Immunotherapies in lung cancer: regulatory perspective

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Challenges for the approval of anti-cancer immunotherapeutic drugs
EMA-CDDF joint meeting, London 4-5 February 2016

disclaimers

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EU-approved immunotherapies in NSCLC

- **nivolumab:** OPDIVO is indicated for the treatment of locally advanced or metastatic **squamous** non-small cell lung cancer (NSCLC) **after prior chemotherapy** in adults

nivolumab dossier

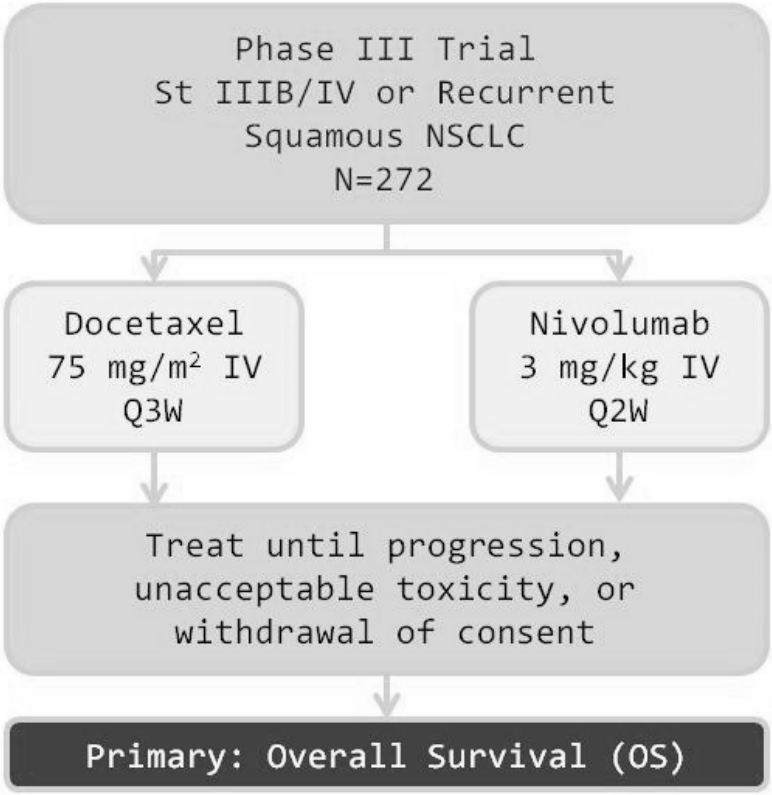
OPDIVO is indicated for the treatment of locally advanced or metastatic **squamous** non-small cell lung cancer (NSCLC) **after prior chemotherapy** in adults

- **CheckMate 017**: phase 3 RCT **nivolumab vs. docetaxel** in **squamous** NSCLC patients progressing during or after **one prior platinum doublet**-based chemotherapy

- **CheckMate 057**: phase 2 nivolumab in advanced/metastatic **squamous** NSCLC patients with ≥ 2 prior systemic regimens

CheckMate 017

Study CA209017: Phase III Study of Nivolumab vs. Docetaxel in 2nd-Line Advanced/Metastatic Squamous NSCLC



