Fattori predittivi di efficacia ed interpretazione della risposta all' immunoterapia

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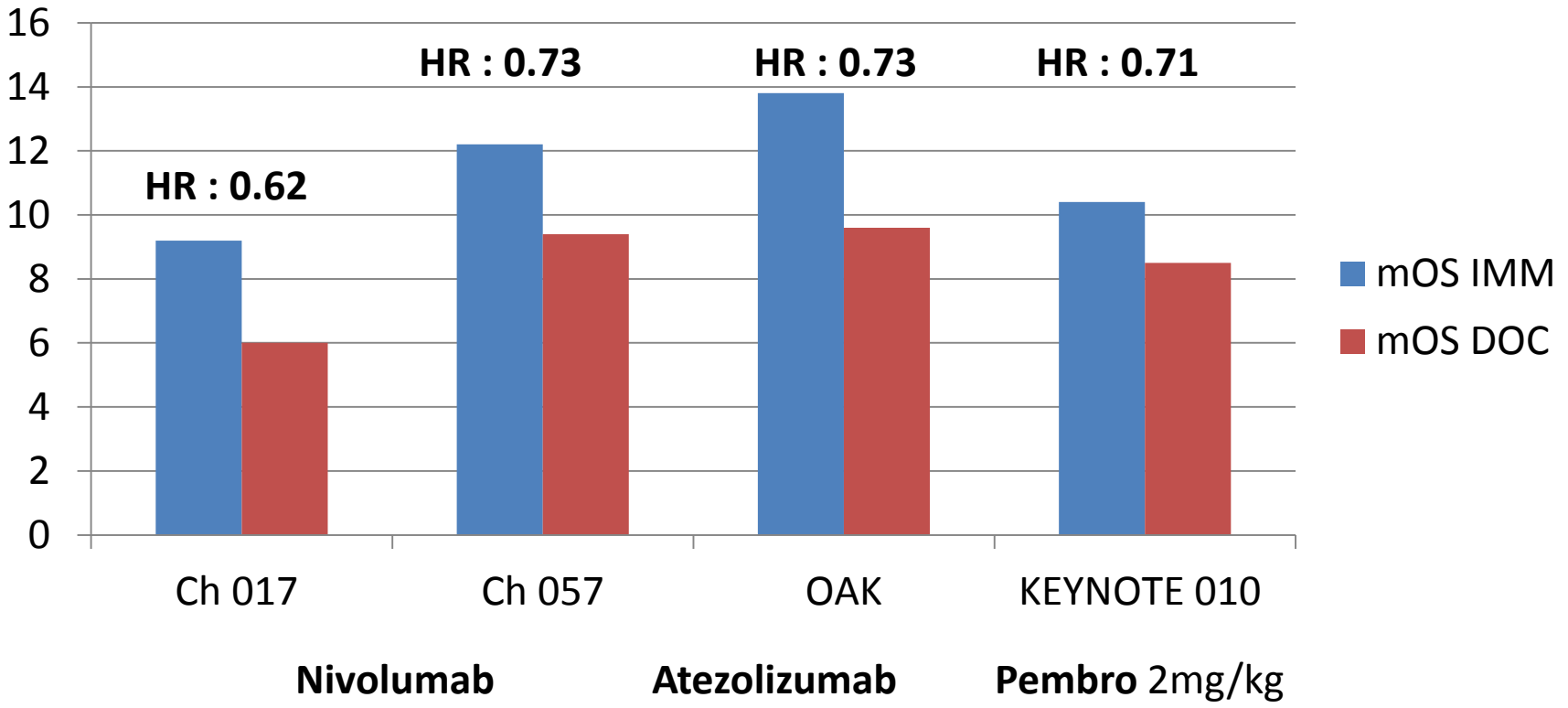
AREA DI RICERCA CLINICA EPIDEMIOLOGICA
ONCOLOGIA CREMONA

mOS in 4 phase III trials in 2° line : immunotherapy is better than docetaxel (and less toxic)



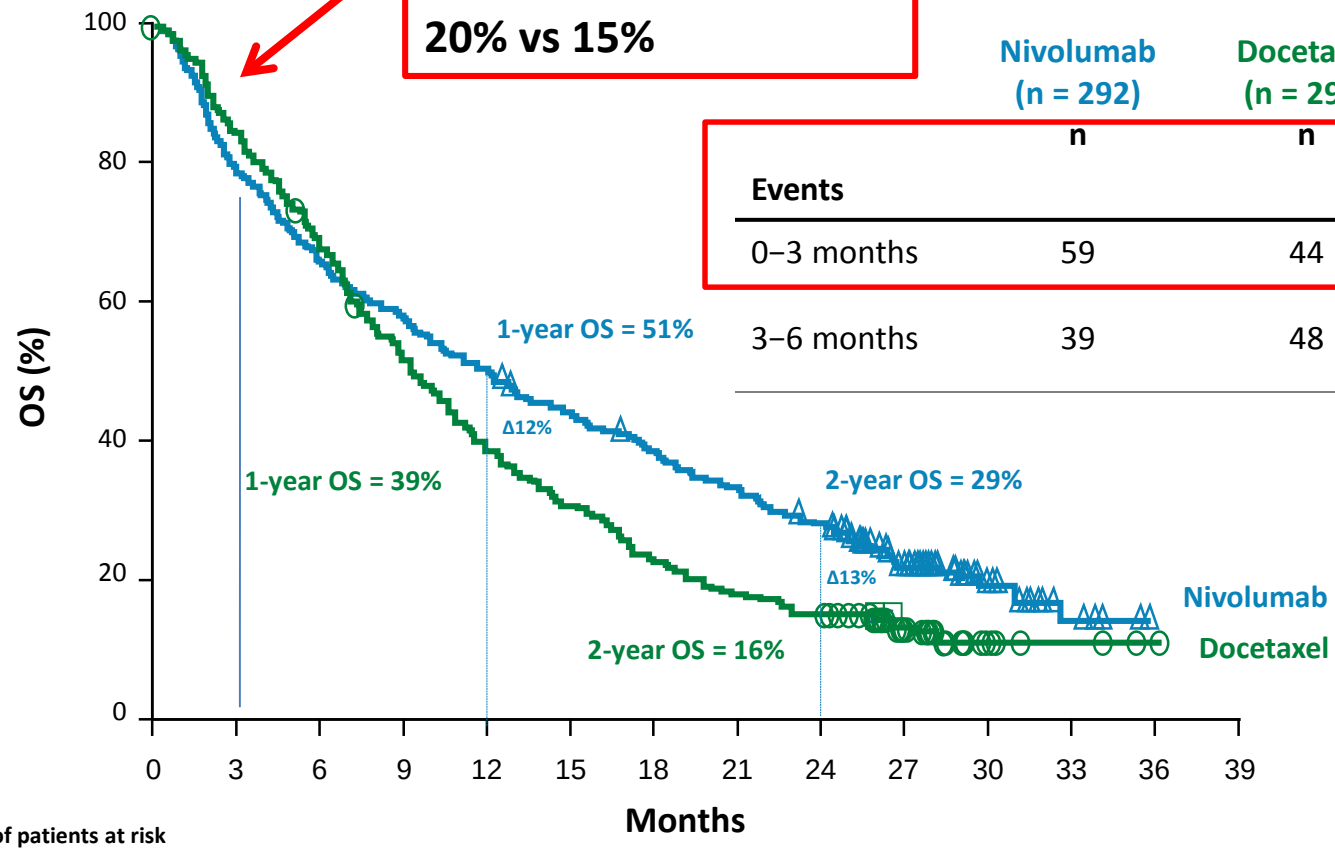
Brahmer et al, N Engl J Med 373:123-135, 2015
Borghaei et al, N Engl J Med 373:1627-1639, 2015
Herbst et al, Lancet 387:1540-150, 2016
Barlesi et al, ESMO 2016

DO WE REALLY NEED PREDICTIVE FACTORS ?

Overall Survival
CheckMate 057: Nivolumab vs Docetaxel in Previously Treated NSQ NSCLC

More events with NIVO in the first 3 months !!!
20% vs 15%

Events	Nivolumab (n = 292) n	Docetaxel (n = 290) n	Difference n
0–3 months	59	44	15
3–6 months	39	48	[9]

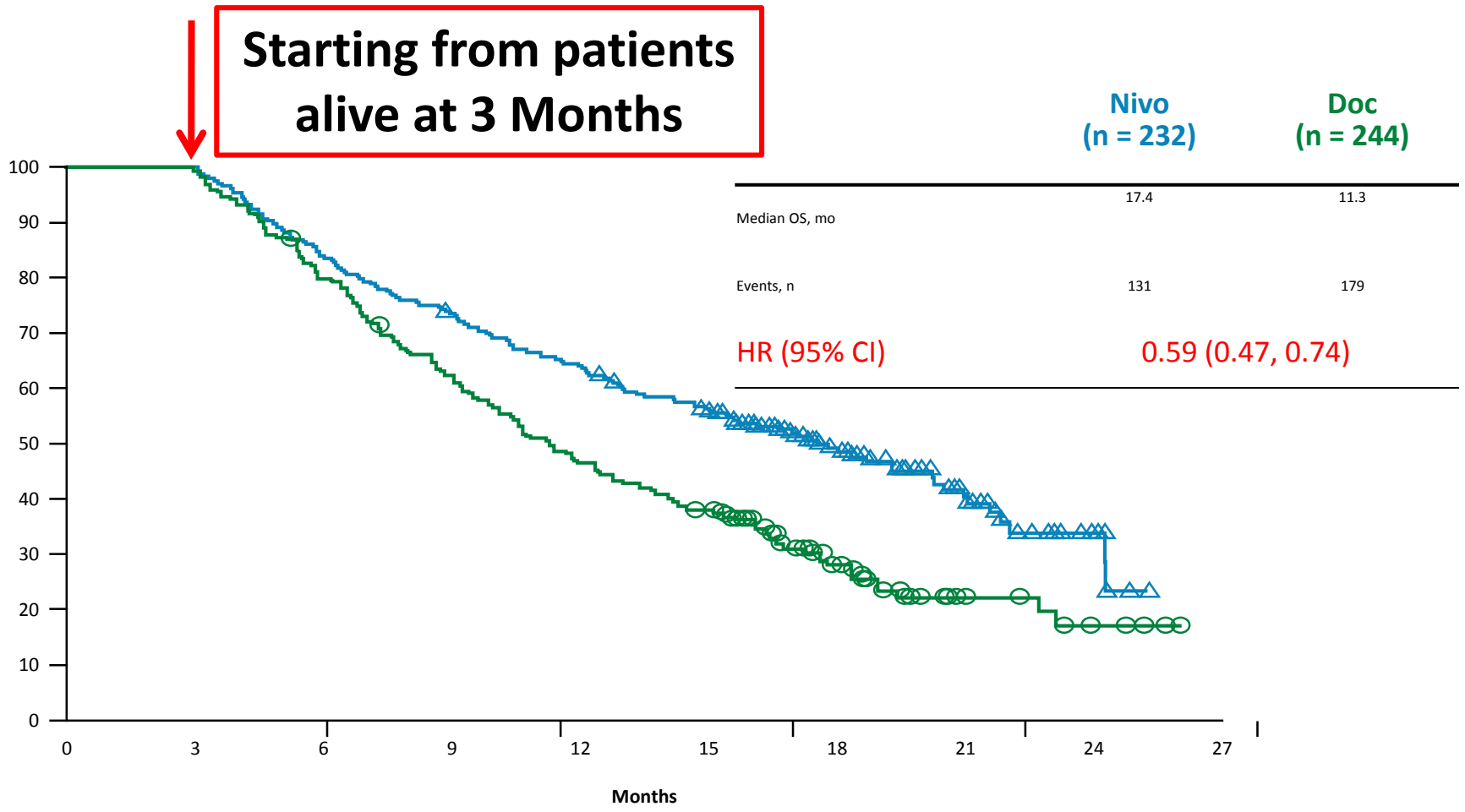


Number of patients at risk

Nivolumab	292	233	194	171	148	128	112	97	81	46	18	6	0	0
Docetaxel	290	243	194	150	111	89	66	53	45	25	6	3	1	0

Based on a February 18, 2016 database lock; minimum follow-up: 2 years
Borghaei H, et al. Presented at the American Society of Clinical Oncology 2016 Annual Meeting; June 3–7, 2016; Chicago, IL, USA. Abstract 9025.

OS with an ideal selection :



3-Month Landmark Analysis of OS
CheckMate 057: Nivolumab vs Docetaxel in Previously Treated NSQ NSCLC

Selection of optimal candidates for immunotherapy

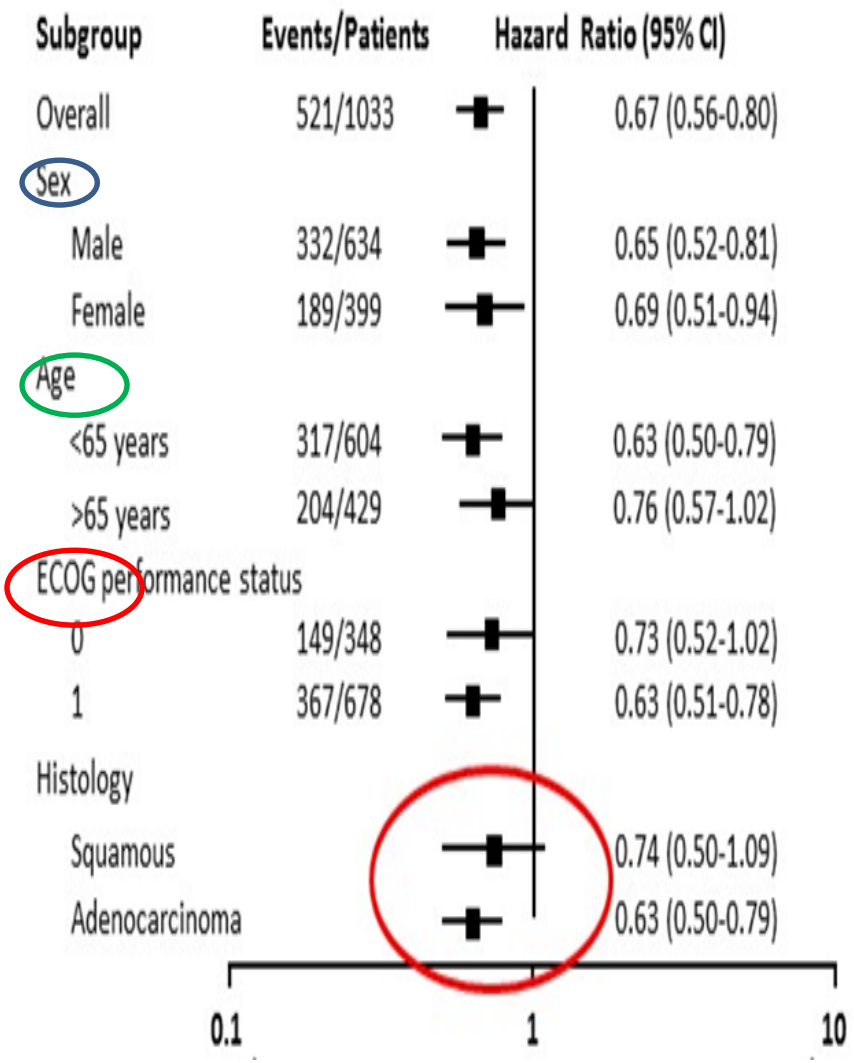
- **Clinical factors**
- **Mutational status (EGFR/ALK/KRAS…)**
- **PDL1**
- **Alternative biomarkers**

Clinical factors :
No influence of age, PS (Ecog 0-1), sex and histology

Checkmate 057 OS

Subgroup	No. of Patients	Unstratified Hazard Ratio (95% CI)
Overall	582	0.75 (0.62–0.91)
Previous use of maintenance therapy		
Yes	233	0.80 (0.58–1.10)
No	349	0.73 (0.57–0.93)
Line of therapy		
Second line	515	0.69 (0.56–0.85)
Third line	66	1.34 (0.73–2.43)
Age		
<65 yr	339	0.81 (0.62–1.04)
≥65 to <75 yr	200	0.63 (0.45–0.89)
≥75 yr	43	0.90 (0.43–1.87)
Sex		
Male	319	0.73 (0.56–0.96)
Female	263	0.78 (0.58–1.04)
ECOG performance-status score		
0	179	0.64 (0.44–0.93)
1	402	0.80 (0.63–1.00)

Keynote 010 OS

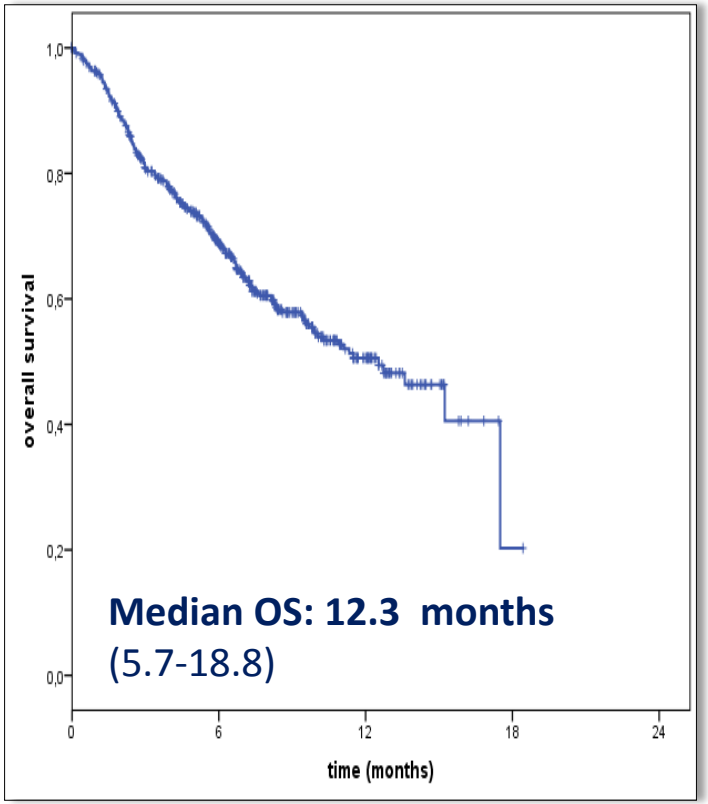


EAP Nivolumab - Elderly patients (≥75 yrs)

Best overall response

	General Population (n = 1585)	Elderly Pts (n=230)
BORR, n (%)	284 (18)	56 (24)
Best overall response, n (%)		
Complete response	10 (<1)	0
Partial response	274 (17)	56 (24)
Stable disease	398 (25)	60 (26)
Mixed response[a]	18 (1)	3 (1)
Progressive disease	664 (42)	87 (38)
Unable to determine[b]	221 (14)	24 (11)

Overall survival



Median follow-up of 6,2 months (1-18,8).

a. Includes pts with different responses (diameter not available) in different metastatic sites.

b. Includes patients without at least one tumor assessment, based on length of treatment.

