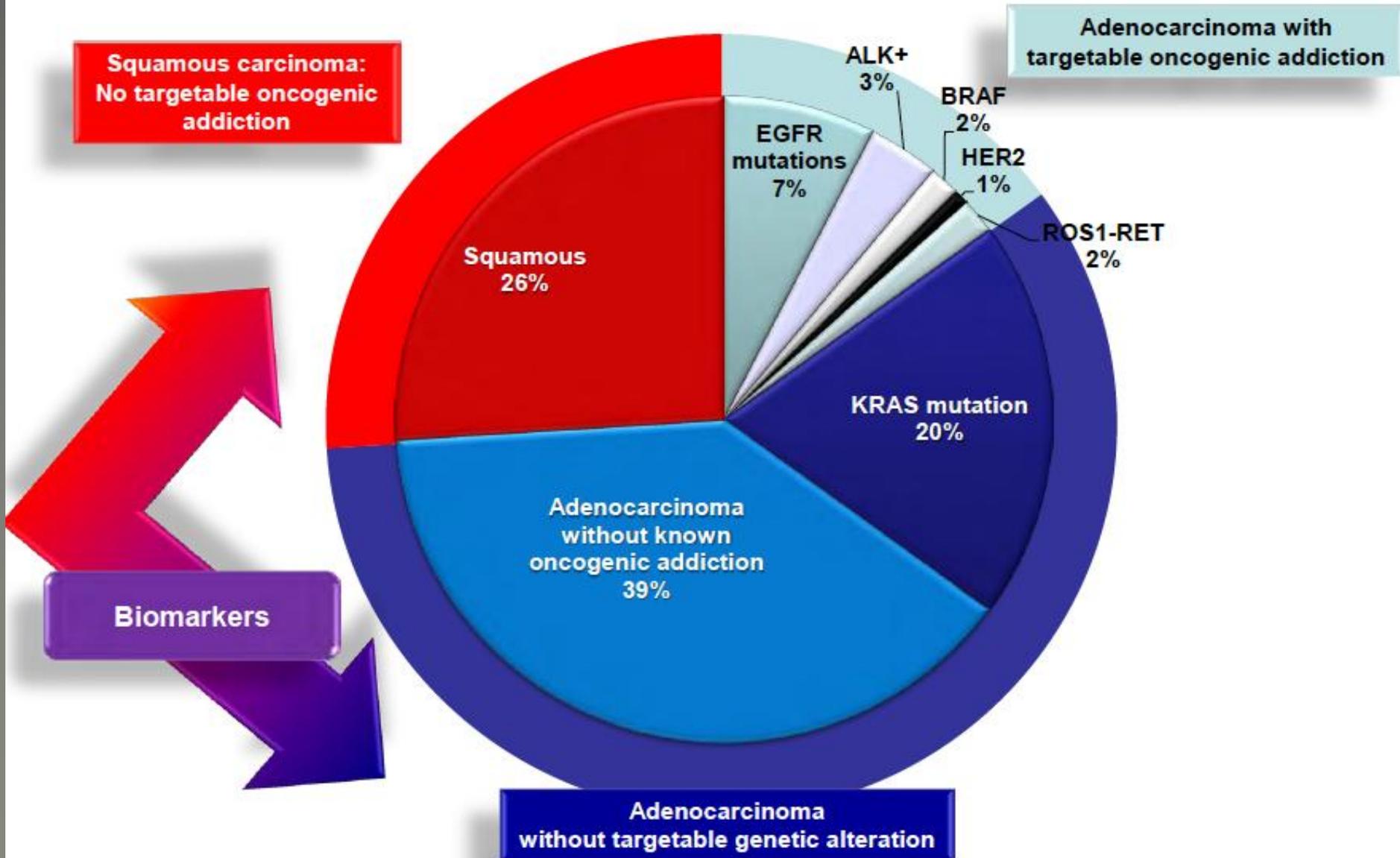


Immunothérapie et Cancer Bronchique

Données récentes

Classifications NAPC



NAPC: algorithme de traitement 2014

		Non-Squamous Carcinoma			Squamous Carcinoma		
		Biomarkers determination					
Decision-making factors	EGFR Mut+	ALK +	Wild-type EGFR and ALK -				
	All PS	All PS	PS 0-1	PS 2 or > 75 years	PS 0-1	PS 2 or > 75 years	
				Comorbidities Bevacizumab eligibility		Comorbidities	
Induction	Gefitinib Erlotinib Afatinib	Platinum-based doublet	Platinum-based doublet ± bevacizumab	Carboplatin-based doublet or single agent ± bevacizumab	Platinum-based doublet except pemetrexed	Carboplatin-based doublet or single agent except pemetrexed	
Maintenance	Gefitinib Erlotinib Afatinib	Bevacizumab Pemetrexed	Bevacizumab Pemetrexed Erlotinib if stable disease	Bevacizumab if used for induction therapy	Erlotinib if stable disease		
2 nd line	Platinum-based doublet ± bevacizumab	Crizotinib	Docetaxel Pemetrexed Erlotinib depending on 1 st line treatment		Docetaxel Erlotinib depending on 1 st line treatment		

Effacité des chimiothérapies de seconde ligne pour les NAPC

	Erlotinib (150 mg /j)	Docetaxel (75mg/m ² /3 sem)	Pemetrexed (500mg/m ² /3 sem)
Taux de Réponse %	8.9	7.8-8.8	9.1
Survie à 1 an %	31	30-37	30
Médiane de survie (mois)	6.7	5.7-7.9	8.3

¹Shepherd F et al. *N Engl J Med.* 2005;353:123-132. ²Erlotinib: product data on file from OSI, Roche. ³Shepherd F et al. *J Clin Oncol.* 2000;18:2095-2103. ⁴Fossella F et al. *J Clin Oncol.* 2000;18:2354-2362. ⁵Hanna N et al. *J Clin Oncol.* 2004;22:1589-1597.

