UT Southwestern
Medical Center

Immunotherapy for Breast Cancer: Current and Future Directions

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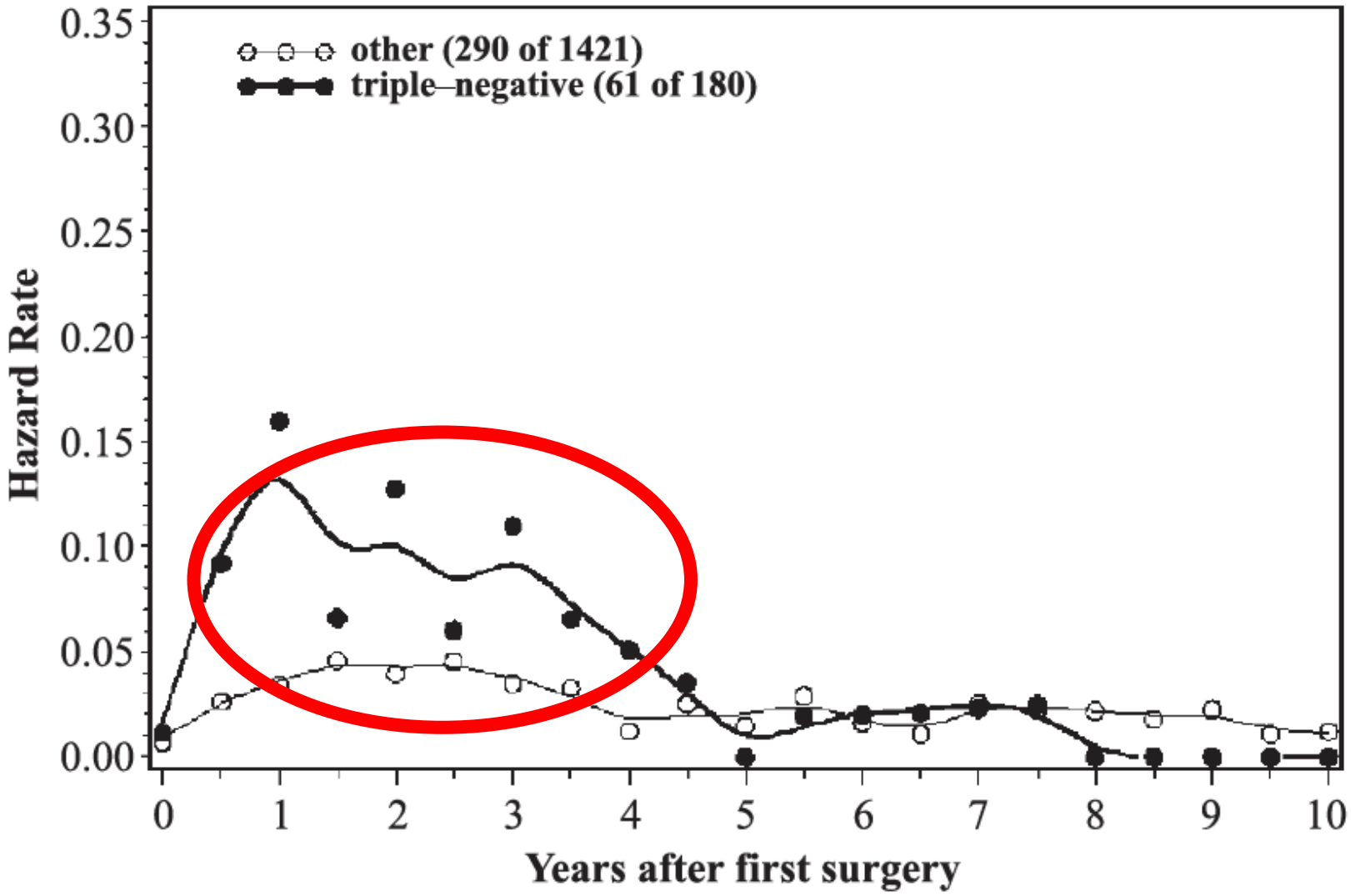
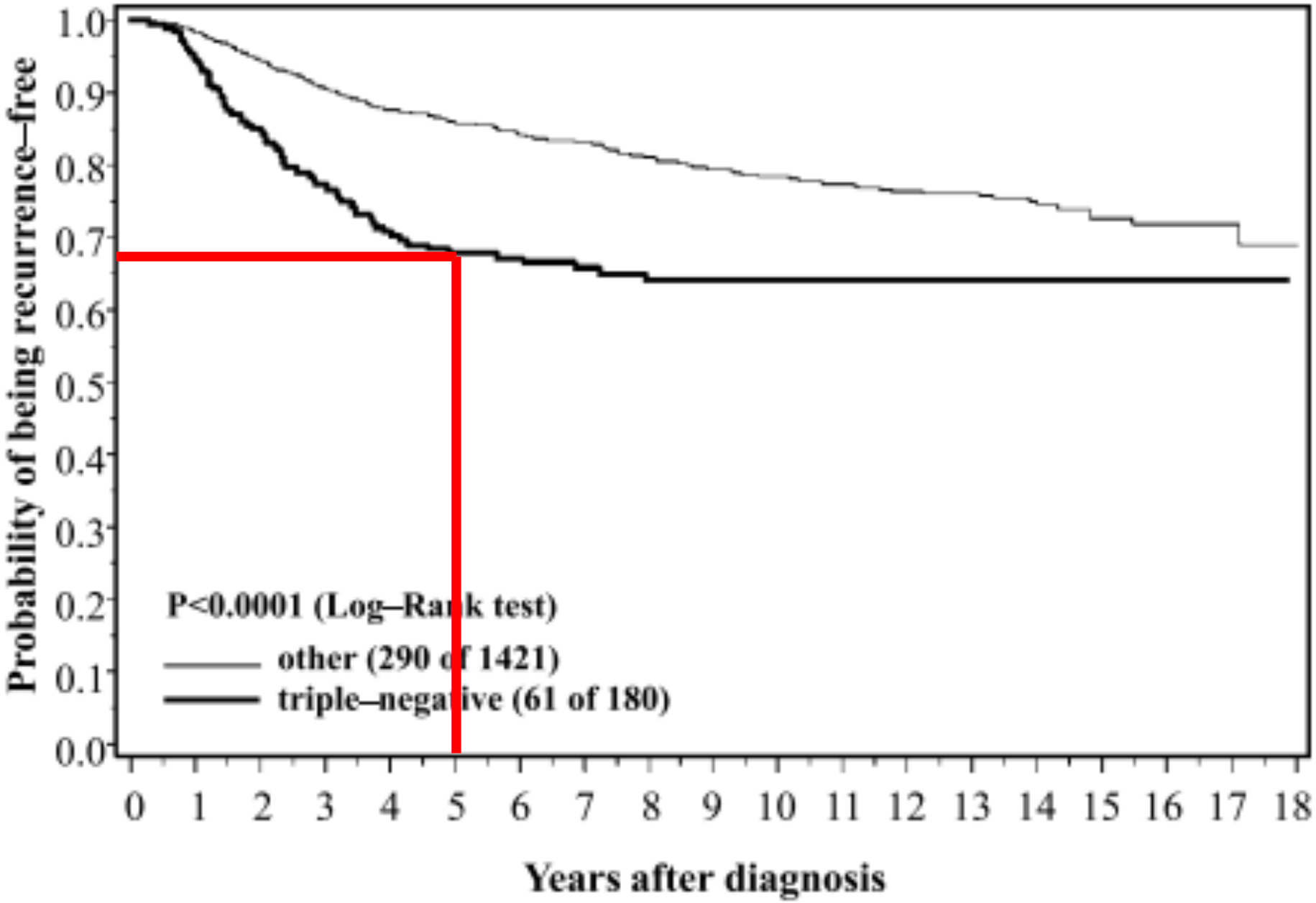
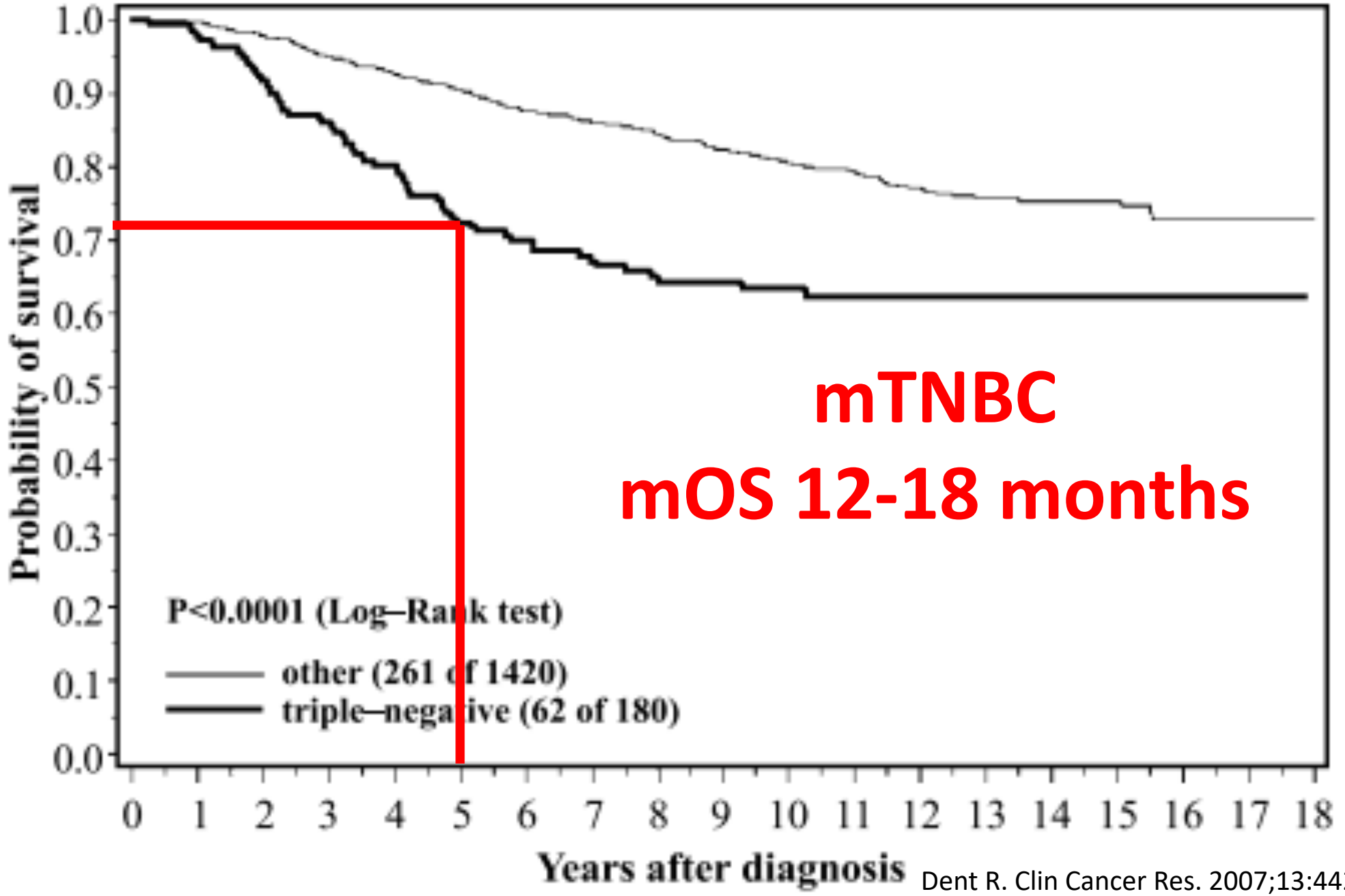
Risk of Recurrence Occurs Early



Dent R. Clin Cancer Res. 2007;13:4429-4434.



Dent R. Clin Cancer Res. 2007;13:4429-4434.



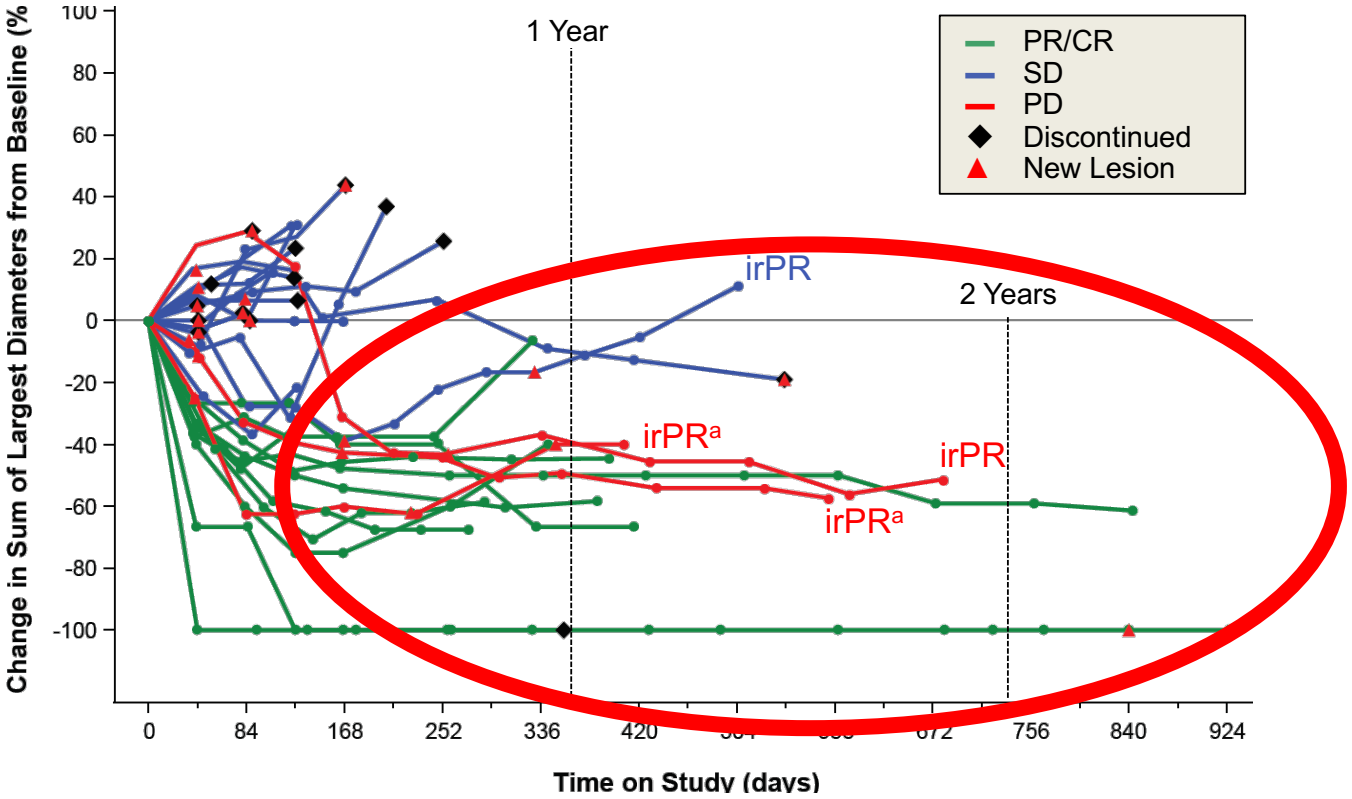
mTNBC

mOS 12-18 months

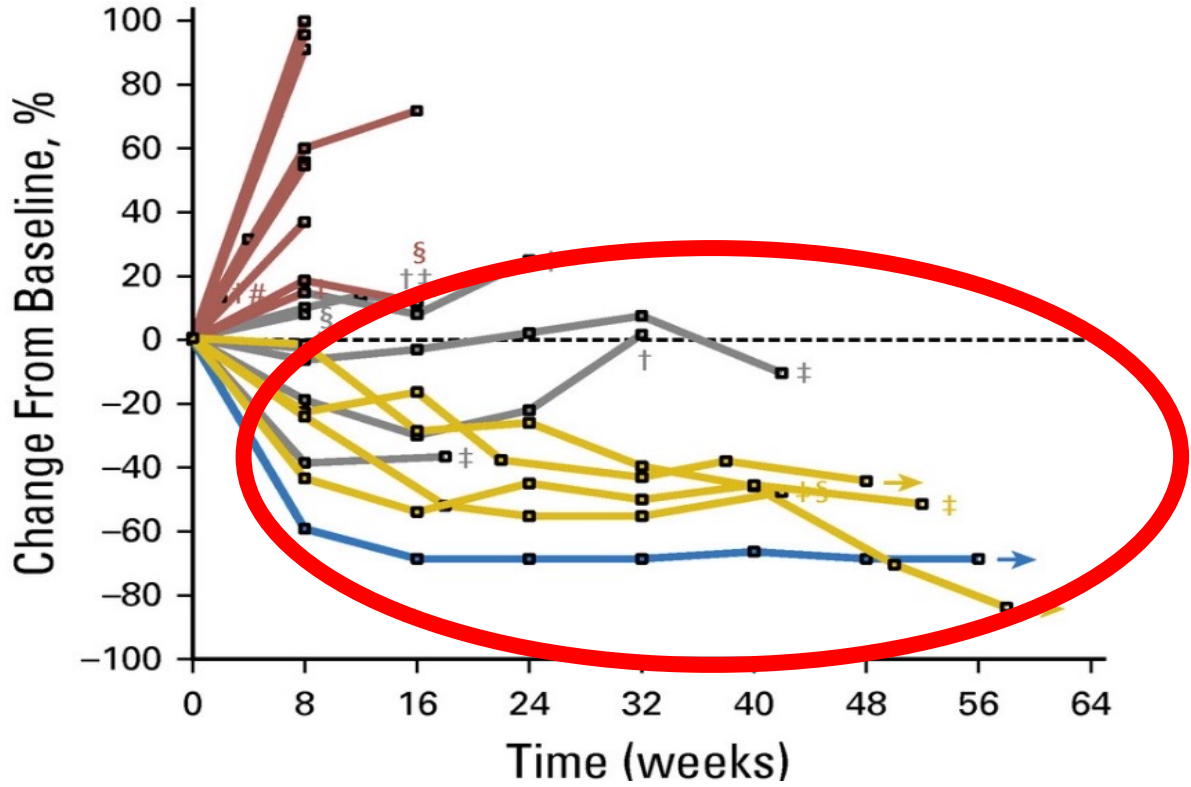
Dent R. Clin Cancer Res. 2007;13:4429-4434.

