Triple Negative Breast Cancer

Beat the Odds Breast Cancer Education Forum
To Life!
Wednesday, August 5, 2020

Jung-Min Lee, M.D.
NIH Lasker Clinical Scholar
Women's Malignancies Branch, Center for Cancer Research,
National Cancer Institute, NIH

NIH NATIONAL CANCER INSTITUTE
Center for Cancer Research

Part 1

Biology and the treatments

Part 2

Advances in the systemic treatment of TNBC

Triple Negative Breast cancer (TNBC)

- What is TNBC ?
- Who gets TNBC ?
- What is the prognosis ?
- How do we treat TNBC ?

What is TNBC ?

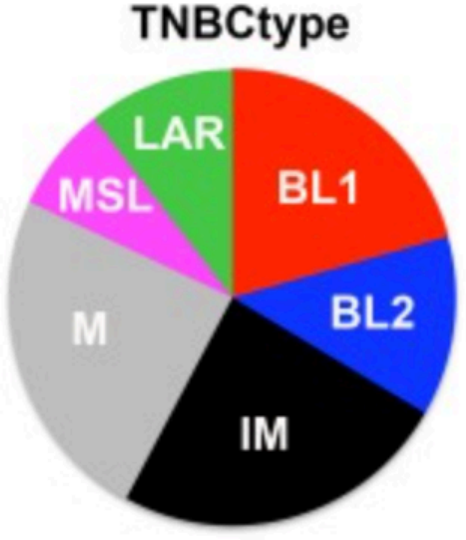
- **Triple-negative breast cancer (TNBC) is a term that has historically been applied to cancers that lack expression of the**
  - **estrogen receptor (ER)**
  - **progesterone receptor (PR)**
  - **and human epidermal growth factor receptor 2 (HER2)**

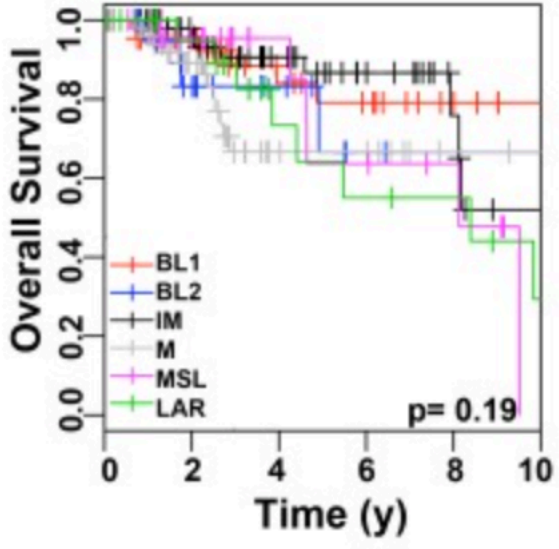
Are all TNBCs the same ?

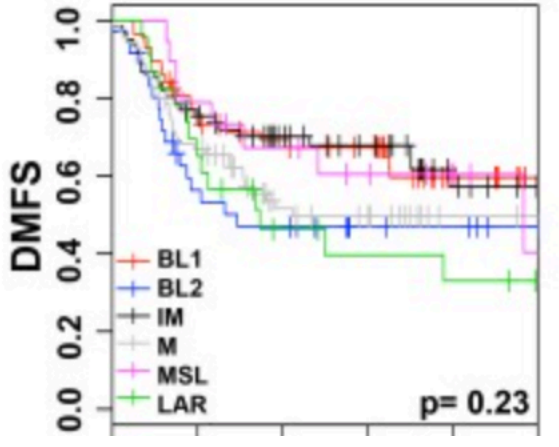
TNBC is a heterogeneous group of breast cancers

Depending on methods used, 4-6 subtypes of TNBC

- **Basal 1 (BL1)**
- **Basal 2 (BL2)**
- **Immunomodulatory (IM)**
- **Mesenchymal (M)**
- **Mesenchymal stem-like (MSL)**
- **Luminal androgen receptor (LAR)**







Lehmann et al. JCI. 2011.
Lehmann et al. J Pathology. 2013.
Lehmann et al. PLOS one. 2016.

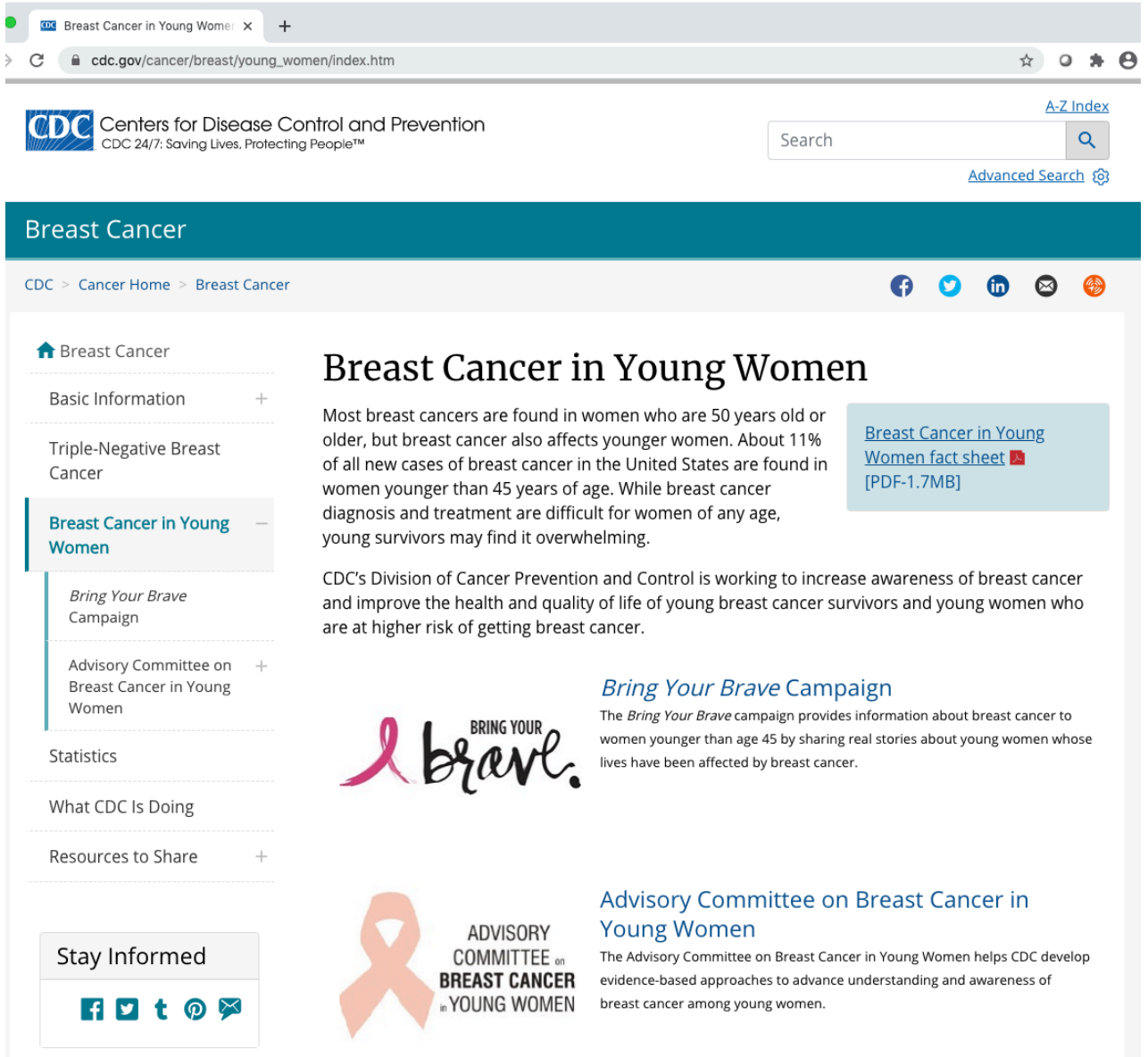
Chance of survival

- **TNBC is often aggressive (fast growing) and has a poorer prognosis than ER positive breast cancer.**
- **However after 5 years, this difference declines and goes away.**

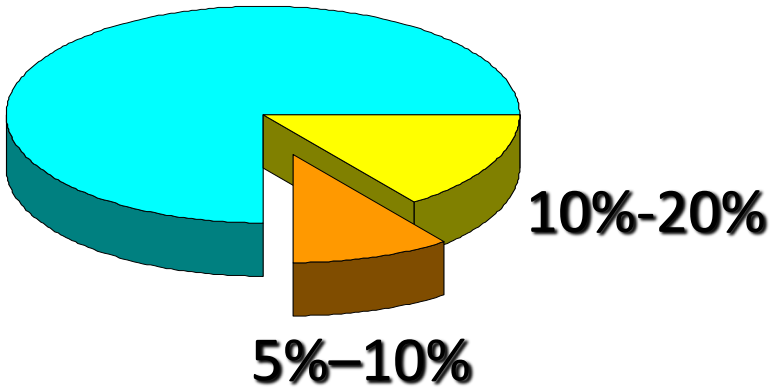
Who gets TNBC ?

- About 15-20% of breast cancers in the US are TNBC.
- Anyone can get TNBC.
- These tumors seem to occur more often in
  - Younger women
  - African-American women
  - Women who have an inherited BRCA1 or BRCA2 gene mutation
    - People diagnosed with TNBC at age 60 or younger should bet their genetic testing for BRCA gene mutations *regardless of family history*

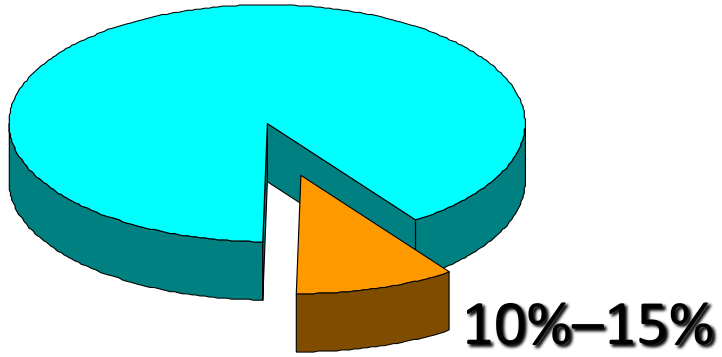
More information available on the CDC website



Most breast and ovarian cancer is not hereditary



Breast Cancer



Ovarian Cancer

Sporadic

Family clusters

Hereditary

Selected hereditary breast cancer genes

Syndrome	Gene	Lifetime risk of developing breast cancer
Hereditary Breast and Ovarian Cancer syndrome	*BRCA1*	40-80%
Hereditary Breast and Ovarian Cancer syndrome	*BRCA2*	30-60%
Li-Fraumeni syndrome	*P53*	90%
Cowden's syndrome	*PTEN*	25-50%
Other genes with low to moderate penetrance	CHEK1, ATM, PALB2 etc	

Hemel and Domchek, Hematol Oncol Clin N Am 2010

Prevalence of BRCA mutation

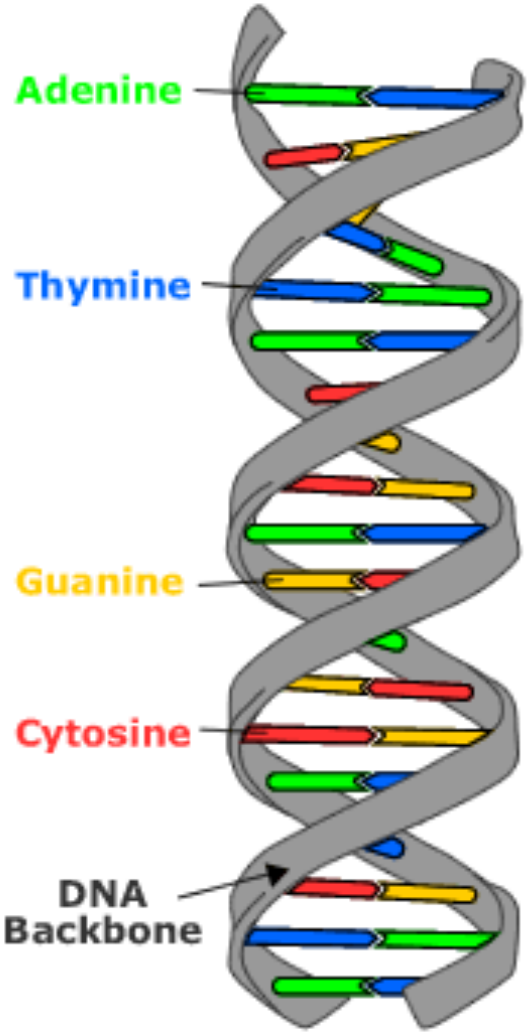
(Percentage of individuals who carry a mutated gene)

- **Overall Population**
  BRCA1 ~1/800 (< 1%)
  BRCA2 ~1/800 (< 1%)

- **Founder Mutations**
  A high frequency of a specific gene mutation in a population due to the presence of that mutation in a single ancestor or a small ancestral group
  Ashkenazi Jewish
  ~1/40 (2.5%) carries a BRCA1 or BRCA2 mutation

What is DNA?

