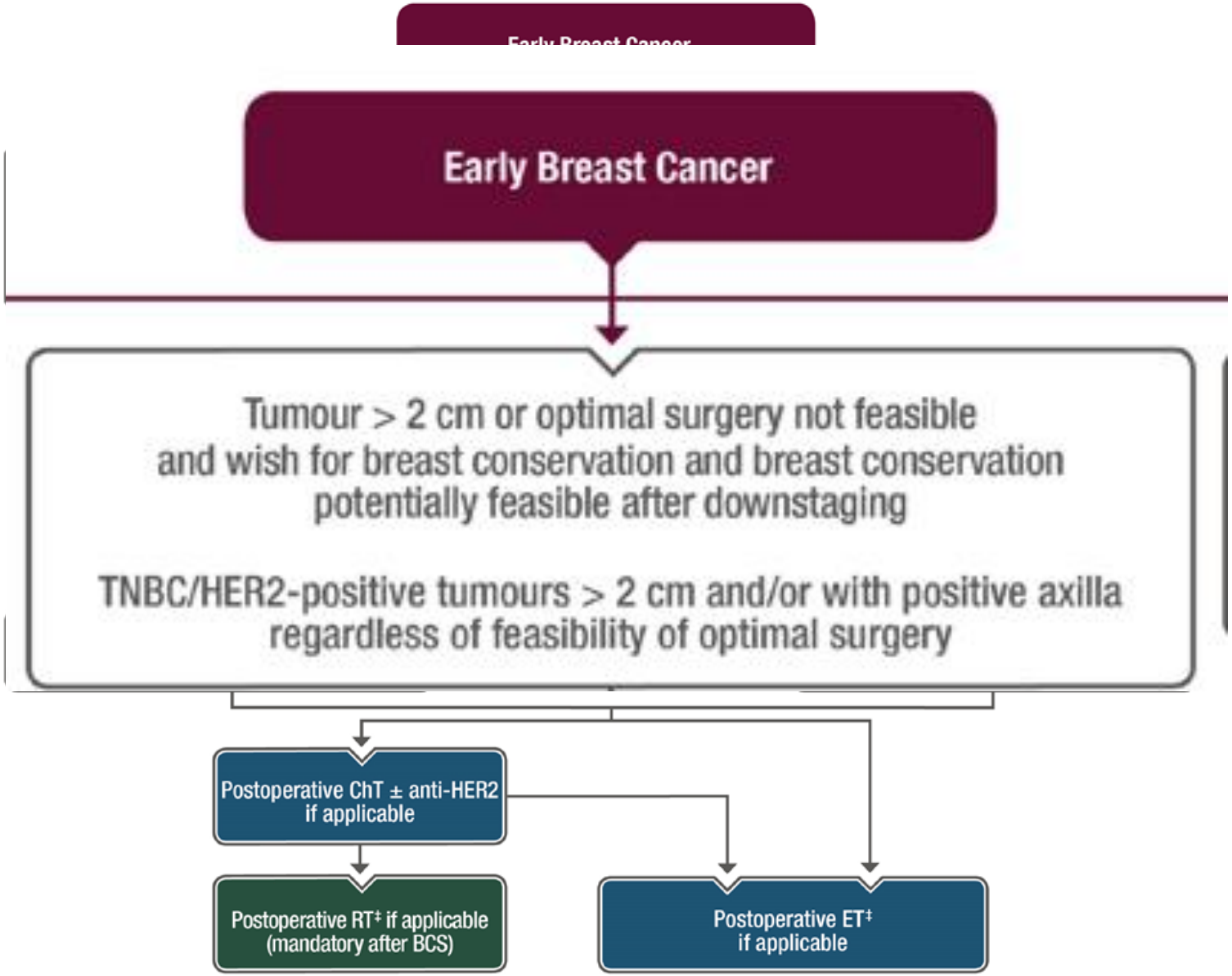
TRIPLE NEGATIVE BREAST CANCER: NEOADJUVANT THERAPY

DR CHETAN DESHMUKH

MEDICAL ONCOLOGIST, PUNE.

CLINICAL PRACTICE GUIDELINES

Treatment



* Biology that requires ChT (TNBC, HER2-positive, luminal B-like), to assess response and prognosis and eventually decide on postoperative therapies, should preferentially receive preoperative ChT

** Aggressive phenotypes: TNBC or HER2-positive breast cancer

† If ChT is planned, it should all be given as neoadjuvant

‡ Concomitant postoperative RT, postoperative ET and anti-HER2 therapy

ESMO

SHIFT TOWARDS NEOADJUVANT - WHY?

- Neoadjuvant chemotherapy(NACT) is the standard strategy in locally advanced disease.
- Helps achieve Breast Conserving Surgery with good cosmesis.
- Chemotherapy delivered when vasculature is intact.
- In vivo marker of chemo-sensitivity.
- Response adaptation possible.
- pathComplete Response - strong predictor of survival in Triple Negative Breast Cancer(TNBC)

