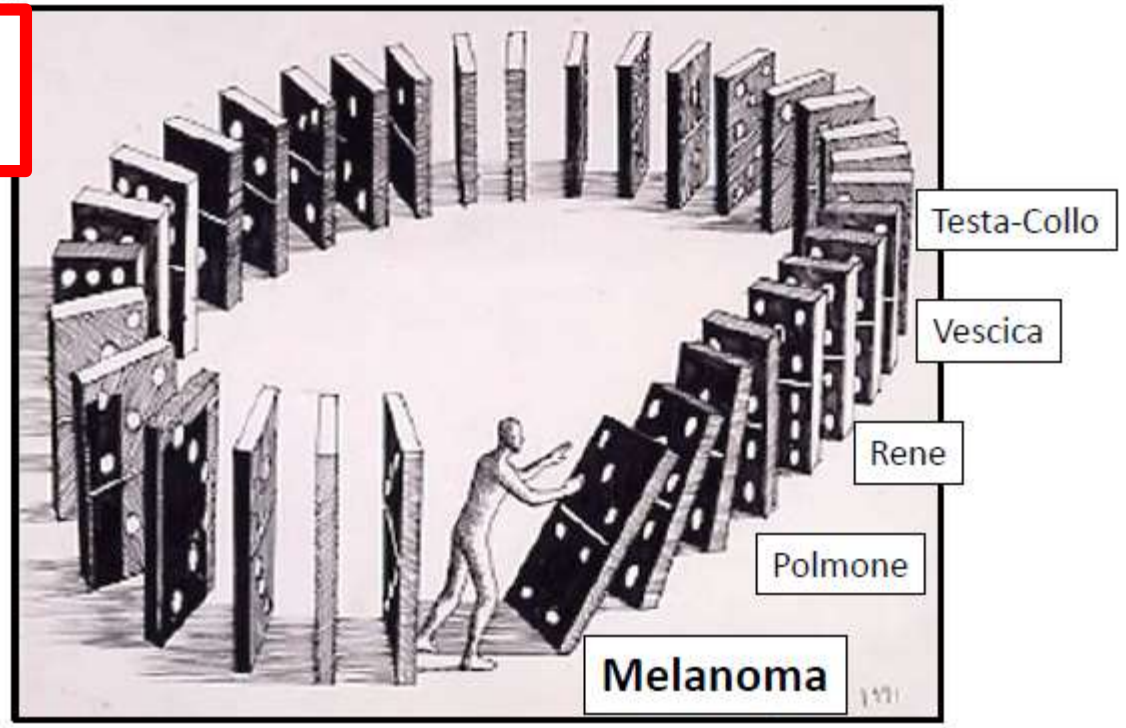
L'immunoterapia: una realtà anche nel carcinoma della mammella

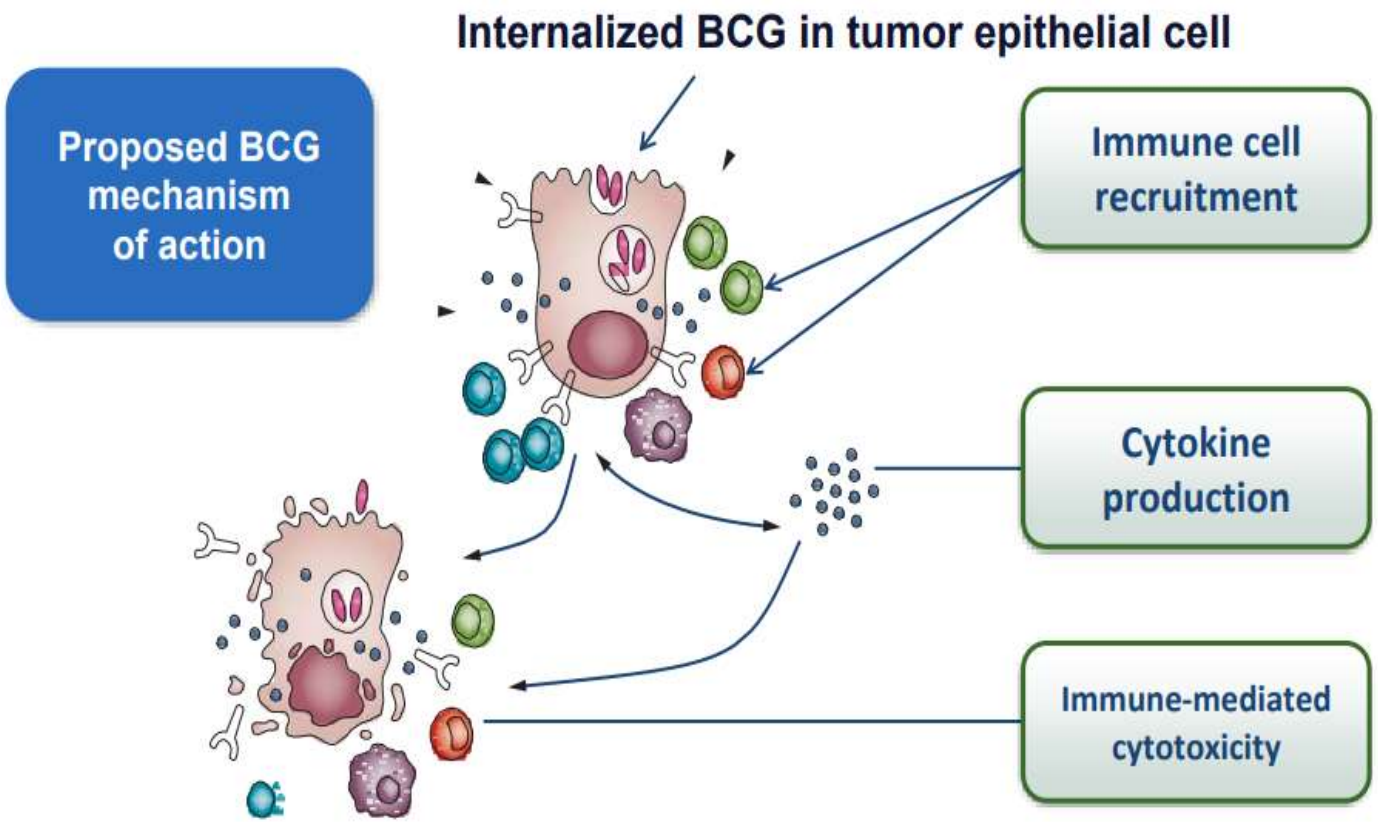


Zelmira Ballatore
CLINICA ONCOLOGICA
Azienda Ospedaliera Universitaria
Ospedali Riuniti-Ancona
***Direttore* Prof.ssa Rossana Berardi**

- ✓ What’s immunotherapy?
- ✓ Breast cancer, mutational burden and TILs
- ✓ Data from clinical trials
- ✓ Looking at the Future: when, who and how?

Immunotherapy in Cancer: Past, Present and Future

BLADDER CANCER

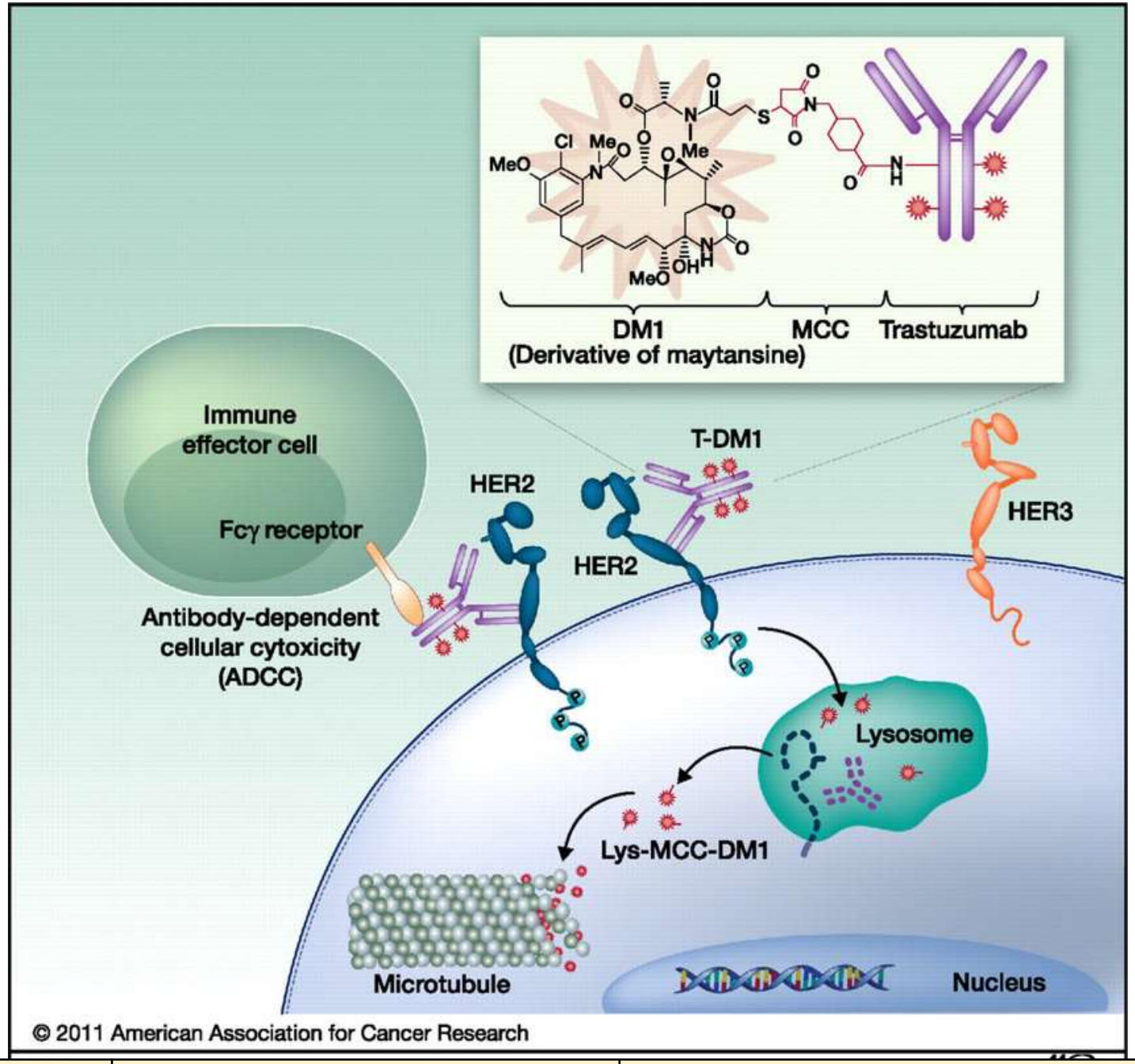


The rationale for immunotherapy in urothelial cancer stems from the breakthrough made with BCG for NMIBC → <u>efficiency in preventing recurrence</u>

Redelman-Sidi G, et al. Nat Rev Urol. 2014;11:153-162.

- **Trastuzumab itself has intrinsic immune-modulating activity with the capacity to mediate antibody-dependent cellular cytotoxicity (ADCC) and promote Her2 specific T cell response.**

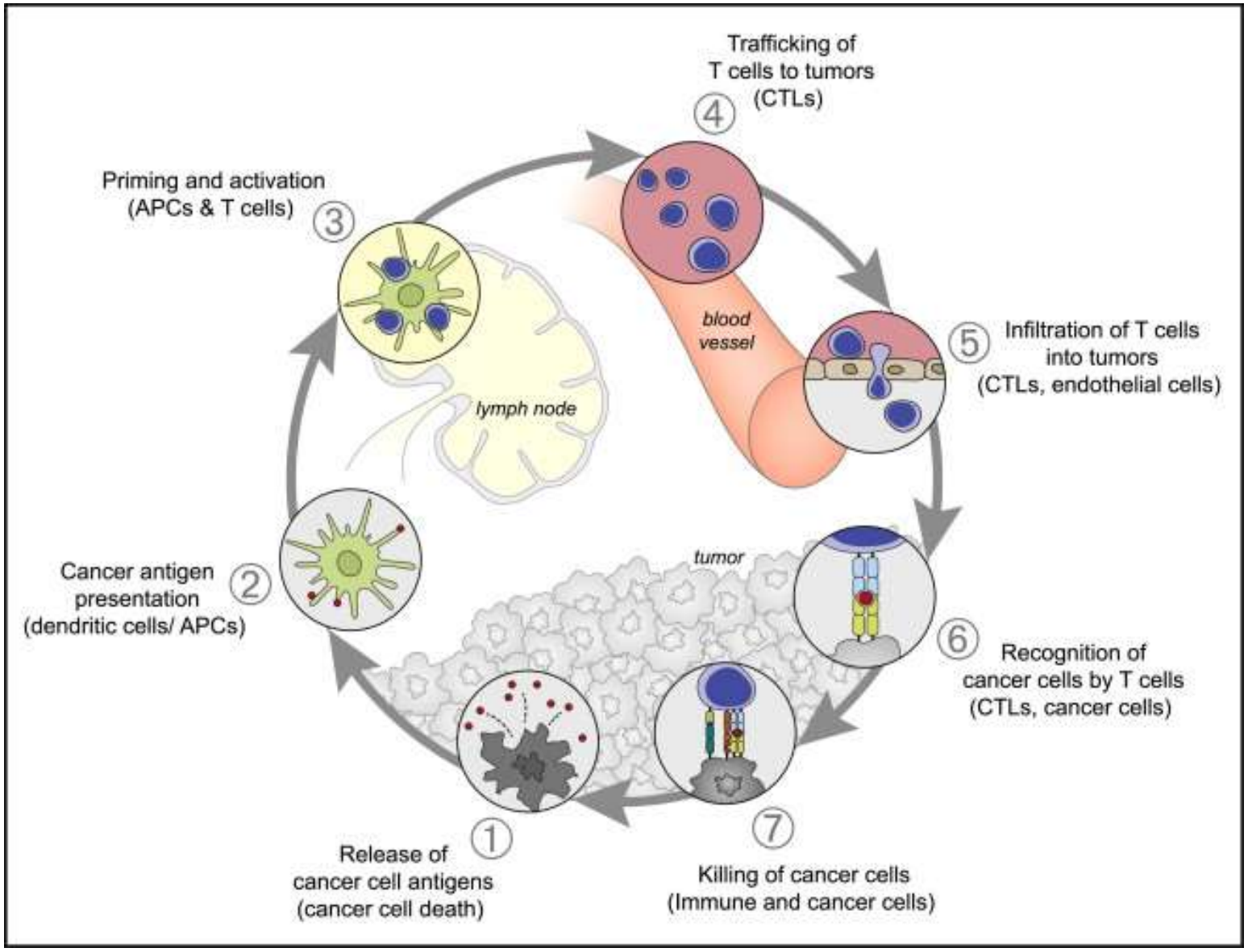
- **The emtansine moiety of TDM1 may further augment immune priming by modulating DC acitivity.**



Leisha A. Emens. Breast Cancer immunotherapy: Facts and Hopes. Clin Canc Res 2017

CANCER IMMUNITY CYCLE

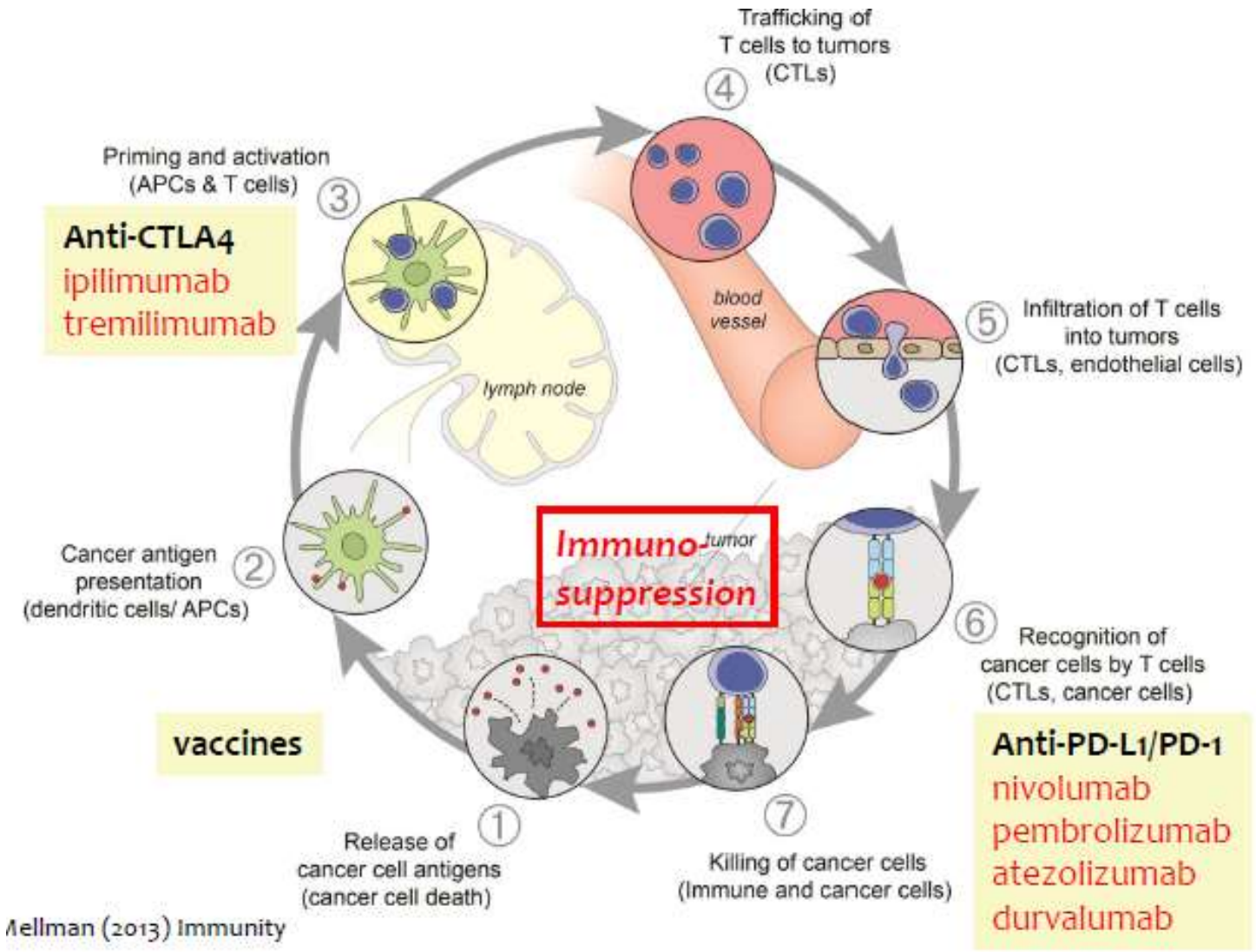
- **PD-L1/PD1 interaction inhibits T cell activation, attenuates effector function, maintain immune homeostasis**
- **Tumors & surrounding cells up-regulate PD-L1 in response to T cell activity**



Chen et al. Immunity Review 2013

What we have learned: immunosoppression is a rate limiting step to effective anti-tumor immunity… *for some patients*

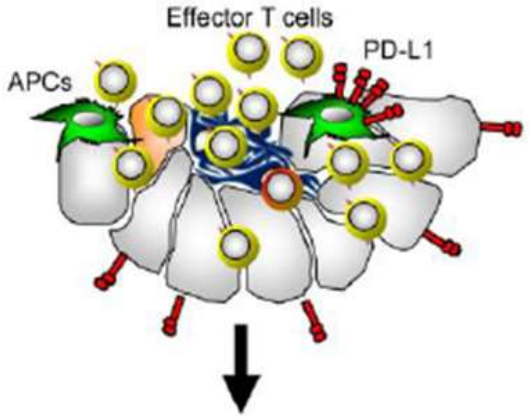
❖**Blocking PD-L1/PD1 restores or prevents loss of T effector function**

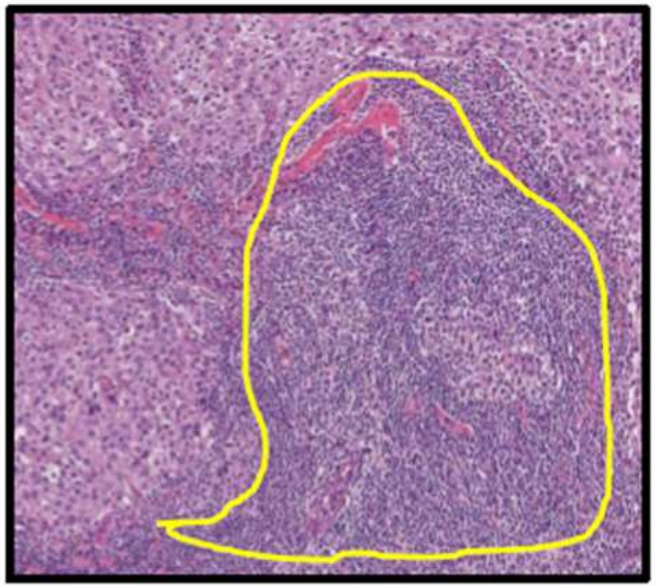


Targeting PD1-PDL1 pathway

Active response to treatment

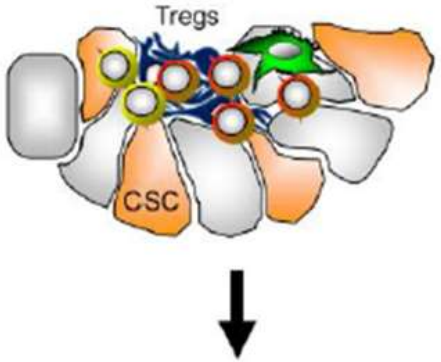
"inflamed cancer"

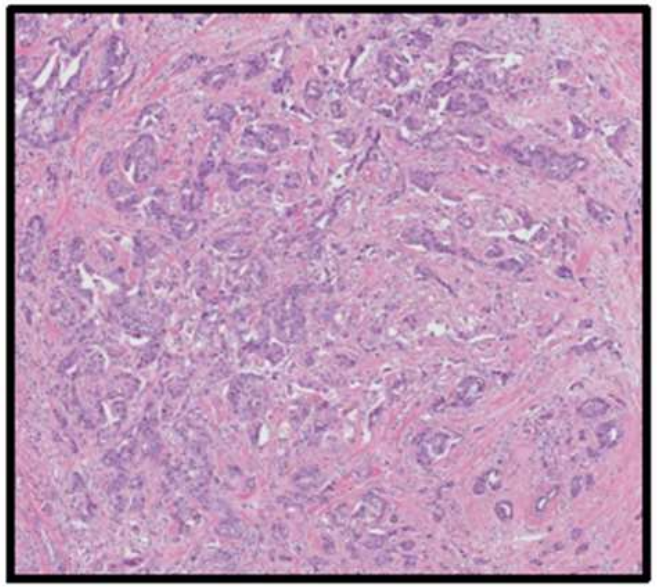




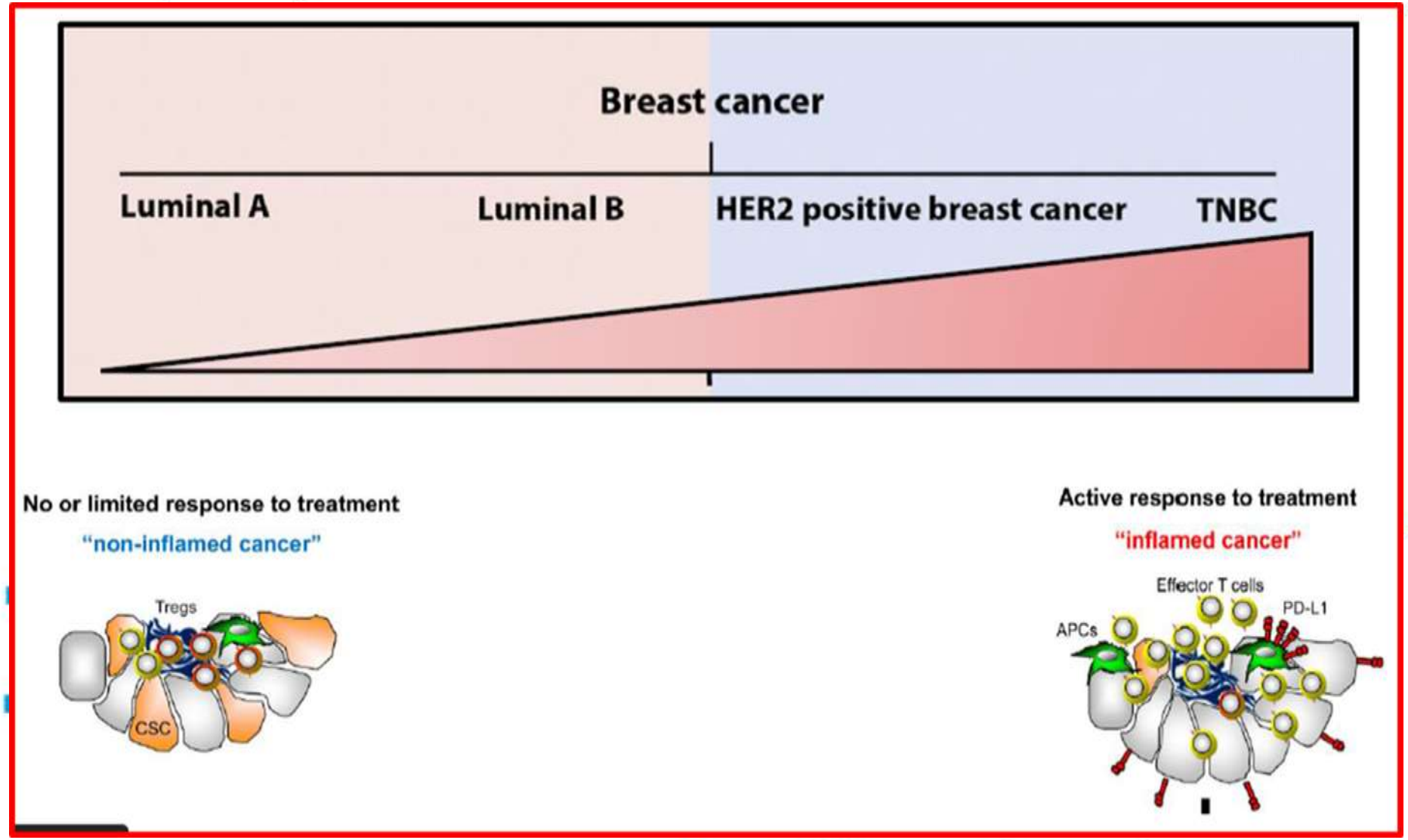
No or limited response to treatment

"non-inflamed cancer"





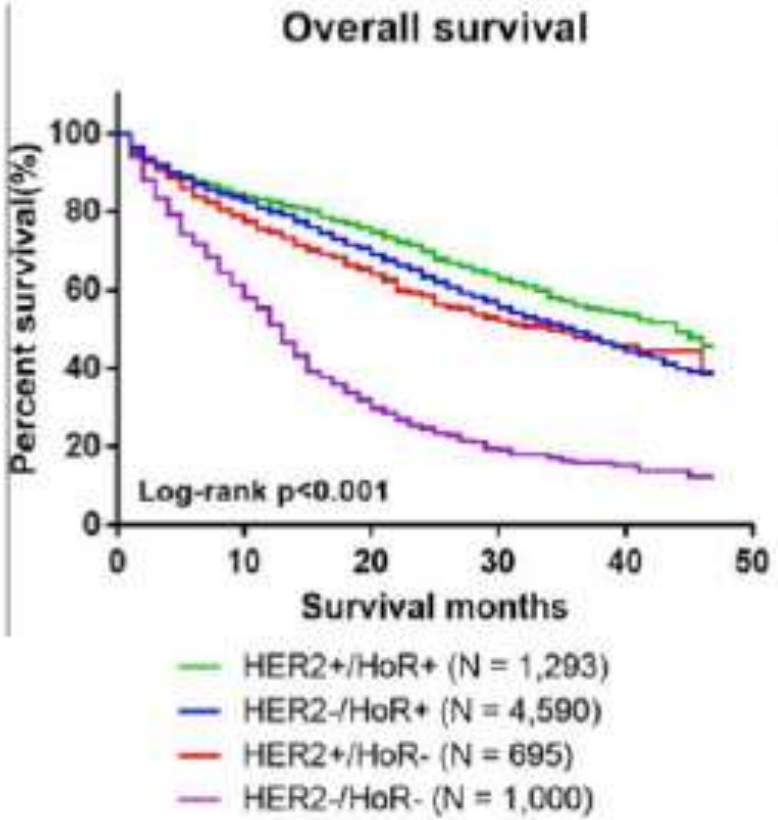
Response Rate correlates with mutation frequency



