Immunotherapy for Triple-Negative Breast Cancer

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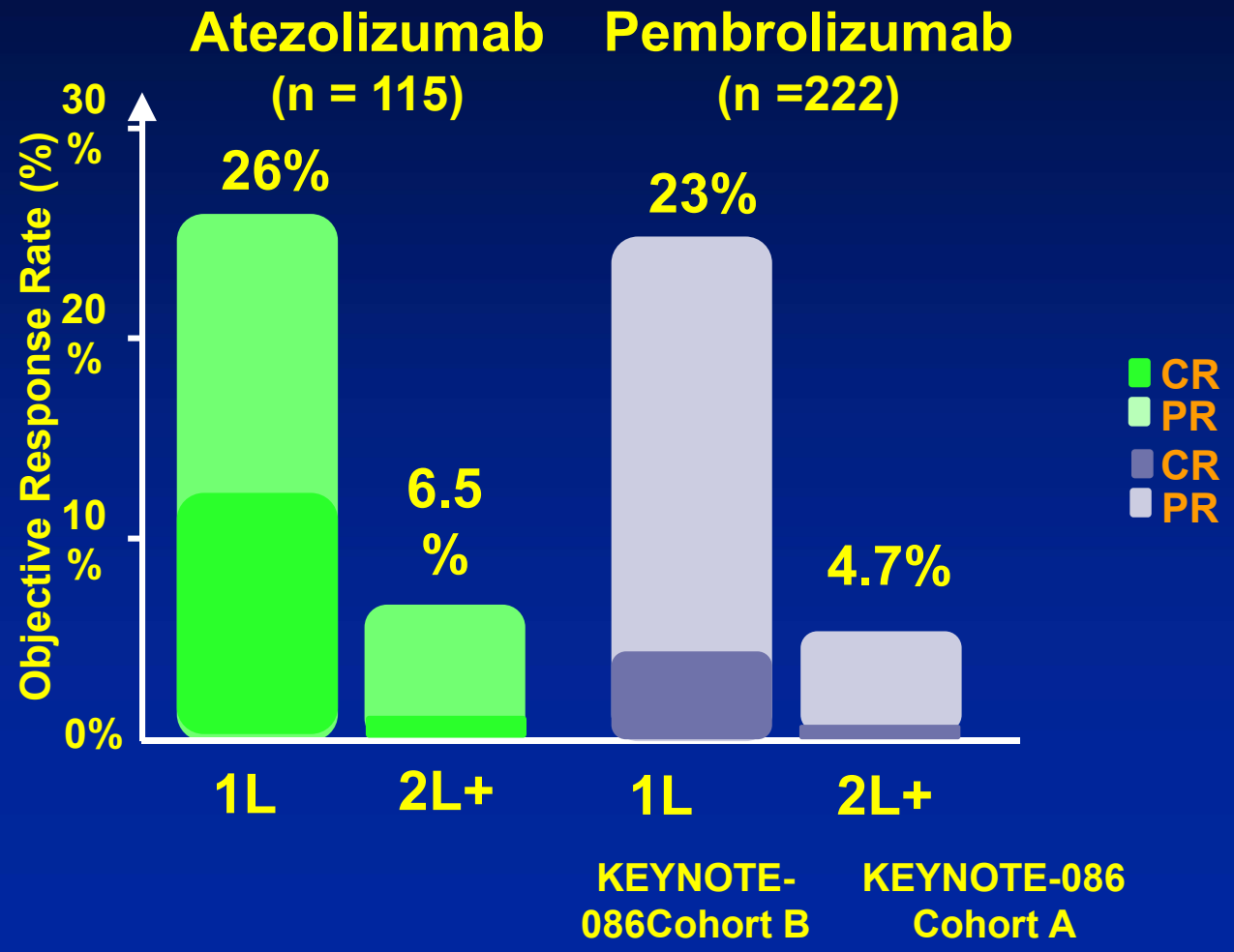
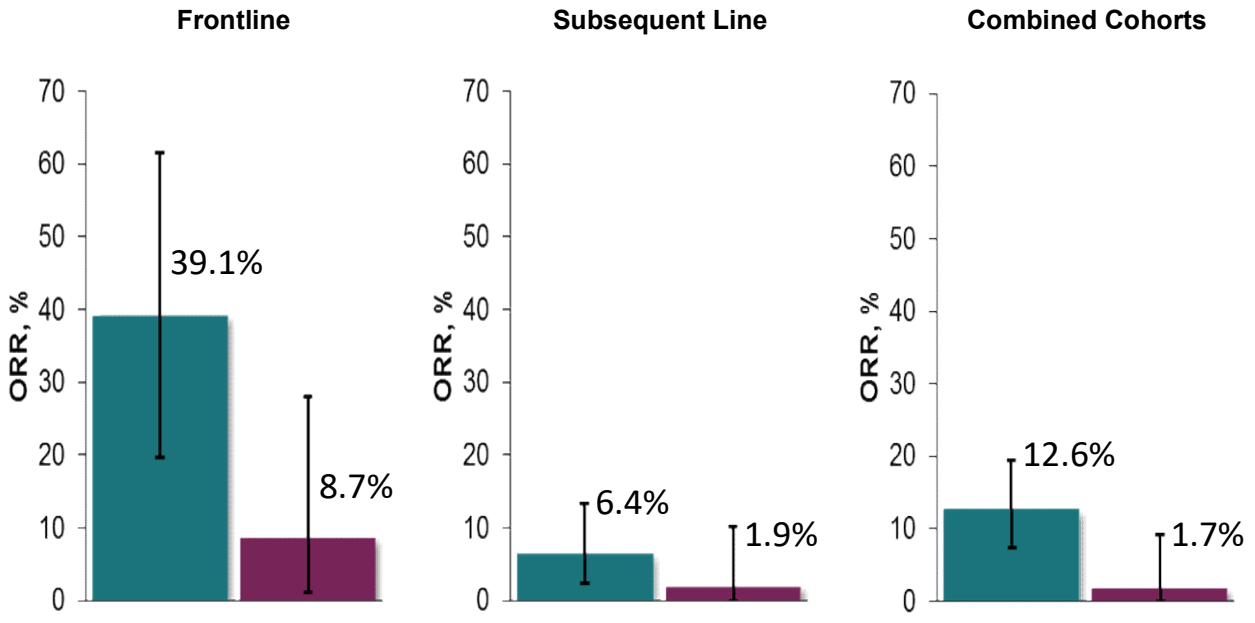
Response to single agent anti-PD-L1/PD-1

Anti-PD-L1/PD-1 single agent in mTNBC ≥1L, PD-L1+/-



Schmid P, et al. AACR 2017; Adams S, et al. ASCO 2017

KEYNOTE 086: Response Rate by Line of Therapy and sTILs with pembrolizumab monotherapy

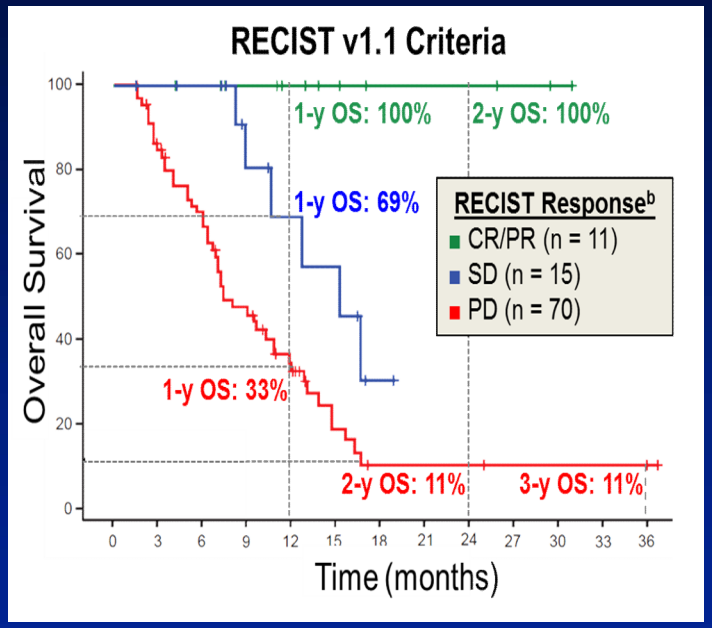


sTIL level	≥17.5 %	<17.5%	≥5%	<5%	≥5%	<5%
n	23	23	94	53	135	58
Responders	9	2	6	1	17	1
Ongoing responses	5	2	3	1	10	1

Loi et al. ESMO 2017

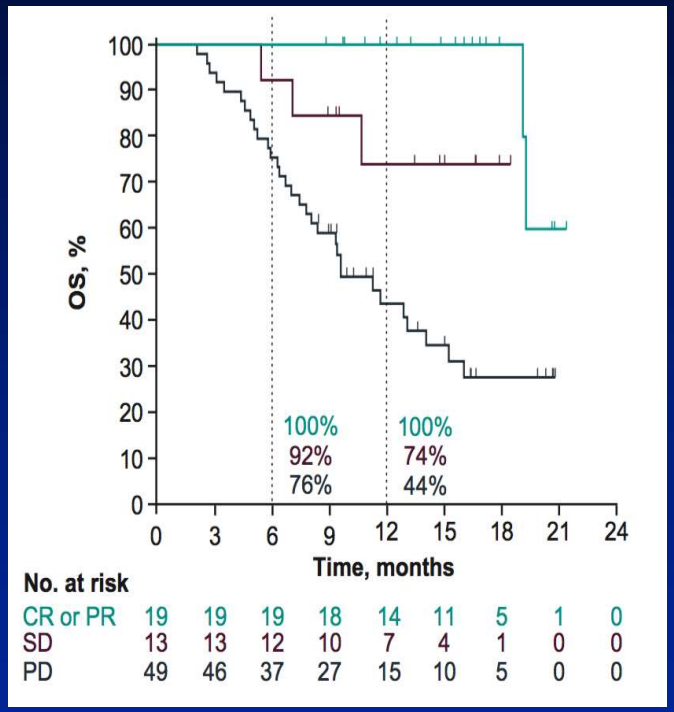
Atezolizumab and Pembrolizumab Monotherapy: Durable Responses

Atezolizumab



N=96
Median OS: 9.3 mo

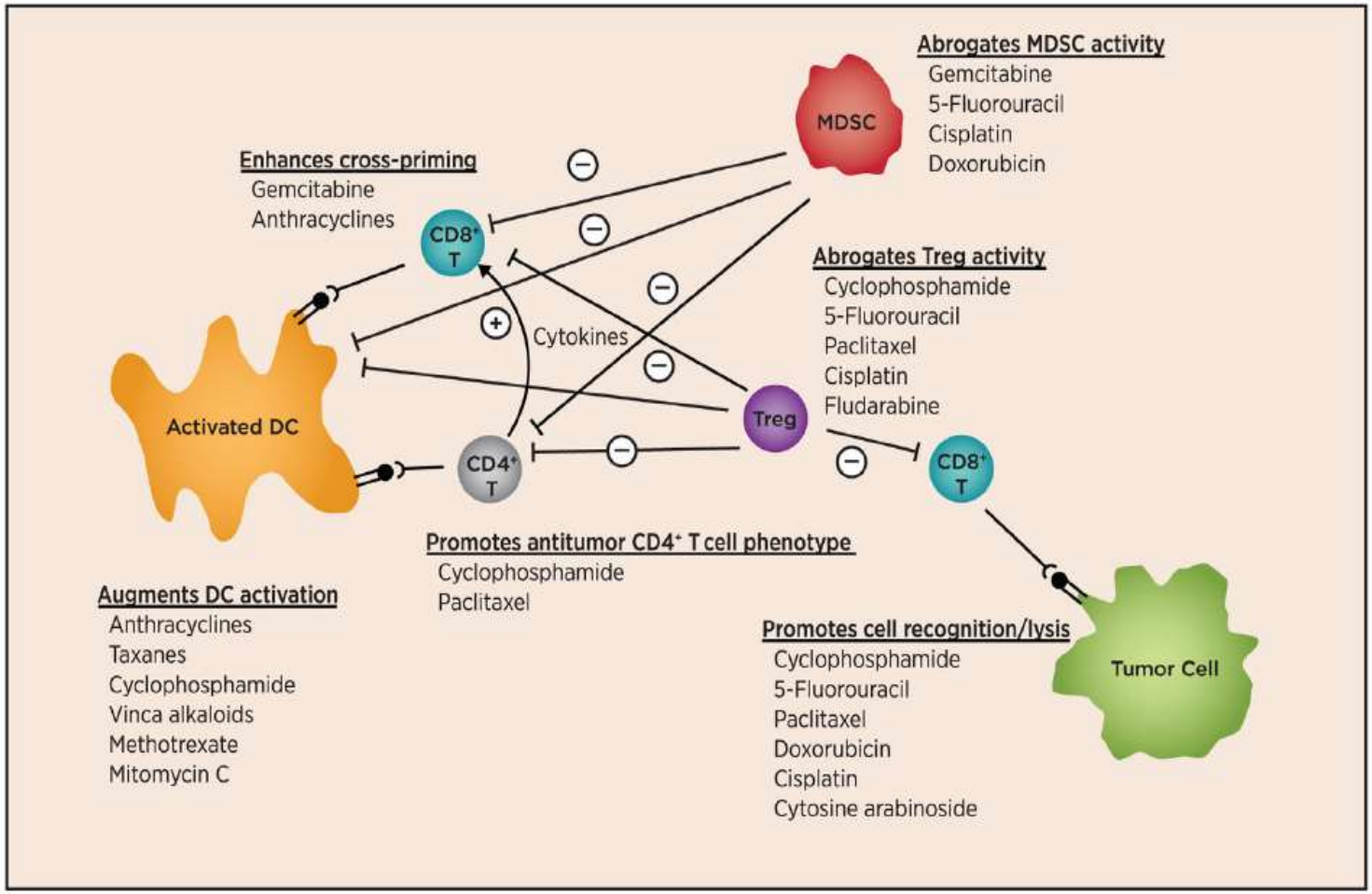
Pembrolizumab



N=81
Median OS: 19.2 mo

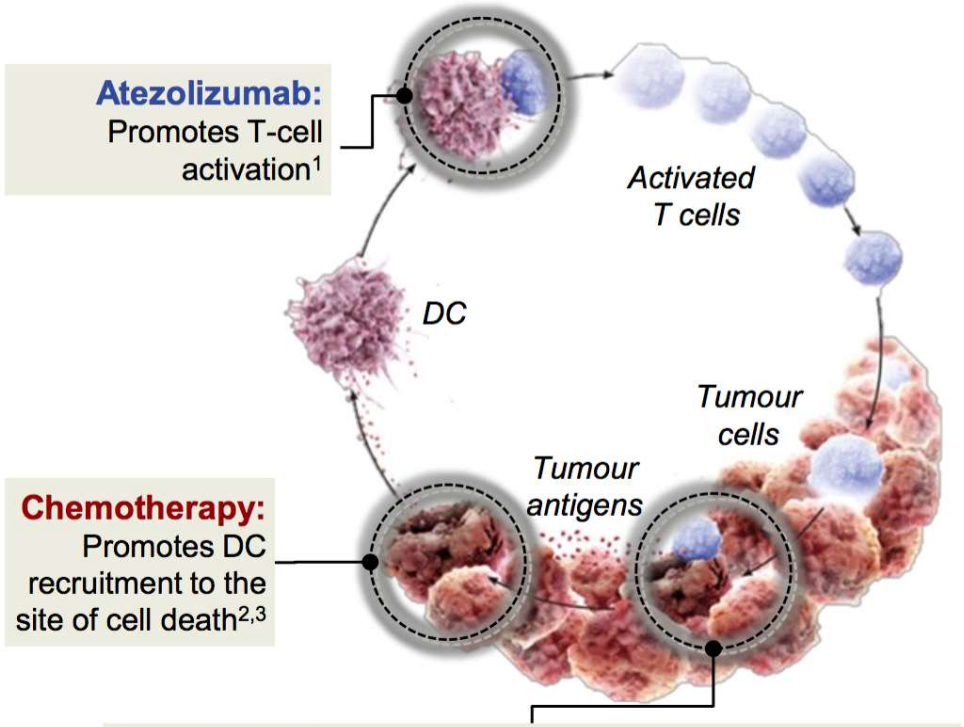
Adams et al, Ann Onc 2018; Emens et al, Jama Onc 2018

Combining Checkpoint Inhibitors with Chemotherapy



Emens et al, Cancer Imm Res 2015

Atezolizumab and chemotherapy



- Atezolizumab (anti–PD-L1) monotherapy is approved in the United States, Europe and elsewhere for certain types of metastatic urothelial carcinoma and lung cancer[4]
- In a Phase I study, atezolizumab monotherapy was active in multiple cancers, including TNBC,[5,6] with greater activity in patients whose tumours had PD-L1 IC ≥ 1%[6]
- The addition of chemotherapy can enhance atezolizumab's anti-tumour activity[7,8]
  - In a Phase Ib study in mTNBC, concurrent administration of *nab*-paclitaxel did not inhibit atezolizumab-mediated immunodynamic effects[8]

DC, dendritic cell.

