Penn Medicine

Metastatic Breast Cancer: Will it Ever Be Curable? What Will it Take To Get There?

Angie DeMichele, MD, MSCE

Jill & Alan Miller Endowed Chair in Breast Cancer Excellence

Co-Leader, Breast Cancer Program, Abramson Cancer Center

Professor of Medicine and Epidemiology

University of Pennsylvania

the cure is within
ABRAMSON CANCER CENTER

Disclosures

- Research funding: Pfizer, Novartis, Genentech, Calithera
- Scientific Consulting: Context Therapeutics

Many of the slides I'll be showing today are Dr. Lisa Carey's.

So she is here in spirit…

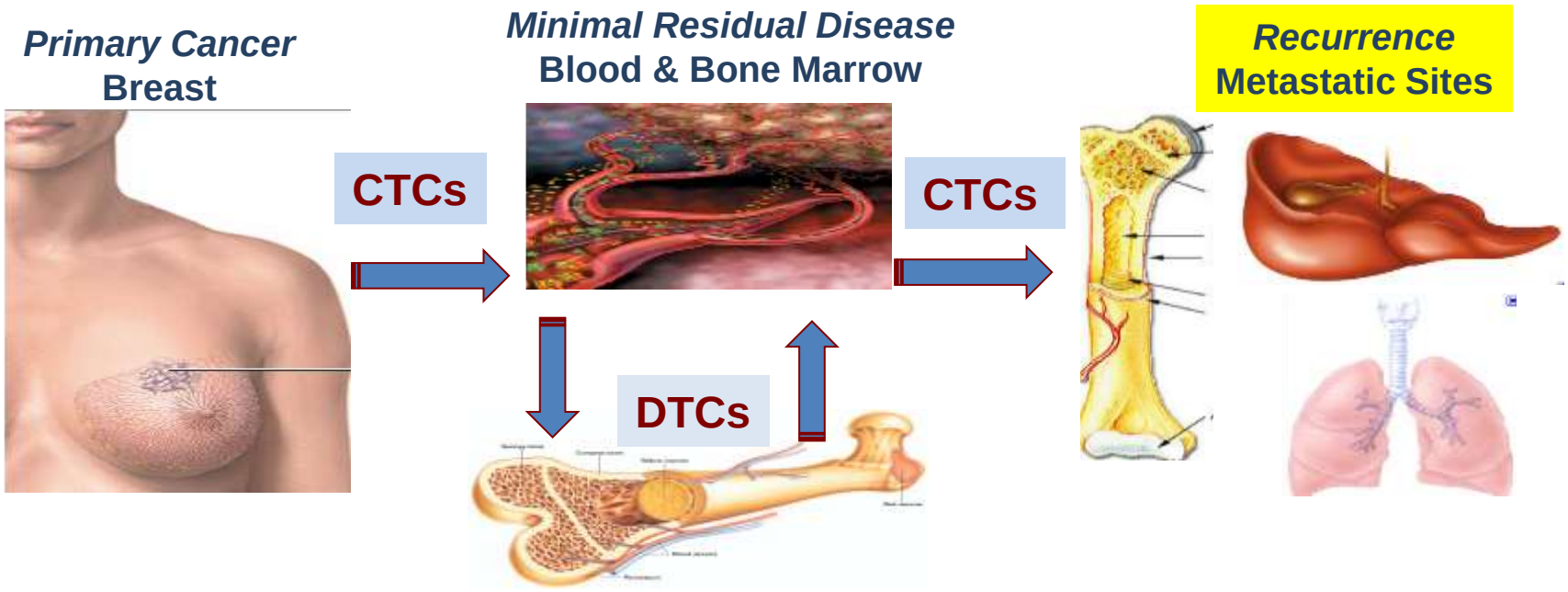
Outline of my talk

- **What is metastatic breast cancer?**
- **New insights into metastatic biology**
  - Tumor genomic testing to target metastatic breast cancer biology
  - How do we apply this to treatment?
- **New therapeutic strategies that are getting us closer to cure**
  - CDK 4/6 inhibitors for hormone-receptor positive cancer
  - Targeting Her2 with multiple approaches
  - Immunotherapy for triple negative disease and beyond

What is “Metastatic Breast Cancer”?

Malignant growth or tumor resulting from the division of abnormal cells ~~in~~ from the breast

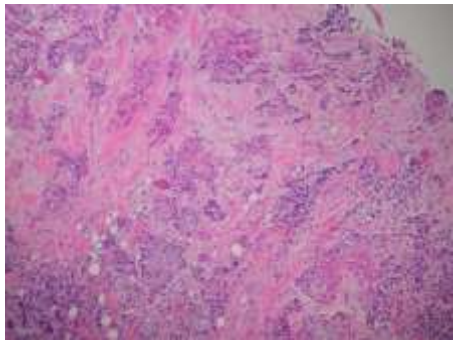
Breast Cancer Metastasis Model

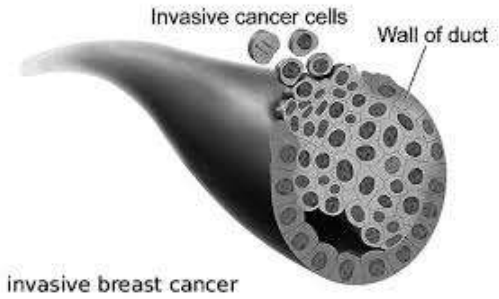


"Seed cells" leave primary tumor → Find sanctuary site, enter dormant state, stop dividing → Awaken, reactivate, start dividing → Travel to distant metastatic sites, begin multiplying

It is Breast Cancer If It…

Arose from cells that comprise the breast
Can divide and grow without normal control
Is able to invade other tissues

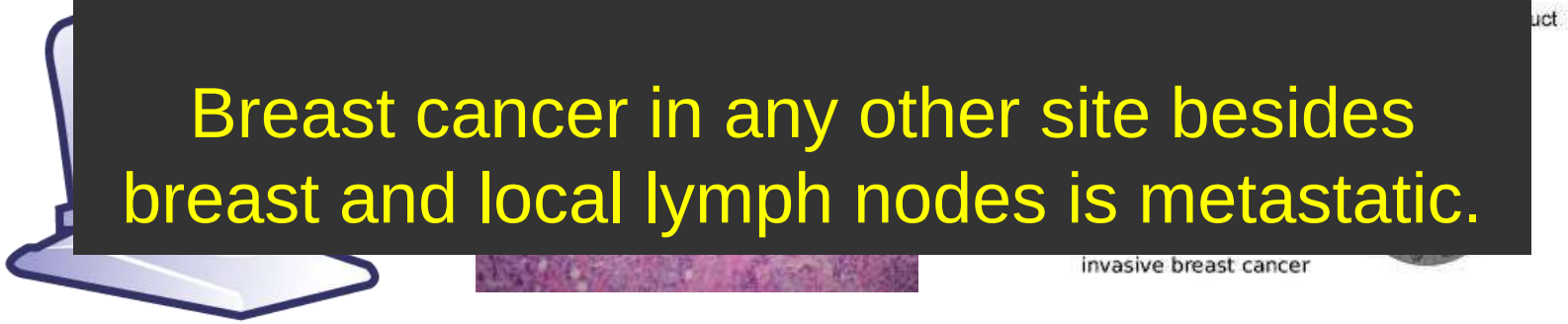




It is Breast Cancer If It…

It does not matter if the tumor is in the breast, lung, or liver.
If the cells came from the breast, it is breast cancer.

Breast cancer in any other site besides breast and local lymph nodes is metastatic.



Goals: From Early to Metastatic

Pre-cancerous changes in breast cells
DCIS

Primary Prevention

"Early" breast cancer (Stages I-III)
90%+ of cancers at diagnosis
Curable
(with surgery, medical therapy, radiation)

Tailoring therapy
Minimizing side effects
Maximizing cure

Secondary Prevention
of Metastatic Disease

Metastatic (Stage IV, spread to other organs)
Incurable
Goals of care: control cancer, quality of life

Maximizing control and longevity
Maximizing quality of life

Someday…cure?

Understanding Metastatic Biology

Who Is Scarier?

Bono:
International
humanitarian

Bernie Madoff:
“Estate planner”

Just like people, cancer’s looks can be deceiving…
We cannot easily identify the “bad” ones

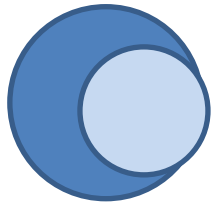
How Do We Better Understand Metastatic Breast Cancer?

Better treatments = understanding tumor genes?

Genes are segments of DNA
A gene is like the *DNA language* for how cells work

DNA sequence

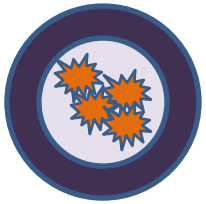
..G G T T A C T G C C..



A mutation is a harmful *spelling change* in the DNA language

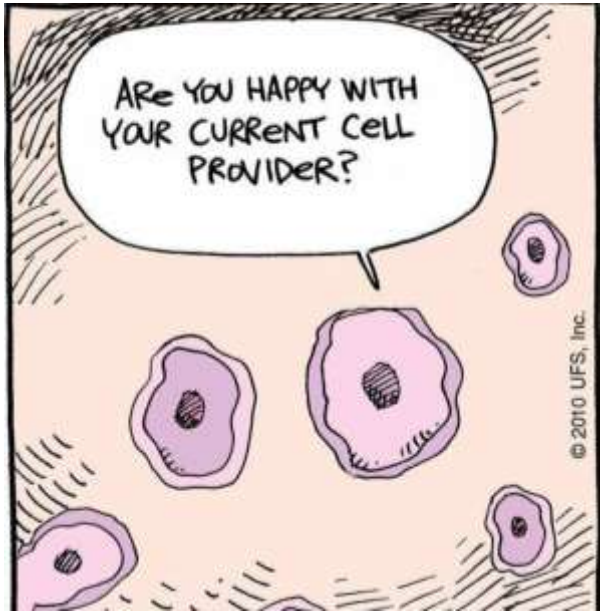
DNA sequence

..G G T C A T T G C C..



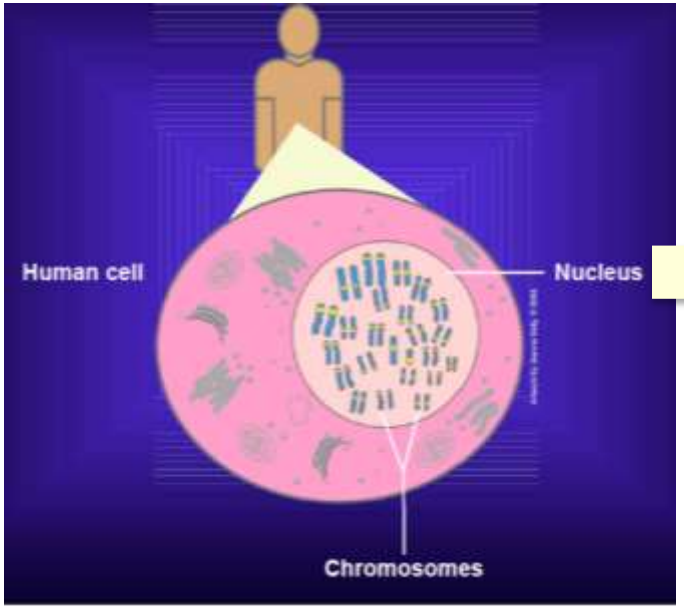
Two Kinds of Genetic Abnormalities in the Cancer

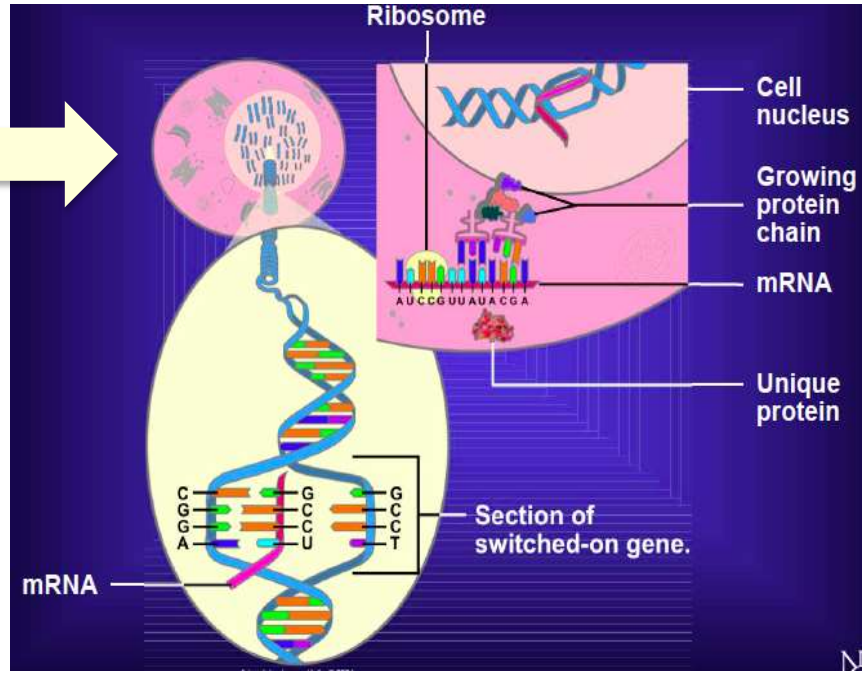
Inherited.
Another thing you can blame on your mother or father.
5-10% of breast cancers are inherited.



"Somatic" errors
(only in the cancer, rest of cells normal).
All cancers have these.

