Immunotherapy for Breast Cancer

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Hollywood, FL

Triple Negative Breast Cancer

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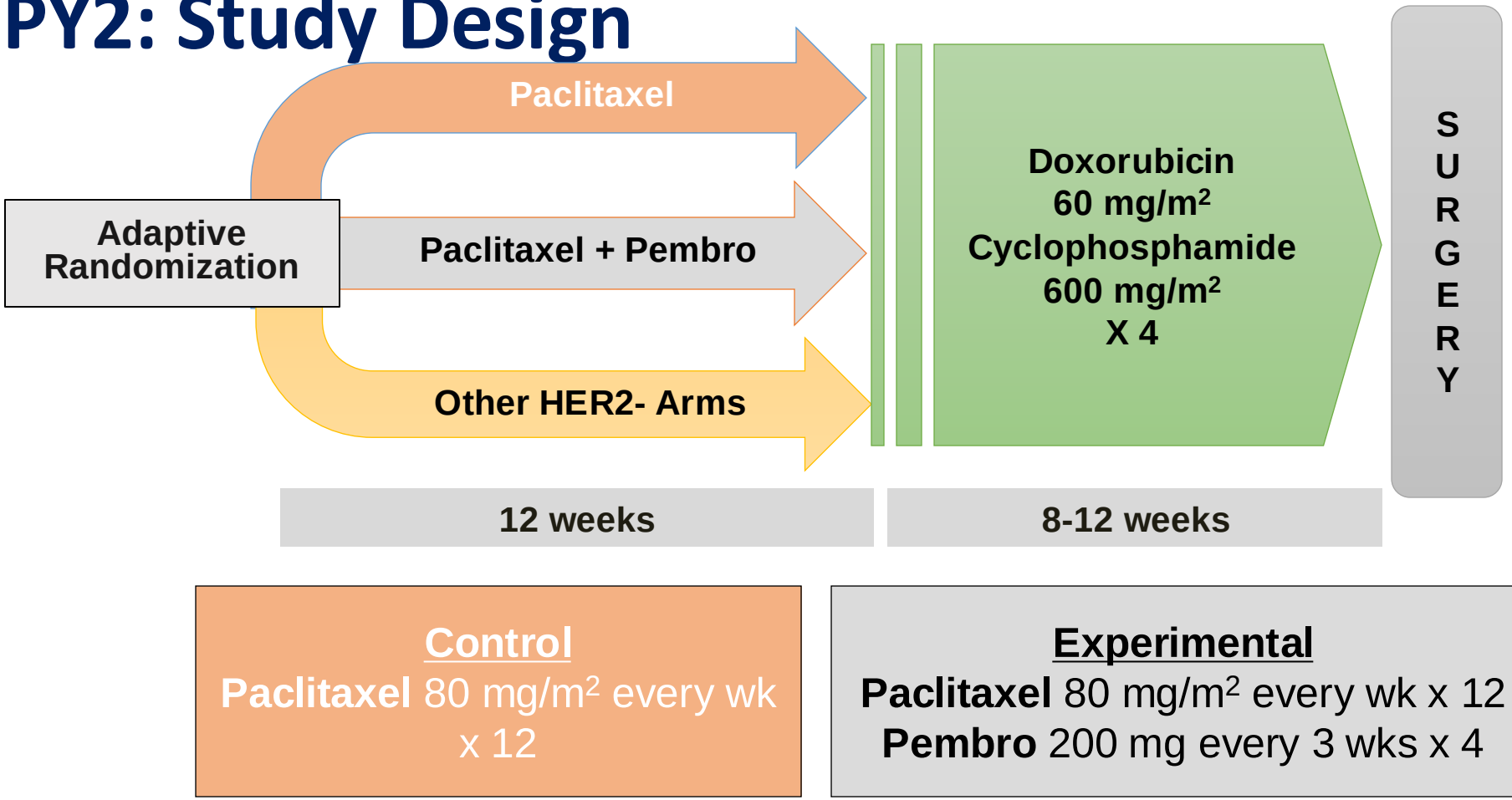
I-SPY2: Study Design



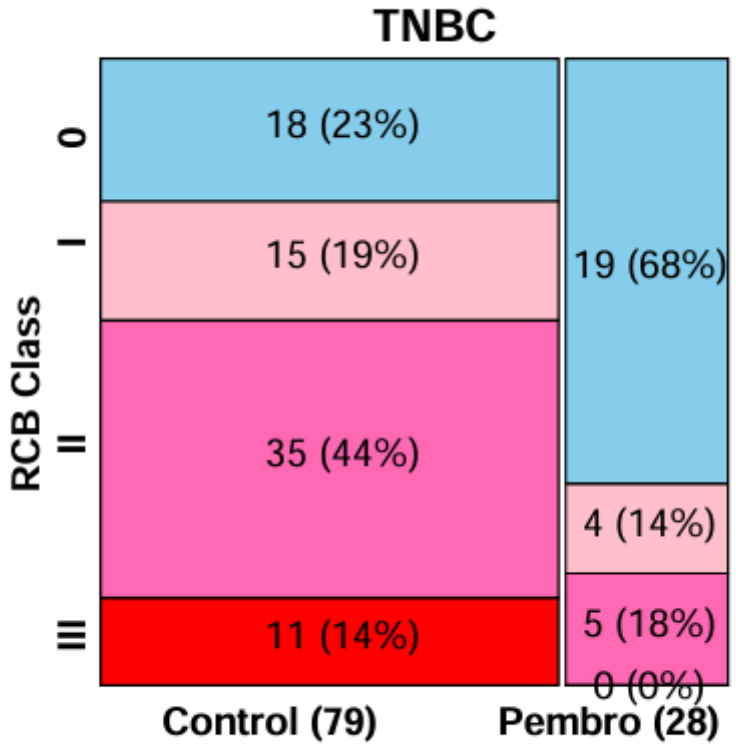
Control
Paclitaxel 80 mg/m² every wk x 12

Experimental
Paclitaxel 80 mg/m² every wk x 12
Pembro 200 mg every 3 wks x 4

Pembrolizumab administered only with paclitaxel

Nanda R et al. 2017 ASCO Annual Meeting. Abstract 506. Nanda R et al. *JAMA Oncol*. 2020;6(5):676-684.

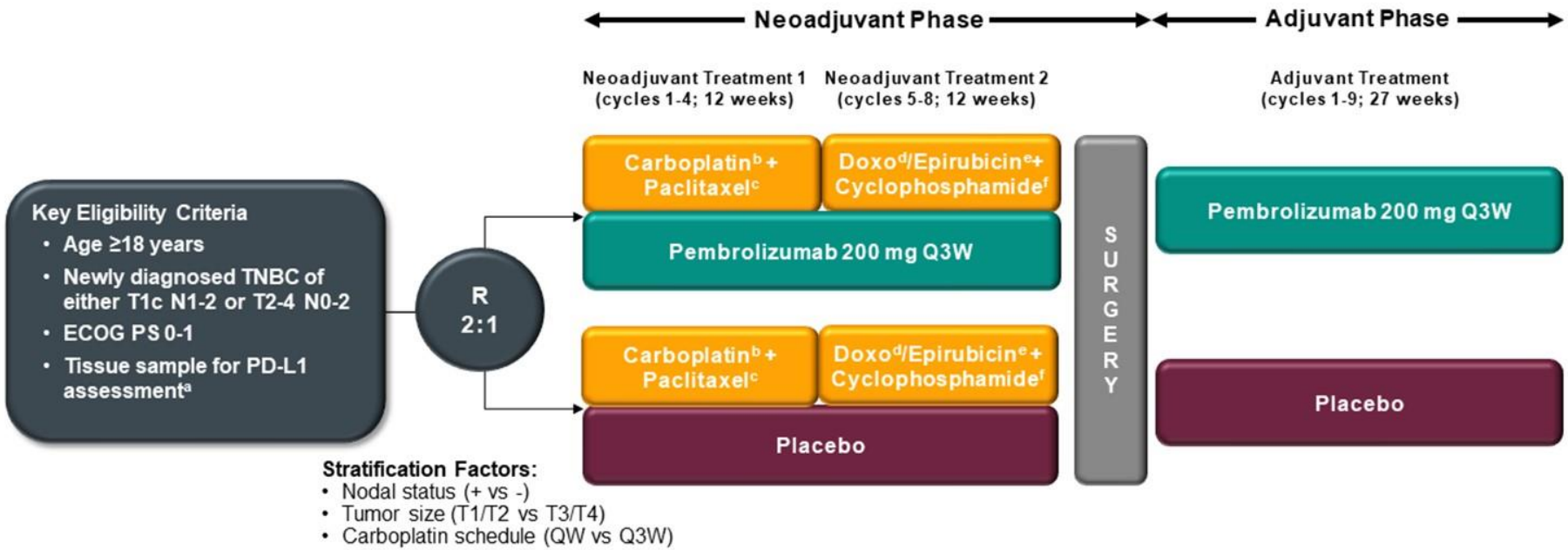
I-SPY 2 Neoadjuvant IO in TNBC



- Pembrolizumab more than doubled the estimated pCR rates
- Pembrolizumab shifted the RCB distribution to a lower disease burden

Nanda R et al. 2017 ASCO Annual Meeting. Abstract 506. Nanda R et al. *JAMA Oncol*. 2020;6(5):676-684.

