IMMUNOTHERAPY IN BREAST CANCER

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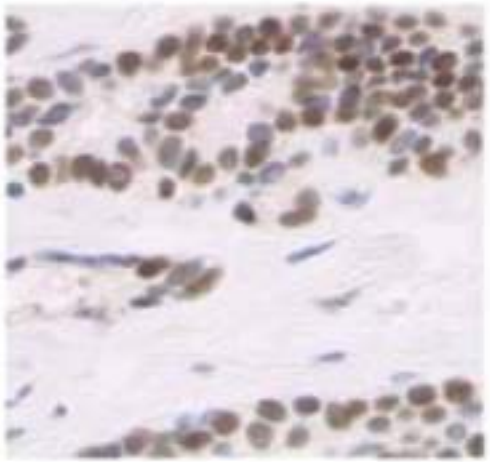
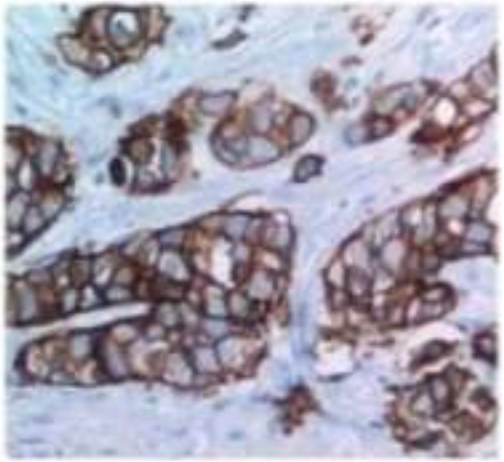
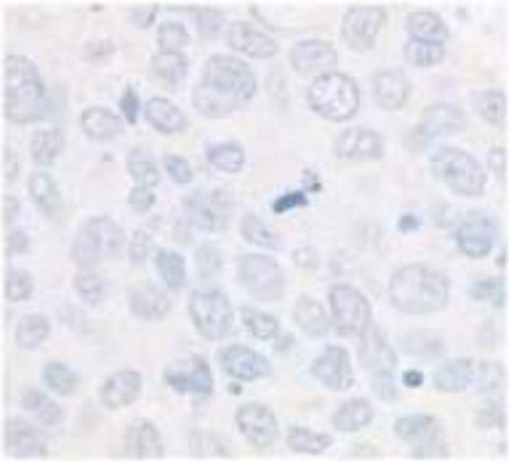
Is breast cancer immunogenic?

Does High TILs correlate with improved survival in node positive TNBC ?

The Simple View:
Three Subtypes of Breast Cancer

HR +ve	HER 2 +ve	TNBC
60 – 70%	15 – 20%	15 – 20%
		
Endocrine therapy	Anti-HER2 therapy	Chemotherapy

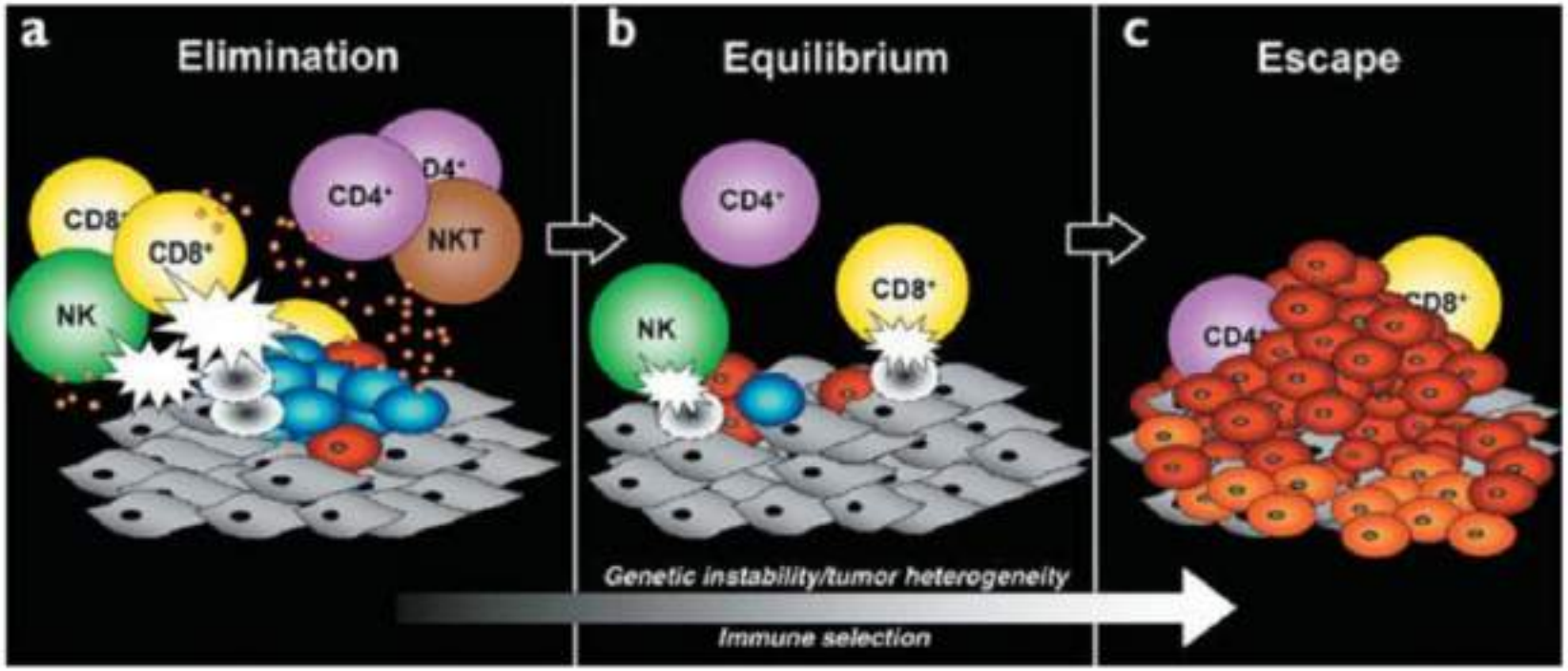
HER2, human epidermal growth factor receptor 2; HR, hormone receptor

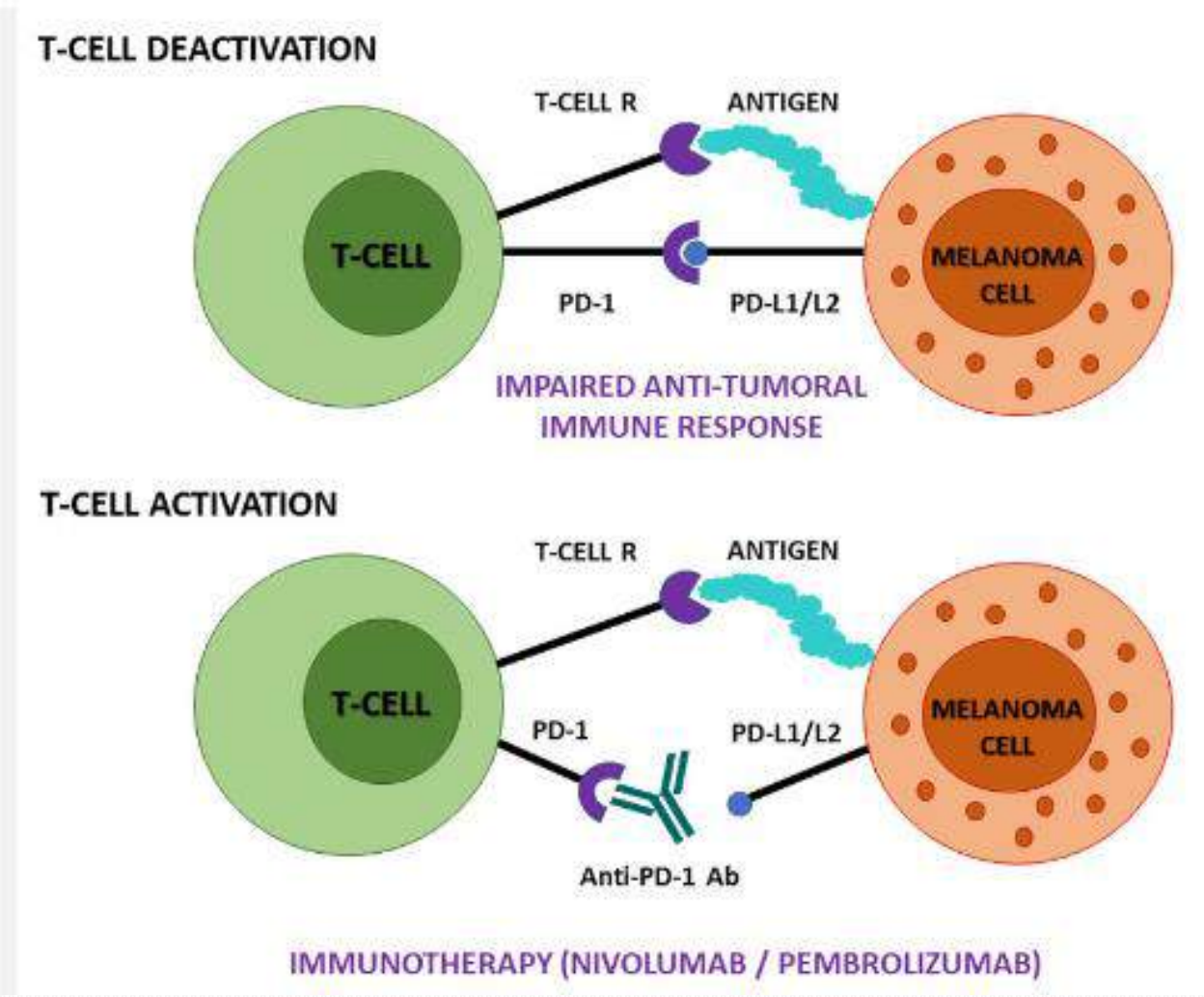
- TNBC is a heterogeneous collection of molecularly distinct disease subtypes with widely differing natural histories

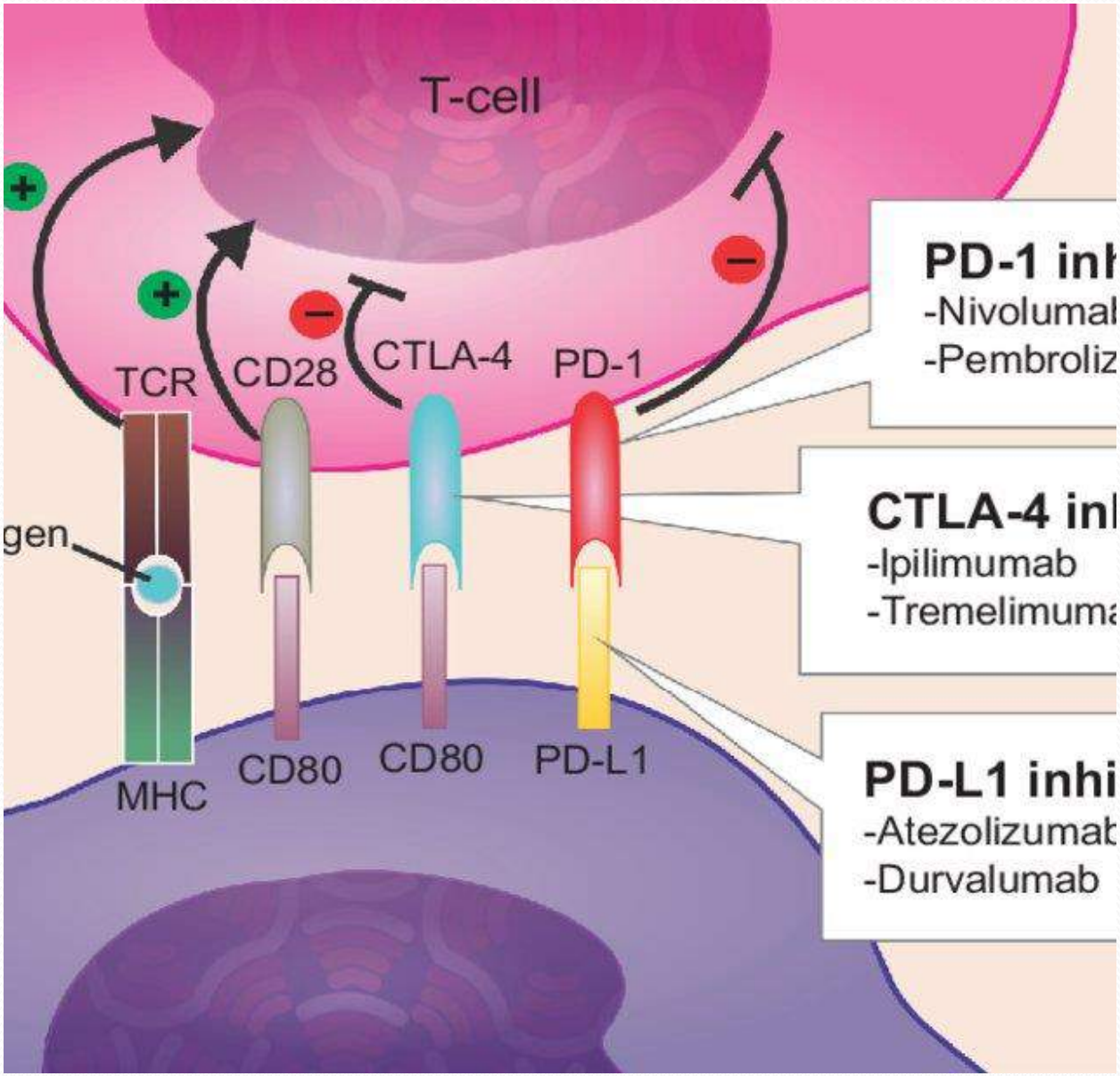
- **TNBC is often associated with genomic instability .**

- Checkpoint inhibitors have shown activity in TNBC. Patient selection remains challenging

