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Triple Negative Breast Cancer: Optimal Strategies

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

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

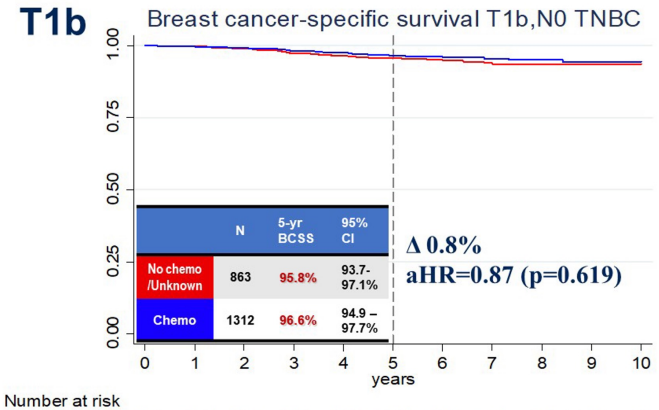
Variables **significantly associated** (all p<0.02) with the use of chemotherapy at multivariate logistic regression were:

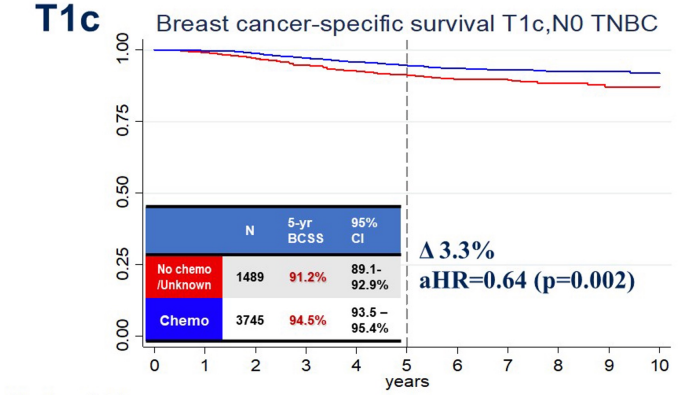
- **Younger age** (<50 vs. >64, **OR=5.19**)
- **Married status** (vs. Single, **OR=1.28**)
- **Ductal histology** (vs. Other, **OR=2.05**)
- **High tumor grade** (vs. low grade, **OR=4.89**)
- **Larger tumors** (Reference T1mic, T1a **OR=2.91**, T1b **OR=19.16**, T1c **OR=31.49**)

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**)

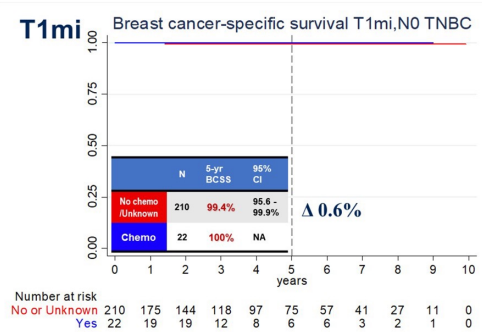


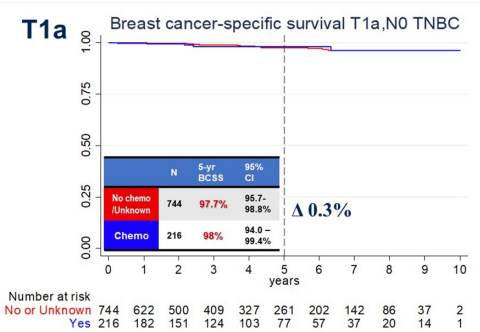


Multivariable cox models adjusted for: age at diagnosis, race, tumor grade, histology, radiation, marital status, income, and rurality.

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.

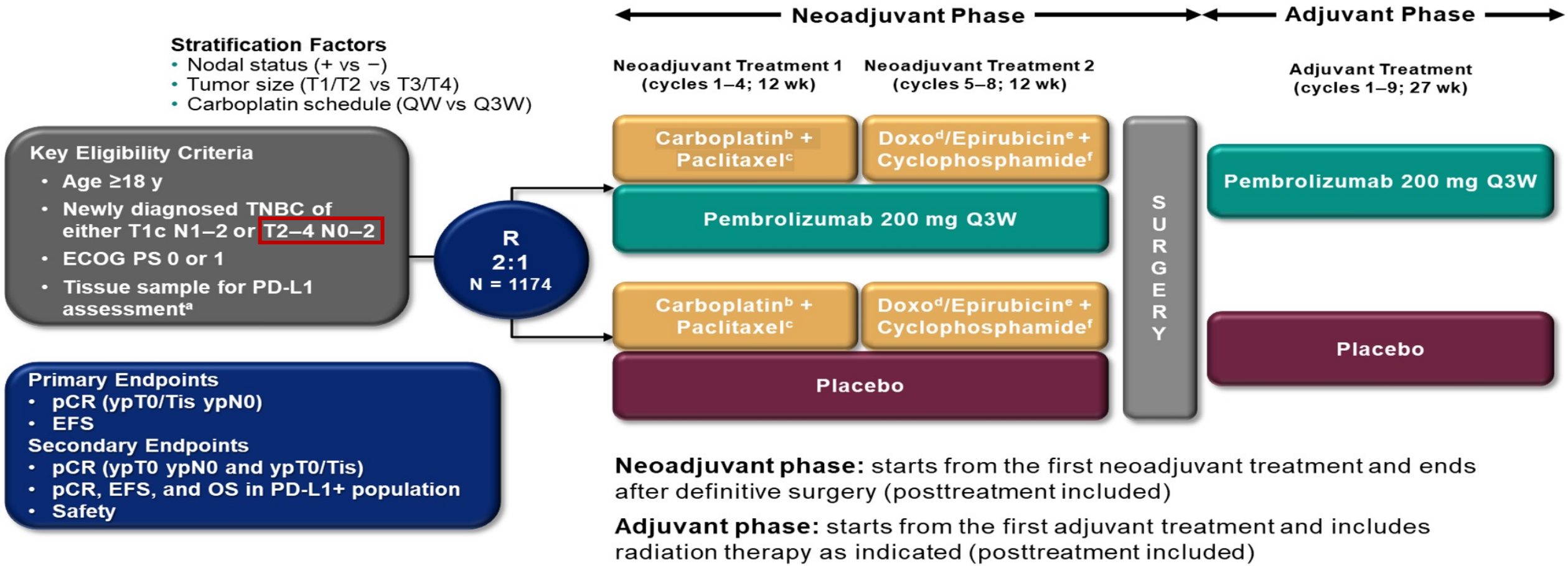
Conclusions/Key Take-Away:

- **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

KN-522 study:

EFS results after a median follow-up of 63.1 months, including results in key subgroups and EFS event types

