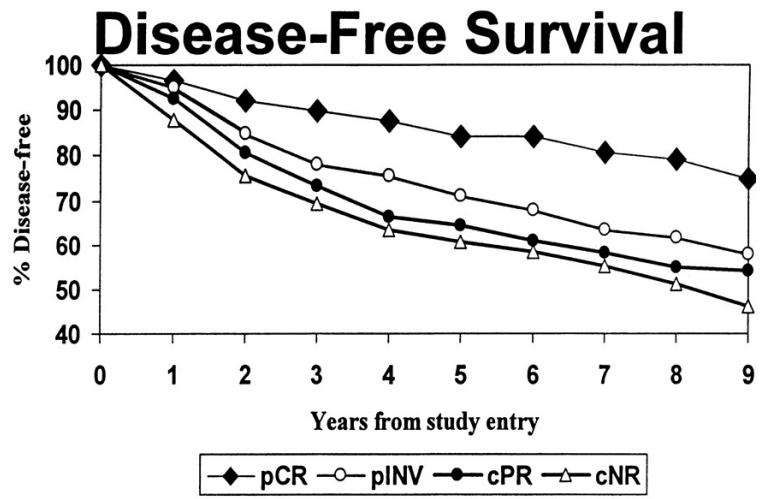
Better Outcomes Due To More Screening and More Adjuvant Therapy

