Immunoterapia e tumori TN

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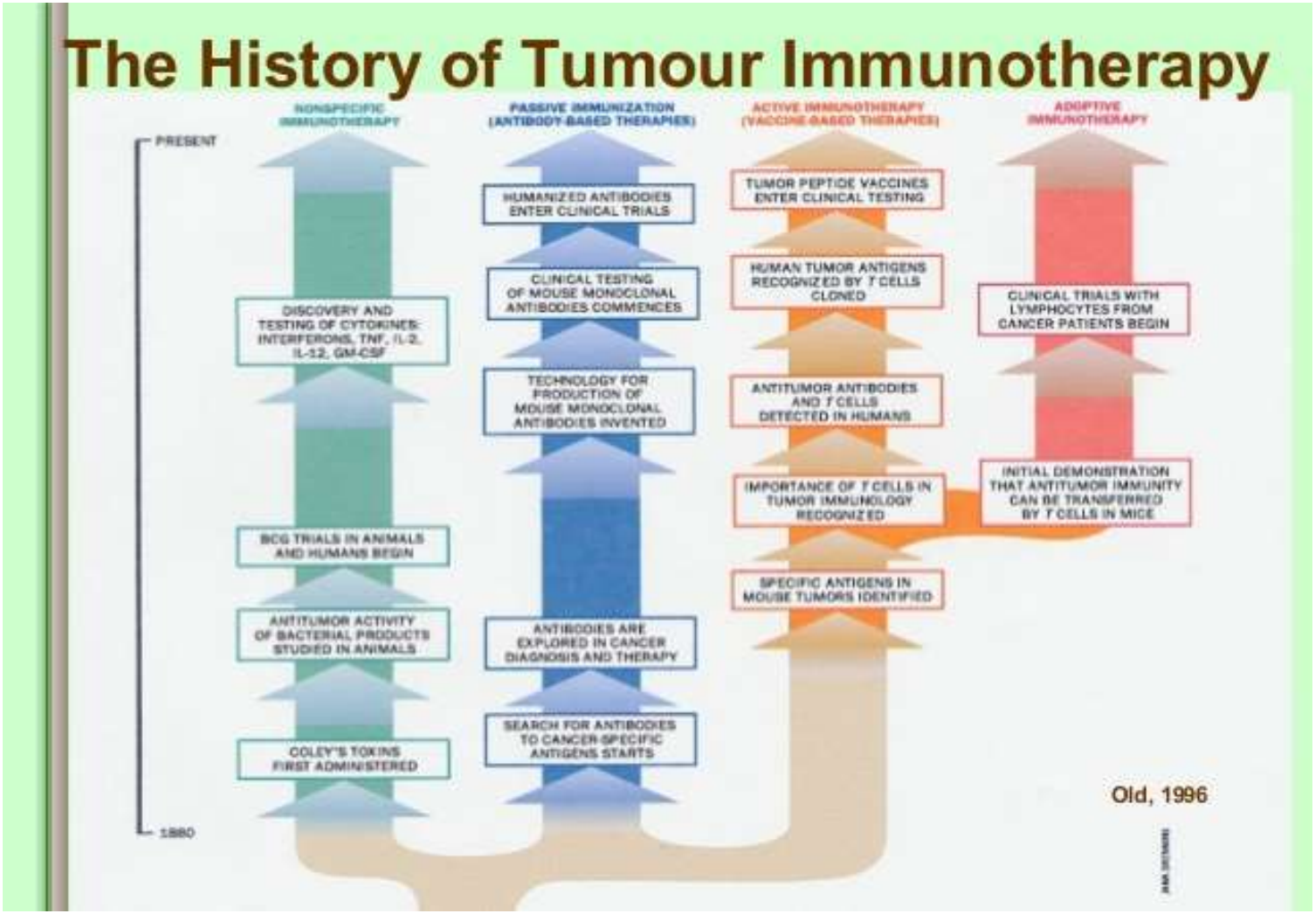
Disclosures (last two years)

- Speaker's Honoraria from
  - Eisai
  - AstraZeneca
  - Pierre Fabre
  - Novartis

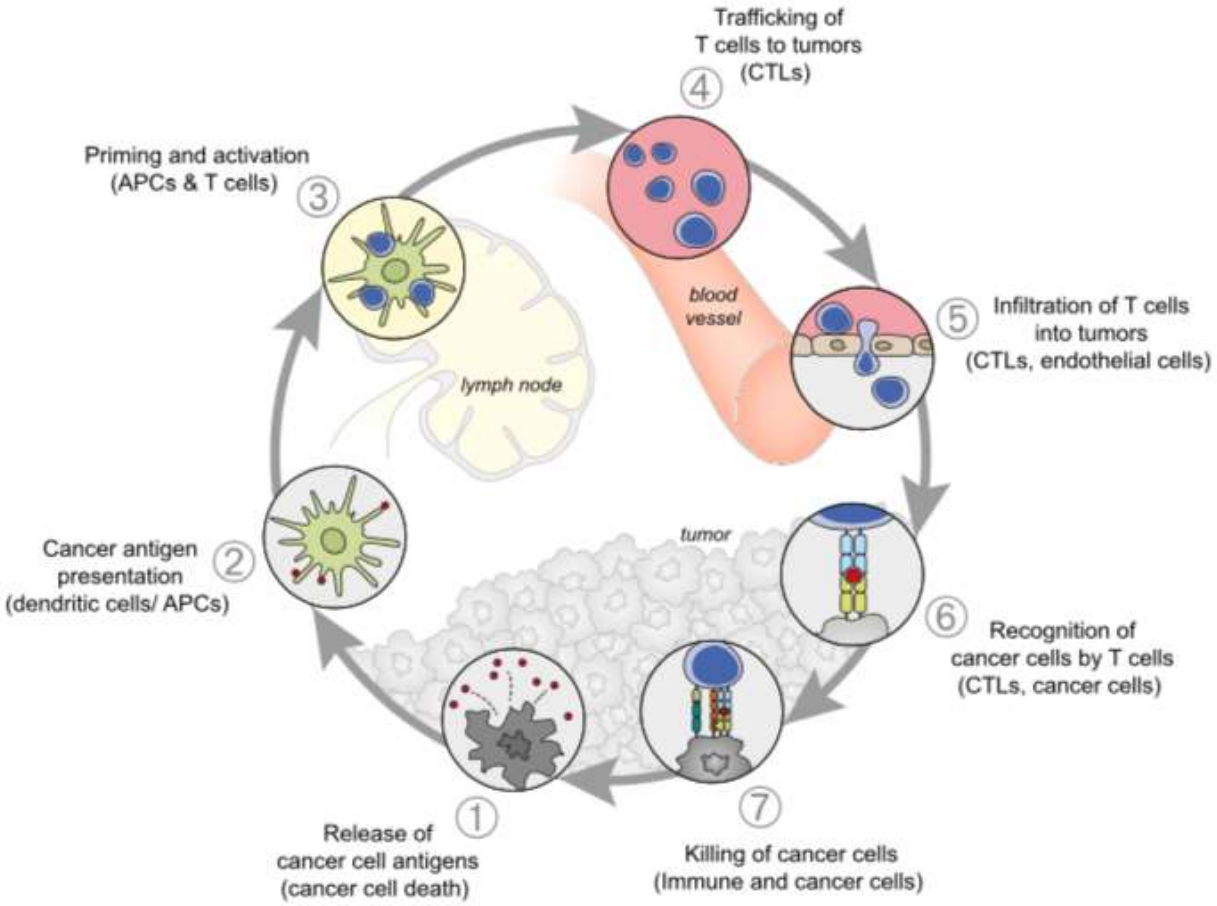
Outline

- Introduction: what's immunotherapy?
- Breast cancer and TILS
- Data from clinical trials
- Future directions: how, when and what

