

# ***Susan G. Komen for the Cure***

## **Virtual Metastatic Breast Cancer Conference 2020**

**Metastatic Breast Cancer Research:**

**Past, Present, and Future**

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***Ann Arbor, Michigan***



# Conflicts

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- **Circulating Tumor Cells**

- **CellSearch**

- **Laboratory and Clinical research funding from Veridex/Janssen Diagnostics/Menarini Silicon BioSystems**
- **Patent regarding circulating tumor cells licensed to MSB**

- **Other**

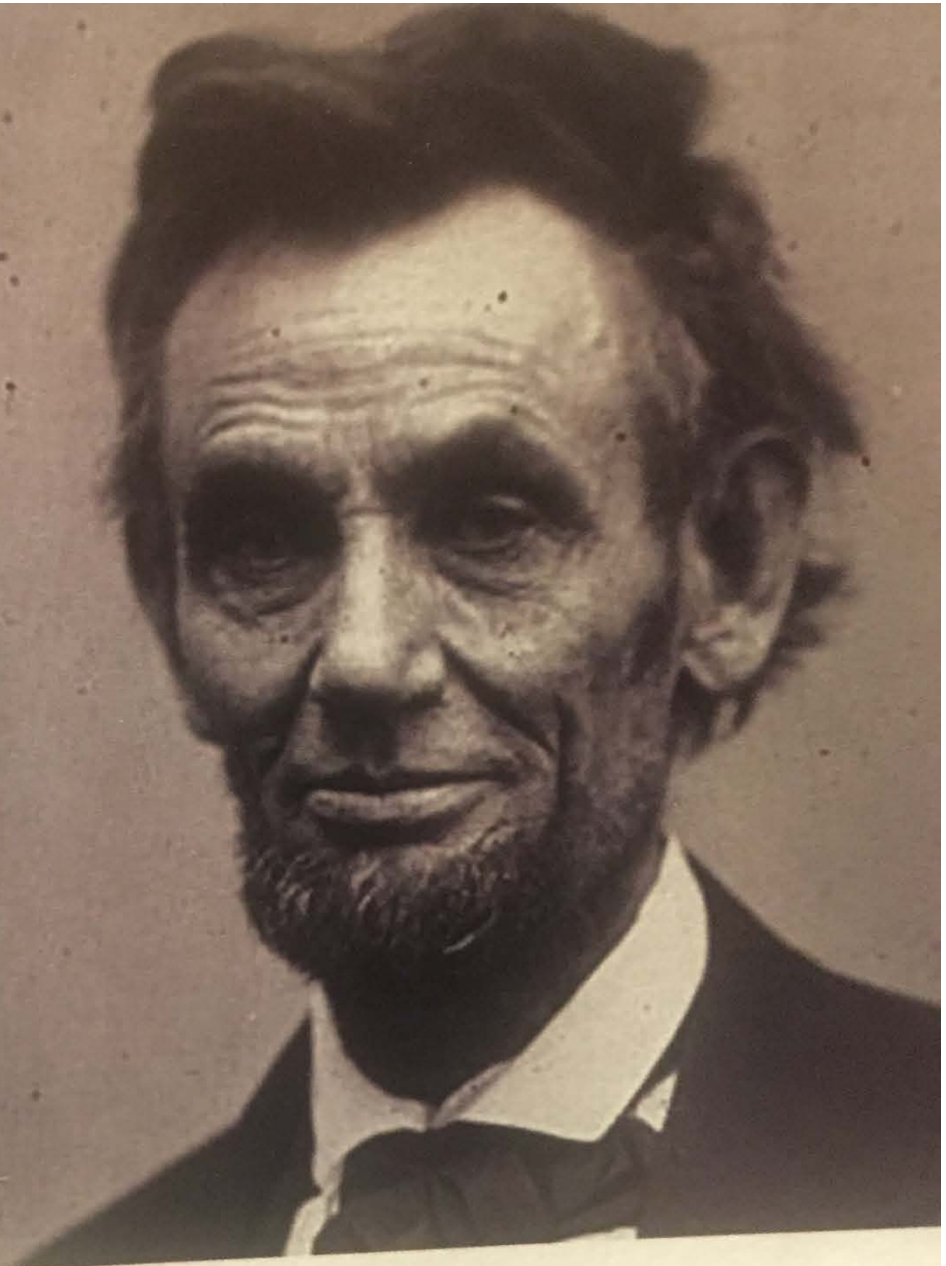
- **Stock Options: OncImmune, InBiomotion**
- **Consultant: Agendia, Cellworks, Cepheid, CVS Caremark**
- **Sponsored Clin Research: Merrimack Pharmaceuticals, Eli Lilly, Menarini/Silicon BioSystems, Puma Biotechnology, Pfizer, Astra Zeneca**
- **Collaborated with GHI, manufacturer of 21-gene RS**