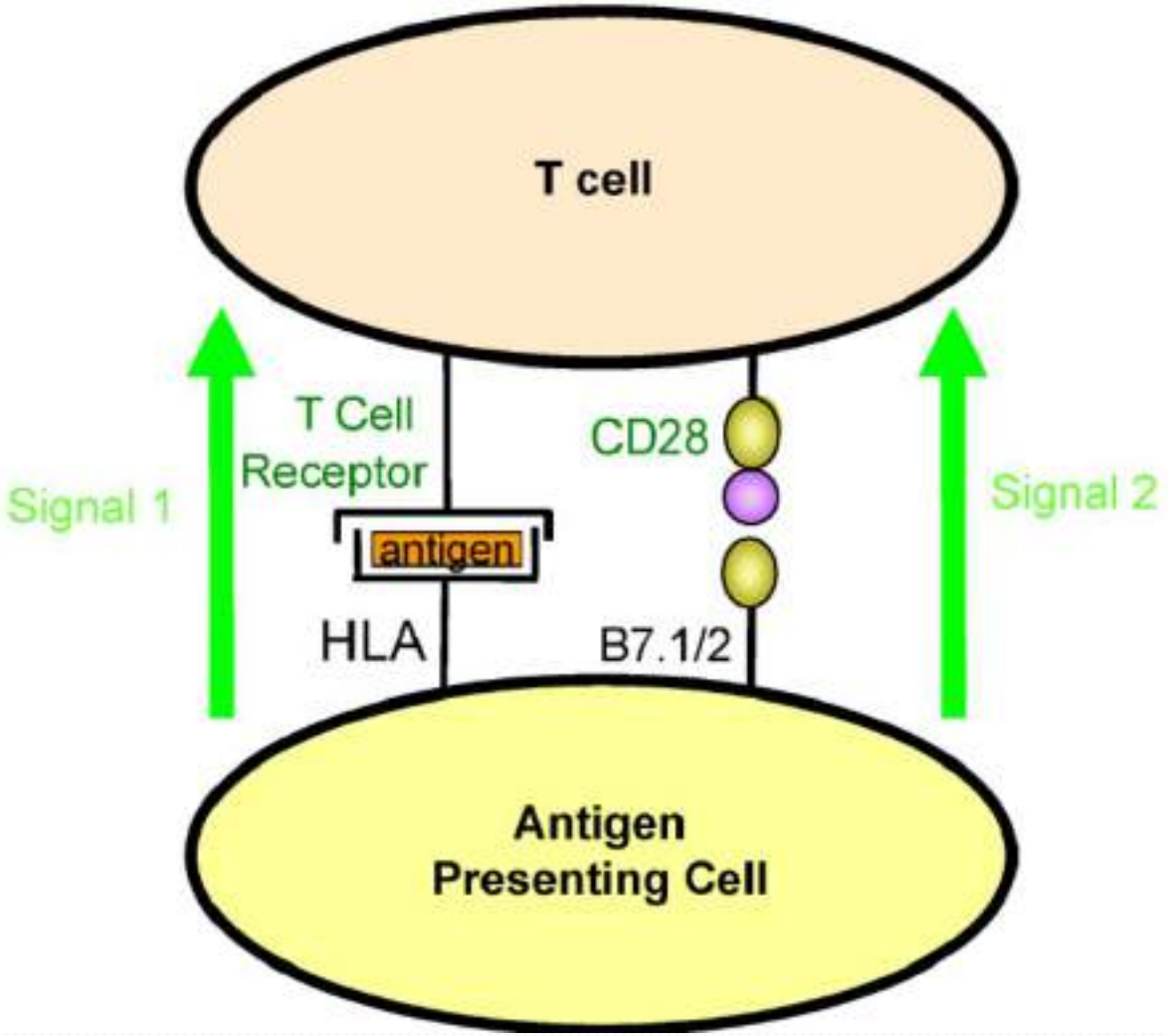
The Immune Editing Hypothesis (3E's)



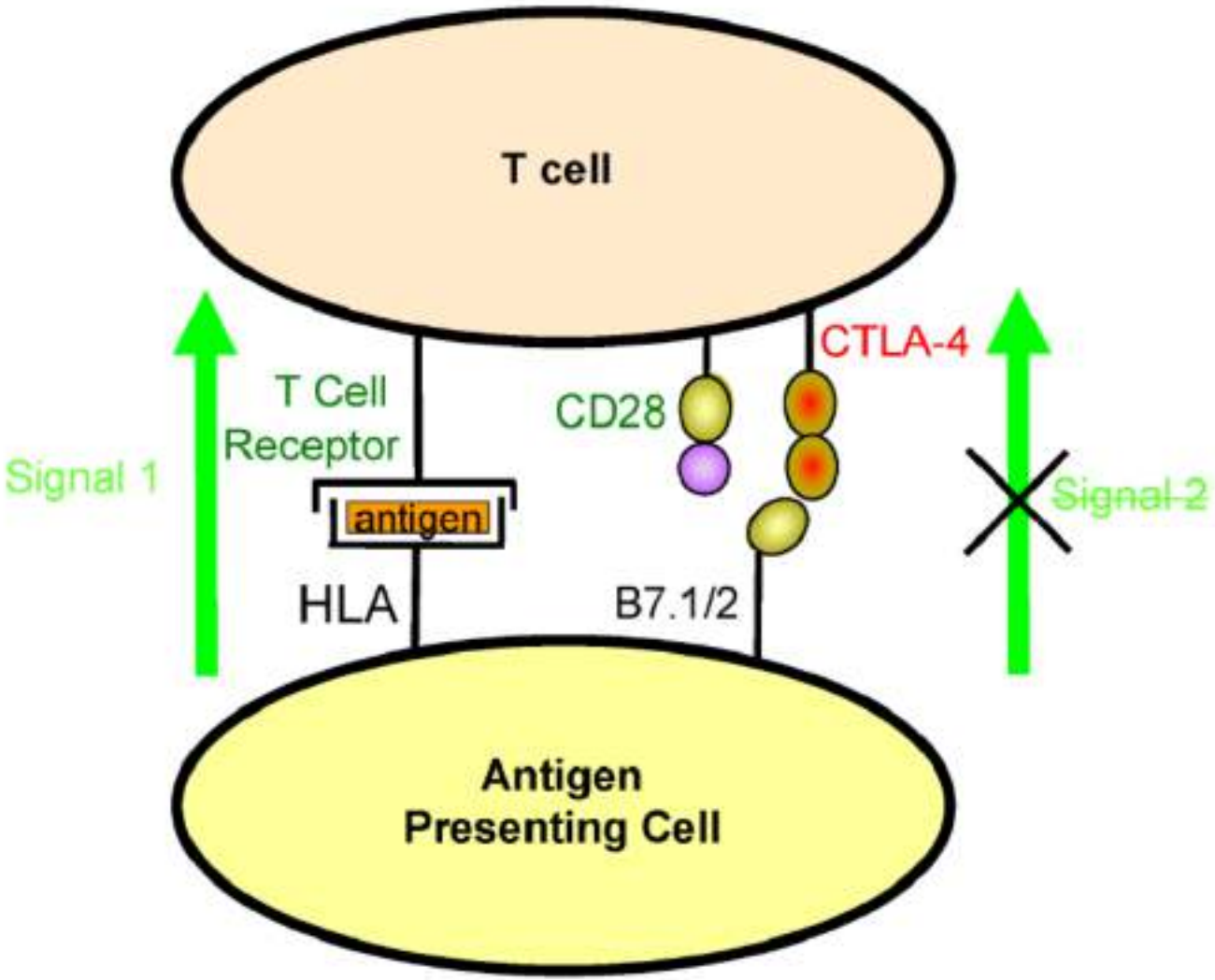

T-CELL DEACTIVATION
T-CELL R
ANTIGEN
T-CELL
MELANOMA CELL
PD-1
PD-L1/L2
IMPAIRED ANTI-TUMORAL IMMUNE RESPONSE
T-CELL ACTIVATION
T-CELL R
ANTIGEN
T-CELL
MELANOMA CELL
PD-1
PD-L1/L2
Anti-PD-1 Ab
IMMUNOTHERAPY (NIVOLUMAB / PEMBROLIZUMAB)


T-cell
TCR
CD28
CTLA-4
PD-1
gen
MHC
CD80
CD80
PD-L1
PD-1 inh
-Nivolumal
-Pembroliz
CTLA-4 inh
-Ipilimumab
-Tremelimuma
PD-L1 inhi
-Atezolizumab
-Durvalumab

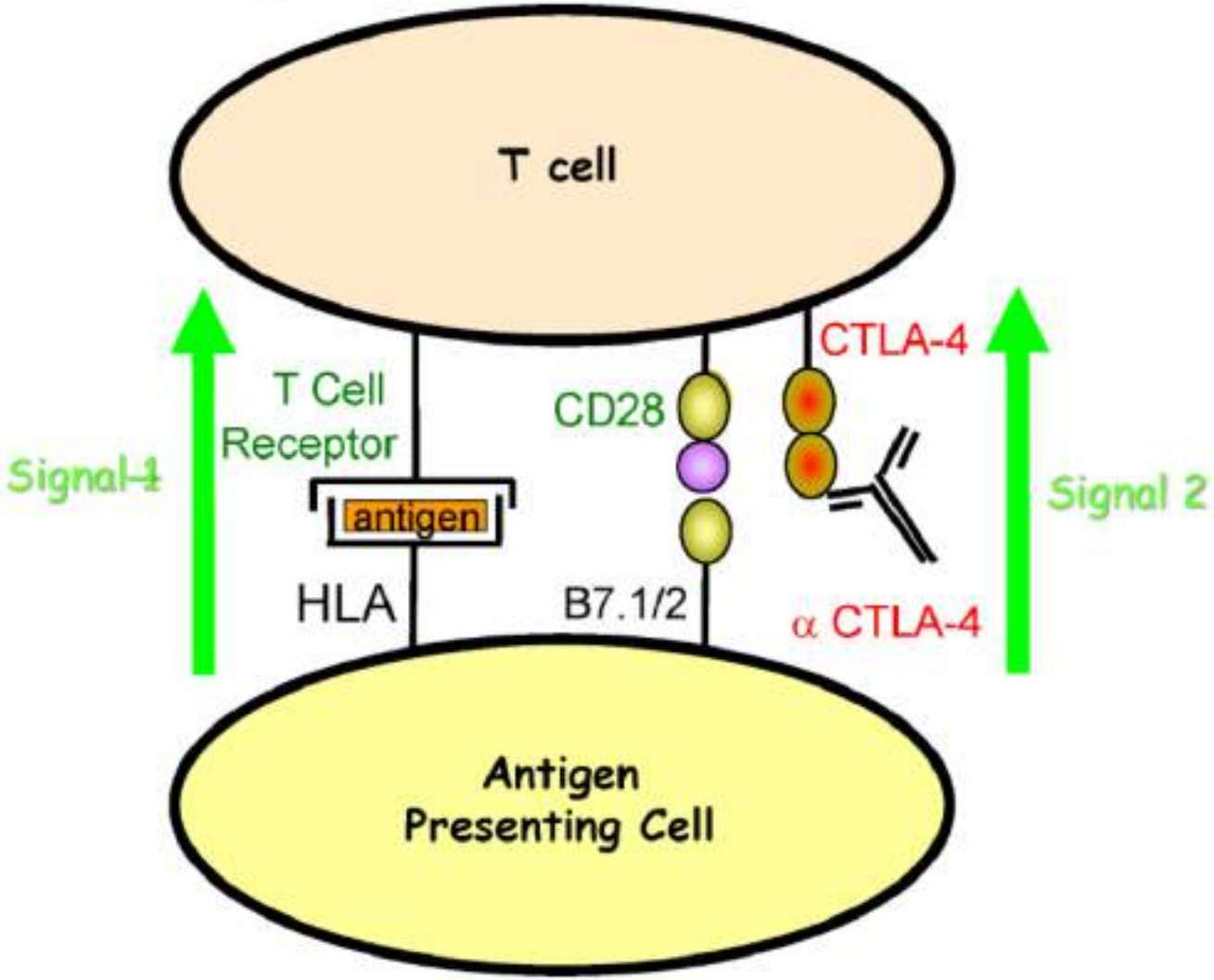
Anti-CTLA-4


T cell
T Cell
Receptor
CD28
Signal 1
Signal 2
antigen
HLA
B7.1/2
Antigen
Presenting Cell

CTLA-4 Prevents Normal T Cell Activation



Ipilimumab (Anti-CTLA-4) Blocks the CTLA-4 Checkpoint, RestoringT Cell Activation



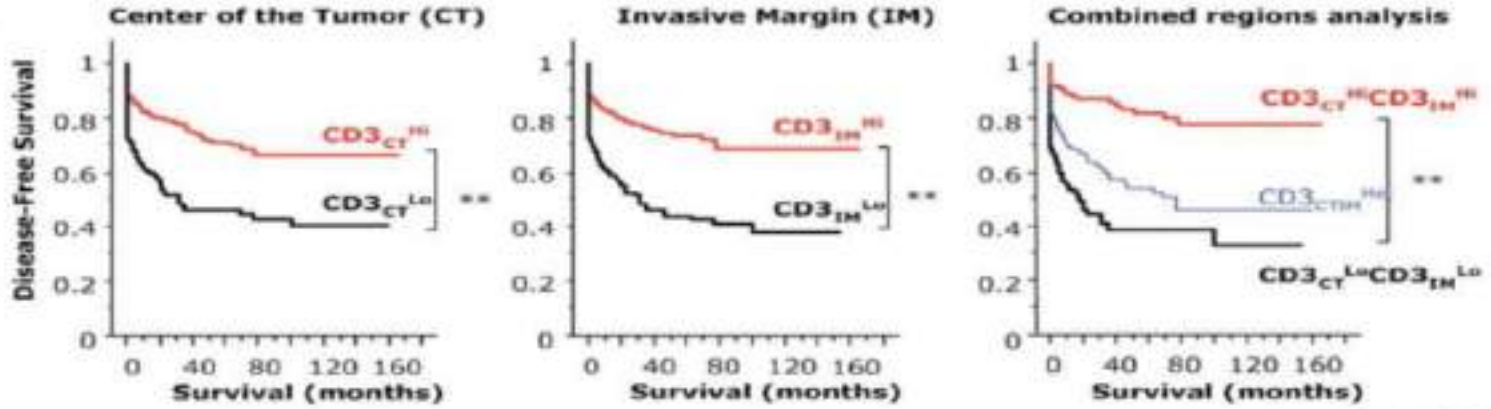
Historical Treatment of TNBC

- Before 2018, primary treatment option for advanced TNBC limited to single-agent chemotherapy
- Combination chemotherapy used to obtain a rapid response for short-term disease-related complications:
  - Large tumor burdens
  - Significant symptoms
  - Impending visceral crisis
- 2018: PARP inhibitors olaparib and talazoparib approved as non chemotherapy treatment options for advanced *HER2*-negative patients (TNBC and ER positive) with germline *BRCA* mutations[a,b]

a. FDA approves olaparib for germline BRCA-mutated metastatic breast cancer. b. FDA approves talazoparib for gBRCAm HER2-negative locally advanced or metastatic breast cancer.