Immunotherapy in cancer

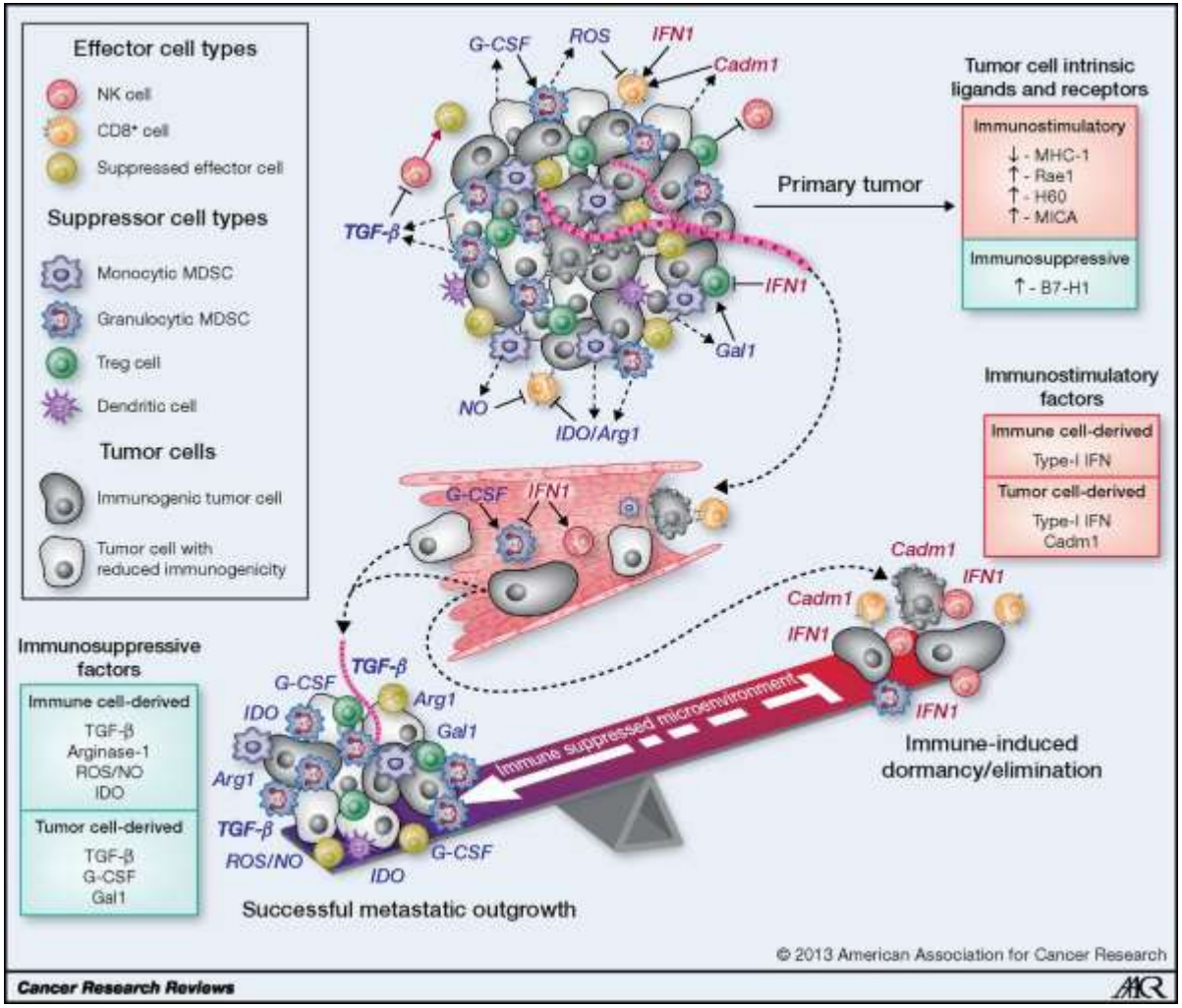


The cancer immunity cycle



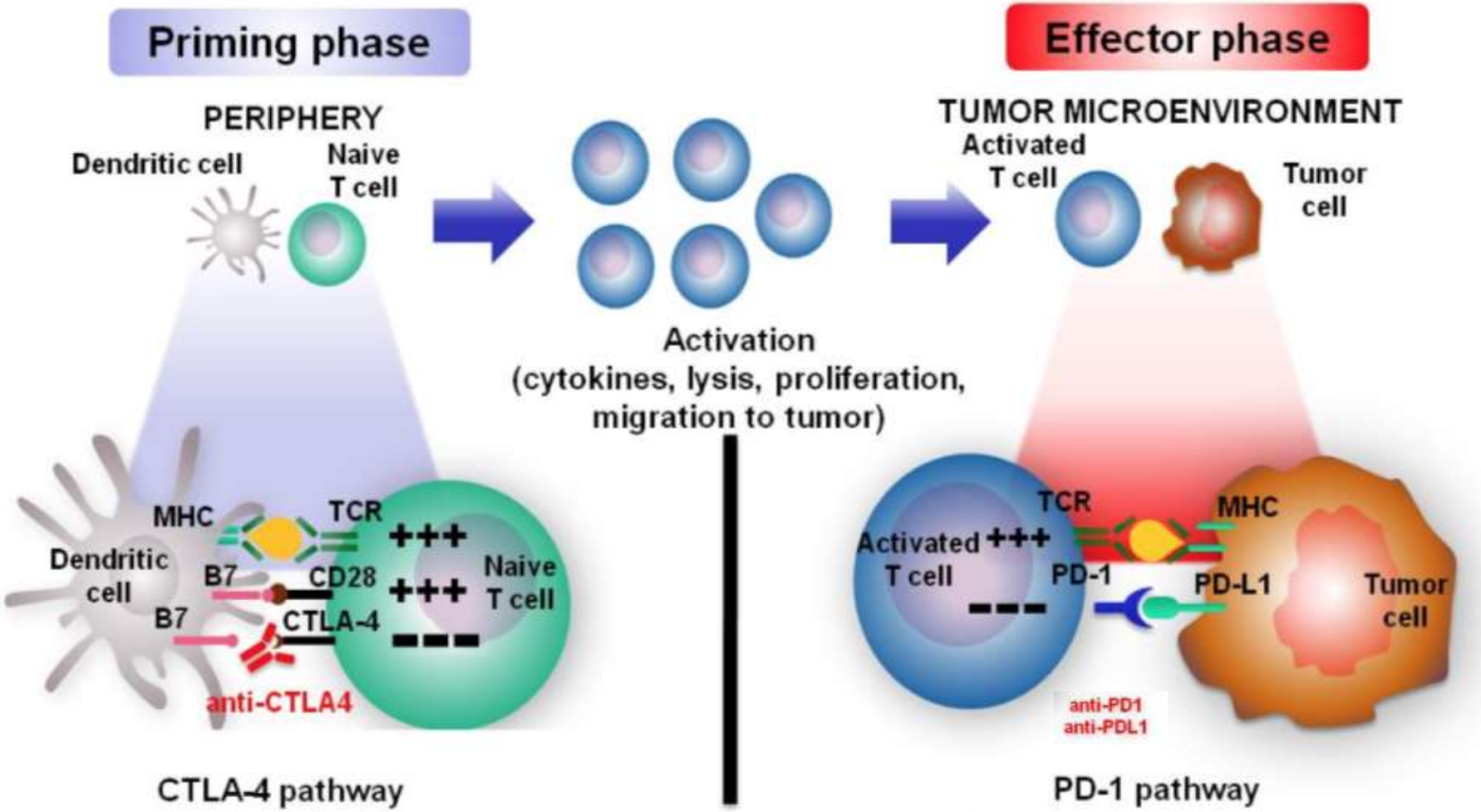
Chen et al, Immunity Review 2013

The immunosurveillance and immunoediting balance



Slaney et al,Cancer Research 2013

Targeting CTLA-4 and PD1 pathways



CTLA-4 = cytotoxic T-lymphocyte-associated antigen 4 ; MHC = major histocompatibility complex; PD-1 = programmed death-1; PD-L1 = programmed death ligand 1; TCR = T-cell receptor

Mod da: Wolchock J, et al. JCO 2013 Volume 31, Issue 15_suppl ; abstr 9012^

Adapted from Bianchini, Back from Madrid, Genova 2017

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

ESTABLISHED IN 1812 MARCH 16, 2017 VOL. 376 NO. 11

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*

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

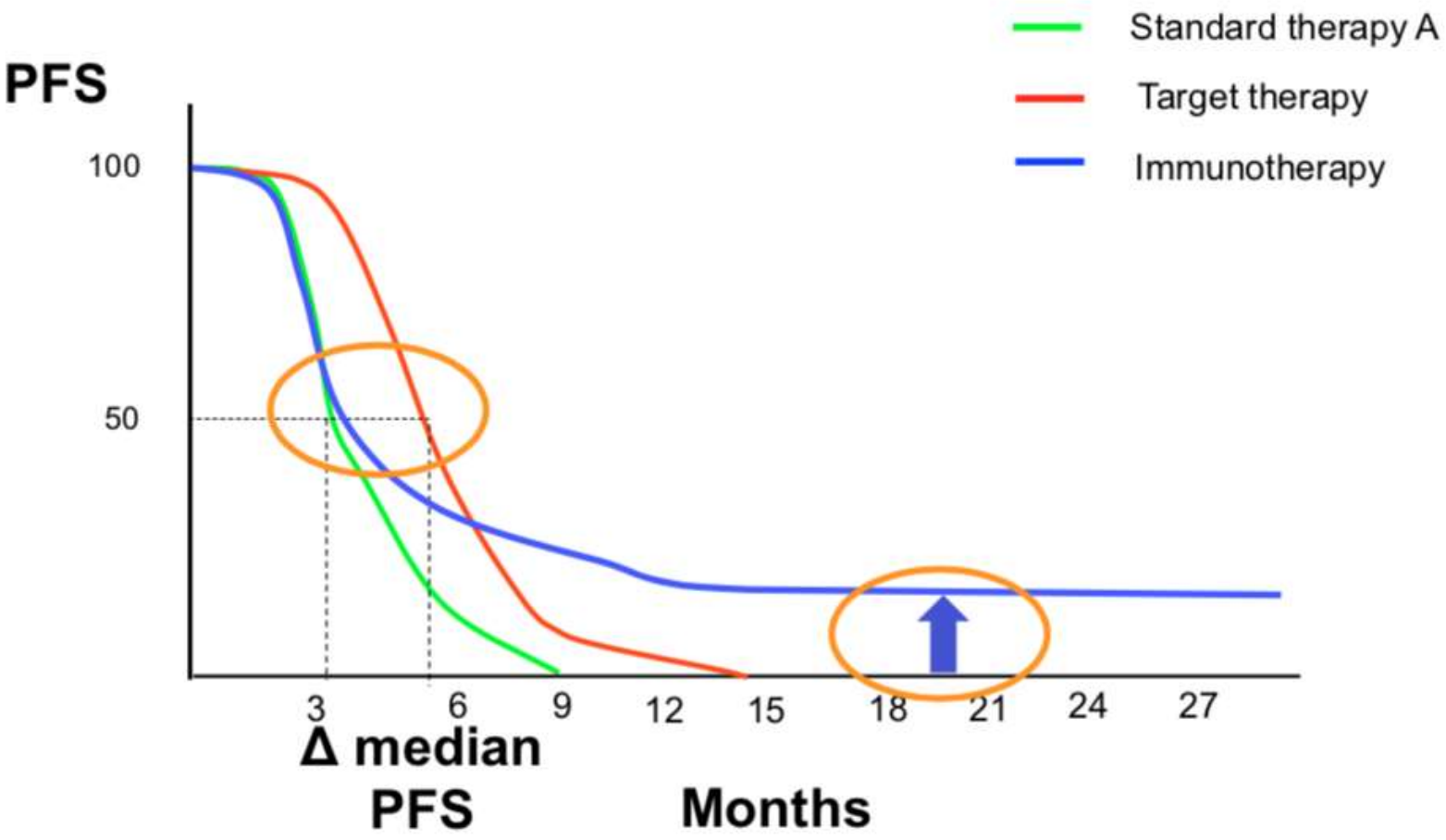
VOLUME 36 · NUMBER 8 · MARCH 10, 2018

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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

Michael J. Overman, Sara Lonardi, Ka Yeung Mark Wong, Heinz-Josef Lenz, Fabio Gelsomino, Massimo Aglietta, Michael A. Morse, Eric Van Cutsem, Ray McDermott, Andrew Hill, Michael B. Sawyer, Alain Hendlisz, Bart Neyns, Magali Svrcek, Rebecca A. Moss, Jean-Marie Ledeine, Z. Alexander Cao, Shital Kamble, Scott Kopetz, and Thierry André

Can we cure cancer with immunotherapy?



Adapted from Bianchini, Back from Madrid, Genova 2017

Mutational Load of Human Cancers

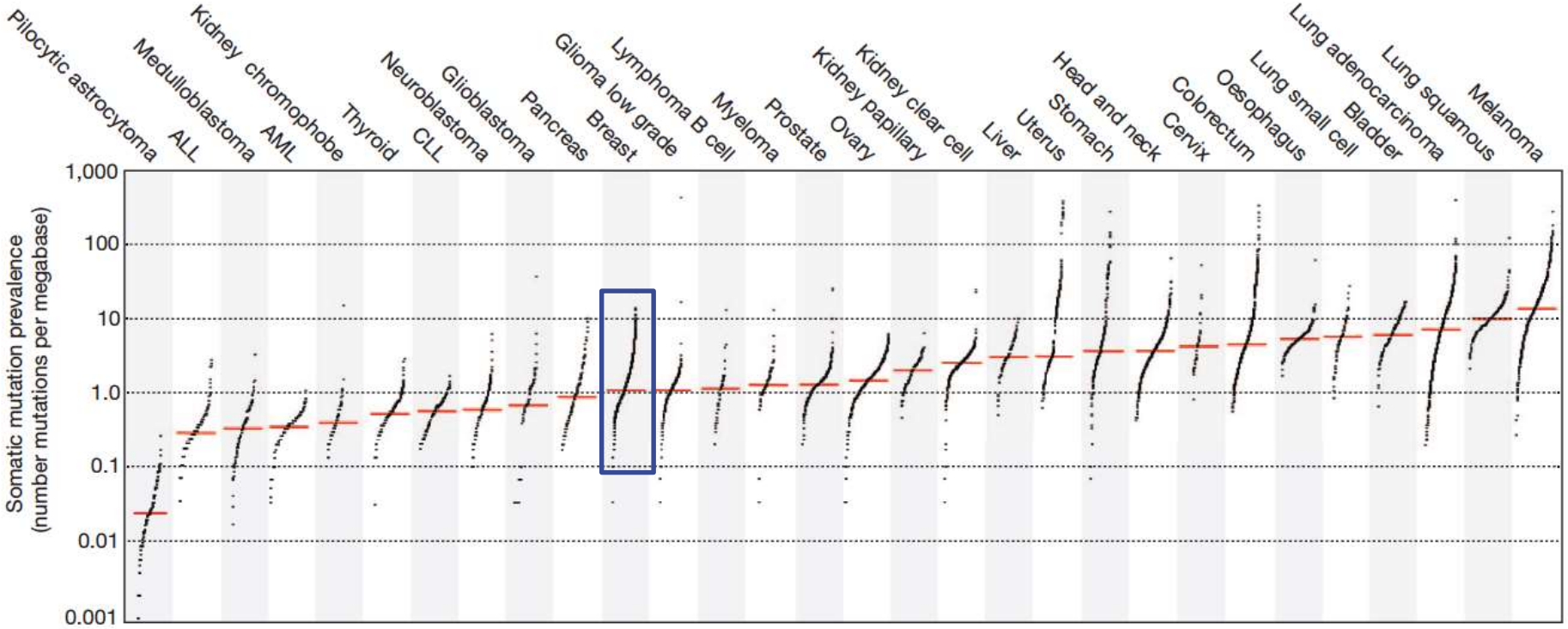
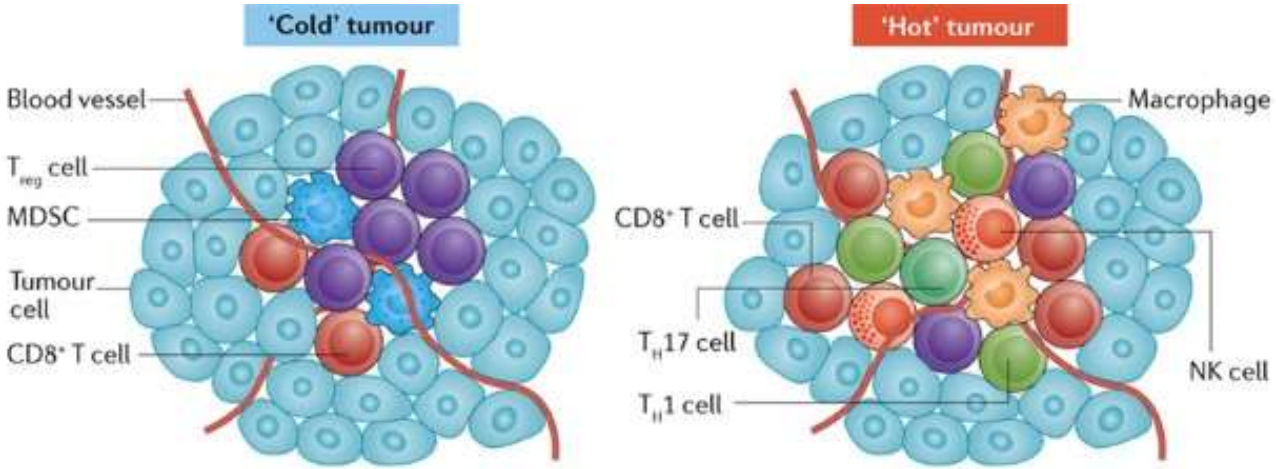


