Current Possibilities and Future Prospects of Immunotherapy in Breast Cancer

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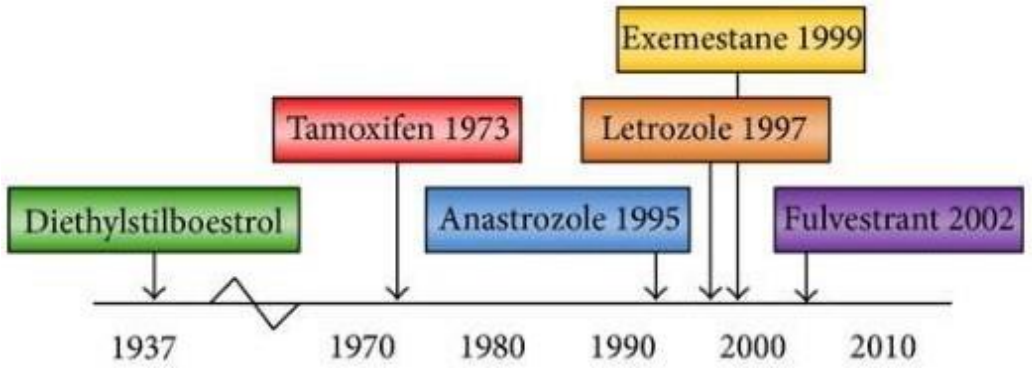
Disclosures

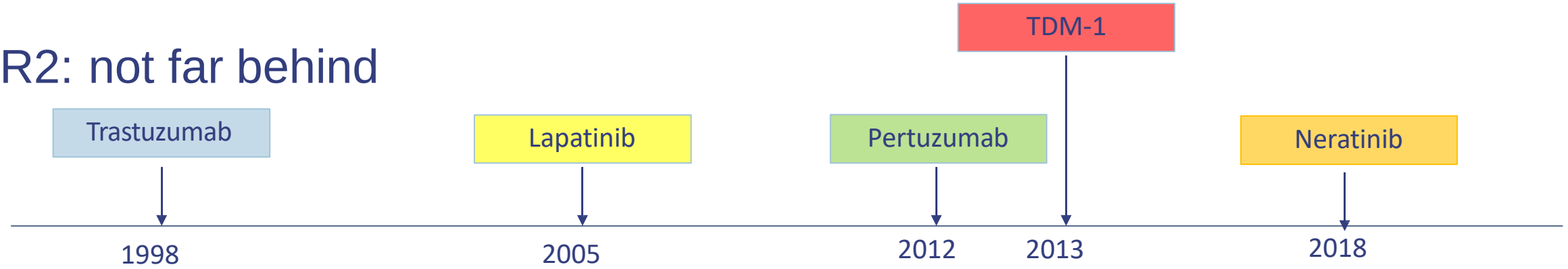
- Advisory boards/consulting: Pfizer, Novartis, Lilly, Roche, MSD
- Institutional/research funding: Novartis, LILT, AstraZeneca

Targeted Therapy for Breast Cancer

- Estrogen: the oldest target



- HER2: not far behind



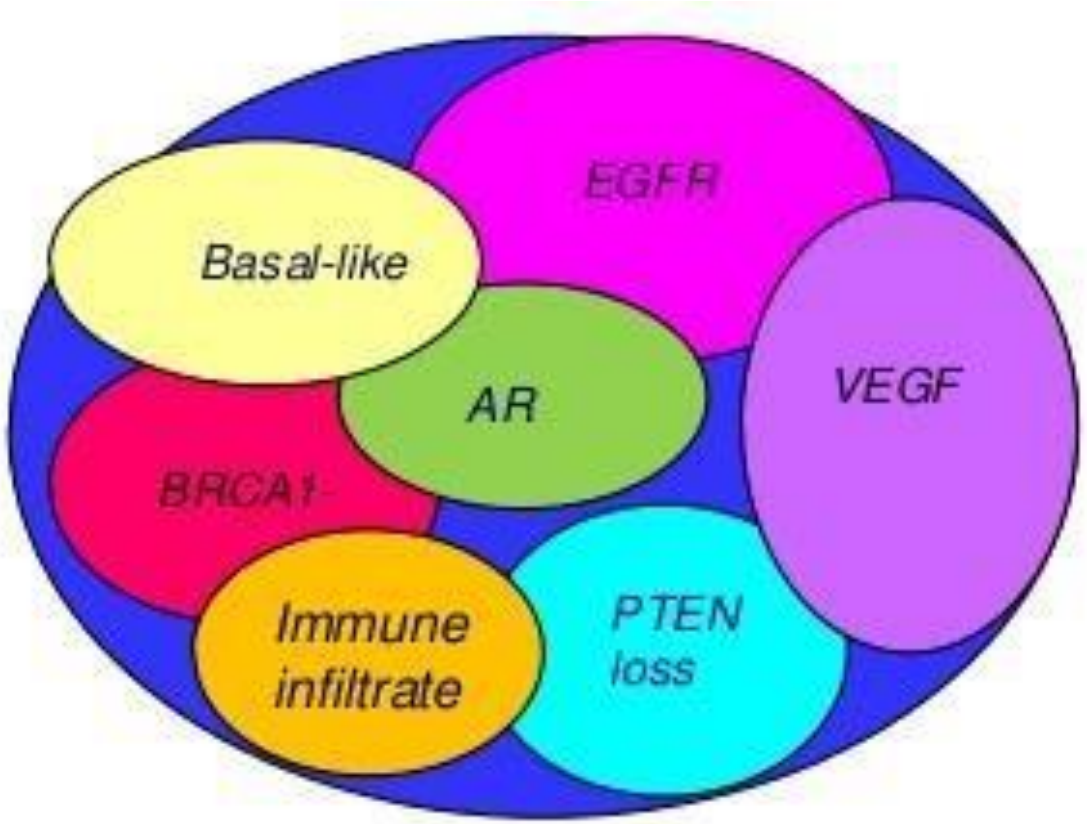
HER2 = human epidermal growth factor receptor 2; TDM-1 = trastuzumab emtansine

TNBC: The Absence of a Target

- Triple-negative breast cancer accounts for 20% of breast cancers worldwide
  - Almost 200,000 cases per year
- More commonly diagnosed in women younger than 40
- Typically present aggressively and have a poorer prognosis compared with other subtypes
- Historically, given the absence of targeted therapy, the mainstay of treatment has been chemotherapy – but this is not enough

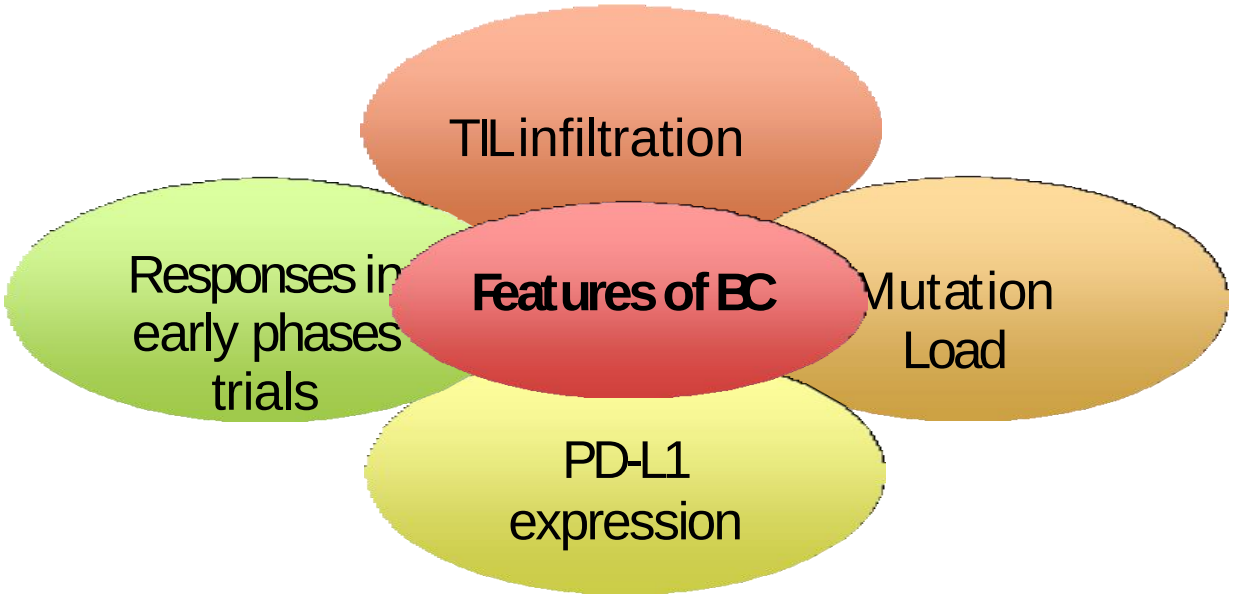
a. Gonzalez-Angulo AM, et al. *Clin Cancer Res.* 2011;17:1082-1089; b. Lin NU, et al. *Cancer*. 2012;118:5463-5472.

Heterogeneity of TNBC



DFCI = Dana-Farber Cancer Institute

Rationale to develop immunotherapy in BC



Why Immunotherapy?

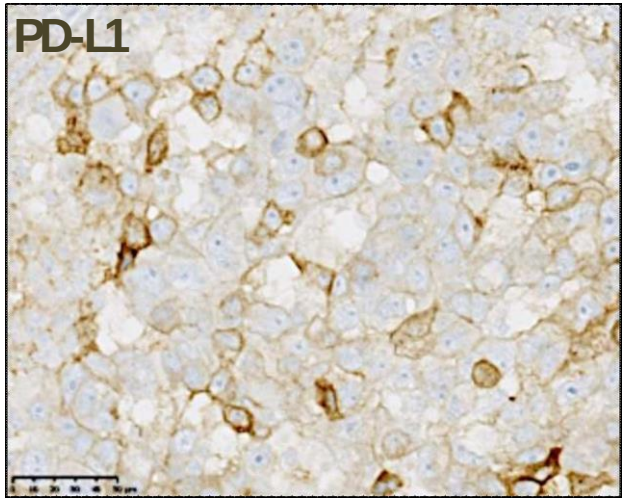
- Higher expression of PD-L1 in TNBC than in HR+ breast cancers[a,b]
  - In one study up to 26% of primary TNBCs expressed PD-L1 on cancer cell surface[b]

- 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[c,d]

HR+ = hormone receptor-positive; PD-L1 = programmed death-ligand 1; TIL = tumor infiltrating lymphoctye

a. Mittendorf EA, et al. *Cancer Immunol Res.* 2014;2:361-370; b. Tung N, et al. *NPJ Breast Cancer*. 2016;2:16002; c. Loi S, et al. *Ann Oncol*. 2014;25:1544-1550; d. Adams S, et al. *J Clin Oncol*. 2014;32:2959-2966.

