Breast Cancer Immunotherapy

Joyce O'Shaughnessy, MD

Celebrating Women Chair in Breast Cancer

Baylor University Medical Center

Texas Oncology

US Oncology

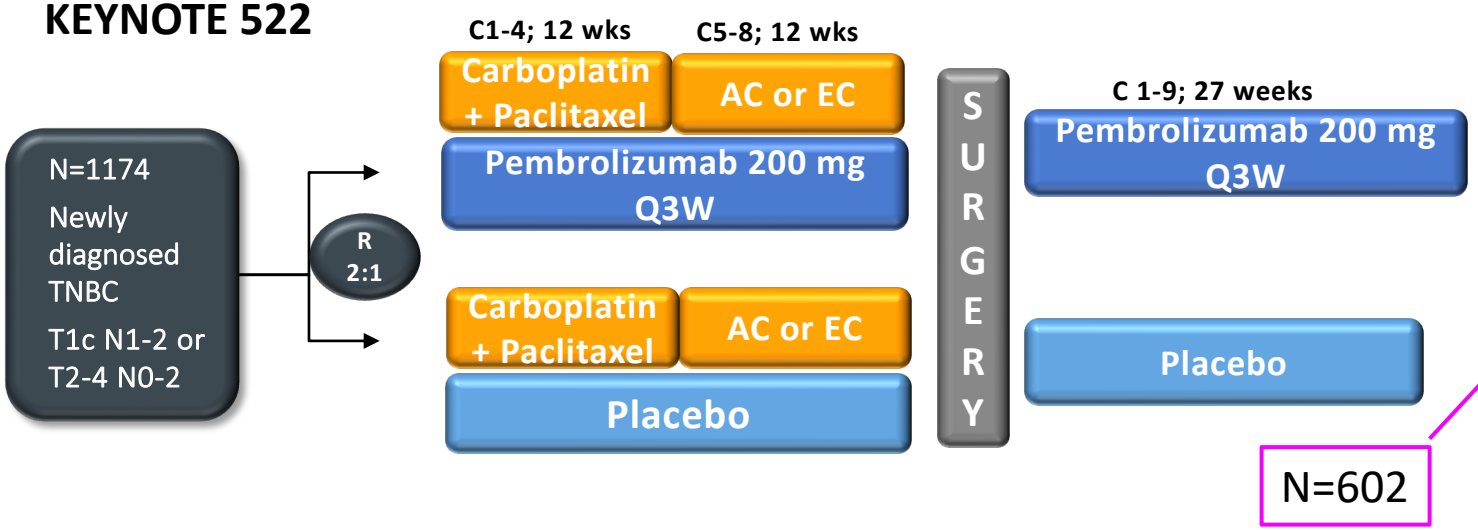
Thanks to Hope Rugo, MD for sharing her SABCS 2021 IO lecture slides

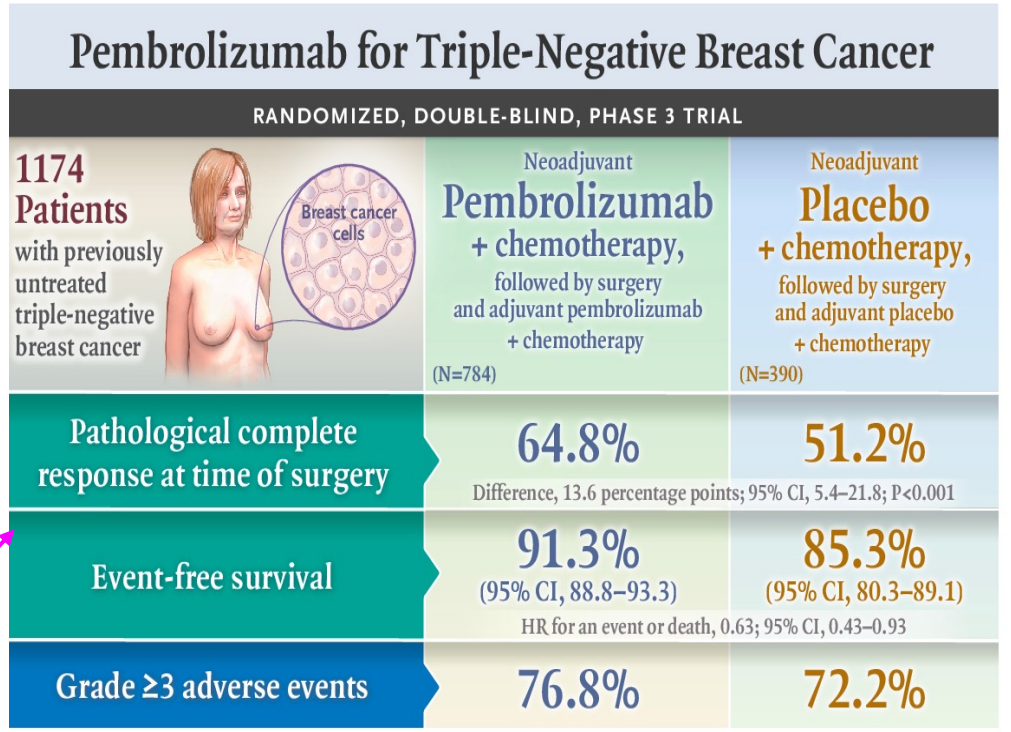
Challenges, Questions and Limitations

- Selecting patients: who benefit from checkpoint inhibitor therapy
- Chemotherapy backbone – de-escalate?
- Adjuvant pembrolizumab following pCR?
- Combining adjuvant pembrolizumab with capecitabine or olaparib?
- How to increase effectiveness of checkpoint inhibitors?
- Benefit for high risk HR+ HER2-?

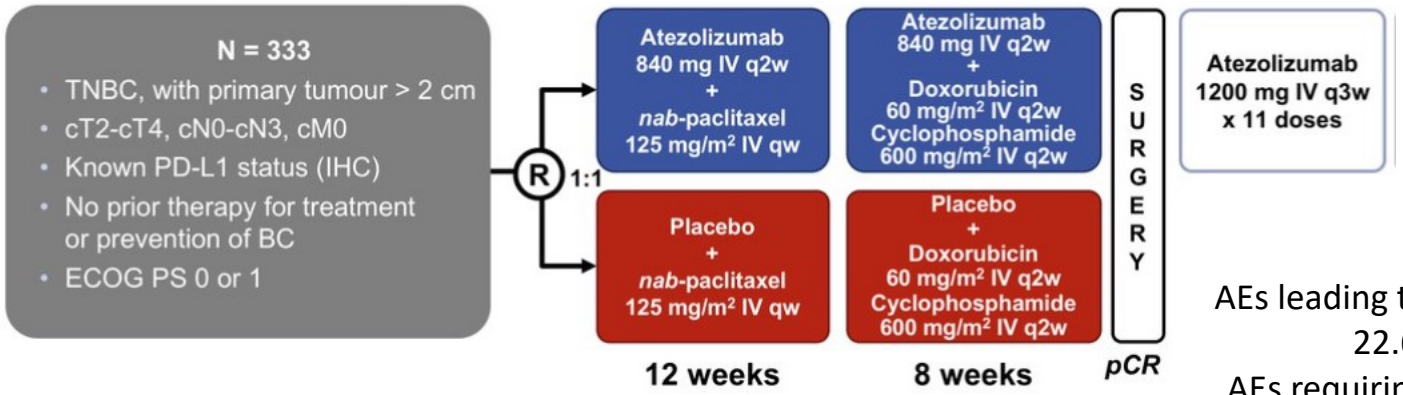
Phase III Neoadjuvant Immunotherapy Trials

KEYNOTE 522

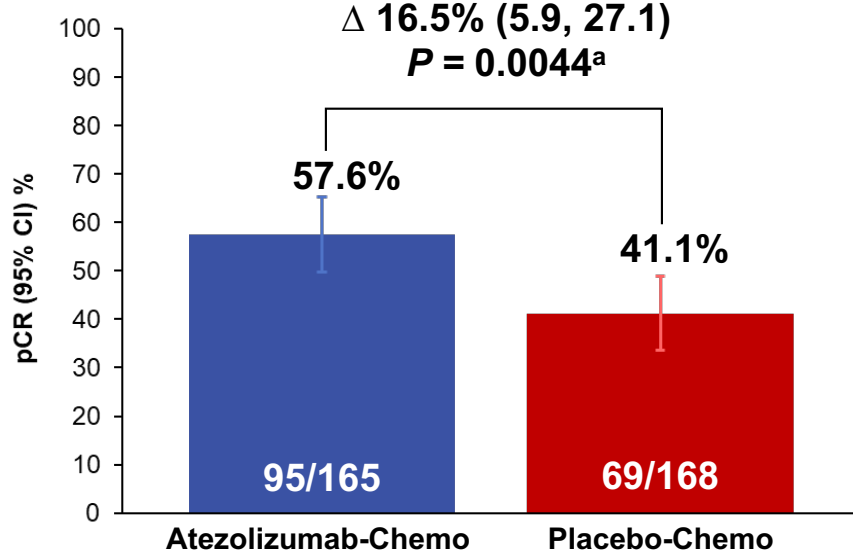




IMpassion 031



AEs leading to D/C of any drug:
22.6 v 19.8%
AEs requiring corticosteroids:
12.8 v 9.6%

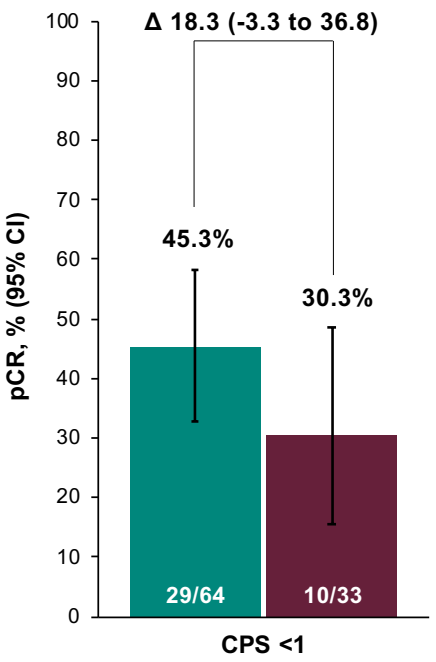


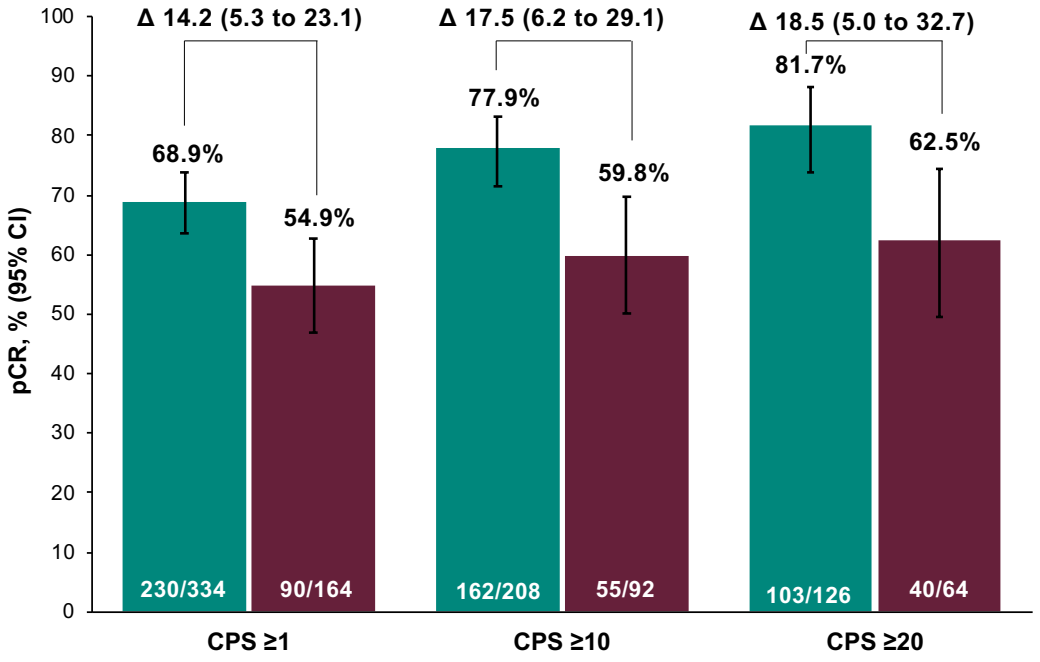
Schmid et al, NEJM 2020; Mittendorf et al, Lancet 2020

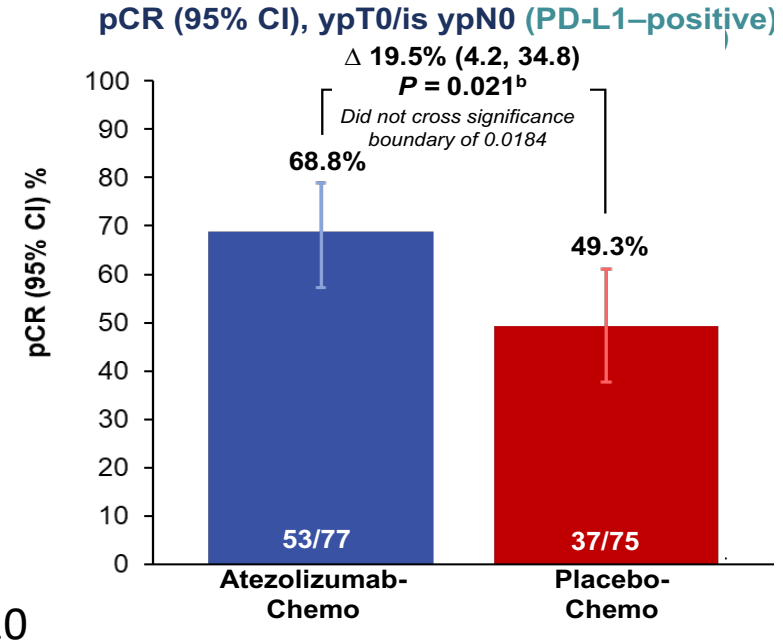
Pembro + Chemo
Placebo + Chemo

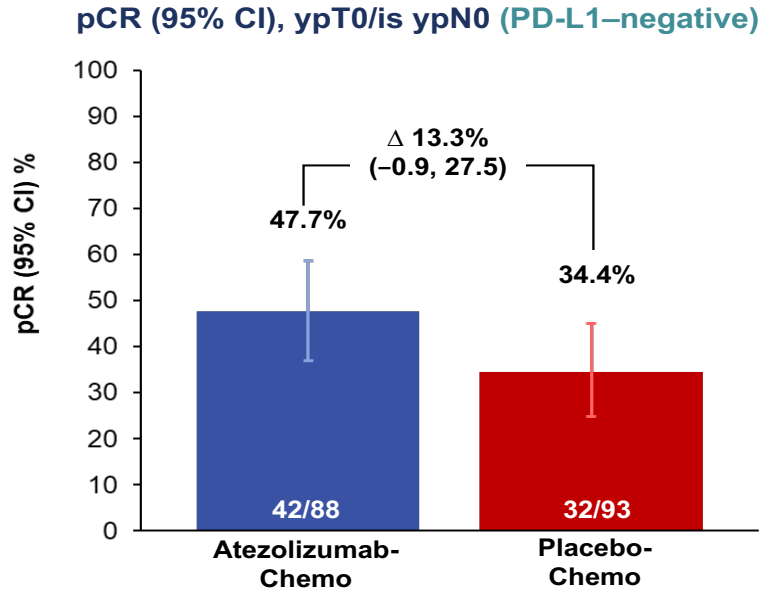
Benefit from Immunotherapy is Independent of PD-L1 status

Is PD-L1 Predictive of Response to Chemotherapy?





