EUROPEAN LUNG CANCER CONFERENCE 2016

IMMUNE ONCOLOGY AS A NEW STANDARD OF CARE

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DKG KREBSGESELLSCHAFT Zertifiziertes Lungenkrebszentrum

LUNGENCLINIC GROSSHANSDORF

DISCLOSURES

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

OUR CURRENT STANDARDS

	SCC	Non Sq NSCLC		
		EGFR mutation	Alk Rearrangement	No oncogene addiction
First-Line	Platinum Doublet	EGFR-TKI	AlK-TKI	Platinum Doublet Chemotherapy (Pem /Bev)
Maintenance	-	EGFR-TKI	ALK-TKI	Pem / Bev
Second line	Docetaxel +/- Ramucirumab Erlotinib Afatinib	Omisertinib (T790M+) Chemotherapy	Ceritinib Chemotherapy	Docetaxel +/- Ramucirumab +/- Nintedanib Pemetrexed Erlotinib

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

IMMUNE – ONCOLOGY IN LUNG CANCER

Where do we come from?

EFFICACY IN PRETREATED PATIENTS?

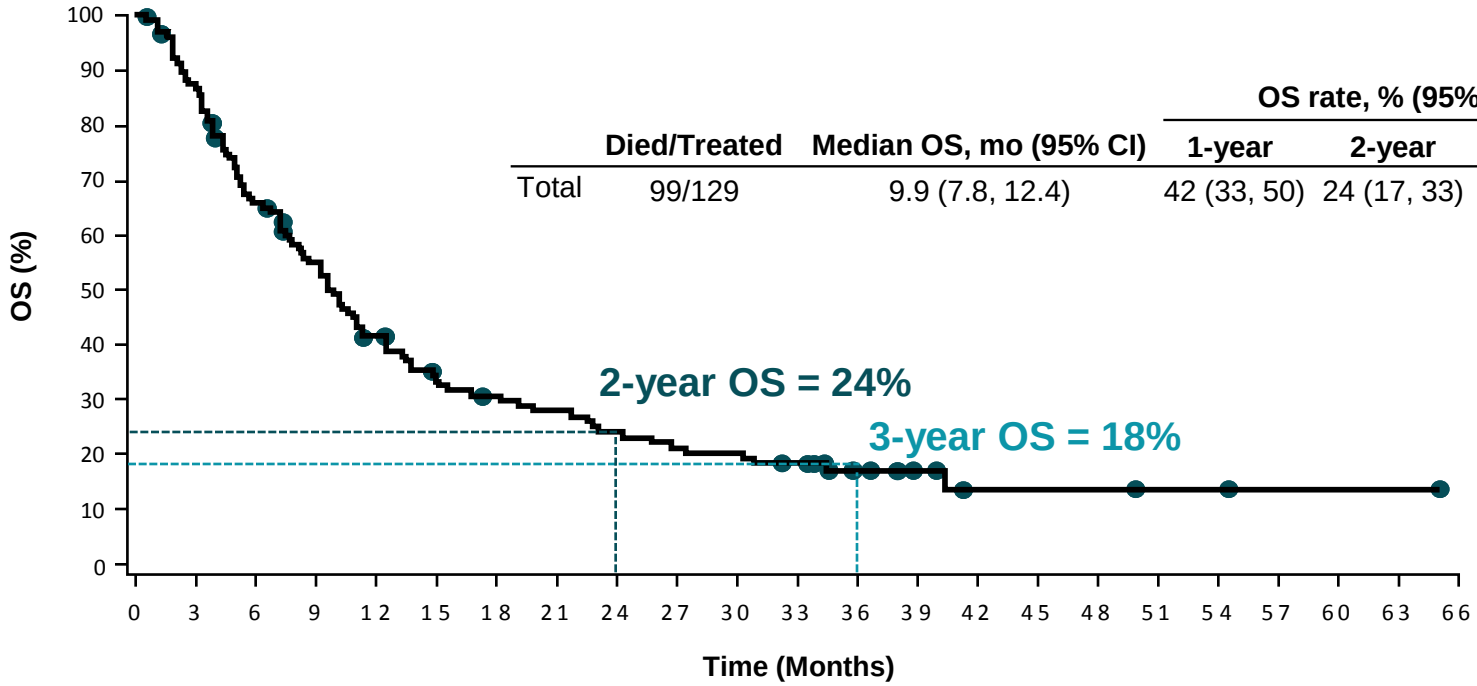
	Nivolumab	Pembrolizumab	Atezolizumab	Durvalumab	Avelumab
N	129	475[1]	175	228	184
RR Squamous Non Sq.	 17% 18%	 23.5% 19%	 27% 21%	 21% 13%	14%
Drug rel AE All grades Grade 3/4	 41% 4.7%	 71% 9.5%	 66% 11%	 50% 8%	 77% 12%
RR PDL-1 + PDL-1 -	 16% 13%	 42% (>50%) 10% (<1%)	 83% (IHC3)		

1: Also treatment naive patients

Gettinger S, J Clin Oncol 2015; 33: 2004-2012; Herbst R, Nature 2014; 515: 563-7; Soria JC, ESMO 2013;
Garon E, NEJM 2015; 372: 2018-28; Rizvi N, ASCO 2015; Guley LJ, ASCO 2015

THE SURPRISE: LONG TERM OS
EXAMPLE: NIVOLUMAB

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

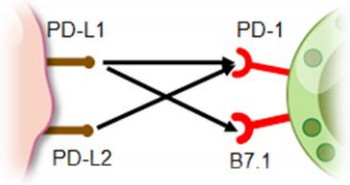


	Died/Treated	Median OS, mo (95% CI)	OS rate, % (95% CI) 1-year	2-year	3-year
Total	99/129	9.9 (7.8, 12.4)	42 (33, 50)	24 (17, 33)	18 (11, 25)

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.