PD-L1 expression in metastatic BC



Adenopathy

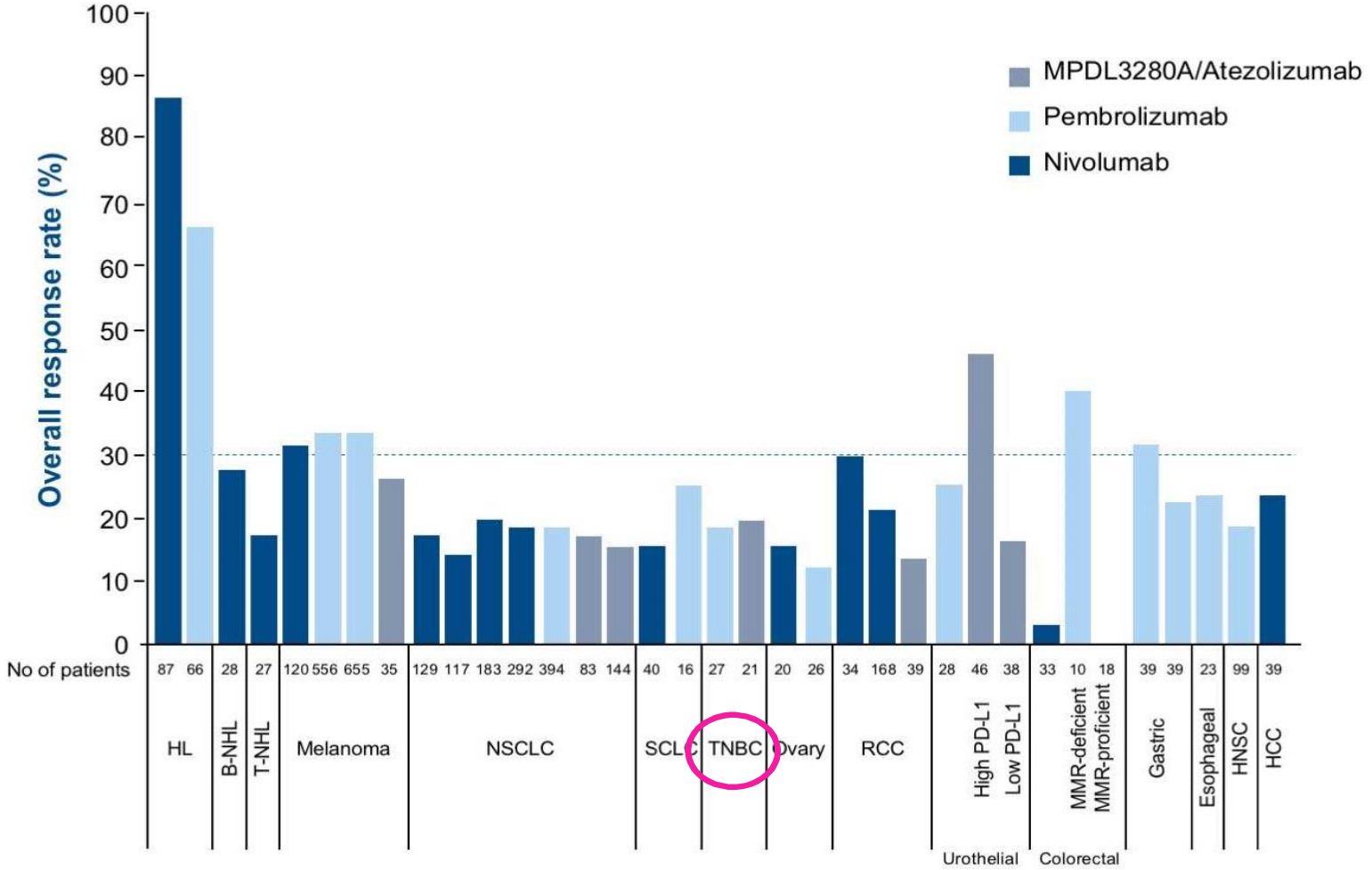
	PD-L1 positivity (%)
Luminal A	0/15 (0)
Luminal B	4/34 (11.7)
HER2+	2/21 (9.5)
TNBC	10/28 (35.7)

111 metastases from 11 sites including skin (40), ipsilateral breast relapse (23), liver (12), soft tissues (7), pleura (6), bone (6), brain (5), peritoneum (3), colon (1), lung (1), nodes (7)

PD-L1 IHC expression on	N = 111 (%)	Median (% cells-positive cases)	25th-75th percentile (%)
Tumor cells	3 (2.7)	1	1-5
Immune cells	12 (10.8)	5	5-10
Stromal cells	9 (8.1)	5	5-10
Any cells	17 (15.3)		

PD-L1 positivity : ≥1% expression on tumor or immune or stromal cells

Single Agent Activity of PD-1/PD-L1 Blockade in Relapsed/Refractory Cancer



B-NHL=B cell non-Hodgkin lymphoma; HCC=hepatocellular carcinoma; HL=Hodgkin lymphoma; HNSCC=head and neck squamous cell carcinoma; MMR=mismatch repair; NSCLC=non-small cell lung cancer; PD-L1=programmed death ligand-1; SCLC=small cell lung cancer, TNBC=triple negative breast cancer; T-NHL=T cell non-Hodgkin lymphoma. Batlevi CL et al. *Nat Rev Clin Oncol*. 2016; 13:25-40.

Why Immunotherapy?

- 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

Budczies J, et al. *J Pathol Clin Res.* 2015;1:225-238; Banerji S, et al. *Nature*. 2012;486:405-409.

Pembrolizumab and Tumor Mutation Burden

- High TMB is an emerging predictive biomarker for checkpoint inhibitor therapy
- TAPUR: a phase II basket study evaluating targeted agents in patients with advanced cancers that have specific genomic alterations
- ASCO 2019: authors reported on a cohort of patients with MBC with high TMB (≥ 9 mutations per megabase) who received pembrolizumab q 3 weeks until progression[a]

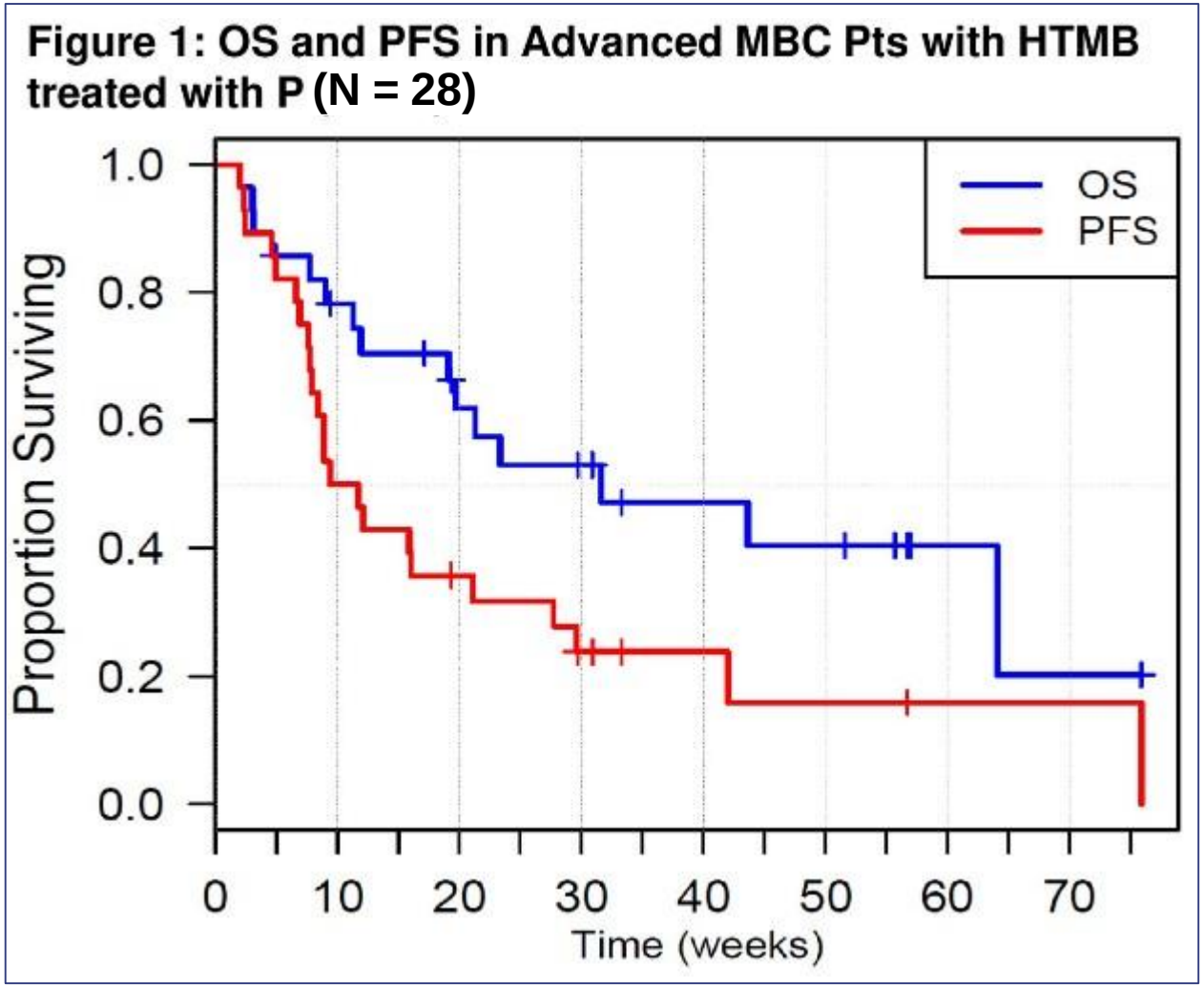
MBC = metastatic breast cancer; q 3 weeks = every three weeks; TMB = tumor mutational burden

a. Alva AS, et al. *J Clin Oncol.* 2019;37(suppl): Abstract 1014.