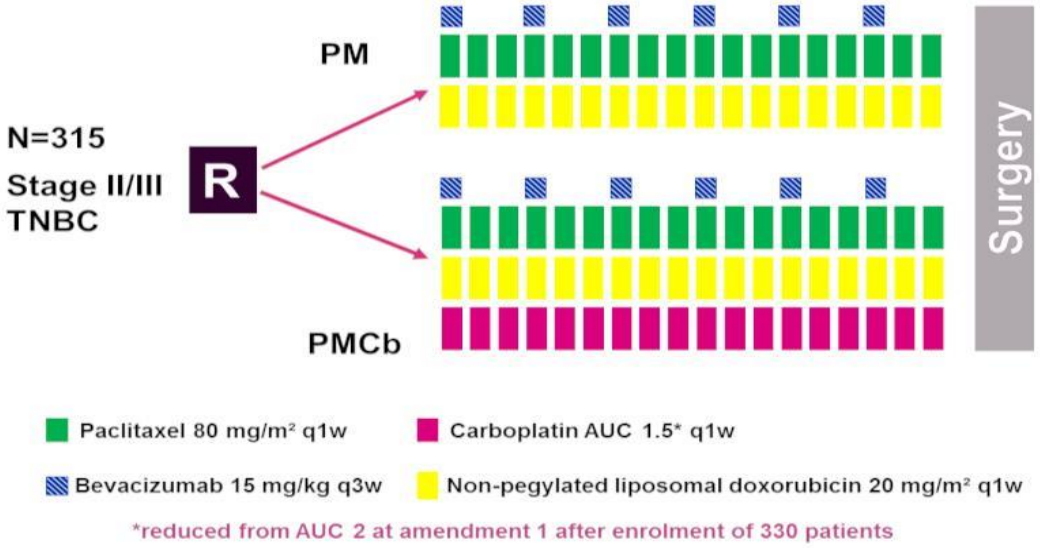
NACT IN TNBC

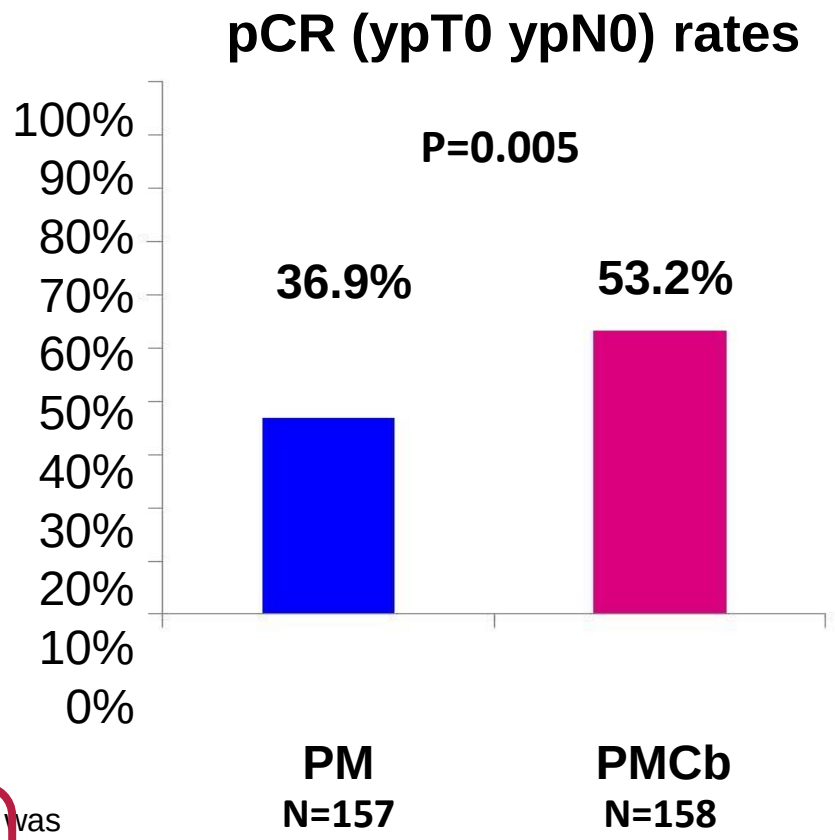
- Commonly used regimes- Sequential Anthracyclines followed by Taxanes with/without Carboplatin or Docetaxel-Carboplatin.
- PathCR achieved in 30-40% patients.
- Strategies to improve this pathCR rate are needed.

ADD-ONS TO CHEMOTHERAPY TO IMPROVE PATHCR

- Carboplatin.
- Poly(ADP Ribosyl Polymerase)(PARP) inhibitors.
- Immunotherapy.

GeparSixto: phase II trial neoadjuvant chemo/bev +/- carbo – pCR rate in TNBC

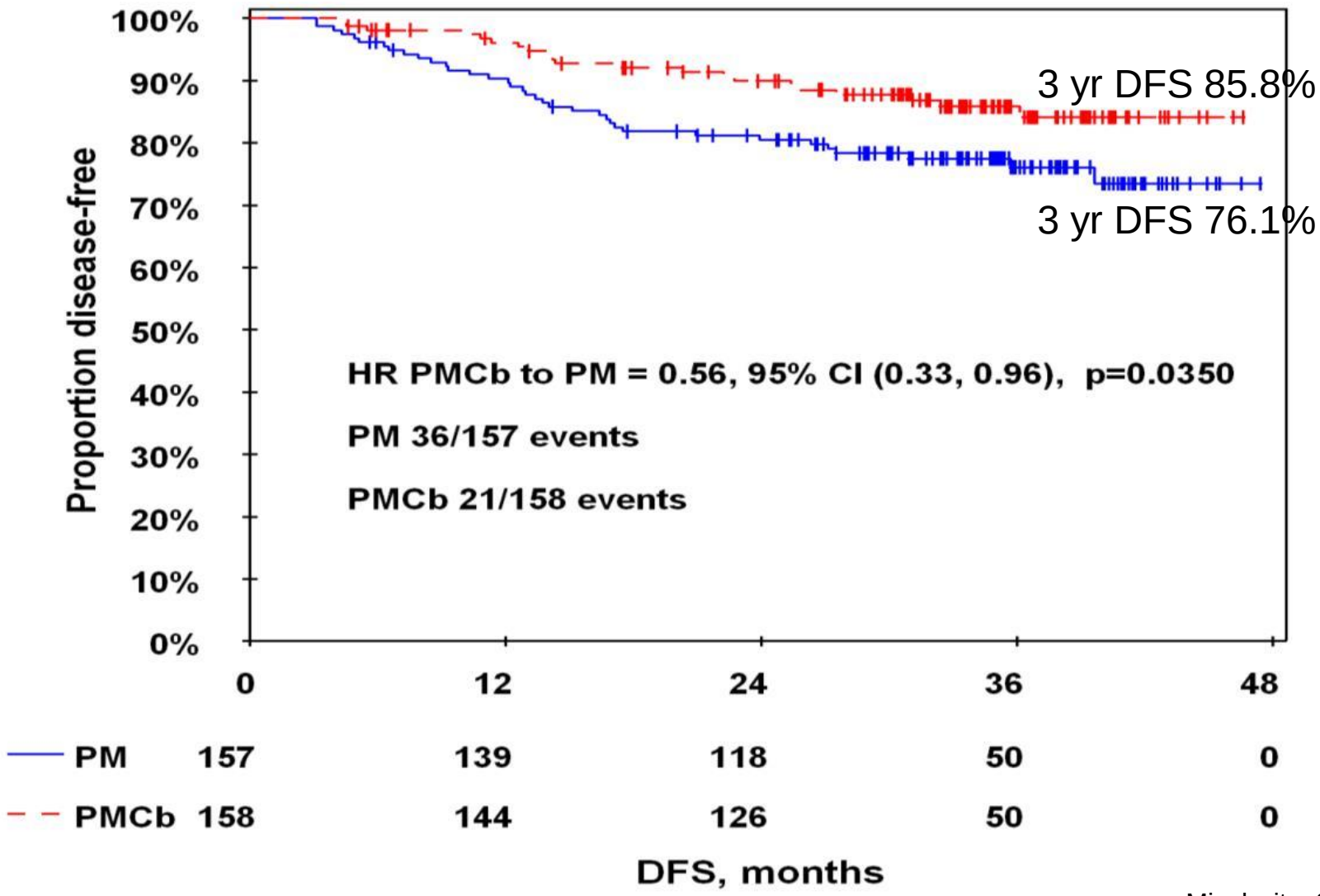




The concomitant use of platinum agents with chemo in GeparSixto was associated with markedly higher toxicity, which resulted in **less than 60% patients completing** all their chemo cycles, compared to the control group.
49 vs 36% patients discontinued due to toxicity

