Breast Cancer Immunotherapy

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Celebrating Women Chair in Breast Cancer

Baylor University Medical Center

Texas Oncology

US Oncology

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

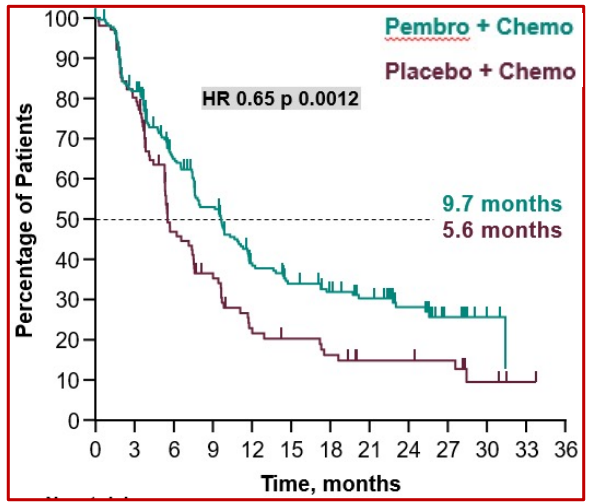
R 2:1

- 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

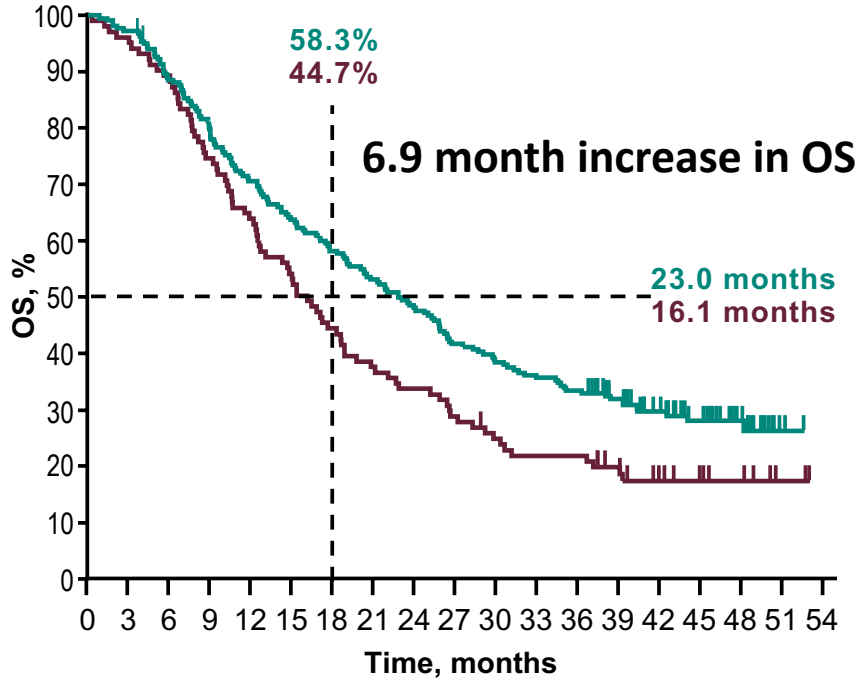


Prespecified *P* value boundary of 0.00411 met

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%		



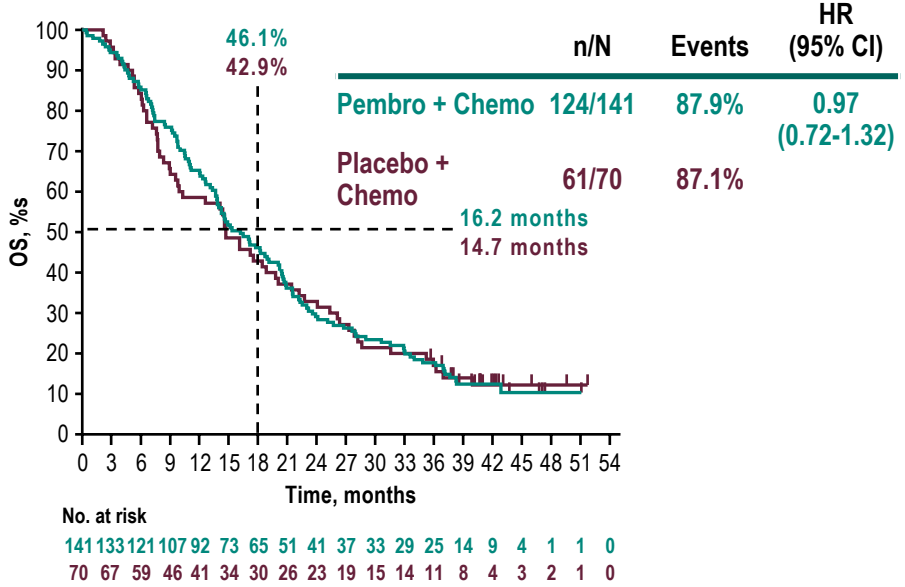
No. at risk

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

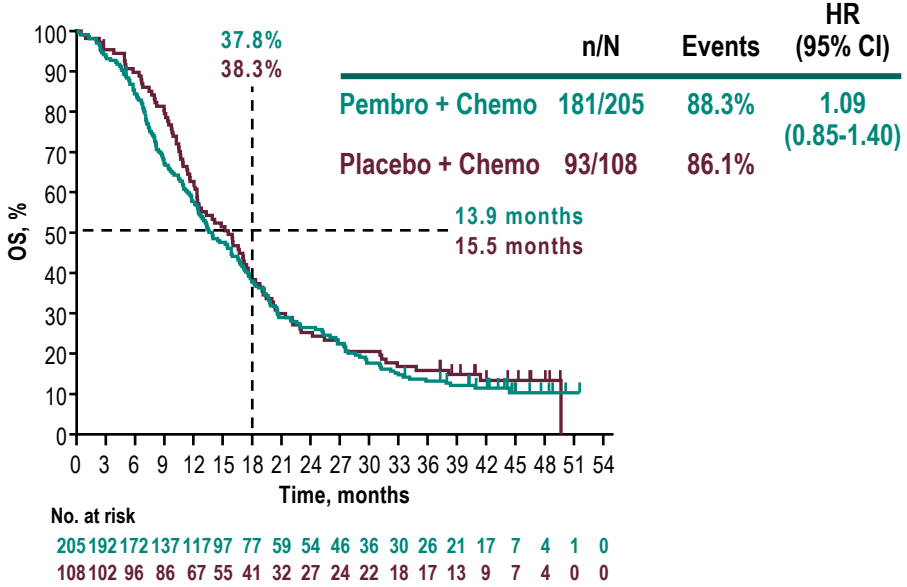
KN-355 Overall Survival in PD-L1 CPS Subgroups

PD-L1 CPS <1



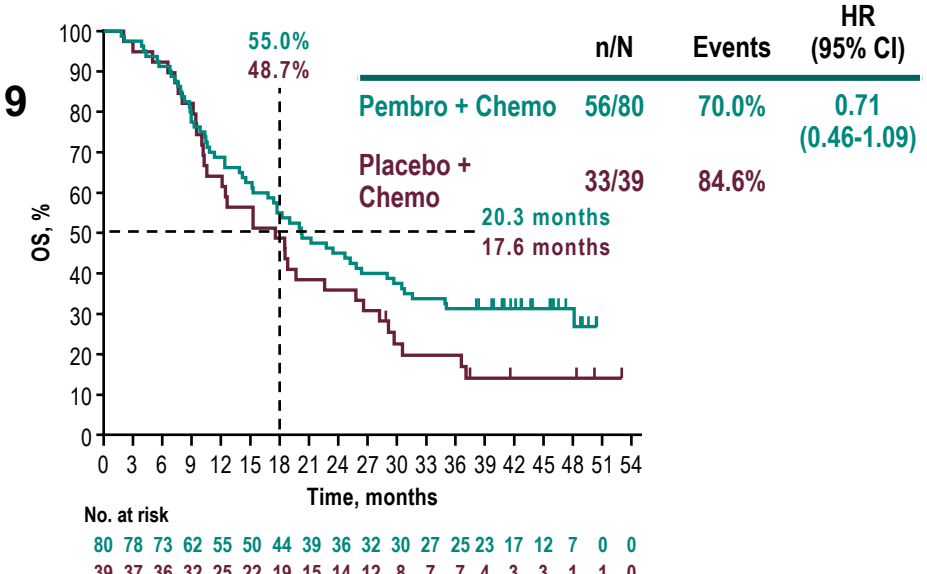
	n/N	Events	HR (95% CI)
Pembro + Chemo	124/141	87.9%	0.97 (0.72-1.32)
Placebo + Chemo	61/70	87.1%	

PD-L1 CPS 1-9



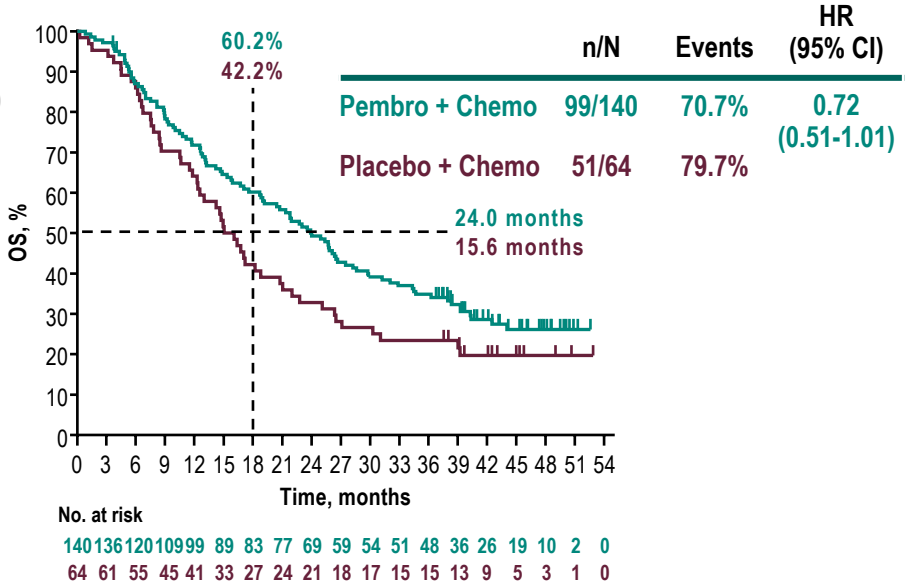
	n/N	Events	HR (95% CI)
Pembro + Chemo	181/205	88.3%	1.09 (0.85-1.40)
Placebo + Chemo	93/108	86.1%	

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



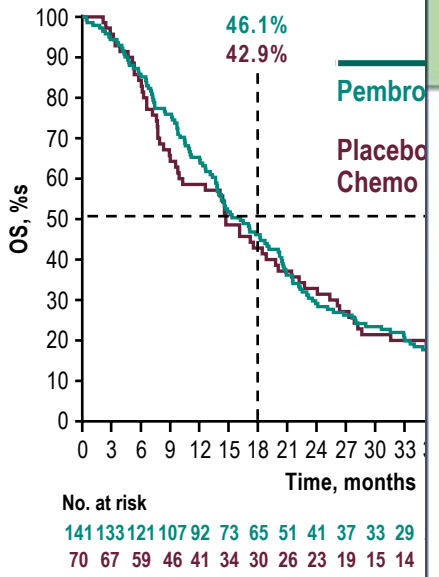
	n/N	Events	HR (95% CI)
Pembro + Chemo	99/140	70.7%	0.72 (0.51-1.01)
Placebo + Chemo	51/64	79.7%	

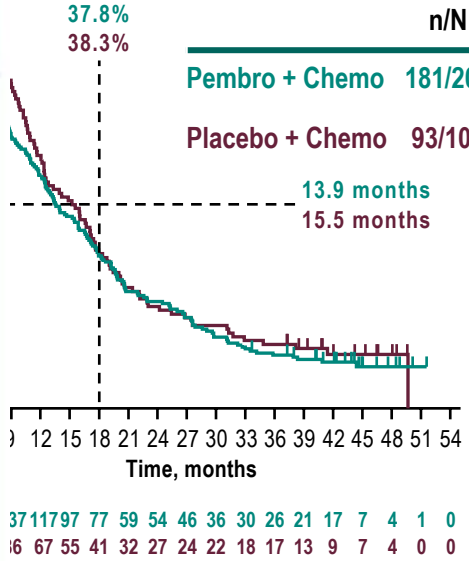
Data cutoff: June 15, 2021.

KN-355 Overall

Subgroups

PD-L1 CPS <1





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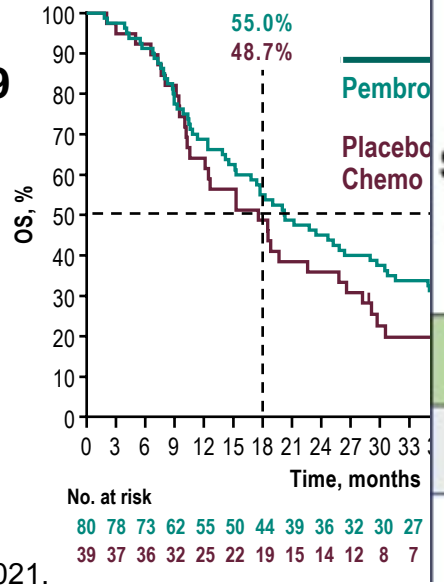
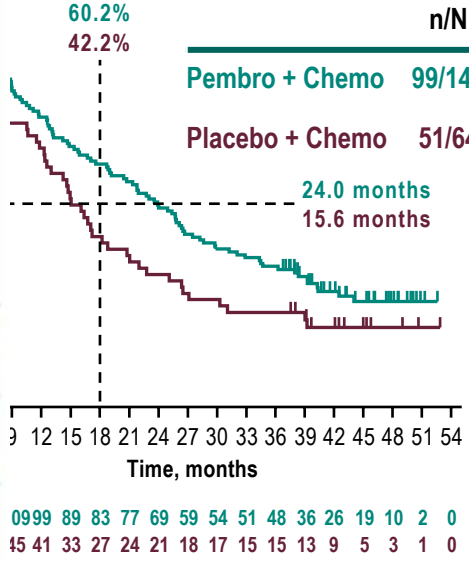
PD-L1 CPS 10-19





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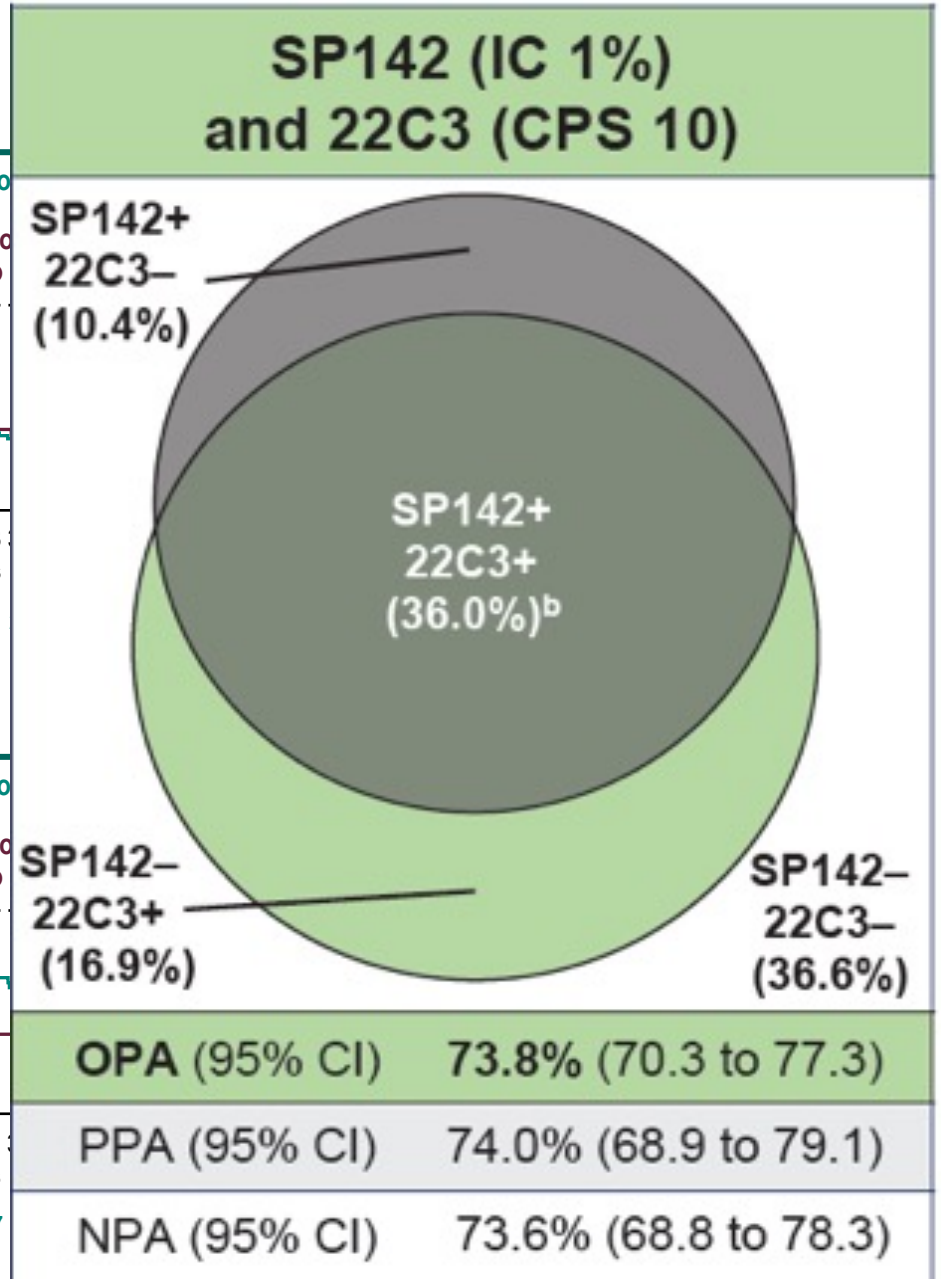


Data cutoff: June 15, 2021.

