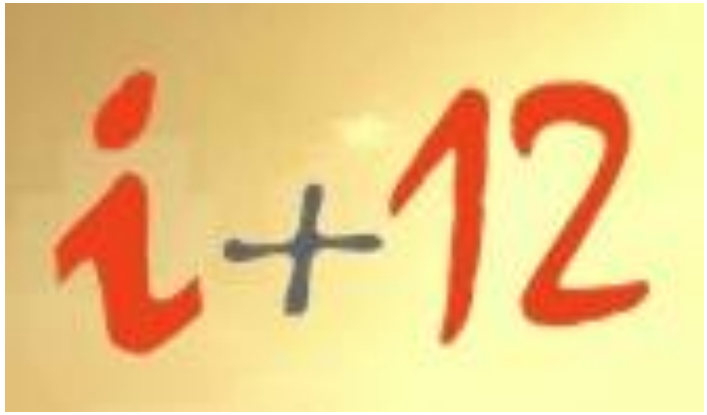


cnio
Centro Nacional de Investigaciones Oncológicas

UNIVERSIDAD COMPLUTENSE MADRID

Influence of the neoantigenic load in the response to immunotherapy. Consequences for the development of new drugs

Luis Paz-Ares

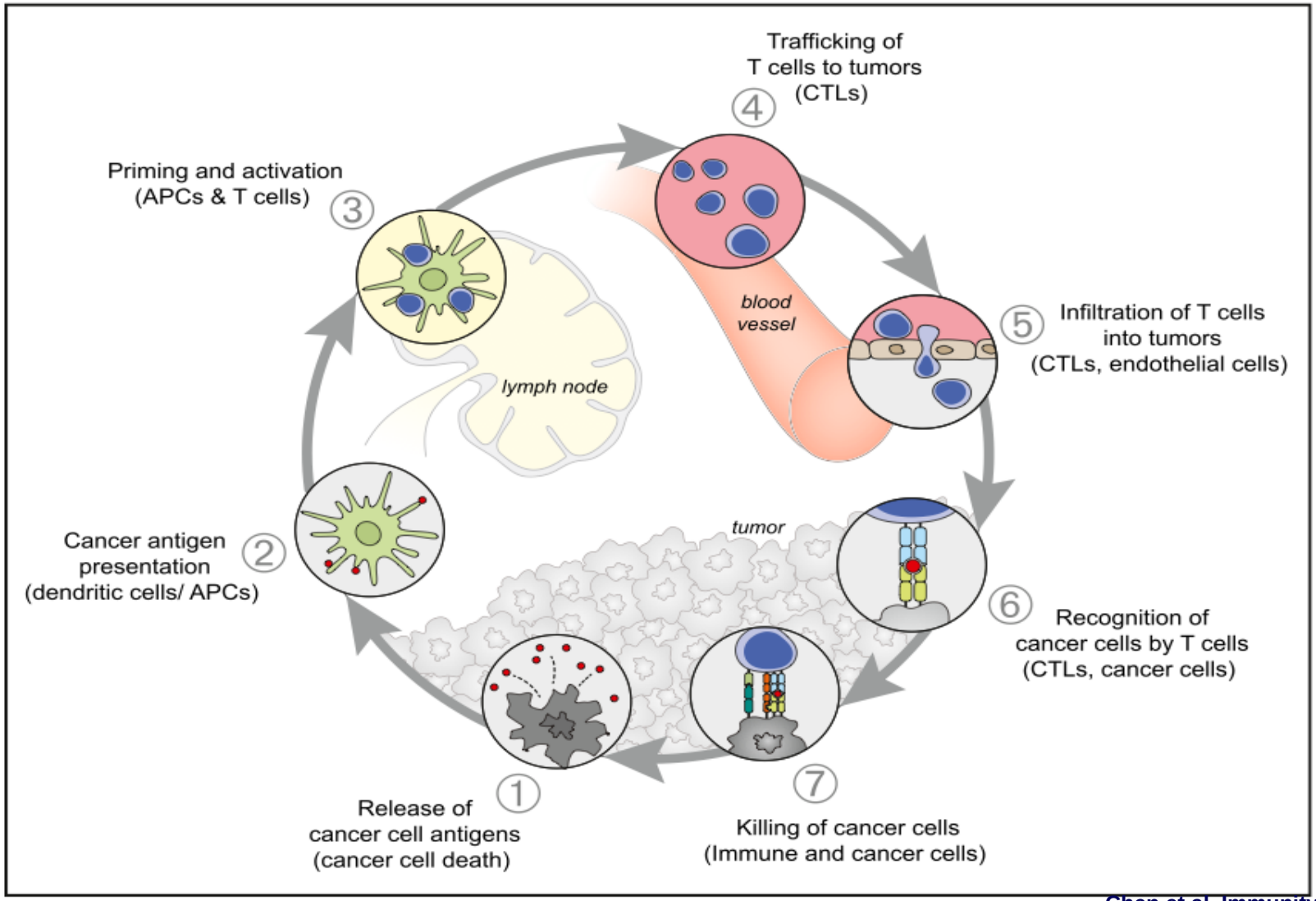
Agenda

- **IO in lung cancer**
- **Beyond PD-L1: TMB (neoantigen load!)**
- **Genomic aberrations and future perspectives**

Agenda

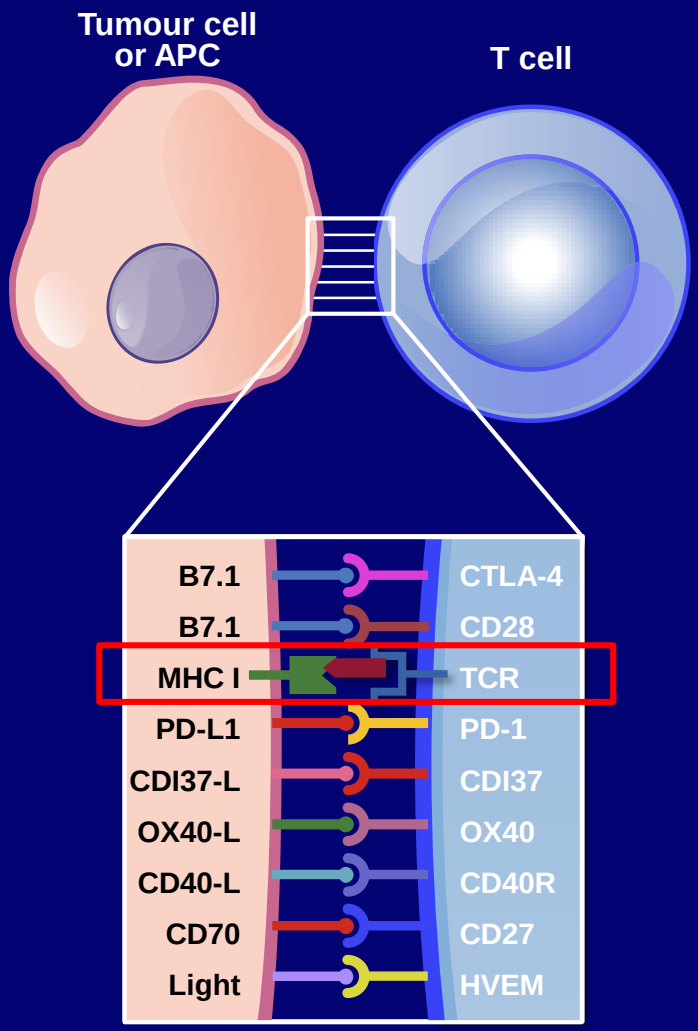
- **IO in lung cancer**
- **Beyond PD-L1: TMB (neoantigen load!)**
- **Genomic aberrations and future perspectives**

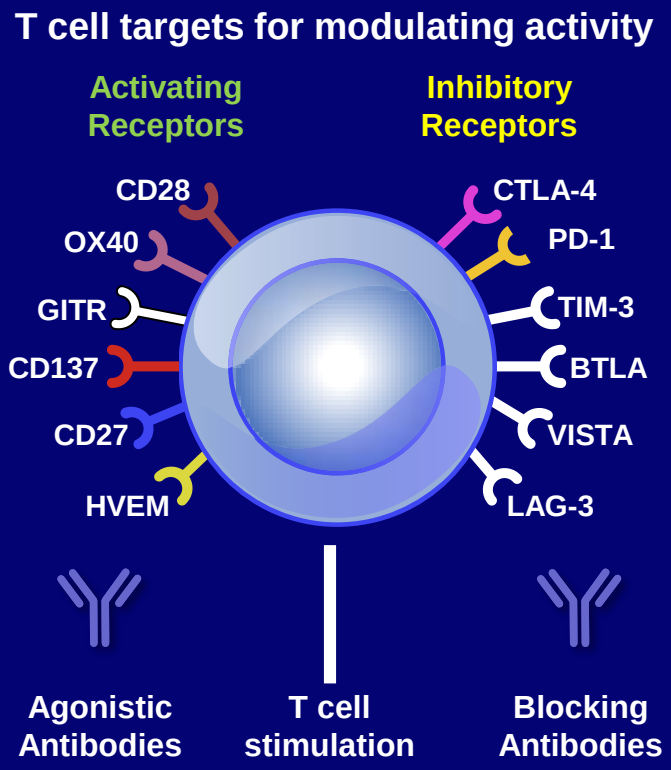
The cancer-immunity cycle



Chen et al. Immunity 2013

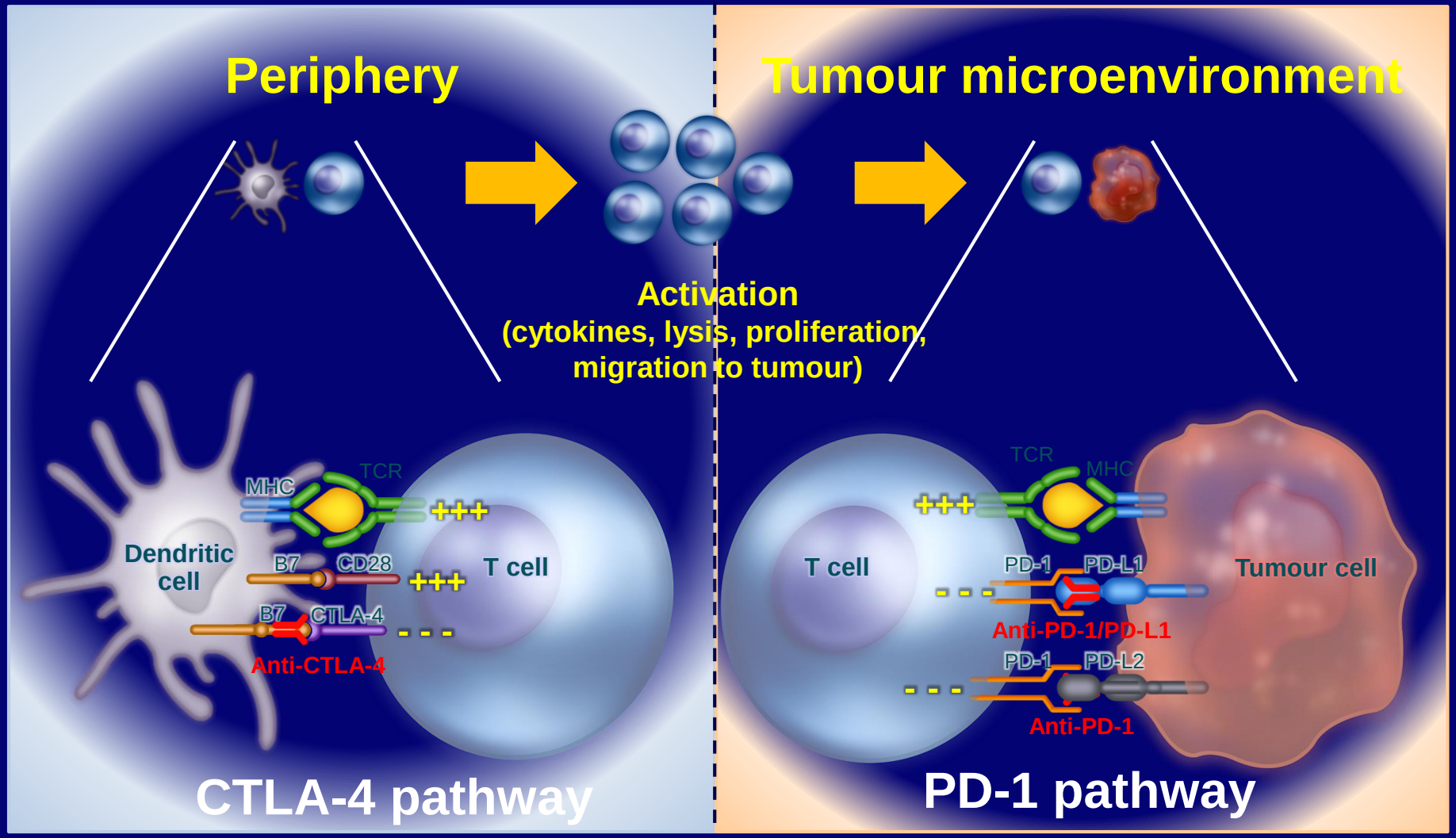
Balance between inhibitory and stimulatory receptors dictates T-cell priming





Mellman Nature 2011; Pardoll Nat Rev Cancer 2012

Targeting CTLA-4 and PD-1 pathways



Wolchock J, et al. *J Clin Oncol* 2013;31(Issue 15_suppl); abstr 9012^

PD-1/PD-L1 Inhibitors in pretreated NSCLC

	CheckMate 017 phase 3[125]		CheckMate 057 phase 3[126]		KEYNOTE-010 phase 3[127]			POPLAR phase 2[128]		Durvalumab phase 1b[129]	Avelumab phase 1b[130]
	Nivolumab	Docetaxel	Nivolumab	Docetaxel	Pembrolizumab 2 mg/kg	Pembrolizumab 10 mg/kg	Docetaxel	Atezolizumab	Docetaxel	Durvalumab	Avelumab
Patients (n)	135	137	292	290	345	346	343	144	143	198	184
Response rate (%)											
All patients	20	9	19	12	18	19	9	15	15	16	14
PD-L1 positive	21	8	36	13	30	29	8	38	13	27	16
PD-L1 negative	15	12	10	14	NA	NA	NA	8	10	5	10
Median progression-free survival (months)											
All patients	3·5	2·8	2·3	4·2	3·9	4·0	4·0	2·7	3·0	NA	2·9
PD-L1 positive	4·8	3·1	5·0	3·8	5·0	5·2	4·1	2·8	3·0	NA	3·0
PD-L1 negative	4·2	2·9	2·1	4·2	NA	NA	NA	1·7	4·1	NA	1·4
Median overall survival (months)											
All patients	9·2	6·0	12·2	9·4	10·4	12·7	8·5	12·6	9·7	NA	8·9
PD-L1 positive	10	6·4	19·4	8·1	14·9	17·3	8·2	15·5	9·2	NA	8·4
PD-L1 negative	8·5	6·1	9·8	10·1	NA	NA	NA	9·7	9·7	NA	4·6
Histology	SCC	SCC	Non-SCC	Non-SCC	All comers	All comers	All comers	All comers	All comers	All comers	All comers
Setting	Second line	Second line	Second line	Second line	Second line	Second line	Second line	Second line	Second line	Pre-treated	Pre-treated
PD-L1 expression											
Positive	≥5%	≥5%	≥5%	≥5%	Highly positive ≥50%; positive ≥1%	Highly positive ≥50%; positive ≥1%	Highly positive ≥50%; positive ≥1%	Tumour cell 1–3 or tumour-infiltrating immune cells 1–3		≥25%	≥1%
Negative	<5%	<5%	<5%	<5%	<1% (not included)	<1% (not included)	<1% (not included)	Tumour cell 0 and tumour-infiltrating immune cells 0		<25%	<1%

Percentages rounded. PD-1=programmed death-1. PD-L1=programmed death ligand-1. SCC=squamous cell cancer. NA=not available.