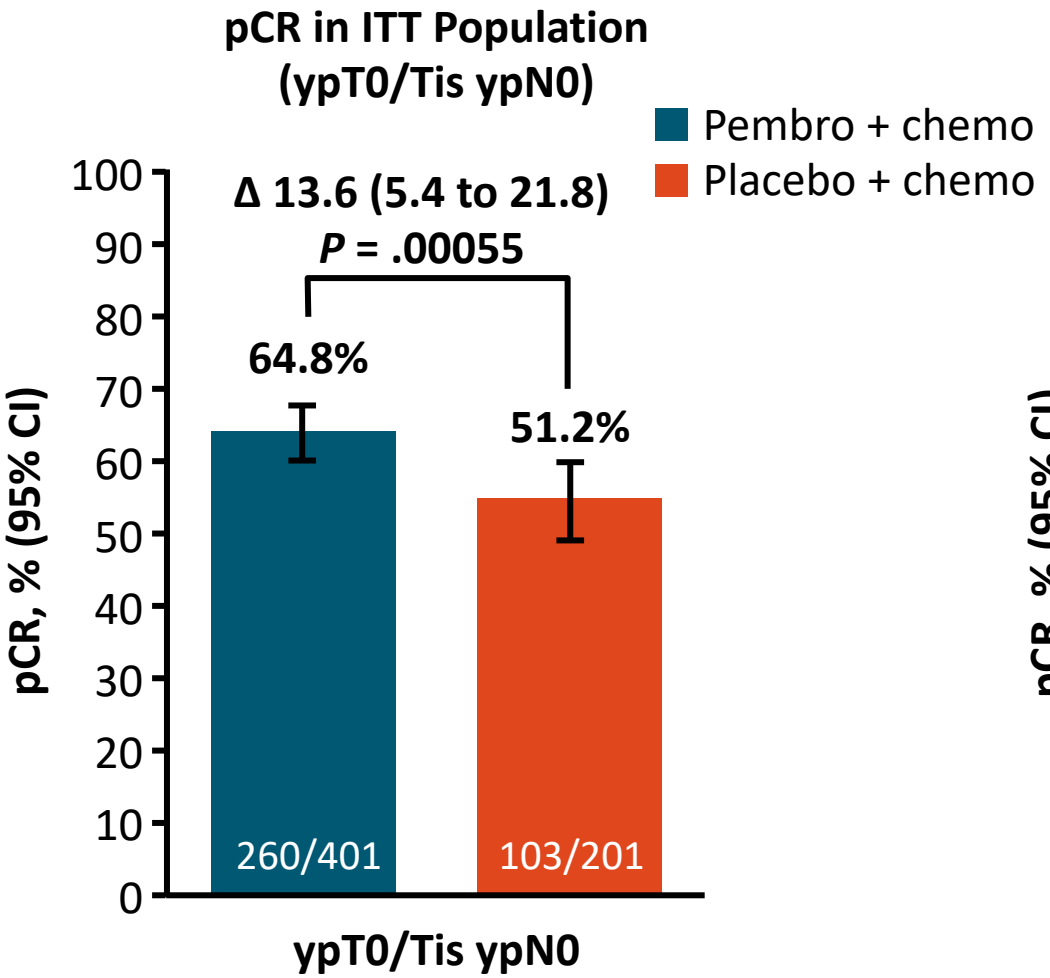


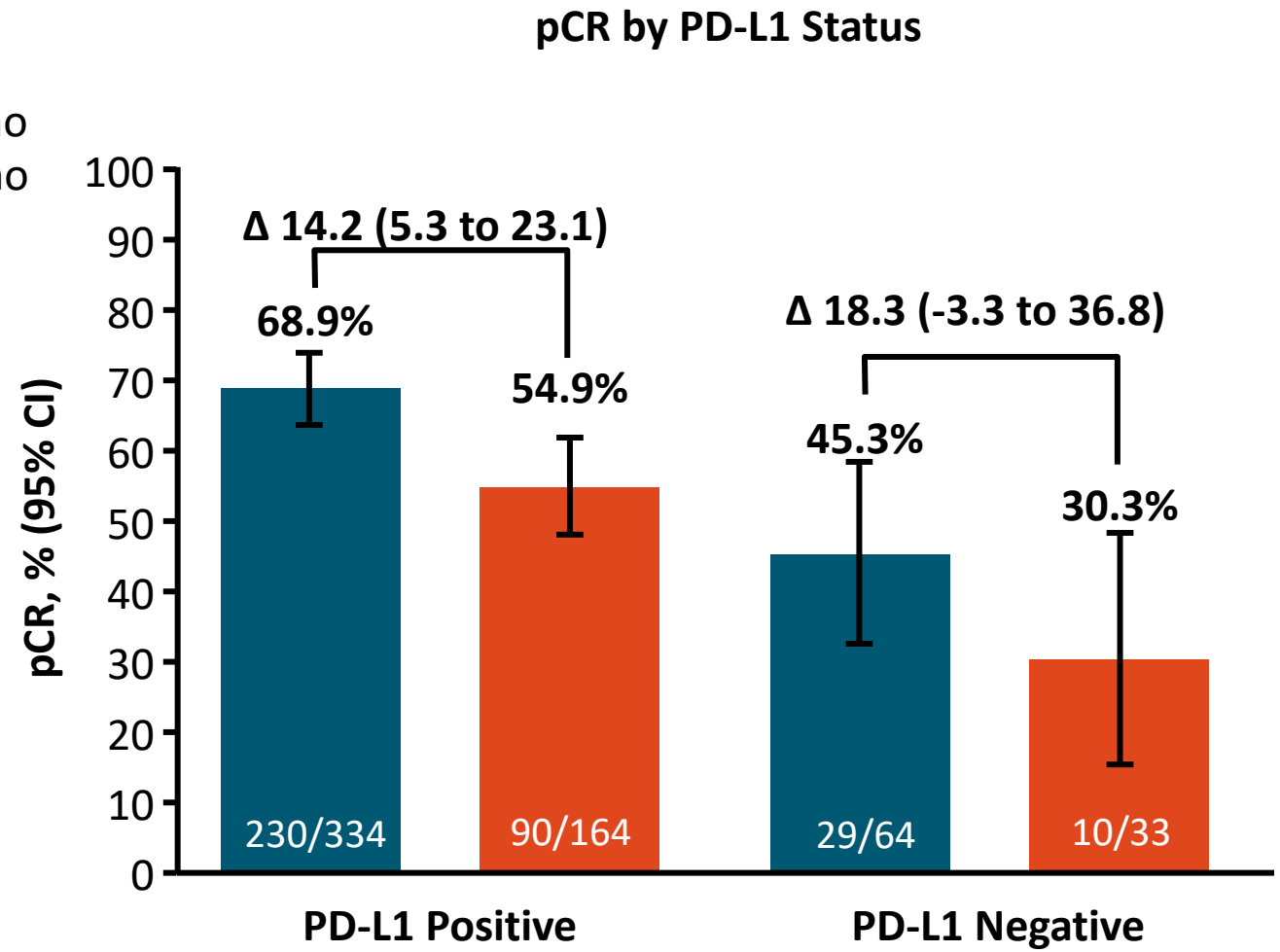
Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (posttreatment included)

Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (posttreatment included)

Schmid P, et al. SABCS 2023

KEYNOTE-522: PD-L1 IHC Did Not Predict Benefit (pCR) From Neoadjuvant Pembrolizumab

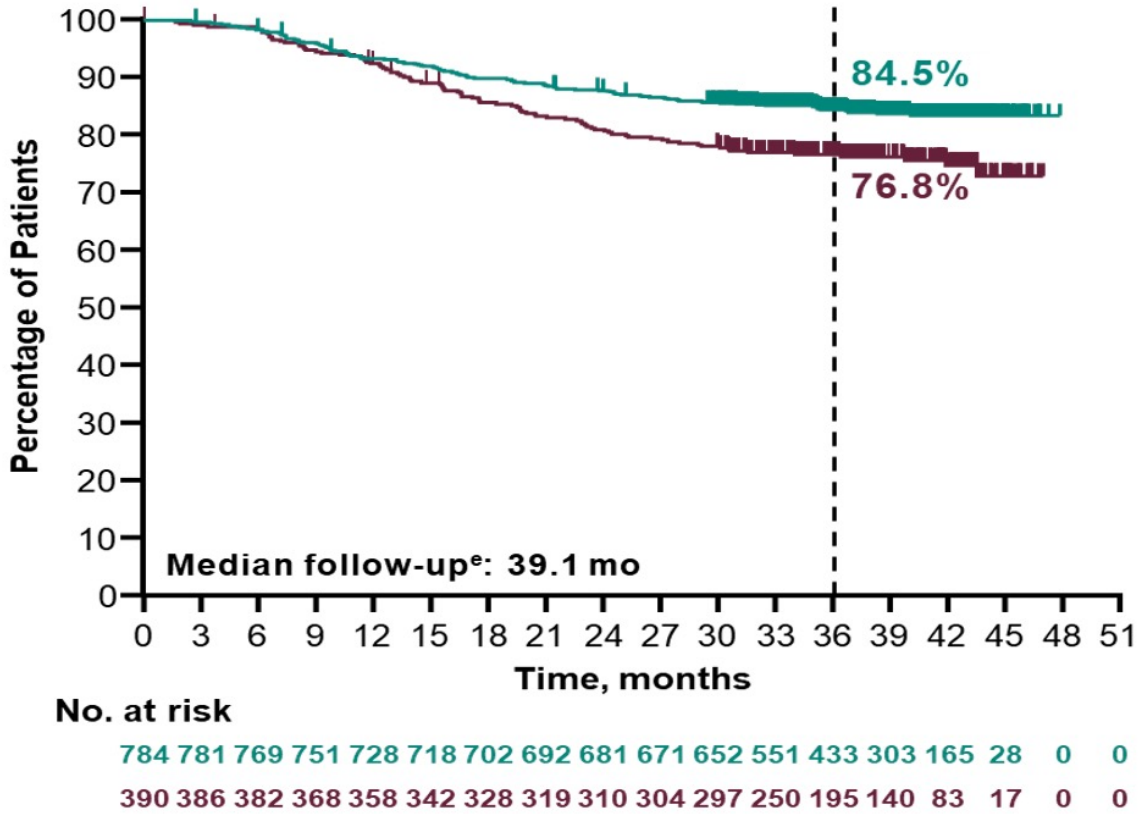




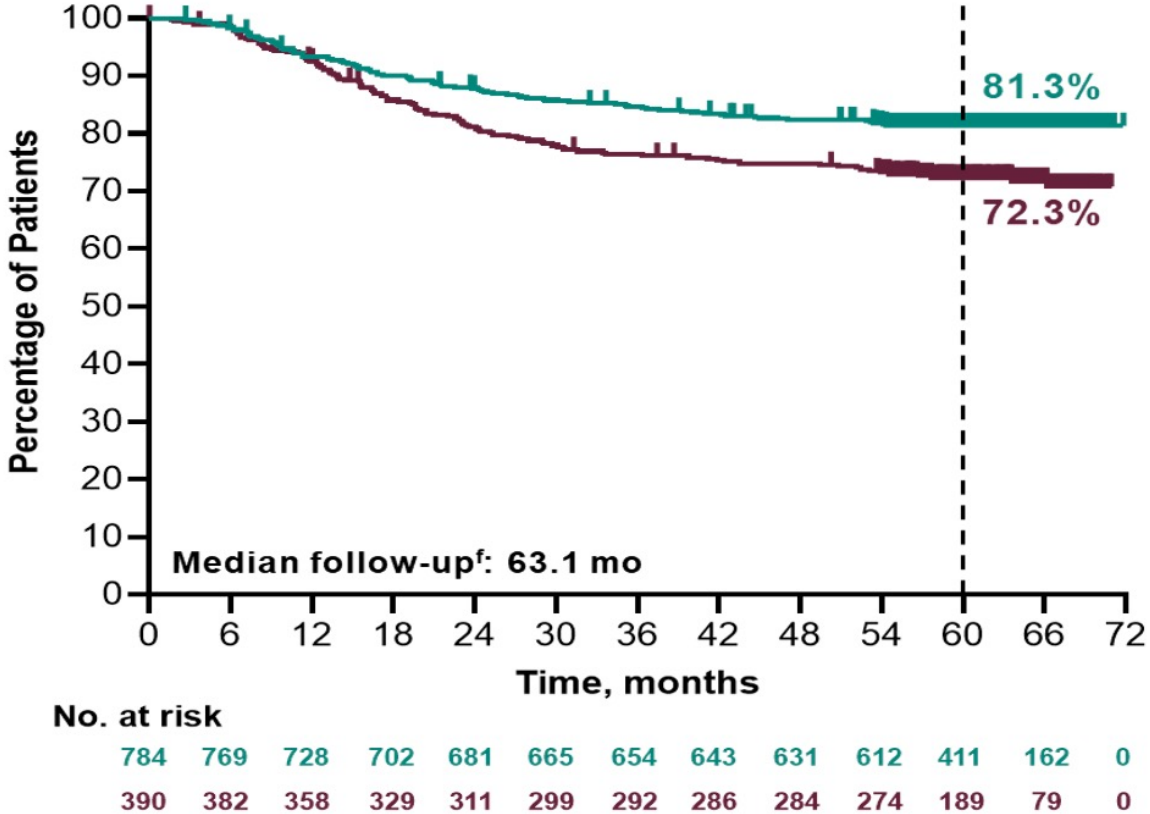
Dent. ESMO Asia 2020. Abstr 10. Schmid. NEJM. 2020;382:810.

