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ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Breast Cancer

Antoinette Tan, MD

Chief of Breast Medical Oncology

Levine Cancer Institute, Atrium Health

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: Celgene, Genentech
- Contracted Research: Genentech, Merck
- I will be discussing non-FDA approved indications during my presentation.

Why Immunotherapy for Breast Cancer?

- Higher expression of PD-L1 in TNBC than in HR+ breast cancers

–In one study up to 26% of primary TNBCs expressed PD-L1 on cancer cell surface

- The presence of TILs suggest an immune response to tumor-associated antigens, and a higher level of TILs is reported in TNBCs and may have prognostic significance

- TNBC is characterized by genomic instability and high rates of genetic mutations, which implicate production of more neoantigens and increased immunogenicity

- The tumor mutational load is higher in TNBC compared with other subtypes

Mittendorf EA, et al. Cancer Immunol Res 2014;2:361-370
Tung N, et al. NPJ Breast Cancer 2016;2:16002
Loi S, et al. Ann Oncol 2014;25:1544-1550
Adams S, et al. J Clin Oncol 2014;32:2959-2966
Budczies J, et al. J Pathol Clin Res 2015;1:225-238
Banerji S, et al. Nature 2012;486:405-409

Modest Response Rate with Checkpoint Inhibitor Monotherapy

Agent	Subtype	N	ORR	ORR (PD-L1+)*
Pembrolizumab				
•Single agent (Keynote-012)	TNBC	32	18.5%	18.5%
•Single agent (Keynote-028)	ER+	25	12.0%	12.0%
•Single agent (Keynote-086-A)	TNBC	170	4.7%	4.8%
•Single agent (Keynote-086-B)	TNBC	84	23.0%	23.0%
•Plus trastuzumab (PANACEA)	HER2+	58		15.0%
Atezolizumab				
•Single agent	TNBC	115	10.0%	13.0%
Avelumab				
•Single agent (Javelin)	All	168	4.8%	33.3%
	ER+/HER2-	72	2.8%	NR
	HER2+	38	3.8%	NR
	TNBC	58	8.6%	44.4%

Nanda et al, JCO 2016; Rugo et al, CCR 2018; Dirix et al, BCRT 2017;
Loi et al, SABCS 2017; Emens et al, JAMA Onc 2018; Adams et al, Ann Onc 2018

*Studies used different antibodies and cutoffs for PD-L1 positivity

KEYNOTE-012: Long-Term Follow-Up

- Median PFS: 1.9 mo
- 12-month PFS: 15%
- 5 responders in original analysis (1 CR, 4 PR)
- 3 patients had long-lasting responses (> 6 mo)
  - Patient 1: D/C pembrolizumab 11 mo after achieving CR; remained in CR with no additional treatment
  - Patient 2: D/C pembrolizumab after 2 y; maintained response for 22.7 mo
  - Patient 3: D/C pembrolizumab after 2 y; developed PD after 7.7 mo and restarted treatment

Nanda R, et al. SABCS 2016. Abstract P6-10-03.

Outline

- FDA approval of atezolizumab and nab-paclitaxel based on IMpassion130 for metastatic triple-negative breast cancer
- Areas of promising investigation for triple-negative breast cancer
  - Neoadjuvant chemotherapy and immunotherapy
  - Adjuvant immunotherapy in patients without a pathologic complete response (pCR) to neoadjuvant chemotherapy
- Using checkpoint inhibitors in other subtypes of breast cancer
- Other immunotherapy-based combinations in the metastatic setting

IMpassion130: Updated OS from a global, randomized, double-blind, placebo-controlled, Phase III study of atezolizumab + *nab*-paclitaxel in previously untreated locally advanced or metastatic triple-negative breast cancer

Peter Schmid,[1] Sylvia Adams,[2] Hope S. Rugo,[3] Andreas Schneeweiss,[4] Carlos H. Barrios,[5] Hiroji Iwata,[6] Véronique Diéras,[7] Volkmar Henschel,[8] Luciana Molinero,[9] Stephen Y. Chui,[9] Amreen Husain,[8] Eric P. Winer,[10] Sherene Loi,[11] Leisha A. Emens[12]

[1]Barts Cancer Institute, Queen Mary University of London, London, UK; [2]New York University Langone Medical Center, New York, NY; [3]University of California San Francisco Comprehensive Cancer Center, San Francisco, CA; [4]University Hospital and German Cancer Research Center Heidelberg, Heidelberg, Germany; [5]Centro de Pesquisa Clínica, HSL, PUCRS, Porto Alegre, Brazil; [6]Aichi Cancer Center Hospital, Nagoya, Japan; [7]Department of Medical Oncology, Centre Eugène Marquis, Rennes, France; [8]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [9]Genentech, Inc, South San Francisco, CA; [10]Dana-Farber Cancer Institute, Boston, MA; [11]Peter MacCallum Cancer Centre, Melbourne, Australia; [12]University of Pittsburgh Medical Center Hillman Cancer Center, Pittsburgh, PA

Rationale of IMpassion130 Trial

- Atezolizumab selectively targets PD-L1 to prevent interaction with PD-1
- Chemotherapy may enhance tumor-antigen-release and anti-tumor responses to checkpoint inhibition

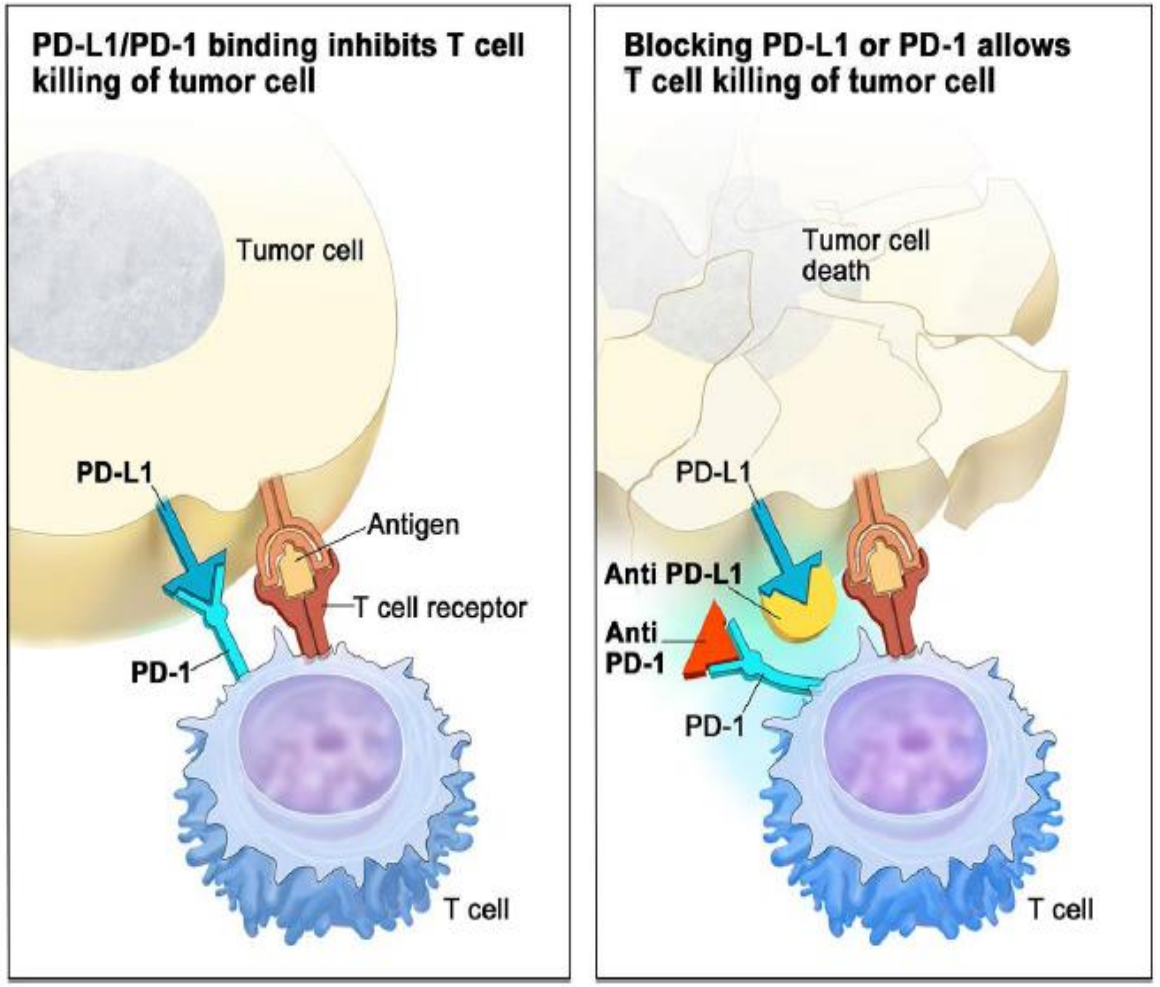
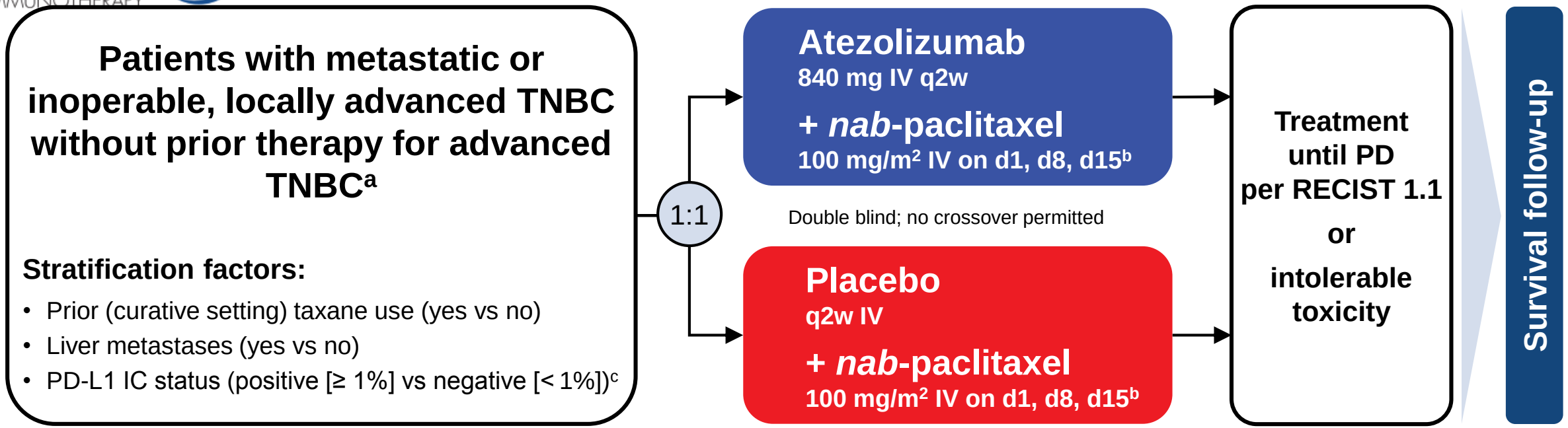