1. Chen *Immunity* 2013. 2. Zitvogel *Immunity* 2013. 3. Emens *CIR* 2015. 4. TECENTRIQ US PI/SmPC 2018. 5. Herbst *Nature* 2014. 6. Emens *JAMA Oncol* 2018. 7. Jotte ASCO 2018. 8. Pohlmann AACR 2018.

Schmid P, et al. IMpassion13(
ESMO 2018 (LBA1_PR
http://bit.ly/2DMhayg

Atezolizumab + Nab paclitaxel

- Immune checkpoint inhibition may be augmented by neoantigen elaboration by chemotherapy (or RT).
  - Nab paclitaxel avoids steroids of other taxanes
- Phase Ib

mTNBC
< 3 prior lines

↓

Atezolizumab (800 iv q2wk)
+
nab paclitaxel (125 iv 3 wks of 4)

Serial biopsies (n=24):
- **pre-Rx**
- **C1 (no atezo)**
- **C2 (+ atezo)**

Adams et al, ASCO 2016

Phase Ib Atezolizumab + Nab paclitaxel

Table 4. Summary of Best Overall Responses by RECIST v1.1

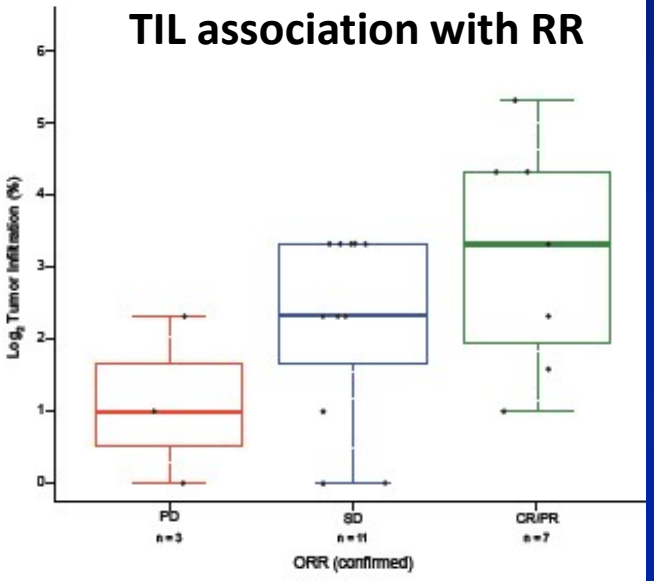
Best Overall Response	First Line (n = 13)	Second Line (n = 9)[b]	Third Line+ (n = 10)[c]	All Patients (N = 32)
Confirmed ORR (95% CI)[a]	46% (19-75)	22% (3-60)	40% (12-74)	38% (21-56)
CR	8%	0%	0%	3%
PR	38%	22%	40%	34%
SD	38%	67%	30%	44%
PD	15%	0%	30%	16%
Missing or NE	0%	11%	0%	3%

Table 2. Treatment-Related Grade 3-4 Adverse Events Occurring in > 1 Patient (> 5%)[a]

Adverse Event, n (%)	Grade 3-4 ≥ 5% N = 32	All Grade N = 32
All	22 (69%)	32 (100%)
Neutropenia and decreased neutrophil count	15 (47%)	21 (66%)
Thrombocytopenia and decreased platelet count	3 (9%)	5 (16%)
Anemia	2 (6%)	7 (22%)
Decreased white blood cell count	2 (6%)	3 (9%)
Diarrhea	2 (6%)	13 (41%)

Adams et al, ASCO 2016

TIL association with RR



IMpassion130 study design

Key IMpassion130 eligibility criteria[a]:

- Metastatic or inoperable locally advanced TNBC
  - Histologically documented[b]
- No prior therapy for advanced TNBC
  - Prior chemo in the curative setting, including taxanes, allowed if TFI ≥ 12 mo
- ECOG PS 0-1

Stratification factors:

- Prior taxane use (yes vs no)
- Liver metastases (yes vs no)
- PD-L1 status on IC (positive [≥ 1%] vs negative [< 1%])[c]

R 1:1

Atezo + nab-P arm:

Atezolizumab 840 mg IV
- On days 1 and 15 of 28-day cycle

+ *nab*-paclitaxel 100 mg/m² IV
- On days 1, 8 and 15 of 28-day cycle

Double blind; no crossover permitted

Plac + nab-P arm:

Placebo IV
- On days 1 and 15 of 28-day cycle

+ *nab*-paclitaxel 100 mg/m² IV
- On days 1, 8 and 15 of 28-day cycle

RECIST v1.1
PD or toxicity

- Co-primary endpoints were PFS and OS in the ITT and PD-L1+ populations[d]
  - Key secondary efficacy endpoints (ORR and DOR) and safety were also evaluated

IC, tumour-infiltrating immune cell; TFI, treatment-free interval. [a] ClinicalTrials.gov: NCT02425891. [b] Locally evaluated per ASCO–College of American Pathologists (CAP) guidelines. [c] Centrally evaluated per VENTANA SP142 IHC assay (double blinded for PD-L1 status). [d] Radiological endpoints were investigator assessed (per RECIST v1.1).

Schmid P, et al. IMpassion130 ESMO 2018 (LBA1_PR) http://bit.ly/2DMhayg

IMpassion130 baseline characteristics

Characteristic	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
Median age (range), y	55 (20-82)	56 (26-86)
Female, n (%)	448 (99%)	450 (100%)
Race, n (%)[a]		
White	308 (68%)	301 (67%)
Asian	85 (19%)	76 (17%)
Black/African American	26 (6%)	33 (7%)
Other/multiple	20 (4%)	26 (6%)
ECOG PS, n (%)[b,c]		
0	256 (57%)	270 (60%)
1	193 (43%)	179 (40%)
Prior (neo)adjuvant treatment, n (%)	284 (63%)	286 (63%)
Prior taxane	231 (51%)	230 (51%)
Prior anthracycline	243 (54%)	242 (54%)

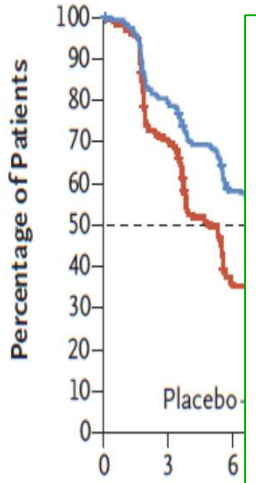
Characteristic	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
Metastatic disease, n (%)	404 (90%)	408 (91%)
No. of sites, n (%)[d]		
0-3	332 (74%)	341 (76%)
≥ 4	118 (26%)	108 (24%)
Site of metastatic disease, n (%)		
Lung	226 (50%)	242 (54%)
Bone	145 (32%)	141 (31%)
Liver	126 (28%)	118 (26%)
Brain	30 (7%)	31 (7%)
Lymph node only[d]	33 (7%)	23 (5%)
PD-L1+ (IC), n (%)	185 (41%)	184 (41%)

Data cutoff: 17 April 2018. [a] Race was unknown in 12 patients in the Atezo + nab-P arm and 15 in the Plac + nab-P arm. [b] Of n = 450 in each arm. [c] ECOG PS before start of treatment was 2 in 1 patient per arm. [d] Of n = 450 in the Atezo + nab-P arm and n = 449 in the Plac + nab-P arm arm.

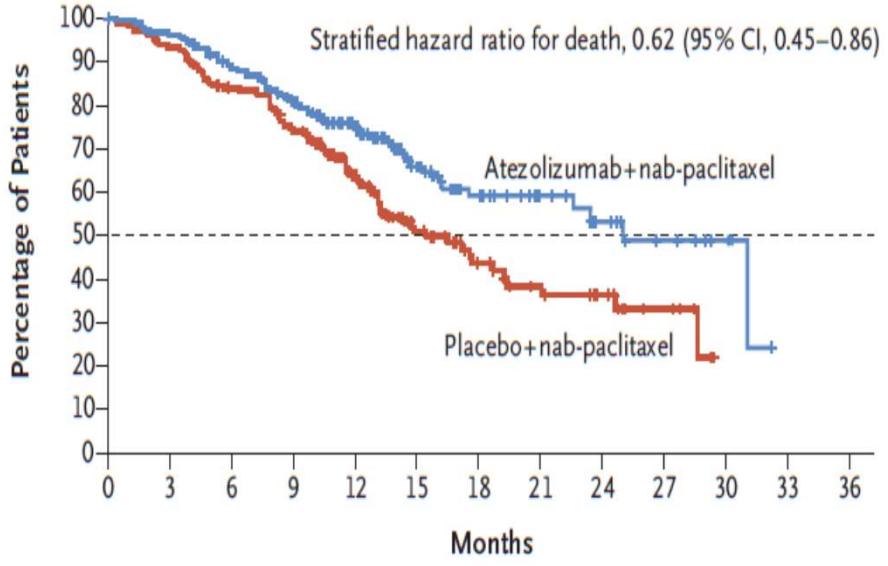
Schmid P, et al. IMpassion130 ESMO 2018 (LBA1_PR) http://bit.ly/2DMhayg

IMPASSION130: PDL1+ COHORT

	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)	1-Yr Rate of Progression-free Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	138/185	7.5 (6.7–9.2)	29.1 (22.2–36.1)
Placebo+Nab-Paclitaxel	157/184	5.0 (3.8–5.6)	16.4 (10.8–22.0)



	No. of Events/ No. of Patients	Median Overall Survival (95% CI)	2-Yr Rate of Progression-free 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)



Schmid P et al. NEJM 2018

IMpassion 130: Overall Survival Update

- Second interim OS analysis with median followup 18 mos with 60% of OS events
- Median OS ITT: 21 mos nP/atezo vs 18.7 mos nP/placebo
  - HR 0.86 (0.72, 1.02) p= 0.078
- PD-L1+ Median OS: 25 mos nP/atezo vs 18 mos nP/placebo
  - HR 0.71 (0.54, 0.93) 2-year OS 51% nP/atezo vs 37% nP/placebo
- Safety nP/atezo/nP/placebo: Steroid use 14%/6%; hypothyroid 18%/5%; hyperthyroid 5%/1%; pneumonitis 4%/<1%

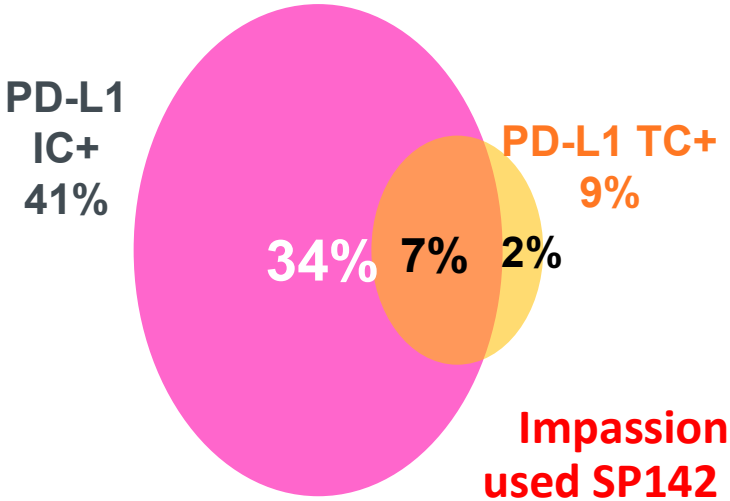
- Clinically meaningful improvement in OS in PD-L1+ population with atezolizumab and no new safety signals/concerns

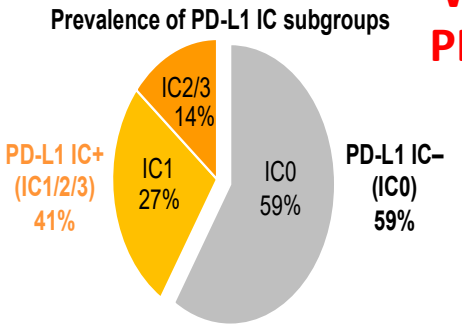
Schmid P et al. ASCO 2019 Abst 1003
Schneeweiss A et al. ASCO 2019 Abst 1068

PD-L1 expression in metastatic TBNC

Different PD-L1 assays provide substantially different results.

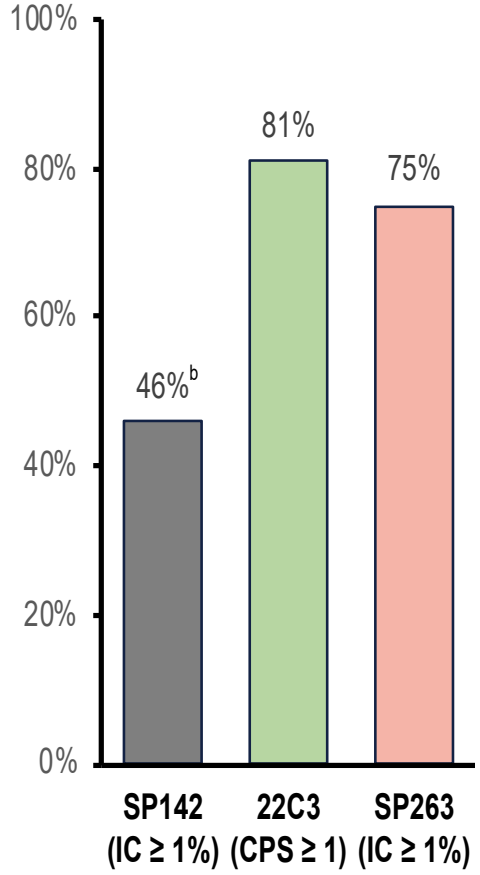
PD-L1 expression with SP142 Assay

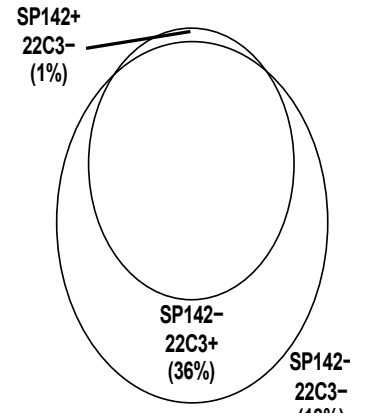


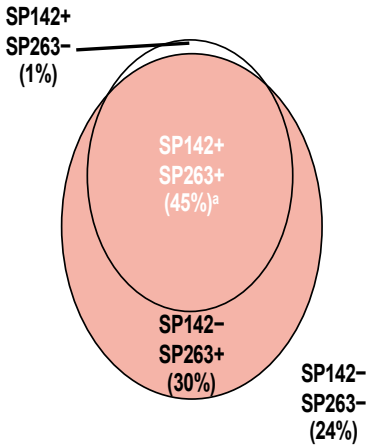


Impassion130 used SP142 assay with cut-off >1% PD-L1 on tumour-infiltrating immune cells

PD-L1 Prevalence with different assays (SP142, 22C3, SP263)



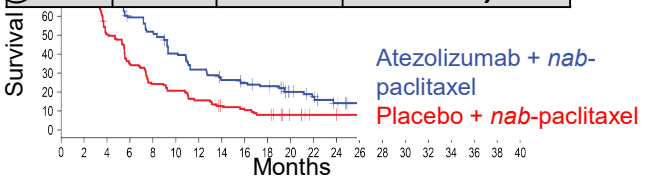


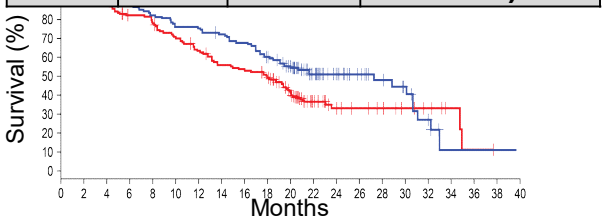


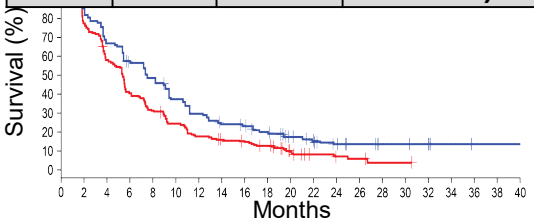
Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04); Rugo, ESMO 2019

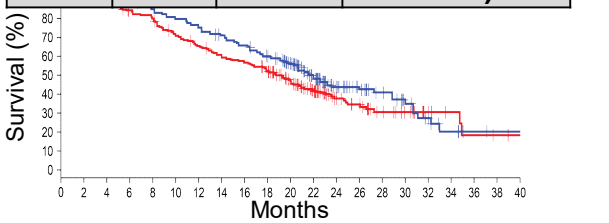
PFS and OS by different PDL1-Assay: SP142, 22C3 and SP263