KN-522 study EFS Endpoint

IA4[a]	Events	HR (95% CI)	*P* value
Pembro + Chemo/Pembro	15.7%	0.63[c] (0.48–0.82)	0.00031[d]
Placebo + Chemo/Placebo	23.8%		



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

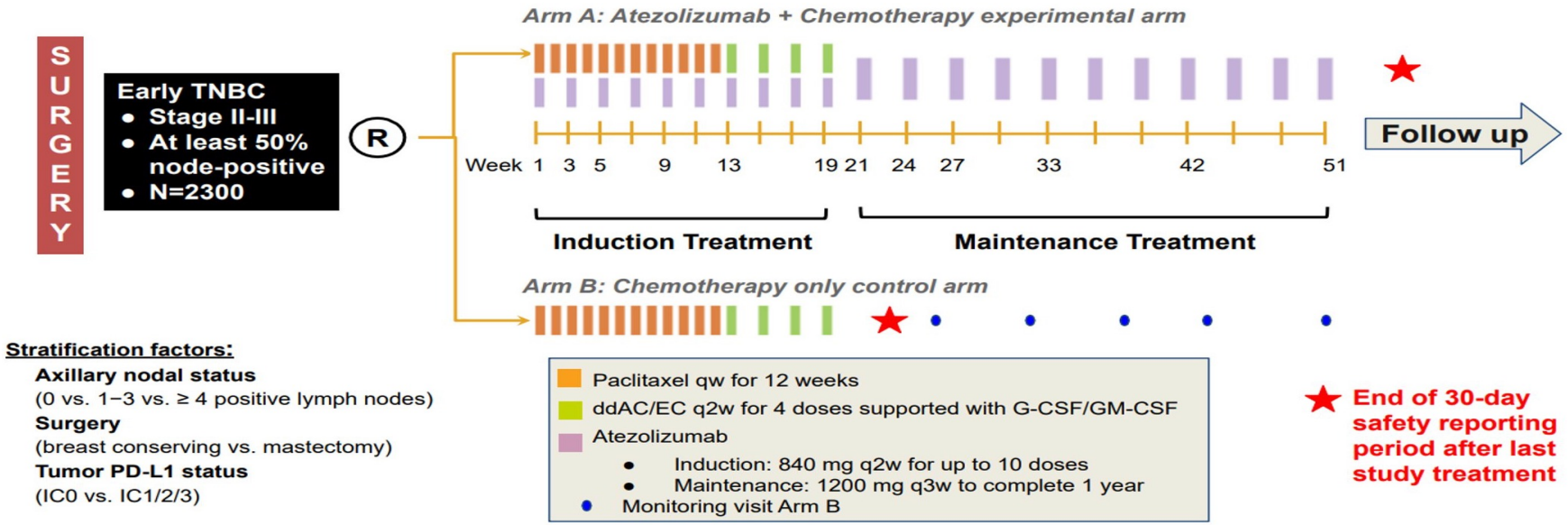


Most common immune-mediated AEs: IRR 18.0 vs 11.6%; hypothyroidism 15.2 vs 5.7%; hyperthyroidism 52. vs 1.8%; severe skin rxn 5.7 vs 1.0%; adrenal insufficiency 2.6 vs 0%, chemo + pembro vs chemo + placebo, respectively.

Schmid P, et al. SABCS 2023

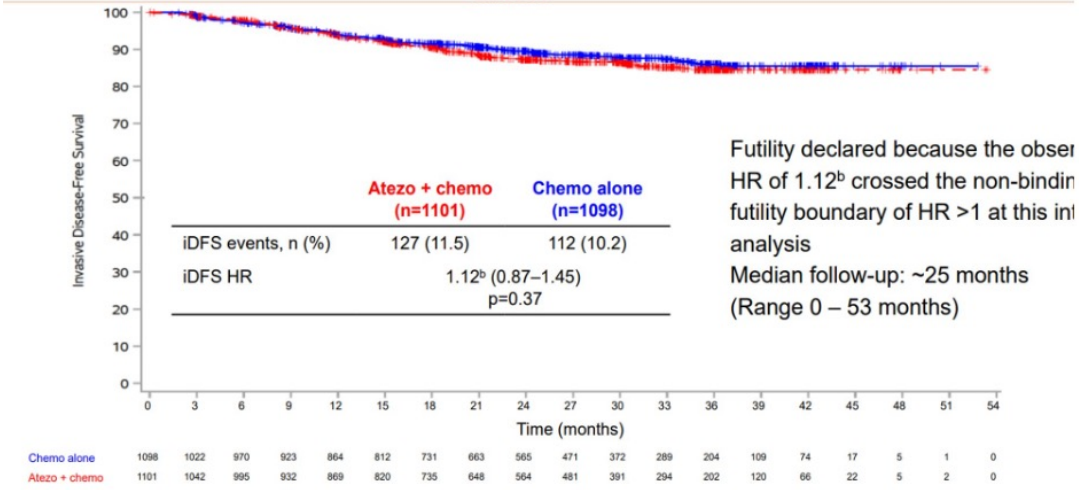
Adjuvant Atezolizumab:

Alexandra/IMpassion030 3 open-label study



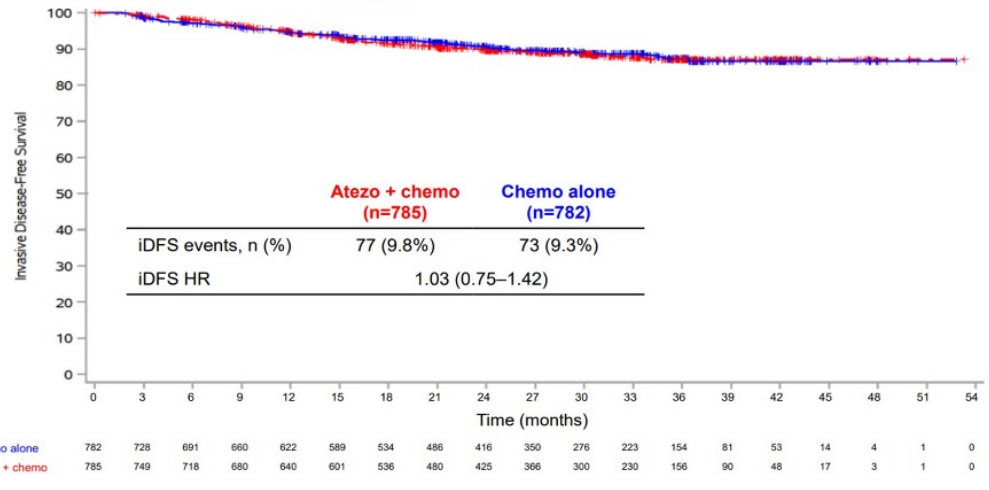
Ignatiadis M, et al. SABCS 2023

Alexandra/IMpassion030 3 open-label study
iDFS in ITT



Ignatiadis M, et al. SABCS

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



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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*

