UNIVERSITÀ DEGLI STUDI
DI MILANO

IEO
Istituto Europeo
di Oncologia

Breast Cancer Subtypes and Immunotherapy

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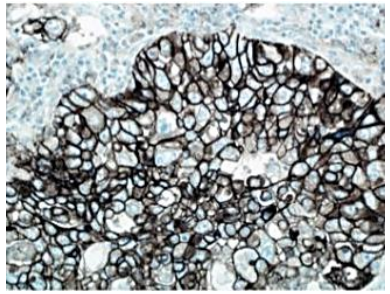
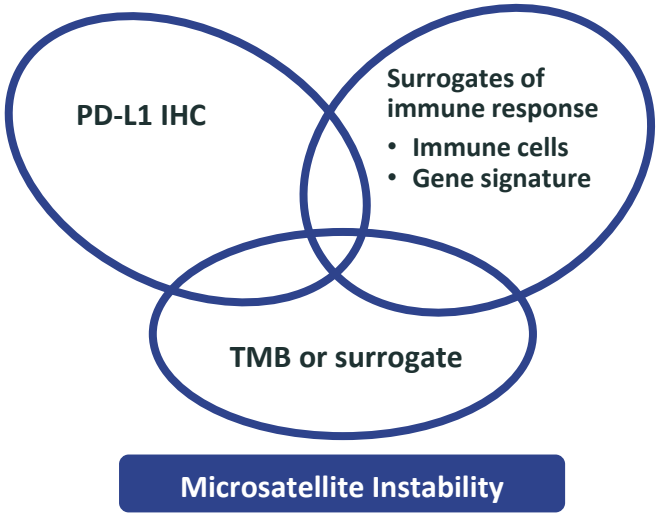
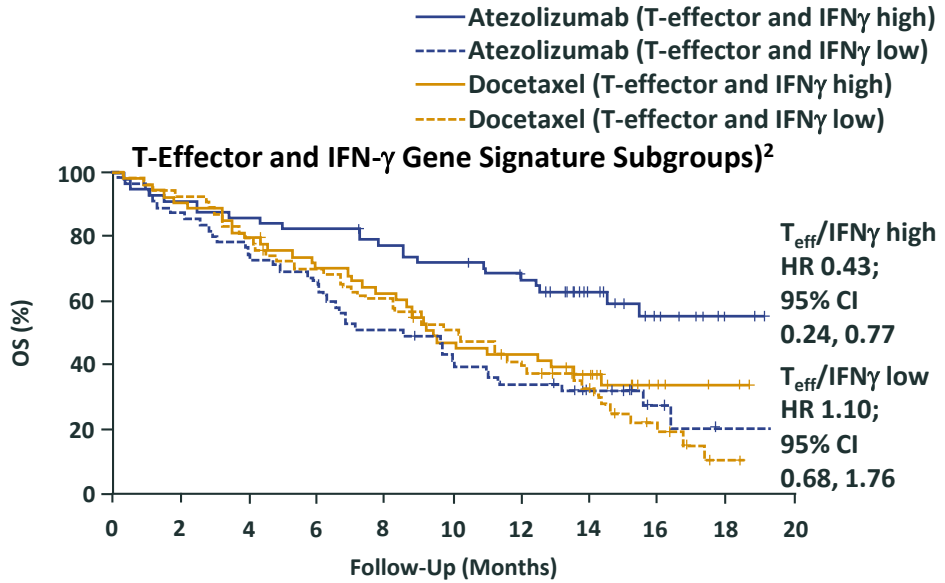
Outline

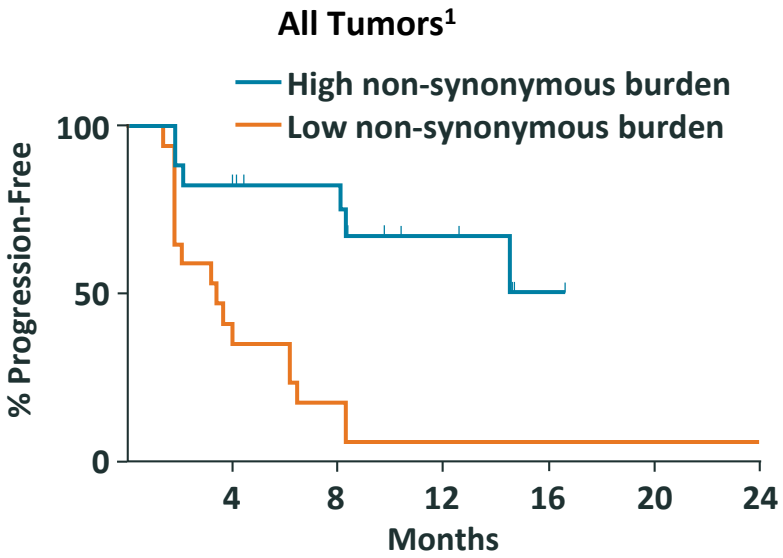
- **Patient Selection for Immunotherapy: Making Sense of Current and Emerging Biomarkers**
- **Molecular characterization of BC immune-phenotypes and TILs**
- **Evidences from clinical trials across BC subtypes**
- **Future perspectives**

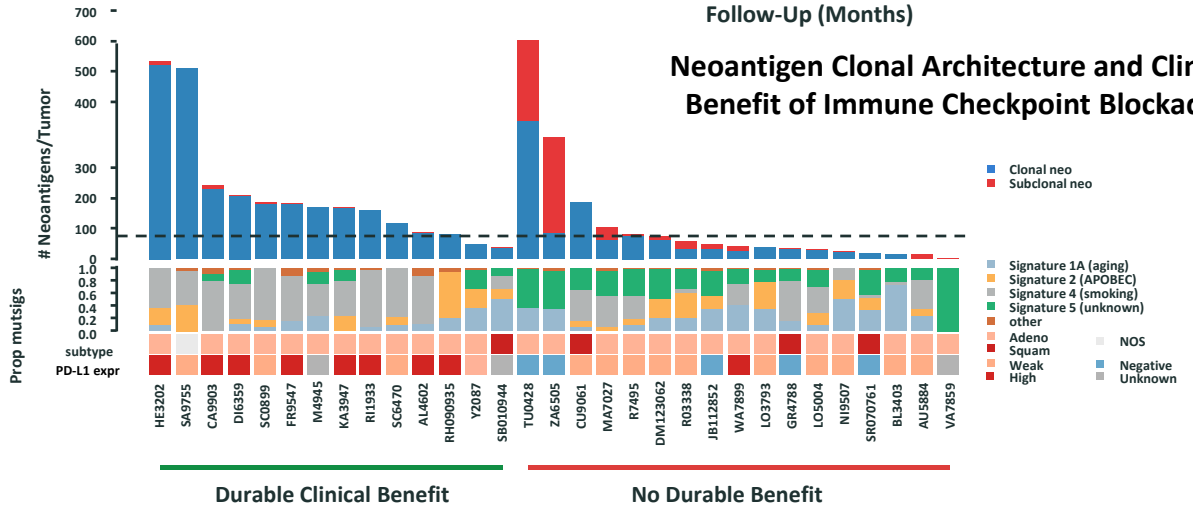
Current Biomarkers for IO











IFN, interferon; IHC, immunohistochemistry; IO, immuno-oncology; NOS, not otherwise specified; OS, overall survival; TMB, tumor mutational burden

1. Rizvi NA, et al. *Science.* 2015;348(6230):124-128. 2. Fehrenbacher L, et al. *Lancet.* 2016;387(10030):1837-1846; 3. McGranahan N, et al. *Science.* 2016;351(6280):1463-1469.

TILs in TNBC

Reference	N	Trial	Endpoint	Subtype Analyzed	Result
Denkert et al. 2010	840	GBG G-3	pCR	All	pCR: 41% in TIL+ BC Validated in G-5
Loi et al. 2013	2009	BIG 2-98	DFS	Preplanned analysis of molecular subtypes	Prognostic impact in TNBC (n = 256): HR: 0.31 (0.11-0.84)
Loi et al. 2014	935	FinHer	DFS	Preplanned analysis of molecular subtypes	Prognostic impact in TNBC (n = 134): HR: 0.31 (0.12-0.8)
Adams et al. 2014	506	ECOG 2197 ECOG 1199	DFS	TNBC	HR: 0.84 (0.74-0.95)
Dieci et al. 2014	278		MFS OS	TNBC	HR: 0.86 (0.77 -0.96) HR: 0.86 (0.77 -0.97)
Denkert et al. 2015	580	Gepar-Sixto trial	pCR	TNBC and HER2	pCR rate was 59.9% in LPBC and 33.8% for non-LPBC (*P*<.001)

Denkert C, et al. *J Clin Oncol.* 2010;28(1):105-113. Loi S, et al. *J Clin Oncol.* 2013;31(7):860-867. Loi S, et al. *Ann Oncol.* 2014 Aug;25(8):1544-1550. Adams S, et al. *J Clin Oncol.* 2014;32(27):2959-2966. Dieci MV, et al. *Ann Oncol.* 2014;25(3):611-618. Denkert C, et al. *J Clin Oncol.* 2015;33(9):983-991.

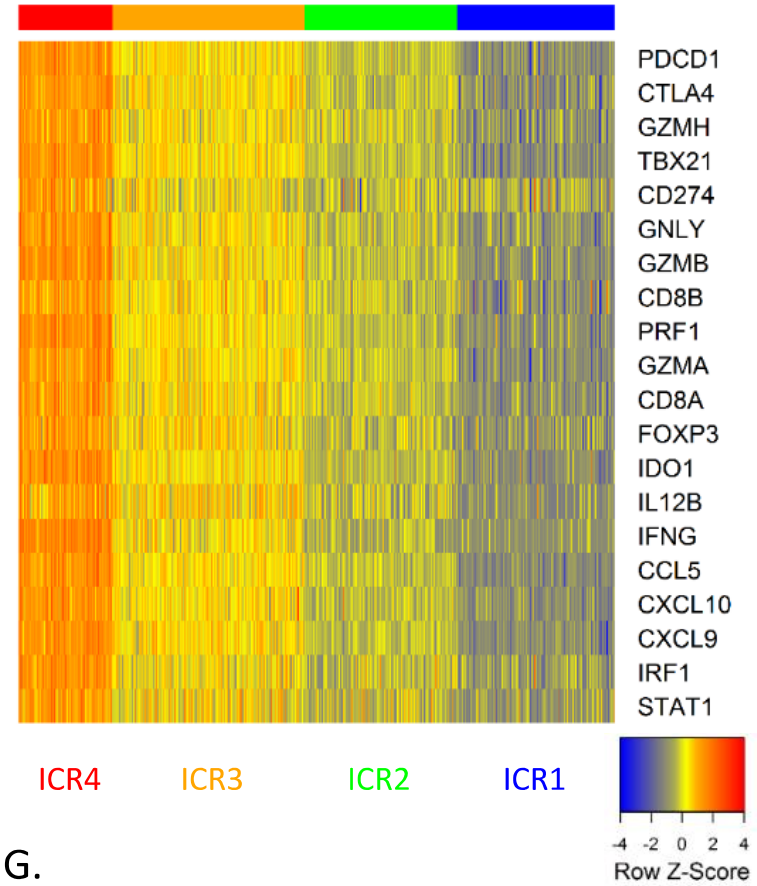
Immune-Signatures

Reference	# of Patients	Signatures	ER-	HER2+	ER+ Lum B	ER+ Lum A
Teschendorff et al. 2007	1056	7-gene immune module	+			
Alexe et al. 2007	286	651 lymphocyte-associated genes		+		
Schmidt et al. 2008	788	B-cell metagene	+	+	+	
Desmedt et al. 2008	1605	Stat1 metagene	+	+		
Rody et al. 2009	1781	Lymphocyte-specific kinase (LCK)	+	+		
Bianchini et al. 2010	684	B-cell/plasma cell metagene	+	+	+	
Criscitiello et al 2018	99	4-gene signature	+	-	-	-

Teschendorff AE, et al. *Genome Biol.* 2007;8(8):R157. Alexe G, et al. *Cancer Res.* 2007;67(22):10669-10676. Schmidt M, et al. *Cancer Res.* 2008;68(13):5405-5413. Desmedt C, et al. *Clin Cancer Res.* 200814(16):5158-5165. Rody A, et al. *Breast Cancer Res.* 2009;11(2):R15. Bianchini G, et al. *Cancer Res.* 2010;70(21):8852-8862.

Top 21 differentially expressed pathways between ICR 1 and ICR 4

C.



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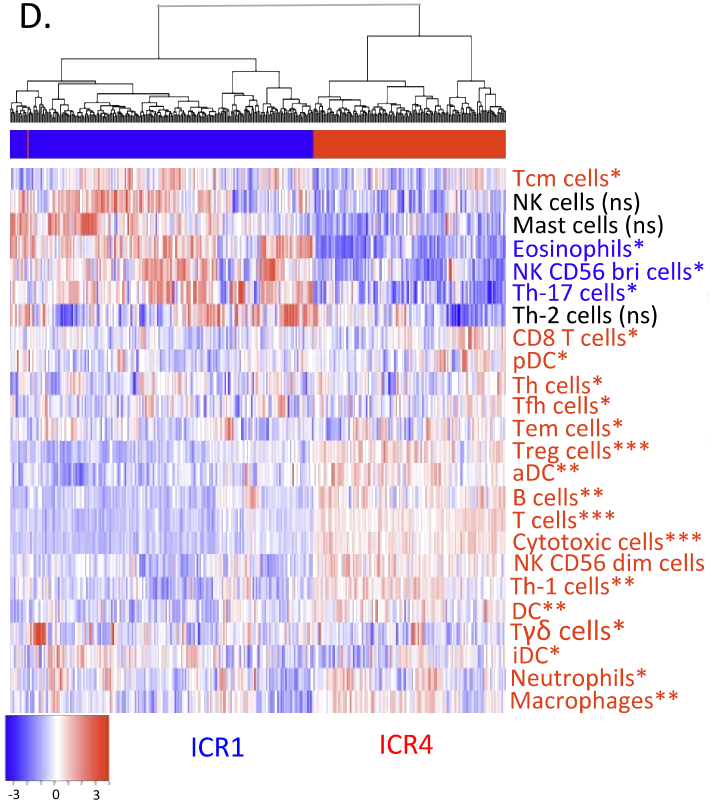


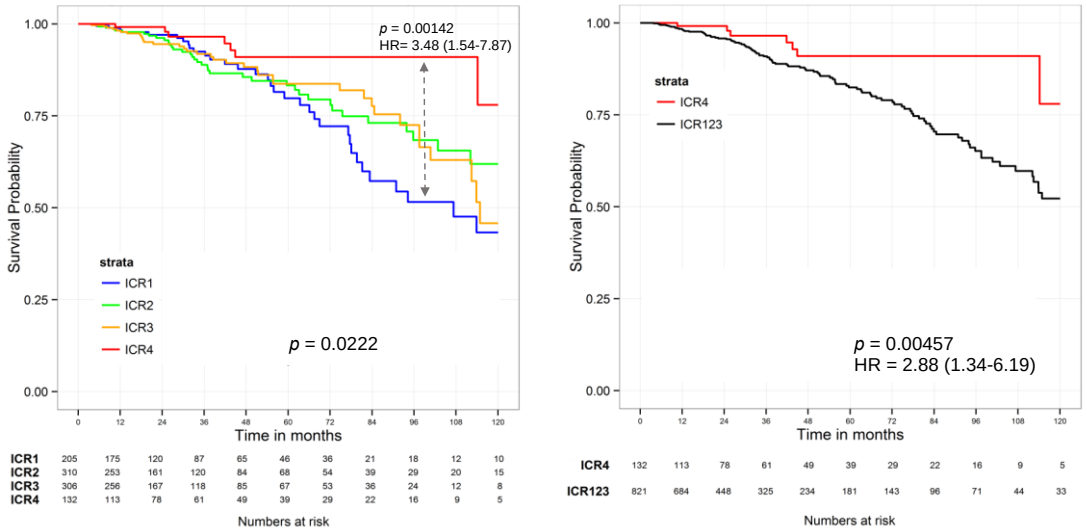
G.

CYTOKINE REGULATION_OF_

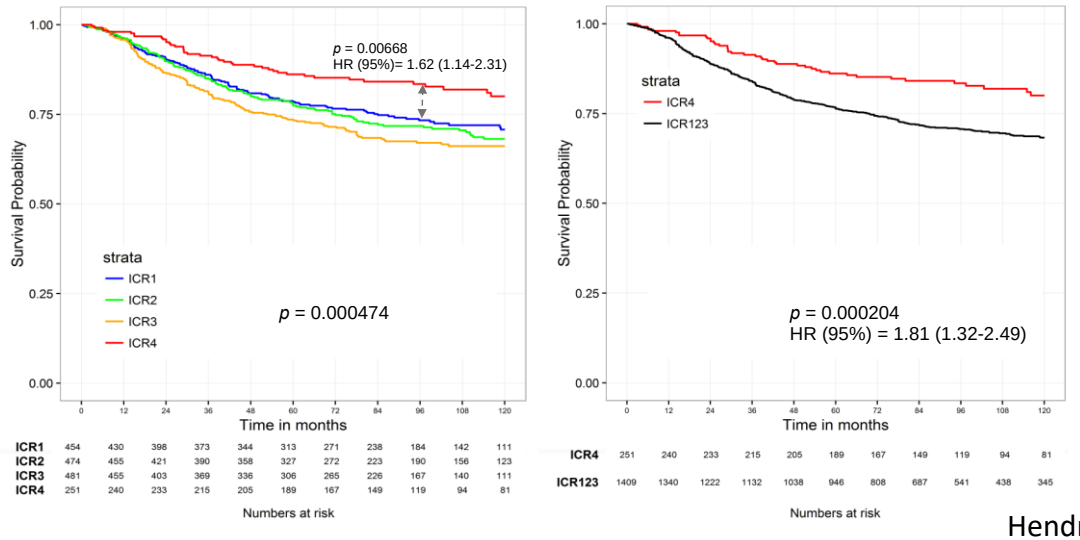
Hendrickx W, et al. *Oncoimmunology.* 2017;6(2):e1253654.

