SESTA SESSIONE
LE NUOVE STRATEGIE ANTITUMORALI:
IMMUNOTARGET THERAPY

Risultati e prospettive nel NSCLC

PD-1 and PD-L1 inhibitors

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Disclosures

- Advisory Boards/Honoraria/Consultant for:
  - Eli-Lilly, Boehringer Ing.

- Research Support / Grants from:
  - E.S.M.O (European Society for Medical Oncology)

Targeting the immune system, not the tumor itself
A paradigm shift

CANCER IMMUNOSURVEILLANCE: WHAT HAPPENS IN NSCLC?

- Evidence of immunosuppressive microenvironment and **immunosurveillance evasion** in lung cancer:
  - increase of functionally Treg cells
  - increase of functionally immunosuppressive cytokines

Woo EY et al, J Immunol 2002

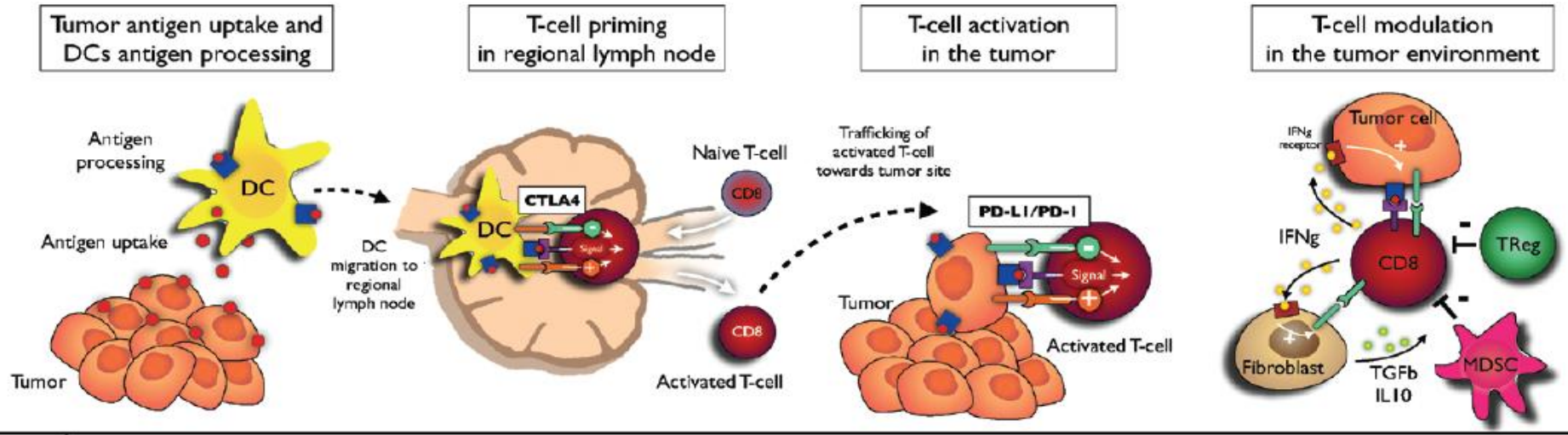
- The magnitude of immune response to lung tumors **correlates with patient outcome**

Al-Shibli et al, Clin Cancer Res 2008
Petersen et al, Cancer 2006

- **Prognostic** immune markers in tumor microenvironment and peripheral blood; genes involved in cancer immunity and inflammation and correlated with recurrence

Suzuki K et al, Clin Cancer Res 2011

Arnessing the immune system against cancer: strategies in NSCLC

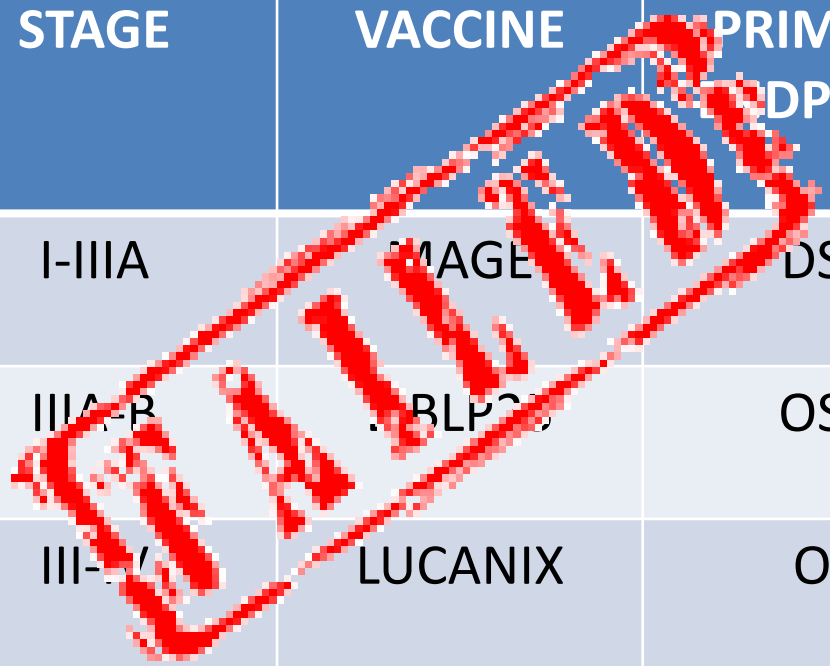


immune system modulation in NSCLC	> down-regulation of MHC-I		> up-regulation of PD-L1 through activation of PI3K/Akt ? MAPK ? Alk ? > up-regulation of TRegs > up-regulation of MDSCs	> IL-10 and TGFß increased concentration by tumor environment > up-regulation of PD-L1 by IFNg secreted by activated T-cell
immuno modulation by NSCLC drugs	**immunogenic cell death** irradiation **vaccination strategies** MAGE-A3, MUC-1, rHU EGF	**up-regulation of MHC-I** paclitaxel, gemcitabine, erlotinib **DC maturation** paclitaxel, docetaxel, bevacizumab **anti-CTLA4** Ipilimumab, Tremelimumab	**anti-PD-1** MDX-1106, CT-011, MK-3475 **anti-PD-L1** MPDL-3280A, MDX-1105 **up-regulation of PD-L1** paclitaxel, etoposide	**TReg inhibition** cisplatin, paclitaxel, bevacizumab **MDSC inhibition** cisplatin, docetaxel, gemcitabine **down-regulation of PD-L1** by PI3Ki ? MEKi ? Crizotinib ?

Champiat S, J Thorac Oncol 2014

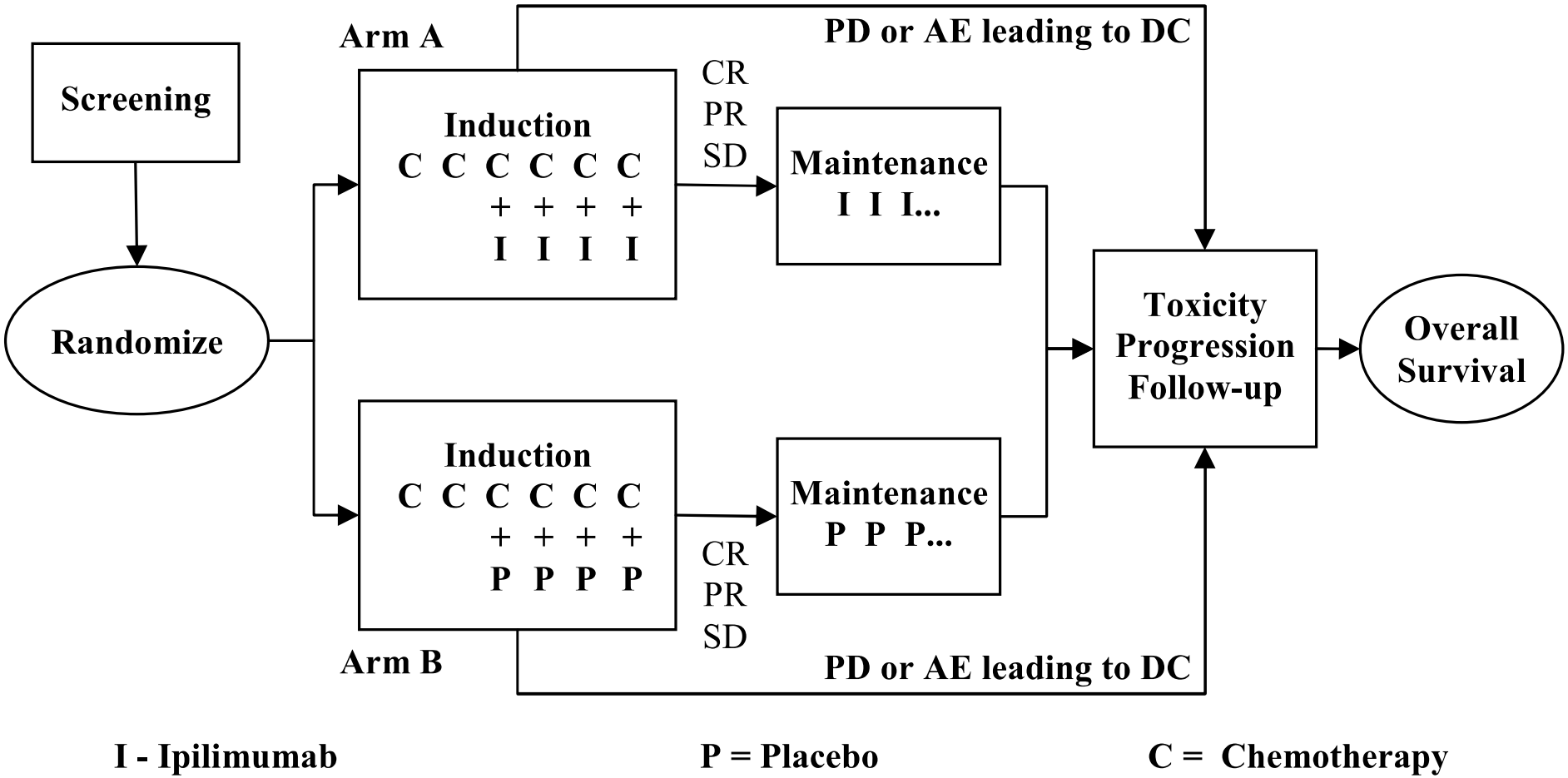
VACCINATION STRATEGIES

PHASE III CLINICAL TRIAL	STAGE	VACCINE	PRIMARY ENDPOINT	RESULTS
MAGRIT	I-IIIA	MAGE	DSF	NEGATIVE
START	IIIA-B	BLP25	OS*	NEGATIVE*
STOP	III-IV	LUCANIX	OS	NEGATIVE



* POSITIVE FOR PATIENTS RECEIVING CONCURRENT CHEMO-RADIOTHERAPY

ANTI-CTLA4 IPILIMUMAB
Ongoing phase III trial design (CA 184104)



I - Ipilimumab P = Placebo C = Chemotherapy

PD-1 and PD-L1 blockade in NSCLC: response across trials with single agents

Table 1. Response rates of PD-1/PD-L1 blockade antibodies used as a monotherapy in advanced NSCLC

Antibody (company)		ORR (RECIST v1.0 or v1.1) All comers		ORR (RECIST v1.0 or v1.1) PD-L1$^+$	
		Untreated	Pretreated	Untreated	Pretreated
PD-1[a]					
Nivolumab (all histologies)	Fully human IgG4	21% ($n = 52$; ref. 60)	17% ($n = 129$; ref. 22)	31% ($n = 26$) ≥5% of tumor cells PD-L1$^+$	15% ($n = 33$)
Nivolumab (squam, ≥2 prior tx)		NA	15% ($n = 117$; ref. 61)	NA ≥5% of tumor cells PD-L1$^+$	24% ($n = 25$)
Pembrolizumab (Merck-MSD)	Humanized IgG4	NA	20% ($n = 194$; ref. 27)	26% ($n = 42$) ≥1% of tumor cells PD-L1$^+$	23%[a]
PD-L1[b]					
BMS-936559 (BMS)	Fully human IgG4	NA	10% ($n = 49$; ref. 62)	NA	
MEDI4736 (AZ/Medimmune)	Fully human engineered IgG1	NA	16% ($n = 58$; ref. 63)	NA PD-L1 threshold undisclosed	25% ($n = 20$)
MPDL3280A (Roche/Genentech)	Fully human IgG4	NA	23% ($n = 53$; ref. 25)	NA ≥1% of tumor immune cells PD-L1$^+$	31% ($n = 26$)
MSB0010718C (Pfizer/Merck Serono)	Human IgG1	NA		NA	

Soria JC, Clin Cancer Res 2015

Good BUT new safety profile

Long lasting tumor response

Clinical benefit in pre-treated and in SQCC

Predictive biomarkers?

NIVOLUMAB

- ✓ Phase I expansion cohort trial (pre-treated)
- ✓ Phase II study (refractory)
- ✓ 2 phase IIIR trials (2L)

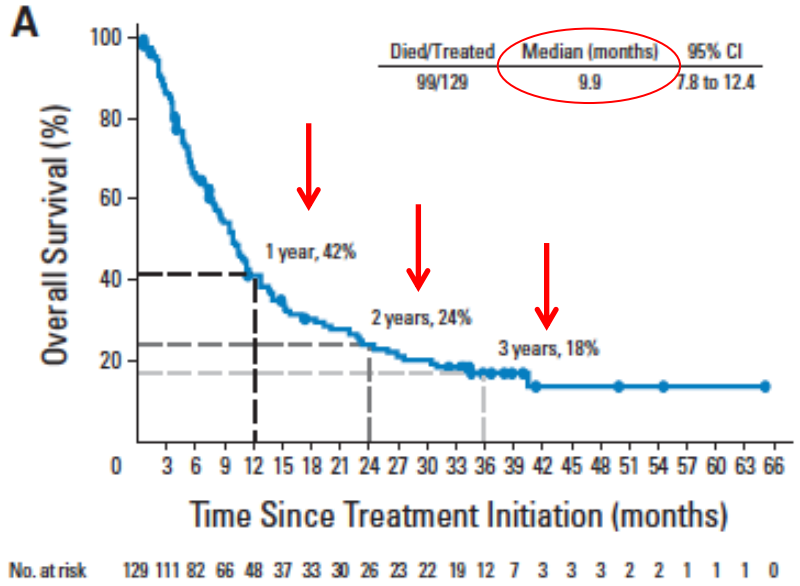
ATEZOLIZUMAB

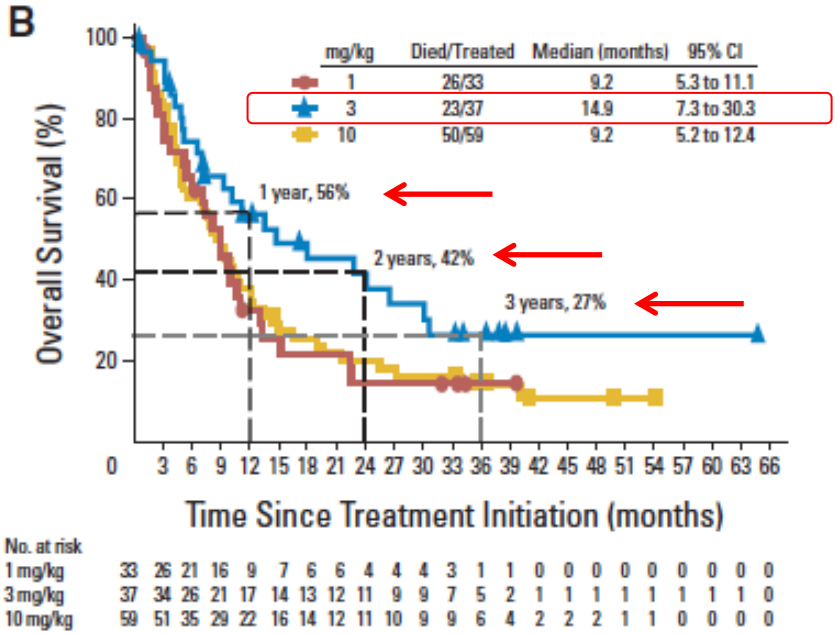
- ✓ Phase IIR trial (2L-3L)