Immunothérapie et cancer bronchique: les principaux agents anti PD1/PD-L1

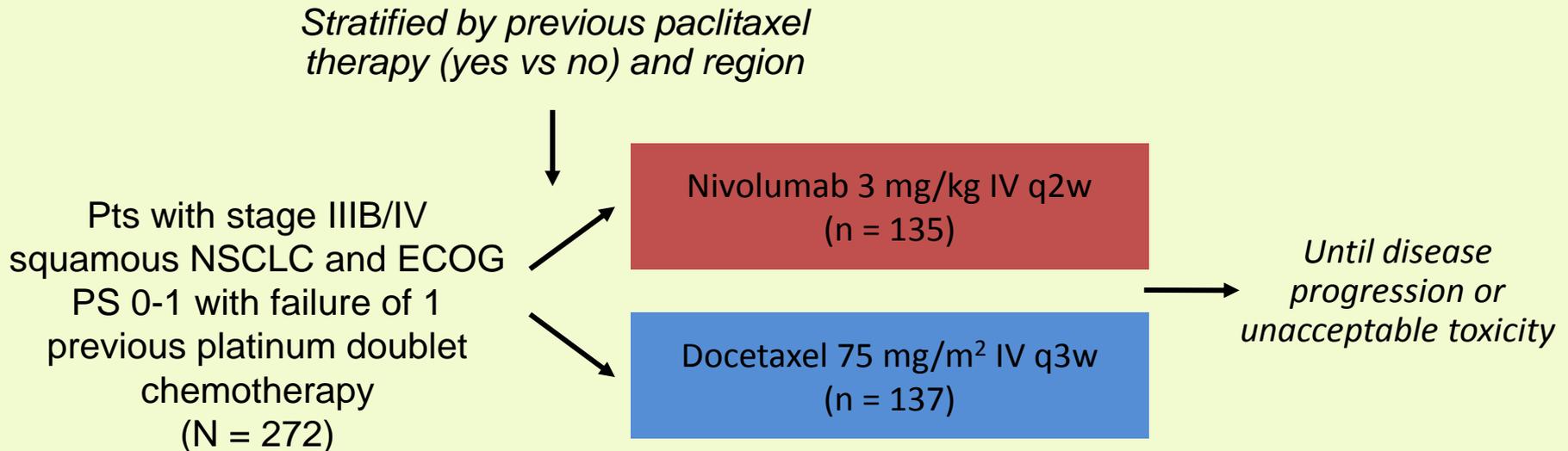
Table 1. PD-1 and PD-L1 Antibodies in Clinical Development

Target and Agent	Class
PD-1	
Nivolumab (MDX1106, BMS-936558)	IgG4 fully human Ab
Pembrolizumab (MK-3475)	IgG4 engineered humanized Ab
Pidilizumab (CT-011)	IgG1 humanized Ab
PD-L1	
BMS935559 (MDX-1105)	IgG4 fully human Ab
MPDL3280A	IgG1 engineered fully human Ab
MEDI4736	IgG1 engineered fully human Ab
MSB0010718C	IgG1 fully human Ab
PD-1–positive T cells	
AMP-224	Fc of human IgG–PD-L2 fusion

Abbreviations: Ab, antibody; IgG, immunoglobulin G; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein 1 ligand.

CheckMate 017: Nivolumab vs Docetaxel in Previously Treated Squamous NSCLC

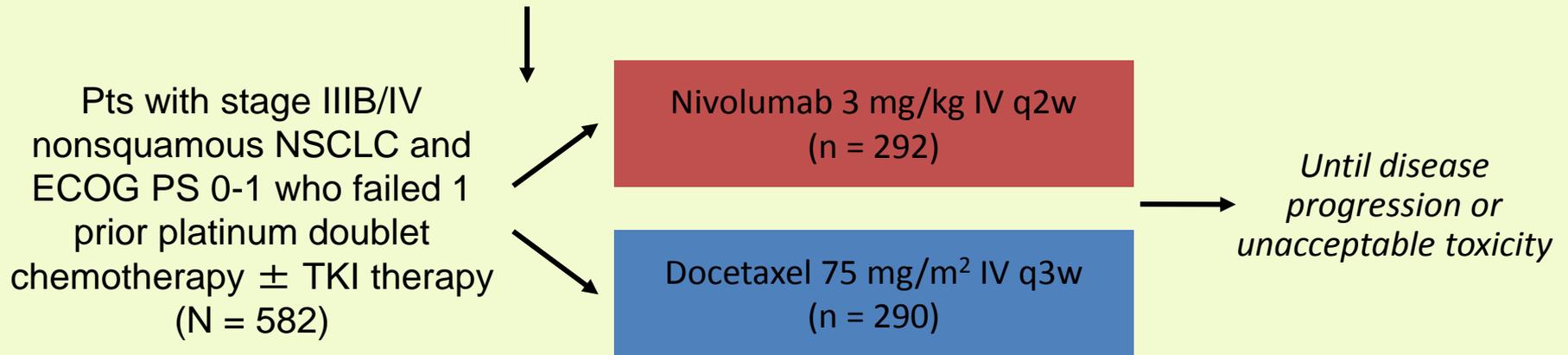
- Open-label, randomized phase III trial



- Primary endpoint: OS
- Secondary endpoints: ORR, PFS, efficacy by PD-L1 expression, safety, QoL

CheckMate 057: Nivo vs Docetaxel in Previously Treated Nonsquamous NSCLC

Stratified by previous maintenance therapy (yes vs no) and line of therapy (second vs third line)



- Primary endpoint: OS
- Secondary endpoints: ORR, PFS, efficacy by PD-L1 expression, safety, QoL

Baseline Characteristics

CHEKMATE 017 Sq

	Nivolumab n = 135	Docetaxel n = 137
Median age, years (range) ≥75, %	62 (39–85) 8	64 (42–84) 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
Prior paclitaxel, %	34	34
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

CHEKMATE 057 non-Sq

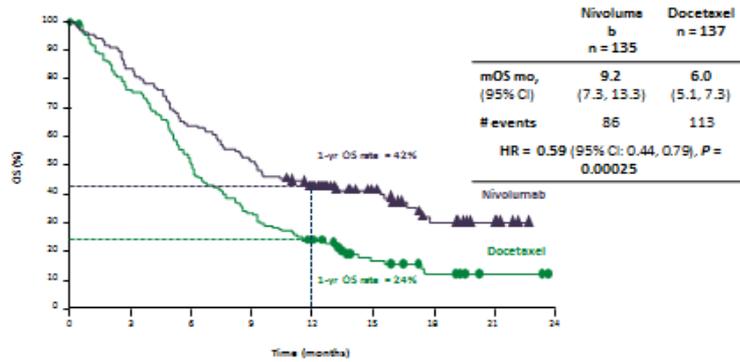
	Nivolumab (n = 292)	Docetaxel (n = 290)
Median age, years (range) ≥75 years, %	61 (37, 84) 7	64 (21, 85) 8
Male, %	52	58
Smoking status, %		
Current/former smoker	79	78
Never smoker	20	21
ECOG PS, ^a %		
0	29	33
1	71	67
Prior maintenance therapy, %	42	38
Number of prior systemic regimens, ^a %		
1	88	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

• 78% (455/582) of randomized patients had quantifiable PD-L1 expression

OS/PFS

CHEKMATE 017 Sq

Overall Survival

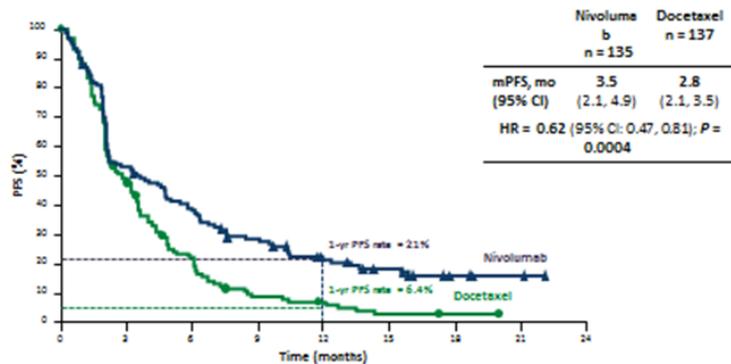


Number of Patients at Risk

	0	3	6	9	12	15	18	21	24
Nivolumab	135	115	86	69	52	31	15	7	0
Docetaxel	137	103	65	45	30	14	7	2	0