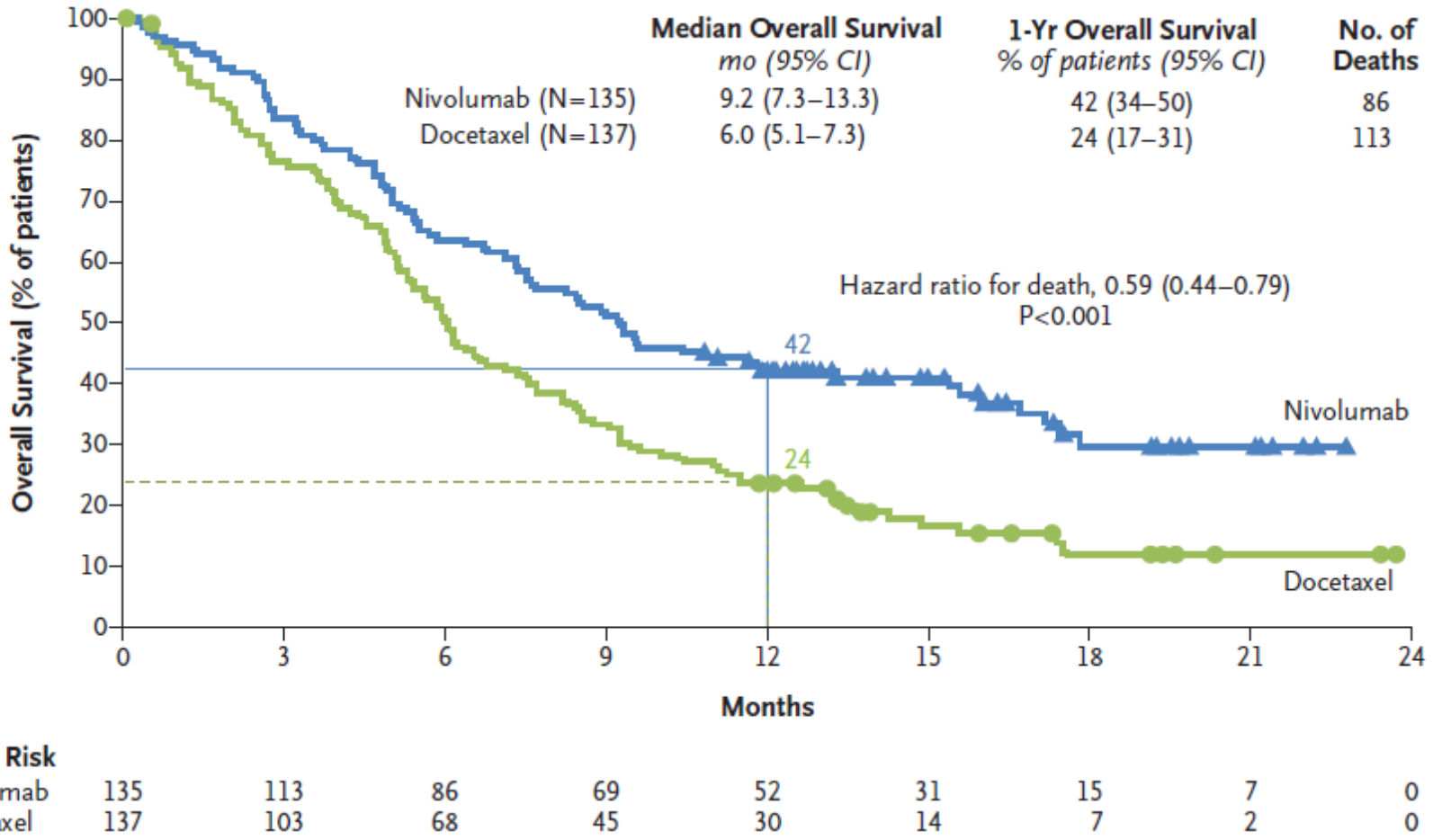
Primary Endpoint

- OS

Secondary Endpoints

- ORR
- PFS
- ORR and OS in PD-L1+ vs. PD-L1– subgroups
- Duration of and time to objective response
- Proportion of patients exhibiting disease-related symptom progression per LCSS

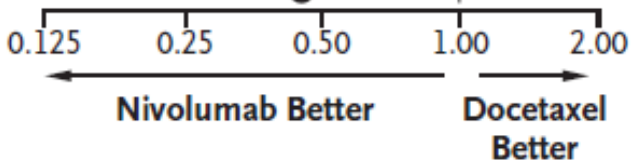
CheckMate 017 (OS)



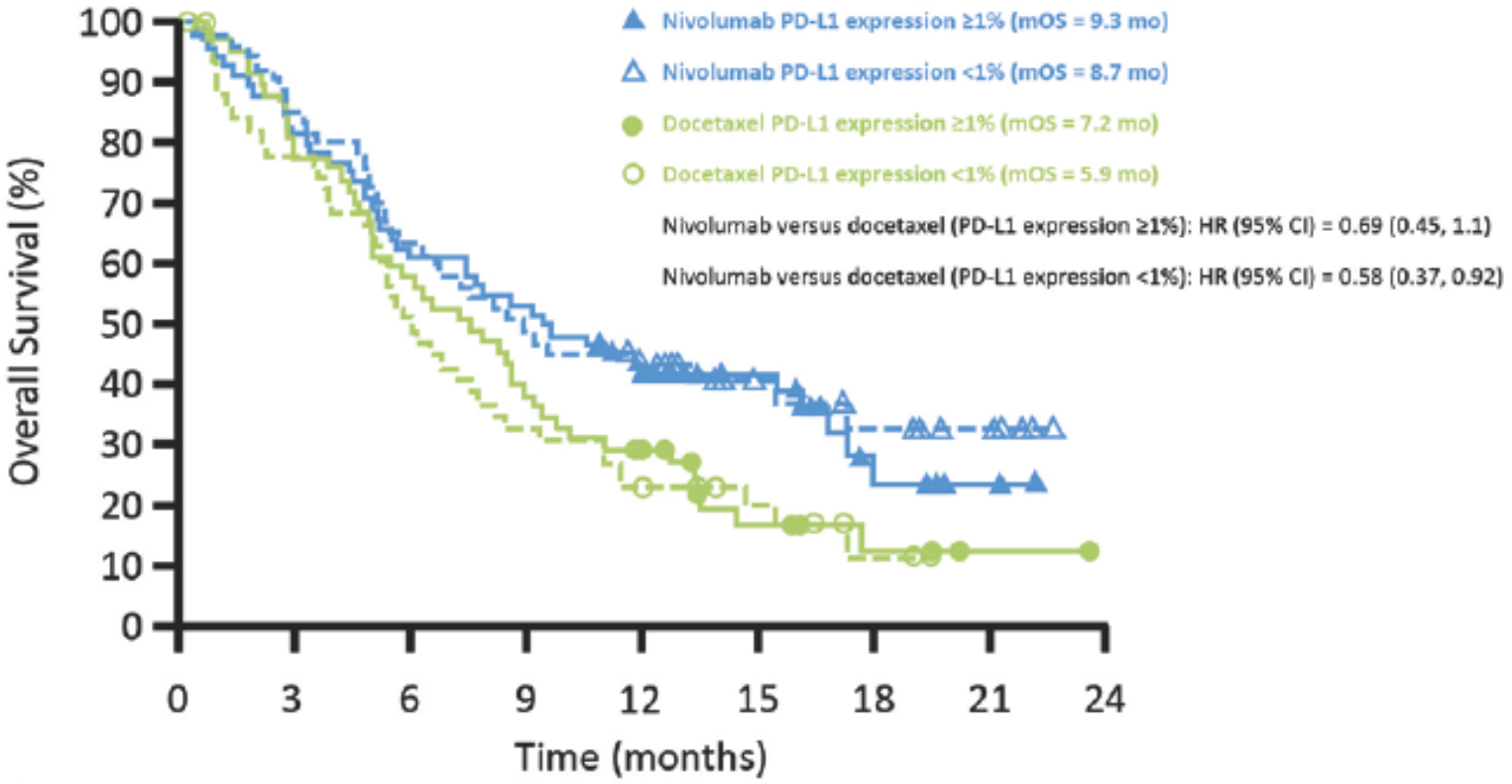
CheckMate 017 (PD-L1)