Table 4: Trials of anti-PD-1/PD-L1 inhibitors in patients with advanced NSCLC who were pre-treated with chemotherapy

Hirsch et al. Lancet 2015

PD-1/PD-L1 Inhibitors in pretreated NSCLC

	CheckMate 017 phase 3[125]		CheckMate 057 phase 3[126]		KEYNOTE-010 phase 3[127]			POPLAR phase 2[128]		Durvalumab phase 1b[129]	Avelumab phase 1b[130]
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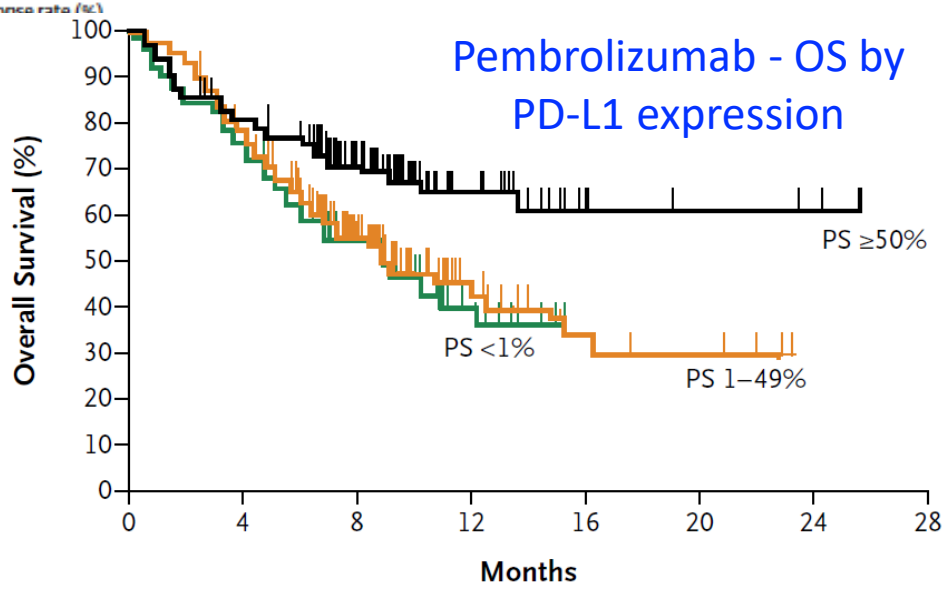
Patients (n)	135	137	292	290	345	346	343	143		184	
Response rate (%)											
	2·8	3·0	NA	3·0							
	1·7	4·1	NA	1·4							
	12·6	9·7	NA	8·9							
	15·5	9·2	NA	8·4							
	9·7	9·7	NA	4·6							
	All comers	All comers	All comers	All comers							
	Second line	Second line	Pre-treated	Pre-treated							
	Tumour cell 1–3 or tumour-infiltrating immune cells 1–3		≥25%	≥1%							
	Tumour cell 0 and tumour-infiltrating immune cells 0		<25%	<1%							



No. at Risk								
PS ≥50%	119	92	56	22	5	4	3	0
PS 1–49%	161	119	58	15	6	4	0	0
PS <1%	76	55	33	8	0	0	0	0

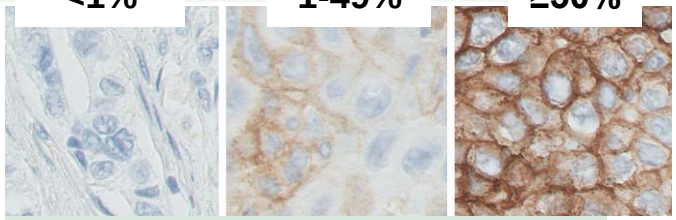


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Table 4: Trials of anti-PD-1/PD-L1 inhibitors in patients with advanced NSCLC who were pre-treated with chemotherapy

Garon E, et al. NEJM 2015

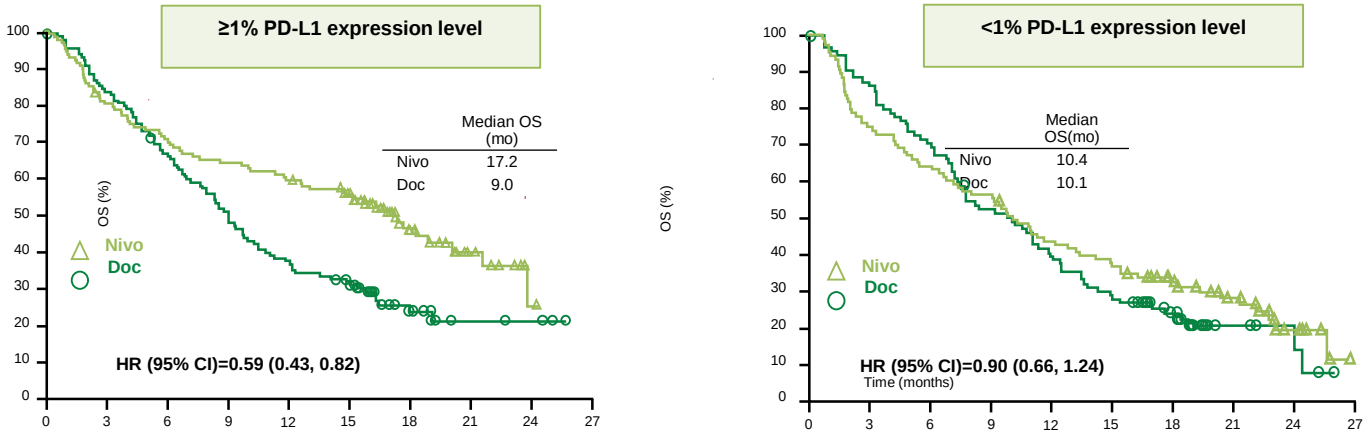
Summary of phase III studies of immunotherapy in previously treated patients

	CheckMate 017[1] Nivolumab vs docetaxel	CheckMate 057[1] Nivolumab vs docetaxel	KEYNOTE-010[2] Pembrolizumab (2mg/kg or 10mg/kg) vs docetaxel	OAK[3] Atezolizumab vs docetaxel
Phase of study	III	III	II/III	III
PD-L1 selected	No	No	Yes (TPS* ≥1%)	No
Study size, n	272 (135 vs 137)	582 (292 vs 290)	1,033 (344 vs 346 vs 343)	1,225 (425 vs 425)*
Histology	Squamous	Non-squamous	All-comers	All-comers
Line of therapy, % 2L 3L >3L Other/unknown	 100 0 0 0	 88 11 <1 0	 69 20 9 <1	 75 25 0 0
Subsequent CIT (immunotherapy arm vs chemo arm), %	<1 vs 2	1 vs 2	0.6 vs 1.7 vs 13.1	4.5 vs 17.2
Crossover from chemo arm to study immunotherapy, %	4	6	Not permitted	Not permitted
Median OS, months **HR vs docetaxel (p value)**	9.2 vs 6.0 0.62 (p=0.0004)	12.2 vs 9.5 0.75 (p<0.001)	10.4 vs 12.7 vs 8.5 2mg/kg: 0.71 (p=0.0008) 10mg/kg: 0.61 (p<0.0001)	13.8 vs 9.6 0.73 (p=0.0003)

Borghaei, et al. ASCO 2016
Herbst, et al. Lancet 2015;
Barlesi, et al. Lancet 2016

OS by PD-L1 expression: CheckMate 057
Nivolumab

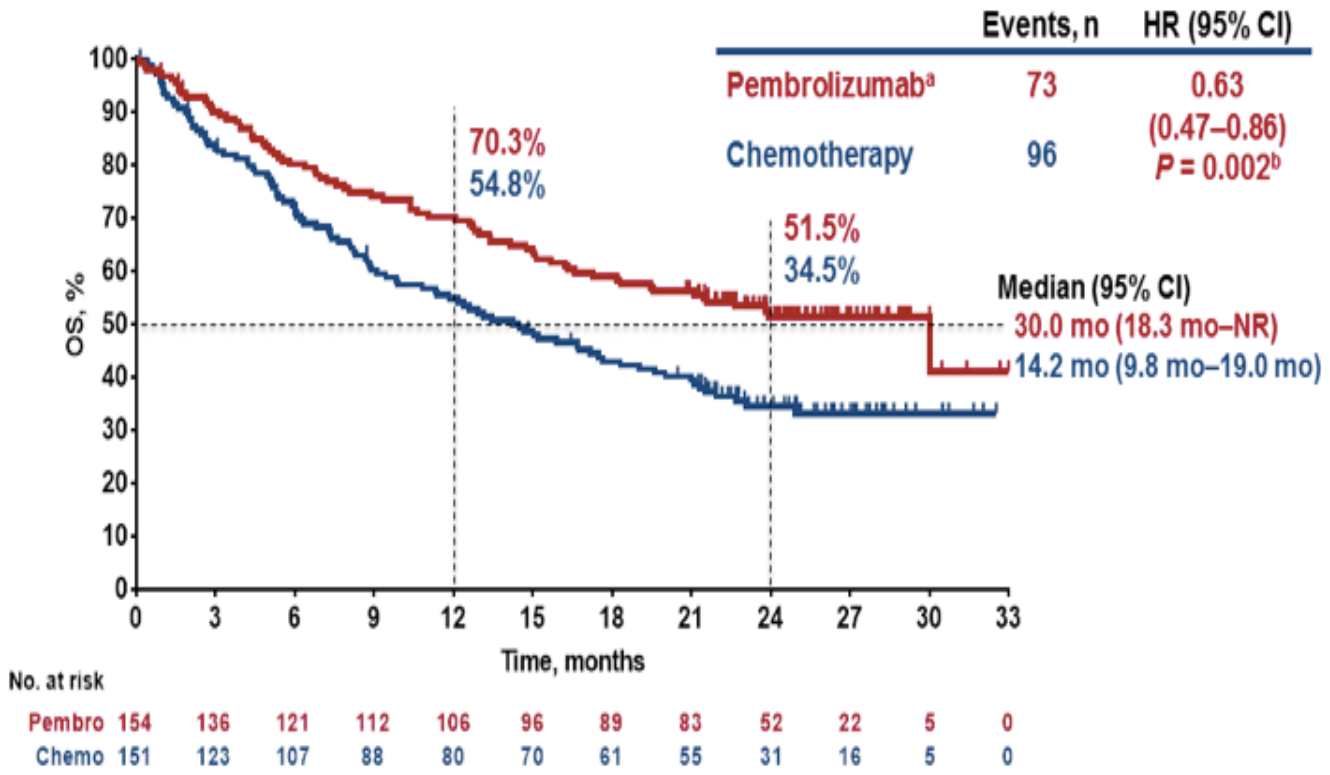
- PD-L1 expression was predictive of benefit with nivolumab



PD-L1 expression level	Median OS (mo)		HR
	Nivolumab	Docetaxel	
≥5%	18.2	8.1	HR (95% CI) = 0.43 (0.30, 0.63)
<5%	9.7	10.1	HR (95% CI) = 1.01 (0.77, 1.34)
≥10%	19.4	8.0	HR (95% CI) = 0.40 (0.26, 0.59)
<10%	9.9	10.3	HR (95% CI) = 1.00 (0.76, 1.31)

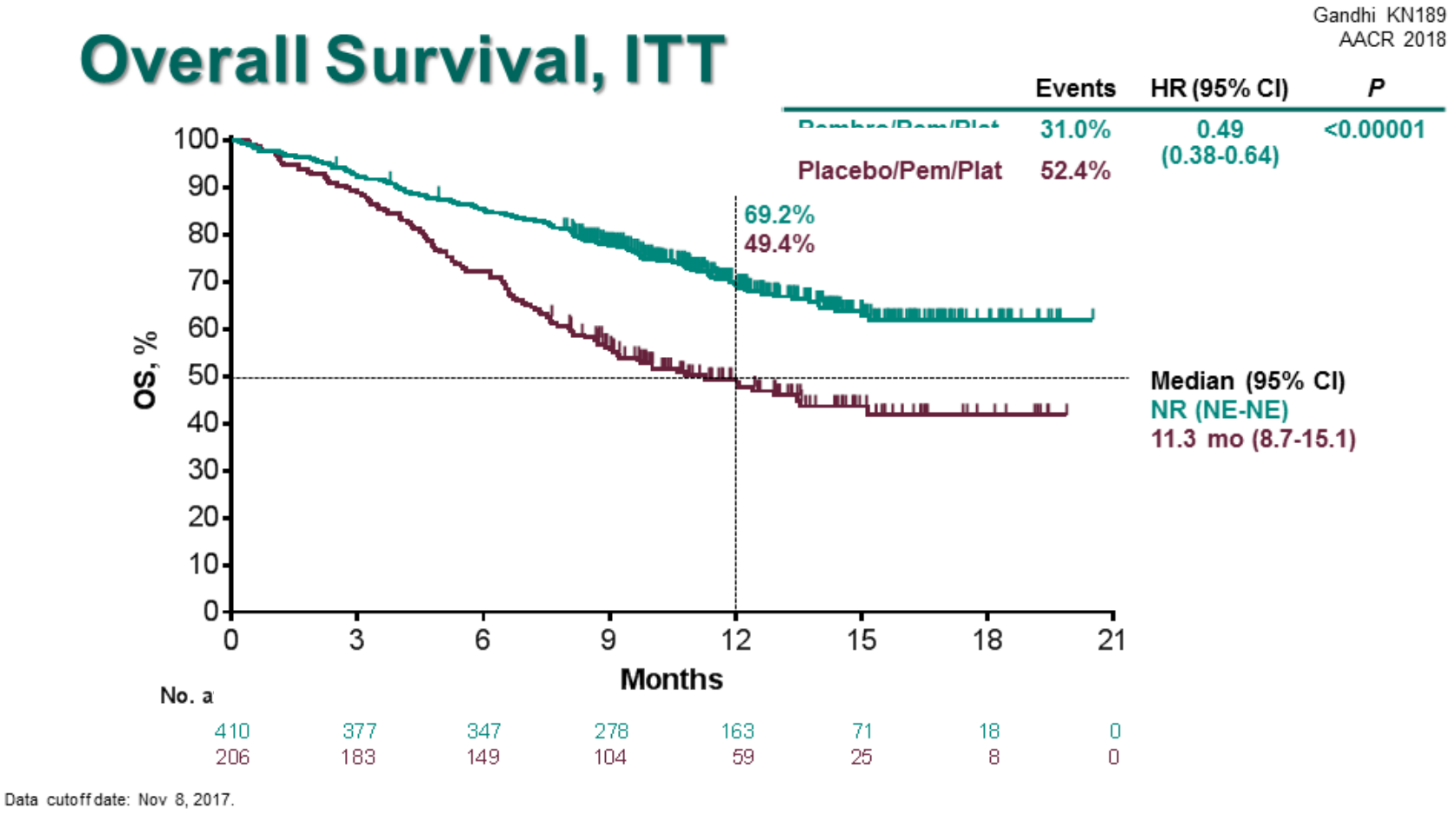
Paz-Ares L, et al. Presented at ASCO 2015, Abstract LBA109.
Borghaei et al., NEJM 2015

KEYNOTE-024 Trial: Pembro v QT
First Line treatment in PD-L1 ≥ 50% NSCLC



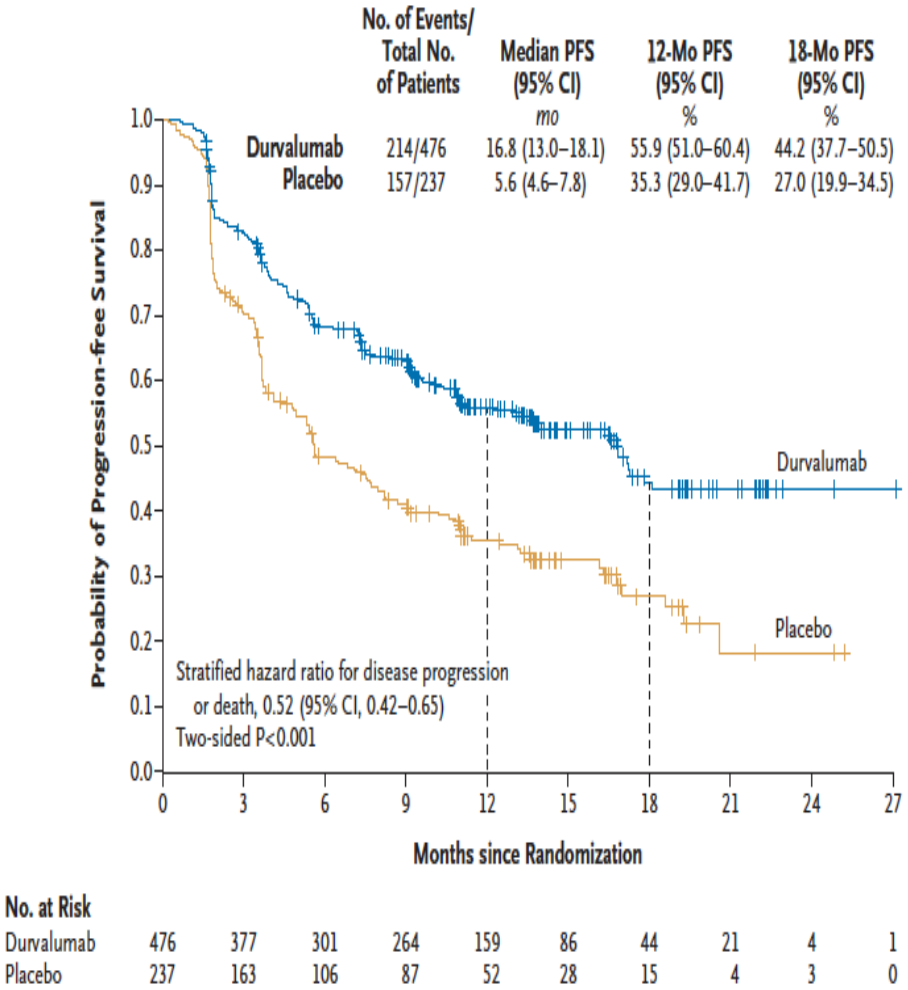
Reck et al NEJM 2017
Brahmer et al. WLCC 2017

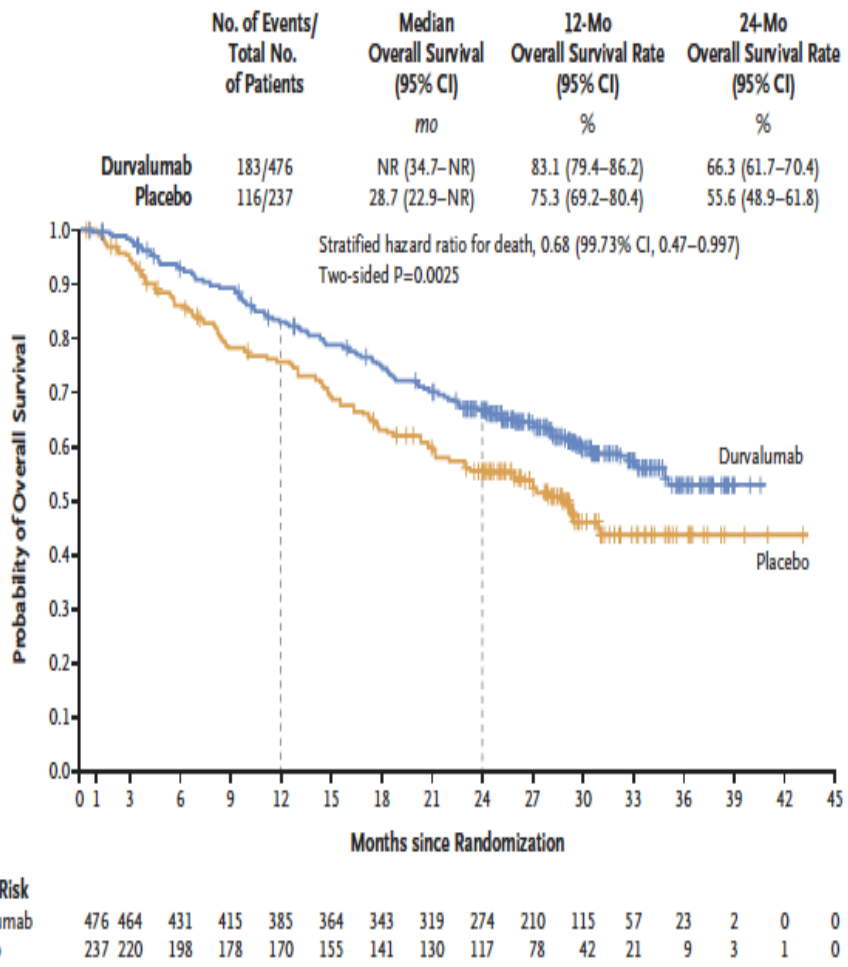
Chemo ± Pembrolizumab in Non-SCC NSCLC
KeyNote 189 Trial



Ghandi et al., NEJM 2018

Stage III: PACIFIC TRIAL
PFS and OS





Antonia S et al., NEJM 2017 and 2018

Vansteenkiste J. et al., atezolizumab in NSCLC (POPLAR)