Behaviour of MBC according to subtype

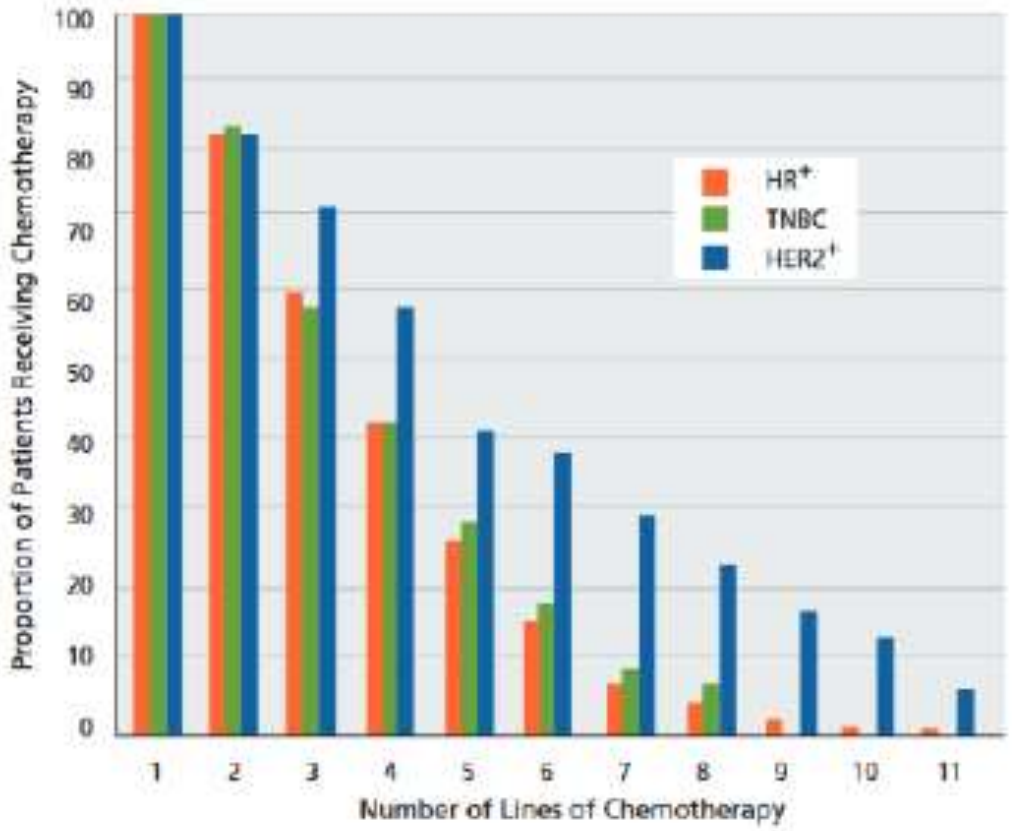
	n	Brain	Liver	Lung	Bone	Distant Nodal	Pleural/ peritoneal	Other
Luminal A	458	7.6	28.6	23.8	66.6	15.9	28.2	13.5
Luminal B	378	10.8	32.4	30.4	71.4	23.3	35.2	19.3
Luminal/HER2	117	15.4	4.4	36.8	65	22.2	34.2	13.7
HER2 enriched	136	28.7	45.6	47.1	59.6	25	31.6	16.9
Basal Like	159	25.2	21.4	42.8	39	39.6	29.6	23.9
TN non basal	109	22	32.1	35.8	43.1	35.8	28.4	25.7
p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.32	0.006

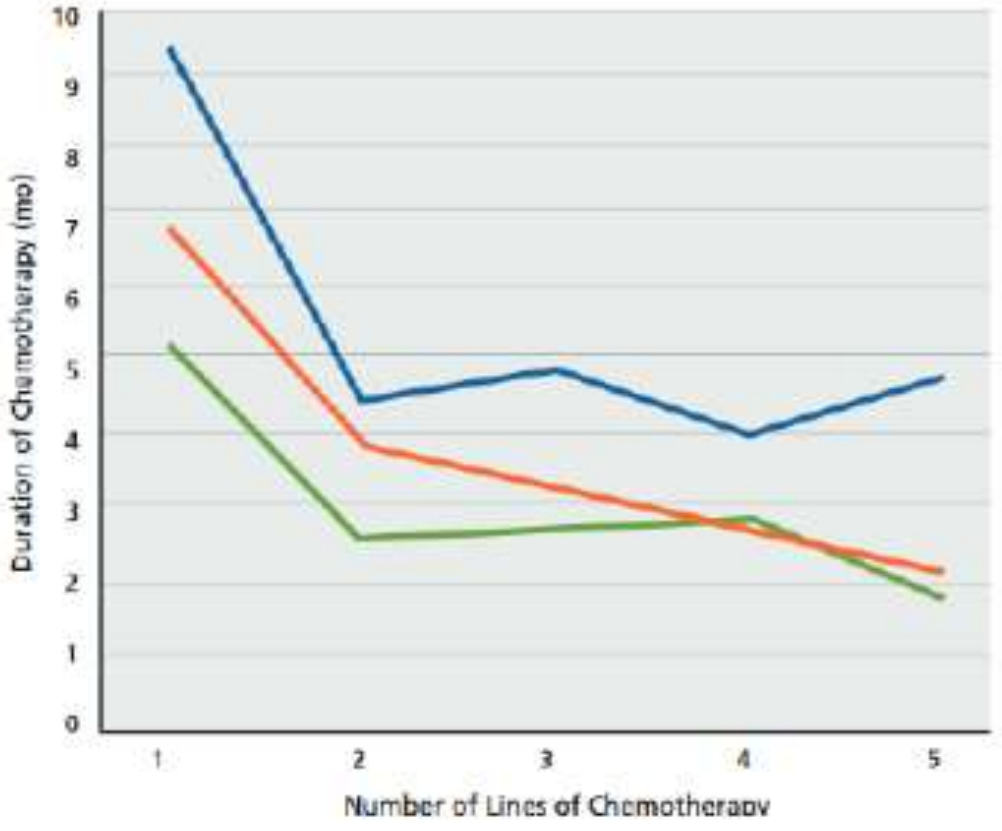
Kennecke H, JCO 2010



Gong Y, Sci Rep 2017

Lines of chemotheray and duration according to BC subtype





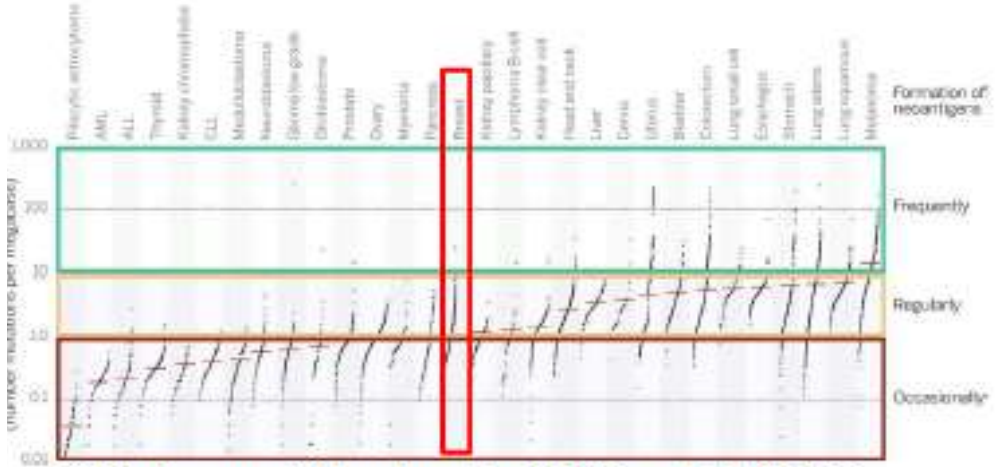
Seah DSE, J Natl Compr Canc Netw 2014

Courtesy Maria Vittoria Dieci, Padua September 22° 2018

Clinical significance of mutation load

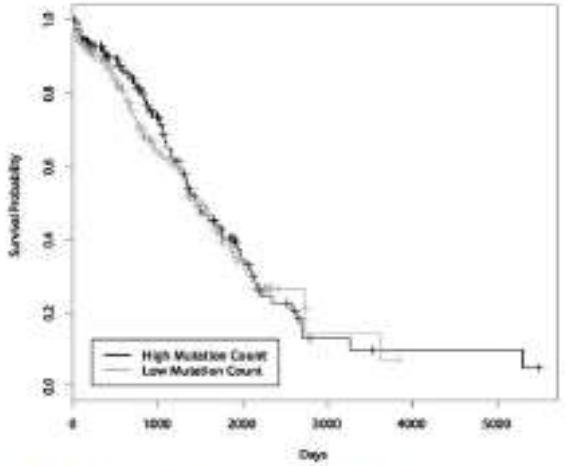
→TIL can recognize somatic mutations and are correlated to the density of predicted mutant epitopes

BC has a moderate mutational load

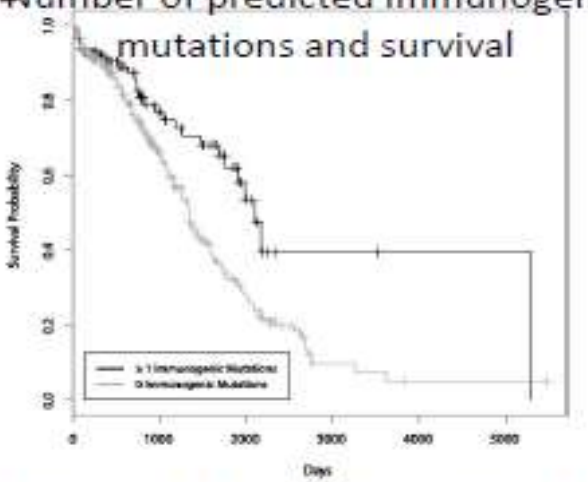


→ Higher mutation load in TNBC and HER2 BC

Total mutations and survival



→Number of predicted immunogenic mutations and survival

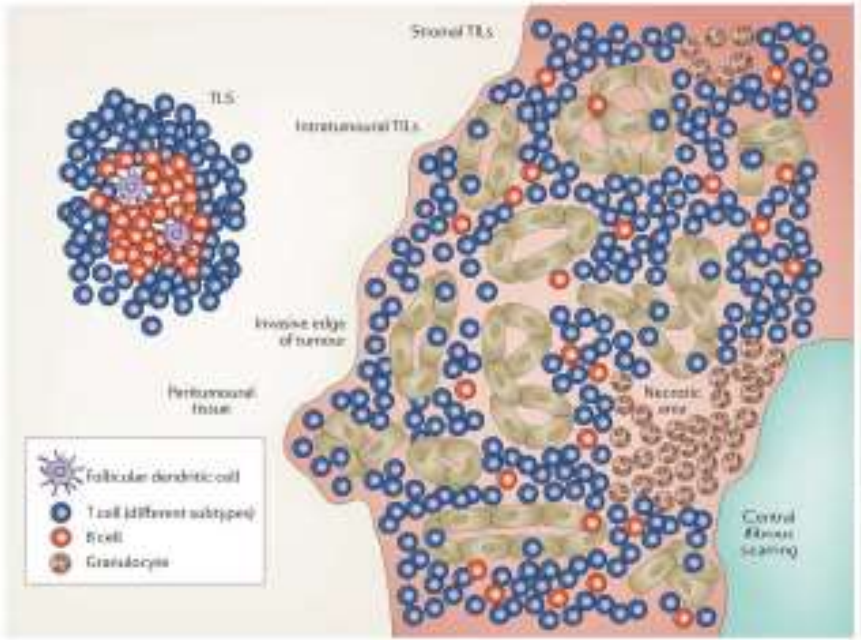


Ton N. Schumacher, and Robert D. Schreiber Science 2015

Scott D. Brown et al. Genome Res. 2014

Clinical Significance of TIL infiltration in BC

→TIL have prognostic and predictive value in early stage BC, particularly in HER2+ and TNBC



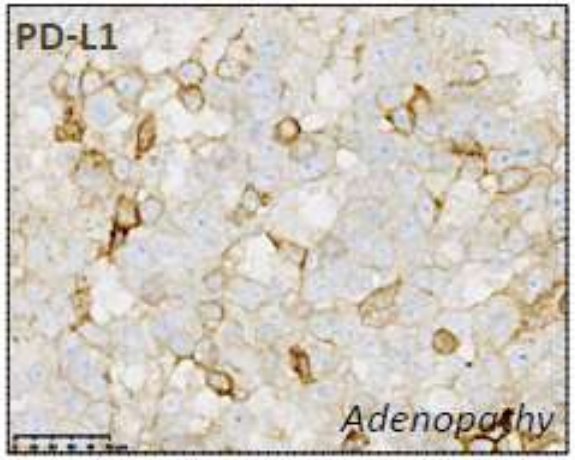
Nature Reviews | Clinical Oncology

Table 3 | Adjuvant trials in which TILs have been assessed

Trial analysed	Trial type	Treatment	TILs assessment	Population	n	Recurrence end points
BIG 2-98 (REF. 10)	Adjuvant Prospective RCT	Doxorubicin Cyclophosphamide CMF Docetaxel	Stromal on H&E	ER+/HER2-	1,079	Not significant
				HER2+	297	Not significant
				TNBC	256	For each 10% increment of sTILs: DFS, HR = 0.84 (95% CI 0.74–0.98, P = 0.025)
FinHER[39]	Adjuvant Prospective RCT	Docetaxel Vinorelbine FEC Trastuzumab	Stromal on H&E	ER+/HER2-	591	Not significant
				HER2+	209	Not significant
				TNBC	134	For each 10% increment of sTILs: DDFS, HR = 0.79 (95% CI 0.64–0.98, P = 0.032)
E2197 and E1199 (REF. 33)	Adjuvant Prospective RCT	Doxorubicin Cyclophosphamide Docetaxel	Stromal on H&E	TNBC	481	For each 10% increment of sTILs: DFS, HR = 0.84 (95% CI 0.74–0.95, P = 0.005)
SEARCH, BCCA, NBCS, NEAT[34]	Prospective Observational RCT (NEAT)	Various, not standardised No trastuzumab	IHC for CD8 in stroma (sCD8) IHC for CD8 in tumour (tCD8)	ER+ (including HER2+)	8,775	Presence versus absence of tCD8: Breast cancer-specific survival, HR = 0.95 (95% CI 0.85–1.07, P = 0.43)
				ER-/HER2+ TNBC	3,501	Presence versus absence of sCD8: Breast cancer-specific survival, HR = 0.79 (95% CI 0.67–0.93, P = 0.004)
NeoALTTO[40]	Neoadjuvant Prospective RCT	Trastuzumab Lapatinib Paclitaxel FEC	Stromal on H&E	HER2+	387	1% decrease in rate of recurrence (event free survival) for every 1% increase in TILs P = 0.002

Trials overall include a total of 15,800 patients. BIG, Breast International Group; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; DDFS, distant disease-free survival; DFS, disease-free survival; ER, oestrogen receptor; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; H&E, haematoxylin and eosin; HR, hazard ratio; IHC, immunohistochemistry; PR, progesterone receptor; RCT, randomized controlled trial; sTIL, stromal TIL; TIL, tumour-infiltrating lymphocyte; TNBC, triple-negative breast cancer.

PD-L1 expression in metastatic BC



	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

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Solinas et al. *In preparation.*

ULB iris

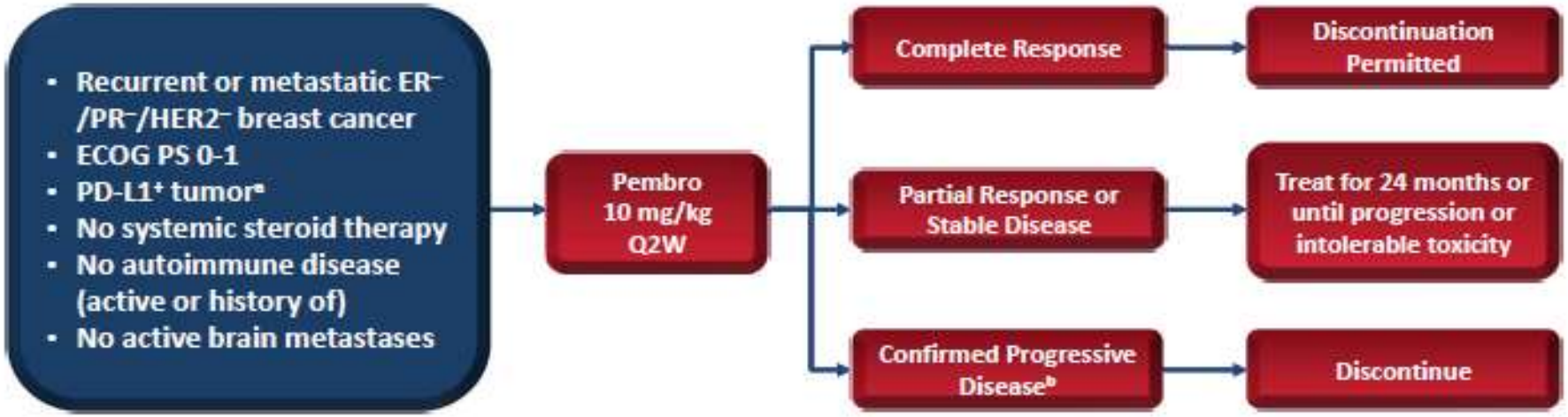
1- Major survival improvements in Her2 positive BC with the uso of mAbs targeting Her2 and their mecchanism of action involve partially the immune system.

2- TILs have a positive prognostic impact on survival and predict a high probability of pathological response to neoadjuvant chemo.

3- PDL1 is expressed in BC and correlates with the presence of TILs, younger age, high grade, lack of ER, overexpression of Her2, **TNBC subtype**

PD-1/PD-L1 Targeting in Breast Cancer – a Literature Review. Cancers 2019

Phase Ib of pembrolizumab in mTNBC KEYNOTE 012

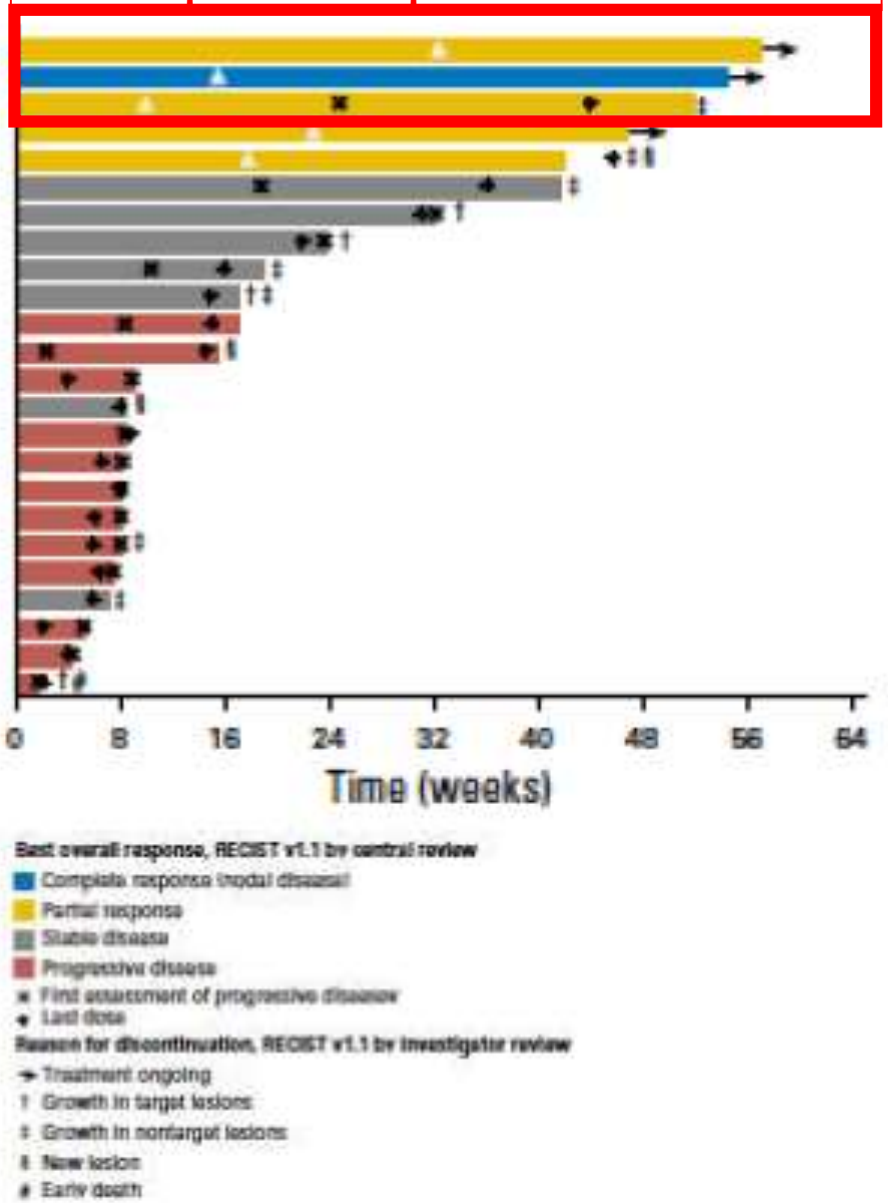


- **PD-L1 positivity:** 58% of all patients screened had PD-L1-positive tumors
- **Treatment:** 10 mg/kg IV Q2W
- **Response assessment:** Performed every 8 weeks per RECIST v1.1

[a]PD-L1 expression was assessed in archival tumor samples using a prototype IHC assay and the 22C3 antibody. Only patients with PD-L1 staining in the stroma or in ≥1% of tumor cells were eligible for enrollment.
[b]If clinically stable, patients are permitted to remain on pembrolizumab until progressive disease is confirmed on a second scan performed ≥4 weeks later. If progressive disease is confirmed, pembrolizumab is discontinued. An exception may be granted for patients with clinical stability or improvement after consultation with the sponsor.

Nanda R et al. San Antonio Breast Cancer Symposium 2014

3 **excecptional responders**



	Patients Evaluable for Response[a] n = 27
Overall response rate	5 (18.5%)
Best overall response	
Complete response	1 (3.7%)
Partial response	4 (14.8%)
Stable disease	7 (25.9%)
Progressive disease	12 (44.4%)
No assessment	3 (11.1%)

- ✓ **32 patients with PDL1 + mTNBC**
- ✓ **ORR 18,5%**
- ✓ **2years survival rate 22%**
- ✓ **Heavily pre-treated pts and 78% with visceral involvement**

Nanda R et al. JCO 2016

Immuno check point inhibitors

Drug	Phase	Subtype	PD-L1	Nb pts *Evaluable*	ORR		References
Pembrolizumab (anti-PD-1)	Ib	TNBC PDL1+	≥ 1% TC Stroma+ *(58% of screened pts)*	32 *27*	**18.5%**	1 CR 4 PR	KEYNOTE 012 Nanda et al. SABC 2014 JCO 2016
Atezolizumab (anti-PD-L1)	Ia	TNBC	≥ 5% IC	115 *112*	**10%**	3 CR 8 PR	Schmid et al. AACR2017
Pembrolizumab (anti-PD-1)	Ib	ER+/HER2- PDL1+	≥ 1% TC Stroma+ *(19% of screened pts)*	25	**12%**	0 CR 3 PR	KEYNOTE 028 Rugo et al. SABC 2015
Avelumab (anti-PD-L1)	Ib	All TNBC ER+/HER2-	≥ 1% TC *(58%)* ≥ 5% TC *(16%)* ≥ 10% IC *(9%)*	168 *153* *58* *72*	**4.8%** 8.6% 2.8%	1 CR 7 PR	JAVELIN Dirix et al. SABC 2015

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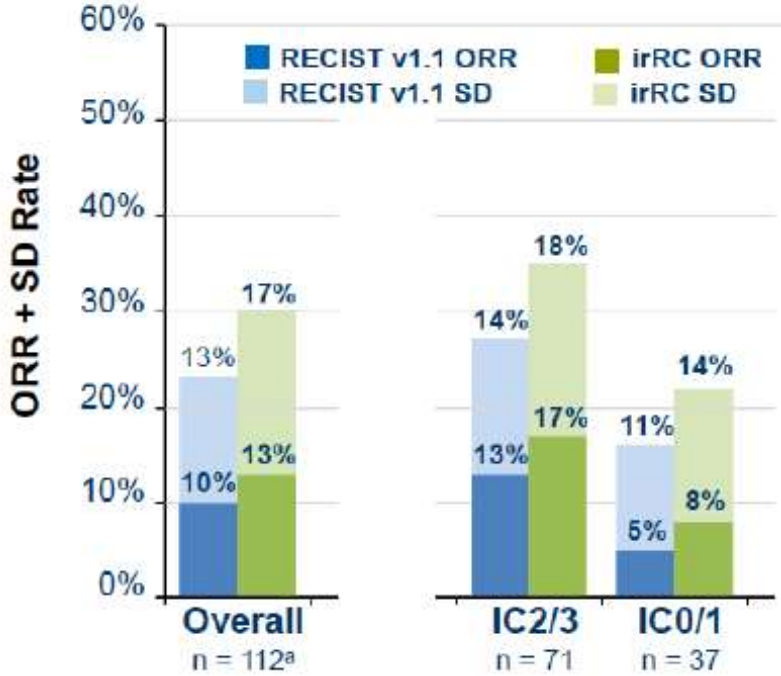
ORR according to PD-L1 expression

Phase Ia: Atezolizumab, an anti-PD-L1 antibody, in patients with locally advanced or metastatic TNBC



Phase Ib: Avelumab, an anti-PD-L1 antibody, in patients with locally advanced or metastatic BC

PD-L1 expression	All patients (N=136)	TNBC (N=48)
≥ 1% TC	3/85 (3.5%)	2/33 (6.1%)
≥ 5% TC	1/23 (4.3%)	1/13 (7.7%)
≥ 25% TC	0/3 (0)	0/2 (0)
≥ 10% IC	4/12 (33.3%)	4/9 (44.4%)

Dirix L et al. SABC 2015

KEYNOTE-086:
Pembrolizumab Monotherapy for Metastatic TNBC

B 1L PD-L1-positive mTNBC n=80 → Pembrolizumab 200 mg IV q 3 weeks

A 2+L mTNBC n=160 Conditional expansion in PD-L1-positive → Pembrolizumab 200 mg IV q 3 weeks

170 pts with documented PD at the first line
61.8% PD-L1 positive

ORR 5.3% in the overall population
5.7% in the PD-L1 positive/ 4.7% in the negative

Disease Control Rate 7.6%
No difference in Survival between PD-L1 pos vs neg

- **Primary Endpoint:**
  - ORR (RECIST 1.1) in first line PD-L1+BC
  - ORR (RECIST 1.1) in 2+ line BC
  - Safety, tolerability
- **Secondary Endpoints:**
  - PFS, DOR, OS

Adams, et al. TIP, SABCS 2015

Keynote-086; sTIL levels correlate with tumor response

Cohort B (1° Line) (n=84 PD-L1+)

ORR 23%
CR 4%
PR 19%
SD 17%
PD 58%

No prior systemic tp and PDL1 positive tumor
Two pts reaching a SD for more than 24 weeks

	Univariate[a]		Multivariate	
	Odds Ratio (95% CI)	P[b]	Odds Ratio (95% CI)	P[a]
sTIL level (continuous)	1.029 (1.012-1.046)	<0.001	1.0212 (1.002-1.041)	0.014
Cohort (B vs A)	6.075 (2.358-16.465)	<0.001	4.191 (1.407-13.005)	0.005
LDH concentration (continuous)	0.683 (0.477-0.896)	0.009	0.688 (0.468-0.924)	0.015

[a]Visceral disease (yes vs no) and ECOG performance status (0 vs 1) were evaluated and found to be nonsignificant based on the likelihood ratio test.
[b]One-sided from logistic regression. Red font indicates statistical significance.
Data cutoff date: Nov 10, 2016.