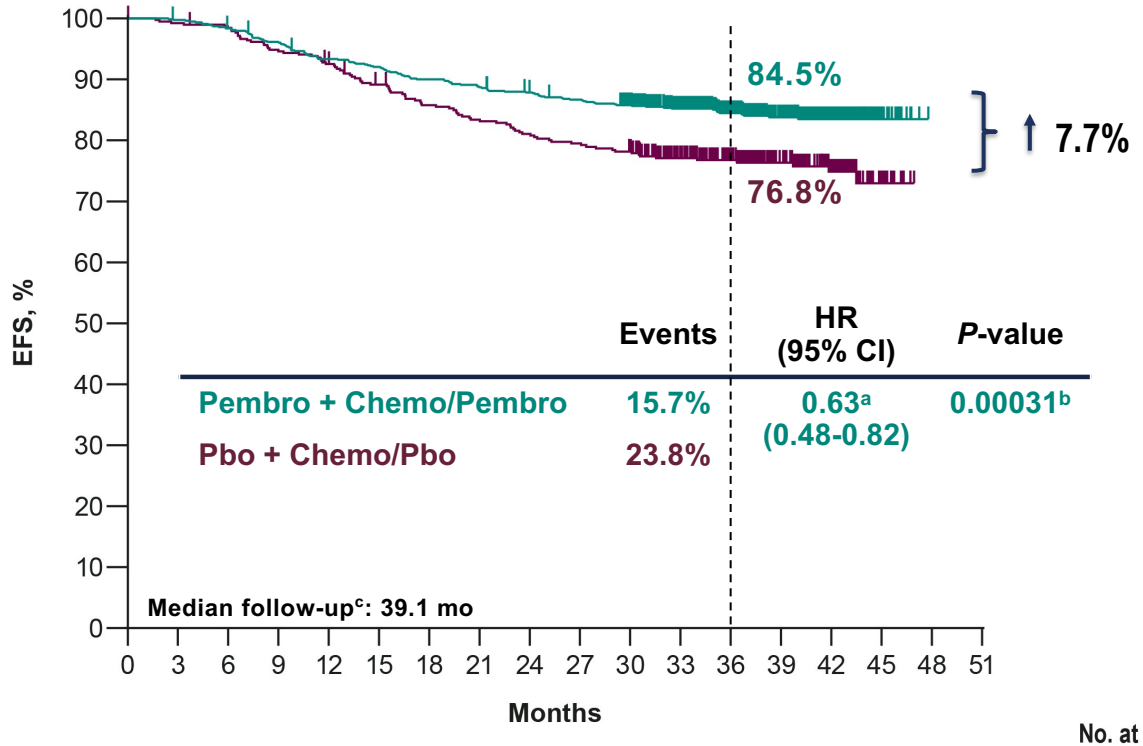




Schmidt et al, SABCS 2019, Mittendorf, Lancet 2020

EFS and DRFS: Statistically Significant at IA4

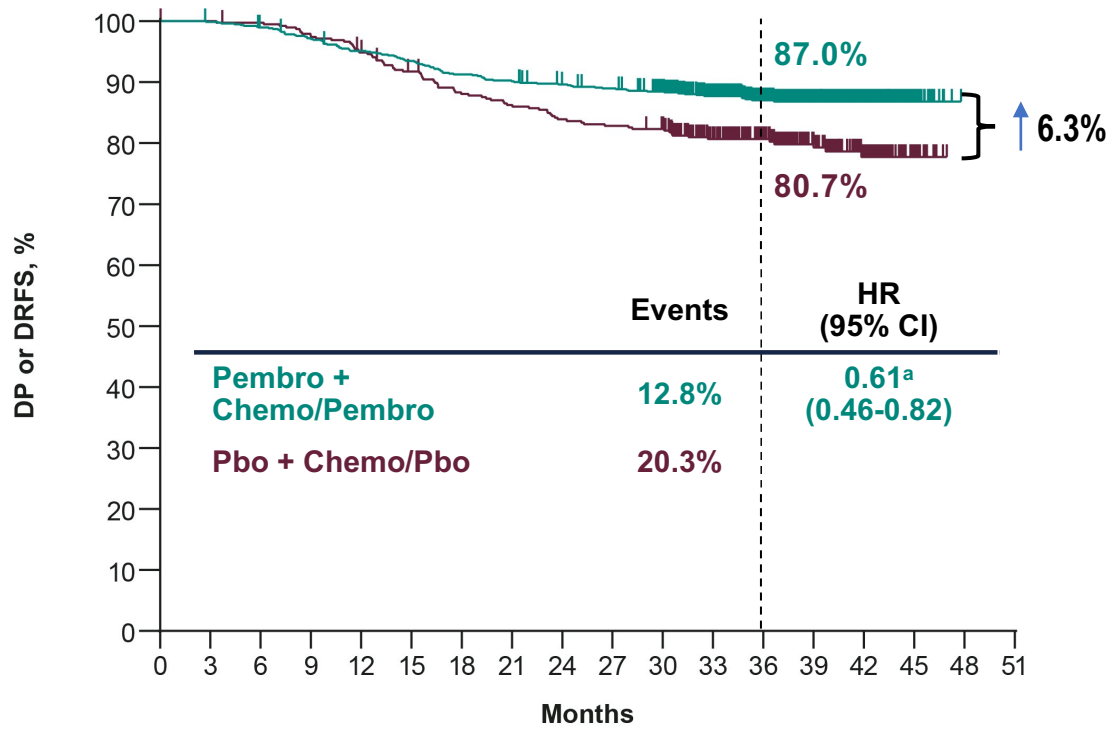
EFS



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

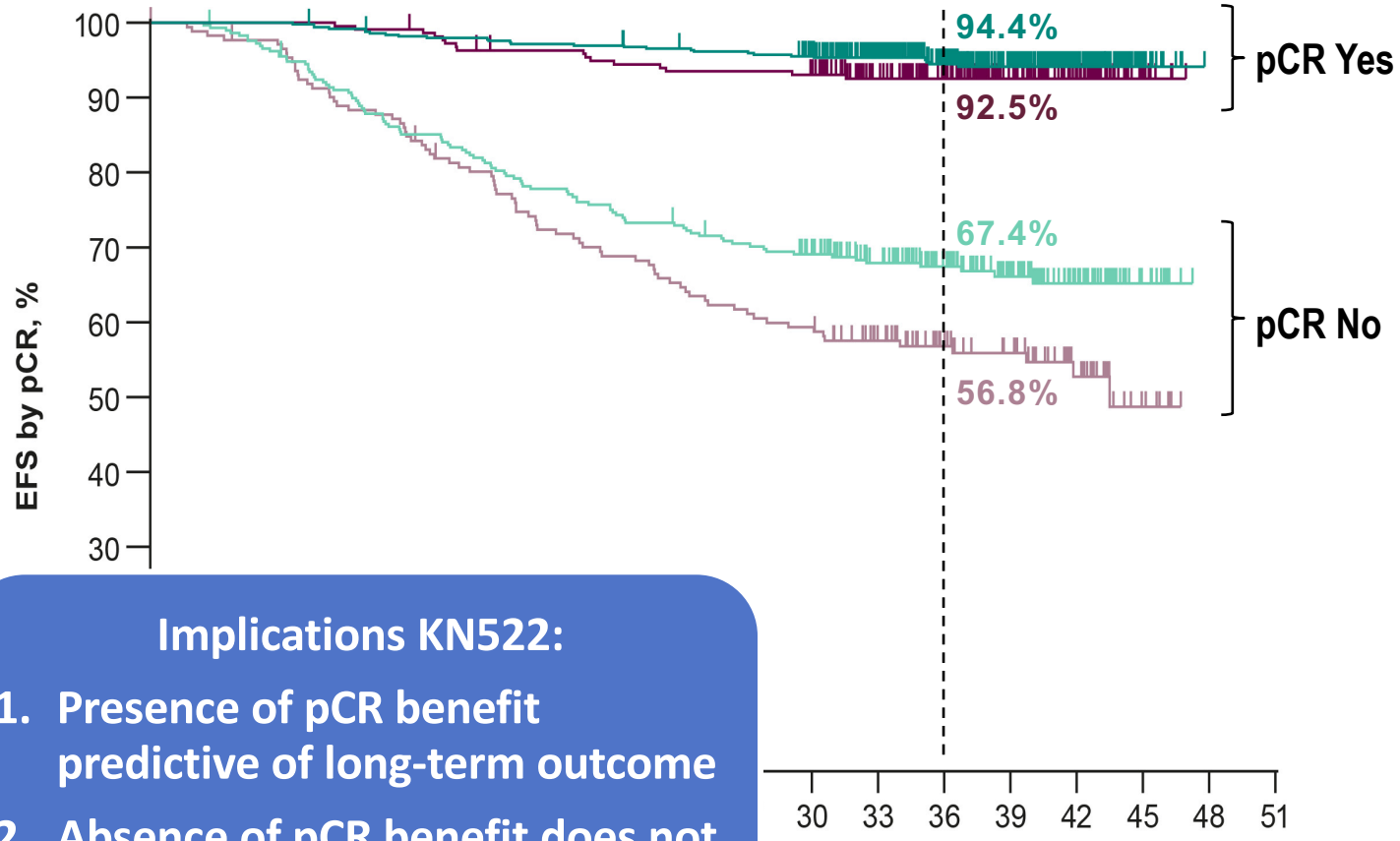
Schmid et al, NEJM 2022

[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.

Do patients with pCR need adjuvant pembrolizumab?

Is there a benefit from CIT beyond achieving a pCR

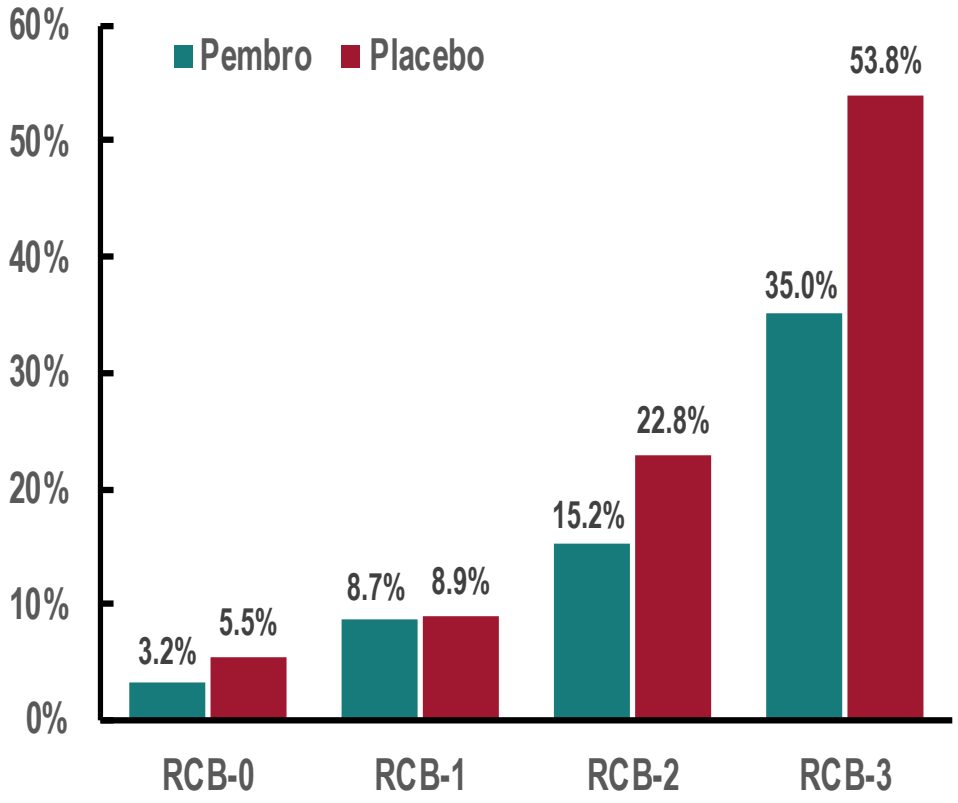
Event-free Survival by pCR



Implications KN522:

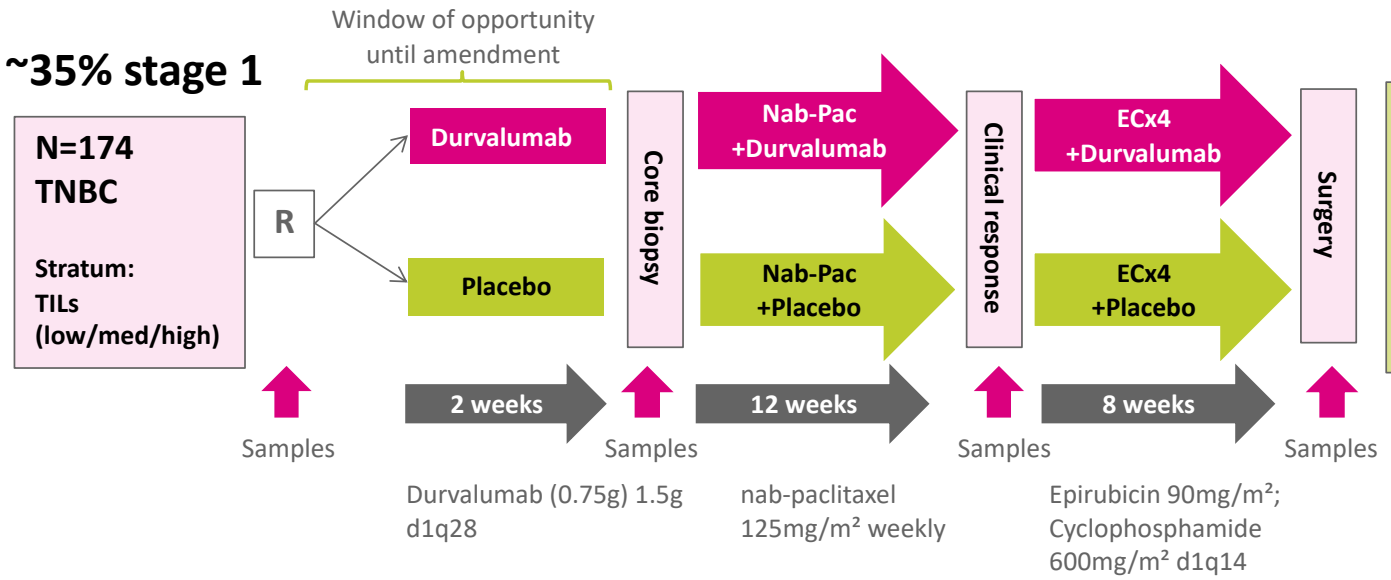
1. Presence of pCR benefit predictive of long-term outcome
2. Absence of pCR benefit does not rule out substantial benefit

Distant recurrences by RCB



Schmid et al, NEJM 2022; Pusztai, ASCO 2022

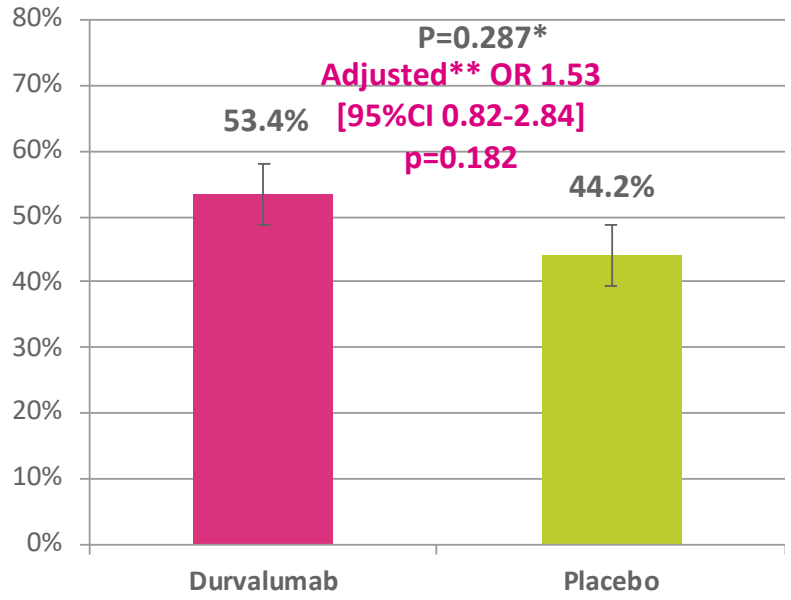
GeparNUEVO: Phase II Durvalumab Neoadjuvant Trial

