Il carcinoma mammario TN e immunoterapia: setting (neo)-adiuvante: dalle evidenze della letteratura ala pratica clinica

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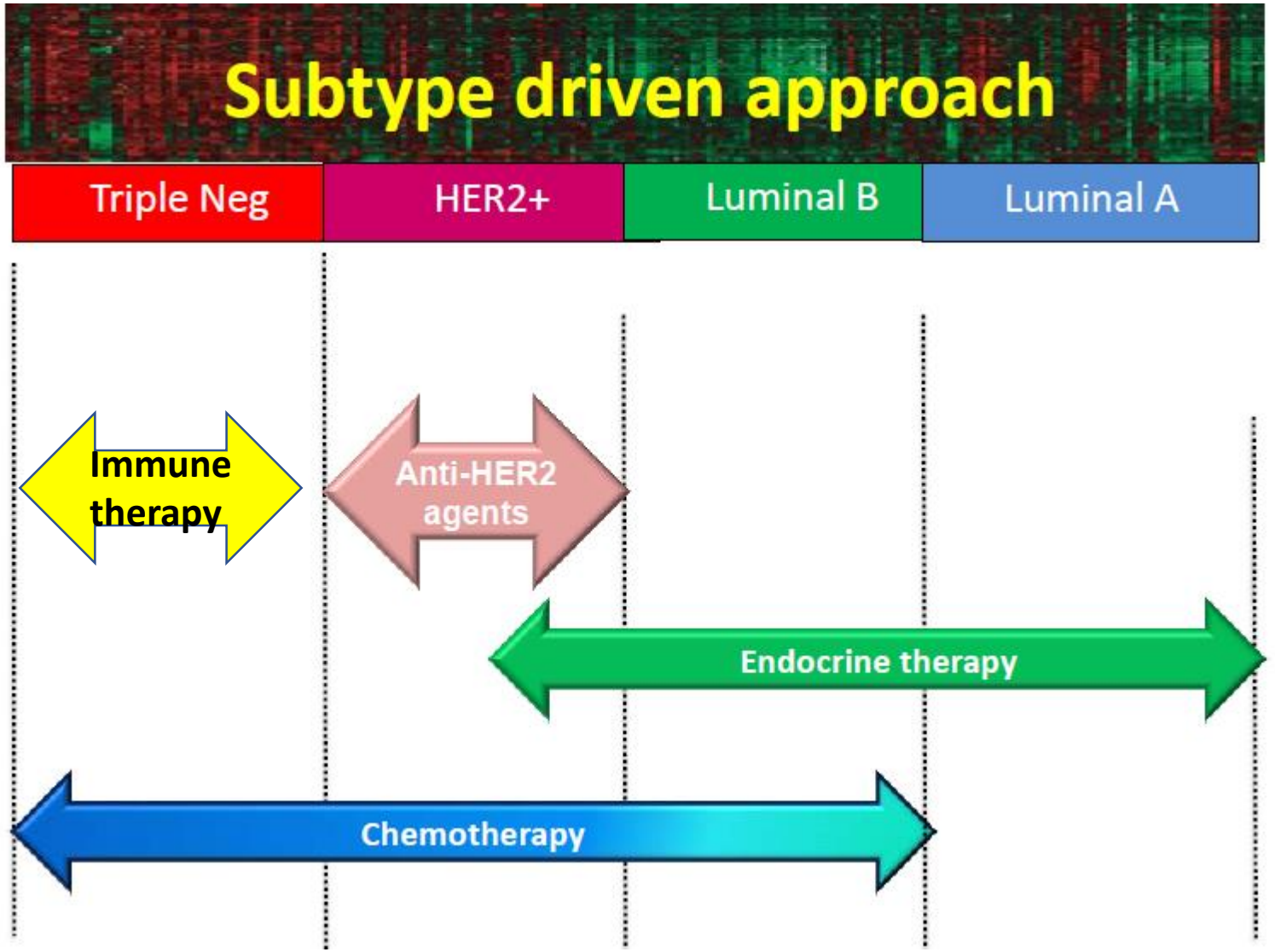
Disclosure

Relationship	**Company/Organization**
Honorary, consultancy or advisory role	Roche – Novartis – Pfizer – Celgene – Takeda – Ipsen – MSD – Genomic Health – Eisai – Eli Lilly – Seattle genetics – Daiichi Sankyo

Adjuvant/neoadjuvant treatment decision



Goals of neoadjuvant therapy in breast cancer

- Make tumors more operable, increase the rate of breast conserving surgeries (breast + axilla)
- Have a better idea of prognosis based on response to neoadjuvant treatment
- Improve DFS and OS using pathological response rate for selection of subsequent treatment in individual patients

Does pCR predict better outcome in different biologic subsets of breast cancer?