KEYNOTE-522 Study Design (NCT03036488)

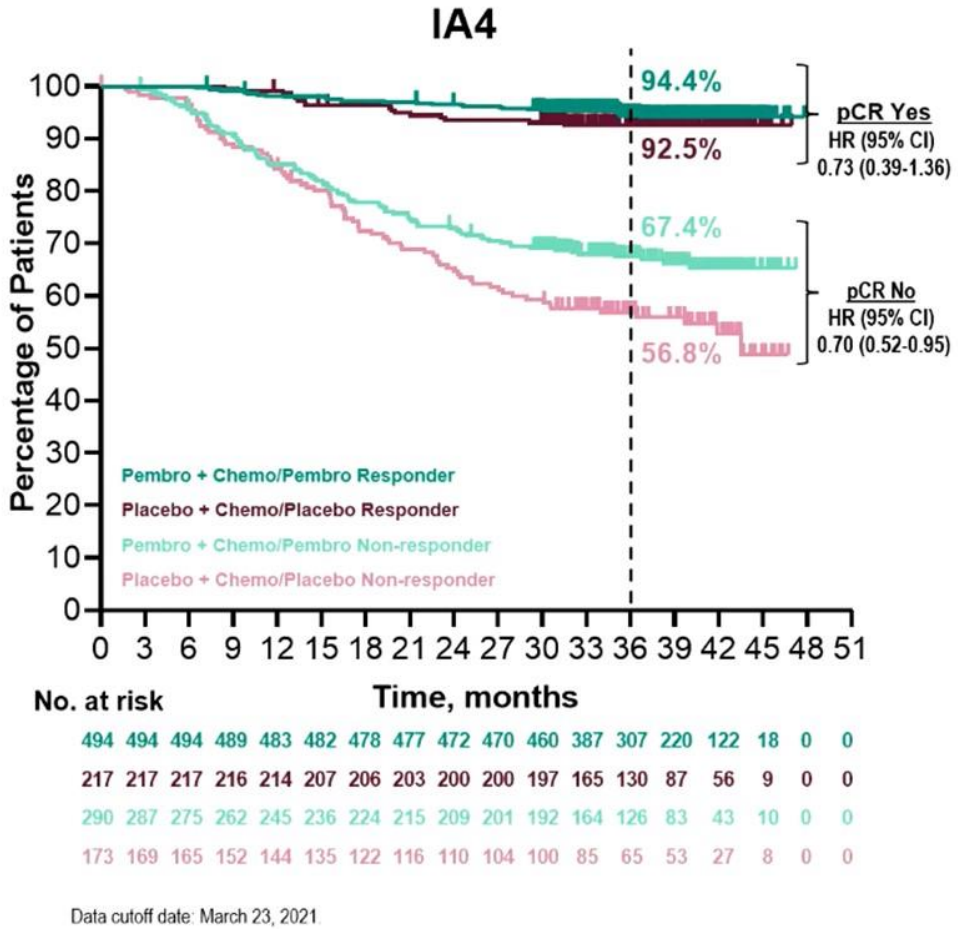


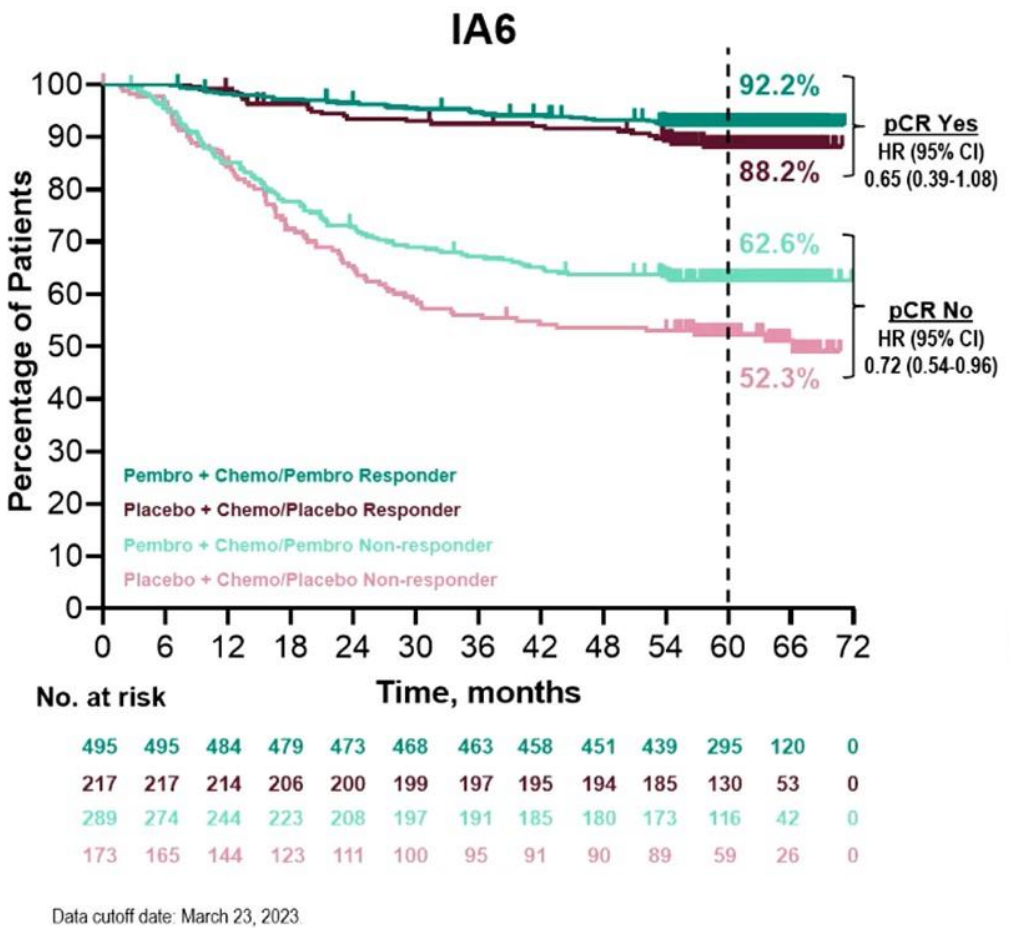
Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

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

Schmid et al. N Engl J Med 2020

KEYNOTE-522 (Phase 3): Efficacy – EFS by pCR (ypT0Tis ypN0)

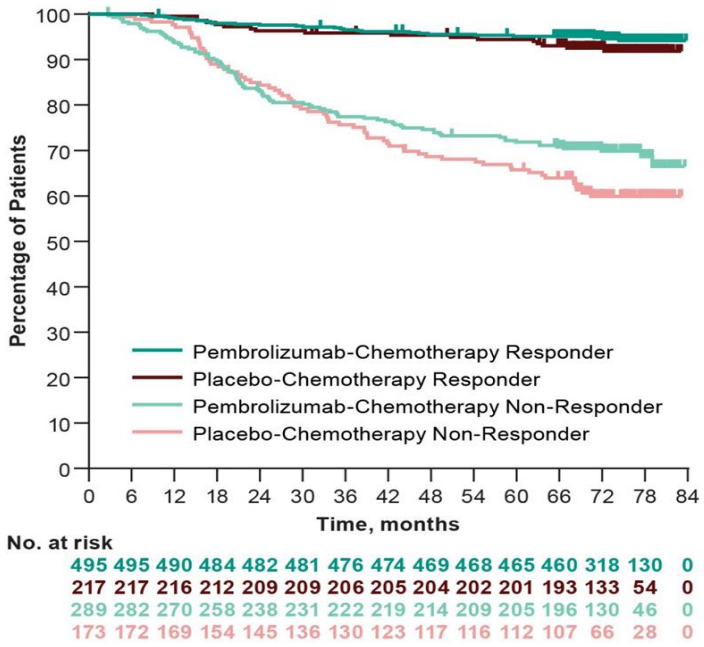




Schmid P, et al. ESMO 2023. Abstract LBA18

KEYNOTE-522 (Phase 3) : OS by pCR

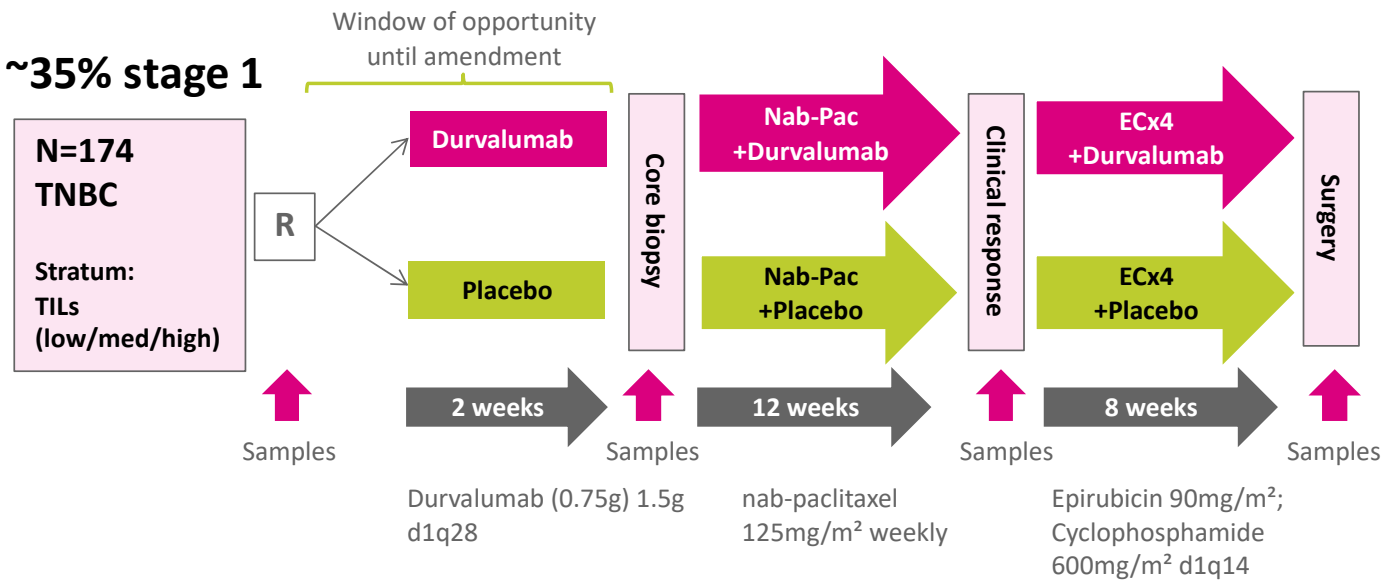
Fig. S4. Kaplan-Meier Estimates of Overall Survival by Pathological Complete Response (ypT0/Tis ypN0) According to Treatment Group in the Intention-to-Treat Population. Tick marks represent data censored at the last time the patient was known to be alive.