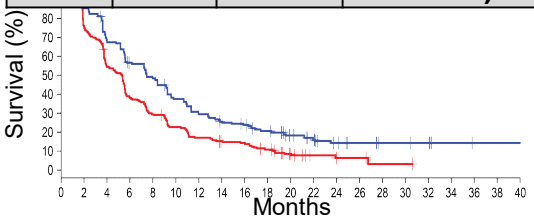
Population	PFS				OS			
	Median PFS, mo			HR (95% CI)	Median OS, mo			HR (95% CI)
	A + nP	P + nP	Δ		A + nP	P + nP	Δ	
SP142 IC ≥ 1%: 46% (285/614)	8.3	4.1	4.2	0.60 (0.47, 0.78)	27.3	17.9	9.4	0.74 (0.54, 1.01)
22C3 CPS ≥ 1: 81% (497/614)	7.5	5.4	2.1	0.68 (0.56, 0.82)	21.6	19.2	2.4	0.78 (0.62, 0.99)
SP263 IC ≥ 1%: 75% (460/614)	7.5	5.3	2.2	0.64 (0.53, 0.79)	22.0	18.7	3.3	0.75 (0.59, 0.96)

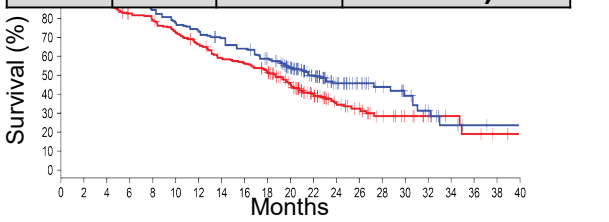










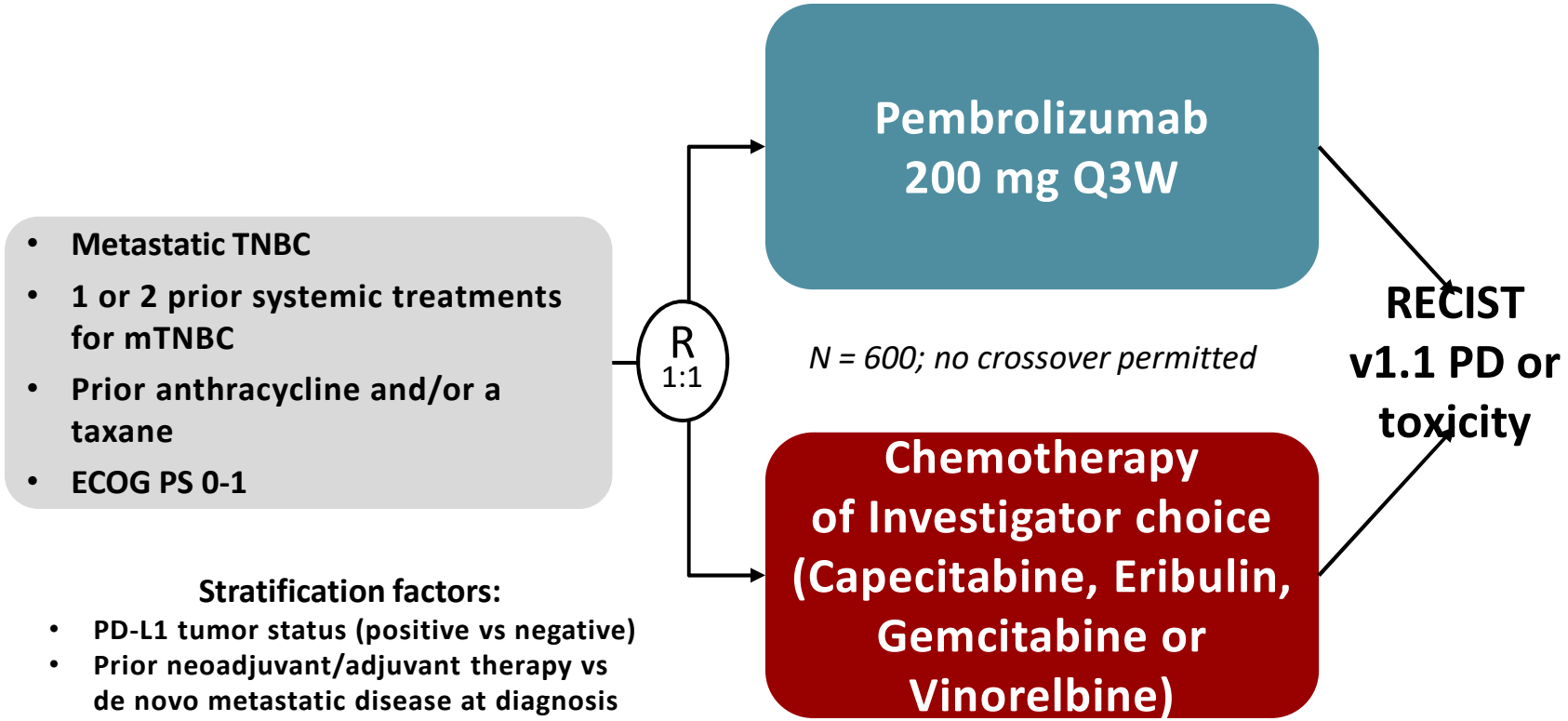


HR adjusted for prior taxanes, presence of liver metastases, age and ECOG PS.

Rugo, et al ESMO 2019

Pembrolizumab versus chemotherapy in 2L/3L TNBC

KEYNOTE 119 study design



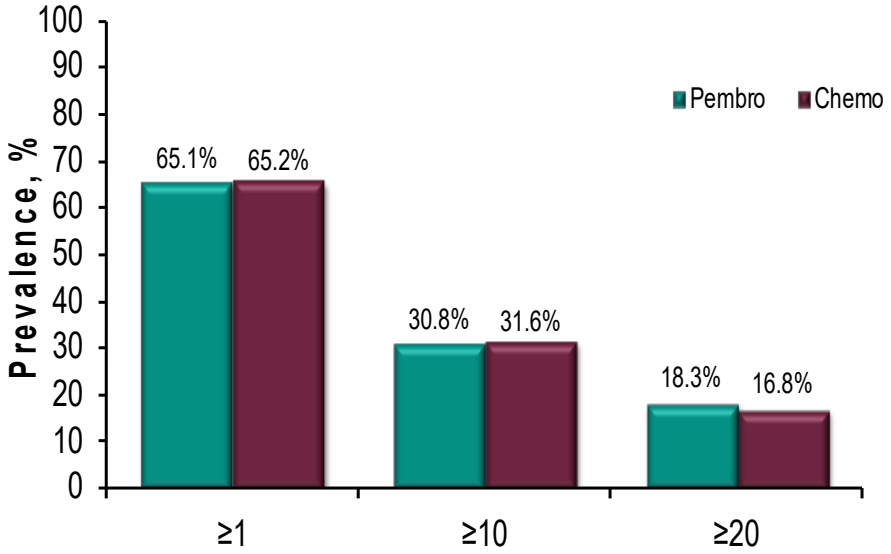
- **Co-primary endpoints were OS in the CPS ≥10, in the CPS ≥1, and in the ITT populations**

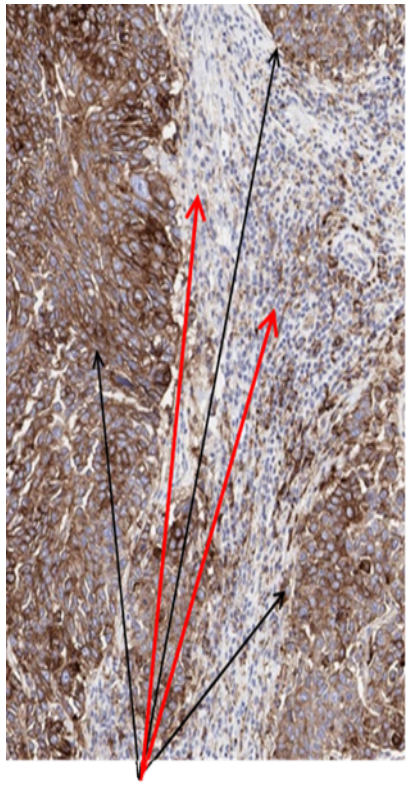
Cortes, et al. ESMO 2019

PD-L1 Expression Analysis: Combined Positive Score (CPS; 22C3)

$$\text{CPS} = \frac{\text{\# PD-L1–staining cells (tumor cells, lymphocytes, macrophages)}}{\text{Total \# viable tumor cells}} \times 100$$

- PD-L1 IHC 22C3 pharmDx (Agilent Technologies)
- Positive PD-L1 expression: CPS ≥10 and CPS ≥1





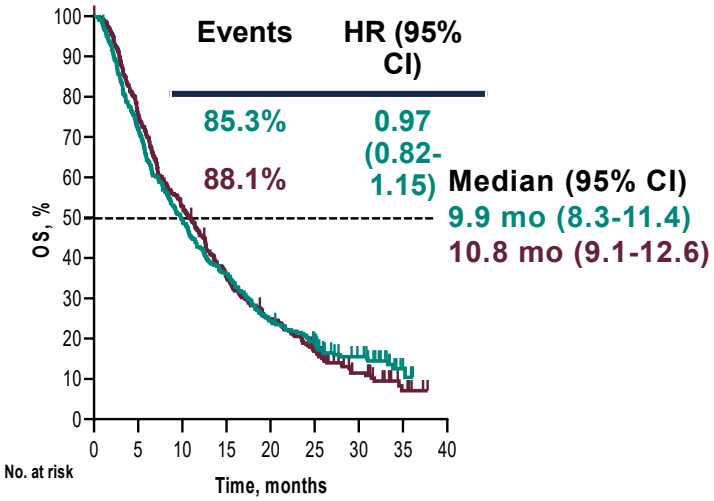
PD-L1 positive cells (Tumor Cells, Immune Cells)

Cortes, et al. ESMO 2019

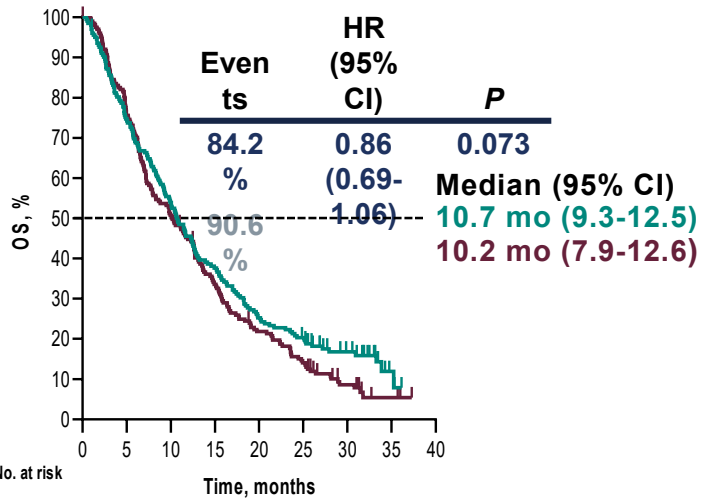
1. Balar AV et al. Presented at ESMO 2016; Oct 7-11, 2016; Copenhagen, Denmark. Abstr. LBA32-PR; 2. Cortes, ESMO 2019.

Pembrolizumab vs chemo in 2L/3L TNBC: OS by PD-L1 CPS (KN119)

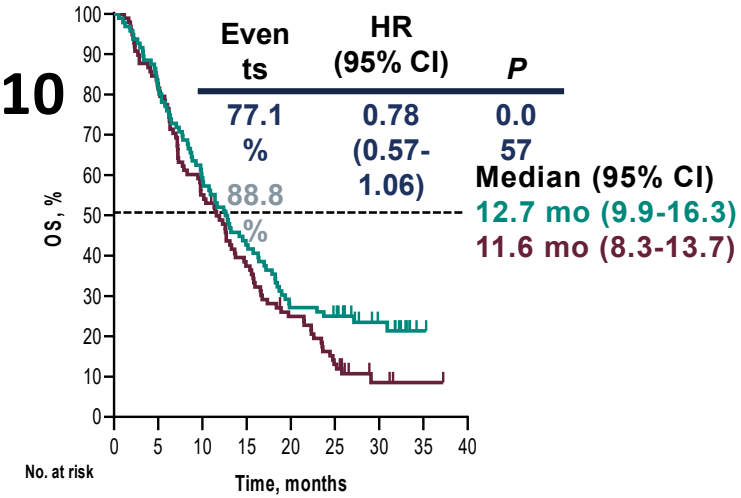
ITT



CPS ≥1

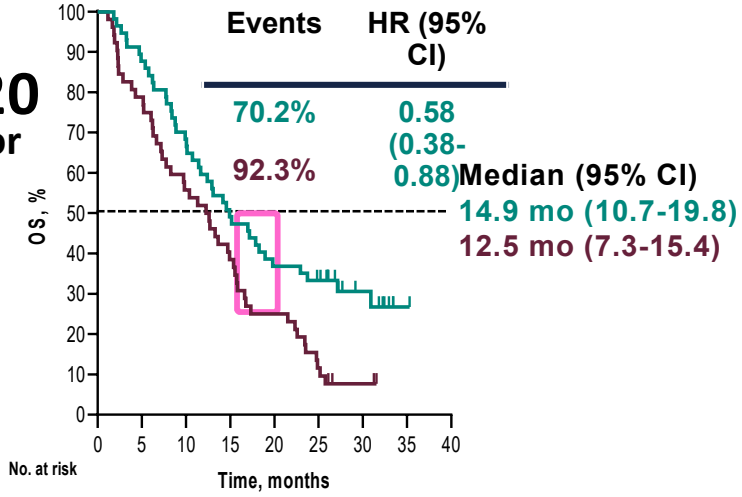


CPS ≥10



CPS ≥20

Exploratory

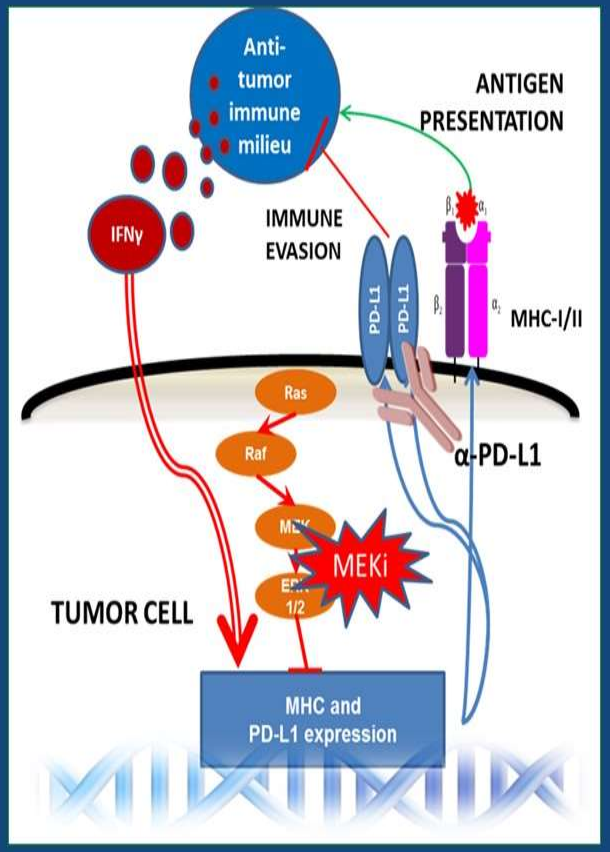


Cortes, et al. ESMO 2019

OS in the ITT, CPS ≥1 and CPS ≥10 populations were primary endpoints; OS in the CPS ≥20 population was an exploratory endpoint.

Can targeted agents improve response?

- The MEK pathway is active in TNBC
- Activation suppresses inflammatory responses to T cells, leading to reduced antigen presentation and PD-L1 expression
- Combining MEK inhibitors with anti-PD-L1 inhibitors may improve antigen presentation while blocking PD-L1-mediated suppression

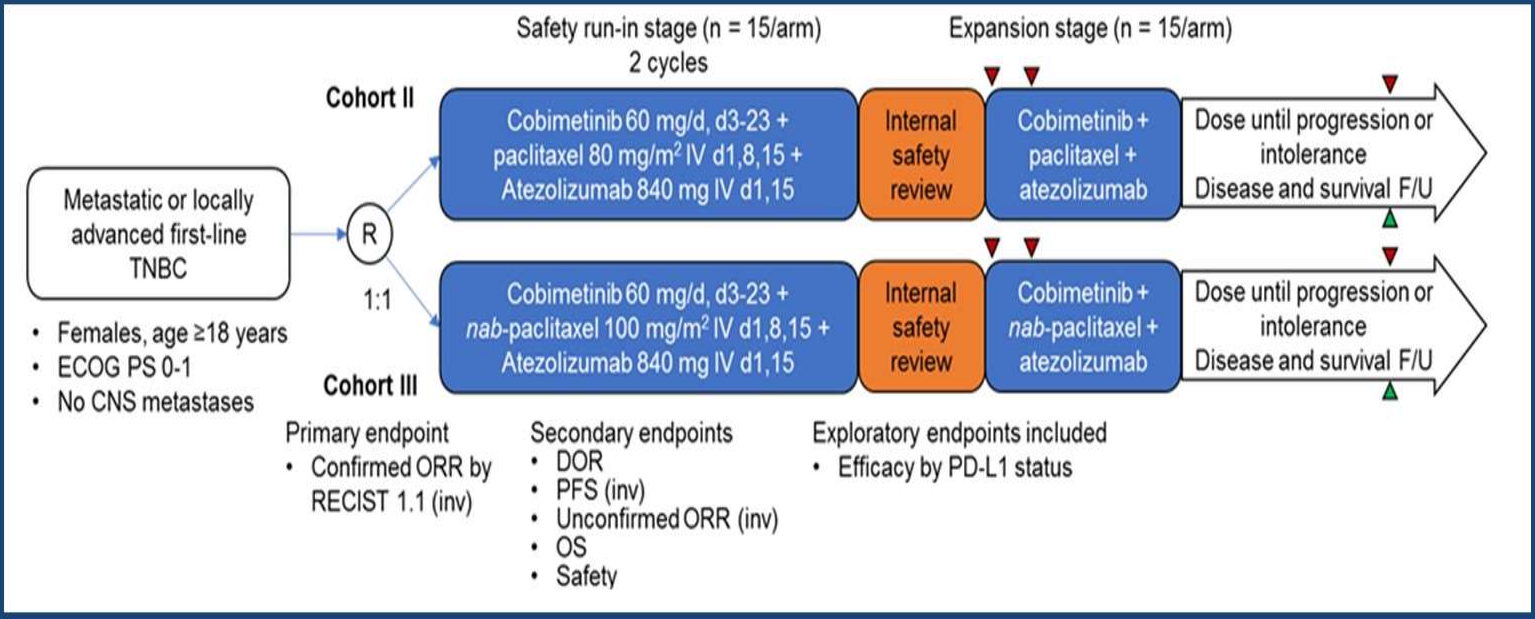


Presented By Justin Balko at 2019 ASCO Annual Meeting

Loi et al...Balko, CCR 2016

Can targeted agents improve response?