Rugo, JNCI 2021

Do patients with pCR need adjuvant pembrolizumab?

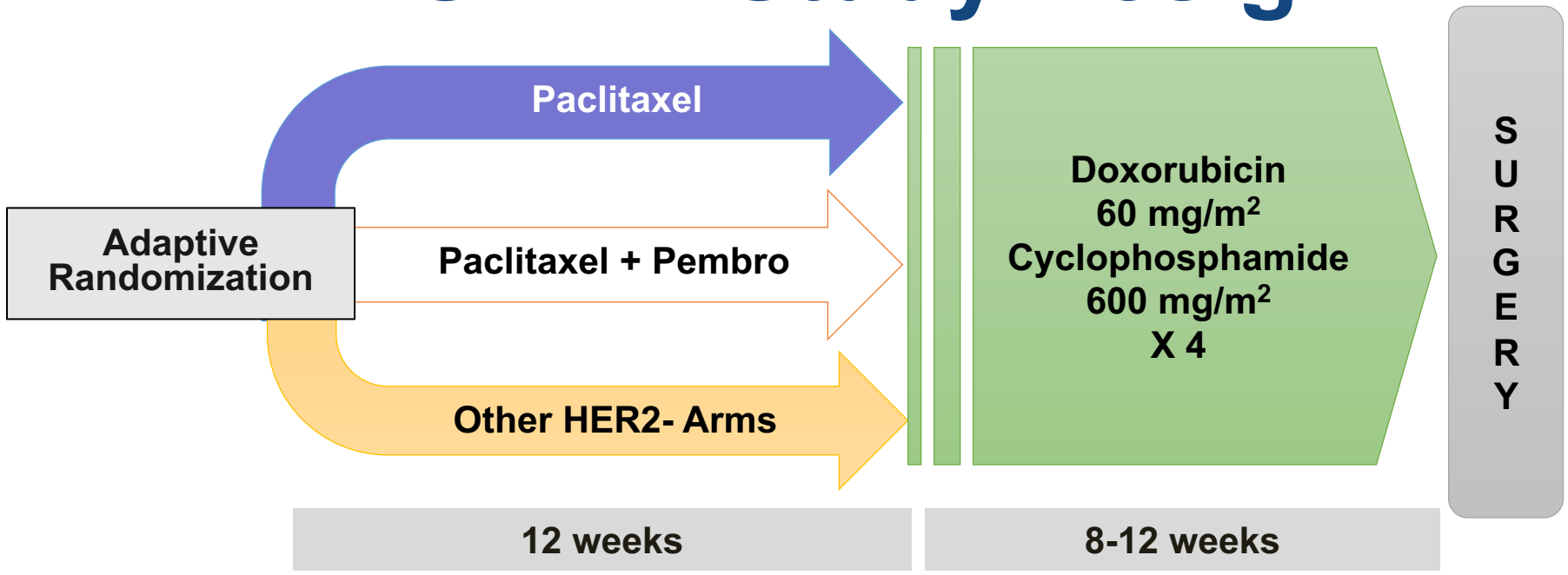
40 yo with Stage II TNBC

- A 40 yo woman presents with rapidly growing 3 cm mass UOQ right breast and no palpable axillary adenopathy
- Biopsy shows grade 3 TNBC ER 0, PR 0, HER2 0, Ki-67 80%
- Mammogram, ultrasound and MRI show no other suspicious lesions or adenopathy
- Germline testing is negative and she has no family h/o breast cancer
- She is treated with preoperative weekly paclitaxel, carboplatin plus pembrolizumab and has a clinical complete response. Shen then receives preoperative doxorubicin/cyclophosphamide + pembrolizumab

40 yo with Stage II TNBC

- She develops rising TSH, is asymptomatic, and is begun on thyroid replacement.
- She undergoes bilateral mastectomy and right SLN biopsy and has no residual disease in the right breast and no cancer nor fibrosis in 3 right axilla SLNs
- She does not need adjuvant cytotoxic therapy nor radiation therapy
- She has an excellent prognosis
- Does she need adjuvant pembrolizumab as was administered in KN-522?

I-SPY2: Study Design



Control
Paclitaxel 80 mg/m^2 every wk x 12

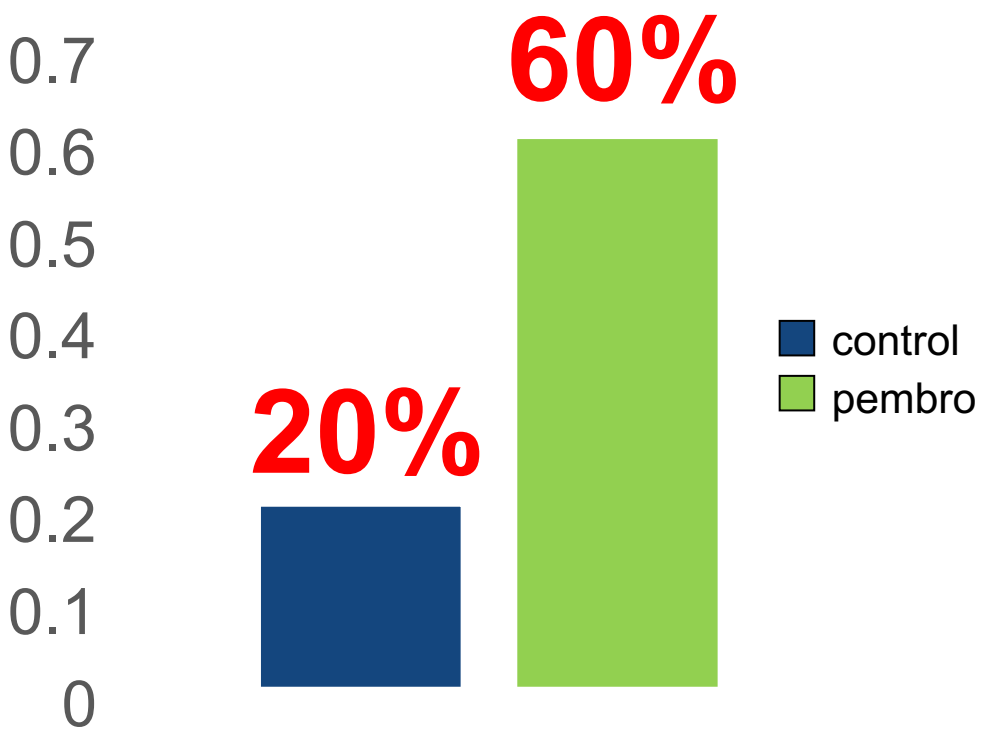
Experimental
Paclitaxel 80 mg/m^2 every wk x 12
Pembro 200 mg every 3 wks x 4

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.

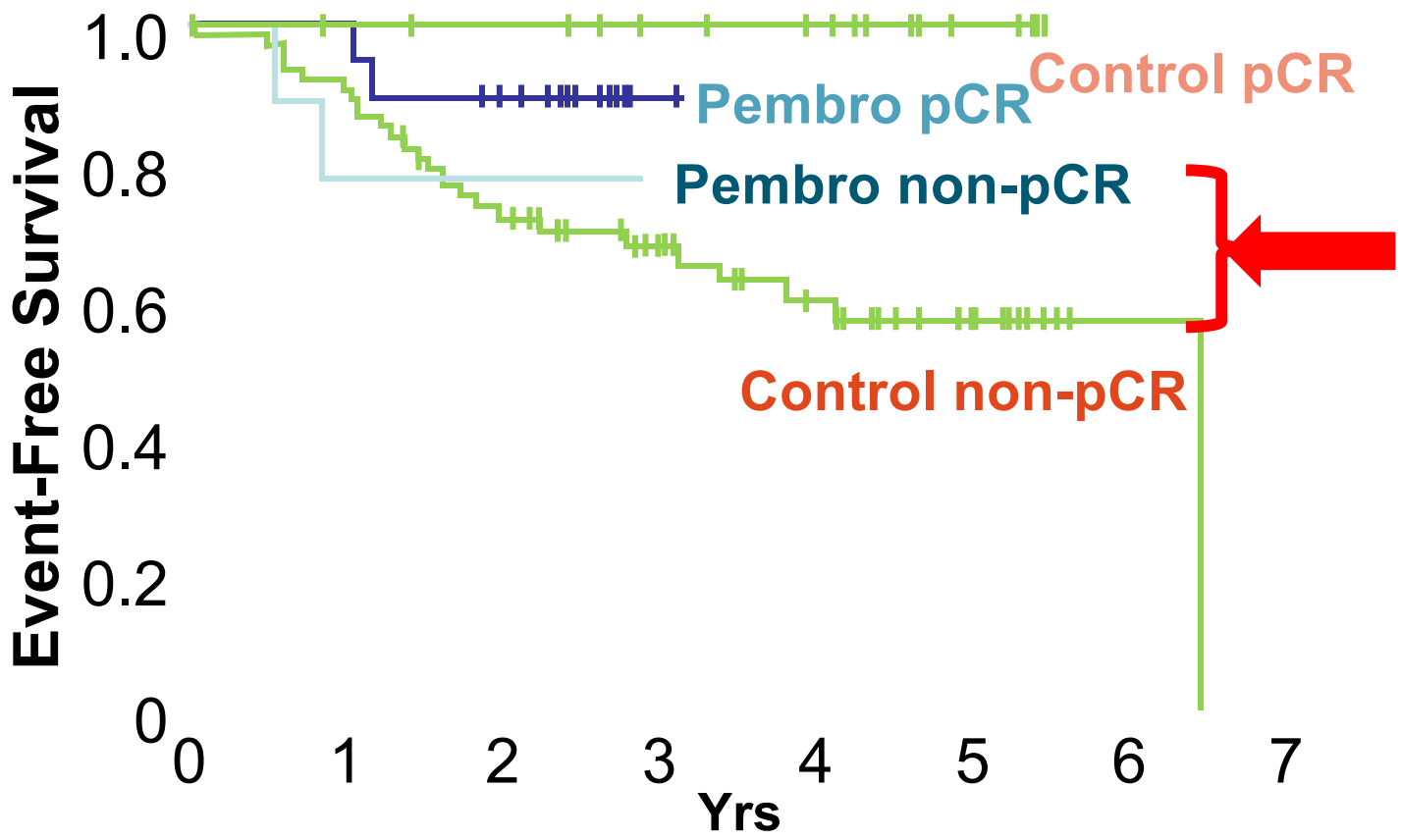
I-SPY2

Estimated pCR



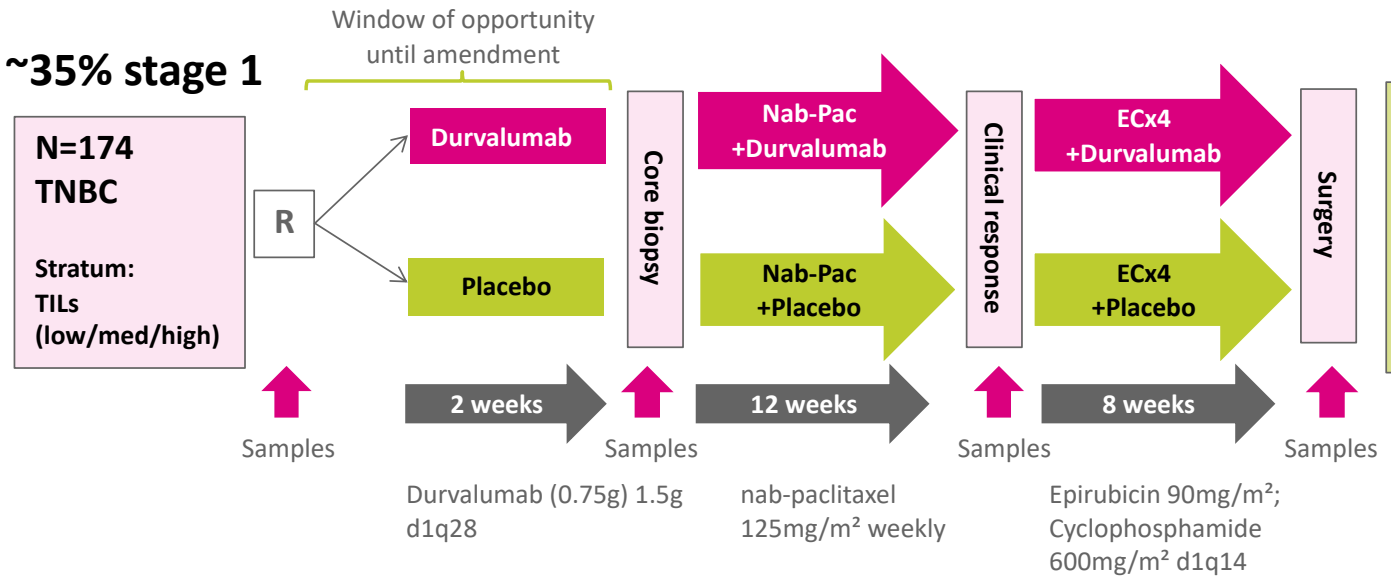
Probability of phase III success: > 99%

EFS by pCR



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

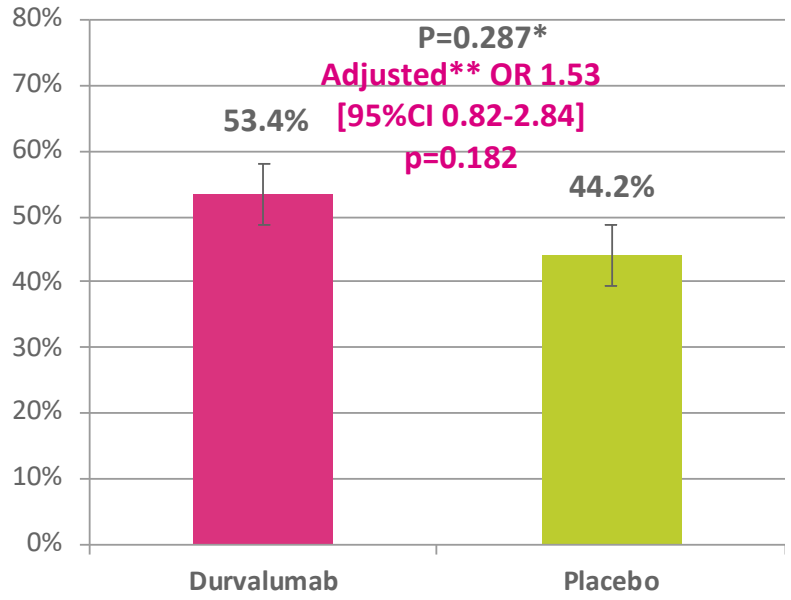
GeparNUEVO: Phase II Durvalumab Neoadjuvant Trial

