Therapeutic Strategies for Patients with Localized Triple-Negative Breast Cancer (TNBC)

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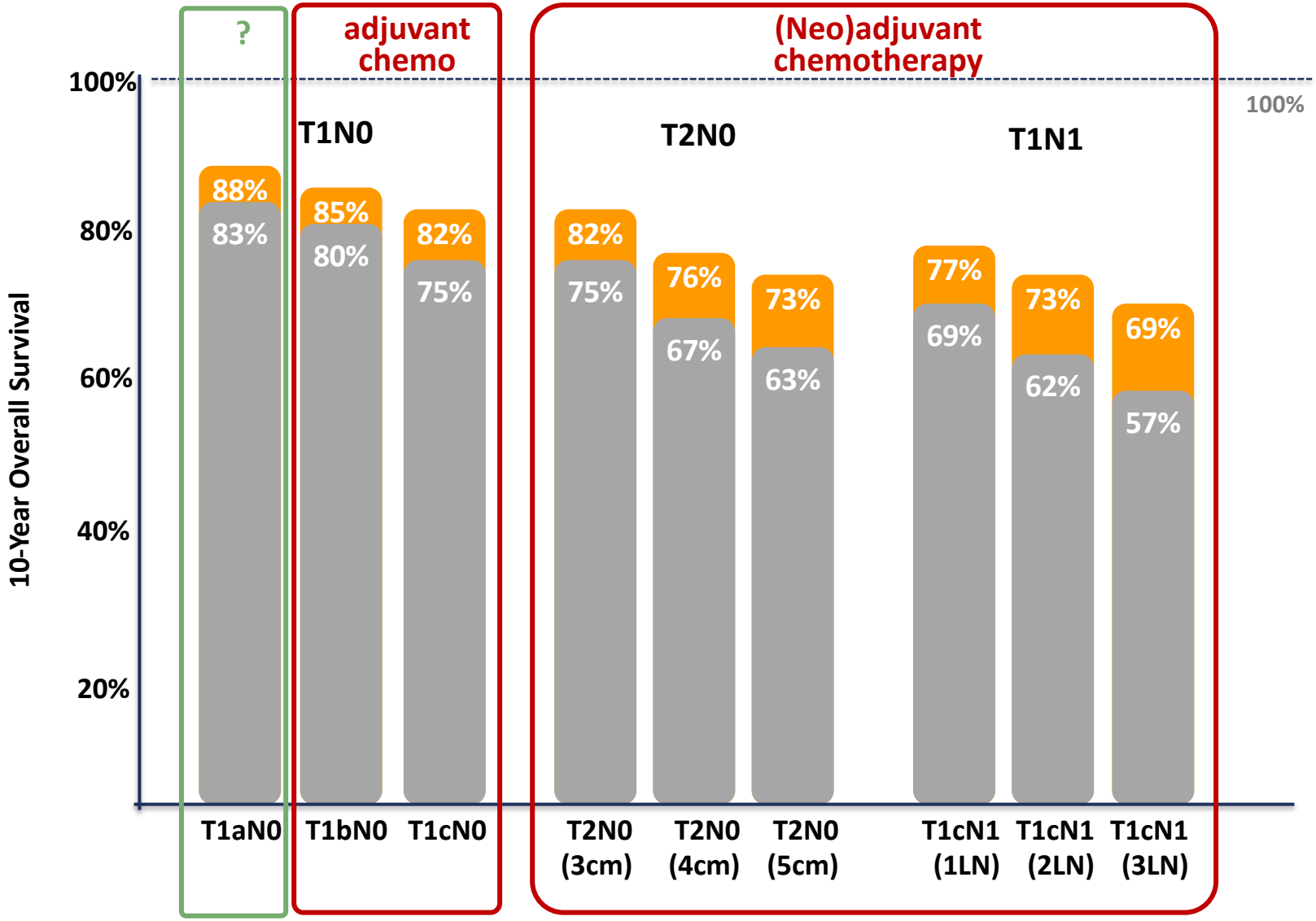
Do all patients with TNBC need chemotherapy?

Survival with/without chemotherapy



10y Survival as per PREDICT NHS, 50y, G2 IDC, ER/HER2/negative, Ki67+

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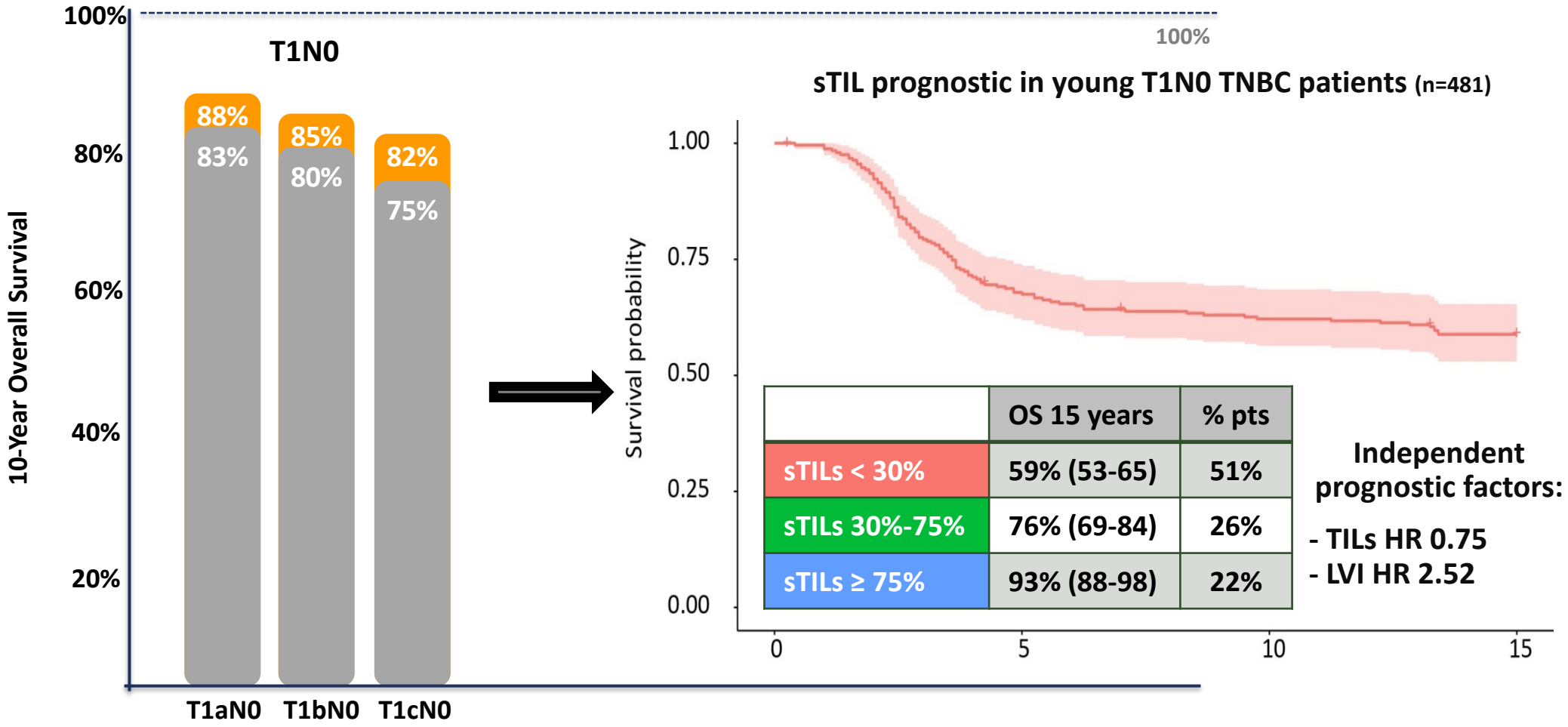


10y Survival as per PREDICT NHS, 50y, G2 IDC, ER/HER2/negative, Ki67+

De Jong et al, ESMO 2020

Preoperative or Postoperative Chemotherapy in TNBC?

RCTs confirm same outcome with adjuvant/neo-adjuvant therapy (eg NSABP18)

Adjuvant Treatment

OP → Chemo

Historically if inoperable

Chemo → OP

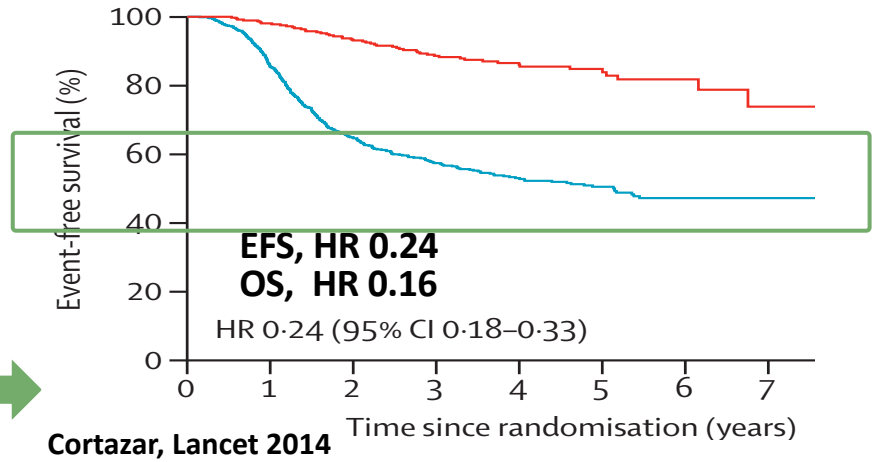
Neoadjuvant Treatment

Downstaging Facilitates less invasive surgery (BCS, SLN, TAD)