Adams, ASCO 2017

Investigative Clinical Oncology

Loi ,LBA13 ESMO 2017

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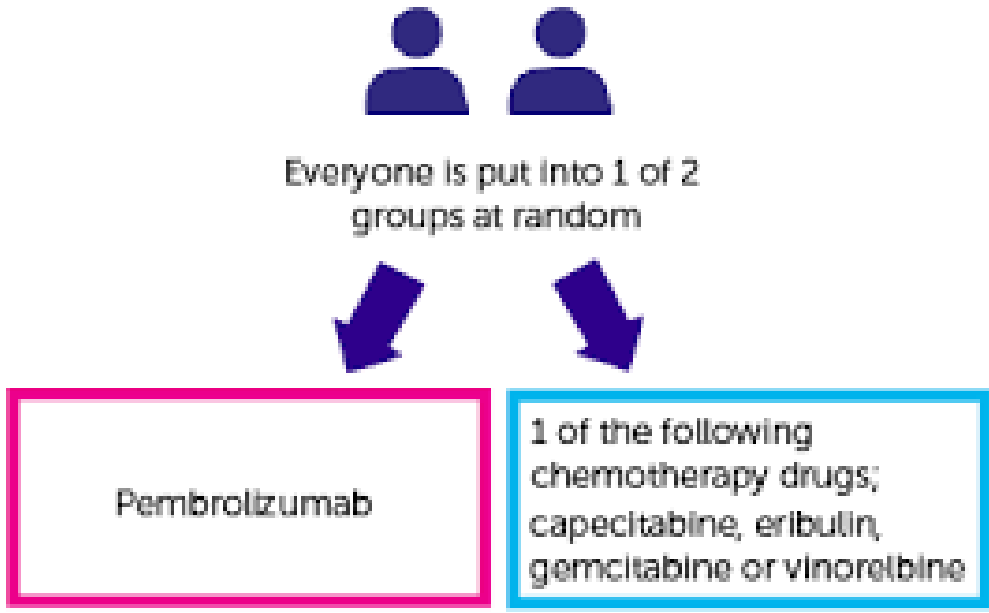
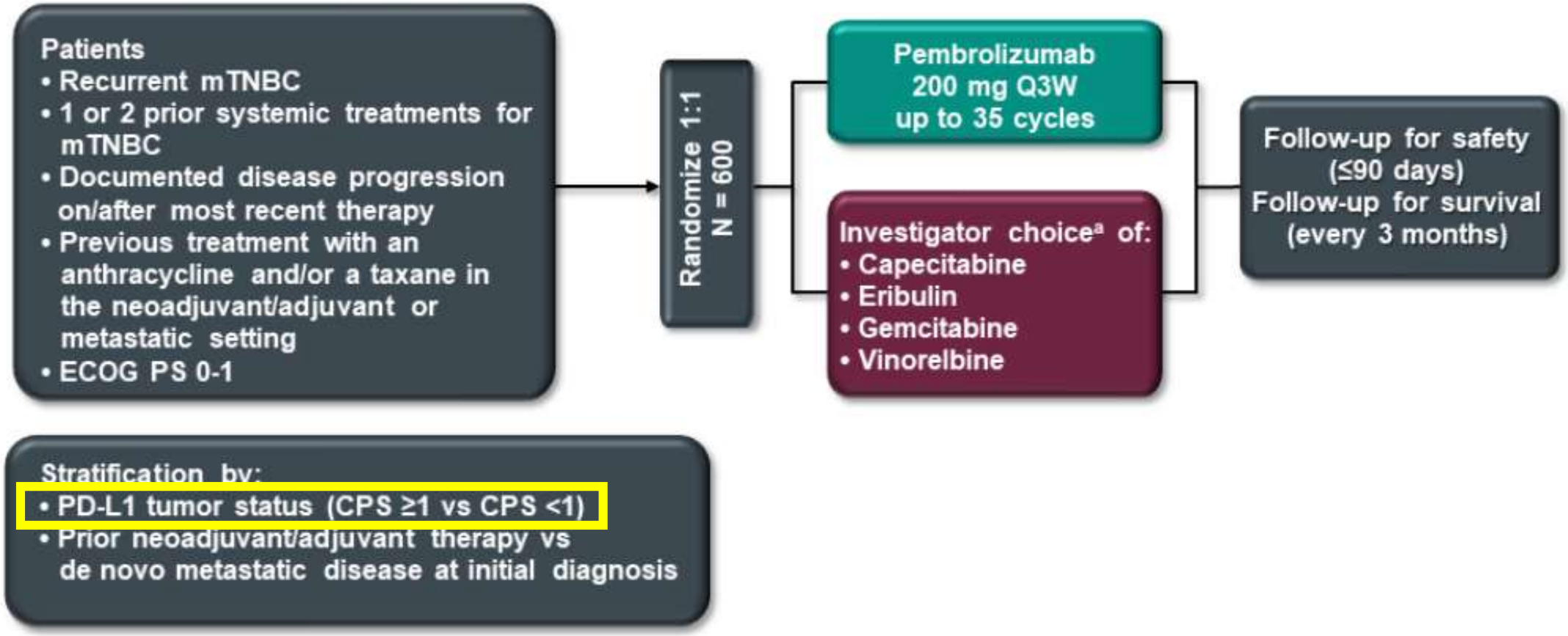


Merck Provides Update on Phase 3 KEYNOTE-119 Study of KEYTRUDA® (pembrolizumab) Monotherapy in Previously-Treated Patients with Metastatic Triple-Negative Breast Cancer

MAY 20, 2019

KENILWORTH, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced that the Phase 3 KEYNOTE-119 trial evaluating KEYTRUDA, Merck's anti-PD-1 therapy, as monotherapy for the second- or third-line treatment of patients with metastatic triple-negative breast cancer (TNBC) did not meet its pre-specified primary endpoint of superior overall survival (OS) compared to chemotherapy (capecitabine, eribulin, gemcitabine or vinorelbine). Other endpoints were not formally tested per the study protocol because the primary endpoint of OS was not met. The safety profile of KEYTRUDA in this trial was consistent with that observed in previously reported studies involving patients treated with KEYTRUDA monotherapy; no new safety concerns were identified. Results will be presented at an upcoming medical meeting.

KEYNOTE-119 Study Design (NCT02555657)



ECOG PS = Eastern Cooperative Oncology Group performance status; mTNBC = metastatic triple-negative breast cancer; PD-L1 = programmed death ligand 1; Q3W = every 3 weeks.
[a]Maximum enrollment cap of 60% of total enrollment for each chemotherapy drug.

Baseline Characteristics

Characteristic, n (%)	Pembro N = 312	Chemo N = 310
Age, median (range), y	50 (28 – 85)	50 (25 – 79)
<65 years	264 (84.6)	260 (83.9)
Post-menopausal	238 (76.3)	239 (77.1)
ECOG PS		
0	169 (54.2)	158 (51.0)
1	141 (45.2)	151 (48.7)
No. prior lines		
1	187 (59.9)	187 (60.3)
2	124 (39.7)	123 (39.7)

Characteristic, n (%)	Pembro N = 312	Chemo N = 310
Prior neoadjuvant/adjuvant	246 (78.8)	246 (79.4)
Time to progression on 1L		
<6 mo	156 (50.0)	151 (48.7)
≥6 mo	156 (50.0)	159 (51.3)
Chemotherapy received		
Eribulin	-	167 (53.9)
Capecitabine	-	85 (27.4)
Vinorelbine	-	43 (13.9)
Gemcitabine	-	15 (4.8)

Study End Points

Primary

- OS in patients with PD-L1 positive tumors (CPS ≥10)[a]
- OS in patients with PD-L1 positive tumors (CPS ≥1)[a]
- OS in all patients

Key Secondary

- PFS in all patients
- ORR in all patients[b]
- Safety and tolerability

Additional Secondary

- DCR and DOR in all patients and patients with PD-L1 positive tumors (CPS ≥1 or CPS ≥10)[a]

Exploratory

- OS, PFS, ORR, and DOR in patients with PD-L1 positive tumors using additional CPS cutpoints

[a]Assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay defined as the combined positive score (CPS), the number of PD-L1–positive cells (tumor cells, lymphocytes, macrophages) divided by total number of tumor cells × 100.
[b]Assessed per RECIST v1.1 by blinded, independent central review.

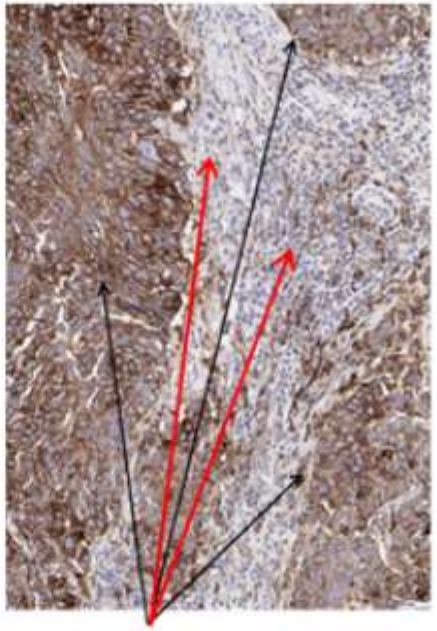
PD-L1 Expression Analysis

- Measure of PD-L1 expression: combined positive score (CPS)

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

- Assessed centrally in newly obtained core or excisional biopsy from metastatic, not previously irradiated, tumor lesion using PD-L1 IHC 22C3 pharmDx (Agilent Technologies)

- Positive PD-L1 expression: CPS ≥10 and CPS ≥1



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

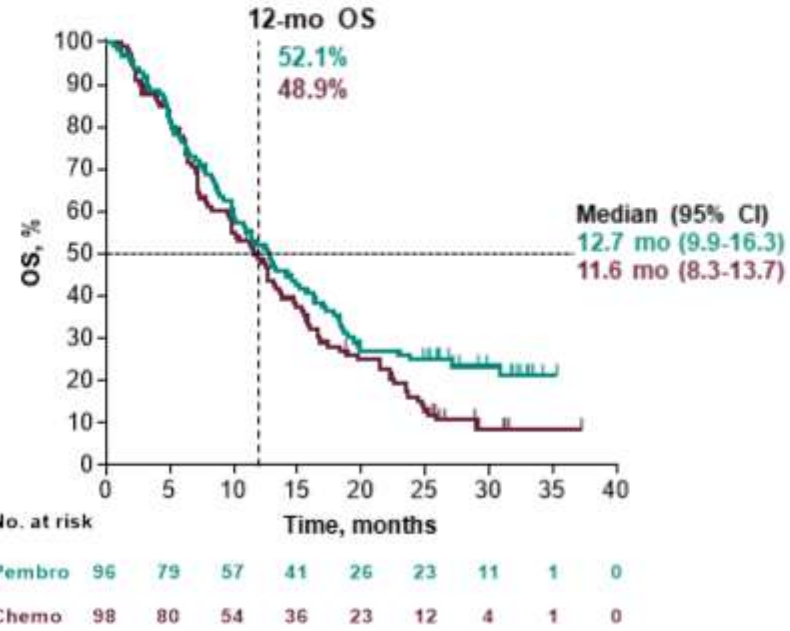
Balar AV et al. Presented at ESMO 2016; Oct 7-11, 2016; Copenhagen, Denmark. Abstr. LBA32-PR.

Cortes KN119 ESMO 2019

Overall Survival: Primary Endpoints

CPS ≥10

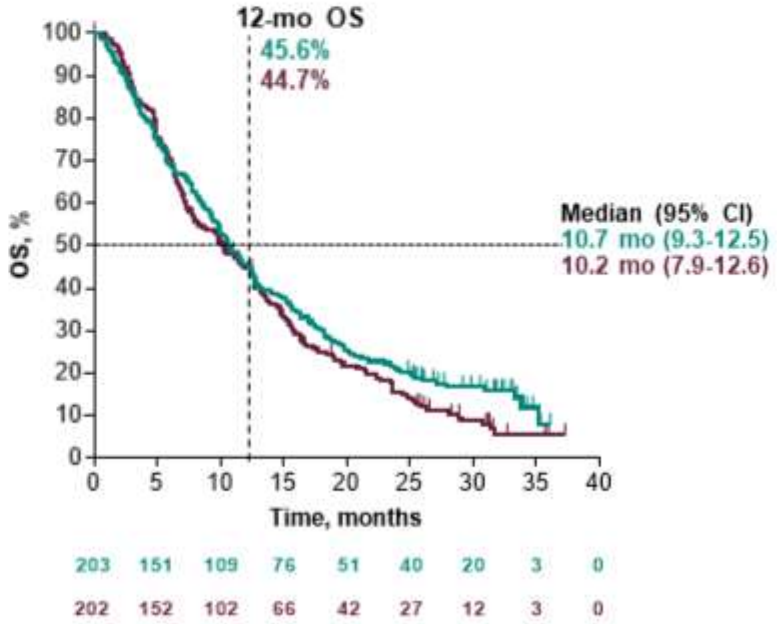
	Events	HR (95% CI)	P
Pembro	77.1%	0.78 (0.57-1.06)	0.057
Chemo	88.8%		



ata cutoff date: April 11, 2019.

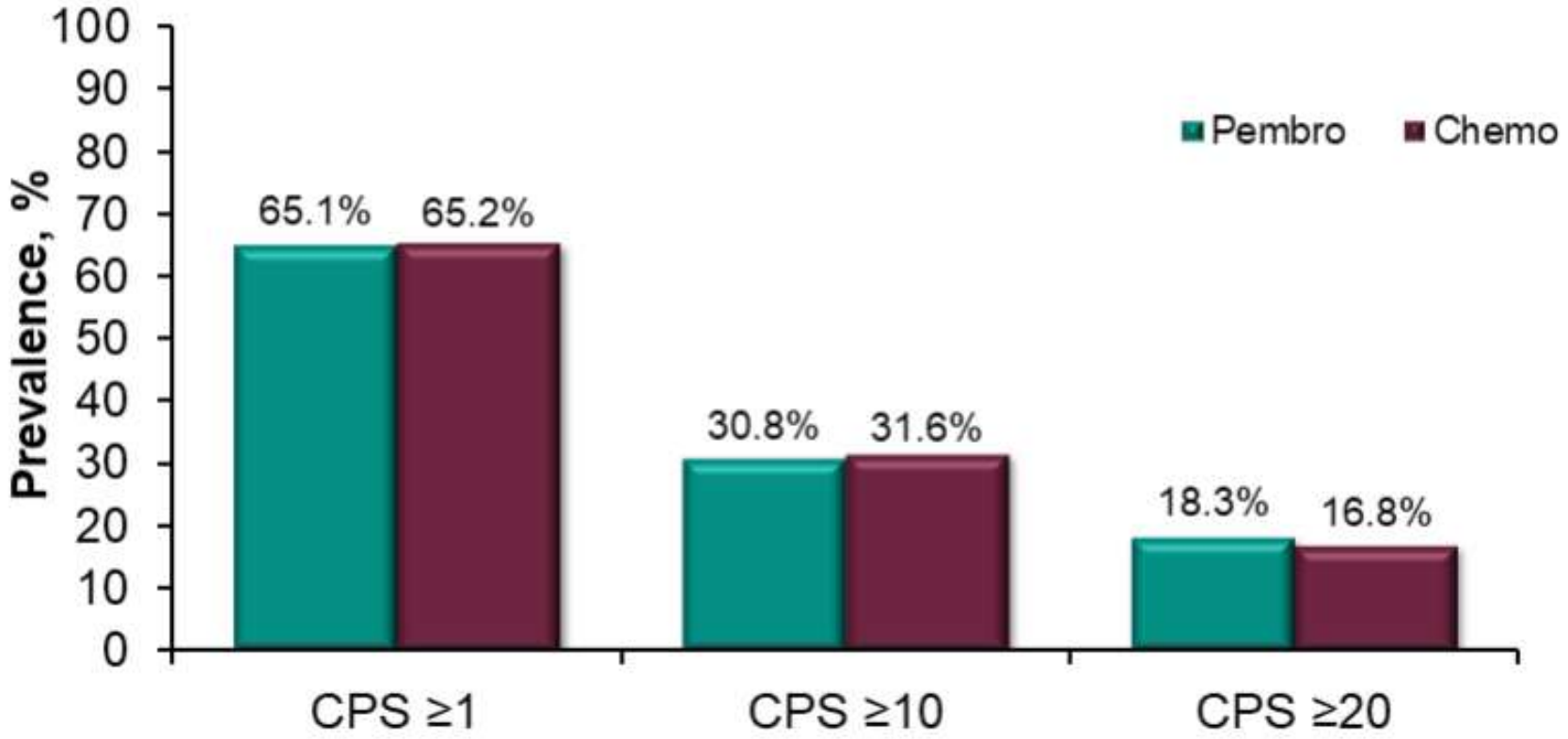
CPS ≥1

	Events	HR (95% CI)	P
Pembro	84.2%	0.86 (0.69-1.06)	0.073
Chemo	90.6%		



Cortes KN119 ESMO 2019

Prevalence of PD-L1 CPS Categories

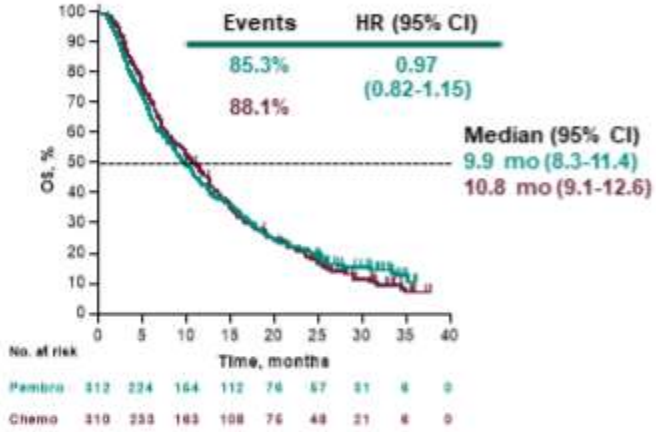


CPS = combined positive score defined as the number of PD-L1–positive cells (tumor cells, lymphocytes, macrophages) divided by total number of tumor cells × 100.
Data cutoff date: April 11, 2019.

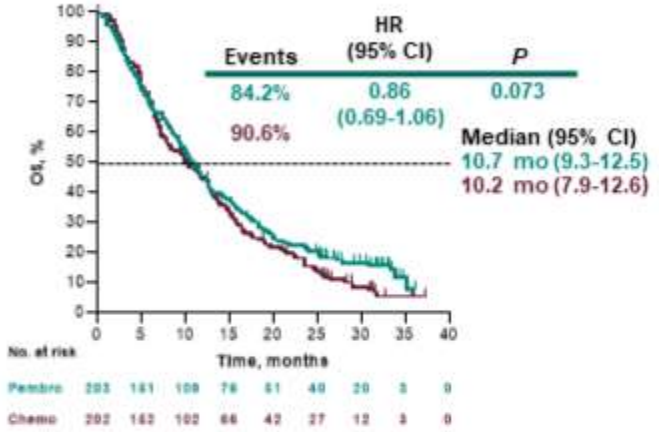
Cortes KN119 ESMO 2019

Overall Survival by PD-L1 CPS

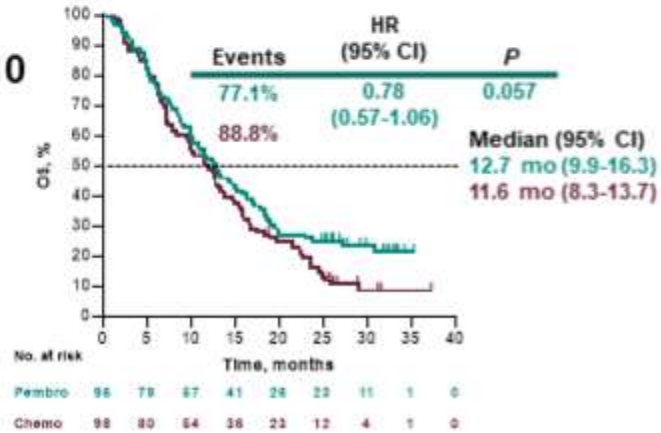
ITT



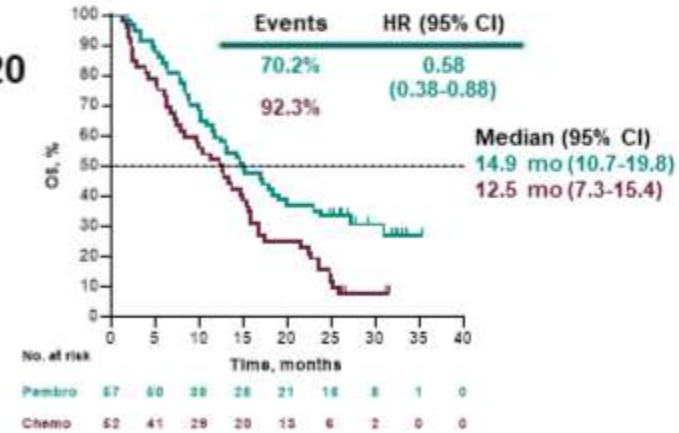
CPS ≥1



CPS ≥10



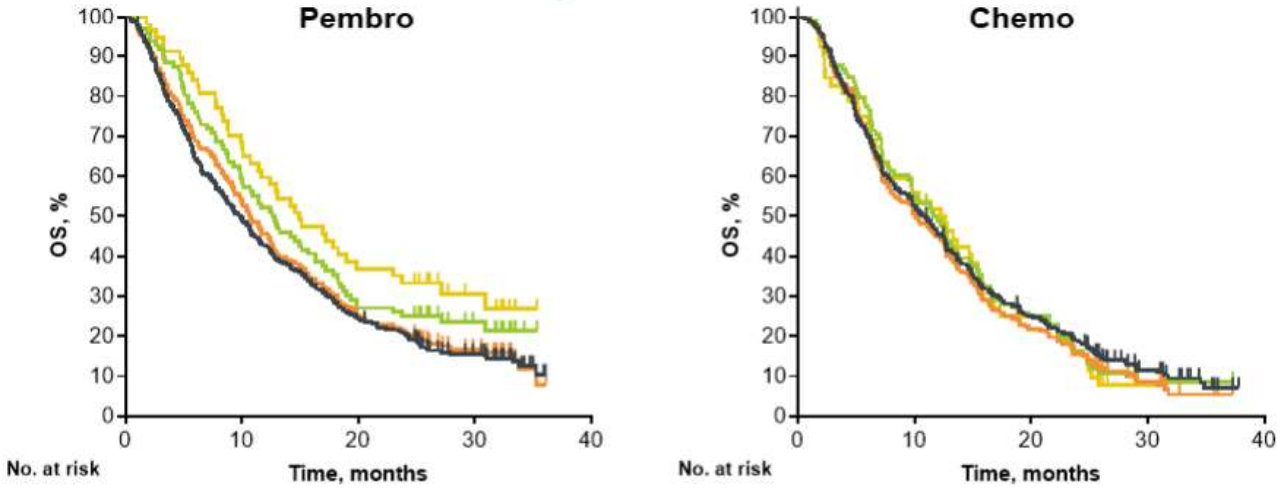
CPS ≥20



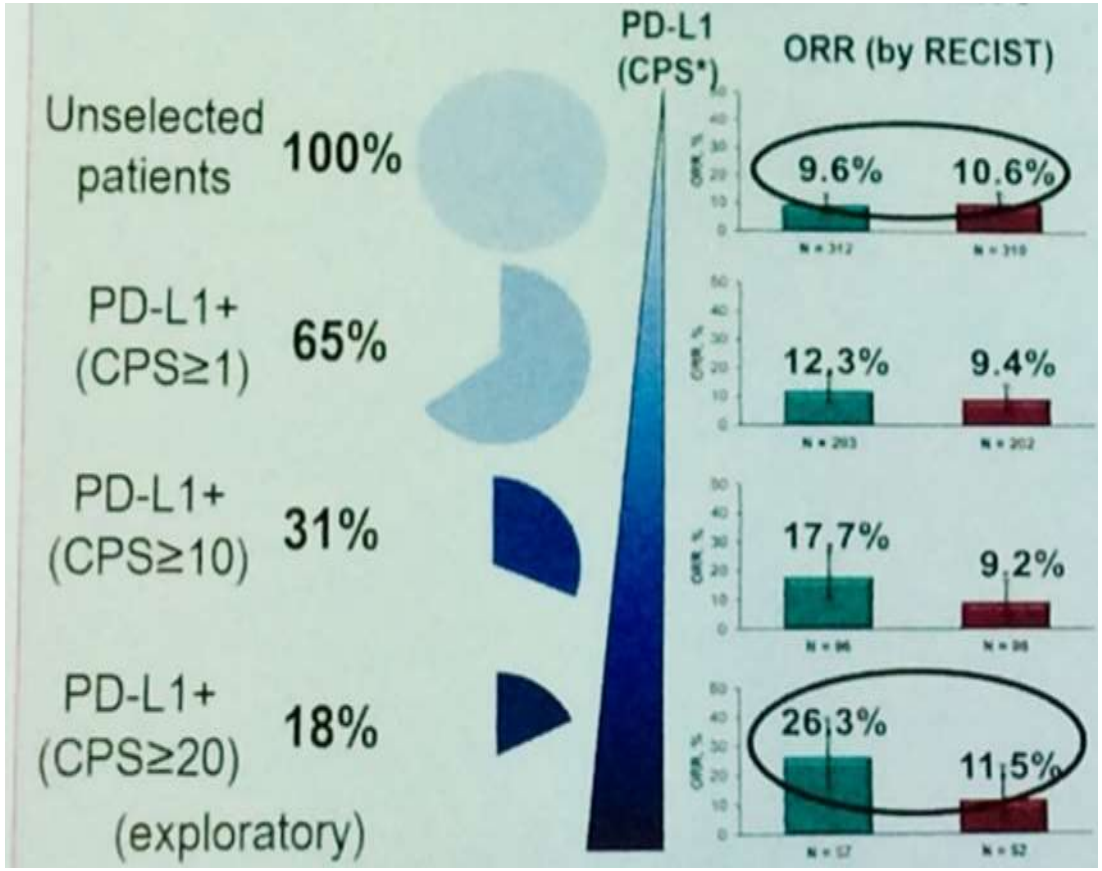
OS in the ITT, CPS ≥1 and CPS ≥10 populations were primary endpoints; OS in the CPS ≥20 population was an exploratory endpoint. Data cutoff date: April 11, 2019

Cortes KN119 ESMO 2019

Overall Survival by PD-L1 CPS



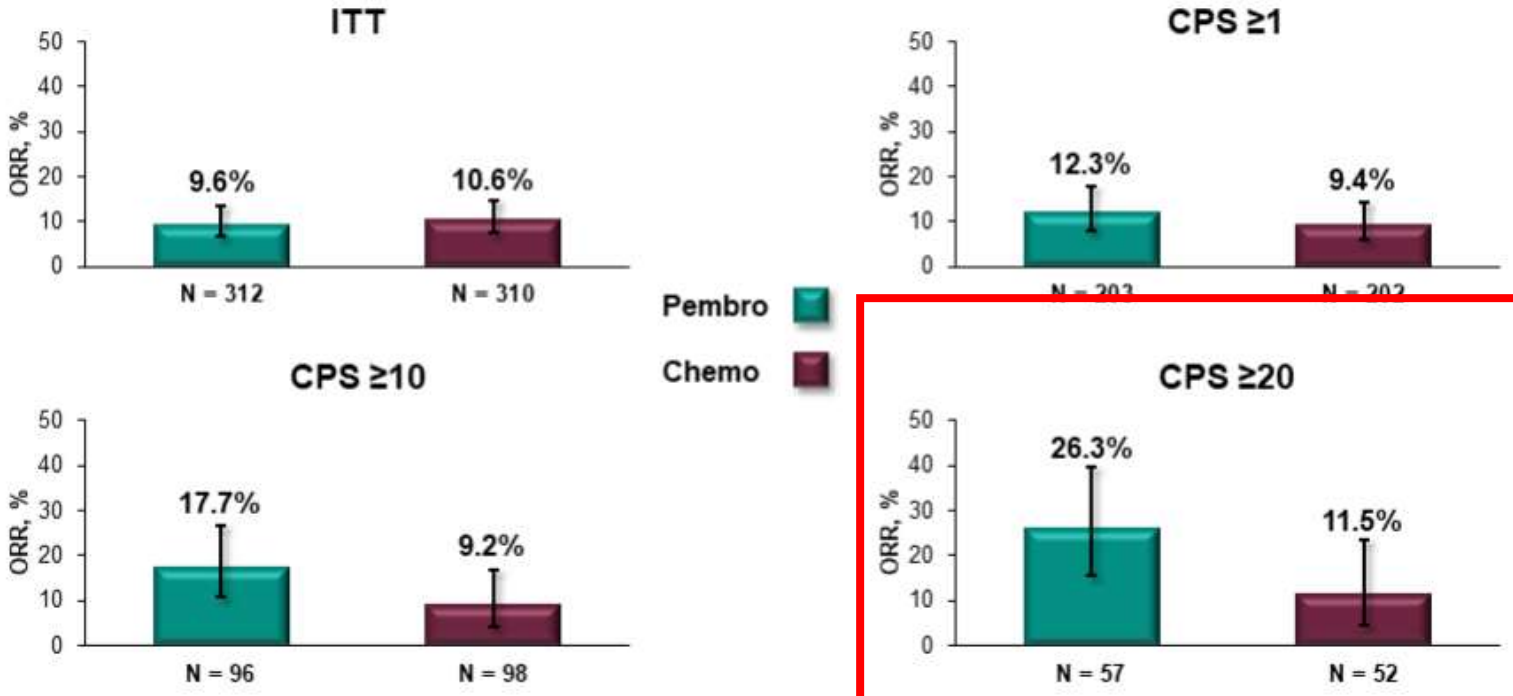
Data cutoff date: April 11, 2019.