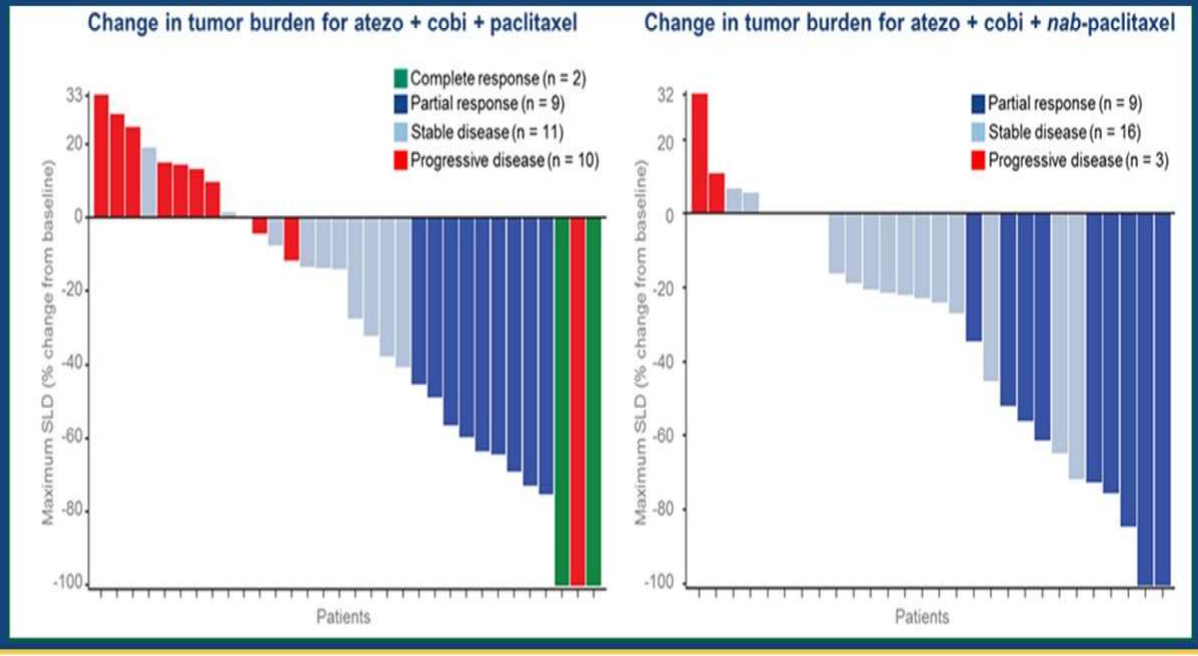
- Phase II COLET Study: Atezolizumab + Cobimetinib + Paclitaxel/*nab*-paclitaxel as First-line Treatment for Patients with Locally Advanced or Metastatic Triple-negative breast Cancer (Brufsky et al)



Brufsky et. al. ASCO 2019

Phase II COLET Study: Atezolizumab + Cobimetinib + Paclitaxel/nab-paclitaxel

- Safety
  - 2 grade 5 events in P arm
  - Diarrhea and rash obvious changes from A + nP (i130)
- Outcomes - positive
- Comparison to IM130?

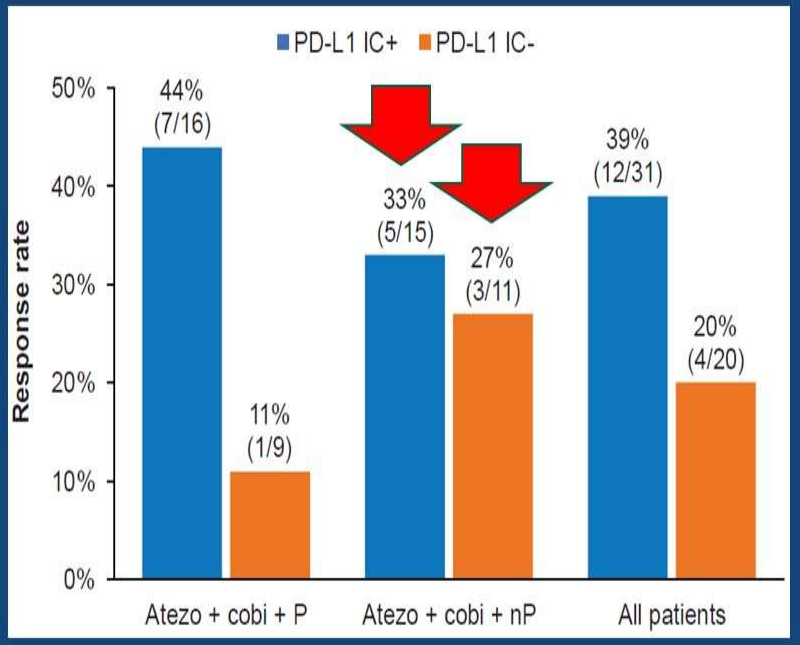


Brufsky et al. ASCO 2019

PD-L1 IC status in COLET

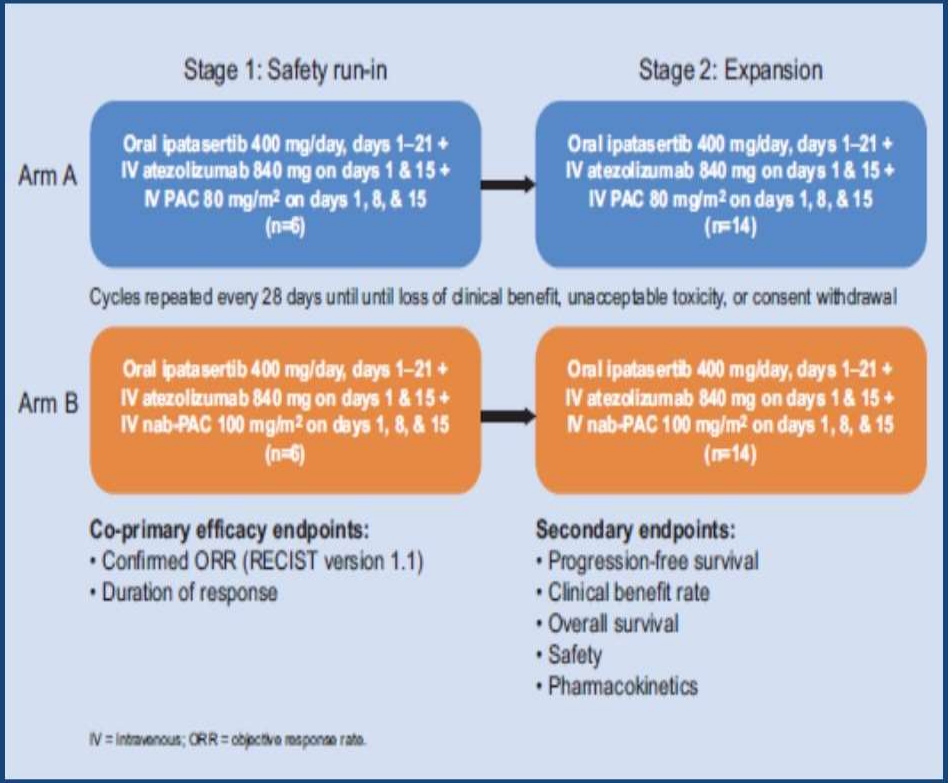
N=63

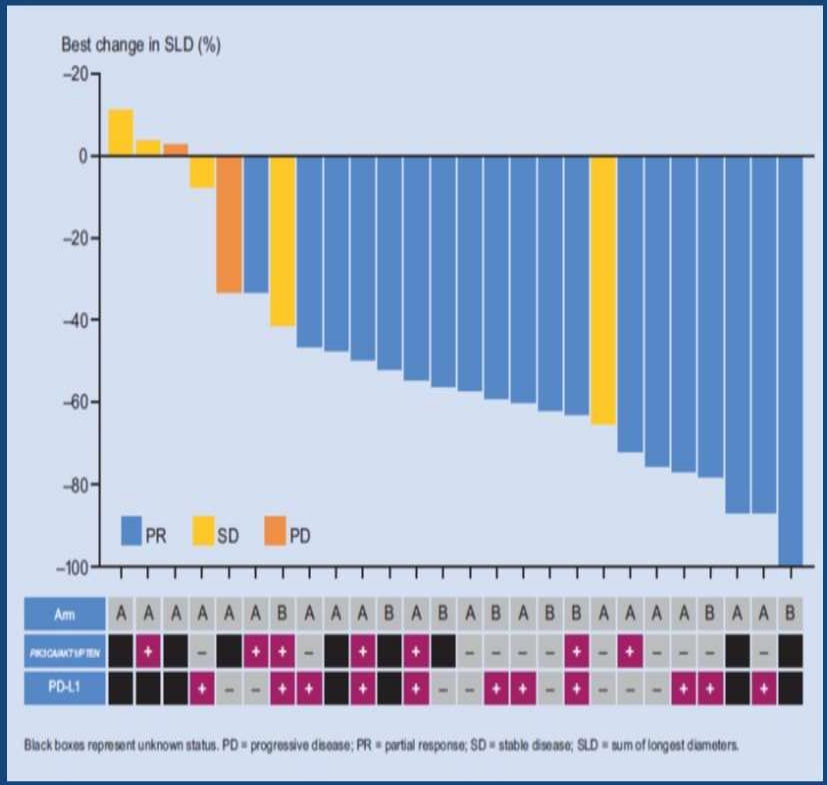
- Generally higher response rates in PD-L1 IC+ tumors
- Does MEKi enhance activity in PD-L1 IC- tumors? What about PD-L1-IC+?
- Biomarkers
  - On-therapy biopsies do not appear to have been collected
  - Open question as to whether MEKi is 'working'



6 months PFS 55% vs 20% in PDL1+ vs PDL-1-
(65% had received neo/adjuvant therapy

MEKi versus AKTi: Phase Ib of ipatasertib, atezo and P/nab-P





Results being confirmed in IPATunity130

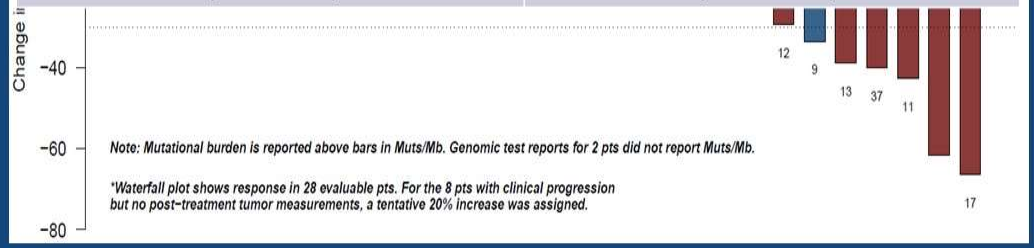
Are high TMB patients better responders to ICI?

- Pembrolizumab in Patients with Metastatic Breast Cancer with reported High TMB (TAPUR) (Alva et al)
  - Advanced MBC without standard treatment options.
  - Single-arm study (pembro).
  - High TMB – platform dependent
  - Primary endpoint is objective response (OR) or stable disease (SD) at 16+ wks.
  - Secondary endpoints are progression-free survival (PFS), overall survival (OS) and toxicity per CTCAE.

Pembrolizumab in Patients with Metastatic Breast Cancer with reported High TMB (TAPUR)

- ~10% of highest TMB mBC patients
- HR status currently unknown
- Activity, particularly in HER2- patients
- No study-internal association with TMB
- Difficult to identify a 'control'

Clinical Outcomes	
DC (OR or SD 16+wks) N (%), [90% CI]	10 (37%), [24%, 46%]
OR (CR or PR) N (%), [95% CI]	6 (21%), [8%, 41%]
mPFS, wks, (95% CI)	10.6 (7.7, 21.1)
mOS, wks, (95% CI)	31.6 (11.9, inf)



Study Design

Key eligibility criteria

- Metastatic breast cancer
- HR + (ER and/or PR >1%, HER2-negative)
- Measurable or evaluable disease
- At least 2 prior lines of hormonal therapy (adjuvant plus metastatic setting) or appropriate candidates for chemotherapy
- 0-2 prior lines of chemotherapy for advanced disease
- No prior eribulin or PD-1/PD-L1 inhibitor therapy
- Archival tumor tissue required (or biopsy)*
- ECOG PS 0-2

N=88

R
1:1

Eribulin + Pembrolizumab

Pembrolizumab 200 mg IV
- On day 1 of 21-day cycle

+ Eribulin 1.4 mg/m^2 IV
- On days 1, 8 of 21-day cycle

Restaging scans obtained every 9 weeks

Eribulin:

Eribulin 1.4 mg/m^2 IV
- On days 1, 8 of 21-day cycle

Pembrolizumab:

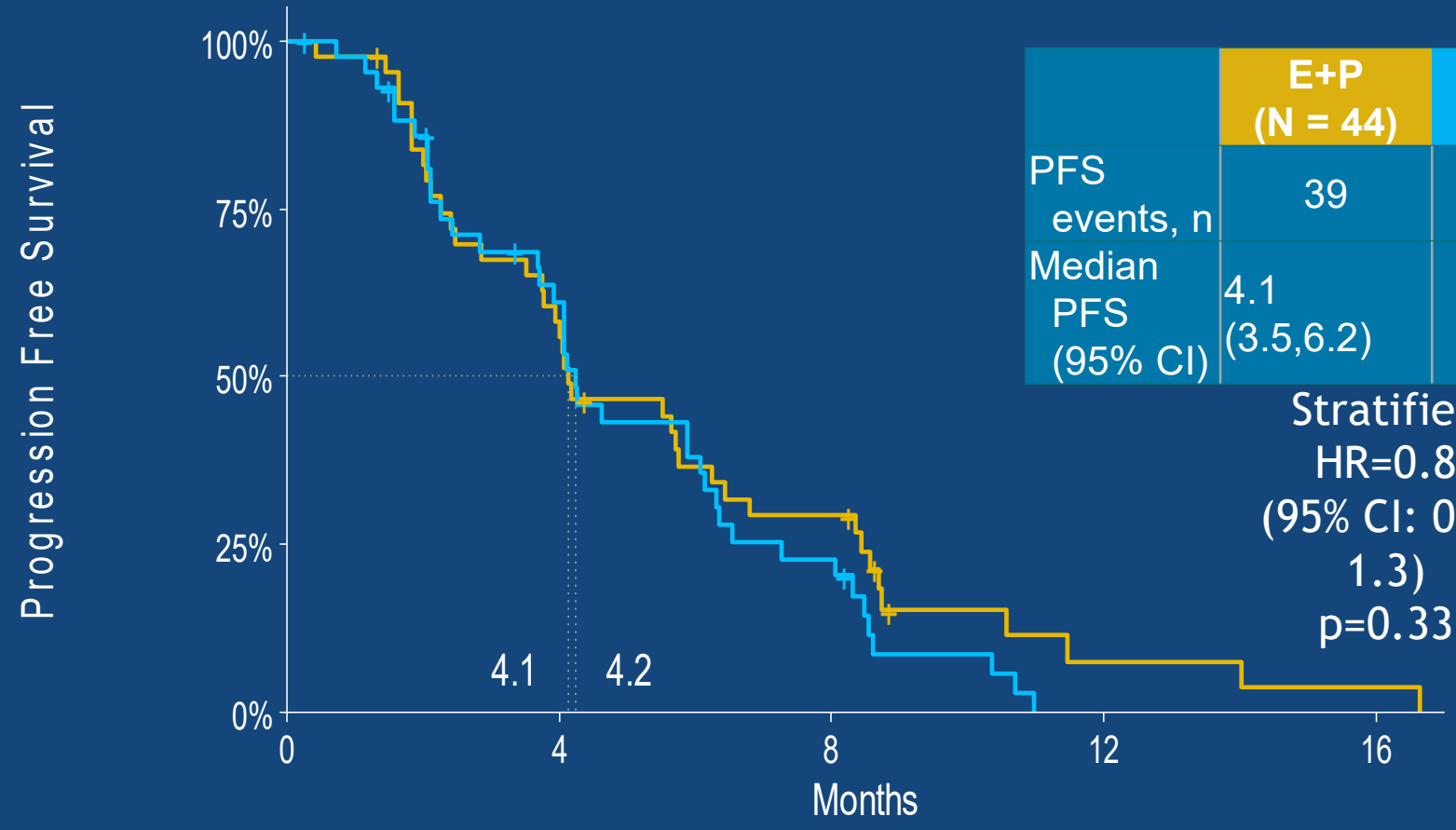
Pembrolizumab 200 mg IV
- On day 1 of 21-day cycle