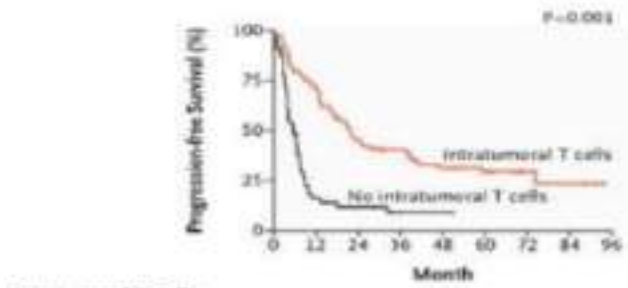
Effect of Immune Infiltration on Overall Survival

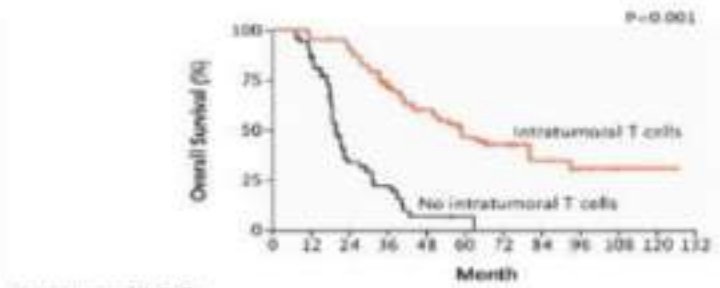
Colon Cancer



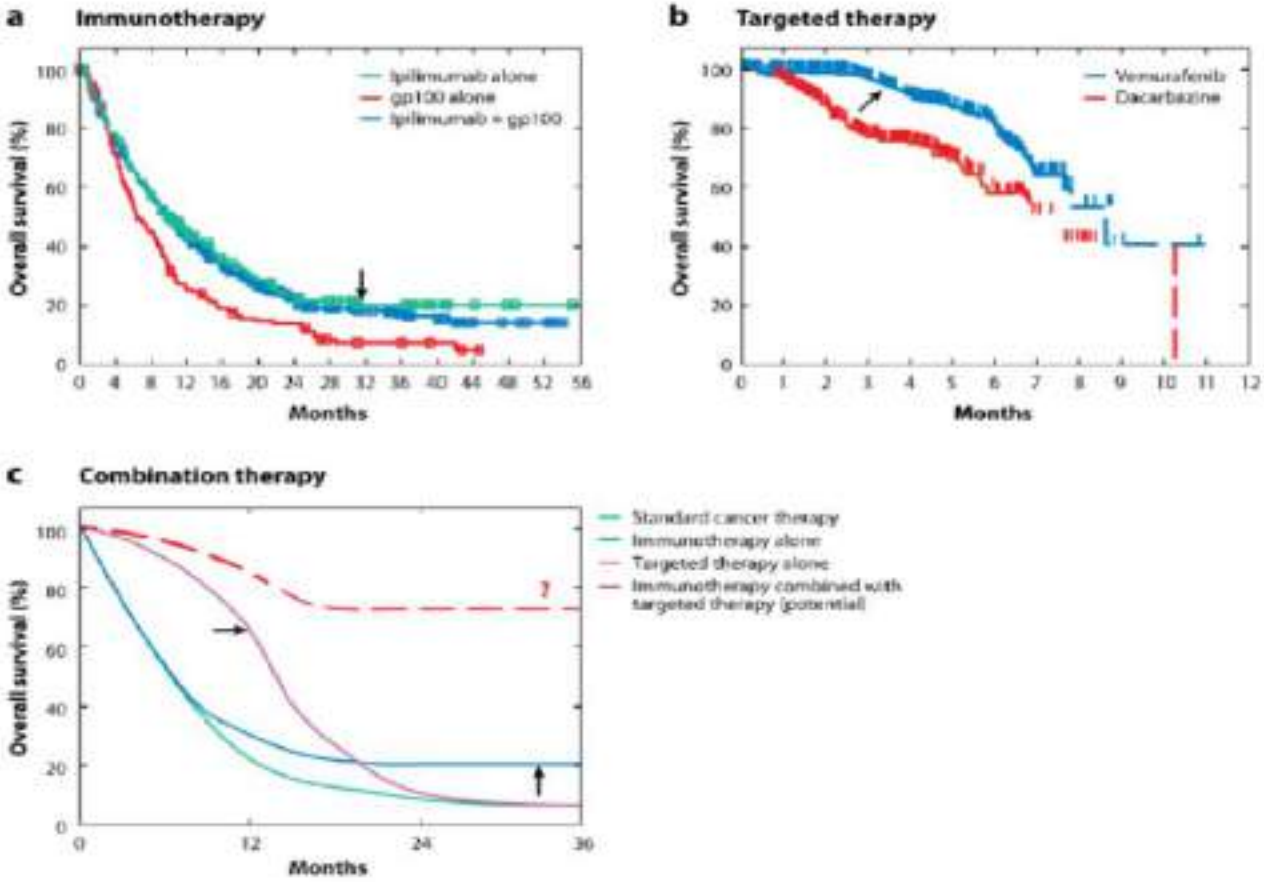
Galon Science 2006

Ovarian Cancer





Rationale for Combination Chemo-Immunotherapy



Maus MV, et al. 2014.
Annu. Rev. Immunol. 32:189–225

Emerging Treatment of TNBC

- 2019: FDA approved of combination nab-paclitaxel and atezolizumab for patients with PD-L1-positive advanced TNBC[a]
- NCCN guidelines recommend PARP inhibitors and atezolizumab for treatment of selected patients with advanced TNBC[b]

Treatment guidelines for advanced TNBC are rapidly evolving.

a. FDA approves atezolizumab with nab-paclitaxel and carboplatin for metastatic NSCLC without EGFR/ALK aberrations. b. NCCN Flash Updates: NCCN Guidelines®, NCCN Compendium®, and NCCN Radiation Therapy Compendium™ for Breast Cancer.

PD-L1 Expression on TCs vs ICs

PD-L1 expression on TCs is typically driven through multiple mechanisms[a]:

- Oncogenic signaling through STAT and MEK
- Proinflammatory cytokines
- Epigenetic modulation of PD-L1 transcription

PD-L1 expression on tumor-associated ICs is due to adaptive regulation from physiological signals[b]

Tumors of different types have different distributions of PD-L1 on TCs and ICs.

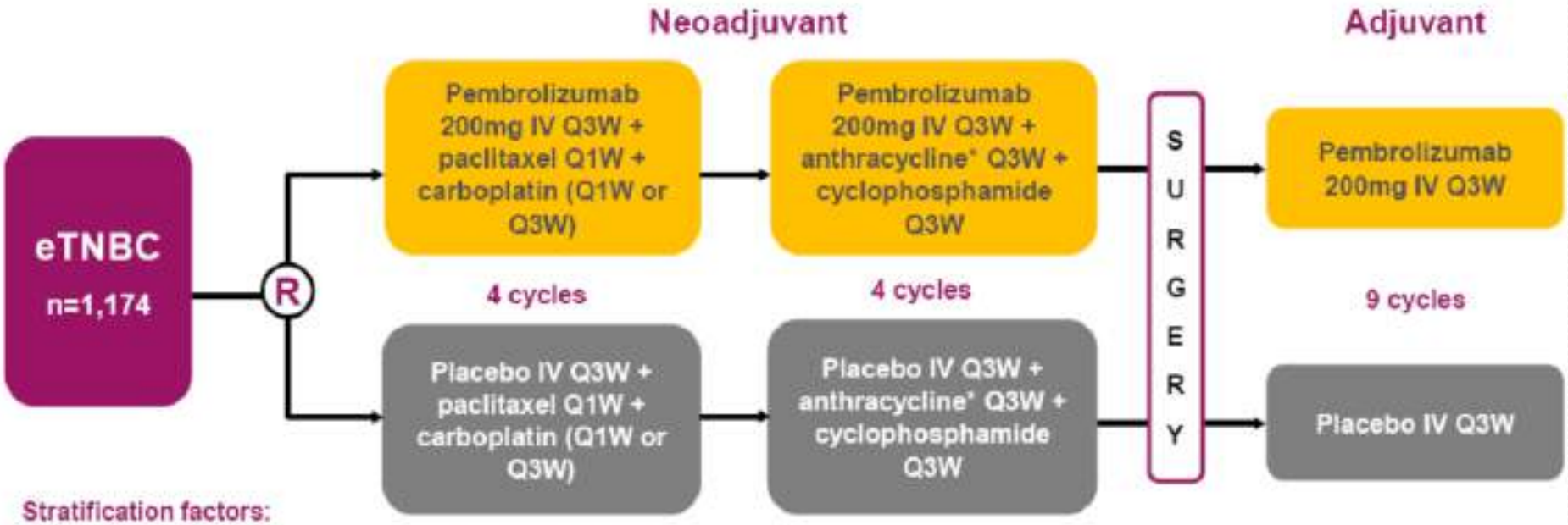
a. Cha JH, et al. *Mol Cell*. 2019;76:359-370; b. Kowanetz M, et al. *Proc Natl Acad Sci U S A*. 2018;115:E10119-E10126.

IMMUNOTHERAPY IN EARLY TNBC

Randomized TNBC neoadjuvant IO trials

	GeparNUEVO	NeoTRIPaPD-L1	KEYNOTE-522	Impassion 031
Chemotherapy backbone	Nab-paclitaxel -> EC q2 week	Nab-palcitaxel + carbo weekly 2 on/1off x8	Paclitaxel + Carbo -> AX/EC q3 week	Nab-paclitaxel –> AC q2 week
CPI	Anti-PD-L1	Anti-PD-L1	Anti-PD-1	Anti-PD-L1
	± Durvalumab (no adj)	± Atezolizumab (no adj)	± Pembrolizumab 1year	± Atezolizumab 1 year
pCR rate	pCR = 53.4% vs 44.2%	pCR = 43.5% vs 40.8%	pCR = 64.8% vs 51.2%	pCR = 57.8% vs 41.1%
	Δ 9.2% (n=174)	Δ 2.7% (n=280)	Δ 13.6% (n=602)	Δ 16.5% (n=333)
			pCR = 63% vs 55.6%	
			Δ 7.5% (n=1174)	
Primary Endpoint	pCR	EFS	pCR EFS	pCR

KEYNOTE-522: phase III neoadjuvant then adjuvant pembrolizumab study in eTNBC



Stratification factors:

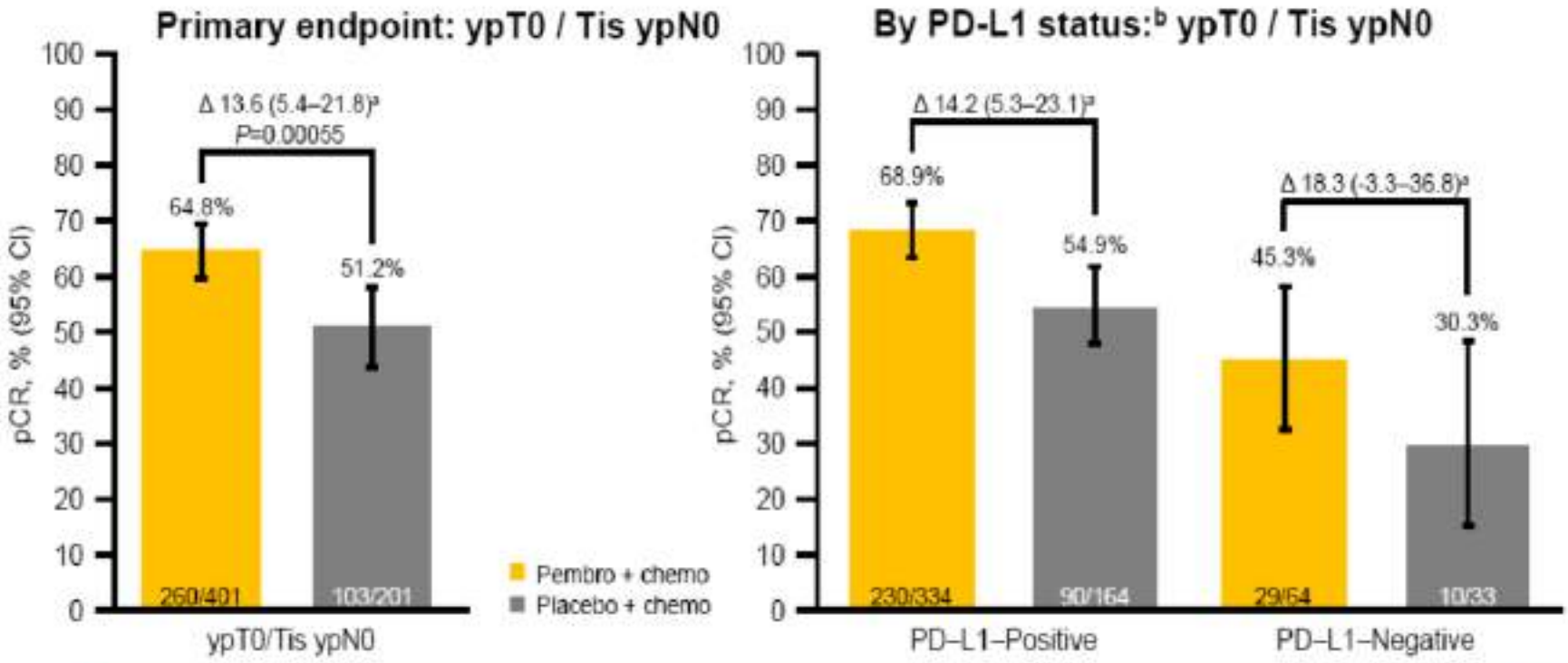
- Nodal status (positive vs negative)
- Tumour size (T1/T2 vs T3/T4)
- Carboplatin schedule (Q1W vs Q3W)

Primary endpoints: pCR (ypT0 / Tis ypN0) by local pathologist assessment (ITT), EFS by investigator assessment (ITT)

Secondary endpoints: pCR per alternative definitions (ypT0 ypN0 and ypT0 / Tis) in patients with PD-L1+ tumours, EFS (PD-L1+), OS (PD-L1+ and ITT), tolerability

