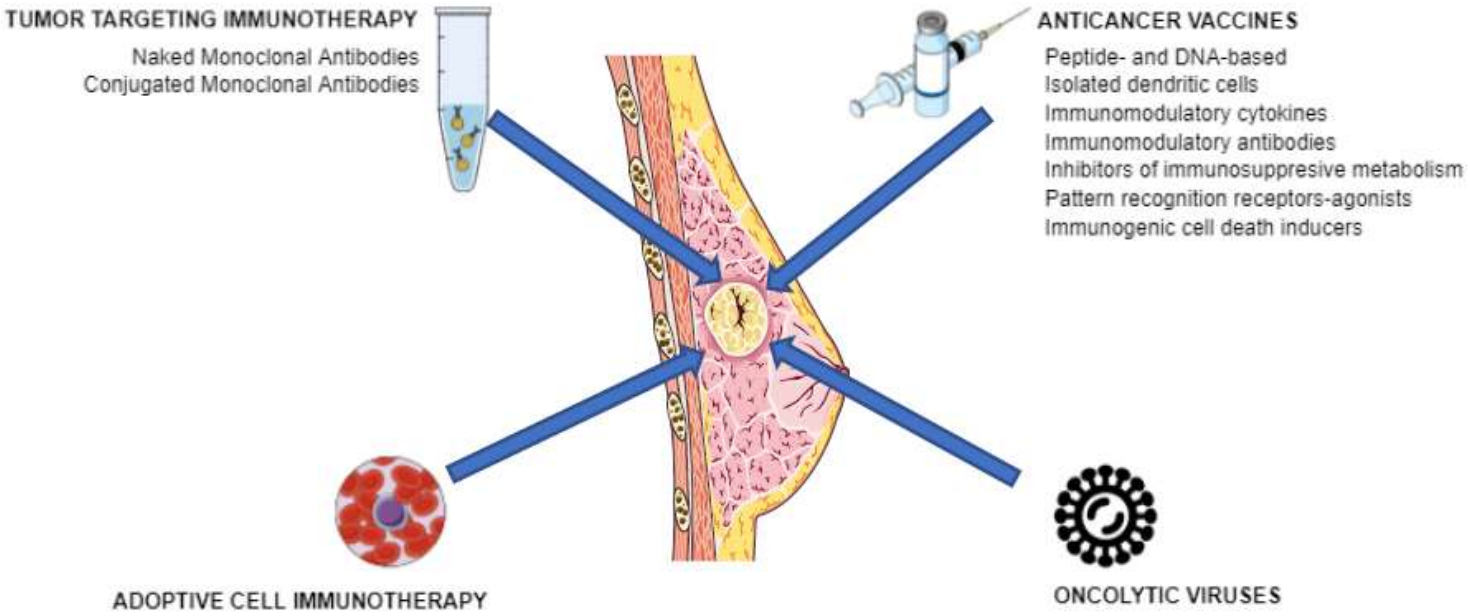
Immunotherapy for Breast Cancer

Richard S. Finn, MD
Professor of Clinical Medicine
Division of Hematology/Oncology
Director, Signal Transduction and Therapeutics Program
Jonsson Comprehensive Cancer Center
Geffen School of Medicine at UCLA

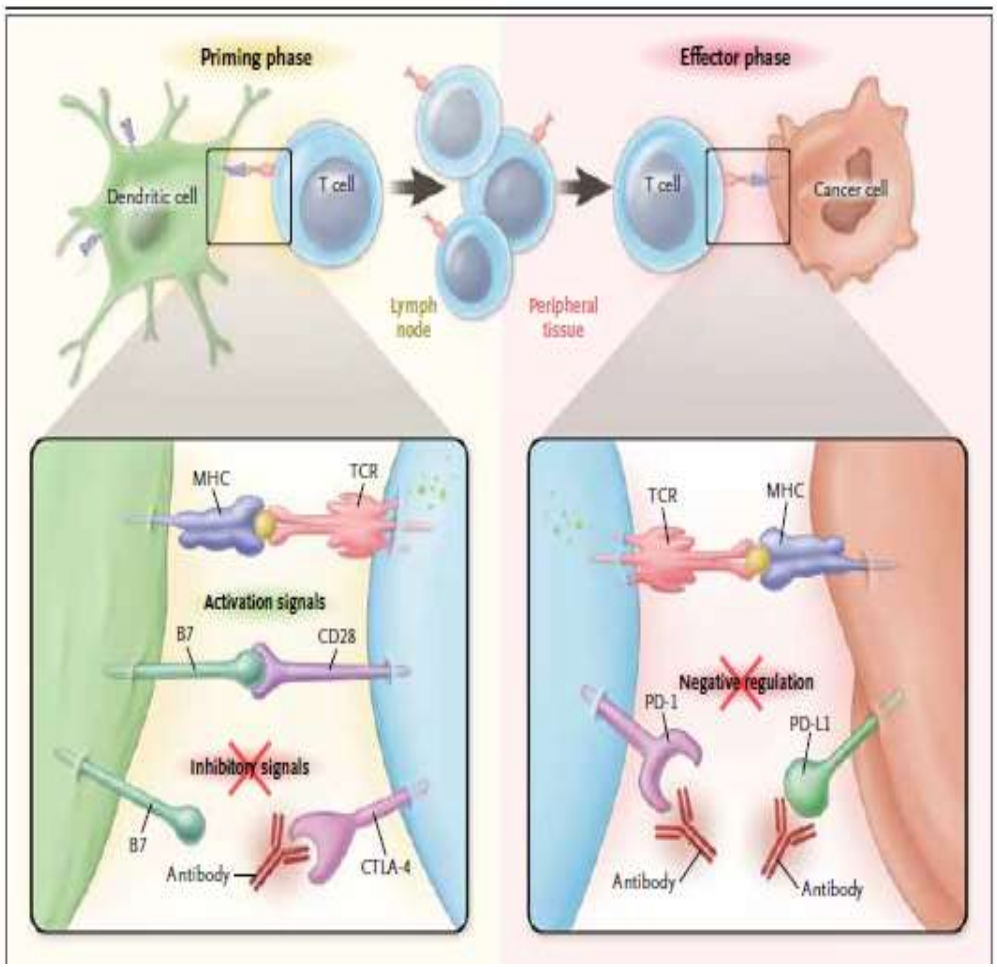
Disclosures

- Consultant: Astra Zeneca, Bayer, BMS, Eisai, Eli-Lilly, Merck, Novartis, Pfizer, Roche/ Genentech