Triangles represent censored observations

Progression-free Survival



Number of Patients at Risk

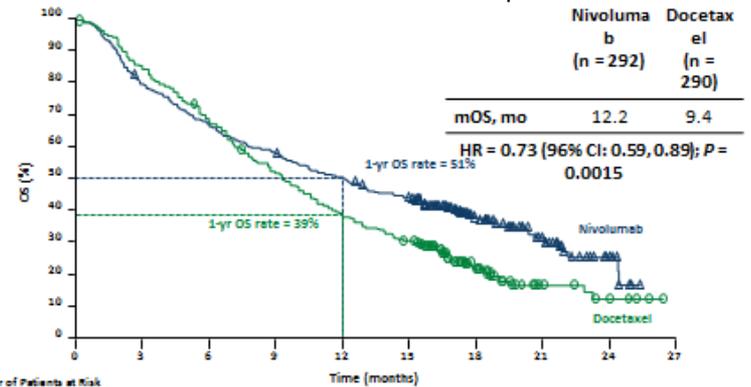
	0	3	6	9	12	15	18	21	24
Nivolumab	135	85	48	35	21	15	6	2	0
Docetaxel	137	62	26	9	6	2	1	0	0

PFS per RECIST

CHEKMATE 057 non-Sq

Overall Survival

Non Sq 057

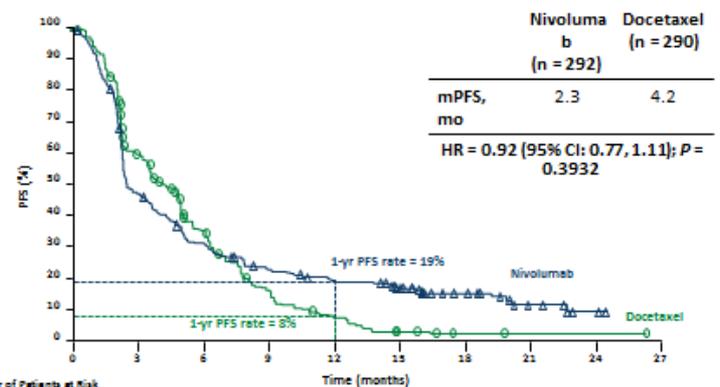


Number of Patients at Risk

	0	3	6	9	12	15	18	21	24	27
Nivolumab	292	232	194	169	145	123	62	32	9	0
Docetaxel	290	244	194	150	111	69	34	10	5	0

Taux de survie à 18 mois : 39% dans bras nivo vs 23% dans bras txt HR 0.72 p=0.0009, médiane du durée de réponse objective de 17.2 mois vs 5.6 mois.

Progression-free Survival



Number of Patients at Risk

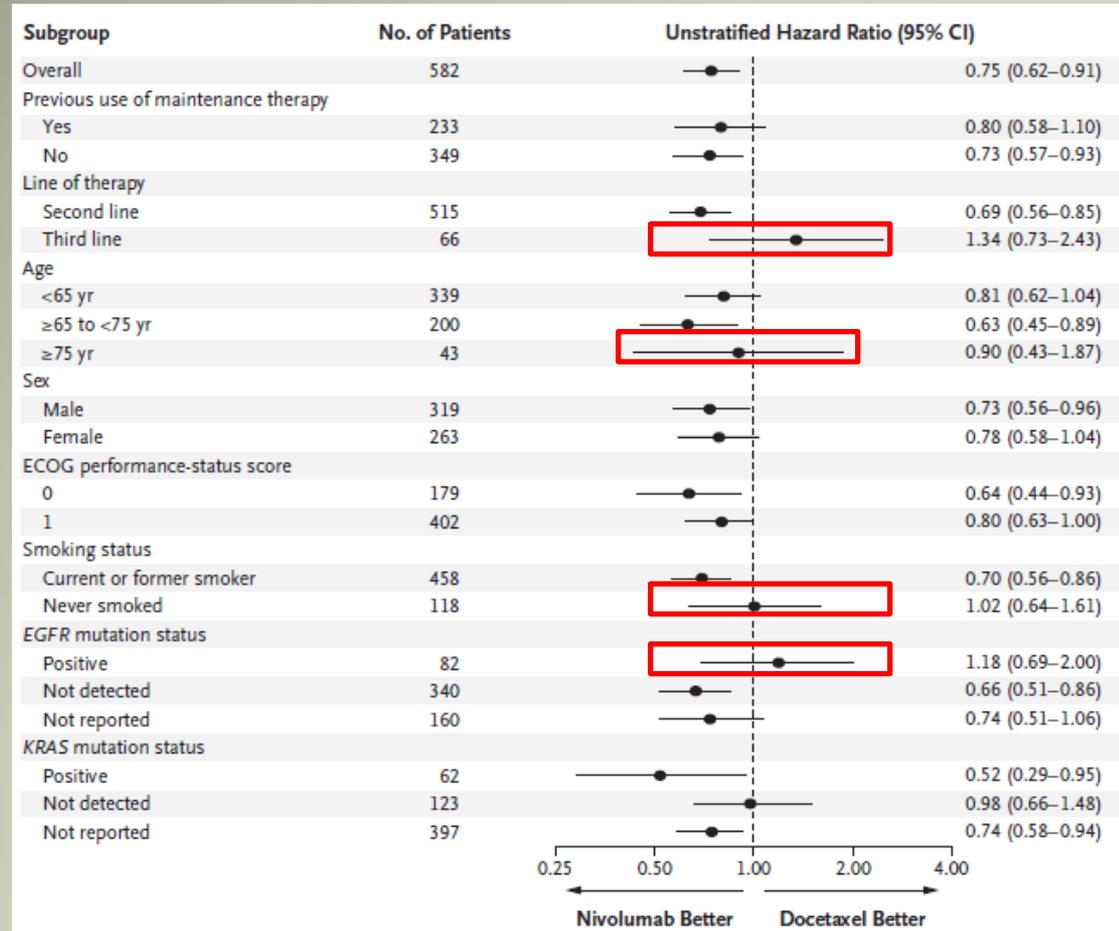
	0	3	6	9	12	15	18	21	24	27
Nivolumab	292	128	82	58	45	25	17	7	2	0
Docetaxel	290	156	87	38	18	6	2	1	1	0