Path CR ypT0/is ypN0

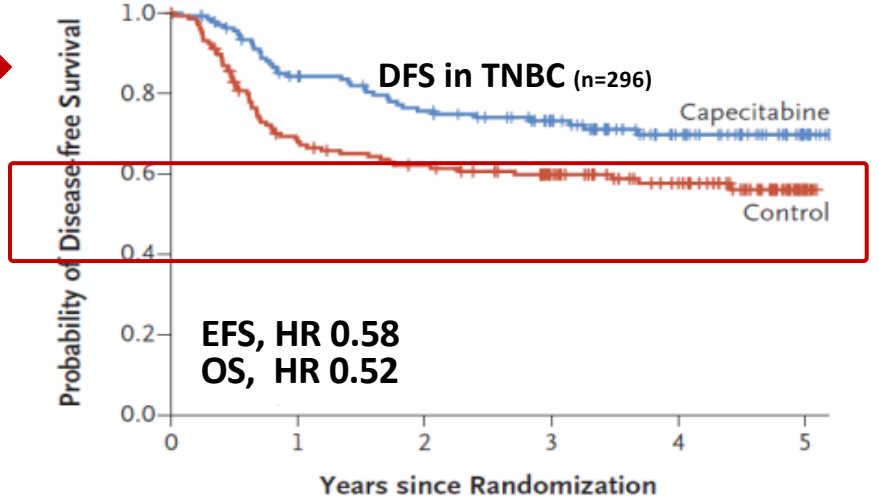
Residual Disease

Metaanalysis: pCR predictive of good outcome



Cortazar, Lancet 2014

Adjuvant Capecitabine improves outcome

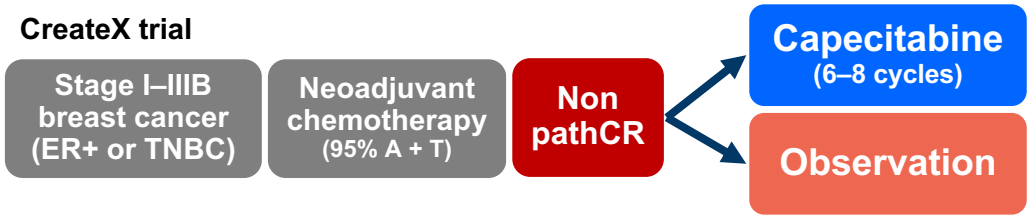


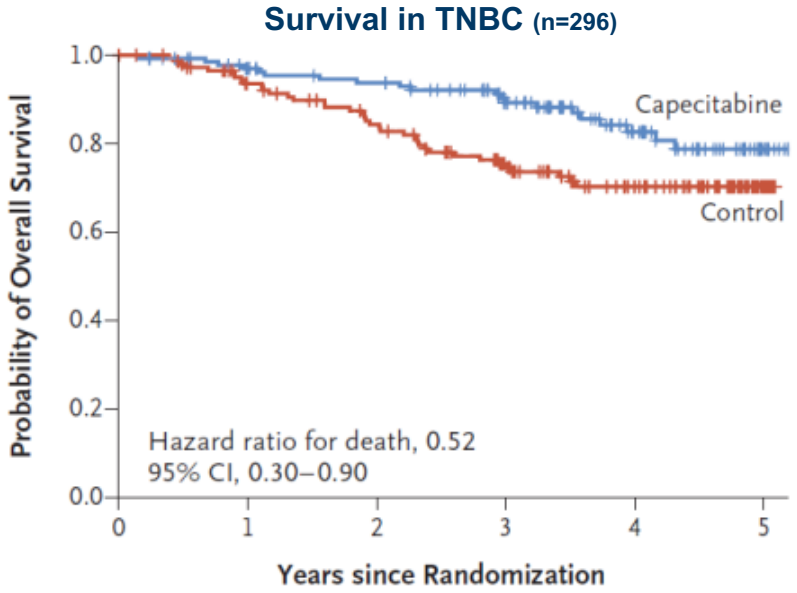
Masuda N, NEJM 2017

Can postoperative treatment improve cure rates in patients with residual disease after preoperative chemo?

