BREAST CANCER REVIEW

Zahi Mitri, MD, MS
Knight Cancer Institute, OHSU
Portland, OR
April 16th, 2022

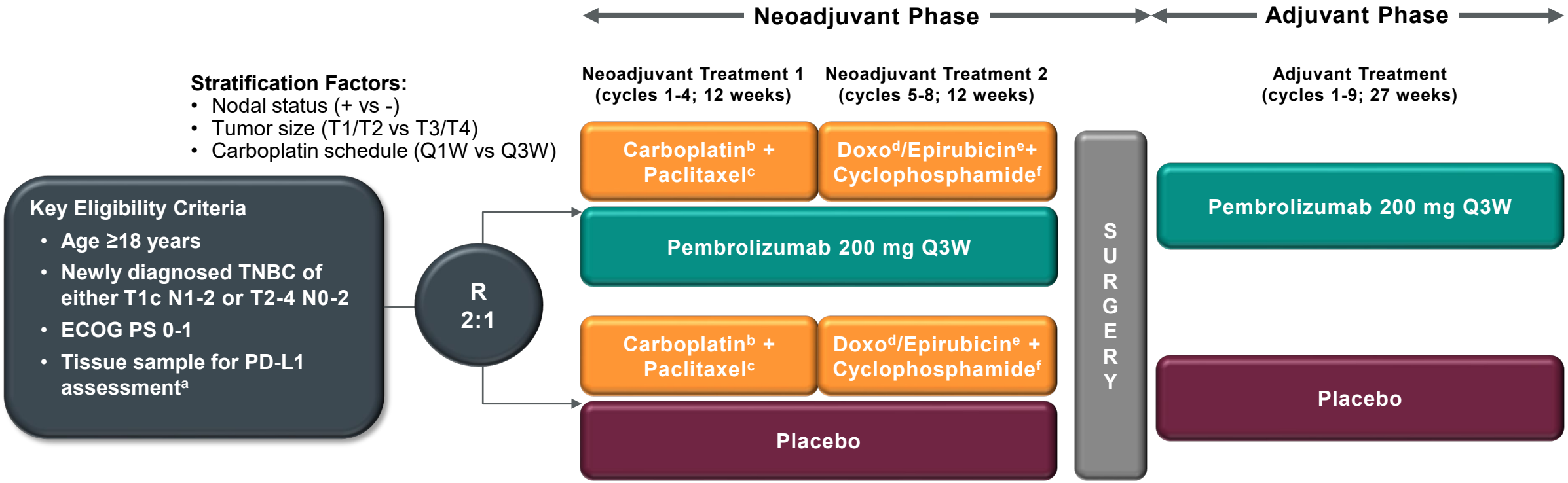
OUTLINE

- Triple Negative Breast Cancer
  - Chemo-Immunotherapy in Early Stage
  - Updates in Metastatic Disease
- BRCA-Associated Breast Cancer
  - Role in Metastatic Disease
  - Adjuvant Olaparib Approval

TRIPLE NEGATIVE BREAST CANCER
EARLY STAGE

Neo-adjuvant Chemo-Immunotherapy Keynote-522

KEYNOTE-522 Study Design (NCT03036488)



[a]Must consist of at least 2 separate tumor cores from the primary tumor.
[b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 Q1W.
[c]Paclitaxel dose was 80 mg/m^2 Q1W.
[d]Doxorubicin dose was 60 mg/m^2 Q3W.
[e]Epirubicin dose was 90 mg/m^2 Q3W.
[f]Cyclophosphamide dose was 600 mg/m^2 Q3W.

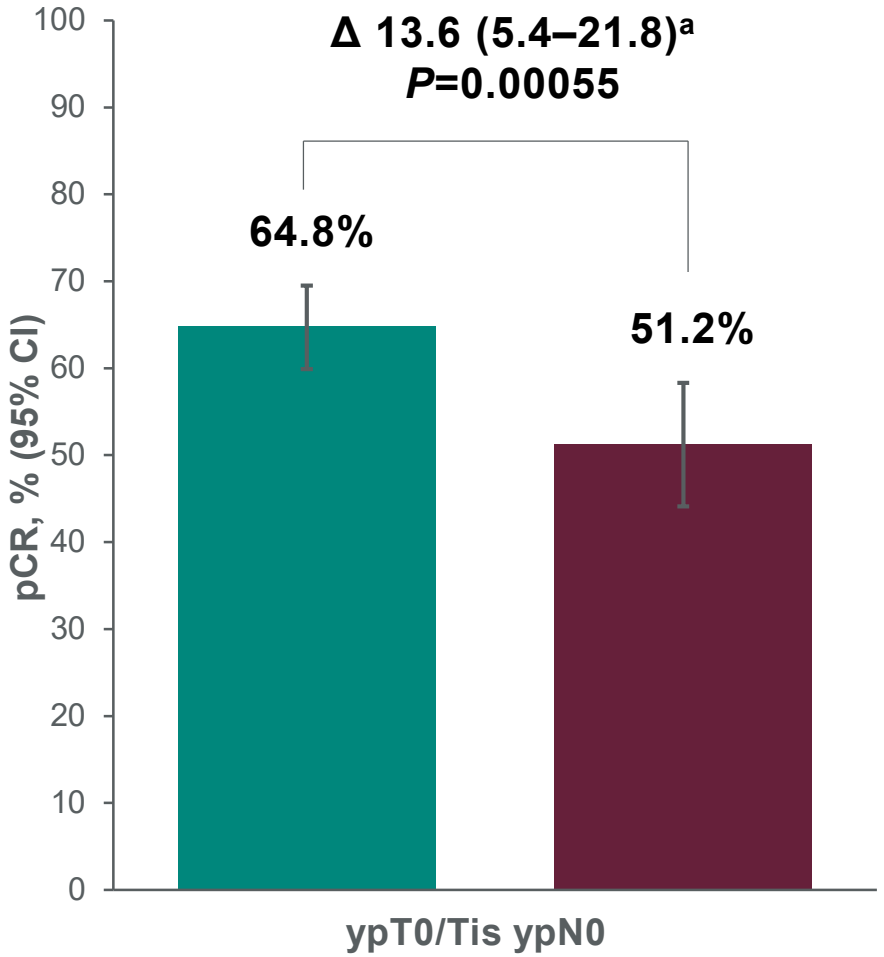
Primary Endpoints

pCR (ypT0/Tis ypN0) assessed by local pathologist in ITT[a]