Pembrolizumab and TMB in MBC

- 28 patients enrolled 10/2016-7/2018
- All patients had TMB ranging 9-27 muts/mb

- Disease control rate of 37% and objective response in 21%
  - impressive in heavily treated MBC (93% patients had 3 or more prior regimens)
- Worthy of further study, and highlights the importance of genomic testing in this population

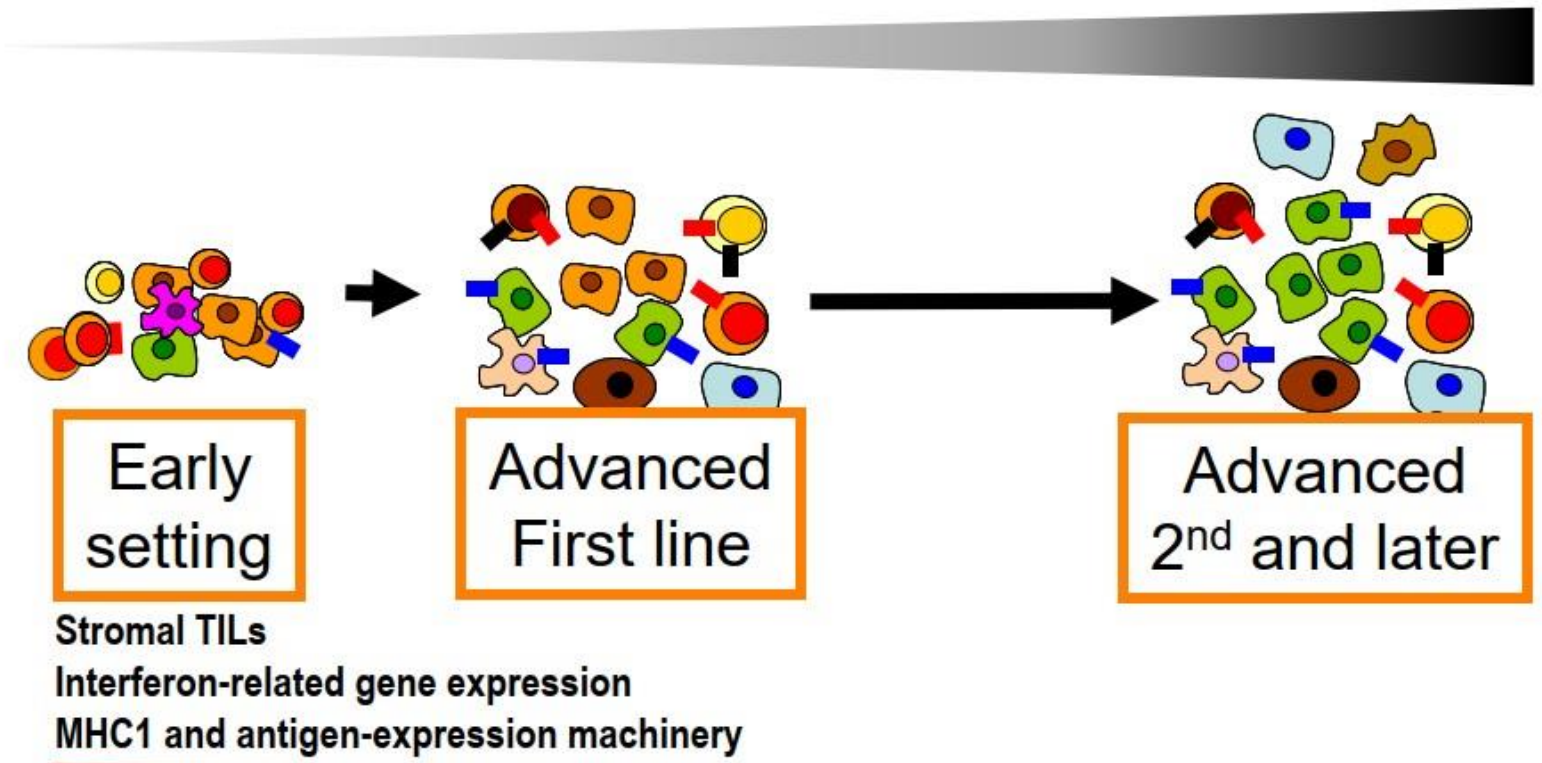


HTMB = high tumor mutational burden; PFS = progression-free survival; Pts = patients

Alva AS, et al. *J Clin Oncol.* 2019;37(suppl): Abstract 1014.

SHOULD WE GIVE IMMUNE CHECKPOINTS INHIBITORS IN FIRST LINE OR SUBSEQUENT LINES OF TREATMENT?

Tumor/immune co-evolution leads to an increasing immunoediting and immune subversion



Bianchini G SABCS 2015; Ogyia R Cancer Sci 2016; Luen SJ Lancet Oncol 2017; SJ Lancet Oncol 2017; Dieci MV Breast Cancer Res 2018; Szekely B Ann Oncol 2018

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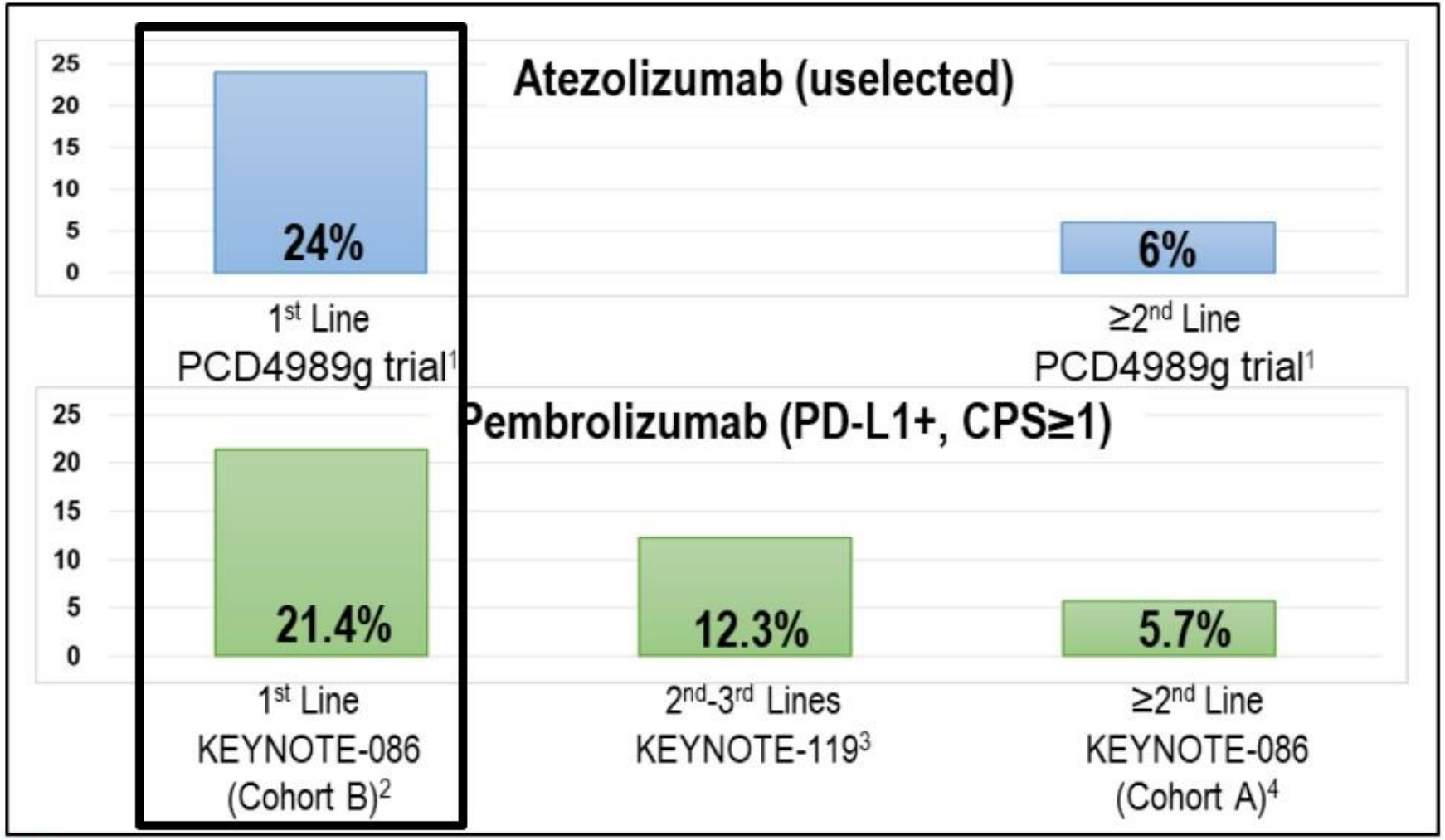
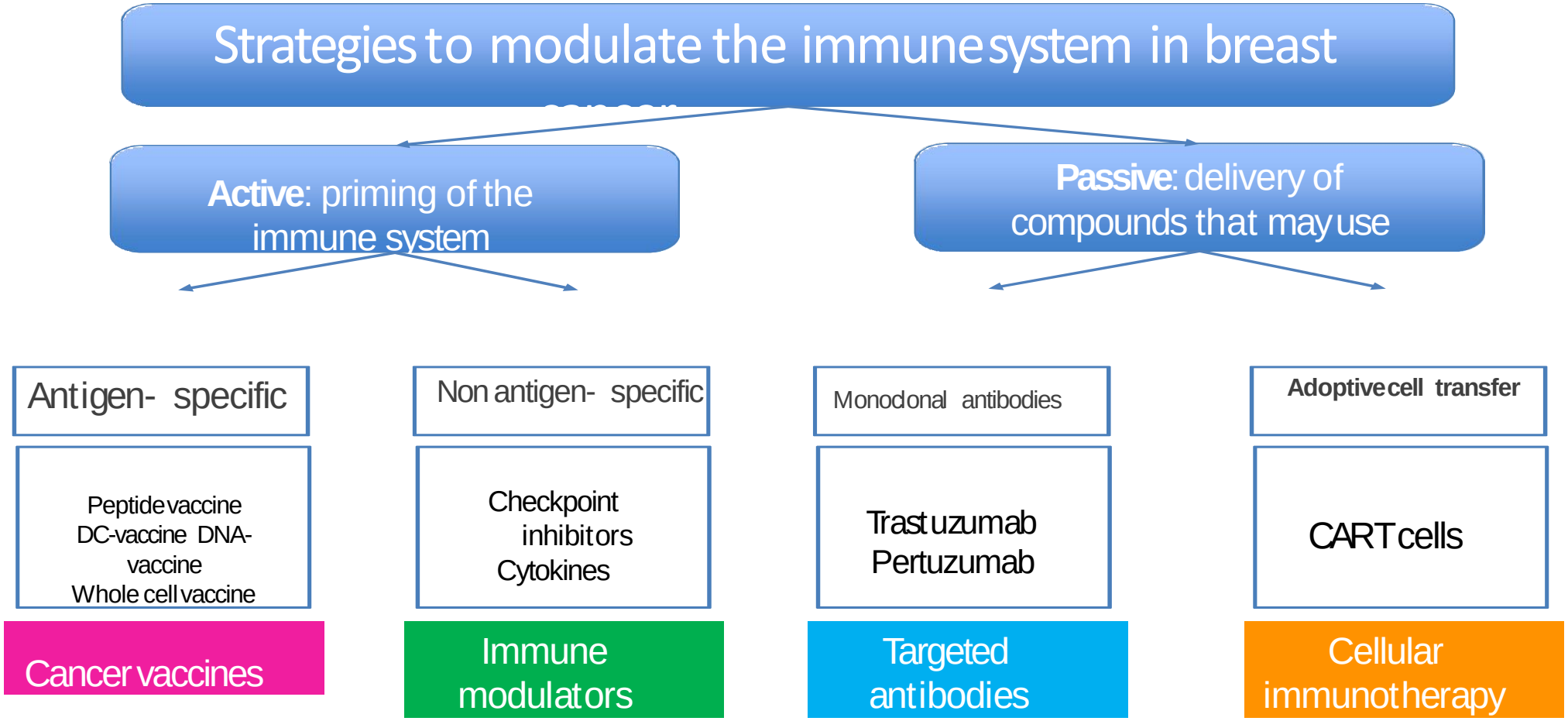


