EUROPEAN LUNG CANCER
CONFERENCE 2016

MONOTHERAPY WITH CHECKPOINT INHIBITORS ANY CHANCE FOR LONG TERM SURVIVAL?

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DISCLOSURES

- Honoraria for lectures and consultancy:
- Hoffmann-La Roche, Lilly, MSD, BMS, AstraZeneca, Boehringer-Ingelheim, Pfizer, Celgene

Abstract 137O

NIVOLUMAB IN PATIENTS WITH ADVANCED REFRACTORY SQUAMOUS (SQ) NSCLC: 2-YEAR FOLLOW-UP FROM CHECKMATE 063 AND EXPLORATORY CYTOKINE PROFILING ANALYSES

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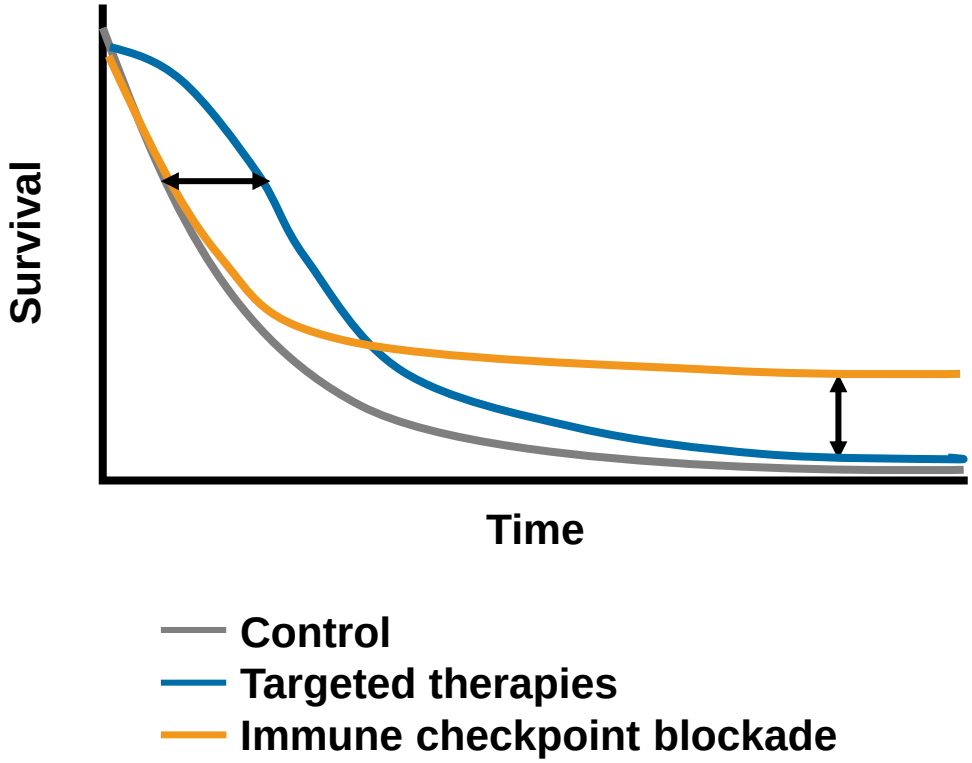
IMMUNOTHERAPY IN LUNG CANCER

- Any chance for long term survival?

SLOPE OR PLATEAU?

ROLLER COASTER OR STEAM RAILWAY?

THE PROMISE
PLATEAU OF LONG TERM OS BY DIFFERENT MOA

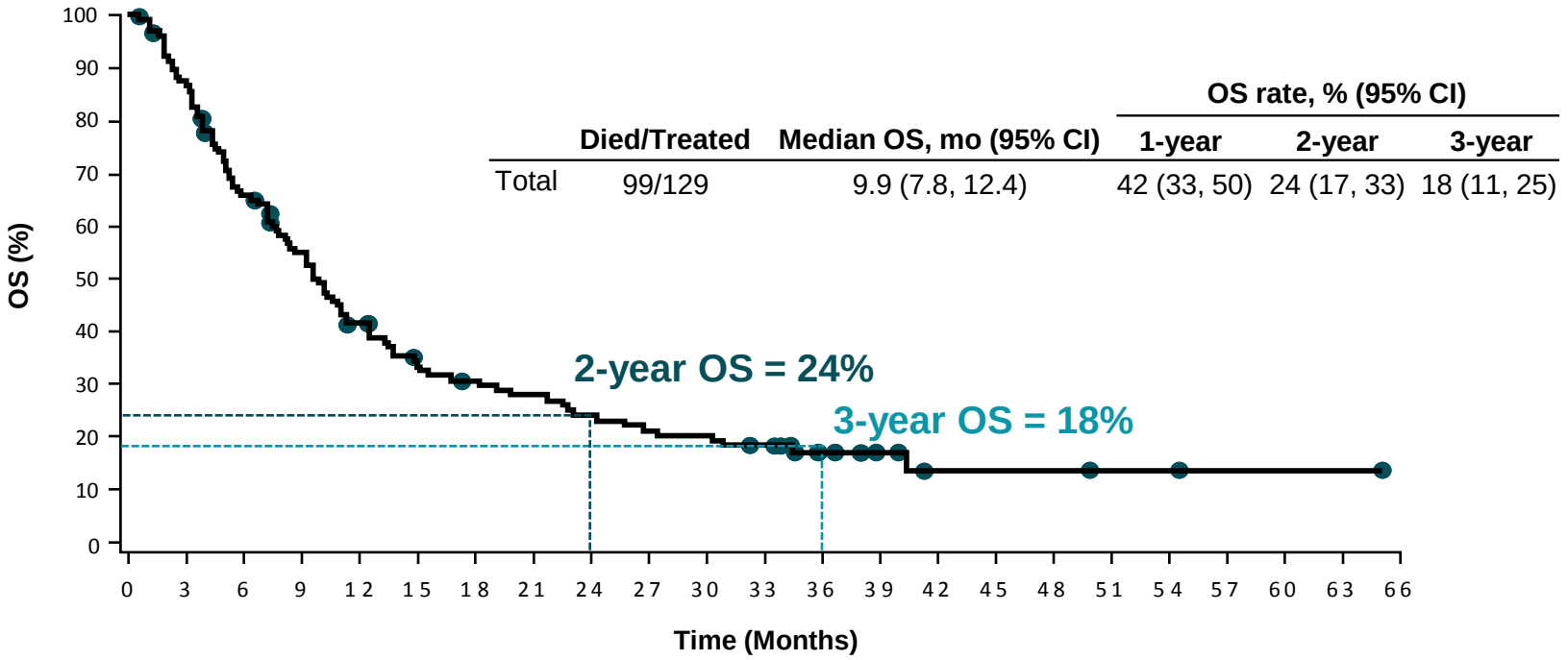


Adapted from Ribas A, presented at WCM, 2013; Ribas A, et al. *Clin Cancer Res* 2012;18:336–341; Drake CG. *Ann Oncol* 2012;23(suppl 8):viii41–viii46

THE TEASER

LONG TERM SURVIVAL IN PRETREATED PATIENTS, EXAMPLE NIVOLUMAB

CA209-003: phase 1 study, stage IIIB/IV NSCLC, up to 5 prior lines of therapy



	Died/Treated	Median OS, mo (95% CI)	OS rate, % (95% CI) 1-year	2-year	3-year
Total	99/129	9.9 (7.8, 12.4)	42 (33, 50)	24 (17, 33)	18 (11, 25)

70% of patients had 3–5 prior lines of therapy; 46% of these patients had received 1–2 prior lines of therapy and 54% had received 3–5 prior lines of therapy.
Gettinger S, et al. Poster presented at CMSTO 2014; Brahmer J, et al. Poster presented at ASCO 2014.

THE CLINICAL QUESTION

- Is this real?
- Is this superior to chemotherapy?

- First of all...

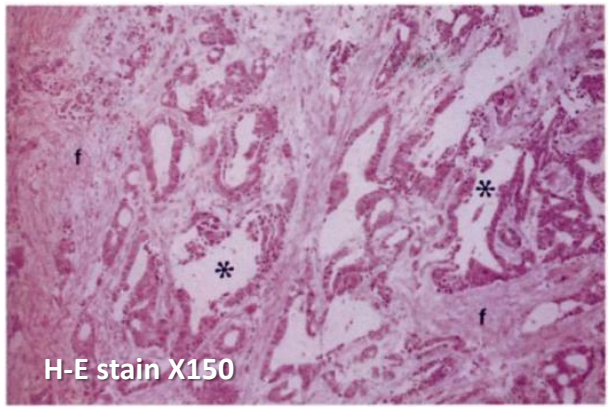
WHAT DO WE KNOW ABOUT LONG TERM SURVIVAL?

- In Second-line treatment of NSCLC?
- In Second-line treatment of squamous cell NSCLC?

WHAT DO WE KNOW ABOUT SQUAMOUS NSCLC?