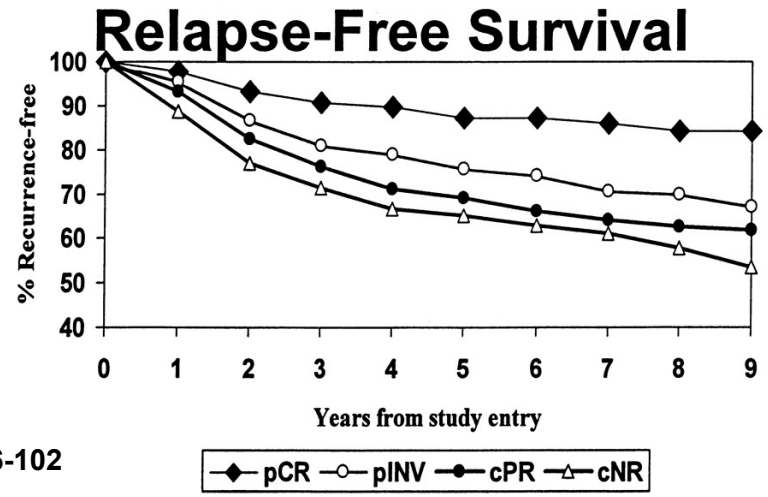


Berry, et al. N Engl J Med 353:1784 2005

Response to pre-surgical chemotherapy correlates with long term outcomes





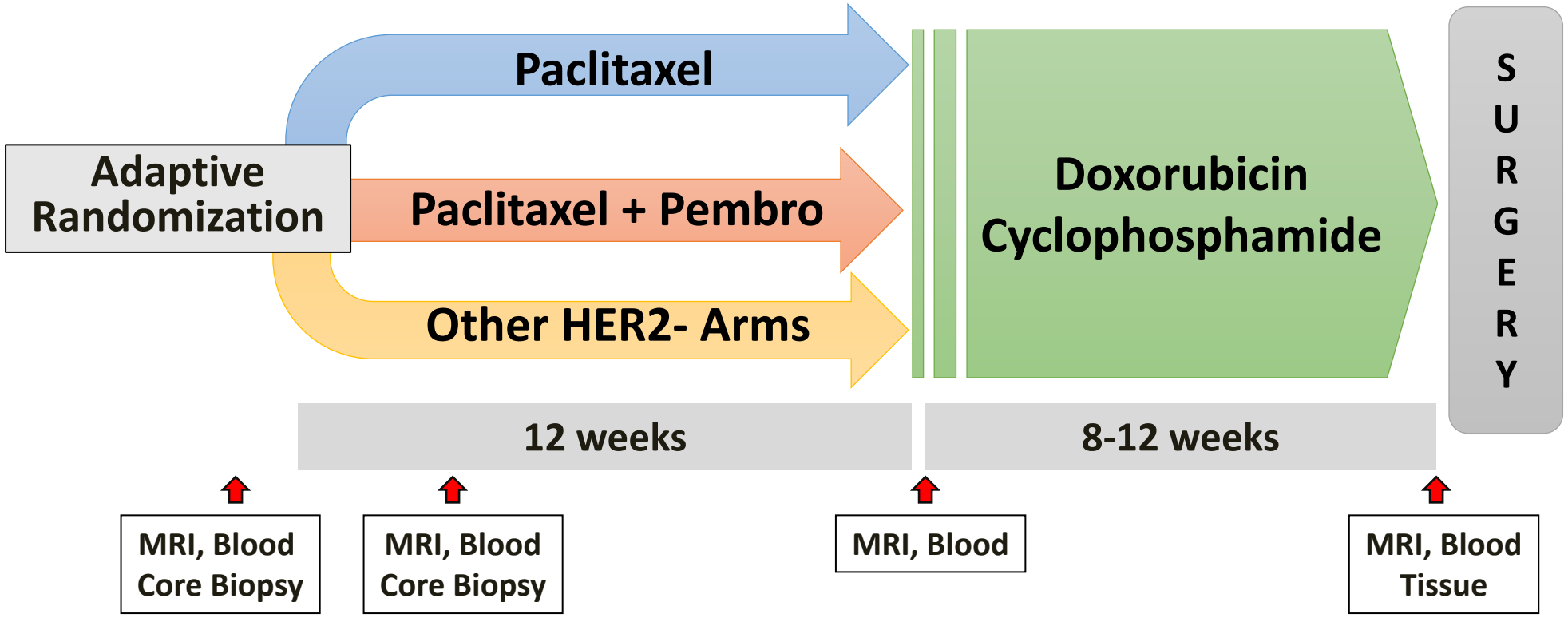


pCR = No residual invasive cancer in breast and lymph nodes

Wolmark N et al. J Natl Cancer Inst Monogr 2001;2001:96-102

JNCI MONOGRAPHS

I-SPY 2 TRIAL Schema: HER2- Signatures



Nanda, et al. JAMA Oncol 2020 PMID: 32053137

JAMA Oncology | Original Investigation

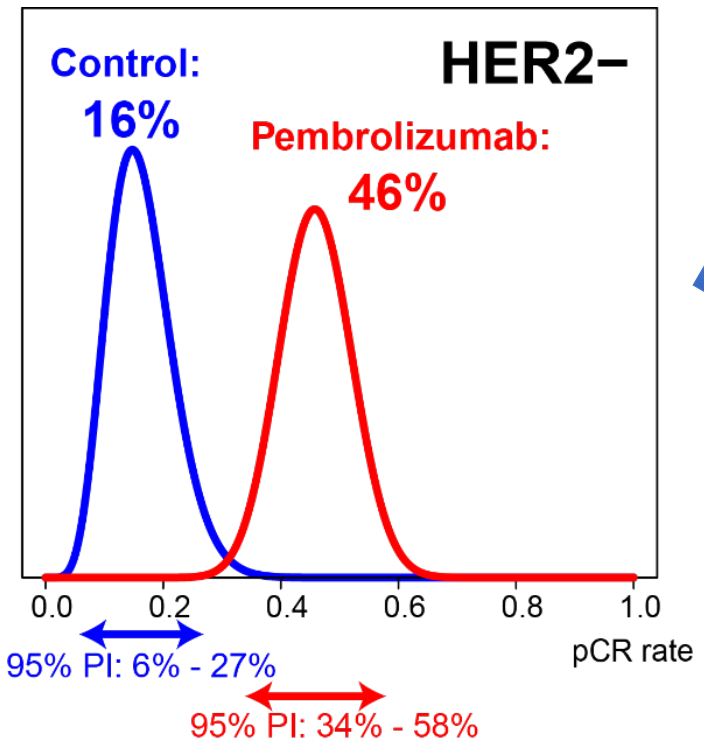
Effect of Pembrolizumab Plus Neoadjuvant Chemotherapy on Pathologic Complete Response in Women With Early-Stage Breast Cancer

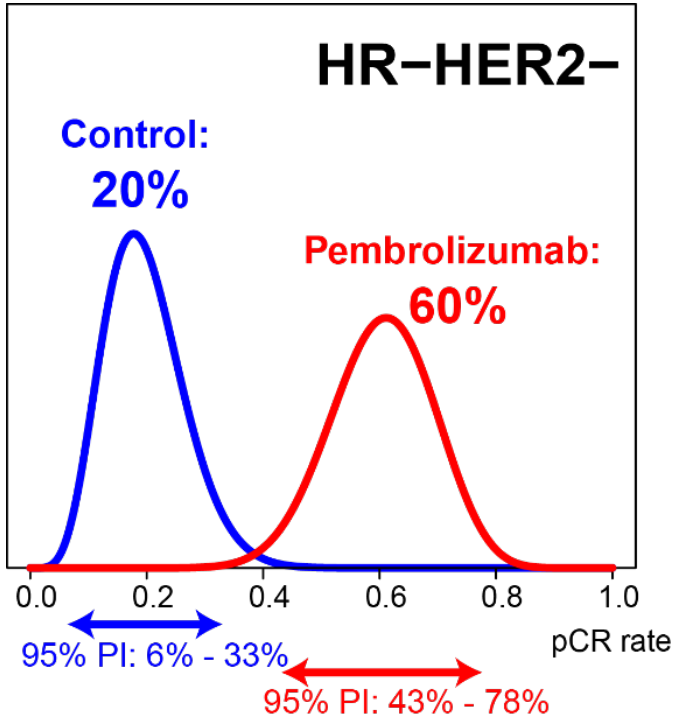
An Analysis of the Ongoing Phase 2 Adaptively Randomized I-SPY2 Trial