BARCELONA 2019 ESMO congress

[1]Emens L JAMA Oncol 2018; [2]Adams S Ann Oncol 2019; [3]Cortes J ESMO LBA21; [4]Adams S Ann Oncol 2019


Strategies to modulate the immune system in breast
Active: priming of the immune system
Passive: delivery of compounds that may use
Antigen- specific
Non antigen- specific
Monodonal antibodies
Adoptive cell transfer
Peptide vaccine
DC-vaccine DNA-vaccine
Whole cell vaccine
Checkpoint inhibitors
Cytokines
Trastuzumab
Pertuzumab
CART cells
Cancer vaccines
Immune modulators
Targeted antibodies
Cellular immunotherapy

Overview

- Current approvals
  - **Atezolizumab + *nab*-paclitaxel in metastatic TNBC – IMpassion trial**

- Areas of promising investigation
  - Neoadjuvant chemotherapy + immunotherapy
    - Adjuvant immunotherapy in patients without a pathologic complete response (pCR) to neoadjuvant chemotherapy
  - Other immunotherapy-based combinations in the metastatic setting

Rationale Behind IMpassion

- Atezolizumab selectively targets PD-L1 to prevent interaction with PD-1[a]
  - This reverses T-cell suppression
- Chemotherapy may enhance tumor-antigen release and antitumor responses to checkpoint inhibition[b]
  - Taxanes, in particular, may additionally activate toll-like receptor activity and promote dendritic cell activity
  - *Nab*-paclitaxel: a convenient choice, as there is no need for glucocorticoid premedication

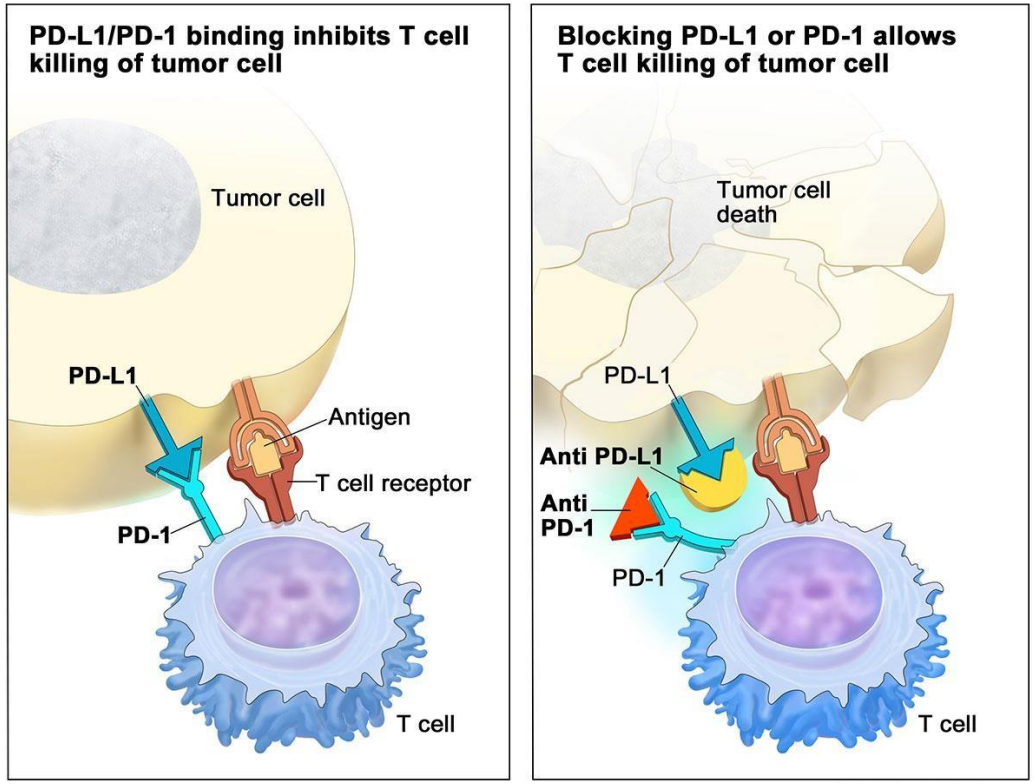


Image courtesy of the NIH.

NIH = National Institute of Health

a. Lee HT, et al. *Sci Rep*. 2017;7:5532; b. Emens LA, et al. *Cancer Immunol Res.* 2015;3:436-443.

IMpassion130 Study Design: Prespecified Analyses in the ITT and PD-L1 IC+ Population

Previously untreated* metastatic or inoperable locally advanced TNBC
N = 902

Double blind; no crossover

R 1:1

Atezo + *nab*-P arm
ITT population: n = 451
PD-L1 IC+ patients: n = 185 (41%)

Plac + *nab*-P arm
ITT population: n = 451
PD-L1 IC+ patients: n = 184 (41%)

Stratification factors:
1. ***Prior taxane use***
2. ***Liver metastases***
3. ***PD-L1 on IC (VENTANA SP142 assay)***

Key study endpoints
- **Coprimary: PFS (ITT and PD-L1 IC+)**
  OS (ITT and PD-L1 IC+)
- **Secondary: ORR and DOR**
- **Safety and tolerability**

***Prior chemotherapy in the curative setting, including taxanes, allowed if treatment-free interval ≥ 12 months**

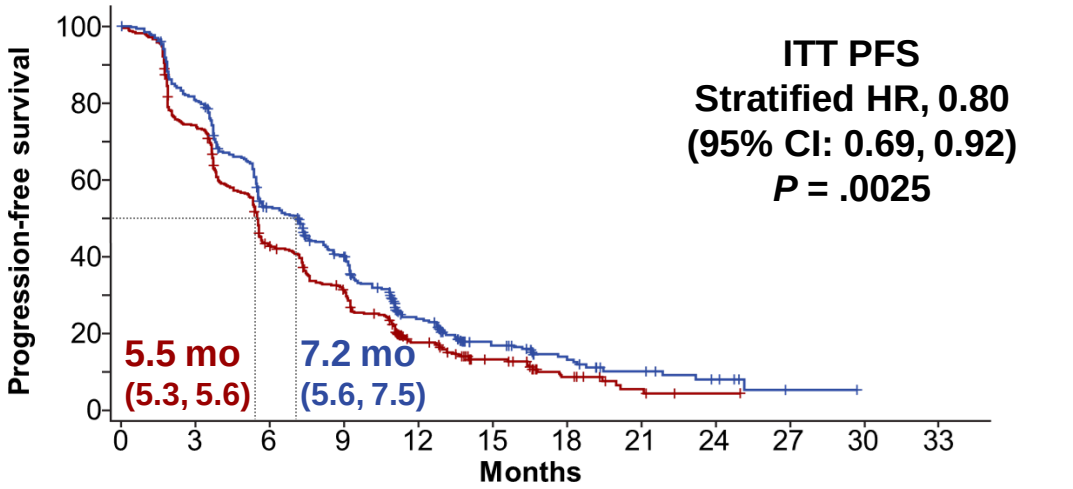
****Atezolizumab or placebo 840 mg IV on days 1 and 15 + *nab*-paclitaxel 100 mg/m^2 IV on days 1, 8, and 15 of 28-day cycle until RECIST v1.1 PD.**

DOR = duration of response; IC = immune cell; ITT = intent to treat; IV = intravenous; ORR = overall response rate; RECIST = response evaluation criteria in solid tumors

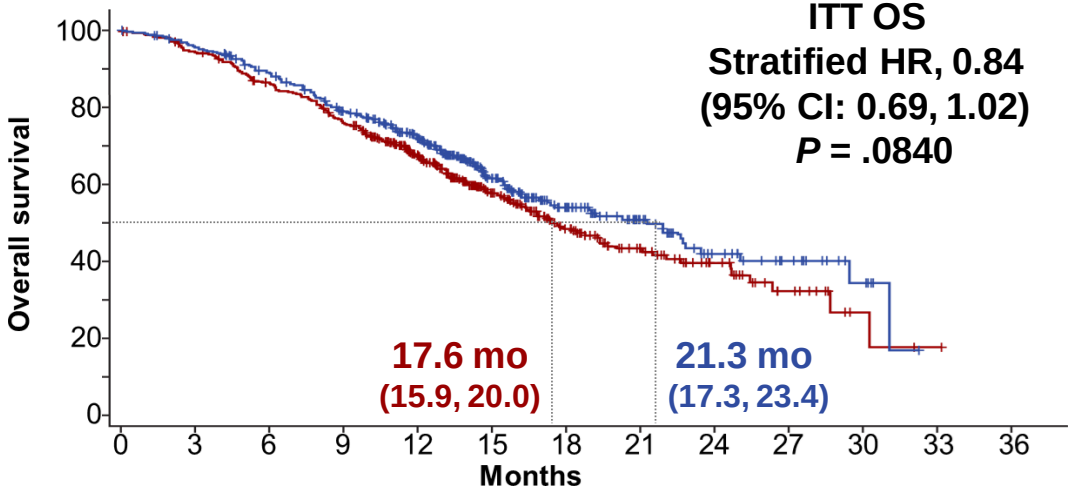
Schmid P, et al. *N Engl J Med.* 2018;379:2108-2121. Emens LA, et al. *Cancer Res.* 2018;78(4 Suppl): Abstract GS1-04.