Median OS: 12.1 months (10.6-13.6) in the general population

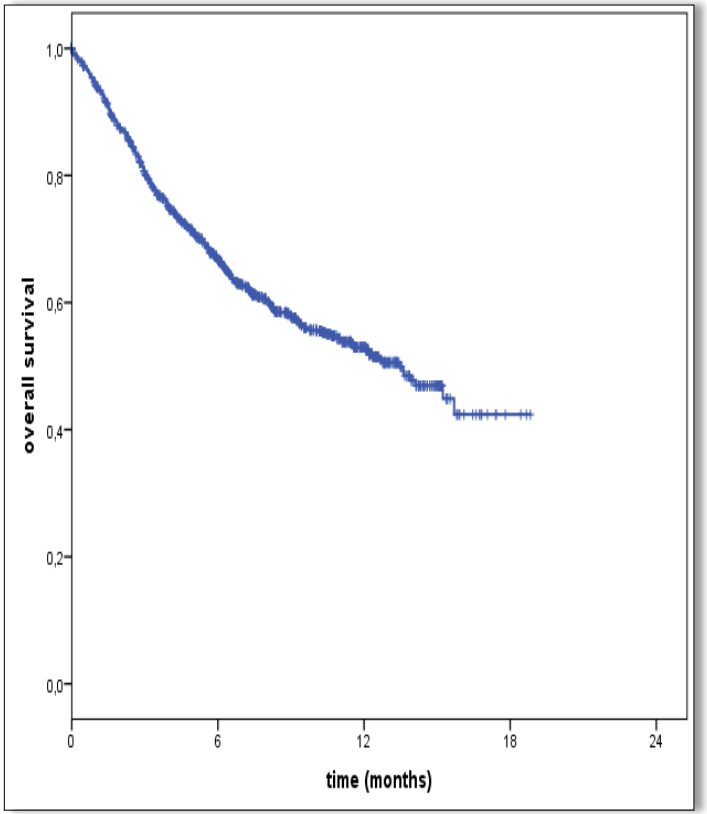
EAP Nivolumab - Pluri-treated (≥ 2 prior lines of therapy) patients

Best overall response

	General Population (n = 1585)	Pluri-treated[a] Pts (n=1128)
BORR, n (%)	284 (18)	203 (18)
Best overall response, n (%)		
Complete response	10 (<1)	8 (<1)
Partial response	274 (17)	195 (17)
Stable disease	398 (25)	307 (27)
Mixed response[b]	18 (1)	12 (1)
Progressive disease	664 (42)	452 (40)
Unable to determine[c]	221 (14)	154 (14)

71%

Overall survival



Median OS: 13.5 months (11.6-15.4)

Median follow-up of 6,2 months (1-18,8).

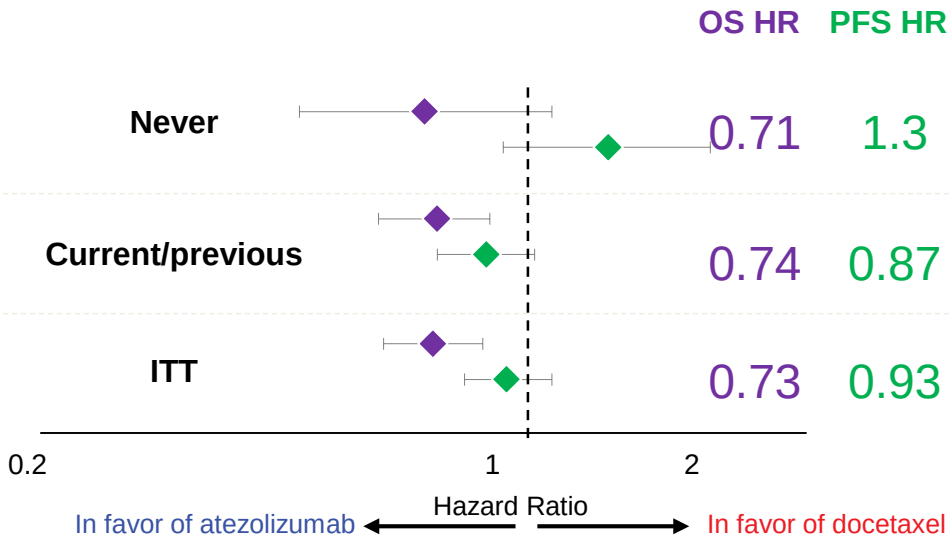
a. **Patients received ≥ 2 prior lines of therapy.**

b. Includes pts with different responses (diameter not available) in different metastatic sites.

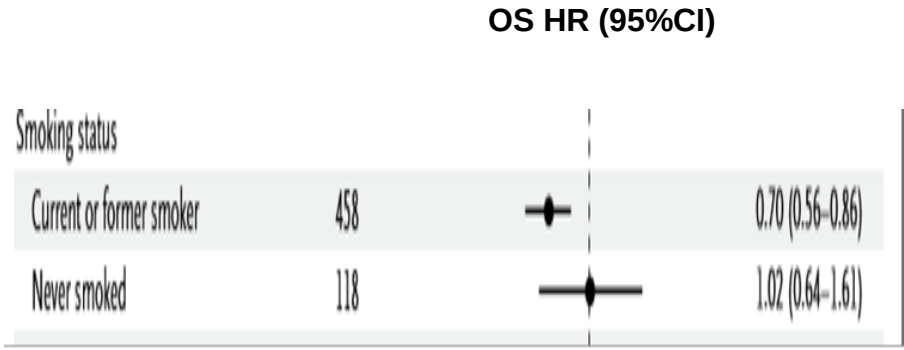
c. Includes patients without at least one tumor assessment, based on length of treatment.

Smoking status: more outcome benefit

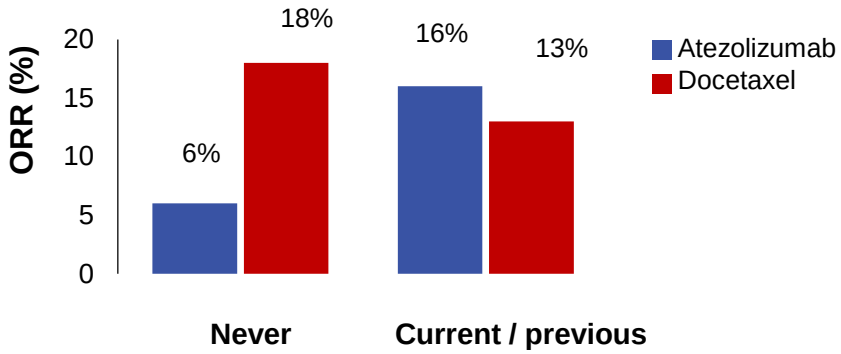
OAK trial



Checkmate 057 OS

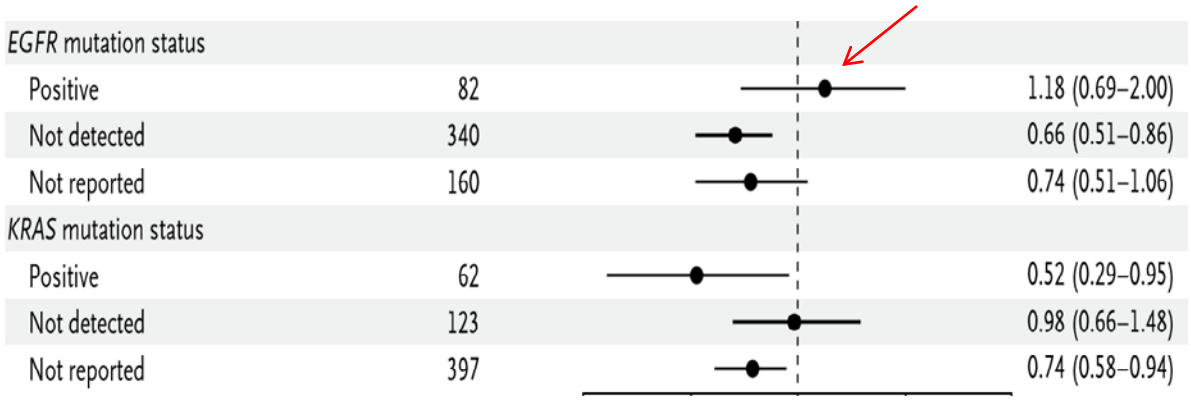


Ph1/2 Durvalumab [*study 1108*]

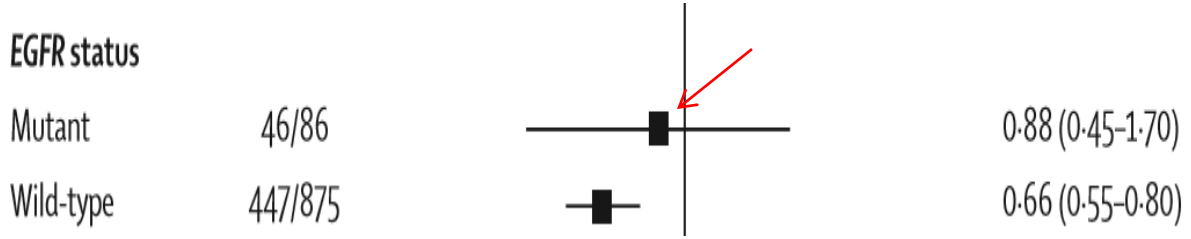


RECIST response (ORR)	
Histology	
Squamous	31/146 (21.2%)
Non-squamous	19/139 (13.7%)
Tobacco use	
Former/current smoker	47/240 (19.6%)
Never smoker	3/45 (6.7%)

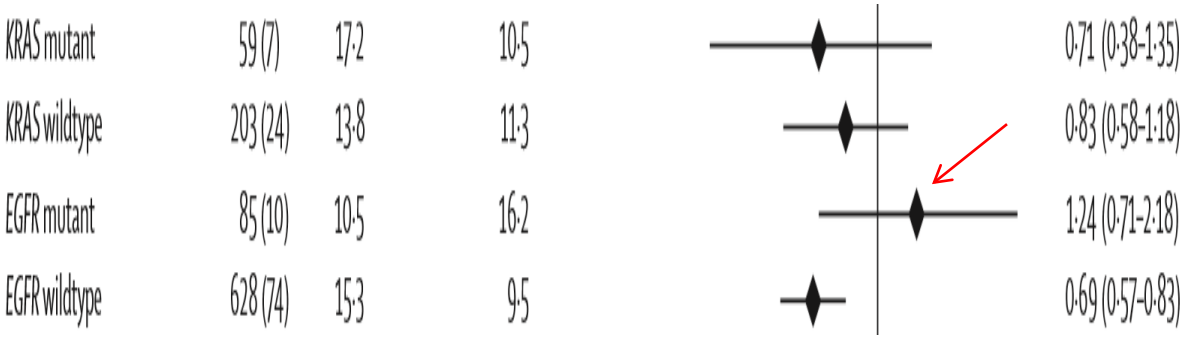
EGFR mutant are not the best candidate for immunotherapy



Checkmate 057 trial
OS HR : 1.18

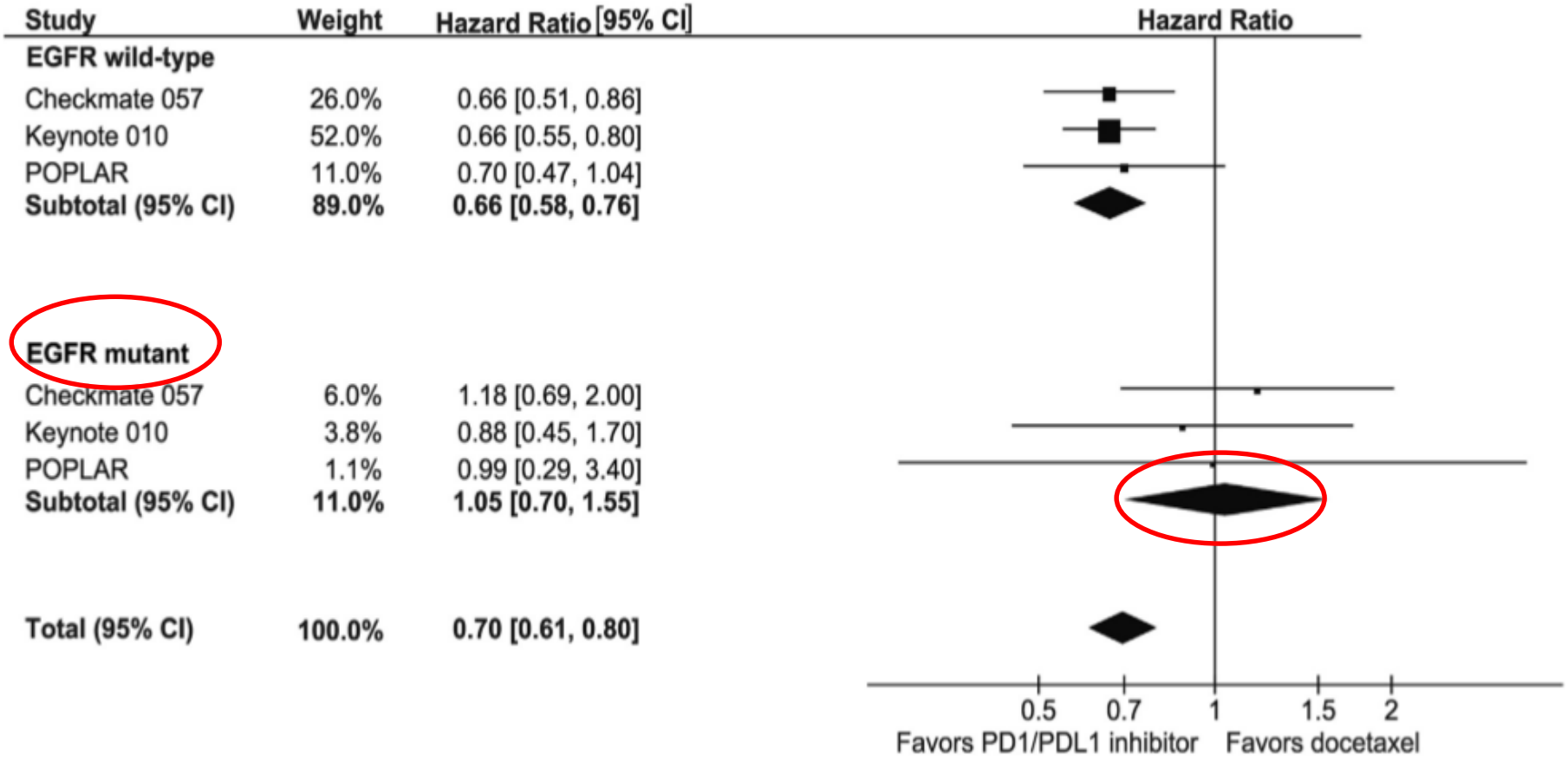


Keynote 010 trial
OS HR : 0.88



OAK trial
OS HR : 1.24

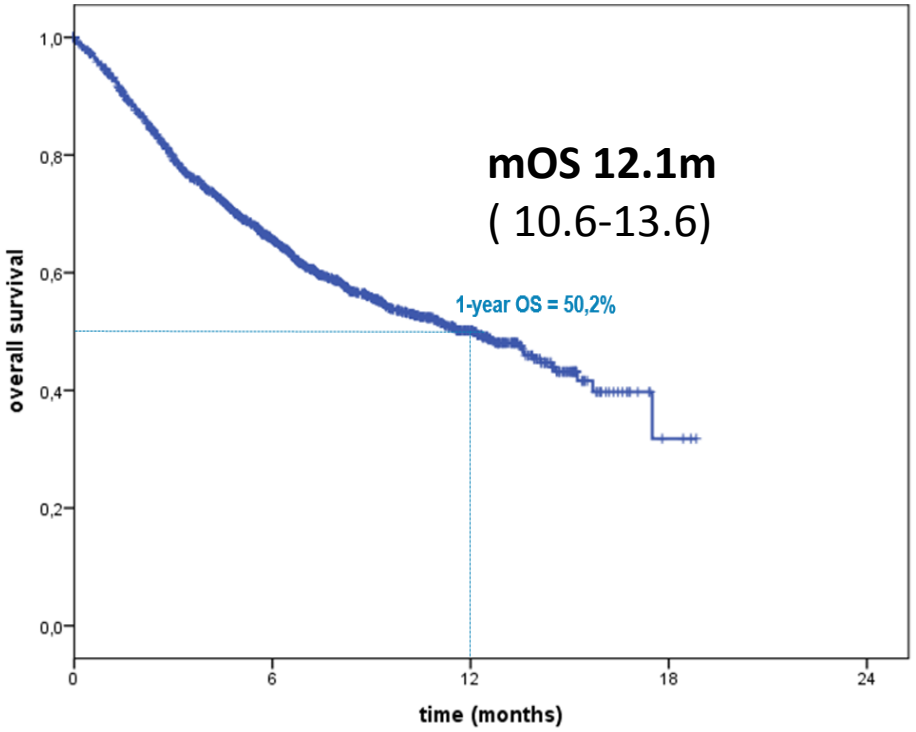
Meta- Analysis of CPI in EGFR mutated



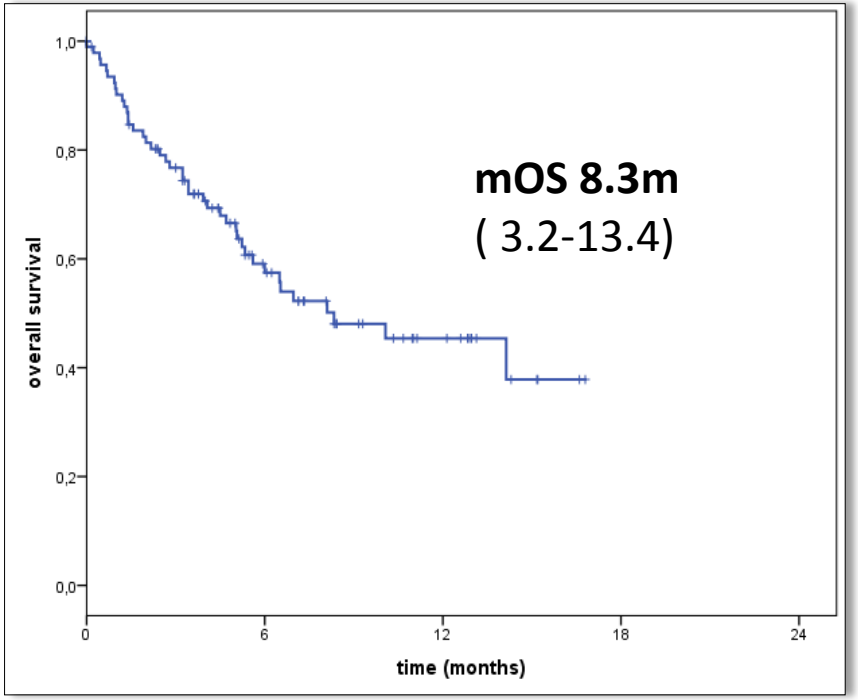
Lee CK et al. JTO 2016

EAP Nivolumab – EGFR-positive Patients

mOS ALL (1585 pts)



mOS EGFR + (101 pts)