- Pembrolizumab significantly improved overall survival as compared with neoadjuvant chemotherapy alone
- A lower risk of death was observed in the Pembrolizumab group than in the SOC group regardless of the outcome with respect to pathological complete response

Schmid P, et al. N Engl J Med 2024;391:1981-1991

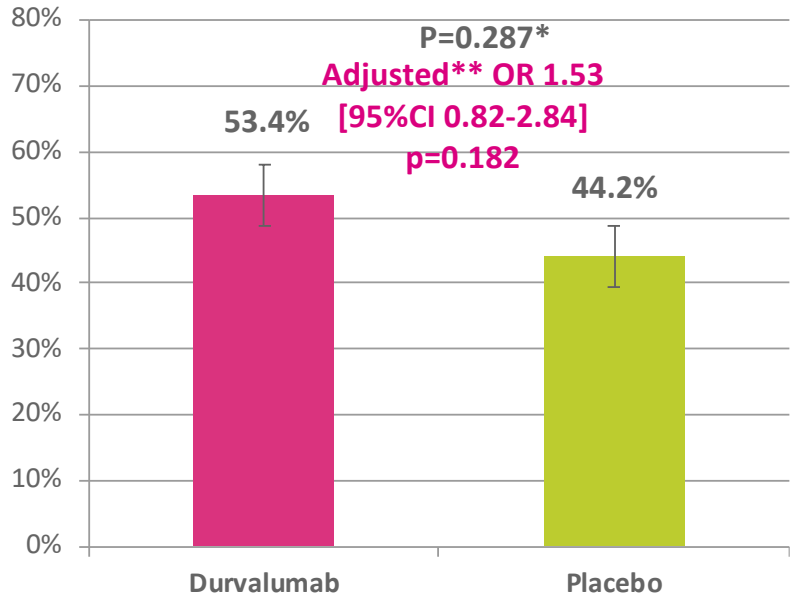
GeparNUEVO: Phase II Durvalumab Neoadjuvant Trial

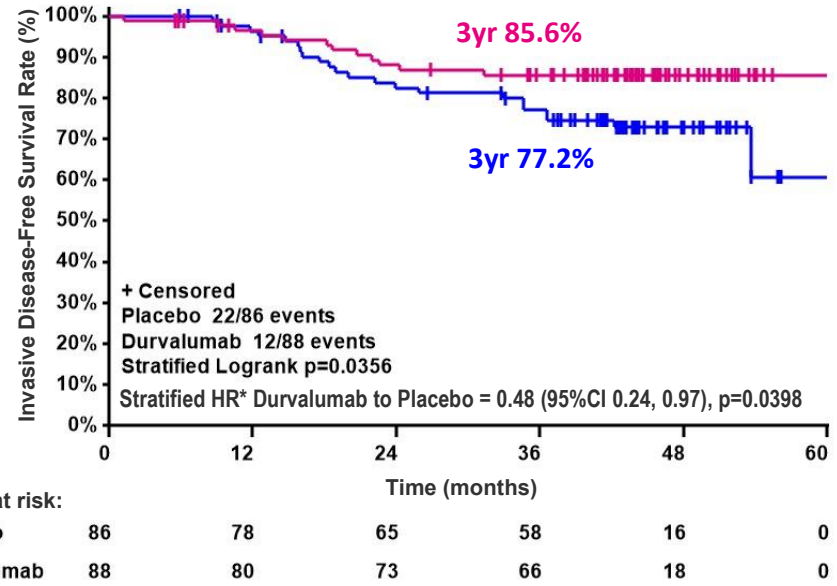


Primary endpoint: pCR (ypT0, ypN0)

Main secondary endpoints: iDFS, DDFS, OS

Primary endpoint: pCR – ypT0, ypN0





Δ8.4%

iDFS between arms

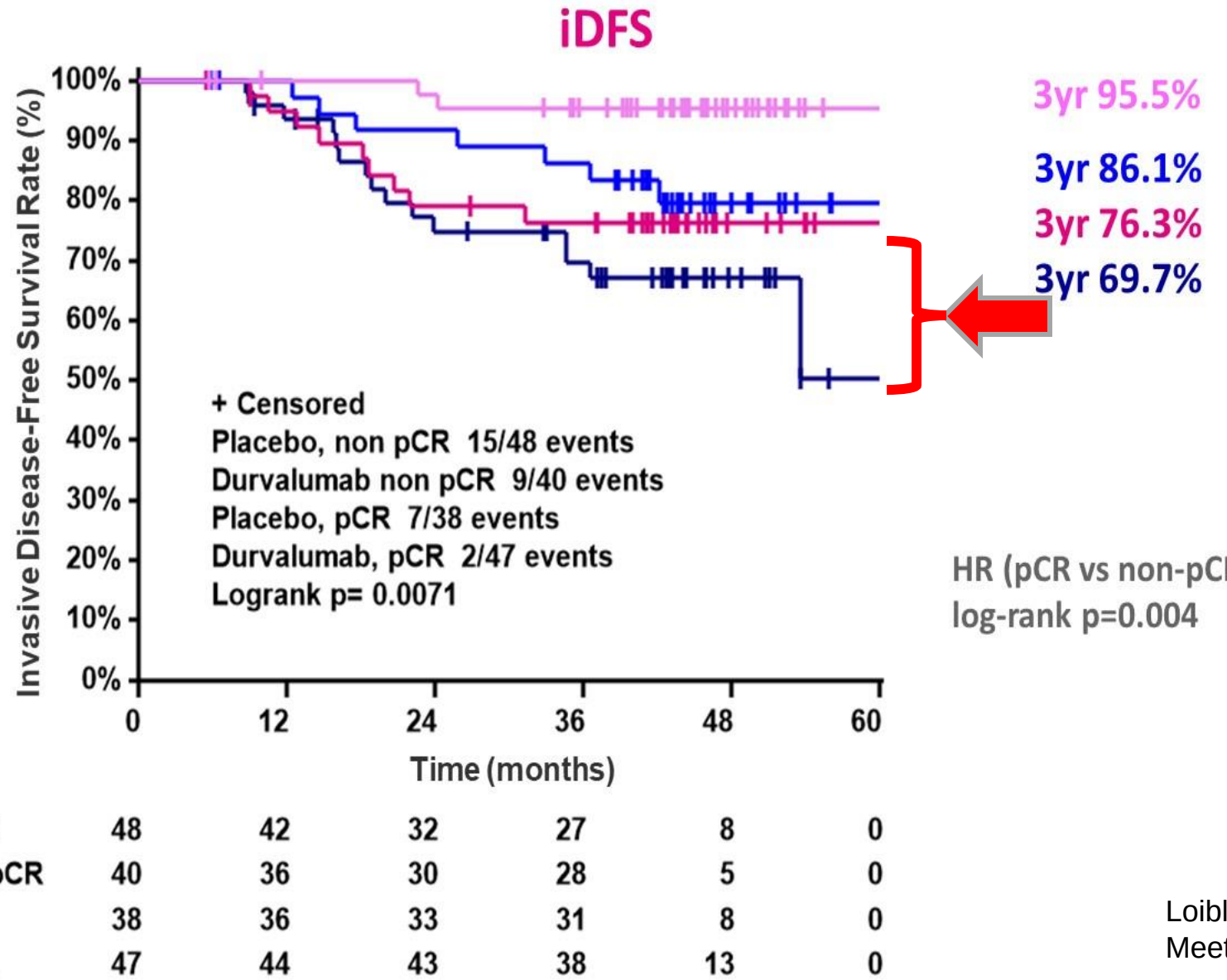
Median FU 43.7 months

* Stratified by sTILs

Immune therapy administered only with neoadjuvant chemo

Loibl S, et al. Ann Oncol 2019; Loibl et al, ASCO 2021

iDFS by pCR and Treatment Arm



HR (pCR vs non-pCR) 0.34 (95%CI 0.16-0.73)
log-rank p=0.004

Loibl S et al. 2021 ASCO Annual Meeting. Abstract 506.

Ongoing Post-Neoadjuvant Studies

Study	Treatment Arms
Pathologic Complete Response After Prior Neoadjuvant Chemotherapy Plus Pembrolizumab	
OptimICE (Alliance) **NCT05812807**	Adjuvant pembrolizumab x 9 cycles vs. No further pembrolizimab
Residual Disease After Prior Neoadjuvant Chemotherapy	
ASCENT-05/OptimICE-RD **NCT05633654**	Sacituzumab Govitecan and Pembrolizumab Vs. Treatment of Physician's Choice
TROPION-Breast03 **NCT05629585**	Dato-DXd Vs. Dato-DXd plus Durvalumab Vs. Investigator's Choice of Therapy

Adjuvant Immunotherapy in TNBC

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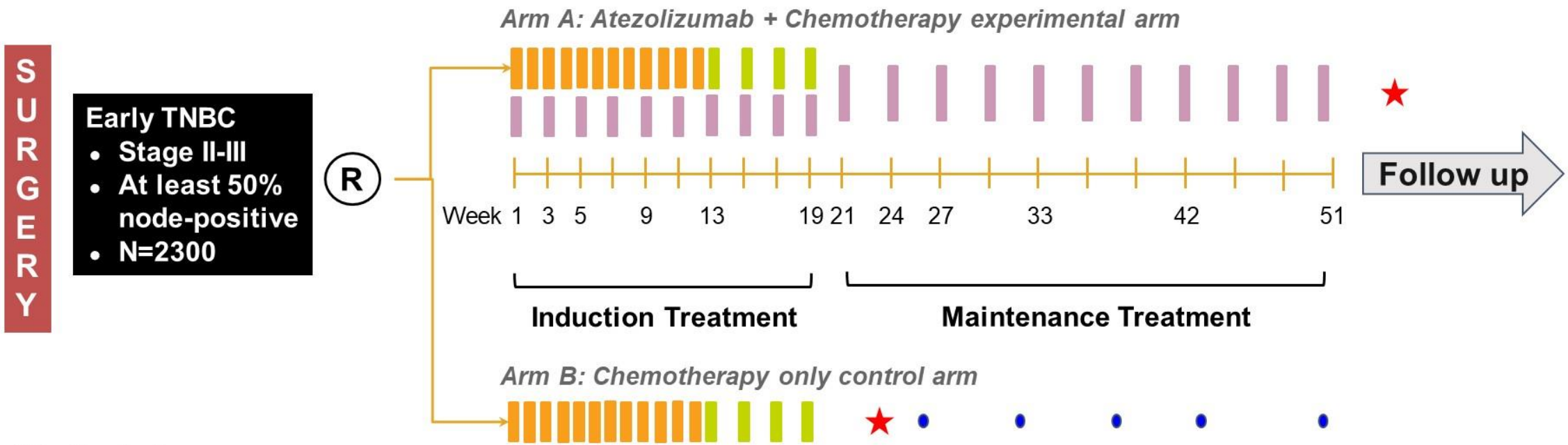
Alexandra/IMpassion030 Phase 3 open-label study design



Stratification factors:

Axillary nodal status
(0 vs. 1–3 vs. ≥ 4 positive lymph nodes)

Surgery
(breast conserving vs. mastectomy)