Immunologic Constant of Rejection

A.#



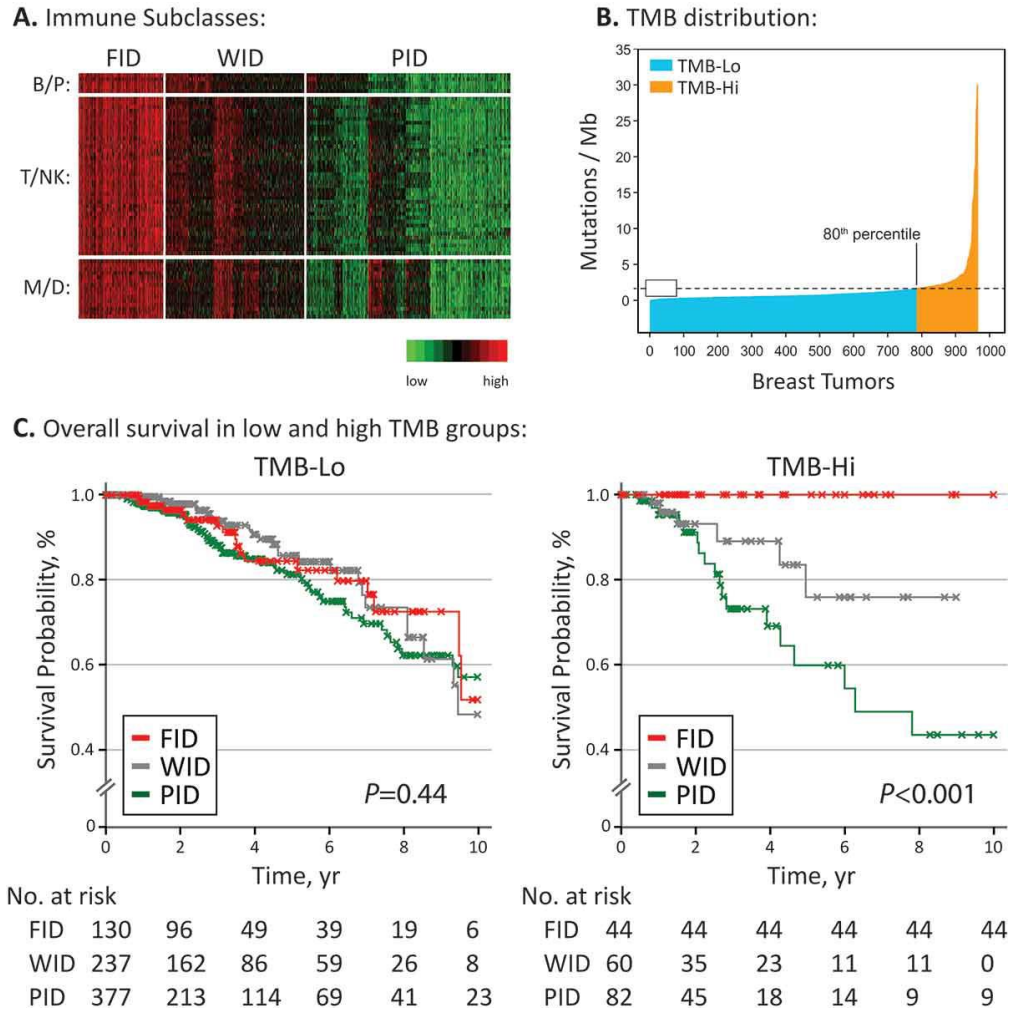
B.#



Hendrickx W, et al. *Oncoimmunology.* 2017;6(2):e1253654.

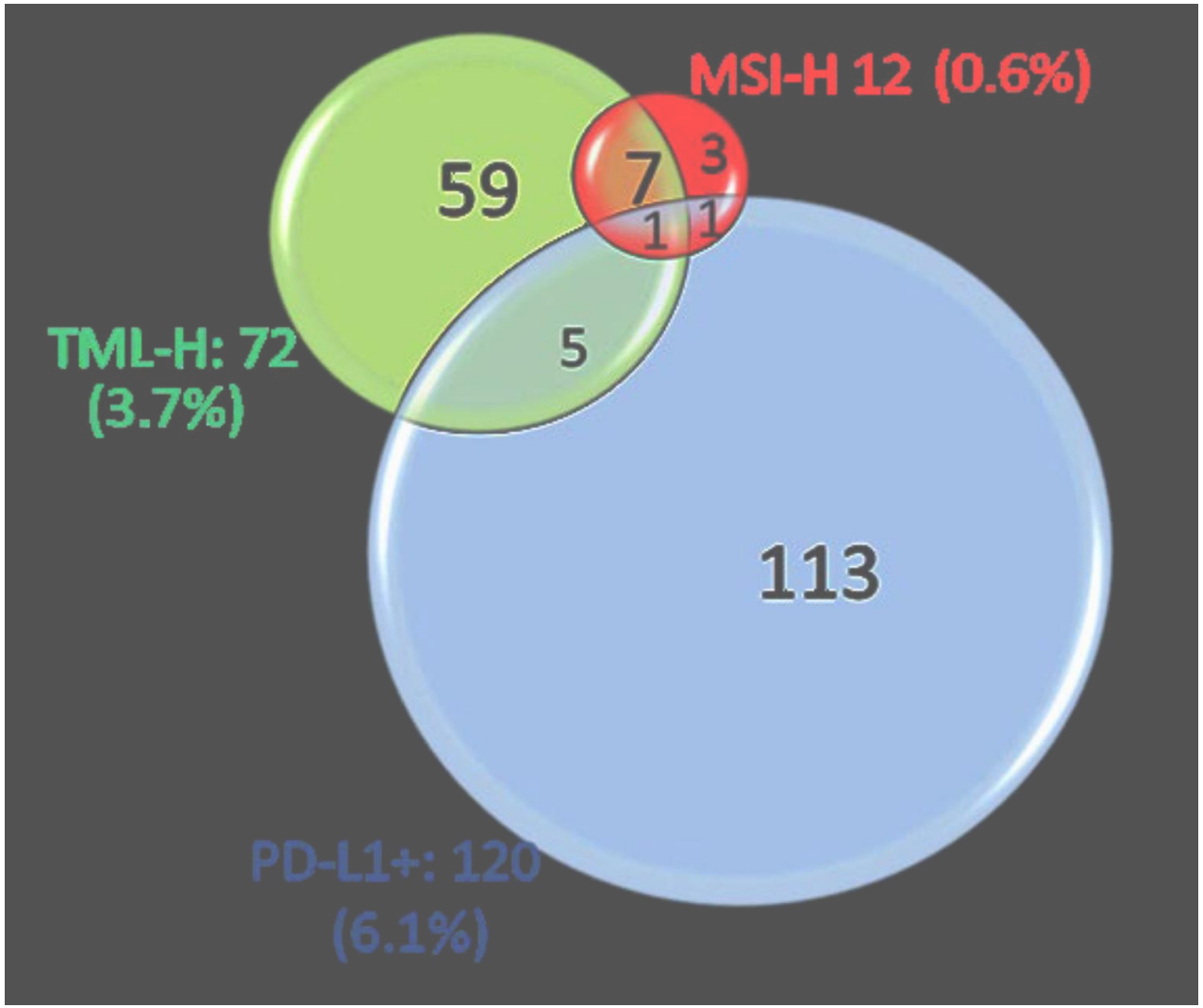
Figure.2)

TMB in breast cancer and survival



Thomas A, et al. *Oncoimmunology.* 2018;10: https://doi.org/10.1080/2162402X.2018.1490854

MSI High and BC



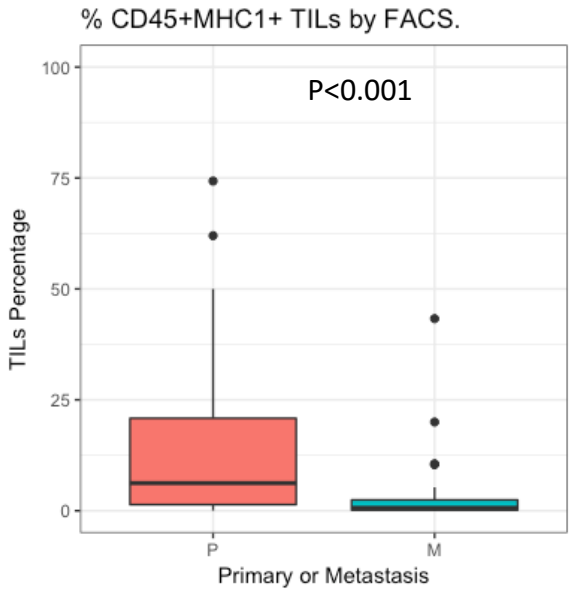
Obeid E et al. SABCS, 2017, Abstract 1416.

TILs in metastatic disease

Majority of metastases lack T cell infiltrate

"no anti-tumour immunity present"

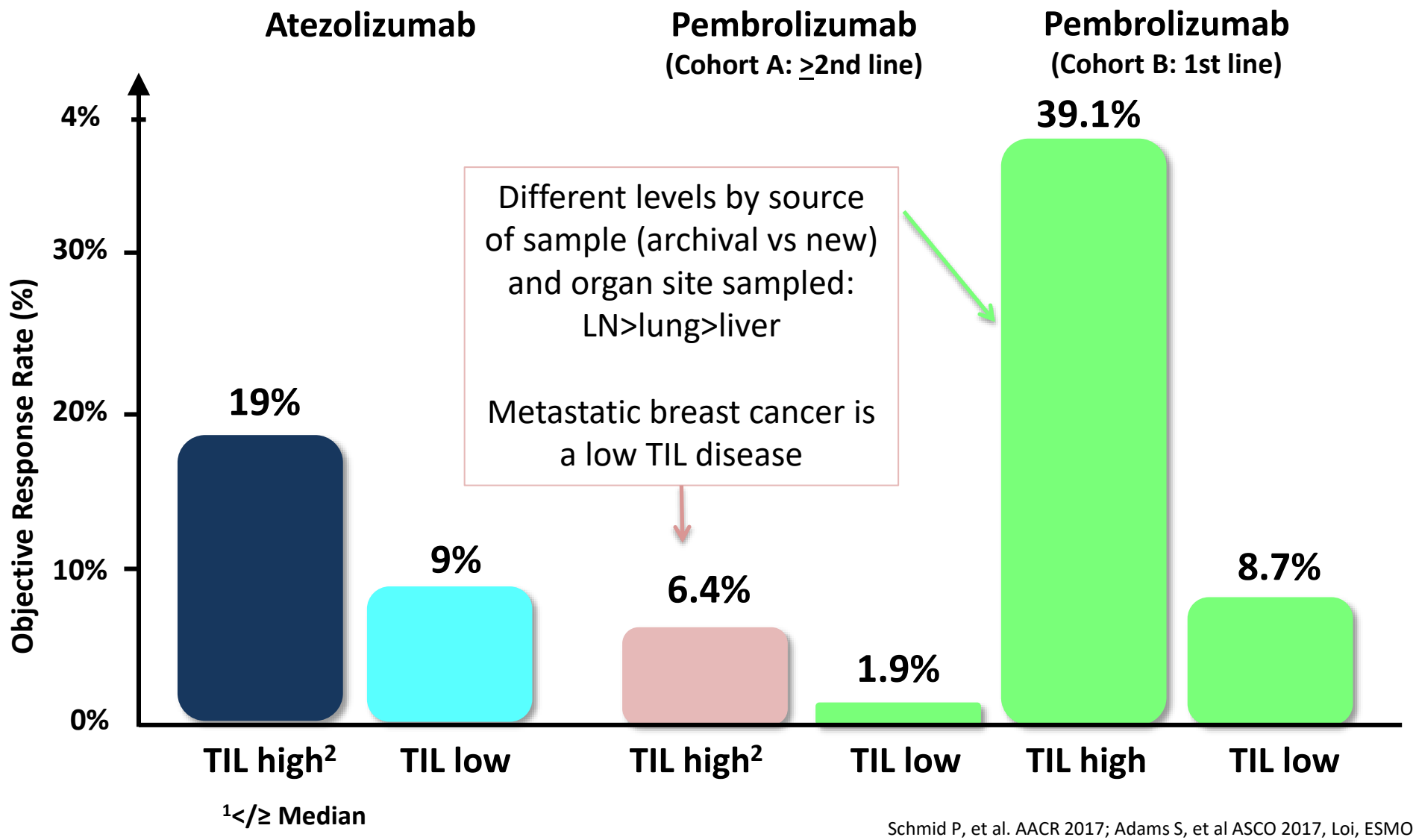
- **Metastatic TNBC grows too fast (high LDH)**
- **Immune escape (subclones)**
- **Large tumour burden is hostile for immune cells (hypoxic, low glucose)**
- **Immunosuppressive local microenvironment and systemically**



Unmatched primary (n=111) and metastatic sites (n=34)

Savas et al Nat Med 2018

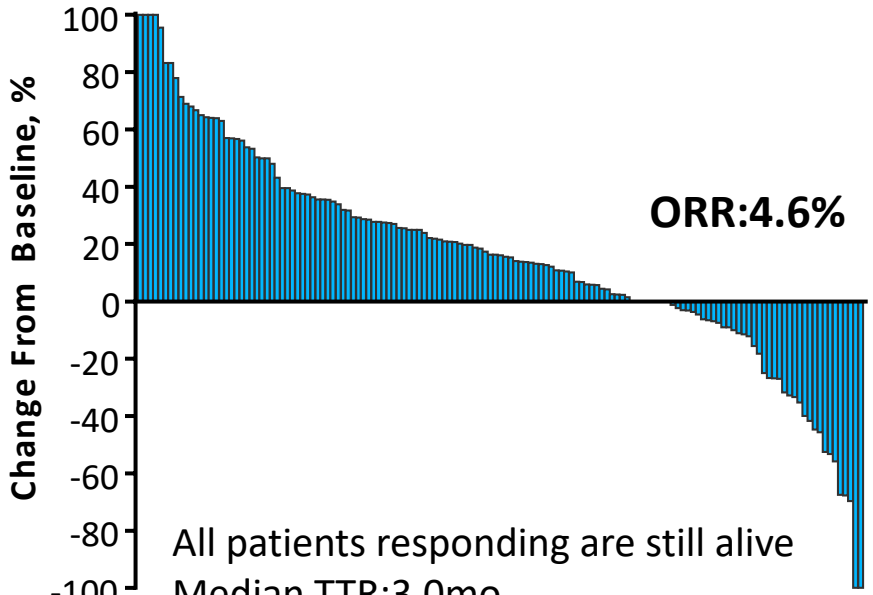
TILs and antitumor activity



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

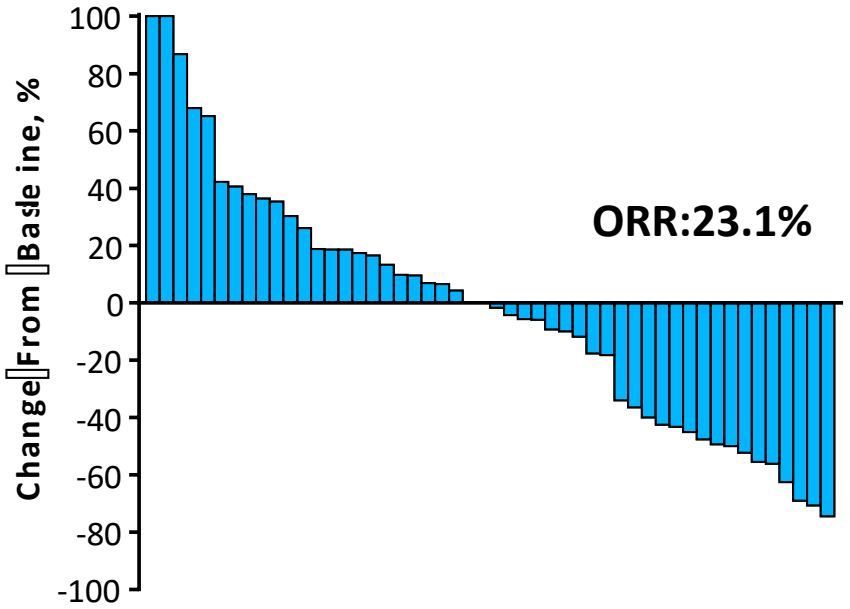
PD-L1 Expression (ICH) As a Predictive Biomarker

Cohort A (N = 170):
Previously Treated,
Regardless of PD-L1 Expression



All patients responding are still alive
Median TTR:3.0mo
Median duration of response: 6.3mo

Cohort B (N = 52)[1]:
Previously Untreated,
PD-L1 Positive



Plots include patients with ≥1 evaluable postbaseline assessment (n = 143 for cohort A, n = 50 for cohort B).

1. Adams S, et al. ASCO Annual Meeting; Jun 2-6, 2017; Chicago, IL; Abstr 1088.

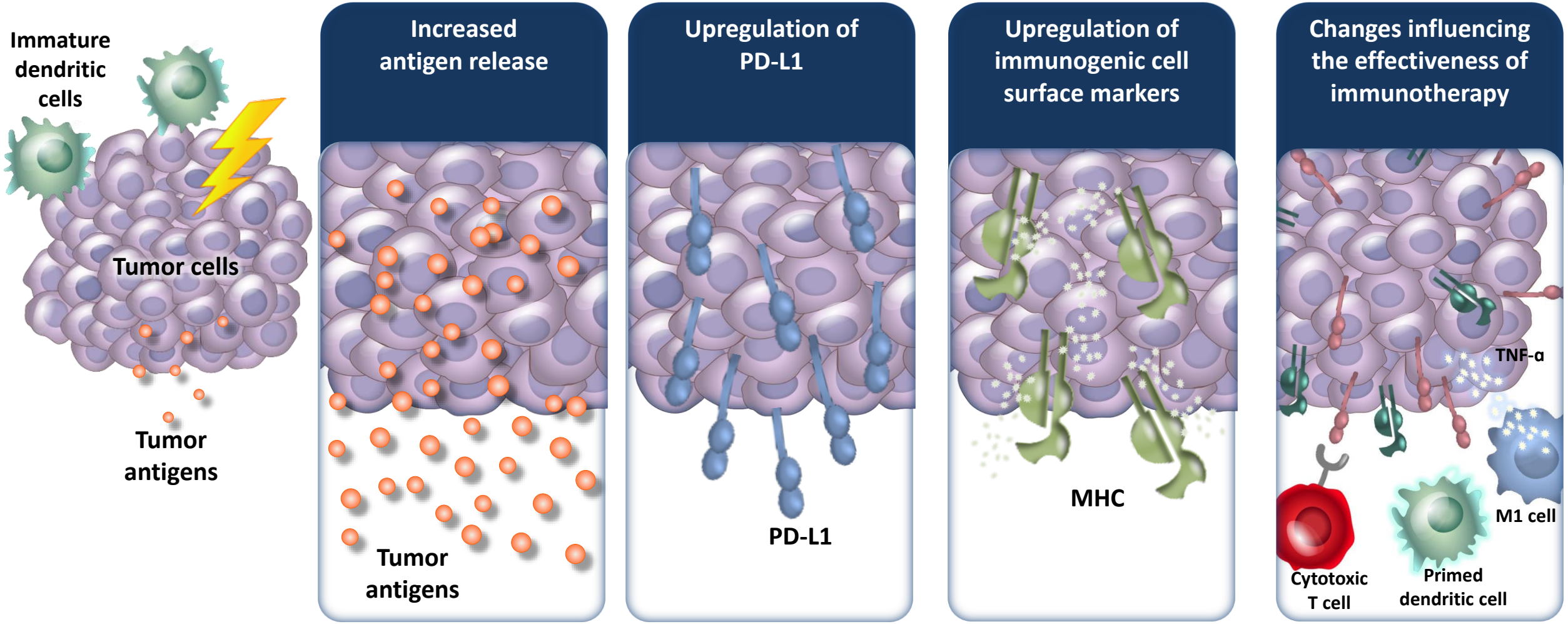
Activity of immune-checkpoint inhibitors monotherapy in BC

- **Modest activity**
- **Impressive outcomes in those with response**
- **PDL1+ and 1st line enriches for responsive tumors**

Antibody	Target	Combination	Breast Cancer Subtype	# Patients	ORR
Avelumab	PD-L1	Single agent	All	168	4.8%
			PD-L1+ All	12	33.3%
			TNBC	58 ★	8.6%
			PD-L1+ TNBC	9 ★	44.4%
			PD-L1- TNBC	39	2.6%
Pembrolizumab	PD-1	Single agent	PD-L1+ TNBC	27 ★	18.5%
		Single agent	TNBC	170 ★	4.7%
			PD-L1+ TNBC	105 ★	4.8%
			PD-L1- TNBC	64	4.7%
		Single agent	PD-L1+ TNBC, 1st line	52 ★	23.1%
			PD-L1+ ER+ HER-2- BC	25	12%
Atezolizumab	PD-L1	Single agent	TNBC	112 ★	10%
			PD-L1+ TNBC	71 ★	13%
			PD-L1- TNBC	37	5%

From Emens LA, CCR 2018

Chemotherapy Induces Multiple Immunomodulatory Changes in the Tumor Microenvironment That May Influence the Effectiveness of Immunotherapy



M1, tumor-associated macrophage; MHC, major histocompatibility complex; TNF-α, tumor necrosis factor alpha

1. Daly ME, et al. *J Thorac Oncol*. 2015;10(12):1685-1693. 2. Kaur P, et al. *Front Oncol*. 2012;2:191; 3. Deng L, et al. *J Clin Invest*. 2014;124(2):687-695.