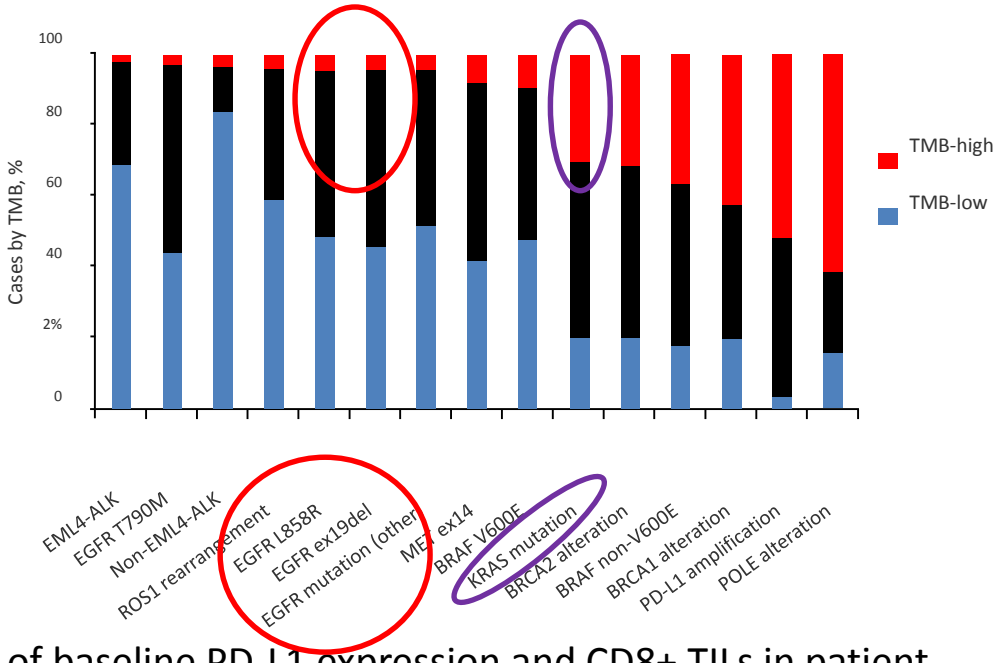


	General Population (n = 1585)	EGFR + (n=101)
BORR, n (%)	284 (18)	8 (8)

Median follow-up of 6,2 months (1-18,8).

EGFR Mutated : low TMB and not inflamed tumor

- Low mutational burden



Spigel et al. ASCO 2016;

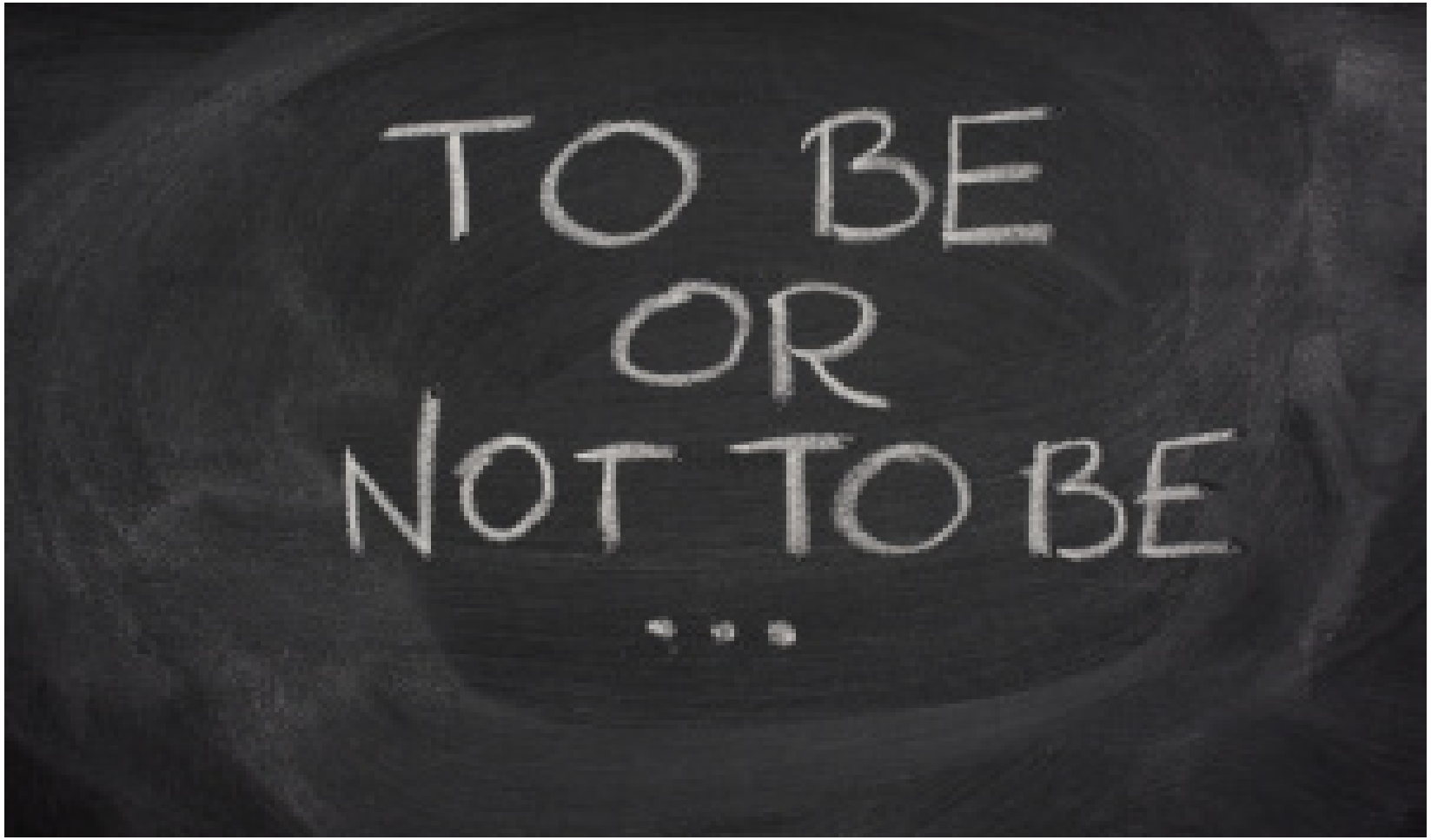
- Less inflamed

Comparison of baseline PD-L1 expression and CD8+ TILs in patient with EGFR vs KRAS mutations

		EGFR mutant	KRAS mutant	P
$CD8^+$TILs(image-based)/mm^2 median		185.1	330.1	0.011
Concurrent PD-L1 expression and CD8		1/48		
PD-L1(≥50%)&high $CD8^+$TILs		1/48	7/56	0.066
PD-L1(≥5%)&high $CD8^+$TILs		1/48	11/56	0.005

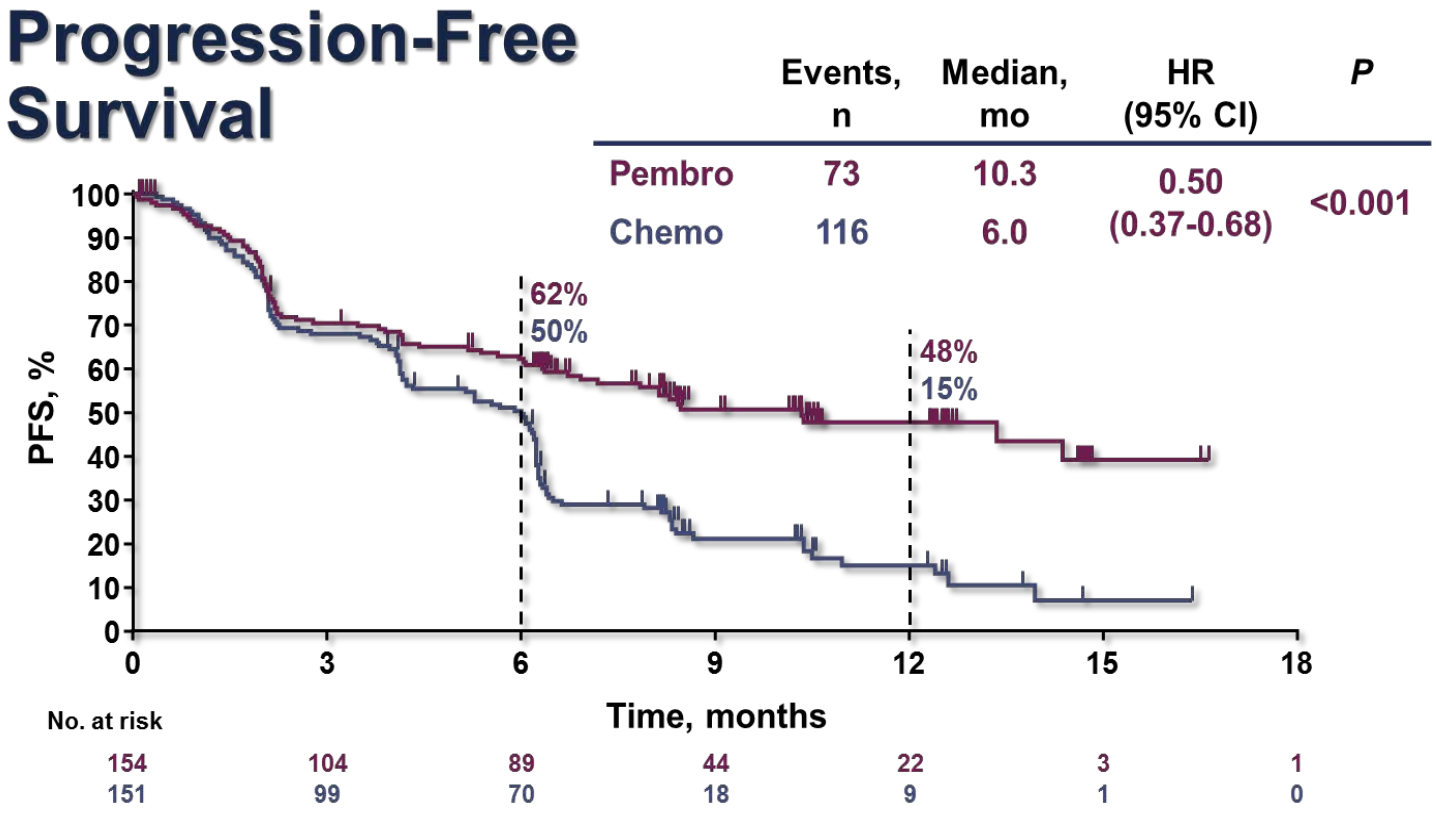
Gainor et al. CCR, 2016

PDL1 : Is it a useful marker ?



…TO BE !

KEYNOTE-024 demonstrated that pembrolizumab had superior efficacy over platinum based chemotherapy as **first-line therapy** for patients with advanced NSCLC with **PD-L1 TPS ≥50%**



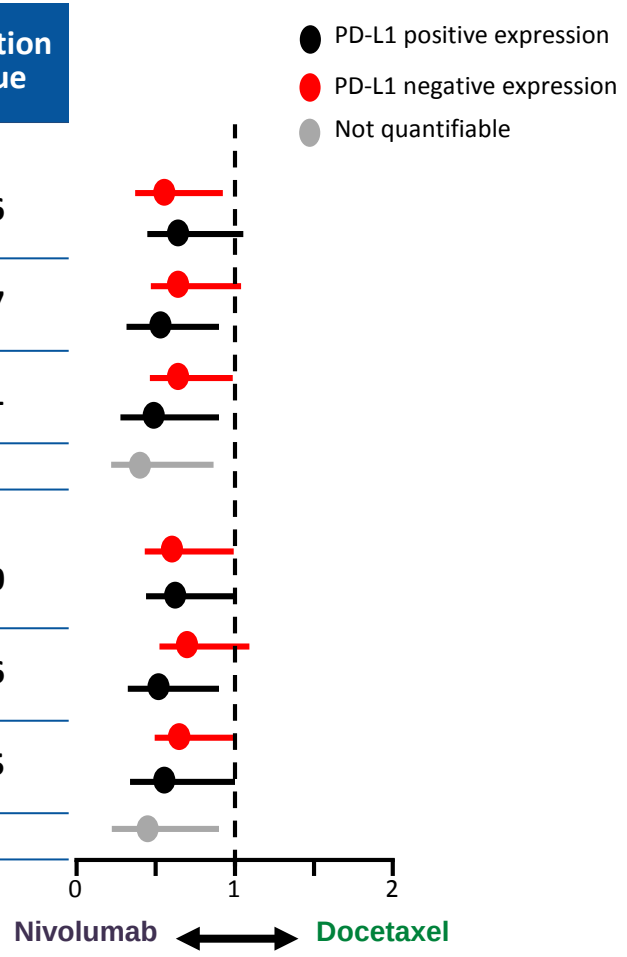
N Engl J Med. Reck,M. et al. Pembrolizumab versus chemotherapy for PD-L1–positive non– small-cell lung cancer. 2016;375:1823-1833.

…NOT TO BE !

CheckMate 017 (Squamous)

OS –PFS- ORR are indipendent of PD-L1 expression

PD-L1 Expression	Patients, n		Unstratified HR (95% CI)	Interaction *P*-value
	Nivolumab	Docetaxel		
OS				
<1%	54	52	0.58 (0.37, 0.92)	**0.56**
≥1%	63	56	0.69 (0.45, 1.05)	
<5%	75	69	0.70 (0.47, 1.02)	**0.47**
≥5%	42	39	0.53 (0.31, 0.89)	
<10%	81	75	0.70 (0.48, 1.01)	**0.41**
≥10%	36	33	0.50 (0.28, 0.89)	
Not quantifiable	18	29	0.39 (0.19, 0.82)	
PFS				
<1%	54	52	0.66 (0.43, 1.00)	**0.70**
≥1%	63	56	0.67 (0.44, 1.01)	
<5%	75	69	0.75 (0.52, 1.08)	**0.16**
≥5%	42	39	0.54 (0.32, 0.90)	
<10%	81	75	0.70 (0.49, 0.99)	**0.35**
≥10%	36	33	0.58 (0.33, 1.02)	
Not quantifiable	18	29	0.45 (0.23, 0.89)	



ORR was independent of PD-L1 expression and consistently higher for nivolumab vs docetaxel

Brahmer et al, NEJM 2015

Issues with PD-L1 detection

Temporal limitations :

- Time between sample collection and treatment with PD-1/PD-L1 inhibitor

Spatial limitations :

- Intrapatient and intratumor heterogeneity

Biological issues :

- PDL1 can be upregulated through either ongogene activation (EGFR, PTEN loss, JACK- STAT disregulation-PI3K/AKT) or through IFNɣ expression.
- Not only tumor cells but also tumor-infiltrating immune cells express PDL1

Technical issues :

-Different antibodies used for different studies
-Definition of threshold of “positivity“

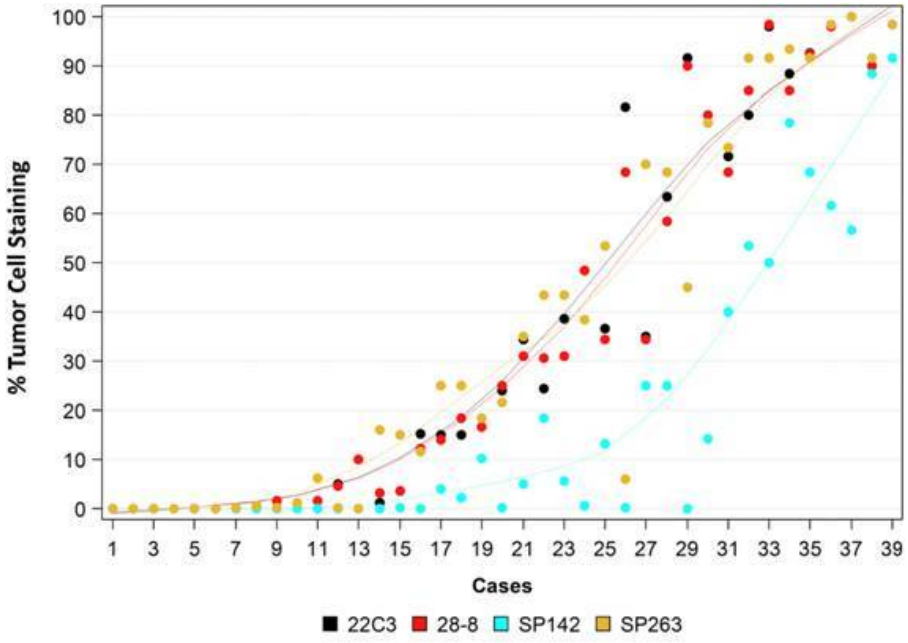
Blueprint PD-L1 IHC Assay Comparison Project