RANDOMIZED TRIALS IN PRETREATED PATIENTS



Nivolumab – CheckMate 017 (PIII)
2nd Line, squamous, PD-L1 All-Comer

- Stage IIIb/IV SQ NSCLC
- 1 prior platinum doublet-based chemotherapy
- ECOG PS 0-1
- Pre-treatment (archival or fresh) tumor samples required for PD-L1 analysis

n=272

R 1:1

Nivolumab
3 mg/kg IV Q2W until PD or unacceptable toxicity
n=135

Docetaxel
75 mg/m² IV Q3W until PD or unacceptable toxicity
n=137

Patients stratified by region and prior Paclitaxel use

Nivolumab – CheckMate 057 (PIII)
2nd Line, non-squamous, PD-L1 All-Comer

- Stage IIIB/IV non-SQ NSCLC
- Pre-treatment (archival or recent) tumor samples required for PD-L1
- ECOG PS 0-1
- Failed 1 prior platinum doublet
- Prior maintenance therapy allowed[a]
- therapy allowed for translocation or ion

.. =582

R 1:1

Nivolumab
3mg/kg IV Q2W
until PD or unacceptable toxicity
n=292

Docetaxel
75mg/m² IV Q3W
until PD or unacceptable toxicity
n=290

Patients stratified by prior maintenance therapy and line of therapy (2nd- vs. 3rd-line)

Pembrolizumab - Keynote 010 (PII/III)
2nd+ Line, PD-L1 TPS ≥1%

- NSCLC
- At least 2 cycles of platinum-containing doublet chemotherapy
- PD-L1+ (central laboratory review)
- ECOG PS 0–1

n=1034

Pembrolizumab high dose (10 mg/kg) iv q3w
n=346

Pembrolizumab low dose (2 mg/kg) iv q3w
n=345

Docetaxel
n=343

Atezolizumab – POPLAR (PII)
2nd+ Line, PD-L1 All-Comer

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

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

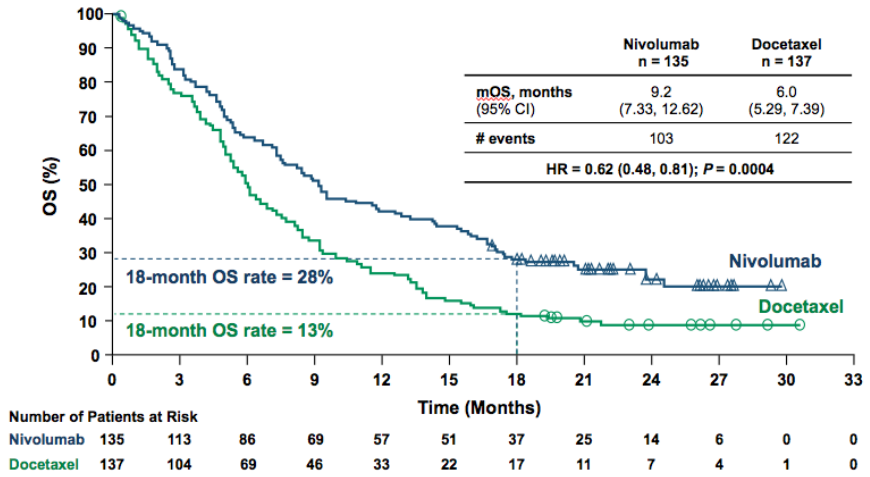
R 1:1

Atezolizumab
1200 mg IV q3w
until loss of clinical benefit

Docetaxel
75 mg/m² IV q3w
until disease progression

IMMUNE ONCOLOGY
A NEW STANDARD IN SECOND LINE SCC?

NIVOLUMAB VS DOCETAXEL IN PRETREATED SCC (CHECKMATE 017)



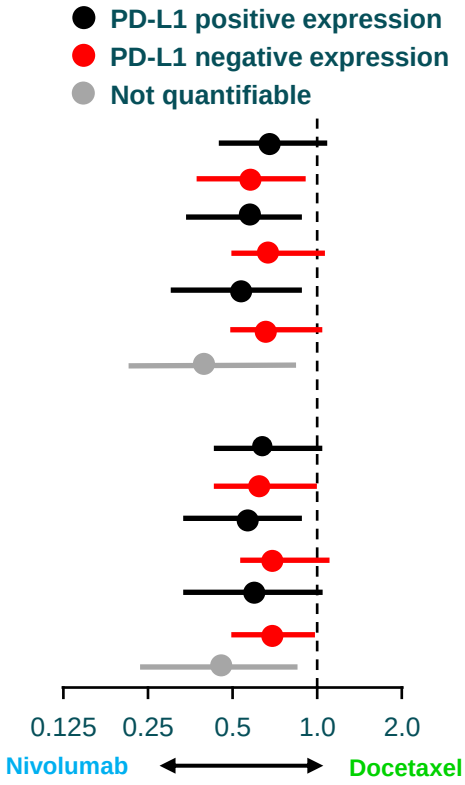
	Nivolumab (n=135)	Docetaxel (n=136)
mPFS	9.2 m	6.0 m
	HR 0.62 (95% CI 0.44, 0.79); p=0.004	
ORR	20%	9%
	P=0.008	
DOR	NR	8.4 m