Activity of immune-checkpoint inhibitors in combination with CT

Antibody	Target	Combination	Breast Cancer Subtype	# Patients	ORR
Avelumab	PD-L1	Single agent	All	168	4.8%
			PD-L1+ All	12	33.3%
			TNBC	58	8.6%
			PD-L1+ TNBC	9	44.4%
			PD-L1- TNBC	39	2.6%
Pembrolizumab	PD-1	Single agent	PD-L1+ TNBC	27	18.5%
		Single agent	TNBC	170	4.7%
			PD-L1+ TNBC	105	4.8%
			PD-L1- TNBC	64	4.7%
		Single agent	PD-L1+ TNBC, 1st line	52	23.1%
			PD-L1+ ER+ HER-2- BC	25	12%
Atezolizumab	PD-L1	Single agent	TNBC	112	10%
			PD-L1+ TNBC	71	13%
			PD-L1- TNBC	37	5%
Atezolizumab	PD-L1	Nab-paclitaxel	TNBC	32	38%
Pembrolizumab	PD-1	Eribulin	TNBC	39	33.3%

From Emens LA, CCR 2018

Atezolizumab and nabpaclitaxel

Key eligibility criteria:

- Metastatic or inoperable TNBC
- 0-2 prior lines of chemo

N=33

Atezo + Nab pac:

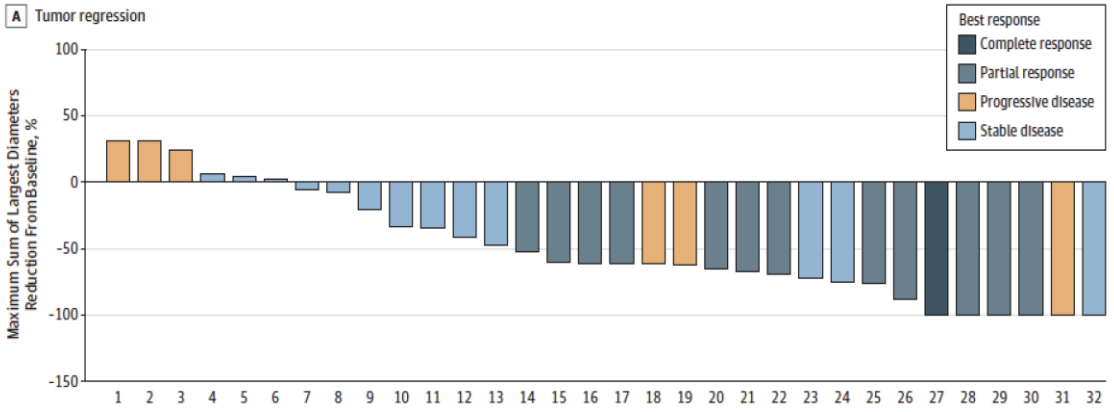
Atezolizumab 800 mg IV D1, 15 q28
+ Nab paclitaxel 125 mg/m2 IV D1, 8, 15 q28

Primary endpoints = safety, ORR

Note: serial biopsy cohort had lead-in nab paclitaxel alone, atezolizumab added C1D15

Adams S et al, JAMA Oncol 2018

Atezolizumab and nabpaclitaxel



	ORR	PFS
1st L	54%	9m
2nd+ L	30%	5m
PDL1+	41%	22m
PDL1-	33%	11m

OS 15m

Exploratory biomarker studies window chemo alone:

- No effect on immune microenvironment
- No ↓ atezo-induced T-cell activation

Key findings:

Activity in 1st and 2nd+ lines

Activity in PDL1+ and –

7 patients with prolonged (> 1y) duration on ICI alone or no Rx

Adams S et al, JAMA Oncol 2018

Pembrolizumab and eribulin

Key eligibility criteria:

- Metastatic or inoperable TNBC
- 0-2 prior lines of Rx for advanced TNBC

Stratification factors:

- 1st line (62%) vs 2nd+ line (38%)
- PD-L1 status on IHC (PDL1+ 46%)

N=107

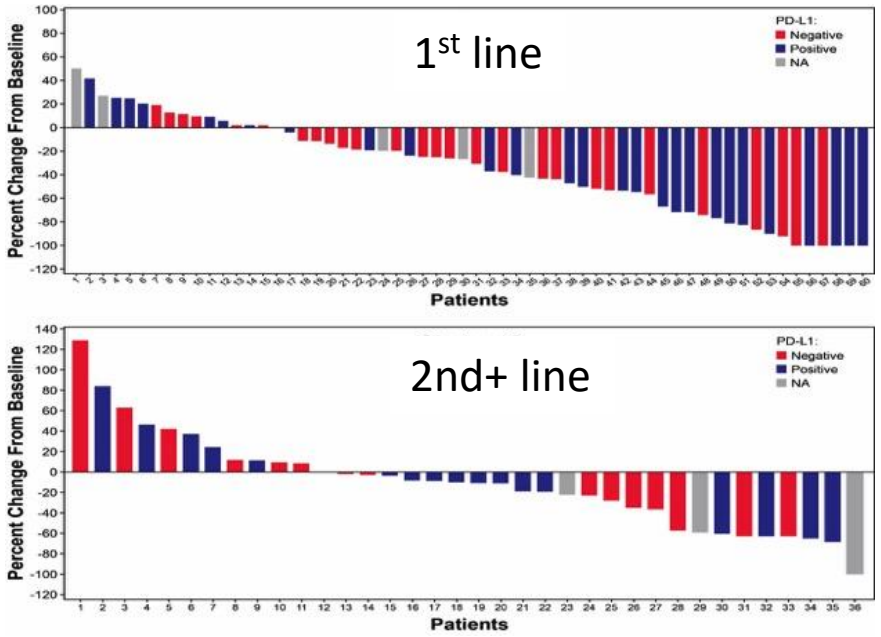
Pembro + eribulin:

Pembrolizumab 200 mg IV D1 q21
+ Eribulin 1.4 mg/m^2 IV D1, 8 q21

Primary endpoints = safety, ORR

Tolaney S et al, SABCS 2017

Pembrolizumab and eribulin



	ORR	PFS
1st L	29%	5m
2nd+ L	22%	4m

DoR (n=28): > 6m 54%, > 12m 14%

OS 18m

Key findings:

Activity in 1st and 2nd+ lines

Activity in PDL1+ and –

Long duration in those that respond

Tolaney S et al, SABCS 2017

Atezolizumab and *nab*-Paclitaxel in mTNBC

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/m^2 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/m^2 IV
- On days 1, 8 and 15 of 28-day cycle

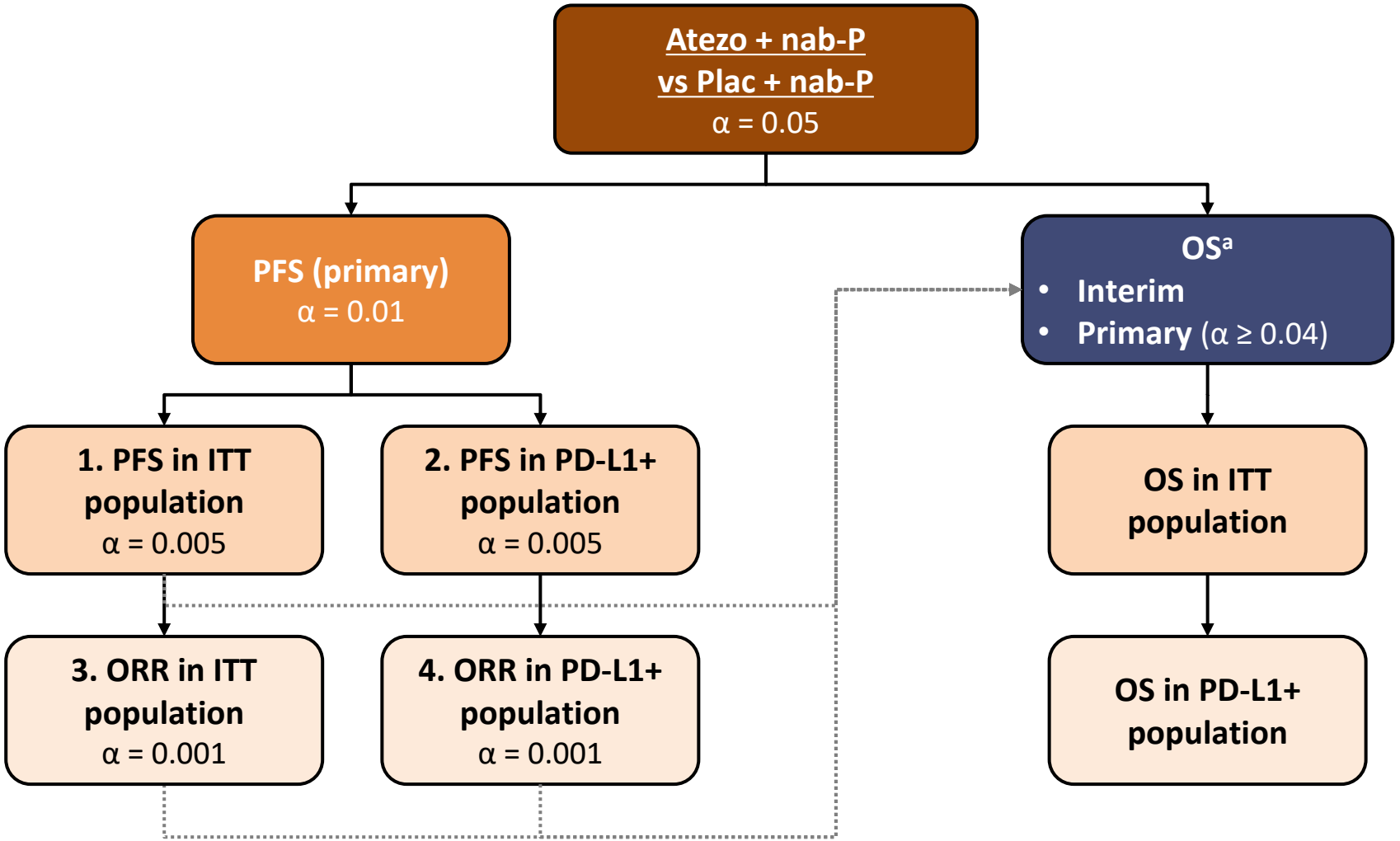
RECIST v1.1 PD or toxicity

- 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. N Engl J Med. 2018 Nov 29;379(22):2108-2121

Statistical design



- Primary PFS analysis (PFS tested in ITT and PD-L1+ populations)
- First interim OS analysis (**OS tested in ITT population, then, if significant, in PD-L1+ population**)

[a] α recycled if PFS/ORR testing is significant. Hazard ratio (HR)/*P* value–stopping boundaries are dependent on the OS analysis timing.

Schmid P, et al. N Engl J Med. 2018 Nov 29;379(22):2108-2121

Patients

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. N Engl J Med. 2018 Nov 29;379(22):2108-2121

Safety

AESI, n (%)[a]	Atezo + nab-P (n = 452)		Plac + nab-P (n = 438)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All	259 (57%)	34 (8%)	183 (42%)	19 (4%)
Important AESIs				
Hepatitis (all)	69 (15%)	23 (5%)	62 (14%)	13 (3%)
Hepatitis (diagnosis)	10 (2%)	6 (1%)	7 (2%)	1 (< 1%)
Hepatitis (lab abnormalities)	62 (14%)	17 (4%)	58 (13%)	12 (3%)
Hypothyroidism	78 (17%)	0	19 (4%)	0
Hyperthyroidism	20 (4%)	1 (< 1%)	6 (1%)	0
Pneumonitis	14 (3%)	1 (< 1%)	1 (< 1%)	0
Meningoencephalitis[b]	5 (1%)	0	2 (< 1%)	0
Colitis	5 (1%)	1 (< 1%)	3 (1%)	1 (< 1%)
Adrenal insufficiency	4 (1%)	1 (< 1%)	0	0
Pancreatitis	2 (< 1%)	1 (< 1%)	0	0
Diabetes mellitus	1 (< 1%)	1 (< 1%)	2 (< 1%)	1 (< 1%)
Nephritis	1 (< 1%)	0	0	0
Other AESIs[c]				
Rash	154 (34%)	4 (1%)	114 (26%)	2 (< 1%)
Infusion-related reactions	5 (1%)	0	5 (1%)	0

- 1 grade 5 AESI per arm (both treatment related):
  - Atezo + nab-P: autoimmune hepatitis
  - Plac + nab-P: hepatic failure
- All hypothyroidism AESIs were grade 1-2; none led to discontinuation
  - Atezo + nab-P: 17%
  - Plac + nab-P: 4%
- Pneumonitis was infrequent with only 1 grade 3-4 event in the Atezo + nab-P arm
  - Atezo + nab-P: 3%
  - Plac + nab-P: < 1%
- Hepatitis rates were balanced

AESI, adverse event of special interest. Data cutoff: 17 April 2018. [a] Baskets of preferred terms according to medical concepts. [b] All events of photophobia. [c] Includes all AESIs occurring in ≥ 1% of patients in either arm.

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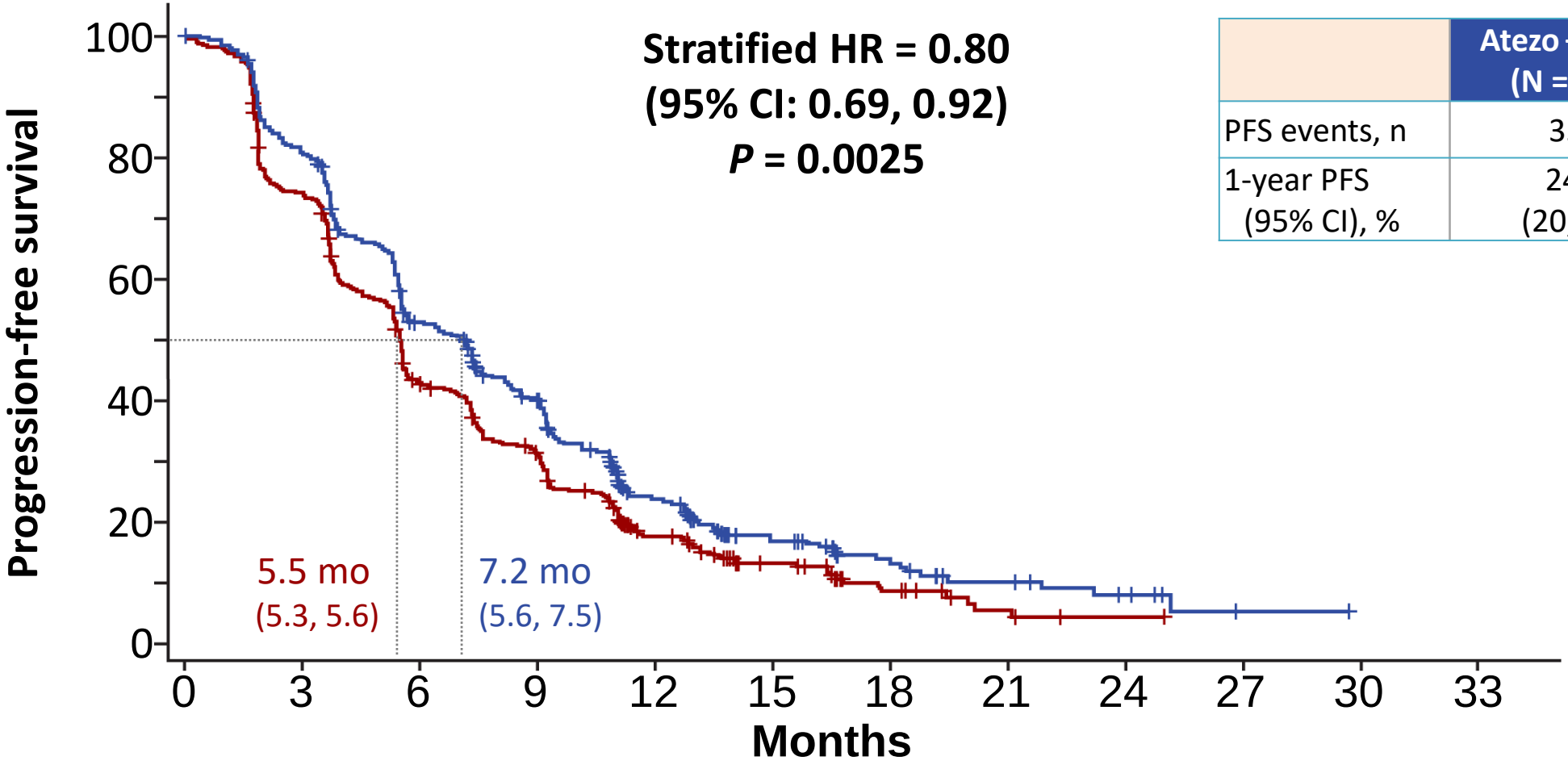
Primary PFS analysis: ITT population



	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
PFS events, n	358	378
1-year PFS (95% CI), %	24% (20, 28)	18% (14, 21)