Figure 1 | The prevalence of somatic mutations across human cancer types. Every dot represents a sample whereas the red horizontal lines are the median numbers of mutations in the respective cancer types. The vertical axis (log scaled) shows the number of mutations per megabase whereas the different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

Cold and Hot Tumours



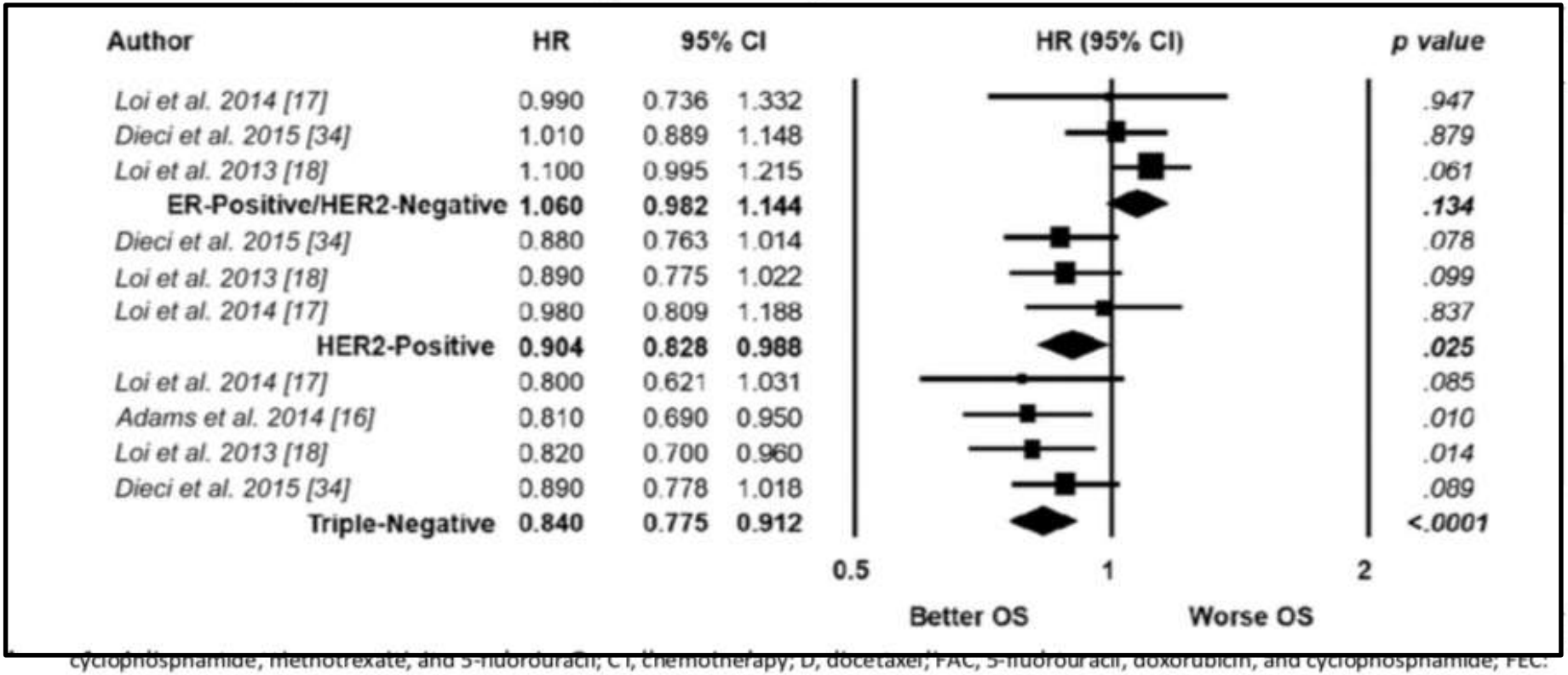
	'Cold' tumour	'Hot' tumour
Biological characteristics	• Epigenetic silencing • Active β-catenin signalling • Mesenchymal-like cells • Stem cell-like cells • Less-differentiated cells	• Epigenetic reprogramming • Suppressed β-catenin signalling • Epithelial cells • Highly differentiated cells • High PDL1 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

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

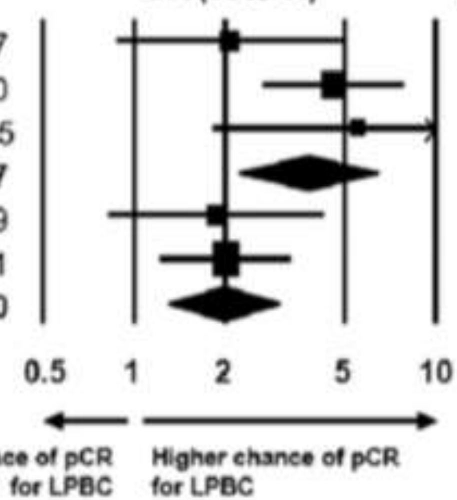
TILs in Early Breast Cancer

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			

B

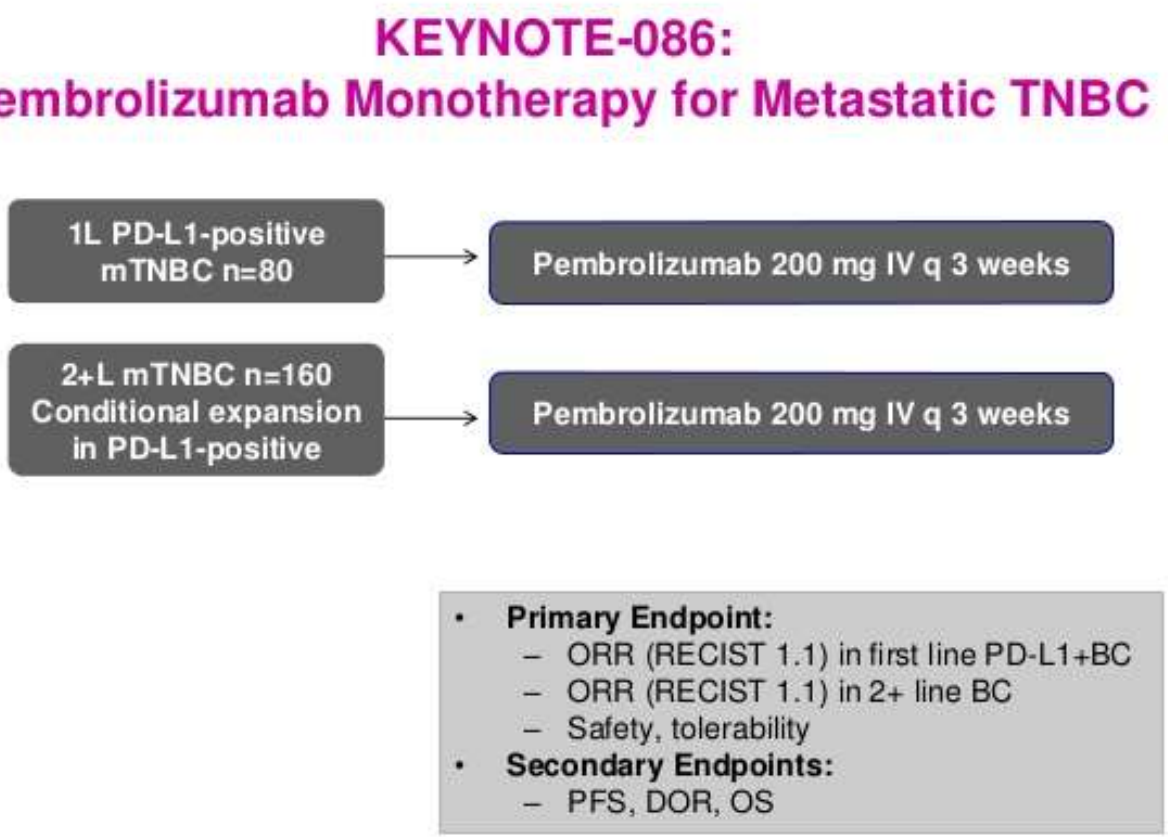
Author	Subtype	OR	95% CI		p value
Denkert et al. 2010 [21]	HER2-Positive	2.081	0.883	4.907	.094
Denkert et al. 2015 [23]	HER2-Positive	4.569	2.673	7.810	<.0001
Dieci et al. 2015 [33]	HER2-Positive	5.500	1.821	16.615	.003
	HER2-Positive	**3.782**	**2.226**	**6.427**	**<.0001**
Issa-Nummer et al. 2013 [22]	Triple-Negative	1.862	0.814	4.259	.141
Denkert et al. 2015 [23]	Triple-Negative	2.013	1.224	3.311	.006
	Triple-Negative	**1.972**	**1.287**	**3.020**	**.002**



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

Pembrolizumab in TNBC: Keynote-086



Pembrolizumab in TNBC: Keynote-086

	Cohort B (1° Line) (n=84 PD-L1+)
ORR, n (%) [95% CI]	ORR 23%
DCR,[b] n (%) [95% CI]	
Best Overall Response, n (%)	
Complete response	CR 4%
Partial response	PR 19%
Stable disease	SD 17%
Progressive disease	PD 58%
Not evaluable,	
Not able to be assessed,[d] n (%)	