Triangles represent censored observations

Treatment Effect on OS in Predefined Subgroups

CHEKMATE 017 Squamous

CHEKMATE 057 non-Squamous



Treatment and Safety Summary

CHEKMATE 017 Squamous

	Nivolumab n = 131		Docetaxel n = 129	
	Any Grade	Grade 3-5*	Any Grade	Grade 3-5
Treatment-related AEs, %	58	7	88	57
Treatment-related AEs leading to discontinuation, %	3 ^b	2	10 ^c	7
Treatment-related deaths, %	0		2 ^d	

* Median number of doses was 8 (range, 1-48) for nivolumab and 3 (range, 1-29) for docetaxel

CHEKMATE 057 non-Sq

	Nivolumab (n = 287)		Docetaxel (n = 268)	
	Any Grade	Grade 3-4*	Any Grade	Grade 3-4*
Median number of doses received (range)	6 (1, 52)		4 (1, 23)	
Relative dose intensity, ≥90%	83		68	
Patients continuing treatment, %	15		0	
Patients who received subsequent systemic therapy, %	42		50	
Treatment-related AEs, %	69	10	88	54
Treatment-related SAEs, %	7	5	20	18
Treatment-related AEs leading to discontinuation, %	5	4	15	7
Treatment-related deaths, %	0 ^b		<1 ^c	

*No grade 5 events were reported in CHEK; 1 grade 5 event was reported for nivolumab (post-CHEK); **1 death attributed to nivolumab (encephalitis); associated to nivolumab changed after CHEK; ***1 death attributed to docetaxel-related drug toxicity (grade 4 fibrile neurogenic).

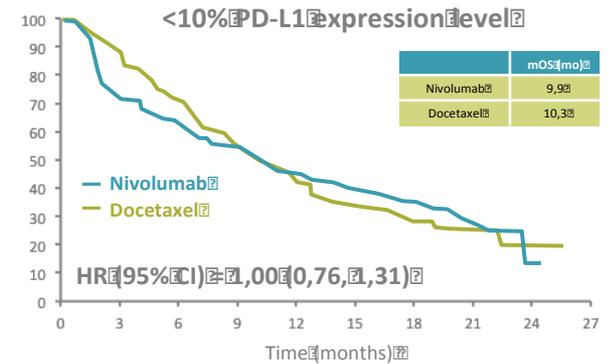
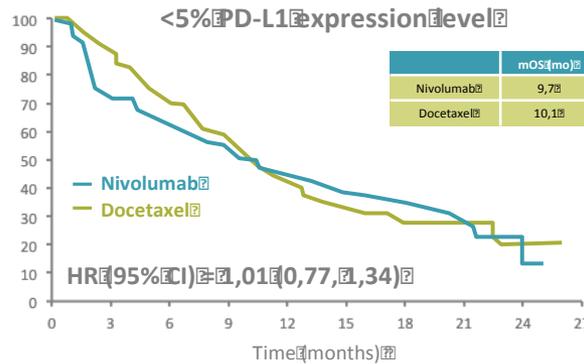
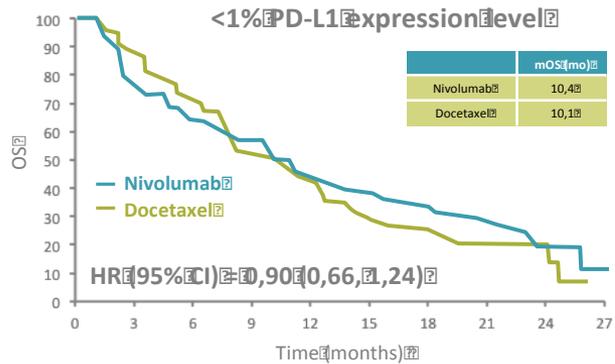
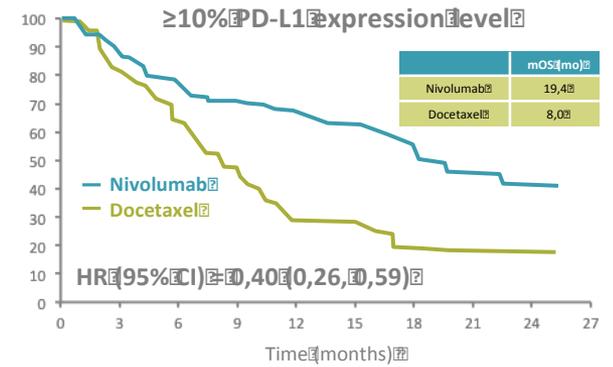
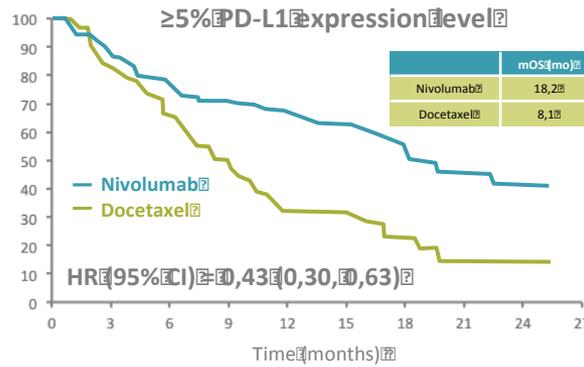
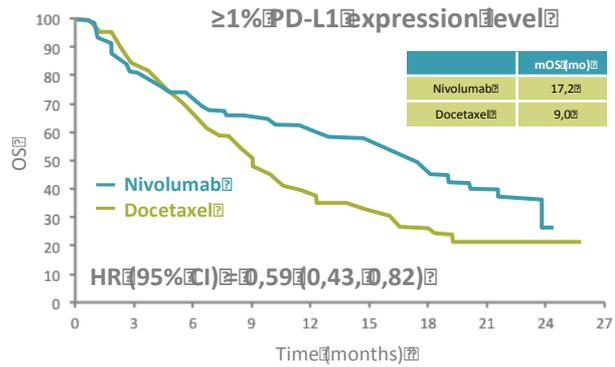
Moins d'effets toxiques de grade 3-5 dans les bras nivo

% comparables de 7 à 10% dans les sq et non-sq

Quelques soient les grades, les AEs les plus fréquents sous nivo sont:

l'asthénie, l'anorexie, nausées/vomissements, diarrhées

Check Mate 057 : OS by PD-L1 Expression



Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial

Roy S Herbst, Paul Baas, Dong-Wan Kim, Enriqueta Felip, José L Pérez-Gracia, Ji-Youn Han, Julian Molina, Joo-Hang Kim, Catherine Dubos Arvis, Myung-Ju Ahn, Margarita Majem, Mary J Fidler, Gilberto de Castro Jr, Marcelo Garrido, Gregory M Lubiniecki, Yue Shentu, Ellie Im, Marisa Dolled-Filhart, Edward B Garon

KEYNOTE-10 Study Design

Patients

- Advanced NSCLC
- Confirmed PD after ≥ 1 line of chemotherapy^a
- No active brain metastases
- ECOG PS 0-1
- PD-L1 TPS $\geq 1\%$
- No serious autoimmune disease
- No ILD or pneumonitis requiring systemic steroids

Stratification factors:

- ECOG PS (0 vs 1)
- Region (East Asia vs non-East Asia)
- PD-L1 status^b (TPS $\geq 50\%$ vs 1%-49%)

R
1:1:1

Pembrolizumab
2 mg/kg IV Q3W
for 24 months

Pembrolizumab
10 mg/kg IV Q3W
for 24 months

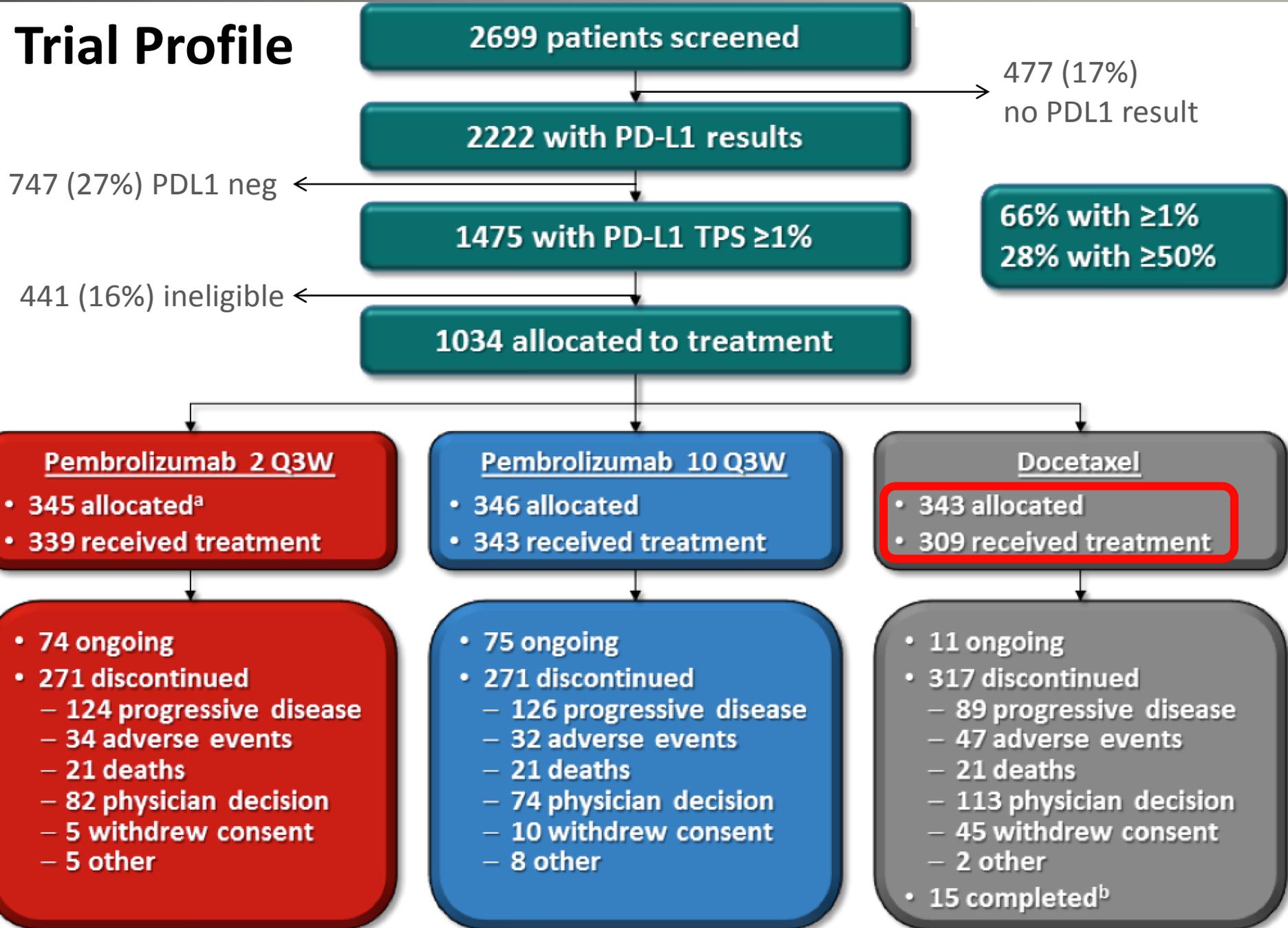
Docetaxel
75 mg/m² Q3W
per local guidelines^c

End points in the TPS $\geq 50\%$ stratum and TPS $\geq 1\%$ population

- Primary: PFS and OS
- Secondary: ORR, duration of response, safety

ClinicalTrials.gov - NCT01905657

Trial Profile



Baseline Characteristics

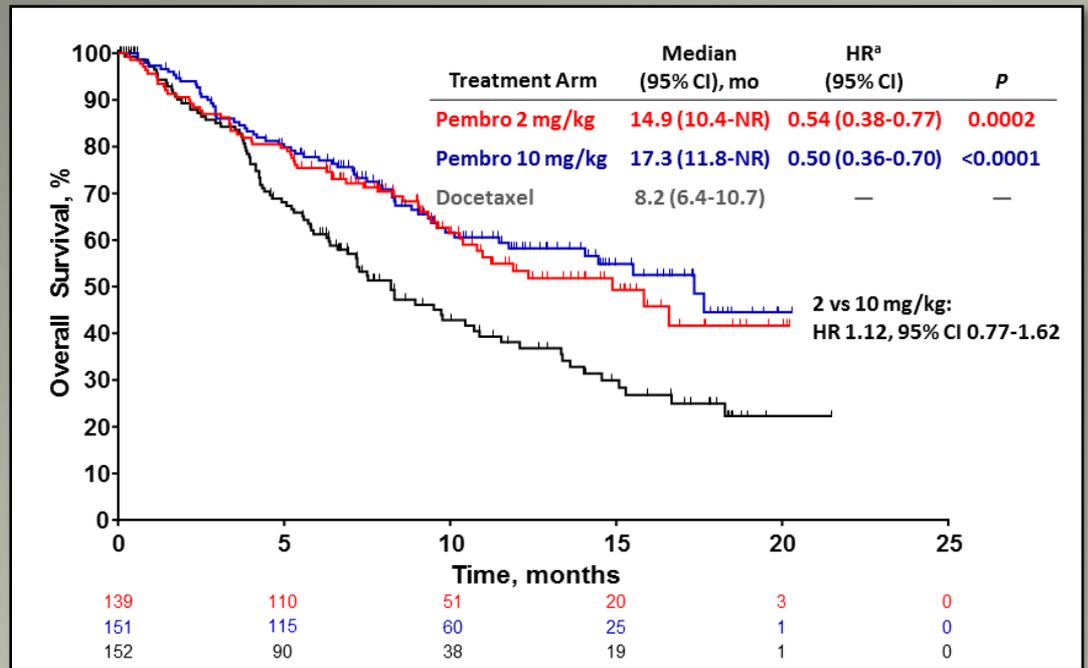
	Pembro 2 Q3W n = 344	Pembro 10 Q3W n = 346	Docetaxel n = 343
Age, median (range), years	63 (29-82)	63 (20-88)	62 (33-82)
Male, %	62	62	61
Race, %			
White	72	72	73
Asian	21	21	21
Other or unknown	7	7	6
ECOG PS, ^a %			
0	33	35	34
1	67	65	65
Smoking status, %			
Former/current	81	82	78
Never	18	17	20
Unknown	1	<1	2
PD-L1 TPS, %			
≥50%	40	44	44
1-49%	60	56	56

Baseline Characteristics cont.

