Quale impatto sulla pratica clinica?

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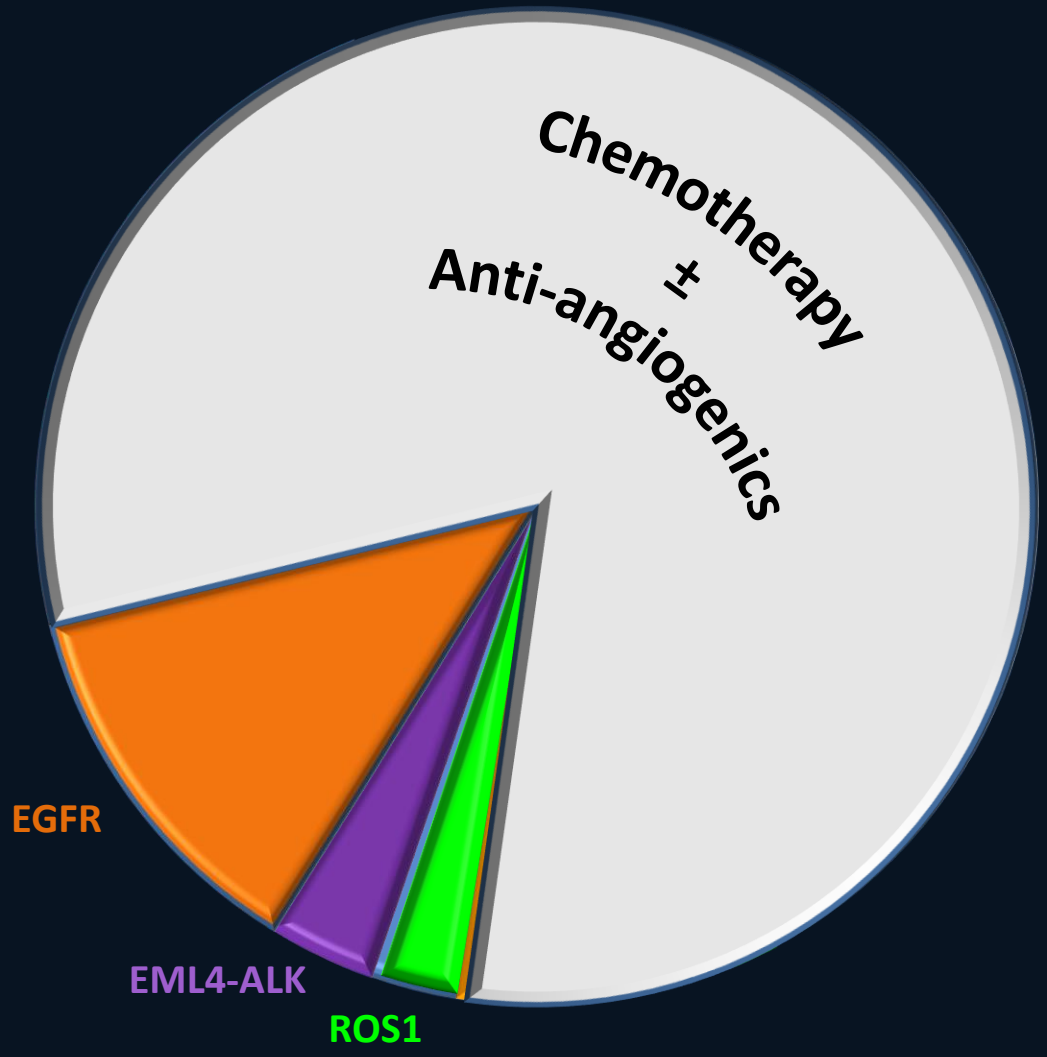
Clinical practice 2015



Chemotherapy in 2nd-line NSCLC

- Docetaxel is standard in 2nd-line NSCLC
- Docetaxel has median survival of ~9 months[1]
- Docetaxel is hampered by important toxicity

- The addition of anti-angiogenics improves docetaxel efficacy
  - ✓ Ramucirumab in all histologies (HR 0.86 [95% CI 0.75, 0.98])[2]
  - ✓ Nintedanib in adenocarcinoma (HR 0.79 [95% CI 0.60, 0.92])[3]

ISTITUTO NAZIONALE
PER LO STUDIO
E LA CURA DEI TUMORI

1. Garassino et al., Lancet Oncol 2013
2. Garon et al., Lancet 2014
3. Reck et al., Lancet Oncol 2014

2015

Scenario attuale

✓ **2 anti PD-1:**

1. **NIVOLUMAB** *All comers (squamoso e non squamoso)*
2. **PEMBROLIZUMAB** *con selezione*

✓ **3 anti PD-L1:**

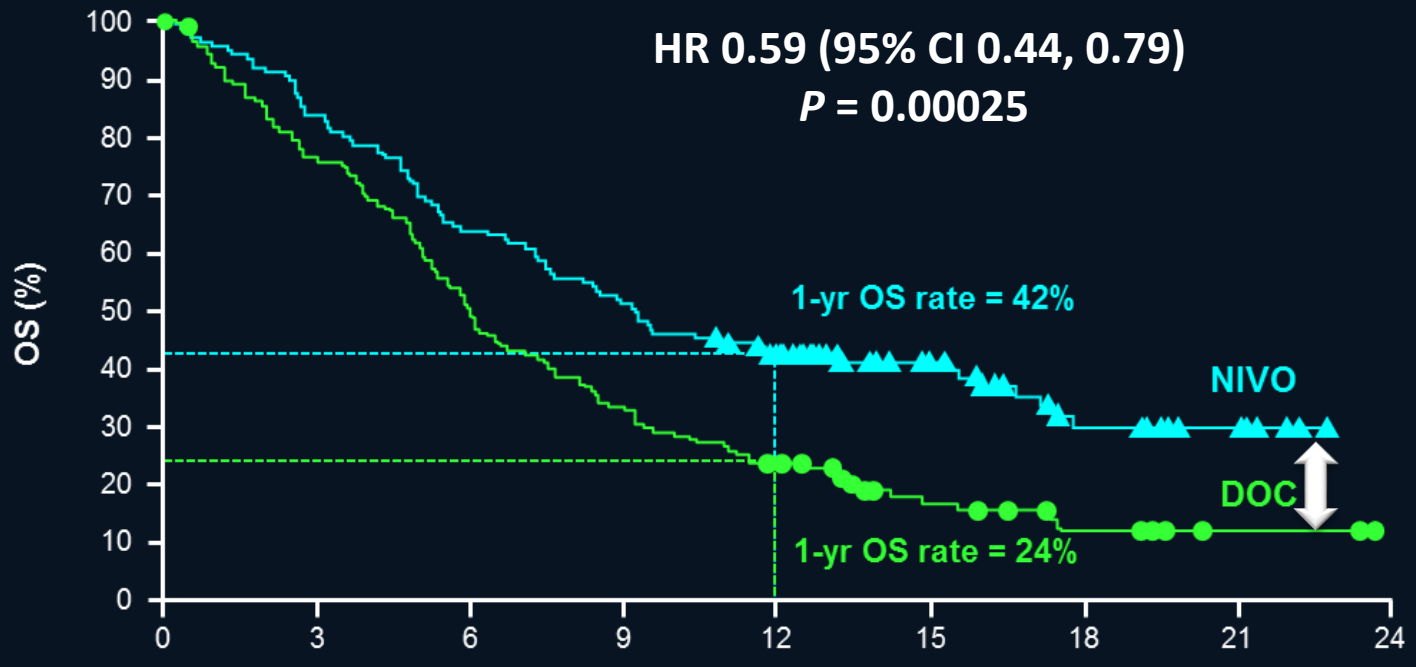
1. **ATEZOLIZUMAB** *con selezione*
2. **DURVALUMAB** *con selezione*
3. **AVELUMAB** *All comers*

Nella pratica clinica

- Anti PD-1 o anti PD-L1 ?
- Abbiamo criteri per la selezione dei pazienti?
- Quale tossicità?
- Quale terapia in seconda linea?

CHECKMATE-017 interim analysis

Nivolumab vs docetaxel squamous 2nd-line



Number of patients at risk									
NIVO	135	113	86	69	52	31	15	7	0
DOC	137	103	68	45	30	14	7	2	0

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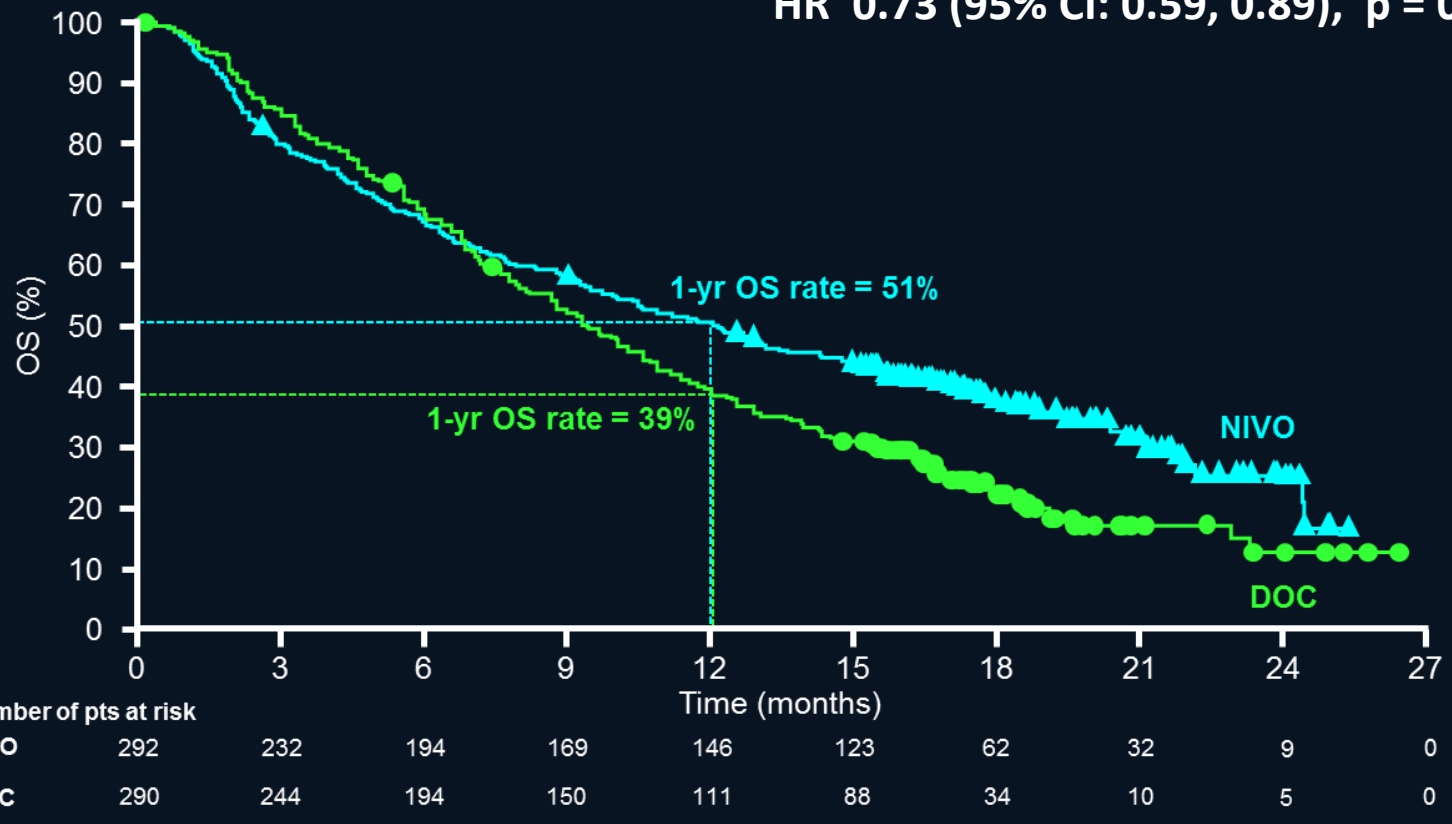
Brahmer J, N Engl J Med 2015