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

PD-L1 Expression Level	Nivolumab	Docetaxel	Unstratified Hazard Ratio (95% CI)
	no. of patients		
Overall survival			
≥1%	63	56	0.69 (0.45–1.05)
<1%	54	52	0.58 (0.37–0.92)
≥5%	42	39	0.53 (0.31–0.89)
<5%	75	69	0.70 (0.47–1.02)
≥10%	36	33	0.50 (0.28–0.89)
<10%	81	75	0.70 (0.48–1.01)
Not quantifiable at baseline	18	29	0.39 (0.19–0.82)
Progression-free survival			
≥1%	63	56	0.67 (0.44–1.01)
<1%	54	52	0.66 (0.43–1.00)
≥5%	42	39	0.54 (0.32–0.90)
<5%	75	69	0.75 (0.52–1.08)
≥10%	36	33	0.58 (0.33–1.02)
<10%	81	75	0.70 (0.49–0.99)
Not quantifiable at baseline	18	29	0.45 (0.23–0.89)



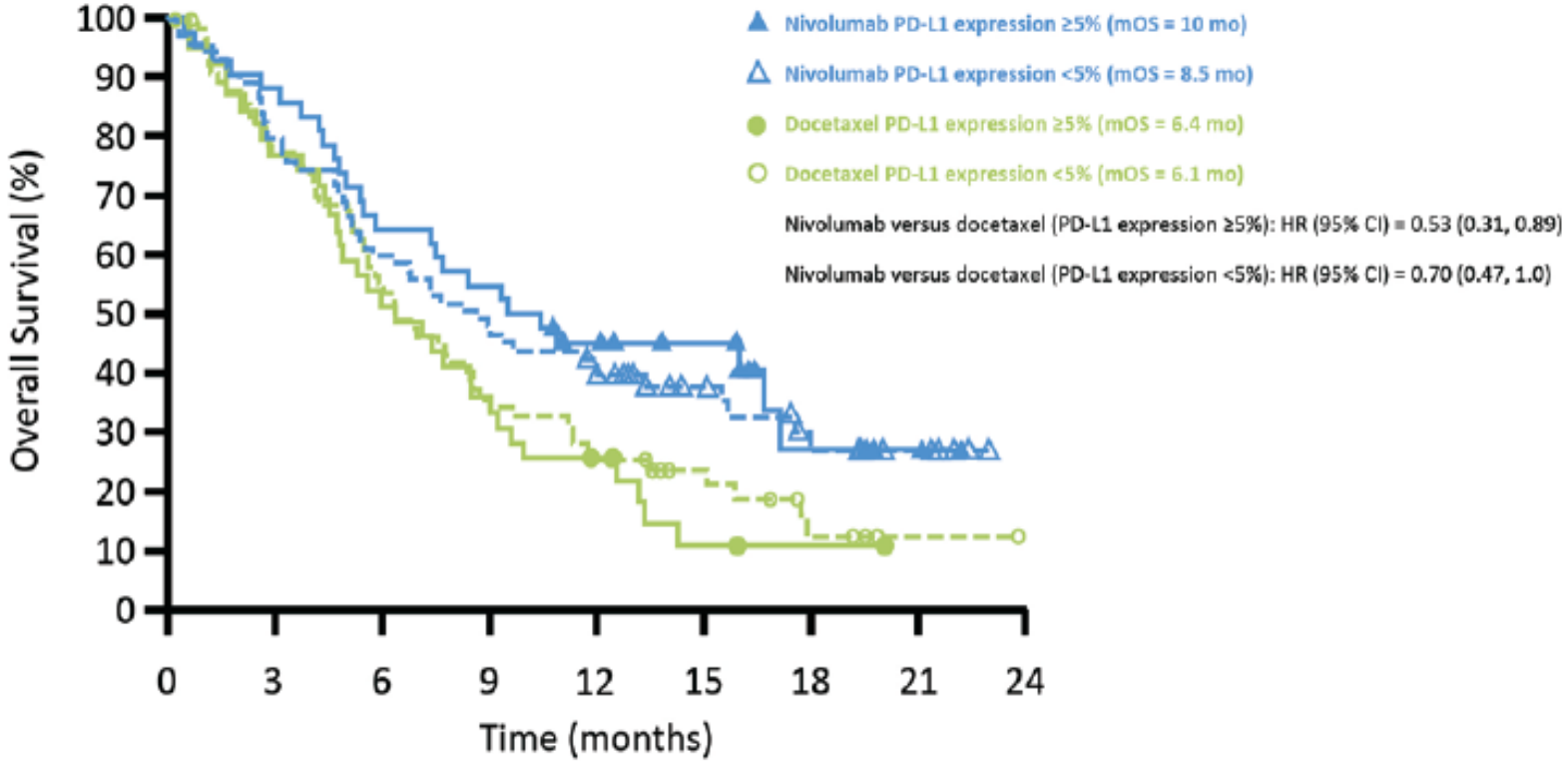
Checkmate 017 (PD-L1 1%)



Number of patients at risk

Nivolumab PD-L1 expression ≥1%	63	51	38	32	23	15	5	2	0
Nivolumab PD-L1 expression <1%	54	46	34	26	21	11	8	5	0
Docetaxel PD-L1 expression ≥1%	56	43	31	21	14	6	3	1	0
Docetaxel PD-L1 expression <1%	52	39	25	16	11	6	2	0	0

Checkmate 017 (PD-L1 5%)