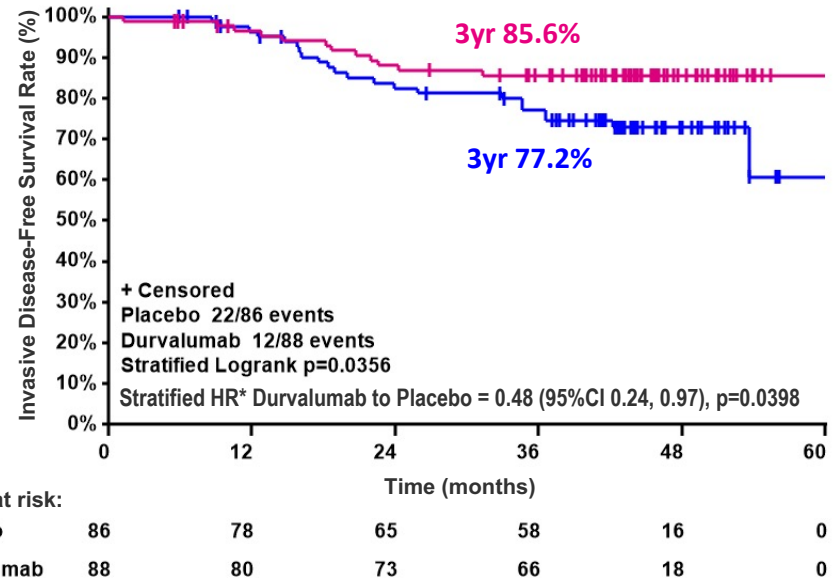


Primary endpoint: pCR (ypT0, ypN0)

Main secondary endpoints: iDFS, DDFS, OS

Primary endpoint: pCR – ypT0, ypN0





Δ8.4%

iDFS between arms

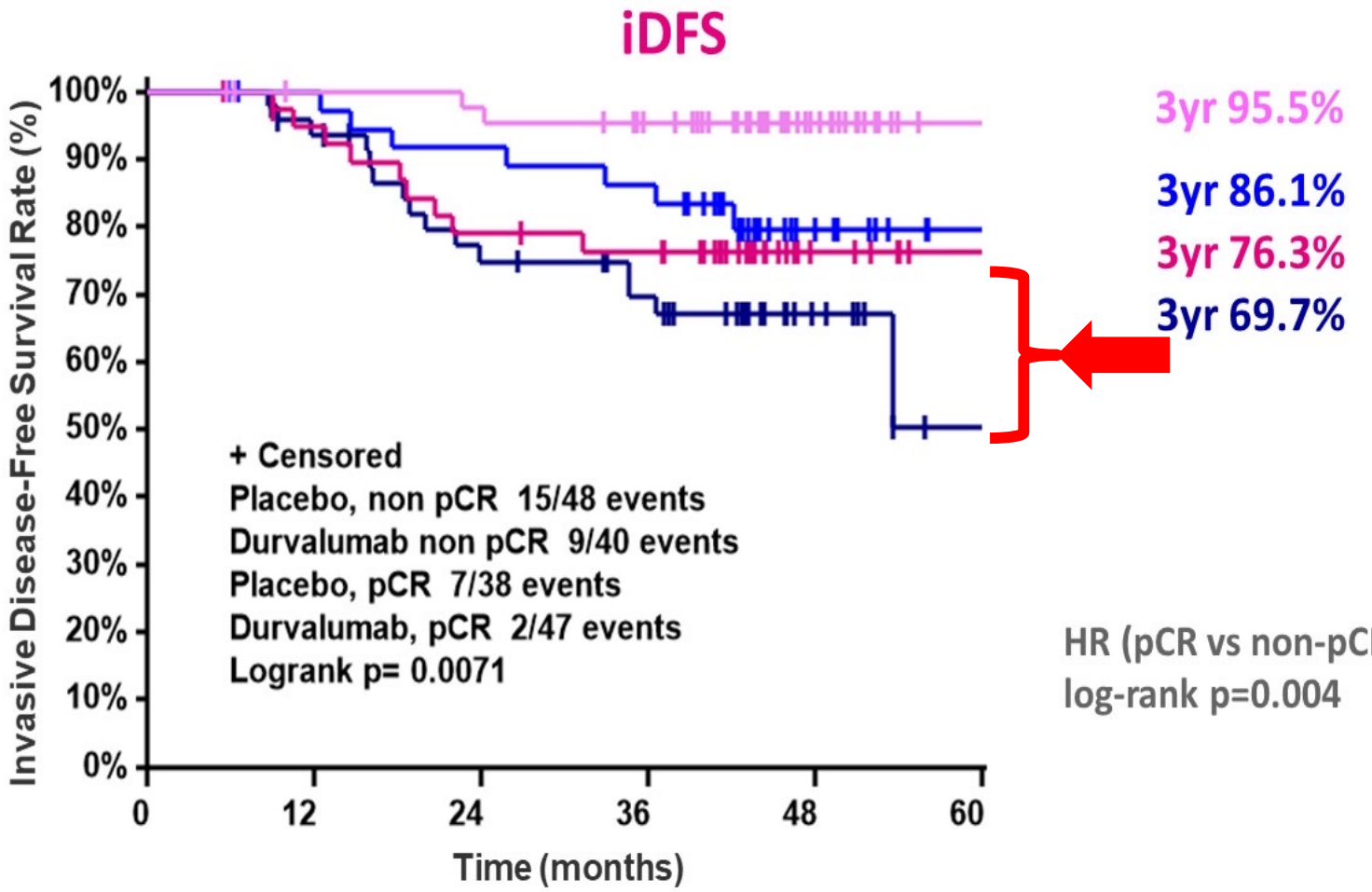
Median FU 43.7 months

* 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

Patients at risk:						
Placebo, non pCR	48	42	32	27	8	0
Durvalumab non pCR	40	36	30	28	5	0
Placebo, pCR	38	36	33	31	8	0
Durvalumab, pCR	47	44	43	38	13	0

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

KEYNOTE-522

Eligibility

- Newly diagnosed TNBC (central confirmation)
- T1c N+ or T≥2 N0-2
- PD-L1+ or PD-L1-

Stratification

- T1/T2 vs T3/T4
- N0 vs N+
- Carboplatin Q1W vs Q3W

N = 1,174

R

Neoadjuvant chemo **+ pembrolizumab**

Neoadjuvant chemo **+ placebo**

Surgery

Adjuvant **pembrolizumab** 9 cycles

Adjuvant **placebo** 9 cycles

Within 3-6 weeks

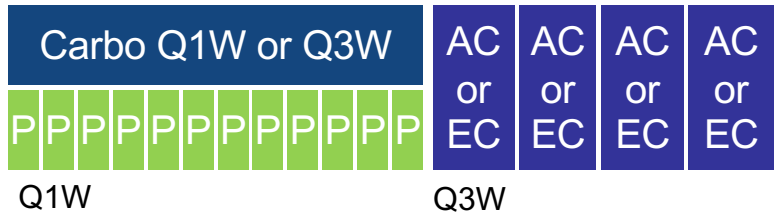
Primary endpoints

- pCR rate (ypT0/Tis ypN0)
- EFS

Secondary endpoints

- Alternative pCR rate (ypT0 ypN0)
- pCR rate in PD-L1+
- EFS in PD-L1+
- OS

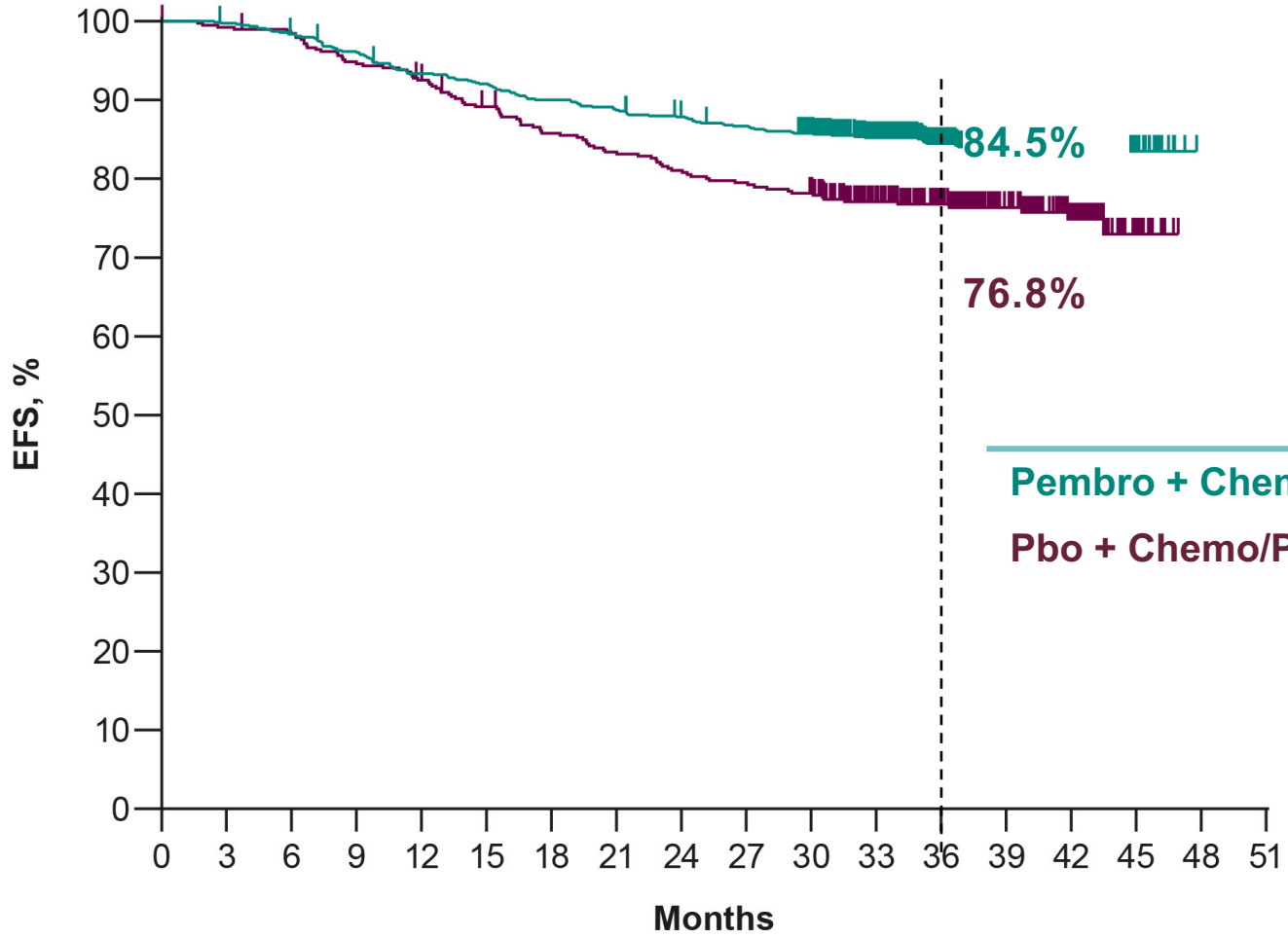
Study Treatment



Paclitaxel 80 mg/m^2 IV weekly
Carboplatin weekly (AUC 1.5) or Q3W (AUC5)
Doxorubicin 60 mg/m^2 IV Q3W
(Epirubicin 90 mg/m^2 IV Q3W)
Cyclophosphamide 600 mg/m^2 IV Q3W
Pembrolizumab 200 mg IV Q3W

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

KEYNOTE-522: EFS update at IA4 (39.1mo)



Δ7.7%

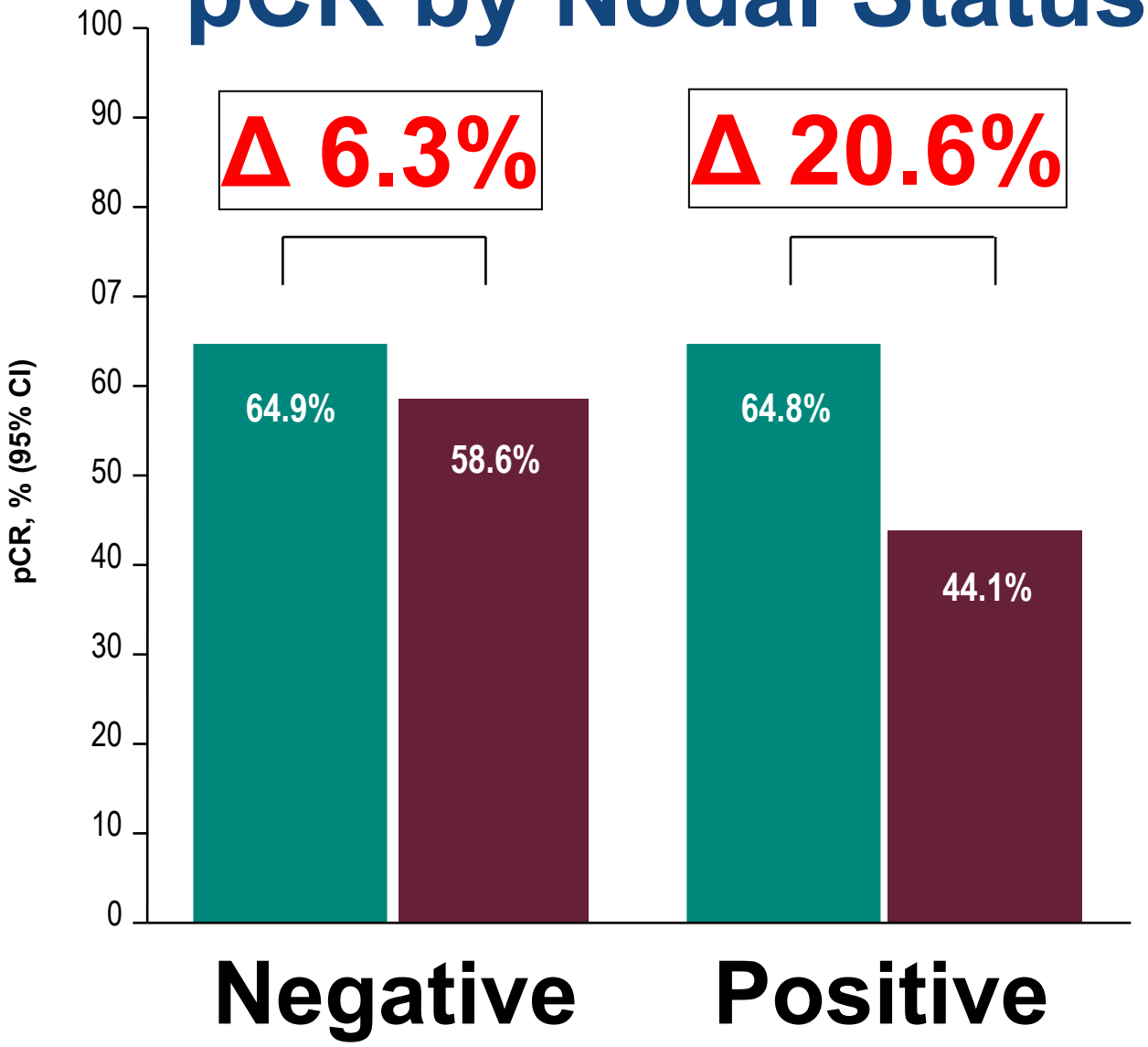
	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	15.7%	0.63[a]	0.00031[b]
Pbo + Chemo/Pbo	23.8%		