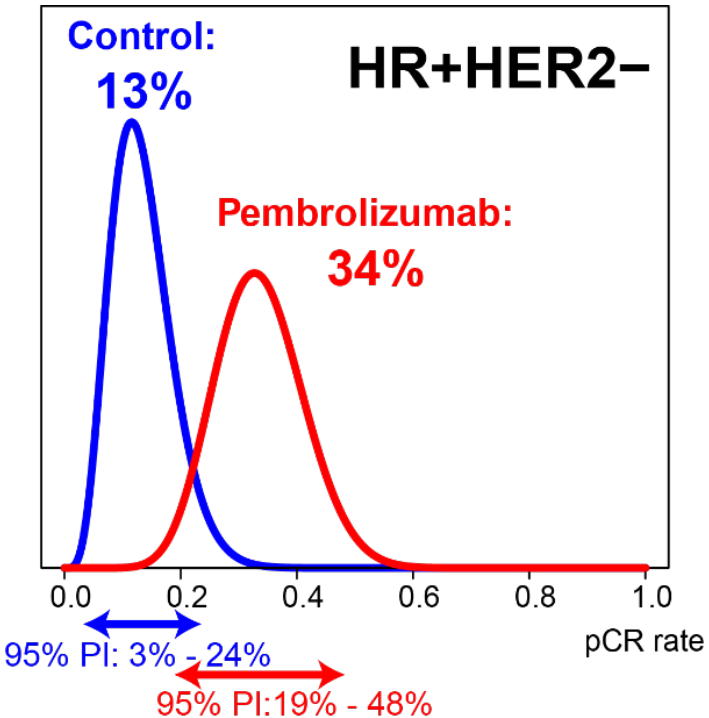
Rita Nanda, MD; Minetta C. Liu, MD; Christina Yau, PhD; Rebecca Shatsky, MD; Lajos Pusztai, MD, DPhil; Anne Wallace, MD; A. Jo Chien, MD; Andres Forero-Torres, MD; Erin Ellis, MD; Heather Han, MD; Amy Clark, MD; Kathy Albain, MD; Judy C. Boughey, MD; Nora T. Jaskowiak, MD; Anthony Elias, MD; Claudine Isaacs, MD; Kathleen Kemmer, MD; Teresa Helsten, MD; Melanie Majure, MD; Erica Stringer-Reasor, MD; Catherine Parker, MD; Marie C. Lee, MD; Tufia Haddad, MD; Ronald N. Cohen, MD; Smita Asare; Amy Wilson; Gillian L. Hirst, PhD; Ruby Singhrao; Katherine Steeg; Adam Asare, PhD; Jeffrey B. Matthews, PhD; Scott Berry, PhD; Ashish Sanil, PhD; Richard Schwab, MD; W. Fraser Symmans, MD; Laura van 't Veer, PhD; Douglas Yee, MD; Angela DeMichele, MD; Nola M. Hylton, PhD; Michelle Melisko, MD; Jane Perlmutter, PhD; Hope S. Rugo, MD; Donald A. Berry, PhD; Laura J. Esserman, MD

Nanda, et al. JAMA Oncol 2020 PMID: 32053137

pCR Probability Distributions by Signature

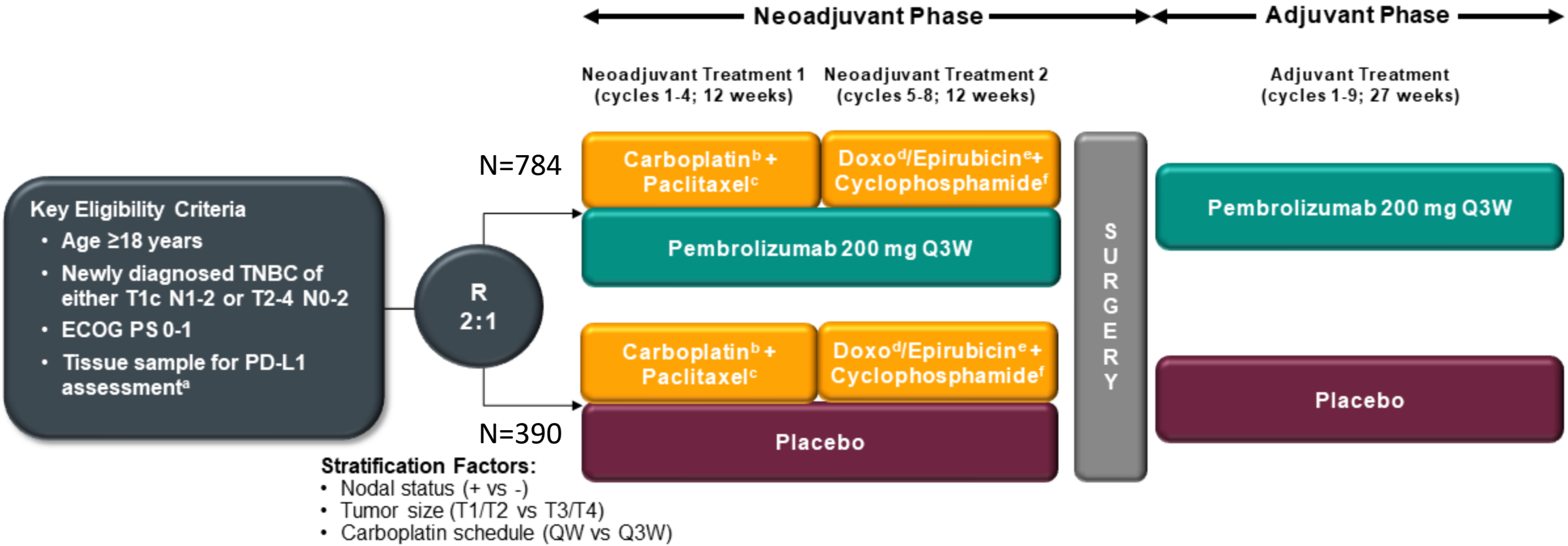






Nanda, et al. JAMA Oncol 2020 PMID: 32053137

KEYNOTE-522 Study Design (NCT03036488)