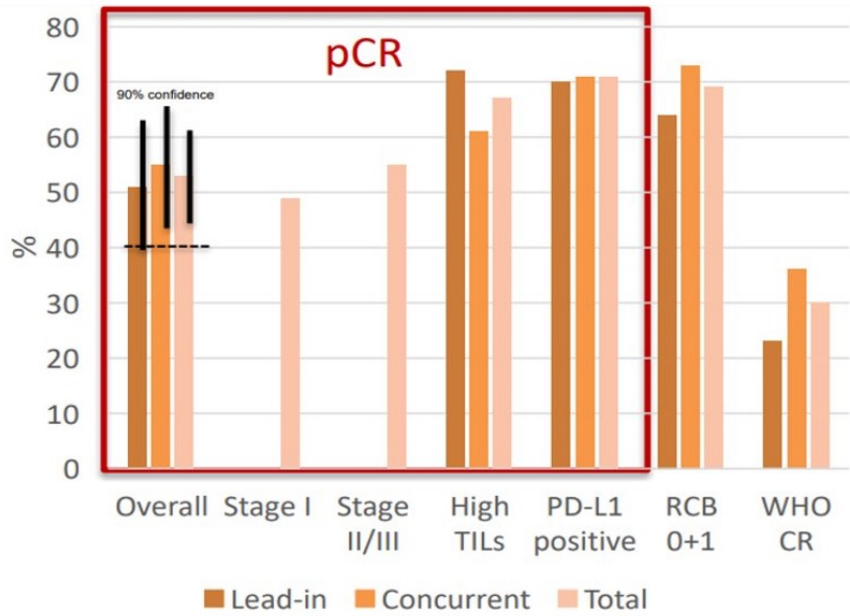
SURGERY*

** 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;

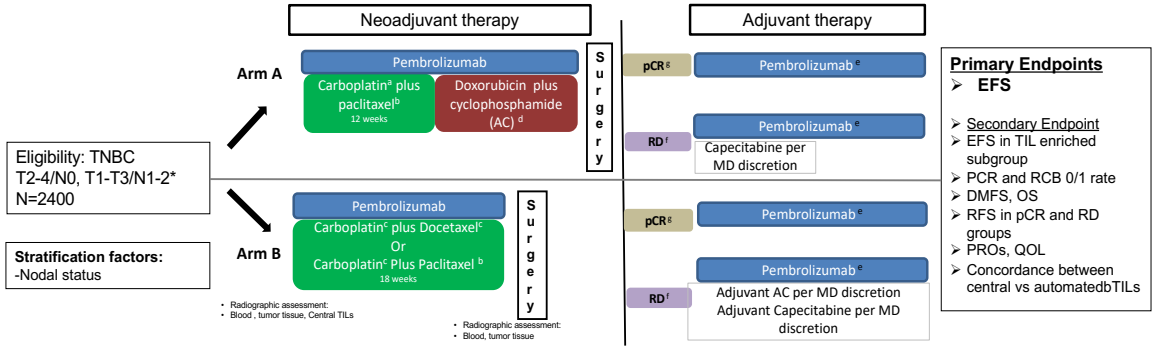
Loi S, et al. SABCS 2023

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

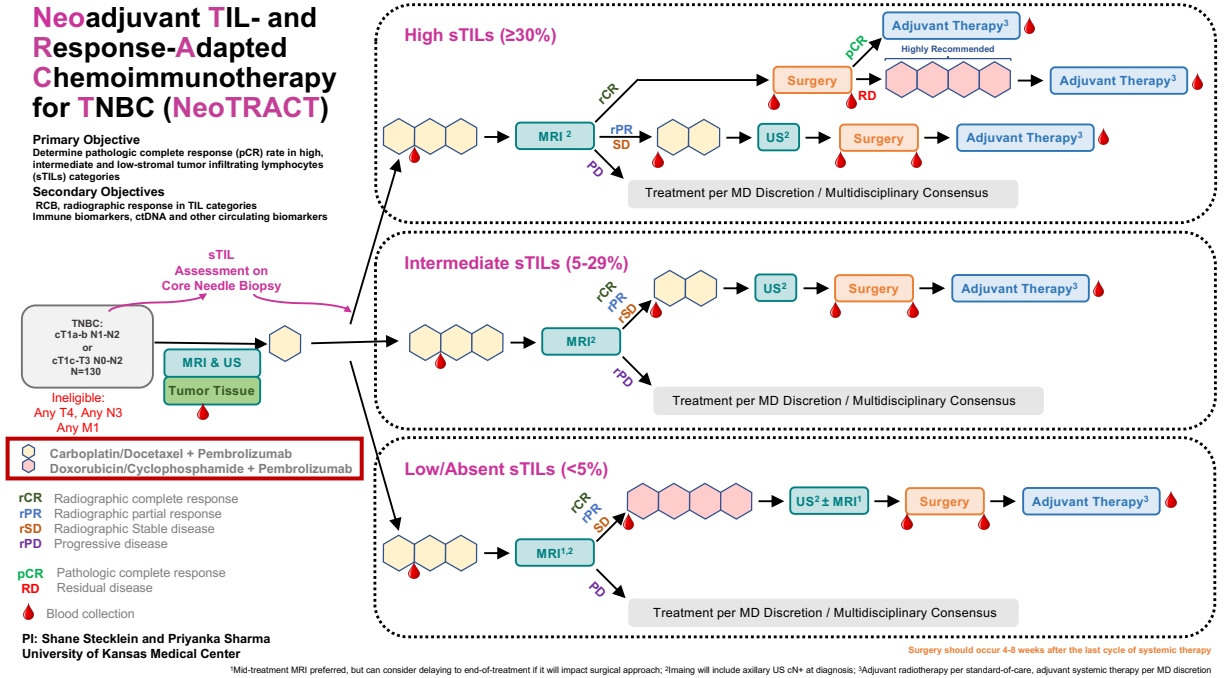
PI: Priyanka Sharma, Zahi Mitri

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

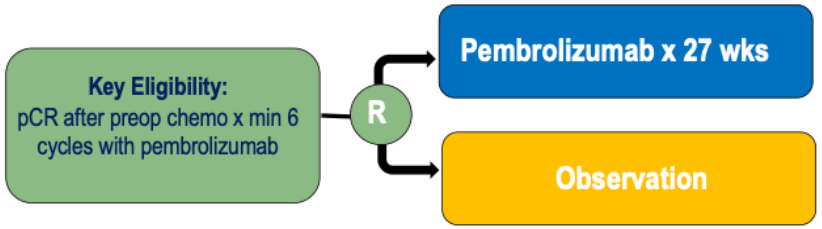
Secondary Objectives
RCB, radiographic response in TIL categories
Immune biomarkers, ctDNA and other circulating biomarkers



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

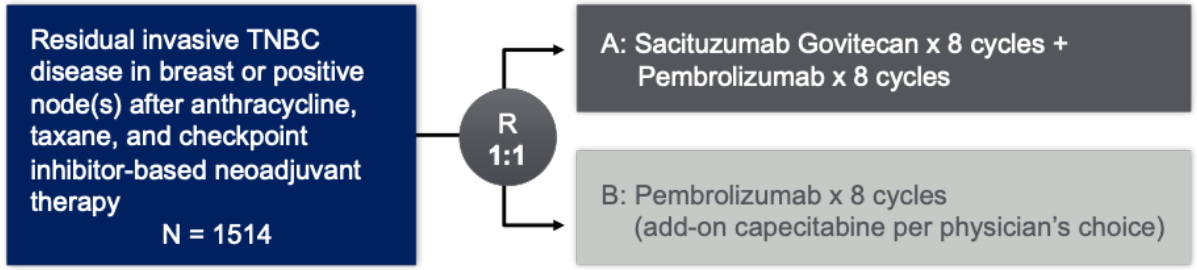


Stratification Factors:
- Baseline nodal status
- Receipt of anthracycline chemotherapy: yes vs. no

PI: Tolaney
Alliance Trial

Phase III Trial: Optimice-RD/ASCENT-05

Residual disease in TNBC



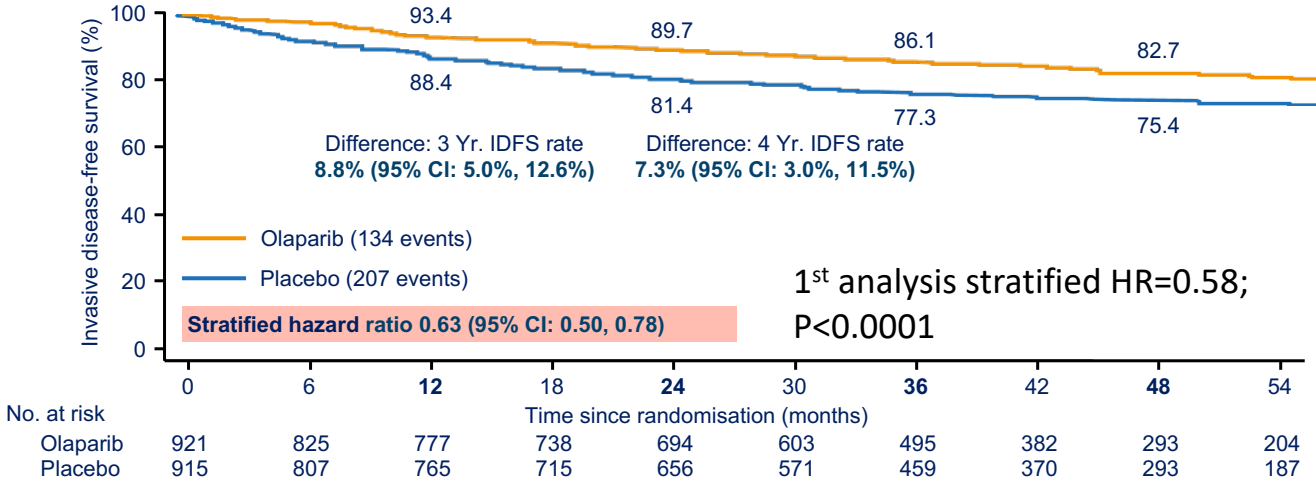
PI: Sara Tolaney
Alliance Foundation Trial

