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Early Stage TNBC: Reviewing Different Strategies and Management

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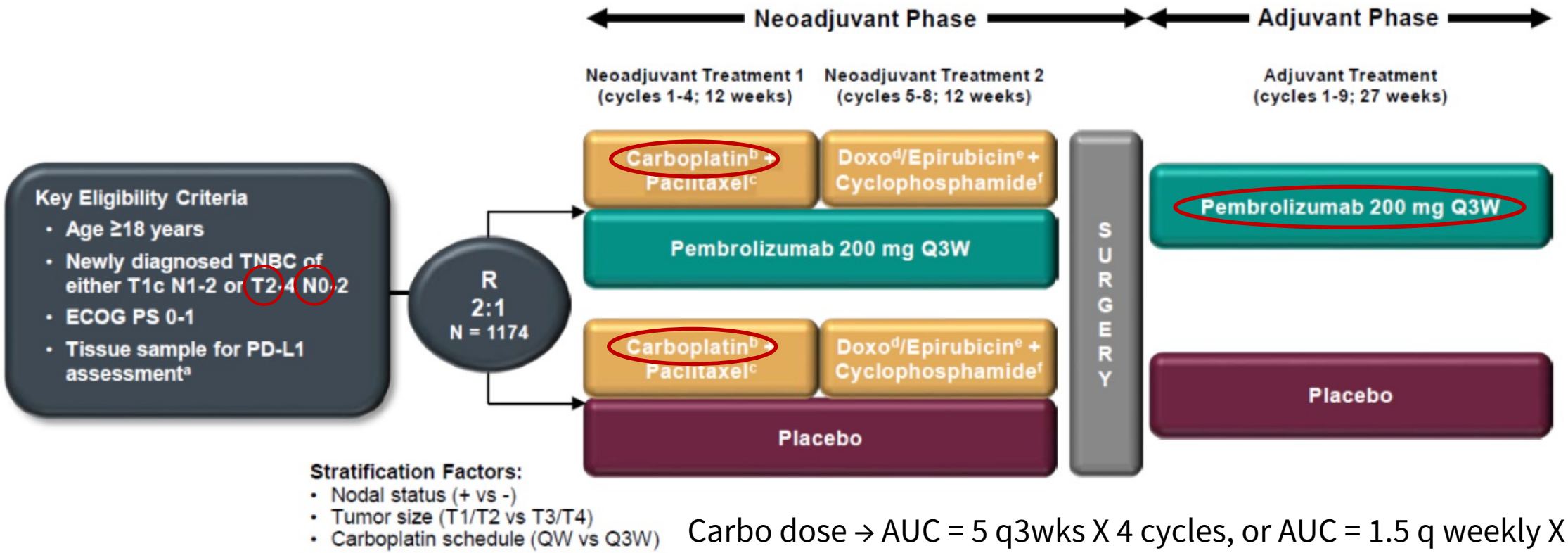
COI declaration relevant to topic: AZ

KEYNOTE-522 Study Design (NCT03036488)



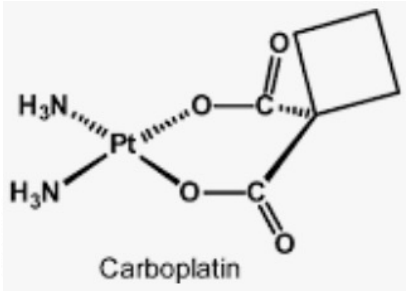
Carbo dose → AUC = 5 q3wks X 4 cycles, or AUC = 1.5 q weekly X 12

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 backbone = paclitaxel/carbo → AC q3 wks X 4
Pembro continued q3 wks adjuvantly X 9 cycles (post-op)

Elements in the same row (period) share physical properties, while elements in the same column (group) share similar reactivity with other elements



Periodic Table of the Elements

Atomic Number | Boiling Point
Symbol
Name
Atomic Mass

1 IA 1A	2 IIA 2A	3 IIIB 3B	4 IVB 4B	5 VB 5B	6 VIB 6B	7 VIIB 7B	8	9 VIII 8	10	11 IB 1B	12 IIB 2B	13 IIIA 3A	14 IVA 4A	15 VA 5A	16 VIA 6A	17 VIIA 7A	18 VIIIA 8A
1 -252.762 H Hydrogen 1.008																	2 -268.93 He Helium 4.003
3 1342 Li Lithium 6.941	4 2471 Be Beryllium 9.012											5 4000 B Boron 10.811	6 graphite 3825 SP C Carbon 12.011	7 -195.798 N Nitrogen 14.007	8 -182.953 O Oxygen 15.999	9 -188.12 F Fluorine 18.998	10 -246.053 Ne Neon 20.180
11 882.940 Na Sodium 22.990	12 1090 Mg Magnesium 24.305											13 2519 Al Aluminum 26.982	14 3265 Si Silicon 28.086	15 white 280.5 P Phosphorus 30.974	16 444.61 S Sulfur 32.066	17 -101.5 Cl Chlorine 35.453	18 -185.847 Ar Argon 39.948
19 759 K Potassium 39.098	20 1484 Ca Calcium 40.078	21 2836 Sc Scandium 44.956	22 3287 Ti Titanium 47.88	23 3407 V Vanadium 50.942	24 2671 Cr Chromium 51.996	25 2061 Mn Manganese 54.938	26 2861 Fe Iron 55.933	27 2927 Co Cobalt 58.933	28 2913 Ni Nickel 58.693	29 2562 Cu Copper 63.546	30 907 Zn Zinc 65.39	31 2204 Ga Gallium 69.732	32 2833 Ge Germanium 72.61	33 616 SP As Arsenic 74.922	34 685 Se Selenium 78.972	35 58.8 Br Bromine 79.904	36 -153.34 Kr Krypton 84.80
37 688 Rb Rubidium 84.468	38 1382 Sr Strontium 87.62	39 3345 Y Yttrium 88.906	40 4409 Zr Zirconium 91.224	41 4744 Nb Niobium 92.906	42 4639 Mo Molybdenum 95.95	43 4265 Tc Technetium 98.907	44 4150 Ru Ruthenium 101.07	45 3695 Rh Rhodium 102.906	46 2963 Pd Palladium 106.42	47 2162 Ag Silver 107.868	48 767 Cd Cadmium 112.411	49 2072 In Indium 114.818	50 2602 Sn Tin 118.71	51 1587 Sb Antimony 121.760	52 988 Te Tellurium 127.6	53 184.4 I Iodine 126.904	54 -108.09 Xe Xenon 131.29
55 671 Cs Cesium 132.905	56 1897 Ba Barium 137.327	57-71	72 4603 Hf Hafnium 178.49	73 5458 Ta Tantalum 180.948	74 5555 W Tungsten 183.85	75 5596 Re Rhenium 186.207	76 5012 Os Osmium 190.23	77 4428 Ir Iridium 192.22	78 3825 Pt Platinum 195.08	79 2856 Au Gold 196.967	80 356.62 Hg Mercury 200.59	81 1473 Tl Thallium 204.383	82 1749 Pb Lead 207.2	83 1564 Bi Bismuth 208.980	84 962 Po Polonium [208.982]	85 337 At Astatine 209.987	86 -61.7 Rn Radon 222.018
87 677 Fr Francium 223.020	88 1737 Ra Radium 226.025	89-103	104 unknown Rf Rutherfordium [261]	105 unknown Db Dubnium [262]	106 unknown Sg Seaborgium [266]	107 unknown Bh Bohrium [264]	108 unknown Hs Hassium [269]	109 unknown Mt Meitnerium [268]	110 unknown Ds Darmstadtium [269]	111 unknown Rg Roentgenium [272]	112 unknown Cn Copernicium [277]	113 unknown Uut Ununtrium unknown	114 unknown Fl Flerovium [289]	115 unknown Uup Ununpentium unknown	116 unknown Lv Livermorium [298]	117 unknown Uus Ununseptium unknown	118 unknown Uuo Ununoctium unknown

Lanthanide Series	57 3464 La Lanthanum 138.906	58 3443 Ce Cerium 140.115	59 3520 Pr Praseodymium 140.908	60 3074 Nd Neodymium 144.24	61 3000 Pm Promethium 144.913	62 1794 Sm Samarium 150.36	63 1529 Eu Europium 151.966	64 3273 Gd Gadolinium 157.25	65 3230 Tb Terbium 158.925	66 2567 Dy Dysprosium 162.50	67 2700 Ho Holmium 164.930	68 2868 Er Erbium 167.26	69 1950 Tm Thulium 168.934	70 1196 Yb Ytterbium 173.04	71 3402 Lu Lutetium 174.967
Actinide Series	89 3198 Ac Actinium 227.028	90 4788 Th Thorium 232.038	91 4027 Pa Protactinium 231.036	92 4131 U Uranium 238.029	93 4174 Np Neptunium 237.048	94 3228 Pu Plutonium 244.064	95 2011 Am Americium 243.061	96 3100 Cm Curium 247.070	97 2627 Bk Berkelium 247.070	98 unknown Cf Californium 251.080	99 unknown Es Einsteinium [254]	100 unknown Fm Fermium 257.095	101 unknown Md Mendelevium 258.1	102 unknown No Nobelium 259.101	103 unknown Lr Lawrencium [262]

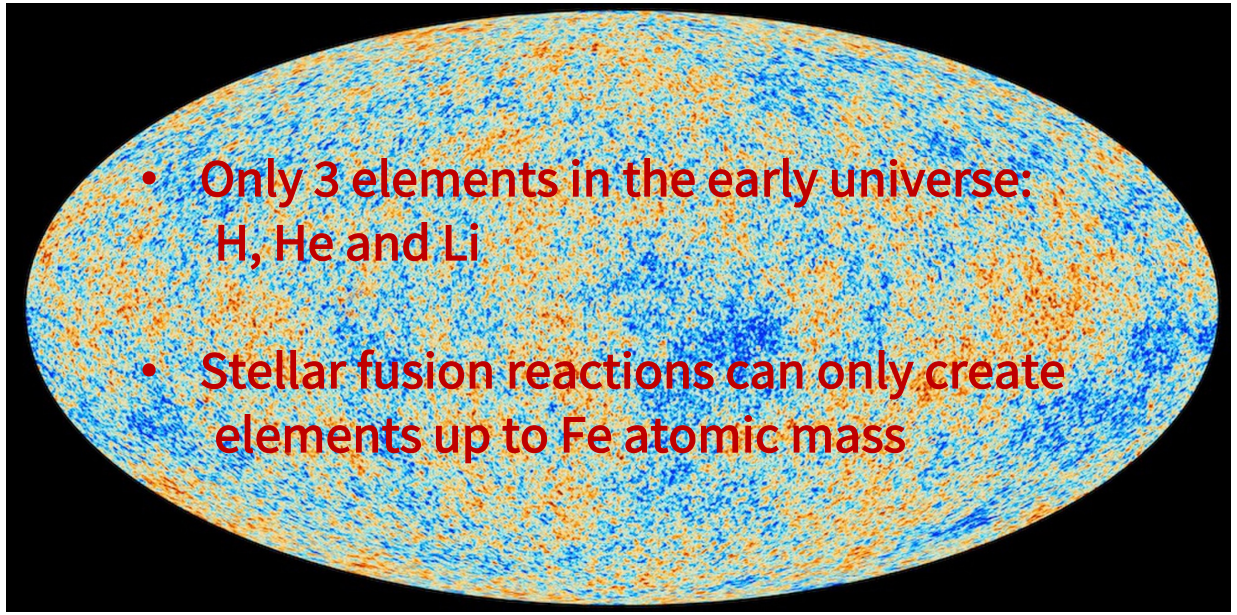
Alkali Metal | Alkaline Earth | Transition Metal | Basic Metal | Semimetal | Nonmetal | Halogen | Noble Gas | Lanthanide | Actinide

78
Pt
Platinum
195.085

Genesis of Elemental Platinum by Rapid Neutron Capture

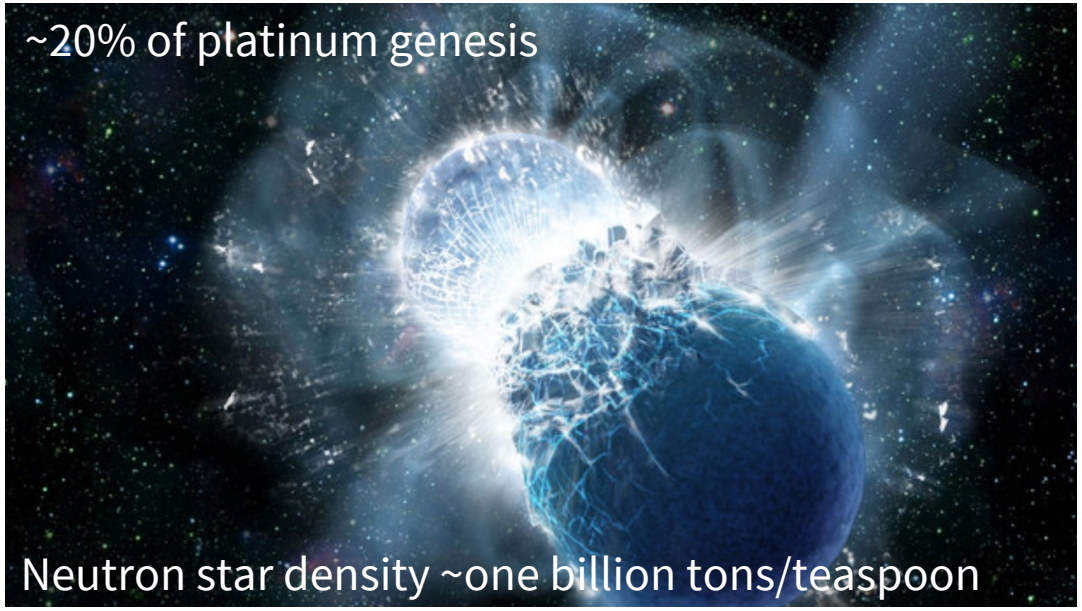
Rare -- 0.005ppm in the earth's crust

The Big Bang: 13.787±0.020 billion years ago

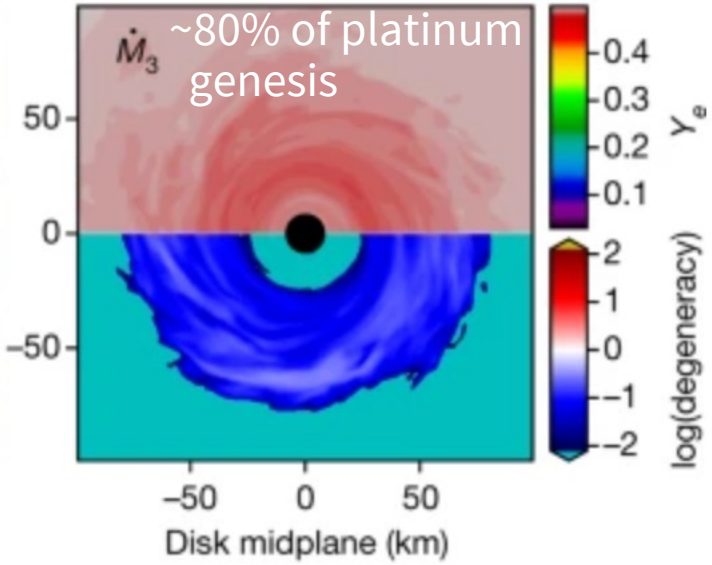


2013 map of cosmic background radiation left over from the Big Bang (discovered by accident in 1964 by American radio astronomers Arno Penzias and Robert Wilson, earning them the 1978 Nobel Prize in Physics)

-- *Taken by the ESA's Planck spacecraft, capturing the oldest light in the universe.*



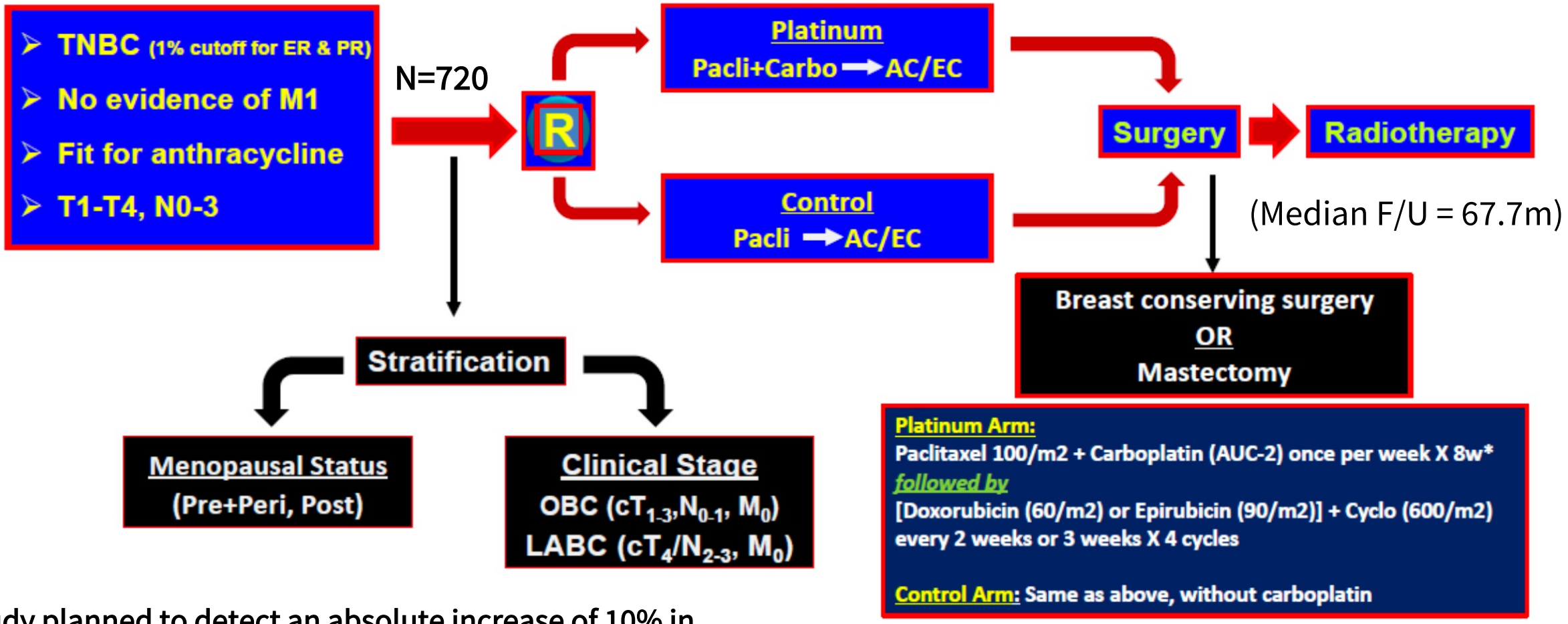
Neutron star merger GW170817 (130 million light-years from earth) – generated ~500 earth masses of Pt



Collapsar accretion model and nucleo-synthetic elemental platinum yields by rapid neutron capture following massive star supernova explosions and collapse to black holes.