IMpassion130: Primary Outcomes in PD-L1+ Pts

ITT population

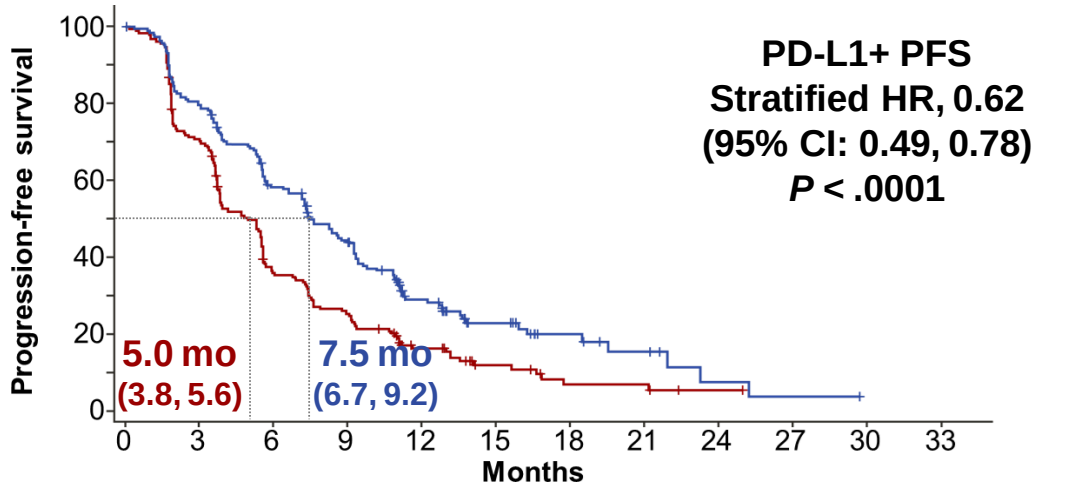


ITT PFS
Stratified HR, 0.80
(95% CI: 0.69, 0.92)
***P* = .0025**

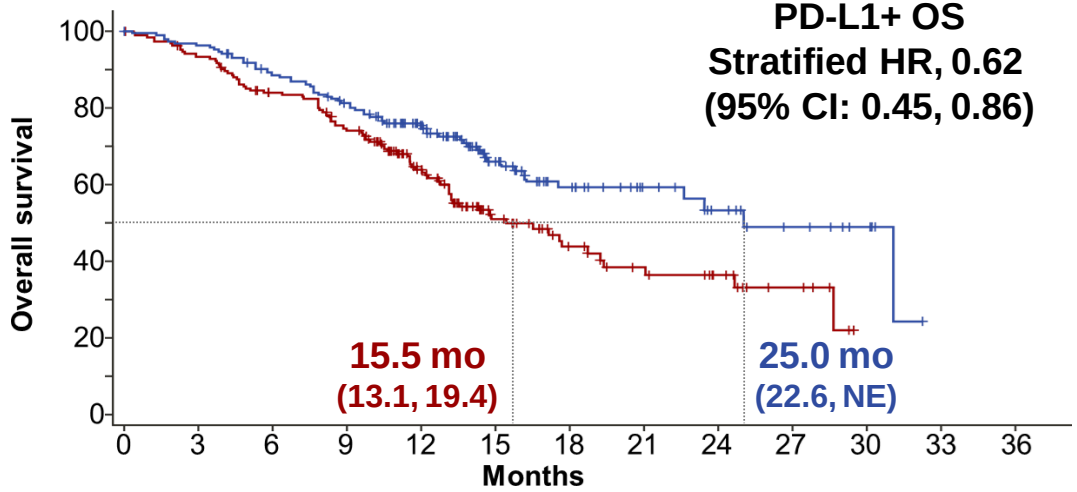


ITT OS
Stratified HR, 0.84
(95% CI: 0.69, 1.02)
***P* = .0840**

PD-L1+ population



PD-L1+ PFS
Stratified HR, 0.62
(95% CI: 0.49, 0.78)
***P* < .0001**

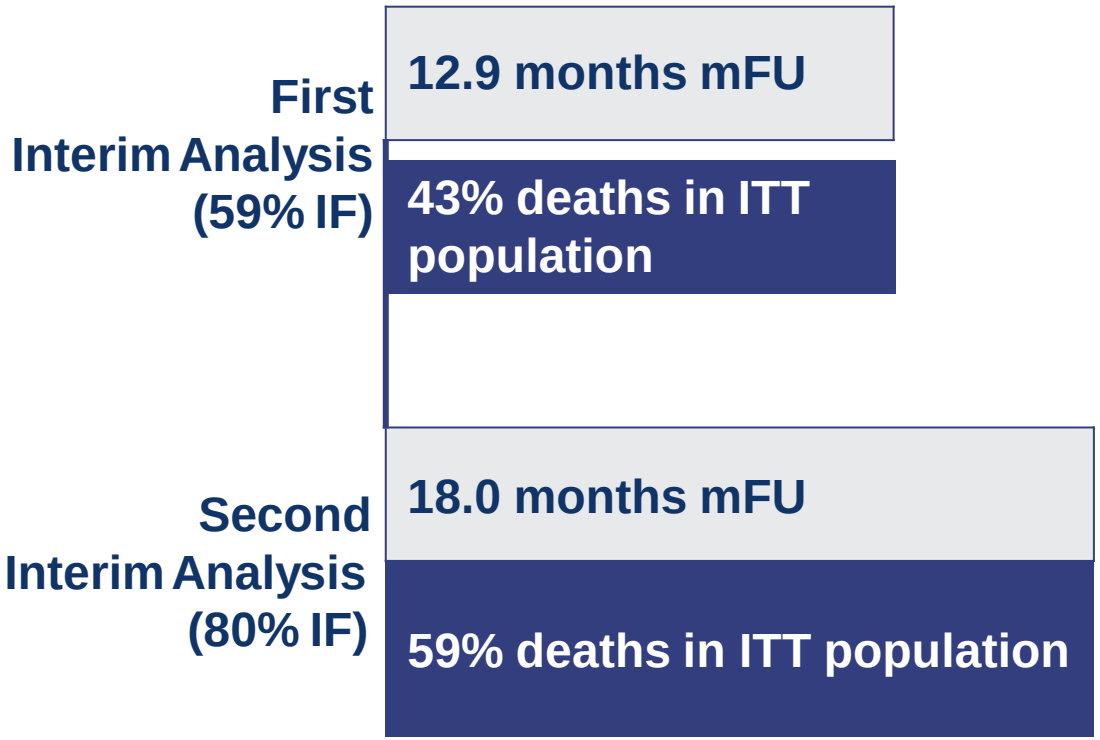


PD-L1+ OS
Stratified HR, 0.62
(95% CI: 0.45, 0.86)

Emens LA, et al. *Cancer Res.* 2018;78(4 Suppl): Abstract GS1-04.

CI = confidence interval; HR = hazard ratio; mo = months; NE = not estimable

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%)

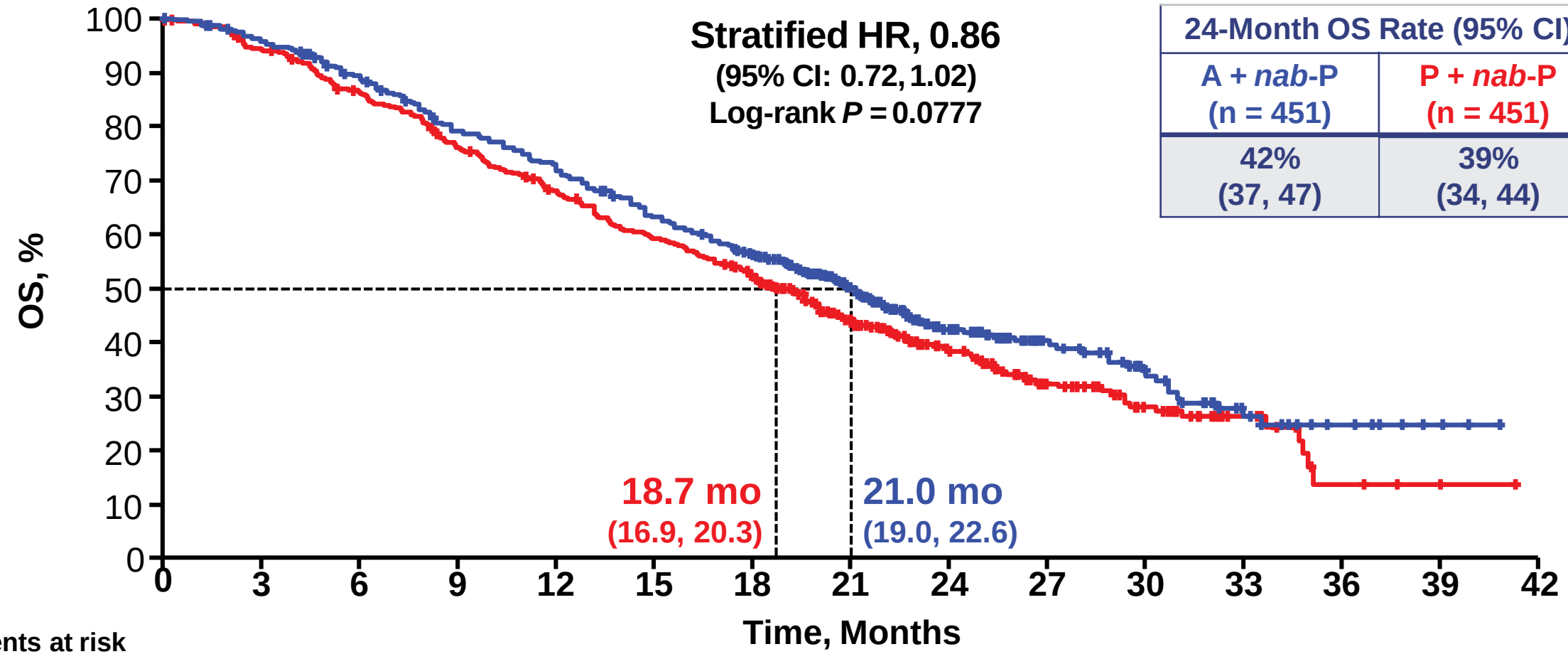
Clinical cutoff date: January 2, 2019.

[a] Compared with Schmid P, et al. *N Engl J Med.* 2018;379:2108-2121.

IF = information fraction; ITT, intention to treat; mFU = median follow-up

Schmid P, et al. *J Clin Oncol.* 2019;37(suppl): Abstract 1003.