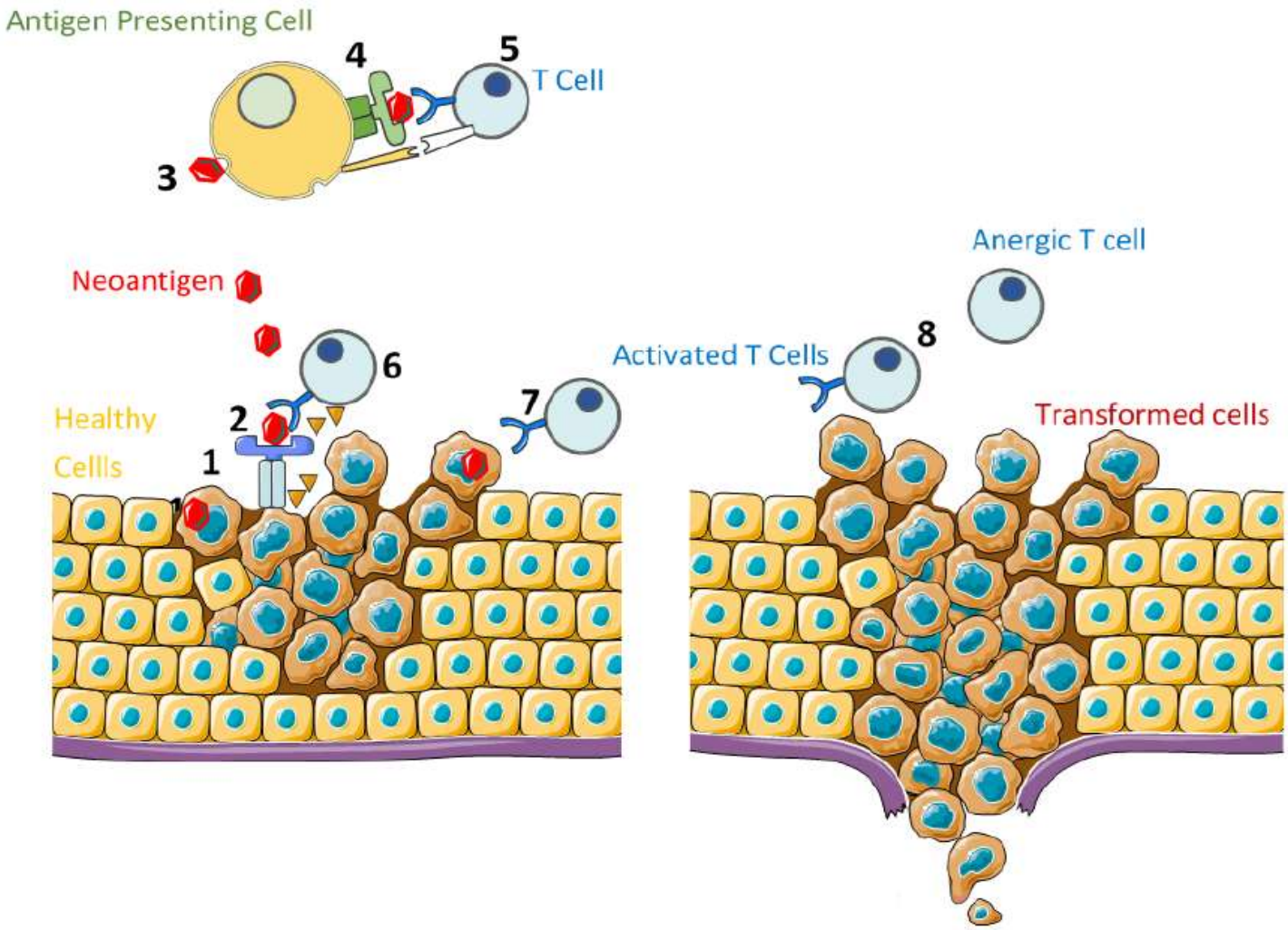
Immunotherapy in Breast cancer



Garcia-Aranda et al Cancers 2019

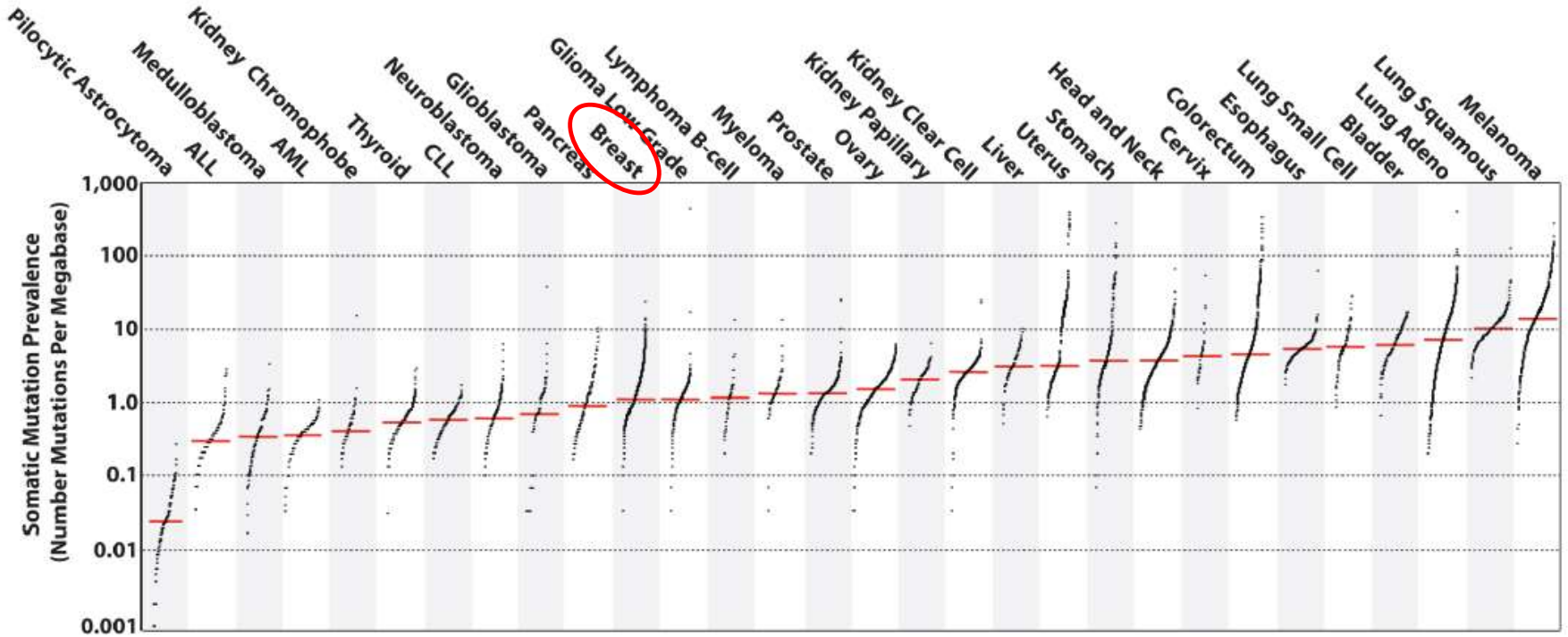


Ribas NEJM 2012



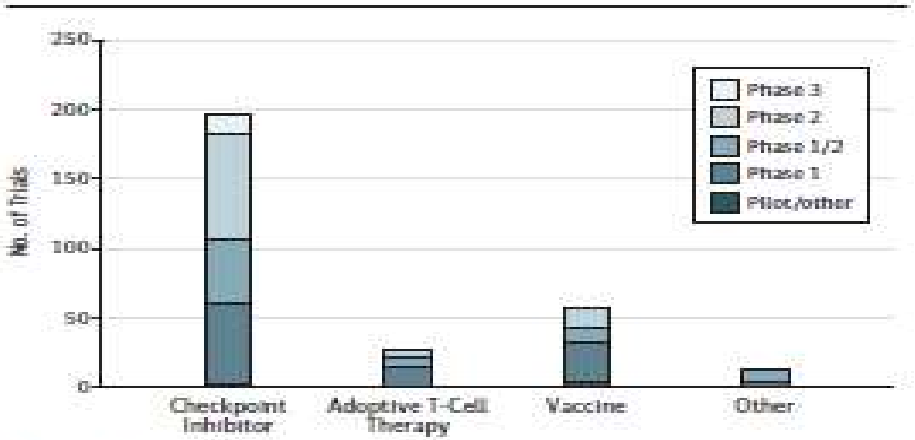
Garcia-Aranda et al Cancers 2019

Tumor Mutational Burden



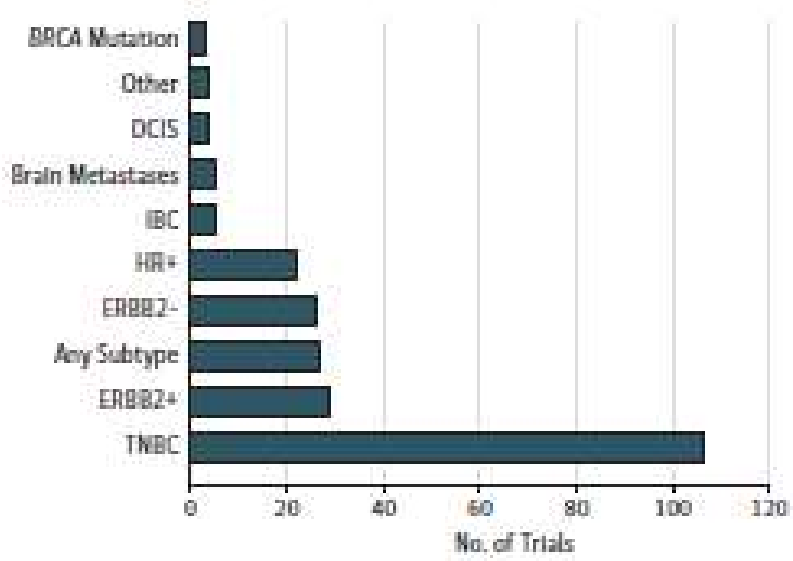
Alexandrov et al Nature 2014

Trials by Immunotherapy Approach



No. of trials	Checkpoint Inhibitor	Adoptive T-Cell Therapy	Vaccine	Other
Phase 3	13	0	0	0
Phase 2	76	6	14	1
Phase 1/2	46	7	11	9
Phase 1	59	14	29	2
Pilot/other	2	0	3	1

Trials by Breast Cancer Subtype



Adams et al JAMA Oncology 2019

Rationale for I-O in Breast Cancer

- Heterogeneous disease representing molecular and clinical sub-types
- Initial single agent studies with PD-1/PDL-1 inhibitors had low response rates (<10%) suggesting breast cancer was not an immunologically active cancer
- Some subtypes more promising
  - HER2 amplified and Triple-negative: higher tumor mutational burden and higher number of tumor infiltrating lymphocytes (TILs)
  - Higher TILs correlated with better response to neoadjuvant therapy

Single agent Checkpoint Studies in Breast cancer

Source (Name)	Population and Line of Therapy	Evaluable Patients, No.	Safety Profile	ORR, %	Median Survival, mo	
					PFS	OS
Monotherapy						
Phase 1b; pembrolizumab; KEYNOTE-012[17]	mTNBC, PD-L1+, 15.6% 1st line	27	15.6% Gr 3-5 AEs; 5 Gr 3 AEs: anemia, aseptic meningitis, lymphopenia, headache, pyrexia; 1 death (DIC)	18.5	1.9	11.2
Phase 1a; atezolizumab[19]	mTNBC, PD-L1+, later expanded to include PD-L1−, 17% 1st line	115	11% Gr 3/4 treatment-related AEs, 2% Gr 5 treatment-related AEs (1 pulmonary hypertension, 1 not specified)	10 (12 for PD-L1+, 0 for PD-L1−	1.4	8.9
Phase 1b; avelumab; JAVELIN[22]	mBC, PD-L1+/− (58 TNBC, 72 HR+/ERBB2−, 26 ERBB2+), 1st to 4th line	168	14.3% Gr 3-5 AEs, immune-related events, autoimmune hepatitis (1.8%); 2 treatment-related deaths (acute liver failure, respiratory distress)	4.8 (33 for PD-L1+, 2.4 for PD-L1−); 5.2 for TNBC, 2.8 for HR+/ERBB2−, 0 for ERBB2+	5.9	8.1
Phase 1b; pembrolizumab; KEYNOTE-028[23]	HR+ mBC, PD-L1+, prior chemo/endocrine therapy allowed	25	16% Gr 3-4 AEs, immune-related AEs included hepatitis, pneumonitis, hyperthyroidism/hypothyroidism	12	1.8	8.6
Phase 2; pembrolizumab; KEYNOTE-086 Cohort A[20]	mTNBC, PD-L1+/−, 2nd line and beyond	170	12% with Gr 3-4 AEs; 19% with irAEs of any grade, of which 1.2% were Gr 3-4 (most common: hypothyroidism/ hyperthyroidism, pneumonitis)	4.7 (4.8 PD-L1+, 4.7 PD-L1−)	2	8.9
Phase 2; pembrolizumab; KEYNOTE-086 Cohort B[21]	mTNBC, PD-L1+, 1st line	84	10% Gr 3-4 AEs; no discontinuations or deaths due of treatment-related AEs	23.1	2.1	NA