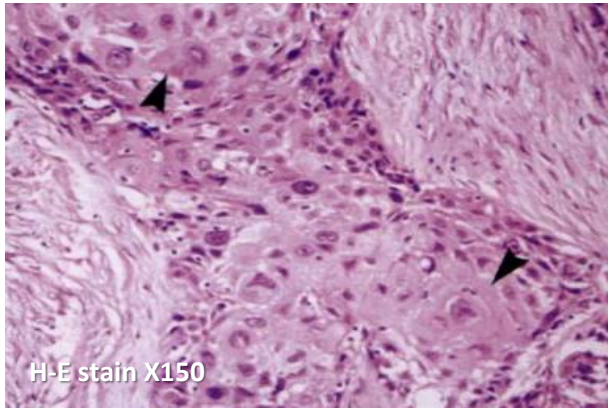
DIFFERENT PATHOLOGY

Adenocarcinoma[1,2]



- Presence of glands and papillary structures (*)
- Neoplastic cells with round to oval nuclei, prominent nucleoli, and moderate amounts of cytoplasm
- Stain for mucin, TTF-1, cytokeratin 7

Squamous[1,2,3]

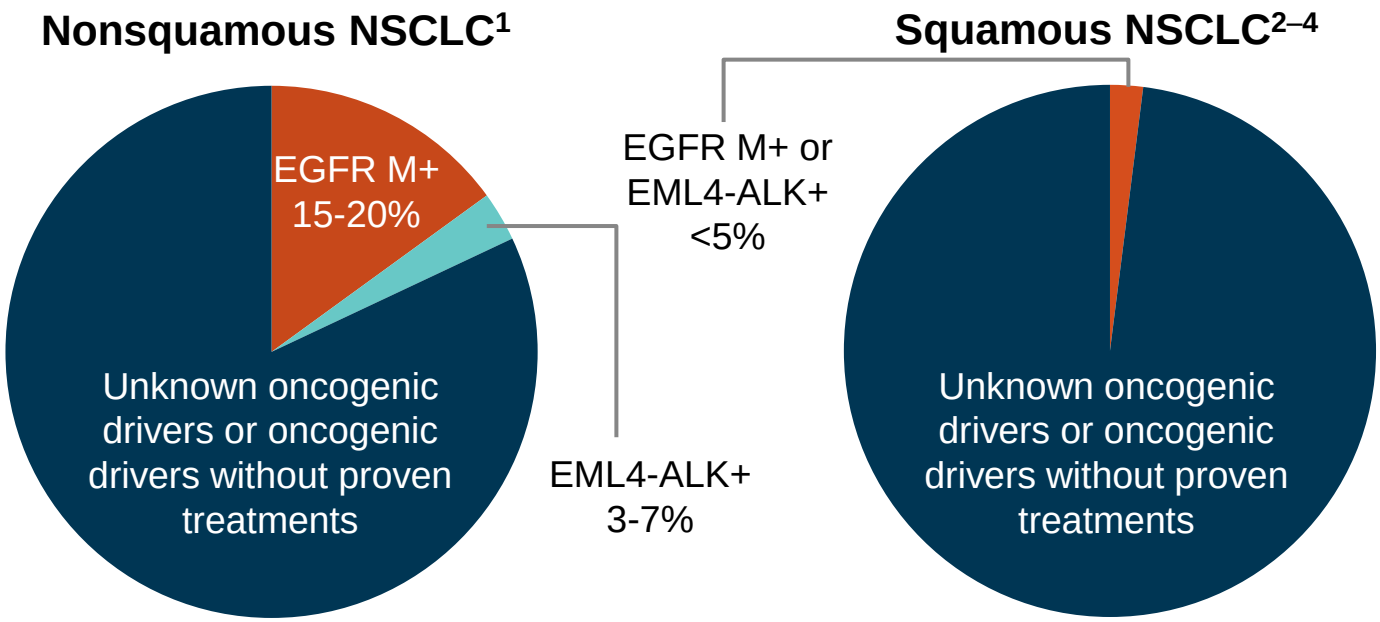


- Flattened appearance (i.e., “squamous”)
- Intercellular bridges
- Individual cell keratinization (arrowhead)
- Keratin pearls
- Stain for p63, p40, cytokeratin 5/6

NSCLC, non-small cell lung cancer

1. Rosado-de-Christenson ML et al. *Radiographics* 1994;14:429–46;
2. Oliver TG et al. *Am J Clin Oncol* 2013;doi: 10.1097/COC.0b013e3182a0e850;
3. Bishop JA et al. *Modern Pathology* 2012; 25: 405–415

FEW TREATABLE ONCOGENIC ALTERATIONS[1-4]



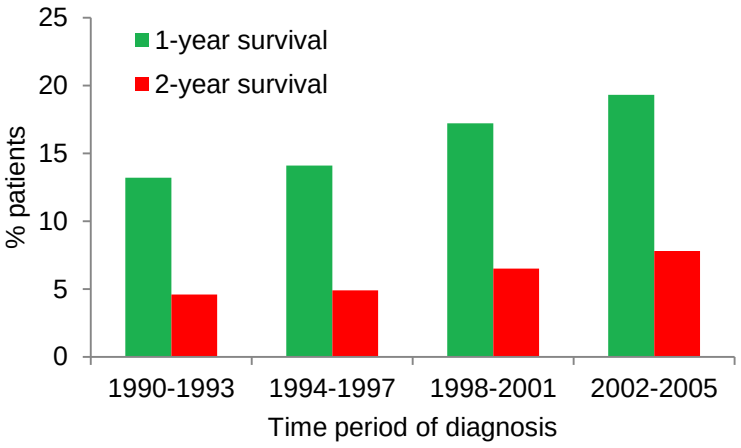
ALK, anaplastic lymphoma kinase;
EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer

1. Gerber DE et al. *Am Soc Clin Oncol Educ Book* 2014;e353–65;;
2. Cancer Genome Atlas Research Network. *Nature* 2012;489:519–25;
3. Pan Y et al. Chest 2014;145:473–9;
4. Rekhtman N et al. Clin Cancer Res 2012;18:1167–76;

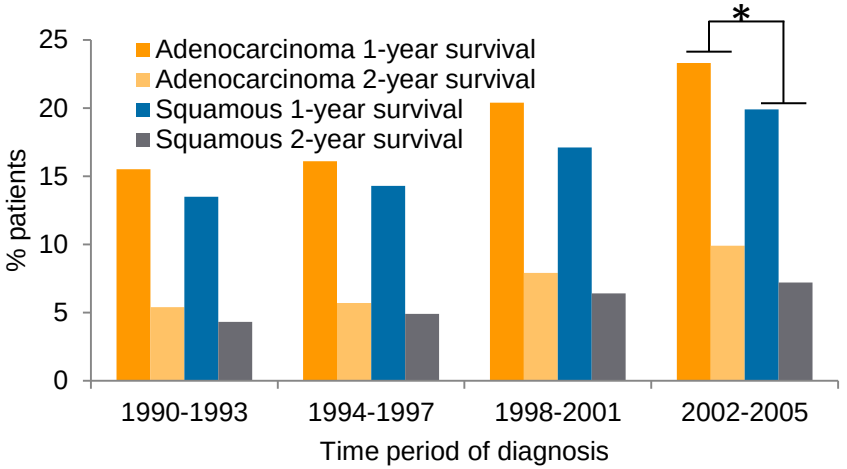
elcc

Improvements in survival over recent decades have been greater in stage IV adenocarcinoma vs squamous NSCLC[1]

Stage IV NSCLC 1 and 2 year survival: all histologies[1]



Stage IV NSCLC 1 and 2 year survival: adenocarcinoma vs squamous[1]



Based on data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program for patients diagnosed between 1990 and 2005 for patients with stage IV NSCLC[1]

- Survival has been improving since 1990 for NSCLC of all histologies[1]
- Significantly increased survival was observed for patients diagnosed in 2002-2005 with adenocarcinoma compared with those diagnosed with squamous cell carcinoma[1]

NSCLC, non-small cell lung cancer

1. Morgensztern D et al. *J Thorac Oncol* 2009;4:1524–9

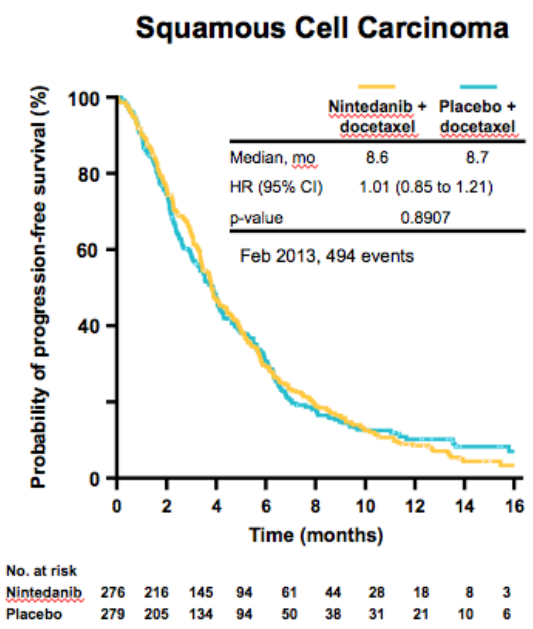
WHAT DO WE KNOW ABOUT SECOND-LINE THERAPY IN NSCLC?

	Docetaxel	Pemetrexed	Erlotinib	Afatinib (SCC)	Docetaxel + Ramucirumab (NSCLC)	Docetaxel + Nintedanib (NSCLC)
RR, %	5.0–12.0	7.1–11.8	7.9–9.0	6	23	4.4 Central Review
Median PFS, m	2.0–3.1	2.6–2.9	2.2–3.6	2.4	4.5	3.4
Median OS, m	5.7–8.0	6.7–8.9	6.7–7.9	7.9	10.5	10.1
1-year OS,%	28.7–37.0	29.7–38.5	31.0–35.7	nr	nr	nr

Shepherd, et al. JCO 2000; Fossella, et al. JCO 2000; Ramlau, et al. JCO 2006; Paz-Ares, et al. BJC 2008 Kim, et al. Lancet 2008; Krzakowski, et al. JCO 2010; Hanna, et al. JCO 2004, Cullen, et al. Ann Oncol 2008 Shepherd, et al. NEJM 2005; Vamvakas, et al. ASCO 2010; Ciuleanu, et al. IASLC Chicago 2010; Reck M , et al, Lancet Oncology 2014; Garon E et al, Lancet 2014; Soria JC, Lancet Oncology 2015