The Promise of Immune Therapy for Breast Cancer

Atezolizumab



Pembrolizumab



Schmid et al. 2017 AACR. Emens LA et al. *JAMA Oncol.* 2019;5(1):74-82.

Nanda R et al. *J Clin Oncol*. 2016;34(21):2460-2467.

KEYNOTE-355 Study Design (NCT02819518)

- paclitaxel,
- nab-paclitaxel
- gemcitabine/carboplatin

Key Eligibility Criteria

- Age ≥18 years
- Central determination of TNBC and PD-L1 expression
- Previously untreated locally recurrent inoperable or metastatic TNBC
- 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[a] + Chemotherapy[b]

Placebo[c] + Chemotherapy[b]

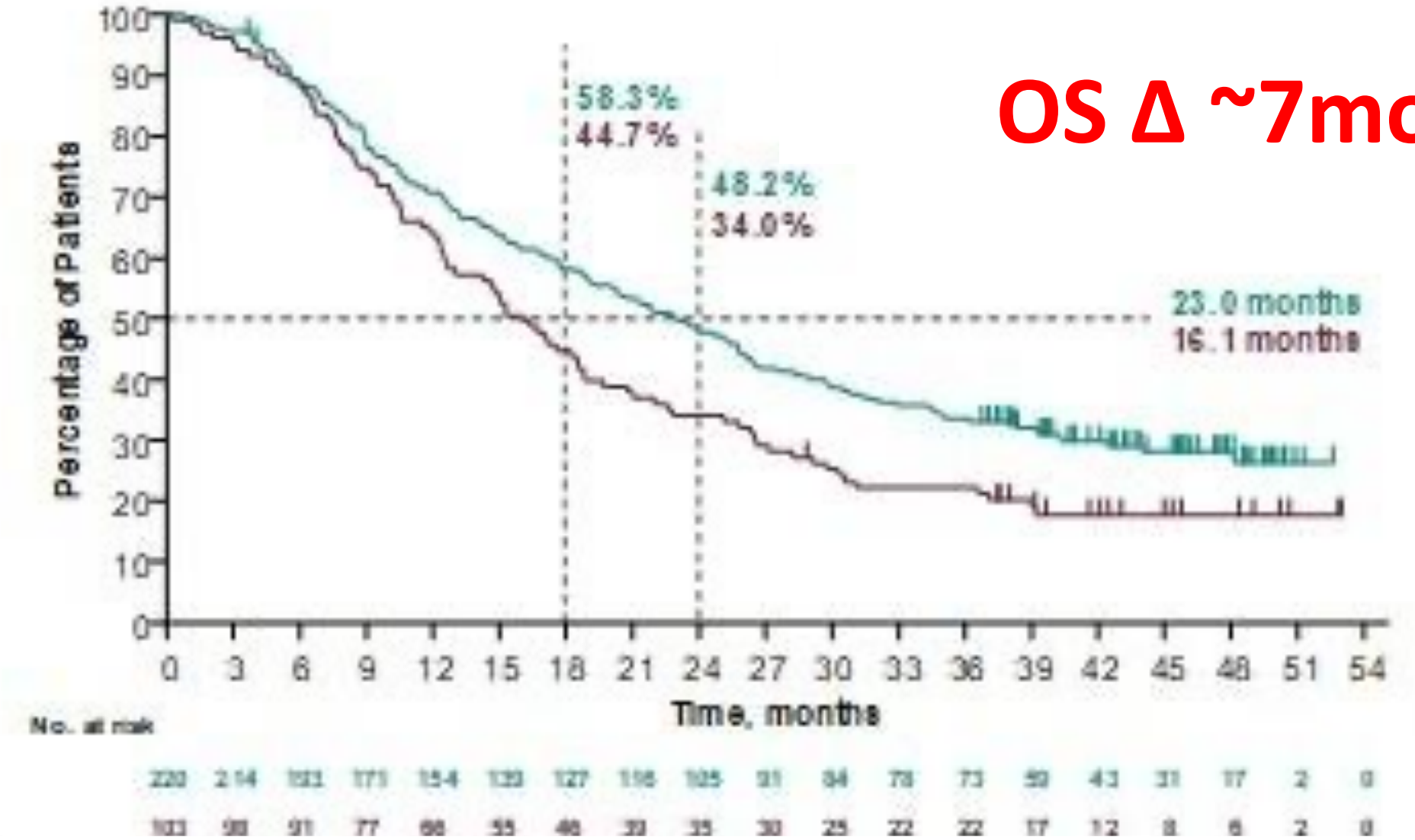
Progressive disease[d]/cessation of study therapy

Stratification Factors:

- Chemotherapy on study (taxane vs gemcitabine/carboplatin)
- PD-L1 tumor expression (CPS ≥1 vs CPS <1)
- Prior treatment with same class chemotherapy in the neoadjuvant or adjuvant setting (yes vs no)

Cortes J et al. ASCO 2020. Abstract 1000.

Overall Survival: PD-L1 CPS ≥10



OS Δ ~7mo

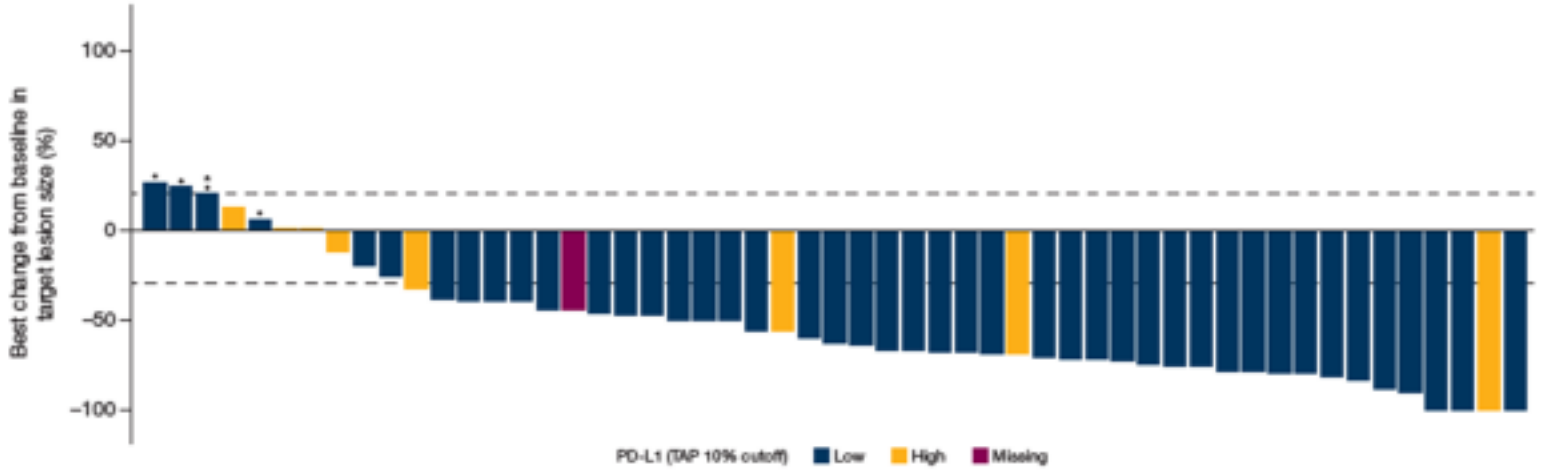
Cortes et al. Abstract LBA16, ESMO 2021

FDA-Approval[1]

On 11/13/20, the FDA granted accelerated approval to **pembrolizumab** in combination with chemotherapy for patients with unresectable or metastatic TNBC whose tumors express **PD-L1 (CPS ≥10)** as determined by an FDA-approved test.

1. www.fda.gov.

BEGONIA: TDxd+Durvalumab



n = 53.
Dotted reference lines at −30% and 20% indicate thresholds for partial response and progressive disease, respectively.
*If the best percentage change from baseline of target lesions cannot be calculated due to progression, withdrawal, or death, the value is imputed at +20%. "•" Patients with progressive disease as best overall response.

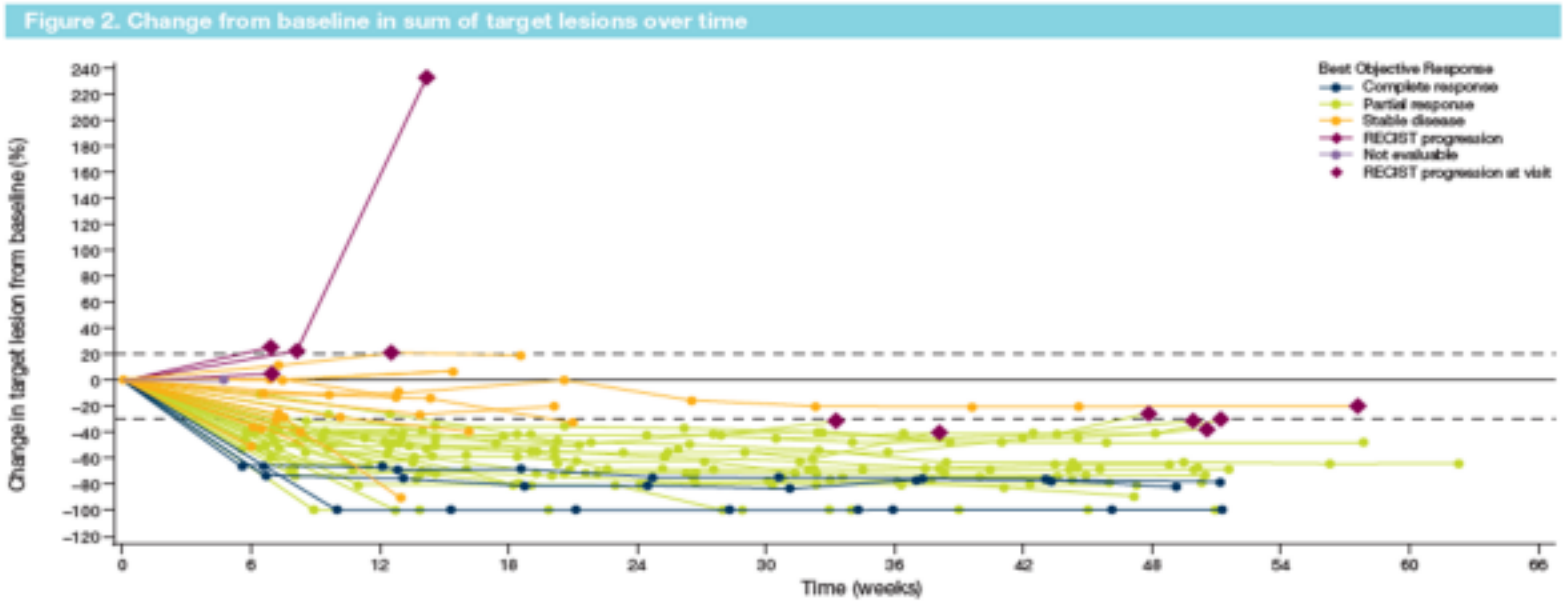
Confirmed ORR = 39 (73.6%)

- Complete Response = 4
- Partial Response = 35

Durable Responses with 82% ongoing at data cutoff
(median follow-up time 7.2 months)

Responses irrespective of

- *PD-L1 status*



Schmid et al. SABCS 2022

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

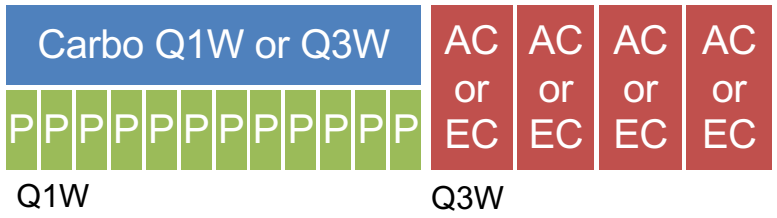
Primary endpoints

- pCR rate (ypT0/Tis ypN0)
- EFS

Secondary endpoints

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

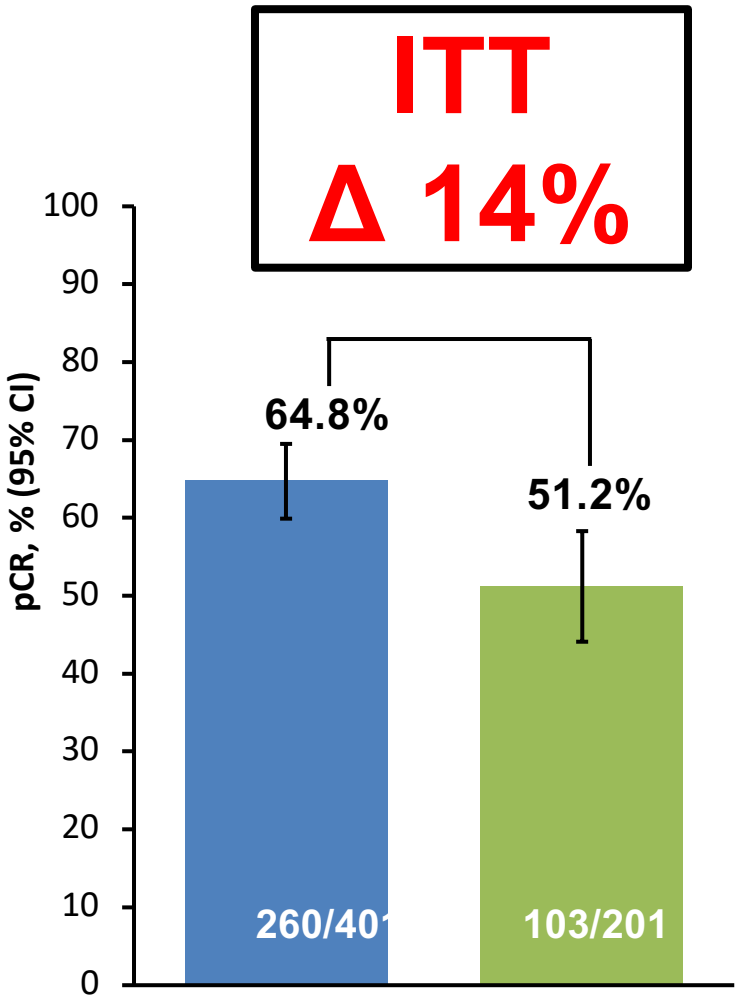
Study Treatment

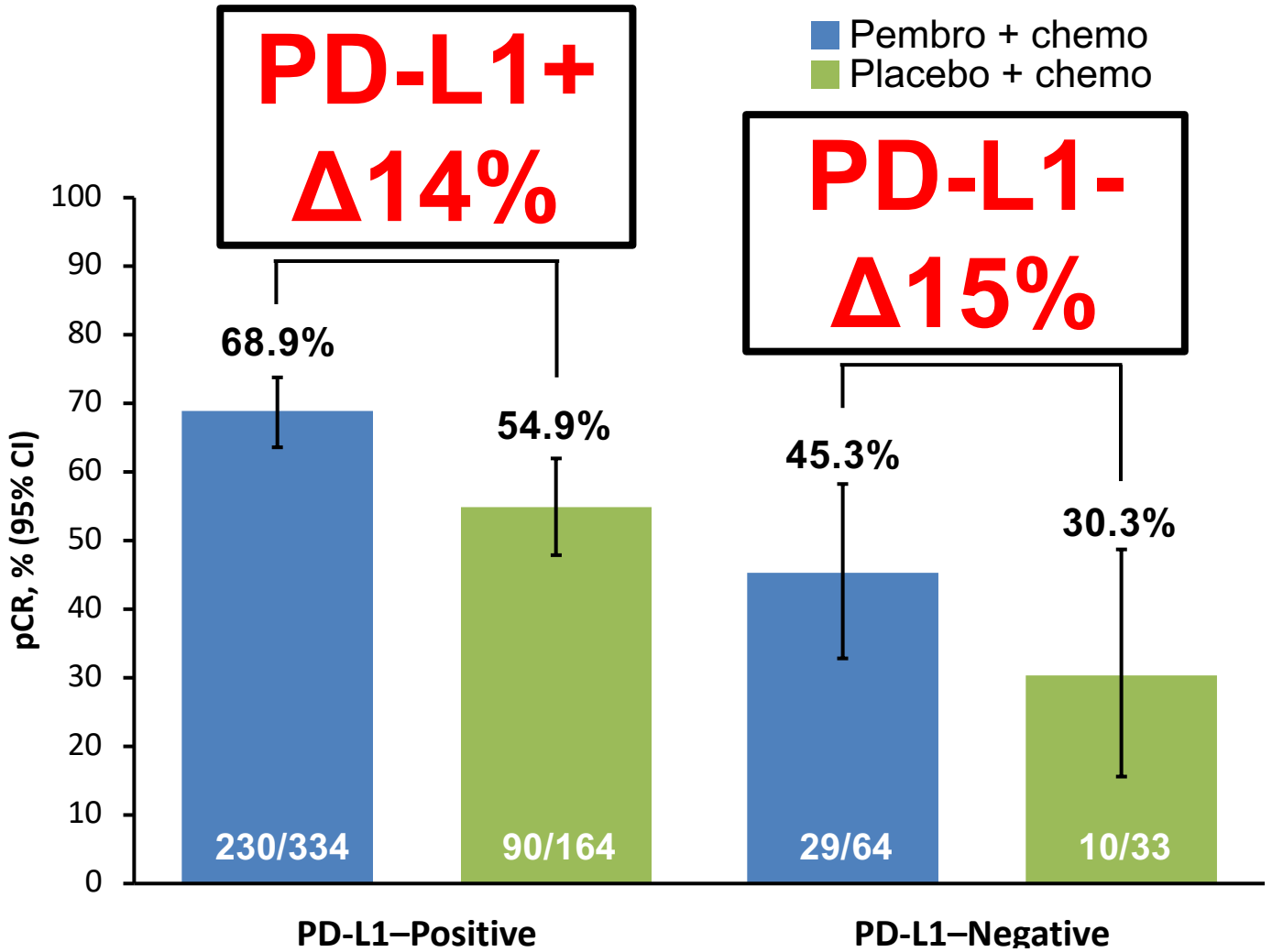


Paclitaxel 80 mg/m^2 IV weekly
Carboplatin weekly (AUC 1.5) or Q3W (AUC5)
Doxorubicin 60 mg/m^2 IV Q3W
(Epirubicin 90 mg/m^2 IV Q3W)
Cyclophosphamide 600 mg/m^2 IV Q3W
Pembrolizumab 200 mg IV Q3W

Schmid P et al. NEJM 2019.