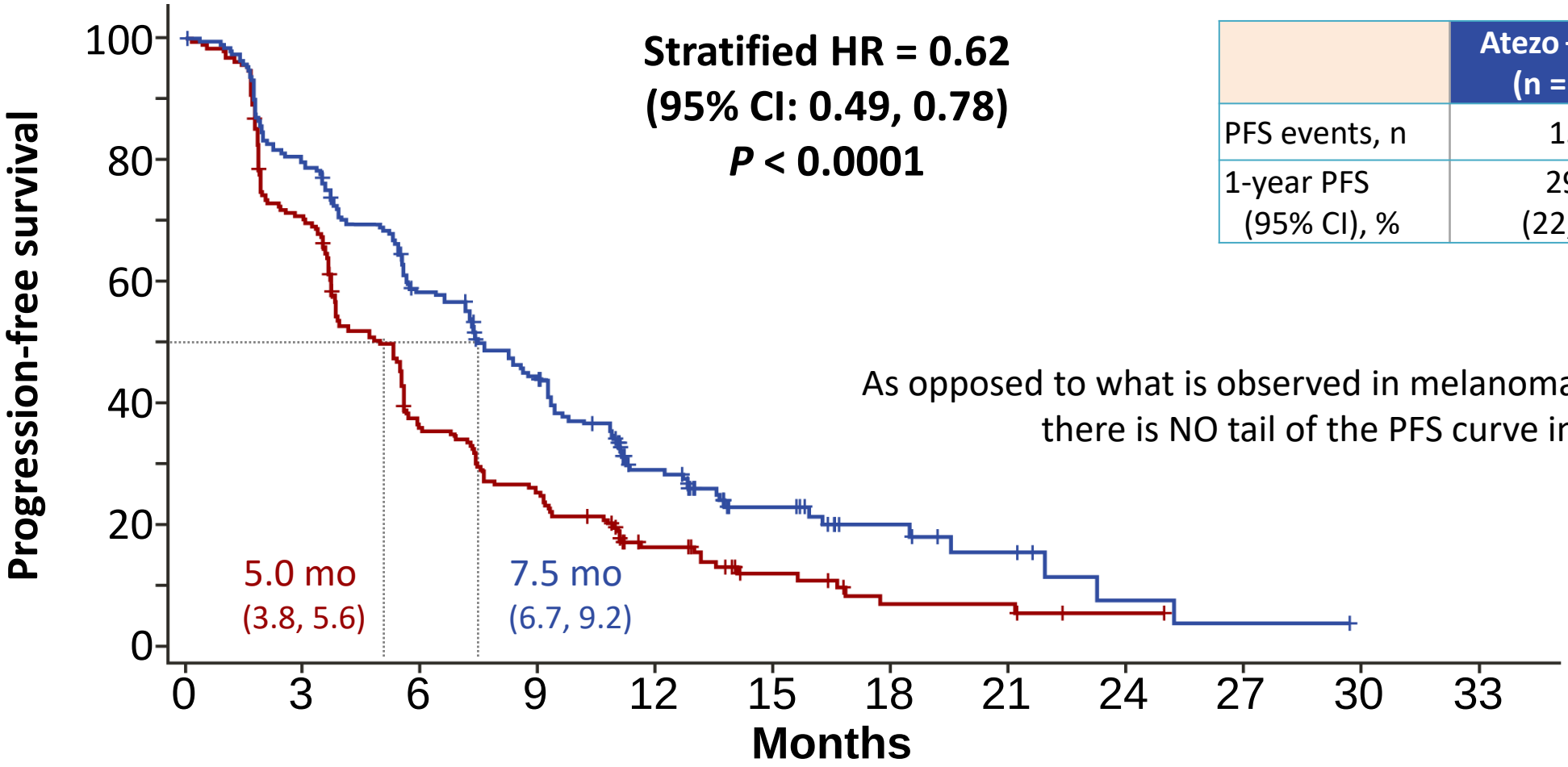
No. at risk:

Atezo + nab-P	451	360	226	164	77	34	20	11	6	1	NE	NE
Plac + nab-P	451	327	183	130	57	29	13	5	1	NE	NE	NE

NE, not estimable. Data cutoff: 17 April 2018. Median PFS durations (and 95% CI) are indicated on the plot. Median follow-up (ITT): 12.9 months.

Schmid P, et al. N Engl J Med. 2018 Nov 29;379(22):2108-2121

Primary PFS analysis: PD-L1+ population



Stratified HR = 0.62
(95% CI: 0.49, 0.78)
***P* < 0.0001**

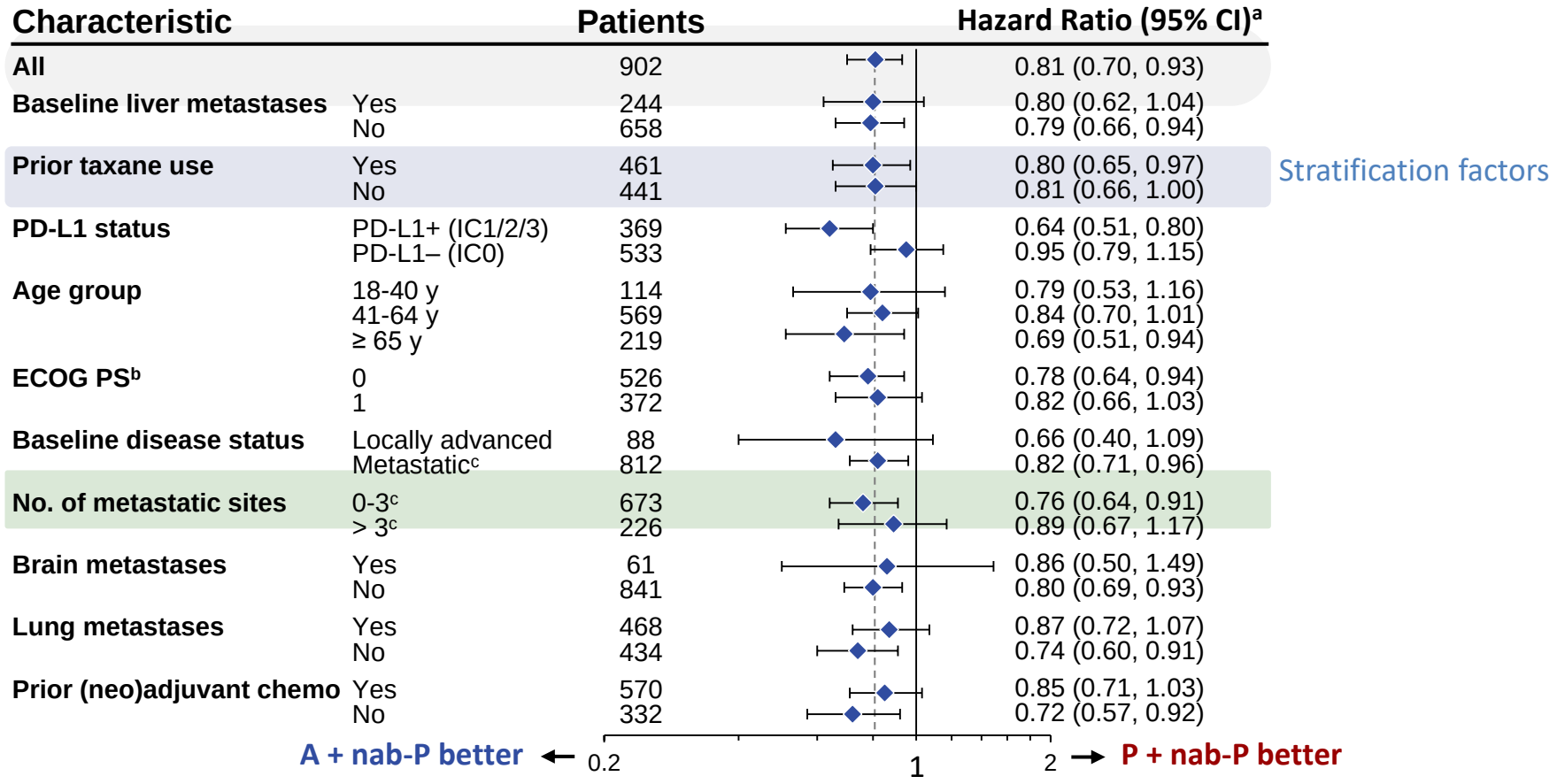
	Atezo + nab-P (n = 185)	Plac + nab-P (n = 184)
PFS events, n	138	157
1-year PFS (95% CI), %	29% (22, 36)	16% (11, 22)

As opposed to what is observed in melanoma and lung cancer, there is NO tail of the PFS curve in TNBC

Data cutoff: 17 April 2018.

Schmid P, et al. N Engl J Med. 2018 Nov 29;379(22):2108-2121

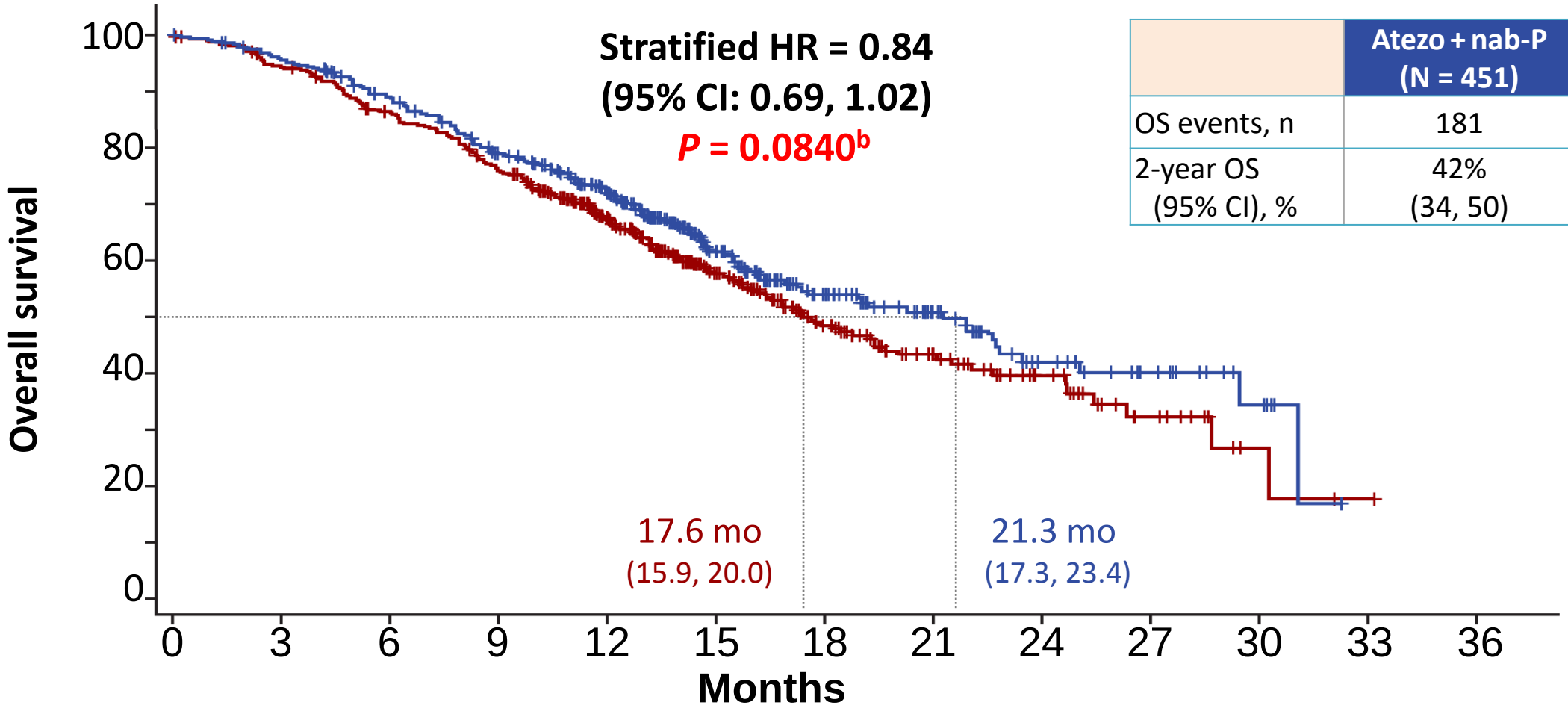
Primary PFS analysis



Stratification factors

Schmid P, et al. N Engl J Med. 2018 Nov 29;379(22):2108-2121

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)

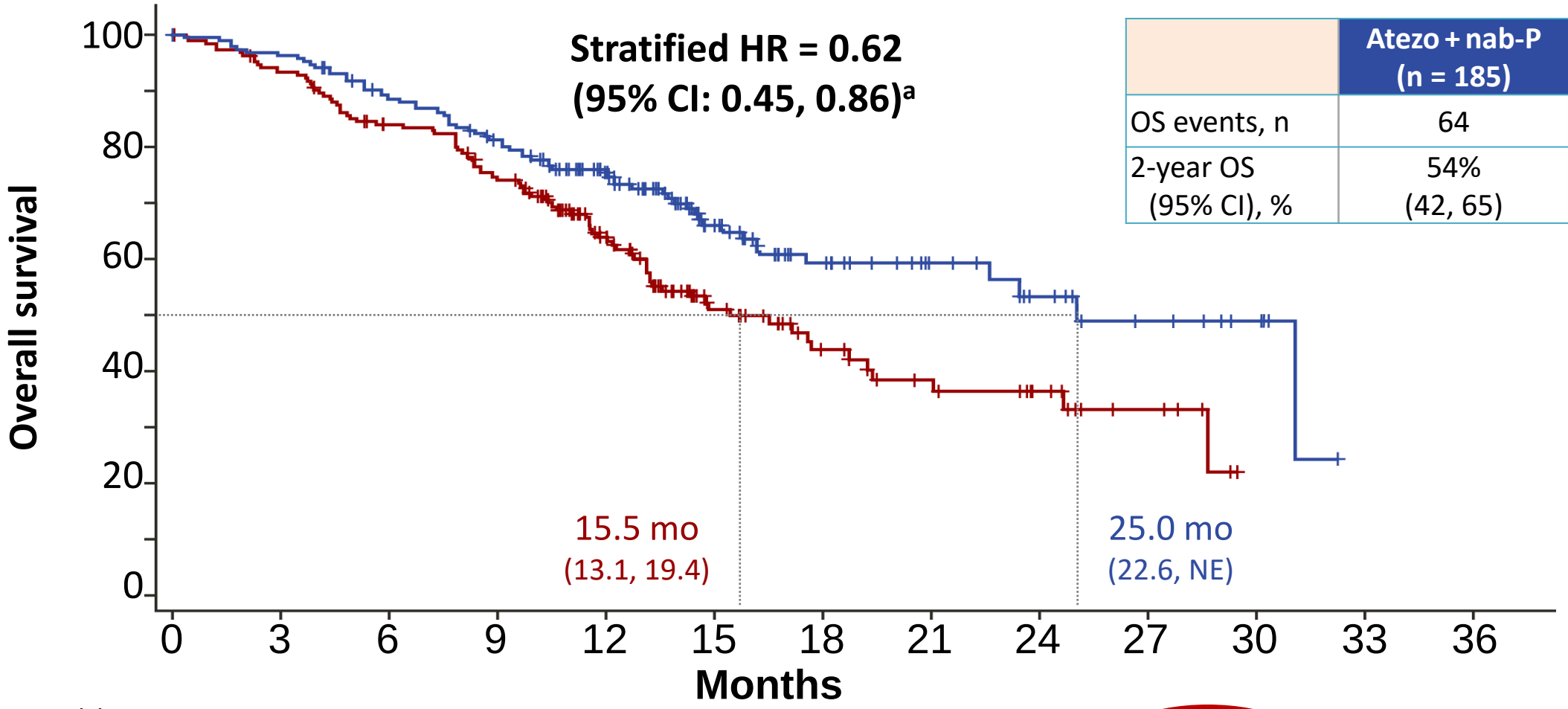
No. at risk:

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

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 death events had occurred. [b] Significance boundary was not crossed.

Schmid P, et al. N Engl J Med. 2018 Nov 29;379(22):2108-2121

Interim OS analysis: PD-L1+ population

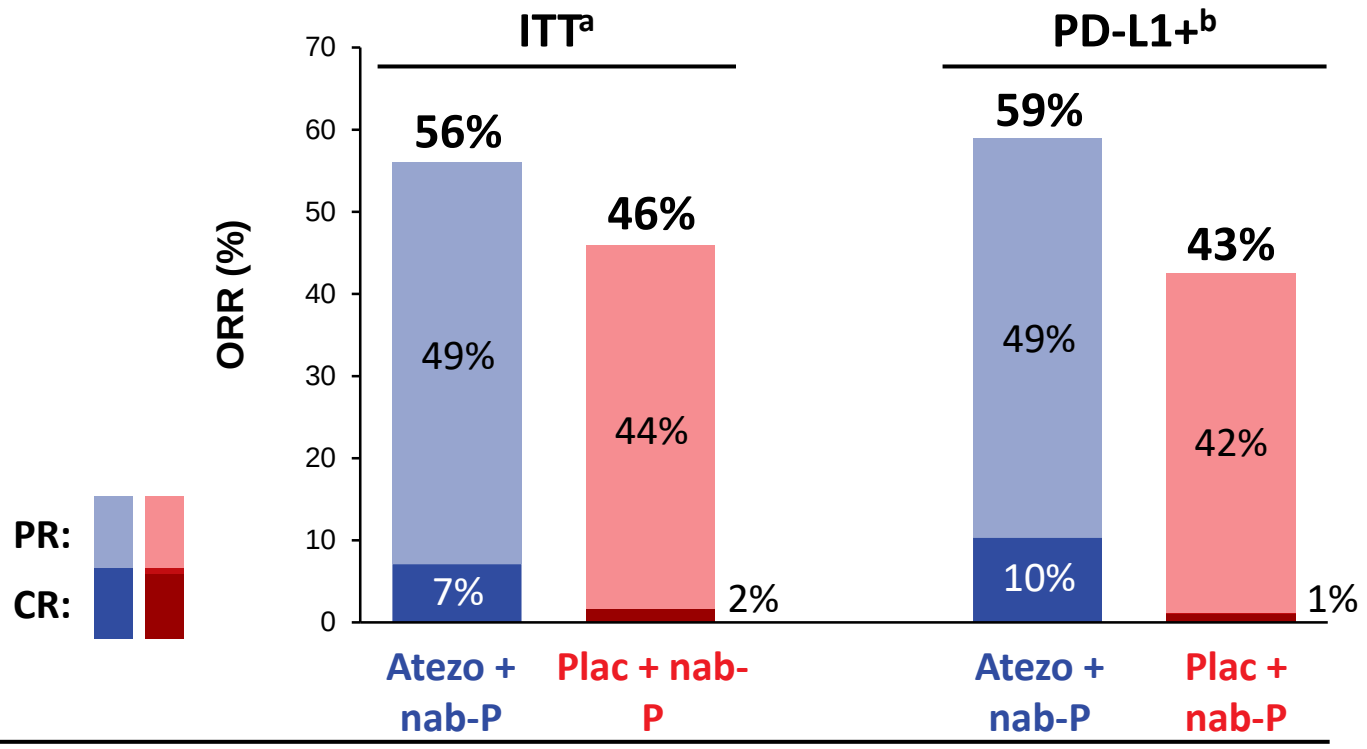


	Atezo + nab-P (n = 185)	Plac + nab-P (n = 184)
OS events, n	64	88
2-year OS (95% CI), %	54% (42, 65)	37% (26, 47)

Data cutoff: 17 April 2018. Median OS durations (and 95% CI) are indicated on the plot. [a] Not formally tested.