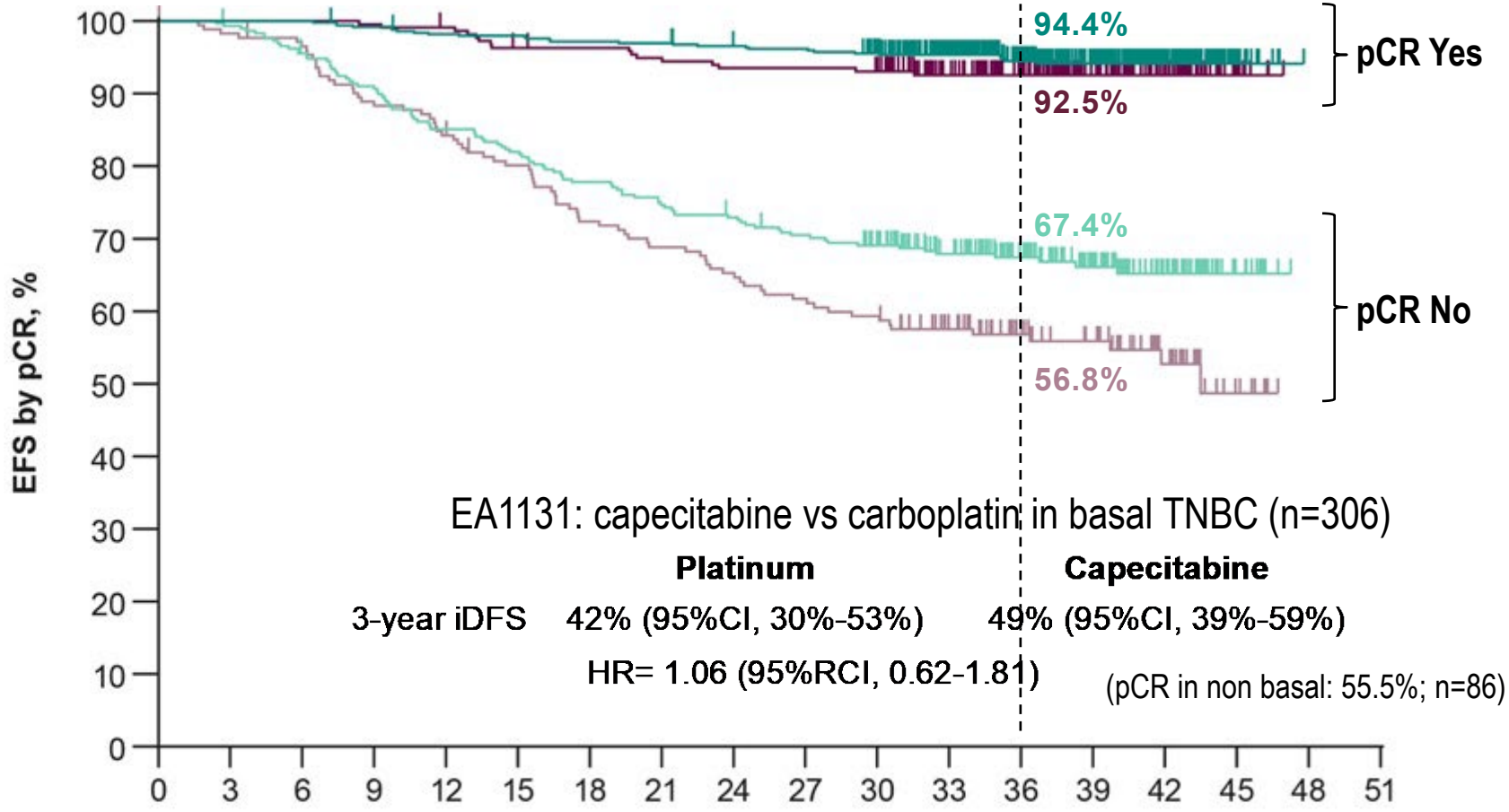
Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

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

Schmid, et al. N Engl J Med 382:810 2020 PMID: 32101663

[a]Must consist of at least 2 separate tumor cores from the primary tumor.
[b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW.
[c]Paclitaxel dose was 80 mg/m^2 QW.
[d]Doxorubicin dose was 60 mg/m^2 Q3W.
[e]Epirubicin dose was 90 mg/m^2 Q3W.
[f]Cyclophosphamide dose was 600 mg/m^2 Q3W.

EFS by pCR (ypT0/Tis ypN0)



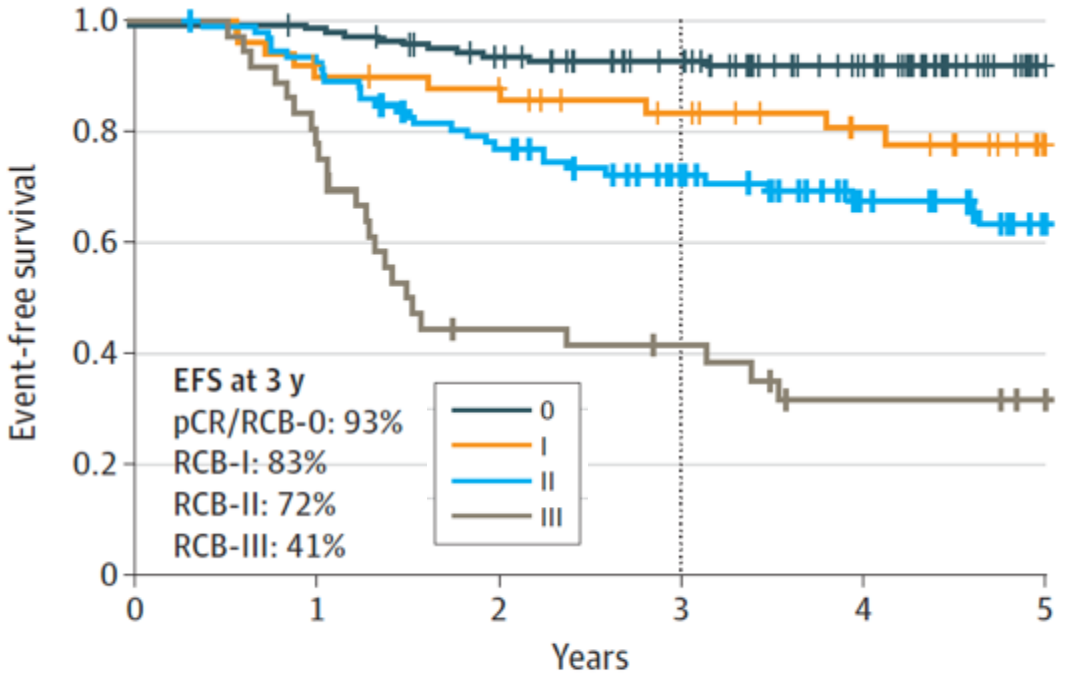
No. at Risk																		
Pembro + Chemo/Pembro Responder	494	494	494	489	483	482	478	477	472	470	460	387	307	220	122	18	0	0
Pbo + Chemo/Pbo Responder	217	217	217	216	214	207	206	203	200	200	197	165	130	87	56	9	0	0
Pembro + Chemo/Pembro Non-Responder	290	287	275	262	245	236	224	215	209	201	192	164	126	83	43	10	0	0
Pbo + Chemo/Pbo Non-Responder	173	169	165	152	144	135	122	116	110	104	100	85	65	53	27	8	0	0