No. at Risk

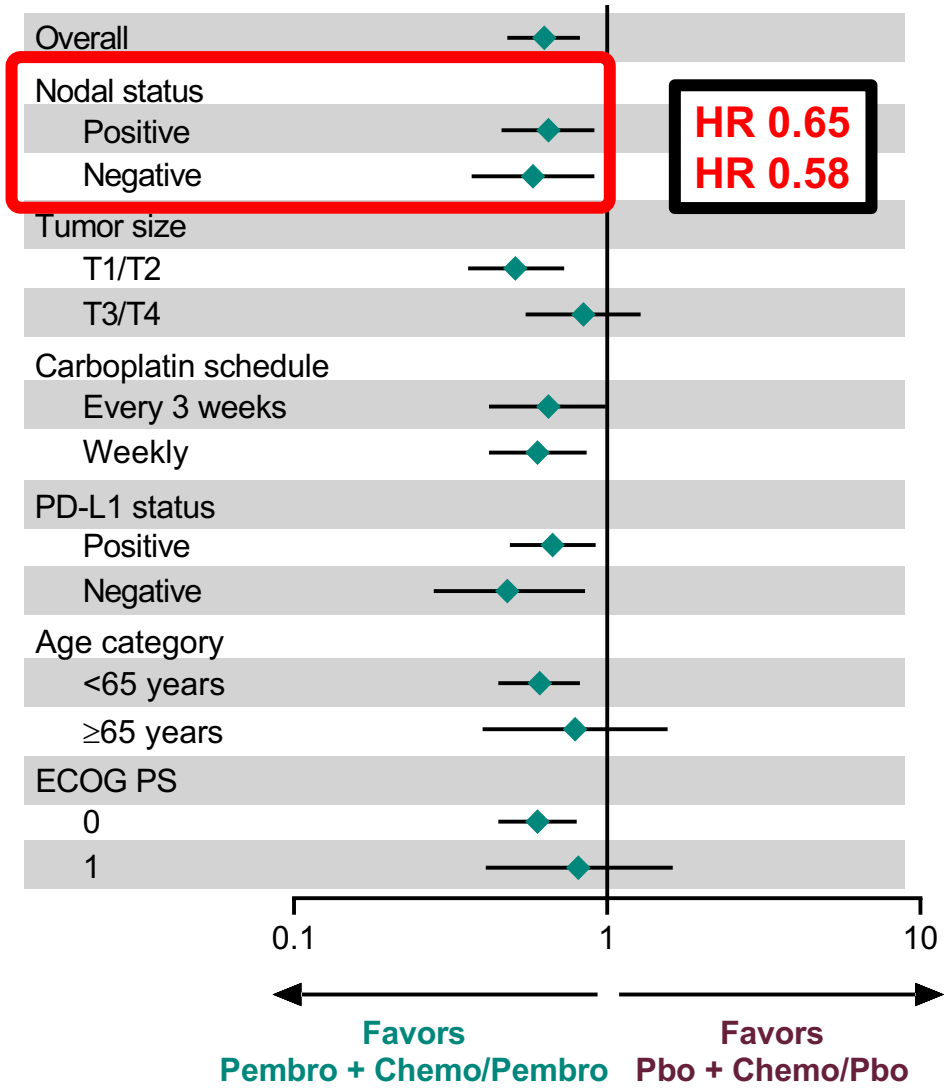
Pembro + Chemo/Pembro	784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
Pbo + Chemo/Pbo	390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

Schmid P et al. 2021 ESMO Virtual Plenary. Abstract VP7-2021. Schmid P et al. *N Engl J Med*. 2022;386:556-567.

pCR by Nodal Status



EFS in Subgroups

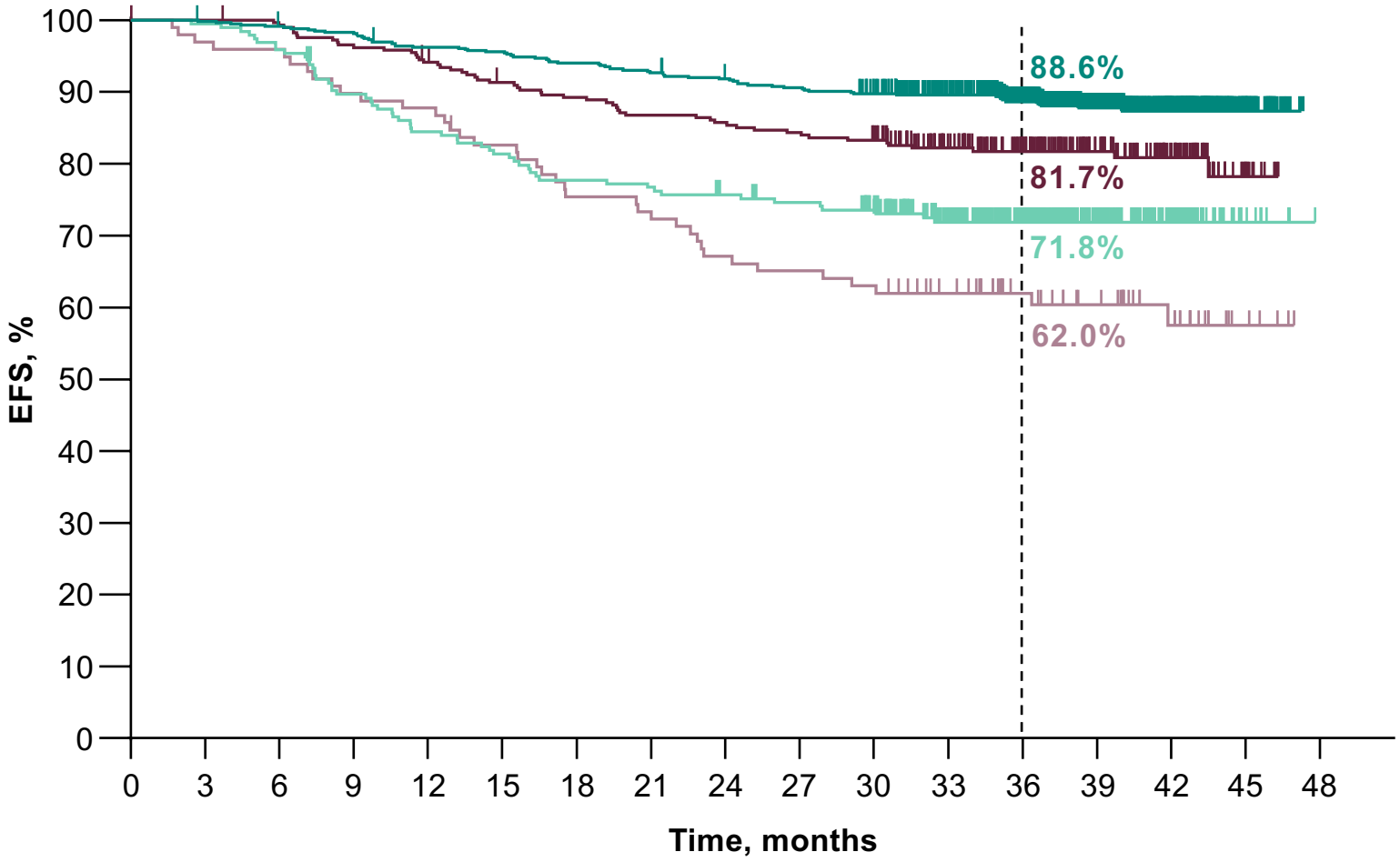


Schmid P et al. 2021 ESMO Virtual Plenary. Abstract VP7-2021.

EFS by Overall Disease Stage

Stage II	Events	HR (95% CI)
Pembro+Chemo/Pembro	11.7%	0.60 (0.42-0.86)
Pbo+Chemo/Pbo	18.6%	

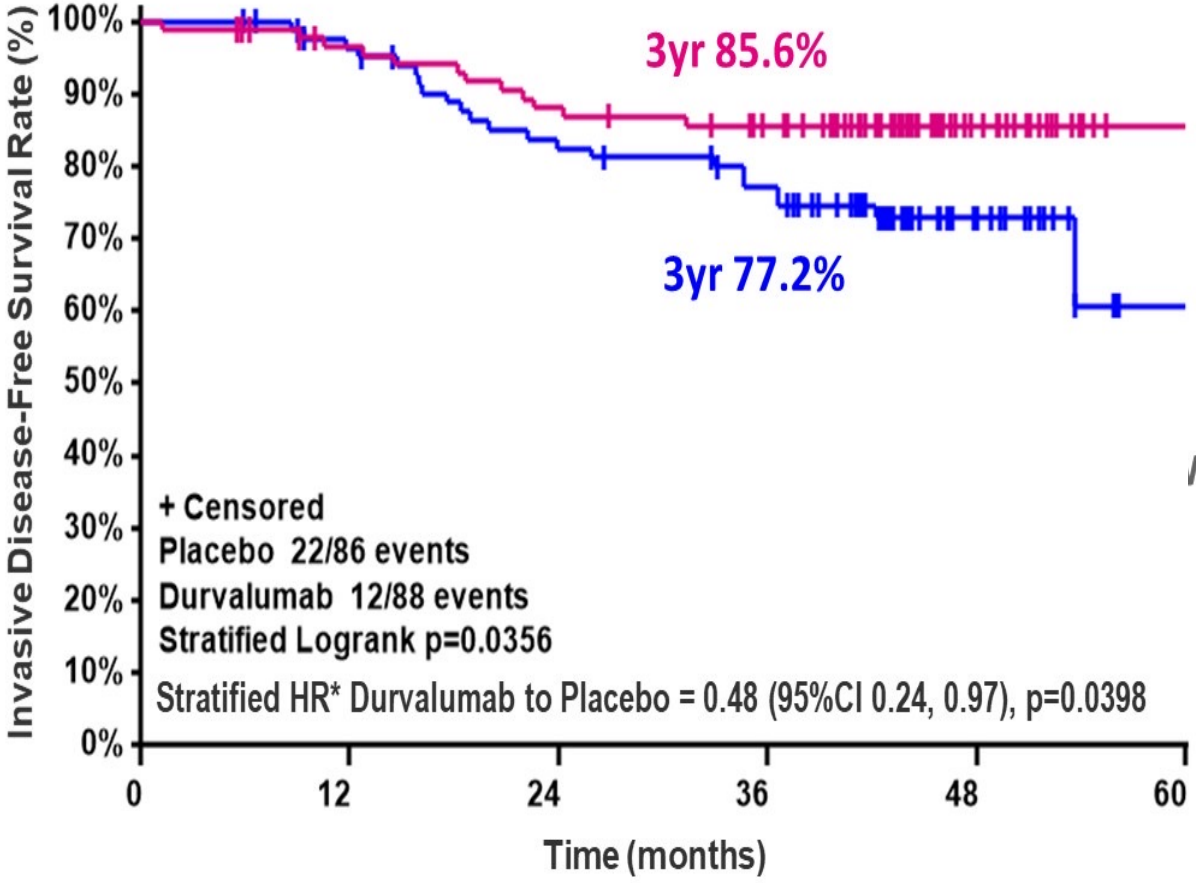
Stage III	Events	HR (95% CI)
Pembro+Chemo/Pembro	27.8%	0.68 (0.45-1.03)
Pbo+Chemo/Pbo	39.8%	



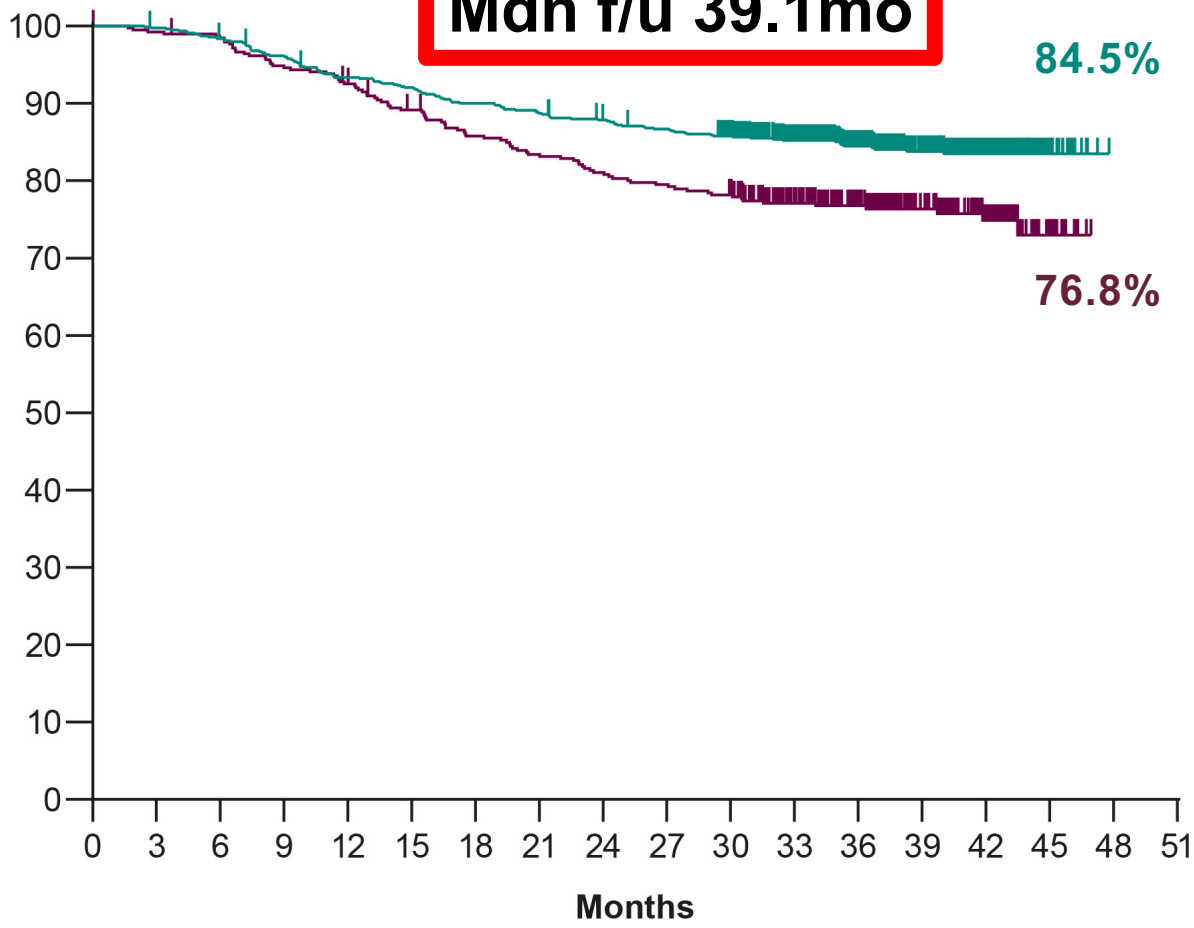
Schmid P et al. 2021 ESMO Virtual Plenary. Abstract VP7-2021. Schmid P et al. *N Engl J Med*. 2022;386:556-567.

Is all the IO benefit conferred with neoadjuvant administration?