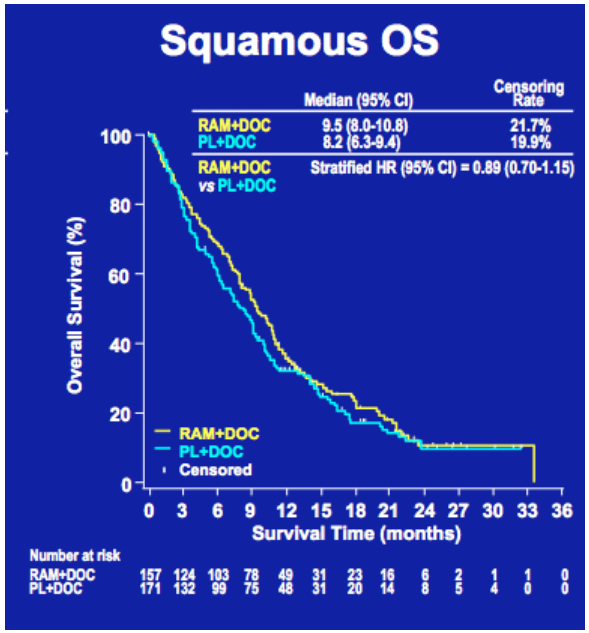
SECOND-LINE TREATMENT IN SCC?
NOT REALLY THE MODEL FOR LONG TERM OS

Nintedanib + Docetaxel
vs Docetaxel



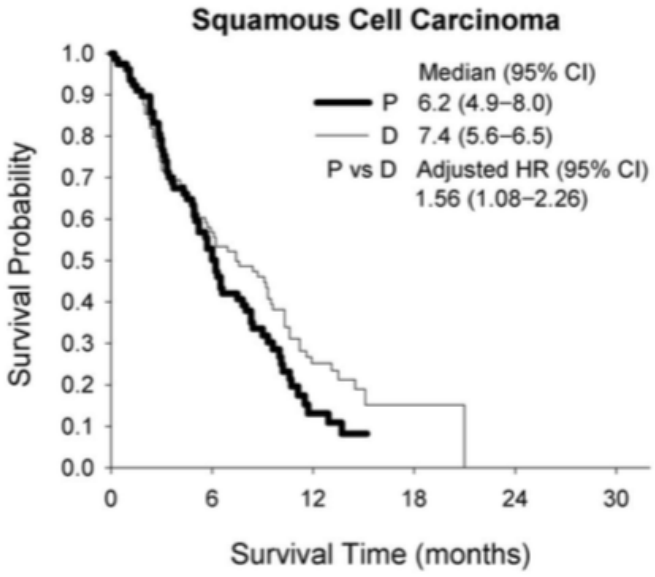
Median OS: 8.6 vs 8.7 m

Ramucirumab + Docetaxel
vs Docetaxel



Median OS: 9.5 vs 8.2 m

Pemetrexed vs Docetaxel



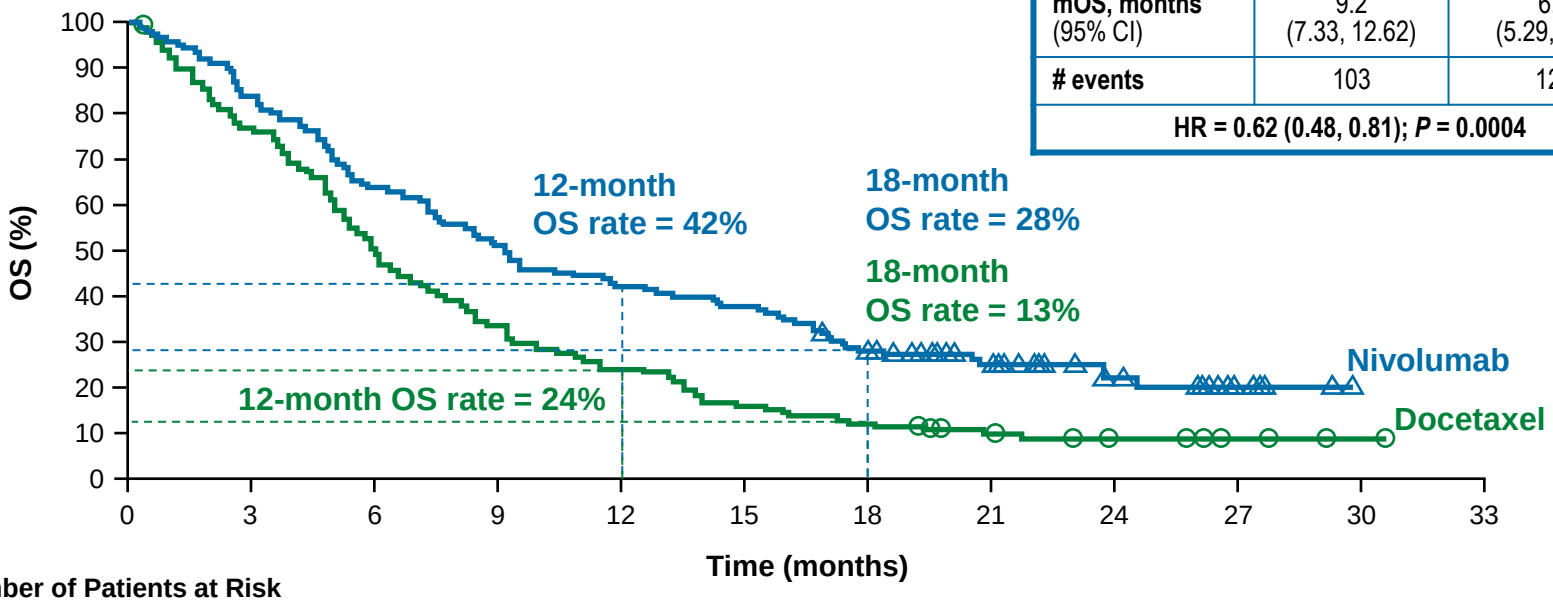
Median OS: 6.2 vs 7.4 m

Reck M et al, Lancet Oncology 2014, Garon E et al, Lancet 2014, Scagliotti GV et al, Oncologist 2009

THIS HAS SOMEWHAT CHANGED...

CHECKMATE 017: OVERALL SURVIVAL

	Nivolumab n = 135	Docetaxel n = 137
mOS, months (95% CI)	9.2 (7.33, 12.62)	6.0 (5.29, 7.39)
# events	103	122
HR = 0.62 (0.48, 0.81); *P* = 0.0004		



Number of Patients at Risk

Nivolumab	135	113	86	69	57	51	37	25	14	6	0	0
Docetaxel	137	104	69	46	33	22	15	11	7	3	1	0

Based on August 2015 DBL.

Minimum follow-up for survival: 18 months

mOS = median overall survival. Symbols refer to censored observations.

Reckamp K, et al. Presented at the 16th World Conference on Lung Cancer; September 6–9, 2015; Denver, Colorado, USA. Oral 02.01.

CHECKMATE 063: STUDY DESIGN AND BASELINE CHARACTERISTICS

Patients
- Stage IIIB/IV SQ NSCLC
- ≥2 prior systemic therapies
- ECOG PS 0–1

(N = 117)

→

Treatment

Nivolumab 3 mg/kg IV q2w, until PD or unacceptable toxicity

Endpoints

Primary
- IRC-assessed confirmed ORR

Secondary
- Investigator-assessed confirmed ORR

Exploratory
- Safety and tolerability
- PFS and OS
- Efficacy by PD-L1 expression

	Nivolumab 3 mg/kg Q2W N = 117
Median age, years (range)	65 (37–87)
Male, %	73
Disease stage, %	
IIIB	17
IV	83
ECOG PS, %	
0	22
1	78
Smoking status, %	
Current/former	92
Never	8
PD-L1 quantifiable, %[a]	65
≥1%	59
≥5%	33
≥10%	33
Number of prior systemic regimens, %	
2	35
3	44
≥4	21

[a]Percentages based on number of patients with evaluable samples (n = 76)

IRC = independent radiology review committee; PD = progressive disease; PFS = progression-free survival

CHECKMATE 063 2-YEAR UPDATE: EFFICACY

Efficacy	Nivolumab 3 mg/kg Q2W, N = 117		
	IRC-assessed, 6 months[a]	Investigator-assessed, 6 months[a]	Investigator-assessed, 24 months[b]
ORR, % (95% CI)	12 (7, 19)	13 (7, 20)	15 (9, 22)
Ongoing responders, % (n/N)	71 (10/14)	93 (14/15)	29 (5/17)[c]
Median TTR, months (range)	3.0 (1.7-4.8)	2.2 (1.3-6.0)	3.3 (1.6-7.4)
Median DOR, months (range)	NR (2.8 to 6.9+)	NR (1.2+ to 7.0+)	19 (4.5+ to 27.5+
Median PFS, months (95% CI)	1.9 (1.8, 3.2)	2.2 (1.8, 3.3)	2.0 (1.8, 3.2)
PFS rate, % (95% CI)	27 (18, 36)	-	9 (4, 15)
Best overall response, %			
CR	0	1	2
PR	12	12	13
SD	29	32	30
PD	43	44	45
Unable to determine/not reported	16	11	10

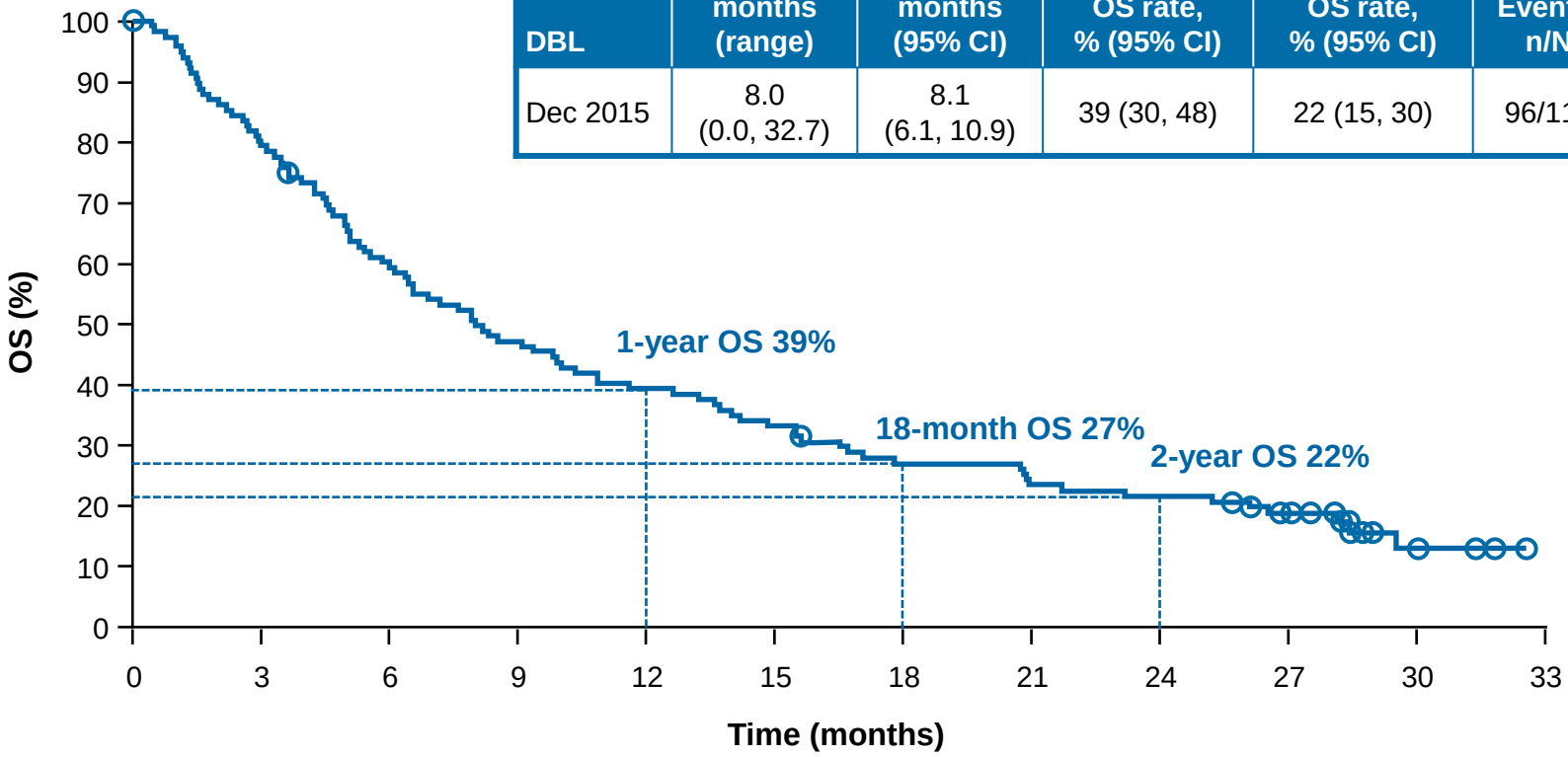
- At the 24-month data cutoff, 4 (3%) patients were still on treatment
- Five of 26 patients treated beyond initial PD demonstrated a non-conventional pattern of benefit