TMC Neoadjuvant Platinum TNBC Study

GeparSixto and BrighTNess showed increased EFS by addition of carbo to neoadj tax/anthra, but CALGB 40603 did not.



→ Study planned to detect an absolute increase of 10% in EFS from a control arm 5-year EFS of 30%, with a 2-sided alpha of 0.05 and power of 80%.

*Gupta S, et al. Single agent weekly paclitaxel as neoadjuvant chemotherapy in locally advanced breast cancer: a feasibility study. Clin Oncol (R Coll Radiol). 2012 Nov;24(9):604-9

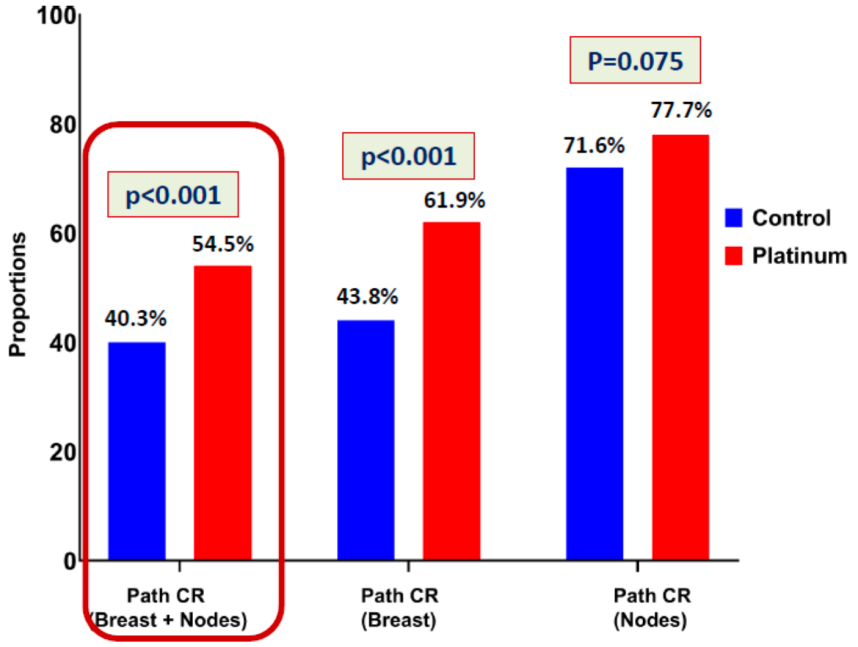
Patient & Tumor Characteristics

	Control Arm (N=356)	Platinum Arm (N=361)	Total (N=717)
Clinical Stage (pre-NACT)			
Operable (cT1-3, N0-1)	142 (39.9%)	143 (39.6%)	285 (39.7%)
Locally Advanced (cT4 / N2-3)	214 (60.1%)	218 (60.4%)	432 (60.3%)
Clinical Node Status (pre-NACT)			
Negative	39 (11.0%)	41 (11.4%)	80 (11.2%)
Positive	317 (89.0%)	320 (88.6%)	637 (88.8%)
Clinical T-size (pre-NACT) (cm)			
Median (Range)	6.0 (1.2-20.0)	6.0 (1.5-20.0)	6.0 (1.2-20.0)
≤ 5 cm	79 (22.2%)	81 (22.4%)	160 (22.3%)
> 5 cm	277 (77.8%)	280 (77.6%)	557 (77.7%)

pCR and EFS in the ITT population

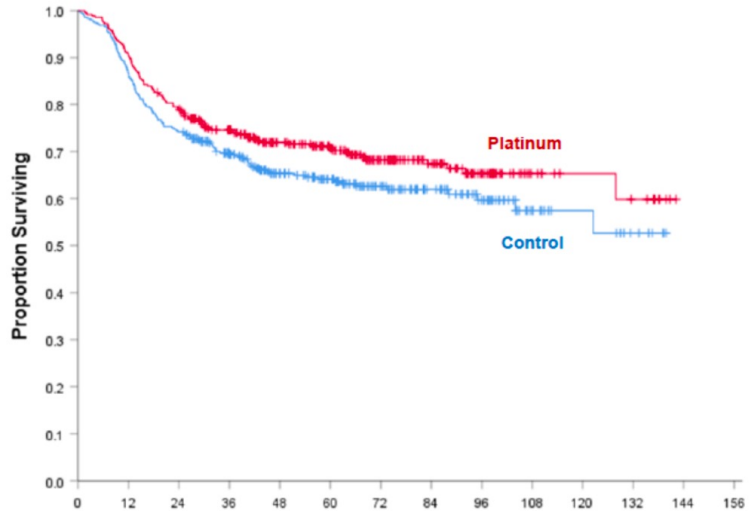
San Antonio Breast Cancer Symposium®, December 6-10, 2022

ITT: Pathological Response to NACT by Rx-Arm



San Antonio Breast Cancer Symposium®, December 6-10, 2022

Event-free Survival in ITT (N=717)



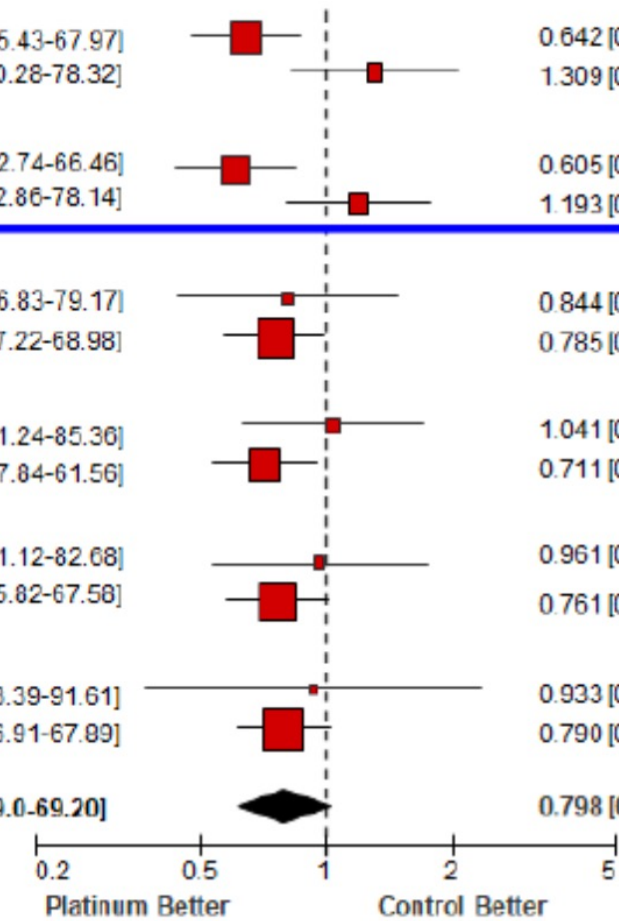
Toxicity

San Antonio Breast Cancer Symposium®, December 6-1

Toxicity	Platinum (N=361)	Control (N=356)		Platinum (N=361)	Control (N=356)
	Any Grade			Grade III or Worse	
Neutropenia	56 (15.5%)	18 (5.1%)		31 (8.6%)	7 (2.0%)
Anemia	23 (6.4%)	9 (2.5%)		7 (1.9%)	1 (0.3%)
Thrombocytopenia	21 (5.8%)	4 (1.1%)		7 (1.9%)	0 (0%)
Neutropenic Fever	-	-		16 (4.4%)	10 (2.8%)

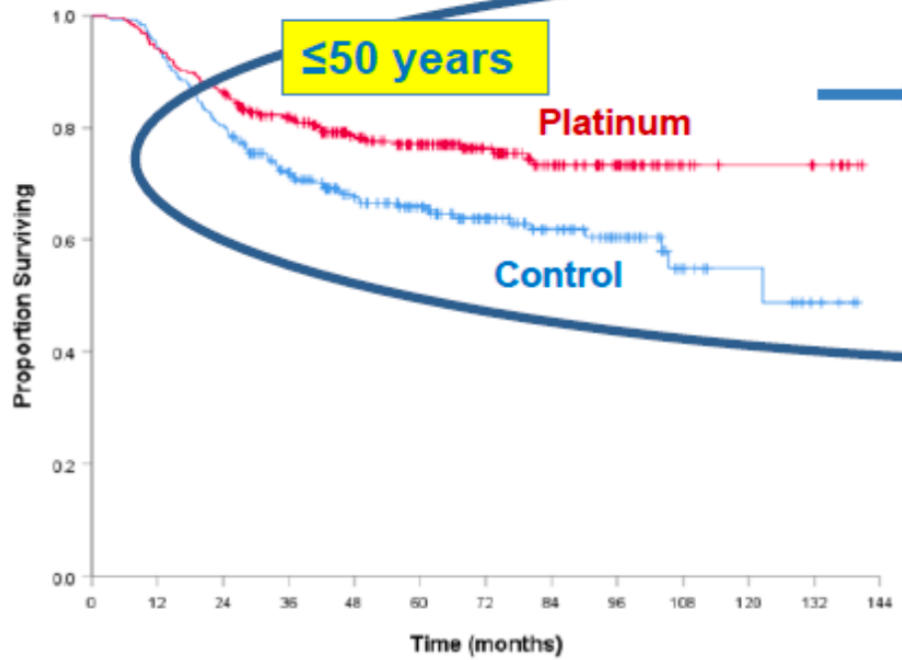
Event-free Survival: Subgroup Analysis

Subgroup	No. of patients with an event/total Platinum	Control	5-Yr Event-free Survival % [95% CI] Platinum	Control	Hazard Ratio [95% CI]	'P' value for Interaction
Age						
<=50 years	71/255	98/245	74.2 [68.71-79.69]	61.7 [55.43-67.97]	0.642 [0.473, 0.871]	0.010
>50 years	40/106	33/111	62.0 [52.20-71.80]	69.3 [60.28-78.32]	1.309 [0.825, 2.076]	
Menopausal Status						
Pre/peri-menopausal	58/209	87/209	75.0 [69.12-80.88]	59.6 [52.74-66.46]	0.605 [0.434, 0.843]	0.010
Post-menopausal	53/152	44/147	64.7 [56.66-72.74]	70.5 [62.86-78.14]	1.193 [0.800, 1.780]	
Family History of Cancer						
Yes	18/62	24/72	75.4 [64.62-86.18]	68.0 [56.83-79.17]	0.844 [0.457, 1.558]	0.836
No	93/299	107/284	69.7 [64.41-74.99]	63.1 [57.22-68.98]	0.785 [0.595, 1.037]	
Clinical Stage						
OBC (T1-3/N0-1)	32/143	31/142	78.6 [71.35-85.85]	78.3 [71.24-85.36]	1.041 [0.635, 1.706]	0.190
LABC (T4/N2-3)	79/218	100/214	65.4 [58.93-71.87]	54.7 [47.84-61.56]	0.711 [0.529, 0.955]	
Clinical T Size						
<=5 cm	21/81	22/79	78.3 [69.09-87.51]	71.9 [61.12-82.68]	0.961 [0.528, 1.749]	0.469
>5 cm	90/280	109/277	68.6 [63.11-74.09]	61.7 [55.82-67.58]	0.761 [0.575, 1.006]	
Clinical Node Status						
Negative	9/41	9/39	76.8 [63.47-90.13]	77.5 [63.39-91.61]	0.933 [0.370, 2.352]	0.744
Positive	102/320	122/317	70.0 [64.90-75.10]	62.4 [56.91-67.89]	0.790 [0.608, 1.028]	
All Patients	111/361	131/356	**70.7 [65.80-75.60]**	**64.1 [59.0-69.20]**	0.798 [0.620, 1.028]	



Overall Survival in Younger and Older Patients

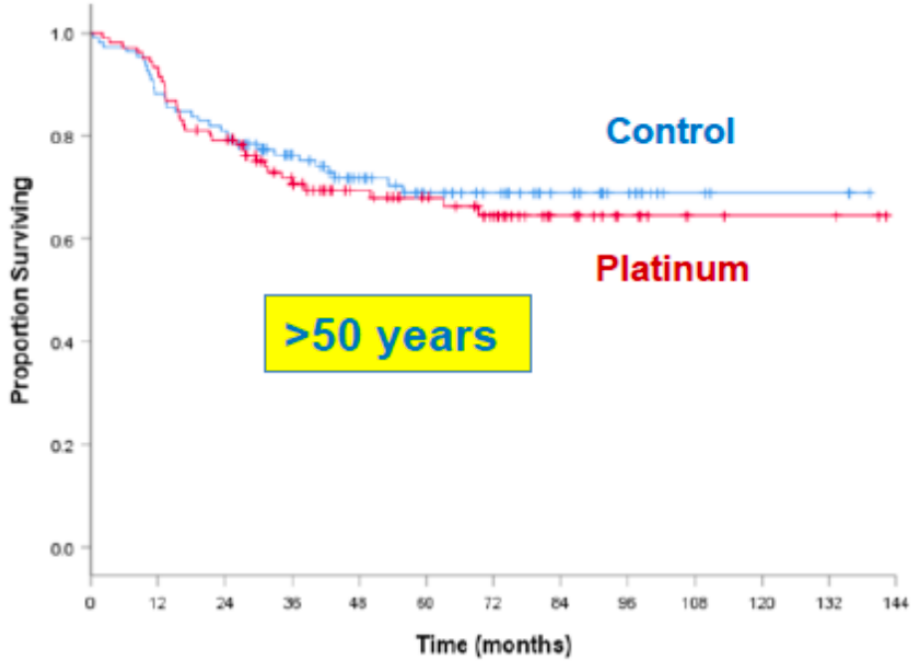
≤50 years



	Control											
Control	245	232	197	160	125	104	74	53	35	15	9	4
Platinum	255	240	220	190	153	127	91	64	40	15	11	9

	Platinum	Control
5-year OS (95% CI)	77.1% (71.81 - 82.39%)	65.9% (59.82 - 71.98%)
HR (95% CI)	0.611 (0.440 - 0.848)	
'p'	0.003	