Key exploratory endpoints: RCB, EFS by pCR, pCR and EFS by TILs

KEYNOTE-522: pCR



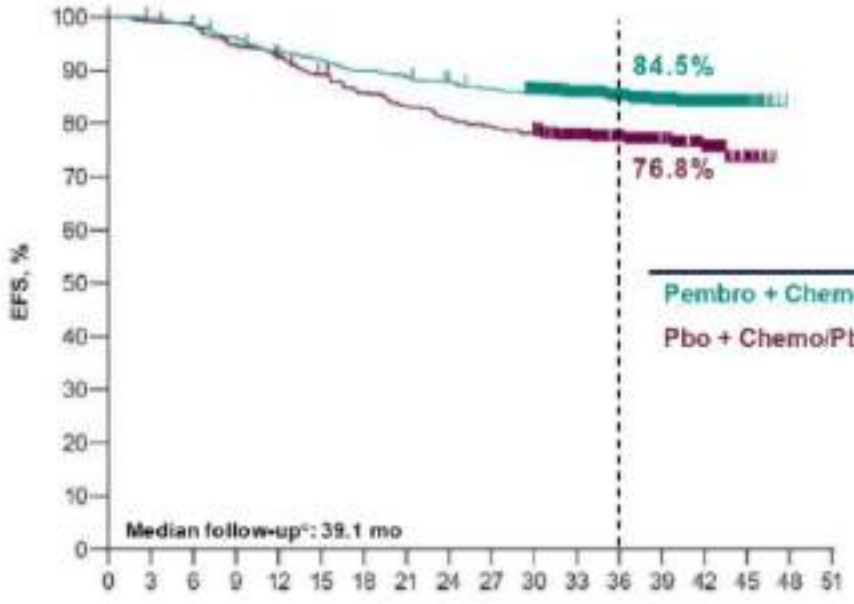
Pembrolizumab showed a statistically significant increase in pCR that was independent of PD-L1 status

[a]Performed after last subject enrolled (data cutoff: 24 September, 2018) based on pre-specified first 602 subjects (pre-calculated boundary for significance: p=0.003); [b]PD-L1 assessed centrally using the PD-L1 IHC 22C3 pharmDx assay and measured by CPS

1. Schmid, et al. ESMO 2019 (Abstract LBA8_PR)

KEYNOTE-522: Event-free survival

Statistically Significant and Clinically Meaningful EFS at IA4



	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	15.7%	0.63[a] (0.48-0.82)	0.00031[b]
Pbo + Chemo/Pbo	23.8%		

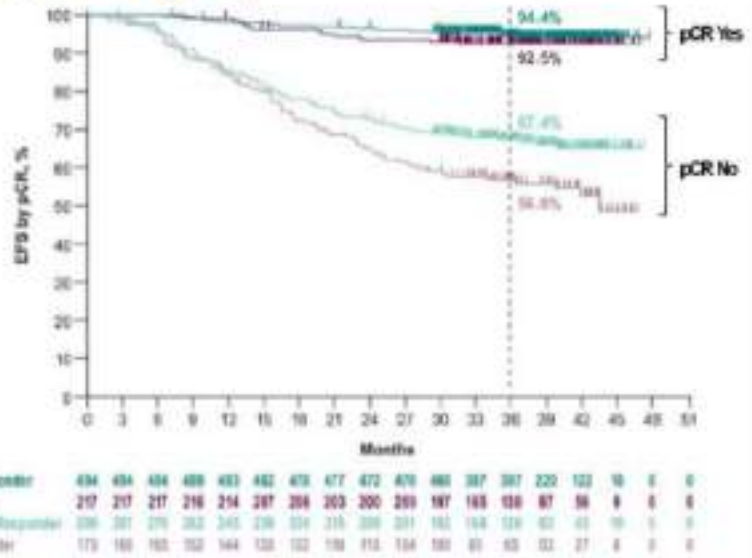
No. at Risk																		
Pembro + Chemo/Pembro	784	781	769	751	726	718	702	692	681	671	652	551	433	303	165	28	0	0
Pbo + Chemo/Pbo	390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [b]Prespecified *P* value boundary of 0.00517 reached at this analysis.
[c]Defined as the time from randomization to the data cutoff date of March 23, 2021.

Schmid P et al, ESMO Virtual Plenary 2021

KEYNOTE-522: EFS subgroup analysis

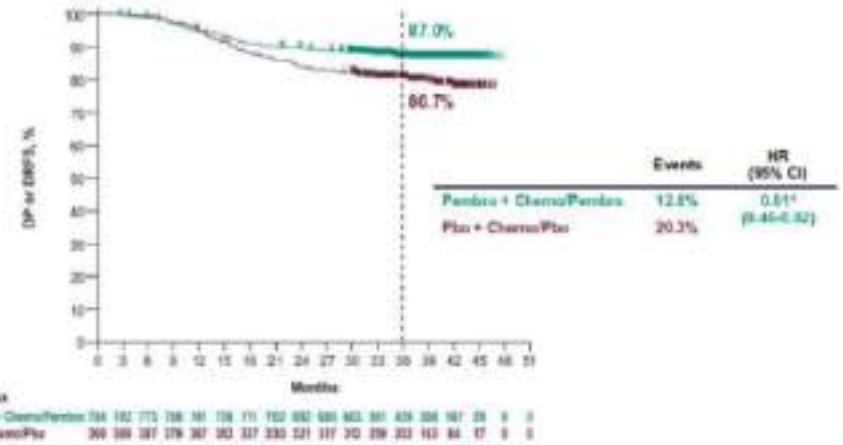
EFS by pCR (ypT0/Tis ypN0)



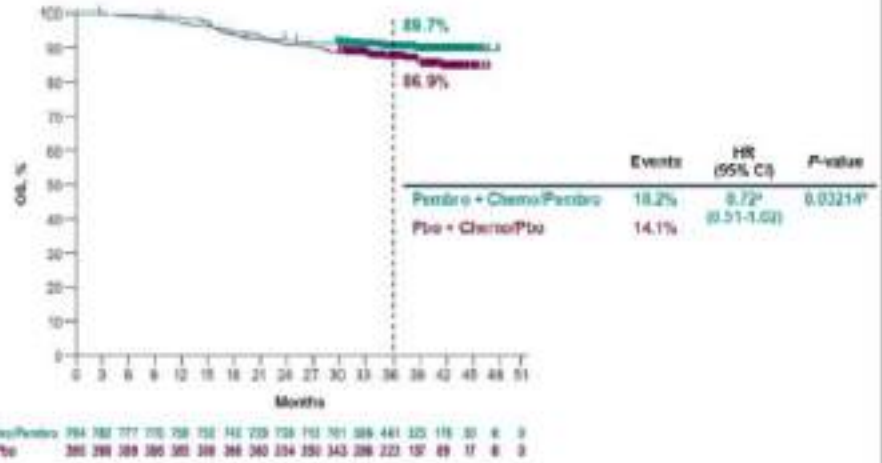
Schmid P et al, ESMO Virtual Plenary 2021

KEYNOTE-522: DRFI and OS

Distant Progression- or Distant Recurrence-Free Survival

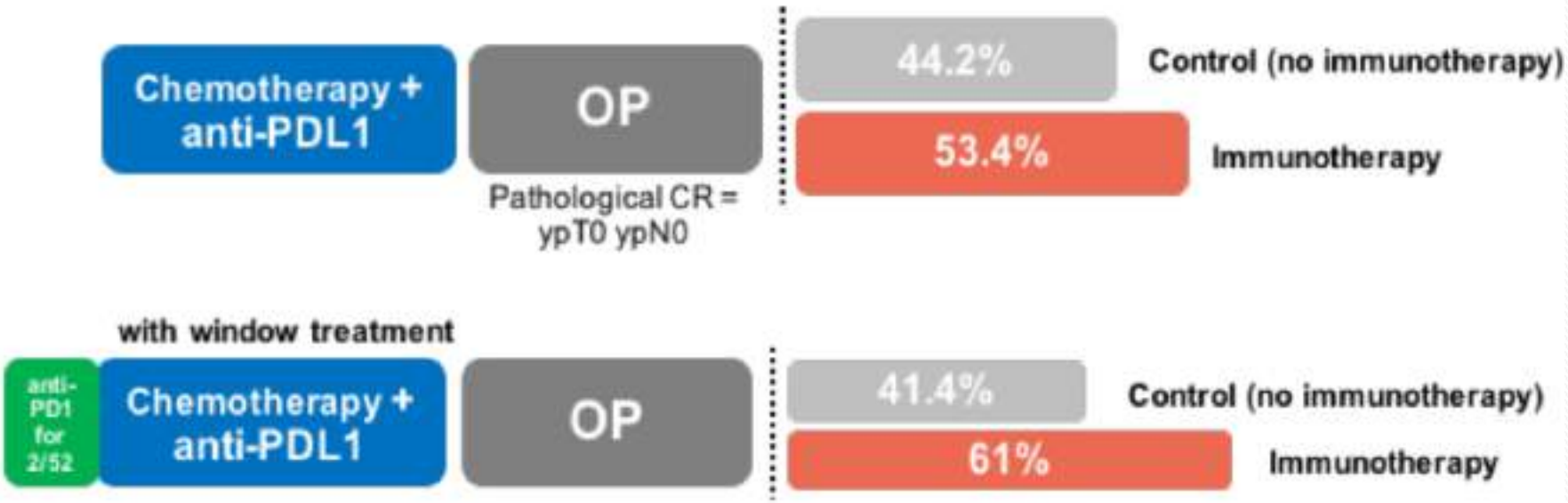


Overall Survival



Schmid P et al, ESMO Virtual Plenary 2021

GepardNuevo Trial: durvalumab in early TNBC



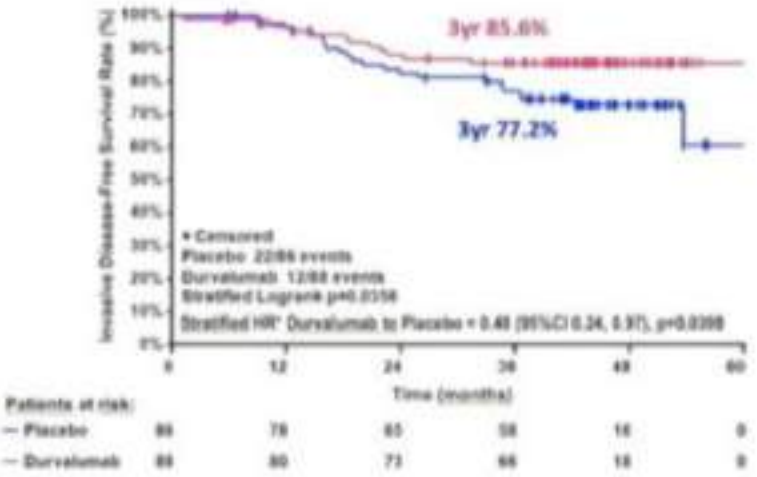
Paclitaxel + carboplatin Q1W x12 + durvalumab Q2W x 6 → AC Q2W x4 + durvalumab Q2W x4

Lobi S et al. ASCO 2018.

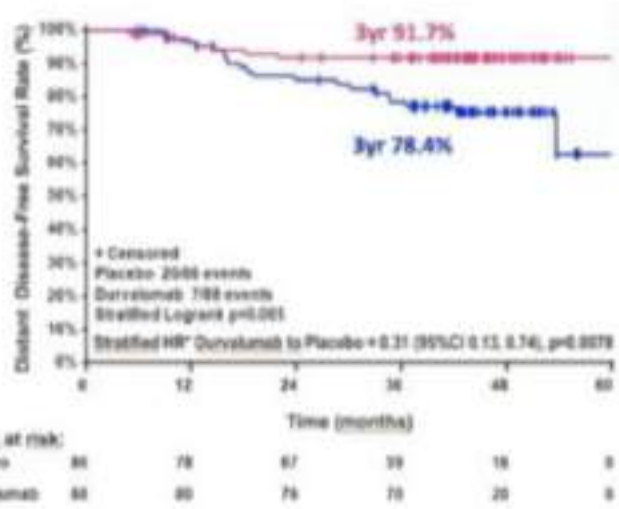
GeparNUEVO: Secondary endpoints

Median follow-up > 3.5 years

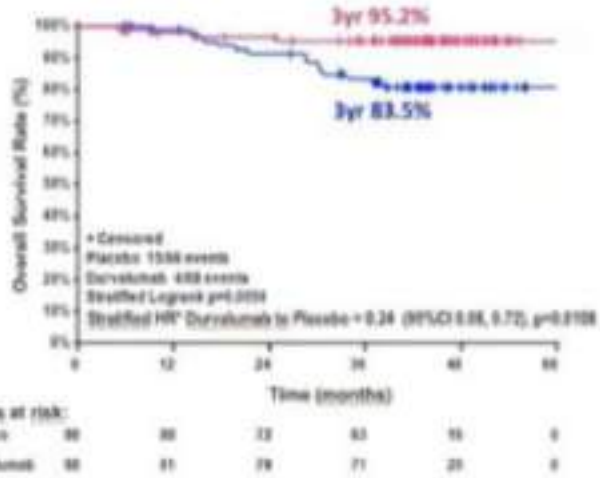
Invasive DFS



Distant DFS



Overall Survival



Loibl S, et al., ASCO 2021

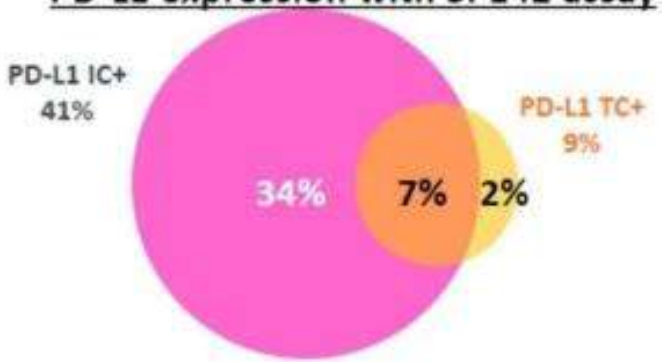
Randomized TNBC neoadjuvant IO trials: Long term outcomes

TRIAL	Regimens	Median FU	Events	HR (95% CI)
GeparNUEVO	Durvalumab+CT vs Placebo+CT	3.5 years	13.6% vs 25.6%	0.48 (0.24-0.97)
KEYNOTE 522	Pembrolizumab+ CT vs placebo+CT	15.5 months	15.7% vs 23.8%	0.63 (0.48-0.82)
Impasssion031	Atezolizumab+CT vs placebo+CT	20.6 months	10.3% vs 13.1%	0.76 (0.4-1.44)

pCR improvement with durvalumab was modest requiring further assessment of association of pCR and longer term outcomes with checkpoints inhibitors

PD-L1 Expression in mTNBC

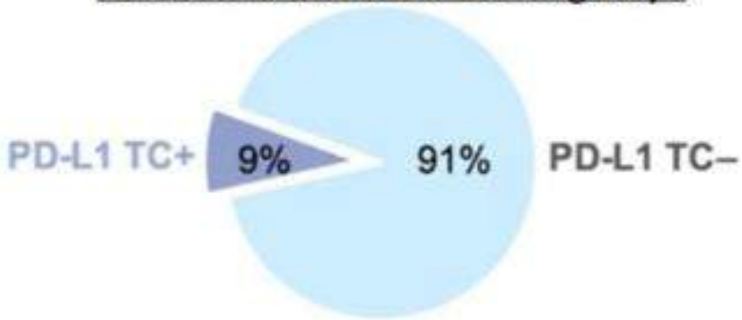
PD-L1 expression with SP142 assay



IMpassion130 used SP142 assay with cut-off >1% PD-L1 on tumor-infiltrating ICs

Prevalence of PD-L1 IC subgroups

Prevalence of PD-L1 TC subgroups



Emens LA. et al. *Cancer Res.* 2019:79. Abstract GS1-04.

