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Triple Negative Breast Cancer: Optimal Strategies

NOLA April, 2024

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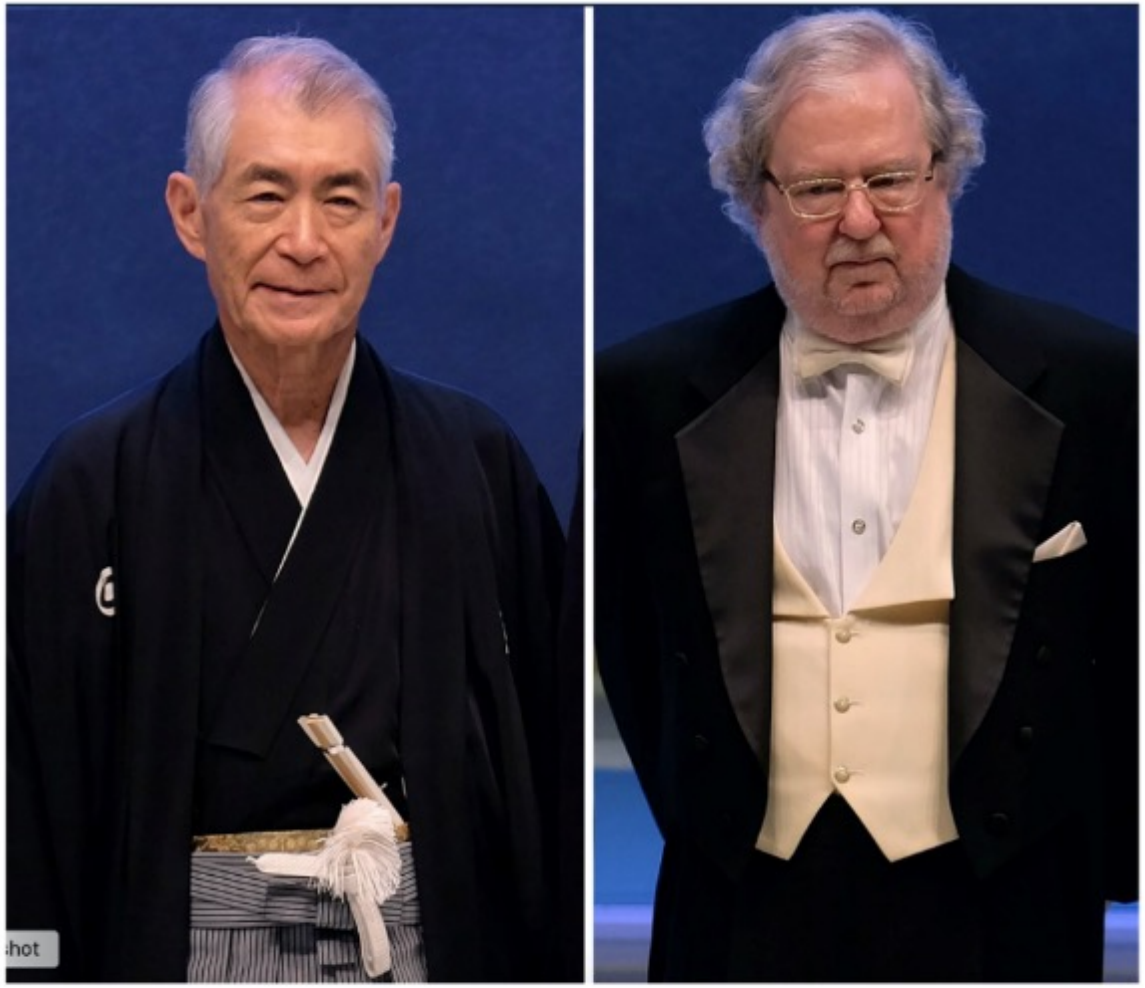
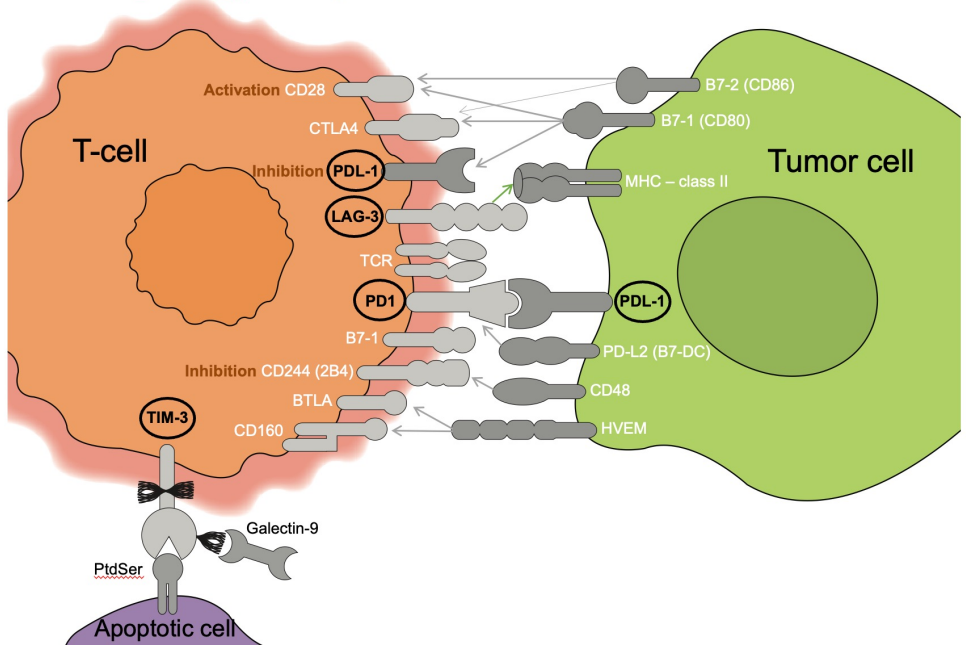
COI declaration relevant to topic: AZ/Daiichi Sankyo, Gilead, Roche/GNE

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–

Immunotherapy in TNBC:KN522

T2-4 N0-2 or
T1c N1-2

TNBC

Pembrolizumab +chemo (taxanes – anthracyclines)

Placebo +chemo (taxanes – anthracyclines)

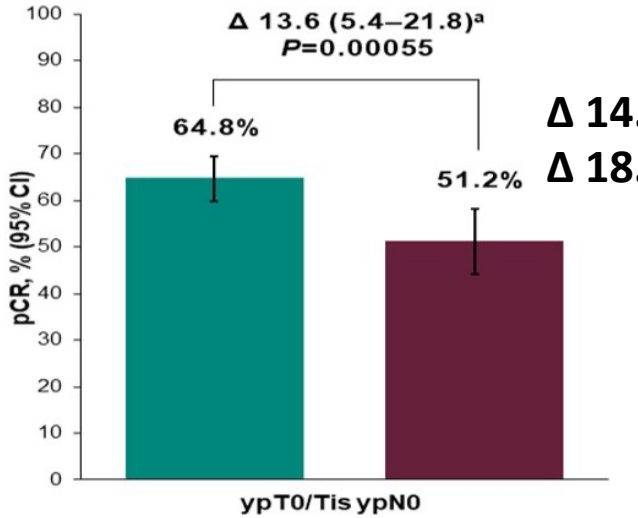
Surgery

Pembrolizumab 9 cycles

Placebo 9 cycles

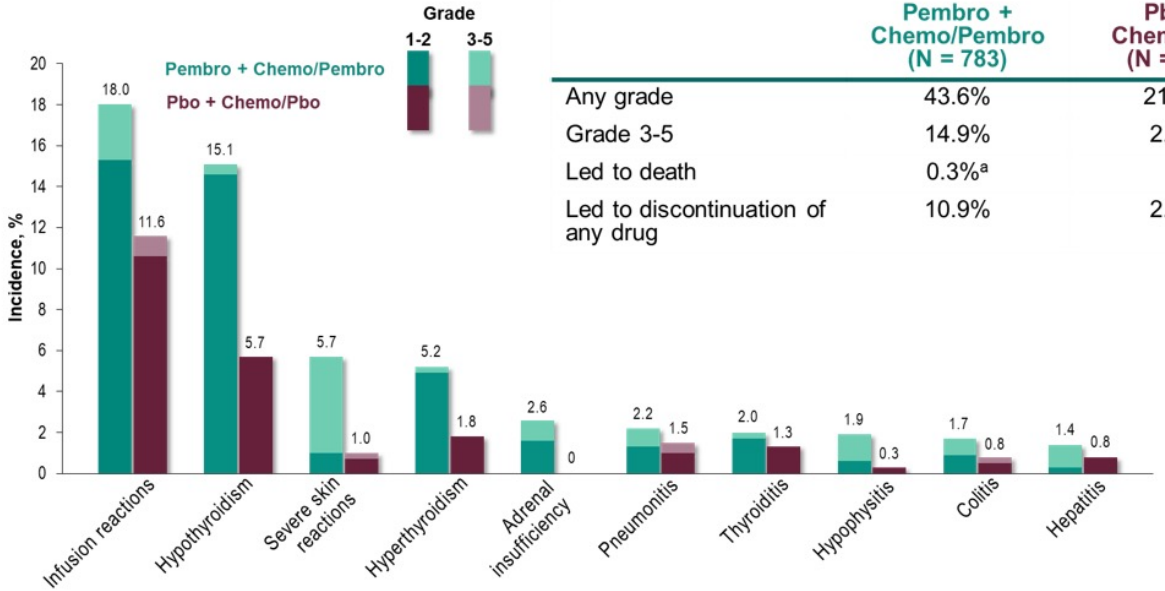
N=1,174

Primary Endpoints:
pCR (ypT0/is ypN0), EFS



Δ 14.2 PD-L1(+)
Δ 18.3 PD-L1(-)

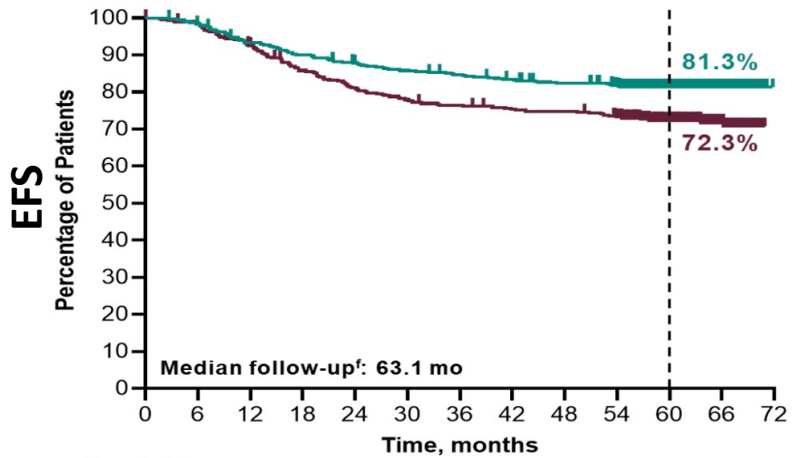
Chemo = PCX4-ACX4



	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

IA6[b]	Events	HR (95% CI)
Pembro + Chemo/Pembro	18.5%	0.63[c] (0.49–0.81)
Placebo + Chemo/Placebo	27.7%	



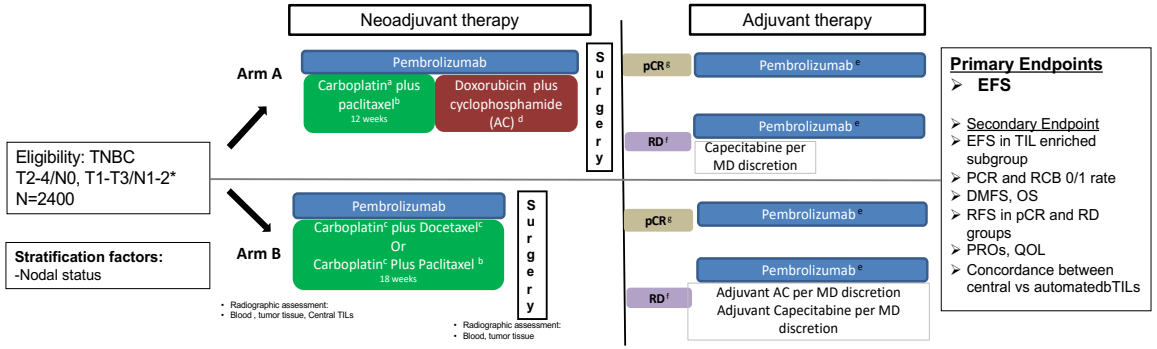
Schmid P, et al. SABCS 2023.

Select Ongoing Phase III Trials with IO in TNBC

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



*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

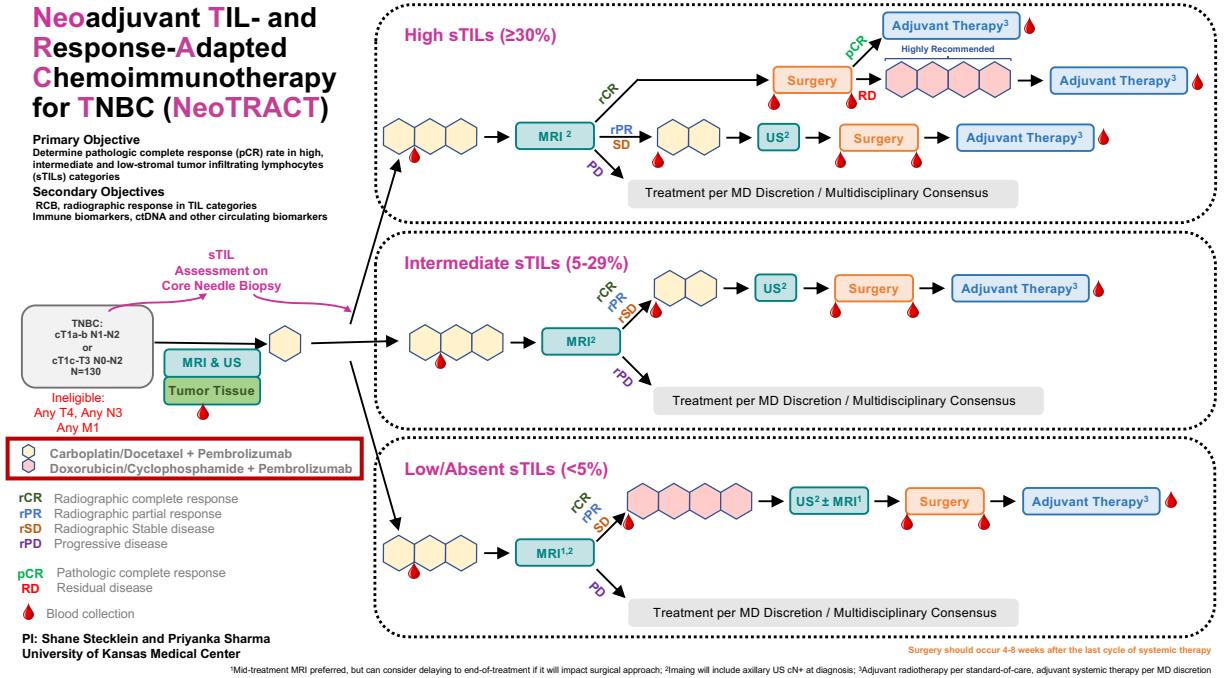
PI: Priyanka Sharma, Zahi Mitri

SWOG CANCER RESEARCH NETWORK

Neoadjuvant TIL- and Response-Adapted Chemoimmunotherapy for TNBC (NeoTRACT)

