STANFORD
CANCER INSTITUTE

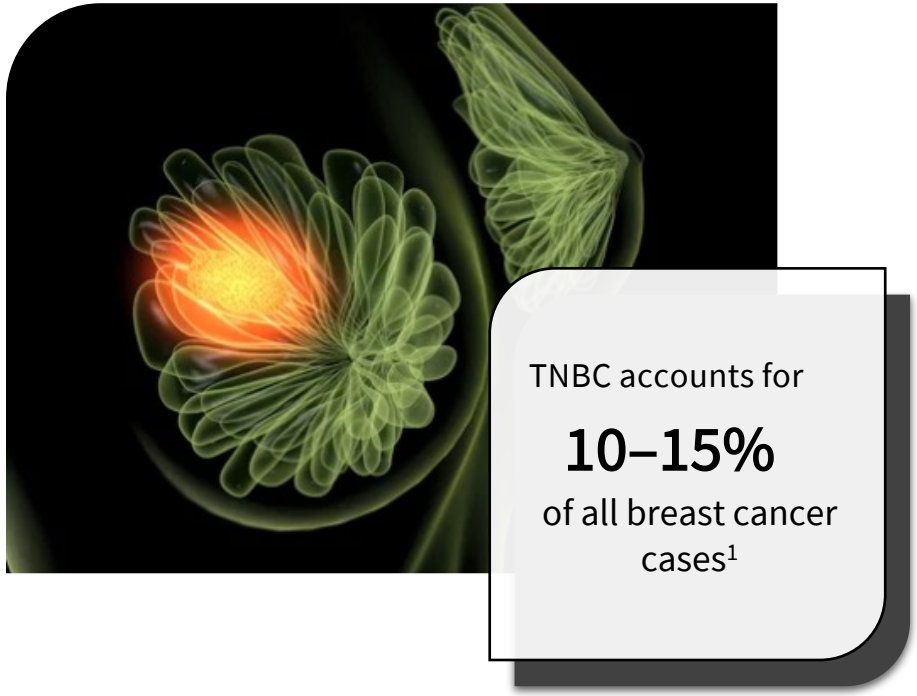
Therapy of Early TNBC: Regulating Intensity

June 2022

Mark Pegram, M.D.
Susy Yuan-Huey Hung Professor of Oncology
Medical Director, Clinical and Translational Research Unit
Associate Dean for Clinical Research Quality
Stanford University School of Medicine

Triple-negative breast cancer (TNBC) is the most aggressive breast cancer subtype

TNBC is highly invasive, exhibiting high metastatic potential, early relapse and poor outcomes



More likely to occur in premenopausal women aged 40–50 years old[1,2]

~46% of TNBC patients will have distant metastasis.[2]
Median survival after metastasis is only 13.3 months

Five-year mortality rate is 30%[2]

- **Varies by ethnicity/race**

NH White:	**11%**
NH Black:	**26%**
Hispanic:	**17%**

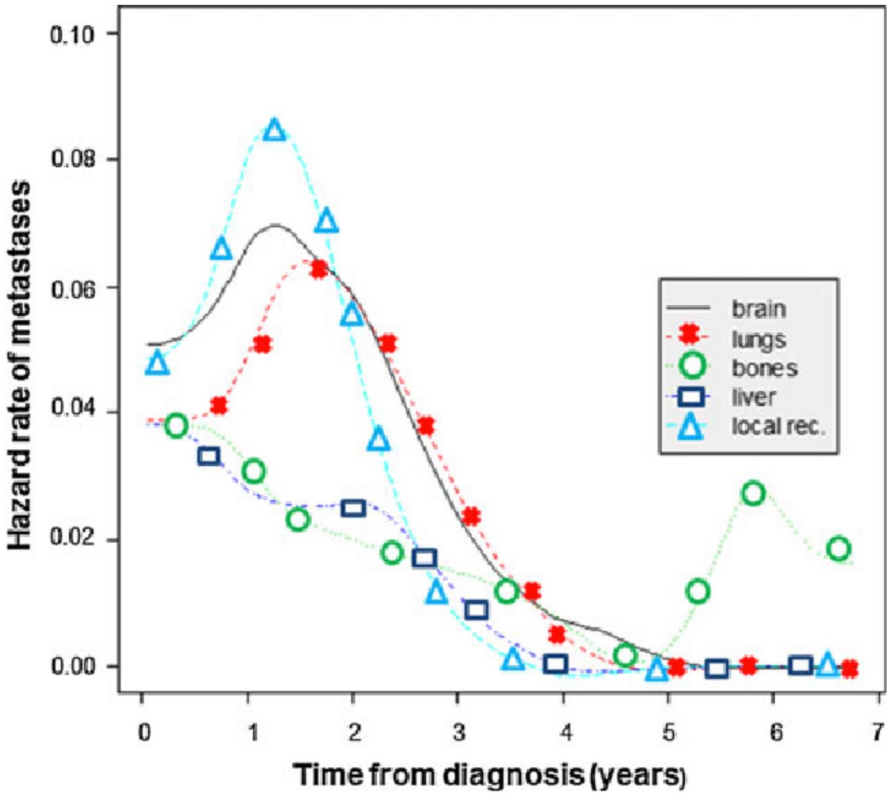
TNBC = triple-negative breast cancer.

1. Furlanetto J and Loibl S. *Breast Care* (Basel) 2020;15:217–226. 2. Schrodi S, et al. *Ann Oncol.* 2021;S0923-7534(21)04218-6. doi: 10.1016/j.annonc.2021.08.1988 [Online ahead of print]. 3. Vi

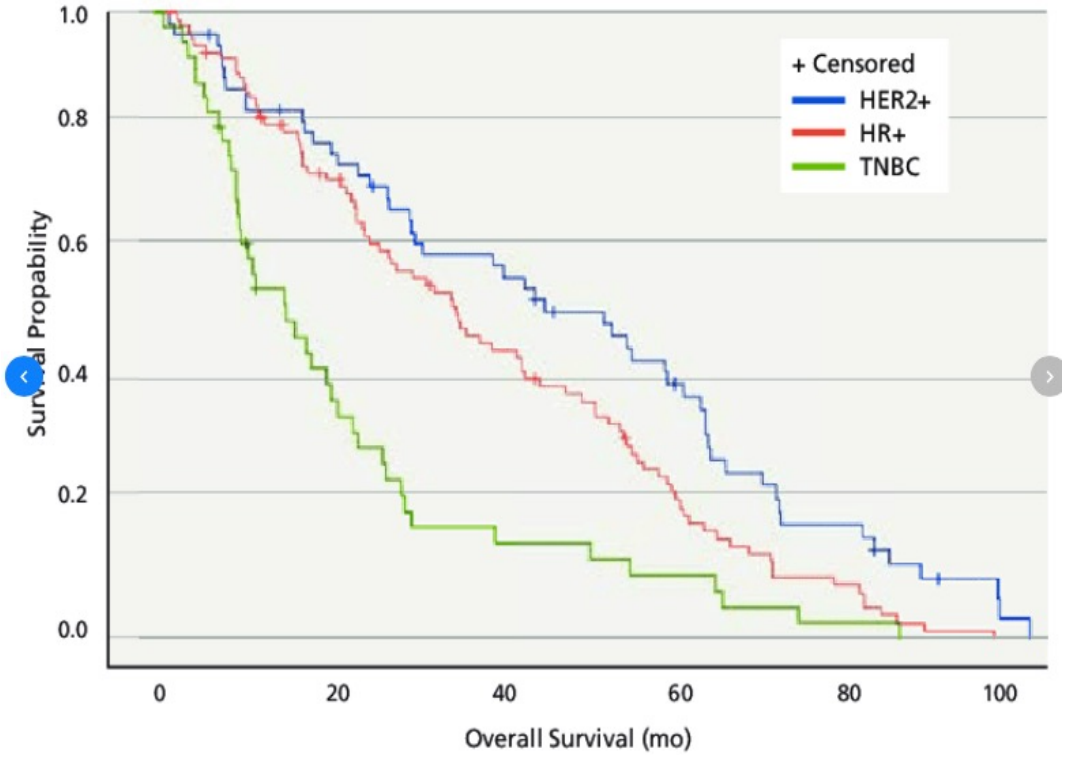
TNBC: Remains an area of unmet need

TNBC represents ~15% of the 279,000 new breast cancer diagnoses in 2020

Recurrence in first 1-3 years



Poorest overall survival



mPFS ~3-6mo

mOS ~12mo

Dent et al Clin Cancer Res 13(15):4429-34, 2007

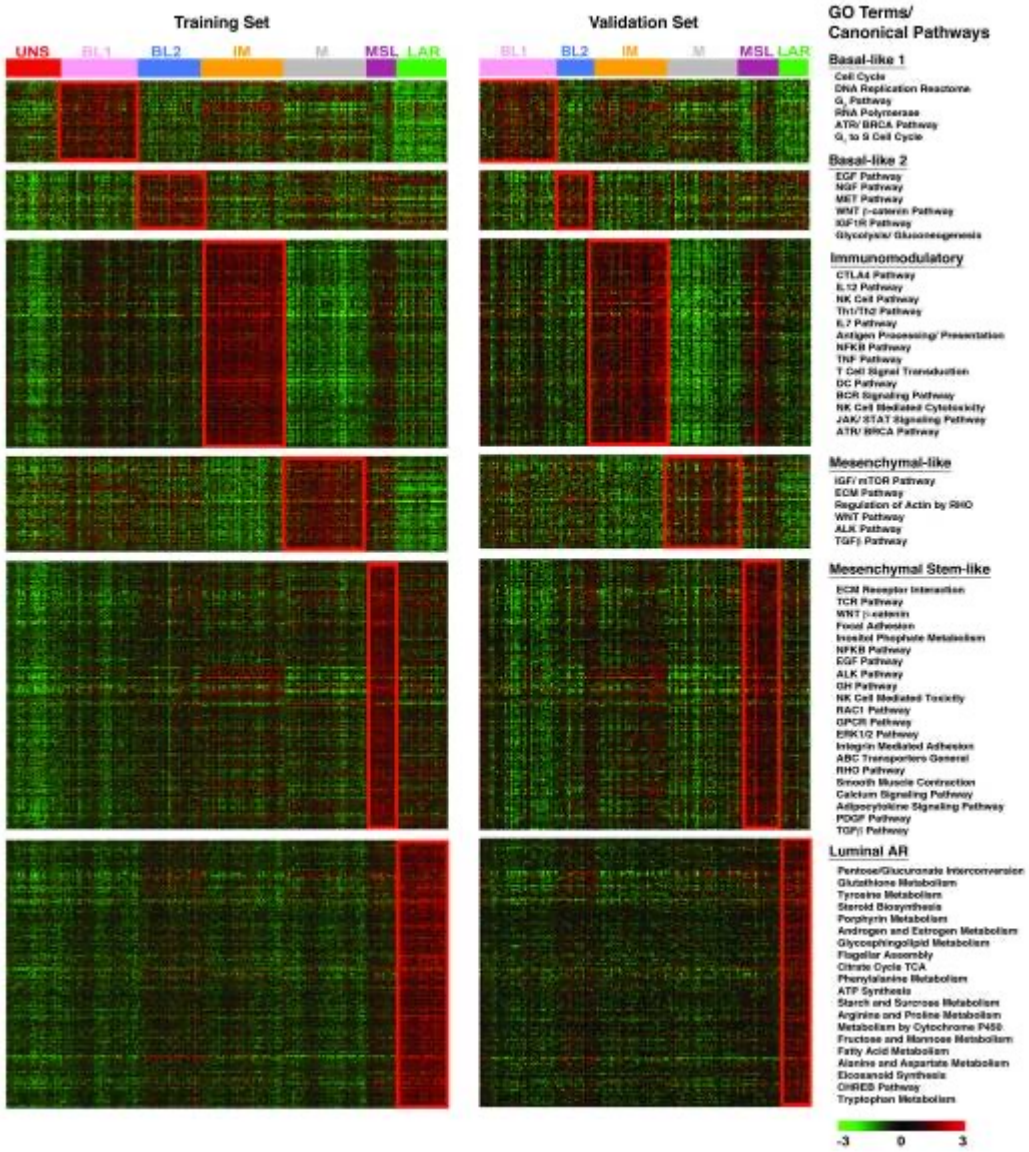
Seah DS et al JNCCN 12(1):71-80, 2014

Pogoda et al Med Onc 2013

Identification of Human TNBC Subtypes

Lehmann, Bauer, Chen, et al.,
J Clin Invest. 2011 Jul;121(7):2750-67.

Lehmann BD,…Pietenpol JA, et al.
PLoS One. 2016; 11(6):e0157368.



1. Basal-like 1: cell cycle, DNA repair and proliferation genes

2. Basal-like 2: Growth factor signaling (EGFR, MET, Wnt, IGF1R)

   - IM: immune cell processes (medullary breast cancer)

3. M: Cell motility and differentiation, EMT processes

   - MSL: similar to M but growth factor signaling, low levels of proliferation genes (metaplastic cancers)

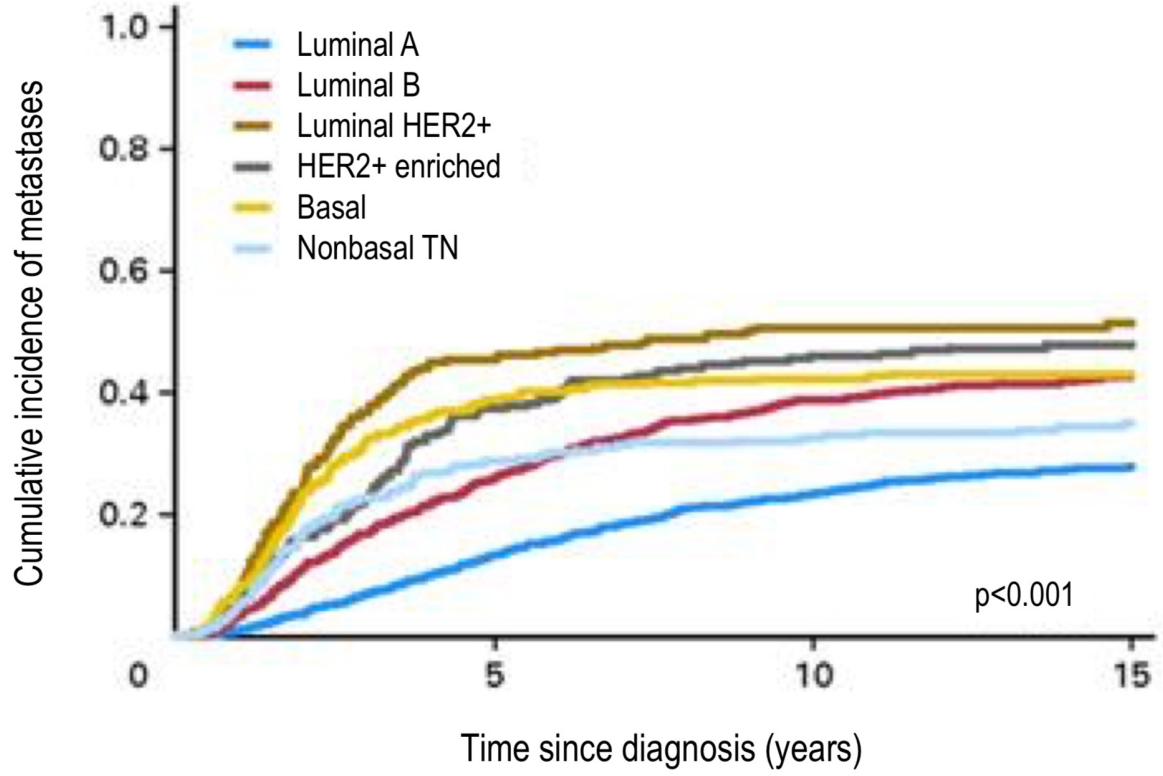
4. LAR: Androgen receptor and downstream genes, luminal features

Microarray Expression Analysis: Breast Tumor Subtype Predictions

Department of Genetics, Stanford University
School of Medicine, Stanford, CA 94305, USA.