CR, complete response; DOR, duration of response; NR, not reached; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TTR, time to response.

[a]March 2014 database lock. [b]December 2015 database lock. [c]Two additional patients had ongoing responses but were censored prior to the database lock (1 was lost to follow-up and 1 withdrew consent).

CHECKMATE 063 2-YEAR UPDATE: OVERALL SURVIVAL

DBL	Median follow-up, months (range)	Median OS, months (95% CI)	1-year OS rate, % (95% CI)	2-year OS rate, % (95% CI)	Events, n/N
Dec 2015	8.0 (0.0, 32.7)	8.1 (6.1, 10.9)	39 (30, 48)	22 (15, 30)	96/117

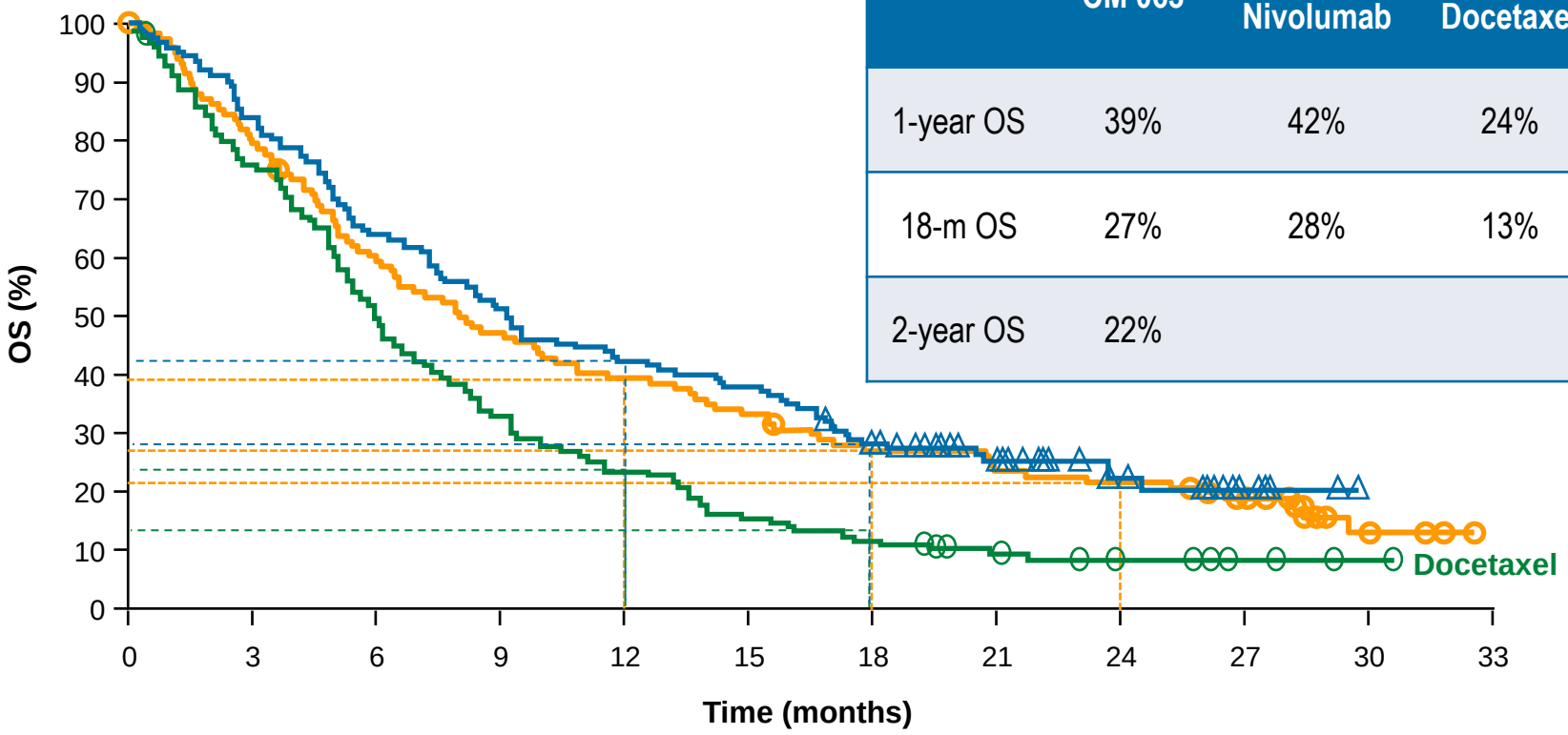


Number of patients at risk:

Dec 2015 database lock	117	93	69	54	45	38	30	27	24	17	5	0

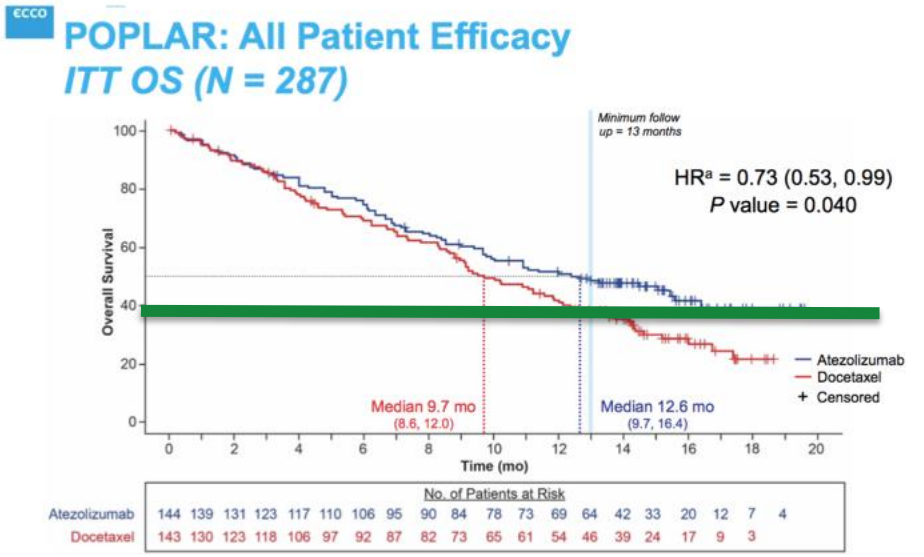
CHECKMATE 063 AND CHECKMATE 17 OVERALL SURVIVAL

	CM 063	CM 017 Nivolumab	CM 017 Docetaxel
1-year OS	39%	42%	24%
18-m OS	27%	28%	13%
2-year OS	22%		

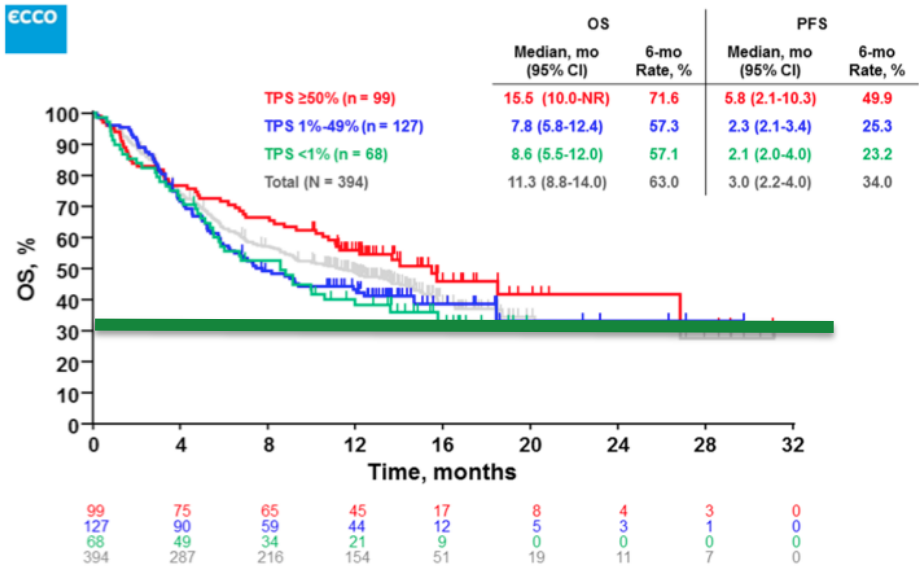


Reckamp K, et al. Presented at the 16th World Conference on Lung Cancer; September 6–9, 2015; Denver, Colorado, USA. Oral 02.01.