Biopsy at time of progression

*Serial blood collected for ctDNA and PBMCs and stool collected for microbiome analyses

NCT03051659

Results: Progression Free Survival (ITT)

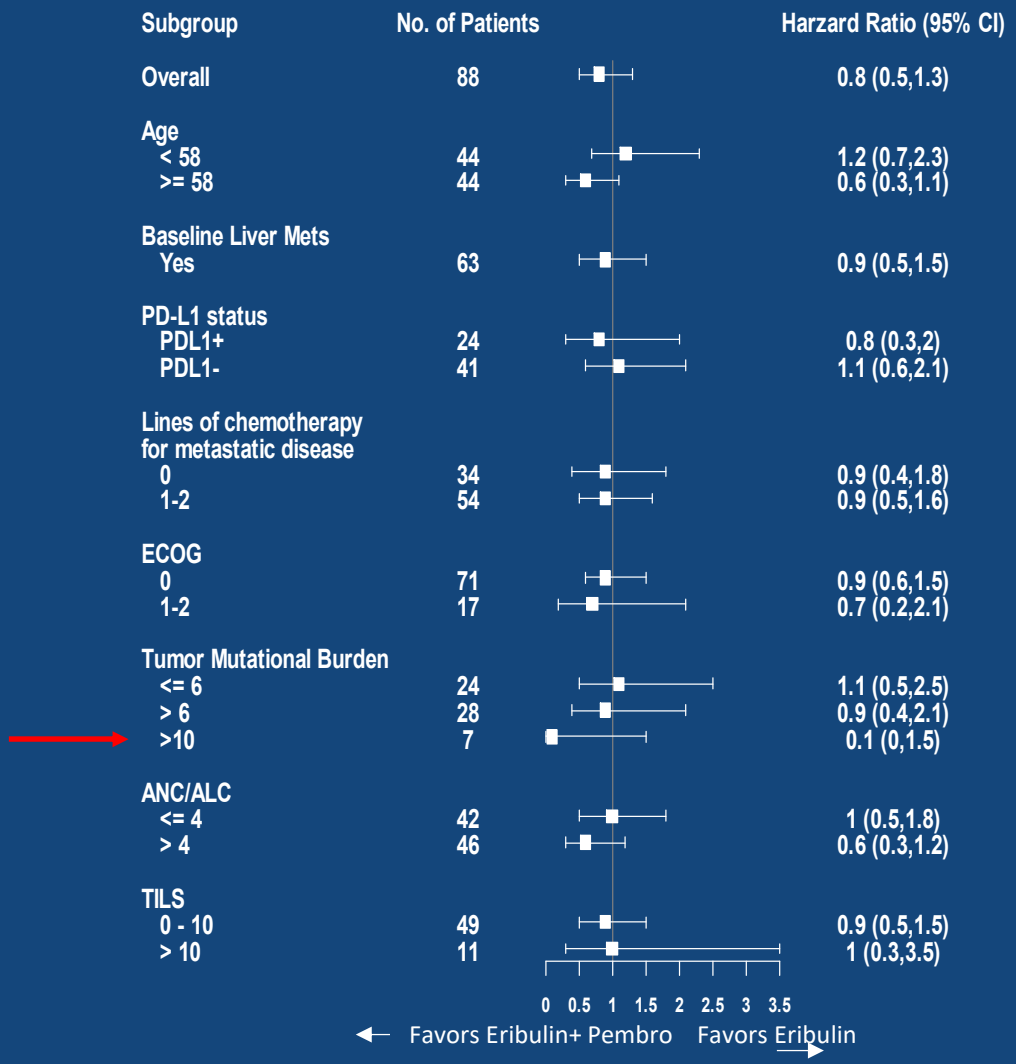


	E+P (N = 44)	E (N = 44)
PFS events, n	39	39
Median PFS (95% CI)	4.1 (3.5,6.2)	4.2 (3.7,6.1)

Stratified HR=0.8 (95% CI: 0.5, 1.3) p=0.33

Eribulin+Pembro	44	25	12	2	1
Eribulin	44	24	9	0	0

PFS subgroup analysis: ITT population



WJOG: West Japan Oncology Group

NEWBEAT

WJOG9917B NEWBEAT study (Phase II)

MBC 1st line
HER2-negative
ECOG PS 0-1
Measurable lesion(+)
n=51

→

Nivolumab
+
Paclitaxel
+
Bevacizumab

Nivolumab 240 mg/body	Days 1 and 15	IV infusion over 30 minutes
Paclitaxel 90 mg/m^2	Days 1, 8 and 15	IV infusion over one hour
Bevacizumab 10 mg/kg	Days 1 and 15	IV infusion over 90 minutes*

(*The duration of infusion may be shortened from the second and subsequent doses.)

Each cycle will consist of 28 days.

[Primary endpoint]

Objective response rate by central assessment

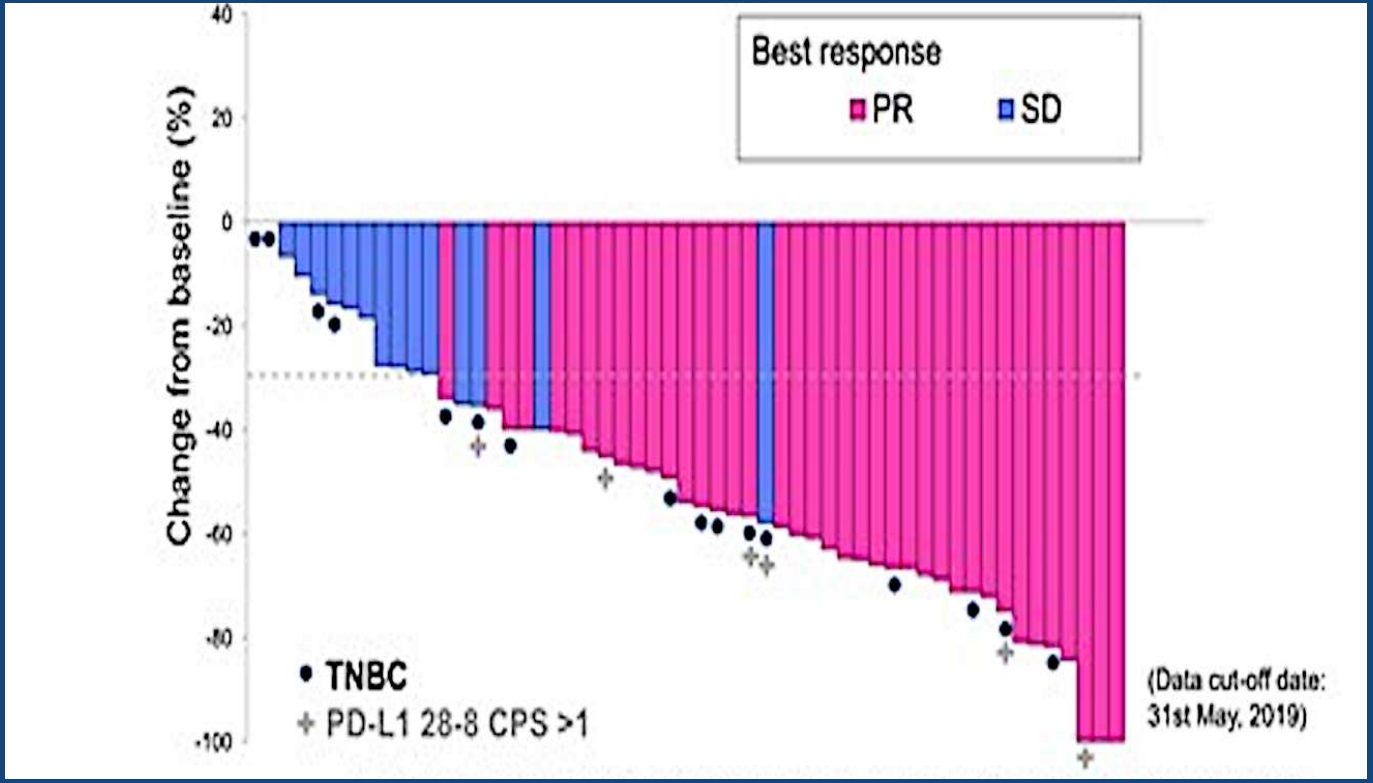
[Secondary endpoints]

Safety, disease control rate, progression free survival, overall survival

Ozaki Y, et al. SABCS 2019, PD1-03

NEWBEAT TRIAL

Best percentage change in tumor size from baseline (N=56)
Central Assessment

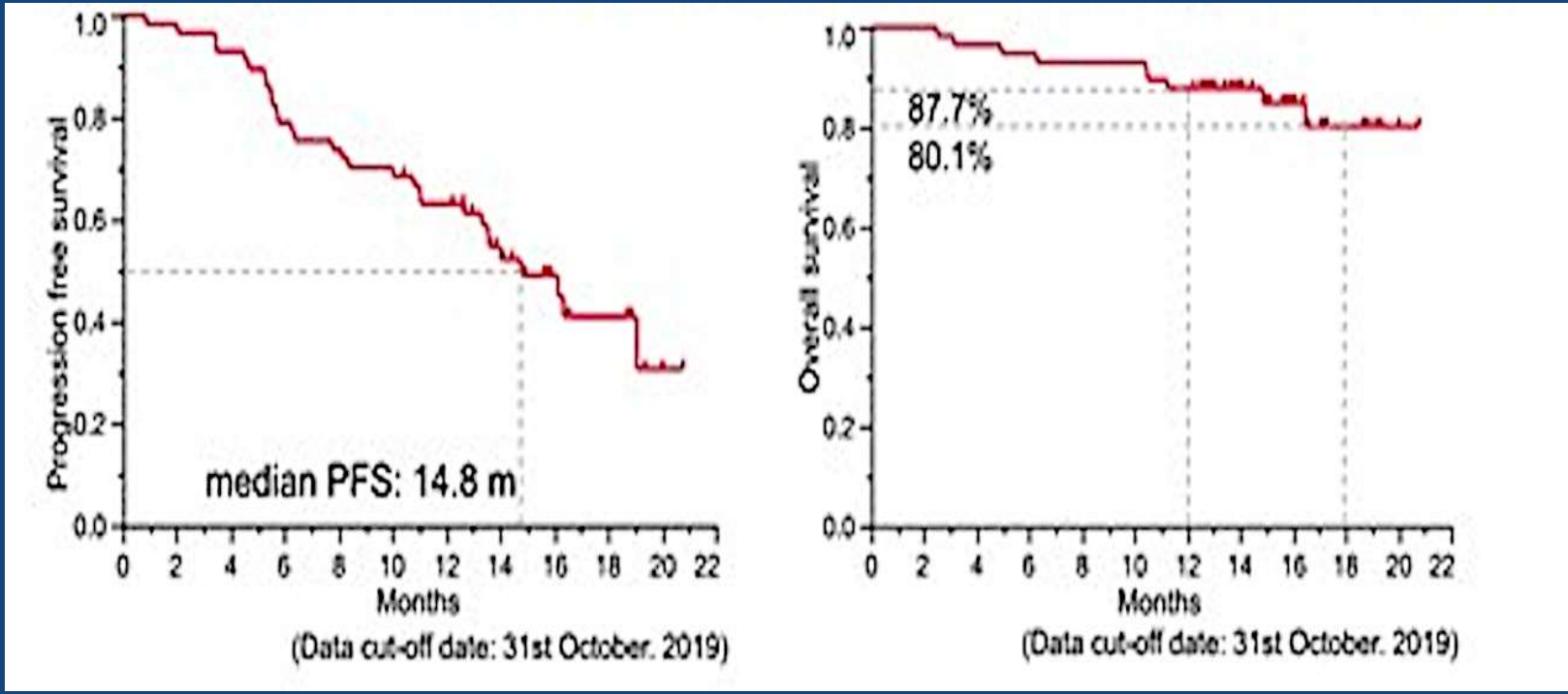


ORR: 70%
(95% CI: 55.9-81.2)

Ozaki Y, et al. SABCS 2019, PD1-03

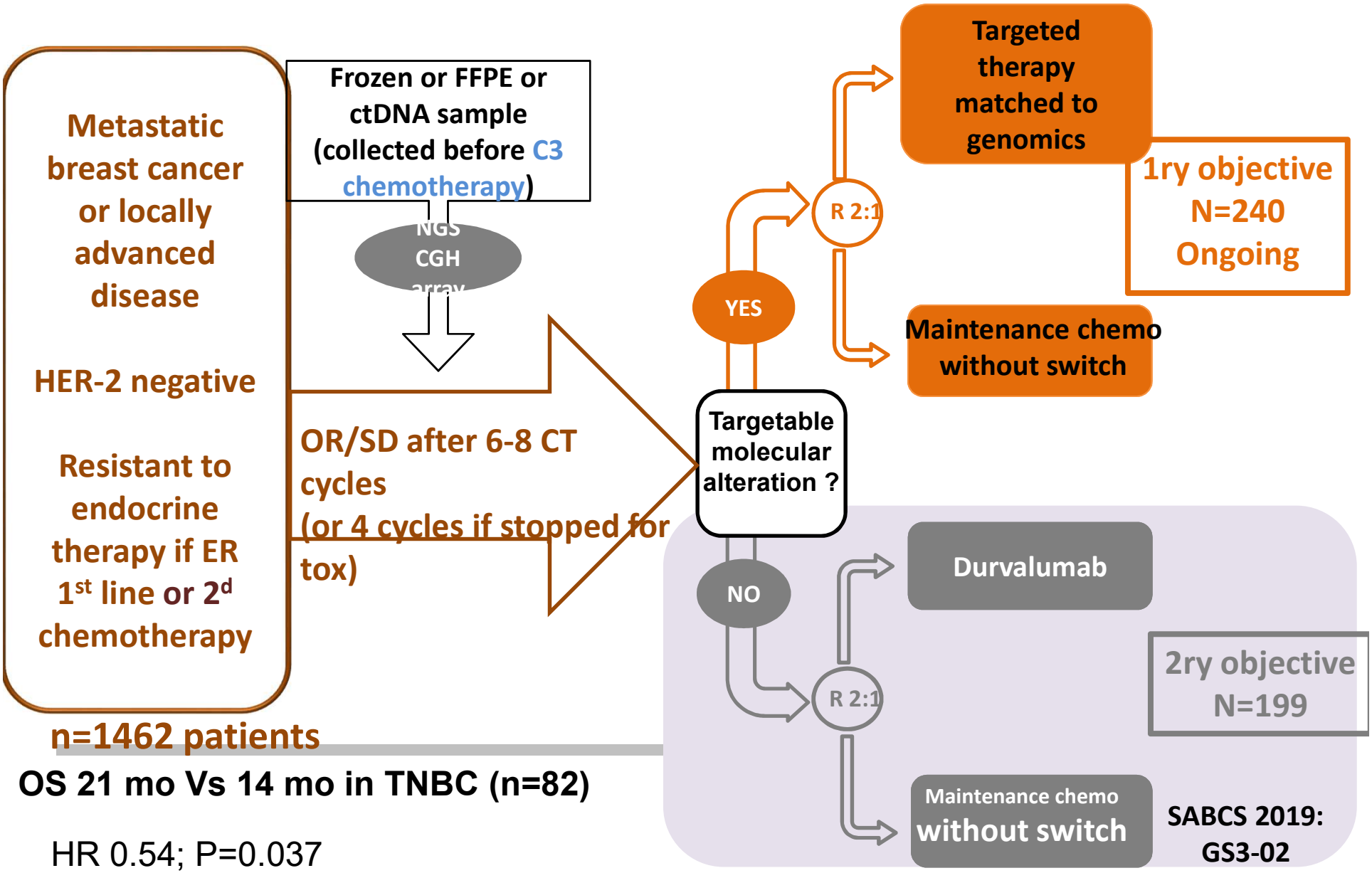
NEWBEAT TRIAL

Kaplan Meier curves for PFS and OS (investigator assessment)