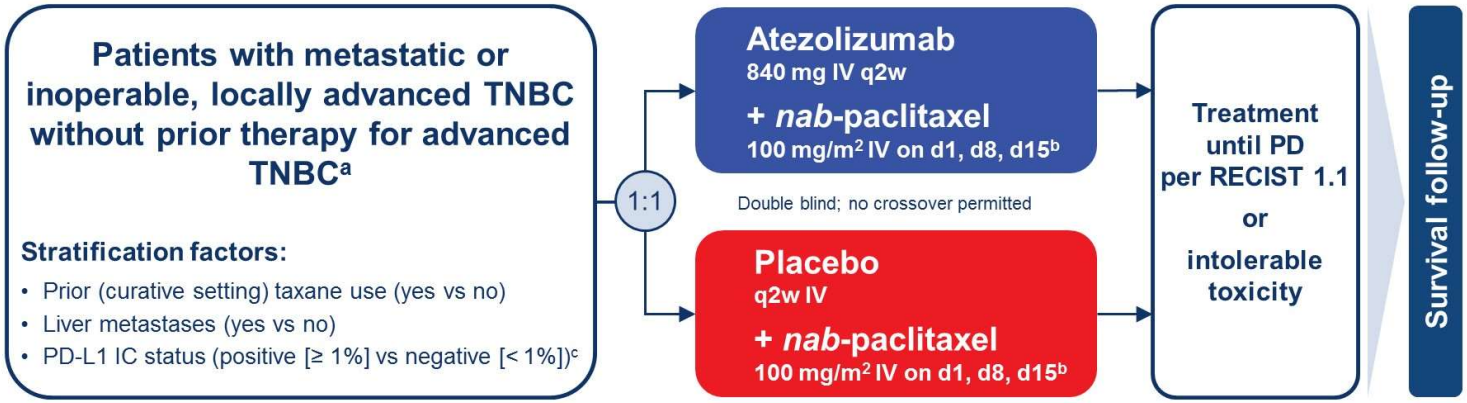
Adams et al JAMA Oncology 2019

Combination Checkpoint Studies in Breast cancer

Combination Therapy						
Phase 1b; atezolizumab + nab-paclitaxel[24]	mTNBC, PD-L1 +/−, 1st to 3rd line	33	73% Gr 3-4 treatment-related AEs, most common: neutropenia, anemia, thrombocytopenia, diarrhea, pneumonia.	39	5.5	14.7
Phase 1b/2; pembrolizumab + eribulin mesylate; ENHANCE[25]	mTNBC, PD-L1 +/−, 1st to 3rd line	107	No DLTs, 66.7% Gr 3-4 AEs; most common, neutropenia and fatigue; most common immune-related AEs hypothyroidism/hyperthyroidism, rash, hyperglycemia, and pneumonitis	26.4	4.2	17.7
Phase 1b; pembrolizumab + abemaciclib; JPCE[26]	HR+, ERBB2− mBC, treatment line NA	28	28.6% serious AEs: Gr 5 AEs, 3.6%; no Gr 4 AEs; Gr 3 AEs: diarrhea (10.7%), neutropenia (28.6%), AST increase (14.3%), ALT (10.7%)	28.6	NA	NA
Phase 2; durvalumab + olaparib; MEDIOLA[27]	*BRCA1/2*-mutated, ERBB2− mBC, 1st and later lines	25	Gr 3-4 AEs were anemia (8%), neutropenia (8%), hemolysis (4%), dyspnea (4%), pancreatitis (4%), fatigue (4%), lymphopenia (4%), and leukopenia (4%)	52 (Includes unconfirmed responses)	NA	NA
Phase 2; niraparib + pembrolizumab; TOPACIO[28]	mTNBC, 1st to 3rd line	46	Gr 3-4 AEs were fatigue (7%), anemia (15%), and thrombopenia (13%)	28 (Includes unconfirmed responses)	NA	NA
Phase 1/2; pembrolizumab + trastuzumab; PANACEA[29]	ERBB2+ mBC, 2nd line and later	58	No DLTs, 19% immune-related AEs (most common, thyroid and pneumonitis)	15.2 for PD-L1+; 0 for PD-L1−	2.7 for PD-L1+,; 2.5 for PD-L1−	17.1 for PD-L1+; 7 for PD-L1−
Phase 1 tremelimumab + exemestane[30]	HR+ mBC	26	5 DLTs	0	NA	NA

Adams et al JAMA Oncology 2019

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.

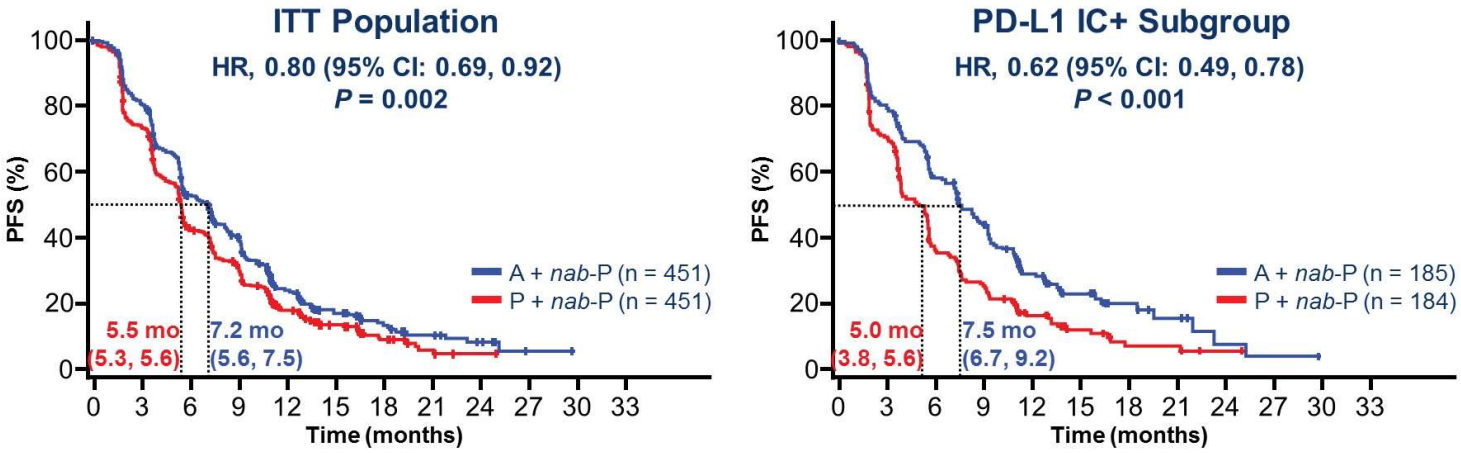
Schmid et al NEJM 2018

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Intention-to-Treat Population		PD-L1–Positive Subgroup	
	Atezolizumab + Nab-Paclitaxel (N = 451)	Placebo + Nab-Paclitaxel (N = 451)	Atezolizumab + Nab-Paclitaxel (N = 185)	Placebo + Nab-Paclitaxel (N = 184)
Age				
Median (range) — yr	55 (20–82)	56 (26–86)	53 (26–82)	53 (28–85)
Distribution — no. (%)				
18–40 yr	63 (14.0)	51 (11.3)	31 (16.8)	24 (13.0)
41–64 yr	284 (63.0)	285 (63.2)	111 (60.0)	117 (63.6)
≥65 yr	104 (23.1)	115 (25.5)	43 (23.2)	43 (23.4)
Female sex — no. (%)	448 (99.3)	450 (99.8)	184 (99.5)	184 (100)
Race or ethnic group — no. (%)†				
White	308 (68.3)	301 (66.7)	125 (67.6)	129 (70.1)
Asian	85 (18.8)	76 (16.9)	38 (20.5)	28 (15.2)
Black	26 (5.8)	33 (7.3)	9 (4.9)	14 (7.6)
Native American	17 (3.8)	23 (5.1)	8 (4.3)	9 (4.9)
Hawaiian or other Pacific Islander	1 (0.2)	0	0	0
Multiple	2 (0.4)	3 (0.7)	0	0
Unknown	12 (2.7)	15 (3.3)	5 (2.7)	4 (2.2)
ECOG performance-status score — no./total no. (%)‡				
0	256/450 (56.9)	270/450 (60.0)	107/185 (57.8)	112/184 (60.9)
1	193/450 (42.9)	179/450 (39.8)	77/185 (41.6)	72/184 (39.1)
2	1/450 (0.2)	1/450 (0.2)	1/185 (0.5)	0
Metastatic disease — no./total no. (%)	404/450 (89.8)	408/450 (90.7)	162/185 (87.6)	159/183 (86.9)
No. of sites of metastatic disease — no./total no. (%)				
0–3	332/450 (73.8)	341/449 (75.9)	149/185 (80.5)	140/183 (76.5)
≥4	118/450 (26.2)	108/449 (24.1)	36/185 (19.5)	43/183 (23.5)
Site of metastatic disease				
Liver — no. (%)§	126 (27.9)	118 (26.2)	44 (23.8)	39 (21.2)
Bone — no. (%)	145 (32.2)	141 (31.3)	54 (29.2)	49 (26.6)
Brain — no. (%)	30 (6.7)	31 (6.9)	15 (8.1)	11 (6.0)
Lung — no. (%)	226 (50.1)	242 (53.7)	86 (46.5)	98 (53.3)
Lymph node only — no./total no. (%)	33/450 (7.3)	23/449 (5.1)	18/185 (9.7)	13/183 (7.1)
Previous therapy — no. (%)				
Neoadjuvant or adjuvant therapy	284 (63.0)	286 (63.4)	125 (67.6)	117 (63.6)
Taxane§	231 (51.2)	230 (51.0)	96 (51.9)	94 (51.1)
Anthracycline	243 (53.9)	242 (53.7)	109 (58.9)	101 (54.9)

Schmid et al NEJM 2018

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



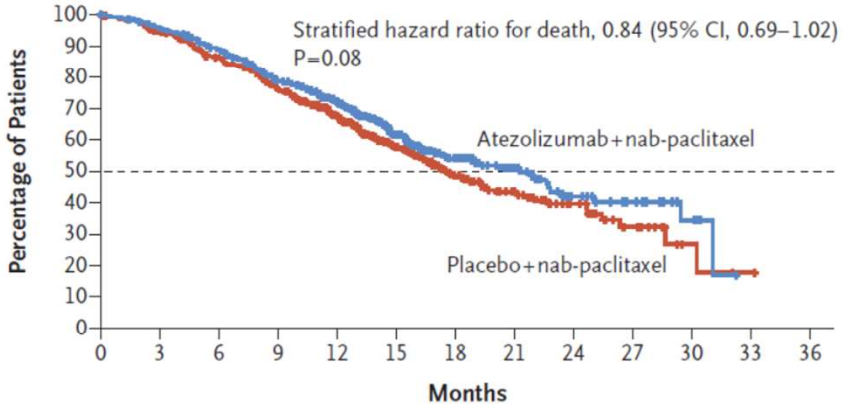
- PFS benefit driven by PD-L1 IC+ patients, as a treatment effect was not observed in PD-L1 IC− patients[1]
- Based on these data,[2] atezolizumab + *nab*-paclitaxel received accelerated approval by the FDA[3] and is recommended for patients with PD-L1 IC+ mTNBC in the NCCN[4] and AGO[5] guidelines

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.