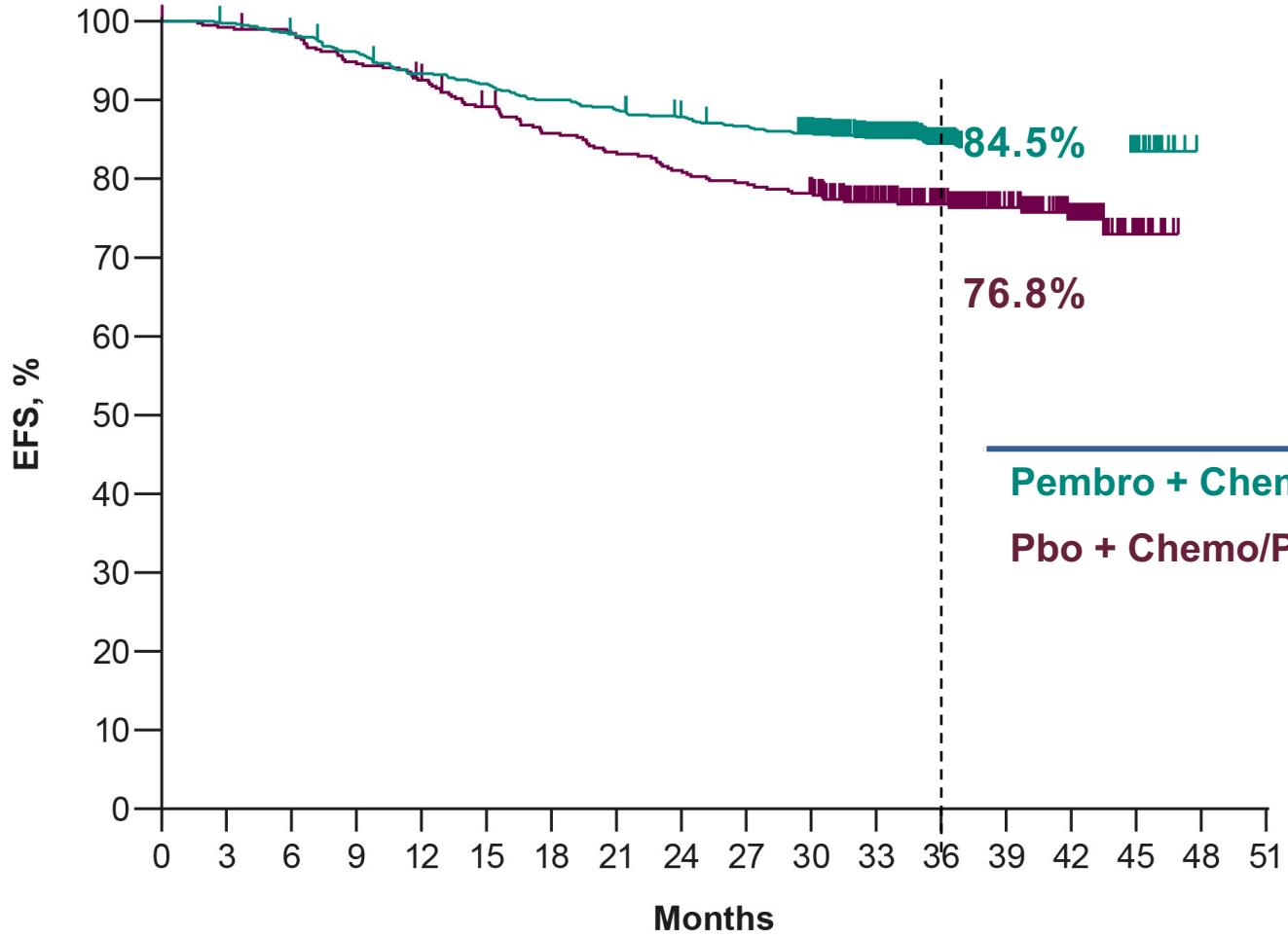
KEYNOTE-522: pCR at IA1





Schmid P et al. NEJM 2019.

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



Δ7.7%

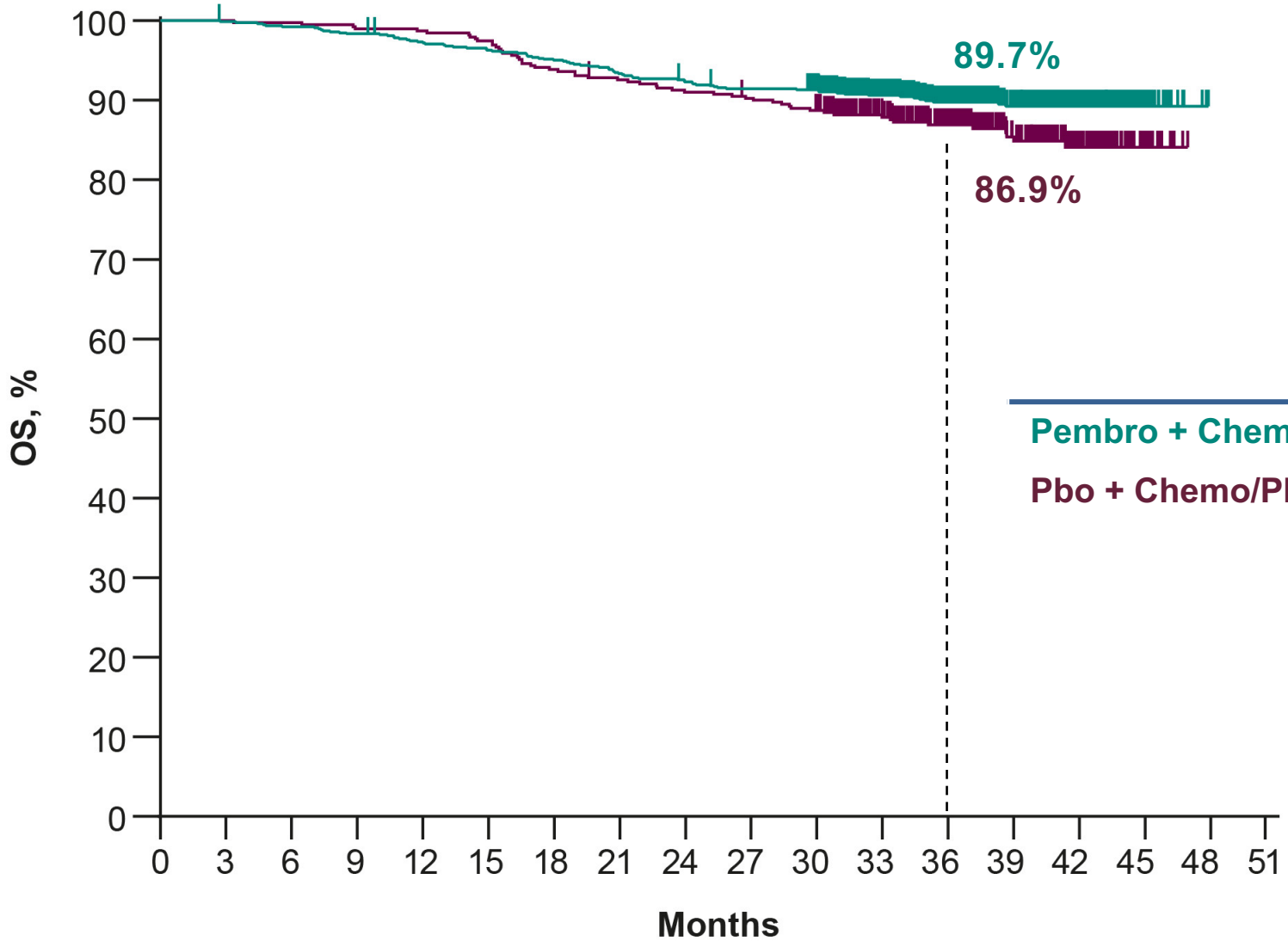
	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	15.7%	0.63[a]	0.00031[b]
Pbo + Chemo/Pbo	23.8%		

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 et al. ESMO Virtual Plenary. Abstract VP7-2021. Presented July 15, 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 et al. ESMO Virtual Plenary. Abstract VP7-2021. Presented July 15, 2021.

FDA-Approval

On **July 27, 2021**, the FDA approved pembrolizumab for high-risk early-stage TNBC with chemotherapy as neoadjuvant treatment and then continued as a single agent as adjuvant treatment after surgery

Based on KEYNOTE-522, the indication for palliative pembrolizumab was converted from accelerated to full approval

www.fda.gov

FDA-Approval

On **July 27, 2021**, the FDA approved
risk early-stage TNBC with ch
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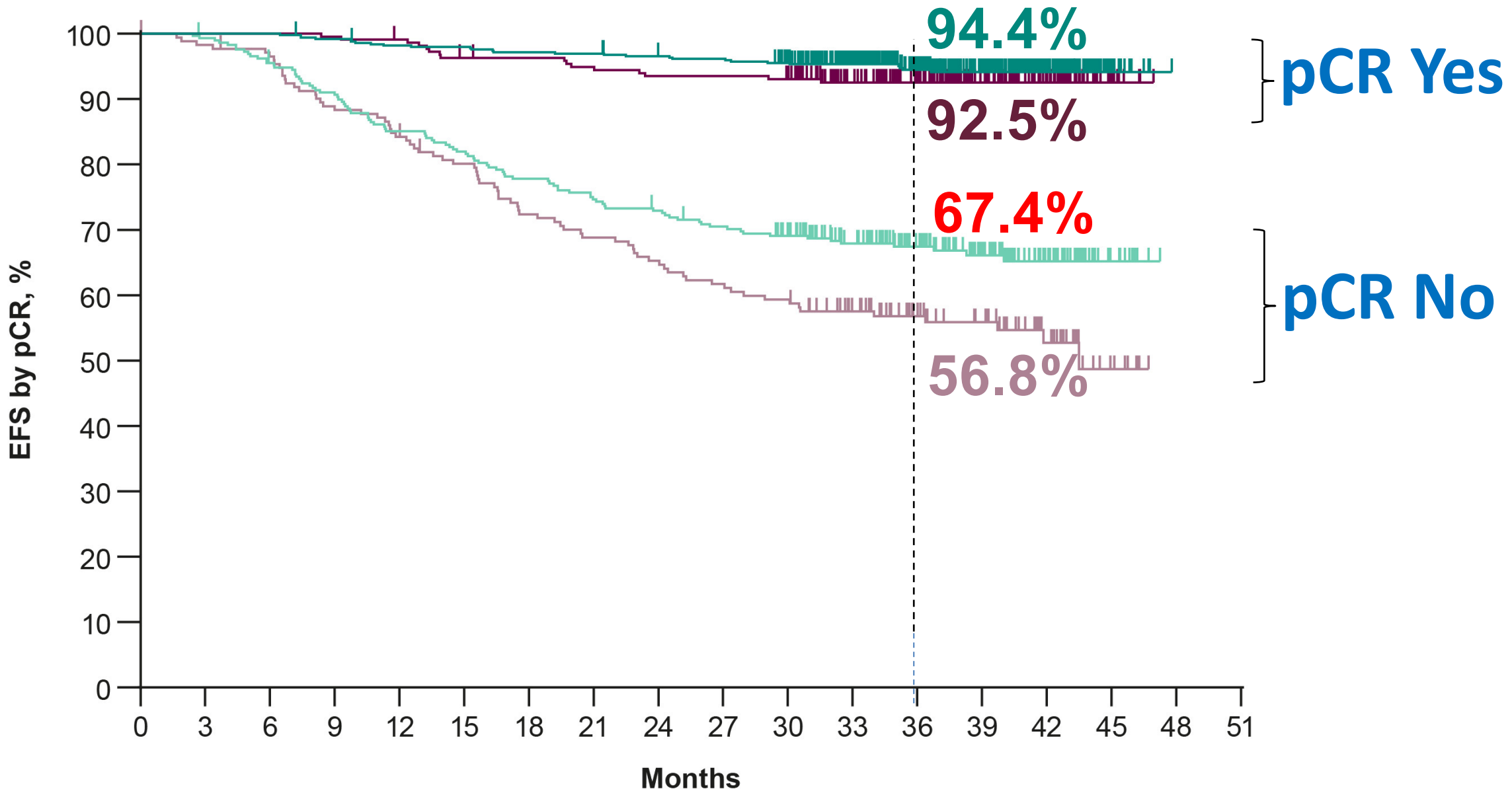
NEW SOC!!
BUT MANY NEW QUESTIONS!

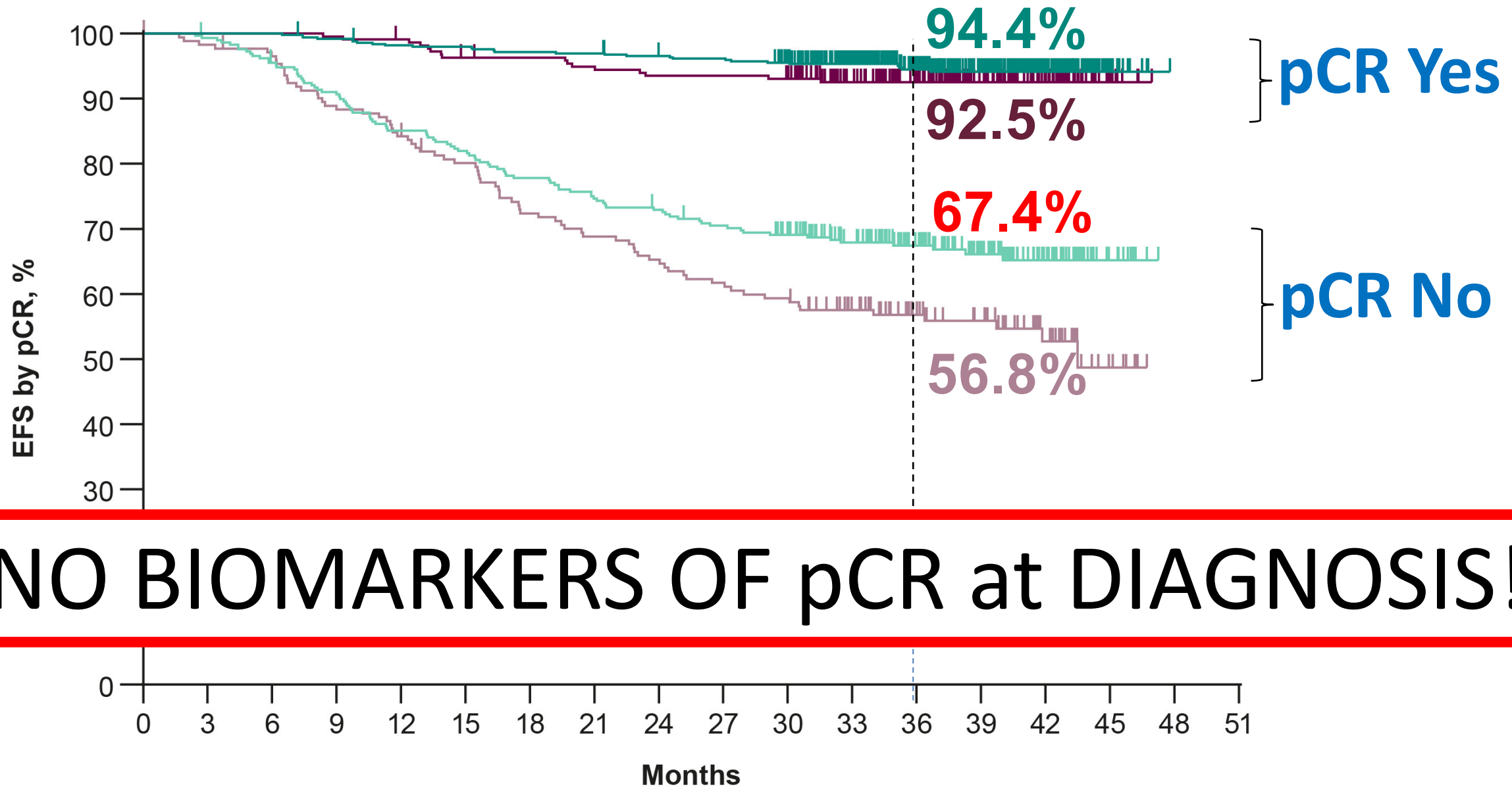
www.fda.gov

Q#1: What Subset Derives Benefit?



Schmid et al. ESMO Virtual Plenary. Abstract VP7-2021. Presented July 15, 2021.