Number of patients at risk

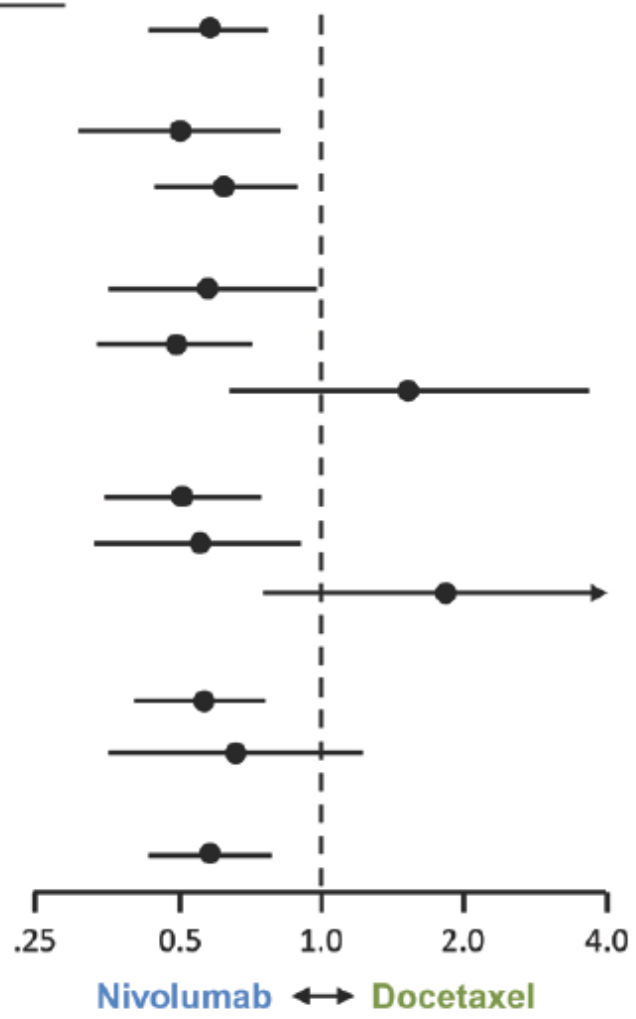
Nivolumab PD-L1 expression ≥5%	42	37	27	23	17	11	4	2	0
Nivolumab PD-L1 expression <5%	75	60	45	35	27	15	9	5	0
Docetaxel PD-L1 expression ≥5%	39	30	20	14	8	3	1	0	0
Docetaxel PD-L1 expression <5%	69	52	36	23	17	9	4	1	0

CheckMate 017 (PD-L1)

	PD-L1 expression level						
	<1%	≥1%	<5%	≥5%	<10%	≥10%	Not evaluable[a]
Nivolumab (N = 135)							
PD-L1 expression,[b] n (%)	54 (40)	63 (47)	75 (56)	42 (31)	81 (60)	36 (27)	18 (13)
Objective response rate,[c] n (%) [95% CI]	9 (17) [8, 29]	11 (17) [9, 29]	11 (15) [8, 25]	9 (21) [10, 37]	13 (16) [9, 26]	7 (19) [8, 36]	7 (39) [17, 64]
Docetaxel (N = 137)							
PD-L1 expression,[b] n (%)	52 (38)	56 (41)	69 (50)	39 (29)	75 (55)	33 (24)	29 (21)
Objective response rate,[c] n (%) [95% CI]	5 (10) [3, 21]	6 (11) [4, 22]	8 (12) [5, 22]	3 (8) [2, 21]	8 (11) [5, 20]	3 (9) [2, 24]	1 (3) [<0.1, 18]

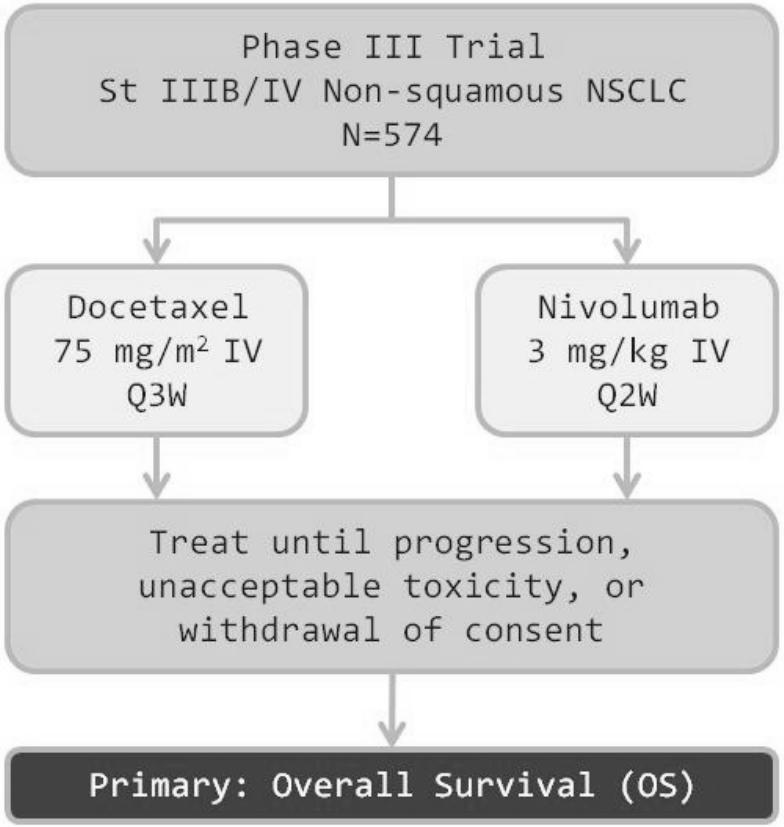
CheckMate 017 OS subgroups

	N	Unstratified HR (95% CI)
Overall	**272**	**0.59 (0.44, 0.78)**
Prior paclitaxel vs other prior treatment		
Prior paclitaxel	92	0.51 (0.31, 0.83)
Another agent	180	0.63 (0.45, 0.90)
Region		
US/Canada	86	0.59 (0.36, 0.98)
Europe	155	0.50 (0.34, 0.72)
Rest of world	31	1.53 (0.65, 3.62)
Age		
<65 years	152	0.52 (0.35, 0.75)
≥65 and <75 years	91	0.56 (0.34, 0.91)
≥75 years	29	1.85 (0.76, 4.51)
Gender		
Male	208	0.57 (0.41, 0.78)
Female	64	0.67 (0.36, 1.25)
Race		
White	252	0.59 (0.44, 0.79)



CheckMate 057

Study CA209057: Phase III Study of Nivolumab vs. Docetaxel in Advanced/Metastatic Non-Squamous Cell NSCLC