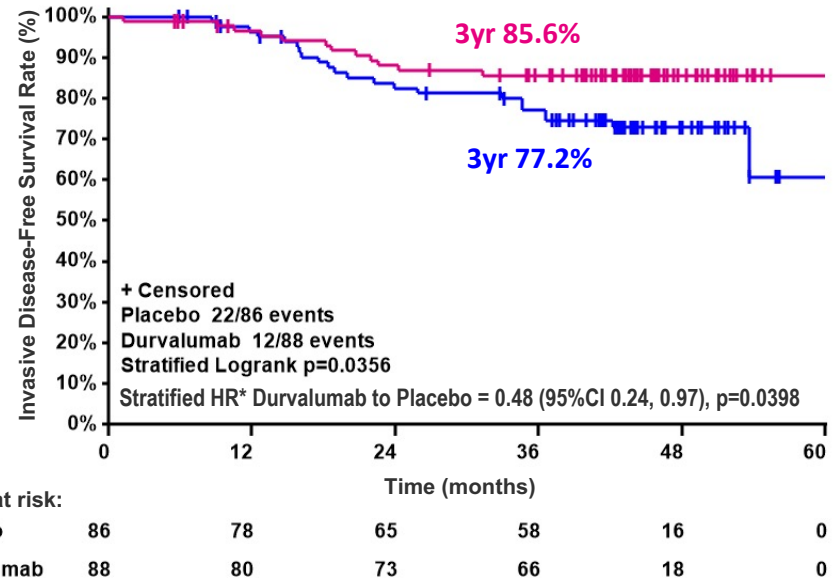


Primary endpoint: pCR (ypT0, ypN0)

Main secondary endpoints: iDFS, DDFS, OS

Primary endpoint: pCR – ypT0, ypN0





iDFS between arms

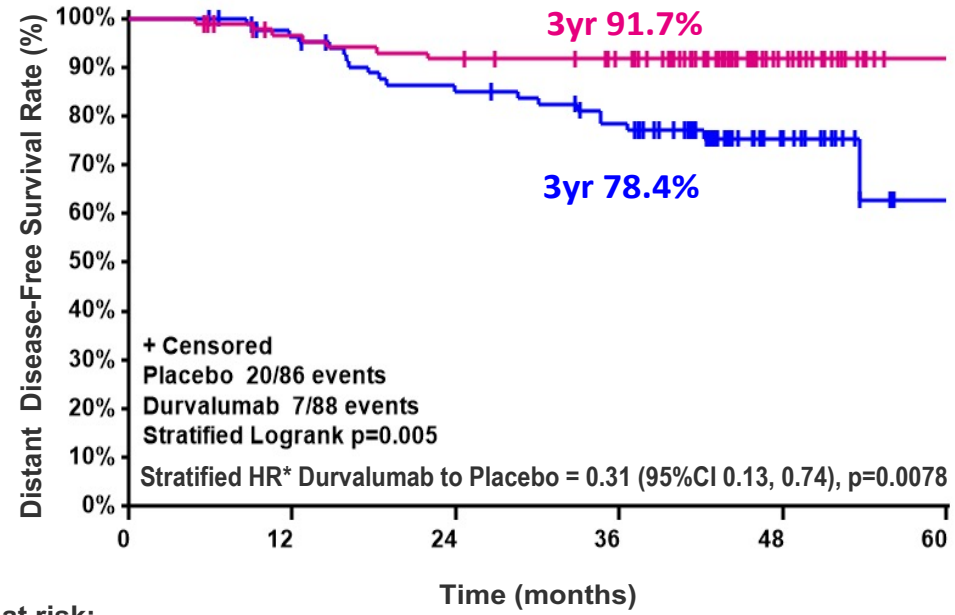
Median FU 43.7 months

* Stratified by sTILs

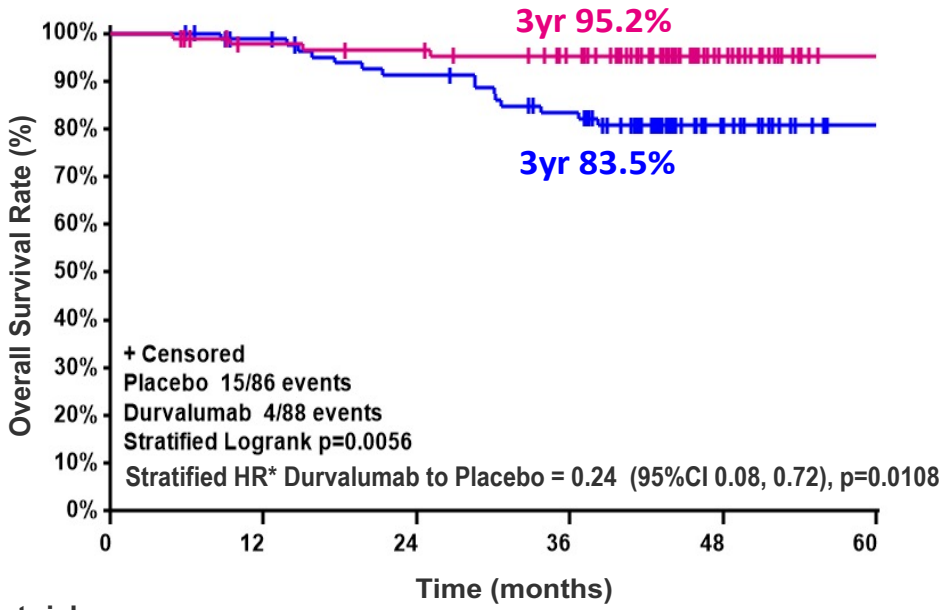
Loibl S, et al. Ann Oncol 2019; Loibl et al, ASCO 2021

Loibl et al, Annals Oncol 2022

DDFS

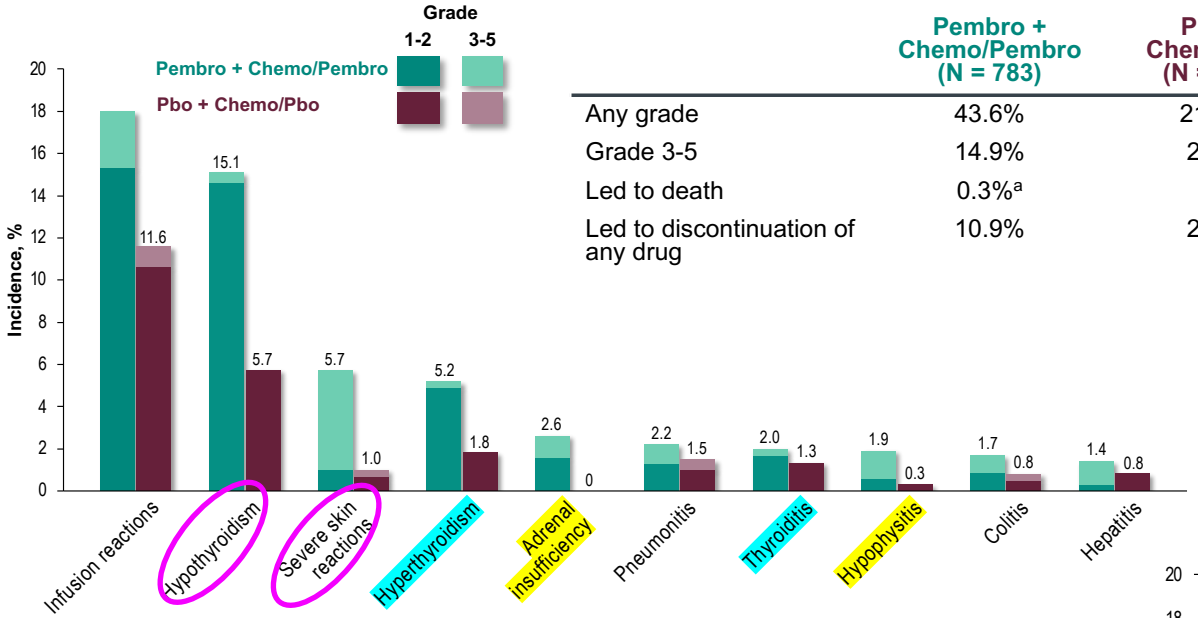


OS



Endpoint	Category	Durvalumab 3-year rates % (95%CI)	Placebo 3-year rates % (95%CI)	HR (durvalumab vs placebo) (95%CI)	Log-rank p-value
iDFS	Non-pCR	76.3% (59.3%, 86.9%)	69.7% (53.4%, 81.2%)	0.67 (0.29-1.54)	0.346
	pCR	95.5% (83.0%, 98.8%)	86.1% (69.8%, 94.0%)	0.22 (0.05-1.06)	0.038
DDFS	Non-pCR	84.3% (68.3%, 92.6%)	71.9% (55.8%, 83.0%)	0.48 (0.18-1.25)	0.124
	pCR	100% (100%, 100%)	86.1% (69.8%, 94.0%)	0.00 (0.00-.)*	0.005
OS	Non-pCR	92.0% (77.1%, 97.3%)	78.8% (63.2%, 88.4%)	0.30 (0.08-1.09)	0.053
	pCR	100% (100%, 100%)	88.9% (73.1%, 95.7%)	0.00 (0.00-.)*	0.024

Neoadjuvant and Adjuvant Immune-Related Toxicities KN-522

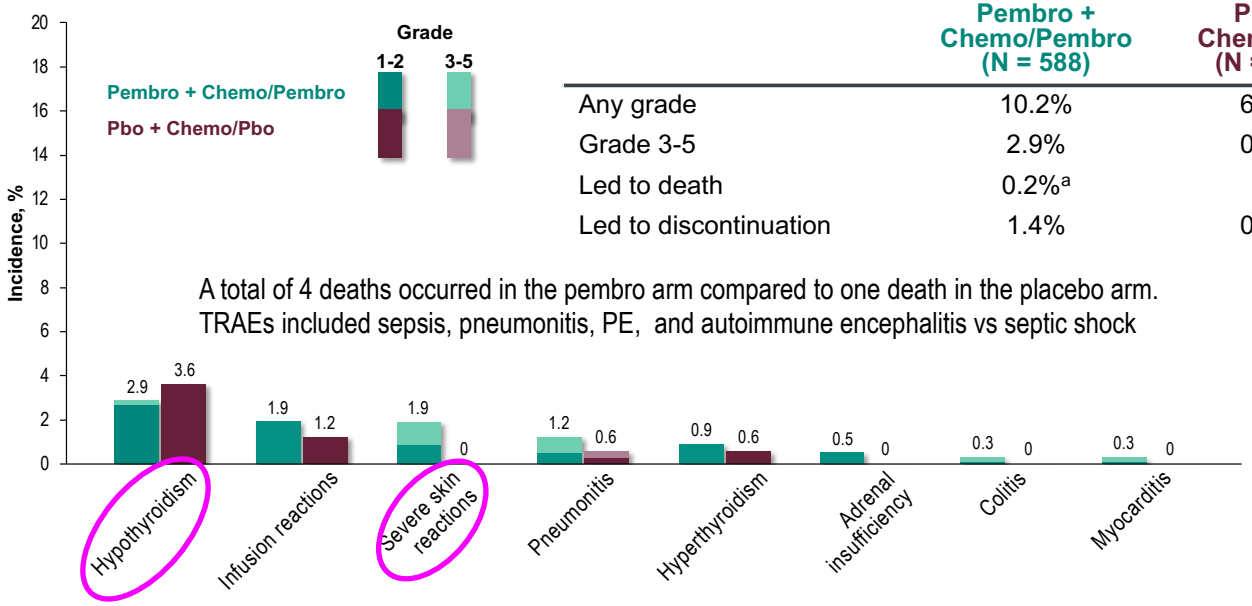


	Pembro + Chemo/Pembro (N = 783)	Pbo + Chemo/Pbo (N = 389)
Any grade	43.6%	21.9%
Grade 3-5	14.9%	2.1%
Led to death	0.3%[a]	0
Led to discontinuation of any drug	10.9%	2.6%

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

Neoadjuvant + chemo

Adjuvant



	Pembro + Chemo/Pembro (N = 588)	Pbo + Chemo/Pbo (N = 331)
Any grade	10.2%	6.0%
Grade 3-5	2.9%	0.3%
Led to death	0.2%[a]	0
Led to discontinuation	1.4%	0.3%

A total of 4 deaths occurred in the pembro arm compared to one death in the placebo arm.
TRAEs included sepsis, pneumonitis, PE, and autoimmune encephalitis vs septic shock

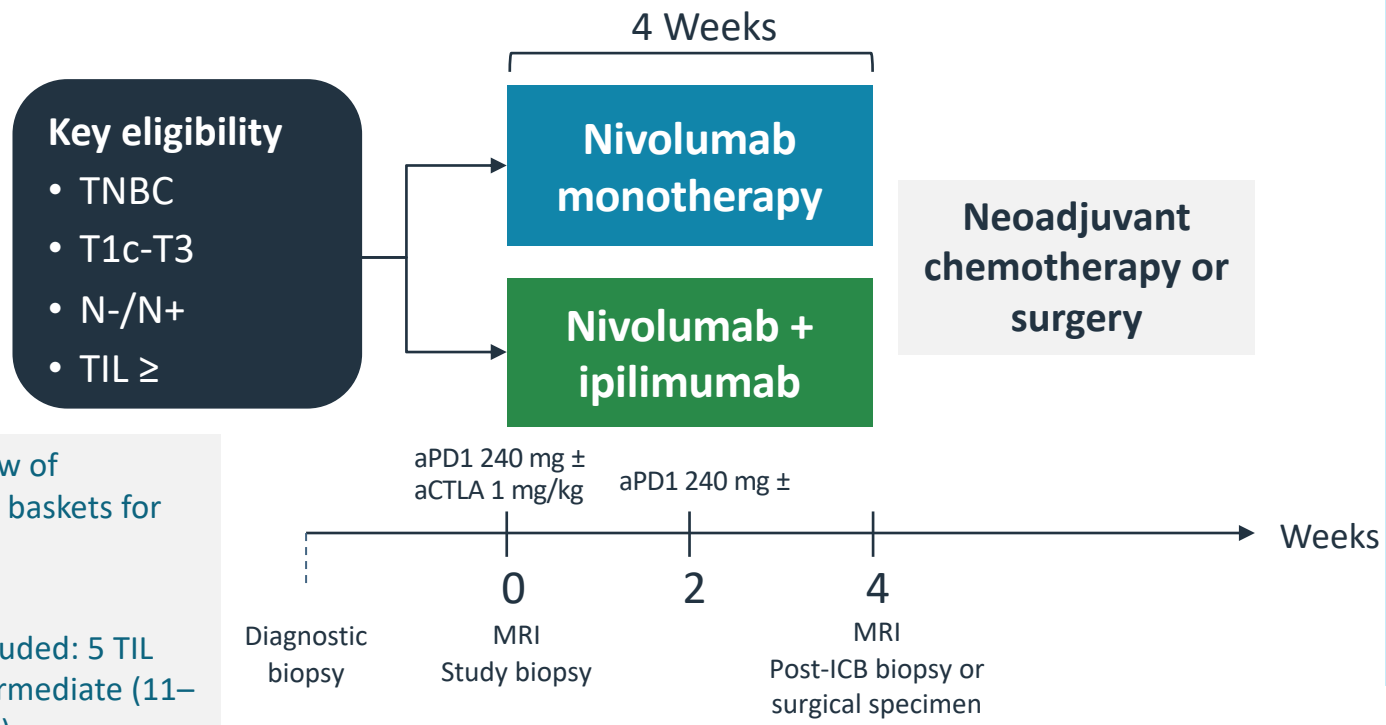
Schmid P et al. SABCS 2021

Do patients with pCR need adjuvant pembrolizumab?