Brahmer J, et al. New Engl J Med. 2015;373:123–135

OS AND PFS BY PD-L1 EXPRESSION: CHECKMATE 017[1]

Survival benefit with nivolumab was independent of PD-L1 expression level

PD-L1 expression[a]	Patients, n		Unstratified 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)	



[a]PD-L1 expression was measured in pretreatment tumor biopsies (DAKO automated IHC assay)[2]

1. Brahmer J, et al. New Engl J Med. 2015;373:123–135. 2. Rizvi NA, et al. Lancet Oncol 2015;16:257–65.

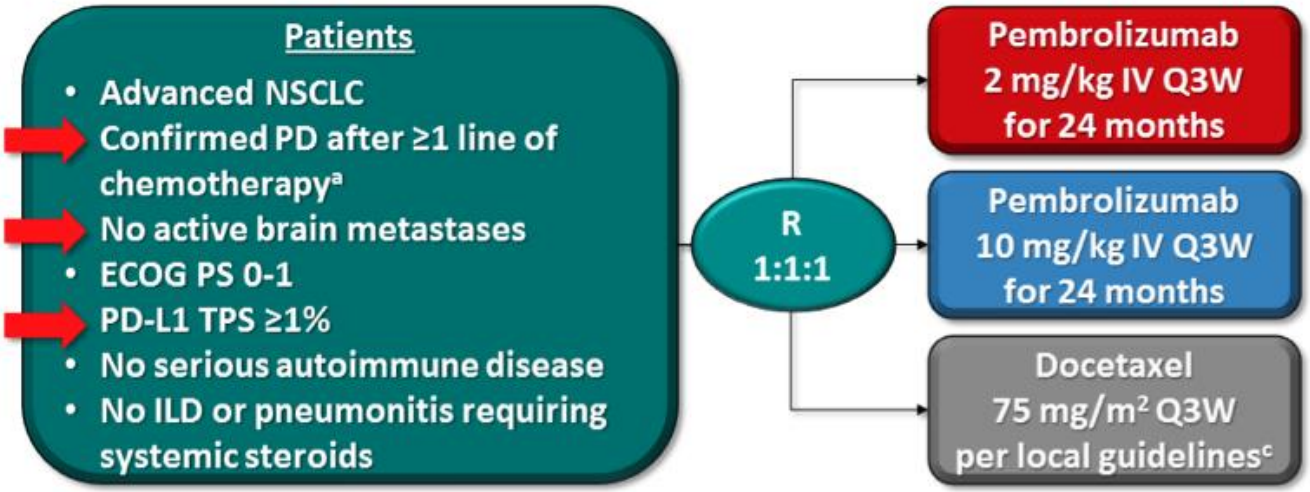
TREATMENT AND SAFETY SUMMARY: CHECKMATE 017

	Nivolumab (n = 131)		Docetaxel (n = 129)	
	Any Grade	Grade 3–5[a]	Any Grade	Grade 3–5
Treatment-related AEs leading to discontinuation, %	3[b]	2	10[c]	7
Treatment-related AEs (≥25% of patients in either arm), %	58	7	86	55
Fatigue	16	1	33	8
Neutropenia	1	0	33	30
Treatment-related select AEs (≥5% of patients in either arm), %				
Gastrointestinal	8	1	20	2
Skin	9	0	9	2
Pulmonary	5	1	1	0
Treatment-related deaths, %	0		2[d]	

[a]No grade 5 events were reported with nivolumab. [b]1% patients had increased ALT/AST, increased lipase, myasthenic syndrome, or rash, and 2% patients had pneumonitis. [c]Peripheral neuropathy (3%) and fatigue (2%). [d]Interstitial lung disease, pulmonary hemorrhage, and sepsis (1 patient each).

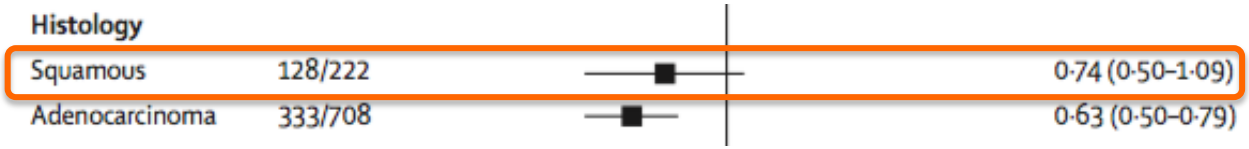
Brahmer J, et al. *New Engl J Med.* 2015;373:123–135.