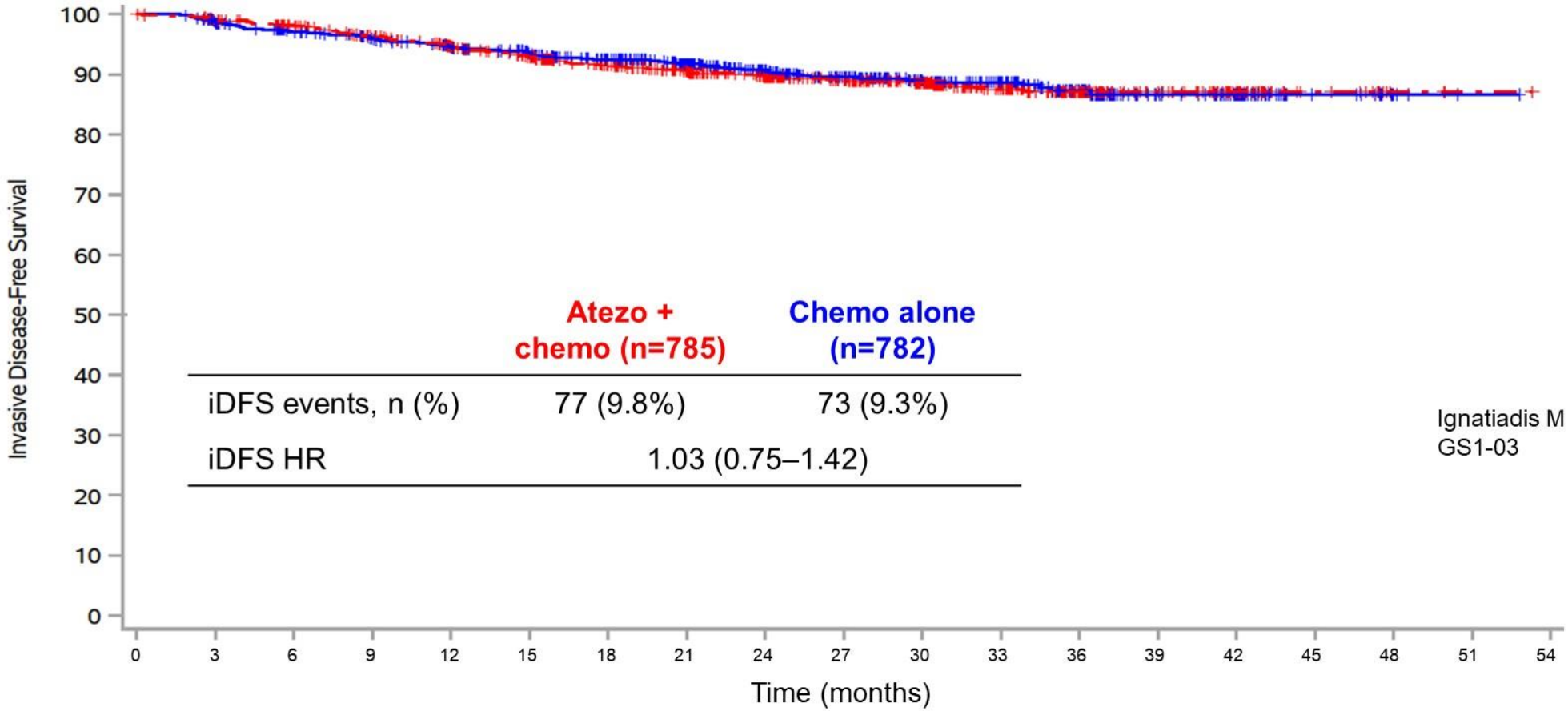
Tumor PD-L1 status
(IC0 vs. IC1/2/3)

- Paclitaxel qw for 12 weeks
- ddAC/EC q2w for 4 doses supported with G-CSF/GM-CSF
- Atezolizumab
  - Induction: 840 mg q2w for up to 10 doses
  - Maintenance: 1200 mg q3w to complete 1 year
- Monitoring visit Arm B

★ End of 30-day safety reporting period after last study treatment

Ignatiadis M SABCS 2023 GS1-03

Key secondary efficacy endpoint: iDFS in the PD-L1+ subgroup (71%)



	Atezo + chemo (n=785)	Chemo alone (n=782)
iDFS events, n (%)	77 (9.8%)	73 (9.3%)
iDFS HR	1.03 (0.75–1.42)	

Chemo alone	782	728	691	660	622	589	534	486	416	350	276	223	154	81	53	14	4	1	0
Atezo + chemo	785	749	718	680	640	601	536	480	425	366	300	230	156	90	48	17	3	1	0

Ignatiadis M SABCS 2023 GS1-03

Immunotherapy in HR+ Breast Cancer

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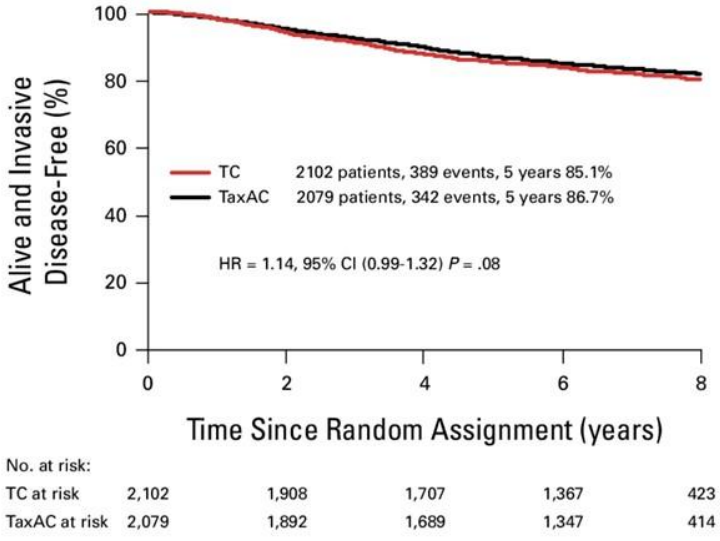
Neoadjuvant Chemotherapy for HR+ EBC

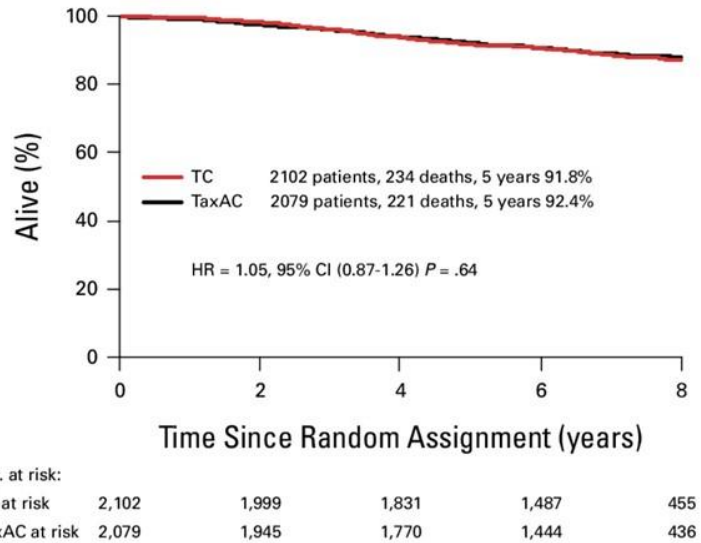
- Use of neoadjuvant chemo for HR+ dz is extrapolated from from adjuvant trials
- ABC Trials compared TC x 6 vs. TaxAC regimens
  - Median follow up at 6.9 years: Noninferiority of TC x 6 for IDFS not demonstrated. TaxAC improved IDFS in HR- subset.
  - Although TaxAC sig. reduced recurrence as IDFS first event, no sig. diff. in OS. & was associated w/ increased leukemias & non-breast cancer deaths.

IDFS



No. at risk:					
TC at risk	2,102	1,908	1,707	1,367	423
TaxAC at risk	2,079	1,892	1,689	1,347	414

OS



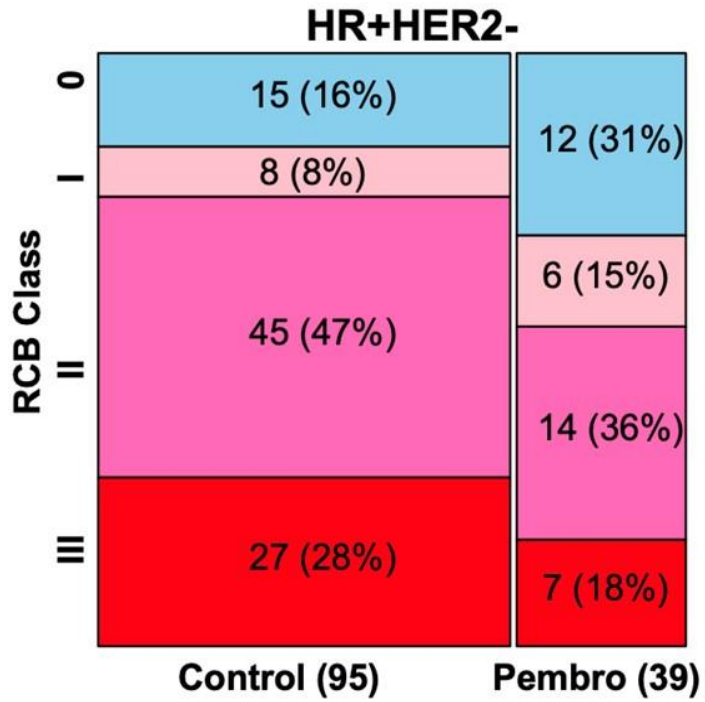
No. at risk:					
TC at risk	2,102	1,999	1,831	1,487	455
TaxAC at risk	2,079	1,945	1,770	1,444	436

Geyer et al. *JCO* 2024

PRESENTED BY: Rebecca Shatsky, MD

Neoadjuvant IO in HR+ EBC

- I-SPY2: adaptively randomized platform trial for high-risk, stage II/III breast cancer
  - 69 pts. randomized to pembrolizumab x 4 cycles with weekly paclitaxel, f/b AC
  - 181 pts. randomized to standard neoadj. chemo control