Schmid P, et al. N Engl J Med. 2018 Nov 29;379(22):2108-2121

Secondary efficacy endpoints



	Atezo + nab-P	Plac + nab-P	Atezo + nab-P	Plac + nab-P
DOR, median (95% CI), mo	7.4 (6.9, 9.0)	5.6 (5.5, 6.9)	8.5 (7.3, 9.7)	5.5 (3.7, 7.1)
No. of ongoing responses, n (%)[c]	78 (31%)	52 (25%)	39 (36%)	19 (24%)

- Numerically higher and more durable responses were seen in the Atezo + nab-P arm
  - Differences were not significant based on α level = 0.1% (ITT: *P* = 0.0021; PD-L1+: *P* = 0.0016)
- The CR rate was higher in the Atezo + nab-P arm vs the Plac + nab-P arm
  - ITT population: 7% vs 2%
  - PD-L1+ patients: 10% vs 1%

Schmid P, et al. N Engl J Med. 2018 Nov 29;379(22):2108-2121

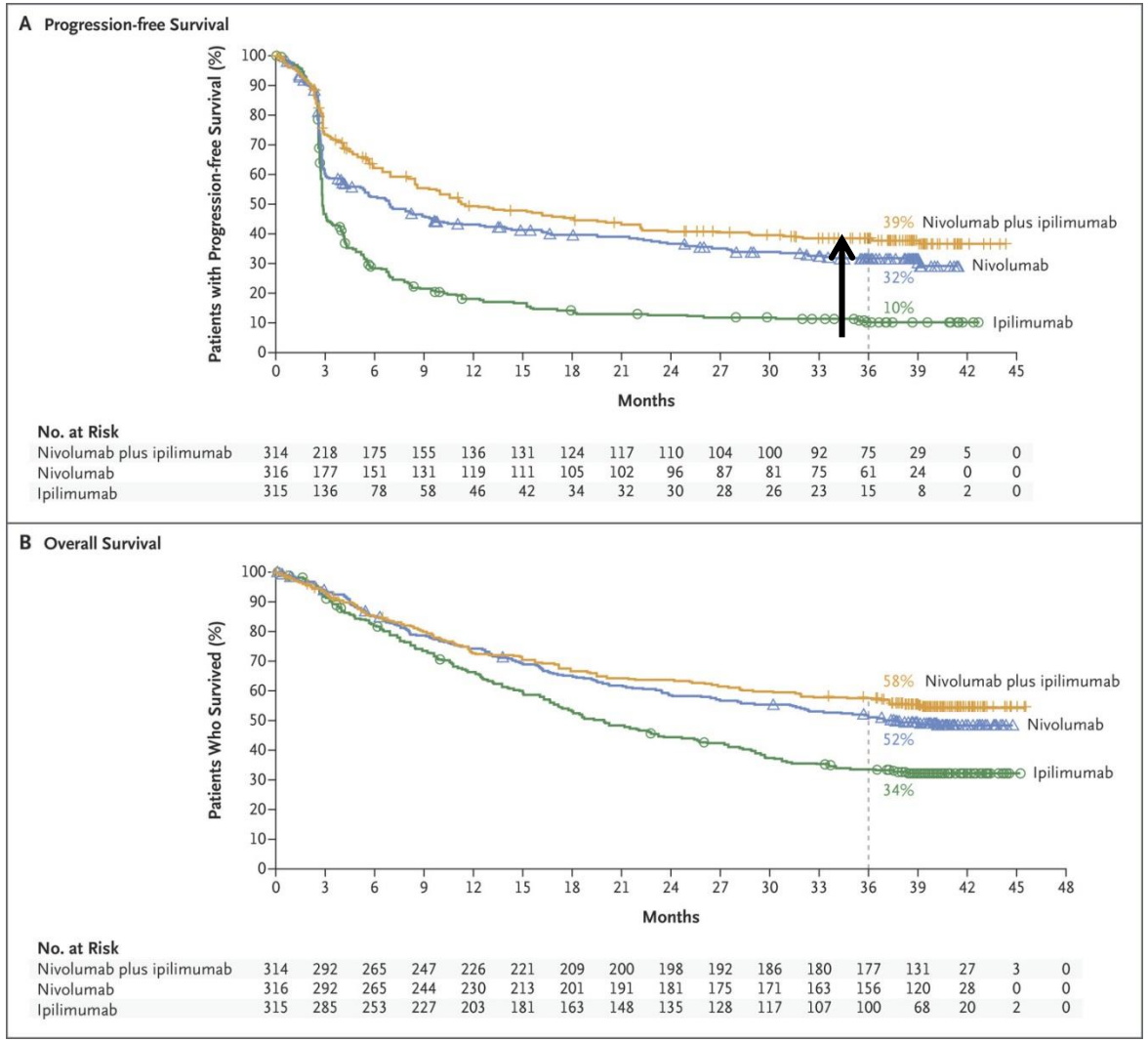
Discussion

- **A positive study for IO in TNBC: this brings breast cancer into the immunotherapy era**
- Subset data for PDL1 expression show clear benefit, which means we have to figure out how best to test tumors
- There is a “missing arm” in the study: atezolizumab alone. Might that be a good option for certain subset?
- What can we learn from other tumor types where IO is established?
- Roadmap: Single agent vs combination therapy with chemotherapy in highly immunogenic selected patients? Chemotherapy followed by consolidation treatment with IO?

Discussion

- Endpoints: should we be more focused on OS than on PFS ?
- Other tumor types (ER+, HER2+) are they as likely to be susceptible? BRCA mutated?
- Neoadjuvant setting: pCR with PD1/PDL1 inhibitors not the ideal endpoint: new data are expected with the potential of biomarker discovery

Is immunotherapy transformative in TNBC?



HER 2+: PANACEA trial: NCT02129556

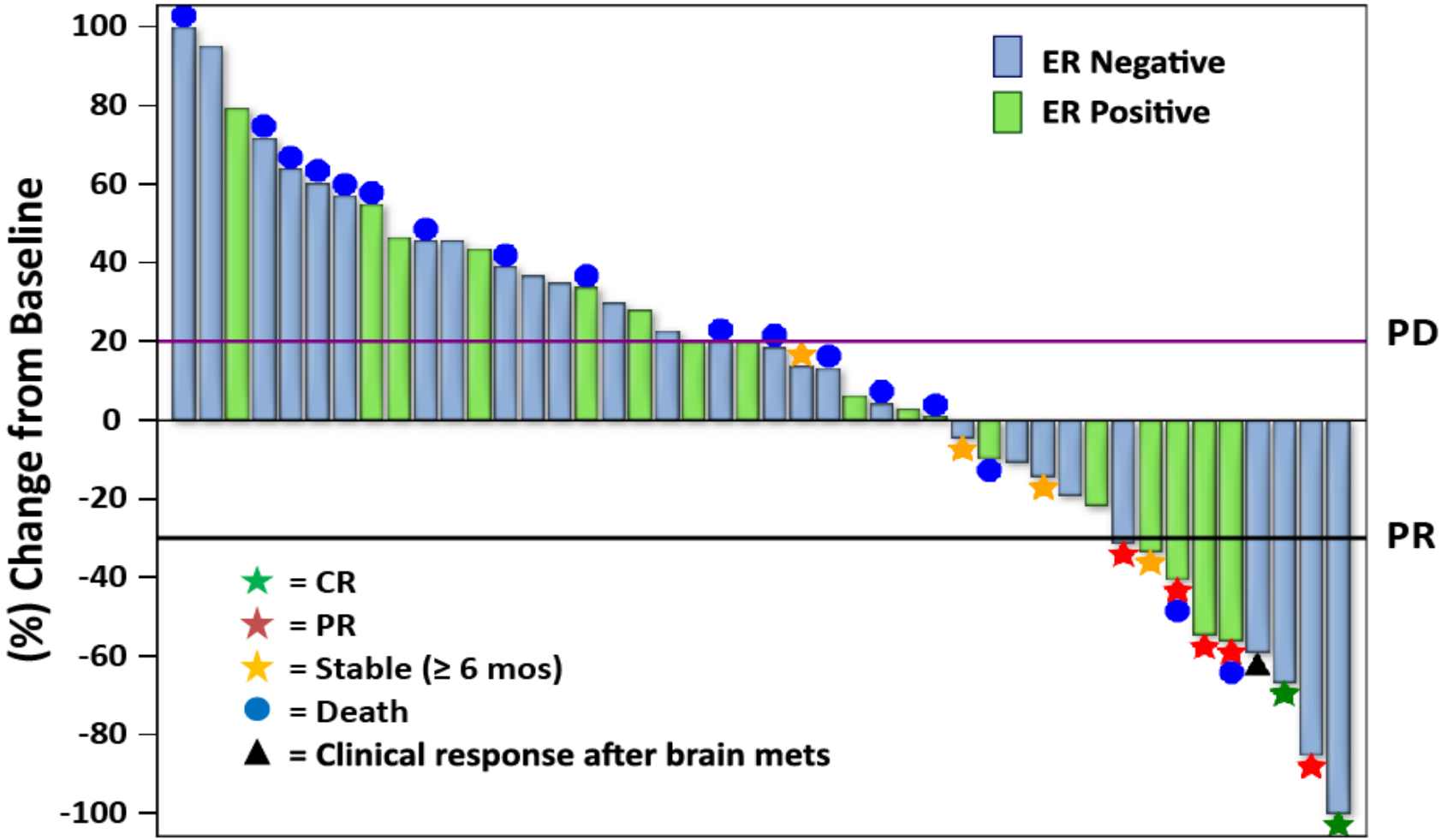
Phase Ib/II trial of anti-PD-1 monoclonal ANtibody in AdvanCed, Trastuzumab-resistant, HER2-positive breast cAncer

Primary Endpoint is efficacy of the combination

Two cohorts PD-L1 positive and negative

Loi et al, Lancet Oncology, 2019

Maximum Change from Baseline in Target Lesions: PD-L1 Positive Cohort (N=44, ORR 20%*)



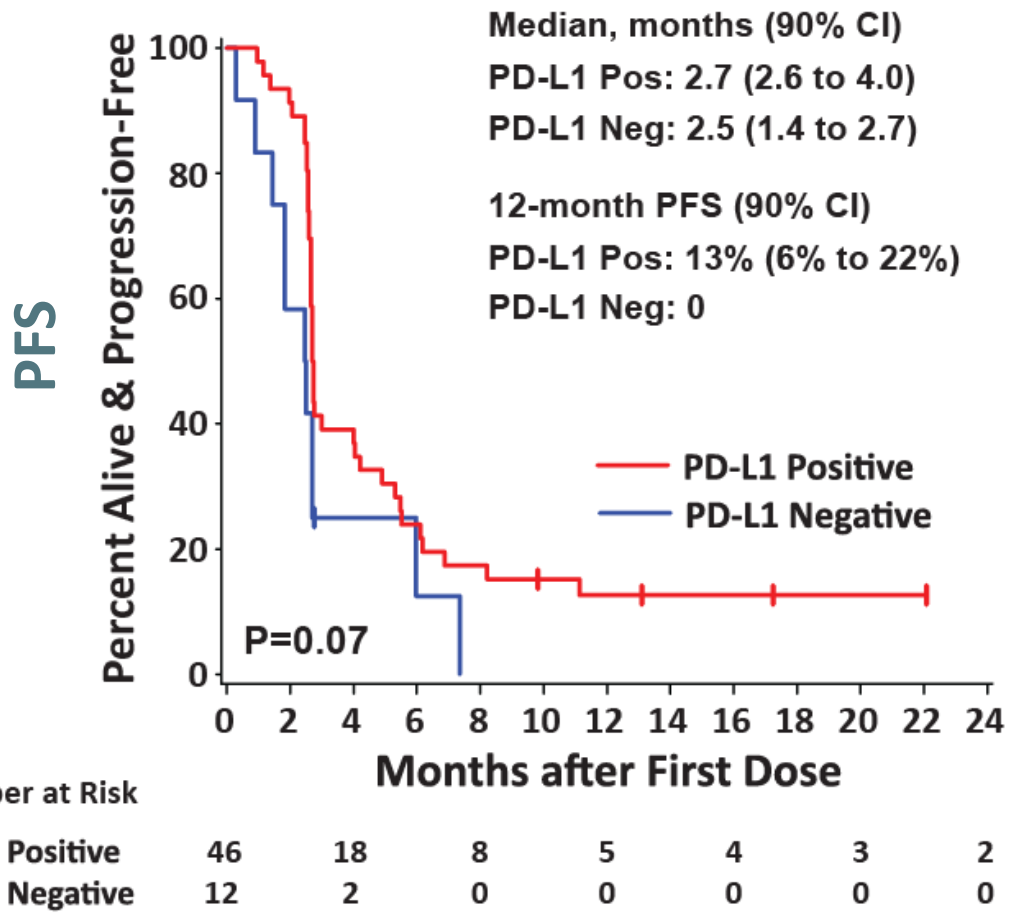
No responses in PD-L1 negative cohort

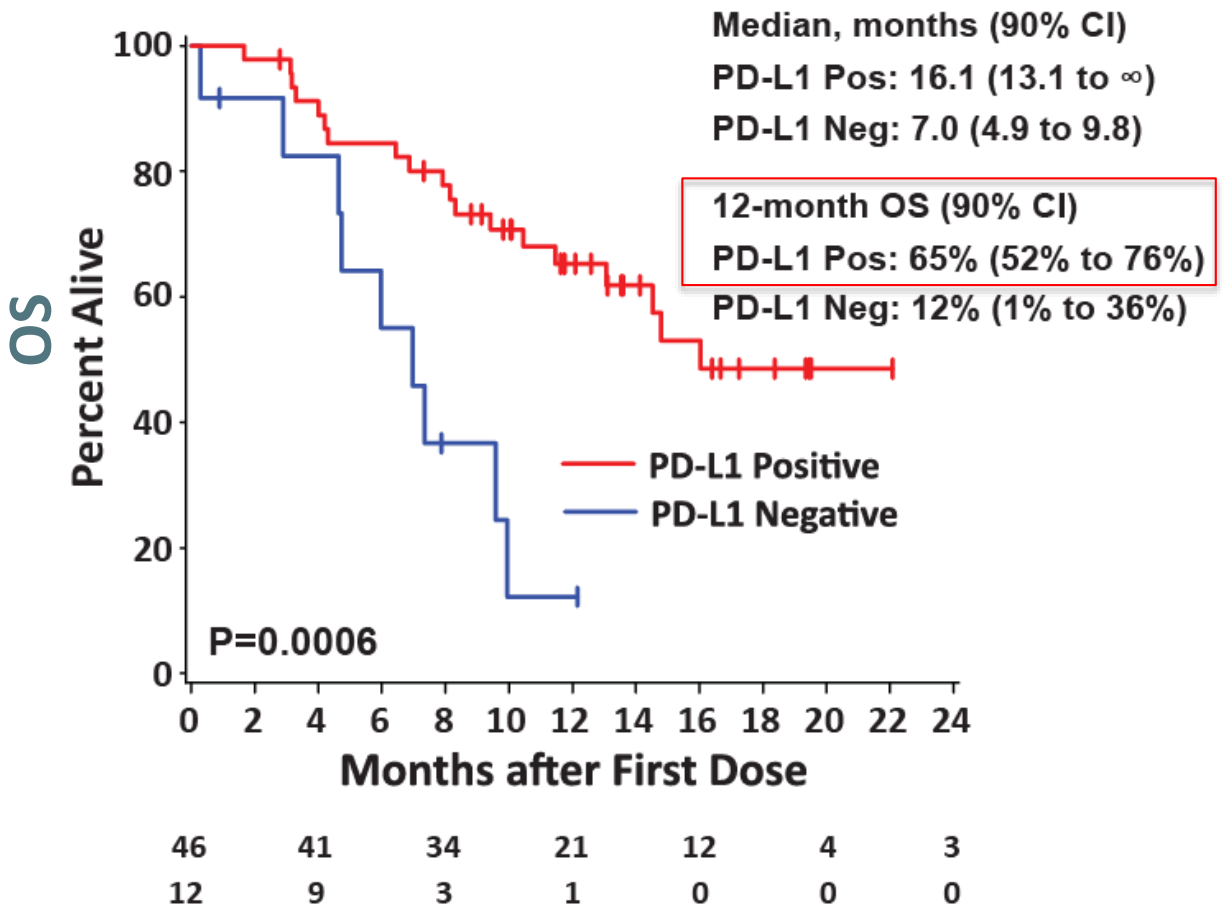
N=44/46 evaluable as excludes 2 patients without follow-up measurements of target lesions

*non-confirmed ORR

Loi et al, Lancet Oncology, 2019

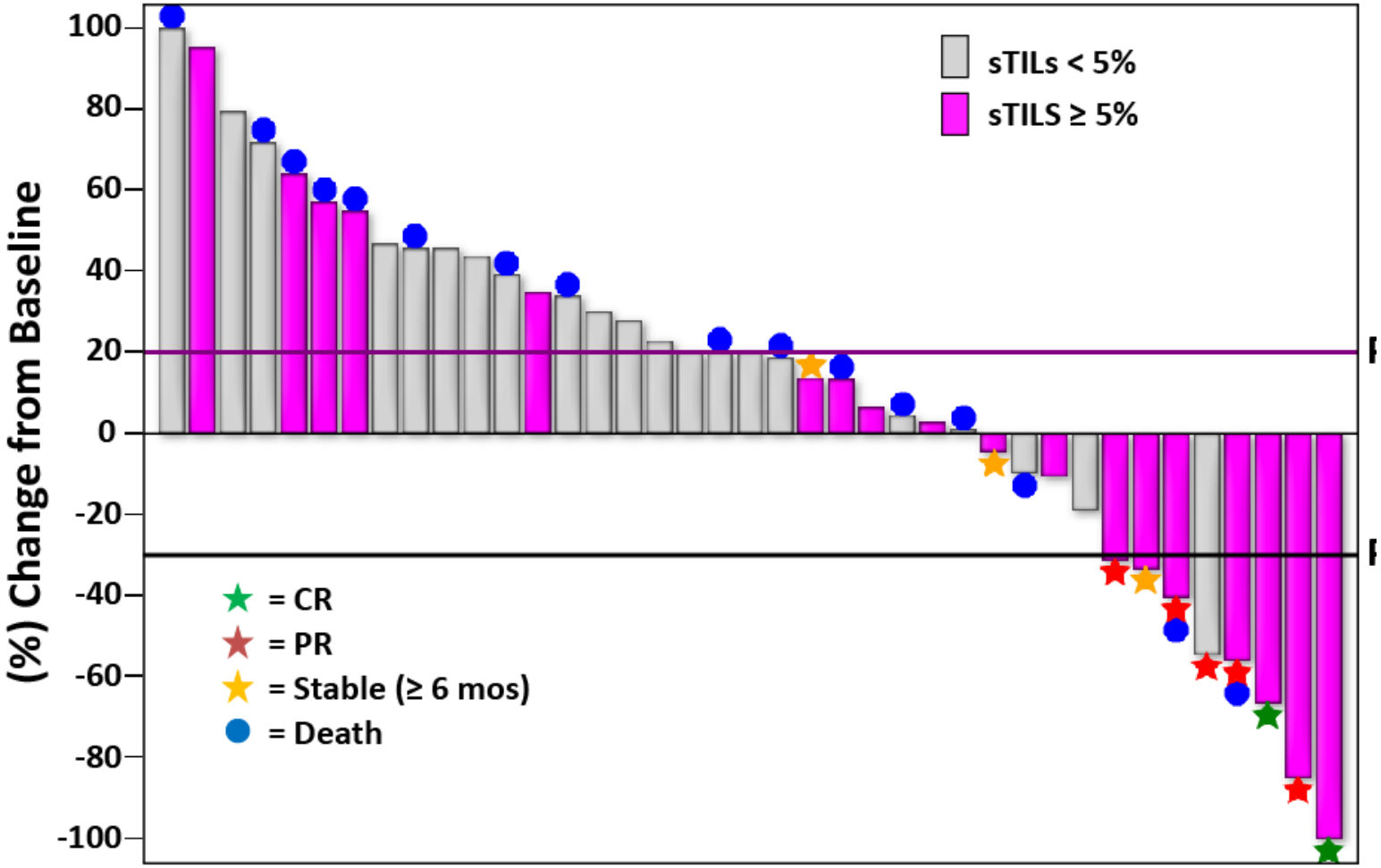
PFS and OS by PD-L1 Status





Loi et al, Lancet Oncology, 2019

sTILs ≥ 5% as Potential Predictive Marker: PD-L1 Positive Cohort



41% of PD-L1 positive cohort had sTILs ≥ 5%

For sTILs ≥ 5% v. sTILs < 5%

ORR

- **39% vs. 5%**
  - Sensitivity: 85.7%
  - Specificity: 61.8%
  - NPV: 95.5%
  - PPV: 31.6%