PEMBROLIZUMAB VS DOCETAXEL IN PDL-1 + TUMORS KEYNOTE 10

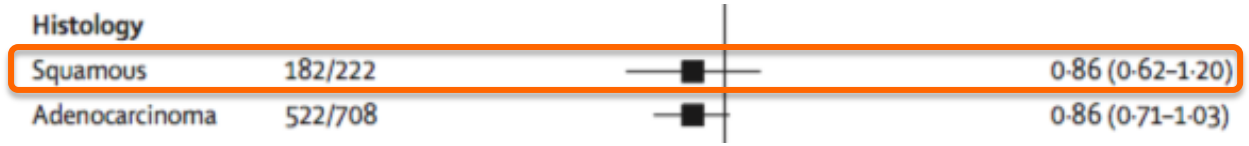


SCC patients:
66 Docetaxel
76 Pembrolizumab (2mg/kg)
80 Pembrolizumab (10 mg/kg)

Overall Survival,
(ITT HR 0.67, p=0.0008)



PFS,
(ITT HR 0.85, p=0.07)



Herbst R et al, Lancet 2015

ATEZOLIZUMAB VS DOCETAXEL IN PRETREATED PATIENTS POPLAR TRIAL

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

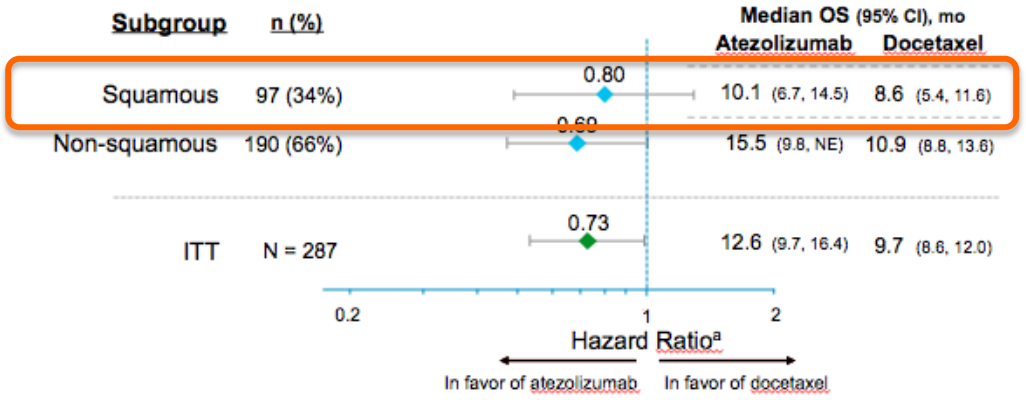
Stratification Factors
- PD-L1 IC expression (0 vs 1 vs 2 vs 3)[a]
- Histology (squamous vs non-squamous)
- Prior chemotherapy regimens (1 vs 2)

R 1:1

Atezolizumab
1200 mg IV q3w
until loss of clinical benefit

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

Overall Survival (ITT HR 0.73, p=0.04)

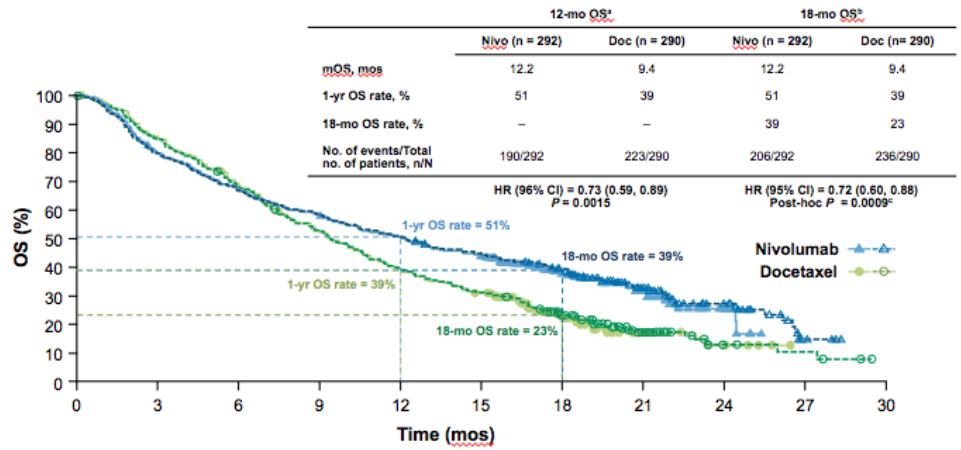


- **Event/patient ratio: Squamous 69%** (63% for atezolizumab, 75% for docetaxel)
  Non-squamous 56% (49% for atezolizumab, 62% for docetaxel)

Vansteenkise J, ECCO ESMO 2015

IMMUNE ONCOLOGY
A NEW STANDARD IN SECOND LINE NON SQ NSCLC?