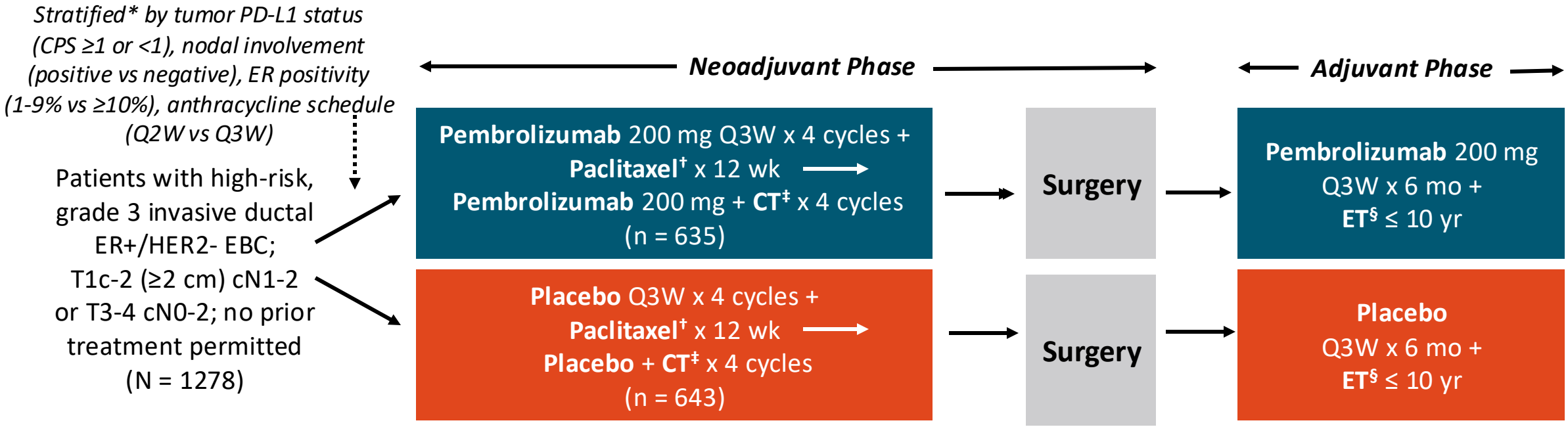


- Important to realize that many "HR"+ cases are actually basal molecular subtypes and benefit from TNBC style regimens

Nanda et al.
JAMA Onc 2020

KEYNOTE-756: Study Design

- International, randomized, open-label phase III trial



*Patients in Eastern Europe stratified by PD-L1 status only; no stratification in China; all other countries stratified by all factors. †80 mg/m^2 QW. ‡Doxorubicin 60 mg/m^2 Q3W, epirubicin 100 mg/m^2 Q3W, cyclophosphamide 600 mg/m^2 Q3W or Q2W. §ET according to institution. Radiotherapy permitted in adjuvant phase.

- Primary endpoints: pCR (ypT0/Tis ypN0) at time of surgery; EFS
- Secondary endpoints: OS; pCR (ypT0 ypN0); pCR (ypT0/Tis); efficacy in PD-L1 CPS ≥1 group; safety

KEYNOTE-756: pCR at First Interim Analysis by Subgroup

Patients With pCR at First Interim Analysis, % (n/N)	Pembrolizumab	Placebo	Estimated Treatment Difference, % (95% CI)
PD-L1 CPS ≥1			
▪ ER+ <10%	57.6 (19/33)	33.3 (13/39)	24.2 (1. to -45.1)
▪ ER+ ≥10%	27.6 (124/449)	18.4 (83/450)	9.2 (3.7 to 14.6)
PD-L1 CPS <1			
▪ ER+ ≥10%	7.2 (11/152)	2.7 (4/150)	4.6 (-0.4 to 10.2)
CT exposure			
▪ Full exposure*	26.2 (142/543)	16.9 (95/563)	9.3 (4.5 to 14.1)
▪ < Full exposure	13.2 (12/91)	6.4 (5/78)	6.8 (-2.6 to 16.2)

*Paclitaxel 10-12 doses, doxorubicin or epirubicin 4 doses, and cyclophosphamide 4 doses.

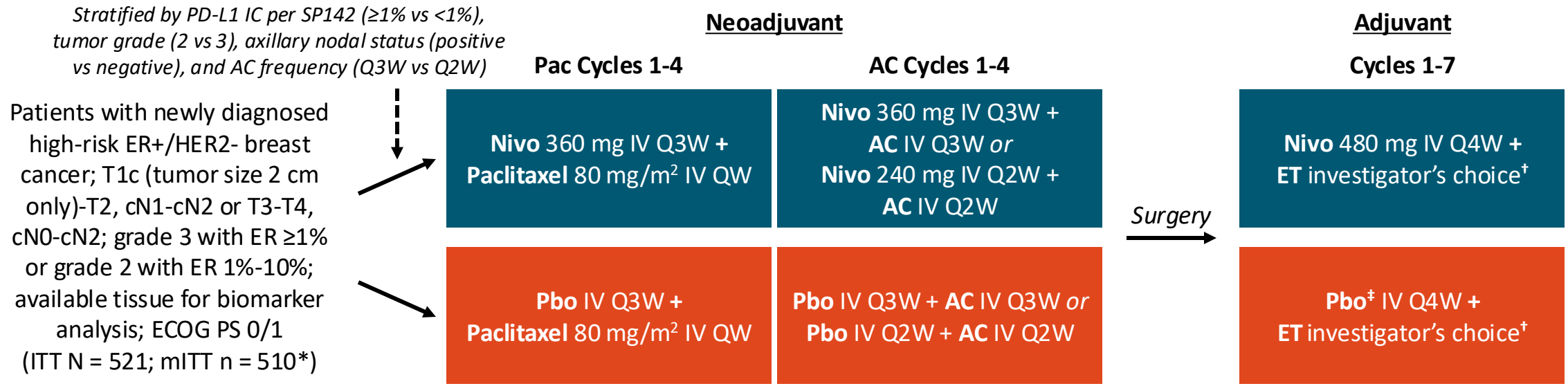
KEYNOTE-756: Residual Cancer Burden After Definitive Surgery

RCB Category After Surgery, % (n/N)	Pembrolizumab	Placebo
RCB 0-1	35.0 (222/635)	23.6 (152/643)
RCB 2	40.8 (259/635)	45.3 (291/643)
RCB 3	20.5 (130/635)	28.9 (186/643)

Bardia. SABCS 2023. Abstr GS01-02.

CheckMate 7FL Biomarker Analysis: Study Design

- Exploratory biomarker analysis of international, randomized, double-blind phase III trial



*mITT population excluded n = 11 enrolled in Russia after site closed before pCR assessment. †Investigator's choice of ET agents included anastrozole, exemestane, letrozole, and tamoxifen. ‡After protocol amendment, adjuvant phase made open label and patients no longer received Pbo.

- **Primary endpoint:** pCR (ypT0/Tis, ypN0) in mITT
- **Secondary endpoints:** pCR in PD-L1+, RCB class frequency and 0-1 rate in mITT and PD-L1+, safety

- **Current analysis:** pCR and RCB 0-1 rates according to PD-L1 expression per SP142 and 28-8 CPS, sTIL score, ER and/or PgR IHC, and Ki67 index

Loi. SABCS 2023. Abstr GS01-01. Loi. ESMO 2023. Abstr LBA20. Loi. ASCO 2020. Abstr TPS604. NCT04109066.

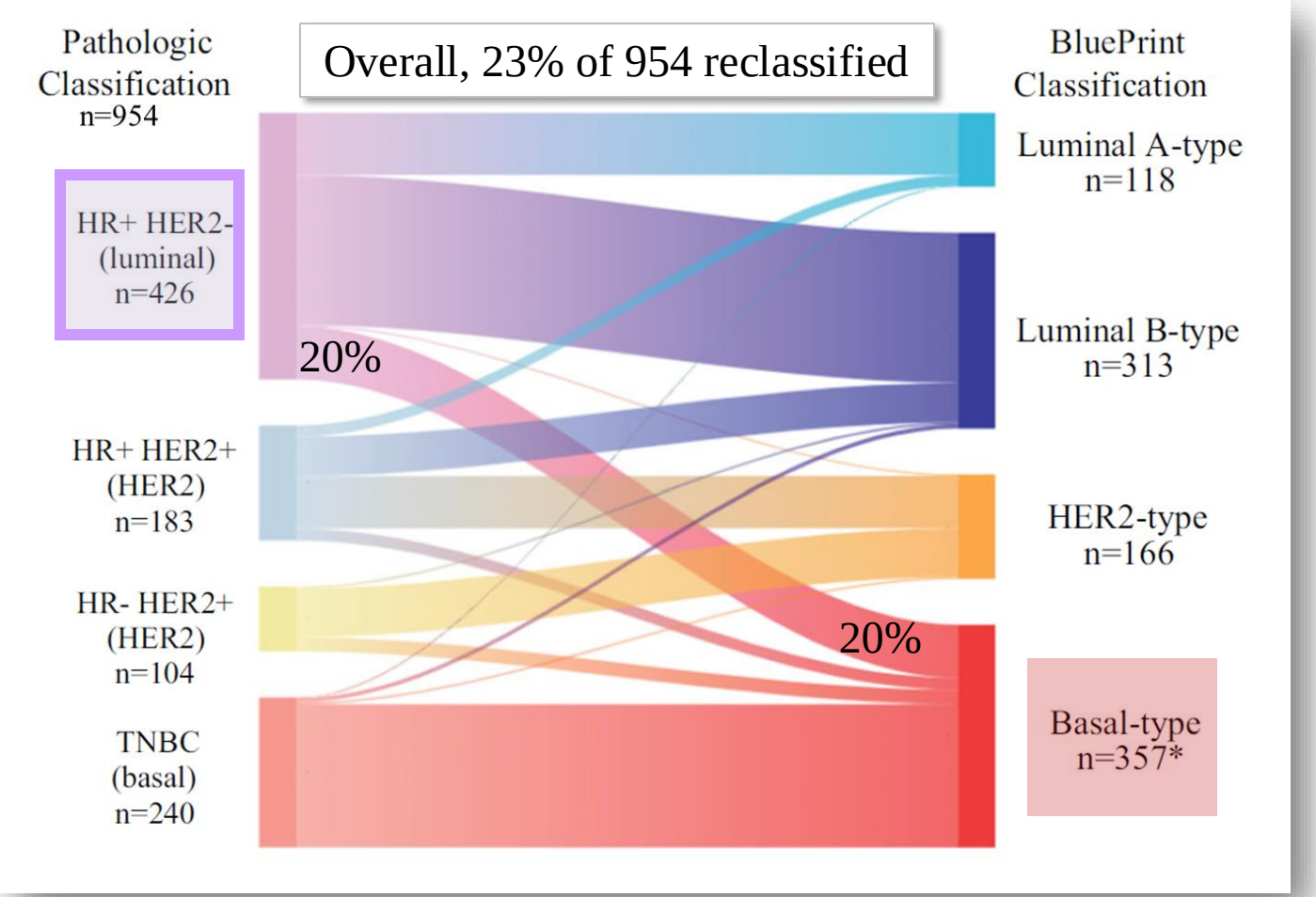
CheckMate 7FL Biomarker Analysis: pCR and sTIL