Olympia: Updated Endpoints

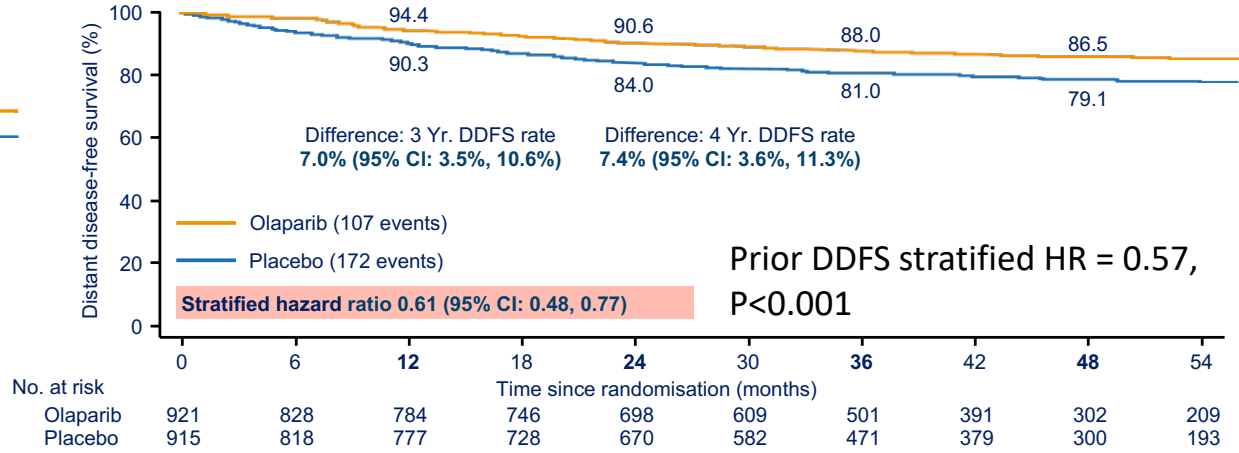
Median FU 3.5 years, 2nd IA

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



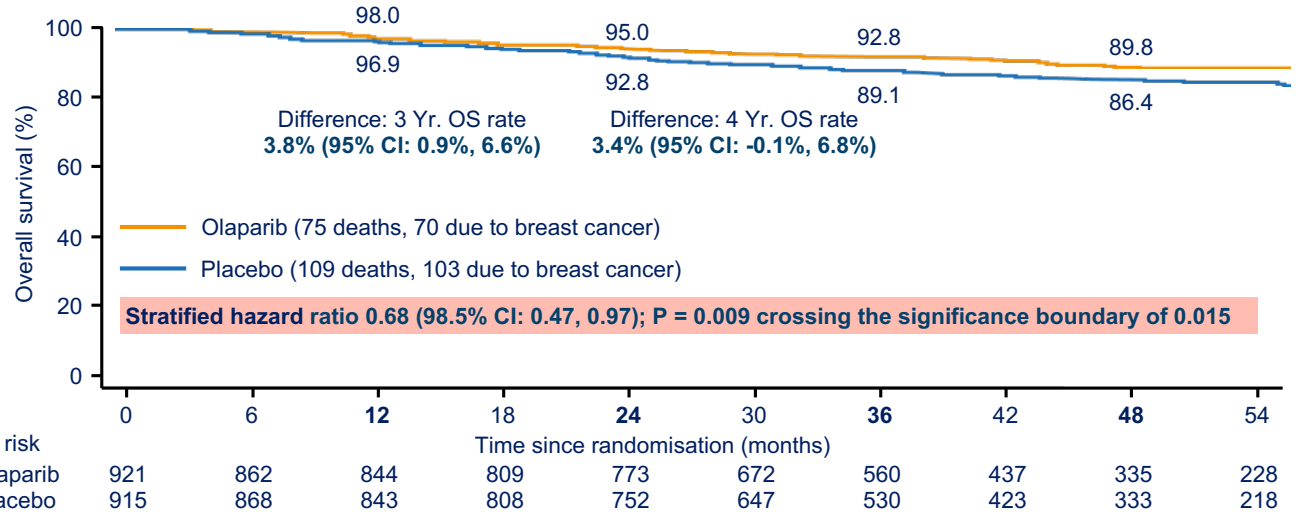
1st analysis stratified HR=0.58; P<0.0001



Prior DDFS stratified HR = 0.57, P<0.001

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

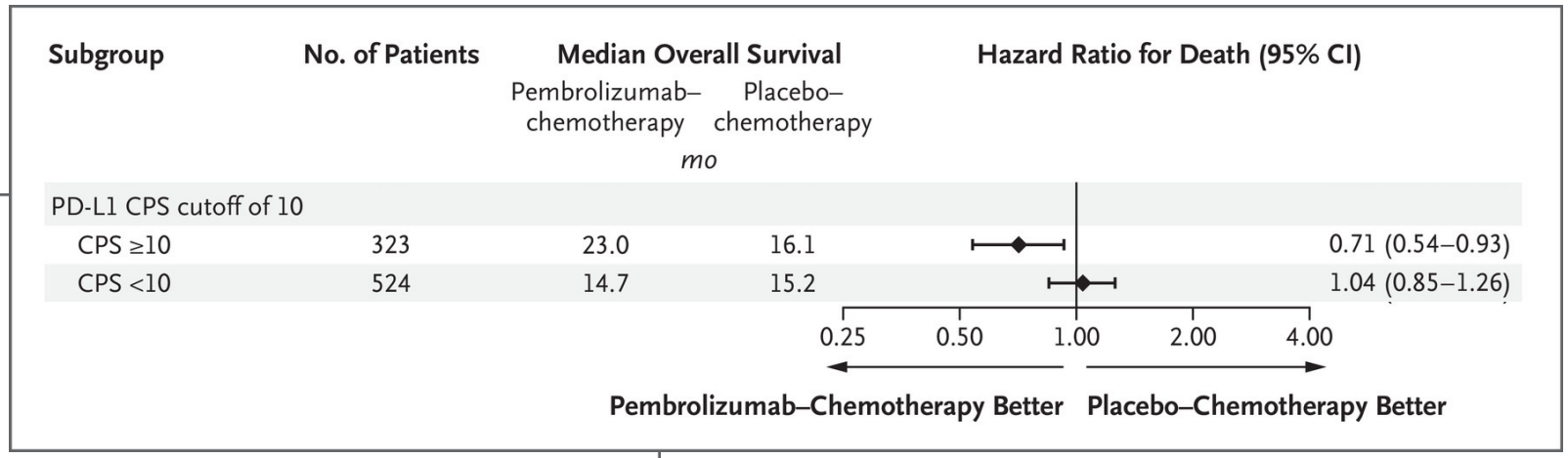
- No increase in MDS/AML compared to placebo
- Most toxicity grade 1/2; nausea most common
- Grade 3
  - Anemia 9%, fatigue 2%, neutropenia 5%



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

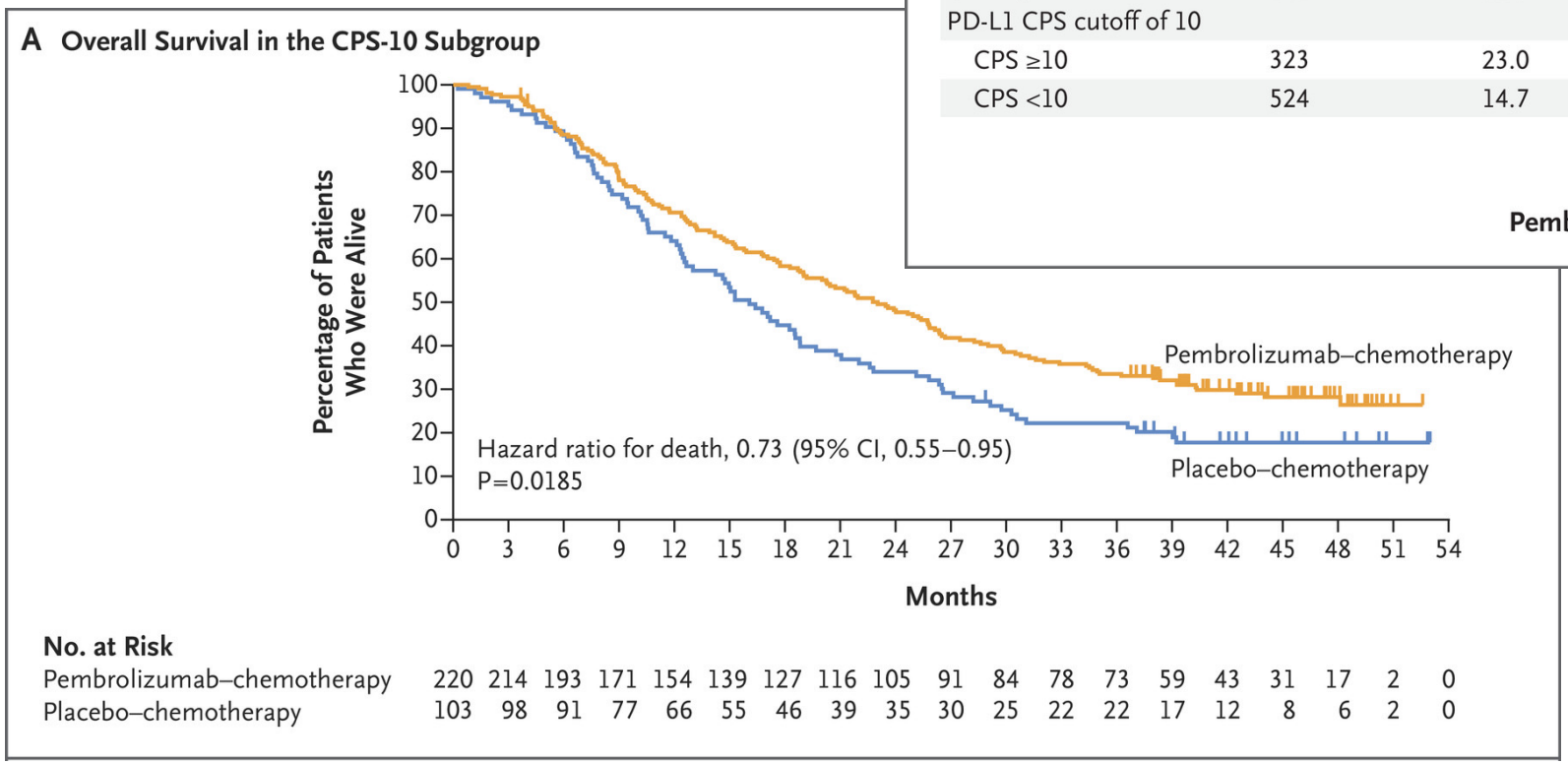
- For CPS ≥ 10%, mOS 23.0 months with chemo + pembro vs 16.1 months with chemo alone.



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.

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)