ER+, HER2-

HER2+

Triple Negative

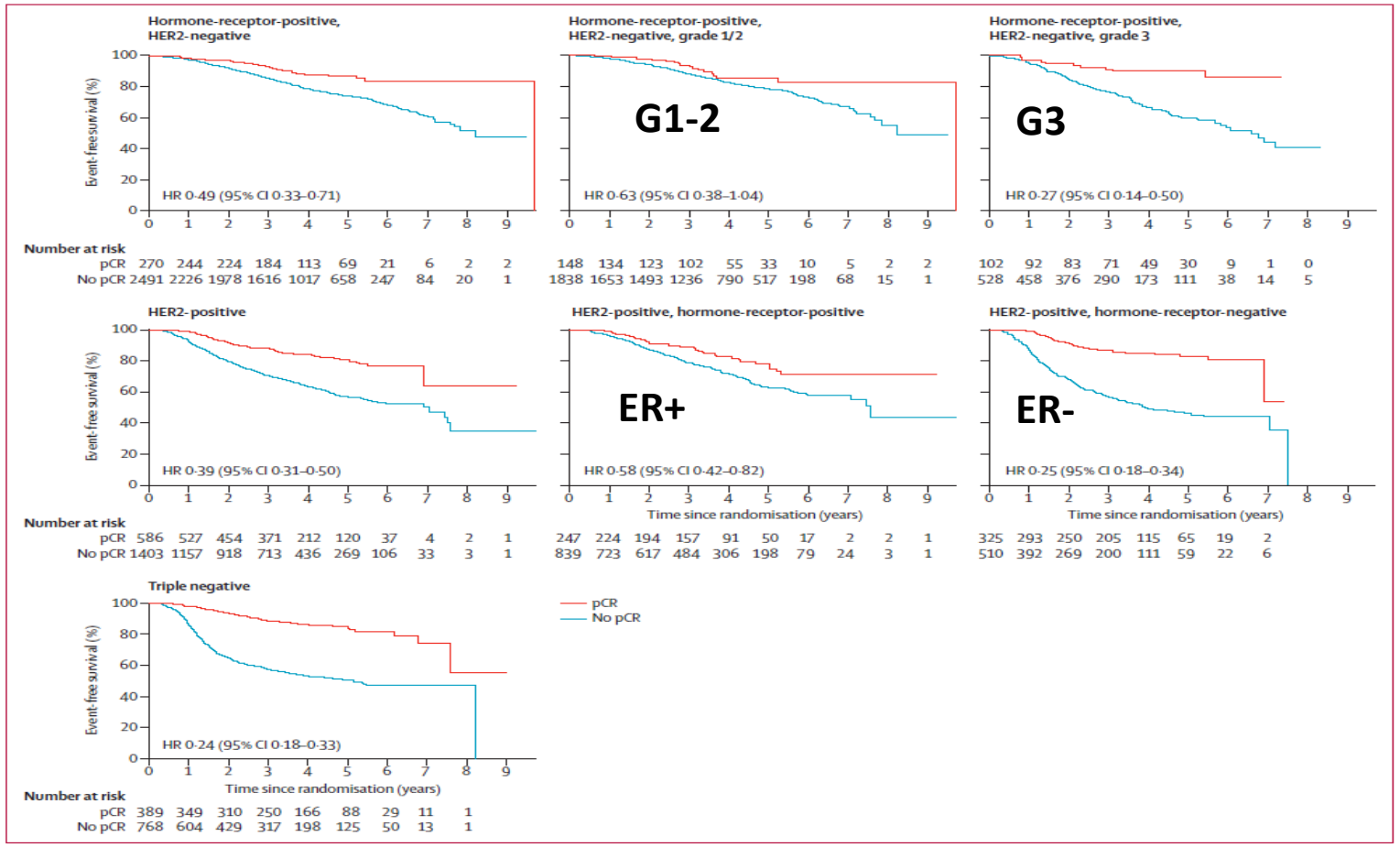
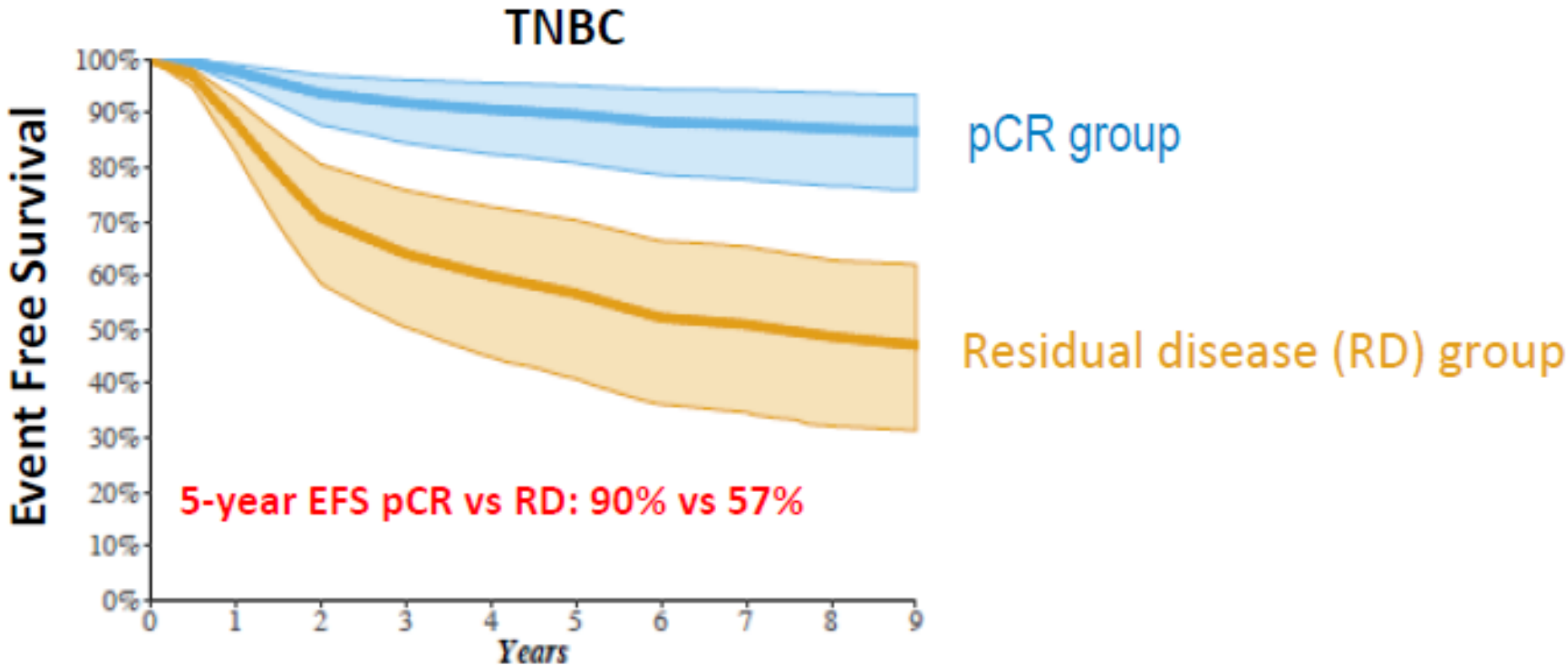


Figure 5: Association between pCR and event-free survival, by breast cancer subtype

Cortazar et al, Lancet 2014

pCR and EFS and OS by Breast Cancer Subtype

Patient level Meta-analysis: 27,000 Patients

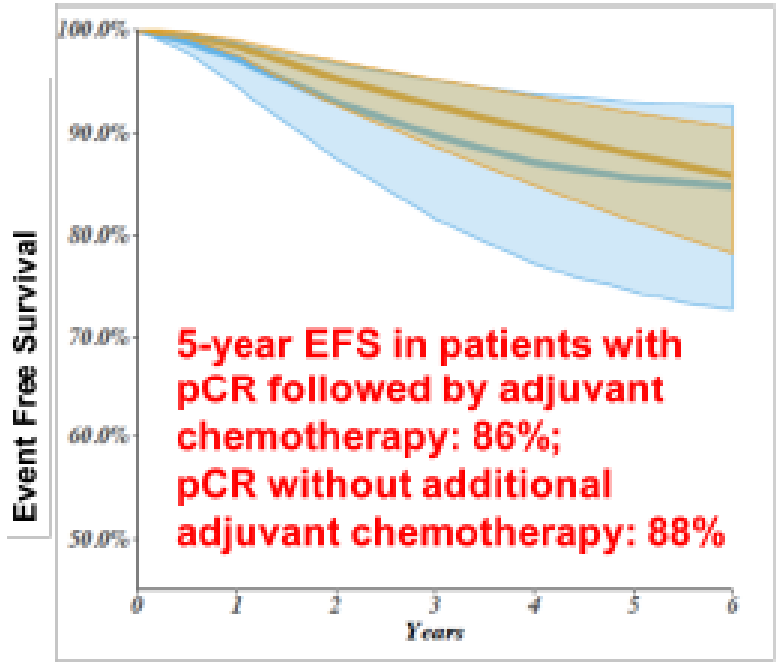


- common theme for neoadjuvant studies, which are typically powered for primary endpoint of pCR and not secondary long-term survival outcomes