Event-free survival (EFS) assessed by investigator in ITT

OHSU

Definitive pCR Analysis



- Definitive pCR analysis to test primary hypothesis of pCR based on prespecified first 602 patients (pre-calculated P value boundary for significance of 0.003)
- Consistent benefit seen with pCR defined as ypT0 ypN0 and ypT0/Tis

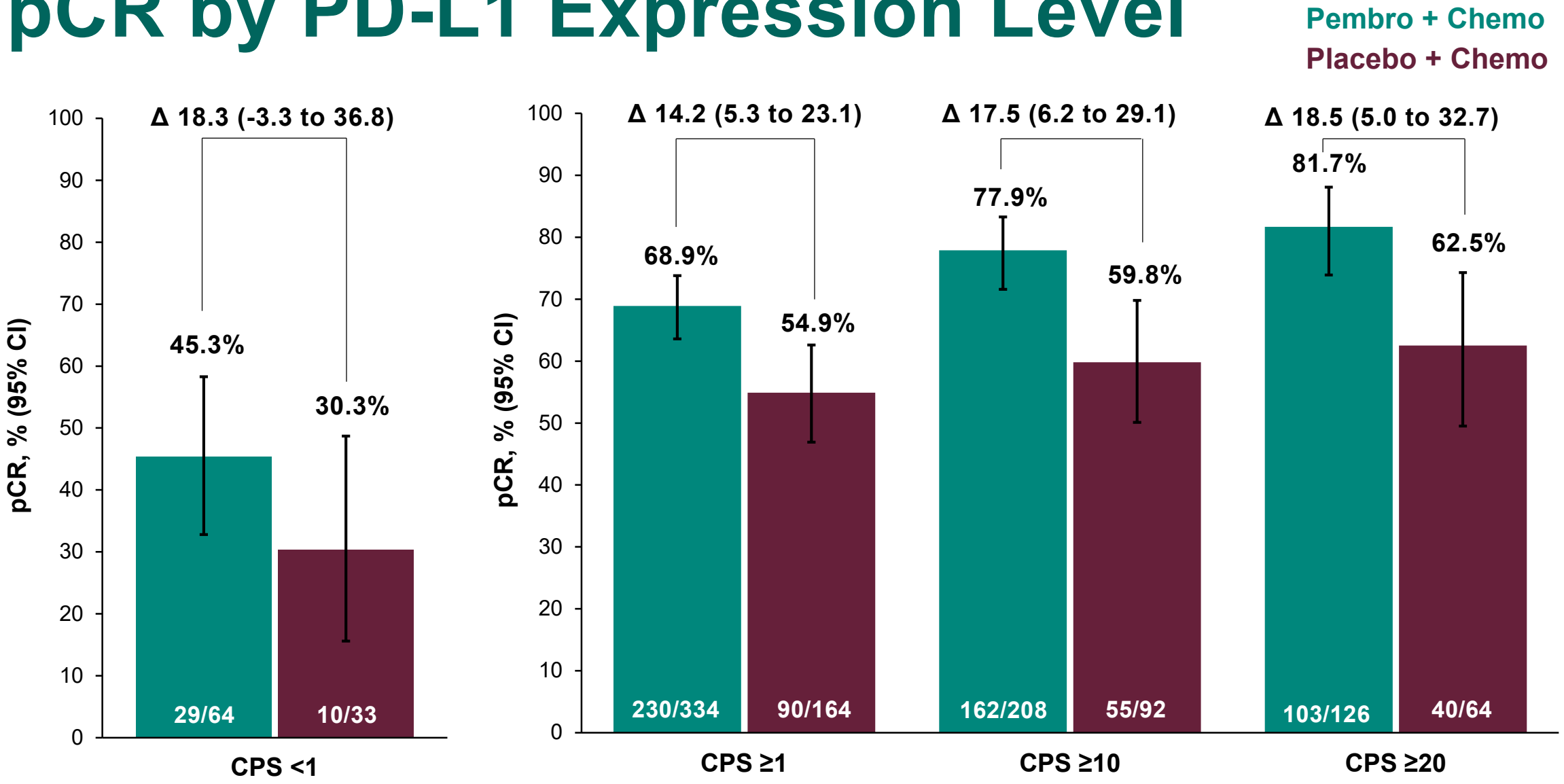
Placebo + Chemo

Pembro + Chemo

[a]Estimated treatment difference based on Miettinen & Nurminen method stratified by randomization stratification factors. Data cutoff date: September 24, 2018.