THE PICTURE IS THE SAME ALSO WITH OTHER COMPOUNDS



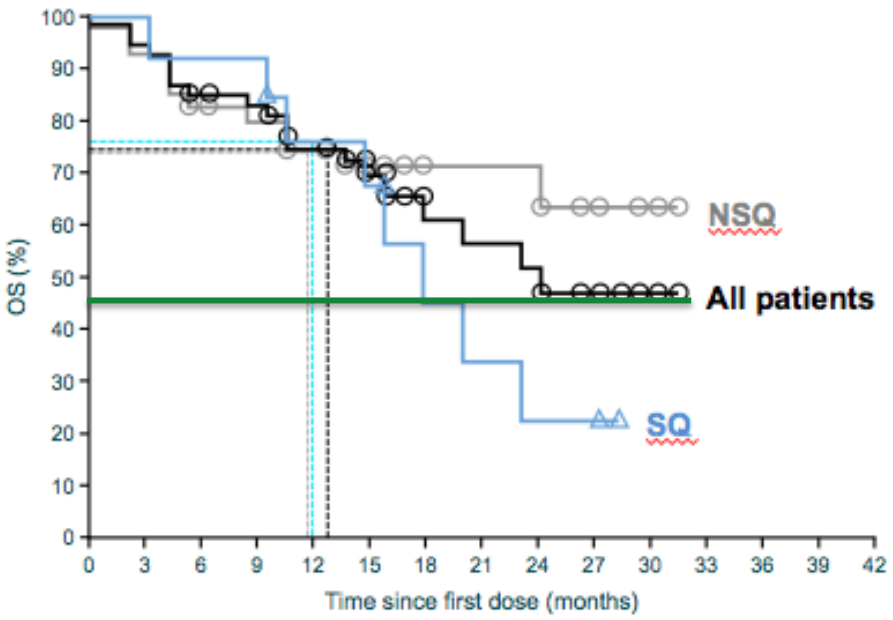
Atezolizumab
(Vansteenkiste ECCO ESMO 2015)



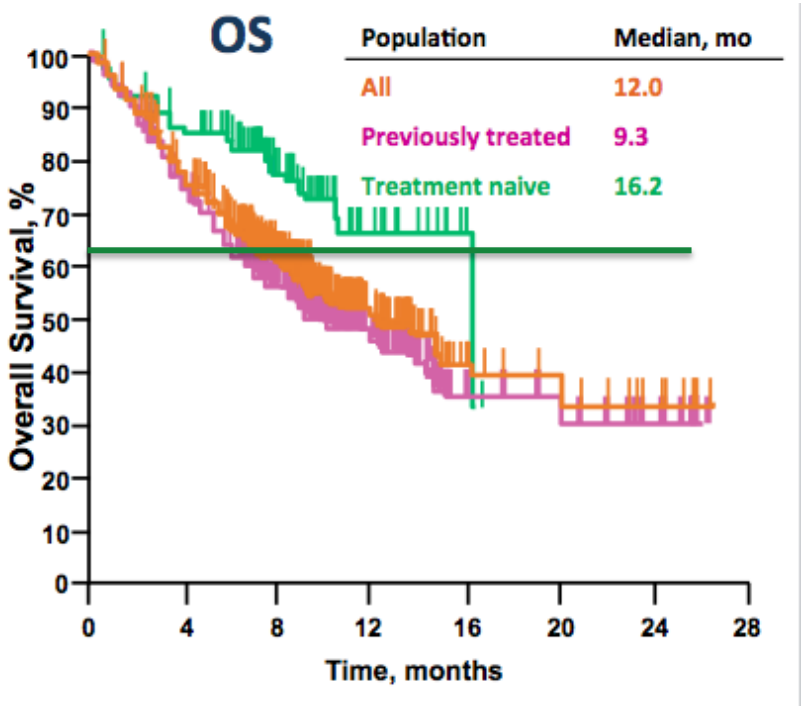
Pembrolizumab
(Soria ECCO ESMO 2015)