The application of incrementally restrictive cut-offs of CPS lends weight to the exploratory analysis showing better survival from pembrolizumab in tumors with CPS≥20

Cortes KN119 ESMO 2019

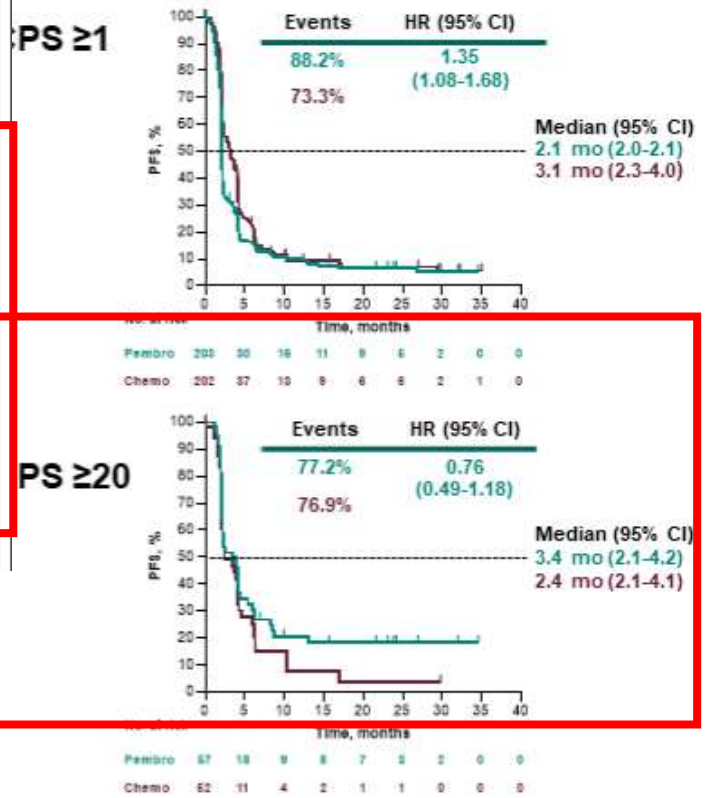
Response Rate (RECIST v1.1, BICR)



ORR in the ITT, CPS ≥1 and CPS ≥10 populations were secondary endpoints; ORR in the CPS ≥20 population was an exploratory endpoint. Data cutoff date: April 11, 2019.

Cortes KN119 ESMO 2019

-L1 CPS (RECIST v1.1, BICR)



PFS in the ITT, CPS ≥1 and CPS ≥10 populations were secondary endpoints; PFS in the CPS ≥20 population was an exploratory endpoint. BICR, blinded, independent central review. Data cutoff date: April 11, 2019

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/2DMhsyg

IMpassion130 baseline characteristics

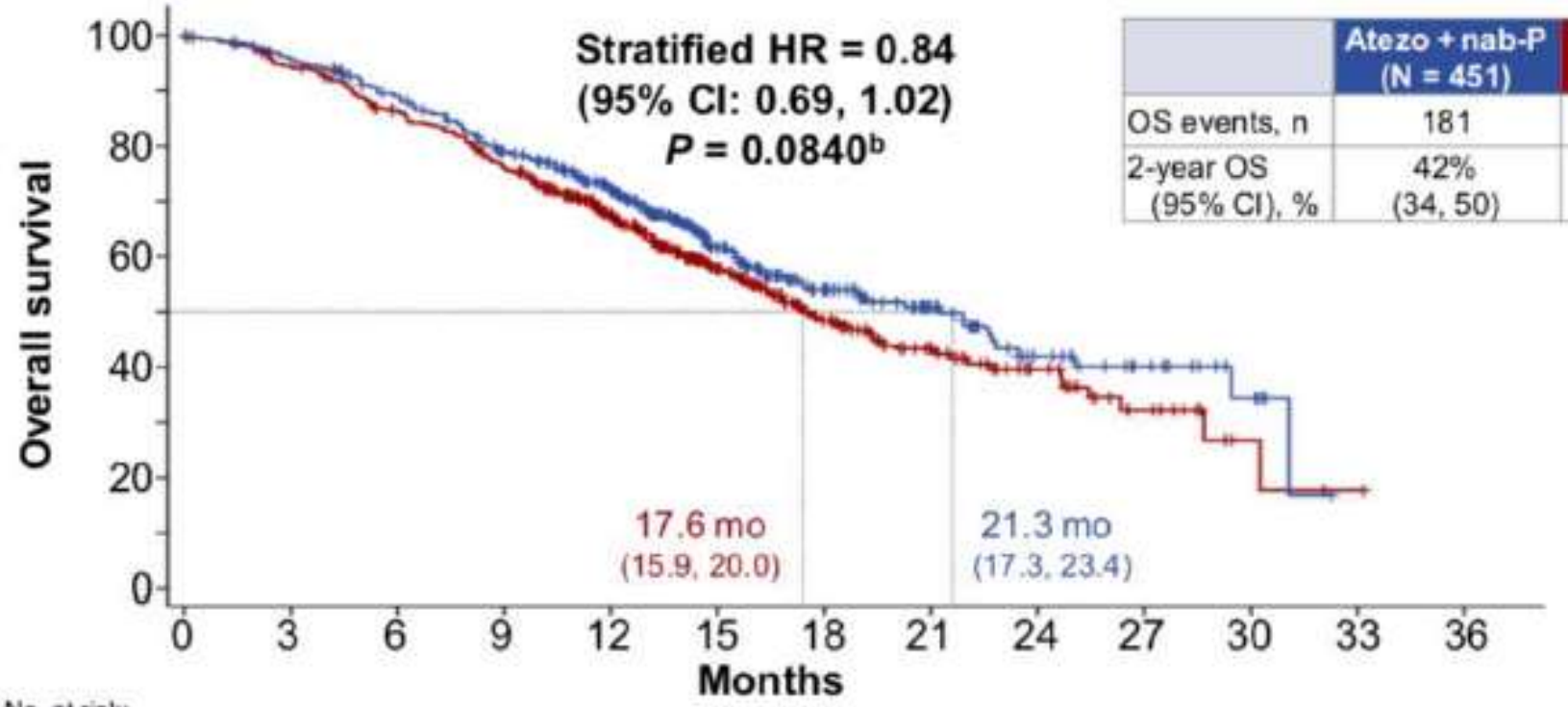
Characteristic	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
Median age (range), y	55 (20-82)	56 (26-86)
Female, n (%)	448 (99%)	450 (100%)
Race, n (%)[a]		
White	308 (68%)	301 (67%)
Asian	85 (19%)	76 (17%)
Black/African American	26 (6%)	33 (7%)
Other/multiple	20 (4%)	26 (6%)
ECOG PS, n (%)[b,c]		
0	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/2DMhevg

Interim OS analysis: ITT population[a]

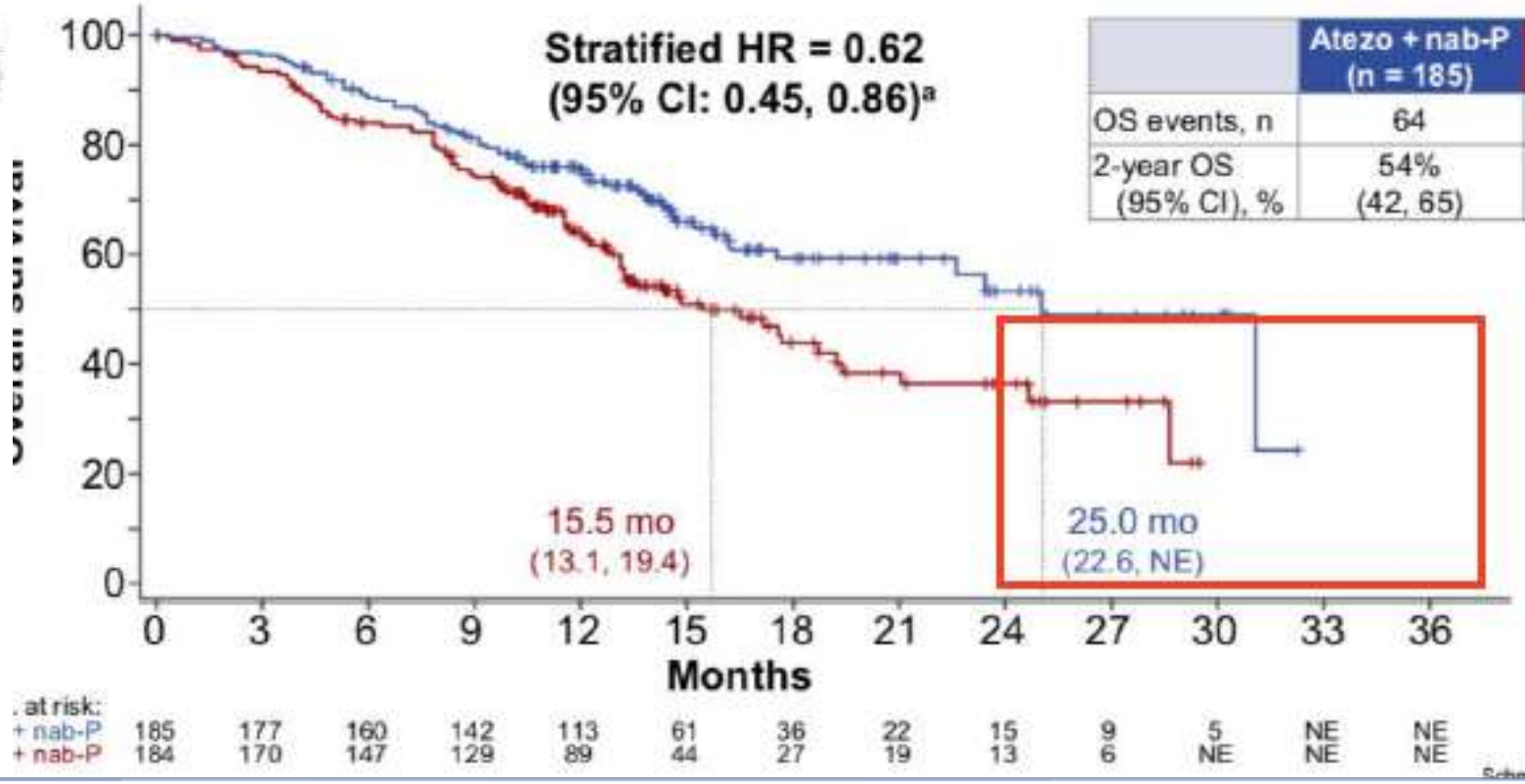


	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
OS events, n	181	208
2-year OS (95% CI), %	42% (34, 50)	40% (33, 46)

Data cutoff: 17 April 2018. Median OS durations (and 95% CI) are indicated on the plot. Median follow-up (ITT): 12.9 months.
[a]For the interim OS analysis, 59% of events had occurred. [b]Significance boundary was not crossed.

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

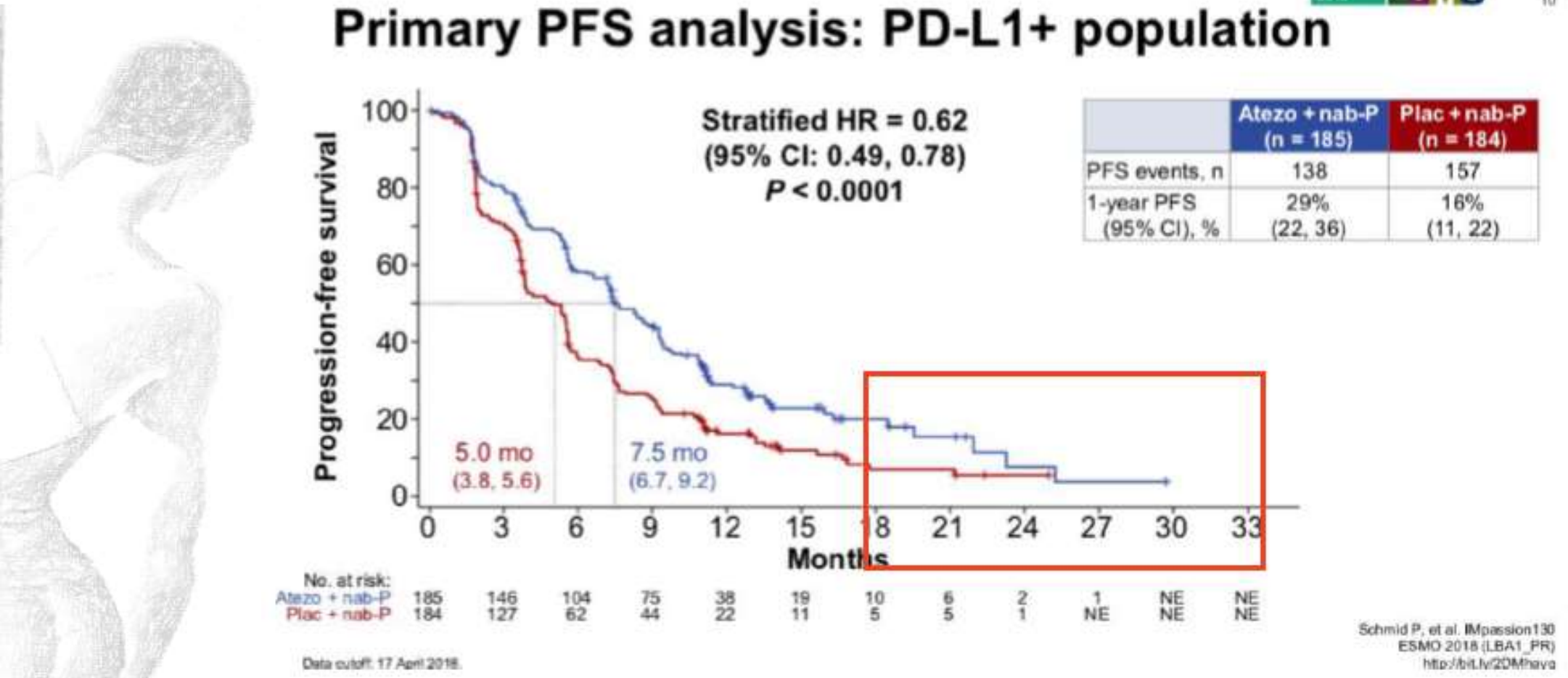
Interim OS analysis: PD-L1+ population



	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)

However, as per protocol, the statistical significance could not be tested in this subgroup, since the OS improvement was not confirmed in the whole population at this time. Of note, in a recently reported update (**second interim analysis after a median follow-up of 18 months), the median OS was still not significantly different between each arm (21 months versus 18.7 months, stratified HR = 0.86, p = 0.07) in the whole population, and the numerical difference in OS in the PD-L1-positive subset tended to decrease** (median OS of 25 months versus 18 months, HR = 0.71, no formal p-value by protocol design).

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)

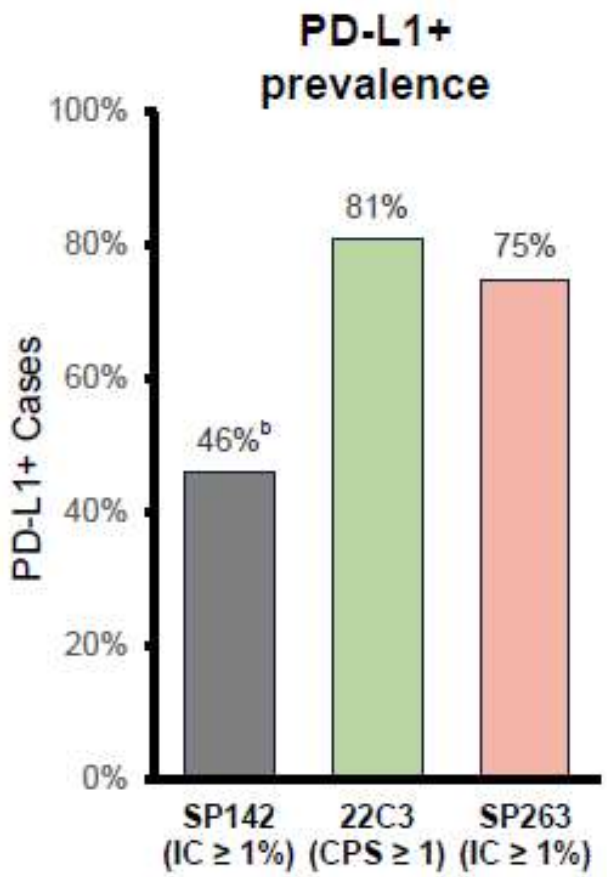
Schmid P, et al. IMpassion130 ESMO 2018 (LBA1_PR)
http://bit.ly/2DMhava

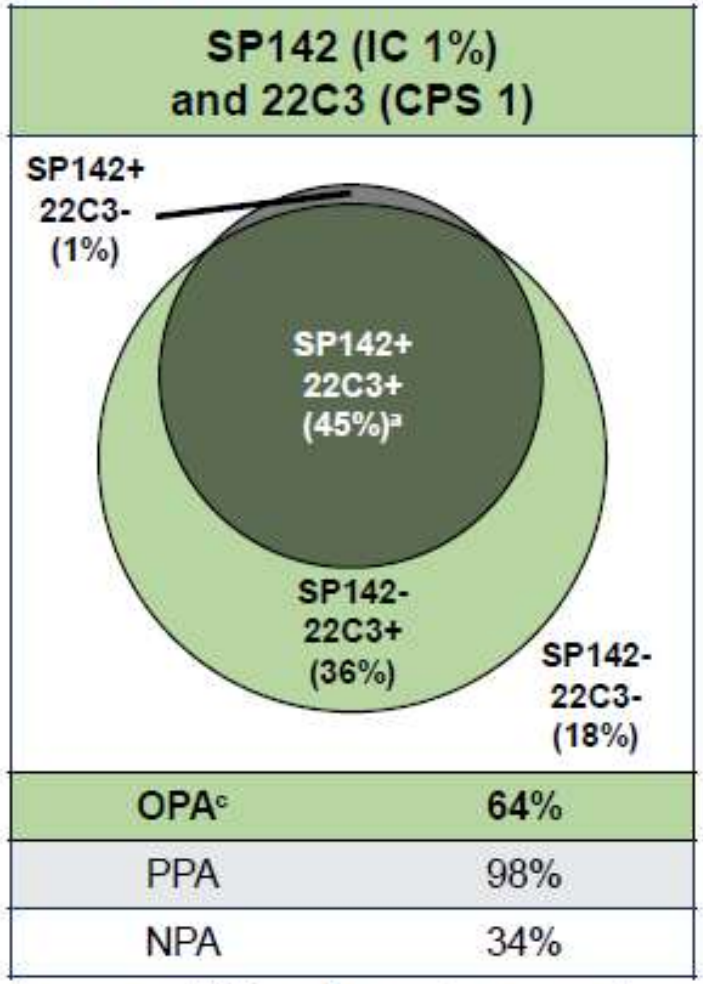
Performance of PD-L1 immunohistochemistry assays in unresectable locally advanced or metastatic triple-negative breast cancer: post hoc analysis of IMpassion130

Methods

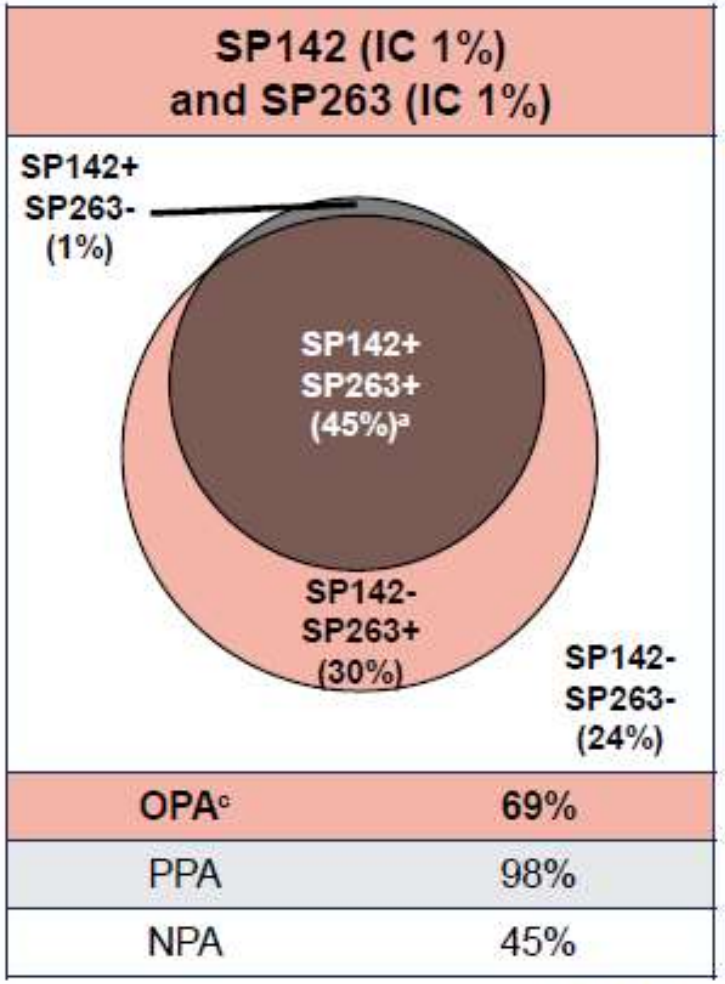
- Central testing of VENTANA PD-L1 SP142, DAKO 22C3 and VENTANA PD-L1 SP263 IHC assays were performed according to the respective package inserts[a]
  - Each slide was read by a single pathologist out of a panel of 8 pathologists[b]
  - Pathologists were trained and qualified to read IC 1% (SP142 and SP263) and CPS 1 (22C3) cutoffs[b]
- The biomarker-evaluable population (BEP) in this retrospective exploratory analysis comprised 614 patients (68% of ITT) with samples tested with the 3 PD-L1 assays
  - Prevalence of PD-L1 IC+ status according to SP142 was higher in the BEP (46%) than the ITT (41%). All other evaluated baseline characteristics were balanced between BEP and ITT
  - PFS outcome with A + nP in the BEP slightly overperformed compared with PFS outcome in the ITT

PD-L1 IHC assays: prevalence and analytical concordance





OPA[c]	64%
PPA	98%
NPA	34%

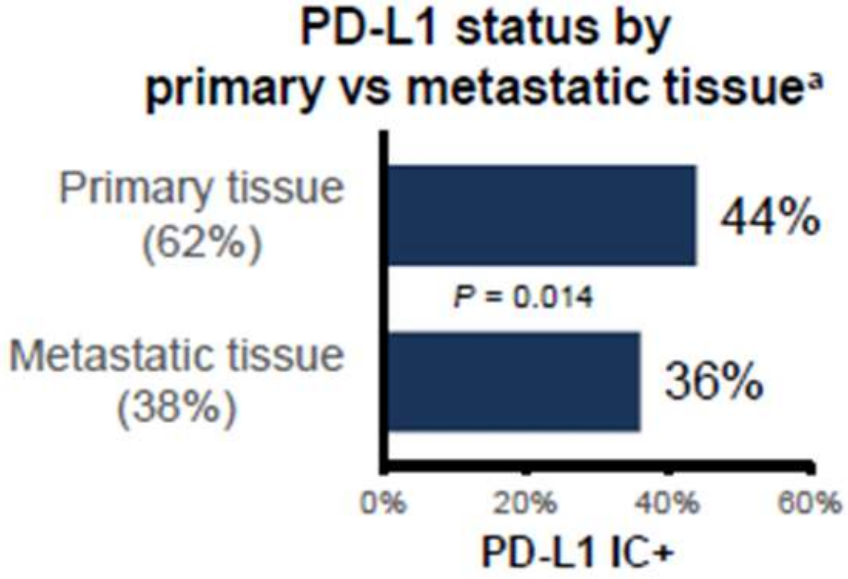


OPA[c]	69%
PPA	98%
NPA	45%

NPA, negative percentage agreement; OPA, overall percentage agreement; PPA, positive percentage agreement.
[a] > 97% of SP142+ samples included in 22C3+ or SP263+ samples. [b] Compared with 41% in ITT (Schmid, *New Engl J Med* 2018).
[c] ≥ 90% OPA, PPA *and* NPA required for analytical concordance.

Rugo et al. Abstract 6571
IMpassion130 PD-L1 IHC
https://bit.ly/30OmOqz

PD-L1 assessment in either primary or metastatic?



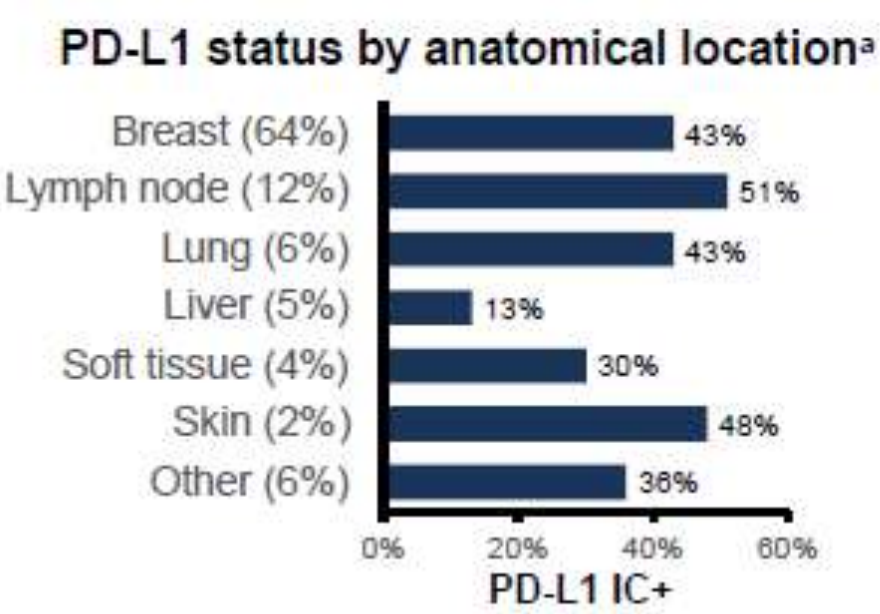
These data do not inform whether PD-L1 assessment in primary and metastatic sites is equally informative!

(a comparison among PD-L1 assessment in different sites of the same patients needed)

Time and spatial heterogeneity of PD-L1 is known. Does site of PD-L1 assessment matter?

When multiple tumor sites are present, what should we prefer to biopsy for PD-L1 assessment?

What about inter tumor heterogeneity?



ay.
in samples collected

Rugo et al. Abstract 657
IMpassion130 PD-L1 IH
https://bit.ly/30OmOq

Most common serious AEs

SAEs occurring in ≥ 1% of patients in either arm (regardless of attribution)

SAE, n (%)	Atezo + nab-P (n = 452)		Plac + nab-P (n = 438)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All	103 (23%)	78 (17%)[a]	80 (18%)	56 (13%)[b]
Pneumonia	10 (2%)	8 (2%)[c]	5 (1%)	0
Urinary tract infection	5 (1%)	2 (< 1%)	0	0
Dyspnoea	5 (1%)	3 (1%)	2 (< 1%)	2 (< 1%)
Pyrexia	5 (1%)	3 (1%)	3 (1%)	0

- A higher proportion of patients in the Atezo + nab-P arm than in the Plac + nab-P arm reported SAEs (23% vs 18%)
- No SAE was reported with a ≥ 2% difference between treatment arms

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

SAE, serious adverse event. Data cutoff: 17 April 2018. [a] Six Grade 5 events occurred. [b] Three Grade 5 events occurred. [c] One Grade 5 event occurred.