Image courtesy of the NIH.

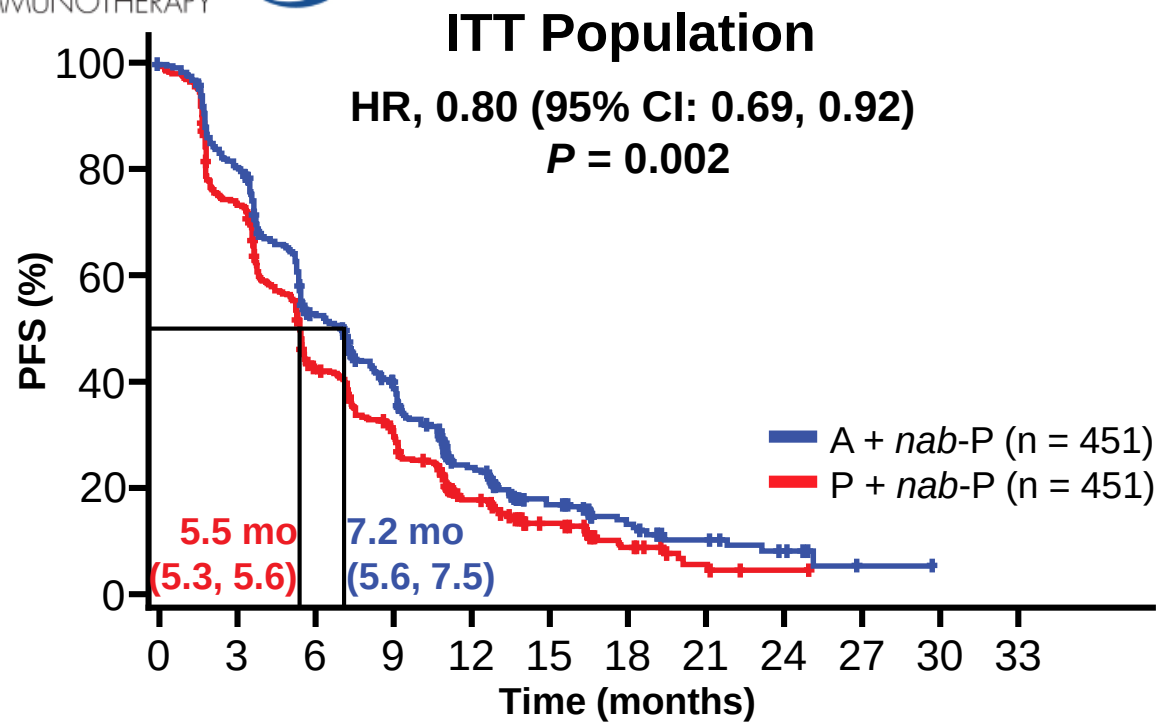
IMpassion130 Study Design

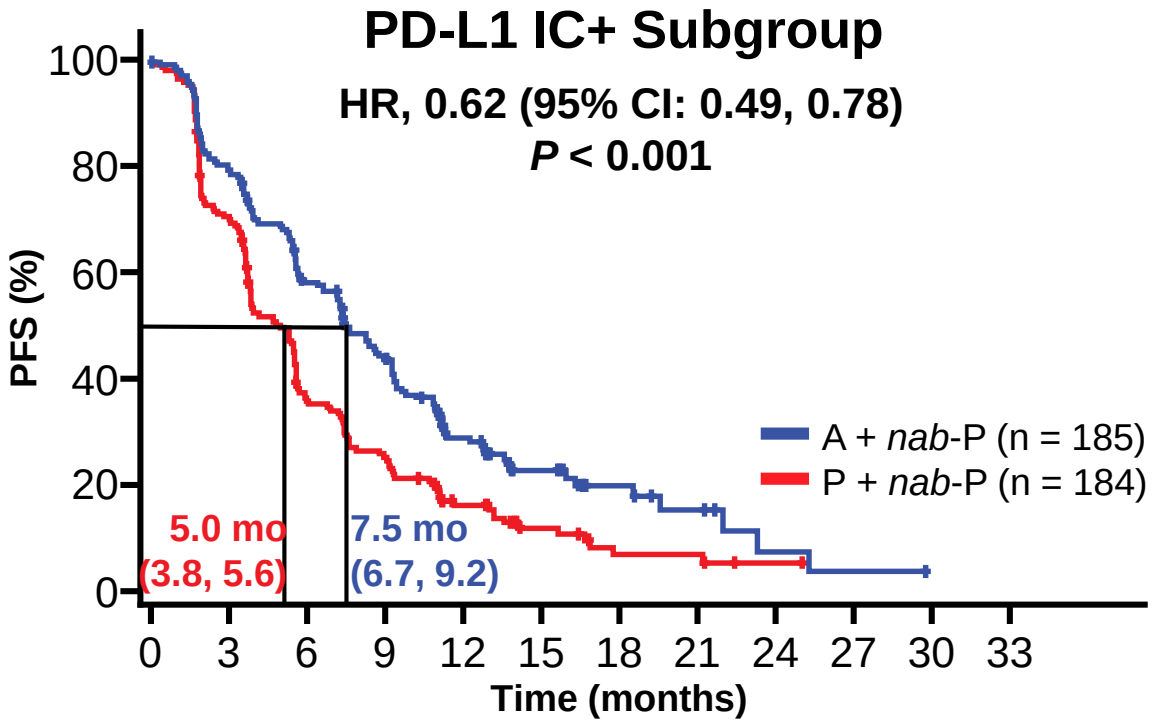


- Co-primary endpoints in ITT and PD-L1 IC+: PFS and OS[d]
- Pre-specified hierarchical testing of OS in ITT and, if significant, in PD-L1 IC+ patients
- In both treatment arms, 41% of patients were PD-L1 IC+

[a] Prior chemotherapy in the curative setting allowed if treatment-free interval ≥ 12 months. [b] 28-day cycle. [c] Centrally evaluated per VENTANA SP142 IHC assay.
[d] Efficacy endpoints assessed by investigators per RECIST 1.1. NCT02425891.