**(no financial support or conflict)**

- *Lo, S. S., et al.; J Clin Oncol; 2010.*
- *Albain, K. S., et al.; Lancet Oncol; 2010*

**The problem  
with quotes on  
the internet is  
that they are  
often not true.**

**—Abraham Lincoln**



# *Early Stage Breast Cancer*

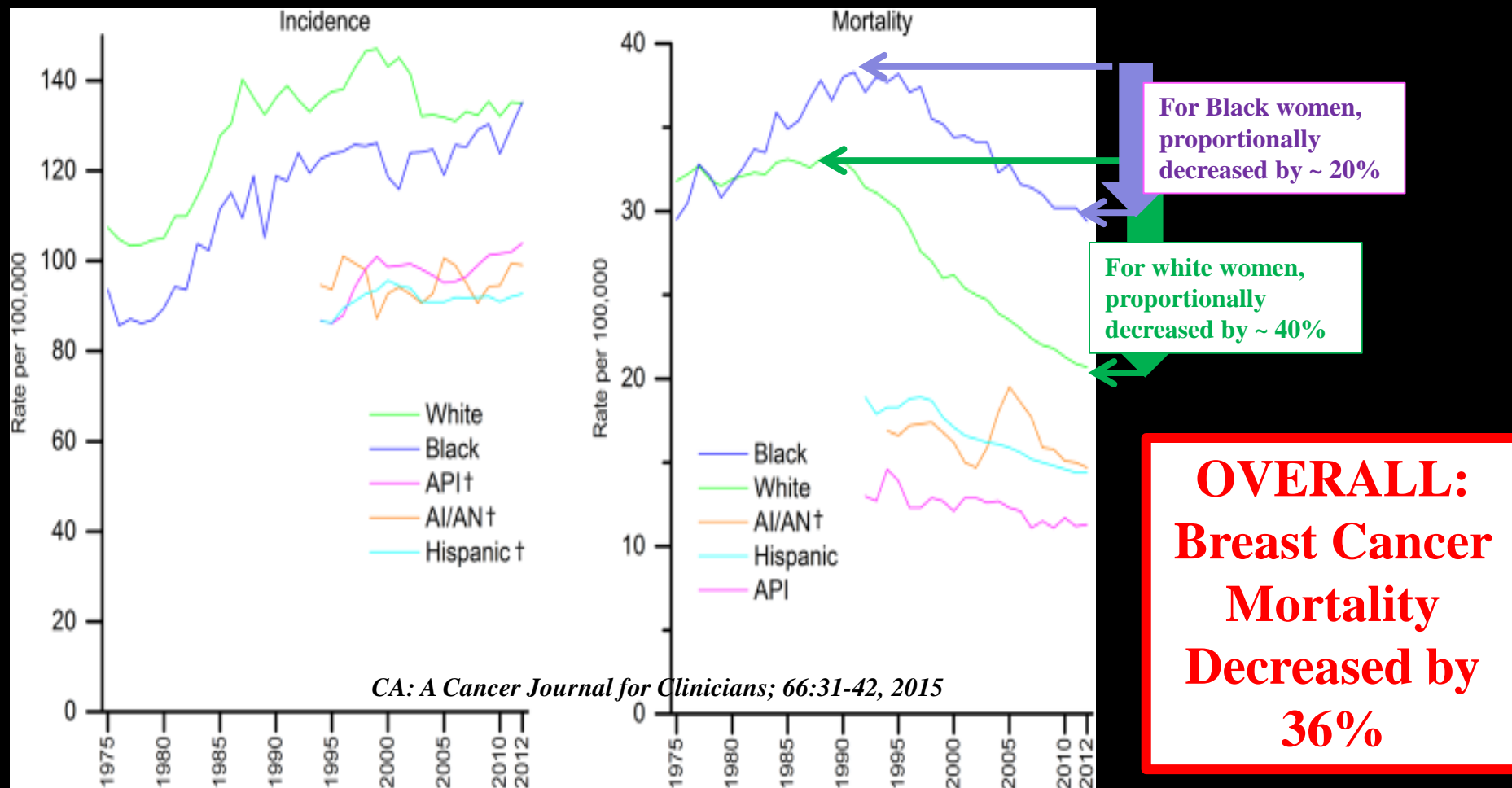
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**First: the Good News-**

