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ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Breast Cancers

Kevin Kalinsky, MD, MS

Director, Glenn Family Breast Center

Director, Breast Medical Oncology

Winship Cancer Institute of Emory University

AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

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Disclosures

- Consulting Fees: Eli-Lilly, Pfizer, Novartis, Eisai, AstraZeneca, Seattle Genetics, Merck
- Contracted Research (Institution): Incyte, Genentech, Eli-Lilly, Pfizer, Calithera Biosciences, Acetylon, Seattle Genetics, Amgen, Zeno Pharmaceuticals, CytomX Therapeutics
- Speakers' Bureau: Eli-Lilly
- I will be discussing non-FDA approved indications during my presentation

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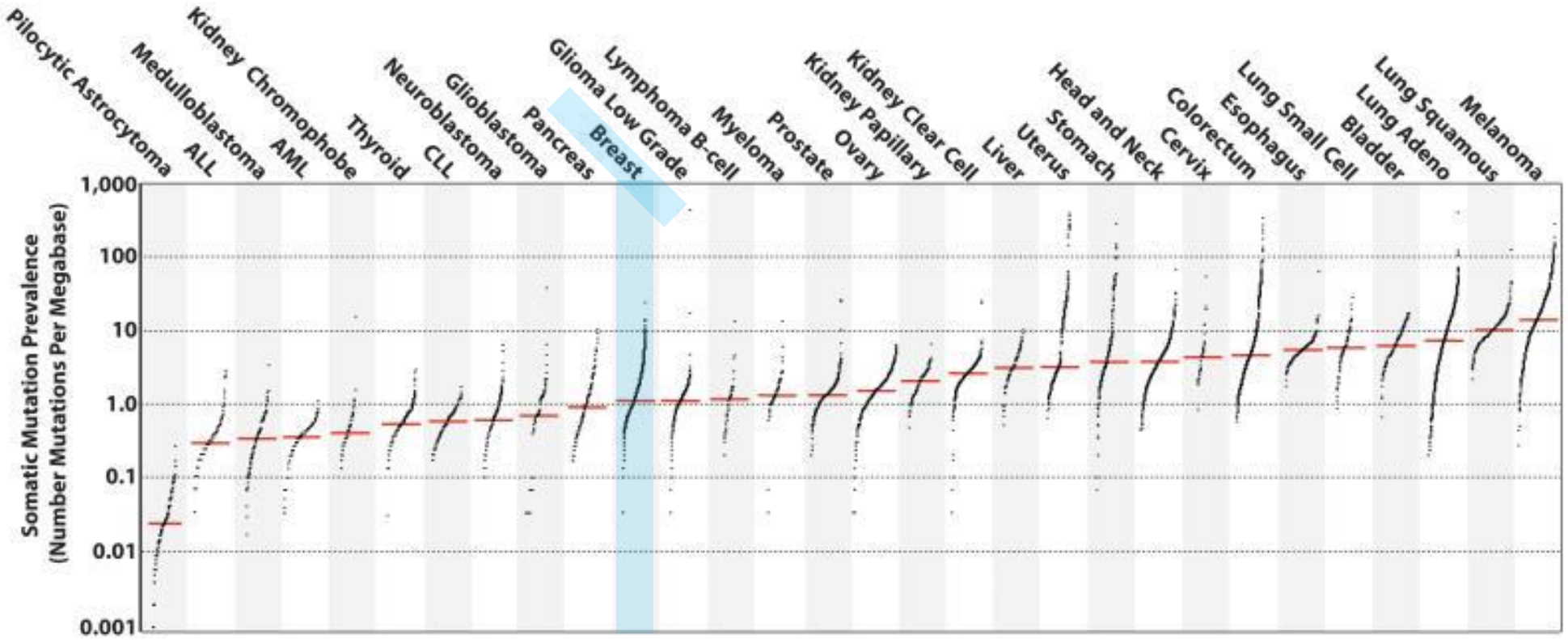
Immunotherapy in breast cancer



Alexandrov, Nature 2013.

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Outline

- Breast cancer
  - Approvals
  - In the pipeline
  - Biomarkers and immunotherapy responsiveness

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Current approvals in breast cancer

Checkpoint inhibitor	Approved	Indication	Dose
Pembrolizumab	2017	MSI-H/dMMR **advanced cancer** with progression on previous treatment	200 mg Q3W or 400 mg Q6W
Atezolizumab + nab-paclitaxel or paclitaxel protein-bound	2019	Advanced/Metastatic **TNBC** with PD-L1 ≥1% immune cells	840 mg atezolizumab Q2W + 100 mg/m^2 nab-paclitaxel on days 1, 8, 15
Pembrolizumab	2020	TMB-high **solid tumors** with progression on prior treatment	200 mg Q3W or 400 mg Q6W
Pembrolizumab	2020	Advanced/Metastatic **TNBC** with PD-L1 ≥10% immune cells	200 mg Q3W or 400 mg Q6W

Antibody-drug conjugate	Approved	Indication	Dose
Ado-trastuzumab emtansine	2019	Adjuvant treatment of **HER2-positive** early breast cancer with residual disease	3.6 mg/kg Q3W
Fam-trastuzumab deruxtecan-nxki	2019	Unresectable/metastatic **HER2-positive** breast cancer after 2+ HER2 regimens	5.4 mg/kg Q3W
Sacituzumab govitecan	2020	Metastatic **TNBC** after two previous therapies	10mg/kg on D1&D8 of 21-day cycle