Primary Objective
Determine pathologic complete response (pCR) rate in high, intermediate and low-stromal tumor infiltrating lymphocytes (sTILs) categories

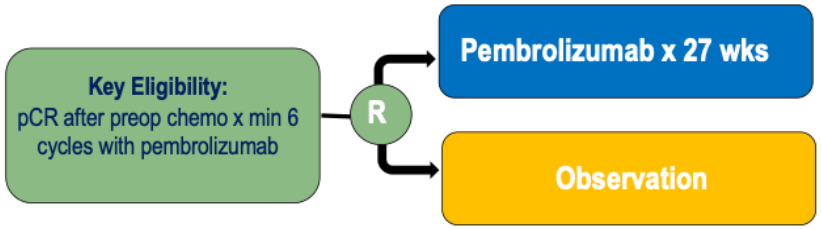
Secondary Objectives
RCB, radiographic response in TIL categories
Immune biomarkers, ctDNA and other circulating biomarkers



PI: Shane Stecklein and Priyanka Sharma
University of Kansas Medical Center

[1]Mid-treatment MRI preferred, but can consider delaying to end-of-treatment if it will impact surgical approach; [2]Imaging will include axillary US cN+ at diagnosis; [3]Adjuvant radiotherapy per standard-of-care, adjuvant systemic therapy per MD discretion

OptimICE-pCR

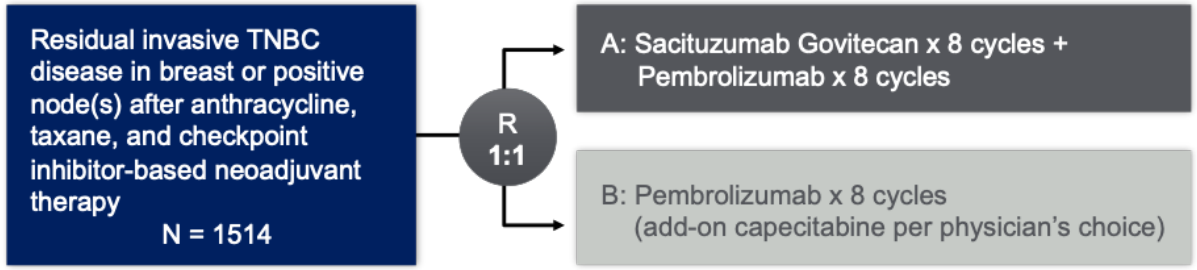


Stratification Factors:
- Baseline nodal status
- Receipt of anthracycline chemotherapy: yes vs. no

PI: Tolaney
Alliance Trial

Phase III Trial: Optimice-RD/ASCENT-05

Residual disease in TNBC



PI: Sara Tolaney
Alliance Foundation Trial

BCT1902/IBCSG 61-20 Neo-N study (non-anthracycline chemo + nivo)

Enrolment: N=108 evaluable at 14 centers from July '20 – Apr '22; Median follow-up 12 months

PATIENT POPULATION

Primary Triple Negative Breast Cancer

Stage I cT1c cN0
Stage IIA cT1 cN1; cT2 cN0
Stage IIB cT2 cN1; cT3 cN0

Stratification according to age: < 40 years, ≥ 40 years

RANDOMISATION

ARM A **N=53**

Nivolumab 240 mg 2 weeks Lead-in

Cycles 1-4
Nivolumab 360 mg D1 Q3W x 4 cycles
Carboplatin AUC5 D1 Q3W x 4 cycles
Paclitaxel 80 mg/m^2 x D1, 8, 15 Q3W x 4 cycles

ARM B **N=55**

Cycles 1-4
Nivolumab 360 mg D1 Q3W x 4 cycles
Carboplatin AUC5 D1 Q3W x 4 cycles
Paclitaxel 80 mg/m^2 x D1, 8, 15 Q3W x 4 cycles

Nivolumab 240 mg

** 14-28 days after last dose of paclitaxel*

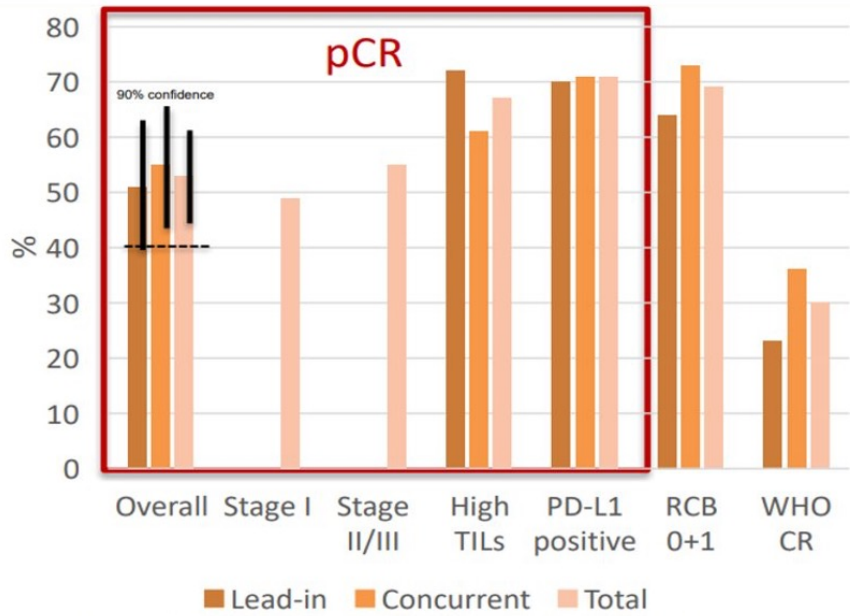
SURGERY*

** 14-28 days after last dose of Nivolumab*

End of Treatment visit 30 days after surgery.

Safety follow-up 100 days after last dose of study treatment

6 monthly follow-up to 3 years post-randomisation



Hypothesis: pCR=ypT0/is ypN0 (lower 90% CI, primary endpoint) greater than 40%

Multivariable logistic regression model (age, study cohort, stage, TILs): High TILs was only predictor of pCR (67 vs 46%; OR 2.47)

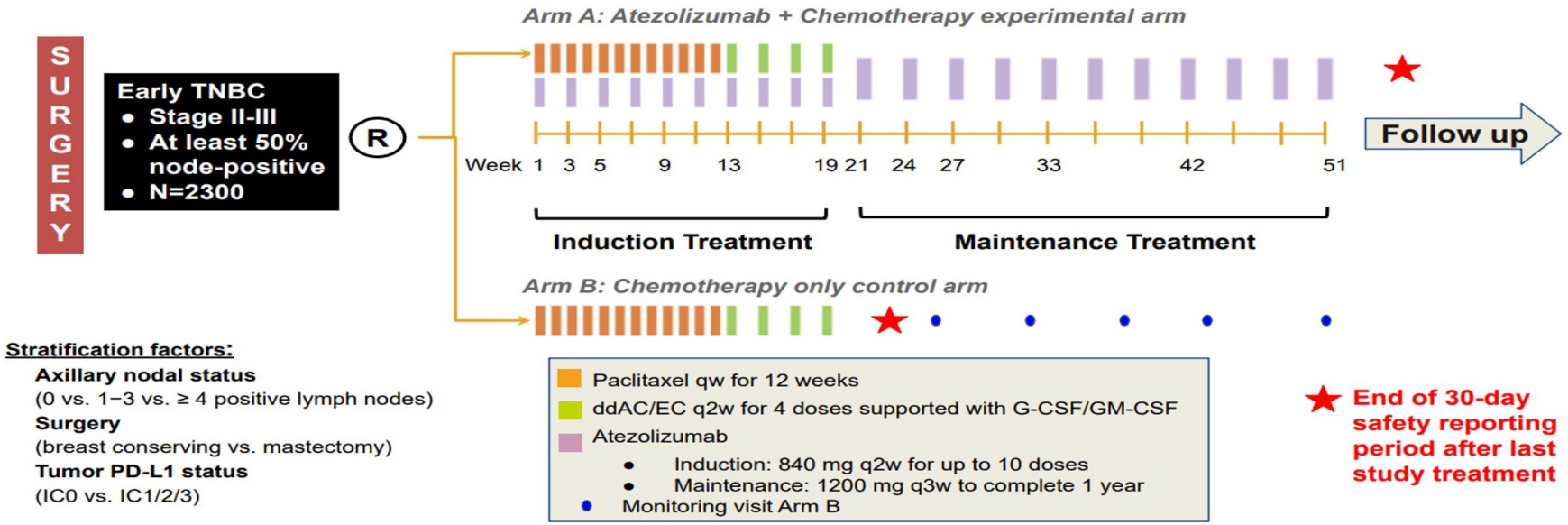
Loi S, et al. SABCS 2023

- pCR rates exceeding 50% support a 12 week neoadjuvant non-anthracycline chemotherapy regimen with nivolumab for Stage I/II TNBC;
  - Total 53% (90%CI 44-61%)
  - Lead-in 51% (90%CI 39-63%)
  - Concurrent 55% (90%CI 43-66%)
  - PD-L1 71% positive vs 33% negative; sTILs 67% high vs 47% low
- No evidence of pCR advantage was seen with Lead-in N;

Loi S, et al. SABCS 2023

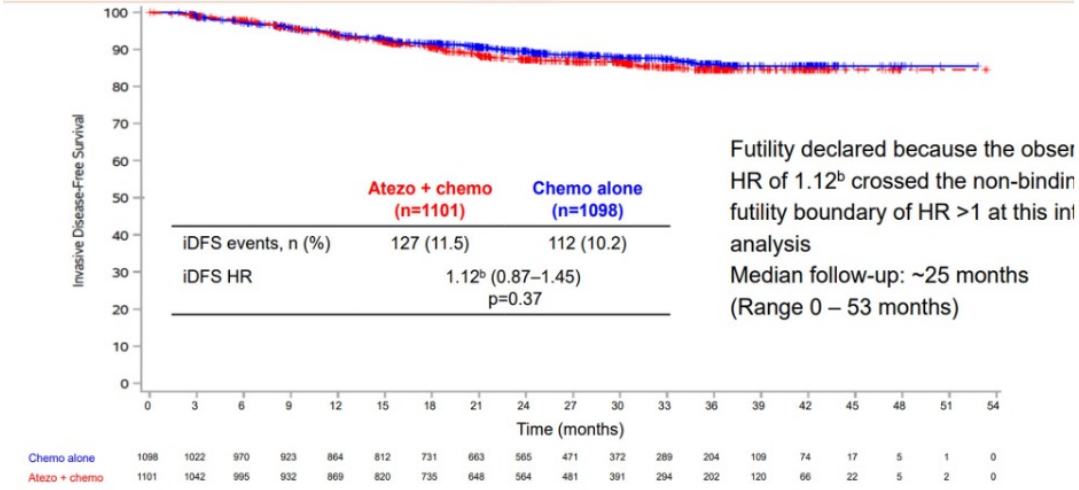
Adjuvant Atezolizumab:

Alexandra/IMpassion030 3 open-label study



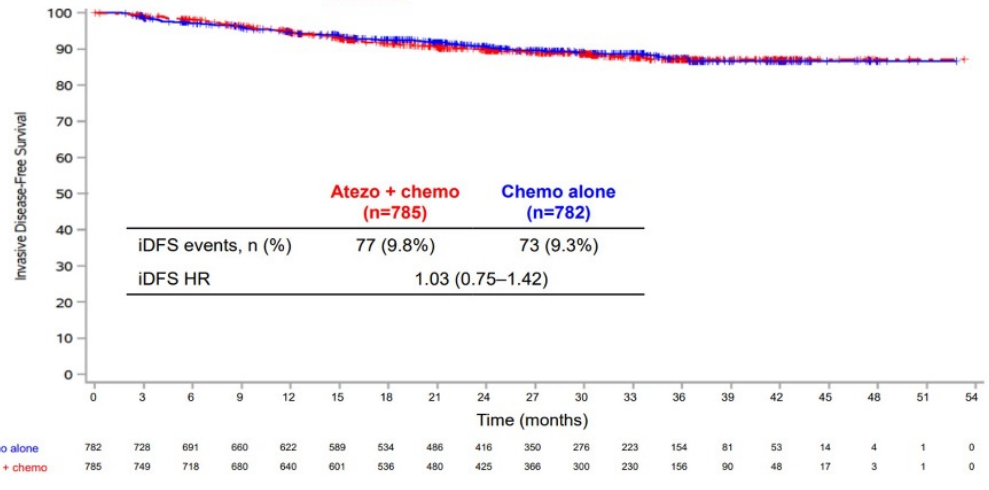
Ignatiadis M, et al. SABCS 2023

Alexandra/IMpassion030 3 open-label study
iDFS in ITT



Ignatiadis M, et al. SABCS

Alexandra/IMpassion030 3 open-label study
iDFS in PDL1+ (71%)



Ignatiadis M, et al. SABCS 2023

Predictors of Chemotherapy Use (N=8,601) Stage I Triple-negative Breast Cancer

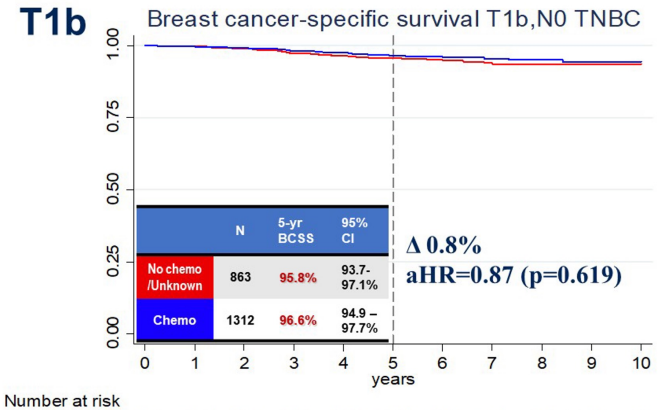
Variables **significantly associated** (all p<0.02) with the use of chemotherapy at multivariate logistic regression were:

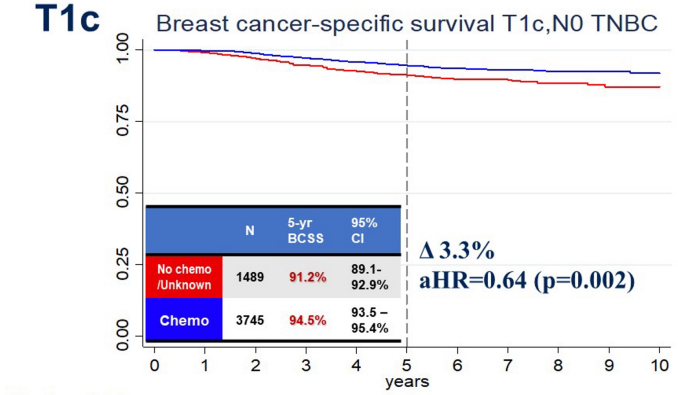
- **Younger age** (<50 vs. >64, **OR=5.19**)
- **Married status** (vs. Single, **OR=1.28**)
- **Ductal histology** (vs. Other, **OR=2.05**)
- **High tumor grade** (vs. low grade, **OR=4.89**)
- **Larger tumors** (Reference T1mic, T1a **OR=2.91**, T1b **OR=19.16**, T1c **OR=31.49**)

Systemic treatment for stage I TNBC is limited to chemotherapy, although its benefit and utilization currently remain unclear.