Adams, ASCO 2017

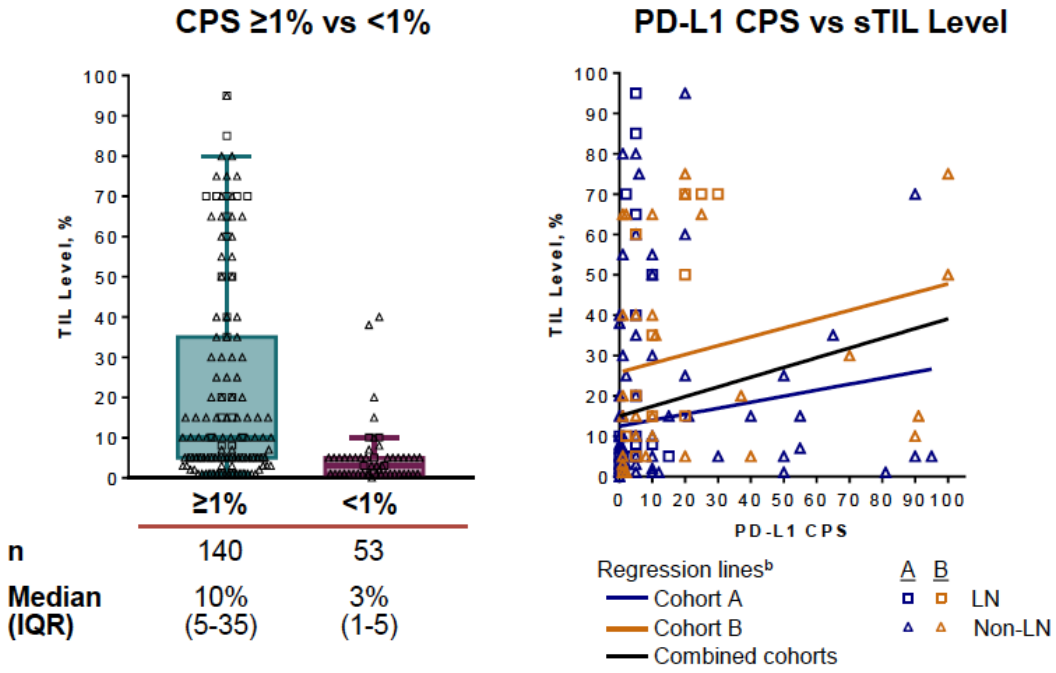
Keynote-086; sTIL levels correlate with tumor response

	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.

Loi ,LBA13 ESMO 2017

Keynote-086: PD-L1 and sTIL levels are correlated



Significant Correlation Between sTIL levels and PD-L1 CPS

- **Cohort A:** ρ = 0.408; *P* < 0.001[a]
- **Cohort B:** ρ = 0.485; *P* = 0.0003[a]
- **Combined cohorts:** ρ = 0.496; *P* < 0.001[a]

- [a]Wilcoxon rank sum (one sided). [b]Cohort A: r = 0.128, *P* = 0.0122; cohort B: r = 0.227, *P* = 0.1296; combined cohorts: r = 0.217, *P* = 0.002.
- In the left figure, Box = 25th and 75th percentiles; line = median; whiskers = 1.5×IQR.
  Data cutoff date: Nov 10, 2016.

Loi ,LBA13 ESMO 2017

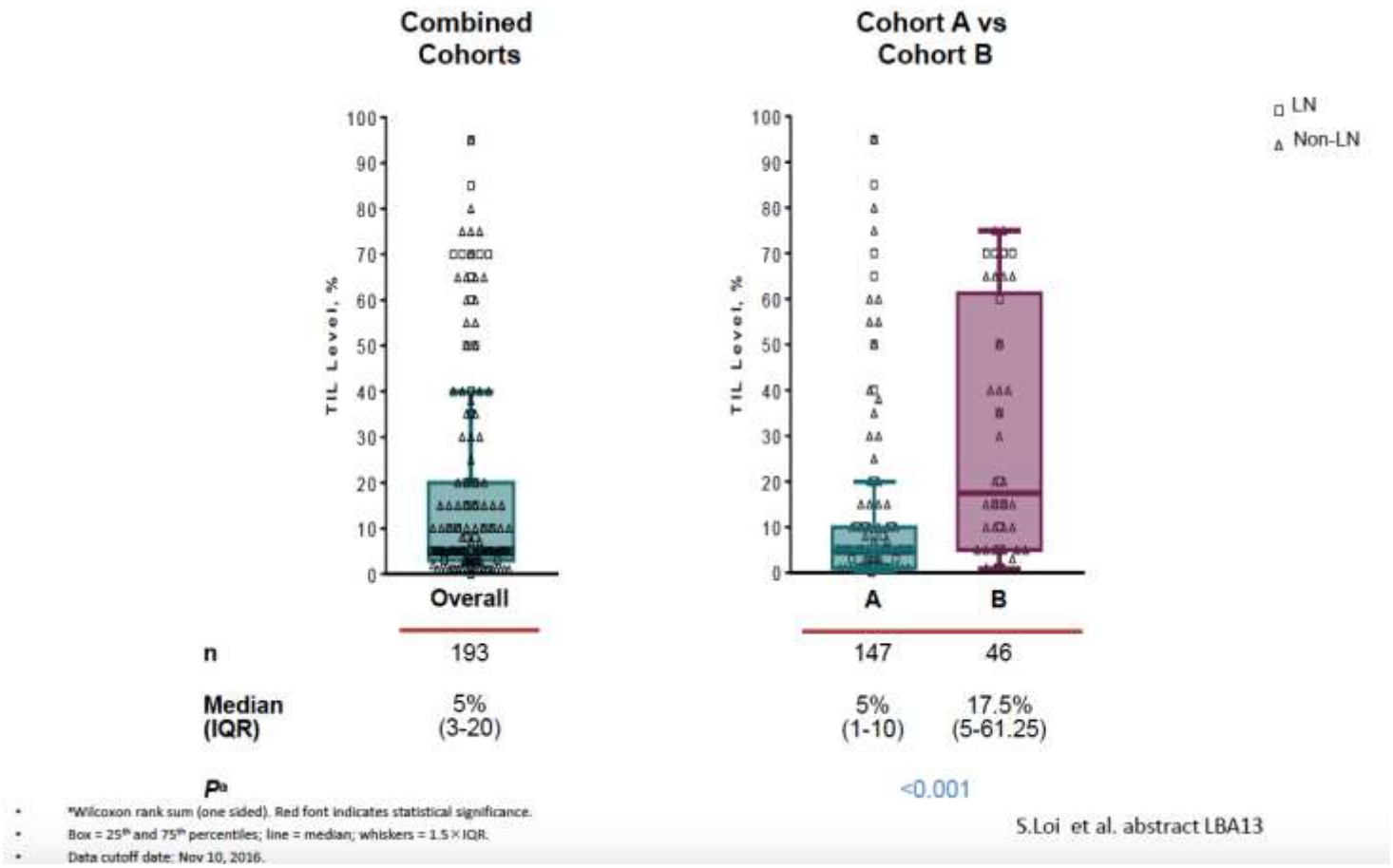
Immune checkpoint inhibitors seems to work better in earlier lines

Molecular subtype	Author	Drug	No. Pts	ORR	Selection	ORR PDL1+§	ORR PDL1-§	ORR 1L	ORR 2L+
TNBC	Nanda R	Pembrolizumab	27	18.5%	PDL1+				
	Adams S	Pembrolizumab	170	4.7%	All	4.8%	4.7%		4.7%
	Adams S	Pembrolizumab	52	23.1%	PDL1+			23.1%	
	Emens L	Atezolizumab	21	19.0%	PDL1+				
	Schmid P	Atezolizumab	112	10.0%	All	13.0%	5.0%	26.0%	7.0%
	Dirix L	Avelumab	58	8.6%	All	44.0%	2.6%		
ER+/HER2-	Hugo R	Pembrolizumab	25	12.0%	PDL1+				
	Dirix L	Avelumab	72	2.8%	All				
HER2+	Dirix L	Avelumab	24	3.8%	All				

§ PDL1+ and PDL1- were defined differently in different studies

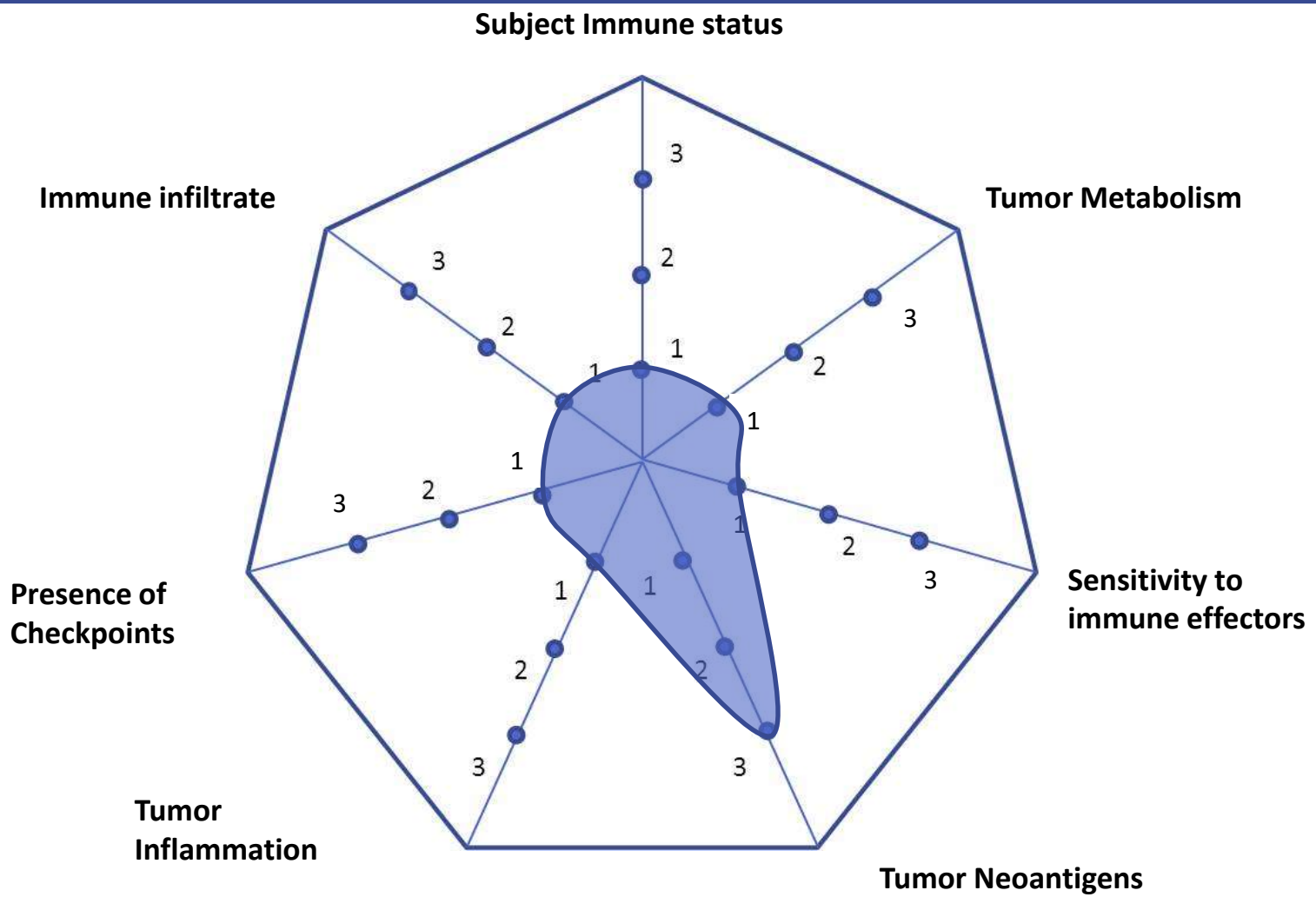
Adapted from Bianchini, Back from Madrid, Genova 2017