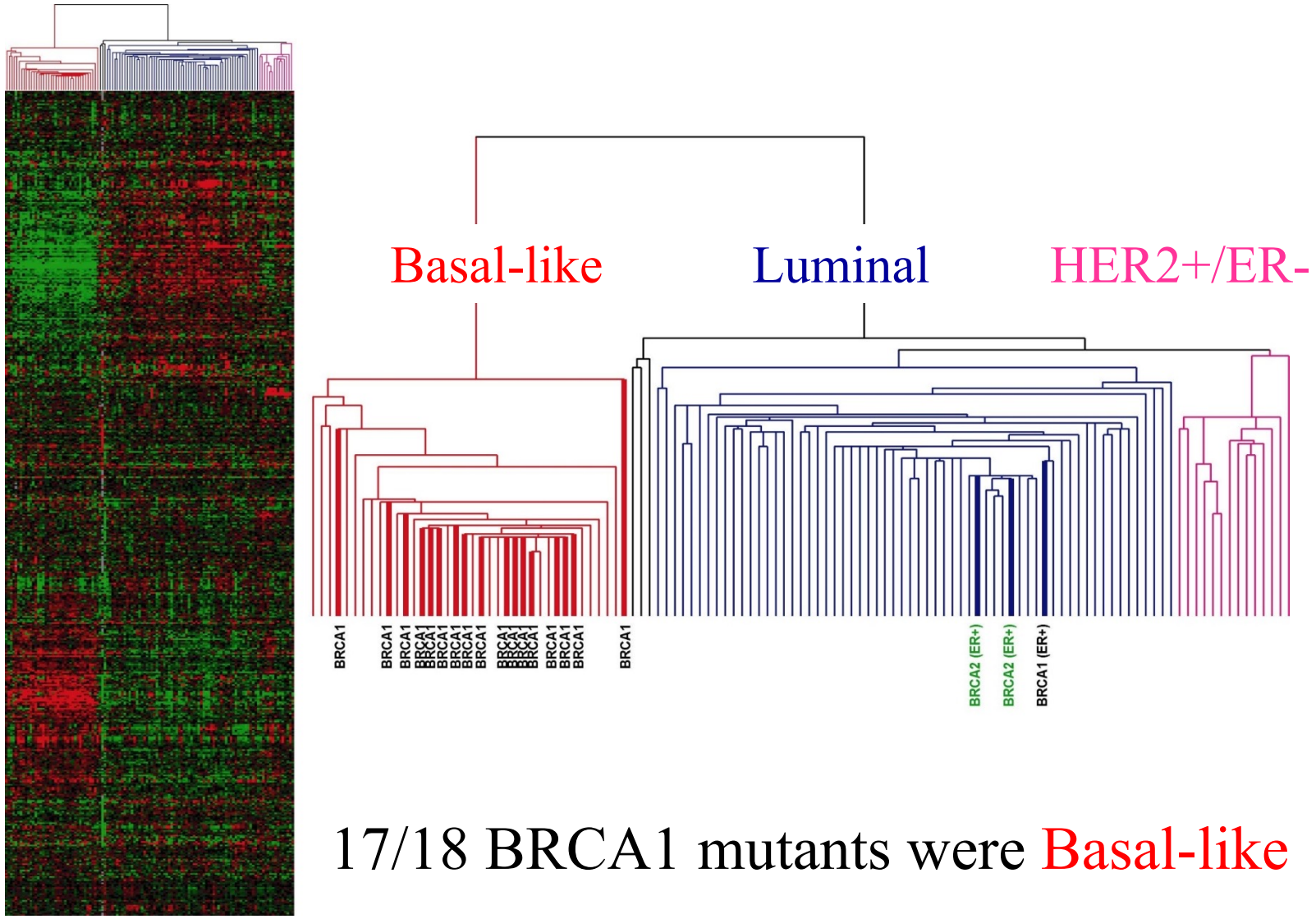
MOLECULAR SUBTYPE

Cumulative incidence curves of first distant metastasis by breast cancer subtype



Sorlie T, *et al.,* Proc Natl Acad Sci U S A. 2003 Jul 8;100(14):8418-23.

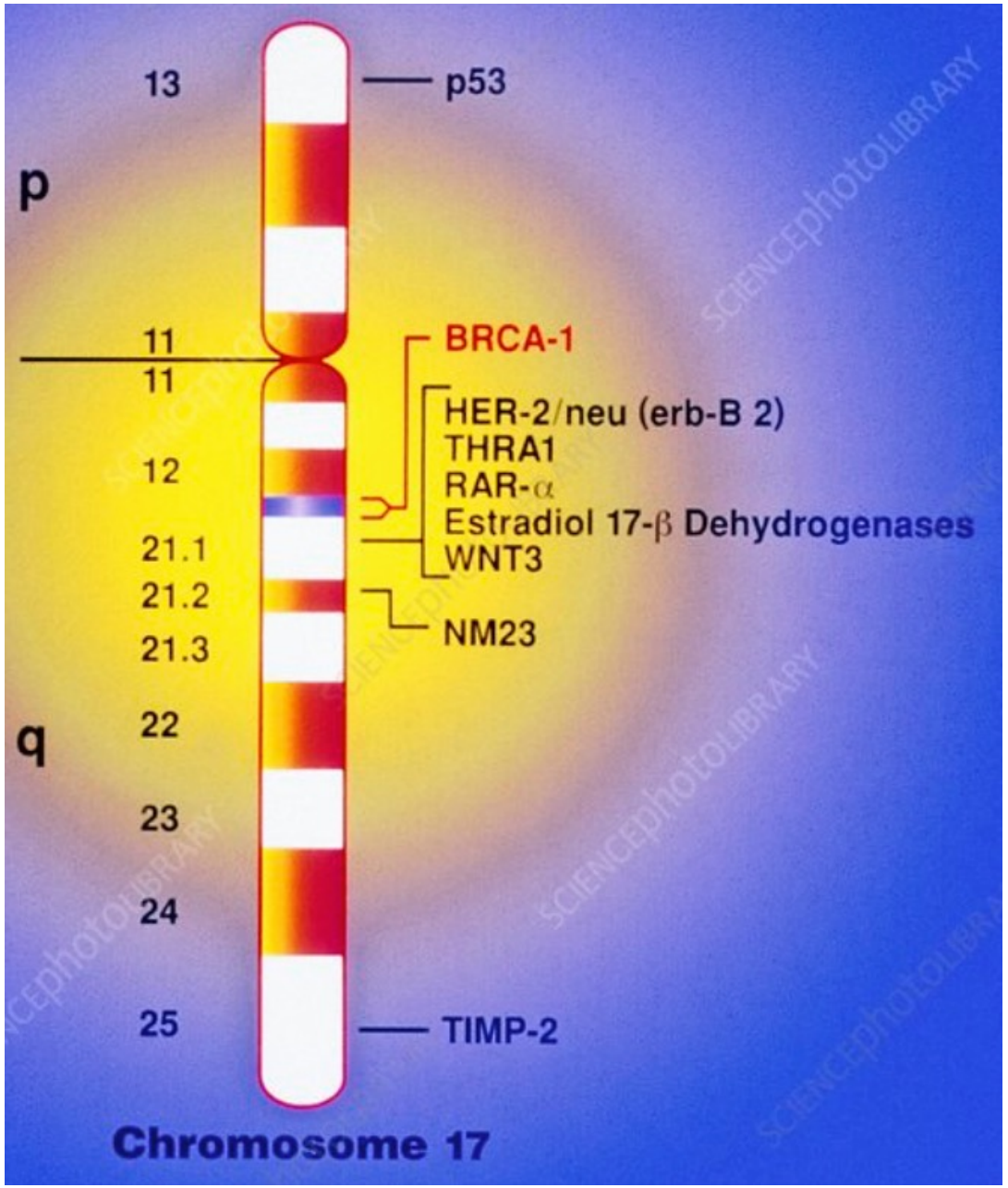
BRCA1 Mutations and Basal-Like Tumors



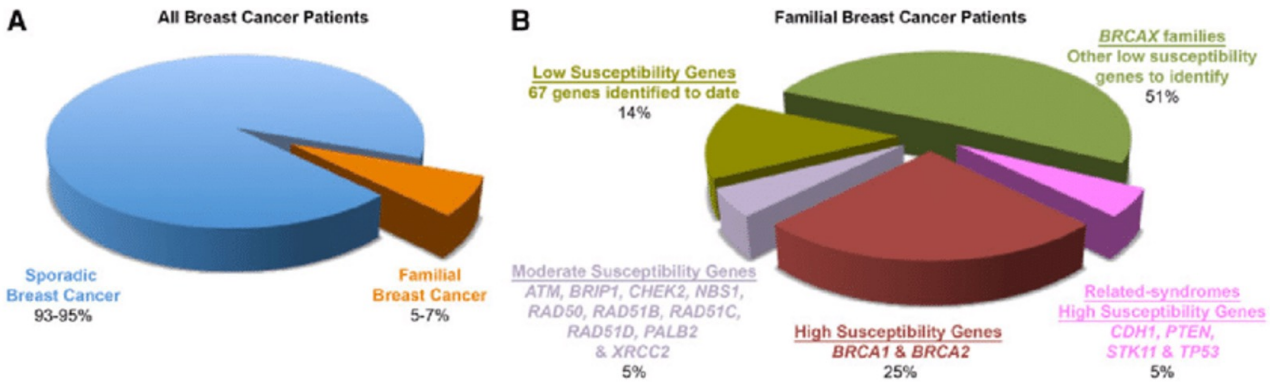
17/18 BRCA1 mutants were Basal-like

Sorlie et al. *PNAS*. 100:8418-8423 (2003), Foulkes et al. JNCI. 95:1482-1485 (2003)

BRCA Mutation and Carrier Frequency



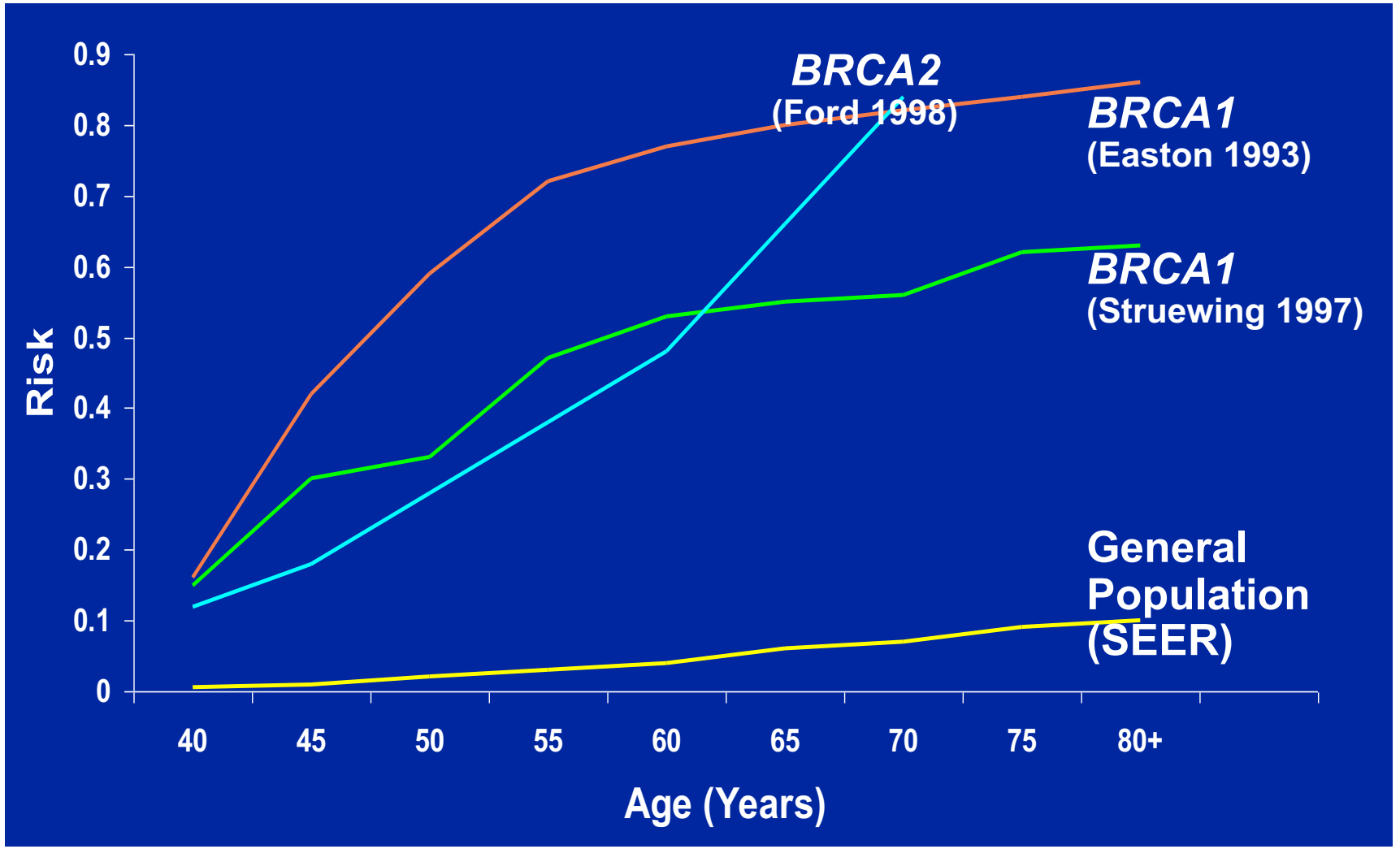
The complex genetic landscape of familial breast cancer



March 22, 2017 Science News: “According to current data, it is estimated that only 30% of breast cancer survivors with the BRCA mutation have been identified, and that number drops significantly to 10% for asymptomatic BRCA carriers”.

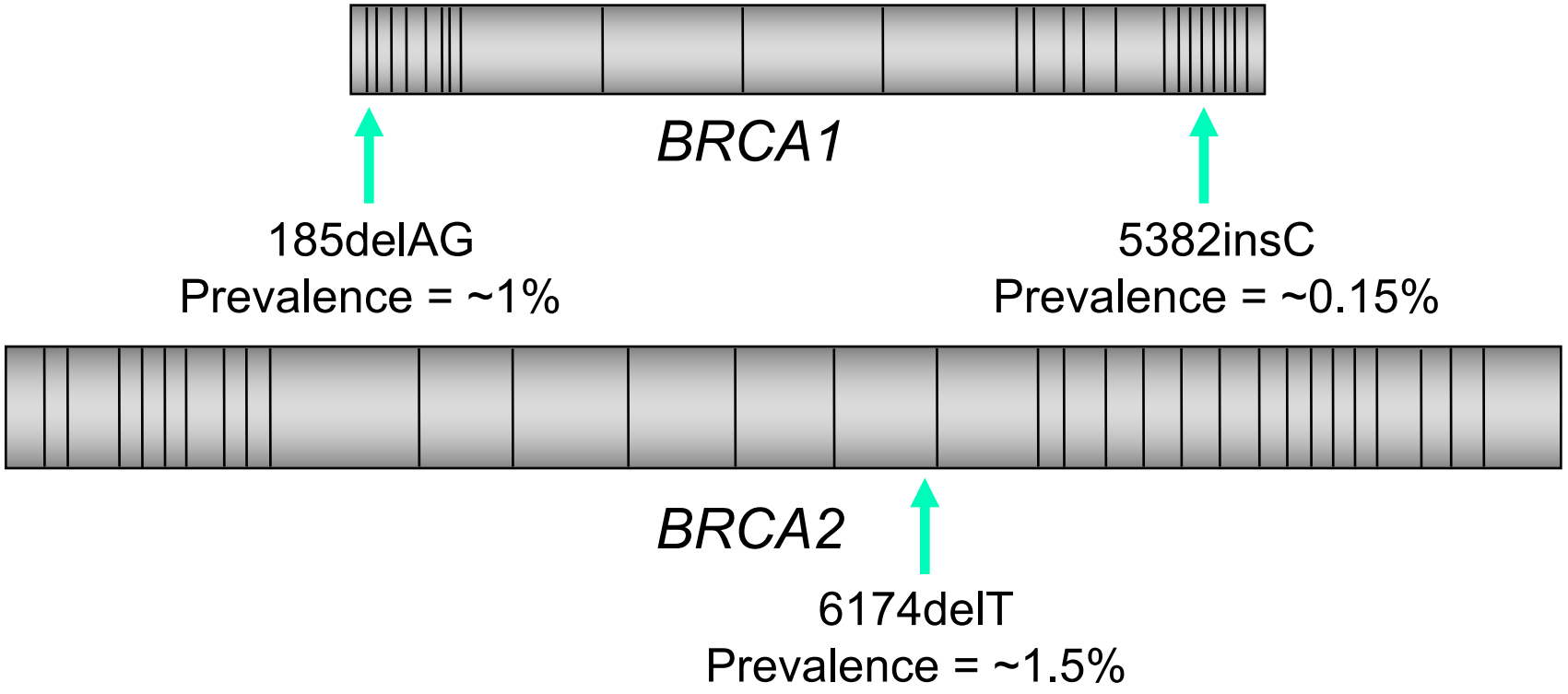
Melchor, Lorenzo & Benítez, Javier. (2013). Human genetics. 132. 10.1007/s00439-013-1299-y.