congress

Spring L et al. SABCS 2018

Adjuvant chemotherapy after pCR



Blue: pCR without adjuvant chemotherapy
Orange: pCR with adjuvant chemotherapy

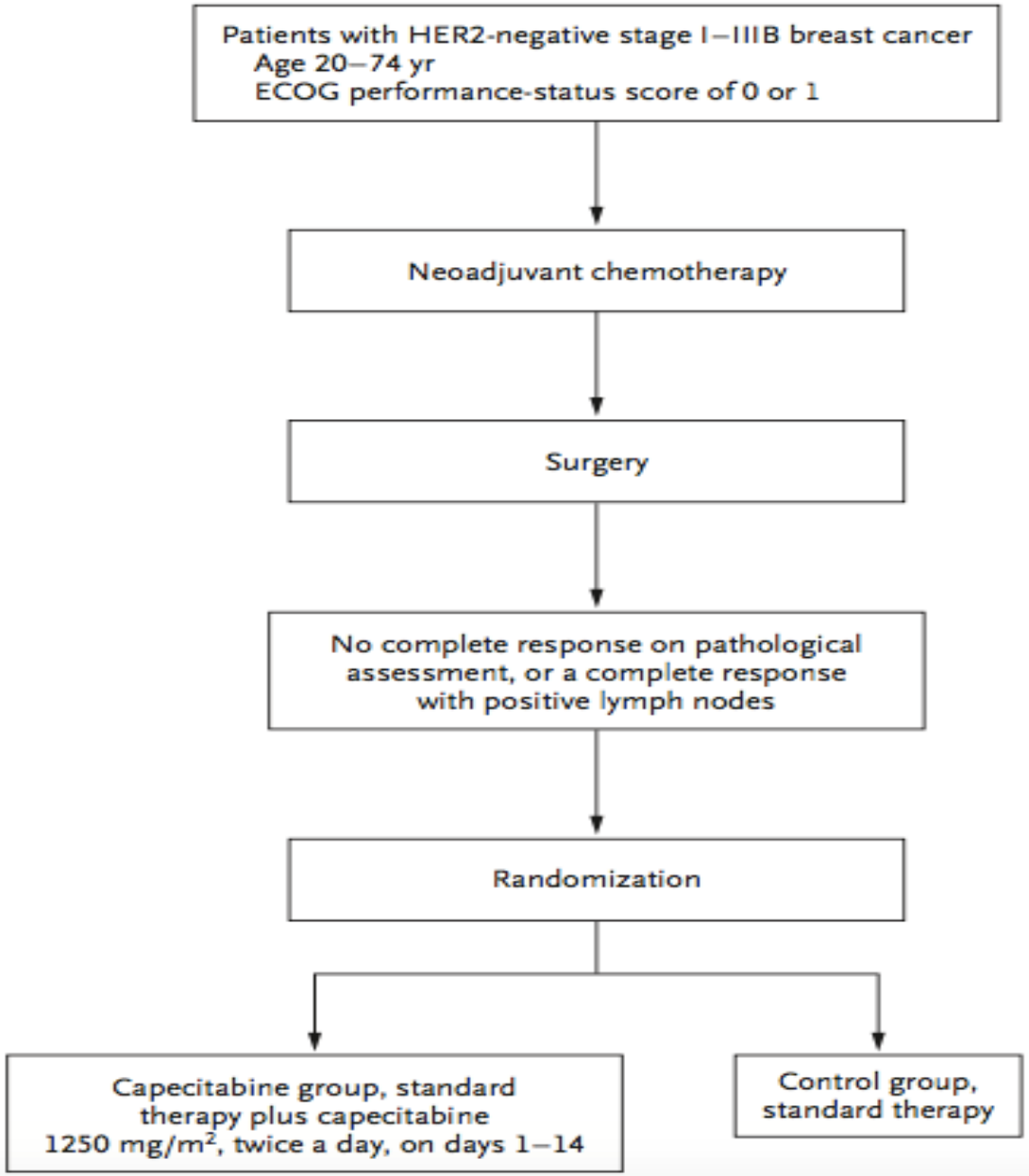
Adjuvant Chemotherapy	Hazard Ratio (pCR and EFS)	95% PI
Yes[1]	0.36	0.19-0.67
No[2]	0.36	0.27-0.54

pCR was associated with significantly improved EFS in both groups, and there was no significant difference in Hazard Ratios between the two groups[3].

[1] >90% of patients received adjuvant chemotherapy
[2] No more than 10% of patients received adjuvant chemotherapy
[3] Paired T-test (difference in log-HR: 0.02, 95% PI: -0.75-0.73; p = 0.60)