PEMBROLIZUMAB

- ✓ Phase I trial (pretreated)

Nivolumab in pretreated patients: phase I expansion cohort



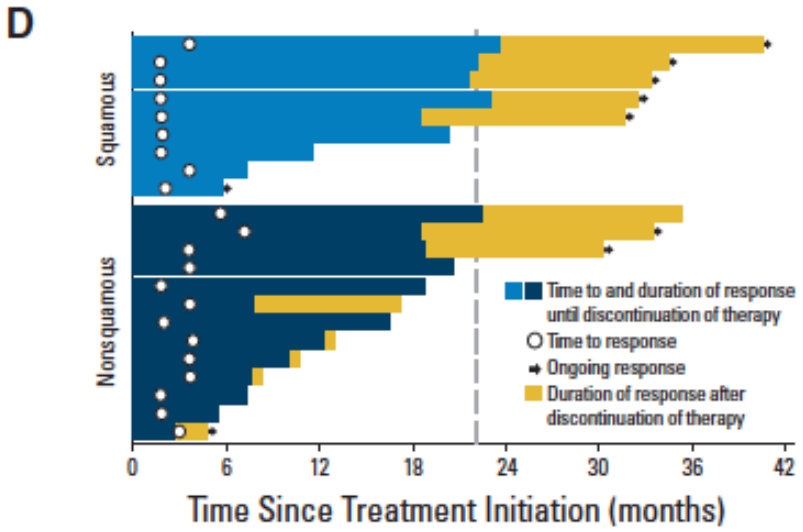


54%: 3 to 5 prior therapies

50% of responders: at the first assessment (**8 weeks**)

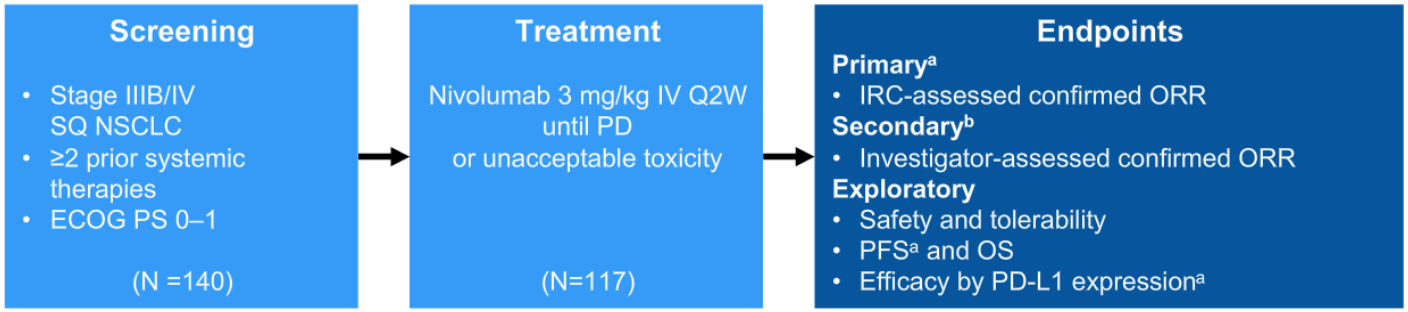
Median **DOR**: **17 months**

41%: responses ongoing (data lock)



Gettinger SN et al, JCO 2015

Nivolumab in refractory NSCLC: CheckMate 063 phase II study



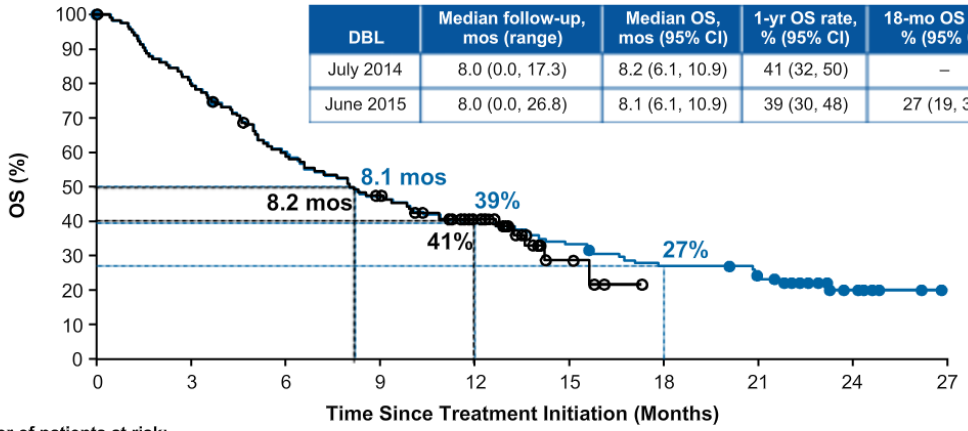
Characteristic	All treated patients (N = 117)
Number of prior systemic regimens, %	
2	35
≥3	65
Best response to most recent prior regimen, %	
Complete or partial response	4
Stable disease	27
Progressive disease	61
Unknown/not reported	8
Time from completion of most recent prior regimen to treatment, %	
<3 months	76
≥3 months	24

Horn L, 16th WCLC

Nivolumab in refractory NSCLC: CheckMate 063 phase II study

Overall Survival (All Treated Patients)

DBL	Median follow-up, mos (range)	Median OS, mos (95% CI)	1-yr OS rate, % (95% CI)	18-mo OS rate, % (95% CI)	Events, n/N
July 2014	8.0 (0.0, 17.3)	8.2 (6.1, 10.9)	41 (32, 50)	–	72/117
June 2015	8.0 (0.0, 26.8)	8.1 (6.1, 10.9)	39 (30, 48)	27 (19, 35)	90/117

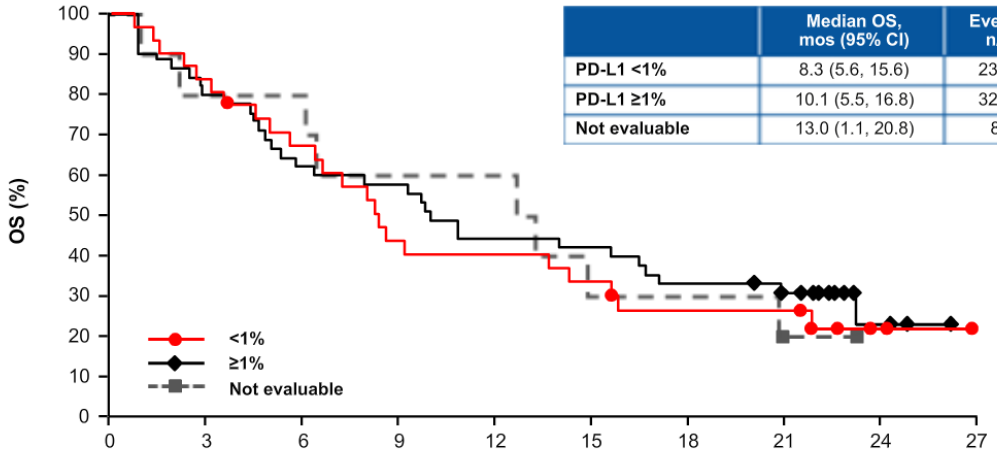


Number of patients at risk:

July 2014 DBL	117	93	68	51	28	5	0	0	0	0
June 2015 DBL	117	93	69	54	45	38	30	24	6	0

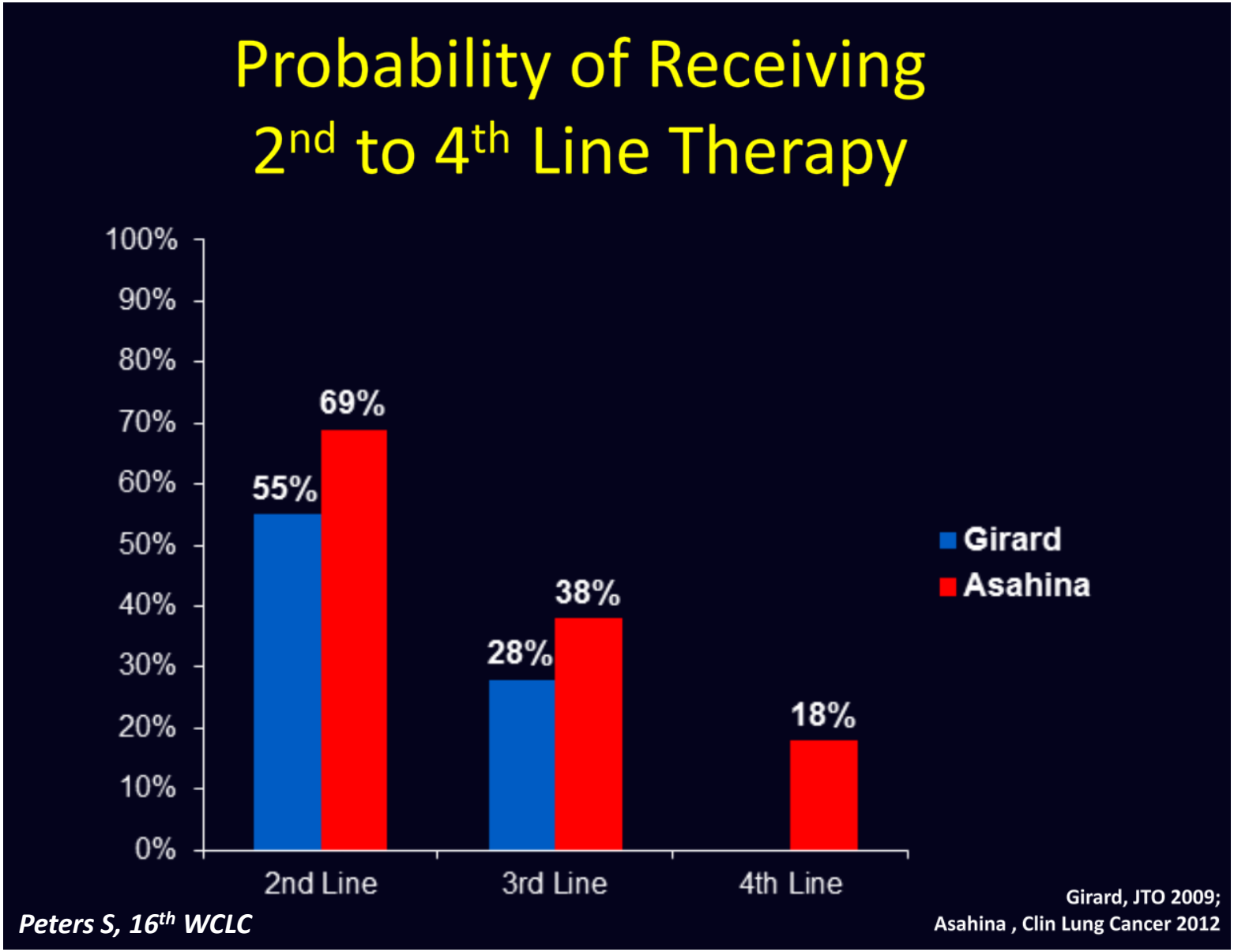
Overall Survival by PD-L1 Expression

	Median OS, mos (95% CI)	Events, n/N
PD-L1 <1%	8.3 (5.6, 15.6)	23/31
PD-L1 ≥1%	10.1 (5.5, 16.8)	32/45
Not evaluable	13.0 (1.1, 20.8)	8/10