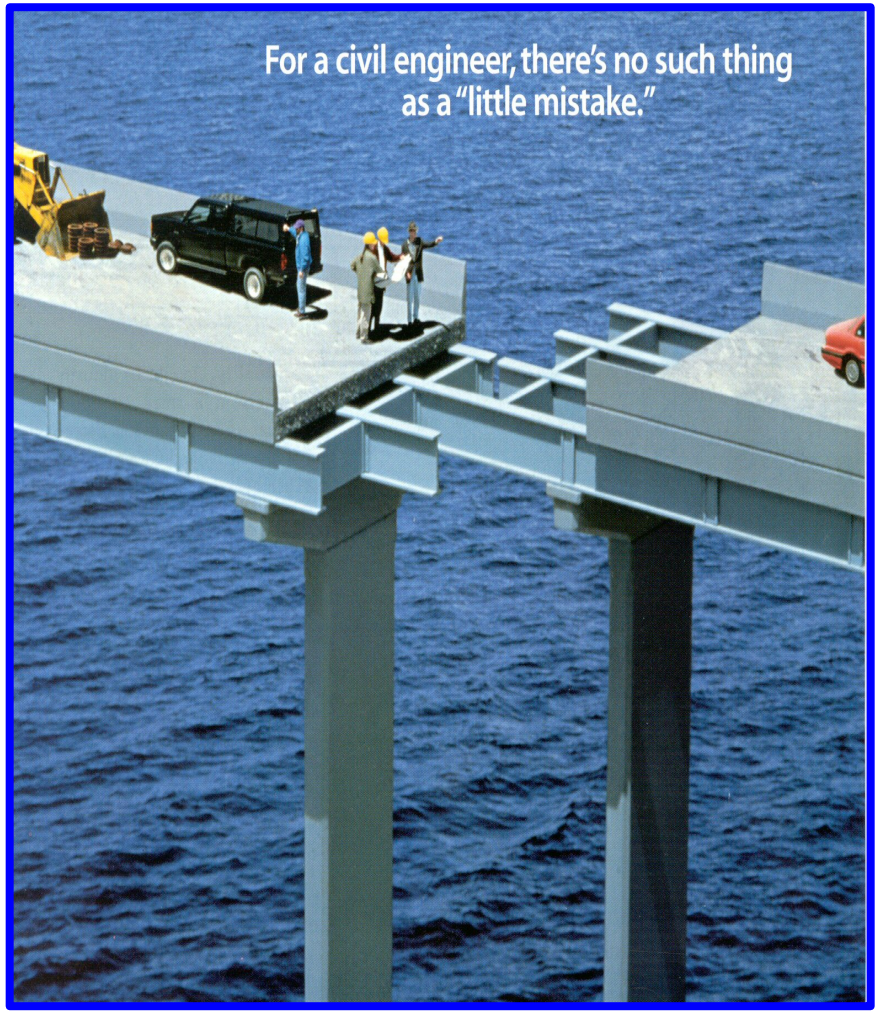
- Building blocks of our genes
- Two complementary strands (double helix, Rosalind Franklin)
- Each chromosome contains 2 copies of each gene, one on each strand
- Germline (what we are born with) mutations, affect only one strand. Cancer needs another (second) hit to happen.



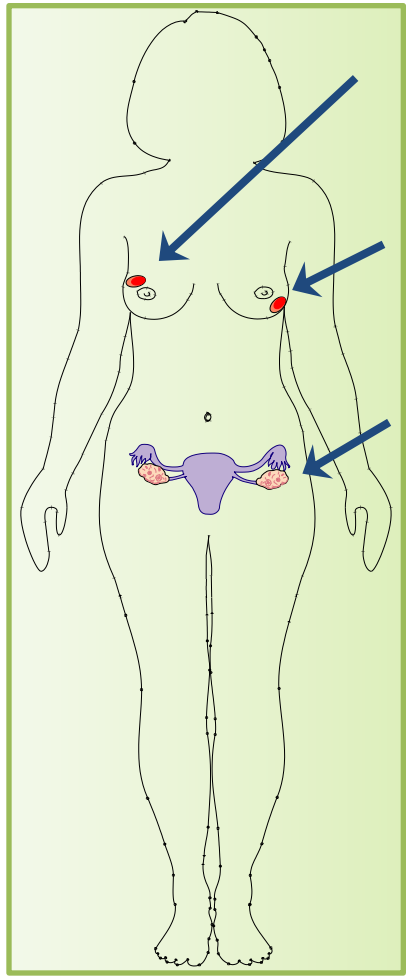
From: evolution.berkeley.edu

When BRCA gene is mutated…

- Normal high fidelity double-stranded DNA repair is lost
- Increased susceptibility to DNA damage
- *Unclear* how/why these genes increase risk of (breast and) ovarian cancers
- 95^{+}% protection by risk reduction surgery; protection against breast cancer also



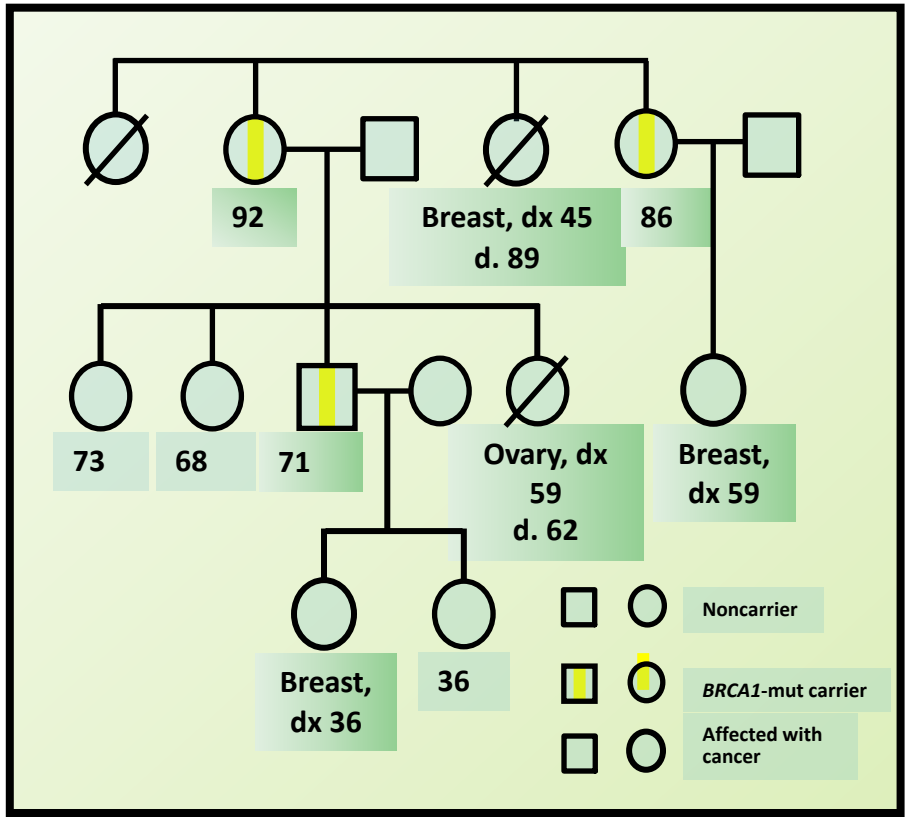
BRCA1 hereditary breast and ovarian cancer



Breast cancer 50%-85%
(often early age at onset)

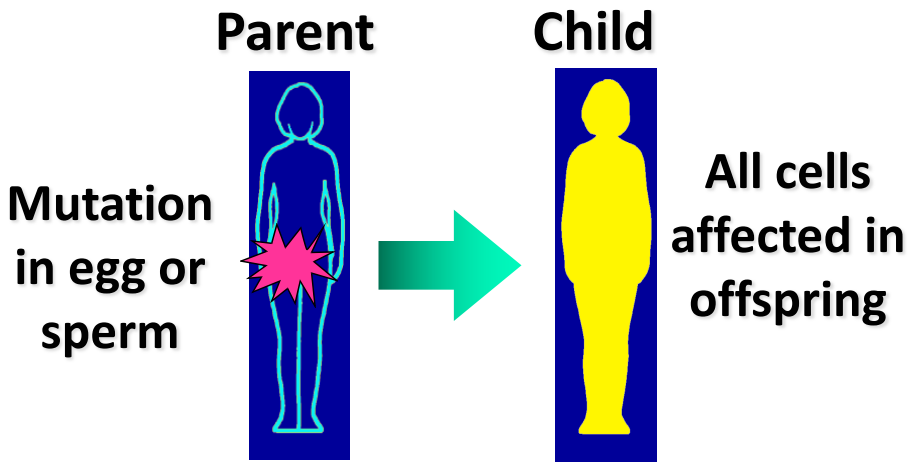
2nd primary breast ca
40%-60%

Ovarian cancer
15%-45%



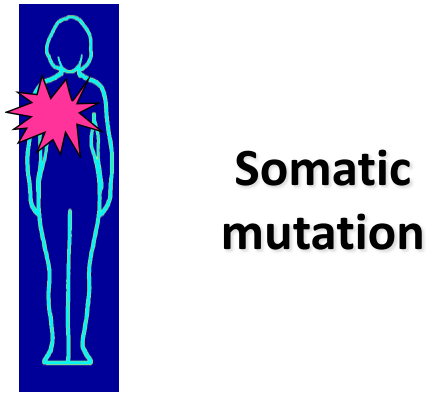
Cancer arises from gene mutations

Germline mutations



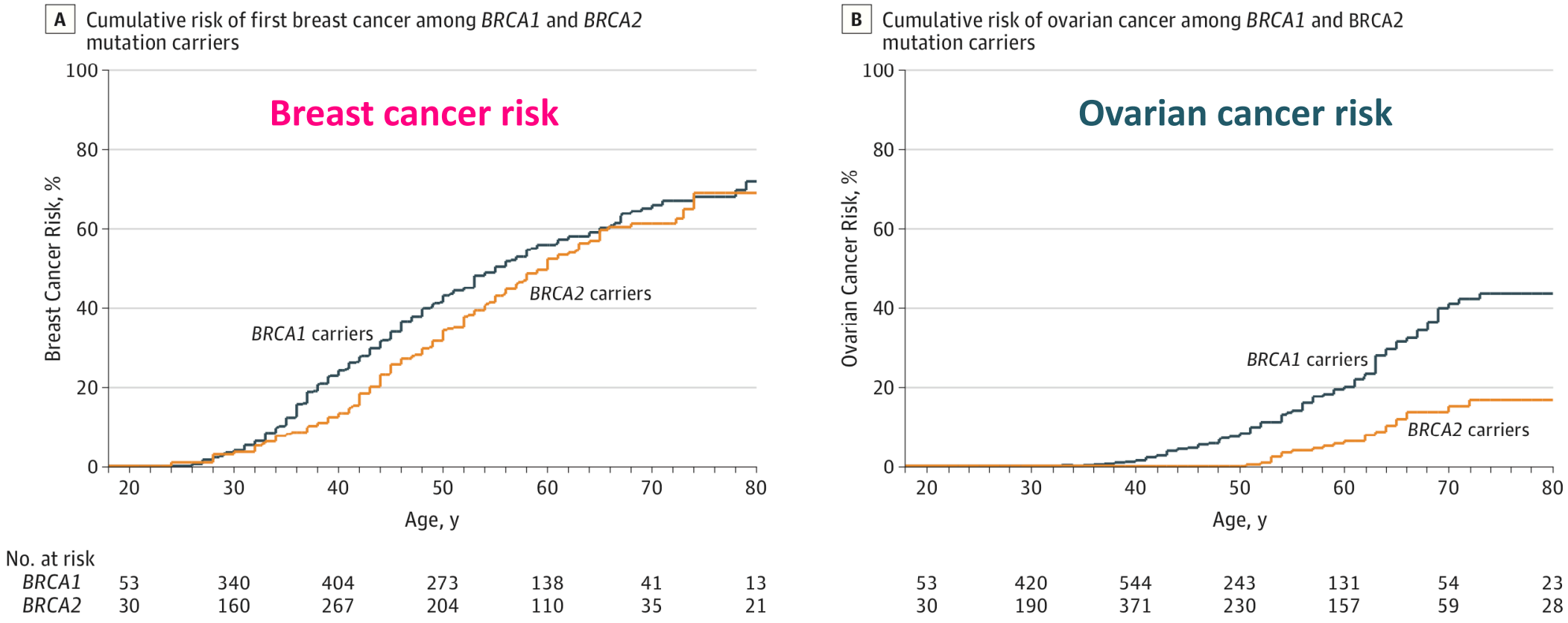
- Present in egg or sperm
- Are heritable
- Cause cancer family syndromes