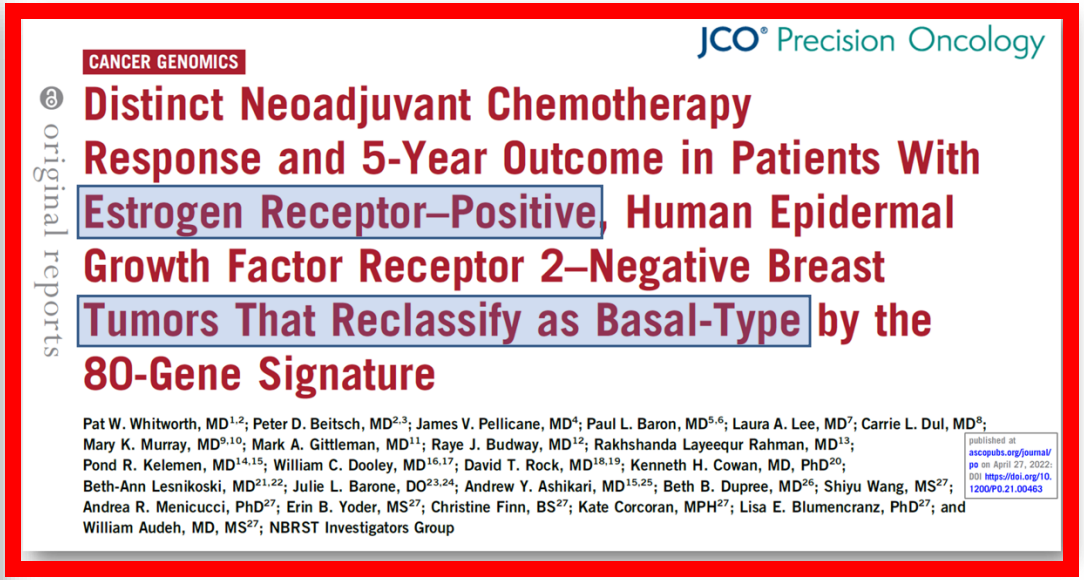
Rate by PD-L1, %		pCR		
		Nivo + NACT	Pbo + NACT	Diff., % (95% CI)
Overall		24.5	13.8	10.7 (3.9 to 17.4)
SP142	<1%	14.2	10.7	3.6 (-3.6 to 10.7)
	≥1%	44.3	20.2	24.1 (10.1 to 36.7)
sTIL	<3	9.2	10.0	-0.8 (-9.5 to 8.3)
	≥3	44.4	21.1	23.4 (8.7 to 36.7)
	<5	9.8	10.5	-0.7 (-9.3 to 8.3)
	≥5	46.1	21.1	24.9 (9.7 to 38.6)
	<10	14.0	11.4	2.7 (-5.9 to 11.4)
	≥10	51.9	22.6	29.2 (10.9 to 44.9)

- Nivo benefit greater in PD-L1+ population defined using SP142 IC ≥1% or 28-8 CPS ≥1
- Greater pCR was observed with nivolumab when tumors had sTIL ≥1%
- RCB 0-1 rate by sTIL status consistent with pCR rate
- Ki67 index (< vs ≥20%) not associated with pCR or RCB 0-1 benefit with nivolumab

Loi. SABCS 2023. Abstr GS01-01. Loi. ESMO 2023. Abstr LBA20. Loi. ASCO 2020. Abstr TPS604. NCT04109066.

20% of ER+, HER2– Clinical "Subtype" → BluePrint Genomic Basal Subtype





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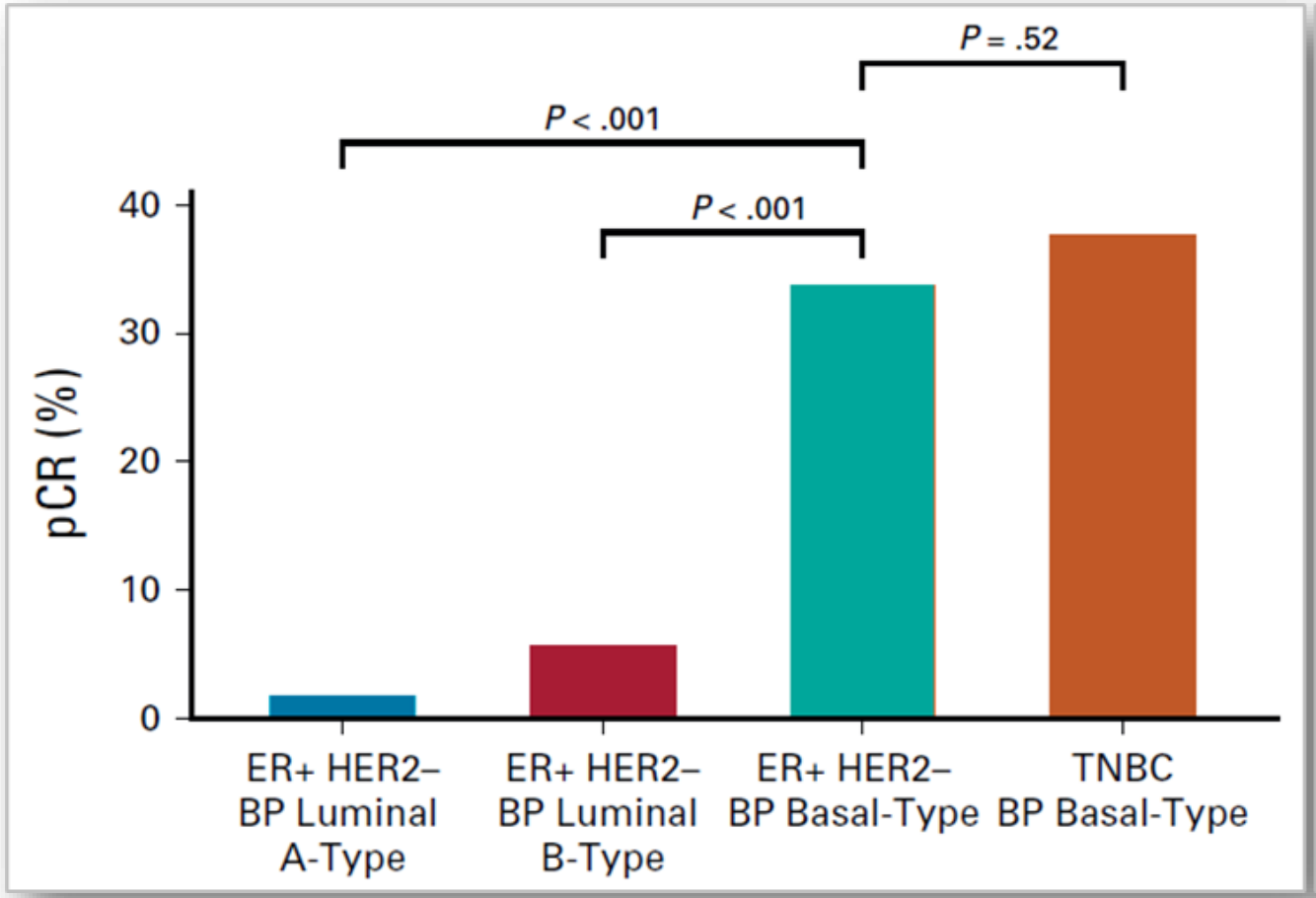
original reports

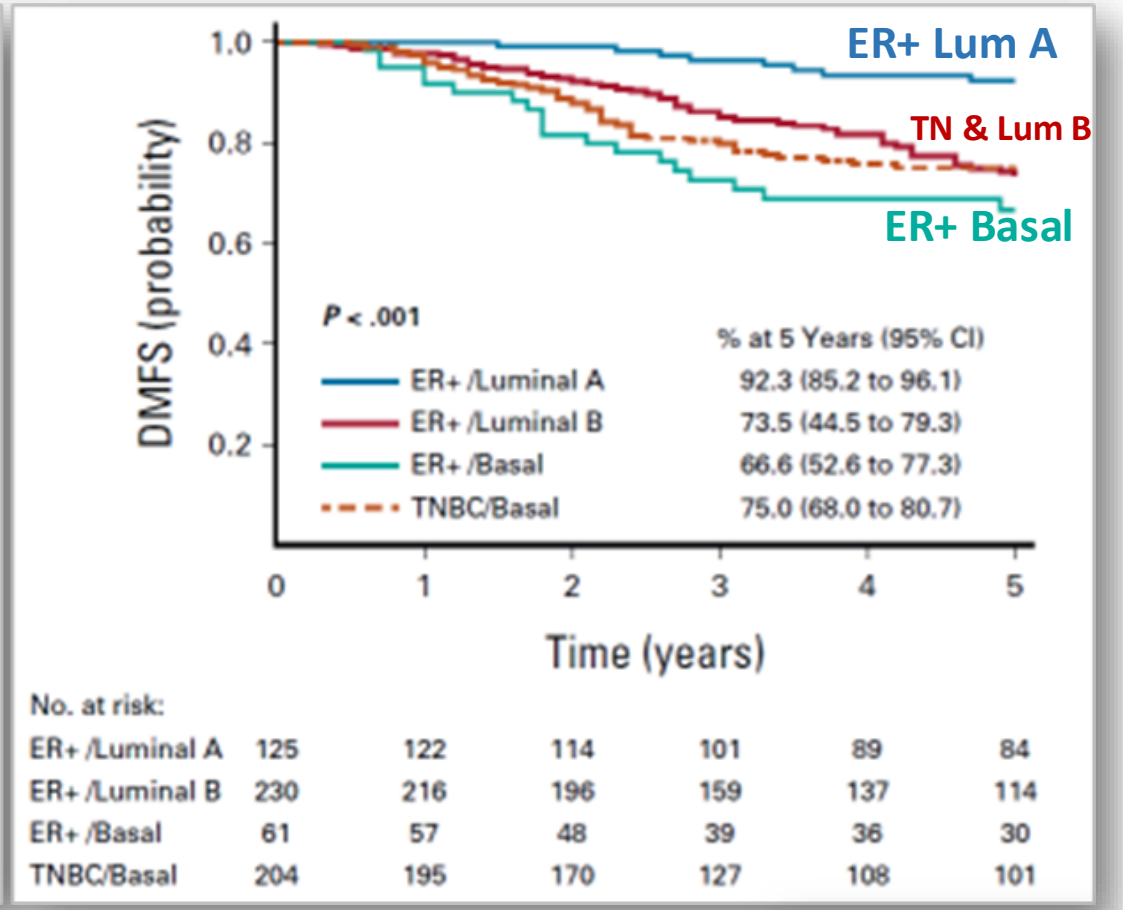
Distinct Neoadjuvant Chemotherapy Response and 5-Year Outcome in Patients With Estrogen Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Breast Tumors That Reclassify as Basal-Type by the 80-Gene Signature