High Cumulative Breast Cancer Risk



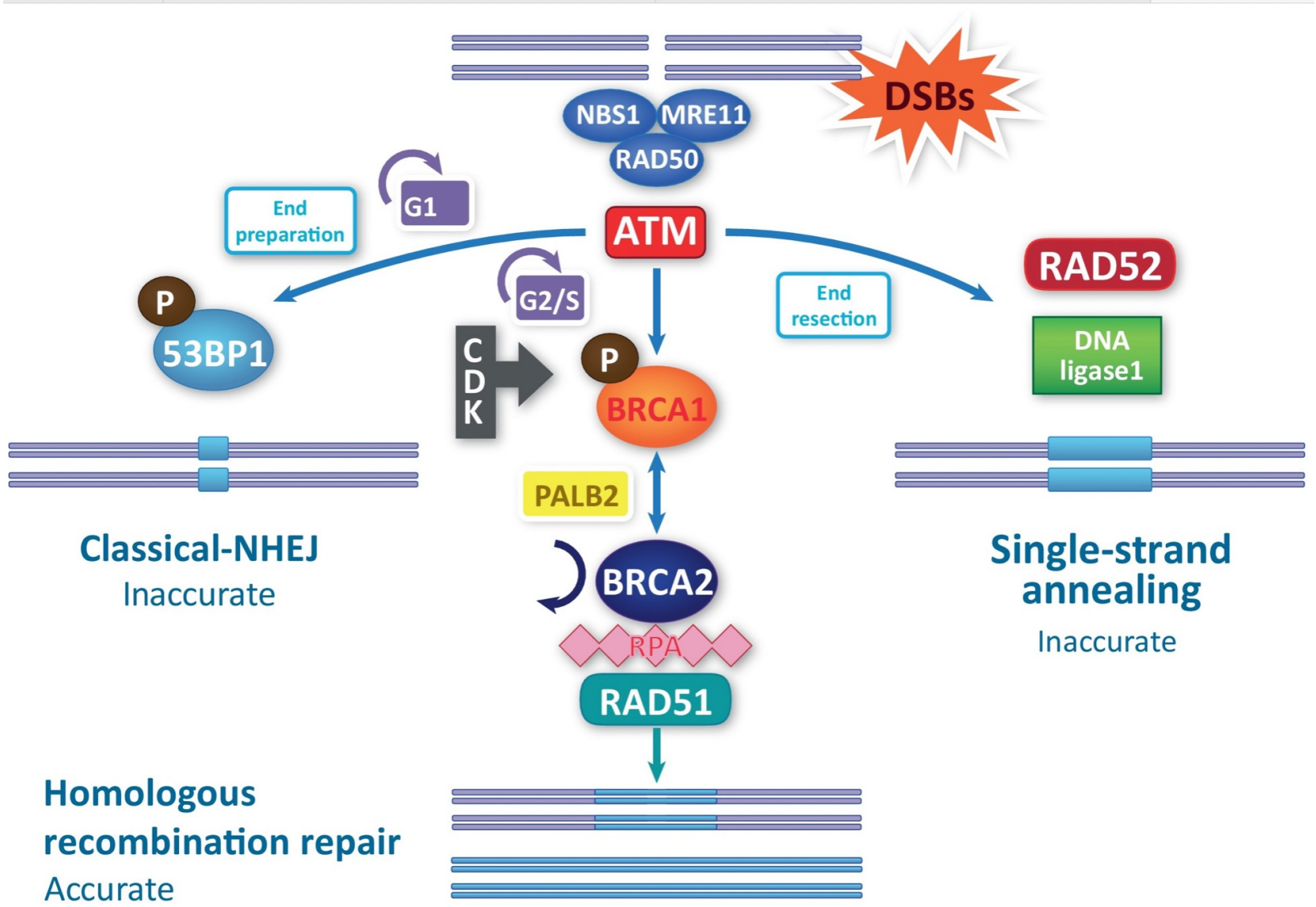
BRCA1 and *BRCA2* Mutations in the Ashkenazi Jewish Population

An estimated 1 in 40 Ashkenazi Jews carries a *BRCA1* or *BRCA2* mutation



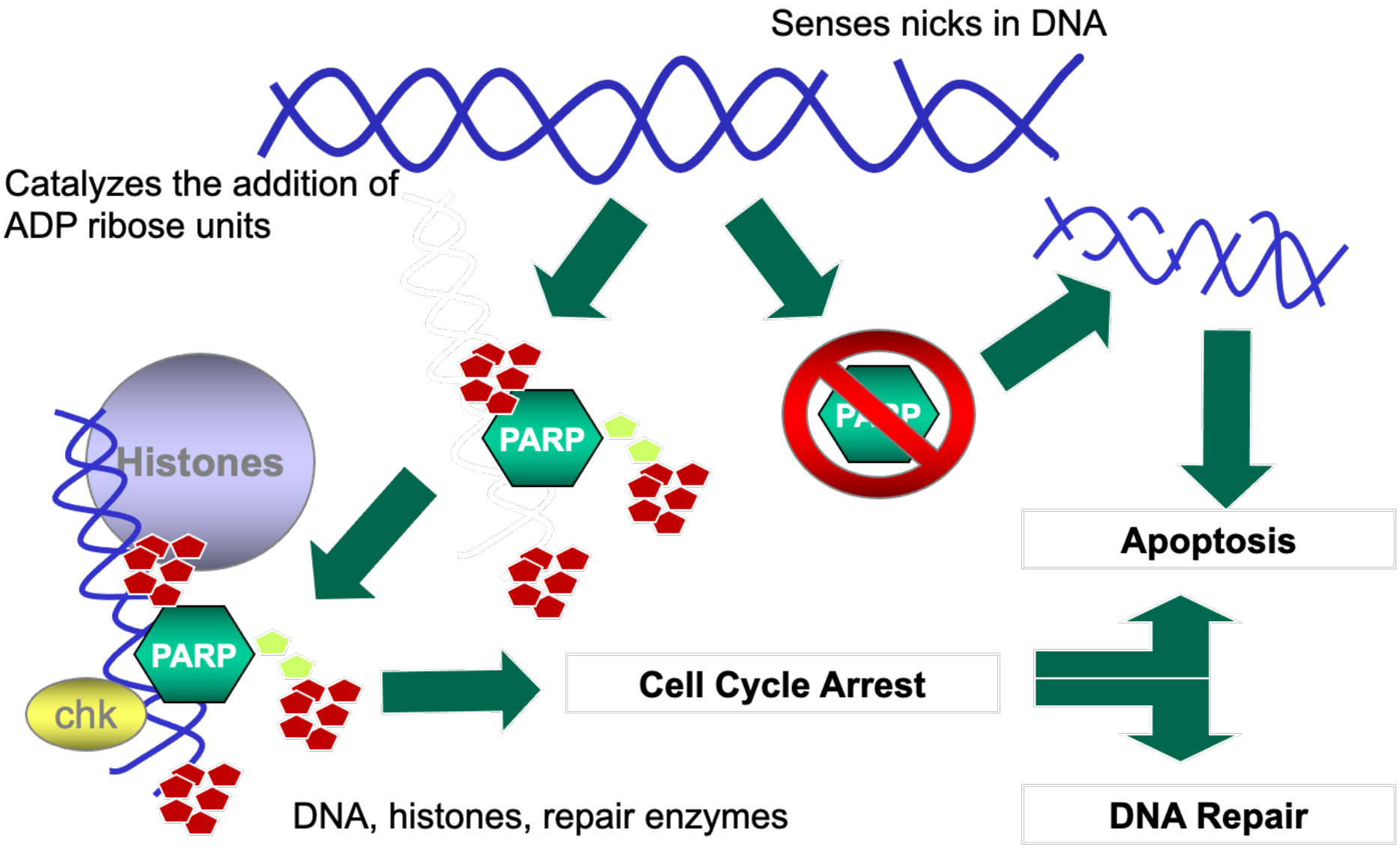
Roa BB et al. *Nat Genet* 14:185, 1996
Oddoux C et al. *Nat Genet* 14:188, 1996
Struewing JP. *N Engl J Med* 336:1401, 1997

DNA Double-Strand Break (DSB) Repair



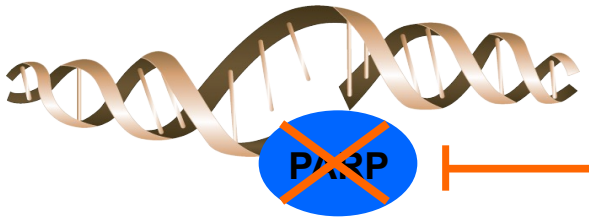
O'Kane GM, et al. Trends in Molecular Medicine Volume 23, Issue 12, December 2017, Pages 1121-1137.

PARP's [Poly(ADP-ribose) polymerase] role in DNA repair



PARP inhibition and tumor-selective synthetic lethality

DNA damage (SSBs)



PARP inhibition

DNA replication
(accumulation of DNA DSBs)

Normal cell with functional HR pathway

HR-deficient tumor cell (e.g. BRCA 1/2$^{-/-}$)

HR-mediated DNA repair

Cell survival

Cell death

Impaired HR-mediated DNA repair

Tumor-selective cytotoxicity

DSB, double-strand break; HR, homologous recombination
SSB, single-strand break

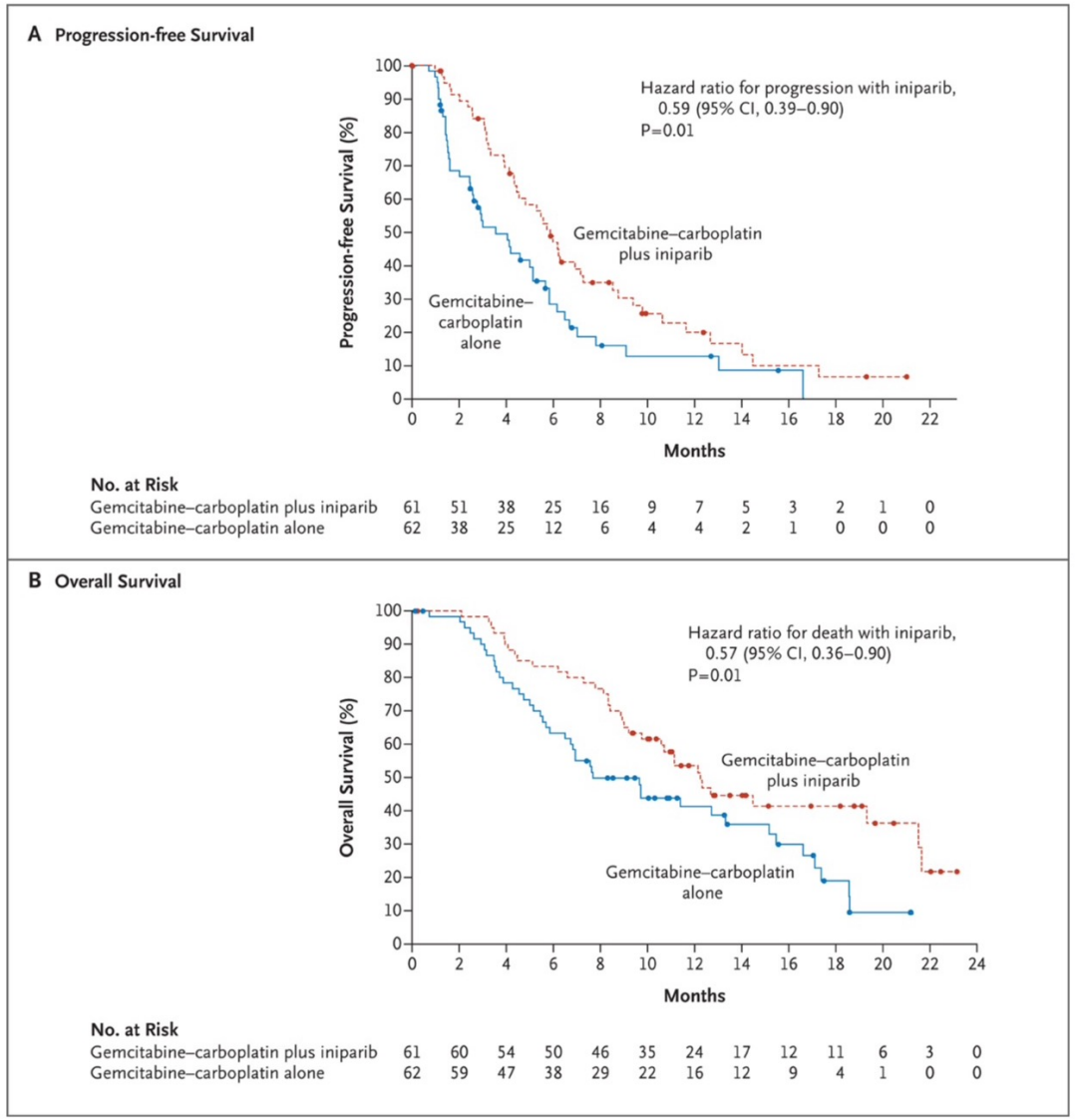
Farmer H *et al. Nature* 2005;434:917–921
Bryant HE *et al. Nature* 2005;434:913–917
McCabe N *et al. Cancer Res* 2006;66:8109–8115

ORIGINAL ARTICLE

The NEW ENGLAND JOURNAL of MEDICINE

Iniparib plus Chemotherapy in Metastatic Triple-Negative Breast Cancer

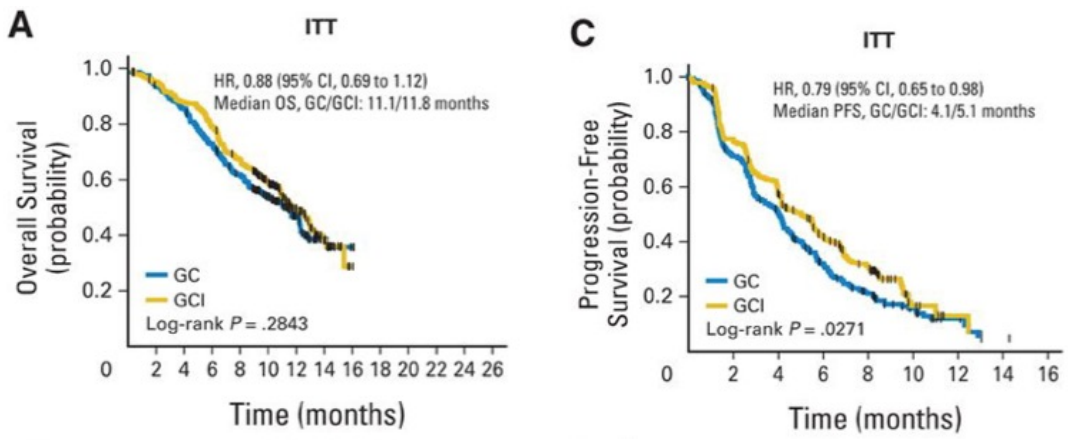
Joyce O'Shaughnessy, M.D., Cynthia Osborne, M.D., John E. Pippen, M.D., Mark Yoffe, M.D., Debra Patt, M.D., Christine Rocha, M.Sc., Ingrid Chou Koo, Ph.D., Barry M. Sherman, M.D., and Charles Bradley, Ph.D.*



ORIGINAL REPORTS | Breast Cancer

Phase III Study of Iniparib Plus Gemcitabine and Carboplatin Versus Gemcitabine and Carboplatin in Patients With Metastatic Triple-Negative Breast Cancer

Joyce O'Shaughnessy, Lee Schwartzberg, Michael A. Danso, Kathy D. Miller, Hope S. Rugo, Marcus NeubauerNicholas Robert, Beth Hellerstedt, Mansoor Saleh, Paul Richards, Jennifer M. Specht, Denise A. Yardley, Robert W. Carlson, Richard S. Finn, Eric Charpentier, Ignacio Garcia-Ribas, Eric P. Winer



Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

Published in final edited form as:
Clin Cancer Res. 2012 March 15; 18(6): 1655–1662. doi:10.1158/1078-0432.CCR-11-2890.