**Breast Cancer Mortality in the U.S. Has **Decreased**  
Substantially Over the Last 30 Years**

# Increase in Breast Cancer Incidence but Decrease in Mortality

## 1975-2012



# *Early Stage Breast Cancer*

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## First: the Good News-

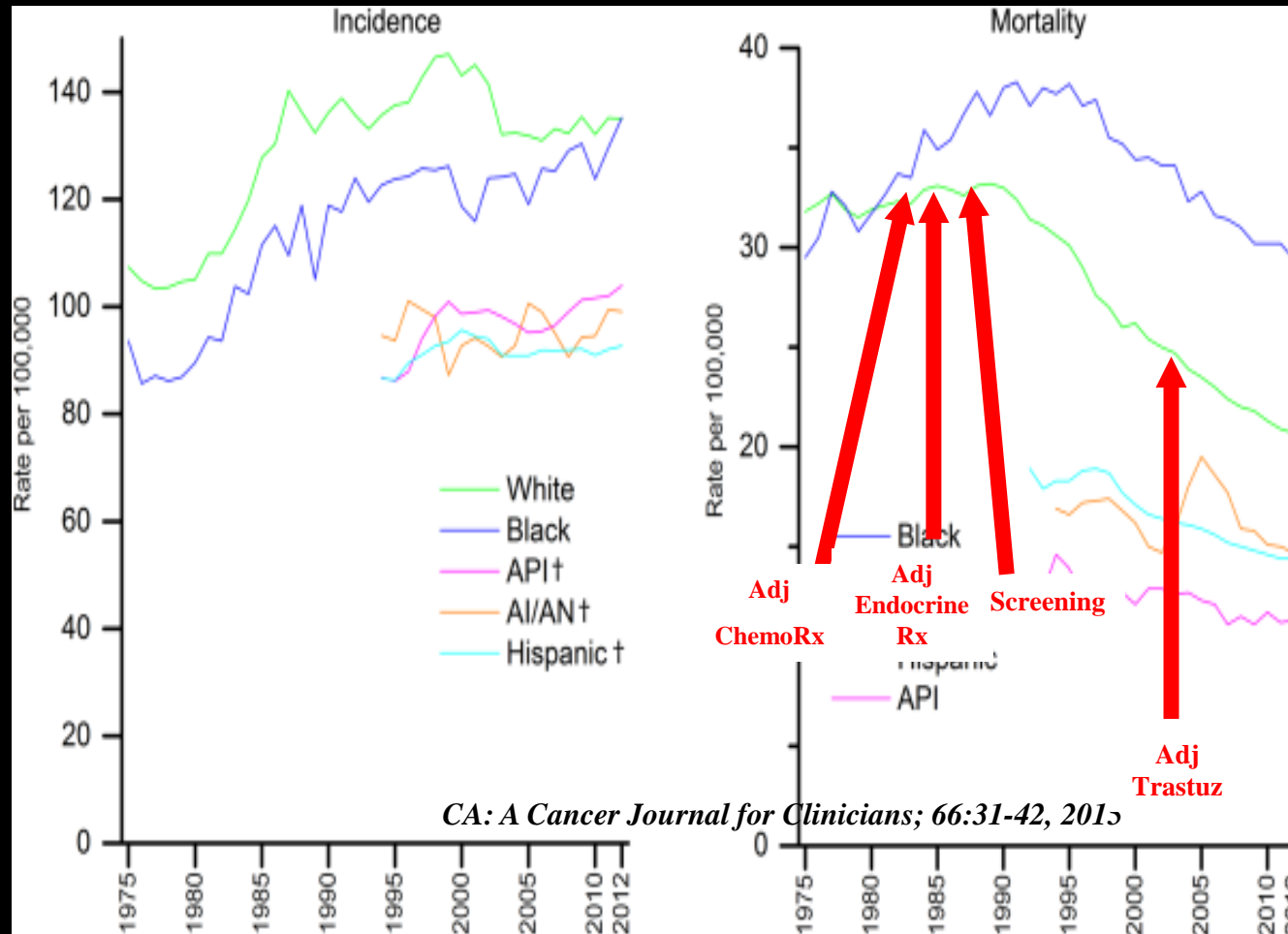
**Breast Cancer Mortality in the U.S. Has  
Decreased Substantially Over the Last 30 Years**