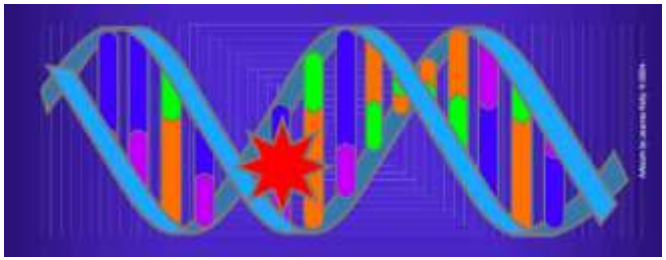
Genes Become RNA, Which Becomes Protein



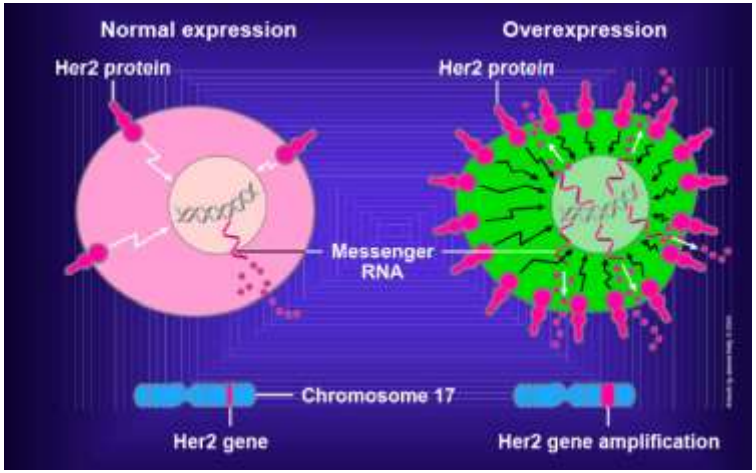


Genetic Errors = Mutation

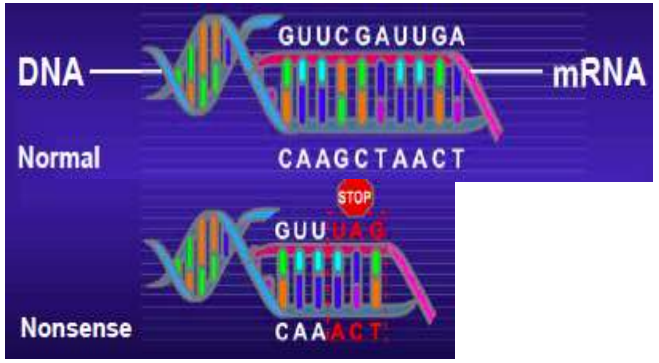
Can cause cell to:



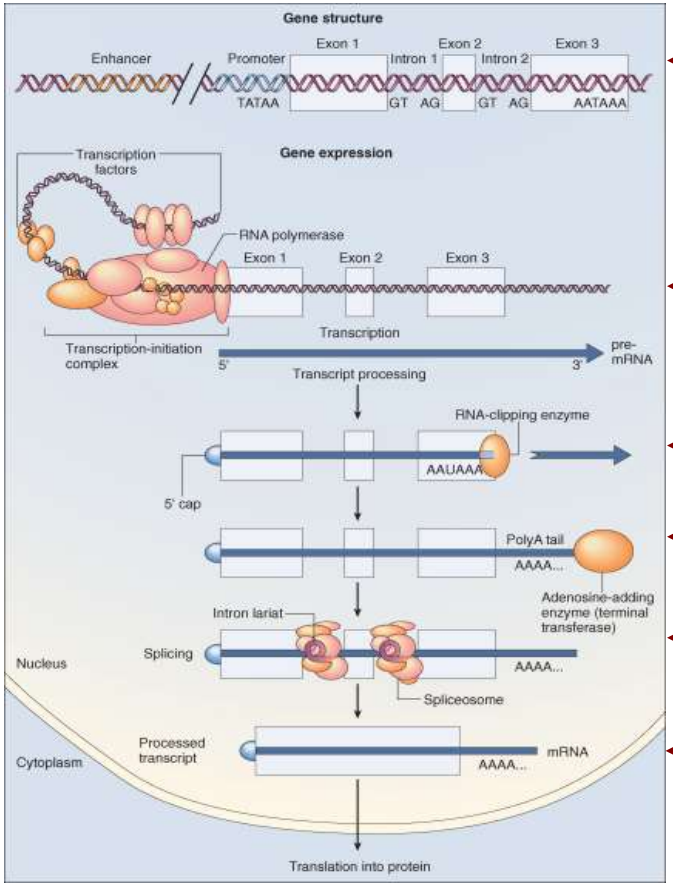
Make too much protein
(e.g. “HER2-positive” disease)



Not make an important protein
(e.g. BRCA1)



Cancer Cell Aberrations Run the Gamut from Gene to Protein



Mutations

"Epigenetic" changes turn genes on & off

"micro" RNAs can alter what is made

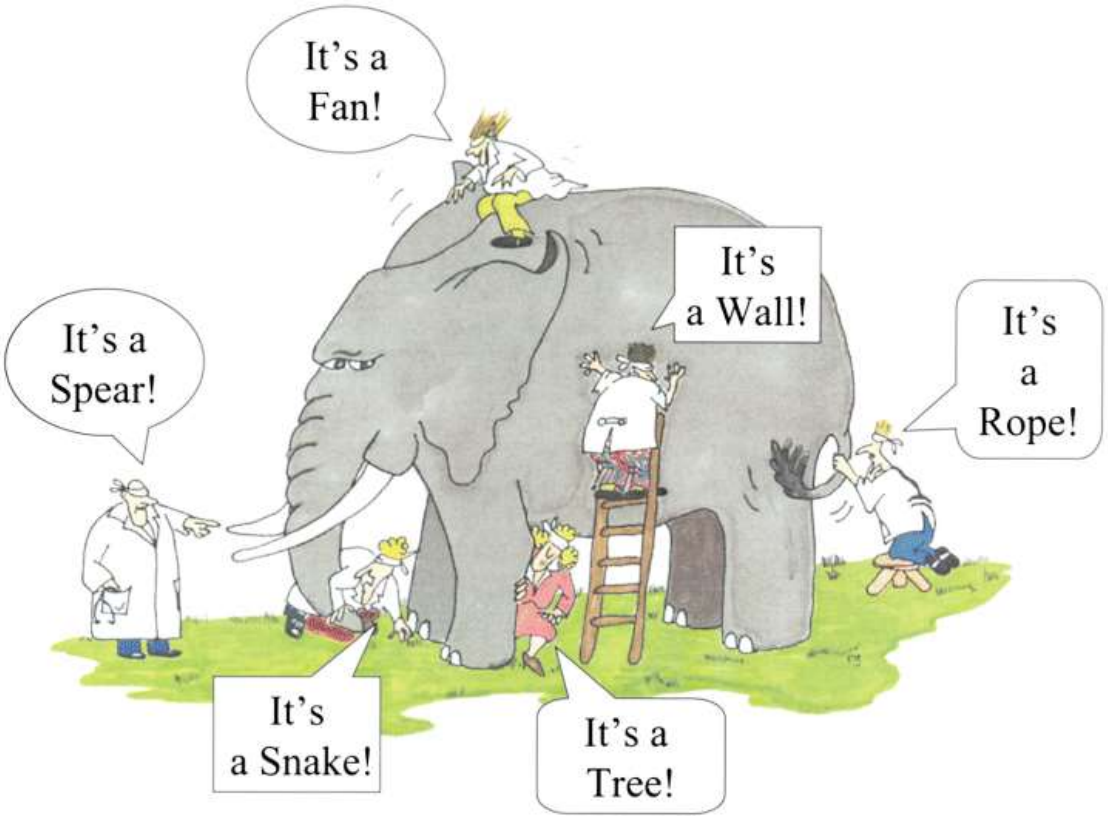
Splicing: making different proteins from the same gene as normal

Proteins can be modified

Protein degradation processes vary

Rosenthal N. NEJM 1994

Collaborative, Integrative Science to the Rescue



"Omics"

Neologism referring to the study of a biologic process using a collective approach

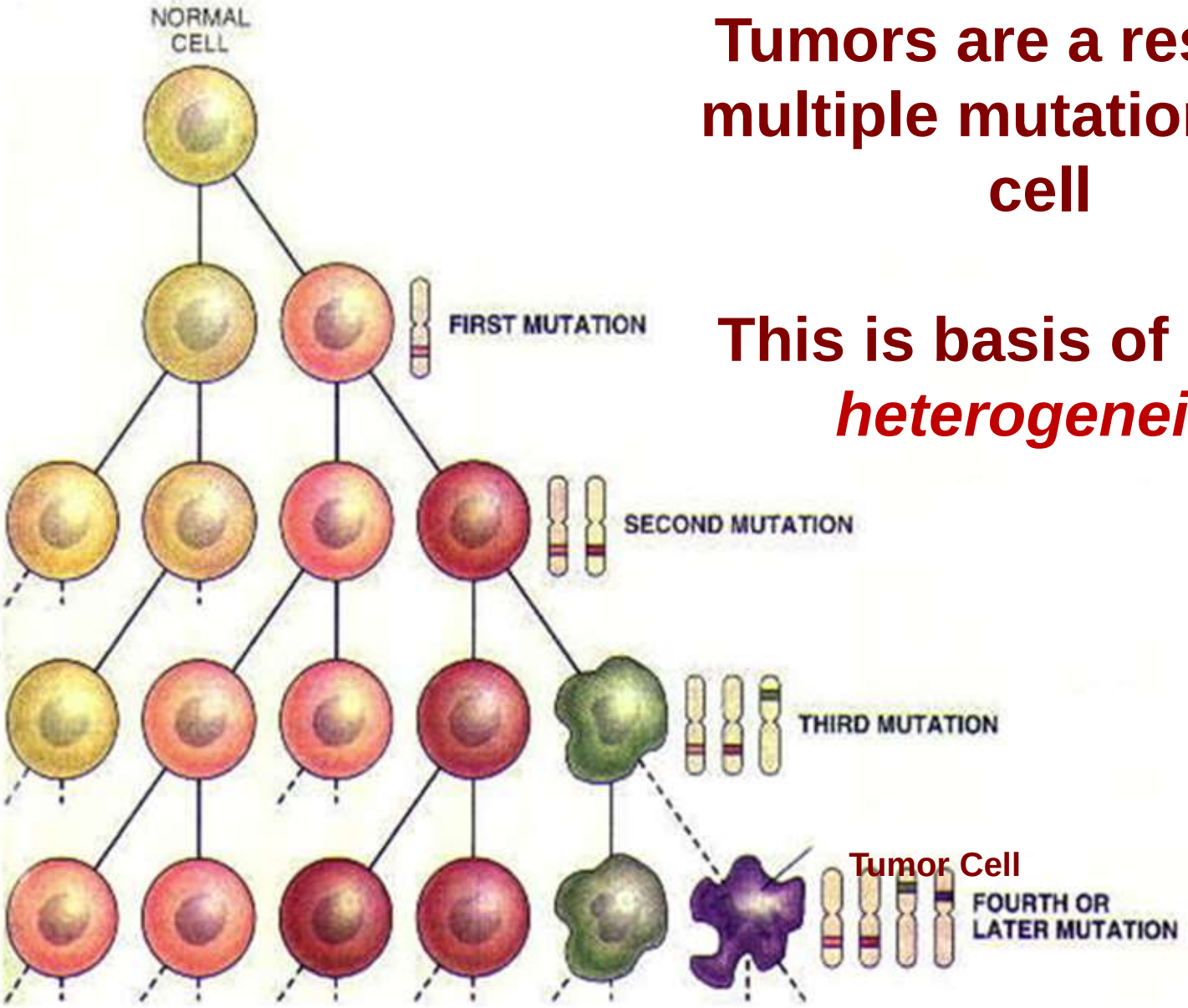
Genome — *Best studied so far*

Proteome

Metabolome

"Poonome"