Primary Endpoint

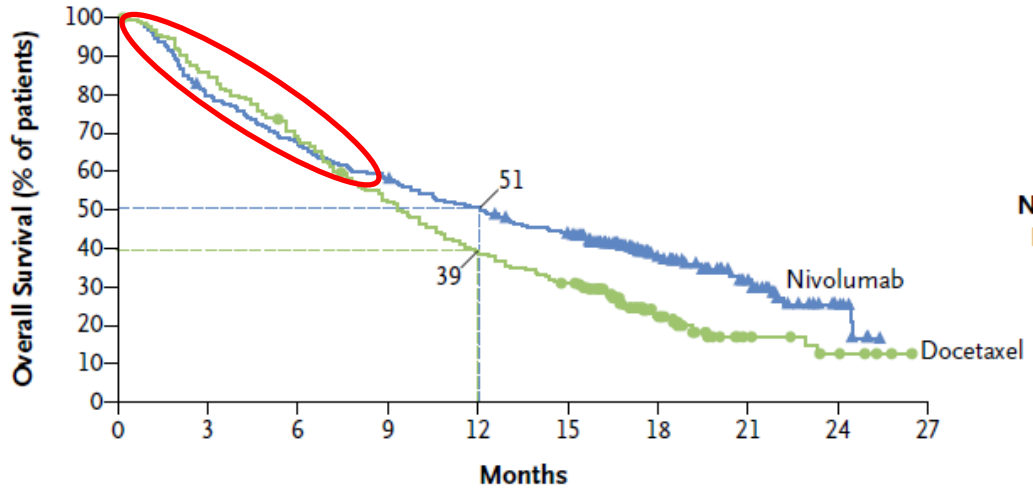
- OS

Secondary Endpoints

- ORR
- PFS
- ORR and OS in PD-L1+ vs. PD-L1– subgroups
- Proportion of patients exhibiting disease-related symptom progression per LCSS

CheckMate 057 (OS)

A Overall Survival



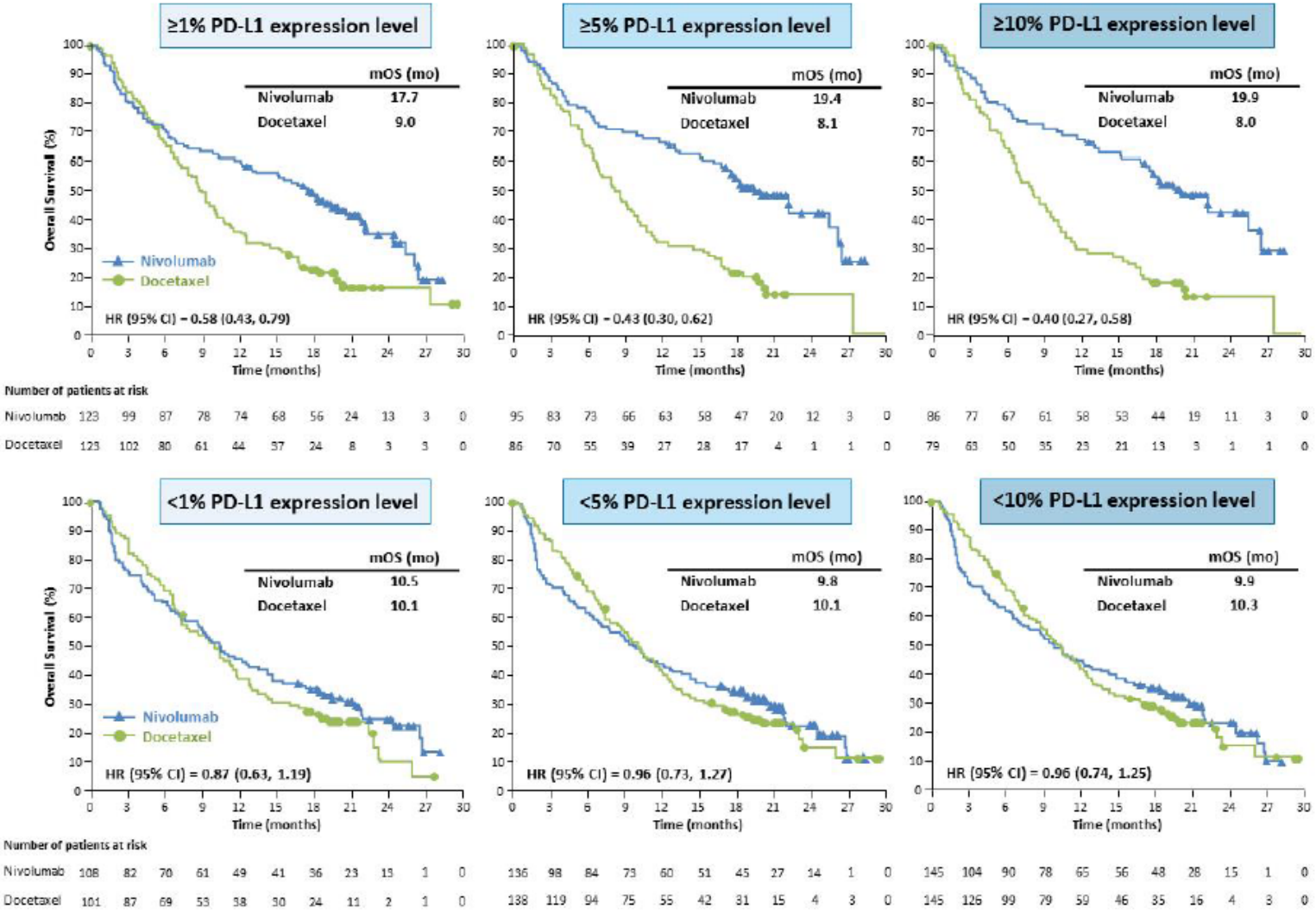
	No. of Deaths/ Total No. of Patients	Median Overall Survival (95% CI)	1-Yr Overall Survival Rate (95% CI)
		mo	%
Nivolumab	190/292	12.2 (9.7–15.0)	51 (45–56)
Docetaxel	223/290	9.4 (8.1–10.7)	39 (33–45)

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

No. at Risk

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

CheckMate 057 (OS PD-L1)