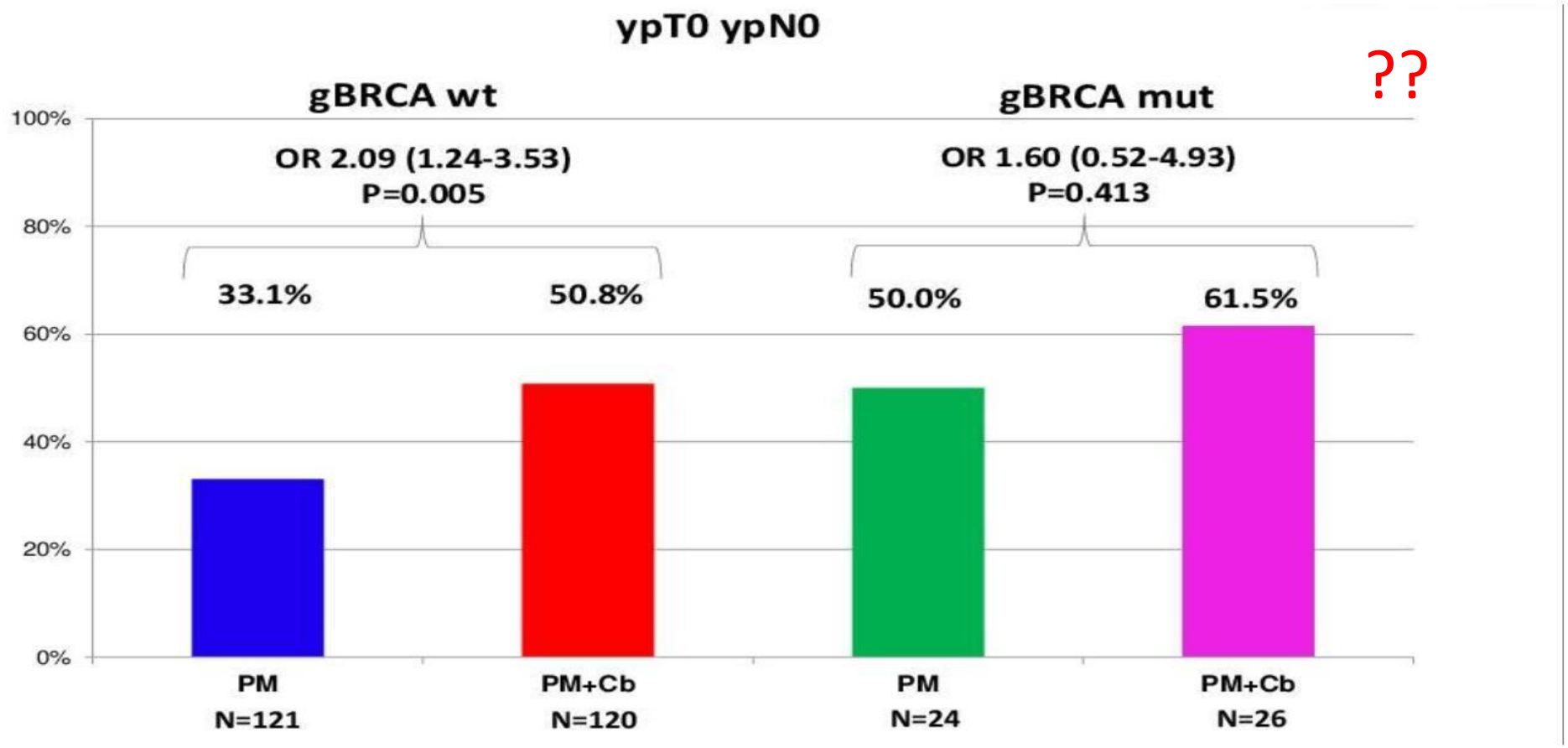
von Minckwitz, Lancet Oncol. 2014

GeparSixto: phase II trial neoadjuvant chemo/bev +/- carbo – DFS in TNBC



von Minckwitz, SABCS 2015

GeparSixto and BRCA status: pCR



Von Minckwitz G, SABCS 2015

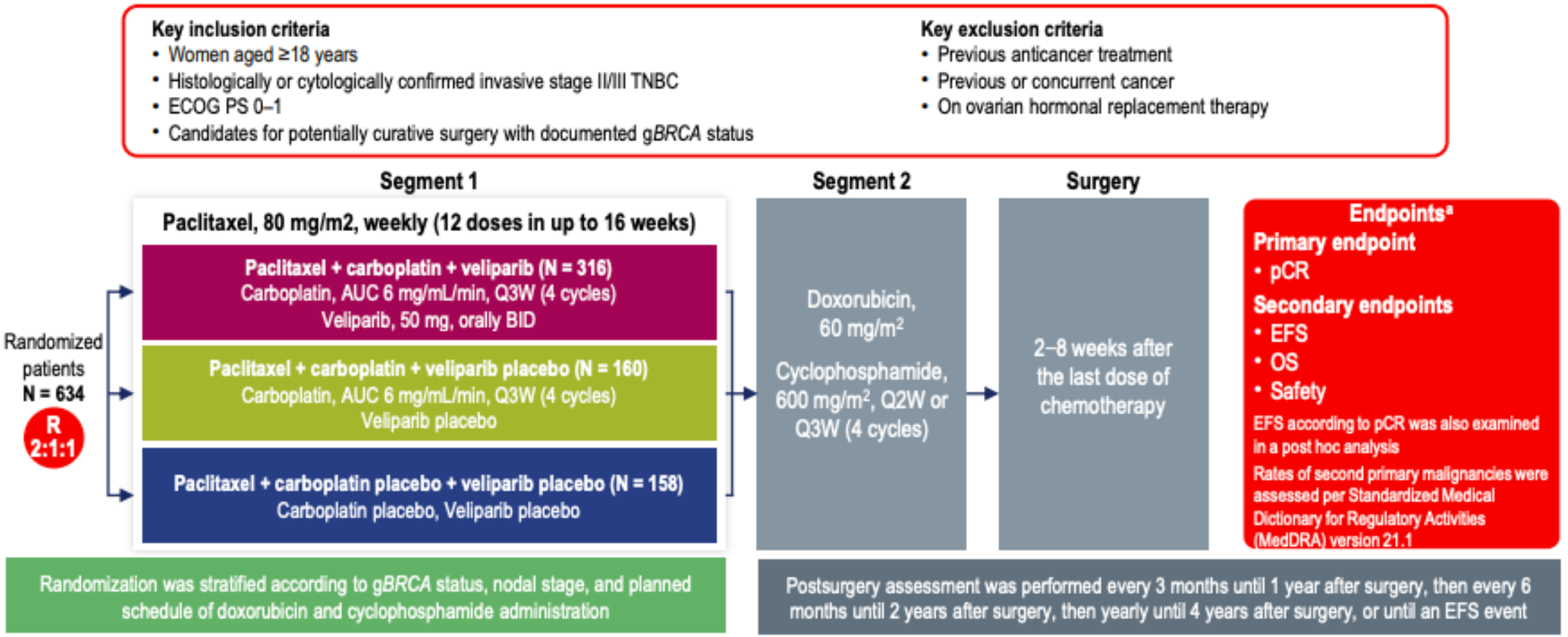
	Treatment without carboplatin (n=293)				Treatment with carboplatin (n=295)				p value*
	Grades 1–2	Grade 3	Grade 4	Grade 5	Grades 1–2	Grade 3	Grade 4	Grade 5	
Anaemia	258 (88%)	1 (<1%)	0	0	242 (82%)	42 (14%)	3 (1%)	0	<0·0001
Neutropenia	135 (46%)	63 (22%)	16 (6%)	0	84 (29%)	126 (43%)	66 (22%)	0	<0·0001
Febrile neutropenia	0	12 (4%)	2 (<1%)	1 (<1%)	0	19 (6%)	6 (2%)	0	0·140
Thrombocytopenia	28 (10%)	1 (<1%)	0	0	155 (53%)	38 (13%)	4 (1%)	0	<0·0001
Nausea	155 (53%)	12 (4%)	0	0	184 (62%)	29 (10%)	0	0	0·009
Vomiting	75 (26%)	6 (2%)	1 (<1%)	0	102 (35%)	16 (5%)	0	0	0·087
Diarrhoea	153 (52%)	32 (11%)	0	0	156 (53%)	49 (17%)	2 (<1%)	0	0·033
Mucositis	212 (72%)	44 (15%)	1 (<1%)	0	193 (65%)	45 (15%)	5 (2%)	0	0·654
Anorexia	88 (30%)	8 (3%)	1 (<1%)	0	99 (34%)	22 (8%)	0	0	0·025