Failure of Iniparib to Inhibit Poly(ADP-ribose) Polymerase *in Vitro*

Anand G. Patel[1,*], **Silvana De Lorenzo**[1,*], **Karen S. Flatten**[1,*], **Guy G. Poirier**[3], and **Scott H. Kaufmann**[1,2]

[1]Division of Oncology Research, Mayo Clinic, Rochester, MN 55905

[2]Department of Molecular Pharmacology, Mayo Clinic, Rochester, MN 55905

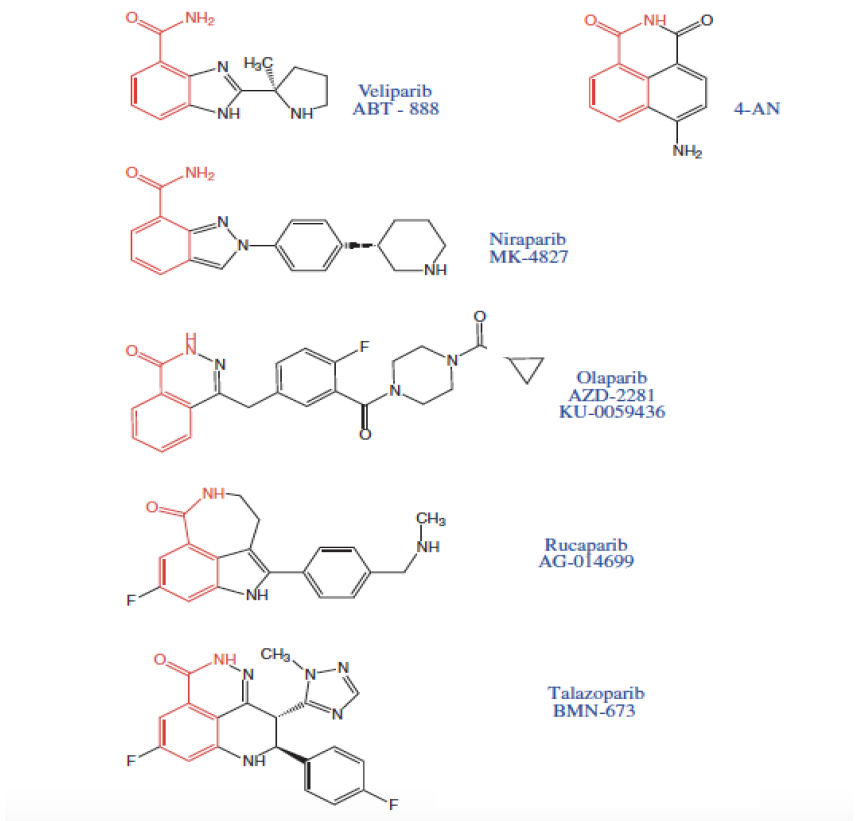
[3]Cancer Axis, Laval University Medical Center, Quebec City, Quebec, Canada G1V 4G2

Downfall of Iniparib: A PARP Inhibitor That Doesn't Inhibit PARP After All FREE

Gunjan Sinha

JNCI: Journal of the National Cancer Institute, Volume 106, Issue 1, January 2014, djt447,
https://doi.org/10.1093/jnci/djt447

PARP Inhibitors



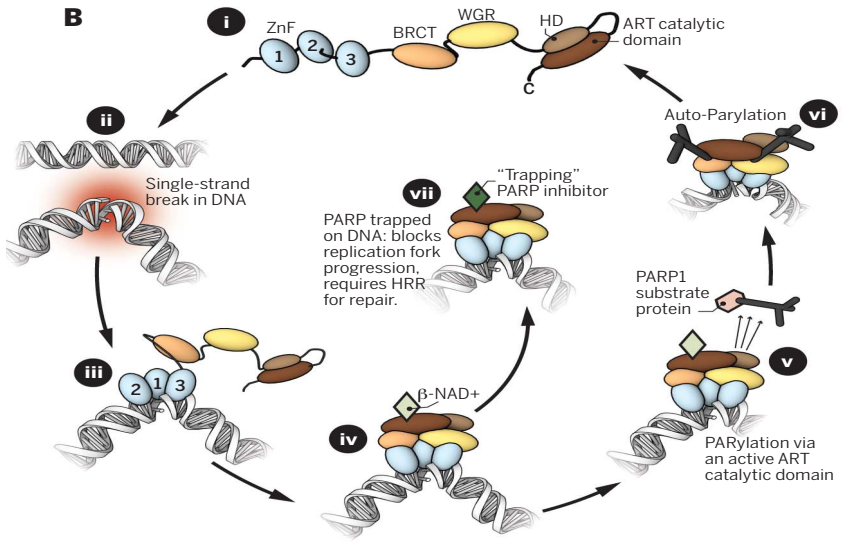
- **Veliparib –** Phase III data presented 9/2019
- **Niraparib**
- **Olaparib -** Approved 1/12/2018
- **Rucaparib**
- **Talazoparib** - Approved 10/16/2018

★ **NCCN guidelines now endorse germline *BRCA1/2* mutation testing for all HER2- MBC patients**

Murai J, Pommier Y. Classification of PARP Inhibitors Based on PARP Trapping and Catalytic Inhibition, and Rationale for Combinations with Topoisomerase I Inhibitors and Alkylating Agents. In: Curtin NJ, Sharma RA, eds. *PARP Inhibitors for Cancer Therapy*. New York: Springer International Publishing;2015:261-274.

PARP inhibitor “trapping” of PARP1 on DNA

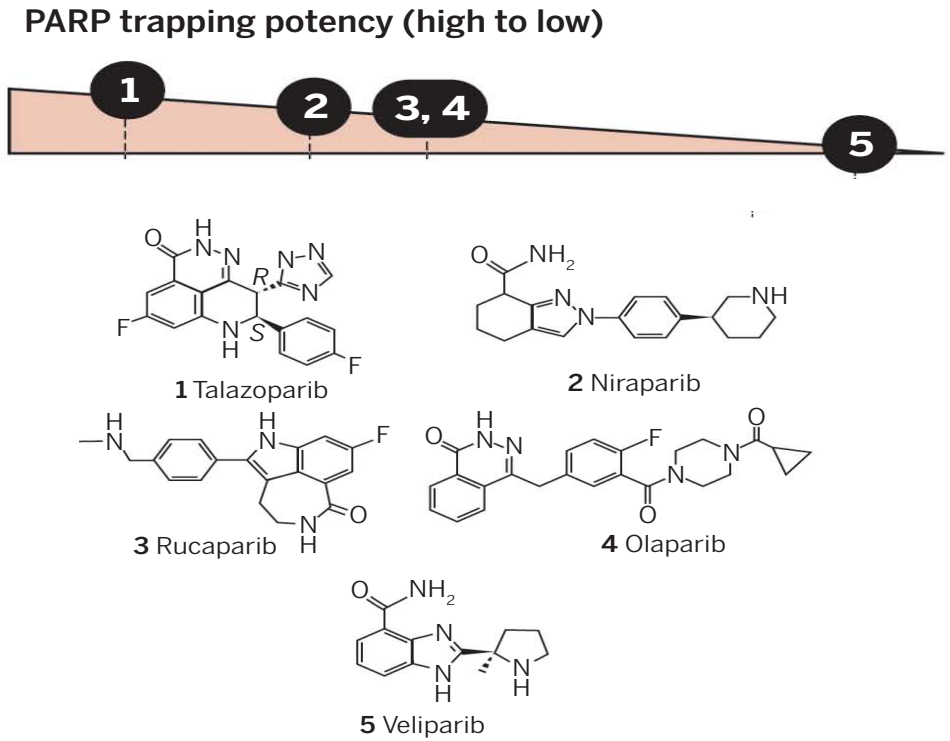
Catalytic inhibition



Talazoparib	0.57 nM
Olaparib	1.9 nM
Rucaparib	2.0 nM
Veliparib	4.7 nM

Shen et al. Clin Cancer Res (2013) 19:5003-5015

Trapping



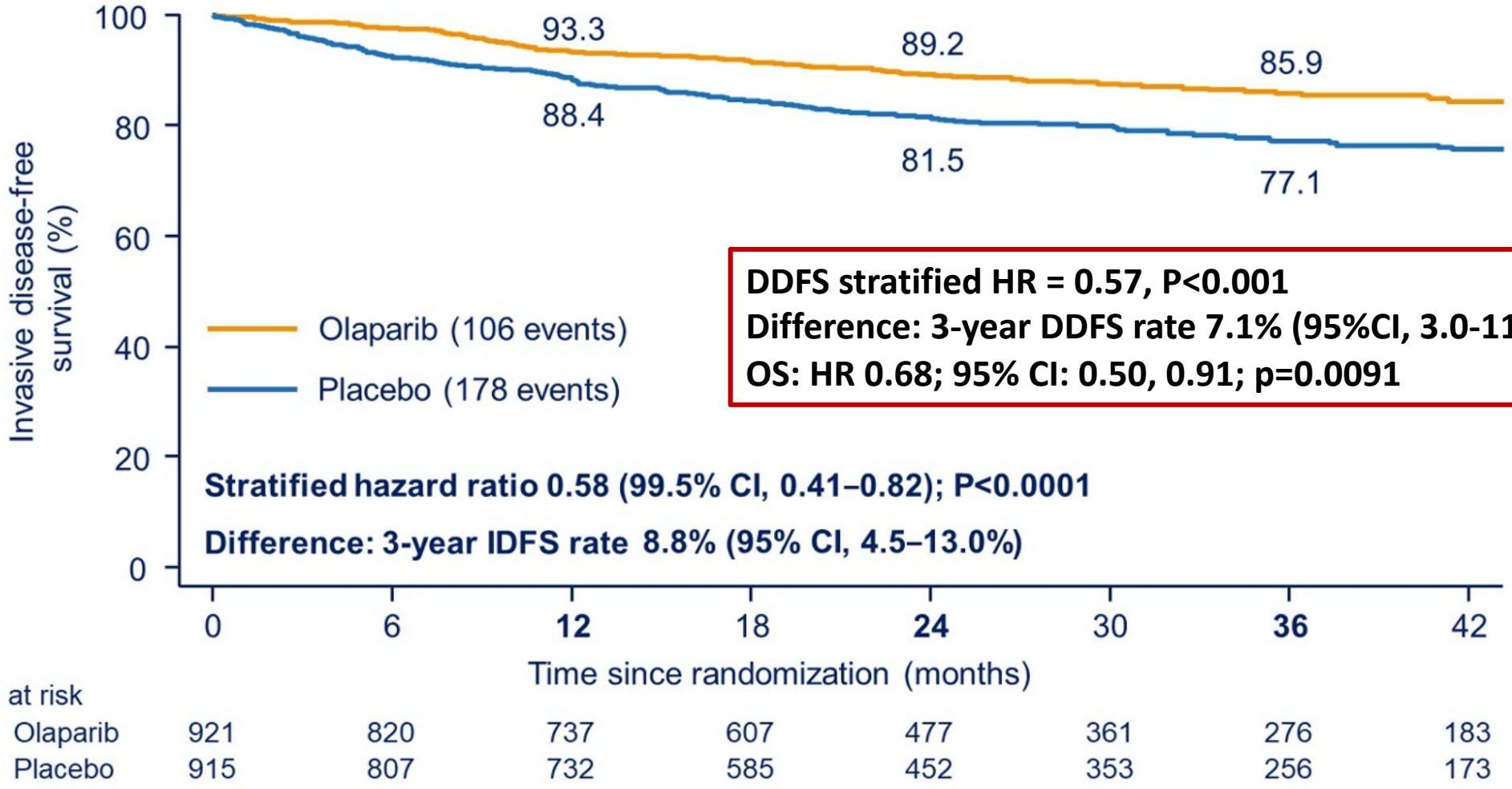
Lord and Ashworth Synthetic lethality in the clinic Science 2017

Oral PARPi Doses and Schedules

Compound	Dose	Phase
Olaparib (AZD2281)	400mg BID	I, II, III
Veliparib (ABT888)	400mg BID	I, II, III
Rucaparib (PF01367338 , AG014699)	600mg BID	I, II, III
Niraparib (MK4827)	300mg BID	I, II, III
Talazoparib (BMN-673)	1mg QD	I, II, III
CEP-9722		I
E7016		I

March 11, 2022: FDA approves olaparib for adjuvant treatment of high-risk early breast cancer

OlympiA: Invasive disease-free survival (ITT)



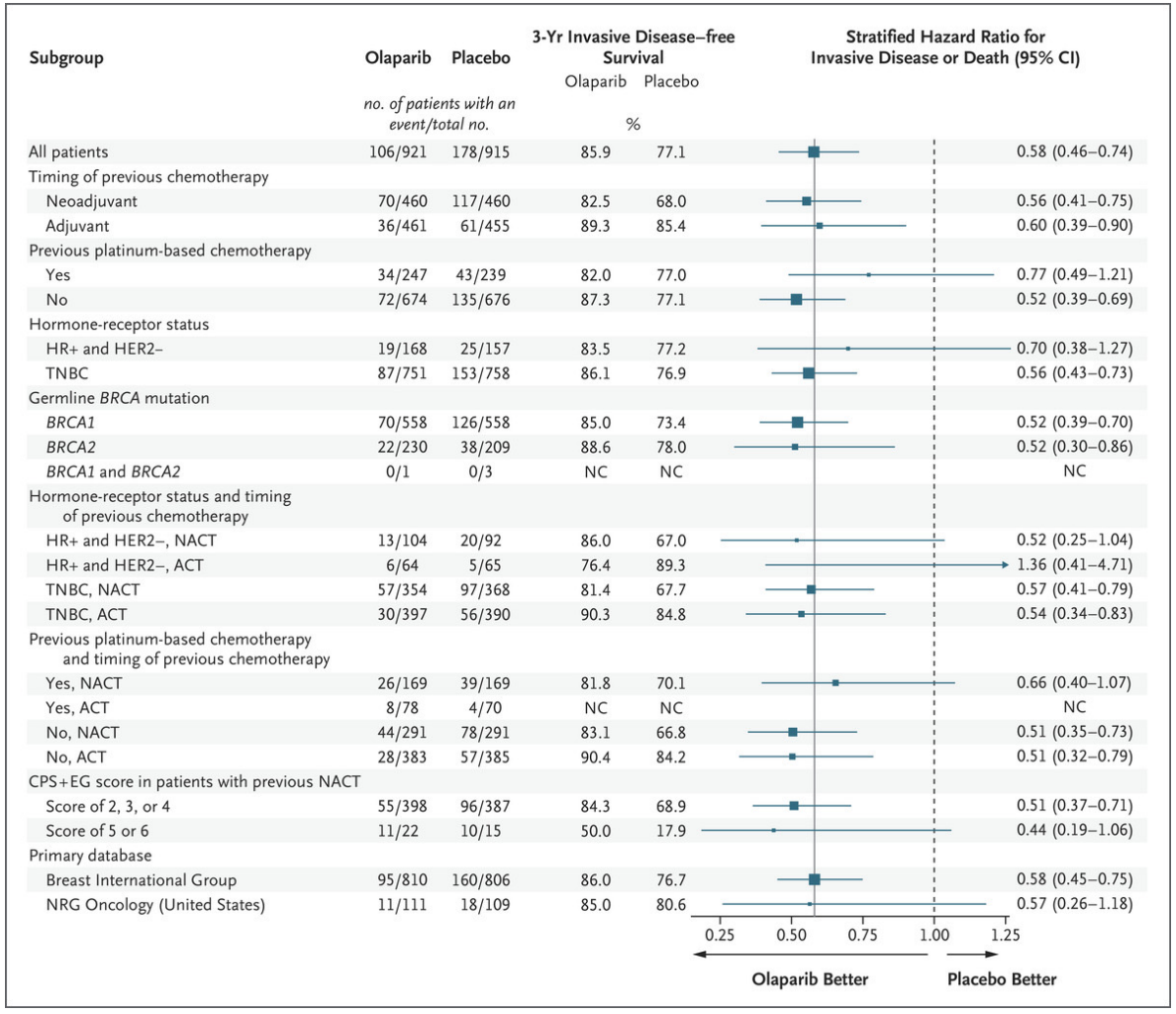
DDFS stratified HR = 0.57, P<0.001
Difference: 3-year DDFS rate 7.1% (95%CI, 3.0-11.1%)
OS: HR 0.68; 95% CI: 0.50, 0.91; p=0.0091

No. at risk

Olaparib	921	820	737	607	477	361	276	183
Placebo	915	807	732	585	452	353	256	173

Presented By: Andrew Tutt MB ChB PhD FMedSci
The Institute of Cancer Research and Kings College London

Adjuvant Olaparib - Subgroup Analysis of Invasive Disease–free Survival.