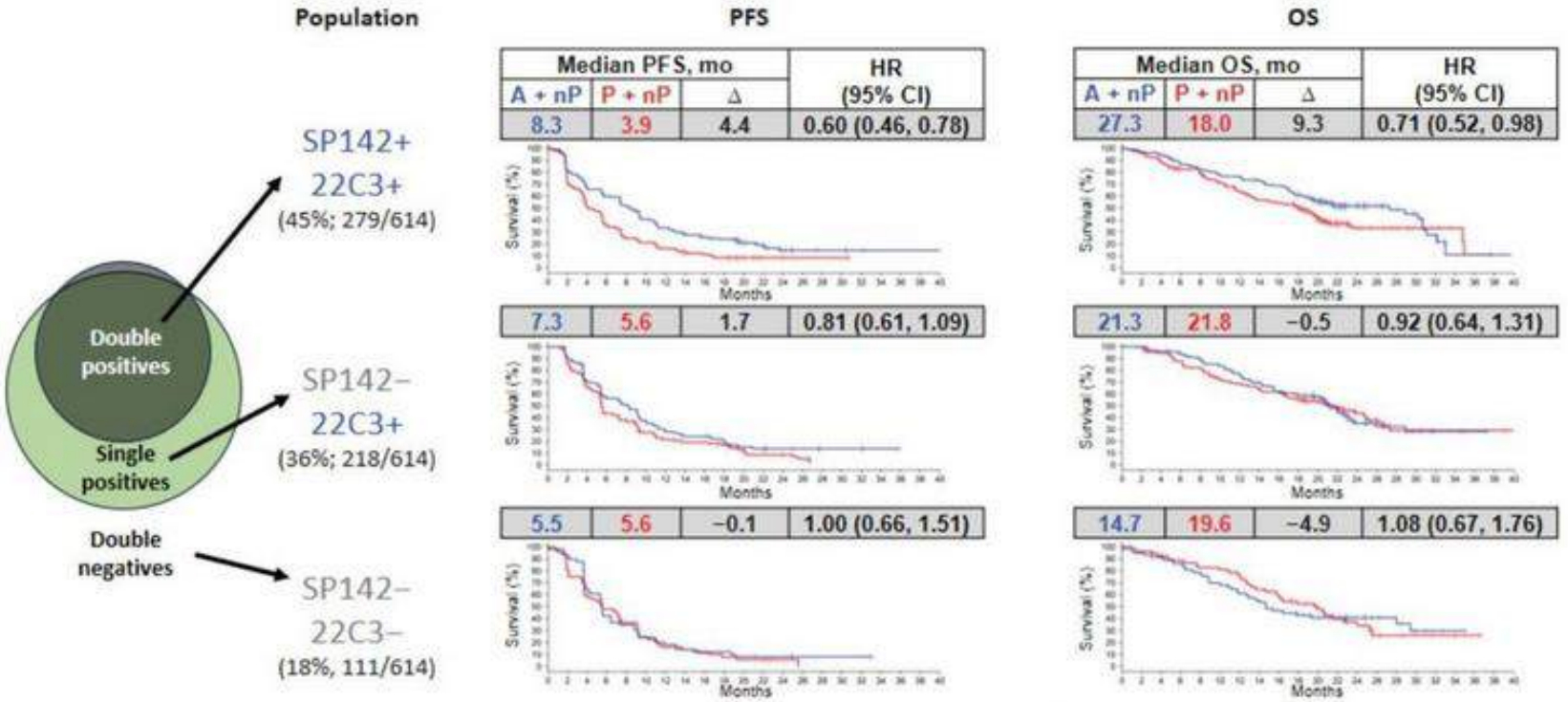
Assays for PD-L1 Expression Testing

	Atezolizumab[a-c]	Avelumab[d-f]	Durvalumab[g,h]	Nivolumab[i]	Pembrolizumab[j,k]
IHC platform	VENTANA SP142 IHC	Dako 73-10 IHC	VENTANA SP263 IHC	Agilent/Dako 28-8 IHC	Dako 22C3 IHC
Cell types and cutoffs for positivity (%)	**NSCLC:** • TCs ≥1, ≥5, ≥50 • ICs ≥1, ≥5, ≥10 **mUC:** ICs ≥1, ≥5 **TNBC:** ICs ≥1	**NSCLC:** • TCs ≥1, ≥5, ≥25 • ICs ≥10 **mUC:** TCs ≥5 **mMCC:** TCs ≥1	**NSCLC:** • TCs ≥25 • ICs ≥25	**NSCLC:** • TCs ≥1, ≥5, ≥10	**NSCLC:** TCs ≥1, ≥50 **mUC:** Combined TCs and ICs ≥1, ≥10

The SP142 assay is FDA approved to identify patients with mTNBC most likely to benefit from adding atezolizumab to nab-paclitaxel.

a.Fehrenbacher L, et al. *Lancet*. 2016;387:1837-1846; b. Rosenberg JE, et al. *Lancet*. 2016;387:1909-1920; c. Schmid P. *N Engl J Med*. 2018;379:2108-2121; d. Gulley JL, et al. *Lancet Oncol*. 2017;18:599-610; e. Patel MR, et al. *Lancet Oncol*. 2018;19:51-64; f. Kaufman HL, et al. *Lancet Oncol*. 2016;17:1374-1385; g. Antonia SJ, et al. *N Engl J Med*. 2018;379:2342-2350; h. Powles T, et al. *JAMA Oncol*. 2017;3:e172411; i. Borghaei H, et al. *N Engl J Med*. 2015;373:1627-1639; j. Herbst RS, et al. *Lancet*. 2016;387:1540-1550. k. Balar AV, et al. *Lancet Oncol*. 2017;18:1483-1492; l. Rugo HS, et al. ESMO 2019. Abstract LBA20.

PFS and OS by Different PD-L1-Assay: SP142 (IC 1%) and 22C3 (CPS 1)

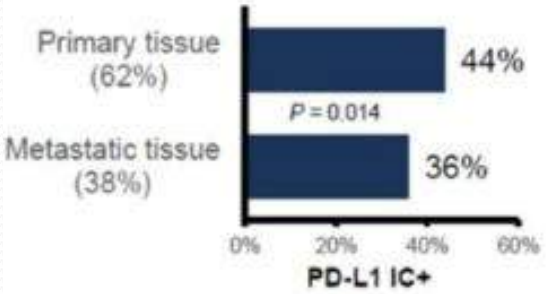


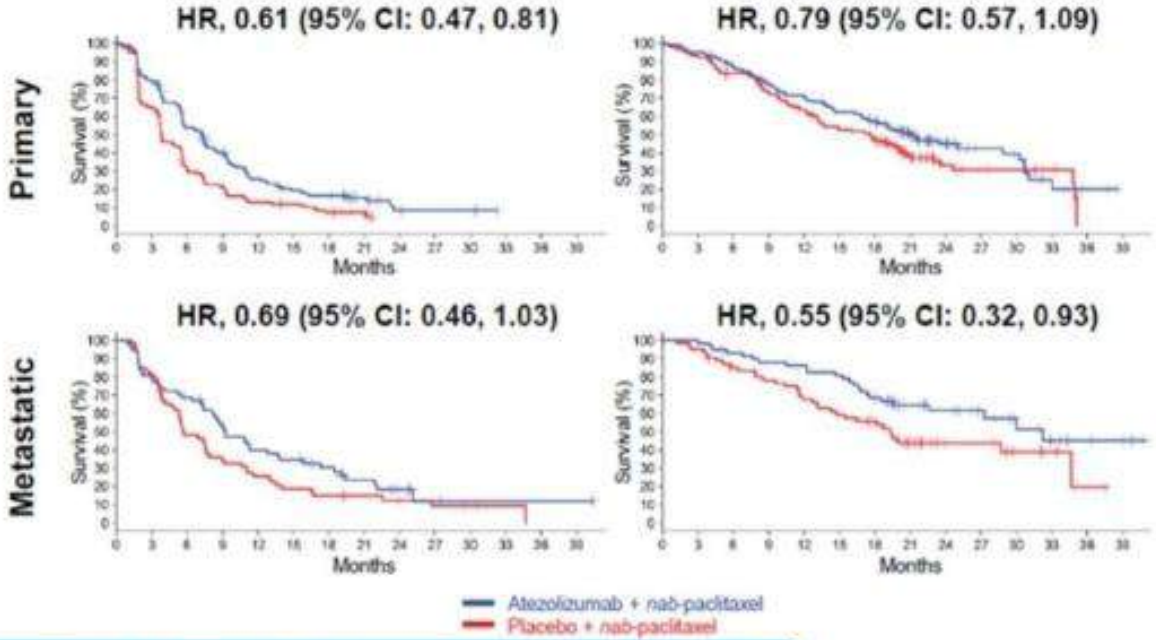
Double positive: SP142 IC ≥ 1%, 22C3 CPS ≥ 1; single positive: SP142 IC < 1%, 22C3 CPS ≥ 1; double negative: SP142 IC < 1%, 22C3 CPS < 1.
HR adjusted for prior taxanes, presence of liver metastases, age and ECOG PS.

Rugo HS, et al. ESMO 2019. Abstract LBA20.

Tissue Source for PD-L1 Testing in TNBC

IMpassion130 allowed testing of either primary tumor or metastatic site





Sampling either the primary tumor or the metastatic site is acceptable for PD-L1 testing.

Rugo HS, et al. ESMO 2019. Abstract LBA20.

Assays for PD-L1 Expression Testing

	Atezolizumab[a-c]
IHC platform	VENTANA SP142 IHC
Cell types and cutoffs for positivity (%)	**NSCLC:** • TCs ≥1, ≥5, ≥50 • ICs ≥1, ≥5, ≥10 **mUC:** ICs ≥1, ≥5 **TNBC:** ICs ≥1

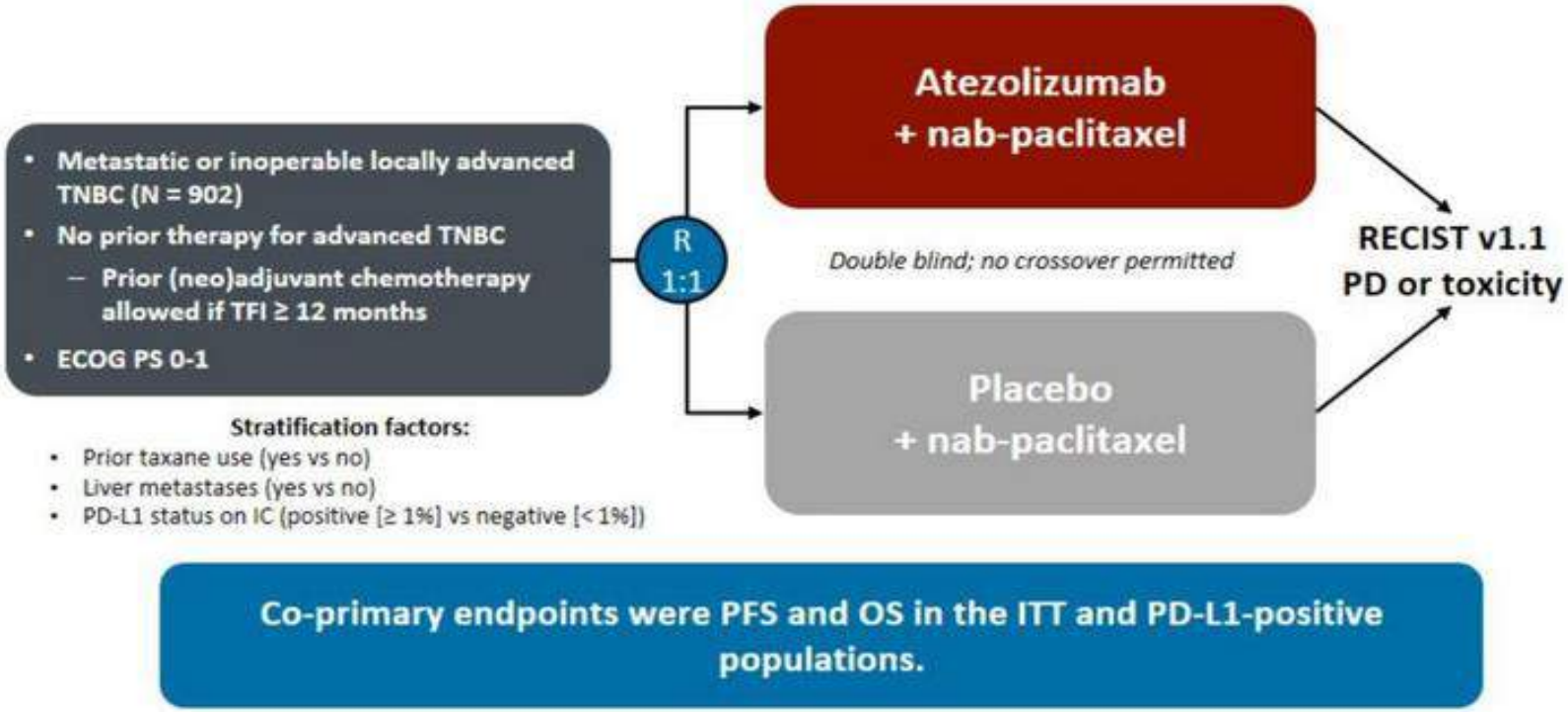
The SP142 assay is FDA approved to identify patients with mTNBC most likely to benefit from adding atezolizumab to nab-paclitaxel.

a.Fehrenbacher L, et al. *Lancet*. 2016;387:1837-1846; b. Rosenberg JE, et al. *Lancet*. 2016;387:1909-1920; c. Schmid P. *N Enal J Med* 2018: 379:2108-2121.