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

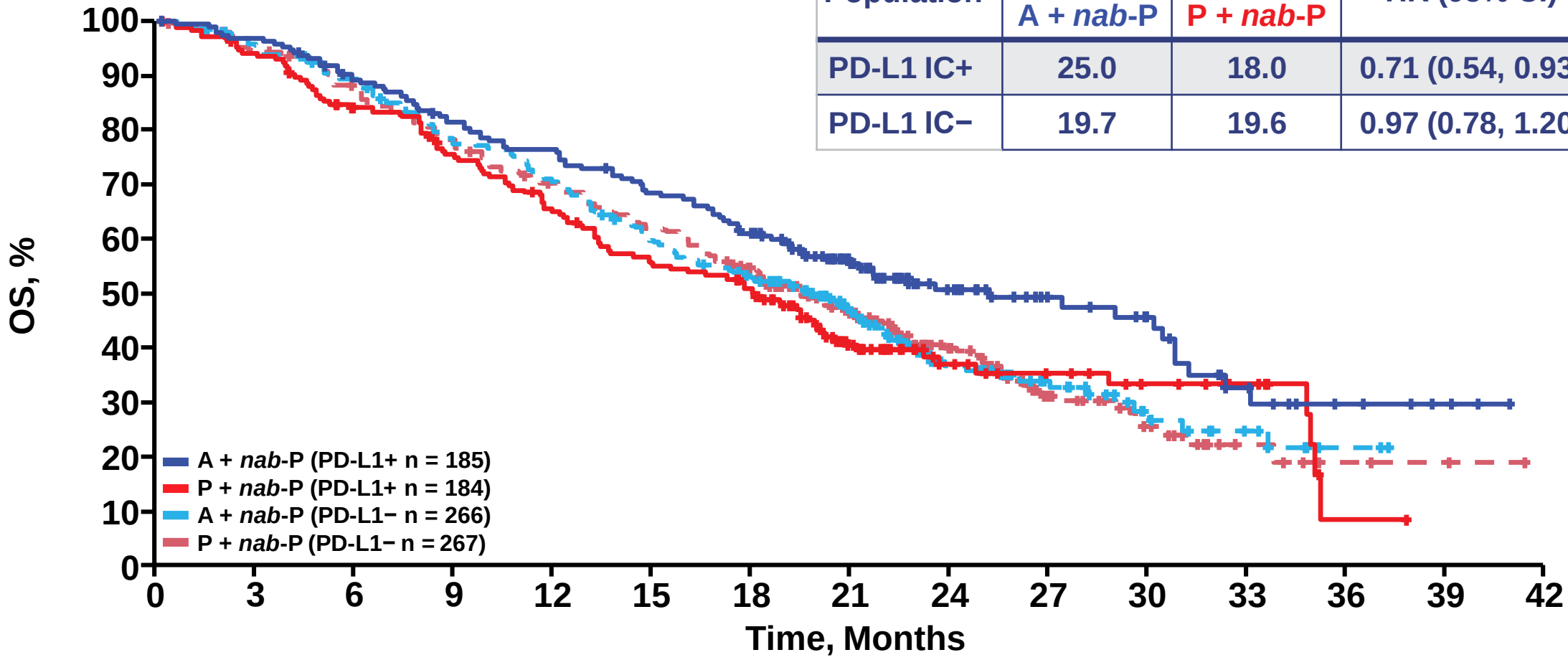
A + *nab*-P	451	426	389	342	312	270	235	162	88	56	35	19	8	3	NE
P + *nab*-P	451	420	376	329	291	252	216	145	87	51	33	17	4	1	NE

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 P, et al. *J Clin Oncol.* 2019;37(suppl): Abstract 1003.

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)



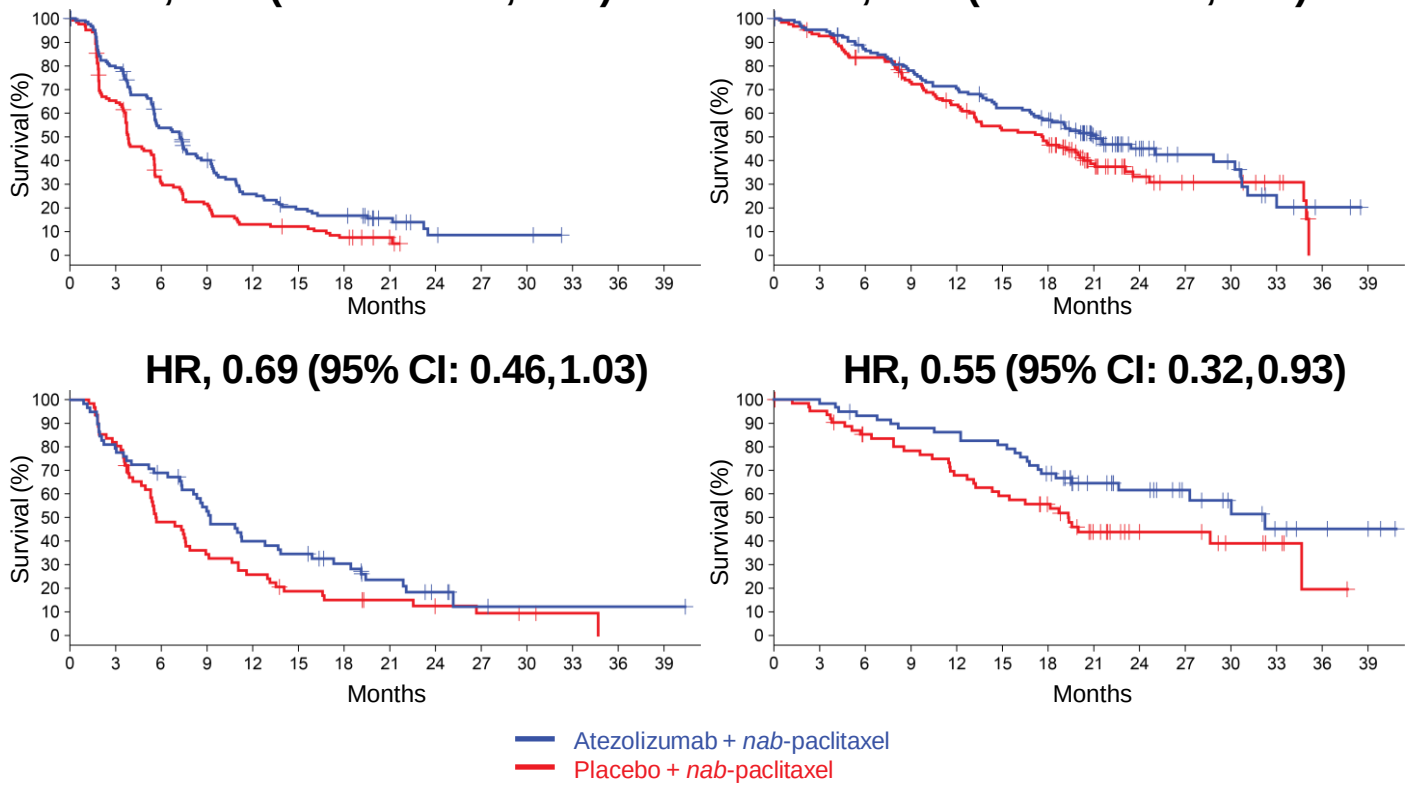
Clinical cutoff date: January 2, 2019.

Schmid P, et al. *J Clin Oncol.* 2019;37(suppl): Abstract 1003.

PD-L1 status in primary vs metastatic tissues

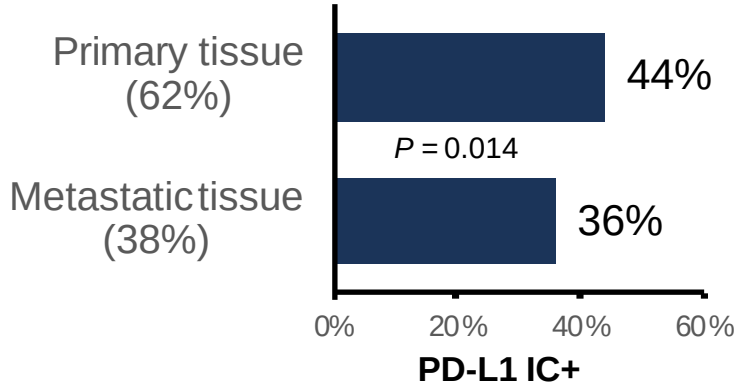
Efficacy in PD-L1

	PFS	OS
Primary	HR, 0.61 (95% CI: 0.47, 0.81)	HR, 0.79 (95% CI: 0.57,1.09)
Metastatic	HR, 0.69 (95% CI: 0.46,1.03)	HR, 0.55 (95% CI: 0.32,0.93)

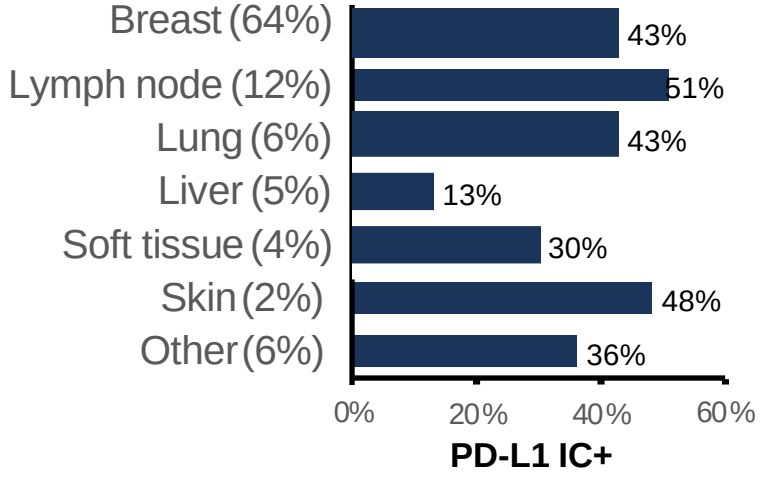


- Median time of sample collection to randomization: 61 days

PD-L1 status by primary vs metastatic tissue[a]

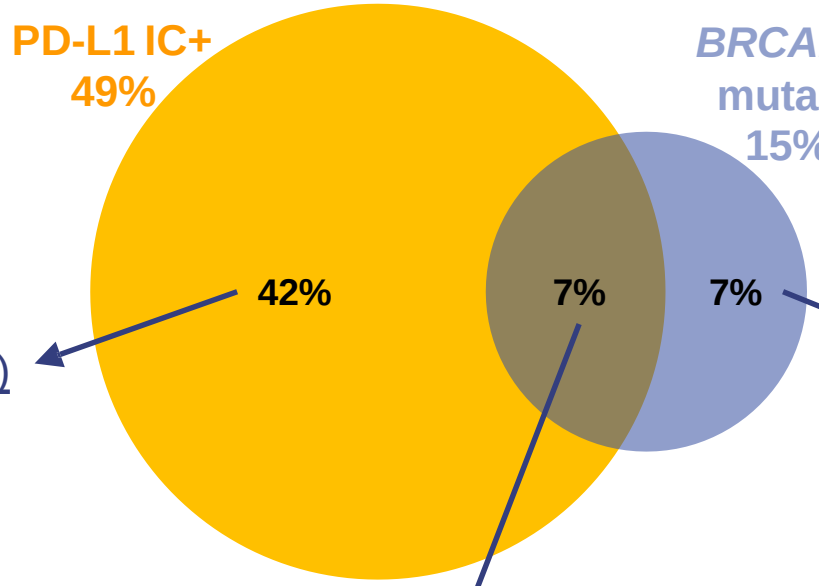


PD-L1 status by anatomical location[a]



[a] Evaluable population (n = 901). PD-L1 IC+: PD-L1 in ≥ 1% of IC as percentage of tumour area assessed with the VENTANA SP142 assay.
HRs adjusted for prior taxanes, presence of liver metastases, age and ECOG PS. No major differences were observed for clinical benefit in samples collected within 61 days of randomization or beyond that period (Emens, et al, manuscript in preparation).

Clinical Benefit in PD-L1 IC+ Patients Independent of *BRCA1/2* Mutation Status



***BRCA1/2* non-mut/PD-L1 IC+** (n = 257)

	HR (95% CI)	*P* Value
PFS	0.63 (0.48, 0.83)	≤ .005
OS	0.62 (0.43, 0.91)	.01

***BRCA1/2* mut/PD-L1 IC–** (n = 44)

	HR (95% CI)	*P* Value
PFS	0.77 (0.37, 1.61)	.49
OS	0.85 (0.29, 2.43)	.76

***BRCA1/2* mut/PD-L1 IC+** (n = 45)

	HR (95% CI)	*P* Value
PFS	0.45 (0.21, 0.96)	.04
OS	0.87 (0.26, 2.85)	.82

- *BRCA1/2* mutants and PD-L1 IC+ are independent from each other (*P* = ns)
- ***Patients with BRCA1/2-mutant tumors derived clinical benefit (PFS/OS) only if their tumors were also PD-L1 IC+***

Emens LA, et al. *Cancer Res.* 2018;78(4 Suppl): Abstract GS1-04.