PERHAPS EVEN BETTER IN UNTREATED PATIENTS

Nivolumab

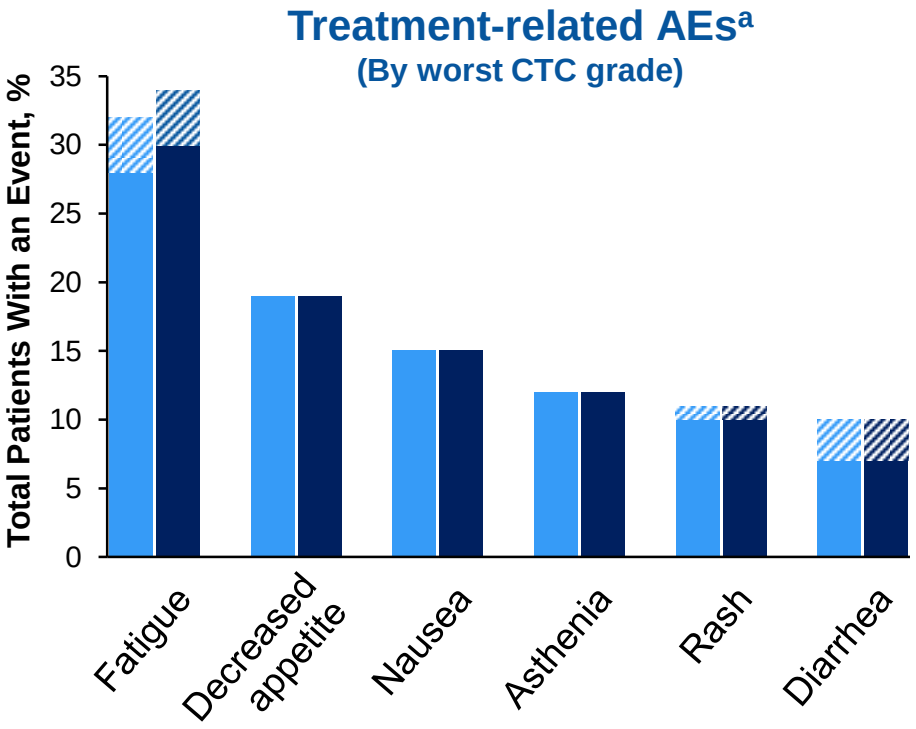


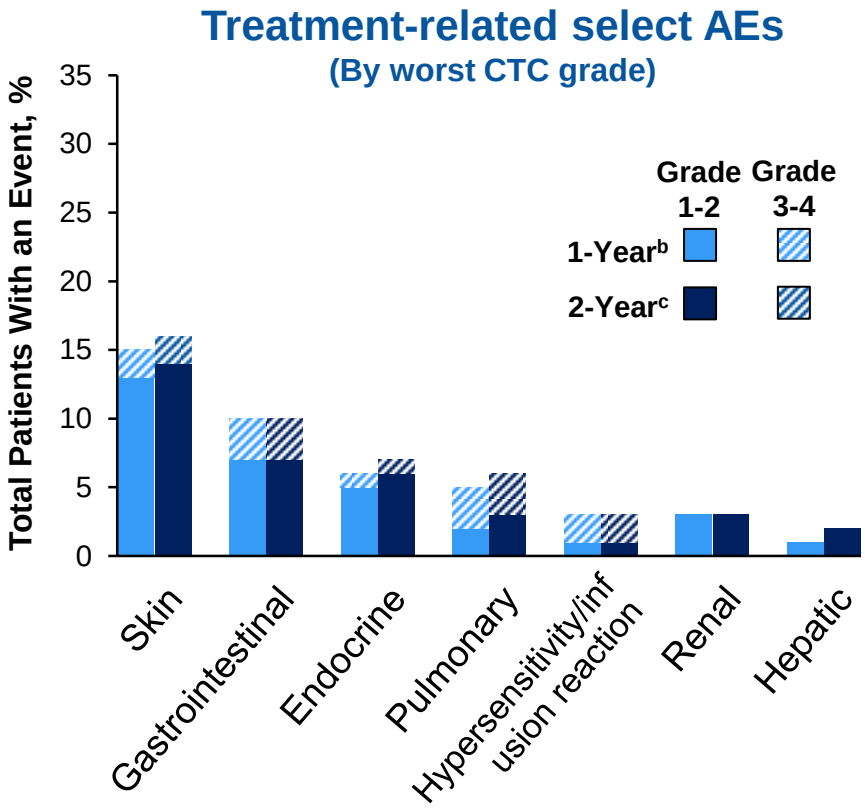
Pembrolizumab



Antonia S, ECCO ESMO 2015; Garon E, AACR 2015

IT IS NOT ONLY EFFICACY: TREATMENT-RELATED AEs AND SELECT AEs

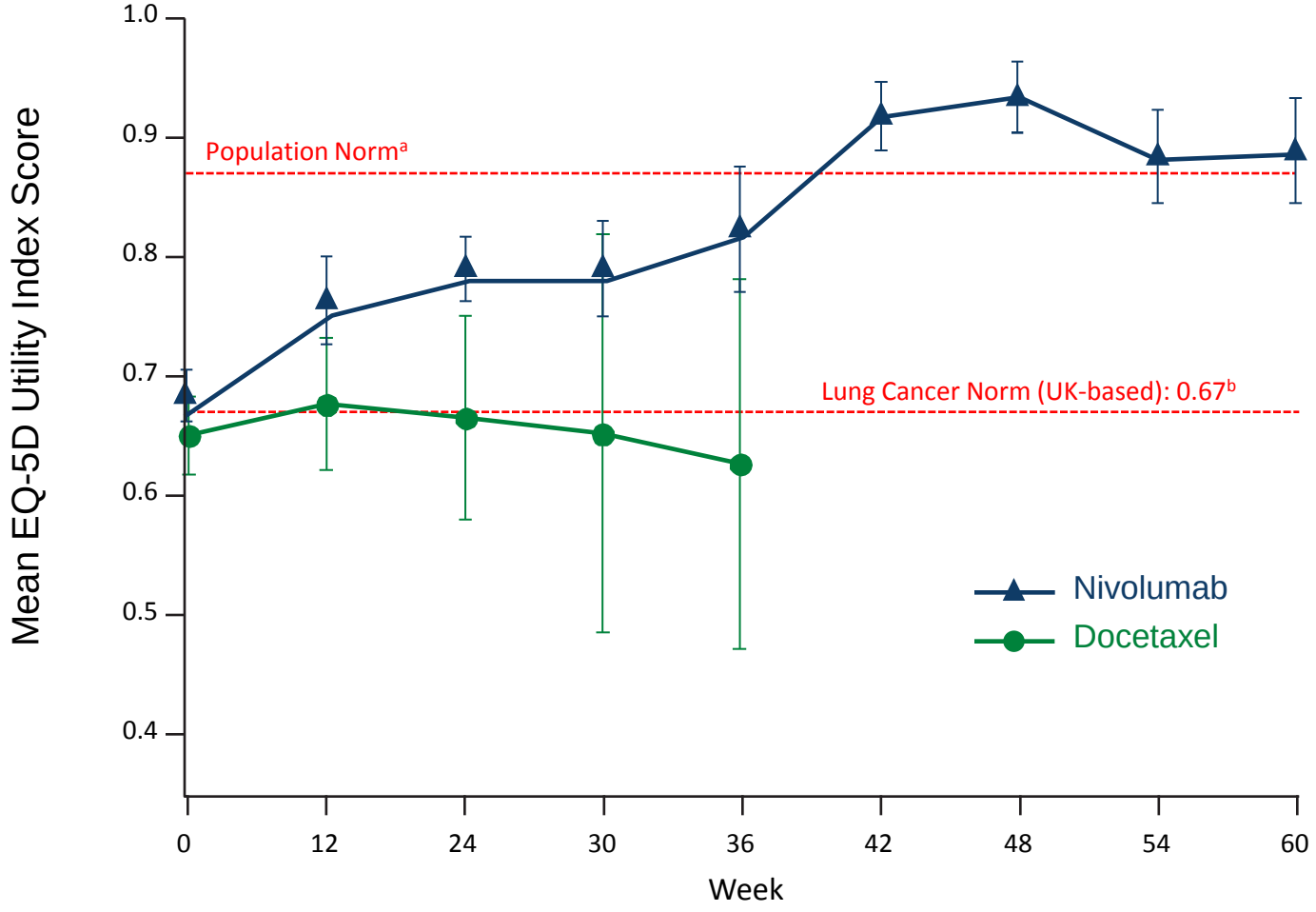




- No new grade 3-4 treatment-related AEs/select AEs have been reported since the 1-year database lock

[a]Reported in >10% of patients. [b]July 2014 database lock. [c]December 2015 database lock.
CTC = common terminology criteria.

SQUAMOUS : EQ-5D UTILITY INDEX WHILE ON TREATMENT

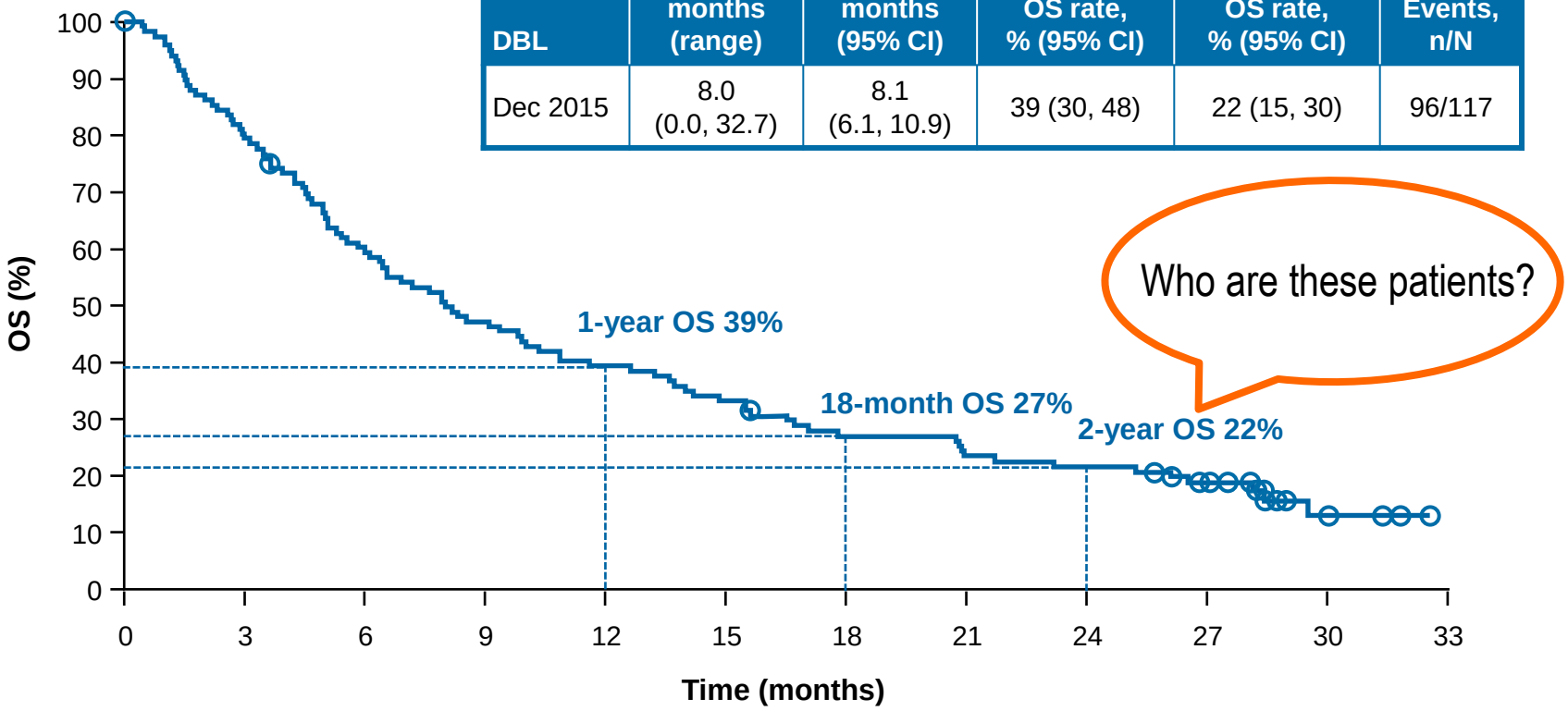


Nivolumab (n = 97)	97	50	32	32	21	18	13	13	8
Docetaxel (n = 89)	88	32	9	5	5	4	4	2	1

Reck, ESMO 2015

THE NEXT QUESTION

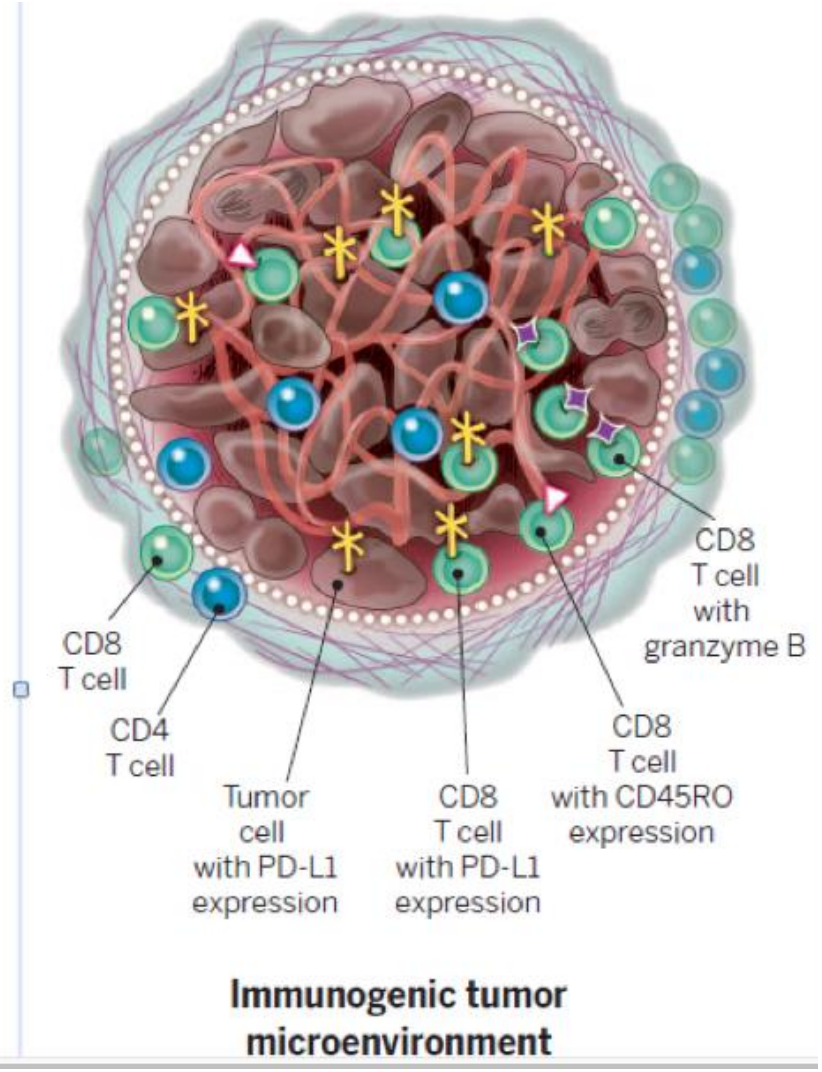
DBL	Median follow-up, months (range)	Median OS, months (95% CI)	1-year OS rate, % (95% CI)	2-year OS rate, % (95% CI)	Events, n/N
Dec 2015	8.0 (0.0, 32.7)	8.1 (6.1, 10.9)	39 (30, 48)	22 (15, 30)	96/117



Number of patients at risk:

Dec 2015 database lock	117	93	69	54	45	38	30	27	24	17	5	0

HOW CAN WE CHARACTERIZE THE „IMMUNOGENIC“ TUMOR?



Sharma P, Allison JP. The future of immune checkpoint therapy. Science 2015;348:56-61.

HOW CAN WE CHARACTERIZE THE „IMMUNOGENIC“ TUMOR?