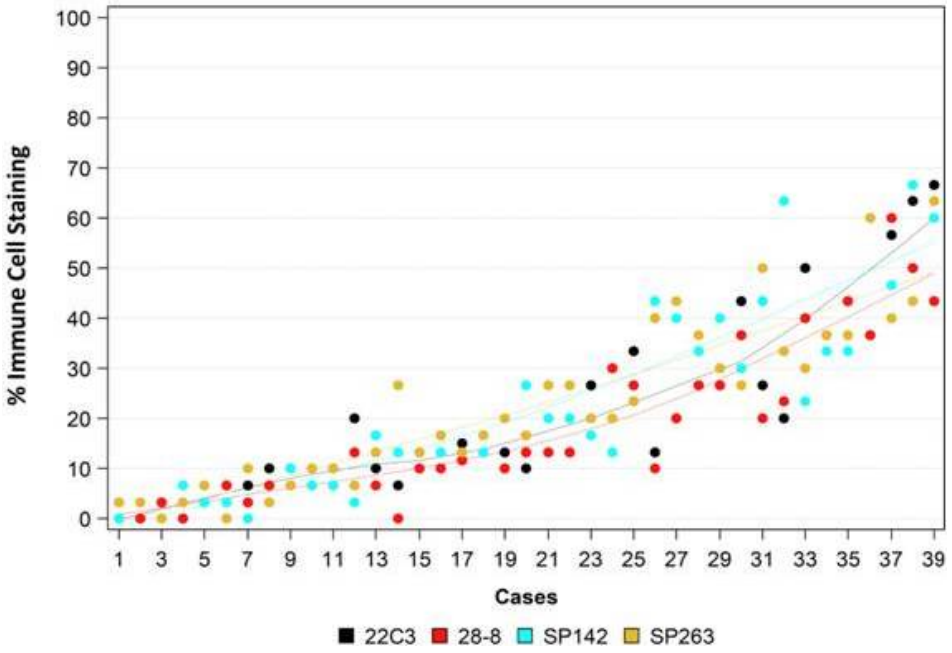
Percentage of PD-L1 stained tumor cells comparable with 223 (dako), 28-8 (dako) and SP263 (Ventana) assays, SP142 (Ventana) assay stained fewer tumor cells

Variability of immune cell staining across 4 assays higher than for tumor cell staining

19/38 (50%) classified above, 5/38 (13%) below selected cutoffs of all assays; **14/38 (37%) different PD-L1 classification depending on assay/scoring system**

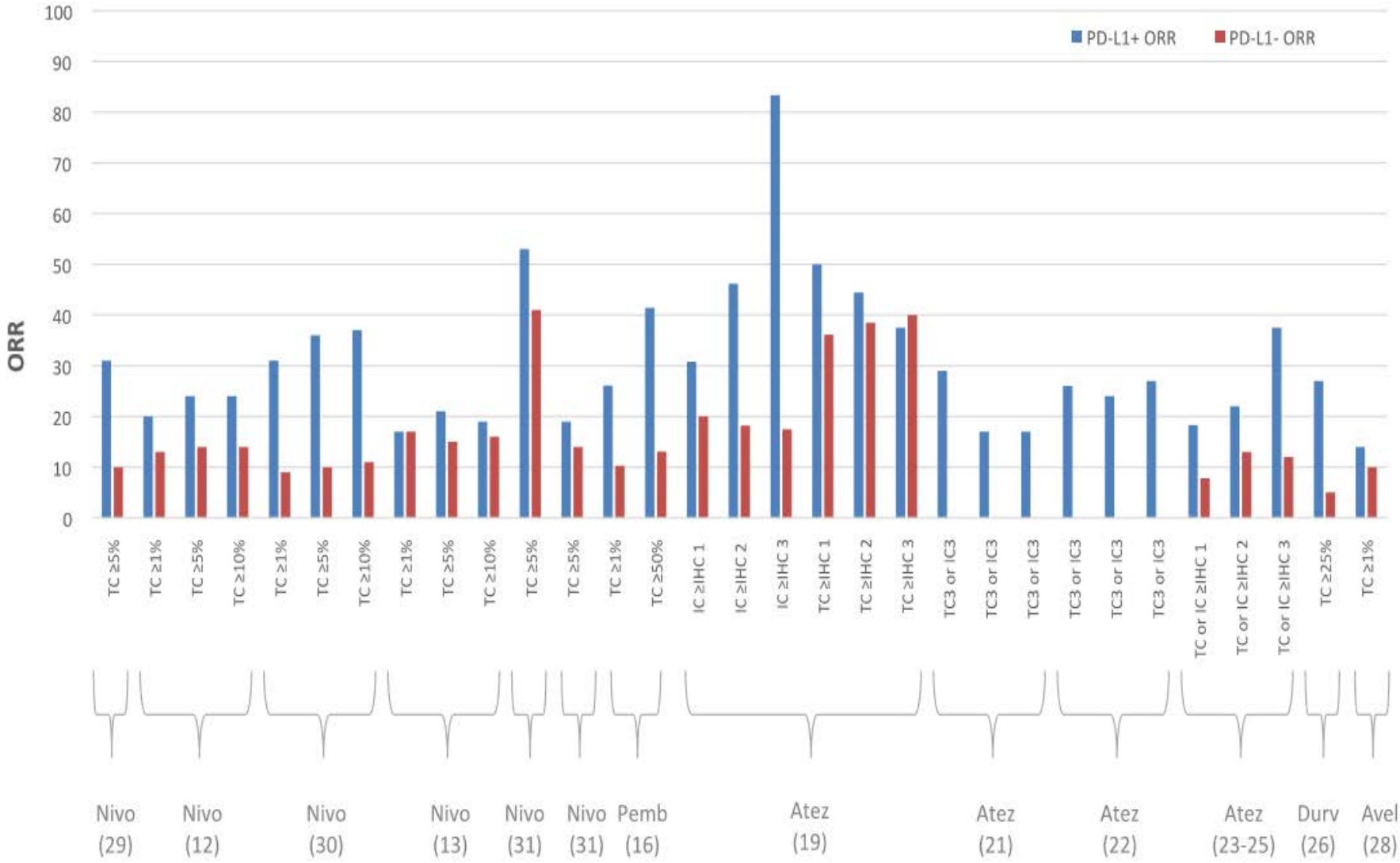
Despite similar performance of PD-L1 expression for 3 assays, interchanging assays and cut-offs may lead to misclassification of PD-L1 status for some patients . More data are necessary





Hirsch et al, JTO 2016

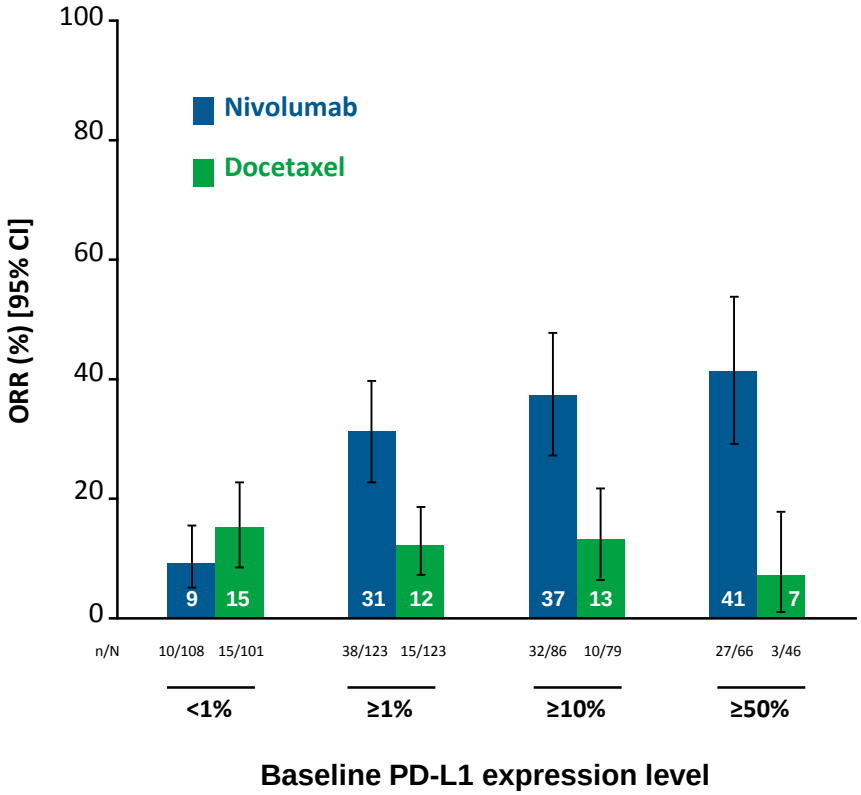
PDL1 and ORR

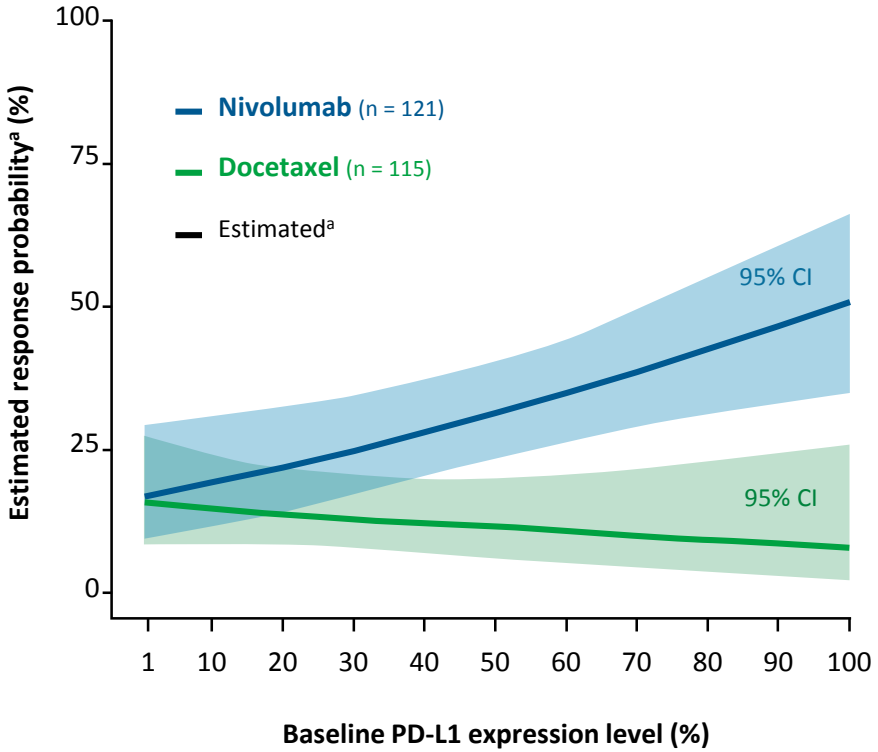


Chae YW et al. Cl Lung Cancer 2016

PD-L1 Expression Continuum and Response Probability

CheckMate 057: Nivolumab vs Docetaxel in Previously Treated NSQ NSCLC





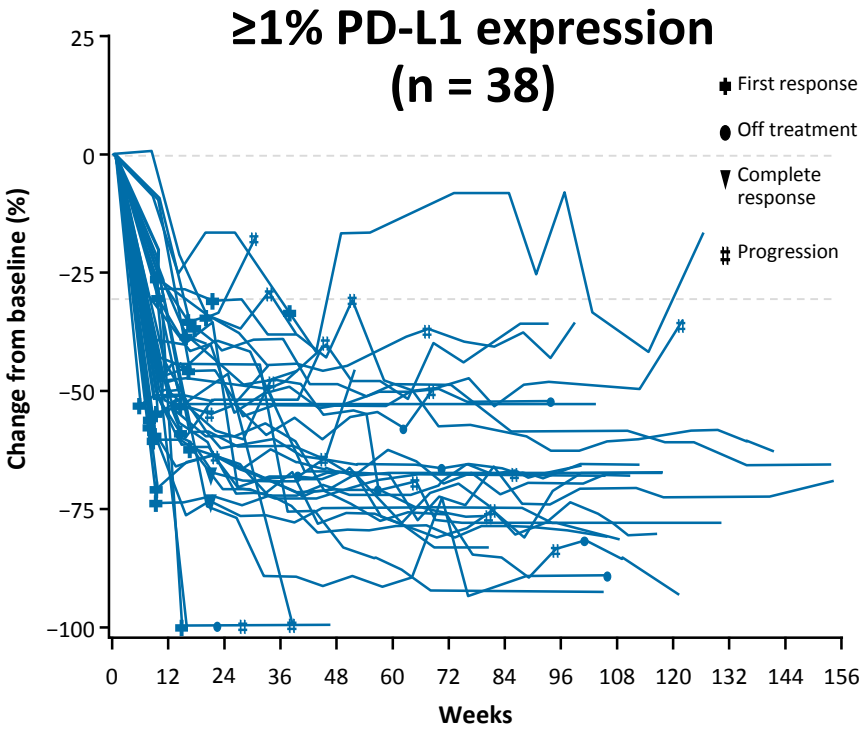
Based on a March 18, 2015 database lock

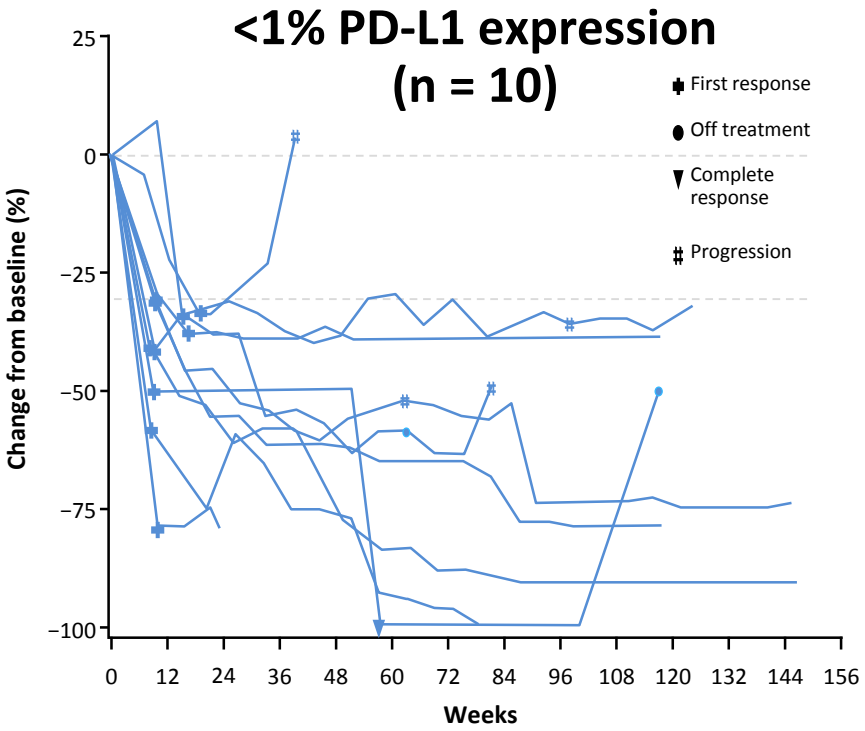
[a]Logistic regression models with baseline PD-L1 expression as continuous covariate

Tumor Burden Change by PD-L1 Expression

CheckMate 057: Nivolumab vs Docetaxel in Previously Treated NSQ NSCLC

Nivolumab-treated responders





- **Deep and durable responses were observed with nivolumab irrespective of tumor PD-L1 expression levels**
  - **Median duration of response: PD-L1 ≥1%, 17.2 months (95% CI: 8.4, NE); PD-L1 <1%, 18.3 months (95% CI: 5.5, NE)**
  - Of 4 complete responders, 2 had PD-L1 ≥1%, 1 had PD-L1 <1%, and 1 had PD-L1 not quantifiable

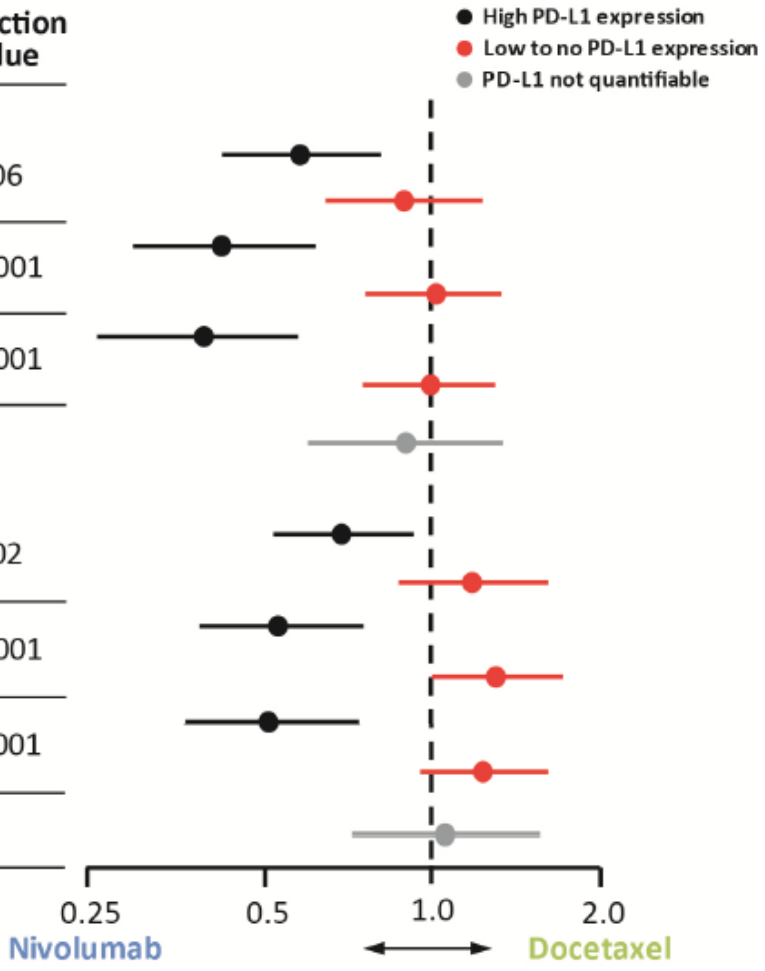
Based on a February 18, 2016 database lock; minimum follow-up: 2 years; NE = not estimable

Barlesi F, et al. Presented at the European Society for Medical Oncology 41st Congress; October 7–11, 2016; Copenhagen, Denmark. Abstract 1215PD.