BCSS in Patients With T1b & T1c TNBC

- No BCSS improvement in **T1b** TNBC (adjusted HR=0.87; p=0.619)
- Significant BCSS improvement in **T1c** TNBC (adjusted HR=0.64; **p=0.002**)

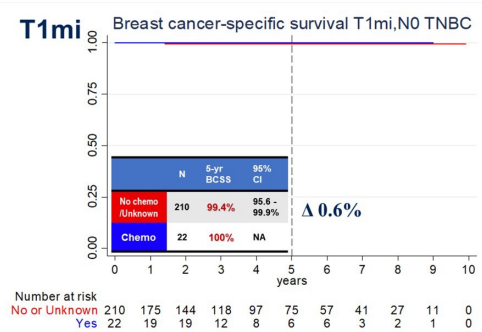


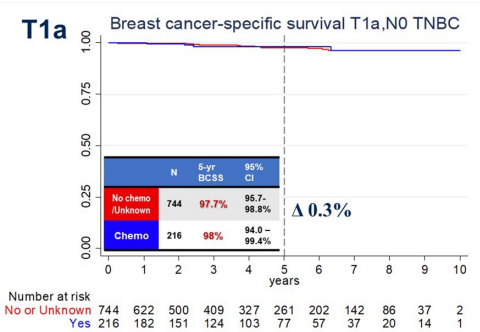


Multivariable cox models adjusted for: age at diagnosis, race, tumor grade, histology, radiation, marital status, income, and rurality.

BCSS in Patients With T1mi & T1a TNBC

- Marginal differences in **5-year BCSS** for **T1mi** and **T1a** TNBC depending on the use of chemotherapy.





Median follow up: 48 months (IQR: 20 – 83)

No adjusted analysis could be performed due to low event rate.

Conclusions/Key Take-Away:

- **In a large cohort of stage I TNBC, 5-year BCSS was favorable**
- **Chemotherapy use increased over time for T1b and T1c TNBC**
- **Chemotherapy significantly increased BCSS for T1c TNBC, (p=0.002)**

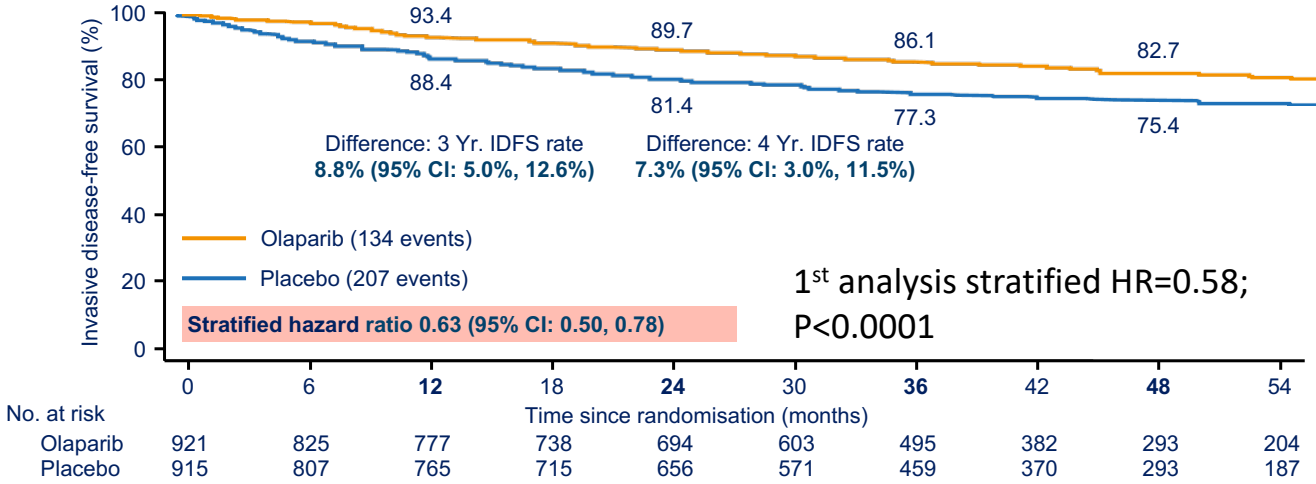
Limitations: retrospective, lack of recurrence data, small #s for T1a/T1mic

Olympia: Updated Endpoints

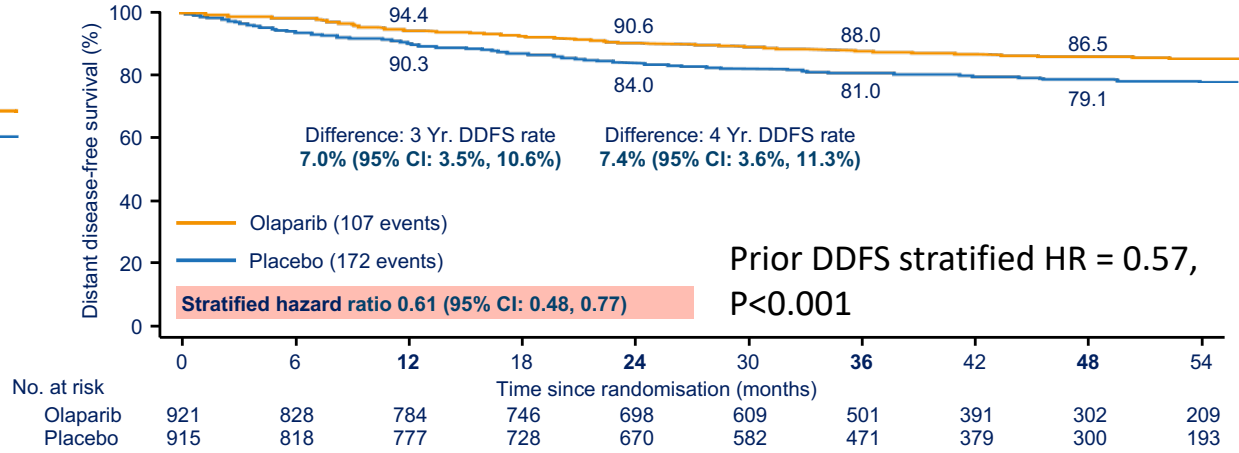
Median FU 3.5 years, 2nd IA

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



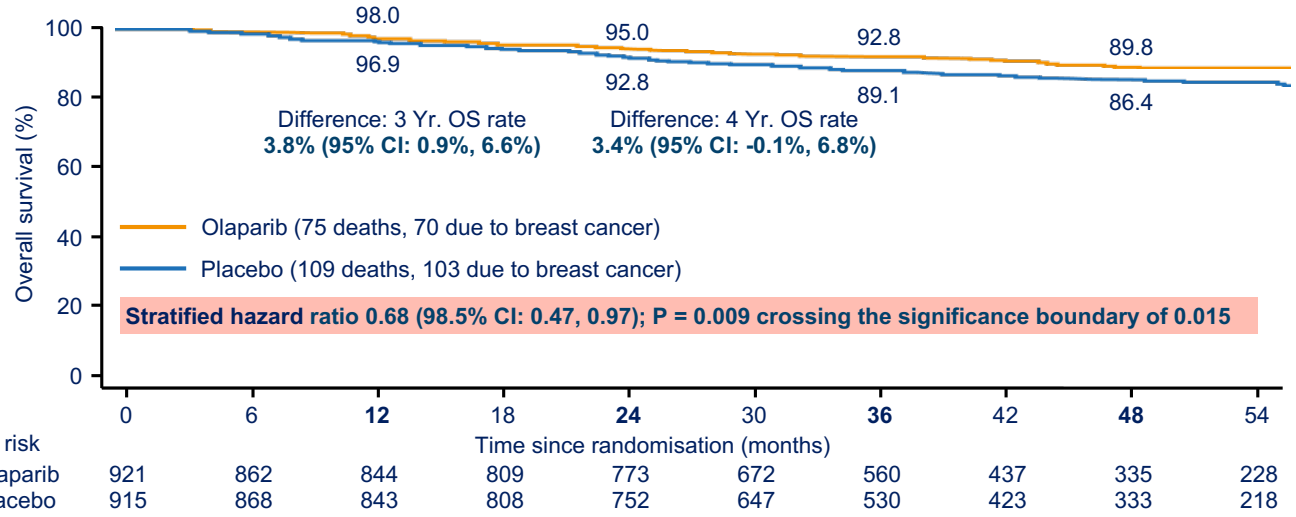
1st analysis stratified HR=0.58; P<0.0001



Prior DDFS stratified HR = 0.57, P<0.001

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

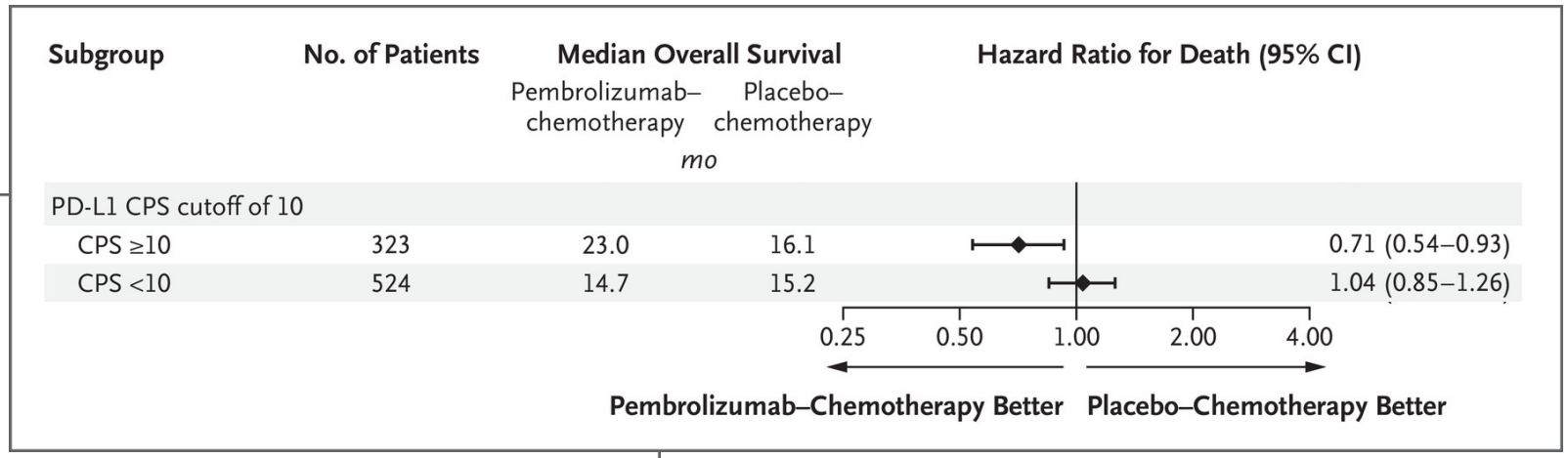
- No increase in MDS/AML compared to placebo
- Most toxicity grade 1/2; nausea most common
- Grade 3
  - Anemia 9%, fatigue 2%, neutropenia 5%



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

Keynote-355: Chemotherapy* +/- Pembrolizumab for Unresectable or Metastatic TNBC in the First-line Setting

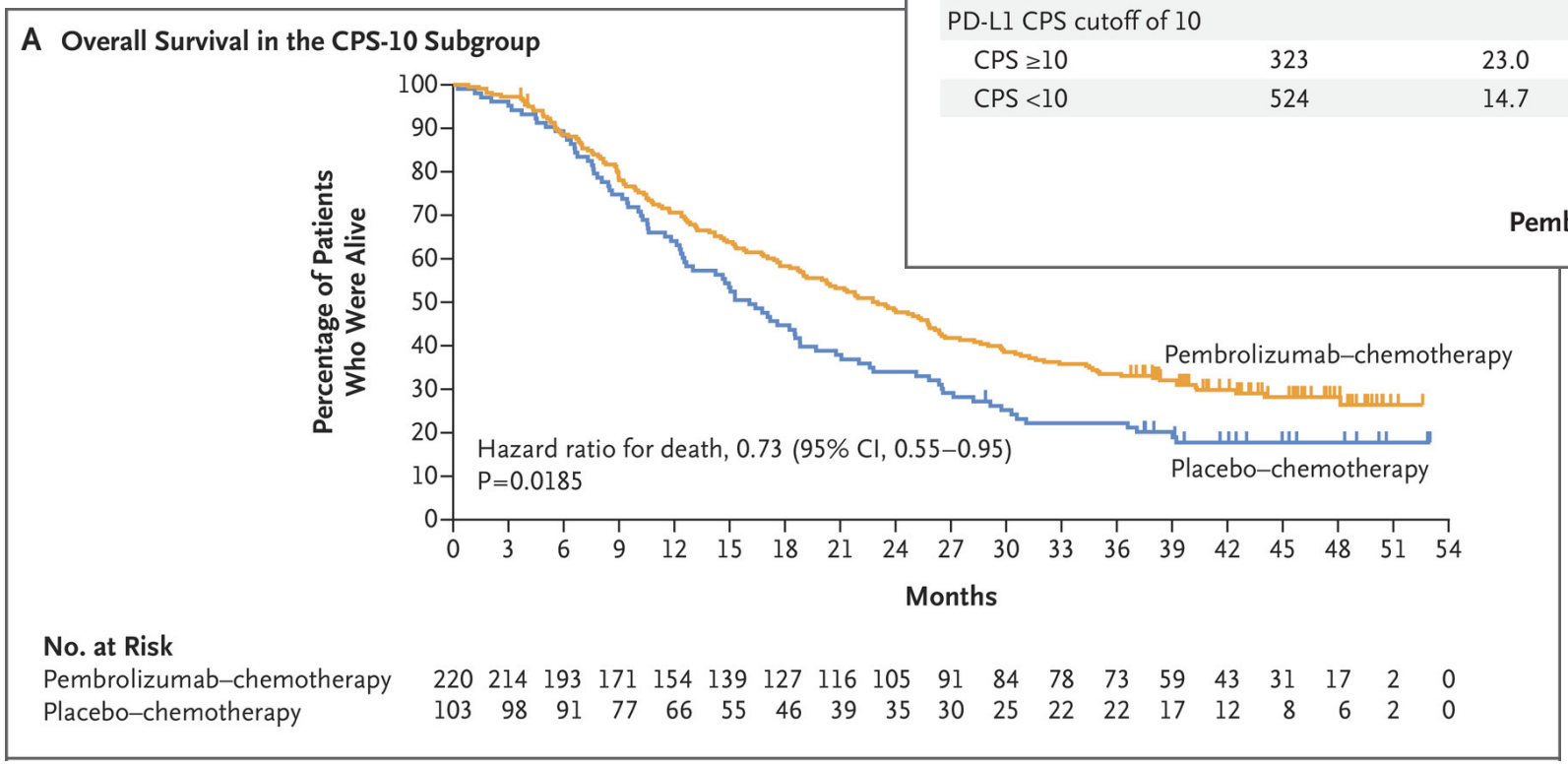
- For CPS ≥ 10%, mOS 23.0 months with chemo + pembro vs 16.1 months with chemo alone.