Yes, in TNBC

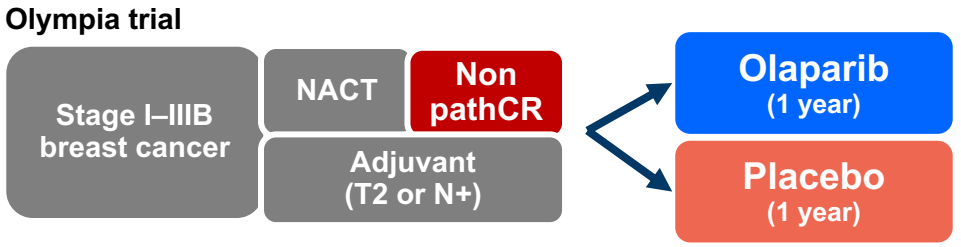
CreateX trial

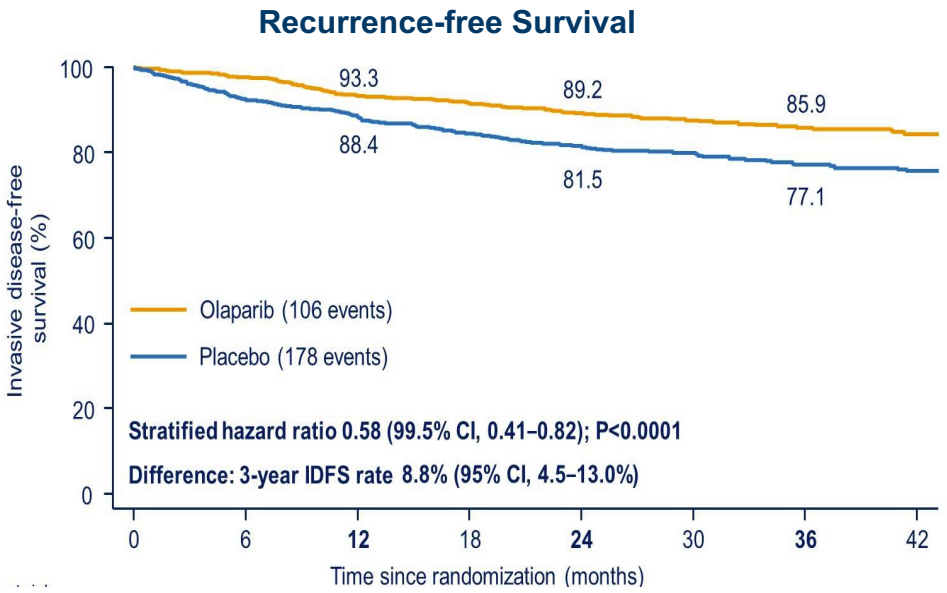




Yes, in patients with gBRCA1/2 mutations

Olympia trial

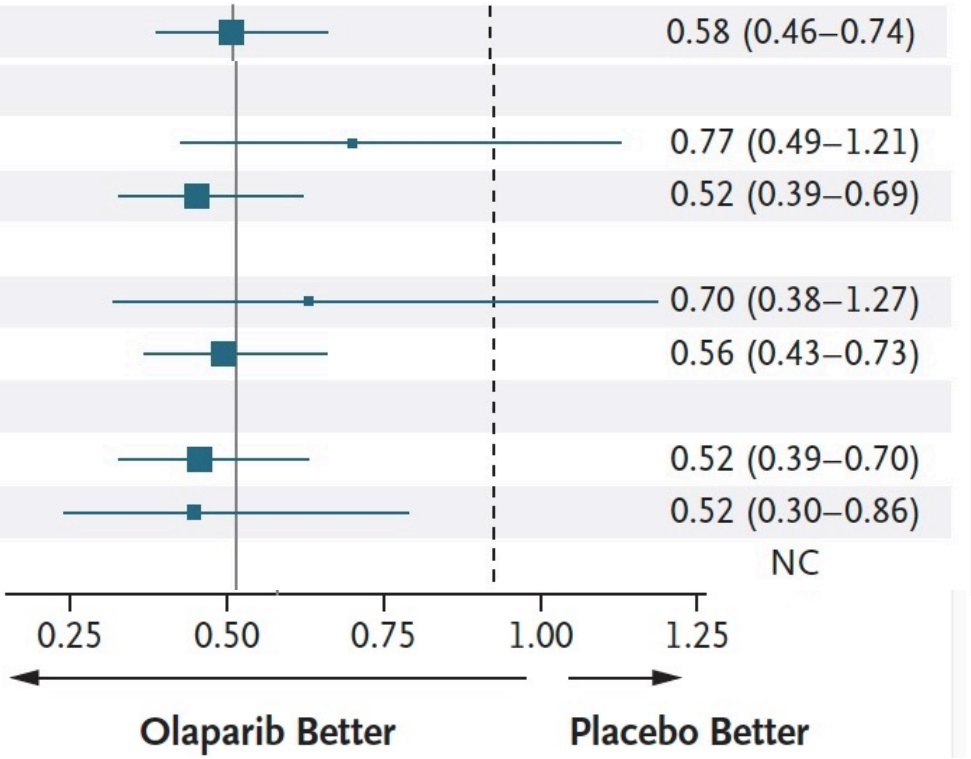




Masuda N, et al. *N Engl J Med*. 2017;376:2147–2159.; Tutt et al, NEJM 2021

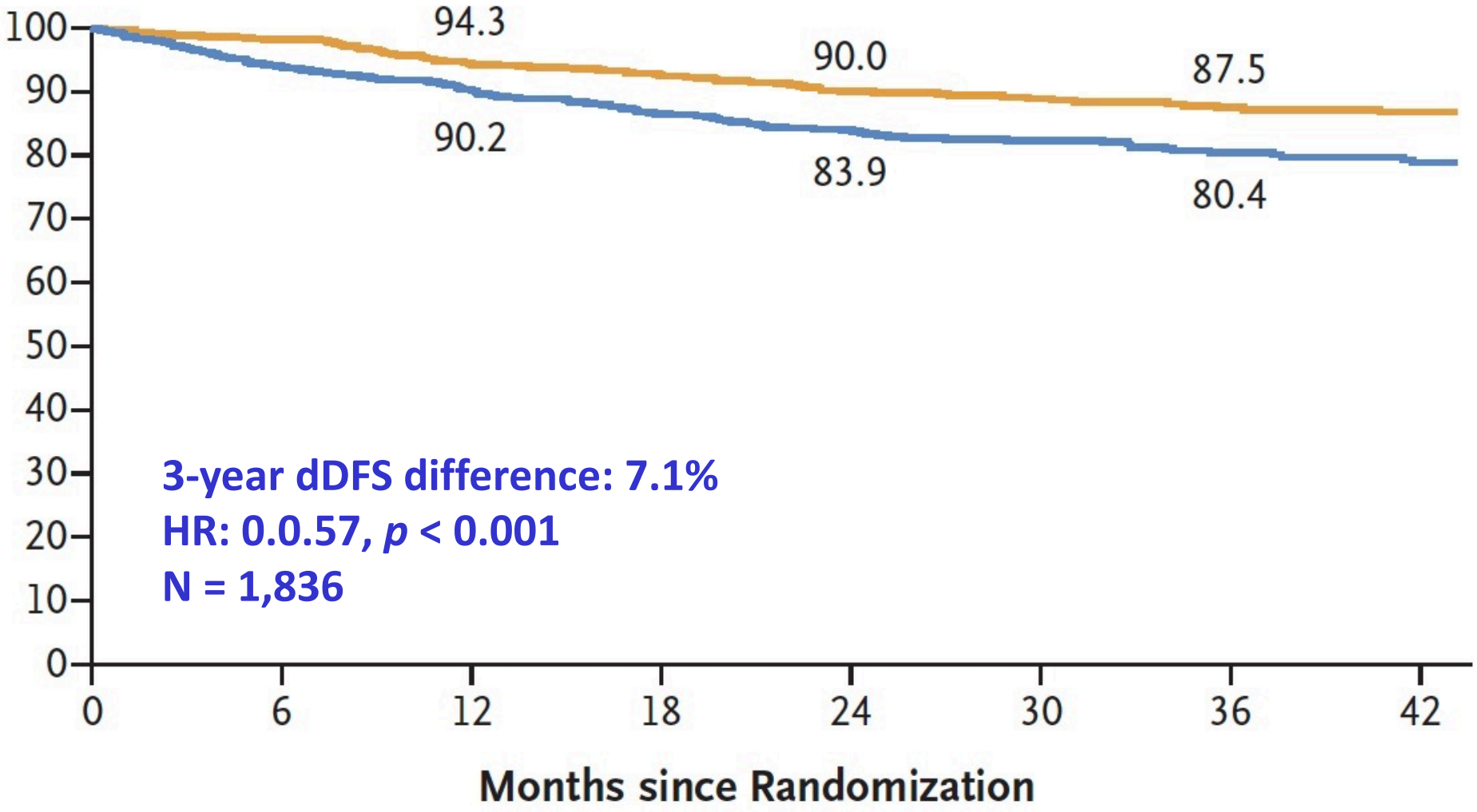
OlympiA: 3-Year Invasive DFS

Subgroup	Olaparib	Placebo	3-Yr Invasive Disease–free Survival		Stratified Hazard Ratio for Invasive Disease or Death (95% CI)
			Olaparib	Placebo	
	no. of patients with an event/total no.		%		
All patients	106/921	178/915	85.9	77.1	0.58 (0.46–0.74)
Previous platinum-based chemotherapy					
Yes	34/247	43/239	82.0	77.0	0.77 (0.49–1.21)
No	72/674	135/676	87.3	77.1	0.52 (0.39–0.69)
Hormone-receptor status					
HR+ and HER2–	19/168	25/157	83.5	77.2	0.70 (0.38–1.27)
TNBC	87/751	153/758	86.1	76.9	0.56 (0.43–0.73)
Germline *BRCA* mutation					
BRCA1	70/558	126/558	85.0	73.4	0.52 (0.39–0.70)
BRCA2	22/230	38/209	88.6	78.0	0.52 (0.30–0.86)
BRCA1 and *BRCA2*	0/1	0/3	NC	NC	NC



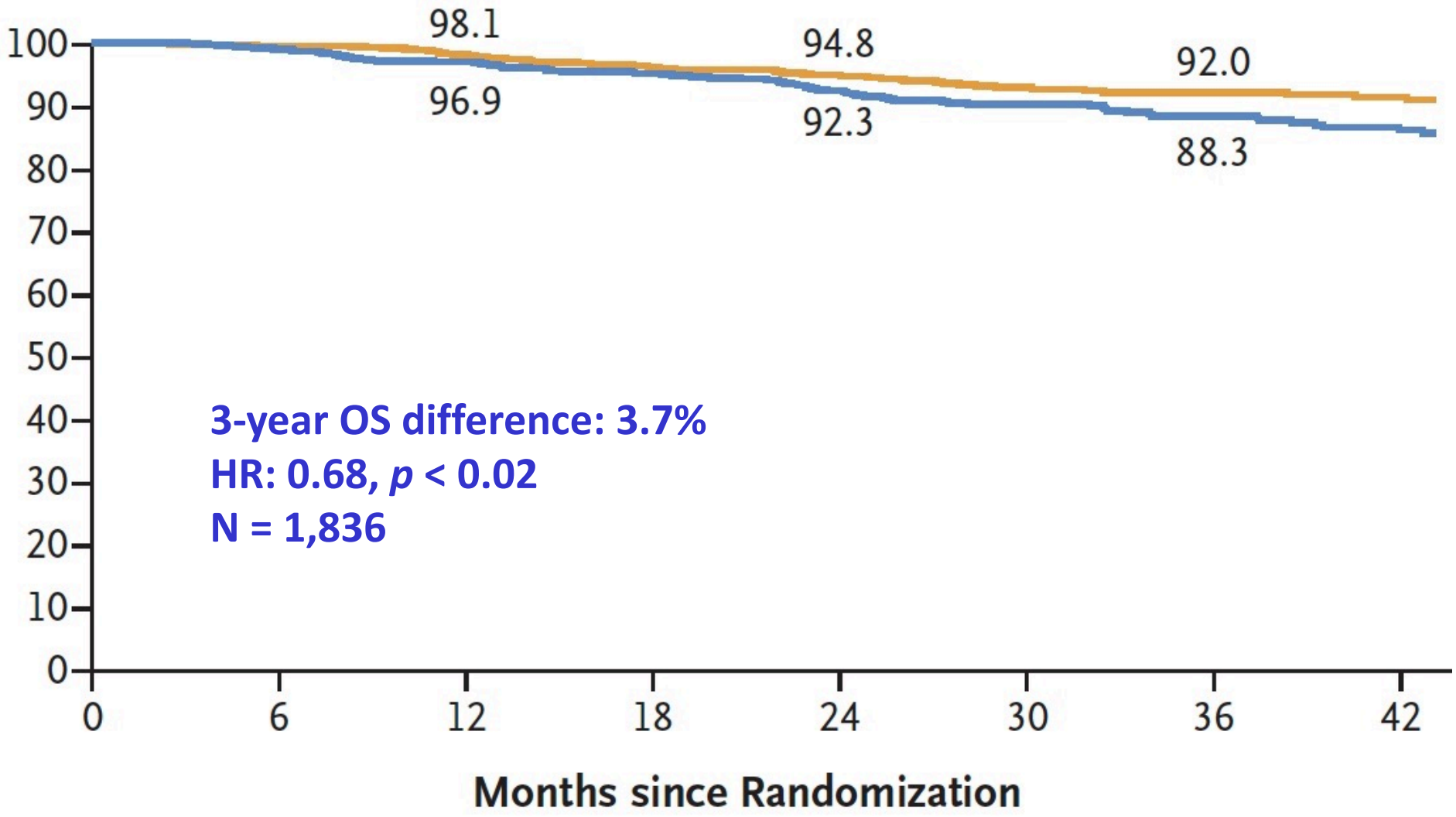
Tutt ANJ et al. *N Engl J Med* 2021;384:2394-405.

OlympiA: Distant Disease-Free Survival



Tutt ANJ et al. *N Engl J Med* 2021;384:2394-405.

OlympiA: Overall Survival



Tutt ANJ et al. *N Engl J Med* 2021;384:2394-405.

OlympiA: Summary of Adverse Events

Adverse Event	Olaparib (N = 911)	Placebo (N = 904)
	no. of patients (%)	
Any adverse event	835 (91.7)	753 (83.3)
Serious adverse event	79 (8.7)	76 (8.4)
Adverse event of special interest†	30 (3.3)	46 (5.1)
MDS or AML	2 (0.2)	3 (0.3)
Pneumonitis‡	9 (1.0)	11 (1.2)
New primary cancer§	19 (2.1)	32 (3.5)
Grade ≥3 adverse event	221 (24.3)	102 (11.3)
Grade 4 adverse event¶	17 (1.9)	4 (0.4)
Adverse event leading to permanent discontinuation of olaparib or placebo‖	90 (9.9)	38 (4.2)
Adverse event leading to death**	1 (0.1)	2 (0.2)

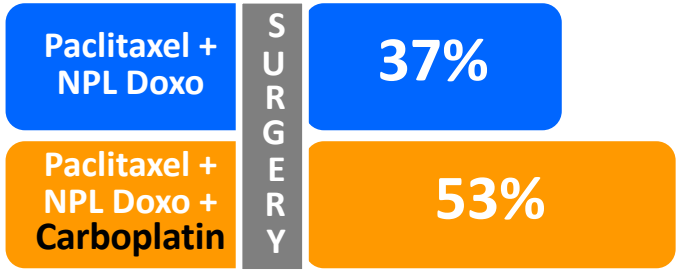
Tutt ANJ et al. *N Engl J Med* 2021;384:2394-405.

Can we increase response to NACT?