Somatic mutations



- Occur in non germline tissues
- Are not heritable

Risk of breast and ovarian cancer in germline BRCA mutation carriers



Kuchenbaecker *et al. JAMA* 2017

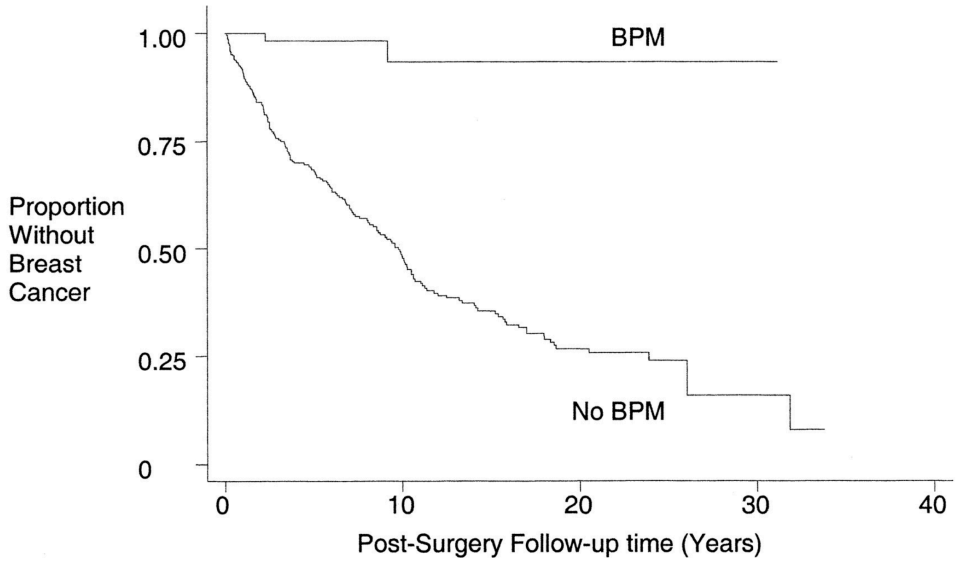
Breast cancer screening in germline BRCA mutation carriers

- **Breast awareness starting at age 18**
- **Age 25: clinical breast exam every 6-12 months**
- **Age 25-29: annual breast MRI**
- **Age 30-75: annual mammogram and consider breast MRI**

NCCN Guidelines: Genetic/Familial High-Risk Assessment: Breast and Ovarian. Version 1.2020.

Role of bilateral prophylactic mastectomy (BPM) in germline BRCA mutation carriers

- **By age of 70, risk of breast cancer in gBRCAm carriers is 40-80%**
- **NCCN guidelines recommend discussion of risks/benefits of BPM on a case-by-case basis**



Rebbeck et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE study group. JCO, March 2004 15(22)

Timing of risk-reducing bilateral salpingo-oophorectomy (RRSO) in germline BRCA mutation carriers

- **Recommended at age 35-40**
- **Can consider delaying until 40-45 in BRCA2 patients**
  - **Ovarian cancer usually develops 8-10 years later in these patients**
- **If does not elect RRSO, consider transvaginal ultrasound + CA=125 starting at age 30-35 although benefit is uncertain**

NCCN Guidelines: Genetic/Familial High-Risk Assessment: Breast and Ovarian. Version 1.2020.

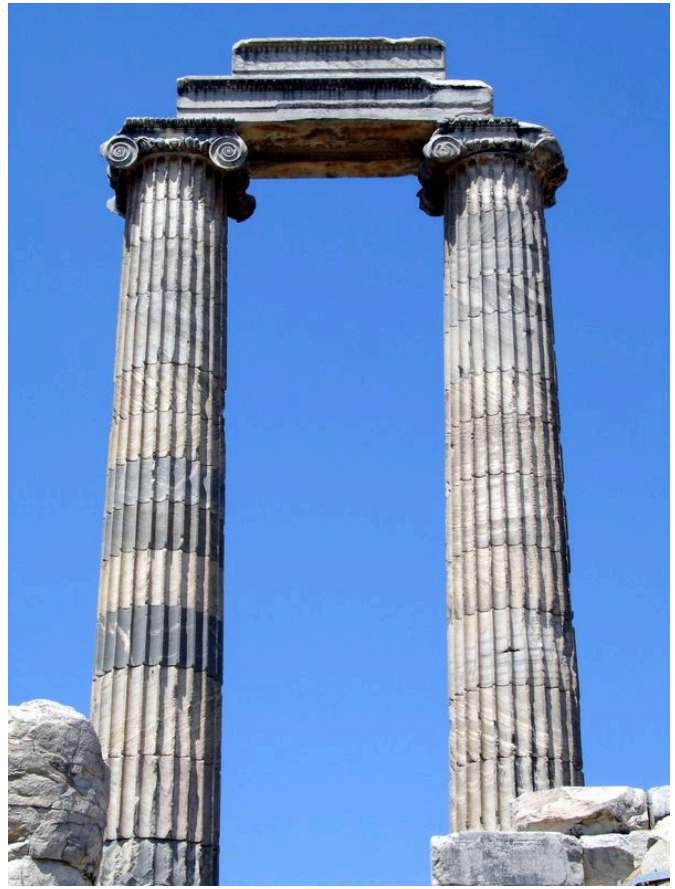
What are the treatment options with TNBC ?

- **Each patient is different and treatment is tailored accordingly.**

Two pillars of breast cancer therapy

- **Local therapy**
  - **Surgery: mastectomy vs lumpectomy**
  - **Radiation therapy**

- **Systemic therapy**
  - **Chemotherapy**
  - **PARP inhibitor**
  - **Immunotherapy**
  - **Antibody-drug conjugates**



How do we treat patients with metastatic/advanced TNBC ?

- Local therapy
  - Surgery: mastectomy vs lumpectomy
  - Radiation therapy

- **Systemic therapy**
  - **Chemotherapy**
  - **PARP inhibitor**
  - **Immunotherapy**
  - **Antibody-drug conjugates**

Commonly used chemotherapy regimens for patients with metastatic/advanced TNBC

- Paclitaxel (taxol)
- Eribulin (halaven)
- Capecitabine (xeloda)
- Vinorelbine (navelbine)
- Nab-paclitaxel (abraxane)
- Carboplatin
- Cisplatin
- Gemcitabine (gemzar)
- Liposomal doxorubicin (doxil)
- Doxetaxel (taxotere)

Choice of chemotherapy

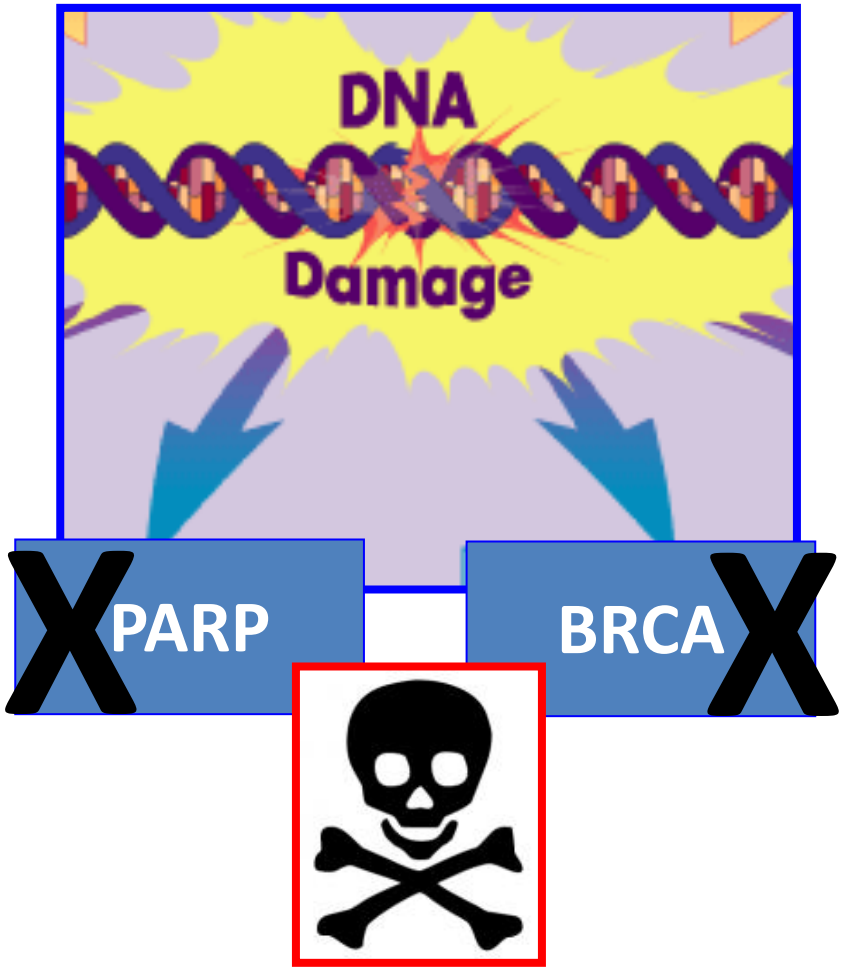
- Order of chemotherapy does not appear to influence survival
- Choose chemotherapy based on
  - Prior treatments
  - Side effects profile (hair loss, neuropathy, hand-foot syndrome, etc)
  - Other health problems (blood counts, neuropathy, diabetes, heart problems, liver function)
  - BRCA mutation status
  - Amount of active cancer/need for rapid response

DNA damage repair and BRCA

- **Everyday your DNA is damaged and also repaired.**
- **BRCA proteins participate in repair of DNA damage.**
- **BRCA mutation carriers have one normal copy and one abnormal copy of BRCA gene in their cells.**
- **Cancer cells in a BRCA carrier: 1 “lost”copy and 1 abnormal copy of BRCA -> PARP inhibitor -> cancer cells not able to repair DNA**

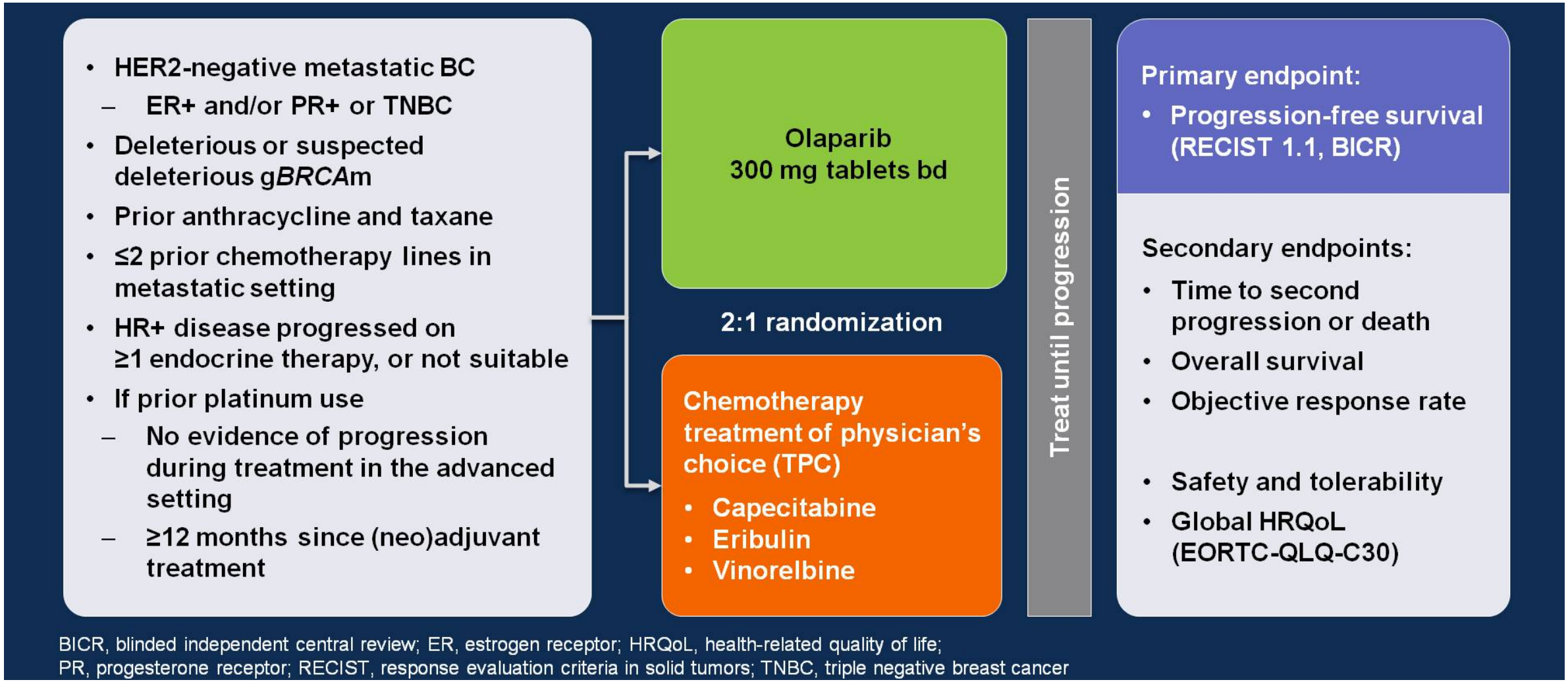
Blocking PARP affects BRCA mutant cancers more