GeparNuevo
Mdn f/u 43.7mo

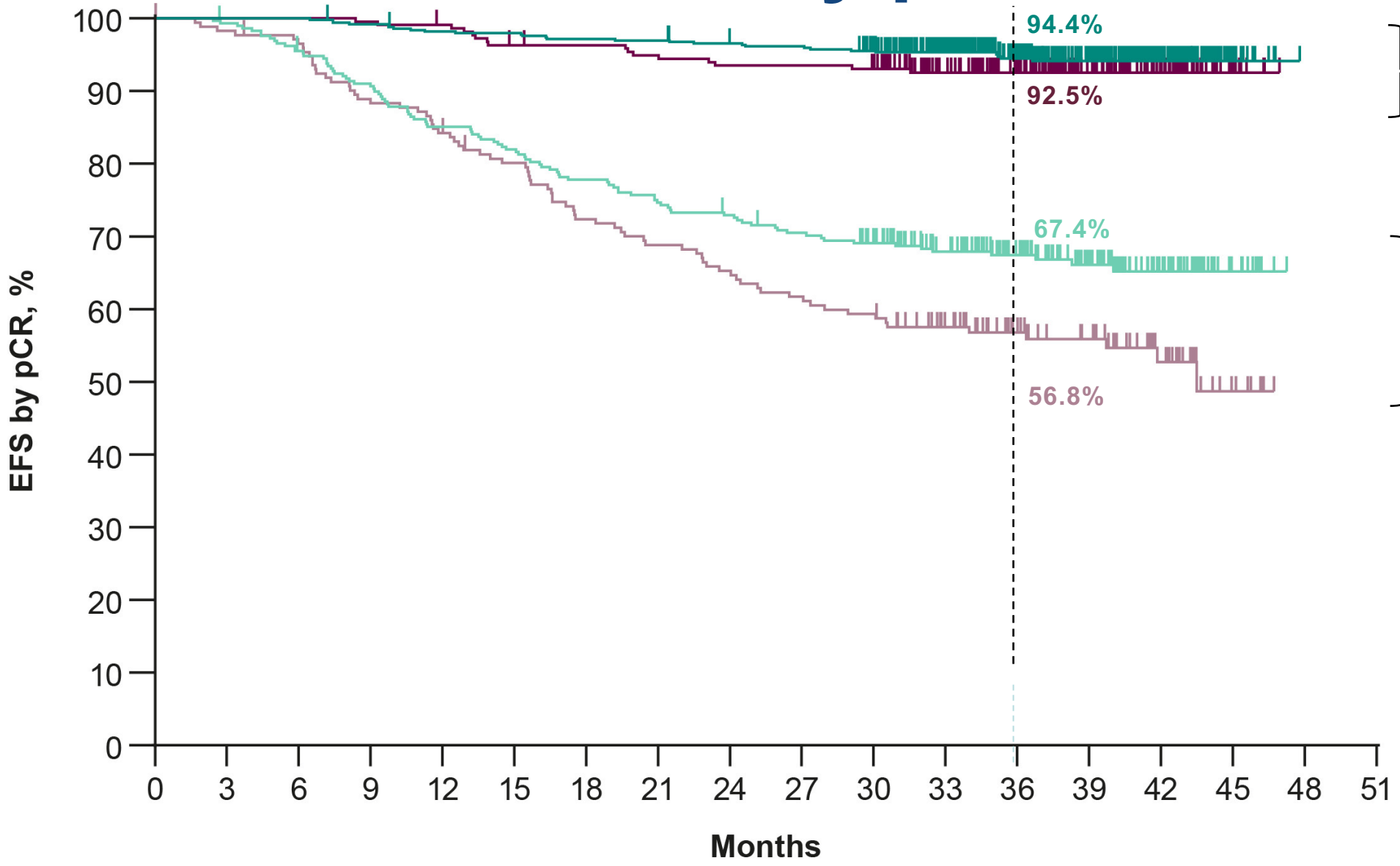


KEYNOTE-522
Mdn f/u 39.1mo



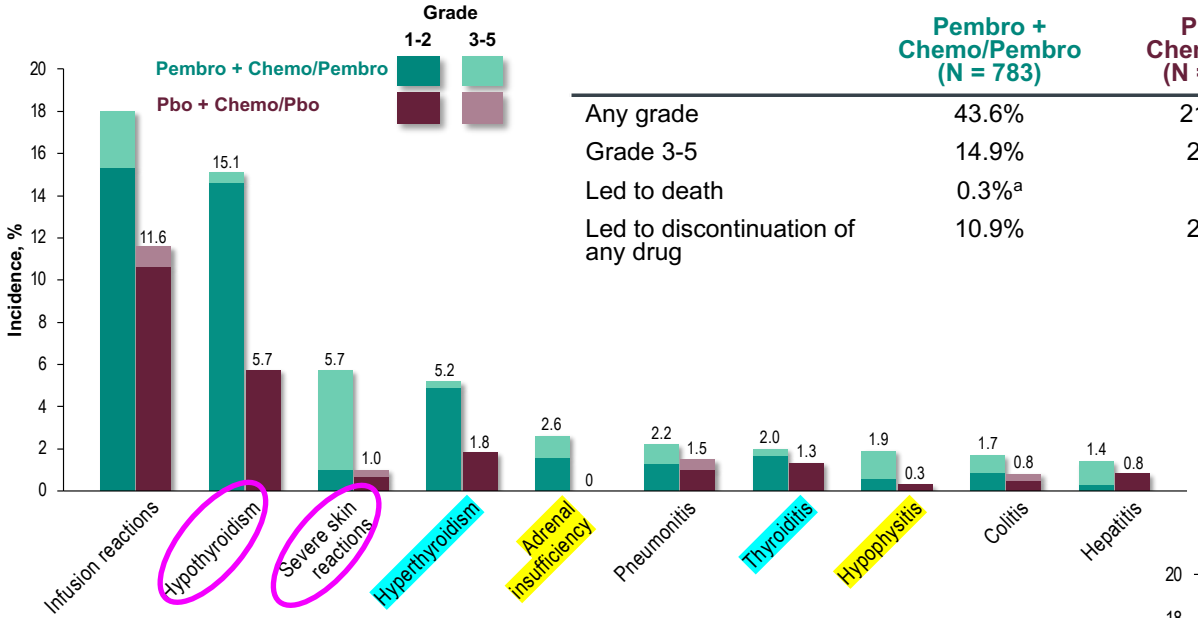
Loibl S et al. 2021 ASCO Annual Meeting. Abstract 506. Schmid P et al. 2021 ESMO Virtual Plenary. Abstract VP7-2021.

EFS by pCR



Schmid P et al. 2021 ESMO Virtual Plenary. Abstract VP7-2021.

Neoadjuvant and Adjuvant Immune-Related Toxicities KN-522

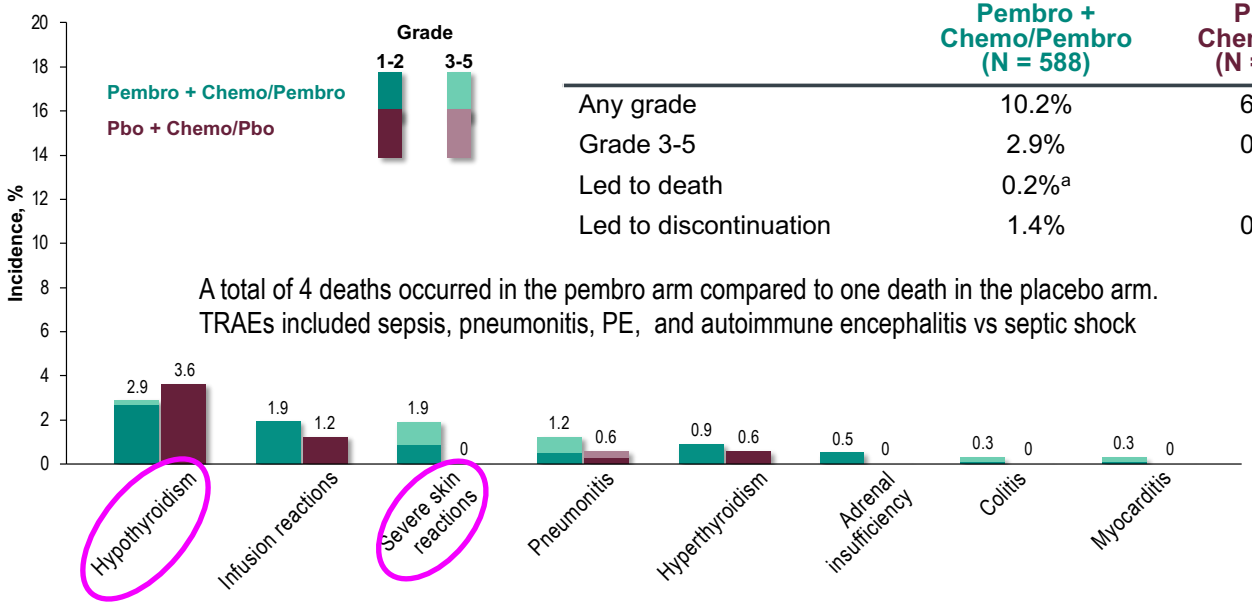


	Pembro + Chemo/Pembro (N = 783)	Pbo + Chemo/Pbo (N = 389)
Any grade	43.6%	21.9%
Grade 3-5	14.9%	2.1%
Led to death	0.3%[a]	0
Led to discontinuation of any drug	10.9%	2.6%

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

Neoadjuvant + chemo

Adjuvant



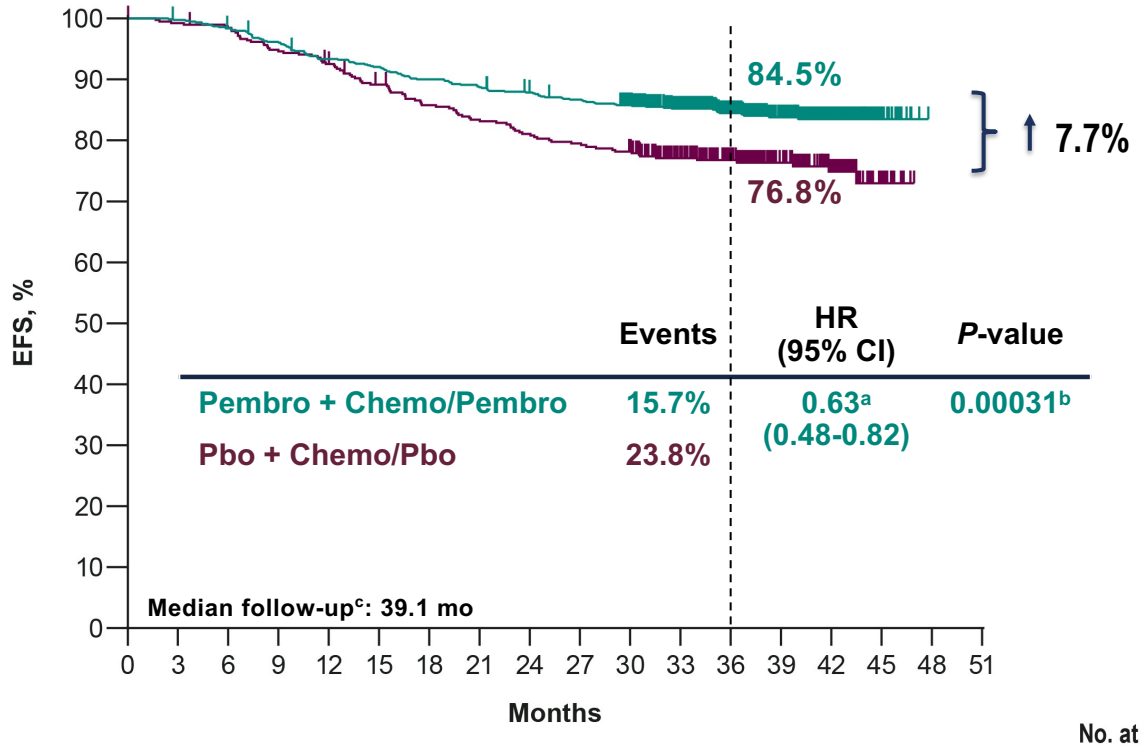
	Pembro + Chemo/Pembro (N = 588)	Pbo + Chemo/Pbo (N = 331)
Any grade	10.2%	6.0%
Grade 3-5	2.9%	0.3%
Led to death	0.2%[a]	0
Led to discontinuation	1.4%	0.3%

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

EFS and DRFS: Statistically Significant at IA4

EFS



No. at Risk

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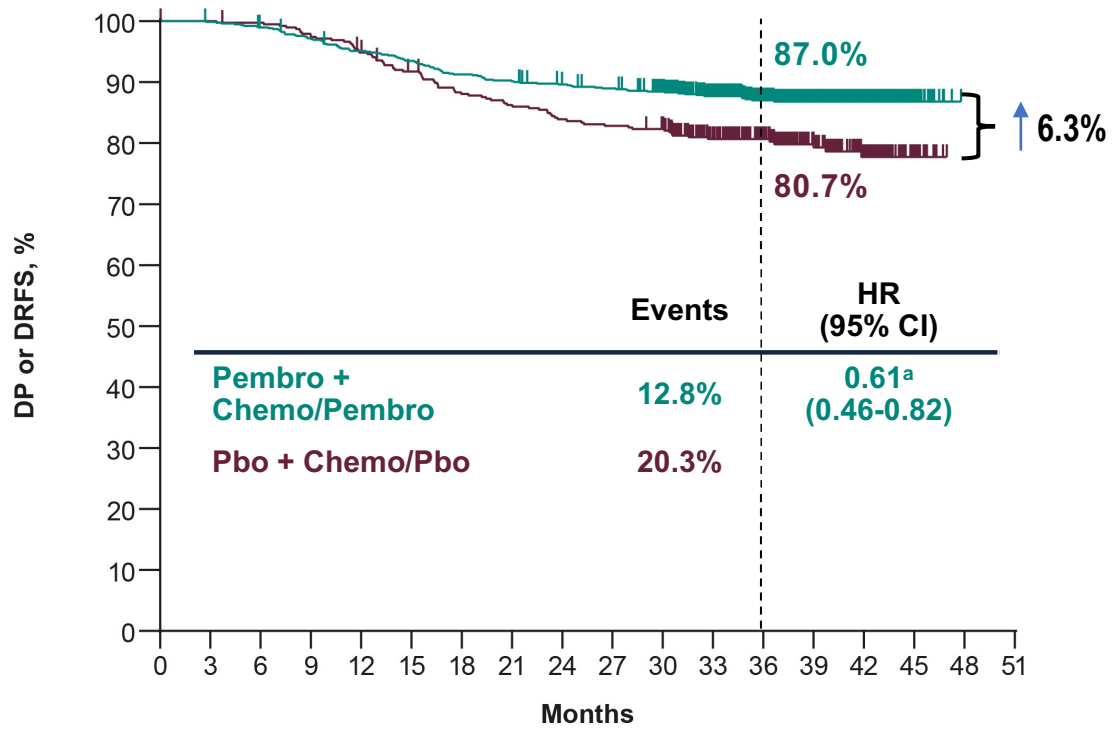
Pbo + Chemo/Pbo	390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

DRFS



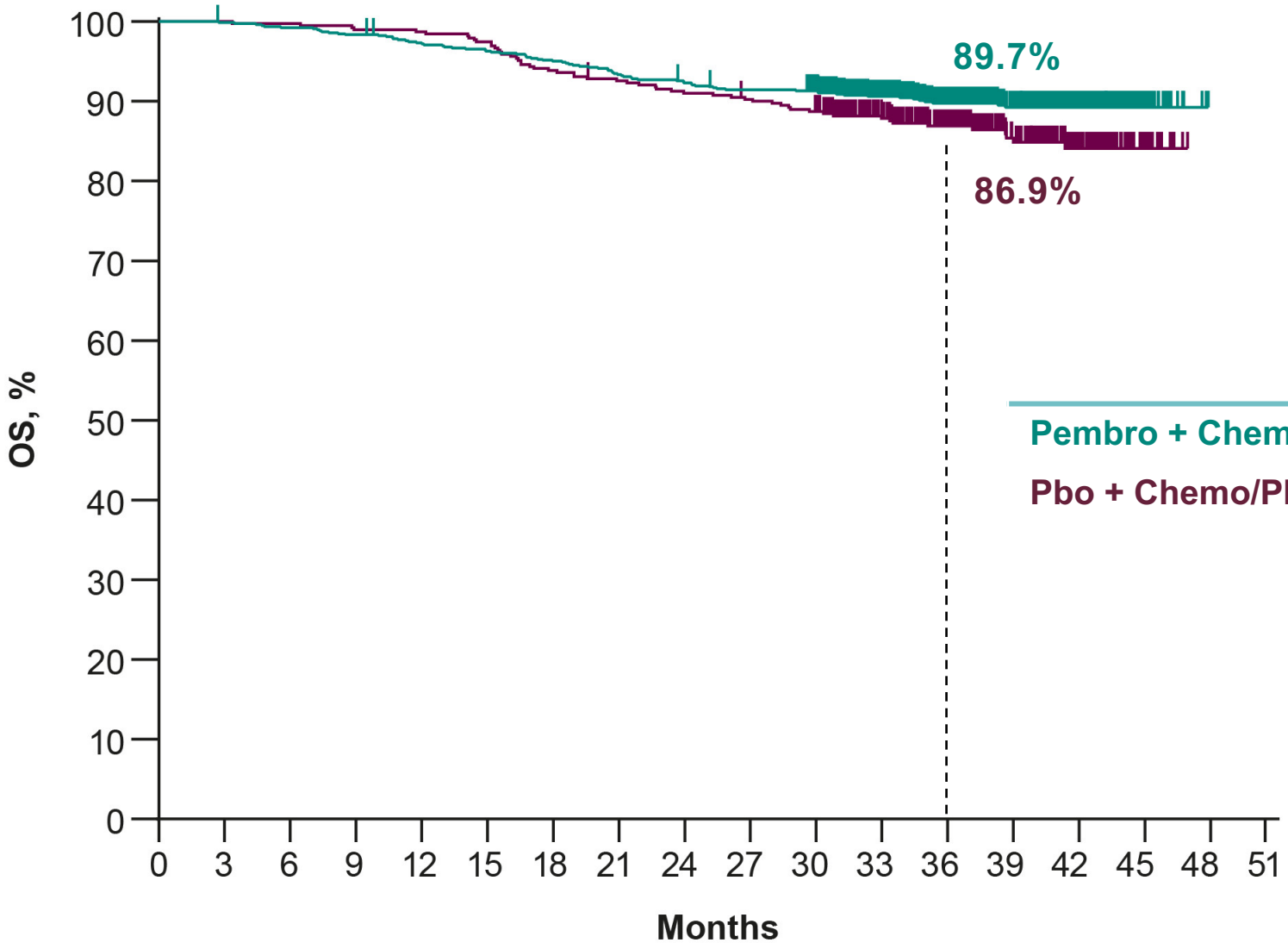
No. at Risk

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

Schmid et al, ESMO virtual plenary 2021

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [b]**Prespecified *P*-value boundary of 0.00517 reached at this analysis.**
[c]Defined as the time from randomization to the data cutoff date of March 23, 2021.