Primary PFS Analysis in the ITT and PD-L1 IC+ Subgroup



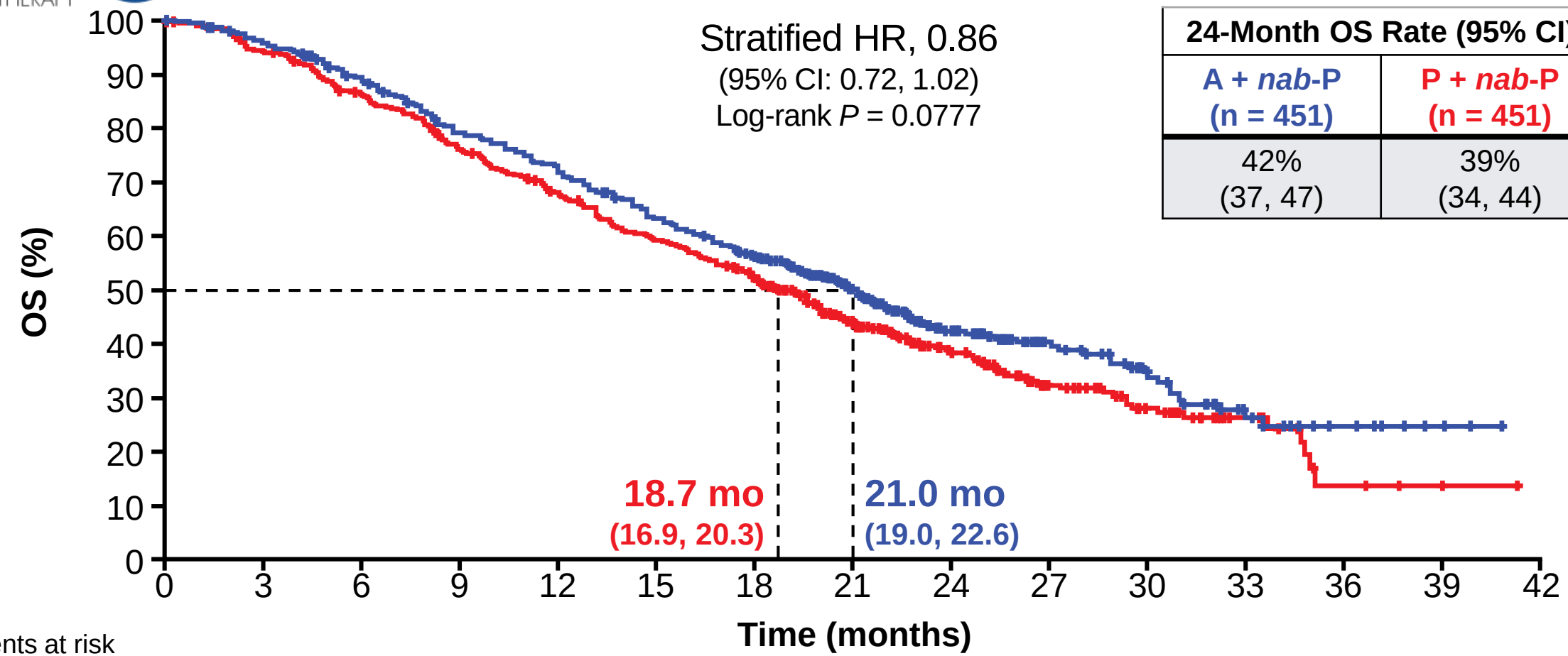


- PFS benefit driven by PD-L1 IC+ patients, as a treatment effect was not observed in PD-L1 IC– patients[1]
- Based on these data,[2] atezolizumab + *nab*-paclitaxel received accelerated approval by the FDA[3] and is recommended for patients with PD-L1 IC+ mTNBC in the NCCN[4] and AGO[5] guidelines

Data cutoff: April 17, 2018. Median follow-up (ITT): 12.9 months.

1. Emens SABCS 2018. 2. Schmid *New Engl J Med.* 2018. 3. Tecentriq (atezolizumab) [package insert]. South San Francisco, CA: Genentech USA, Inc; 2019.
4. NCCN Clinical Practice Guidelines. Breast Cancer. V1.2019. 5. AGO Guidelines Breast Version 2019.1.

OS in ITT Population



24-Month OS Rate (95% CI)	
A + *nab*-P (n = 451)	P + *nab*-P (n = 451)
42% (37, 47)	39% (34, 44)

Patients at risk

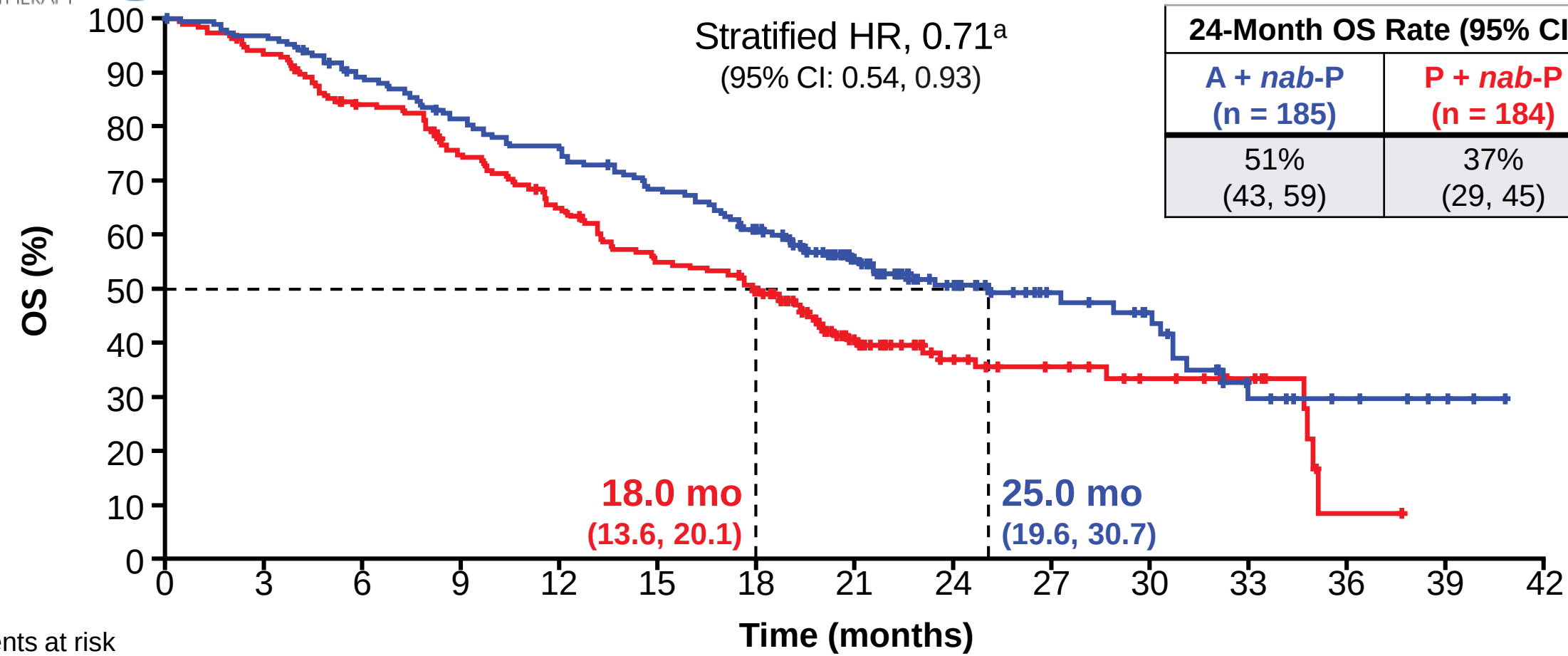
A + *nab*-P	451	426	389	342	312	270	235	162	88	56	35	19	8	3	NE
P + *nab*-P	451	420	376	329	291	252	216	145	87	51	33	17	4	1	NE

NE, not estimable. Clinical cutoff date: January 2, 2019. Median PFS (95% CI) is indicated on the plot. Median FU (ITT): 18.0 mo.

OS in PD-L1+ Population

Stratified HR, 0.71[a]
(95% CI: 0.54, 0.93)

24-Month OS Rate (95% CI)	
A + *nab*-P (n = 185)	P + *nab*-P (n = 184)
51% (43, 59)	37% (29, 45)