Agenda

- IO in lung cancer
- **Beyond PD-L1: TMB (neoantigen load!)**
- Genomic aberrations and future perspectives

IO Monotherapy benefits a subset of patients

	CheckMate 017 phase 3[125]		CheckMate 057 phase 3[126]		KEYNOTE-010 phase 3[127]			POPLAR phase 2[128]		Durvalumab phase 1b[129]	Avelumab phase 1b[130]
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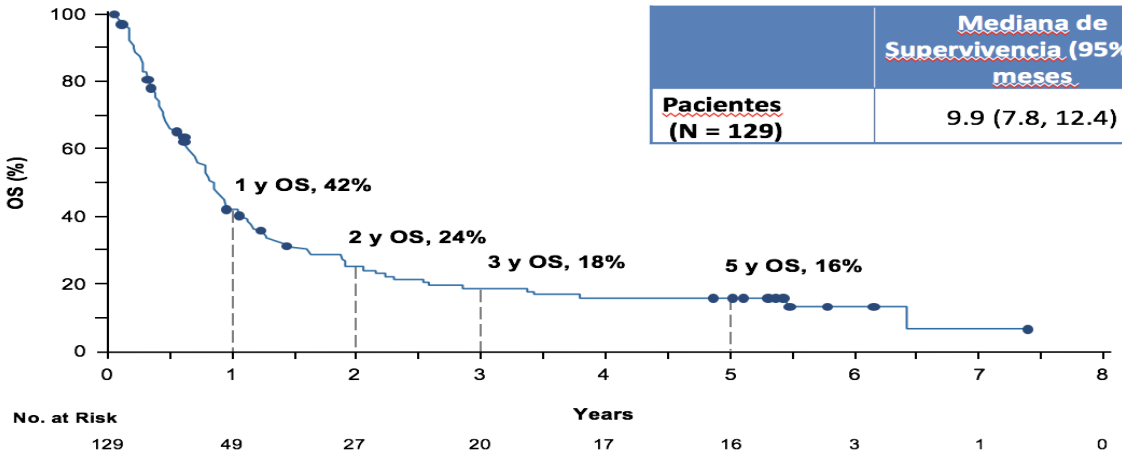
Median progression-free survival (months)											
All patients											
PD-L1 positive											
PD-L1 negative											
Median overall su											
All patients											
PD-L1 positive											
PD-L1 negative											
Histology											
Setting											
PD-L1 expression											
Positive											
Negative											

Percentages rounde

Table 4: Trials of a

Nivolumab NSCLC Phase I Cohort 5 Year Survival

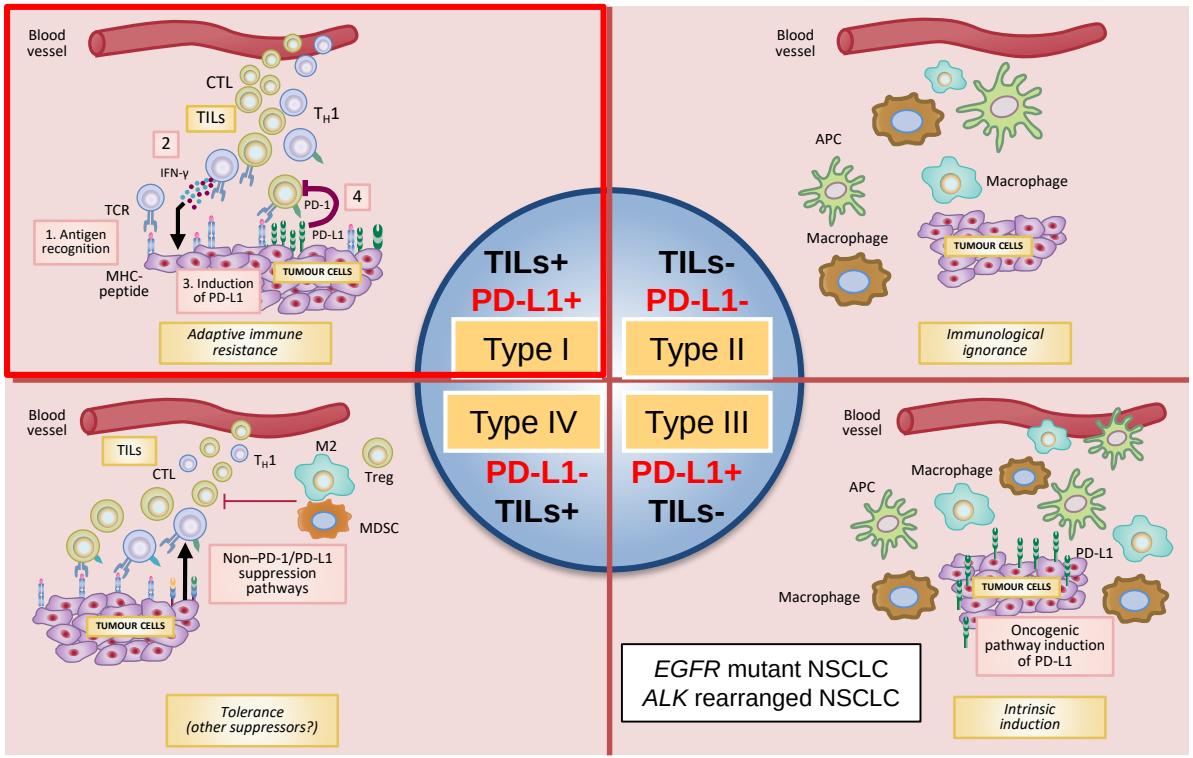


	Mediana de Supervivencia (95% CI), meses
Pacientes (N = 129)	9.9 (7.8, 12.4)

Brahmer et al. AACR 2017

Hirsch et al. Lancet 2016

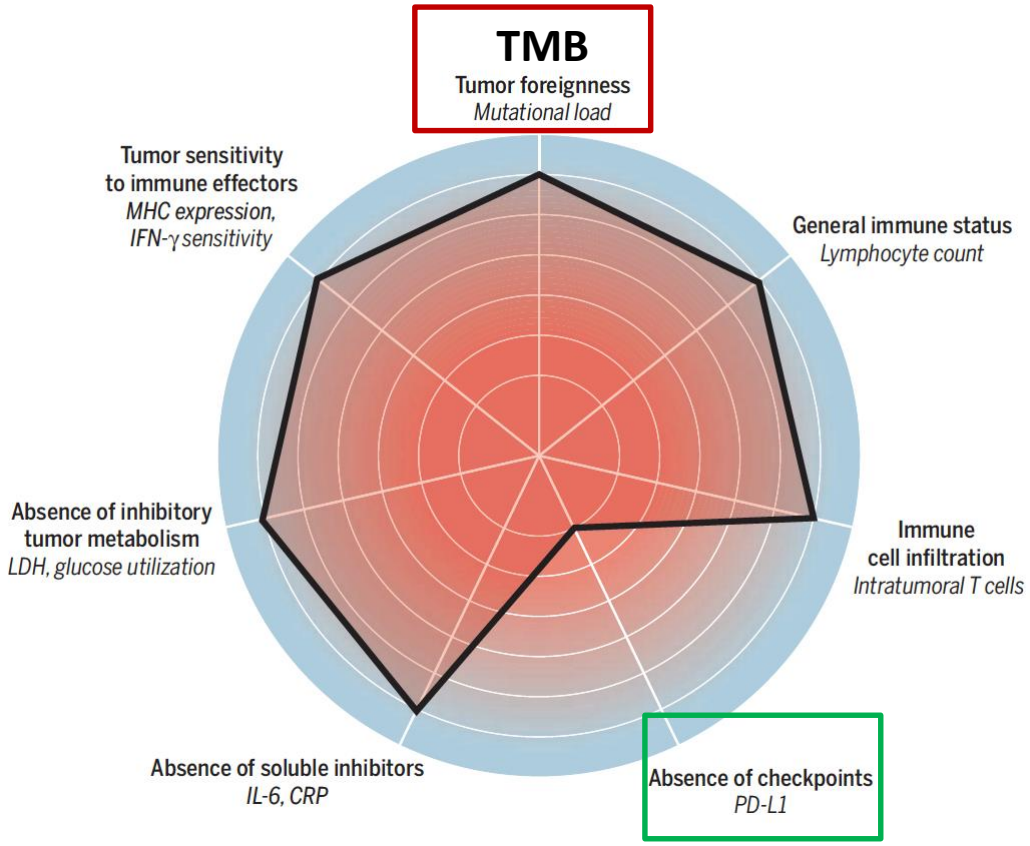
Tumour Microenvironment Types Based on TILs and PD-L1



APC, antigen-presenting cell; CTL, cytotoxic T cell; IFN-γ, interferon gamma; M2, M2 macrophage; MDSC, myeloid derived suppressor cell; MHC, major histocompatibility complex; PD-1, programmed death protein 1; PD-L1, programmed death ligand 1; TCR, T cell receptor; T_H1, T helper 1; TIL, tumour infiltrating lymphocyte; Treg, regulatory T cell.

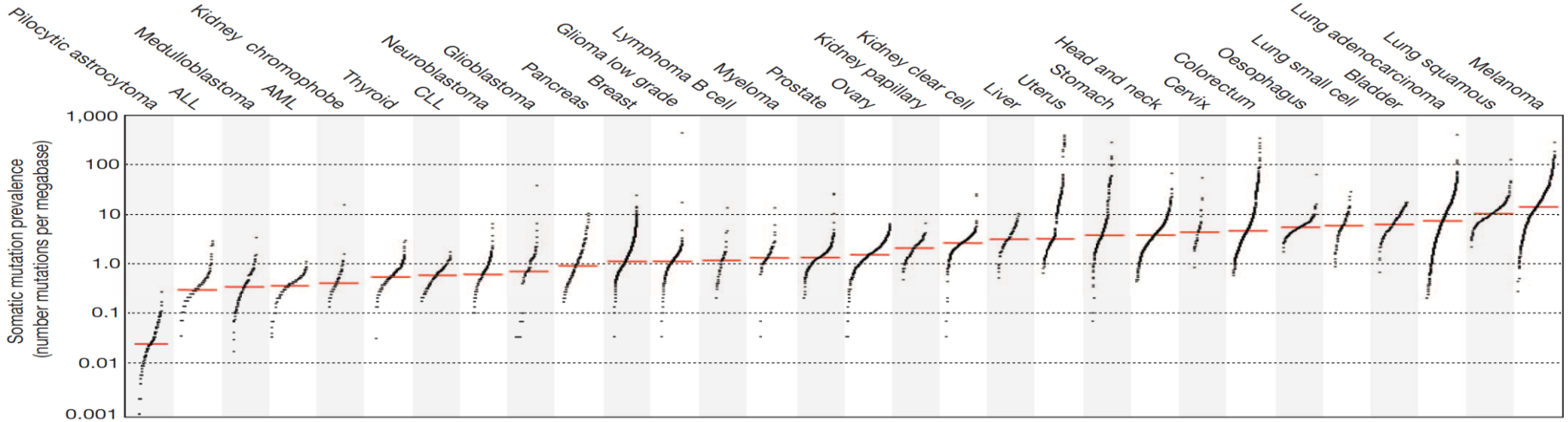
Teng MWL et al. *Cancer Res.* 2015;75(11):2139-2145.

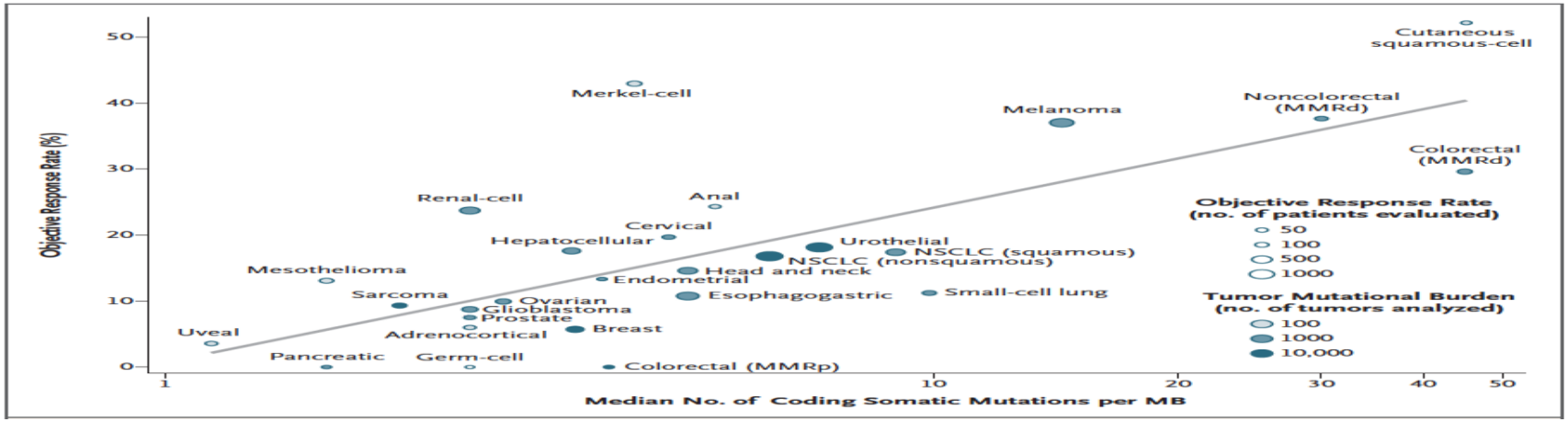
The cancer inmunogram



Blank CU et al. Science 2016; 352:658

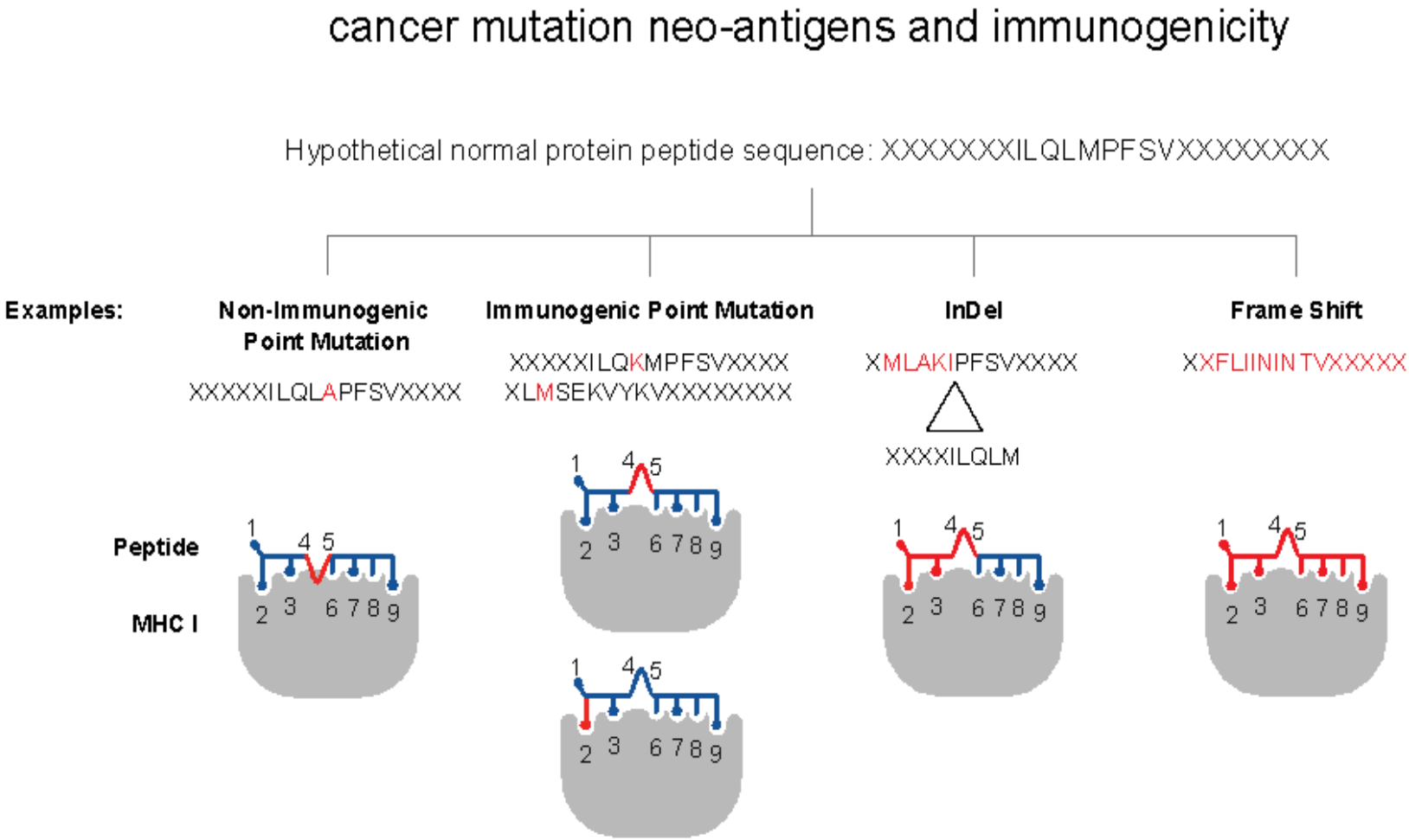
Tumour Mutation Burden and Response to PD-1 Inhibitors