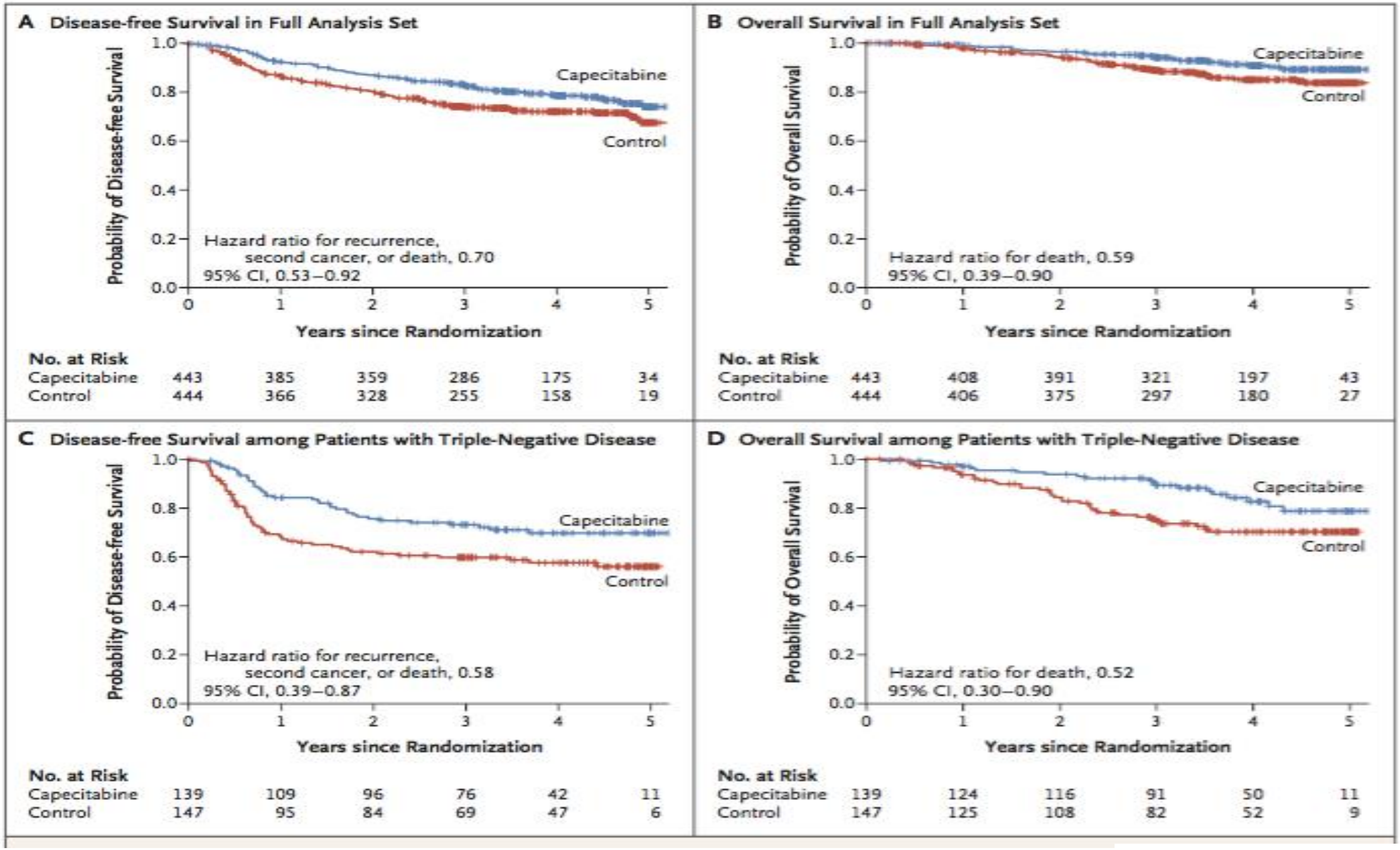
Spring L, et al. SABCS 2018

Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy



	Capecitabine group (N=443)	Control Group (N=444)
Characteristics		
Median age **Range**	**48** **25-74**	**48** **25-74**
ER+ or PgR+ no. (%) **ER-and PgR-**	**304 (69)** **139 (31)**	**297 (67)** **147 (33)**
Neoadj CT no. (%) **Seq anthra and tax** **Concurr anthra and tax**	 **357 (81)** **63 (14)**	 **372 (84)** **53 (12)**

Masuda N N Engl J Med 2017;376:2147-59.



Masuda N

N Engl J Med 2017;376:2147-59.

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Neoadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast Cancer: ASCO Guideline

Korde et al.

Summary of Recommendations

Recommendation 1.3

- Neoadjuvant systemic therapy should be offered to patients with high-risk HER2-positive or triple negative breast cancer (TNBC) in whom the finding of residual disease would guide recommendations related to adjuvant therapy.

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
High	Strong

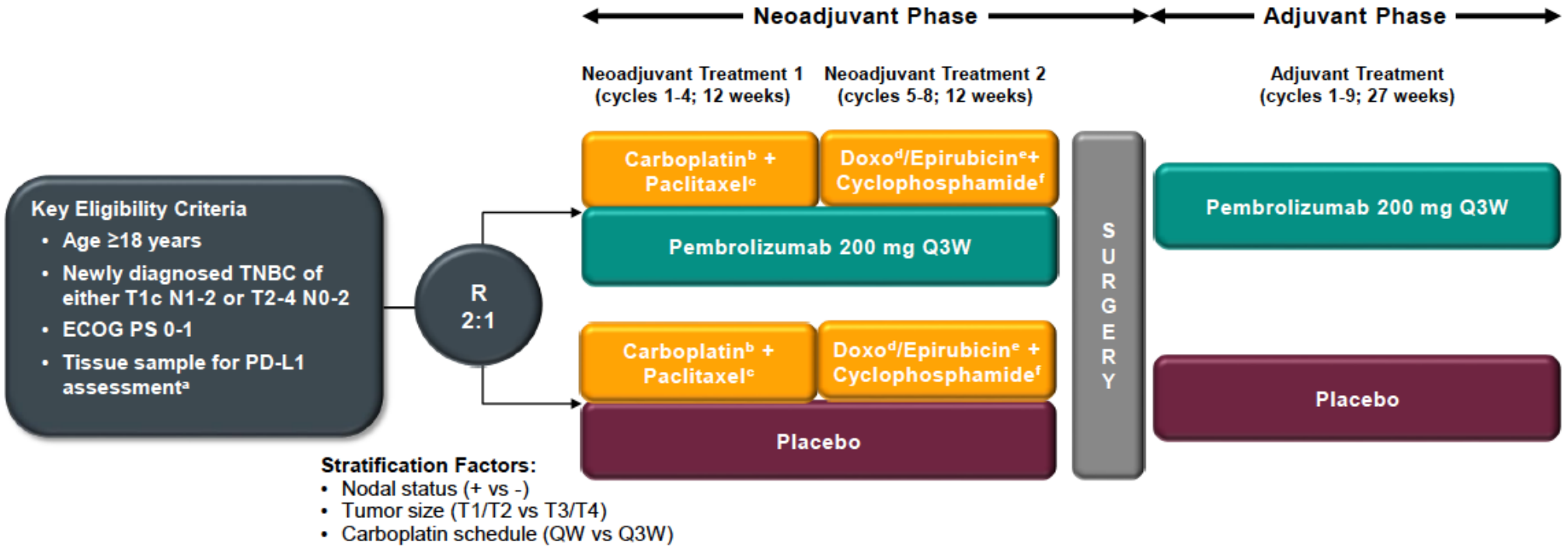
Summary of Recommendations

Recommendation 3.2

- Patients with cT1a or cT1bN0 TNBC should not routinely be offered neoadjuvant therapy outside of a clinical trial.

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
High	Strong

KEYNOTE-522: study design



Primary End Point:

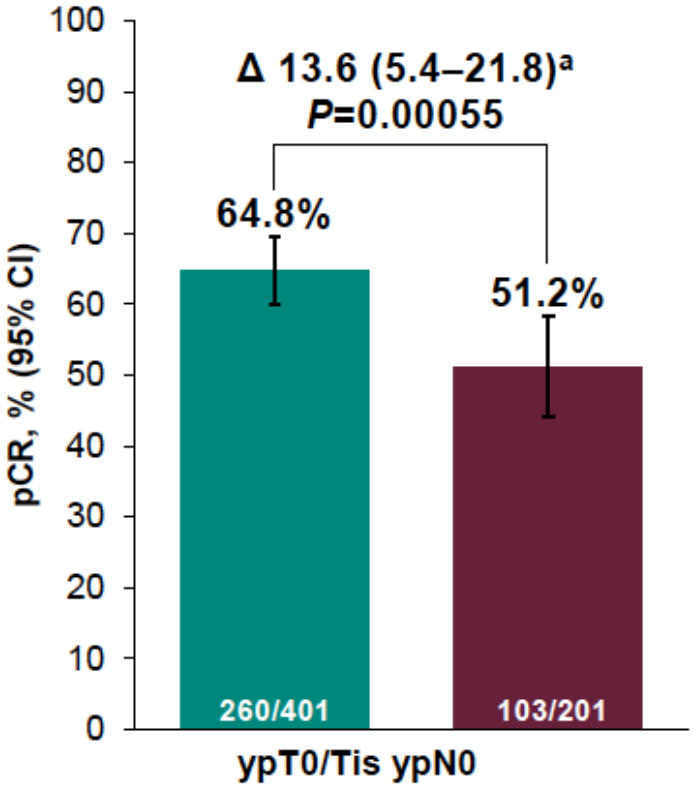
pCR /ypT0/is ypN0) assessed by local pathologist in ITT population