Conclusions IMpassion130 Presentation

- PD-L1 expression on IC is a predictive biomarker for selecting patients who clinically benefit from first-line atezolizumab + *nab*-paclitaxel treatment for mTNBC
  - PFS and OS benefit was observed in patients with a PD-L1 IC of ≥ 1% (by VENTANA SP142 IHC assay)
  - A treatment effect was not seen for adding atezolizumab to chemotherapy in the PD-L1–negative subgroup

- PD-L1 IC expression was the best predictor of clinical benefit as the patient subgroups with tumor-infiltrating immune cells (stromal TILs+) or cytotoxic T cells (CD8+) derived clinical benefit with atezolizumab + *nab*-paclitaxel if their tumors were also PD-L1 IC+

- PFS and OS results were consistent regardless of *BRCA1/2* mutation status

- Patients with newly diagnosed metastatic and unresectable locally advanced TNBC should be routinely tested for PD-L1 IC status to determine whether they might benefit from atezolizumab + *nab*-paclitaxel

Overview

- Current approvals
  - Atezolizumab + *nab*-paclitaxel in metastatic TNBC – IMpassion trial

- Areas of promising investigation
  - **Neoadjuvant chemotherapy + immunotherapy**
    - Adjuvant immunotherapy in patients without a pathologic complete response (pCR) to neoadjuvant chemotherapy
  - Other immunotherapy-based combinations in the metastatic setting

Ongoing Neoadjuvant Trials

- Carboplatin + paclitaxel +/- atezolizumab (NCT02883062)
  - Mayo, UC Davis, Hopkins, Wash U, UNC, Duke
- *Nab*-paclitaxel + atezolizumab (NCT02530489)
  - MDACC

- I-SPY 2 (NCT01042379)*
  - Pembrolizumab + paclitaxel → ddAC
  - SD-101 + pembrolizumab + paclitaxel → ddAC
  - Durvalumab + olaparib + paclitaxel→ ddAC

*Open at Emory as of June 2019

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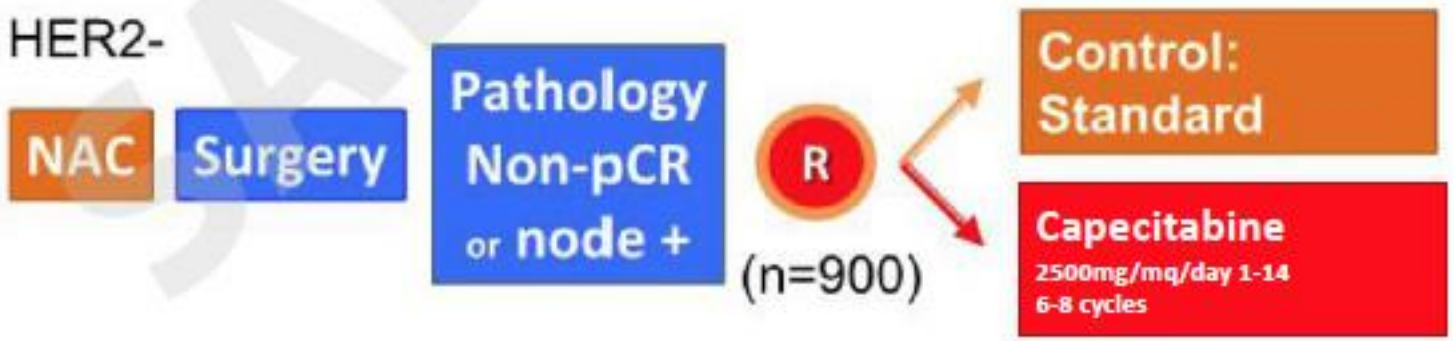
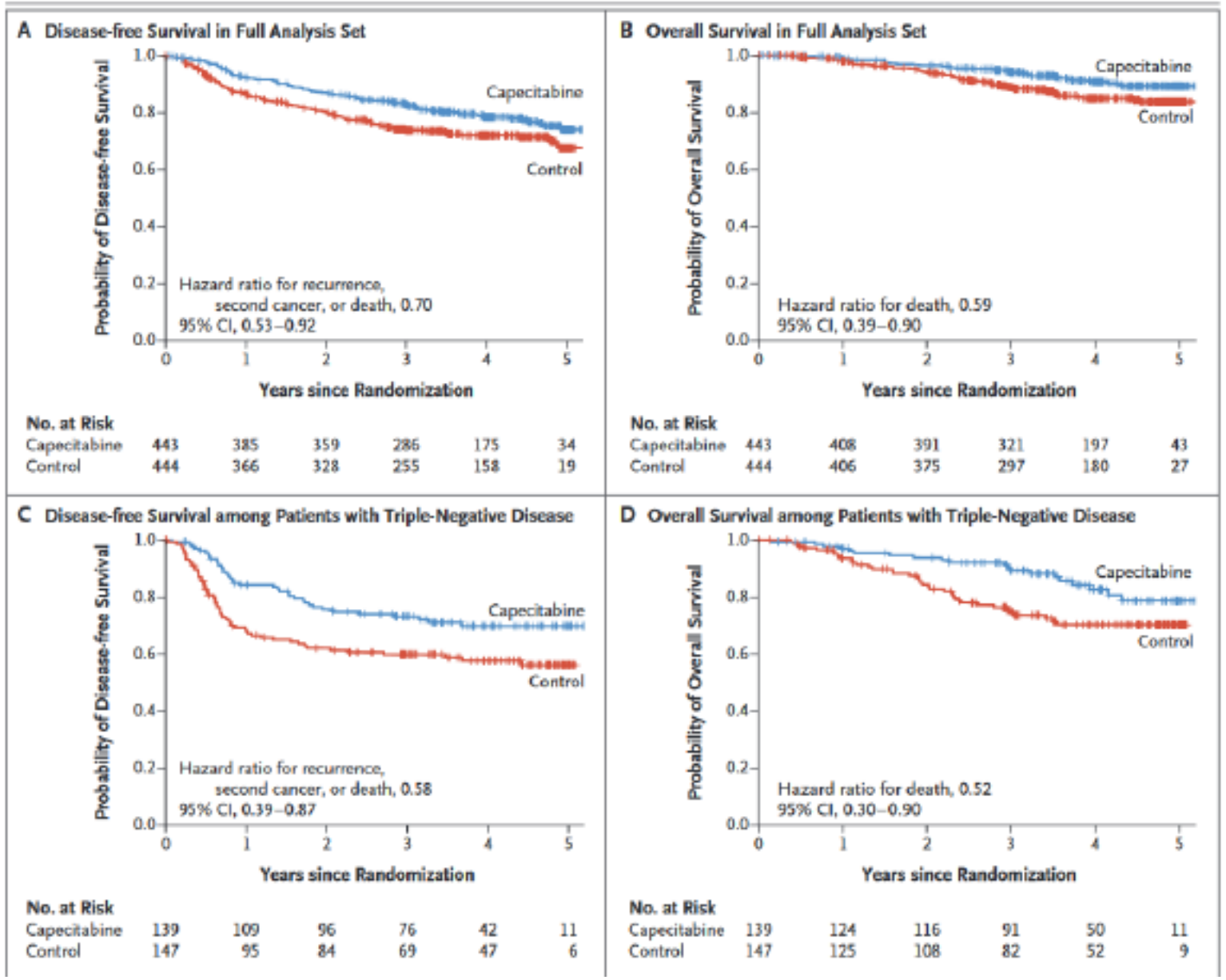
CREATE-X



Stratification factors:
ER, Age, NAC, ypN, 5FU and institution

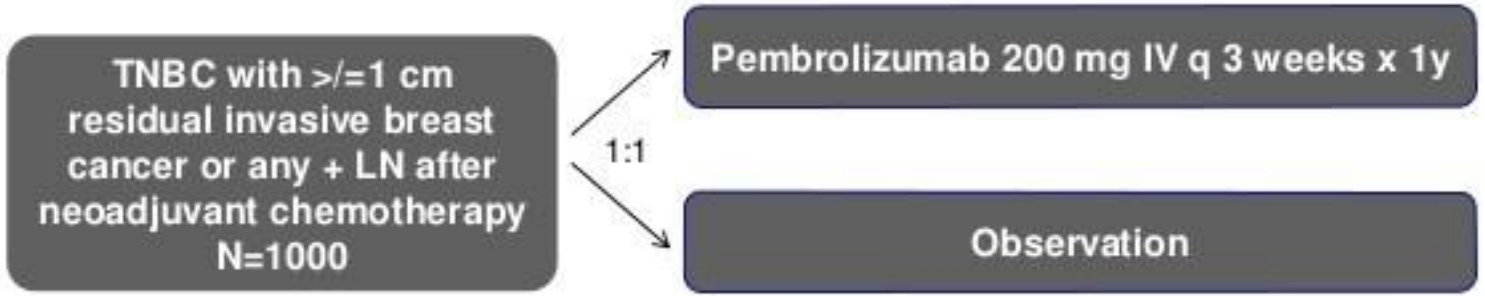
Standard therapy:
HR+: Hormone therapy
HR-: No further systemic treatment

Masuda N, NEJM 2017



Masuda N, NEJM 2017

SWOG S1418: Randomized, Phase III Trial of Pembrolizumab for Residual TNBC Post-NAC



Stratification
-Nodal stage (ypNo vs ypN+)
-Residual tumor (≥ 2cm vs < 2cm)
-PD-L1+ vs PD-L1-
-Prior adjuvant chemo (y or n)

HYPOTHESIS: pembrolizumab reduces IDFS by 33% compared with observation alone

PRIMARY ENDPOINT: invasive DFS in PD-L1+ and overall cohort

IDFS = invasive disease-free survival; LN = lymph node

National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT02954874. Accessed: July 8, 2019.