>50 years



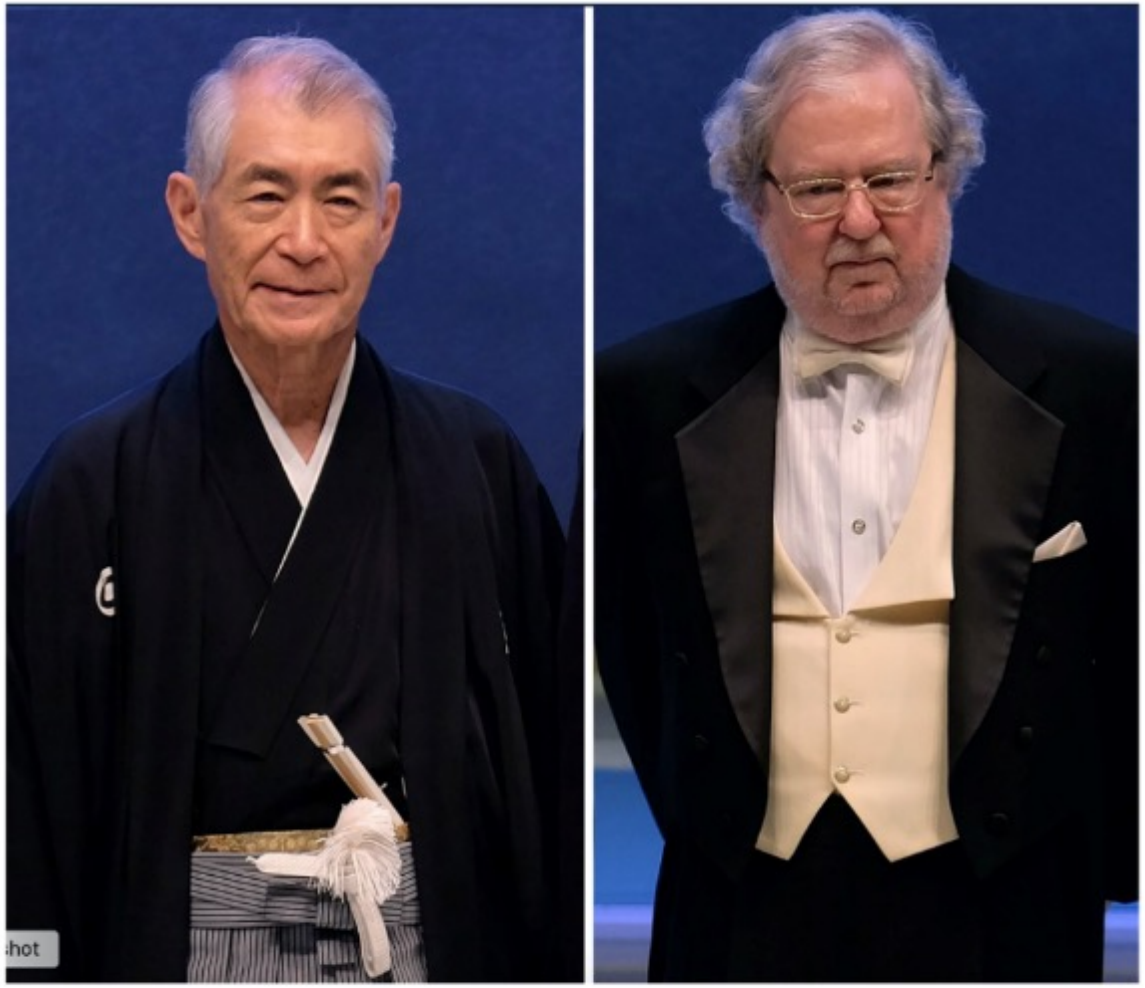
	Control											
Control	111	98	90	69	54	43	32	21	13	5	3	3
Platinum	106	99	83	62	48	41	31	19	11	4	3	3

	Platinum	Control
5-year OS (95% CI)	68.0% (58.79 - 77.21%)	68.9% (59.69 - 78.11%)
HR (95% CI)	1.132 (0.698 - 1.835)	
'p'	0.615	

CONCLUSIONS

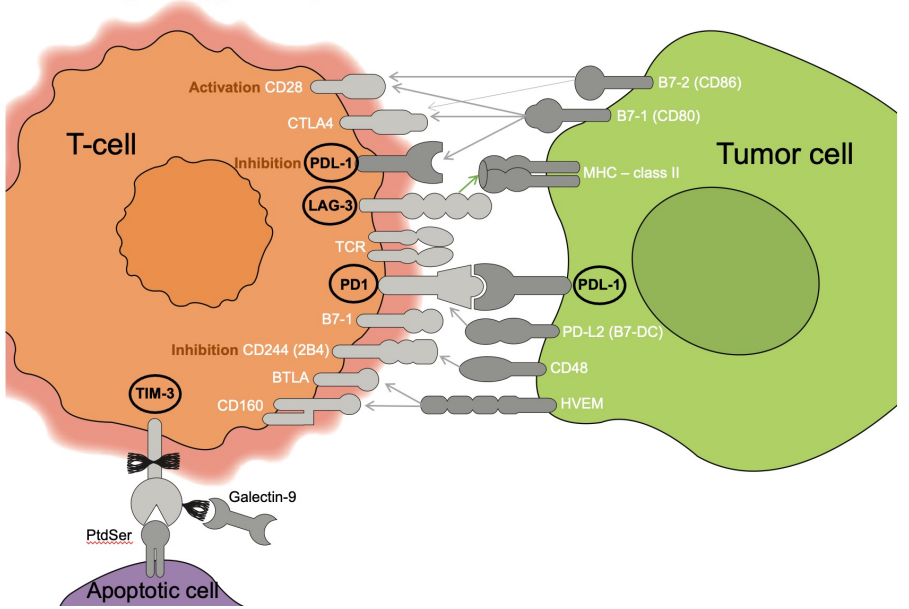
- Addition of carboplatin to sequential taxane-anthracycline neoadjuvant chemotherapy significantly improves overall survival and tends to improve event-free survival among patients with operable and locally-advanced TNBC.
  - The benefit seems confined to younger or premenopausal patients in whom there is substantial and significant improvement in EFS and OS.
- Addition of carboplatin to taxane-anthracycline neoadjuvant chemotherapy should be the standard of treatment of patient who are ≤50 or pre-MP

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



Tasuku Honjo and James Allison

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

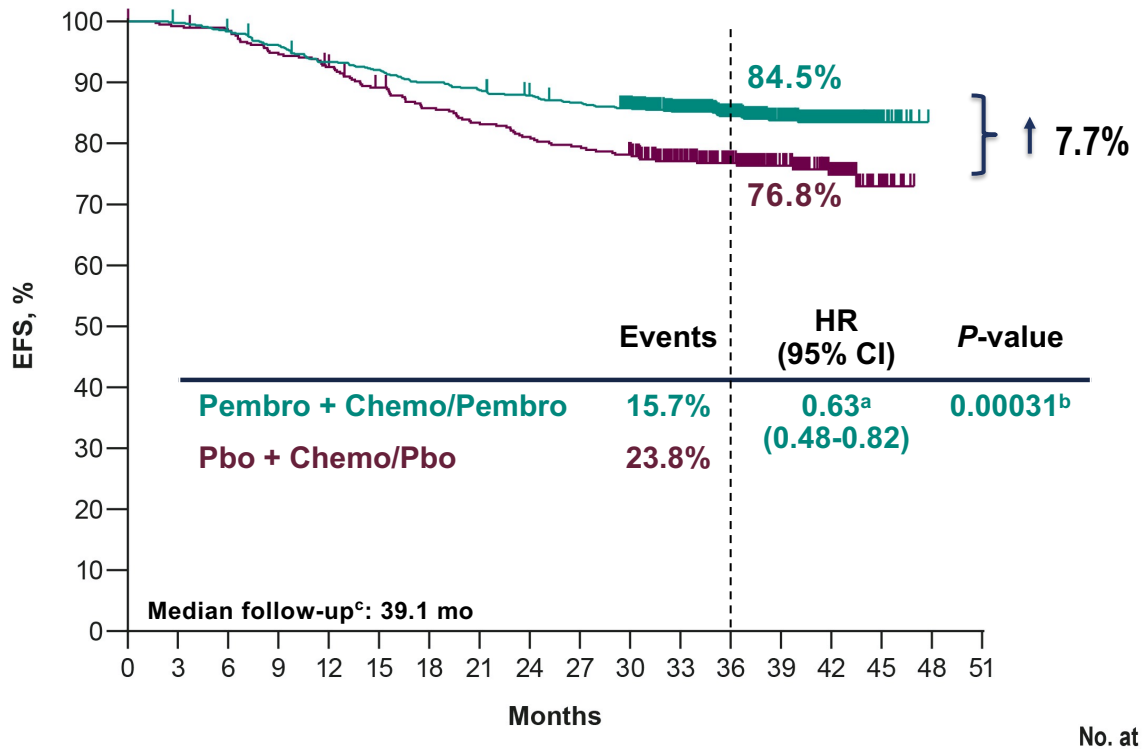


Immunoregulatory interactions principally involving immune checkpoint blockade[2]

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.

EFS and DRFS: Statistically Significant at IA4

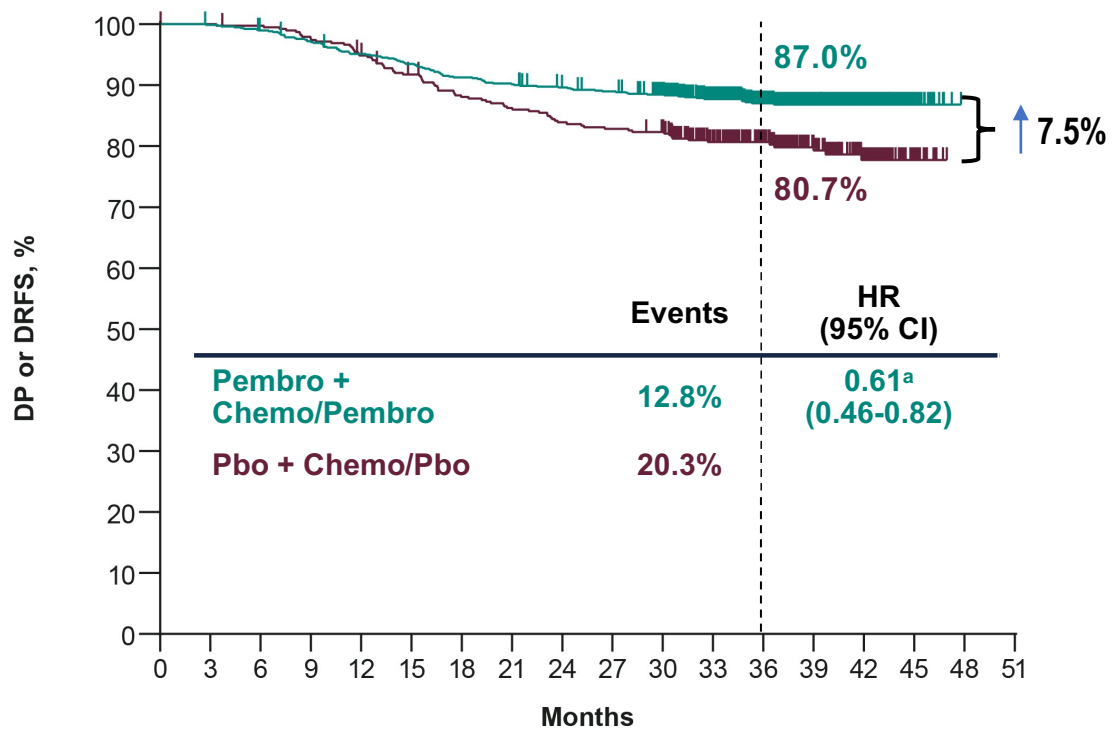
EFS



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

DRFS



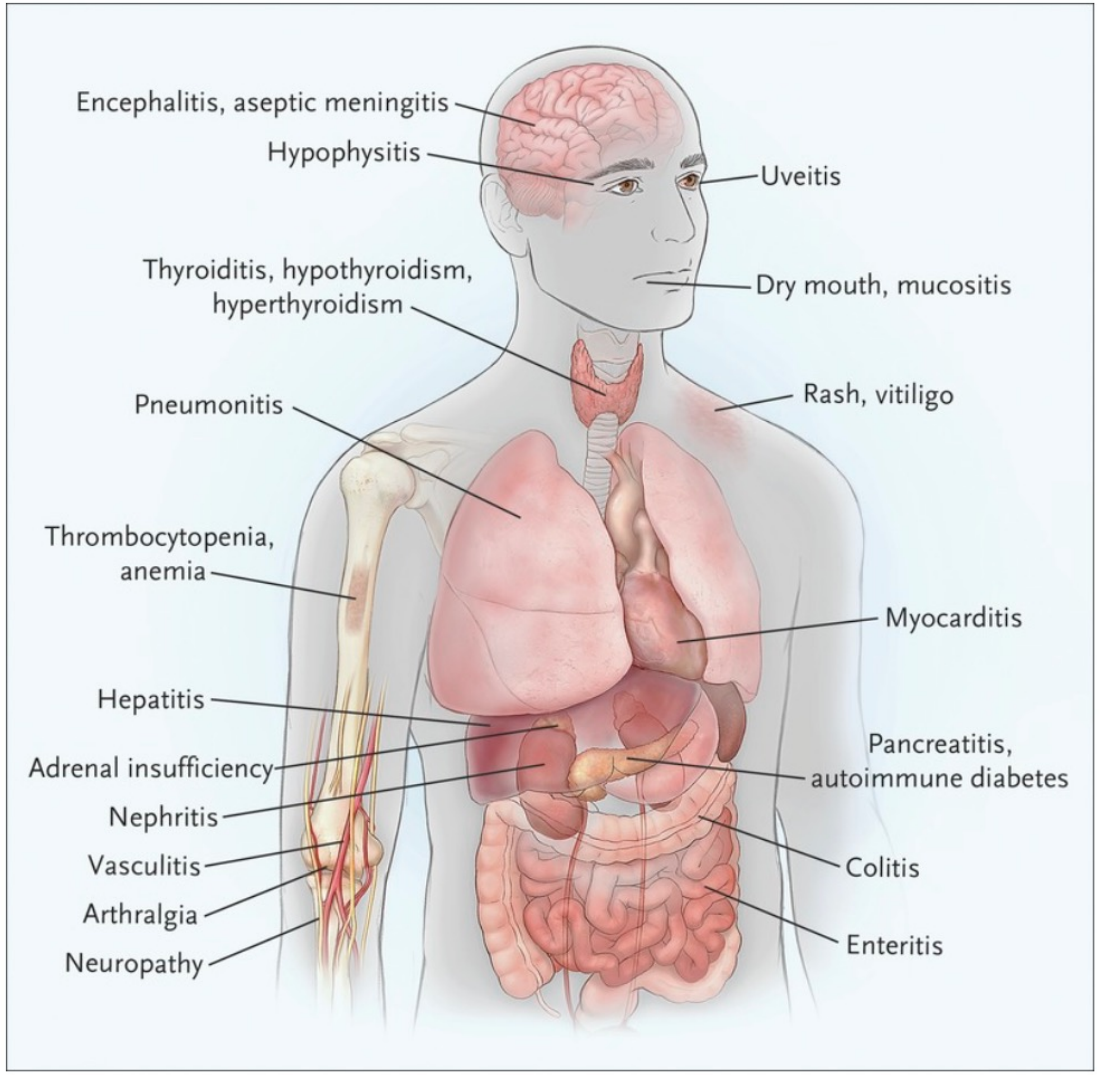
No. at Risk

Pembro + Chemo/Pembro	784	782	773	758	741	728	711	702	692	685	663	561	439	308	167	29	0	0
Pbo + Chemo/Pbo	390	389	387	379	367	352	337	330	321	317	312	259	202	143	84	17	0	0

Schmid et al, ESMO virtual plenary 2021.

[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.

