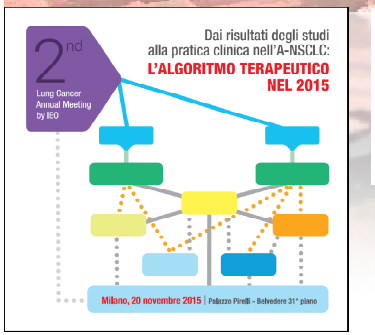

AntiPD1/PDL1e attuale loro applicazione pratica nella II/III linea del NSCLC

Filippo de Marinis

Thoracic Oncology Division, IEO, Milan, Italy

IEO
European Institute
of Oncology

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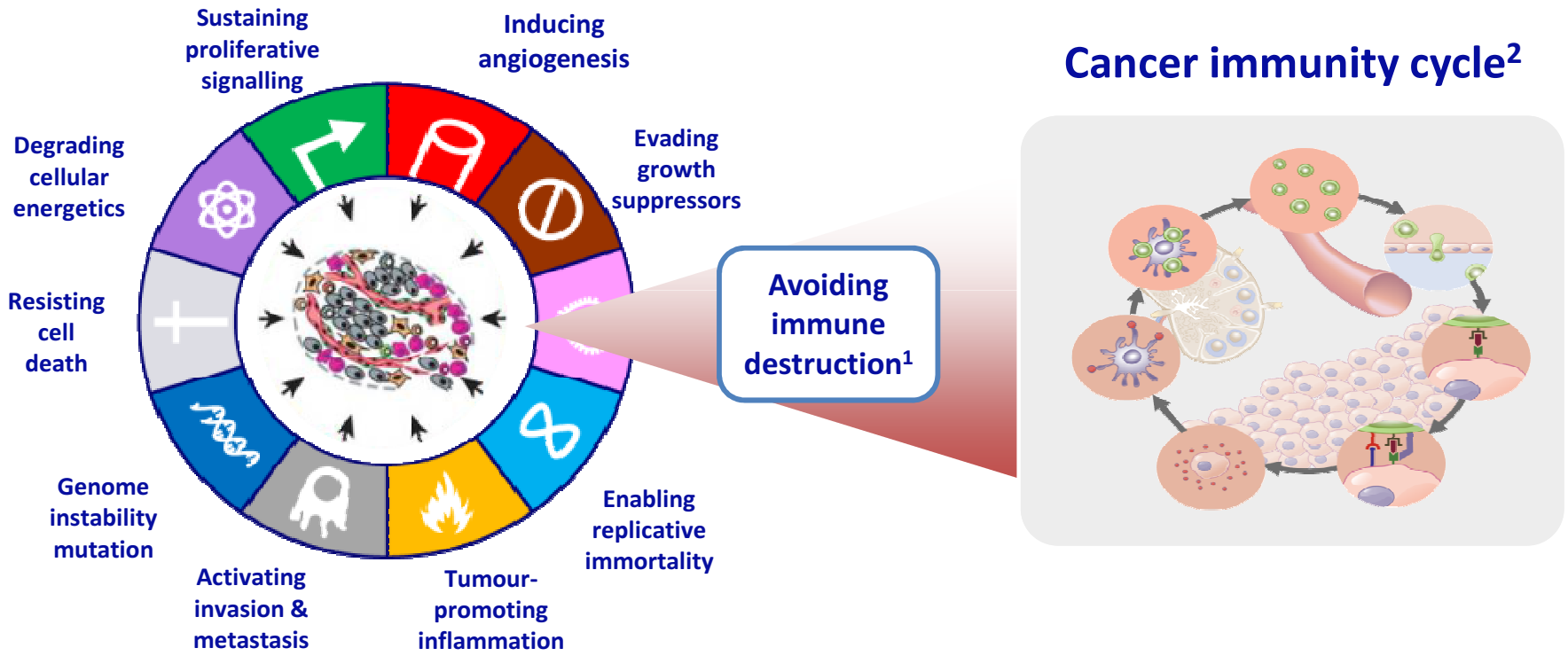
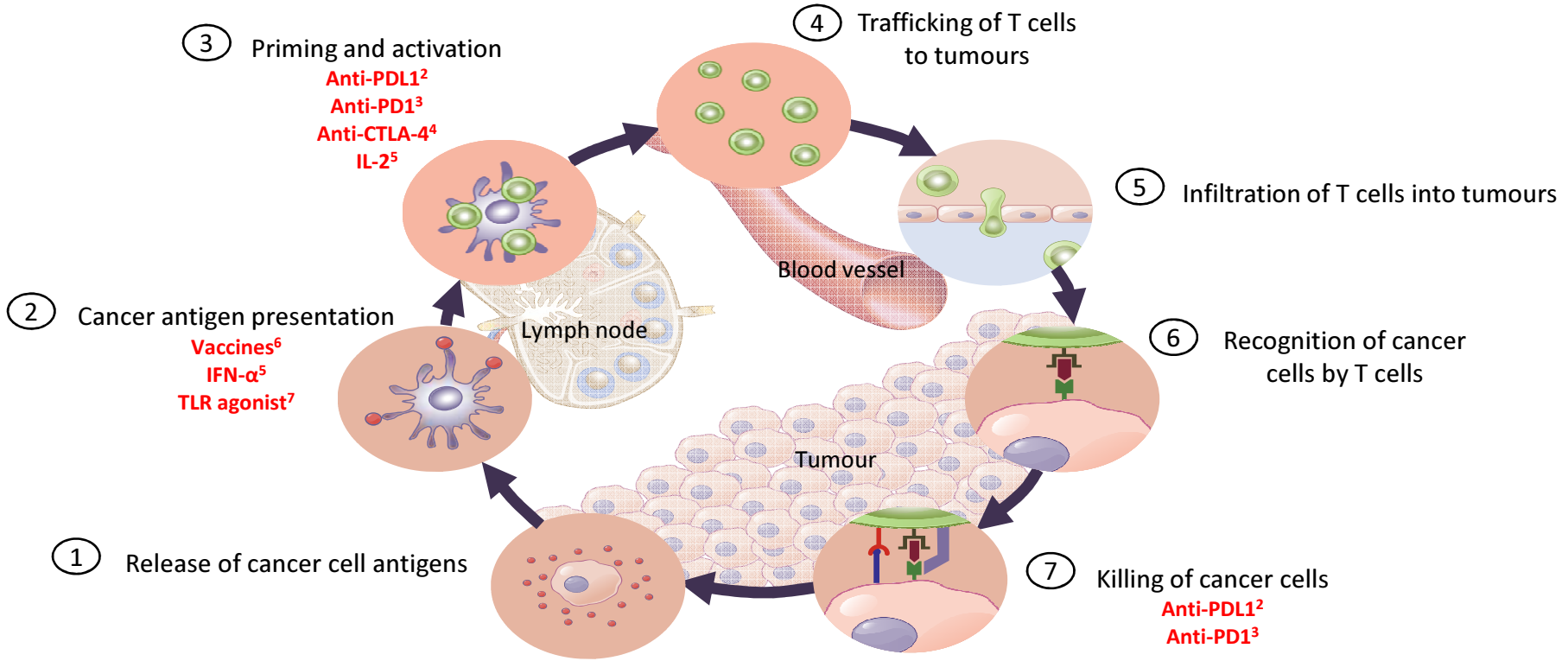
Avoiding Immune Destruction is a Hallmark of Cancer



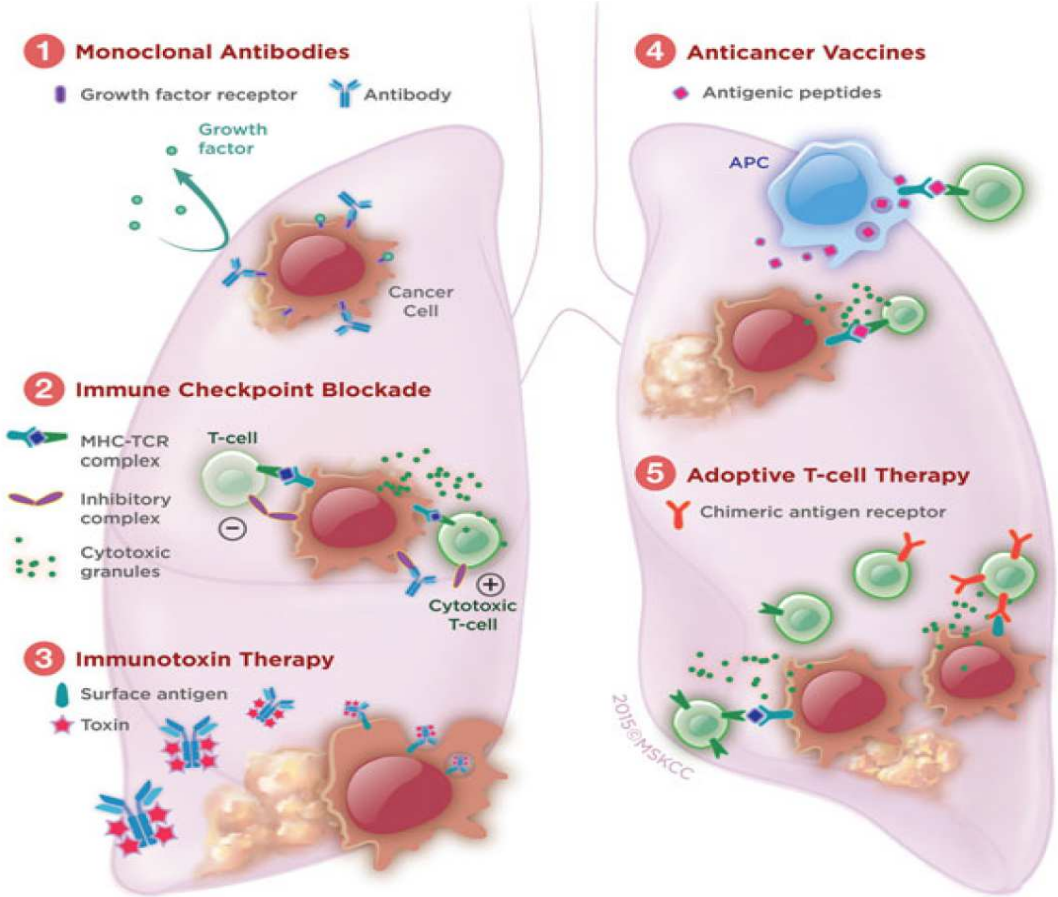
1. Hanahan & Weinberg. Cell 2011 2. Chen & Mellman. Immunity 2013

Immunotherapy in NSCLC can Target Several Steps in the Cancer Immunity



1. Chen and Mellman. Immunity 2013; 2. Soria, et al. ECC 2013; 3. Brahmer, et al. ASCO 2014 4. Lynch, et al. JCO 2012; 5. Jansen, et al. J Immunother 1992; 6.Vansteenkiste, et al. JCO 2013 7. Manegold, et al. JCO 2008

Current immunotherapeutic strategies for non-small cell lung cancer.



M Major et al, Eur J Cardio-Thor Surg 2015

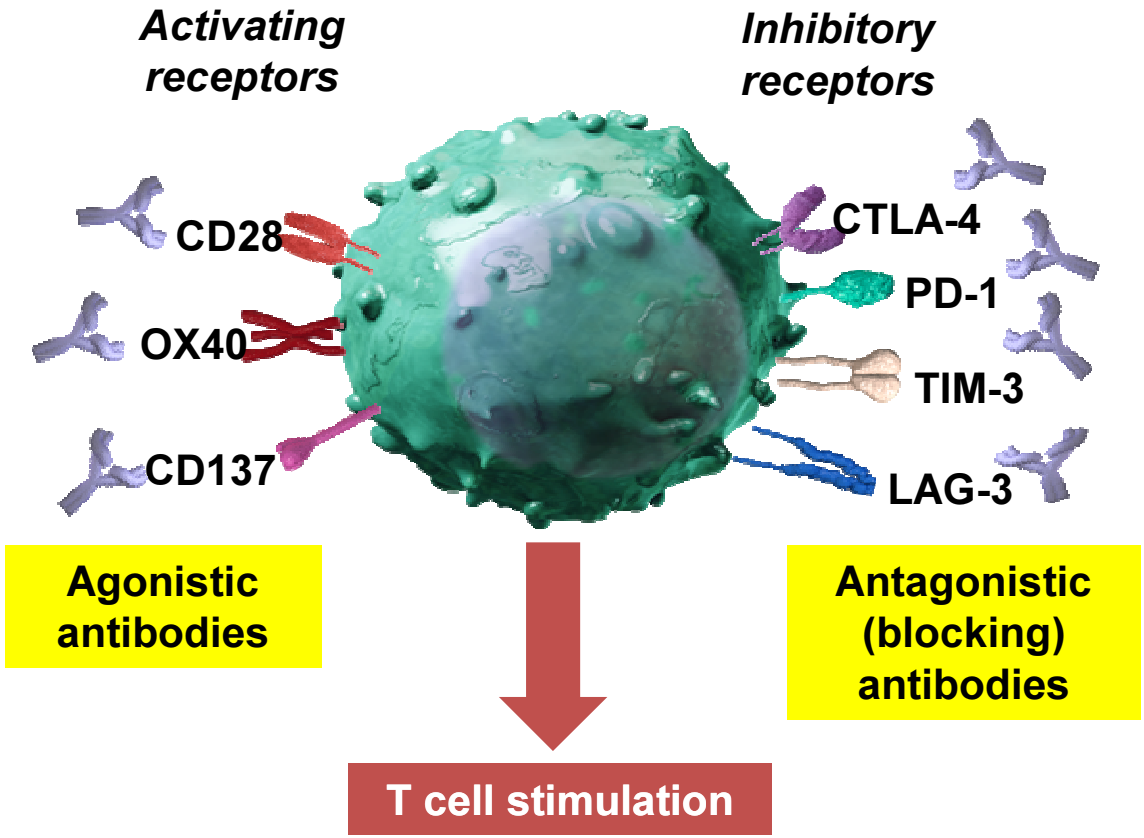
Failed Immunotherapies Tested in NSCLC

Agent	Immunotherapeutic Approach	Study Design	Patient Population	Results
SRL172	Nonspecific vaccine (killed *Mycobacterium*)	Open label: Chemotherapy ± SLR172 (phase III)	Stage III/IV unresectable NSCLC	Primary OS endpoint not met[29]
Tecemotide (L-BLP25)	Tumor-specific MUC1 vaccine	START: Tecemotide *v* placebo (phase III)	Stage III NSCLC after chemoradiation	Primary OS endpoint not met[30]
MAGE-A3	Tumor-specific MAGE-A3 vaccine	MAGRIT: MAGE-A3 *v* placebo (phase III)	Stage IB-IIIA resected MAGE-A3-positive NSCLC (adjuvant therapy)	Primary DFS endpoint not met[31]
GVAX	Autologous tumor cell vaccine with "bystander" GM-CSF-secreting cells	GVAX alone (phase I/II)	Advanced NSCLC	No objective responses[32]
Belagenpumatucel-L	TGF-β-blocking allogeneic tumor cell vaccine	STOP: Maintenance belagenpumatucel-L *v* placebo (phase III)	Stage III/IV NSCLC; no disease progression after frontline therapy	Primary OS endpoint not met; however, predefined subgroups derived substantial OS benefit[33]
Talactoferrin	Dendritic cell activation	FORTIS-M: Talactoferrin *v* placebo (phase III)	Stage III/IV NSCLC refractory to 2 or more therapies	Primary OS endpoint not met[34]
CPG 7909	Dendritic cell activation	Chemotherapy ± CPG 7909 (phase III)	Stage III/IV NSCLC naïve to chemotherapy	Primary OS endpoint not met[35]

Abbreviations: DFS, disease-free survival; GM-CSF, granulocyte-macrophage colony-stimulating factor; NSCLC, non-small cell lung cancer; OS, overall survival; TGF-β, transforming growth factor-beta.

NA Pennel, Semin Oncol 2015

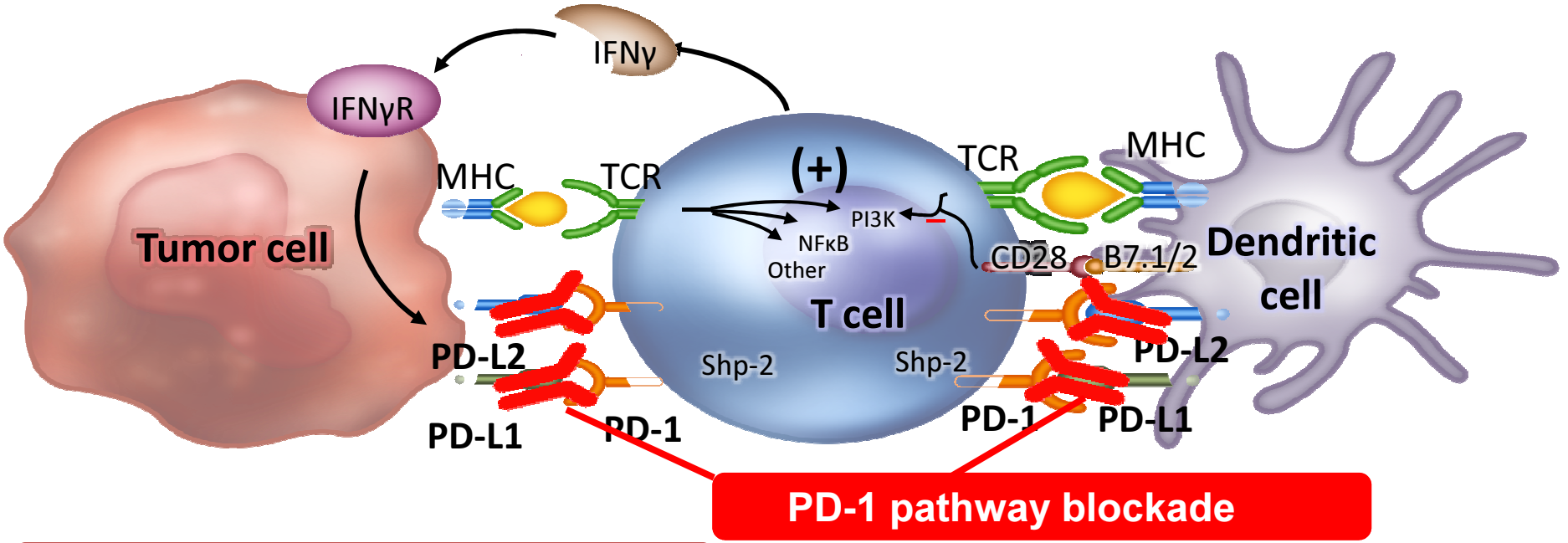
Regulating the T cell Immune Response



- T cell responses are regulated through a complex balance of inhibitory ('checkpoint') and activating signals
- Tumours can dysregulate checkpoint and activating pathways, and consequently the immune response
- Targeting checkpoint and activating pathways is an evolving approach to cancer therapy, designed to promote an immune response

Adapted from Mellman I, et al. *Nature.* 2011:480;481–489;
Pardoll DM. *Nat Rev Cancer.* 2012;12:252–264.