CheckMate 057 (interim analysis)

Nivolumab vs docetaxel non squamous 2nd-line

HR 0.73 (95% CI: 0.59, 0.89), p = 0.0015



Number of pts at risk										
NIVO	292	232	194	169	146	123	62	32	9	0
DOC	290	244	194	150	111	88	34	10	5	0

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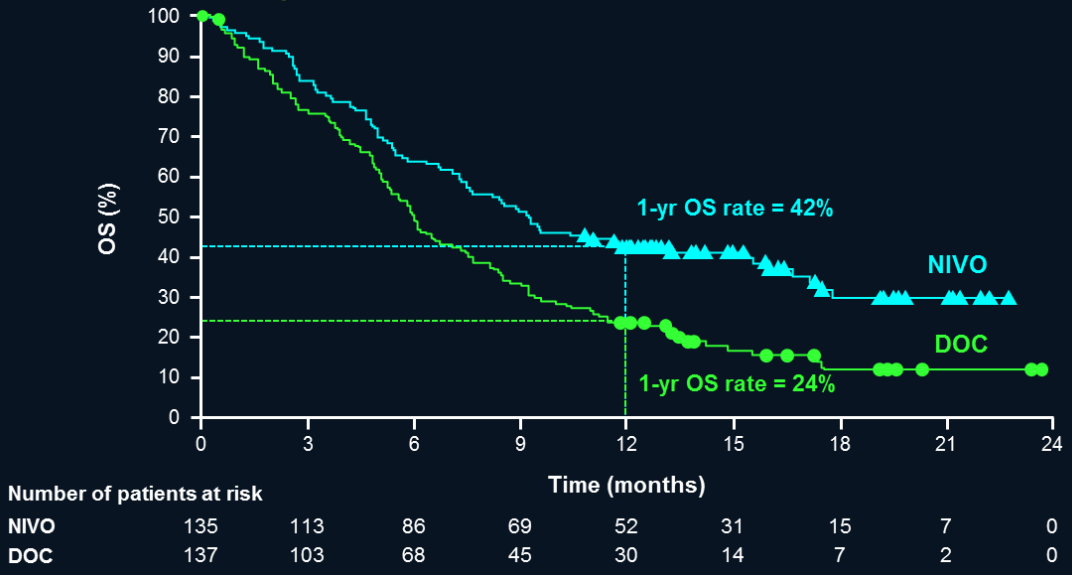
Borghaei H, N Engl J Med 2015

Is nivolumab more effective in squamous than adenocarcinoma?