Patients at risk

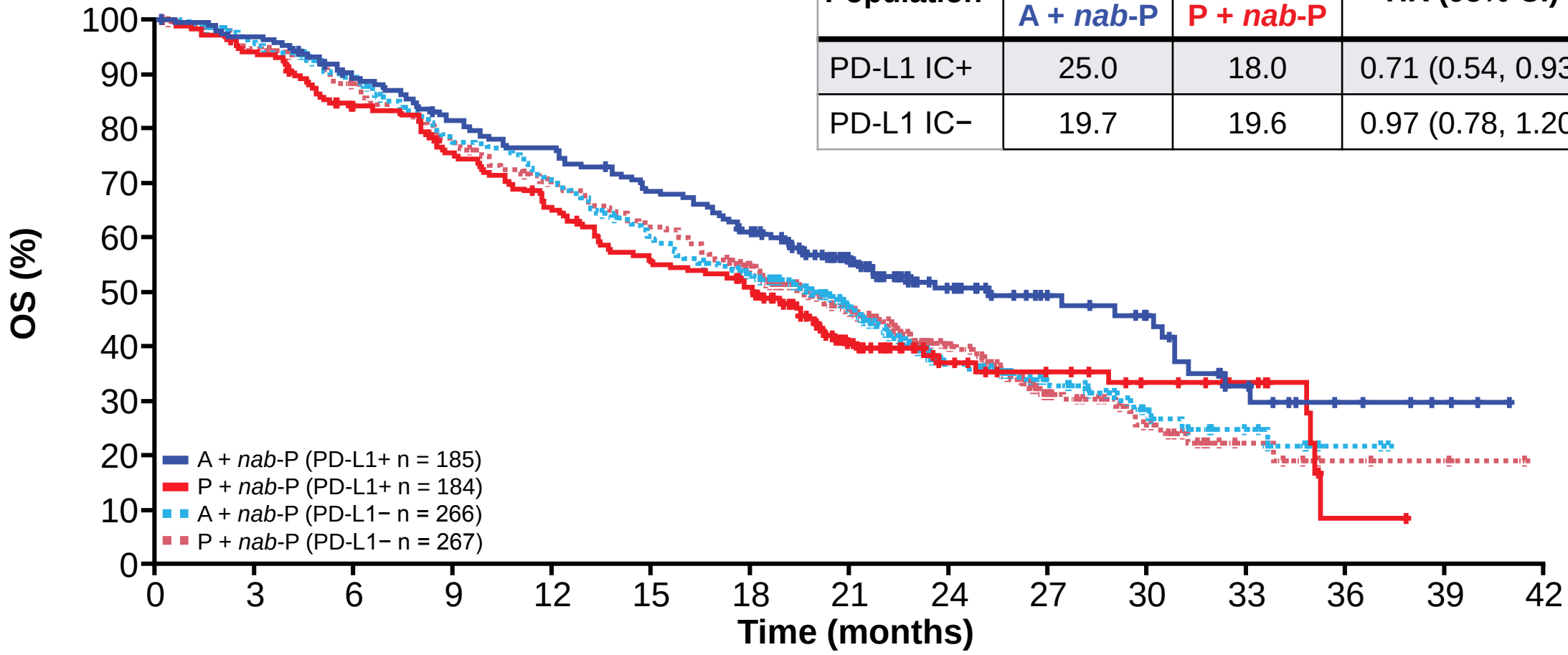
A + *nab*-P	185	177	160	145	135	121	106	69	43	28	21	10	6	3	NE
P + *nab*-P	184	170	147	129	111	93	81	47	26	20	15	10	1	NE	NE

[a] Not formally tested due to pre-specified hierarchical analysis plan.

Clinical cutoff date: January 2, 2019. Median PFS (95% CI) is indicated on the plot. Median FU (ITT): 18.0 months.

Comparison of OS in PD-L1+ and PD-L1− Populations

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)



Clinical cutoff date: January 2, 2019.

Conclusions

- IMpassion130 is the first and only Phase III study to show the clinically meaningful benefit of first-line immunotherapy in mTNBC
- PD-L1 IC status predicts clinical benefit with atezolizumab + *nab*-paclitaxel
- Although not formally testable due to the pre-specified statistical analysis plan, a median OS improvement from 18 to 25 months was observed in the PD-L1+ population (HR, 0.71)
- Atezolizumab + *nab*-paclitaxel was well tolerated, with no cumulative toxicities and no new- or late-onset safety signals
- Atezolizumab + *nab*-paclitaxel sets a new benchmark as the first therapy to cross the 2-year landmark OS benefit in first-line therapy for PD-L1+ mTNBC
- Atezolizumab + *nab*-paclitaxel is approved by the FDA[1] and recommended for the treatment of patients with PD-L1 IC+ mTNBC in the NCCN[2] and AGO[3] guidelines

1. Tecentriq (atezolizumab) [package insert]. South San Francisco, CA: Genentech USA, Inc; 2019. 2. NCCN Clinical Practice Guidelines. Breast Cancer. V1.2019. 3. AGO Guidelines Breast Version 2019.1.

IMPassion130: Summary and Implications

- **FDA accelerated approval for atezolizumab and nab-paclitaxel in PD-L1+ metastatic TNBC on 3/8/19**
  - Continued approval may be contingent upon verification of clinical benefit in confirmatory trials

- **PD-L1+ (PD-L1 stained tumor-infiltrating immune cells [IC]) as "determined by an FDA-approved test"**
  - Ventana PD-L1 (SP142) assay approved as a companion diagnostic for selecting TNBC patients

- **If PD-L1 ≥ 1%, consider atezolizumab and *nab*-paclitaxel if**
  - No previous treatment in the metastatic setting **i.e. first-line**
  - Previous curative chemotherapy completed ≥ 12 months
  - Counsel modest PFS benefit, undefined OS benefit

Phase III Clinical Trials with Immunotherapy for Breast Cancer

Study of Pembrolizumab plus Chemotherapy vs Placebo plus Chemotherapy for Previously Untreated Metastatic TNBC	NCT02819518 KEYNOTE-355	Metastatic with no prior systemic therapy for metastatic disease	Not recruiting	858	Experimental: 1) nab-paclitaxel + pembrolizumab 2) paclitaxel + pembrolizumab 3) gemcitabine + carboplatin + pembrolizumab Comparator: 1) nab-paclitaxel + placebo 2) paclitaxel + placebo 3) gemcitabine + carboplatin + placebo
A Study of Atezolizumab and Paclitaxel vs Placebo and Paclitaxel in Participants with Previously Untreated Metastatic TNBC	NCT03125902 IMpassion131	Metastatic with no prior systemic therapy for metastatic disease	Not recruiting	540	Experimental: paclitaxel + atezolizumab Comparator: paclitaxel + placebo
A Study of the Efficacy and Safety of Atezolizumab plus Chemotherapy for Patients with Early Relapsing Recurrent TNBC	NCT03371017 IMpassion132	Metastatic; disease progression within 12 months from last treatment of curative intent	Recruiting	350	Experimental: gemcitabine + carboplatin + atezolizumab OR capecitabine + atezolizumab Comparator: gemcitabine + carboplatin + placebo OR capecitabine + placebo

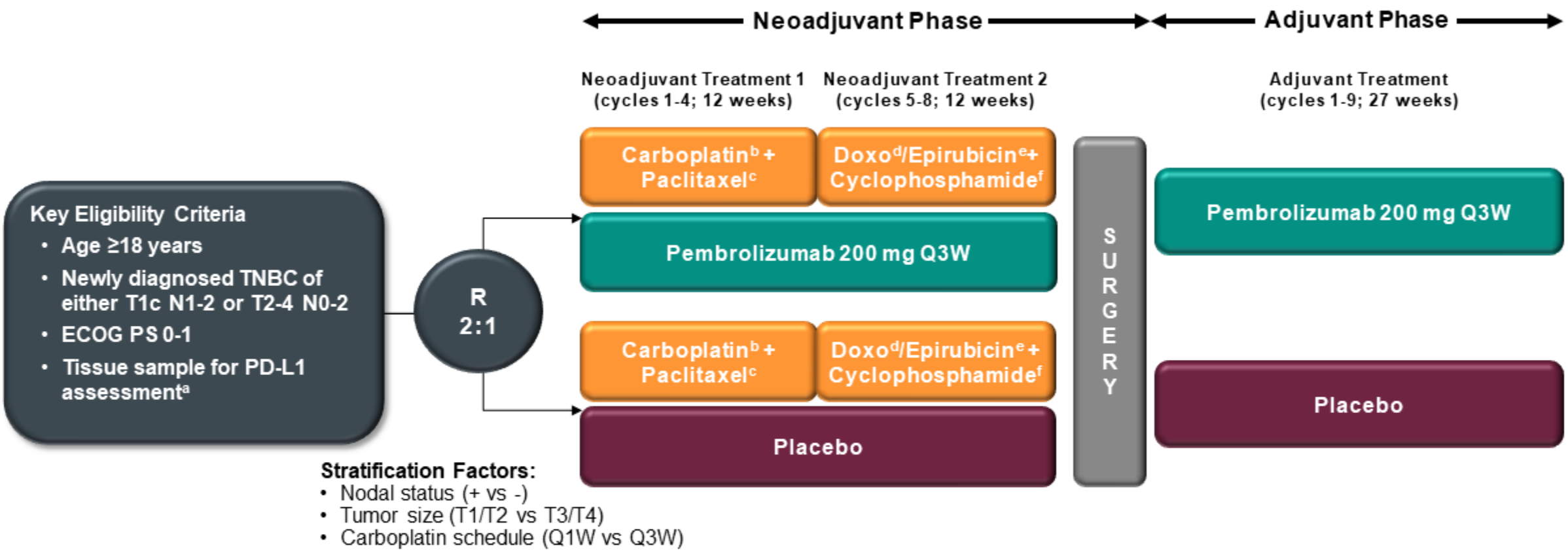
Neoadjuvant Setting

Background

- Patients with TNBC who achieve pathological complete response (pCR) after neoadjuvant chemotherapy have sustained clinical benefit[1,2]
- Taxane- and anthracycline-based neoadjuvant regimens produce pCR rates of ~40%[3]; addition of platinum increases pCR rates to ~50-55%[4-7]
- Meta-analysis of individual patient data showed a strong association of pCR after neoadjuvant chemotherapy with improved long-term EFS (HR 0.24) and OS (HR 0.16) benefit[8]
- Neoadjuvant pembrolizumab + chemotherapy showed manageable safety and antitumor activity in early TNBC[9,10]

1. Cortazar P et al. *Lancet* 2014;384:164-72. 2. Huang M et al. Poster. ESMO Breast Cancer; May 2-4, 2019; Berlin, Germany. 3. Loibl S et al. *Ann Oncol* 2019;30:1279-88. 4. von Minckwitz G et al. *Lancet Oncol* 2014;15:747-56. 5. Sikov WM et al. *J Clin Oncol* 2015;33:13-21. 6. Petrelli F et al. *Breast Cancer Res Treat* 2014;14:223-32. 7. Loibl S et al. *Lancet Oncol* 2018;19:497-509. 8. Spring LM et al. *Cancer Research* 2019;79:Abstract GS2-03. 9. Schmid P et al. *J Clin Oncol* 2017;35(15S):Abstract 556. 10. Nanda R et al. *J Clin Oncol* 2017;35;(15S):Abstract 506.