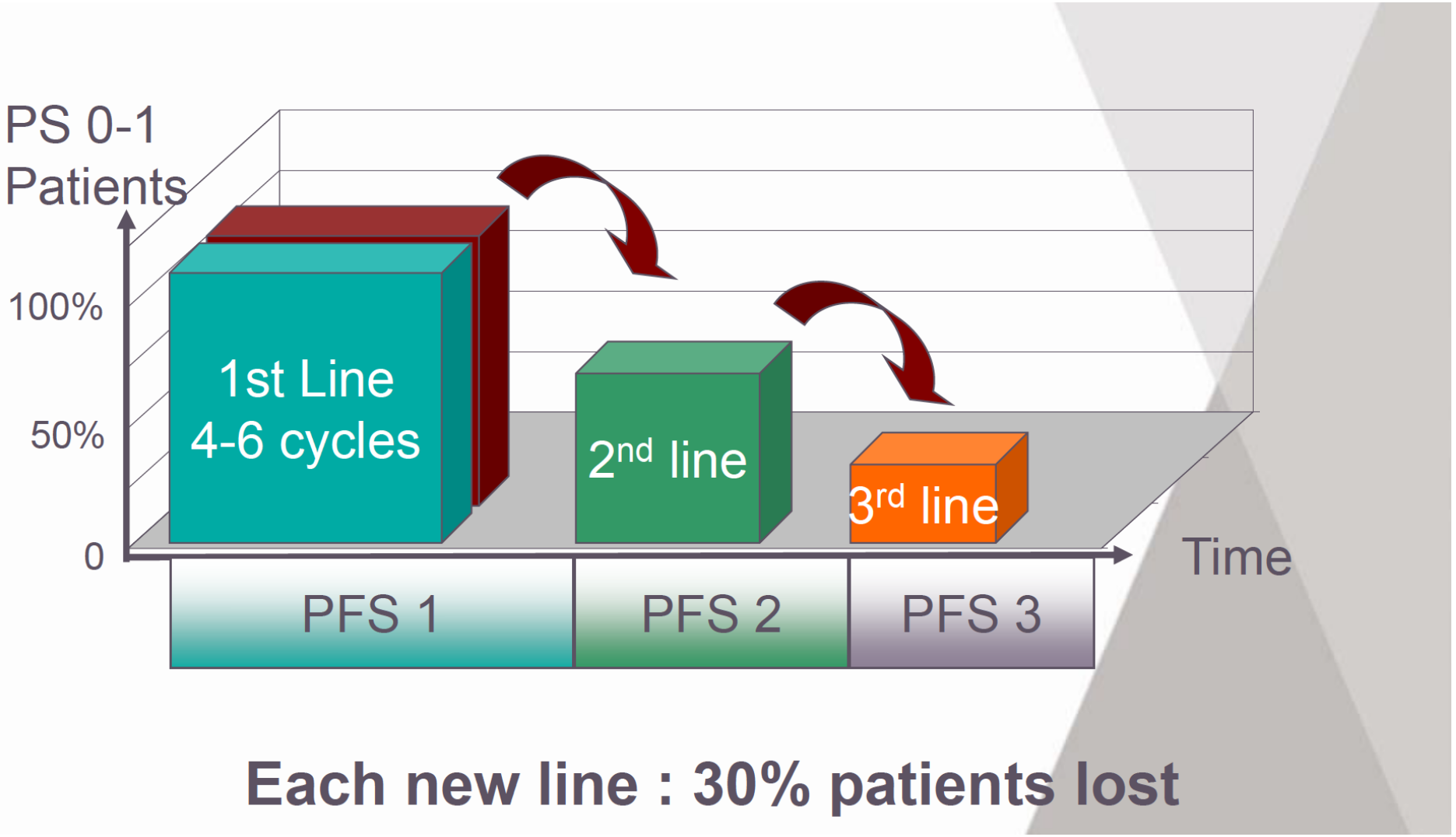


Horn L, 16th WCLC

Clinical relevance of long-term response in NSCLC



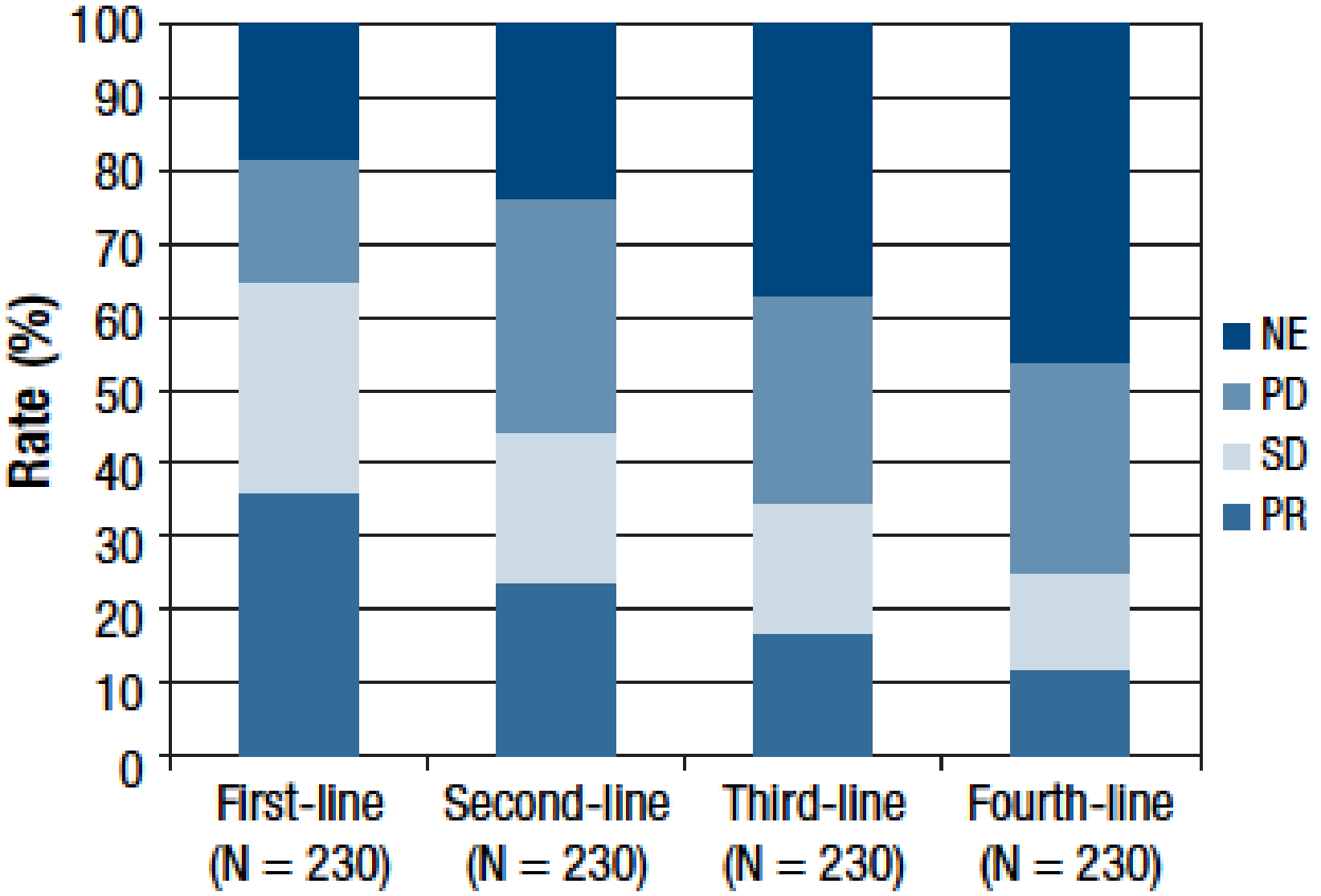
Clinical relevance of long-term response in NSCLC



Each new line : 30% patients lost

Besse B, 2014 ESMO

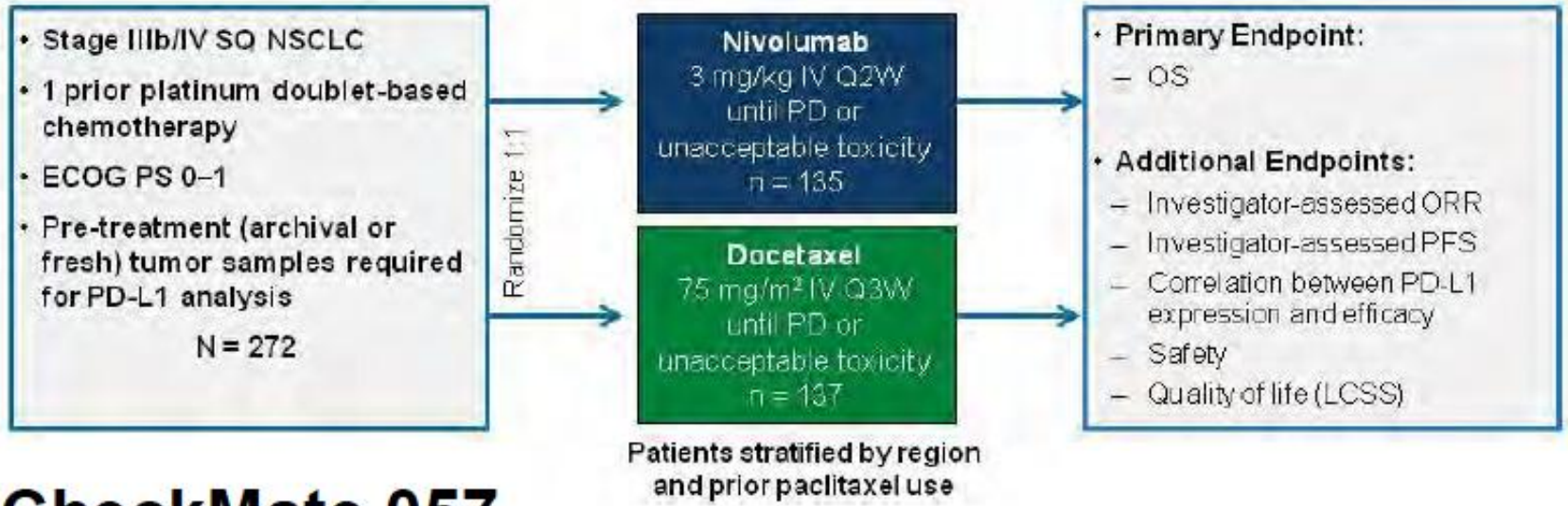
Clinical relevance of long-term response in NSCLC



Asahina H et al, Clin Lung Cancer 2012

Nivolumab: phase III trials in all comers NSCLC, 2L

CheckMate 017



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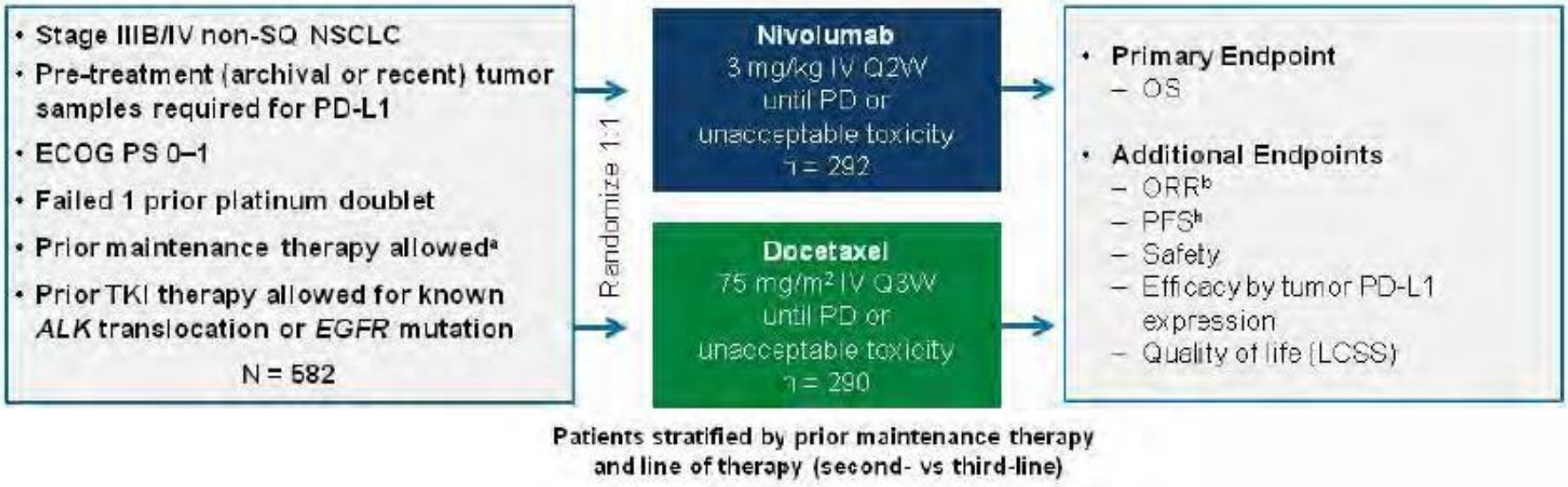
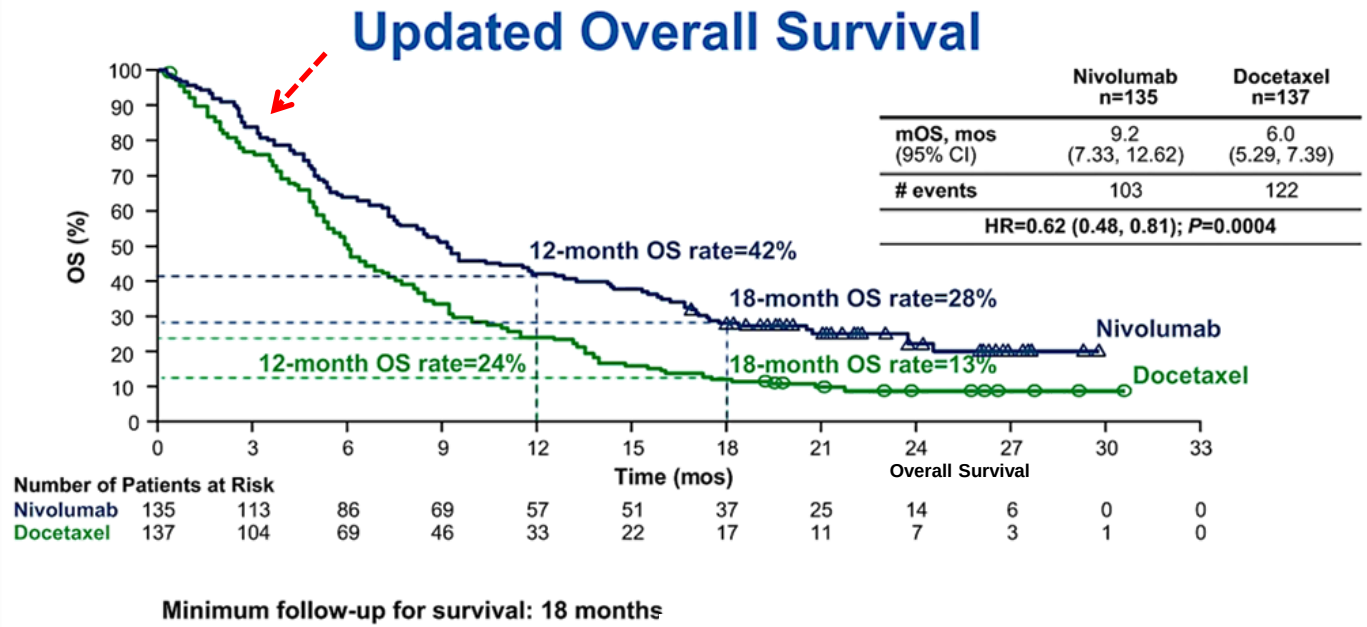
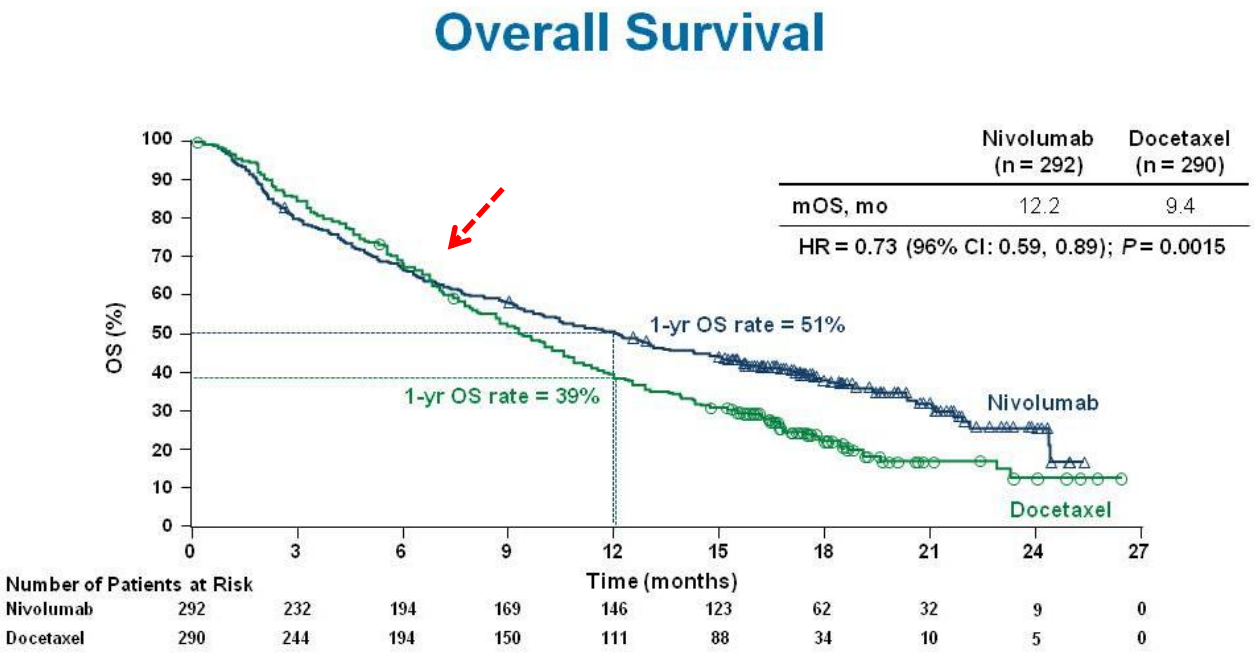