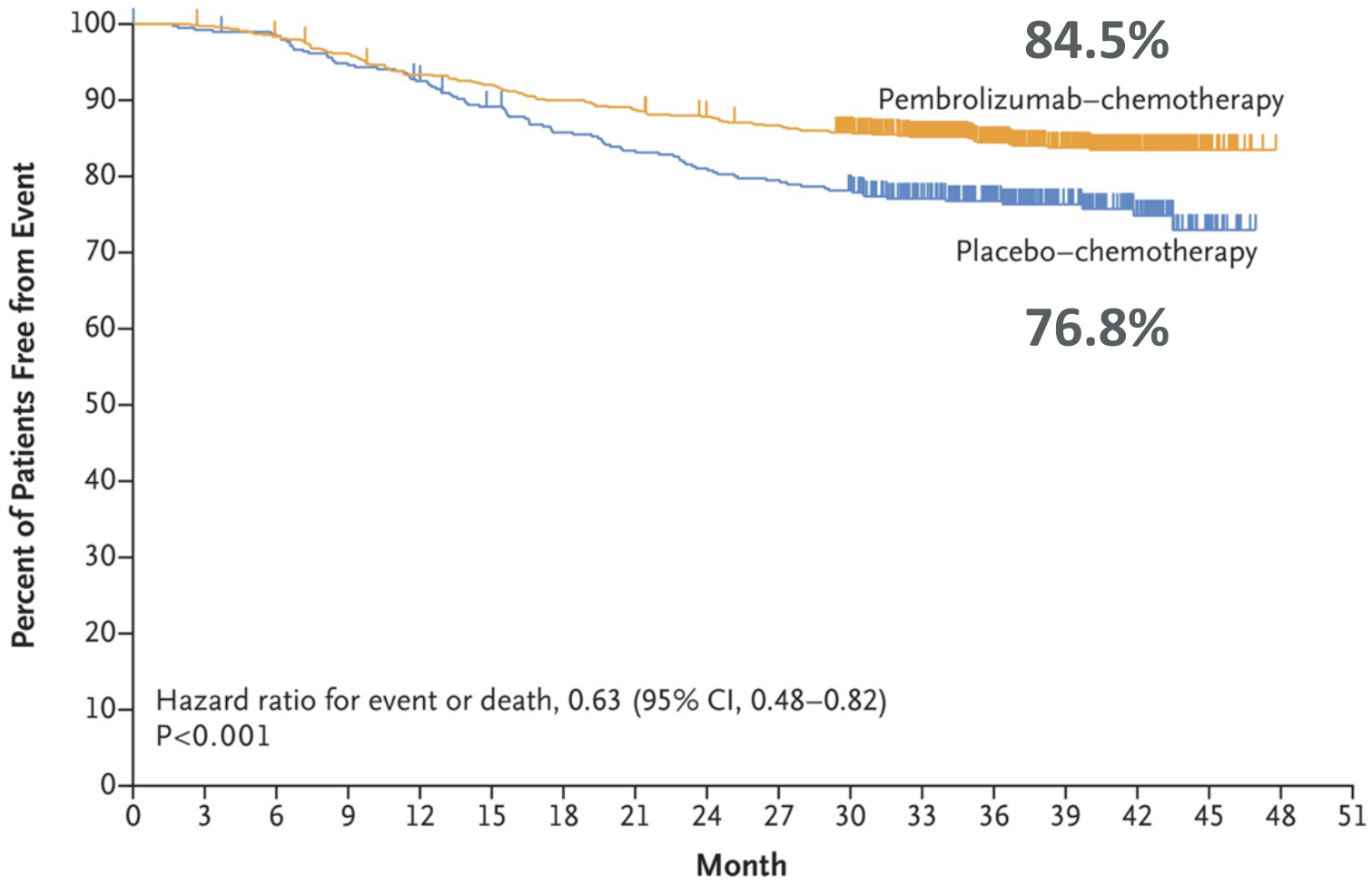
OHSU

pCR by PD-L1 Expression Level



Pre-specified analysis. PD-L1 assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay and measured using CPS; number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by total number of tumor cells x 100); PD-L1–positive = CPS ≥1. Estimated treatment difference based on Miettinen & Nurminen method stratified by nodal status (positive vs negative), tumor size (T1/T2 vs T3/T4) and choice of carboplatin (Q3W vs QW). Data cutoff date: September 24, 2018.

EFS (ITT Population)



No. at Risk

Pembrolizumab–chemotherapy	784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
Placebo–chemotherapy	390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

Schmid P et al. N Engl J Med 2022;386:556-567

Summary of First Events in Analysis of Event-free Survival.

Table 1. Summary of First Events in Analysis of Event-free Survival.

First Event	Pembrolizumab–Chemotherapy (N=784)	Placebo–Chemotherapy (N=390)
	number (percent)	
Any first event	123 (15.7)	93 (23.8)
Progression of disease that precluded definitive surgery	14 (1.8)	15 (3.8)
Local recurrence*	28 (3.6)	17 (4.4)
Distant recurrence	60 (7.7)	51 (13.1)
Second primary cancer†	6 (0.8)	4 (1.0)
Death	15 (1.9)	6 (1.5)

The NEW ENGLAND JOURNAL of MEDICINE

OHSU

Schmid P et al. N Engl J Med 2022;386:556-567

Table 2. Adverse Events in the Combined Neoadjuvant and Adjuvant Phases (As-Treated Population).*

Event	Pembrolizumab–Chemotherapy (N=783)		Placebo–Chemotherapy (N=389)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Immune-mediated adverse event‡	262 (33.5)	101 (12.9)	44 (11.3)	4 (1.0)
Hypothyroidism	118 (15.1)	4 (0.5)	22 (5.7)	0
Severe skin reaction	45 (5.7)	37 (4.7)	4 (1.0)	1 (0.3)
Hyperthyroidism	41 (5.2)	2 (0.3)	7 (1.8)	0
Adrenal insufficiency	20 (2.6)	8 (1.0)	0	0
Pneumonitis	17 (2.2)	7 (0.9)	6 (1.5)	2 (0.5)
Thyroiditis	16 (2.0)	2 (0.3)	5 (1.3)	0
Hypophysitis	15 (1.9)	10 (1.3)	1 (0.3)	0