Data cutoff date: March 23, 2021.

Schmid et al, ESMO plenary 2021; Mayer et al. JCO 2021

I-SPY2: Less Tumor, Bettor Outcome

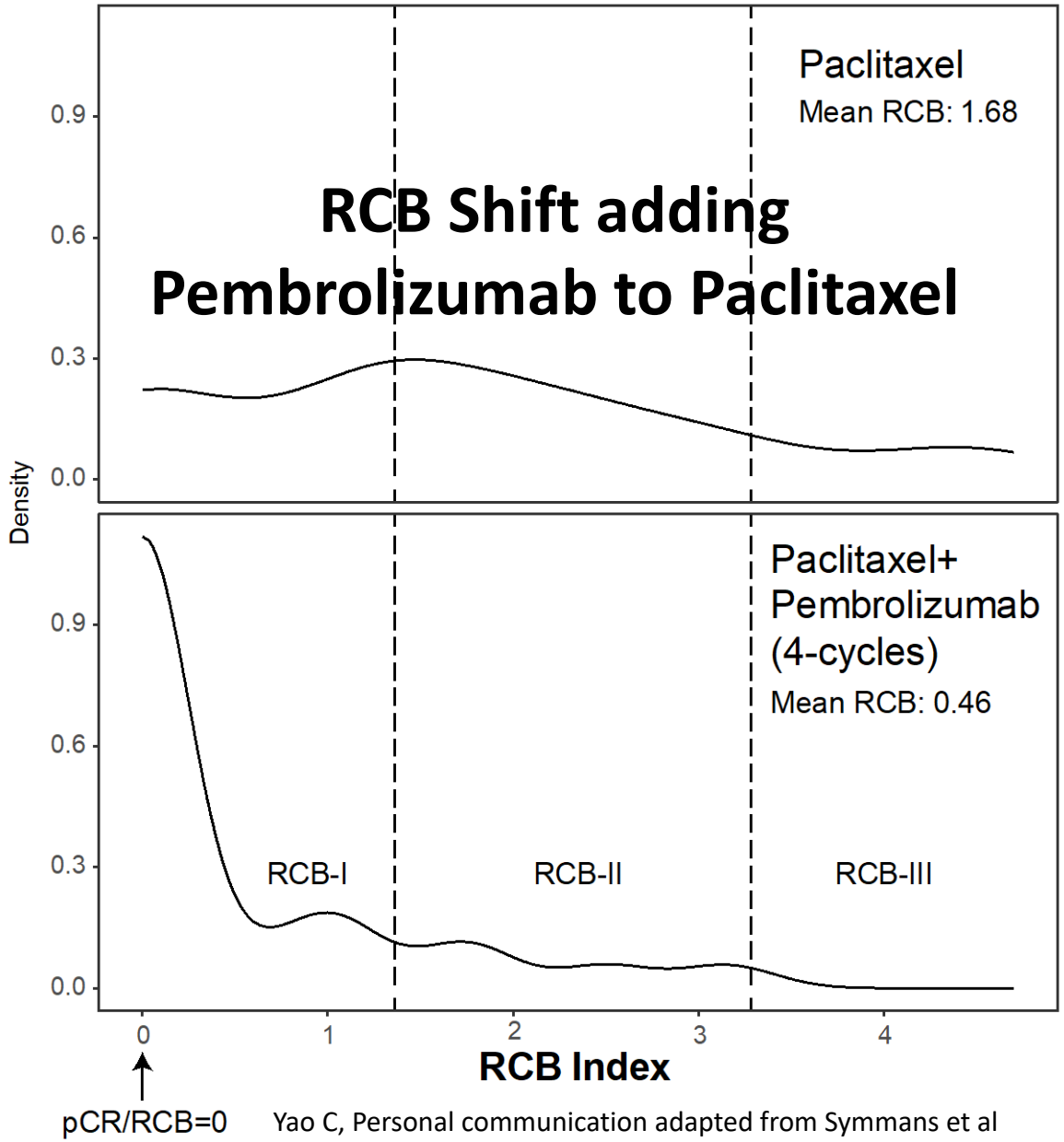
3 year EFS by RCB for TNBC



No. at risk

0	140	138	126	109	86	52
I	50	44	42	35	26	15
II	93	85	68	54	36	24
III	36	28	15	13	8	6

Symmans WF, *et al*. JAMA Oncol. 2021; Nanda et al, JAMA Onc 2020



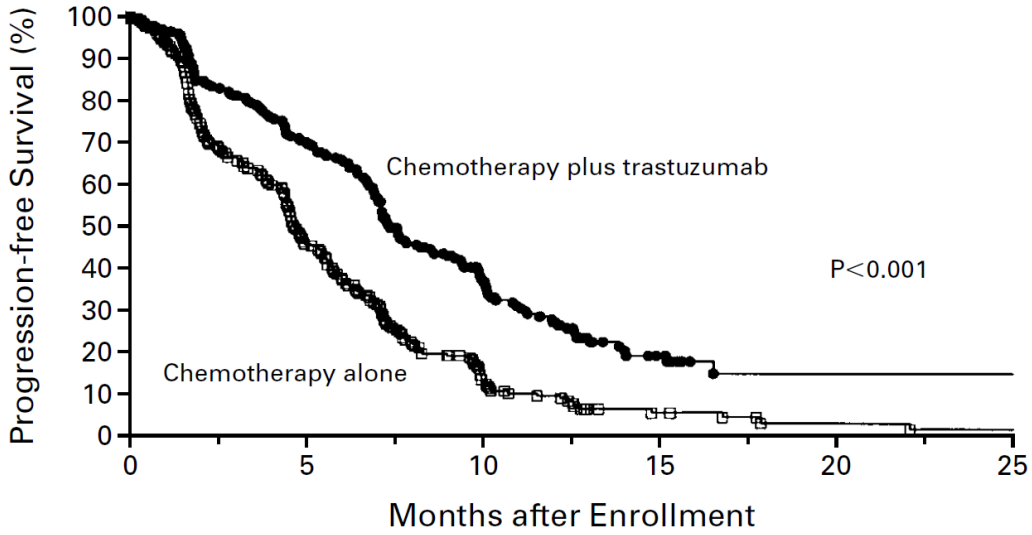
Yao C, Personal communication adapted from Symmans et al

Immune Checkpoint Inhibitors Approved For Therapy in Breast Cancer

- Atezolizumab (anti-PD-L1) with nab-paclitaxel approved in metastatic TNBC when immune effector cells stain positive for PDL1
  - Approval subsequently withdrawn by the sponsor
- Pembrolizumab (anti-PD1) approved for metastatic TNBC staining positive for PDL1 in tumor or immune cells (CPS Score)
  - Tumors with high level of Tumor Mutational Burden
- Pembrolizumab (anti-PD1) approved for neoadjuvant therapy of TNBC regardless of PDL1 staining

Trastuzumab (Herceptin®) Humanized Anti-HER2 Antibody