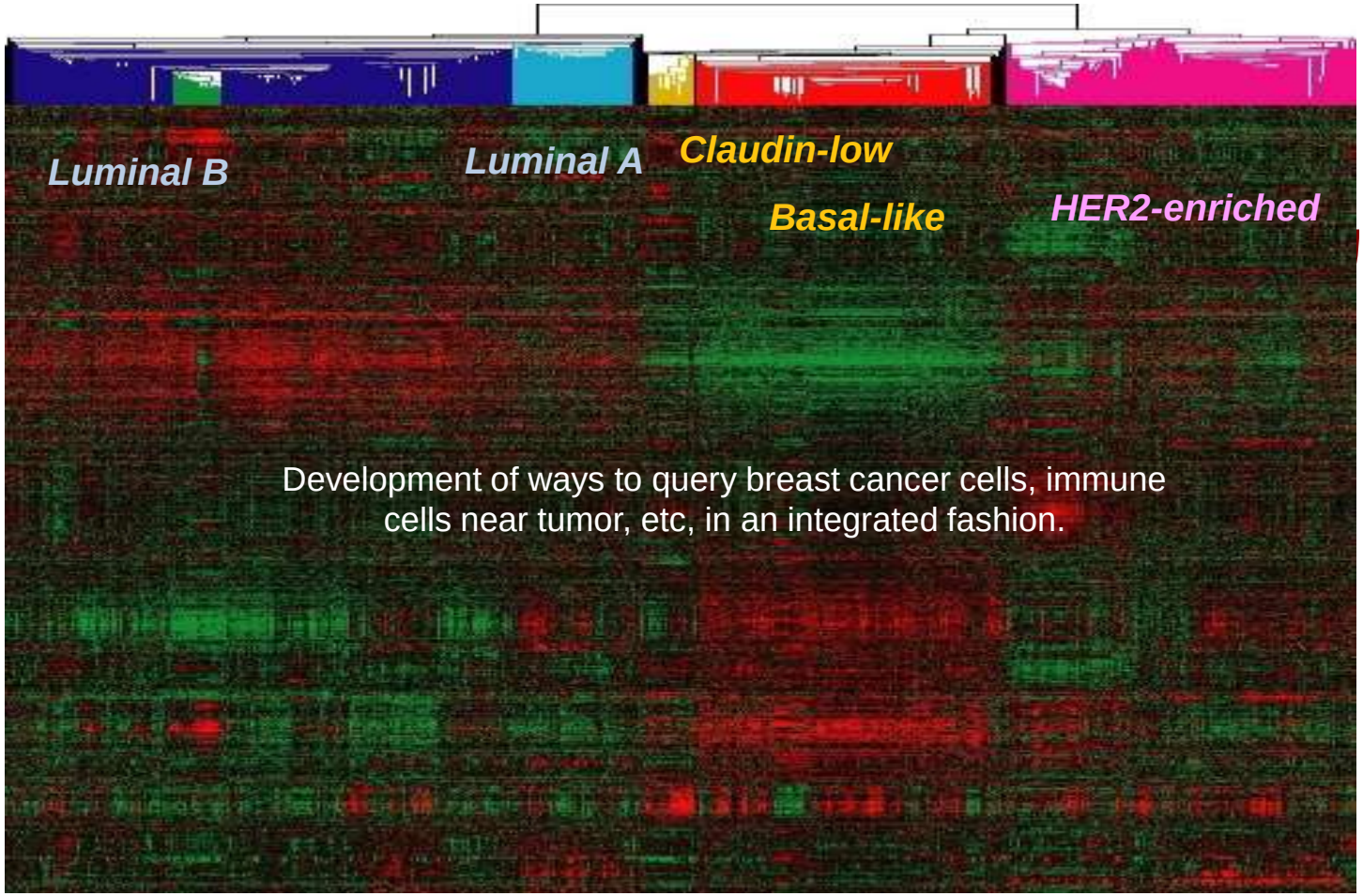
…



Tumors are a result of multiple mutations in a cell

This is basis of *tumor heterogeneity*

Breakthrough Technology



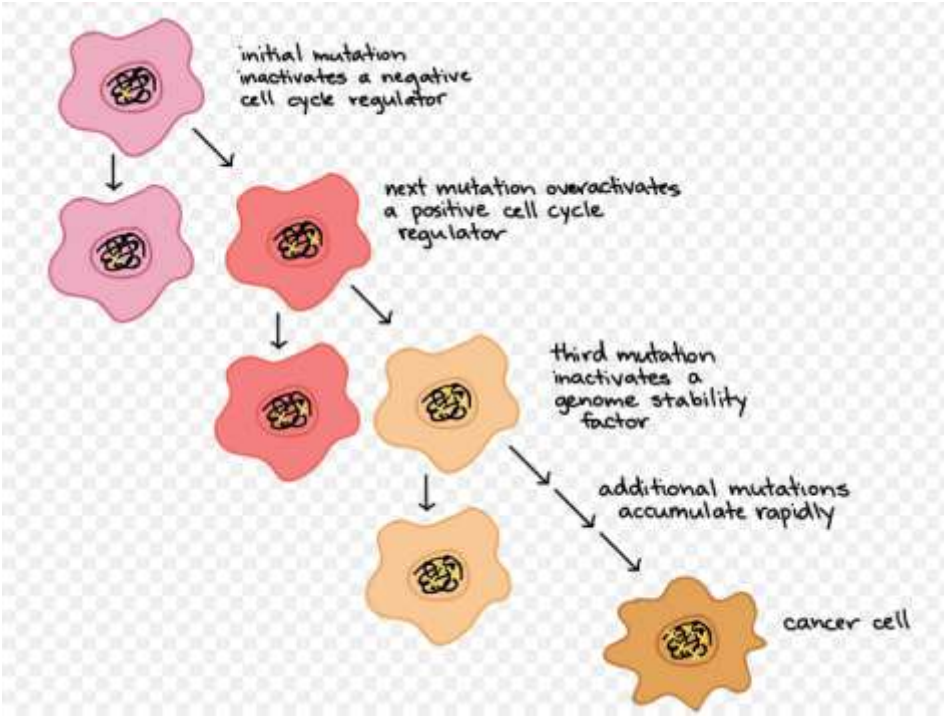
Development of ways to query breast cancer cells, immune cells near tumor, etc, in an integrated fashion.

Chuck Perou, PhD

NAME	BC/FUMI0	BC/FUMI4	BC/FUMI4	BC601B-A	BC601A-B	BC/FUMI1	BC/FUMI2	BC/FUMI2	BC/FUMI1	BC/FUMI1	BC102B-B	BC/FUMI2	BC/FUMI3	BC/FUMI3	BC/FUMI1	BC/FUMI1
adipose differentiation-related prote	0.242	1.21	-0.253	-0.841	-0.423	-0.363	-0.852	-1.383		-2.642	0.501	-0.25	-0.605	-0.636	0.229	-0.626
plasminogen activator, urokinase re	0.908	0.485	-0.397	-0.767	-0.886	-0.251	-0.683	0.057	-0.317	-1.2	0.125		-0.536	-0.248		-0.365
plasminogen activator, urokinase re	0.4635	0.3545	-0.8975	-1.23	-0.8335	0.0175	-1.002	0.1555	-0.4325	-1.008	-0.1785		-0.7445	-0.1485	0.0555	0.2055
coronin, actin binding protein, 1C A	0.551	0.151	-0.422	0.007	-0.638	0.087		-0.689	-0.91	-0.853	0.052	-0.492	-0.201	-0.152	-0.368	-0.741
**coatomer protein complex, subun	-1.061	-0.8655	-0.1235	-0.9895	0.3815	-0.4955	-0.2775	-0.1465	-1.109	-0.8635	0.2615	-0.0905	-0.3225	-0.6035	0.0195	-0.9345
coactosin-like protein R78490	-0.8835	-0.4545	0.2375	-1.177	0.2155	-0.2975	-0.9385	-0.2815	-1.494	-0.5985	0.4095	-0.3465	0.2185	-0.1345	-0.2895	-0.5525
folylpolyglutamate synthase R4486	0.686	1.583	1.313	0.048	-0.272	-0.143	-0.394	0.423	-0.445	-0.854	0.322	-0.03	-0.412	0.214	-1.098	-0.175
lysozyme (renal amyloidosis) N639	-0.18	1.155	1.575	-1.635	0.355	0.295	-0.805	0.135	-2.145	-0.955	0.575	0.735	-0.435	-0.855	-0.8	-1.705
chemokine (C-C motif) receptor 1 AA036881		0.524	1.233	-1.459	-0.095	-0.122	-0.196	0.101		-0.942	-0.2	-0.133	-0.549	-0.763		-0.059
interferon, gamma-inducible protei	-0.181	-0.062	0.37	0.064	0.418	-0.33	-0.098	-0.289	-1.042	-0.332	0.907	1.056	-0.8	-0.193	-0.789	-1.25
cystatin B (stefin B) H22919	-0.188	-0.489	-0.603	0.074	-0.212	-0.295	-0.54	-0.535	-0.453	-0.479	-0.021	0.291	-0.651	-0.536	-0.401	-0.511
cathepsin S AA236164	-0.791		0.334	-0.316	0.723	-0.46	0.39	-0.452		-0.413		1.063	-0.849	-1.088	-0.94	-1.291
small inducible cytokine A2 (monoc	0.2665	0.2955	0.5315	-0.1285	0.4255	-1.099	-0.7265	-0.6035	-1.052	-1.438	0.1355	0.0365	-0.4335	0.0875	-1.218	-0.7785
natural killer cell transcript 4 AA458	0.483	0.348	0.575	-0.685	0.971	-0.335	-0.222	-0.116	-1.644	-0.66	-0.322	0.885	-0.08	-0.02	-0.441	-0.51
superoxide dismutase 2, mitochonc	0.431	0.301	-0.836	0.519		-0.492	-0.834	-0.86		0.781	0.005	-1.163	-1.283	-0.969		-0.586
superoxide dismutase 2, mitochondrial AA487		0.3185	-0.6835	0.4865	0.6925	-0.7895	-0.6005	-0.5815	0.4995	0.0165	0.3755	-0.1225	-1.129	-1.137		-0.6935
transforming growth factor, beta-in	0.0235	0.6525	-0.3785	-0.5505	-0.3675	-0.4755	-0.1105	0.3435	0.0785	-0.4735	0.7925	1.532	-0.3355	-0.0885	0.2495	-0.1985
glycine dehydrogenase (decarboxy	-1.122	-1.412	-1.275	-1.764	-0.611	1.259	-1.25	-0.76	-2.159	-1.72	-1.017	-0.972	-0.715	-0.543	-0.658	-0.818
syndecan 2 (heparan sulfate proteo	-1.828	-1.7	-1.409	-1.964	-0.975	1.516	-1.24	-1.75	-2.219	-2.477	-1.08	0.29	-1.641	-2.045	-0.315	-1.356
glutathione S-transferase pi R3364	-1.726	-1.892	-1.568			1.528	-1.346	-2.157	-3.114	-3.146	-0.943	0.236	-1.349	-1.674	-0.416	-1.557
chitinase 3-like 2 AA668821				-0.771	-1.436	-1.454	-0.813	-1.578	0.312	-0.167	0	-0.469	0.129	-0.566		-0.489
nuclear factor I/B W87528	0.464	-1.314	-0.187								825		-0.441	-0.928	0.316	-1.188
ras homolog gene family, member	-1.382	-0.471	-0.421								713	-0.167	0.09	1.074		-0.393
ras homolog gene family, member	-1.311	-0.763	-0.61								486	-0.778	-0.579	0.812	0.348	-0.222
**zinc finger, DHHC domain containing 5 AA4		-0.965	-0.571								926	-1.153	-0.462	-0.683	0.828	0.347
keratin 5 (epidermolysis bullosa sin	-0.309	-0.485	-0.748	-0.909	-0.403	-0.127	-0.371	-0.778	-1.596	-1.787	-0.782	0.242	-0.559	-0.804	0.79	0.374
keratin 5 (epidermolysis bullosa simplex, Dowl		-0.655	-2.421	0.301	0.689	-0.38	-0.131	-1.647		-1.396	0.248	-1.118	-0.389	-1.423	1.963	-0.068
keratin 17 AA026100		-0.593	-2.294	0.181	-0.45	0.457	-1.132	-0.754		-2.708	-0.641	-0.148	-0.201	0.161	2.264	1.758
tripartite motif-containing 29 AA055	-0.523	-0.763		-0.726	-0.155	-0.401		-1.8	-1.591	-1.789	-1.076	-0.929	-1.132	-1.051		-0.24
pleiomorphic adenoma gene-like 1 AA463204		-0.7035	-0.5595	-0.7765	-0.2835		-0.1885		-1.466	-2.035	-0.1475	-0.7075	-0.4025	-1.054	0.3535	-0.5835
secreted frizzled-related protein 1 AA002080		-1.951	-2.022	-1.982	0.069	-0.117	-1.543	-2.996		-2.657	-0.275	-1.187	-0.262	-0.688	3.135	0.295
Homo sapiens cDNA FLJ11796 fis, clone HEN		-1.425		-0.74	-0.798	0.243	-0.225	-0.061		-0.957	-0.001		-0.491	-0.28	0.595	-0.721
ESTs AA074677		-0.411	-0.412	-0.879	-0.78	-0.401	-0.135	-0.508		-2.237	0.077		-0.72	-1.057		-1.301
pellino homolog 1 (Drosophila) W8	-0.3805	-1.159	-0.6945	-0.3935	-0.1785	-0.3665	-0.3835	-0.2825	0.1245	0.3185	0.2735	-1.329	-0.9455	-1.313		-0.4235
matrix metalloproteinase 7 (matrilys	-0.887			-2.32	0.16	-1.65		-1.54		-1.065	1.453		-1.55	-2.859		-0.04
moesin R22977	0.452	-0.759	-0.433	-0.691	0.148	-0.538	-0.28	-0.478	-0.477	0.019	0.062		-0.001	0.259	-0.24	-0.314
prion protein (p27-30) (Creutzfeld-	-0.8095	-1.302	-0.5695	-1.843	-0.8355	-0.3325	-0.7305	0.2015	-0.3825	-0.2335	-0.4605	-1.181	-0.6875	-0.3315	0.2825	-0.0605
chitinase 3-like 1 (cartilage glycoprotein-39) A		1.474	1.071	0.678	0.987	-1.357		-2.185		-1.619	3.517	-0.465	-1.549	-1.699		-1.262
annexin A8 AA235002		-0.55		-0.832	0.209	0	-0.576	-0.199		-1.046	-0.454	-0.221	0.134	-0.015	0.619	0.519
hypothetical protein FLJ20481 N32	-0.078	-0.939	-1.002	0.058	-0.058	-0.158	-1.65	-0.794		-1.612	0.17	1.318	0.404	-0.312		-0.039
ADP-ribosylation factor-like 7 N353	-0.9415	-0.0585	-0.3685	-0.9365	-0.2155	0.0715	-0.2825	-0.5505		-1.107	-0.5855	0.2285	-0.2475	0.1635		-0.1405
cystatin A (stefin A) W72207		-0.532	-0.941	0.909	1.783	0.164	-0.106	-0.577		-1.496	0.588	3.351	-0.73			-0.855
inhibitor of DNA binding 3, dominar	-0.46	-0.587	-0.421	-0.358	0.326		0.638		-0.642		-0.224	-0.143	-0.445	-0.58	0.377	
complement component 1, r subcor	0.116		0.475	-1.506	0.089	-0.624	0.876	-1.115		-1.773	-0.505	-0.276	-0.204	-1.308	0.584	-0.431
nicotinamide N-methyltransferase T	0.675	-0.083	0.035	-0.244	0.053	-0.021	-0.365	-1.174	-1.235	-1.789	-0.688	0.972	-0.261	-0.532	0.606	0
myosin IE AA029956	-0.6075		-0.5465	-0.8195	-0.3755	-0.3535	-0.5545	-0.6505		-1.089	0.0005	-0.0205	0.1535	-0.1775		-0.0005
major histocompatibility complex, c	-0.494	-0.582	-1.091	-0.32	0.305	-0.098	-0.085	0.262	-1.668	-1.457	-0.039	-0.362	-0.218	-0.838	-0.197	-0.537
fatty acid binding protein 7, brain W72051			-1.595	-2.086	-1.717	-0.387	-2.433	-0.184			-1.441		-0.603	0.446		0.728
kynureninase (L-kynurenine hydrolase) H874	-0.342	-0.591	1.233	0.358	-0.954	-1.687	-1.194	-1.515	-2.291	-0.198	0.075	-0.657	-1.675	-0.58	-1.138	
cytochrome P450, subfamily I (dio	1.065	-0.579	0	-0.767	0.392	-0.386	-0.479	-0.752	-0.401	-0.549	0.165	0.11	-0.605	-0.779	0.499	-0.131
cytochrome P450, subfamily I (dio	2.202	-0.047	-0.231	-0.604	-0.234	-0.713	-0.836	-1.99	-1.558	-1.474	0.425	0.622	-0.872	-1.706		-0.579
S100 calcium binding protein A8 (c	-1.641	0.014	-1.05	4.29	-0.162	-0.899	-1.625	-1.818		-2.268	-1.165	-1.2	-1.797	-1.329		-1.087
signal transducer and activator of transcription	-0.2855	-0.6135	2.59	-0.0555	-0.4895	-0.3215	-1.224	-1.718	-1.387	-0.4765	-0.7565	-1.143	-0.8755			-0.9545
gamma-aminobutyric acid (GABA) A receptor	3.044		-1.498	0.076	0.153	-0.766	-0.789		-1.485	-0.69		-0.823	-0.104			-0.235
EphB6 AA609284		0.6365	-1.062	-0.5295	-0.1345		-0.6565				-0.0415	-0.0885	0.0535			-0.3235
secretory leukocyte protease inhibi	-2.088	-1.806	-1.596	0.434	-1.378	-1.269	-0.849	-1.961	-2.645	-3.187	-1.637		-0.996	-1.568	0.538	-1.344
aldo-keto reductase family 1, member C1 (dih	0.83	0.835	-0.435	1.743	1.173	-0.558	-1.21			-1.547		-0.834	0.712	0.104		-0.296
latrophilin W74533	-1.28	0.216	-0.322	-0.467	-0.563	0.111	0.383	-0.648	-0.95	-1.333	-0.903		0.469	0		0.274
echinoderm microtubule associated	-0.0045	-0.1755	-0.1055	0.1595	-0.2585	-0.5155	-1.05	-0.3895	-0.1395	-0.8335	-0.0445	-0.4845	0.0045	-0.7135	0.1435	-0.2125
epidermal growth factor receptor (erythroblast	-0.676	-1.527	-0.203	-1.07	-1.157	-0.979	-1.085			-2.181	-1.547	-0.782	-0.768			0.432
ERO1-like (S. cerevisiae) AA18680	0.3395	0.4075	-0.6115	-0.3415		-0.4095	-0.8285	-0.4075	-0.4405	-0.4075	-1.335	-0.2325	-0.7075	-0.7125		-0.3035
**hypothetical protein FLJ20624 R9	-0.232	-0.341		-0.153	-0.446	0.838	-1.658	0.466	-0.553	-0.909	-0.199	-0.662	-0.334	0.371	-0.029	0.617
forkhead box D1 AA069132	-1.192	-0.07	-0.666	-0.596	0.02	0.388	-0.54	0.11		-1.016	-1.28	-1.077	-0.051	-0.477	-0.561	0.796
met proto-oncogene (hepatocyte growth factor receptor) AA410591				-1.151	-0.373	0.228		0.322		-0.654	-0.23	0.176	0.74	0.446		0.177
ESTs, Weakly similar to TRHY_HUMAN TRICH	-0.137	-0.378	-0.339	0.263	0.618	0.02	0.518			-1.656	1.242	0.885	0.19	0.389		-0.164
ESTs AA149250				1.847	-0.295	0.293		-0.215		-1.641	-0.868	-0.33	-0.395	0.21		-0.185
Homo sapiens mRNA; cDNA DKFZp564O2364	3.135	0.0215	0.3145	0.7915	-0.2245	1.343	-0.0505			-0.1155	1.125		-0.1125	-0.5255		-0.3445
hypothetical protein FLJ10337 AA1	-0.6325	0.8375	0.2155	-0.7935	-0.1815	-0.3315	-0.4795	-0.6435	-0.6095	-0.4435	0.2225	0.0585	-0.3355	0.2375		0.1205
integral membrane protein 3 AA034	-0.998	-0.313	0.52	-1.106	-0.005	-0.618	-0.901	-0.847	-2.533	-2.828	-1.247	-0.647	-1.005	-1.651	-0.119	-0.465