OS and PFS HR regarding PD-L1 expression

Checkmate 057

PD-L1 expression level	Nivolumab n	Docetaxel n	Unstratified HR (95% CI)	Interaction *P*-value
OS				
≥1%	123	123	0.59 (0.43, 0.82)	0.06
<1%	108	101	0.90 (0.66, 1.24)	
≥5%	95	86	0.43 (0.30, 0.63)	<0.001
<5%	136	138	1.01 (0.77, 1.34)	
≥10%	86	79	0.40 (0.26, 0.59)	<0.001
<10%	145	145	1.00 (0.76, 1.31)	
Not quantifiable at baseline	61	66	0.91 (0.61, 1.35)	
PFS				
≥1%	123	123	0.70 (0.53, 0.94)	0.02
<1%	108	101	1.19 (0.88, 1.61)	
≥5%	95	86	0.54 (0.39, 0.76)	<0.001
<5%	136	138	1.31 (1.01, 1.71)	
≥10%	86	79	0.52 (0.37, 0.75)	<0.001
<10%	145	145	1.24 (0.96, 1.61)	
Not quantifiable at baseline	61	66	1.06 (0.73, 1.56)	

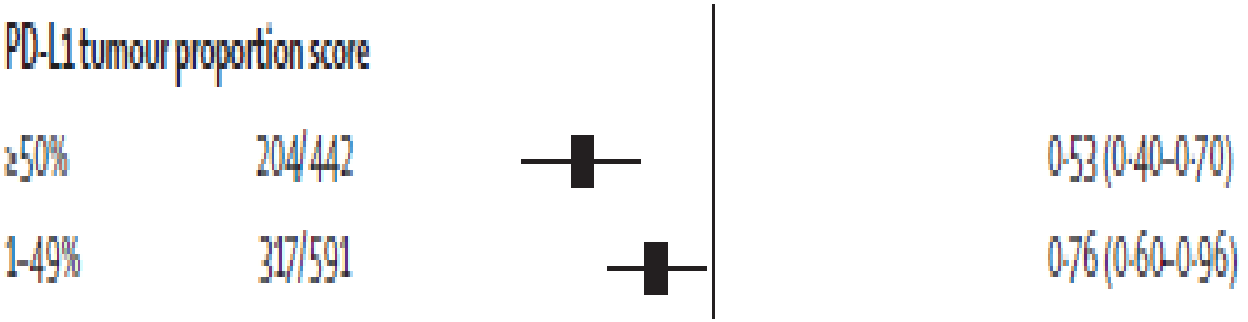


Borghaei et al, NEJM 2015

OS HR regarding PD-L1 expression

KEYNOTE 010

Herbst R et al. ,Lancet 2016

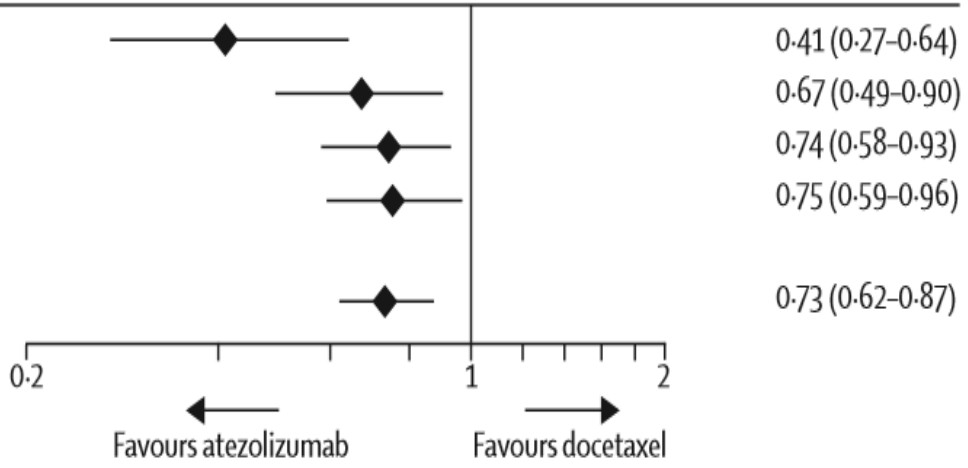


OAK

PD-L1 tumour cell scoring		PD-L1 tumour-infiltrating immune cell scoring	
Score	Percentage of PD-L1-expressing cells	Score	Percentage of PD-L1-expressing cells
TC3	≥50%	IC3	≥10%
TC2	≥5% and <50%	IC2	≥5% and <10%
TC1	≥1% and <5%	IC1	≥1% and <5%
TC0	<1%	IC0	<1%

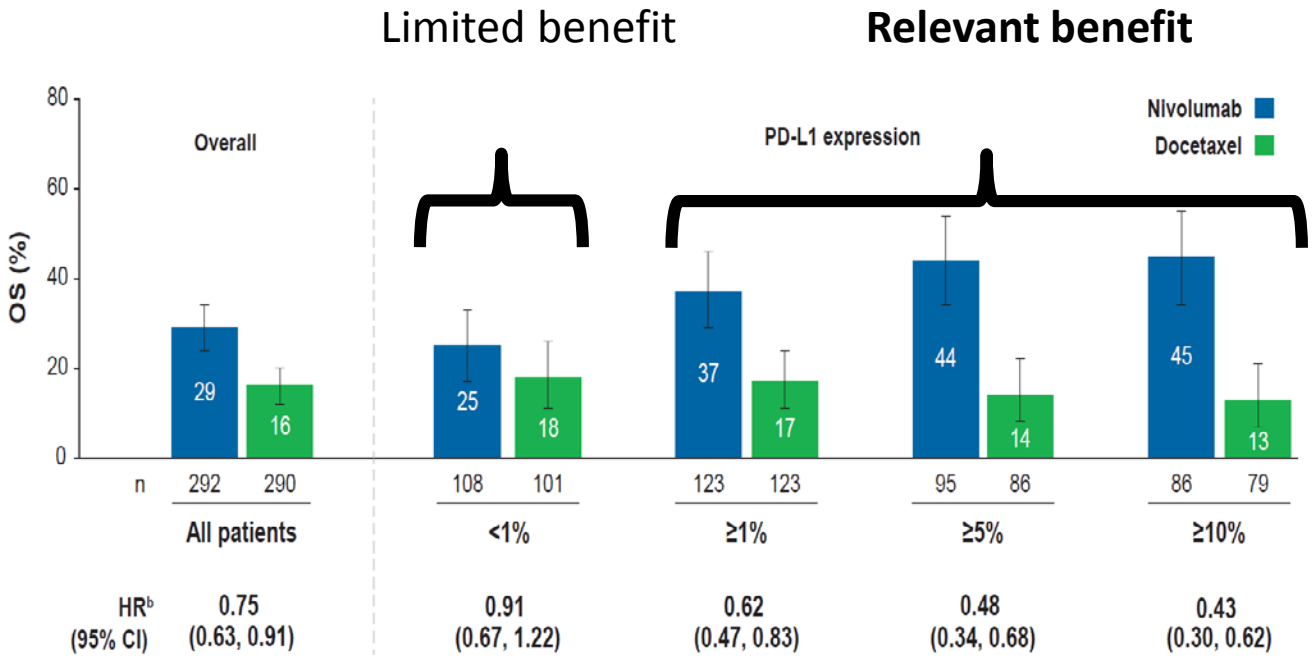
F

	n (%)	Median overall survival (months)	
		Atezolizumab	Docetaxel
TC3 or IC3	137 (16)	20·5	8·9
TC2/3 or IC2/3	265 (31)	16·3	10·8
TC1/2/3 or IC1/2/3	463 (54)	15·7	10·3
TC0 and IC0	379 (45)	12·6	8·9
ITT	850 (100)	13·8	9·6



Rittmeye A Lancet 2017

2-year OS Rates Overall and by PD-L1 Expression Level in CheckMate 057 (non-SQ NSCLC)



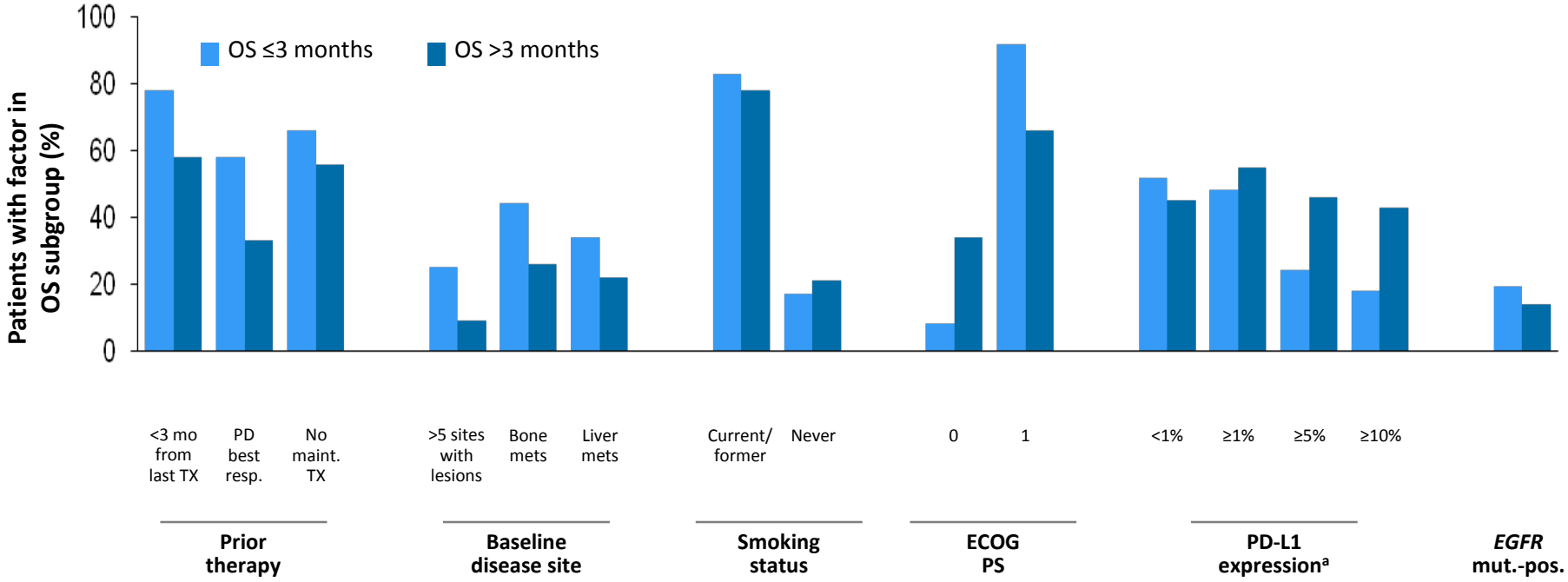
- In CheckMate 057, consistent with the primary analysis,[2] PD-L1 expression level was associated with the magnitude of OS benefit at 2 years starting at the lowest level studied (1%)

[a]Kaplan–Meier estimates, with error bars indicating 95% CIs
[b]For the comparison of the full Kaplan–Meier survival curves for each treatment group

Borghaei H et al ASCO 2016

Single Baseline Characteristics by OS With Nivolumab

CheckMate 057



- **Post-hoc, exploratory multivariate analysis suggested that nivolumab-treated patients with poorer prognostic features and/or aggressive disease when combined with lower or no tumor PD-L1 expression may be at higher risk of death within the first 3 months**

-> These included the following known prognostic factors: <3 months since last treatment, PD as best response to prior treatment, and ECOG PS = 1

Based on a March 18, 2015 database lock; [a]Percentages of patients are based on numbers of patients with quantifiable PD-L1 expression at baseline; maint. = maintenance; mets = metastases; mut. = mutation; pos. = positive; resp. = response; TX = treatment

ALTERNATIVE BIOMARKERS

LEADING TUMOR BIOMARKER STRATEGIES UNDER DEVELOPMENT FOR CHECKPOINT IMMUNOTHERAPY

	Details of approach	Malignancies studied	Improved clinical outcome association
PD-L1[10,12,13,19-25]	Immunohistochemistry-based assessment of the proportion of PD-L1-positive tumour cells, immune cells, or both	Multiple tumour types	Positive PD-L1 tumour status
Tumour-infiltrating lymphocyte[26-28]	Immunohistochemistry-based assessment of T cells at invasive tumour margin or tumour parenchyma	Melanoma; multiple tumour types	Increased CD8+ tumour-infiltrating lymphocyte density
T-cell receptor clonality[27]	Involves next-generation sequencing of T-cell receptor β chain	Melanoma	Restricted, clonal T-cell receptor β chain
Mutational burden[29-37]	Whole or targeted exome sequencing to assess non-synonymous somatic mutations	Melanoma, NSCLC, bladder cancer	High mutational count
Neoantigen burden[31-33,37]	Predicted neoantigens derived from whole-exome sequencing data	Melanoma, NSCLC	High neoantigen count
Immune gene signatures[38,39]	Assessment of gene expression from the tumour microenvironment using an automated platform	Melanoma	Interferon γ or T-cell inflamed profile
Multiplex immunohistochemistry[27]	Direct assessment of multiple protein markers on tumour cells and immune cells, including spatial relationships	Multiple tumour types	Physical interaction with PD-1-positive and PD-L1-positive cells; others likely to be determined

PD-L1=programmed death-ligand 1. NSCLC=non-small-cell lung cancer. PD-1=programmed death-1.

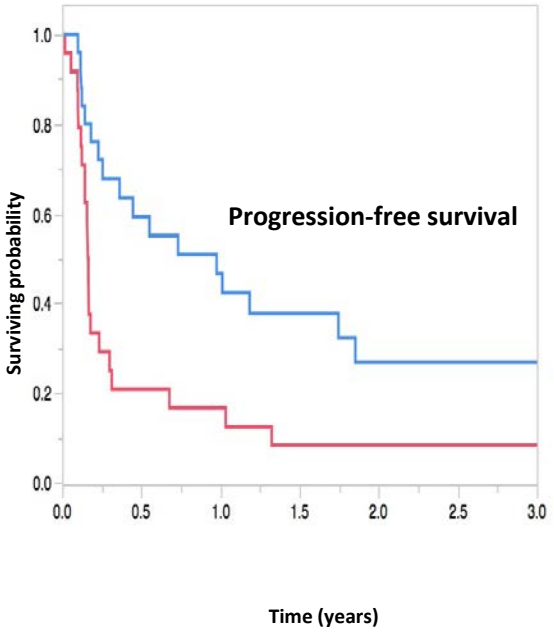
Gibney et al. Lancet Onc. Dec 2016

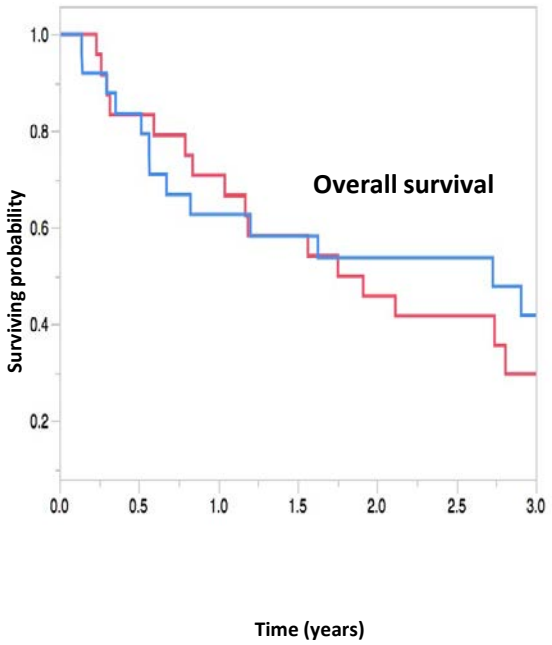
Predictive Value of Measuring Somatic Mutations and Tumor Infiltrating Lymphocytes for PD-1 Axis Therapy in NSCLC

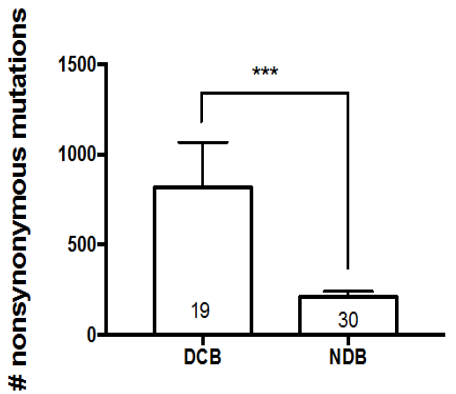
Kurt A. Schalper – IASLC 2016

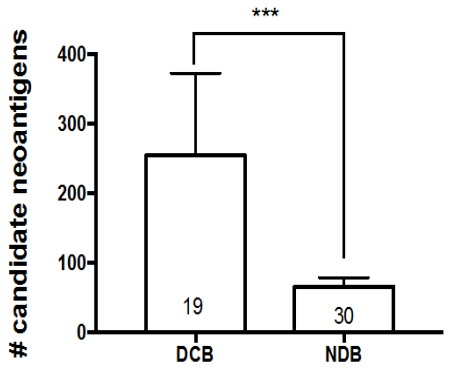
-Pre-treatment FFPE tumor from 49 NSCLC patients treated with PD-1 axis blockers at the Yale Cancer Center between 2009-2014.

