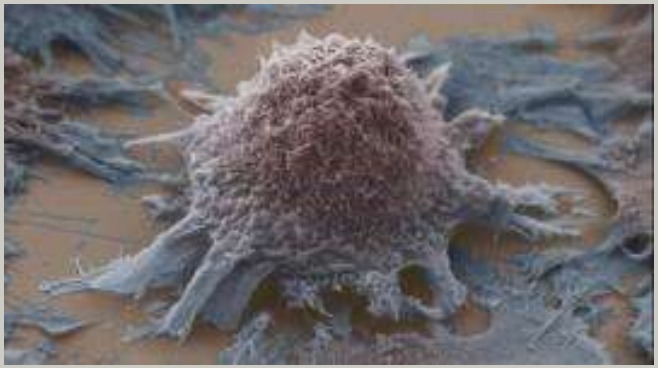


Immuntherapie beim Lungenkarzinom

Dr. med. R. Müller

Chefarzt Klinik f. Innere Medizin V
Lungenzentrum
Heinrich-Braun-Klinikum
Standort Zwickau

Zwickau, 18. März 2017

The Hallmarks of Cancer

verändert nach: Hanahan D und Weinberg RD, DOI 10.1016/j.cell.2011.02.013

Tumor-Zellen können der Immun-Antwort durch verschiedene Mechanismen entgehen

1. Stopp der Antigen-Expression[1]

2. Sekretion immunsuppressiver Cytokine und Rekrutierung immunosuppressiver Zellen[2,3]

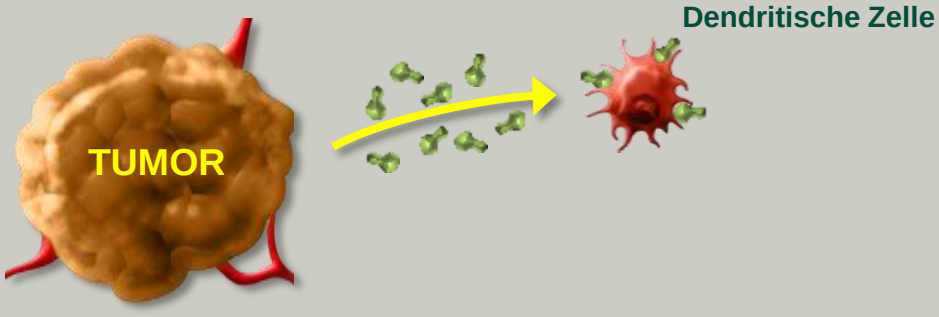
3. Ausnutzen von Immun-Checkpoint-Signalwegen, wie den PD-1-Signalweg[4]

PD-1 = programmed cell death protein 1.

1. Ahmad M et al. *Cancer Immunol Immunother.* 2004;53:844–854; **2.** Zou W. *Nat Rev Immunol*. 2006;6:295–307;
3. Finn OJ. *N Engl J Med*. 2008;358:2704–2715; **4.** Pardoll DM. *Nat Rev Cancer*. 2012;12:252–264.

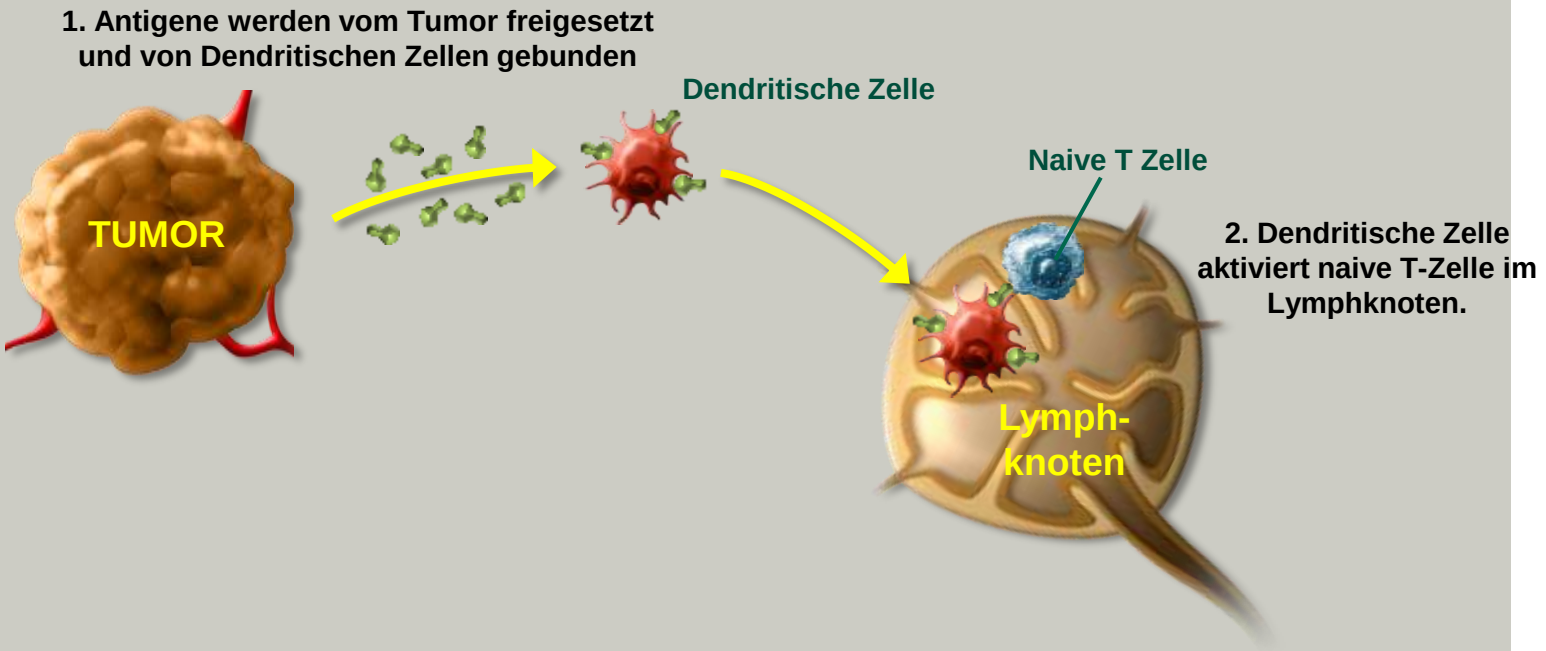
T-Zellen sind wichtig, um Tumor-Zellen zu entdecken und zu zerstören[1]

1. Antigene werden vom Tumor freigesetzt und von Dendritischen Zellen gebunden



1. May KF Jr et al. In: Prendergast GC et al. *Cancer Immunotherapy*. 2nd ed. Elsevier; 2013:101–113.

T-Zellen sind wichtig, um Tumor-Zellen zu entdecken und zu zerstören[1]



1. May KF Jr et al. In: Prendergast GC et al. *Cancer Immunotherapy*. 2nd ed. Elsevier; 2013:101–113.

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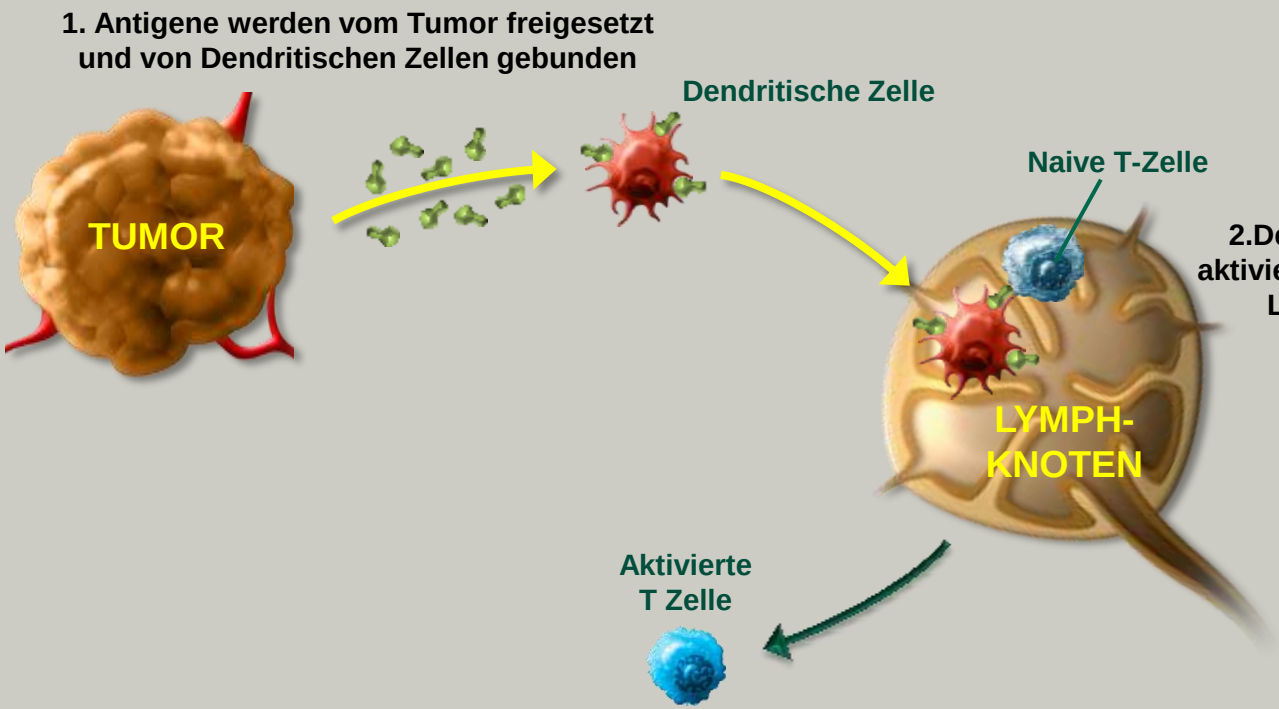

1. May KF Jr et al. In: Prendergast GC et al. *Cancer Immunotherapy*. 2nd ed. Elsevier; 2013:101–113.

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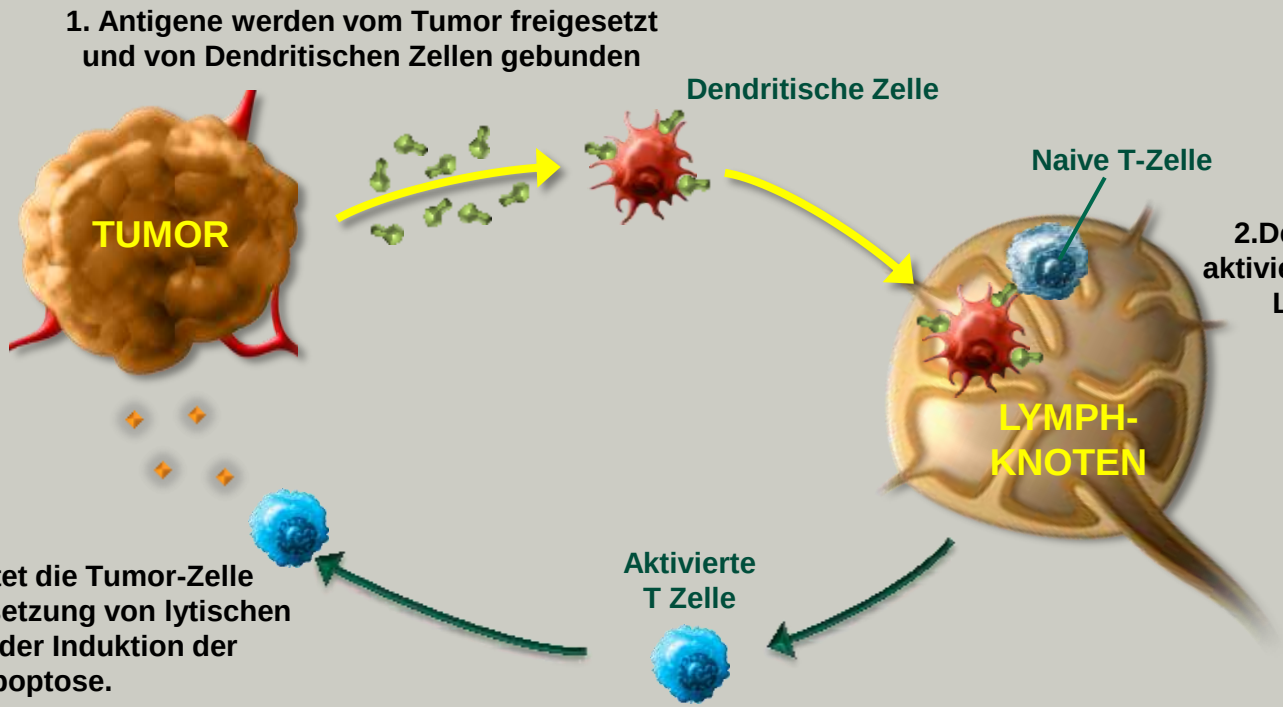
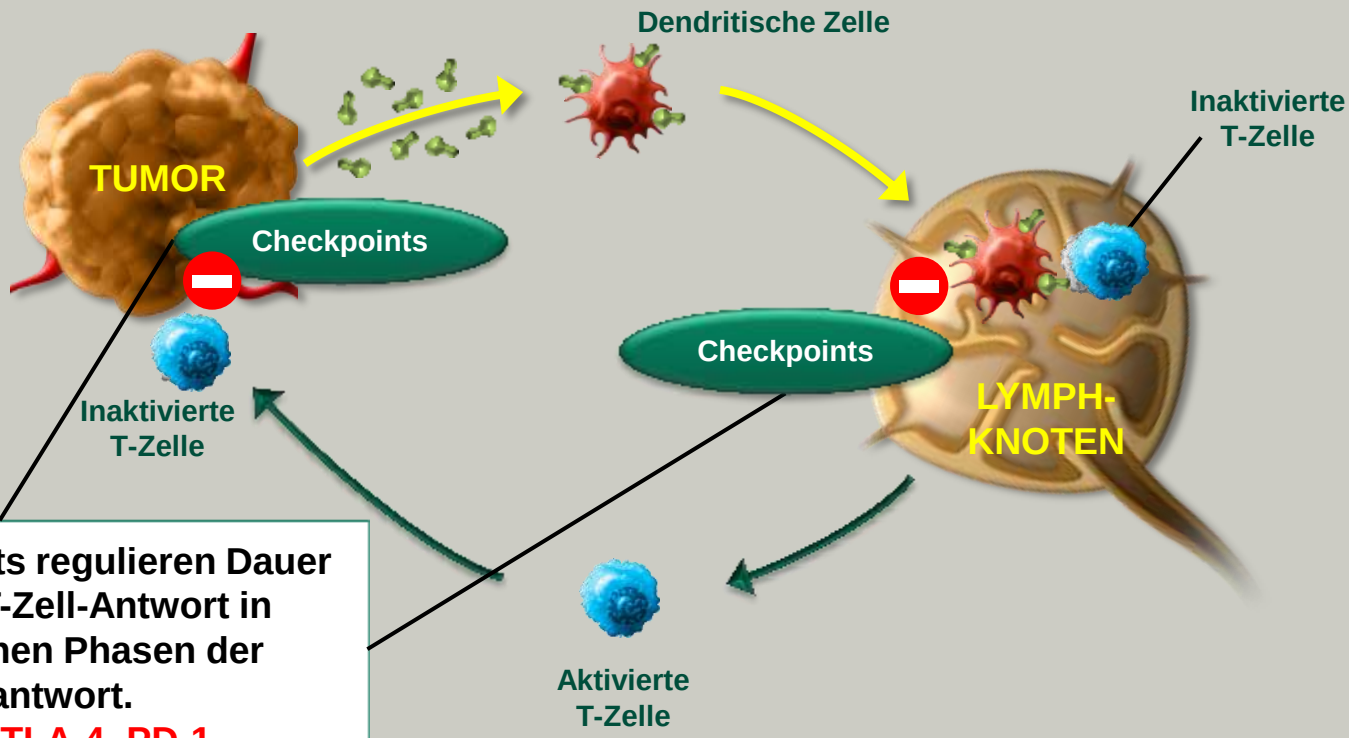
T-Zellen sind wichtig, um Tumor-Zellen zu entdecken und zu zerstören[1]



1. May KF Jr et al. In: Prendergast GC et al. *Cancer Immunotherapy*. 2nd ed. Elsevier; 2013:101–113.

Immun-Checkpoints regulieren die T-Zell-Aktivität



Immun-Checkpoints regulieren Dauer und Level der T-Zell-Antwort in unterschiedlichen Phasen der Immunantwort.
Beispiele: CTLA-4, PD-1

CTLA-4 = cytotoxic T-lymphocyte antigen 4; PD-1 = programmed cell death protein 1.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12:252–264.