- DNA in the BRCA mutant cancer cell is not properly repaired.
- It gets worse with addition of DNA repair inhibitors.
- Triggers cancer cell death



OlympiAD:

The first PARP inhibitor trial for gBRCA mutant breast cancer

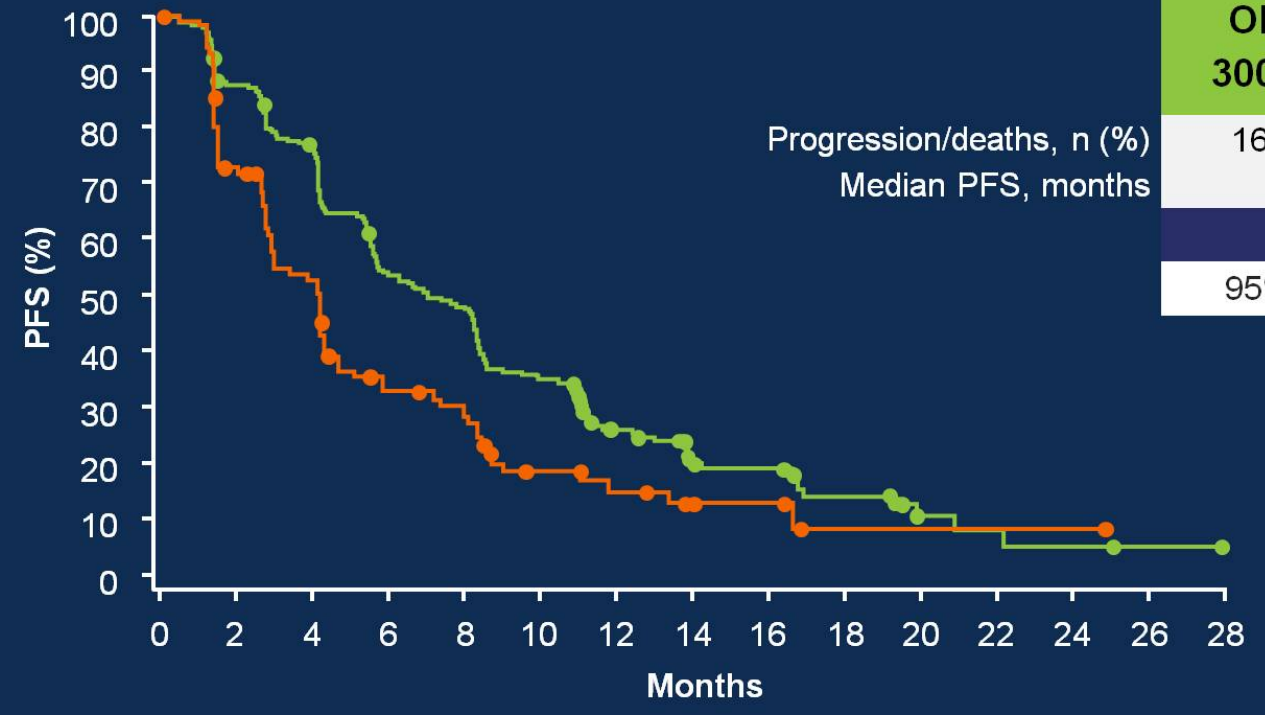


BICR, blinded independent central review; ER, estrogen receptor; HRQoL, health-related quality of life; PR, progesterone receptor; RECIST, response evaluation criteria in solid tumors; TNBC, triple negative breast cancer

Robson *et al. NEJM* 2017

OlympiAD: progression-free survival

Primary endpoint: progression-free survival by BICR



	Olaparib 300 mg bd	Chemotherapy TPC
Progression/deaths, n (%)	163 (79.5)	71 (73.2)
Median PFS, months	7.0	4.2
HR 0.58		
95% CI 0.43 to 0.80; *P*=0.0009		

At risk, n															
Olaparib 300 mg bd	205	177	154	107	94	69	40	23	21	11	4	3	2	1	0
Chemotherapy TPC	97	63	44	25	21	11	8	4	4	1	1	1	1	0	0

Robson *et al. NEJM* 2017

OlympiAD: additional findings

Compared to standard chemotherapy:

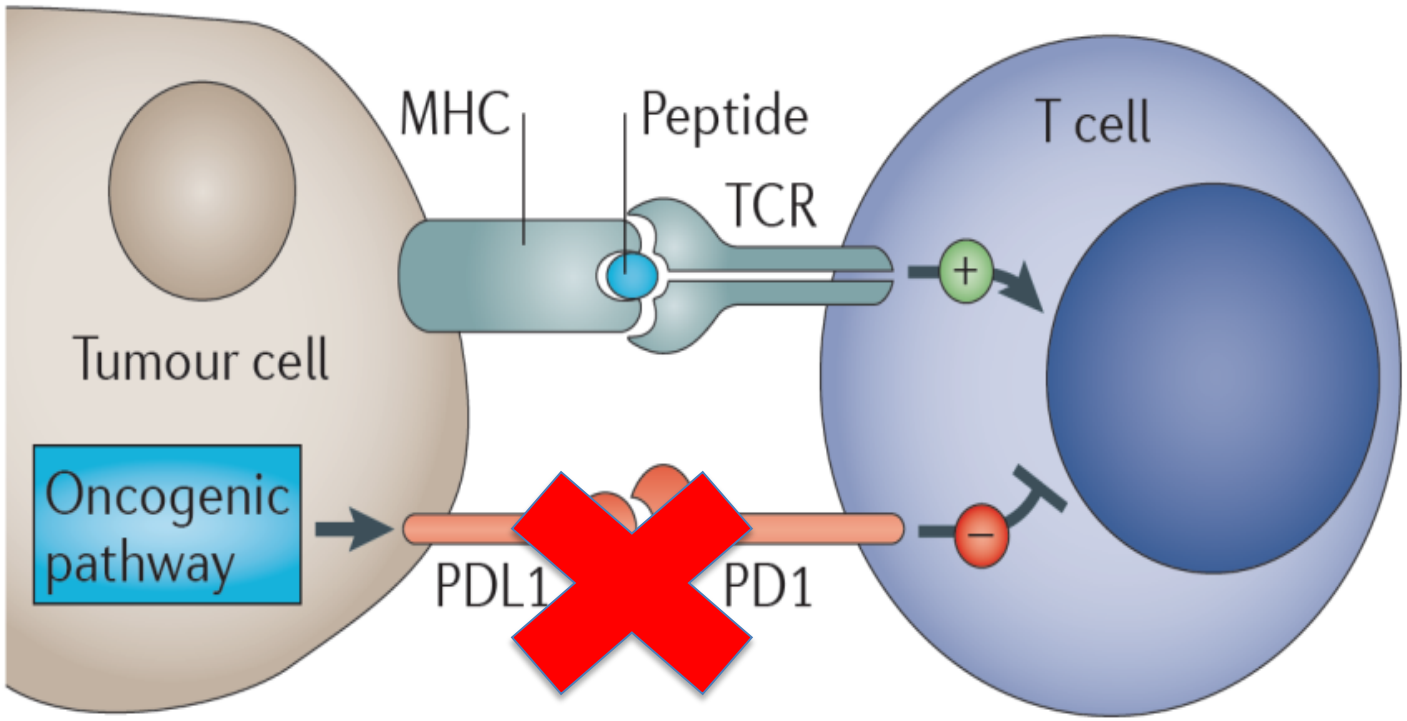
- **Similar activity regardless of prior chemotherapy exposure**
- **More effective in TNBC than ER+ breast cancer**
- **Similar activity with or without prior platinum chemotherapy**
- **Side effects generally similar:**
  Olaparib had more nausea
  Chemotherapy had more low white count
- **Olaparib had improved Quality of Life**

Olaparib (OlympiAD) and Talazoparib (EMBRACA); FDA-approved in 2018 for BRCA mutant, HER2 negative breast cancer patients with prior chemotherapy

Therapeutic approach of targeting immune systems

- Our immune systems evolved to recognize “foreign invaders” such as bacteria or viruses etc
- Our immune system also can recognize cancer cells but
  - More difficult because cancer cells are our own cells that have mutated
  - More difficult because cancers find ways to escape or hide
  - We want to avoid unnecessarily activating all of our immune cells as this can cause so much trouble such as autoimmune disease etc.

Immune checkpoint blockade



IMpassion130:

PD-L1 inhibitor plus chemotherapy for TNBC

Patients with metastatic or advanced TNBC; no prior therapy for advanced setting (prior RT or CT in curative setting allowed if ≥ 12-mo DFI); tumor evaluable for PD-L1* (N = 902)

Stratified by prior taxane use in curative setting (yes vs no), liver metastases (yes vs no), PD-L1 IC status (≥ 1% vs < 1%)

Atezolizumab 840 mg IV Q2W + nab-Paclitaxel 100 mg/m² IV on D1, 8, 15 28-day cycles (n = 451)

Placebo IV Q2W + nab-Paclitaxel 100 mg/m² IV on D1, 8, 15 28-day cycles (n = 451)

Treatment until progression or intolerable toxicity

No crossover Allowed

Survival follow-up

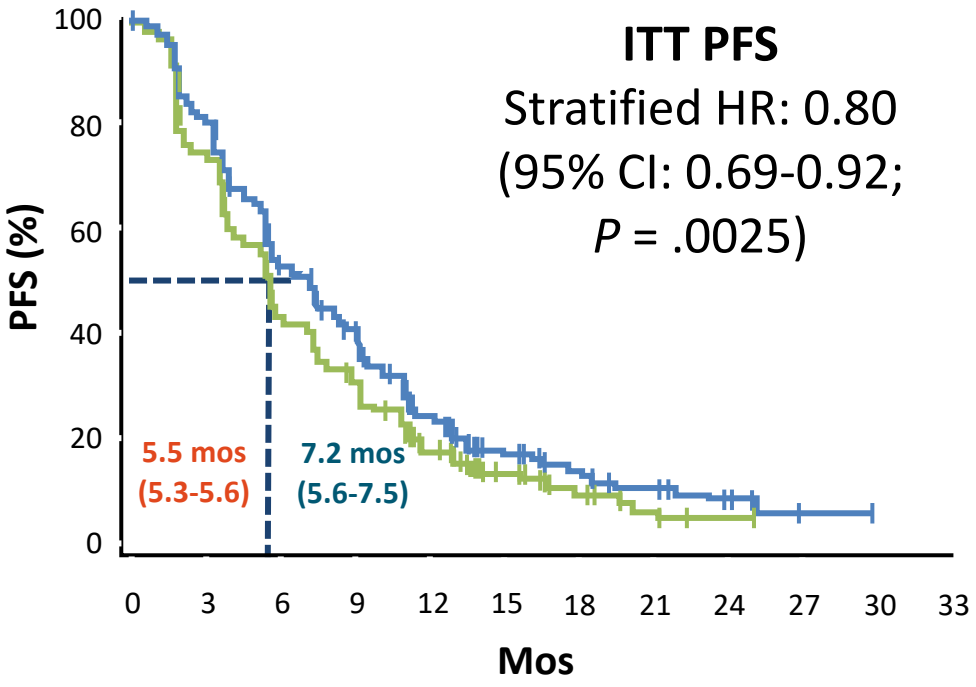
- **Coprimary endpoints: PFS and OS (ITT population and PD-L1+ subgroup)**

***By prospective central testing with SP142 PD-L1 IHC assay. 41% of patients in each arm were PD-L1+ (≥ 1 % IC).**

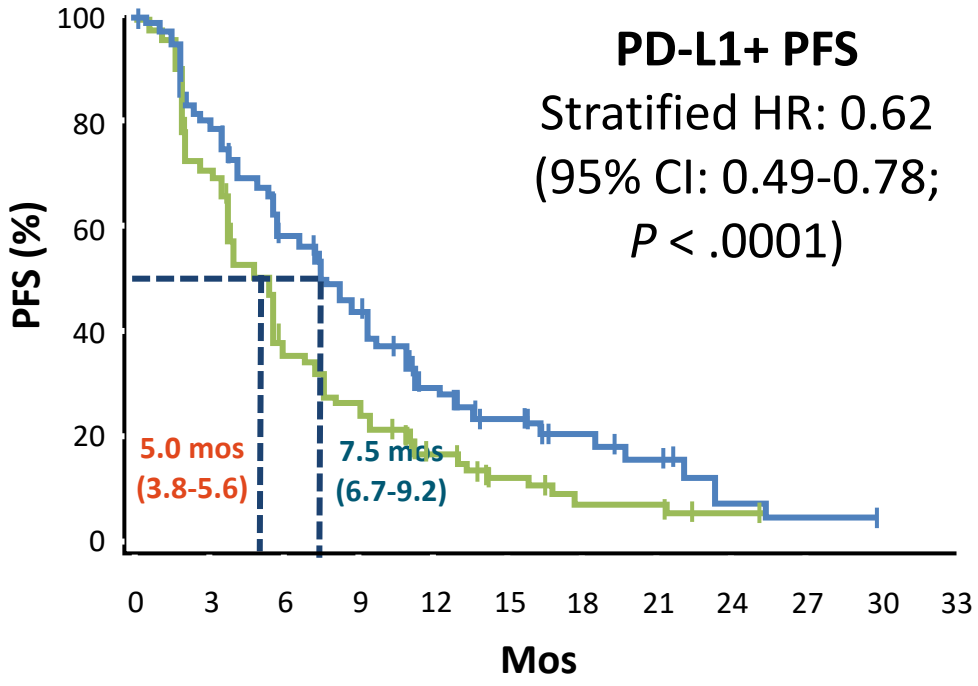
Schmid. NEJM. 2018;379:2108.