DCR

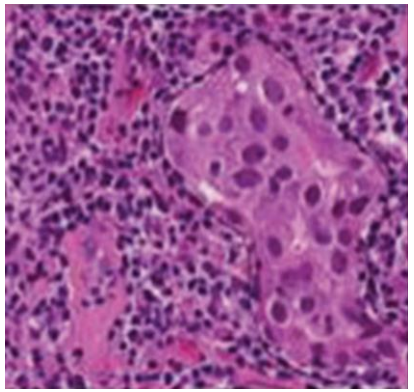
- **47% vs. 5%**
  - Sensitivity: 90.0%
  - Specificity: 67.7%
  - NPV: 95.5%
  - PPV: 47.4%

Loi et al, Lancet Oncology, 2019

TIL in ER-positive BC

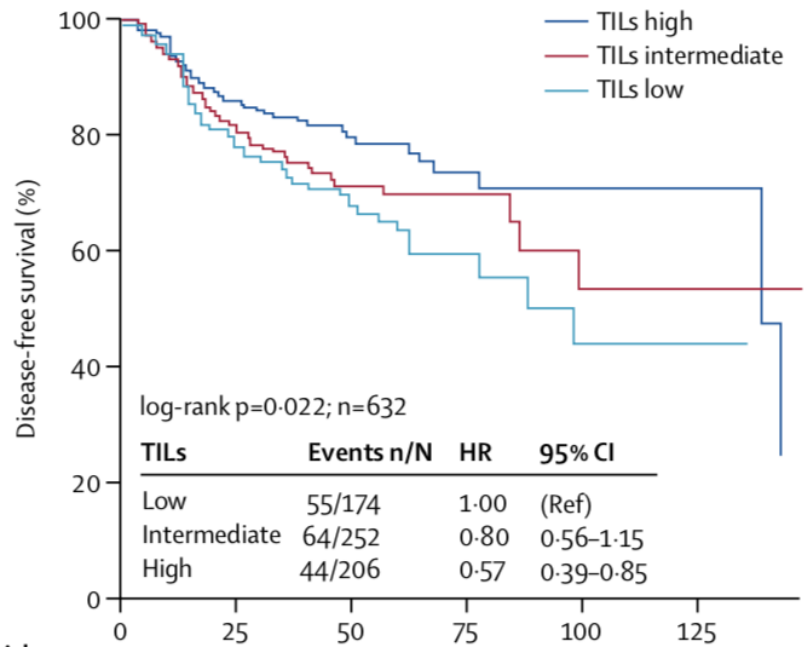
Table 2. Lymphocytic Infiltration in Breast Cancer Subtypes

Subtype	Patients, No.	Median (Range), %		
		None[a]	<49%	LBPC
TN	1640	15 (10-20)	80 (60-89)	20 (4-37)
HR+	2410	20	94 (88-97)	6 (3-12)
HER2+	929	9	84 (86-89)	16 (11-24)

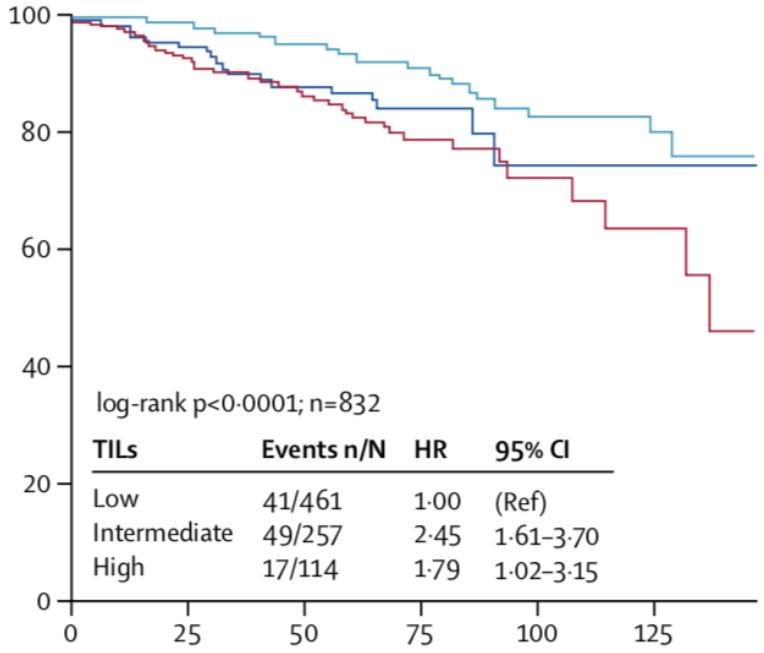


LPBC= lymphocyte-predominant breast cancer

TNBC



ER-positive



Stanton et al. JAMA Oncol 2017
Salgado et al. Ann Oncol 2014
Denkert et al. Lancet Oncol 2017

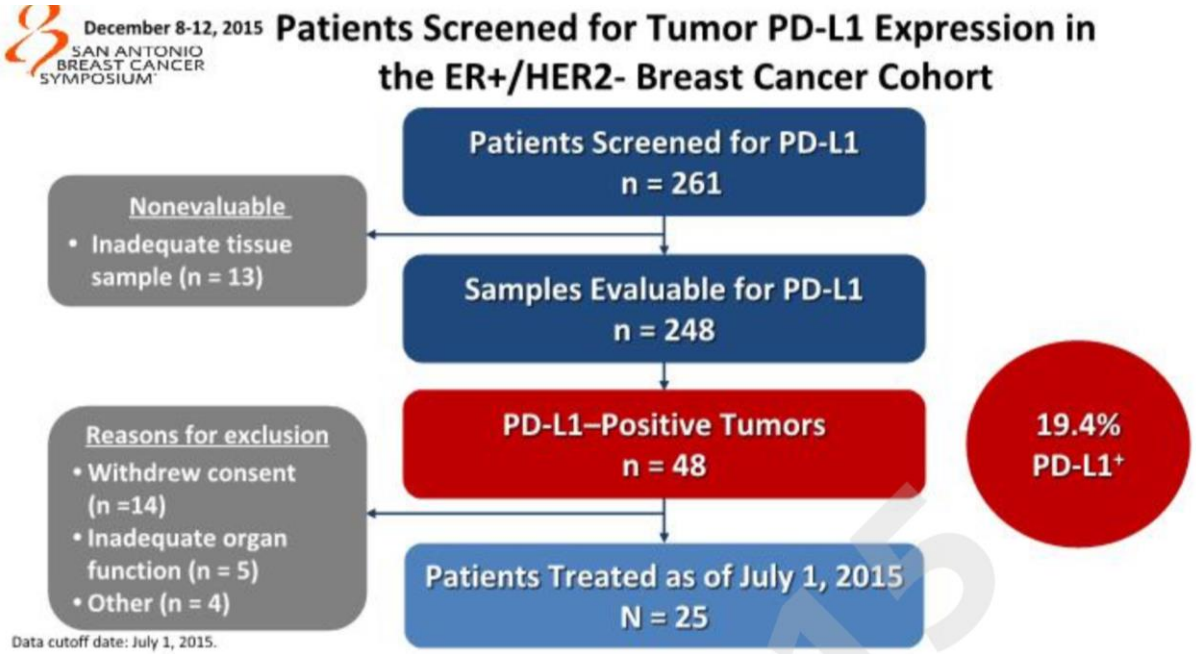
Anti-PD-L1 in end-stage ER-positive BC

Subgroup	*n*/*N*1	ORR % (95% CI)
TNBC	3/58	5.2 (1.1, 14.4)
HER2− (ER+ or PR+)	2/72	2.8 (0.3, 9.7)
HER2+	0/26	0 (0, 13.2)

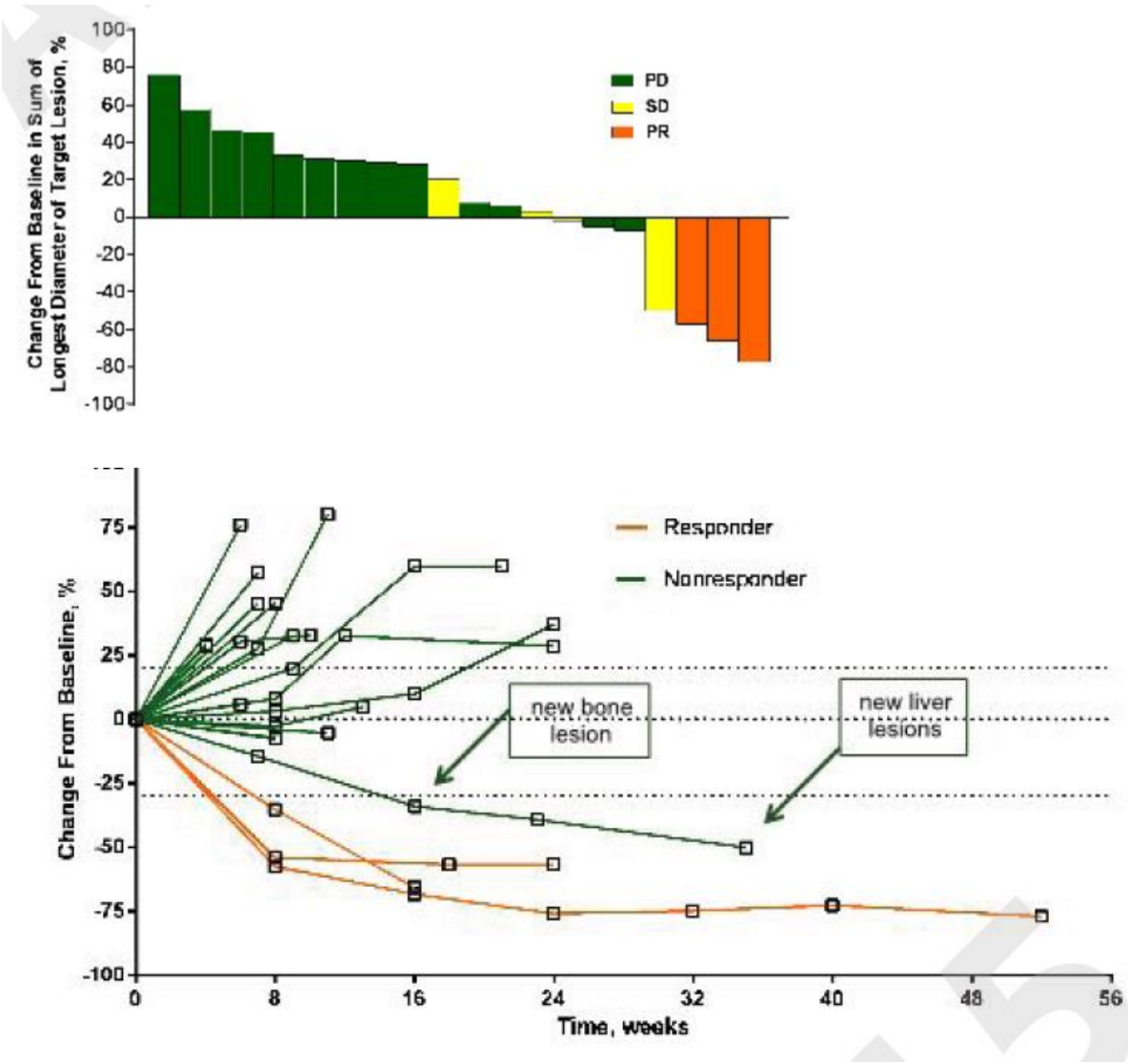
Avelumab, an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase 1b JAVELIN Solid Tumor study

Luc Y. Dirix[1] · Istvan Takacs[2] · Guy Jerusalem[3] · Petros Nikolinakos[4] · Hendrik-Tobias Arkenau[5,6] · Andres Forero-Torres[7] · Ralph Boccia[8] · Marc E. Lippman[9] · Robert Somer[10] · Martin Smakal[11] · Leisha A. Emens[12] · Borys Hrinczenko[13] · William Edenfield[14] · Jayne Gurtler[15] · Anja von Heydebreck[16] · Hans Juergen Grote[16] · Kevin Chin[17] · Erika P. Hamilton[18]

Anti-PD-1 in PD-L1 positive ER+ MBC



22 patients (PD-L1 positive tumor)
Response rate: 12%



Rugo et al. Clin Canc Res 2018

Cancer Therapy: Clinical

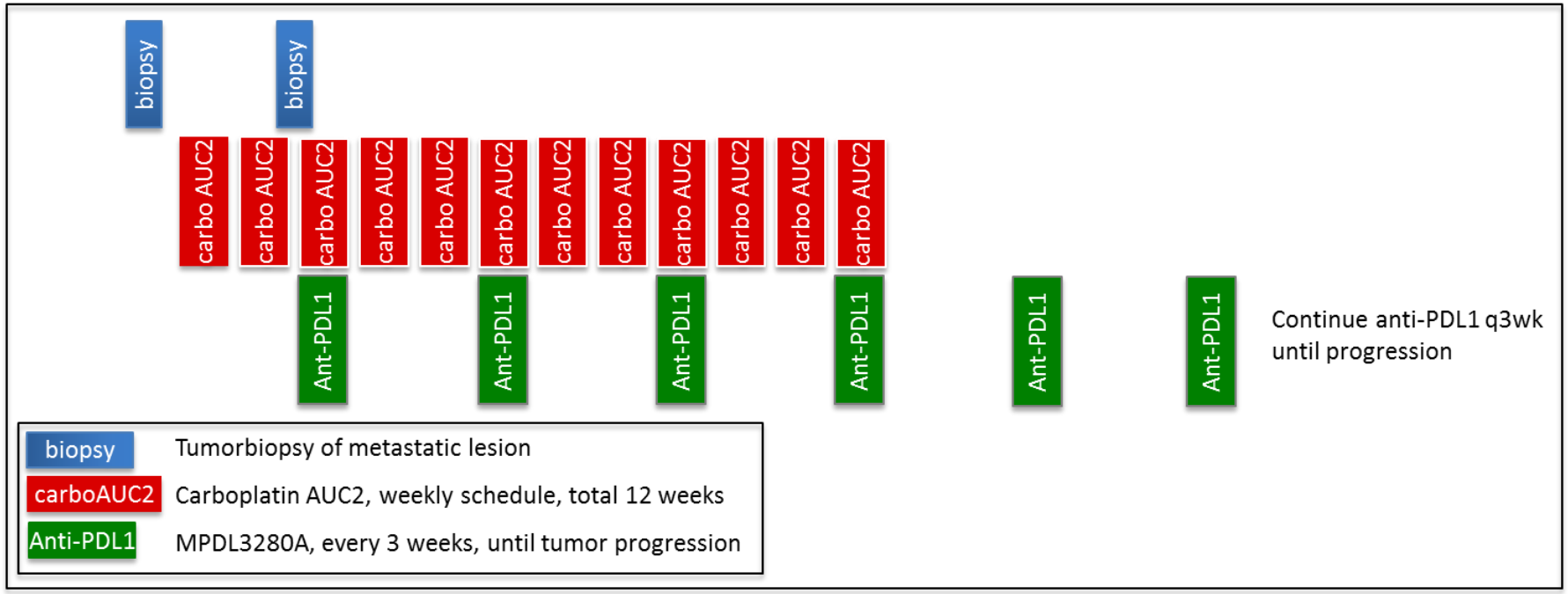
Clinical Cancer Research

Tremelimumab in Combination with Exemestane in Patients with Advanced Breast Cancer and Treatment-Associated Modulation of Inducible Costimulator Expression on Patient T Cells

Robert H. Vonderheide[1], Patricia M. LoRusso[2], Magi Khalil[1], Elaina M. Gartner[2], Divis Khaira[3], Denis Soulieres[4], Prudence Dorazio[5], Jennifer A. Trosko[1], Jens Rüter[1], Gabriella L. Mariani[6], Tiziana Usari[6], and Susan M. Domchek[1]