CheckMate 017 SQCC



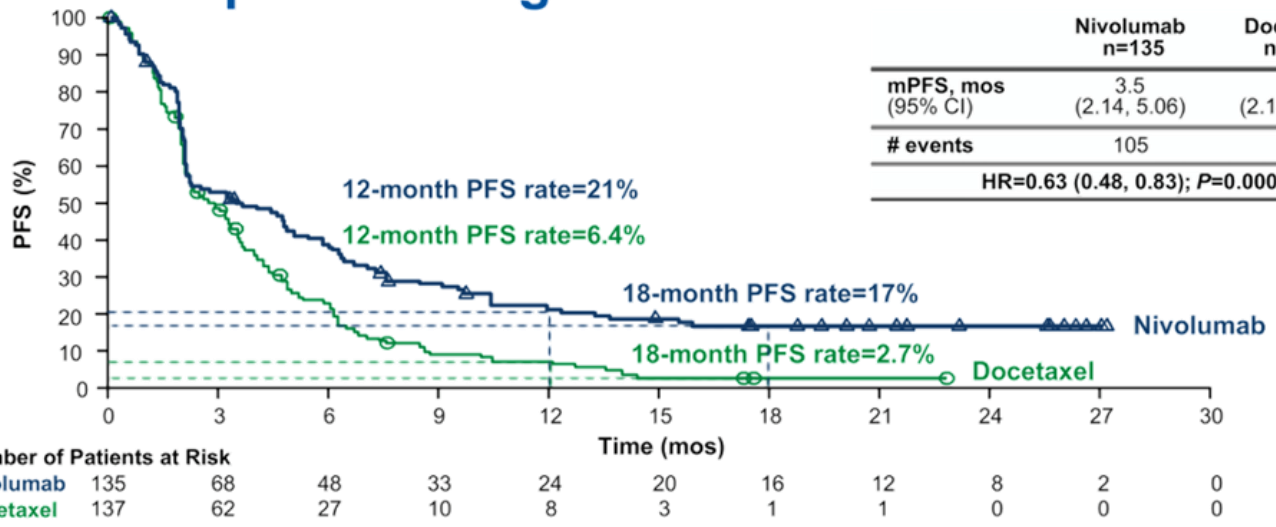
Minimum follow-up for survival: 18 months

CheckMate 057 non-SQCC



Spigel D and Paz-Ares L, 2015 ASCO Annual Meeting; Reckamp K, 16th WCLC

Updated Progression-free Survival



	Nivolumab n=135	Docetaxel n=137
mPFS, mos (95% CI)	3.5 (2.14, 5.06)	2.8 (2.14, 3.52)
# events	105	122
HR=0.63 (0.48, 0.83); *P*=0.0008		

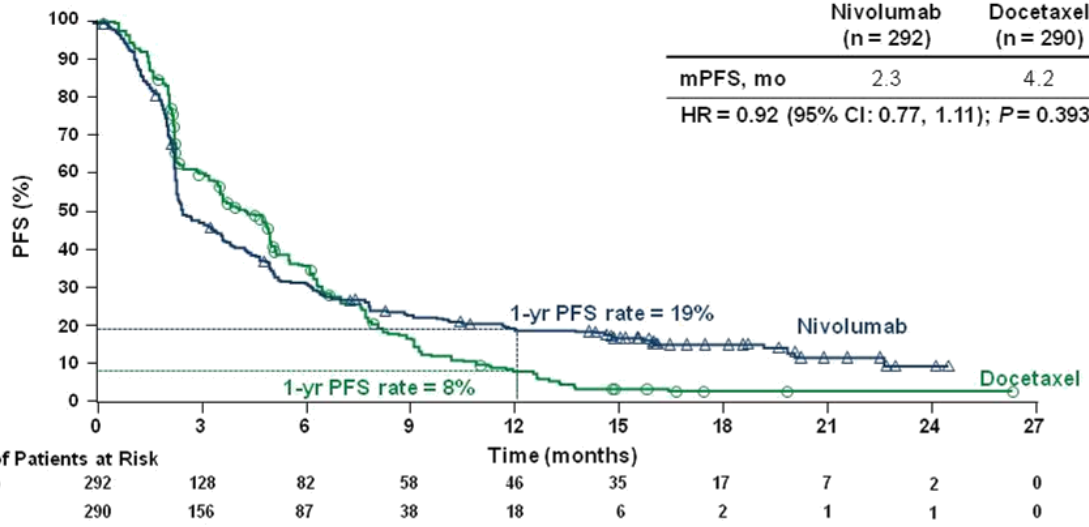
Number of Patients at Risk

Nivolumab	135	68	48	33	24	20	16	12	8	2	0
Docetaxel	137	62	27	10	8	3	1	1	0	0	0

Minimum follow-up for survival: 18 months

CheckMate 017 SQCC

Progression-free Survival



	Nivolumab (n = 292)	Docetaxel (n = 290)
mPFS, mo	2.3	4.2
HR = 0.92 (95% CI: 0.77, 1.11); *P* = 0.3932		

Number of Patients at Risk

Nivolumab	292	128	82	58	46	35	17	7	2	0
Docetaxel	290	156	87	38	18	6	2	1	1	0

CheckMate 057 non-SQCC

Spigel D and Paz-Ares L, 2015 ASCO Annual Meeting; Reckamp K, 16th WCLC

CheckMate 017 in squamous NSCLC

Updated Treatment and Safety Summary

	Nivolumab n=131		Docetaxel n=129	
	Any grade	Grade 3–5[a]	Any grade	Grade 3–5
Treatment-related AEs, %	59	8	87	58
Treatment-related AEs leading to discontinuation, %	5[b]	3	10[c]	7
Treatment-related deaths, %	0		2[d]	

- Median number of doses was 8 (range, 1–56) for nivolumab and 3 (range, 1–29) for docetaxel

Reckamp K, 16th WCLC

Nivolumab as second line treatment of advanced squamous NSCLC

MARCH 2015

MAY 2015

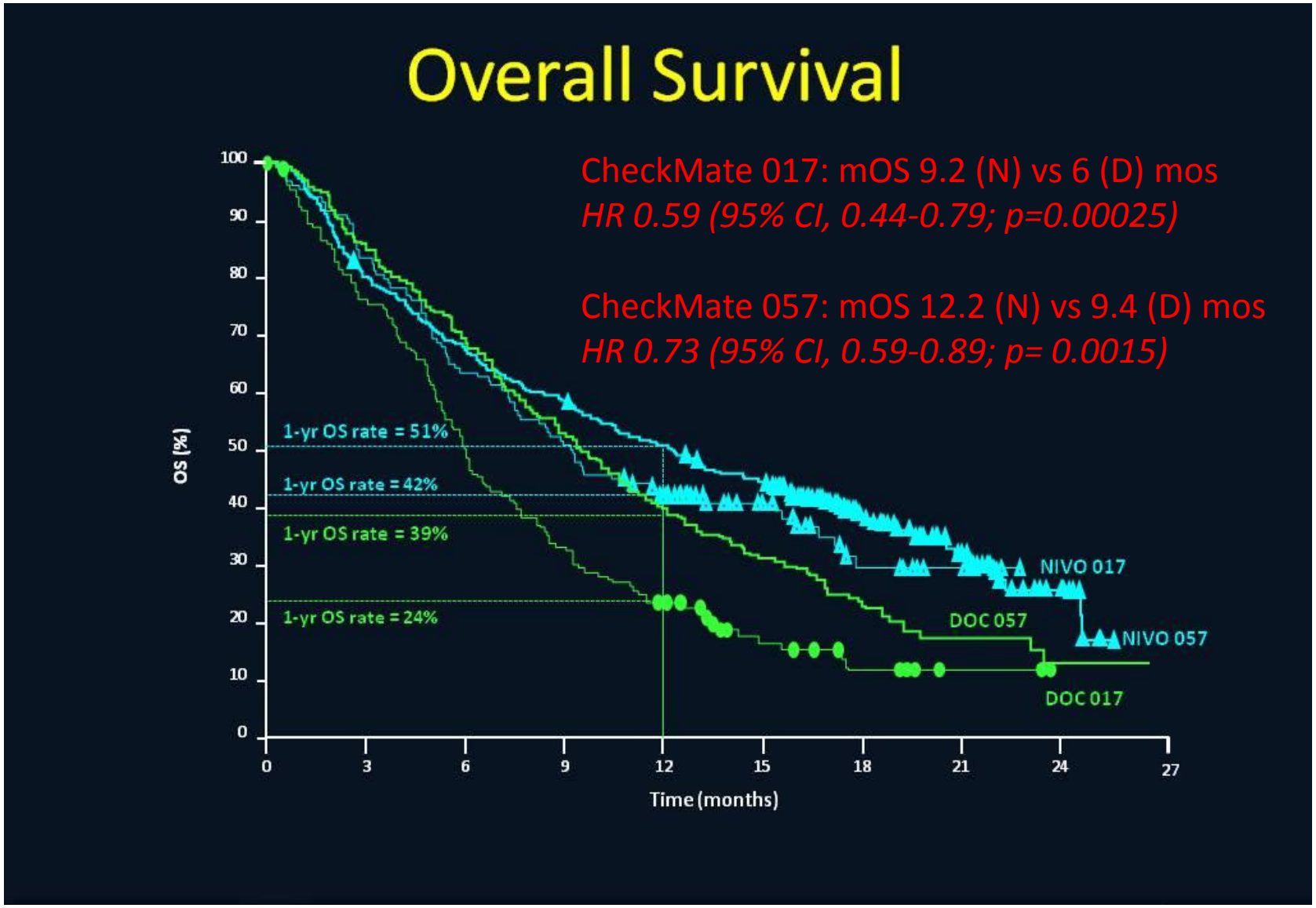
EUROPEAN MEDICINES AGENCY

SCIENCE MEDICINES HEALTH

CheckMate 017 and 057 : key points

- **Nivolumab: different trials, different ‘performance’?**
- **2015 scenarios for squamous and non-squamous NSCLC**
- **PD-L1 status and selection criteria for treatment**

Nivolumab: different trials, different 'performance'?



Modified from Garassino MC, 2015 ASCO Annual Meeting

Nivolumab: different trials, different 'performance'?

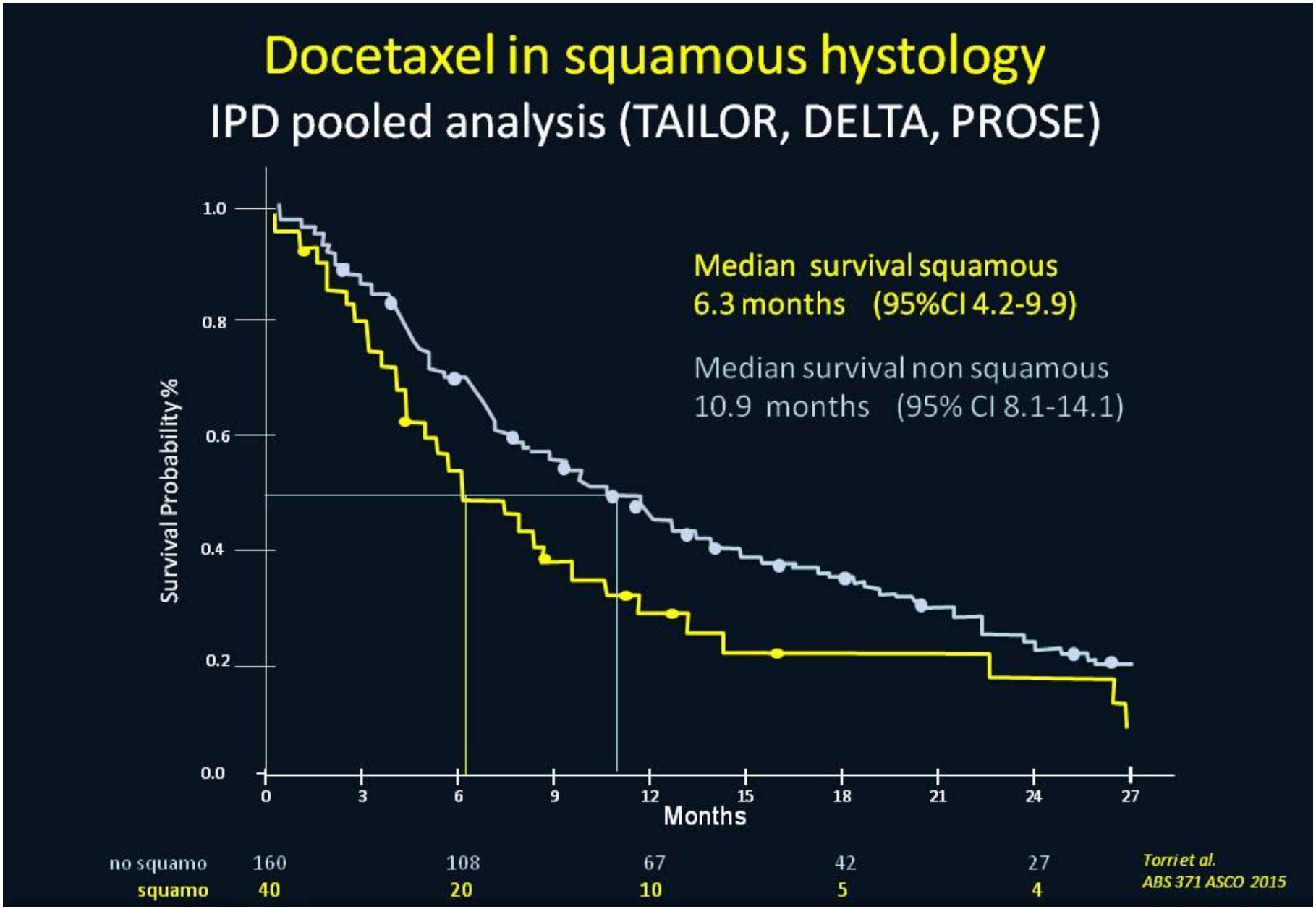
Clinical trial	OS all	OS non squamous	OS squamous
Docetaxel vs BSC	7 vs 4.6	NA	NA
Docetaxel vs Pem	7.9 vs 8.3	8 vs 9.3	7.4 vs 6.2
Docetaxel vs Erlotinib	8.2 vs 5.4	NA	NA (24%)
Docetaxel ramucirumab vs Docetaxel	10.5 vs 9.1	11.1 vs 9.7	9.5 vs 8.2
Docetaxel nintendanib vs Docetaxel	10.1 vs 9.1	12.6 vs 10.3	8.6 vs 8.7
Nivolumab vs Docetaxel	NA	12.2 vs 9.4	9.2 vs 6.0
Atezolizumab vs Docetaxel	11.4 vs 9.5	NA	NA

nonSQCC: mOS 8-10 months

SQCC: mOS 6-8.7 months

Peters S, 16th WCLC

Nivolumab: different trials, different 'performance'?