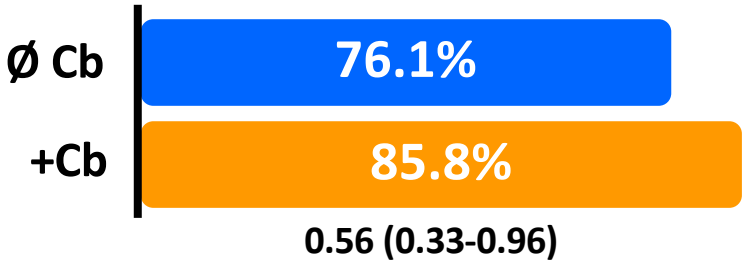
Role of Platinum for TNBC

pCR Rates without Platinum around 35%
Addition of carboplatin increases pCR rate in TNBC to >50% with improvement of EFS/OS

GeparSixto

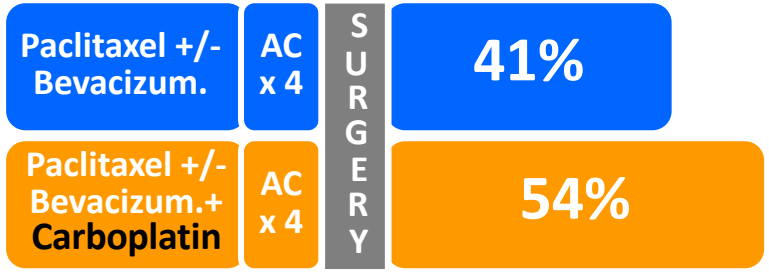


Paclitaxel 80 mg/m² q1w x18 + NPLD 20 mg/m² q1w x18 + Carboplatin AUC 1.5 q1w

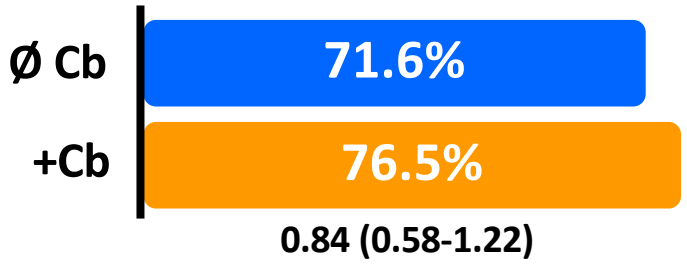


0.56 (0.33-0.96)

CALGB 40603

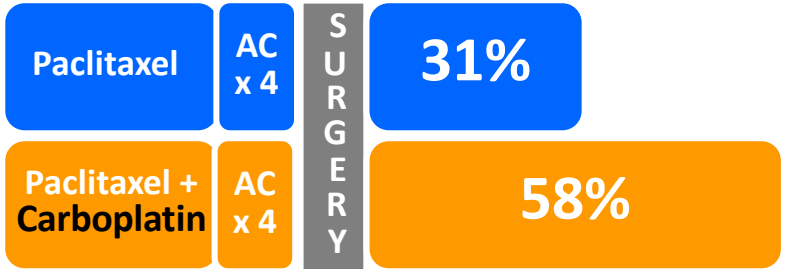


Paclitaxel 80 mg/m² q1w x 12 + Carboplatin AUC 6 q3w x 4



0.84 (0.58-1.22)

BrighTNess



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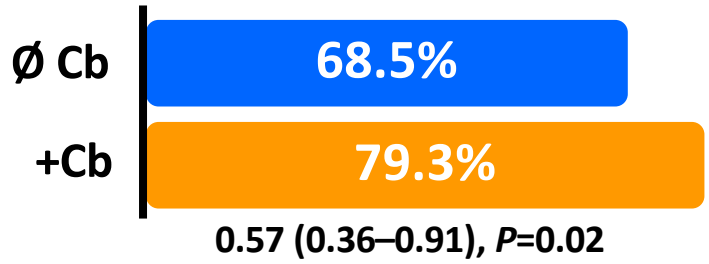


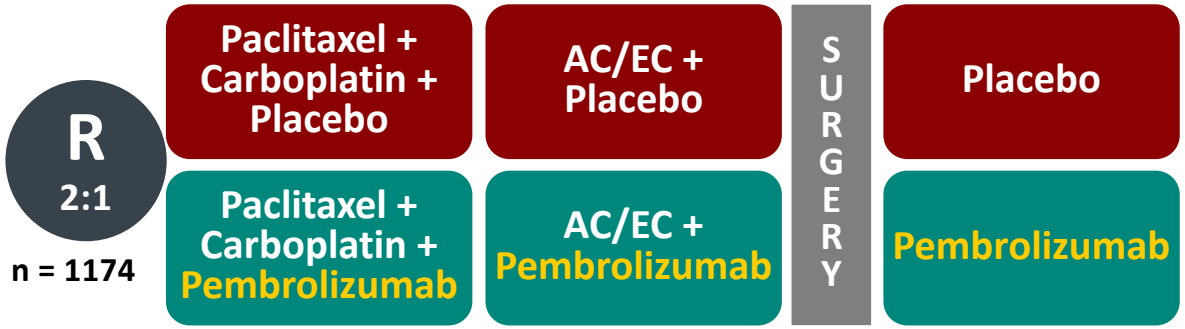
0.57 (0.36–0.91), *P*=0.02

von Minckwitz G, SABCS 2015. #S2-04; von Minckwitz G. *Lancet Oncol.* 2014; Castrellon AB, *Oncol Rev* 2017, Sikov, *JCO* 2015, Sikov, SABCS 2015 S2-05; Loibl, S, et al. *Lancet Oncol.* 2018.

Neoadjuvant Immunotherapy in early TNBC

Phase 3 trials of Immunotherapy in Stage II/III TNBC

Keynote 522



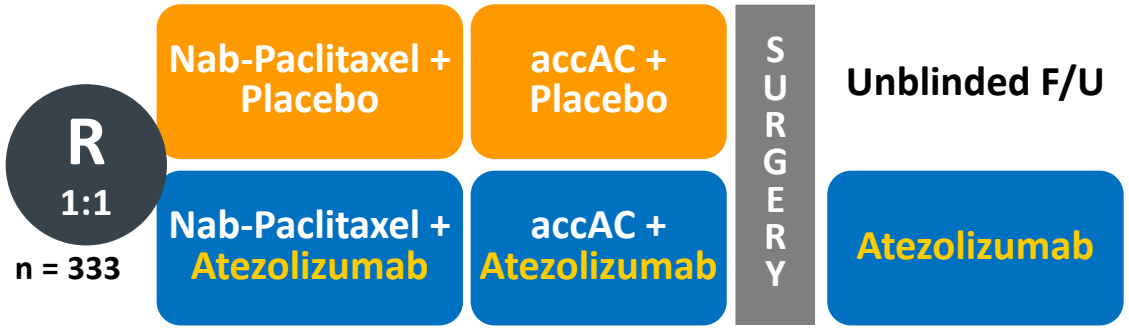
- PDL1+ (22C3 CPS1) 82%
- N+ 52%, T3/4 26%
- Carbo QW 41%

Co-primary endpoints:

- pCR (ypT0/Tis ypN0)
- Event-free Survival

Pembrolizumab: 200 mg given IV q3w
Paclitaxel: 80 mg/m^2 given IV qw for 12 weeks;Carboplatin: AUC5 q3w x 4 or AUC1.5 qw x 12
Doxorubicin: 60 mg/m^2 given IV q2w/Cyclophosphamide: 600 mg/m^2 given IV q2w

IMpassion031



- PDL1+ (SP142≥1%) 53%
- N+ 38% (34% Ate; 43% Pla)
- T3/4 28%

Co-primary endpoints:

- pCR (ypT0/Tis ypN0) in ITT & PD-L1+

Atezolizumab: 840 mg given IV q2w (neoadjuvant); 1200 mg IV q3w x 11 (adjuvant)
Nab-paclitaxel: 125 mg/m^2 given IV qw for 12 weeks
Doxorubicin: 60 mg/m^2 given IV q2w/Cyclophosphamide: 600 mg/m^2 given IV q2w

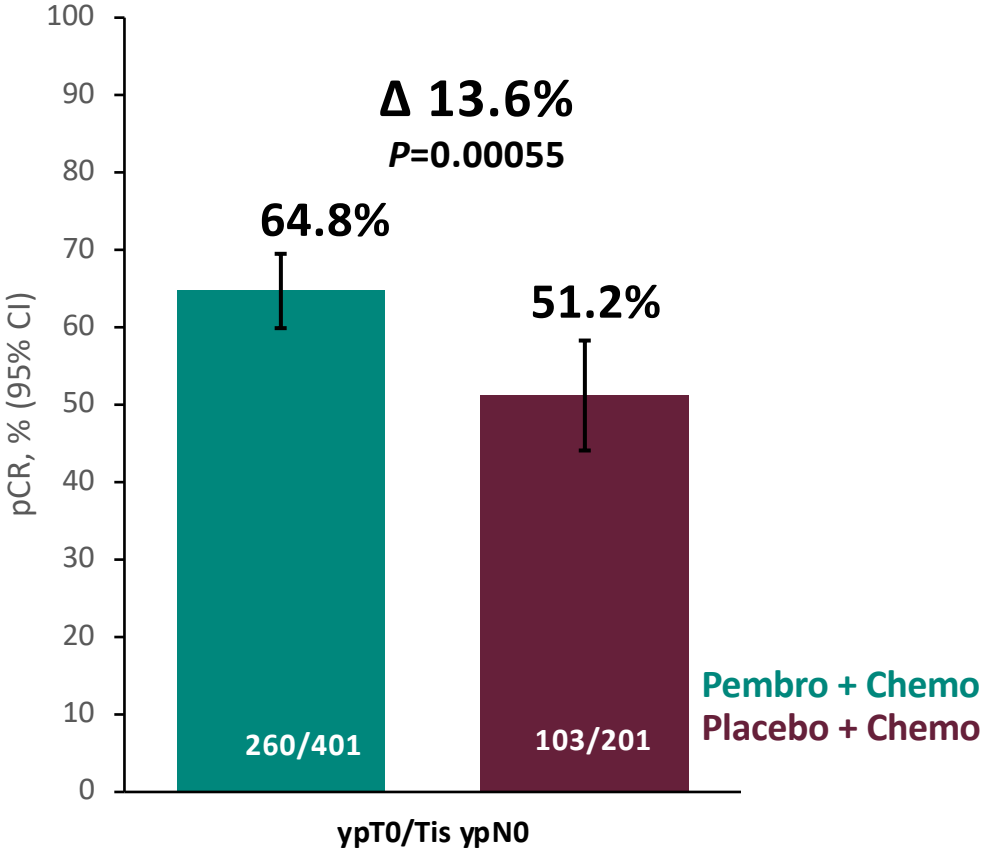
Cross-trial comparison between Keynote 522 and IMpassion031 should be avoided

Schmid P, et al *NEJM* 2020; Mittendorf E, et al *Lancet* 2020.