Keynote-086; sTILS levels tend to decrease during the natural history of breast cancer



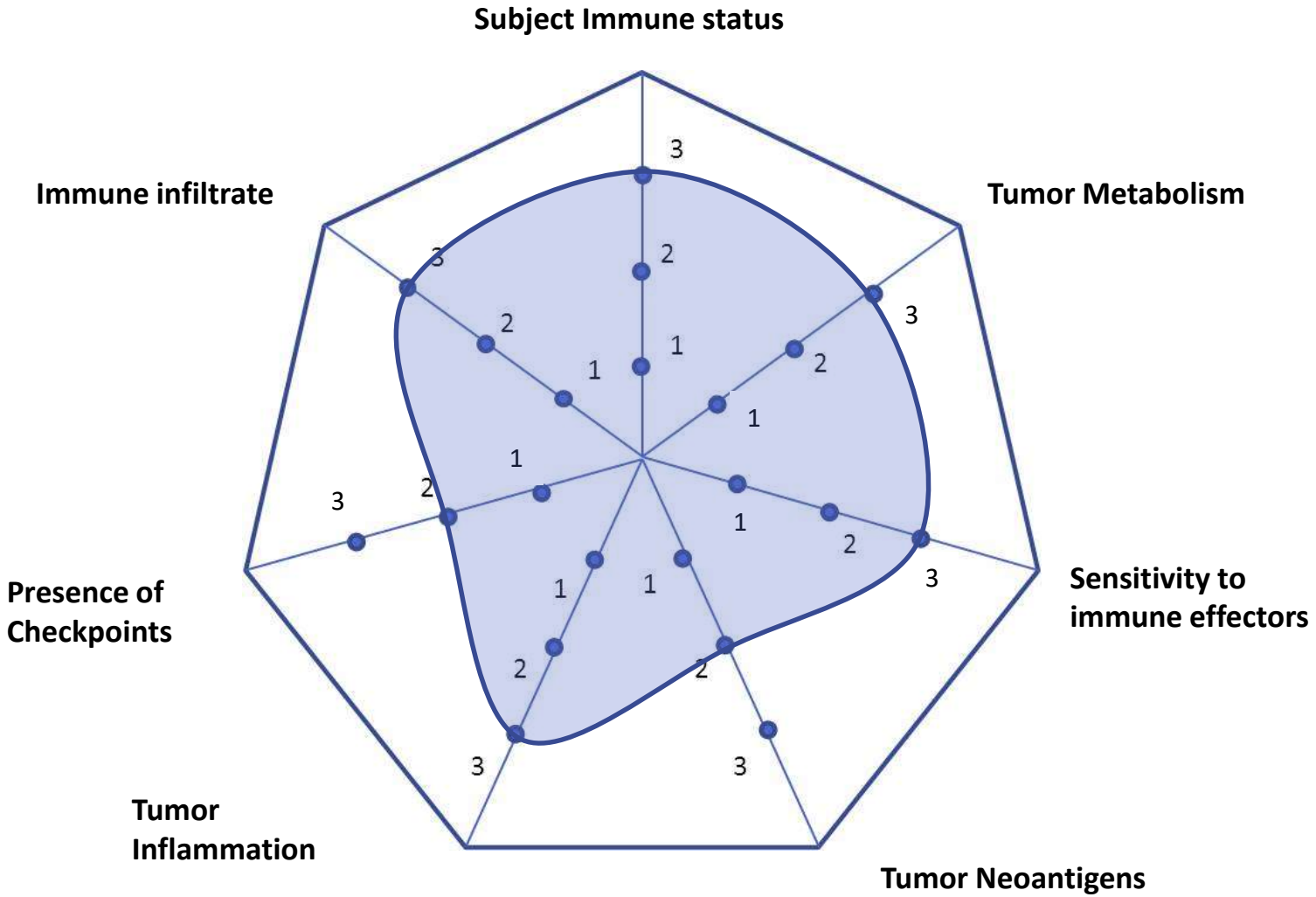
Loi ,LBA13 ESMO 2017

Immunogram; late stage disease



Courtesy of Dr Filippo Montemurro

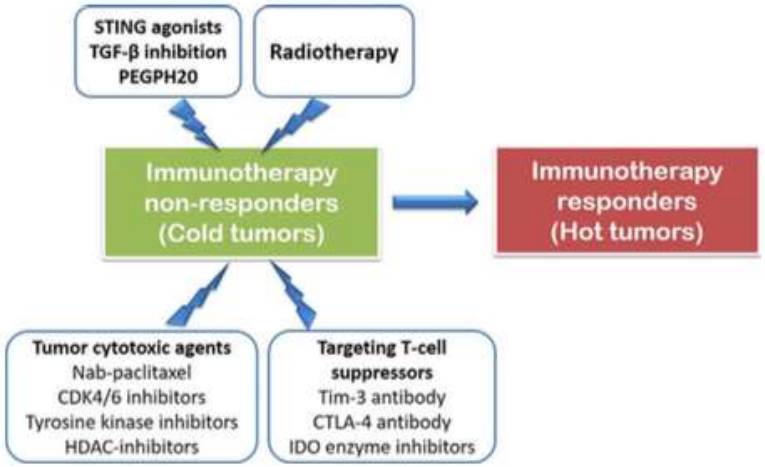
Immunogram; earlier stage disease



Courtesy of Dr Filippo Montemurro

Combinatorial strategies

- Novel Vaccines
- Oncolytic Virus
- Co-Stimulatory Molecules
- **Targeted Therapy**
- **Radiation**
- **Chemotherapy**
- Adoptive Cell Therapy



Tolba et al. Critcal Review in Oncology, 2018

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].

Phase III Trial: Impassion 130

MUNICH 2018 ESMO congress

IMpassion130 study design

Key IMpassion130 eligibility criteria[a]:

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

Stratification factors:

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

R 1:1

Atezo + nab-P arm:

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

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

Double blind; no crossover permitted

Plac + nab-P arm:

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

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

RECIST v1.1
PD or toxicity

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

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

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

Phase III Trial: Impassion 130

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IMpassion130 baseline characteristics

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

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

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

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

Phase III Trial: Impassion 130

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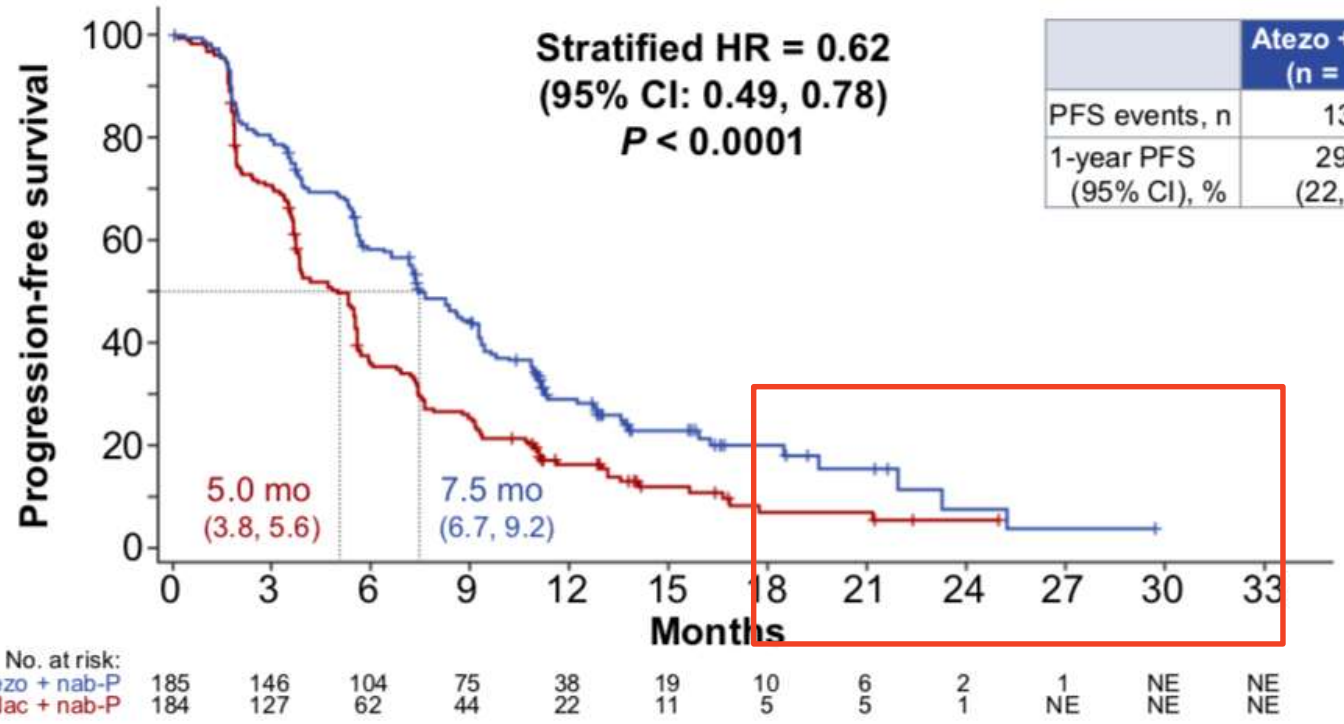
Primary PFS analysis: PD-L1+ population