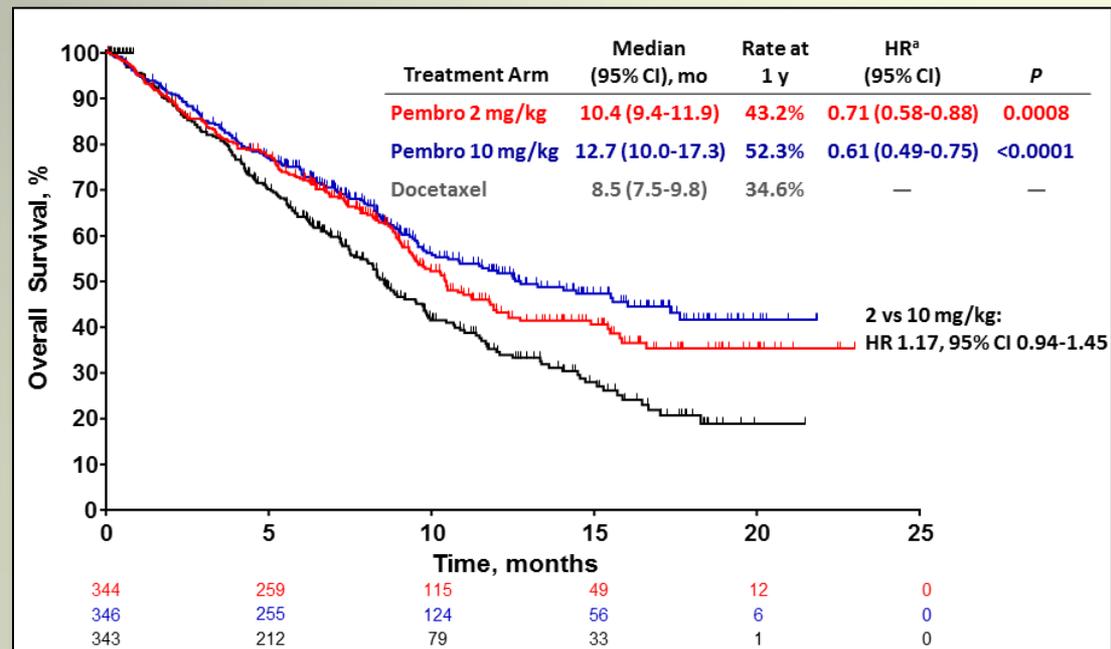
	Pembro 2 Q3W n = 344	Pembro 10 Q3W n = 346	Docetaxel n = 343
Histology, %			
Squamous	22	23	19
Nonsquamous	70	71	70
Other/unknown	8	6	11
EGFR mutant, %	8	9	8
ALK translocated, %	1	1	1
Prior therapy, %			
Adjuvant	2	2	1
Neoadjuvant	<1	<1	0
Prior lines, advanced disease			
1	71	68	69
≥2	27	20	22