- Clinical Factors?
  - Age
  - PS
  - Gender
  - Histology
  - Stage

Not really

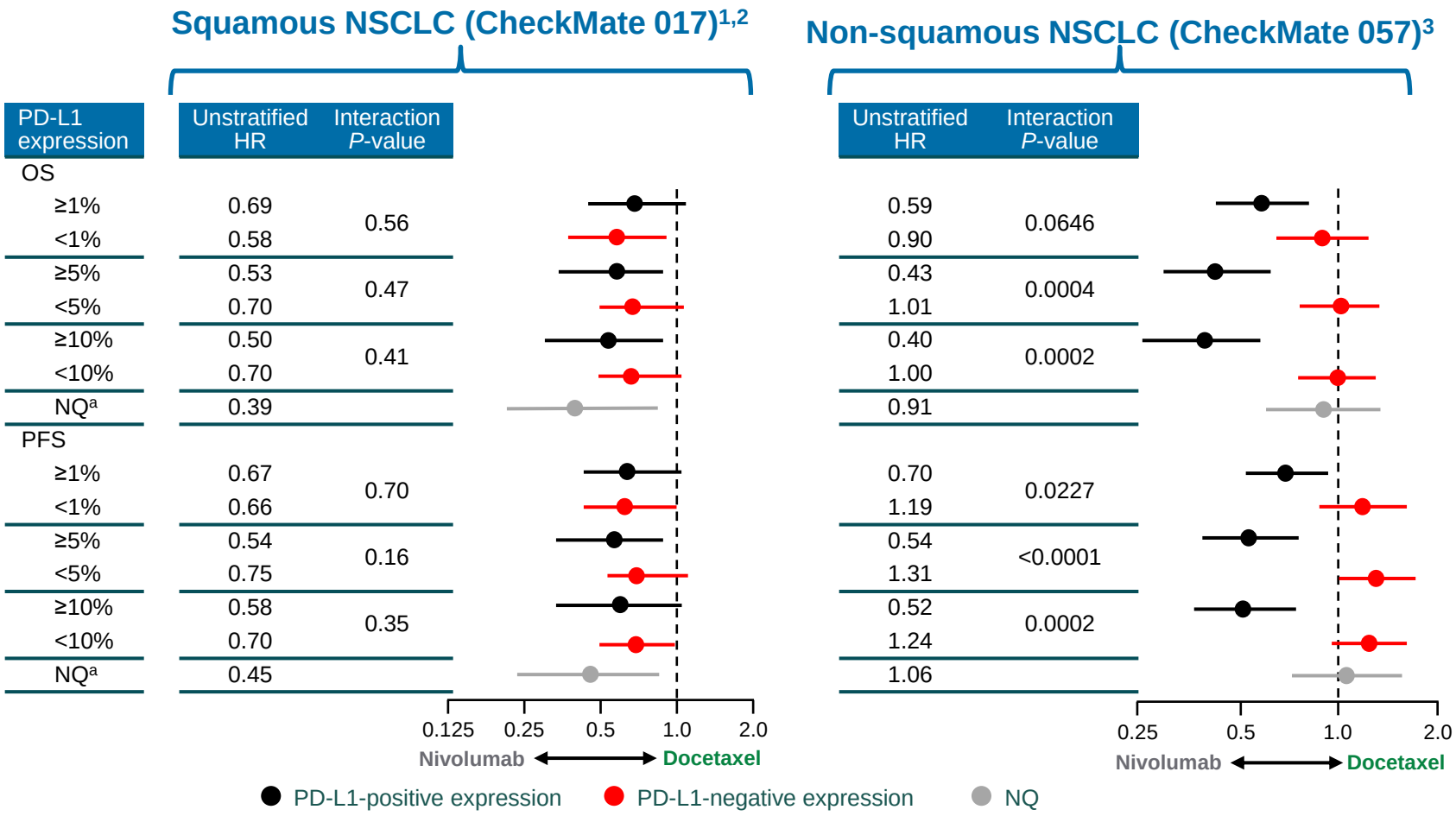
HOW CAN WE CHARACTERIZE THE „IMMUNOGENIC“ TUMOR?

- Clinical Factors? **Not suitable**
- PDL-1 Expression?

THE CHALLENGE IN PD-L1 TESTING: CURRENTLY FOUR TESTS IN DEVELOPMENT

	Merck	BMS	Roche	AZ	Pfizer
	KEYTRUDA pembrolizumab	**Opdivo nivolumab**	**Atezolizumab MPDL3280a**	**Durvalumab MEDI-4736**	**Avelumab MSB0010718C**
Clone	22C3	28-8	SP142	SP263	–
Dxy	Dako	Dako	Ventana	Ventana	Dako
Cutoffs	TC: ≥1, ≥50	TC: ≥1, ≥5, ≥10	TC: ≥1, ≥10, ≥50 IC: ≥1, ≥5, ≥10	TC: ≥25, ≥90	TC: ≥1
Prospective	**Yes**	**No**	**Yes**	**Yes**	**Yes**
Inter Observer	**95.6 (50%)**	**97.8 (1%) 98.5 (5%)**	**>90**	**96.7 (25%)**	**–**
Inter Site	**91.3 (50%)**	**90.2 (1%) 94.8 (5%)**	**–**	**–**	**–**

DIFFERENT IMPACT OF PD-L1 EXPRESSION RELATED TO HISTOLOGY? PERHAPS NOT THE BEST IDEA IN SCC



[a]at baseline.

1. Brahmer J, et al. *New Engl J Med.* 2015;373:123–135. 2. Spigel DR, et al. Presented at ASCO 2015, Abstract 8009. 3. Paz-Ares L, et al. Presented at ASCO 2015, Abstract LBA109.

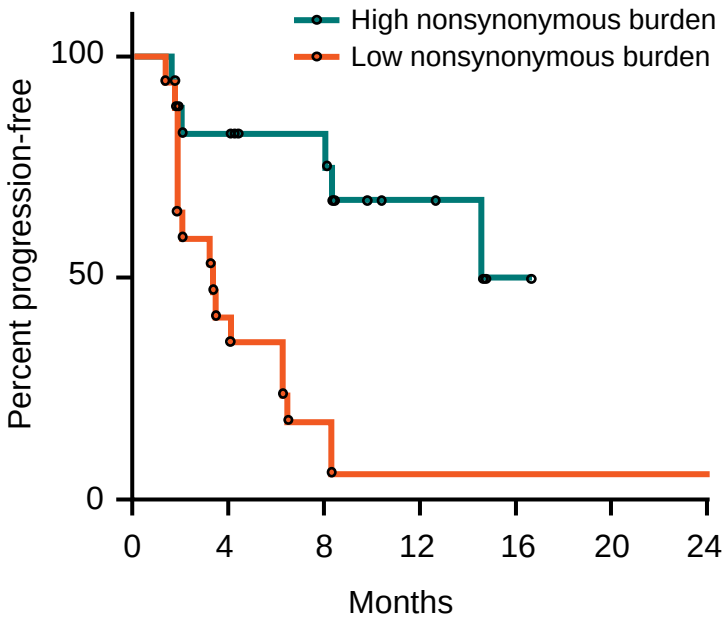
HOW CAN WE CHARACTERIZE THE „IMMUNOGENIC“ TUMOR?

- Clinical Factors? **Not suitable**
- PDL-1 Expression? **Not helpful in SCC**
- Other?

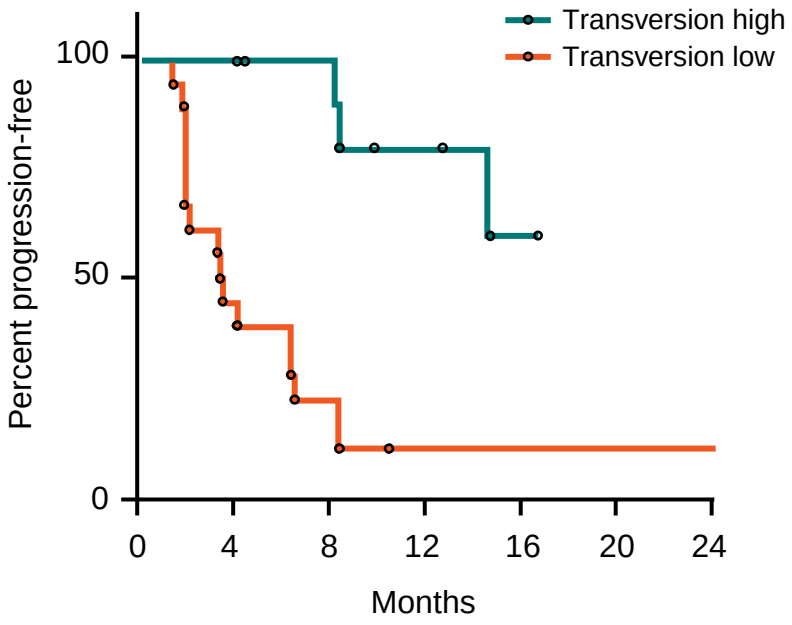
MUTATIONAL BURDEN AND SENSITIVITY TO IO AGENTS

EXAMPLE: PEMBROLIZUMAB

Mutational burden



Molecular smoking signature



Rizvi NA, et al. *Science*. 2015;348:124–128.

IMPACT OF AN IFNY SIGNATURE ON EFFICACY
EXAMPLE PEMBROLIZUMAB (HEAD AND NECK C)

Table 3. Association of Immune-Related Gene Expression Signatures and Best Overall Response and PFS in Patients With Head and Neck Cancer[a]

Signature	Nominal 1-Sided *P* Value[b]	
	Best Overall Response N = 40	PFS N = 43
IFN-γ (6 genes)	0.005	<0.001
TCR signaling (13 genes)	0.071	0.002
Expanded immune (18 genes)	0.015	<0.001
De novo (33 genes)	0.018	<0.001

[a]Best overall response and PFS assessed by investigator.
[b]From logistic or Cox regression for overall response and PFS, respectively, using signature scores as a continuous variable.