Fatigue	211 (72%)	40 (14%)	0	0	205 (70%)	48 (16%)	1 (<1%)	0	0·358
Hand-foot syndrome	146 (50%)	48 (16%)	0	0	135 (46%)	27 (9%)	0	0	0·009
Skin rash (acneiform)	31 (11%)	6 (2%)	0	0	25 (9%)	0	0	0	0·015
Nail changes	98 (33%)	11 (4%)	0	0	81 (28%)	2 (1%)	0	0	0·012
Peripheral sensory neuropathy	190 (65%)	21 (7%)	0	0	173 (59%)	19 (6%)	0	0	0·746
Fever	85 (29%)	17 (6%)	3 (1%)	0	67 (23%)	11 (4%)	0	0	0·100
Infection	119 (41%)	37 (13%)	7 (2%)	1 (<1%)	126 (43%)	37 (13%)	3 (1%)	1 (<1%)	0·642
Thromboembolic events	12 (4%)	7 (2%)	3 (1%)	0	14 (5%)	7 (2%)	3 (1%)	0	1·000
Pneumonitis	6 (2%)	6 (2%)	3 (1%)	0	0	1 (<1%)	0	0	0·011
Arterial hypertension	33 (11%)	9 (3%)	0	0	29 (10%)	5 (2%)	0	0	0·295
LVEF decrease, congestive heart failure (NYHA), and myocardial infarction	6 (2%)	0	0	1 (<1%)	5 (2%)	2 (<1%)	0	0	1·000
Other cardiac disorders	24 (8%)	3 (1%)	1 (<1%)	1 (<1%)	20 (7%)	0	0	0	0·030
Surgical complications	3 (1%)	2 (<1%)	0	0	5 (2%)	4 (1%)	0	0	0·450
Other non-haematological adverse events	219 (75%)	67 (23%)	6 (2%)	0	212 (72%)	76 (26%)	1 (<1%)	0	0·777