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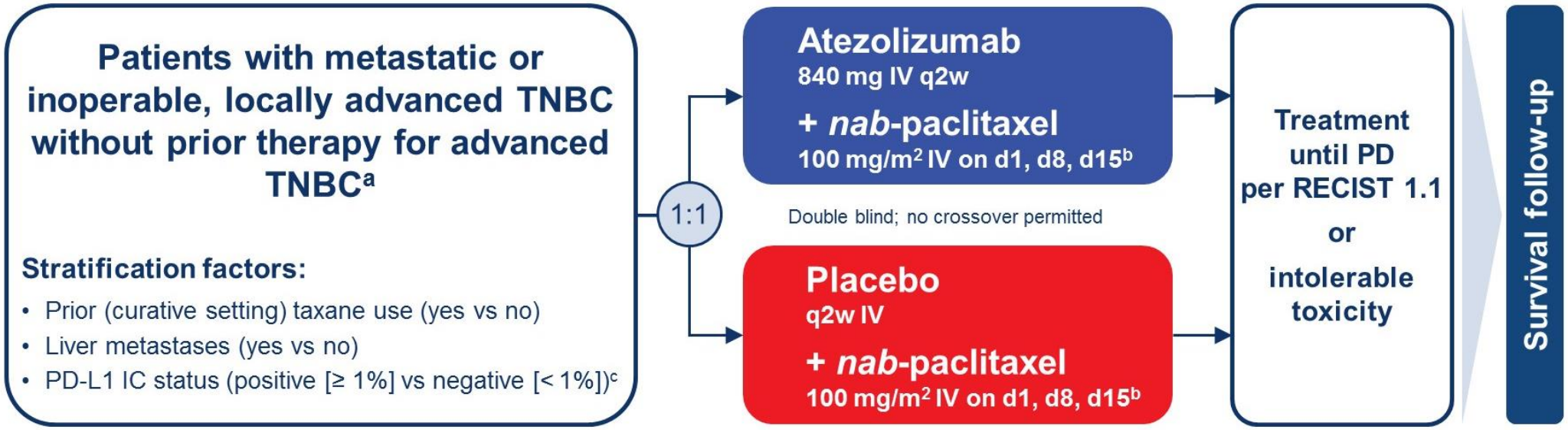
Clinical Data – IMpassion130 PD-L1+ TNBC



- Co-primary endpoints in ITT and PD-L1 IC+: PFS and OS[d]
- Pre-specified hierarchical testing of OS in ITT and, if significant, in PD-L1 IC+ patients
- In both treatment arms, 41% of patients were PD-L1 IC+

Schmid, ASCO 2019.

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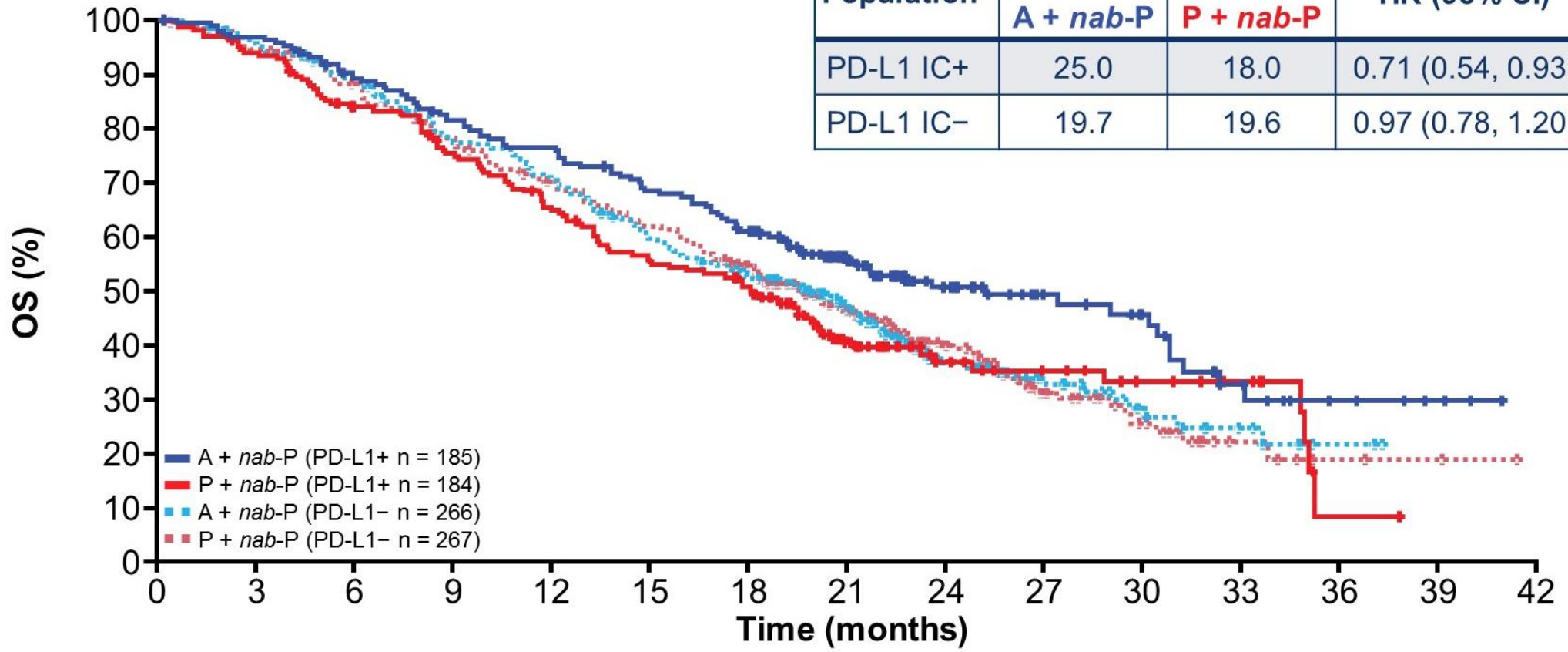
Clinical Data – IMpassion130 PD-L1+ TNBC

Population	Median OS, mo		HR (95% CI)
	A + *nab*-P	P + *nab*-P	
PD-L1 IC+	25.0	18.0	0.71 (0.54, 0.93)
PD-L1 IC−	19.7	19.6	0.97 (0.78, 1.20)



Schmid, ASCO 2019.

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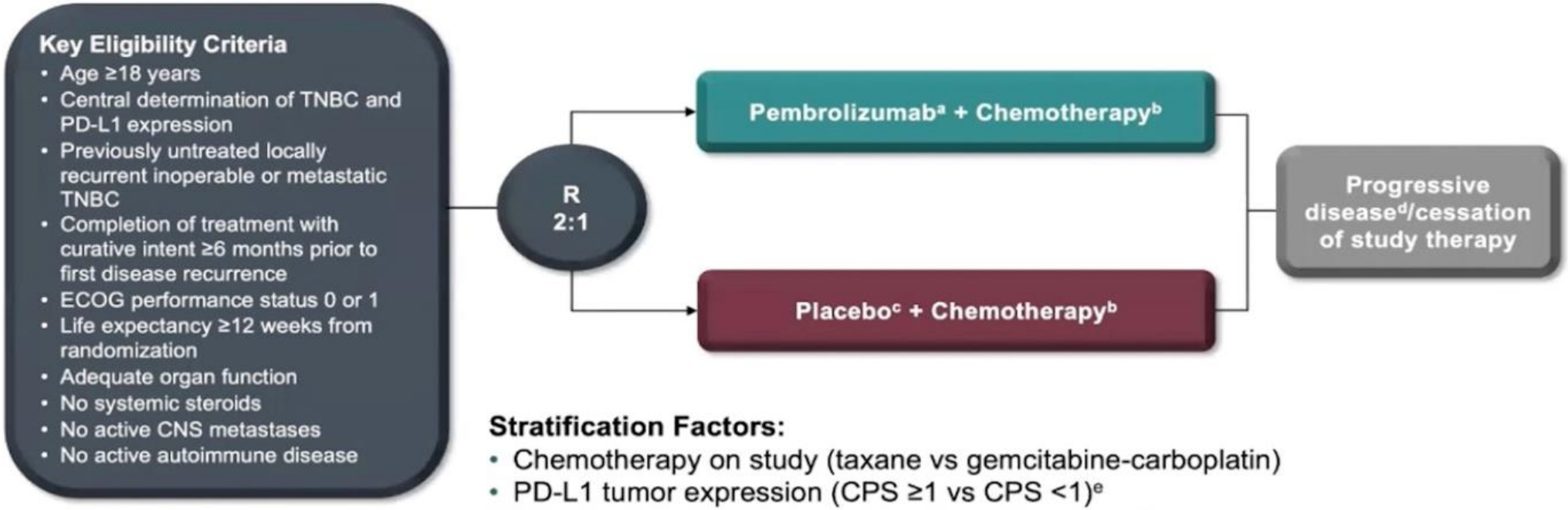
Keynote 355 Study Design