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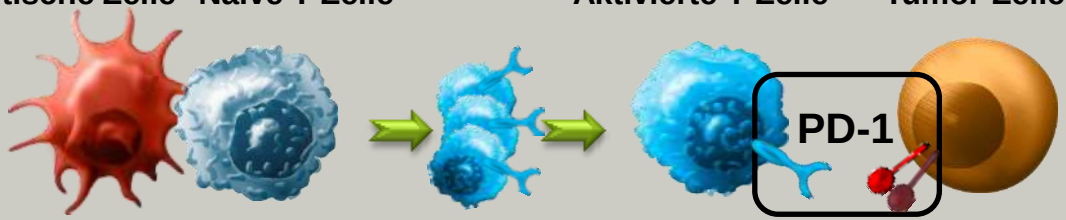
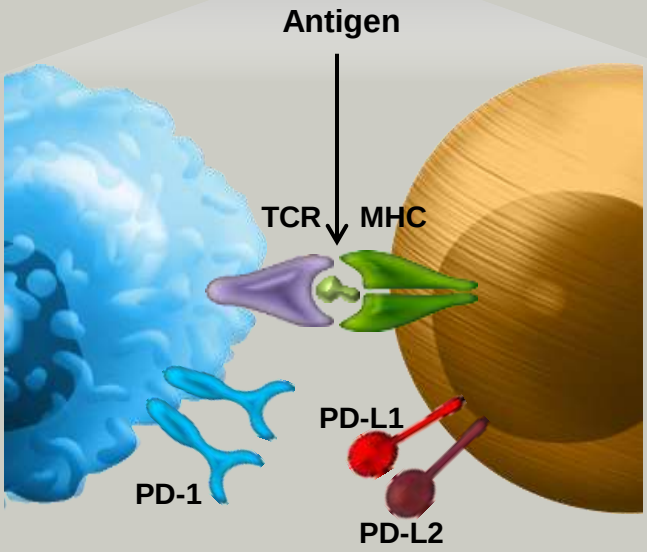
Ausnutzen des PD-1 Immun-Checkpoint-Signalweges durch die Tumorzelle[1]

Präge-Phase der Aktivierung

Effektor-Phase

Dendritische Zelle **Naïve T-Zelle** **Aktivierte T-Zelle** **Tumor-Zelle**





- Der PD-1-Immun-Checkpoint-Signalweg wurde als ein Weg identifiziert, wie Tumor-zellen den Angriff durch das Immun-System überleben können
- Tumor-Zellen blockieren die Immun-Antwort über den PD-1 Immun-Checkpoint-Signalweg durch die Expression der PD-1-Liganden, PD-L1 and PD-L2

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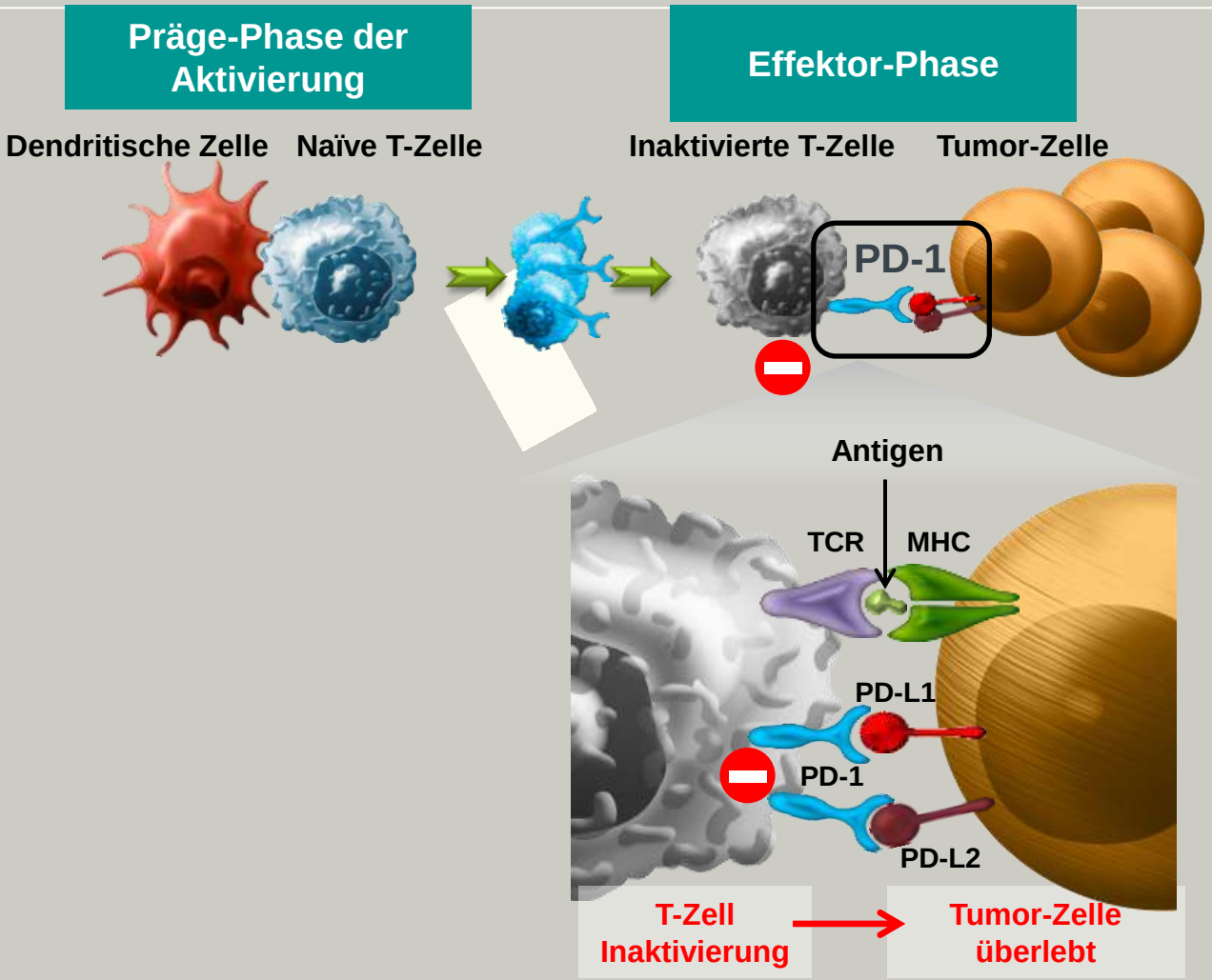
PD-1 = programmed cell death protein 1; TCR = T-cell receptor; MHC = major histocompatibility complex; PD-L1 = programmed; cell death ligand 1; PD-L2 = programmed cell death ligand 2.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12:252–64.

R. Müller

Ausnutzen des PD-1 Immun-Checkpoint-Signalweges durch die Tumorzelle[1]



- PD-1 ist während der Effektor-Phase der Immunantwort auf aktivierten T-Zellen hoch-reguliert.
- PD-L1 und PD-L2 binden den PD-1-Rezeptor der T-Zelle und hemmen so ihre Aktivität in der Effektor-Phase.

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PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1;
PD-L2 = programmed cell death ligand 2.

1. Pardoll DM. *Nat Rev Cancer*. 2012;12:252–264.

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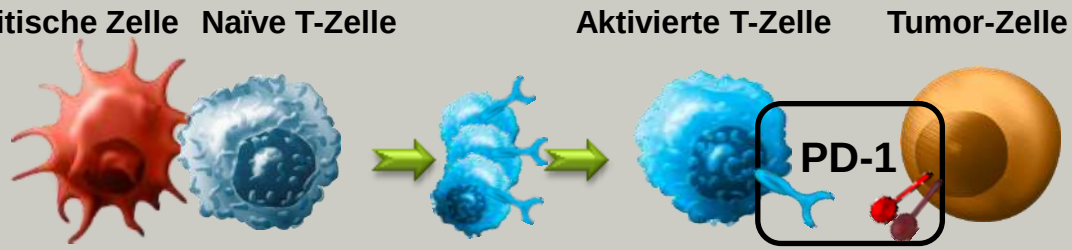
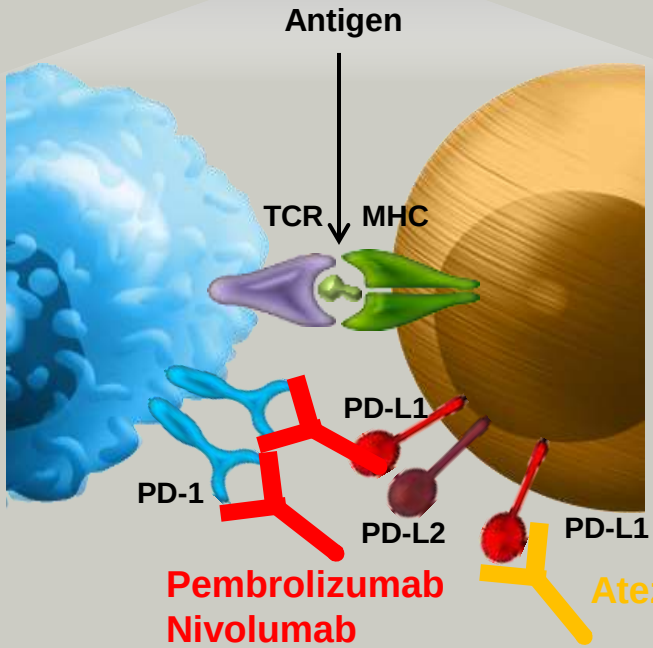
Gezielte Blockade des PD-1 Immun-Checkpoint-Signalweges durch einen Anti-PD-1-/PD-L1 Antikörper[1]

Präge-Phase der Aktivierung

Effektor-Phase





- Der Anti-PD-1-Antikörper bindet selektiv an den PD-1-Rezeptor der T- Zelle und verhindert die Bindung von PD-L1 und PD-L2
- Durch die Blockade der PD-1-Rezeptoren bleibt die T-Zell-Aktivität erhalten
- Der Anti-PD-L1-Antikörper bindet an das PD-L1-Protein auf der Tumorzelle und an B7.1 der APC und verhindert die Bindung von PD-L1 und dem PD1-Rezeptor, sowie eine Hemmung der T-Zellaktivierung. PD-L2 kann weiterhin binden.

Reprinted by permission from Macmillan Publishers Ltd: *Nat Rev Cancer,*[1] copyright 2012.
PD-1 = programmed cell death protein 1; TCR = T-cell receptor; MHC = major histocompatibility complex; PD-L1 = programmed; cell death ligand 1; PD-L2 = programmed cell death ligand 2.
1. verändert nach Pardoll DM. *Nat Rev Cancer*. 2012;12:252–64.

NSCLC und Nivolumab

8009: A phase III study (CheckMate 017) of nivolumab (NIVO; anti-programmed death-1 [PD-1]) vs docetaxel (DOC) in previously treated advanced or metastatic squamous (SQ) cell non-small cell lung cancer (NSCLC) – Spigel DR et al

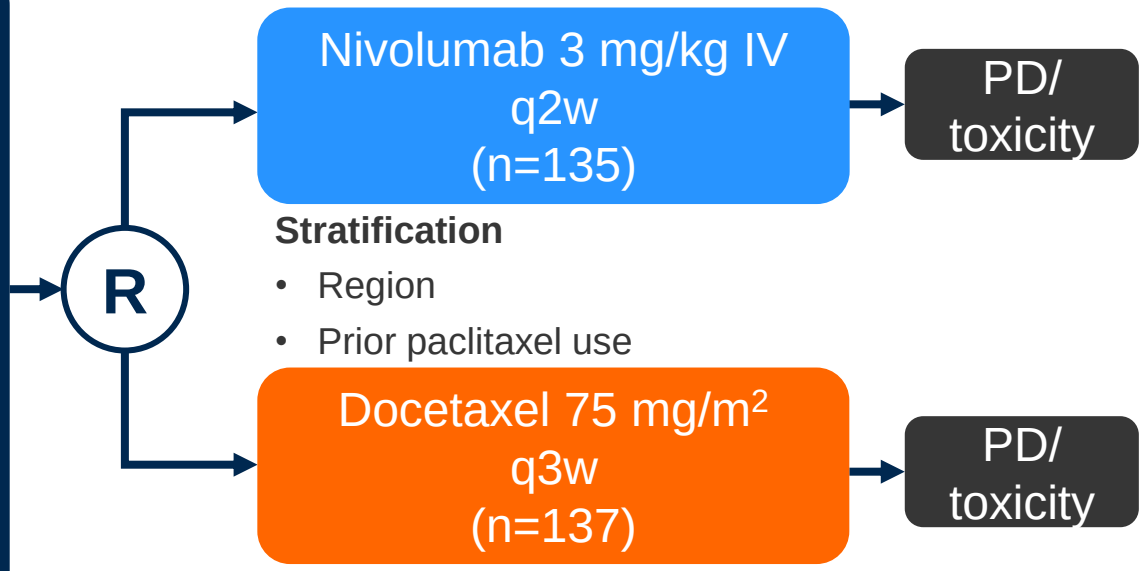
Study objective

- To investigate the efficacy and safety of nivolumab, a human anti-PD-1 antibody, vs. docetaxel in patients with squamous NSCLC

Key patient inclusion criteria

- Squamous NSCLC
- Stage IIIb/IV
- ECOG PS 0−1
- 1 prior platinum doublet
- Pre-treatment (archival or fresh) tumour samples available for PD-L1 analysis

(n=272)



Primary endpoint

- OS

Secondary endpoints

- ORR, PFS, efficacy by PD-L1 expression, quality-of-life, safety

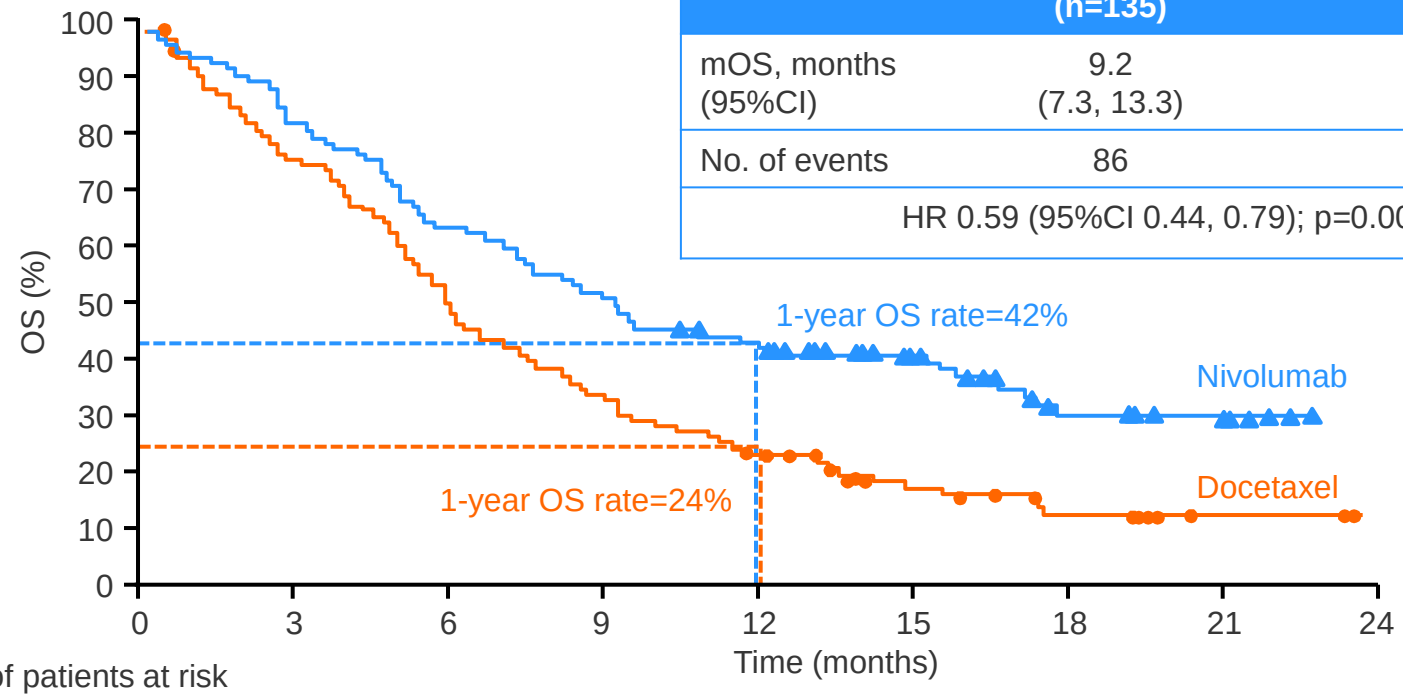
Spigel et al. J Clin Oncol 2015; 33 (suppl): abstr 8009

8009: A phase III study (CheckMate 017) of nivolumab (NIVO; anti-programmed death-1 [PD-1]) vs docetaxel (DOC) in previously treated advanced or metastatic squamous (SQ) cell non-small cell lung cancer (NSCLC) – Spigel DR et al

- **Key results**
  - Nivolumab was associated with a 41% reduction in risk of death

OS

	Nivolumab (n=135)	Docetaxel (n=137)
mOS, months (95%CI)	9.2 (7.3, 13.3)	6.0 (5.1, 7.3)
No. of events	86	113
HR 0.59 (95%CI 0.44, 0.79); p=0.00025		



Number of patients at risk

Nivolumab	135	113	86	69	52	31	15	7	0
Docetaxel	137	103	68	45	30	14	7	2	0

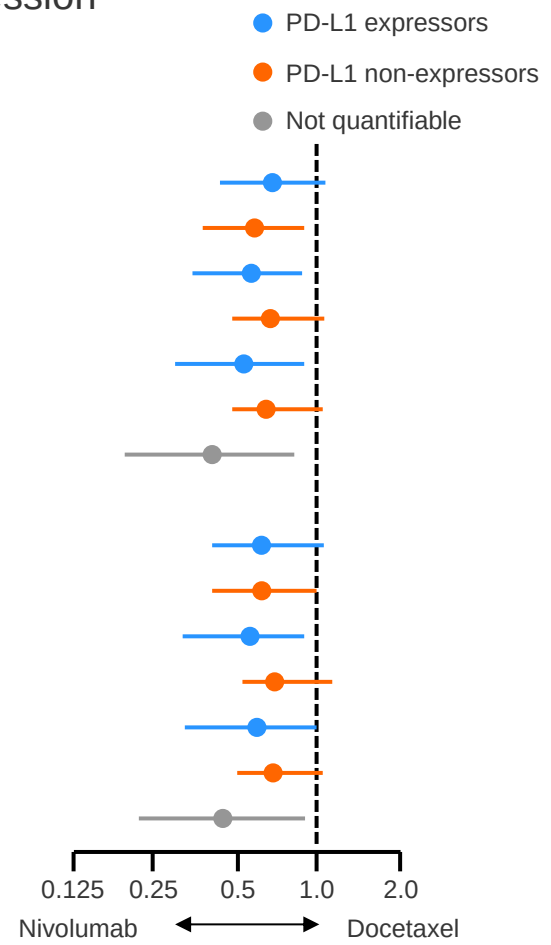
Symbols represent censored observations

Spigel et al. J Clin Oncol 2015; 33 (suppl): abstr 8009

8009: A phase III study (CheckMate 017) of nivolumab (NIVO; anti-programmed death-1 [PD-1]) vs docetaxel (DOC) in previously treated advanced or metastatic squamous (SQ) cell non-small cell lung cancer (NSCLC) – Spigel DR et al