Immune-Related Adverse Events Associated with Immune Checkpoint Blockade



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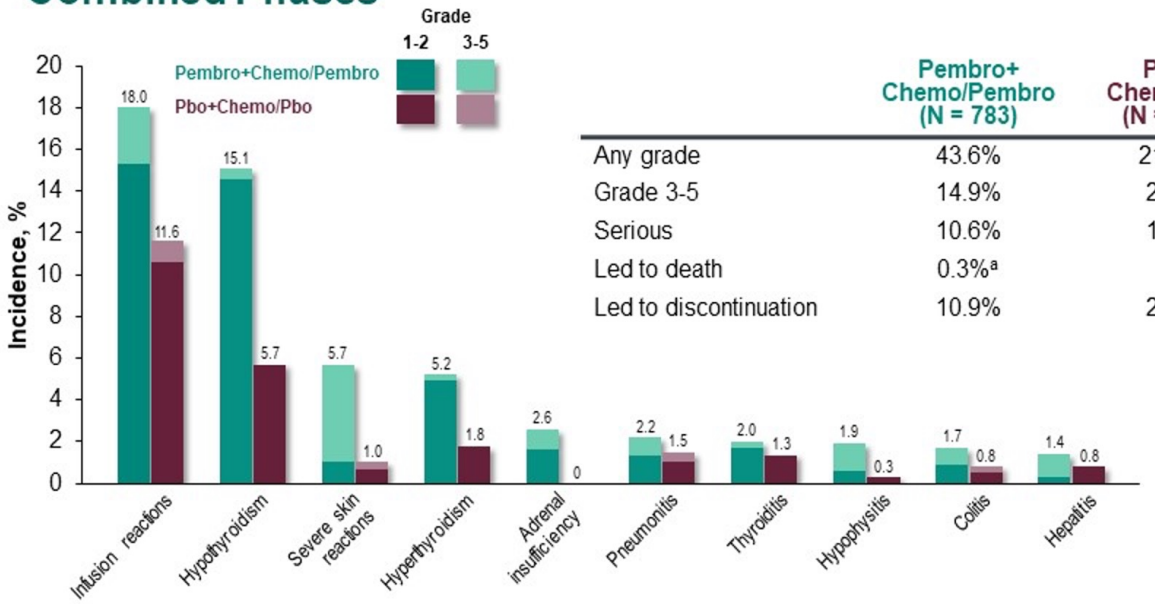
Immune-Mediated AEs and Infusion Reactions in Combined Phases



	Pembro+ Chemo/Pembro (N = 783)	Pbo+ Chemo/Pbo (N = 389)
Any grade	43.6%	21.9%
Grade 3-5	14.9%	2.1%
Serious	10.6%	1.3%
Led to death	0.3%[a]	0
Led to discontinuation	10.9%	2.6%

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

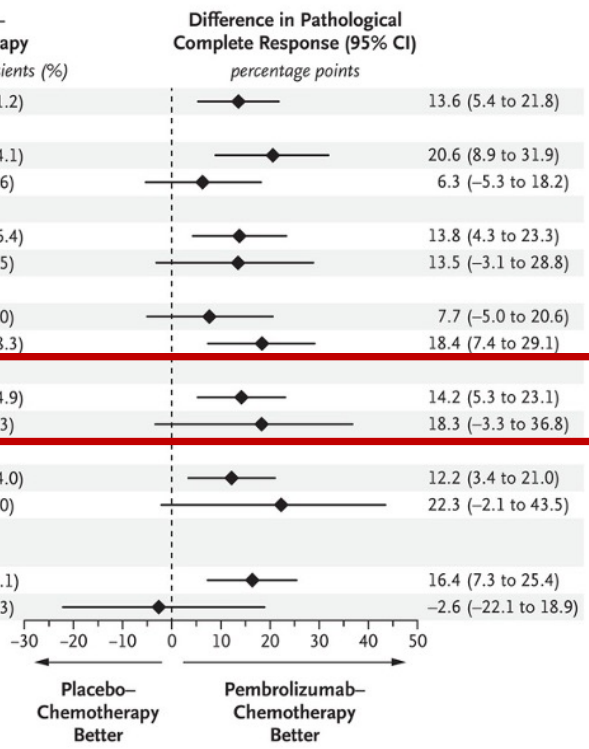
1 patient from pneumonitis and 1 patient from autoimmune encephalitis. Considered regardless of attribution to treatment or immune relatedness by the investigator. Related terms included in addition to preferred terms listed. Data cutoff date: March 23, 2021.

Postow MA, Sidlow R, Hellmann MD. N Engl J Med. 2018 Jan 11;378(2):158-168.
Schmid P, et al. SABCS 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)



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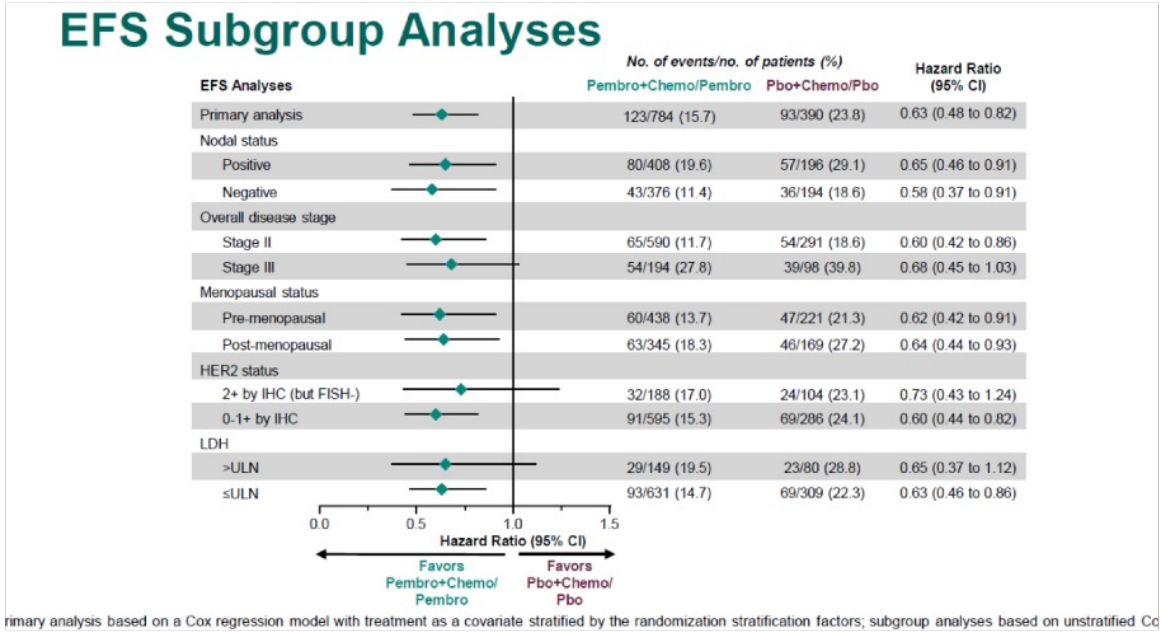
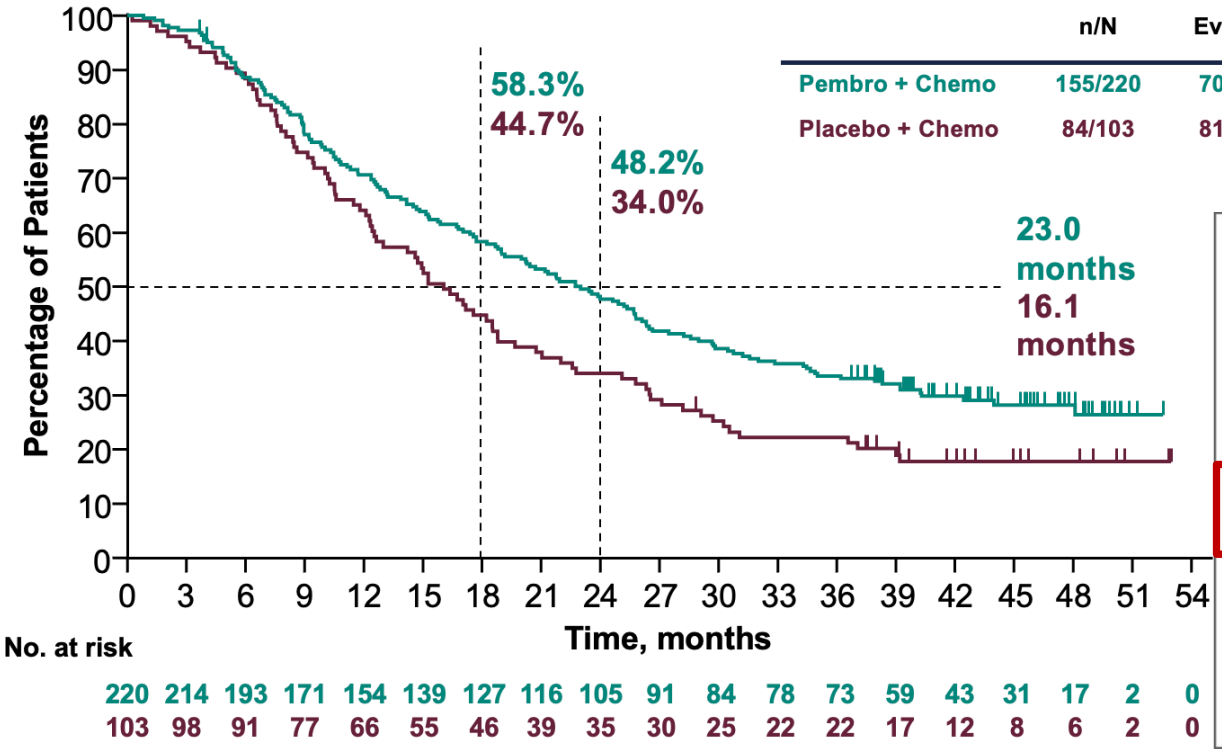
P Schmid et al. N Engl J Med 2020;382:810-821.



*PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies) Combined Positive Score, = # of PD-L1–positive cells (tumor cells, lymphocytes, and macrophages) ÷ total number of tumor cells, multiplied by 100.

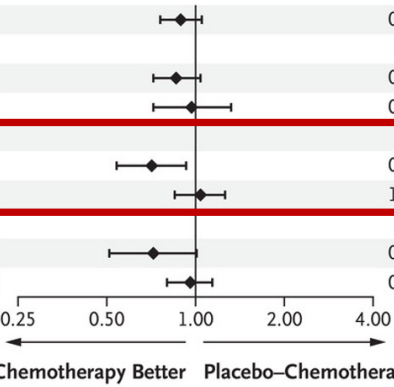
Immune Checkpoint Inhibition in Metastatic TNBC

KEYNOTE-355: Overall Survival at PD-L1 CPS ≥10



	n/N	Events	HR (95% CI)	P-value (one-sided)
Pembro + Chemo	155/220	70.5%	0.73 (0.55-0.95)	0.0093*
Placebo + Chemo	84/103	81.6%		

Subgroup	No. of Patients	Median Overall Survival: Pembrolizumab–chemotherapy (mo)	Median Overall Survival: Placebo–chemotherapy (mo)	Hazard Ratio for Death (95% CI)
Overall	847	17.2	15.5	0.89 (0.76–1.05)
PD-L1 CPS cutoff of 1				
CPS ≥1	636	17.6	16.0	0.86 (0.72–1.04)
CPS <1	211	16.2	14.7	0.97 (0.72–1.32)
PD-L1 CPS cutoff of 10				
CPS ≥10	323	23.0	16.1	0.71 (0.54–0.93)
CPS <10	524	14.7	15.2	1.04 (0.85–1.26)
PD-L1 CPS cutoff of 20				
CPS ≥20	204	24.0	15.6	0.72 (0.51–1.01)
CPS <20	643	15.9	15.5	0.96 (0.80–1.14)



*Prespecified P value boundary of 0.0113 met.
Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff: June 15, 2021.
Rugo HS, et al. ESMO 2021. Abstract LBA16.

J Cortes et al. N Engl J Med 2022;387:217-226.

“Concordance” of Programmed Death-Ligand 1 Expression between SP142 and 22C3/SP263 Assays in Triple-Negative Breast Cancer

Journal of Breast Cancer JBC

Programmed Death-Ligand 1 SP142 Assay in Triple-Negative Breast Cancer

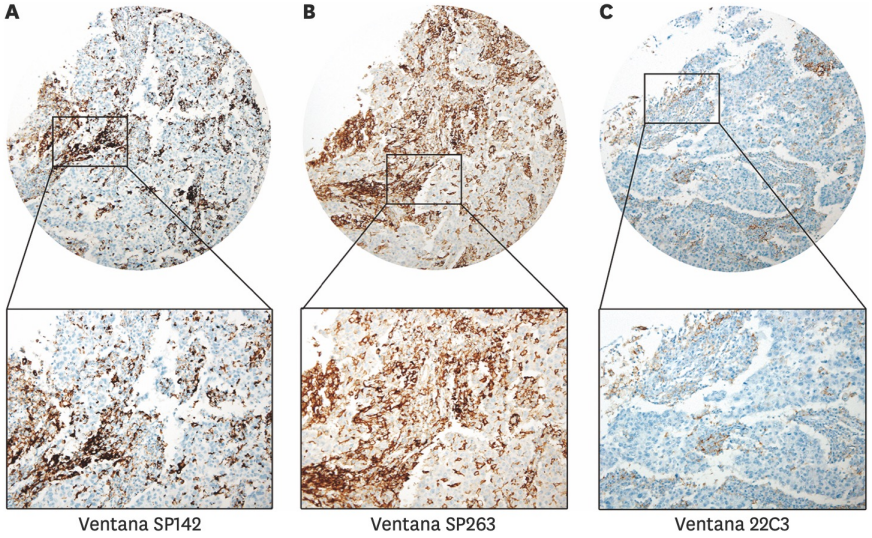
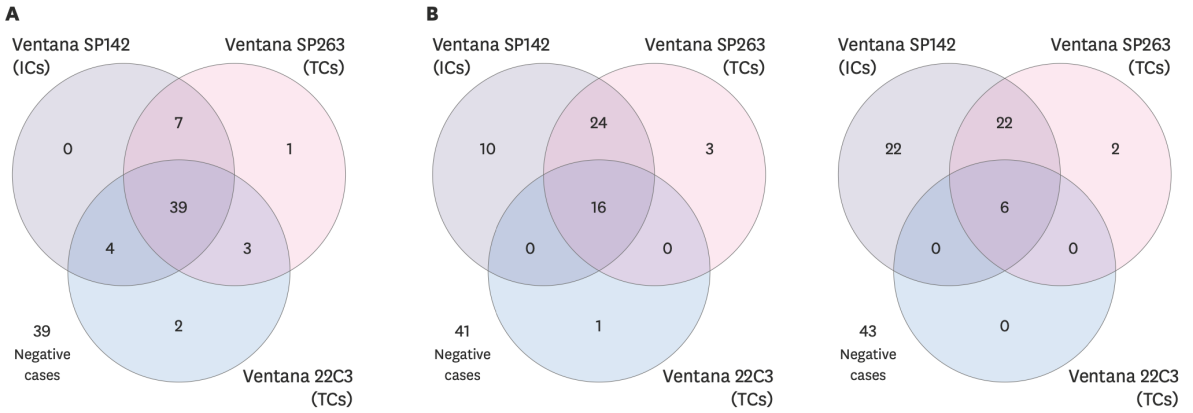


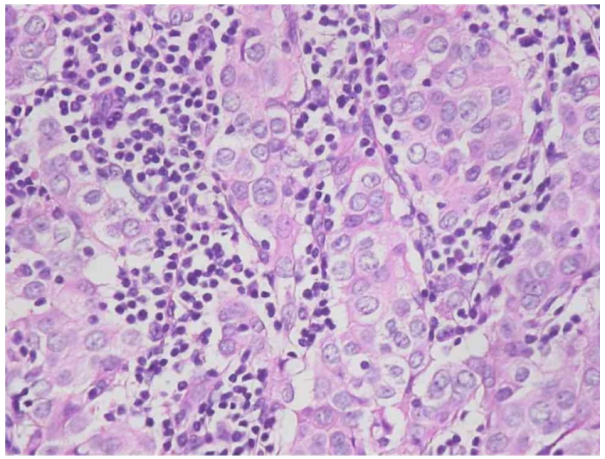
Figure 1. Representative IHC image of the same TMA core stained with 3 PD-L1 assays. (A) An SP142 assay on the Ventana platform showed prominent granular staining in infiltrating immune cells (IHC staining, 20× magnification). (B) An SP263 assay on the Ventana platform showed membranous staining in TCs (IHC staining, 20× magnification). (C) A 22C3 assay on the Ventana platform showed membranous staining in TCs (IHC staining, 20× magnification).
IHC = immunohistochemistry; TMA = tissue microarray; PD-L1 = programmed death-ligand 1; TC = tumor cell.