IMpassion 130: progression-free survival

ITT Population

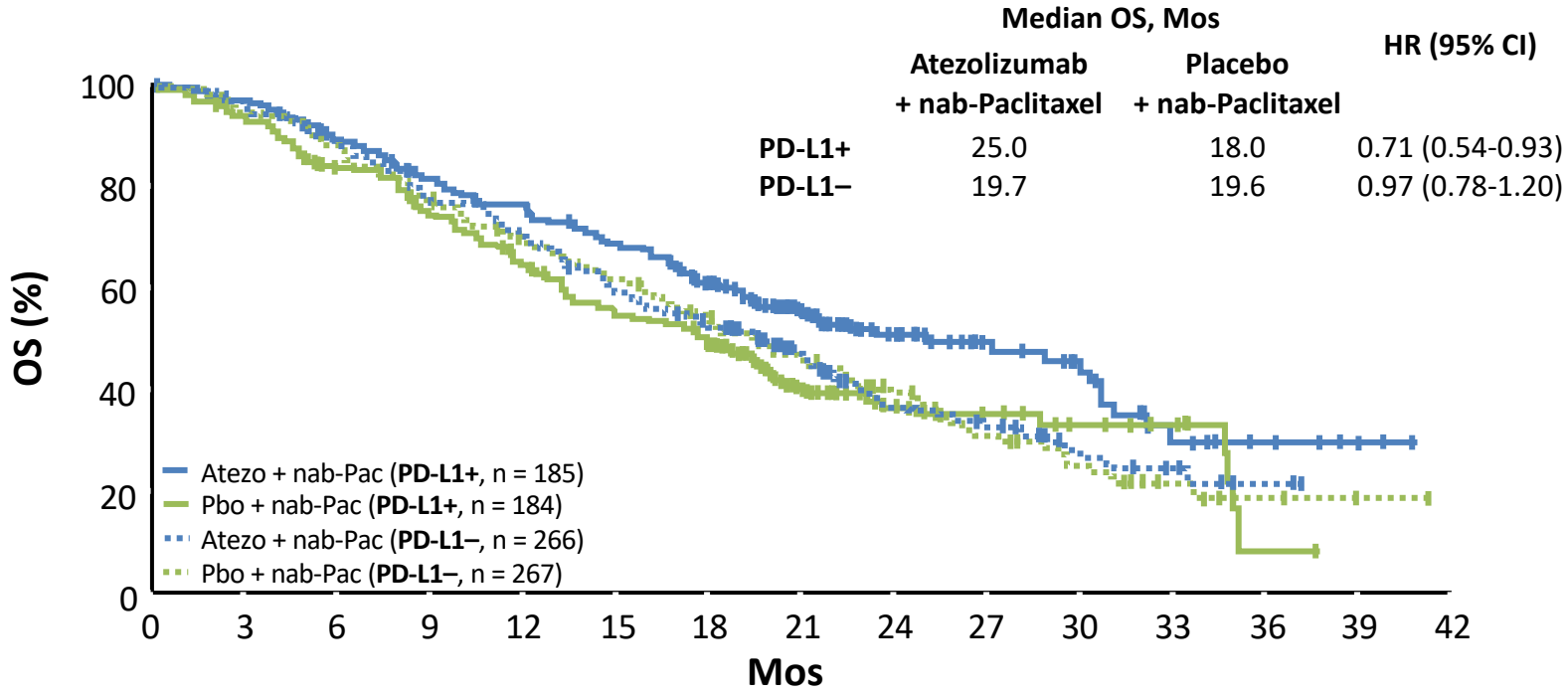


PD-L1+ Population



Schmid. NEJM. 2018;379:2108.

IMpassion130: overall survival by PD-L1 status



Treatment benefit limited to PD-L1+ tumors: FDA approval on March 8, 2019

Summary

- **TNBC is heterogenous disease with more aggressive features.**
- **BRCA mutation testing if ≤60 yo but most patients with TNBC *do not carry* a hereditary BRCA mutation.**
- **Treatments for advanced/metastatic disease**
  - **Doublet chemotherapy for visceral crisis (no survival benefit, increased toxicity)**
  - **If BRCA1/2+, PARPi monotherapy (OlympiAD, EMBRACA)**
  - **Biopsy if tumor changes behavior, check PD-L1 (Ventana SP142 assay)**
    - **If PD-L1+, atezolizumab + nab-paclitaxel**
    - **If PD-L1- or progressed, single agent chemotherapy**

Triple Negative Breast Cancer
Part 2

Advances in the systemic treatment of TNBC; recently approved drugs and clinical trials

Jung-Min Lee, MD
NIH Lasker Clinical Research Scholar
Women's Malignancies Branch, Center for Cancer Research
National Cancer Institute

What do different clinical trial phases do?

- **Phase 1 clinical trials**
  - ask questions regarding safety and side effects to help define the best dose(s) for further study
  - may often be open to a wide array of cancer types
  - do not have benefit as a primary endpoint

- **Phase 2 clinical trials**
  - treat a more homogeneous population of patients
  - use a predefined and consistent dose and schedule
  - look for signs of activity as the primary endpoint of therapy
  - may be randomized, between regimens or with placebo controls

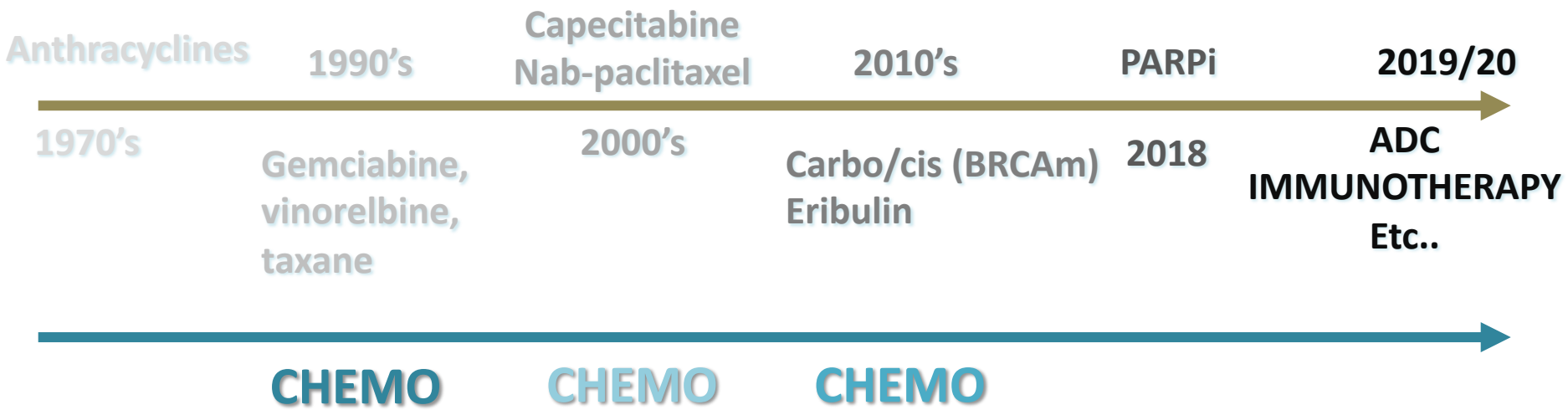
In courtesy of Dr E.C.Kohn

What do different clinical trial phases do?

- **Phase 3 clinical trials**
  - compare a new promising approach to standard therapy(s)
  - have intent to change clinical practice patterns (eg FDA registration)
  - may do so by showing superiority or non-inferiority to the standard of care
  - may commonly use blinded treatment and placebo controls

In courtesy of Dr E.C.Kohn

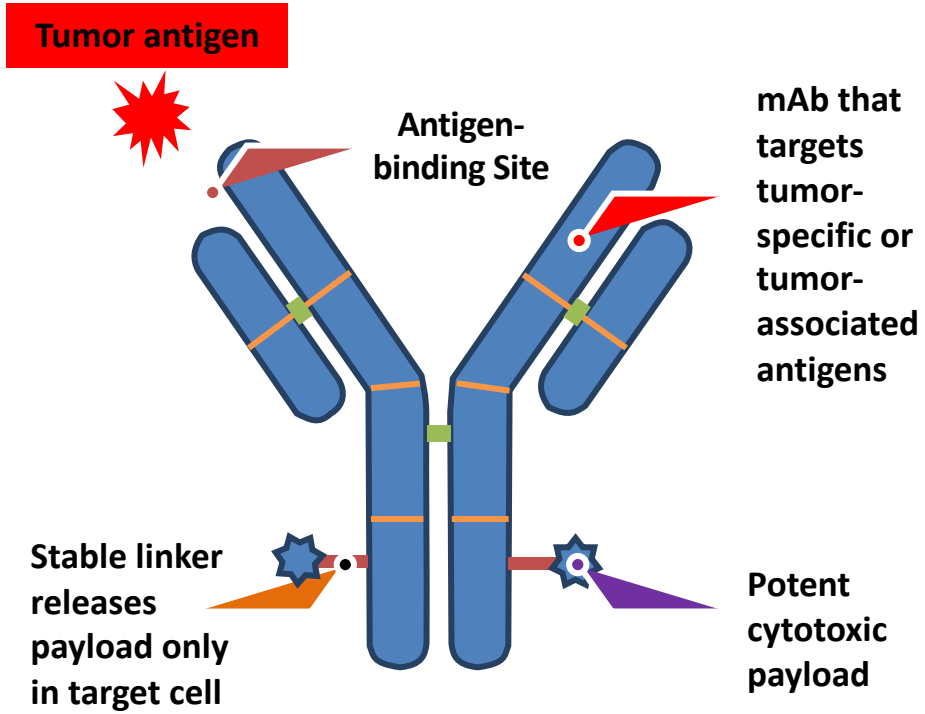
Progress in the systemic treatments of TNBC



PARP inhibitors (2018)
Immunotherapy plus chemo (2019)
Antibody drug conjugates (2020)

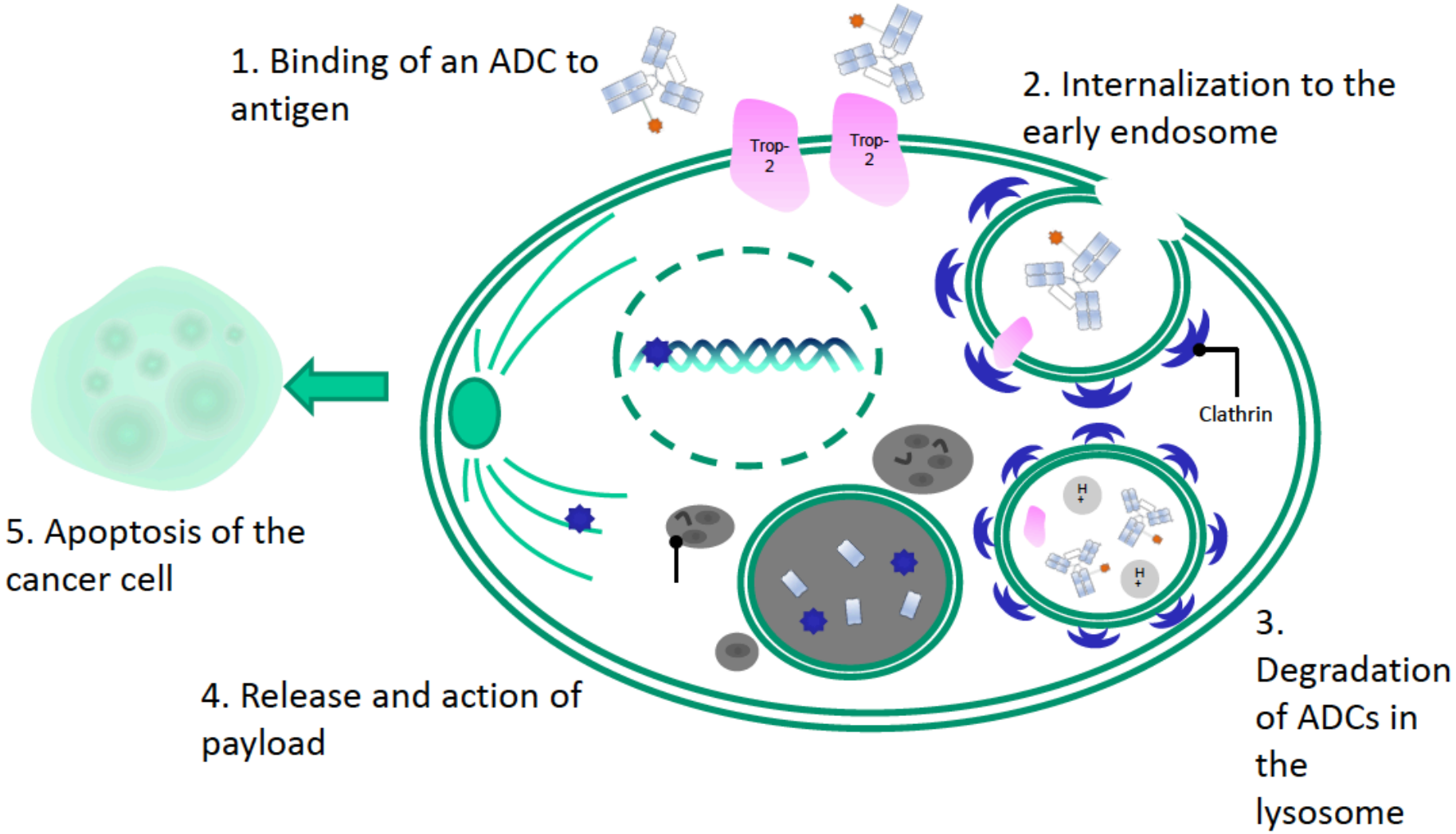
Antibody-drug conjugates (ADC)