ADDITION OF CARBOPLATIN

- Better pathCR but associated with significant toxicity.
- Dose of Carboplatin reduced from AUC 2 to AUC 1.5 due to toxicity
- Benefit confined to TNBC subset only.
- Benefit irrespective of BRCA status.
- Commonly used drug, easily available, economical, toxicity known and preventable.

STUDY DESIGN

Addition of PARPi- BRIGHTNESS Study

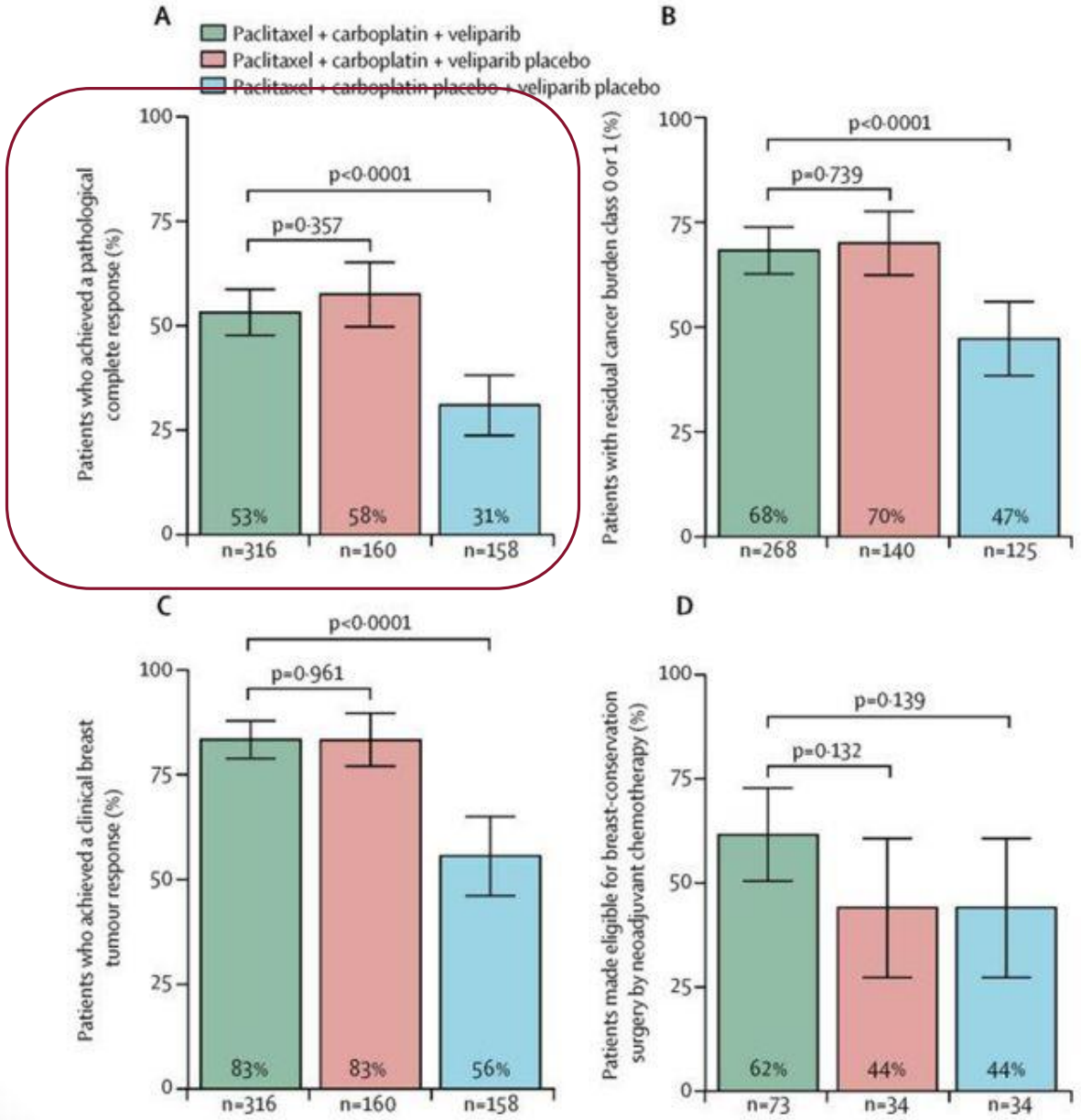


2021 ESMO congress

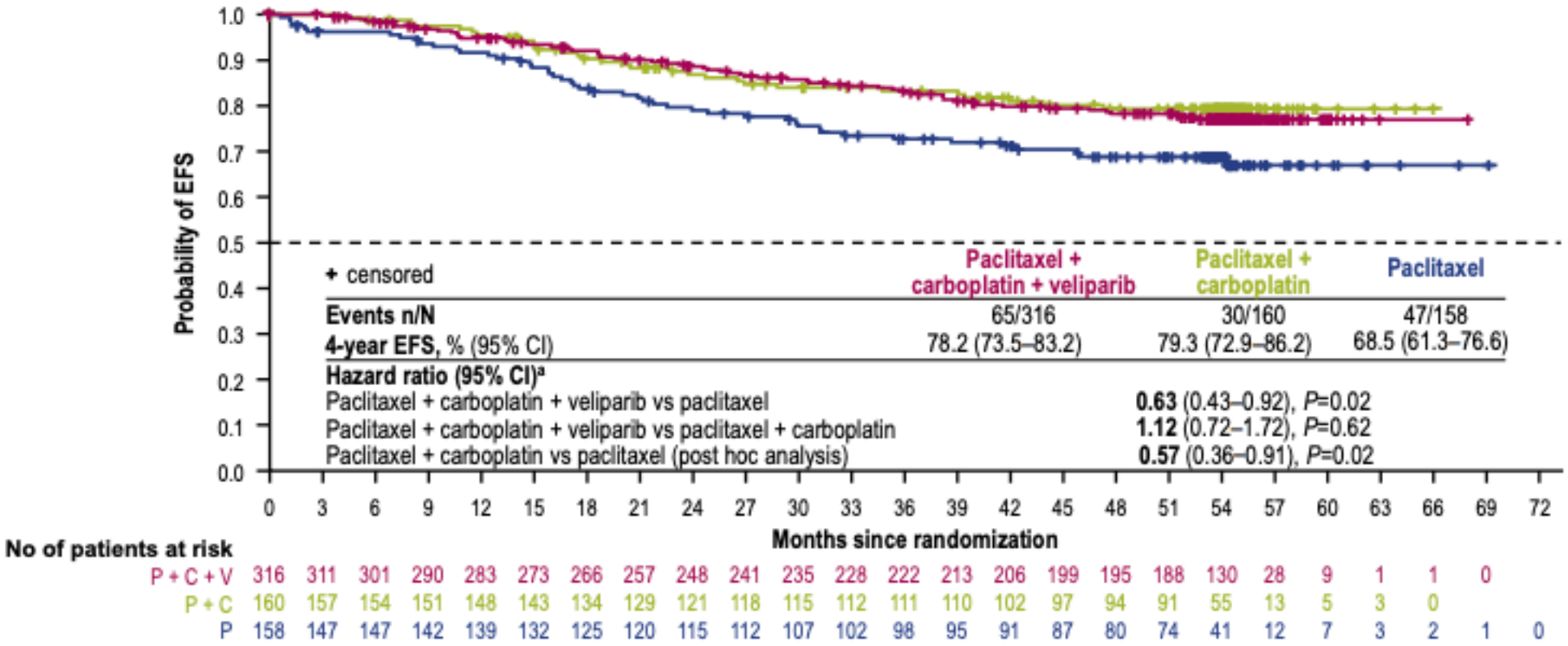
[a]Efficacy was assessed in all randomized patients and safety in all patients who received ≥1 dose

AUC, area under the curve; BID, twice a day; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; OS, overall survival; pCR, pathological complete response; Q2W, every 2 weeks; Q3W, every 3 weeks; R, randomization; TNBC, triple negative breast cancer.

BrighTNess Trial: Results



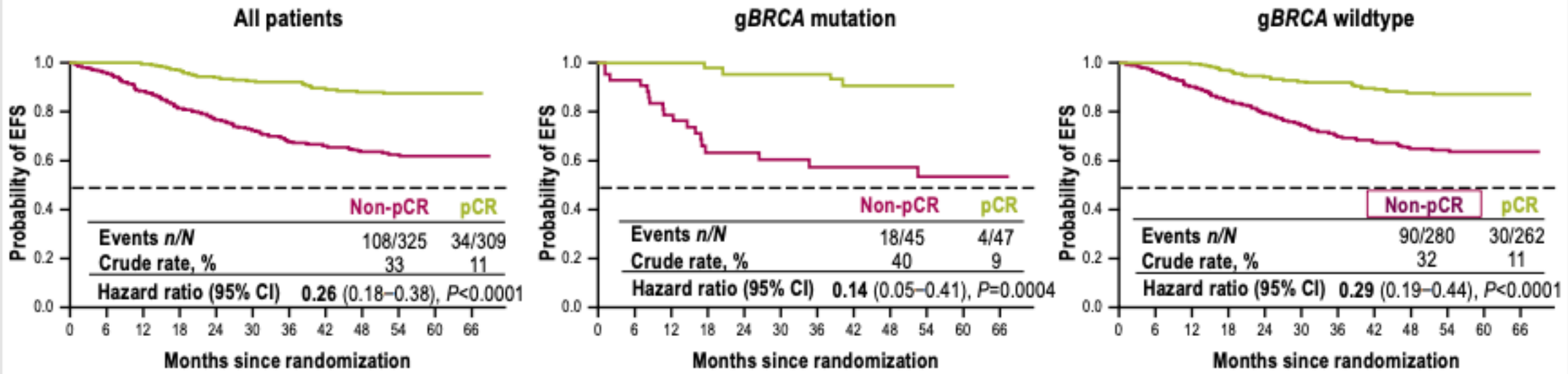
STRATIFIED ANALYSIS OF EFS WITH MEDIAN FOLLOW-UP OF 4.5 YEARS



2021 ESMO congress

[a]Stratified by *BRCA* status, lymph node status, and planned doxorubicin/cyclophosphamide dose intensity.