Schmid P et al. N Engl J Med 2022;386:556-567

KN-522: Conclusions

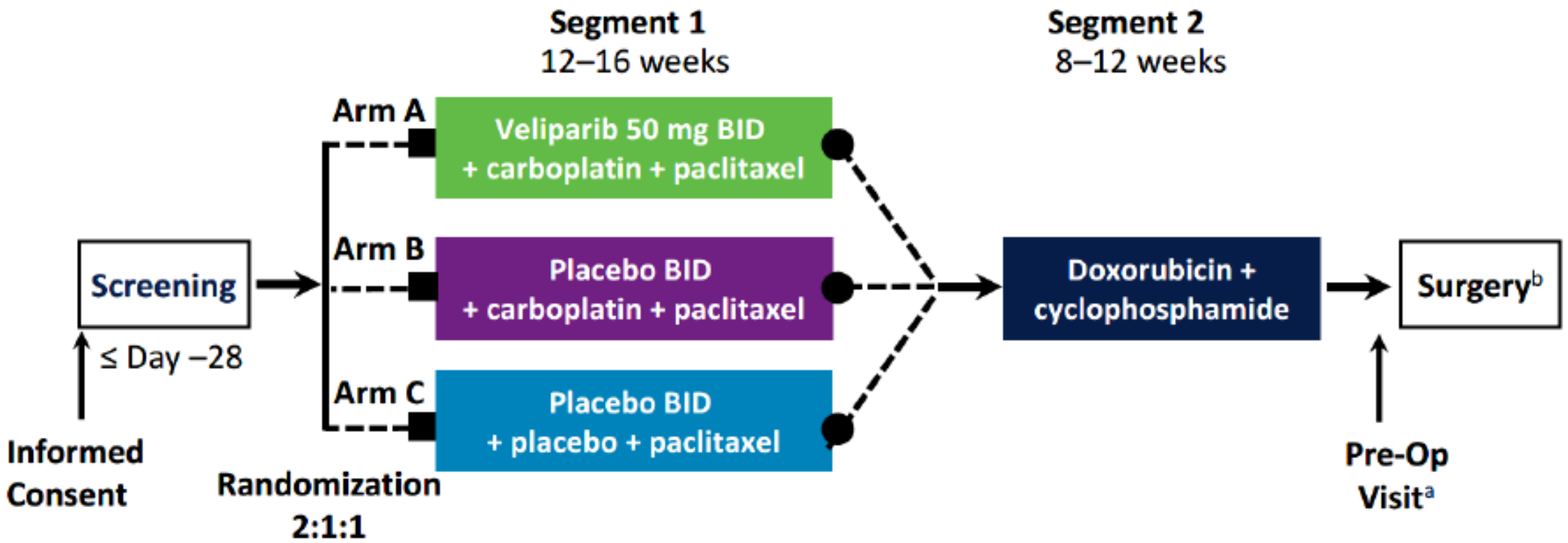
- Chemo + Pembrolizumab approved as neoadjuvant therapy
- No PD-L1 testing restriction / requirement
- Improves pCR, EFS
- OS analysis premature

KN-522: Questions?

- Four chemo backbone needed for everyone?
- Role of carboplatin?
- Adjuvant therapy for residual disease
  - Capecitabine + Pembrolizumab?
- Pembrolizumab maintenance in pCR?

BRIGHTNESS TRIAL

STUDY SCHEMA



pCR Analysis

REGIMEN	pCR
Paclitaxel / Carboplatin / Veliparib	53% (168/316)
Paclitaxel / Carboplatin	58% (92/160)
Paclitaxel	31% (49/158)

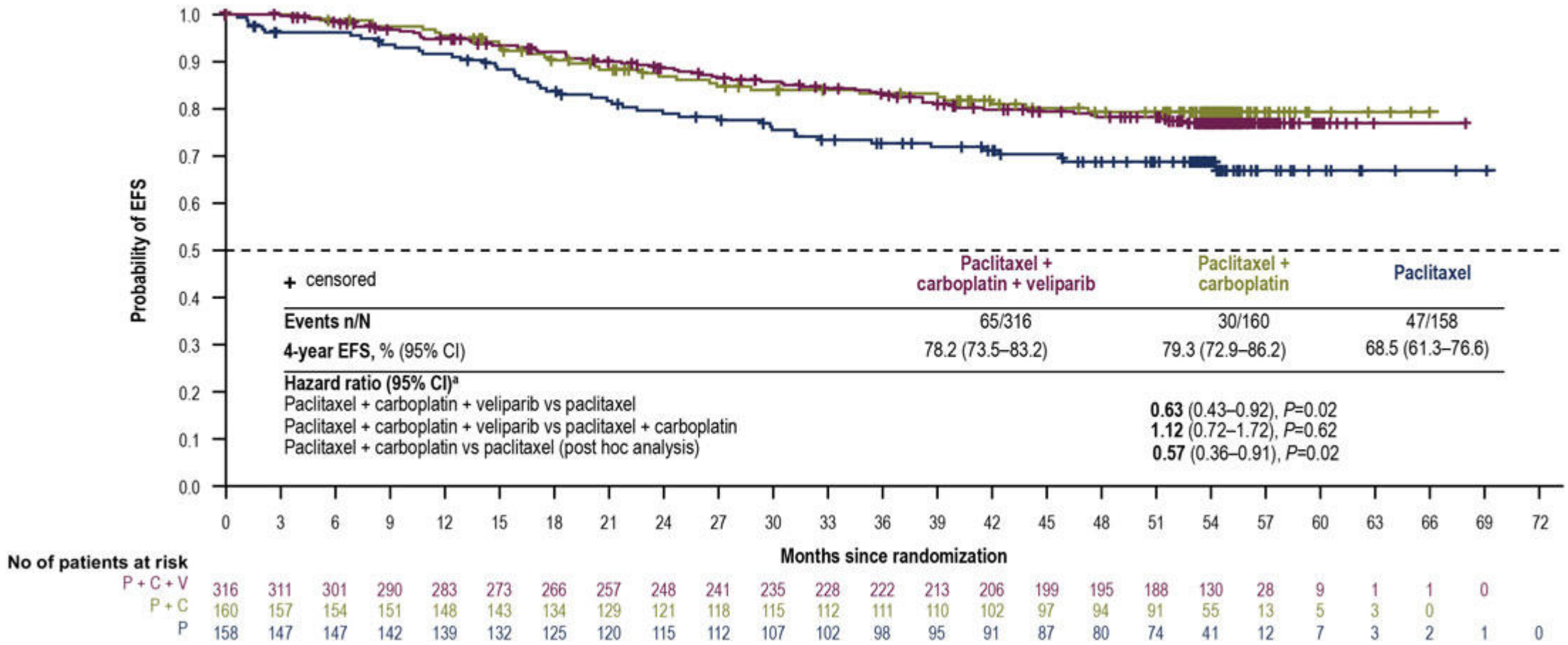
Loibl et al, Lancet Oncology 2018

EFS Analysis

REGIMEN	4-Year EFS
Paclitaxel / Carboplatin / Veliparib	78.2%
Paclitaxel / Carboplatin	79.3%
Paclitaxel	68.5%