Garassino MC, 2015 ASCO Annual Meeting

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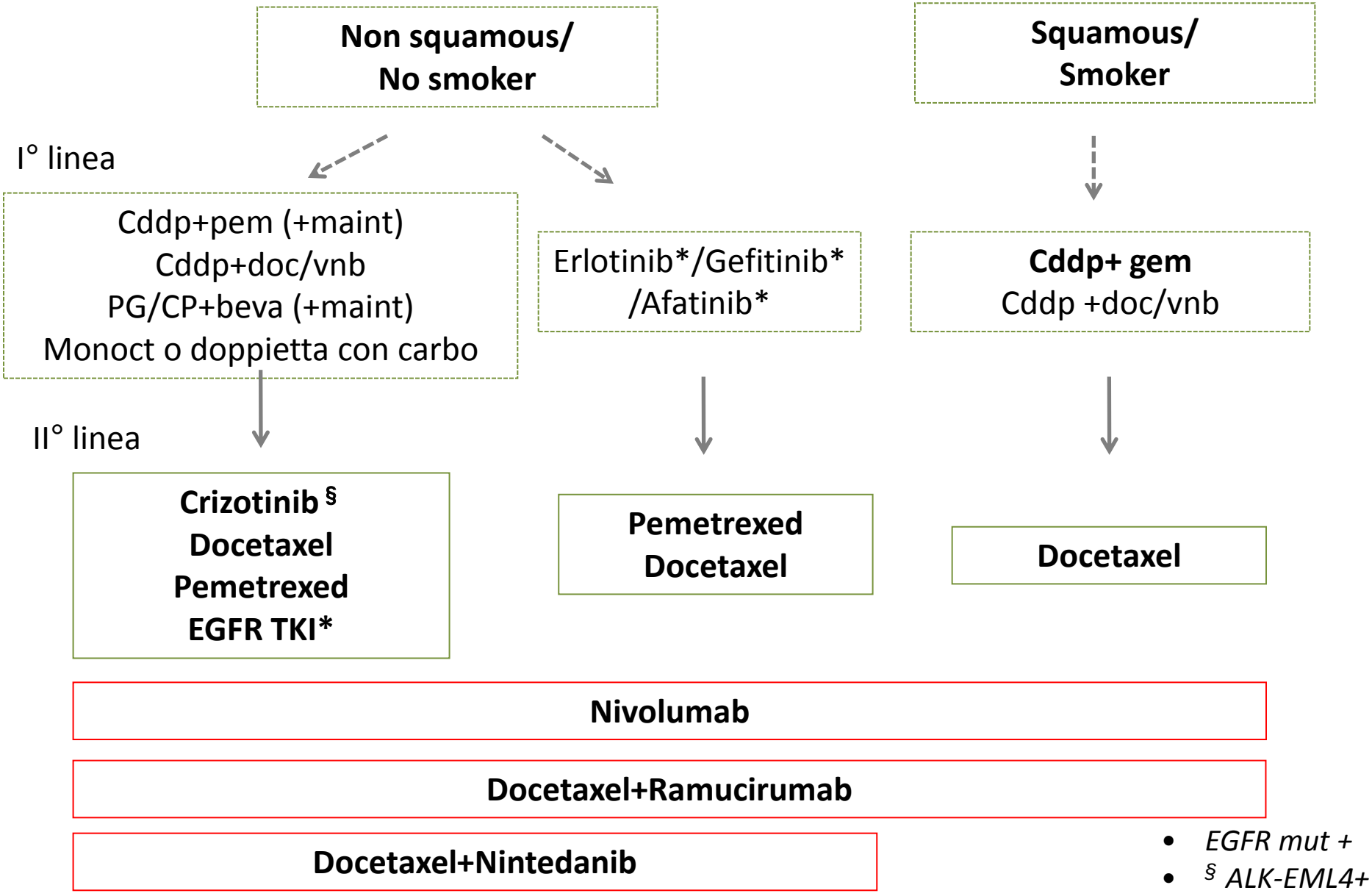
- **Nivolumab: different trials, different 'performance'?**

Different performance of docetaxel in the two histologies?
Delayed effect of nivolumab in non-squamous cell carcinoma?
Mixed populations? Subsequent therapies?

- **2015 scenarios for squamous and non-squamous NSCLC**

- **PD-L1 status and selection criteria for treatment**

Second line treatment options in NSCLC patients



- *EGFR mut +*
- *§ ALK-EML4+*

Meaningful advantage? Raising the bar!

Table 1. Summary of Recommended Targets for Meaningful Clinical Trial Goals

Cancer Type	Patient Population	Current Baseline Median OS (months)	Primary End Point: Improvement Over Current OS That Would Be Clinically Meaningful (months)	Primary End Point: Target HRs	Secondary End Point: Improvement in 1-Year Survival Rate (%)*	Secondary End Point: Improvement in PFS (months)
Pancreatic cancer	FOLFIRINOX-eligible patients	10 to 11[19]	4 to 5	0.67 to 0.69	48 → 63	4 to 5
Pancreatic cancer	Gemcitabine or gemcitabine/nab-paclitaxel–eligible patients	8 to 9[20,21]	3 to 4	0.6 to 0.75	35 → 50	3 to 4
Lung cancer	Nonsquamous cell carcinoma	13[22]	3.25 to 4	0.76 to 0.8	53 → 61	4
Lung cancer	Squamous cell carcinoma	10[23]	2.5 to 3	0.77 to 0.8	44 → 53	3
Breast cancer	Metastatic triple negative, previously untreated for metastatic disease	18[24,25]	4.5 to 6	0.75 to 0.8	63 → 71	4
Colon cancer	Disease progression with all prior therapies (or not a candidate for standard second- or third-line options)	4 to 6[26]	3 to 5	0.67 to 0.67	25 → 35	3 to 5

Abbreviations: FOLFIRINOX, leucovorin, fluorouracil, irinotecan, and oxaliplatin; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
*Current → target.

Ellis ME et al, J Clin Oncol 2014

- SURVIVAL ADVANTAGE/CLINICAL BENEFIT
- SAFETY
- COSTS
- **PREDICTIVE BIOMARKERS**
- **PATIENT SELECTION**

New second line treatment options in non-oncogene addicted NSCLC

	SQCC (mOS months)	**Non-SQCC** (mOS months)
Docetaxel+Ramucirumab vs Docetaxel	**9.5 vs 8.2 (HR 0.88)**	**11.1 vs 9.7 (HR 0.83)**
Docetaxel+Nintedanib vs Docetaxel	**/**	**12.6 vs 10.3[§] (HR 0.83)**
Nivolumab vs docetaxel	**9.2 vs 6 (HR 0.62)**	**12.2 vs 9.4 (HR 0.73)**

[§]secondary endpoint

Nivolumab safety in PS 2 patients
a " real life study"

Summary of Adverse Events

	Nivolumab 3 mg/kg N = 824			Nivolumab 3 mg/kg ECOG PS 0–1 (n = 742)			Nivolumab 3 mg/kg ECOG PS 2 (n = 65)		
	Any Grade n (%)	Grade 3–4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3–4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3–4 n (%)	Grade 5 n (%)
All adverse events	762 (93)	311 (38)	158 (19)	683 (92)	268 (36)	131 (17)	62 (95)	33 (51)	24 (37)
All serious adverse events (SAEs)	309 (38)	223 (27)	158 (19)	257 (35)	185 (25)	131 (17)	42 (65)	29 (45)	24 (37)
All select adverse events	282 (34)	37 (5)	5 (1)	253 (34)	32 (4)	3 (<1)	22 (34)	3 (5)	2 (3)
All treatment-related adverse events	439 (53)	59 (7)	1 (<1)	403 (54)	52 (7)	1 (<1)	27 (42)	4 (6)	0
All treatment-related SAEs	23 (3)	19 (2)	1 (<1)*	18 (2)	14 (2)	1 (<1)	3 (5)	3 (5)	0
All treatment-related select AEs	199 (24)	20 (2)	0	181 (24)	16 (2)	0	14 (22)	2 (3)	0
All AEs leading to discontinuation	87 (11)	53 (6)	34 (4)	69 (9)	42 (6)	27 (4)	16 (25)	9 (14)	7 (11)
All treatment-related SAEs leading to discontinuation	14 (2)	12 (2)	1 (<1)	11 (2)	9 (1)	1 (<1)	2 (3)	2 (3)	0
All treatment-related select AEs leading to discontinuation	12 (2)	11 (1)	0	9 (1)	8 (1)	0	2 (3)	2 (3)	0

CA209-153

Hussein M, 16th WCLC

CheckMate 017 and 057 : key points

- **Nivolumab: different trials, different 'performance'?**

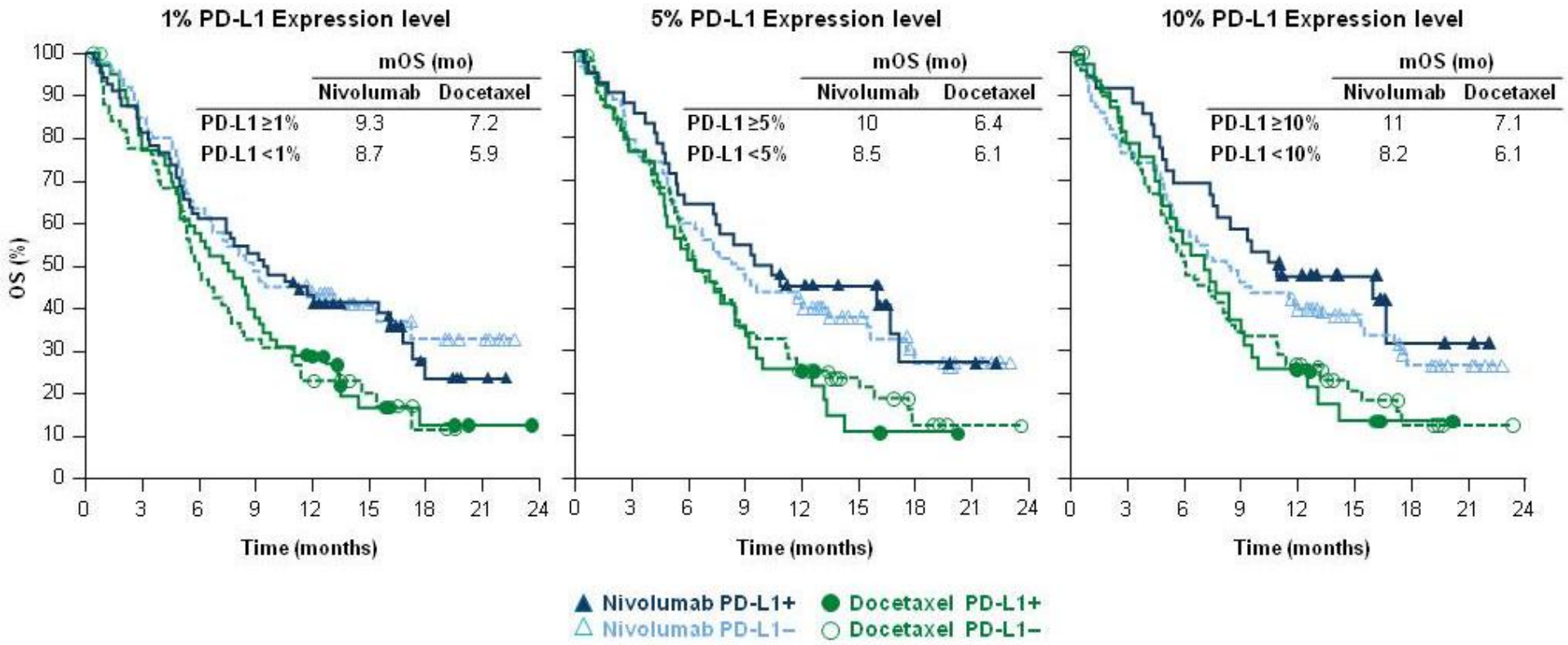
Different performance of docetaxel in the two histologies?
Delayed effect of nivolumab in non-squamous cell carcinoma?
Mixed populations? Subsequent therapies?