C Overall Survival in the Intention-to-Treat Population

	No. of Events/ No. of Patients	Median Overall Survival (95% CI)	2-Yr Rate of Overall Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	181/451	21.3 (17.3–23.4)	42.1 (34.3–49.9)
Placebo+Nab-Paclitaxel	208/451	17.6 (15.9–20.0)	39.7 (33.2–46.3)

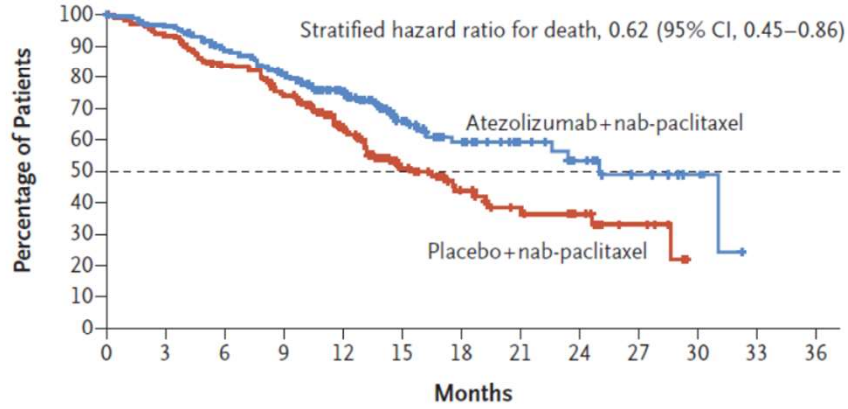


No. at Risk

Atezolizumab+ nab-paclitaxel	451	426	389	337	271	146	82	48	26	15	6	NE	NE
Placebo+ nab-paclitaxel	451	419	375	328	246	145	89	52	27	12	3	1	NE

D Overall Survival in the PD-L1–Positive Subgroup

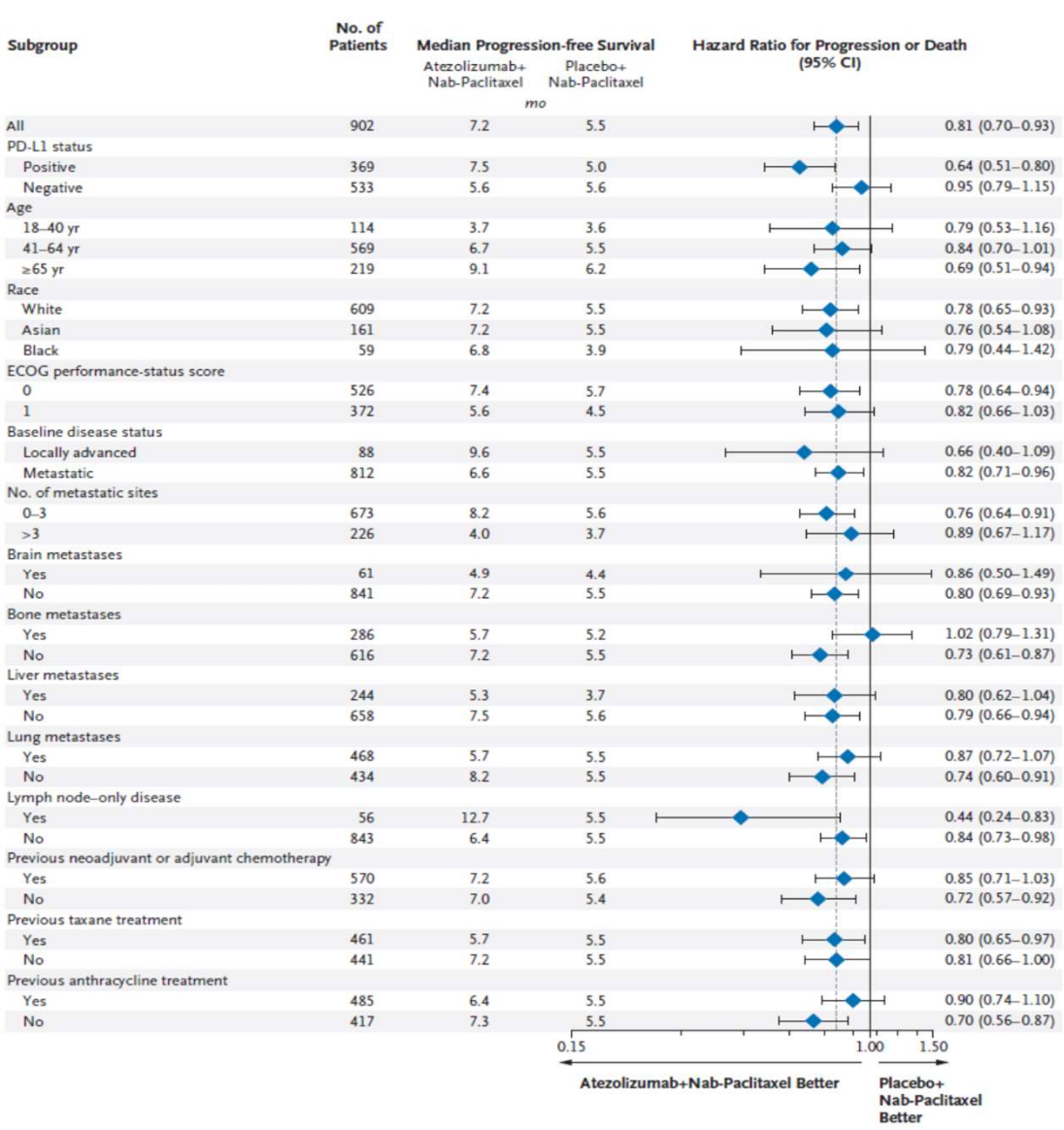
	No. of Events/ No. of Patients	Median Overall Survival (95% CI)	2-Yr Rate of Overall Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	64/185	25.0 (22.6–NE)	53.5 (42.3–64.6)
Placebo+Nab-Paclitaxel	88/184	15.5 (13.1–19.4)	36.6 (26.4–46.7)



No. at Risk

Atezolizumab+ nab-paclitaxel	185	177	160	142	113	61	36	22	15	9	5	NE	NE
Placebo+ nab-paclitaxel	184	170	147	129	89	44	27	19	13	6	NE	NE	NE

Schmid et al NEJM 2018

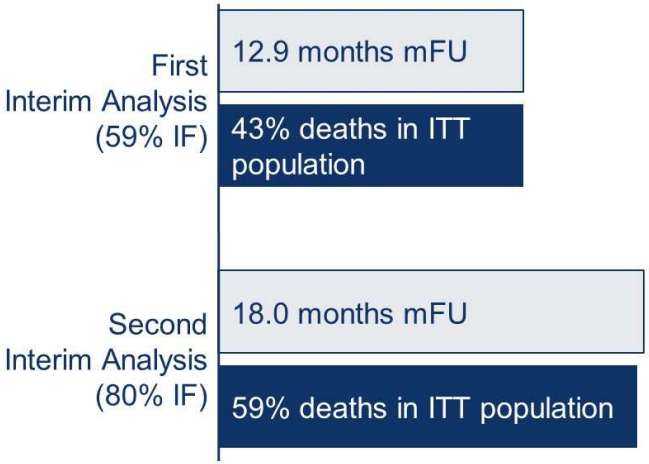


Schmid et al NEJM 2018

Variable	Atezolizumab + Nab-Paclitaxel	Placebo + Nab-Paclitaxel	Difference (95% CI) *percentage points*	P Value	Odds or Hazard Ratio (95% CI)
Response					
Intention-to-treat population — no. of patients†	450	449			
Objective response					
No. of patients	252	206			
% of patients (95% CI)	56.0 (51.3–60.6)	45.9 (41.2–50.6)	10.1 (3.4–16.8)	0.002	1.52 (1.16–1.97)‡
Complete response					
No. of patients	32	7			
% of patients (95% CI)	7.1 (4.9–9.9)	1.6 (0.6–3.2)			
Partial response					
No. of patients	220	199			
% of patients (95% CI)	48.9 (44.2–53.6)	44.3 (39.7–49.1)			
Stable disease					
No. of patients	113	119			
% of patients (95% CI)	25.1 (21.2–29.4)	26.5 (22.5–30.8)			
Progressive disease					
No. of patients	69	104			
% of patients (95% CI)	15.3 (12.1–19.0)	23.2 (19.3–37.4)			
Patients who had missing data or could not be evaluated — no. (%)	16 (3.6)	20 (4.5)			
PD-L1–positive subgroup — no. of patients†	185	183			
Objective response					
No. of patients	109	78			
% of patients (95% CI)	58.9 (51.5–66.1)	42.6 (35.4–50.1)	16.3 (5.7–26.9)	0.002	1.96 (1.29–2.98)‡
Complete response					
No. of patients	19	2			
% of patients (95% CI)	10.3 (6.3–15.6)	1.1 (0.1–3.9)			
Partial response					
No. of patients	90	76			
% of patients (95% CI)	48.6 (41.3–56.1)	41.5 (34.3–49.0)			
Stable disease					
No. of patients	38	49			
% of patients (95% CI)	20.5 (15.0–27.1)	26.8 (20.5–33.8)			
Progressive disease					
No. of patients	31	46			
% of patients (95% CI)	16.8 (11.7–22.9)	25.1 (19.0–32.1)			
Patients who had missing data or could not be evaluated — no. (%)	7 (3.8)	10 (5.5)			
Duration of response§					
Intention-to-treat population — no. of patients	252	206			
Median duration of response (95% CI) — mo	7.4 (6.9–9.0)	5.6 (5.5–6.9)			0.78 (0.63–0.98)
Patients with ongoing response at data-cutoff date — no. (%)¶	78 (31.0)	52 (25.2)			
PD-L1–positive subgroup — no. of patients	109	78			
Median duration of response (95% CI) — mo	8.5 (7.3–9.7)	5.5 (3.7–7.1)			0.60 (0.43–0.86)
Patients with ongoing response at data-cutoff date — no. (%)¶	39 (35.8)	19 (24.4)			

Schmid et al NEJM 2018

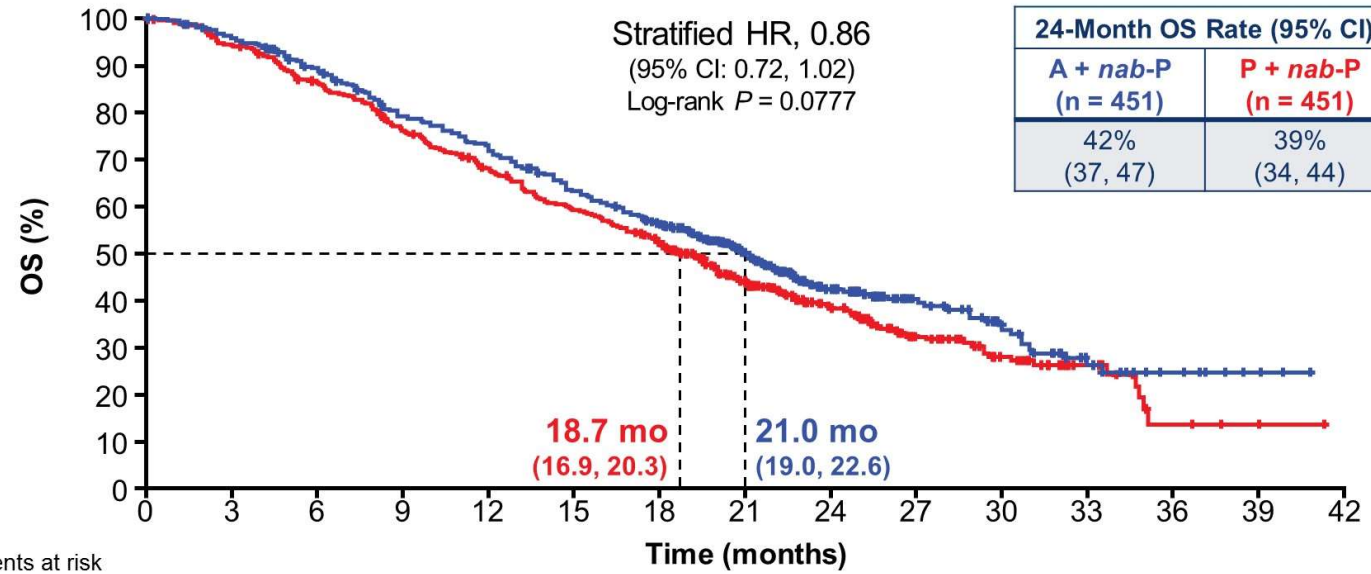
Patient Disposition at Second Interim OS Analysis



Second Interim OS Analysis		
Patient Disposition	**Atezolizumab + *nab*-paclitaxel (n = 451)**	**Placebo + *nab*-paclitaxel (n = 451)**
Patients on study, n (%)		
Alive on treatment	39 (9%)	13 (3%)
Alive in survival follow-up	133 (30%)	135 (30%)
Patients who discontinued study, n (%)		
Dead	255 (57%)	279 (62%)
Lost to follow-up	24 (5%)	24 (5%)

IF, information fraction; mFU, median follow-up.
Clinical cutoff date: January 2, 2019.
[a] Compared with Schmid et al. *New Engl J Med.* 2018.