Stratification Factors:

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

[a]Pembrolizumab 200 mg IV 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.
[e]PD-L1 CPS at cutoff 10 was not a stratification factor.

Rugo et al SABCS 2020

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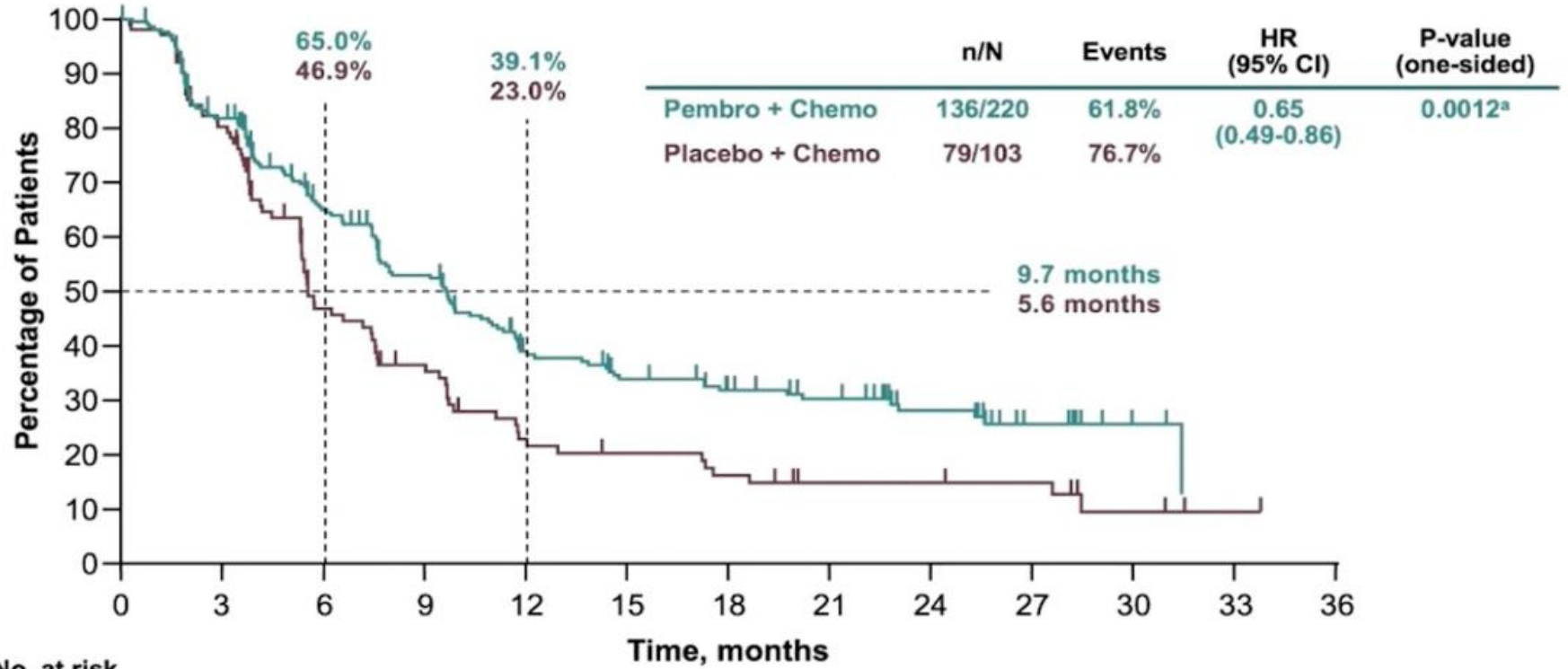
Progression Free Survival CPS ≥ 10



	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.