Immune checkpoint inhibitors seem to work better in erlier setting

Ph.	Anti-PD(L)-1	Single (S) or Combination	Study Title	Conditions or Disease	Treatment Line	Comparative Arm (for Phase IIR/III)	ORR (+/− 95% CI)	Duration of Response Median, Months (+/− 95% CI)	PFS Median, Months (+/− 95% CI)	OS Median, Months (+/− 95% CI)	Ref.
II	Atezolizumab	(Nab) paclitaxel + Cobimetinib	COLET	LA or M+ TNBC	1 L	/	34%	NA	6-mo PFS rate: 40.5%	6-mo OS rate: 84.1%	Brufski ASCO 2019 (#1013)
II-R	Pembrolizumab	Standard Chemo	I-SPY 2 trial	LA TNBC	Neo-adj	Placebo	Pembro: 62% Placebo: 22%	NA	NA	NA	Nanda ASCO 2017
II-R	Pembrolizumab	Eribulin	KEYNOTE-150 (ENHANCE 1) (Study 218)	M+ TNBC	1 L to 3 L	Eribulin +/− Pembrolizumab	26.4% (2017) Equal in 2 arms (2019)	8.3 mo (SABCS 2017)	P + E = 4.1 mo (ASCO 2019) E = 4.2 mo (ASCO 2019)	Median 17.7 (13.7–NR) (SABCS 2017)	Tolaney, SABCS 2017 Tolaney, ASCO 2019 (#1004)
II-R	Nivolumab	Doxo or Cyclo or RT (3*8 Gy)	TONIC	M+ TNBC	1 L to ≥3 L	Doxo or Cyclo or RT	Doxo = 35% Cyclo = 8% RT = 8%	NA	NA	NA	Voorwerk Nature Med 2019
II-R	Durvalumab	Nab-paclitaxel + standard EC	GeparNuevo	LA TNBC (cT2-cT4a-d)	Neo-adj						
III	Pembrolizumab	S	KEYNOTE-119	M+ TNBC	2 L or 3 L	single-agent CT (physician's choice)	4.8%	NA	NA	not superior to CT	Merck press release
III	Atezolizumab	Nab-paclitaxel	IMPASSION-130	LA or M+ TNBC	1 L	Nab-paclitaxel	Atezo: 56% Placebo: 46%	HR= 0.78 (0.63–0.98) Median DOR Atezo: 7.4 mo Median DOR placebo: 5.6	HR 0.62 (0.49–0.78) Median PFS Atezo: 7.2 mo Median PFS placebo: 5.5 mo	HR 0.86 (0.72–1.02 Median OS Atezo: 21.0 mo Median OS placebo: 18.7 mo	Schmid NEJM 2018 Schmid ASCO 2019

The pCR was higher in durvalumab-arm (53.4% vs. 44.2% placebo), but not statistically significant

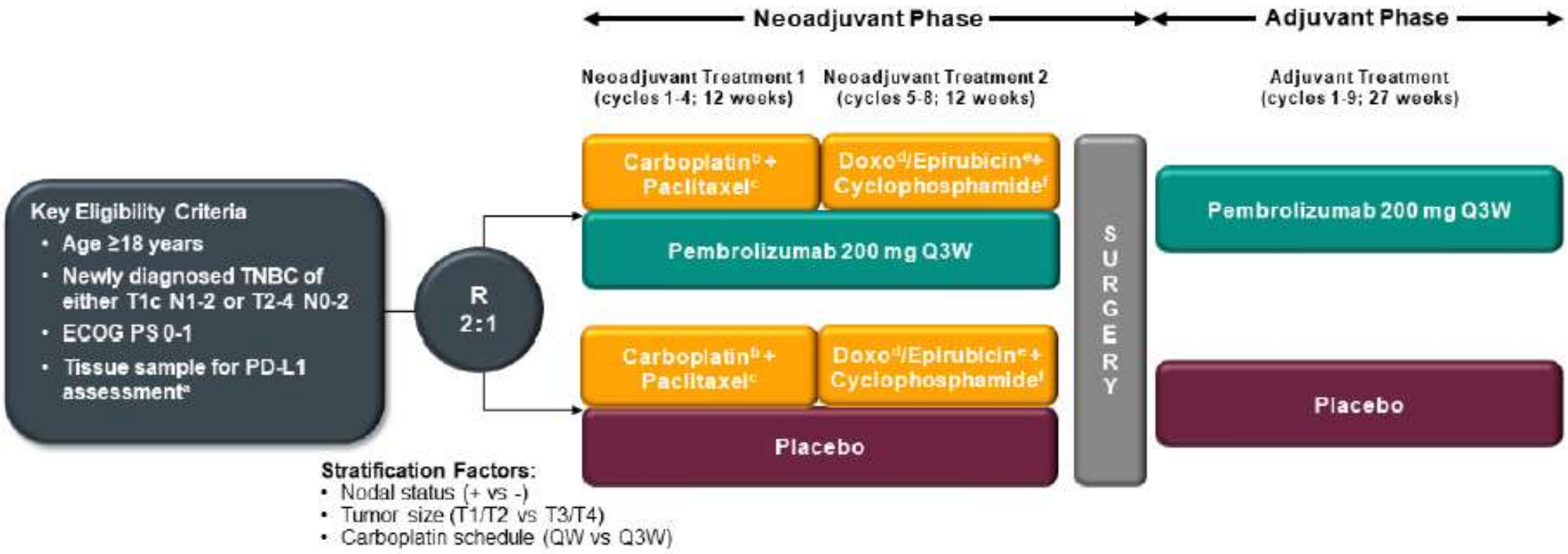
Abbreviations: Ph = phase; IIR = phase II Randomized; TNBC: Triple Negative Breast Cancer; LA = Locally Advanced; M+ = metastatic; ORR = Objective Response Rate; DOR = Duration of Response; PFS = Progression-Free-Survival; OS = Overall Survival; L = Line; mo = months; NR = Not Reached; gBRCAm = germline BRCA-mutated;

KEYNOTE-522: Phase 3 Study of Pembrolizumab + Chemotherapy versus Placebo + Chemotherapy as Neoadjuvant Treatment, Followed by Pembrolizumab versus Placebo as Adjuvant Treatment for Early Triple-Negative Breast Cancer (TNBC)

Peter Schmid[1], Javier Cortes[2], Rebecca Dent[3], Lajos Pusztai[4], Heather McArthur[5], Sherko Kümmel[6], Jonas Bergh[7], Carsten Denkert[8], Yeon Hee Park[9], Rina Hui[10], Nadia Harbeck[11], Masato Takahashi[12], Theodoros Foukakis[7], Peter A. Fasching[13], Fatima Cardoso[14], Liyi Jia[15], Vassiliki Karantza[15], Jing Zhao[15], Gursel Aktan[15], Joyce O'Shaughnessy[16]

1. Barts Cancer Institute, Queen Mary University London, London, UK; 2. IOB Institute of Oncology, Quiron Group; Vall d'Hebron Institute of Oncology (VHIO), Madrid & Barcelona, Spain; 3. University of Toronto, Toronto, Ontario, Canada; 4. Yale School of Medicine, Yale Cancer Center, New Haven, CT, USA; 5. Cedars-Sinai Medical Center, Los Angeles, CA, USA; 6. Breast Unit, Kliniken Essen-Mitte, Essen, Germany; 7. Department of Oncology-Pathology, Karolinska Institutet and Breast Cancer Centre, Cancer theme, Karolinska University Hospital, Solna, Sweden; 8. Institute of Pathology, Philipps-University Marburg and University Hospital Marburg (UKGM), Marburg, Germany; 9. Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; 10. Westmead Breast Cancer Institute, Westmead Hospital and the University of Sydney, Sydney, NSW, Australia; 11. Breast Center, University of Munich (LMU), Munich, Germany; 12. Hokkaido Cancer Center, Sapporo, Japan; 13. University Hospital Erlangen, Comprehensive Cancer Center Erlangen-EMN, Erlangen, Germany; 14. Breast Unit, Champalimaud Clinical Center/Champalimaud Foundation, Lisbon, Portugal; 15. Merck & Co., Inc., Kenilworth, NJ, USA; 16. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, TX, USA

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.

Study Endpoints

- Primary Endpoints
  - pCR (ypT0/Tis ypN0) assessed by local pathologist in ITT population[a]
  - Event-free survival (EFS) assessed by investigator in ITT population
- Secondary Endpoints
  - pCR as per alternative definitions (ypT0 ypN0 and ypT0/Tis)
  - Overall survival (OS)[b]
  - pCR, EFS[a] and OS[b] in the PD-L1–positive population[c]
  - Safety in all treated patients
- Key Exploratory Endpoints
  - Residual cancer burden (RCB)[b]
  - EFS by pCR[b]
  - pCR and EFS by TILs[b]

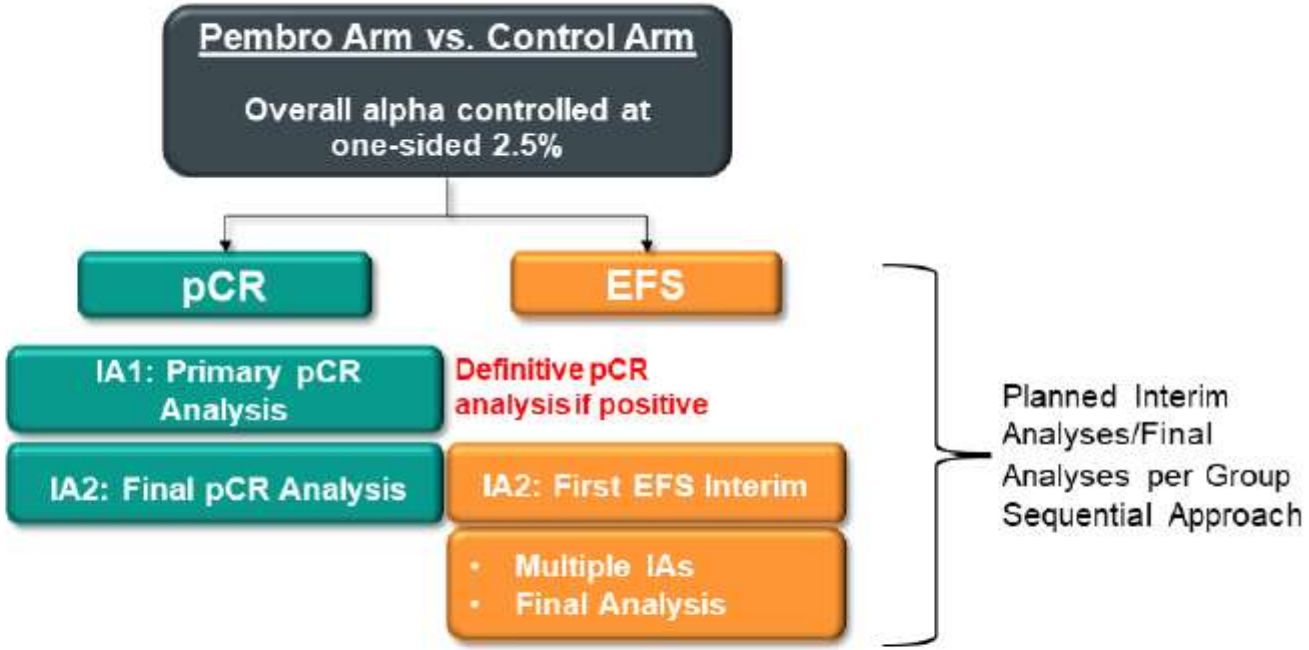
[a]Subjects without pCR data due to any reason or who received neoadjuvant chemotherapy not specified in the protocol were counted as non-pCR. [b]To be presented at a later date. [c]PD-L1 assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay and measured using the combined positive 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.

Statistical Considerations

Interims Completed:

✓First IA (IA1) performed after last subject enrolled; Data Cutoff: Sep 24, 2018

✓Second IA (IA2) performed ~24 mo after first subject enrolled; Data Cutoff: Apr 24, 2019



- **IA1:** Primary pCR analysis to test primary hypothesis of pCR based on prespecified first 602 subjects (pre-calculated *P* value boundary for significance of 0.003)
- **IA2:** If pCR hypothesis successful at IA1 (thus definitive), pCR will not be formally tested at IA2
- EFS at IA2 (first interim of EFS): precalculated *P* value boundary for significance of 0.000051 (HR <0.4)
- Prespecified analysis plan allows alpha passing from successful endpoint(s) to other(s)

Schmid KN522 ESMO 2019

Summary of Study Treatment and Analysis Populations: IA2

1174 patients randomized 2:1 from Mar 2017 to Sep 2018

Pembrolizumab + Chemotherapy Arm

- 784 allocated
- 778 (99.2%) started Carboplatin/Paclitaxel
- 726 (92.6%) started AC or EC
- 758 (96.7%) had documented surgery[b]
- 547 (69.8%) started adjuvant treatment

10 (1.3%) discontinued neoadjuvant treatment due to PD[a]

Placebo + Chemotherapy Arm

- 390 allocated
- 389 (99.7%) started Carboplatin/Paclitaxel
- 369 (94.6%) started AC or EC
- 380 (97.4%) had documented surgery[b]
- 314 (80.5%) started adjuvant treatment

9 (2.3%) discontinued neoadjuvant treatment due to PD[a]

Analysis Populations

- ITT: N = 784
- Safety-evaluable: N = 781[c]

Median follow-up[d]: 15.3 mo

Analysis Populations

- ITT: N = 390
- Safety-evaluable: N = 389[c]

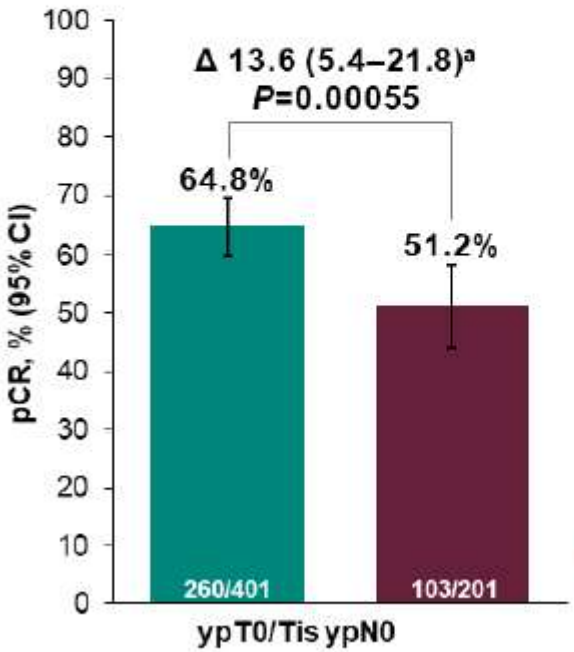
Median follow-up[d]: 15.8 mo

[a]Includes radiographic and clinical PD. [b]Patients did not have to complete all neoadjuvant therapy to undergo surgery. [c]Includes all patients who received ≥1 dose of study treatment or underwent surgery. [d]Defined as the time from randomization to the date of death or database cutoff date of April 24, 2019, if the patient was alive.

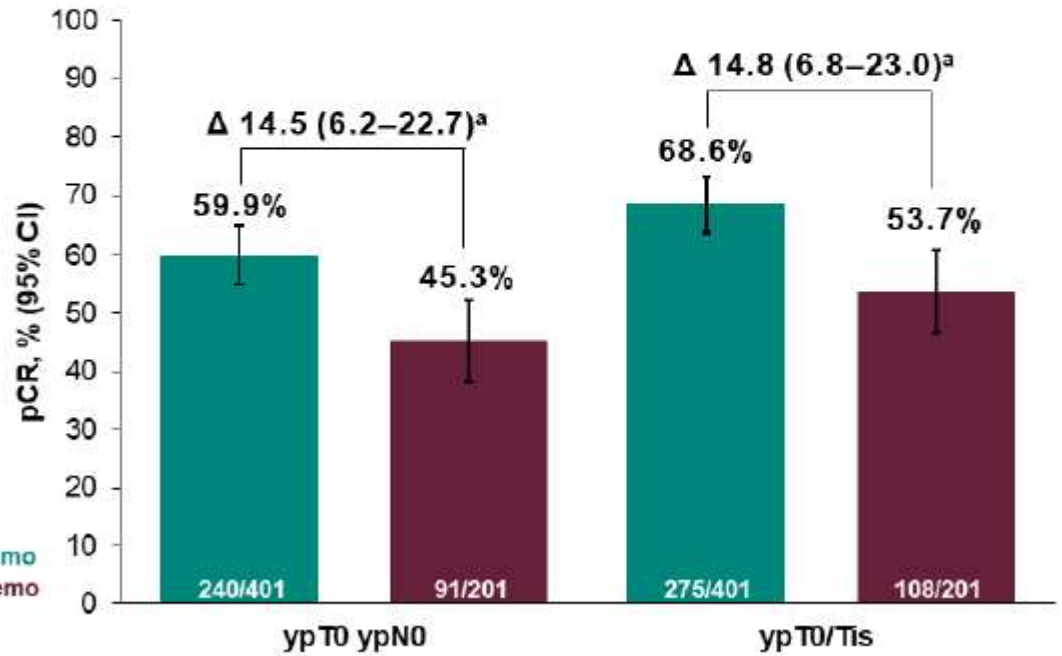
Schmid KN522 ESMO 2019

Pathological Complete Response at IA1

Primary Endpoint



Secondary Endpoints: Other pCR Definitions

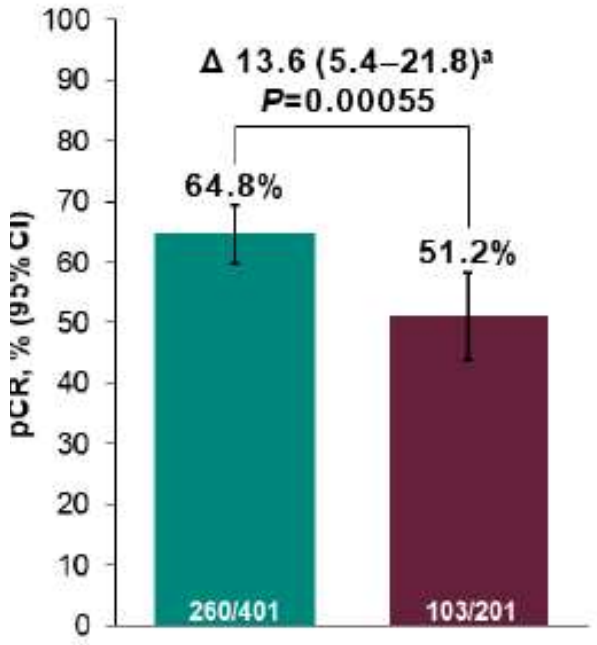


Pembro + Chemo
Placebo + Chemo

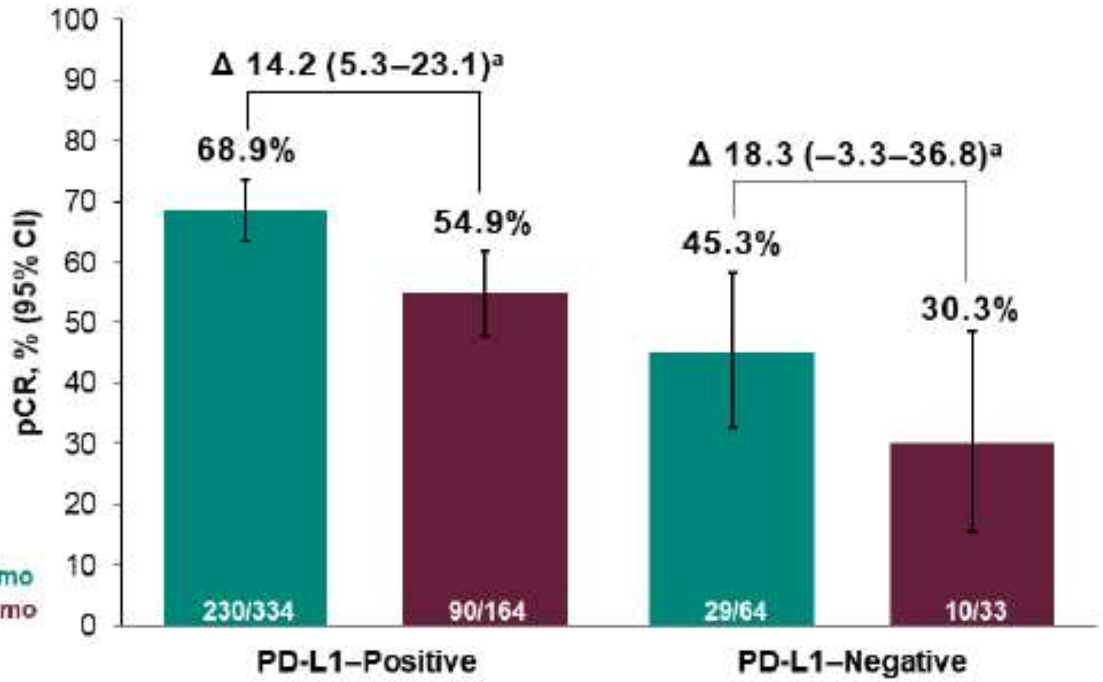
[a]Estimated treatment difference based on Miettinen & Nurminen method stratified by randomization stratification factors.
Data cutoff date: September 24, 2018.

Pathological Complete Response at IA1

Primary Endpoint: ypT0/Tis ypN0



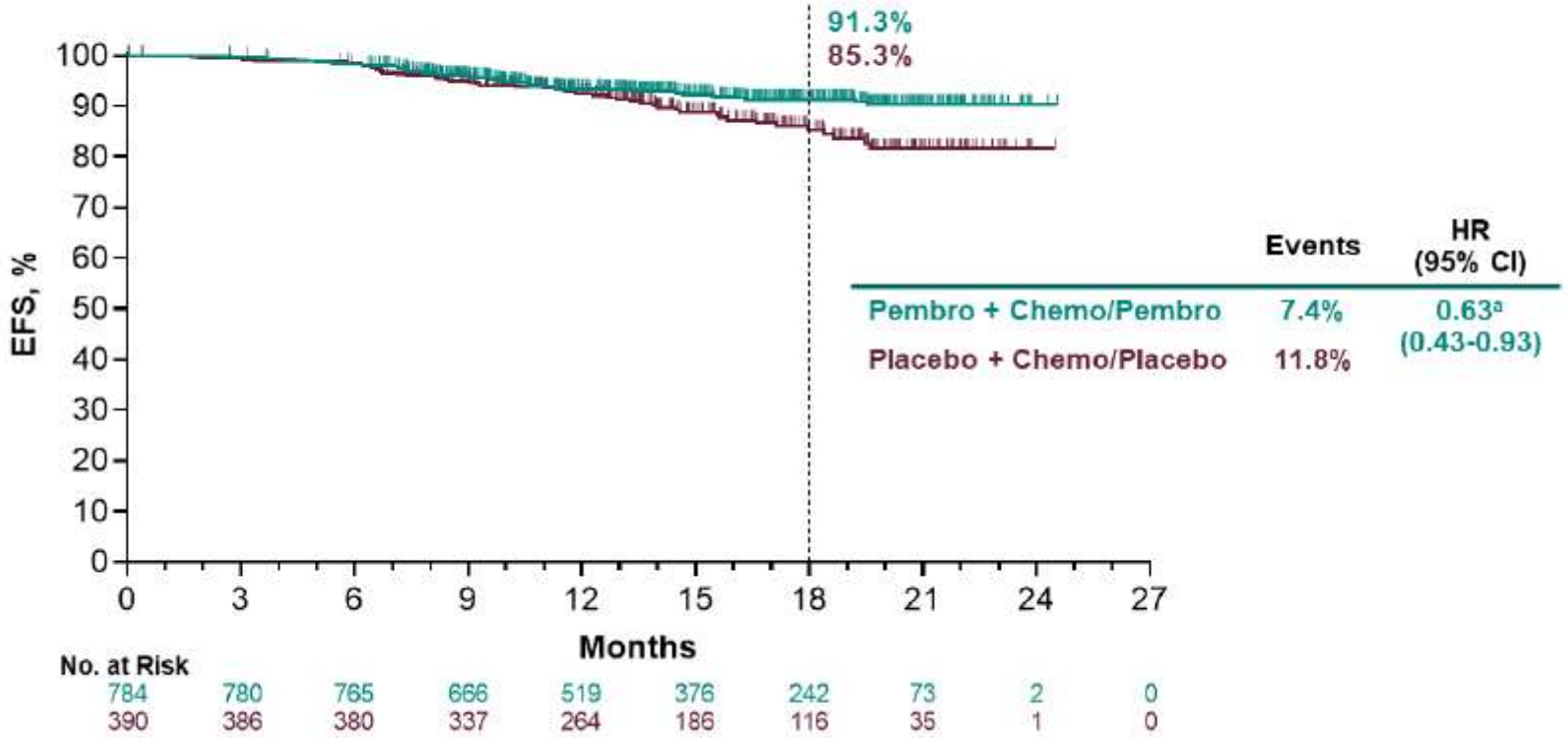
By PD-L1 Status[b]: ypT0/Tis ypN0



Pembro + Chemo
Placebo + Chemo

ited 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 harmDx 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 100); PD-L1–positive = CPS ≥1. Data cutoff date: September 24, 2018.

Event-Free Survival at IA2



	Events	HR (95% CI)
Pembro + Chemo/Pembro	7.4%	0.63[a] (0.43-0.93)
Placebo + Chemo/Placebo	11.8%	

[a]Prespecified *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.

Summary

- KEYNOTE-522 is the first prospective randomized placebo controlled phase 3 trial of pembrolizumab in early TNBC in the neoadjuvant/adjuvant setting
- Addition of pembrolizumab to platinum-containing neoadjuvant chemotherapy resulted in a statistically significant and clinically meaningful increase in pCR (ypT0/Tis ypN0) of 13.6 percentage points (P=0.00055)
  - Consistent benefit seen with pCR defined as ypT0 ypN0 and ypT0/Tis
  - Benefit of pembrolizumab independent of PD-L1 status
- Safety was consistent with the known profiles of each regimen; long-term safety follow-up is ongoing

Aiom Associazione Italiana di Oncologia Medica

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2019
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

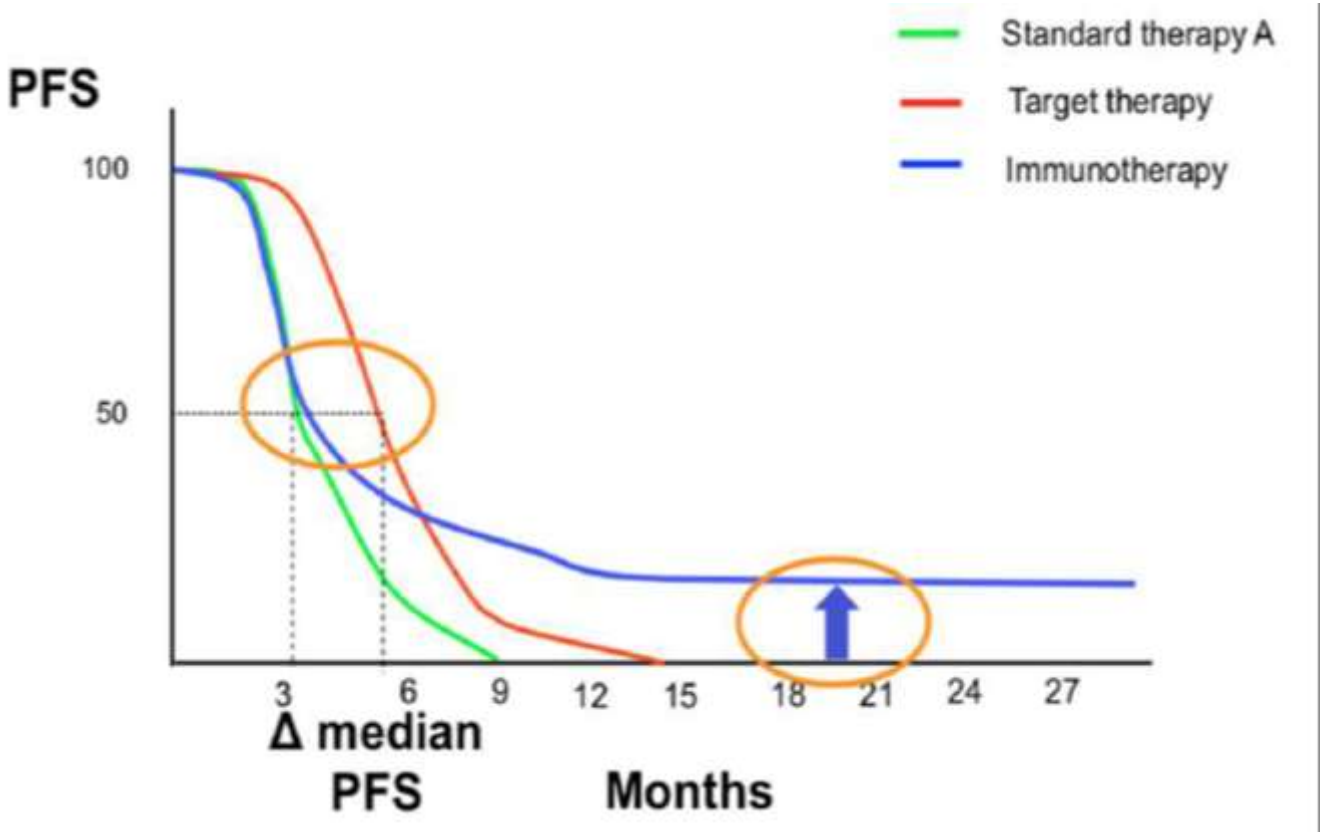
PREOPERATIVE/ADJUVANT THERAPY REGIMENS[a,b,c,d,e,f]

HER2-Negative[g]
Preferred regimens: • Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks[h] • Dose-dense AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel[h] • TC (docetaxel and cyclophosphamide) • If triple-negative breast cancer and residual disease after preoperative therapy with taxane-, alkylator-, and anthracycline-based chemotherapy: capecitabine[i]
Useful in certain circumstances: • Dose-dense AC (doxorubicin/cyclophosphamide) • AC (doxorubicin/cyclophosphamide) every 3 weeks (category 2B) • CMF (cyclophosphamide/methotrexate/fluorouracil) • AC followed by weekly paclitaxel
Other recommended regimens: • AC followed by docetaxel every 3 weeks • EC (epirubicin/cyclophosphamide) • TAC (docetaxel/doxorubicin/cyclophosphamide)

TNBC : the candidate for immunotherapy

Can we cure cancer with immunotherapy?

- ✓Single agent response rate : 5-20%
- ✓ Higher Rationale in TNBC (most of all in PD-L1 positivity)
- ✓ Long-lasting responses and survival in a subset of pts
- ✓Acceptable safety profile in early phases trials in metastatic setting



Immuno checkpoint inhibitors in BC

✓ Identification of biomarkers of response for a better selection of patients **(Different PDL1 IHC test for each IMP)**

SP142 the most accurate in BC!

- Limitations in defining PD-L1 as the biomarker
- Expression is dynamic and focal
- < Biopsies / full sections
- < location of the metastases
- Expression depend of the antibody used
- Responses in PD-L1-negative cases
- 5-20% objective response rate in PD-L1 negative tumors (melanoma & NSCLC)
- Studies have used different threshold of positivity / different cells type
- Stratification < PD-L1 status in clinical trials

PEMBROLIZUMAB	**22C3**
	SP263
NIVOLUMAB	**28-8**
	SP263
ATEZOLIZUMAB	**SP142**
DURVALUMAB	**SP263**

Curr Opin Pharmacol 2015; 23:32-38

Immuno checkpoint inhibitors in BC

"PD-L1 continues to be the most common biomarker assessed across cancer types, but a standardized protocol needs to be developed to facilitate data interpretation across clinical trials."