Planned ALLIANCE trial of adjuvant pembrolizumab vs not in pts with pCR following preop chemotherapy + pembrolizumab regimen:

OptimICE-pCR Trial

BELLINI (first results): Nivolumab and ipilimumab in early stage TNBC with tumor-infiltrating lymphocytes



- Nonrandomized window of opportunity study with baskets for nivolumab and nivolumab/ipilimumab
- Each basket (n=15) included: 5 TIL low (5–10%), 5 TIL intermediate (11–49%), 5 TIL high (≥ 50%)

Primary endpoint:

- 2-fold increase in CD8 and/or IFNy after 4 weeks treatment

Secondary endpoints:

- Safety
- Radiological responses
- Translational analyses

Statistics

- Simon's two-stage design, expansion to stage II allowed if at least 5 out of 15 patients show a 2-fold increase in CD8 and/or IFNy

Primary endpoint result: 2-fold increase in CD8 (IHC) and/or IFNy (gene expression):

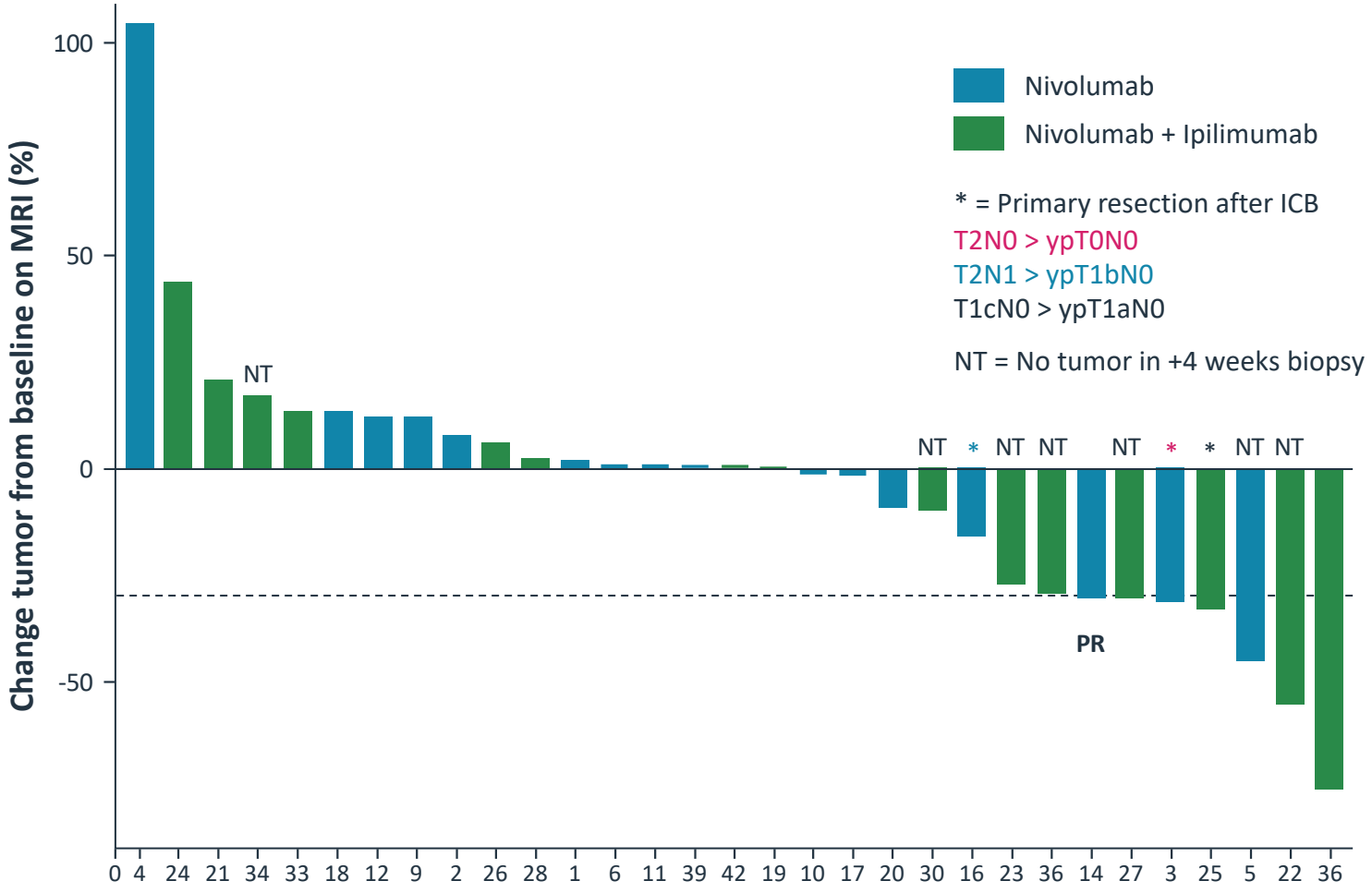
- Nivolumab: 8 (53.3%)
- Nivolumab + ipilimumab: 9 (60.0%)

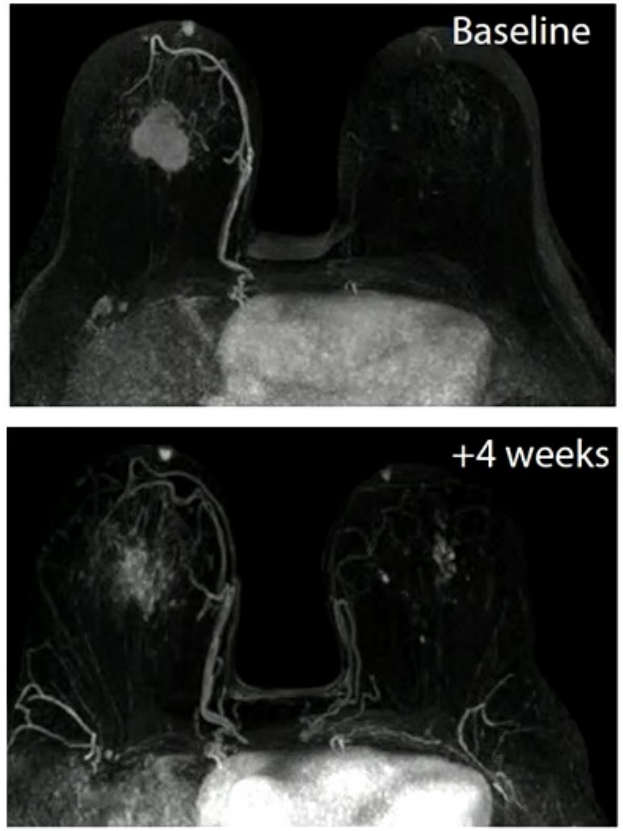
Basket expansion to stage II allowed if ≥30% of patients showed immune activation: both cohorts met the criterion

Tumors very high I CD8/IFNy at baseline, less likely to have 2-fold increase

Nederlof I, et al. ESMO 2022. Abstract LBA13

BELLINI (first results): MRI and pathological response

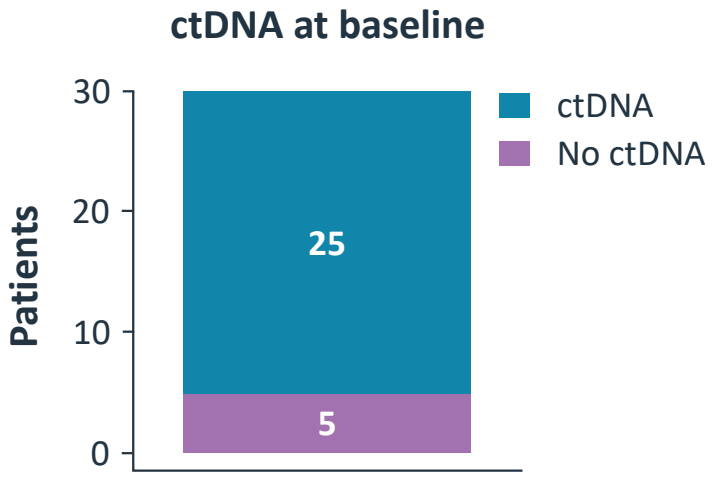


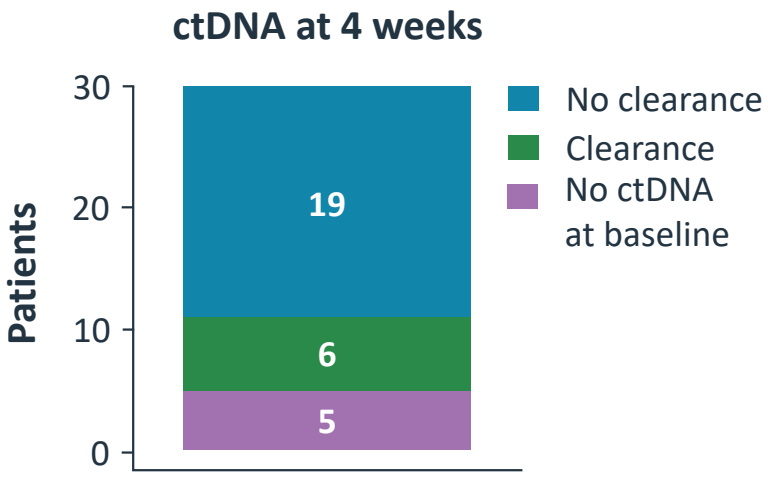


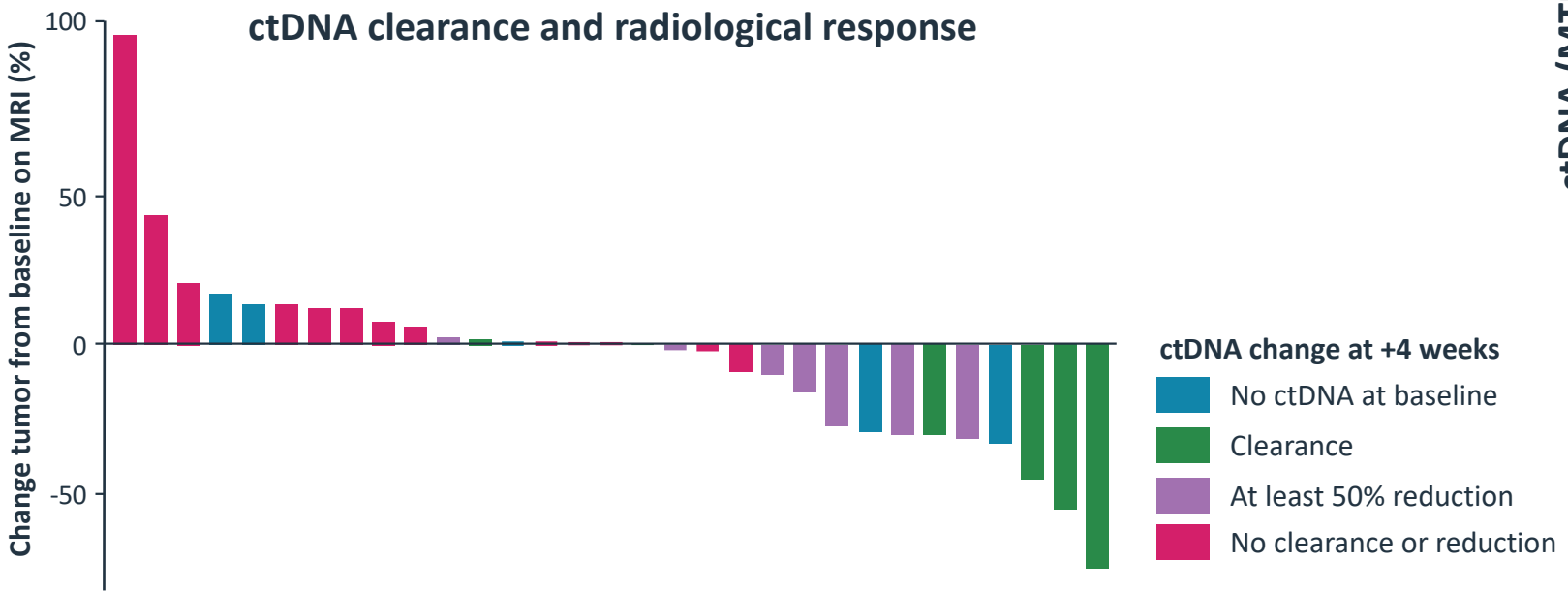
MRI changes after 2 cycles of nivolumab in a patient with pCR

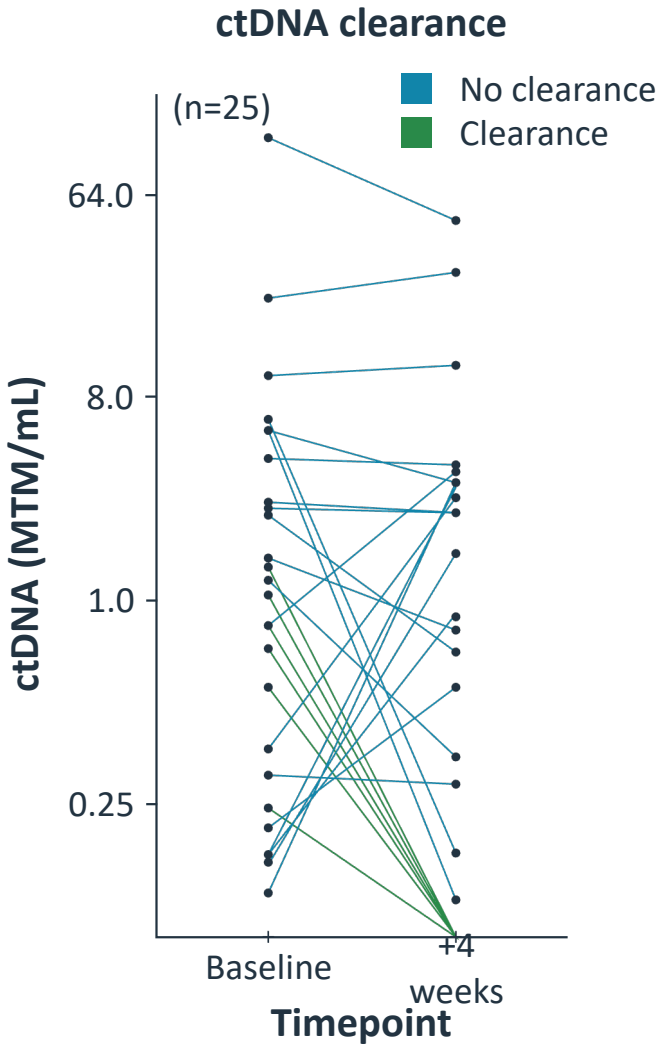
Nederlof I, et al. ESMO 2022. Abstract LBA13

BELLINI (first results): ctDNA clearance after 4 weeks





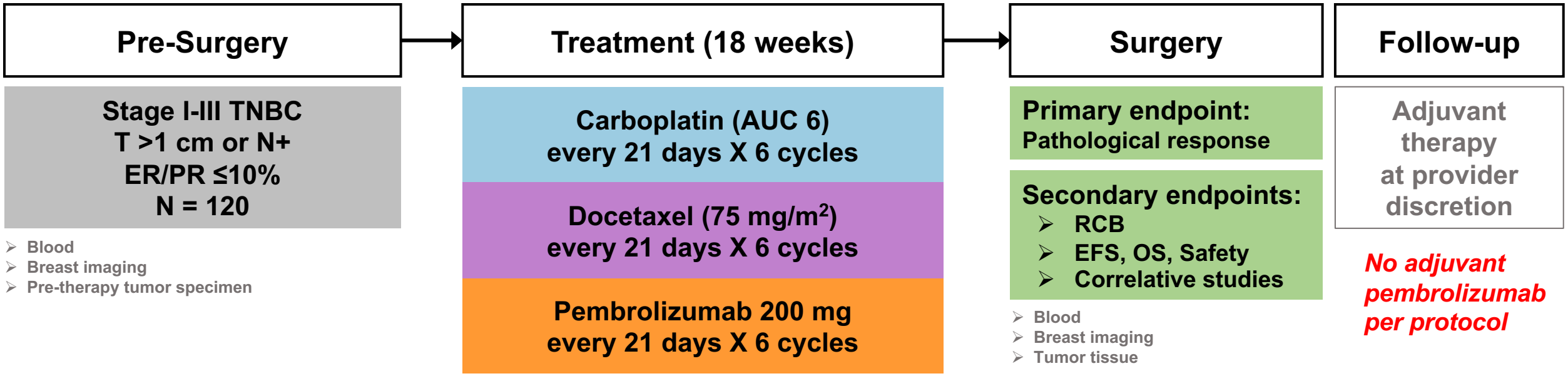




Nederlof I, et al. ESMO 2022. Abstract LBA13

De-Escalating or Escalating Neo/Adjuvant Therapy for Stage II/III TNBC

Neoadjuvant Phase II Study of Pembrolizumab and Carboplatin plus Docetaxel in Triple Negative Breast Cancer (NeoPACT)



Sites: University of Kansas and Baylor University Medical Center

NCI Designated Cancer Center

NCI Community Oncology Research Program
A program of the National Cancer Institute of the National Institutes of Health

THE UNIVERSITY OF KANSAS CANCER CENTER

PRESENTED BY:
Priyanka Sharma, M.D.