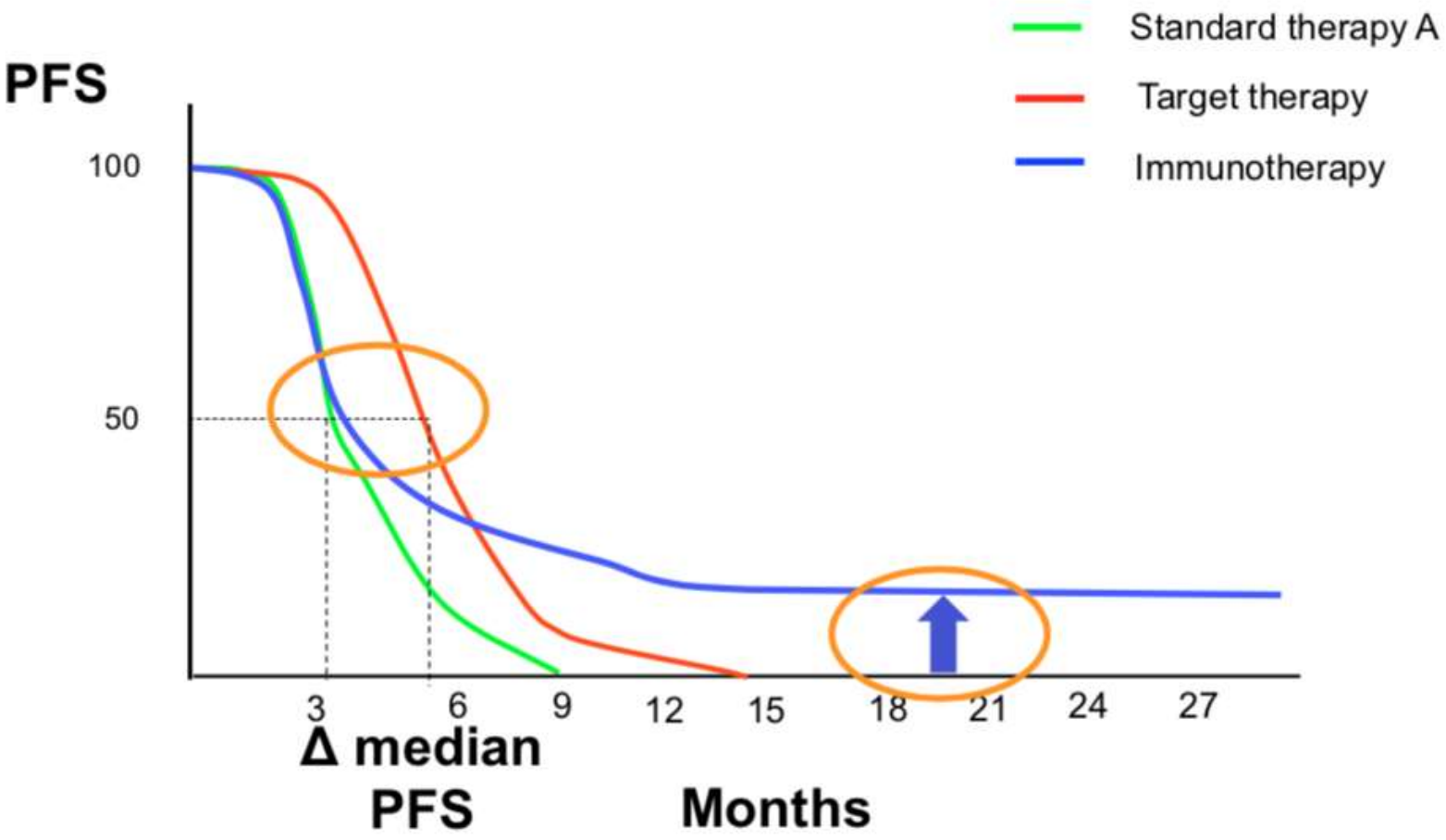


	Atezo + nab-P (n = 185)	Plac + nab-P (n = 184)
PFS events, n	138	157
1-year PFS (95% CI), %	29% (22, 36)	16% (11, 22)

Data cutoff: 17 April 2018.

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

Can we cure cancer with immunotherapy?



Adapted from Bianchini, Back from Madrid, Genova 2017

Phase III Trial: Impassion 130

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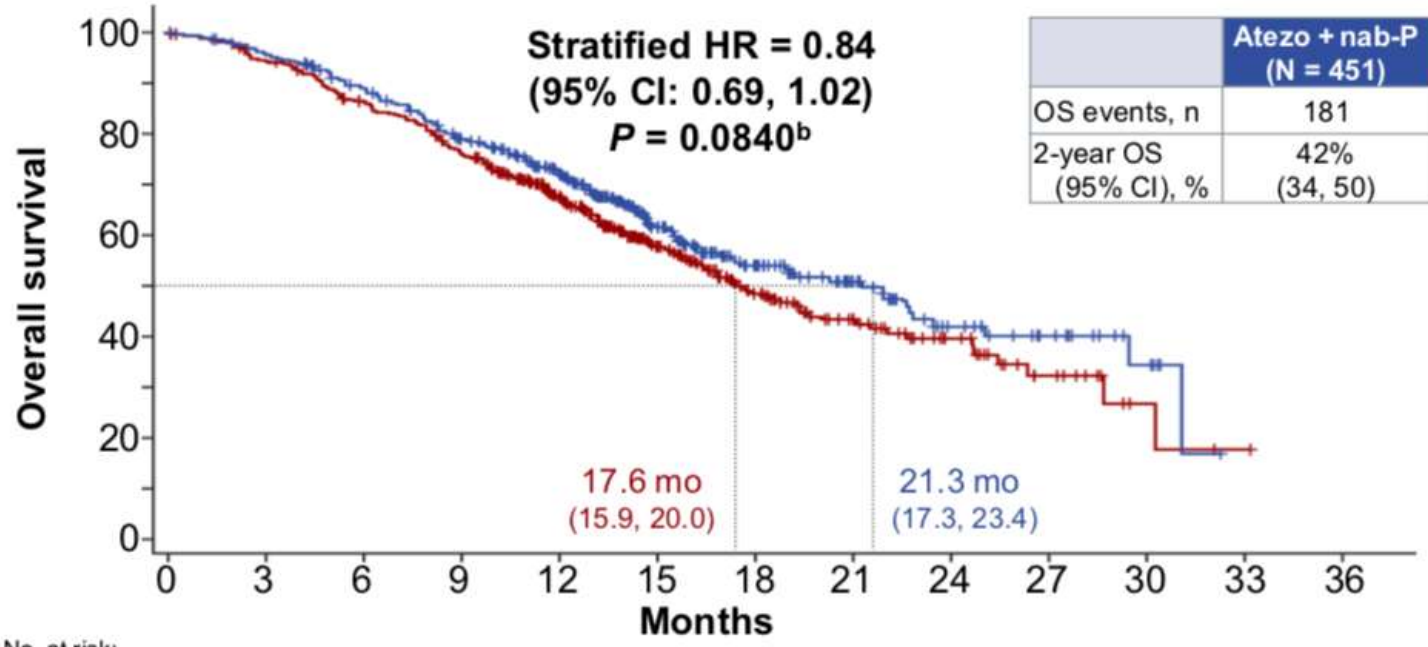
Interim OS analysis: ITT population[a]



	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:

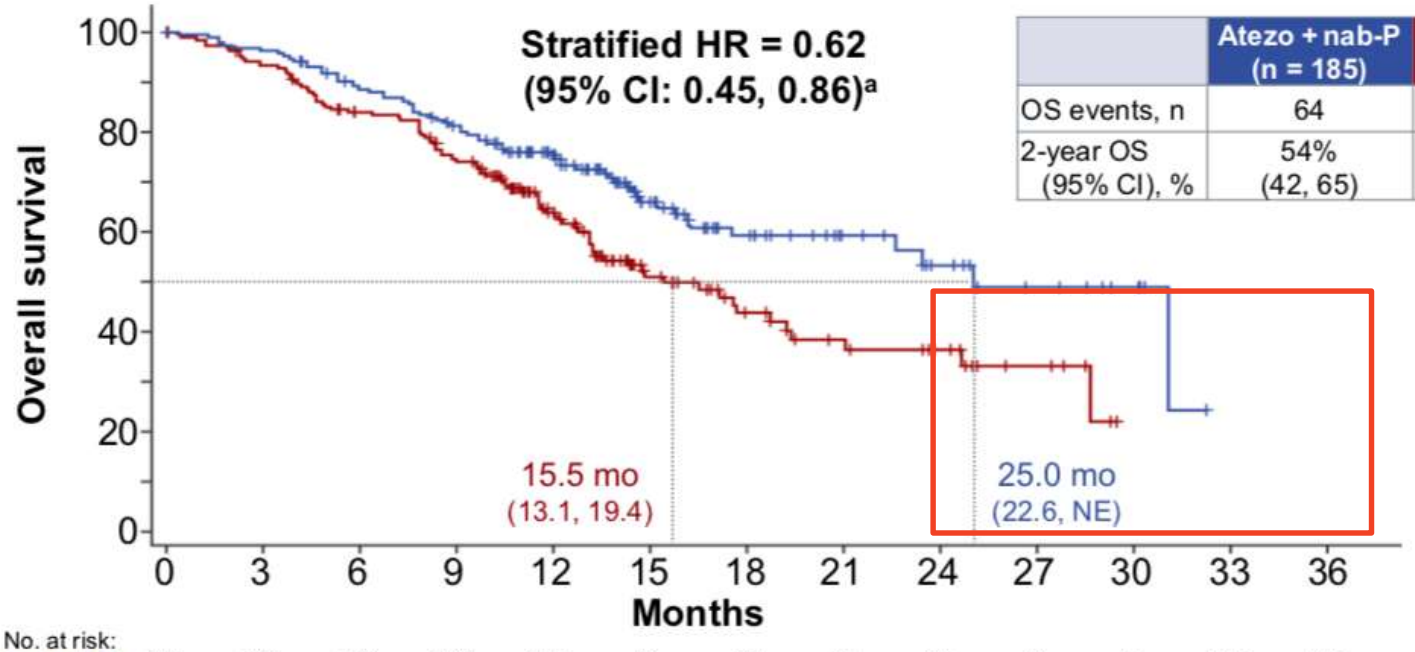
Atezo + nab-P	451	426	389	337	271	146	82	48	26	15	6	NE	NE
Plac + nab-P	451	419	375	328	246	145	89	52	27	12	3	1	NE

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

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

Phase III Trial: Impassion 130

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)

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

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

Phase III Trial: Impassion 130

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

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.

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

Tonic Trial

Adaptive phase II randomized non-comparative trial of nivolumab after induction treatment in triple negative breast cancer: TONIC-trial

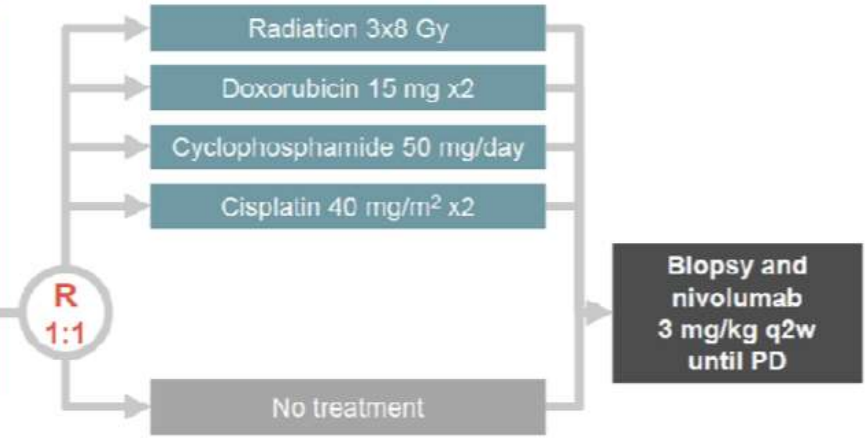
Study objective

- To assess if short-term induction with radiation or chemotherapy modulates the anticancer immune response

Key patient inclusion criteria

- Metastatic triple-negative BC
- ≤3 lines of chemotherapy for metastatic disease
- LDH <2x ULN
- Accessible lesion for biopsy
- WHO PS 0–1
- No history of leptomeningeal disease, no symptomatic CNS disease