- **Key results (cont.)**
  - Survival benefit with nivolumab was independent of PD-L1 expression

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



- **Conclusion**
  - Nivolumab was superior to docetaxel in OS, PFS and ORR in patients with advanced or metastatic squamous NSCLC, regardless of tumour PD-L1 levels

Spigel et al. J Clin Oncol 2015; 33 (suppl): abstr 8009

LBA109: Phase III, randomized trial (CheckMate 057) of nivolumab (NIVO) versus docetaxel (DOC) in advanced non-squamous cell (non-SQ) non-small cell lung cancer (NSCLC) – Paz-Ares L et al

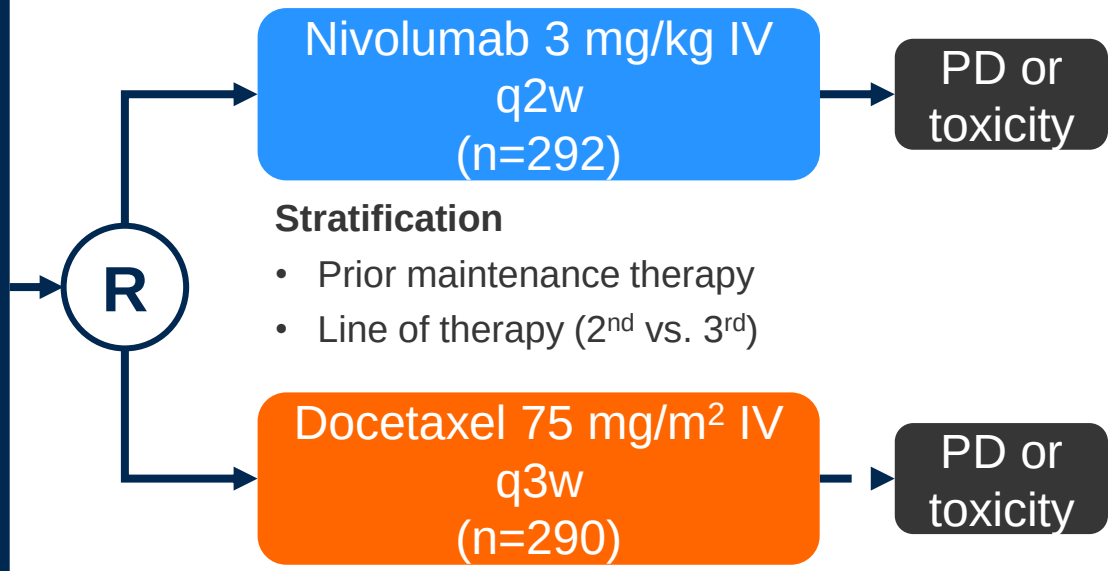
Study objective

- To evaluate the efficacy and safety of nivolumab vs. docetaxel in patients with advanced non-squamous NSCLC after failure of platinum-based doublet chemotherapy

Key patient inclusion criteria

- Stage IIIB/IV non-squamous NSCLC
- Pre-treatment (archival or recent) tumor samples available for PD-L1 testing
- ECOG PS 0–1
- Failed 1 prior platinum doublet

(n=582)



Primary endpoint

- OS

Secondary endpoints

- ORR, PFS, safety, efficacy by PD-L1 expression, QoL

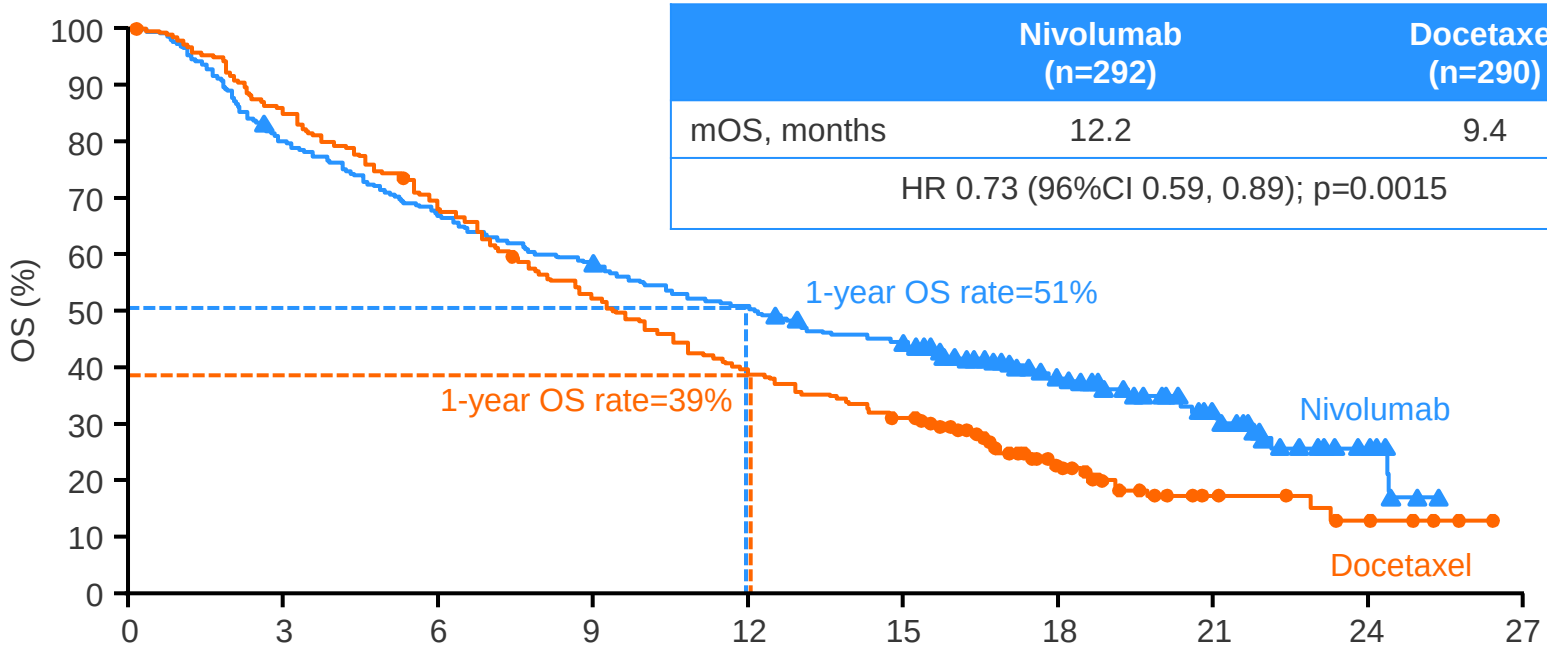
Paz-Ares et al. J Clin Oncol 2015; 33 (suppl): abstr LBA109

LBA109: Phase III, randomized trial (CheckMate 057) of nivolumab (NIVO) versus docetaxel (DOC) in advanced non-squamous cell (non-SQ) non-small cell lung cancer (NSCLC) – Paz-Ares L et al

- **Key results**
  - Nivolumab was associated with a 27% reduction in risk of death

OS

	Nivolumab (n=292)	Docetaxel (n=290)
mOS, months	12.2	9.4
HR 0.73 (96%CI 0.59, 0.89); p=0.0015		



Number of Patients at Risk

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

Symbols represent censored observations

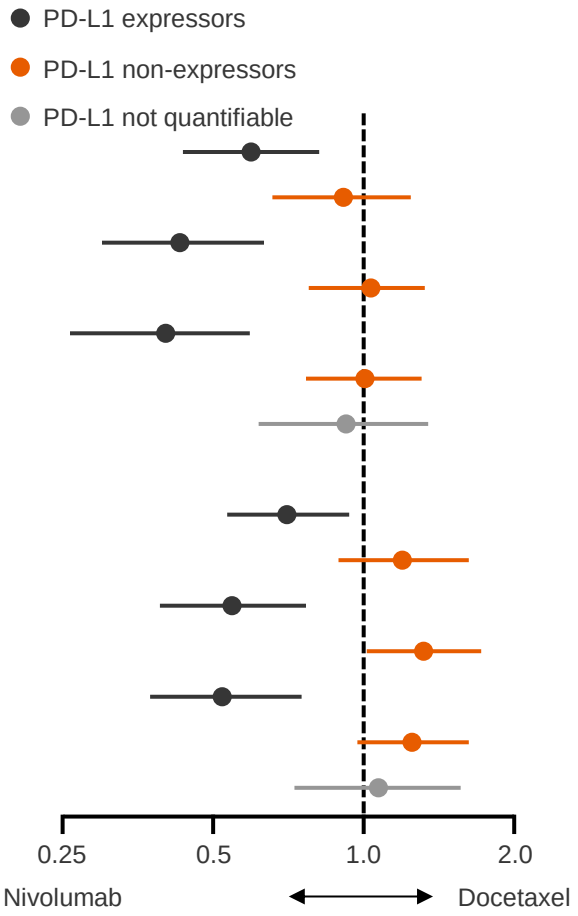
Paz-Ares et al. J Clin Oncol 2015; 33 (suppl): abstr LBA109

LBA109: Phase III, randomized trial (CheckMate 057) of nivolumab (NIVO) versus docetaxel (DOC) in advanced non-squamous cell (non-SQ) non-small cell lung cancer (NSCLC) – Paz-Ares L et al

- **Key results**
  - PD-L1 expressors benefitted more from nivolumab than PD-L1 non-expressors

PD-L1 expression level	Nivolumab (n)	Docetaxel (n)	Unstratisfied HR (95% CI)	Interaction p-value*
OS				
≥1%	123	123	0.59 (0.43, 0.82)	0.0646
<1%	108	101	0.90 (0.66, 1.24)	
≥5%	95	86	0.43 (0.30, 0.63)	0.0004
<5%	136	138	1.01 (0.77, 1.34)	
≥10%	86	79	0.40 (0.26, 0.59)	0.0002
<10%	145	145	1.00 (0.76, 1.31)	
Not quantifiable at baseline	61	66	0.91 (0.61, 1.35)	
PFS				
≥1%	123	123	0.70 (0.53, 0.94)	0.0227
<1%	108	101	1.19 (0.88, 1.61)	
≥5%	95	86	0.54 (0.39, 0.76)	<0.0001
<5%	136	138	1.31 (1.01, 1.71)	
≥10%	86	79	0.52 (0.37, 0.75)	0.0002
<10%	145	145	1.24 (0.96, 1.61)	
Not quantifiable at baseline	61	66	1.06 (0.73, 1.56)	

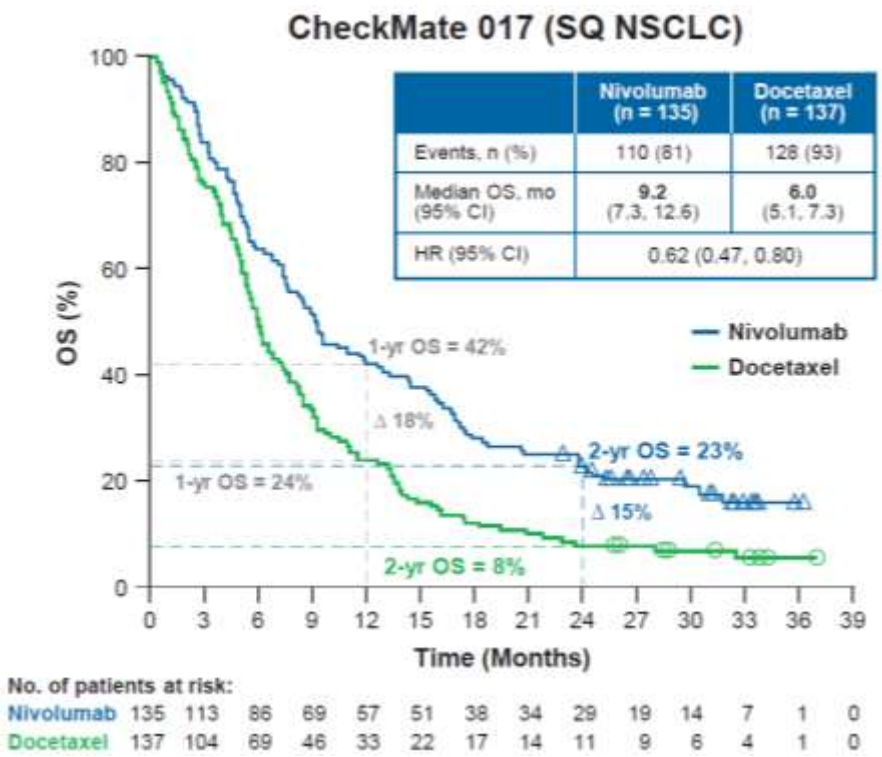
*Interaction p-value from Cox proportional hazard model with treatment, PD-L1 expression and treatment by PD-L1 expression interaction



- **Conclusion**
  - Nivolumab improved survival vs. docetaxel in previously treated patients with advanced non-squamous NSCLC with efficacy being correlated with PD-L1 expression

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

Figure 4. Kaplan–Meier Estimates of OS (2 Years Minimum Follow-up)



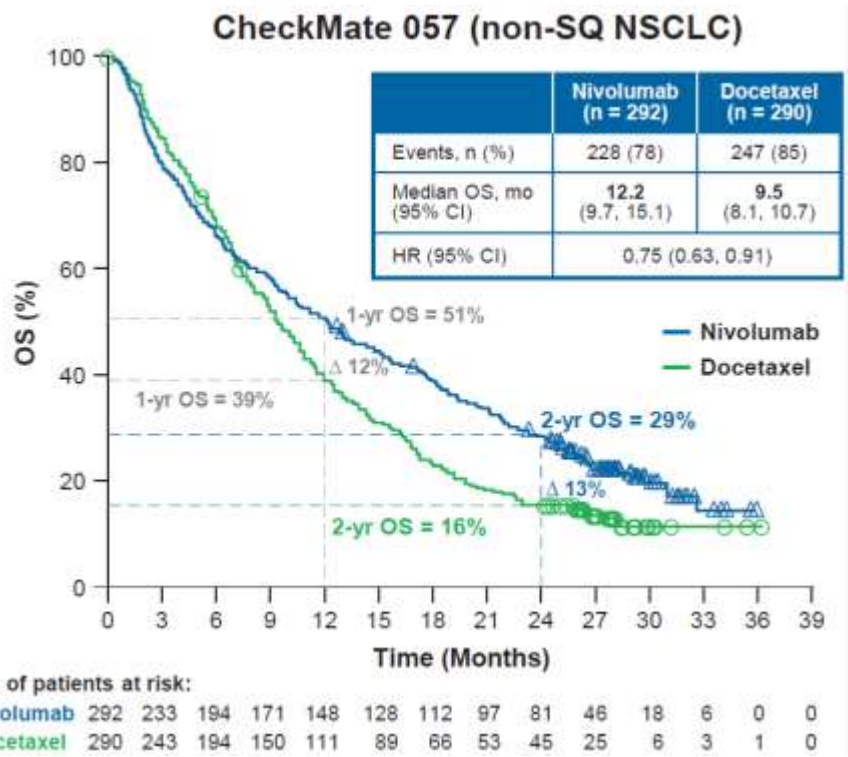
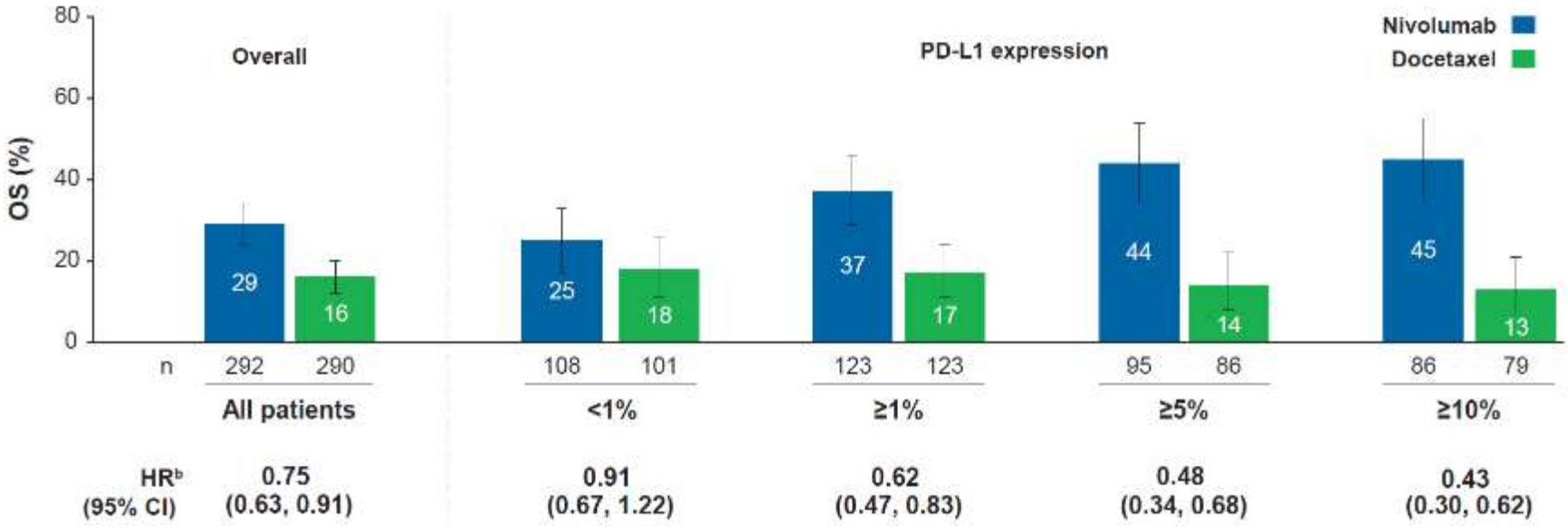


Figure 6. 2-year OS Rates[a] Overall and by PD-L1 Expression Level in CheckMate 057 (non-SQ NSCLC)



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

Immunvermittelte Nebenwirkungen Checkmate 017

	Nivolumab n = 131	
	Alle Grade	**Grad 3-4**
Endokrin, % (n)	**3,8 (5)**	**0**
Hypothyreose	3,5 (5)	0
Gastrointestinal, % (n)	**8,4 (11)**	**0,8 (1)**
Diarrhoe	7,6 (10)	0
Kolitis	0,8 (1)	0,8 (1)
Hepatisch, n (%)	**1,5 (2)**	**0**
Alanin-Aminotransferase erhöht	1,5 (2)	0
Aspartat-Aminotransferase erhöht	1,5 (2)	0
Bilirubin im Blut erhöht	0	0
Pulmonal, n (%)	**5,3 (7)**	**0,8 (1)**
Pneumonitis	4,6 (6)	0,8 (1)
Lungeninfiltration	0,8 (1)	0
Interstitielle Lungenerkrankung	0	0

Modifiziert nach:
Reckamp K et al. Oral presentation at WCLC 2015, Abstract No: 55806.