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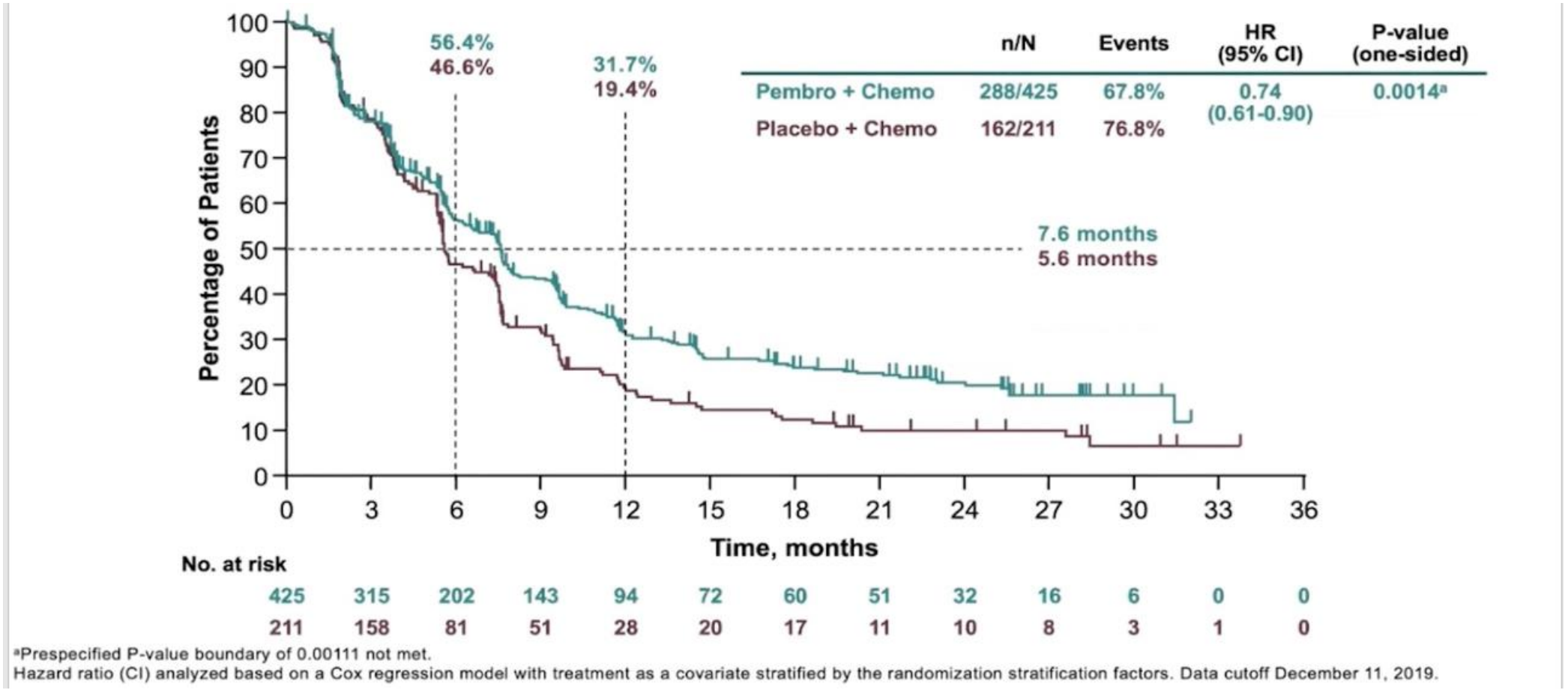
Progression Free Survival CPS ≥ 1



	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.

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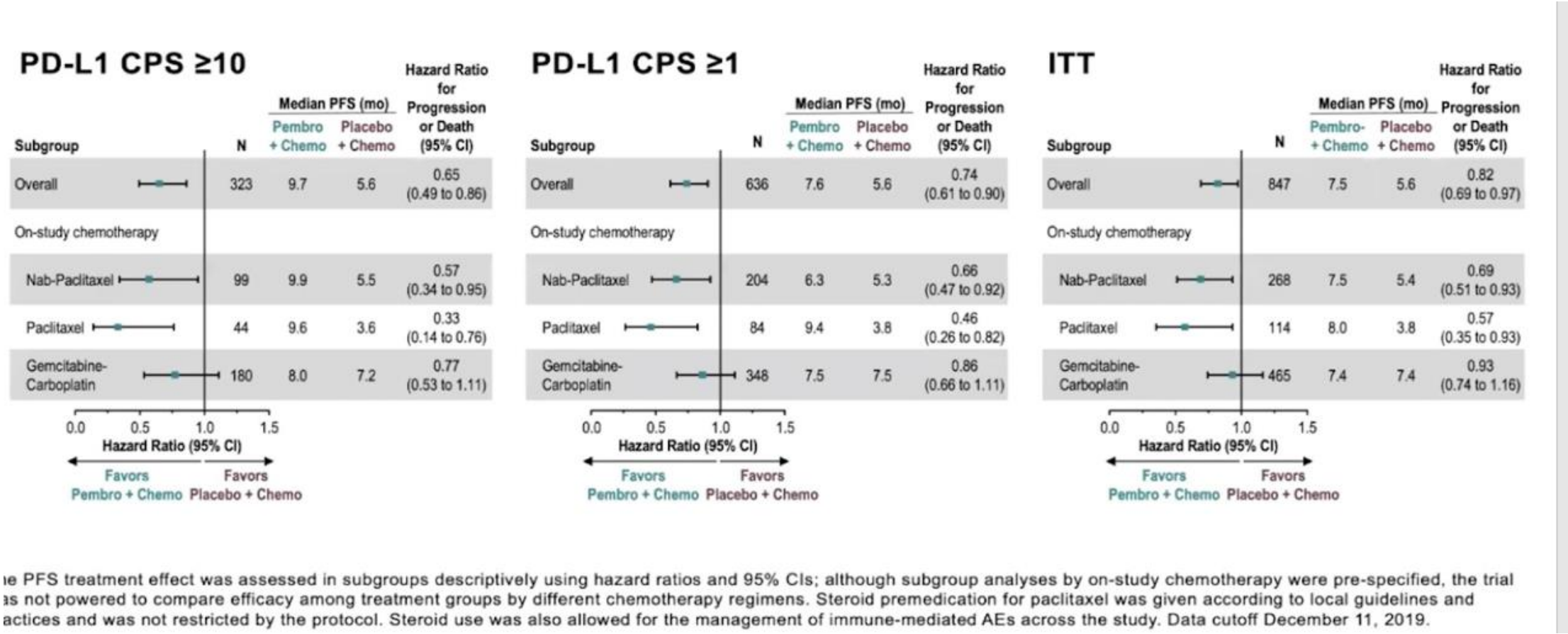
Progression free survival in chemotherapy subgroups



ıe PFS treatment effect was assessed in subgroups descriptively using hazard ratios and 95% CIs; although subgroup analyses by on-study chemotherapy were pre-specified, the trial ıs not powered to compare efficacy among treatment groups by different chemotherapy regimens. Steroid premedication for paclitaxel was given according to local guidelines and actices and was not restricted by the protocol. Steroid use was also allowed for the management of immune-mediated AEs across the study. Data cutoff December 11, 2019.

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Outline

- Breast cancer
  - Approvals
  - In the pipeline
  - Biomarkers and immunotherapy responsiveness
- Gynecologic cancers
  - Approvals
  - In the pipeline