Overall Survival

PD-L1 TPS $\geq 50\%$

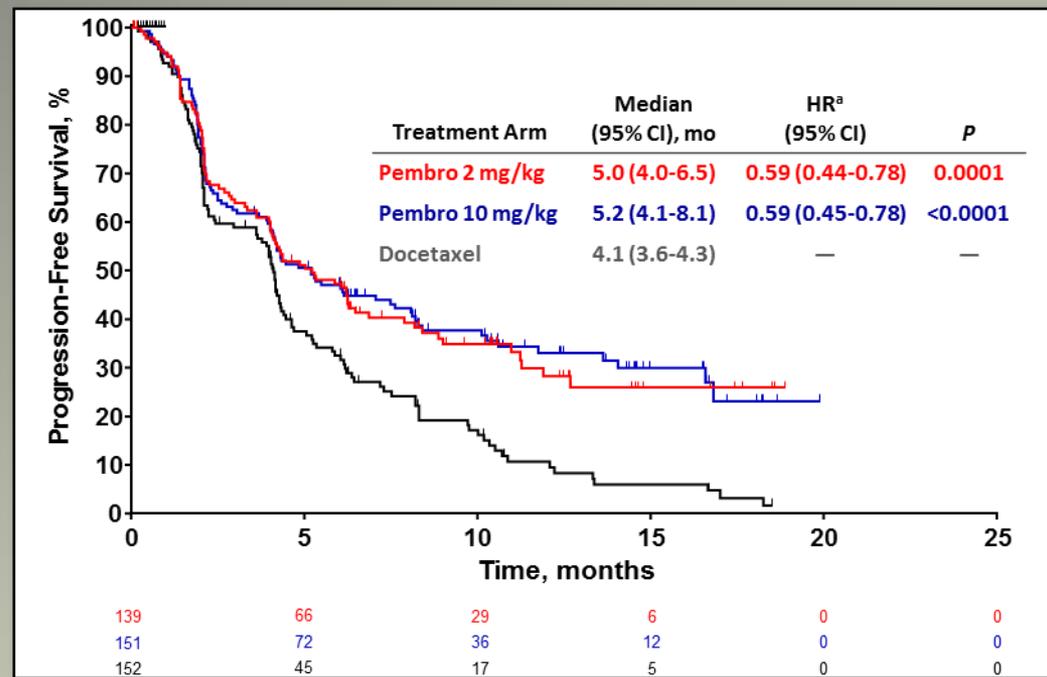


Total Population
PD-L1 TPS $\geq 1\%$

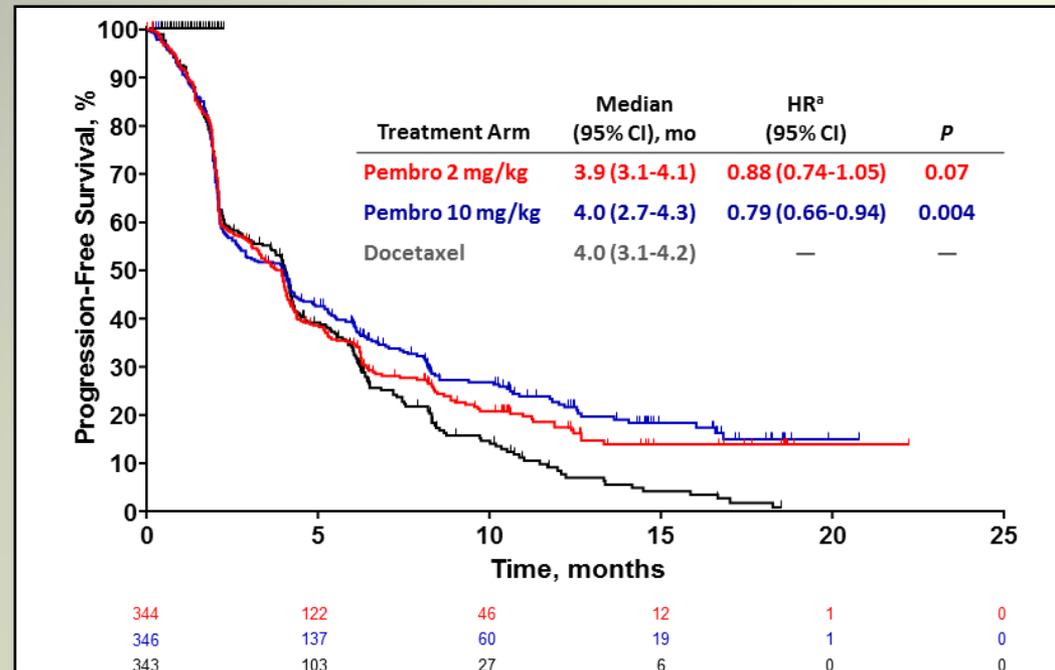


Progression Free Survival

PD-L1 TPS $\geq 50\%$



Total Population
PD-L1 TPS $\geq 1\%$



ORR (RECIST v1.1, Central Review)

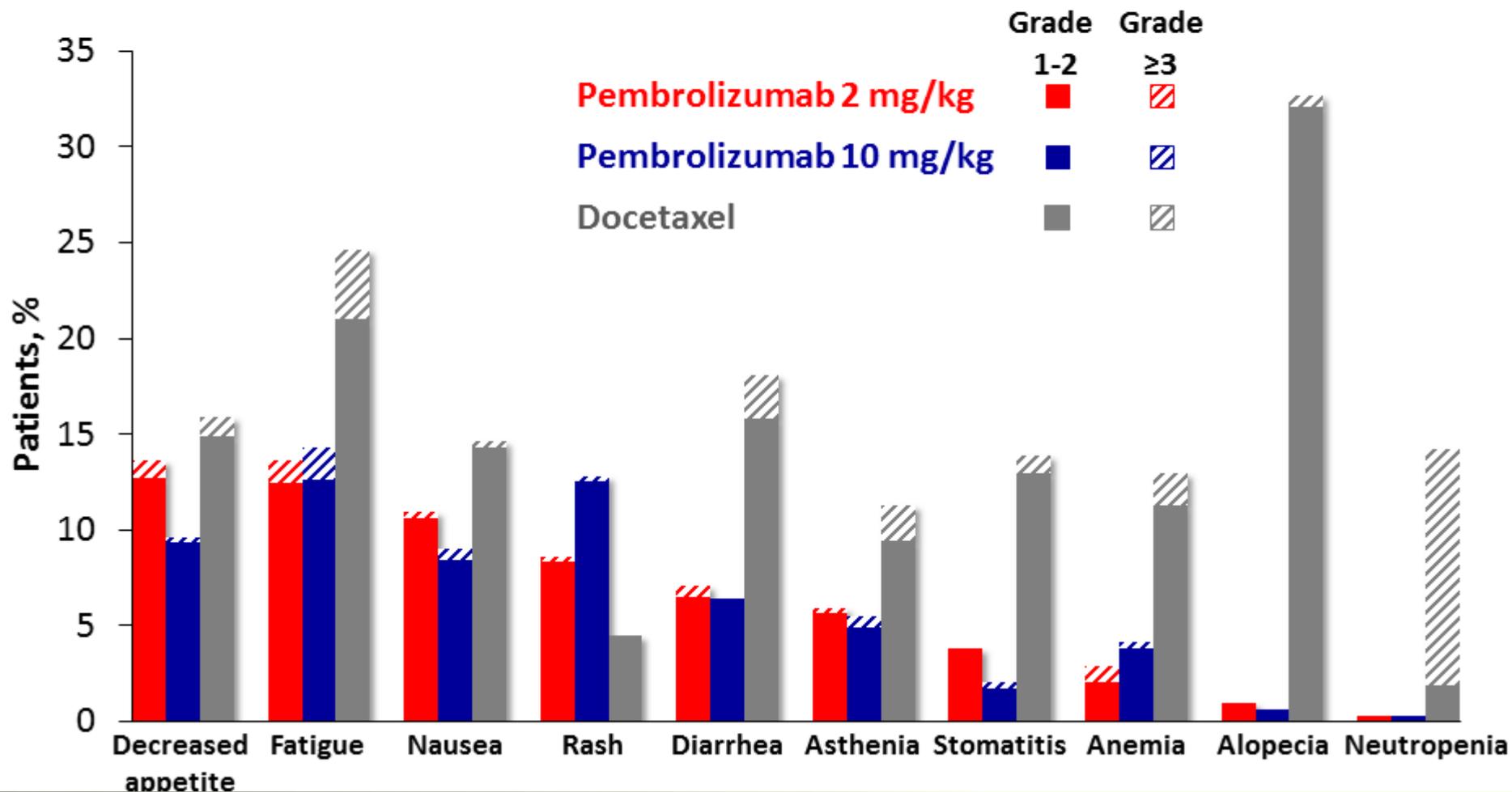
	Pembro 2 mg/kg n = 139	Pembro 10 mg/kg n = 151	Docetaxel n = 152
PD-L1 TPS ≥50%			
ORR, % (95% CI)	30 (23-39) <i>P</i> < 0.0001^a	29 (22-37) <i>P</i> < 0.0001^a	8 (4-13)

	Pembro 2 mg/kg n = 344	Pembro 10 mg/kg n = 346	Docetaxel n = 343
PD-L1 TPS ≥1%			
ORR, % (95% CI)	18 (14-22) <i>P</i> = 0.0005^a	18 (14-23) <i>P</i> = 0.0002^a	9 (6-13)