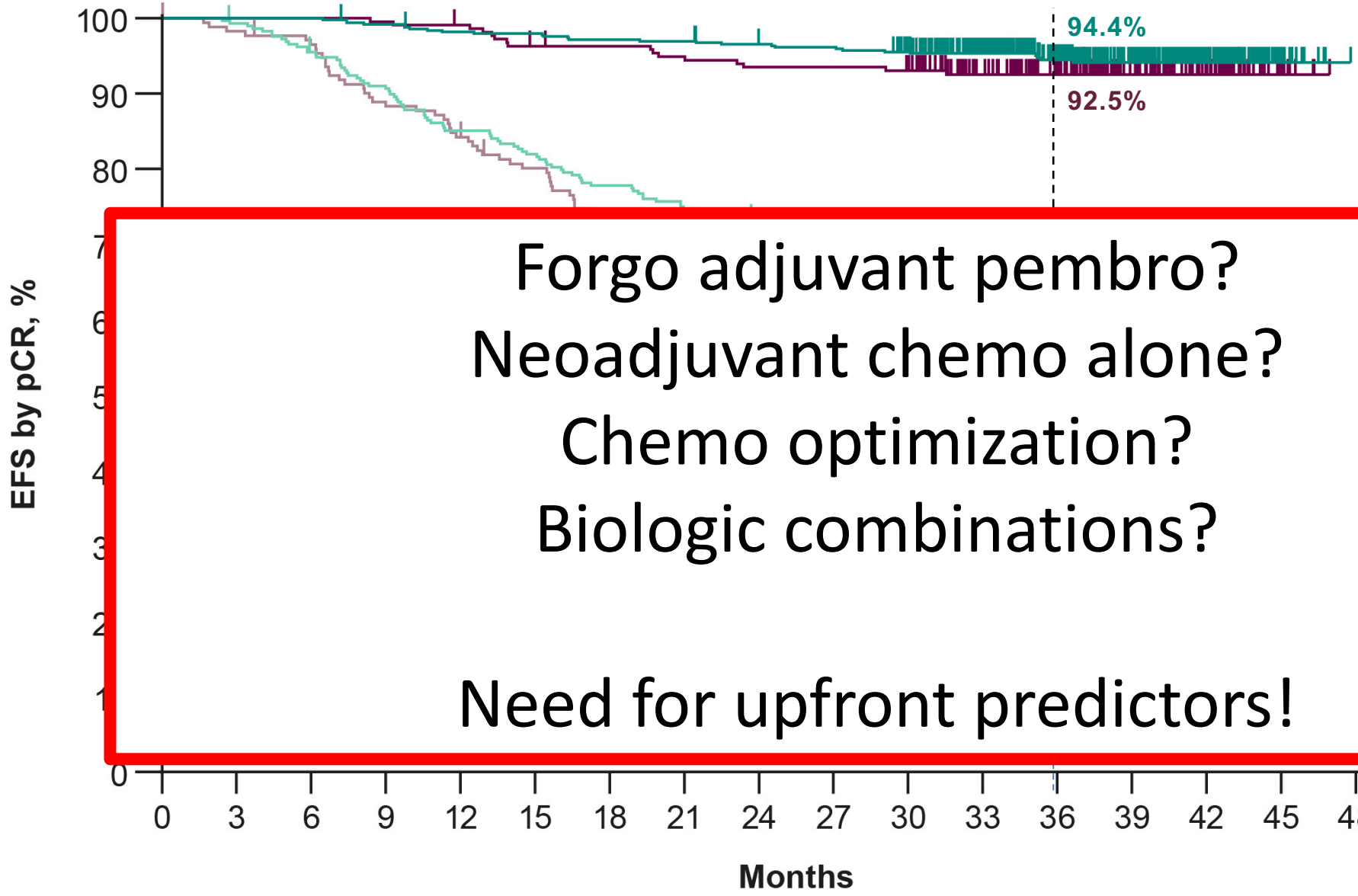
Q#1: What Subset Derives Benefit?



NO BIOMARKERS OF pCR at DIAGNOSIS!

Schmid et al. ESMO Virtual Plenary. Abstract VP7-2021. Presented July 15, 2021.

EFS by pCR



pCR Yes

Forgo adjuvant pembro?

Neoadjuvant chemo alone?

Chemo optimization?

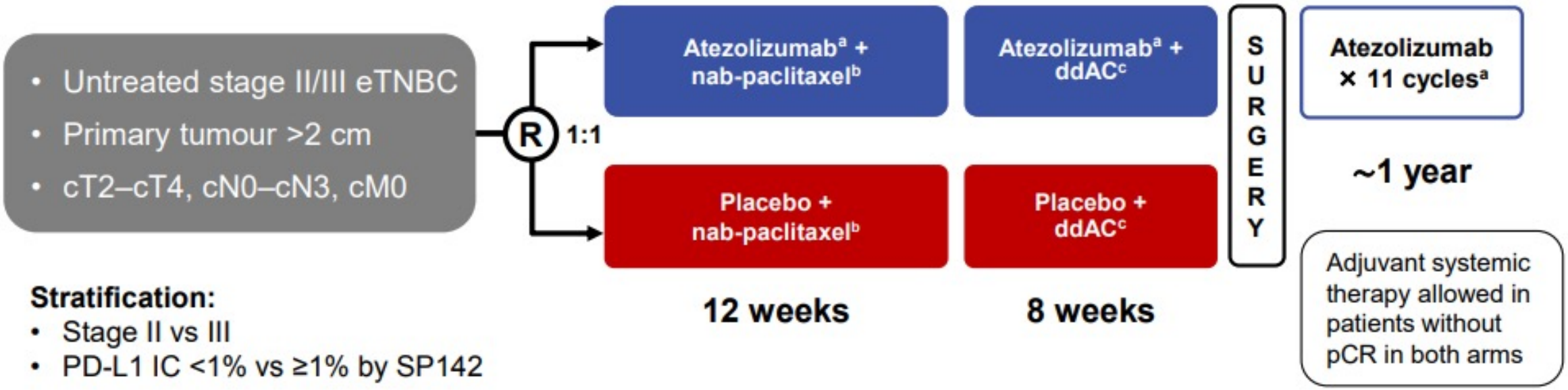
Biologic combinations?

Need for upfront predictors!

Schmid et al. ESMO Virtual Plenary. Abstract VP7-2021. Presented July 15, 2021.

IMpassion031 TRIAL DESIGN

Randomised international phase 3 trial



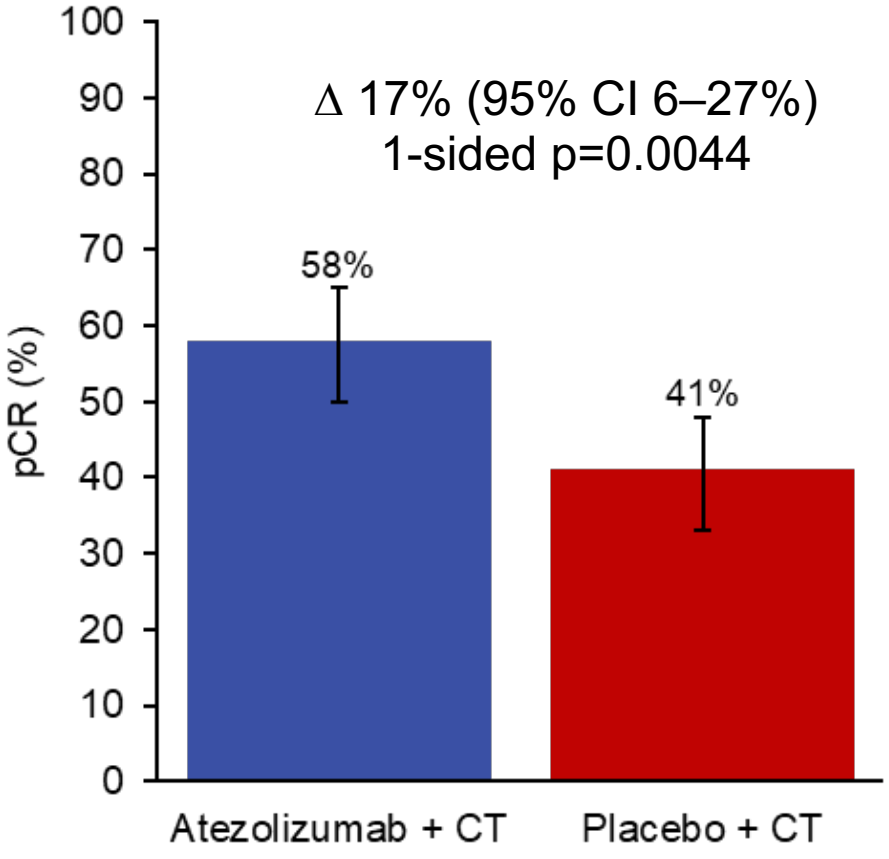
Co-primary endpoints: pCR (ypT0/is ypN0) in ITT and PD-L1+ (IC ≥1%) populations

Secondary endpoints: EFS, DFS and OS in ITT and PD-L1+ populations (no formal statistical comparison), safety, PROs

[a]Atezolizumab 840 mg every 2 weeks (neoadjuvant) and 1200 mg every 3 weeks (adjuvant). [b]nab-paclitaxel 125 mg/m² every week. [c]Doxorubicin 60 mg/m² + cyclophosphamide 600 mg/m² every 2 weeks. ddAC = dose-dense doxorubicin + cyclophosphamide; eTNBC = early-stage TNBC; IC = immune cell; ITT = intent-to-treat; nab = nanoparticle albumin-bound; PRO = patient-reported outcome; R = randomisation

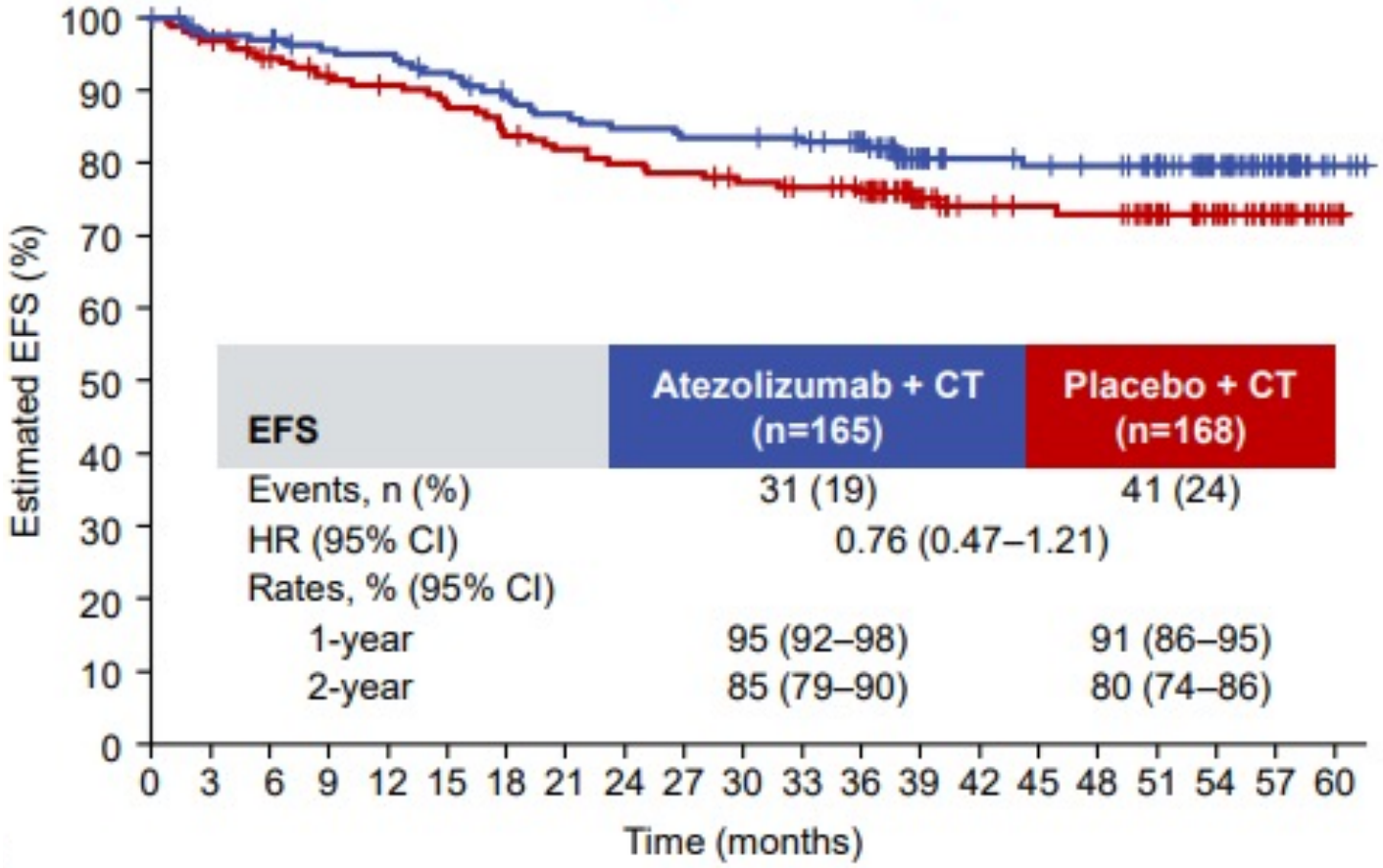
IMpassion031

pCR



Mittendorf et al. Lancet Oncol 2020

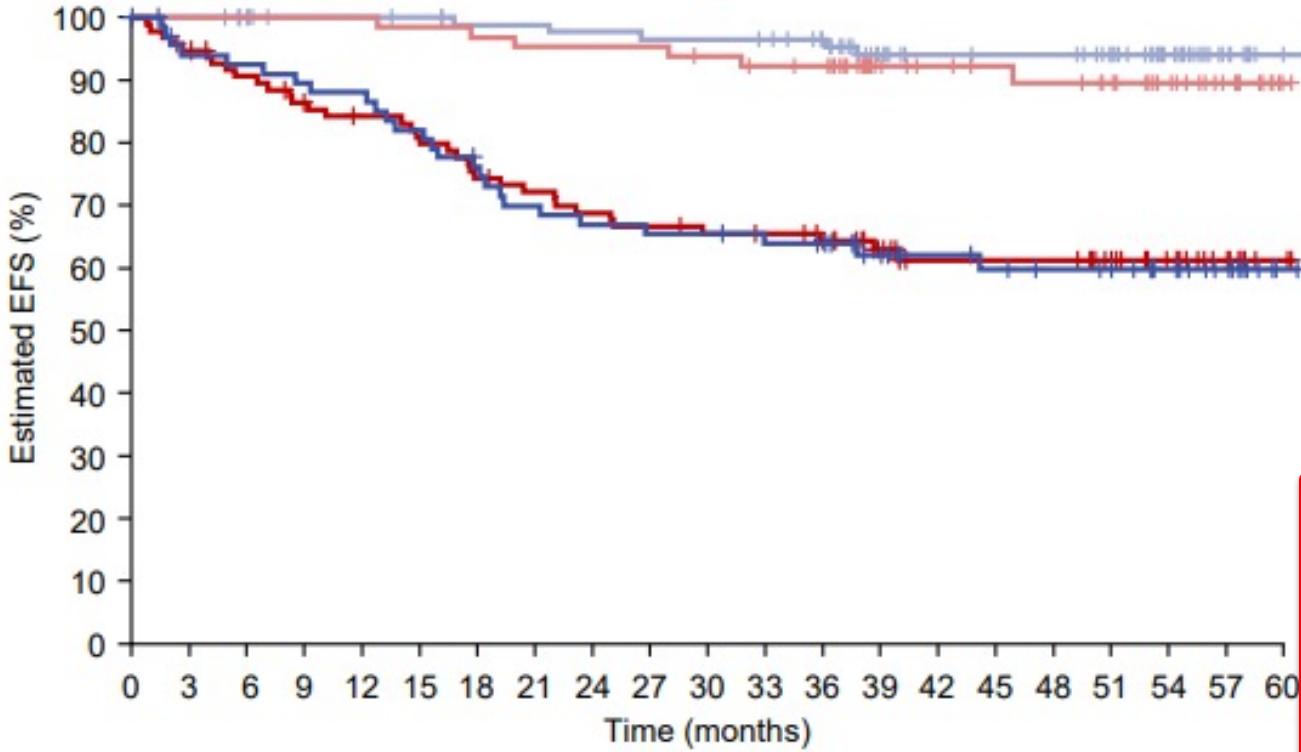
EFS



Barrios et al. ESMO Breast 2023

EXPLORATORY ANALYSIS: EFS BY pCR STATUS

pCR is highly prognostic for long-term outcome



pCR subgroup

Atezolizumab: 95/165 (58%)
Placebo: 69/168 (41%)

Non-pCR subgroup

Atezolizumab: 70/165 (42%)
Placebo: 99/168 (59%)

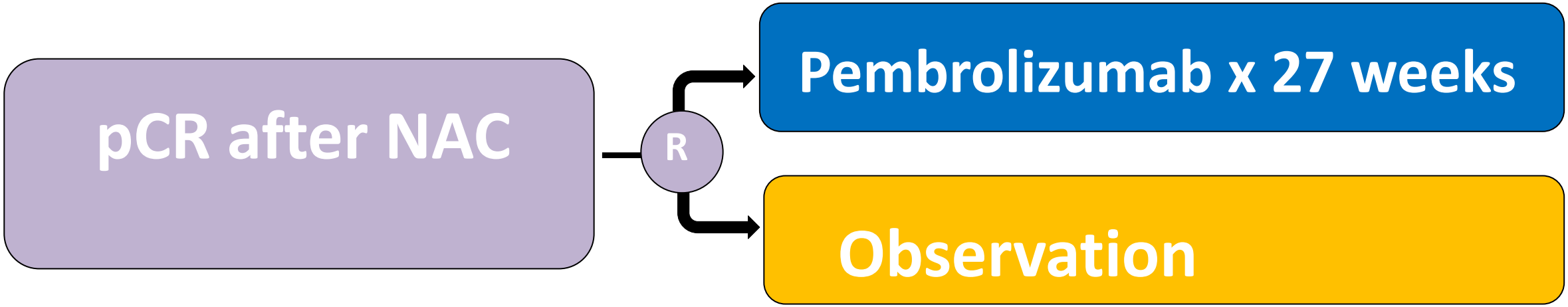
No. at risk

pCR atezolizumab	95	95	95	92	92	91	89	89	88	87	87	86	80	56	49	48	48	42	30	12	2
pCR placebo	69	69	67	66	66	65	64	63	63	63	61	59	58	38	35	33	32	29	20	10	1
Non-pCR atezolizumab	70	63	62	60	59	55	50	46	44	43	43	41	40	33	29	27	25	24	18	12	1
Non-pCR placebo	99	92	86	80	77	74	68	65	62	60	58	57	54	41	34	34	34	27	17	11	2

Adjuvant systemic therapy in:

- 20% of patients in the atezolizumab arm
- 33% in the placebo arm

Planned study for patients with pCR

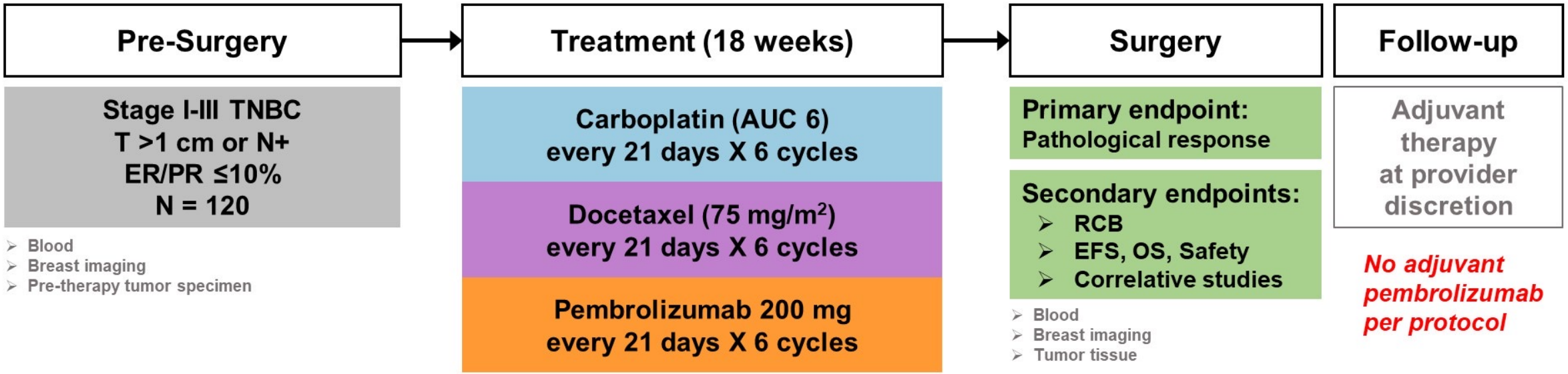


Stratification Factors:

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

Slide courtesy of Sara Tolaney

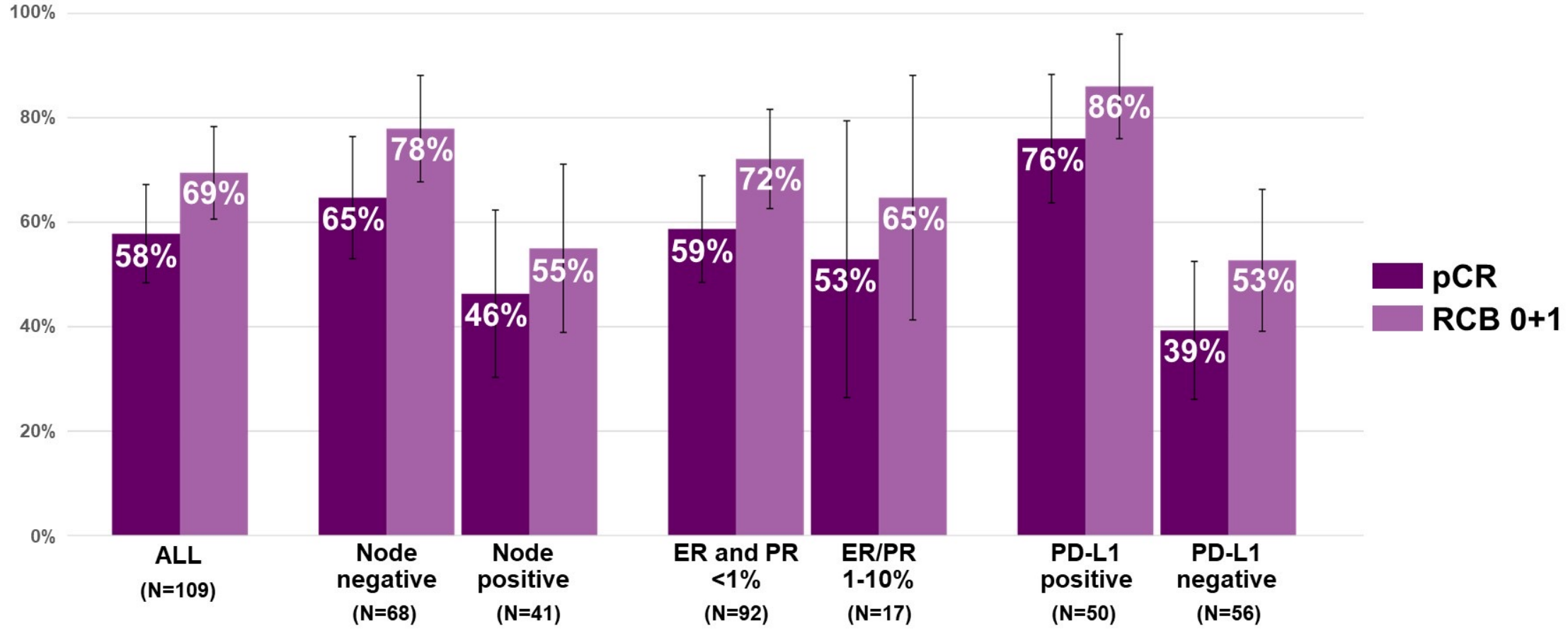
Neoadjuvant Phase II Study of Pembrolizumab and Carboplatin plus Docetaxel in Triple Negative Breast Cancer (NeoPACT)



Sites: University of Kansas and Baylor University Medical Center

PRESENTED BY:
Priyanka Sharma, M.D.

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

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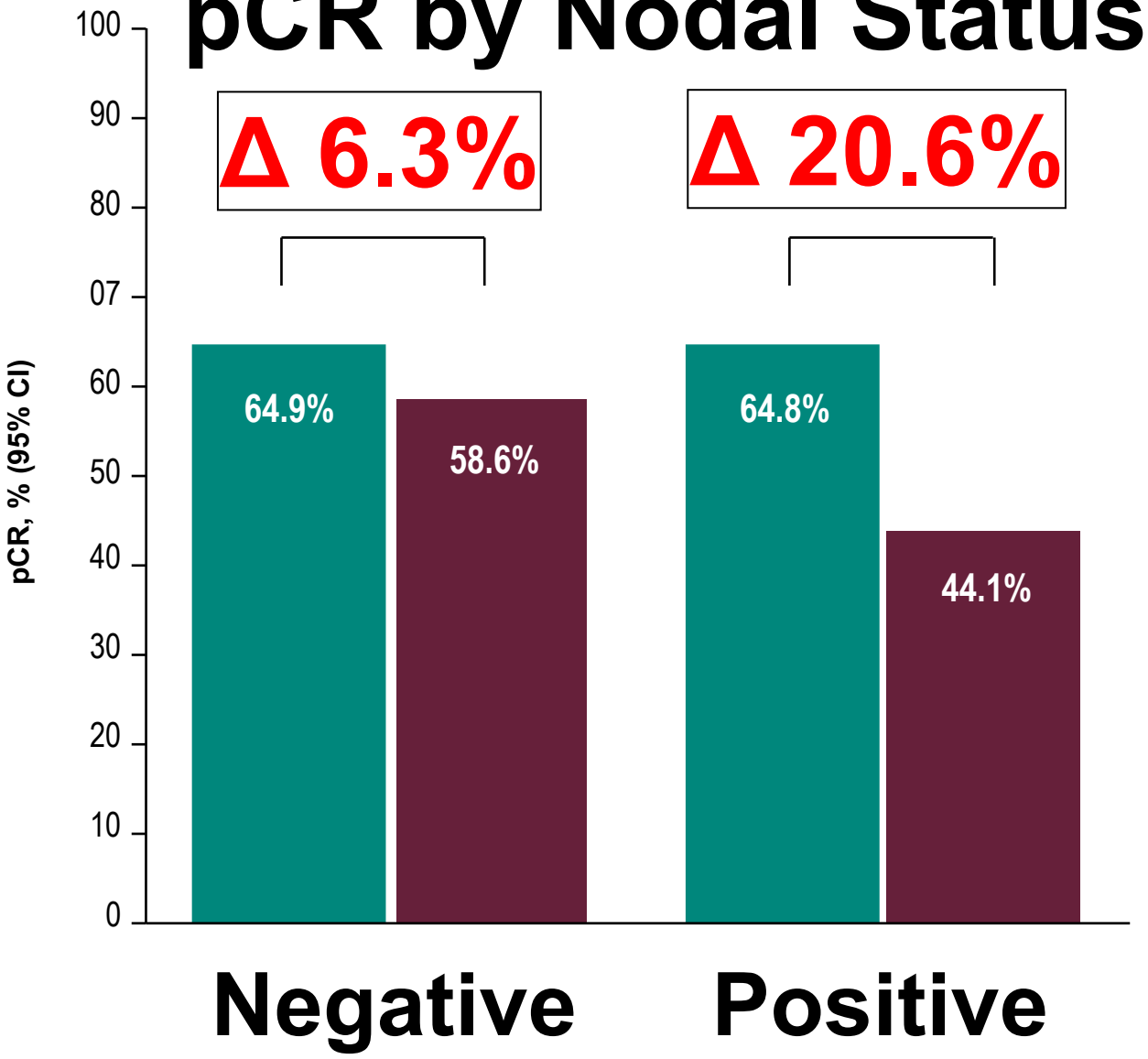
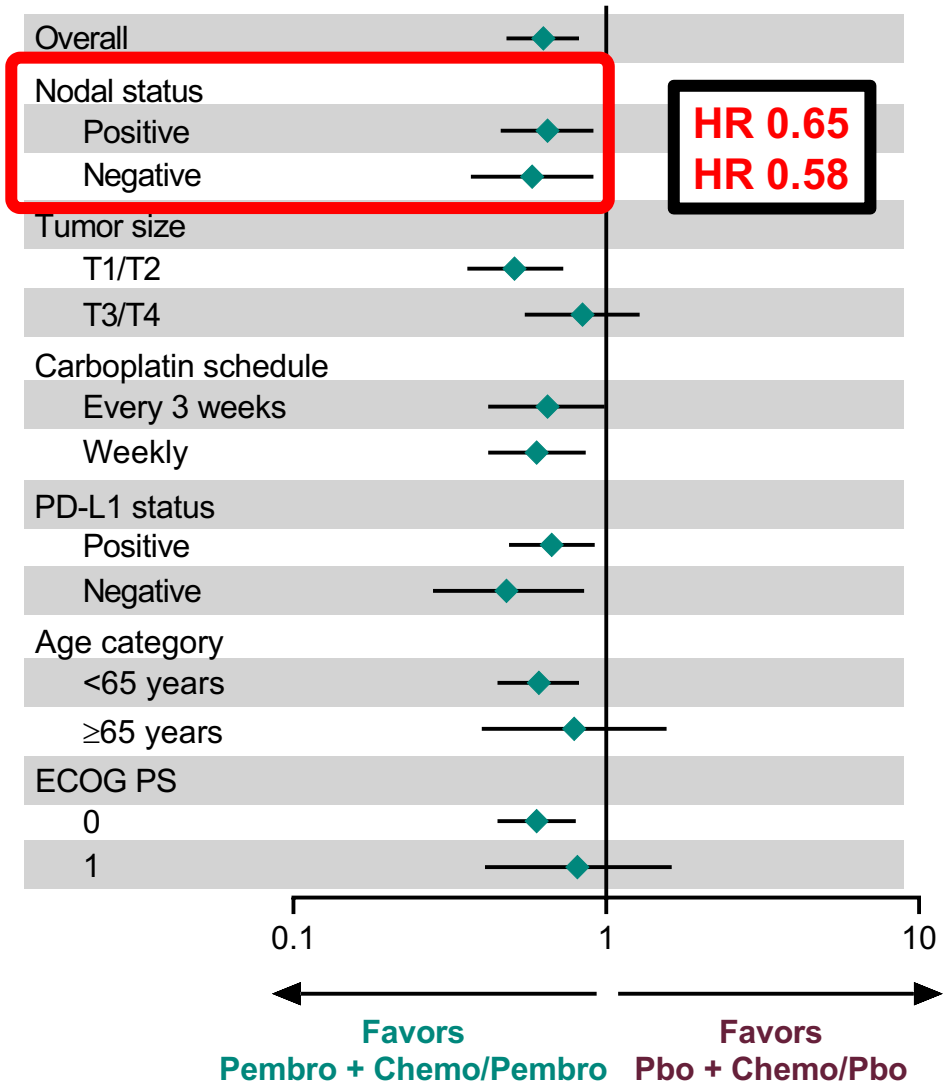
pCR by Nodal Status



EFS in Subgroups

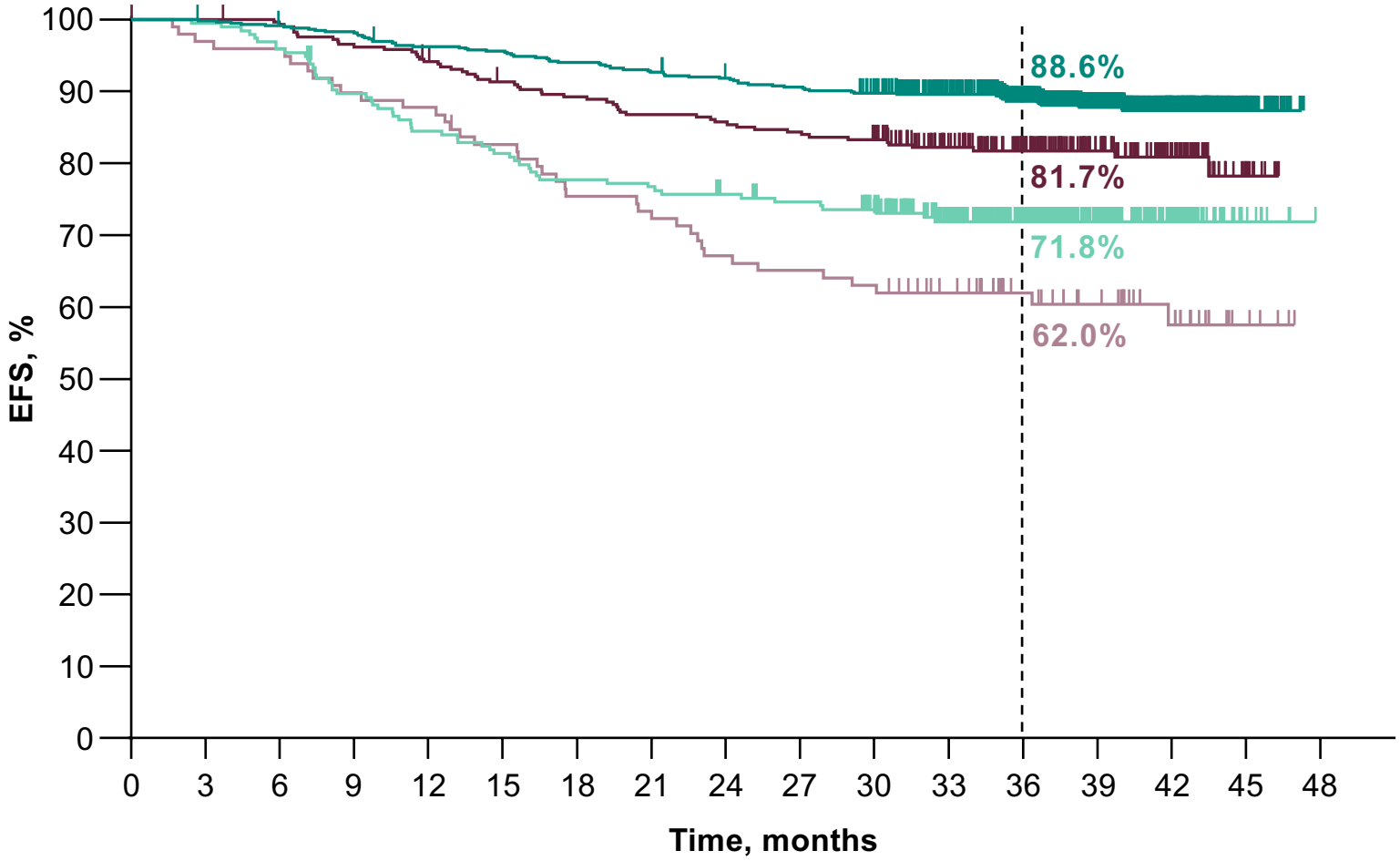


Schmid et al. ESMO Virtual Plenary. Abstract VP7-2021. Presented July 15, 2021.