NIVOLUMAB VS DOCETAXEL IN NON SQ NSCLC CHECKMATE 057



- Minimum follow-up for 12-mo OS rate, 13.2 mos; for 18-mo OS rate, 17.1 mos

	Nivolumab (n = 292)	Docetaxel (n = 290)
Med OS	12.2 m	9.4 m
	HR 0.72 (95% CI 0.6,0.88) p=0.009	
Med PFS	2.3 m	4.2 m
1 y PFS	19%	8%
	HR 0.92 (95% CI 0.77, 1.11) p= 0.39	
ORR	19%	12%
	P= 0.025	
DOR	17.2 m	5.6 m

elcc

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Borghaei H et al, NEJM 2016;

TREATMENT AND SAFETY SUMMARY: CHECKMATE 057

	Nivolumab (n = 287)		Docetaxel (n = 268)	
	Any Grade	Grade 3–4[a]	Any Grade	Grade 3–4[a]
Treatment-related AEs leading to discontinuation, %	5	4	15	7
Treatment-related SAEs, %	7	5	20	18
Treatment-related AEs (≥25% of patients in either arm), %	69	10	88	54
Fatigue	16	1	29	5
Nausea	12	1	26	1
Alopecia	<1	0	25	0
Neutropenia	<1	0	31	27
Treatment-related select AEs, % (≥5% of patients in either arm)				
Rash	9	<1	3	0
Pruritus	8	0	1	0
Diarrhea	8	1	23	1
Hypothyroidism	7	0	0	0

[a]No grade 5 events were reported at DBL; 1 grade 5 event was reported for nivolumab post-DBL, death attributed to nivolumab (encephalitis) the association to nivolumab changed after DBL; 1 death attributed to docetaxel-related drug toxicity (grade 4 febrile neutropenia).

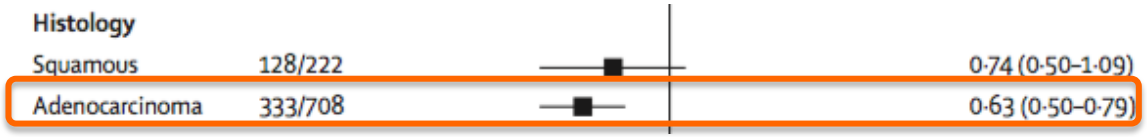
AE = adverse event; SAE = serious adverse event.

Borghaei H et al, NEJM 2016;

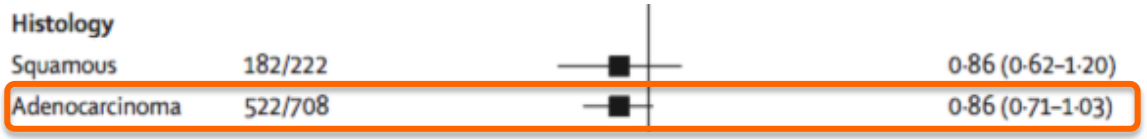
PEMBROLIZUMAB / ATEZOLIZUMA VS DOCE IN NON-SQUAMOUS NSCLC

Pembrolizumab – KN 10

OS (ITT HR 0.67, p=0.0008)

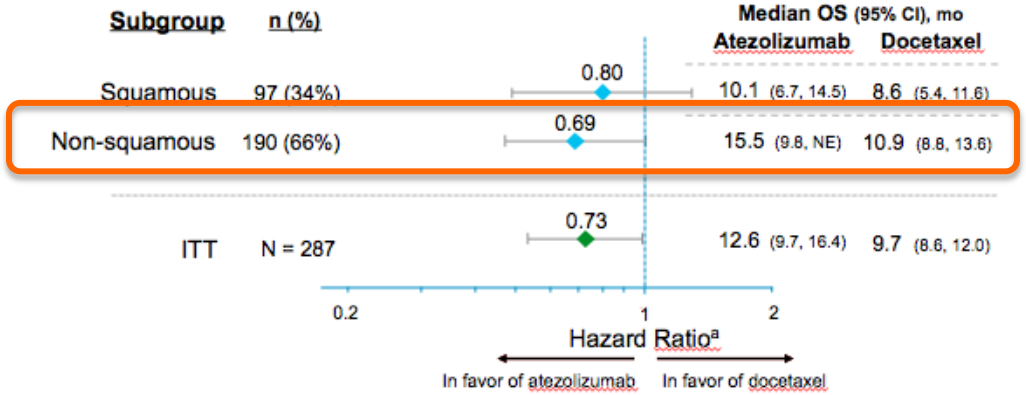


PFS (ITT HR 0.85, p=0.07)



Atezolizumab – Poplar

OS (ITT HR 0.73, p=0.04)



- **Event/patient ratio: Squamous 69%** (63% for atezolizumab, 75% for docetaxel)
  Non-squamous 56% (49% for atezolizumab, 62% for docetaxel)