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Clinical trials in TNBC

Trial	Treatment arm(s)	Patient selection criteria	n	ORR	Median PFS (months)	Median OS (months)
IMpassion130	Atezolizumab + nab-paclitaxel* **FDA-approved*	Metastatic TNBC without prior therapy	902	ITT: 56.0% PD-L1+: 58.9%	ITT: 7.2 PD-L1+: 7.5	ITT: 21.3 PD-L1+: 25.0
	Placebo + nab-paclitaxel			ITT: 45.9% PD-L1+: 42.6%	ITT: 5.5 PD-L1+: 5.0	ITT: 17.6 PD-L1+: 15.5
KEYNOTE-086	Pembrolizumab	A: Metastatic TNBC at 2nd line or greater	170	5.3% CR: 1.2%	2.0	9.0
		B: PD-L1+ metastatic TNBC without prior therapy	84	21.4% CR: 4.7%	2.1	18.0
IMMU-132-01	Sacituzumab govitecan-hziy* (Anti-Trop-2)	Advanced TNBC with at least 2 prior therapies	108	33.3%	5.5	13.0
KEYNOTE-355	Pembrolizumab + chemotherapy	Locally recurrent inoperable or metastatic TNBC without prior therapy	566		ITT: 7.5 CPS >10: 9.7	
	Placebo + chemotherapy		281		ITT: 5.6 CPS >10: 5.6	
KEYNOTE-522	Neoadjuvant pembrolizumab + paclitaxel/carboplatin, adjuvant pembrolizumab	Stage II or III TNBC without prior therapy	1174	Pathological complete response rates: ITT: 64.8% vs 51.2% PD-L1+: 68.9% vs 54.9% PD-L1-: 45.3% vs 30.3%		
	Neoadjuvant placebo + paclitaxel/carboplatin, adjuvant placebo					

Cortes, ASCO 2020; Schmid, N Engl J Med 2018; Schmid, N Engl J Med 2020;
Adams, Ann Oncol 2019; Loi, Lancet Oncol 2019; Bardia, N Engl J Med 2019.

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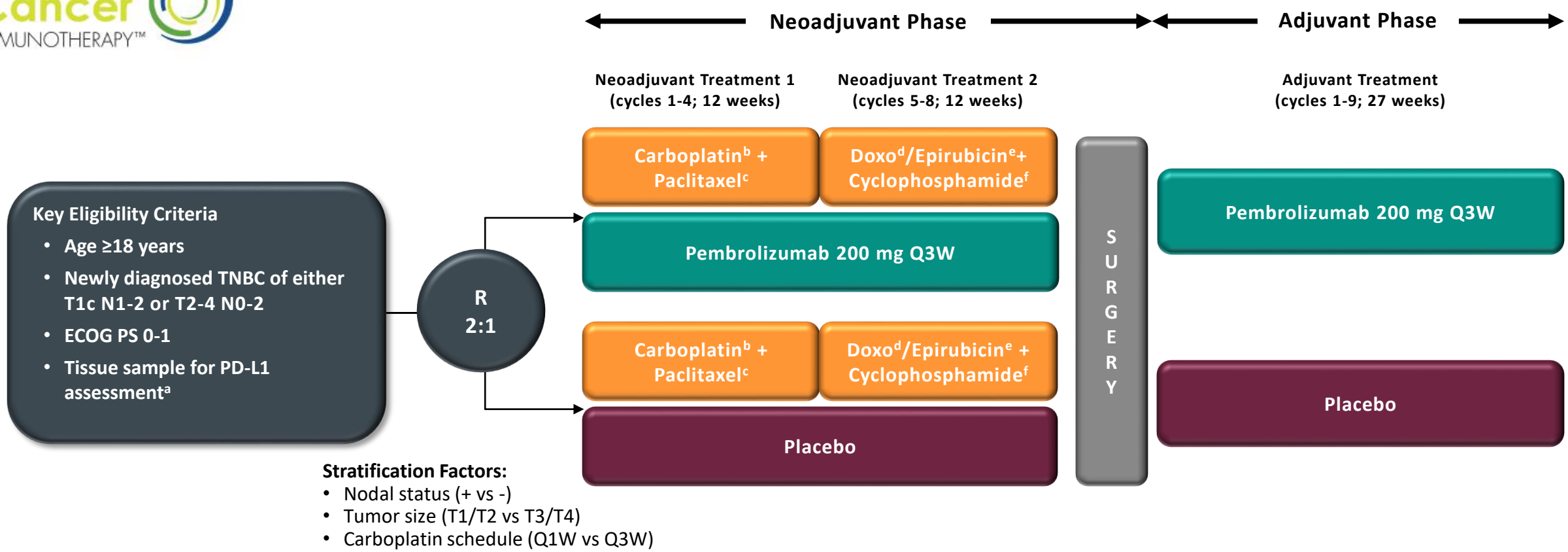
KEYNOTE-522 Study Design (NCT03036488)



Stratification Factors:
- Nodal status (+ vs -)
- Tumor size (T1/T2 vs T3/T4)
- Carboplatin schedule (Q1W vs Q3W)

Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

[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.

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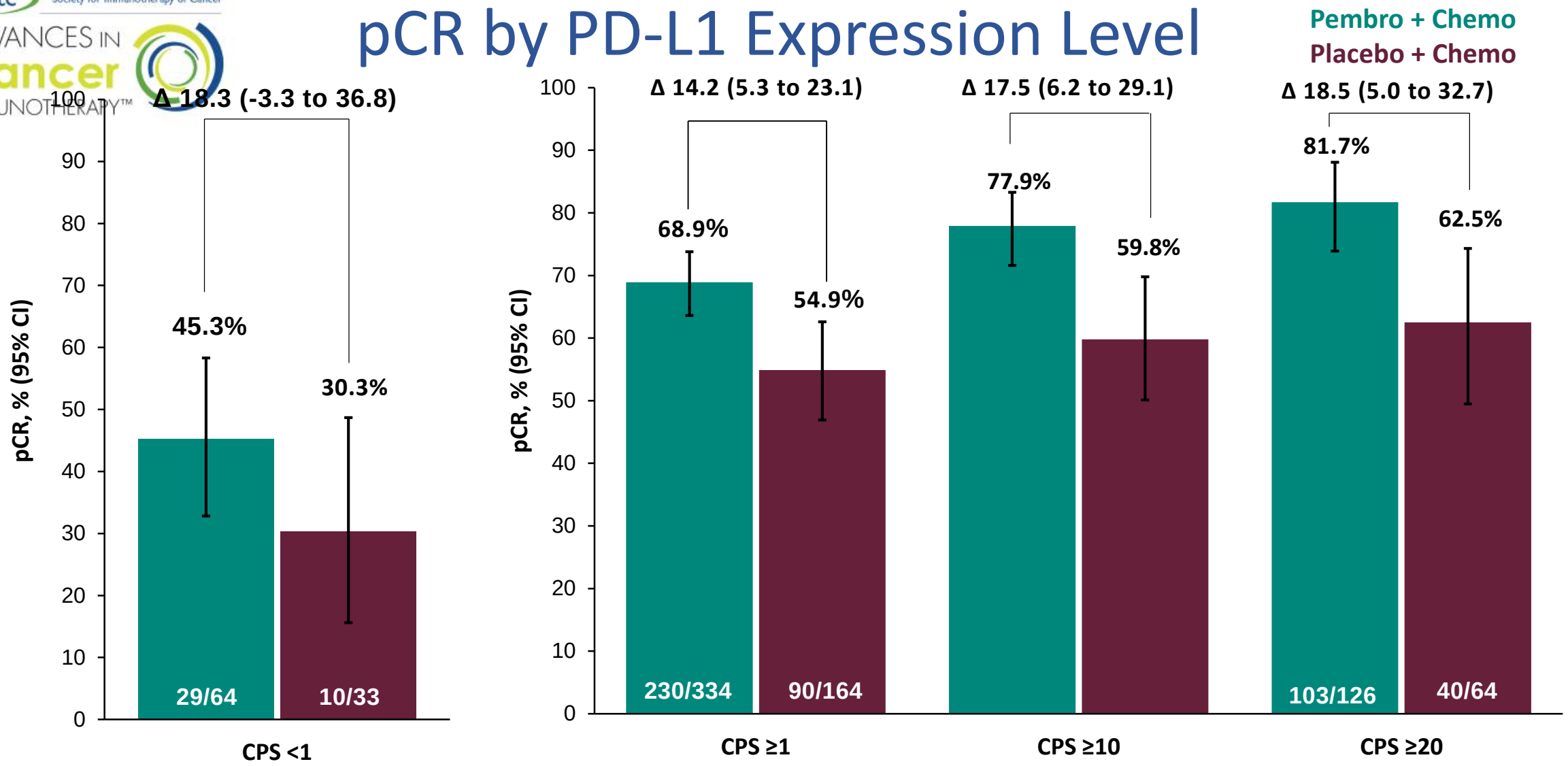
pCR by PD-L1 Expression Level