Loibl et al, ESMO 2021

EFS Analysis



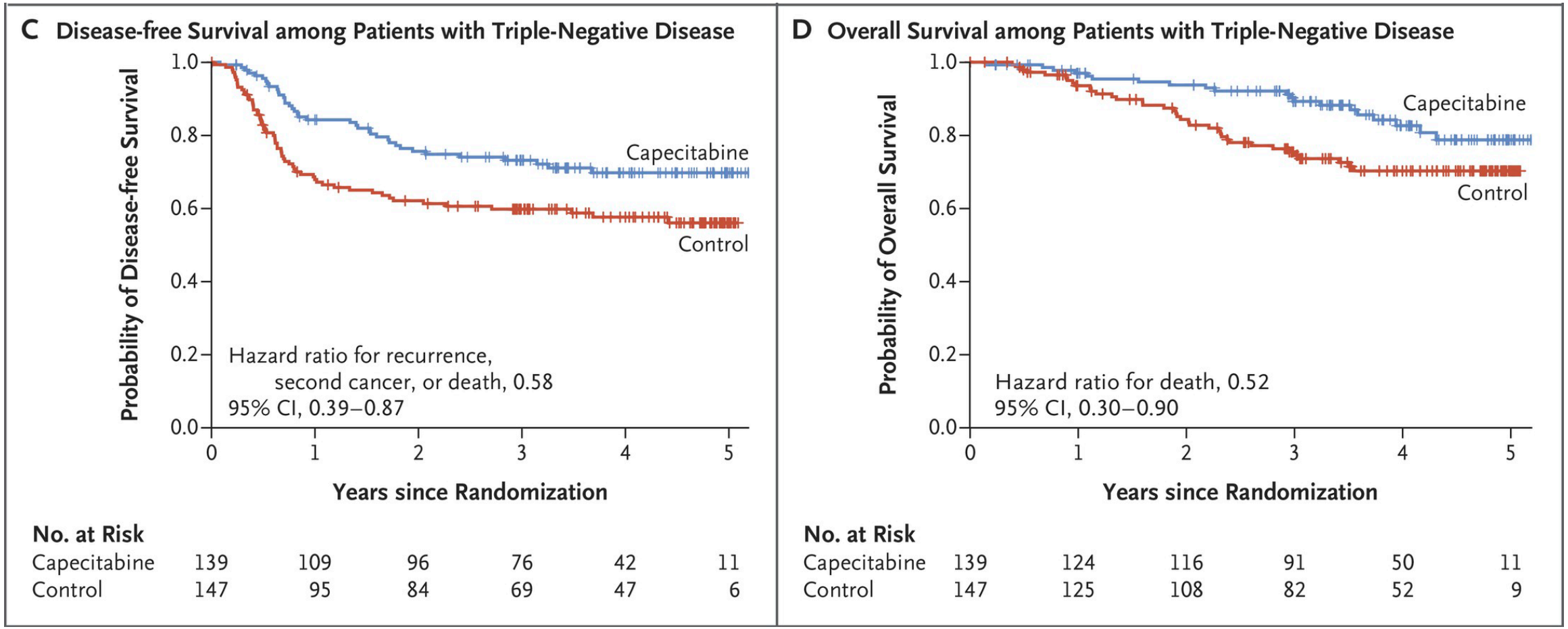
Loibl et al, ESMO 2021

OUTLINE

- Triple Negative Breast Cancer
  - Neoadjuvant Chemo-Immunotherapy (KN-522)
  - Carboplatin Impact (Brightness)
  - Sacituzumab for Metastatic

ADJUVANT THERAPY – RESIDUAL DISEASE

CREATE-X Trial



Masuda et al, NEJM 2017

Combine Cape & Pembro?