Seiwert TY et al, ASCO 2015

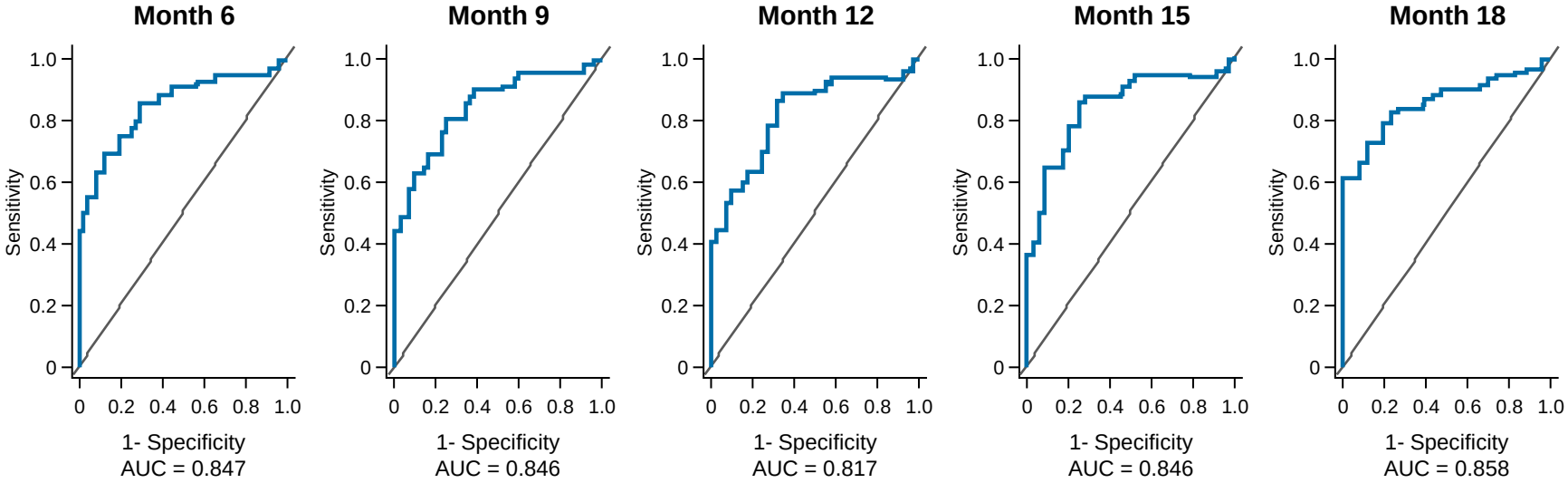
CYTOKINES ASSOCIATED WITH OS IN PATIENTS WITH SQ NSCLC

Cytokines associated with OS[a] identified via stepwise variable selection in Cox model using AIC:

IL-8	VWF	MICA	CRP	IL-6	FRTN	MIG
IP-10	IL-18	MIP1B	ICAM1	IL-1RA	MMP3	VDBP

Some key cytokines, such as IFNγ and TNF, were not evaluable, so were not considered in the cytokine selection

Model Evaluation of the Selected Cytokines in the Validation Set

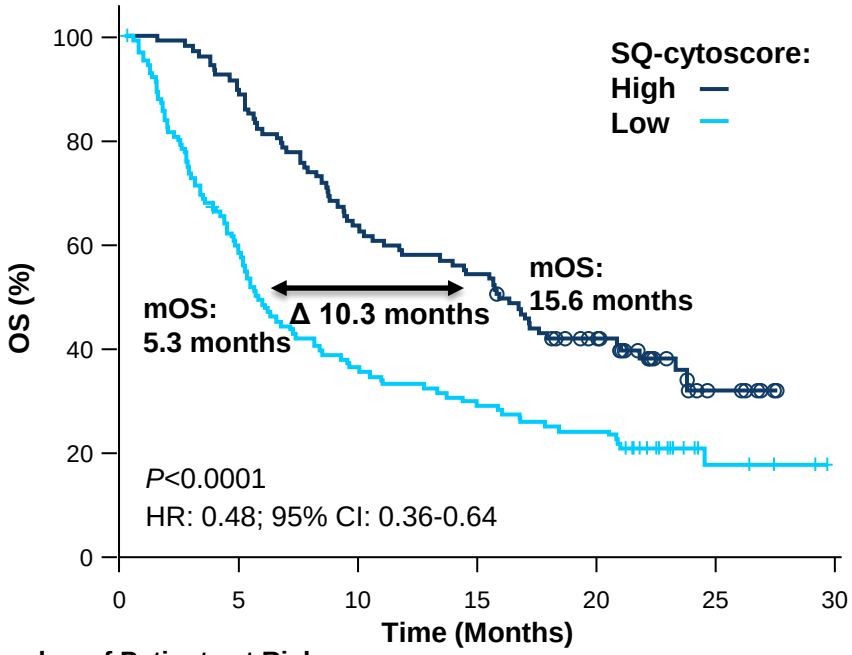


[a]Based on 18-month data from CheckMate 063 (June 2015 database lock) and CheckMate 017 (August 2015 database lock).

AIC = Akaike information criterion. AUC = area under the curve.

PATIENTS WITH HIGH SQ-CYTOSCORE SHOWED LONGER MEDIAN OS – PROGNOSTIC FACTOR

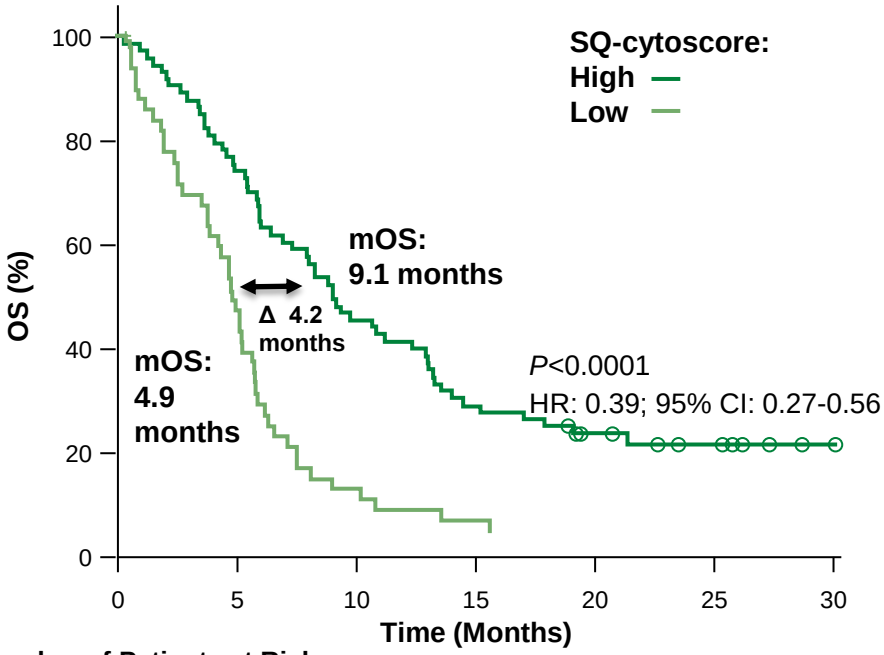
Nivolumab-treated patients



Number of Patients at Risk

High	102	62	33	0
Low	120	38	24	0

Docetaxel-treated patients



Number of Patients at Risk

High	70	30	11	1
Low	48	4	0	--

- mOS in patients with high SQ-cytoscore (nivolumab vs docetaxel): 15.6 vs 9.1 months (*P* = 0.0051; HR:0.63; 95% CI: 0.45-0.88)
- mOS in patients with low SQ-cytoscore (nivolumab vs docetaxel): 5.3 vs 4.9 months (*P* = 0.0009; HR:0.51; 95% CI: 0.37-0.71)

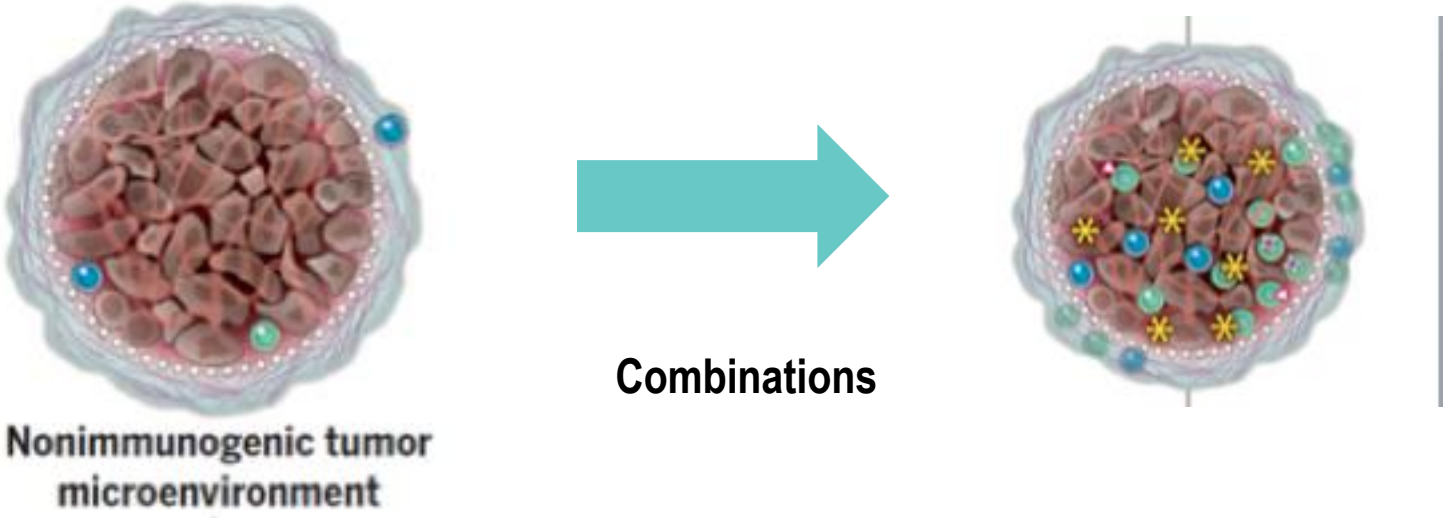
Based on 18-month data from CheckMate 063 (June 2015 database lock) and CheckMate 017 (August 2015 database lock).

QUESTIONS

- Association of dynamic changes in cytokine levels with efficacy of checkpoint inhibitors? (Pharmacodynamic marker)
- Besides cytokines could circulating immune cells serve as a marker of interest (baseline markers as well as dynamic marker?)
- Do we see similar outcomes also in non-squamous NSCLC?
- Analyses of CM-057 will be presented at ASCO 2016!

CONCLUSION

- Is there a chance for long term survival by checkpoint-inhibitors?
- Yes, it seems so,
- ,....but
  - We are still on the way to identify these patients
    - ***(because these patients should receive IO-treatment!)***
  - We will need to improve this plateau!



Sharma P, Allison JP. The future of immune checkpoint therapy. Science 2015;348:56-61.