KEYNOTE-522 Study Design (NCT03036488)



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)

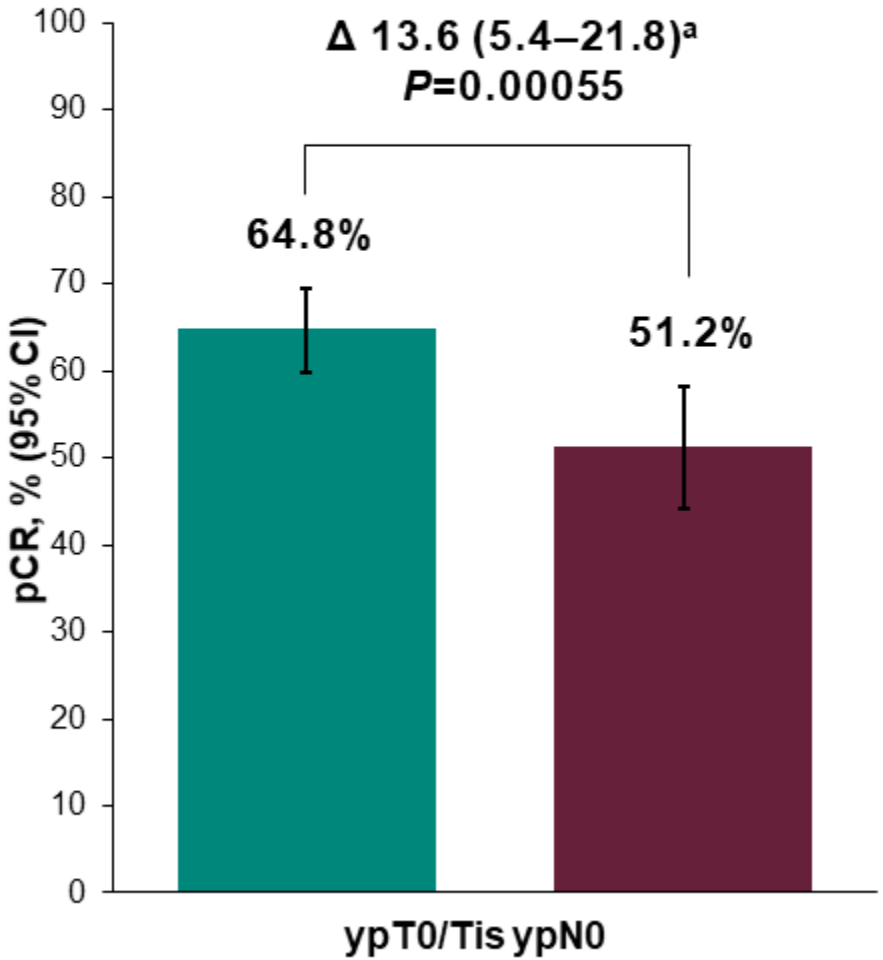
[a]Must consist of at least 2 separate tumor cores from the primary tumor.
[b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 Q1W.
[c]Paclitaxel dose was 80 mg/m^2 Q1W.
[d]Doxorubicin dose was 60 mg/m^2 Q3W.
[e]Epirubicin dose was 90 mg/m^2 Q3W.
[f]Cyclophosphamide dose was 600 mg/m^2 Q3W.

Baseline Characteristics, ITT Population

Characteristic, n (%)	All Subjects, N = 602	
	Pembro + Chemo N = 401	Placebo + Chemo N = 201
Age, median (range), yrs	49 (22-80)	48 (24-79)
ECOG PS 1	73 (18.2)	28 (13.9)
PD-L1–positive[a]	334 (83.3)	164 (81.6)
Carboplatin schedule		
Q1W	167 (41.6)	83 (41.3)
Q3W	234 (58.4)	118 (58.7)
Tumor size		
T1/T2	296 (73.8)	148 (73.6)
T3/T4	105 (26.2)	53 (26.4)
Nodal involvement		
Positive	208 (51.9)	104 (51.7)
Negative	193 (48.1)	97 (48.3)

[a]PD-L1 assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay and measured using the combined positive score (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. Data cutoff date: September 24, 2018.

Definitive pCR Analysis



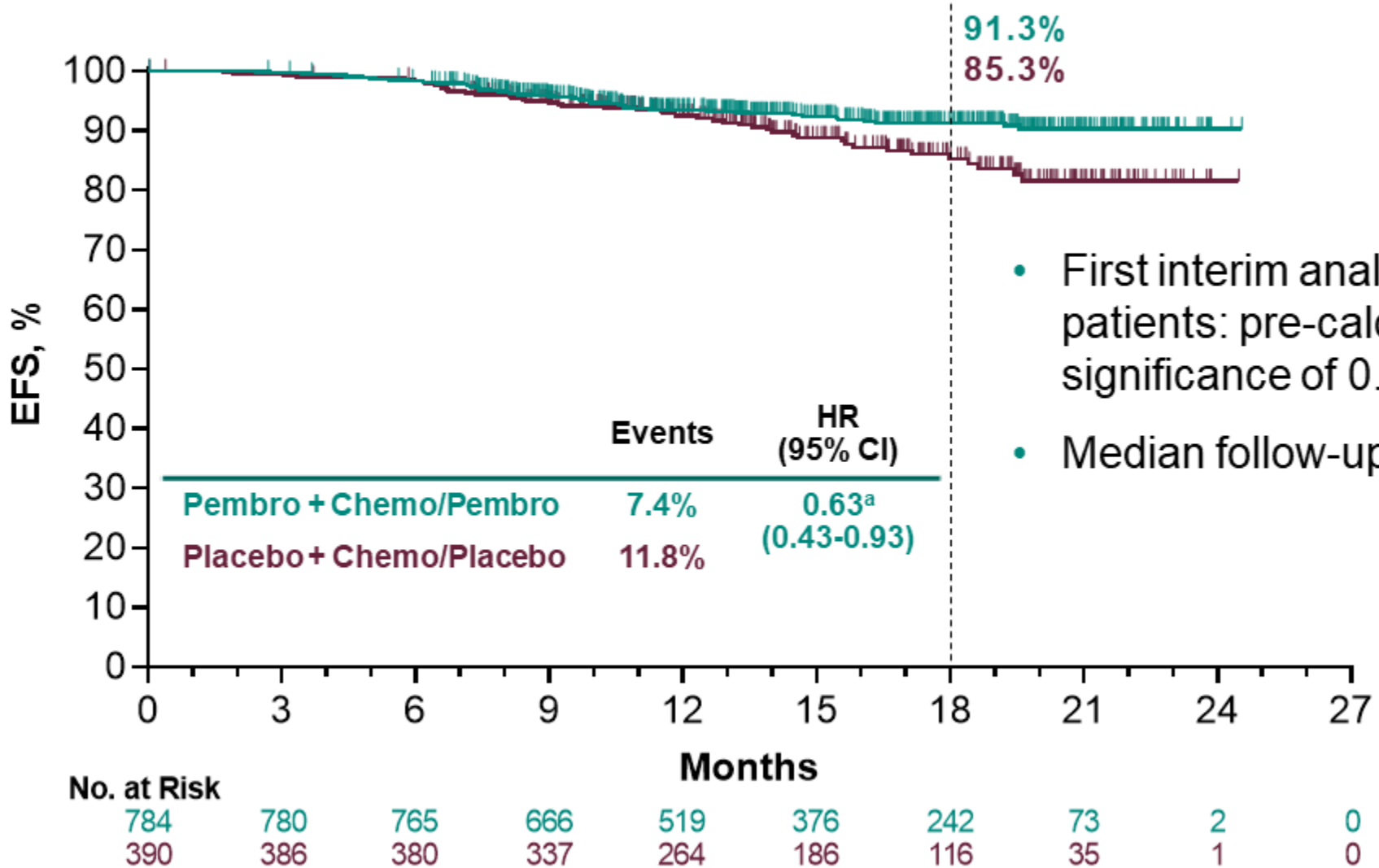
- Definitive pCR analysis to test primary hypothesis of pCR based on prespecified first 602 patients (pre-calculated P value boundary for significance of 0.003)
- Consistent benefit seen with pCR defined as ypT0 ypN0 and ypT0/Tis

Placebo + Chemo

Pembro + Chemo

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

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.