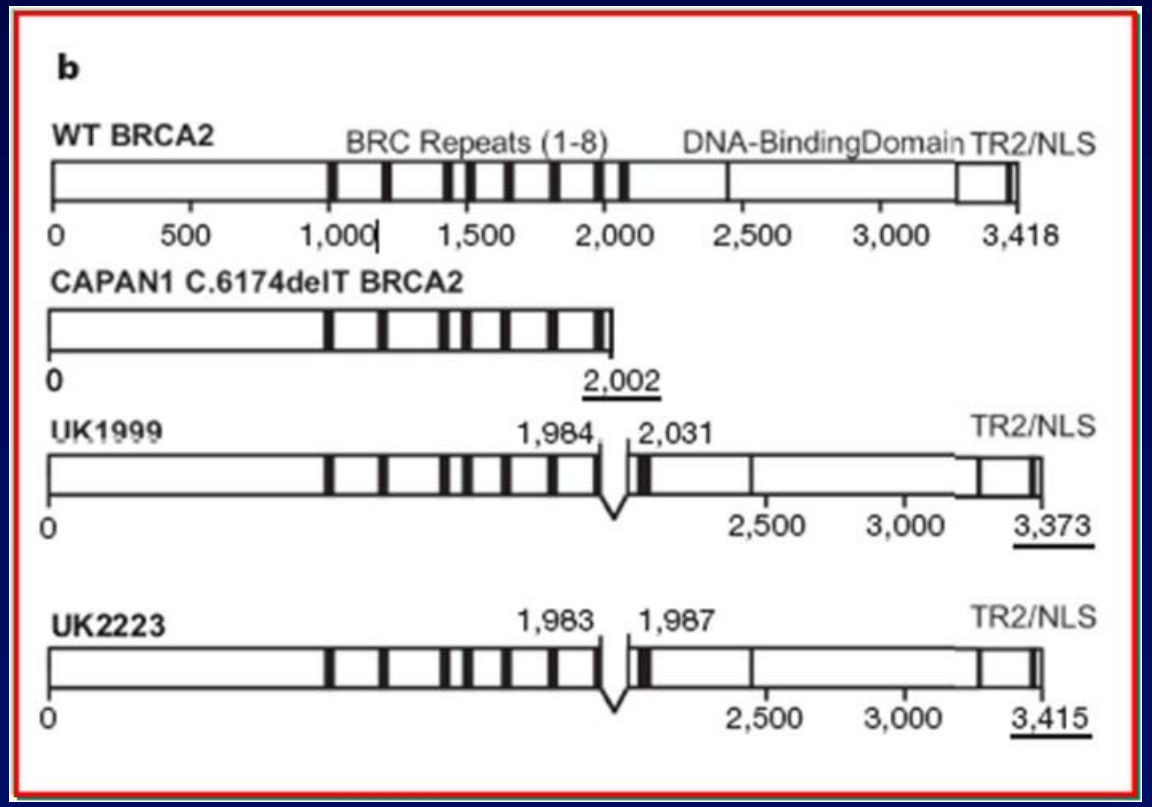


Subgroup	Olaparib	Placebo	3-Yr Invasive Disease–free Survival		Stratified Hazard Ratio for Invasive Disease or Death (95% CI)
			Olaparib	Placebo	
	no. of patients with an event/total no.		%		
All patients	106/921	178/915	85.9	77.1	0.58 (0.46–0.74)
Timing of previous chemotherapy					
Neoadjuvant	70/460	117/460	82.5	68.0	0.56 (0.41–0.75)
Adjuvant	36/461	61/455	89.3	85.4	0.60 (0.39–0.90)
Previous platinum-based chemotherapy					
Yes	34/247	43/239	82.0	77.0	0.77 (0.49–1.21)
No	72/674	135/676	87.3	77.1	0.52 (0.39–0.69)
Hormone-receptor status					
HR+ and HER2–	19/168	25/157	83.5	77.2	0.70 (0.38–1.27)
TNBC	87/751	153/758	86.1	76.9	0.56 (0.43–0.73)
Germline *BRCA* mutation					
BRCA1	70/558	126/558	85.0	73.4	0.52 (0.39–0.70)
BRCA2	22/230	38/209	88.6	78.0	0.52 (0.30–0.86)
BRCA1 and *BRCA2*	0/1	0/3	NC	NC	NC
Hormone-receptor status and timing of previous chemotherapy					
HR+ and HER2–, NACT	13/104	20/92	86.0	67.0	0.52 (0.25–1.04)
HR+ and HER2–, ACT	6/64	5/65	76.4	89.3	1.36 (0.41–4.71)
TNBC, NACT	57/354	97/368	81.4	67.7	0.57 (0.41–0.79)
TNBC, ACT	30/397	56/390	90.3	84.8	0.54 (0.34–0.83)
Previous platinum-based chemotherapy and timing of previous chemotherapy					
Yes, NACT	26/169	39/169	81.8	70.1	0.66 (0.40–1.07)
Yes, ACT	8/78	4/70	NC	NC	NC
No, NACT	44/291	78/291	83.1	66.8	0.51 (0.35–0.73)
No, ACT	28/383	57/385	90.4	84.2	0.51 (0.32–0.79)
CPS+EG score in patients with previous NACT					
Score of 2, 3, or 4	55/398	96/387	84.3	68.9	0.51 (0.37–0.71)
Score of 5 or 6	11/22	10/15	50.0	17.9	0.44 (0.19–1.06)
Primary database					
Breast International Group	95/810	160/806	86.0	76.7	0.58 (0.45–0.75)
NRG Oncology (United States)	11/111	18/109	85.0	80.6	0.57 (0.26–1.18)

AN Tutt et al. N Engl J Med 2021;384:2394-2405.

The NEW ENGLAND JOURNAL of MEDICINE

Resistance to therapy caused by intragenic deletion in BRCA2



Restored ORF

Edwards, et al., NATURE| Vol 451|28 February 2008

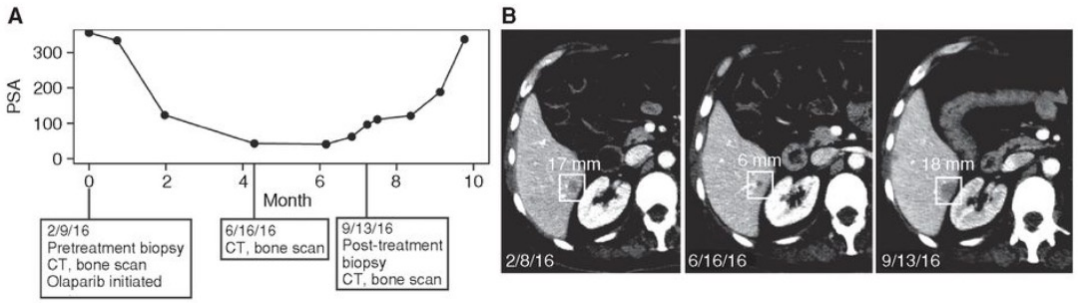
CANCER DISCOVERY 10

Home About Articles For Authors Alerts News COVID-19 Webinars 10th Anniversary Search

Research Briefs

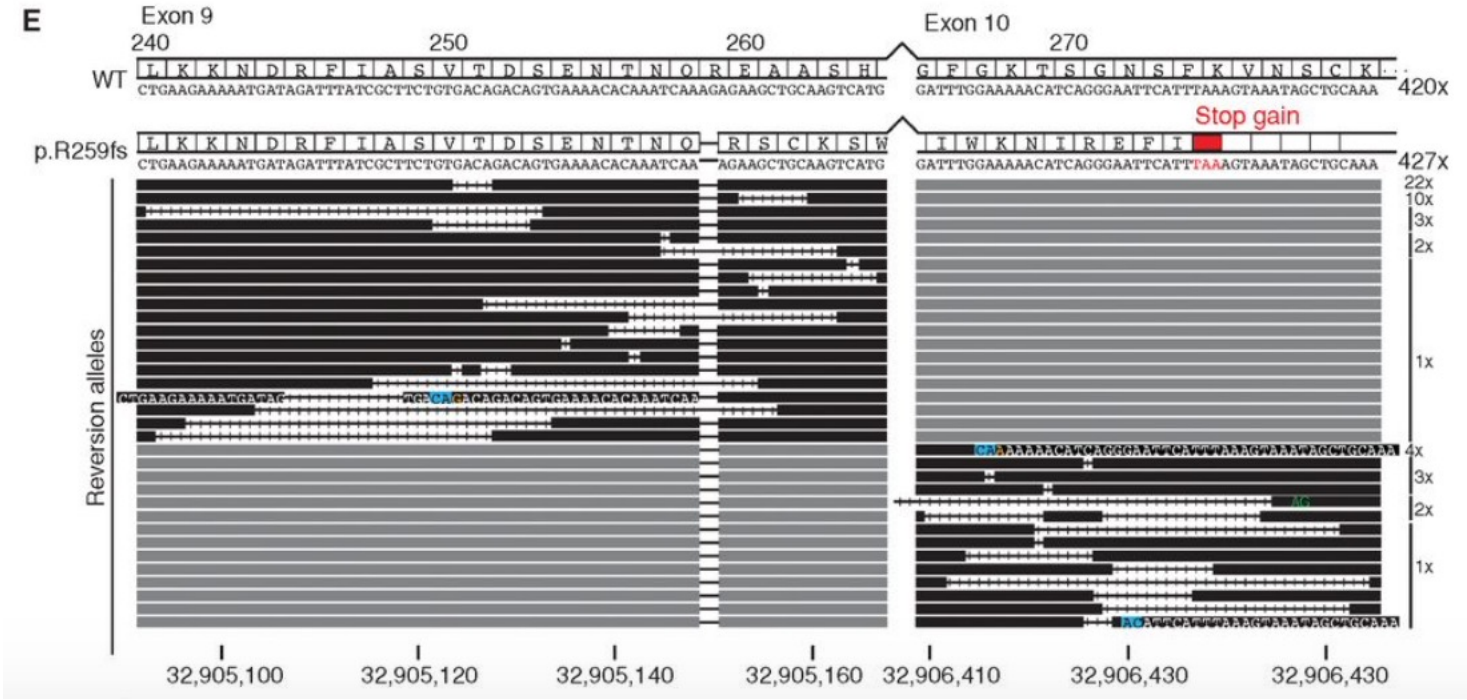
Analysis of Circulating Cell-Free DNA Identifies Multiclonal Heterogeneity of *BRCA2* Reversion Mutations Associated with Resistance to PARP Inhibitors

David Quigley, Joshi J. Alumkal, Alexander W. Wyatt, Vishal Kothari, Adam Foye, Paul Lloyd, Rahul Aggarwal, Won Kim, Eric Lu, Jacob Schwartzman, Kevin Beja, Matti Annala, Rajdeep Das, Morgan Diolaiti, Colin Pritchard, George Thomas, Scott Tomlins, Karen Knudsen, Christopher J. Lord, Charles Ryan, Jack Youngren, Tomasz M. Beer, Alan Ashworth, Eric J. Small, and Felix Y. Feng



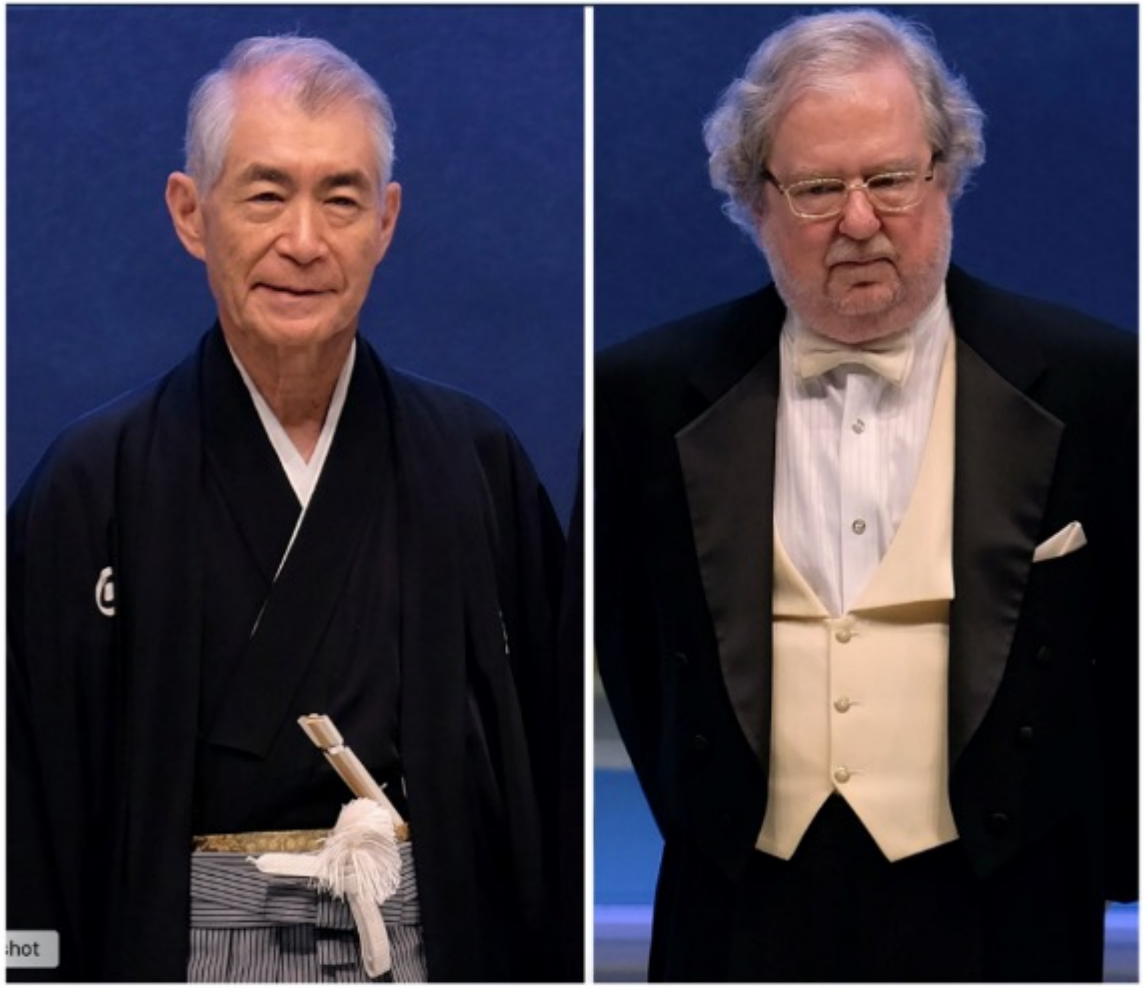
David Quigley et al. Cancer Discov 2017;7:999-1005

AACR American Association for Cancer Research
CANCER DISCOVERY

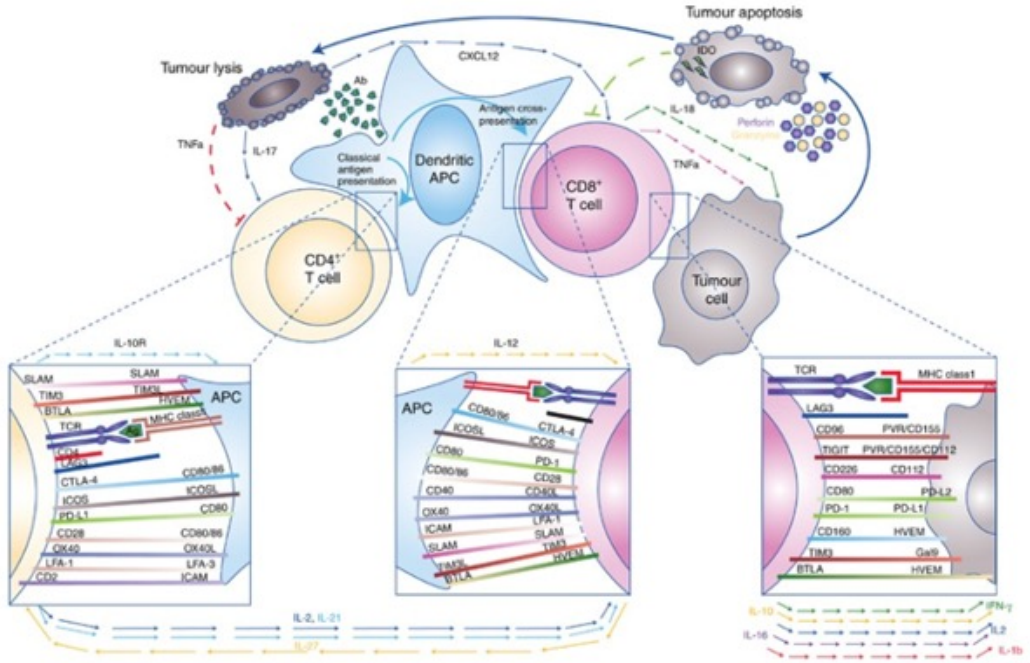


Here, we report the first mechanistic description of talazoparib resistance, the first BRCA2 reversion mutations identified in prostate cancer, and the first cases of multiclonal BRCA2 reversion mutations as a mechanism of PARPi resistance. The multiclonal nature resistance in metastatic disease, in the context of a single evolutionary stimulus, was striking.