Content Outline

- Clinical trial safety and efficacy data of immunotherapy in patients with mTNBC
- PD-L1 biomarker for assessing patients with advanced TNBC to receive immunotherapy in combination with nab-paclitaxel
- Interpretation of diagnostic PD-L1 testing results to guide biomarker-driven therapy selection in patients with TNBC

Atezolizumab + nab-Paclitaxel for Advanced TNBC
IMpassion130 Study Design



Co-primary endpoints were PFS and OS in the ITT and PD-L1-positive populations.

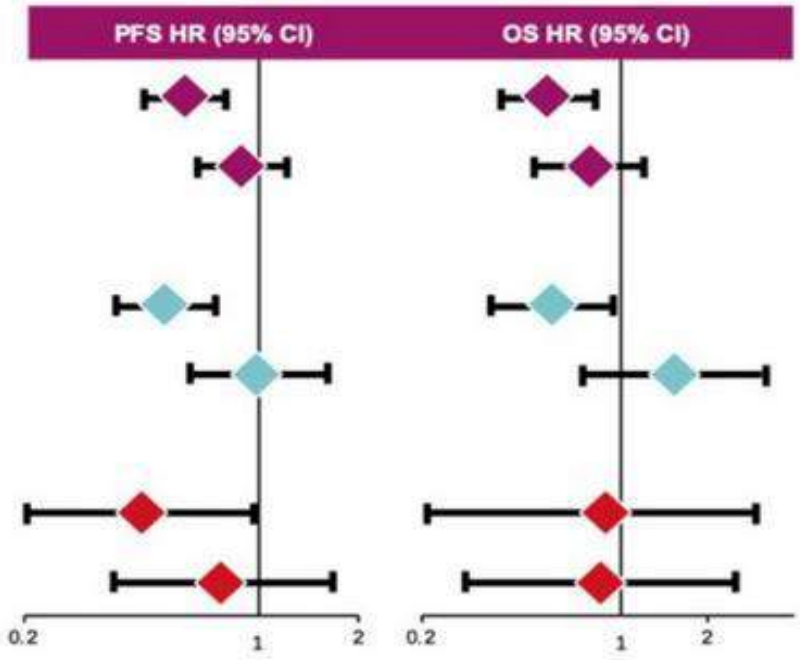
Schmid P, et al. *N Engl J Med.* 2018;379:2108-2121; Schmid P, et al. *Ann Oncol.* 2018;29. Abstract LBA1.

IMpassion130 Outcomes With Other Biomarkers

Patients with CD8+ tumors derived clinical benefit only if their tumors were also PD-L1 IC+

Patients with TIL+ tumors derived clinical benefit only if their tumors were also PD-L1 IC+

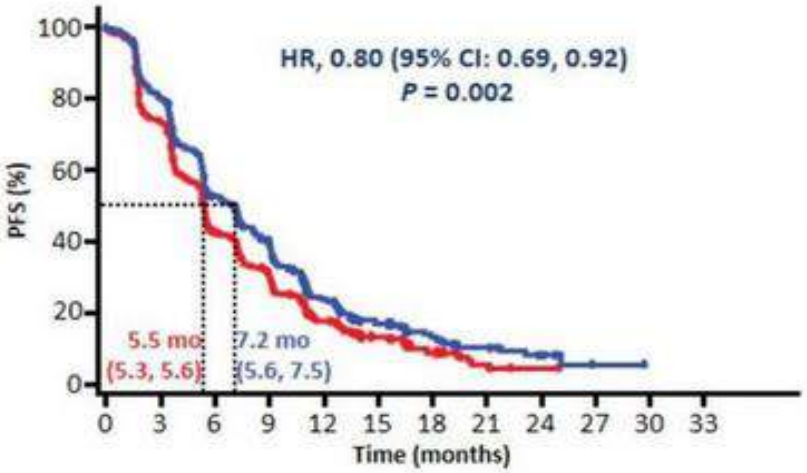
Patients with BRCA1/2-mutant tumors derived clinical benefit only if their tumors were also PD-L1 IC+



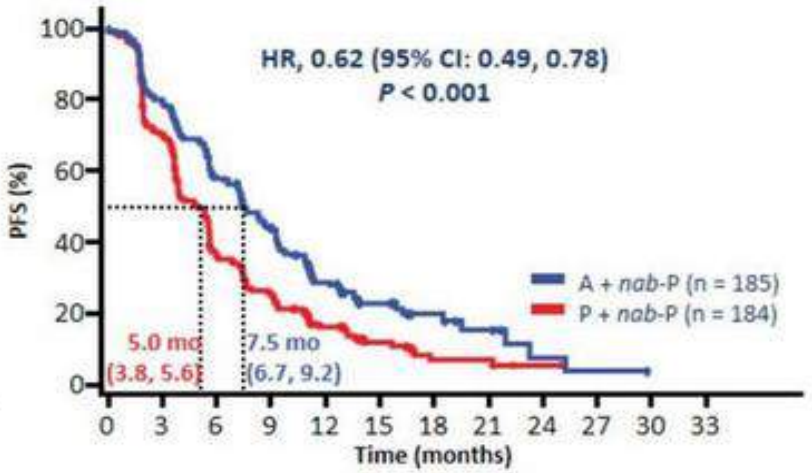
Emens LA, et al. *Cancer Res.* 2019;79. Abstract GS1-04.

Atezolizumab + nab-Paclitaxel for Advanced TNBC
IMpassion130 PFS Findings

ITT population[a]



PFS: PD-L1-positive population[a]



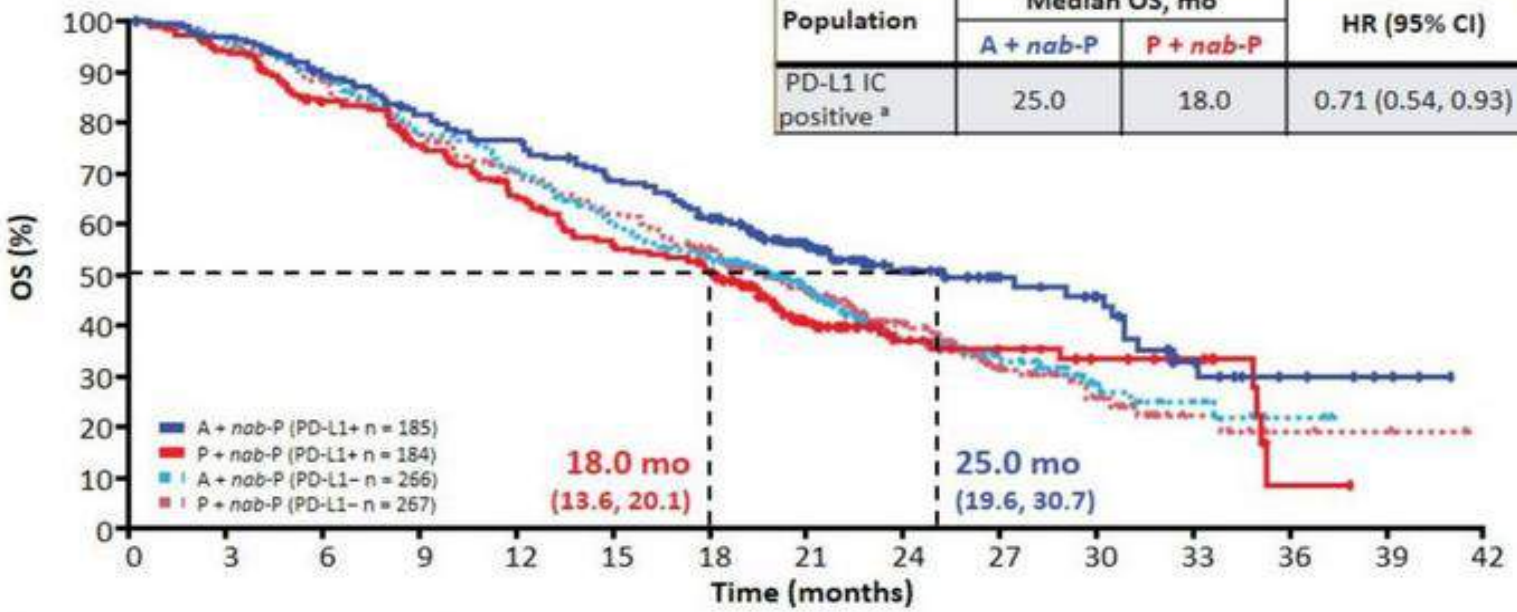
- **PFS benefit driven by PD-L1 IC-positive patients, as a treatment effect was not observed in PD-L1 IC-negative patients**
- **Based on these data, atezolizumab + nab-paclitaxel received accelerated approval by the FDA and is recommended for patients with PD-L1 IC-positive mTNBC in the NCCN[b] and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

a. Schmid P. *N Engl J Med.* 2018;379:2108-2121; b. NCCN Guidelines Breast Cancer, Version 3.2019; c. Thill M, et al. *Breast Care*. 2019;14:247-255.

Atezolizumab + nab-Paclitaxel for Advanced TNBC
IMpassion130 OS Findings

OS in PD-L1-Positive Patients

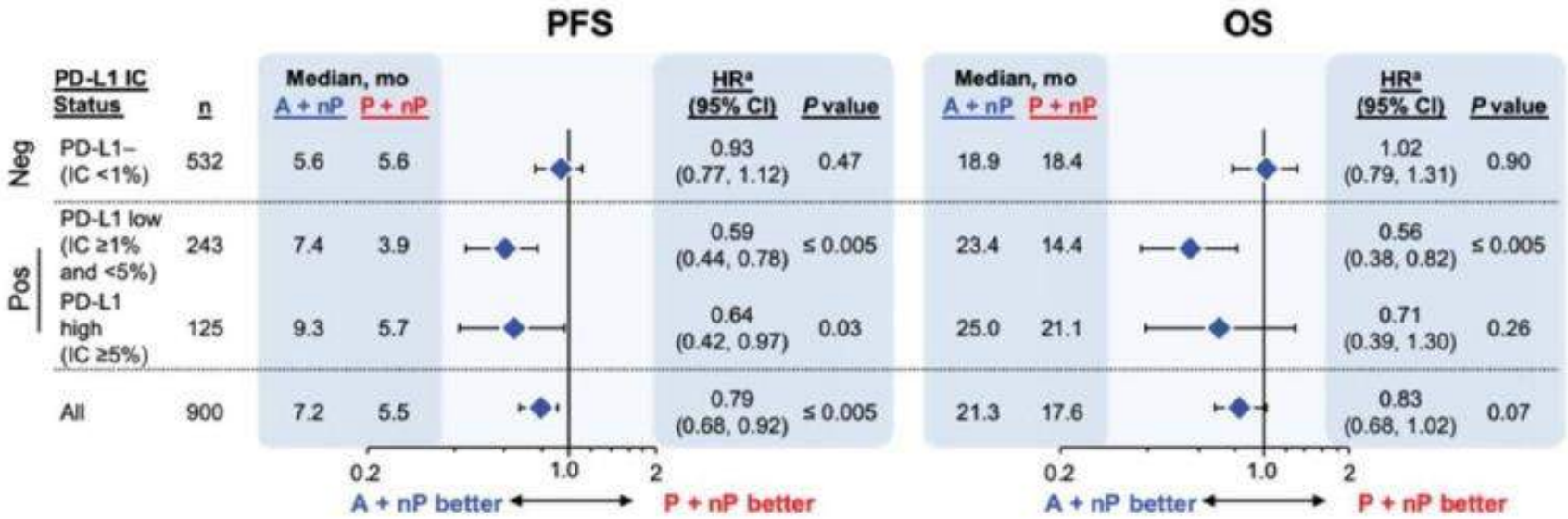
Population	Median OS, mo		HR (95% CI)
	A + *nab*-P	P + *nab*-P	
PD-L1 IC positive [a]	25.0	18.0	0.71 (0.54, 0.93)



[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.

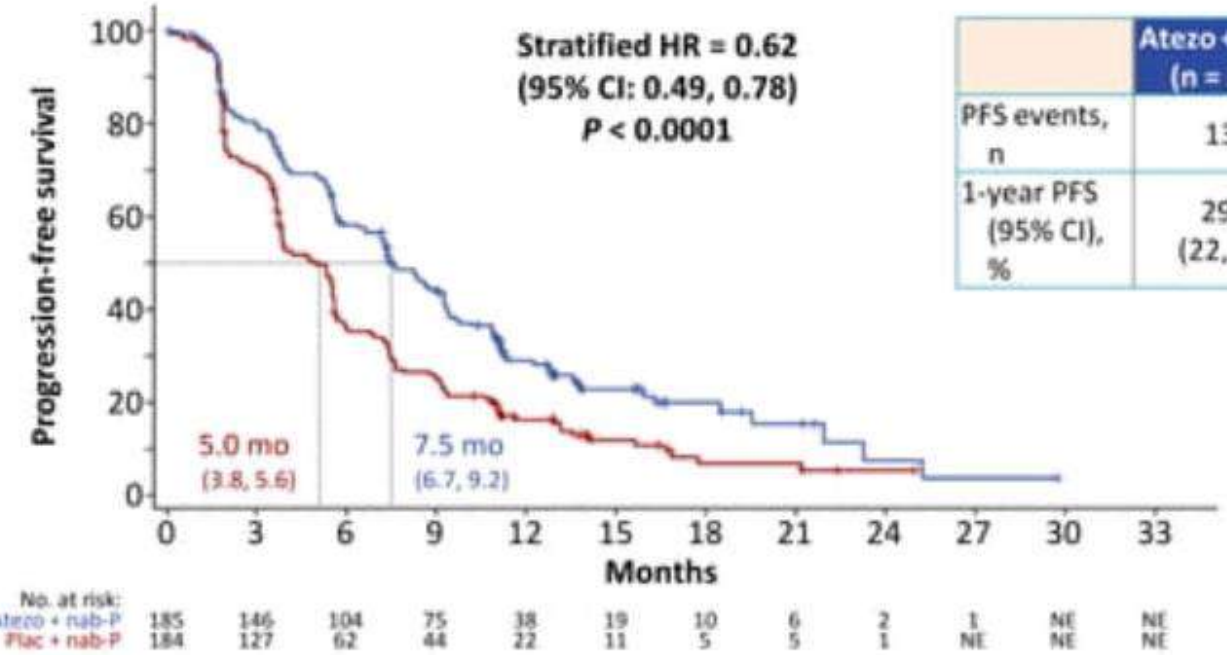
Schmid P, et al. *J Clin Oncol.* 2019;37. Abstract 1003.