- **Tumor antigen:** abundant in tumors, minimal in normal tissues; internalized upon ADC binding
- **Antibody:** high affinity, avidity for antigen; internalized
- **Linker:** stable in plasma; efficient release of cytotoxic agent inside tumor cells
- **Payload:** drug cytotoxic to targeted tumor cells; not hydrophobic; must be potent since limited number of molecules can be attached to antibody



Thomas. Lancet Oncol. 2016;17:e254.

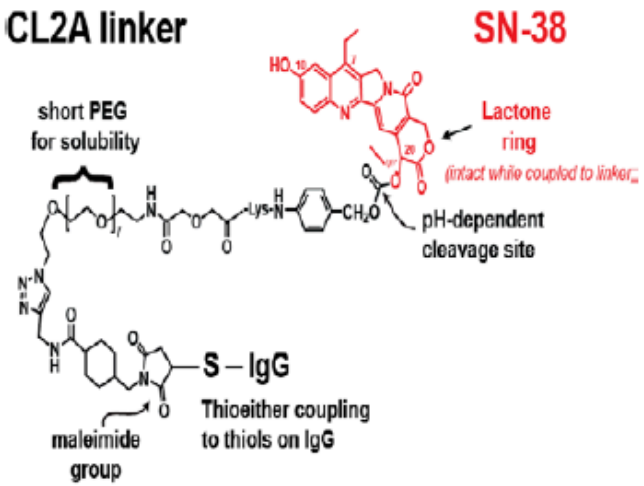
Selective delivery of toxic payload

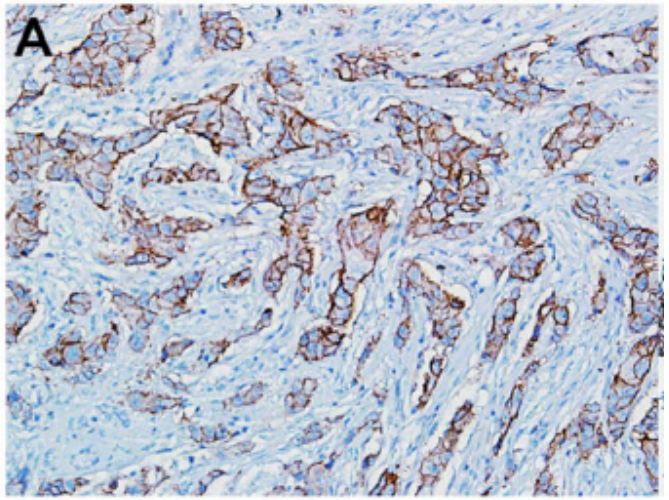


Nagayma et al. Target Onc 2017

Sacituzumab govitecan; ADC targeting trop-2 in TNBC

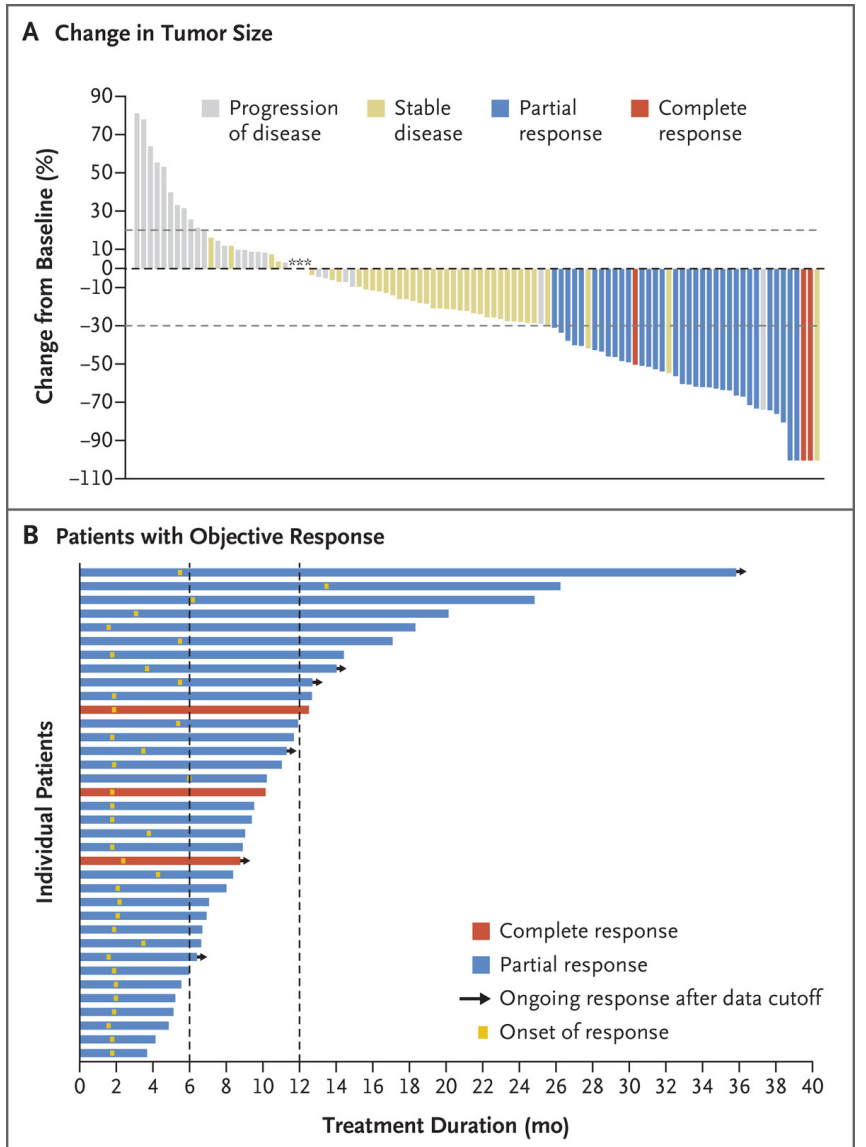
- Trop-2/EGP-1 is a pan-epithelial cancer antigen
- Trop-2 is seen in all types of breast cancer but especially more in luminal A, basal and TNBC
- Trop-2 expression does not appear to be associated with age, menopause or stage
- SN-38: the active metabolite of irinotecan





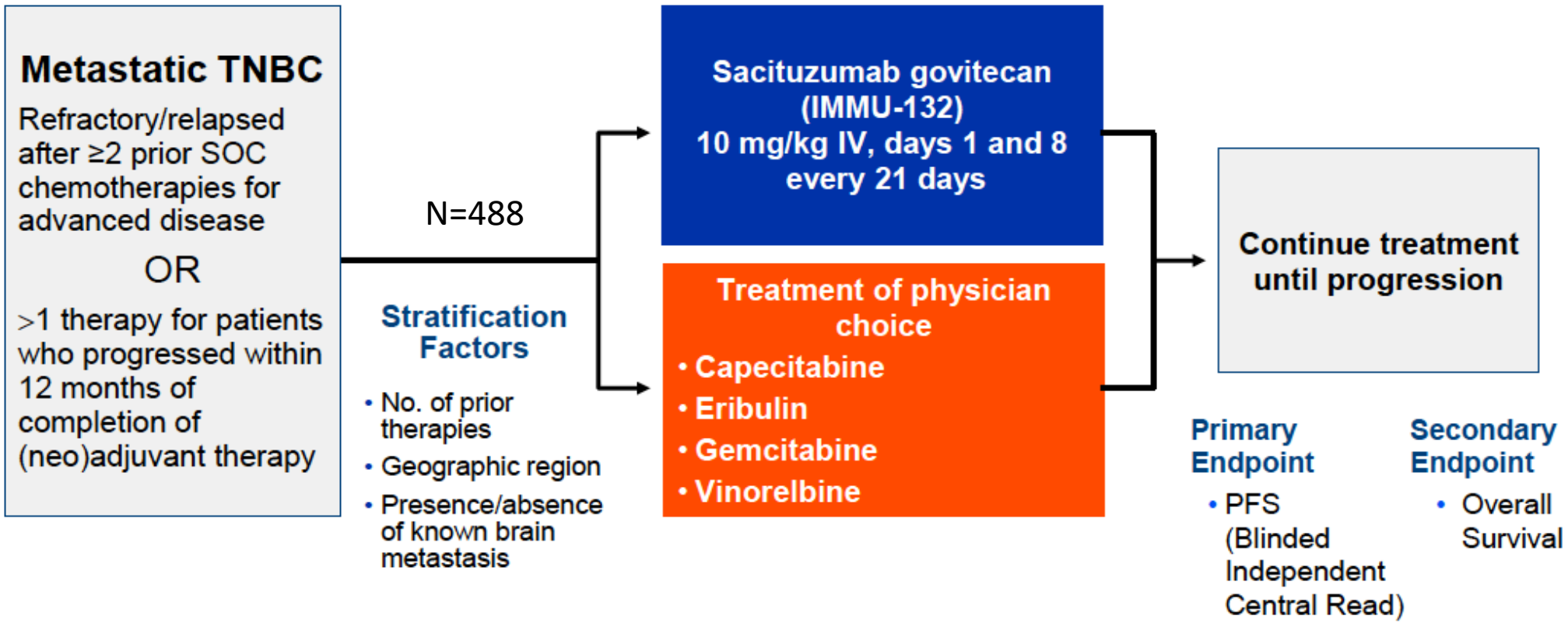
Sacituzumab Govitecan
durable response in phase I/II trial

- 108 heavily pretreated patients with TNBC (median of 3 previous therapies; range, 2-10).
- The response rate was 33.3% (95% CI, 4.9-10.8), and the median duration of response was 7.7 months (95% CI, 4.9-10.8).
- Median progression-free survival was 5.5. months (95% CI, 4.1-6.3), and overall survival was 13.0 months (95% CI, 11.2-13.7).



Bardia et al. NEJM 2019

ASCENT phase 3



Opened in late 2017

cancernetwork.com/view/s ascent pfs sacituzumab - Google Search rated-in-breast-cancer-risk-predication-models

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Phase III ASCENT Study of Metastatic TNBC Halted Due to Compelling Efficacy

April 10, 2020
Hannah Slater

April 10, 2020

RELEVANT TOPICS

The decision to halt the study was based on the unanimous recommendation by an independent data safety monitoring committee during its routine review of the ASCENT study.

The phase III confirmatory ASCENT study will be halted due to compelling evidence of efficacy, according to Immunomedics, the company leading the study.[1]

The decision was based on the unanimous recommendation by an independent data safety monitoring committee (DSMC) during its routine review of the ASCENT study.

ASCENT is designed to validate the promising safety and efficacy data of sacituzumab govitecan observed in a phase II study of heavily pretreated patients with metastatic triple-negative breast cancer (mTNBC). The primary endpoint for the study is progression-free survival, and secondary endpoints include overall survival and objective response, among others.

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FDA NEWS RELEASE

FDA Approves New Therapy for Triple Negative Breast Cancer That Has Spread, Not Responded to Other Treatments

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Press Announcements

For Immediate Release: April 22, 2020

Today, the U.S. Food and Drug Administration granted accelerated approval to Trodelvy (sacituzumab govitecan-hziy) for the treatment of adult patients with triple-negative breast cancer that has spread to other parts of the body. Patients must have received at least two prior therapies before taking Trodelvy.