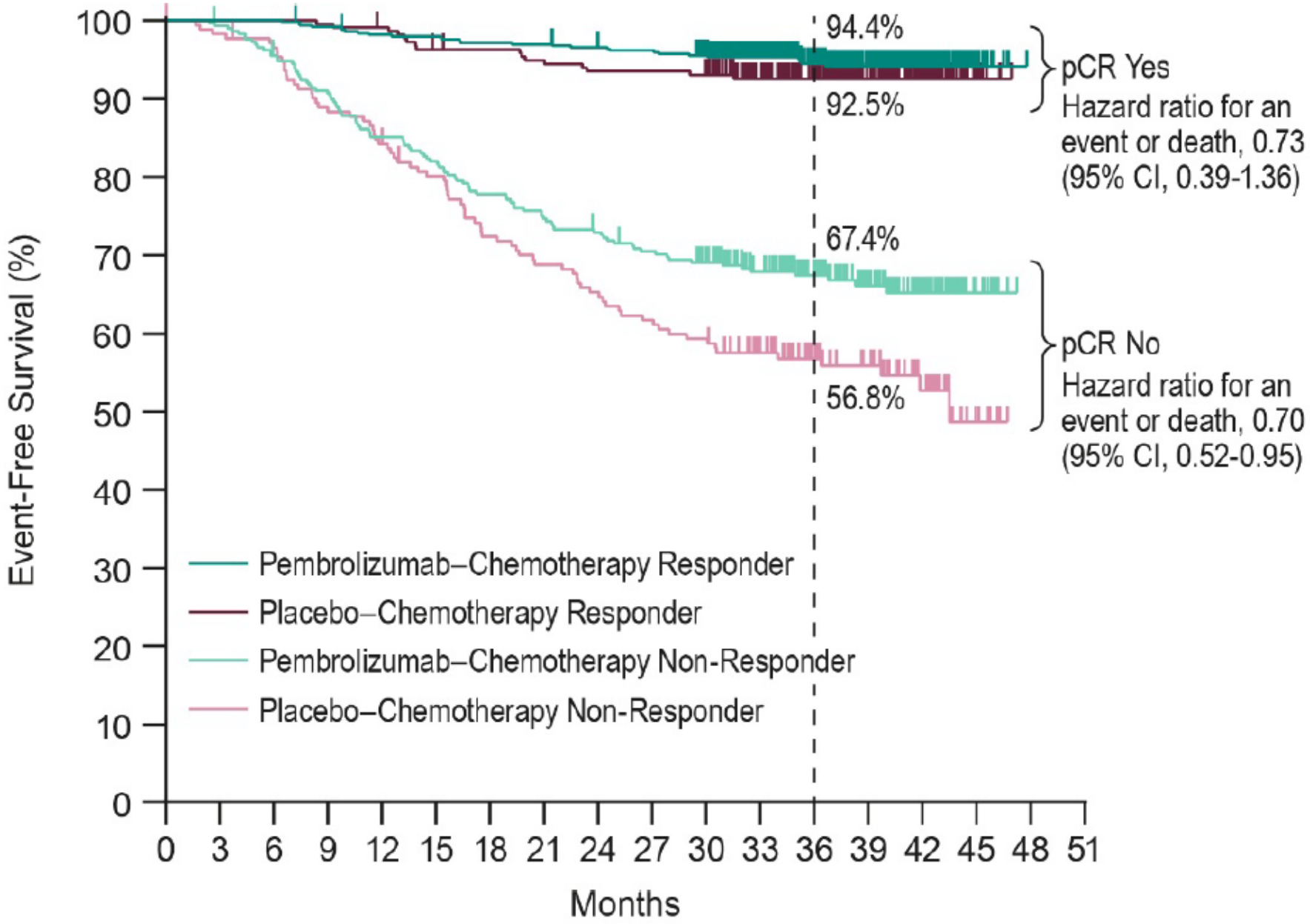
- Combination in stage IV disease
  - Safe, AEs similar to capecitabine monotherapy
  - Signal of efficacy in subgroup of patients

Page et al, AACR 2019
Shah et al, Journal of Immunotherapy for Cancer, 2020

OHSU

ADJUVANT THERAPY – pCR

KN-522


Event-Free Survival (%)
100
90
80
70
60
50
40
30
20
10
0
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51
Months
94.4%
92.5%
67.4%
56.8%
pCR Yes
Hazard ratio for an event or death, 0.73 (95% CI, 0.39-1.36)
pCR No
Hazard ratio for an event or death, 0.70 (95% CI, 0.52-0.95)
Pembrolizumab–Chemotherapy Responder
Placebo–Chemotherapy Responder
Pembrolizumab–Chemotherapy Non-Responder
Placebo–Chemotherapy Non-Responder

Continue Pembro?

- KN-522 completed 1 year of pembrolizumab regardless of pathologic response
- Excellent outcomes for pCR in pembro / control arm
- Trials to address pembrolizumab maintenance question

TRIPLE NEGATIVE BREAST CANCER METASTATIC DISEASE

KEYNOTE – 355
CHEMO +/- PEMBRO

KEYNOTE-355 Study Design (NCT02819518)

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

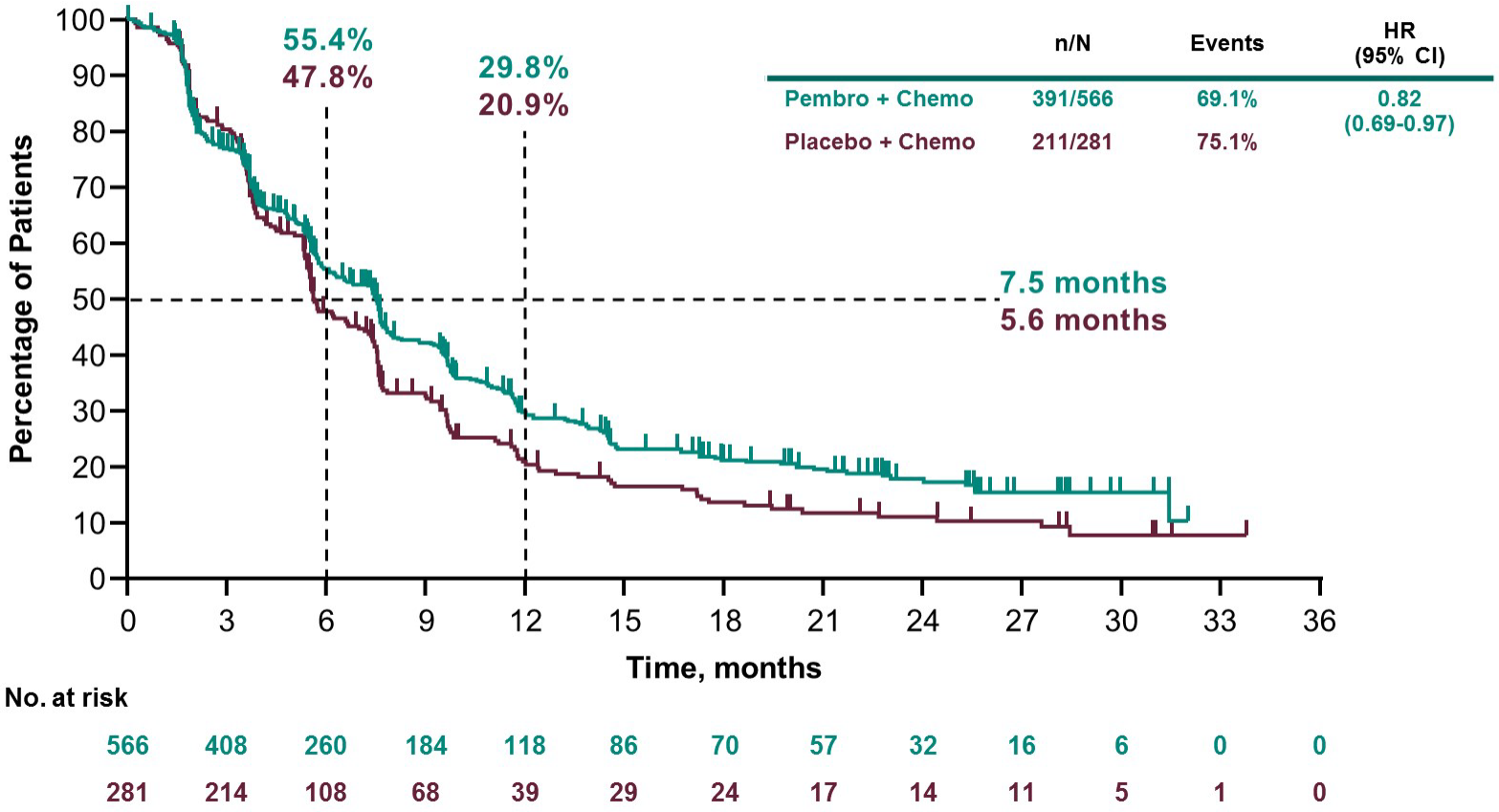
Stratification Factors:
- Chemotherapy on study (taxane vs gemcitabine/carboplatin)
- PD-L1 tumor expression (CPS ≥1 vs CPS <1)
- Prior treatment with same class chemotherapy in the neoadjuvant or adjuvant setting (yes vs no)