EFS

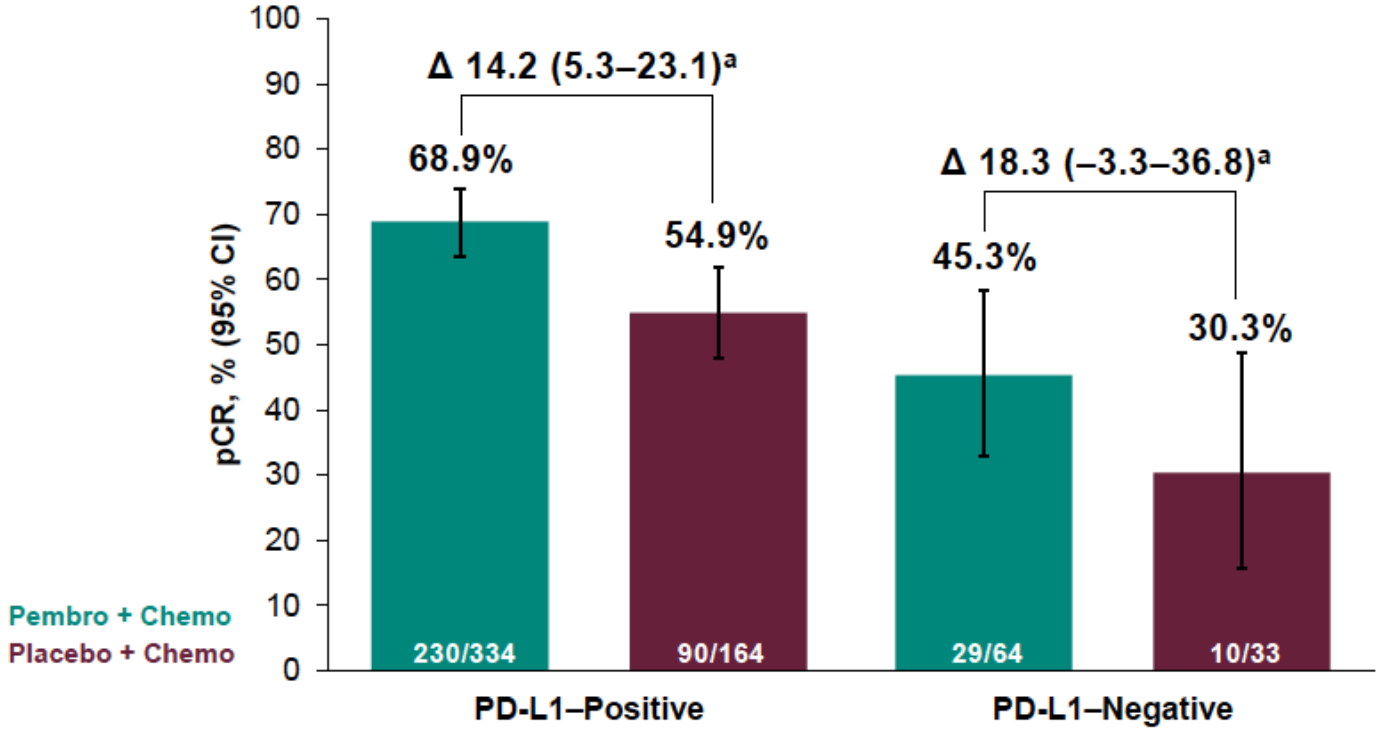
Schmid, NEJM 2020

KEYNOTE-522: pCR

Primary End Point: ypT0/is N0



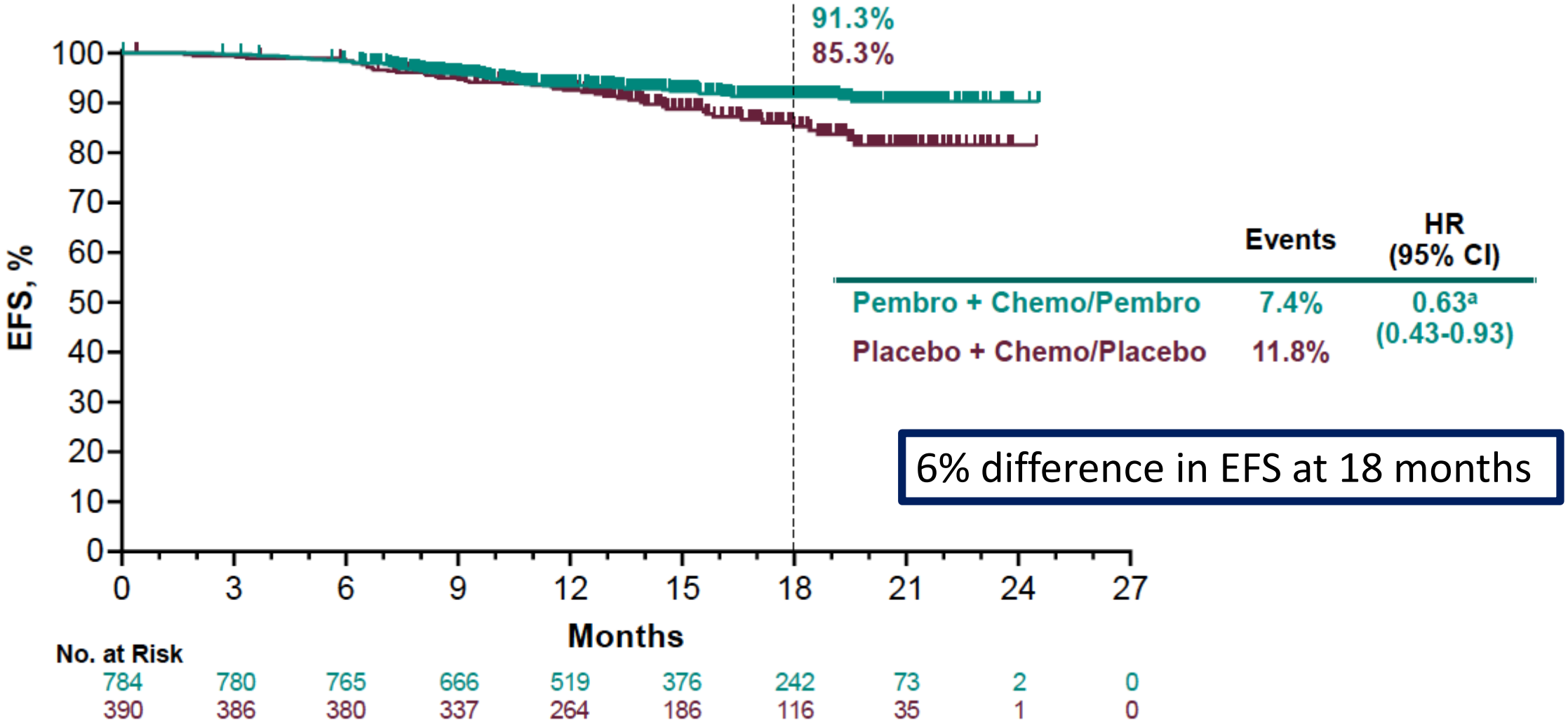
Primary End Point: by PD-L1 status*



* PD-L1 assessed using the IHC 22C3 assay and measured using the CPS; PD-L!-positive = CPS ≥ 1