A

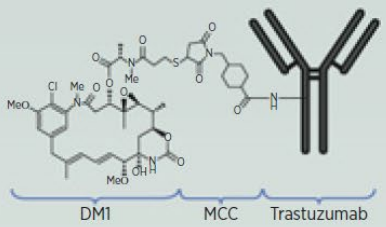
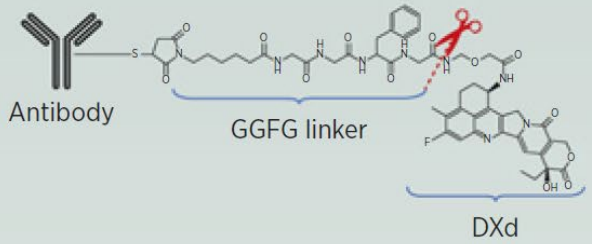
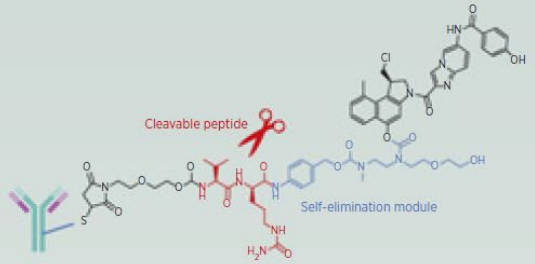


No. at Risk				
Chemotherapy plus trastuzumab	235	152	63	15
Chemotherapy alone	234	103	25	6

- Effective only in HER2 overexpressing or amplified breast cancer
- Synergy with chemotherapy in metastatic disease
- Unexpected cardiac toxicity (CHF) observed in clinical trials

Slamon, et al. N Engl J Med 344:783 2001 PMID: 11248153

Trastuzumab as a drug targeting agent

Characteristics	T-DM1 (36)	DS-8201a (37)	SYD985 (39)
			
Trial phase	Approved	Approved	Phase III
Antibody	Trastuzumab	Trastuzumab	Trastuzumab
Payload	Maytansinoids (mitotic inhibitor)	Deruxtecan (topoisomerase I inhibitor)	Duocarmycin (alkylating agents)
Linker	Noncleavable thioether linker (MCC)	Cleavable tetrapeptide linker	Cleavable dipeptide valine-citrulline linker
Drug-antibody ratio	3.5	8	2.8
Bystander killing effect	No bystander killing effect in vitro	Potent bystander killing (38)	Potent bystander killing (40)