Subgroup	No. of Patients	Median Overall Survival (mo)		Hazard Ratio for Death (95% CI)
		Pembrolizumab–chemotherapy	Placebo–chemotherapy	
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)

0.25 0.50 1.00 2.00 4.00

Pembrolizumab–Chemotherapy Better | Placebo–Chemotherapy Better



- No OS benefit for CPS <10%.
- Grade 3-5 immune-related toxicities observed in 5.3% with pembro vs 0% of those given placebo.
  - Thyroid-related (19.0%)
  - Pneumonitis (2.5%)

***Chemotherapy of physician choice**

Nab-paclitaxel (~1/3)
Paclitaxel (~10-15%)
Gem/carbo (~50%)

Combined PD-L1 positive cells, including tumor cells, lymphocytes, and macrophages.

Cortes J, et al. Lancet 2020;396:1817-1828.

Discordance

~~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

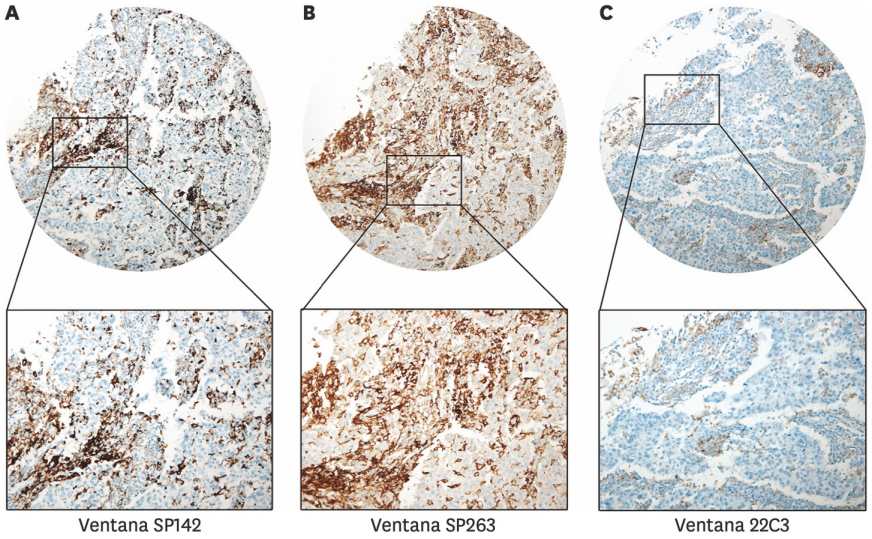
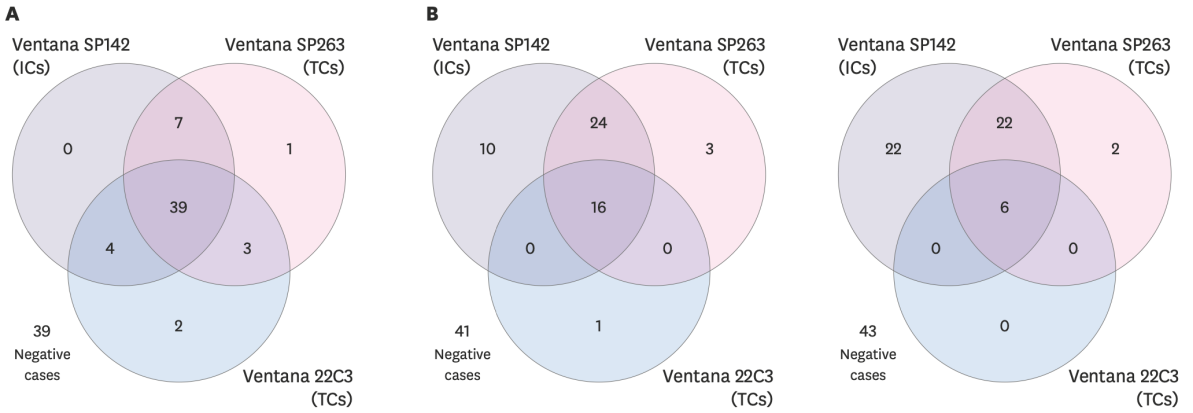


Figure 1. Representative IHC image of the same TMA core stained with 3 PD-L1 assays. (A) An SP142 assay on the Ventana platform showed prominent granular staining in infiltrating immune cells (IHC staining, 20× magnification). (B) An SP263 assay on the Ventana platform showed membranous staining in TCs (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.

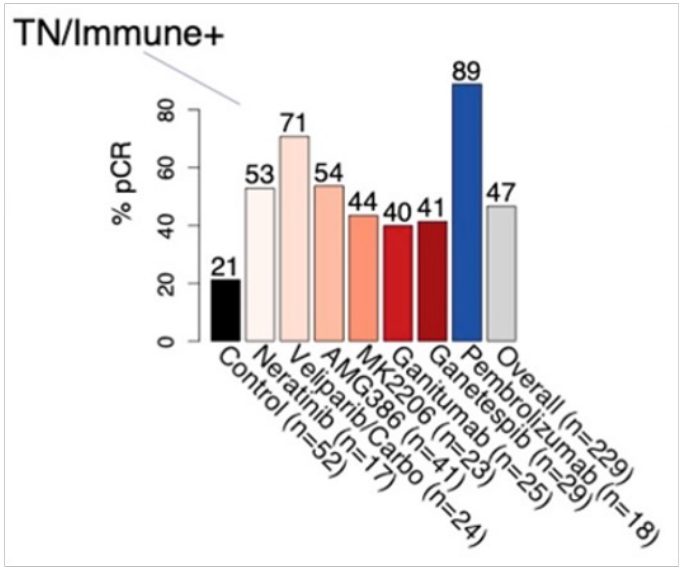
Indeed, PD-L1 expression is NOT a predictor of response to neoadjuvant pembrolizumab + chemotherapy in early TNBC [Schmid P, et al. N Engl J Med 2020; 382:810-821].



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.

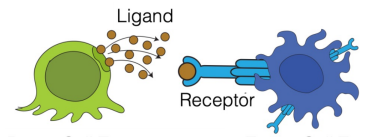
Lee SE, et al. J Breast Cancer. 2020 Jun;23(3):303-313.

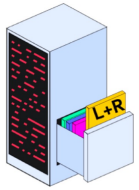
Immune response signature and pCR with ICI in I-SPY2



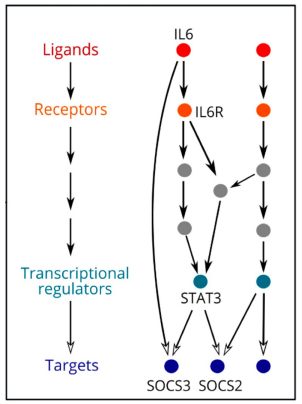
Yee D, et al. ASCO 2022, abstr 591, poster 362

Inference of cell-cell interactions from single cell data





CellPhoneDB: *Efremova et al.* **Nature Protocols** 2020



NicheNet: *Browaeys et al.* **Nature Methods** 2020

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.

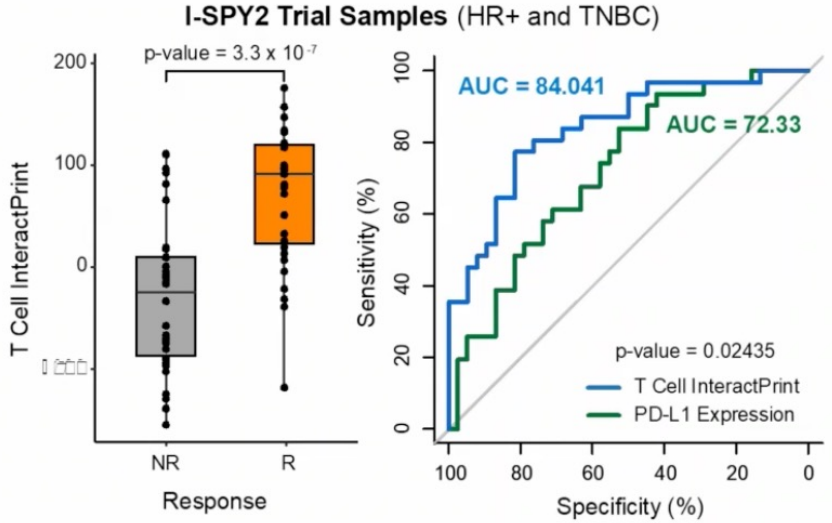
$$InteractPrint = \sum_{i=1}^{10}(e_i)(R_i)(w)$$

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

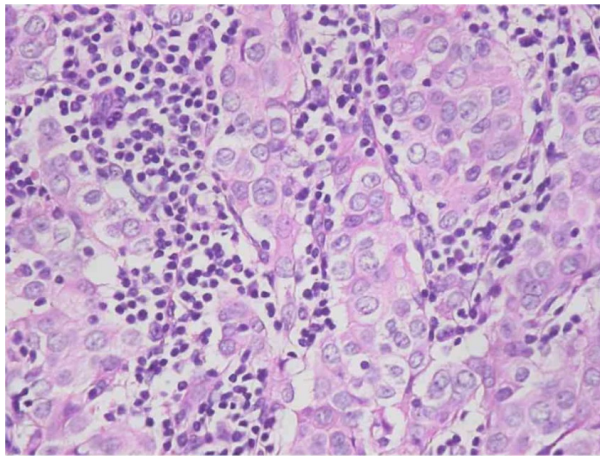
T Cell InteractPrint predicts response to anti-PD-1 therapy in I-SPY2

- 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; $p < 0.05$).

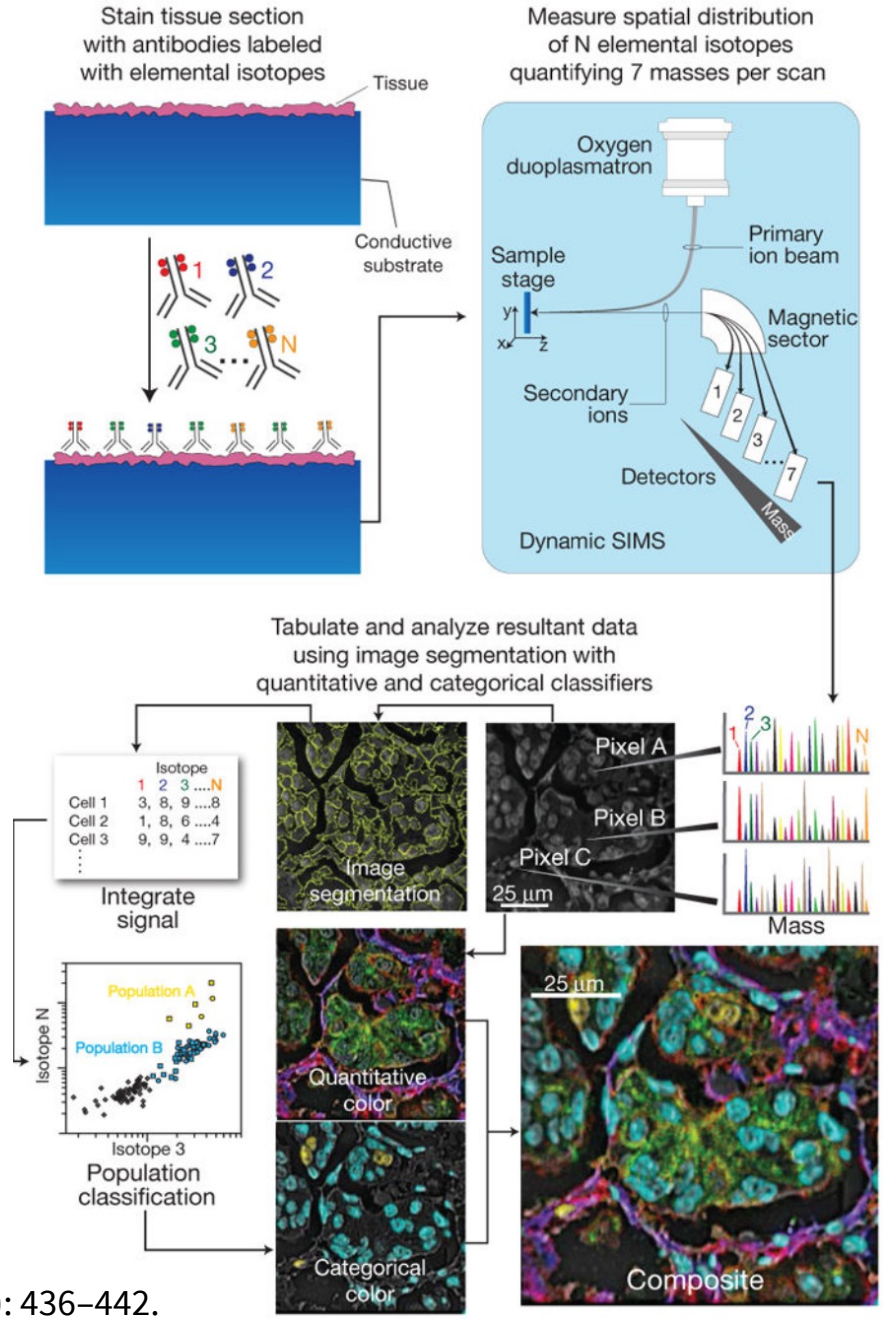


[5] Nanda et al., JAMA Oncol 2020.

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.