"Metastatic triple-negative breast cancer is an aggressive form of breast cancer with limited treatment options. Chemotherapy has been the mainstay of treatment for triple-negative breast cancer. The approval of Trodelvy today represents a new targeted therapy for patients living with this aggressive malignancy," said Richard Pazdur, M.D., director of the FDA's Oncology

Content current as of:
04/22/2020

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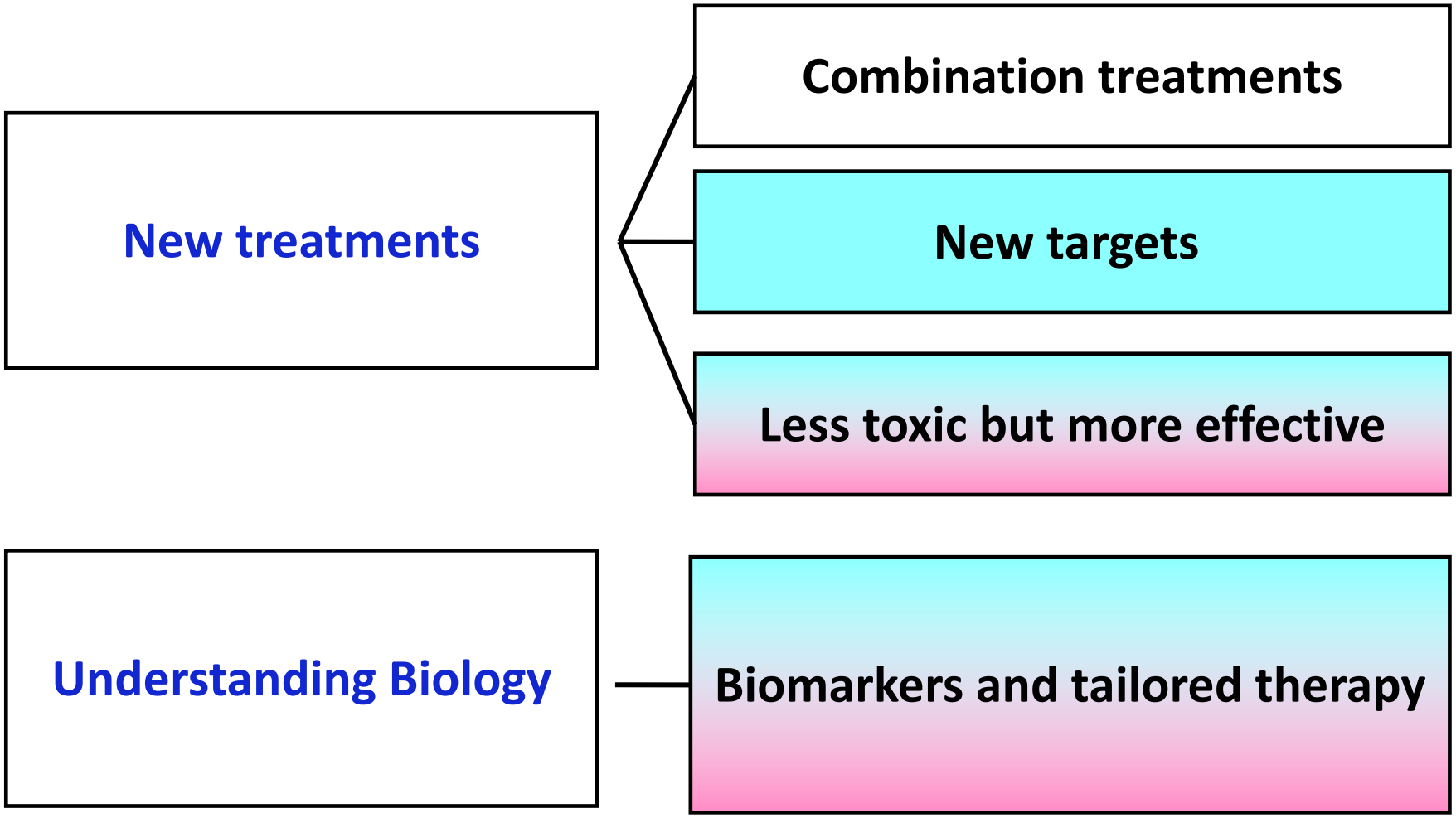
recently announced the study met the primary endpoint

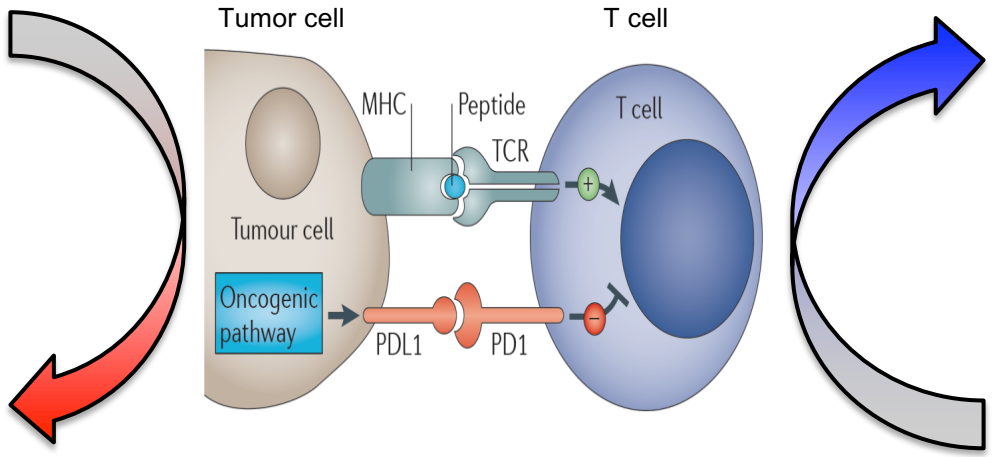
Ongoing research efforts to improve the outcome of TNBC



Clinical trials

Taking PARP inhibitors to the next level:

Augmenting Immunotherapy?



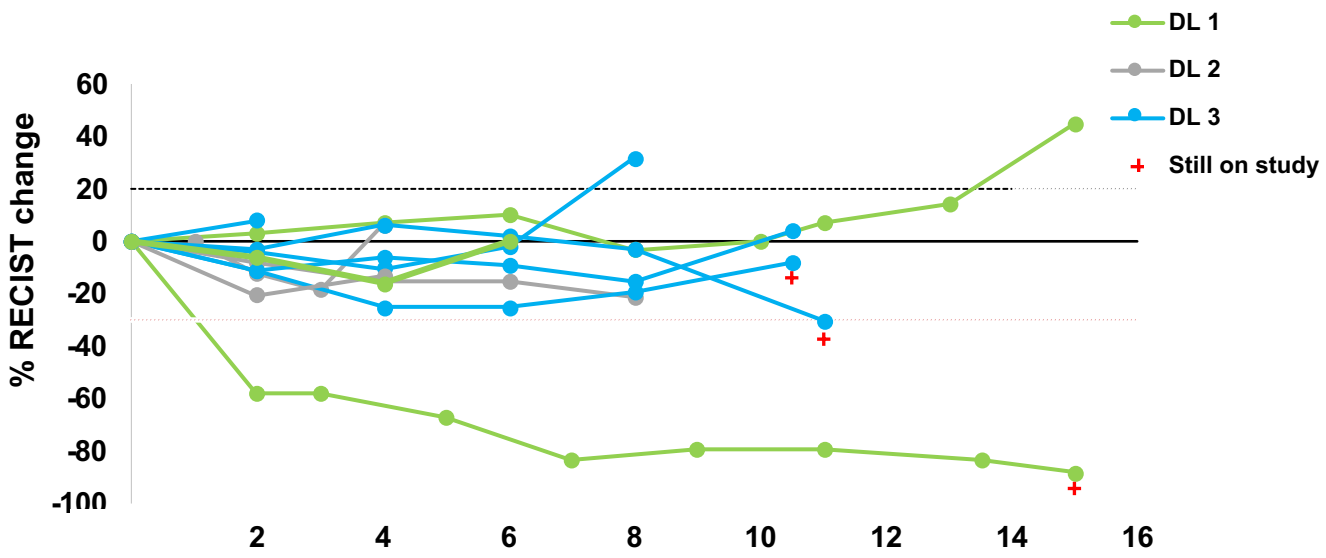
⬆ Tumor mutational burden through DNA damage

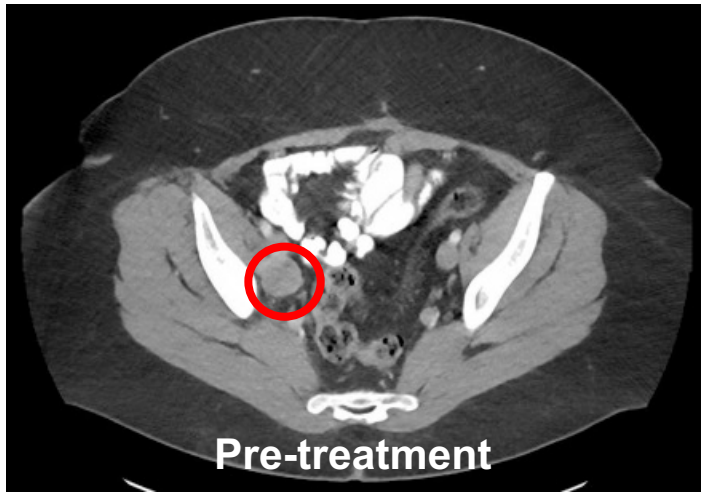
Immunomodulation by PARP inhibition

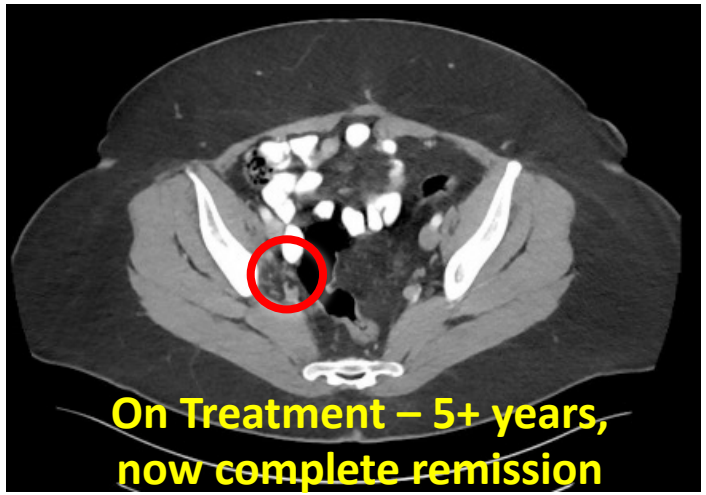
⬆ PD-L1 upregulation and IFNg expression

First-in-human combination of PARP inhibitor + anti-PD-L1

Phase I olaparib + durvalumab





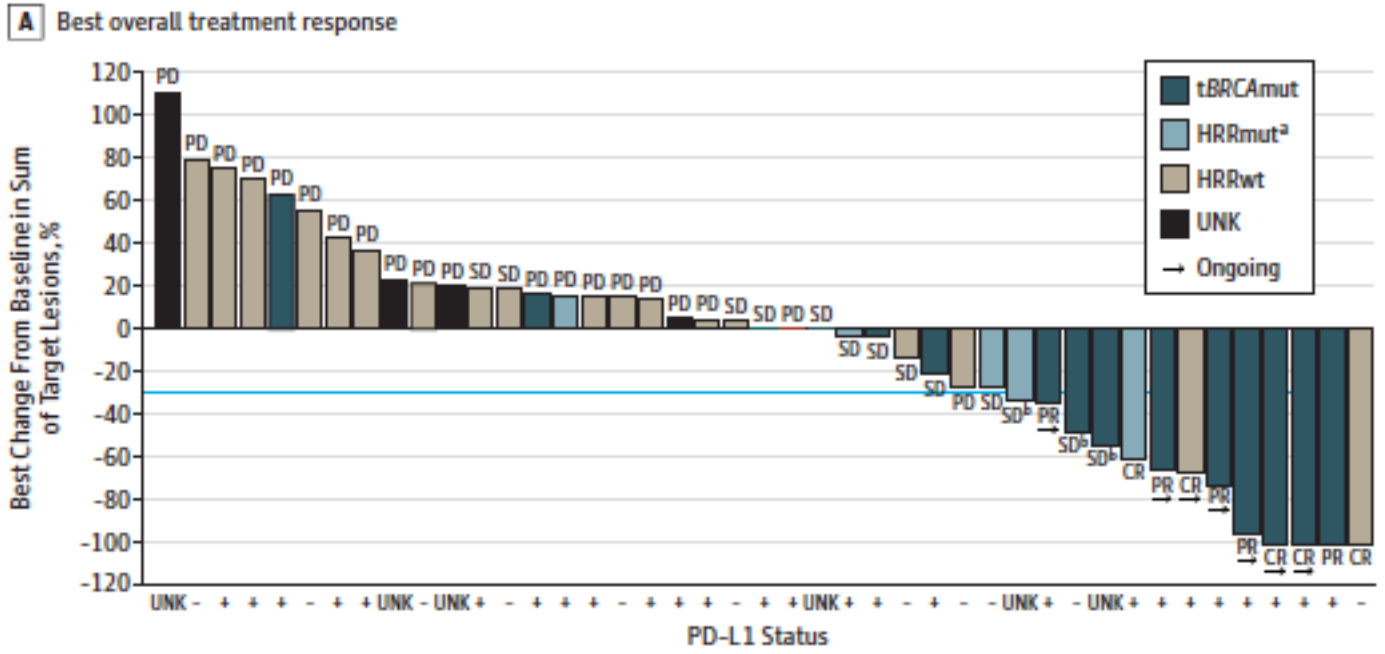


NCT02484404

Lee *et al, J Clin Oncol* 2017

Phase I/II TOPACIO study of pembrolizumab and niraparib (KEYNOTE 162) in advanced/metastatic TNBC