-49 Whole exome DNA sequencing: (Mutational load-HLA-typing -Candidate class-I neoantigens)



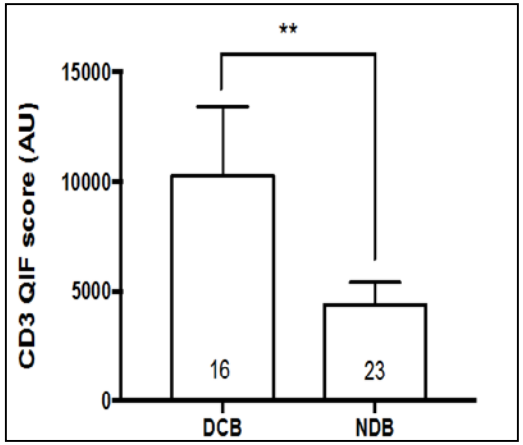


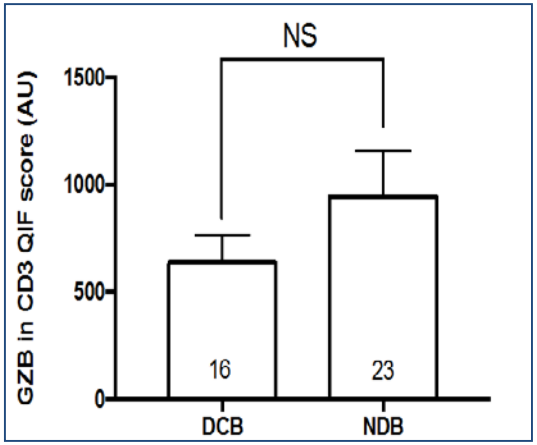


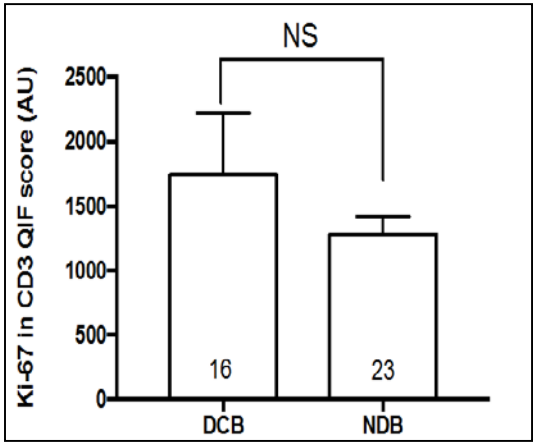


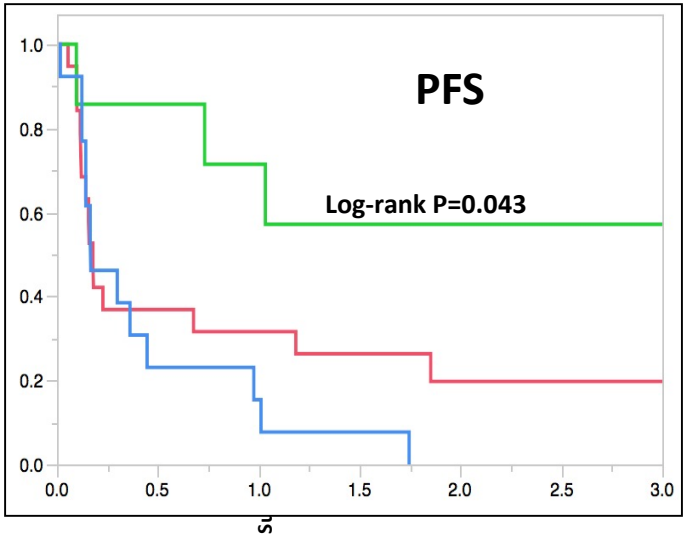
Increased mutational load or candidate class-I neoantigens is significantly associated with durable clinical benefit and PFS in NSCLC pts treated with PD-1 axis blockers.

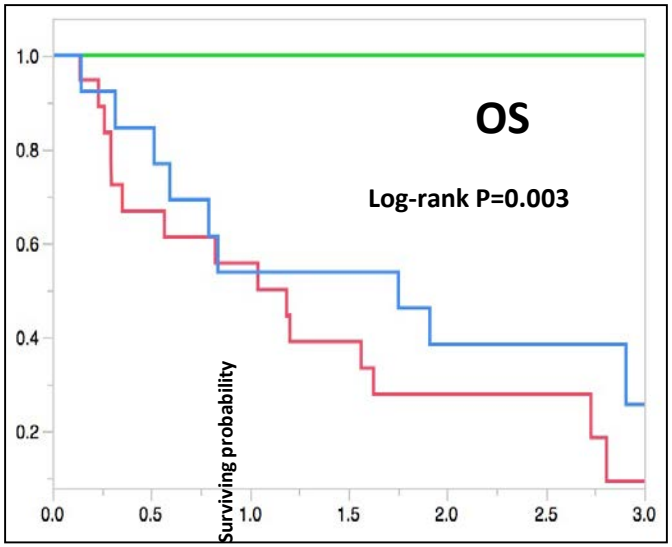
-39 Multiplex quantitative immunofluorescence (QIF): (DAPI-Cytokeratin-Ki-67)

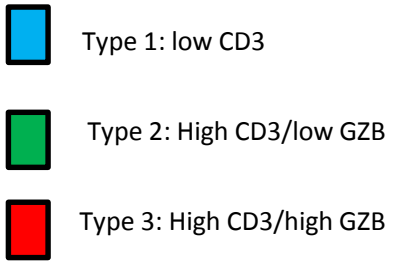






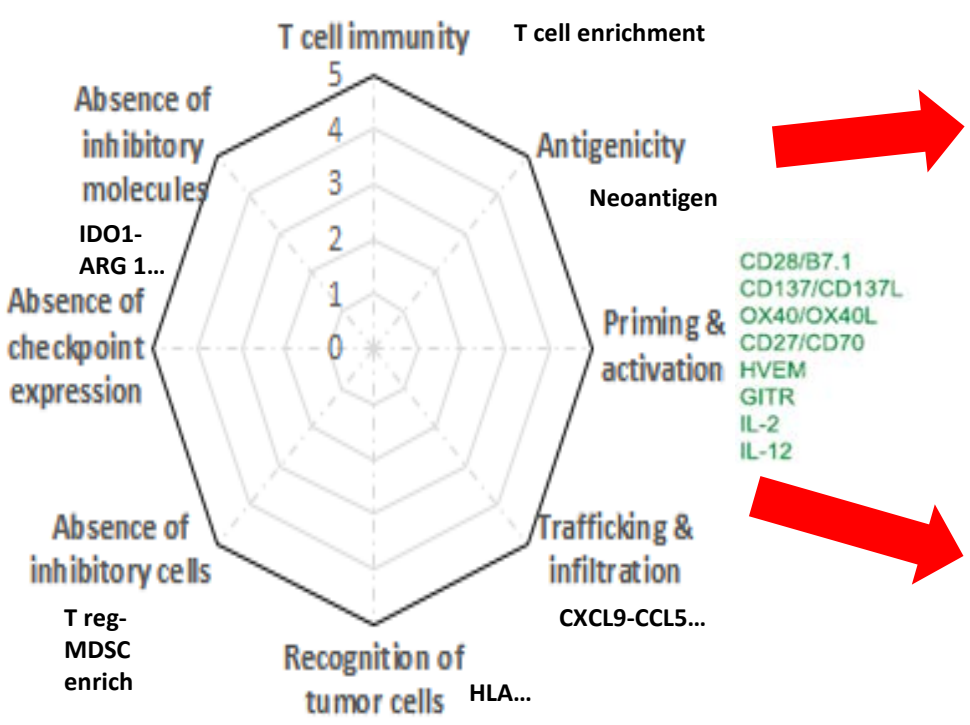


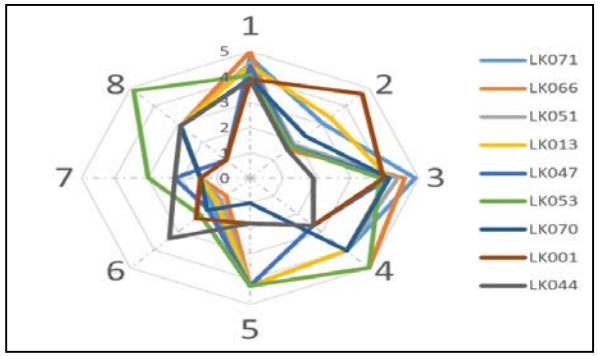




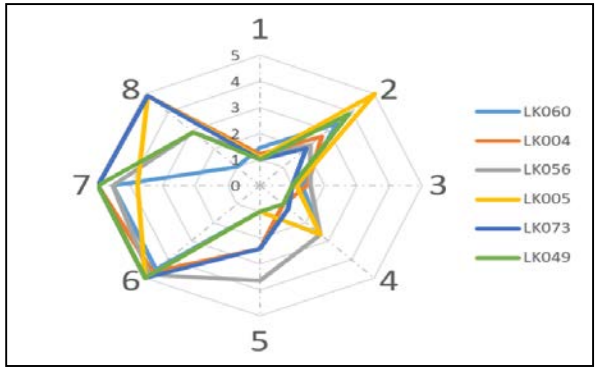
Tumors with high T-cell infiltration but low *in situ* activation/proliferation show the highest clinical benefit (e.g. Type 2 or "dormant" TIL phenotype) after PD-1 axis blockade in NSCLC

Immunogram for Cancer-Immunity Cycle towards Personalized Immunotherapy of Lung Cancer- IASLC 2016 Takahiro Karasaki





T cell **rich**



T cell **poor**

Immunogram for the Cancer-Immunity Cycle using NGS data

-can **visualize** the landscape of **cancer-immunity interaction** in each patient.
-can translate cumbersome **omics data** into easily comprehensible **"report cards"** of immune status for clinicians.
-can be used as an **integrated biomarker.**
- may thus become a valuable resource for **personalized immunotherapy.**

CONCLUSIONS

We are at the beginning of the IO revolution in thoracic oncology

There are no patients who can be excluded from immunotherapy based on predictive markers of efficacy

The category of patients with mutations (EGFR/ALK) is the one that is less likely to get a benefit

Pdl1 should be considered as an indicator of the likelihood of response to immunotherapy in NSCLC not squamous in 2° line.

Patients with aggressive disease (no response to chemotherapy and rapid progression) and PDL1 <1% are those that are less likely to respond

Personalized strategies for IO therapeutics will be developed

How we can valuate and monitor efficacy of immunotherapy ?

Assessing Immunotherapy response

The response kinetics of I-O are more heterogeneous than conventional anti-cancer therapies

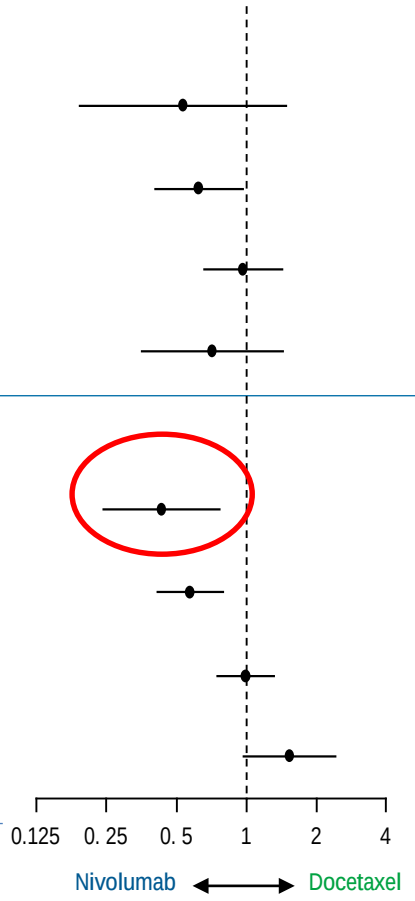
The degree of immune response and the amount of time needed to mount an effective immune response can vary between patients

Response to ICP are generally faster than the response to anti CTLA4

Responses to immunotherapy may become apparent only after a period of pseudo-progression, in which immune cell infiltration is manifest as new lesions or growth of old lesions that are mistaken for tumor progression

The response matter ?
Treatment Effect on OS by Best Overall Response

Best overall response	Nivolumab, n	Median OS, mo (95% CI)	Docetaxel, n	Median OS, mo (95% CI)	Unstratified HR (95% CI)
CheckMate 017 (SQ NSCLC)					
Complete/partial response[a]	27	NR (30.5, NR)	12	NR (5.4, NR)	0.53 (0.19, 1.49)
Stable disease	39	11.9 (9.2, 17.1)	47	8.4 (6.0, 11.1)	0.62 (0.40, 0.97)
Progressive disease	56	4.9 (4.2, 5.7)	48	5.3 (4.4, 7.3)	0.96 (0.65, 1.43)
Response not available[b]	13	2.7 (0.5, 5.8)	30	1.5 (1.0, 2.6)	0.71 (0.35, 1.44)
CheckMate 057 (non-SQ NSCLC)					
Complete/partial response[a]	56	NR (25.5, NR)	36	19.2 (14.5, 23.3)	0.43 (0.24, 0.77)
Stable disease	74	19.9 (14.7, 24.4)	122	11.9 (10.6, 13.9)	0.57 (0.41, 0.80)
Progressive disease	129	6.9 (5.3, 9.2)	85	6.0 (5.0, 7.5)	0.99 (0.74, 1.32)
Response not available[b]	33	1.5 (1.0, 1.9)	47	2.1 (1.8, 4.8)	1.52 (0.96, 2.43)



[a]Confirmed complete and partial responses per RECIST v1.1 criteria, as assessed by the investigator
[b]Includes death prior to disease assessment, never treated, early discontinuation due to toxicity, and other
NR = not reached; RECIST = Response Evaluation Criteria in Solid Tumors

Objective response rate CH. 057 : RECIST 1.1

	Nivolumab (n=292)	Docetaxel (n=290)
Objective response rate[a] (95% CI)	**19%** (15, 24)	**12%** (9, 17)
Odds ratio (95% CI)	1.7 (1.1, 2.6)	
***P* value[a]**	0.02	
Best overall response, %		
Complete response	1	<1
Partial response	18	12
Stable disease	25	42
Progressive disease	44	29
Unable to determine	11	16
Median time to response, months (range)[b,c]	2.1 (1.2, 8.6)	2.6 (1.4, 6.3)
Median duration of response, months (range)[b,d]	**17.2** (1.8, 22.6+)	**5.6** (1.2+, 15.2+)
Ongoing response, %[e]	52	14

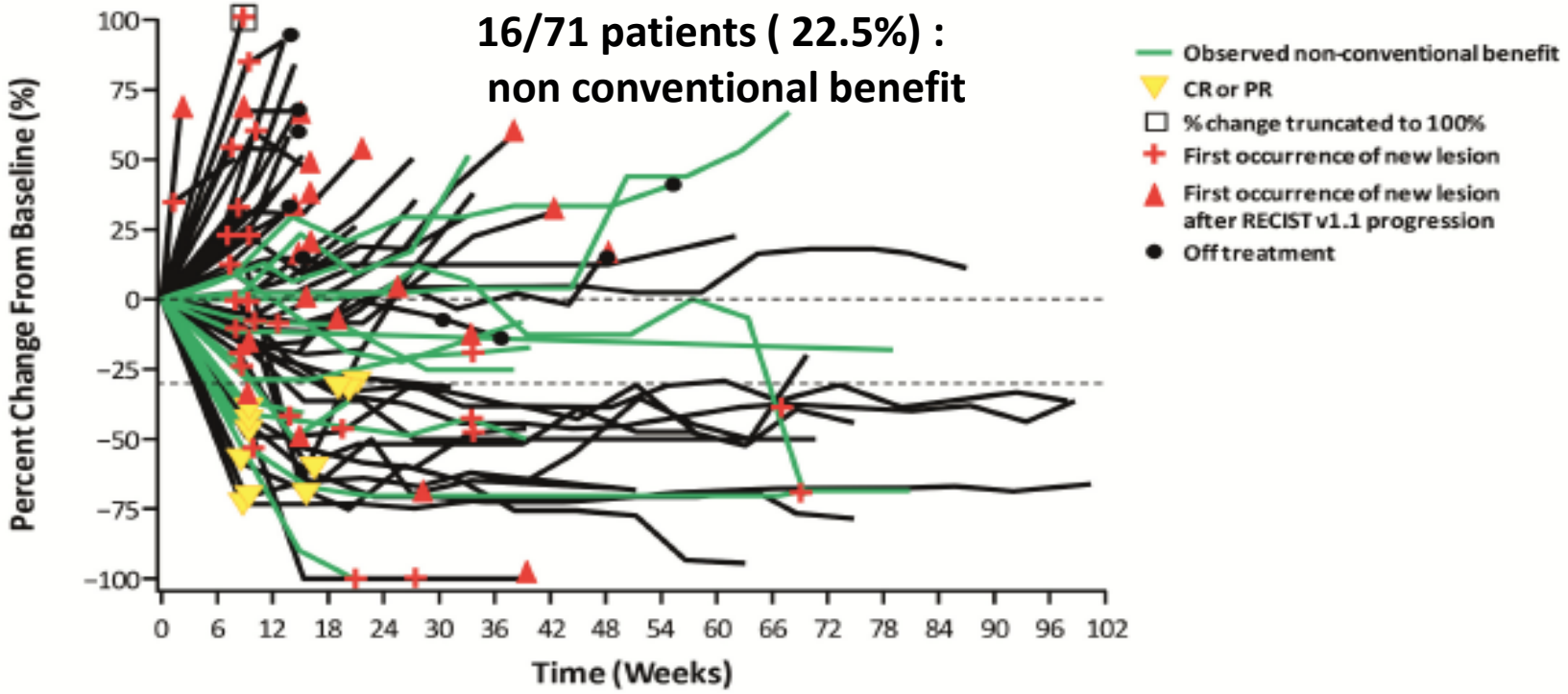
- **71 (24%) patients on nivolumab were treated beyond RECIST v1.1–defined progression**
- **<u>Non-conventional benefit was observed in 16 patients- 5.4%</u> (not included in best overall response)**
- **Med OS : 16.9 months (6.5 - 22.2)**

Non conventional benefit : reduction in size or number (or both) of target with simultaneous appareance of new lesion or a PD followed by either tumor reduction or no further PD for at least 2 tumor assessments

[a]Responses assessed according to RECIST, version 1.1. Adapted from Borghaei H, et al. *N Engl J Med*. 2015.