Pat W. Whitworth, MD[1,2]; Peter D. Beitsch, MD[2,3]; James V. Pellicane, MD[4]; Paul L. Baron, MD[5,6]; Laura A. Lee, MD[7]; Carrie L. Dul, MD[8]; Mary K. Murray, MD[9,10]; Mark A. Gittleman, MD[11]; Raye J. Budway, MD[12]; Rakhshanda Layeequr Rahman, MD[13]; Pond R. Kelemen, MD[14,15]; William C. Dooley, MD[16,17]; David T. Rock, MD[18,19]; Kenneth H. Cowan, MD, PhD[20]; Beth-Ann Lesnikoski, MD[21,22]; Julie L. Barone, DO[23,24]; Andrew Y. Ashikari, MD[15,25]; Beth B. Dupree, MD[26]; Shiyu Wang, MS[27]; Andrea R. Menicucci, PhD[27]; Erin B. Yoder, MS[27]; Christine Finn, BS[27]; Kate Corcoran, MPH[27]; Lisa E. Blumencranz, PhD[27]; and William Audeh, MD, MS[27]; NBRST Investigators Group

published at ascopubs.org/journal/po on April 27, 2022: DOI https://doi.org/10.1200/PO.21.00463

pCR Rates and DMFS in Basal and ER+ Luminal Subtypes
ER Basal Behaves Like TNBC but looks like ER positive

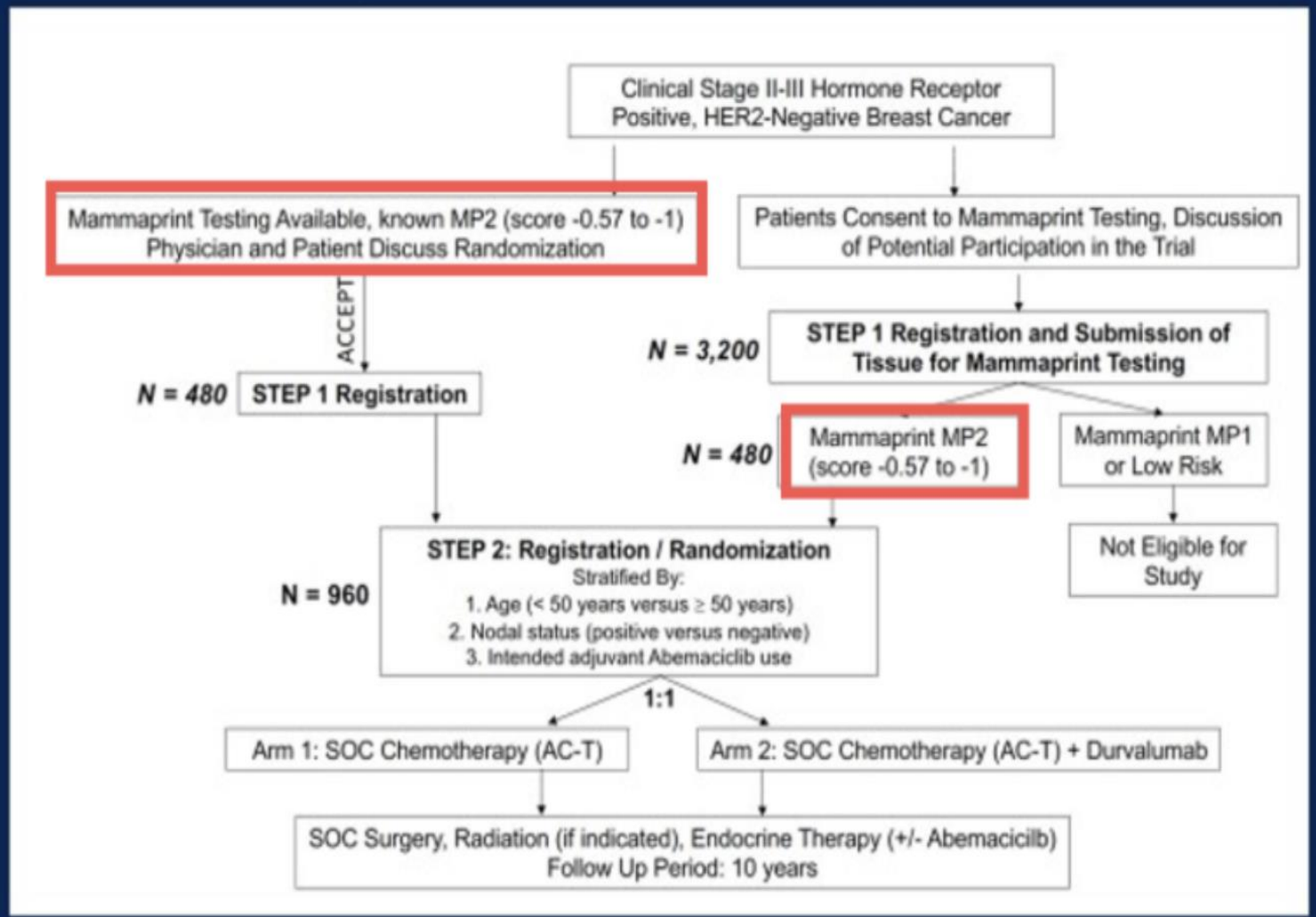




ascopubs.org/journal/po on April 27, 2022: DOI https://doi.org/10.1200/PO.21.00463

SWOG S2206

MammaPrint High 2 for Immunotherapy in ER+ Breast Cancer



Metastatic Triple Negative Breast Cancer

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KEYNOTE-355 Study Design (NCT02819518)

Key Eligibility Criteria
- Age ≥18 years
- Central determination of TNBC and PD-L1 expression[a]
- Previously untreated locally recurrent inoperable or metastatic TNBC
- De novo metastasis or completion of treatment with curative intent ≥6 months prior to first disease recurrence
- ECOG performance status 0 or 1
- Life expectancy ≥12 weeks from randomization
- Adequate organ function
- No systemic steroids
- No active CNS metastases
- No active autoimmune disease

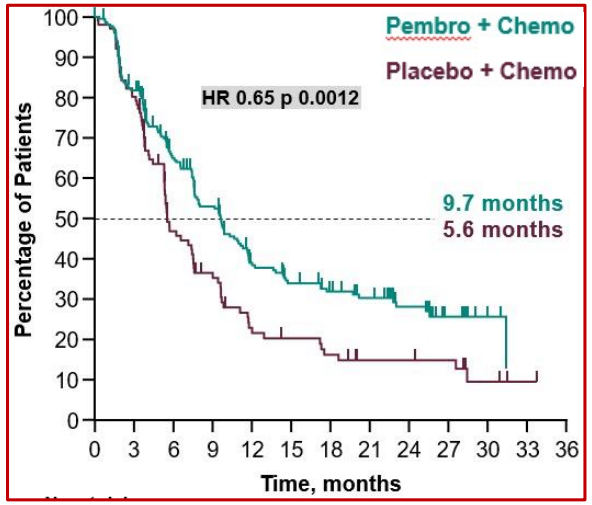
R 2:1

- Pembrolizumab[b] + Chemotherapy[c]
- Placebo[d] + Chemotherapy[c]

→ Progressive disease[e]/cessation of study therapy

Stratification Factors:
- Chemotherapy on study (taxane or gemcitabine-carboplatin)
- PD-L1 tumor expression (CPS ≥1 or CPS <1)[f]
- Prior treatment with same class chemotherapy in the neoadjuvant or adjuvant setting (yes or no)

PFS: PD-L1 CPS ≥10

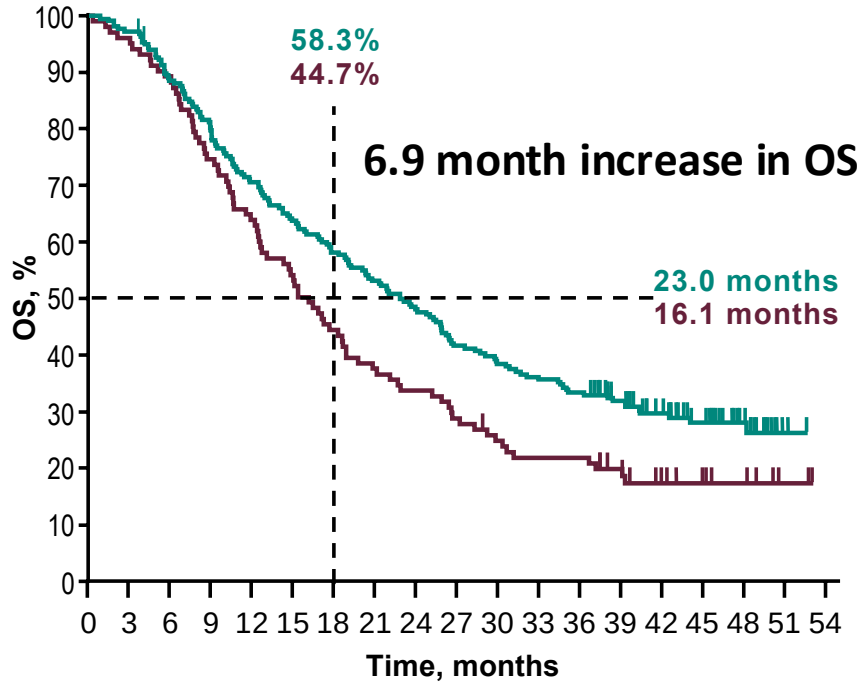


Prespecified *P* value boundary of 0.00411 met

38% of pts

OS: 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[a]
Placebo + Chemo	84/103	81.6%		