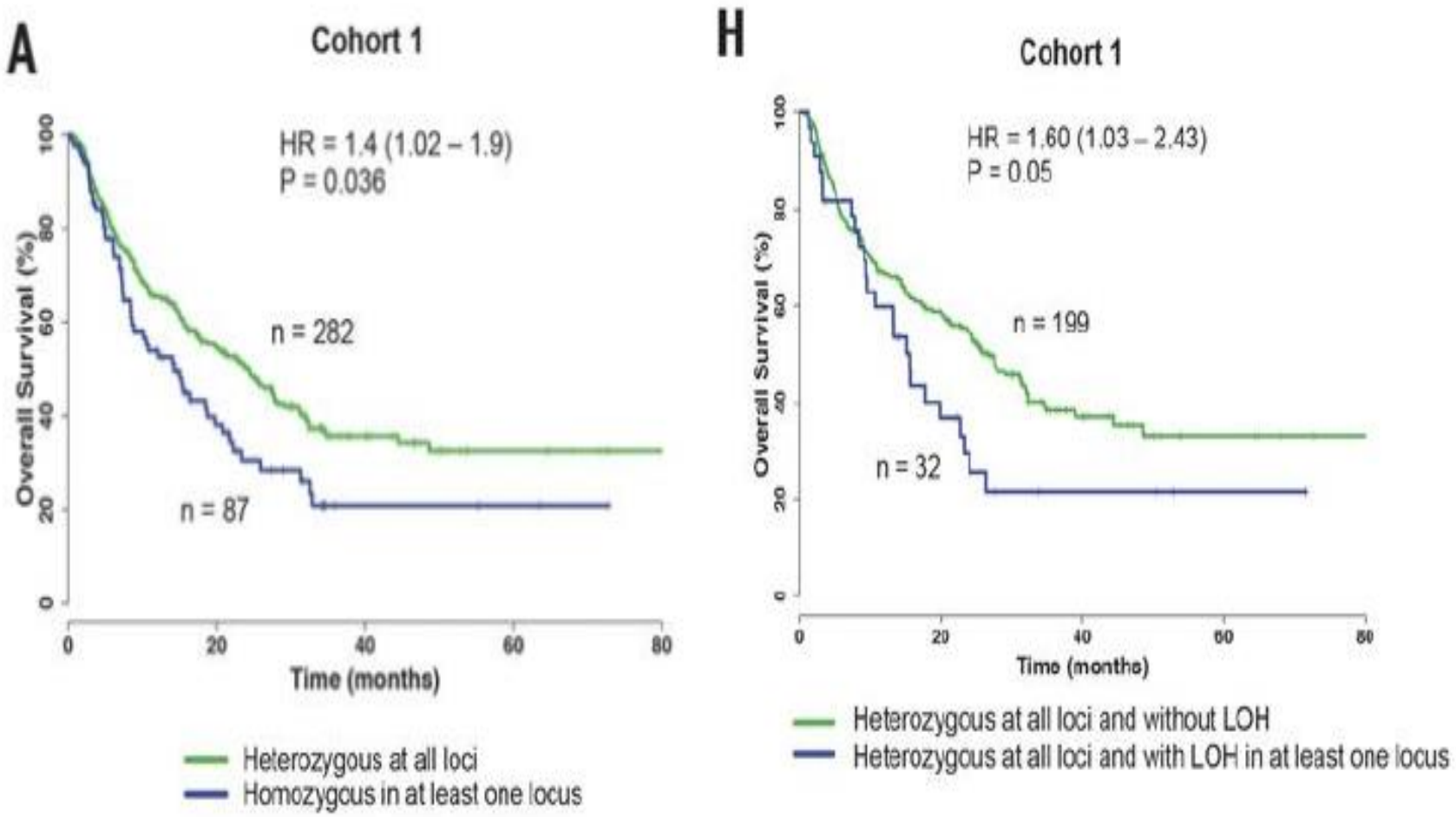
Alexandrov *et al.*, Science 2013
Rosemberg *et al.*, Lancet 2016
Yarchoan *et al.*, NEJM 2017

Mutated Peptides are presented to the Inmune System



Chen and Mellman. Nature 2017

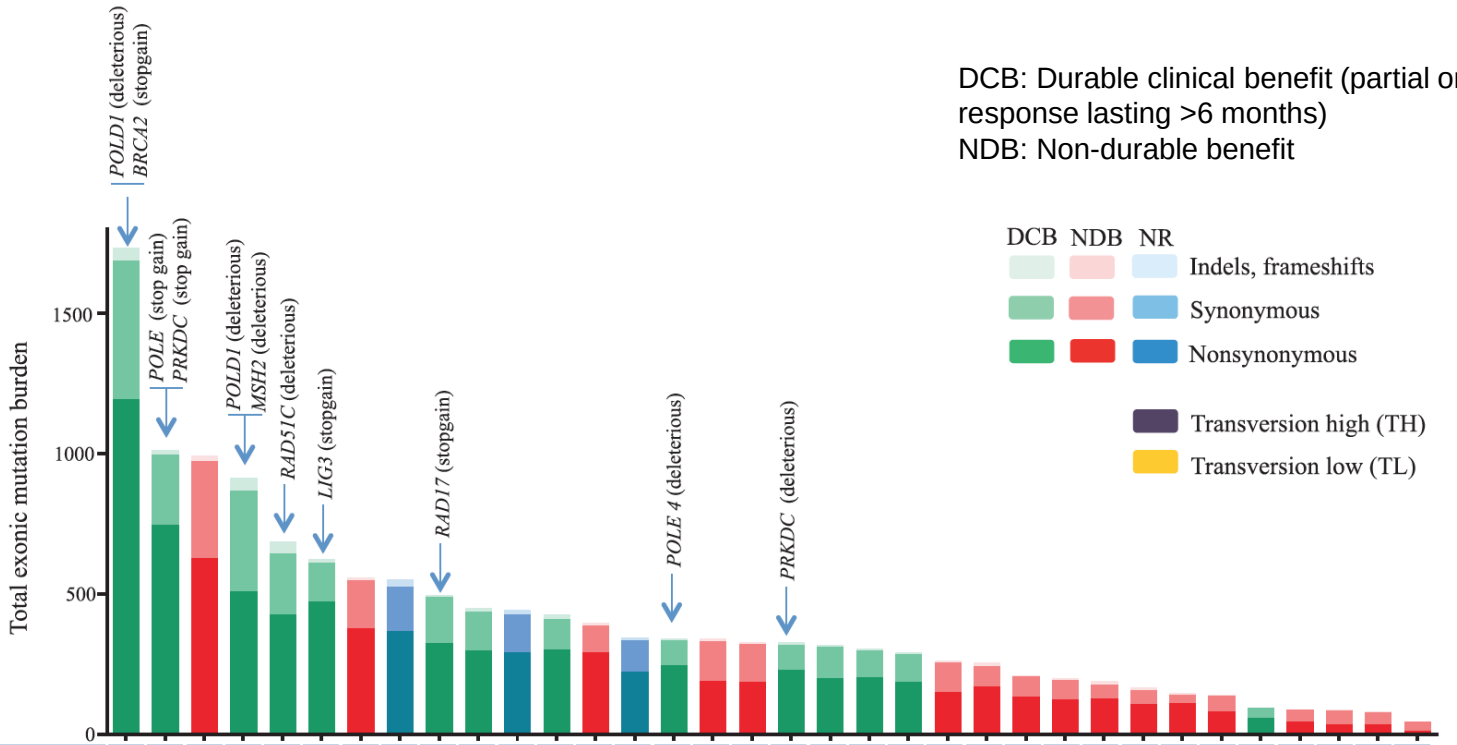
HLA Cigosity
The influence of genetics



Chowell et al., Science 2018

Mutational landscape determines sensitivity to PD-1 blockade in NSCLC

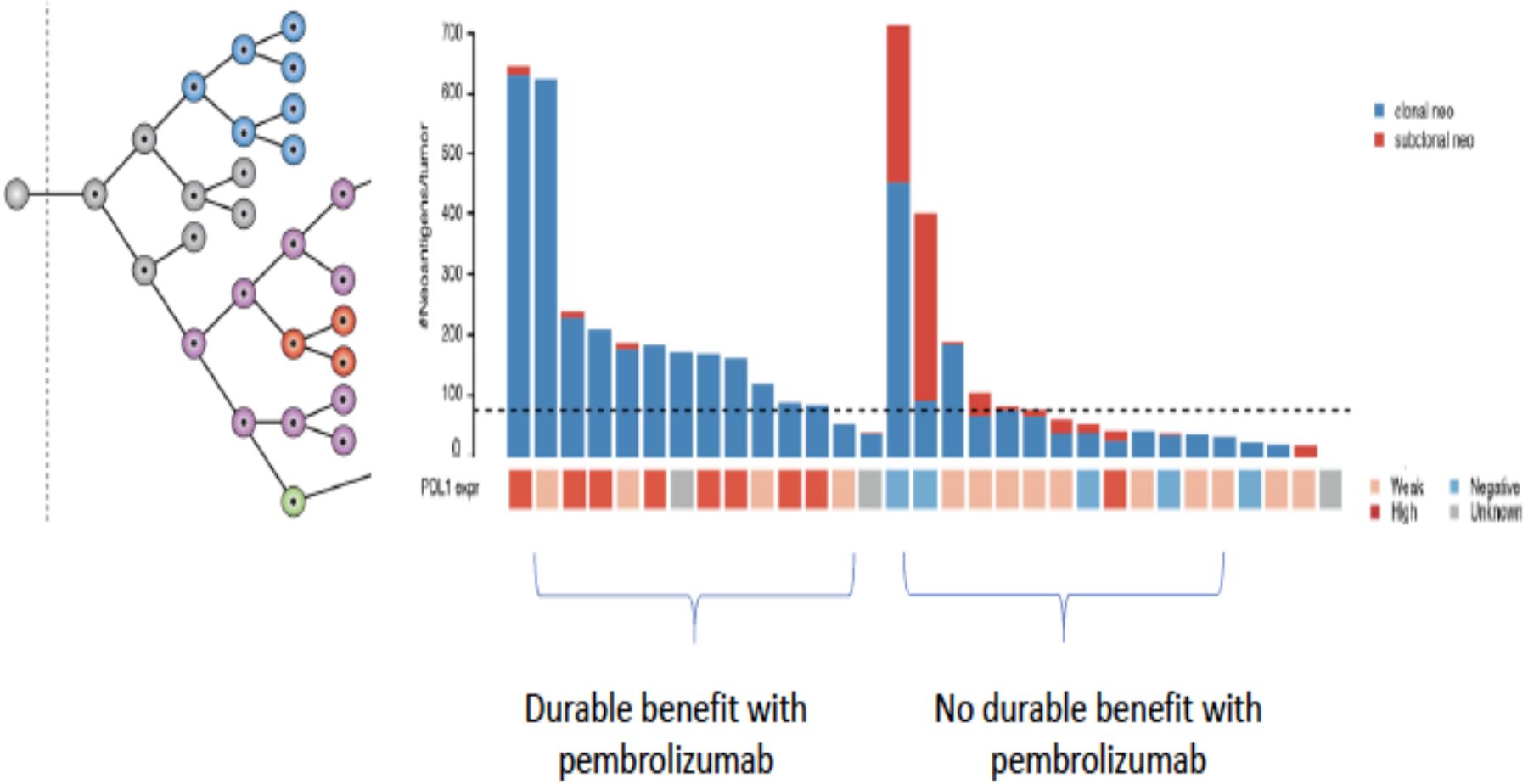
DCB: Durable clinical benefit (partial or stable response lasting >6 months)
NDB: Non-durable benefit



Study ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34
Cohort	V	D	D	V	V	D	V	V	D	D	V	D	D	V	V	V	D	D	V	V	D	D	D	V	V	V	D	V	V	V	D	V	D	D
Objective Response	PR	PR	PD	SD	PR	PR	PD	SD	PR	PR	PR	SD	PD	PR	SD	PD	PD	PR	PR	PR	SD	SD	PD	PD	PD	PD	PD	SD	SD	PR	SD	PD	PD	SD
PFS (months)	8	14	2	8	14	16	2	4	15	13	4	8	2	4	8	3	3	10	27	10	8	7	2	2	1	2	2	4	6	8	4	2	2	6
Ongoing response	++	++			++	++		++		++	++			++	++			++	++	++														
Smoking signature	TH	TH	TH	TL	TH	TH	TL	TH	TH	TH	TH	TH	TH	TH	TH	TL	TL	TH	TL	TL	TH	TL	TH	TL	TL	TL	TL	TL	TL	TL	TL	TL	TL	TL

Rizvi *et al*, Science 2015
TMB and PD-L1 blockade sensitivity

Clonal Neoantigens
Predictor for anti-PD-1Treatment Benefit



McGranaham et al., Science 2016

Checkmate 227: TMB as predictor of response with nivo+ipi

The NEW ENGLAND JOURNAL of MEDICINE

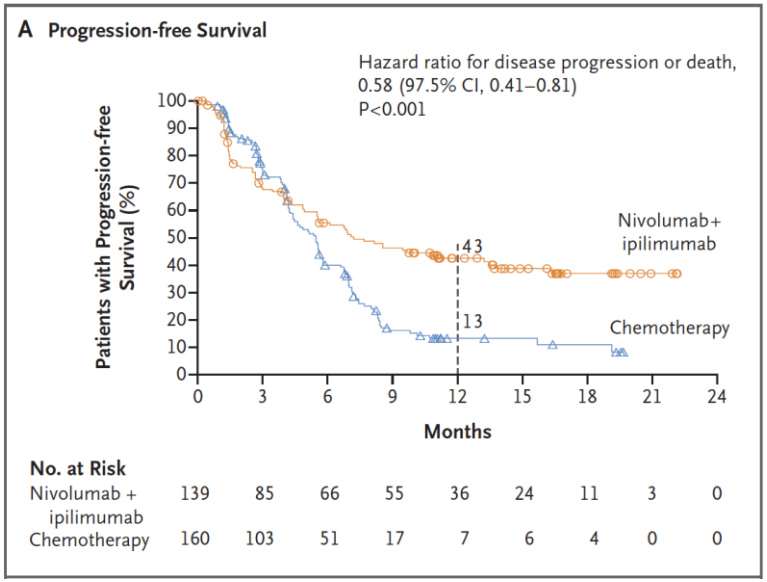
ORIGINAL ARTICLE

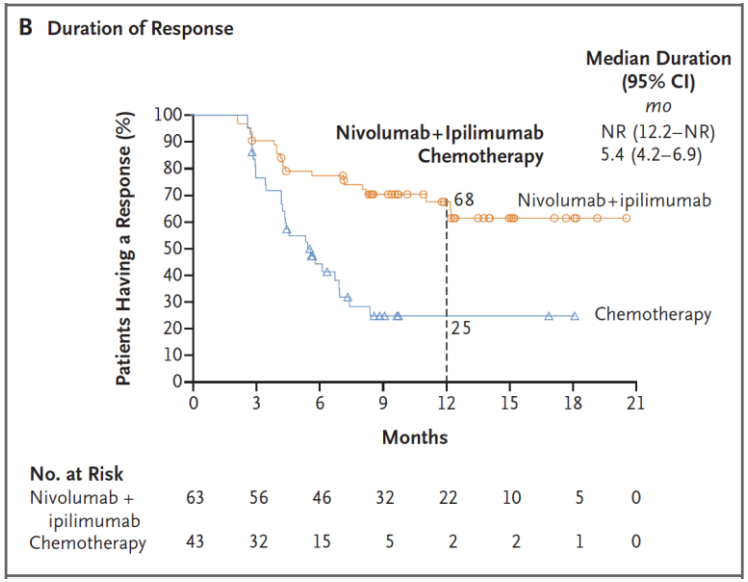
Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden

M.D. Hellmann, T.-E. Ciuleanu, A. Pluzanski, J.S. Lee, G.A. Otterson, C. Audigier-Valette, E. Minenza, H. Linardou, S. Burgers, P. Salman, H. Borghaei, S.S. Ramalingam, J. Brahmer, M. Reck, K.J. O'Byrne, W.J. Geese, G. Green, H. Chang, J. Szustakowski, P. Bhagavatheeswaran, D. Healey, Y. Fu, F. Nathan, and L. Paz-Ares

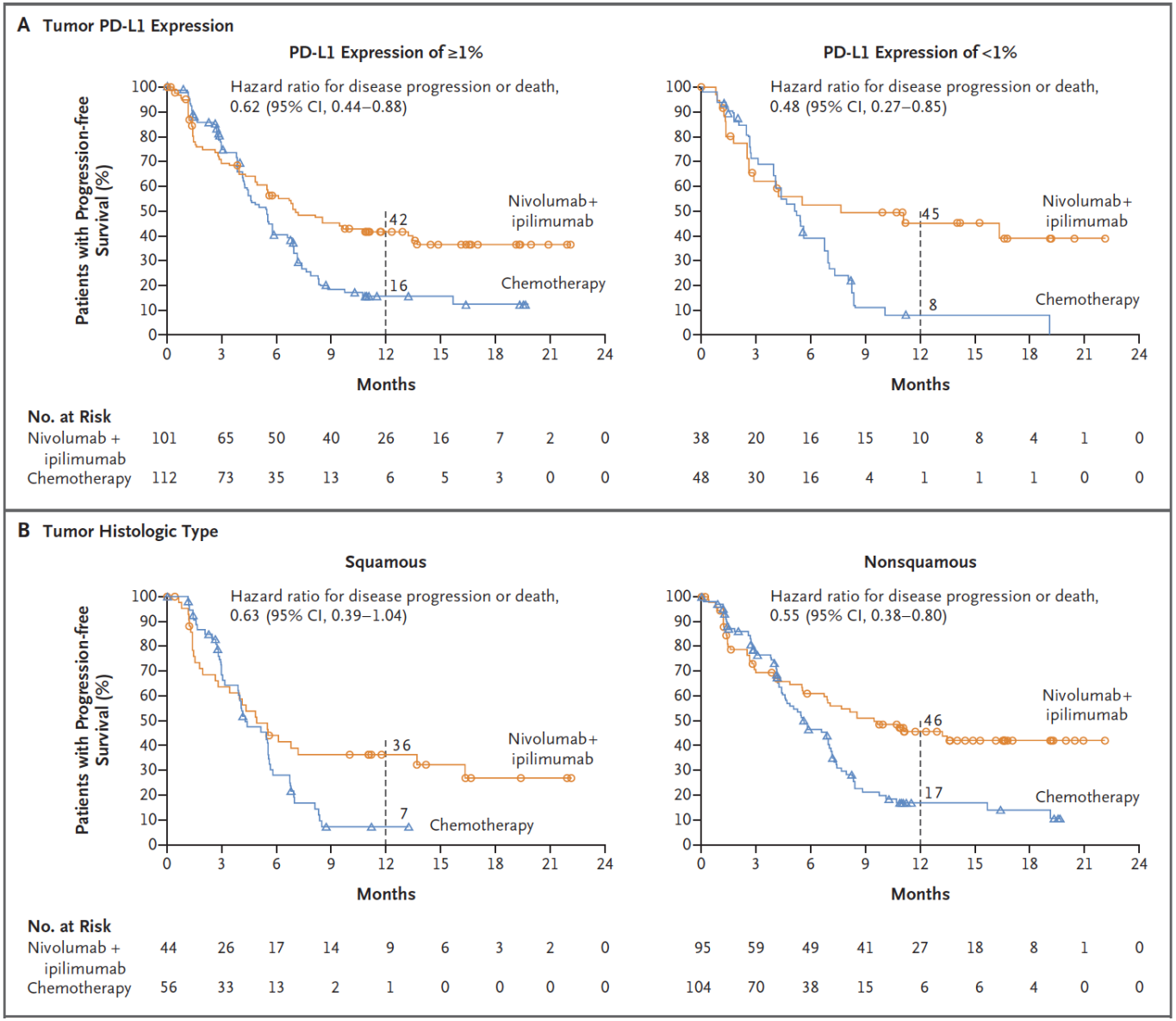
This article was published on April 16, 2018, at NEJM.org.