EFS BY pCR IN ALL PATIENTS AND SUBGROUPS BY g*BRCA* STATUS



Patients with pCR had improved EFS compared to those without pCR (HR 0.26, 95% CI 0.18–0.38; P<0.0001), regardless of *BRCA* mutation status

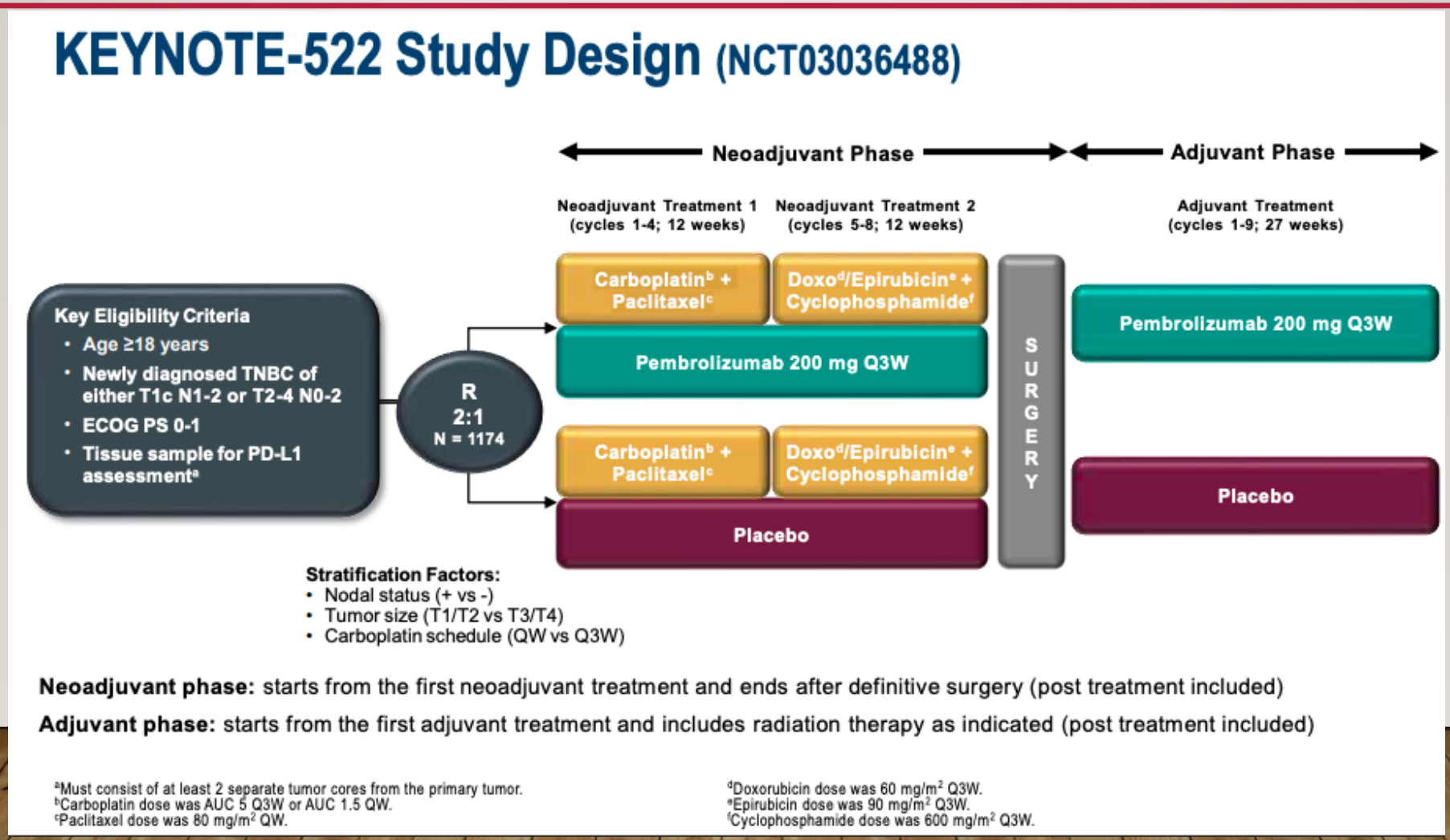
2021 ESMO congress

[a]Stratified by *BRCA* status, lymph node status, and planned doxorubicin/cyclophosphamide dose intensity.

BRIGHTNESS STUDY

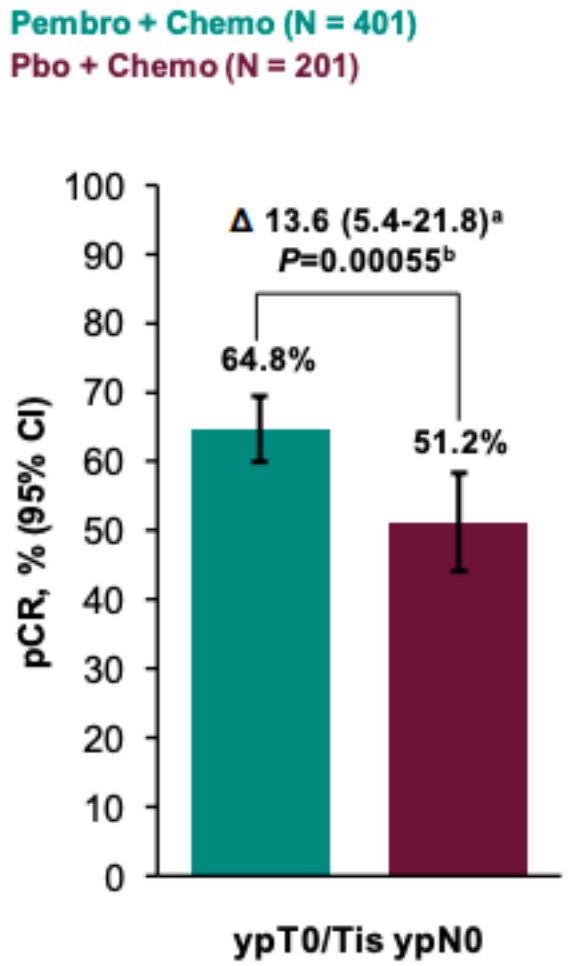
- Addition of Carboplatin improved survival, not Veliparib.
- pathCR was better in BRCA wildtype patients(however, number of gBRCA was < 20%)
- Event free survival correlated with pathCR and not BRCA status.