KEYNOTE-522: Conclusions

- In patients with early-stage TNBC, neoadjuvant pembrolizumab + chemotherapy associated with a larger pCR benefit vs chemo alone
  - Particularly for patients with stage III or node-positive disease
  - Benefit seen in patients who received less than planned full chemotherapy
  - Similar benefit observed regardless of PD-L1 expression level

- Neoadjuvant pembrolizumab added to chemotherapy associated with higher rate of lower residual cancer burden

- Rate of immune-mediated adverse events in study consistent with that reported previously and no new safety signal observed

- Additional follow-up needed to confirm EFS benefit and long-term safety profile

Schmid. SABCS 2019. Abstr GS3-03.

Design of the NeoTRIP trial

*HER-2 negative, ER and PgR negative early high-risk **(T1cN1; T2N1; T3N0)** or locally advanced unilateral breast cancer

N = 280

R

Carboplatin (AUC2) + *nab*-paclitaxel (125 mg/m²) weekly for 2 wks every 3; 8 cy → **S** → **AC/EC/FEC** for 4 cycles

Carboplatin (AUC2) + *nab*-paclitaxel (125 mg/m²) weekly for 2 wks every 3; 8 cy **+ Atezolizumab (1200 mg)** day 1 every 3 wks for 8 cycles → **S** → **AC/EC/FEC** for 4 cycles

→ **FOLLOW UP**

Tumour & Blood banked for correlative studies

*Estrogen receptor, progesterone receptor, HER2 and PD-L1 were centrally assessed before randomization

NeoTrip ITT Analysis: pCR rate

	ITT population	
	With atezo (138)	**No atezo** (142)
% pCR rate	**43.5**	**40.8**
95% CI	35.1-52.2	32.7-49.4
Difference: atezo vs no atezo (95% CI)	**2.63** (14.0-8.8)	
***Odds ratio (95% CI)**	**1.11 (0.69-1.79)**	
***p-value**	**0.66**	

*Cochran-Mantel-Haenszel test, controlling for PD-L1 expression and disease stage and quantified by OR and rate difference

NeoTrip Conclusions

- The addition of atezolizumab to *nab*-paclitaxel and carboplatin did not significantly increase the rate of pCR in women with TNBC
- In multivariate analysis the presence of PD-L1 expression was the most significant factor influencing rate of pCR (OR 2.08)
- Treatment-related adverse events were similar with either regimen except for a significantly higher overall incidence of SAEs and liver transaminases abnormalities with atezolizumab.
- Continuous follow up for the primary endpoint of EFS and other efficacy end points is ongoing, and molecular studies are under way

Toxicities with Adding Checkpoint Inhibitor to Neoadjuvant Chemotherapy in Breast Cancer

Any immune-mediated adverse events

AE	KN 522		NeoTRIP	
	Pembro	No Pembro	Atezo	No Atezo
Thyroid abnormalities	21.7%	8.5%	8.0%	1.4%
Skin reaction	5.5%	1.0%	0%	0%
Adrenal insufficiency + Hypophysitis	4.5%	0.3%	0%	0%
Pneumonitis	1.9%	1.5%	0%	0%
Hepatitis	1.4%	0.5%	0.7%	0%
Colitis	1.8%	1.0%	1.5%	0%

Schmid P et al SABCS 2019; Gianni L et al SABCS 2019; Nanda R et al ASCO meeting 2017
Slide courtesy from Dr. Kevin Kalinsky

Post-Neoadjuvant Immunotherapy

- Given that patients with residual disease after neoadjuvant chemotherapy for TNBC have a very poor prognosis, there are a number of clinical trials attempting to optimize therapy for this extremely high-risk population

- Immunotherapy may be a good opportunity for a subset of these patients

Residual Disease after Neoadjuvant Chemotherapy: Role of Checkpoint Inhibitor?

Surgery: Pathologic Complete Response → Cure

Adjuvant checkpoint inhibitor trials

Trial	N	Intervention
A-BRAVE	335	Avelumab x 1 year vs. observation
IMPASSION030	2300	Weekly paclitaxel, DDAC (or EC) +/- atezolizumab x 1 year

SWOG S1418: Residual disease

TNBC: ≥ 1 cm residual invasive cancer or + LN

Randomization

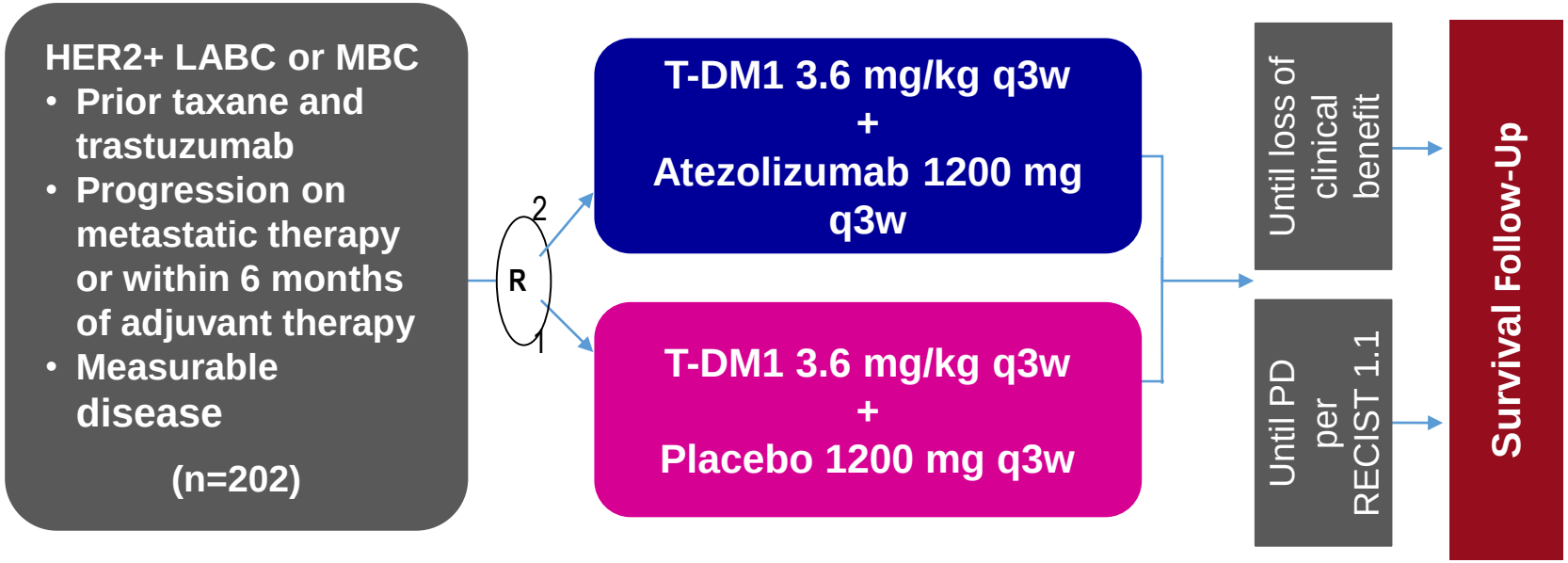
- Pembrolizumab
- Observation

Primary Endpoint: IDFS Overall and PD-L1+

Adapted from Adams S et al JAMA Oncology 2019

Slide courtesy from Dr. Kevin Kalinsky

KATE2: STUDY DESIGN
Efficacy endpoints in the ITT population



Primary endpoint:
- Investigator-assessed PFS

Secondary endpoints:
- OS
- Objective response rate
- Duration of response

Exploratory endpoints:
- PFS in patients with PD-L1+ disease
- Exploratory biomarker subgroups (PD-L1, PIK3CA mutation status, HER2 expression, immune-related [TILs, CD8 IHC expression])

Post hoc endpoint:
- ***OS in PD-L1 subgroups***

Stratification factors:
- Tumour PD-L1 IC status (IC0 [<1%] vs IC1/2/3 [≥1%])[a]
- World region (Western Europe vs North America vs rest of world)
- Presence of liver metastases (yes or no)