Nivolumab anti-PD1
Ipilimumab anti-CTLA-4



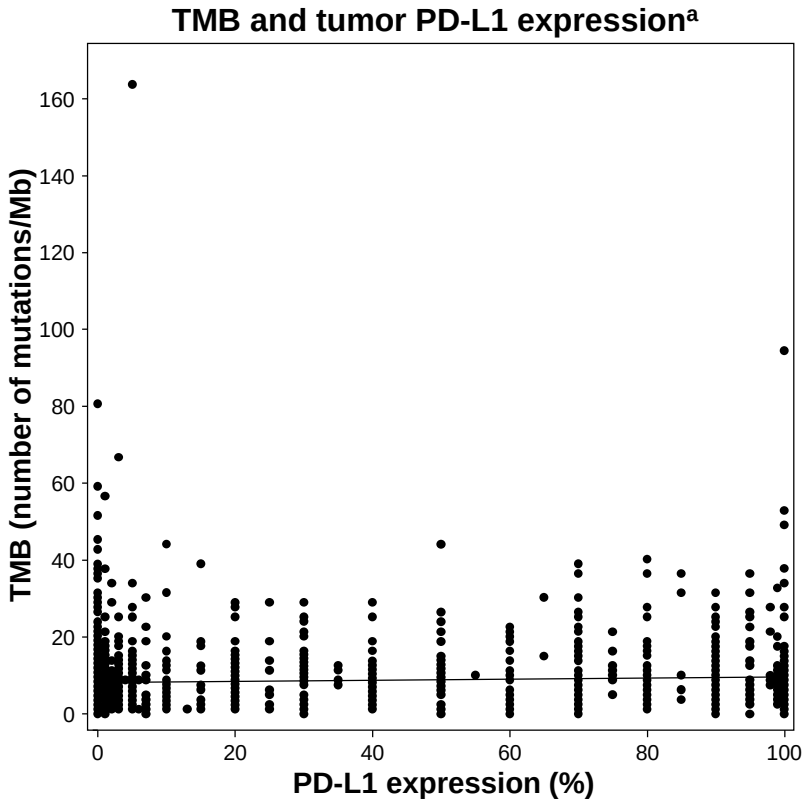


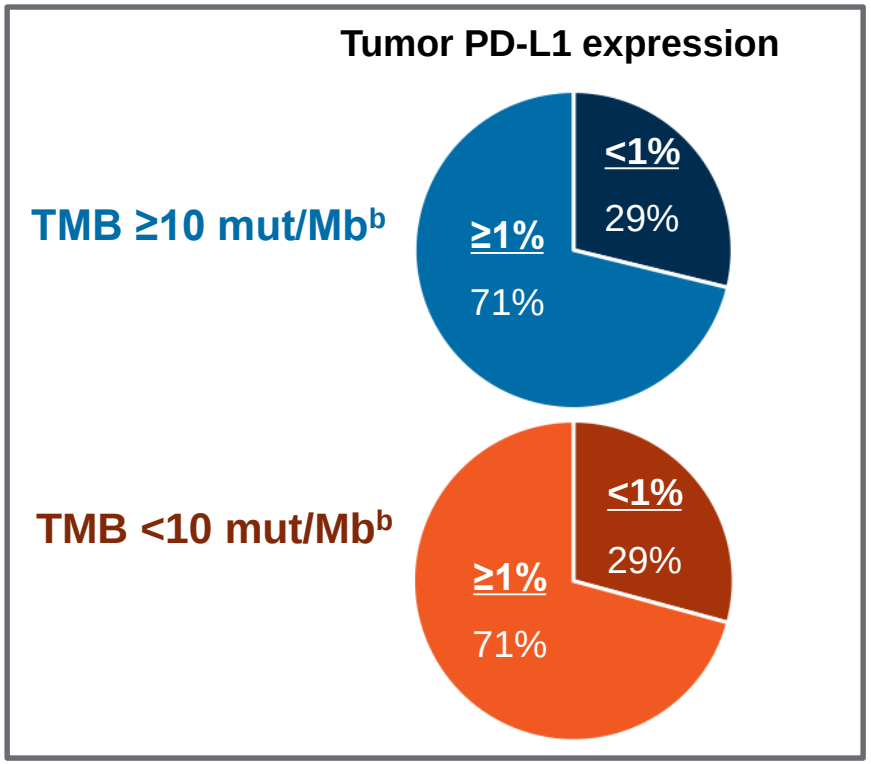
Checkmate 227: TMB as predictor of response with nivo+ipi



Hellmann MD,…Paz-Ares L. New Eng J Med 2018

TMB and Tumor PD-L1 Expression Identify Distinct and Independent Populations of NSCLC



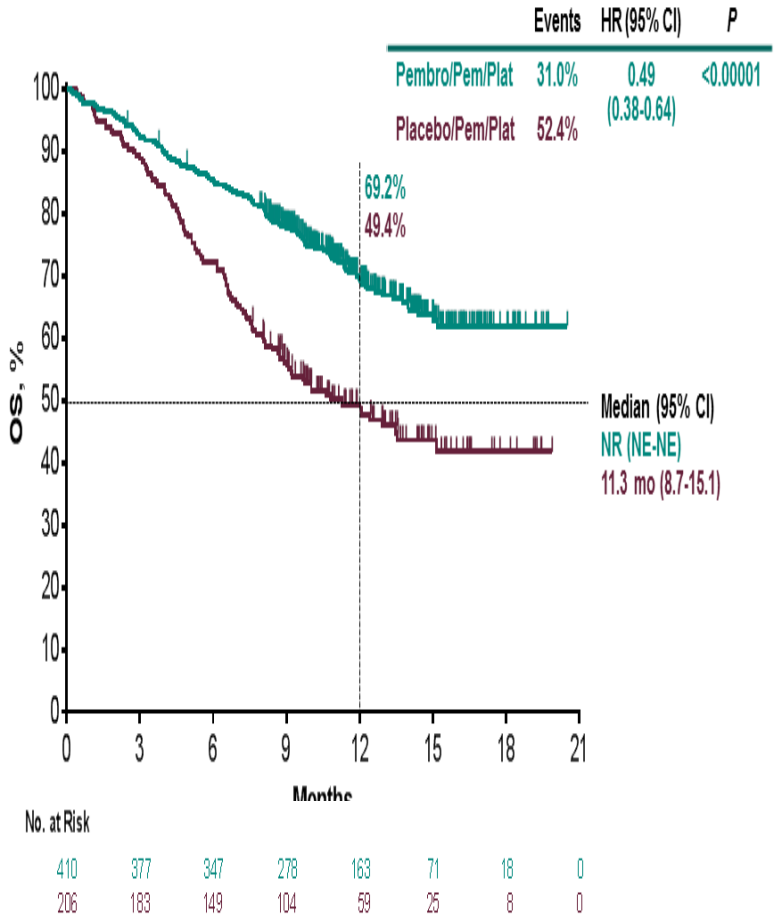


[a]Symbols (dots) in the scatterplot may represent multiple data points, especially for patients with <1% tumor PD-L1 expression. The black line shows the relationship between TMB and PD-L1 expression as described by a linear regression model; [b]Among patients in the nivolumab +ipilimumab and chemotherapy arms; TMB ≥10 mut/Mb, n = 299; TMB <10 mut/Mb, n = 380

Hellmann MD,…Paz-Ares L. New Eng J Med 2018

Chemo ± Pembrolizumab in NSCLC

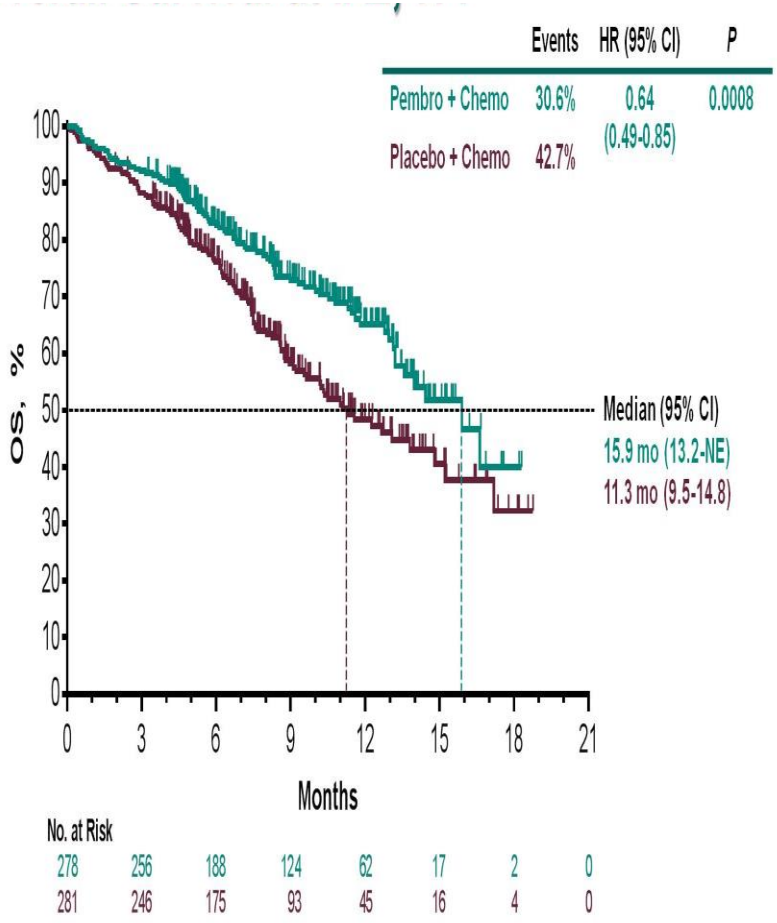
Non SCC KeyNote 189 Trial



Data cutoff date: Nov 8, 2017.

Ghandi et al., NEJM 2018

Non SCC KeyNote 407 Trial

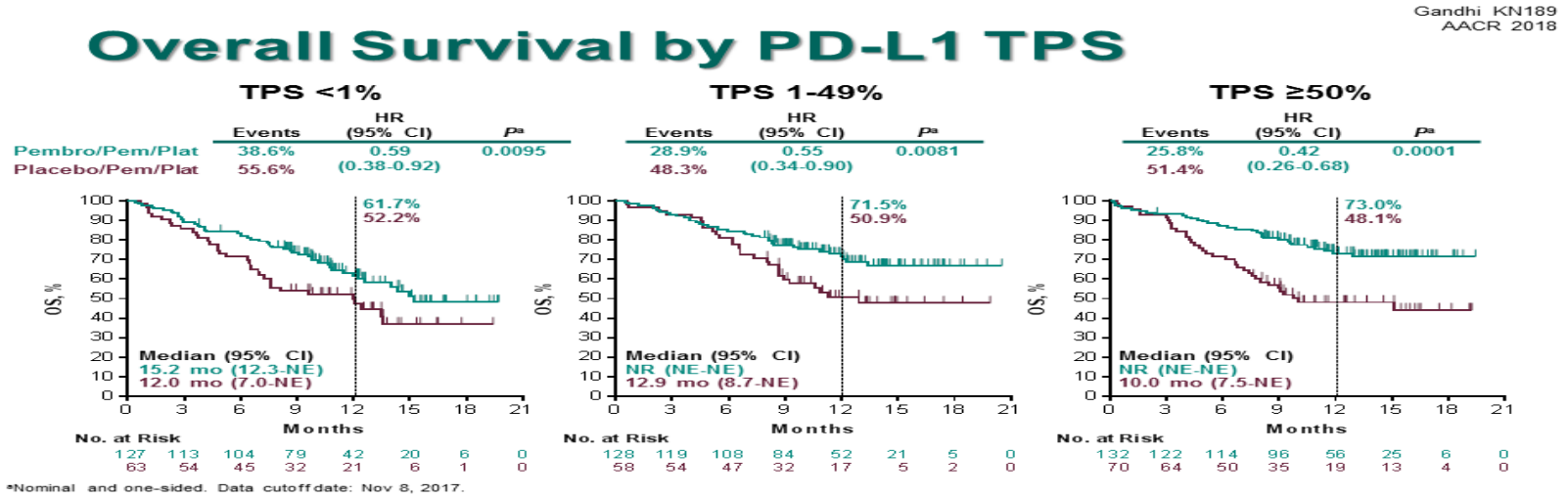


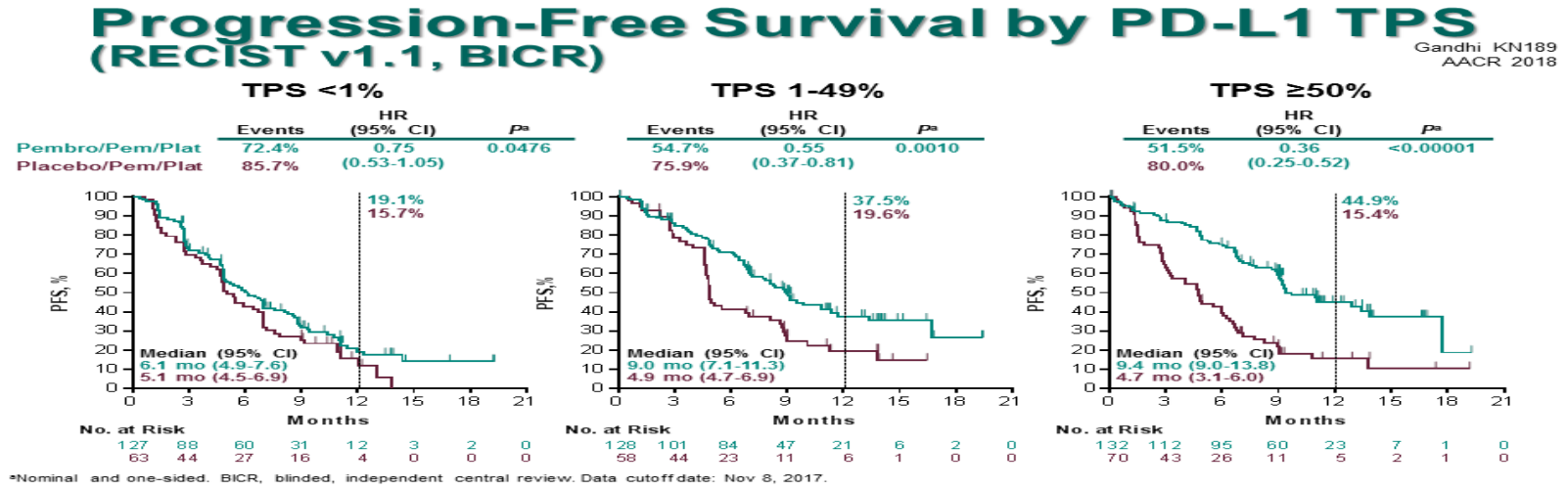
Data cutoff date: Apr 3, 2018.

Paz-Ares et al., NEJM 2018

Not all patients are benefitting fron QT+IO

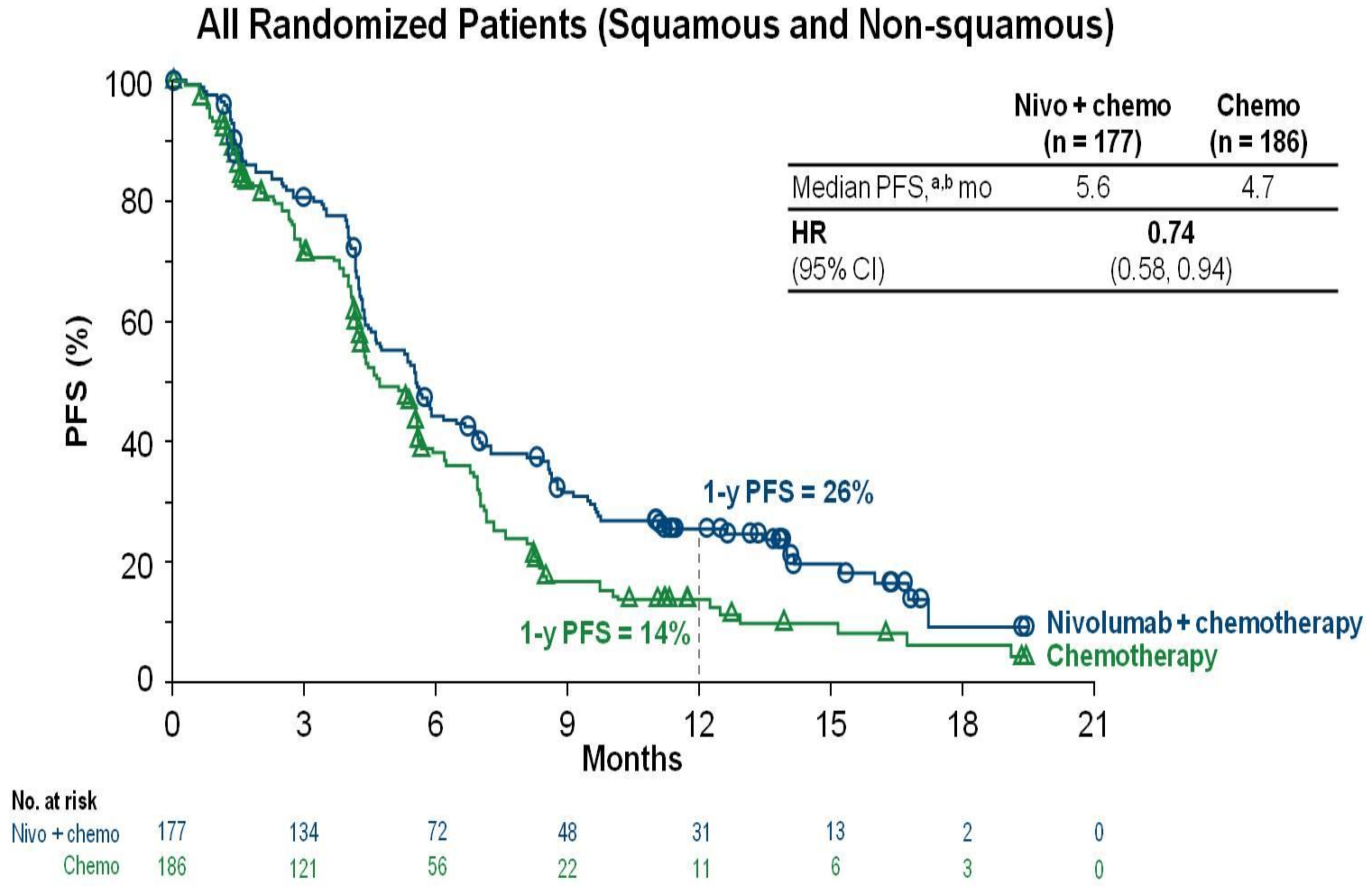
KeyNote 189/407 Trial Benefit according to PD-L1 expression