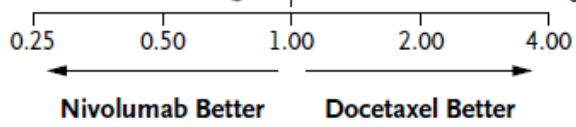


CheckMate 057 (ORR PD-L1)

	PD-L1 Expression Level						Not quantifiable[b]
	1%[a]		5%[a]		10%[a]		
	<1%	≥1%	<5%	≥5%	<10%	≥10%	
Nivolumab							
n (%)	108 (47)	123 (53)	136 (59)	95 (41)	145 (63)	86 (37)	61 (21)
Objective response rate,[c] n (%) [95% CI]	10 (9) [5, 16]	38 (31) [23, 40]	14 (10) [6, 17]	34 (36) [26, 46]	16 (11) [6, 17]	32 (37) [27, 48]	8 (13) [6, 24]
Median DOR, mos (95% CI) n	18.3 (4.2, NE) 10	16.0 (8.4, NE) 38	18.3 (5.5, NE) 14	16.0 (8.4, NE) 34	18.3 (7.5, NE) 16	16.0 (6.9, NE) 32	7.3 (2.2, NE) 8
Docetaxel							
n (%)	101 (45)	123 (55)	138 (62)	86 (38)	145 (65)	79 (35)	66 (23)
Objective response rate,[c] n (%) [95% CI]	15 (15) [9, 23]	15 (12) [7, 19]	19 (14) [9, 21]	11 (13) [7, 22]	20 (14) [9, 21]	10 (13) [6, 22]	6 (9) [3, 19]
Median DOR, mos (95% CI) n	5.6 (4.2, 9.9) 15	5.6 (3.0, 5.7) 15	5.6 (4.2, 7.1) 19	5.6 (3.0, 7.0) 11	5.6 (4.2, 7.1) 20	5.6 (1.6, 6.2) 10	6.6 (2.8, 14.2) 6
Odds ratio[d] (95% CI)	0.6 (0.2, 1.5)	3.2 (1.6, 6.7)	0.7 (0.3, 1.6)	3.8 (1.7, 9.0)	0.8 (0.4, 1.7)	4.1 (1.8, 10.1)	1.5 (0.4, 5.6)

CheckMate 057 OS subgroups

Subgroup	No. of Patients	Unstratified Hazard Ratio (95% CI)
Overall	582	0.75 (0.62–0.91)
Previous use of maintenance therapy		
Yes	233	0.80 (0.58–1.10)
No	349	0.73 (0.57–0.93)
Line of therapy		
Second line	515	0.69 (0.56–0.85)
Third line	66	1.34 (0.73–2.43)
Age		
<65 yr	339	0.81 (0.62–1.04)
≥65 to <75 yr	200	0.63 (0.45–0.89)
≥75 yr	43	0.90 (0.43–1.87)
Sex		
Male	319	0.73 (0.56–0.96)
Female	263	0.78 (0.58–1.04)
ECOG performance-status score		
0	179	0.64 (0.44–0.93)
1	402	0.80 (0.63–1.00)
Smoking status		
Current or former smoker	458	0.70 (0.56–0.86)
Never smoked	118	1.02 (0.64–1.61)
EGFR mutation status		
Positive	82	1.18 (0.69–2.00)
Not detected	340	0.66 (0.51–0.86)
Not reported	160	0.74 (0.51–1.06)
KRAS mutation status		
Positive	62	0.52 (0.29–0.95)
Not detected	123	0.98 (0.66–1.48)
Not reported	397	0.74 (0.58–0.94)



CheckMate 057 uncertainties

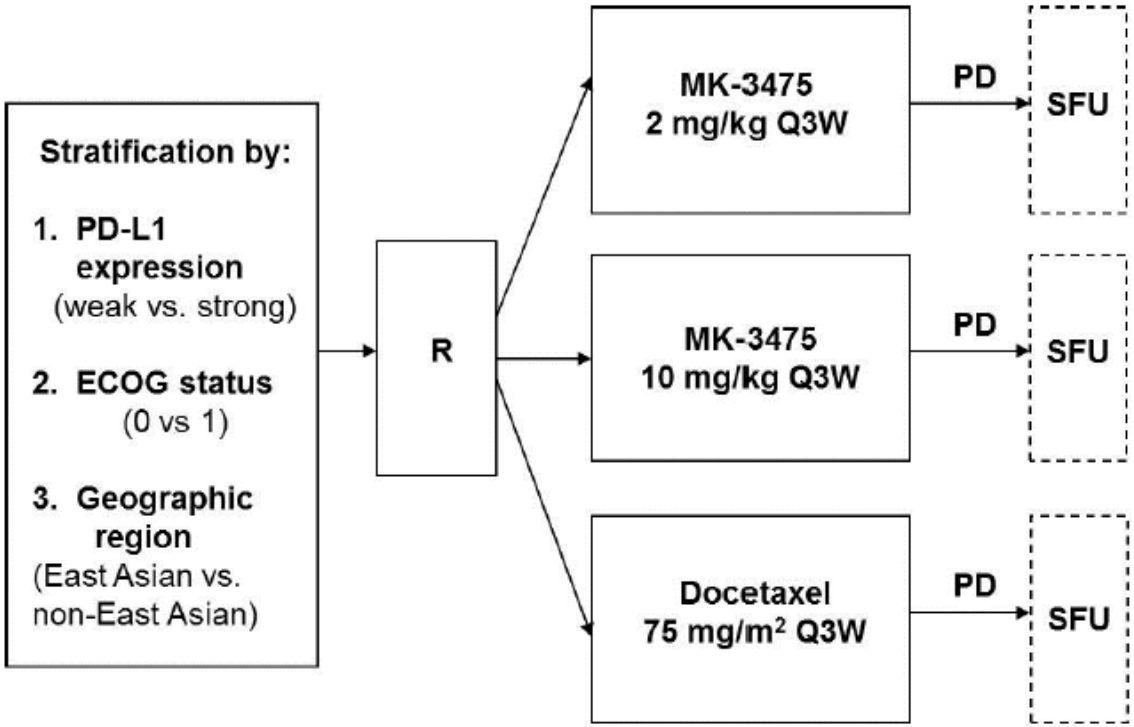
- >ORR and longer survival for PD-L1+
- EGFRm?
- lack of benefit vs. docetaxel in PD-L1 low
- > deaths with nivolumab in first 6 months

WHY?