Aktueller Zulassungsstatus (EMA)

Nivolumab Bronchialkarzinom :

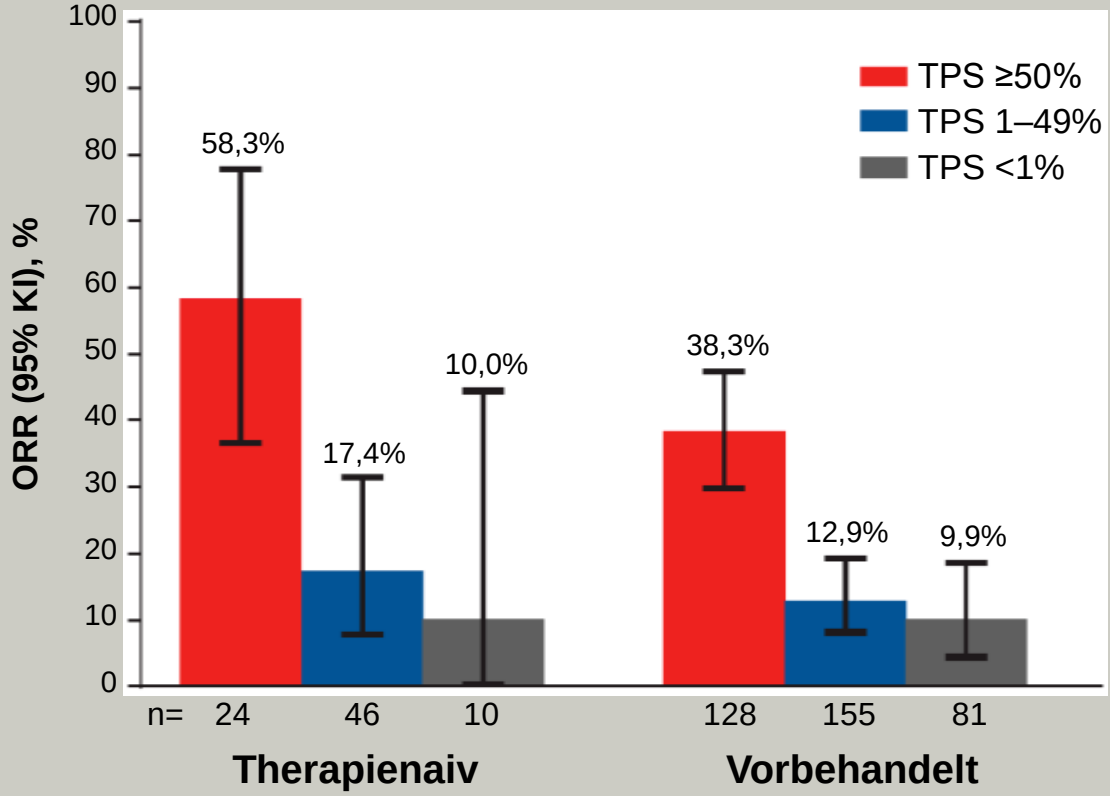
- Behandlung des lokal fortgeschrittenen oder metastasiereten nicht-kleinzelligen Lungenkarzinoms (NSCLC) nach vorheriger Chemotherapie bei Erwachsenen

NSCLC und Pembrolizumab

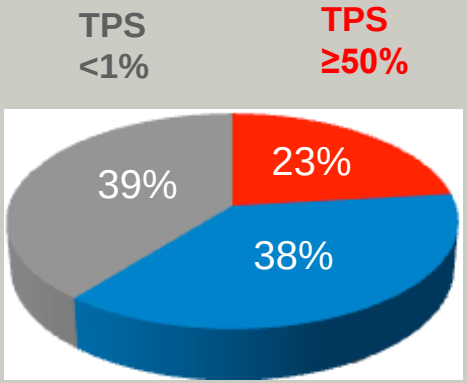
Objektive Ansprechrate nach PD-L1 Expression

KEYNOTE-001 (n=550)

ORR* bei therapienaiven und vorbehandelten Patienten nach PD-L1 TPS (Tumor Proportion Score)



Prävalenz der PD-L1-Expression (n=824)[a]



[a]KN-001 Garon EB et al NEJM 2015 (372) 2018-2028, Supplement

*Nur Patienten mit messbarer Erkrankung (unabhängige, zentrale Beurteilung nach RECIST v1.1.-Kriterien) waren auswertbar für die ORR. Alle Fälle von Therapieansprechen wurden bestätigt. Patienten mit unbekanntem PD-L1 TPS wurden ausgeschlossen.

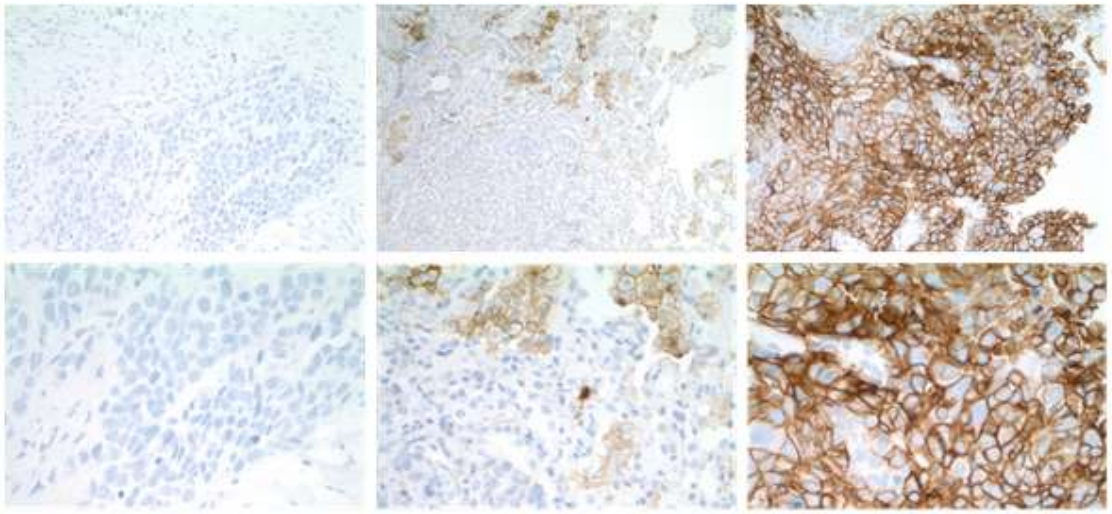
Hui R et al. ASCO 2016 abstract 9026

R. Müller

M Reck. ESMO 2016.

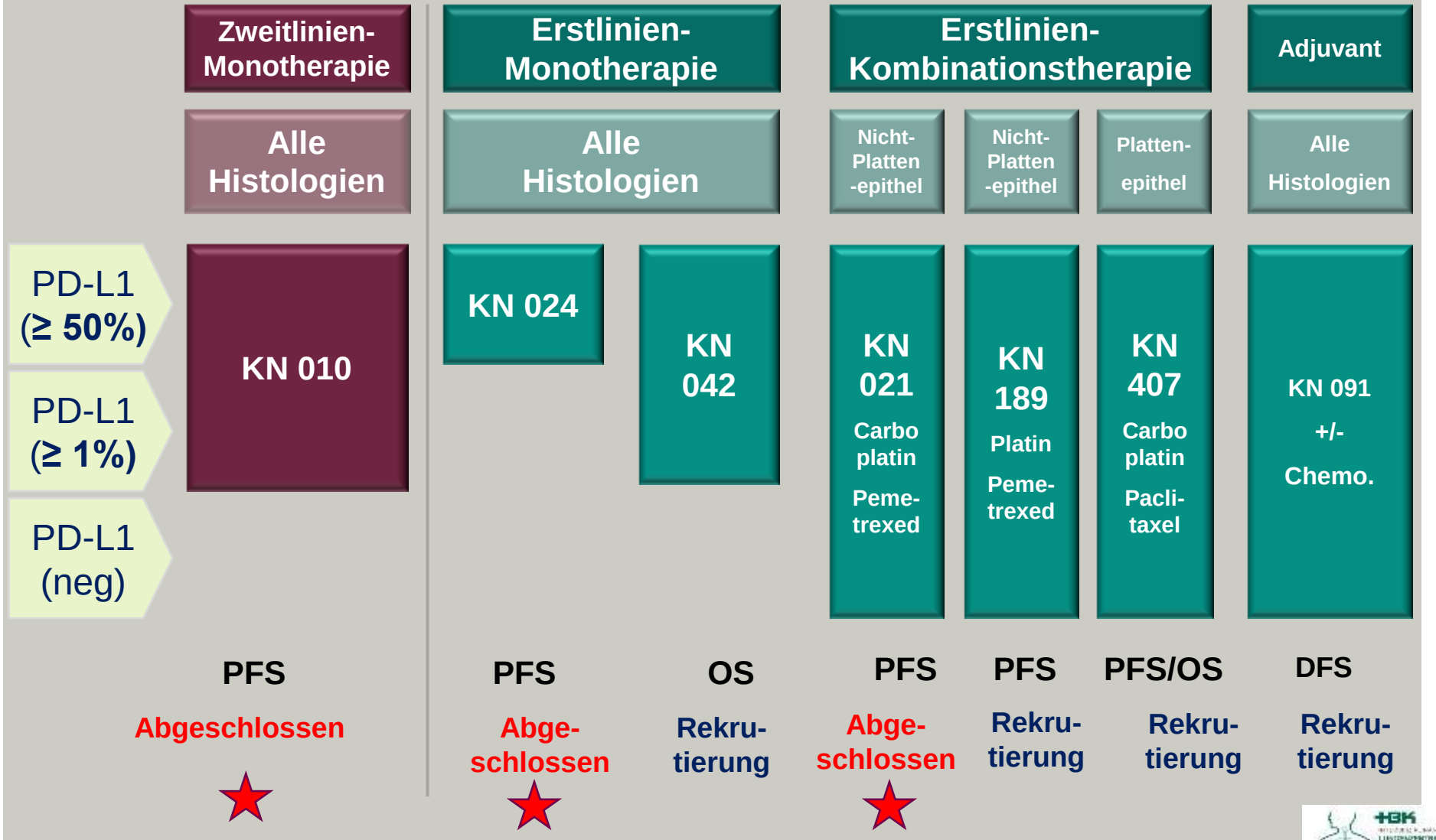
PD-L1 Expression and Pembrolizumab

- PD-L1 TPS cutpoint of 50% was identified in KEYNOTE-001 using independent training and validation sets[1]
- FDA-approved and CE-marked companion diagnostic: PD-L1 IHC 22C3 pharmDx (Dako)



1. Garon EB et al. *N Engl J Med*. 2015;372:2018-2028.
PD-L1 staining images from Herbst RS et al. *J Clin Oncol*, 2016;34(15_suppl): abstr 3030.

Pembrolizumab NSCLC Studien-Programm



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Pembrolizumab + NSCLC

KEYNOTE-010 (n=1.034)

Patienten

- Fortgeschrittenes NSCLC
- Bestätigte Krankheitsprogression nach ≥ 1 Erstlinien-Chemotherapie
- Keine aktiven Hirnmetastasen
- ECOG PS 0–1
- PD-L1 TPS ≥ 1%
- Keine schwerwiegende Autoimmunerkrankung[b]
- Keine interstitielle Lungenerkrankung oder Pneumonitis mit Erfordernis systemischer Steroide

R 1:1:1

- **Pembrolizumab 2 mg/kg i.v. alle 3 Wochen über 24 Monate**
- **Pembrolizumab 10 mg/kg i.v. alle 3 Wochen über 24 Monate**
- **Docetaxel 75 mg/m² alle 3 Wochen nach lokalen Leitlinien[d]**

Stratifizierung nach:

- ECOG PS (0 vs. 1)
- Region (Ost-Asien vs. Nicht Ost-Asien)
- PD-L1 Status[c] (TPS 1–49% vs. ≥50%)

Endpunkte im TPS ≥ 50% Stratum und in der TPS ≥ 1% Population:

Primär: PFS und OS

Sekundär: ORR, Dauer des Ansprechens, Sicherheit

[a] Die Vorbehandlung musste ≥ 2 Zyklen einer Platin-Dubletten-Chemotherapie beinhaltet haben. Bei Patienten, deren Tumore eine EGFR- sensibilisierende Mutation oder eine ALK-Translokation aufwiesen, war ein geeigneter Tyrosin-Kinase-Inhibitor erforderlich.[b] Keine aktive oder anamnestisch dokumentierte Autoimmunerkrankung mit Erfordernis systemischer Steroide oder Immunsuppressiva, ausgenommen Patienten mit Vitiligo, mit geheiltem Asthma / geheilter Atopie in der Kindheit oder Patienten mit inhalativen oder lokal injizierten Steroiden.[c] Auf Basis der KEYNOTE-0013-Ergebnisse; nach Rekrutierung von 441 Patienten hinzugefügt, um eine gleichmäßige Verteilung der Fälle von TPS ≥50 und 1–49% bei den nachfolgend aufgenommenen Patienten sicherzustellen. [d] Die Patienten erhielten die durch die lokalen Zulassungbehörden maximal zugelassene Anzahl Zyklen.

ECOG: Eastern Cooperative Oncology Group Performance Status; NSCLC: Nicht-kleinzelliges Lungenkarzinom; TPS: Tumor Proportion Score.; R = Randomisiert

Herbst, ESMO 2016, LBAA48 Poster; Herbst RS et al. Lancet 2015 (387) 1540–1550

Patientencharakteristika

KEYNOTE-010 (n=1.034)

			Pembro 2 mg/kg n=344	Pembro 10 mg/kg n=346	Docetaxel n=343
Medianes Alter (Bereich), Jahre			63 (29–82)	63 (20–88)	62 (33–82)
Männer, %			62	62	61
Ethnische Zugehörigkeit, %	Kaukasier		72	72	73
	Asiaten		21	21	21
	Andere oder unbekannt		7	7	6
ECOG PS, %	0		33	35	34
	1		67	65	65
Raucherstatus, %	Früher/derzeitig		81	82	78
	Niemals		18	17	20
	Unbekannt		1	<1	2
PD-L1 TPS, %	≥50%		40	44	44
	1–49%		60	56	56
Histologiebefund, %	Plattenepithel		22	23	19
	Nicht Plattenepithel		70	71	70
	Anderes/unbekannt		8	6	11
***EGFR*-Mutation, %**			8	9	8
***ALK*-Translokation, %**			1	1	1
Vorbehandlung, %	Adjuvant		2	2	1
	Neoadjuvant		<1	<1	0
	Bisherige Therapielinien, fortgeschrittenes Stadium	1	71	68	69
		≥2	27	30	31

Herbst, ESMO 2016, LBAA48 Poster; Herbst RS et al. Lancet 2015 (387) 1540–1550

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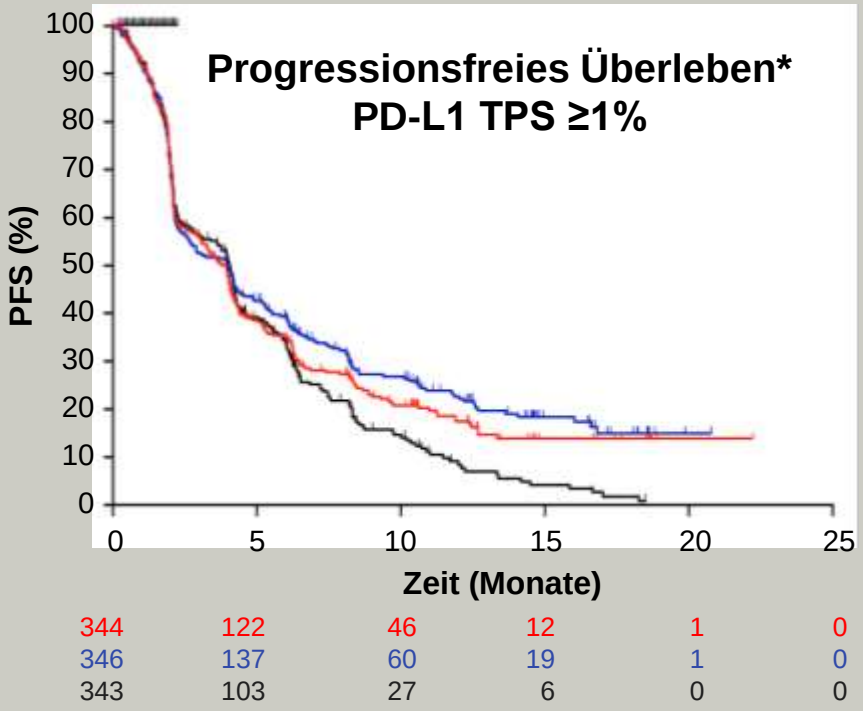
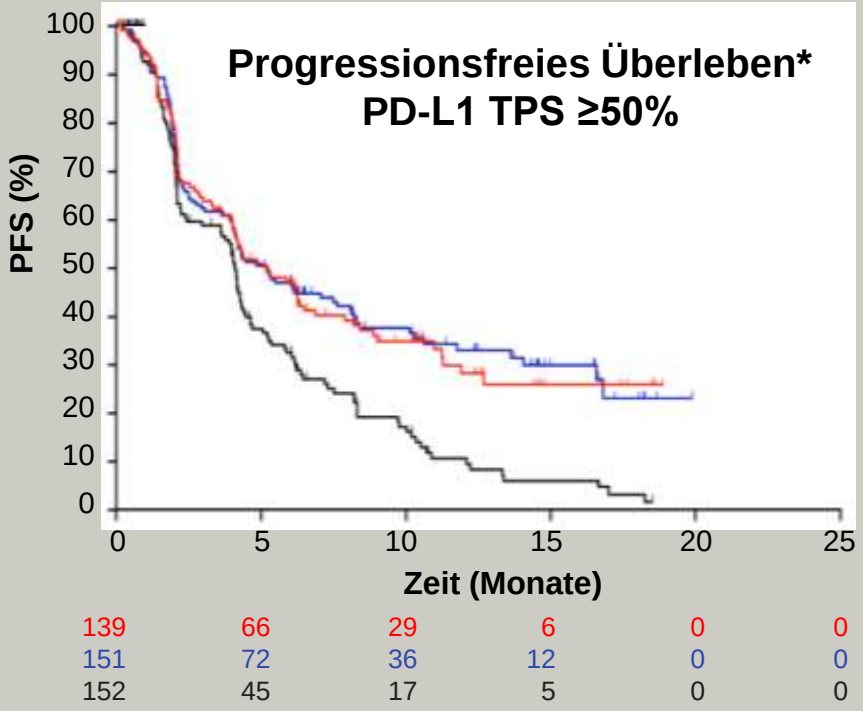
Signifikant höherer PFS-Vorteil unter Pembrolizumab bei Patienten mit PD-L1 ≥50%