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)

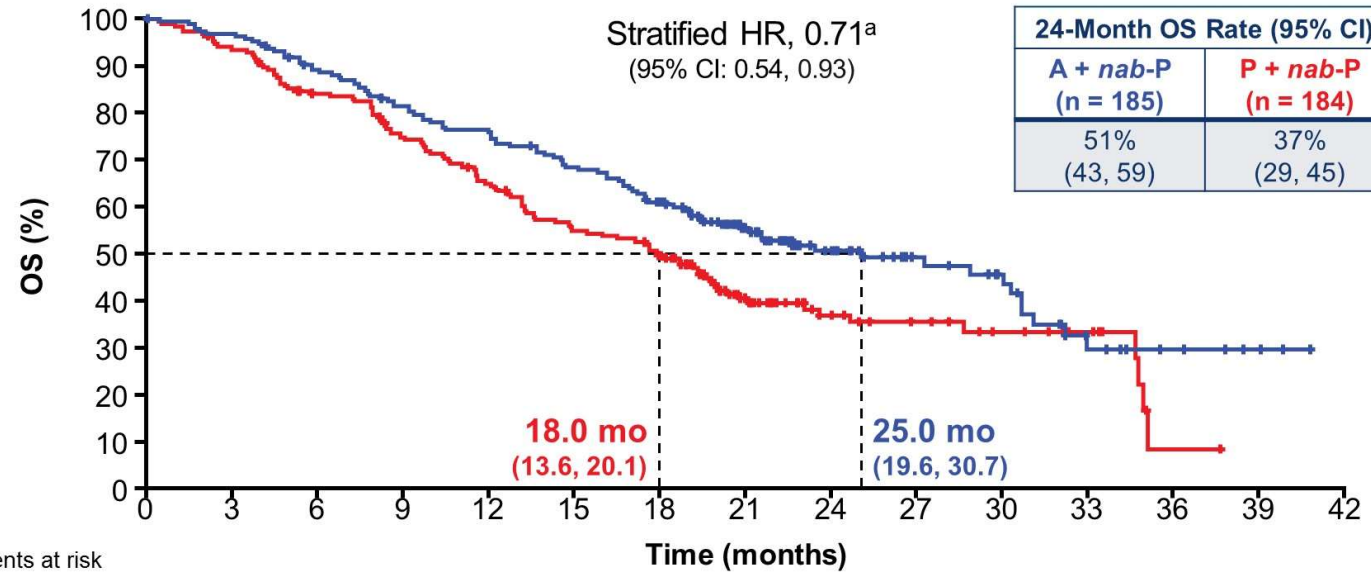
Patients at risk

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.

Schmid et al NEJM 2018

OS in PD-L1+ Population



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

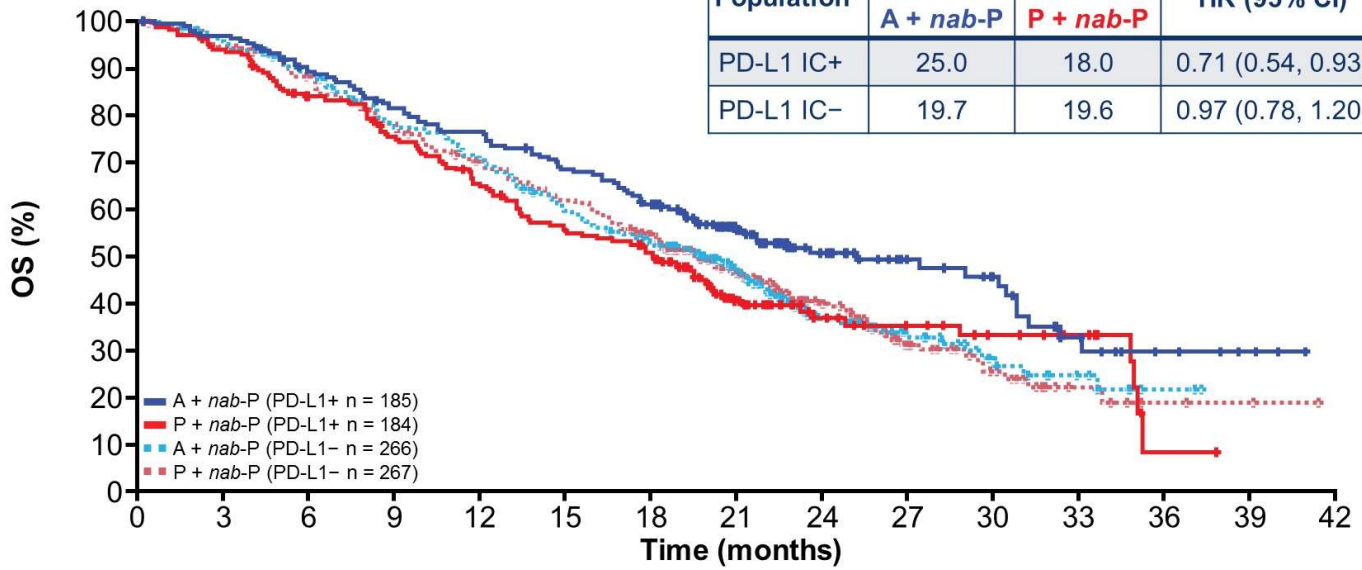
Patients at risk

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.

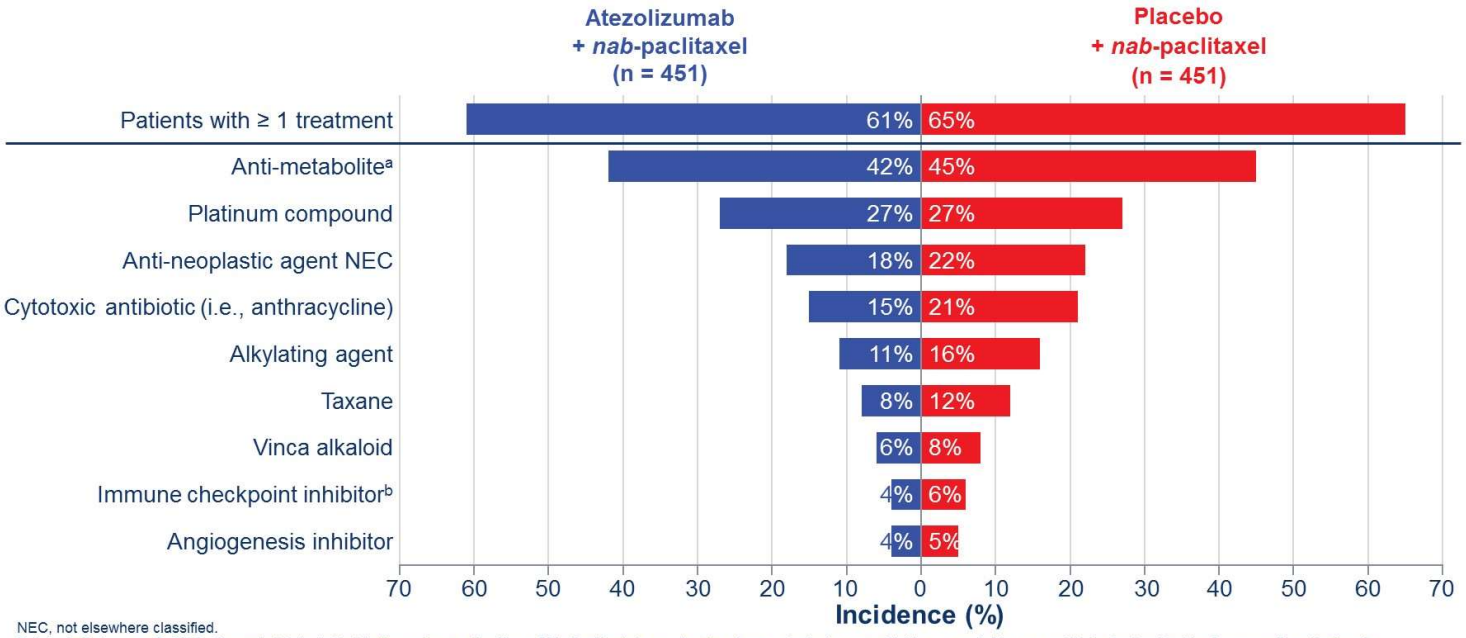
Comparison of OS in PD-L1+ and PD-L1− Populations

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.

Subsequent Therapies



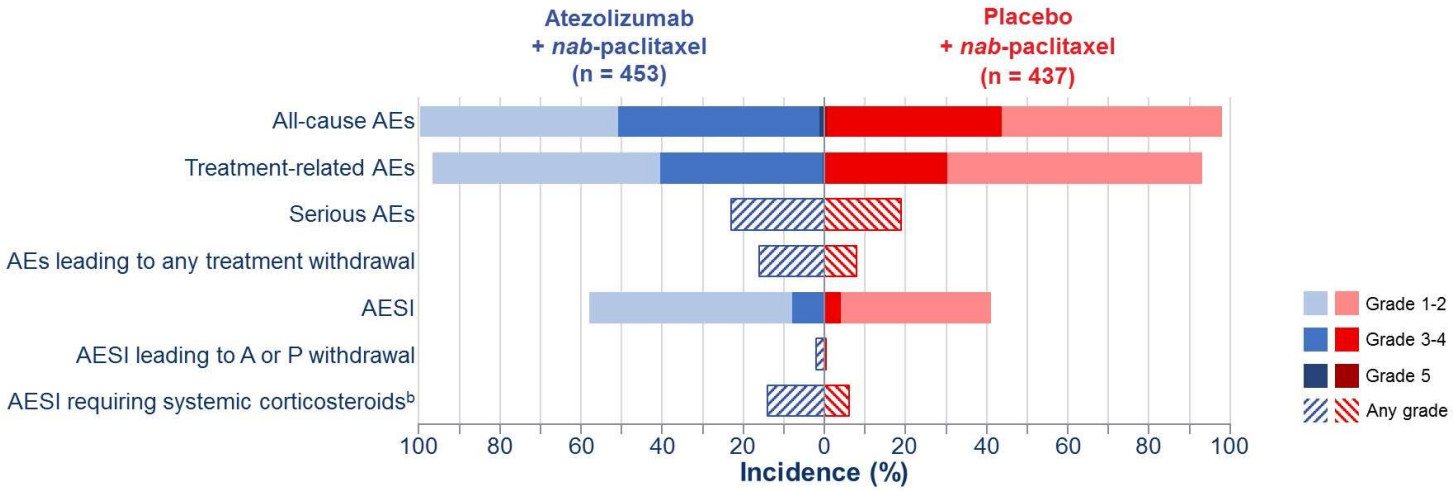
NEC, not elsewhere classified.
Data cutoff: January 2, 2019. Presented data limited to therapies received by ≥ 5% of patients in any treatment arm. [a] Includes capecitabine, gemcitabine, gemcitabine hydrochloride, fluorouracil, methotrexate, cytarabine, decitabine, floxuridine, methotrexate sodium, pemetrexed, tegafur. [b] Includes monoclonal antibodies targeting PD-L1, PD-1 and CTLA-4.