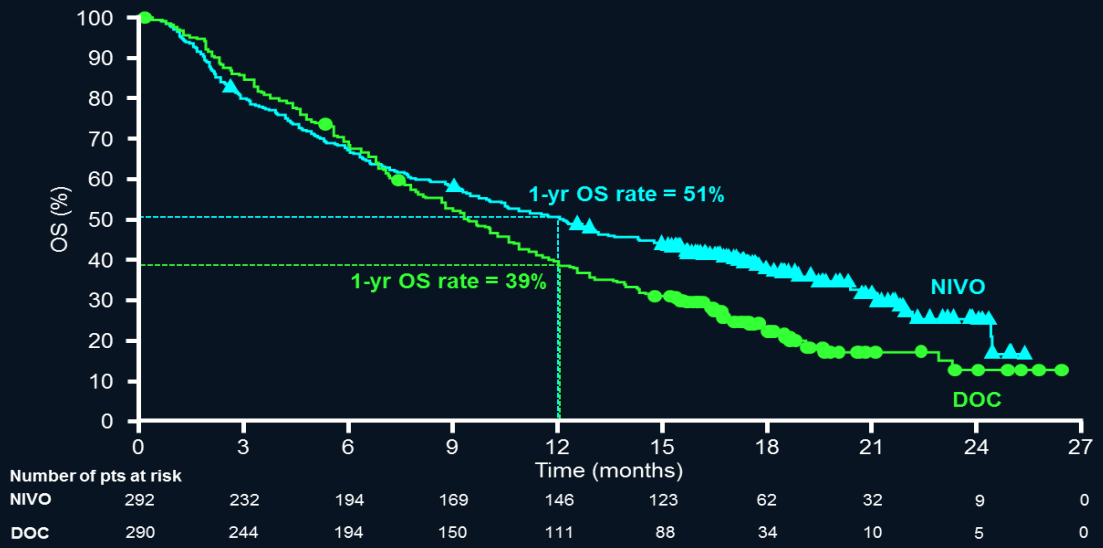
CHECKMATE-017
Squamous

HR 0.59 (95% CI 0.44, 0.79)
***P* = 0.00025**

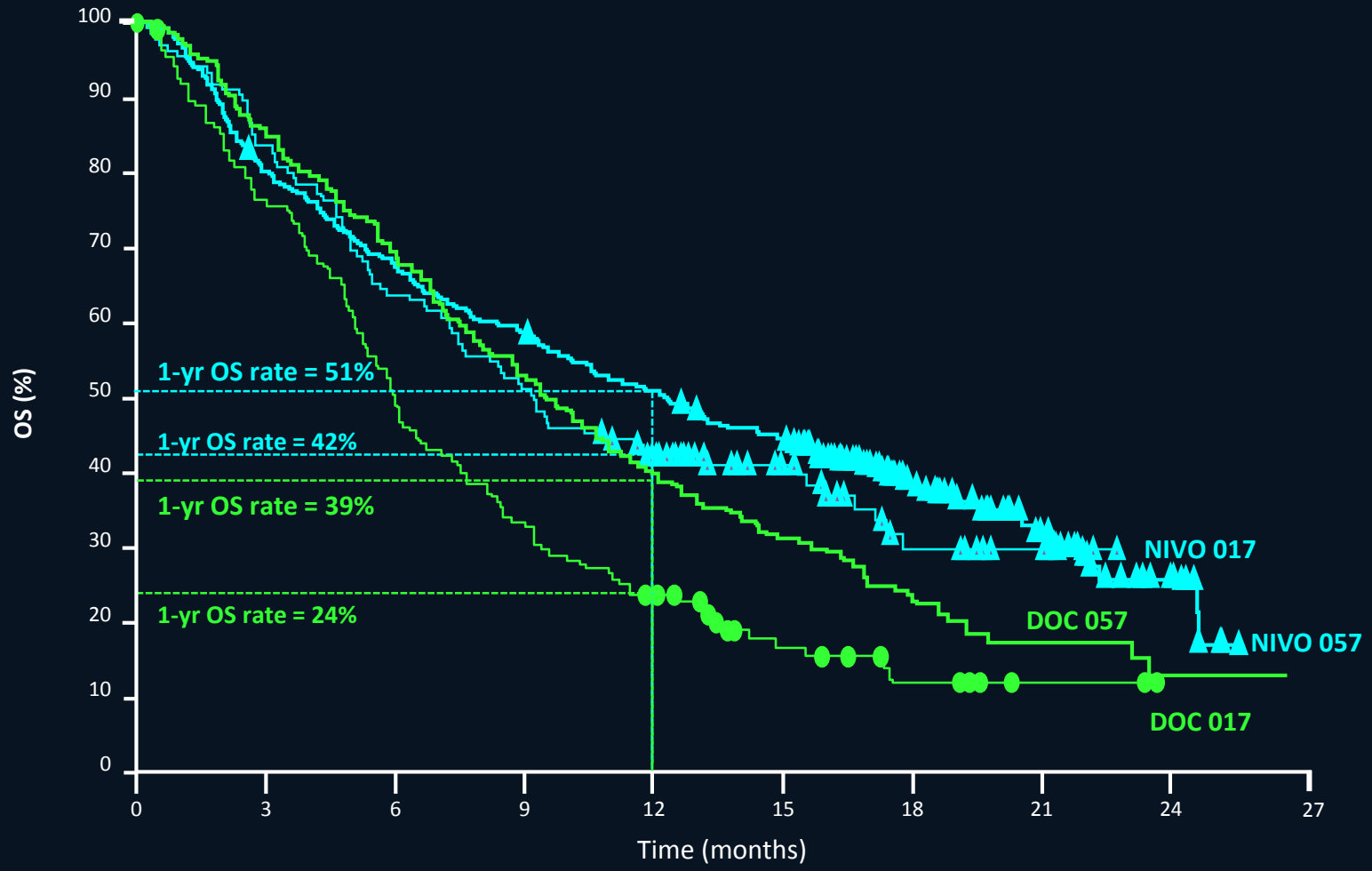


CHECKMATE-057
Non-squamous

HR 0.73 (96% CI 0.59, 0.89)
***P* = 0.0015**



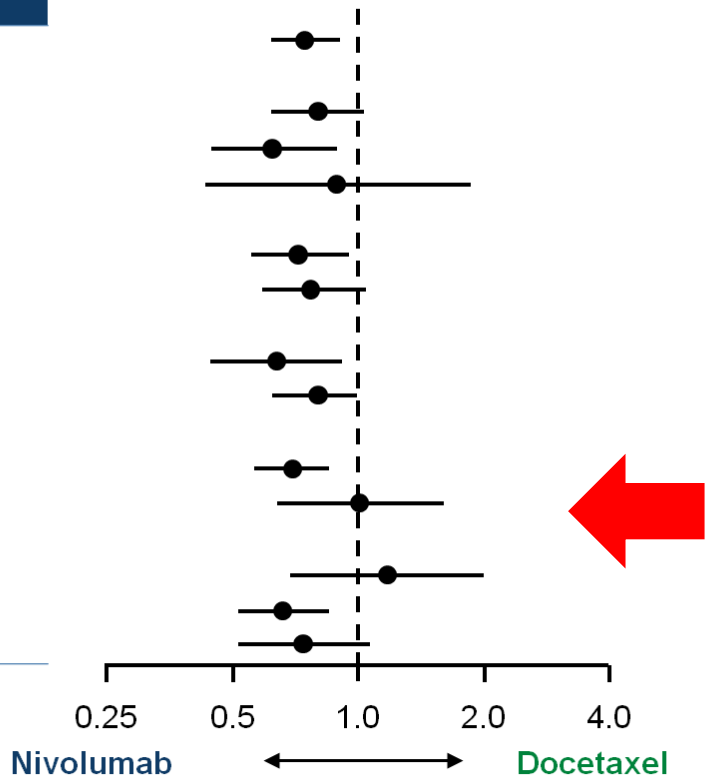
Overall survival-ASCO discussion



Minimum follow-up of approximately 10.6 months

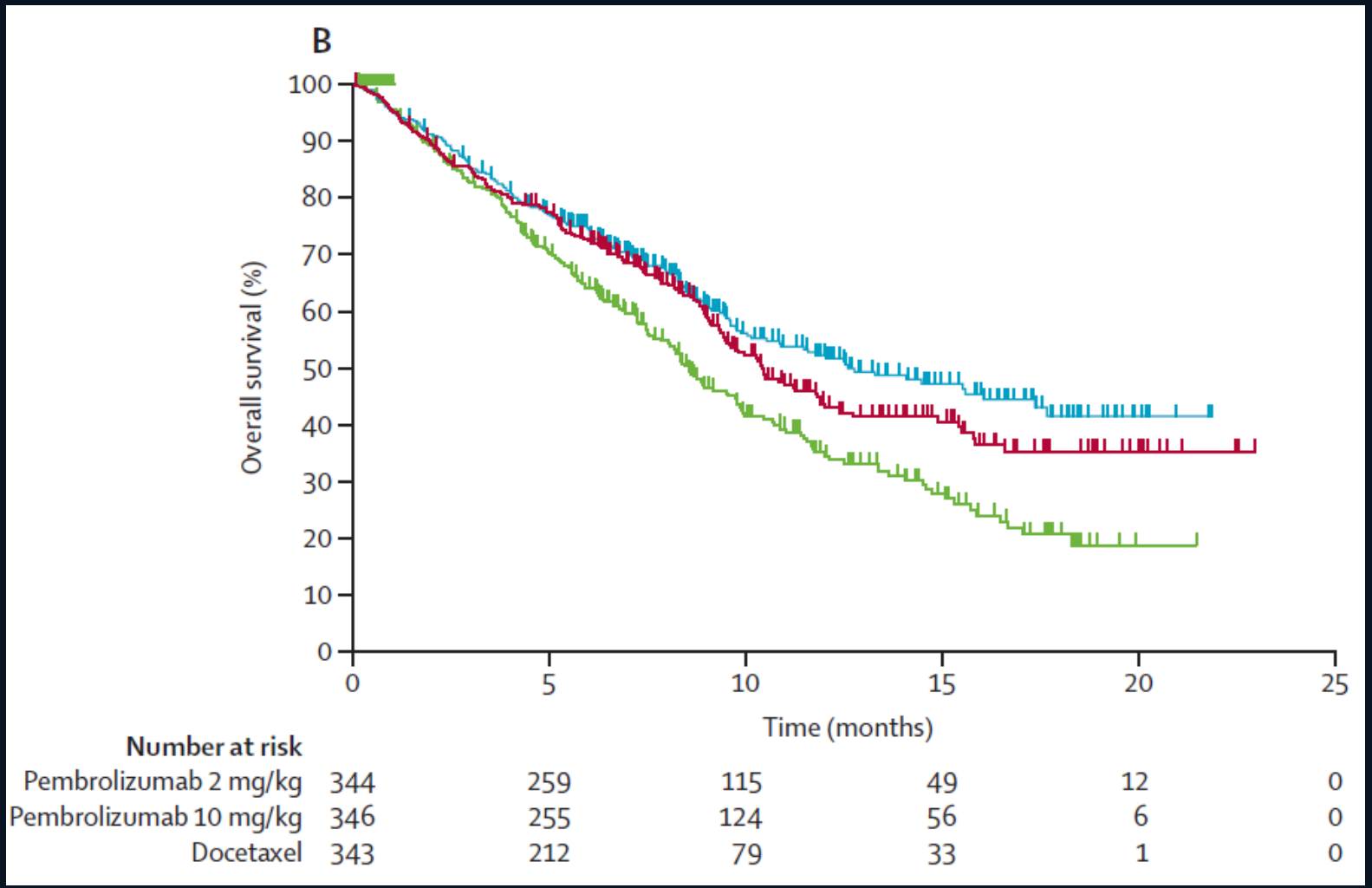
Treatment Effect on OS in Predefined Subgroups

	N	Unstratified HR (95% CI)
Overall	582	0.75 (0.62, 0.91)
Age Categorization (years)		
<65	339	0.81 (0.62, 1.04)
≥65 and <75	200	0.63 (0.45, 0.89)
≥75	43	0.90 (0.43, 1.87)
Gender		
Male	319	0.73 (0.56, 0.96)
Female	263	0.78 (0.58, 1.04)
Baseline ECOG PS		
0	179	0.64 (0.44, 0.93)
≥1	402	0.80 (0.63, 1.00)
Smoking Status		
Current/Former Smoker	458	0.70 (0.56, 0.86)
Never Smoked	118	1.02 (0.64, 1.61)
***EGFR* Mutation Status**		
Positive	82	1.18 (0.69, 2.00)
Not Detected	340	0.66 (0.51, 0.86)
Not Reported	160	0.74 (0.51, 1.06)



All randomized patients (nivolumab, n = 292; docetaxel, n = 290).

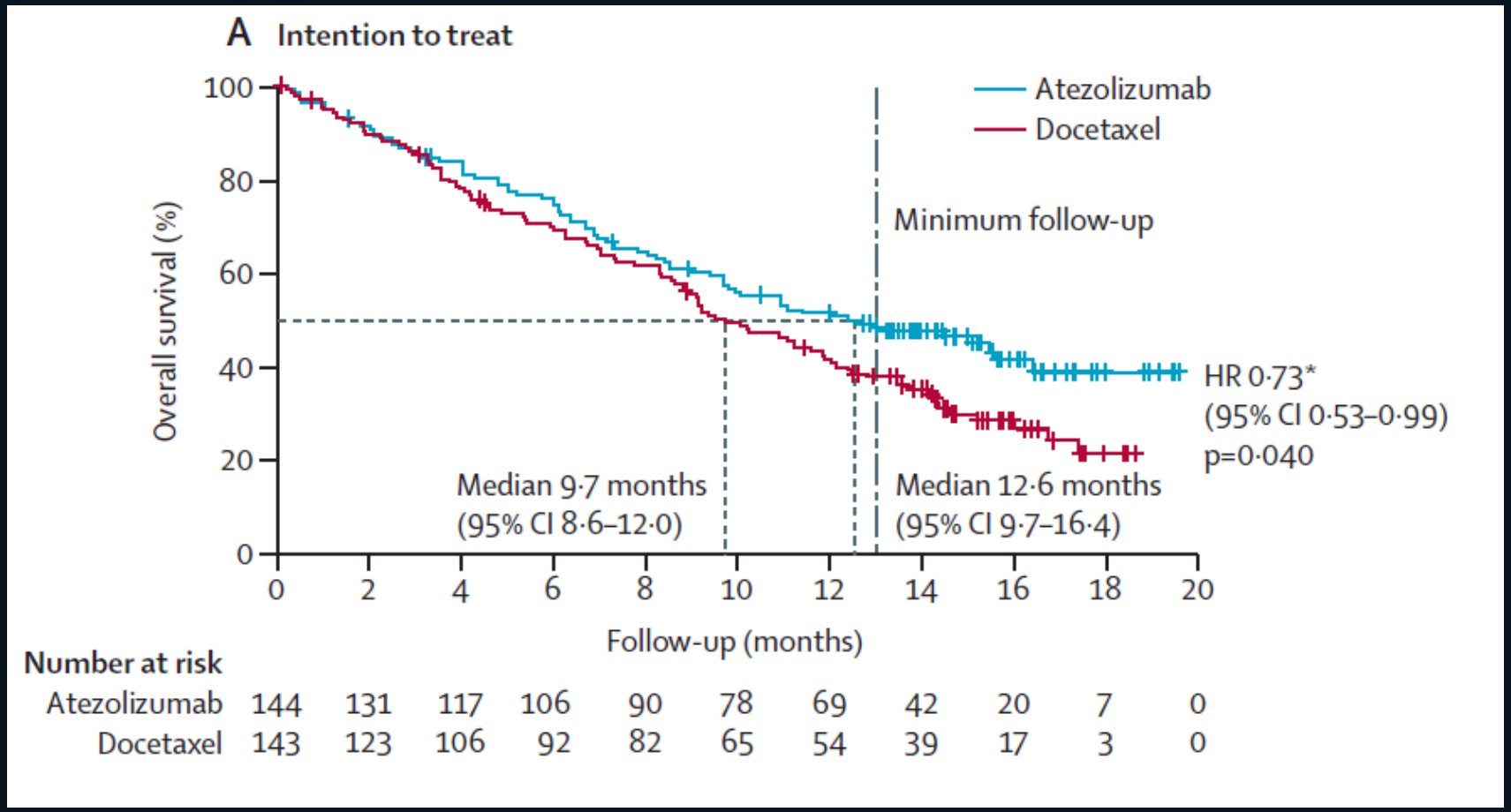
KEYNOTE – 010 (pembro PS≥1%)



Number at risk						
Pembrolizumab 2 mg/kg	344	259	115	49	12	0
Pembrolizumab 10 mg/kg	346	255	124	56	6	0
Docetaxel	343	212	79	33	1	0

Herbst RS et al, Lancet 2015

POPLAR: all patient efficacy



Fehrenbacher L., Lancet 2016

PD-L1 as a predictive biomarker ?

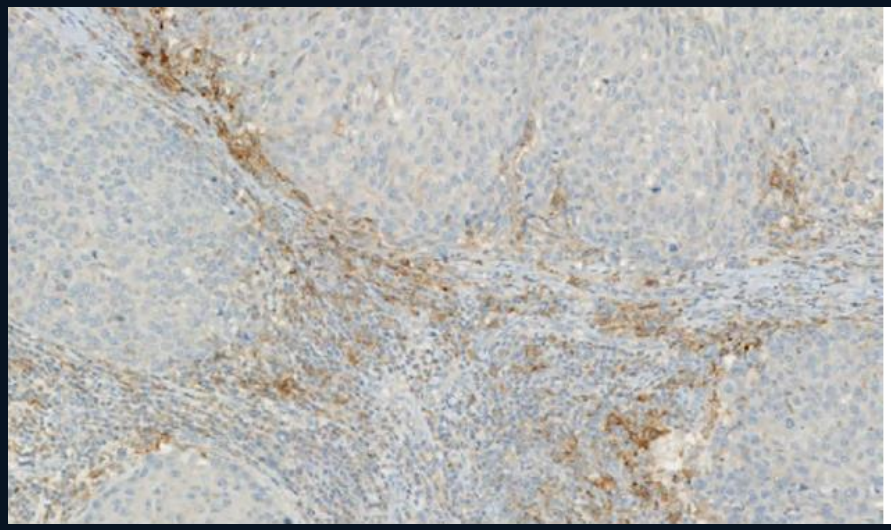
- **Discordance**

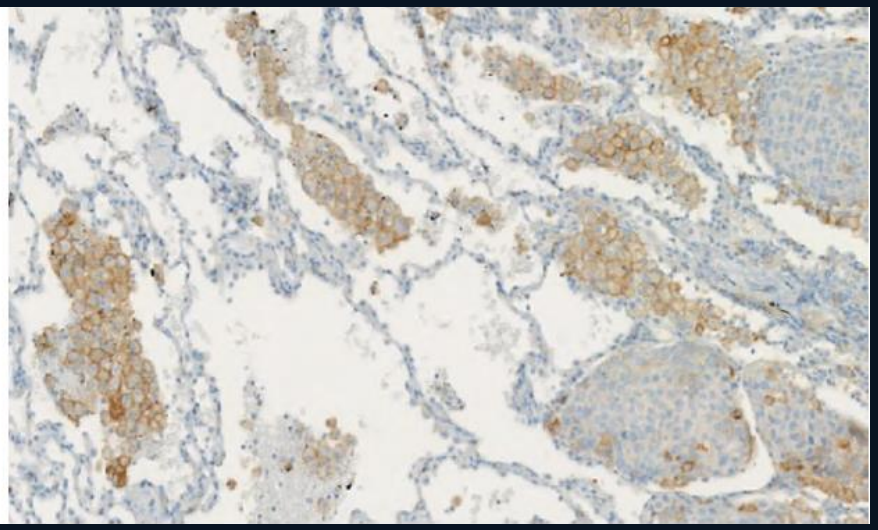
6% in multisampled cases

30% primary vs metastatic sites

- **Expression**

on tumour and immune cells





PD-L1 expression (ICH) as a predictive biomarker

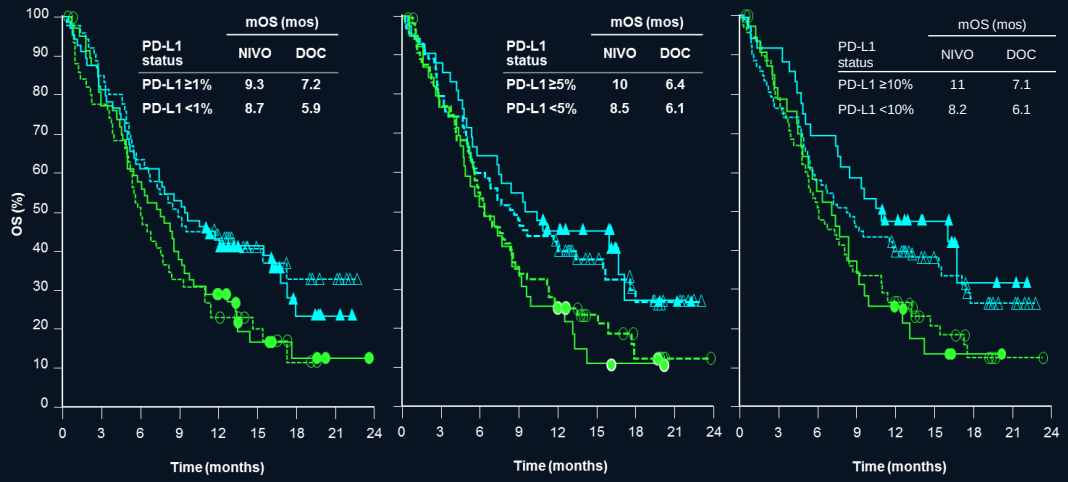
TABLE 1. Summary of Published Findings for PD-L1 Immunohistochemistry in Therapeutic Trials