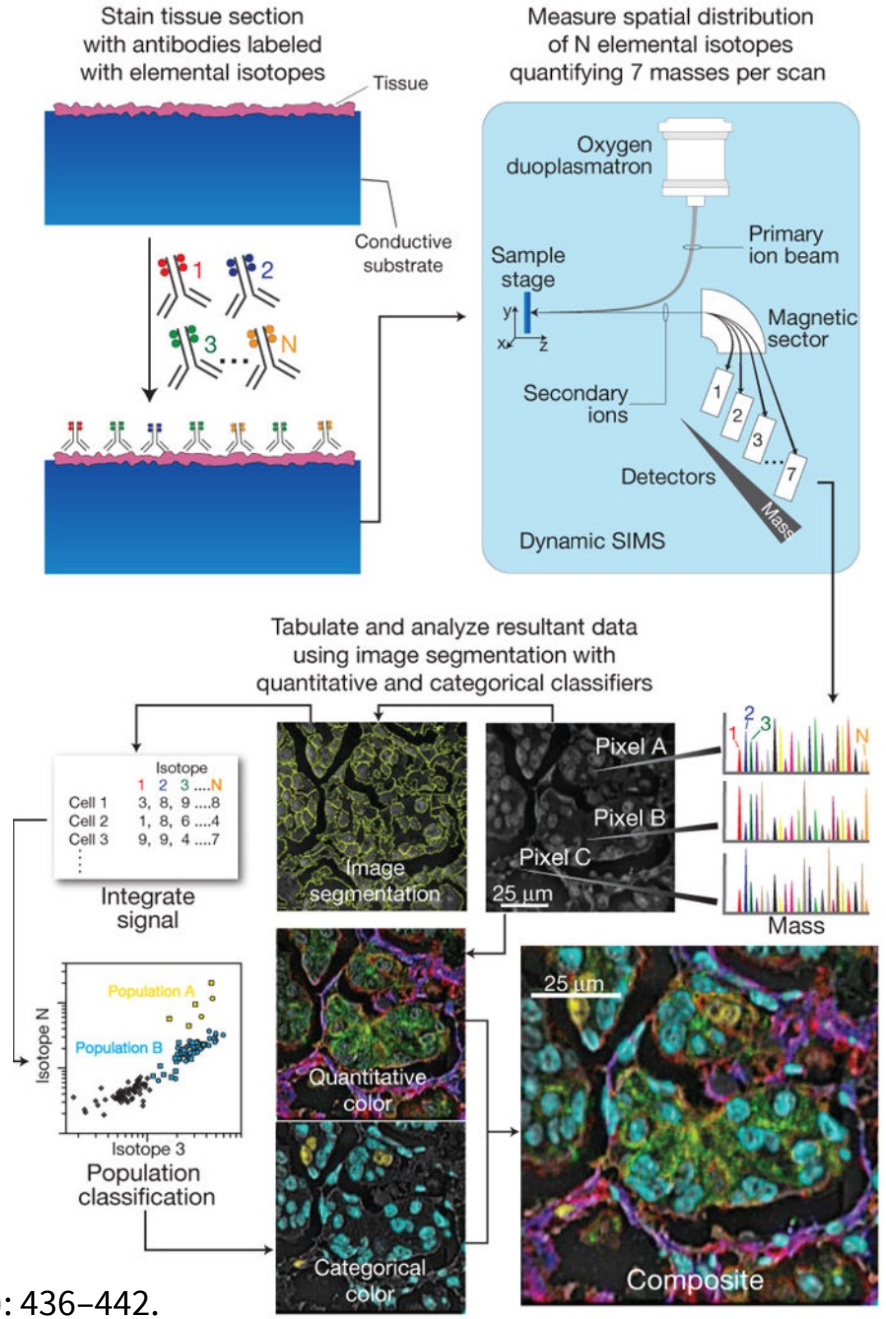
Venn diagram representing the concordance or discordance between the SP142 assay (≥ 1% of immune cells) and the 22C3/SP263 assays. (A) 22C3/SP263 assays at a 1% cut-off value, (B) 22C3/SP263 assays at a 5% cut-off value, (C) 22C3/SP263 assays at a 10% cut-off value.

Lee SE, et al. J Breast Cancer. 2020 Jun;23(3):303-313.

Multiplexed ion beam imaging (MIBI) of human breast tumors



H&E – TILs in breast CA



Multiplexed ion beam imaging (MIBI) is capable of analyzing up to 100 targets simultaneously over a five-log dynamic range. Here, we used MIBI to analyze formalin-fixed, paraffin-embedded (FFPE) human breast tumor tissue sections. The resulting data suggest that MIBI will provide new insights by integrating tissue microarchitecture with highly multiplexed protein expression patterns, and will be valuable for basic research, drug discovery and clinical diagnostics.

Angelo M, et al. Nat Med. 2014 April ; 20(4): 436–442.

NeoTRIP trial results and sample collection

OFFICIAL best of SABCS

Multiplexed ion beam imaging (MIBI) of human breast tumors

Angelo M, et al. Nat Med. 2014 April ; 20(4): 436–442.

TN high-risk **(T1cN1; T2N1; T3N0)** or locally advanced ***N=280***

R

Carboplatin+*nab*-paclitaxel

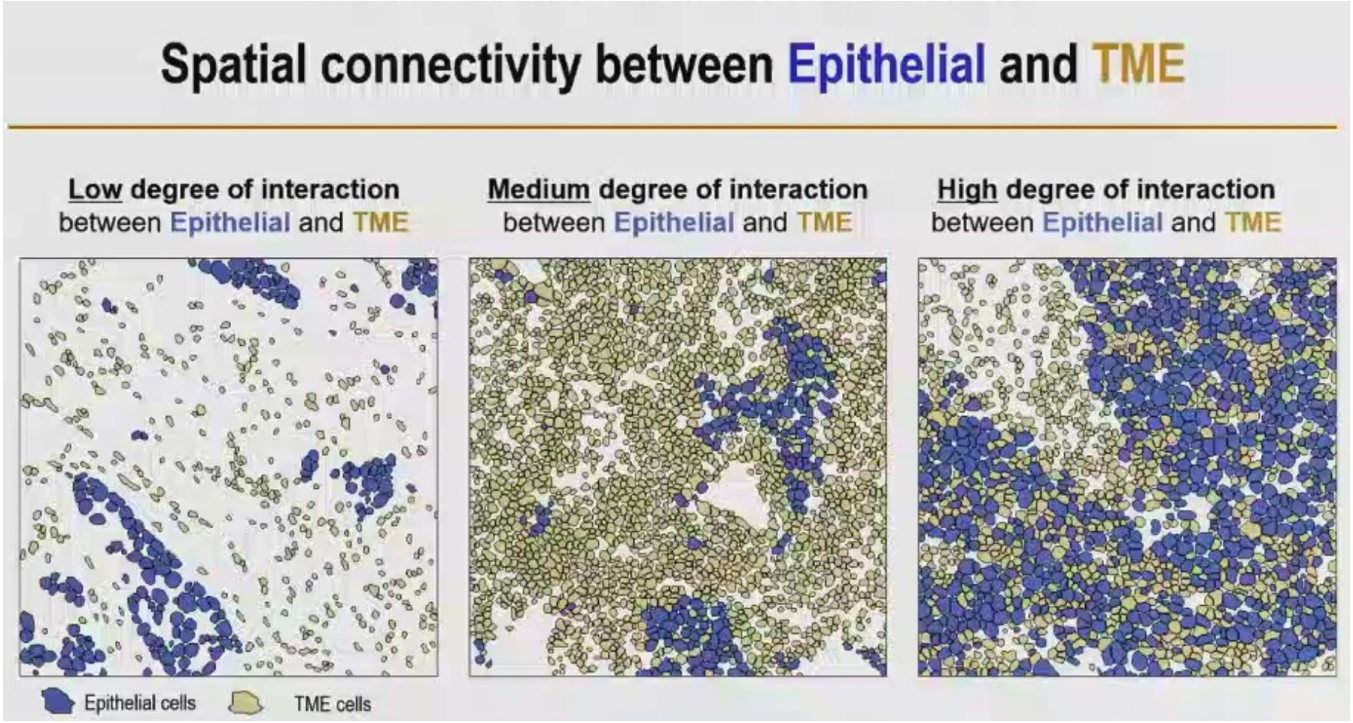
Carboplatin + *nab*-paclitaxel + Atezolizumab

Surgery

Pre-treatment tissue biopsies ***N=243*** (87%)
RNA-sequencing & Imaging Mass Cytometry of 43 proteins

Checkpoint	Lymphoid	Epithelial	Life & Death
PD-L1 (SP142)	CD56	CK5/14	c-PARP
PD-L1 (73-10)	CD20	CK8/18	pH2AX
IDO	CD79a	PanCK	Ki67
PD-1	CD3	Heterogeneity	DNA
OX40	CD4	AR	H3
ICOS	CD8	GATA3	Ir
Myeloid	FOXP3	CD15	
CD11c	GATA3	Mesenchymal	
CD15	Helios	Caveolin-1	
CD163	T-bet	CD31	
CD68	TCF	PDPN	
MPO	TOX	PDGFRB	
MHC I&II	GZMB	SMA	
HLA-ABC	Pan-Immune	Vimentin	
HLA-DR	CD45	Calponin	

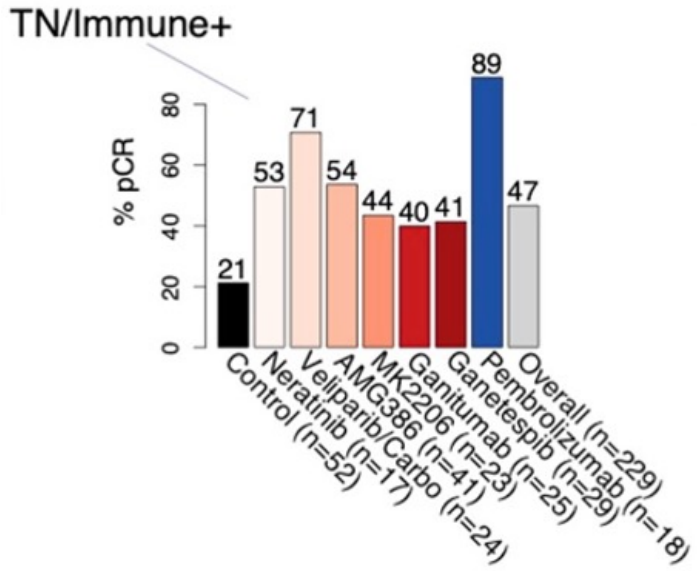
Is there a better marker than PDL1 to identify patients that selectively benefitted from ICI?



Giampaolo Bianchini, MD, et al. SABCS 2021.

1. **High degree of *spatial* connectivity between epithelial and specific TME cell phenotypes (e.g. CD8+PD1+T_{EX}; CD8+GZMB+; CD20+B) is predictive of higher pCR rate with the addition of atezolizumab, independently by PD-L1 and sTILs**
2. **Spatial Epithelial-TME interactions outperform cell phenotype density in predicting differential response to immunotherapy**

Immune response signature and pCR with ICI in I-SPY2



Yee D, et al. ASCO 2022, abstr 591, poster 362

UTSouthwestern Medical Center

InteractPrint predicts the degree of immune cell interaction for a patient's tumor

- We developed **InteractPrint**, a score that predicts the degree of immune cell interaction for a patient's tumor.

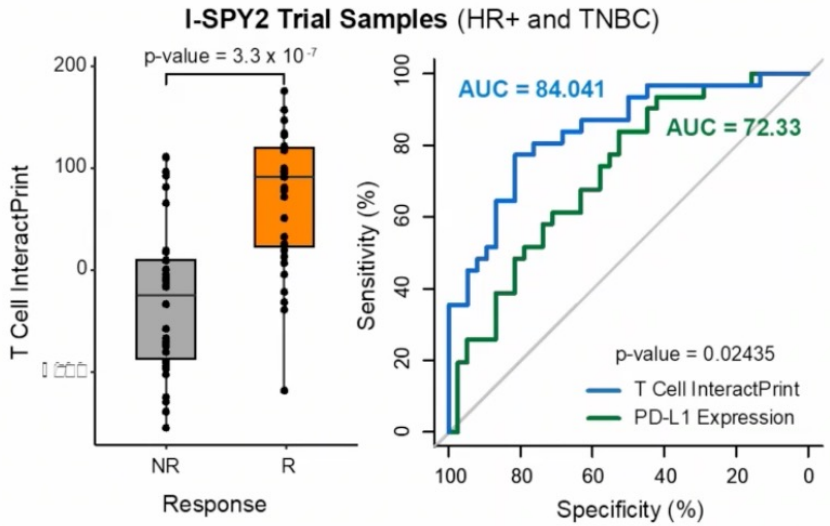
$$InteractPrint = \sum_{i=1}^{10} (e_i)(R_i)(w)$$

i = GE
e_i = GE expression
R_i = Number of predicted R-L pairs
w = Multiplier for activating GE (1) or inactivating GE (-1)

Medical Center

T Cell InteractPrint predicts response to anti-PD-1 therapy in I-SPY2

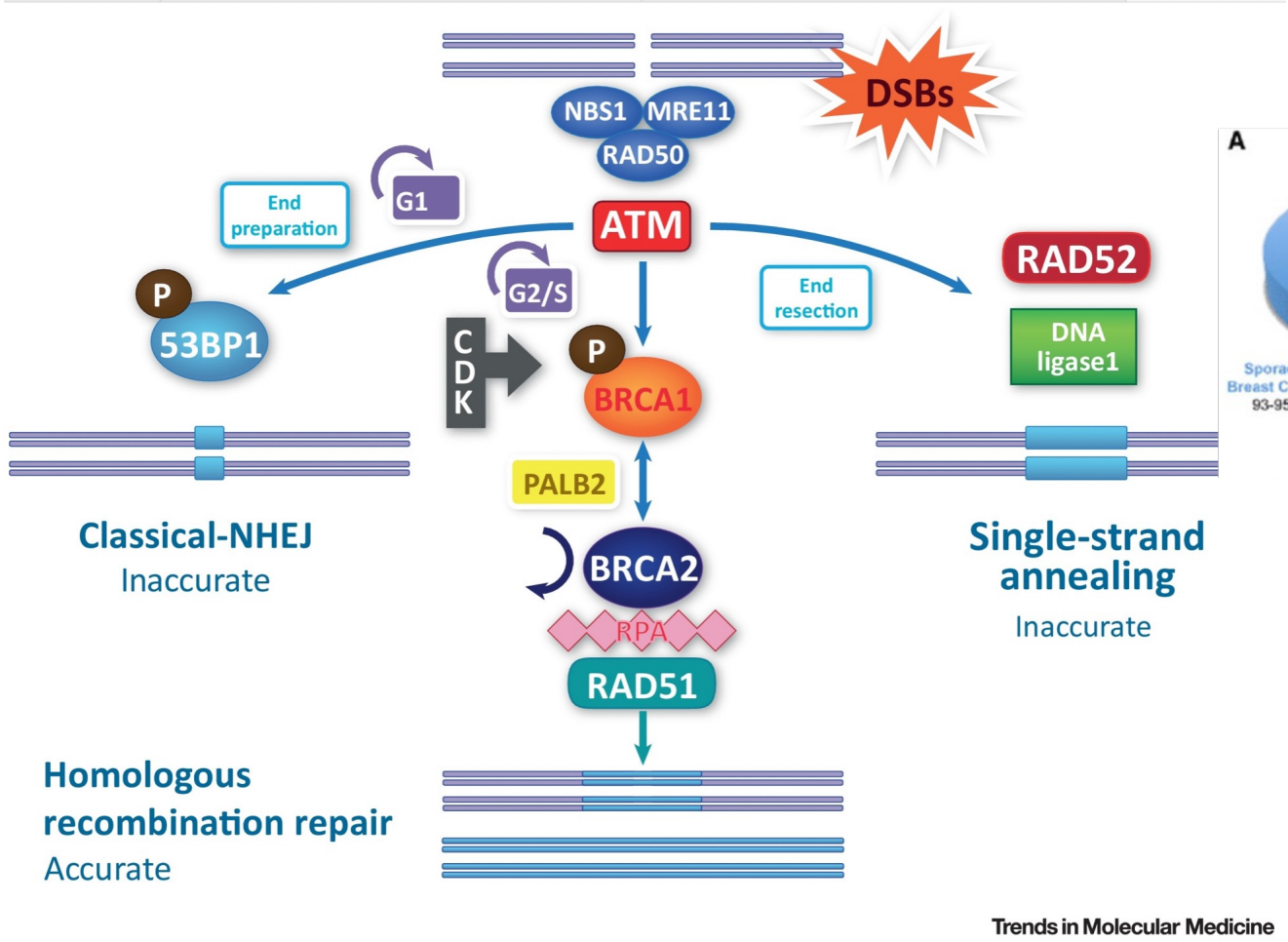
- In this trial, **T Cell InteractPrint predicted response to anti-PD-1 + neoadjuvant chemo with an AUC of 84.0** ($p < 1 \times 10^{-6}$).
- This was a **significant improvement over PD-L1** (assessed by average PD-L1 transcript levels; $p < 0.05$).