KEYNOTE-010 (n=1.034)





	Monate, median (95% KI)	HR (95% KI)	p
Pembro 2 mg/kg	3,9 (3,1–4,1)	0,88 (0,74–1,05)	0,07
Pembro 10 mg/kg	4,0 (2,7–4,3)	0,79 (0,66–0,94)	0,004
Docetaxel	4,0 (3,1–4,2)	–	–

	Monate, median (95% KI)	HR (95% KI)	p
Pembro 2 mg/kg	5,0 (4,0–6,5)	0,59 (0,44–0,78)	0,0001
Pembro 10 mg/kg	5,2 (4,1–8,1)	0,59 (0,45–0,78)	<0,0001
Docetaxel	4,1 (3,6–4,3)	–	–

*Zentrale Beurteilung gemäß RECIST v1.1-Kriterien

Herbst, ESMO 2016, LBAA48 Poster; Herbst RS et al. Lancet 2015 (387) 1540–1550

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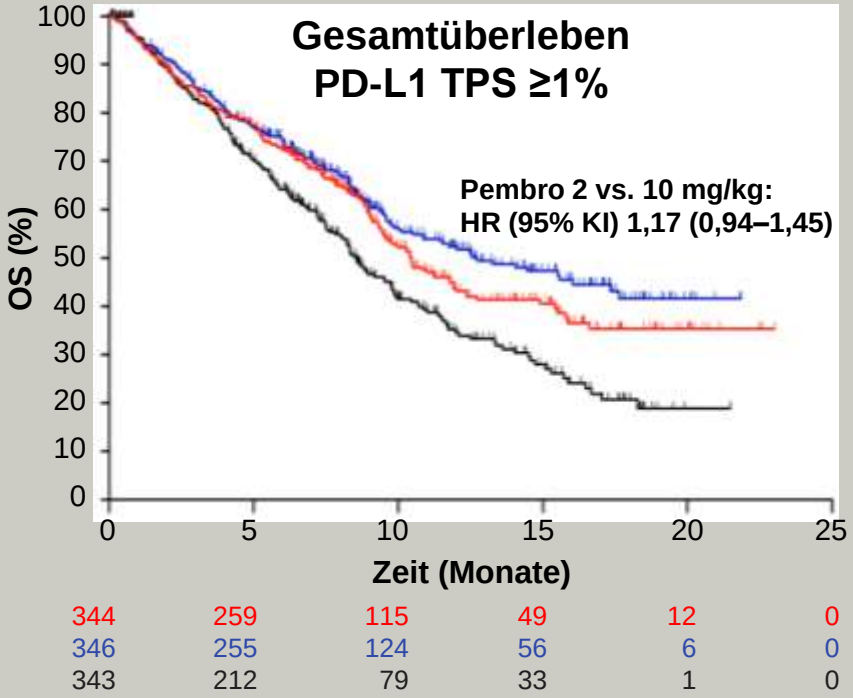
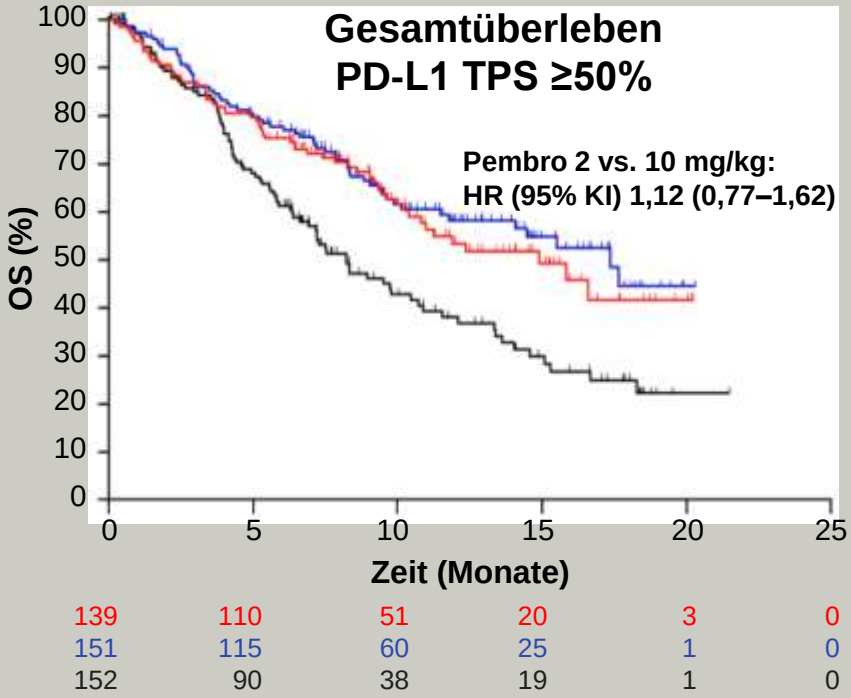
Gesamt-Überlebensvorteil bei allen Patienten unter Pembrolizumab

KEYNOTE-010 (n=1.034)





	Monate, median (95% KI)	Rate nach 1 Jahr	HR (95% KI)	p
Pembro 2 mg/kg	10,4 (9,4–11,9)	43,2%	0,71 (0,58–0,88)	0,0008
Pembro 10 mg/kg	12,7 (10,0–17,3)	52,3%	0,61 (0,49–0,75)	<0,0001
Docetaxel	8,5 (7,5–9,8)	34,6%	–	–

	Monate, median (95% KI)	HR (95% KI)	p
Pembro 2 mg/kg	14,9 (10,4–NR)	0,54 (0,38–0,77)	0,0002
Pembro 10 mg/kg	17,3 (11,8–NR)	0,50 (0,36–0,70)	<0,0001
Docetaxel	8,2 (6,4–10,7)	–	–

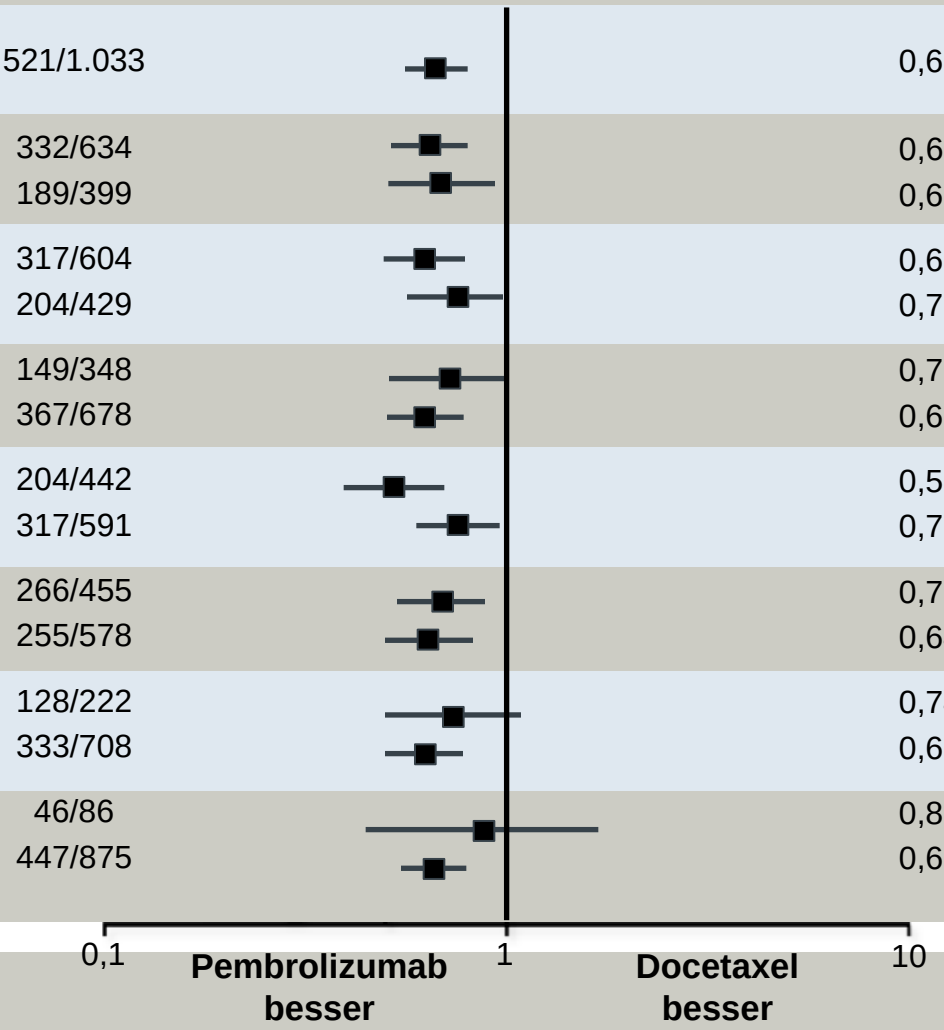
NR = not reached

Herbst, ESMO 2016, LBAA48 Poster; Herbst RS et al. Lancet 2015 (387) 1540–1550

Gesamtüberleben in den wichtigsten Subgruppen (PD-L1 TPS ≥1%)

KEYNOTE-010 (n=1.034)

Subgruppe		Ereignisse /Patienten (n)	Hazard ratio (95% KI)
Gesamtkollektiv	Alle Patienten	521/1.033	0,67 (0,56–0,80)
Geschlecht	Männer	332/634	0,65 (0,52–0,81)
	Frauen	189/399	0,69 (0,51–0,94)
Alter	< 65 Jahre	317/604	0,63 (0,50–0,79)
	≥ 65 Jahre	204/429	0,76 (0,57–1,02)
ECOG PS	0	149/348	0,73 (0,52–1,02)
	1	367/678	0,63 (0,51–0,78)
PD-L1 TPS	≥ 50%	204/442	0,53 (0,40–0,70)
	1–49%	317/591	0,76 (0,60–0,96)
Tumorprobe	Archiviert	266/455	0,70 (0,54–0,89)
	Neu	255/578	0,64 (0,50–0,83)
Histologie	Plattenepithel	128/222	0,74 (0,50–1,09)
	Adenokarzinom	333/708	0,63 (0,50–0,79)
***EGFR* Status**	Mutation	46/86	0,88 (0,45–1,70)
	Wildtyp	447/875	0,66 (0,55–0,80)



Cut-off-Datum der Analyse: 30. September 2015
Daten der Pembrolizumab-Dosierungen gepoolt.

Modifiziert nach Herbst,ESMO ASIA 2015; Herbst RS et al. Lancet 2015 (387) 1540–1550

R. Müller

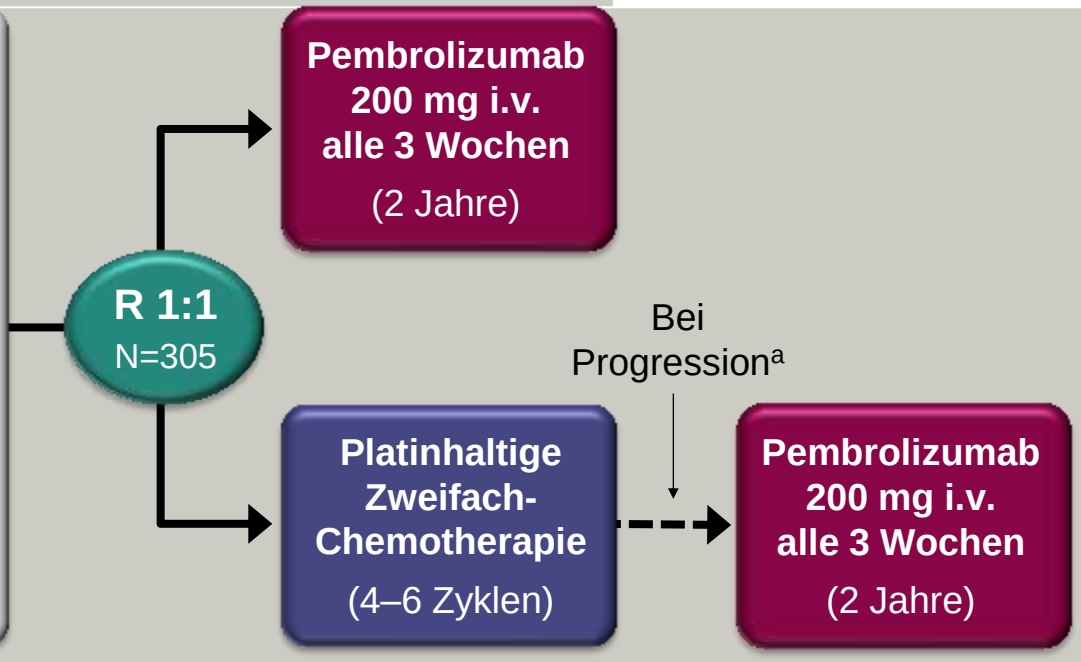
Studiendesign

NCT02142738

KEYNOTE-024
(Ph 3)

Haupteinschlusskriterien

- Unbehandeltes NSCLC Stadium IV
- PD-L1 TPS ≥ 50%
- ECOG PS 0–1
- Keine aktivierende EGFR-Mutation oder ALK-Translokation
- Keine unbehandelten Hirnmetastasen
- Keine aktive Autoimmunerkrankung mit Erfordernis einer systemischen Therapie



Hauptendpunkte

Primär: PFS (verblindete, unabhängige, zentrale Bewertung nach RECIST 1.1-Kriterien)

Sekundär: OS, ORR, Sicherheit

Exploratorisch: DOR

[a]Um für das Cross-over auswertbar zu sein, musste die Progression der Erkrankung mittels verblindeter, unabhängiger radiologischer Begutachtung bestätigt worden sein

Reck M et al. ESMO 2016; Reck M et al NEJM 2016 (375) 1823-1833

Patientencharakteristika

KEYNOTE-024 (Ph 3)

	Pembrolizumab N=154	**Chemotherapie** N=151
Medianes Alter (Bereich), Jahre	64,5 (33–90)	66,0 (38–85)
Männer, n (%)	92 (60)	95 (63)
Studieneinschluss in Ostasien, n (%)	21 (14)	19 (13)
ECOG PS 1, n (%)	99 (64)	98 (65)
Plattenepithel, n (%)	29 (19)	27 (18)
Raucherstatus[a], n (%)		
Derzeitig	34 (22)	31 (21)
Früher	115 (75)	101 (67)
Niemals	5 (3)	19 (13)
Hirnmetastasen, n (%)	18 (12)	10 (7)

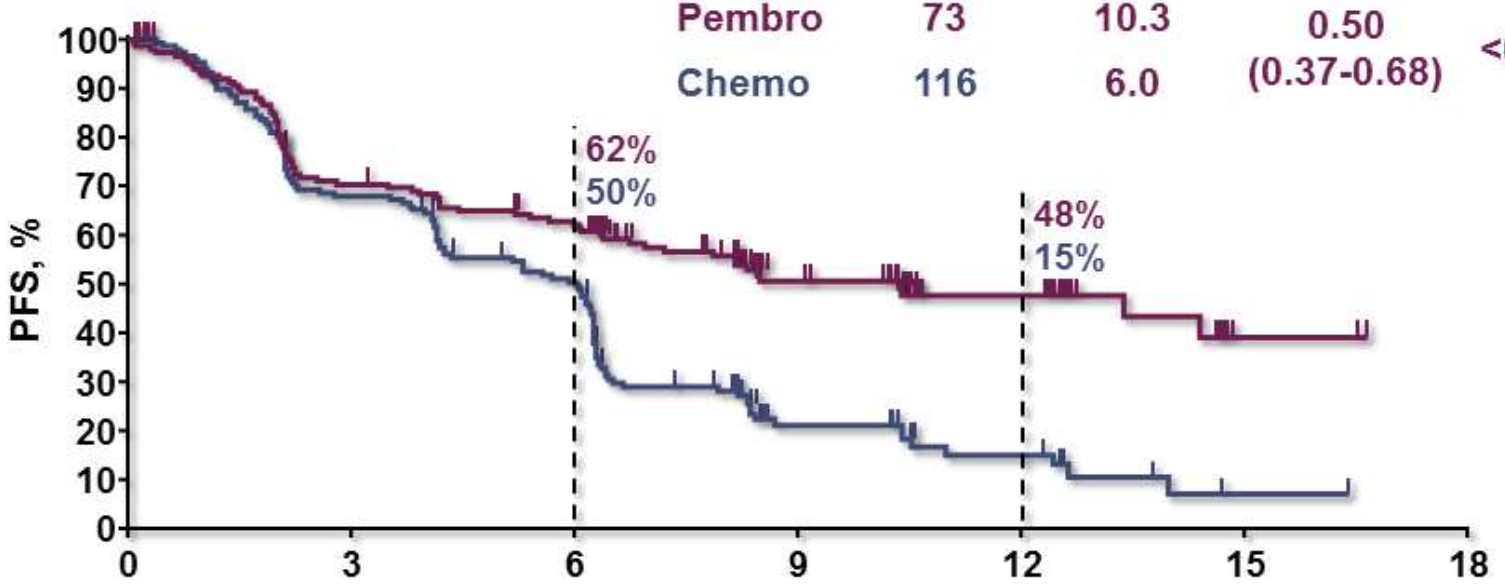
[a]Wie definiert und vom Patienten berichtet. Daten-Cut-off: 9. Mai 2016

Reck M et al. ESMO 2016; Reck M et al NEJM 2016 (375) 1823-1833

M Reck. ESMO 2016.