Drug	Biomarker Antibody	Rx Line	Definition of "Positive"[a] (%)	N Positive (%)	Positive Predictive Outcome	ORR % IHC pos. Cases	ORR % IHC neg. Cases	Ref.
Nivolumab	Dako 28-8	1st	≥5 in >100 cells	59	Yes	31[b]	10	7,8[f]
Nivolumab	Dako 28-8	≥2nd	≥5, ≥1	49, 56	No	15, 13	14, 17	9,10
Nivolumab + Ipilimumab	Dako 28-8	1st	≥5 in >100 cells	42	No	19	14	11
Nivolumab	Dako 28-8	≥2nd	≥5	33[c]	Yes	24	14	12[f]
Nivolumab	5H1[d]	≥2nd	≥5, also studied TIICs	67	Yes	No data for lung	No data for lung	13
Pembrolizumab	Dako 22C3	Any	"Strong" ≥50, "Weak" 1–49	25, 70	Yes, Yes	37, 17	9	14
Pembrolizumab	Dako 22C3	1st	≥50, ≥1	?	Yes	47, 26	?	15
MPDL3280A	Roche Ventana, SP142	≥2nd	≥10,[e] ≥5, ≥1 TIICs	13, 28, 56	Yes	83, 46, 31	18, 18, 20	16–18
MEDI-4736	Roche Ventana, SP263	≥2nd	Data not available	41	Yes	25	3	19,20

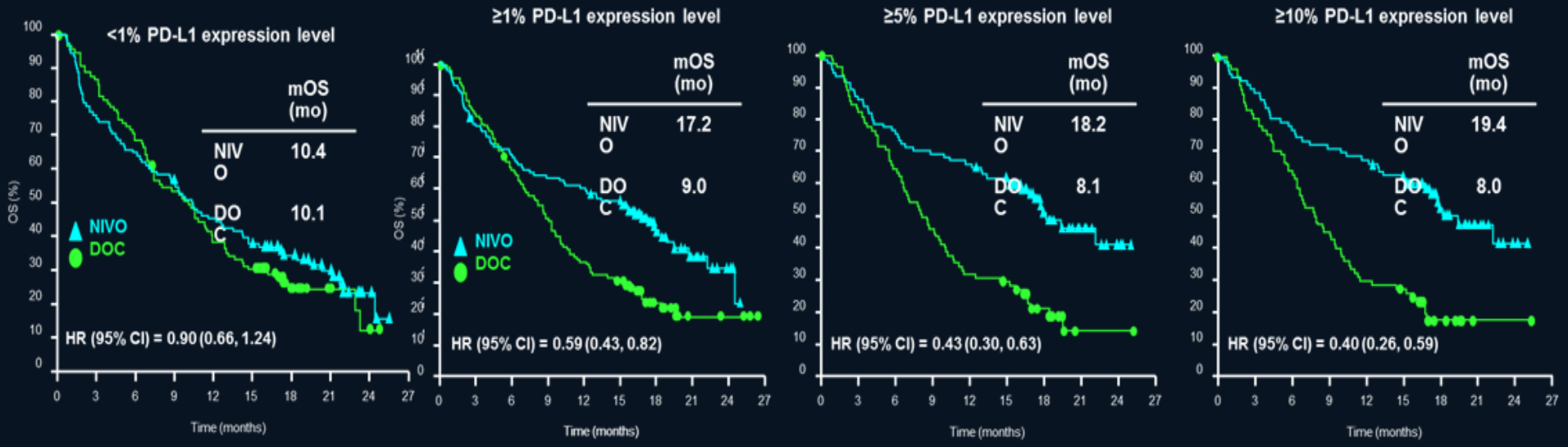
[a]Expression in tumor cells unless otherwise stated.
[b]The 31% figure is for all tumors. The ORR was 37% in nonsquamous tumors and 12% in squamous cases. In PDL-1 negative cases, ORR was 14% in nonsquamous tumors and 0% in squamous tumors.
[c]This study concerned squamous cell carcinomas only.
[d]These authors also used the anti-PD-1 monoclonal M3 in their immunohistochemical analysis.
[e]IHC score 3, ≥10% TIICs positive; IHC score 2–3, ≥5% TIICs positive; IHC score 1–2–3, ≥1% TIICs positive.
[f]ORR quoted are those actually presented, as opposed to those published in the abstract
IHC, immunohistochemistry; TIICs, tumor infiltrating immune cells; ORR, overall response rate (response evaluation criteria in solid tumors).

K.Kerr J, Thorac Oncol 2015

PD-L1 NOT predictive for OS in squamous!



PD-L1 predictive for OS in NON-squamous?



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Paz-Ares et al. J Clin Oncol 2015;33 (suppl; abstr LBA109)
Spigel et al. J Clin Oncol 2015;33 (suppl; abstr 8009)

Proportion score and pembrolizumab

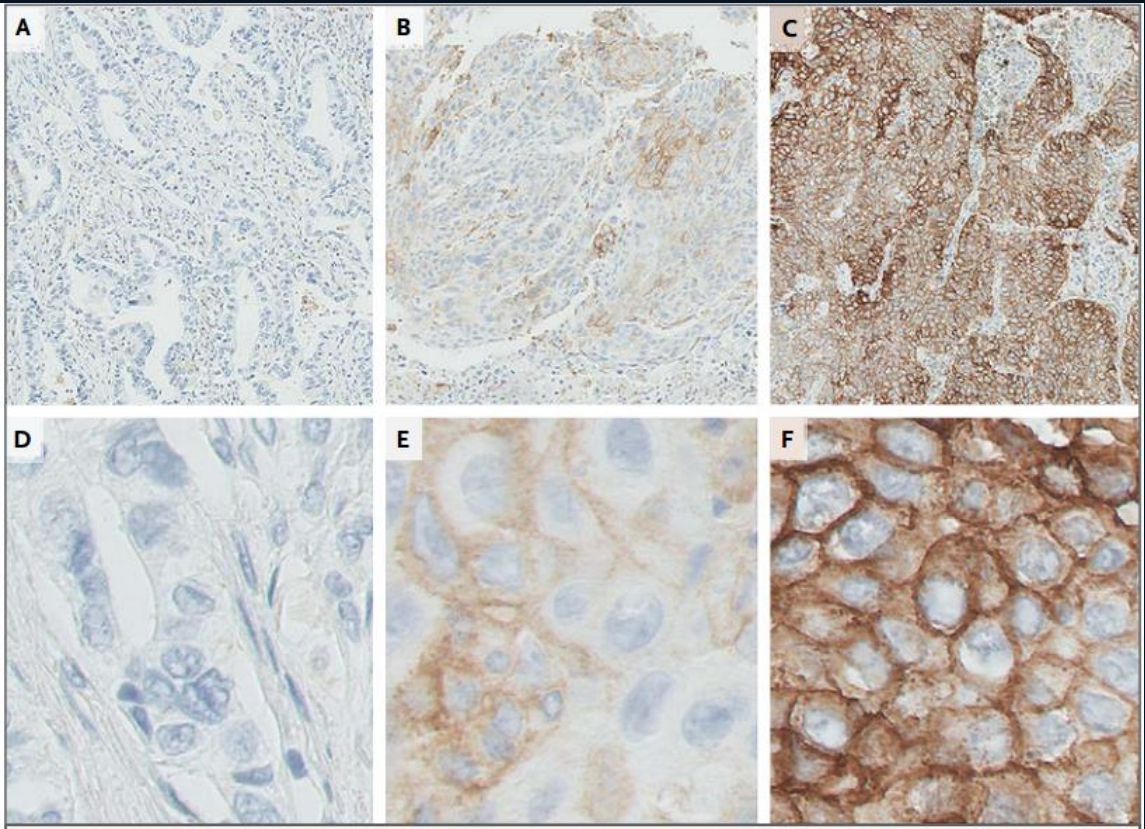
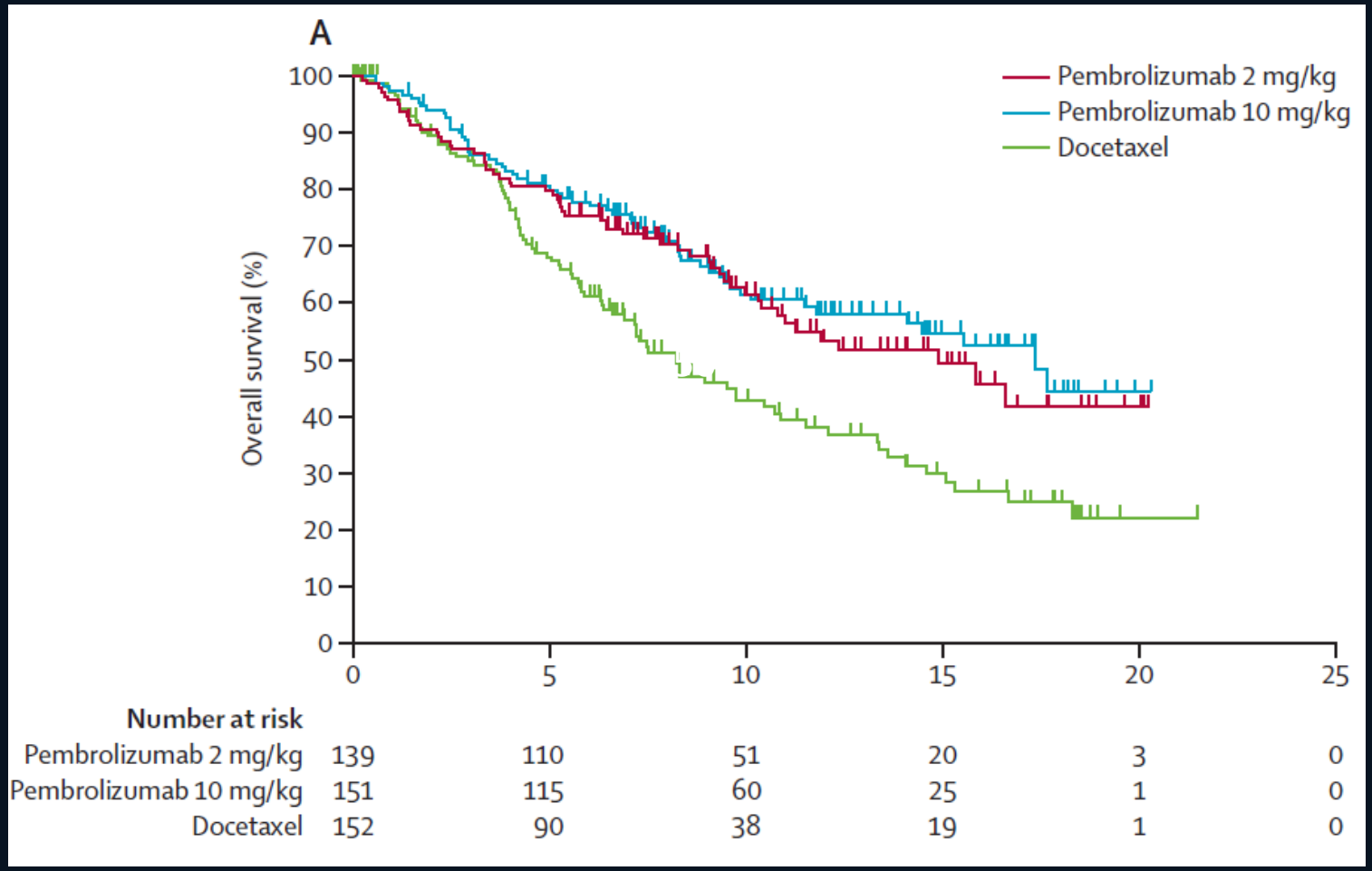


Figure 1. PD-L1 Expression in Non–Small-Cell Lung Cancers.