Thank god for computers

Mutability of Cancer



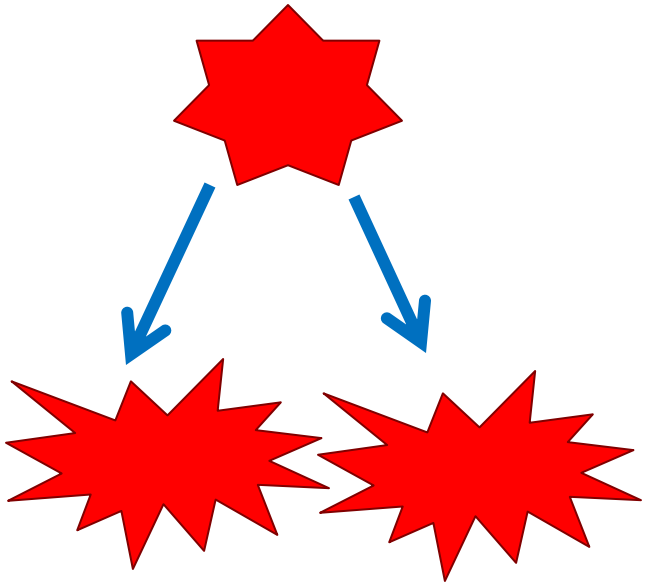
Cancer DNA is inherently unstable.

Changes over time and under the pressure of drugs.

Why does this matter?

40,000 Die of Metastatic Breast Cancer Yearly

2015- original breast cancer

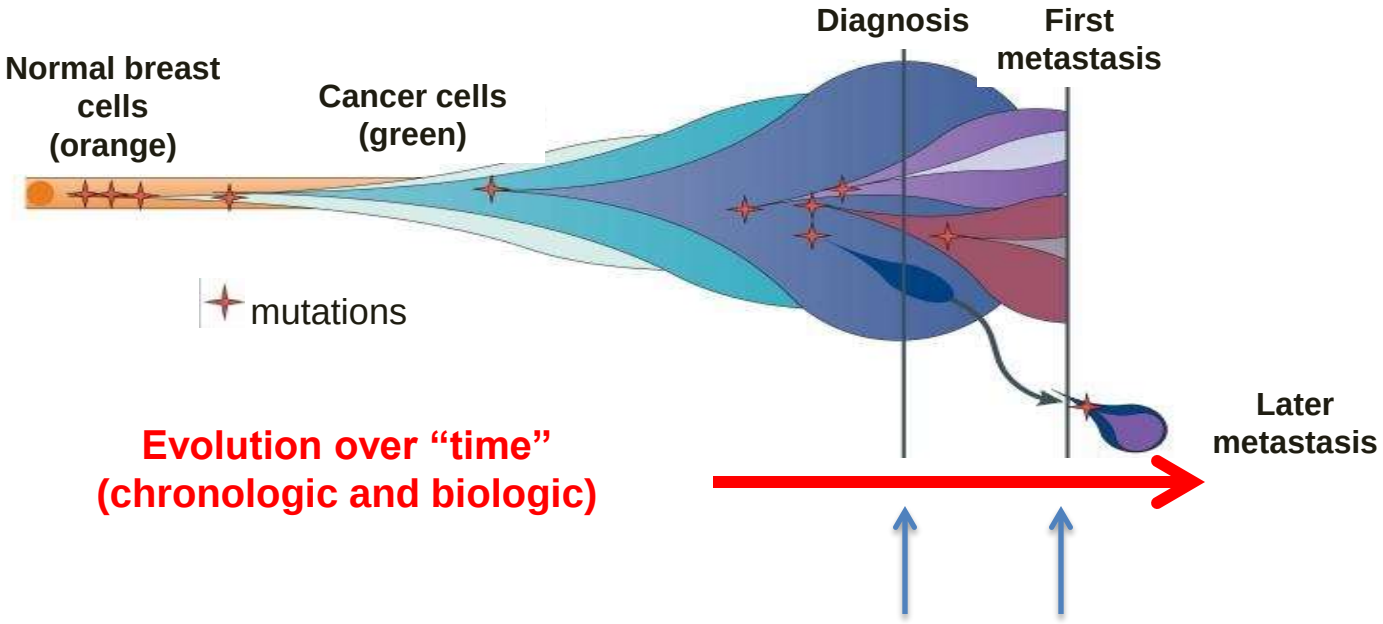


2019 - metastasis in liver, brain

- **We have the 2015 tumor for testing and "precision medicine"**

However…
The 2015 tumor is not the problem, the 2019 tumors are.

Cancer Evolves



These are not the same

Metastatic profiles differ by subtype

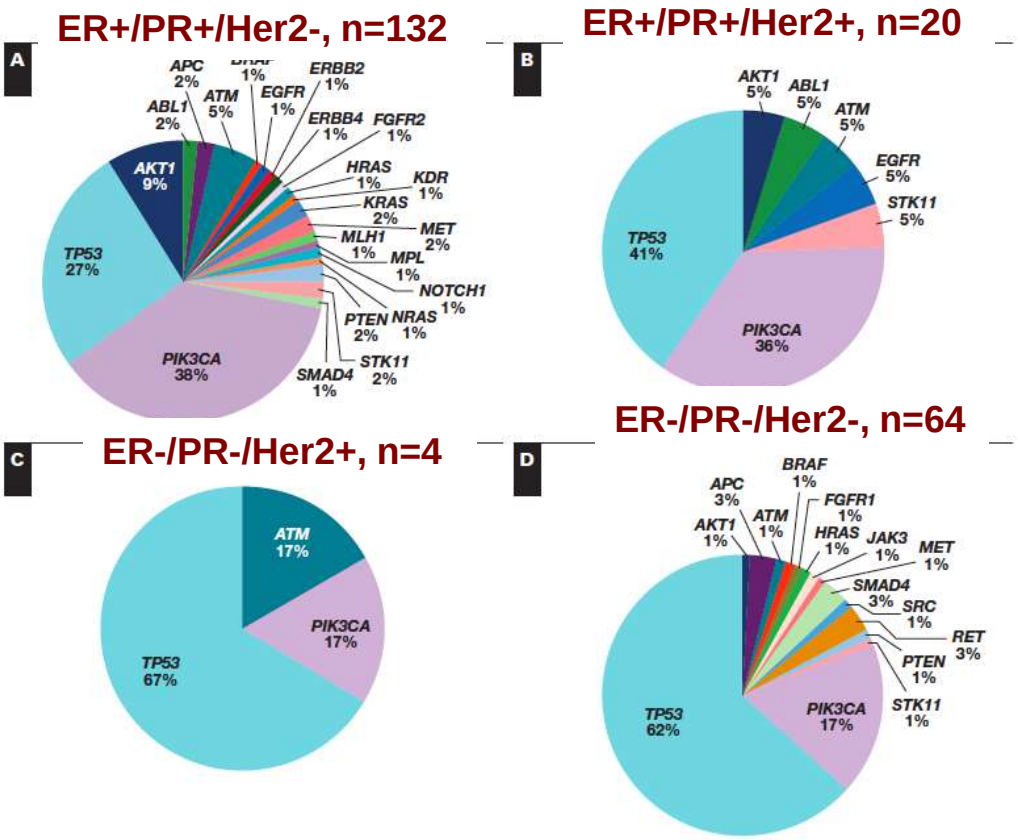


Figure 1 Distribution of mutations with relative frequencies seen in the four clinically relevant therapeutic groups. **A**, ER/PR+HER2–: n = 132, No. of mutations = 176. **B**, ER/PR+HER2+: n = 20, No. of mutations = 22. **C**, ER/PR–HER2+: n = 4, No. of mutations = 6. **D**, ER/PR/HER2–: n = 64, No. of mutations = 77.

- 415 metastatic samples from 354 patients
- Used CLIA Next Gen panel testing
- 62% of patients had a mutation
- Mutational spectrum differs by subtype

Roy-Chowdhury, Meric-Bernstam, Am J Clin Path, 2015

Presented by:

PENN METAMORPH Study

Understanding biology of the metastatic disease

Biopsy of metastatic disease or Blood collection

Patient counseled and educated about testing

Patient counseled about results, given treatment recommendation

Progression: Rebiopsy or Blood testing

CLINICAL LAB:
Tumor profiling (CPD): 64 gene panel
Blood cell-free DNA (Guardant)

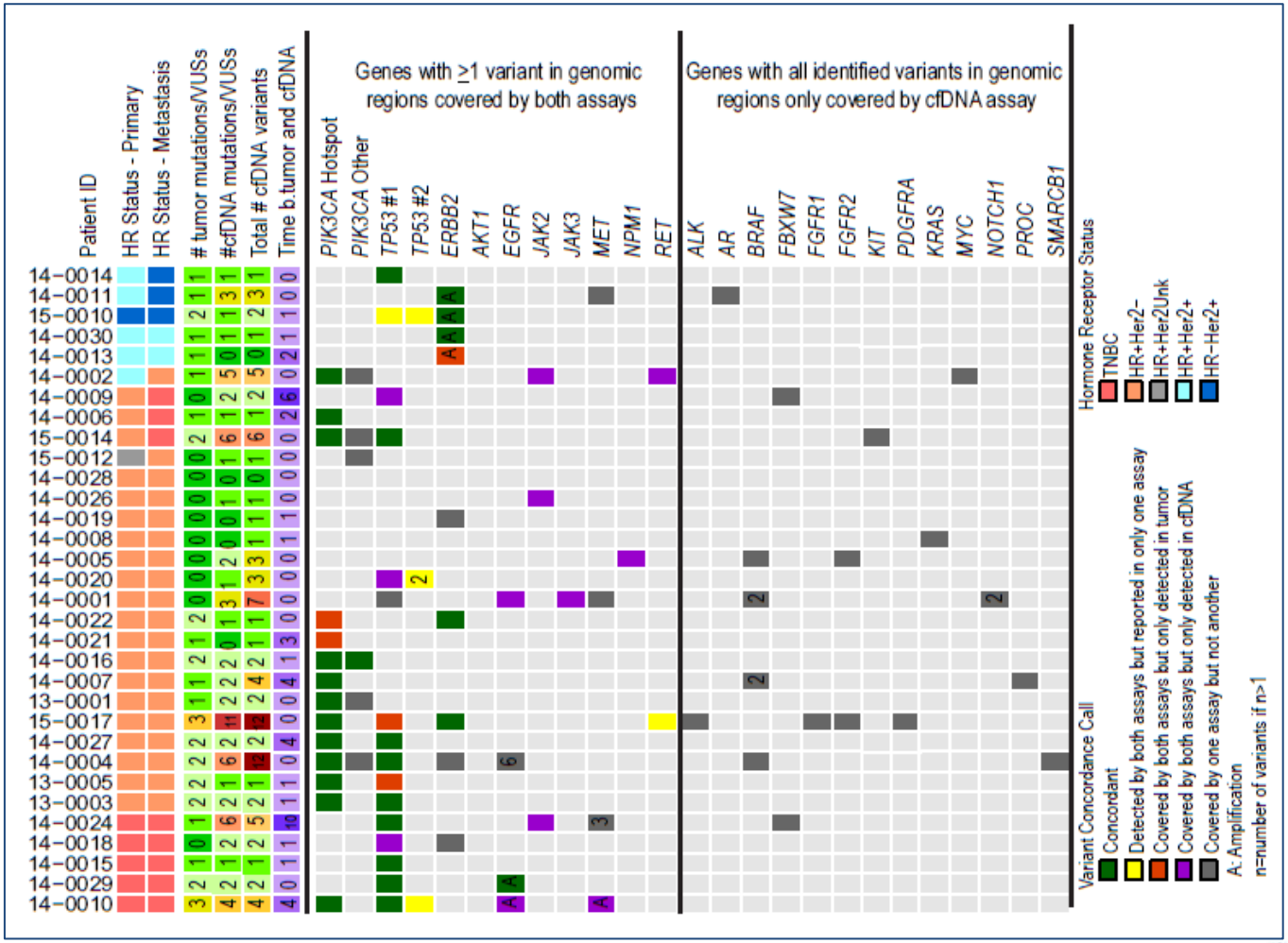
TUMOR BOARD
Physicians/scientists review results and treatment recommendations

RESEARCH ENGINE:
Samples to research lab to study biology of metastasis
Information used to develop new clinical trials

Mutation can be shed into the blood

"Liquid biopsy"

- Patients with concurrent tumor biopsy and blood sample
- 18%: change in subtype (receptors)
- Forest Green: same in tumor and blood
- Red: Only in tumor
- Purple & Gray: Found only in the blood



Penn Medicine

Maxwell, DeMichele, BCRT, 2017

the cure is within
ABRAMSON CANCER CENTER

How Could this Affect Curability?