Biomark. Med 2018; 12: 97-100

- ✓ Early stage! **(challenges with EndPoint)**
- ✓ Development of multiple intriguing rationale combinations (**Difficulty in assessing the success of a given combination when one agent is significantly more active than the other)** with compatible mechanisms that act synergistically to:
  - Increase anti-tumor efficacy **(Recist 1.1? imRecist? What about cross-over?)**
  - Reduce on-target side effects **(Different AEs profile! Different Management!)**

New Therapies.....
New Toxicities

- ✓ Adjuvant/neoadjuvant and metastatic settings **(133 trials, 92 recruiting)**

NIH U.S. National Library of Medicine
ClinicalTrials.gov

THANKS!

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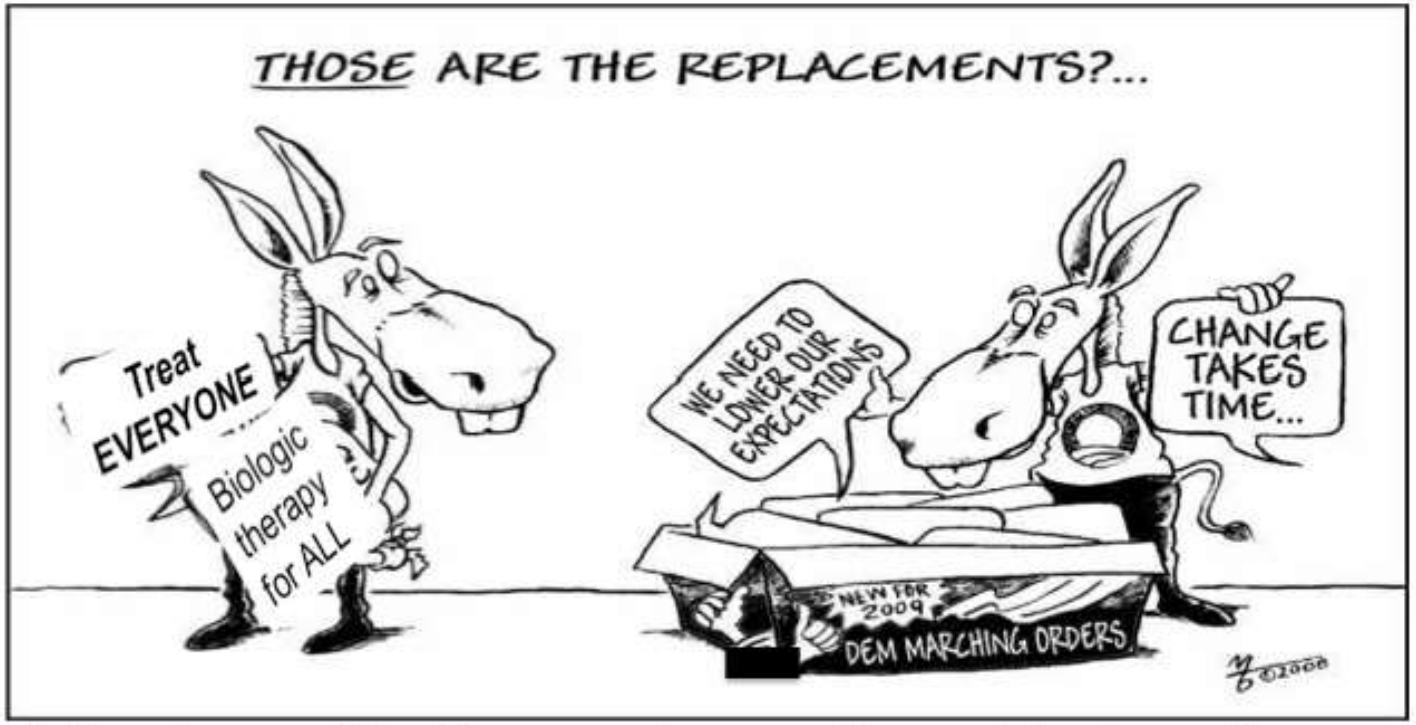
www.oncologiamarche.it

What Have we Learned?



The benefit of experience is not in treating everyone, but in treating wisely.

Nelle donne con carcinoma mammario TRIPLO NEGATIVO (recettori ormonali negativi ed HER2-negativo) candidate a ricevere chemioterapia primaria/neoadiuvante, è raccomandabile l'aggiunta del platino ad uno schema standard con antracicline e taxani rispetto alla sola chemioterapia a base di antracicline e taxani?

Qualità Globale delle evidenze GRADE	Raccomandazione clinica	Forza della raccomandazione clinica
Moderata	Nelle donne con carcinoma mammario triplo negativo (recettori ormonali negativi ed HER2 negativo) candidate a ricevere chemioterapia primaria/neoadiuvante, l'aggiunta del platino ad uno schema standard con antracicline e taxani può essere preso in considerazione.	**Positiva debole**

Leggere capitolo 14- Raccomandazioni prodotte secondo metodologia GRADE

Una recente revisione sistematica e metanalisi ha incluso 9 studi randomizzati (n=2109) che hanno confrontato regimi chemioterapici neoadiuvanti contenenti platino vs regimi privi di platino per pazienti con carcinoma mamamrio triplo negativo[37]. Dei 9 studi inclusi, 7 confrontavano carboplatino + antracicline e taxani vs antracicline e taxani, di cui 5 (GEICAM/2006-3, GeparSixto GBG66, CALGB 40603 Alliance, UMIN000003355 and BrighTNess) presentavano lo stesso backcbone chemioterapico con antracicline e taxani nei due bracci di randomizzazione. La metanalisi di questi 5 studi ha mostrato come l'aggiunta di platino si associ ad un'aumentata probabilità di ottenere una risposta patologica completa (54.2% vs 37.1% OR 2.04; 95% CI 1.39-3.00). Tuttavia, l'utilizzo del platino non è risultato associato ad una significativamente migliore sopravvivenza in termini di event-free survival o overall survival.
Nel CALGB 40603, l'aggiunta di carboplatino ogni tre settimane a paclitaxel settimanale seguita da AC "dose-densa" non ha dimostrato a distanza di 3 anni alcun beneficio in EFS[38]; al contrario, nello studio GeparSixto l'aggiunta di carboplatino, a uno schema chemioterapico non convenzionale, ha permesso di osservare un miglioramento assoluto del 10% in termini di sopravvivenza (EFS)[39]. Infine, dall'analisi di tutti e 9 gli studi inclusi, il trattamento con platino è risultato associato ad un maggior rischio di tossicità ematologiche di grado 3-4.

La terapia biologica

Incorporazione dei farmaci antiHER2 - Nelle pazienti con carcinoma mammario HER2+ candidate a

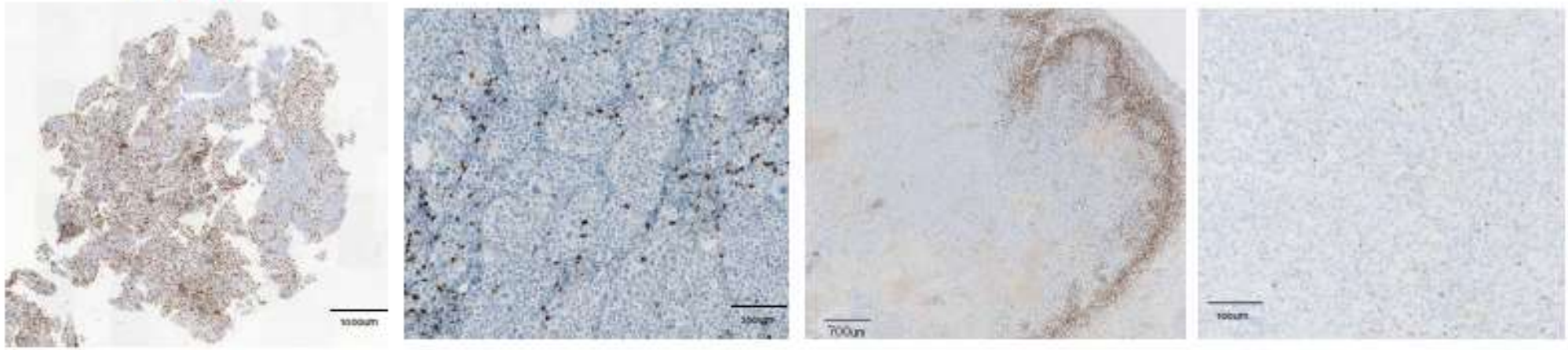
Current approaches largely address patients with pre-existing immunity

Pre-existing Immunity (20-30%?)

Non-functional immune response

Excluded infiltrate

Immune desert



CD8/IFNγ signature

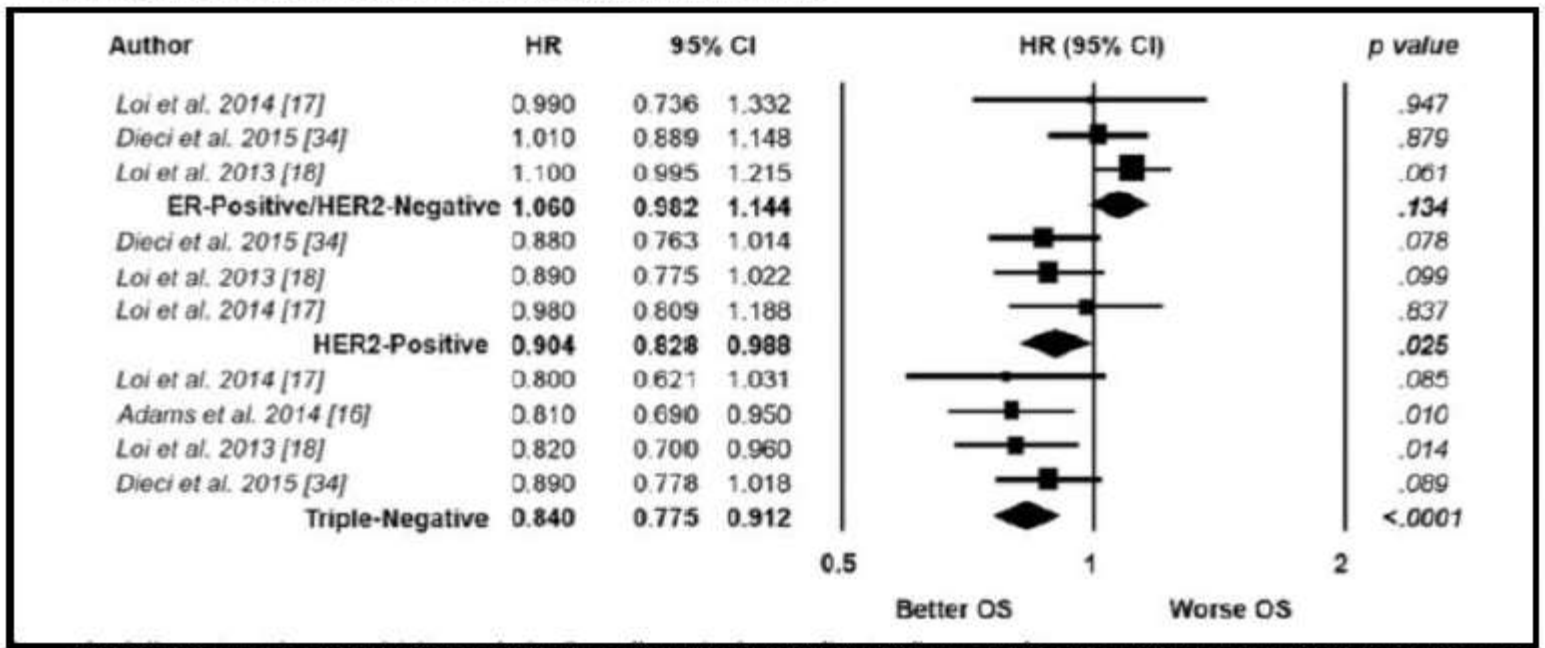
Response to immunotherapy

Many or most patients may lack pre-existing immunity

- Challenges with endpoints in combination trials
- Difficulty in assessing the success of a given combination when one agent is significantly more active than the other
- The utility of traditional radiographic response criteria for cancer immunotherapy (CIT) may be limited by the non-classical tumor kinetics (“pseudoprogression”) observed in some patients with clinical benefit
- ORR and PFS have underestimated the overall survival (OS) benefit in monotherapy studies with PD1/PDL-1 inhibitors: how do we keep later line cross-over from confounding and prolonging studies?
- Immune modified RECIST may capture of benefit of atypical responses otherwise missed with RECIST 1.1
- oAll atezolizumab trials include RECIST 1.1 and imRECIST

TILs in Early Breast Cancer

Table 2. Characteristics of adjuvant randomized trials evaluating tumor-infiltrating lymphocytes in stromal compartments as continuous variable per 10% increase according to disease subtype



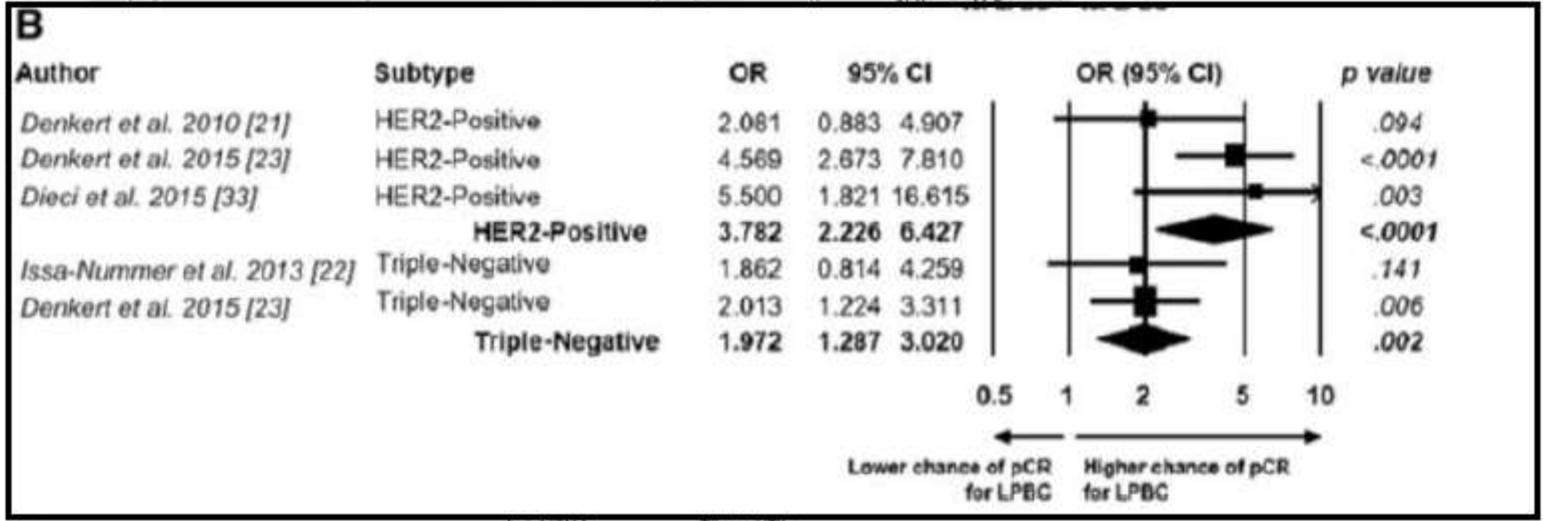
cyclophosphamide, methotrexate, and 5-fluorouracil; CT, chemotherapy; D, docetaxel; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide; FinHER, Finland Herceptin; H&E, hematoxylin and eosin staining; HER2-pos, HER2-positive breast cancer; HR, hazard ratio; iTILs, intratumoral-infiltrating lymphocytes; LPBC, lymphocyte-predominant breast cancer (defined as ≥60% infiltration of stromal or intratumoral lymphocytes); NR, not reported; OS, overall survival; P, paclitaxel; sTILs, stromal tumor-infiltrating lymphocytes; TN, triple-negative breast cancer; TR, trastuzumab; V, vinorelbine.

Carbognin et al, The Oncologist 2016

TILs in Early Breast Cancer

Table 1. Characteristics of neoadjuvant randomized trials evaluating tumor-infiltrating lymphocytes, including lymphocyte-predominant breast cancer assay, according to disease subtype

Author, Year [Reference]	Study	Disease subtype	Patients (n)	Treatment arms	TIL assay	TIL cutoff value	pCR definition	pCR in LPBC (%)	pCR in non-LPBC (%)
Denkert et al., 2010 [21]	GeparTrio	HER2-neg HER2-pos	442 254	TAC ×6 vs. TAC ×8 vs.	sTILs, iTILs in H&E,	Noninfiltrate, partial	ypT0 ypN0	48.1 31.0	12.6 17.8
				+ L vs. P + TR + L→FEC + TR + L		sTILs and iTILs as continuous variable			



Abbreviations: Beva, bevacizumab; CA, carboplatin; EC, epirubicin and cyclophosphamide; EVE, everolimus; FEC: 5-fluorouracil, epirubicin, and cyclophosphamide; H&E, hematoxylin and eosin staining; HER2-neg, HER2-negative breast cancer; HER2-pos, HER2-positive breast cancer; IHC, immunohistochemistry; iTILs, intratumoral-infiltrating lymphocytes; L, lapatinib; LPBC, lymphocyte-predominant breast cancer (defined as ≥60% infiltration of stromal or intratumoral lymphocytes); nplA, nonpegylated lyposomal doxorubicin; P, paclitaxel; pCR, pathological complete response; sTILs, stromal tumor-infiltrating lymphocytes; T, docetaxel; TAC, docetaxel, doxorubicin, and cyclophosphamide; TN, triple-negative breast cancer; TR, trastuzumab; VCAp, vinorelbine and capecitabine.

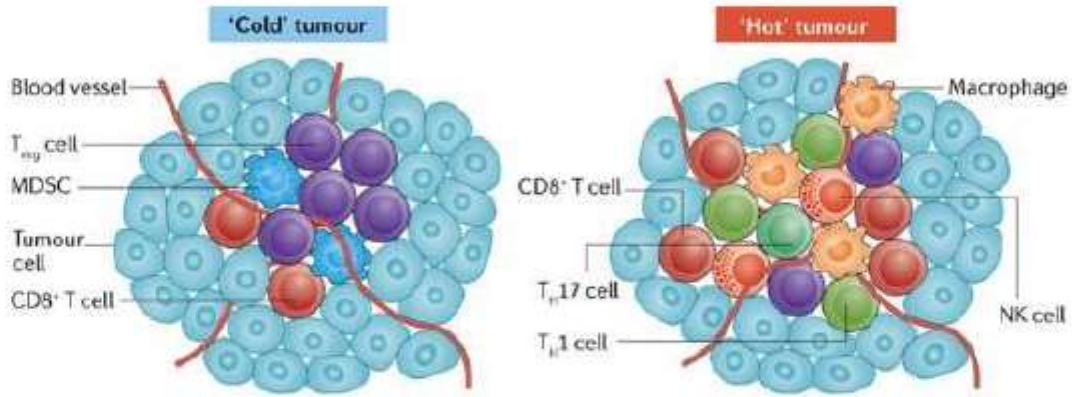
Carbognin et al, The Oncologist 2016

Classifying Cancers Based on T-cell Infiltration and PD-L1

Tumor Microenvironment		Early BC	Ovarian	Melanoma
Type I	TIL+/PD-L1+	21%	57.4%	38%
Type II	TIL-/PD-L1-	24%	5.1%	41%
Type III	TIL-/PD-L1+	2%	0%	1%
Type IV	TIL+/PD-L1-	53%	37.4%	20%
References		Buisseret 2016	Webb 2016	Teng 2015

Type I: Adaptive immune resistance
Type II: Immunological ignorance
Type III: Intrinsic Induction
Type IV: Tolerance

Cold and Hot Tumours

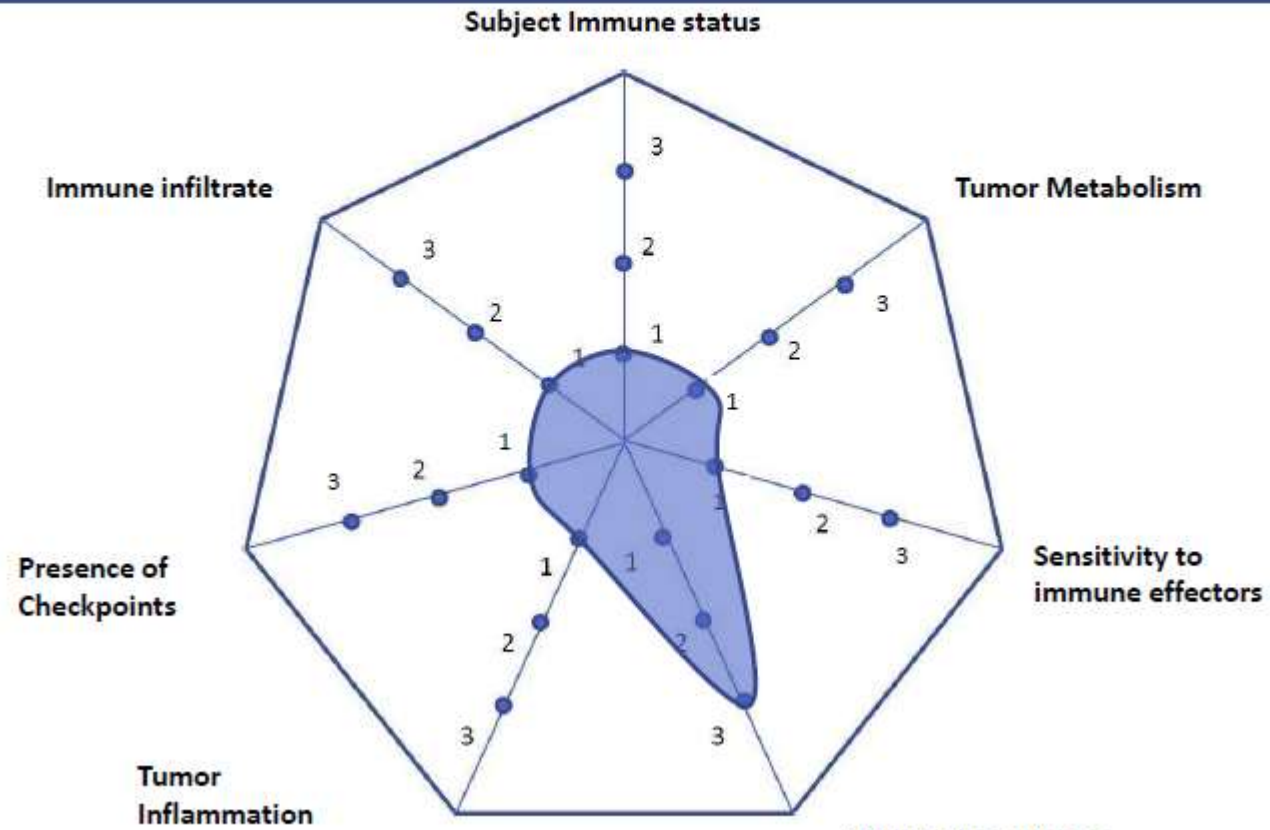


	'Cold' tumour	'Hot' tumour
Biological characteristics	• Epigenetic silencing • Active β-catenin signalling • Mesenchymal-like cells • Stem cell-like cells • Less-differentiated cells	• Epigenetic reprogramming • Suppressed β-catenin signalling • Epithelial cells • Highly differentiated cells • High PDL1 expression
Immunological characteristics	• Enriched in immunosuppressive cytokines • High numbers of T_{reg} cells and MDSCs • Few T_H1 cells, NK cells and CD8⁺ T cells • Few functional APCs	• Enriched in T_H1-type chemokines • High numbers of effector immune cells (T_H1 cells, NK cells and CD8⁺ T cells) • High numbers of functional APCs

Nature Reviews | Immunology

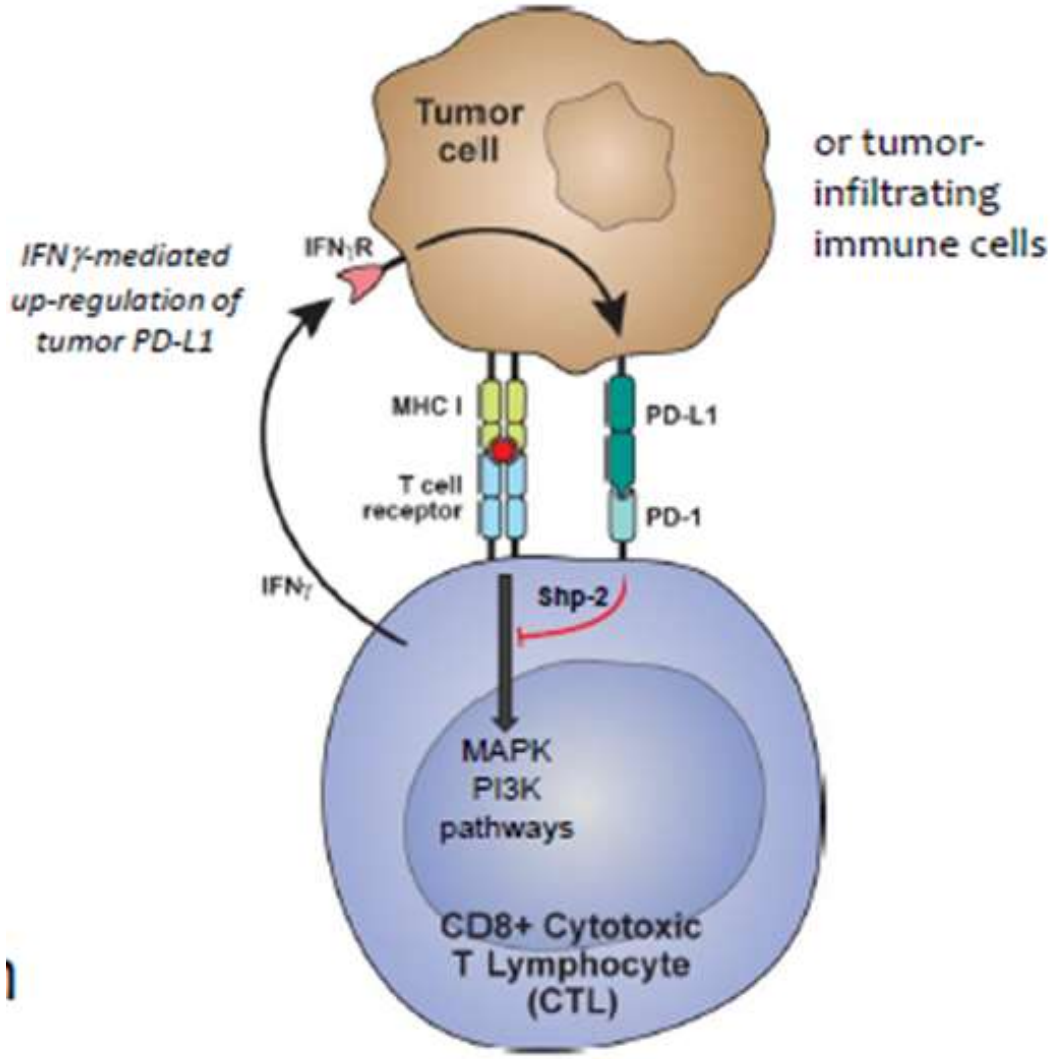
Nagasheth et al, Nature Reviews Imunology 2017