- onset of mechanism of action?
- imbalances in prognostic factors?
- PD-L1 expression?

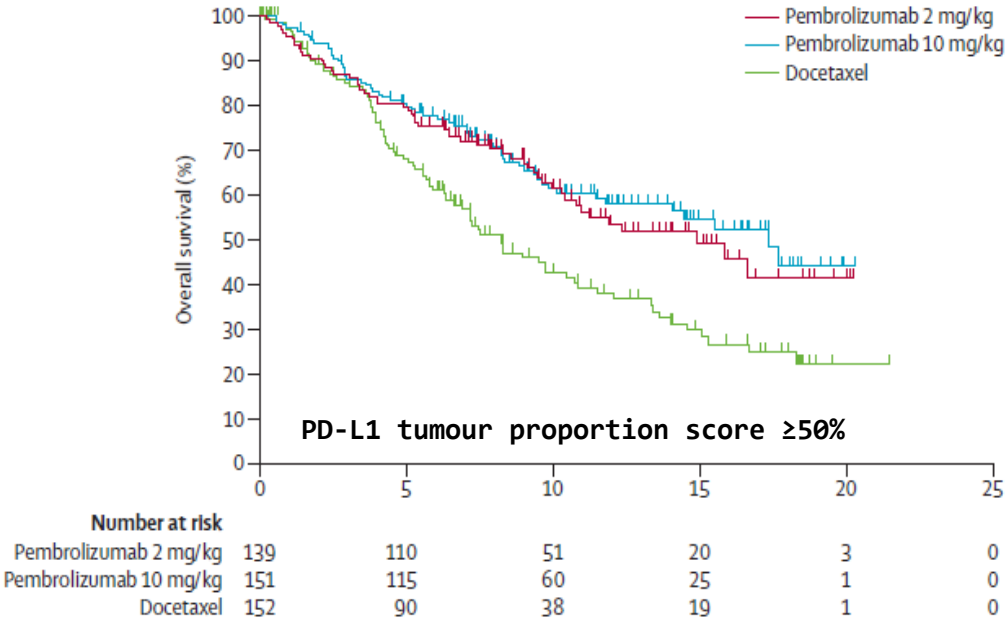
pembrolizumab dossier

- **KEYNOTE 010**: phase 2/3 RCT **pembrolizumab vs. docetaxel** for **previously treated, PD-L1-positive,** advanced NSCLC

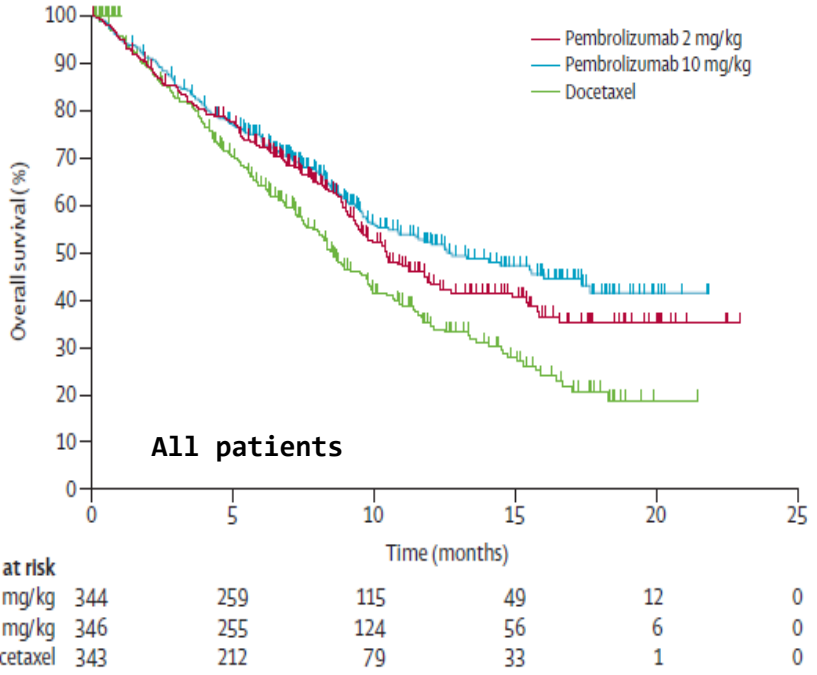


OS & PFS primary endpoints

KEYNOTE 010 (OS)



2 mg/kg HR 0.54 (95% CI 0.38–0.77)
10 mg/kg HR 0.50 (95% CI 0.36–0.70)