If you knew a sub-cancer was important.

And you knew what drug it was sensitive to.

You would look for and treat that needle in the haystack.

Do mutations predict response?

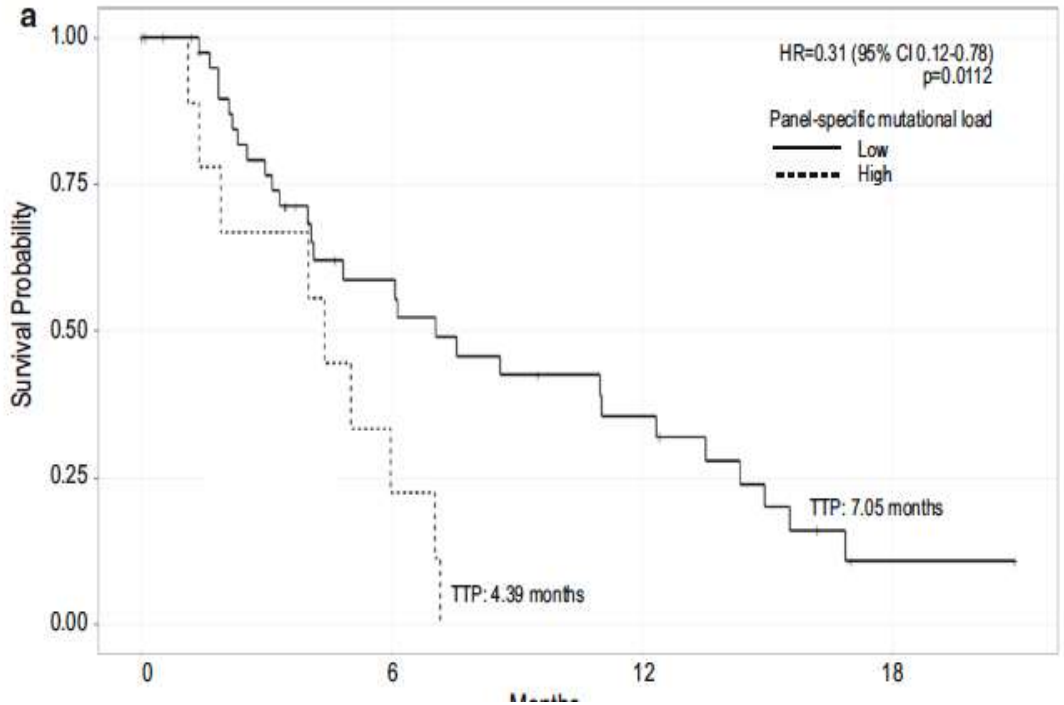
Gene	Therapy	Trial(s)	Association
BRCA 1, 2	**PARP inhibitors**	OLYMPIAD, ICEBERG	**Positive** predictor **GERMLINE**
	Platinums	TNT	**Positive** predictor
ERBB2 (Her2)	**Trastuzumab**		N/A
	Neratinib	Case report	Studies ongoing
PIK3CA	**Everolimus**	BOLERO-1, 2, 3	**Mixed**
	Palbociclib	PALOMA-3	No association
ESR-1	**AI**	SoFEA	**Negative** predictor
	Fulvestrant	FERGI, SoFEA	**Mixed**
	Palbociclib	PALOMA-3	No association

“Mutational Load”

- Number of mutations on panel testing of tumor or plasma tumor DNA

- **7.05 months low**
- **4.4 months high**

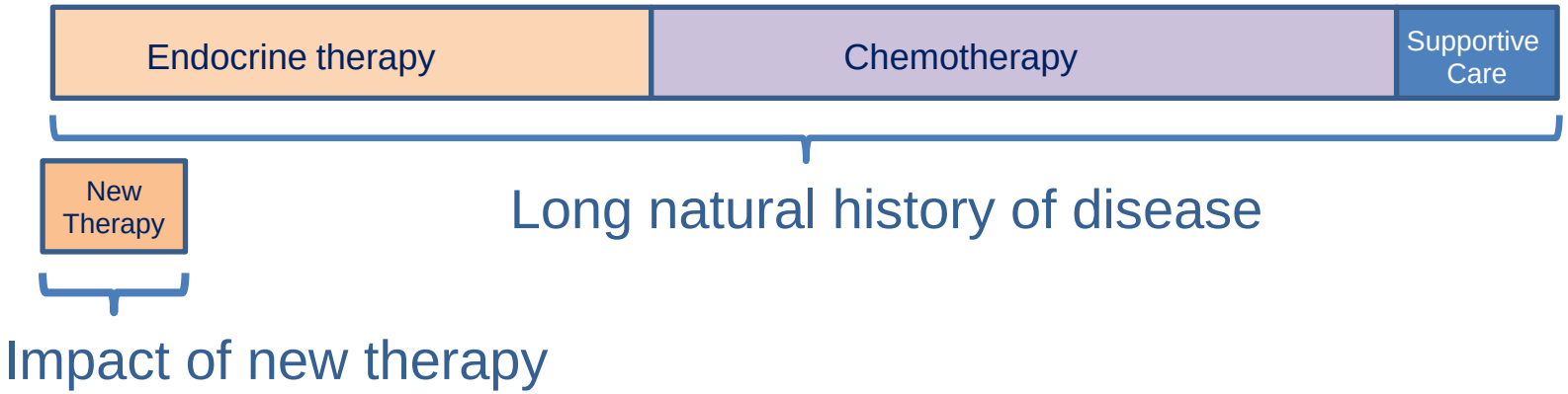
HR 0.31, p=0.0112



May predict response to immunotherapy

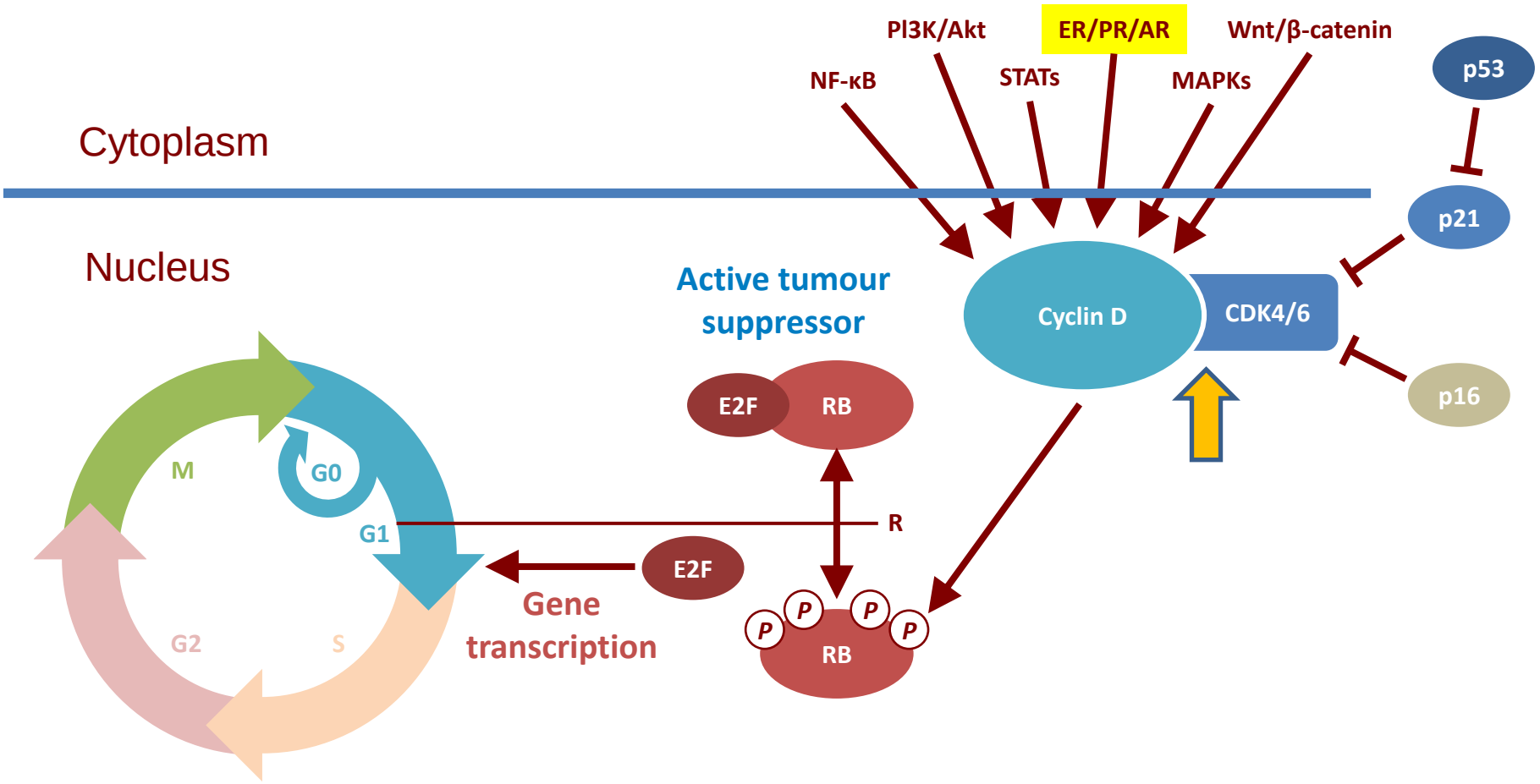
New Treatment Strategies: Are they getting us closer to "cure"?

Showing improvements in survival in clinical trials is tricky



- Treatment at early point in trajectory
- Response time small proportion of overall time
- Impact of subsequent therapy and crossover

G1/S Checkpoint in Breast Cancer



CDK 4/6 inhibitors: FDA-approved indications

	Dose	Schedule	Indications:
Palbociclib (Ibrance, Pfizer)	125 mg daily	3 weeks on/1 week off	• **First line** with AI • **Progressing after ET**, with fulvestrant
Ribociclib (Kisqali, Novartis)	600 mg daily	3 weeks on/1 week off	• **First line** with AI • **Progressing after ET**, with fulvestrant • **Premenopausal** breast cancer
Abemaciclib (Verzenio, Lilly)	150 or 200 mg twice daily	**Continuous**	• **First line** with AI • **Progressing after ET,** with fulvestrant • **Monotherapy after progression** on ET and CT

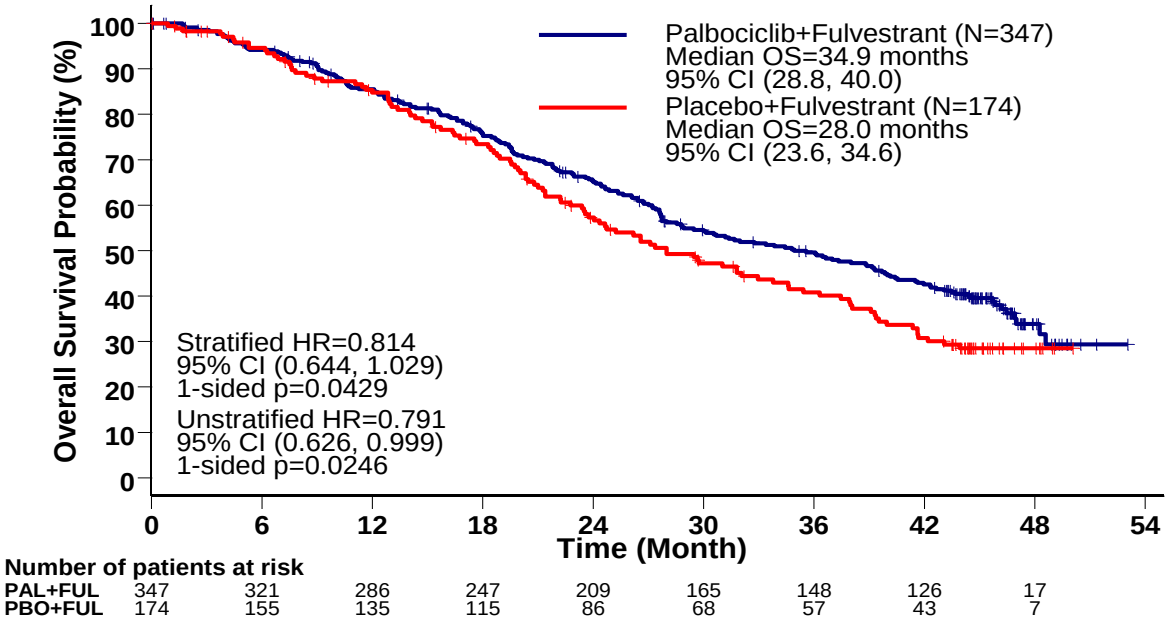
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer

N.C. Turner, D.J. Slamon, J. Ro, I. Bondarenko, S.-A. Im, N. Masuda, M. Colleoni, A. DeMichele, S. Loi, S. Verma, H. Iwata, N. Harbeck, S. Loibl, F. André, K.P. Theall, X. Huang, C. Giorgetti, C. Huang Bartlett, and M. Cristofanilli