IMpassion130 Outcomes by PD-L1 Expression Level



Emens LA, et al. *Cancer Res.* 2019:79. Abstract GS1-04.

Primary PFS analysis: PD-L1+ population

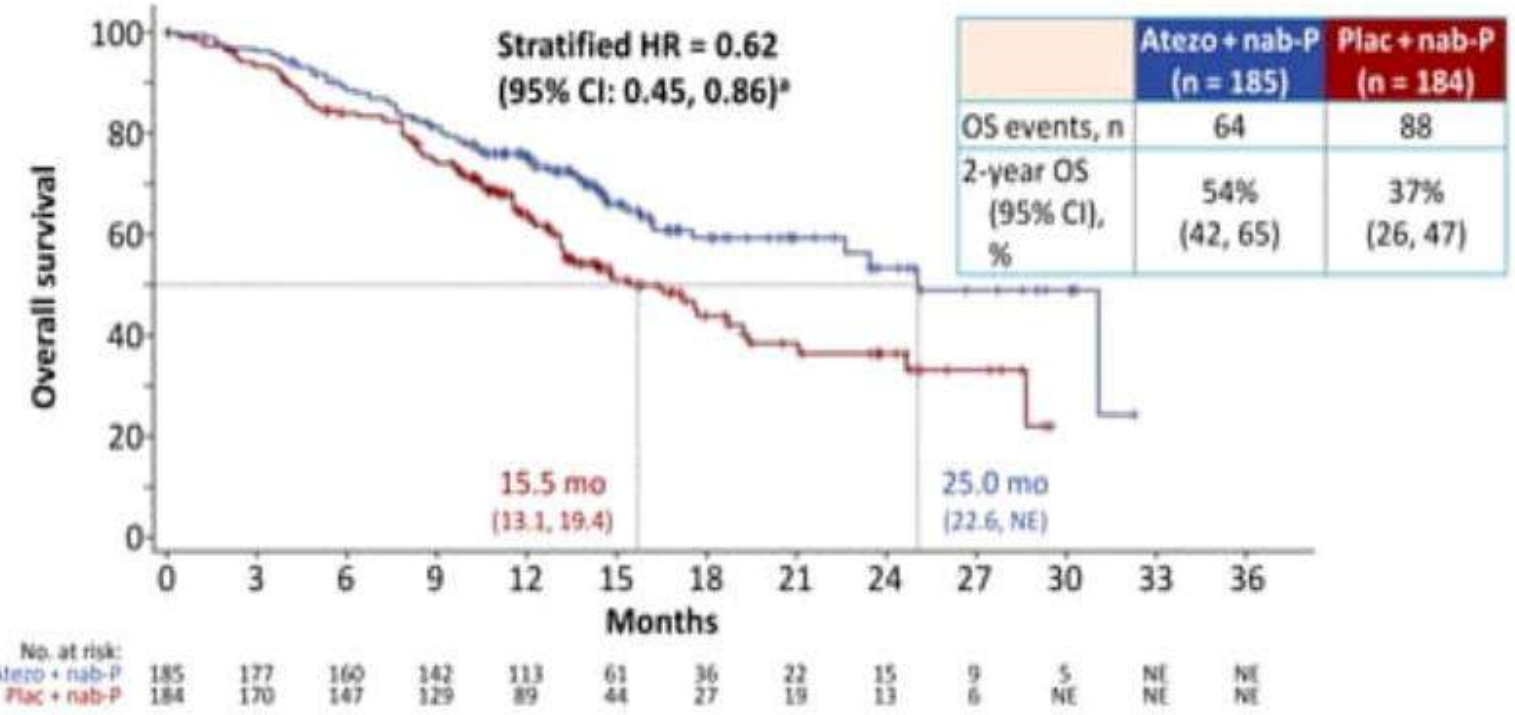


	Atezo + nab-P (n = 185)	Plac + nab-P (n = 184)
PFS events, n	138	157
1-year PFS (95% CI), %	29% (22, 36)	16% (11, 22)

Data cutoff: 17 April 2018.

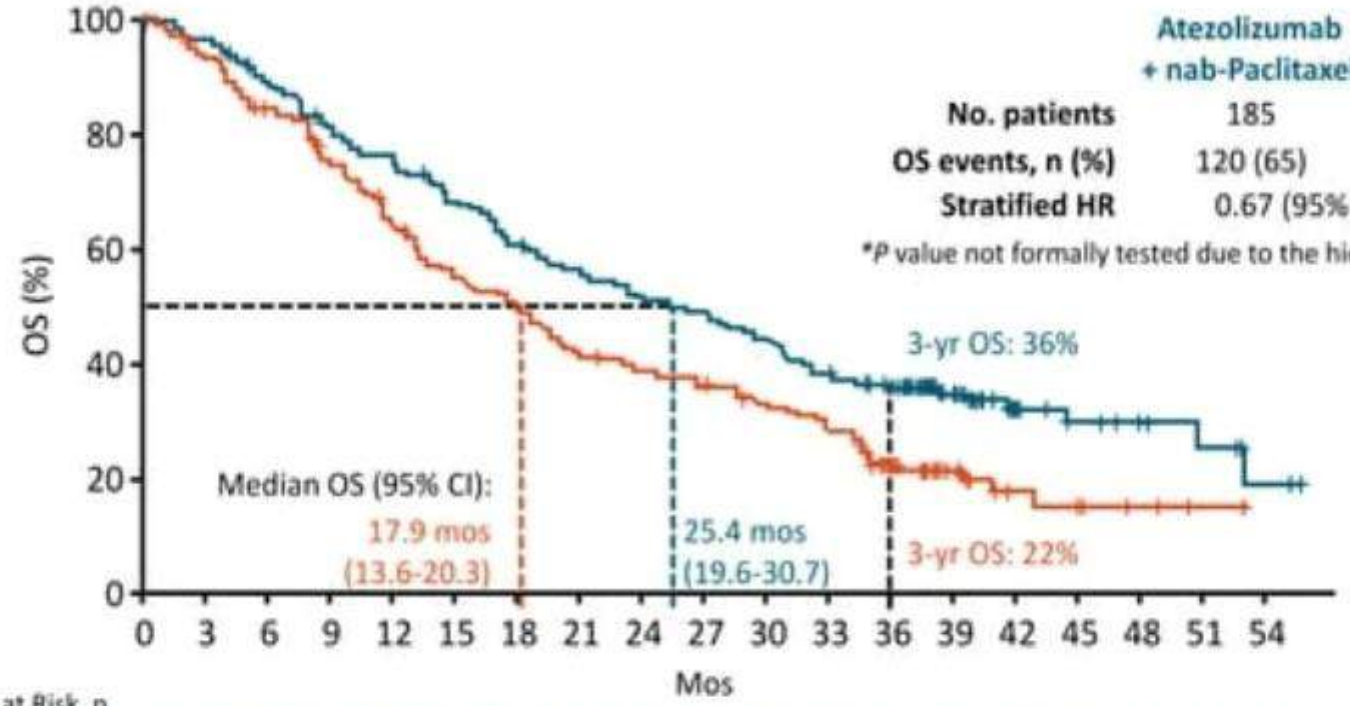
Schmid P, et al. IMpassion130 ESMO 2018 (LBA1_PR) http://bit.ly/2DMhayg

Interim OS analysis: PD-L1+ population



	Atezo + nab-P (n = 185)	Plac + nab-P (n = 184)
OS events, n	64	88
2-year OS (95% CI), %	54% (42, 65)	37% (26, 47)

IMpassion130: Final OS Analysis in PD-L1 IC+ Population



	Atezolizumab + nab-Paclitaxel	Placebo + nab-Paclitaxel
No. patients	185	184
OS events, n (%)	120 (65)	139 (76)
Stratified HR	0.67 (95% CI: 0.53-0.86)*	

*P value not formally tested due to the hierarchical study design.

Patients at Risk, n

Atezo + nab-Pac	185	177	160	145	135	121	108	98	90	86	77	67	56	32	17	11	9	6	3
Pbo + nab-Pac	184	170	150	132	113	95	85	72	66	62	54	47	28	14	7	6	3	1	NE

Emens. ESMO 2020. Abstr LBA16.

IMpassion130: Key Adverse Events[a]

	Atezolizumab + nab-P (n = 452)		Placebo + nab-P (n = 438)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Alopecia	255 (56%)	3 (1%)	252 (58%)	1 (< 1%)
Fatigue	211 (47%)	18 (4%)	196 (45%)	15 (3%)
Nausea	208 (46%)	5 (1%)	167 (38%)	8 (2%)
Diarrhea	147 (33%)	6 (1%)	150 (34%)	9 (2%)
Anemia	125 (28%)	13 (3%)	115 (26%)	13 (3%)
Constipation	113 (25%)	3 (1%)	108 (25%)	1 (< 1%)
Cough	112 (25%)	0	83 (19%)	0
Headache	105 (23%)	2 (< 1%)	96 (22%)	4 (1%)
Peripheral neuropathy	98 (22%)	25 (6%)	97 (22%)	12 (3%)
Neutropenia	94 (21%)	37 (8%)	67 (15%)	36 (8%)
Decreased appetite	91 (20%)	3 (1%)	79 (18%)	3 (1%)
Neutrophil count decreased	57 (13%)	21 (5%)	48 (11%)	15 (3%)
Hypertension	22 (5%)	4 (1%)	24 (5%)	11 (3%)

Patient-reported outcomes from IMpassion130 indicated maintenance of HRQoL and day-to-day function from baseline[b]

a. Schmid P. et al. *Ann Oncol.* 2018:29. Abstract LBA1; b. Adams S. et al. *J Clin Oncol.* 2019:37. Abstract 1067.

FDA Approval for Atezolizumab

Based on IMpassion130 study results, atezolizumab is now approved in combination with nab-paclitaxel for adult patients with unresectable locally advanced or metastatic, PD-L1-positive (≥ 1% IC) TNBC

US FDA Press Release.

IMpassion130: Summary

- PD-L1 expression on IC is a predictive biomarker for selecting patients who clinically benefit from first-line atezolizumab + nab-paclitaxel treatment for mTNBC
- PD-L1 expression on TC did not provide additional information beyond PD-L1 IC status
- PD-L1 (IC ≥ 1%) is the strongest biomarker to predict benefit vs $CD8^+$ and TILs

Concluding Remarks

- Immunotherapy is now available for the management of advanced, PD-L1--positive TNBC
- The SP142 assay should be used to test for eligibility of atezolizumab-based therapy, and it cannot be exchanged for other assays
- Novel immunotherapy-based therapeutic regimens are currently being explored across numerous settings of breast cancer

KEYNOTE-355: Study Design

- Randomized, double-blind, multicenter phase III trial

Stratified by chemotherapy (taxane vs gem/carbo); PD-L1 tumor expression (CPS > 1 vs < 1); previous Tx with same class of chemotherapy for EBC (Y vs N)

Adults with previously untreated locally recurrent inoperable or metastatic TNBC; completed curative intent Tx ≥ 6 mos before first recurrence (N = 847)

→ **Pembrolizumab** 200 mg IV Q3W + **chemotherapy*** (n = 566)

→ **Placebo** + **chemotherapy*** (n = 281)

→ *Until progression, toxicity, or completion of 35 cycles of pembrolizumab/placebo*

*Investigator's choice of chemotherapy:

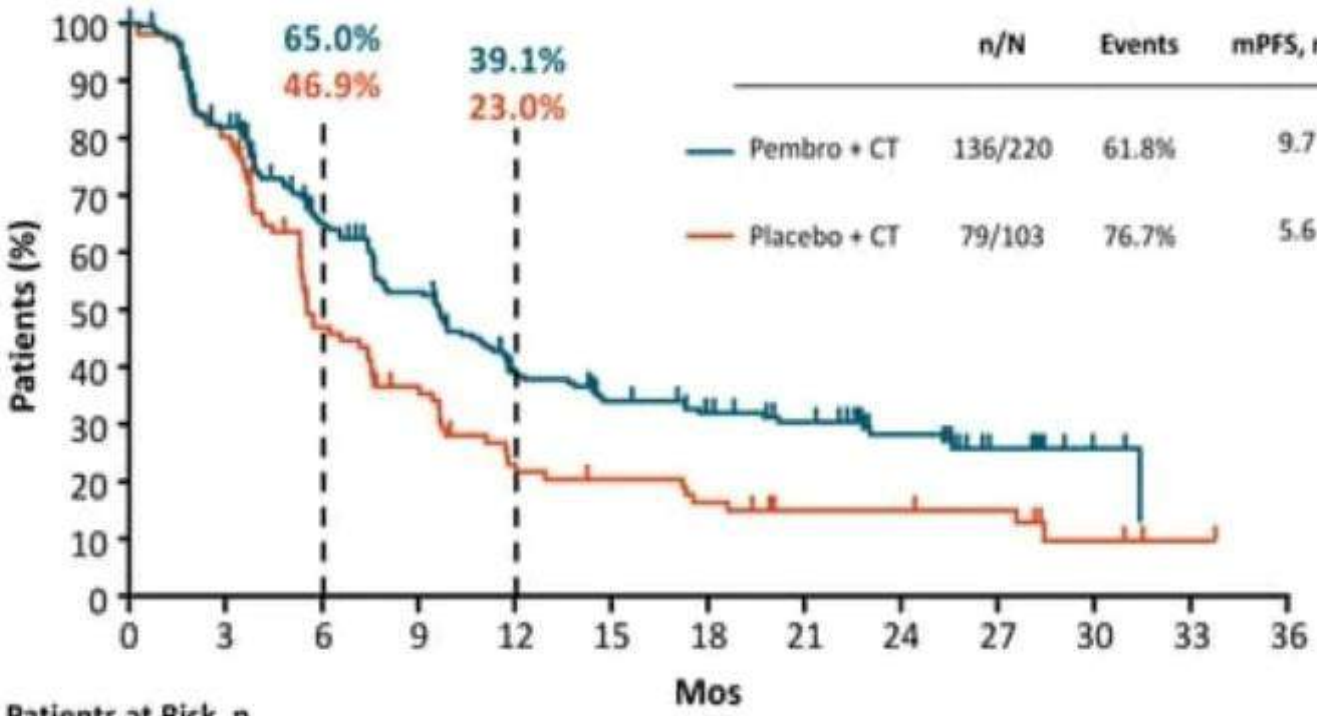
- Nab-paclitaxel 100 mg/m² IV on Days 1, 8, 15 of 28-day cycle
- Paclitaxel 90 mg/m² IV on Days 1, 8, 15 of 28-day cycle
- Gem 1000 mg/m² + carbo AUC 2 on Days 1, 8 of 21-day cycle

- Primary endpoints: PFS and OS (PD-L1 CPS ≥ 10, PD-L1 CPS ≥ 1, and ITT)
- Secondary endpoints: ORR, DoR, DCR, safety

Cortes. ASCO 2020. Abstr 1000.