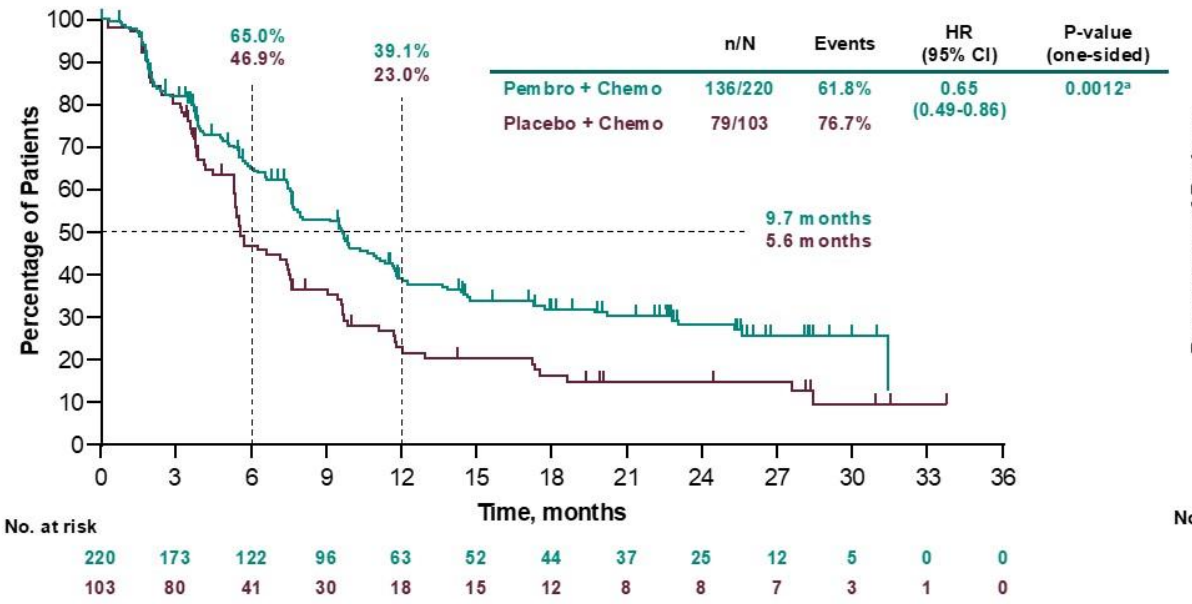
No. at risk

220	214	193	171	154	139	127	116	105	91	84	78	73	59	43	31	17	2	0
103	98	91	77	66	55	46	39	35	30	25	22	22	17	12	8	6	2	0

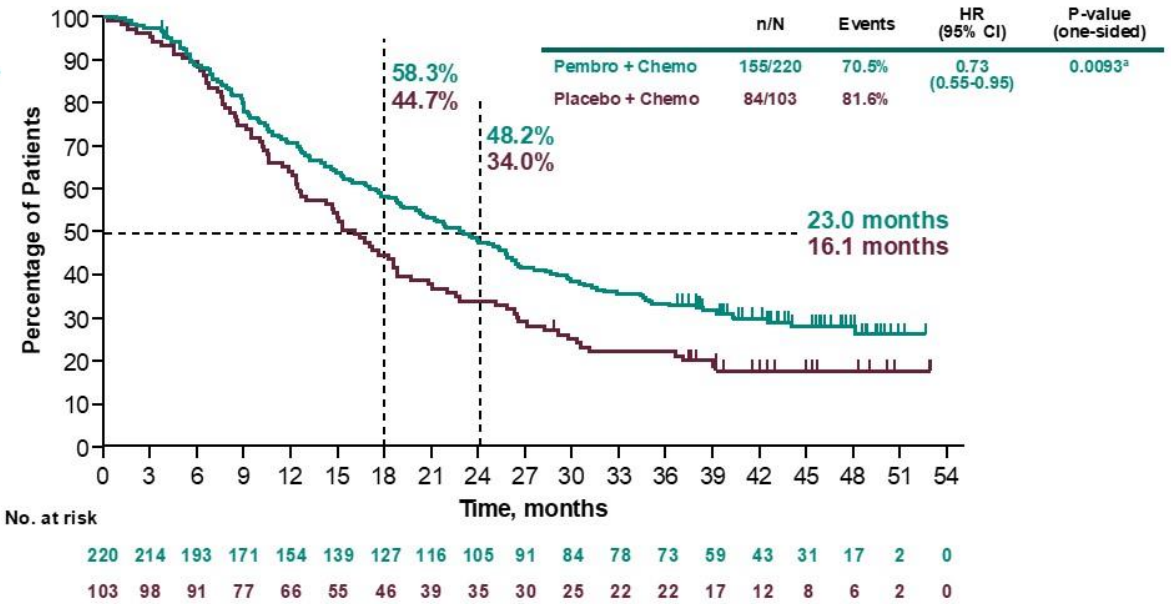
Cortes et al, Lancet 2020; Rugo et al , ESMO 2021

KN355: Addition of Pembrolizumab to Chemotherapy Improves Survival as 1L Treatment for PD-L1+ mTNBC

PFS in PD-L1+ (CPS ≥10)



OS in PD-L1+ (CPS ≥10)

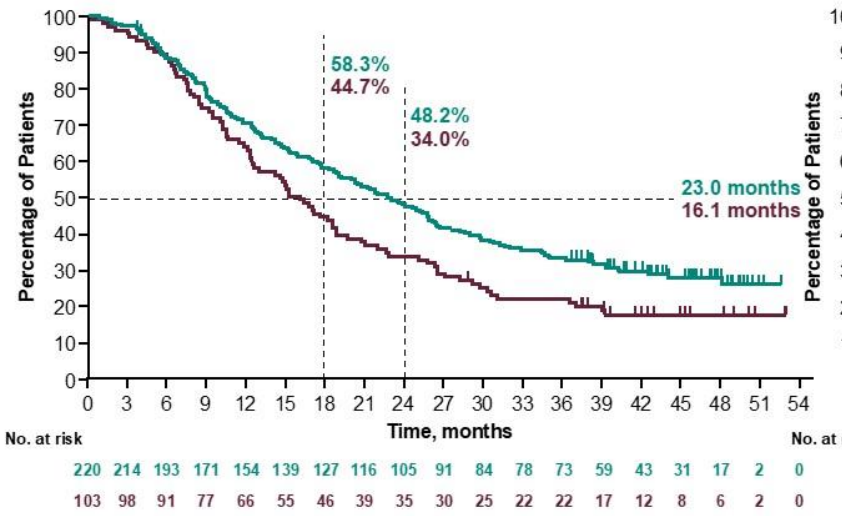


Cortes J et al. ASCO 2020; Rugo H et al. SABCS 2020; Cortes J et al. Lancet. 2020;396:1817-28; Rugo H et al. ESMO 2021; Cortes J et al. N Engl J Med. 2022;387:217-26.

KN355: Pembrolizumab Benefit in PD-L1 CPS ≥10

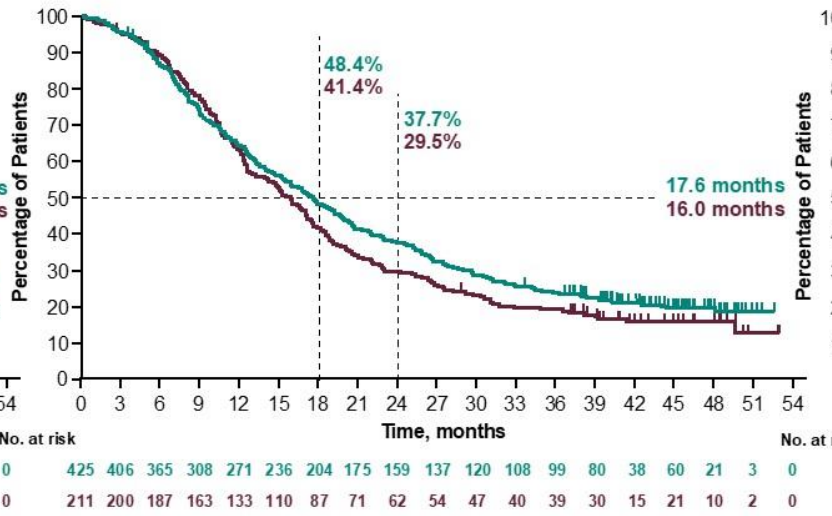
CPS ≥10

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



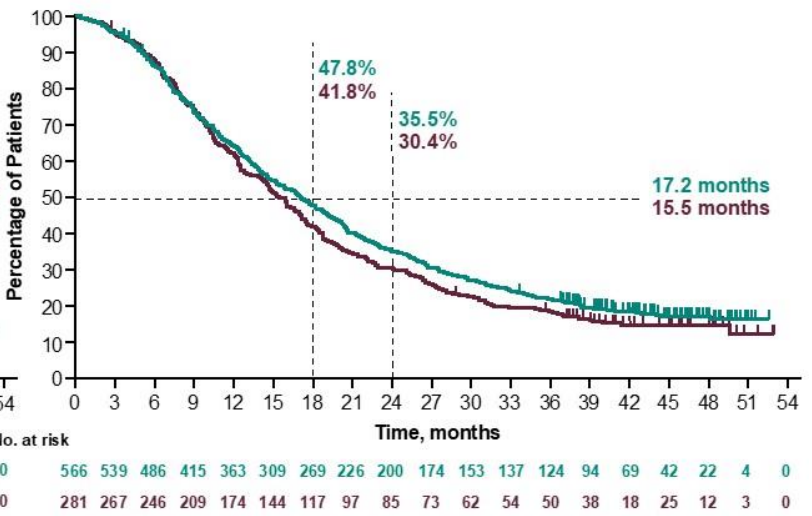
CPS ≥1

	n/N	Events	HR (95% CI)	P-value (one-sided)
Pembro + Chemo	336/425	79.1%	0.86 (0.72-1.04)	0.0563[a]
Placebo + Chemo	177/211	83.9%		



ITT

	n/N	Events	HR (95% CI)
Pembro + Chemo	460/566	81.3%	0.89 (0.76-1.05)
Placebo + Chemo	238/281	84.7%	



Cortes J et al. ASCO 2020; Rugo H et al. SABCS 2020; Cortes J et al. Lancet. 2020;396:1817-28; Rugo H et al. ESMO 2021; Cortes J et al. N Engl J Med. 2022;387:217-26.

Take Home Message

- Neoadjuvant Chemoimmunotherapy is now SOC in patients with Stage II/III TNBC based on results from Keynote-522
- In patients with early-stage triple-negative breast cancer, the addition of Atezolizumab to standard adjuvant chemotherapy provided no benefit over chemotherapy alone in the final analysis of the phase III ALEXANDRA/IMpassion030 trial
- Neoadjuvant Chemoimmunotherapy significantly improved pCR and RCB 0–1 rates in High Risk HR (+) Her2 Negative Breast cancer patients
- Chemoimmunotherapy in advanced triple-negative breast cancer whose tumors expressed PD-L1 with a CPS of 10 or more resulted in significantly longer overall survival than chemotherapy alone.

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