IMMUNE CHECKPOINT INHIBITORS IN NSCLC



PD-L1 As A Predictive Immune Biomarker: Assays Sample Collection And Analysis In NSCLC Studies

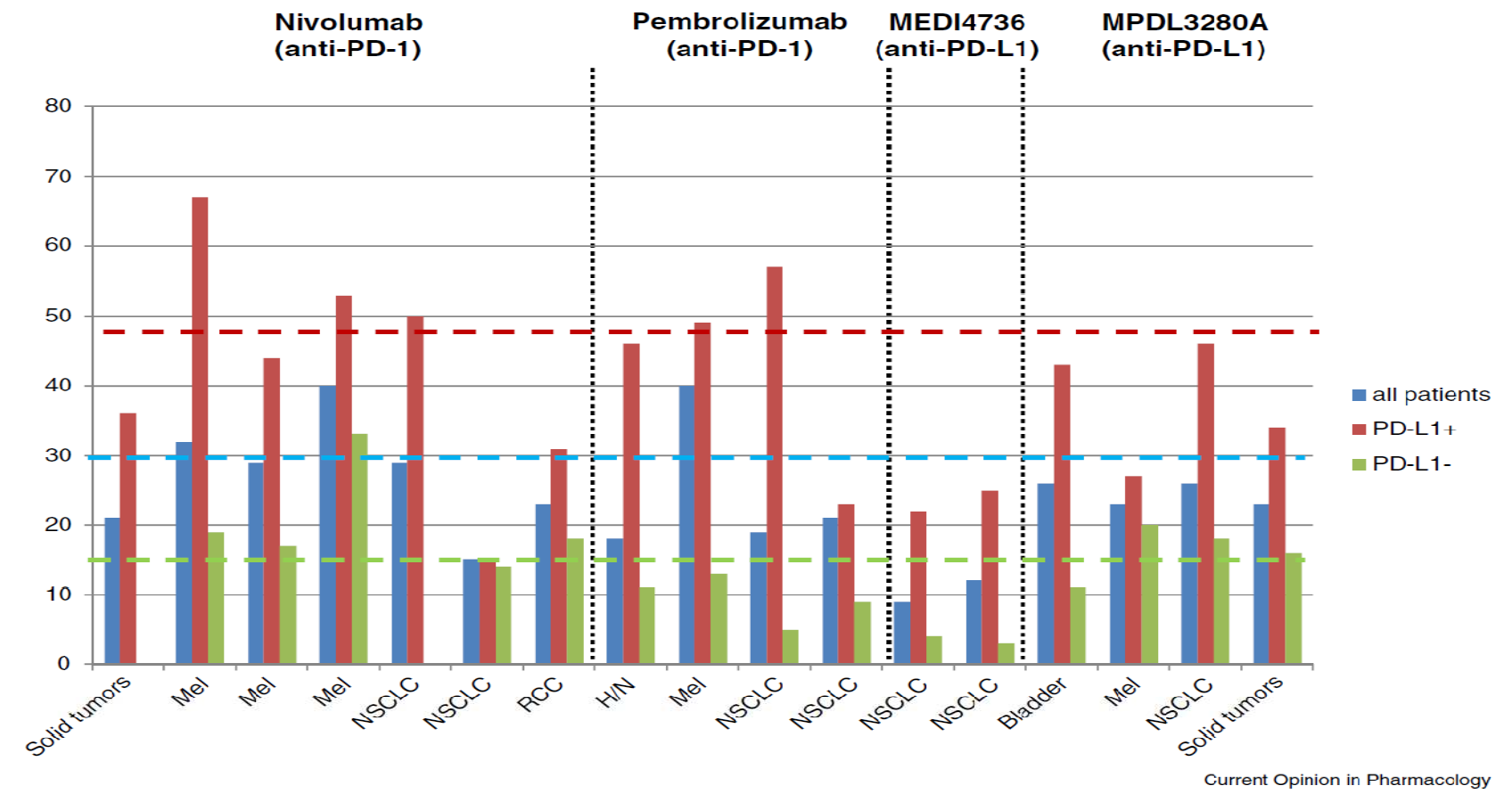
	Pembrolizumab Merck	Nivolumab Bristol-Myers Squibb	ATEZOLIZUMAB Roche/Genentech	DURVALUMAB AstraZeneca
PD-L1 Assay	• Prototype or clinical trial IHC assay (22C3 Ab)[1,2]	• Dako automated IHC assay (28-8 Ab)[3,4]	• Central laboratory IHC assay[6]	• Ventana automated IHC (BenchMark ULTRA using Ventana PD-L1 (SP263) clone)[8,9]
Sample Source and Collection	• Surface expression of PD-L1 on tumour specimen[1,2] • Ph I: Fresh or archival tissue[1,2]	• Surface expression of PD-L1 on tumour cells[3,4] • Archival or fresh tissue[3,4]	• Surface expression of PD-L1 on TILs or tumour cells[6,7] • Archival or fresh tissue[6]	• Surface expression of PD-L1 on tumour cells[8,9] • Unknown
Definition of Positivity†	**IHC Staining:** • Strong vs weak expression[1,2] • PD-L1 expression required for NSCLC for enrollment[1] • Note that one arm of KEYNOTE 001 trial requires PD-L1⁻ tumours[1] **Tumour PD-L1 expression:**[1,2] • ≥50% PD-L1⁺ cut-off:32% (41/129) • 1–49% PD-L1⁺ cut-off: 36% 46/129)	**IHC Staining:** • Strong vs weak expression[3,4] • Patients not restricted by PD-L1 status in 2nd- & 3rd-line • Ph III 1st-line trial in PD-L1+[5] **Tumour PD-L1 expression:** • 5% PD-L1⁺ cut-off: 59% (10/17)[3] • 5% PD-L1⁺ cut-off: 49% (33/68)[4]	**IHC Staining Intensity (0, 1, 2, 3):** •IHC 3 (≥10% PD-L1⁺)[6,7] •IHC 2,3 (≥5% PD-L1⁺)[6,7] •IHC 1,2,3 (≥1% PD-L1⁺)[6,7] •IHC 0,1,2,3 (all patients with evaluable status)[6,7] •PD-L1 expression required for NSCLC for enrolment in Ph II trials[6] **TIL PD-L1 expression:**[6] IHC 3 (≥10% PD-L1⁺): 11% (6/53) PD-L1 low (IHC 1, 0): 62% (33/53)	**IHC Staining Intensity:** •Not presented to date[8–10] **Tumour PD-L1 expression (all doses):**[8] •PD-L1⁺: 34% (20/58) •PD-L1⁻: 50% (29/58)

Ab, antibody;
IHC, immunohistochemistry

†Definition of PD-L1 positivity differs between assay methodologies.

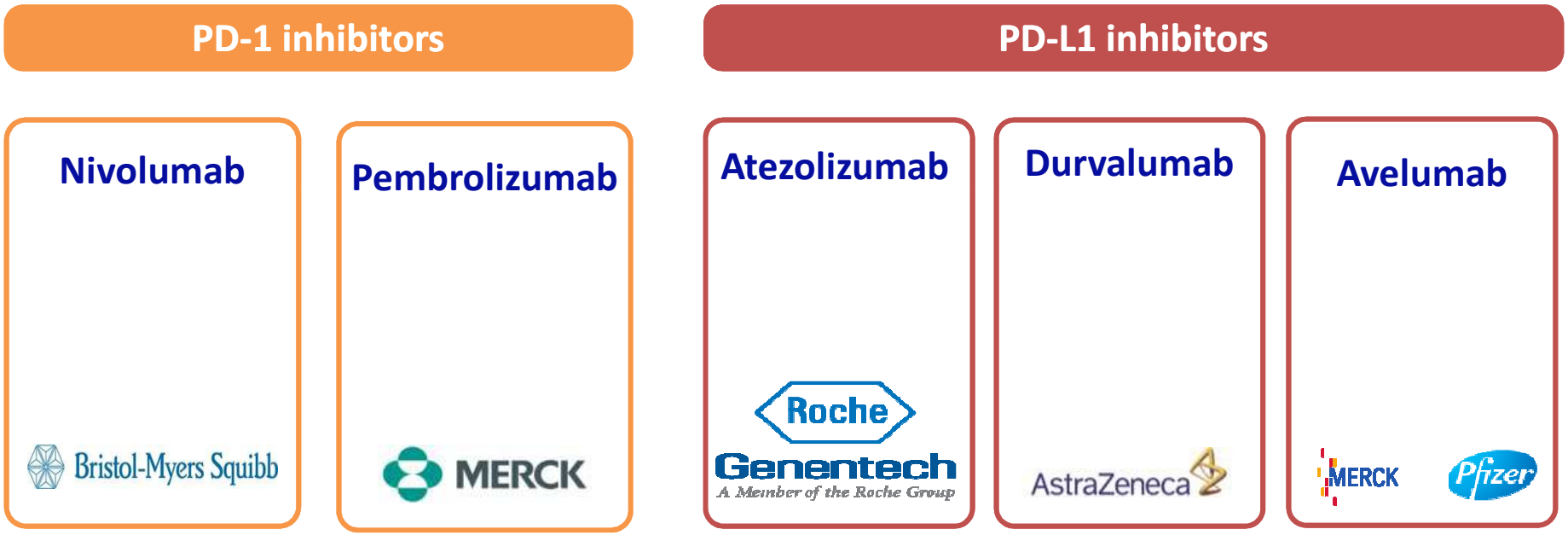
1. Garon EB, et al. Presented at ESMO 2014 (abstr. LBA43); 2. Rizvi NA, et al. Presented at ASCO 2014 (abstr. 8007); 3. Gettinger S et al. Poster p38 presented at ASCO 2014 (abstr. 8024); 4. Brahmer JR et al. Poster 293 presented at ASCO 2014 (abstr. 8112^); 5. http://www.clinicaltrials.gov/ct2/show/NCT02041533 Accessed January 2015; 6 . Rizvi NA et al. Poster presented at ASCO 2014 (abstr. TPS8123); 7. Soria J-C, et al. ESMO 2014 (abstr. 1322P); 8. Brahmer JR, et al. Poster presented at ASCO 2014 (abstr. 8021^); 9. Segal NH, et al. Presented at ASCO 2014 (abstr. 3002^); 10. Segal NH, et al. ESMO 2014 (abstr. 1058PD).

Association of PD-L1 expression in pre-treatment tumor specimens with objective response to anti-PD-1/PD-L1 therapy.



J Sunshine et al, Curr Op Pharma 2015

PD-1 And PD-L1 Inhibitors In Development for NSCLC



Immune Checkpoint Inhibitors in Development for NSCLC

Checkpoint Inhibitor	Phase	Patient Population
Nivolumab	FDA-approved	Recurrent advanced squamous NSCLC
Pembrolizumab	FDA-approved	Previously untreated advanced NSCLC (PD-L1–positive or unselected)
Durvalumab	III	Recurrent NSCLC after EGFR inhibition Previously untreated advanced NSCLC Stage III unresectable NSCLC Completely resected NSCLC
Atezolizumab	III	Chemotherapy-naïve stage IV NSCLC (PD-L1-positive or unselected)
Avelumab	III	Recurrent advanced NSCLC
Ipilimumab	III	Stage IV/recurrent squamous NSCLC
Tremelimumab	III	Previously untreated advanced NSCLC Stage III/IV NSCLC after $\geq$2 prior therapies

Abbreviations: EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1.

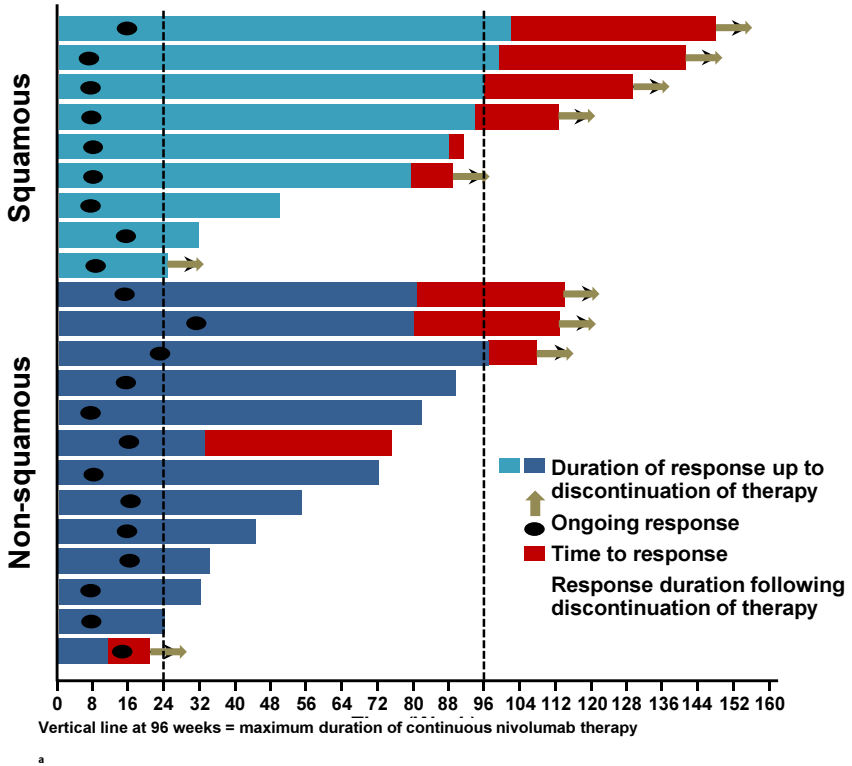
Mod from NA Pennel, Semin Oncol 2015

Clinical studies of nivolumab in non-small cell lung cancer.

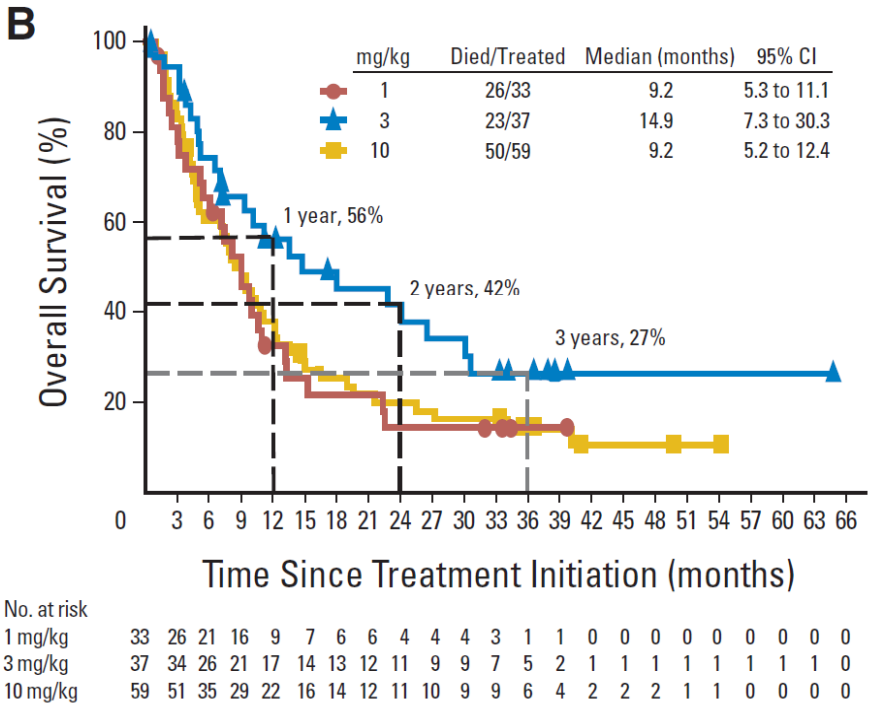
Study	Agent	Phase	Population	Treatment Arms	No. Patients	Primary Endpoint	ORR	OS and/or PFS	Grade 3+ AEs (Related to Checkpoint Inhibitor)
Gettinger et al[2]	Nivolumab	I	Advanced, refractory NSCLC	Nivolumab monotherapy at varying doses	129	OS	17%	OS: 9.9 mo (across all doses tested)	4.7%
CheckMate 063[26]	Nivolumab	II	Advanced, refractory squamous NSCLC	Nivolumab monotherapy (single arm)	117	ORR	14.5%	Median PFS: 1.9 mo Median OS: 8.2 mo	17% (Pneumonitis 3%)
CheckMate 017[27]	Nivolumab	III	Advanced, refractory squamous NSCLC	Nivolumab vs docetaxel	N: 135 DOC: 137	OS	20% vs 9%, favoring N ($P = 0.008$)	OS: 9.2 vs 6 mo, favoring nivolumab (HR, 0.59; $P < 0.001$)	7% (Pneumonitis 0%)
CheckMate 057[28]	Nivolumab	III	Advanced, refractory nonsquamous NSCLC	Nivolumab vs docetaxel	N: 292 DOC: 290	OS	19% vs 12%, favoring N ($P = 0.0246$)	OS: 12.2 vs 9.4 mo, favoring nivolumab (HR, 0.73; $P = 0.0015$)	10.5%

NA Rizvi, Cancer J 2015

Overall Survival and Long-Term Safety of Nivolumab (Anti–Programmed Death 1 Antibody, BMS-936558, ONO-4538) in Patients With Previously Treated Advanced Non–Small-Cell Lung Cancer



NSCLC Responders[a,b] by Histology



Gettinger SN, et al. JCO 2015

Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial

	Patients (n=117)
Previous systemic therapy	
Platinum-based therapy	117 (100%)
Other	117 (100%)
EGFR TKI	39 (33%)
Experimental treatment	13 (11%)
Number of previous systemic treatments	
2	41 (35%)
3	52 (44%)
≥4	24 (21%)
Previous radiotherapy	87 (74%)
Best response to most recent previous treatment	
CR or PR	5 (4%)
SD	32 (27%)
Progressive disease	71 (61%)
Unknown	9 (8%)

Patients received nivolumab 3 mg/kg as an intravenous infusion every 2 weeks (1 cycle) until disease progression or unacceptable toxic effects.

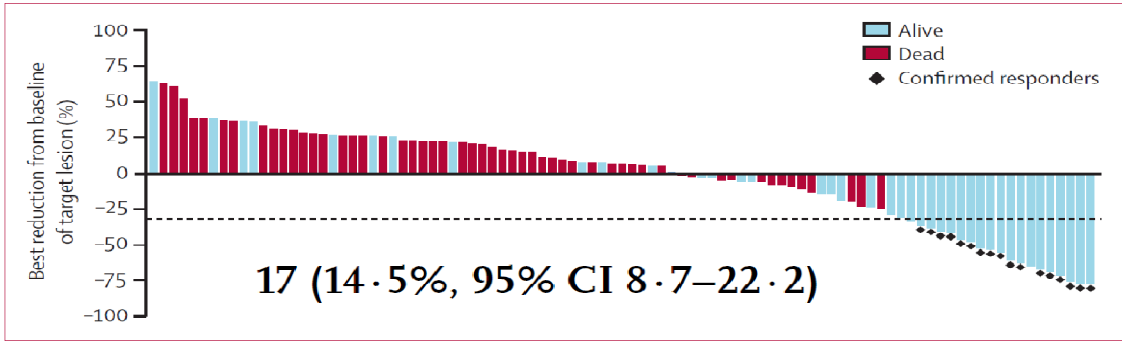
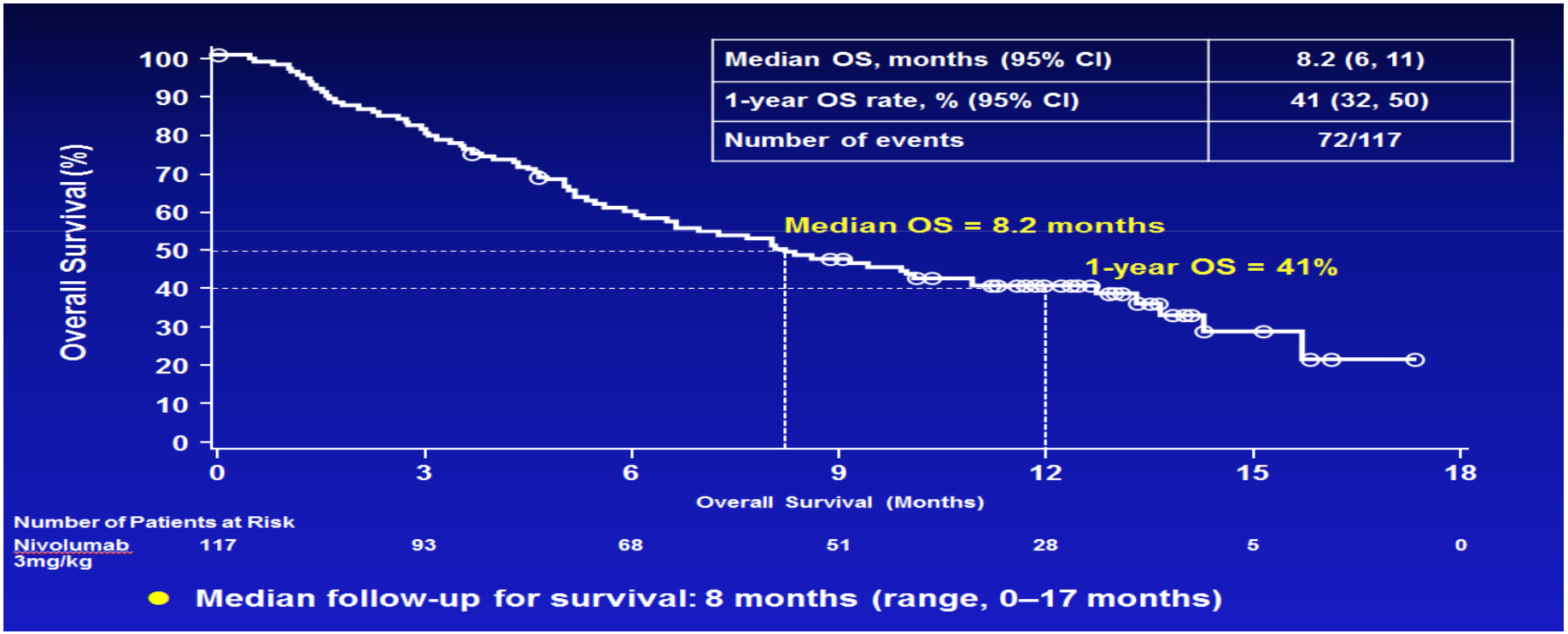