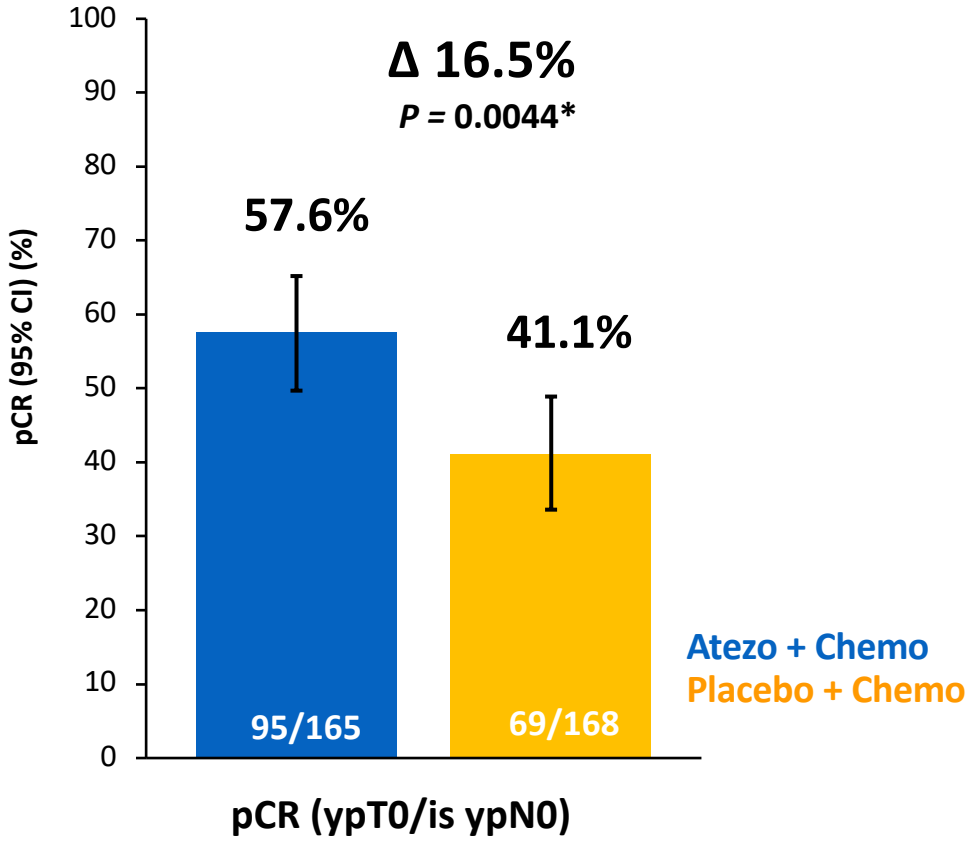
Neoadjuvant CIT in TNBC: Pathological complete response

Addition of CIT significantly improves pCR in ITT Population

Keynote 522



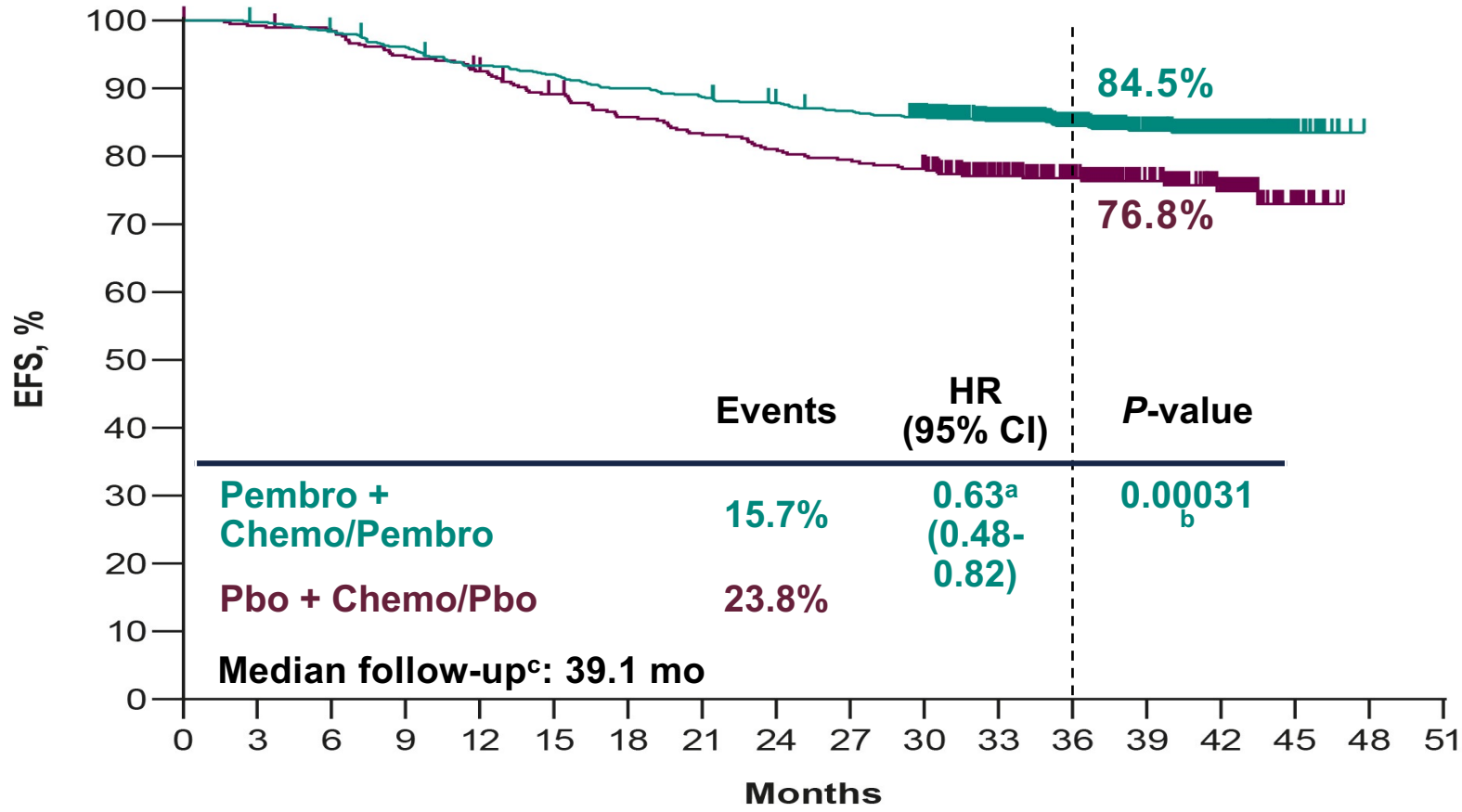
Impassion 031



Schmid P, et al. ESMO 2019, Schmid, et al NEJM 2020, Harbeck et al, ESMO 2020

Neoadjuvant CIT in TNBC: Event-free Survival

Addition of CIT significantly improves EFS in ITT population



No. at Risk

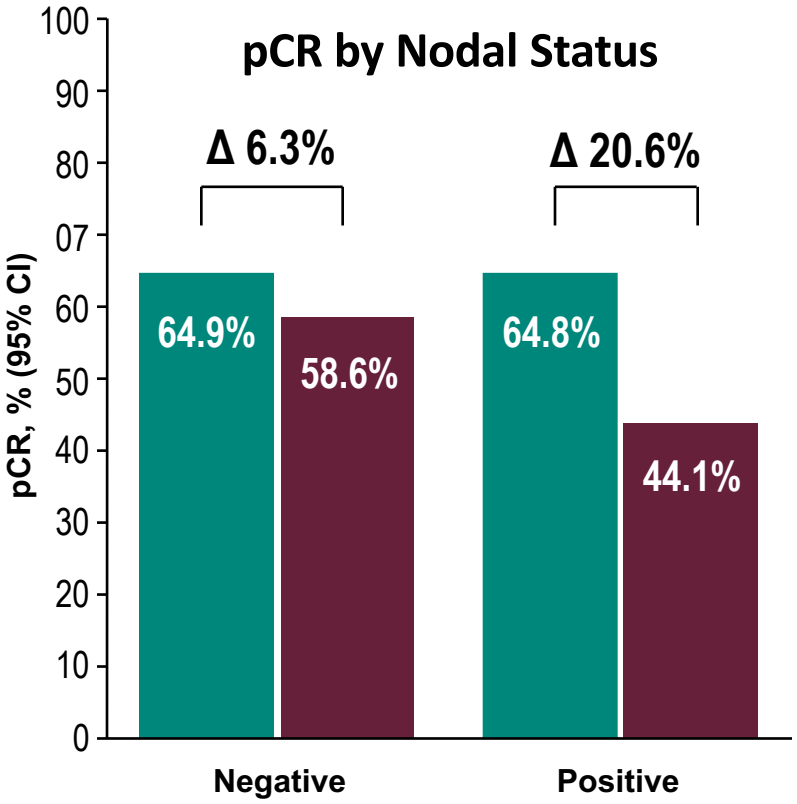
Pembro + Chemo/Pembro	784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
Pbo + Chemo/Pbo	390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

[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.