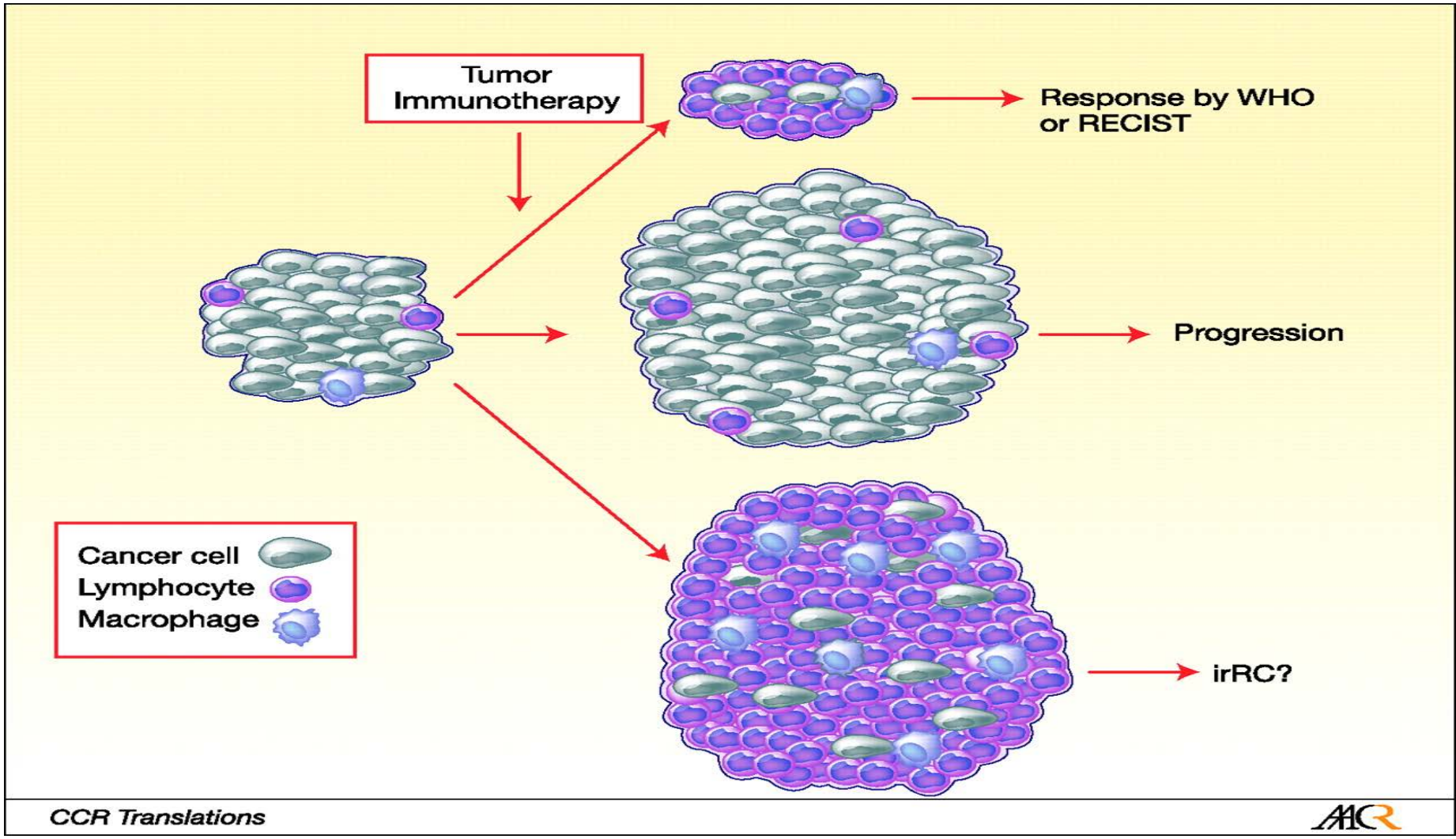
Checkmate 057

Figure S6. Change in Target Lesions from Baseline in Patients Treated with Nivolumab After Initial RECIST v1.1-defined Progression.



Data are based on a March 18, 2015 database lock. Assessments are per Investigator using RECIST v1.1 criteria, confirmation of response required. Patients treated beyond progression are defined as patients with last available dose after RECIST v1.1 progression date.

Pseudoprogression



Antoni Ribas et al. Clin Cancer Res 2009;15:7116-7118

Response criteria summarised

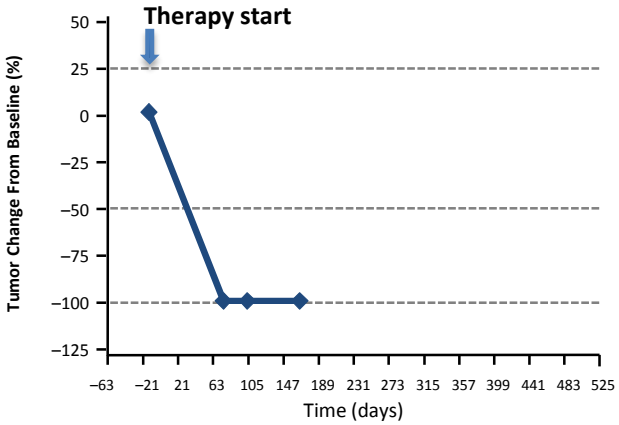
	RECIST 1.1	irRC (+ unidimensional variant)	"irRECIST /irRECIST1.1" variants
Bi/unidimen.?	Unidimensional	**Bidimensional**	Unidimensional
N Target	5	**15; (≥5 × 5mm)**	10 / 5 (≥10mm/ ≥10mm (15 for nodes))
New target lesions added to sum or measures (SOM)?	No **PD for new lesion**	(≥5 × 5mm); **Yes** - does not automatically define PD	(RECIST or RECIST 1.1 rules) **Yes**
How many ?	NA	10 visceral, 5 cutaneous	10 / 5 (RECIST 1.1 rules)
Definition of progression (PD)	≥ 20% ↑ compared to nadir (≥ 5mm ↑)	≥ 25% ↑ compared to baseline (BL), nadir/**reset BL**	≥ 20% ↑ compared to nadir (≥ 5mm ↑)
Confirmation ?	No	Yes, required	Yes, recommended

*If an increase in tumor burden is observed at the first scheduled assessment, the baseline is reset to the value observed at the first assessment.

Wolchok et al. Clin Cancer Res 2009
Hodi et al JCO 2016
www.eortc.org in Press the Lancet Oncology

Potential response patterns to I-O agents

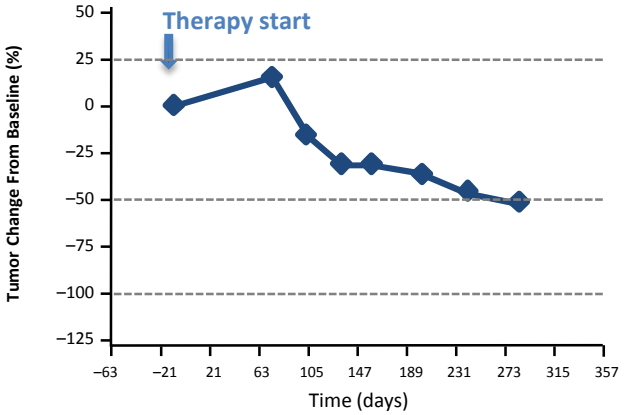
Response in baseline lesions:
Typically seen with chemotherapy, but also I-O therapies.
Captured by existing RECIST and WHO criteria



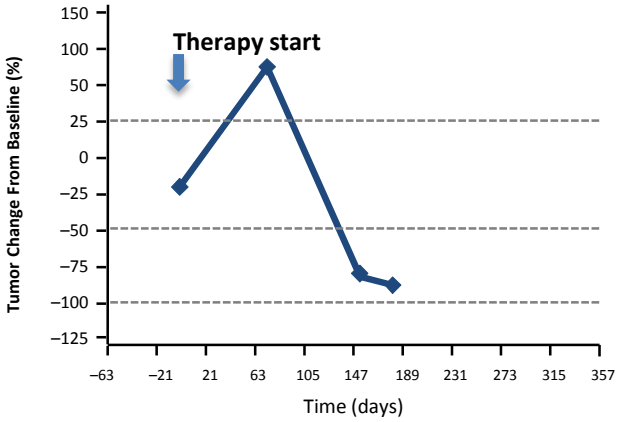
Thresholds for response or PD (RECIST)

Graphs for illustrative purposes showing responses to ipilimumab in advanced melanoma

SD: Slow, steady decline in tumor volume seen with chemotherapy, targeted, and I-O therapies.
Captured by existing RECIST and WHO criteria

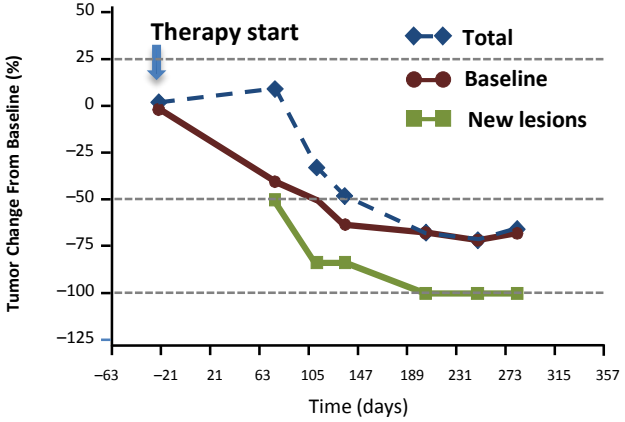


Response after initial increase in tumor volume.
Novel and specific to I-O therapy
(RECIST or WHO criteria may not be appropriate to assess)

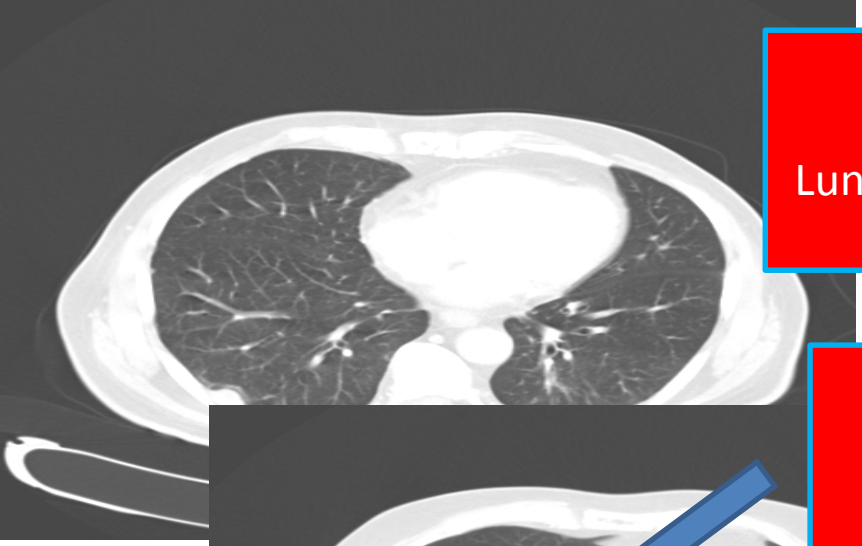


Atypical responses

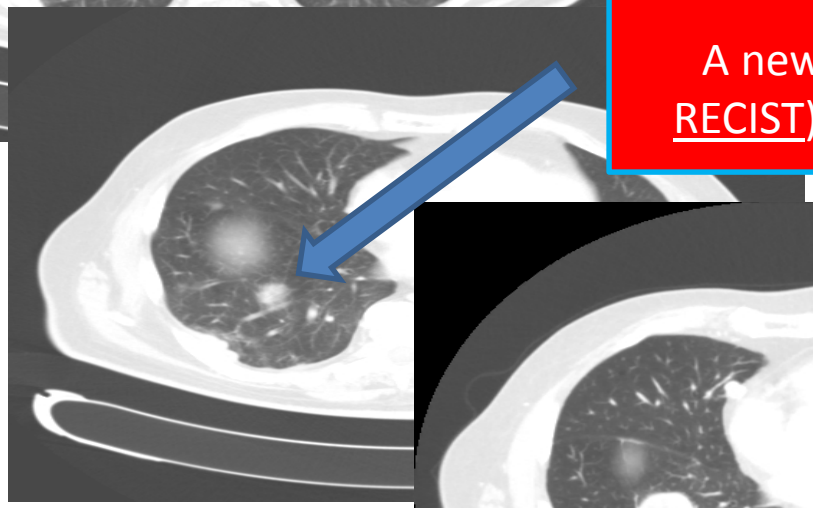
Reduction in tumor burden after appearance of new lesions.
Novel and specific to I-O therapy
(RECIST or WHO criteria may not be appropriate to assess)



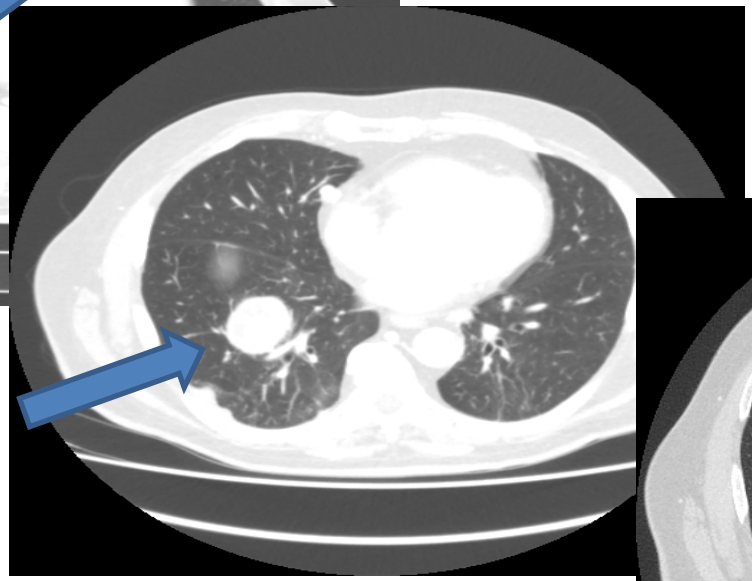
Figures adapted from Wolchok JD et al. *Clin Cancer Res*. 2009;15:7412–7420; Hoos A et al. *Ann Oncol*. 2012;23(suppl 8):viii47–viii52.



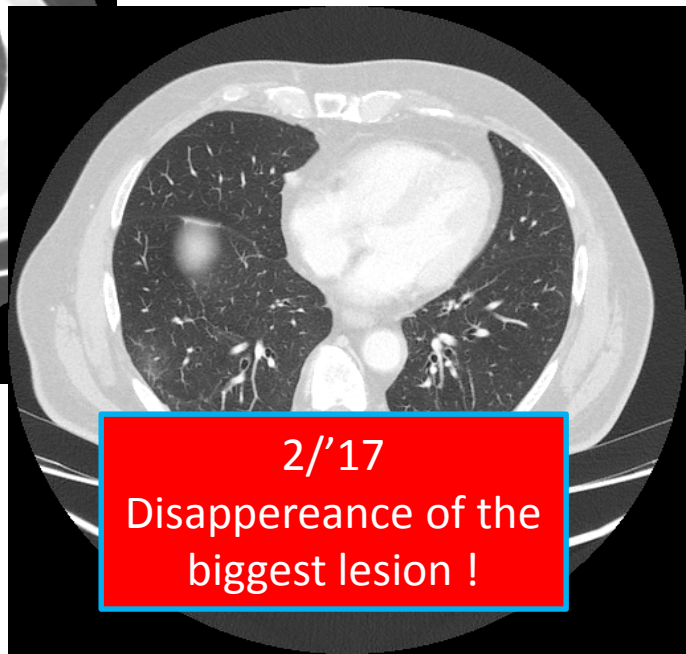
2/’16
Starting Nivo.
Lung metastasis from renal cancer



6/’16
A new lesion in LIS (PD for RECIST) . Stable other lesions.



10/’16
Increase in tumor volume
Improve clinical conditions
Continue Nivo



2/’17
Disappereance of the biggest lesion !