Figure 1: Best reduction of tumour size

NA Rizvi et al, Lancet Oncology 2015

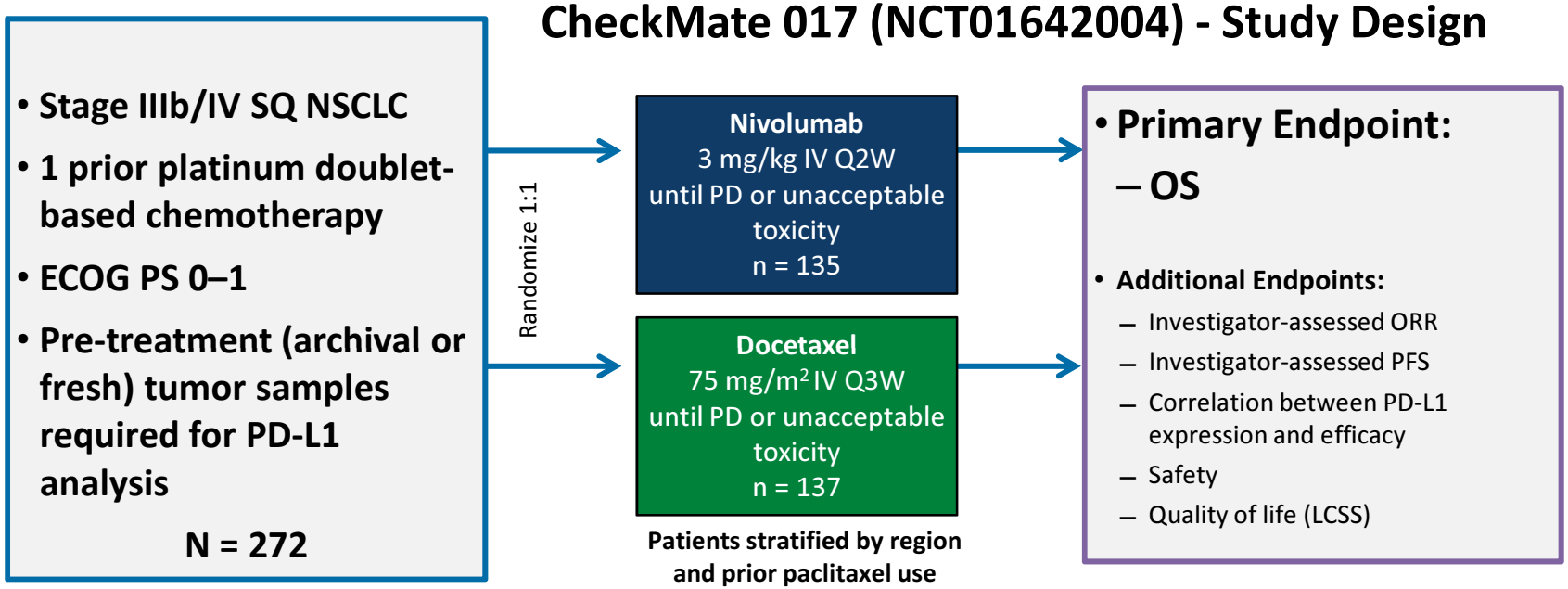
Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial



NA Rizvi et al, Lancet Oncol 2015

Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

CheckMate 017 (NCT01642004) - Study Design



- One pre-planned interim analysis for OS
- At time of DBL (December 15, 2014), 199 deaths were reported (86% of deaths required for final analysis)
- The boundary for declaring superiority for OS at the pre-planned interim analysis was P <0.03

LCSS = Lung cancer symptom scale

Spigel et al, ASCO 2015; Brahmer et al, NEJM 2015

CheckMate 017 – Baseline Characteristics

	Nivolumab n = 135	Docetaxel n = 137
Median age, years (range)	62 (39–85)	64 (42–84)
≥75, %	8	13
Male, %	82	71
Disease stage,[a] %		
Stage IIIb	21	18
Stage IV	78	82
Performance status, %		
0	20	27
1	79	73
CNS metastasis, %	7	6
Current/former smoker, %	90	94
PD-L1 expression,[b] %		
≥1%	47	41
≥5%	31	29
≥10%	27	24
Not quantifiable	13	21

- **83% (225/272) of patients had quantifiable PD-L1 expression**

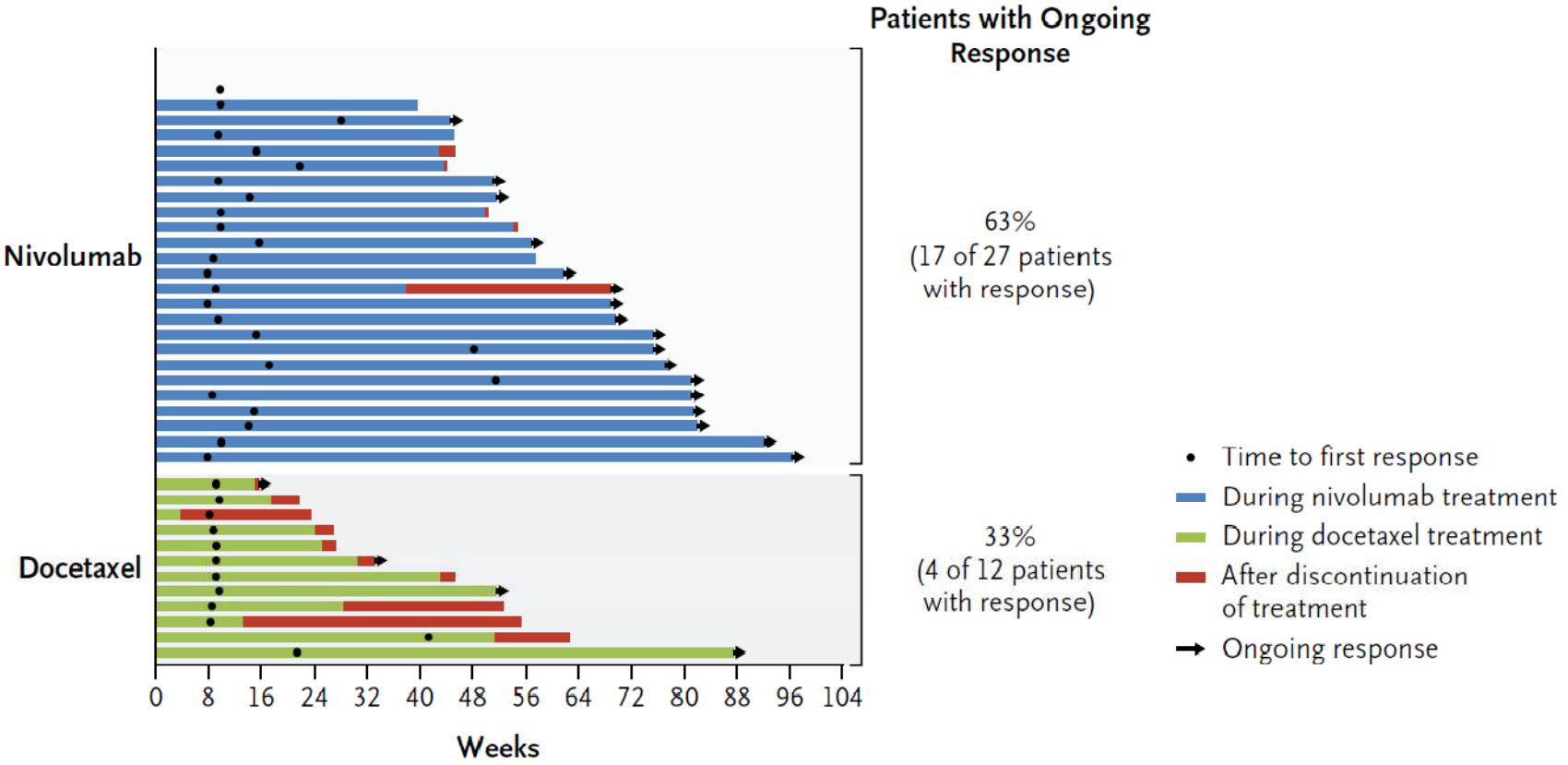
Spigel et al, ASCO 2015; Brahmer et al, NEJM 2015

Table 2. Clinical Activity of Nivolumab versus Docetaxel in Patients with Advanced Squamous-Cell Non–Small-Cell Lung Cancer.*

Variable	Nivolumab (N = 135)	Docetaxel (N = 137)
Objective response†		
No. of patients	27	12
% of patients (95% CI)	20 (14–28)	9 (5–15)
Estimated odds ratio (95% CI)	2.6 (1.3–5.5)	
P value	0.008	
Best overall response — no. (%)		
Complete response	1 (1)	0
Partial response	26 (19)	12 (9)
Stable disease	39 (29)	47 (34)
Progressive disease	56 (41)	48 (35)
Could not be determined	13 (10)	30 (22)
Time to response — mo‡§		
Median	2.2	2.1
Range	1.6–11.8	1.8–9.3
Duration of response — mo‡¶		
Median	NR	8.4
Range	2.9 to 20.5+	1.4+ to 15.2+

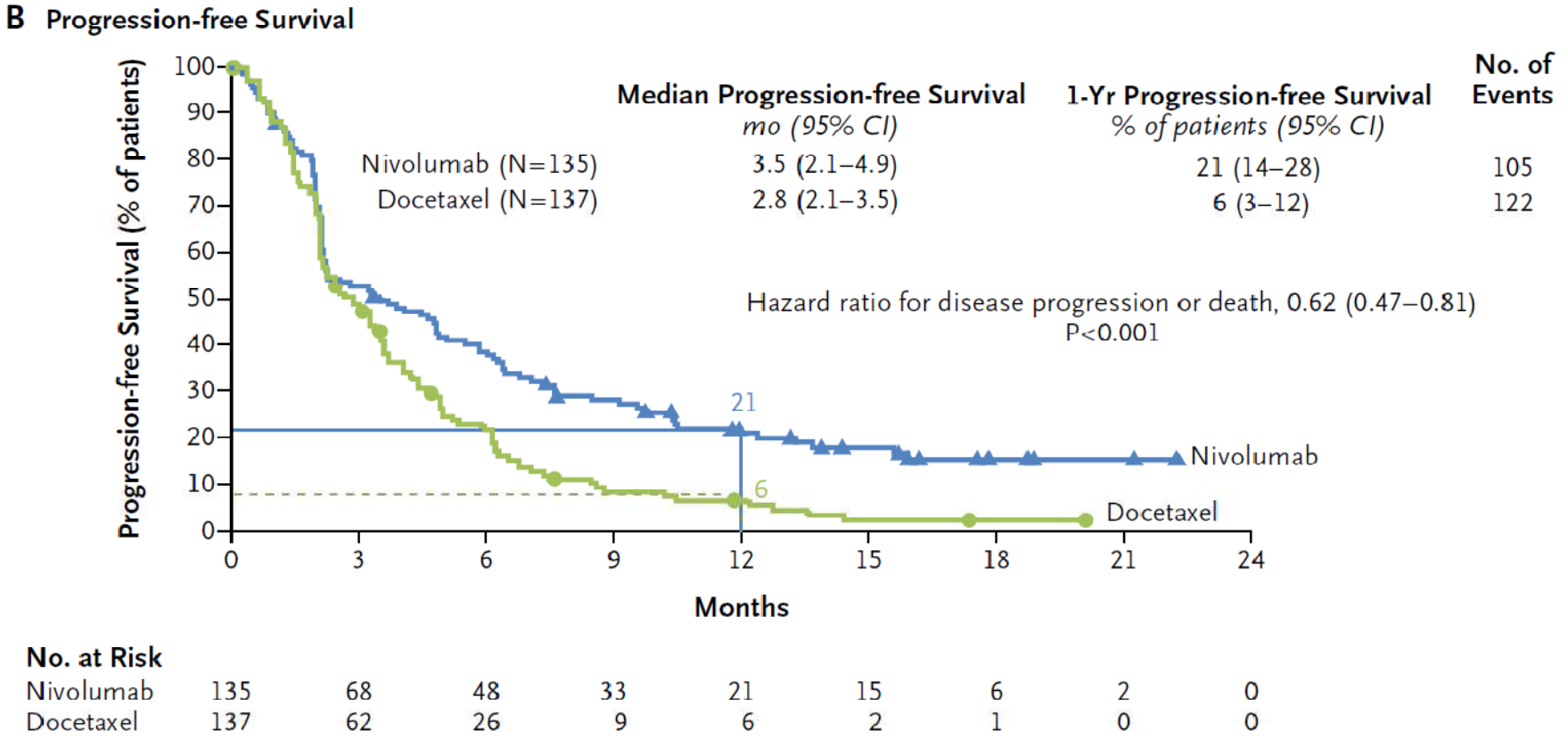
Spigel et al, ASCO 2015; Brahmer et al, NEJM 2015

CheckMate 017 – Duration of Response



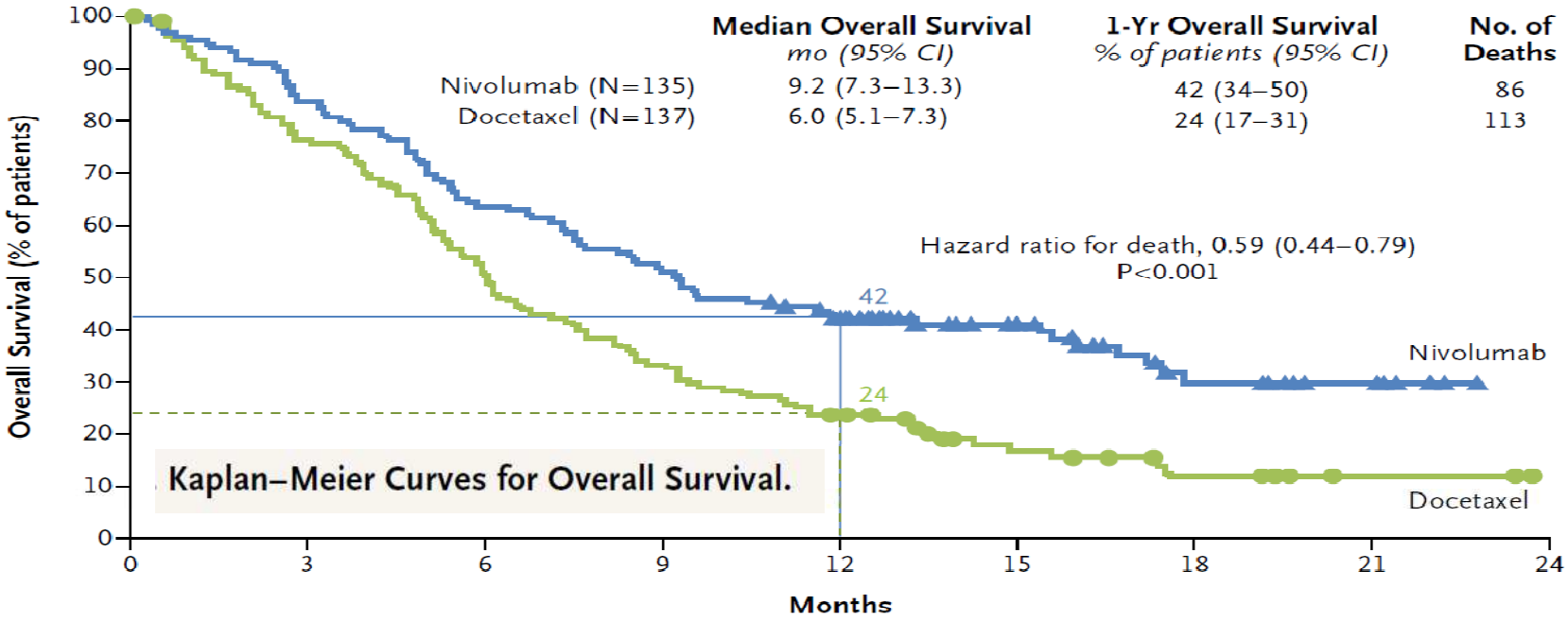
Spigel et al, ASCO 2015; Brahmer et al, NEJM 2015

CheckMate 017 – Progression Free Surviuval



Spigel et al, ASCO 2015; Brahmer et al, NEJM 2015

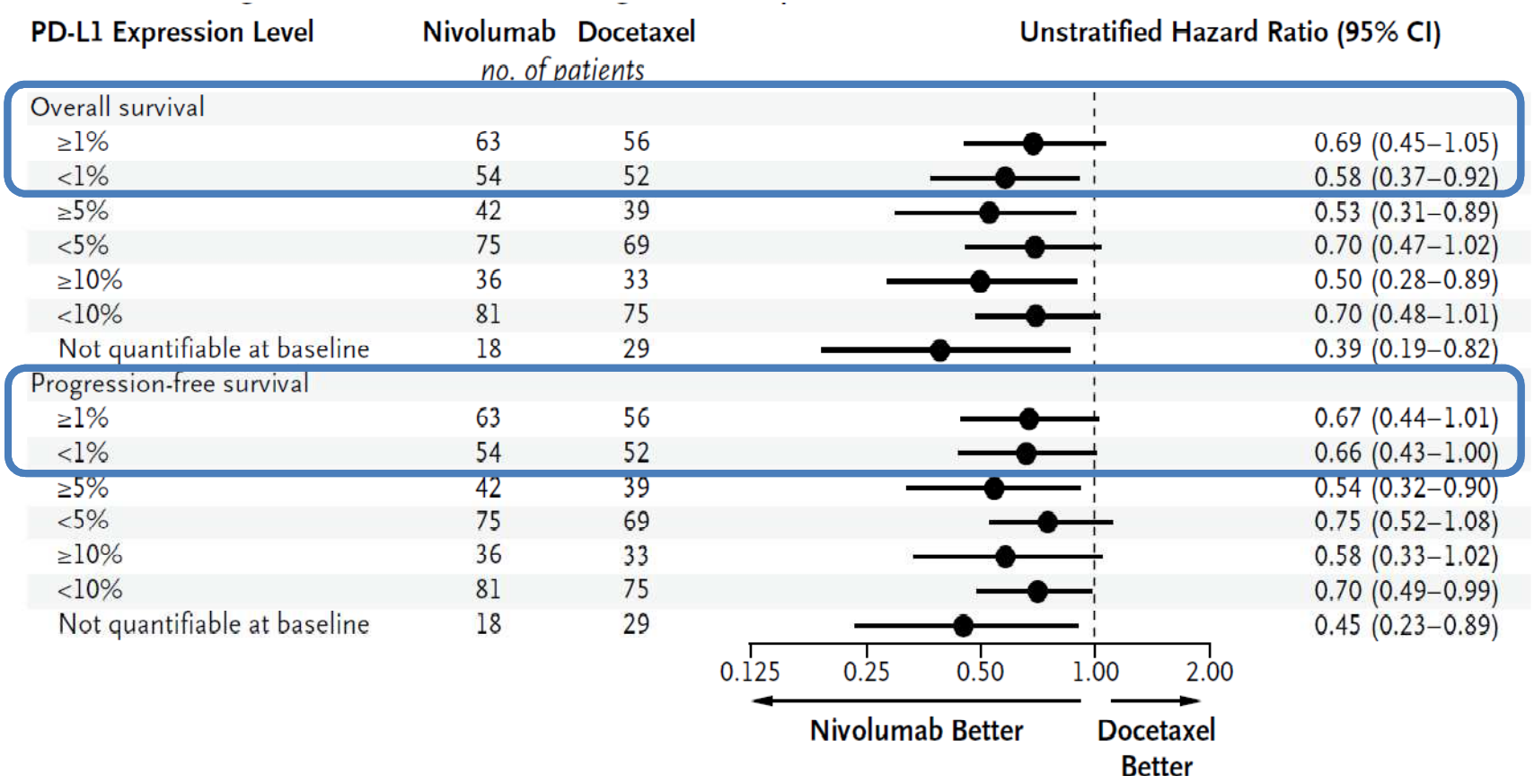
Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer



No. at Risk									
Nivolumab	135	113	86	69	52	31	15	7	0
Docetaxel	137	103	68	45	30	14	7	2	0