Table 3. Key Adverse Events.*

Event	Atezolizumab + Nab-Paclitaxel (N=452)		Placebo + Nab-Paclitaxel (N=438)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with event (percent)			
Alopecia	255 (56.4)	3 (0.7)	252 (57.5)	1 (0.2)
Nausea	208 (46.0)	5 (1.1)	167 (38.1)	8 (1.8)
Cough	112 (24.8)	0	83 (18.9)	0
Peripheral neuropathy	98 (21.7)	25 (5.5)	97 (22.1)	12 (2.7)
Neutropenia	94 (20.8)	37 (8.2)	67 (15.3)	36 (8.2)
Pyrexia	85 (18.8)	3 (0.7)	47 (10.7)	0
Hypothyroidism	62 (13.7)	0	15 (3.4)	0

Schmid et al NEJM 2018

Updated Safety Analysis[a]



- Safety data remain consistent with those previously published[1]
- **See poster #149 for further safety analysis details (Schneeweiss et al.) and poster #148 for patient-reported outcomes (Adams et al.)**

AESI, adverse events of special interest. Clinical data cutoff: September 3, 2018.
[a] Median follow-up 15.6 mo (4.5 months after primary PFS analysis). [b] Within 30 days of AESI onset. 1. Schmid et al. *N Engl J Med.* 2018.

Merck's KEYTRUDA® (pembrolizumab) in Combination with Chemotherapy Met Primary Endpoint of Progression-Free Survival (PFS) as First-Line Treatment for Metastatic Triple-Negative Breast Cancer (mTNBC)

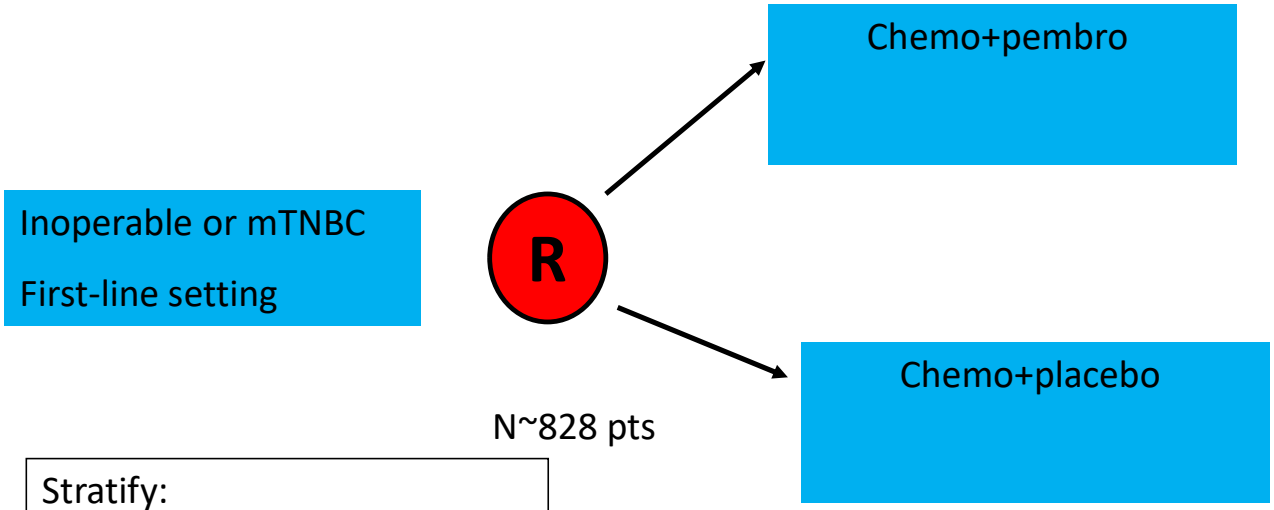
FEBRUARY 12, 2020

In Pivotal Phase 3 KEYNOTE-355 Study, KEYTRUDA Plus Chemotherapy Significantly Improved PFS Compared to Chemotherapy Alone in Patients with mTNBC Whose Tumors Expressed PD-L1 (CPS ≥10)

Data to be Presented at an Upcoming Medical Congress and Discussed with Regulatory Authorities

https://investors.merck.com/news/press-release-details/2020/Mercks-KEYTRUDA-pembrolizumab-in-Combination-with-Chemotherapy-Met-Primary-Endpoint-of-Progression-Free-Survival-PFS-as-First-Line-Treatment-for-Metastatic-Triple-Negative-Breast-Cancer-mTNBC/default.aspx

KEYNOTE 355



Primary endpoints:

PFS and OS

Stratify:

-chemo choice

-PDL-1 +/1

-prior chemo with same agent

Chemo options:

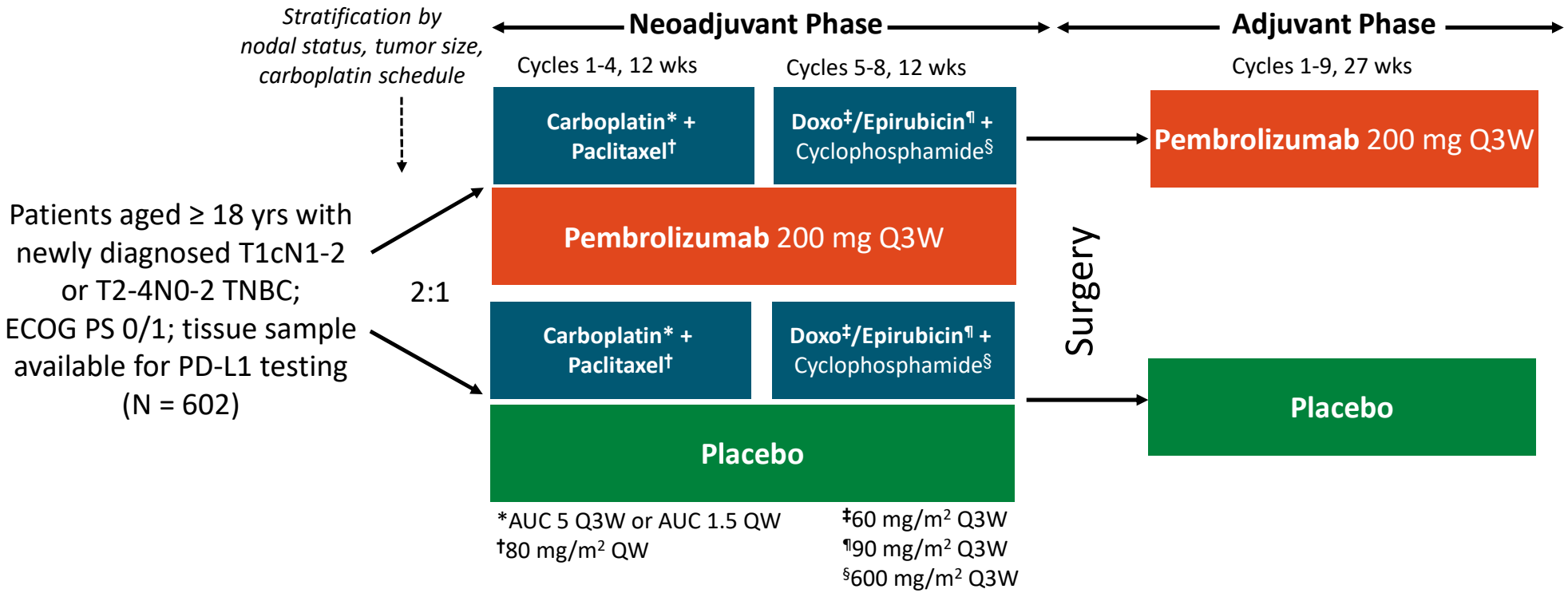
- Taxane (paclitaxel or nab-paclitxel)
- gem/carbo

KEYNOTE-522: Background

- Sustained clinical benefit observed in patients with TNBC who achieve pCR with neoadjuvant chemotherapy[1,2]
  - Approximately 40% to 55% of patients achieve pCR with current neoadjuvant chemotherapy[3-7]
- pCR after neoadjuvant chemotherapy associated with increased long-term EFS (HR: 0.24) and OS (HR: 0.16)[8]
- Addition of pembrolizumab to neoadjuvant chemotherapy has demonstrated antitumor activity and tolerable safety in early-stage TNBC[9,10]
- Previously phase III KEYNOTE-522 reported a significant improvement in pCR with addition of pembrolizumab vs placebo in the neoadjuvant and adjuvant settings in patients with early-stage TNBC[11]
- Current KEYNOTE-522 analysis of pCR rates in key patient subgroups, by treatment exposure, residual cancer burden, and immune-mediate adverse events[12]

1. Cortazar. Lancet. 2014;384:164. 2. Huang. Ann Oncol. 2019;30 (suppl3):iii34. 3. Loibi. Ann Oncol. 2019;30;1279. 4. von Minckwitz. Lancet Oncol. 2014;15:747. 5. Sikov. JCO. 2015;33:13. 6. Petrelli. Breast Cancer Res Treat. 2014;14:223. 7. Loibi. Lancet Oncol. 2018;19:497. 8 Spring. AACR 2019. Abstr GS2-03. 9. Schmid. ASCO 2017. Abstr 556. 10. Nanda. ASCO 2017. Abstr 506. 11. Schmid. ESMO 2019. Abstr LBA8_PR. 12. Schmid. SABCS 2019. Abstr GS3-03

KEYNOTE-522: Study Design



- Primary endpoints: pCR (ypT0/Tis ypN0) by local review, EFS by local review
- Secondary endpoints: pCR (ypT0 ypN0 and ypT0/Tis), OS, EFS, AE
- Exploratory endpoints: RCB, pCR by subgroups, EFS by pCR

Schmid. Et al NEJM 2020.

KEYNOTE-522: Baseline Characteristics

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

*Assessed by centralized laboratory.

Schmid. Et al NEJM 2020.