EFS by Overall Disease Stage

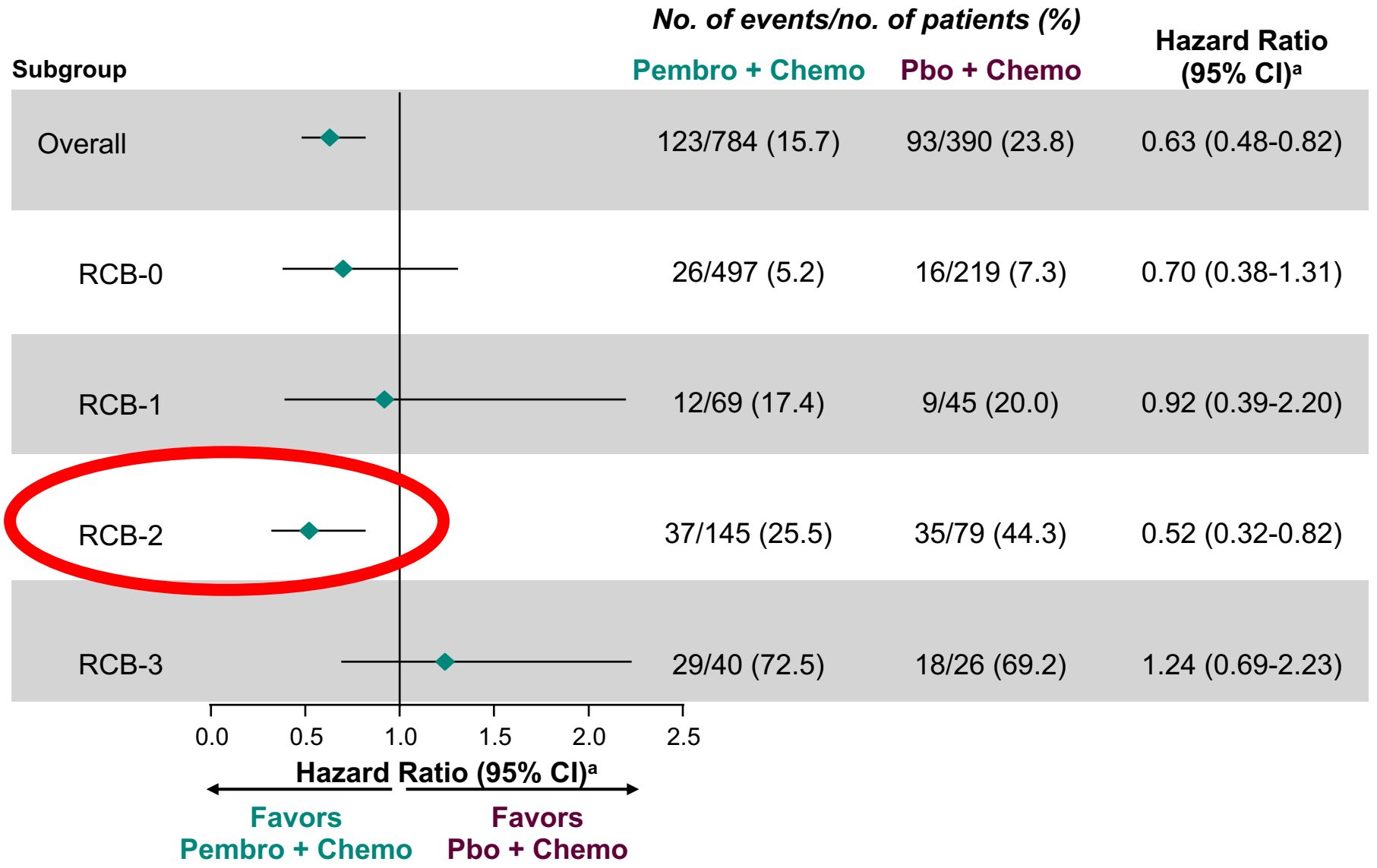
Stage II	Events	HR (95% CI)
Pembro+Chemo/Pembro	11.7%	0.60 (0.42-0.86)
Pbo+Chemo/Pbo	18.6%	

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



Schmid et al. SABCS 2021.

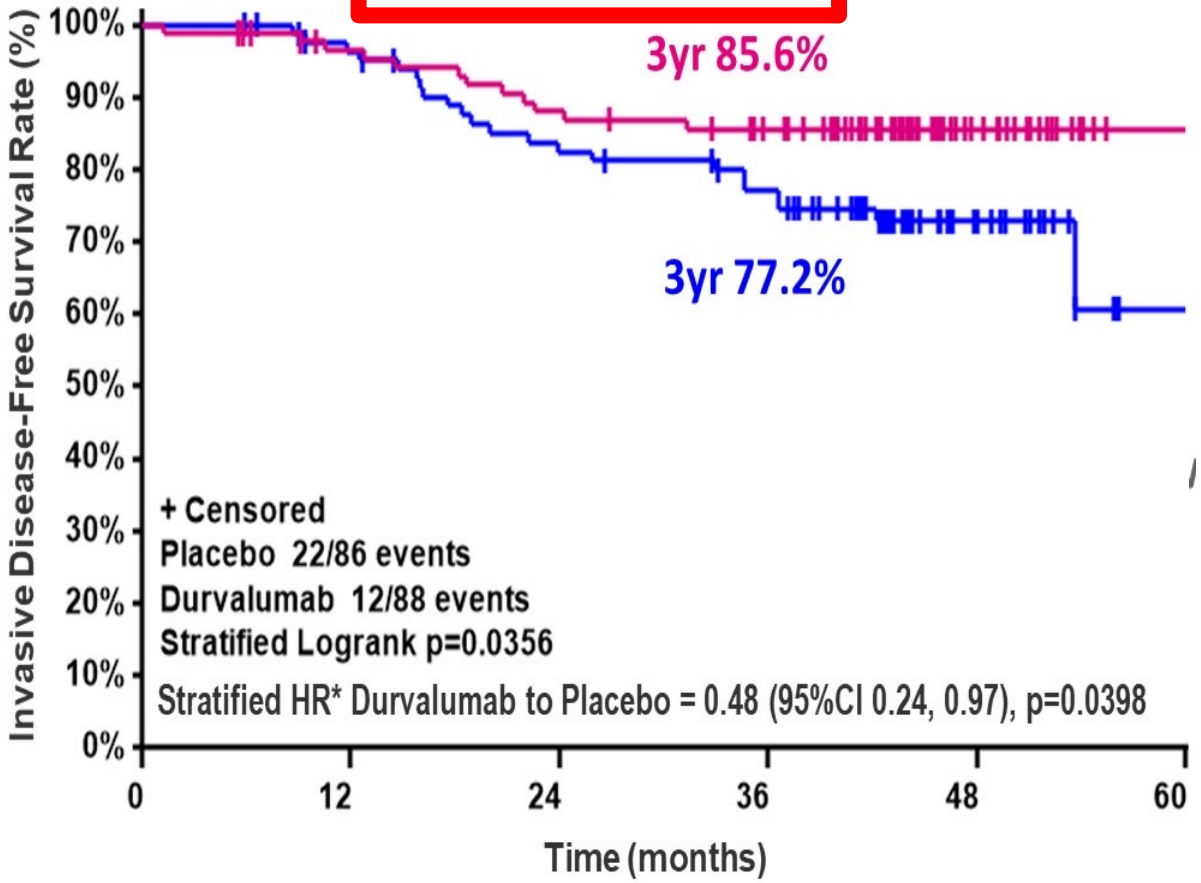
EFS Analysis by RCB Category



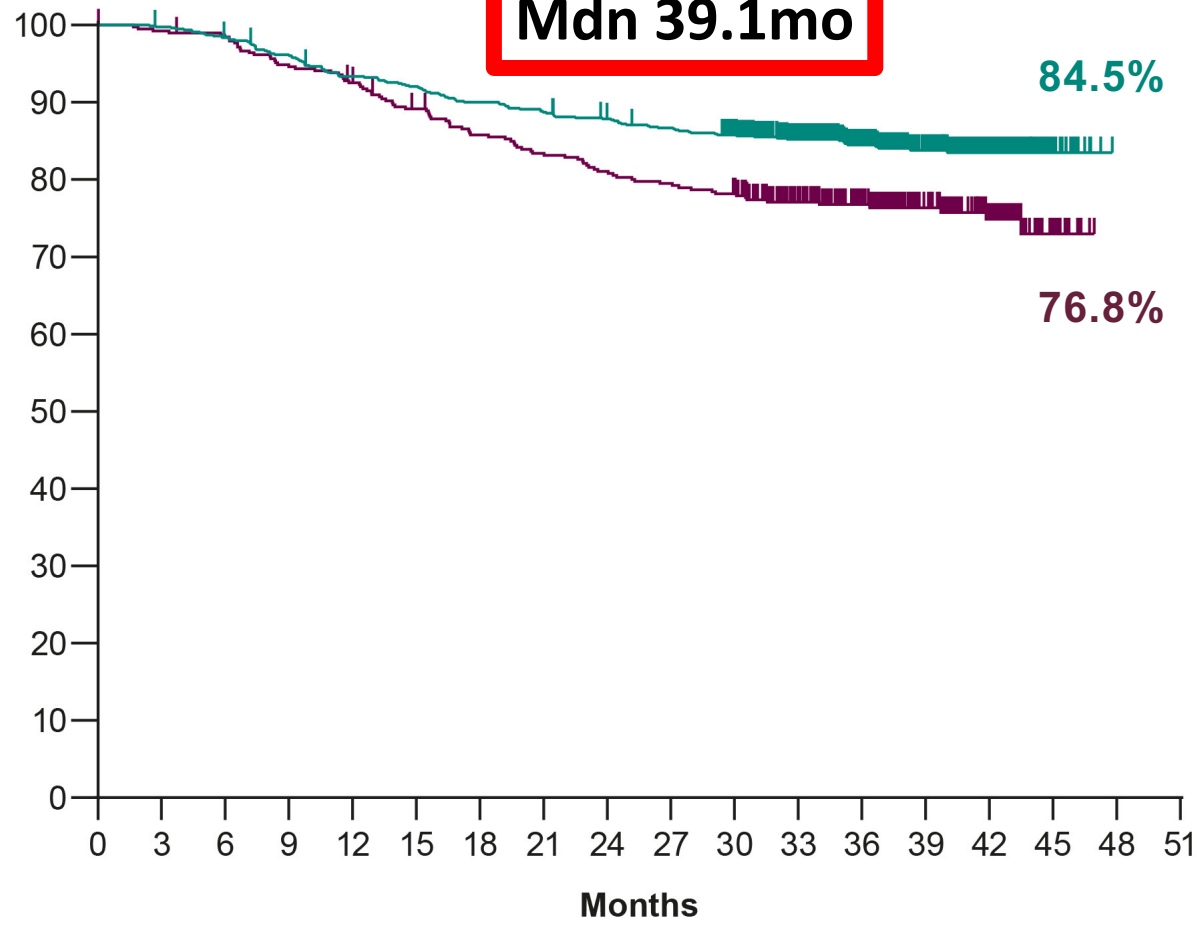
Pusztai et al. ASCO 2022

Question #2: Is all the IO benefit conferred with neoadjuvant administration?

GeparNuevo
Mdn 43.7mo

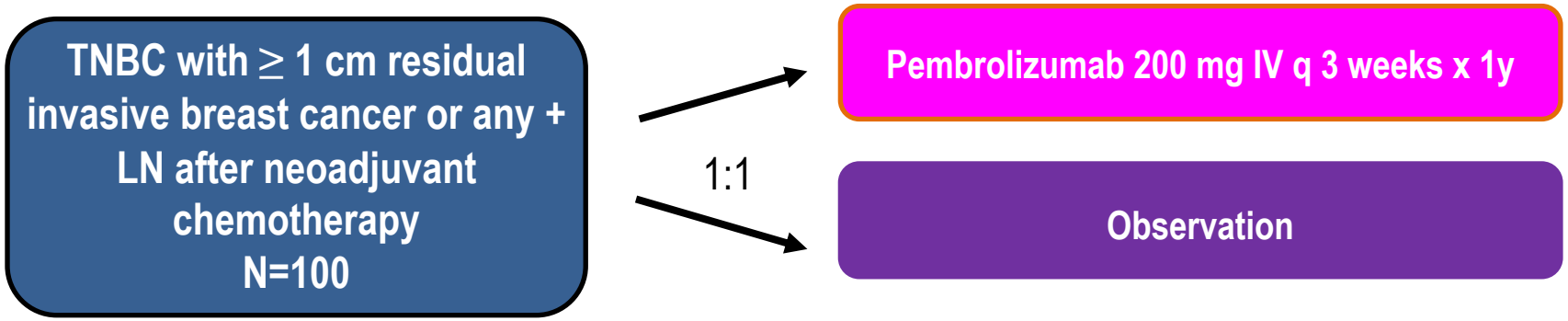


Keynote-522
Mdn 39.1mo



Loibl et al. ASCO 2021; Schmid ett al ESMO 2021.

SWOG 1418/NRG BR006



- **Registration:**
  - Central PD-L1 testing
- **Stratification:**
  - Nodal stage ypNo vs ypN+
  - Residual tumor ≥2 vs < 2cm
  - PD-L1 pos vs neg
  - Prior adjuvant chemo yes vs no

- **Hypothesis:**
  - Pembrolizumab reduces IDFS by 33% c/w observation alone
- **Primary Endpoint:**
  - Invasive DFS in PD-L1-positive and overall cohort
- **Secondary Endpoints:**
  - Toxicity
  - OS
  - DRFS
  - QOL (PROMIS, PRO-CTCAE forms, inflammatory markers)
  - Tissue banking

PI Lajos Pusztai
NCT02954874

ALEXANDRA/IMpassion030

Eligibility

- **Adequately excised primary invasive TNBC (stage II/III)** 50:50 node negative/positive–enriched population

Stratification

- Axillary nodal status (0 vs 1-3 vs ≥4 positive lymph nodes)
- Surgery (breast conserving vs mastectomy)
- PD-L1 IC0 vs IC1/2/3

N = 2,300

R

1:1

1 year

Paclitaxel weekly for 12 weeks

Doxorubicin + cyclophosphamide every 2 weeks for 4 cycles

Atezolizumab

Atezolizumab

Post-chemo XRT per SOC

Paclitaxel weekly for 12 weeks

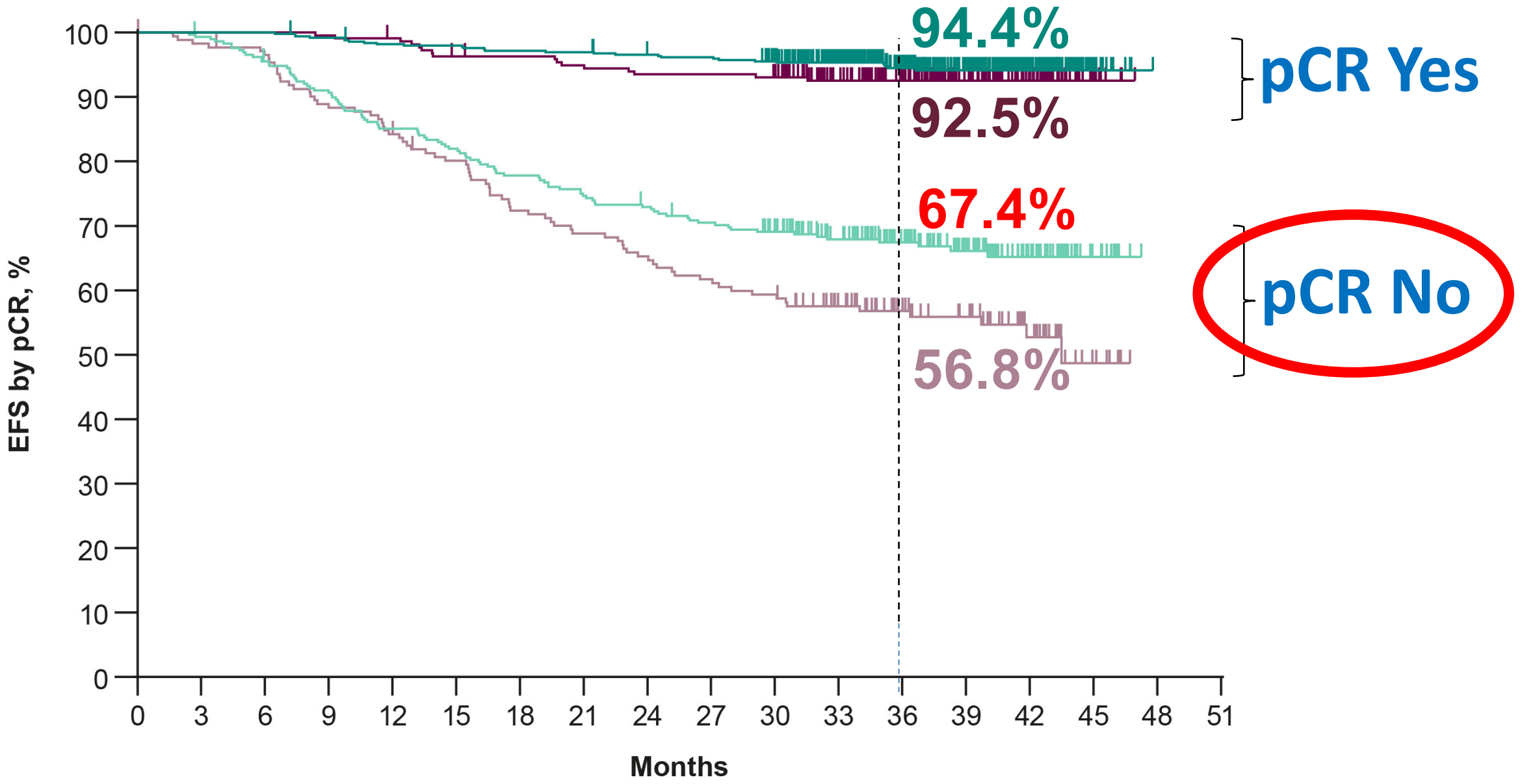
Doxorubicin + cyclophosphamide every 2 weeks for 4 cycles

- **Primary endpoint:** iDFS in ITT
- **Secondary endpoints:** iDFS PD-L1 IC1/2/3, OS, RFI, distant RFI, safety, and health-related QoL

Co-PIs: Ignatiadis, McArthur, Saji

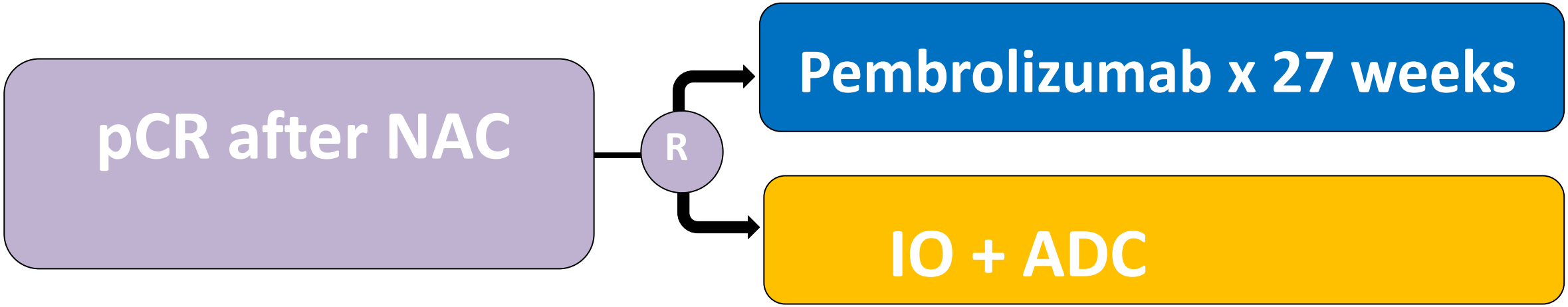
NCT03498716

Q#3: Impact of response on adjuvant decision making?