Overall Survival



	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	10.2%	0.72[a] (0.51-1.02)	0.03214[b]
Pbo + Chemo/Pbo	14.1%		

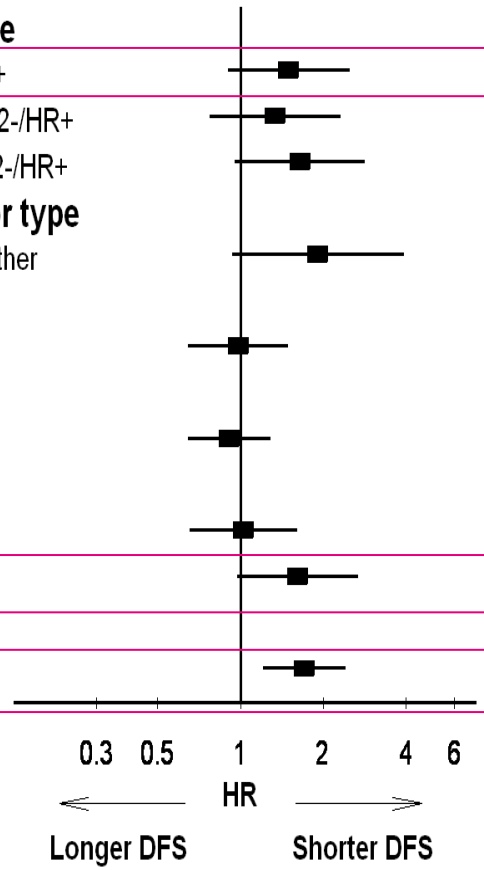
Schmid P et al. 2021 ESMO Virtual Plenary. Abstract VP7-2021. Schmid P et al. *N Engl J Med*. 2022;386:556-567.

GBG Metaanalysis of Outcomes of pCR Patients

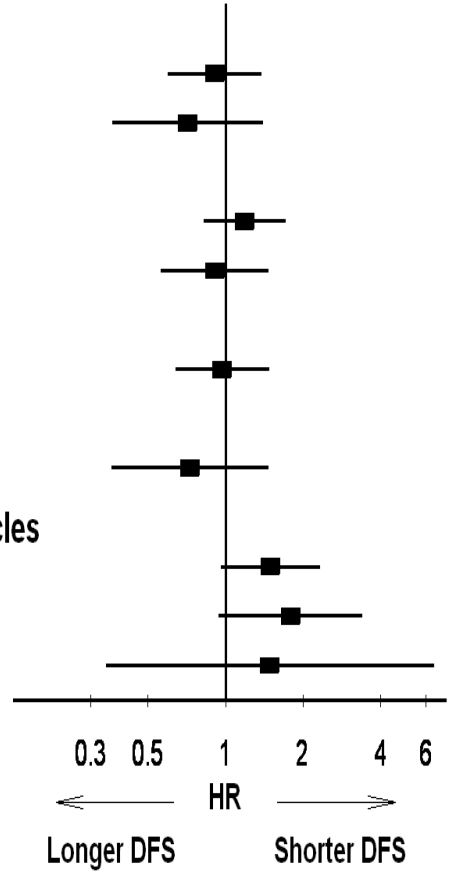
- 2188 patients with pCR (ypT0/is ypN0) from GeparTrio, GeparQuattro, GeparQuinto, GeparSixto and GeparSepto trial were included
- Objectives were disease-free survival (DFS), distant DFS (DDFS), overall survival (OS)
- Multivariate Cox regression models included potential risk factors as well as study ID
- After a median follow up of 59 months 290 DFS, 197 DDFS and 130 OS events were observed

DFS, multivariate Cox regression

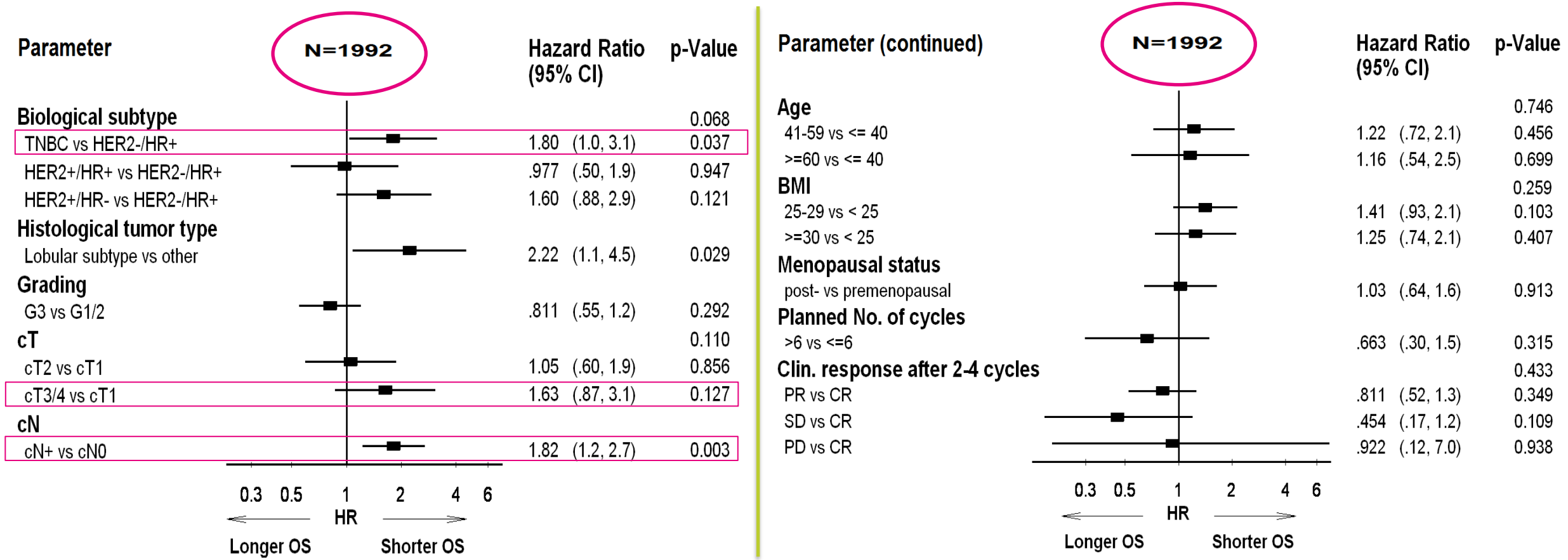
Parameter	N=1217	Hazard Ratio (95% CI)	p-Value
Biological subtype			0.308
TNBC vs HER2-/HR+		1.50 (.90, 2.5)	0.120
HER2+/HR+ vs HER2-/HR+		1.34 (.77, 2.3)	0.300
HER2+/HR- vs HER2-/HR+		1.64 (.96, 2.8)	0.071
Histological tumor type			
Lobular subtype vs other		1.91 (.93, 3.9)	0.076
Ki-67			
>20% vs <= 20%		.981 (.65, 1.5)	0.926
Grading			
G3 vs G1/2		.911 (.65, 1.3)	0.593
cT			0.050
cT2 vs cT1		1.02 (.66, 1.6)	0.915
cT3/4 vs cT1		1.61 (.97, 2.7)	0.064
cN			
cN+ vs cN0		1.70 (1.2, 2.4)	0.002



Parameter (continued)	N=1217	Hazard Ratio (95% CI)	p-Value
Age			0.598
41-59 vs <= 40		.907 (.60, 1.4)	0.647
>=60 vs <= 40		.713 (.36, 1.4)	0.321
BMI			0.512
25-29 vs < 25		1.19 (.82, 1.7)	0.358
>=30 vs < 25		.908 (.56, 1.5)	0.691
Menopausal status			
post- vs premenopausal		.972 (.64, 1.5)	0.893
Planned No. of cycles			
>6 vs <=6		.727 (.36, 1.5)	0.373
Clin. response after 2-4 cycles			0.259
PR vs CR		1.50 (.96, 2.3)	0.073
SD vs CR		1.79 (.94, 3.4)	0.076
PD vs CR		1.49 (.34, 6.4)	0.595



OS, multivariate Cox regression (without Ki-67)



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

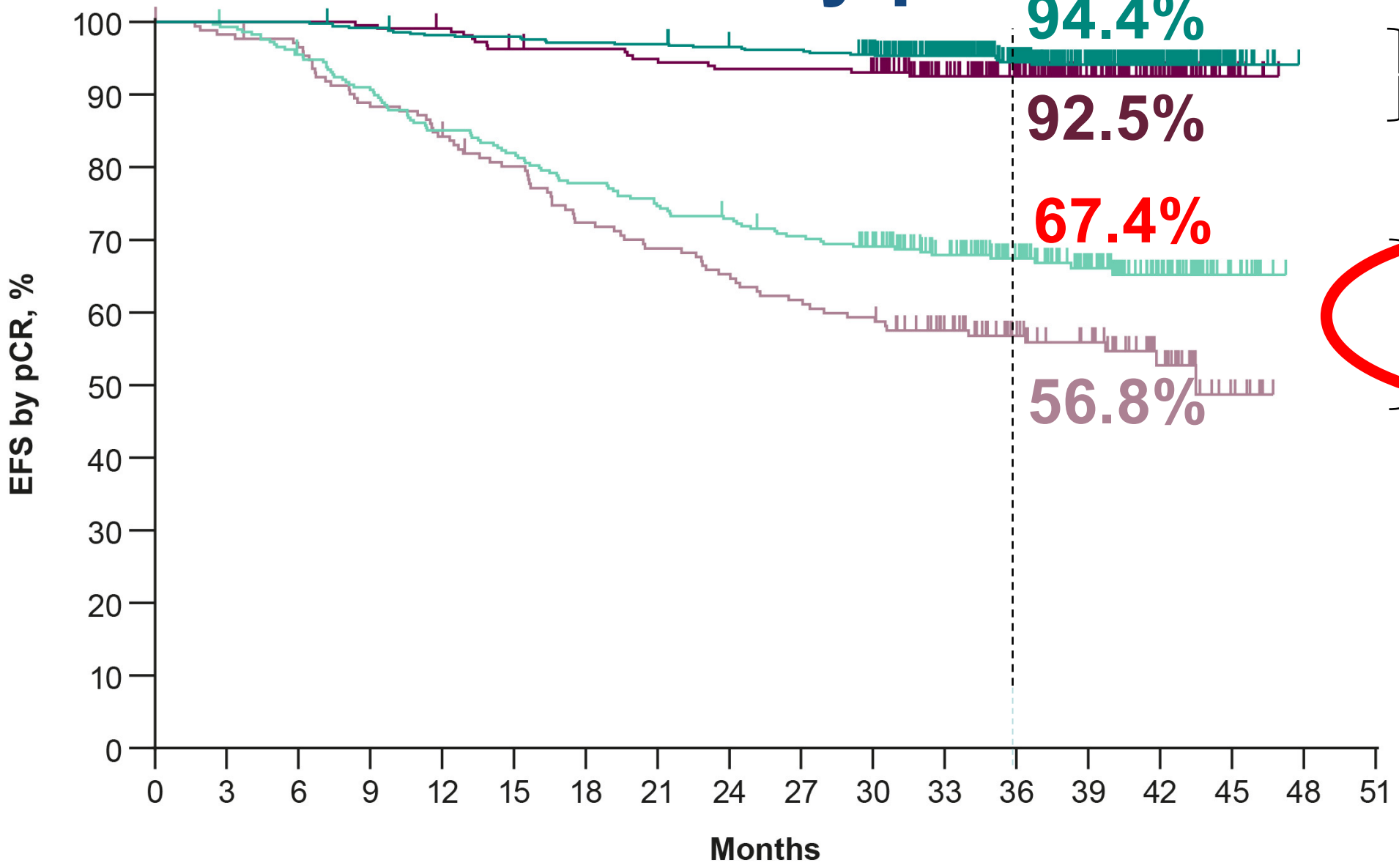
Stage III TNBC Patient with Residual Disease following preop KN-522 Regimen

- 36 yo African American woman presented with T3, cN1 right breast
- Breast and axillary biopsy showed grade 3 TNBC with LVI and nodal metastasis
- Staging showed no distant metastatic disease
- Germline testing showed gBRCA1 mutation
- She tolerated preop KN-522 regimen well, working full time as a teacher and caring for her family
- At bilateral mastectomy she had 1 cm RD in her breast and 1 of 4 positive axillary LN positive for disease

Stage III TNBC Patient with Residual Disease following preop KN-522 Regimen

- She underwent post-mastectomy radiation therapy
- BSO is planned
- She is currently receiving therapy with olaparib 300mg bid plus pembrolizumab
- She had low grade nausea for 8 weeks requiring intermittent prochlorperazine, which then resolved, and has ongoing grade 1 fatigue
- She continues to work full time and care for her family

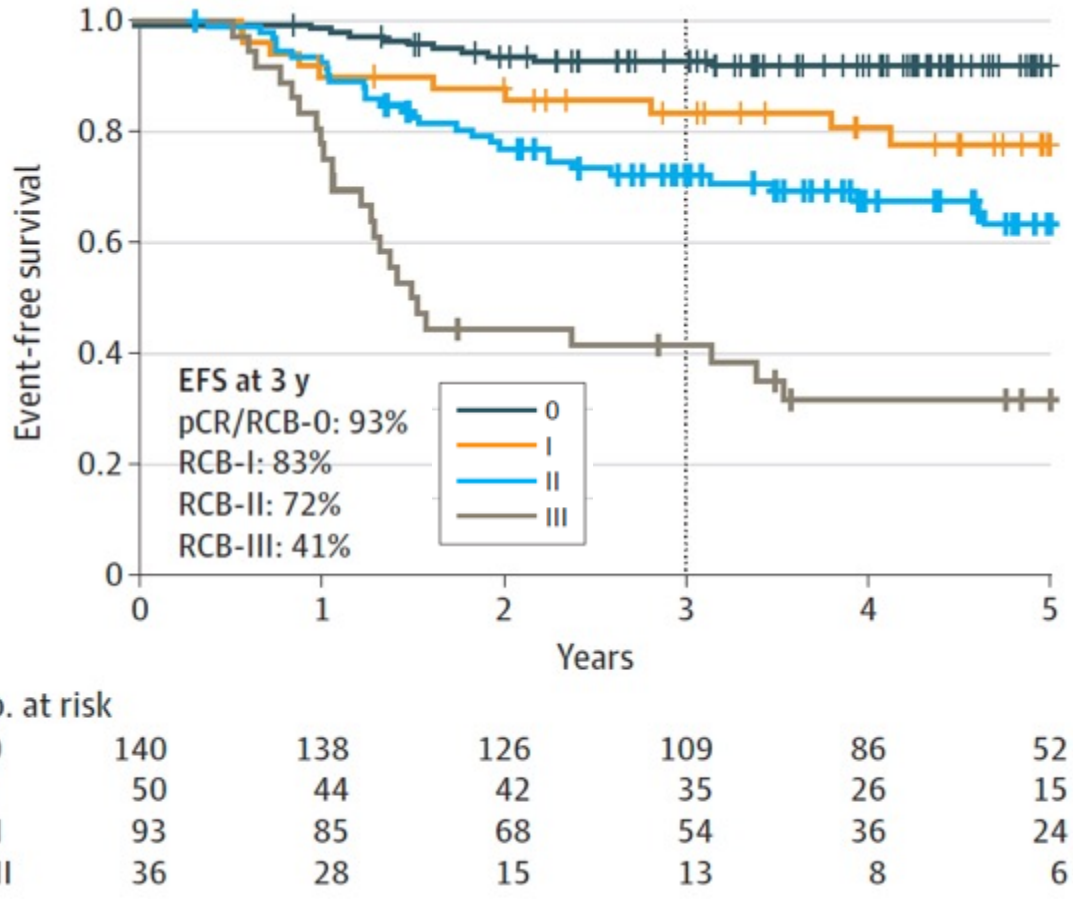
EFS by pCR



Schmid P et al. 2021 ESMO Virtual Plenary. Abstract VP7-2021.