KEYNOTE-522: pCR and EFS

Endpoint	Pembrolizumab + Chemotherapy (n = 401)	Placebo + Chemotherapy (n = 201)
Definitive pCR analysis, %	64.8	51.2
	Δ 13.6 (95% CI: 5.4-21.8) *P* = .00055	
EFS, %	91.3	85.3
▪ Events, %	7.4	11.8
	HR: 0.63 (95% CI: 0.43-0.93)	

- Definitive pCR analysis based on prespecified first 602 patients
  - Precalculated *P* value boundary for significance: .003
- Consistent benefit seen with pCR defined as ypT0 ypN0 vs ypT0/Tis
- First interim analysis of EFS based on 1174 patients at median follow-up of 15.5 mos
  - Precalculated *P* value boundary for significance: .000051 (HR < 0.4)

Schmid. Et al NEJM 2020.

KEYNOTE-522: pCR by Key Patient Subgroups

pCR, % (n/N)		Pembrolizumab + Chemotherapy (n = 401)	Placebo + Chemotherapy (n = 201)	Δ (95% CI)
Disease stage	▪ IIA	73.1 (133/182)	62.1 (54/87)	11.0 (-0.7 to 23.2)
	▪ IIB	56.2 (68/121)	48.4 (30/62)	7.8 (-7.4 to 22.8)
	▪ IIIA	66.7 (40/60)	42.1 (16/38)	24.6 (4.3 to 43.1)
	▪ IIIB	48.6 (18/37)	23.1 (3/13)	25.6 (-6.1 to 48.9)
Lymph node involvement	▪ Negative	64.9 (124/191)	58.6 (58/99)	6.3 (-5.3 to 18.2)
	▪ Positive	64.8 (136/210)	44.1 (45/102)	20.6 (8.9 to 39.1)
PD-L1 expression	▪ CPS < 1	45.3 (29/64)	30.3 (10.33)	18.3 (-3.3 to 36.8)
	▪ CPS ≥ 1	68.9 (230/334)	54.9 (90/164)	14.2 (5.3 to 23.1)
	▪ CPS ≥ 10	77.9 (162/208)	59.8 (55/92)	17.5 (6.2 to 29.1)
	▪ CPS ≥ 20	81.7 (103/126)	62.5 (40/64)	18.5 (5.0 to 32.7)
Chemotherapy exposure*	▪ Full exposure	69.7 (314/307)	55.3 (88/159)	14.4 (5.1 to 3.6)
	▪ < Full exposure	51.1 (46/90)	35.7 (15/42)	15.4 (-3.0 to 32.1)

*Full exposure comprised paclitaxel weekly 10-12 doses, carboplatin weekly 10-12 doses or Q3W 4 doses, doxorubicin or epirubicin Q3W 4 doses, and cyclophosphamide Q3W 4 doses, regardless of exposure to pembrolizumab.

Schmid. Et al NEJM 2020.

KEYNOTE-522: Residual Cancer **Burden** and AEs

Residual Cancer Burden, %	Pembrolizumab + Chemotherapy (n = 401)	Placebo + Chemotherapy (n = 201)
RCB 0	65.6	52.7
RCB I	8.5	10.9
RCB II	16.2	21.9
RCB III	4.5	8.5

AE, %	Pembrolizumab + Chemotherapy (n = 781)	Placebo + Chemotherapy (n = 389)
Any grade	32.1	10.8
Grade 3-5	12.0	1.0
Grade 5*	0.1	0
D/c due to AE	6.5	0.8

*Death from pneumonitis, n = 1.

Immune-Mediated AE (All Grades) in ≥ 10 Patients, %	Pembrolizumab + Chemotherapy (n = 781)	Placebo + Chemotherapy (n = 389)
Hypothyroidism	14.9	5.7
Skin reaction	5.5	1.0
Hyperthyroidism	5.1	1.8
Adrenal insufficiency	2.7	0
Pneumonitis	1.9	1.5
Colitis	1.8	0.8
Hypophysitis	1.8	0.3
Thyroiditis	1.7	1.0
Hepatitis	1.4	0.5

Schmid. Et al NEJM 2020.

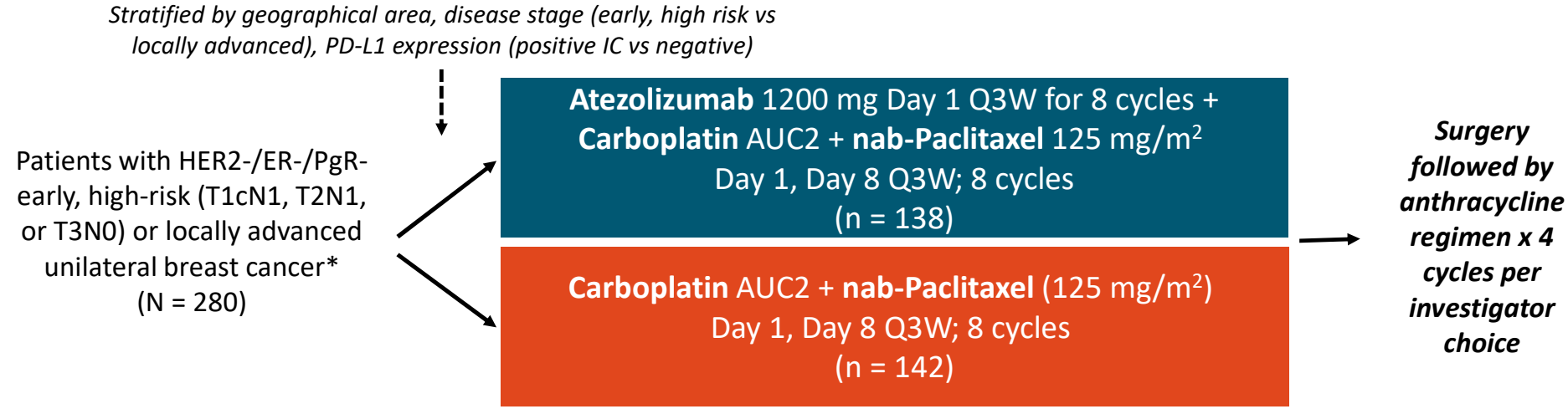
NeoTRIPaPDL1: Background

- TNBC associated with poor prognosis and rapid progression to distant metastases and development of resistance to chemotherapy
  - Setting in need of new therapeutic approaches
- Prognosis and probability of response to chemotherapy correlated with immune infiltration of TNBC
- Whether as single agent or in combination with SoC chemotherapy, blocking PD-L1/PD1 may promote durable responses in TNBC by immune mechanisms
  - In phase III IMpassion130 trial, addition of anti–PD-L1 antibody atezolizumab to nab-paclitaxel achieved significant PFS and OS benefit in PD-L1–positive metastatic TNBC[1,2]
- Current analysis evaluated efficacy, safety of carboplatin/nab-paclitaxel ± atezolizumab in patients with early, high-risk and locally advanced TNBC[3]

1. Schmid. NEJM 2018;379:2108. 2. Schmid. ASCO 2019. Abstr 1003. 3. Gianni. SABCS 2019. Abstr GS3-04.

NeoTRIPaPDL1: Study Design

- Open-label, randomized phase III trial



*ER, PgR, HER2, and PD-L1 centrally assessed before randomization. Tumor and blood banked for correlative studies.

- Primary endpoint: EFS at 5 yrs after randomization of last patient
- Key secondary endpoint: pCR rate (defined as absence of invasive cells in breast and lymph nodes)
- Other secondary endpoints: tolerability; predictive biomarkers of benefit and/or resistance

Gianni. SABCS 2019. Abstr GS3-04.

NeoTRIPaPDL1: Baseline Characteristics (ITT)

Characteristic		Atezolizumab + Carboplatin/nab-Paclitaxel (n = 138)	Carboplatin/nab-Paclitaxel (n = 142)
Median age, yrs (range)		49.5 (25-79)	50 (24-77)
Disease stage, n (%)	▪ Early high risk ▪ Locally advanced	69 (50) 69 (50)	73 (51) 69 (49)
PD-L1, n (%)	▪ Negative ▪ Positive	79 (57) 59 (43)	77 (54) 65 (46)
T stage, n (%)	▪ cT1c ▪ cT2 ▪ cT3 ▪ cT4a-d	13 (9) 61 (44) 47 (34) 17 (12)	8 (6) 75 (53) 41 (29) 18 (13)
Nodal status, n (%)	▪ cN0 ▪ cN1 ▪ cN2 ▪ cN3	18 (13) 85 (62) 16 (12) 19 (14)	19 (13) 79 (56) 22 (15.5) 22 (15.5)

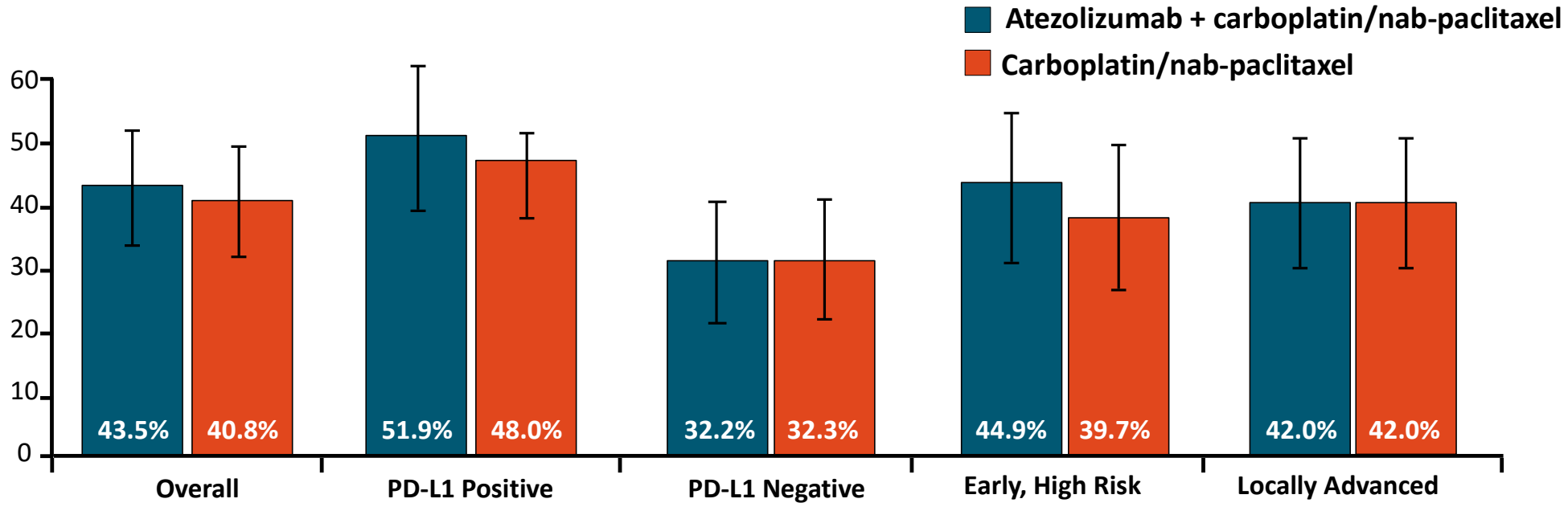
Gianni. SABCS 2019. Abstr GS3-04.