Schmid, NEJM 2020

KEYNOTE-522: EFS

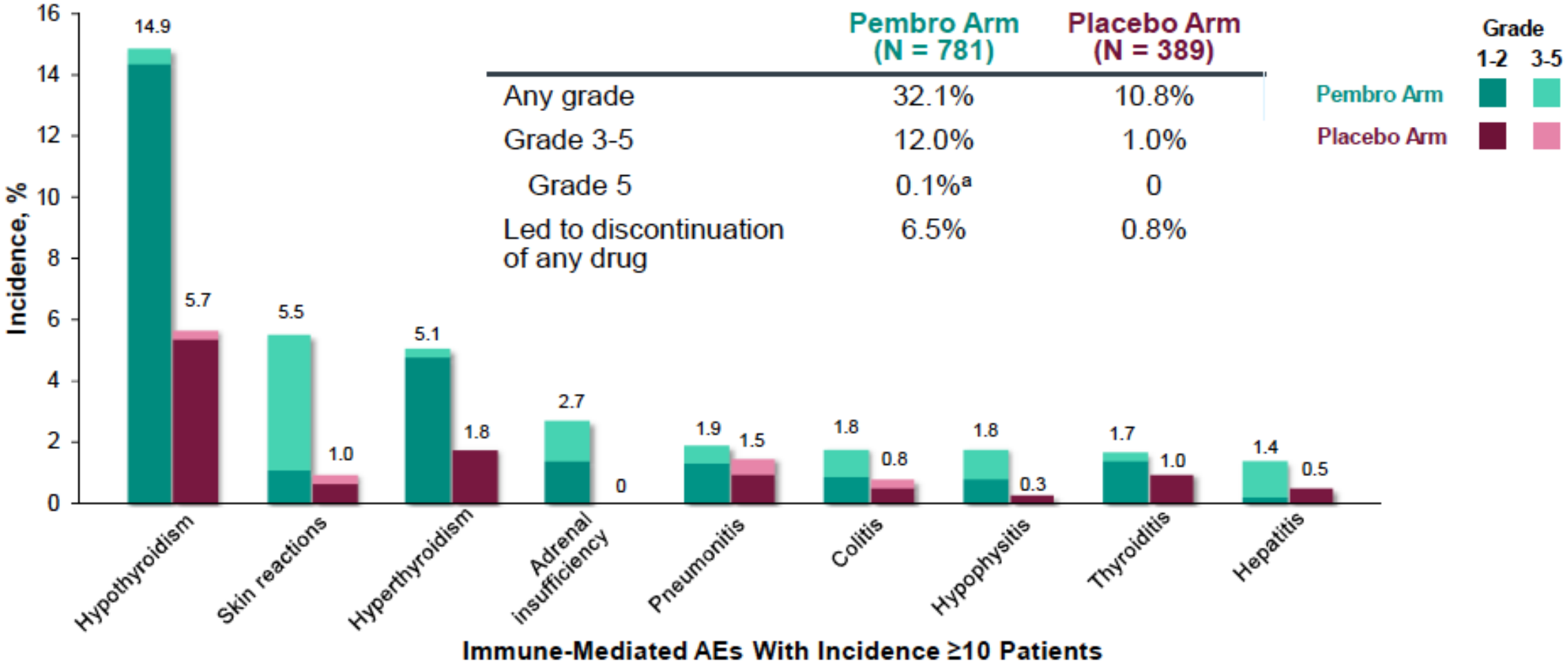


6% difference in EFS at 18 months

Schmid, NEJM 2020

KEYNOTE-522: Immune mediate EAs in the combined phase

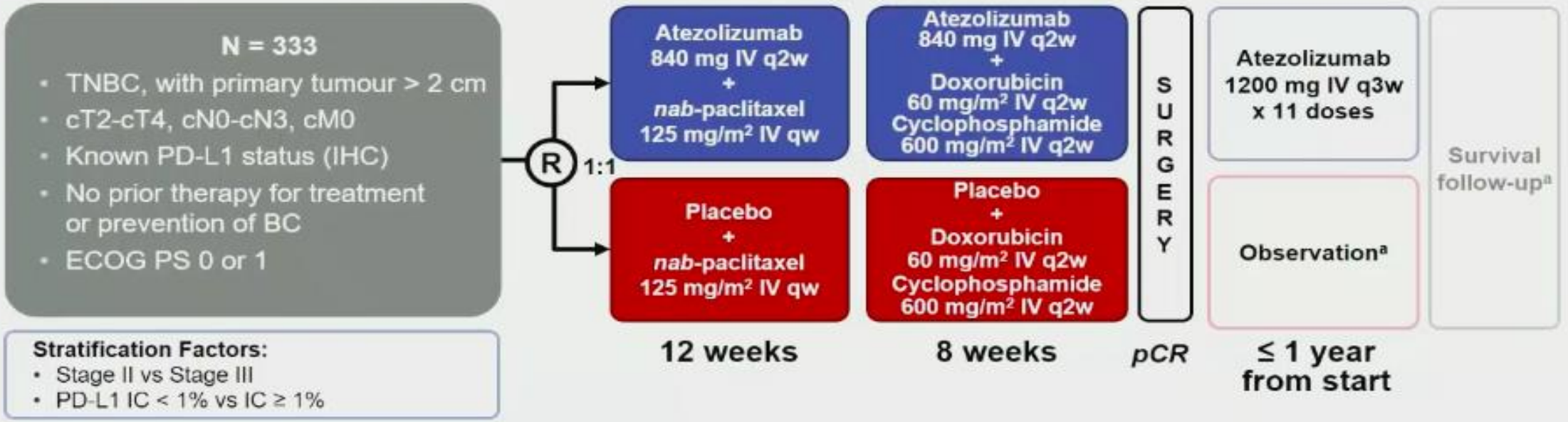
	Pembro Arm (N = 781)	Placebo Arm (N = 389)
Any grade	32.1%	10.8%
Grade 3-5	12.0%	1.0%
Grade 5	0.1%[a]	0
Led to discontinuation of any drug	6.5%	0.8%



Schmid, NEJM 2020

IMpassion031:
Phase III atezolizumab neoadjuvant study in eTNBC[1,2]