Vansteenkise J, ECCO ESMO 2015;
Herbst R, Lancet 2015

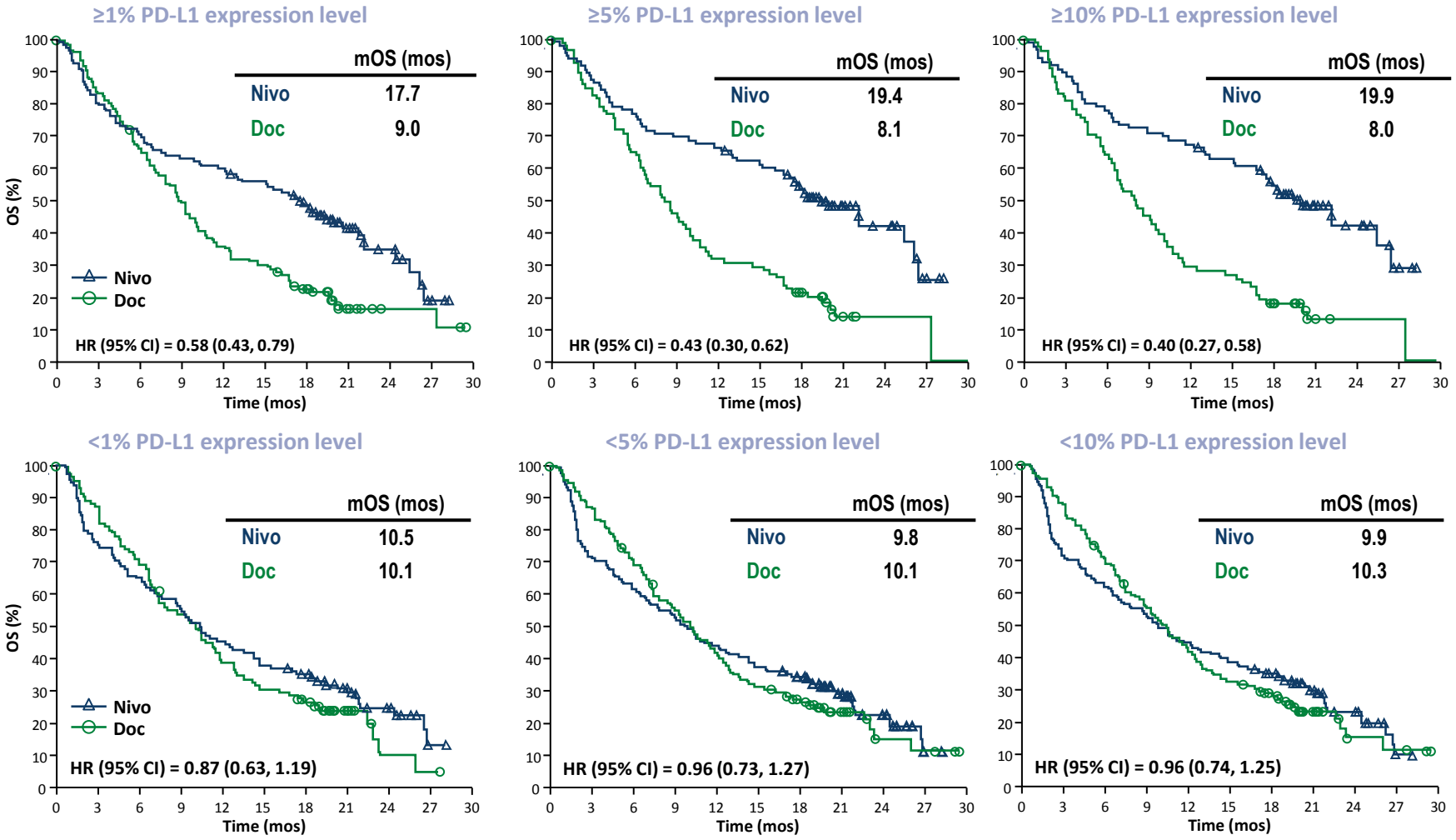
IMMUNE ONCOLOGY
A NEW STANDARD
IN SECOND LINE NON SQ NSCLC?

Impact of PD-L1 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%)**	**–**	**–**	**–**

NIVOLUMAB – CM-057: OVERALL SURVIVAL BY PD-L1 EXPRESSION



Based on a July 2, 2015 DBL. Symbols represent censored observations

Horn L, ESMO Asia 2015

HOWEVER

PD-L1 expression level	ORR,[a] %		Median DOR, mos	
	Nivolumab	Docetaxel	Nivolumab	Docetaxel
≥1%	31	12	16.0	5.6
≥5%	36	13	16.0	5.6
≥10%	37	13	16.0	5.6
<1%	9	15	18.3	5.6
<5%	10	14	18.3	5.6
<10%	11	14	18.3	5.6
Not quantifiable	13	9	7.3	6.6

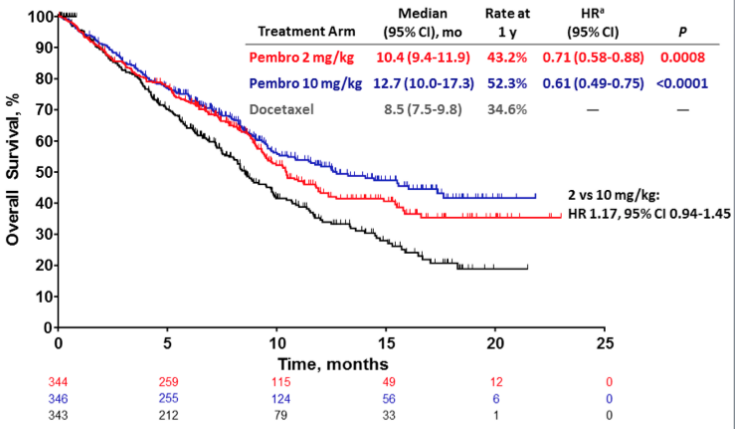
Response Rate lower in PD-L1 negative patients but there are responses
Duration of response independent from PD-L1 status