Nobel Prize in Medicine (2018) – Immune checkpoint blockade[1]



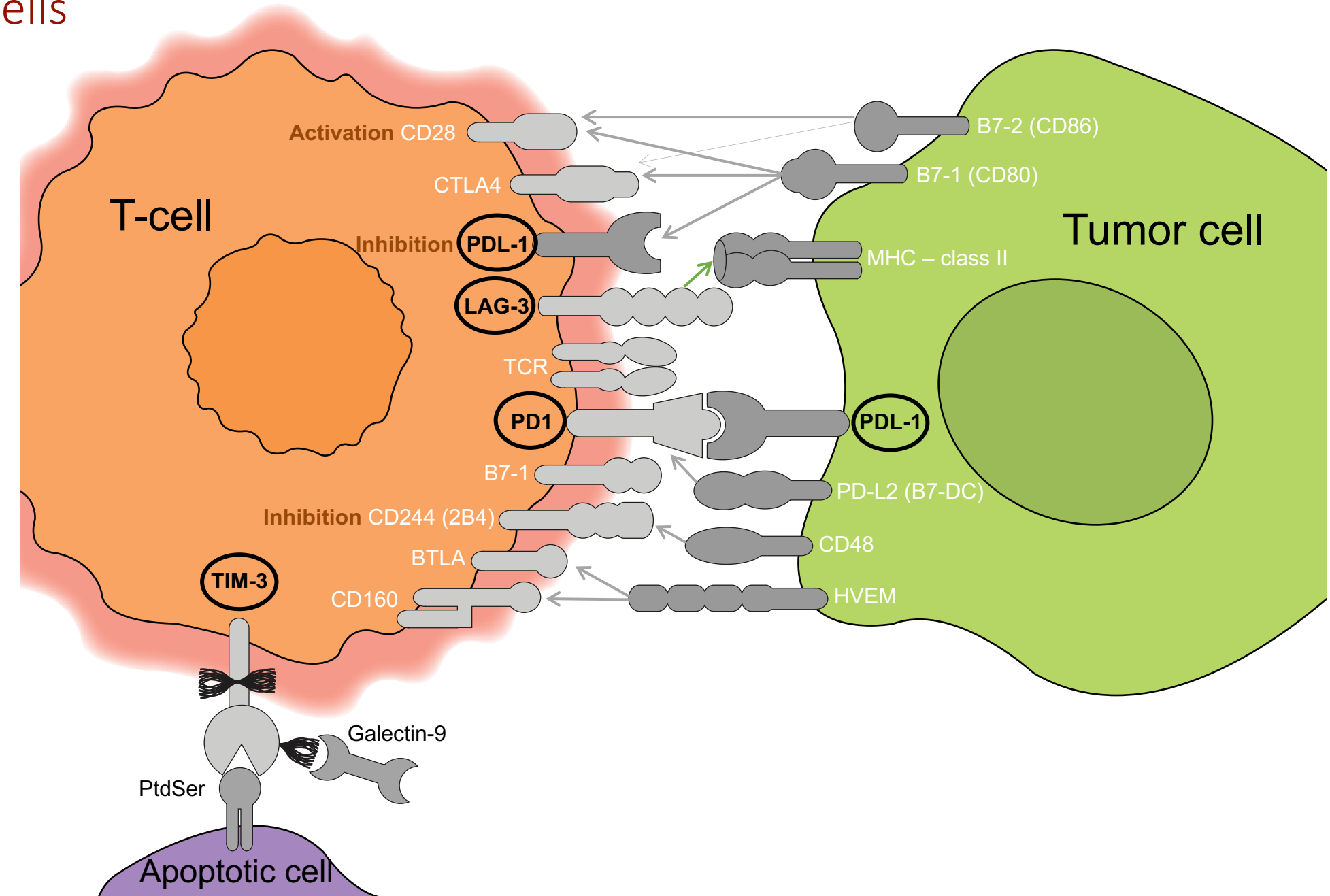
Tasuku Honjo and James Allison



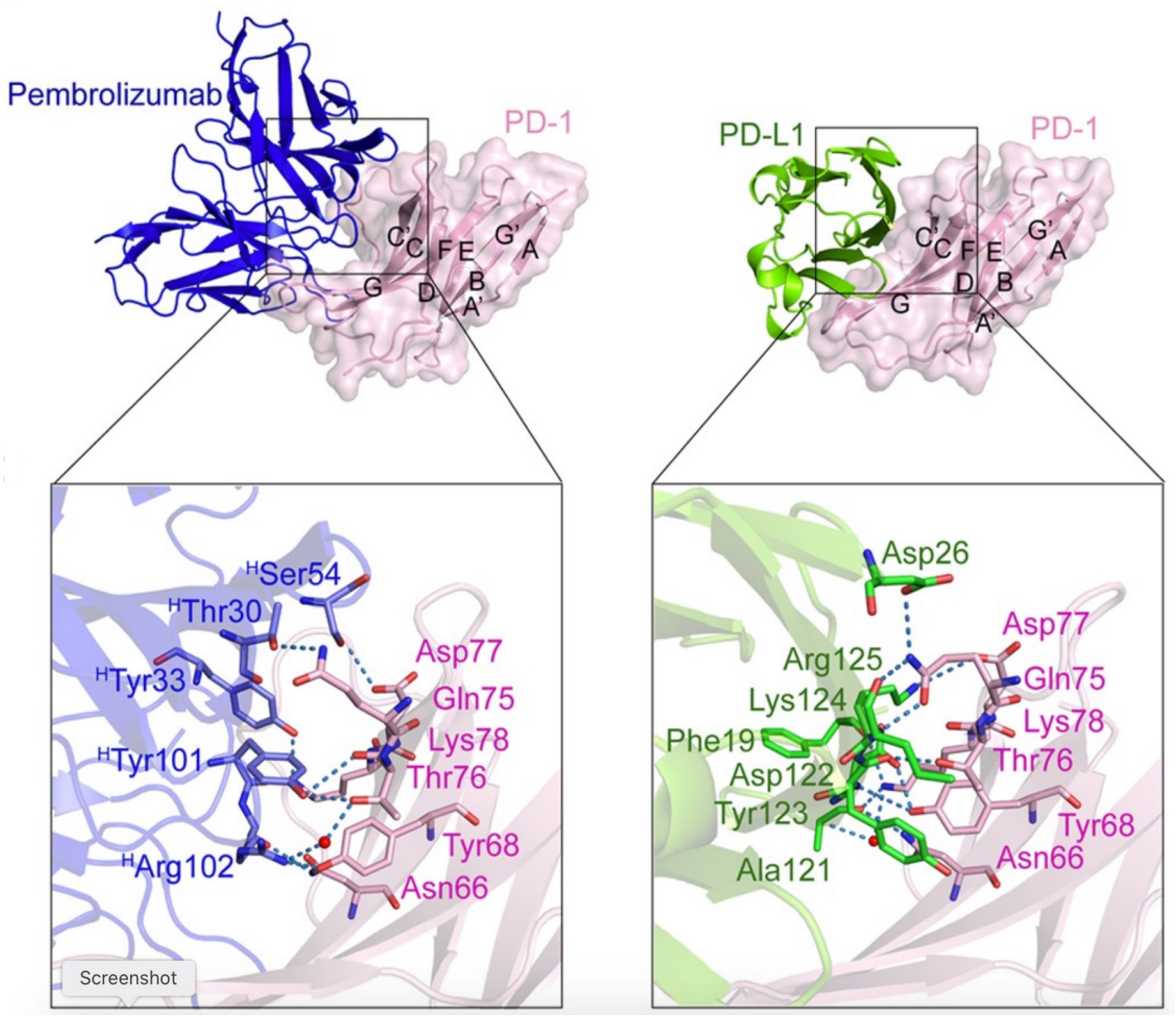
Immunoregulatory interactions principally involving immune checkpoint blockade[2]

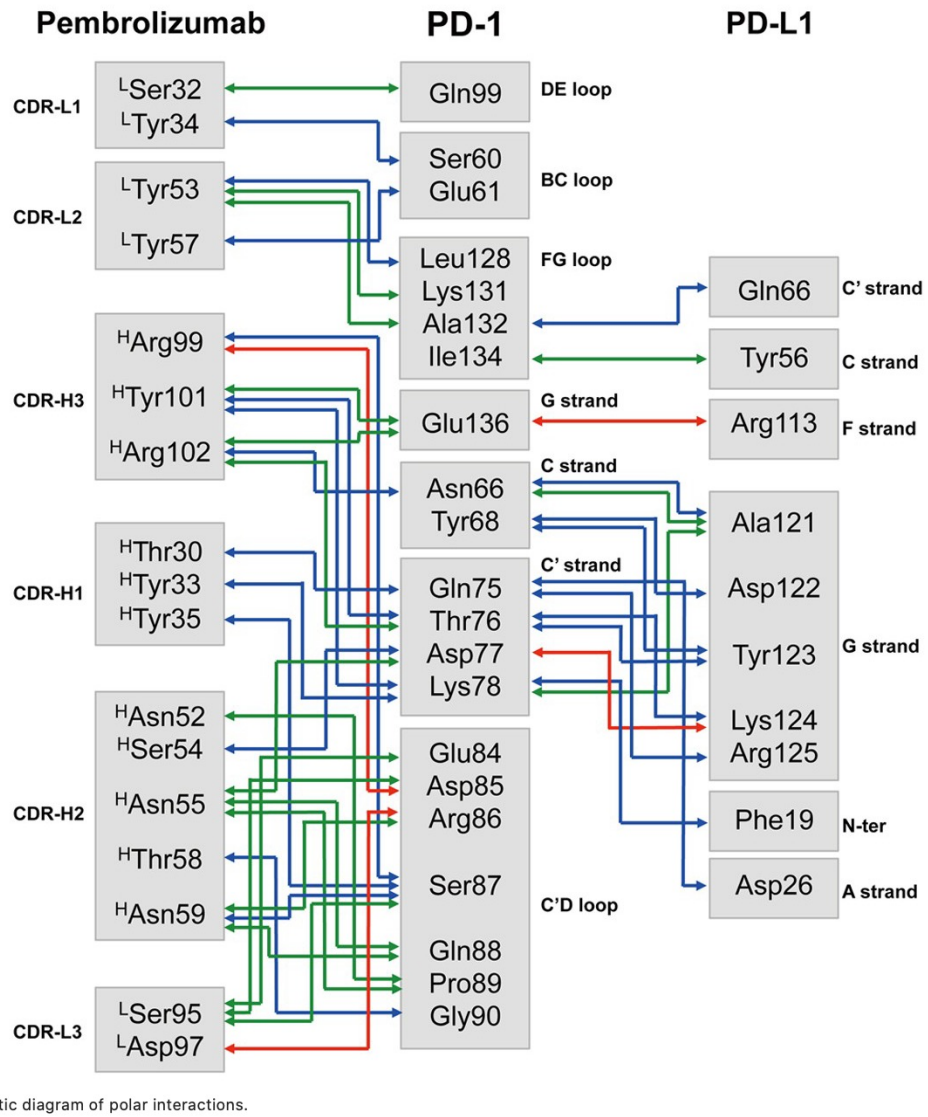
1. Huang P-W and Chang J W-C. *Biomed J.* 2019;42(5):299–306. 2. Cogdill AP, et al. *Br J Cancer.* 2017;117(1):1–7.

Multiple immune signaling pathways modulate interactions between T-cells and tumor cells



High-resolution crystal structure of the therapeutic antibody pembrolizumab bound to the human PD-1



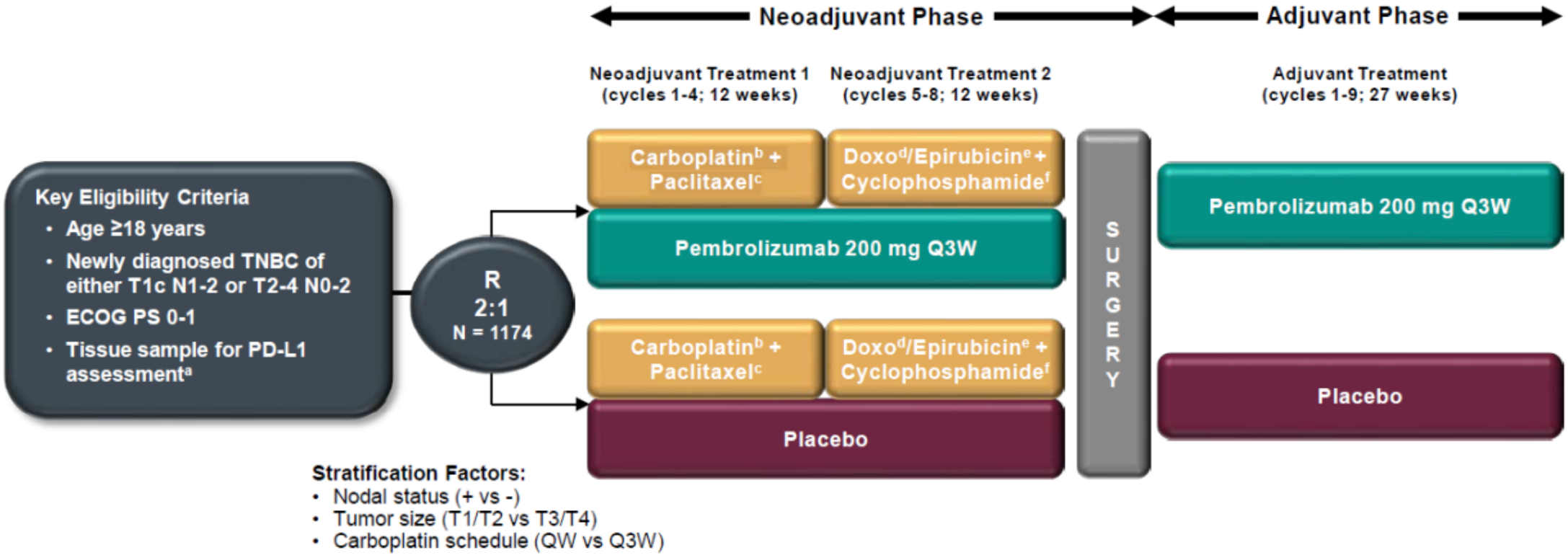


A schematic diagram of polar interactions.

Direct protein/protein hydrogen bonds are in blue; water-mediated hydrogen bonds are in green; and salt bridges are in red.

Horita, S., Nomura, Y., Sato, Y. et al. High-resolution crystal structure of the therapeutic antibody pembrolizumab bound to the human PD-1. Sci Rep 6, 35297 (2016).

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)

Chemo= paclitaxel/carbo→AC Q3 wks x 4

Pembro continued Q3wks adjuvantly x 9 cycles

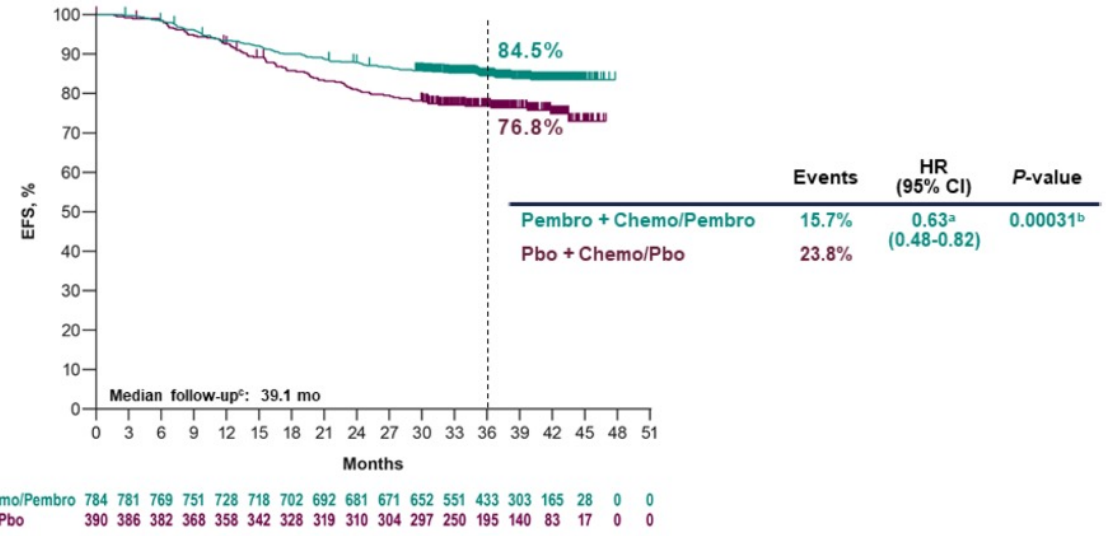
On July 26, 2021, the Food and Drug Administration approved pembrolizumab for high-risk, early-stage, triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

ESMO VIRTUAL PLENARY

KEYNOTE-522: Phase 3 Study of Neoadjuvant Pembrolizumab + Chemotherapy versus Placebo + Chemotherapy, Followed by Adjuvant Pembrolizumab versus Placebo for Early-Stage Triple-Negative Breast Cancer

Schmid KN522 ESMO Virtual Plenary 2021

Statistically Significant and Clinically Meaningful EFS at IA4



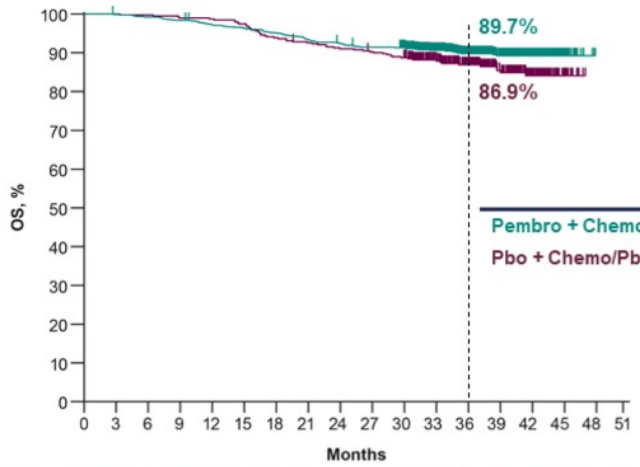
	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	15.7%	0.63[a] (0.48-0.82)	0.00031[b]
Pbo + Chemo/Pbo	23.8%		

No. at Risk																		
Pembro + Chemo/Pembro	784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
Pbo + Chemo/Pbo	390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [b]Prespecified *P*-value boundary of 0.00517 reached at this analysis.
[c]Defined as the time from randomization to the data cutoff date of March 23, 2021.