A randomised, multicentre, international, double-blind, placebo-controlled trial

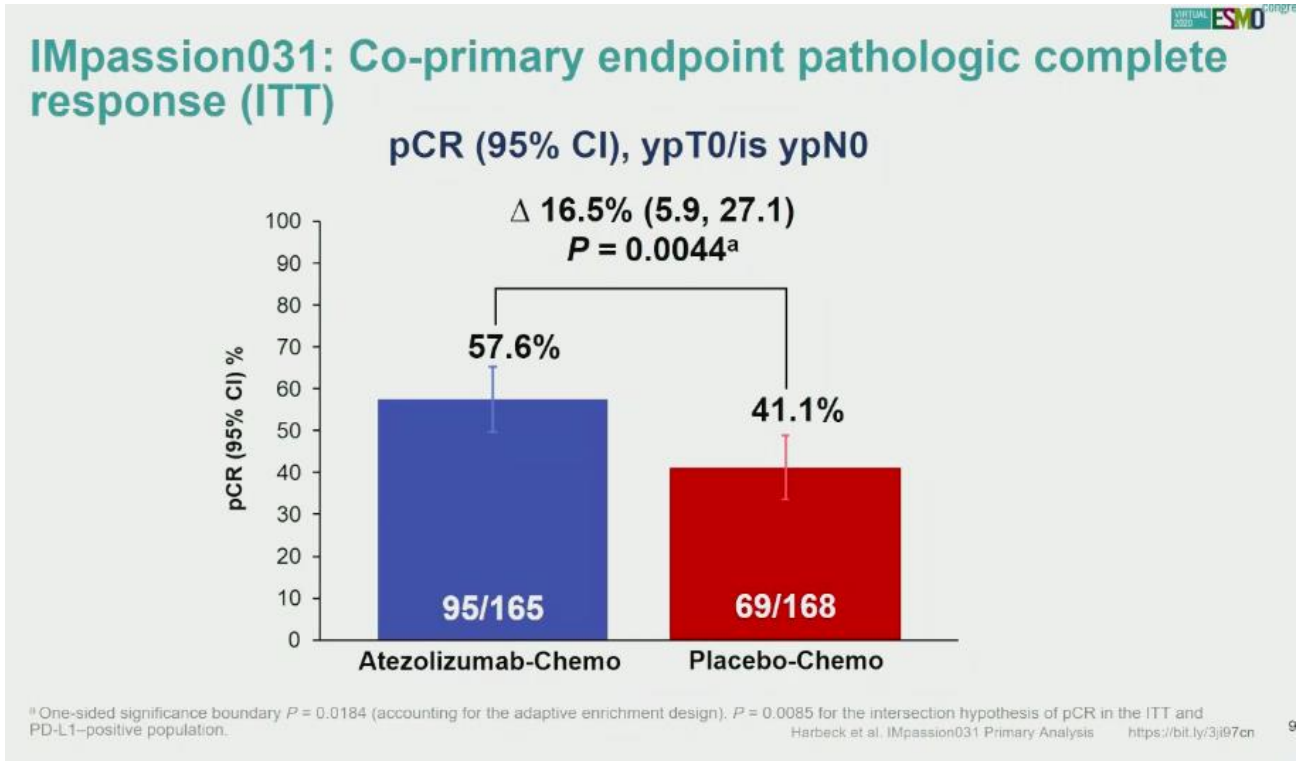


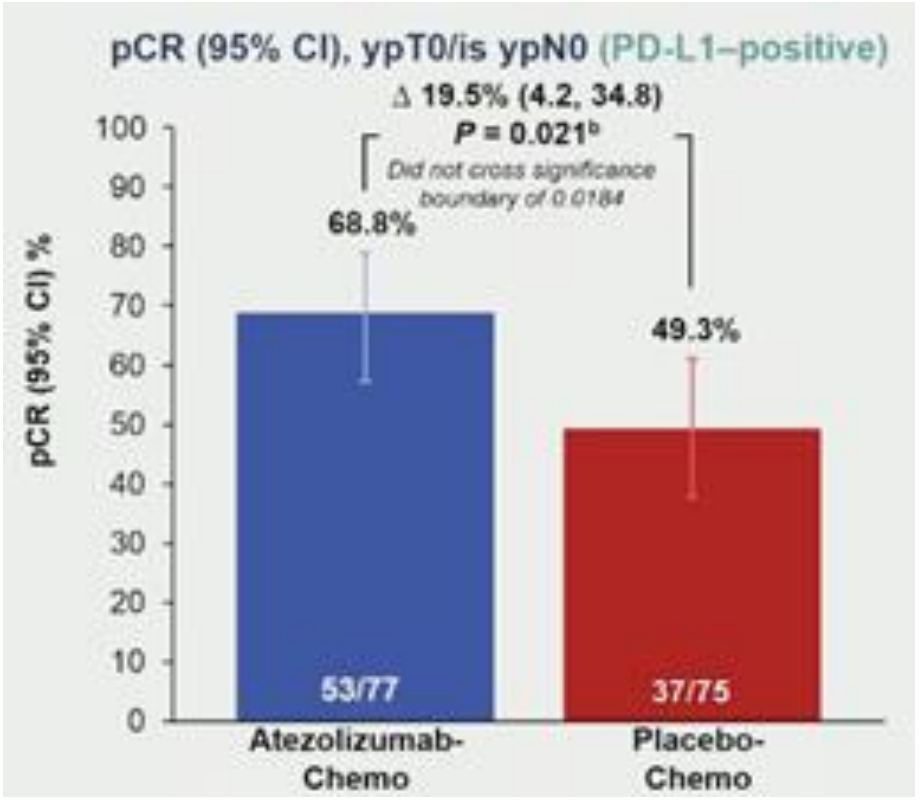
Co-primary endpoints: pathologic complete response (pCR, ypT0/is ypN0) in ITT and PD-L1–positive (IC ≥ 1%) subpopulation

Secondary endpoints: EFS, DFS, and OS in ITT and in PD-L1–positive subpopulation, safety, PROs

[a] Postsurgical management of patients was at the discretion of the treating investigator and based on local practice guidelines.
pCR, pathologic complete response; PD-L1 IC, PD-L1–expressing tumor-infiltrating immune cells as percentage of tumor area using the VENTANA SP142 assay; PRO, patient-reported outcome; q2w, every 2 weeks, q3w, every 3 weeks, qw, every week.

1. Mittendorf E, et al. SABCS 2017 [abstract 17-OT2-07-03]. 2. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/study/NCT03197935. Accessed 11 August 2020.