Stanford University

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

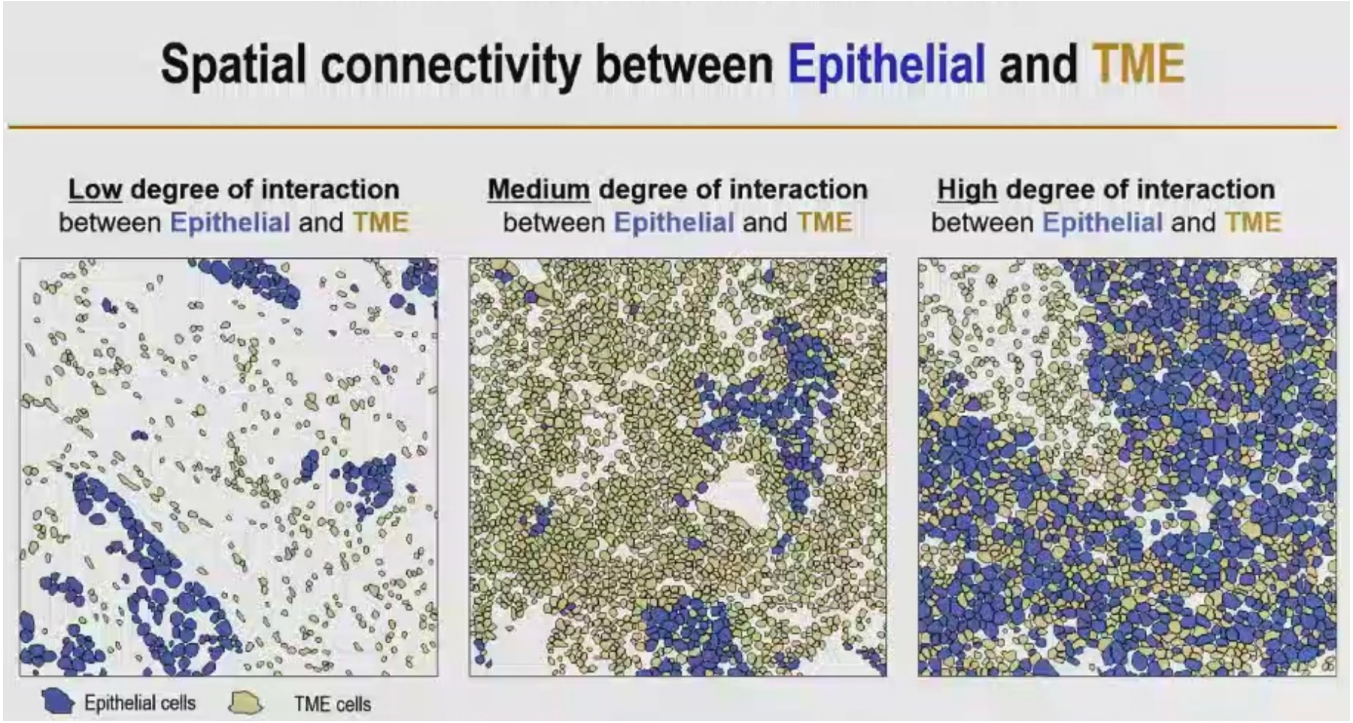
Carboplatin + *nab*-paclitaxel + Atezolizumab

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**

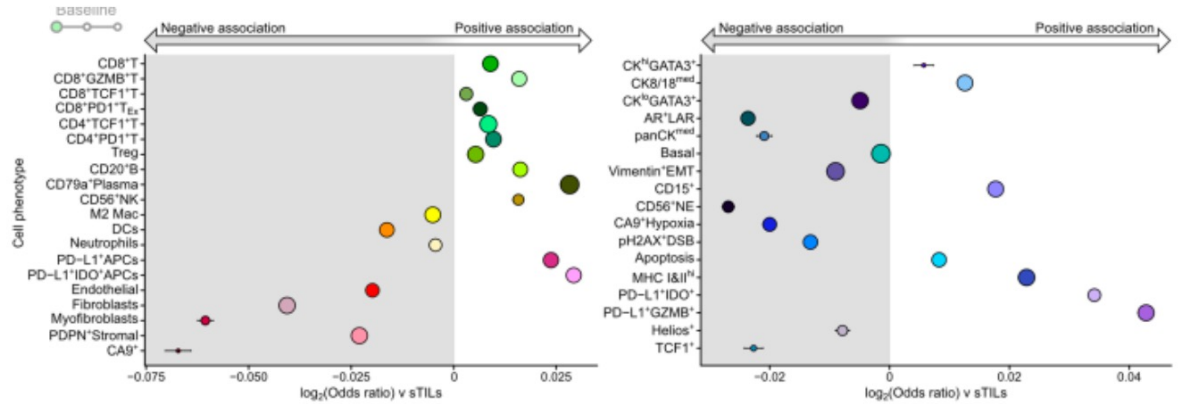
Article

Spatial predictors of immunotherapy response in triple-negative breast cancer

Xiao Qian Wang[1], Esther Danenberg[1], Chiun-Sheng Huang[2], Daniel Egle[3], Maurizio Callari[4], Begoña Bermejo[5,6,7], Matteo Dugo[8], Claudio Zamagni[9], Marc Thill[10], Anton Anton[11], Stefania Zambelli[8], Stefania Russo[12], Eva Maria Ciruelos[13], Richard Greil[14,15,16], Balázs Győrffy[17,18], Vladimir Semiglazov[19], Marco Colleoni[20], Catherine M. Kelly[21], Gabriella Mariani[22], Lucia Del Mastro[23,24], Olivia Biasi[20], Robert S. Seitz[25], Pinuccia Valagussa[4], Giuseppe Viale[20,26], Luca Gianni[4,28], Giampaolo Bianchini[4,8,28] ✉ & H. Raza Ali[1,27,28] ✉

Nature

Can we identify predictors of response to immunotherapy for TNBC

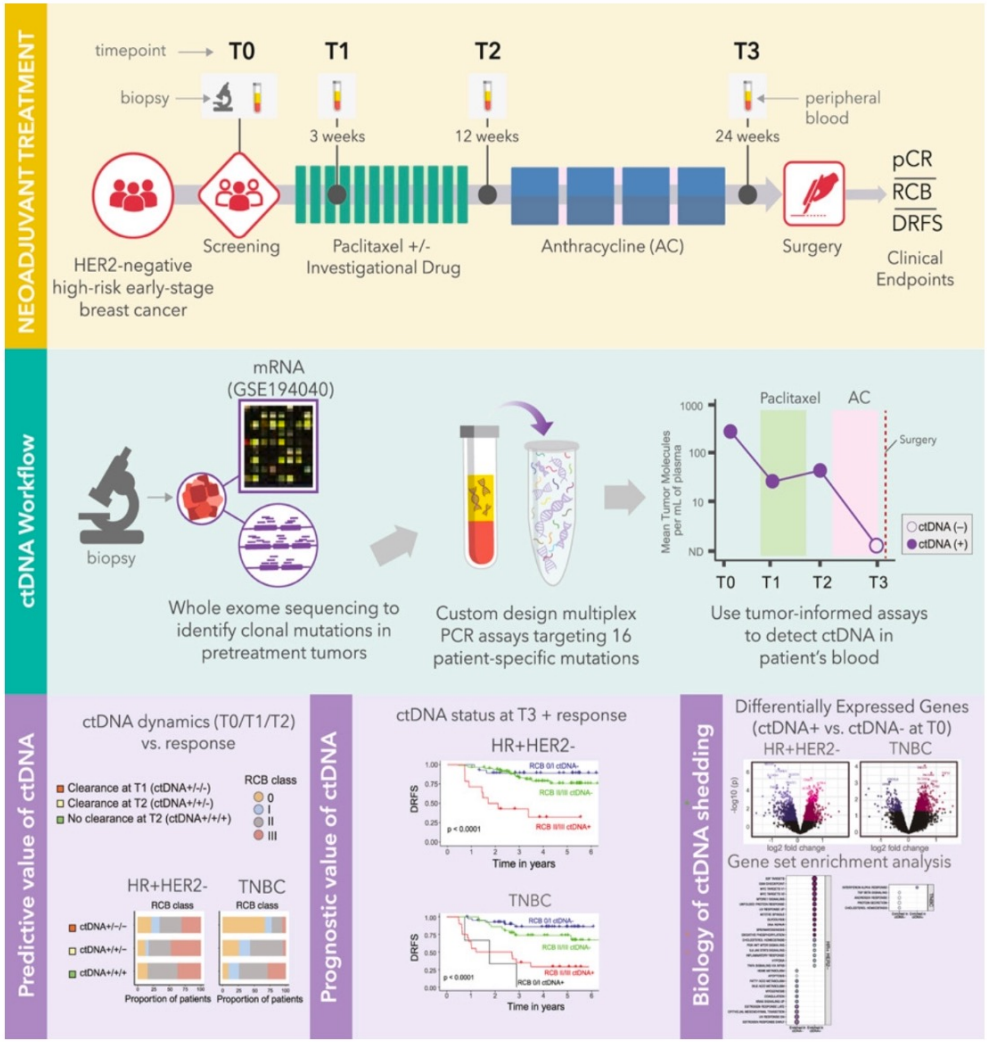


- Multicellular spatial organization and response to immunotherapy in tumors from patients with TNBC in the NeoTRIP trial, a randomized trial of neoadjuvant chemotherapy alone vs with anti-PD-L1 atezolizumab.
- Cellular composition and spatial organization of 43 proteins in TNBC at baseline (n=243), on treatment (n=207), and post-treatment (n=210), found CD8+TCF1+T cells and MHCII+ cancer cells were predictors of response, followed by cancer cell interactions with B cells and granzyme B+ T cells.
- Responsive tumors contained abundant granzyme B+ T cells, while resistant tumors contained CD15+ cancer cells, although how these cells resist IBC is unclear.
- **PMID: 37674077**

Cancer Cell

Article

Clinical significance and biology of circulating tumor DNA in high-risk early-stage HER2-negative breast cancer receiving neoadjuvant chemotherapy



Can we use ctDNA monitoring as an early predictor of response?

Mark Jesus M. Magbanua,[1,14,*] Lamorna Brown Swigart,[1] Ziad Ahmed,[1] Rosalyn W. Sayaman,[1] Derrick Renner,[2] Ekaterina Kalashnikova,[2] Gillian L. Hirst,[1] Christina Yau,[1] Denise M. Wolf,[1] Wen Li,[1] Amy L. Delson,[3] Smita Asare,[4] Minetta C. Liu,[2,5,13] Kathy Albain,[6] A. Jo Chien,[1] Andres Forero-Torres,[7] Claudine Isaacs,[8] Rita Nanda,[9] Debu Tripathy,[10] Angel Rodriguez,[2] Himanshu Sethi,[2] Alexey Aleshin,[2] Matthew Rabinowitz,[2] Jane Perlmutter,[3] W. Fraser Symmans,[10] Douglas Yee,[11] Nola M. Hylton,[1] Laura J. Esserman,[1] Angela M. DeMichele,[12] Hope S. Rugo,[1] and Laura J. van 't Veer[1]

- Serial ctDNA analysis was performed for ER+/HER2- BC and TNBC patients receiving neoadjuvant chemotherapy (NAC) in the I-SPY2 trial.
- ctDNA positivity rates before, during, and after NAC were higher in patients with TNBC than in ER+/HER2- BC patients.
- Early clearance of ctDNA 3 weeks after treatment initiation predicts a favorable response to NAC in TNBC only. ctDNA positivity associates with reduced distant recurrence-free survival in both subtypes.
- Gene expression analysis revealed pathways associated with ctDNA shedding at baseline in both subtypes, including active metabolism, proliferation, and high indicators of immune activity.
- On the basis of these findings, the I-SPY2 trial will prospectively test ctDNA for utility in redirecting therapy to improve response

Magbanua et al., 2023, Cancer Cell 41, 1091–1102.

KEYLYNK-009 study

Key Eligibility Criteria

- Locally recurrent inoperable or metastatic TNBC not previously treated in the metastatic setting
- Measurable disease per RECIST v1.1 by local radiology review
- Interval between treatment with curative intent and recurrence ≥6 months
- Confirmed PD-L1 status

ITT Population

271 pts

Induction

Carboplatin AUC 2 on days 1 and 8 of each 21-day cycle and gemcitabine 1000 mg/m² on days 1 and 8 of each 21-day cycle
+
Pembro 200 mg Q3W

(4 to 6 cycles)

RANDOMIZATION[c] (1:1)

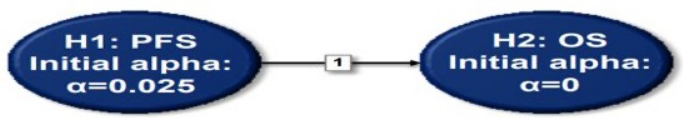
Post-induction

Olaparib 300 mg twice daily[a,b]
+
Pembro 200 mg Q3W up to 35 cycles including induction[b]

Carboplatin AUC 2 on days 1 and 8 of each 21-day cycle and gemcitabine 1000 mg/m² on days 1 and 8 of each 21-day cycle[b]
+
Pembro 200 mg Q3W for up to 35 cycles including induction[b]

Randomization was stratified by
- Induction response (CR or PR vs SD)
- Tumor PD-L1 status (CPS ≥1 vs <1)
- Genomic tumor status (*BRCA*m vs *BRCA*wt)

- Primary Endpoints[a]
  - PFS per RECIST v1.1 by BICR in ITT population
  - OS in ITT populatic