(n=50)*



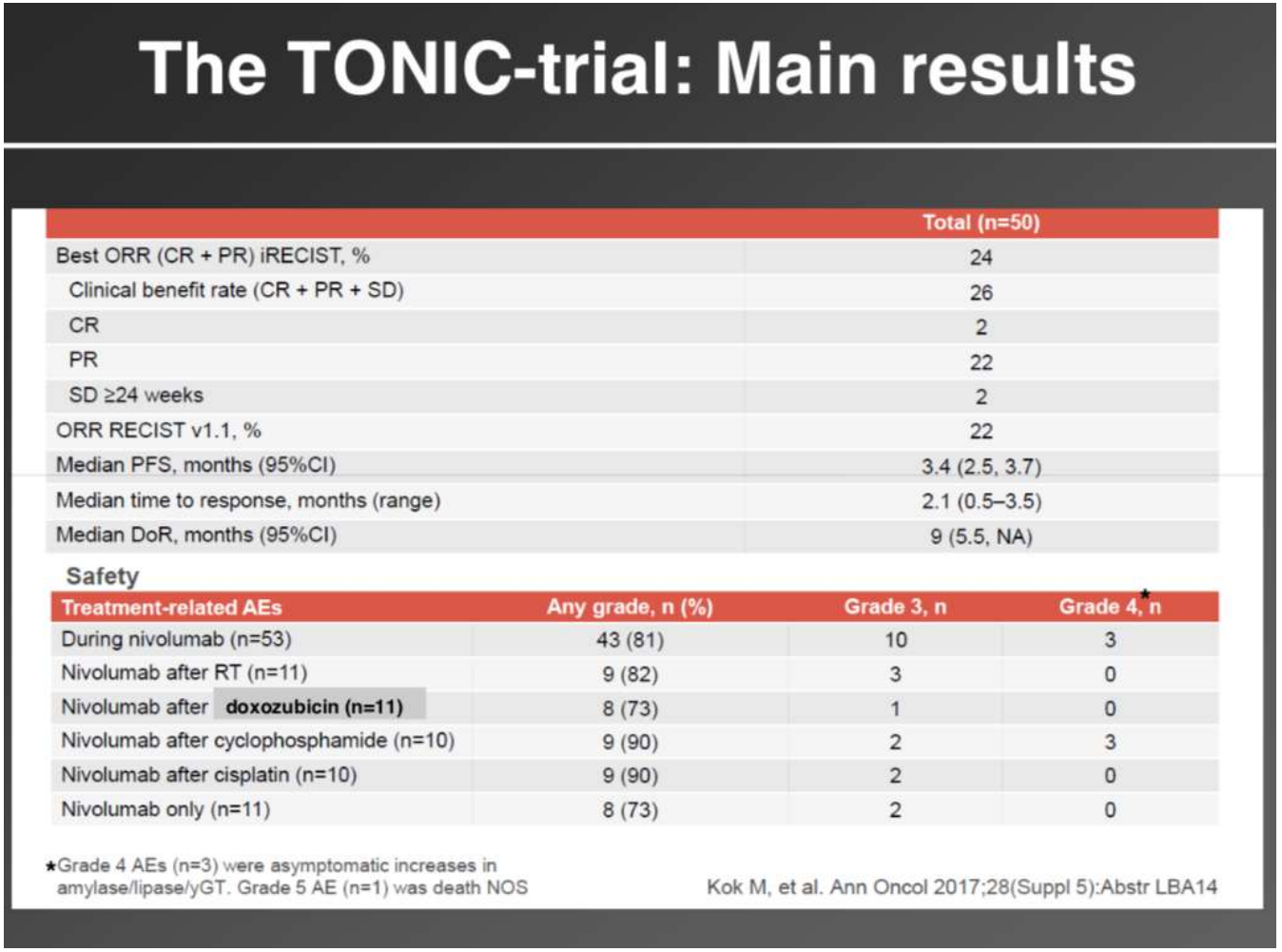
ENDPOINTS

- PFS (RECIST, iRECIST), ORR, clinical benefit, safety, OS, translational endpoints

*Minimum sample of 10 allows early discontinuation if in cohort ≤30% of the patients respond

Kok M, et al. Ann Oncol 2017;28(Suppl 5):Abstr LBA14

Tonic Trial



The TONIC-trial: Main results

	Total (n=50)
Best ORR (CR + PR) iRECIST, %	24
Clinical benefit rate (CR + PR + SD)	26
CR	2
PR	22
SD ≥24 weeks	2
ORR RECIST v1.1, %	22
Median PFS, months (95%CI)	3.4 (2.5, 3.7)
Median time to response, months (range)	2.1 (0.5–3.5)
Median DoR, months (95%CI)	9 (5.5, NA)

Safety

Treatment-related AEs	Any grade, n (%)	Grade 3, n	Grade 4, n
During nivolumab (n=53)	43 (81)	10	3
Nivolumab after RT (n=11)	9 (82)	3	0
Nivolumab after **doxozubicin (n=11)**	8 (73)	1	0
Nivolumab after cyclophosphamide (n=10)	9 (90)	2	3
Nivolumab after cisplatin (n=10)	9 (90)	2	0
Nivolumab only (n=11)	8 (73)	2	0

★Grade 4 AEs (n=3) were asymptomatic increases in amylase/lipase/γGT. Grade 5 AE (n=1) was death NOS

Kok M, et al. Ann Oncol 2017;28(Suppl 5):Abstr LBA14

New Therapies ➔ New Toxicities

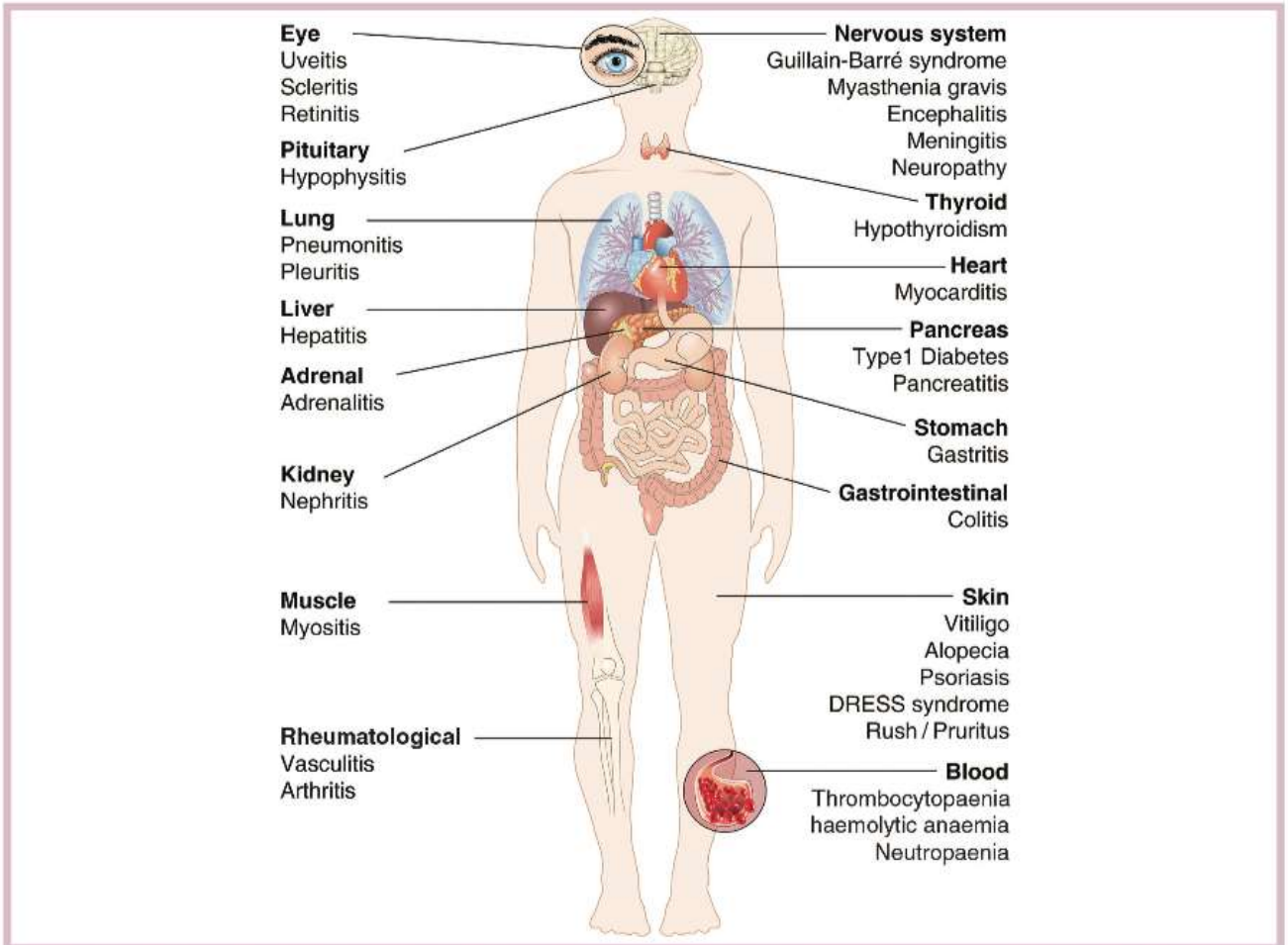


Figure 3 Some of the immune-related adverse effects (IRAEs) associated with checkpoints inhibitors in patients with cancer. DRESS, drug rash with eosinophilia and systemic symptoms.

Varicchi et al. ESMO Open, 2017

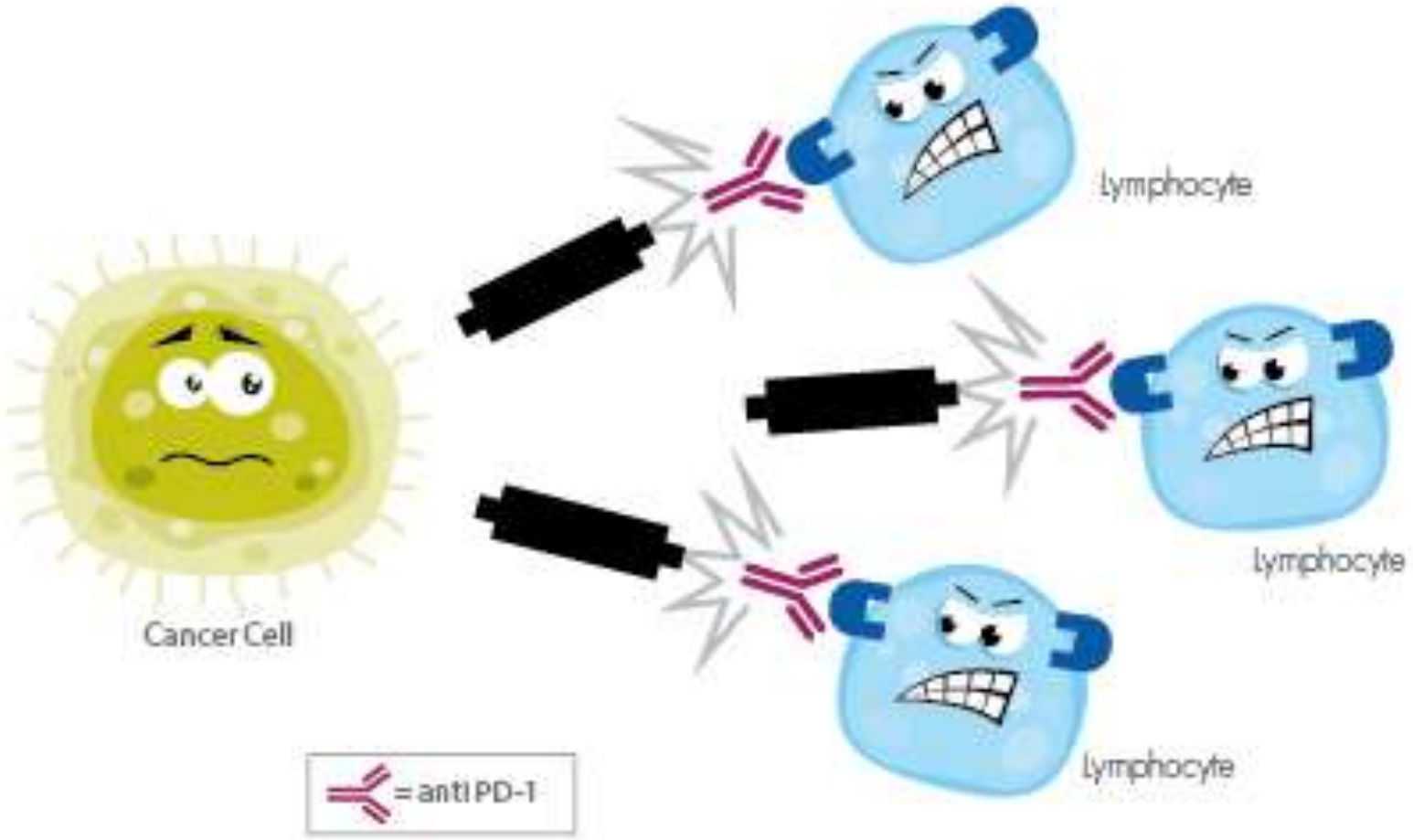
Main Ongoing Trials

Agents	Subtype	Phase	Trial Name	Trial ID
Neoadjuvant Pembrolizumab + chemotherapy ➔ adjuvant pembrolizumab	Early TNBC	III	KEYNOTE-522	NCT03036488
Standard surgery, neo- or adjuvant chemotherapy, radiotherapy ➔adjuvant avelumab/observation	Early TNBC	III	A-BRAVE	NCT02926196
Atezolizumab + nab-paclitaxel + carboplatin ➔ surgery + EC or CEF Paclitaxel + carboplatin	Early TNBC	III	Neo-TRIP	NCT02620280
Pembrolizumab Capecitabine/Eribulin/ gemcitabine/vinorelbine (physician choice)	Metastatic TNBC	III	KEYNOTE-119	NCT02555657
Induction treatment: radiation or doxorubicin (low dose) or CTX (low dose) or no treatment ➔ Nivolumab	Metastatic TNBC	II	Tonic	NCT02499367
Atezolizumab + Gem-Carbo and Atezolizumab + Paclitaxel	Metastatic TNBC	III	Impassion 131 and 132	NCT02425891