IMMUNOTHERAPY IN ADDITION TO NACT

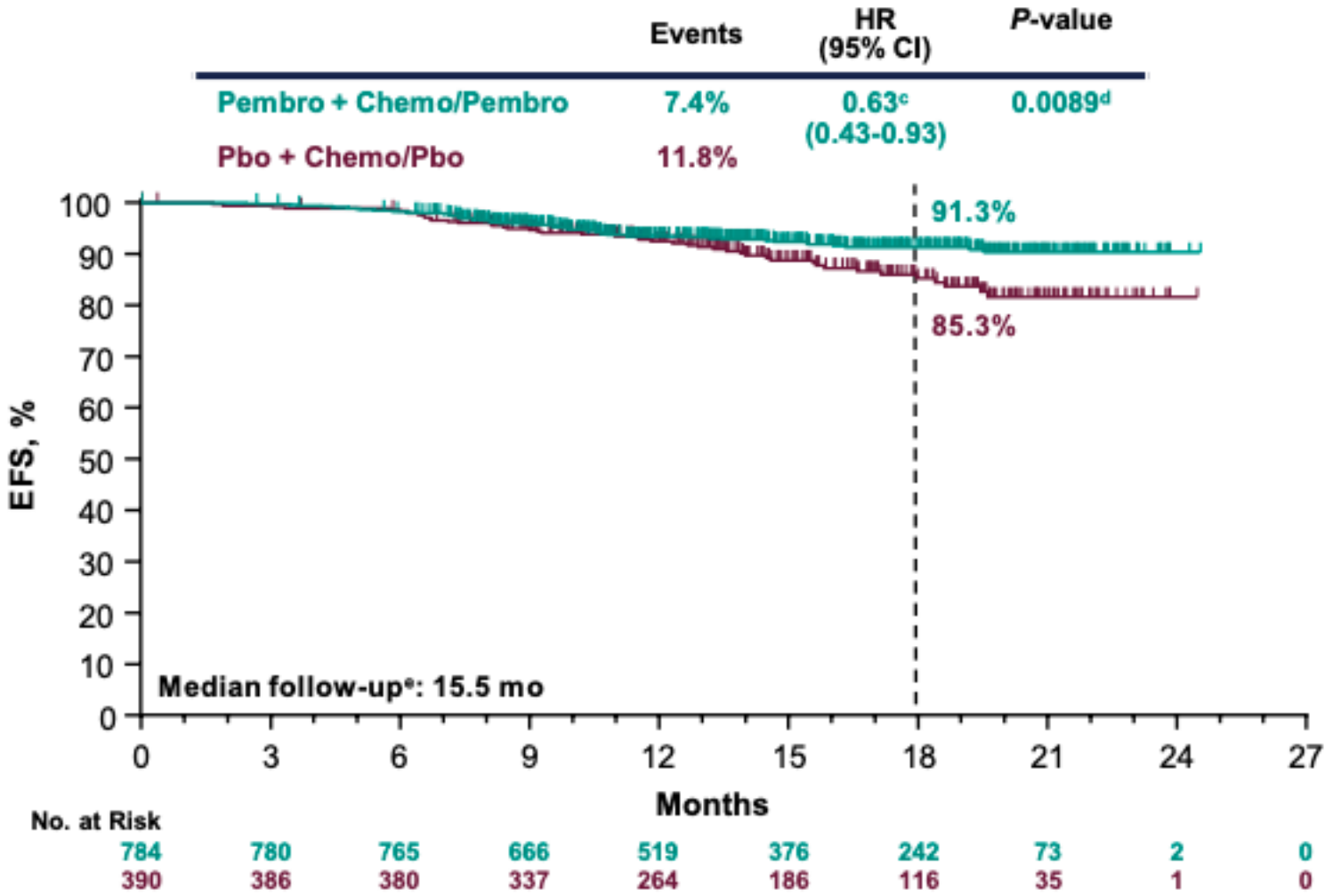


Prior Analyses of KEYNOTE-522

Primary pCR Endpoint at IA1[1]

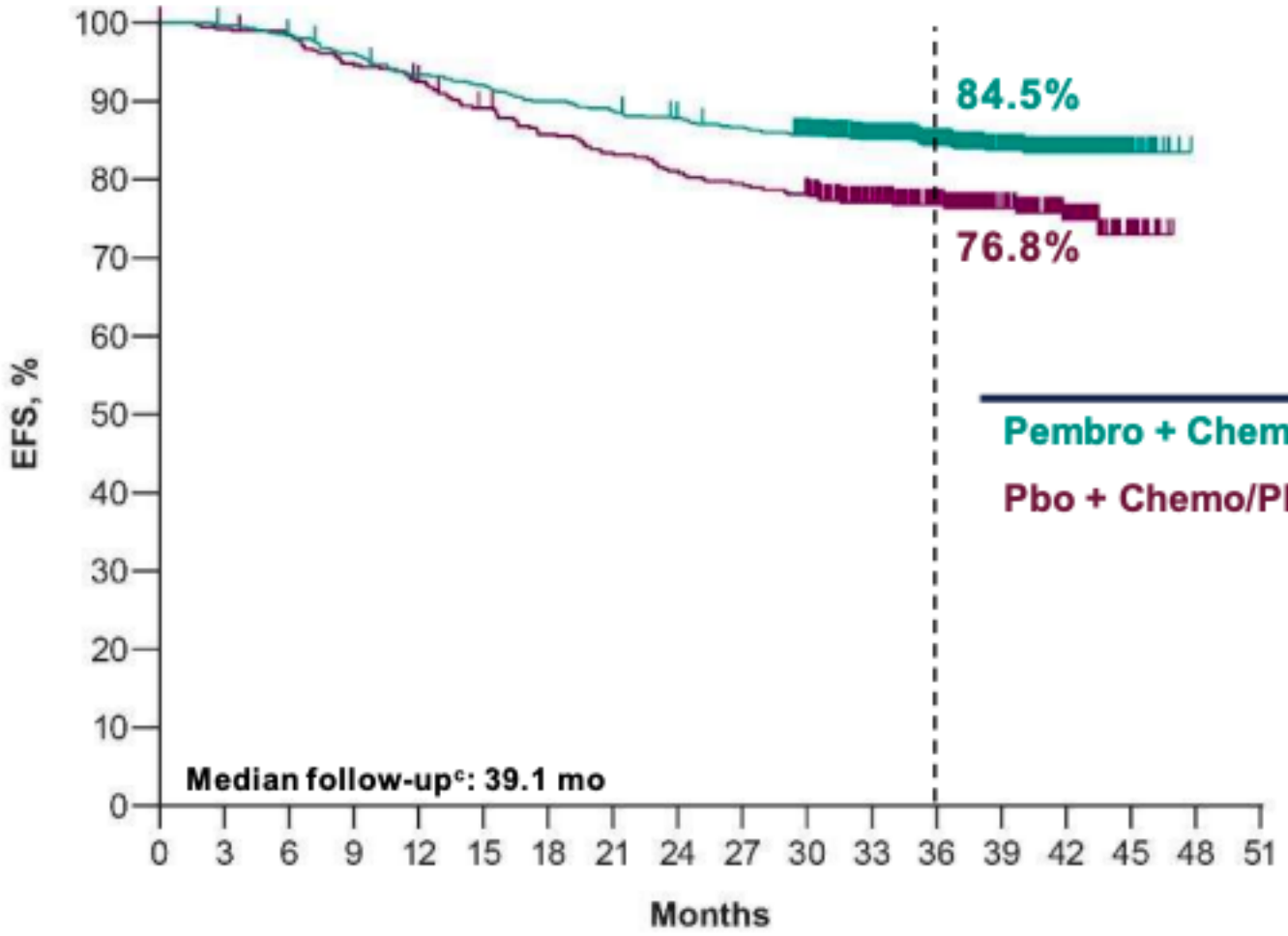


First EFS Analysis at IA2[1]



[a]Estimated treatment difference based on Miettinen & Nurminen method stratified by randomization stratification factors. [b]Prespecified *P*-value boundary for significance of 0.003 was crossed; data cutoff date: September 24, 2018. [c]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [d]Prespecified *P*-value boundary for significance of 0.000051 not reached at this analysis. [e]Defined as the time from randomization to the date of death or data cutoff date of April 24, 2019, if the patient was alive. 1. Schmid P, et al. *N Engl J Med* 2020;382:810-21.