Immunogram; late stage disease

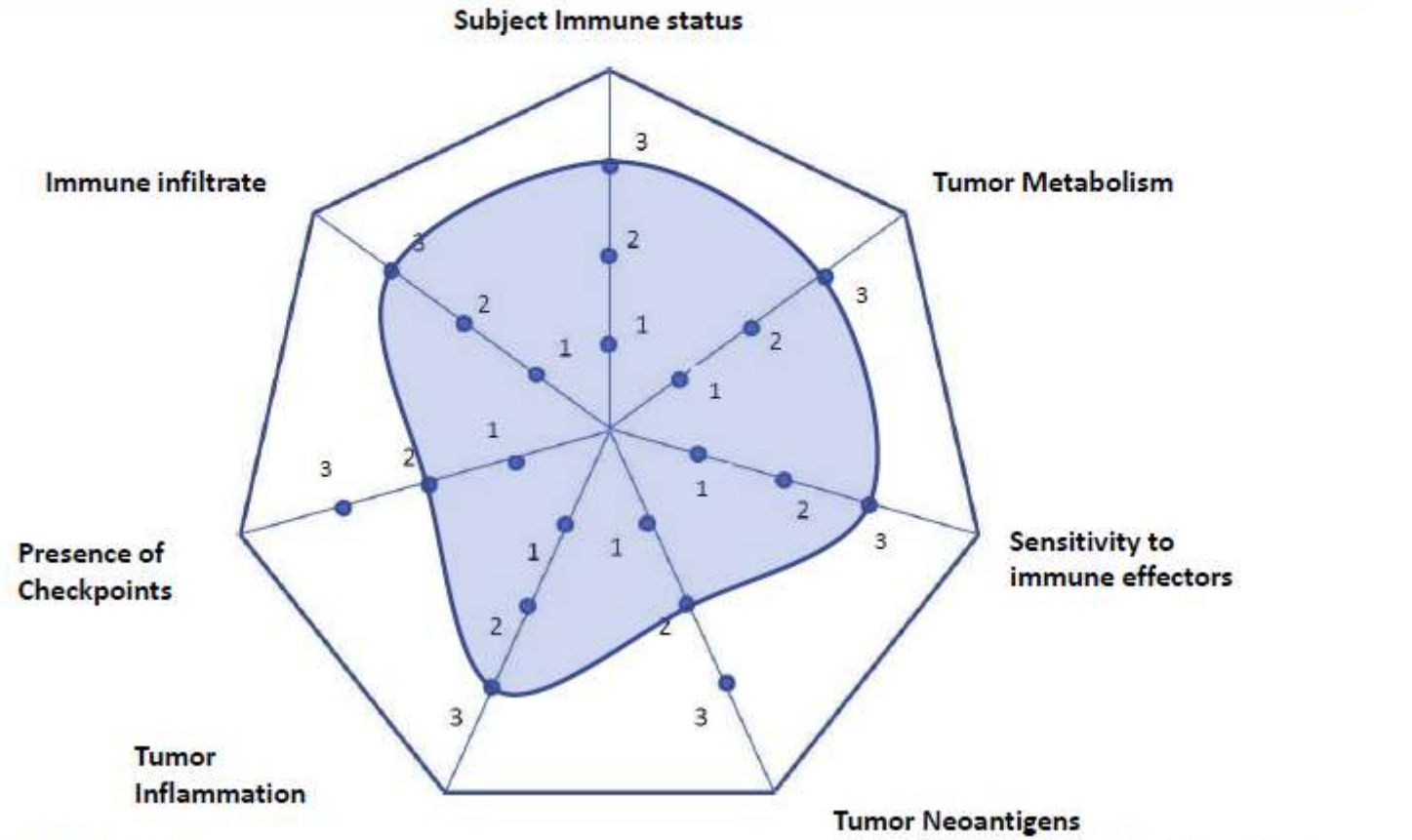


Courtesy of Dr Filippo Montemurro

What we have learned: immunosoppression is a rate limiting step to effective anti-tumor immunity… *for some patients*



Immunogram; earlier stage disease

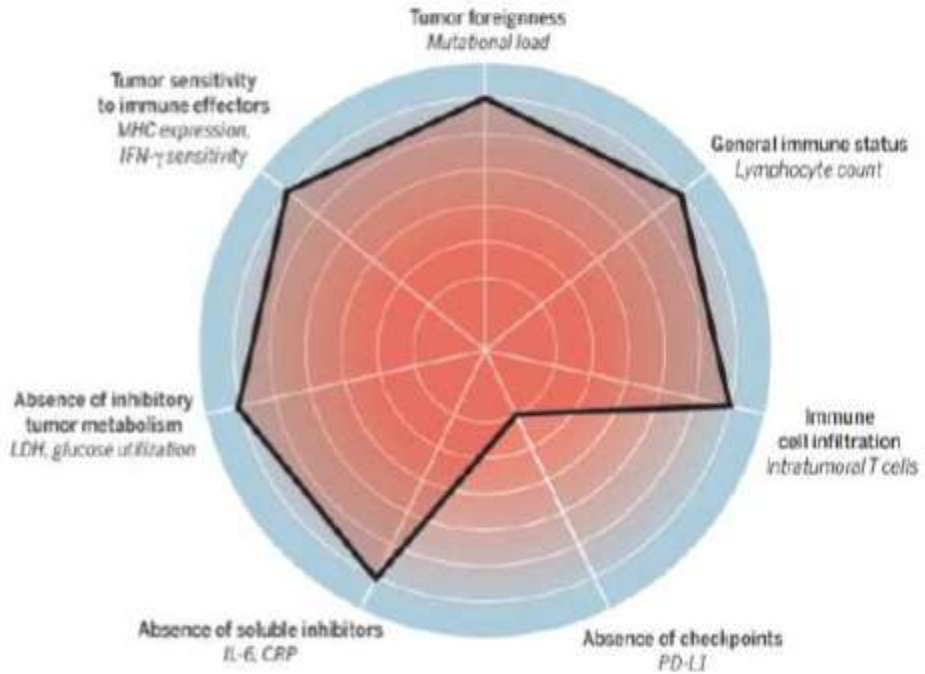


Courtesy of Dr Filippo Montemurro

Conclusion

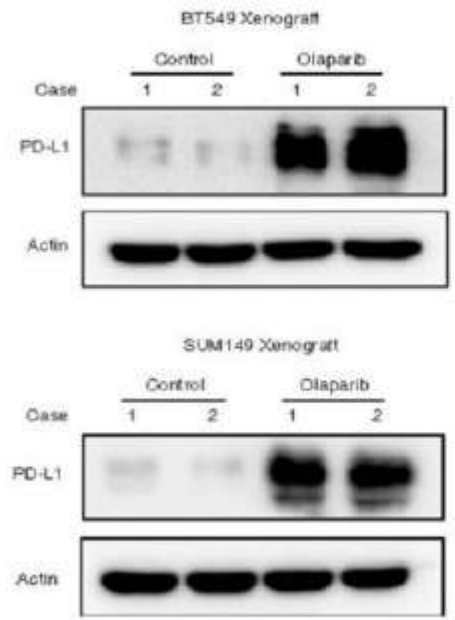
- Immunotherapy represents an intringuing and potentially
- revolutionary approach in BC
- • Immune Checkpoint Inhibitors are active and promising
- especially in TN subtype and in earlier lines of treatment
- • Novel strategies and novel combinations to enhance activity and
- extend spectrum of efficacy of immunotherapy are needed and
- under investigation

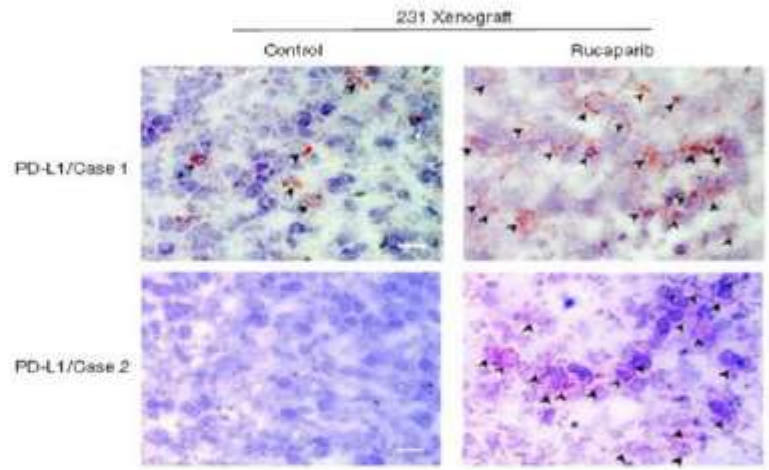
The cancer immunogram



Blank et al, Science 2016

Rationale for combining PARP inhibitors + immune checkpoint inhibitors

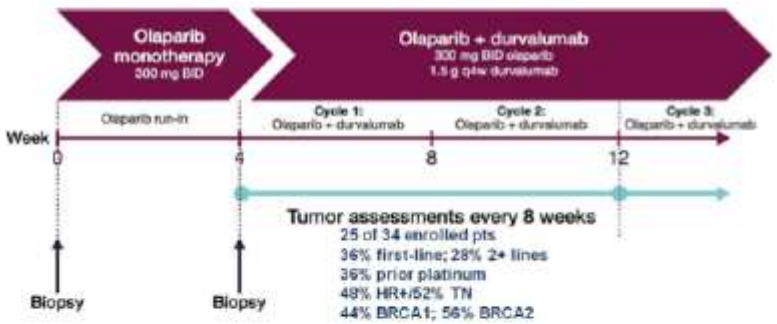




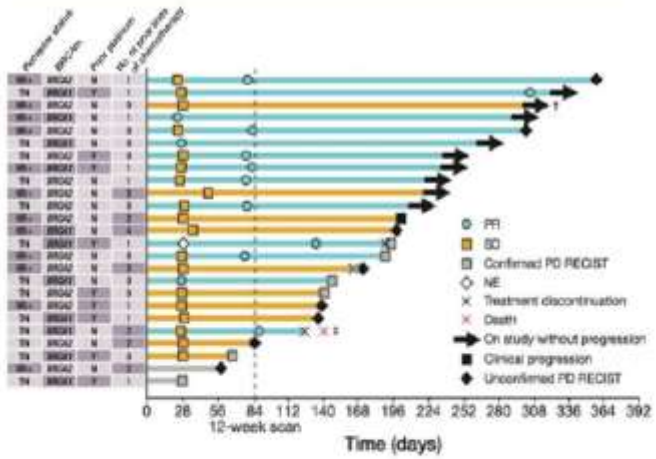
Jiao et al, Clin Cancer Res 2017

MEDIOLA, phase II basket study of olaparib and durvalumab: gBRCAmut HER2- MBC (n=25)

Best Response by Line of Chemotherapy				
Response	1L	2L	3L	4L
CR	0	0	0	0
PR	6	6	1	0
SD	2	2	2	2
PD	1	1	2	0
Total #	9	9	5	2
ORR	6/9=67%	6/9=67%	1/5=20%	0/2=0%



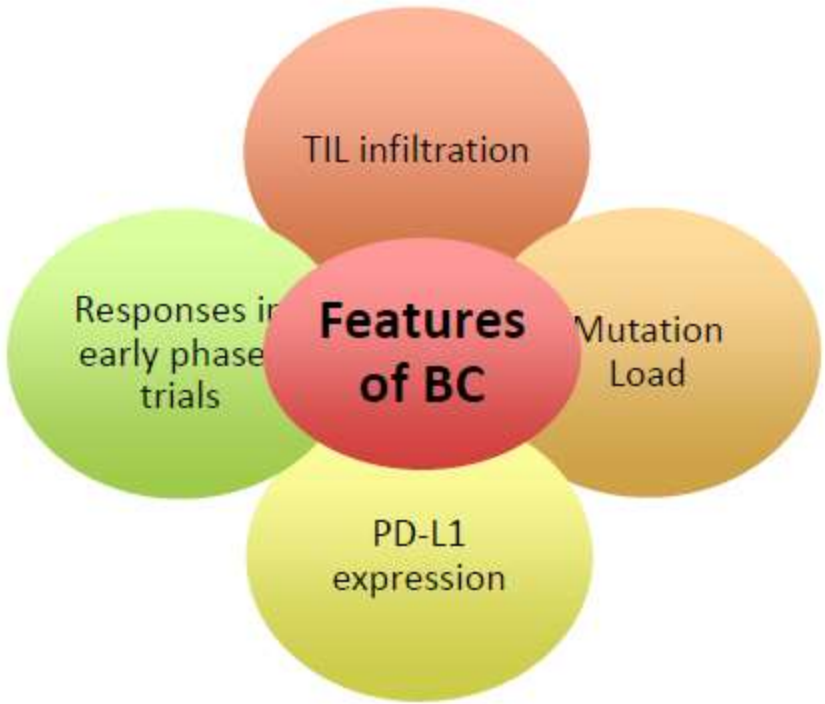
Domcheck et al, SABCS 2017



What is going to challenge the already unstable algorithm for mTNBC?

- Increasing use of platinum in early setting will challenge its role in MBC
  - «ovarian cancer-like» model based on platinum sensitivity for platinum rechallenge or PARPi for gBRCAmut? Need for data and biomarkers.
- Immunotherapy combinations in early lines (CT, PARPi)
  - In patients subgroups (which role of immune biomarkers in I/O combos?)
  - Opportunity for maintenance treatment
  - PARPi in BRCA non mut
- AKT inhibitors + taxane in 1st line

Rationale to develop immunotherapy in BC



Goals of cancer immunotherapy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab versus Ipilimumab in Advanced Melanoma

Caroline Robert, M.D., Ph.D., Jacob Schachter, M.D., Georgina V. Long, M.D., Ph.D., Ana Arance, M.D., Ph.D., Jean Jacques Grob, M.D., Ph.D., Laurent Mortier, M.D., Ph.D., Adil Daud, M.D., Matteo S. Carlino, M.B., B.S., Catriona McNeil, M.D., Ph.D., Michal Lotem, M.D., James Larkin, M.D., Ph.D., Paul Lorigan, M.D., Bart Neyns, M.D., Ph.D., Christian U. Blank, M.D., Ph.D., Omid Hamid, M.D., Christine Mateus, M.D., Ronnie Shapira-Frommer, M.D., Michele Kosh, R.N., B.S.N., Honghong Zhou, Ph.D., Nageatte Ibrahim, M.D., Scot Ebbinghaus, M.D., and Antoni Ribas, M.D., Ph.D., for the KEYNOTE-006 investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer

H. Borghaei, L. Paz-Ares, L. Horn, D.R. Spigel, M. Steins, N.E. Ready, L.Q. Chow, E.E. Vokes, E. Felip, E. Holgado, F. Barlesi, M. Kohlhäufl, O. Arrieta, M.A. Burgio, J. Fayette, H. Lena, E. Poddubskaya, D.E. Gerber, S.N. Gettinger, C.M. Rudin, N. Rizvi, L. Crinò, G.R. Blumenschein, Jr., S.J. Antonia, C. Dorange, C.T. Harbison, F. Graf Finckenstein, and J.R. Brahmer

The NEW ENGLAND JOURNAL of MEDICINE

MARCH 16, 2017

Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma

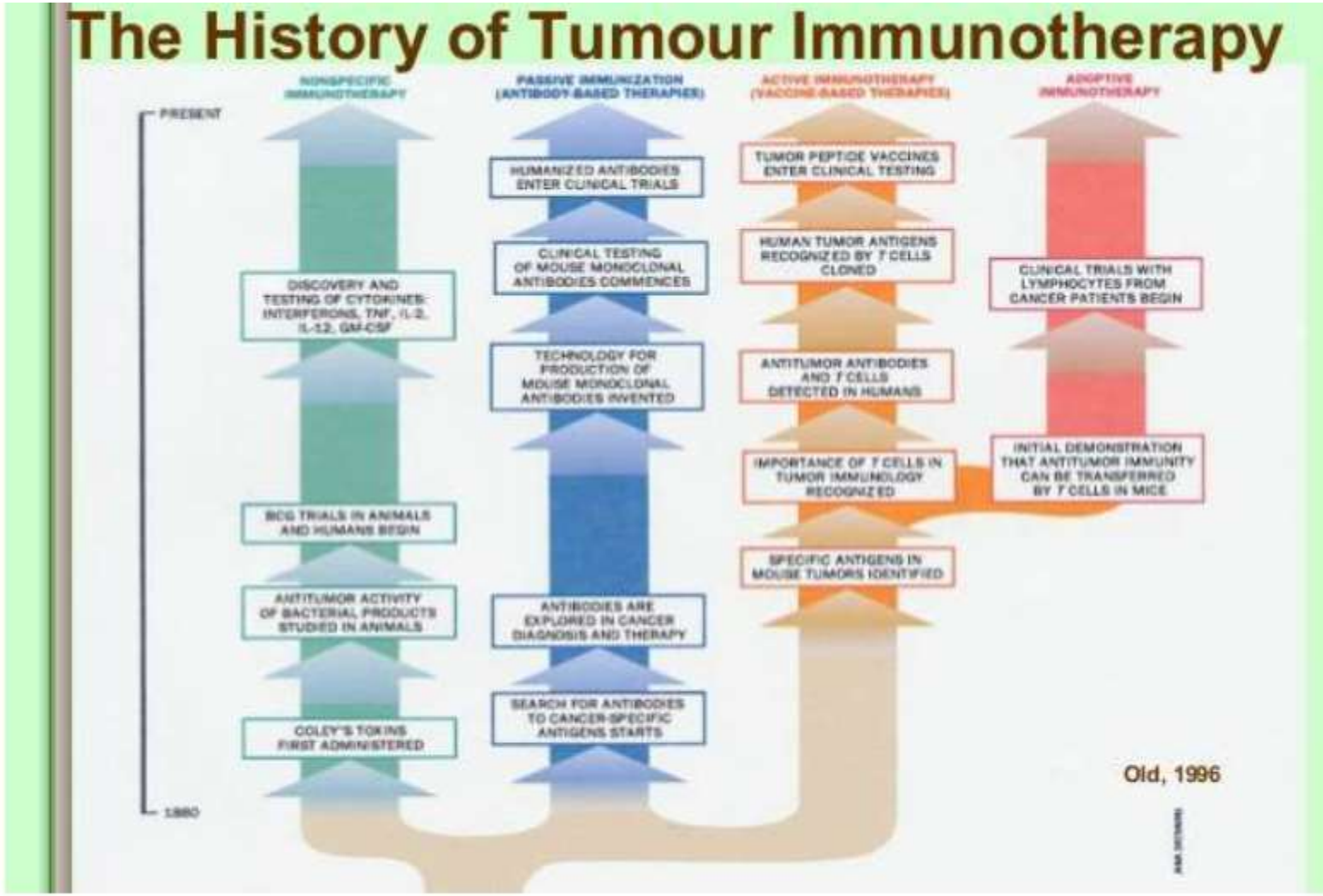
J. Bellmunt, R. de Wit, D.J. Vaughn, Y. Fradet, J.-L. Lee, L. Fong, N.J. Vogelzang, M.A. Climent, D.P. Petrylak, T.K. Choueiri, A. Necchi, W. Gerritsen, H. Gurney, D.I. Quinn, S. Culine, C.N. Sternberg, Y. Mai, C.H. Poehlein, R.F. Perini, and D.F. Bajorin, for the KEYNOTE-045 Investigators*

VOLUME 36 · NUMBER 8 · MARCH 10, 2018

JOURNAL OF CLINICAL ONCOLOGY

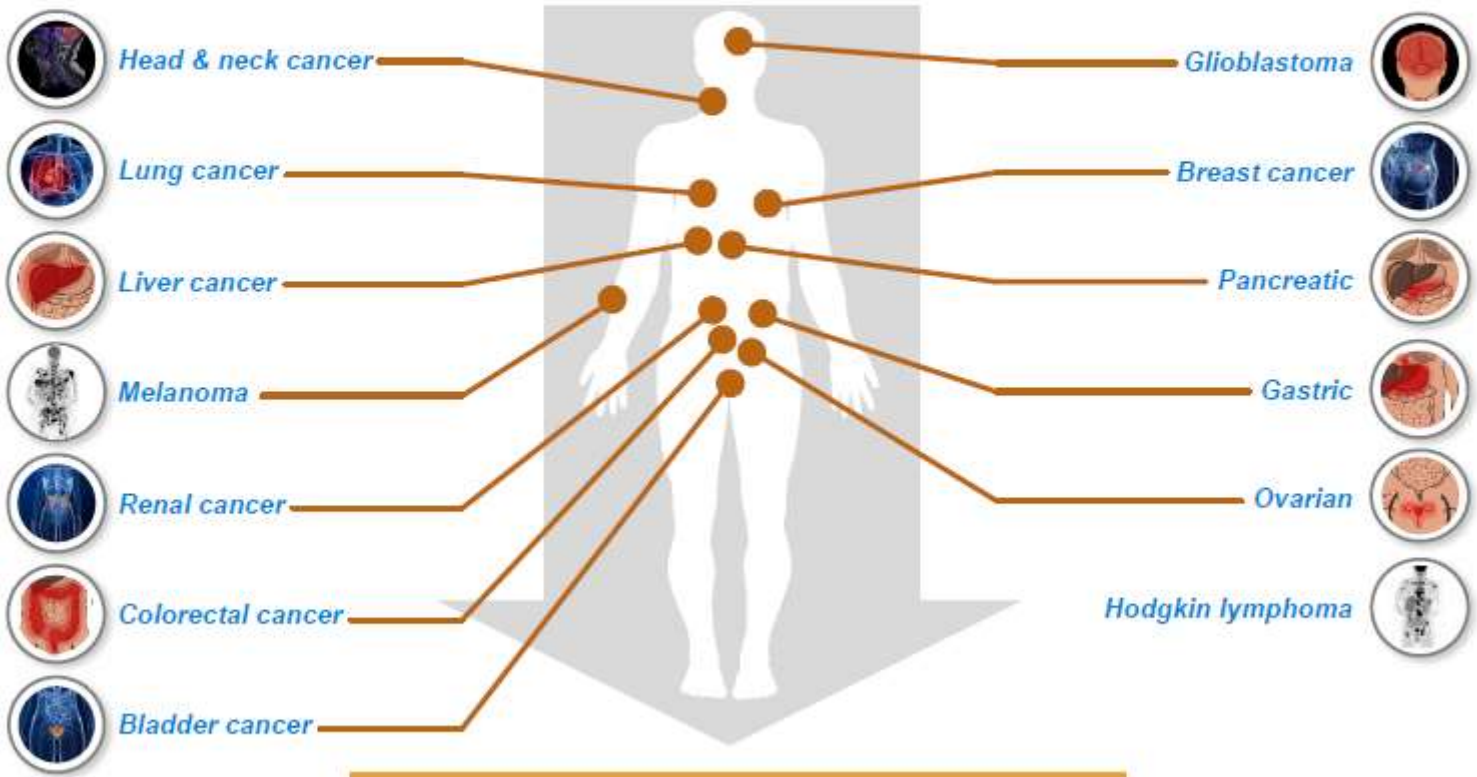
ORIGINAL REPORT

Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair–Deficient/Microsatellite Instability–High Metastatic Colorectal Cancer



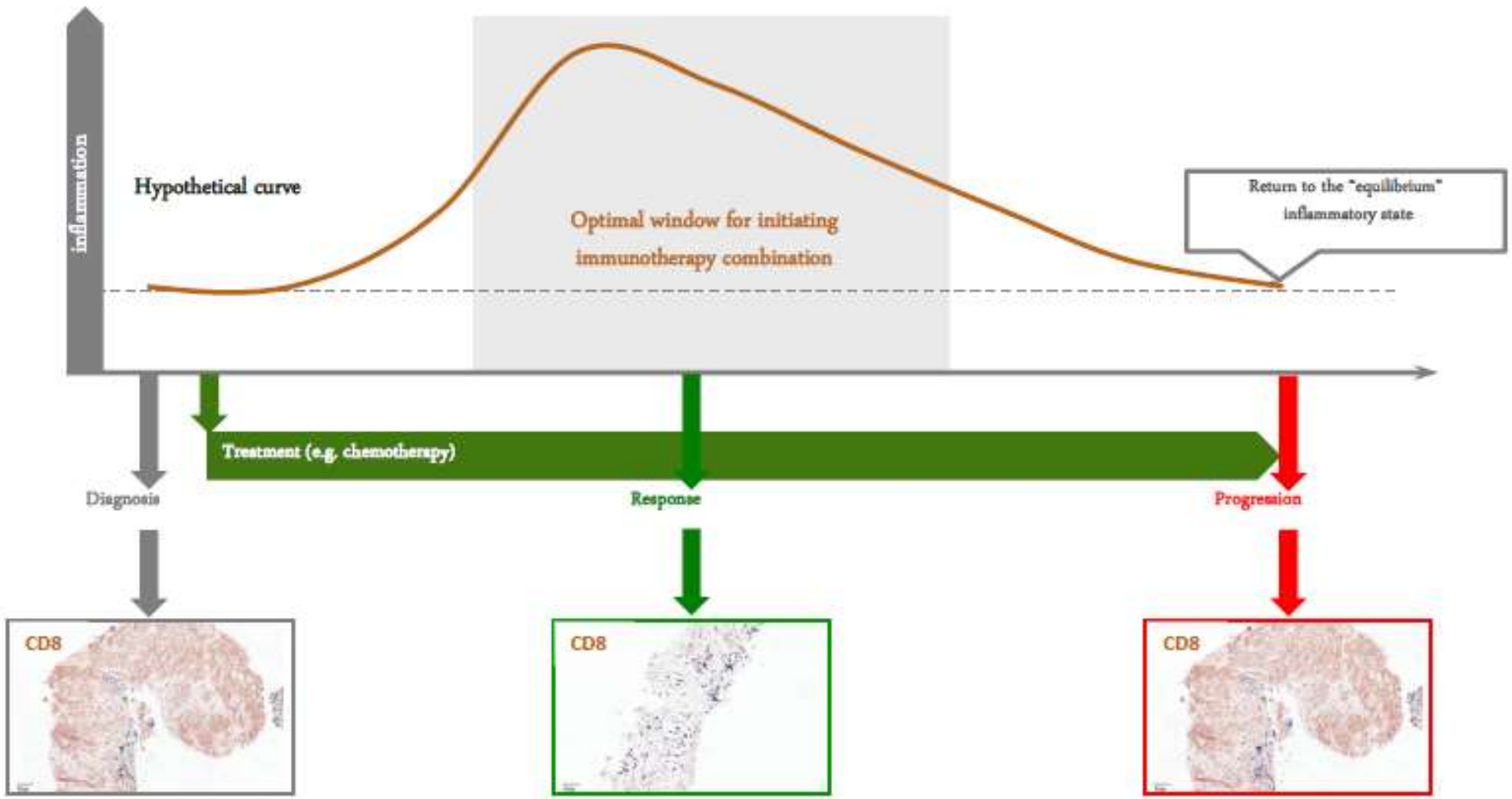
Investigative Clinical Oncology

Broad activity for anti-PD-L1/PD-1 in human cancer



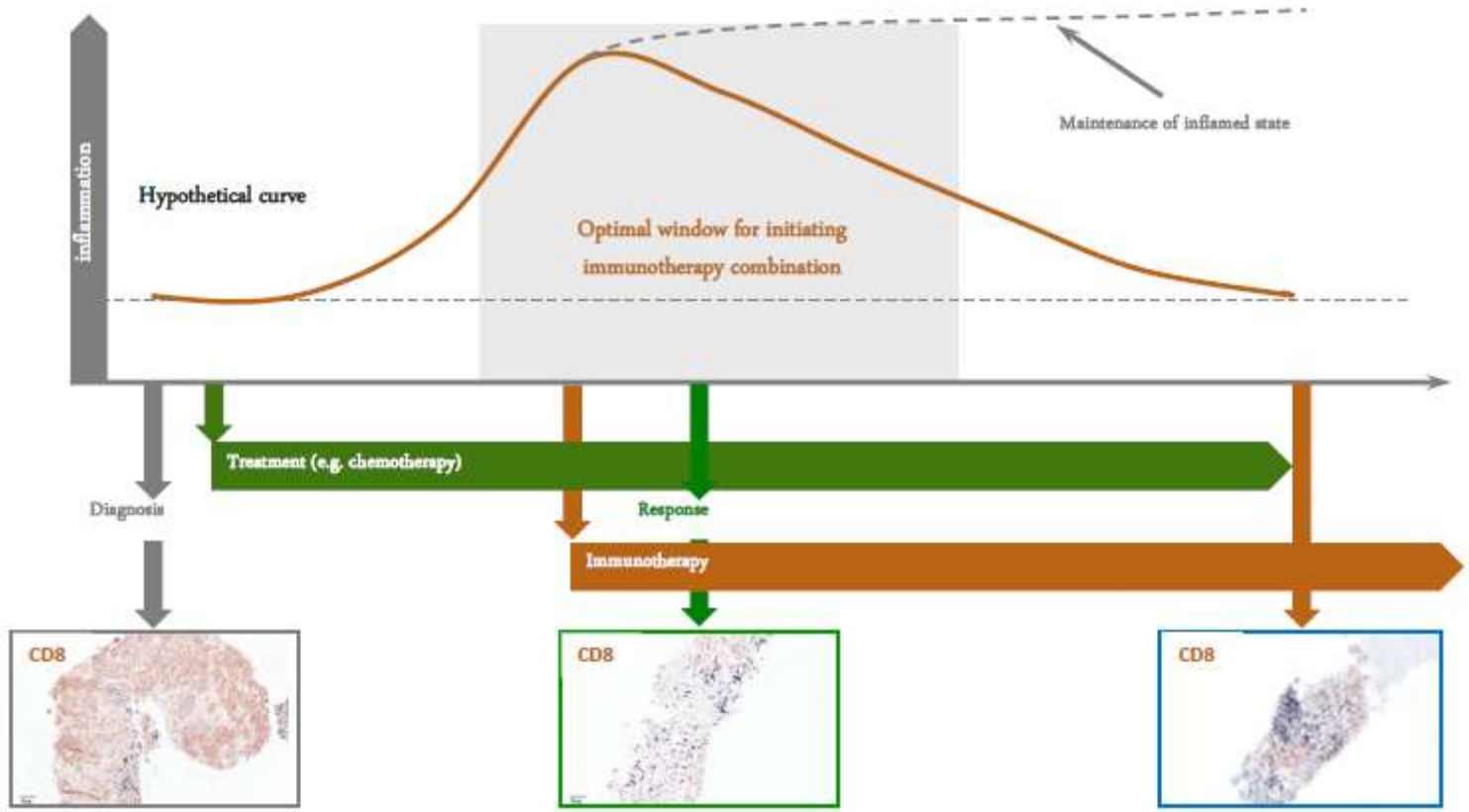
Broad activity, but only subset of patients benefit: ~10-30%