Horn L, ESMO Asia 2015

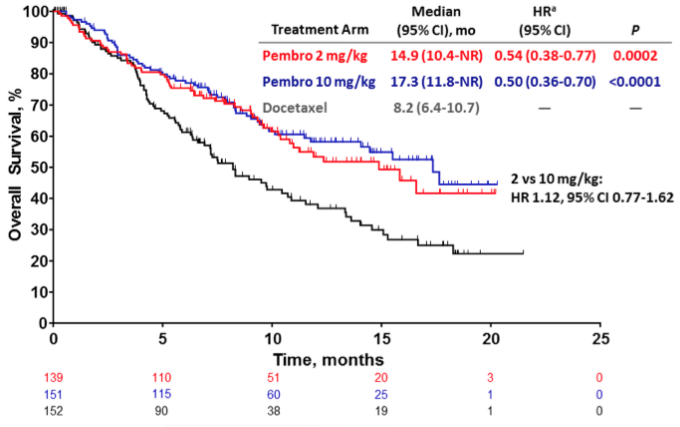
PEMBROLIZUMAB VS DOCETAXEL KEYNOTE 10

Efficacy of Docetaxel seems to be independent from PD-L1 status

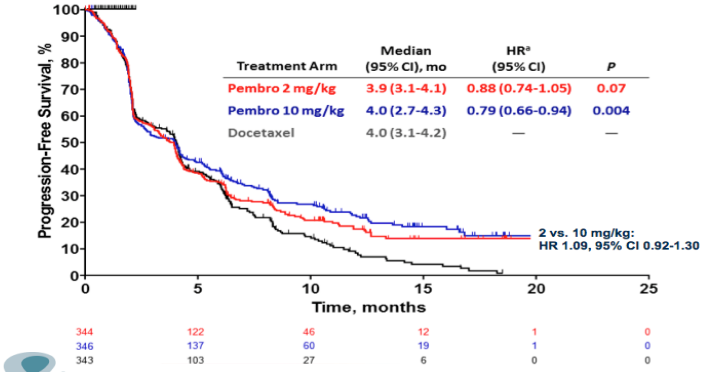
OS, PD-L1 TPS ≥1% (Total Population)



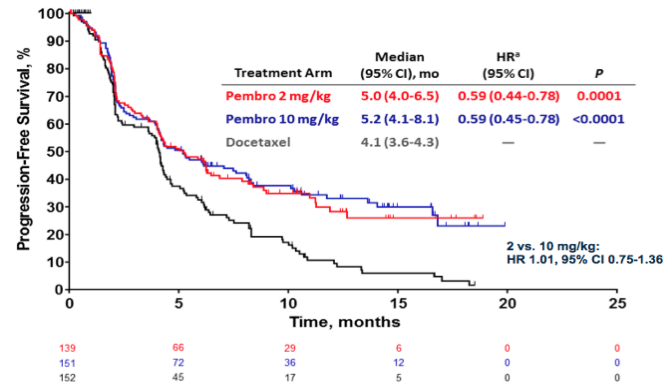
OS, PD-L1 TPS ≥50% Stratum



PFS (RECIST v1.1, Central Review), PD-L1 TPS ≥1%



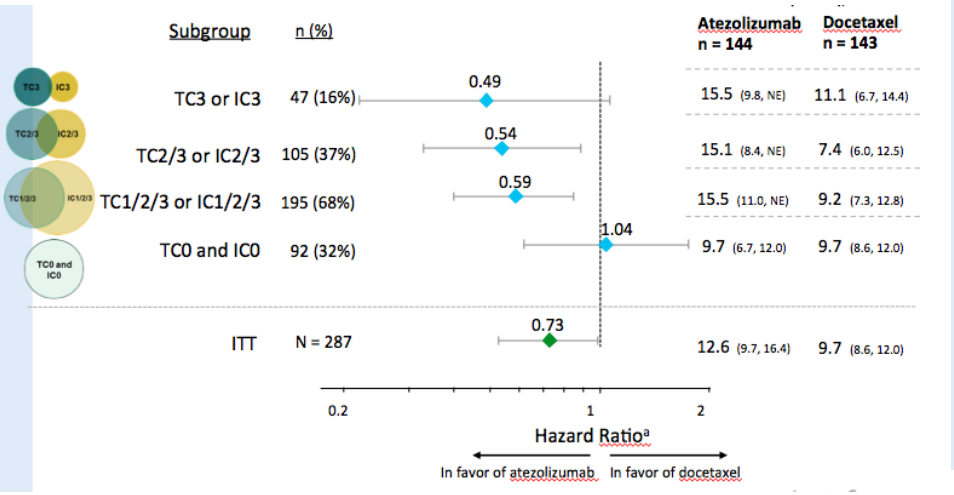
PFS (RECIST v1.1, Central Review), PD-L1 TPS ≥50%