Results were reported as the percentage of neoplastic cells showing membranous staining of programmed cell death ligand 1 (PD-L1) (proportion score). Shown are tumor samples obtained from patients with a proportion score of less than 1% (Panel A), a score of 1 to 49% (Panel B), and a score of at least 50% (Panel C) (all at low magnification). Tumor samples with the corresponding proportion scores are shown at a higher magnification in Panels D through F. PD-L1 staining is shown by the presence of the brown chromogen. The blue color is the hematoxylin counterstain.

Garon et al., N Engl J Med 2015

KEYNOTE - 010
Survival benefit by PD-L1 expression (PS≥50%)



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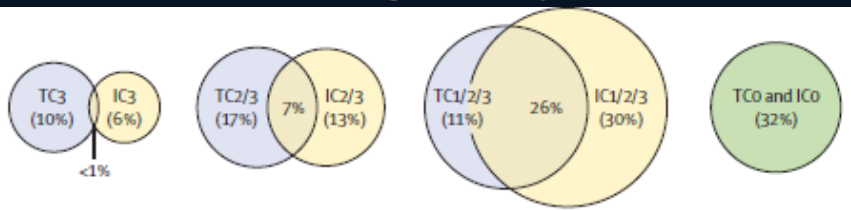
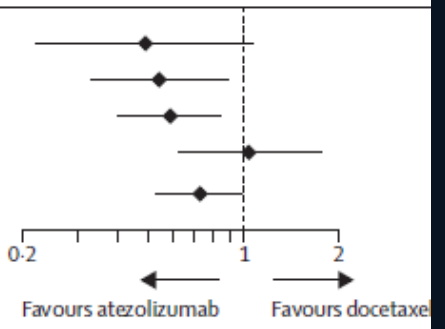
Herbst RS et al, lancet 2015

POPLAR: OS in programmed death ligand 1 subgroups



PD-L1 tumour cell scoring		PD-L1 tumour-infiltrating immune cell scoring		Overall prevalence	
Score	Percentage of PD-L1-expressing cells	Score	Percentage of PD-L1-expressing cells	Subgroup	Proportion
TC3	≥50%	IC3	≥10%	TC3 or IC3	16%
TC2	≥5% and <50%	IC2	≥5% and <10%	TC2/3 or IC2/3	37%
TC1	≥1% and <5%	IC1	≥1% and <5%	TC1/2/3 or IC1/2/3	68%
TC0	<1%	IC0	<1%	TC0 and IC0	32%

	n (%)	HR*	95% CI	p value	Median overall survival (months [95% CI])	
					Atezolizumab (n=144)	Docetaxel (n=143)
TC3 or IC3	47 (16%)	0·49	0·22–1·07	0·068	15·5 (9·8–NE)	11·1 (6·7–14·4)
TC2/3 or IC2/3	105 (37%)	0·54	0·33–0·89	0·014	15·1 (8·4–NE)	7·4 (6·0–12·5)
TC1/2/3 or IC1/2/3	195 (68%)	0·59	0·40–0·85	0·005	15·5 (11·0–NE)	9·2 (7·3–12·8)
TC0 and IC0	92 (32%)	1·04	0·62–1·75	0·871	9·7 (6·7–12·0)	9·7 (8·6–12·0)
Intention to treat	287	0·73	0·53–0·99	0·040	12·6 (9·7–16·4)	9·7 (8·6–12·0)



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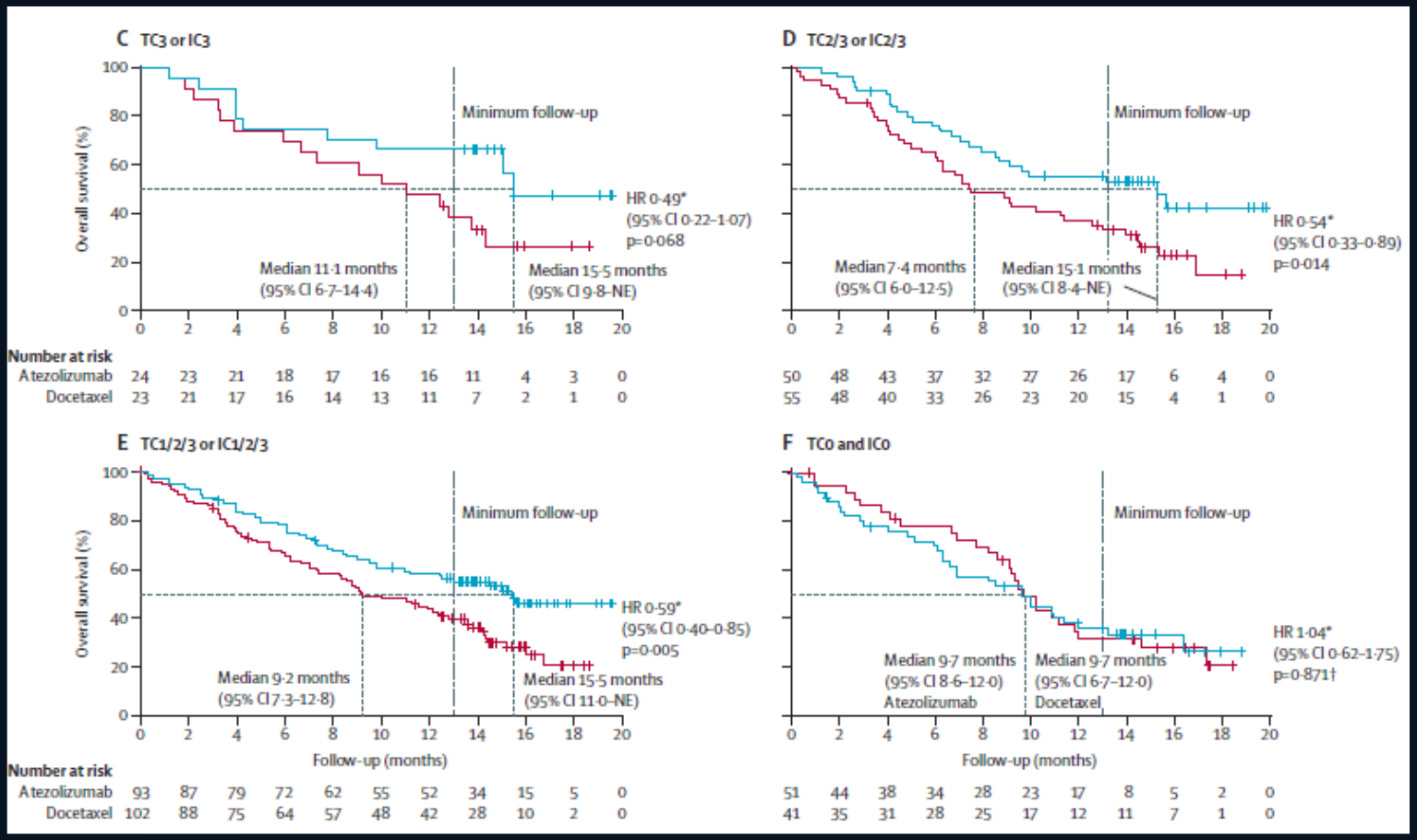
Fehrenbacher L., Lancet 2016

POPLAR: OS in programmed death ligand 1 subgroups



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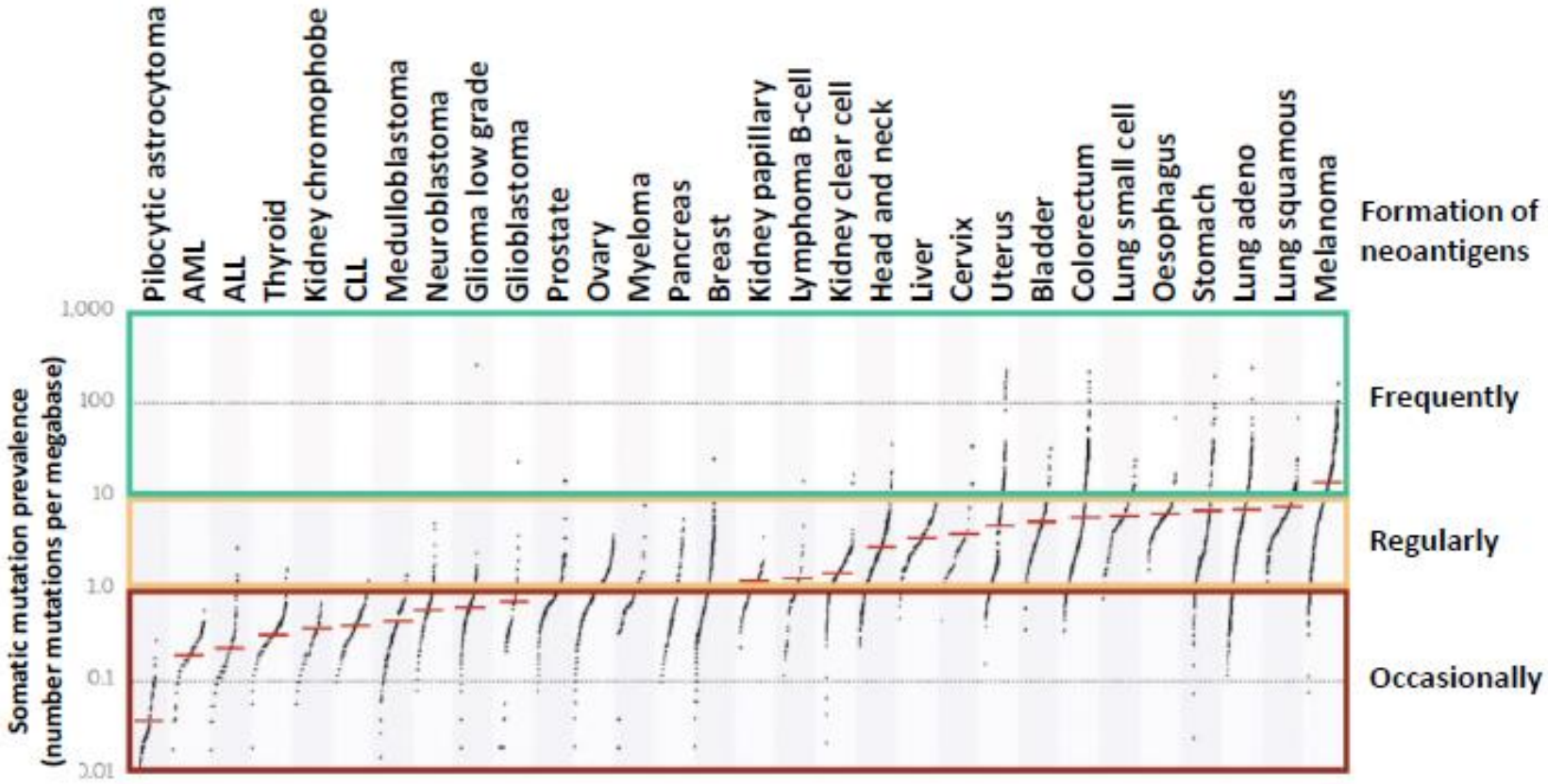
Fehrenbacher L., Lancet 2016