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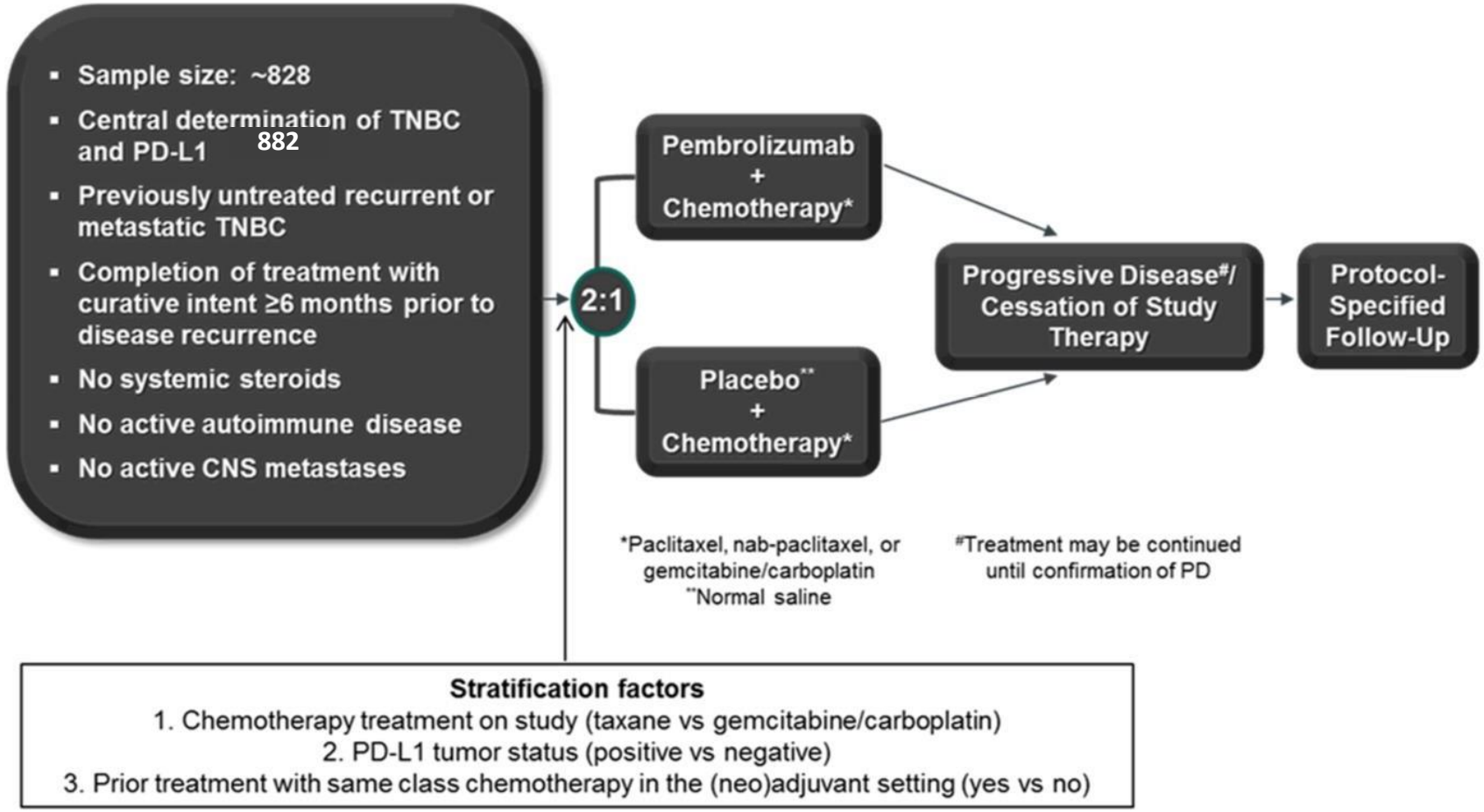
KEYNOTE-355



CNS = central nervous system; PD = progressive disease

National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT02819518. Accessed: July 8, 2019.

KEYNOTE in Second- and Third-Line

- KEYNOTE 086[a]
  - Cohort A: Pembrolizumab in second or later lines for mTNBC
  - Cohort B: Pembrolizumab as first-line for mTNBC
  - Cohort C: Expansion of cohort A restricted to PD-L1+ positive patients

- KEYNOTE 119[b]
  - Pembrolizumab vs chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) in second- or third-line treatment for mTNBC

a. National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT02447003. Accessed: July 8, 2019.
b. National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT02555657. Accessed: July 8, 2019.

Morpheus-TNBC

- A study evaluating the efficacy and safety of multiple immunotherapy-based treatment combinations in patients with metastatic or inoperable locally advanced TNBC
  - Capecitabine
  - Atezolizumab + ipatasertib
  - Atezolizumab + SGN-LIV1A
  - Atezolizumab + bevacizumab
  - Atezolizumab + bevacizumab + cobimetinib
  - Atezolizumab + capecitabine
  - Atezolizumab + chemo (gem/carbo or eribulin)
  - Atezolizumab + RO6874281
  - Atezolizumab + selicrelumab + bevacizumab

All patients (except on have the option to continue on atezo + chemo arm) have the option to switch to atezo + chemo at the time of progression

National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT03424005. Accessed: July 8, 2019.

JAVELIN-Medley

- A phase Ib/II study evaluating avelumab in combination with other immune modulators in TNBC as well as several other tumor types (NSCLC, melanoma, etc)

Avelumab + utomilumab

Avelumab + PF-04518600

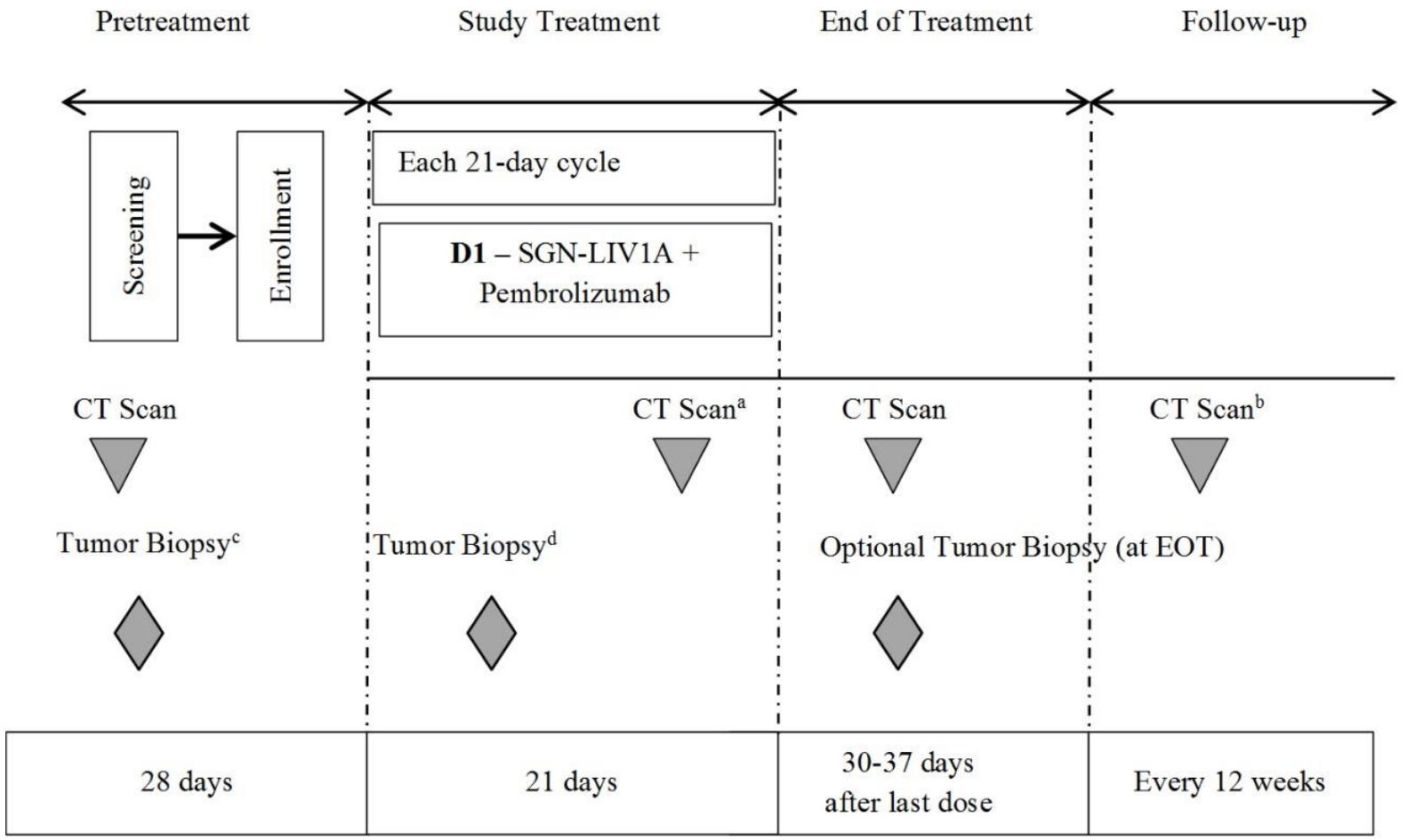
Avelumab + PD 0360324

Avelumab + utomilumab + PF-04518600

NSCLC = non-small cell lung cancer

National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT02554812. Accessed: July 8, 2019.

SGN-LIV1A + Pembrolizumab



National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT03310957. Accessed: July 8, 2019.

PARP + Immunotherapy

- Olaparib + durvalumab for metastatic TNBC[a]
  - Olaparib PO BID x 28 days (lead in)
  - Olaparib PO BID + durvalumab IV q 4 weeks
    - Treatment is for up to 12 courses in the absence of progression or unacceptable toxicity (participants may continue on therapy beyond progression at the investigator's discretion)
- Rucaparib + atezolizumab (for TNBC and gyn malignancies)[b]
  - 21-day run in of rucaparib
  - Rucaparib BID and atezolizumab IV q 21 days
    - Treatment is until unacceptable toxicity or progression

BID = twice daily; PO = by mouth; q 4 weeks = every 4 weeks; q 21 days = every 21 days

a. National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT03801369. Accessed: July 8, 2019.
b. National Institutes of Health. https://clinicaltrials.gov/ct2/show/NCT03101280. Accessed: July 8, 2019.

Where Are We Now?

- Atezolizumab + abraxane = standard of care in first line for PD-L1+ mTNBC
  - I think also very reasonable to use in second line or third line in this population if they haven't received it sooner
- Ongoing neoadjuvant trials and adjuvant are exciting and a good opportunity for patients when logistically feasible, given pCR ~30% with chemotherapy and poor prognosis with residual disease
- Lots of studies in the metastatic setting looking at finding the right immunotherapy combinations for the right patients
  - PARP + immunotherapy for BRCA+?

With Progress, More Questions Will Follow

- Patient selection is a huge issue
  - PD-L1+ IC very helpful for atezolizumab/abraxane
  - Will the same test, or different ones, prove appropriate for other IO agents?
- Optimizing upfront therapy
  - Neoadjuvant? If so, for whom? And do we continue adjuvantly or stop if pCR?
  - Biomarkers to predict benefit from adjuvant use for those with residual disease
- Are all drugs equal?
  - Eventually, choosing among various anti-PD1 and –PD-L1 agents may pose a challenge for clinicians (and for patients)

IO = immuno-oncology

Thank You!

- The meeting organizers for the opportunity to present today
- Most importantly….all the patients who have participated in the important trials that are helping to push the envelope forward