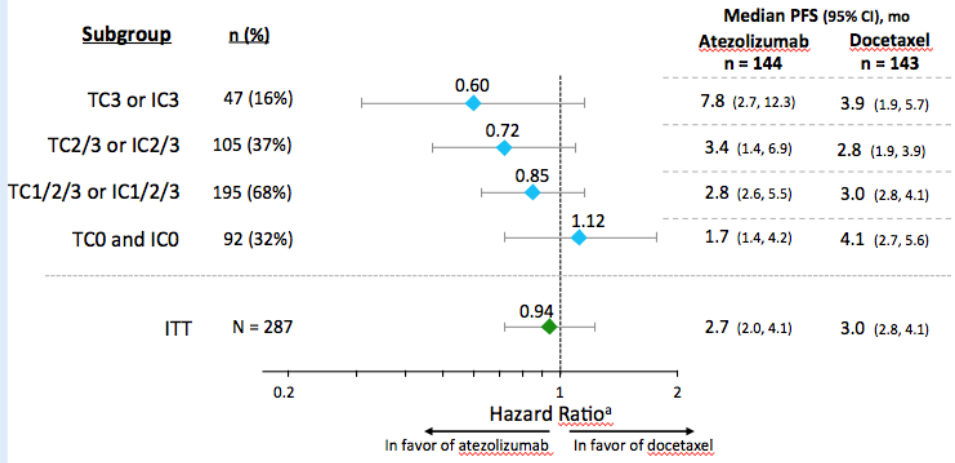
Herbst R et al, Lancet 2015

ATEZOLIZUMAB VS DOCETAXEL POPLAR

Overall Survival



Progression Free Survival



Either TC or IC expression seems to be predictive independent from each other (low number of patients)

Vansteenkiste J, ECCO ESMO 2015

HOW TO DEAL WITH PD-L1 EXPRESSION?

- Not an ideal marker
- Supportive for enrichment of patients
- Not an exclusion marker in case of PD-L1 negativity
- Testing will come following the results of IO First-line trials
- Harmonization eagerly awaited

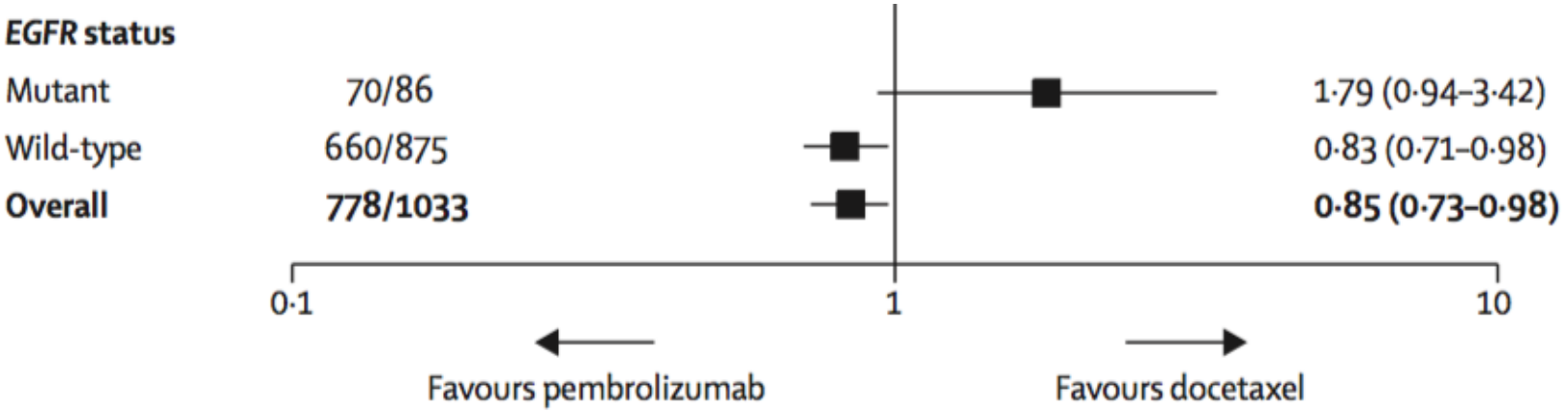
REMAINING QUESTIONS I
WHAT ABOUT EFFICACY IN FREQUENT SUBGROUPS?

	CM 017	CM 057	KN 10	Poplar
CNS Met.	6-7%	nr	14-16%	nr
PS 2	1% PS nr	1% PS nr	1 %	20-29% PS 2/3
> 2nd line	nr	11-12% 3rd line	27-30% 3rd line + > 3rd line	33-35% 3rd line

Brahmer J et al, NEJM 2015; Borghaei H et al, NEJM 2016;
Herbst R et al, Lancet 2015;
Fehrenbacher L et al Lancet Oncology 2016

REMAINING QUESTIONS II
WHAT ABOUT EFFICACY IN PATIENTS WITH EGFR MUTATIONS?

Pembrolizumab (KN 10)



Nivolumab (CM 057)

Borghaei H et al, NEJM 2016;
Herbst R et al, Lancet 2015

IO – A NEW STANDARD IN NSCLC?

- In second-line treatment
  - Confirmed superior efficacy to docetaxel
  - Lower incidence of AEs
  - PD-L1 expression may be used as enrichment factor (in non squamous NSCLC)
  - Not compared to combined second-line regimen (docetaxel + nintedanib/ramucirumab)
- Open important questions
  - Efficacy and safety in PS 2/3 patients and in patients with CNS metastasis
  - Efficacy > 2nd line
  - Duration of treatment?
- In first-line treatment
  - Trial results expected soon (Dr. Carbone)