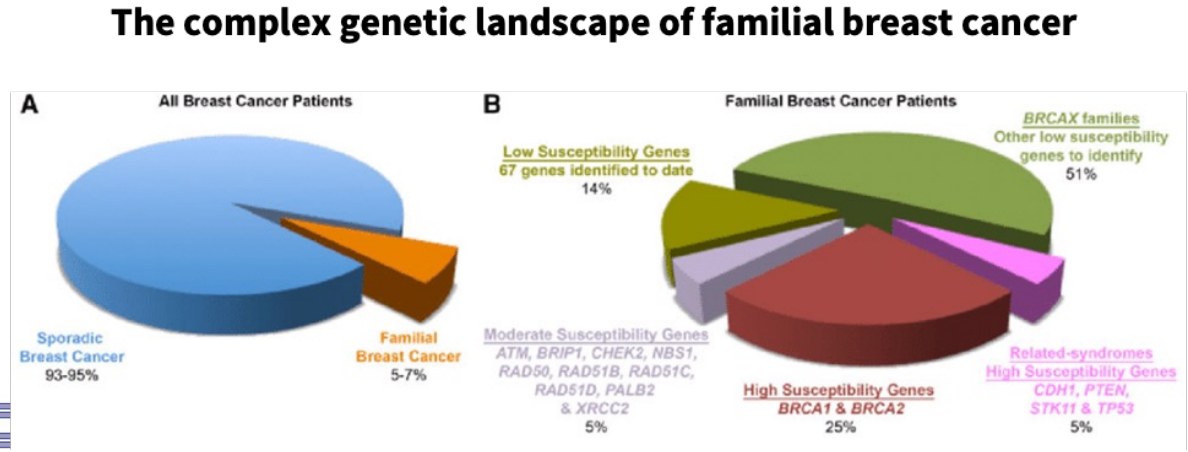
[5] Nanda et al., JAMA Oncol 2020.

Xu L, et al. Single-cell RNAseq,…SABCS 2022, GS5-06.

DNA Double-Strand Break (DSB) Repair



Trends in Molecular Medicine

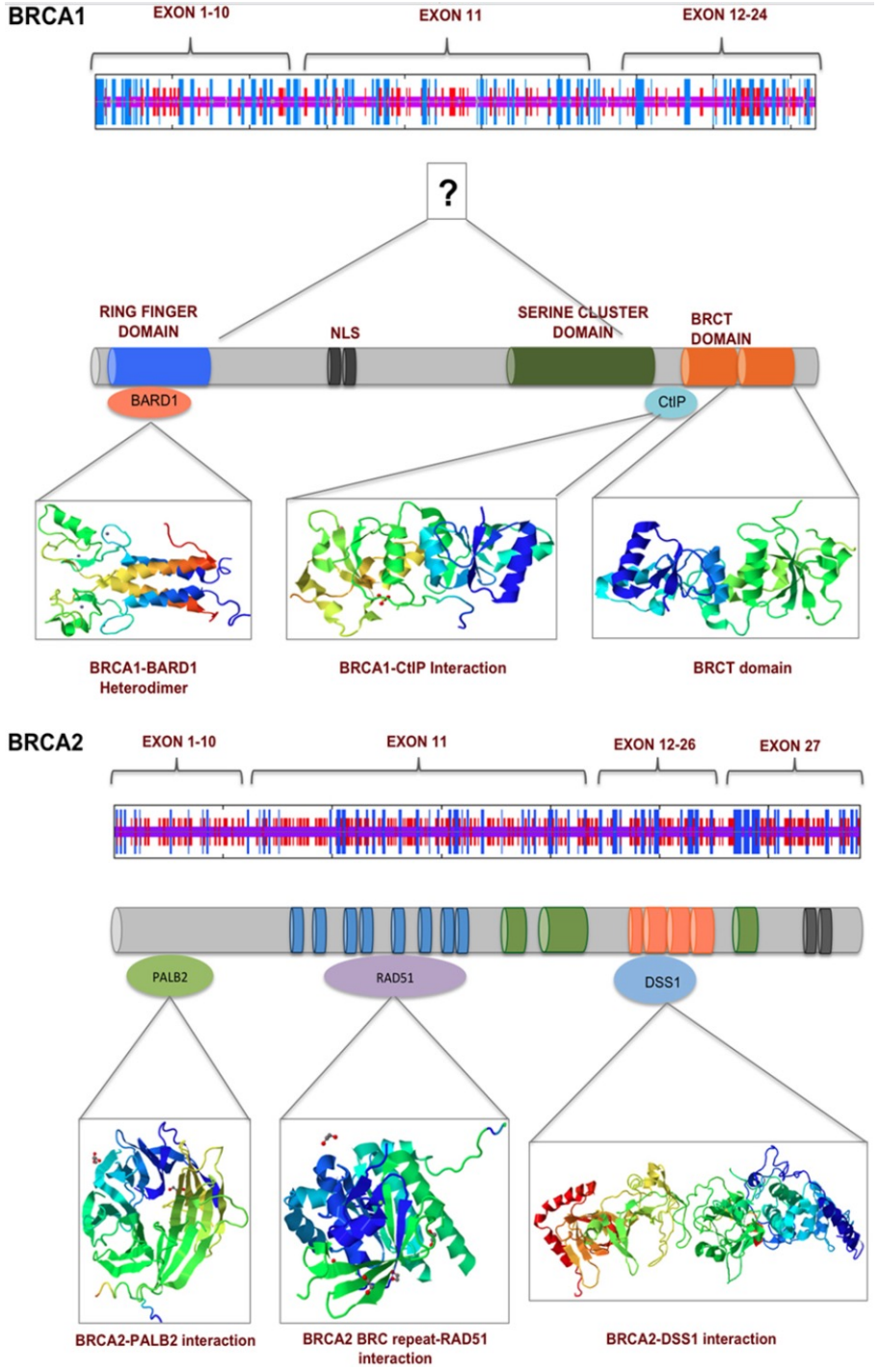


March 22, 2017 Science News: "According to current data, it is estimated that only 30% of breast cancer survivors with the BRCA mutation have been identified, and that number drops significantly to 10% for asymptomatic BRCA carriers".

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

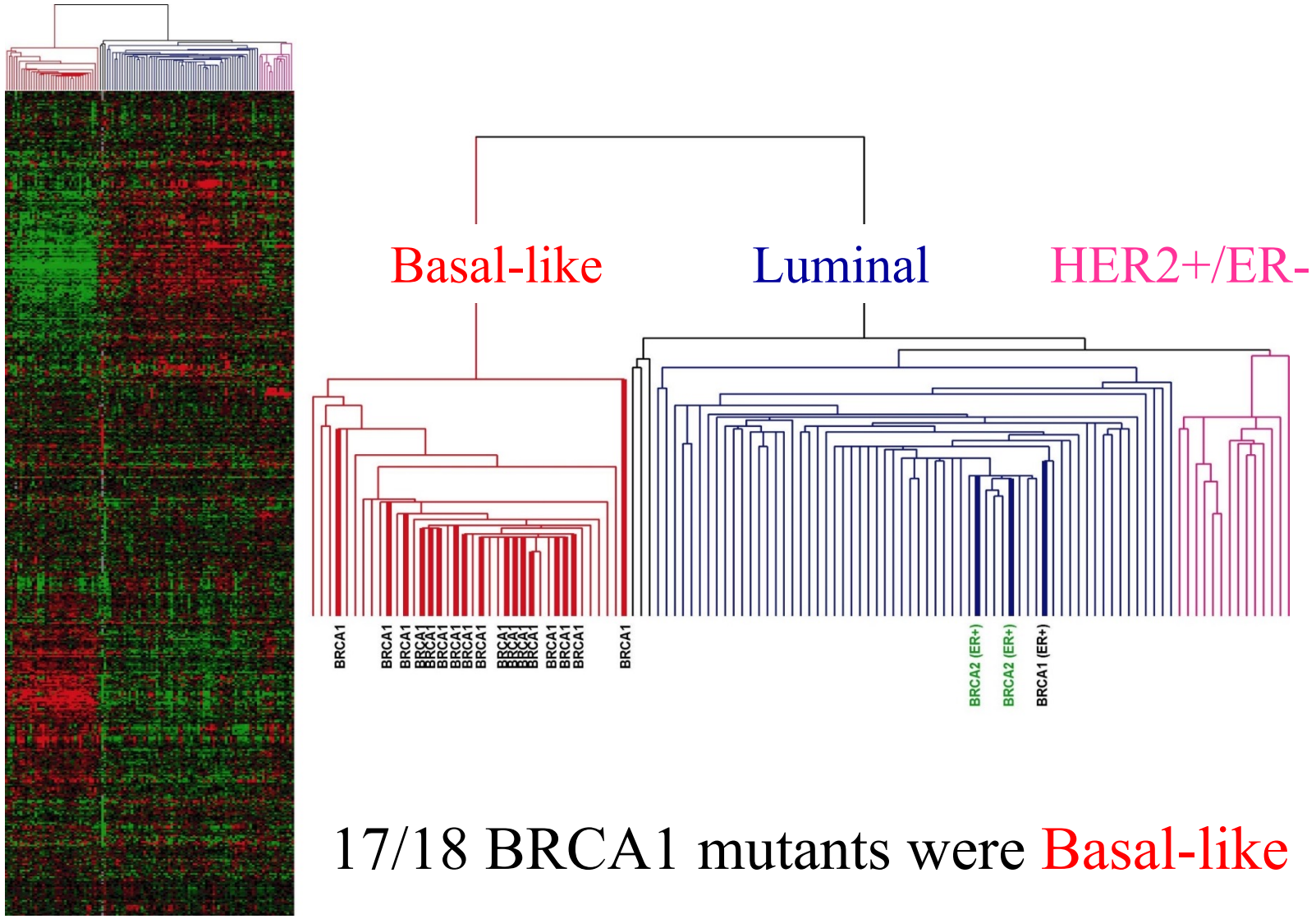
BRCA Structure/Function Relationships

BRCA1 and BRCA2 interact with numerous proteins via their multiple functional domains. The N and C termini of BRCA1 have structural motifs that allow multiple protein–protein interaction. Exons 11–13 in the middle of BRCA1 are more unstructured, which contains two nuclear localization signals. BRCA2 secondary structure prediction indicate a more helical middle region, which contains BRC repeats and binding sited for various proteins of the DNA damage response pathway.



Mylavarapu S, Das A, Roy M. Front Oncol. 2018 Feb 5;8:16.

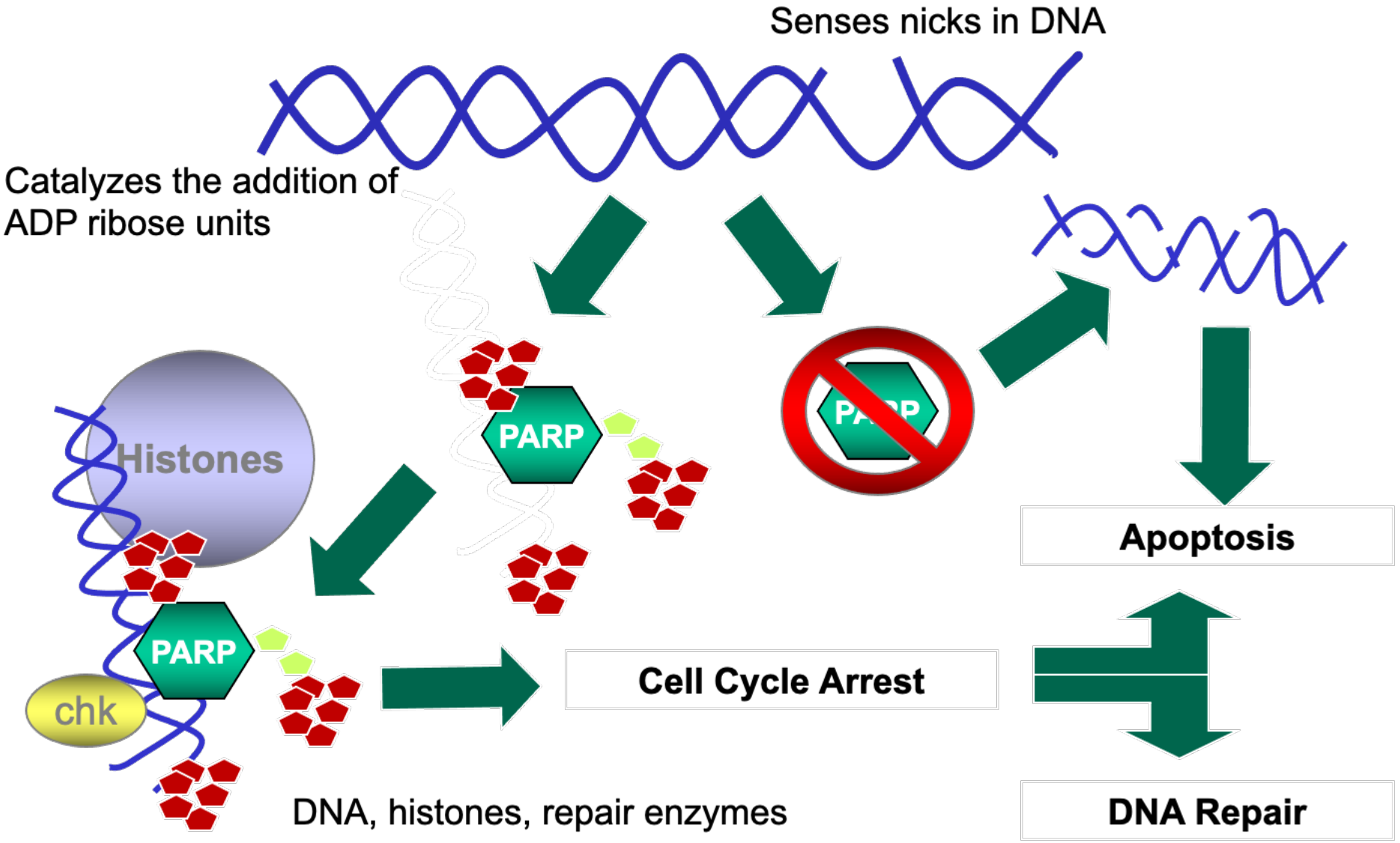
BRCA1 Mutations and Basal-Like Tumors



17/18 BRCA1 mutants were Basal-like

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

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

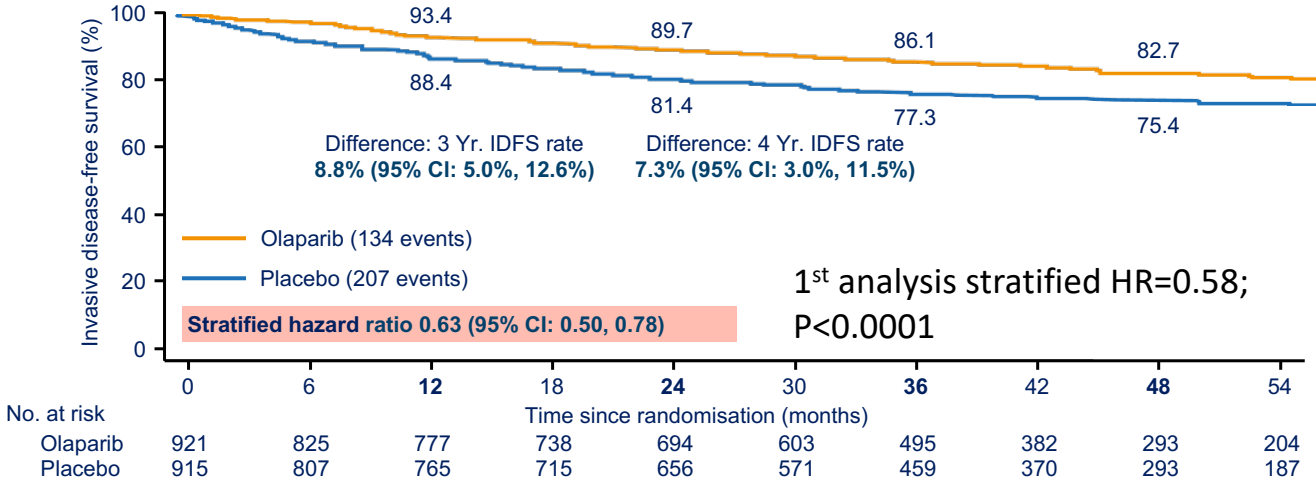


Olympia: Updated Endpoints

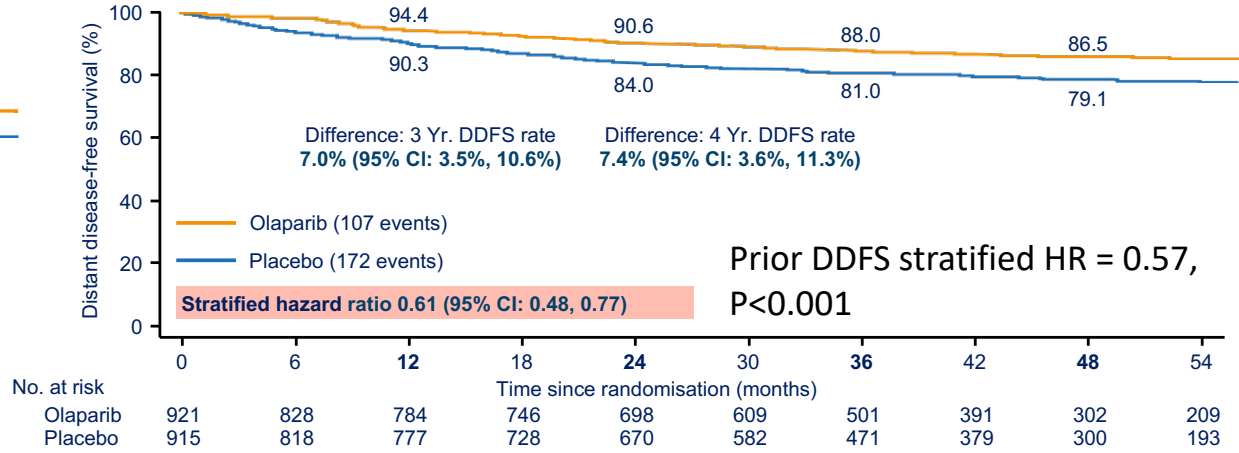
Median FU 3.5 years, 2nd IA

Neoadjuvant Group
- *TNBC:* non-pCR
- *Hormone receptor–positive:* non-pCR and CPS+EG score ≥ 3