- Schmid et al. ESMO Virtual Plenary. Abstract VP7-2021. Presented July 15, 2021.

Planned study for patients w/o pCR



ADC

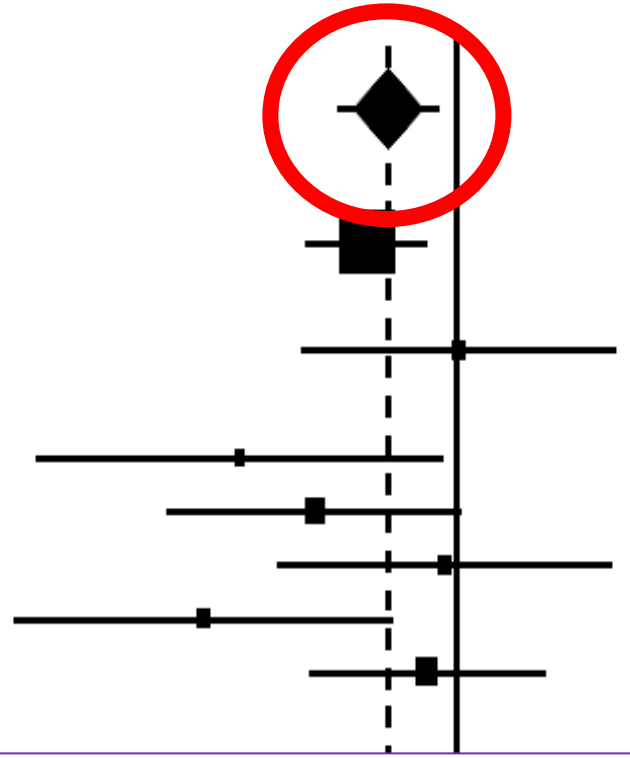
- Sacituzumab govitecan (Alliance)
- DatoDXd (SWOG)

Q4: How to reconcile with adjuvant capecitabine?

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
CreateX	296	0.493 (0.291, 0.837)	0.009
CIBOMA/2004-01	876	0.922 (0.665, 1.278)	0.625

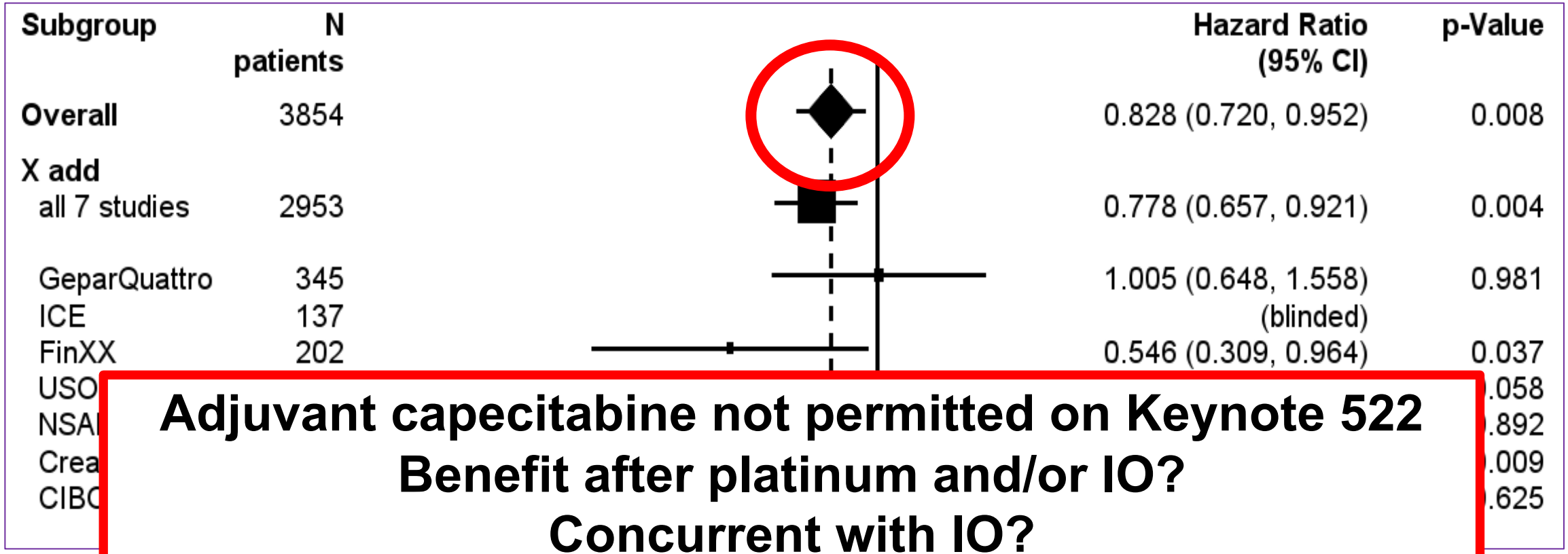


van Mackelenbergh et al. SABCS 2019.
van Mackelenbergh et al. Eur J Cancer. 2022;166:185-201.

Q4: How to reconcile with adjuvant capecitabine?

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

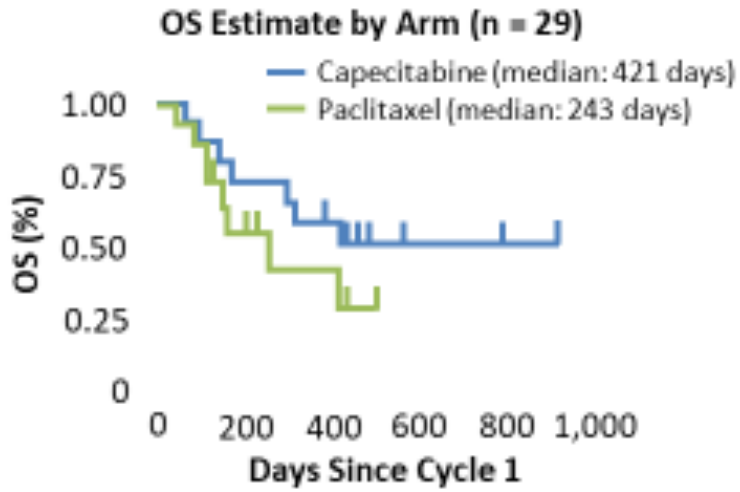
OS benefit in TNBC

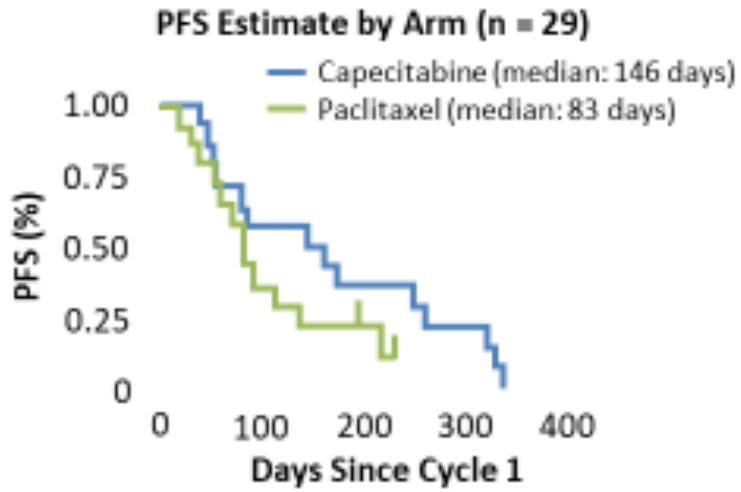


Adjuvant capecitabine not permitted on Keynote 522
Benefit after platinum and/or IO?
Concurrent with IO?

van Mackelenbergh et al. SABCS 2019.
van Mackelenbergh et al. Eur J Cancer. 2022;166:185-201.

First- or Second-line Pembrolizumab with Paclitaxel or Capecitabine in mTNBC

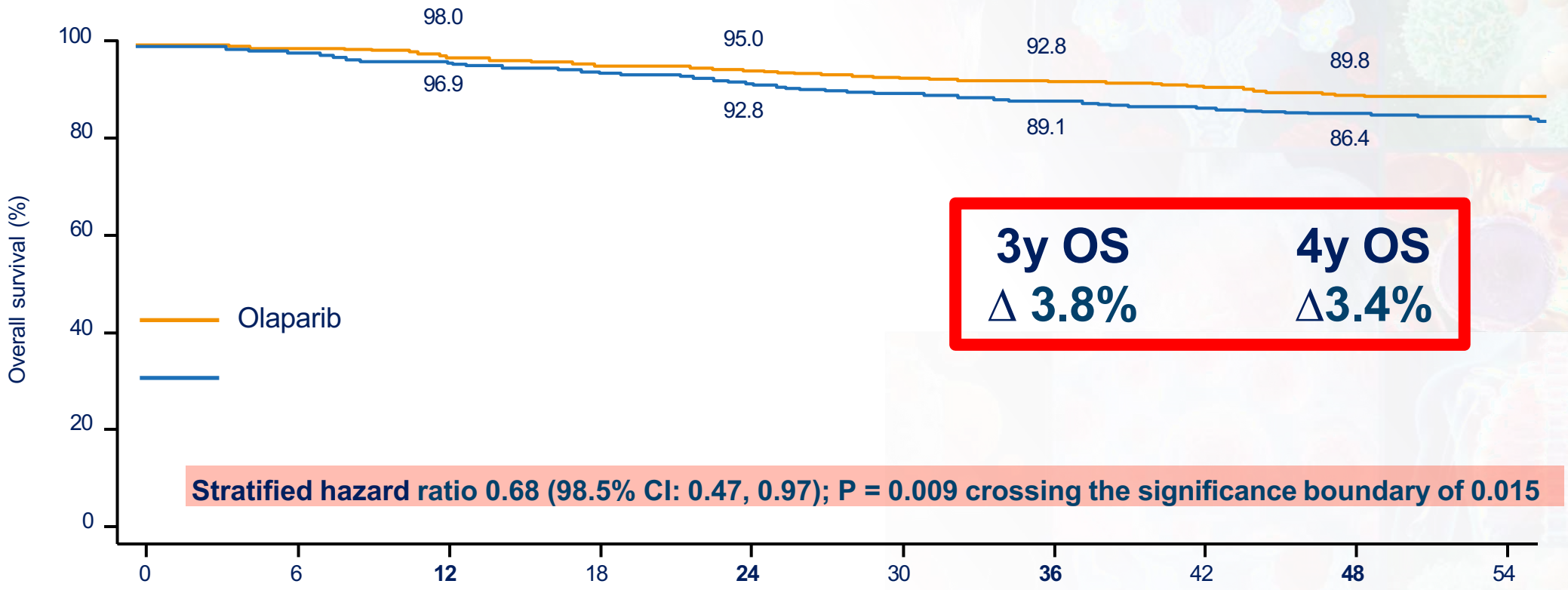




- Week 12 ORR: 43% with pembro/capecitabine
- Co-administration was safe
- Co-administration of adjuvant pembro/capecitabine may be reasonable in selected high-risk patients with residual TNBC after NAC

Page et al. ASCO 2019. Abstr 1015. Page et al. NPJ Breast 2023.
Chun et al. J Immunother Cancer 2022;10(1):e004033.

OlympiA OS with PARPi



No. at risk

Olaparib	921	862	844	809	773	672	560	437	335	228
Placebo	915	868	843	808	752	647	530	423	333	218

Tutt et al, *Annals of Oncology*, March 2022

Endpoint	TOPACIO (N=47)[1]	Mediola (n = 30)[2]	Olympiad (n = 205)[3]
Treatment	Pembro+ niraparib	Durvalumab+ olaparib	Olaparib
ORR, %	21	63	60
DoR, mos	NR	9.2	6.4
PFS, mos	2.3	8.2	7.0

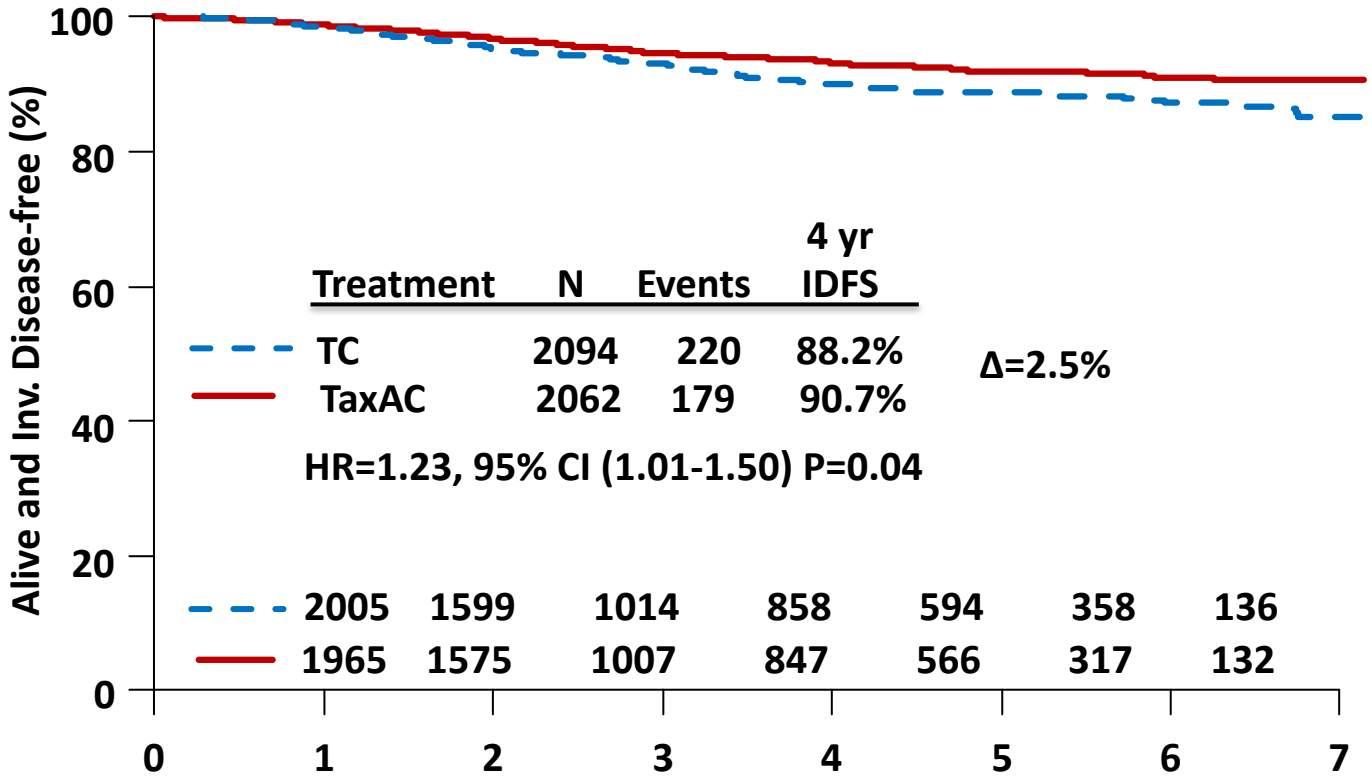
No new safety signals with PARPi + IO

Co-administration of adjuvant pembro/PARPi may be reasonable in selected high-risk patients with early stage gBRCA-associated TNBC

[1]Vinayak et al. JAMA Oncol. 2019;5(8):1132-40 [2]Domchek et al. Lancet Oncol. 2020;21(9):1155-1164. [3]Robson et al. NEJM. 2017;377:523.

Q5: Optimal Chemo Partner?

ABC Trials: Invasive Disease-Free Survival

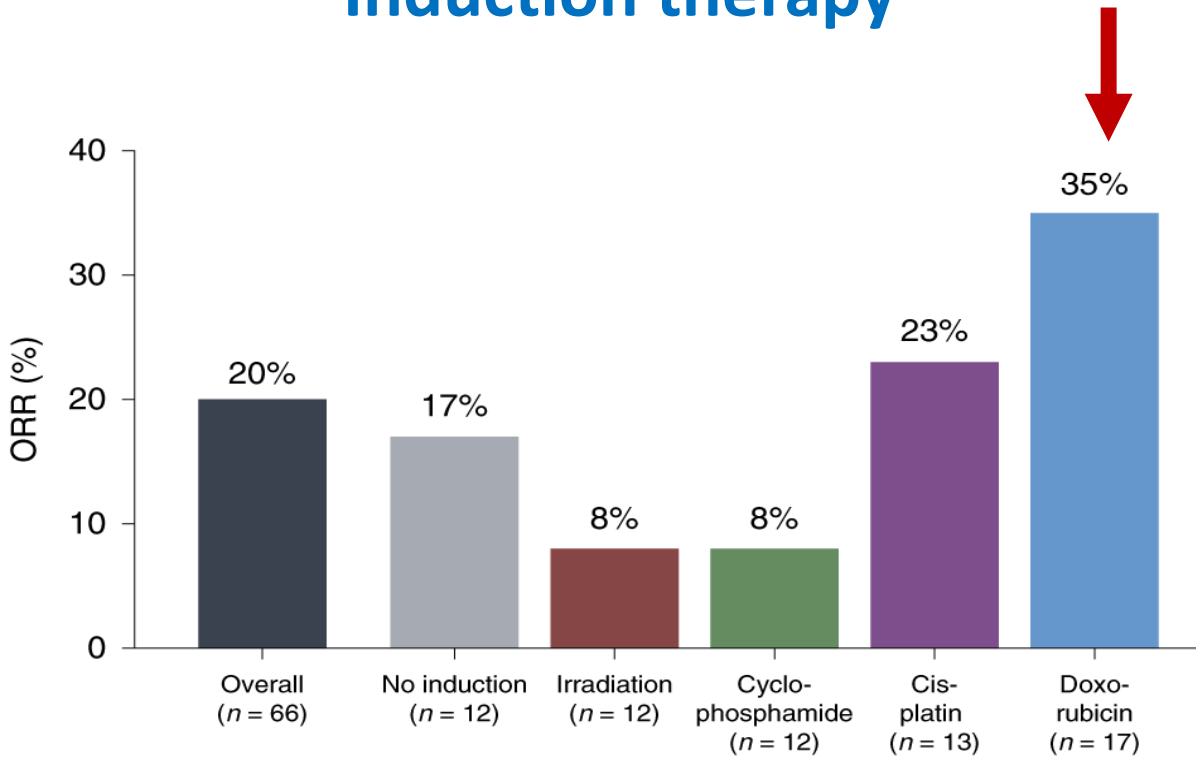


Status	No. of Patients		No. of Events		4-Year IDFS (%)		4-Year IDFS Δ (%)	HR (95% CI)
	TaxAC	TC	TaxAC	TC	TaxAC	TC		
HR negative								
Node negative	459	488	37	52	89.5	87.0	2.5	1.31 (0.86 to 1.99)
1-3 positive nodes	153	119	21	28	85.5	74.6	10.9	1.58 (0.90 to 2.79)
≥ 4 positive nodes	42	40	11	16	71.8	60.8	11.0	1.34 (0.62 to 2.91)

Blum J, et al. J Clin Oncol. 2017;35:2647-2655.