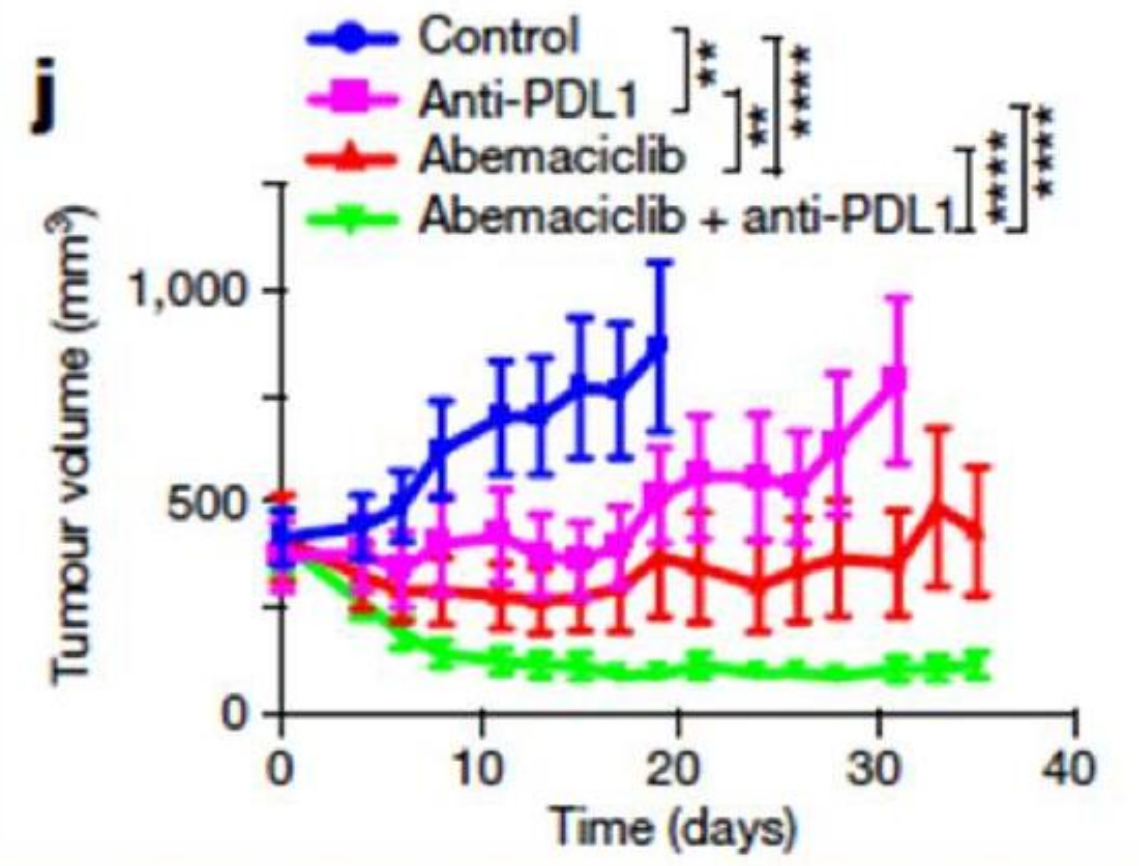
phase 1b
n=26
best ORR (SD>=12 wks) 42%

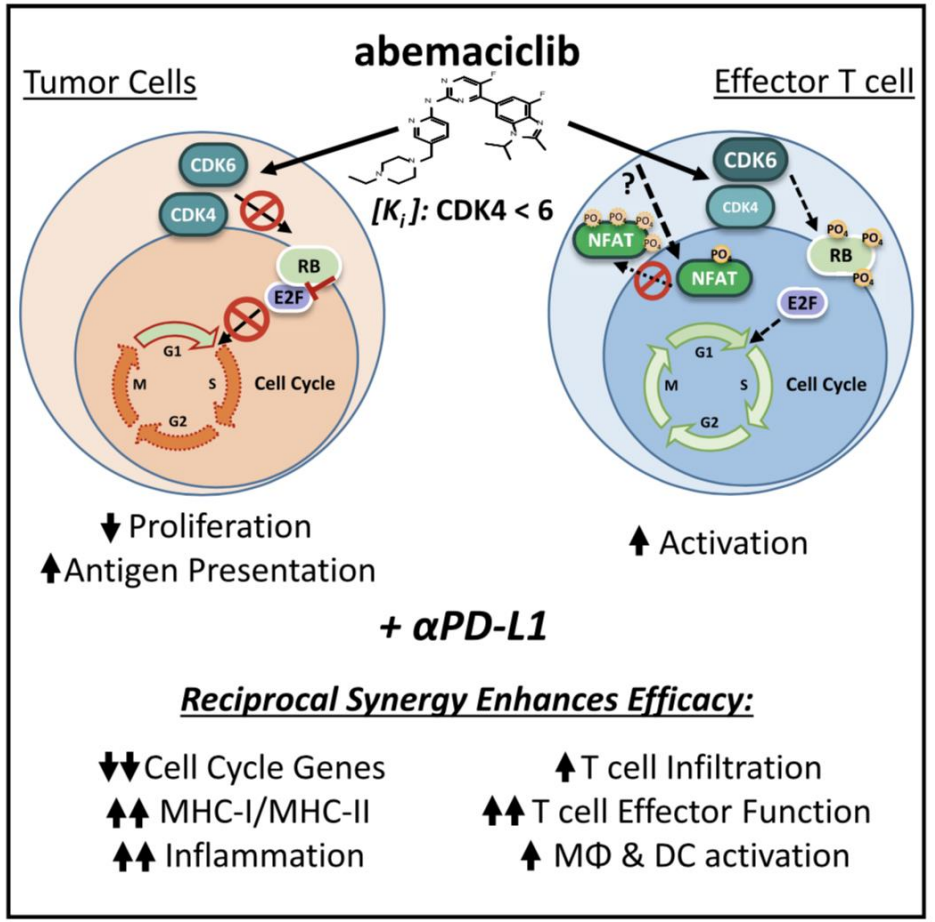
Platinum+atezo in mILC: GELATO trial



ClinicalTrials.gov Identifier: NCT03147040

Immunomodulatory capacity CDK4/6-i?





Goel et al. Nature 2017, Deng et al Cancer Discovery 2017, Schaer et al. Cell Reports 2018

CDK4/6-i + pembro in ER+ MBC

A Stage IV NSCLC, KRAS mutation (N=25)

B Stage IV NSCLC, Squamous (N=25)

C HR+, HER2- MBC (N=25)[a]

Inclusion Criteria
- Measurable disease per RECIST v1.1
- 1-2 prior chemotherapy
- No prior treatment with CDK4 & 6 or PD-1 & PD-L1 inhibitors
- ECOG PS ≤ 1

Figure 1. Study Design

Treatments
abemaciclib: 150 mg BID
+
pembrolizumab: 200 mg IV on Day 1 per 21-day cycle

16-wks Analysis

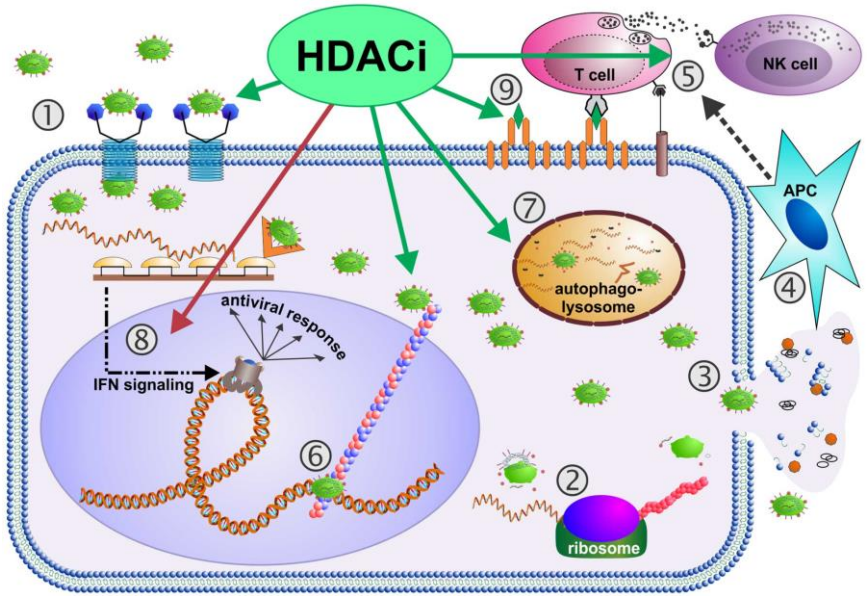
24-wks Primary Outcome

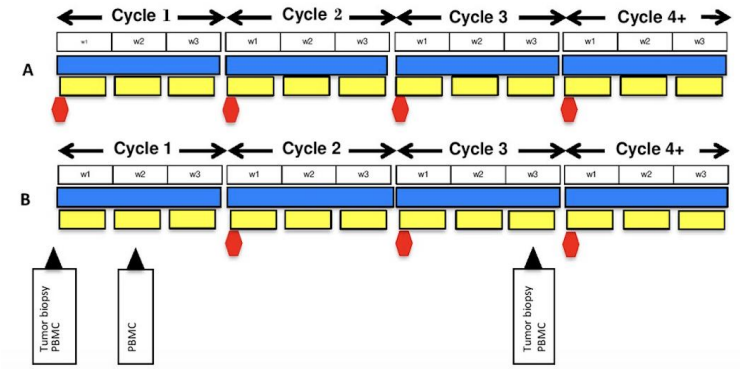
- **Primary objective**
  Safety Profile per CTCAE v4.0

Investigator-assessed Response	N=28
Confirmed ORR (CR+PR) (95% CI)	28.6% (13.2-48.7)
CR	0%
PR (confirmed) (95% CI)	28.6% (13.2-48.7)
CBR (CR+PR+SD ≥6 months) (95% CI)	46.4% (27.5-66.1)

Tolaney et al. ASCO 2018

Immunomodulatory capacity of HDAC-i?

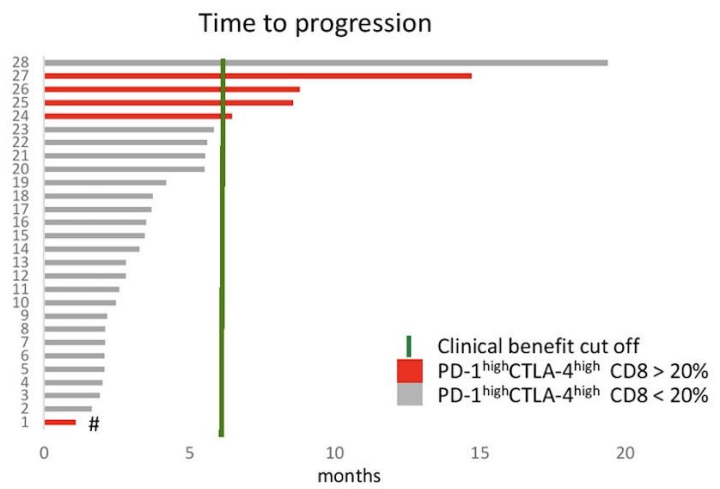


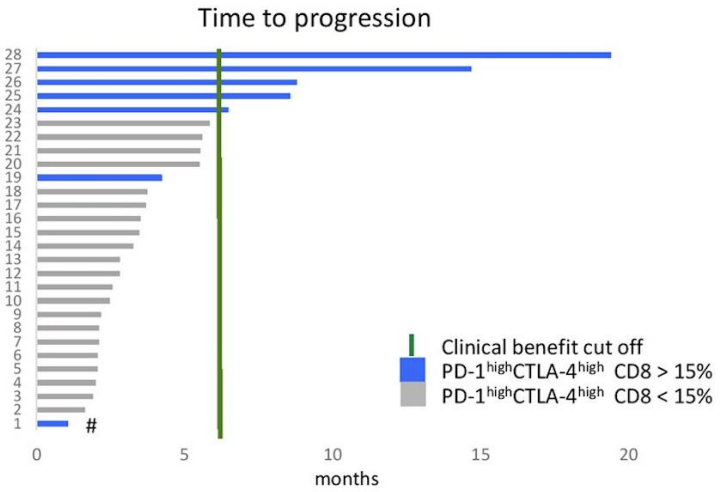


Tamoxifen: 20mg daily PO
Vorinostat: 400mg 5 days/week PO
Pembrolizumab: 200mg every 3 weeks IV

Figure 1: Schematic of dosing schedule. Phase II study - testing if HDACi can prime anti-PD-1 therapy and reverse hormone therapy resistance in (ER)$^{+}$ breast cancer.
A – concurrent priming; B – sequential priming with HDAC inhibitor. Blood and tumor samples were obtained for correlative analysis. PBMCs – peripheral blood mononuclear cells.

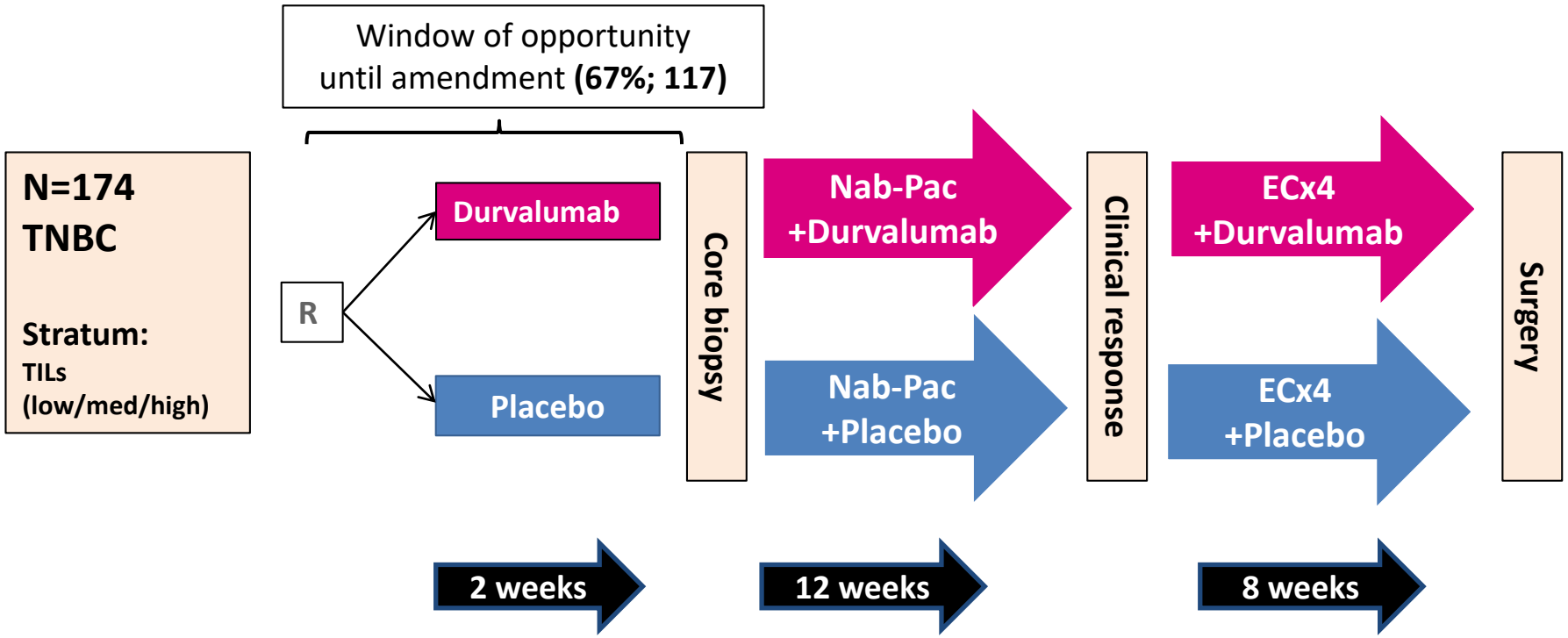
Dual positivity PD-1/CTLA-4 in CD8 cells in pretreatment blood or tumor correlates with clinical benefit





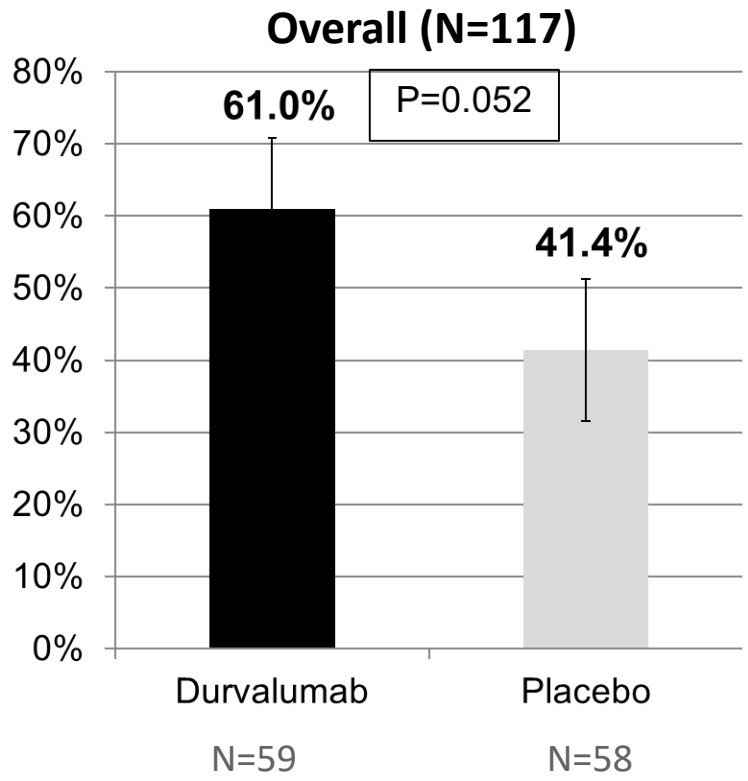
Ellerhof et al. Int J Oncol. Munster et al. ASCO 2018

Neoadjuvant setting



Loibl et al, ASCO 2018

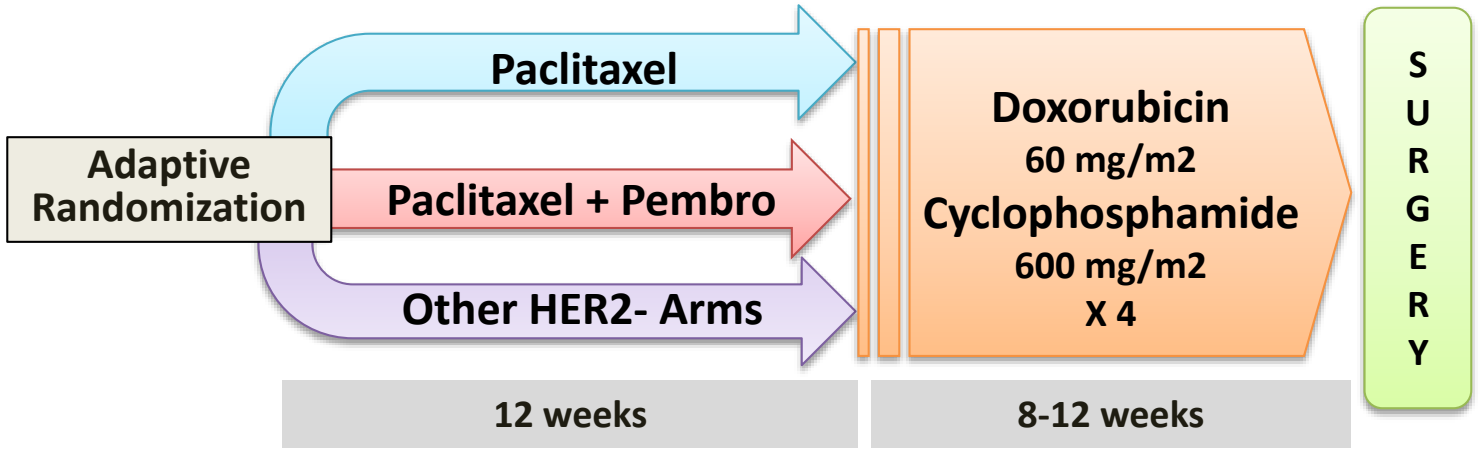
Neoadjuvant setting



Induction ICI to augment responsiveness?