[a]Pembrolizumab 200 mg intravenous (IV) every 3 weeks (Q3W)
[b]Chemotherapy dosing regimens are as follows:
Nab-paclitaxel 100 mg/m^2 IV on days 1, 8, and 15 every 28 days
Paclitaxel 90 mg/m^2 IV on days 1, 8, and 15 every 28 days
Gemcitabine 1000 mg/m^2/carboplatin AUC 2 on days 1 and 8 every 21 days

[c]Normal saline
[d]Treatment may be continued until confirmation of progressive disease
CNS=central nervous system; ECOG=Eastern Cooperative Oncology Group; PD-L1=programmed death ligand 1; R=randomized; TNBC=triple-negative breast cancer

OHSU

Progression-Free Survival: ITT



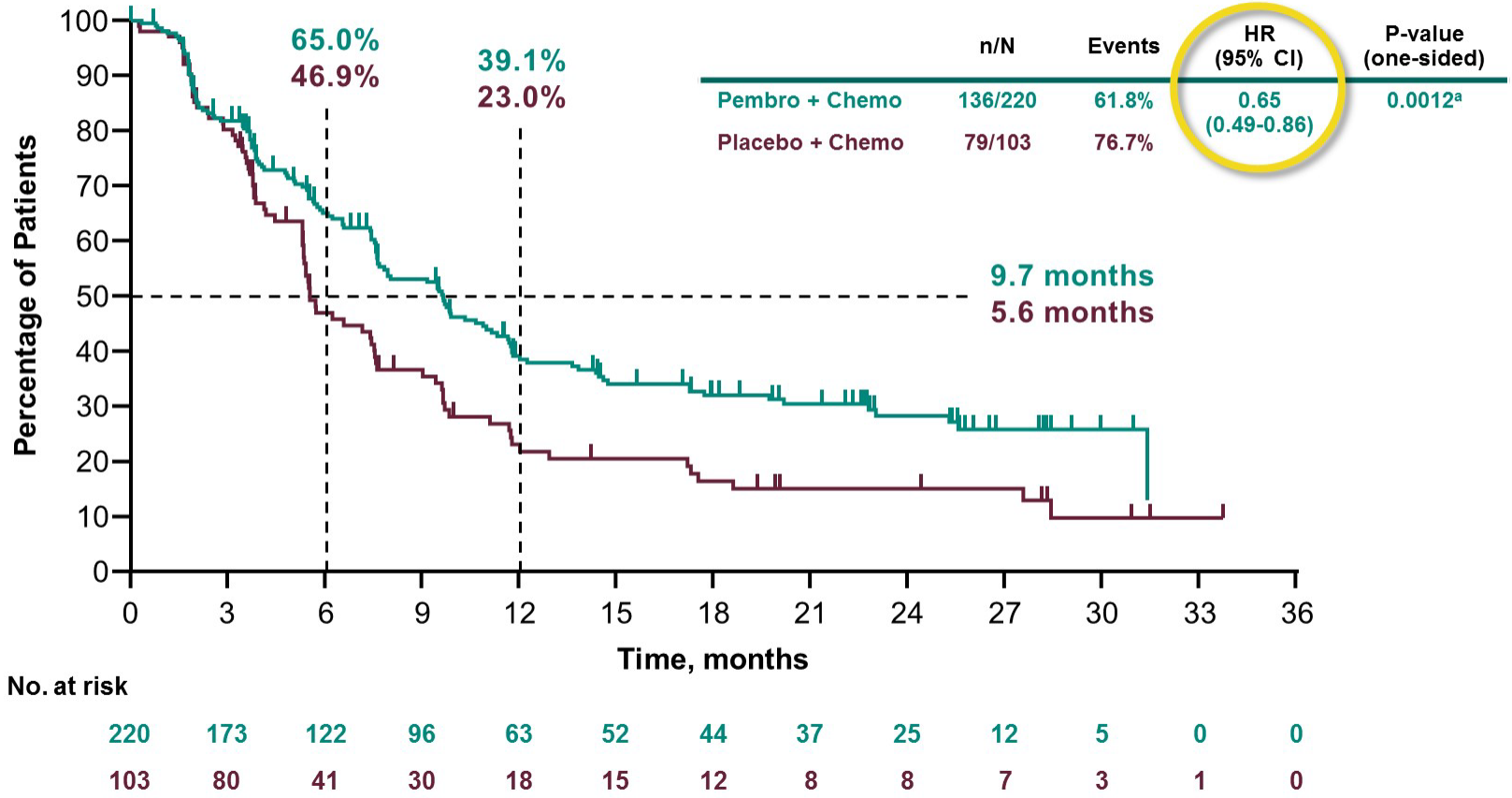
	n/N	Events	HR (95% CI)
Pembro + Chemo	391/566	69.1%	0.82 (0.69-0.97)
Placebo + Chemo	211/281	75.1%	