## Why?

- **Screening**
- **Better and More Well Tolerated Therapies**

# *Increase in Breast Cancer Incidence but Decrease in Mortality*

1975-2012



**OVERALL:  
Breast Cancer  
Mortality  
Decreased by  
36%**

## *Early Stage Breast Cancer*

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### **Second: Mixed News-**

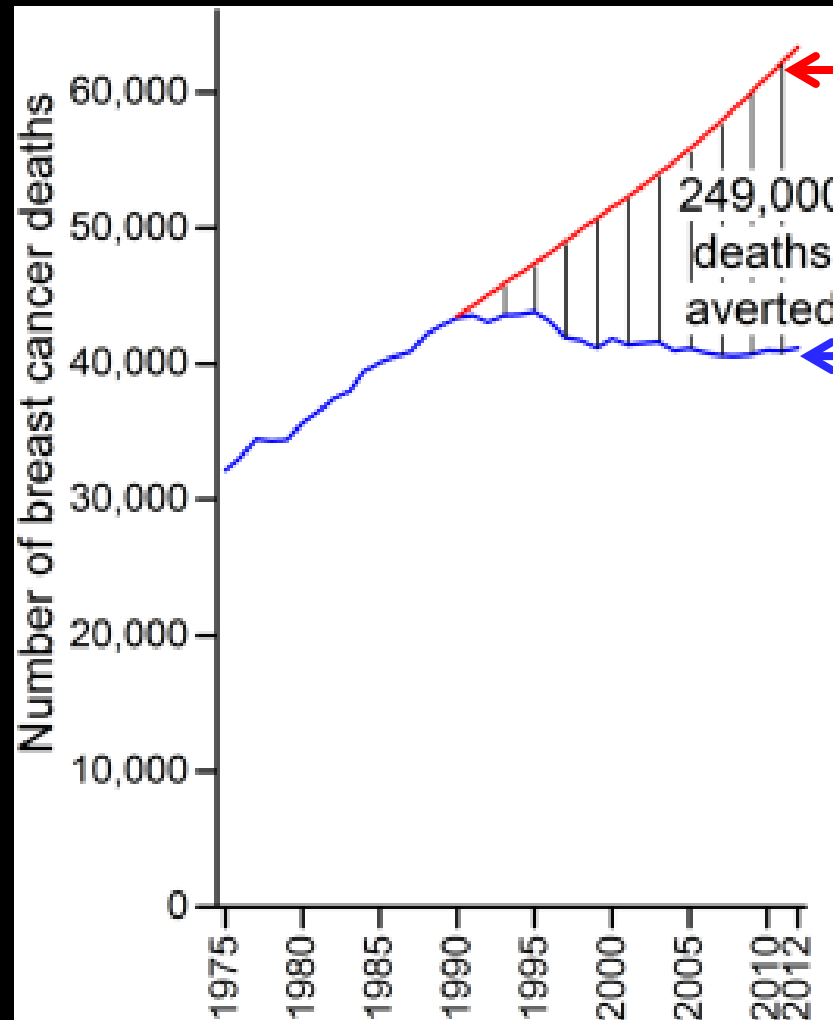
**Although We Would Have Lost Many More Patients to Breast Cancer Without the Advances,**