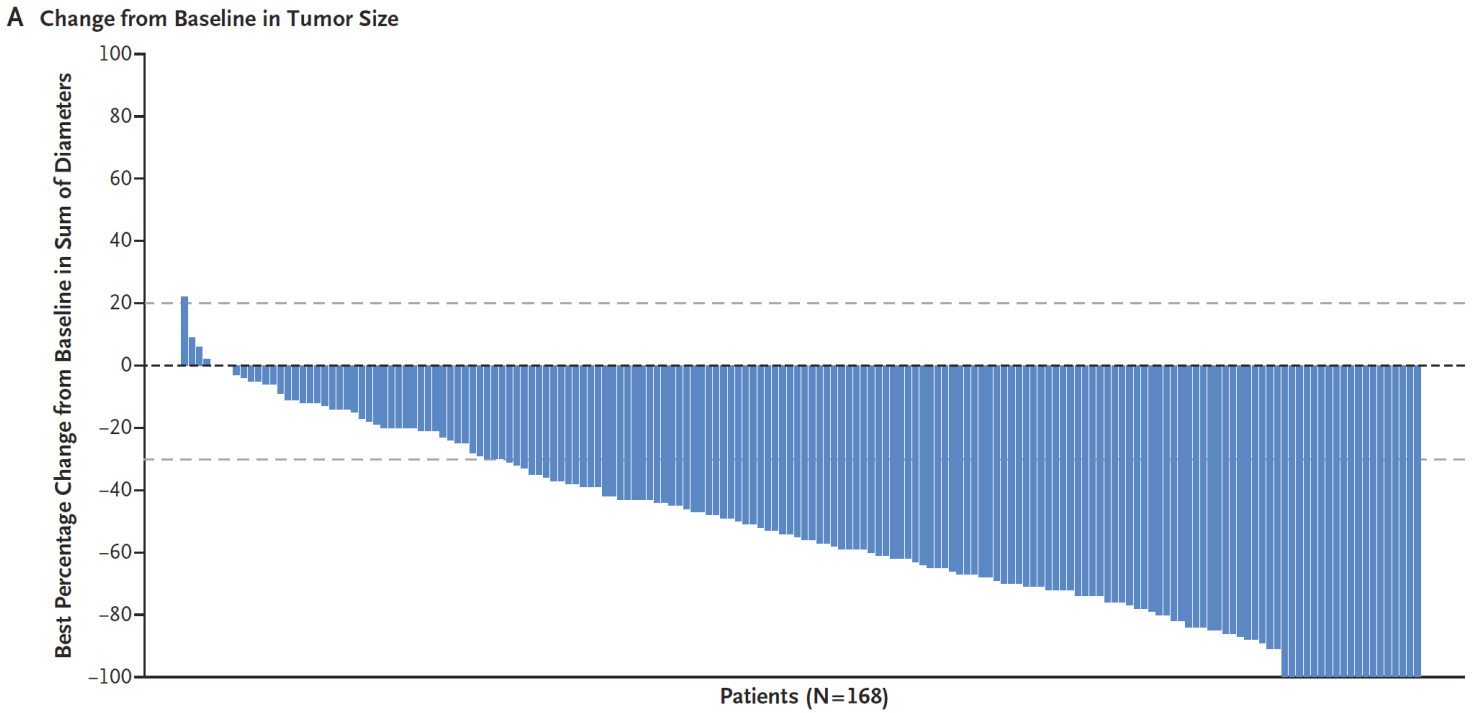
Adapted from Pegram, et al. Clin Cancer Res 26:775 2020 PMID: 31582515

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer

S. Modi, C. Saura, T. Yamashita, Y.H. Park, S.-B. Kim, K. Tamura, F. Andre, H. Iwata, Y. Ito, J. Tsurutani, J. Sohn, N. Denduluri, C. Perrin, K. Aogi, E. Tokunaga, S.-A. Im, K.S. Lee, S.A. Hurvitz, J. Cortes, C. Lee, S. Chen, L. Zhang, J. Shahidi, A. Yver, and I. Krop, for the DESTINY-Breast01 Investigators*

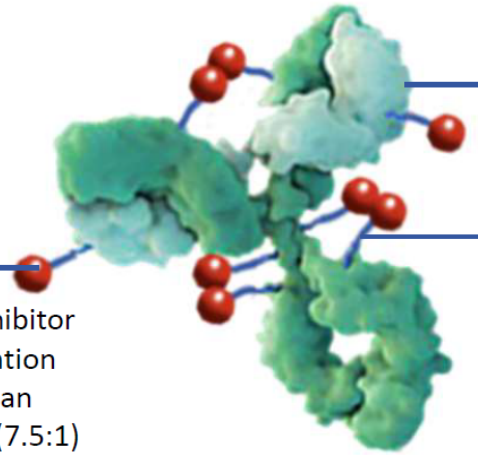


Response rate

Previous TDM1	64% (36/56)
No TDM1	59% (76/128)
HER2 3+	63% (97/154)
HER2 1+/2+	46% (13/28)

Modi, et al. N Engl J Med 382:610 2020 PMID: 31825192

Sacituzumab Govitecan: A Novel Trop-2 Directed ADC



Monoclonal antibody (hRS7)

- Binds to Trop-2, a surface protein overexpressed by many solid tumors, including TNBC

Hydrolyzable linker (CL2A)

- Helps to ensure an active concentration of SN-38 is maintained in the tumor
- Hydrolysis of the linker releases the toxic payload to kill cells in the tumor microenvironment