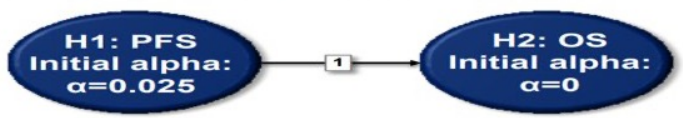
Post-induction

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



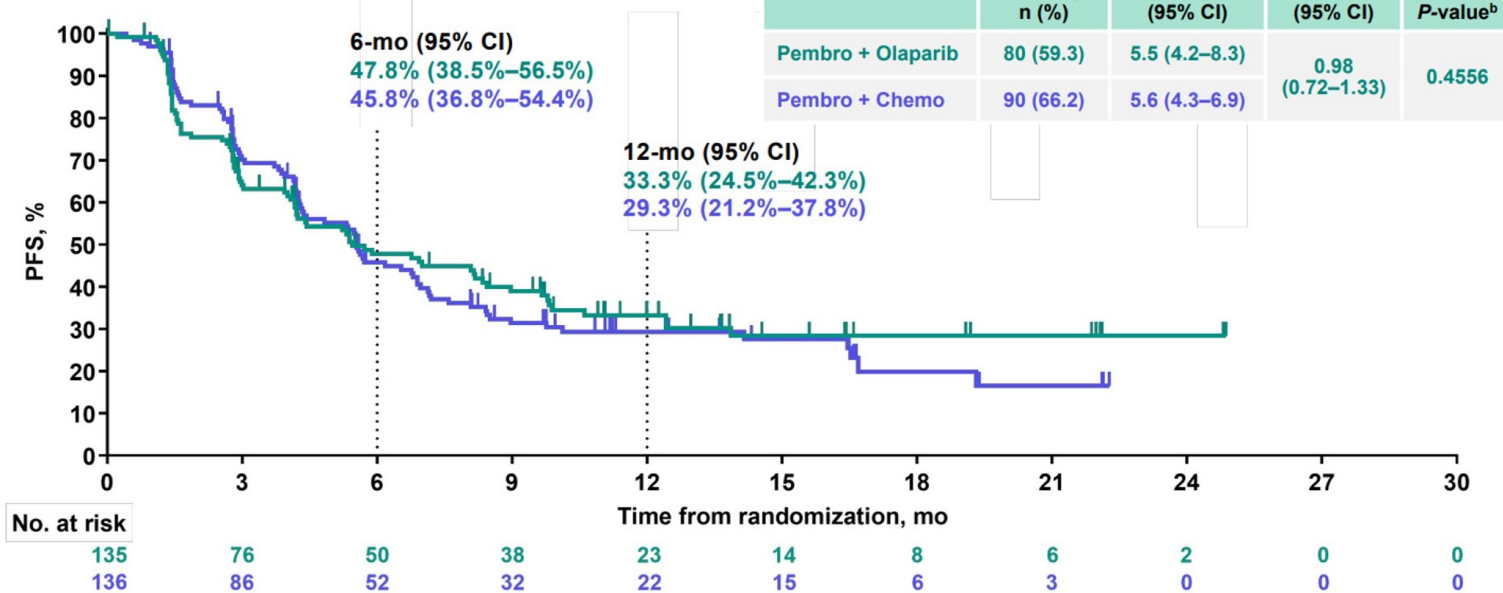
All α=2.5% will be allocated to PFS first, and if superiority is demonstrated, the full alpha 2.5% from the superiority test for PFS will be passed to the superiority test for OS

Rugo H, et al. SABCS 2023

KEYLYNK-009 study

KEYLYNK-009 study

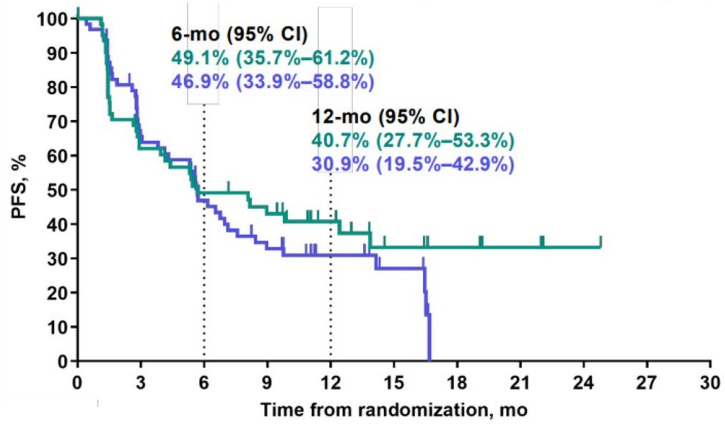
	Events, n (%)	Median, mo (95% CI)	HR[a] (95% CI)	*P*-value[b]
Pembro + Olaparib	80 (59.3)	5.5 (4.2–8.3)	0.98 (0.72–1.33)	0.4556
Pembro + Chemo	90 (66.2)	5.6 (4.3–6.9)		



Rugo H, et al. SABCS 2023

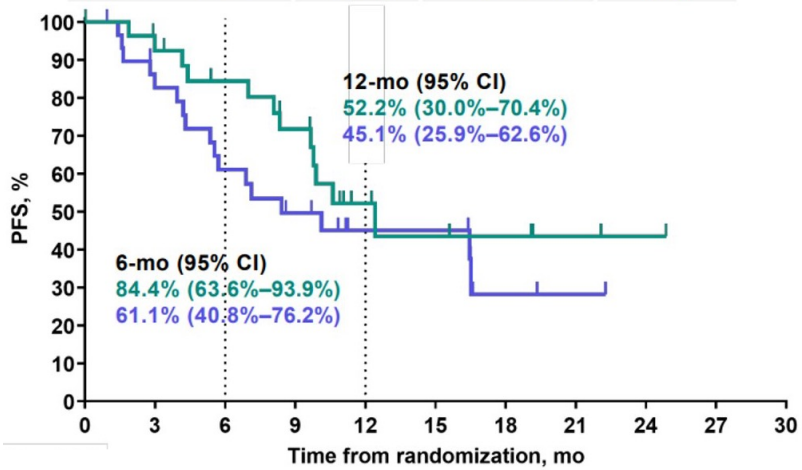
Tumor PD-L1 CPS ≥10 Population (~48%)

	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)	



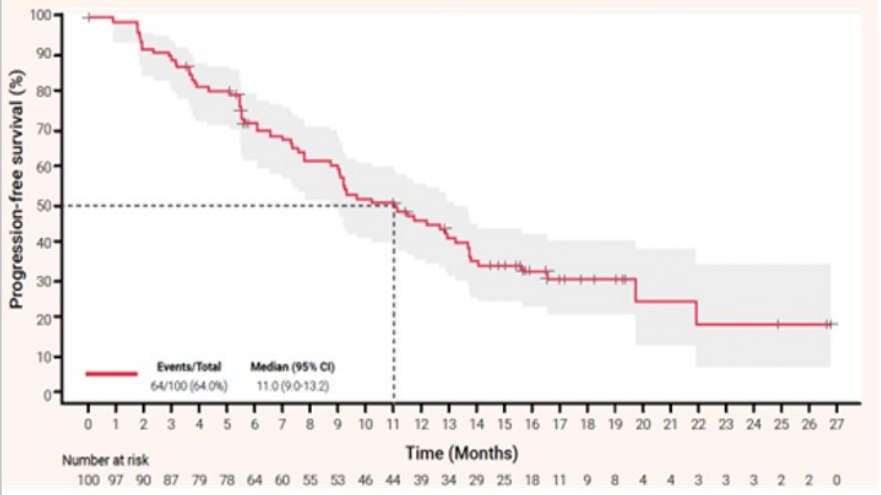
t*BRCA*m Population (~21%)

	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)	

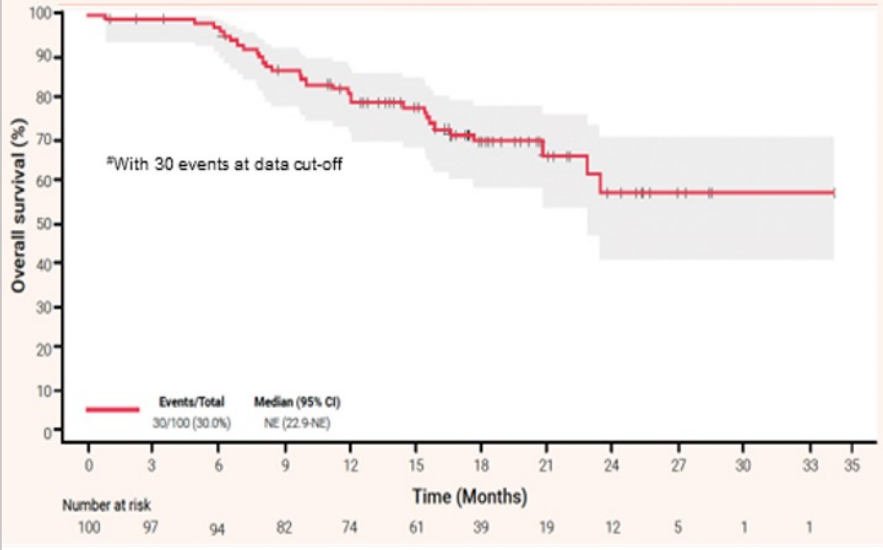


1st line TNBC: ATRACTIB study (Atezolizumab + Paclitaxel + Bevacizumab)

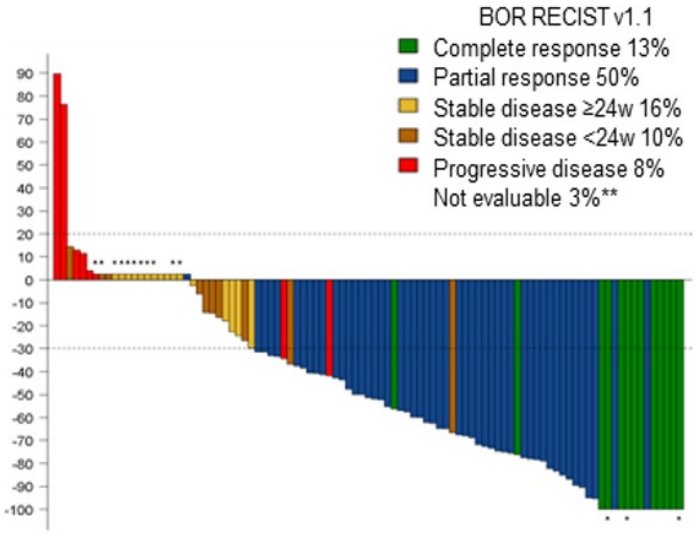
mPFS 11.0 months (95% CI, 9.0 – 13.2)



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(%)

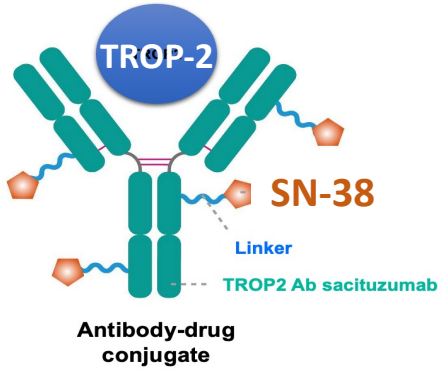
TEAEs, n (%)	Overall (N=100)	Treatment-related
Any TEAEs	100 (100.0%)	97 (97.0%)
Grade 3/4 TEAEs	61 (61.0%)	47 (47.0%)
Any serious TEAEs	34 (34.0%)	18 (18.0%)
ECIs	42 (42.0%)	42 (42.0%)
TEAEs leading to treatment discontinuation of:		
Atezolizumab	14 (14%)	-
Bevacizumab	15 (15%)	-
Paclitaxel	40 (40%)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