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.

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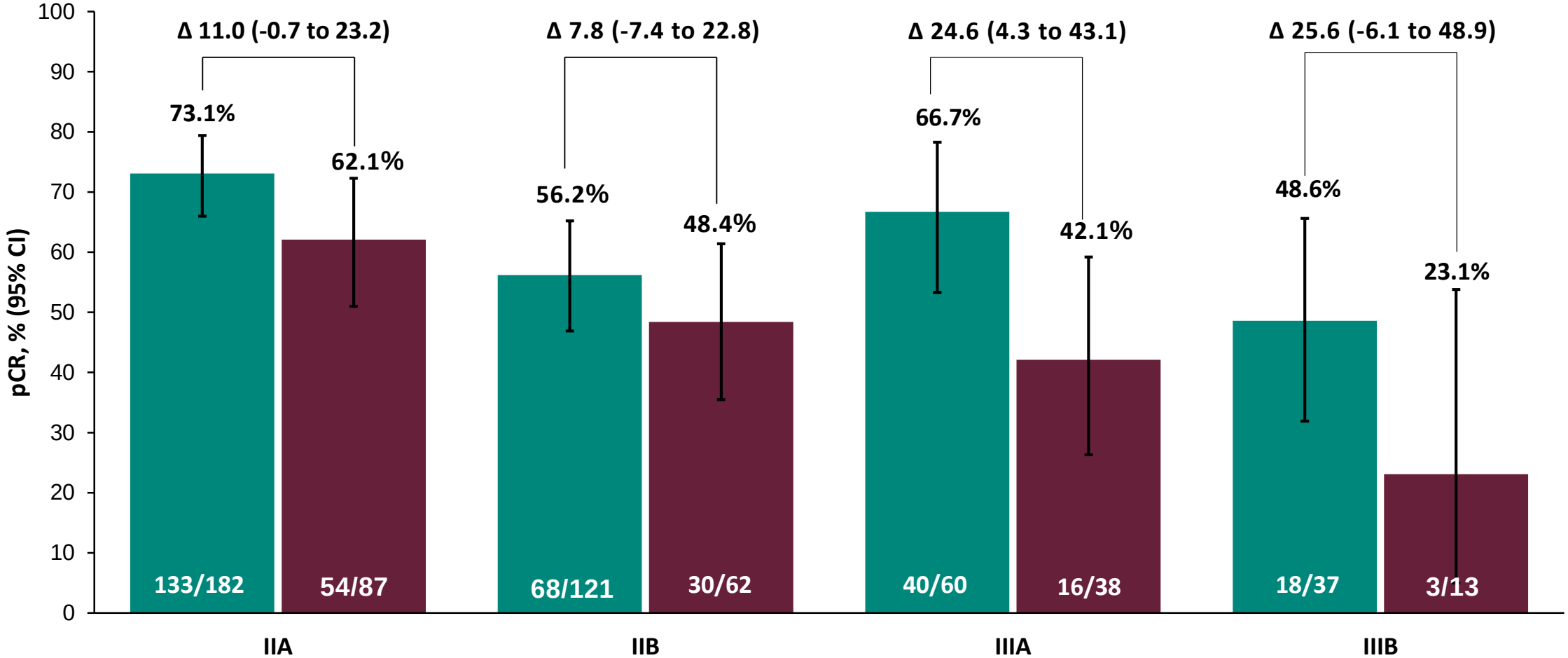
pCR by Disease Stage



Post-hoc analysis. Estimated treatment difference based on unstratified Miettinen & Nurminen method. Data cutoff date: September 24, 2018.