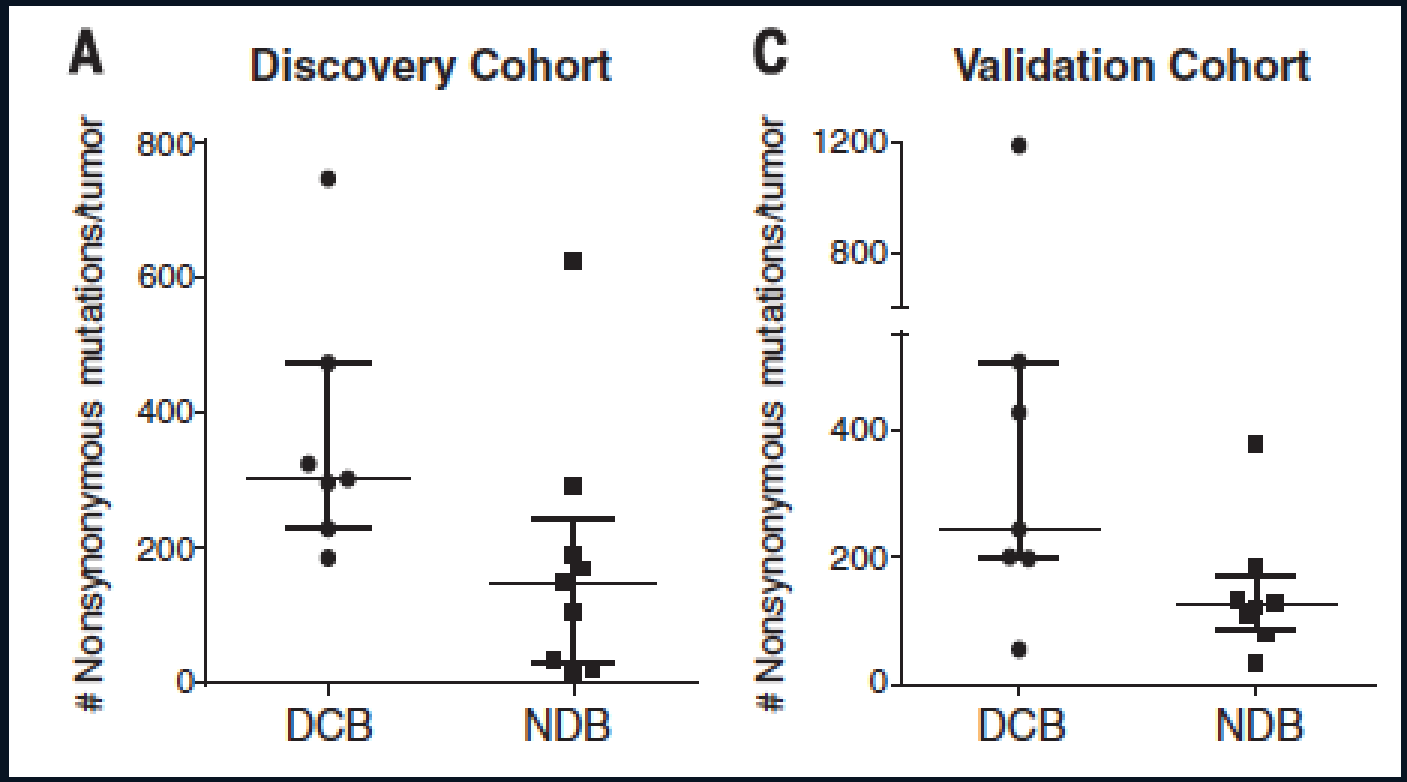
Esistono altre ipotesi di selezione?

Neoantigens



Schumacher TN and Schreiber RD. Science 2015

Mutation burden associated with clinical benefit to anti-PD1 therapies



DCB: Durable clinical benefit: partial or stable disease >6 months
NDB: Non durable benefit

Rizvi NA et al, Science 2015

Ci vuole MB, ma bassa eterogeneità!

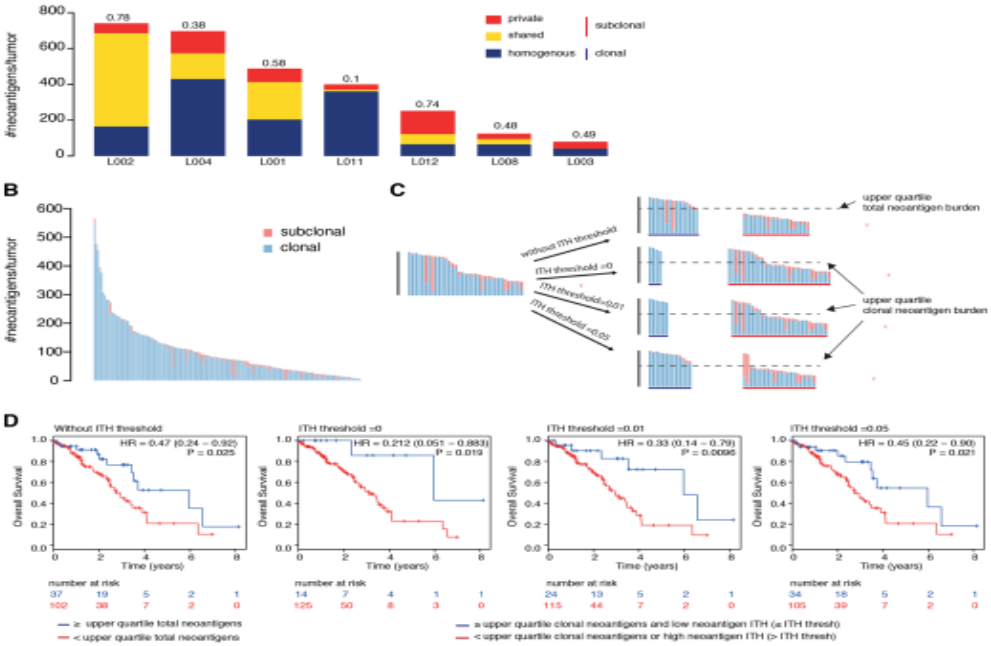


Fig. 1. Heterogeneity and prognostic value of neoantigen landscape in primary NSCLC. (A) Total putative neoantigen burden in multi-region sequenced NSCLC tumors. Proportion of clonal neoantigens, identified ubiquitously in every tumor region are shown in blue, while shared subclonal neoantigens, identified as shared in multiple tumor regions, but not all, are shown in yellow, and private subclonal neoantigens, identified in only one tumor region, are in red. **(B)** Total putative neoantigen burden in TCGA LUAD tumors. Proportion of neoantigens arising from clonal (blue) or subclonal (red) mutations is shown. **(C)** Schematic illustrating use of different neoantigen ITH thresholds, with bar plot showing separation into the two groups. Without an ITH threshold, samples are simply grouped according to upper quartile of total neoantigen burden. For each ITH threshold, the upper quartile of clonal neoantigens is used to separate tumors with high and low clonal neoantigen burden, and the neoantigen ITH threshold further groups samples. For example, an ITH threshold =0 involves grouping tumors with high clonal neoantigen burden and zero neoantigen heterogeneity separately from those with low clonal neoantigen burden or any neoantigen heterogeneity. **(D)** Overall survival curves for samples using different ITH thresholds: without an ITH threshold (log-rank, $P = 0.028$, HR = 0.46 [0.23–0.94]); ITH threshold = 0 (log-rank, $P = 0.019$, HR = 0.21 [0.051–0.88]); ITH threshold = 0.01 (log-rank, $P = 0.0096$, HR = 0.33 [0.14–0.79]); ITH threshold = 0.05 (log-rank, $P = 0.021$, HR = 0.45 [0.22–0.90]). The number of patients in each group is listed below the survival curves.

Le tossicità

Toxicity: pre-treated advanced NSCLC

Treatment related AEs (%)	Nivolumab squamous	Nivolumab non-squamous	Atezolizumab all comers
Any AE	58	69	67
Grade ≥3	7	10	11
Grade 5 (death)	0	0	0*
Any AE leading to discontinuation	3	5	8

* Grade 5 4%

Immune Related Adverse Events (IRAEs)

System	Adverse Events
Gastrointestinal	Colitis (Diarrhea, perforation)
Renal	Acute Interstitial Nephritis (Increased serum Creatinine)
Pulmonary	Pneumonitis (dyspnea, cough)
Dermatologic	Dermatitis (Lichenoid/ spongiotic dermatitis, rash), Vitaligo
Hepatic	Hepatitis (elevated LFTs)
Neurologic	Central and Peripheral (Aseptic Meningitis, Guillan-Barre Syndrome, Myasthenia Gravis
Endocrine	Hypophysitis, thyroiditis, adrenal insufficiency
Ocular	Uveitis, Iritis

Immune Related Adverse Events (IRAEs)

- Average time to onset of irAEs is 6-12 weeks after initiation of therapy
  - Within days of the first dose
  - After several months of treatment
  - After discontinuation of therapy

- Severity: can be mild and asymptomatic to severe and life threatening

review

Annals of Oncology 00: 1–17, 2015
doi:10.1093/annonc/mdv383

Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies

J. Naidoo[1*], D. B. Page[2], B. T. Li[3], L. C. Connell[3], K. Schindler[4], M. E. Lacouture[5,6], M. A. Postow[3,6] & J. D. Wolchok[3,6]

ANTI PDL-1 AGENTS

Durvalumab (MEDI4736)

Agent	First author (year)	Phase	Tumor type	No. of patients receiving anti-PD-1/PD-L1 agent (*N*)	Therapy schedule	Treatment-related toxicities (grade 1–5)	Treatment-related grade 3–4 toxicities
	Segal	I	Multiple solid tumors[a]	346	10 mg/kg every 2 weeks × 1 year	Total = 39% (*n* = 135) Fatigue (13%, *n* = 45) Rash (9%, *n* = 30) Pneumonitis (1%, *n* = 5) AST/ALT elevation (4%, *n* = 13) Hypothyroidism (2%, *n* = 8)	Total = 6% (*n* = 20) Fatigue (1%, *n* = 2) Rash (<1%, *n* = 1) AST/ALT elevation (1%, *n* = 3) Hypothyroidism (<1%, *n* = 1)
	Rizvi (2015)	I	NSCLC	228	10 mg/kg every 2 weeks × 1 year	Total = 93% (*n* = 213) Fatigue = 18% Low appetite = 9% Nausea = 8% Hyperthyroidism (4%, *n* = 9) Diarrhea (7%, *n* = 15) Rash (8%, *n* = 17) Pneumonitis (1%, *n* = 3)	Total = 53% (*n* = 121) Diarrhea (<1%, *n* = 1) Rash (0%, *n* = 0) Hyperthyroidism (<1%, *n* = 1)

Atezolizumab (MPDL3280A)

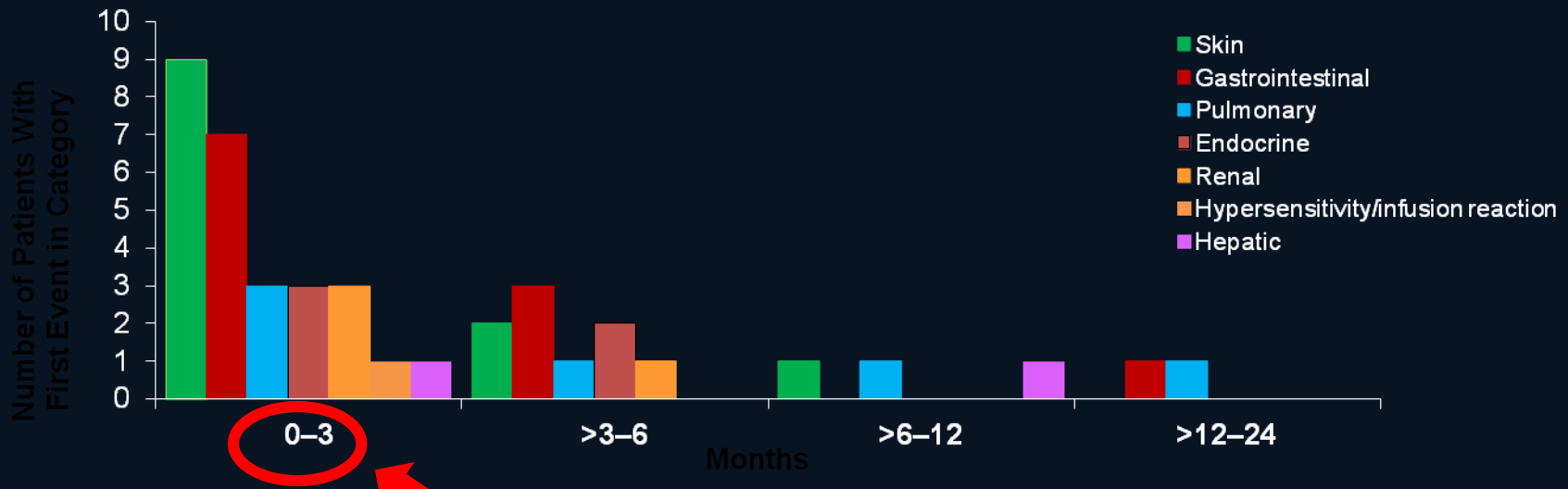
	Herbst (2014)	I	Multiple solid tumors + hematologic malignancies	277	0.01–20 mg/kg every 3 weeks	Total = 70% (*n* = 194) Fatigue (24%, *n* = 67) Low appetite (12%, *n* = 33) Rash (11%, *n* = 29) Influenza-like illness (6%, *n* = 16) AST/ALT elevation (4%, *n* = 10) Tumor lysis syndrome (<1%, *n* = 2)	Total = 13% (*n* = 35) Fatigue (2%, *n* = 5) Low appetite (0%, *n* = 0) Rash (0%, *n* = 0) Influenza-like illness (<1%, *n* = 1) AST/ALT elevation (2%, *n* = 6) Tumor lysis syndrome (<1%, *n* = 2)
	Powles (2014)	I	Urothelial carcinoma	68	15 mg/kg every 3 weeks × 1 year	Total = 57% (*n* = 39) Low appetite (12%, *n* = 8) Fatigue (12%, *n* = 8) Pyrexia (12%, *n* = 8) Influenza-like illness (4%, *n* = 3) Thrombocytopenia (3%, *n* = 2)	Total = 4% (*n* = 3) Asthenia (1.5%, *n* = 1) Thrombocytopenia (1.5%, *n* = 1) Phosphorus elevation (1.5%, *n* = 1)