NeoTRIPaPDL1: Patient Disposition

	Atezolizumab + Carboplatin/nab-Paclitaxel (n = 138)	Carboplatin/nab-Paclitaxel (n = 142)
Protocol population	125	126
Nonevaluable		
▪ Failed eligibility after randomization	3	2
▪ Withdrew consent	2	5
▪ Missing surgery in absence of PD	5	6
▪ Other	4	3

Gianni. SABCS 2019. Abstr GS3-04.

NeoTRIPaPDL1: pCR Rate (ITT)



- Overall pCR rate difference: 2.63%; odds ratio: 1.11 (95% CI: 0.69-1.79); *P* = .66

Gianni. SABCS 2019. Abstr GS3-04. Reproduced wit permission.

NeoTRIPaPDL1: Multivariate Analysis of Factors Associated With pCR

Variable	Odds Ratio (95% CI)	*P* Value
Treatment: with atezolizumab vs without	1.11 (0.88-1.40)	.39
PD-L1 expression: positive vs negative	2.08 (1.64-2.65)	< .0001
Disease stage: early, high risk vs locally advanced	0.84 (0.66-1.06)	.15

Gianni. SABCS 2019. Abstr GS3-04.

NeoTRIPaPDL1: Clinical Overall Response and Disease Progression During Neoadjuvant Therapy

Response	Atezolizumab + Carboplatin/nab-Paclitaxel (n = 138)	Carboplatin/nab-Paclitaxel (n = 142)
Clinical ORR, % (95% CI)	76.1 (68.1-82.9)	68.3 (60.0-75.9)
CR, %	29.0	26.1
PR, %	47.1	42.3
SD, %	3.6	4.9
PD, %	5.8	8.4
Not assessed, %	14.5	18.3
PD during neoadjuvant therapy, n (%) ▪ Overall ▪ Locoregional ▪ Distant	 8 (5.8) 4 (2.9) 4 (2.9)	 12 (8.4) 9 (6.3) 3 (2.1)

Gianni. SABCS 2019. Abstr GS3-04.

NeoTRIPaPDL1: Safety

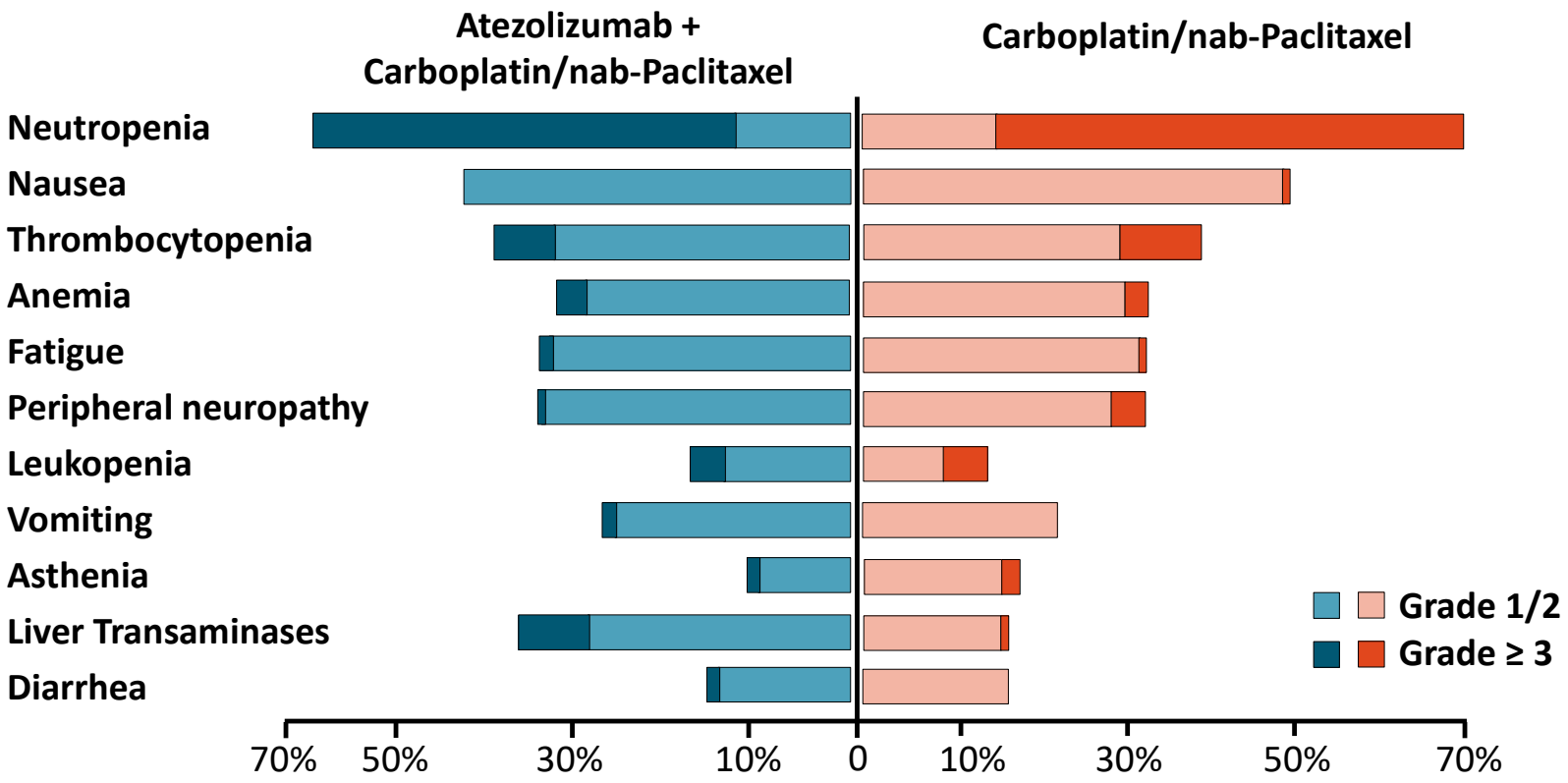
Adverse event	Atezolizumab + Carboplatin/nab-Paclitaxel (n = 138*)		Carboplatin/nab-Paclitaxel (n = 140*)	
Treatment-related AEs, %				
▪ Any grade	97.8		98.6	
▪ Grade ≥ 3	77.5		70.0	
▪ Serious AEs	18.1†		5.7†	
▪ Led to death (unknown causes)	0.7		--	
▪ Led to treatment discontinuation‡	25.4		25.0	
Immune-mediated AEs and infusion reactions	**Any grade**	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**
▪ Infusion reactions	8.0	1.4	5.7	0.7
▪ Hypothyroidism	5.8	--	1.4	--
▪ Thyroiditis	1.5	--	--	--
▪ Hyperthyroidism	0.7	--	--	--
▪ Colitis	1.5	0.7	--	--
▪ Pancreatitis	1.5	1.5	--	--
▪ Hepatitis	0.7	--	--	--
▪ Interstitial nephritis	0.7	--	--	--
▪ Coombs positive hemolytic anemia	0.7	0.7	--	--
▪ Thrombotic thrombocytopenia purpura	0.7	0.7	--	--

*Safety population included all patients who received ≥ 1 dose. †*P* = .003.

‡Median no. of cycles before discontinuation: 6 (range: 1-7) for both study arms.

Gianni. SABCS 2019. Abstr GS3-04.

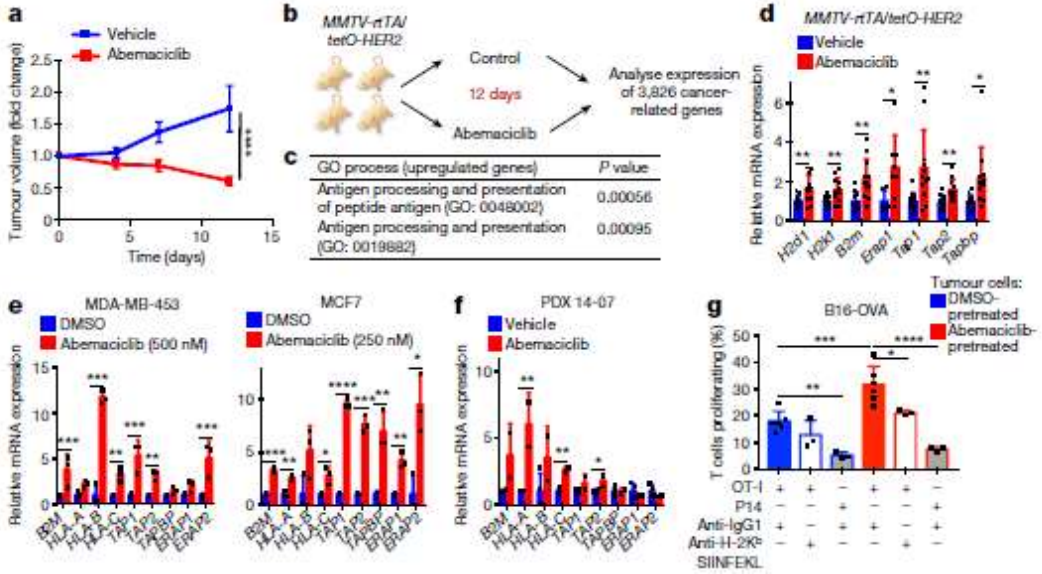
NeoTRIPaPDL1: Treatment-Related AEs in ≥ 15% of Patients



Gianni. SABCS 2019. Abstr GS3-04.

CDK4/6 inhibition triggers anti-tumour immunity

Shom Goel[1,2*], Molly J. DeCristo[3,4*], April C. Watt[1], Haley BrinJones[1], Jaclyn Sceneay[3,4], Ben B. Li[1], Naveed Khan[1], Jessalyn M. Ubellacker[3,4], Shaozhen Xie[1], Otto Metzger-Filho[2], Jeremy Hoog[5], Matthew J. Ellis[6], Cynthia X. Ma[5], Susanne Ramm[7,8], Ian E. Krop[2], Eric P. Winer[2], Thomas M. Roberts[1], Hye-Jung Kim[9,10]§, Sandra S. McAllister[3,4,11,12]§ & Jean J. Zhao[1,12,13]§



Conclusions:

- Immune checkpoint inhibitors and chemotherapy are showing significant activity in breast cancer
  - No new safety signals
- To date, most mature data in triple-negative breast cancer
  - Phase 3 Impassion 130: Atezo-nab-paclitaxel in PDL-1 +
  - Impressive path CR rates in the neo-adjuvant setting (KEYNOTE 522)
- Ongoing studies will establish role in other breast cancer settings
  - Adjuvant
  - HER2 positive
  - ? ER+