**~40,000 U.S. Women Will Die of Br Ca in 2020**



# *Deaths Averted by Advances in Breast Cancer Screening and Therapy*

1990-2012



**Anticipated Breast  
Cancer Deaths in US  
at unabated 1989 rate**

**Actual Number of  
Breast Cancer Deaths  
recorded in each year**

# *Early Stage Breast Cancer*

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## **Second: Mixed News-**

**Although We Would Have Lost Many More Patients to Breast Cancer Without the Advances,**

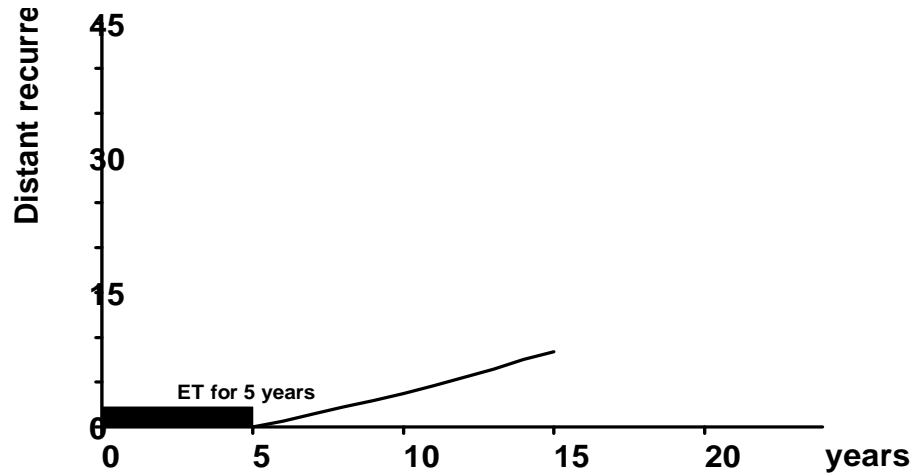
**~40,000 U.S. Women Will Die of Br Ca in 2020**

## **Who Are These Patients?**

- **All Types of Breast Cancers**
- **Disproportionally those with ER Positive Disease Who Will Experience Late Recurrences**

# Distant Recurrence by Nodal Status & T Size

**Patients Without Recurrence @ 5  
Yrs; Years 5-20**



	No. at risk	(and, in each 5-year period, no. of events and a
T1N4-9	3832	(391, 10.2%) (68, 2.6%) (11, 2.2%)
T1N1-3	14342	(734, 5.1%) (162, 1.5%) (35, 1.7%)
T1N0	19402	(509, 2.6%) (218, 1.1%) (58, 1.4%)

# ***Why Do These Patients Keep Suffering Recurrences?***

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- **They are not taking their drugs**
  - **Adherence/Toxicity**
- **They still have cells but the current therapy isn't working**
  - **Prediction/Resistance**
- **They still have cells but the current therapy isn't working**
  - **Prognosis/Dormancy**

# ***Does Everyone Need to Take Extended ET?***

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- Potential determinants of late risk other than nodal

status: ***NONE OF THESE HAS BEEN CLINICALLY***

- ***VALIDATED AND SHOULD NOT BE*** assays,

***MONITORED OR USED TO MAKE THE***

- ***DECISION REGARDING EXTENDED ET!!*** e

potential:

- Disseminated or circulating tumor cells (DTC, CTC)
- Circulating cell free tumor DNA (cftDNA)
- Circulating protein or metabolites?

# New Advances in Metastatic Disease

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- **Goal of Therapy (2020)**

- Very few if any patients with established metastatic disease are cured
- But, the length of time patients live with their disease is much longer than 35 years ago
  - Median was ~ 18 months
  - Now ~ 35 months
- Why?
  - Better understanding of the biology of Breast Cancer
  - Ability to target the biology

# New Advances in Metastatic Disease

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- **Goal of Therapy (2020)**

- Therefore, main goal of therapy is “Palliation”
  - Keeping you feeling as good as you can for as long as you can
- In addition, longer survival
- Taken together: *living longer, living well.*

- **How?**

- Pick therapies most likely to work with the fewest side effects
- Assess whether:
  - You are tolerating the therapy
  - It is working
- Change if
  - Not tolerating
  - Not working

# Breast Cancer Biology

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- **Estrogen Receptor**
  - MTOR activation
  - CDK4/6 activation
  - PIK3CA mutations
- **HER2**
- **BRCA1/2 mutations**
- **Programmed Death Ligand 1 (PD-L1)**