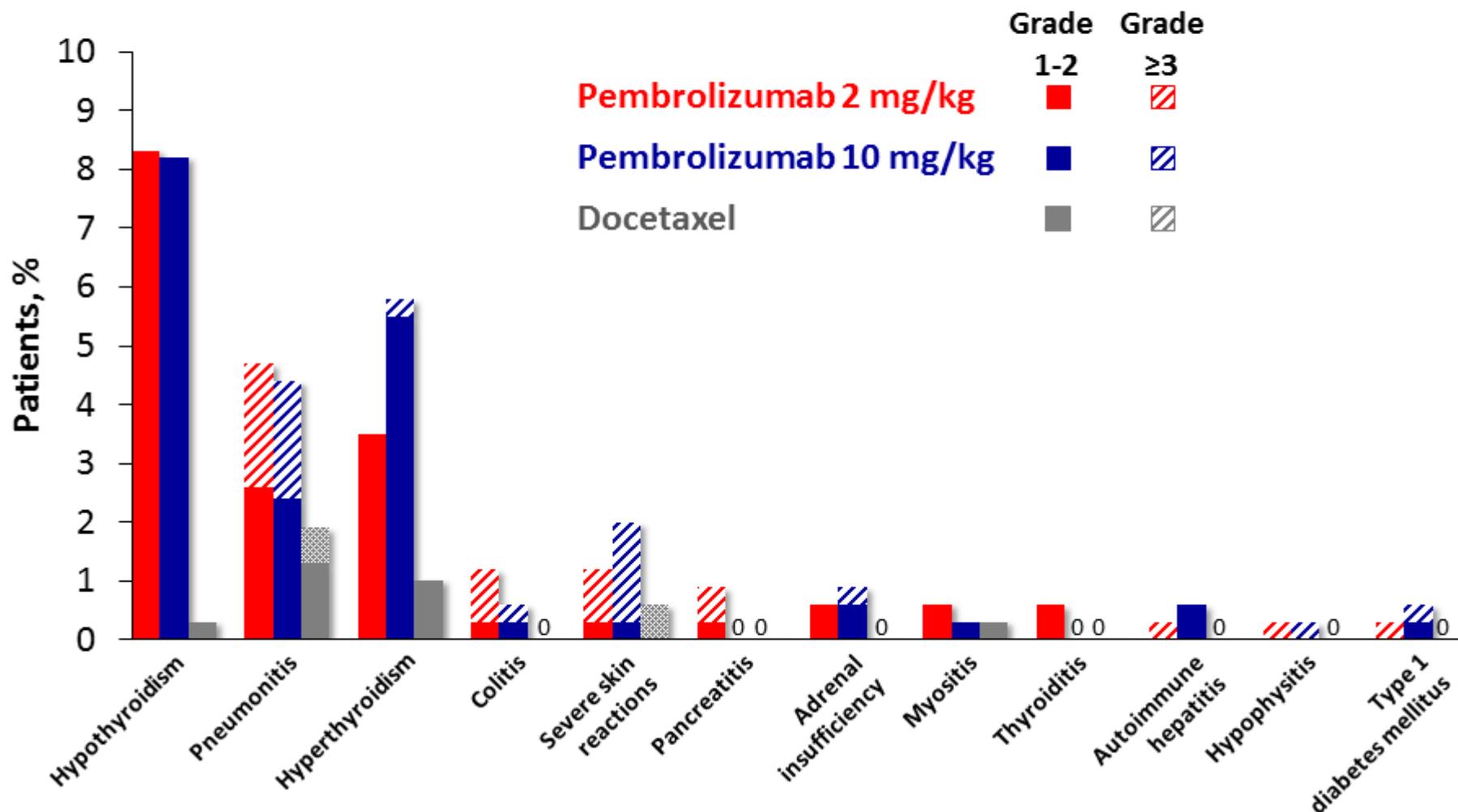
Treatment Exposure and Adverse Event Summary

	Pembro 2 Q3W n = 339	Pembro 10 Q3W n = 343	Docetaxel n = 309
Months on therapy, median (range)	3.5 (0.03-22.4)	3.5 (0.03-20.8)	2.0 (0.03-13.7)
≥1 Treatment-related AE, %			
Any grade	63	66	81
Grade 3-5	13	16	35
Led to discontinuation	4	5	10
Led to death	1 ^a	1 ^b	2 ^c

Treatment-Related AEs With Incidence $\geq 10\%$ in Any Arm, TPS $\geq 1\%$



Immune-Mediated AEs Occurring in ≥ 2 Patients in the Pembrolizumab Arms



Futur (1): Anti-PD1/ PD-L1 en monothérapie en première ligne

	Trial	Indication	Control Arm	N	Endpoint
Nivolumab	CA209-026	CBNPC, PDL1 + (≥ 1%)	Platinum-based doublet	495	PFS PD-L1 (≥ 5%)
Pembrolizumab	024	CBNPC, PD-L1++ (≥ 50%)	Platinum-based doublet	300	PFS
Pembrolizumab	042	CBNPC, PD-L1 + (≥ 1%)	Platinum-based doublet	1240	OS
MPDL3280A	GO29431	Non-squamous, PDL1++/+++	Cisplatin- pemetrexed	400	PFS
Nivolumab	 08-2015	CBNPC, PS=2 or ≥70 y	SOC	248	%1 Y OS

Futur (2): Anti-PD1/ PD-L1 en association (chimio ou anti-CTLA4)

Combinations	Trial	Indication	Control Arm	n	Endpoint
Atezolizumab +CT	GO29436	Non-squamous	Carboplatin-paclitaxel ± bevacizumab	1200	PFS PFS PD-L1+
Atezolizumab +CT	GO29437	Squamous	Carboplatin-Nab-paclitaxel	1200	PFS PFS PD-L1+
Atezolizumab +CT	GO29537	Non-squamous	Carboplatin-Nab-paclitaxel	500	PFS PFS PD-L1+
Durvalumab	MYSTIC	NSCLC, PD-L1 + or -	Platinum-based doublet	675	PFS
Durvalumab + tremelimumab	MYSTIC	NSCLC, PD-L1 + or -	Platinum-based doublet		PFS
Nivolumab	CA209-227	NSCLC, PD-L1+ (≥ 1%)	Platinum-based doublet	990	OS and PFS
Nivolumab + ipilimumab	CA209-227	NSCLC, PD-L1+ (≥ 1%)	Platinum-based doublet		OS and PFS
Nivolumab + ipilimumab	CA209-227	NSCLC, PD-L1- (< 1%)	Platinum-based doublet	990	OS and PFS
Nivolumab + Platinum doublet chemotherapy	CA209-227	NSCLC, PD-L1- (< 1%)	Platinum-based doublet		OS and PFS
Pembrolizumab +CT	189	Non Squamous (all)	Platinum- pemetrexed	570	PFS

Conclusion et encore quelques questions

- Supériorité du nivolumab et du pembrolizumab / docétaxel en 2ème ligne pour les adénocarcinomes et les carcinomes épidermoïdes
 - Standard thérapeutique de 2ème ligne pour les CBNPC épidermoïdes
 - Sélection des adénocarcinomes ?
 - Sélection des patients sur l'expression de PD-L1 ?
- L'efficacité possible pour les PDL-1 < 1% impose d'encore affiner la valeur prédictive du test, ou de développer d'autres tests plus discriminants
- L'immunothérapie en 1ère ligne se positionne soit en monothérapie soit en association (chimio ou anti-CTLA4): résultats à suivre
- Migration de ligne pour les traitements existants en seconde ligne
 - Quelle troisième ligne pour les longs répondeurs à l'immunothérapie
 - Quelles efficacité imprévue des médicaments après l'immunothérapie
 - Quelle troisième ligne pour les non répondeurs l'immunothérapie
 - Rechallenge anti PD1 , PD-L1
- Problématique du coût des traitements



Taxe Carbone

Traitements innovants