Gandhi et al., NEJM 2018
Paz-Ares et al NEJM 2018

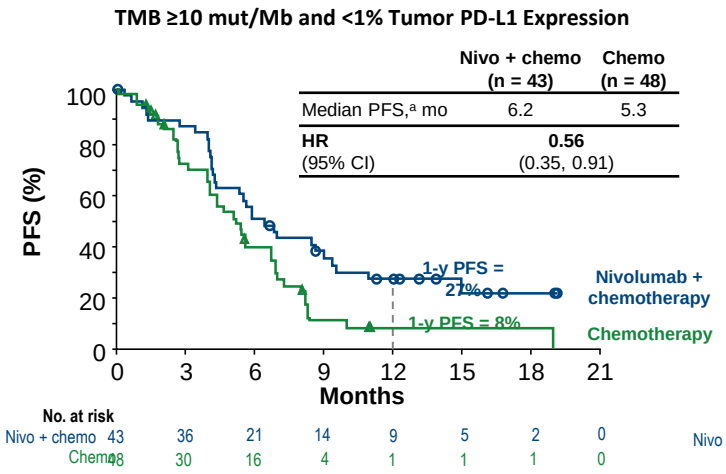
CM 227- PD-L1 Negative Tumors Chemo ± NivolumabTrial

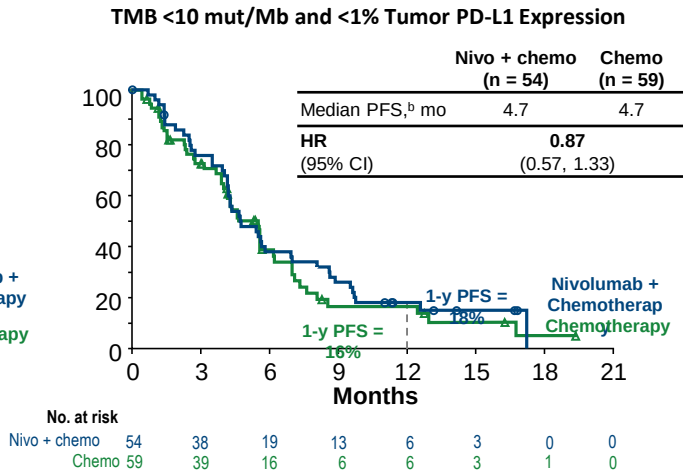


[a]95% CI: nivo + chemo (4.6, 6.7 mo), chemo (4.3, 5.6 mo); [b]In the nivo + ipi arm (n = 187), median (95% CI) PFS was 4.4 (3.1, 6.0), 1-y PFS was 29%, and HR vs chemo was 0.79 (0.62, 1.01)

Hellmann MD *et al*, (Paz-Ares L) New Eng J Med 2018;
Borghaei H et al. ASCO 2018

CM 227- PD-L1 Negative Tumors Chemo ± NivolumabTrial





- TMB ≥10 mut/Mb: ORR was 60.5% with nivo + chemo and 20.8% with chemo
- TMB <10 mut/Mb: ORR was 27.8% with nivo + chemo and 22.0% with chemo

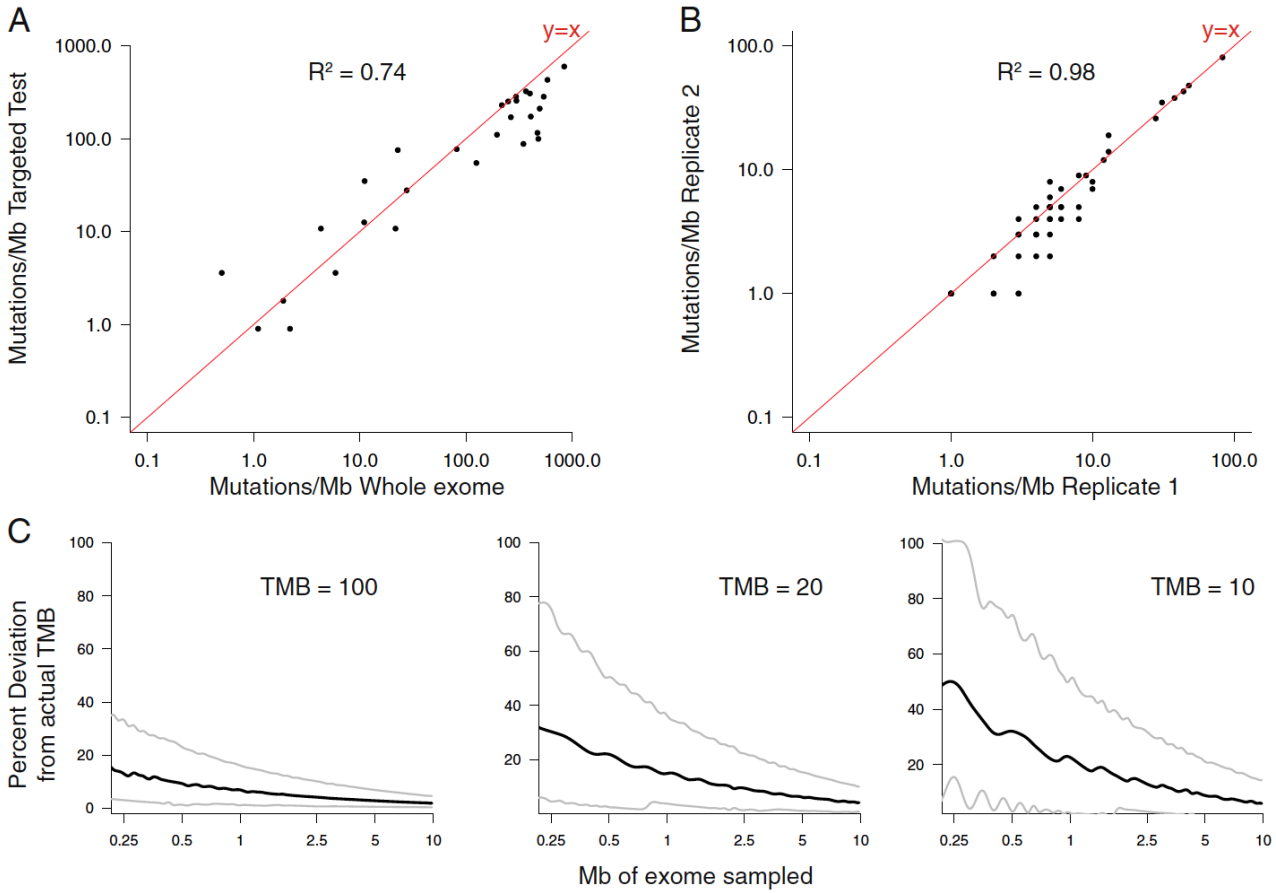
Hellmann MD *et al*, (Paz-Ares L) New Eng J Med 2018;
Borghaei H etal. ASCO 2018

Standard of practice: Foundation One

Comprehensive genomic profiling assay
315 genes
1.1 Mb of coding genome
Correlation to WES:

Exome: 38Mb

FoM cutoffs:
TMB^{low} 1-5 mut/Mb
TMB^{med} 5-10 mut/Mb
TMB^{high} >10 mut/Mb



Chalmers ZR *et al*, Genome Med 2017

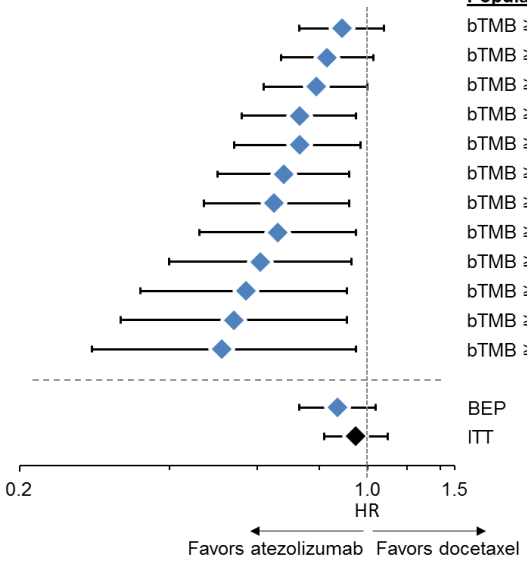
Other available NGS panels for TMB calculation

Panel	Brand	FDA approved for diagnostic use	Technology	Genes	Horizontal coverage	Bibliography
TruSight Tumour TST170	Illumina	No	Hybrid capture (DNA+RNA)	170	0,524 Mb	
AmpliSeq Comprehensive Cancer Panel	Thermo Fisher	No	Amplicons (DNA)	409	1,7 Mb	
Foundation One CDx	**Roche**	**Yes**	**Hybrid capture**	**324**	**1,1 Mb**	**Goodman AM, Mole Canc Ther 2017 Hellmann MD NEJM 2018**
CGP+ Sureselect ST Caris Molecular Int	Agilent	No	Hybrid capture	592	1,4 Mb	Gatalica Z EJC 2018 Vandervalde A Cancer Med 2018
MSK-IMPACT	MSKCC	Yes	Hybrid capture	468	1,22 Mb	Rizvi H et al, JCO 2018
TruSight Oncology TSO500	Ilumina	No	Hybrid capture	523	1,95 Mb	
Oncomine Tumour Mutation Load	Thermo Fisher	No	Amplicons (DNA)	409	1,7 Mb	
QiaSeq Human Comprehensive cancer panel	Qiagen	No	Single primer extension (+UMIs)	275	0,83 Mb	

For Research Use Only. Not for use in diagnostic procedures.

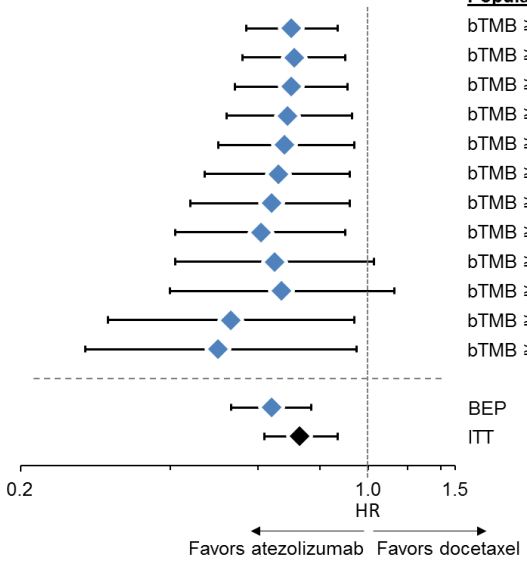
Increasing Atezolizumab benefit with higher bTMB cut-points in OAK Trial

Progression-Free Survival – OAK



Population	PFS HR (95% CI)	n (%)
bTMB ≥4	0.89 (0.73, 1.08)	441 (76%)
bTMB ≥6	0.83 (0.67, 1.03)	371 (64%)
bTMB ≥8	0.79 (0.62, 1.00)	302 (52%)
bTMB ≥10	0.73 (0.56, 0.95)	251 (43%)
bTMB ≥12	0.73 (0.54, 0.97)	211 (36%)
bTMB ≥14	0.68 (0.50, 0.92)	188 (32%)
bTMB ≥16	0.65 (0.47, 0.92)	158 (27%)
bTMB ≥18	0.66 (0.46, 0.95)	136 (23%)
bTMB ≥20	0.61 (0.40, 0.93)	105 (18%)
bTMB ≥22	0.57 (0.35, 0.91)	84 (14%)
bTMB ≥24	0.54 (0.32, 0.91)	69 (12%)
bTMB ≥26	0.51 (0.28, 0.95)	54 (9%)
BEP	0.87 (0.73, 1.04)	583 (100%)
ITT	0.95 (0.82, 1.10)	850

Overall Survival – OAK



Population	OS HR (95% CI)	n (%)
bTMB ≥4	0.70 (0.57, 0.87)	441 (76%)
bTMB ≥6	0.71 (0.56, 0.90)	371 (64%)
bTMB ≥8	0.70 (0.54, 0.91)	302 (52%)
bTMB ≥10	0.69 (0.52, 0.93)	251 (43%)
bTMB ≥12	0.68 (0.50, 0.94)	211 (36%)
bTMB ≥14	0.66 (0.47, 0.92)	188 (32%)
bTMB ≥16	0.64 (0.44, 0.92)	158 (27%)
bTMB ≥18	0.61 (0.41, 0.90)	136 (23%)
bTMB ≥20	0.65 (0.41,1.03)	105 (18%)
bTMB ≥22	0.67 (0.40, 1.13)	84 (14%)
bTMB ≥24	0.53 (0.30, 0.94)	69 (12%)
bTMB ≥26	0.50 (0.27, 0.95)	54 (9%)
BEP	0.64 (0.53, 0.77)	583 (100%)
ITT	0.73 (0.62, 0.87)	850

- Enrichment of PFS benefit was observed in the bTMB ≥16 subgroup, while OS was consistent between the bTMB ≥16 subgroup and the BEP

Gandara DR et al.., Nat Med 2018

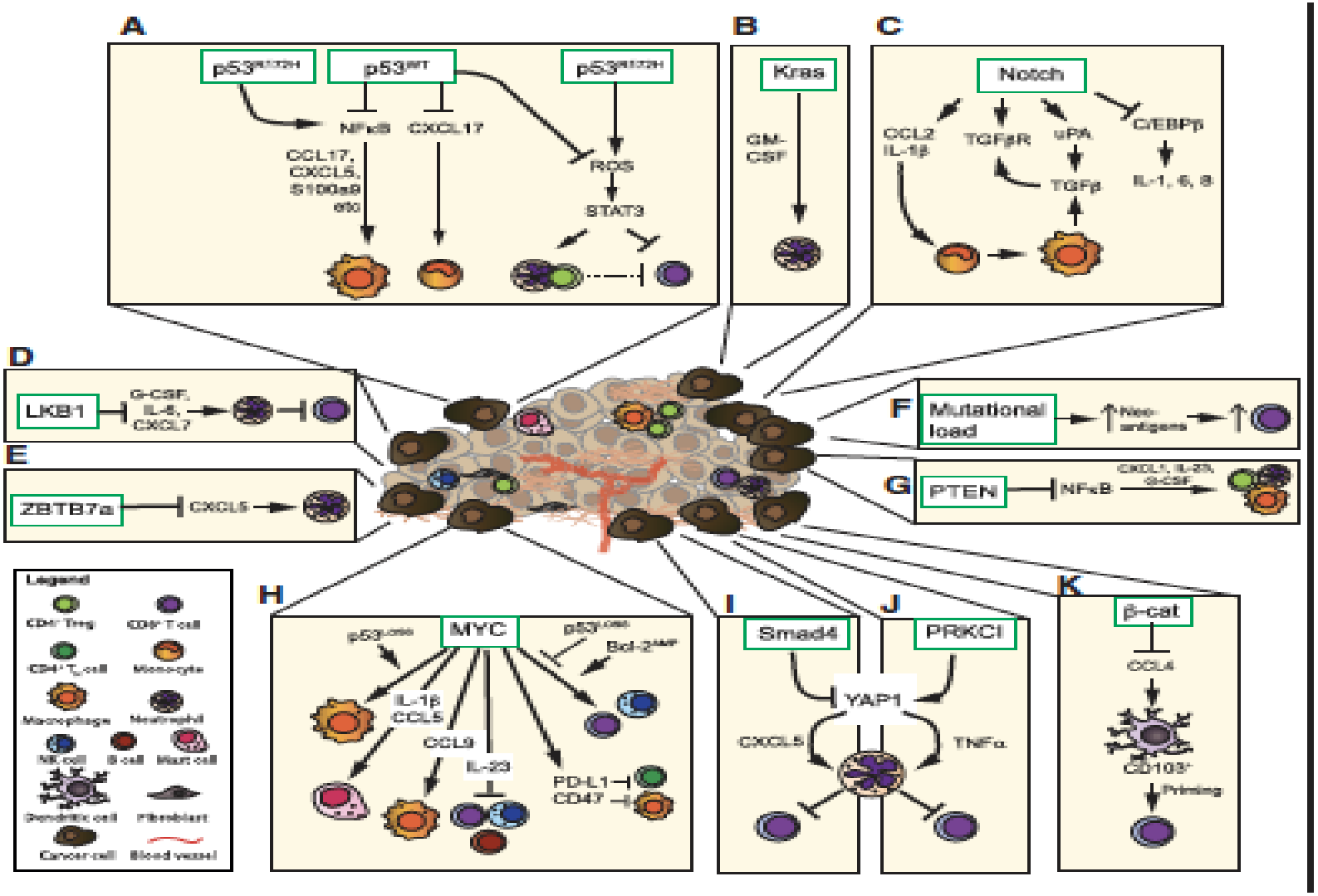
Issues at implementation of TMB into routine clinical practice

- ✓ **Expertise and technology**
- ✓ **Bioinformaticians**
- ✓ **Open algorithms**
- ✓ **Standardization/Harmonization studies**
- ✓ **Availability of sequencers of high capacity**
- ✓ **Data storage with encrypted data**
- ✓ **Time around time**

Agenda

- IO in lung cancer
- Beyond PD-L1: TMB (neoantigen load!)
- **Genomic aberrations and future perspectives**

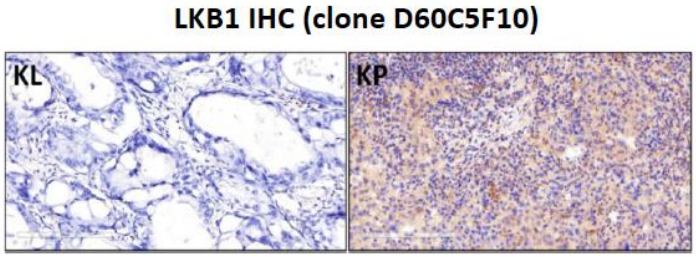
Cancer Genotypes shapes the immune landscape