- **2015 scenarios for squamous and non-squamous NSCLC**

Clinical benefit, safety and costs should be integrated with predictive biomarkers for patients selection
Importance of a 'personalized' sequence

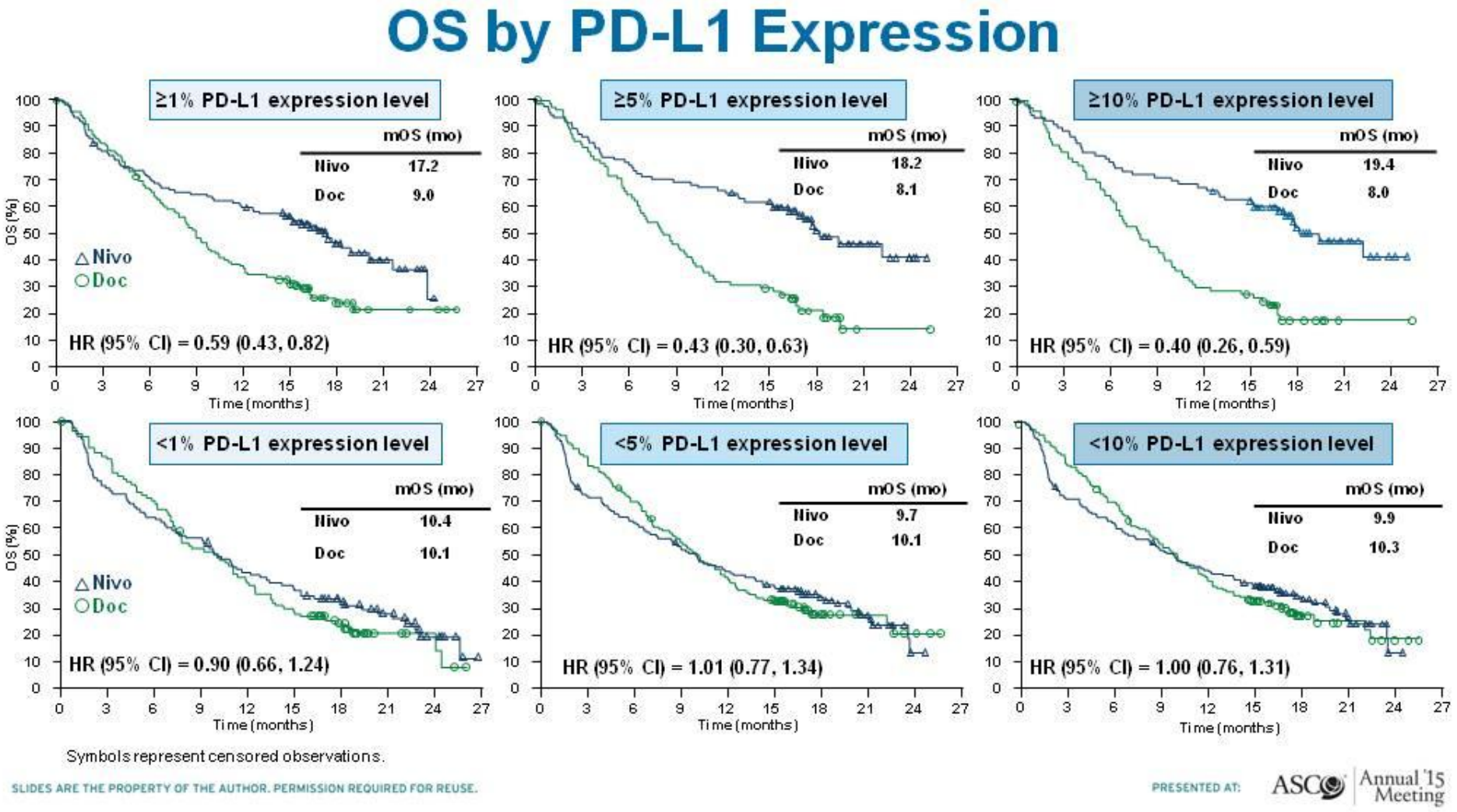
- **PD-L1 status and selection criteria for treatment**

PD-L1 status and selection criteria for treatment CheckMate 017



Spigel D 2015 ASCO Annual Meeting; Reckamp K, 16th WCLC

PD-L1 status and selection criteria for treatment CheckMate 057

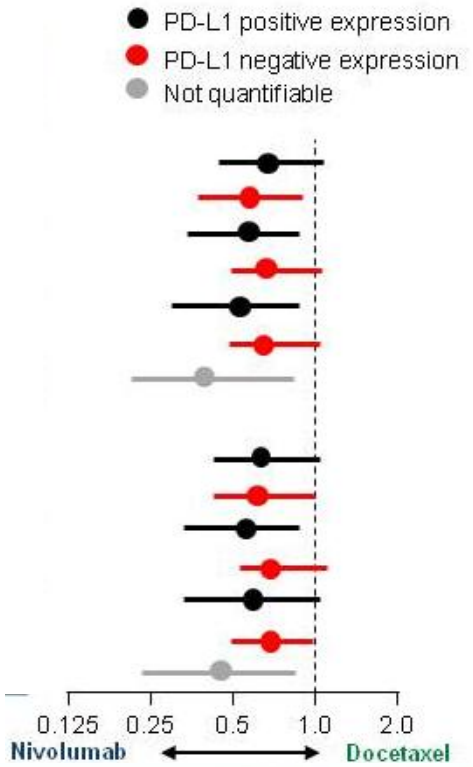


PRESENTED AT: ASCO Annual '15 Meeting

Paz-Ares L, 2015 ASCO Annual Meeting;

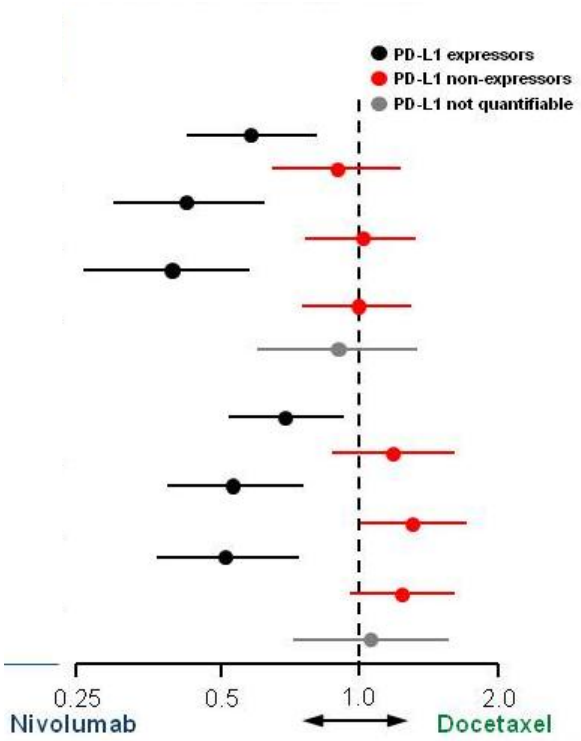
Treatment outcome according to PD-L1 expression

CheckMate 017



	PD-L1 Expression Level						
	≥1%	<1%	≥5%	<5%	≥10%	<10%	Not quantifiable[a]
Nivolumab							
ORR,[b] % (n/N)	18 (11/63)	17 (9/54)	21 (9/42)	15 (11/75)	19 (7/36)	16 (13/81)	39 (7/18)
Docetaxel							
ORR,[b] % (n/N)	11 (6/56)	10 (5/52)	8 (3/39)	12 (8/69)	9 (3/33)	11 (8/75)	3 (1/29)
Interaction *P*-value	0.94		0.29		0.64		

CheckMate 057



	ORR,[a] %		
PD-L1 expression level	Nivolumab	Docetaxel	Interaction *P*-value
≥1%	31	12	0.0019
<1%	9	15	
≥5%	36	13	0.0020
<5%	10	14	
≥10%	37	13	0.0021
<10%	11	14	
Not quantifiable	13	9	

Spigel D and Paz-Ares L, 2015 ASCO Annual Meeting; Reckamp K, 16th WCLC

Dumb and smart tumors

EGFR+ NSCLC: Example of dumb cancer

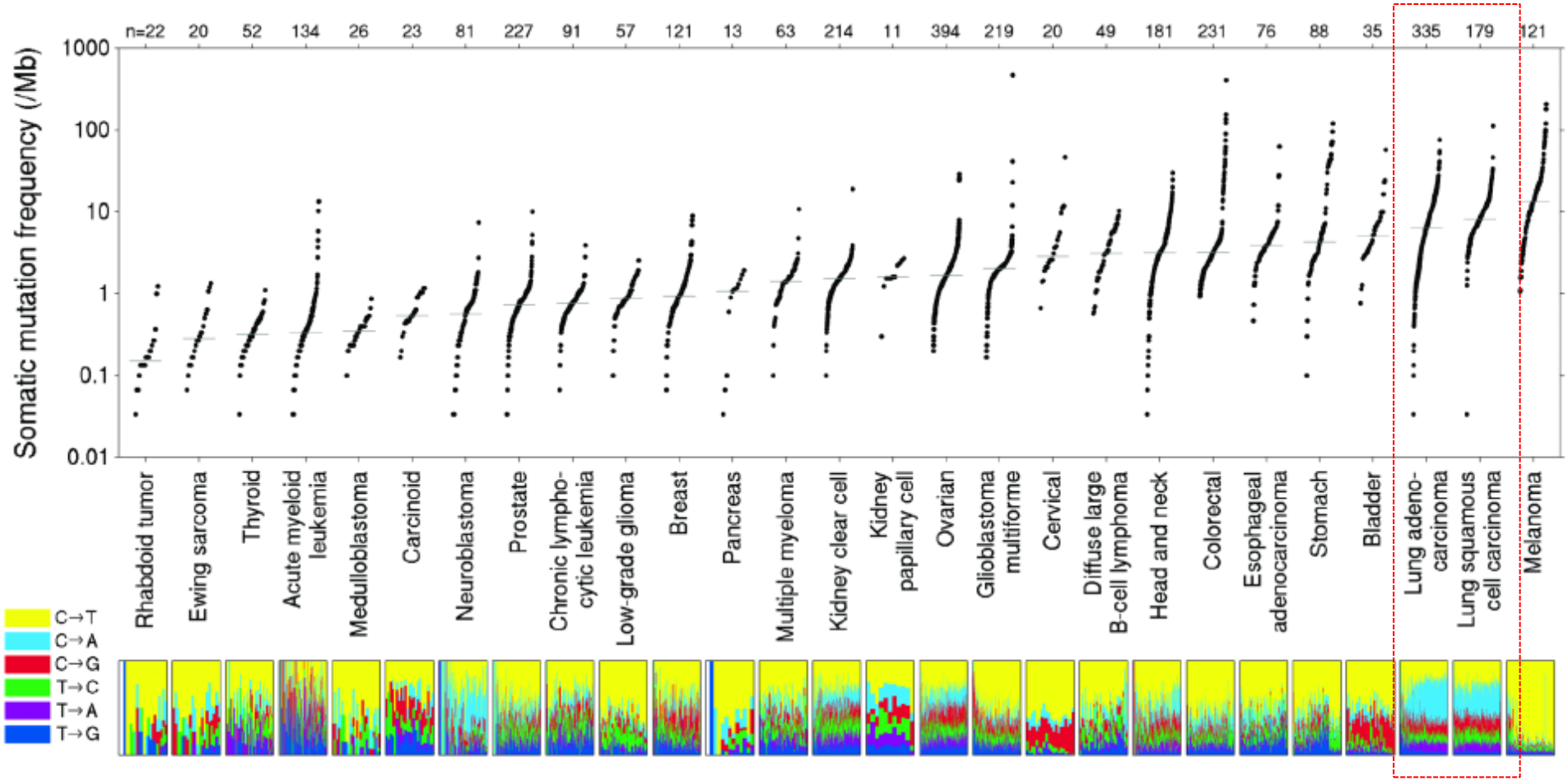
- **Single dominant mutation**
- **Small mutational load**
- **Monotherapy is effective**
- **Resistance rare, late, same pathway**

NSCLC in smokers: Example of smart cancer

- **Multiple mutational drivers**
- **Large mutational load**
- **Multi-targeted therapy required**
- **Resistance common, early**

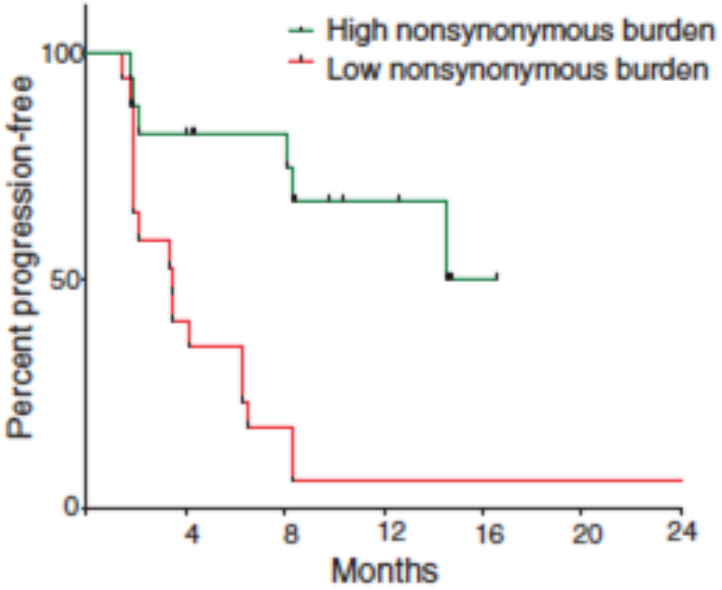
Sledge GW, ASCO Meeting 2010

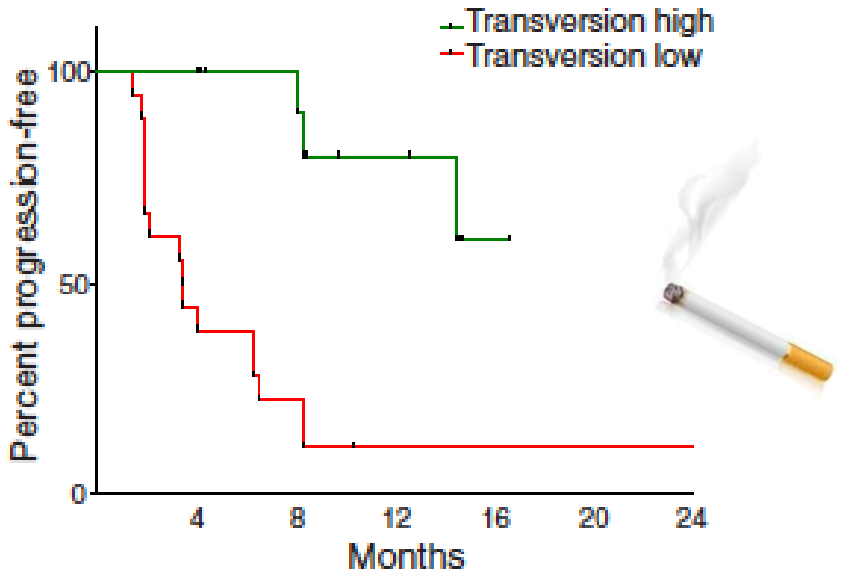
Somatic mutation frequencies in cancer

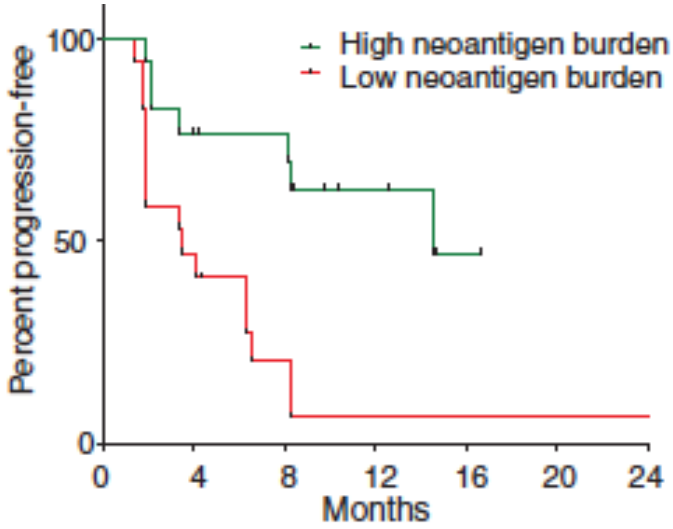


Lawrence MS et al, Nature 2014

Mutational load, smoking signature, neoantigen burden and response to checkpoint inhibitors







Rizvi NA et al, Science 2015

CheckMate 017 and 057 : key points

- **Nivolumab: different trials, different 'performance'?**

Different performance of docetaxel in the two histologies?
Delayed effect of nivolumab in non-squamous cell carcinoma?
Mixed populations? Subsequent therapies?