# Breast Cancer Drugs: Generic – Brand Names

Condition	Type drug	Generic	Brand	
ER Pos	LHRH agonists	Goserelin	Zoladex	
		Leuprolide	Leupron	
		Triptorelin	Triptodur	
	SERM	Tamoxifen	Nolvadex	
		Toremifene	Fareston	
		Raloxifene	Evista	
	Arom Inhibitor	Anastrozole	Arimidex	
		Letrozole	Femara	
		Exemestane	Aromasin	
	SERD	Fulvestrant	Faslodex	
		CDK inhibitor	Palbociclib	Ibrance
			Ribociclib	Kisqali
Ambemaciclib	Versenio			
PIK3CA Mut	MTOR inhibitor	Everolimus	Afinitor	
		TKI	Alpelisib	Piqray
		HER2 Pos	Antibody	trastuzumab
Pertuzumab	Perjeta			
Margetuximab	Not yet approved			
	subQ trastuz	Trastuzumab-PKRB	Hylecta	
		ADC	TDM-1	Kadcyla
			Ado-trastuzumab emtamsine	
Fam-trastuzumab deruxtecan	Enhertu			
	TKI	Lapatinib	Tykerb	
		Neratinib	Nerlynx	
		Tucatinib	Tukysa	
Triple Neg	ADC	Sacituzumab govitecan	Trodelvy	
		ImChPoint inhib	Atezolizumab	Tecentriq
			Pembrolizumab	Keytruda
BRCA1/2 Mut	PARP Inhib	Olaparib	Lynparza	
		Talazoparib	Talzenna	
Bone: Different Brand Names		Cancer	BMD	
Bisphosphonate	Zoledronic Acid	Zometa	ReClast	
Anti-RANKL	Denosumab	XGeva	Prolia	

# Estrogen Receptor (ER)

- **Too much ER – “Endocrine” (or anti-estrogen) therapies:**

- Selective ER Modulator (SERM) Tamoxifen (Nolvadex)
- Suppression of ovarian function Zoladex, Leupron
- Aromatase inhibitors Arimidex, Femara, Aromasin
- Selective ER DownRegulator (SERD) Faslodex

- **Mutated ER**

- SERD (Oral) in trials

- **Add to Endocrine therapies**

- MTOR inhibitor Afinitor
- CDK 4/6 inhibitor Ibrance, Kisqaly, Versinio
- PIK3CA inhibitor Piqray

# HER2

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- **Too much HER2 – anti-HER2 therapies:**

- Antibodies directly against HER2

Herceptin, Perjeta,  
(Margetuxumab)

- Subcutaneous Herceptin

Hylecta

- Herceptin+drug conjugates (Trojan Horse)

Kadcyla (Herceptin plus emtansine),  
Enhertu (Herceptin plus deruxtecan)