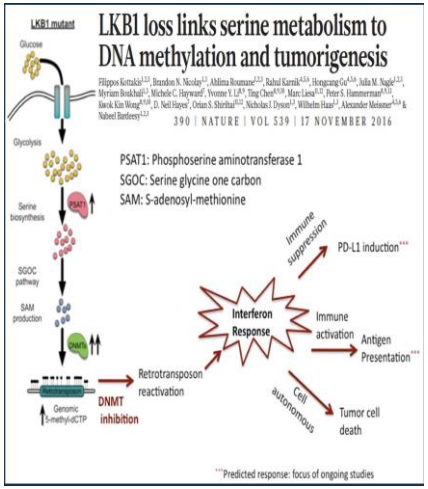


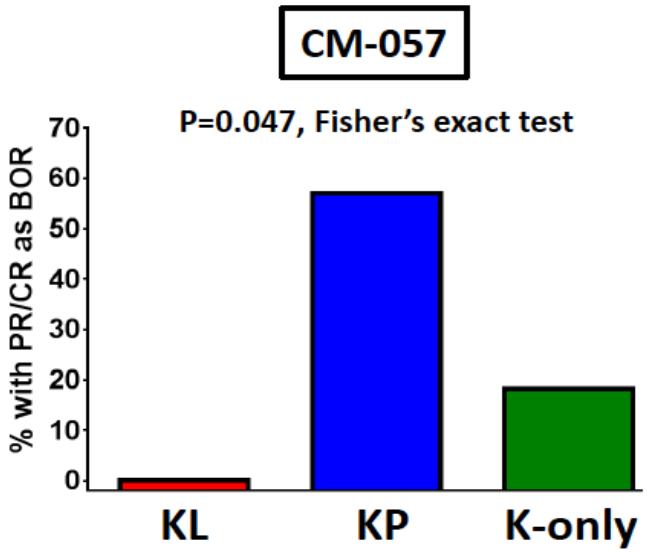
H Borghaei et al.,. ASCO 2018

Underlying Genomic Aberrations

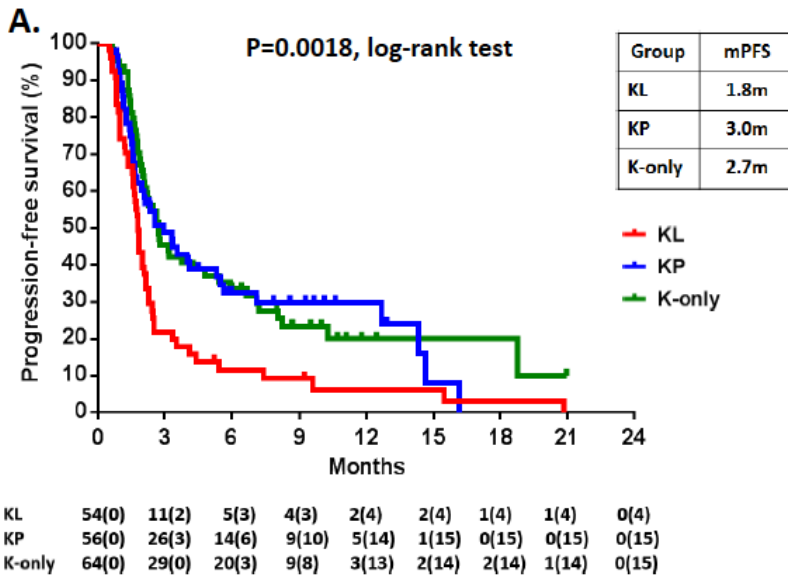
KRAS and LKB1







Group	KL	KP	K-only
ORR	0% (0/6)	57.1% (4/7)	18.2% (2/11)



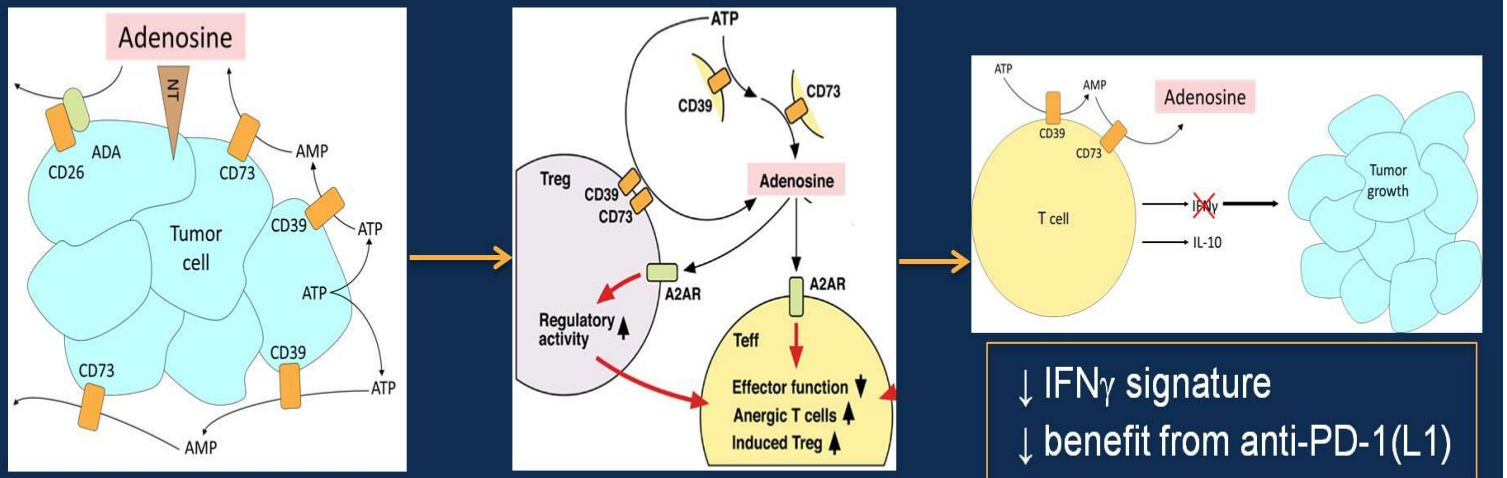
Group	mPFS
KL	1.8m
KP	3.0m
K-only	2.7m

KL	54(0)	11(2)	5(3)	4(3)	2(4)	2(4)	1(4)	1(4)	0(4)
KP	56(0)	26(3)	14(6)	9(10)	5(14)	1(15)	0(15)	0(15)	0(15)
K-only	64(0)	29(0)	20(3)	9(8)	3(13)	2(14)	2(14)	1(14)	0(15)

Skoulidis et al., Cancer Discovery 2018

Relevance of a specific genomic aberration on the immune landscape

Hypothesis: Over-expression of CD73 in EGFRm tumors creates an immunosuppressive microenvironment



EGFR activation induces CD73 expression,
↑ Adenosine

Immunosuppression
↓ T cell activation/
effector function

Martin, F et al. Trends in Mol Med. 18: 2012;
Luca A et al. Nat Rev Cancer 13: 2013;
Borghaei, H., et al. NEJM 73:2015.
Herbst, R.S., et al. Lancet. 387: 2015;
Fehrenbacher, et al. Lancet. 387: 2016;
Ohta A and Sitkovsky M. Front. Immunol., 2014.

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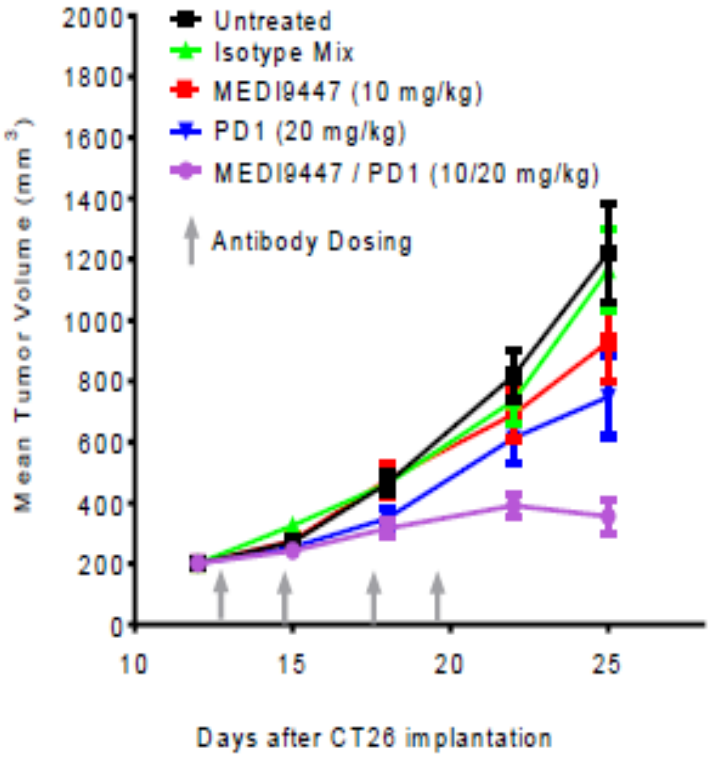
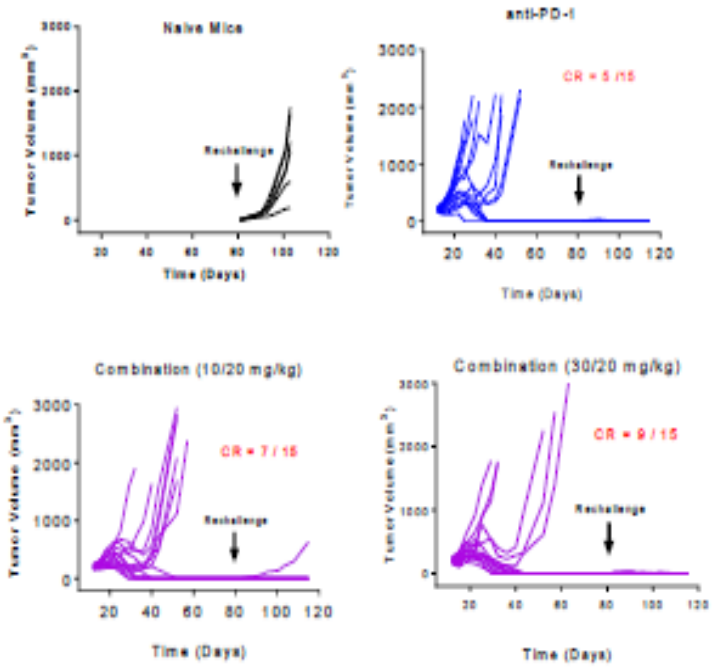
MEDI9447+Anti-PD1: demonstration of synergistic effect

MEDI9447 + Anti-PD-1: Additive Activity at Optimal Doses

Tumor Growth Inhibition



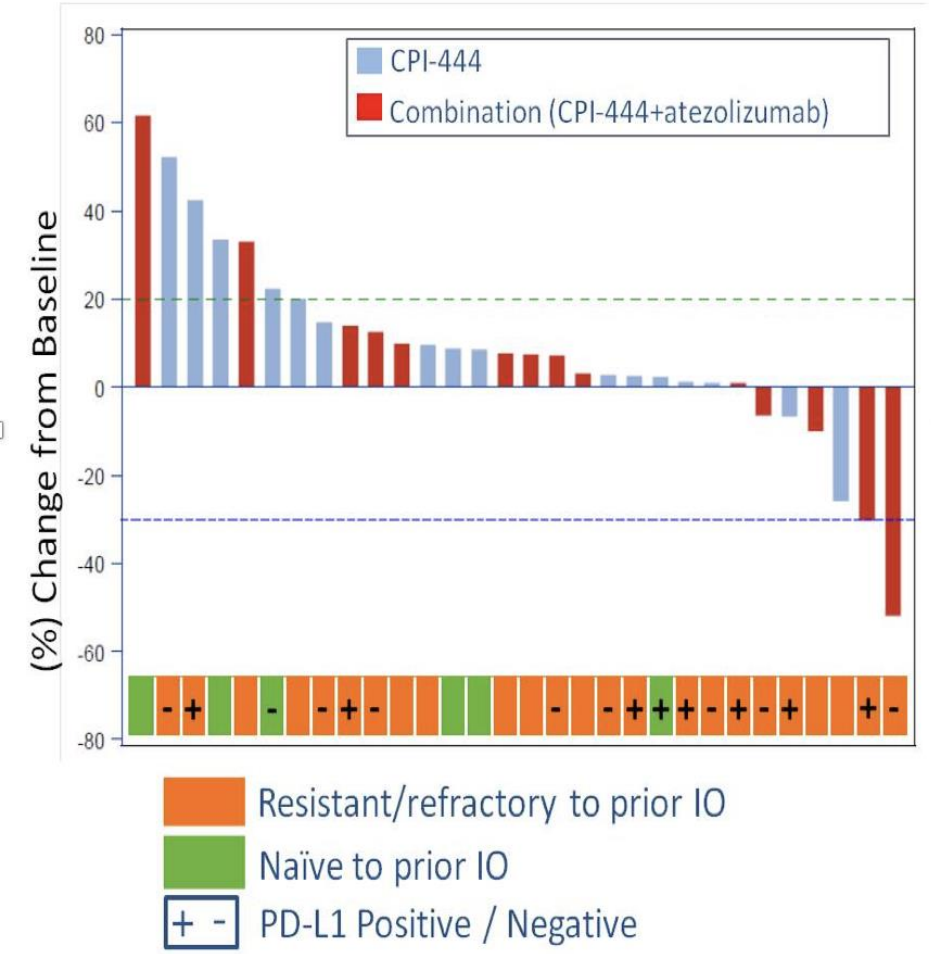
Complete Response and Memory

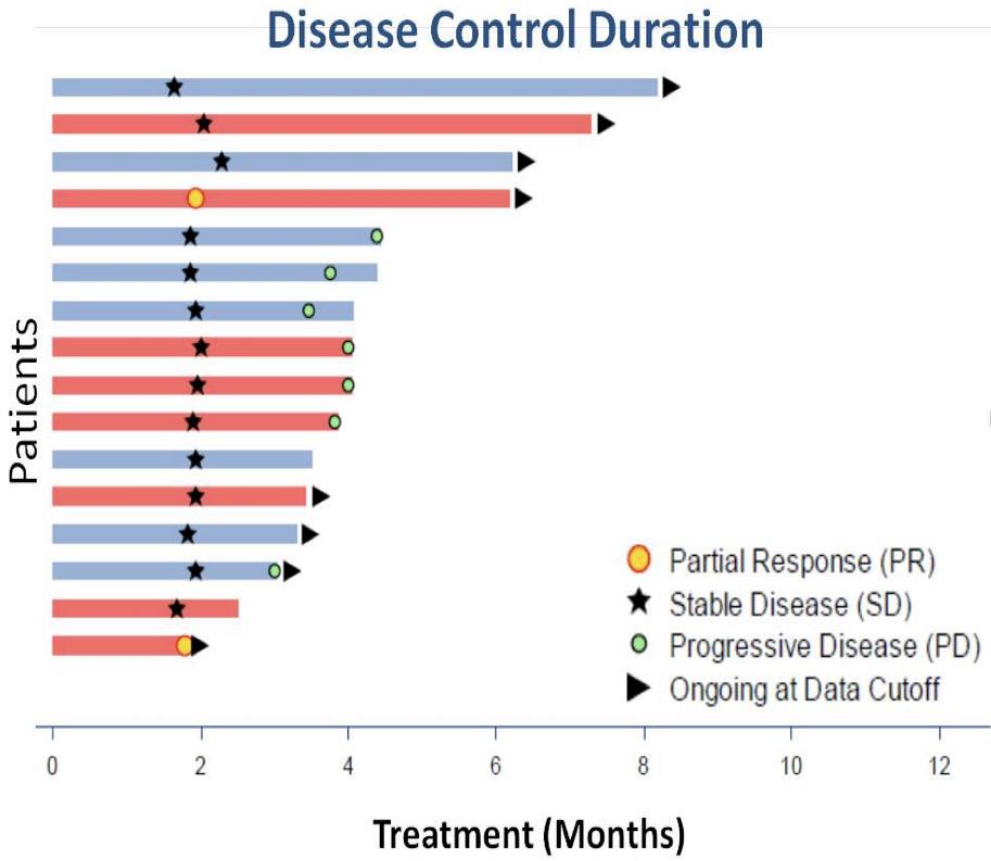


Hay et al., 2016

Hay et al OncoImmunology 2016

Adenosine Receptor Inhibitors
CPI-444 ± Atezo

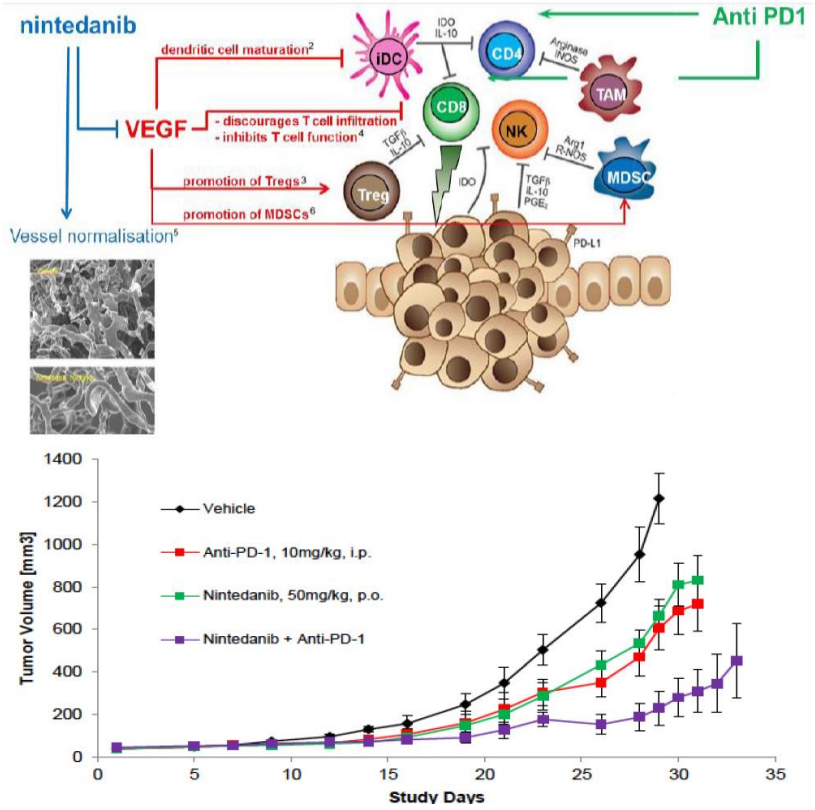




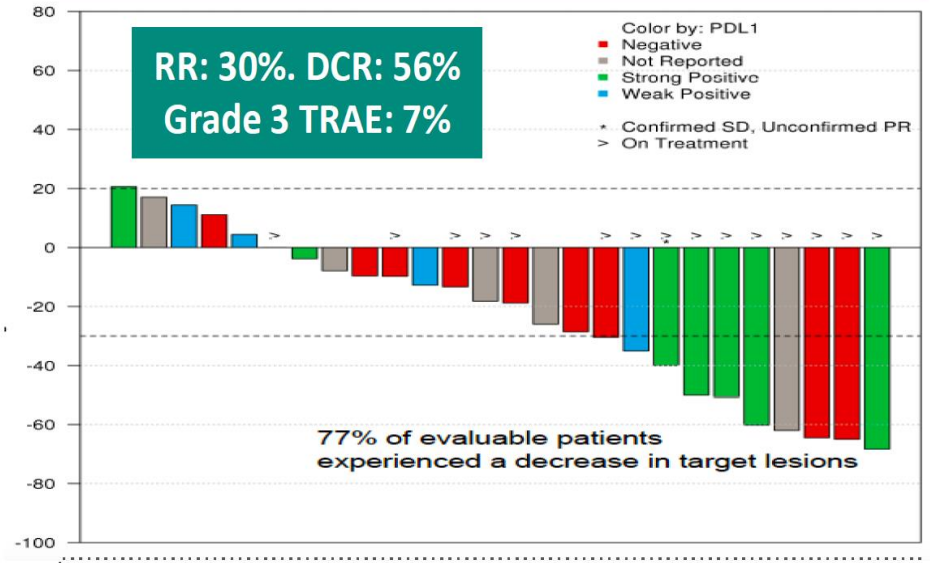
Fong et al., ASCO 2017

Targeted agent not directed against a genomic aberration: IO Agents + Antiangiogenics