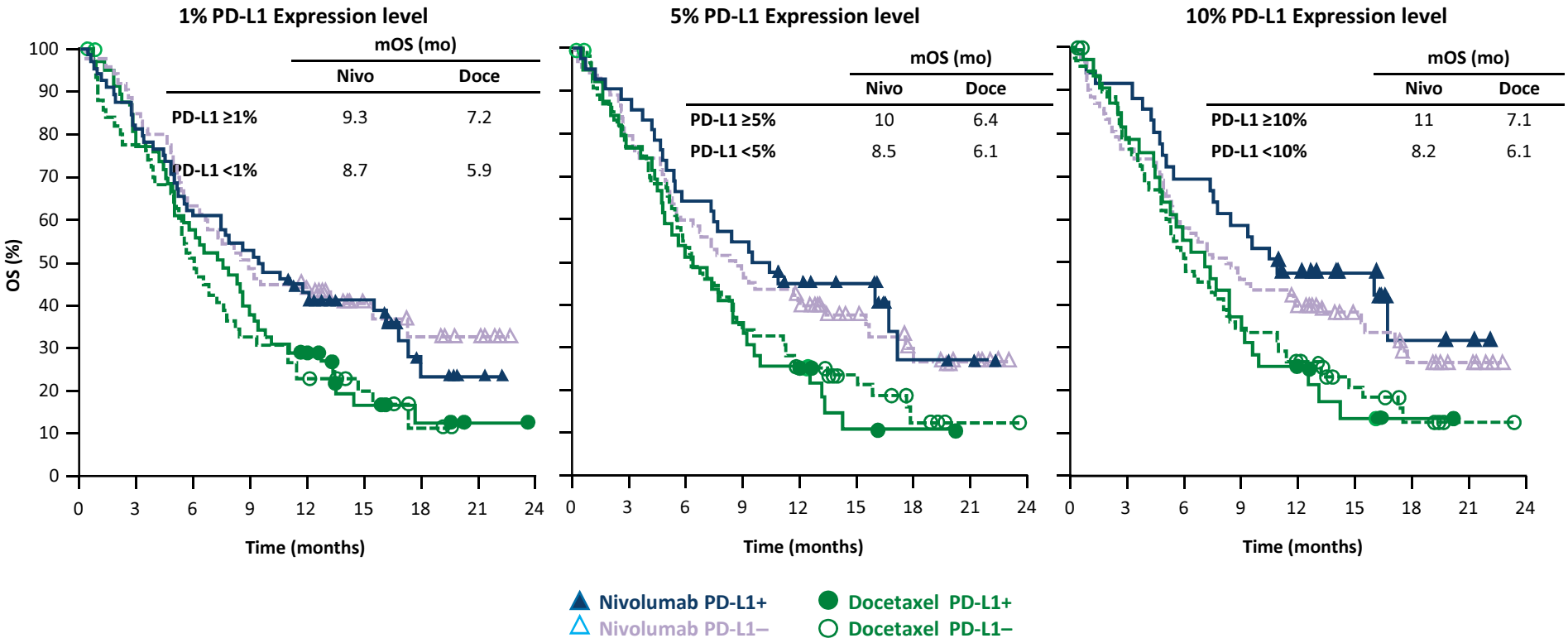
Spigel et al, ASCO 2015; Brahmer et al, NEJM 2015

Overall and Progression-free Survival According to PD-L1 Expression Level



Spigel et al, ASCO 2015; Brahmer et al, NEJM 2015

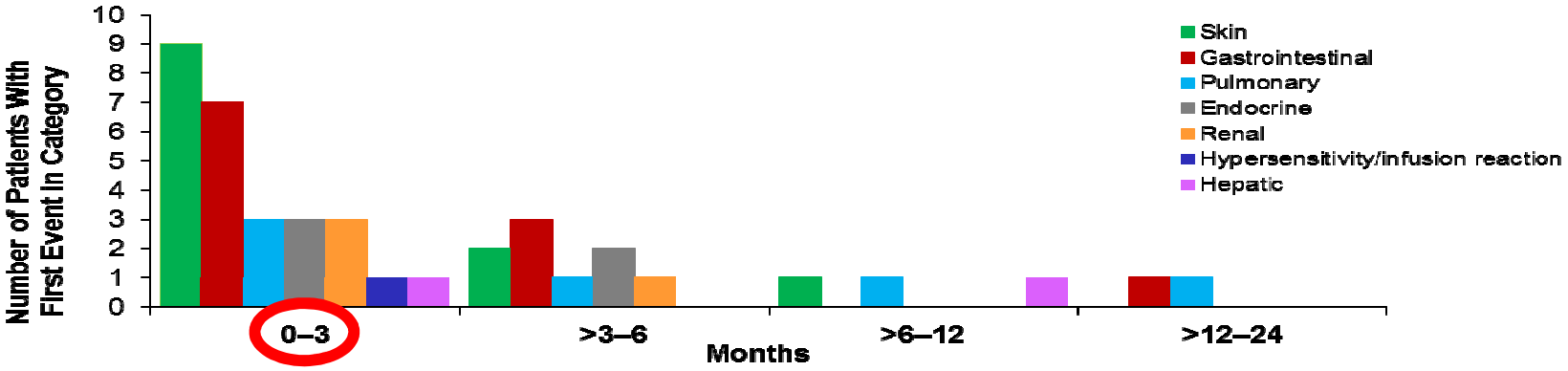
CheckMate 017 – OS by PD-L1 Expression



Spigel et al, ASCO 2015; Brahmer et al, NEJM 2015

CheckMate 017: Updated Safety

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



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

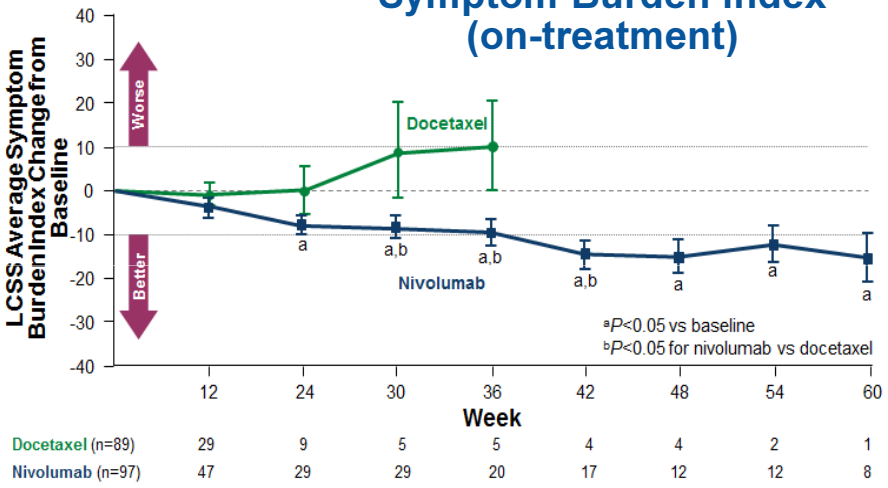
- The majority of patients who experienced treatment-related select AEs with nivolumab experienced their first event within the first 3 months of treatment

Select AEs: AEs with potential immunologic etiology that require frequent monitoring/intervention.
Based on December 2014 DBL. Includes events reported between first dose and 30 days after last dose of study therapy.
Within each time interval, patients with ≥1 event were counted only once in each category but could be classified into more than one category

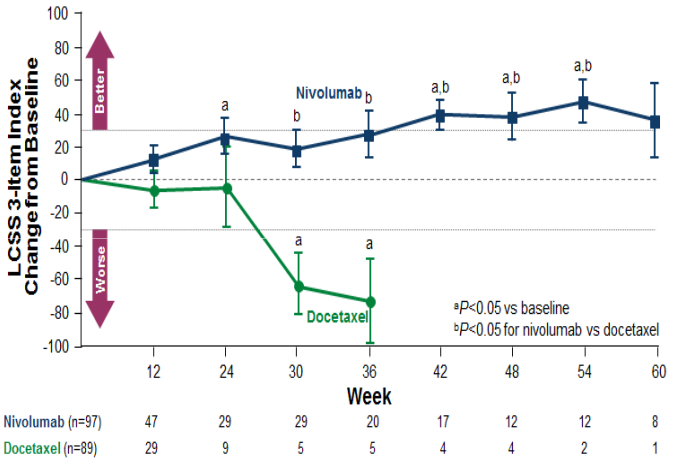
Reckamp K ORAL02.01

CheckMate 017: Patient Reported Outcomes (PROs)

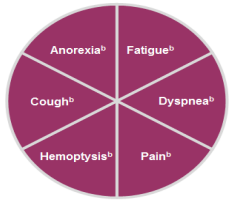
LCSS Average Symptom Burden Index (on-treatment)



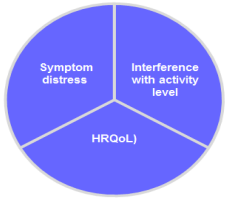
LCSS-3 Item Index (on treatment)



Average Symptom Burden Index (0–100)
(MID ≥10; higher is worse)



3-Item Index (0–300)b
(MID ≥30; higher is better)



Gralla R et al, WCLC 2015 ORAL31.03

CheckMate 017 - SUMMARY

- Nivolumab is the first PD-1 inhibitor to demonstrate a survival benefit versus standard-of-care docetaxel in previously-treated patients with **advanced SQ NSCLC**
  - 41% reduction in risk of death **(HR 0.59; *P* = 0.00025)**
  - 1-yr OS: 42% vs 24%
  - mOS: 9.2 vs 6.0 mo
- Nivolumab demonstrated superiority over docetaxel across all secondary efficacy endpoints
  - ORR: 20% vs 9% (*P* = 0.0083)
  - 1-yr PFS: 21% vs 6.4%; mPFS: 3.5 vs 2.8 mo (HR 0.62; *P* = 0.0004)
- **Nivolumab benefit was independent of PD-L1 expression**
- The safety profile of nivolumab was favorable versus docetaxel and consistent with prior studies

- **Nivolumab received FDA approval in the US on March 4, 2015 for metastatic SQ-NSCLC with progression on or after platinum-based chemotherapy**

VOLUME 33 · NUMBER 30 · OCTOBER 20 2015

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Systemic Therapy for Stage IV Non–Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

CLINICAL QUESTION B2

What is the most effective second-line therapy for patients with stage IV NSCLC with negative or unknown *EGFR*/*ALK* status and SCC?

On March 14, 2015, the FDA approved nivolumab for the treatment of patients with metastatic squamous cell NSCLC with disease progression who had received ≥ one prior platinum-based regimen on the basis of an RCT with 272 participants, in which patients were randomly assigned to receive single-agent nivolumab versus docetaxel. Median OS was 9.2 versus 6 months, favoring nivolumab (HR, 0.59; 95% CI, 0.44 to 0.79; $P < .001$). This trial was published while this ASCO guideline update was in press; therefore, the final impact cannot yet be determined.[101] The Update Committee awaits fuller data on adverse events before full incorporation into this guideline.

101. Brahmer J, Reckamp KL, Baas P, et al: Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 373: 123-135, 2015

EXPANDED ACCESS GUIDANCE DOCUMENT CA209254

EXPANDED ACCESS SINGLE NAMED PATIENT GUIDANCE DOCUMENT FOR THE USE OF NIVOLUMAB FOR THE TREATMENT OF SQUAMOUS CELL NONSMALL CELL LUNG CARCINOMA

Version of 06 March 2015

GAZZETTA UFFICIALE

AGENZIA ITALIANA DEL FARMACO

DETERMINA 17 settembre 2015

Inserimento del medicinale per uso umano «nivolumab» nell'elenco dei medicinali erogabili a totale carico del Servizio sanitario nazionale ai sensi della legge 23 dicembre 1996, n. 648, per il trattamento di seconda linea del carcinoma polmonare non a piccole cellule avanzato ad istologia squamosa. (Determina n. 1215/2015). (15A07159) (GU Serie Generale n.220 del 22-9-2015)

LINEE GUIDA PER LA GESTIONE INTEGRATA DEL PAZIENTE CON TUMORE POLMONARE

IMMUNOTERAPIA

AIOT
ASSOCIAZIONE ITALIANA ONCOLOGIA TORACICA

RACCOMANDAZIONI

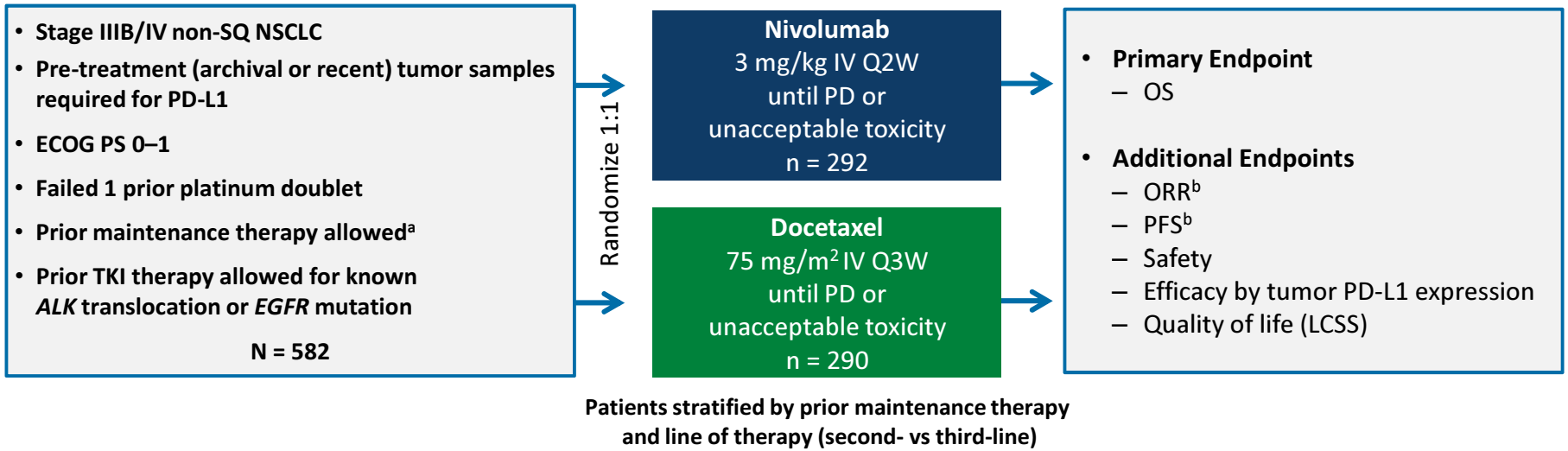
- **Per i pazienti affetti da NSCLC avanzato ad istologia squamosa, il trattamento di seconda linea con nivolumab come agente singolo è raccomandato**

  LIVELLO DI EVIDENZA IB

  GRADO DI RACCOMANDAZIONE A

Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer

CheckMate 057 - Study Design



Patients stratified by prior maintenance therapy and line of therapy (second- vs third-line)

- PD-L1 expression measured using the Dako/BMS automated IHC assay[14,15]
  - Fully validated with analytical performance having met all pre-determined acceptance criteria for sensitivity, specificity, precision, and robustness

[a] Maintenance therapy included pemetrexed, bevacizumab, or erlotinib (not considered a separate line of therapy); [b] Per RECIST v1.1 criteria as determined by the investigator.

Paz-Ares et al, ASCO 2015; Borghaei et al, NEJM 2015

CheckMate 057 - Baseline Characteristics

	Nivolumab (n = 292)	Docetaxel (n = 290)
Median age, years (range)	61 (37, 84)	64 (21, 85)
≥75 years, %	7	8
Male, %	52	58
Smoking status, %		
Current/former smoker	79	78
Never smoker	20	21
ECOG PS,[a] %		
0	29	33
1	71	67
Prior maintenance therapy, %	42	38
Number of prior systemic regimens,[b,c] %		
1	88	89
2	12	11
***EGFR*-positive mutation status, %**	15	13
***ALK*-positive translocation status, %**	4	3
Baseline PD-L1 expression		
Quantifiable (% of evaluable patients)		
≥1%	53	55
≥5%	41	38
≥10%	37	35
Not quantifiable (% of randomized patients)	21	23

Paz-Ares et al, ASCO 2015; Borghaei et al, NEJM 2015

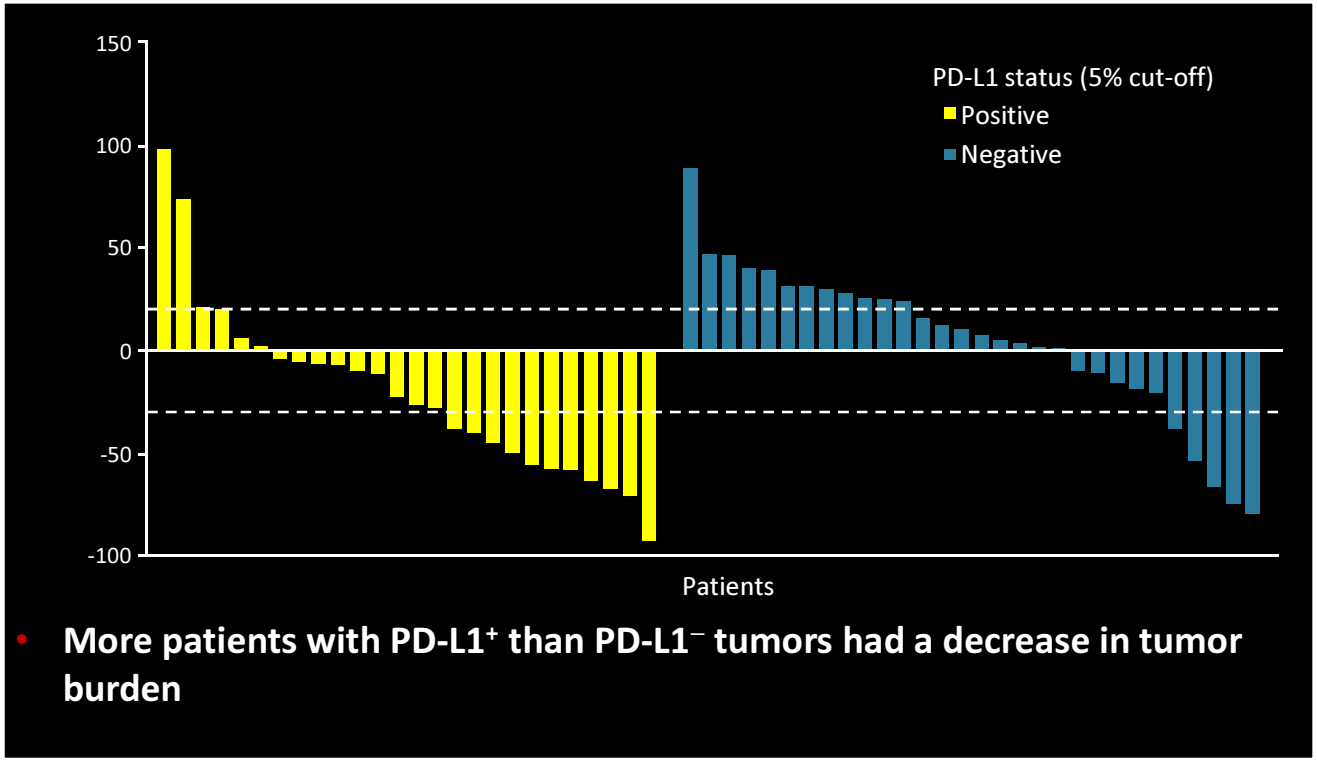
CheckMate 057 – Objective Response Rate

	Nivolumab (n = 292)	Docetaxel (n = 290)
ORR (95% CI)	**19%** (15, 24)	**12%** (9, 17)
***Odds Ratio* (95% CI)**	1.72 (1.1, 2.6)	
***P*-value[a]**	0.0246	
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,[b] mo (range)	2.1 (1.2, 8.6)	2.6 (1.4, 6.3)
Median DOR,[b] mo (range)	**17.2** (1.8, 22.6+)	**5.6** (1.2+, 15.2+)
Ongoing response,[c] %	52	14

- 71 (24%) patients on nivolumab were treated beyond RECIST v1.1-defined progression
- Non-conventional benefit was observed in 16 patients (not included in best overall response)

Paz-Ares et al, ASCO 2015; Borghaei et al, NEJM 2015

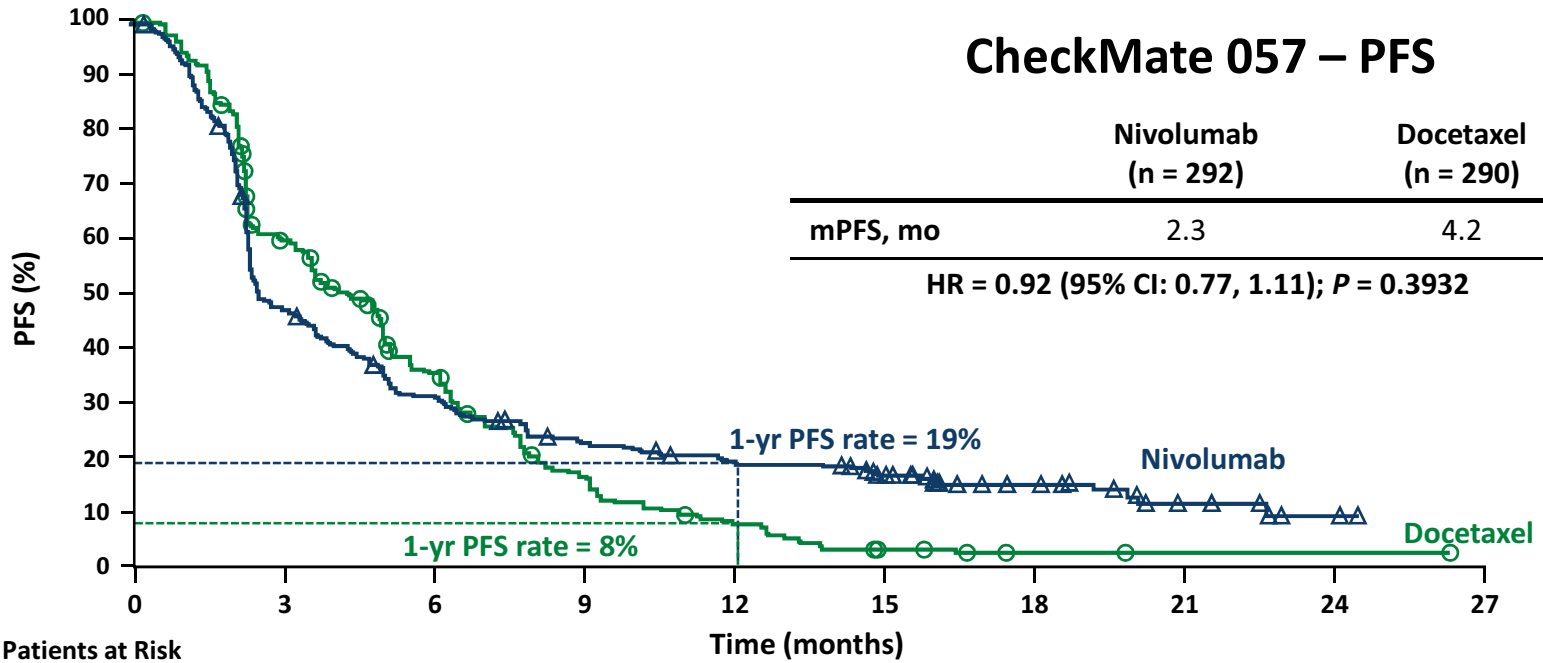
Nivolumab activity was observed in patients with PD-L1^{+} tumors and also in some patients with PD-L1^{-} tumors



- More patients with PD-L1^{+} than PD-L1^{-} tumors had a decrease in tumor burden

Brahmer JR, et al. ASCO 2014 (abstr. 8112).

Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer



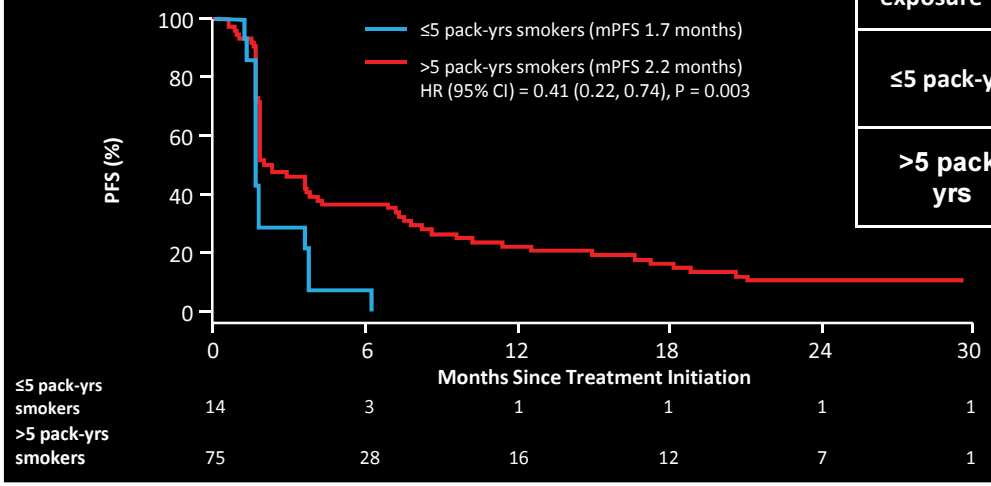
Symbols represent censored observations.

Paz-Ares et al, ASCO 2015; Borghaei et al, NEJM 2015

Smoking Status and Response to Immunotherapy in NSCLC

In studies of nivolumab, a history of smoking in patients with NSCLC was associated with improved clinical response and PFS

PFS by smoking exposure

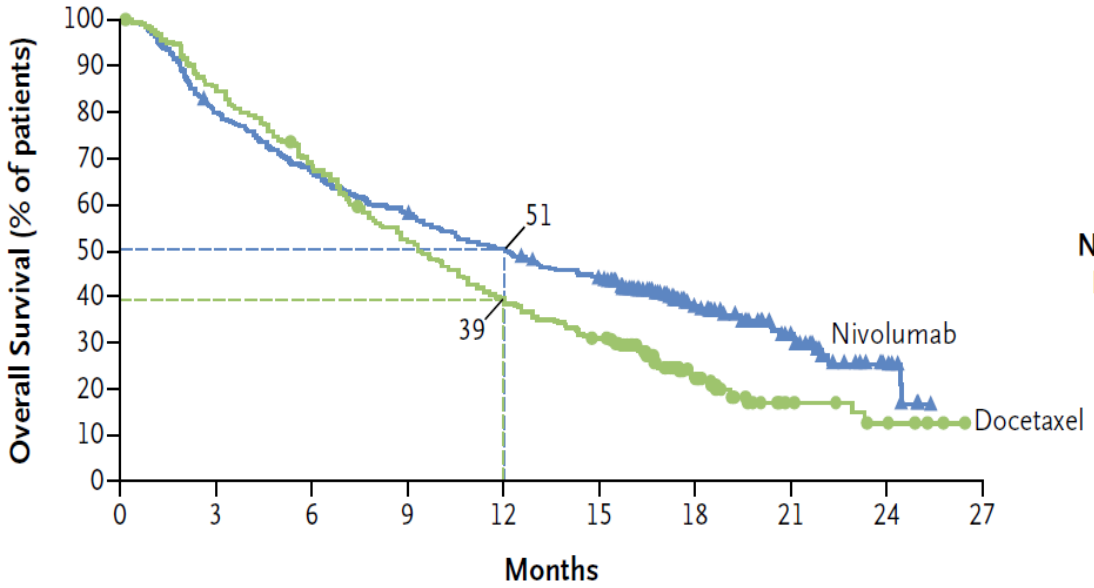


Variable	ORR, % (n/N) [95% CI]	*P*-value
Smoking exposure		
≤5 pack-yrs	0 (0/14) [0, 23]	0.018
>5 pack-yrs	30 (20/66) [20, 43]	

HR = hazard ratio; mPFS = median progression-free survival; ORR = objective response rate; PFS = progression-free survival.
Hellmann MD, et al. Poster presented at ESMO 2014 (asbtr. 1229PD).

Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer

A Overall Survival



	No. of Deaths/ Total No. of Patients	Median Overall Survival (95% CI)	1-Yr Overall Survival Rate (95% CI)
		mo	%
Nivolumab	190/292	12.2 (9.7–15.0)	51 (45–56)
Docetaxel	223/290	9.4 (8.1–10.7)	39 (33–45)

Hazard ratio for death, 0.73 (96% CI, 0.59–0.89)
P=0.002

No. at Risk

Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

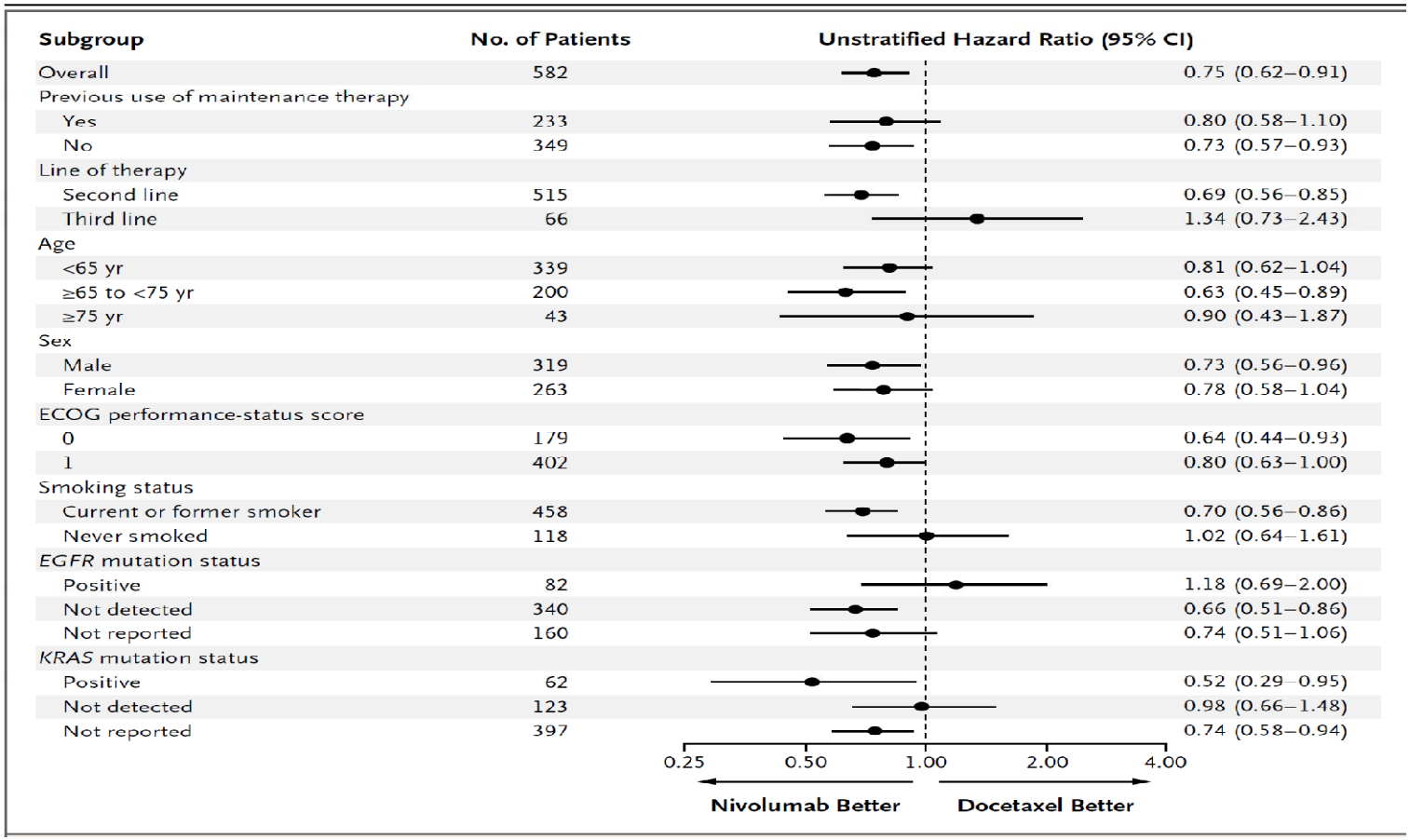
Paz-Ares et al, ASCO 2015; Borghaei et al, NEJM 2015

Treatment-Related Adverse Events Reported in at Least 10% of the Patients Treated with Nivolumab or Docetaxel.*

Event	Nivolumab (N = 287)		Docetaxel (N = 268)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with an event (percent)			
Any event	199 (69)	30 (10)	236 (88)	144 (54)
Fatigue	46 (16)	3 (1)	78 (29)	13 (5)
Nausea	34 (12)	2 (1)	70 (26)	2 (1)
Decreased appetite	30 (10)	0	42 (16)	3 (1)
Asthenia	29 (10)	1 (<1)	47 (18)	6 (2)
Diarrhea	22 (8)	2 (1)	62 (23)	3 (1)
Peripheral edema	8 (3)	0	28 (10)	1 (<1)
Myalgia	7 (2)	1 (<1)	30 (11)	0
Anemia	6 (2)	1 (<1)	53 (20)	7 (3)
Alopecia	1 (<1)	0	67 (25)	0
Neutropenia	1 (<1)	0	83 (31)	73 (27)
Febrile neutropenia	0	0	27 (10)	26 (10)
Leukopenia	0	0	27 (10)	22 (8)

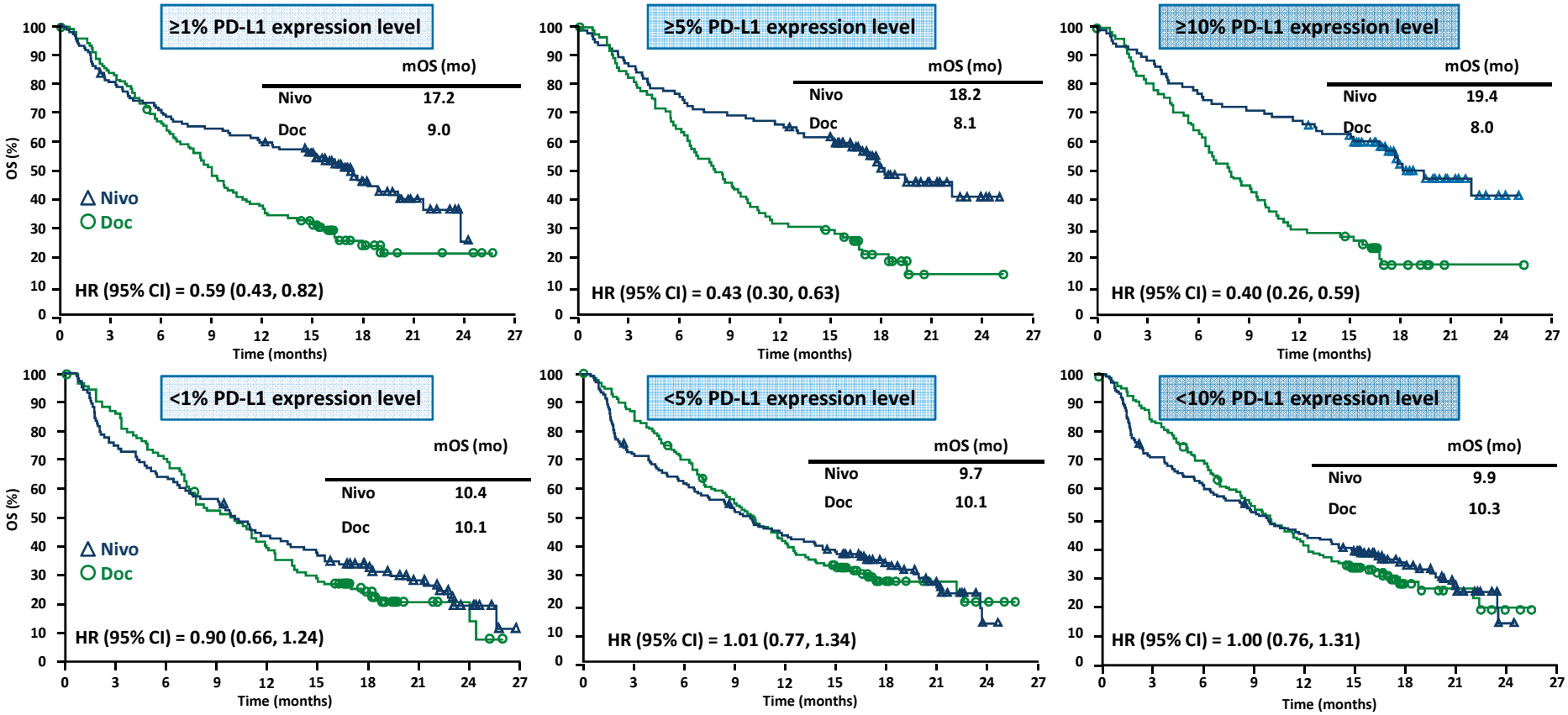
Paz-Ares et al, ASCO 2015; Borghaei et al, NEJM 2015

Treatment Effect on Overall Survival, According to Subgroup.



Paz-Ares et al, ASCO 2015; Borghaei et al, NEJM 2015

OS by PD-L1 Expression



Paz-Ares et al, ASCO 2015; Borghaei et al, NEJM 2015

LINEE GUIDA PER LA GESTIONE INTEGRATA DEL PAZIENTE CON TUMORE POLMONARE

IMMUNOTERAPIA

AIOT
ASSOCIAZIONE ITALIANA ONCOLOGIA TORACICA

RACCOMANDAZIONI

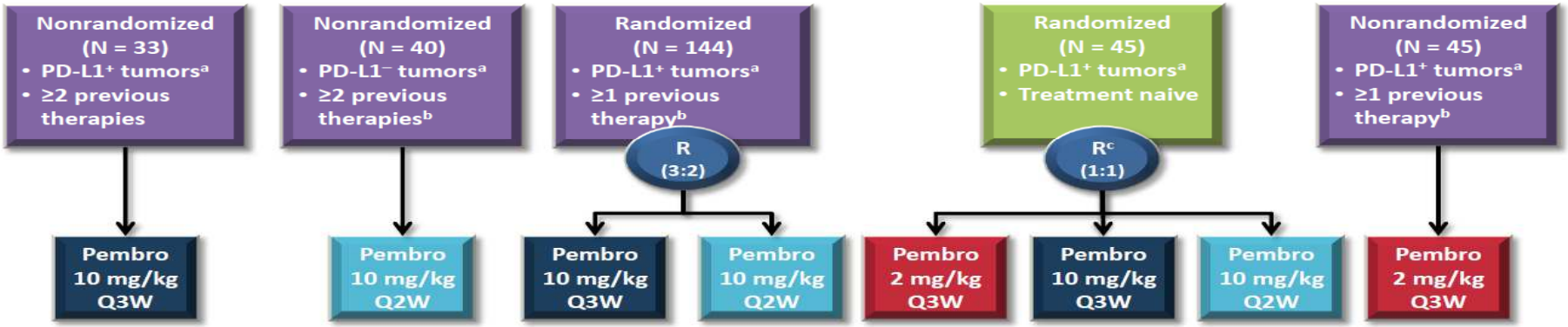
- **Per i pazienti affetti da NSCLC avanzato ad istologia non-squamosa, il trattamento di seconda linea con nivolumab come agente singolo è raccomandato. Al momento della stesura delle presenti linee guida, il nivolumab non è ancora registrato in Italia nei pazienti con istologia non-squamosa**

  LIVELLO DI EVIDENZA IB

  GRADO DI RACCOMANDAZIONE A

Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer

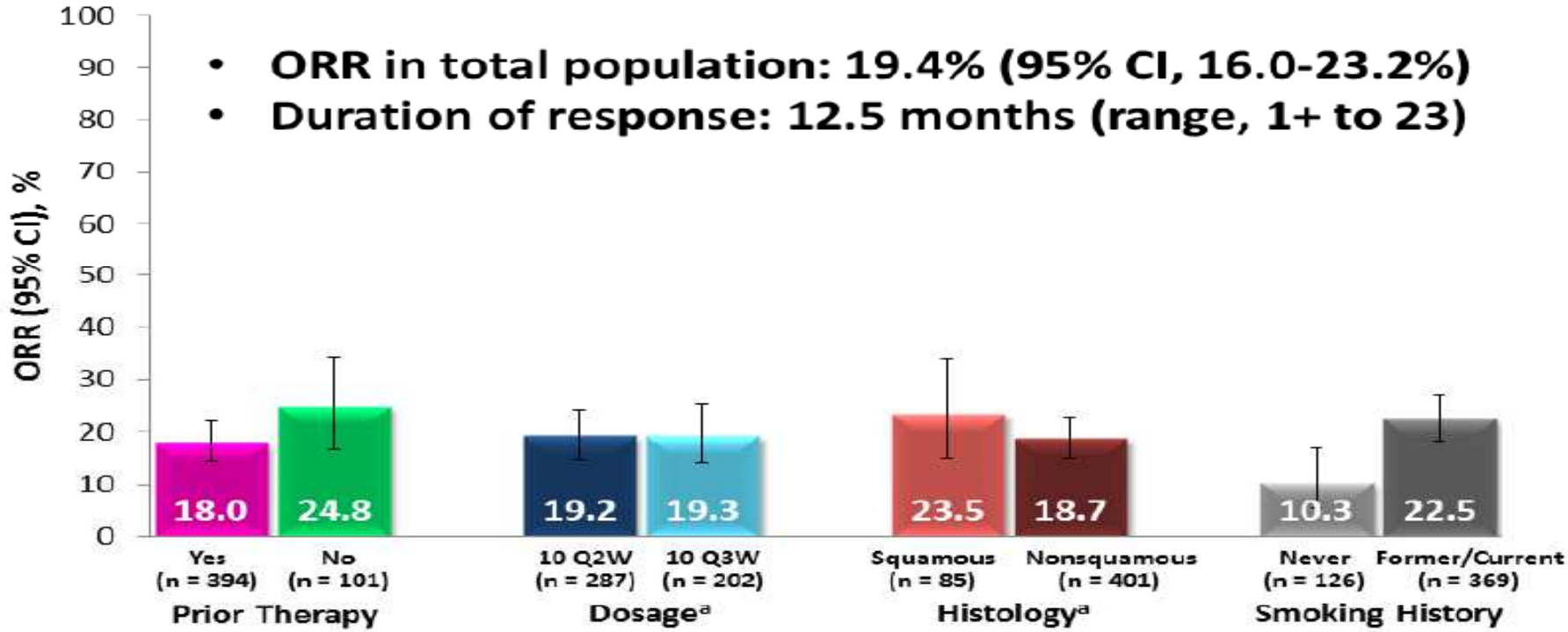
KEYNOTE-001 Study: NSCLC Expansion Cohorts (N = 307)