- Tyrosine Kinase Inhibitors

Tykerb, Nerlynx, Tukysa

- **Mutated HER2**

Nerlynx

# Antibody-Drug Conjugates

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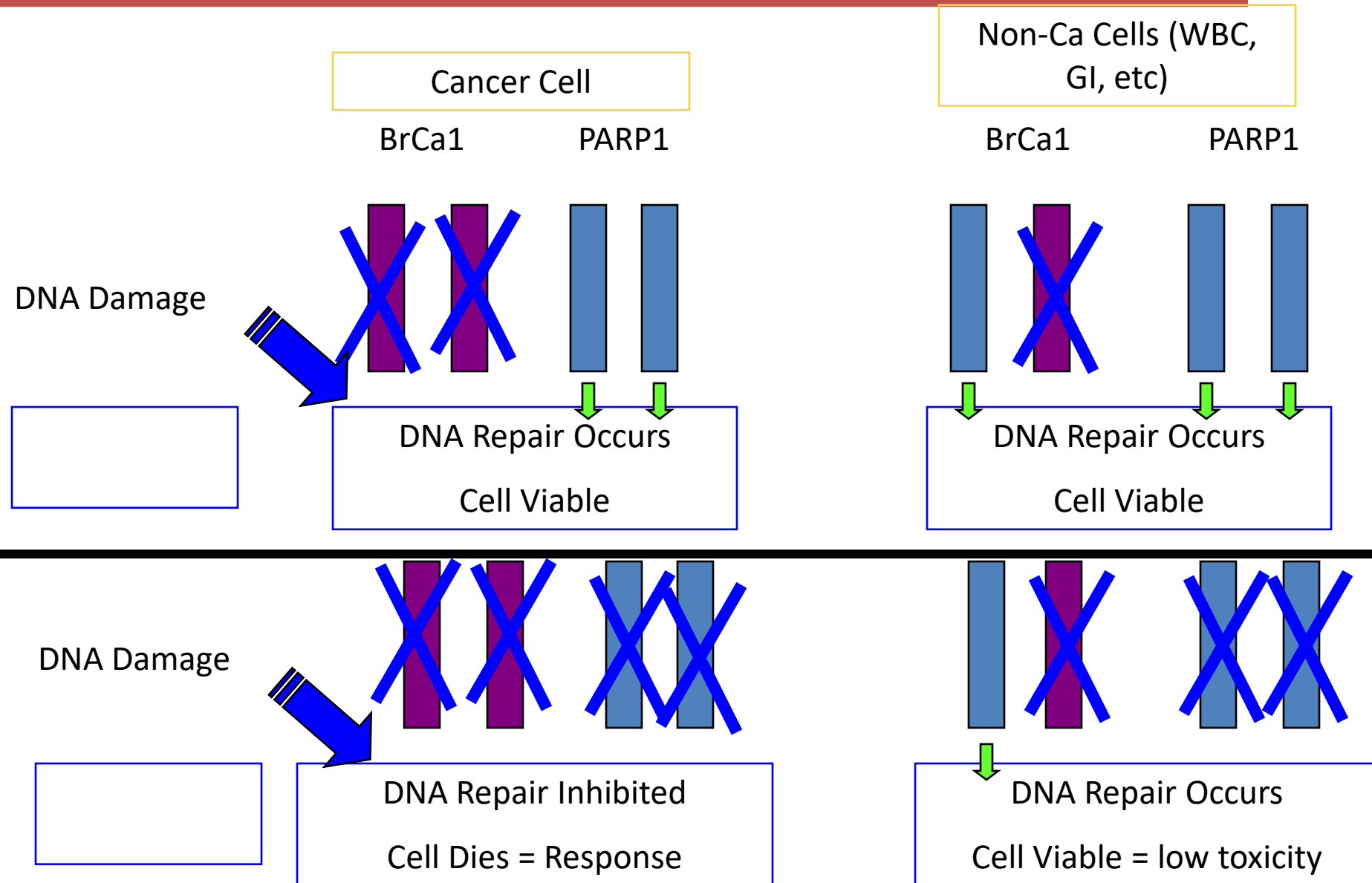
- Chemotherapy “payload” is linked to antibody
- Antibody binds to a target on the cancer cell
- Entire Complex internalized
- Link broken
- Chemotherapy kills cell
- Chemotherapy leaks out but at much lower concentrations in blood – less toxicity than if infused as free chemotherapy

# “Triple Negative”

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- **BRCA1/2 mutated OR “mutated like”**
- **Inhibitors of PARP**  
Lynparza, Talzenna  
Veliparib (not approved)
- **PD-L1 over-expressed (ImmunoRx)**  
– Immune Checkpoint inhibitors  
Tecentriq, Keytruda
- **Antibody-Drug Conjugate**  
*Trodelvy*

# Proposed Mechanism of PARP1 Inhibition in "BRCA-like" (germ line and/or somatic) Breast Cancer



# *Innovations in Immune Therapies Against Cancer*

**Bacteria**



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The immune system is designed to get rid of invading germs from outside our bodies

**BUT** the immune system cannot go after our own cells, even when they become malignant!

*They have a cloak of invisibility!!*

**Cancer Cell**



# *Innovations in Immune Therapies Against Cancer*

At least 7 new drugs that break the cloak of invisibility and allow the immune system to go after the cancer cells:

Scientists have figured out how to break through the “cloak of invisibility”!!

These work for:

- **Melanoma**
- **Colon Cancer**
- **Lung Cancer**
- **Others (NOBEL PRIZE: 2018)**
- **And now: selected Triple Negative Breast Cancers!**





# Research in Metastatic Breast Cancer

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- **Diagnostics**
  - “Next Generation Sequencing” - looking for needles in big haystack that might be targets for therapy
  - “Circulating” Tumor biomarkers in blood
    - Circulating tumor cells
    - Circulating cell free tumor DNA
  - Novel Imaging approaches

# Research in Metastatic Breast Cancer

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- **Summary**

- Lots better than 35 years ago
- New stuff almost every month
- Still not good enough

- **RESEARCH RESEARCH RESEARCH**

- Participate in clinical trials if they make sense to you
- Raise more money (Komen for the Cure!!)