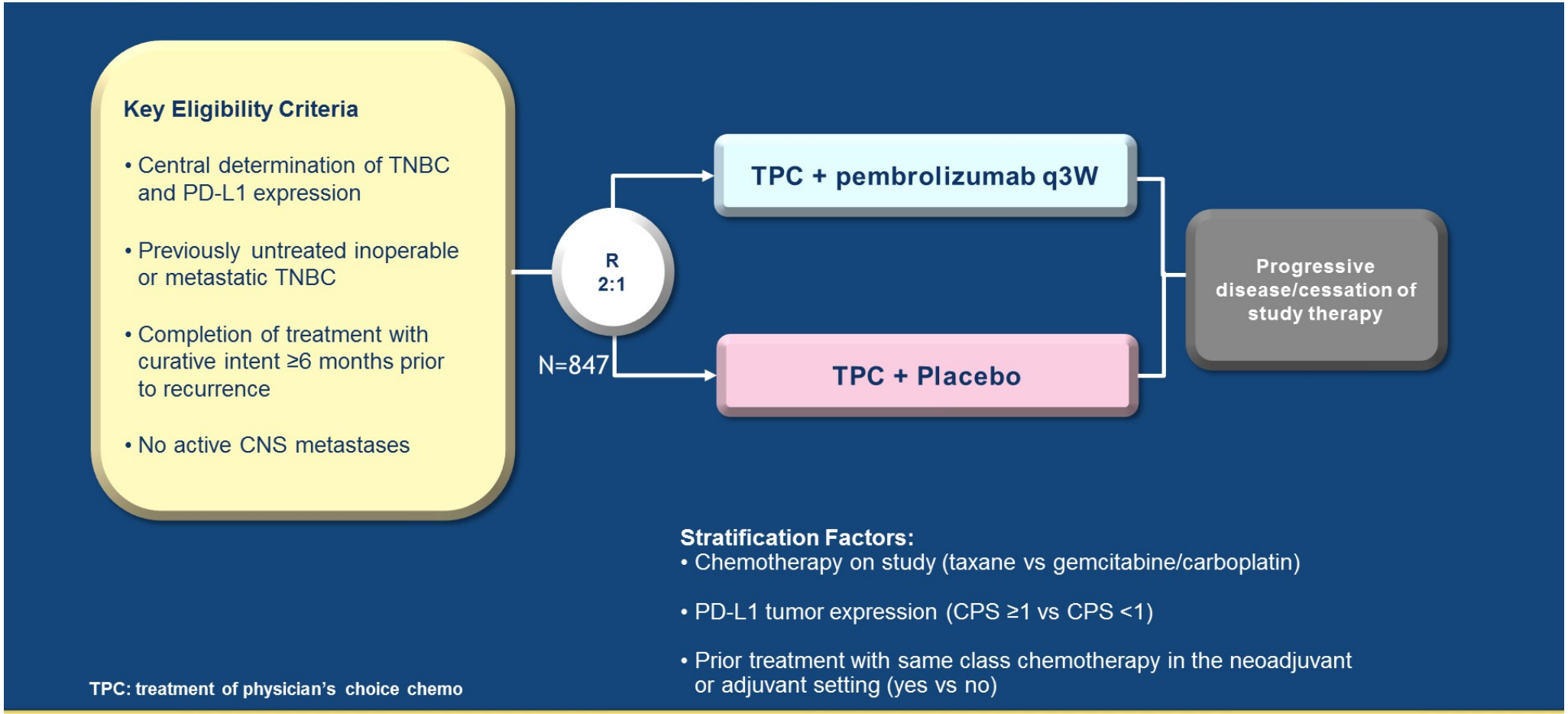
- **Early durable clinical activity (response rate of 22% (10/47) and disease control rate of 49 % (23/47)**
- **Activity was seen not only in BRCA mutant TNBC but also in BRCA wild type TNBC**



Vinayak et al, JAMA Onc 2019

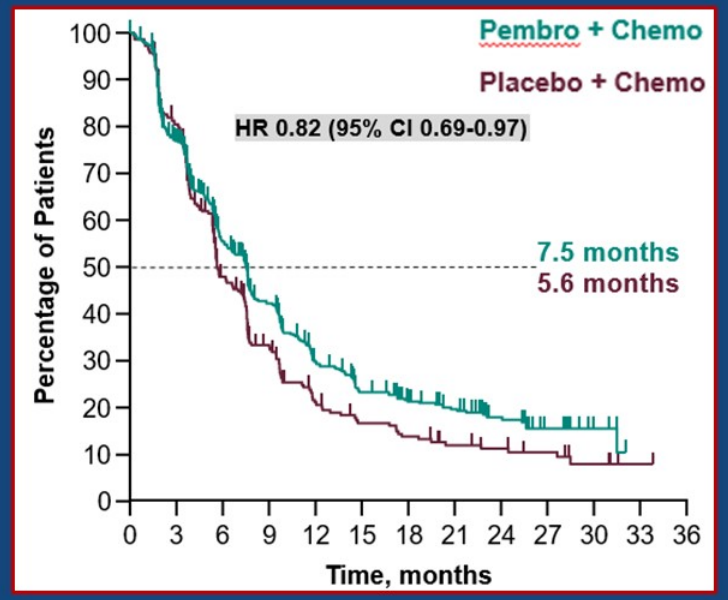
KEYNOTE 355

pembrolizumab plus chemotherapy in 1st line metastatic TNBC



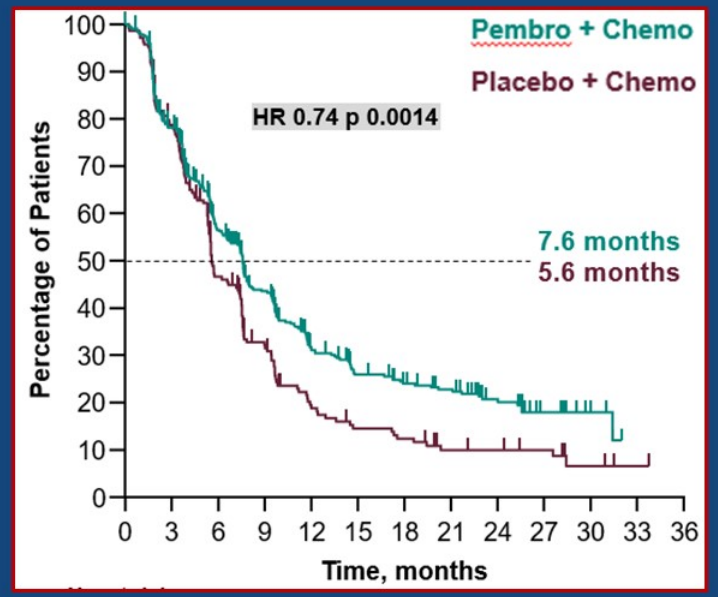
KEYNOTE 355: progression-free survival

ITT



Statistical significance was not tested due to the prespecified hierarchical testing strategy

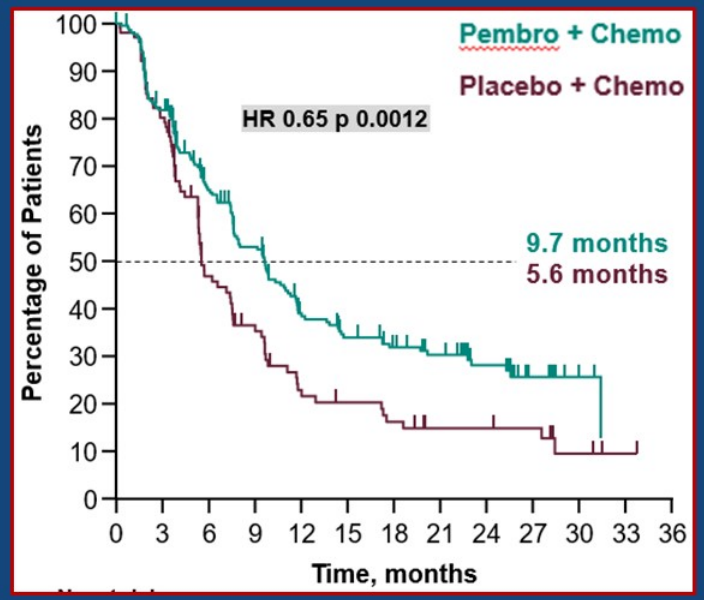
PD-L1 CPS ≥1



Prespecified *P* value boundary of 0.00111 not met

75% of pts

PD-L1 CPS ≥10



Prespecified *P* value boundary of 0.00411 met

38% of pts

Results of key immunotherapy trials in advanced/metastatic TNBC thus far

Setting	Study name	Study treatment	Outcome - ITT
Neo adjuvant	KEYNOTE-522[1]	Paclitaxel+Carboplatin → AC/EC Pembrolizumab/Placebo (24 wks) Pembro/placebo (29 weeks)	pCR 64.8% with P vs 51.2%
	NeoTRIPa PDL1[2]	Nab-Paclitaxel+Carboplatin Atezolizumab/Placebo (24 wks) AC/EC/FEC (12 weeks)	pCR 43.5% with A vs 40.8%
1L Metastatic	IMpassion 130[3]	Nab-paclitaxel +/- Atezolizumab	PFS: HR 0.80, p =0.0021
	KEYNOTE-355[4]	Pembrolizumab vs Nab-paclitaxel/ Paclitaxel/Carboplatin+Gemcitabine	PFS: HR 0.82 (0.69-0.97)

In courtesy of 2020 ASCO Presentation By Erika Hamilton

1. P. Schimd et al ESMO 2019
2. L. Gianni et al SABCS 2019 GS3-04
3. P. Schimd et al Lancet Oncol 2020; 21: 44-59
4. J. Cortes et al ASCO 2020

Examples of ADCs in trials for breast cancer

Drugs	Targets
IMMU-132	Trop2
U3-1402	HER3
DS-8201a	HER2
SGN-LIV1A	LIV1
DS-1062	Trop2

- Different ADC combinations either with chemotherapy or targeted drugs e.g., PARP inhibitor or immunotherapy, etc.
- Various settings including different treatment life cycle: adjuvant vs neoadjuvant, or primary vs late-line therapy, brain metastasis yes or no etc.

Other targets and drugs

- AKT1, PTEN, PIK3CA; Ipatasertib, capivasert, etc.
- Androgen receptor
- DNA repair inhibitors
- Cell cycle regulators; ATRi or CHK1i
- MYC
- Bromodomain inhibitors, CDK7 or CDK9 inhibitors, aurora kinase inhibitors

Summary

- Patients with TNBC constitute subsets of the patient population with unmet needs
- Continue to dissect and advance understanding in TNBC biology
- Tailored therapy for metastatic disease
  - Doublet chemotherapy for visceral crisis (no survival benefit, increased toxicity)
  - If BRCA1/2+, PARPi monotherapy
  - Biopsy if tumor changes behavior, check PD-L1 (Ventana SP142 assay)
    - If PD-L1+, atezolizumab + nab-paclitaxel
    - If PD-L1- or progressed, single agent chemotherapy
  - Newer agents/combinations (Sacituzumab Govitecan-hziy) and clinical trials!

TNBC trials at NCI in Bethesda, MD

- **Phase II trial Olaparib plus durvalumab (TNBC arm)**
- **Phase I/Ib: BN-Brachyury, entinostat, adotrastuzumab emtansine and M7824 in advanced stage breast cancer (BrEAsT) (TNBC arm, open also at the OSU)**

- **Travel is provided for patients living beyond a defined travel limit once enrollment is complete**
- **Small allowance for travelers to assist with outpatient costs while in Bethesda**
- **Drugs, tests, inpatient (Bethesda) care provided at no cost**
- **Patient referrals: Cynthia Boyle, RN, Oncology Referral Nurse, NCI Referral Office**
- **cynthia.boyle@nih.gov, Ph: 240-760-6006 (Direct Line), Fax: 301-451-5433, Toll Free: 888-624-1937 option 4 (Referral Office Line)**

Thank you for your attention