Adjuvant Group
- *TNBC:* ≥ pT2 or ≥ pN1
- *Hormone receptor–positive:* ≥ 4 positive lymph nodes



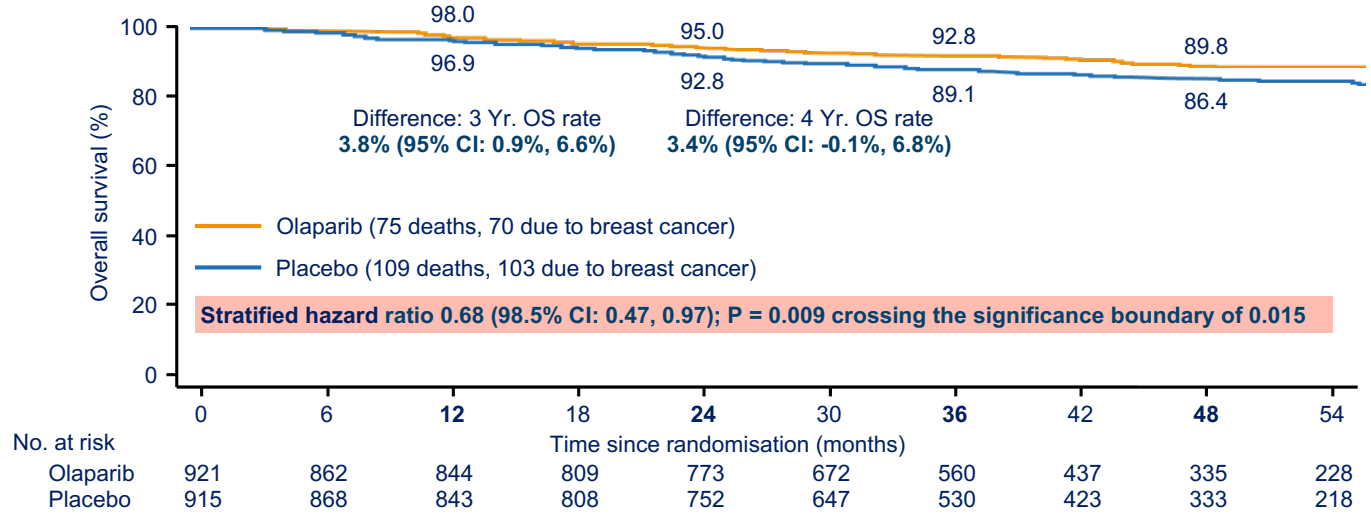
1st analysis stratified HR=0.58; P<0.0001



Prior DDFS stratified HR = 0.57, P<0.001

- 72% BRCA1, 82% TNBC, 50% post NACT

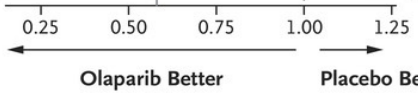
- No increase in MDS/AML compared to placebo
- Most toxicity grade 1/2; nausea most common
- Grade 3
  - Anemia 9%, fatigue 2%, neutropenia 5%



Tutt et al. N Engl J Med. 2021;384(25):2394-2405;
Tutt et al. ESMO Plenary 2022.

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.

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CANCER DISCOVERY 10

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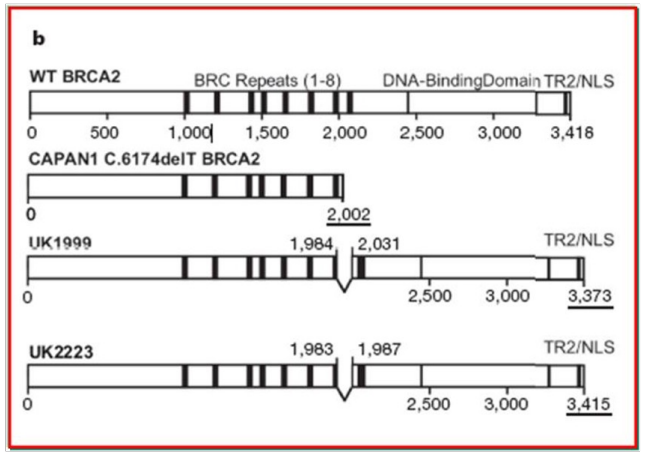
Research Briefs

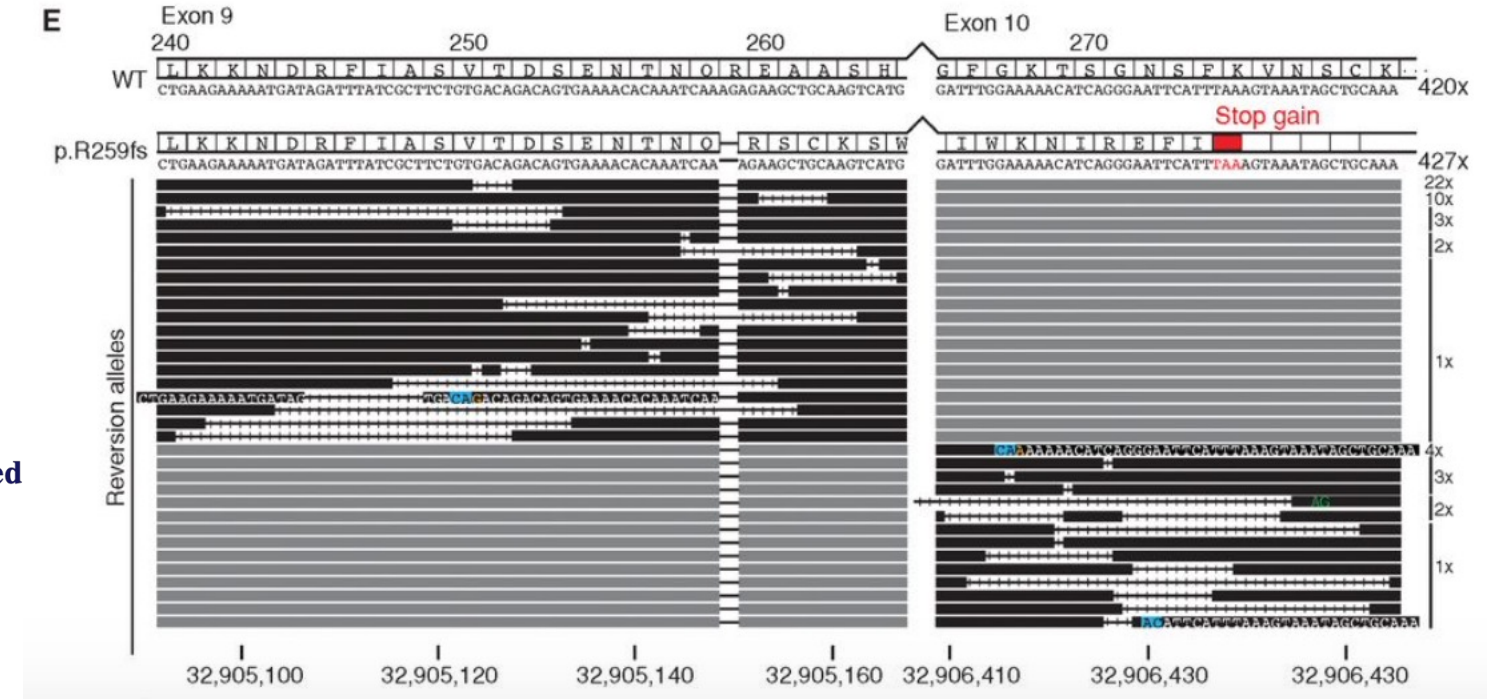
Analysis of Circulating Cell-Free DNA Identifies Multiclonal Heterogeneity of *BRCA2* Reversion Mutations Associated with Resistance to PARP Inhibitors

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

Resistance to therapy caused by intragenic deletion in BRCA2



Restored ORF



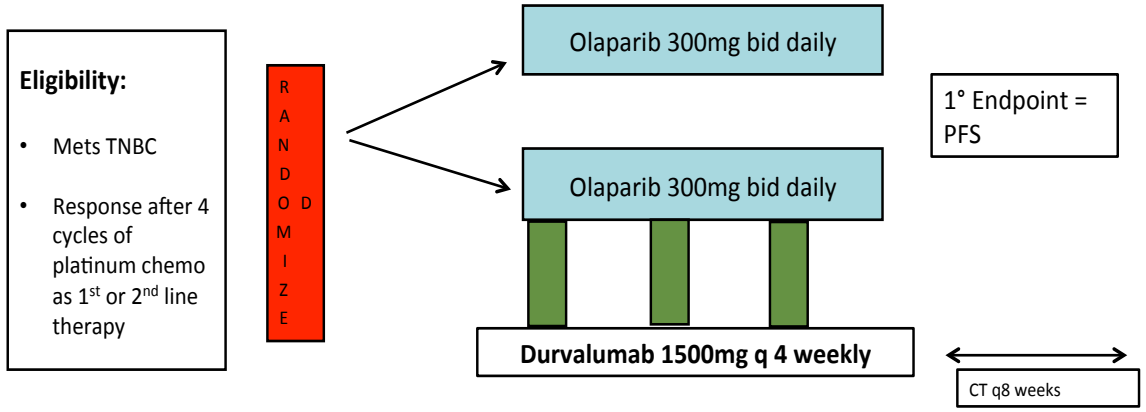
Edwards, et al., NATURE| Vol 451|28 February 2008.

"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."

PARPi + checkpoint inhibition as maintenance?

DORA study[1]

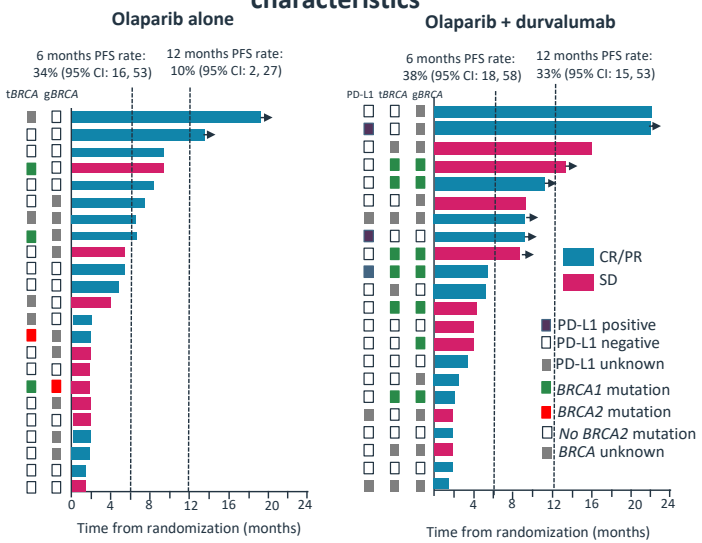
Phase II maintenance study of PARPi + anti-PD-L1 vs PARPi



Primary and subgroup PFS analysis

Median PFS (95% CI)	Olaparib alone (n=23)	Olaparib + durvalumab (n=22)
All patients	4.0 (2.6, 6.1)	6.1 (3.7, 10.1)
X^2 P value vs historical control	0.0023	<0.0001
Subgroups according to prior platinum sensitivity		
CR/PR to prior platinum	5.4 (3.0, 9.7)	7.6 (3.8, 15.1)
SD to prior platinum	2.2 (1.2, 4.3)	4.4 (2.1, 9.3)

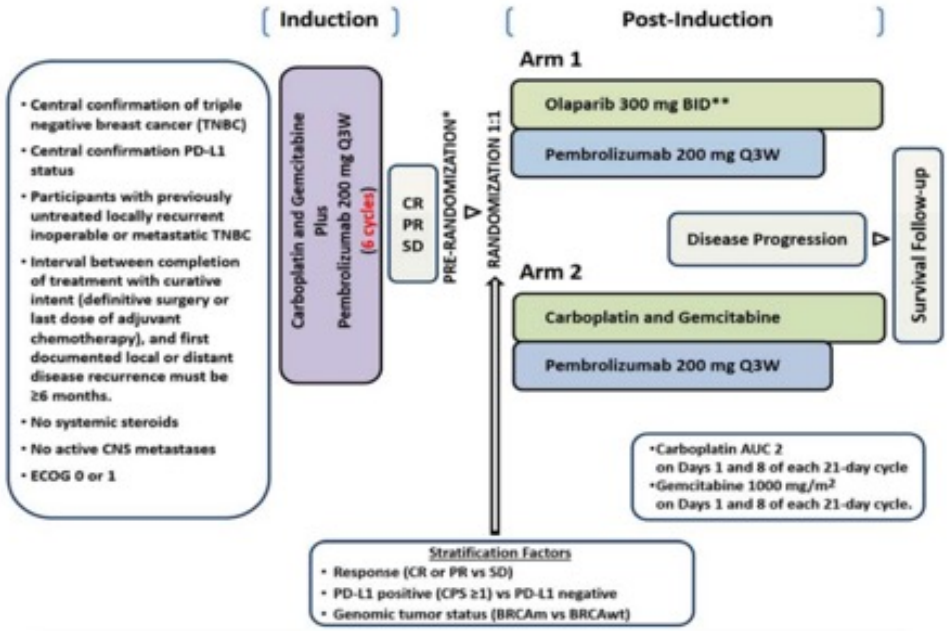
Treatment exposure/response according to tumor characteristics



CR, complete response; PR, partial response; SD, stable disease
Sammons SL, et al. SABCS 2022. Abstract PD11-12

KEYLYNK-009[2]

Phase II study of post-induction pembrolizumab + PARPi



Sammons et al, SABCS 2022, PD11-12

*1. Dent R, et al. Cancer Research. 2018; 78(4); 2. Rugo H, et al. JCO. 2020; 38 (suppl 15); 2. Rugo H, et al. Presented at SABCS 2020. Abstract #OT-30-31

Ongoing Phase III Trials with IO in TNBC

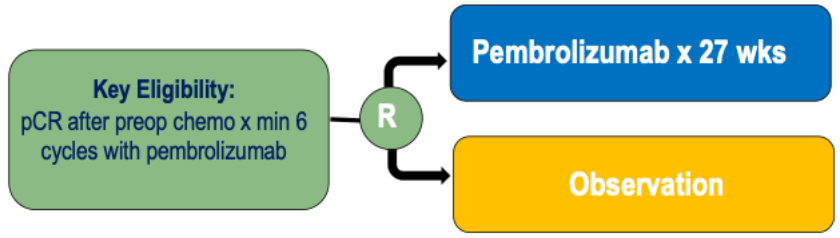
Neoadjuvant/adjuvant

- Atezolizumab
  - NSABP B59/GeparDouze (n=1520)
    - Pac/carbo → AC/EC
  - EFS NeoTRIPaPDL1 (n=272)
  - EFS Impassion 031 (n=333)
- Pembrolizumab
  - NeoPACT (n=100)
    - Docetaxel/carbo/pembro x 6

Adjuvant

- Atezolizumab
  - Impassion 30 (n=2300)
    - Pac → AC/EC
- Avelumab
  - A-Brave (n=335)
    - Adjuvant and post NAC high risk: avelumab alone
- Pembrolizumab*
  - SWOG S1418/NRG BR006 (n=1155)
    - Post NAC: Pembro vs Obs x 1 yr