Progression-Free Survival

	Events, n	Median, mo	HR (95% CI)	*P*
Pembro	73	10.3	0.50 (0.37-0.68)	<0.001
Chemo	116	6.0		



No. at risk

154	104	89	44	22	3	1
151	99	70	18	9	1	0

Assessed per RECIST v1.1 by blinded, independent central review.
Data cut-off: May 9, 2016.

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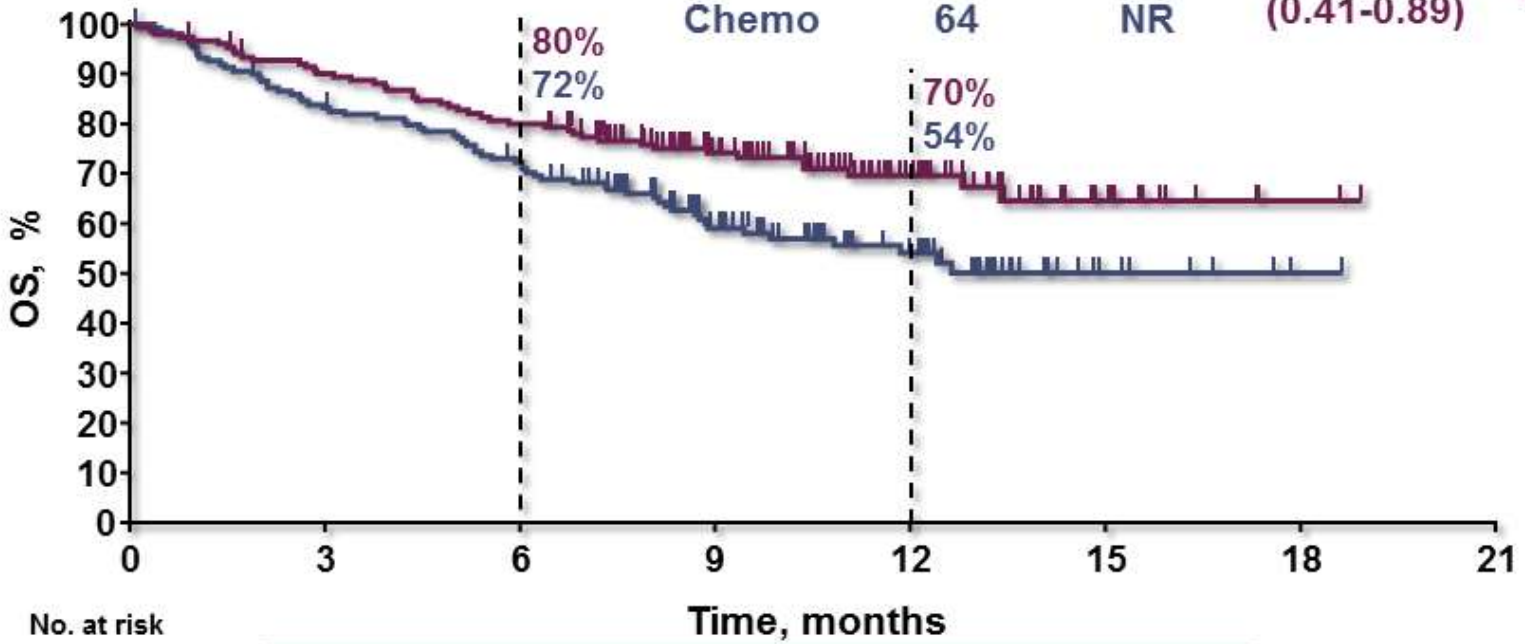
M Reck. ESMO 2016.

Overall Survival

	Events, n	Median, mo	HR (95% CI)	P
Pembro	44	NR	0.60 (0.41-0.89)	0.005
Chemo	64	NR		



No. at risk

154					2		0
151					1		0

DMC recommended stopping the trial because of superior efficacy observed with pembrolizumab

Data cut-off: May 9, 2016.

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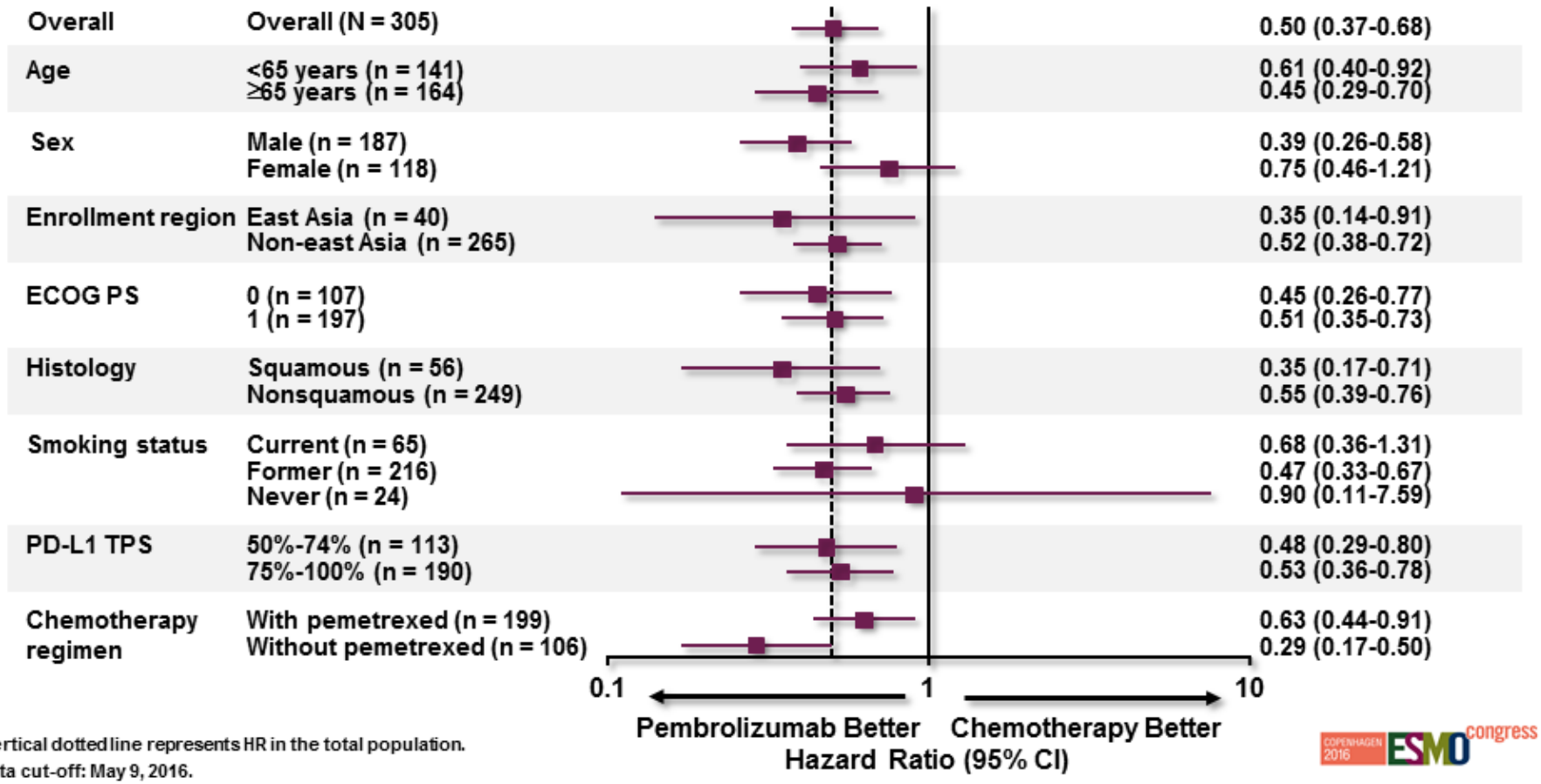
M Reck. ESMO 2016.

Progression-Free Survival in Subgroups



Vertical dotted line represents HR in the total population.
Data cut-off: May 9, 2016.

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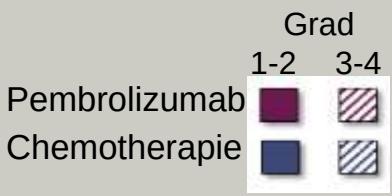
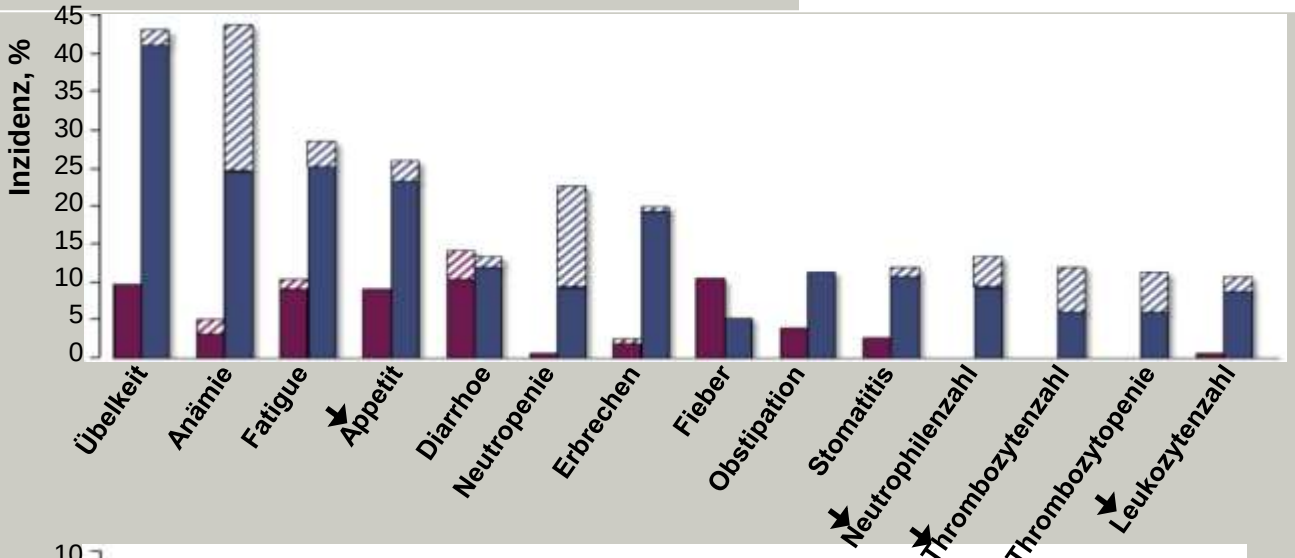
Unerwünschte Ereignisse

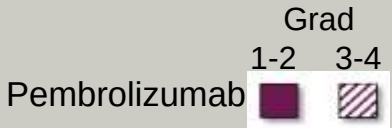
KEYNOTE-024 (Ph 3)

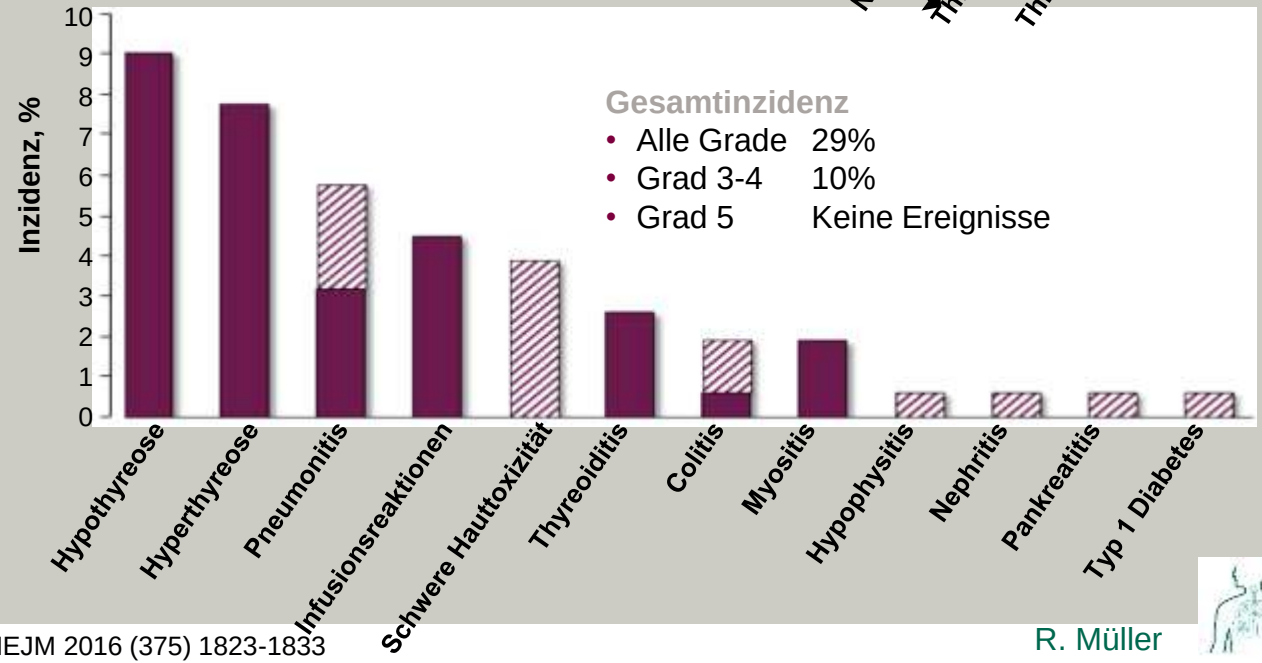
UEs im Zusammenhang mit der Studienmedikation (Inzidenz >10%)





Immunvermittelte UEs im Pembrolizumab-Arm





Daten-Cut-Off: 9. Mai 2016

Reck M et al. ESMO 2016; Reck M et al NEJM 2016 (375) 1823-1833

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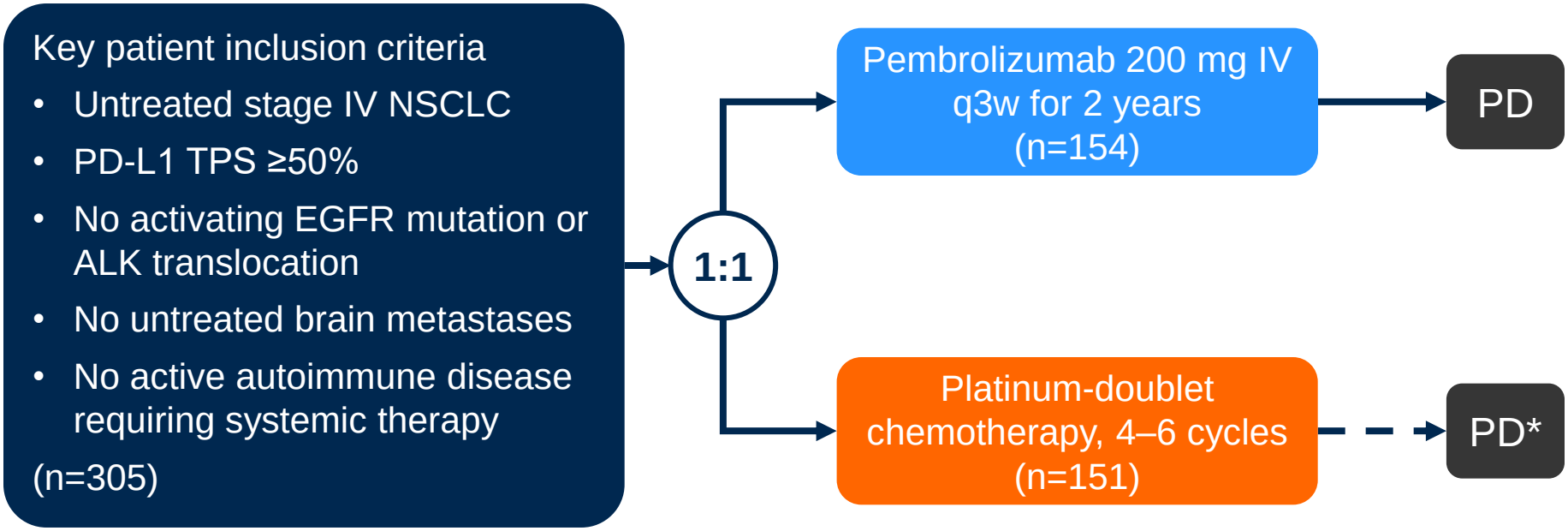
PL04a.01: Health-Related Quality of Life for Pembrolizumab vs Chemotherapy in Advanced NSCLC with PD-L1 TPS ≥50%: Data from KEYNOTE-024 – Brahmer J, et al

- **Study objective**
  - To investigate the efficacy and safety of pembrolizumab vs. platinum-doublet chemotherapy as first-line treatment of stage IV NSCLC