- Response assessment
  - Primary measure: ORR by RECIST v1.1[1] per independent central review
  - Secondary measure: immune-related response criteria (irRC)[2] per investigator assessment
- Pembrolizumab was given until disease progression, unacceptable toxicity, or death
- Analysis cut-off date: March 3, 2014[d]

Garon EB, et al. *N Engl J Med.* 2015;372:2018-2028

Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer

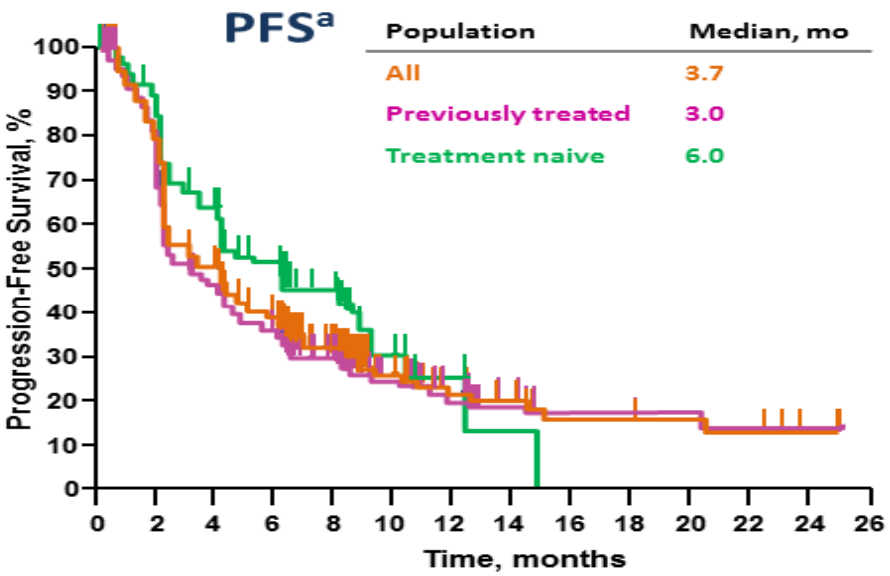


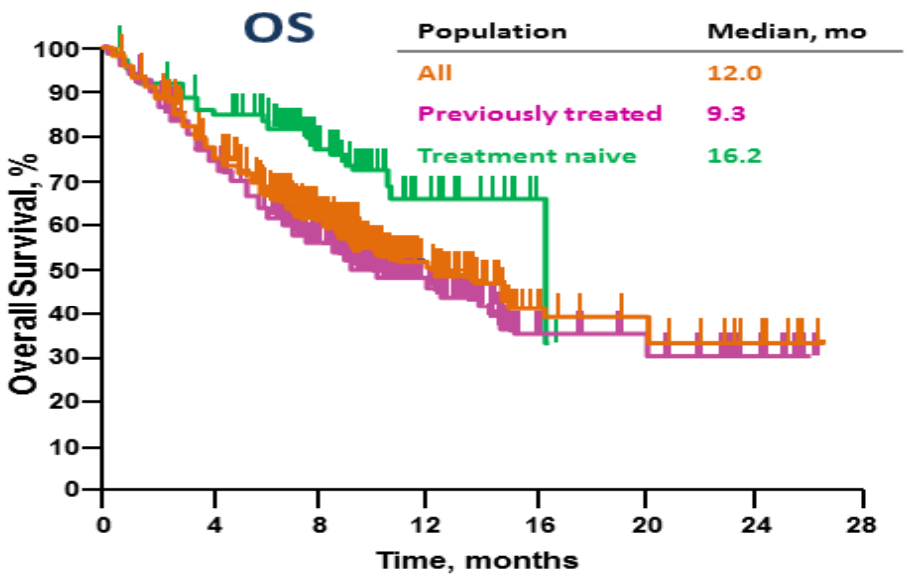
[a]Because of small patient numbers, data for patients treated with pembrolizumab 2 mg/kg Q3W (n = 6) and those with other histology (n = 9) are not shown.
ORR was assessed per RECIST v1.1 by central review.
Analysis cut-off date: August 29, 2014.

Garon EB, et al. *N Engl J Med.* 2015;372:2018-2028

PEMBROLIZUMAB FOR NON–SMALL-CELL LUNG CANCER

Longitudinal Outcome in All Treated Patients





n at risk

495	361	230	167	97	47	26	12	7	6	6	5	2	0
394	275	173	125	75	40	23	11	7	6	6	5	2	0
101	86	57	42	22	7	3	1	0	0	0	0	0	0

495	368	209	67	18	14	7	0
394	284	165	52	16	14	7	0
101	84	44	15	2	0	0	0

Garon EB, et al. *N Engl J Med.* 2015;372:2018-2028

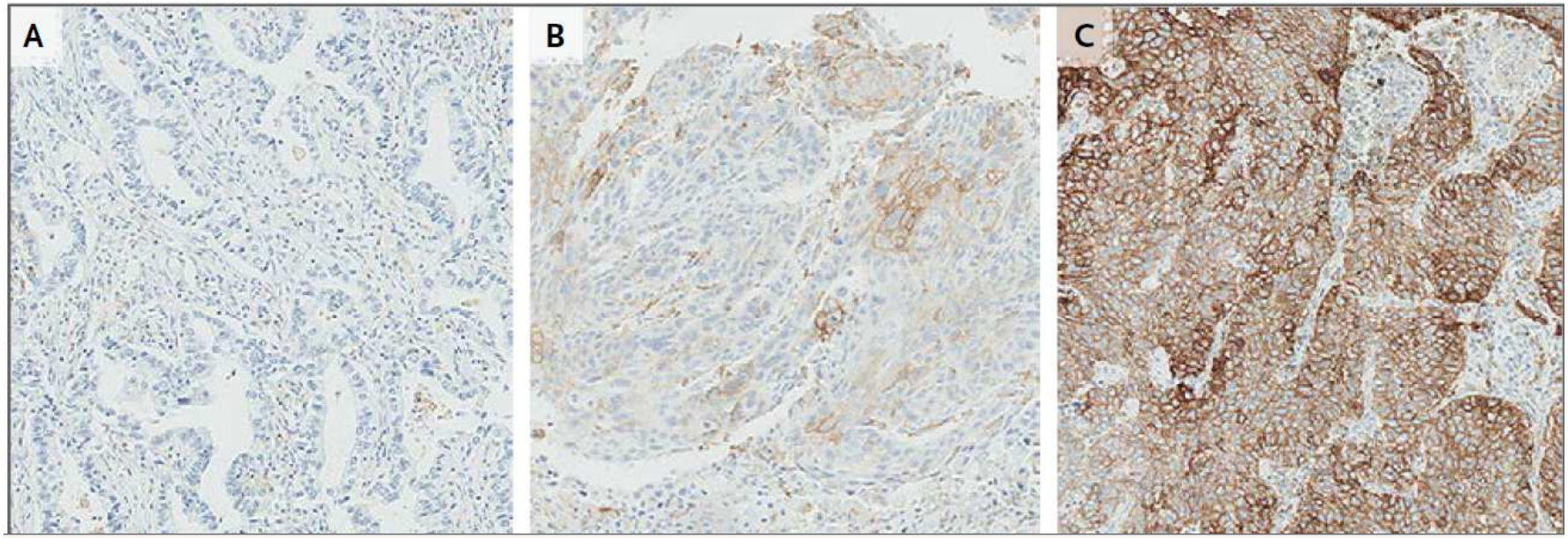


Figure 1. PD-L1 Expression in Non–Small-Cell Lung Cancers.

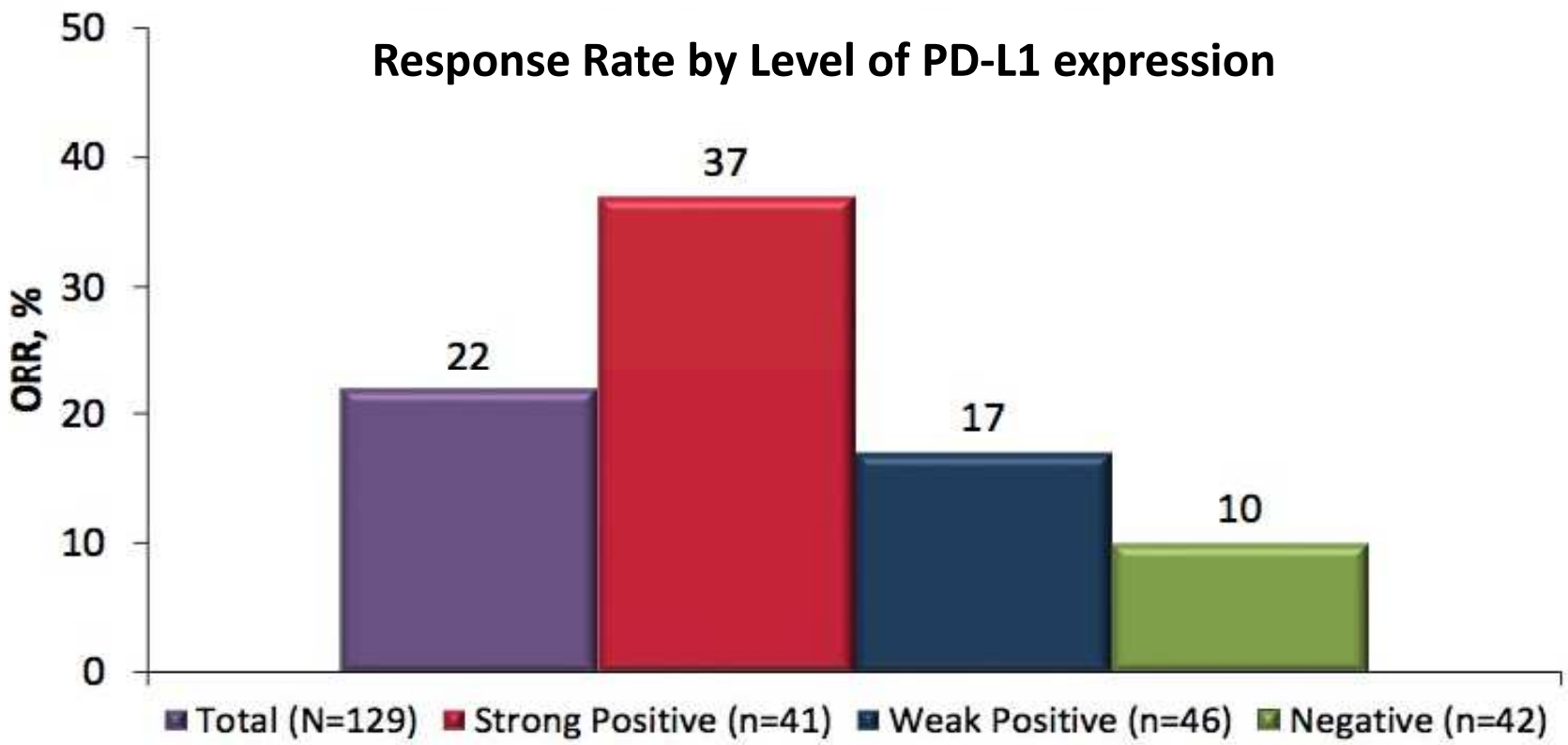
Results were reported as the percentage of neoplastic cells showing membranous staining of programmed cell death ligand 1 (PD-L1) (proportion score). Shown are tumor samples obtained from patients with a proportion score of less than 1% (Panel A), a score of 1 to 49% (Panel B), and a score of at least 50% (Panel C) (all at low magnification).

Brown chromogen: PD-L1 staining.
Blue color: hematoxylin counterstain.

PDL-1 IHC 22C3 pharmDx Test

Garon EB, et al. *N Engl J Med.* 2015;372:2018-2028

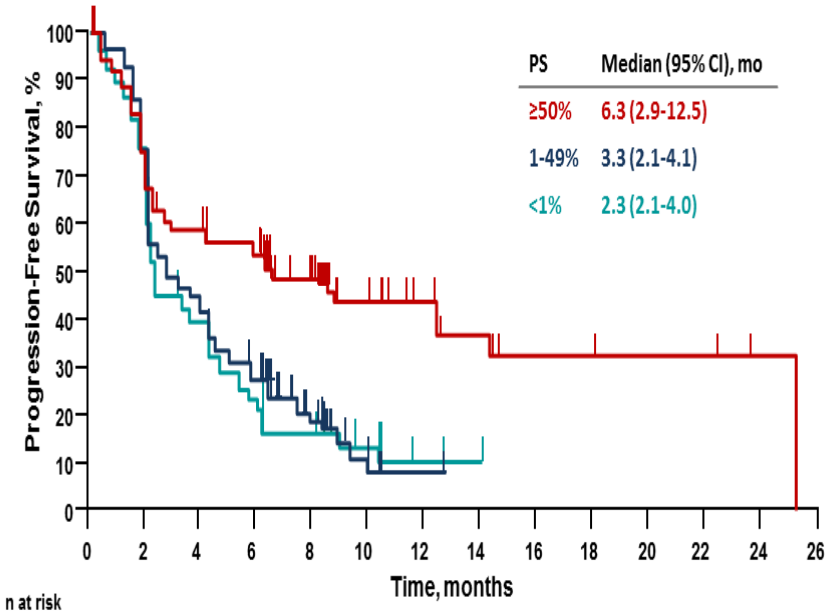
PEMBROLIZUMAB FOR NON–SMALL-CELL LUNG CANCER



Garon EB, et al. *N Engl J Med.* 2015;372:2018-2028

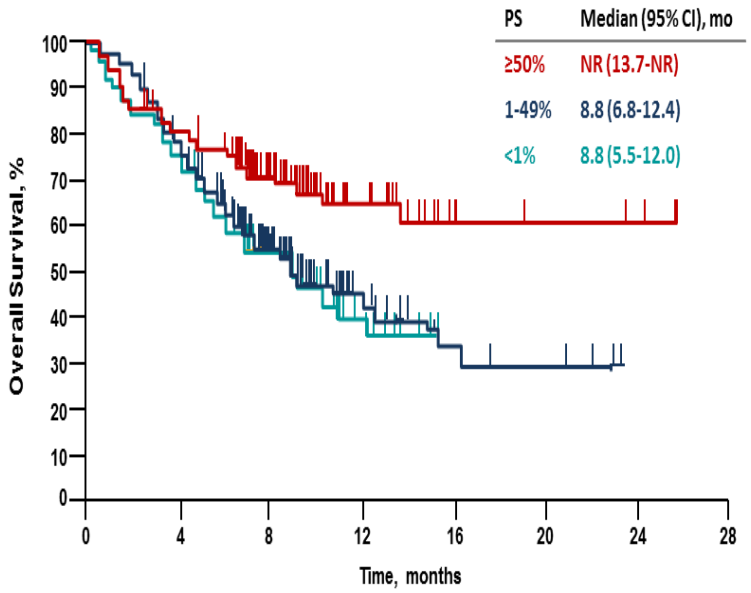
Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer

EFFICACY by PD-L1 Expression: ALL CTA-Evaluable Patients



n at risk

PS ≥50%	119	86	66	60	38	20	13	8	4	3	3	3	1	0
PS 1-49%	161	122	70	45	21	4	1	0	0	0	0	0	0	0
PS <1%	76	52	29	17	11	6	2	0	0	0	0	0	0	0

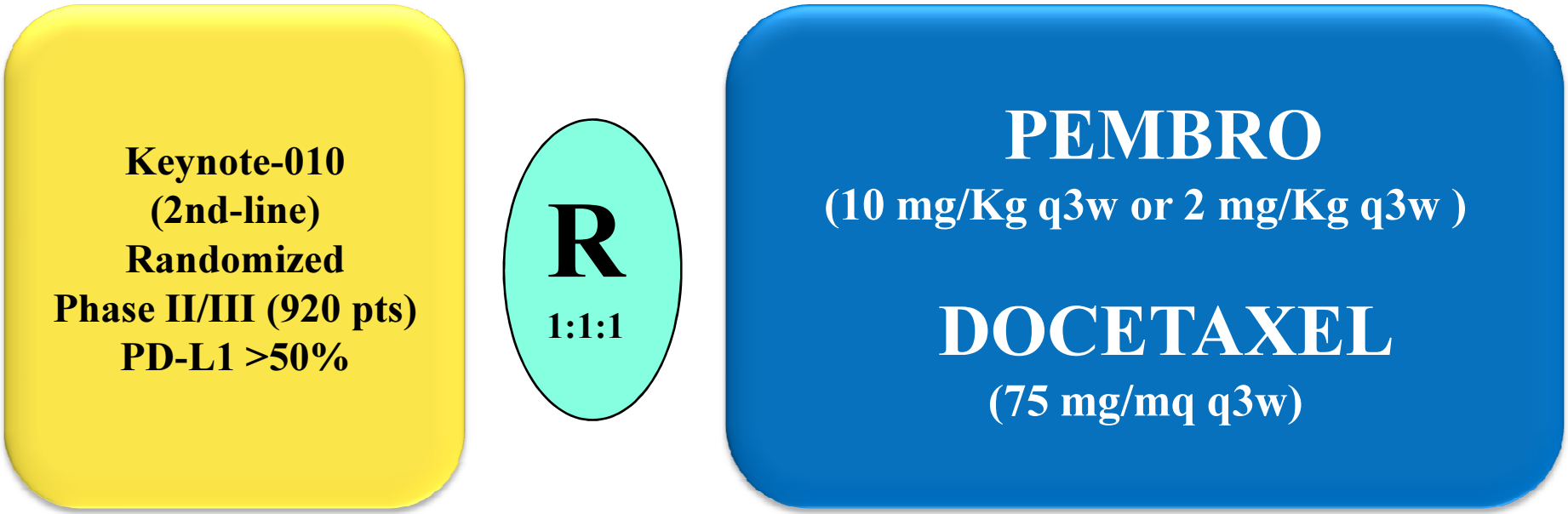


n at risk

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

Garon EB, et al. *N Engl J Med.* 2015;372:2018-2028

Pembrolizumab (MK-3475) in NSCLC: KEYNOTE 010 randomized phase III trial with pending results in A-NSCLC

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FDA approves Keytruda for advanced non-small cell lung cancer
First drug approved in lung cancer for patients whose tumors express PD-L1
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October 2, 2015
Release
The U.S. Food and Drug Administration today granted accelerated approval for Keytruda (pembrolizumab) to treat patients with advanced (metastatic) non-small cell lung cancer (NSCLC) whose disease has progressed after other treatments and with tumors that express a protein called PD-L1. Keytruda is approved for use with a companion diagnostic, the PD-L1 IHC 22C3 pharmDx test, the first test designed to detect PD-L1 expression in non-small cell lung tumors.