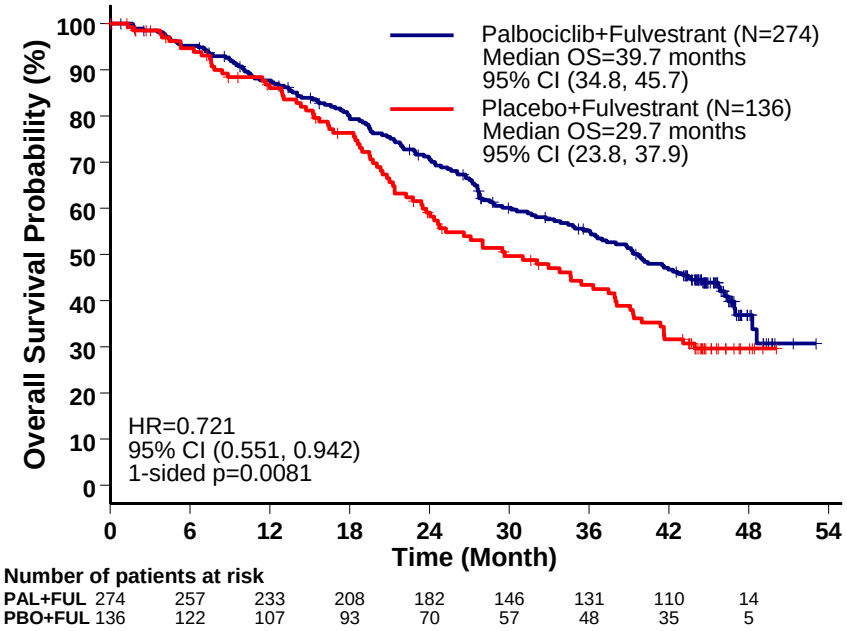
Living longer overall



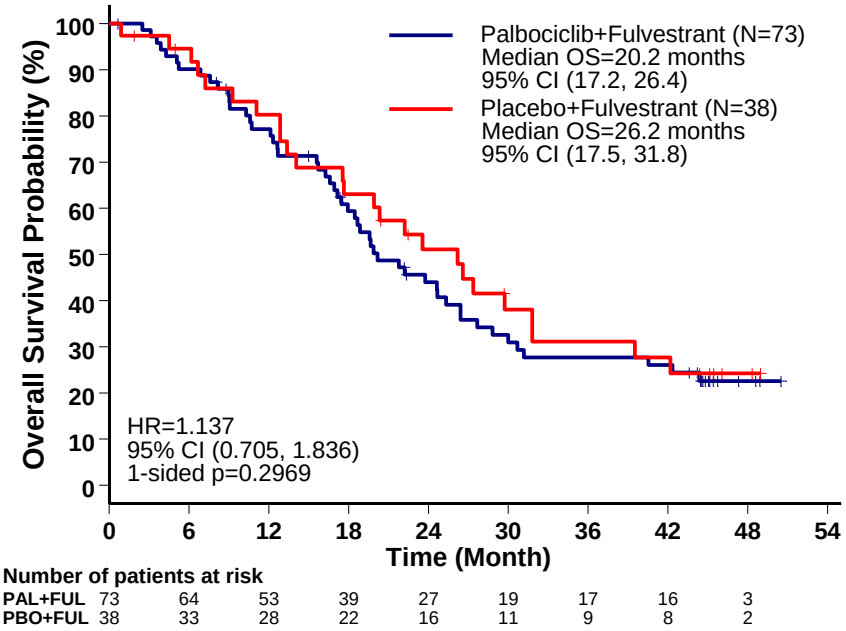
- **Absolute improvement in median OS in the palbociclib arm vs the placebo arm was 6.9 months.**

Prolonging sensitivity to hormonal therapy

- **Patients With Sensitivity to Prior ET**

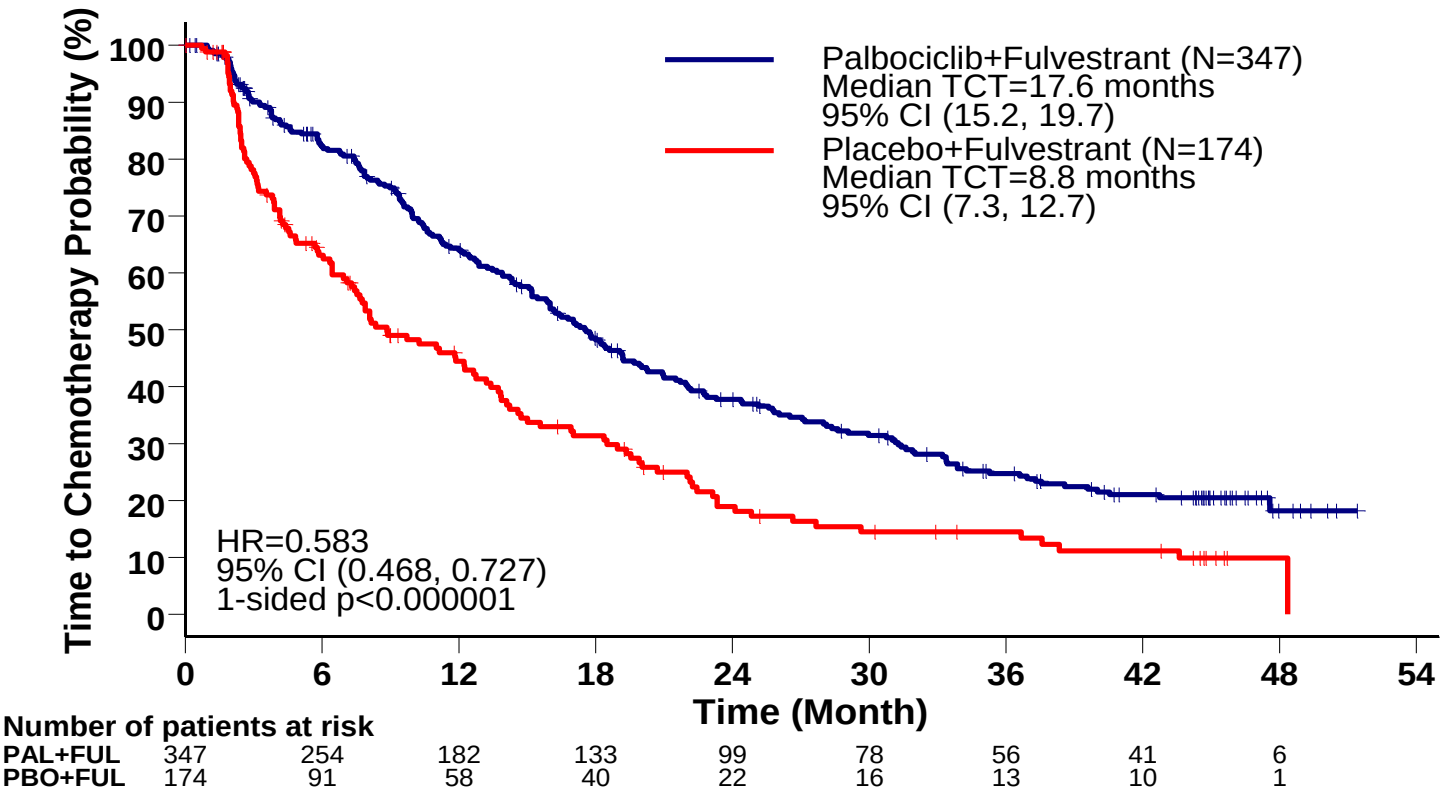


Patients Without Sensitivity to Prior ET



- **In patients with sensitivity to prior ET, absolute improvement in median OS in the palbociclib arm vs the placebo arm was 10.0 months.**

Delaying time to chemotherapy



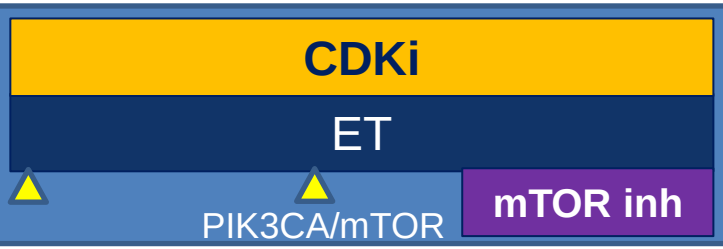
TCT=time to chemotherapy.

What should we do when the cancer gets resistant?

Switch endocrine therapy, maintain CDKi

Switch to something else, maintain endocrine therapy

Maintain ET and CDKi, Target a collateral pathway



HER2-Positive Metastatic Breast Cancer

- **Multiple anti-HER2 drugs approved**
- **Longevity <u>after</u> metastatic disease increasing!**

Not a cure, but getting better

Lessons from a Trial About Drug Response

Newly diagnosed women with HER2+ disease

Randomized clinical trial

50% of the women in each arm

Chemo +
1 antiHER2 drug

Chemo +
2 antiHER2 drugs

How much better are 2 antiHER2 drugs than 1?

Response to Therapy: The Whole Story

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Molecular Heterogeneity and Response to Neoadjuvant Human Epidermal Growth Factor Receptor 2 Targeting in CALGB 40601, a Randomized Phase III Trial of Paclitaxel Plus Trastuzumab With or Without Lapatinib

Clinical trial, <u>mandatory biopsies for research</u>

Factor	Response
Drug therapy: Two vs one drug	38% ↑
Better vs worse drug	60% ↑
HER2-Enriched molecular subtype	300% ↑
Immune cells in tumor	60% ↑

Drugs mattered… but not as much as cancer biology and patient factors

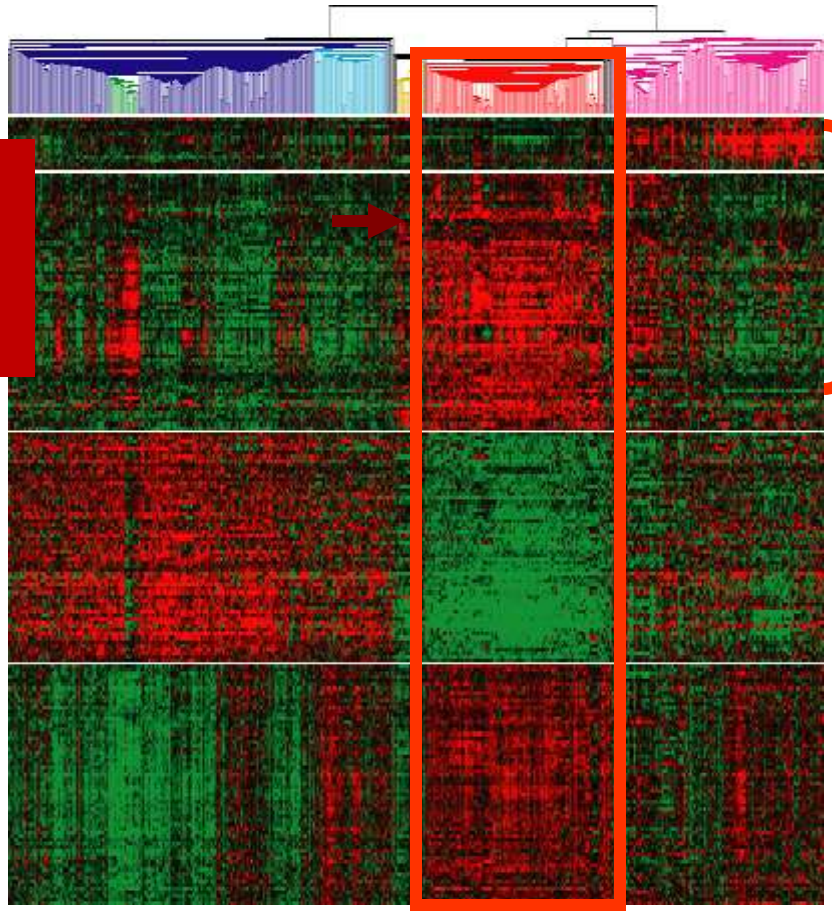
Triple Negative Metastatic Breast Cancer

- **Defined by the absence of targeted therapy**
  - **Chemotherapy is mainstay of treatment**
- **Improved survival recently but not by much**

The subtype with the most need

Triple Negative Breast Cancer

The infamous "triple negative" breast cancer subtype



EGFR/HER1
CRYAB
TCF4
Frizzled 7
LY6D
c-KIT
Keratin 5
Keratin 17
P-Cadherin

We have drugs that inhibit this gene

Clinical trials in metastatic triple negative didn't work

Why didn't it work?

Very few had good tumor control with anti-EGFR therapy.

- **Sometimes the target gene wasn't there**
- **Sometimes the gene was there but didn't seem to be working**
- **Sometimes it looked like it should have worked, but didn't…**
  - **The tumor was smarter than we were, and had a back door in.**

We need to understand each cancer better to truly develop personalized cancer therapy

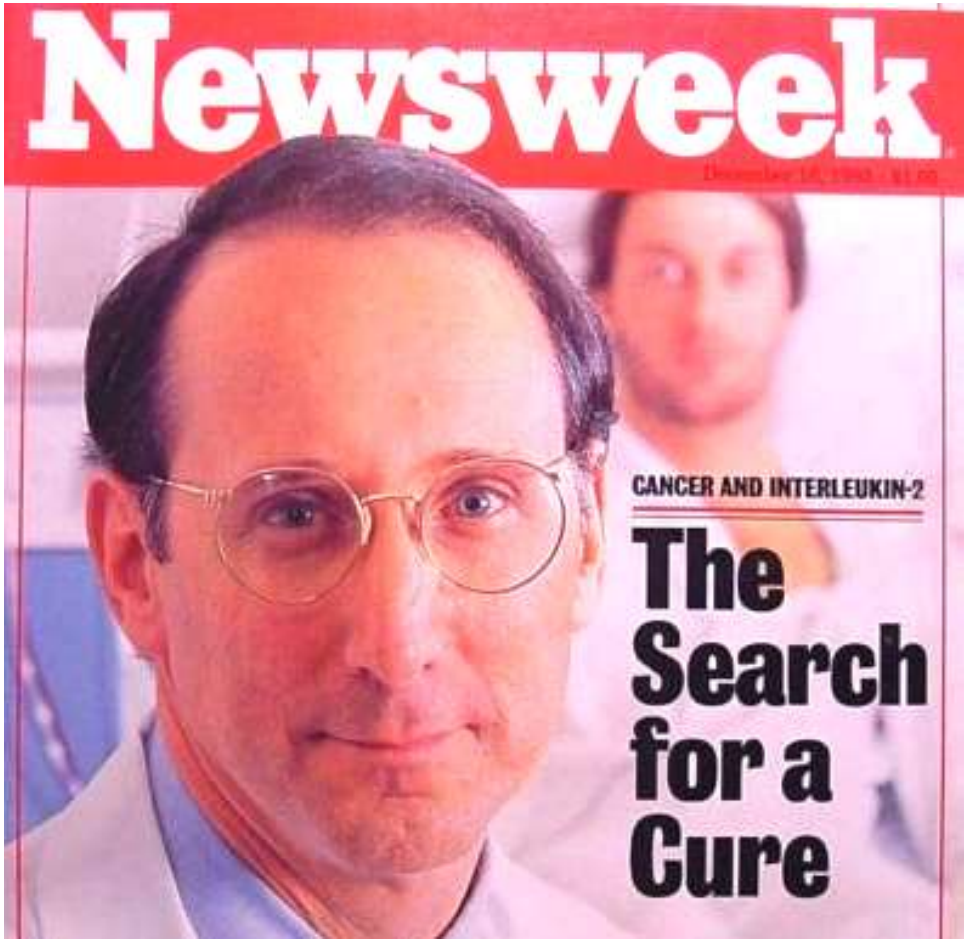
Getting the Immune System to Help

Importance of the Immune System

1. It already exists in the body
2. It is designed to attack foreign invaders (infections…cancer?)
3. It turns on and off naturally
4. The cells are stable, they don't mutate all the time