Schmid et al, ESMO 2021

Nodal Status and Benefit from Immunotherapy

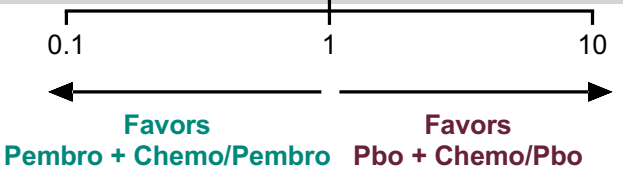
N0 and N+ patients have similar pCR when treated with CIT



N0 and N+ patients have similar EFS Benefit when treated with CIT

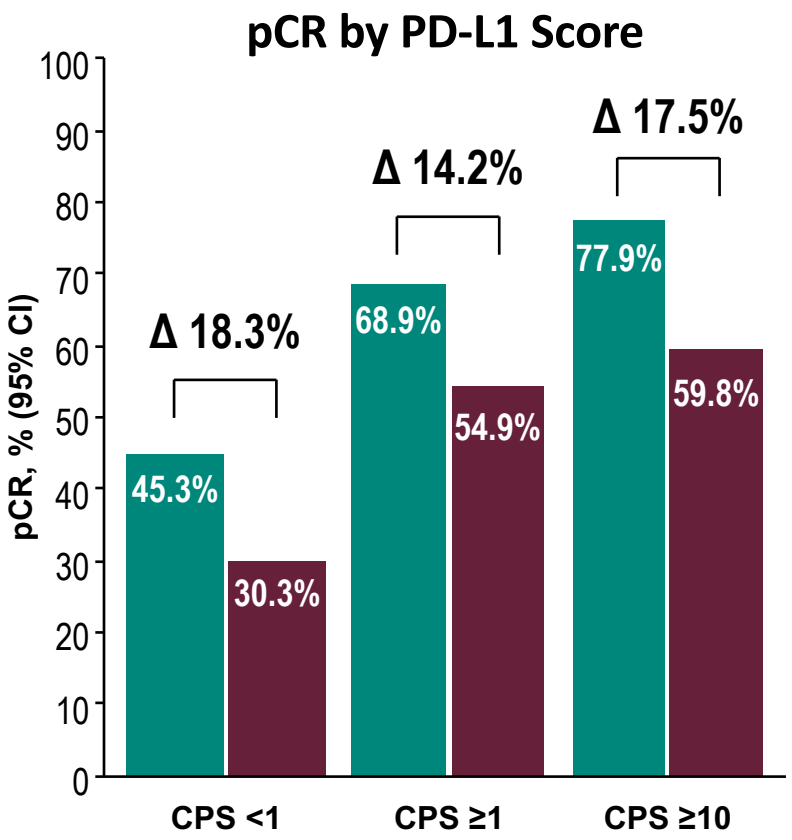
EFS in Subgroups

	No. Events/No. Patients (%)		Hazard Ratio (95% CI)
	Pembro + Chemo/Pembro	Pbo + Chemo/Pbo	
Overall	123/784 (15.7)	93/390 (23.8)	0.63 (0.48 to 0.82)
Nodal status			
Positive	80/408 (19.6)	57/196 (29.1)	0.65 (0.46 to 0.91)
Negative	43/376 (11.4)	36/194 (18.6)	0.58 (0.37 to 0.91)
Tumor size			
T1/T2	64/581 (11.0)	59/290 (20.3)	0.51 (0.36 to 0.73)
T3/T4	59/203 (29.1)	34/100 (34.0)	0.84 (0.55 to 1.28)
Carboplatin schedule			
Every 3 weeks	50/334 (15.0)	37/167 (22.2)	0.65 (0.42 to 0.99)
Weekly	71/444 (16.0)	56/220 (25.5)	0.60 (0.42 to 0.86)
PD-L1 status			
Positive	98/656 (14.9)	68/317 (21.5)	0.67 (0.49 to 0.92)
Negative	25/128 (19.5)	25/69 (36.2)	0.48 (0.28 to 0.85)
Age category			
<65 years	103/700 (14.7)	79/342 (23.1)	0.61 (0.45 to 0.82)
≥65 years	20/84 (23.8)	14/48 (29.2)	0.79 (0.40 to 1.56)
ECOG PS			
0	101/678 (14.9)	80/341 (23.5)	0.60 (0.45 to 0.80)
1	22/106 (20.8)	13/49 (26.5)	0.81 (0.41 to 1.62)



PD-L1 Status and Benefit from Immunotherapy

PD-L1+ and PD-L1- patients have similar EFS and pCR Benefit when treated with CIT



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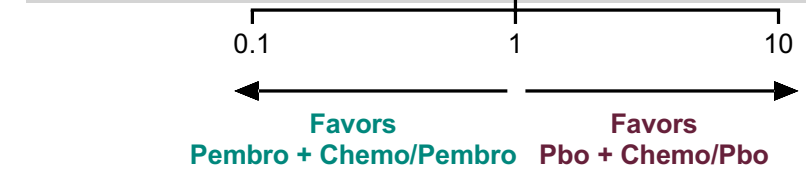
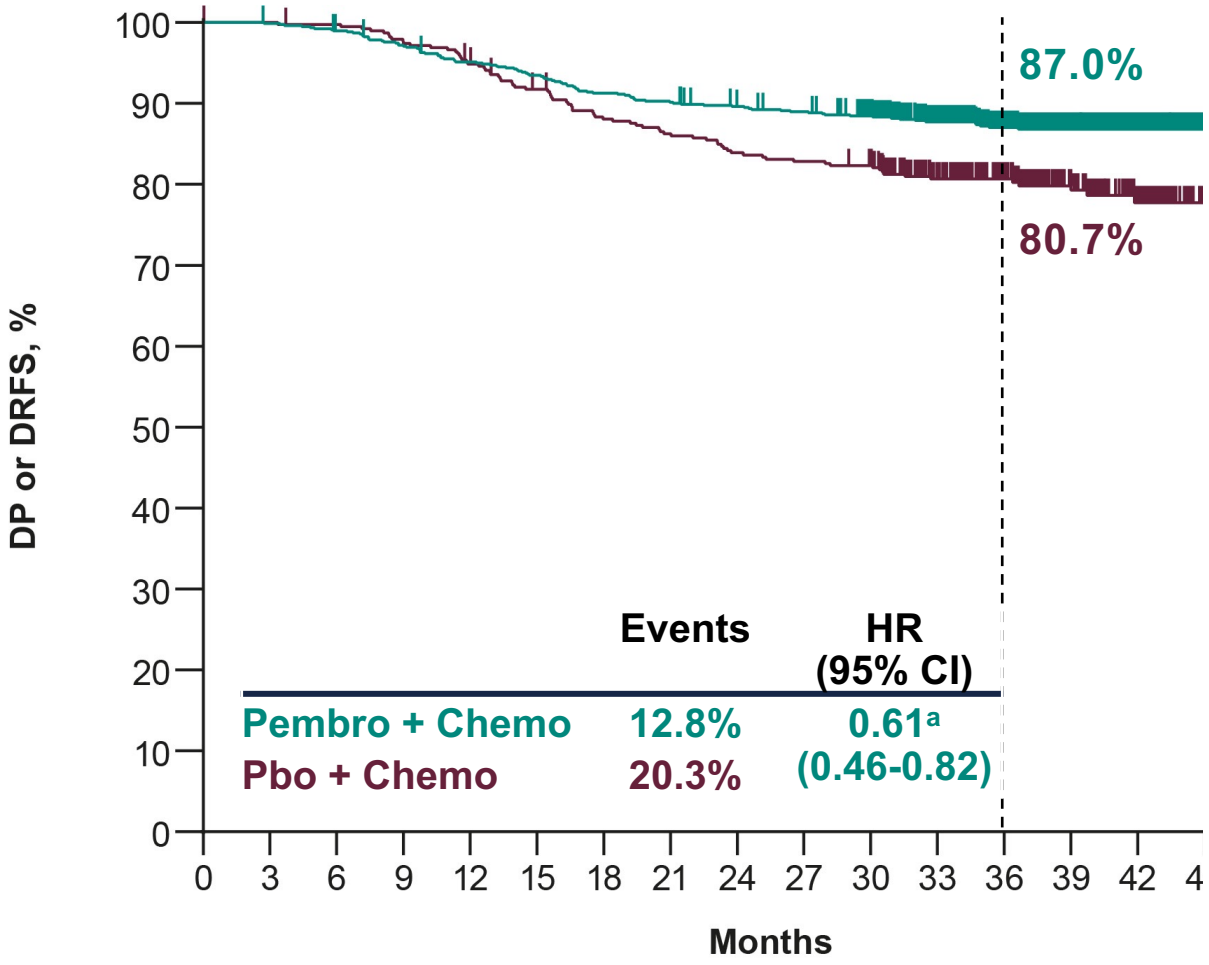
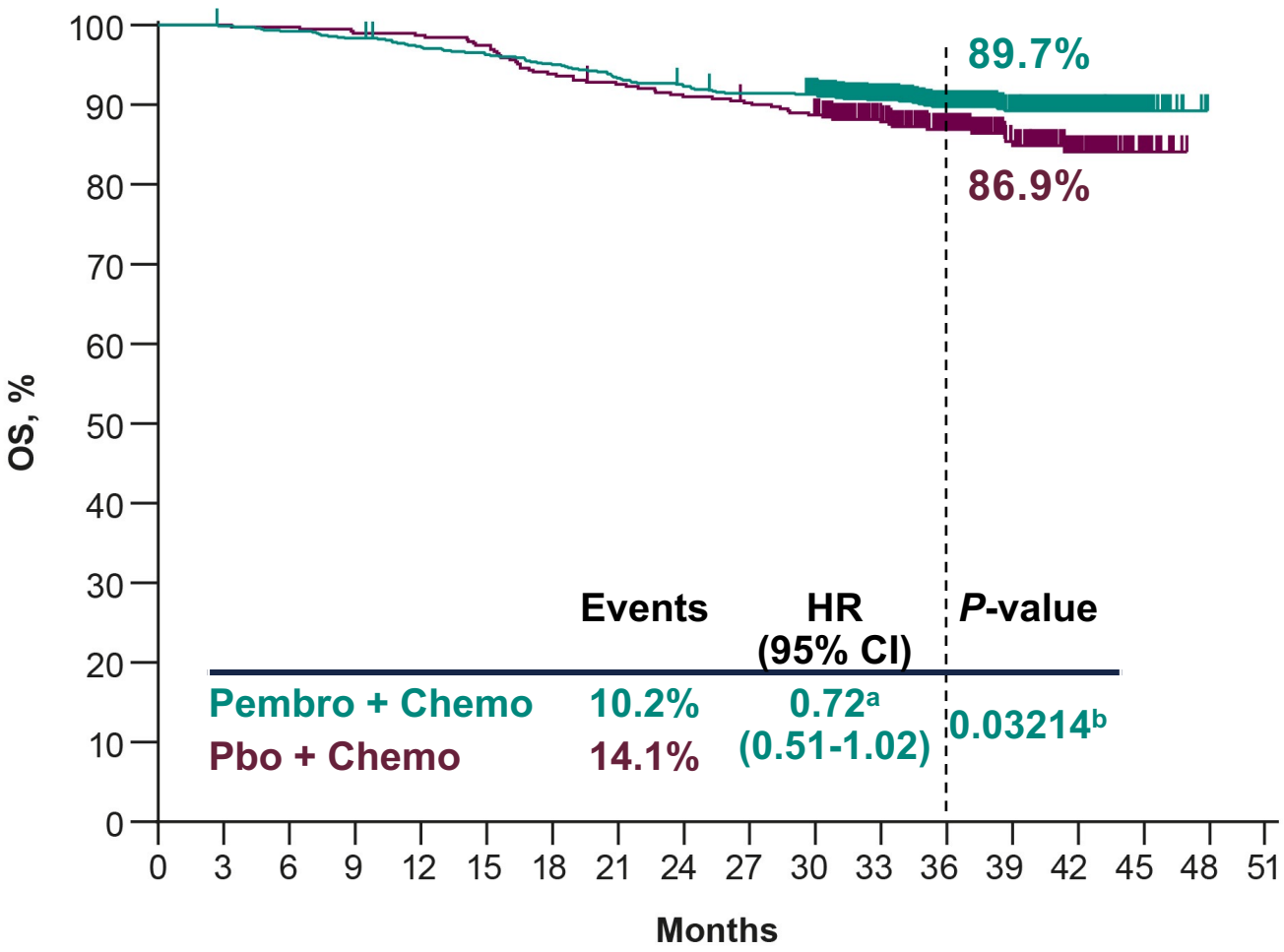