Differentiating a real PD from a Pseudo progression

	REAL PD	PSEUDO PD
PS	WORSEN	MAY IMPROVE
SYMPTOMS	WORSEN	MAY GET BETTER
BIOPSY	TUMOR GROWTH	T CELL INFILTRATION

Pseudoprogression NSCLC

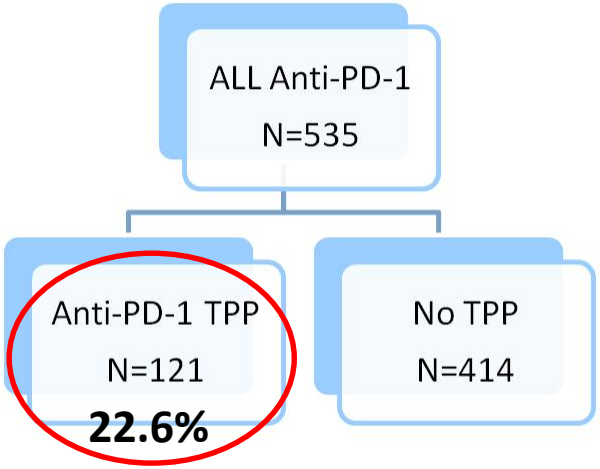
Methods

- Three multi-center clinical trials submitted to FDA evaluating anti-PD-1 monotherapy in 535 patients for the treatment of patients with mNSCLC who progressed after initial therapy were pooled.
- Patients imaged every 6 weeks after 1st scan and allowed to receive TPP with anti-PD-1 if in the opinion of the investigator,
  - Patient not experiencing rapid disease progression
  - Investigator determined clinical benefit received
  - Had stable performance status and drug tolerated
  - Written informed consent obtained

Pseudoprogression NSCLC

Methods cont'd

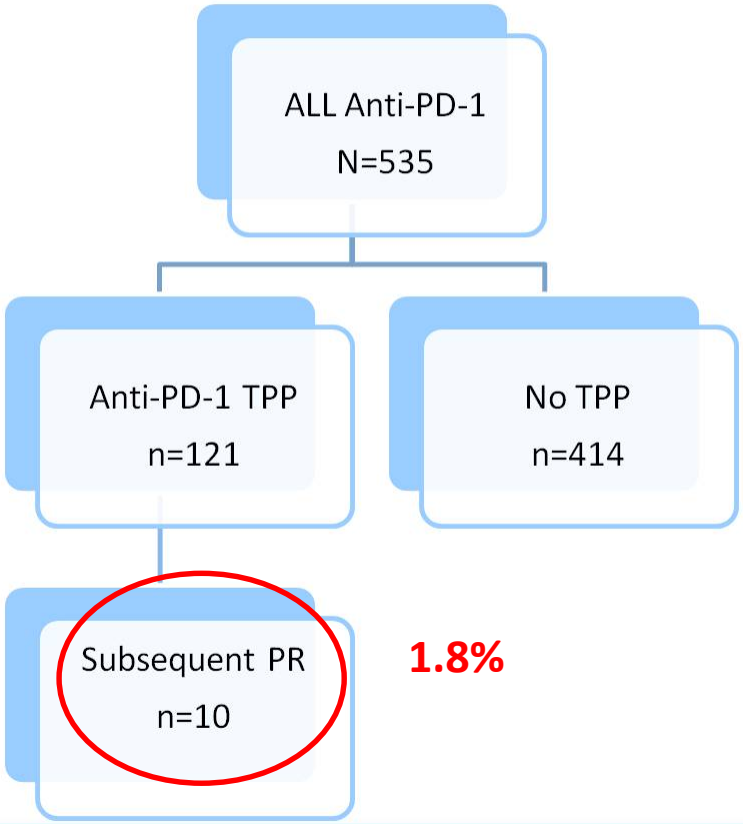
- 121 anti-PD-1-treated patients with TPP from the pooled trials identified
- Changes in tumor burden from radiographic tumor measurement data *following* RECIST-defined progression evaluated.
- Objective in this group was to determine
  - Demographic and disease characteristics
  - Best overall response (BoR) per RECIST prior to conventional progression
  - Cause of 1st progression per RECIST
  - At time of receiving TPP, how many patients received benefit as defined by a ≥ 30% decrease from baseline in the sum of the longest diameter (SLD) of target lesions (TL)



Pseudoprogression NSCLC

Results

- Ten patients (8.3%) receiving TPP experienced additional tumor shrinkage defined as a subsequent ≥ 30% decrease in the SLD of TLs compared to baseline.
- BoRs prior to TPP were PR: 4; SD 2; PD: 4 patients



TGR CAN BE A NEW RESPONSE CRITERIA ?

Cancer Therapy: Clinical

Clinical Cancer Research

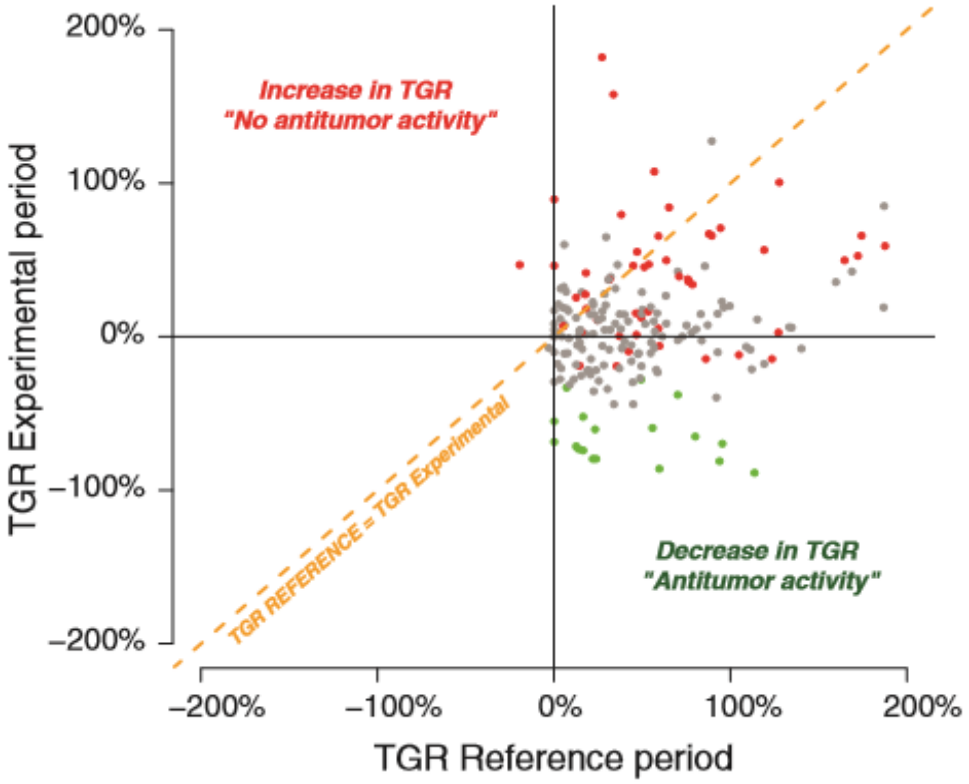
2014

Tumor Growth Rate Is an Early Indicator of Antitumor Drug Activity in Phase I Clinical Trials

Charles Ferté[1,3,6,7], Marianna Fernandez[3], Antoine Hollebecque[1,3], Serge Koscielny[2,3], Antonin Levy[3,5], Christophe Massard[1,3,6], Rastislav Balheda[1,3], Brian Bot[7], Carlos Gomez-Roca[3], Clarisse Dromain[4], Samy Ammari[4], and Jean-Charles Soria[1,3,6]

253patients prospectively treated in 20 phase I trials. TGR was computed during the pretreatment period (reference) and the experimental period.

TGR allows for an earlier and more precise detection of signs of antitumor activity as compared with the RECIST criteria
It is independently associated with PFS



● : PD Recist ● : RP Recist
● : SD Recist

Immune Checkpoint inhibitors induce paradoxical progression in a subset of Non-Small Cell Lung Cancer (NSCLC).

J. Lahmar[1]*, L. Mezquita[1], S. Koscielny[2], F. Facchinetti[1], M.V. Bluthgen[1], J. Adam[3], A. Gazzah[4], J. Remon[1], D. Planchard[1], J-C. Soria[4], C. Caramella[5], B. Besse[1]

[1]Department of Medical Oncology, [2]Department of Biostatistics, [3]Department of Pathology, [4] Drug Development Department, [5]Department of Radiology. Gustave Roussy - 114 rue Edouard Vaillant - 94805 Villejuif – France

*jihene.lahmar-bach-hambe@gustaveroussy.fr

1222P

BACKGROUND

- Immune Checkpoint inhibitors (IC) represent a major step forward in treating advanced NSCLC by improving survival and clinical outcomes.
- In patients (pts) with non-squamous NSCLC with negative PD-L1 tumors, IC increases the risk of early death compared to docetaxel. Risks later reverse for the two study groups to increasingly favor IC, as shown in the phase III study Checkmate 057.

OBJECTIVE

We used Tumor Growth Rate (TGR) estimations to identify a subset of patients in which IC could accelerate tumor progression, leading to early death.

PATIENTS AND METHODS

- We performed a clinical and radiological retrospective case study of all NSCLC patients treated by IC in a single institution between Dec 12 and Feb 18.
- CT scan were centrally reviewed by a senior radiologist and assessed according to RECIST 1.1 criteria.
- We calculated TGR at baseline of IC (baseline CTscan (n) vs. n-1 CTscan) and TGR during IC (n+2 CTscan vs. n+1 CTscan).
- We further estimated the difference (deltaTGR) between TGR during IC and TGR at baseline.
  - deltaTGR<0 means that the treatment slows down tumor progression whereas
  - deltaTGR>0 means that the treatment speeds up tumor growth.

METHOD

TGR Estimation

- Tumor Growth Rate (TGR) is calculated using 2 CT scans and the time interval between the 2 exams.
- Let D0 and D1 be the RECIST sum of tumor diameters at times t0 and t1, respectively.
- $TGR = 3(\ln(D1/D0))/(t1-t0)$
  ln represents natural logarithms.
  (t1-t0) is the time between evaluations in months,
- TGR is expressed as a %change in tumor volume per month
- $TGR\% = 100\ (\exp(TGR)-1)$

Figure 1.Hypothetical representation of TGR across treatment periods

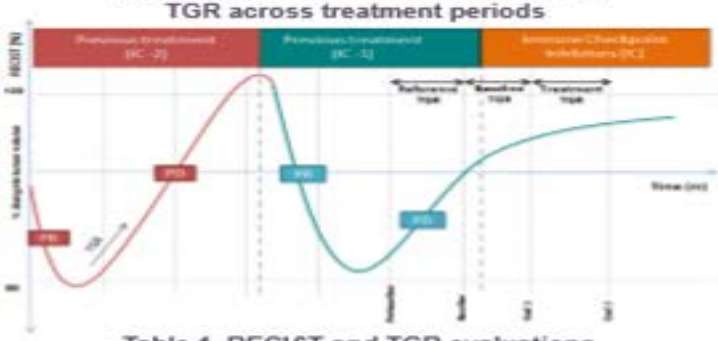


Table 1. RECIST and TGR evaluations

Variable	N (%) or median (min; max)
RECIST	
Complete response	3 (3%)
Partial response	22 (25%)
Stable disease	31 (35%)
Progression	30 (34%)
Pseudo Progression	3(3%)
Baseline TGR% (IC start period)	
Median (range)	40% (-53% - >200%)
Regressing tumors (TGR<0)	12 (13%)
Treatment TGR% (IC period)	
Median (range)	0% (-98% - 188%)
Regressing tumors (TGR<0)	41 (46%)

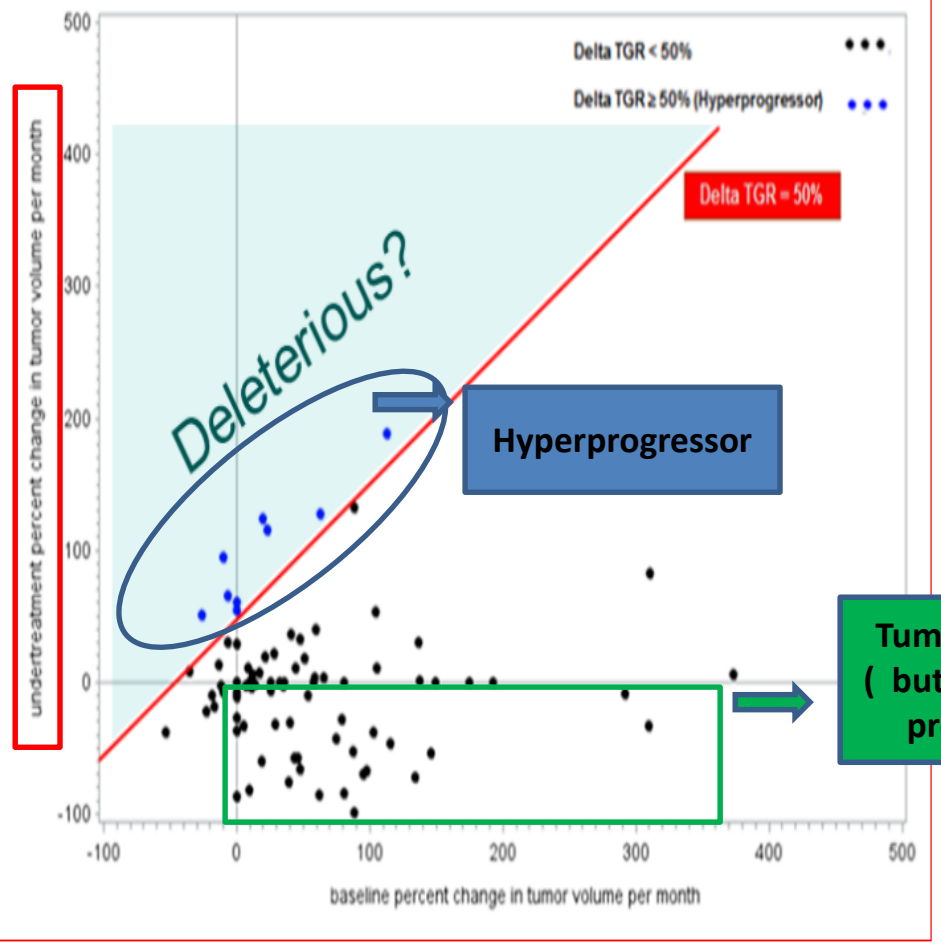
PATIENTS

Table 2. Patient characteristics at diagnosis

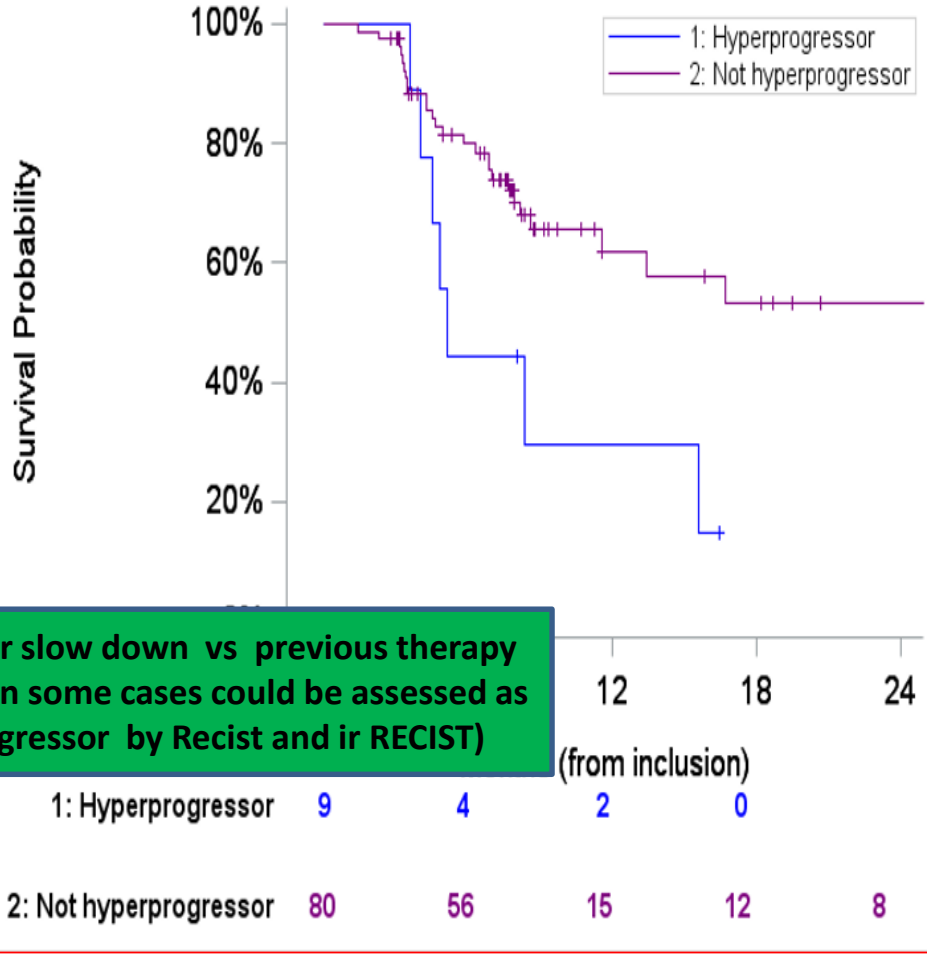
	Frequency n=89 (%)
Age (year)	
Median (range)	62 (41-78)
Sex	
Female	37 (42%)
Male	52 (58%)
Smoking status	
Never smoker	13 (15%)
Former smoker	43 (48%)
Current smoker	29 (33%)
Stage	
IIIb	28 (31%)
IV	61 (69%)
Histology	
Adenocarcinoma	62 (70%)
Squamous cell	21 (24%)
Other	6 (6%)
PD-L1 expression	
Positive	7 (22%)
Negative	25 (78%)
Not monitored	57
IC Treatment	
Nivolumab	52 (58%)
Pembrolizumab	25 (28%)
Atezolizumab	12 (13%)

References:
- Gomez-Roca C et al. Eur J Cancer 47: 2512–6 (2011)
- Brahmer J et al. N Eng J Med 373(2):123-35 (2015)
- Borghaei H et al. N Eng J Med 373(17):1627-39 (2015)

Percent change in tumor volume: undertreatment vs. Baseline



Overall survival according to DeltaTGR>50%



Tumor slow down vs previous therapy (but in some cases could be assessed as progressor by Recist and ir RECIST)

- **Paradoxical Progressive Disease (PPD) was defined as deltaTGR>50%**, corresponding to an absolute increase in TGR greater than 50% per month. As an example: a TGR of 10% per month before IC initiation had to increase to at least 60% per month after IC initiation.
- Among the 20 patients with deltaTGR>0, 9 had paradoxical progressive disease. Characteristics (age, sex, smoking status, pathology, number of previous lines, PD-L1 status) of the 9 patients were not different from others.
- Only one patient among the "hyper progressors " had pseudo progression.

CONCLUSIONS

RECIST 1.1 are the response criteria used in all the immunotherapy trails and are actually our standard; however they may not always adequately capture the unique patterns of response of ICK

Although PSPD is now well described, it remains unusual (around 5%); it is well captured only by immuno- relater response criteria.

Treatment past RECIST 1.1 progression should only be considered in carefully selected scenarios, when the patient is stable (or improving) symptomatically and where there is a short period before reassessment.

In the future it will be possible to quantify the differences in outcome estimation between RECIST 1.1 and iRECIST

TGR could be a new response criteria for ICK but needs to be validated

Grazie per l’ attenzione

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