- **2015 scenarios for squamous and non-squamous NSCLC**

Clinical benefit, safety and costs should be integrated with predictive biomarkers for patients selection

- **PD-L1 status and selection criteria for treatment**

Different mutational load in the two histologies?
Different proportion of smokers?
Gene signature as predictive to PD-1/PD-L1 inhibition?

NIVOLUMAB

- ✓ Phase I expansion cohort trial (pre-treated)
- ✓ Phase II study (refractory)
- ✓ 2 phase IIIR trials (2L)

ATEZOLIZUMAB

- ✓ Phase IIR trial (2L-3L)

PEMBROLIZUMAB

- ✓ Phase I trial (pretreated)

The POPLAR phase IIR study in NSCLC all comers, 2L-3L

Metastatic or locally advanced NSCLC (2L/3L)
Disease progression on a prior platinum therapy
N = 287

Stratification Factors
- PD-L1 IC expression (0 vs 1 vs 2 vs 3)[a]
- Histology (squamous vs non-squamous)
- Prior chemotherapy regimens (1 vs 2)

R 1:1

Atezolizumab
1200 mg IV q3w
until loss of clinical benefit

Docetaxel
75 mg/m^2 IV q3w
until disease progression

Primary study objective:
- **Estimate OS in PD-L1 selected and ITT populations**

Secondary study objectives:
- Evaluate PFS, ORR and DOR in PD-L1 selected and ITT populations
- Evaluate safety

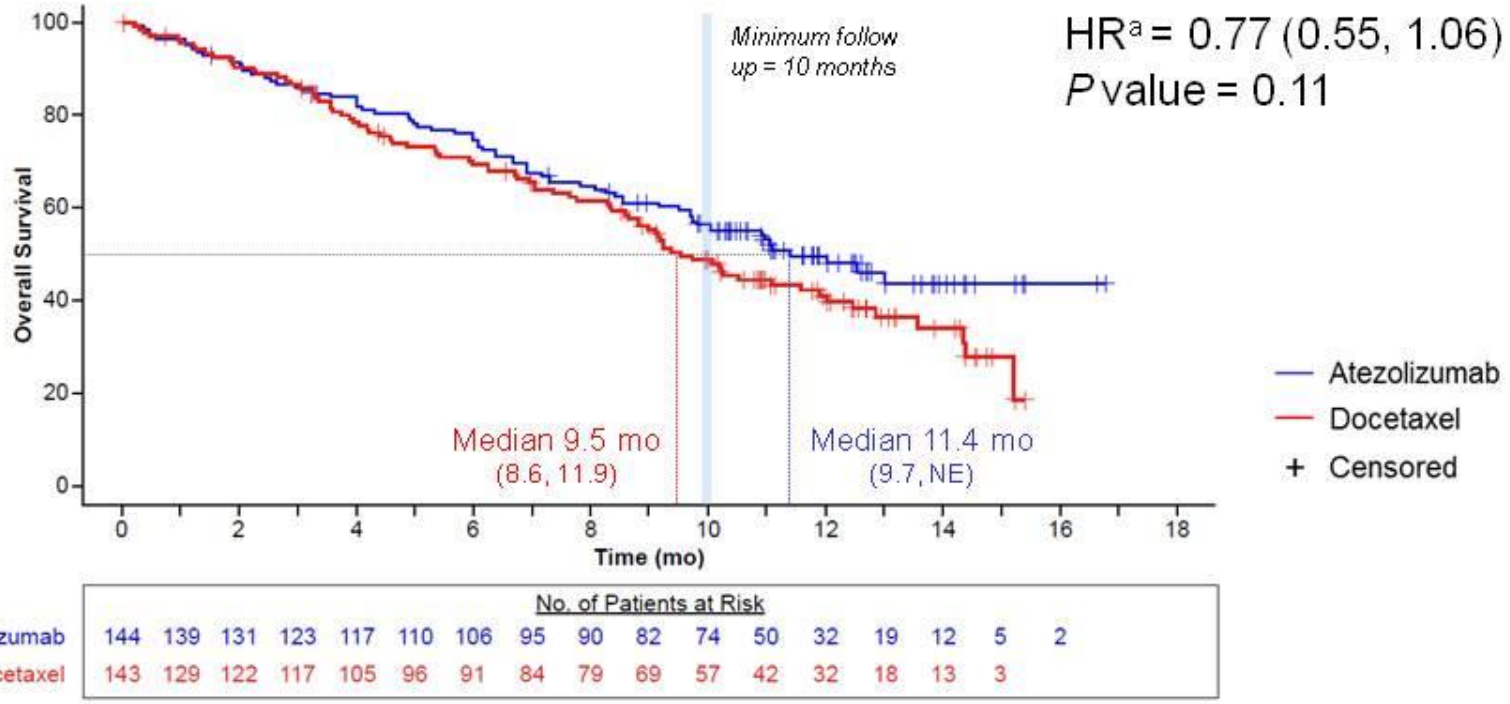
Interim analysis is based on 153 events with a minimum follow-up 10 months

[a]Archival or fresh tissue required for pre-dose testing.

Spira A et all, 2015 ASCO Annual Meeting

The POPLAR phase IIR study in NSCLC

POPLAR: All Patient Efficacy
ITT interim OS (N = 287)

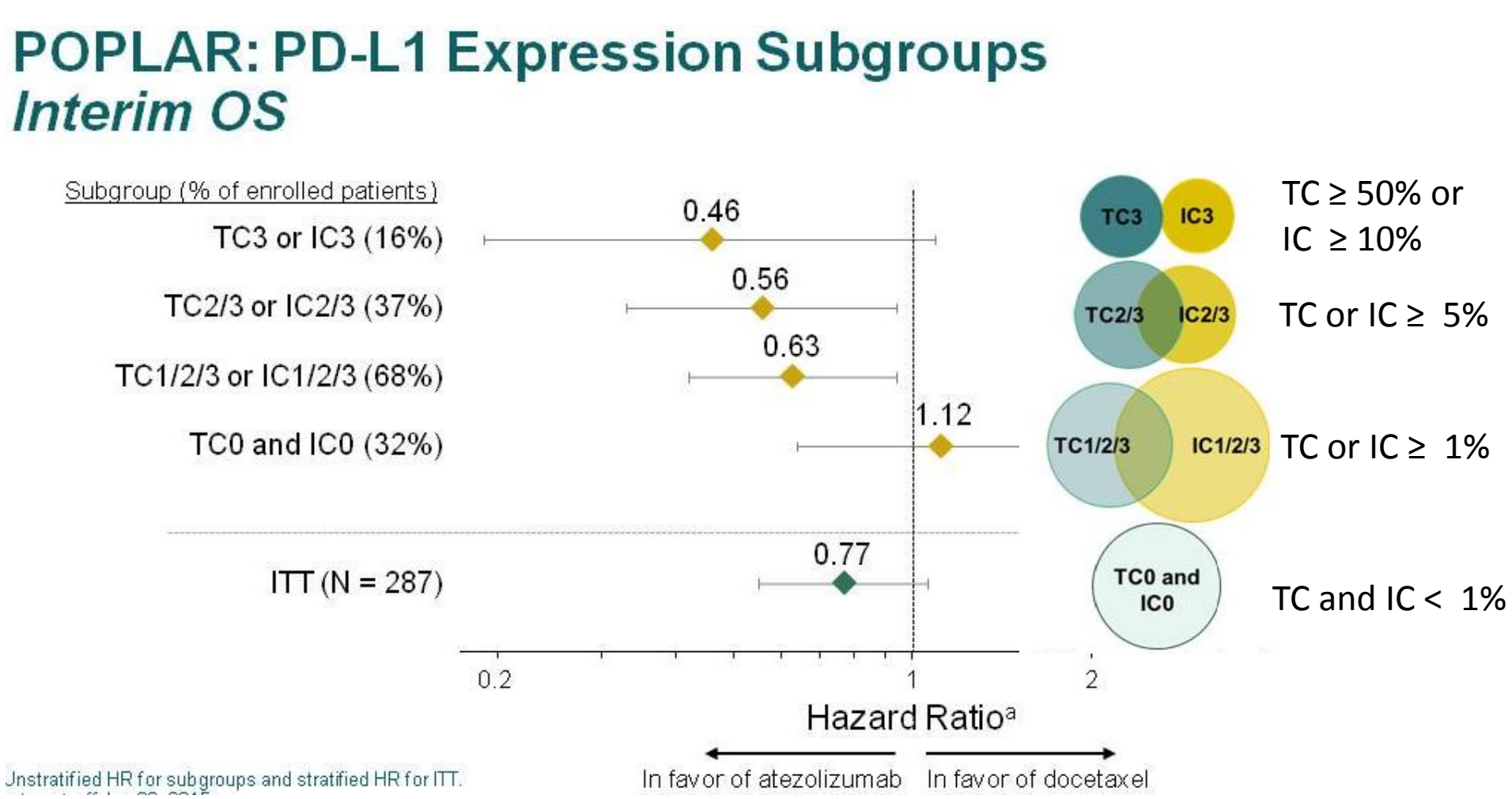


[a]Stratified HR.
Data cut-off Jan 30, 2015.

PRESENTED AT: ASCO Annual '15 Meeting

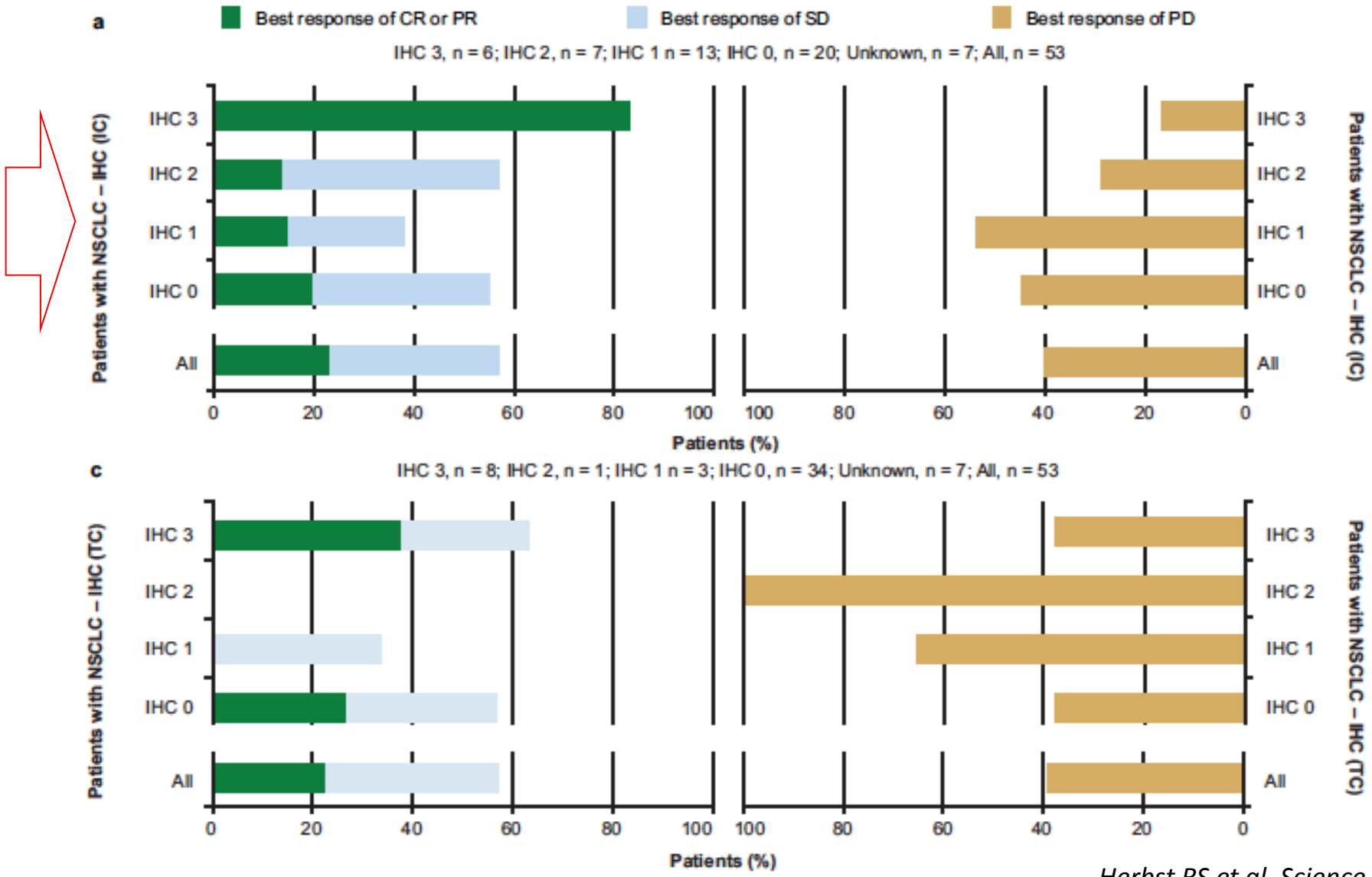
Spira A et all, 2015 ASCO Annual Meeting

The POPLAR phase IIR study in NSCLC



Modified from Spira A et all, 2015 ASCO Annual

Atezolizumab: predictive correlates of response



Herbst RS et al, Science 2014

NIVOLUMAB

- ✓ Phase I expansion cohort trial (pre-treated)
- ✓ Phase II study (refractory)
- ✓ 2 phase IIIR trials (2L)

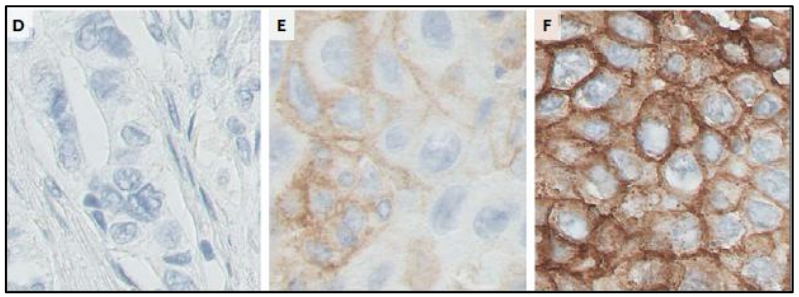
ATEZOLIZUMAB

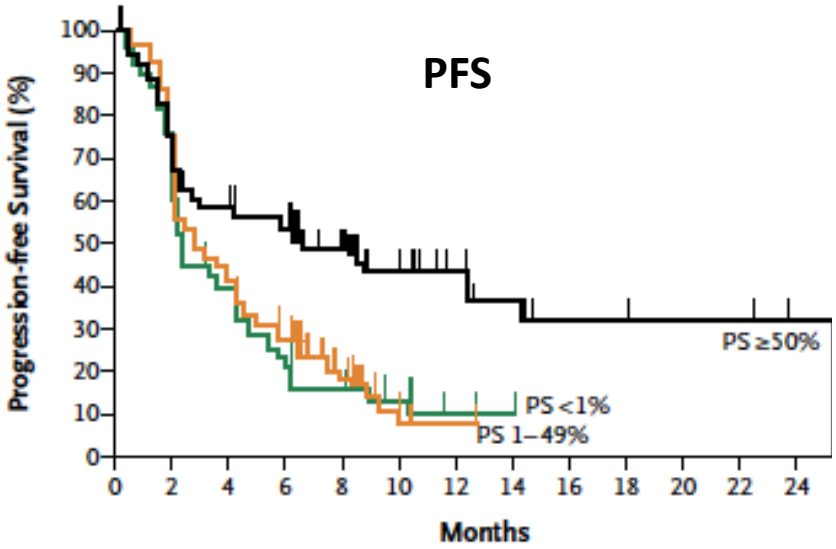
- ✓ Phase IIR trial (2L-3L)