Statistically Significant and Clinically Meaningful EFS at IA4



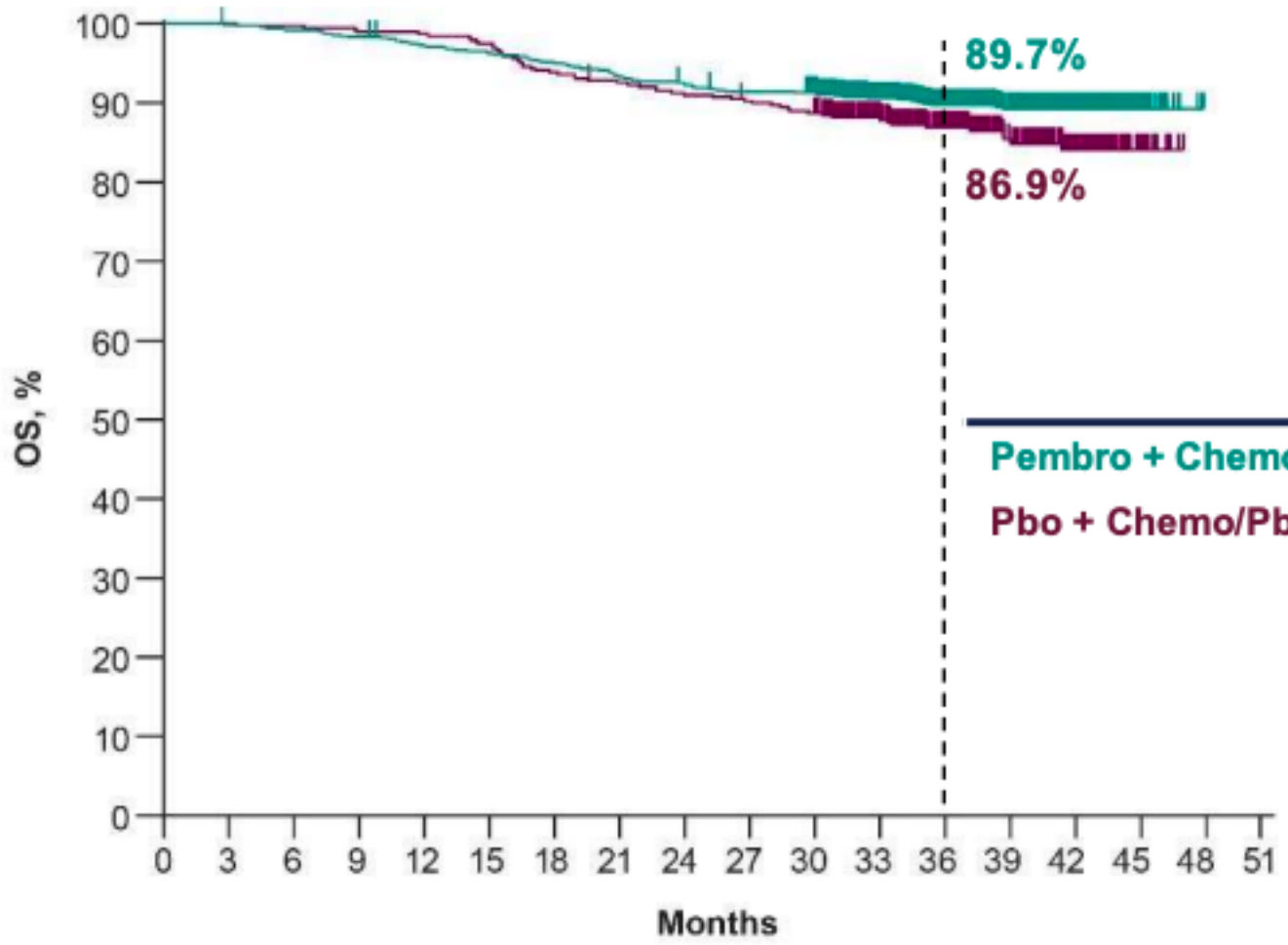
	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	15.7%	0.63[a] (0.48-0.82)	0.00031
Pbo + Chemo/Pbo	23.8%		

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

[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%		

No. at Risk

Pembro + Chemo/Pembro	784	782	777	770	759	752	742	729	720	712	701	586	461	323	178	30	0	0
Pbo + Chemo/Pbo	390	390	389	386	385	380	366	360	354	350	343	286	223	157	89	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 0.00086 not reached at this analysis.
Data cutoff date: March 23, 2021.

Table 3. Adverse Events during the Neoadjuvant Phase at the Second Interim Analysis.*

Event	Pembrolizumab–Chemotherapy (N = 781)		Placebo–Chemotherapy (N = 389)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	777 (99.5)	633 (81.0)	389 (100.0)	295 (75.8)
Treatment-related adverse event†	773 (99.0)	600 (76.8)	388 (99.7)	281 (72.2)
Nausea	490 (62.7)	26 (3.3)	246 (63.2)	5 (1.3)
Alopecia	471 (60.3)	14 (1.8)	220 (56.6)	8 (2.1)
Anemia	430 (55.1)	142 (18.2)	215 (55.3)	58 (14.9)
Neutropenia	365 (46.7)	270 (34.6)	183 (47.0)	129 (33.2)
Fatigue	321 (41.1)	27 (3.5)	147 (37.8)	6 (1.5)
Diarrhea	230 (29.4)	17 (2.2)	92 (23.7)	5 (1.3)
Elevated alanine aminotransferase level	199 (25.5)	41 (5.2)	96 (24.7)	9 (2.3)
Vomiting	199 (25.5)	18 (2.3)	85 (21.9)	6 (1.5)
Asthenia	191 (24.5)	25 (3.2)	99 (25.4)	9 (2.3)
Constipation	185 (23.7)	0	82 (21.1)	0
Decreased neutrophil count	185 (23.7)	146 (18.7)	112 (28.8)	90 (23.1)
Rash	170 (21.8)	7 (0.9)	59 (15.2)	1 (0.3)
Peripheral neuropathy	154 (19.7)	15 (1.9)	82 (21.1)	4 (1.0)
Adverse event of interest‡	304 (38.9)	101 (12.9)	71 (18.3)	7 (1.8)
Infusion reaction	132 (16.9)	20 (2.6)	43 (11.1)	4 (1.0)
Hypothyroidism	107 (13.7)	3 (0.4)	13 (3.3)	0
Hyperthyroidism	36 (4.6)	2 (0.3)	4 (1.0)	0
Severe skin reaction	34 (4.4)	30 (3.8)	4 (1.0)	1 (0.3)
Adrenal insufficiency	18 (2.3)	10 (1.3)	0	0

KEYNOTE 522

- Pembrolizumab given to all comers.
- Magnitude of response was better in PDL-1 positive patients but PDL-1 negative patients were very few(< 20%)
- pathCR in control arm was also good.
- Overall survival not very impressive numerically inspite of giving Pembrolizumab in the adjuvant setting too.

NACT IN TNBC

- Neoadjuvant chemotherapy being offered earlier and to smaller tumours may improve results.
- No biomarker(BRCA, PDL-1) has helped in selecting patients for NACT.
- Addition of Carboplatin has improved pathCR rates but at the cost of significant toxicity.
- However, it may be a good choice for young, fit patients desiring breast conservation.
- Better access to Immunotherapy may help it to become a standard frontline therapy