Schmid KN522 ESMO Virtual Plenary 2021

Overall Survival



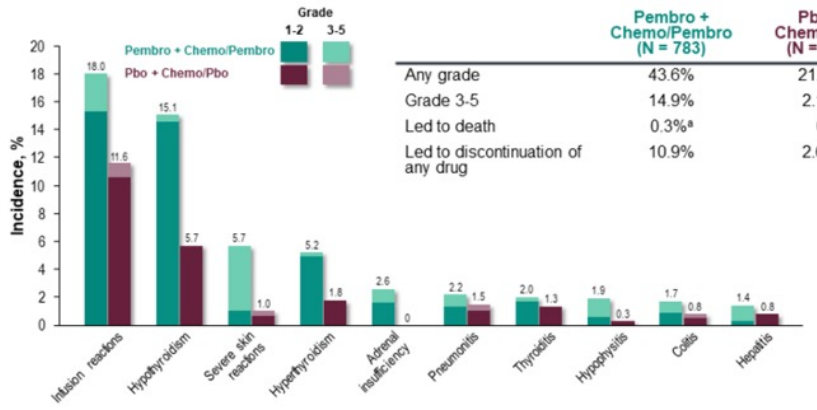
	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	10.2%	0.72[a] (0.51-1.02)	0.03214[b]
Pbo + Chemo/Pbo	14.1%		

No. at Risk																		
Pembro + Chemo/Pembro	784	782	777	770	759	752	742	729	720	712	701	586	461	323	178	30	0	0
Pbo + Chemo/Pbo	390	390	389	386	385	380	366	360	354	350	343	286	223	157	89	17	0	0

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [b]Prespecified *P*-value boundary of 0.00086 not reached at this analysis.
Data cutoff date: March 23, 2021.

Schmid KN522 ESMO Virtual Plenary 2021

Immune-Mediated AEs and Infusion Reactions in Combined Phases



	Pembro + Chemo/Pembro (N = 783)	Pbo + Chemo/Pbo (N = 389)
Any grade	43.6%	21.9%
Grade 3-5	14.9%	2.1%
Led to death	0.3%[a]	0
Led to discontinuation of any drug	10.9%	2.6%

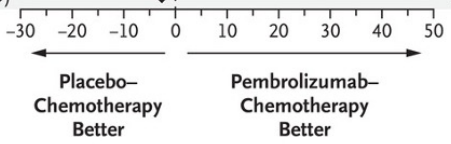
Immune-Mediated AEs and Infusion Reactions with Incidence ≥10 Patients

[a]1 patient from pneumonitis and 1 patient from autoimmune encephalitis. Considered regardless of attribution to treatment or immune relatedness by the investigator. Related terms included in addition to preferred terms listed. Data cutoff date: March 23, 2021.

KN522 Subgroup Analysis

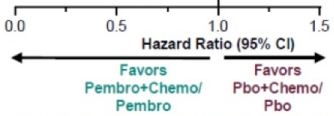
Subgroup Analysis of Difference in Percentages of Patients with a Pathological Complete Response (Stage ypT0/Tis ypN0).

Subgroup	Pembrolizumab–Chemotherapy	Placebo–Chemotherapy	Difference in Pathological Complete Response (95% CI)
	no. of patients with response/no. of patients (%)		*percentage points*
Overall	260/401 (64.8)	103/201 (51.2)	13.6 (5.4 to 21.8)
Nodal status			
Positive	136/210 (64.8)	45/102 (44.1)	20.6 (8.9 to 31.9)
Negative	124/191 (64.9)	58/99 (58.6)	6.3 (–5.3 to 18.2)
Tumor size			
T1 to T2	207/295 (70.2)	84/149 (56.4)	13.8 (4.3 to 23.3)
T3 to T4	53/106 (50.0)	19/52 (36.5)	13.5 (–3.1 to 28.8)
Carboplatin schedule			
Every 3 wk	105/165 (63.6)	47/84 (56.0)	7.7 (–5.0 to 20.6)
Weekly	154/231 (66.7)	56/116 (48.3)	18.4 (7.4 to 29.1)
PD-L1 status			
Positive	230/334 (68.9)	90/164 (54.9)	14.2 (5.3 to 23.1)
Negative	29/64 (45.3)	10/33 (30.3)	18.3 (–3.3 to 36.8)
Age			
<65 yr	235/355 (66.2)	95/176 (54.0)	12.2 (3.4 to 21.0)
≥65 yr	25/46 (54.3)	8/25 (32.0)	22.3 (–2.1 to 43.5)
ECOG performance-status score			
0	215/328 (65.5)	85/173 (49.1)	16.4 (7.3 to 25.4)
1	45/73 (61.6)	18/28 (64.3)	–2.6 (–22.1 to 18.9)



EFS Subgroup Analyses

EFS Analyses	No. of events/no. of patients (%) Pembro+Chemo/Pembro	Pbo+Chemo/Pbo	Hazard Ratio (95% CI)
Primary analysis	123/784 (15.7)	93/390 (23.8)	0.63 (0.48 to 0.82)
Nodal status			
Positive	80/408 (19.6)	57/196 (29.1)	0.65 (0.46 to 0.91)
Negative	43/376 (11.4)	36/194 (18.6)	0.58 (0.37 to 0.91)
Overall disease stage			
Stage II	65/590 (11.7)	54/291 (18.6)	0.60 (0.42 to 0.86)
Stage III	54/194 (27.8)	39/98 (39.8)	0.68 (0.45 to 1.03)
Menopausal status			
Pre-menopausal	60/438 (13.7)	47/221 (21.3)	0.62 (0.42 to 0.91)
Post-menopausal	63/345 (18.3)	46/169 (27.2)	0.64 (0.44 to 0.93)
HER2 status			
2+ by IHC (but FISH-)	32/188 (17.0)	24/104 (23.1)	0.73 (0.43 to 1.24)
0-1+ by IHC	91/595 (15.3)	69/286 (24.1)	0.60 (0.44 to 0.82)
LDH			
>ULN	29/149 (19.5)	23/80 (28.8)	0.65 (0.37 to 1.12)
≤ULN	93/631 (14.7)	69/309 (22.3)	0.63 (0.46 to 0.86)

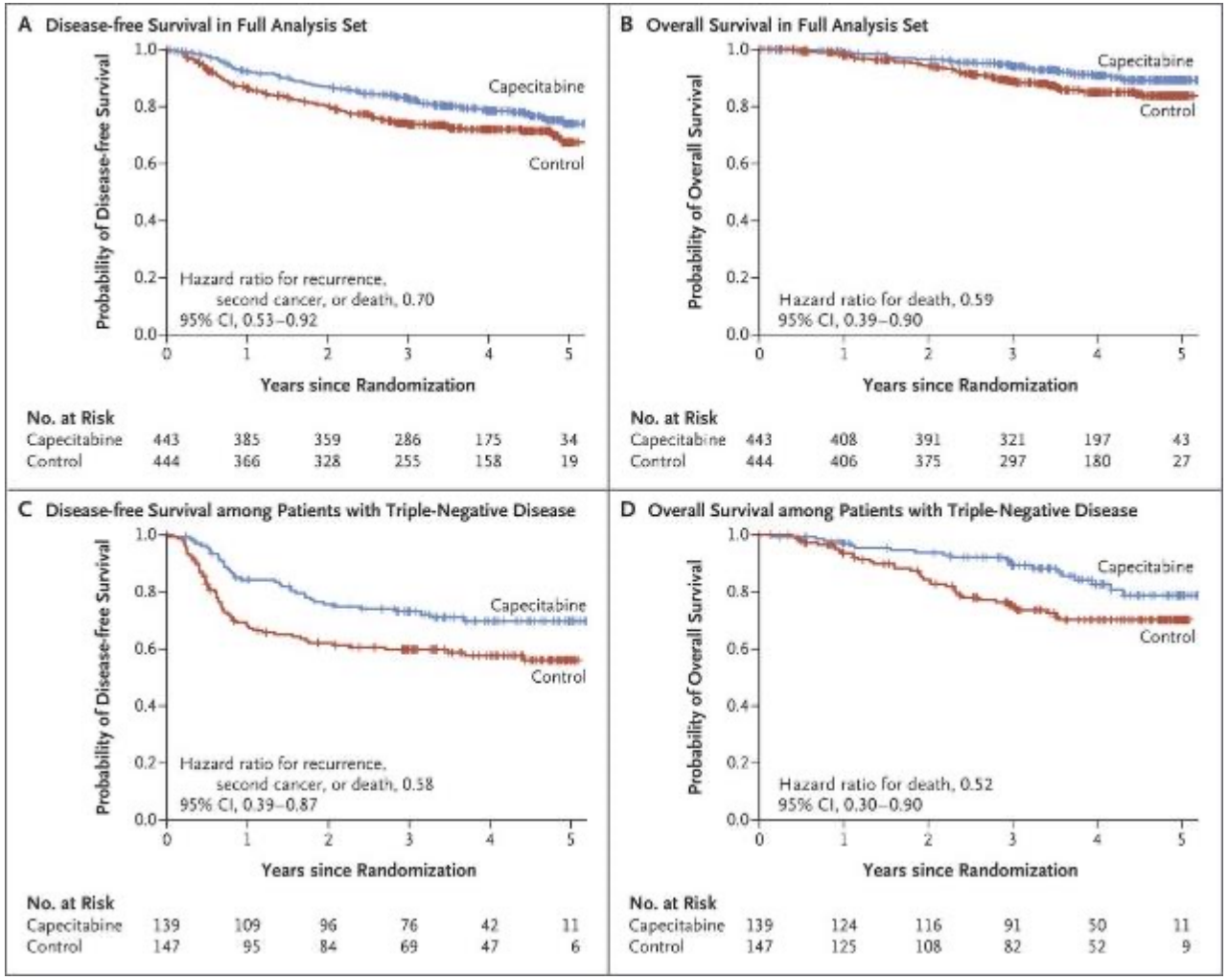


rimary analysis based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors; subgroup analyses based on unstratified Co

P Schmid et al. N Engl J Med 2020;382:810-821.

Adjuvant Capecitabine after Preoperative Chemotherapy

Kaplan–Meier Estimates of Disease-free Survival and Overall Survival.



The NEW ENGLAND JOURNAL of MEDICINE

Masuda N et al. N Engl J Med 2017;376:2147-2159.

Open access Original research

Journal for ImmunoTherapy of Cancer

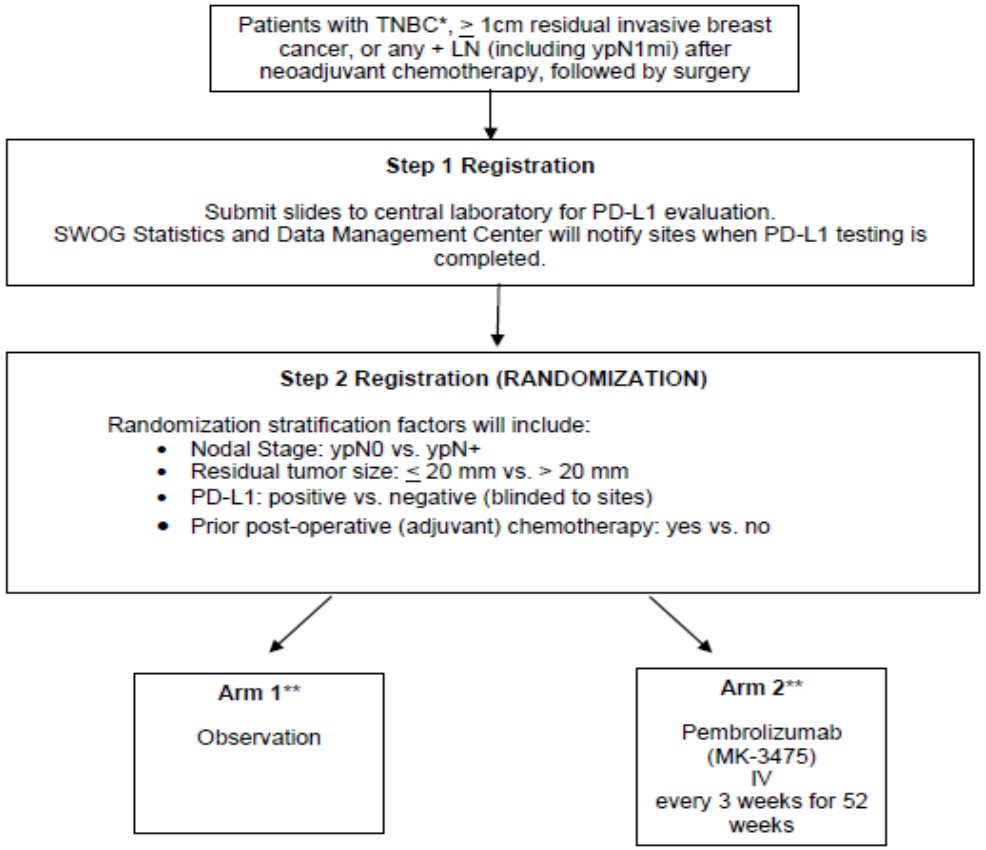
Phase II study of pembrolizumab and capecitabine for triple negative and hormone receptor-positive, HER2–negative endocrine-refractory metastatic breast cancer

Ami N Shah [1], Lisa Flaum,[1] Irene Helenowski,[1] Cesar A Santa-Maria,[2] Sarika Jain,[1] Alfred Rademaker,[1] Valerie Nelson,[1] Dean Tsarwhas,[1] Massimo Cristofanilli,[1] William Gradishar[1]

SWOG S1418:

Version Date 10/15/2021

SCHEMA



* Patients with low ER- and/or PR- positive cancers (less than or equal to 5% positivity) and/or HER2 borderline cancers by ASCO CAP guidelines are also eligible.

** Patients must complete adjuvant chemotherapy, if given, prior to Step 1 Registration. Radiation therapy may be given concurrently with protocol treatment on Arm 1 or Arm 2 (see Section 7.0).

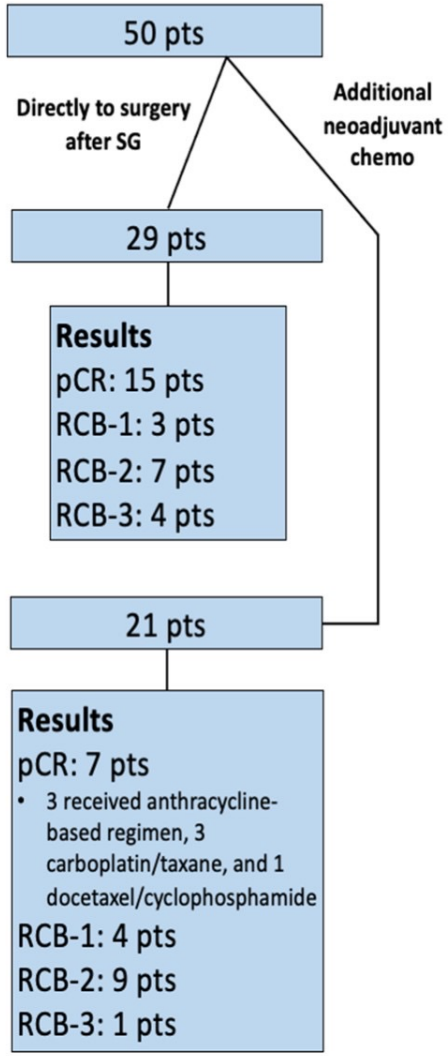
Trial allowed the patients to complete capecitabine and then start Pembro

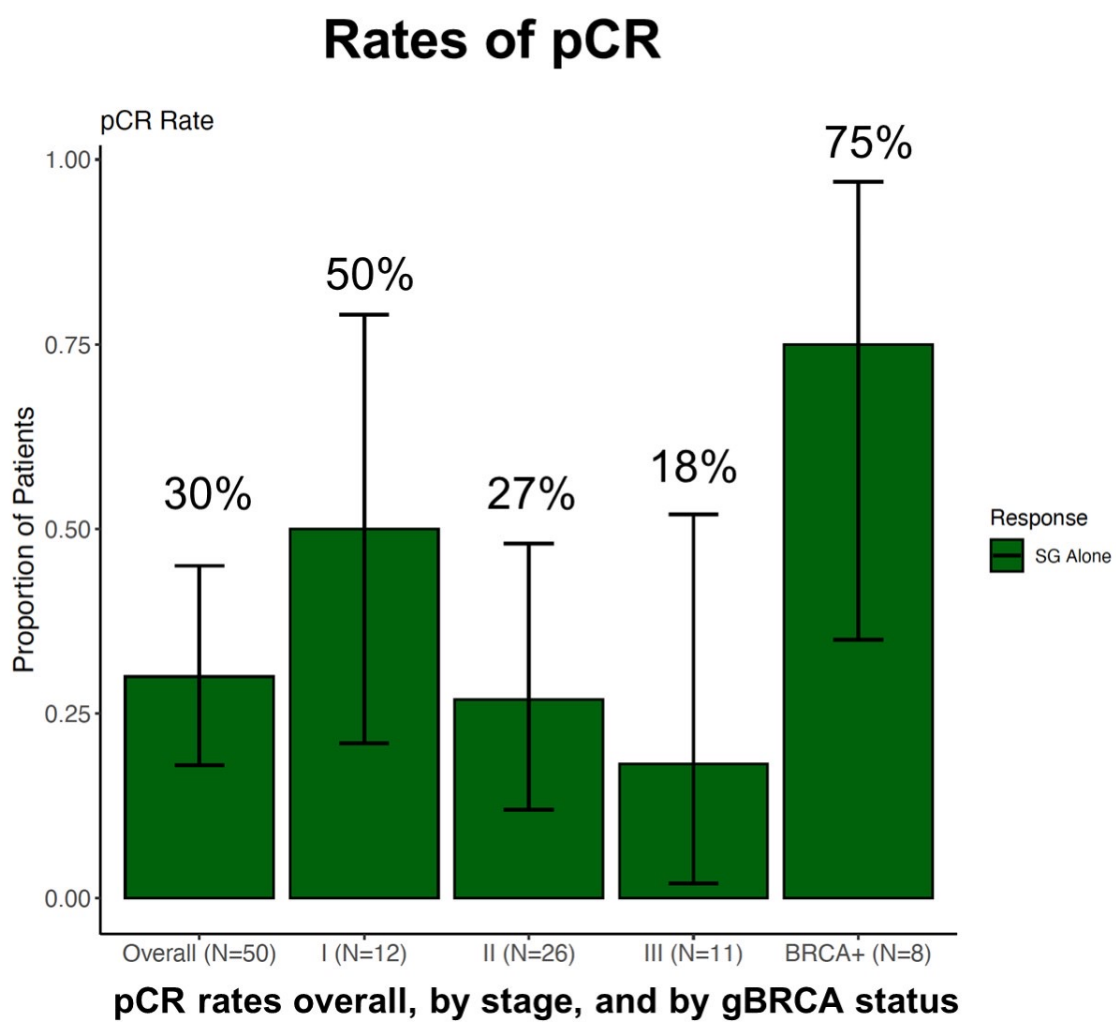
Olaparib+Pembro?