Slide credit: clinicaloptions.com

KEYNOTE-355: PFS in PD-L1 CPS ≥ 10 Population



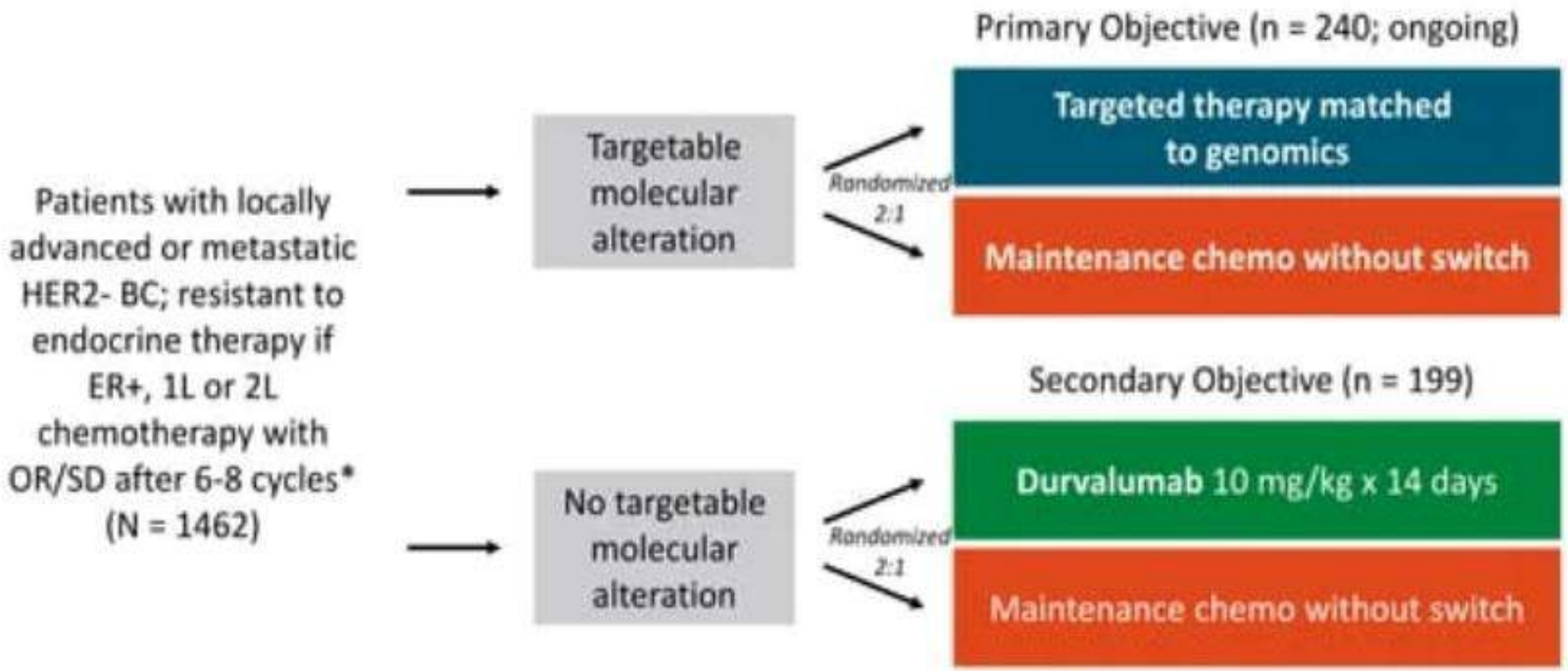
	n/N	Events	mPFS, mos	HR (95% CI)	*P* value (1-sided)
Pembro + CT	136/220	61.8%	9.7	0.65 (0.49-0.86)	.0012
Placebo + CT	79/103	76.7%	5.6		

Patients at Risk, n

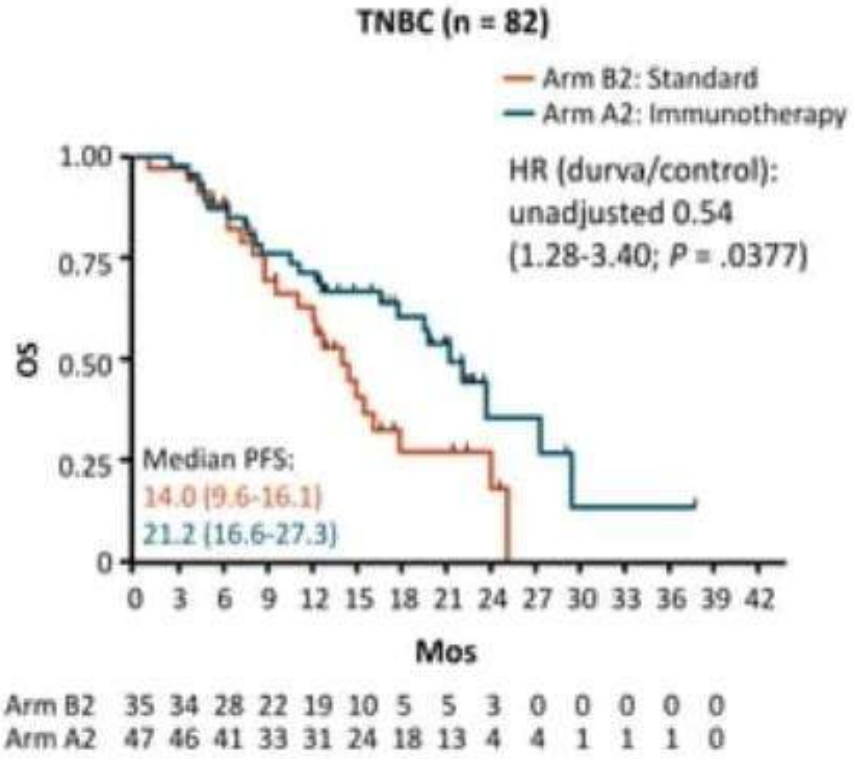
220	173	122	96	63	52	44	37	25	12	5	0	0
103	80	41	30	18	15	12	8	8	7	3	1	0

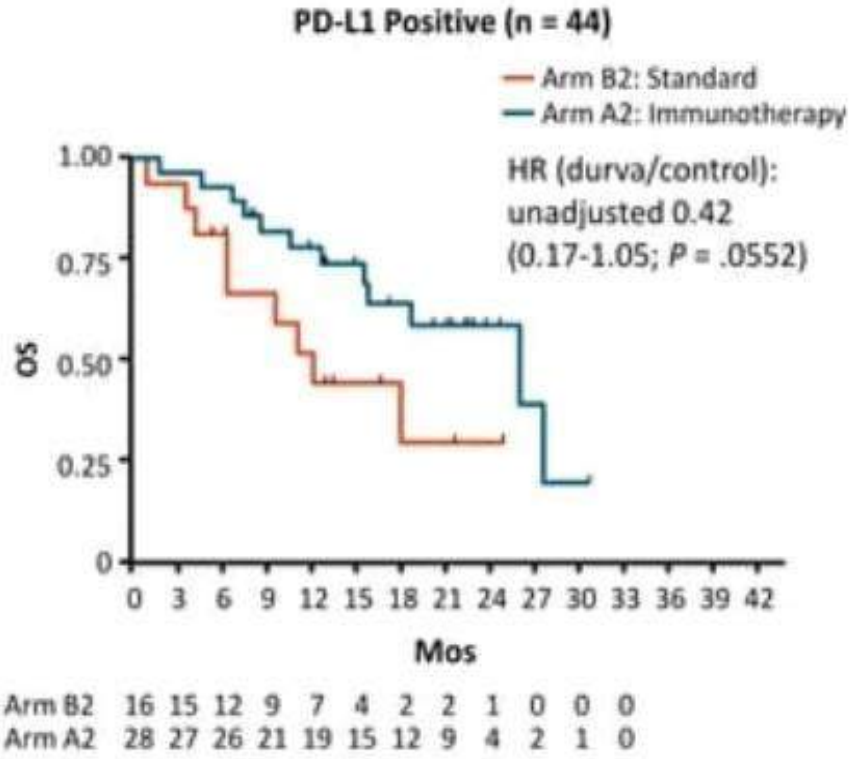
Cortes. ASCO 2020. Abstr 1000.

SAFIR-02 BREAST: Study Design



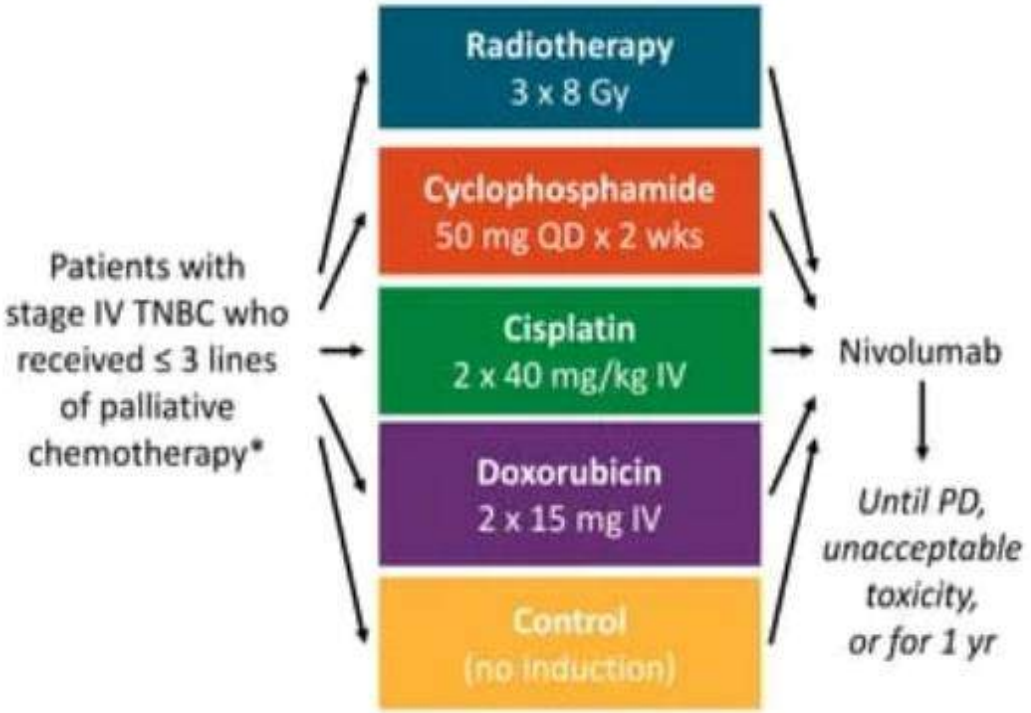
SAFIR-02 BREAST: OS in Patients With TN and PD-L1+ Tumors (Exploratory Analysis)

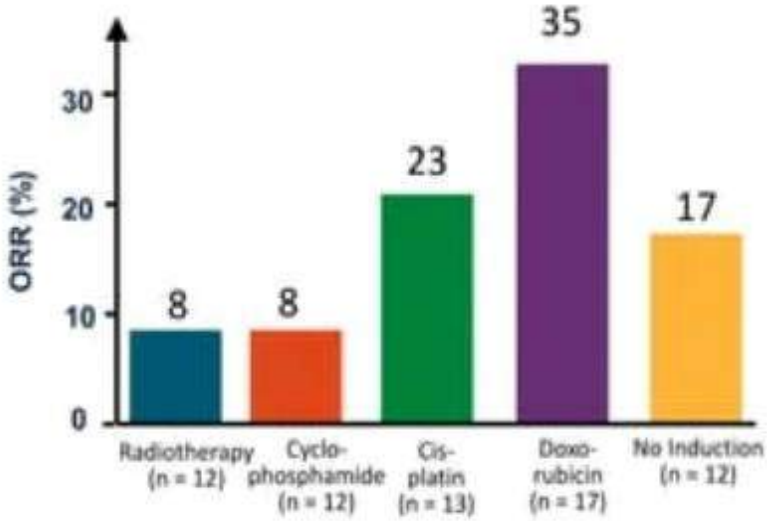




Dalenc. SABCS 2019. Abstr GS3-02.

TONIC: Induction Followed by Nivolumab Monotherapy in Metastatic TNBC





*Biopsy and blood taken at baseline, 2 wks, and 8 wks.

Kok. ASCO 2018. Abstr 1012. Voorwerk. Nat Med. 2019;25:920.

Future Directions for Immunotherapy in Breast Cancer

Phase 3 trials incorporating immunotherapy into treatment for advanced breast cancer:

- As part of neoadjuvant therapy for operable TNBC
- As adjuvant therapy, with or without chemotherapy, for operable TNBC
- In combination with other chemotherapy regimens for metastatic TNBC
- In combination with frontline anti-*HER2* and chemotherapy treatment for advanced, *HER2*-positive breast cancer
- Adding immunotherapy to radiation treatment for hormone receptor--positive and TNBC

Adams S, et al. *JAMA Oncol*. 2019. [Epub ahead of print]

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THANK YOU