- But…

- Cancer isn't really foreign
- The immune system is ridiculously complex
- It sometimes gets it wrong (autoimmune diseases)



Newsweek
1985

~ 30 Years Later

Approaches to Breast Cancer Immunotherapy

Modality	Phase I	Phase II	Phase III	Approved?	Comment
CTLA-4	→			No	Minimal activity
PD-1/PD-L1	→	→	→	yes	ORR <20% in TNBC; combinations being tested
Therapeutic vaccines	→	→	X	No	Negative randomized studies; combinations critical
Prevention vaccines	→			No	First-in-human studies underway
T-cell agonists	→			No	Unlikely to offer single-agent activity in breast cancer
Adoptive T cells	→			No	Initial CAR T-cell studies underway

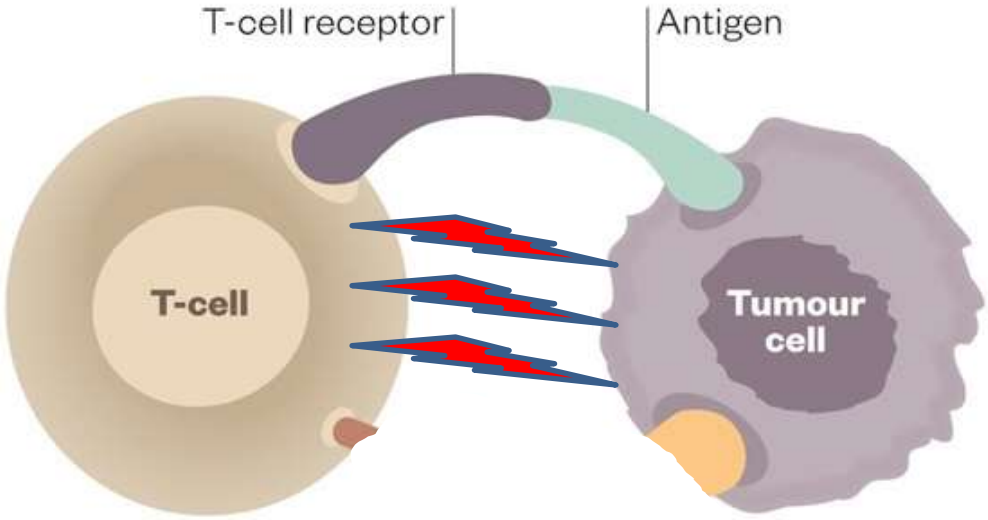
Now approved with chemo in triple negative breast cancer

How This Kind of Immunotherapy Works: The Short Answer

- **Cancer hides from the immune system using an invisibility cloak**

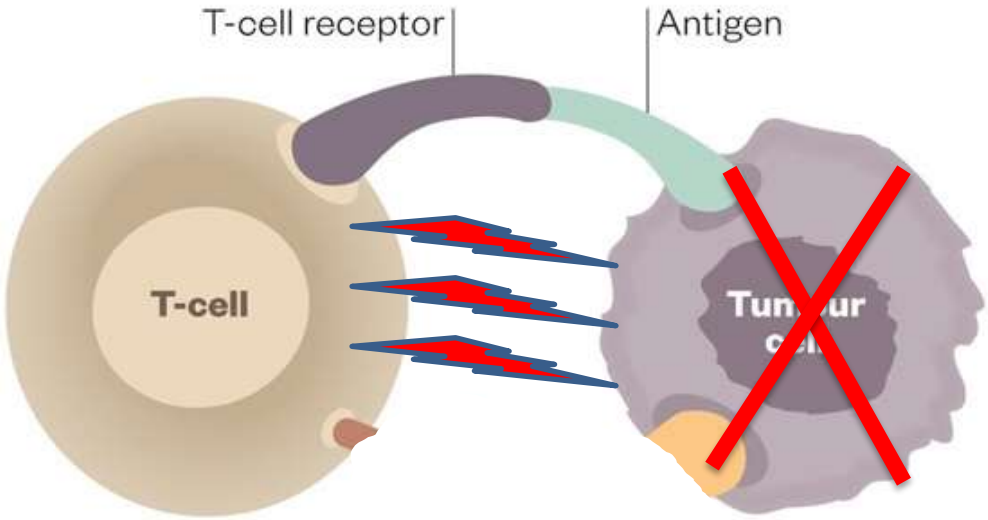
How This Kind of Immunotherapy Works: The Longer Answer

T-cells are designed to recognize and kill tumor cells



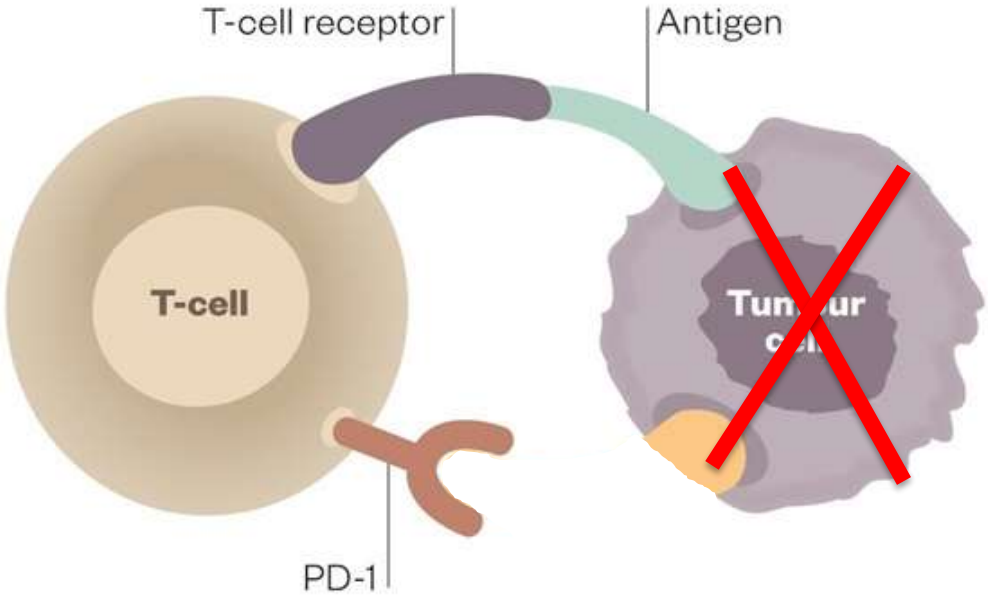
How This Kind of Immunotherapy Works: The Longer Answer

T-cells are designed to recognize and kill tumor cells



How This Kind of Immunotherapy Works: The Longer Answer

PD-1 acts as an "off switch" for T-cells



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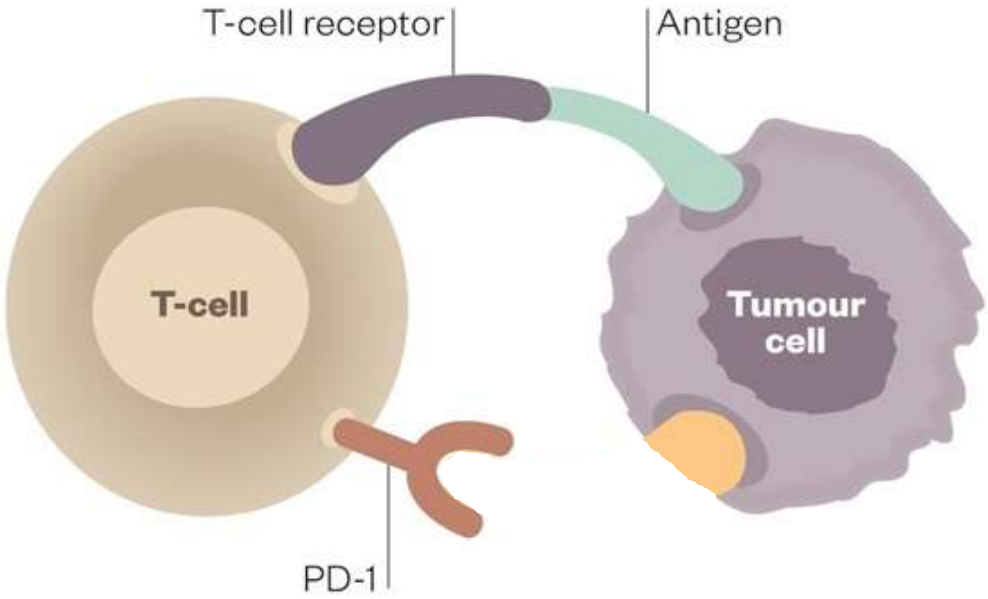
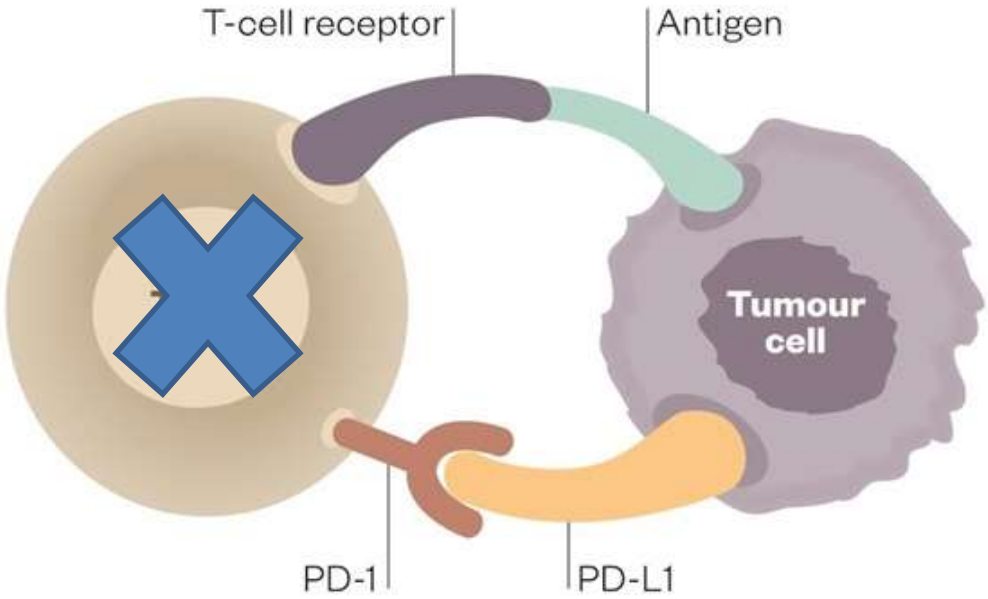


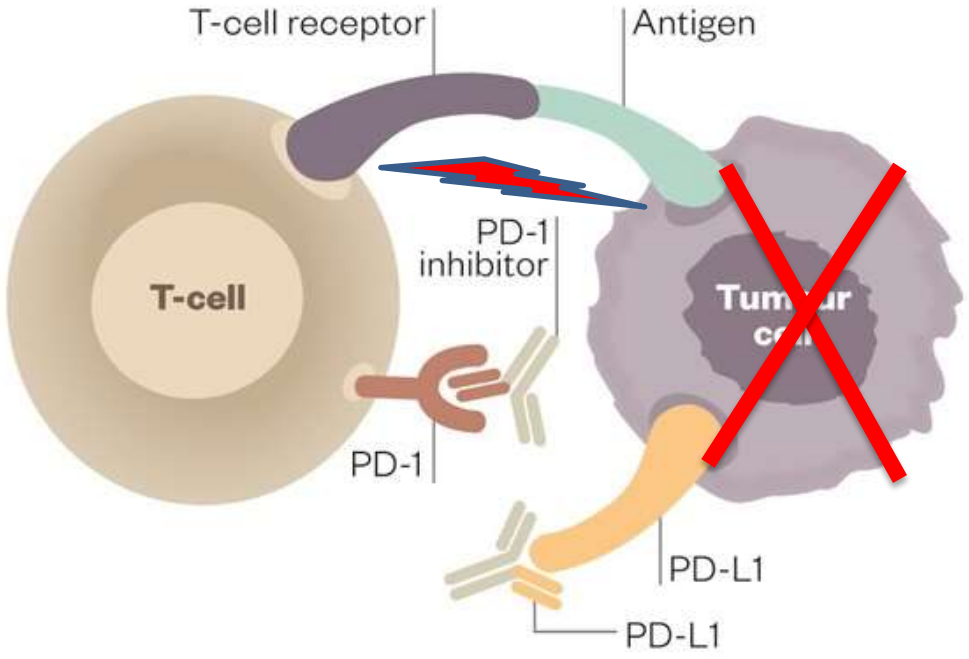
How This Kind of Immunotherapy Works: The Longer Answer

Tumor PD-L1 binds to T cell PD-1 inactivates T-cells



How This Kind of Immunotherapy Works: The Longer Answer

Drugs that inactivate PD-1 or PD-L1 prevent tumor cells from inactivating T-cells