ANTI PD-1 AGENTS

Agent	First author (year)	Phase	Tumor type	No. of patients receiving anti-PD-1/PD-L1 agent (*N*)	Therapy schedule	Treatment-related toxicities (grade 1–5)	Treatment-related grade 3–4 toxicities
Nivolumab							
	Weber (2015)	III	Ipilimumab-refractory melanoma	272	3 mg/kg every 2 weeks versus chemotherapy	Total = 67% ($n = 181$) Fatigue (25%, $n = 67$) Pruritus (16%, $n = 43$) Diarrhea (11%, $n = 30$) Nausea (9%, $n = 25$)	Total = 9% ($n = 24$) Lipase elevation (1%, $n = 3$) ALT elevation (1%, $n = 2$) Anemia (1%, $n = 2$) Fatigue (1%, $n = 2$)
	Brahmer	III	NSCLC (squamous)	131	3 mg/kg every 2 weeks versus docetaxel	Total = 58% ($n = 76$) Fatigue (16%, $n = 21$) Low appetite (14%, $n = 11$) Asthenia (10%, $n = 13$) Diarrhea (8% $n = 10$) Pneumonitis (5%, $n = 6$) Hypothyroidism (4%, $n = 5$)	Total = 7% ($n = 9$) Fatigue (<1%, $n = 1$) Low appetite (<1%, $n = 1$) Leucopenia (<1%, $n = 1$) Pneumonitis (<1%, $n = 1$) Colitis (<1%, $n = 1$) Interstitial nephritis (<1%, $n = 1$)
Pembrolizumab							
	Ribas (2015)	II	Melanoma	357	2 or 10 mg/kg every 3 weeks versus standard chemotherapy	Total = 71% ($n = 252$) Fatigue (26%, $n = 92$) Pruritus (22%, $n = 79$) Rash (8%, $n = 29$) Hypothyroidism (6% $n = 22$) Pneumonitis (1%, $n = 3$)	Total = 13% ($n = 45$) Fatigue (<1%, $n = 2$) Myalgia (<1%, $n = 2$) Edema (<1%, $n = 2$) Colitis (<1%, $n = 2$) Hypophysitis (<1%, $n = 2$) Pneumonitis (<1%, $n = 2$)
	Robert (2015)	III	Untreated melanoma	556	10 mg/kg every 2 or 3 weeks versus ipilimumab	Total = 76% ($n = 423$) Fatigue (20%, $n = 111$) Pruritus (14%, $n = 79$) Rash (14%, $n = 77$) Hypothyroidism (9%, $n = 52$) Hyperthyroidism (5%, $n = 27$) Colitis (3%, $n = 15$) Hepatitis (1%, $n = 8$) Pneumonitis (1%, $n = 6$) Uveitis (<0.1%, $n = 4$)	Total = 12% ($n = 65$) Colitis (2%, $n = 11$) Diarrhea ($n = 10$) Hepatitis ($n = 8$) Hypophysitis ($n = 2$) Pneumonitis ($n = 1$) Type 1 diabetes ($n = 1$)

CheckMate 017: Updated Safety

Time to Onset of First Treatment-related Select AE With Nivolumab by Category (Any Grade)



	0–3	>3–6	>6–12	>12–24
Pts still on study, n	131	112	85	52
Pts still on treatment, n	131	73	51	25
Total pts with first event,[a] n	24	6	2	1

- The majority of patients who experienced treatment-related select AEs with nivolumab experienced their first event within the first 3 months of treatment

Immunoterapia in combinazione

Agent	Author(s)	Phase	Tumor type	Total patients (*N*)	Treatment schedule	Treatment-related toxicities (grade 1–5)	Grade 3–4 treatment-related toxicities
Pembrolizumab + ipilimumab	Patnaik et al. [37]	I	NSCLC	18	P (2 or 10 mg/kg every 3 weeks) + I (1 or 3 mg/kg every 3 weeks × 4) + maintenance P	Total = 83% (*n* = 15) Fatigue (33%, *n* = 4) Low appetite (17%, *n* = 2) Pruritus (17%, *n* = 2) Rash (17%, *n* = 2) Myasthenia gravis (6%, *n* = 1) Myocarditis (6%, *n* = 1) Pneumonitis (6%, *n* = 1) Uveitis (6%, *n* = 1)	Total = 17% (*n* = 3) Rash (17%, *n* = 2) Adrenal insufficiency (6%, *n* = 1)
MEDI4736 + tremelimumab	Antonia et al. [38]	Ib	NSCLC	102	M (3–20 mg/kg every 4 weeks or 10 mg/kg every 2 weeks) + T (1–3 mg/kg every 2 or 4 weeks × 6 doses) for 1 year	Total = 93% (*n* = 95) Diarrhea (27%, *n* = 28) Fatigue (26%, *n* = 27) Colitis (12%, *n* = 12) ALT elevation (10%, *n* = 10) AST elevation (6%, *n* = 6) Hypothyroidism (6%, *n* = 6) Pneumonitis (5%, *n* = 5)	Total = 61% (*n* = 63) Diarrhea (8%, *n* = 8) Colitis = (9%, *n* = 9) ALT elevation (3%, *n* = 3) AST elevation (4%, *n* = 4) Myasthenia gravis (*n* = 1) Polymyositis (*n* = 1) Pneumonitis (4%, *n* = 4) Hypothyroidism (1%, *n* = 1)
Chemotherapy							
Nivolumab + platinum-doublet chemotherapy	Antonia et al. [39]	I	NSCLC	56	N (10 mg/kg every 3 weeks or 5 mg/kg every 3 weeks) + chemotherapy × 4) + N alone (10 mg/kg every 3 weeks or 5 mg/kg every 3 weeks)	Total = 93% (*n* = 52) Fatigue (71%, *n* = 40) Nausea (46%, *n* = 26) Low appetite (36%, *n* = 20) Alopecia (30%, *n* = 17) Pneumonitis (13%, *n* = 7)	Total = 45% (*n* = 25) Fatigue (5%, *n* = 3) Anemia (4%, *n* = 2) Rash (4%, *n* = 2) Acute renal failure (5%, *n* = 3) Pneumonitis (7%, *n* = 4)
Targeted therapy							
Durvalumab + AZD9291	Oxnard et al. [40]	Ib	EGFR-mutant T790M-positive NSCLC	14	M (3 or 10 mg/kg every 2 weeks) + A (80 mg daily)	Total: not reported[b] Diarrhea (50%, *n* = 7) Vomiting (50%, *n* = 7) Anemia (45%, *n* = 6) Pneumonitis (21%, *n* = 3)	Total: 1% (*n* = 2)[b] Neutropenia = 2
Durvalumab + gefitinib	Creelan et al. [41]	Ib	NSCLC	10	M (3 or 10 mg/kg every 4 weeks) + G (250 mg daily) × 1 year	Total = 100% (*n* = 10) ALT elevation (50%, *n* = 5) AST elevation (50%, *n* = 5) Diarrhea (50%, *n* = 5)	Total = 30% (*n* = 3) Dyspnea (1%, *n* = 1) Fatigue (1%, *n* = 1) ALT elevation (1%, *n* = 1)

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Review

Optimal management of immune-related toxicities associated with checkpoint inhibitors in lung cancer

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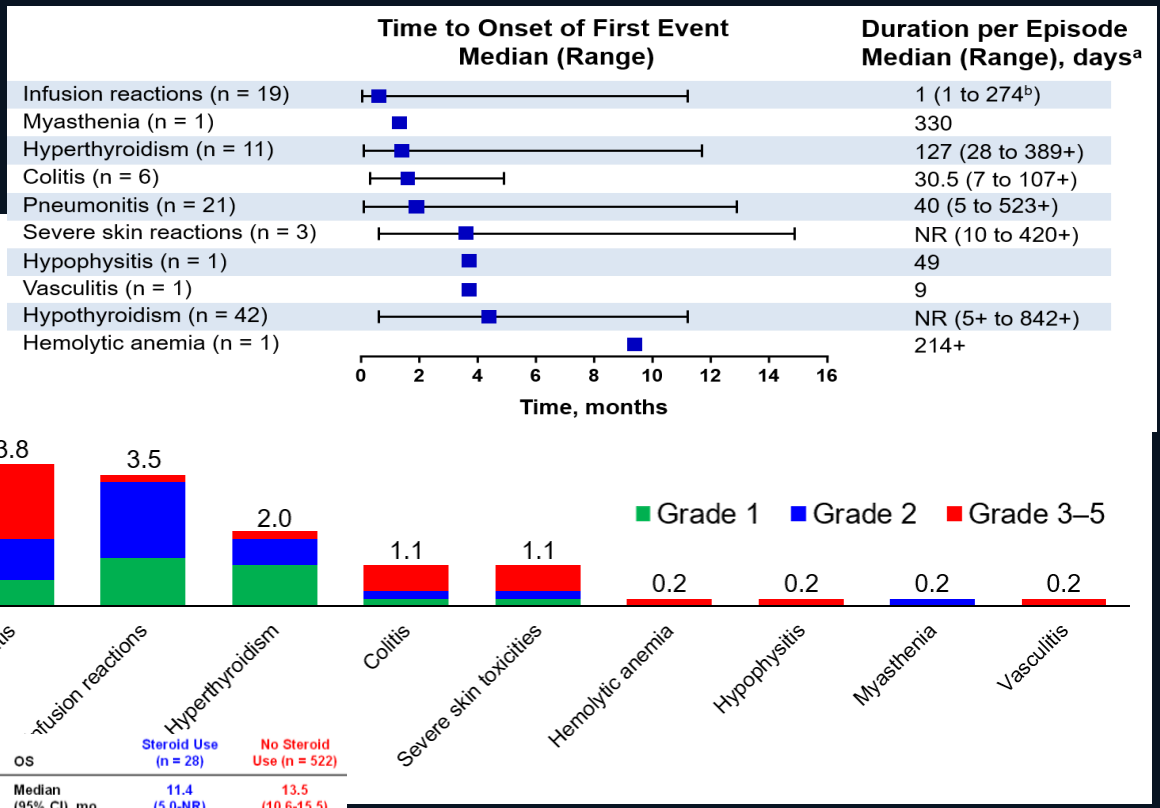
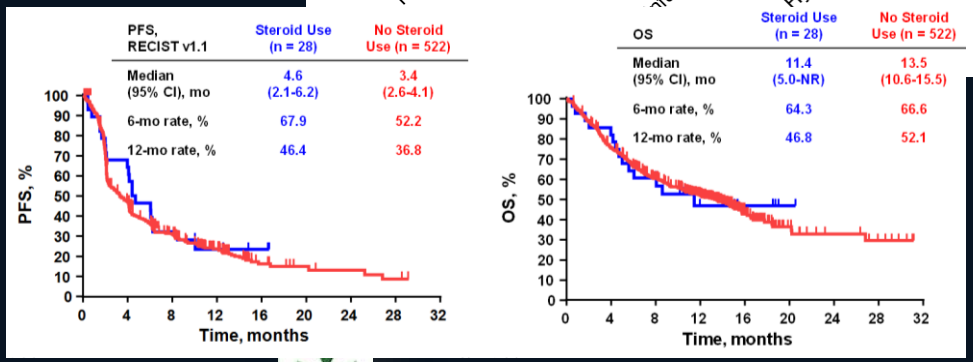
General management algorithm for immune related toxicity.