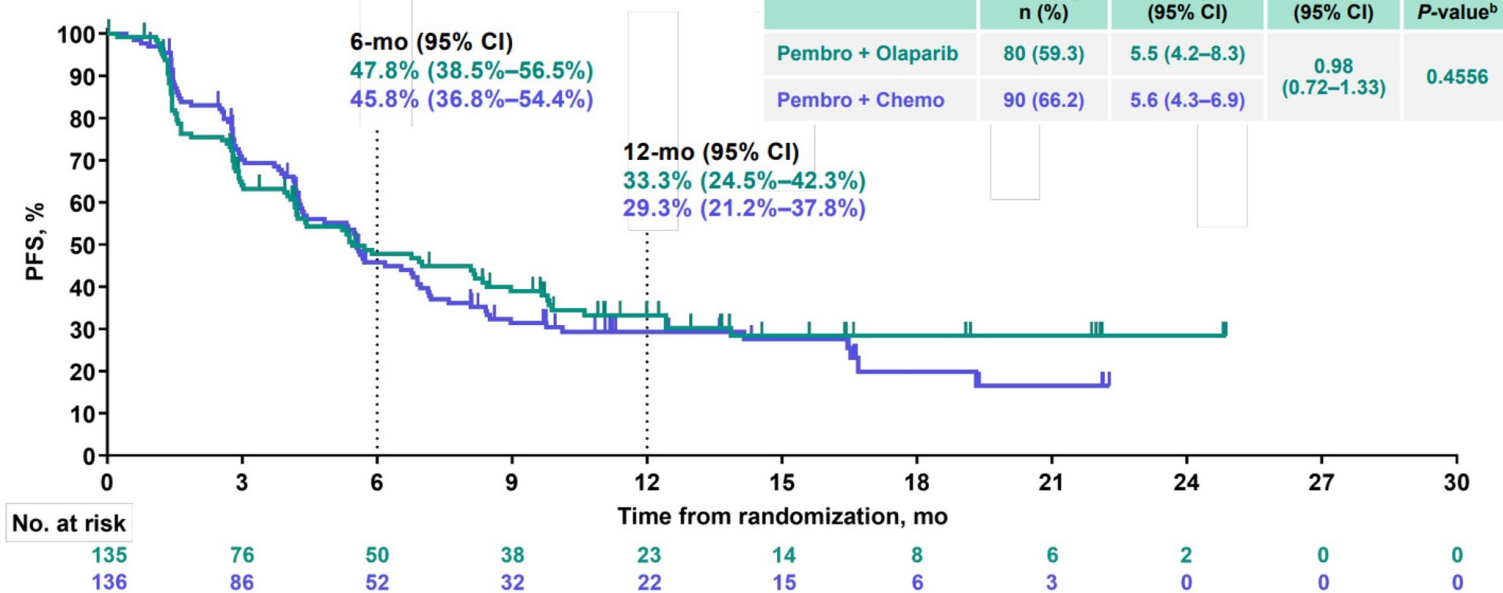
All α=2.5% will be allocated to PFS first, and if superiority is demonstrated, the full alpha 2.5% from the superiority test for PFS will be passed to the superiority test for OS

Rugo H, et al. SABCS 2023

KEYLYNK-009 study

KEYLYNK-009 study

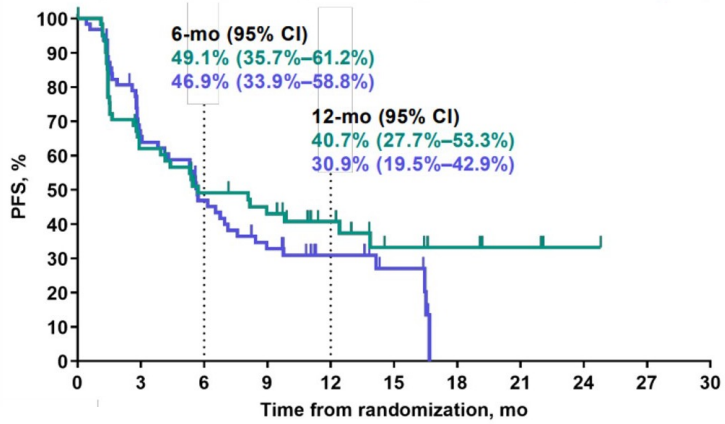
	Events, n (%)	Median, mo (95% CI)	HR[a] (95% CI)	*P*-value[b]
Pembro + Olaparib	80 (59.3)	5.5 (4.2–8.3)	0.98 (0.72–1.33)	0.4556
Pembro + Chemo	90 (66.2)	5.6 (4.3–6.9)		



Rugo H, et al. SABCS 2023

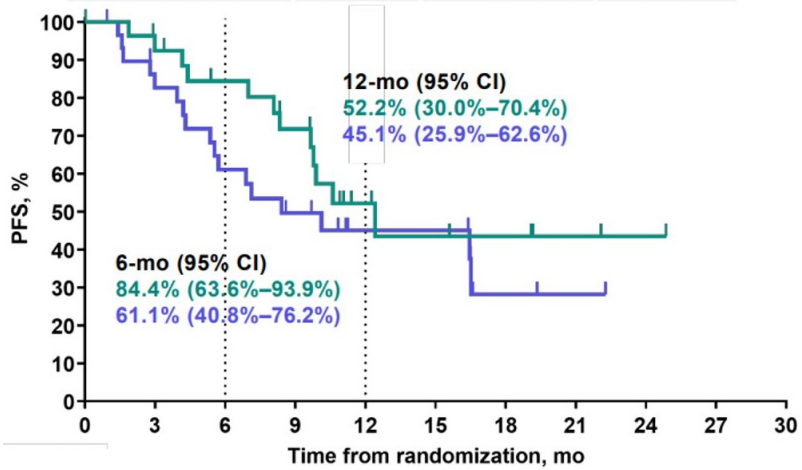
Tumor PD-L1 CPS ≥10 Population (~48%)

	Events, n (%)	Median, mo (95% CI)	HR[a] (95% CI)
Pembro + Olaparib	36 (55.4)	5.7 (2.9–13.9)	0.92 (0.59–1.43)
Pembro + Chemo	45 (69.2)	5.7 (3.8–7.6)	



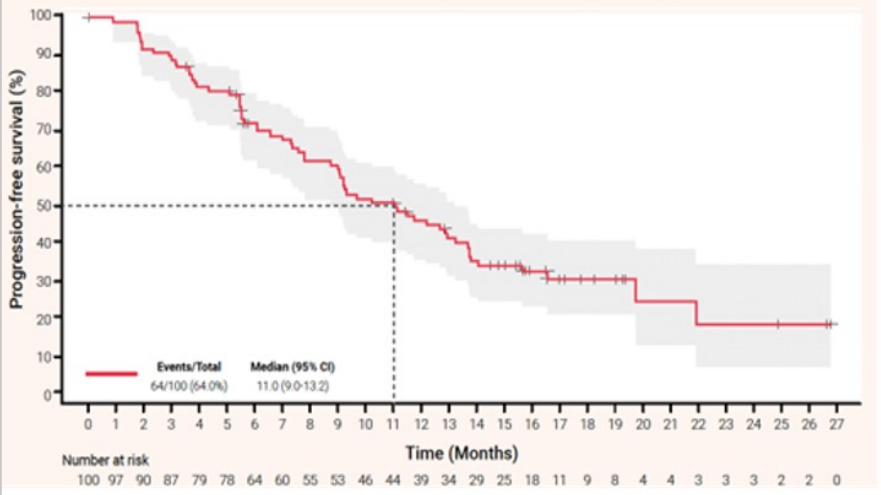
t*BRCA*m Population (~21%)

	Events, n (%)	Median, mo (95% CI)	HR[b] (95% CI)
Pembro + Olaparib	12 (41.4)	12.4 (8.3–NR)	0.70 (0.33–1.48)
Pembro + Chemo	17 (56.7)	8.4 (5.4–NR)	

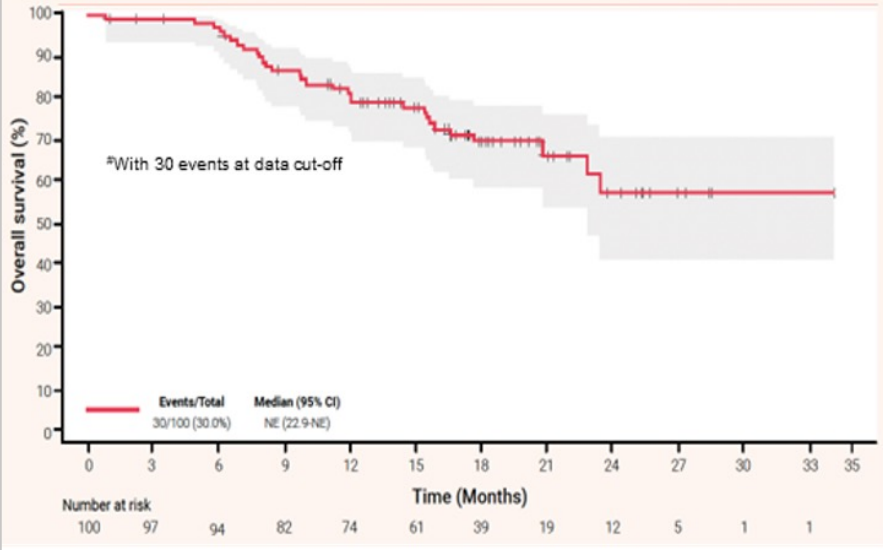


1st line TNBC: ATRACTIB study (Atezolizumab + Paclitaxel + Bevacizumab)

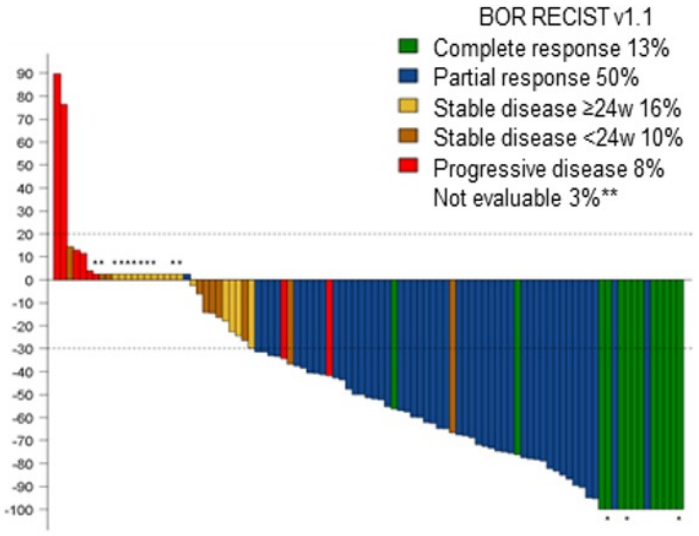
mPFS 11.0 months (95% CI, 9.0 – 13.2)



Estimated 18-month OS# 69.4% (95% CI, 58.4% - 78.1%)



Best percentage change in sum of target lesions (%)



Tumor response, n (%)	Confirmed	Unconfirmed
ORR	55.0% (95% CI, 44.7% - 65.0%)	63.0% (95% CI, 52.8% - 72.4%)
CR	11	13
PR	44	50
SD ≥24 w	22	16
SD <24 w	12	10
PD	8	8
NE	4	3
CBR	77.0% (95% CI, 67.5% - 84.8%)	79.0% (95% CI, 69.7% - 86.5%)
Duration of response (median), months		
10.0 (95% CI, 7.2 – 13.8)		

Summary of TEAEs, most frequent TEAEs (>25%) and irAEs n(%)

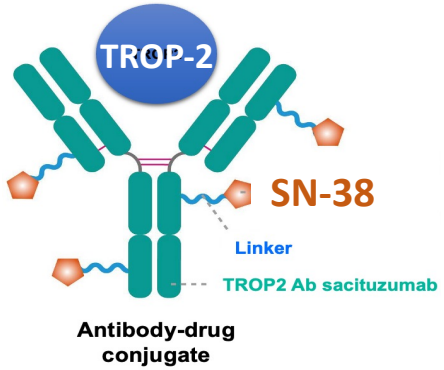
TEAEs, n (%)	Overall (N=100)	Treatment-related
Any TEAEs	100 (100.0%)	97 (97.0%)
Grade 3/4 TEAEs	61 (61.0%)	47 (47.0%)
Any serious TEAEs	34 (34.0%)	18 (18.0%)
ECIs	42 (42.0%)	42 (42.0%)
TEAEs leading to treatment discontinuation of:		
Atezolizumab	14 (14%)	-
Bevacizumab	15 (15%)	-
Paclitaxel	40 (40%)	-
TEAEs leading to death	0 (0.0%)	0 (0.0%)
Dose adjustments		
Reduction of Paclitaxel	22 (22.0%)	22 (22.0%)

Most frequent TEAEs, n (%)	Any grade	Grade 3/4
Non-hematologic		
Peripheral neuropathy‡	68 (68.0%)	13 (13.0%)
Fatigue	62 (62.0%)	7 (7.0%)
Diarrhea	42 (42.0%)	3 (3.0%)
Alopecia	41 (41.0%)	0 (0.0%)
Stomatitis	37 (37.0%)	3 (3.0%)
Nausea	31 (31.0%)	0 (0.0%)
Hypertension	30 (30.0%)	9 (9.0%)
Hematologic		
Neutropenia	27 (27.0%)	12 (12.0%)

irAEs, n (%)	Any grade	Grade 3/4
Any irAEs	12 (12.0%)	5 (5.0%)
Thyroid disorders	6 (6.0%)	0 (0.0%)
Immune-mediated hepatitis	3 (3.0%)	3 (3.0%)
Nephritis	2 (2.0%)	2 (2.0%)
Addison's disease	1 (1.0%)	0 (0.0%)

*Patients with only non-target lesions. **Three patients discontinued before post-baseline assessment due to Progressive Disease in one patient and to withdrawal of consent in two patients. ‡ Peripheral neuropathy (SMQ), includes Neuropathy peripheral, Neurotoxicity, Polyneuropathy, and Toxic neuropathy (MedDRA v.25.1).
ATZ, atezolizumab; BVZ, bevacizumab; BOR, best overall response; CBR, Clinical Benefit Rate; CI, confidence interval; CR, Complete Response; ECI, events of clinical interest; NE, Not Evaluable; PR, Partial Response; PTX, paclitaxel; SD, Stable Disease; TEAEs, treatment-emergent adverse events.