PRO endpoints

- Change from baseline to Week 15 in EORTC QLQ-C30 global health status/QoL score
- Time to deterioration in EORTC QLQ-LC13 composite endpoint of cough, chest pain and dyspnoea

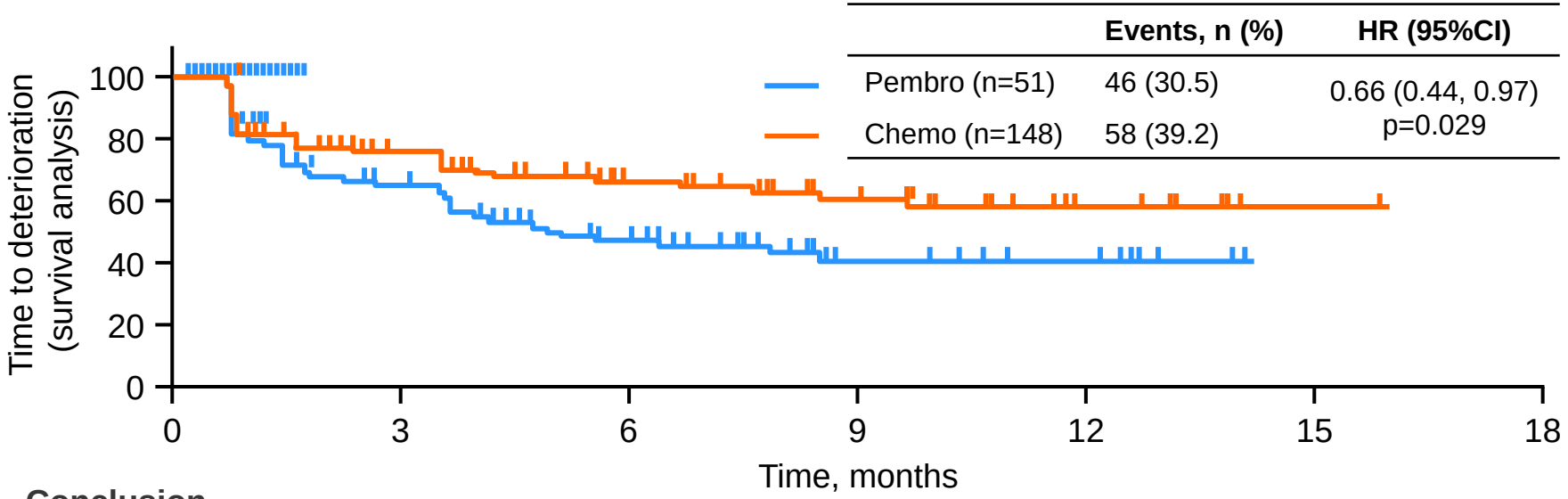
*Patients could switch to pembrolizumab IV 200 mg q3w for 2 years

Brahmer et al. J Thorac Oncol 2016; 11(suppl): abstr PL04a.01

PL04a.01: Health-Related Quality of Life for Pembrolizumab vs Chemotherapy in Advanced NSCLC with PD-L1 TPS ≥50%: Data from KEYNOTE-024 – Brahmer J, et al

- **Key results**
  - Pembrolizumab was associated with a significantly greater improvement from baseline to Week 15 in HRQoL vs. platinum-doublet therapy (difference in LS mean 7.8 [95%CI 2.8, 12.8], p=0.002)
  - Pembrolizumab showed slower deterioration in HRQoL due to symptoms (p=0.029)

Time to deterioration (EORTC QLQ-LC13 composite endpoint of cough, chest pain and dyspnea)



- **Conclusion**
  - For first-line treatment of advanced NSCLC with PD-L1 expression TPS ≥50%, pembrolizumab may be a new standard of care showing superior PFS and OS and HRQoL benefits

Brahmer et al. J Thorac Oncol 2016; 11(suppl): abstr PL04a.01

Aktueller Zulassungsstatus (EMA)

Pembrolizumab Bronchialkarzinom :

- Monotherapie zur Erstlinienbehandlung des metastasierenden nicht-kleinzelligen Lungenkarzinoms (NSCLC) mit PD-L1 exprimierenden Tumoren (Tumor Proportion Score [TPS] ≥ 50 %) ohne EGFR- oder ALK-positive Tumormutationen bei Erwachsenen angezeigt.

- Behandlung des lokal fortgeschrittenen oder metastasierenden nicht-kleinzelligen Lungenkarzinoms (NSCLC) mit PD-L1 exprimierenden Tumoren nach vorheriger Chemotherapie bei Erwachsenen. Patienten mit EGFR- oder ALK-positiven Tumormutationen sollten vor der Therapie mit KEYTRUDA® bereits eine für diese Mutationen zugelassene Therapie erhalten haben.

NSCLC und Atezolizumab

LBA44_PR: Primary analysis from OAK, a randomized phase III study comparing atezolizumab with docetaxel in 2L/3L NSCLC – Barlesi F, et al

Study objective

– To evaluate the efficacy and safety of atezolizumab vs. docetaxel in patients with previously treated NSCLC

Key patient inclusion criteria

- Locally advanced or metastatic NSCLC
- 1–2 prior lines of chemotherapy including at least 1 platinum based
- Any PD-L1 status

(n=1225)

R

Atezolizumab 1200 mg IV q3w (n=425) → PD / loss of benefit

Stratification

- PD-L1 status
- Prior chemotherapy regimens (1 vs. 2)
- Histology

Docetaxel 75 mg/m^2 IV q3w (n=425) → PD

Primary endpoint

- OS in ITT and PD-L1-expression on ≥1% TC or IC

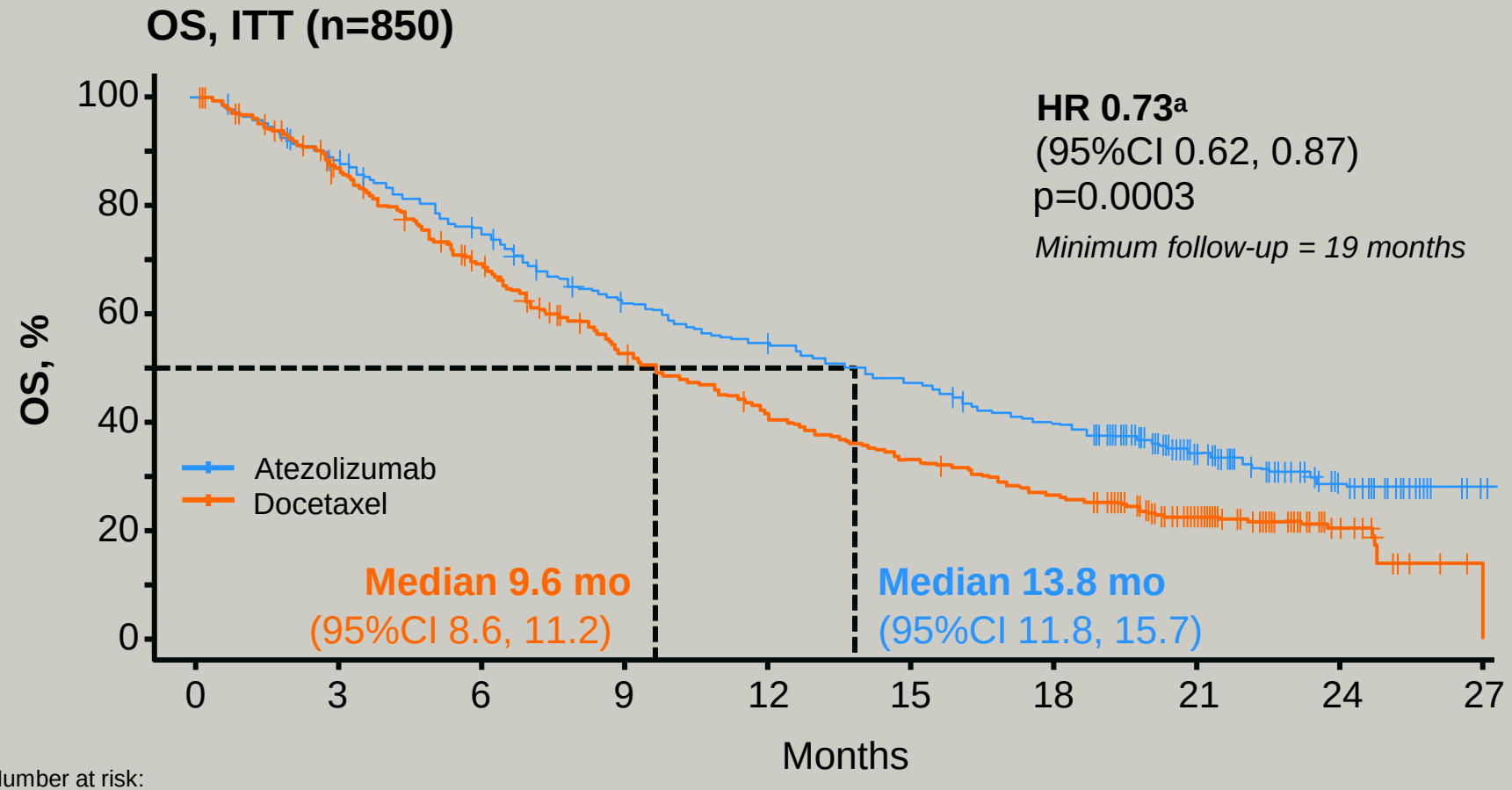
Secondary endpoints

- ORR, PFS, DoR, safety

Barlesi et al. Ann Oncol 2016; 27 (suppl 6): abstr LBA44_PR

LBA44_PR: Primary analysis from OAK, a randomized phase III study comparing atezolizumab with docetaxel in 2L/3L NSCLC – Barlesi F, et al

Key results



[a]Stratified HR

Barlesi et al. Ann Oncol 2016; 27 (suppl 6): abstr LBA44_PR

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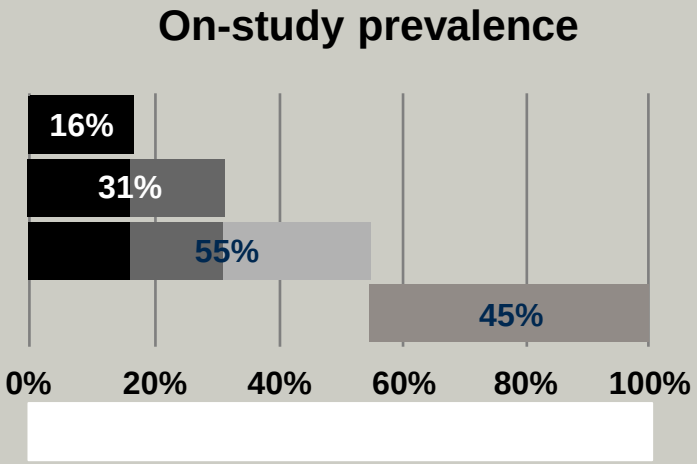
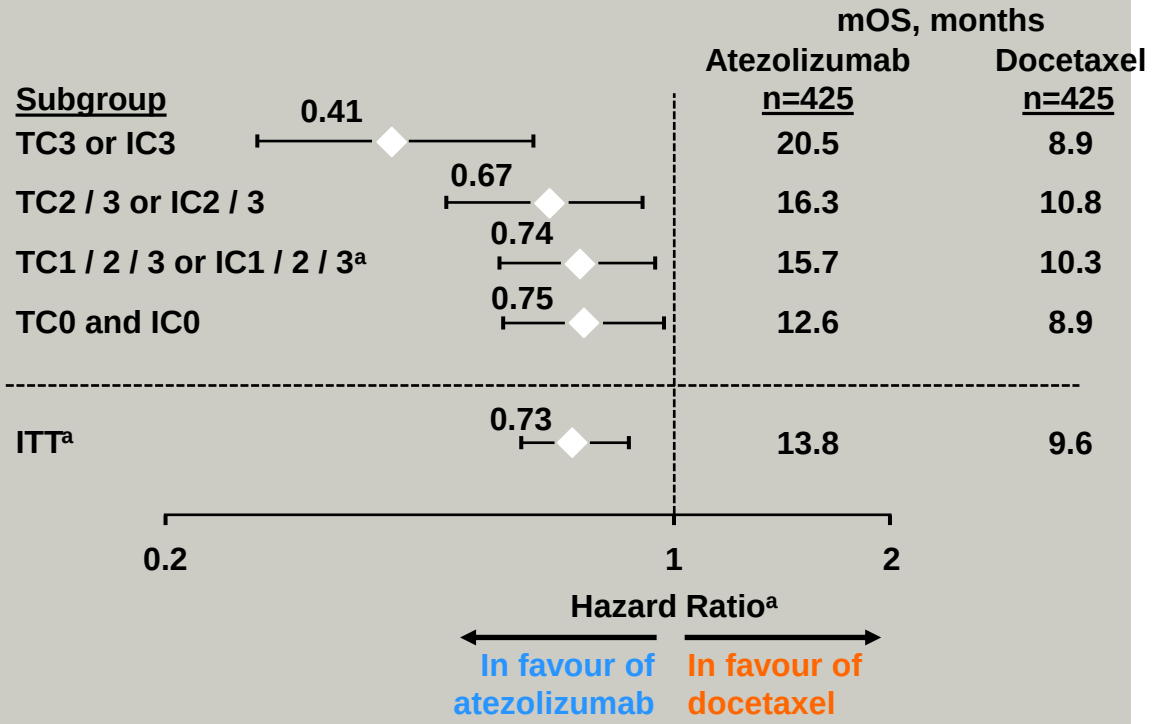
Key results (cont.)

OS by PD-L1 expression





[a]Stratified HRs for ITT and TC1 / 2 / 3 or IC1 / 2 / 3. Unstratified HR for subgroups

Barlesi et al. Ann Oncol 2016; 27 (suppl 6): abstr LBA44_PR

R. Müller

LBA44_PR: Primary analysis from OAK, a randomized phase III study comparing atezolizumab with docetaxel in 2L/3L NSCLC – Barlesi F, et al

Conclusions

- Atezolizumab improved OS in all patients, and benefit was seen regardless of PD-L1 expression levels (HR 0.75 in <1% PD-L1 expression population and 0.41 in ≥50% TC or ≥10% IC expression population)
  - OS benefit was consistent across subgroups, including histology (HR 0.73 for both), patients with CNS mets (HR 0.54) and never smokers (HR 0.71)
- Atezolizumab was well tolerated and had a favourable safety profile compared with docetaxel

Barlesi et al. Ann Oncol 2016; 27 (suppl 6): abstr LBA44_PR

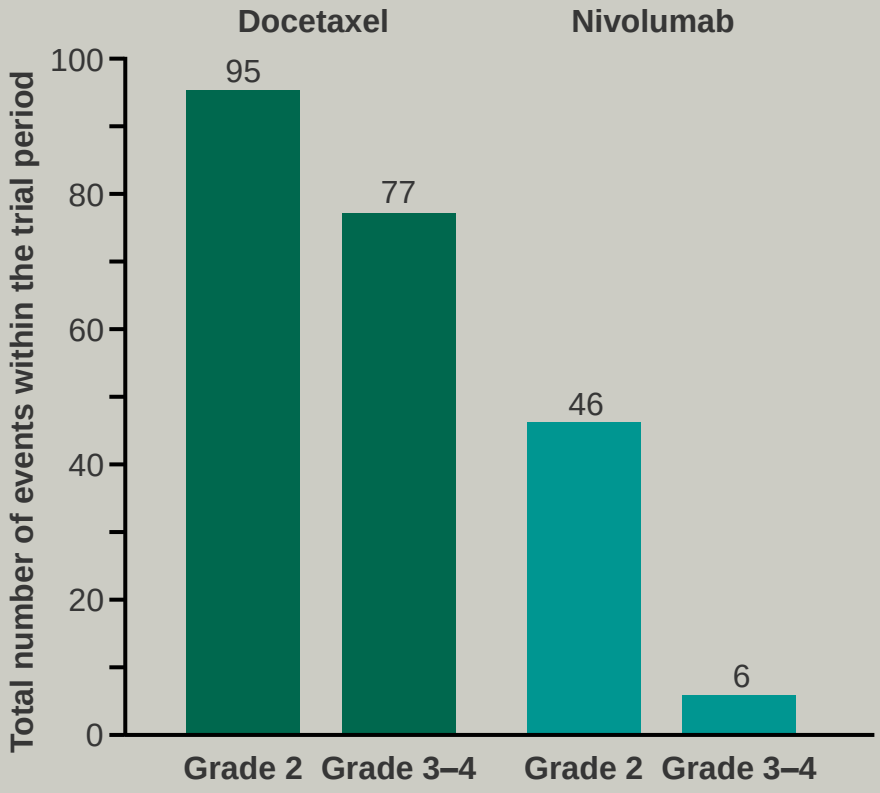
Behandlungskosten ?