CTCAE grade	Management
1	• Supportive treatment • Increased monitoring of symptoms • Exclude infection • Patient education
2	As per grade 1 but in addition: • Withhold immunotherapy until toxicity has resolved to grade 1 or less • Consider oral steroids if persistent symptoms >5 days
3	• Supportive therapy • Commence intravenous steroids (typical dose 1–2 mg/kg methyprednisolone) • If not resolving within 48 h consider addition of other immunosuppressants (e.g. infliximab, mycophenolate) • Consider system specific investigations (e.g. colonoscopy) • Seek expert opinion of relevant specialist • Investigate and treat infection • Withhold immunotherapy, consider restarting if toxicity grade 1 or less on individual basis • Steroids will need to be tapered over 3–6 weeks
4	• As for grade 3 but permanently discontinue immunotherapy

Pembro: Immune-Related Events & Steroids

KEYNOTE-001, Data from 505 pts





PER LO STUDIO
E LA CURA DEI TUMORI

WCLC 2015, Leighl N ORAL31.02

CHECKMATE 057

NIVO vs DOC non squamous 2nd line

Would it be better than the BEST CURRENT RESULT in ADENO?

i.e. DOC + Antiangiogenics

INDIRECT COMPARISON

	DOC + ANTI ANGIOGENIC		NIVO	TEST FOR INTERACTION
	REVEL	LUME-LUNG1	CM-057	
HR-OS	0.83	0.83	0.73	χ_2 1.14
CI95%	0.71-0.97	0.70-0.99	0.59-0.89	p 0.29
P	0.020	0.0359	0.00155	

Toxicity: pre-treated advanced NSCLC

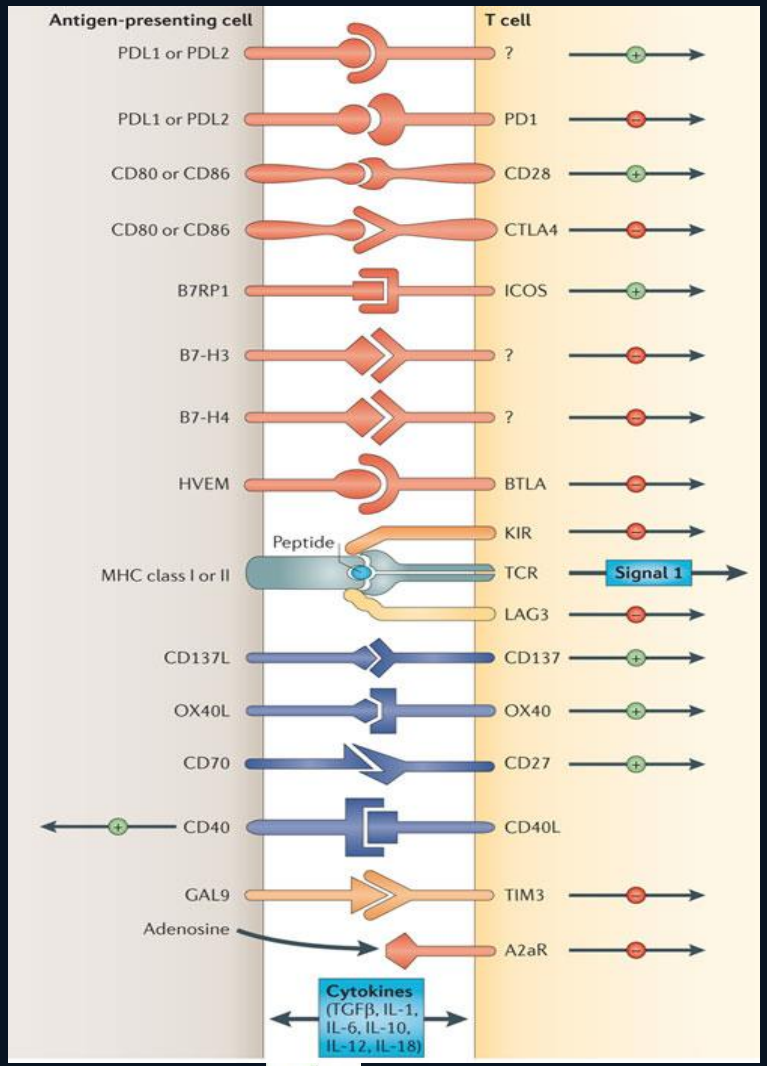
Treatment related AEs (%)	Nivolumab squamous	Nivolumab non-squamous	Atezolizumab all comers	Ramucirumab + docetaxel*	Nintedanib + docetaxel
Any AE	58	69	67	98	94
Grade ≥3	7	10	11	79	71
Grade 5 (death)	0	0	0	5	5
Any AE leading to discontinuation	3	5	8	-	23

PD-1/PD-L1 inhibitors in Phase III clinical development for first-line advanced NSCLC

IMT	Target	PD-L1 selection criteria	Monotherapy/ combination	Comparator	Trials
Nivolumab	PD-1	PD-L1 unselected	Monotherapy or +ipilimumab	Platinum-doublet chemotherapy	Checkmate-227
		PD-L1+	Monotherapy	Chemotherapy (investigator choice)	Checkmate-026
Pembrolizumab	PD-1	PD-L1+	Monotherapy	Platinum-doublet chemotherapy	Keynote-042
		PD-L1 strong	Monotherapy	Platinum-doublet chemotherapy	Keynote-024
Durvalumab	PD-L1	PD-L1 unselected	Monotherapy or + tremelimumab	Platinum-doublet chemotherapy	MYSTIC
		PD-L1 unselected	+tremelimumab	Platinum-doublet chemotherapy	NEPTUNE
Atezolizumab	PD-L1	PD-L1 unselected	+ carboplatin/paclitaxel or + carboplatin/nab-paclitaxel	Carboplatin/ nab-paclitaxel	IMpower 131
		PD-L1 unselected	+carboplatin/paclitaxel +/-bevacizumab	Carboplatin/paclitaxel /bevacizumab	IMpower 150
		PD-L1 unselected	+carboplatin/nab-paclitaxel	Carboplatin/ nab-paclitaxel	IMpower130
		PD-L1+	Monotherapy	Carboplatin/pemetrexed or cisplatin/pemetrexed	IMpower110
		PD-L1+	Monotherapy	Carboplatin/gemcitabine or Cisplatin/gemcitabine	IMpower111

Source: clinicaltrials.gov

Regulation of T cell responses via multiple co-stimulatory and inhibitory interactions



- T cells require 2 signals from dendritic cells to become fully activated:

1) binding of the MHC-antigen to the T-cell receptor and

2) binding of costimulatory molecules expressed on mature dendritic cells (e.g., B7) to CD28 on the T cell.

- CTLA4 and PD-1 receptors are up-regulated following T-cell activation and bind to CD80 or PDL1 or 2, sending an inhibitory signal that down-regulates T-cell activation.

Nuovi farmaci e possibili combinazioni

B7 family member combinations

PD-1, CTLA-4

Novel immunogloblulin superfamily targets

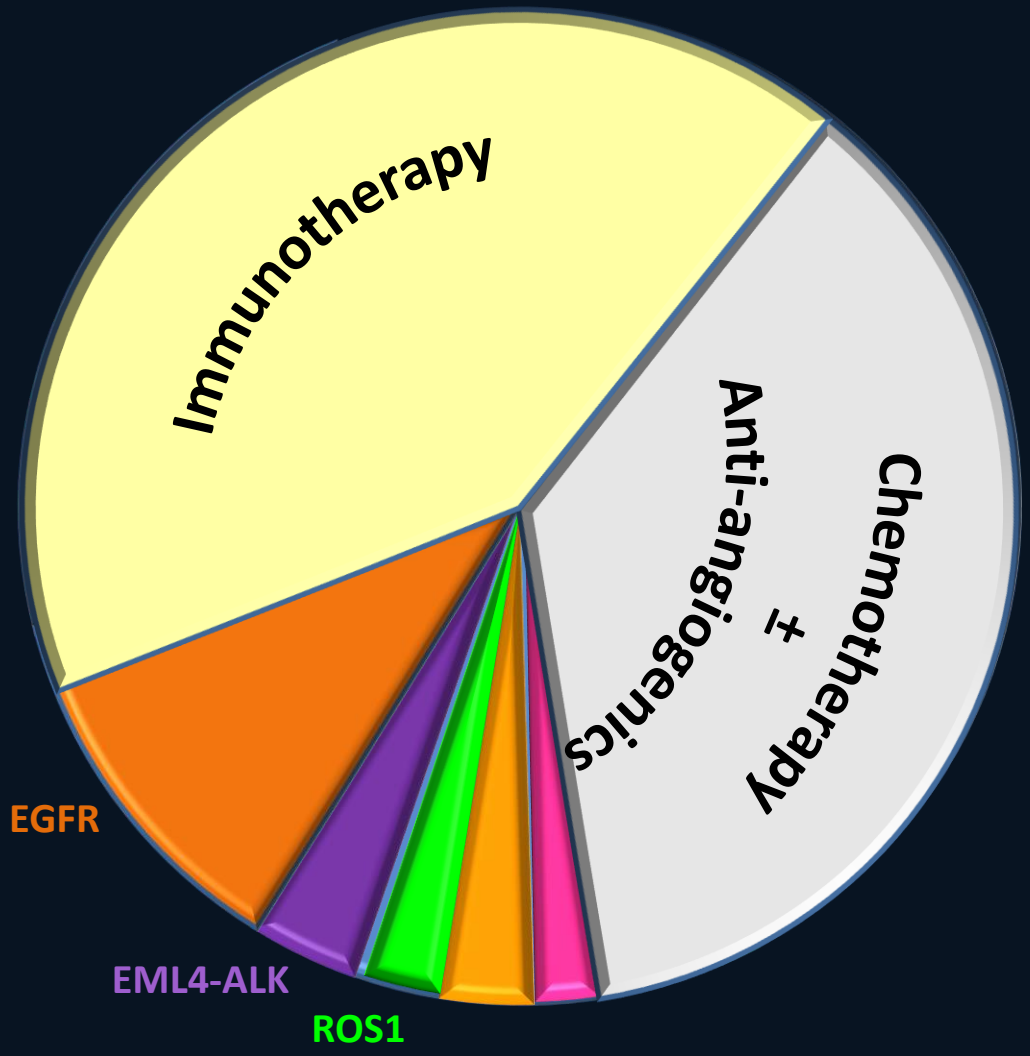
TIM-3, LAG-3, VISTA

TNFR superfamily

OX40, GITR, CD137, CD27

Soluble inhibitors

IDO, arginase, adenosine



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Conclusioni

- L'immunoterapia è una NUOVA arma terapeutica nel trattamento delle neoplasie del polmone

Biomarcatori

- L'istologia non è un criterio di selezione
- L' intensità di espressione di PD-L1 su tumore e su infiltrato è sicuramente un biomarcatore, ma non l' unico
- E' necessaria una armonizzazione della valutazione di PD-L1

Futuro

- Combinazioni (con chemio, TT, altre immunoterapie,etc)
- Definire criteri di selezione e durata dei trattamenti e

Grazie per la Vostra Attenzione !!!