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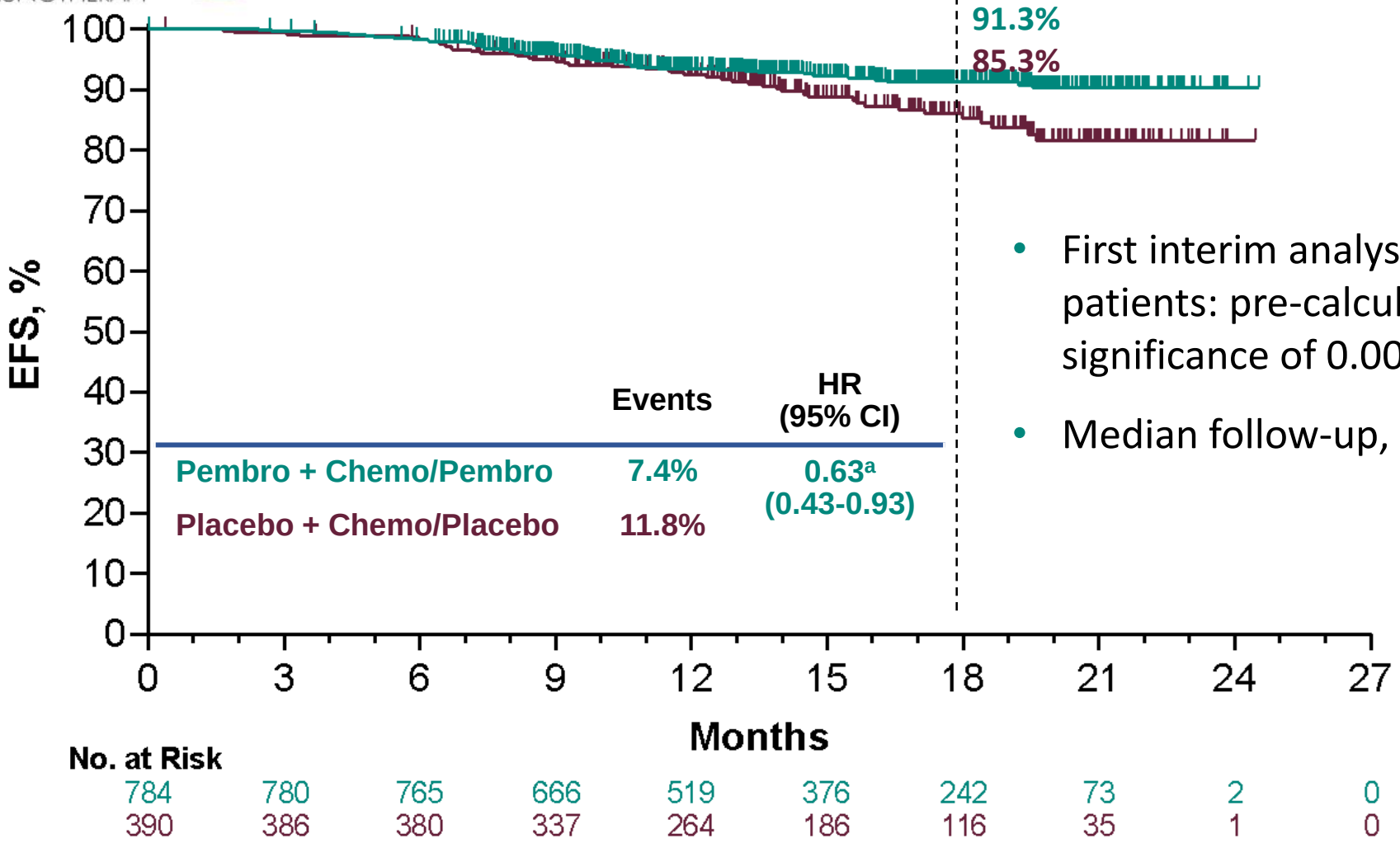
First Pre-planned Interim Analysis for EFS



- First interim analysis of EFS based on 1174 patients: pre-calculated P value boundary for significance of 0.000051 (HR <0.4)
- Median follow-up, 15.5 months

[a]Pre-specified P value boundary of 0.000051 not reached at this analysis (the first interim analysis of EFS). Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff April 24, 2019.

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I-SPY 2 TRIAL
AEs of Special Interest

	Pembrolizumab (n=69) % (n)		Control (n=180) % (n)	
	All grades	Grade 3-5	All grades	Grade 3-5
Hypothyroidism	**8.7 (6)**	**1.4 (1)**	**0.6 (1)**	**0 (0)**
Hyperthyroidism	**4.3 (3)**	**0 (0)**	**0 (0)**	**0 (0)**
Adrenal Insufficiency^	**8.7 (6)**	**7.2 (5)**	**0 (0)**	**0 (0)**
Hepatitis	2.9 (2)	2.9 (2)	0 (0)	0 (0)
Pneumonitis	2.9 (2)	0 (0)	1.1 (2)	0.6 (1)
Colitis	1.4 (1)	1.4 (1)	0.6 (1)	0.6 (1)
Pruritis	24.6 (17)	0 (0)	11.1 (20)	0.6 (1)

*includes both hyperthyroidism and hypothyroidism
^includes primary and secondary causes of AI

Nanda R, et al. ASCO 2017

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Trials in HR+ or HER2+ breast cancer

Trial	Treatment arm(s)	Patient selection criteria	n	ORR	Median PFS (months)	Median OS (months)
KEYNOTE-028	Pembrolizumab	ER+/HER2-, PD-L1+ breast cancer	25	12.0% CR: 0%	1.8	8.6
KEYNOTE-014/PANACEA	Pembrolizumab + trastuzumab	HER2+ breast cancer with progression on trastuzumab	58	PD-L1+: 15% CR: 4% PD-L1-: 0%		
KATE2	Atezolizumab + trastuzumab emtansine	HER2+ advanced breast cancer with previous trastuzumab and a taxane	133	ITT: 45% PD-L1+: 54%	ITT: 8.2 PD-L1+: 8.5	ITT 1-year: 89.1% PD-L1+: 94.3%
	Trastuzumab emtansine		69	ITT: 43% PD-L1+: 33%	ITT: 6.8 PD-L1+: 4.1	ITT 1-year: 89.0% PD-L1+: 87.9%
KATHERINE	Trastuzumab emanstine* (Anti-HER2)	HER2-positive early breast cancer after neoadjuvant therapy	1486	3-year invasive disease-free survival: 88.3% vs. 77.0%		
DESTINY-Breast01	Trastuzumab deruxtecan*	HER2-positive metastatic breast cancer after trastuzumab emanstine	184	60.9%	16.4	NR

Rugo, Clin Cancer Res 2018; Loi, Lancet Oncol 2019; Emens ESMO 2019 and SABCS 2018; von Minckwitz, N Engl J Med 2019; Modi, N Engl J Med 2020.

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Biomarkers and immunotherapy responsiveness in breast cancers

- Potential markers of responsiveness include:
  - PD-L1
  - Tumor infiltrating lymphocytes

FDA-approved biomarkers only include:
- PD-L1+ by SP142 (≥1%)
- PD-L1 by CPS (≥10%)
- TMB 10 or more
- MSI high

ADDITIONAL TARGETED THERAPIES AND ASSOCIATED BIOMARKER TESTING FOR RECURRENT OR STAGE IV (M1) DISEASE

Biomarkers Associated with FDA-Approved Therapies					
Breast Cancer Subtype	**Biomarker**	**Detection**	**FDA-Approved Agents**	**NCCN Category of Evidence**	**NCCN Category of Preference**
Any[a]	*BRCA1* mutation *BRCA2* mutation	Germline sequencing	Olaparib	Category 1	Preferred
			Talazoparib	Category 1	Preferred
HR-positive/ HER2-negative[b]	*PIK3CA* mutation	PCR (blood or tissue block if blood negative), molecular panel testing	Alpelisib + fulvestrant[d]	Category 1	Preferred second-line therapy
HR-negative/ HER2-negative[c]	PD-L1 expression • Threshold for positivity: ≥1% on tumor-infiltrating immune cells	IHC	Atezolizumab + albumin-bound paclitaxel	Category 2A	Preferred
Any	*NTRK* fusion	FISH, NGS, PCR (tissue block)	Larotrectinib[e]	Category 2A	Useful in certain circumstances[e]
			Entrectinib[e]	Category 2A	Useful in certain circumstances[e]
Any	MSI-H/dMMR	IHC, PCR (tissue block)	Pembrolizumab[f]	Category 2A	Useful in certain circumstances[f]

NCCN Guidelines.