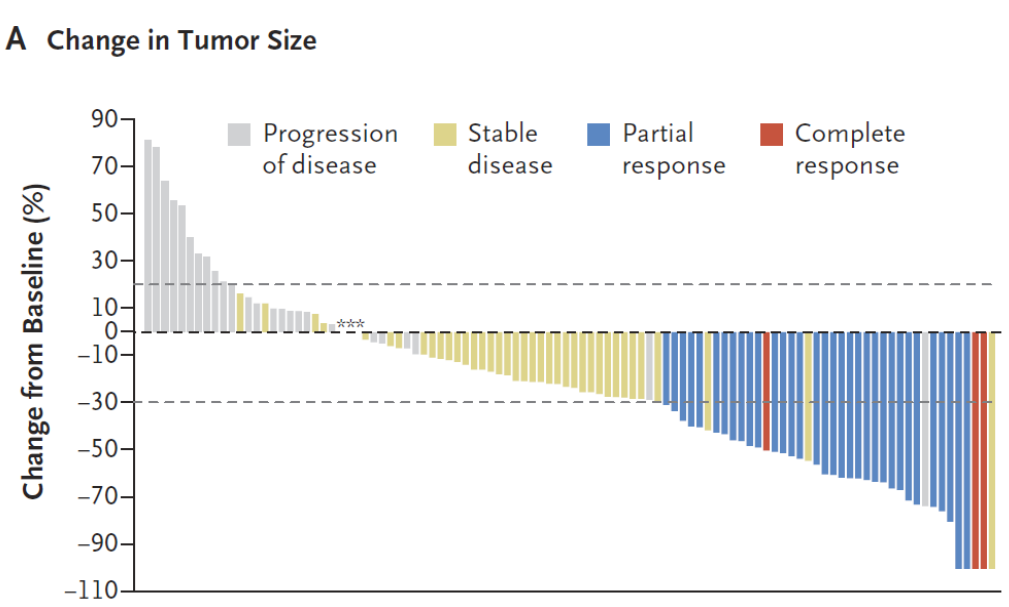
Cytotoxic (SN-38)

- SN-38 is a topoisomerase inhibitor thought to block DNA replication
- Active metabolite of irinotecan
- High drug-to-antibody ratio (7.5:1)

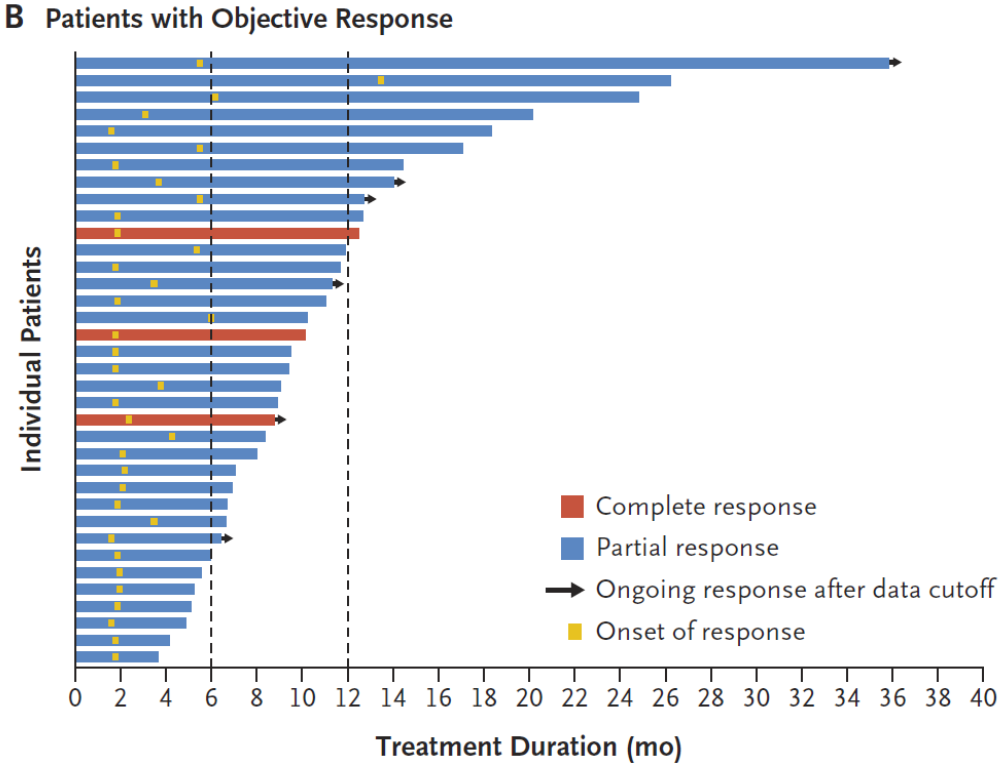
Due to the unique cleavable linker, SN-38 is released in tumors both intracellularly and in the tumor microenvironment, allowing for delivery of therapeutic concentrations of the drug in tumors. Sacituzumab-bound tumor cells are killed by intracellular uptake of SN-38; adjacent tumor cells are killed by extracellular release of SN-38

Bardia, et al. N Engl J Med 380:741 2019 PMID: 30786188

Sacituzumab Govitecan In TNBC



Previous anticancer regimens — median no. (range)	3 (2–10)
Previous use of taxanes or anthracyclines for metastatic or nonmetastatic disease — no. (%)	
Taxanes	106 (98.1)
Anthracyclines	93 (86.1)
Previous use of chemotherapy drugs for metastatic disease — no. (%)	
Cyclophosphamide	20 (18.5)
Platinum agents	74 (68.5)
Gemcitabine	59 (54.6)
Fluoropyrimidine agents	56 (51.9)
Eribulin	49 (45.4)
Vinorelbine	17 (15.7)



Bardia, et al. N Engl J Med 380:741 2019 PMID: 30786188

What Are We Learning In The War?

- Breast cancer is not a single disease
- Improved cancer therapies translate directly from basic science
  - Gene expression profiling to identify benefit from chemotherapy
  - Small molecule drugs targeting estrogen receptor signaling
  - Immune checkpoint inhibitor drugs
  - Antibody drug conjugates
- Breast cancer heterogeneity needs to be addressed in clinical cancer research and care
  - “Individualized” therapy is possible
  - New technologies will further