Nintedanib improves anti-tumor efficacy in combination with anti-PD-1 in syngeneic lung tumor models sensitive and refractory to IO inhibition



Phase I: Pembroliz 200 mg D1+ **Ramucir.** 10 mg/kg/ 21 d
N=27. 78% Adenocarcinoma. ≥ 2nd Line
PD-L1 +: 41% (PD-L1 > 50%: 26%* by 22C3)

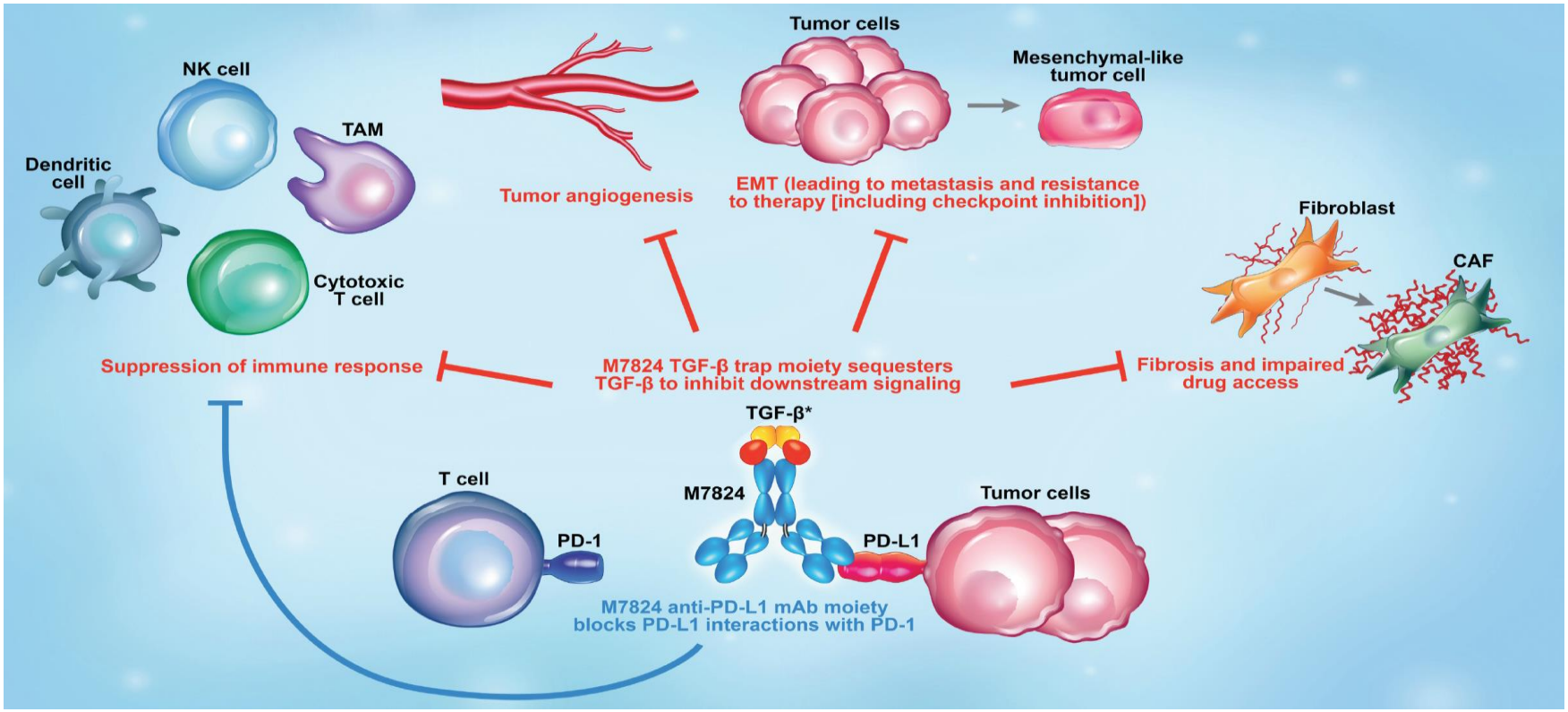


NCT02856425: Phase I Trial of Pembrolizumab and **Nintedanib** (PEMBIB)
NCT03074513: Phase II Trial of Atezolizumab and **Bevacizumab** (15 mg/kg)

Herbst et al. al. ESMO 2016

Pembrolizumab+ramucirumab is not in the label of ramucirumab in The Netherlands

Bifunctional PD-L1/TGF β Inhibitor M7824

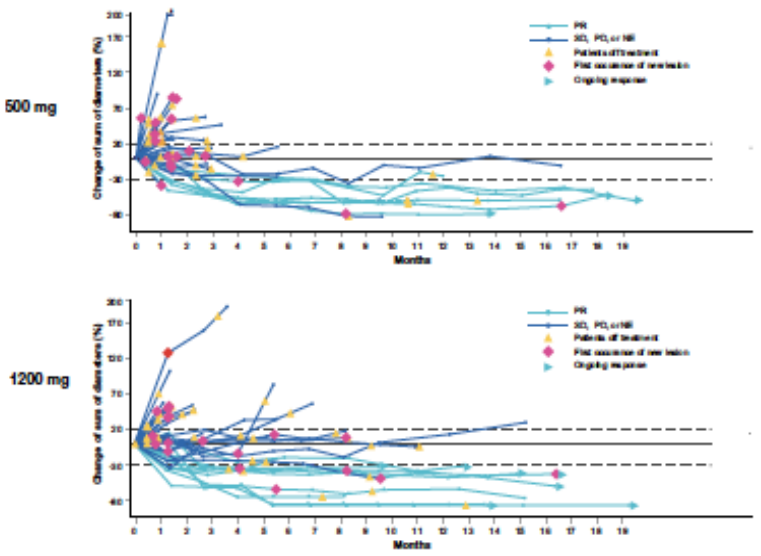


Paz-Ares et al. ASCO 2018

Results from a second-line (2L) NSCLC cohort treated with M7824 (MSB0011359C), a bifunctional fusion protein targeting TGF-β and PD-L1

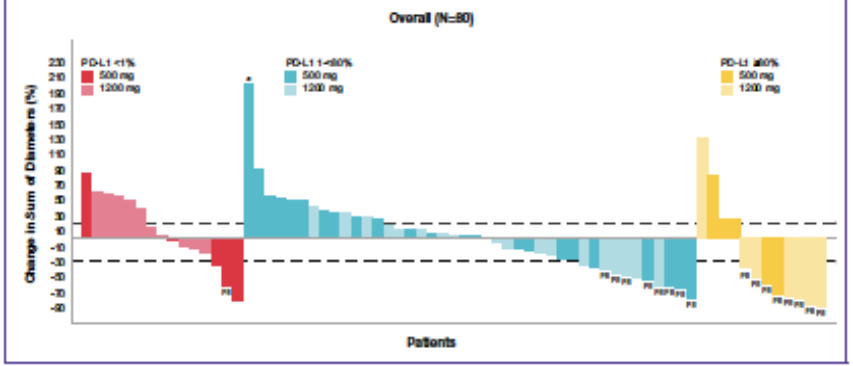
L.G. Paz-Ares[1], T.M. Kim[2], D. Vicente[3], E. Felip[4], D.H. Lee[5], K.H. Lee[6], C-C. Lin[7], M.A. Di Nicola[8], R.M. Alvarez[9], I. Dussault[10], C. Helwig[11], L.S. Ojalvo[10], J.L. Gulley[12], B.C. Cho[13]

Figure 2. Efficacy according to RECIST v1.1 adjudicated by IRC



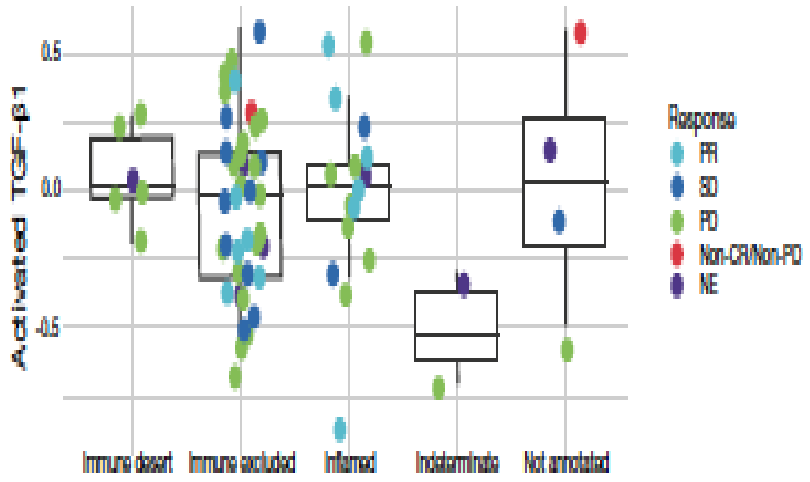
*Value >200

Figure 3. Change in target lesions from baseline by PD-L1 status adjudicated by the IRC



- All doses: ORR overall patient population 21.5%
- High dose: ORR 37% and 86% for PD-L1+ and PD-L1 high, respectively

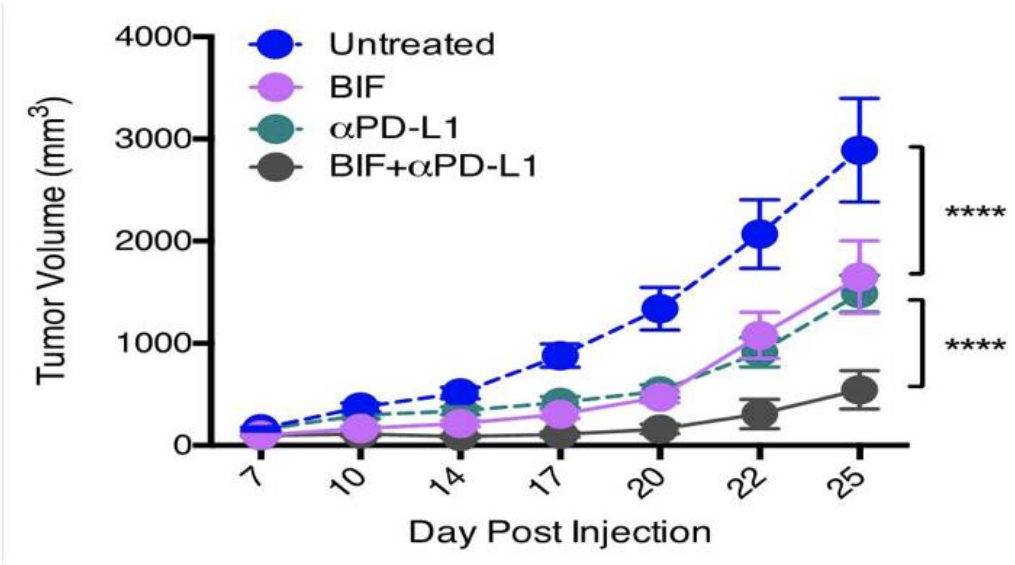
Figure 5. Response by immune phenotype

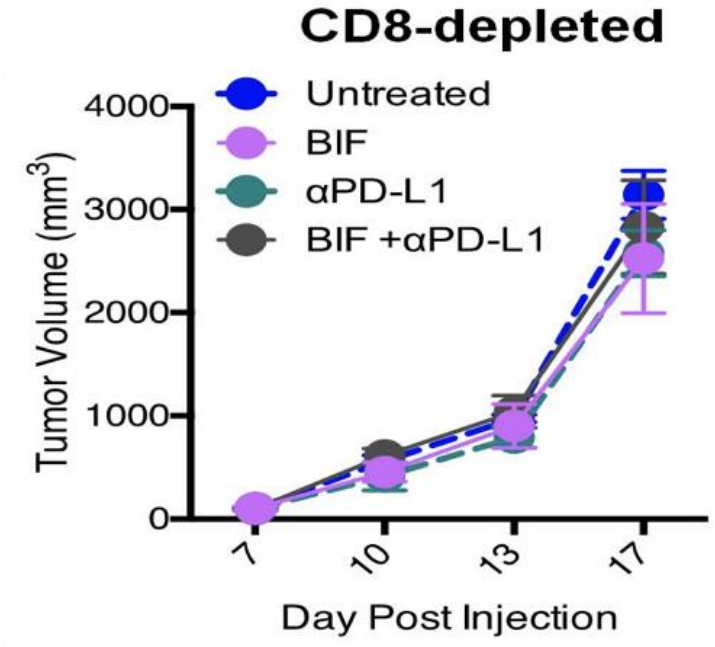


Paz-Ares et al. ASCO & ESMO 2018

Get Cold Tumors Inflammed Microbiota

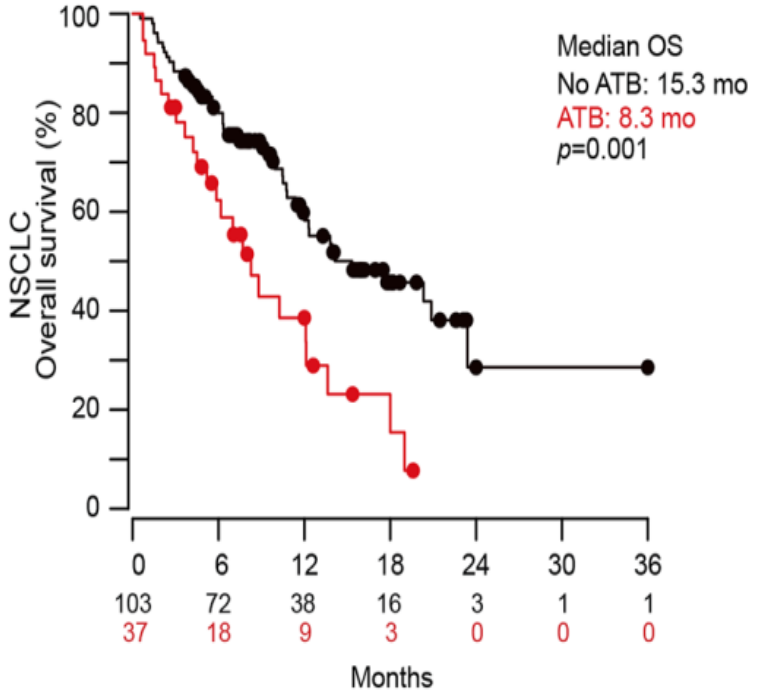
Commensal microbiota: Bifidobacterium species can improve anti-tumor immunity and response to anti-PD-L1 antibody in vivo

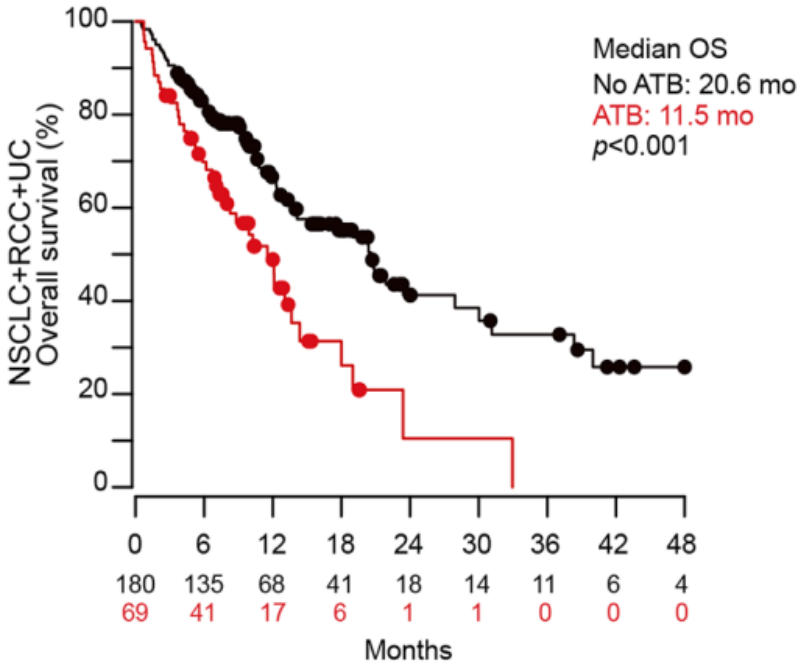




Sivan et al., Science 2015

Patients who had received antibiotics showed decreased PFS and OS following anti-PD-1/PD-L1 treatment





Derosa et al., Science 2018

Adoptive T-Cell Therapy

TCR	CAR-T (LIQUID TUMORS)	TIL (SOLID TUMORS)
Few solid tumors treated so far	No examples of successful utility in solid tumors	Available data in melanoma, head & neck and cervical cancers
One-time treatment	One-time treatment	One-time treatment
Genetic modification	Genetic modification	Currently, no genetic modification
Potential on-target, off-tissue effects	Potentially immunogenic: cytokine release syndrome	Minimal chance of unpredicted on-target, off-tissue effects found to date
Target only single tumor antigen	Mainly target only single/ surface tumor antigen	Target multiple tumor antigens
Autologous	Autologous	Autologous
HLA restriction	No HLA restriction	No HLA restriction

Gracias

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stop cancer

GECI