- Olaparib Plus Pembrolizumab Treatment Safe in Advanced Cholangiocarcinoma

- KEYLYNK-009: A phase II/III, open-label, randomized study of pembrolizumab (pembro) plus olaparib vs pembro plus chemotherapy after induction with first-line pembro plus chemotherapy in patients with locally recurrent inoperable or metastatic triple-negative breast cancer (TNBC).

Phase 2 study of response-guided neoadjuvant sacituzumab govitecan (IMMU-132) in patients with localized triple-negative breast cancer: results from the NeoSTAR trial.





pCR rates overall, by stage, and by gBRCA status

ASCO June 6, 2022 – Abstract ID: 591, Poster Board 362

Improved Pathologic Complete Response Rates for Triple-Negative Breast Cancer in the I-SPY2 Trial

Douglas Yee, Rebecca Arielle Shatsky, Christina Yau, Denise M. Wolf, Rita Nanda, Laura van 't Veer, Donald A. Berry, Angela DeMichele, Laura Esserman, I-SPY2 Consortium

Masonic Cancer Center, University of Minnesota, Minneapolis, MN; UCSD Medical Center, San Diego, CA; UC San Francisco, San Francisco, CA; University of Chicago Medical Center, Chicago, IL; Berry Consultants, Austin, TX; Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; University of California, San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA

BACKGROUND

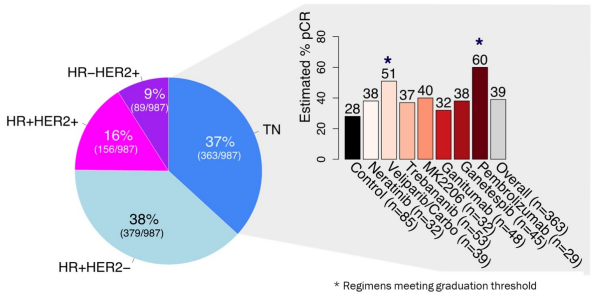
- Triple Negative Breast Cancer (TNBC) is composed of multiple distinct biologic and genomic subtypes.
- Recent trials have shown that drugs targeting DNA repair, immune activators, and conventional cytotoxic agents all improve outcomes.
- I-SPY2 is a platform phase 2 trial utilizing an adaptive design to compare new regiments with conventional chemotherapy using the primary endpoint of pathologic complete response (pCR).
- To date, 7 investigational agents have been tested in I-SPY 2 trial (I-SPY2-990) and compared to control chemotherapy. All agents have numerically superior pCR rates compared to control.

METHODS

- Eligible patients had tumors with one of the following: Stage II or III, or T4, any N, M0, or Regional Stage IV, where supraclavicular lymph nodes are the only metastatic sites.
- The I-SPY2 platform trial tests novel agents given neo-adjuvantly with a control backbone of paclitaxel (T) followed by doxorubicin and cyclophosphamide. Agents investigated in TNBC breast cancer were (control), neratinib (N), veliparib/carboplatin (VC), Trebananib, MK2206, ganitumab, ganetespib, and pembrolizumab. Molecular subtyping based on gene expression was utilized to categorize tumors into 5 response predictive subtypes (RPS-5) Wolf, D., et al *Cancer Cell*, 2022.
- MammaPrint categorization is by Agendia, Inc., using a predefined threshold applied to the MP 70-gene risk score evaluated on Agilent 44K arrays.

RESULTS

Prevalence of TNBC in I-SPY2 and Bayesian-estimated pCR rates



* Regimens meeting graduation threshold

Classification of TNBC by Enhanced Immune (Immune+) and DNA Repair Deficient (DRD+) gene signatures

	TN/Immune-	TN/Immune+
TN/DRD-	26%	7%
TN/DRD+	11%	56%

TN Response Predictive Subtypes based on Immune and DRD

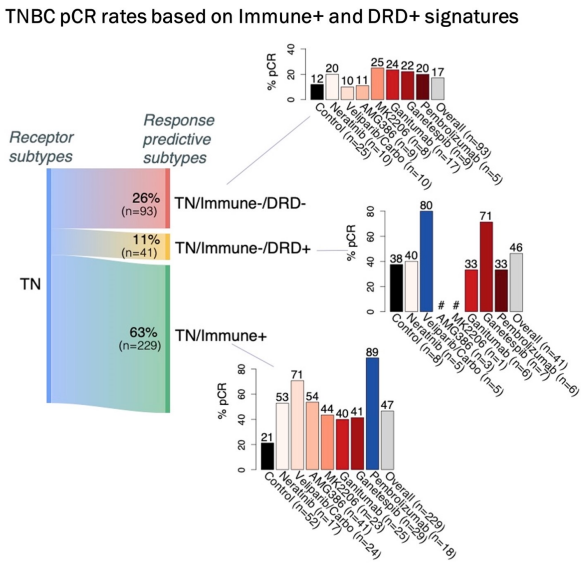
1. TN/Immune-/DRD-
2. TN/Immune-/DRD+
3. TN/Immune+

Enhanced Immune+ signature = average of Dendritic Cell (Danaher, et al. J Immunother Cancer 5:18 2017 PMID: 28239471) and STAT1 (Rody, et al. Breast Cancer Res 11:R15 2009 PMID: 19272155) signatures

DNA Repair Deficient+ signature = PARPi7 signature (Daemen, et al. Breast Cancer Res Treat 135:505 2012 PMID: 22875744)

RESULTS

TNBC pCR rates based on Immune+ and DRD+ signatures



SUMMARY

- Only pembrolizumab and veliparib/carboplatin reached the threshold for graduation in TNBC.
- Gene expression profiling identified tumors with an Enhanced Immune and DNA Damage Repair Deficient signatures.
- 56% of TNBC were both Immune+ and DRD+.
- TNBC with Immune + signatures had a high pCR rate in patients treated with paclitaxel/pembrolizumab.
- TNBC with DRD+ signatures had a high pCR rate to veliparib/carboplatin therapy. These tumors also had a higher pCR rate to control chemotherapy; pembrolizumab did not have superior pCR rates compared to non-pembrolizumab therapies.
- Classification of TNBC into subtypes may reveal efficacy for specific drugs that are not evident in the entire group, e.g. ganetespib has a pCR rate of 71% (5/7) in the Immune-/DRD+ group.
- TNBC with neither signature have poor responses to the drugs tested thus far in I-SPY2.

CONCLUSIONS

- TNBC is a molecular heterogeneous disease.
- Classification of TNBC into specific subtypes associates with response to individual therapies.
- Identifying molecular subtypes of TNBC shows that not all subtypes benefit from addition of an immune checkpoint inhibitor to neoadjuvant treatment.
- Advances in molecular classification will allow improved precision application of neoadjuvant therapy.

I-SPY2's ADAPTIVE TRIAL DESIGN

I-SPY 2 is a multicenter, phase 2 trial using response-adaptive randomization within biomarker subtypes to evaluate a series of novel agents when added to standard neoadjuvant therapy for women with high-risk stage II/III breast. Within each patient subtype, participants are assigned to one of several investigational therapies or the control regimen (4:1). Randomization probabilities are proportional to current probabilities that the respective therapies have a higher pCR rate than control rate in the respective subtypes. ***The primary endpoint is pathologic complete response (pCR, no residual disease in breast or nodes) at surgery.***

The goal is to identify/graduate regimens that have ≥85% Bayesian predictive probability of success (statistical significance) in a 300-patient phase 3 neoadjuvant trial, defined by hormone-receptor (HR) & HER2 status & MammaPrint (MP).

Regimens may leave the trial for one of four reasons: Graduate, Drop for futility (< 10% probability of success), Drop for safety issues, or accruing maximum sample size (10%< probability of success <85%).

I-SPY2 study schema and adaptive randomization based on probabilities of agents of achieving pCR within a given subtype

Regimen specific pCR rates for TNBC based on Immune+ and DRD+ signatures

pCR rates	Control	Neratinib	V/C	Trebaninib	MK2206	Ganitumab	Ganetespib	Pembro
All TNBC	28% (21-35%)	38% (22-50%)	51% (36-66%)	37% (21-53%)	40% (25-55%)	32% (17-46%)	38% (23-53%)	60% (44-75%)
Immune-/DRD-	12% (3-31%)	20% (3-56%)	10% (0-45%)	11% (0-48%)	25%(3%-65%)	24% (7-50%)	22% (3-60%)	20% (1-72%)
Immune-/DRD+	38% (9-76%)	40% (5-85%)	80% (28-99%)	#	#	33% (4-78%)	71% (29-96%)	33% (4-78%)
Immune+	19% (10-33%)	53% (28-77%)	71% (49-87%)	54% (37-69%)	43% (23-66%)	40% (21-61%)	41% (24-61%)	89% (65-99%)
					Graduated			

*** Observed pCR rate with 95% binomial exact (Clopper and Pearson) confidence interval**

 # Not evaluated. Subset with <5 samples

ACKNOWLEDGEMENTS:

With support from Quantum Leap Healthcare Collaborative, FNIH, NCI (Grant 28XS197 P-0518835, P01 CA210961), Safeway Foundation, William K. Bowes, Jr. Foundation, The Breast Cancer Research Foundation, UCSF, the Biomarkers Consortium, Salesforce, Novella Clinical, CCS Associates, Berry Consultants, Agendia, OpenClinica, Give Breast Cancer the Boot, Stand up for Cancer, Atwater Trust, CA Breast Cancer Research Program, Seagen, AstraZeneca, Daiichi-Sankyo, Merck, Dynavax, Pfizer, Puma Biotechnology, AbbVie, Madrigal Pharmaceuticals, Genentech, Amgen, Plexxikon, Regeneron, G1 Therapeutics, GSK, Byondis, Eli Lilly, Sanofi, Apotex, Trisalus Life Sciences. Initial support from IQVIA, Johnson & Johnson, San Francisco Foundation, Eisai Company, Side Out Foundation, Harlan Family, Avon Foundation for Women, Alexandria Real Estate Equities. Sincere thanks to Anna Barker, our DSMB (Harold Burstein, Elizabeth Frank, Steven Goodman, Robert Mass, Janet Wittes, Tiffany Traina and Deborah Laxague), Ken Buetow and CaBIG, our patients, advocates and investigators.

Pembrolizumab label language:

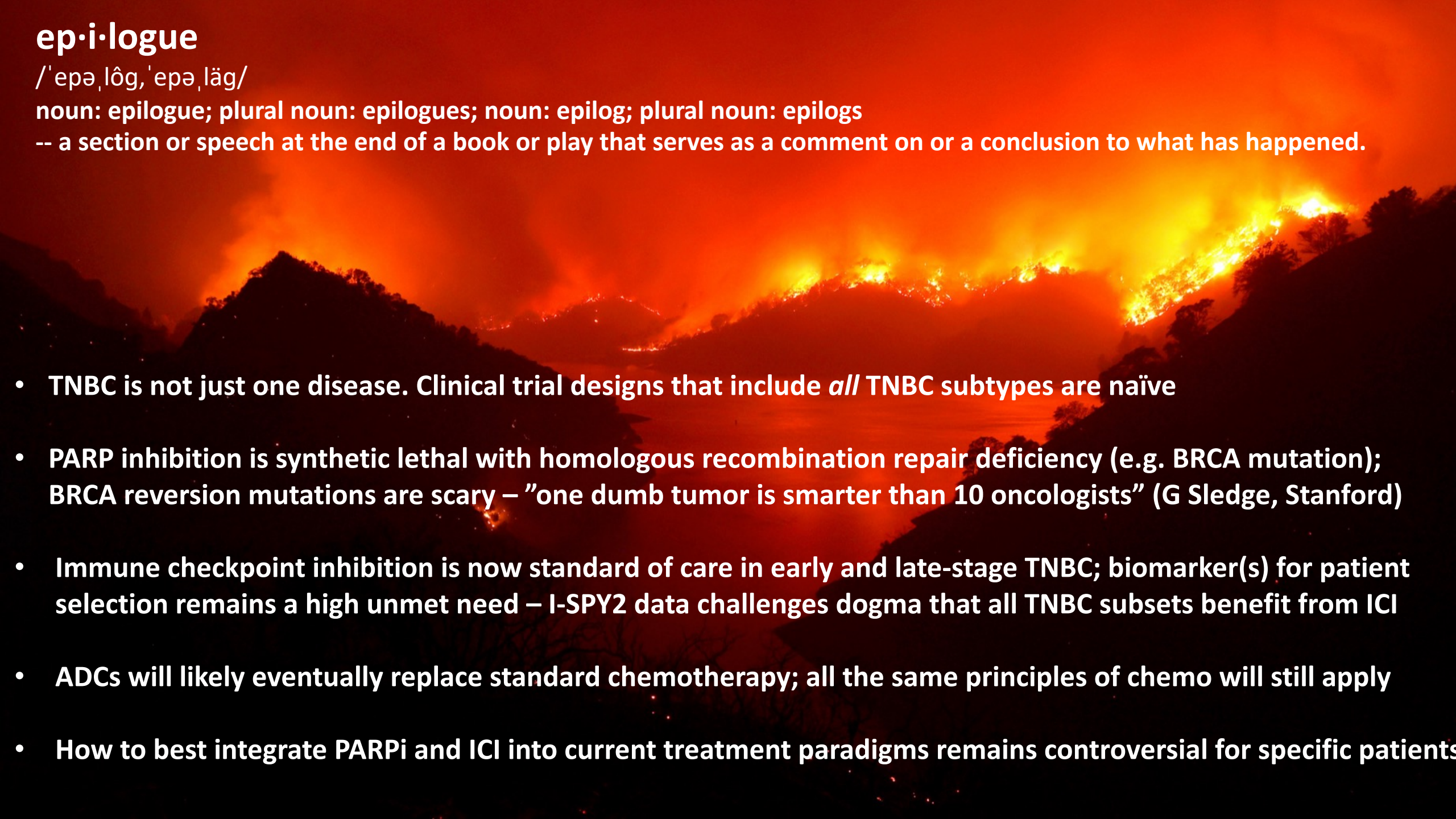
Triple-Negative Breast Cancer (TNBC)

- for the treatment of patients with high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery. (1.18)

Olaparib label language:

Breast cancer

- for the adjuvant treatment of adult patients with deleterious or suspected deleterious g*BRCA*m human epidermal growth factor receptor 2 (HER2)-negative high risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for olaparib (1.5, 2.1).



ep·i·logue

/ˈepəˌlôg,ˈepəˌläg/

noun: epilogue; plural noun: epilogues; noun: epilog; plural noun: epilogs

-- a section or speech at the end of a book or play that serves as a comment on or a conclusion to what has happened.

- **TNBC is not just one disease. Clinical trial designs that include *all* TNBC subtypes are naïve**
- **PARP inhibition is synthetic lethal with homologous recombination repair deficiency (e.g. BRCA mutation); BRCA reversion mutations are scary – ”one dumb tumor is smarter than 10 oncologists” (G Sledge, Stanford)**
- **Immune checkpoint inhibition is now standard of care in early and late-stage TNBC; biomarker(s) for patient selection remains a high unmet need – I-SPY2 data challenges dogma that all TNBC subsets benefit from ICI**
- **ADCs will likely eventually replace standard chemotherapy; all the same principles of chemo will still apply**
- **How to best integrate PARPi and ICI into current treatment paradigms remains controversial for specific patients**