OptimICE-pCR



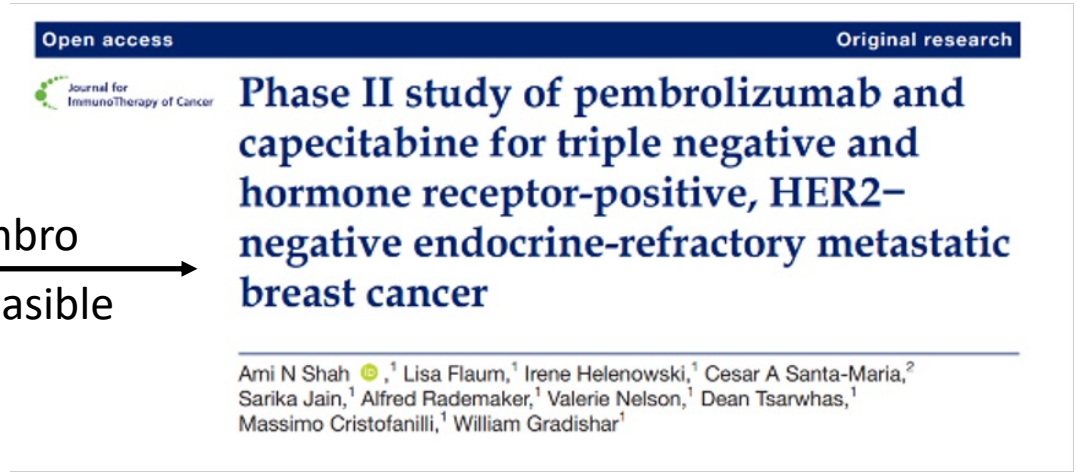
Stratification Factors:
- Baseline nodal status
- Receipt of anthracycline chemotherapy: yes vs. no

PI: Tolaney
Alliance Trial

- Completed
- Closed early, results pending

***S1418 allowed patients to complete capecitabine, then start pembrolizumab (as precedent).**

Cape + Pembro → Clinically feasible



Open access Original research

Journal for ImmunoTherapy of Cancer

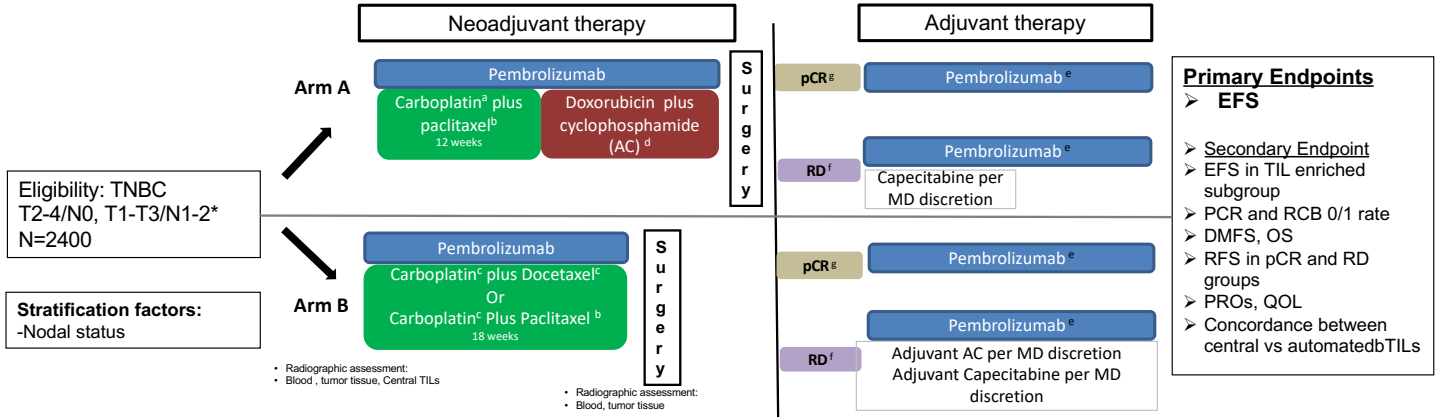
Phase II study of pembrolizumab and capecitabine for triple negative and hormone receptor-positive, HER2– negative endocrine-refractory metastatic breast cancer

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]

S2212: Shorter Anthracycline-free Chemoimmunotherapy Adapted to pathological Response in Early TNBC (SCARLET)

Randomized non-inferiority trial

Hypothesis: In patients with early stage TNBC, carboplatin-taxane chemoimmunotherapy is non-inferior to taxane-platinum-anthracycline-based chemoimmunotherapy



Primary Endpoints

- **EFS**
- Secondary Endpoint
- EFS in TIL enriched subgroup
- PCR and RCB 0/1 rate
- DMFS, OS
- RFS in pCR and RD groups
- PROs, QOL
- Concordance between central vs automatedbTILs

*T4/N+ , any N3 and inflammatory breast cancer excluded

[a]Carboplatin QW or Q 3W

[b] Paclitaxel QW.

[c] Carboplatin Q3W, Docetaxel Q 3W

[d] AC every 3 weeks

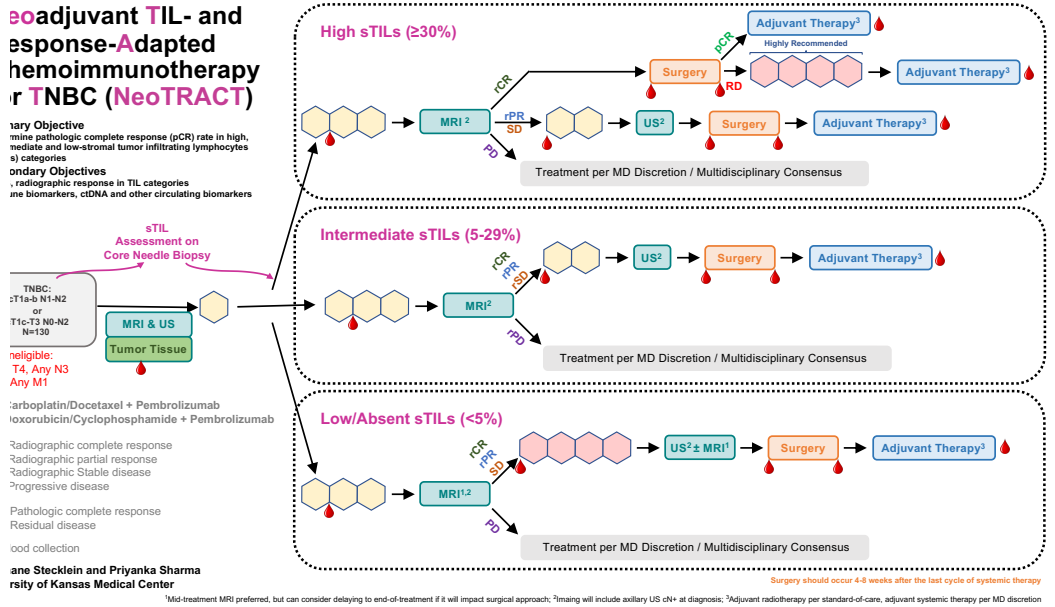
[e] Total duration of neo plus adjuvant pembrolizumab = 51 weeks (17 q 3 week doses)

[f] Co-enrollment in adjuvant NCTN escalation trials will be allowed after discussion with CTEP/study teams

[g] No Further Adjuvant chemotherapy. Co-enrollment in adjuvant NCTN de-escalation trials will be allowed after discussion with CTEP/study teams

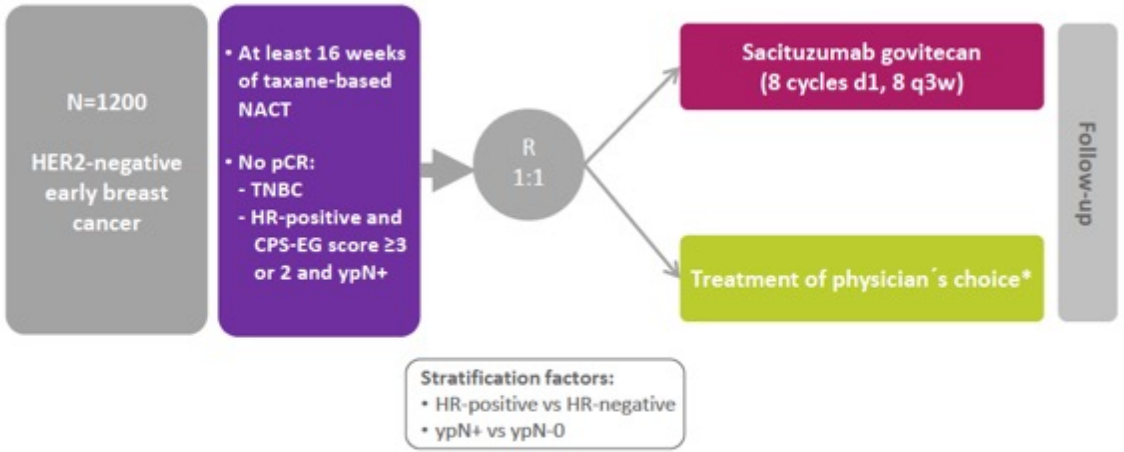
PI: Priyanka Sharma, Zahi Mitri

SWOG CANCER RESEARCH NETWORK



GBG: SASCIA Post-Neoadjuvant Trial

NCT04595565

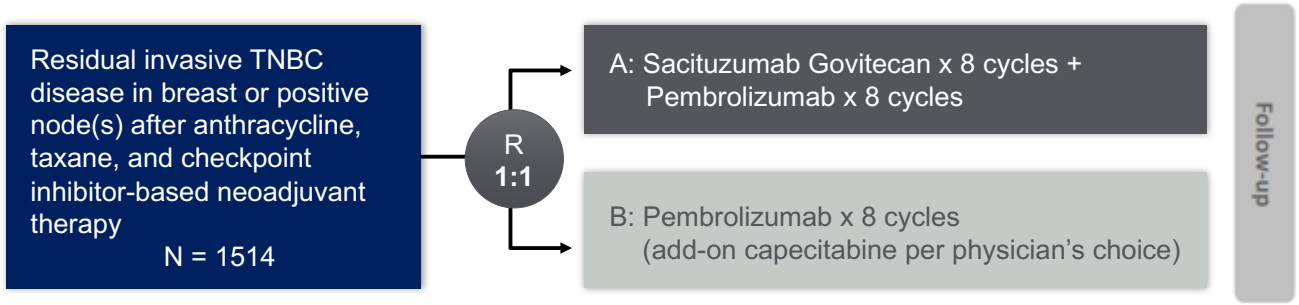


Challenge combining ER+ and TNBC pts

*Capecitabine (8 cycles) or platinum-based chemotherapy (8 cycles) or observation.
Background therapy: in patients with HR-positive breast cancer, endocrine-based therapy will be administered according to local guidelines.

Phase III Trial: Optimice-RD/ASCENT-05

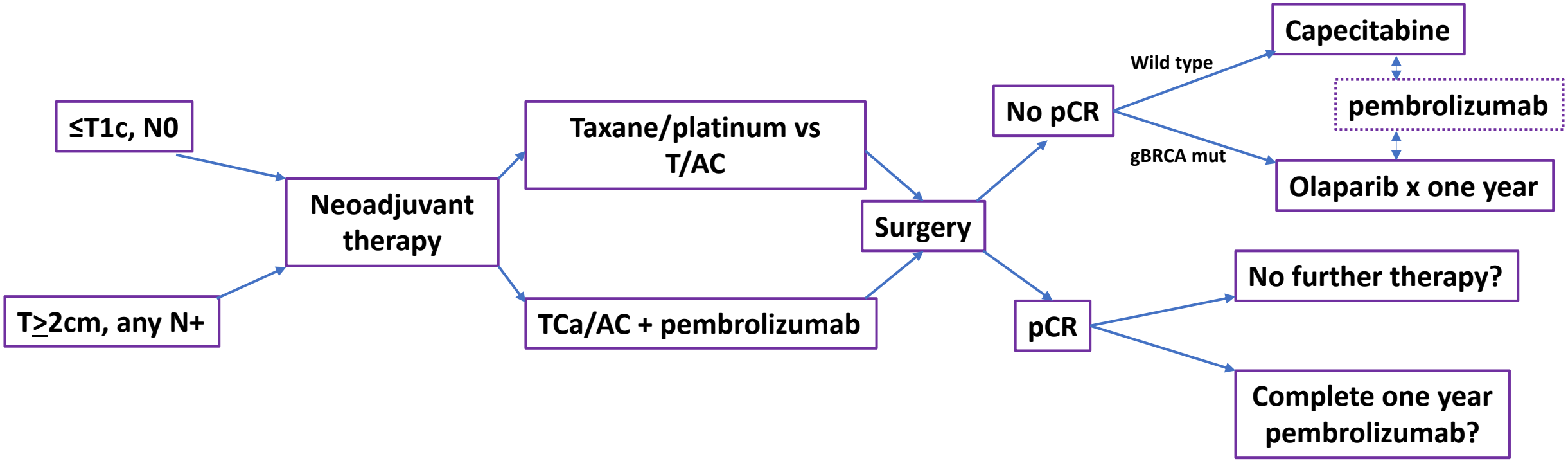
Residual disease in TNBC

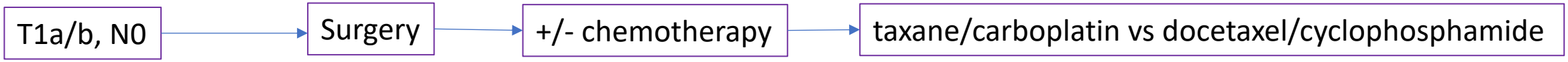


PI: Sara Tolaney

Alliance Foundation Trial

Roadmap for Early TNBC





Ongoing Trials: Tailoring neoadjuvant therapy to response; optimizing post-neoadjuvant therapy – ADCs, checkpoint inhibitor?

AC: anthracycline/cyclophosphamide; Ca: carboplatin

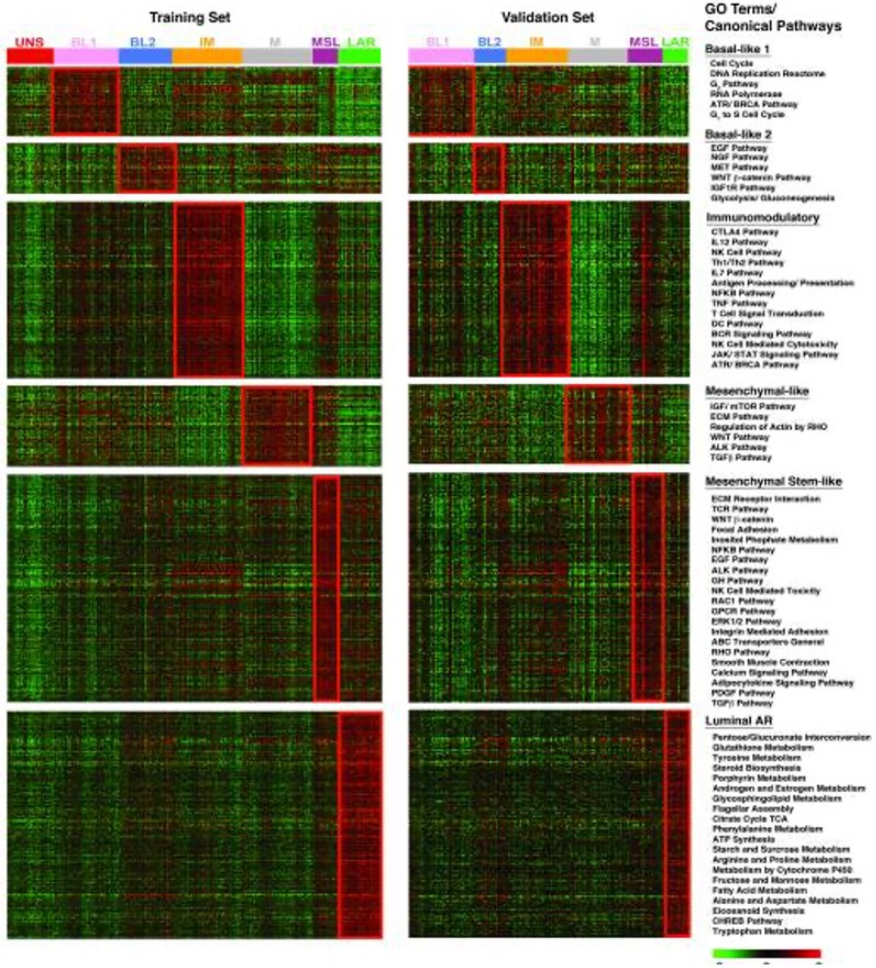
gBRCA mutation: neoadjuvant PARP inhibitors?

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.

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



- Platinum, formed in kilonova and collapsar events, increases pCR, EFS, and OS in pre-MP women with TNBC.
- TNBC is not just one disease. Clinical trial designs that include all TNBC subtypes (unless exploratory) are naïve.
- Immune checkpoint inhibition is now standard of care in high-risk early-, and (PD-L1+) late-stage TNBC; robust biomarker(s) for patient selection remains a high unmet need. New data challenges dogma that PD-L1 expression is a useful biomarker.
- Consider adjuvant Olaparib in gBRCAmut early TNBC, based upon the strength of significant OS benefit in the ITT population in OlympiA. Integration of PARPi with I/O is ongoing, as is the integration of ADC (Sacituzumab govitecan) with I/O in the post-neoadjuvant setting.

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