Results: Patient characteristics

115 eligible patients enrolled from 9/2018-1/2022
109 evaluable for pathologic response

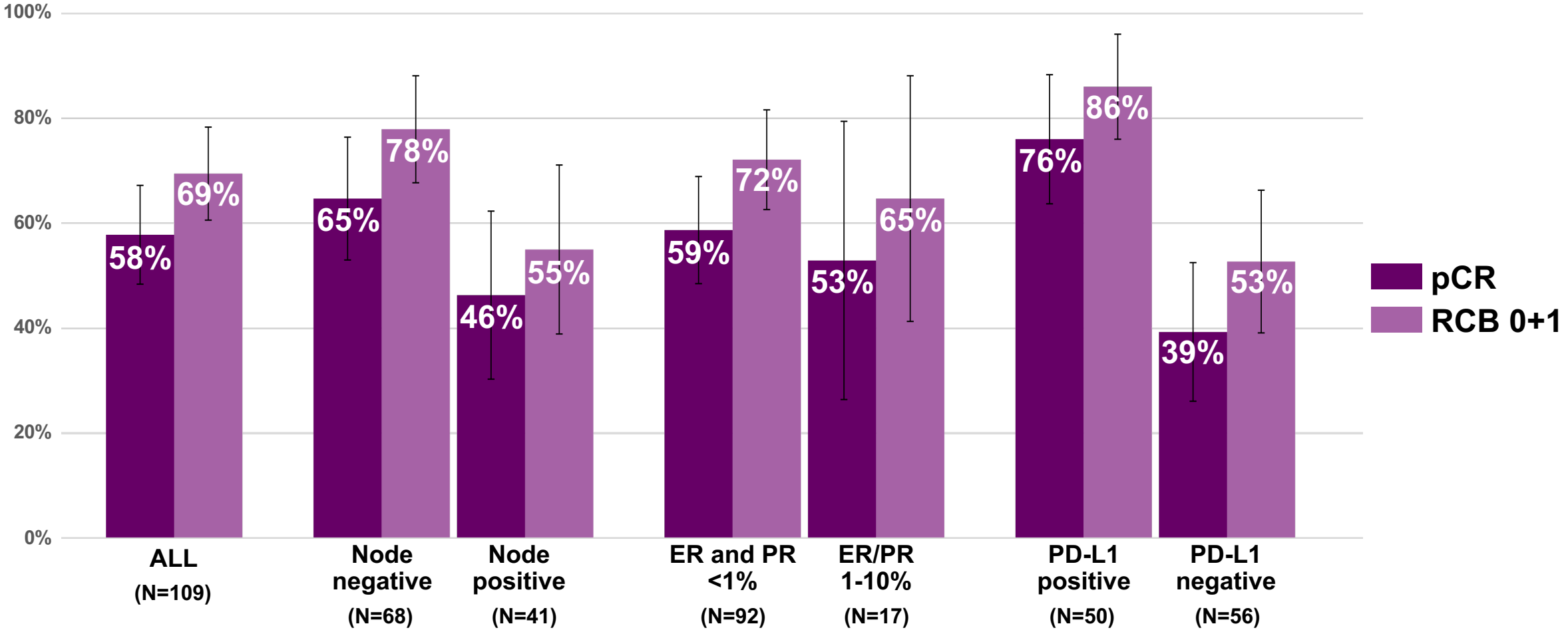
Characteristic – N (%)		N=115
Age at diagnosis, yrs – median (range)		50 (27-70)
Race	White	84 (73%)
	Black	20 (17%)
	Other	10 (9%)
Ethnicity[a]	Non-Hispanic	111 (97%)
	Hispanic	3 (3%)
Menopausal status	Pre	58 (50%)
	Post	57 (50%)
Germline *BRCA1/2* mutation	Yes	9 (8%)
	No	95 (83%)
	Unknown	11 (10%)
T stage	1	21 (18%)
	2	73 (63%)
	3	21 (18%)
Nodal status	Negative	70 (61%)
	Positive[b]	45 (39%)
TNM stage	I	14 (12%)
	II	86 (75%)
	III	15 (13%)
ER/PR (IHC)	ER and PR <1%	97 (84%)
	ER and/or PR 1-10%	18 (16%)

Characteristic – N (%), cont.		N=115
sTILs, % – median (range)[c]		20 (1-95)
sTILs[c]	<30%	56 (52%)
	≥30%	51 (48%)
PD-L1 (CPS ≥10)[d]	Positive	52 (46%)
	Negative	60 (54%)
Surgery type[e]	Lumpectomy	54 (48%)
	Mastectomy	58 (52%)
Adjuvant radiation therapy[f]		80 (74%)
Adjuvant immunotherapy[f]		5 (5%)
Adjuvant chemotherapy[f]		38 (35%)
Anthracycline + cyclophosphamide (AC)		18 (17%)
Capecitabine		11 (10%)
AC and capecitabine		7 (6%)
Other		2 (2%)

[a] Ethnicity data available for n=114.
[b] Subjects with clinically/radiologically abnormal axillary lymph nodes were required to have pathological confirmation of N+ disease with image-guided biopsy/fine needle aspiration.
[c] sTILs data available for n=107.
[d] PD-L1 data available for n=112.
[e] Surgery data available for n=112.
[f] Adjuvant therapy data available for n=109.

NeoPACT required a more stringent criterion for N+ status (biopsy/FNA) compared to other contemporary neoadjuvant chemoimmunotherapy studies, where N+ status was determined clinically

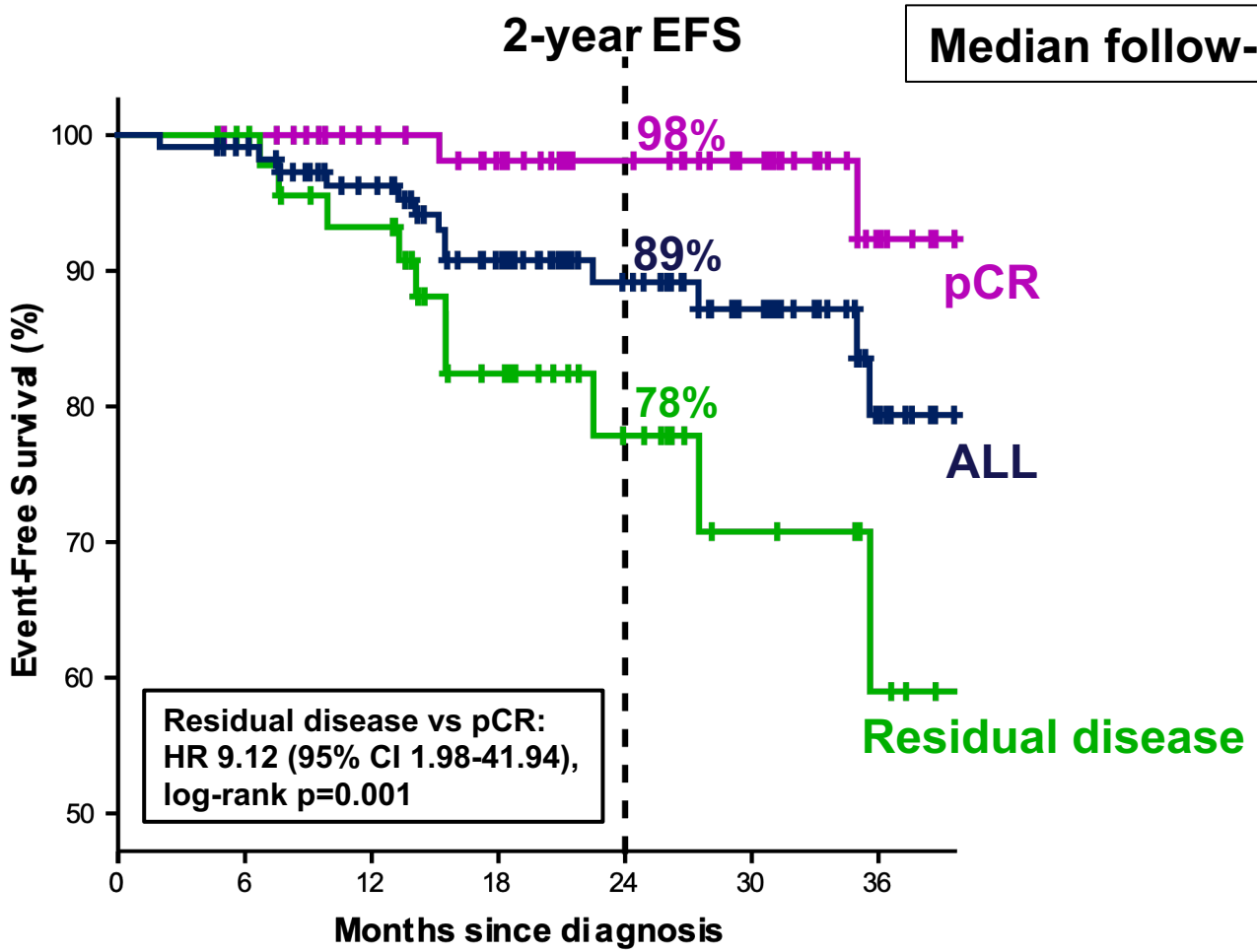
RESULTS: Pathologic response



- No patients had disease progression during neoadjuvant treatment.
- Among patients with stage II-III disease and ER & PR IHC <1%, pCR and RCB 0+1 rates were 59% and 69%, respectively.
- pCR in TNM stage I, II, and III disease was 69%, 59%, and 43%, respectively.

Error bars represent 95% binomial confidence intervals

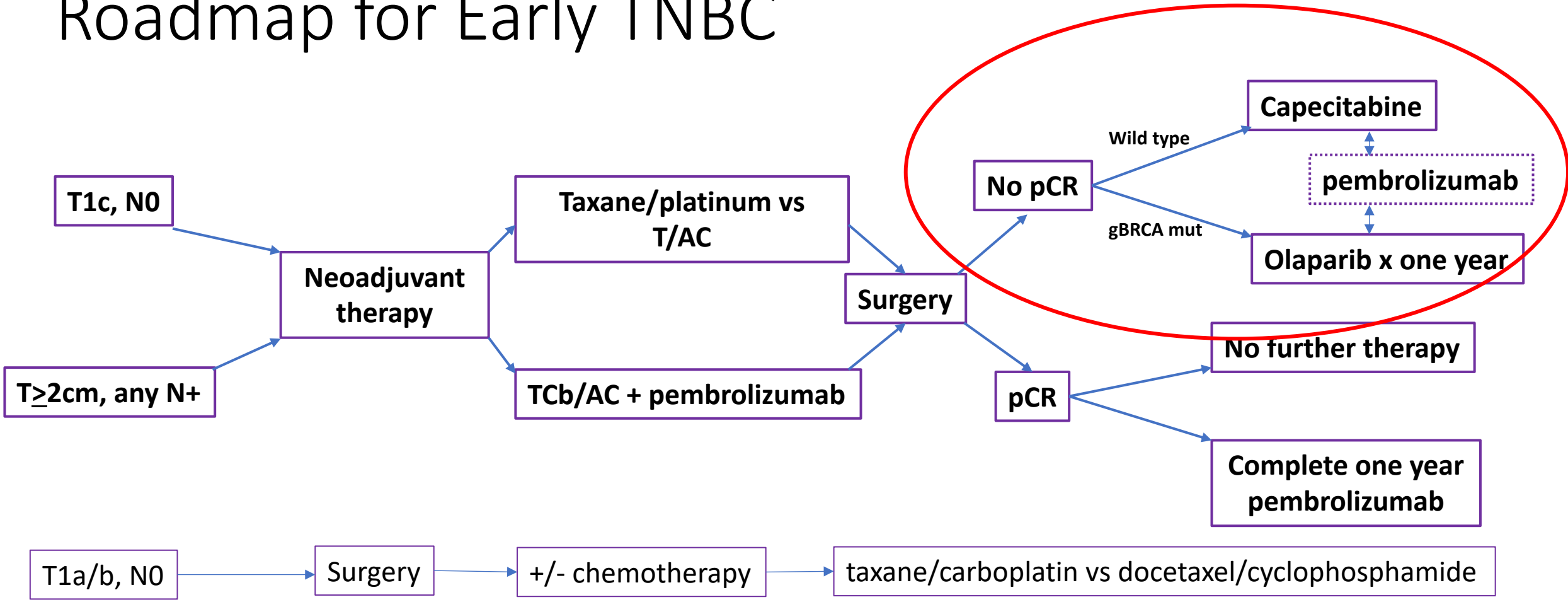
Event-free survival



	Number at risk						
All	113	108	95	75	54	37	18
pCR	63	62	55	48	38	28	13
Residual disease	49	46	40	27	16	9	5

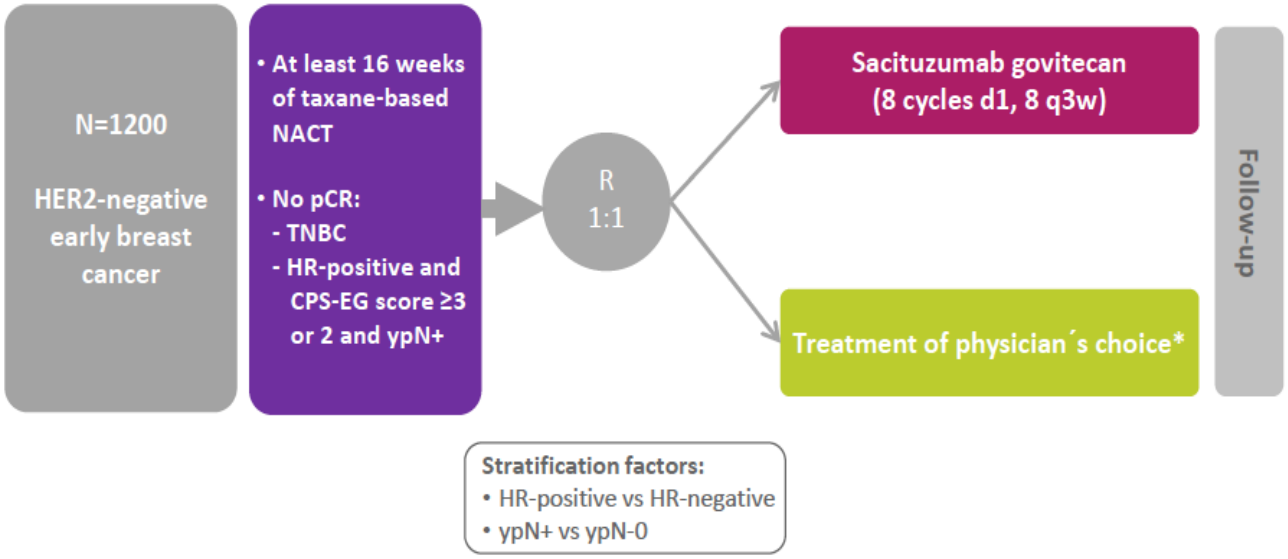
Survival analysis includes all patients in the ITT population except for N=2 who are awaiting surgery