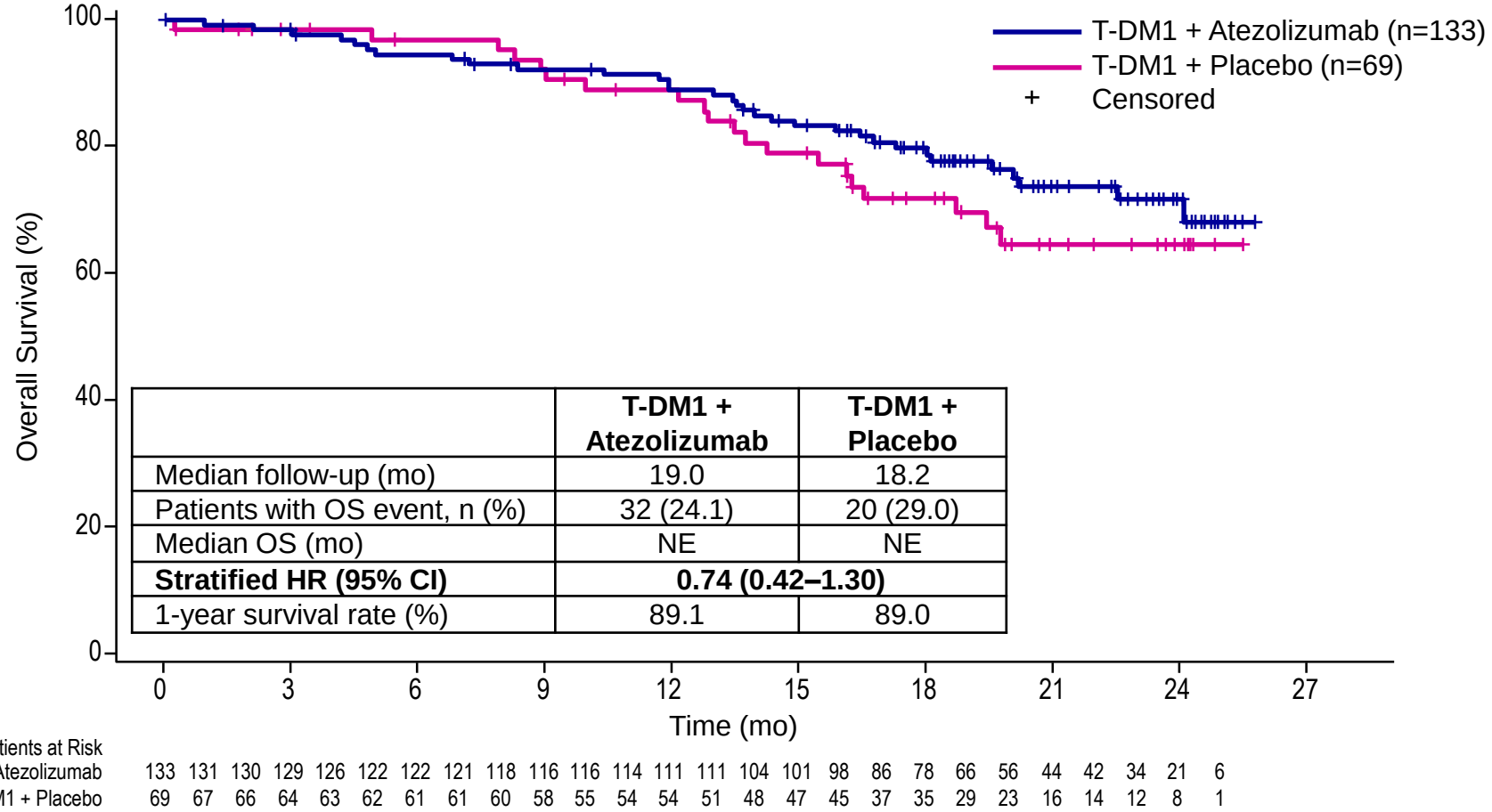
[a] Determined using VENTANA SP142.

- Data cutoff for primary analysis: 11 December 2017
- Data cutoff for OS analysis: 11 December 2018

IC, tumour-infiltrating immune cell; IHC, immunohistochemistry; ITT, intention-to-treat; LABC, locally advanced breast cancer; MBC, metastatic breast cancer; OS, overall survival; PD, progressive disease; PFS, progression-free survival; TIL, tumour-infiltrating lymphocyte.

Access slides at: https://bit.ly/2NGiaqZ

KATE2: Overall Survival in ITT Population



	T-DM1 + Atezolizumab	T-DM1 + Placebo
Median follow-up (mo)	19.0	18.2
Patients with OS event, n (%)	32 (24.1)	20 (29.0)
Median OS (mo)	NE	NE
Stratified HR (95% CI)	**0.74 (0.42–1.30)**	
1-year survival rate (%)	89.1	89.0

No. of Patients at Risk

T-DM1 + Atezolizumab	133	131	130	129	126	122	122	121	118	116	116	114	111	111	104	101	98	86	78	66	56	44	42	34	21	6
T-DM1 + Placebo	69	67	66	64	63	62	61	61	60	58	55	54	54	51	48	47	45	37	35	29	23	16	14	12	8	1

- With 52 OS events reported, median OS was not reached in either arm
- 1-year OS was similar in both arms

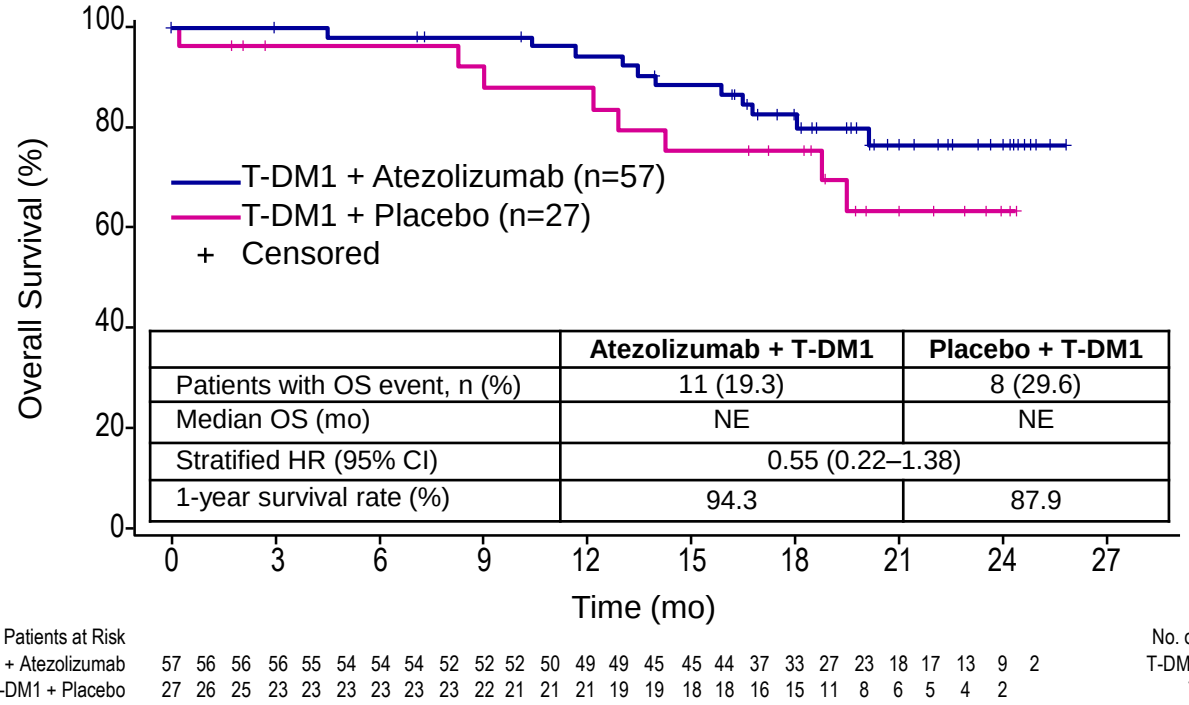
Access slides at: https://bit.ly/2NGiaqZ

11 December 2018 cutoff date

CI, confidence interval; HR, hazard ratio; NE, not estimable; ITT, intention-to-treat; OS, overall survival.

KATE2: Overall Survival in PD-L1 IC+ and PD-L1 IC− Subgroups

OS in PD-L1 IC+ Subgroup (IC 1/2/3)