I-SPY2: Prognostic Role of RCB

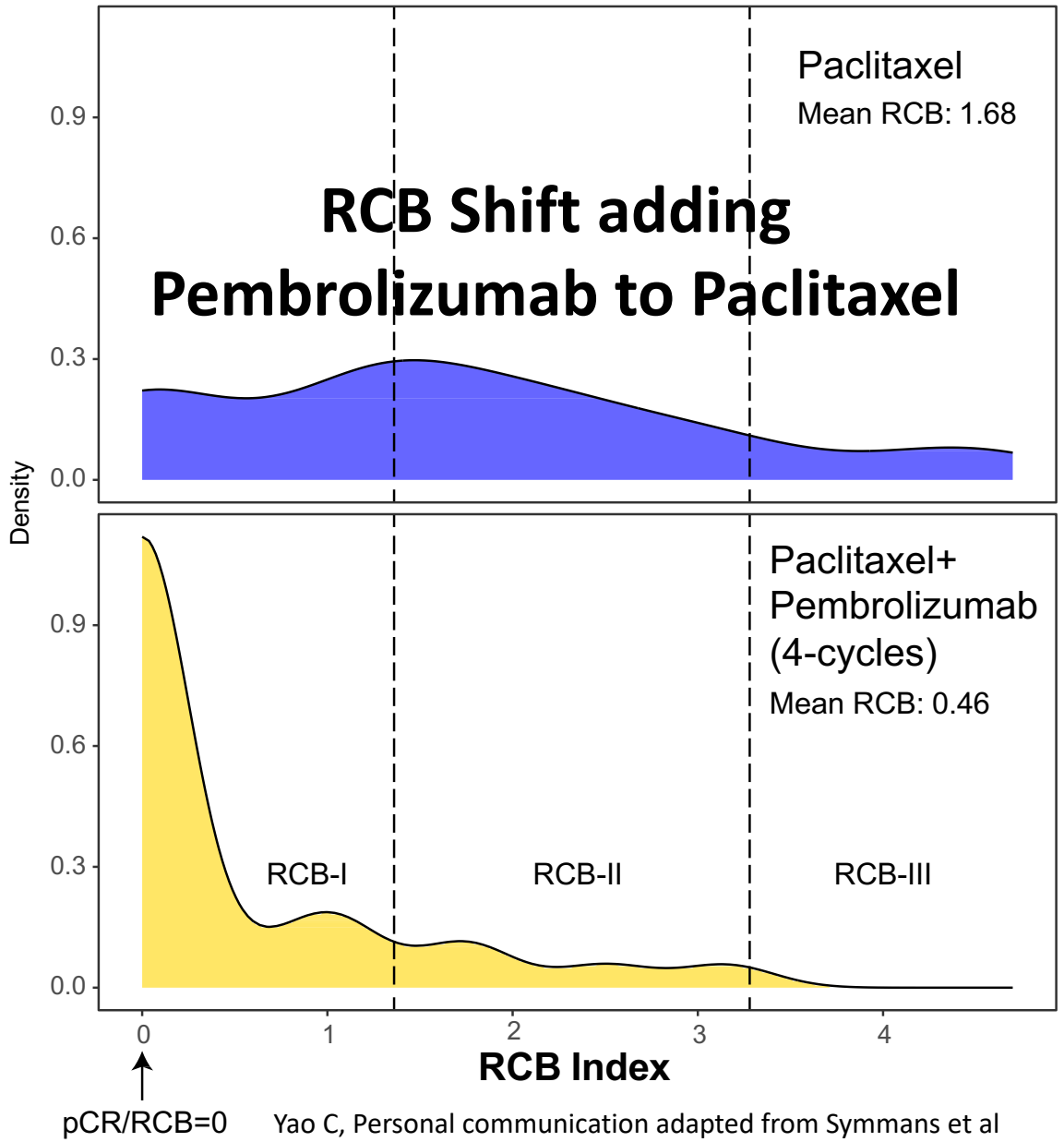
3 year EFS by RCB for TNBC



No. at risk

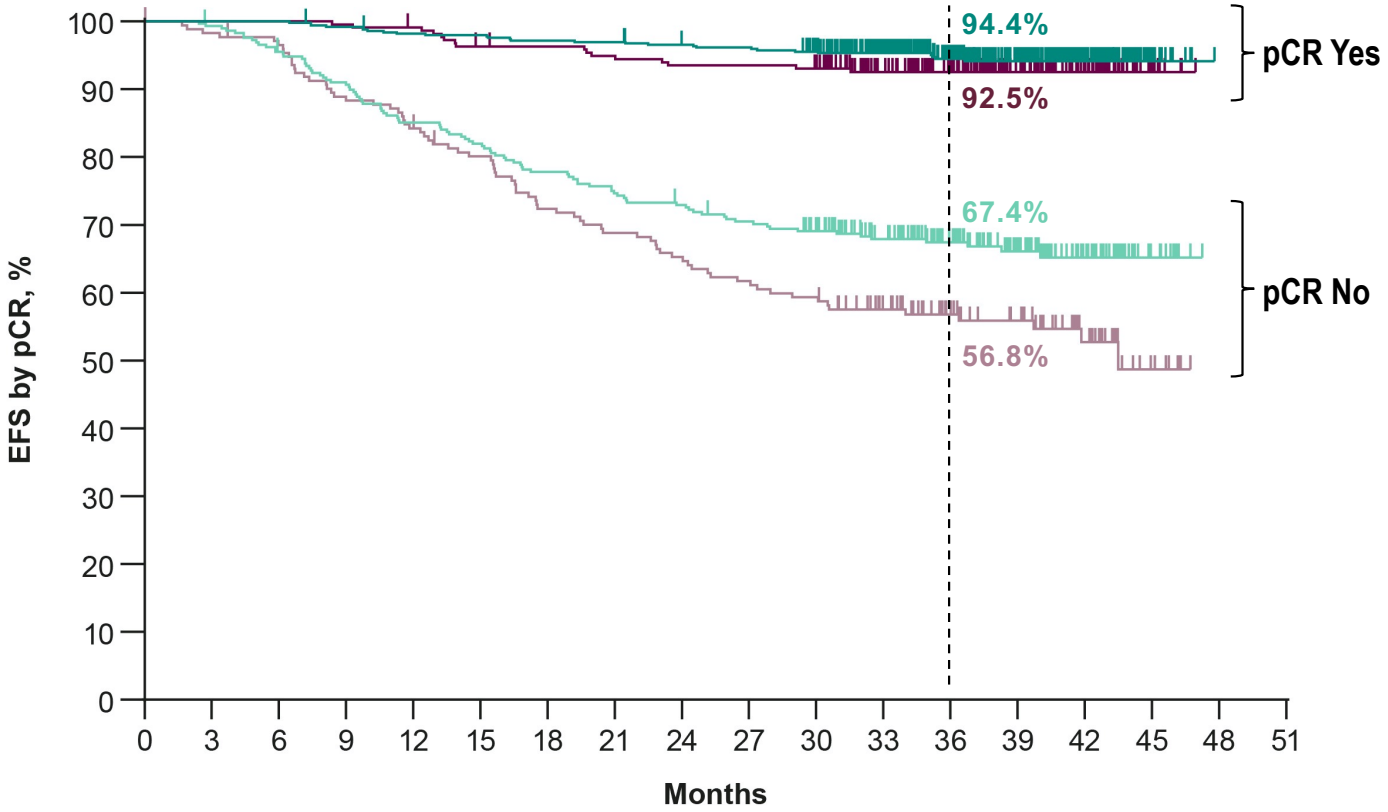
0	140	138	126	109	86	52
I	50	44	42	35	26	15
II	93	85	68	54	36	24
III	36	28	15	13	8	6

Symmans WF, *et al*. JAMA Oncol. 2021; Nanda et al, JAMA Onc 2020

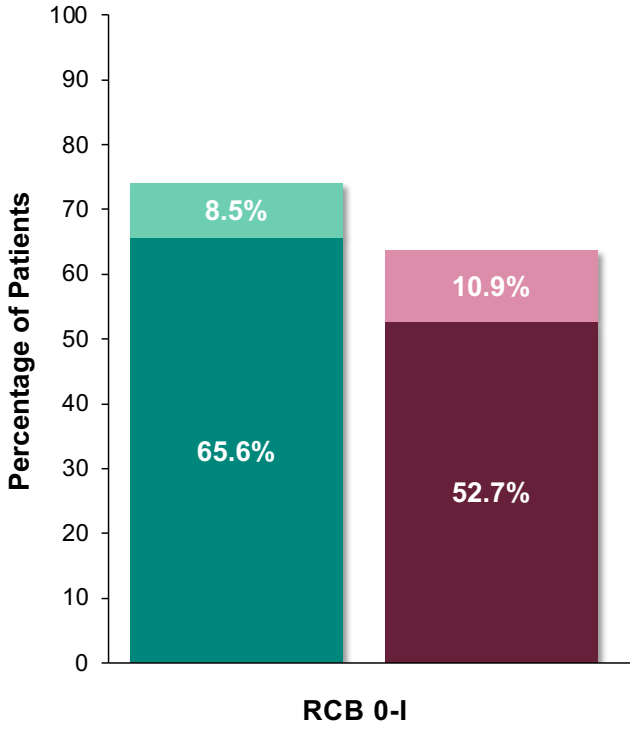


Yao C, Personal communication adapted from Symmans et al

EFS by pCR (ypT0/Tis ypN0)



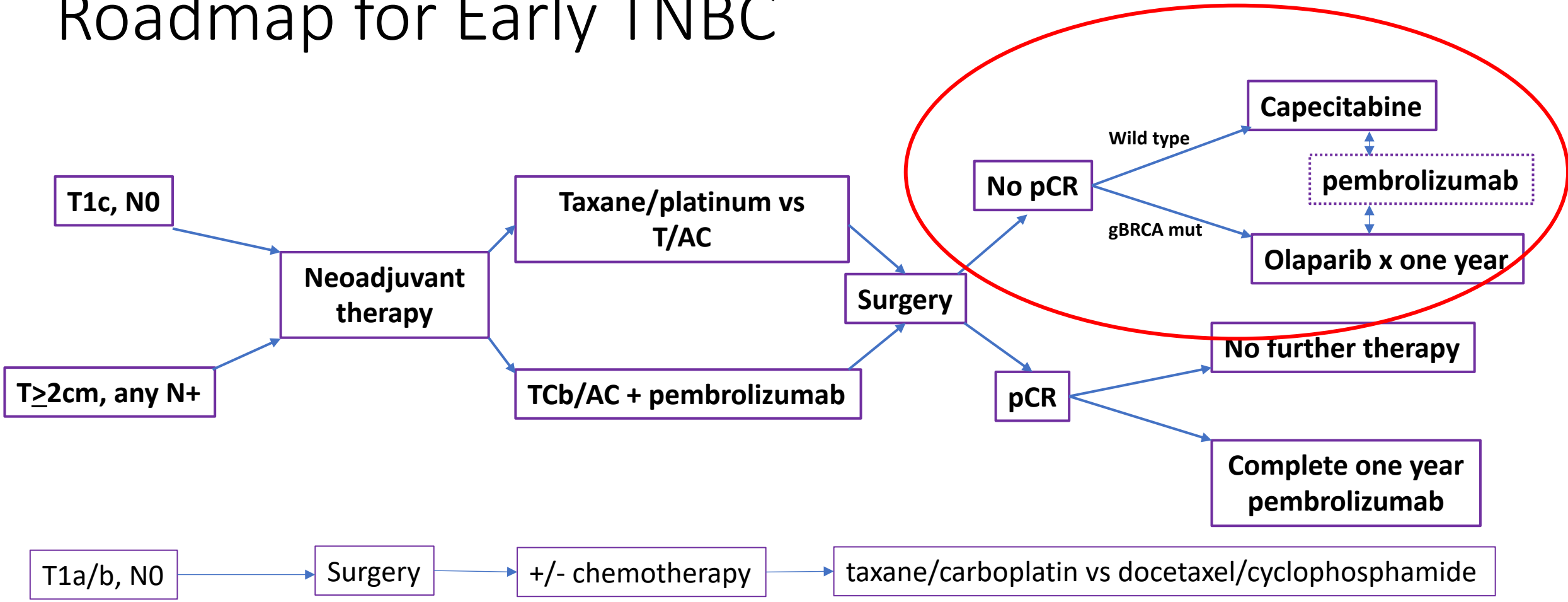
No. at Risk																		
Pembro + Chemo/Pembro Responder	494	494	494	489	483	482	478	477	472	470	460	387	307	220	122	18	0	0
Pbo + Chemo/Pbo Responder	217	217	217	216	214	207	206	203	200	200	197	165	130	87	56	9	0	0
Pembro + Chemo/Pembro Non-Responder	290	287	275	262	245	236	224	215	209	201	192	164	126	83	43	10	0	0
Pbo + Chemo/Pbo Non-Responder	173	169	165	152	144	135	122	116	110	104	100	85	65	53	27	8	0	0



RCB Frame Shift with Pembrolizumab at IA1

Schmid et al, SABCS 2019; Data cutoff date: April 24, 2019

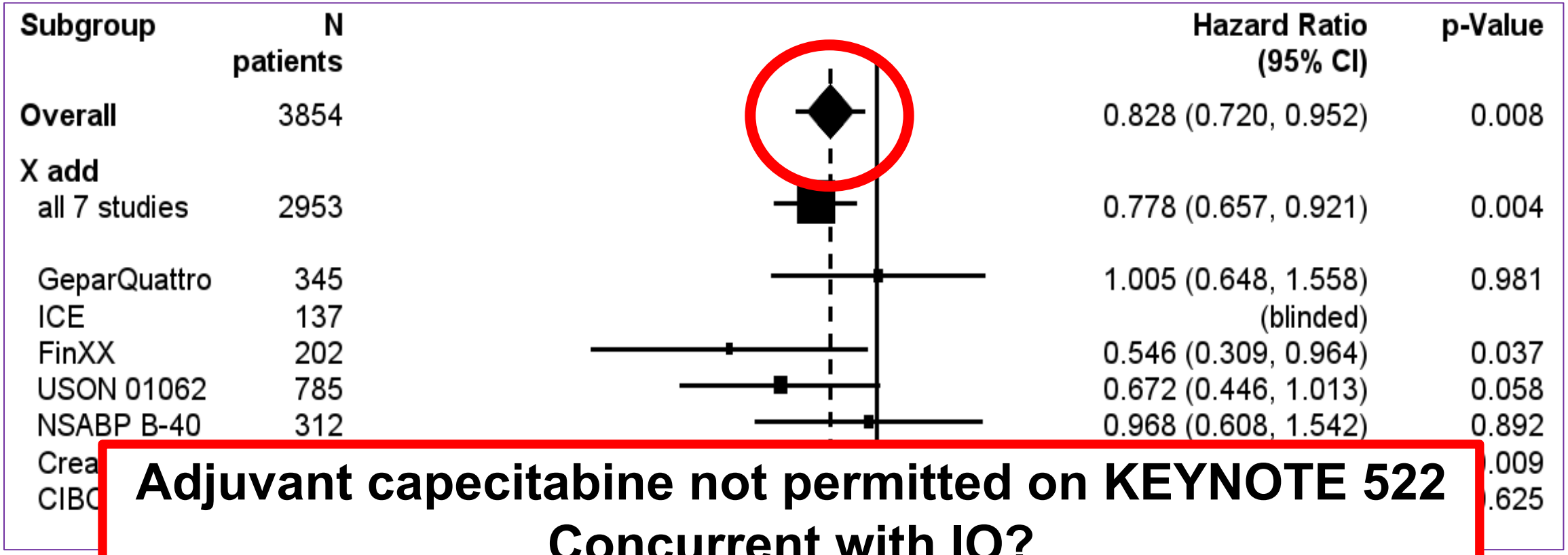
Roadmap for Early TNBC



- 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

A meta-analysis of individual patient data from 12 randomized trials including 15,457 patients

OS benefit in TNBC

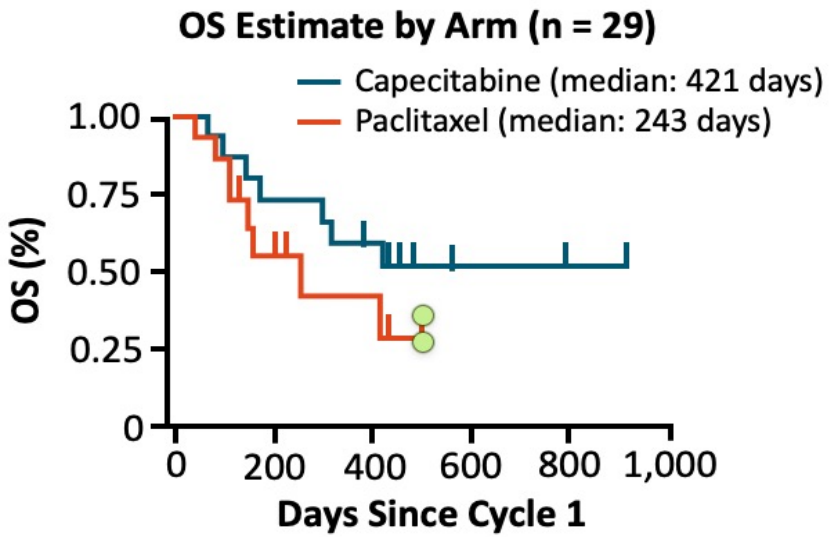


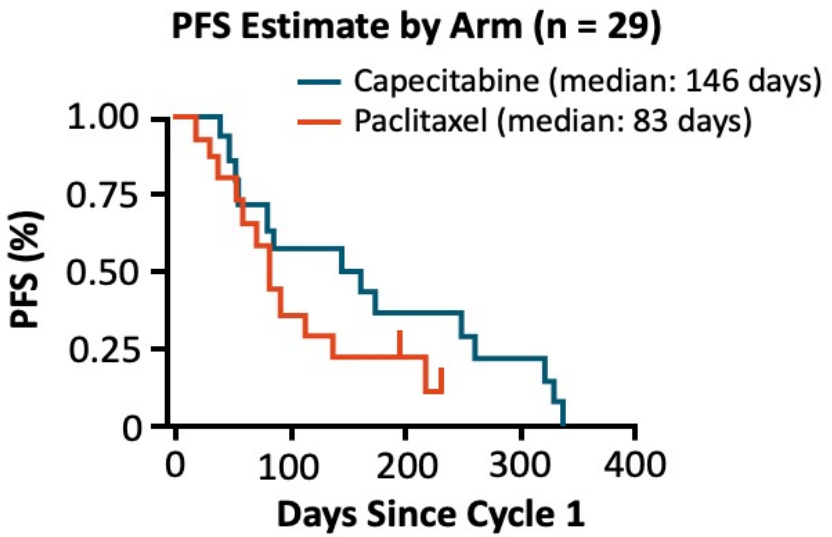
Subgroup	N patients	Hazard Ratio (95% CI)	p-Value
Overall	3854	0.828 (0.720, 0.952)	0.008
X add			
all 7 studies	2953	0.778 (0.657, 0.921)	0.004
GeparQuattro	345	1.005 (0.648, 1.558)	0.981
ICE	137	(blinded)	
FinXX	202	0.546 (0.309, 0.964)	0.037
USON 01062	785	0.672 (0.446, 1.013)	0.058
NSABP B-40	312	0.968 (0.608, 1.542)	0.892
Crea			.009
CIBC			.625

Adjuvant capecitabine not permitted on KEYNOTE 522
Concurrent with IO?

van Mackelenbergh M et al. 2019 SABCS. Abstract GS1-07.