Roadmap for Early TNBC



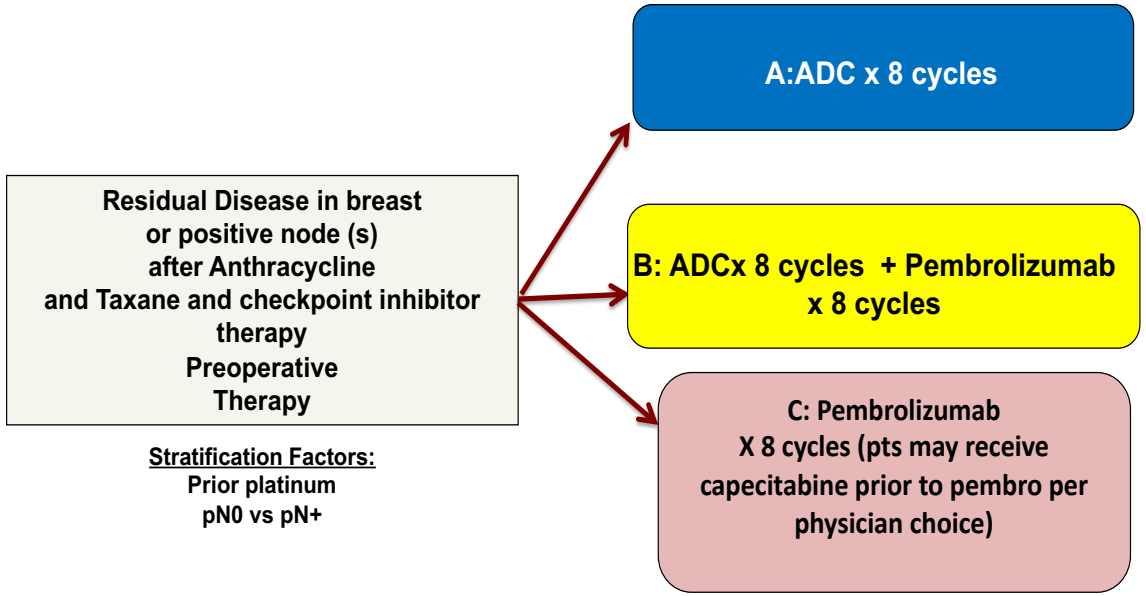
- Unknown whether adjuvant capecitabine or olaparib improves outcomes in pts with RD post-preop chemotherapy/pembrolizumab, alone or in combination with adjuvant pembrolizumab
- Safety is acceptable with pembrolizumab with olaparib or with capecitabine
- Reasonable to combine adjuvant pembrolizumab + capecitabine or olaparib in high risk pts with RD

GBG: SASCIA Post-Neoadjuvant Trial



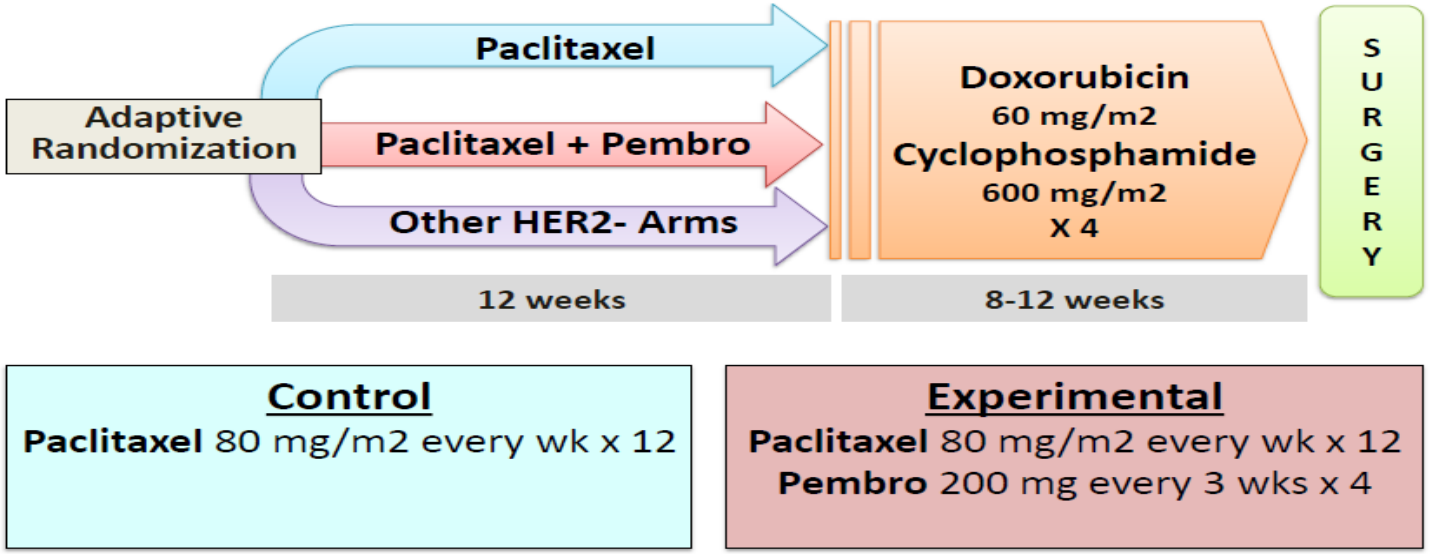
*Capecitabine (8 cycles) or platinum-based chemotherapy (8 cycles) or observation.
Background therapy: in patients with HR-positive breast cancer, endocrine-based therapy will be administered according to local guidelines.

Potential Future Trial



Courtesy of Sara Tolaney; Alliance for Clinical Trials in Oncology

I-SPY2: Pembrolizumab Graduated for Efficacy in HER2 Neg Cohorts

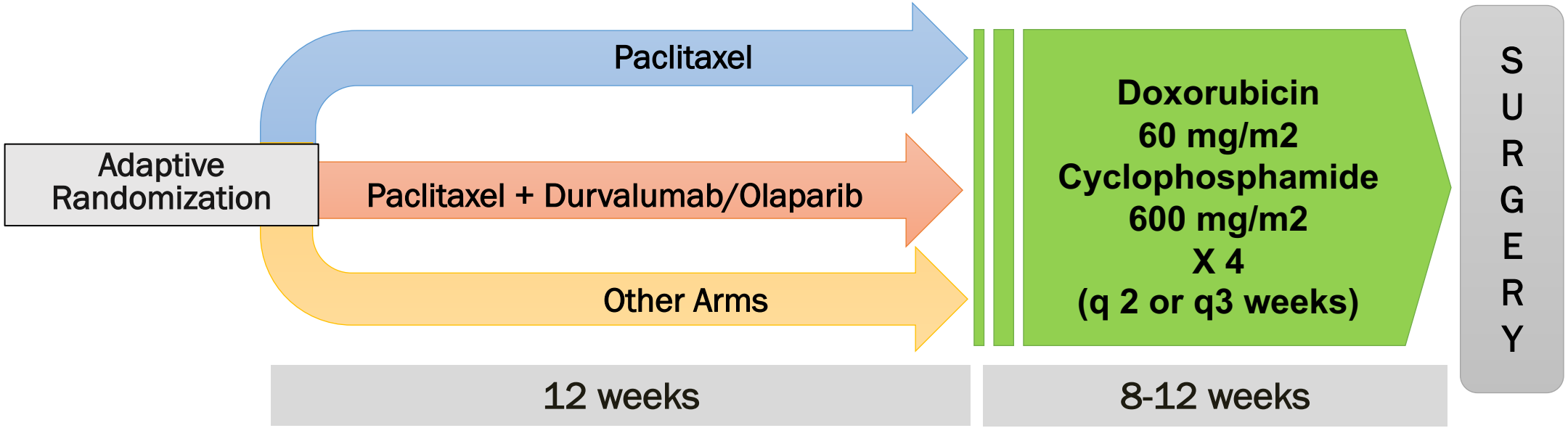


Final Predictive Probability of Success in Phase III Testing by Signature

Biomarker Signature	Estimated Rate of Pathologic Complete Response (95% Probability Interval)		Probability, %	
	Pembrolizumab (n = 69)	Control (n = 181)	Probability Superior to Control	Predictive Probability of Success in Phase 3 Trial
ERBB2 negative	44 (33-55)	17 (11-23)	>99.9	98.5
HR positive/*ERBB2* negative	30 (17-43)	13 (7-19)	>99.9	99.6
TNBC	60 (44-75)	22 (13-30)	99.6	83.4

Nanda et al, JAMA Oncol 2020

I-SPY 2 TRIAL Schema



Control Arm

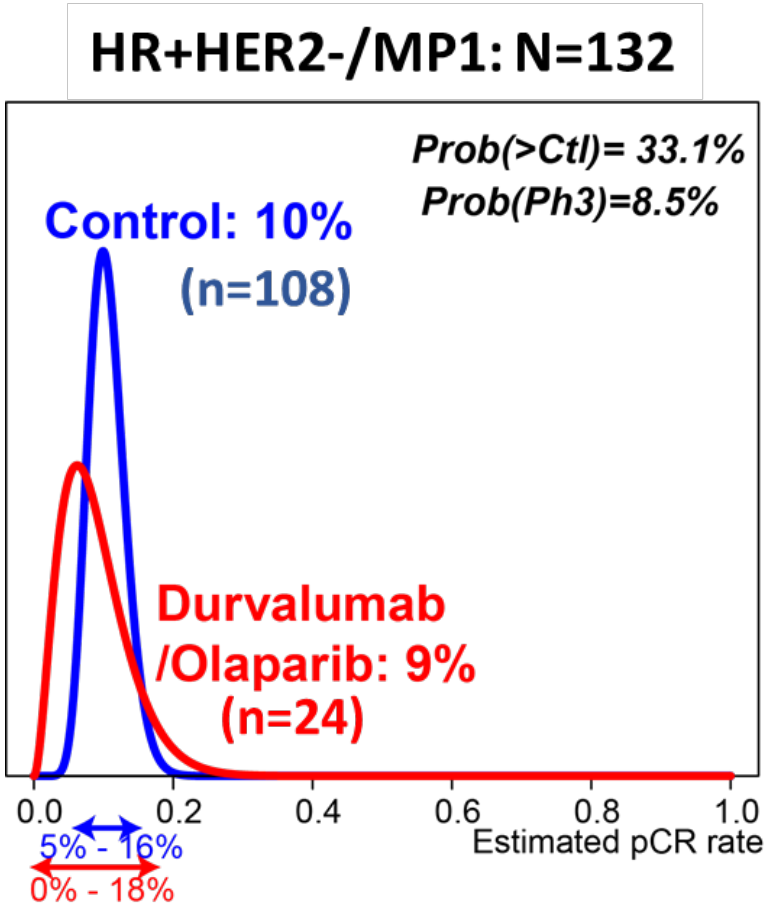
Paclitaxel 80 mg/m2 every wk x 12

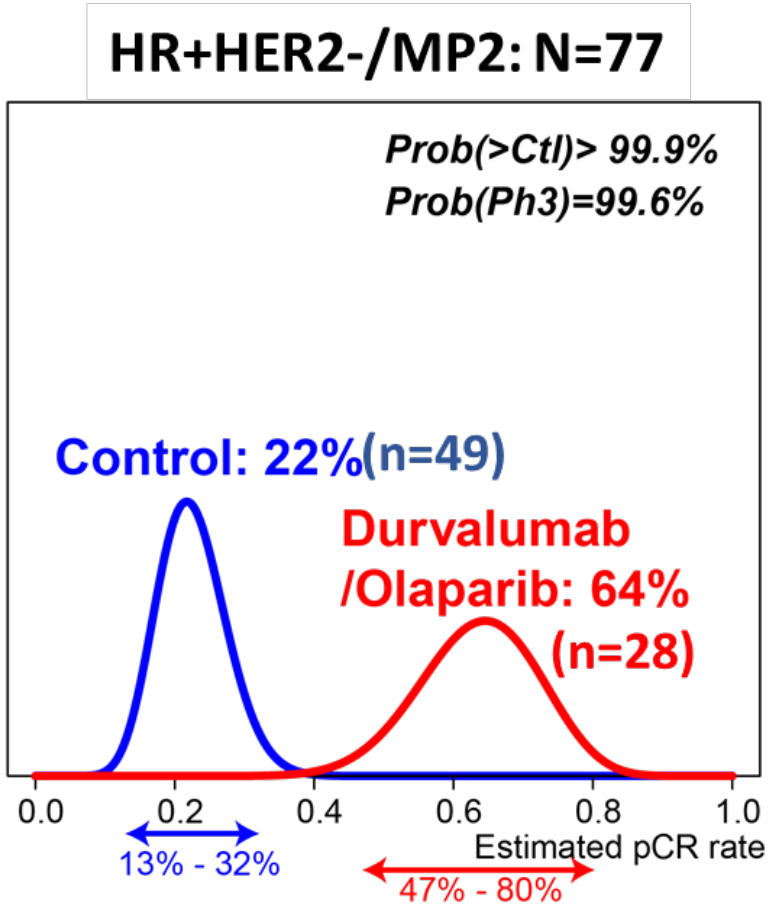
Experimental Arm

Paclitaxel 80 mg/m2 every wk x 12
Durvalumab 1500 mg every 4 wks x 3
Olaparib 100 mg twice daily wks 1-11

Puzstai, Cancer Cell, 2021

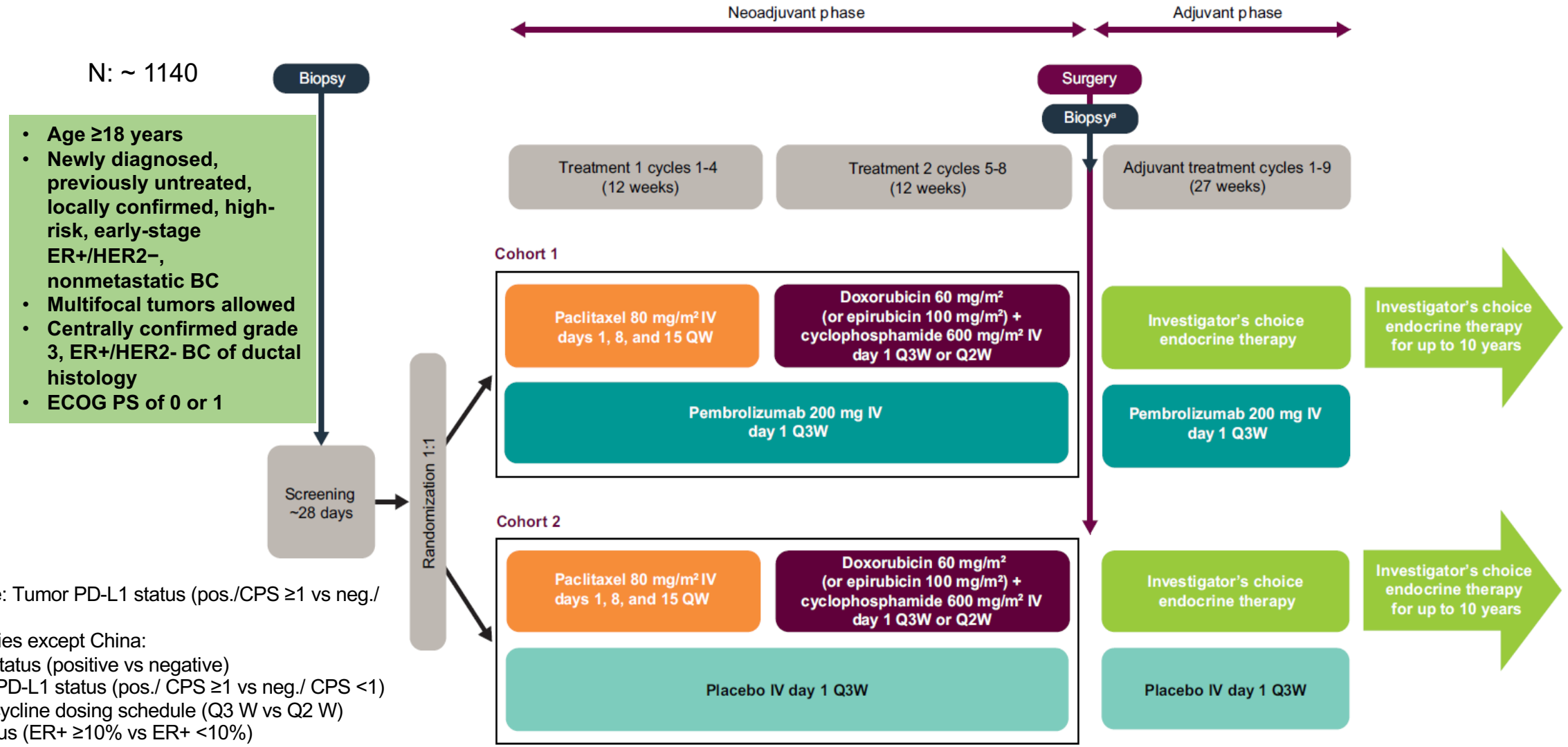
HR+ with “Ultra-high (MP2)” MammaPrint Scores Benefit From Durvalumab/Olaparib





Puzstai, Cancer Cell, 2021

KEYNOTE-756 is a randomized, double-blind, placebo-controlled, phase 3 study in patients with newly diagnosed, previously untreated, high-risk (based on clinicopathological criteria), early-stage ER+/HER2− breast cancer



Stratification

- Eastern Europe: Tumor PD-L1 status (pos./CPS ≥1 vs neg./ CPS <1)
- All other countries except China:
  - Nodal status (positive vs negative)
  - Tumor PD-L1 status (pos./ CPS ≥1 vs neg./ CPS <1)
  - Anthracycline dosing schedule (Q3 W vs Q2 W)
  - ER status (ER+ ≥10% vs ER+ <10%)
- China is not further substratified

IV, intravenously; QW, every week; Q2W, every 2 weeks; Q3W, every 3 weeks.
[a]Optional biopsy to be used for biomarker studies.