Gion M, et al. SABCS 2023

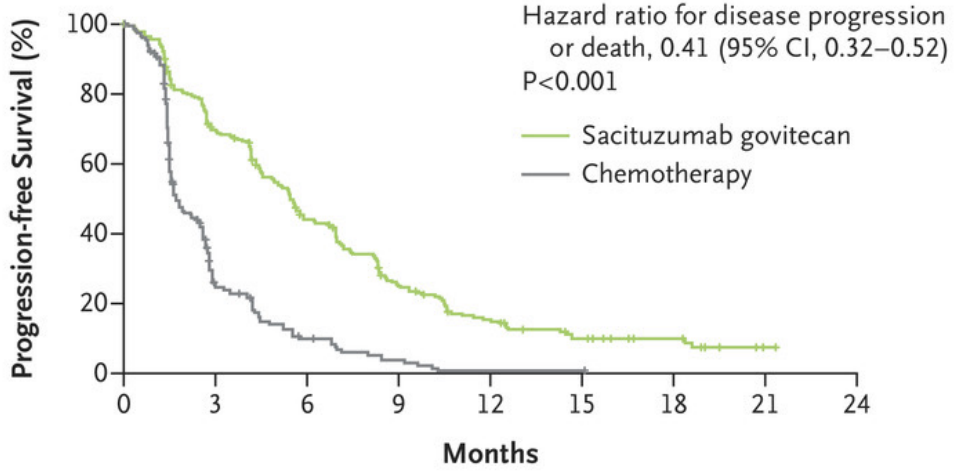


Antibody-drug conjugate

ASCENT: A phase III Trial of Antibody-Drug Conjugate Sacituzumab Govitecan vs TPC in Metastatic Triple Negative Breast Cancer – Level One Evidence for OS Benefit

A Progression-free Survival among Patients without Brain Metastases

	No. of Patients	No. of Events	Median Progression-free Survival (mo (95% CI))
Sacituzumab Govitecan	235	166	5.6 (4.3–6.3)
Chemotherapy	233	150	1.7 (1.5–2.6)

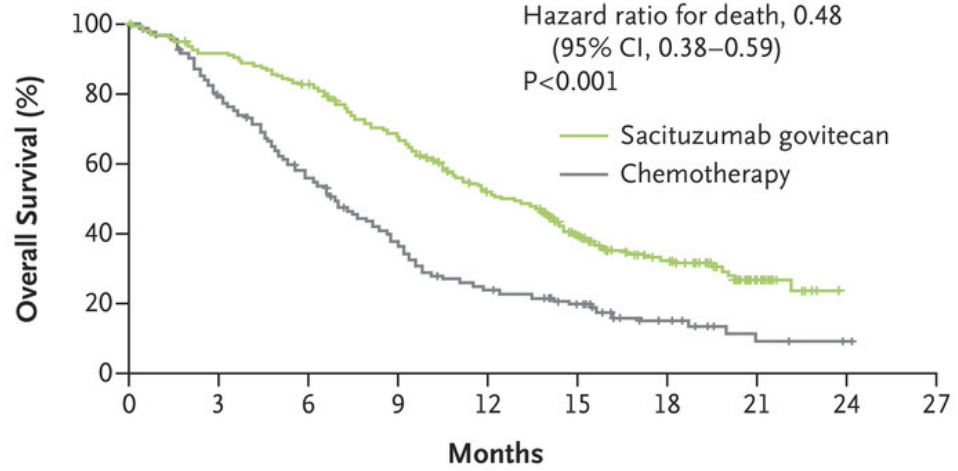


No. at Risk								
Sacituzumab govitecan	235	154	91	49	28	15	9	1
Chemotherapy	233	39	14	5	1	1	0	0

B Overall Survival among Patients without Brain Metastases

Most common AEs (incidence >25%): cytopenias, N/V/D, fatigue, alopecia, anorexia, rash and abdominal pain

	No. of Patients	No. of Events	Median Overall Survival (mo (95% CI))
Sacituzumab Govitecan	235	155	12.1 (10.7–14.0)
Chemotherapy	233	185	6.7 (5.8–7.7)

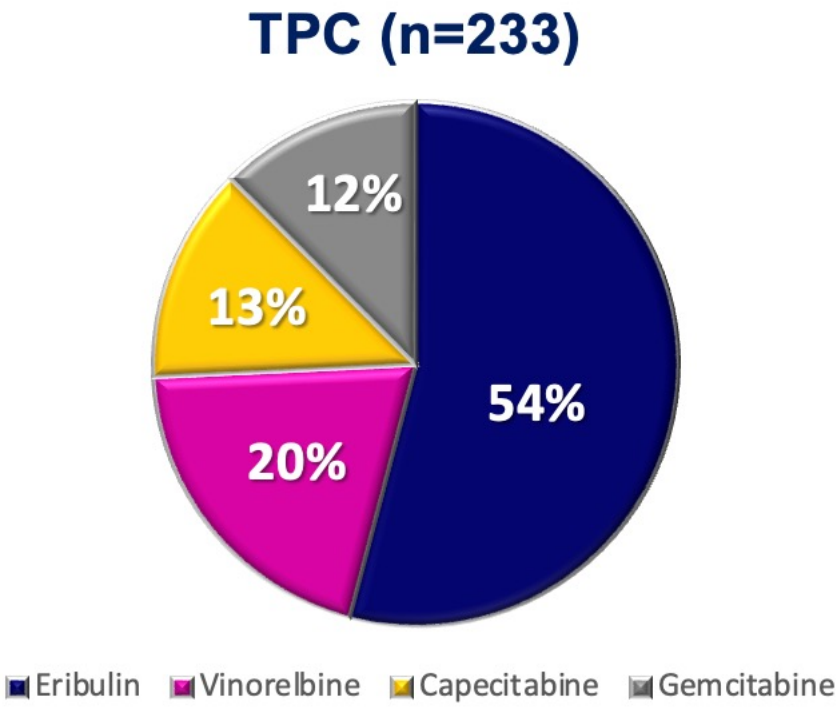


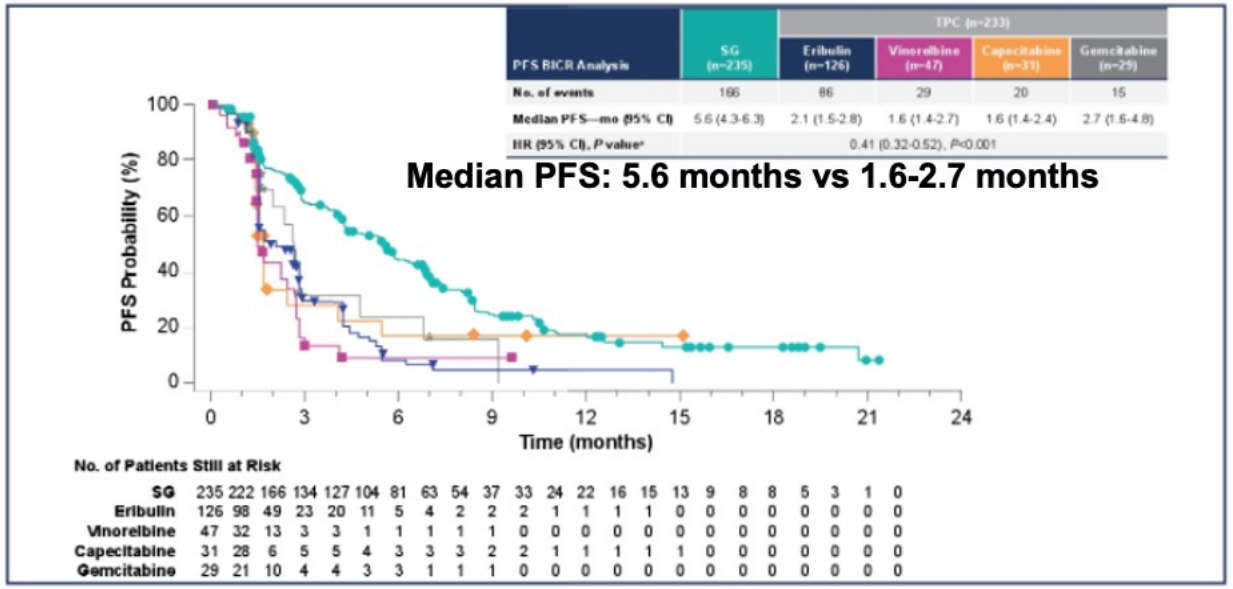
No. at Risk									
Sacituzumab govitecan	235	214	190	153	107	70	37	13	0
Chemotherapy	233	173	117	74	45	30	11	3	1

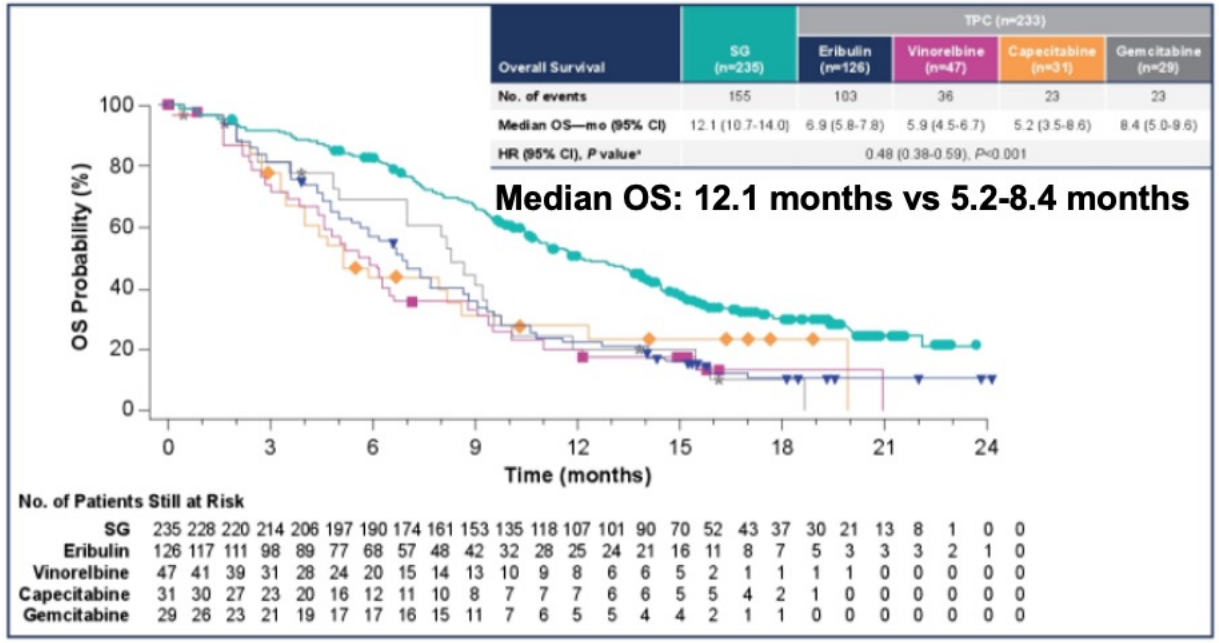
Ongoing Phase III Trials ASCENT 3 and 4 will test SG and SG ± pembro in 1L MBC.

Bardia A, et al. *N Engl J Med* 2021; 384:1529-1541.

ASCENT: Outcomes by Treatment of Physician's Choice (TPC)







O'Shaughnessy J, et al. ASCO 2021. Abstract 1077.

ASCENT and TROPiCS-02: Safety Outcomes by UGT1A1 Status

UTG1A1

- ✓ Variants affect enzymatic function, causing reduced metabolic capacity
- ✓ Over 50% of individuals may harbor an UTG1A1 polymorphism, dependent on genetic ancestry

	ASCENT		TROPiCS-02	
SG patients (n=250)	UTG1A1 Status n(%)	Dose Intensity (%)	UTG1A1 Status n(%)	Dose Intensity (%)
*1/*1 (wt)	113 (44)	99.8	104 (38)	99
*1/*28	96 (37)	99.5	119 (44)	98
*28/*28	34 (13)	99.8	25 (9)	94

Grade ≥3 TEAEs Overall (%)	SG (n=268)
Neutropenia	52
Diarrhea	10
Anemia	8
Febrile neutropenia	6

	ASCENT			TROPiCS-02		
Grade ≥3 TEAEs By UTG1A1 Status (%)	*1/*1 (wt)	*1/*28	*28/*28	*1/*1 (wt)	*1/*28	*28/*28
Neutropenia	53	47	59	45	57	64
Diarrhea	10	9	15	6	13	24
Anemia	4	6	15	6	8	8
Febrile neutropenia	3	5	18	6	7	4

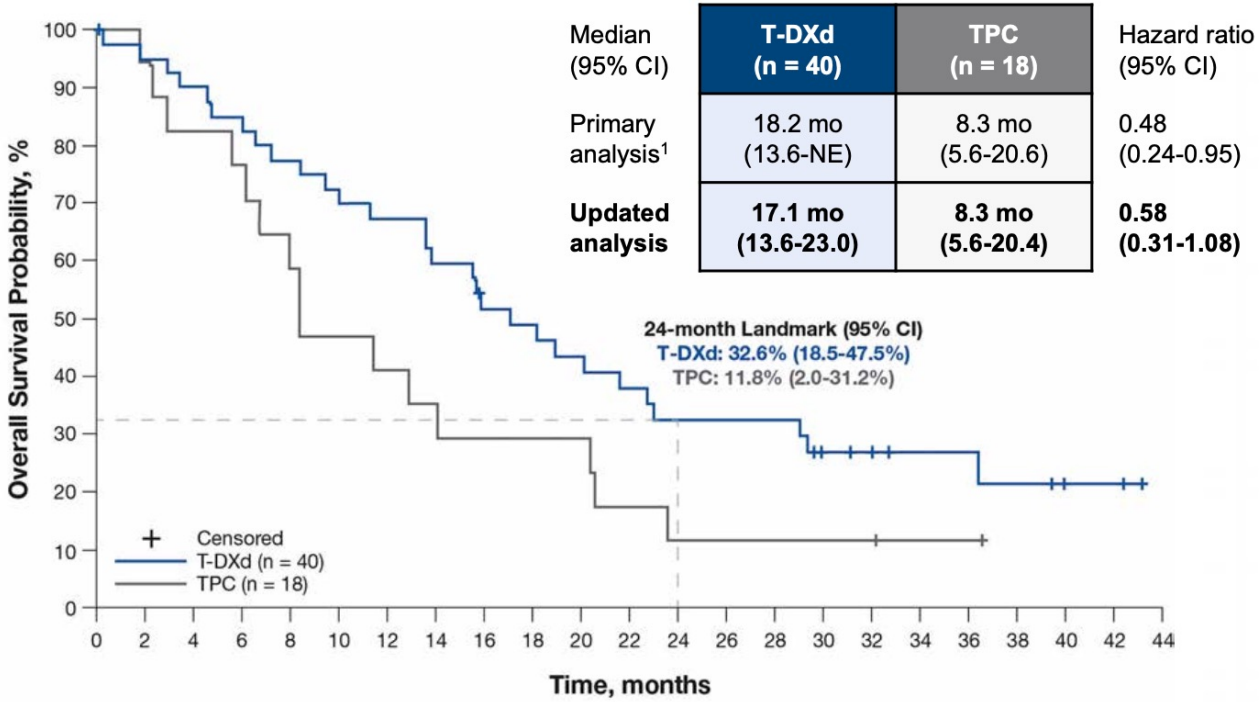
ASCENT: Treatment discontinuation due to TRAEs more common in *28 homozygous genotype

Nelson, RS, et al. *Cancers.* 2021;13:1566.
Rugo, HS, et al. *npj Breast Cancer.* 2022;8:98.
Marmé, F, et al. *Annals of Oncol.* 2023;8(1suppl_4):101223-101223.