First- or Second-line Pembrolizumab With Capecitabine in mTNBC





Week 12 ORR: 43% with pembro/capecitabine

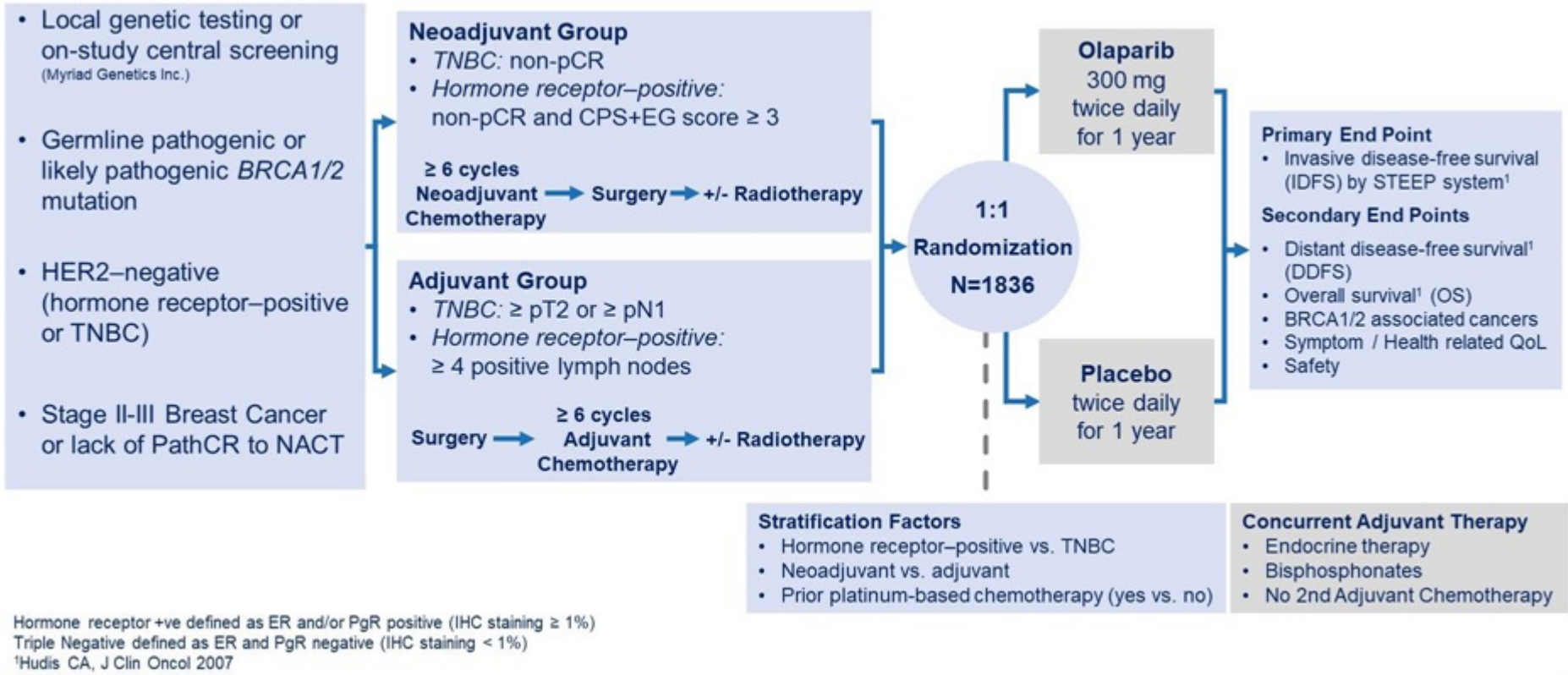
Co-administration was safe

Co-administration of adjuvant pembro/capecitabine may be

reasonable in selected high-risk patients with residual TNBC after NAC

Page DB et al. 2019 ASCO Annual Meeting. Abstract 1015.

OlympiA phase III Adjuvant Olaparib trial in gBRCA1/2 High Risk Patients



Hormone receptor +ve defined as ER and/or PgR positive (IHC staining ≥ 1%)
Triple Negative defined as ER and PgR negative (IHC staining < 1%)
[1]Hudis CA, J Clin Oncol 2007

Eligibility

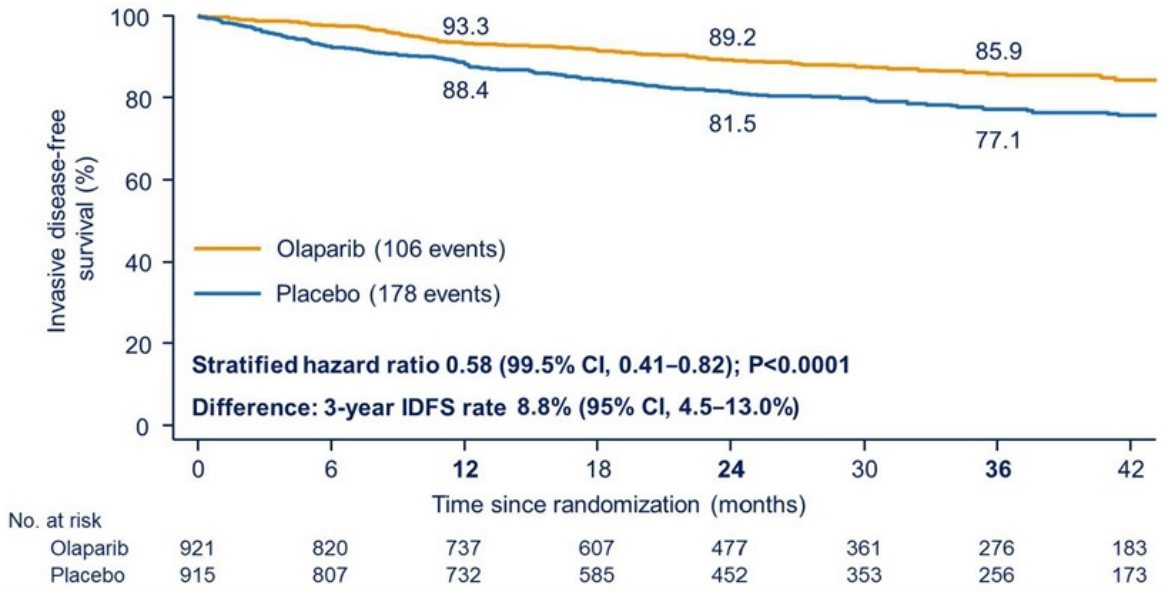
- **TNBC (82%) - non-pCR <u>OR</u> if adjuvant, ≥ pT2 or ≥ N1**
- **HR+HER2 negative (18%) - non-pCR AND CPS+EG ≥ 3 <u>OR</u> if adjuvant, ≥ 4 nodes**

CPS score-pretreatment clinical stage and post-treatment pathologic stage; EG- estrogen receptor status and tumor grade. Scores range 0-6

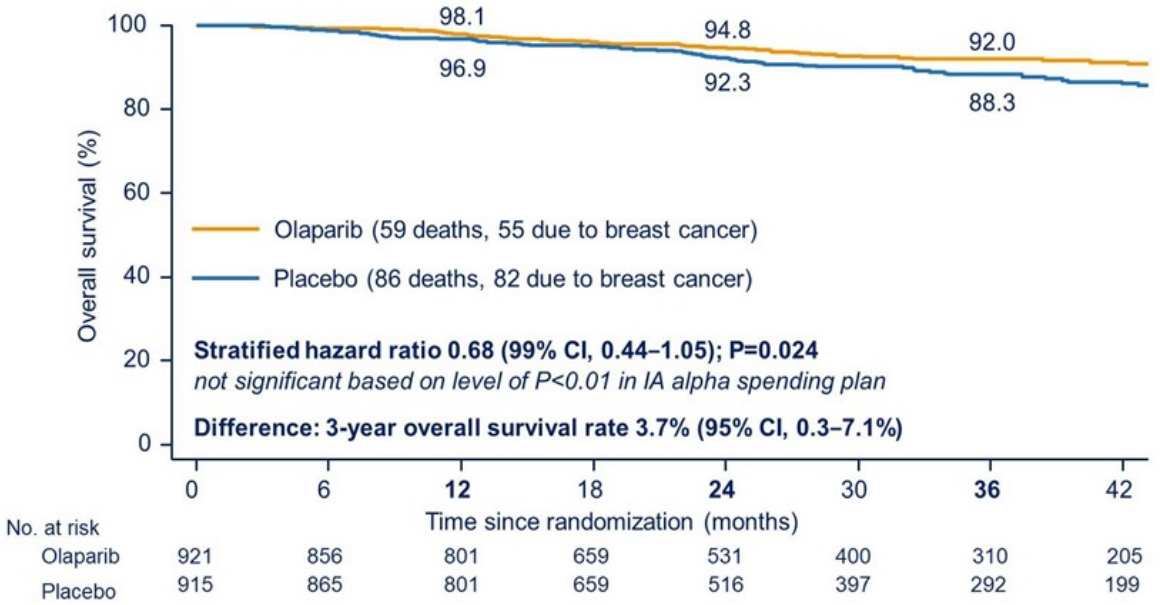
Tutt et al. ASCO 2021
Tutt et al. NEJM 2021

ADJUVANT OLAPARIB FDA APPROVED!!!!

OlympiA: Invasive disease-free survival (ITT)



OlympiA: Overall survival



HR 0.68 p=0.009 3.5 yrs follow-up
3-year OS 92% vs 89.1%

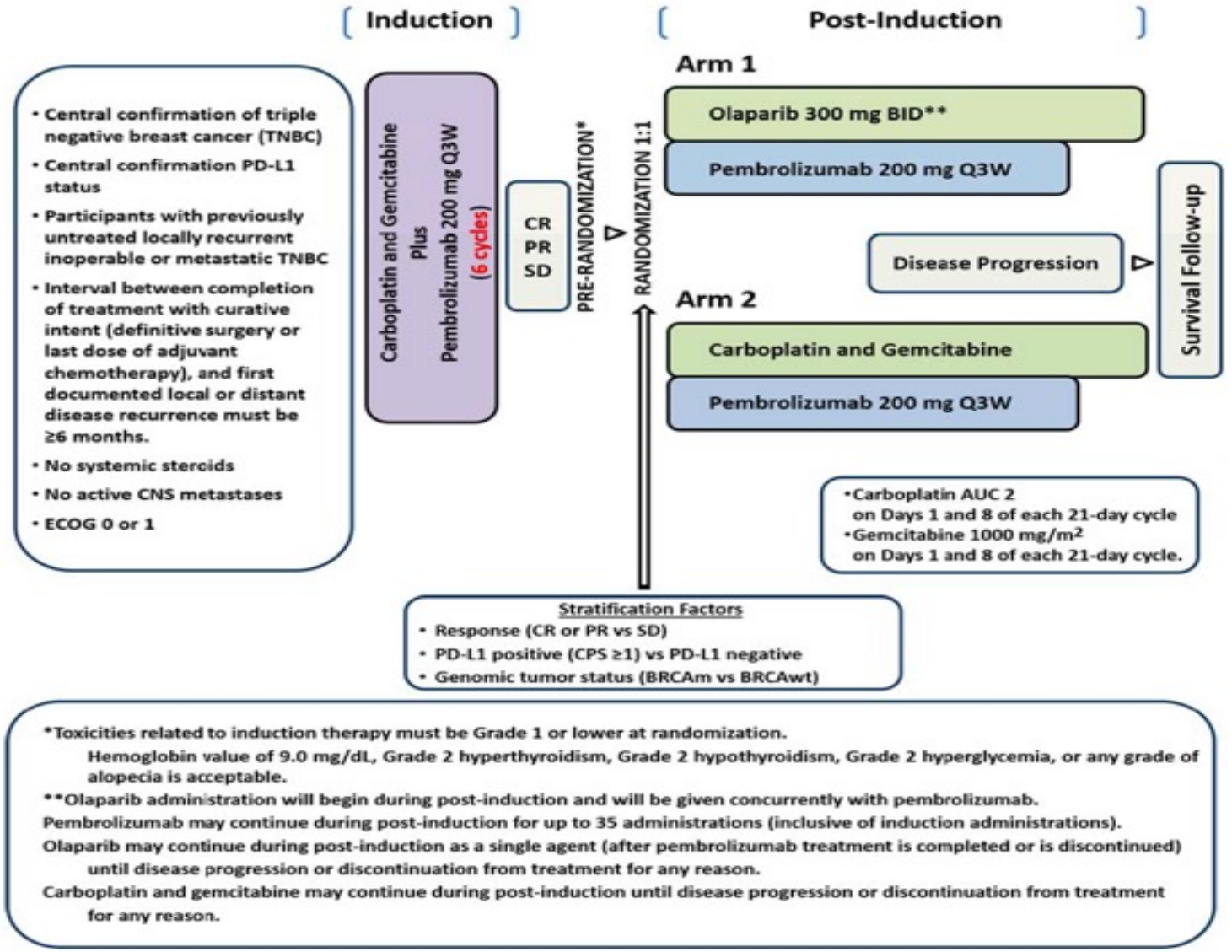
- **Treatment discontinuation - 9.9% with O and 4.2% with P**
- **SAEs - 8.7% with O and 8.4% with P**
- **No additional MDS/AML or new primary malignancy**
- **Expected to be superior to adjuvant capecitabine based on OlympiAD where ~45% received capecitabine**
- **Capecitabine underperformed in basal subtype patients in EA1131 & g*BRCA* commonly basal**

Practice-changing. NCCN germline genetic testing guidelines now updated. Clinicians should pay attention to improved equity & utilization of genetic testing.

Tutt et al. ASCO 2021
Tutt et al. NEJM 2021
Tutt et al ESMO VP 2022

Olaparib + Pembrolizumab is Safe in Multiple Ongoing Trials

KEYLYNK-009



PI: Hope Rugo

Immunotherapy for Breast Cancer

- Adjuvant pembrolizumab needed post-pCR? Longer term trials show about 15% chance of recurrence or DFS event in pCR pts
- Adjuvant pembrolizumab may synergize with radiation therapy
- Adjuvant pembrolizumab needed post-pCR? - randomized trial planned but for now, YES, as stage II/III TNBC is high risk population
- 33% chance of recurrence at 3 years in patients with RD in KN-522 with pembrolizunab
- Safe and reasonable to combine adjuvant pembrolizumab + olaparib or capecitabine in high risk pts with RD
- Trial of Topoisomerase-1 ADCs plus pembrolizumab in RD pts planned