Conclusions

- 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

Thank You



Backup slides

Pembrolizumab in HER2 positive mBC: Panacea Trial

Baseline Characteristics

Characteristic N (%)	Phase Ib PD-L1 positive; n=6	Phase II PD-L1 positive; n=40	Phase II PD-L1 negative; n=12	Overall n=58
Age yrs. median (range)	49 (38-57)	49 (28-72)	56.5 (43-61)	50.5 (28-72)
ER negative	4 (66%)	23 (57.5%)	6 (50%)	33 (56.9%)
positive (≥ 1%)	2 (33%)	17 (42.5%)	6 (50%)	25 (43.1%)
Prior trastuzumab-containing therapy	6 (100%)	40 (100%)	12 (100%)	58 (100%)
Additional anti-HER2 therapy				
No	1 (16.7%)	6 (15%)	0 (0%)	7 (12.1%)
Yes	5 (83.3%)	34 (85%)	12 (100%)	51 (87.9%)
T-DM1	4	29	9	42
Pertuzumab	3	10		
Other	1	17		
Prior chemotherapy (Anth/Taxane)	6 (100%)	40 (100%)		
Median time from Dx met disease to enrolment; months (range)	15.5 (6-83.6)	40.8 (1.1-		

Best Overall Response (RECIST 1.1)

	PD-L1 Positive Phase Ib, n=6	PD-L1 Positive Phase II, n=40
ORR n (%) [90%CI]	1 (17%) [1-58]	6 (15%) [7-29]
DCR[1] n (%) [90%CI]	1 (17%) [1-58]	10 (25%) [14-49]
Best overall response, n (%)		
Complete Response	1 (17%)	1 (2.5%)
Partial Response	-	5 (12.5%)
Stable Disease	-	7 (17.5%)
Progressive Disease	5 (83%)	25 (62.5%)
Not Evaluable	-	2 (5.0%)
Overall PD-L1 + cohort	ORR 15.2% [7-27]	DCR 24% [14-36]

[1]DCR: CR, PR, or SD ≥ 6 months

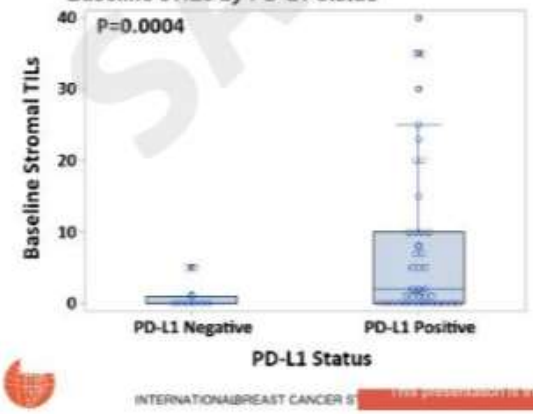
Loi ,SABSC 2017

Pembrolizumab in HER2 positive mBC: Panacea Trial

sTILs by PD-L1 Status and Site of Biopsy

Stromal TILs Median 1%, Mean 4.8%, IQR 0-5%, all <1 yr old biopsies from metastatic lesions

Baseline sTILs by PD-L1 status



Baseline sTILs by site of biopsy

2017 SAN ANTONIO BREAST CANCER SYMPOSIUM December 5-9, 2017

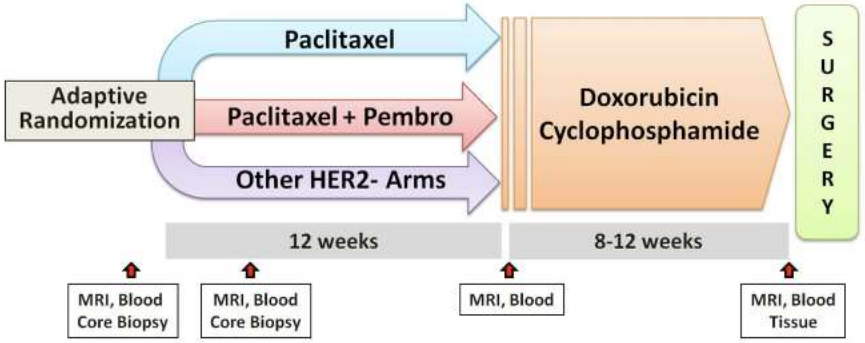
Summary and Conclusions

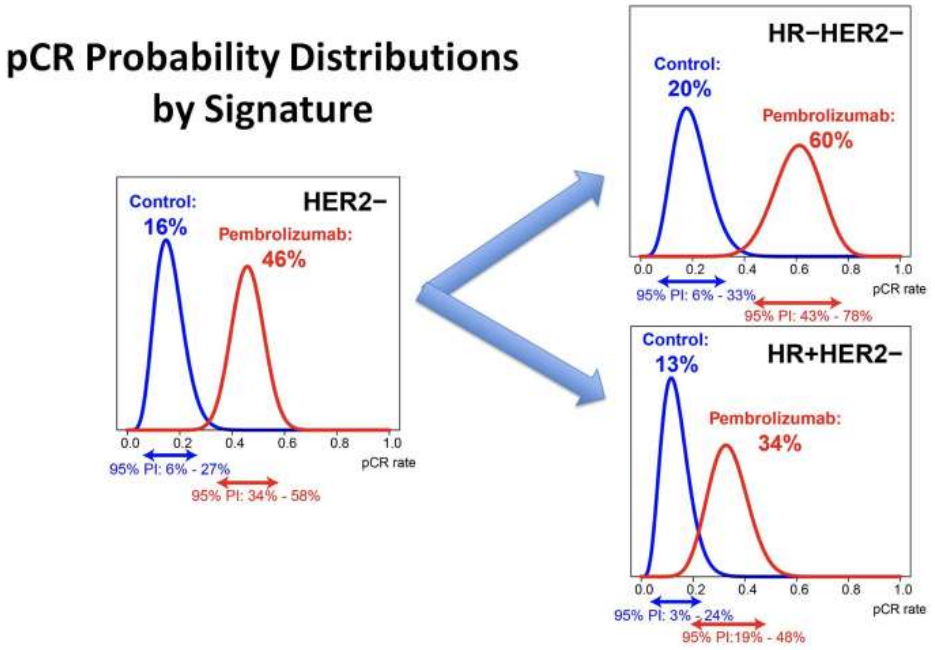
- PANACEA study of pembrolizumab with trastuzumab in trastuzumab-resistant mHER2+ patients met its primary endpoint in the PD-L1 positive cohort (ORR 15%, DCR 25%)
  - No responses observed in PD-L1 negative patients
  - Stromal TIL levels associated with responses: sTILs ≥ 5% patients (ORR 39%, DCR 47%)
  - For responders: combination offers durable control without chemotherapy
- Metastatic HER2+ disease in the heavily pretreated setting is poorly immunogenic (majority of patients had low TILs in their metastatic lesions)
- Future directions in IO in mHER2+ should focus on combinations with effective anti-HER2 therapy, especially in low TIL patients

Loi ,SABSC 2017

Neoadjuvant Pembrolizumab; the I-SPY 2 study

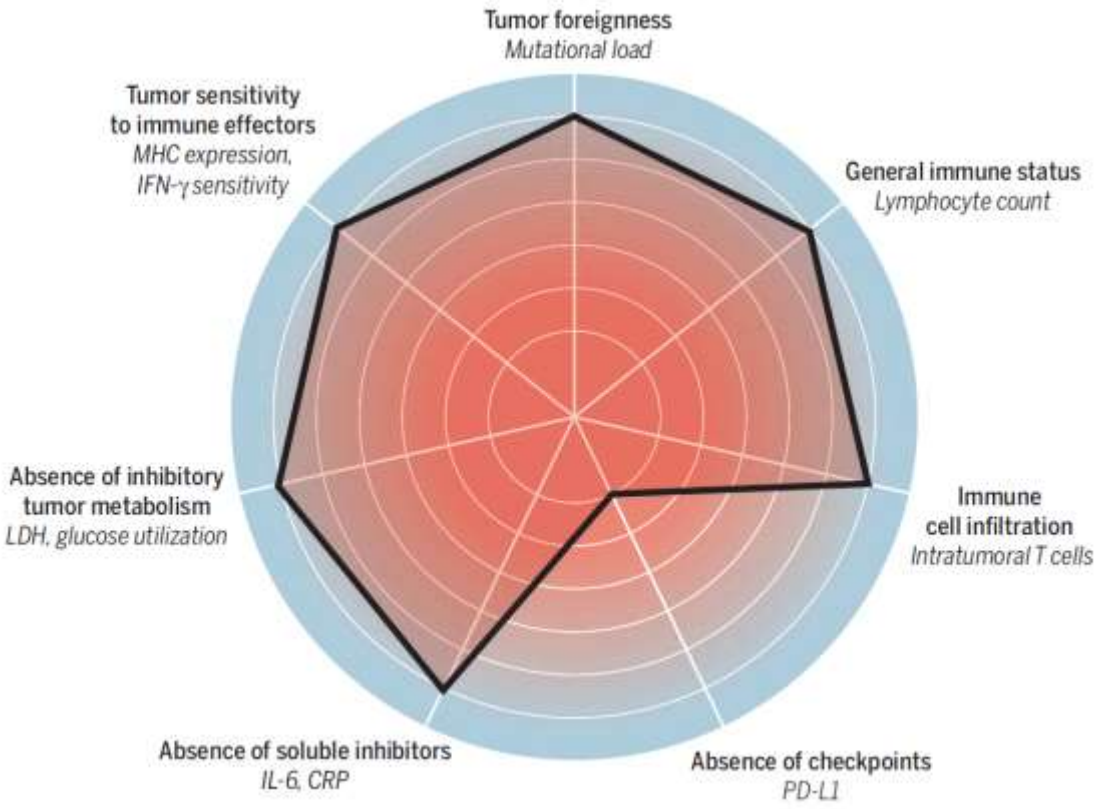
46pts





Nanda; ASCO 2017

The cancer immunogram



Blank et al, Science 2016