Ozaki Y, et al. SABCS 2019, PD1-03

SAFIR-02 BREAST : Study Design

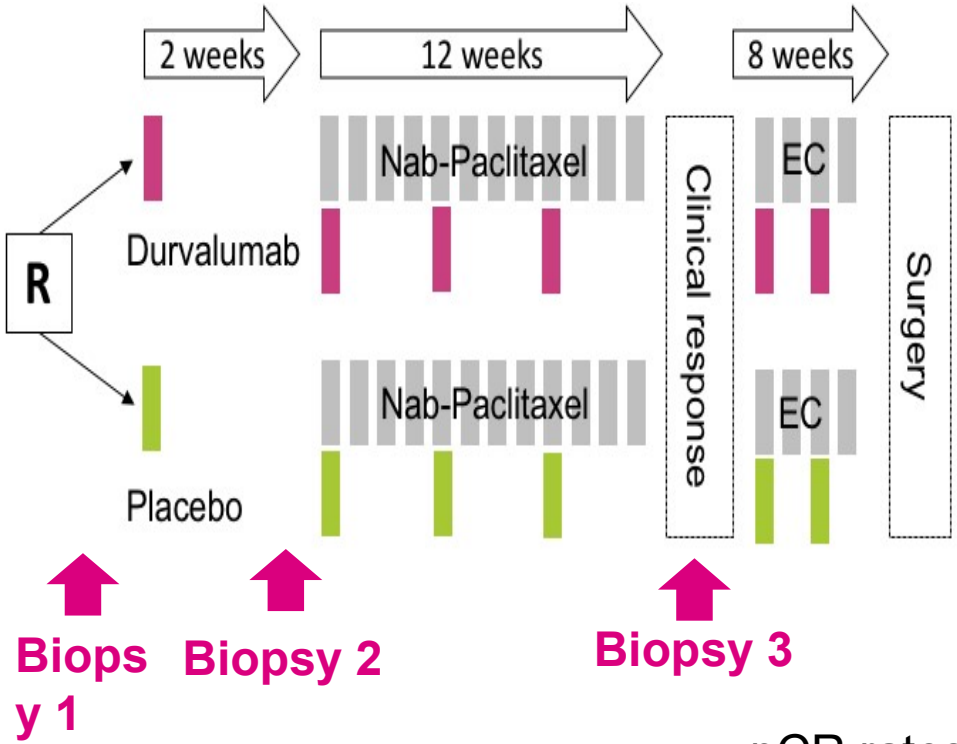


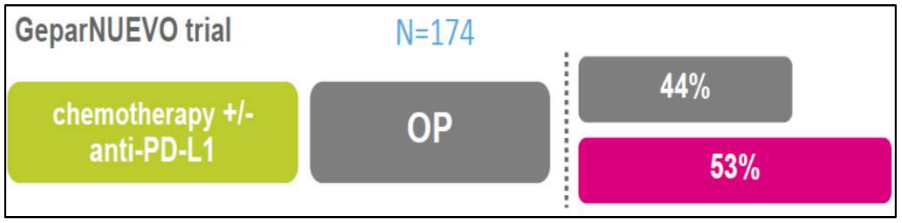
OS 21 mo Vs 14 mo in TNBC (n=82)

HR 0.54; P=0.037

Neoadjuvant/Adjuvant Clinical Trials

GeparNeuvo: Neoadjuvant Durvalumab

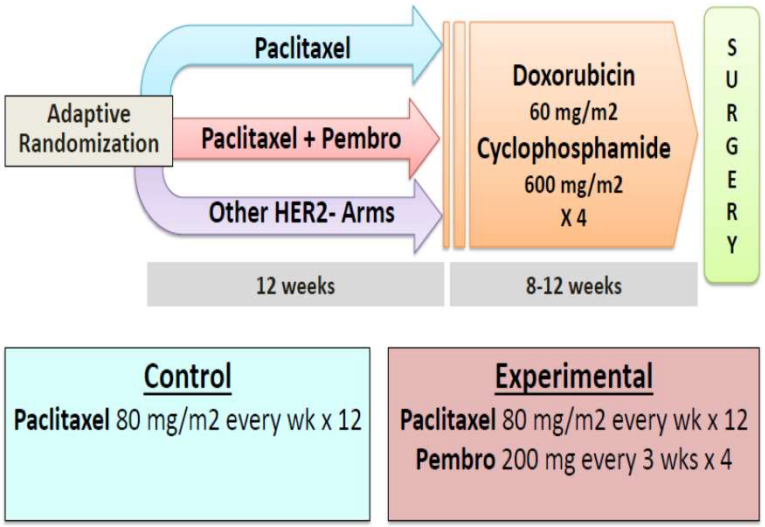




pCR rates:
Window cohort (61 vs 41.4%)
Stage ≥ IIa (55.5 vs 38.6%)

Loibl et al, ASCO 2018; Loibl et al, Ann Onc 2019

Neoadjuvant Pembrolizumab: Efficacy Results from the I-SPY2 Adaptively Randomized Platform Trial



Signature	Estimated pCR rate (95% probabilty interval)		Probability pembro is superior to control	Predictive probability of success in phase 3
	Pembro	Control		
All HER2-	0.46 (0.34 – 0.58)	0.16 (0.06 – 0.27)	> 99%	99%
TNBC	0.60 (0.43 – 0.78)	0.20 (0.06 – 0.33)	>99%	>99%
HR+/HER2-	0.34 (0.19 – 0.48)	0.13 (0.03 – 0.24)	>99%	88%

Current I-SPY2 Immunotherapy Arms:

- **Pembolizumab/Paclitaxel-> Pembrolizumab (no AC): SABCS 2019 (P3-09-12)**
- Olaparib/Durvalumab/Paclitaxel->AC
- SD-101/Pembrolizumab/Paclitaxel->AC

Nanda et al, ASCO 2017

Neoadjuvant Pembrolizumab: Immune-related Adverse Events from the I-SPY2 Adaptively Randomized Platform Trial

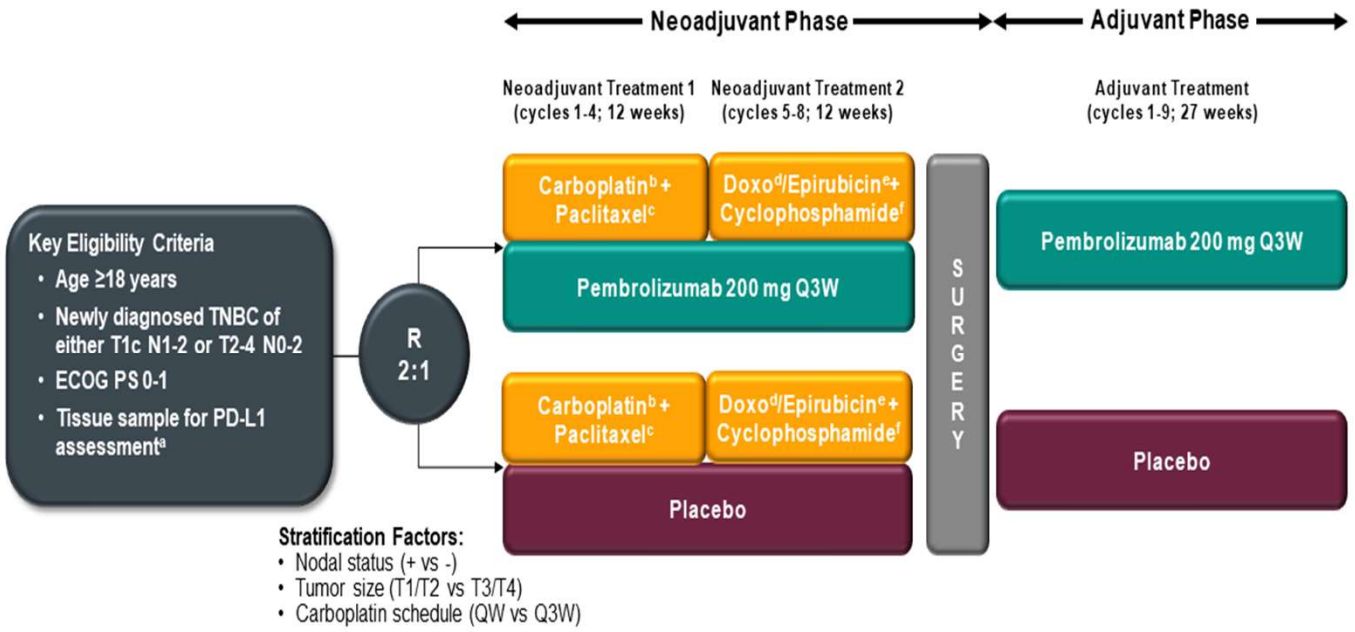
	Pembrolizumab (n=69) % (n)		Control (n=180) % (n)	
	All grades	Grade 3-5	All grades	Grade 3-5
Hypothyroidism	8.7 (6)	1.4 (1)	0.6 (1)	0 (0)
Hyperthyroidism	4.3 (3)	0 (0)	0 (0)	0 (0)
Adrenal Insufficiency^	8.7 (6)	7.2 (5)	0 (0)	0 (0)
Hepatitis	2.9 (2)	2.9 (2)	0 (0)	0 (0)
Pneumonitis	2.9 (2)	0 (0)	1.1 (2)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

Adrenal insufficiency

- 5/6 presented >10 wks after last pembro dose
- 1/6 presented during pembro (5 wks after 1st pembro dose)
- Rates of primary/secondary AI across studies are 0.8% and 0.6%

Schmid KN522 ESMO 2019

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 QW.
[c]Paclitaxel dose was 80 mg/m² QW.
[d]Doxorubicin dose was 60 mg/m² Q3W.
[e]Epirubicin dose was 90 mg/m² Q3W.
[f]Cyclophosphamide dose was 600 mg/m² Q3W.

Primary Endpoints:
- pCR
- EFS

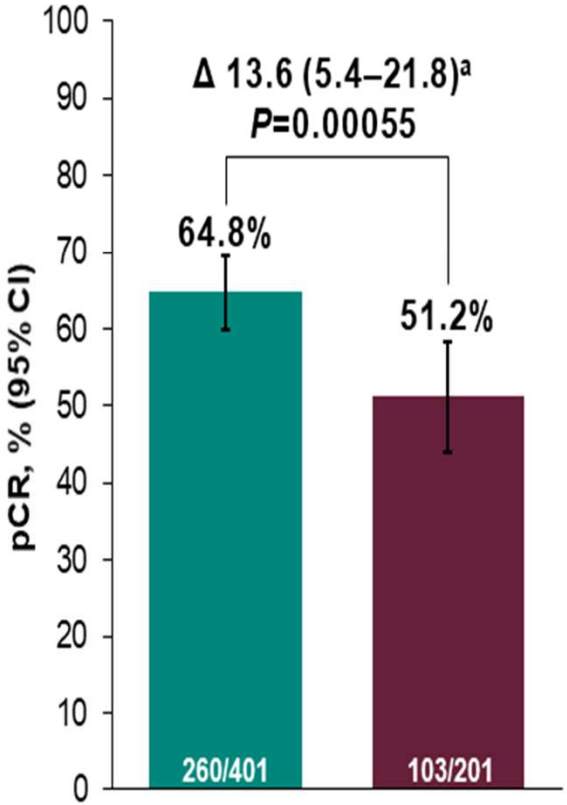
Secondary Endpoints:
- OS
- pCR/EFS/OS in PD-L1+
- Safety

Exploratory Endpoints:
- RCB
- EFS by pCR
- EFS/pCR by TILs

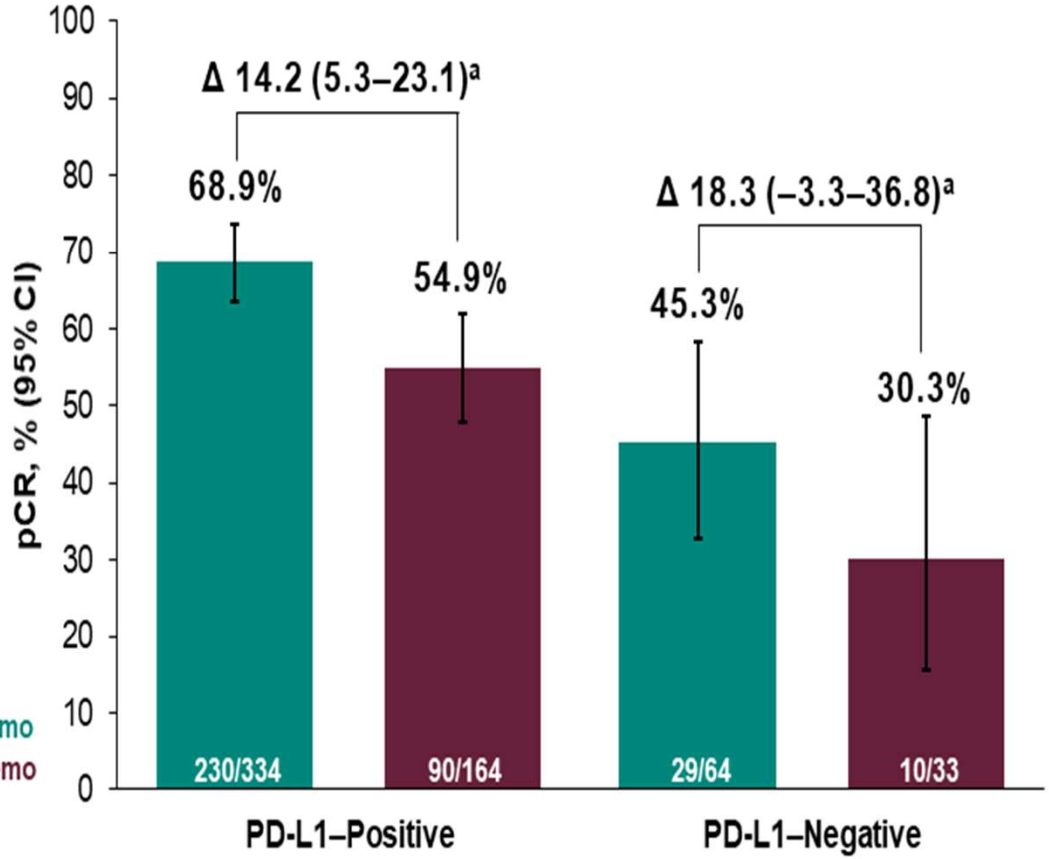
SABCS 2019 (GS3-03)
- **RCB**
- **EFS updates**
- **pCR in subgroups**

Pathological Complete Response at IA1

Primary Endpoint: ypT0/Tis ypN0



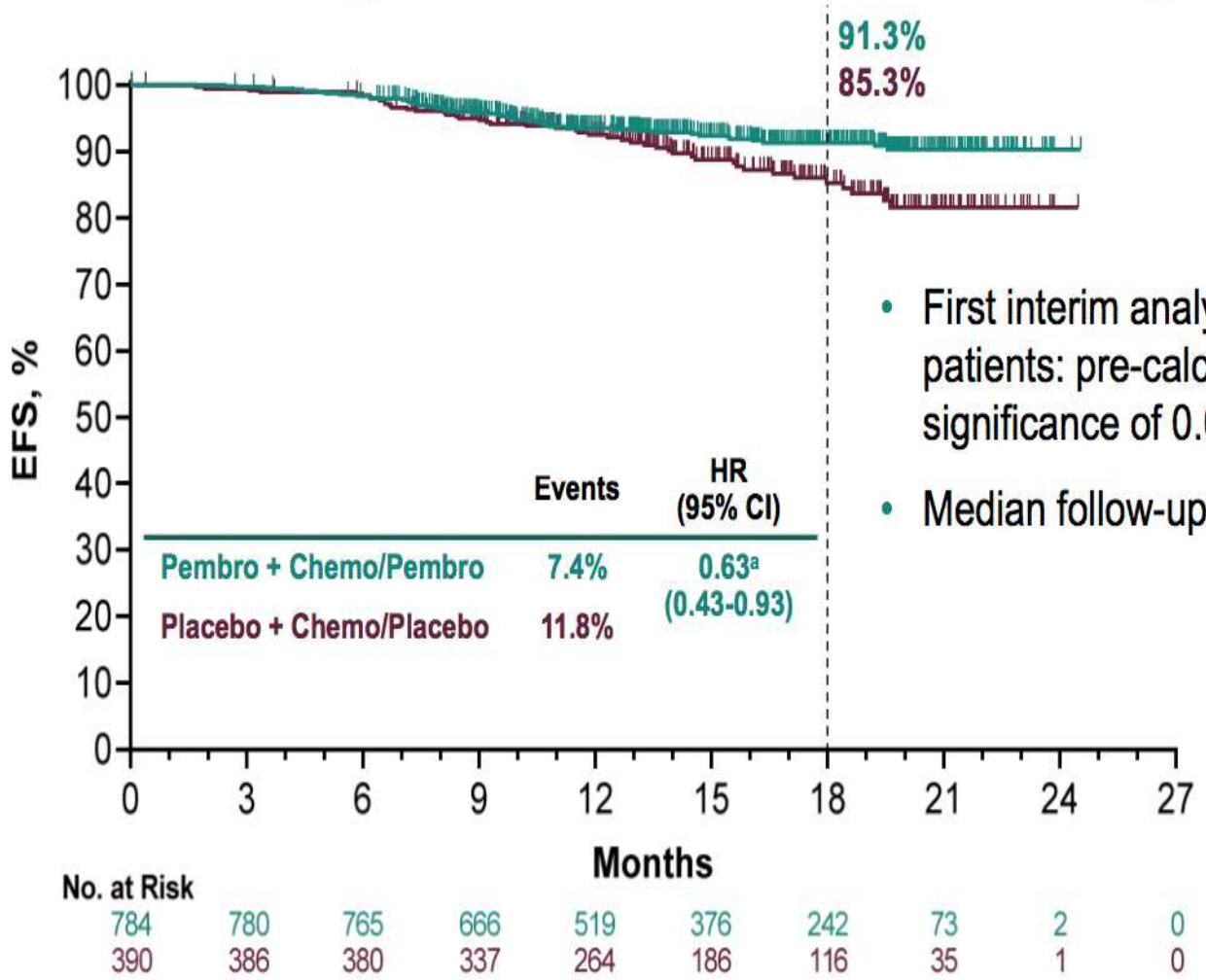
By PD-L1 Status[b]: ypT0/Tis ypN0



Pembro + Chemo
Placebo + Chemo

[a]Estimated treatment difference based on Miettinen & Nurminen method stratified by randomization stratification factors. [b]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.