Increasing Effectiveness of ICIs in Metastatic TNBC

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

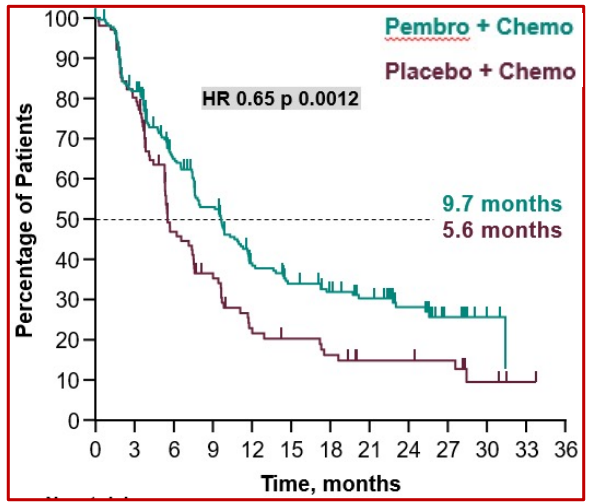
R 2:1

- 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

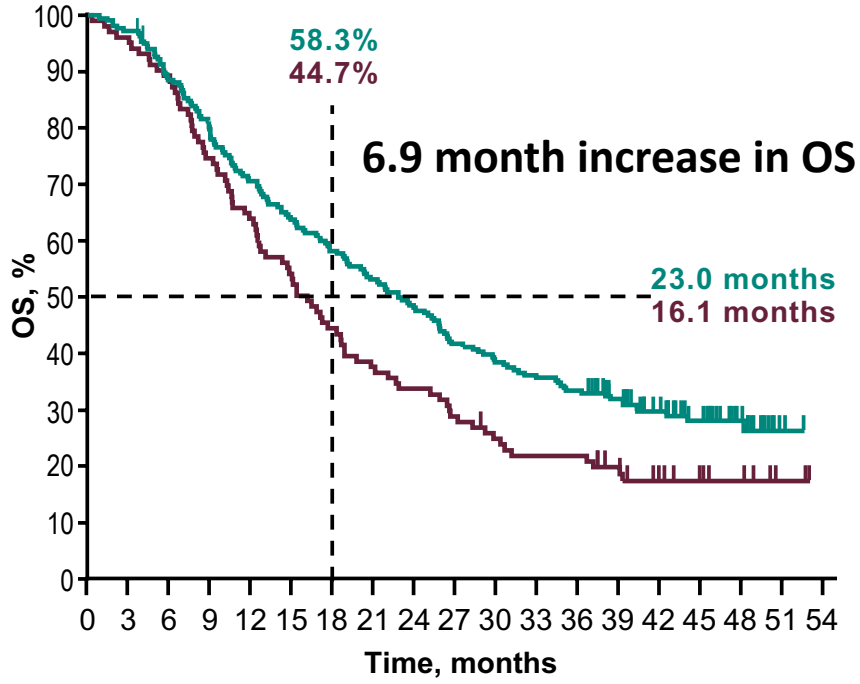


Prespecified *P* value boundary of 0.00411 met

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%		



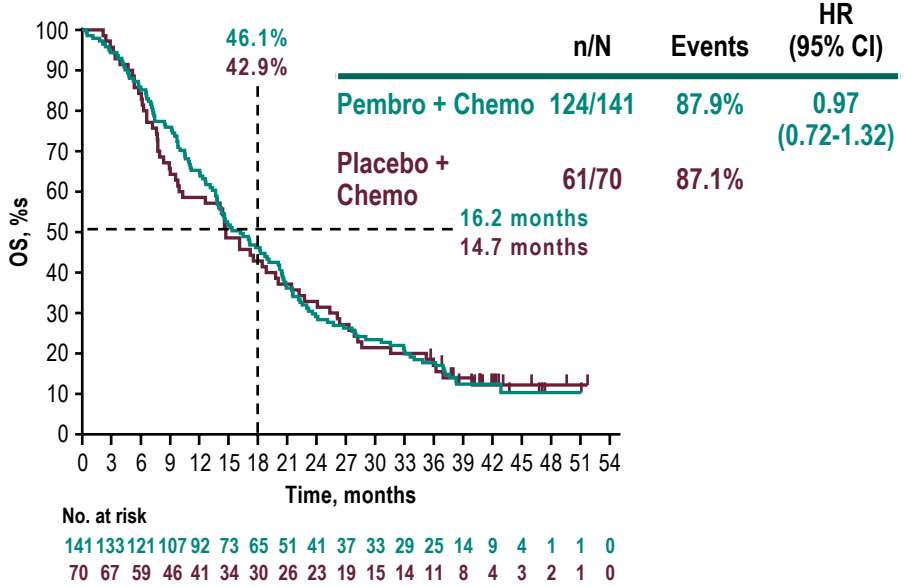
No. at risk

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

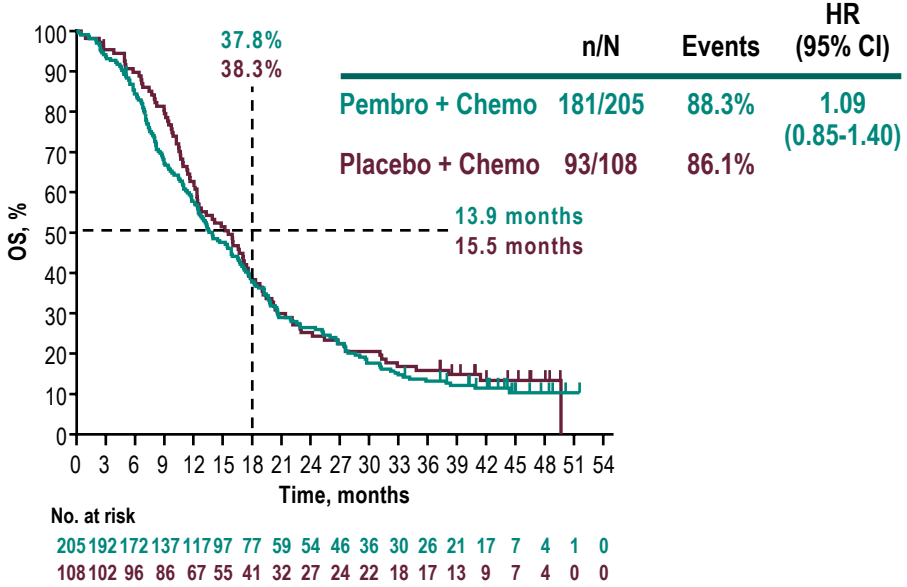
KN-355 Overall Survival in PD-L1 CPS Subgroups

PD-L1 CPS <1



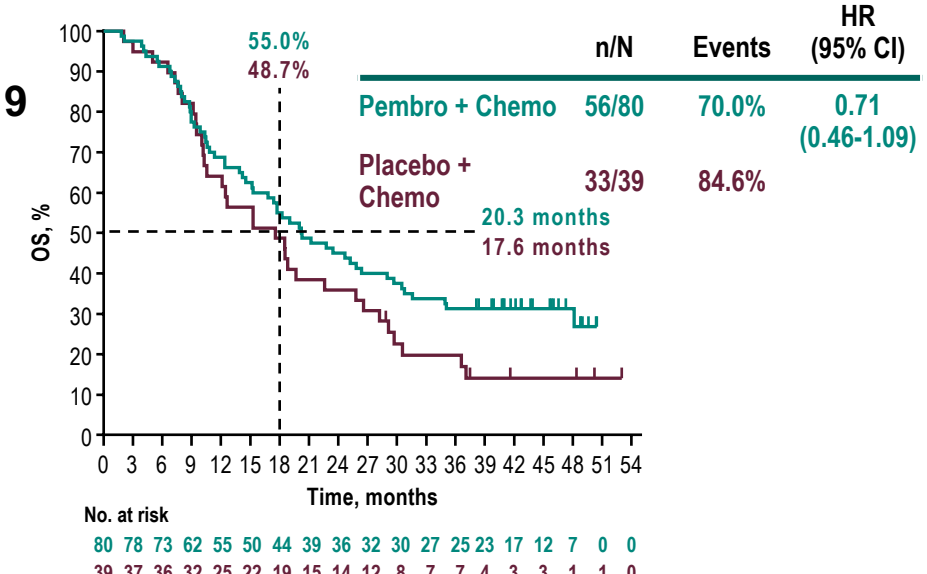
	n/N	Events	HR (95% CI)
Pembro + Chemo	124/141	87.9%	0.97 (0.72-1.32)
Placebo + Chemo	61/70	87.1%	

PD-L1 CPS 1-9



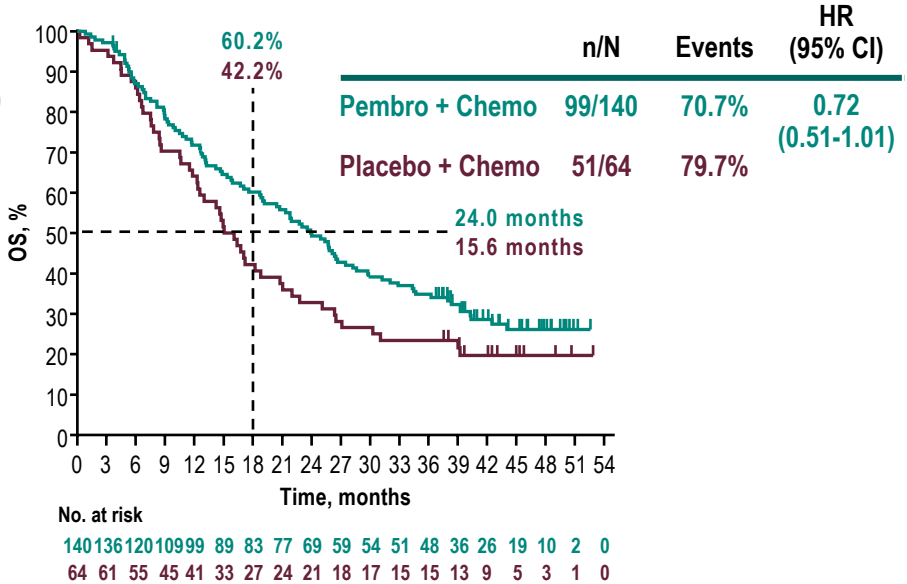
	n/N	Events	HR (95% CI)
Pembro + Chemo	181/205	88.3%	1.09 (0.85-1.40)
Placebo + Chemo	93/108	86.1%	

PD-L1 CPS 10-19



	n/N	Events	HR (95% CI)
Pembro + Chemo	56/80	70.0%	0.71 (0.46-1.09)
Placebo + Chemo	33/39	84.6%	

PD-L1 CPS ≥20



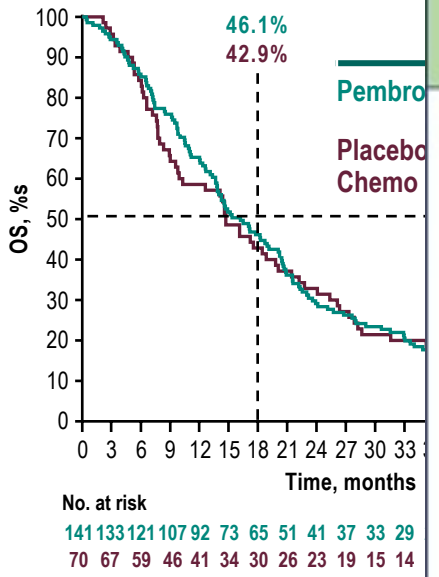
	n/N	Events	HR (95% CI)
Pembro + Chemo	99/140	70.7%	0.72 (0.51-1.01)
Placebo + Chemo	51/64	79.7%	

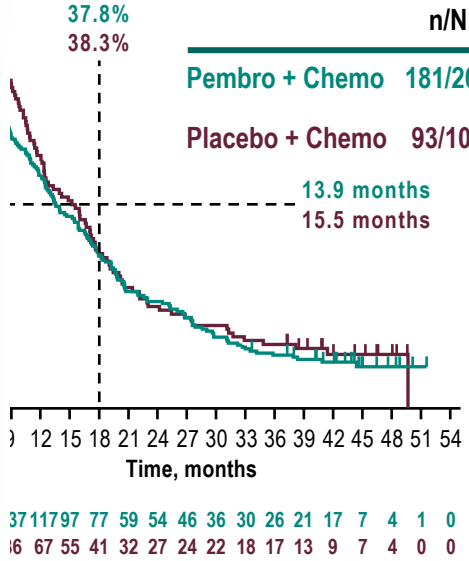
Data cutoff: June 15, 2021.