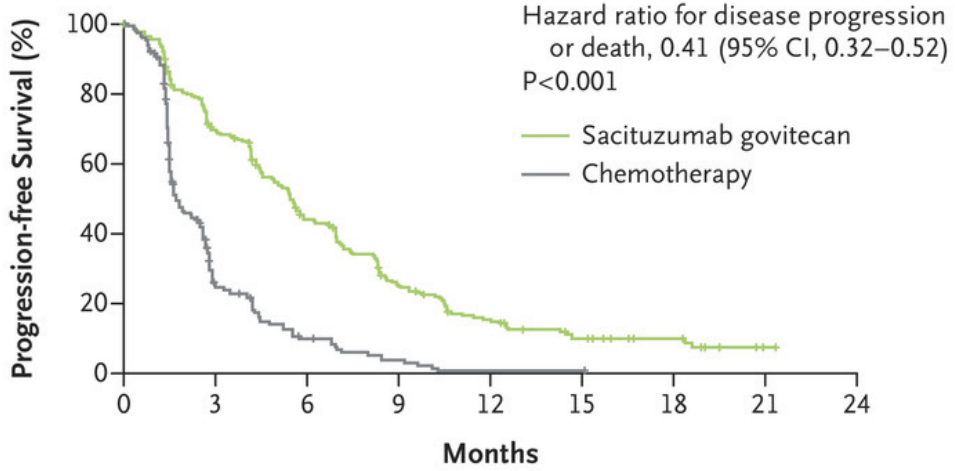


Antibody-drug conjugate

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)

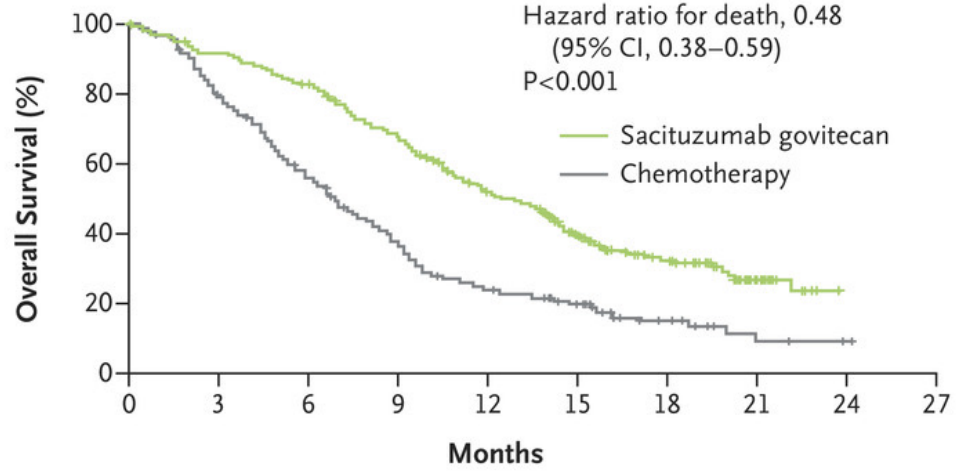


No. at Risk								
Sacituzumab govitecan	235	154	91	49	28	15	9	1
Chemotherapy	233	39	14	5	1	1	0	0

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

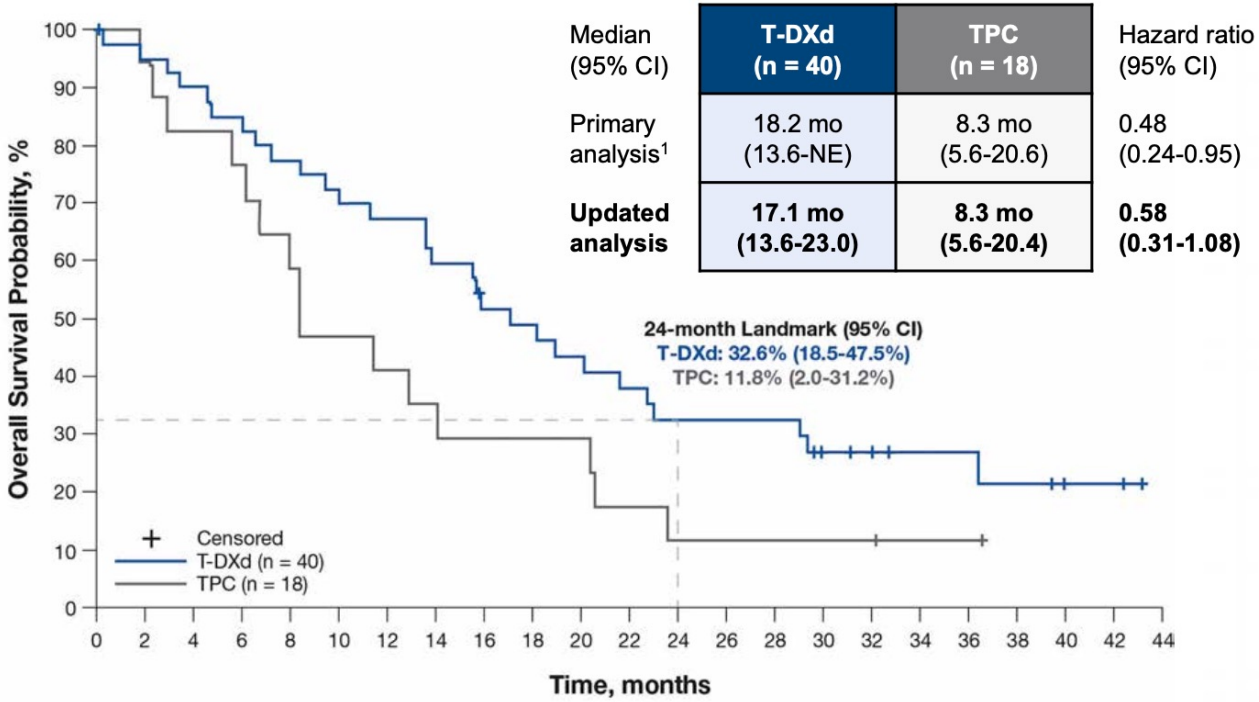
Ongoing Phase III Trials ASCENT 3 and 4 will test SG and SG ± pembro in 1L MBC.

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

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

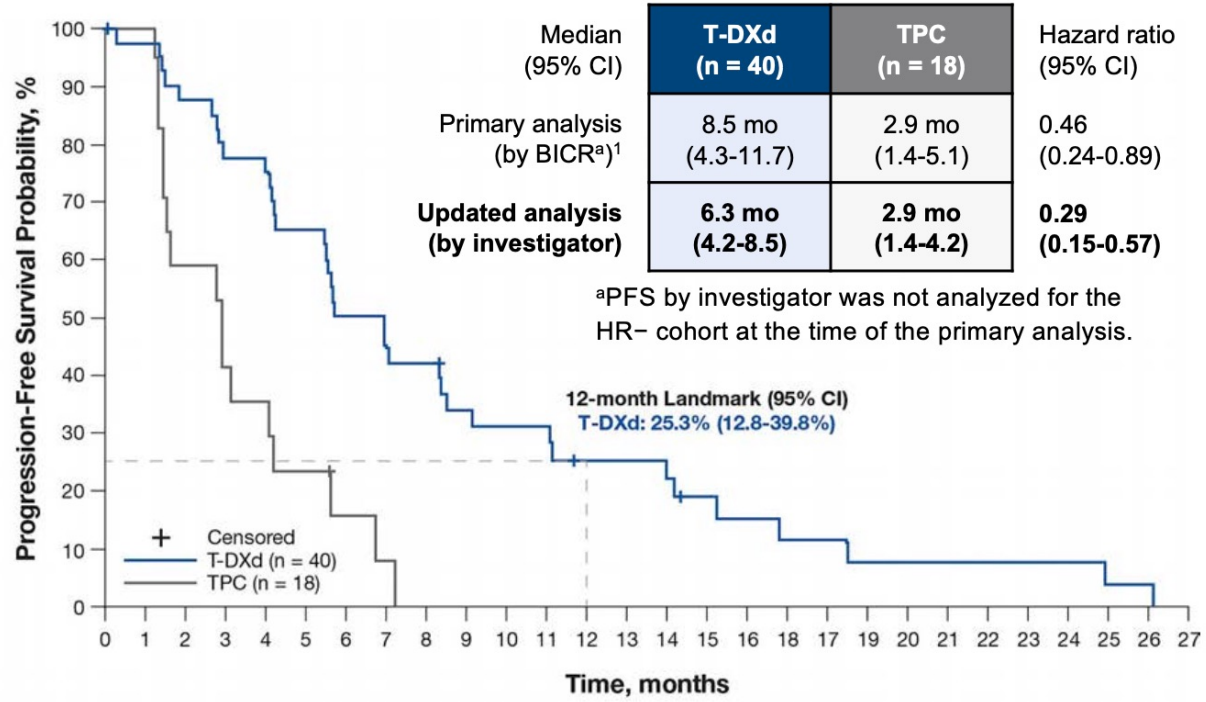
Med 32 mo followup

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)