First Pre-planned Interim Analysis for EFS

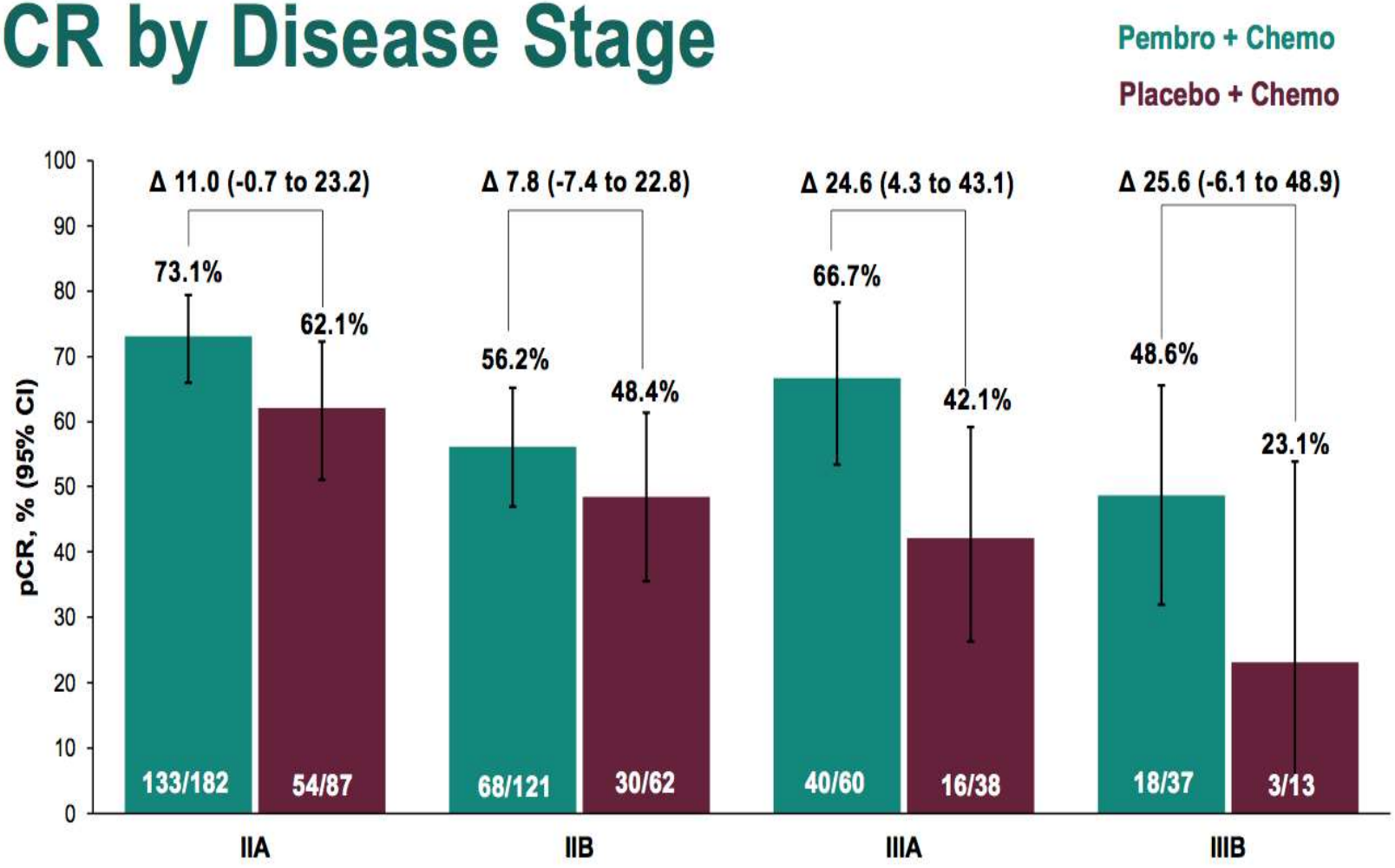


- First interim analysis of EFS based on 1174 patients: pre-calculated P value boundary for significance of 0.000051 (HR <0.4)
- Median follow-up, 15.5 months

[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.

San Antonio Breast Cancer Symposium®, December 10-14, 2019

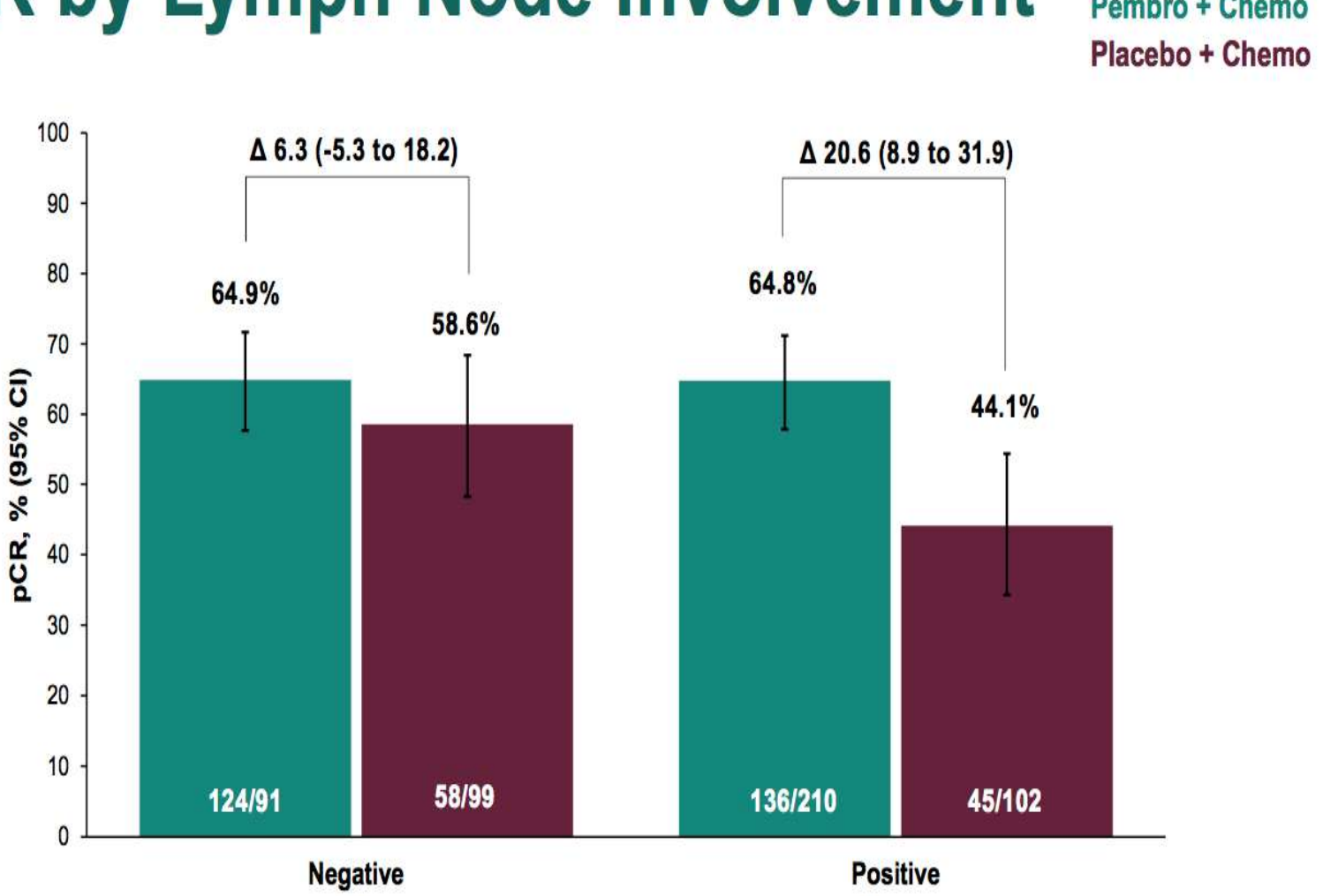
pCR by Disease Stage



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

San Antonio Breast Cancer Symposium®, December 10-14, 2019

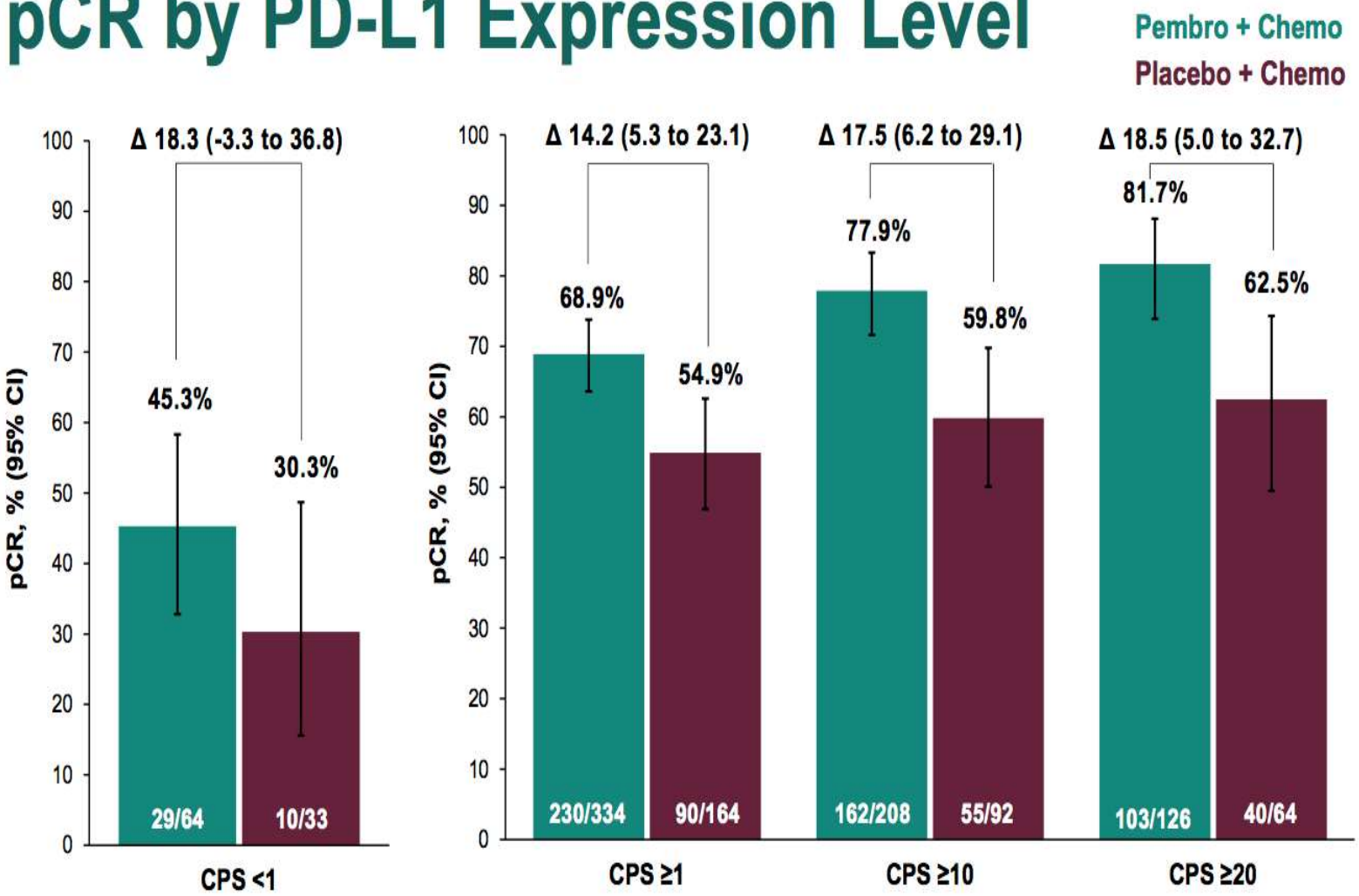
pCR by Lymph Node Involvement



Pre-specified analysis. Lymph node involvement was determined by the study investigator by physical exam, sonography/MRI and/or biopsy. Estimated treatment difference based on unstratified Miettinen & Nurminen method. Data cutoff date: September 24, 2018.

San Antonio Breast Cancer Symposium®, December 10-14, 2019

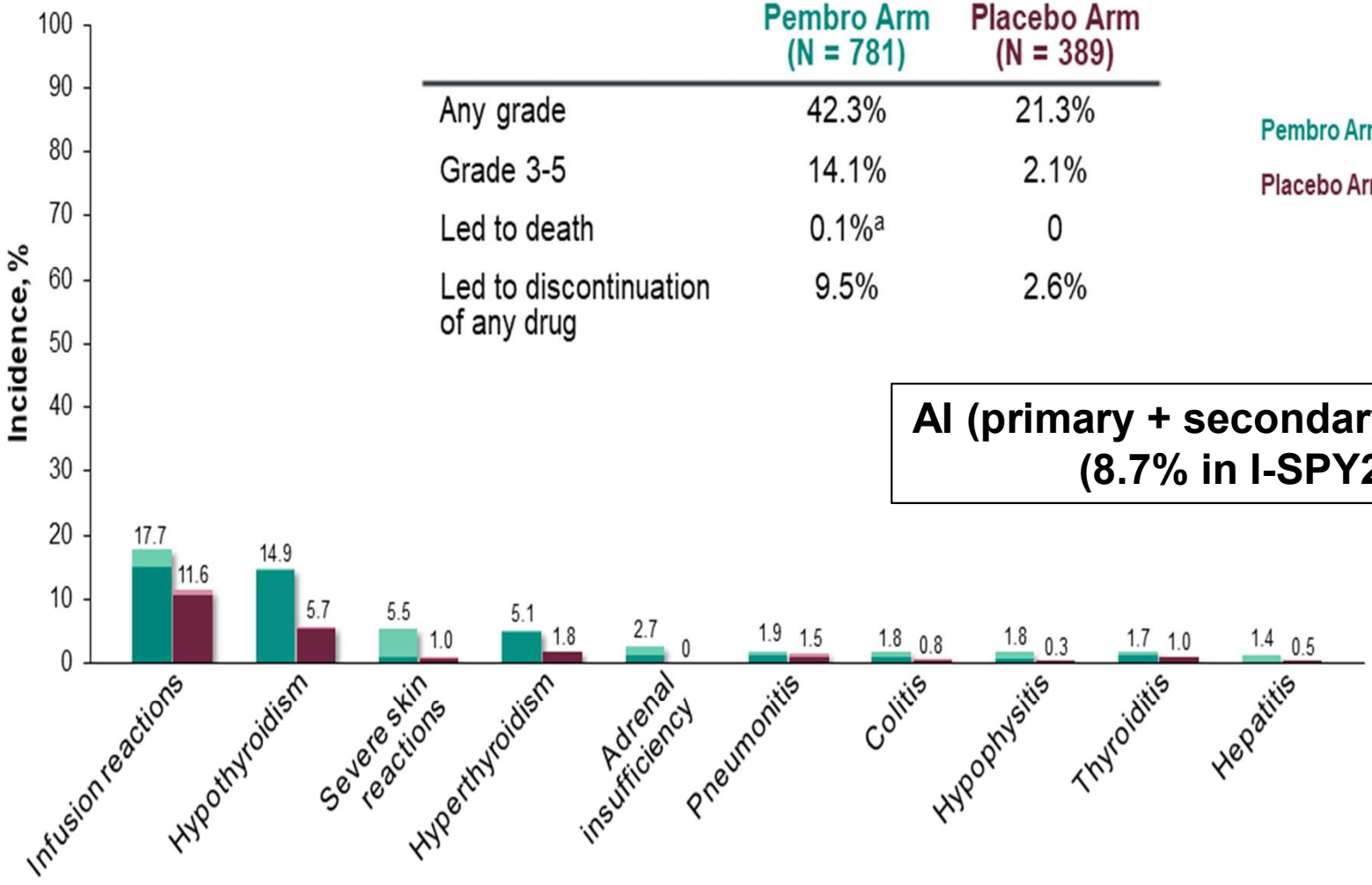
pCR by PD-L1 Expression Level



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.