Trastuzumab Deruxtecan in HER2-low TNBC: Updated Efficacy in the HR− Cohort (Exploratory Analyses)

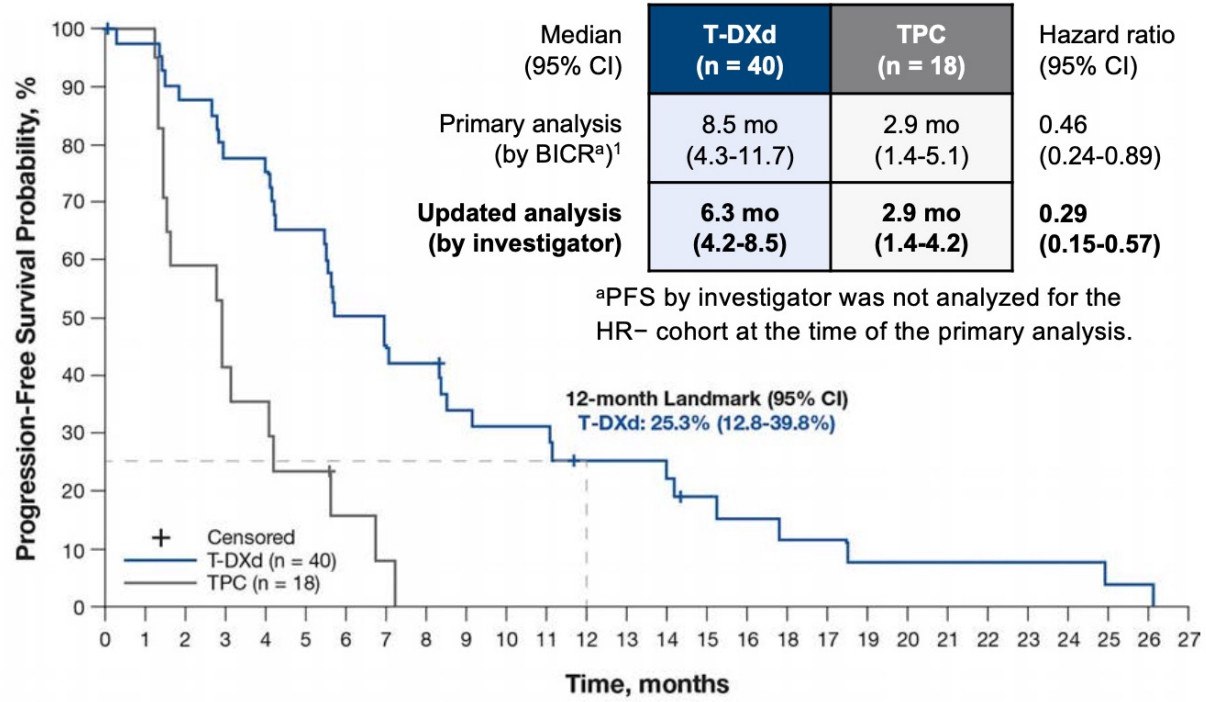
Med 32 mo followup

Overall Survival



Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis[1]	18.2 mo (13.6-NE)	8.3 mo (5.6-20.6)	0.48 (0.24-0.95)
Updated analysis	**17.1 mo (13.6-23.0)**	**8.3 mo (5.6-20.4)**	**0.58 (0.31-1.08)**

Progression-Free Survival (by Investigator)



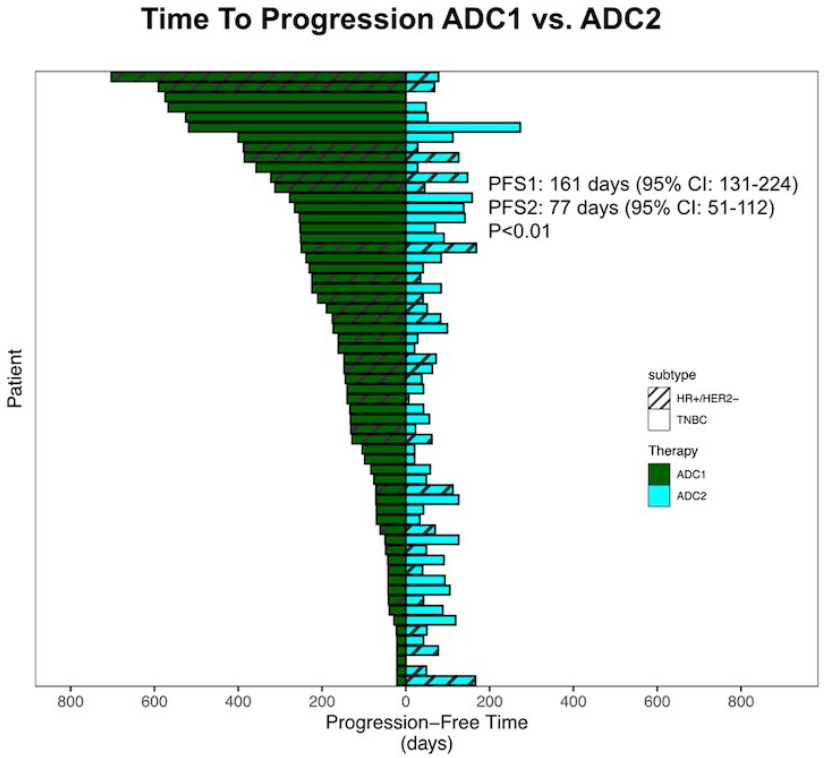
Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis (by BICR[a])[1]	8.5 mo (4.3-11.7)	2.9 mo (1.4-5.1)	0.46 (0.24-0.89)
Updated analysis (by investigator)	**6.3 mo (4.2-8.5)**	**2.9 mo (1.4-4.2)**	**0.29 (0.15-0.57)**

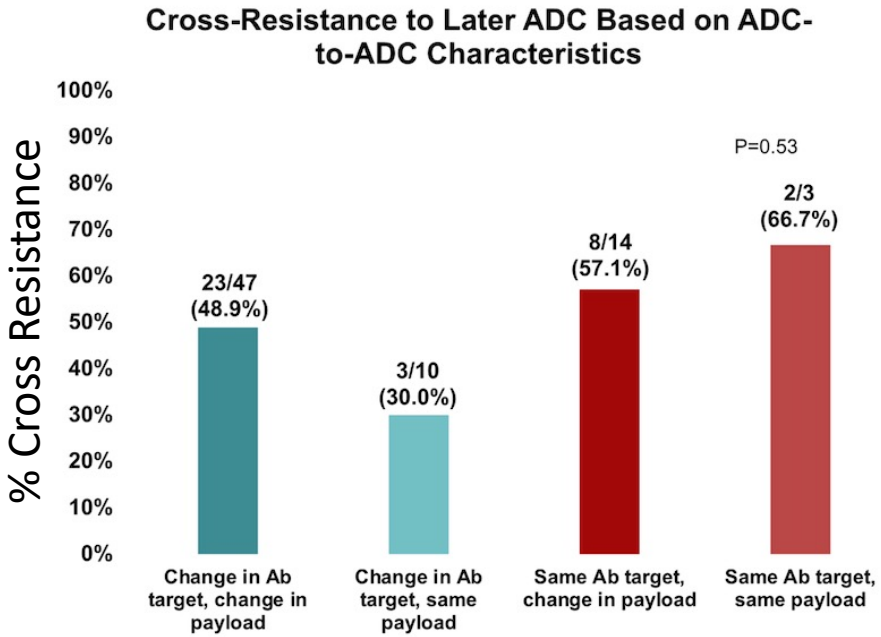
[a]PFS by investigator was not analyzed for the HR− cohort at the time of the primary analysis.

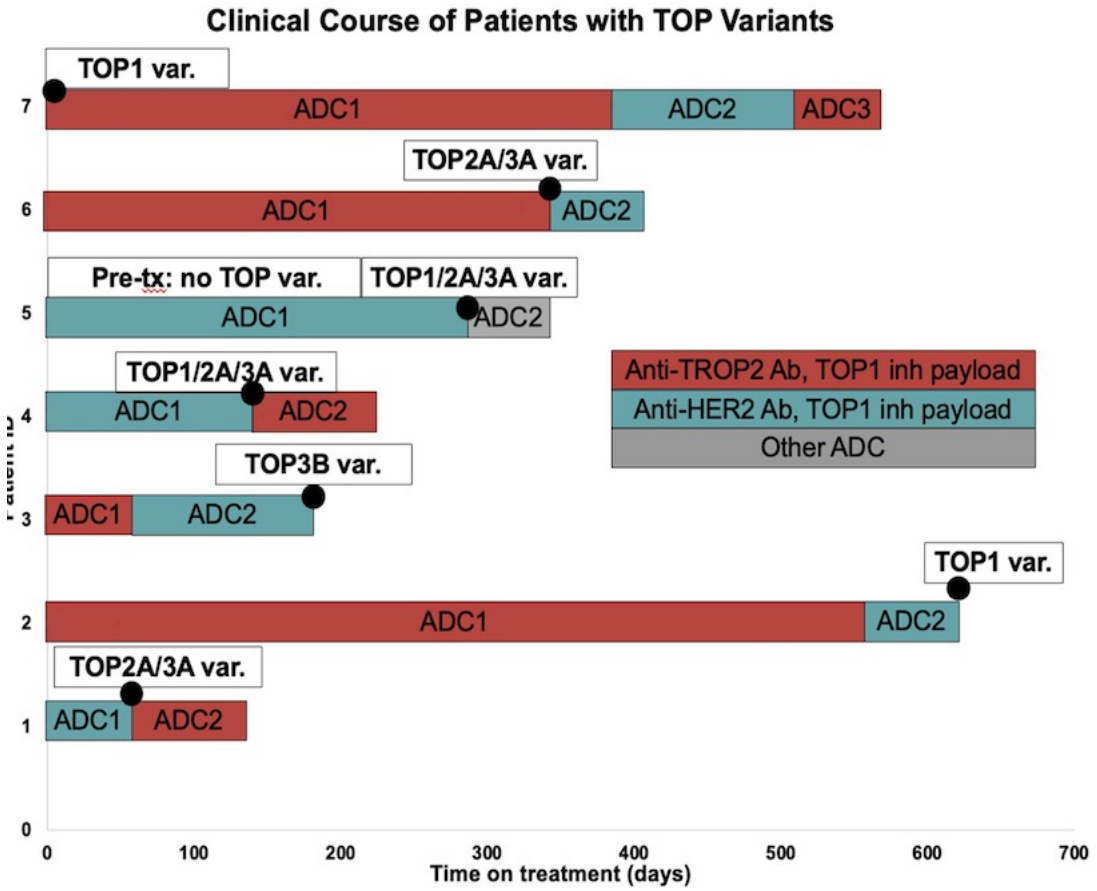
- There was a 42% reduction in risk of death and 71% reduction in risk of disease progression or death for HR− patients receiving T-DXd compared with TPC
- Most common AEs (≥20%): N/V/D, anorexia, cytopenias, inc LFTs, hypokalemia, MS pain and resp infection

Modi S, et al. ESMO 2023.

Sequencing Antibody-Drug Conjugate after Antibody-Drug Conjugate in Metastatic Breast Cancer (A3 study): Multi-Institution Experience and Biomarker Analysis







CONCLUSIONS AND FUTURE DIRECTIONS

- This multi-institution update of patients receiving ADC after ADC includes biomarker data from tissue sequencing.
- Cross-resistance to ADC2 appears to be driven by antibody target in some patients versus payload in others.
- Mechanisms of resistance to ADCs are likely heterogeneous given the complex structure of ADCs.
- Tumor sequencing identified candidate resistance mutations including variants in TOP family.
- These data emphasize the ongoing role of tissue samples in determining resistance mutations to novel agents.

Abelman RO, et al. SABCS 2023.

Conclusions

- GS01-03 Adding atezolizumab to adjuvant chemotherapy for stage II and III triple-negative breast cancer is unlikely to improve efficacy: interim analysis of the **ALEXANDRA/IMpassion030** phase 3 trial. Michail Ignatiadis, et al
- LBO1-01 Neoadjuvant pembrolizumab or placebo plus chemotherapy followed by adjuvant pembr nab or placebo for early-stage triple- TE-522** study. Peter Schmid, e
- PS14-05 Safety plus chemotherapy f east cancer (TNBC). Javier
- LBO1-03 Rando eks of concurrent N+carboplatin p CT1902/IBCSG **61-20 Neo-N**). S
- GS01-05 Pembr zumab + Chemotherapy f **KEYLYNK-009** Study. Hope Ru
- PS16-02 Efficac safety of first-line atezolizumab + bevacizumab + paclitaxel in patients with advanced triple-negative breast cancer: the **ATRACTIB** phase 2 trial. Maria Gión, et al

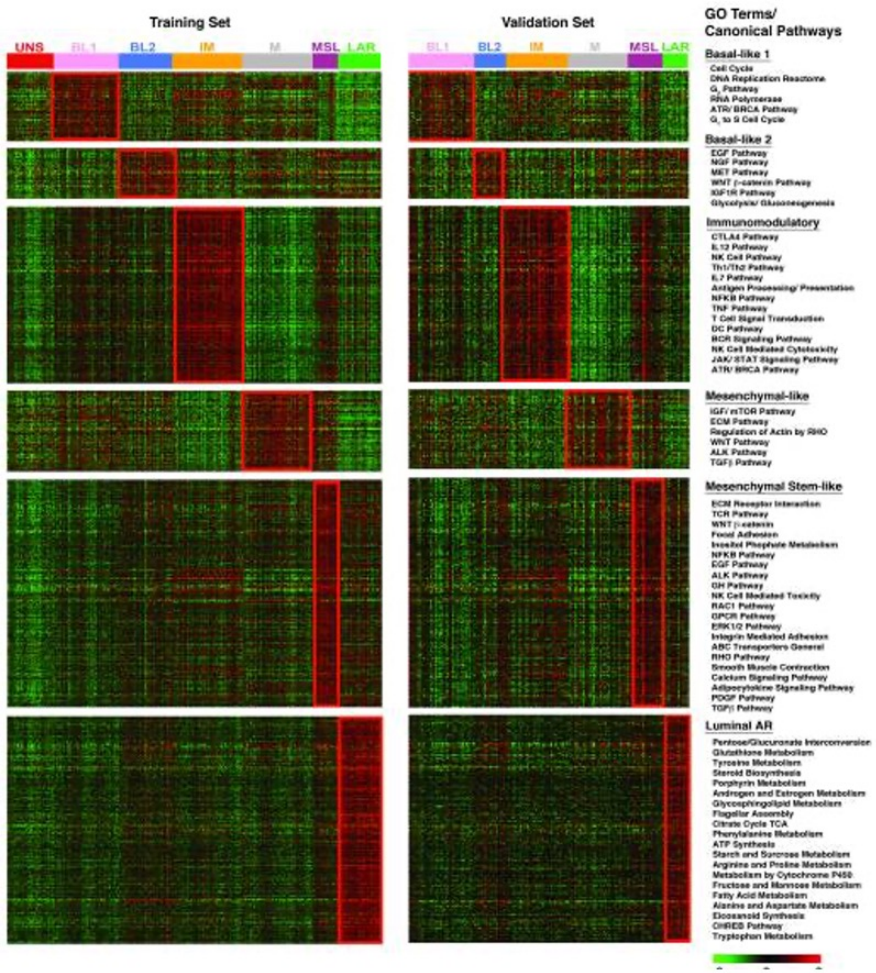
No practice changing data from SABCS 2023 in TNBC

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



- 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.

Questions/Comments/Debate/Discussion/Criticism

THANK YOU!