The New Era Dawns

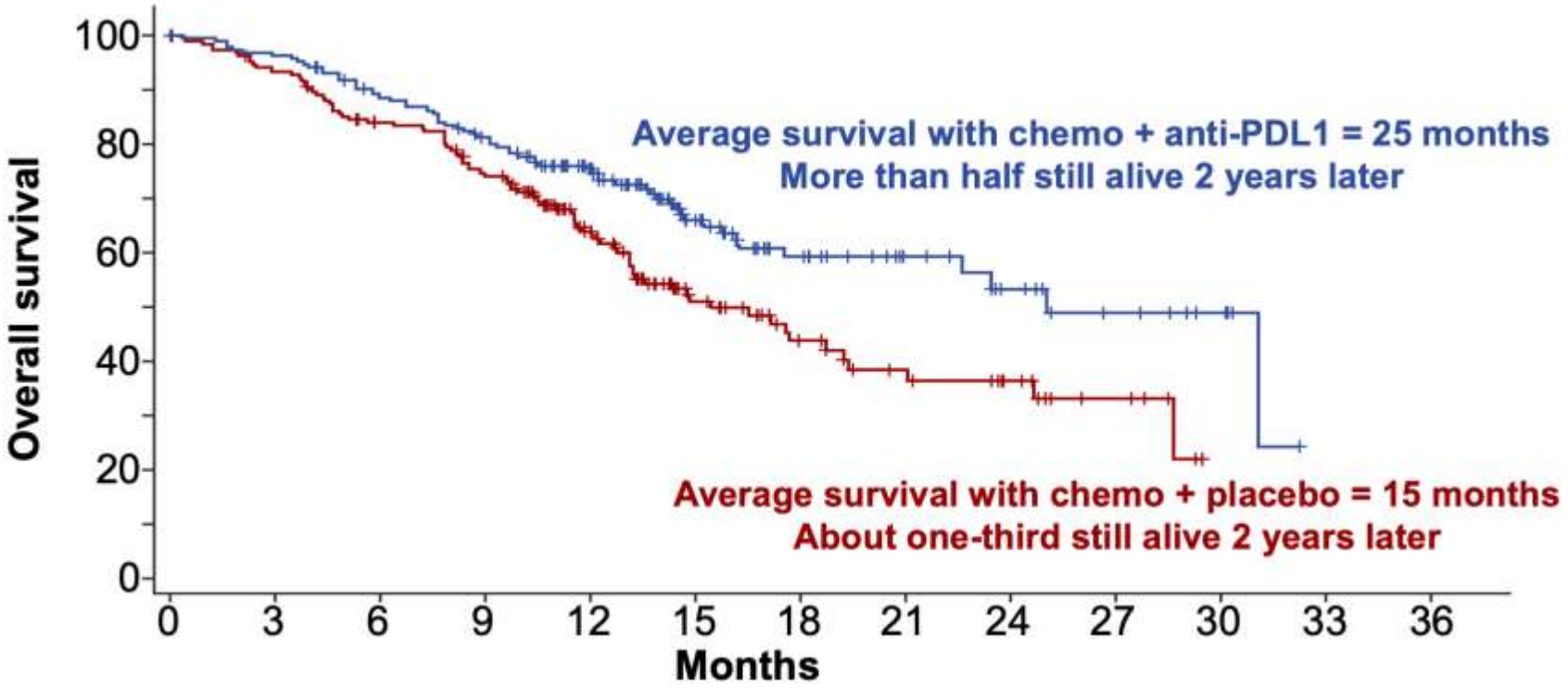
The NEW ENGLAND JOURNAL of MEDICINE

Metastatic untreated triple negative breast cancer

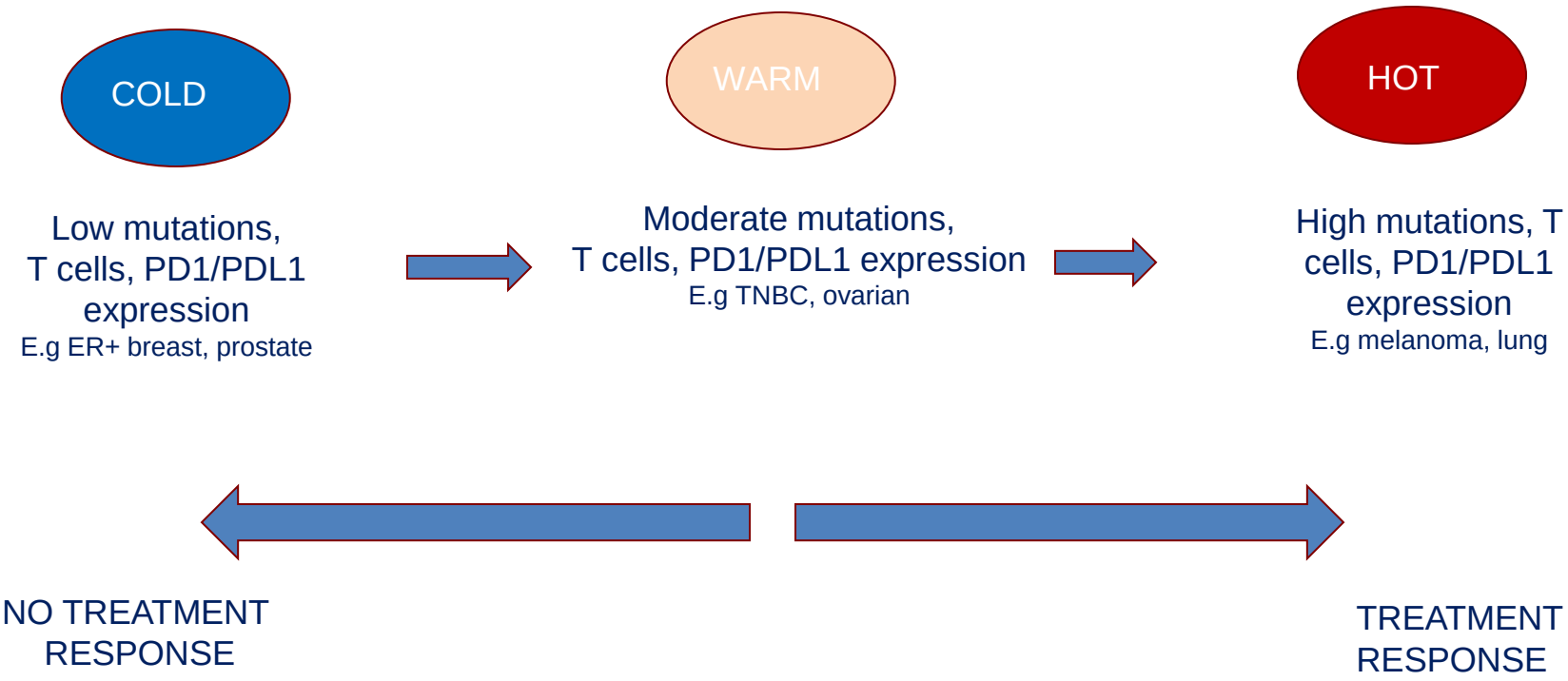
Chemotherapy + anti-PDL1 antibody

Chemotherapy + placebo

Real Improvement in PDL1+ Triple Negative Disease

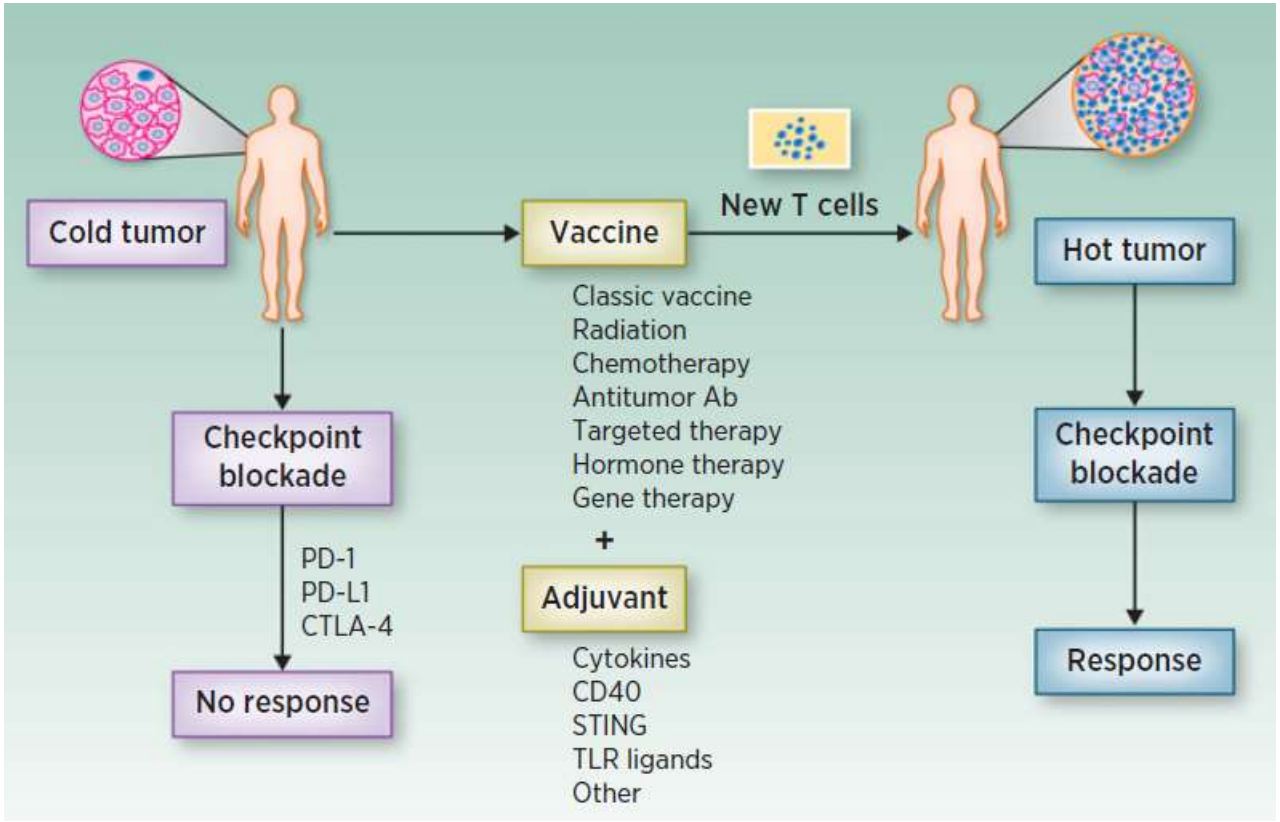


"COLD" AND "HOT" TUMORS



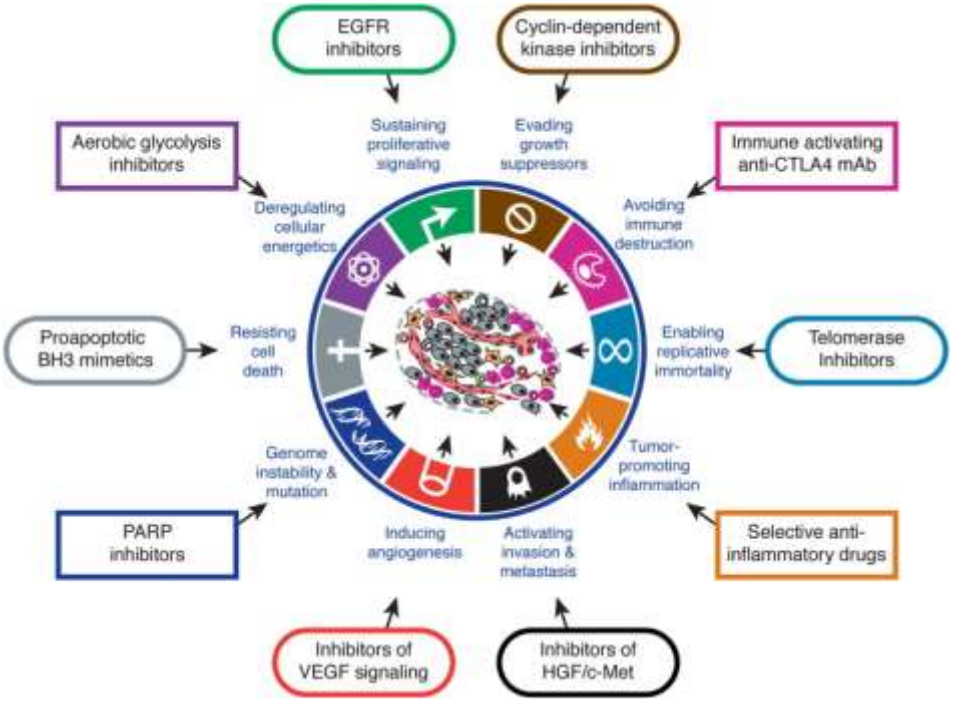
Converting Cold Tumors to Hot

Works in progress



Some success here

Curing Metastatic Breast Cancer May Need a Multipronged Approach

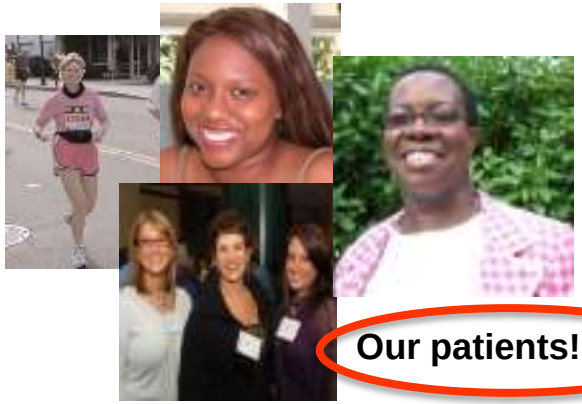


Breast Cancer Research is a Partnership

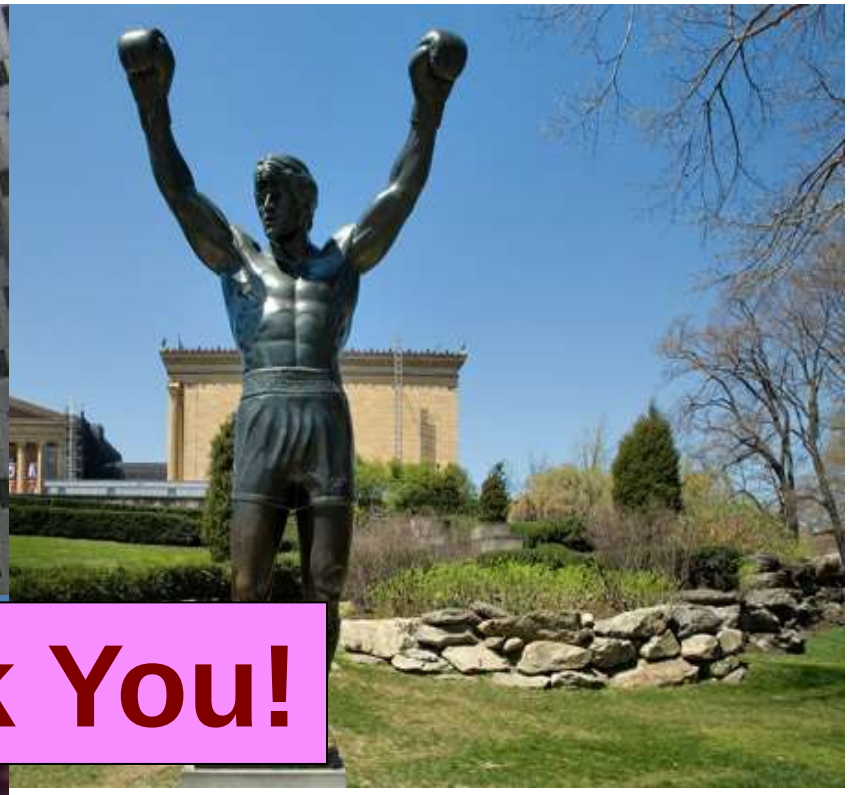
medical colleagues

Clinical oncology staff

Research staff



Our patients!



Thank You!

Penn
UNIVERSITY of PENNSYLVANIA

the cure is with in
ABRAMSON CANCER CENTER