6617: Estimated costs of managing treatment-related adverse events (TRAEs) of nivolumab (nivo) and docetaxel (doc) in the CheckMate 017 and CheckMate 057 phase III non-small cell lung cancer (NSCLC) trials – Venkatachalam M et al

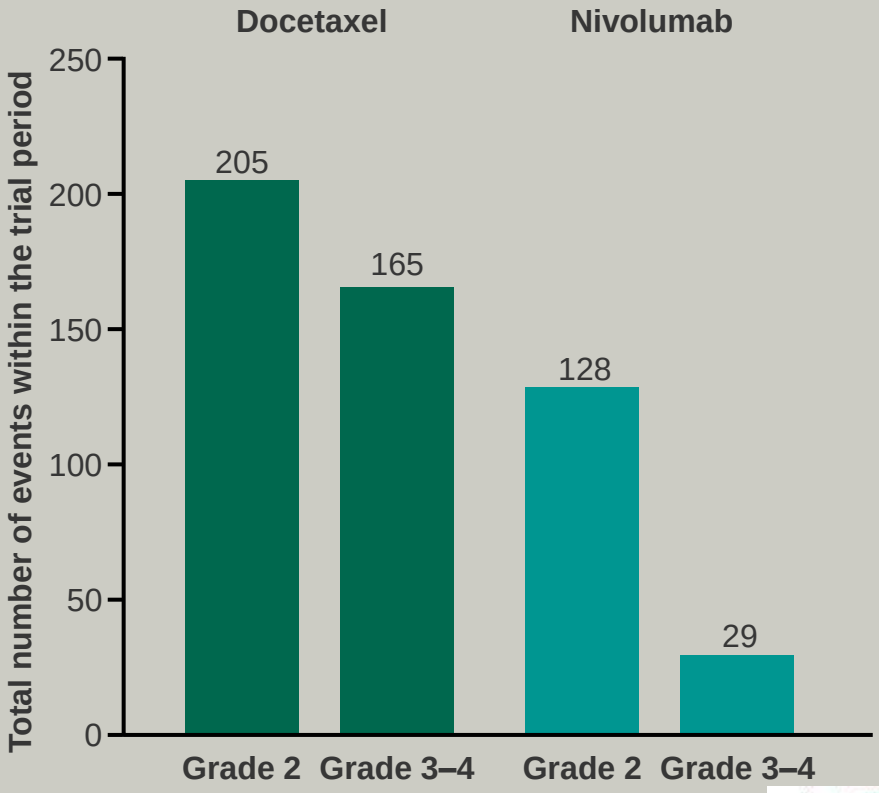
Key results

- In both trials, more treatment-related AEs were observed with docetaxel than with nivolumab

CheckMate 017



CheckMate 057



Venkatachalam et al. J Clin Oncol 2016; 34 (suppl): abstr 6617

R. Müller

6617: Estimated costs of managing treatment-related adverse events (TRAEs) of nivolumab (nivo) and docetaxel (doc) in the CheckMate 017 and CheckMate 057 phase III non-small cell lung cancer (NSCLC) trials – Venkatachalam M et al

Key results (cont.)

- The cost of managing treatment-related AEs was 15.8 and 10.7 times higher in the docetaxel arm vs. the nivolumab arm for the CheckMate 017 and 057 trials, respectively

	CheckMate 017		CheckMate 057	
	Docetaxel (n=129)	**Nivolumab (n=131)**	**Docetaxel (n=268)**	**Nivolumab (n=287)**
Number of TRAEs	172	52	370	157
Total cost of managing TRAEs, $	906,104	57,506	1,591,987	148,603
Cost per TRAE, $	5,268	1,106	4,303	947
Cost per treated patient in each trial, $	7,024	439	5,940	518

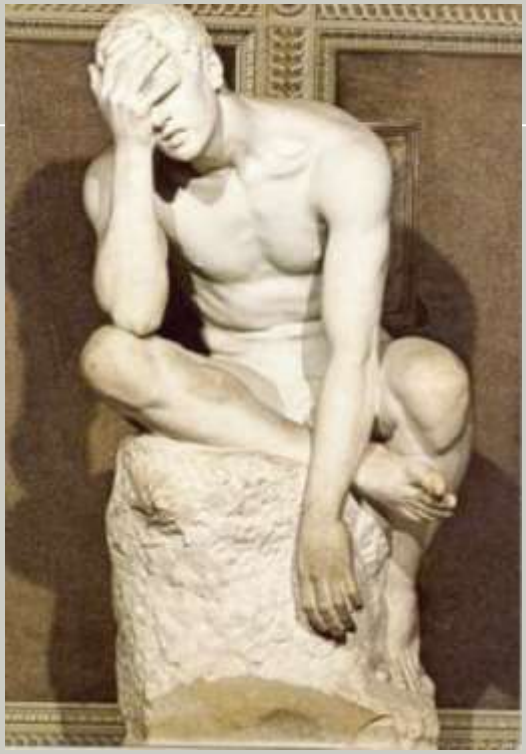
Conclusions

- Consistent with the higher frequency of treatment-related AEs associated with docetaxel, there were large estimated differences in the costs of management, favoring nivolumab
- The reduction in costs for managing AEs with the use of nivolumab should be considered when assessing the value of nivolumab in this patient population

Venkatachalam et al. J Clin Oncol 2016; 34 (suppl): abstr 6617

Laufende Studien

- Rolle Ipilimumab (CTLA 4-AK) in Komb. mit Chemotherapie beim NSCLC
- PD1/PDL1-AK + Ipilimumab bei NSCLC
- Immuntherapie +/- Ipilimumab beim SCLC



+ Vielen Dank für Ihre Aufmerksamkeit +

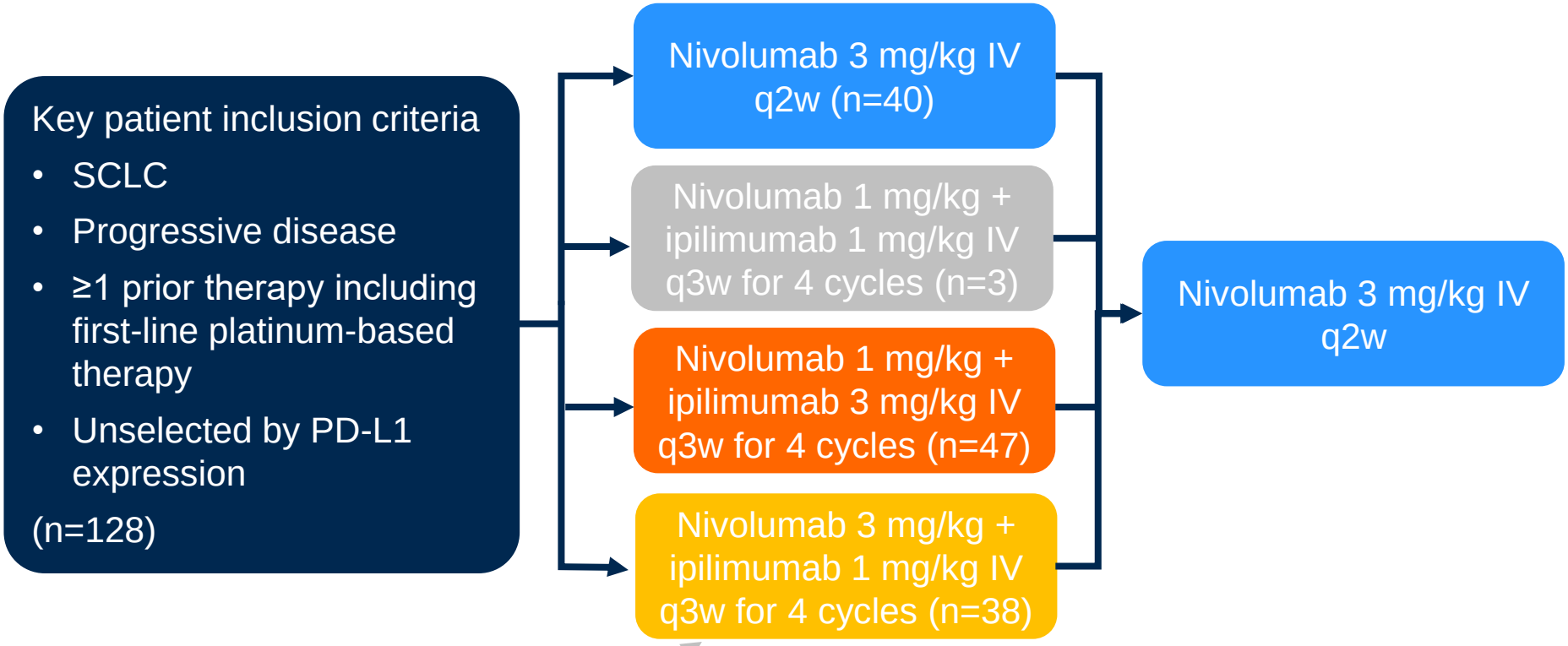

Hey du ...
rauchen ist
OUT

SCLC und Nivolumab +/- Ipilimumab

7503: Phase I/II study of nivolumab with or without ipilimumab for treatment of recurrent small cell lung cancer (SCLC): CA209-032 – Antonia SJ et al

Study objective

- To assess the efficacy and safety of nivolumab, an IgG4 PD-1 immune checkpoint inhibitor, with or without ipilimumab, a CTLA-4 checkpoint inhibitor, in previously treated SCLC patients



Primary endpoint

- ORR per RECIST v1.1

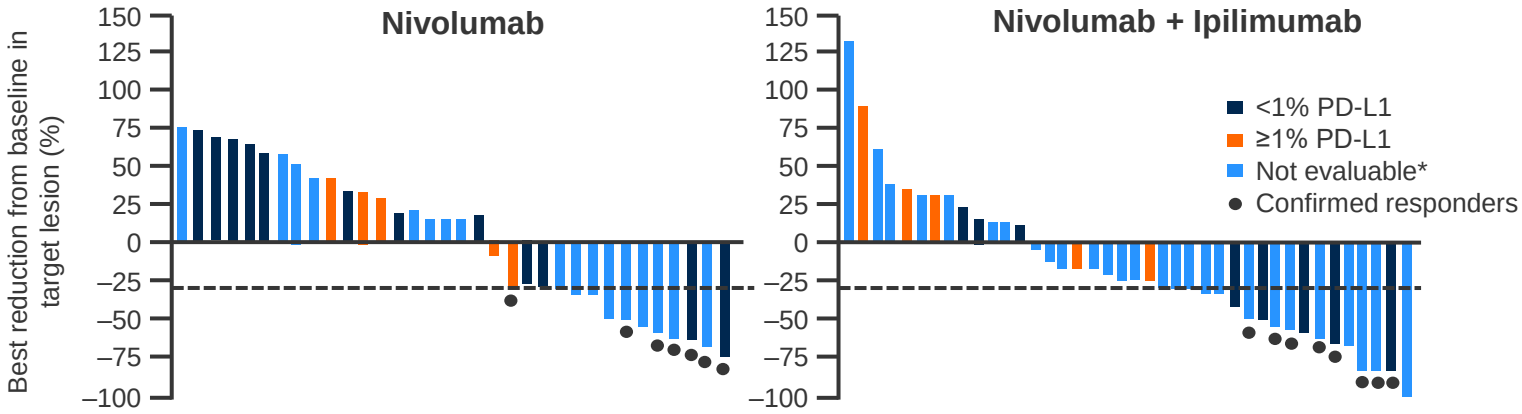
Secondary endpoints

- Safety, PFS, OS, biomarker analysis

Antonia et al. J Clin Oncol 2015; 33 (suppl): abstr 7503

7503: Phase I/II study of nivolumab with or without ipilimumab for treatment of recurrent small cell lung cancer (SCLC): CA209-032 – Antonia SJ et al

- **Key results**
  - Clinical responses occurred in patients regardless of PD-L1 expression



Evaluable samples (40 of 96)	PD-L1 expression level, n (%)	
	<1%	≥1%
Nivolumab (n=22)	15 (68)	7 (32)
Nivolumab + ipilimumab (n=18)	12 (67)	6 (33)

- **Conclusions**
  - Nivolumab alone or in combination with ipilimumab showed activity and durable responses in patients with SCLC and progressive disease
  - Nivolumab alone or in combination with ipilimumab had a manageable safety profile
  - These regimens will be explored in future trials of patients with SCLC

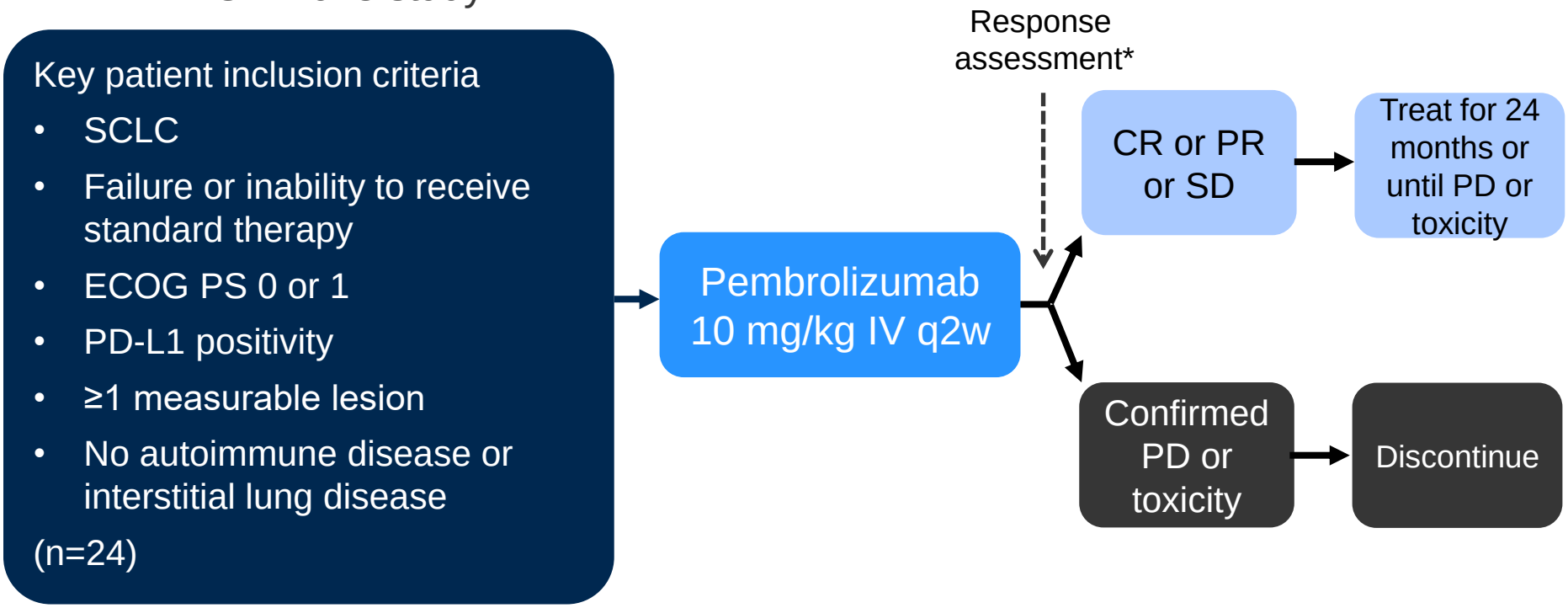
Antonia et al. J Clin Oncol 2015; 33 (suppl): abstr 7503

SCLC und Pembrolizumab

R. Müller

OA05.01: Pembrolizumab in Patients with Extensive-Stage Small Cell Lung Cancer: Updated Survival Results from KEYNOTE-028 – Ott P, et al

- **Study objective**
  - To assess the long-term follow-up data of pembrolizumab in SCLC from the KEYNOTE-028 study



Primary endpoints

- ORR (RECIST v1.1; investigator assessed) and safety

Secondary endpoints

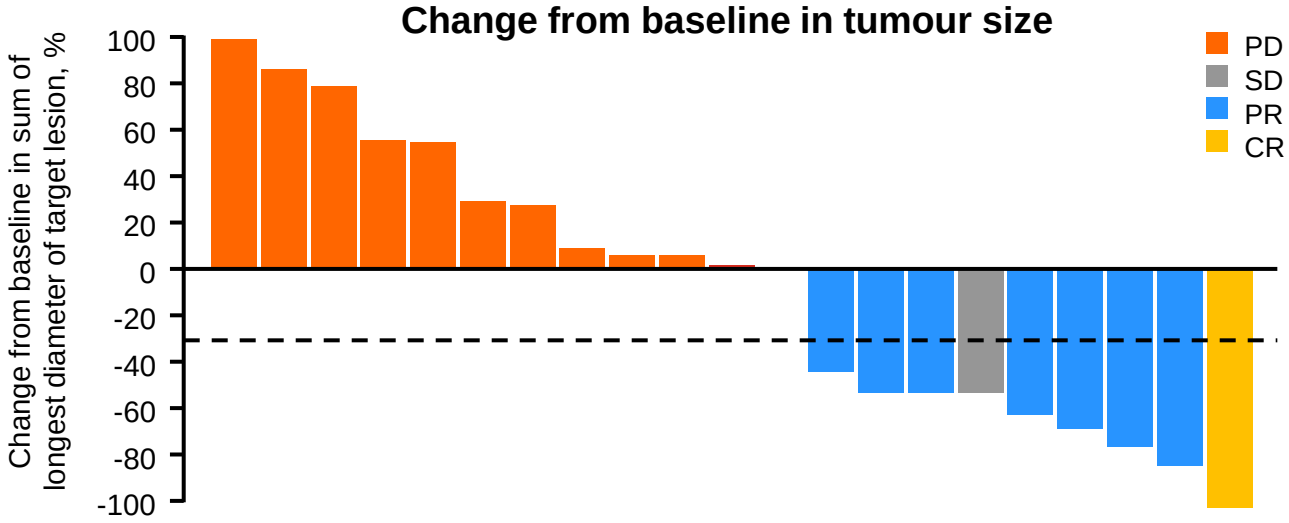
- PFS, OS, DoR

*Response assessment, q8w for the first 6 months, q12w thereafter

Ott et al. J Thorac Oncol 2016; 11(suppl): abstr OA05.01

OA05.01: Pembrolizumab in Patients with Extensive-Stage Small Cell Lung Cancer: Updated Survival Results from KEYNOTE-028 – Ott P, et al

- **Key results**
  - ORR 33.3% (95%CI 15.6, 55.3); median DoR 19.4 months (range 3.6+–20.0+)
  - Median PFS 1.9 months (95%CI 1.7, 5.9) and OS 9.7 months (95%CI 4.1, NR)



  - AEs of any grade occurred in 16 (66.7%) patients, grade ≥3 in 2 (8.3%) patients
- **Conclusion**
  - In previously treated patients with PD-L1-positive SCLC, pembrolizumab demonstrated anti-tumour activity, with a safety profile consistent with other tumour types

Ott et al. J Thorac Oncol 2016; 11(suppl): abstr OA05.01