LINEE GUIDA PER LA GESTIONE INTEGRATA DEL PAZIENTE CON TUMORE POLMONARE

IMMUNOTERAPIA

AIOT
ASSOCIAZIONE ITALIANA ONCOLOGIA TORACICA

RACCOMANDAZIONI

- **Per i pazienti affetti da NSCLC avanzato, il trattamento di seconda-linea con pembrolizumab come agente singolo è raccomandato solo in presenza di espressione di PD-L1 ≥ 50% determinata con il test PD-L1 IHC 22C3 pharmDx. Al momento della stesura delle presenti linee guida pembrolizumab non è ancora registrato in Italia**

  LIVELLO DI EVIDENZA IIA

  GRADO DI RACCOMANDAZIONE B

ATEZOLIZUMAB ONGOING PHASE III TRIALS

PD-L1 Inhibitor	Study Design	Population	NCT No.
Atezolizumab	Carboplatin + *nab*-paclitaxel ± atezolizumab: IMpower 130	Untreated metastatic nonsquamous NSCLC	NCT02367781
Atezolizumab	Carboplatin + *nab*-paclitaxel + (atezolizumab or bevacizumab + atezolizumab or bevacizumab): IMpower 150	Untreated metastatic nonsquamous NSCLC	NCT02366143
Atezolizumab	Carboplatin + *nab*-paclitaxel *v* carboplatin + *nab*-paclitaxel + atezolizumab *v* carboplatin + paclitaxel + atezolizumab: IMpower 131	Untreated metastatic nonsquamous NSCLC	NCT02367794
Atezolizumab	Atezolizumab *v* platinum + pemetrexed: IMpower 110	Untreated metastatic nonsquamous NSCLC	NCT02409342
Atezolizumab	Atezolizumab *v* platinum + gemcitabine: IMpower 111	Untreated metastatic squamous PD-L1–positive NSCLC	NCT02409355
Atezolizumab	Atezolizumab *v* best supportive care	Completely resected stage IB-IIIA NSCLC	NCT02486718
Atezolizumab (MPDL3280A)	Atezolizumab *v* docetaxel: OAK	Recurrent locally advanced or metastatic NSCLC	NCT02008227

MPDL3280A (Atezolizumab)
Phase Ia: safety/efficacy summary – NSCLC

Population: patients with metastatic NSCLC (median 4 prior regimens)

Diagnostic: multi-modality biomarkers being evaluated, including PD-L1

MPDL3280A IV every 3 weeks

Safety overview (n=88)

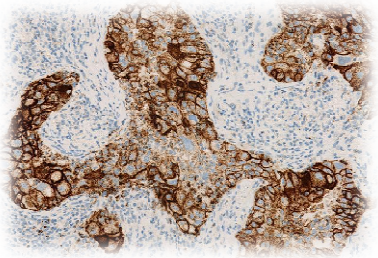
- No maximum tolerated dose, dose-limiting toxicities or treatment-related deaths
- The majority of AEs were grade 1–2 and did not require intervention, grade 3-4 in 11% of pts

Efficacy overview (n=88)

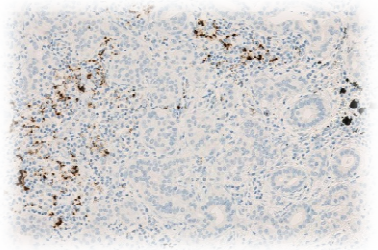
	ORR* per RECIST 1.1, %	24 weeks PFS or longer, %	1-yrs OS, %
NSCLC (n=88)	21	42	82
TC0/1/2 & IC0/1/2 (n=58)	14	36	78
TC3 or IC3 (n=20)	45	45	89

Horn L et al, ASCO 2015

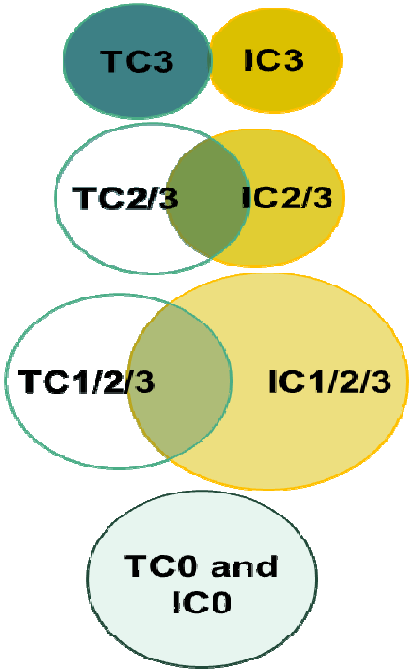
PD-L1 Expression on TC (tumor cells) and IC (infiltrating tumor cells) is a Potential Predictive Biomarker for Atezolizumab in NSCLC



***Intrinsic* PD-L1 expression in tumor cells (TC)**



***Adaptive* PD-L1 expression in tumor-infiltrating immune cells (IC)**



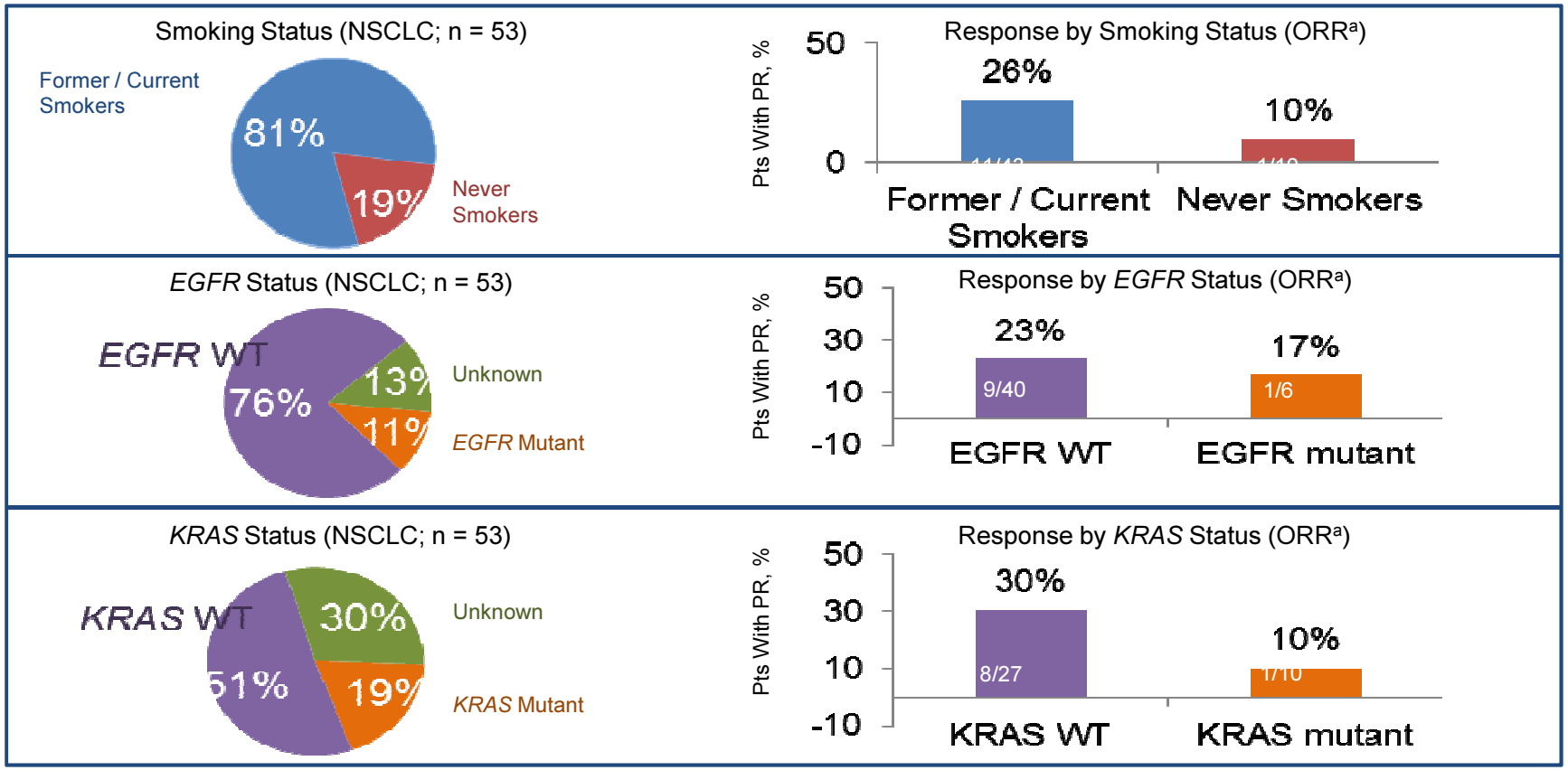
PD-L1 expression levels and TC/IC overlap in POPLAR

- SP142 IHC assay is sensitive and specific for PD-L1 expression on both TC and IC
- Distinct TC and IC sub-populations exist at each of four cutoff levels[a] (Gettinger et al., ASCO 2015)
- PD-L1 expression on TC and IC was independently predictive of response (Horn et al. and Spigel et al., ASCO 2015)

[a]TC scored as percentage of tumor cells and IC scored as percentage of tumor area. **TC3 or IC3** = TC ≥ 50% or IC ≥ 10% PD-L1+; **TC2/3 or IC2/3** = TC or IC ≥ 5% PD-L1+; **TC1/2/3 or IC1/2/3** = TC or IC ≥ 1% PD-L1+; **TC0 and IC0** = TC and IC < 1% PD-L1+, respectively.

AI Spira et al, ASCO 2015

MPDL3280A Phase Ia: Response by Smoking and Mutational Status



[a] ORR includes investigator-assessed u/c PR by RECIST 1.1. Patients first dosed at 1-20 mg/kg by Oct 1, 2012. Data cutoff: Apr 30, 2013.

BIRCH: Phase II Trial of Atezolizumab in PD-L1-Selected Advanced NSCLC

- Locally advanced or metastatic NSCLC
- Tumor PD-L1 expression by IHC (TC2/3 and/or IC2/3)
- ECOG PS 0 or 1
- No brain mets

N = 667

→ Cohort 1 (1L) No prior chemo n = 142 → PD

→ Cohort 2 (2L) 1 prior platinum chemo n = 271 → Until loss of clinical benefit

→ Cohort 3 (3L+) > 1 prior platinum chemo n = 254 → Until loss of clinical benefit

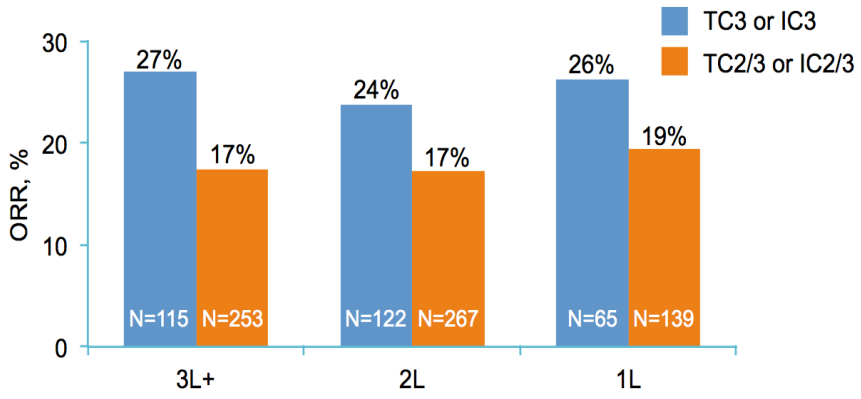
Atezolizumab dosed at 1200 mg IV q3w in all cohorts.

- Primary endpoint: Objective response rate assessed by Independent Review Facility (IRF-assessed ORR) per RECIST v1.1

	3L+ (n = 253)	2L (n = 267)	1L (n = 139)	All Patients (N = 659)
Median age (range), y	64.0 (38-84)	63.0 (28-83)	67.0 (35-88)	64.0 (28-88)
Male, %	60	61	51	59
ECOG PS 1, %	68	63	57	64
TC3 or IC3 status, %	45	46	47	46
Current/previous tobacco use, %	83	82	84	83
Non-squamous histology, %	72	69	76	72
EGFR mutation[a]				
n	124	130	73	327
Positive	14 (11%)	15 (12%)	10 (14%)	39 (12%)
KRAS mutation[a]				
n	75	62	40	177
Positive	24 (32%)	21 (34%)	14 (35%)	59 (33%)

BIRCH: IRF-assessed ORR by Line of Therapy

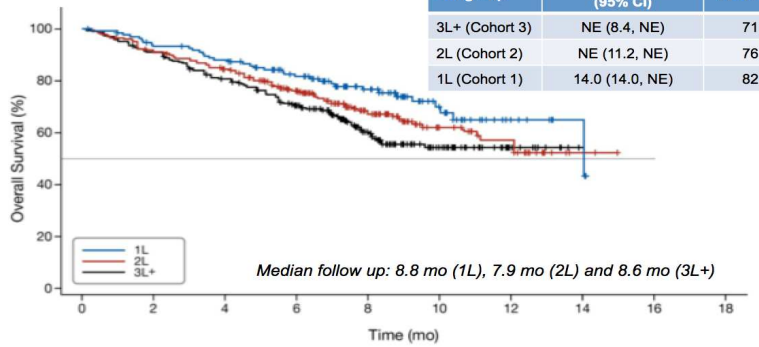
TC3 or IC3 and TC2/3 or IC2/3 subgroups



BIRCH: Overall Survival by Line of Therapy

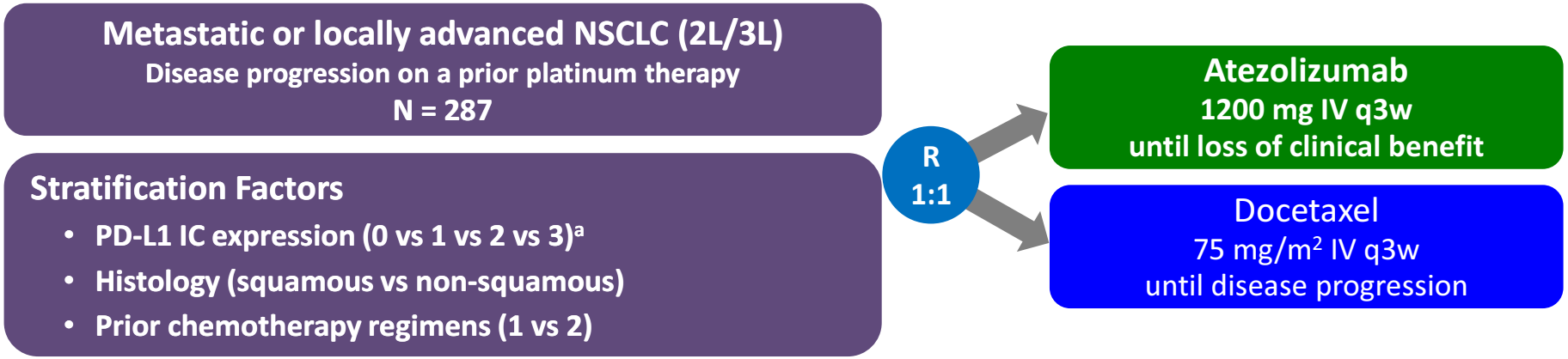
TC2/3 or IC2/3

Subgroup	Median OS, mo (95% CI)	6-mo OS, %
3L+ (Cohort 3)	NE (8.4, NE)	71%
2L (Cohort 2)	NE (11.2, NE)	76%
1L (Cohort 1)	14.0 (14.0, NE)	82%



Besse B et al, ECCO 2015

Efficacy, safety and predictive biomarker results from a randomized Phase II study comparing atezolizumab (MPDL3280A) vs docetaxel in 2L/3L NSCLC (POPLAR)



Primary study objective:

- **Estimate OS in PD-L1 selected and ITT populations**

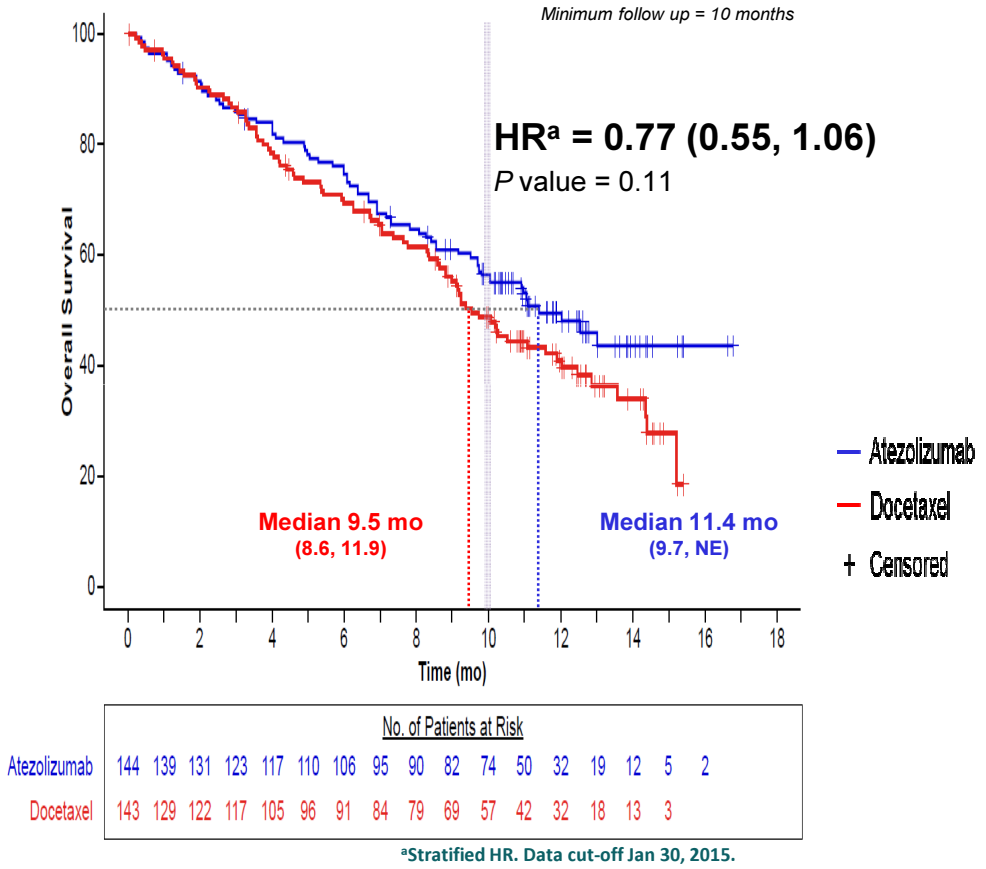
[a]Archival or fresh tissue required for pre-dose testing.

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

Al Spira et al, ASCO 2015

POPLAR: Characteristics *ITT and Interim OS*

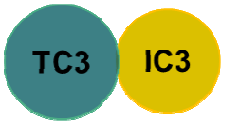
Characteristics of Patients with NSCLC	Atezolizumab (n = 144)	Docetaxel (n = 143)
Median age, y	62	62
≥ 65 y	40%	39%
Male	65%	53%
Histology		
Non-squamous	66%	66%
Squamous	**34%**	**34%**
ECOG score, 0 / 1	33% / 67%	32% / 68%
No. of prior chemotherapies, 1 / 2	65% / 35%	67% / 33%
History of tobacco use		
Never	19%	20%
Current	**17%**	**15%**
Previous	**64%**	**65%**

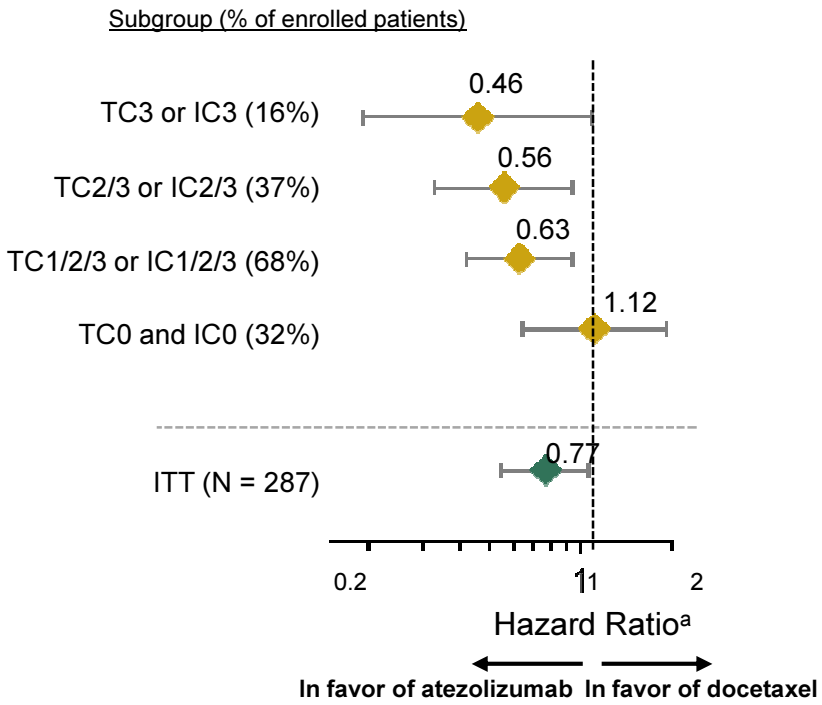


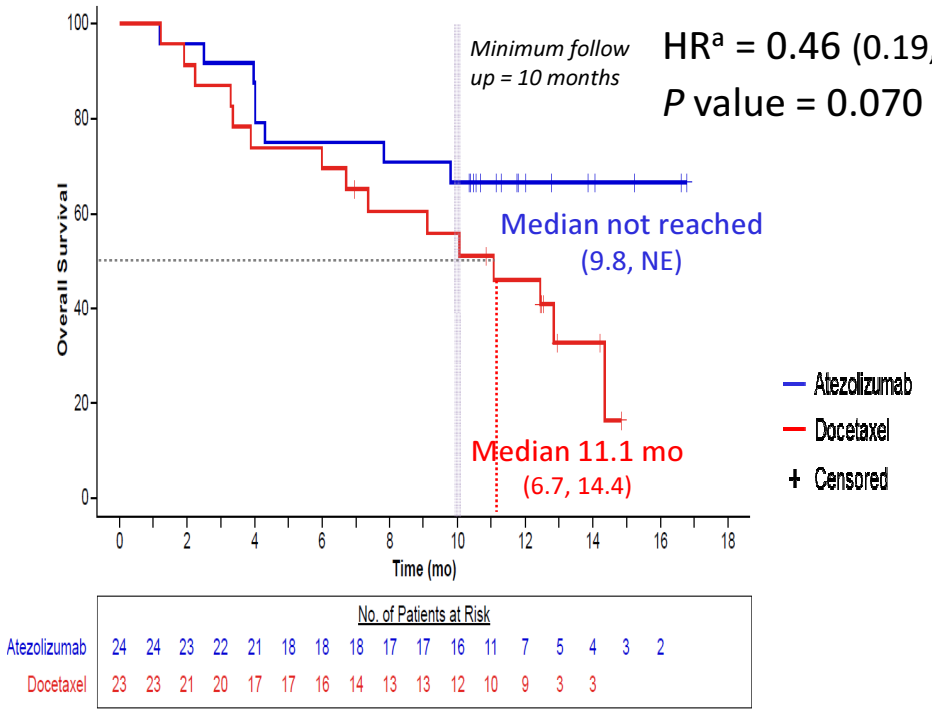
[a]Stratified HR. Data cut-off Jan 30, 2015.