Q5: Optimal Chemo Partner?

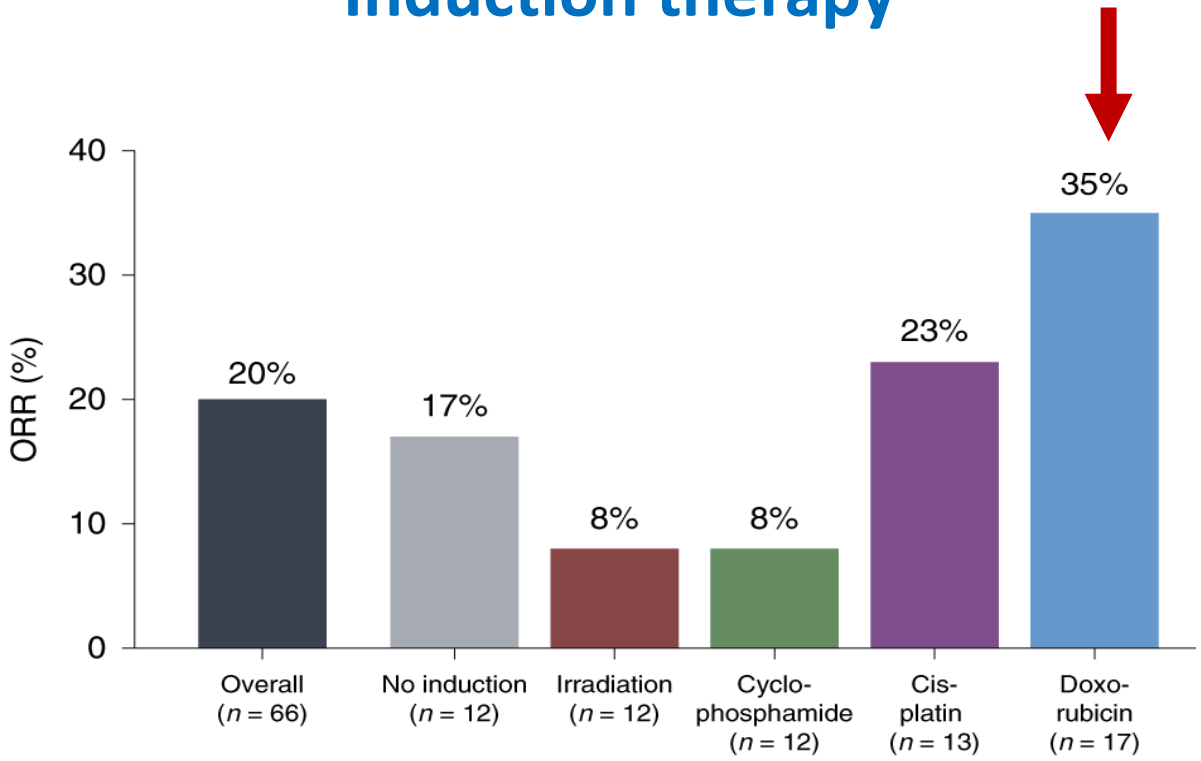
TONIC trial (metastatic): Induction therapy



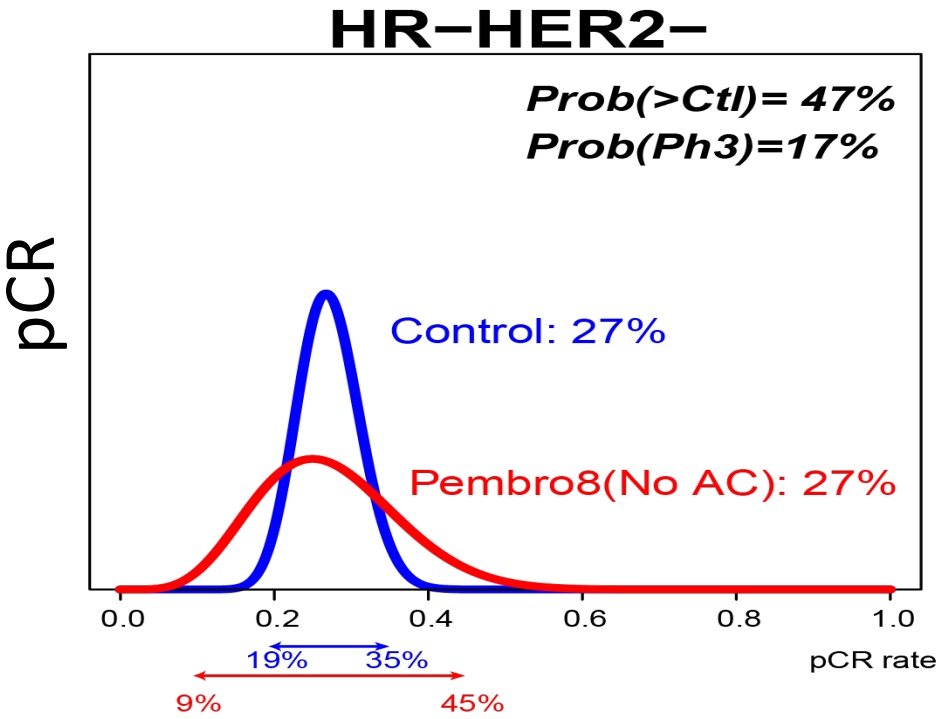
Alizadeh D et al, Cancer Research 2014; Sistigu A et al, Nature Medicine 2014; Casares N et al J Exp Med 2005; Voorkerk et al Nature Medicine 2019; Liu MC et al SABCS 2019

Q5: Optimal Chemo Partner?

TONIC trial (metastatic): Induction therapy



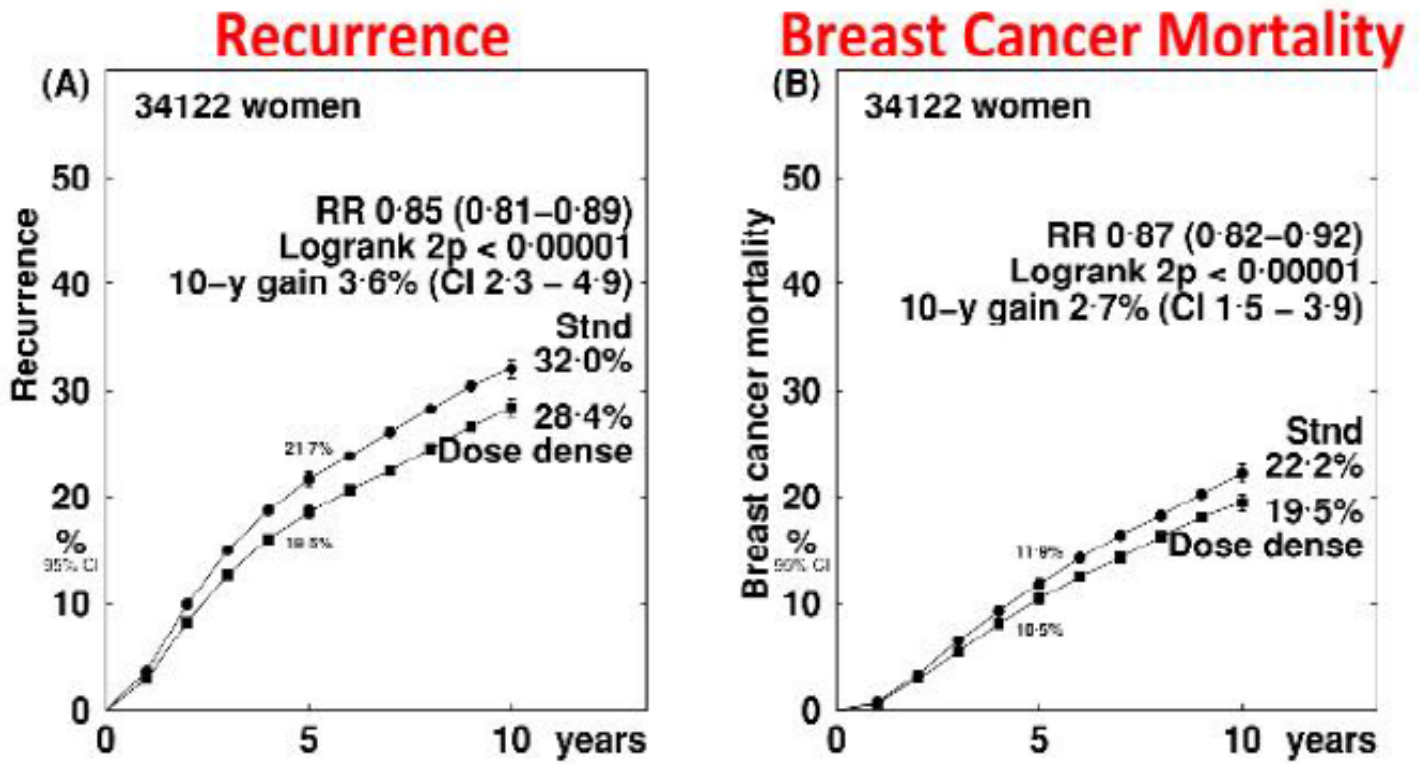
ISPY-2 (neoadjuvant): Pembro x 8 Pembro + Paclitaxel, Pembro (no AC)



Alizadeh D et al, Cancer Research 2014; Sistigu A et al, Nature Medicine 2014; Casares N et al J Exp Med 2005; Voorkerk et al Nature Medicine 2019; Liu MC et al SABCS 2019

Q#6: Impact of Dose Density?

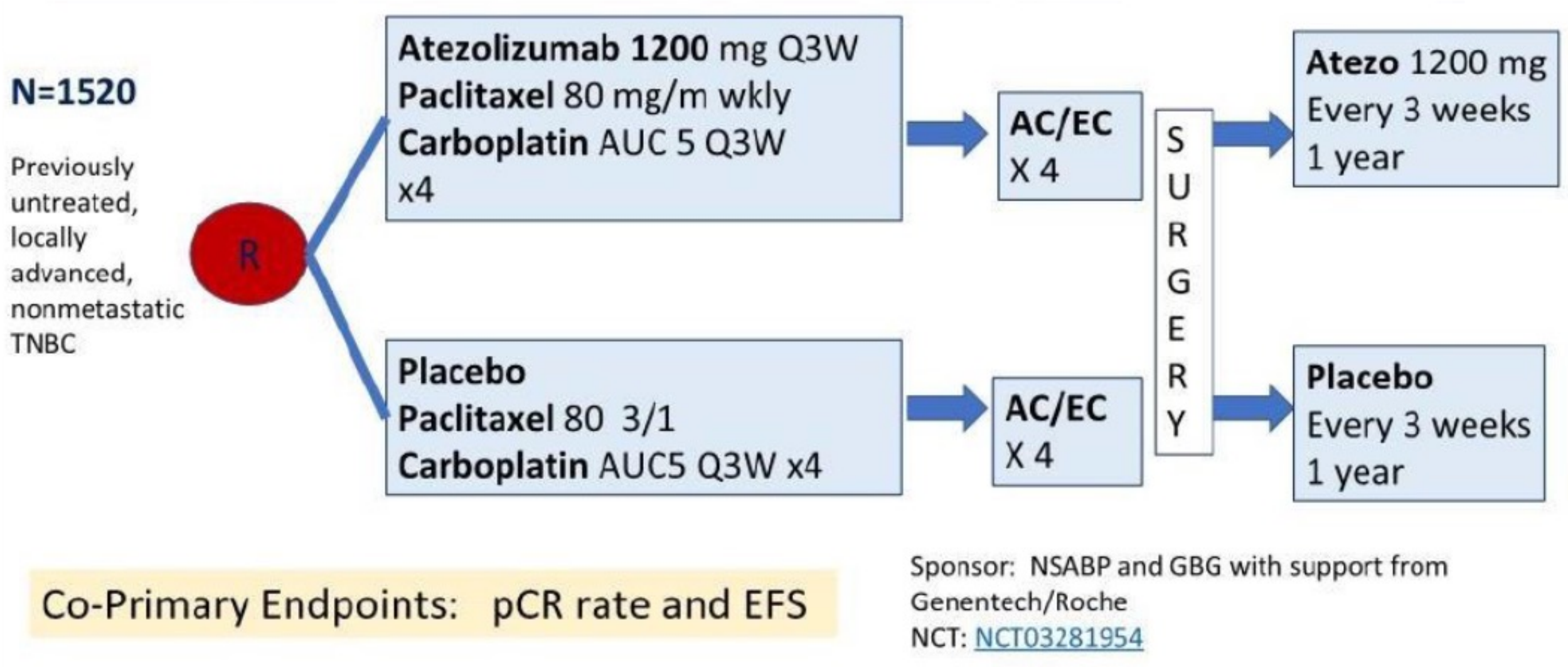
Pooled analysis of all 25 dose-dense and sequential trials



Impact of growth factor support on IO efficacy?

Gray R, et al. SABCS, December 2017. Abstract GS1-01; EBCTCG Lancet 2019;393(10179)1440-1452

GeparDouze



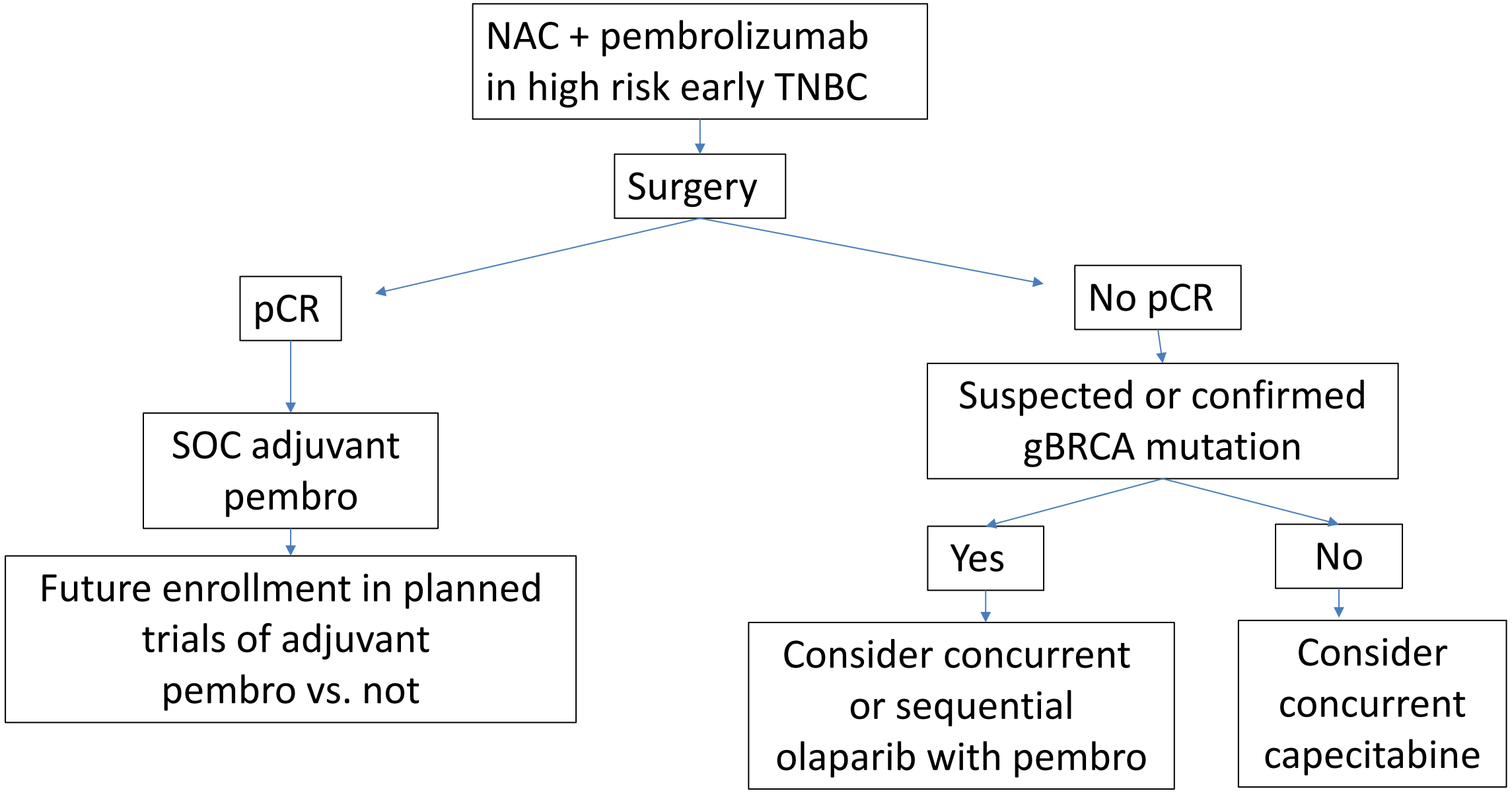
AC q2-3 weeks TPC

PI Wolmark
NCT03281954

Question #7: Locoregional Implications: When should RT be administered with adjuvant pembro?

- "If post-operative radiation therapy is indicated, adjuvant pembro or placebo may be started either concurrently with radiation therapy or 2 weeks post-radiation therapy."
- 40% received adjuvant radiation[1]
- Safe with sequential (65%) or concurrent RT (35%)

McArthur et al. SABCS 2022; PD3-01



Consider concurrent pembro with radiation

Thank you!