Neoadjuvant CIT in TNBC: Distant RFS and Overall Survival

Distant Recurrence-Free Survival



Overall Survival

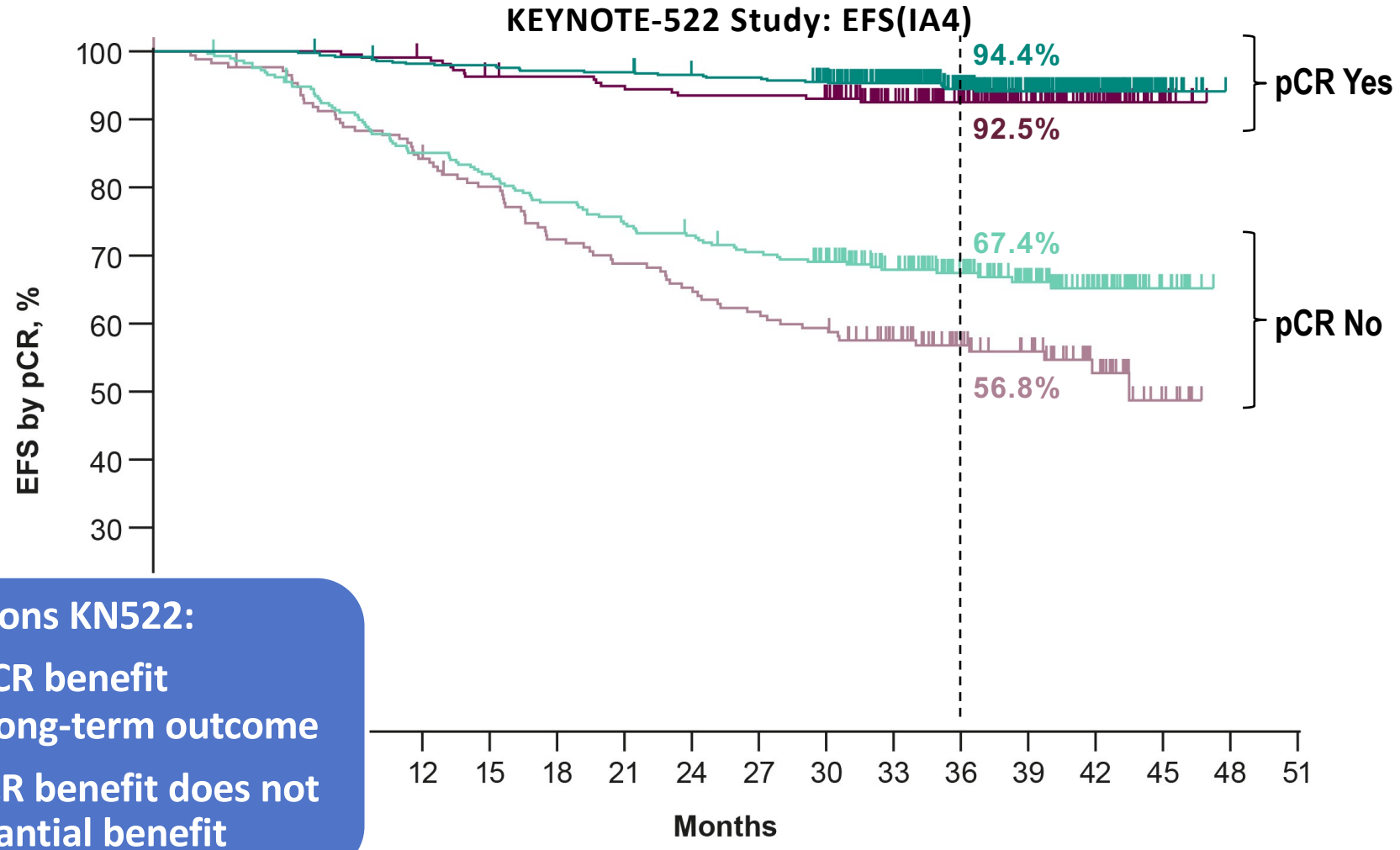


[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff date: March 23, 2021.

Schmid et al, ESMO 2021

Does pCR-benefit with CIT translate into survival benefit?

Is there a benefit beyond achieving a pCR? Event-free Survival by pCR

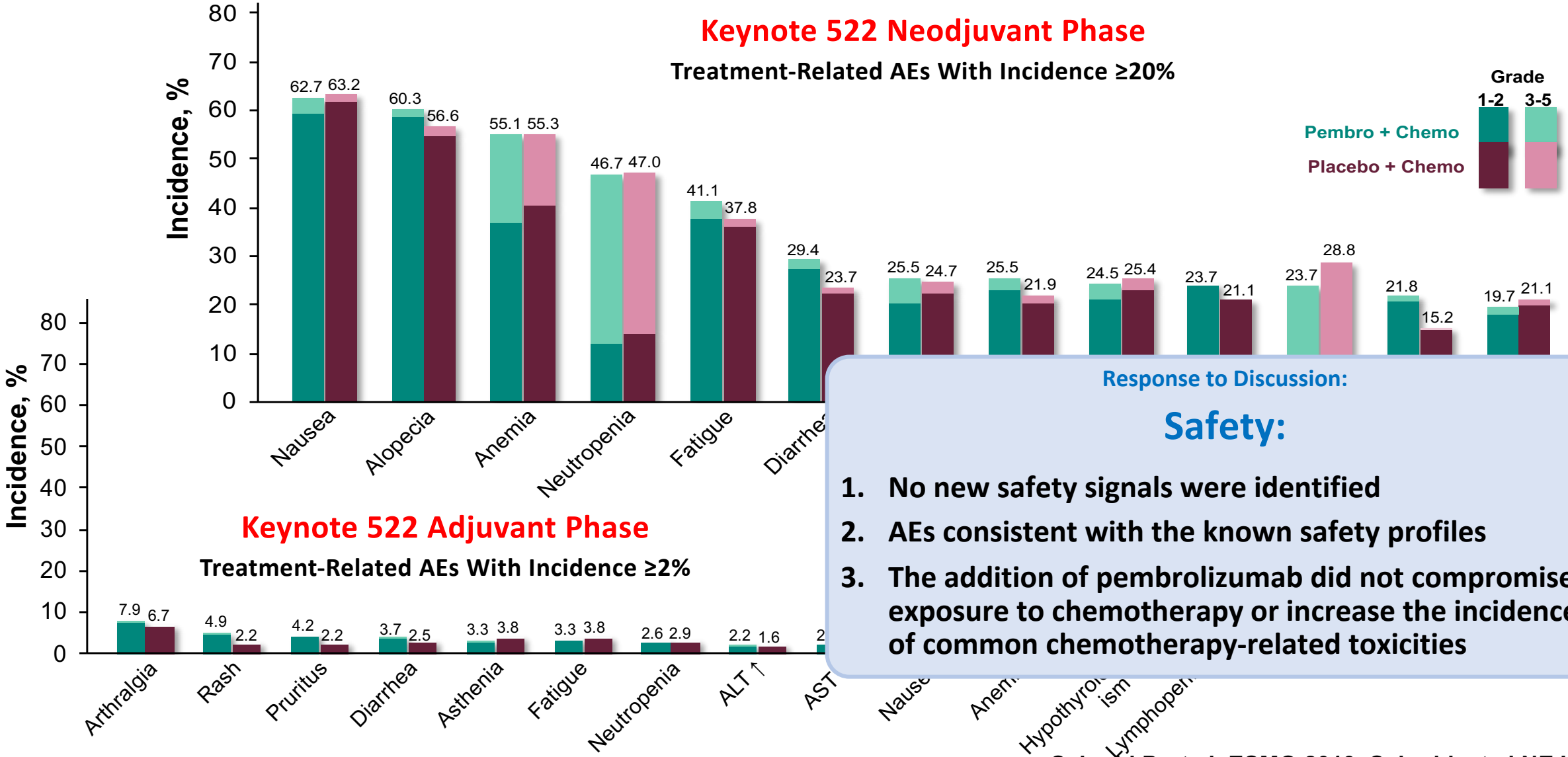


Implications KN522:

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

Schmid et al, ESMO 2021

Neoadjuvant CIT: Treatment-related side effects



Response to Discussion:

Safety:

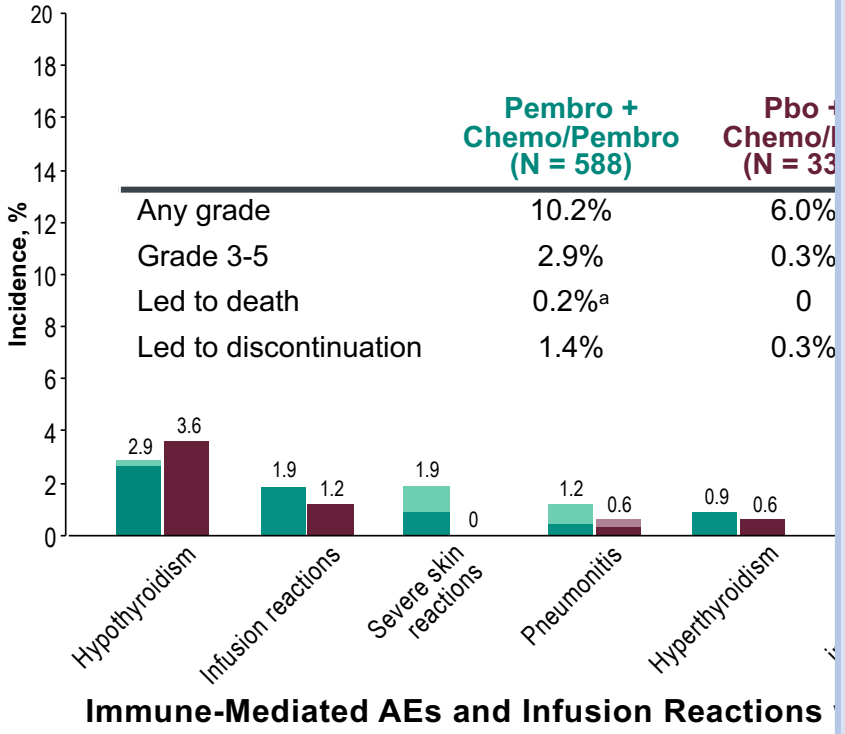
1. **No new safety signals were identified**
2. **AEs consistent with the known safety profiles**
3. **The addition of pembrolizumab did not compromise exposure to chemotherapy or increase the incidence of common chemotherapy-related toxicities**

Schmid P, et al. ESMO 2019, Schmid, et al NEJM 2020

Neoadjuvant CIT: Immune-mediated side effects

Immune-Mediated AEs in Adjuvant Phase

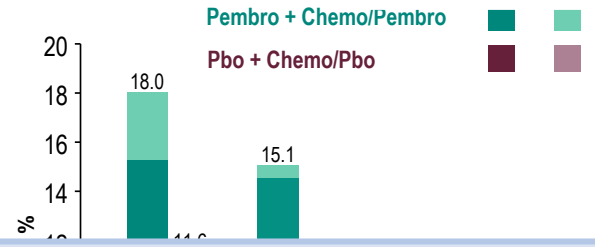
	Pembro + Chemo/Pembro (N = 588)	Pbo + Chemo/P (N = 33
Any grade	10.2%	6.0%
Grade 3-5	2.9%	0.3%
Led to death	0.2%[a]	0
Led to discontinuation	1.4%	0.3%



Immune-Mediated AEs and Infusion Reactions

[a]1 patient from autoimmune encephalitis. Considered regardless of attribution to treatment or immune relatedn
preferred terms listed. Data cutoff date: March 23, 2021.

Immune-Mediated AEs in Combined Phases



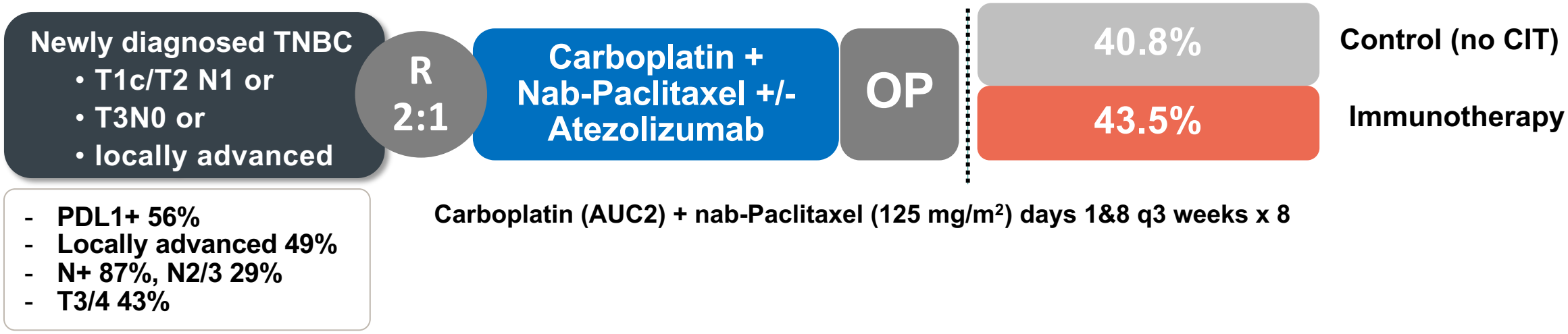
	Pembro + Chemo/Pembro (N = 783)	Pbo + Chemo/Pbo (N = 389)
Any grade	43.6%	21.9%
Grade 3-5	14.9%	2.1%

Response to Discussion:

Immune-Mediated AEs:

1. Higher incidence of immune-mediated AEs primarily driven by endocrinopathies and skin reactions
2. AEs mostly occurred during the neoadjuvant phase with a very low incidence during the adjuvant phase
3. AEs generally low-grade, and successfully managed with treatment interruption, steroid administration, and/or hormone replacement, underscoring the importance of early identification and intervention to minimize risk and ensure continued treatment benefit
4. Although some immune-mediated AEs may be irreversible, analyses from other cancer types support the long-term safety of pembrolizumab, with no signal for late toxicities
5. Additional follow-up will inform the long-term safety of this regimen

Neoadjuvant Chemo + anti-PDL1 in TNBC: NeoTRIP Study



Primary endpoint: Event-free survival at 5 years

Key secondary endpoints: pCR rates (ypT0/TisypN0), safety, predictive markers

Gianni, L, SABCS 2019

CIT trial designs in Early TNBC

Neoadjuvant Chemo
Immunotherapy
OP
+/- Immunotherapy

Keynote 522, Impassion031, NSABP B-59/GBG96

- Optimal antigen release
- Possible over-treatment (pCR with CT)
- pCR with CIT predictive of EFS?
- Contribution of adjuvant therapy unclear

Neoadjuvant Chemo
OP
+/- Immunotherapy

If suboptimal response: Immunoth.

- Reduced antigen release
- Selection of high risk group
- No validated definition of subop response

OP
Neoadjuvant Chemo
Immunotherapy
+/- Immunotherapy

Impassion030

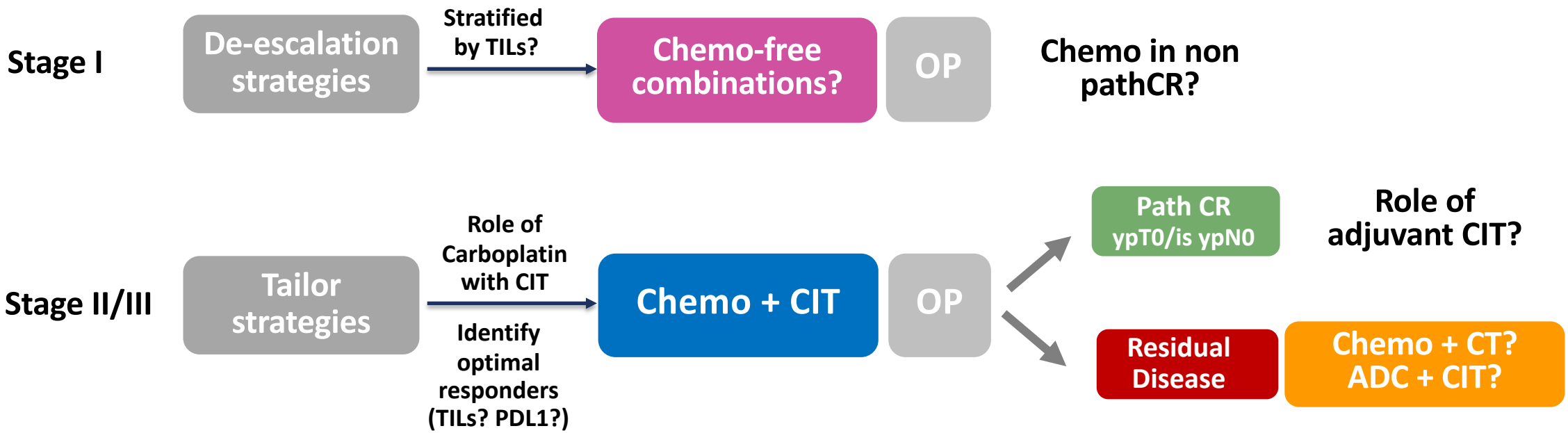
- No/minimal antigen release
- Possible over-treatment
- NACT increasingly standard

Neoadjuvant Chemo
OP
non-path CR Immunotherapy

A-BRAVE, SWOG

- No/minimal antigen release
- Single CIT agent efficacy limited

Future directions in early TNBC



Based on personal communication from Prof. P. Schmid, Barts Cancer Institute.