No. at risk

566	408	260	184	118	86	70	57	32	16	6	0	0
281	214	108	68	39	29	24	17	14	11	5	1	0

Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Statistical significance was not tested due to the prespecified hierarchical testing strategy. Data cutoff December 11, 2019.

Progression-Free Survival: PD-L1 CPS ≥10



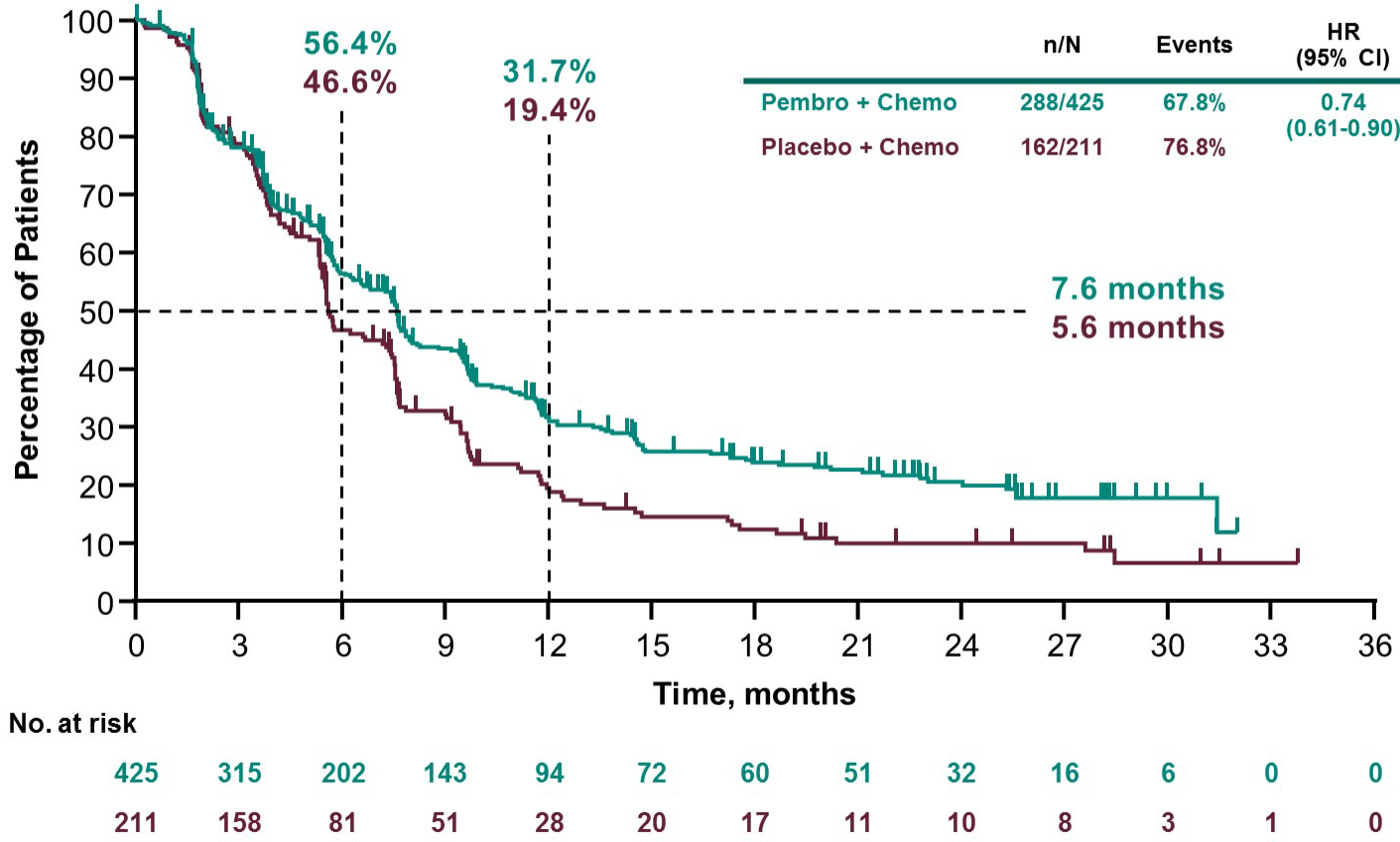
	n/N	Events	HR (95% CI)	P-value (one-sided)
Pembro + Chemo	136/220	61.8%	0.65 (0.49-0.86)	0.0012[a]
Placebo + Chemo	79/103	76.7%		

No. at risk

220	173	122	96	63	52	44	37	25	12	5	0	0
103	80	41	30	18	15	12	8	8	7	3	1	0

[a]Prespecified *P* value boundary of 0.00411 met.
Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff December 11, 2019.

Progression-Free Survival: PD-L1 CPS ≥1



	n/N	Events	HR (95% CI)	P-value (one-sided)
Pembro + Chemo	288/425	67.8%	0.74 (0.61-0.90)	0.0014[a]
Placebo + Chemo	162/211	76.8%		

No. at risk

425	315	202	143	94	72	60	51	32	16	6	0	0
211	158	81	51	28	20	17	11	10	8	3	1	0

[a]Prespecified *P* value boundary of 0.00111 not met.
Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff December 11, 2019.