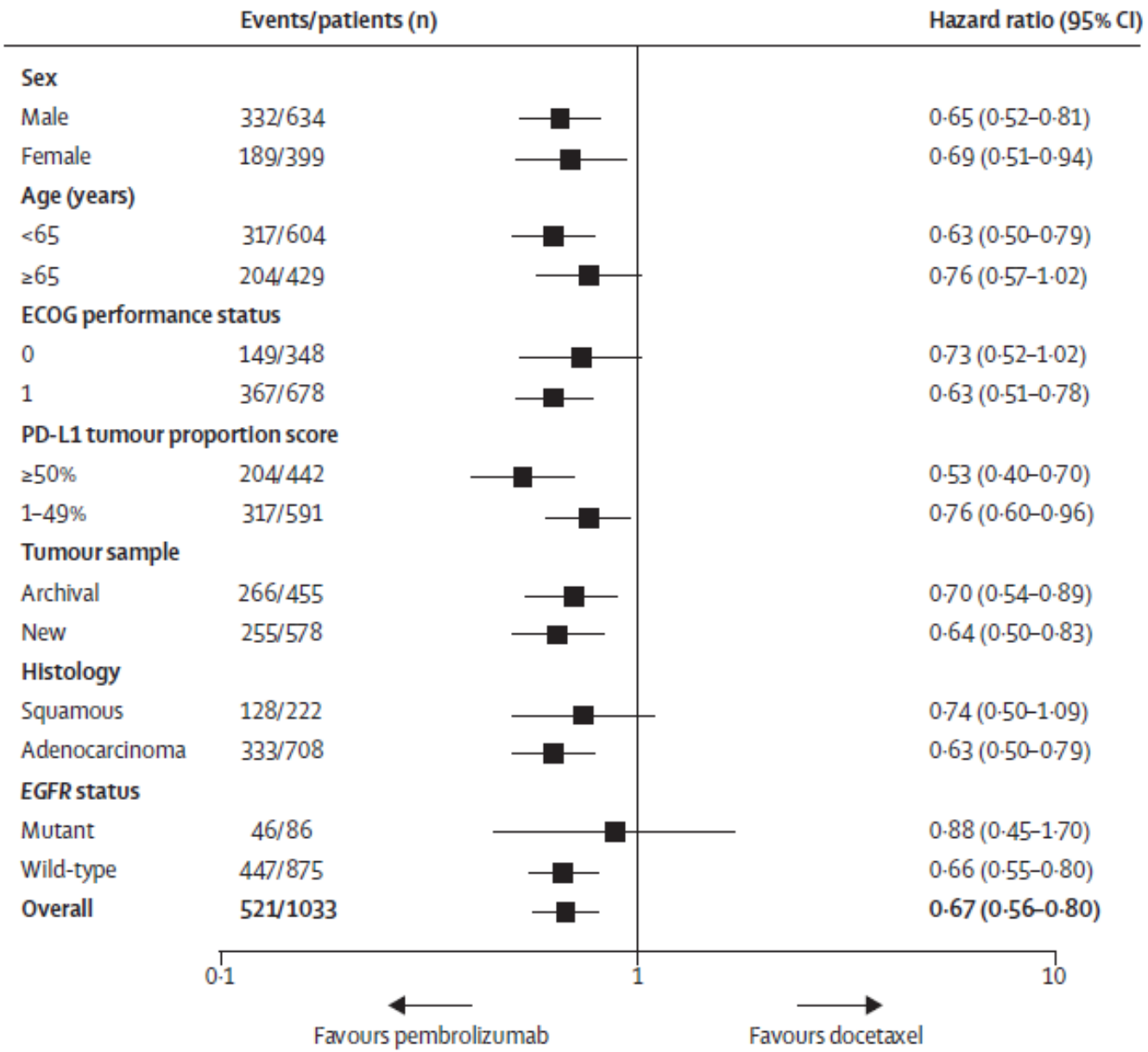


2 mg/kg HR 0.71 (95% CI 0.58–0.88)
10 mg/kg HR 0.61 (95% CI 0.49–0.75)

KEYNOTE 010 (ORR PD-L1)

	Tumour Proportion Score ≥50% Stratum			Total Population		
	Pembrolizumab 2 mg/kg n=139	Pembrolizumab 10 mg/kg n=151	Docetaxel n=152	Pembrolizumab 2 mg/kg n=344	Pembrolizumab 10 mg/kg n=346	Docetaxel n=343
Overall response rate						
No. of responses	42	44	12	62	64	32
% (95% CI)	30·2 (22·7-38·6)	29·1 (22·0-37·1)	7·9 (4·1-13·4)	18·0 (14·1-22·5)	18·5 (14·5-23·0)	9·3 (6·5-12·9)
Estimated difference *vs* docetaxel,* % (95% CI)	23·3 (14·8-32·1)	22·2 (14·0-30·7)	—	8·7 (3·6-13·9)	9·1 (4·1-14·3)	—
One-sided p value†	<0·0001	<0·0001	—	0·0005	0·0002	—
Median time to response (IQR),‡ weeks	9 (9-17)	9 (9-13)	9 (9-18)	9 (9-18)	9 (9-17)	9 (9-18)
Median duration of response (IQR),‡ months	Not reached (4·2-10·4)	Not reached (4·4-12·6)	8 (2·6-8·3)	Not reached (4·2-10·5)	Not reached (4·2-12·5)	6 (2·7-6·1)
Patients without progression,‡ n (%)	37 (88·1)	35 (79·5)	7 (58·3)	50 (80·6)	48 (75·0)	19 (59·4)

KEYNOTE 010 subgroups OS

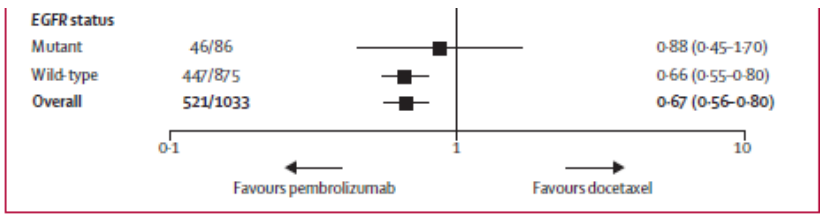


KEYNOTE 010 uncertainties

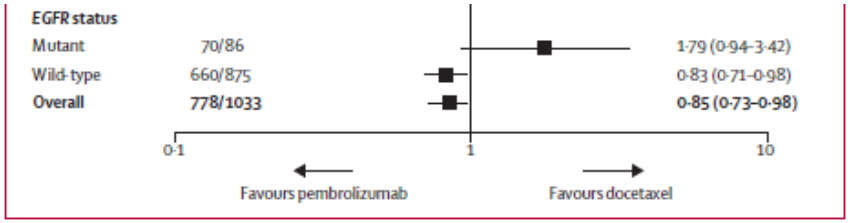
- longer survival for PD-L1 ≥50%
- > ORR for PD-L1 ≥50%

- efficacy results for PD-L1 low expression?

- EGFRm?
- histology?



OS



PFS

Thank you!

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