Modulation of tumor immune status by chemotherapy may be transient



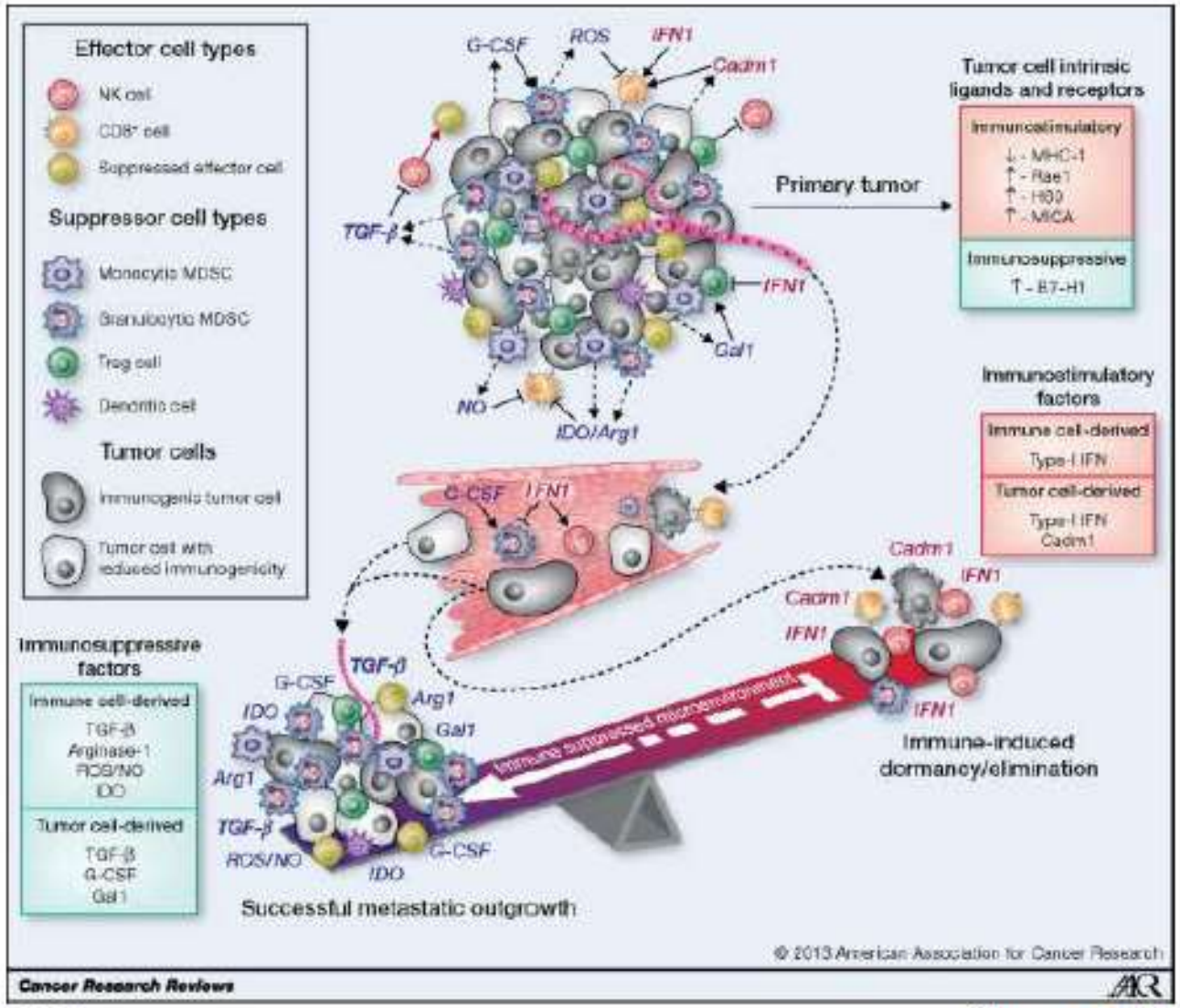
CD8 staining images are illustrative

Simultaneous combinations may help to maintain and extend tumor inflamed state



CD8 staining images are illustrative

Immunosurveillance and immunoediting balance



Clinical Oncology

Slaney et al,Cancer Research 2013

Attempt to design a treatment algorithm for mTNBC: key considerations

- Metastatic TNBC pts
  - Most received A-T as adjuvant/neoadjuvant treatment
  - Visceral metastases
  - Poor survival from the onset of MBC
  - Limited options available with limited efficacy

→ Clinical trials!
→ A long-term treatment sequence is not possible (high attrition rate)
→ Best option first

Treatment options for metastatic TNBC

Platinum for gBRCAmut metastatic TNBC

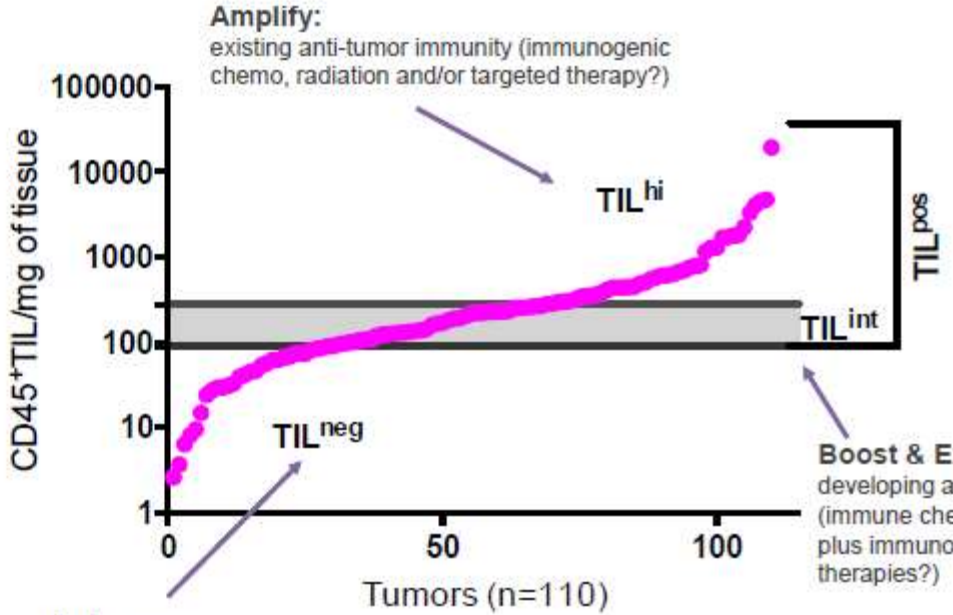
			ORR %		
Study	Drug	Setting	All/ Unselected	BRCA wt	BRCA mut
TBCR009[1]	Cisplatin or Carboplatin	1-2 line	26%	20%	54.5%
BALI[2]	Cisplatin	1-2 line	10%	--	--
Byrski[3]	Cisplatin	1-2 line	--	--	80%

1. Isakoff SJ, J Clin Oncol 2015; 2. Baselga J et al, J Clin Oncol 2013; 3. Byrski T et al, Breast Cancer Res 2012

What is going to challenge the already unstable algorithm for mTNBC?

- Increasing use of platinum in early setting will challenge its role in MBC
  - «ovarian cancer-like» model based on platinum sensitivity for platinum rechallenge or PARPi in gBRCAmut? Need for data and biomarkers.
- Immunotherapy combinations in early lines (CT, PARPi)

TIL infiltration



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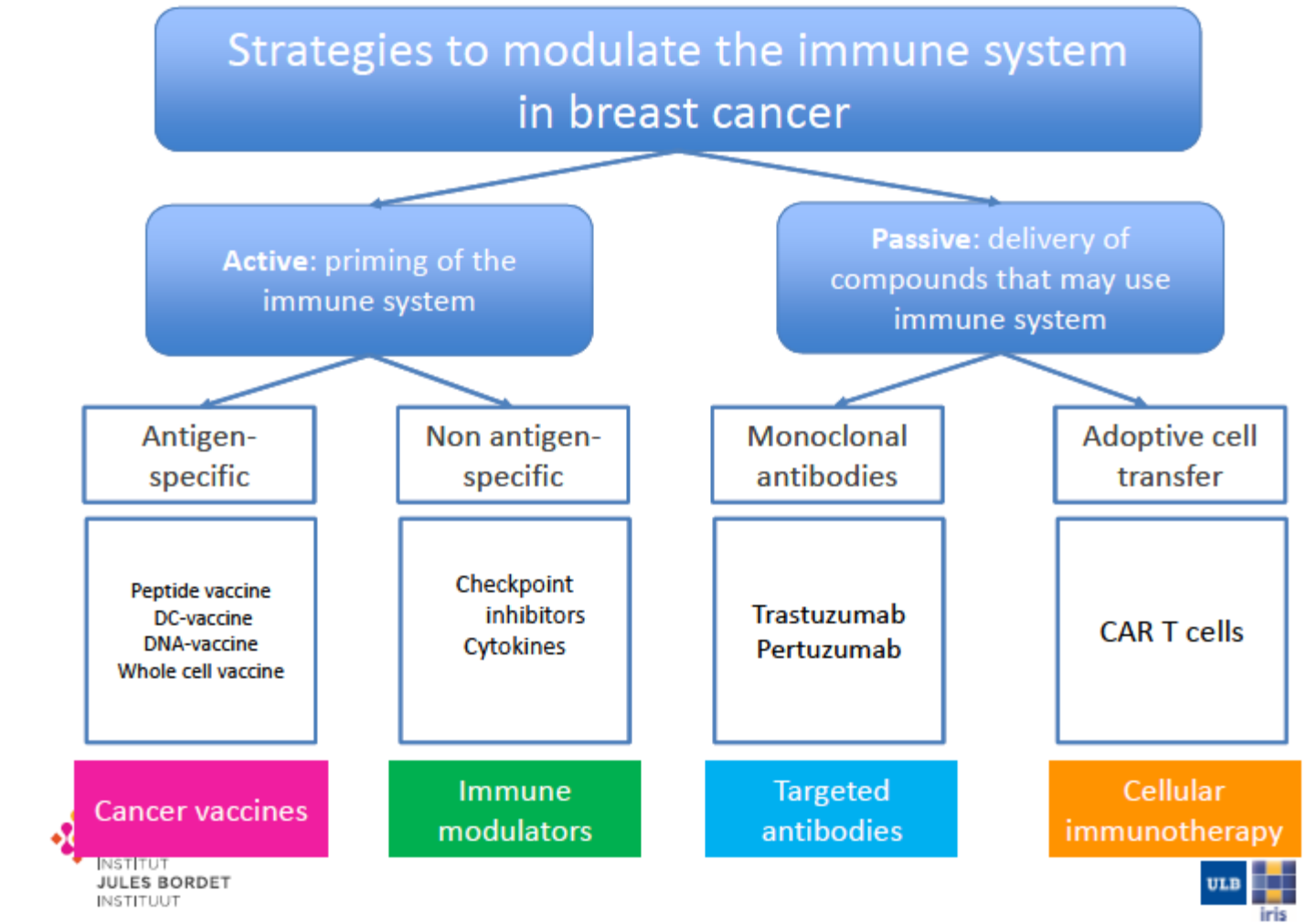
Buisseret et al. Oncoimunology 2017

ULB iris


Strategies to modulate the immune system in breast cancer
Active: priming of the immune system
Passive: delivery of compounds that may use immune system
Antigen-specific
Non antigen-specific
Monoclonal antibodies
Adoptive cell transfer
Peptide vaccine
DC-vaccine
DNA-vaccine
Whole cell vaccine
Checkpoint inhibitors
Cytokines
Trastuzumab
Pertuzumab
CAR T cells
Cancer vaccines
Immune modulators
Targeted antibodies
Cellular immunotherapy
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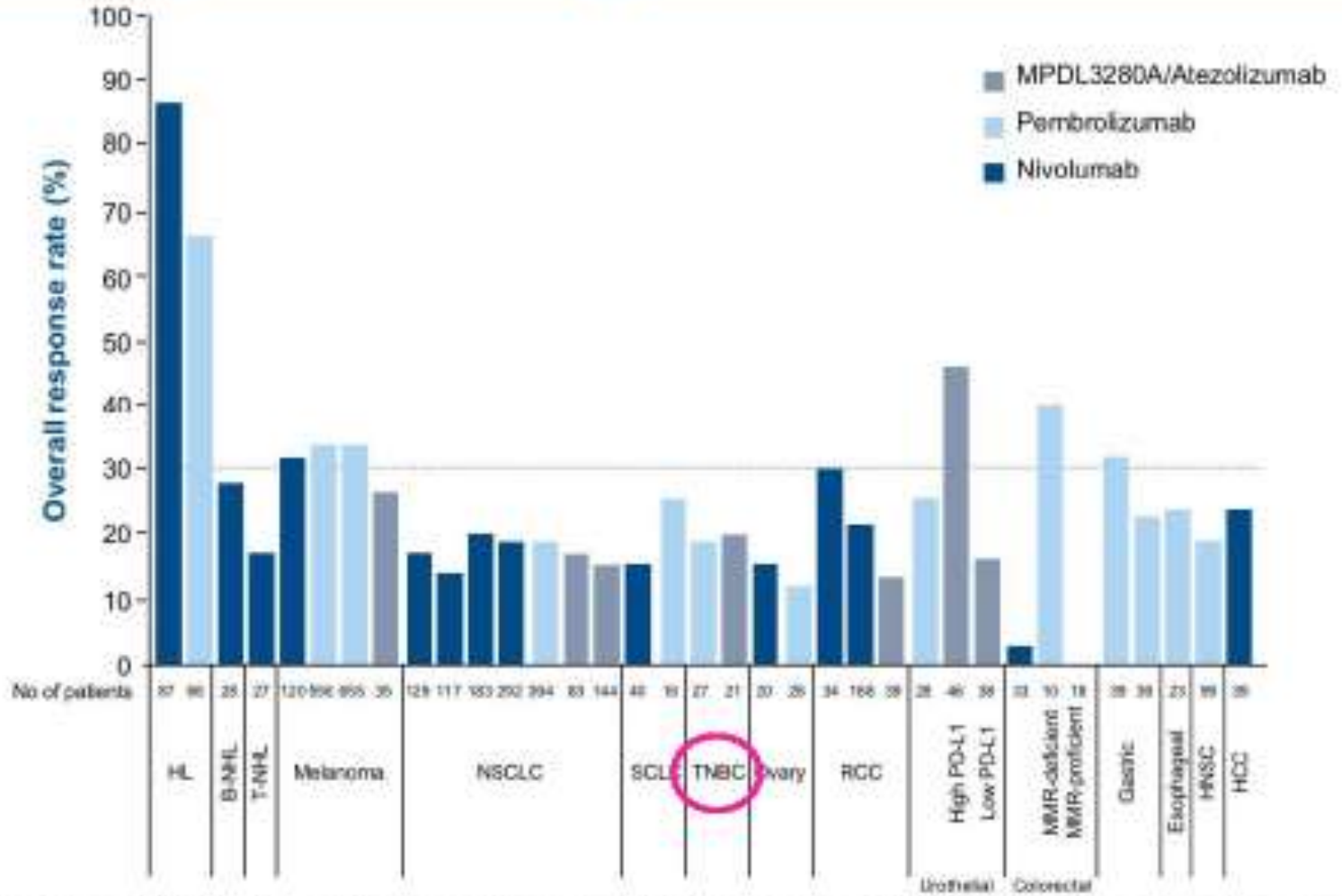
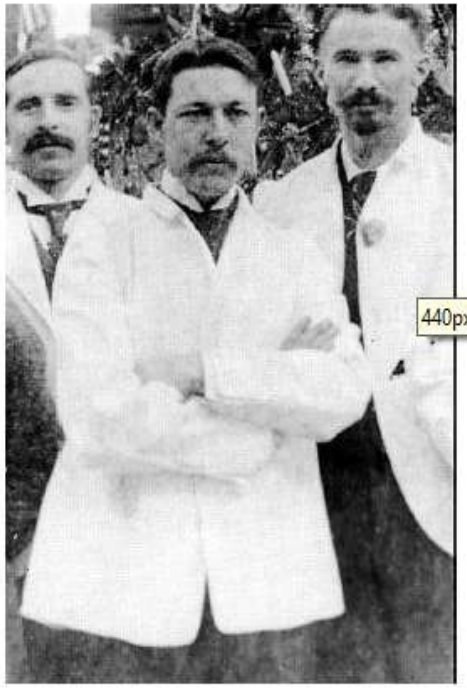
Single Agent Activity of PD-1/PD-L1 Blockade in Relapsed/Refractory Cancer



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.

William Coley and the birth of cancer immunotherapy



New York Times - July 29, 1908

ERYSIPELAS GERMS AS CURE FOR CANCER

Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

MANY CASES CURED HERE

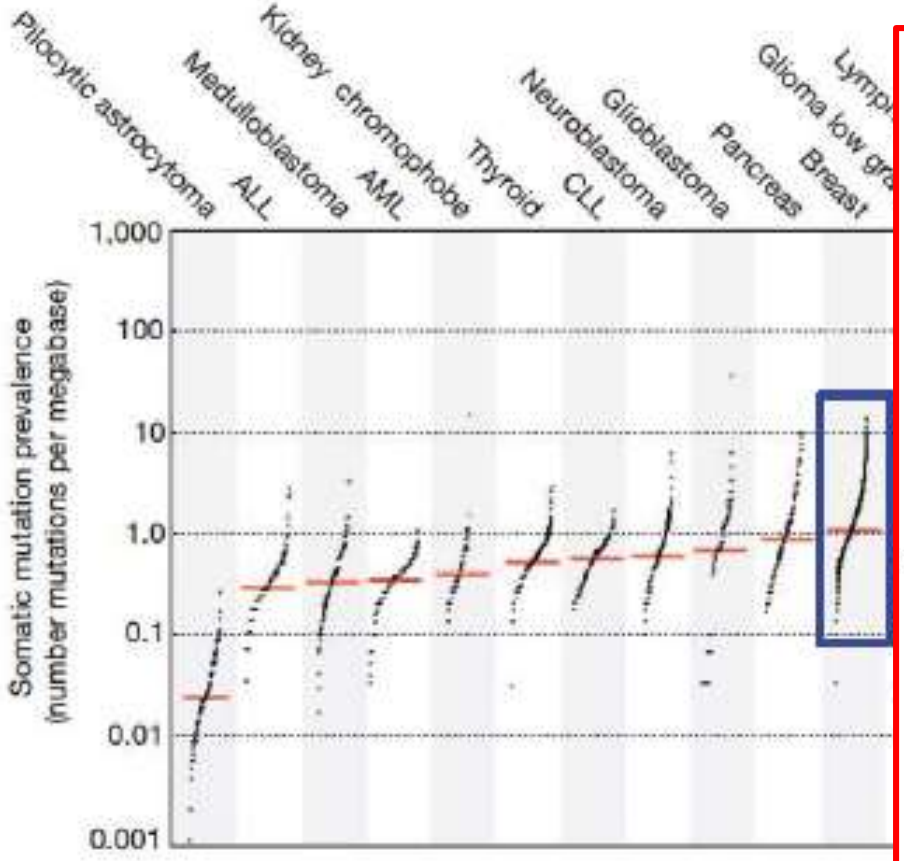
Physician Has Used the Cure for 15 Years and Treated 430 Cases— Probably 150 Sure Cures.

Following news from St. Louis that two men have been cured of cancer in the City Hospital there by the use of a fluid discovered by Dr. William B. Coley of New York. It came out yester-

Elie Metchnikoff & Paul Ehrlich won the Nobel Prize 3 months later

….Ever since the nineteenth-century observation by William Coley that postoperative infections were correlated with cancer regression and subsequently that injections for the treatment of erysipelas induced tumor regression, **the immune system has been suspected to play a role in cancer.**

Since then, a wealth of in vitro and in vivo data has led to an **immunosurveillance /immunoediting** model of cancer progression proposed by Schreiber and colleagues.



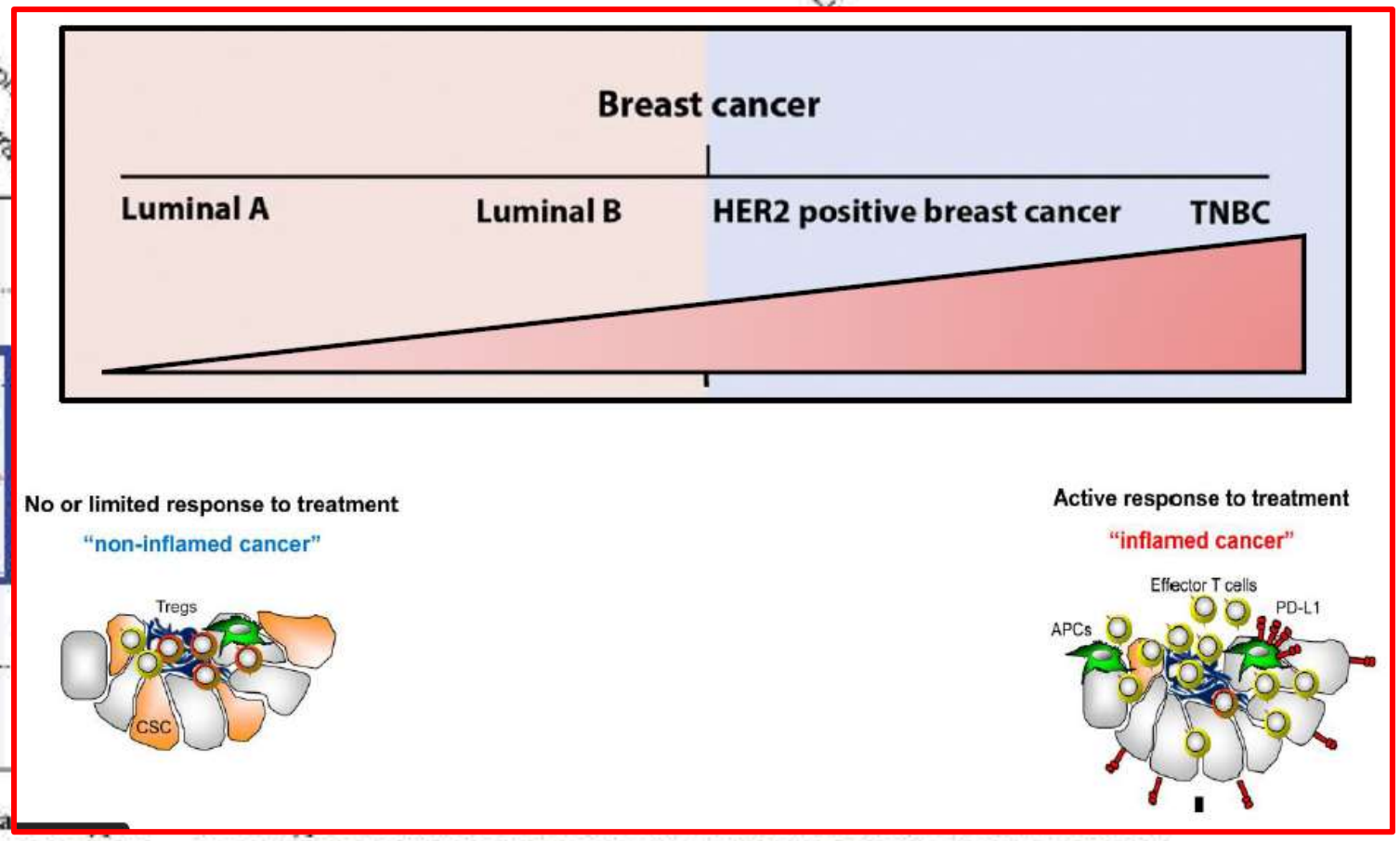
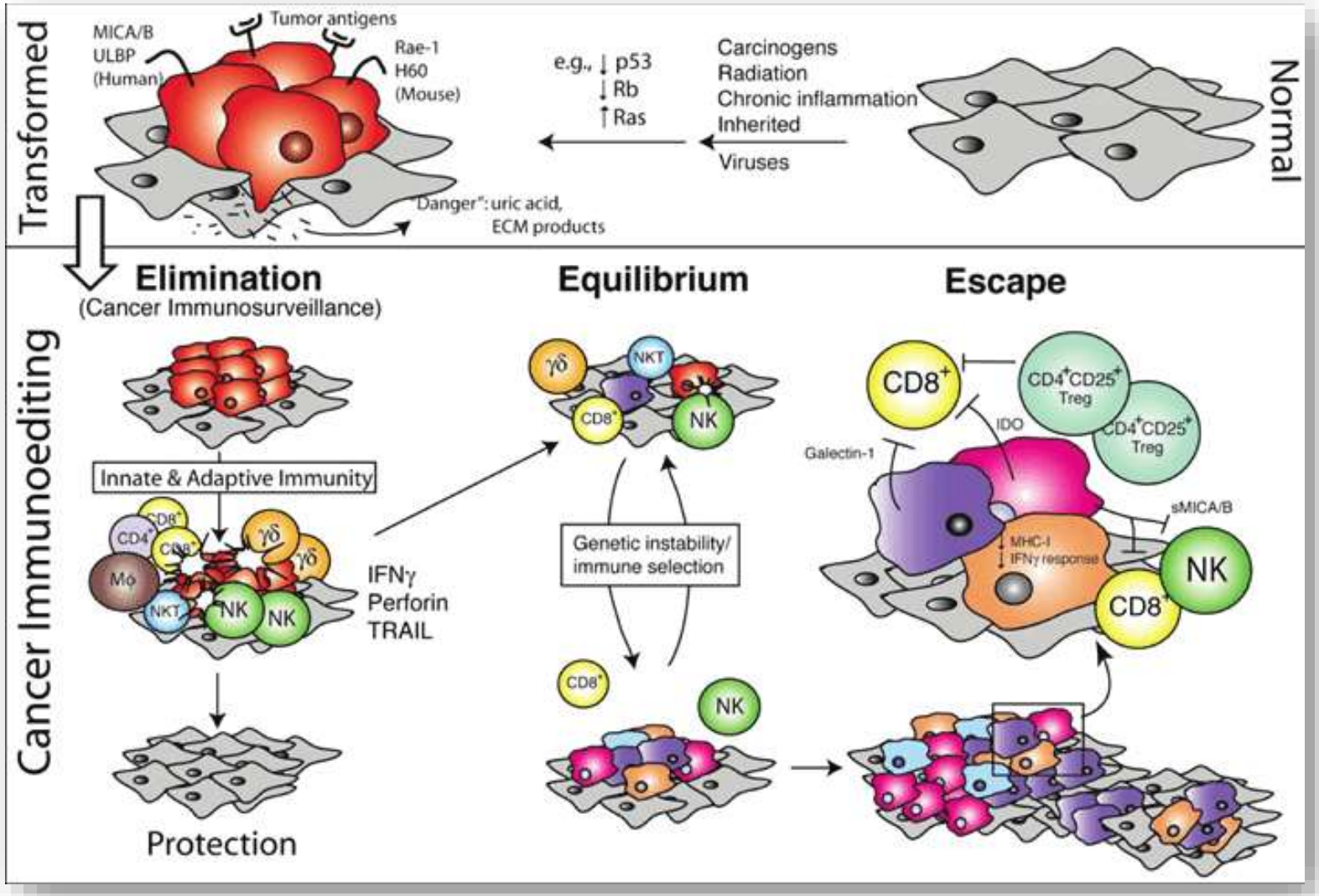


Figure 1 | The prevalence of somatic mutations across human ca
Every dot represents a sample whereas the red horizontal lines are the median numbers of mutations in the respective cancer types. The vertical axis (log scaled) shows the number of mutations per megabase whereas the different

of somatic mutations. We thank G. Getz and colleagues for the design of this figure[26]. ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia.

Alexandrov et al, Nature 2013

Immunotherapy in Cancer: Past, Present and Future



Atezolizumab and Nab-Paclitaxel in metastatic TNBC

Best Overall Response	1L (n = 9)	2L (n = 8)	3L+ (n = 7)	All Patients N = 24
Confirmed ORR (95% CI)[a]	66.7% (29.9, 92.5)	25% (3.2, 65.1)	28.6% (3.7, 71.0)	41.7% (22.1, 63.4)
ORR (95% CI)[b]	88.9% (51.7, 99.7)	75.0% (34.9, 96.8)	42.9% (9.9, 81.6)	70.8% (48.9, 87.4)
CR	11.1%	0	0	4.2%
PR	77.8%	75.0%	42.9%	66.7%
SD	11.1%	25.0%	28.6%	20.8%
PD	0	0	28.6%	8.3%

Response rates were higher for patients who received atezolizumab/nab-paclitaxel treatment as 1L therapy compared to 2L+

[a] Confirmed ORR defined as at least 2 consecutive assessments of complete or partial response.
[b] Including investigator-assessed unconfirmed responses.
Efficacy-evaluable patients were dosed by June 1, 2015, and were evaluable for response by RECIST v1.1. Minimum efficacy follow up was ≥ 3 months.

Adams S, et al. SABCS. 2015 [abstract 850477].