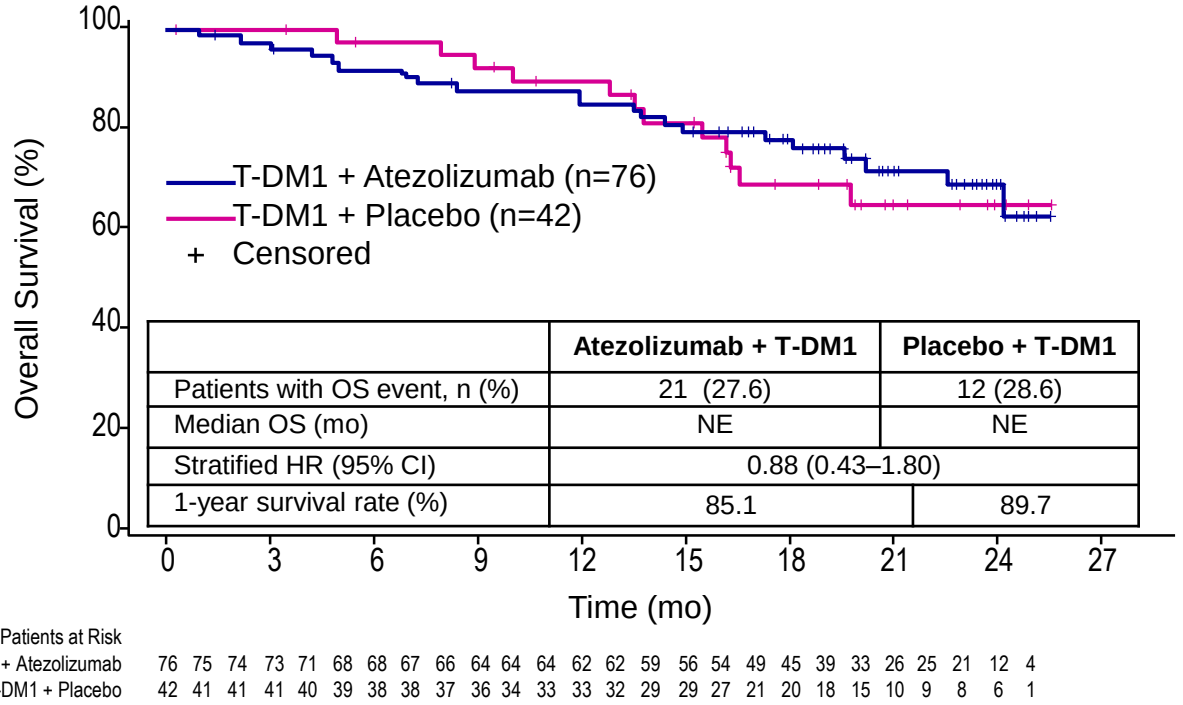


	Atezolizumab + T-DM1	Placebo + T-DM1
Patients with OS event, n (%)	11 (19.3)	8 (29.6)
Median OS (mo)	NE	NE
Stratified HR (95% CI)	0.55 (0.22–1.38)	
1-year survival rate (%)	94.3	87.9

No. of Patients at Risk

T-DM1 + Atezolizumab	57	56	56	56	55	54	54	54	52	52	52	50	49	49	45	45	44	37	33	27	23	18	17	13	9	2
T-DM1 + Placebo	27	26	25	23	23	23	23	23	23	22	21	21	21	19	19	18	18	16	15	11	8	6	5	4	2	

OS in PD-L1 IC− Subgroup (IC 0)



	Atezolizumab + T-DM1	Placebo + T-DM1
Patients with OS event, n (%)	21 (27.6)	12 (28.6)
Median OS (mo)	NE	NE
Stratified HR (95% CI)	0.88 (0.43–1.80)	
1-year survival rate (%)	85.1	89.7

No. of Patients at Risk

T-DM1 + Atezolizumab	76	75	74	73	71	68	68	67	66	64	64	64	62	62	59	56	54	49	45	39	33	26	25	21	12	4
T-DM1 + Placebo	42	41	41	41	40	39	38	38	37	36	34	33	33	32	29	29	27	21	20	18	15	10	9	8	6	1

- In the PD-L1 IC+ subgroup, the 1-year OS rate was numerically higher in the atezolizumab + T-DM1 arm than in the placebo + T-DM1 arm

Access slides at: https://bit.ly/2NGiaqZ

CI, confidence interval; HR, hazard ratio; IC, tumour-infiltrating immune cell; NE, not estimable; OS, overall survival.

11 December 2018 cutoff date

NRG BR-004 Schema

HER2-Positive, First-line Metastatic Breast Cancer

STRATIFICATION

- Prior adjuvant or neoadjuvant trastuzumab (yes; no)
- Prior pertuzumab or neratinib in adjuvant or neoadjuvant setting (yes; no)
- Estrogen receptor status (positive; negative)
- PD-L1 status (positive; negative)

RANDOMIZATION

Arm 1

Weekly Paclitaxel
+
Trastuzumab + Pertuzumab every 3 weeks until progression
+
Placebo every 3 weeks until progression or 2 years

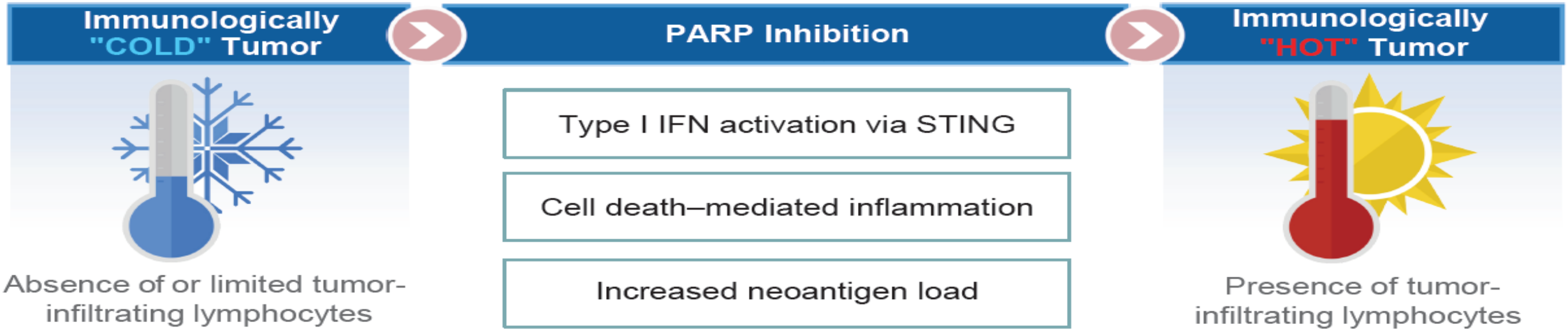
Arm 2

Weekly Paclitaxel
+
Trastuzumab + Pertuzumab every 3 weeks until progression
+
Atezolizumab 1200 mg every 3 weeks until progression or 2 years

Weekly Paclitaxel (WP): 80 mg/m2 IV Days 1, 8, 15, 22, 29, and 36 every 6 weeks for 4 cycles

NCT03199885

PARP Inhibition May Enhance Immune Surveillance Through Multiple Mechanisms



- Phase II trial in TNBC (TOPACIO)
  - Niraparib and pembrolizumab
  - Primary endpoint: ORR
- 55 patients enrolled, 47 evaluable for efficacy
- 5 CRs, 5 PRs, 13 SD
- In 15 evaluable patients with tumor *BRCA* mutations, ORR included 7 patients (47%)
- In 27 evaluable patients with *BRCA* wild-type tumors, ORR included 3 patients (11%)

- Phase II trial in TNBC (MEDIOLA)
  - Olaparib and durvalumab
  - Primary endpoint: ORR
- 30 patients enrolled
- 19 responders, ORR 63.3%
- Median duration of response: 9.2 months

Vinayak S, et al. JAMA Oncol 2019; 5:1132-1140
Domchek S, et al. ESMO 2019 (abstr 11910)

Case Studies

Case Study 1

A 46-year-old premenopausal female presents with a palpable mass in the right breast.

On mammogram, there is a 4 cm mass in the right breast and a 1.5 cm mass in the right axilla.

Ultrasonography-guided core needle biopsy of the breast mass reveals a poorly differentiated, estrogen receptor-negative, progesterone receptor-negative, *HER2*-negative invasive ductal cancer. Biopsy of the right axillary node is also positive.

She undergoes genetic testing and does not have germline BRCA 1/2 mutation.

She undergoes neoadjuvant doxorubicin and cyclophosphamide followed by paclitaxel and carboplatin followed by lumpectomy and sentinel lymph node biopsy. Nodes are clear but she has residual 2 cm of breast tumor.

She undergoes radiation therapy and 6 cycles of adjuvant capecitabine.

Case Study 1

Fifteen months after completing chemotherapy, she presents with abdominal pain.

CT scan CAP reveals numerous liver lesions.

Do you:

A. Start gemcitabine and carboplatin
B. Biopsy the liver lesion and then start gemcitabine and carboplatin
C. Biopsy the liver lesion and then start nab-paclitaxel and atezolizumab
D. Biopsy the liver lesion, send sample for PD-L1 testing, and if positive, start nab-paclitaxel and atezolizumab

Case Study 2

A 31 year old female presents with de novo metastatic breast cancer. She presents with a palpable left breast mass measuring 4.5 cm and left axillary adenopathy. Both the breast mass and left axillary node undergo biopsy and consistent with a ER0%, PR0%, and HER2-negative (IHC0) breast cancer. Staging studies performed. A CT scan shows numerous pulmonary nodules. She is asymptomatic.

What would you do next?

A. Start nab-paclitaxel and atezolizumab immediately

B. Biopsy the lung nodule to confirm is TNBC and refer to genetic counselor for BRCA testing.

C. Biopsy the lung nodule, send it for PD-L1 testing, and refer to genetic counselor for BRCA testing.

Case Study 2

You find out that her lung nodule is consistent with triple-negative breast cancer. It is PD-L1 positive immune cells. Her genetic test comes back as having a pathogenic mutation in BRCA1.

What would you do next?

A. Start nab-paclitaxel and atezolizumab.

B. Start PARP inhibitor.

C. Start gemcitabine and carboplatin.

D. Start PARP inhibitor and a checkpoint inhibitor.