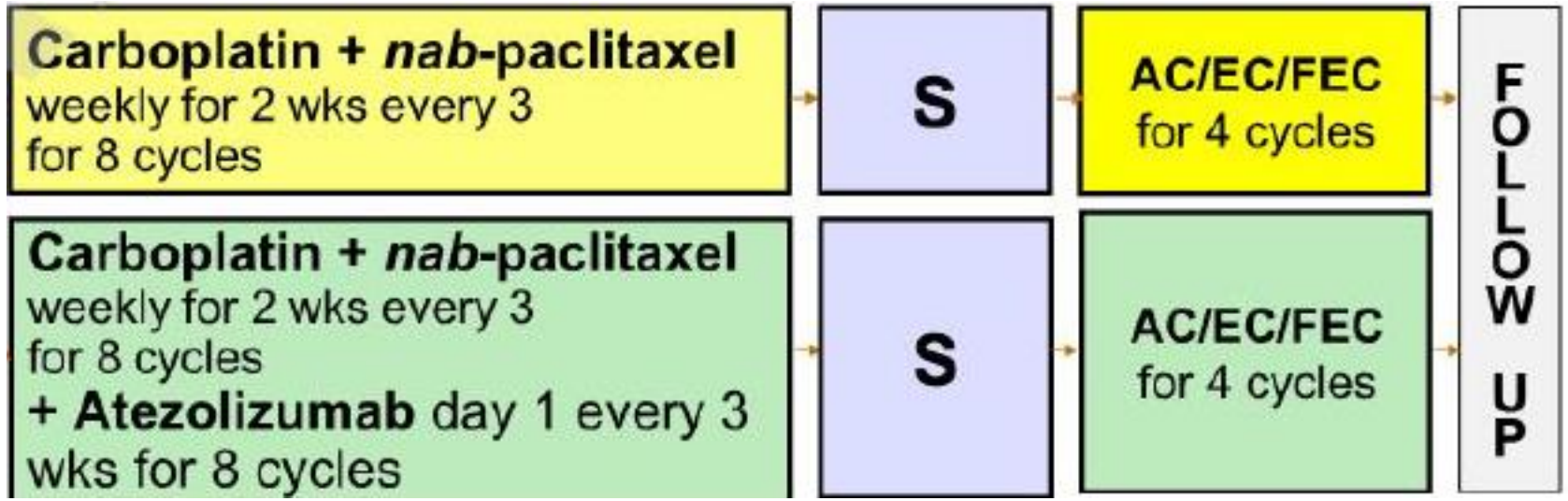


Implications of all the available evidence

The IMpassion031 results showed that addition of atezolizumab to neoadjuvant chemotherapy with nab-paclitaxel followed by doxorubicin plus cyclophosphamide provides clinical benefit in the potentially curable setting of early-stage TNBC. Patients derived pathological complete response benefit regardless of PD-L1 status.

NeoTRIP: study design

ER and PgR negative, HER2-negative, early high risk (cT1N1; T2N1; T3N0) or locally advanced unilateral breast cancer

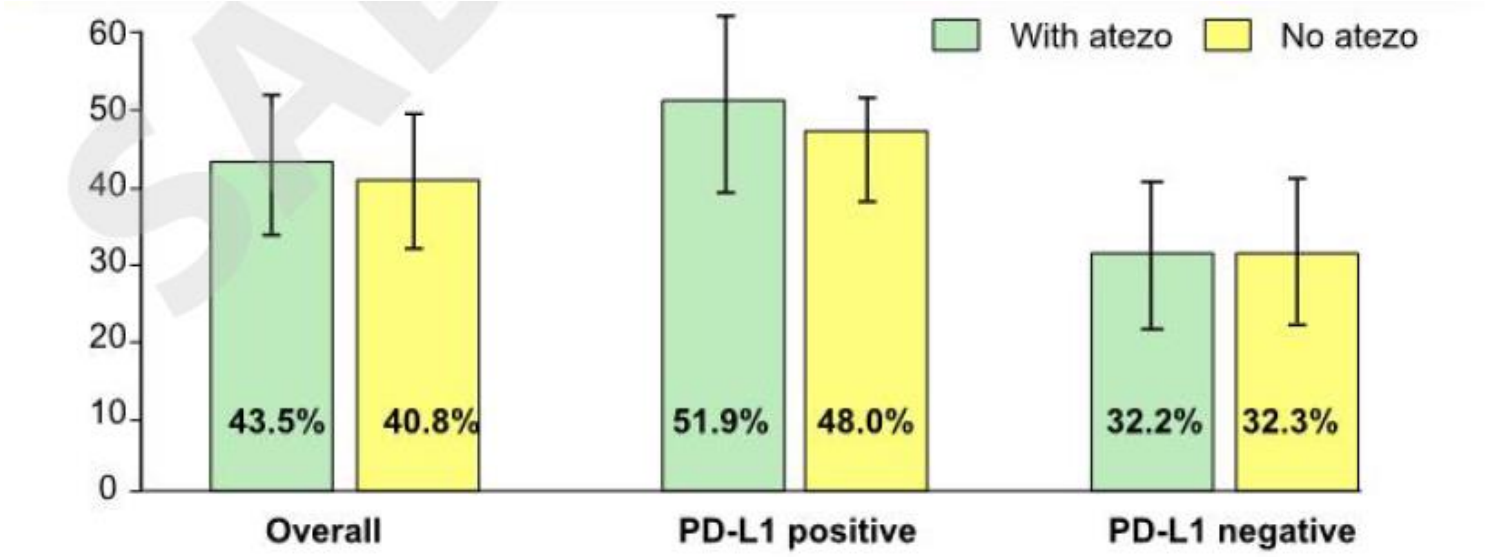


Primary End Point: EFS (5 years)

Secondary End Point: pCR, tolerability

Gianni L, SABCS 2019

NeoTRIP: pCR



Variable	Effect	OR (95%CI)	*P* value
Treatment	With Atezo vs. no Atezo	1.11 (0.88-1.40)	0.39
PD-L1 expression	Positive vs. negative	0.84 (0.66-1.06)	0.15

Gianni L, SABCS 2019

Summary of Recommendations

Clinical Question 3

- What neoadjuvant systemic therapy regimens are recommended for patients with TNBC?

Recommendation 3.1

- Patients with TNBC who have clinically node positive and/or at least T1c disease should be offered an anthracycline- and taxane-containing regimen in the neoadjuvant setting.

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
High	Strong

Summary of Recommendations

Recommendation 3.2

- Patients with cT1a or cT1bN0 TNBC should not routinely be offered neoadjuvant therapy outside of a clinical trial.

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
High	Strong

Recommendation 3.3

- Carboplatin may be offered as part of a neoadjuvant regimen in patients with TNBC to increase likelihood of pCR. The decision to offer carboplatin should take into account the balance of potential benefits and harms.

Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
Intermediate	Moderate

Summary of Recommendations

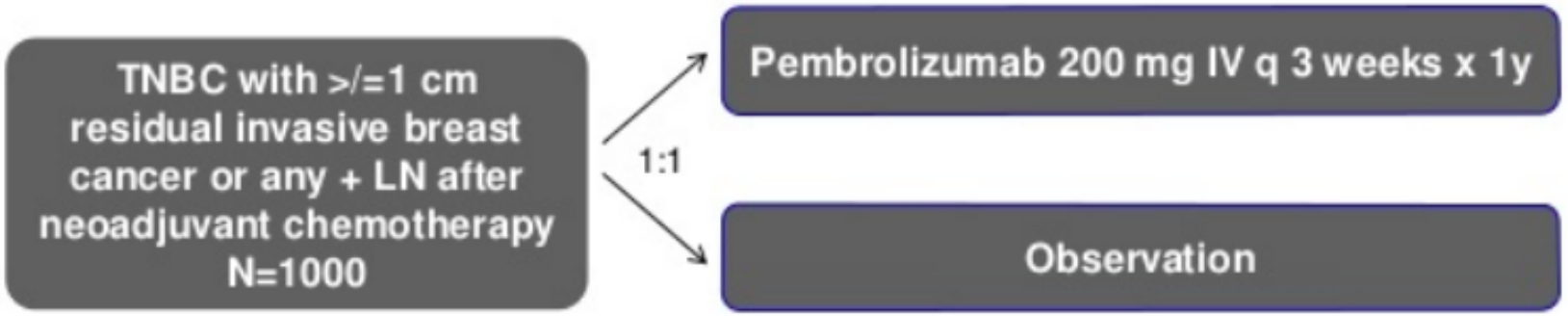
Recommendation 3.4

- There is insufficient evidence to recommend routinely adding the immune checkpoint inhibitors to neoadjuvant chemotherapy in patients with early-stage TNBC.

Informal consensus	
Evidence Quality	**Strength of Recommendation**
Intermediate	Moderate

Post-neoadjuvant: trial in progress

SWOG S1418



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