KN-355 Overall

Subgroups

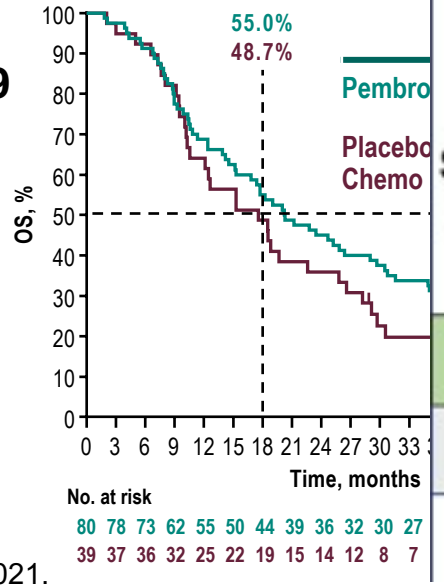
PD-L1 CPS <1

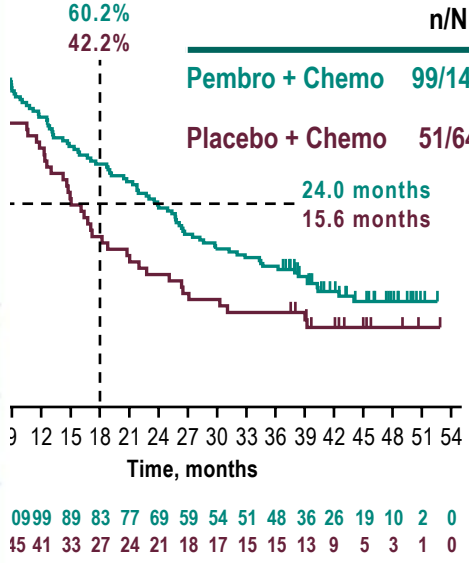




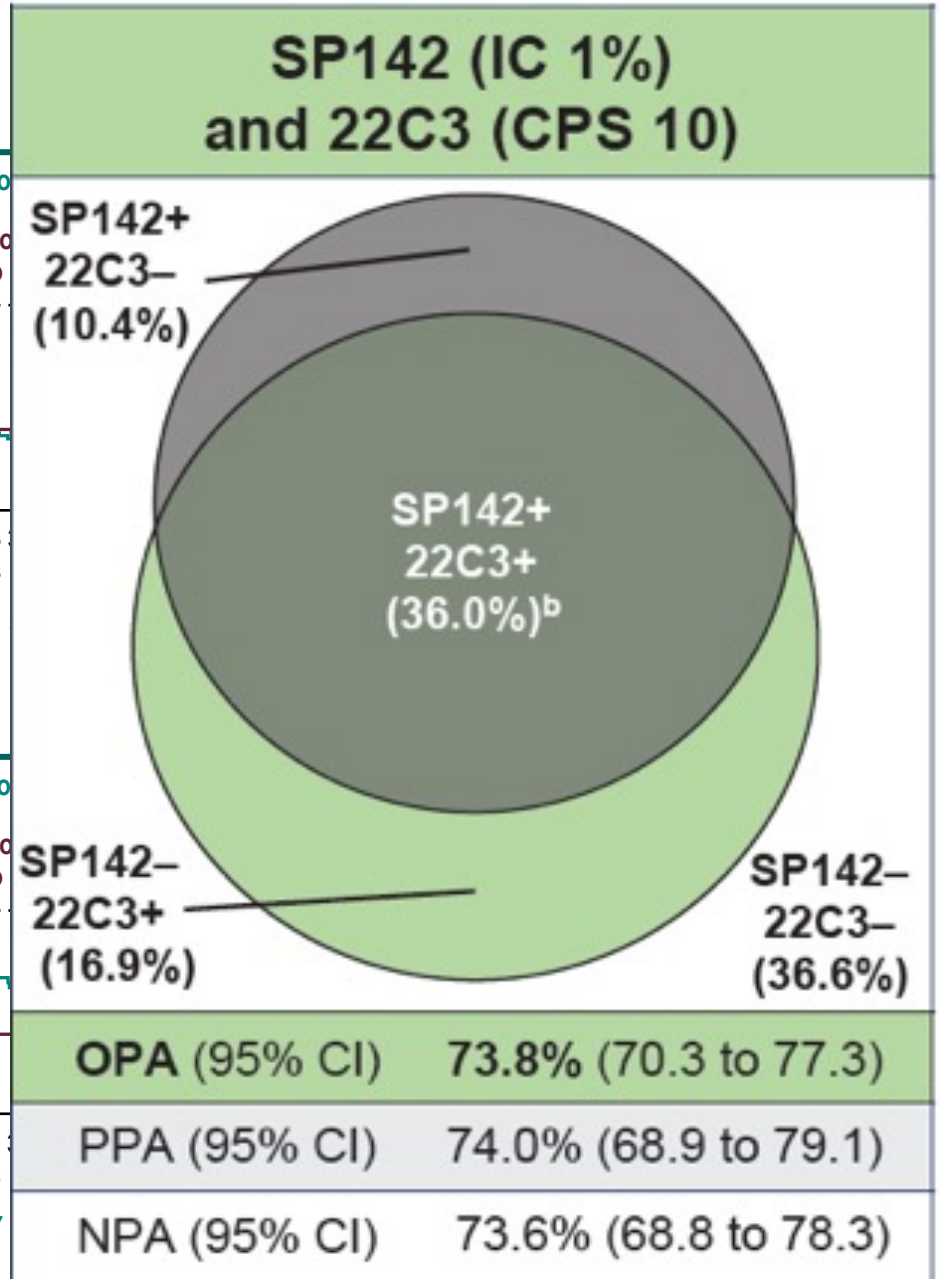
	n/N	Events	HR (95% CI)
Pembro + Chemo	181/205	88.3%	1.09 (0.85-1.40)
Placebo + Chemo	93/108	86.1%	

PD-L1 CPS 10-19





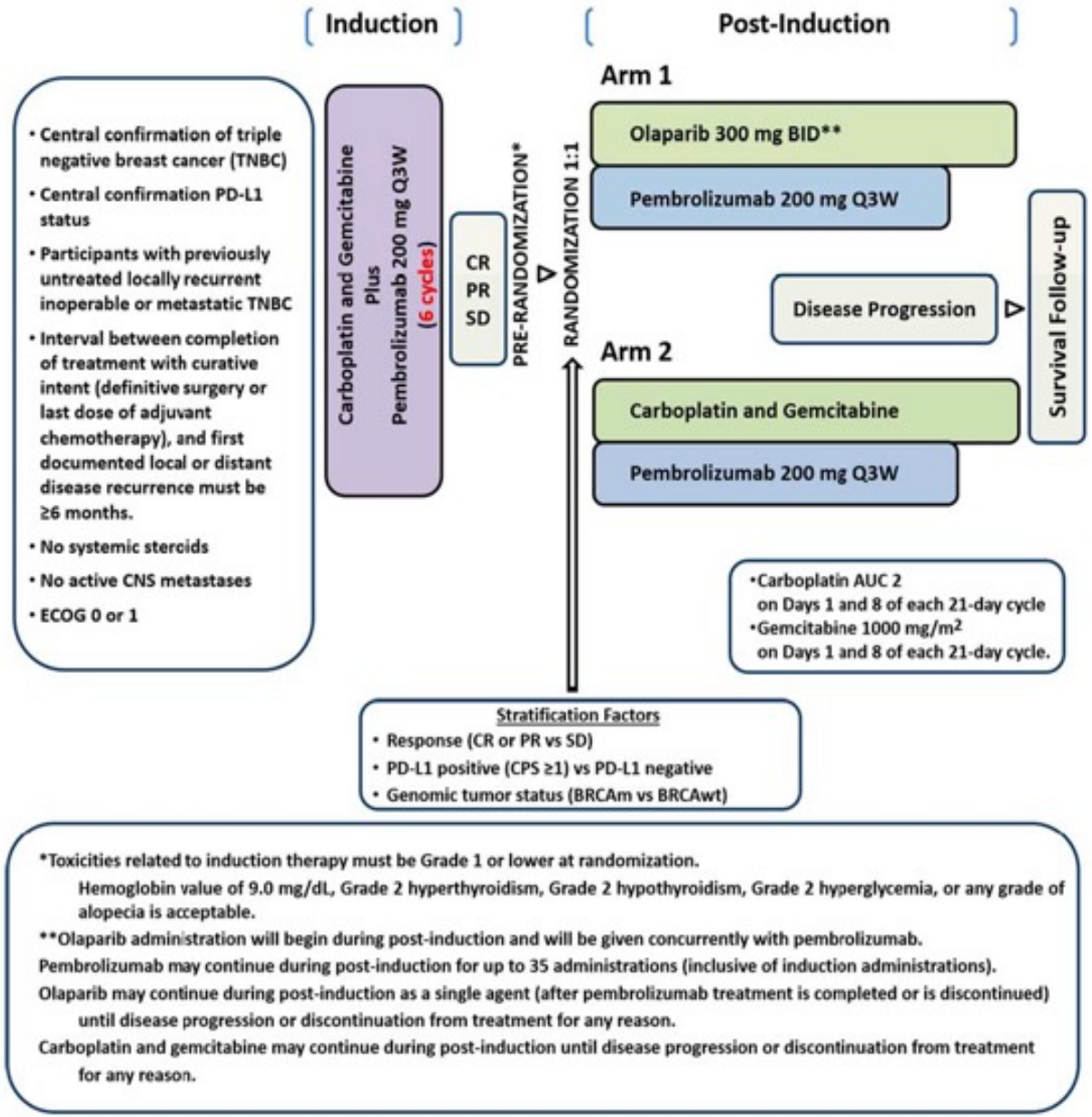
	n/N	Events	HR (95% CI)
Pembro + Chemo	99/140	70.7%	0.72 (0.51-1.01)
Placebo + Chemo	51/64	79.7%	



Data cutoff: June 15, 2021.

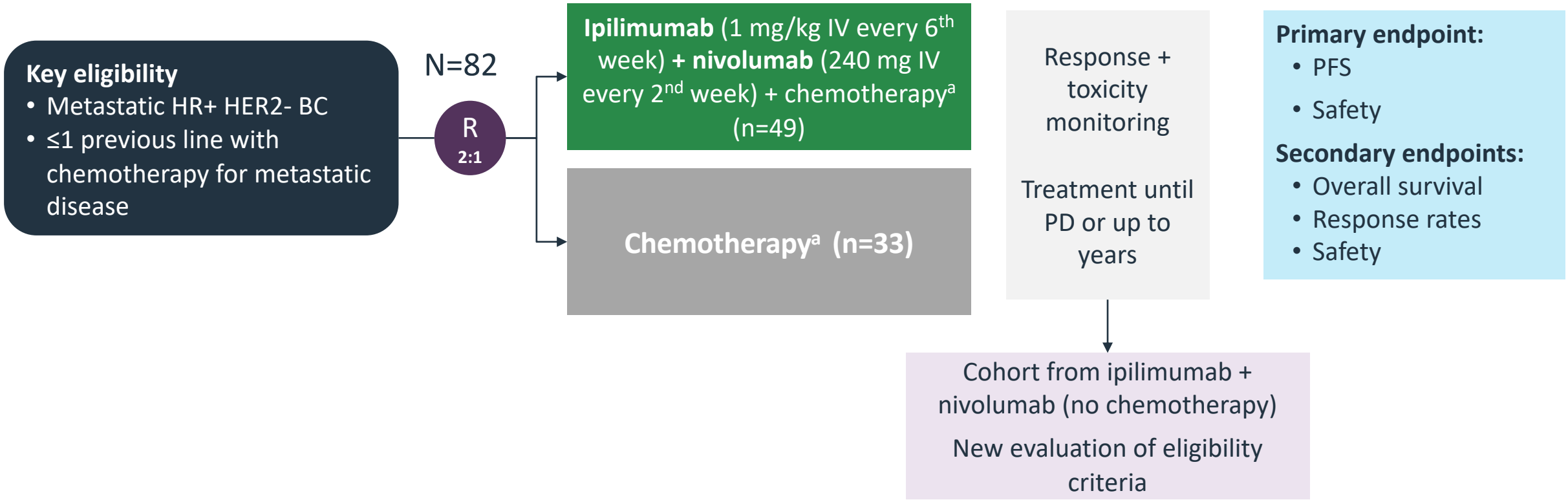
Rugo, JNCI 2021

PARP Inhibition May Increase Immunogenicity of TNBC with ICI



KEYLYNK-009

ICON (Phase 2b): chemotherapy + ipilimumab and nivolumab in HR+ mBC

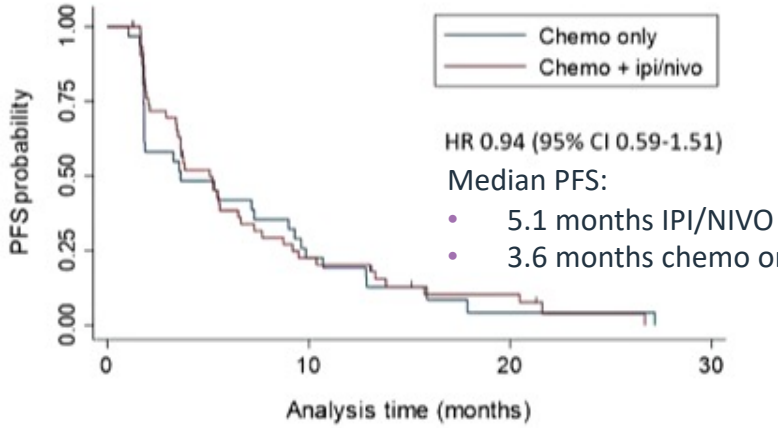


[a]Pegylated liposomal doxorubicin (PDL; 200 mg/m2 IV Q2W + oral cyclophosphamide (50 mg/day, 2/4 weeks

)Kyte JA, et al. ESMO 2022. Abstract 215MO

ICON (Phase 2b): Efficacy (PP population[a])

Progression-free survival

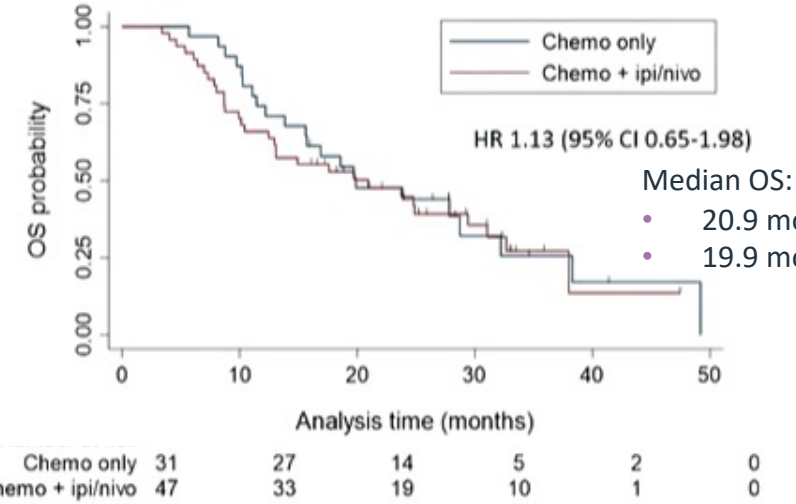


HR 0.94 (95% CI 0.59-1.51)

Median PFS:

- 5.1 months IPI/NIVO + chemo
- 3.6 months chemo only

Overall survival

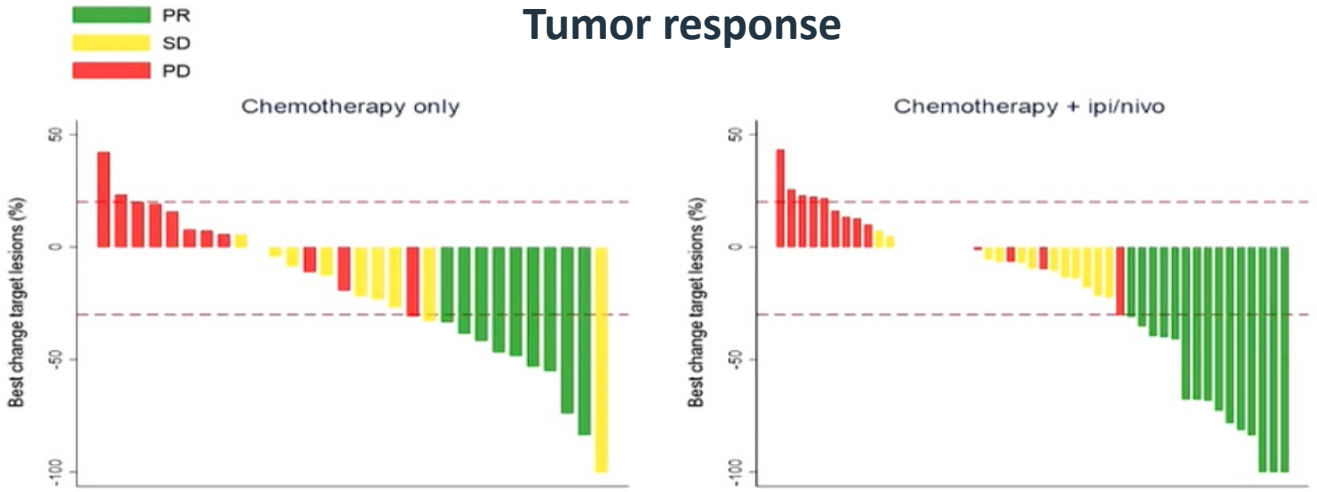


HR 1.13 (95% CI 0.65-1.98)

Median OS:

- 20.9 months IPI/NIVO + chemo
- 19.9 months chemo only

Tumor response



Treatment response

	IPI/NIVO + chemo (n=47)	Chemo only (n=31)
OR, % (95% CI)	32 (20, 46)	29 (16,47)
Clinical benefit,[b] % (95% CI)	55 (41, 69)	48 (32, 65)

[a]Patients who received ≥2 doses of PLD and nivoluab (arm B), ≥700 mg cyclophosphamide, ≥1 dose of ipilimumab (arm B). [b]CR/PR or SD until Week 24 evaluation

Kyte JA, et al. ESMO 2022. Abstract 215MO

Challenges with ICI Therapy for Breast Cancer

- Patient selection: preop pembrolizumab for Stage II/III – who doesn't benefit and who is cured with chemotherapy alone?
- May be able to de-escalate preop chemotherapy with Txt/Cb + pembrolizumab – randomized trial needed
- Reasonable to combine adjuvant pembrolizumab + olaparib or capecitabine in high risk pts with RD post-KN522 preop regimen
- Adjuvant pembrolizumab needed post-pCR? - randomized trial planned
- High grade (MP high 2) HR+ HER2- pts may benefit from preop ICI – KN-756 trial
- 22C3 IHC CPS testing needed to select PD-L1+ mTNBC pts for pembrolizumab
- Can olaparib replace chemotherapy in combination with pembrolizumab for PDL1+ metTNBC? KEYLYNK-009 trial