Immune-Mediated AEs and Infusion Reactions in Combined Phases: IA2

	Pembro Arm (N = 781)	Placebo Arm (N = 389)
Any grade	42.3%	21.3%
Grade 3-5	14.1%	2.1%
Led to death	0.1%[a]	0
Led to discontinuation of any drug	9.5%	2.6%



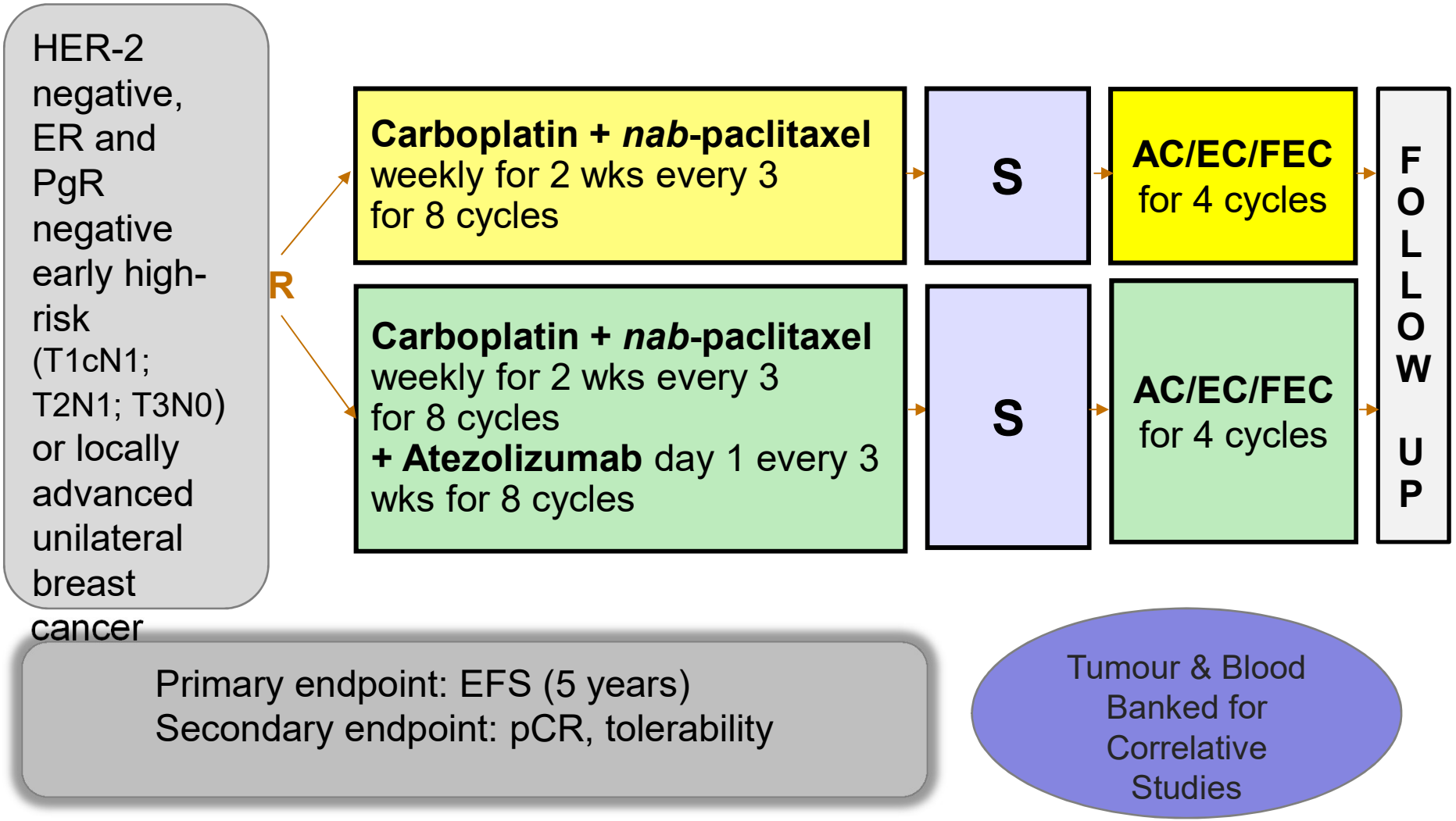
AI (primary + secondary) = 4.5 %
(8.7% in I-SPY2)

Immune-Mediated AEs and Infusion Reactions With Incidence ≥10 Patients

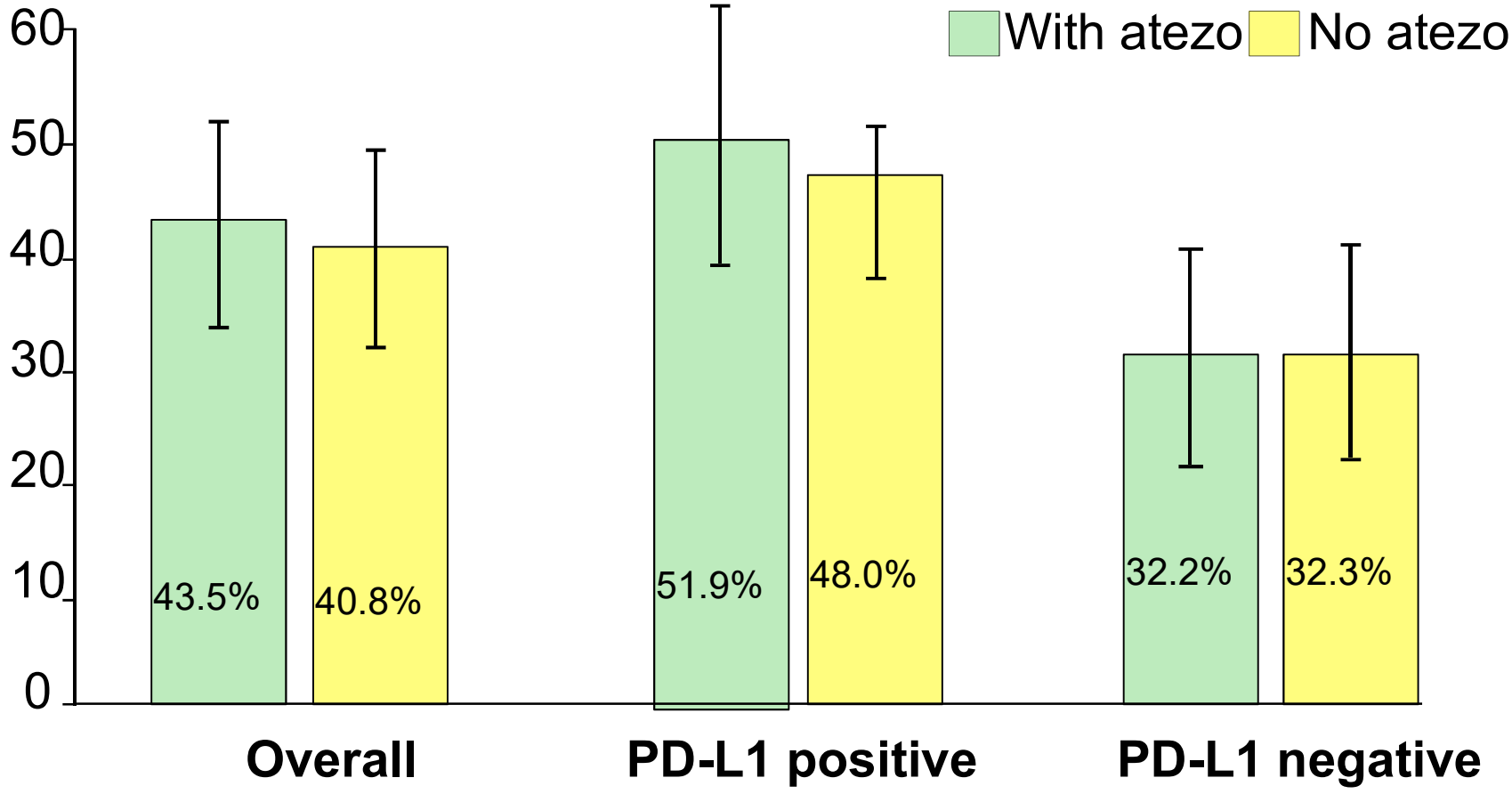
[a]1 patient from pneumonitis.

Considered regardless of attribution to treatment or immune relatedness by the investigator. Related terms included in addition to preferred terms listed. Data cutoff date: April 24, 2019.

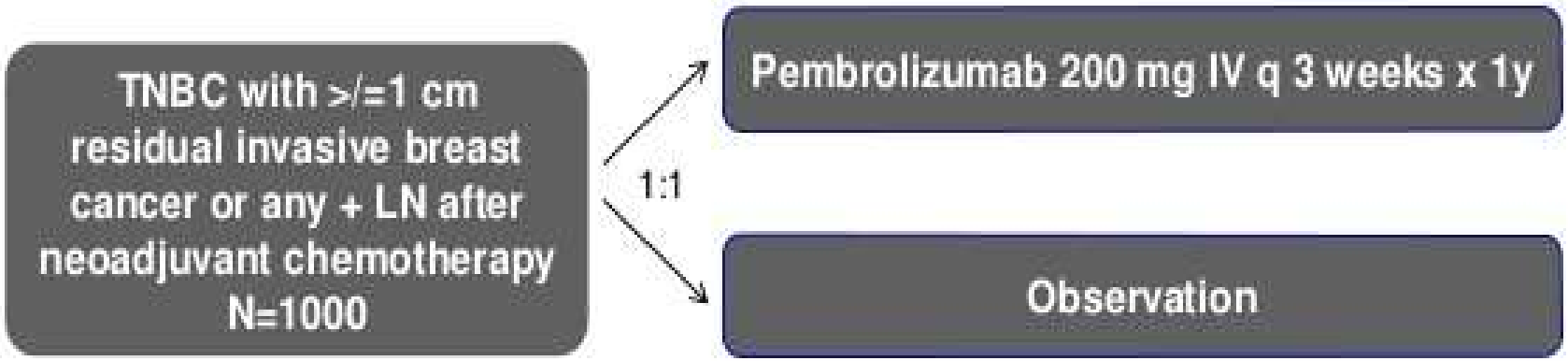
Design of the NeoTRIP trial (GS3-04)



pCR rate and *PD-L1 expression*



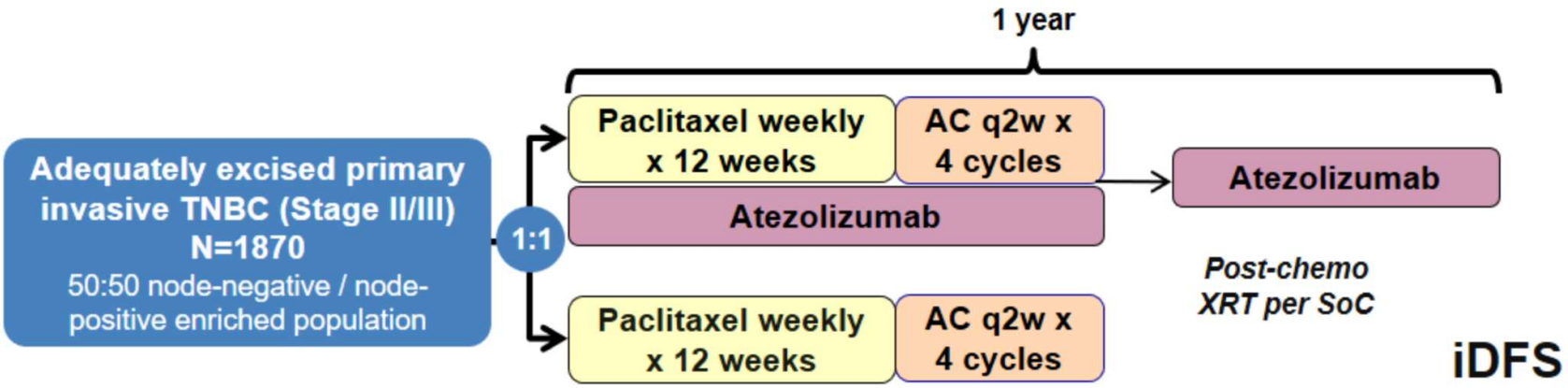
Post NAC residual disease: SWOG 1418



- **Registration:**
  - Central PD-L1 testing
- **Stratification:**
  - Nodal stage ypNo vs ypN+
  - Residual tumor ≥2 vs < 2cm
  - PD-L1 pos vs neg
  - Prior adjuvant chemo yes vs no

- **Hypothesis:**
  - Pembrolizumab reduces IDFS by 33% c/w observation alone
- **Primary Endpoint:**
  - Invasive DFS in PD-L1-positive and overall cohort
- **Secondary Endpoints:**
  - Toxicity
  - OS
  - DRFS
  - QOL (PROMIS, PRO-CTCAE forms, inflammatory markers)
  - Tissue banking

IMpassion030: Phase III randomized, open label adjuvant TNBC trial (Alliance/BIG)



Stratification factors:

- Axillary nodal status (0 vs. 1-3 vs. ≥4 positive lymph nodes)
- Surgery (breast conserving vs mastectomy)
- PD-L1 IC0 vs IC1/2/3

- **Primary endpoint:**
  - iDFS in ITT
- **Assumptions:**
  - iDFS HR=0.75
  - 3-yr iDFS +4.4% *(81% ➔ 85.4%)*
  - 80% power, alpha =5% (two sided)

- **Secondary endpoints:**
  - iDFS PD-L1 IC1/2/3
  - OS
  - Recurrence-free interval (RFI)
  - Distant RFI
  - Safety
  - Health-related QoL

Candidate Biomarkers for Immunotherapy

Tumor antigens

- Biomarkers indicative of hypermutation & neoantigens may predict response to immuno-oncology therapies

Examples:

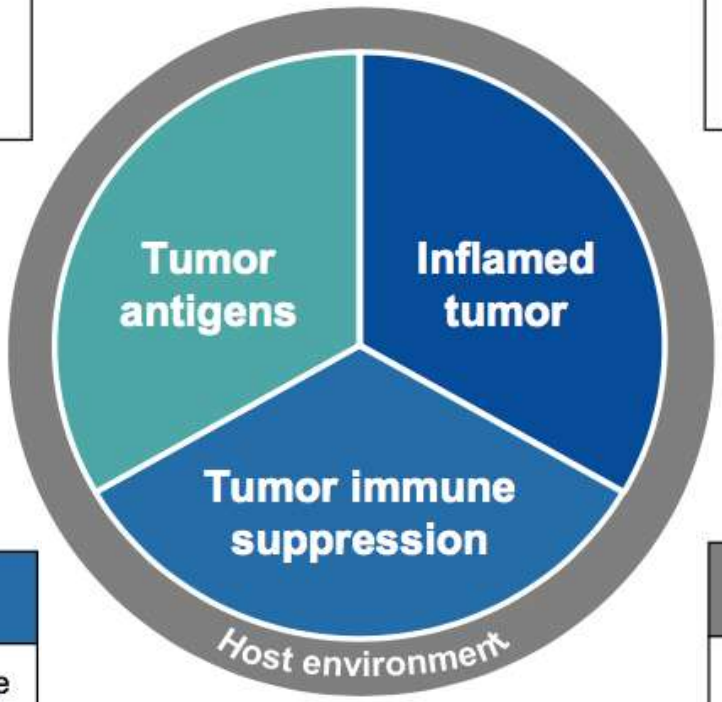
– ***TMB, MSI-high, neoantigens***

Inflamed tumor microenvironment

- Biomarkers (intra- or peri-tumoral) indicative of an inflamed phenotype may predict response to immuno-oncology therapies

Examples:

– ***PD-L1, inflammatory signatures***



Tumor immune suppression/evasion

- Biomarkers that identify tumor immune system evasion beyond PD-1/CTLA-4 to inform new immuno-oncology targets and rational combinations

Examples:

– ***Tregs, MDSCs, IDO, LAG-3***

Host environment

- Biomarkers that characterize the host environment, beyond tumor microenvironment, may predict response to immuno-oncology therapies

Examples:

– ***Microbiome, germline genetics***

Adapted from Blank CU, et al. Science 2016;352:658-660; Presented by Peters S. et al. AACR 2017

Summary

- Monotherapy responses in mTNBC are modest
  - Line of therapy, PD-L1, TILs
- Atezolizumab + nab-paclitaxel approved for PD-L1+ advanced TNBC
  - VENTANA SP142, immune cells
- Trials with non-taxane backbones appear promising
  - Induction, maintenance
- Combination of checkpoint blockade and targeted therapies for mTNBC look promising; phase III trials planned/ongoing
- Addition of pembrolizumab to NACT in TNBC significantly improves pCR rates but with immune-related toxicities

Acknowledgement

I am grateful to Dr. Rita Nanda for providing slides from her San Antonio Educational Presentation

MOC Question

- In Impassion-130, 41% of the patients were found to be PDL-1 positive by which of the following antibodies?
- 1. 22C3
- **2. SP142**
- 3. SP263
- 4. PDL123
- 5. None of the above