Al Spira et al, P ASCO 2015

POPLAR: PD-L1 Expression Subgroups
TC3 or IC3 interim OS (n = 47)



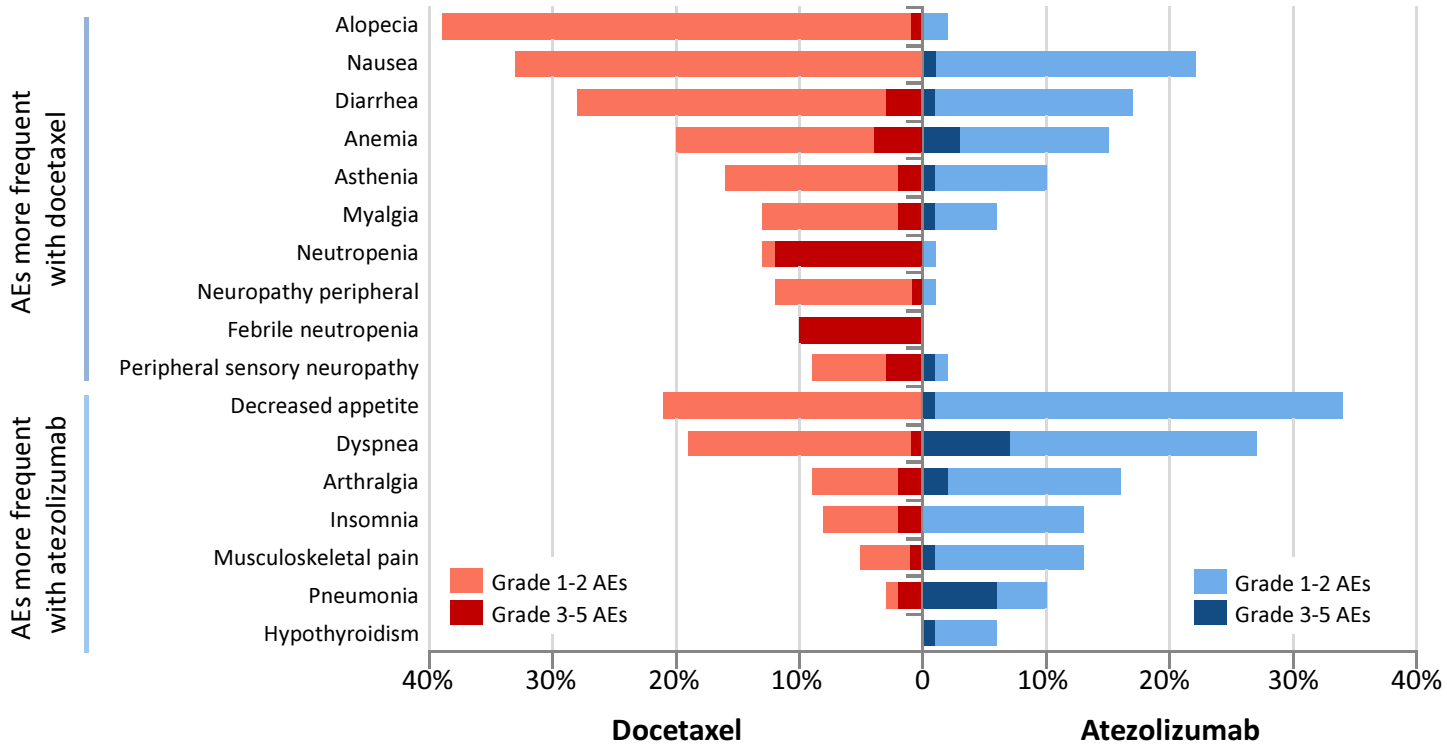




[a]Unstratified HR. Data cut-off Jan 30, 2015.

Al Spira et al, ASCO 2015

POPLAR: All-cause AEs *(≥ 5% difference between arms)*

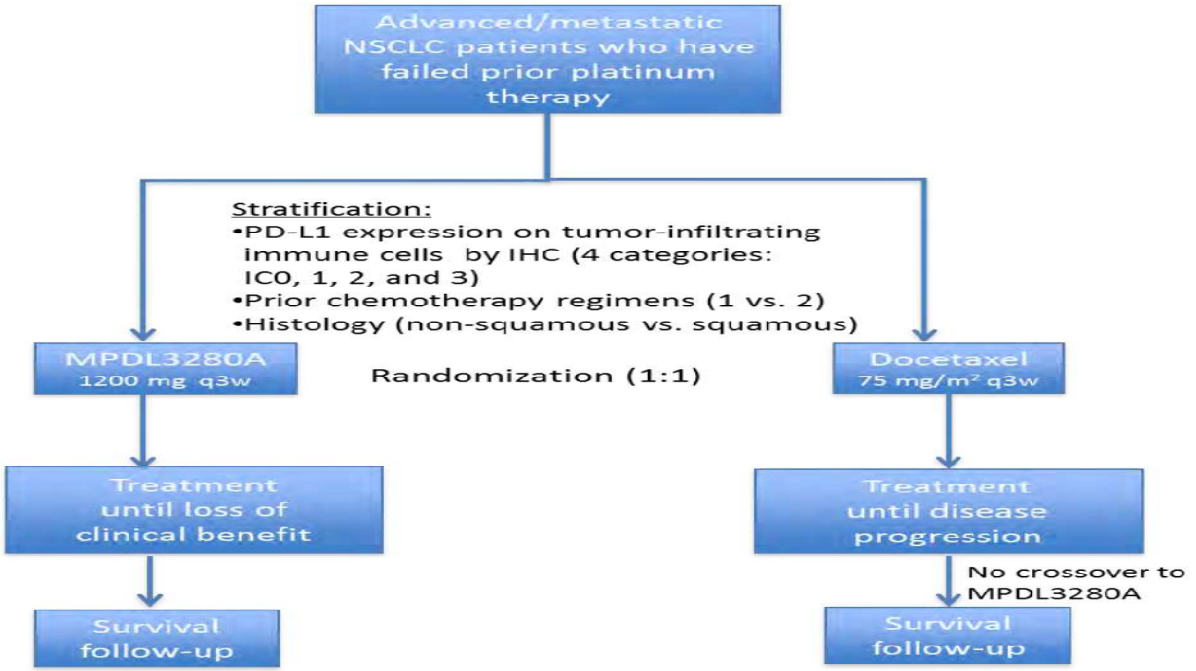


- AE profiles consistent with previous studies
- For atezolizumab, other immune-mediated AEs (any grade) included:
  - AST increased (4%)
  - ALT increased (4%)
  - **Pneumonitis (2%)**
  - Colitis (1%)
  - Hepatitis (1%)

Al Spira et al, ASCO 2015

A PHASE III, OPEN-LABEL, MULTICENTER, RANDOMIZED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF MPDL3280A (ANTI–PD-L1 ANTIBODY) COMPARED WITH DOCETAXEL IN PATIENTS WITH NON–SMALL CELL LUNG CANCER AFTER FAILURE WITH PLATINUM-CONTAINING CHEMOTHERAPY (OAK)

Figure 1 Study Schema



DURVALUMAB. Phase I results in NSCLC

	MEDI4736 10 mg/kg q2w (n=200); PD-L1 status		
	All patients	PD-L1+	PD-L1-
RECIST response (ORR),[b] n/N (%) 95% CI	32/200 (16) 11.2–21.8	23/84 (27) 18.2–38.2	5/92 (5) 1.8–12.2
DCR,[c] n/N (%) 95% CI	84/200 (42) 35.1–49.2	40/84 (48) 36.6–58.6	35/92 (38) 28.1–48.8
Range for duration of ongoing response, wks	0.1+–54.4+	0.1+–54.4+	9.9+–41.7+
Ongoing responders, n/N (%)	21/32 (66)	17/23 (74)	2/5 (40)

NA Rizvi – ASCO 2015

DURVALUMAB. Phase I results in NSCLC

Table 6. Tumor Response by Subgroup

	ORR[a]			DCR[b]		
	All patients	PD-L1+	PD-L1−	All patients	PD-L1+	PD-L1−
No. of prior lines of therapy, n/N (%)						
Any	32/200 (16)	23/84 (27)	5/92 (5)	84/200 (42)	40/84 (48)	35/92 (38)
0	5/20 (25)	3/11 (27)	1/7 (14)	11/20 (55)	5/11 (46)	5/7 (71)
1	10/54 (19)	8/25 (32.0)	0/19 (0)	29/54 (54)	15/25 (60)	8/19 (42)
≥2	17/124 (14)	12/48 (25)	4/66 (6)	44/124 (36)	20/48 (42)	22/66 (33)
Histology, n/N (%)						
Squamous	18/88 (21)	14/43 (33)	3/37 (8)	42/88 (48)	21/43 (49)	18/37 (49)
Non-squamous	14/112 (13)	9/41 (22)	2/55 (4)	42/112 (38)	19/41 (46)	17/55 (31)
Tobacco use,[c] n/N (%)						
Former/current smoker	28/166 (17)	20/72 (28)	5/73 (7)	67/166 (40)	33/72 (46)	26/73 (36)
Never smoker	4/34 (12)	3/12 (25)	0/19 (0)	17/34 (50)	7/12 (58)	9/19 (47)

[a]ORR includes RECIST response (confirmed/unconfirmed CR or PR); [b]DCR = confirmed/uncofirmed CR or PR + SD ≥12 weeks; [c]Smoker defined as having any history of smoking.

NA Rizvi – ASCO 2015

A Phase III open-label, multicenter trial of avelumab (MSB0010718C) versus docetaxel in subjects with non-small cell lung cancer that has progressed after a platinum-containing doublet

Subjects with histologically confirmed Stage IIIb/IV or recurrent NSCLC who have experienced disease progression

Approximately 650 subjects, among them 522 PD-L1 assay positive subjects, will be randomized in a 1:1 ratio to receive either

- avelumab at a dose of 10 mg/kg as a 1-hour intravenous (IV) infusion once every 2 weeks, or
- docetaxel at a starting dose of 75 mg/m^2 (per label) by IV infusion once every 3 weeks.

Primary objective

To demonstrate superiority with regard to overall survival (OS) of avelumab versus docetaxel in subjects with programmed death ligand 1 (PD-L1) positive (+; as determined by a companion diagnostic test under development), non-small cell lung cancer (NSCLC) after failure of a platinum-based doublet

The trial will be conducted at approximately 290 sites globally in North America, South America, Asia, Africa, and Europe.

Coordinating Investigator Fabrice Barlesi, MD, PhD

Summary of PD-1/PD-L1 Blockade Immune-Mediated Toxicities

Occasional (5% to 20%)

•Fatigue, headache, arthralgia, fevers, chills,

•**Rash**: maculopapular, pruritus, vitiligo

•**Diarrhea/colitis**

•**Hepatitis**, liver/pancreatic enzyme abnormalities

- Infusion reactions
- **Endocrinopathies**: thyroid, adrenal, hypophysitis

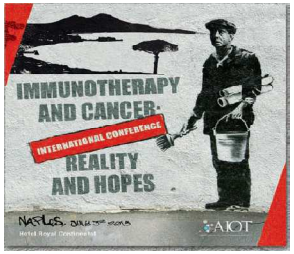
Rare (< 5%)

- **Pneumonitis**
- Nefritis

Weber JS, et al. J Clin Oncol. 2012;30:2691-2697. -
Weber JS, et al. J Clin Oncol. 2015

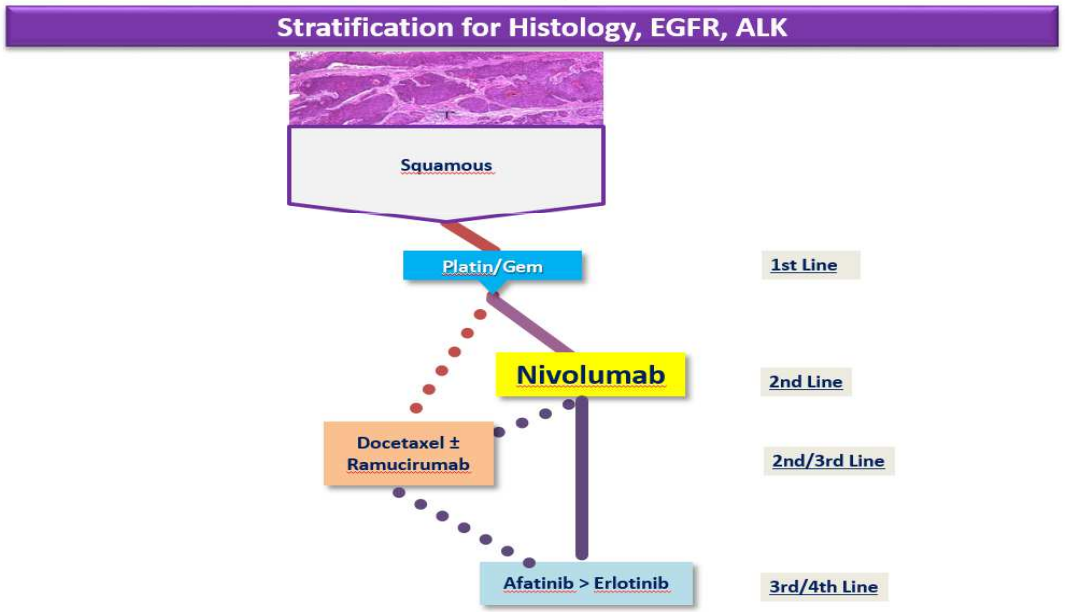
QUESTIONS GOING FORWARD IN ADVANCED NSCLC TREATMENT

- **Anti -PD1 vs Anti –PDL1**
- **Doses**
- **Duration of therapy (1 yr, 2 yrs, until PD)**
- **PDL1 status predictive?**
  (if yes different assays, activity in PDL1 negative pts, contrasting results)
- **Single agent or combined?**
  (chemo, targeted therapies, other immunotherapy)
- **Treatment strategy (upfront, maintenance,2nd line)**



The evolving role of nivolumab in non-small-cell lung cancer for second-line treatment: a new cornerstone for our treatment algorithms. Results from an International Experts Panel Meeting of the Italian Association of Thoracic Oncology

ALGORITHM IN A-SqNSCLC TREATMENT



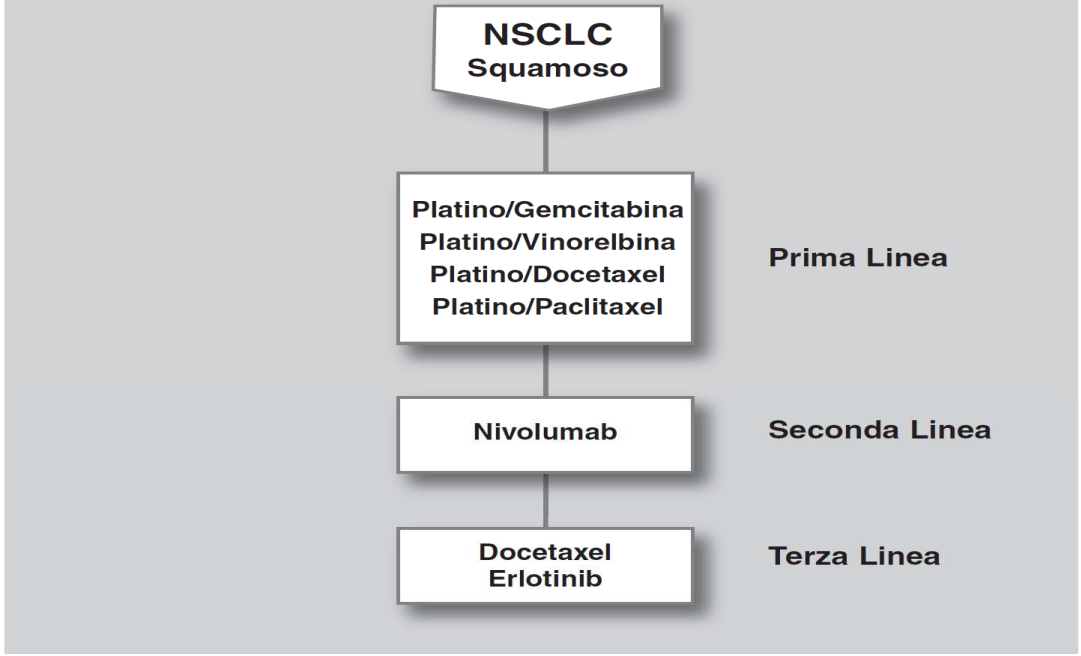
Gridelli C[1], Besse B[2], Brahmer JR[3], Crino' L[4], Felip E[5] Rizvi NA[6], de Marinis F[7]

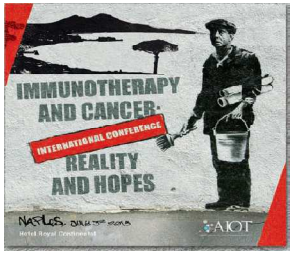
LINEE GUIDA PER LA GESTIONE INTEGRATA DEL PAZIENTE CON TUMORE POLMONARE

IMMUNOTERAPIA

AIOT
ASSOCIAZIONE ITALIANA ONCOLOGIA TORACICA

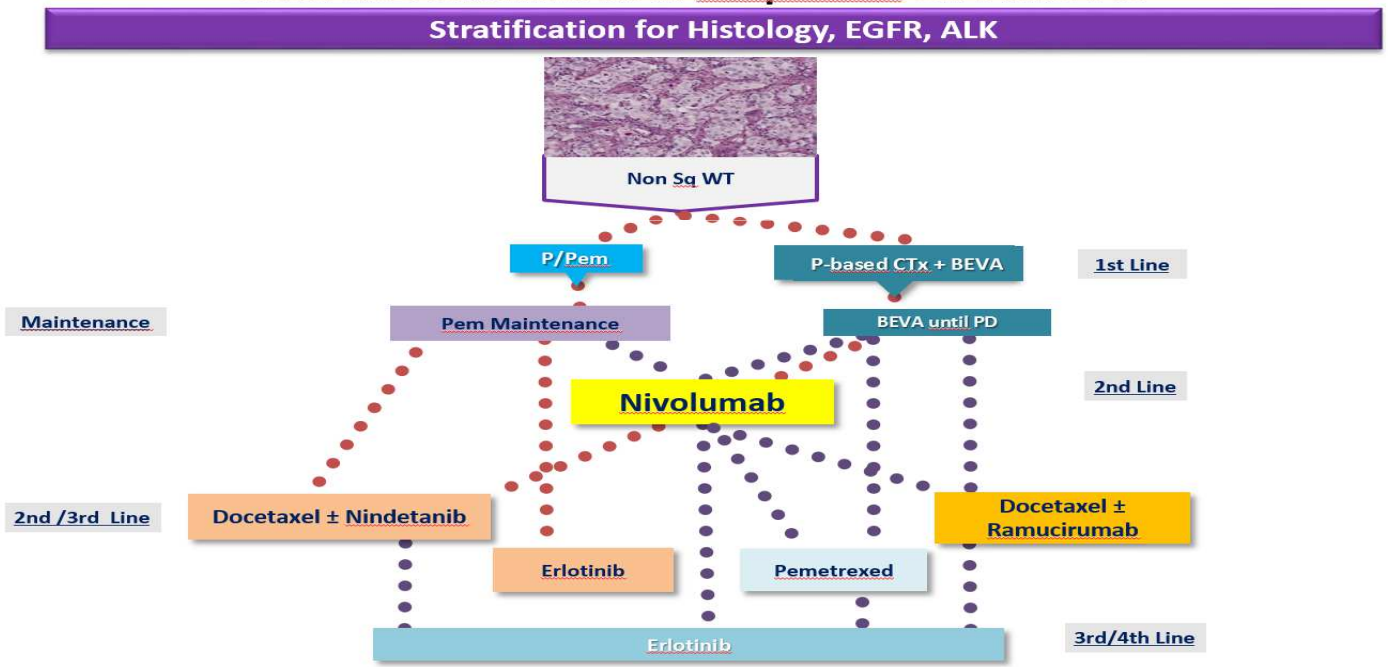
FIGURA 1. Algoritmo suggerito per il trattamento di seconda linea del carcinoma squamoso del polmone con farmaci rimborsabili in Italia





The evolving role of nivolumab in non-small-cell lung cancer for second-line treatment: a new cornerstone for our treatment algorithms. Results from an International Experts Panel Meeting of the Italian Association of Thoracic Oncology

EBM ALGORITHM IN A-NSqNSCLC TREATMENT



Gridelli C[1], Besse B[2], Brahmer JR[3], Crino' L[4], Felip E[5] Rizvi NA[6], de Marinis F[7]

Thank You

filippo.demarinis@ieo.it

Illustration by Brett Ryder