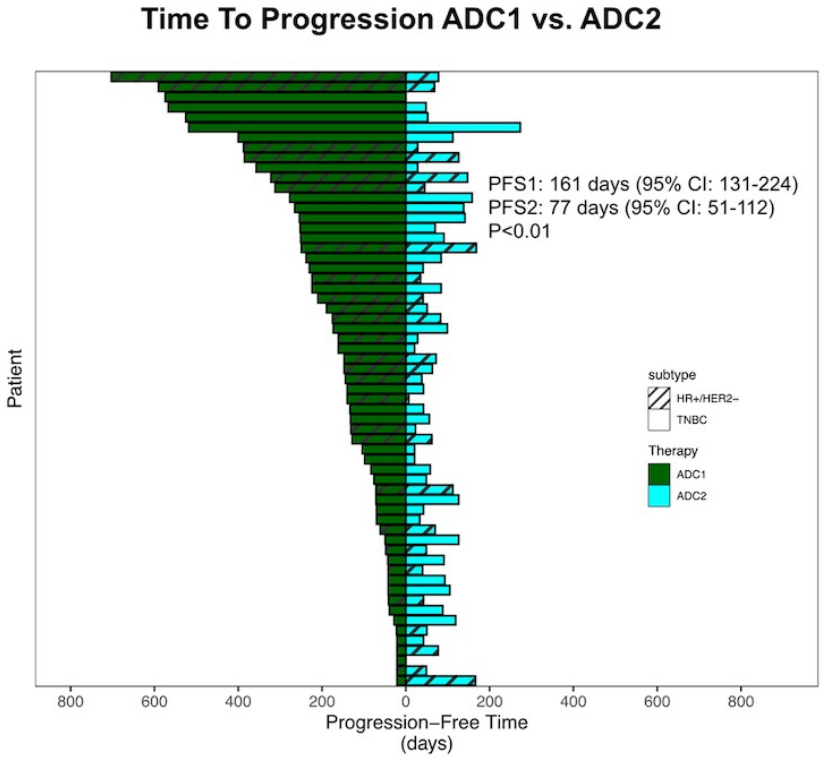
Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis (by BICR[a])[1]	8.5 mo (4.3-11.7)	2.9 mo (1.4-5.1)	0.46 (0.24-0.89)
Updated analysis (by investigator)	**6.3 mo (4.2-8.5)**	**2.9 mo (1.4-4.2)**	**0.29 (0.15-0.57)**

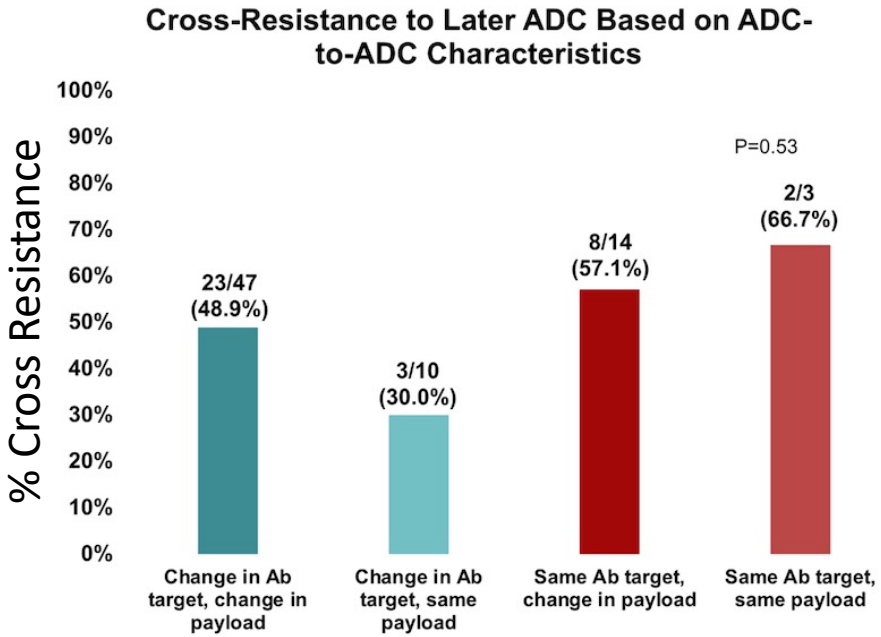
[a]PFS by investigator was not analyzed for the HR− cohort at the time of the primary analysis.

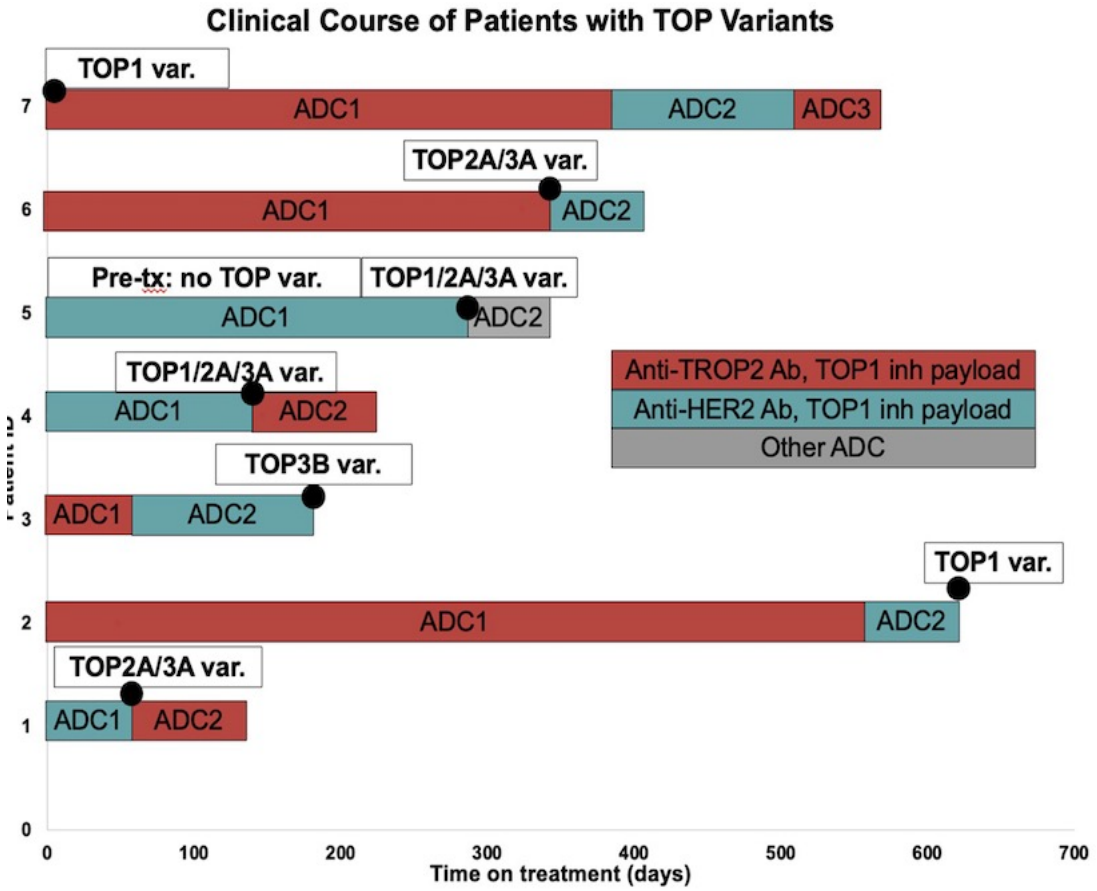
- There was a 42% reduction in risk of death and 71% reduction in risk of disease progression or death for HR− patients receiving T-DXd compared with TPC
- Most common AEs (≥20%): N/V/D, anorexia, cytopenias, inc LFTs, hypokalemia, MS pain and resp infection

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

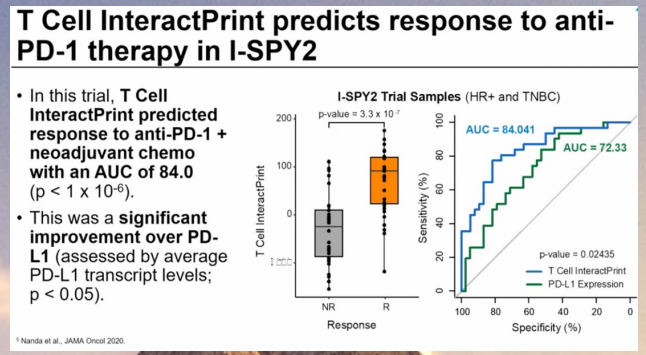
- GS01-03 Adding atezolizumab to adjuvant chemotherapy for stage II and III triple-negative breast cancer is unlikely to improve efficacy: interim analysis of the **ALEXANDRA/IMpassion030** phase 3 trial. Michail Ignatiadis, et al
- LBO1-01 Neoadjuvant pembrolizumab or placebo plus chemotherapy followed 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

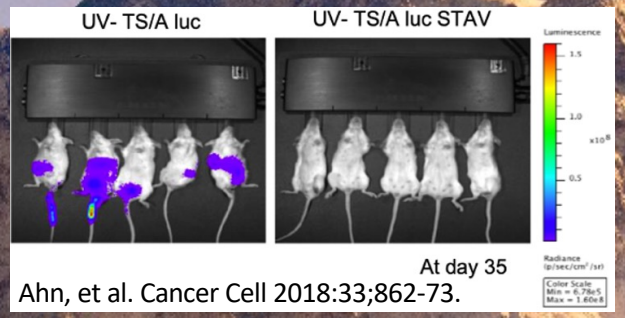
Questions/Comments/Debate/Discussion/Criticism

Future Directions:

1. Better diagnostics for ICI response

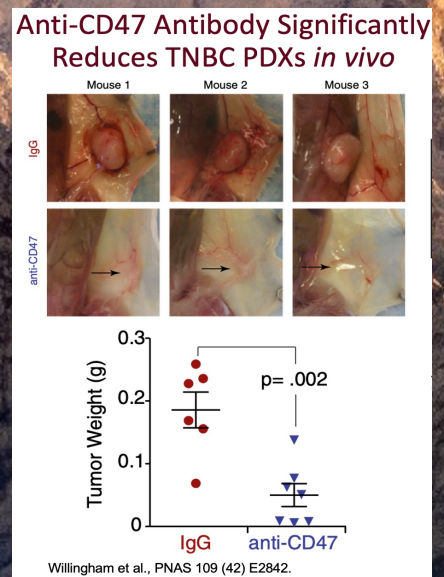


2. STING agonists



Ahn, et al. Cancer Cell 2018:33;862-73.

3. CD47/SIRPα MΦ checkpoint inhibition



Willingham et al., PNAS 109 (42) E2842.

THANK YOU!