Loibl et al, ASCO 2018

Neoadjuvant setting



Control

Paclitaxel 80 mg/m2 every wk x 12

Experimental

Paclitaxel 80 mg/m2 every wk x 12

Pembro 200 mg every 3 wks x 4

Nanda et al, ASCO 2017

Neoadjuvant setting

	Est pCR + pembro	Est pCR control
All HER2-	0.46 (0.34-0.58)	0.16 (0.06-0.27)
TNBC	**N=29** **0.60 (0.43-0.78)**	**N=89** **0.20 (0.06-0.33)**
HR+HER2-	0.34 (0.19-0.48)	0.13 (0.03-0.24)

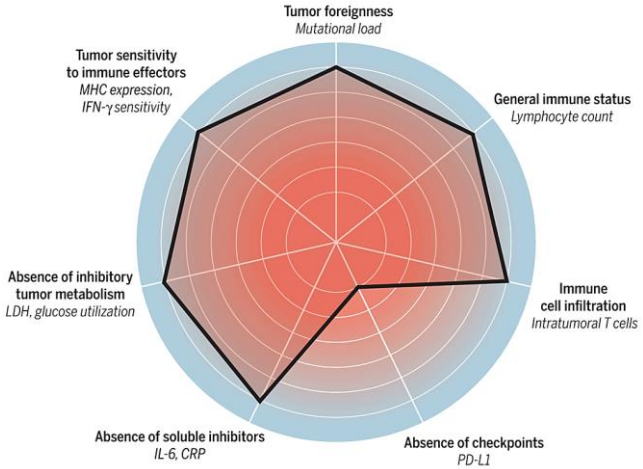
Likelihood of significant difference > 99%

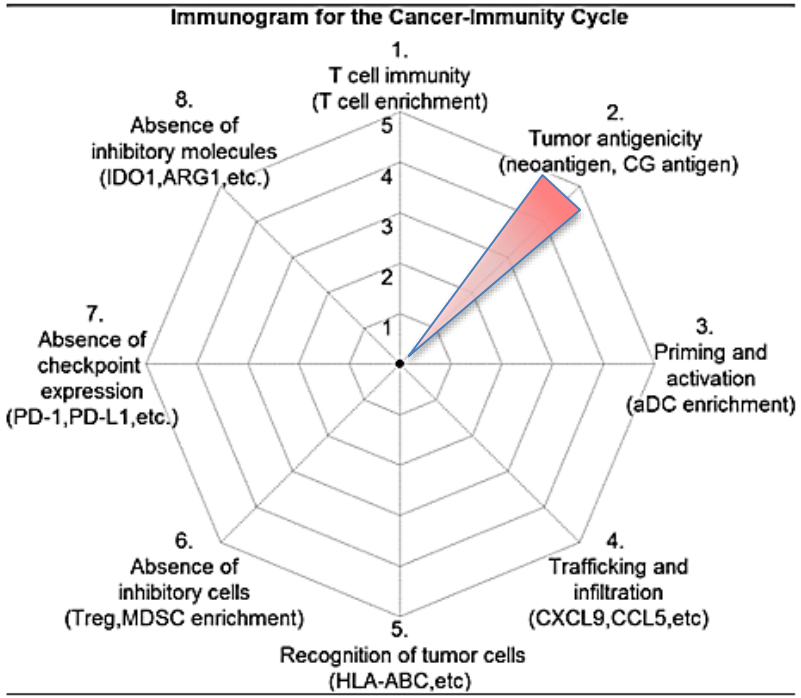
Exciting, however:

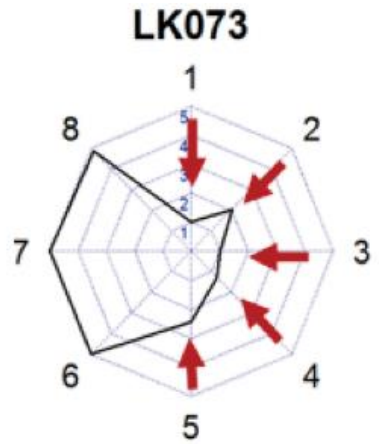
- Estimation of an intermediate endpoint (caveat emptor)
- grade 3+ adrenal insufficiency in ~ 7%, other immune toxicities seen

Nanda et al, ASCO 2017

The Cancer Immunogram

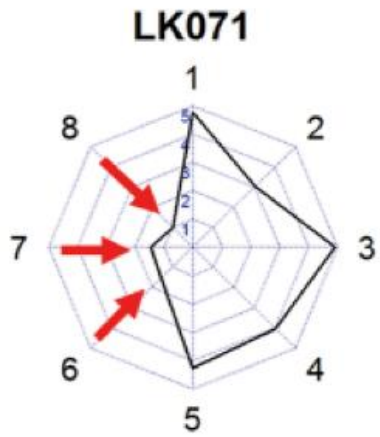






T cell-poor

- ✓Induce immunogenic cell death
- ✓Neoantigen vaccine
- ✓Anti–CTLA-4
- ✓IFNα, CD40-agonist, microbiota
- ✓Epigenetic therapy
- ✓CAR-T cell therapy

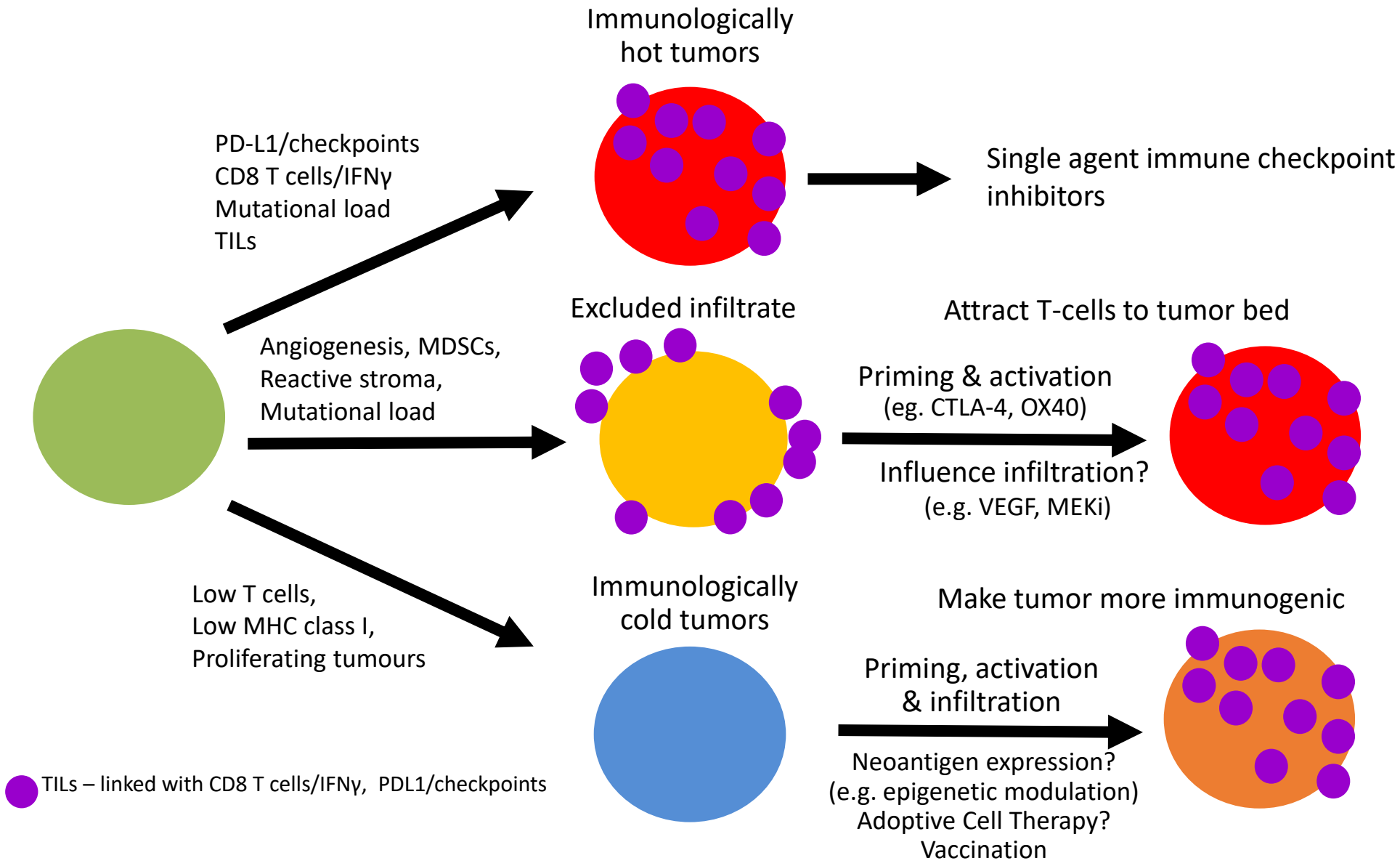


T cell-rich

- ✓Deprivation of Treg/MDSC
- ✓Anti–PD-1/PD-L1
- ✓IDO/arginase inhibitor
- ✓Control of glucose metabolism

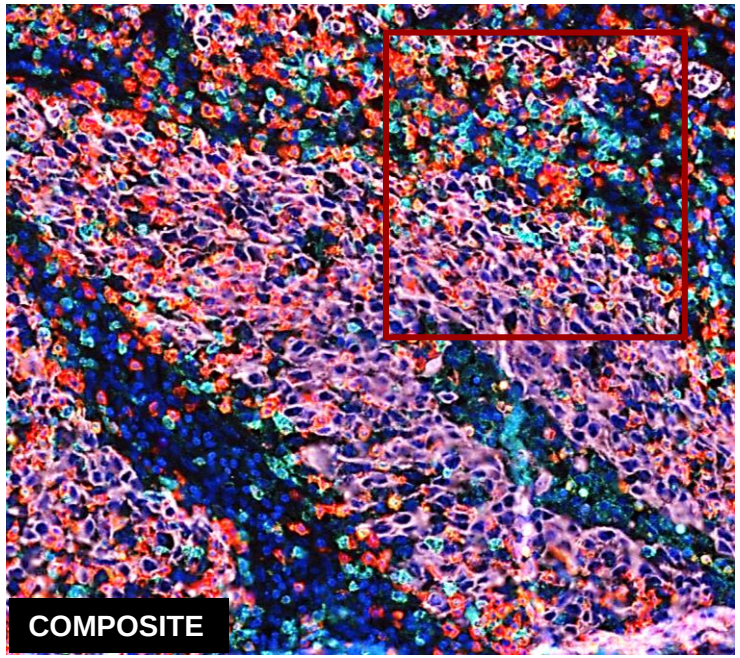
Blank CU, et al. *Science.* 2016;352(6286):658-660. Karasaki T, et al. *J Thorac Oncol.* 2017;12(25):791-803.

MDSC, Myeloid-derived suppressor cells


Immunologically hot tumors
PD-L1/checkpoints
CD8 T cells/IFNγ
Mutational load
TILs
Single agent immune checkpoint inhibitors
Excluded infiltrate
Attract T-cells to tumor bed
Angiogenesis, MDSCs,
Reactive stroma,
Mutational load
Priming & activation
(eg. CTLA-4, OX40)
Influence infiltration?
(e.g. VEGF, MEKi)
Low T cells,
Low MHC class I,
Proliferating tumours
Immunologically cold tumors
Make tumor more immunogenic
Priming, activation & infiltration
Neoantigen expression?
(e.g. epigenetic modulation)
Adoptive Cell Therapy?
Vaccination
TILs – linked with CD8 T cells/IFNγ, PDL1/checkpoints

Breast Cancer Immune Landscape:
Analysis of CD3, CD8, CD4, FoxP3 Immune infiltrates in tumors (CK)

Inflamed



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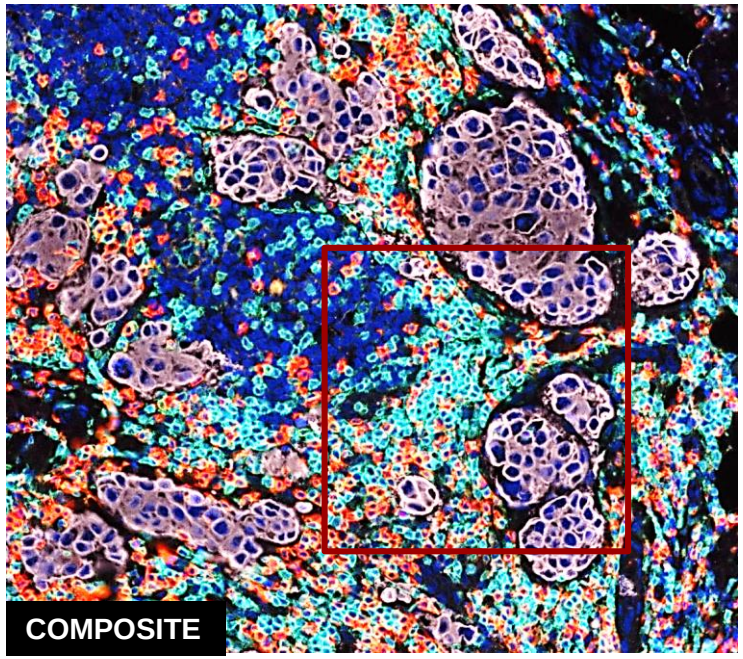
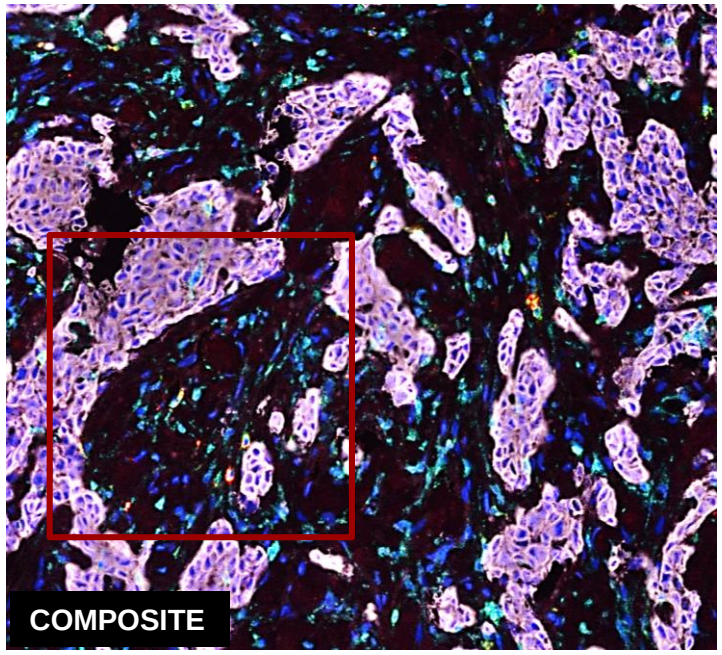


Immune desert



LUDWIG CANCER RESEARCH

Courtesy, George Coukos lab
Rusakiewicz Sylvie

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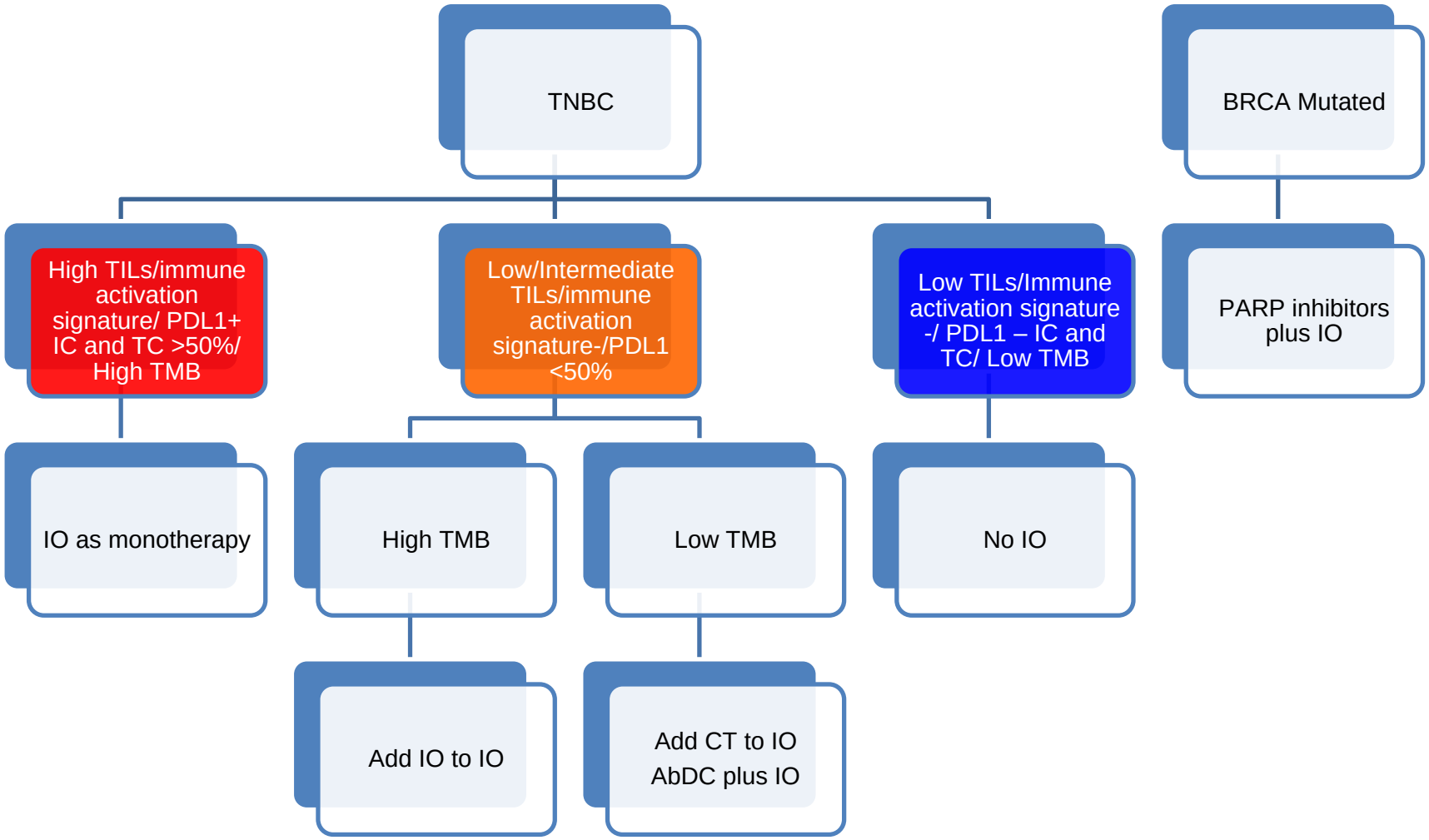
CHUV

Immunogenic TNBC: A road map for future



Conclusions

- The tumour genome as a driver of cancer immunity
- The immune response to cancer is dependent on T cells that are specific for cancer-associated antigens
- Changes in gene expression in tumours owing to epigenetic modifications and the expression of microRNAs probably contribute directly to determining the immune microenvironment and immunogenicity of a tumour
- Limited data on host (microbiome)

Thank You

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