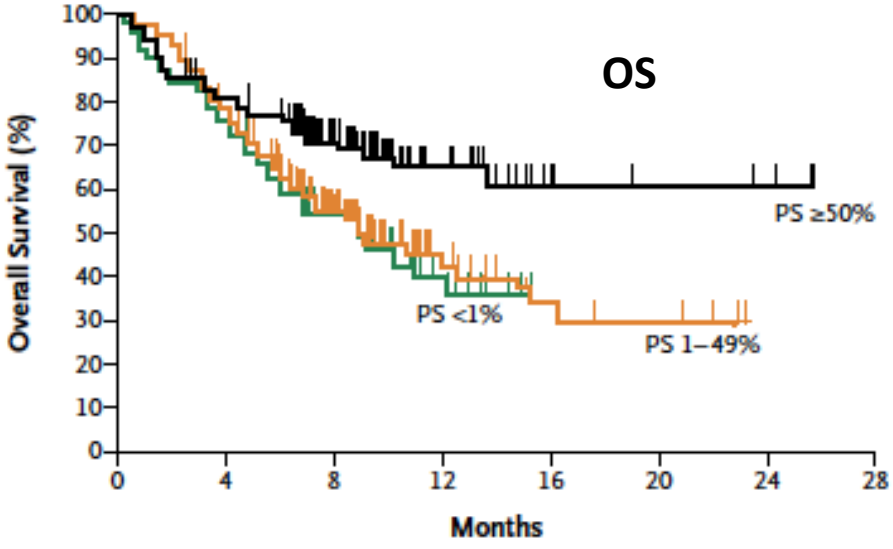
PEMBROLIZUMAB

- ✓ Phase I trial (pretreated)

The KEYNOTE 001 phase I study in pretreated NSCLC







No. at Risk													
PS ≥50%	119	86	66	60	38	20	13	8	4	3	3	3	1
PS 1–49%	161	122	70	45	21	4	1	0	0	0	0	0	0
PS <1%	76	52	29	17	11	6	2	0	0	0	0	0	0

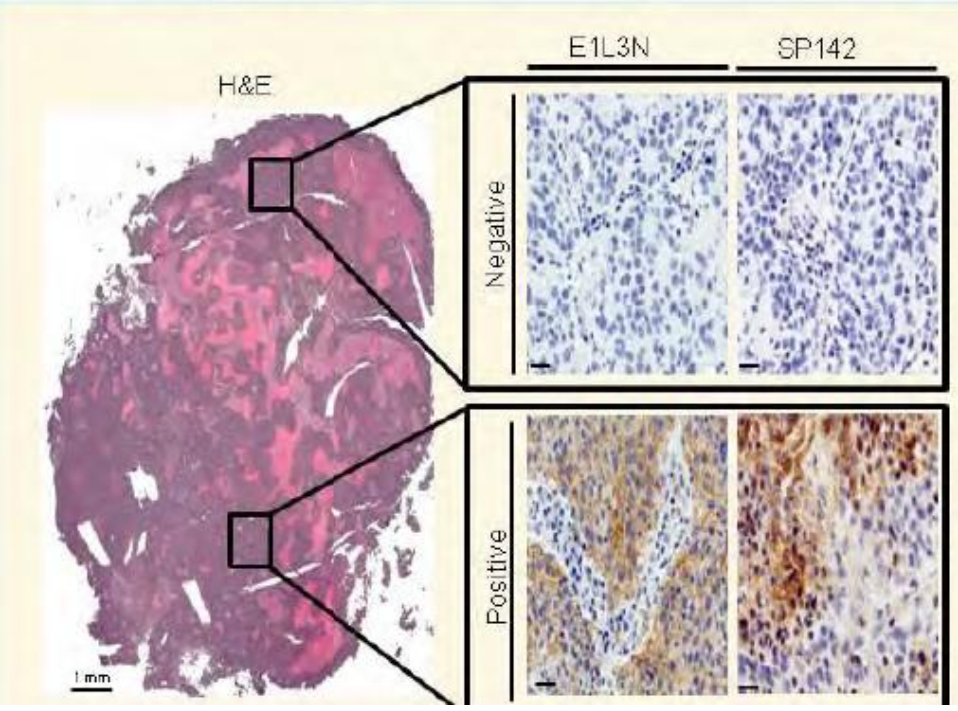
No. at Risk								
PS ≥50%	119	92	56	22	5	4	3	0
PS 1–49%	161	119	58	15	6	4	0	0
PS <1%	76	55	33	8	0	0	0	0

→ Estimated prevalence of PD-L1: approximately 20-25%

Garon EB et al, NEJM 2015

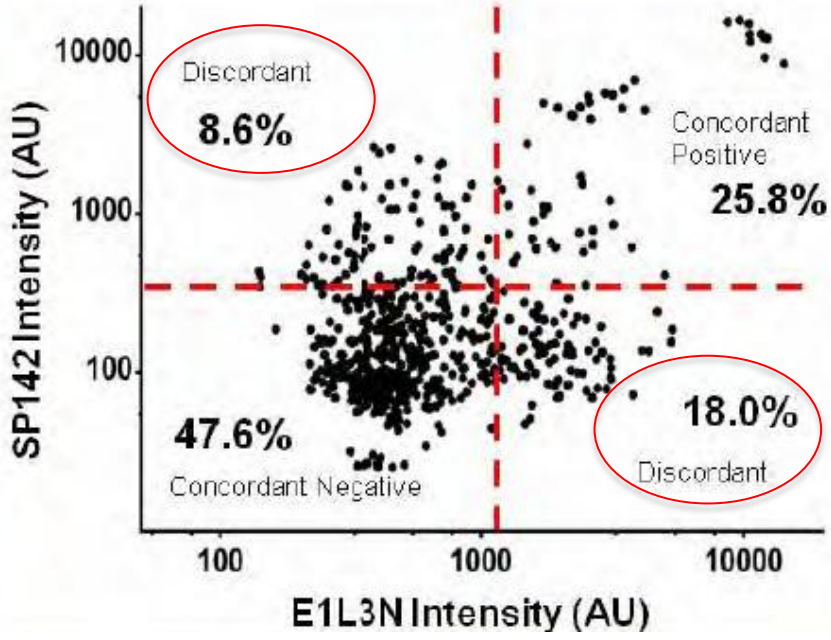
PD-L1 as a predictive immune biomarker: assays, sample collection and analysis in NSCLC studies

	Pembrolizumab Merck	Nivolumab Bristol-Myers Squibb	MPDL3280A Roche/Genentech	MEDI4736 AstraZeneca
PD-L1 Assay	• Proprietary IHC assay[1]	• Dako automated IHC assay (28-8 Ab)[2]	• Ventana automated IHC assay	• 1st generation or Ventana automated IHC BenchMark ULTRA) assay (Ventana PD-L1 (SP263) clone)[5,6]
Sample Source and Collection	• Surface expression of PD-L1 on tumour specimen* • Ph I: Fresh tissue • Ph II/III: Archival or fresh tissue[1]	• Surface expression of PD-L1 on tumour cells* • Archival[3] or fresh tissue	• Surface expression of PD-L1 on TILs[4] • Archival or fresh tissue	• Surface expression of PD-L1 on TILs • PhI: Fresh tissue
Definition of Positivity†	**IHC Staining:** • Strong vs weak expression[1] • PD-L1 expression required for NSCLC for enrollment[1] **Tumour PD-L1 expression** • PD-L1+ cut-point: 24% (4/7) • PD-L1+ ≥0 : 61% (23/38)	**IHC Staining:** • Strong vs weak expression[2,3,4] • Patients not restricted in PD-L1 status in 2nd- & 3rd-line[3] • Ph III 1st-line trial in PD-L1+[2] **Tumour PD-L1 expression:** • 5% PD-L1+ cut-off: 49% (33/68)[3]	**IHC Staining intensity (0, 1, 2, 3):** • IHC 3 (≥10% PD-L1+): Ph III trial[4] • IHC 2,3 (≥5% PD-L1+)[4] • IHC 1,2,3 (≥1% PD-L1+)[4] • IHC 1, 0, or unknown • PD-L1 expression required for NSCLC for enrollment **TIL PD-L1 expression:** • 11% (6/53) IHC 3 (≥10% PD-L1+) • 75% (40/53) PD-L1 low (IHC 1, 0)	**IHC Staining intensity :** • Not presented to date[5,6] **TIL PD-L1 expression:** • Not presented to date[5,6]



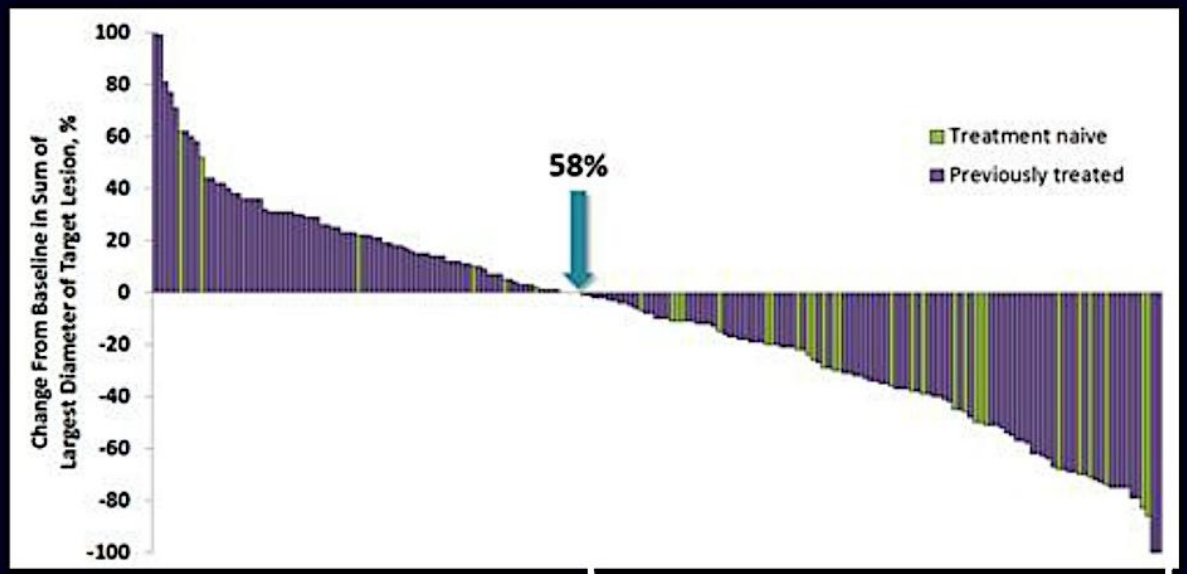
PD-L1 is dynamic and heterogeneous…..

…and variable according to the antibody



Herbst R, 2015 ASCO meeting

Patients who might benefit

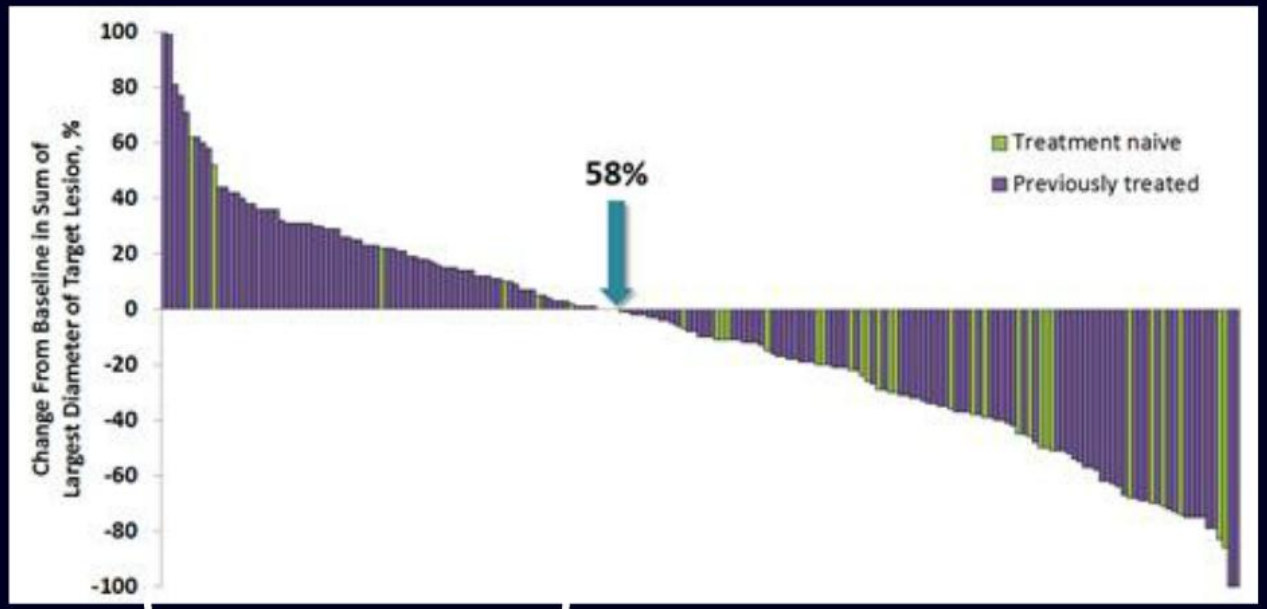


Are we confident in accurately identifying these patients?

Functional MHC class 1 presentation ***AND***
Probably (but not exclusively):
-PD-L1 positivity ***AND/OR***
-Specific TILs tumour infiltration ***AND/OR***
-High mutation load (smoking, mismatch repair…) ***AND/OR***
-Expression of potent neo-antigens ***AND/OR***
-Others: interferon signature, …?

Peters S, 16th WCLC

Patients who probably don't benefit



Need to induce T-cell response

- Combinations with other immunotherapy strategies: checkpoints modulators/ TLR agonists / oncolytic viruses /cytokines / vaccines /targeted therapies

Do we exect a potential role for immunotherapy in this patient population?

Peters S, 16th WCLC

Future perspectives