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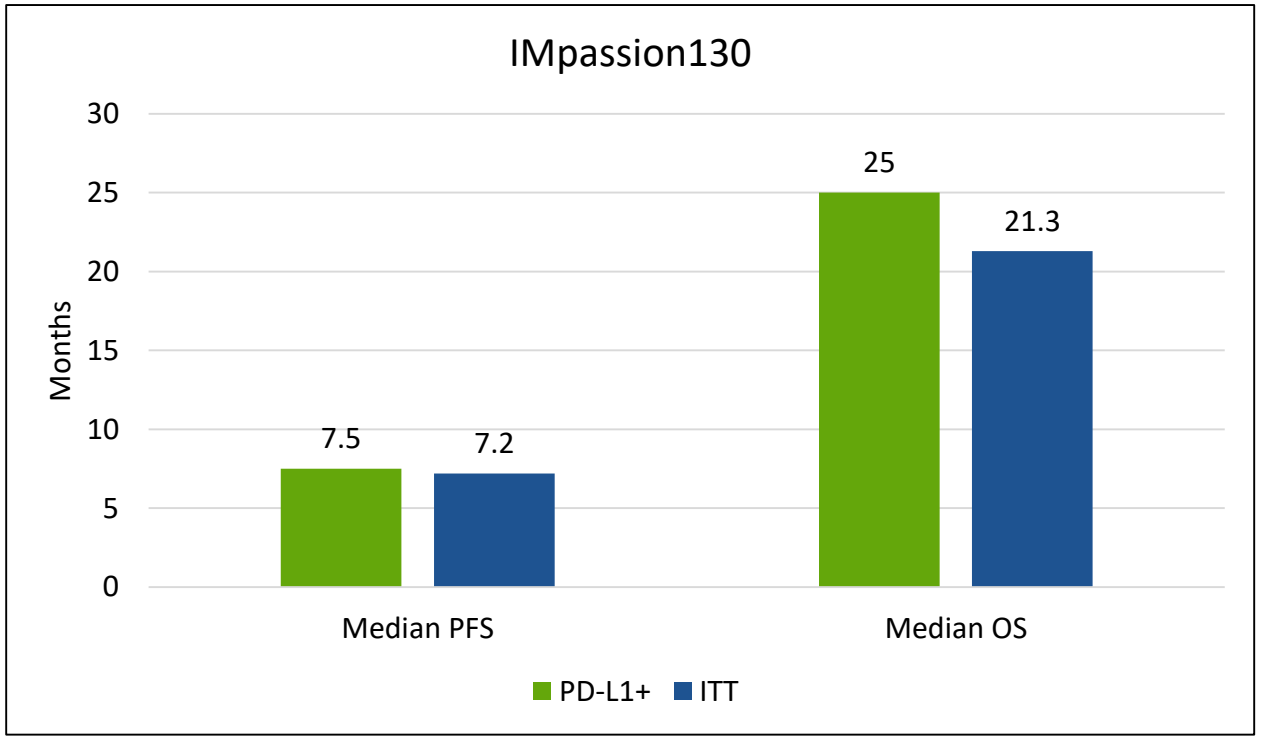
Biomarkers and immunotherapy responsiveness in breast cancers

- Potential markers of responsiveness include:
  - PD-L1
  - Tumor infiltrating lymphocytes

Here, patients with PD-L1 on ≥ 1% of tumor-infiltrating immune cells had improved outcomes on atezolizumab + chemotherapy compared to the general population (OS HR 0.62 vs 0.84)

However, PD-L1 expression does not always correlate with response to all ICIs.



Schmid, N Engl J Med 2018.

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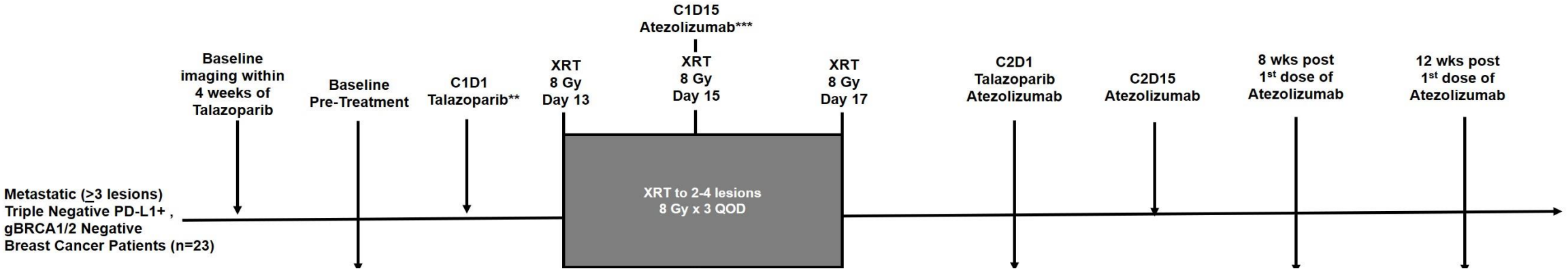
Clinical Trials at Emory

- Neoadjuvant: ISPY-2
- Residual Disease TNBC: S1418 (pembro vs. observiation)
- Metastatic TNBC and HR+/HER2- (DS-1062: TROP2 ADC)
- Metastatic HR+/HER2-: Sacituzumab +/- pembrolizumab
- Metastatic TNBC: TARA trial below



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Conclusions

- Immunotherapy in breast is expanding rapidly
- Immunotherapy in breast cancer shows promise in certain subtypes
- Clinical trials are actively ongoing with various breast cancer subtypes in the early-stage and metastatic setting

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Case Studies

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ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

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Instructions - Case Study 1

Case Study Format

45 year old female presents with newly metastatic TNBC. Which PDL1 assay predicts benefit to atezolizumab?

A. SP142
B. 22C3
C. SP263
D. None

SP142 is the predictive assay for atezolizumab. 22C3 for pembrolizumab

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