Post ESMO / WCLC 2017: Immunotherapie

ESMO: Madrid 8 – 12 sept
WCLC: Yokohama, 15 – 18 oktober

Ben van den Borne

Gedreven door het leven.

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Inhoud presentatie:

- Situatie voor ESMO / WCLC (2e en 1e lijn stadium IV)
- Advies NVALT t.a.v. inzetten immunotherapie (mei 2017)
- Nieuws ESMO / WCLC
  - 1e lijn stadium IV
  - 2E lijn stadium IV
  - Stadium III
  - (O.h.a.) beperkt tot gerandomiseerde studies
- Huidige / toekomstige situatie

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Wat was de situatie voor ESMO / WCLC?

Wat was de situatie voor ESMO / WCLC?

2e lijn stadium IV

Checkmate 017

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

Julie Brahmer, M.D., Karen L. Reckamp, M.D., Paul Baas, M.D., Lucio Crinò, M.D., Wilfried E.E. Eberhardt, M.D., Elena Poddubskaya, M.D., Scott Antonia, M.D., Ph.D., Adam Pluzanski, M.D., Ph.D., Everett E. Vokes, M.D., Esther Holgado, M.D., Ph.D., David Waterhouse, M.D., Neal Ready, M.D., Justin Gainor, M.D., Osvaldo Arén Frontera, M.D., Libor Havel, M.D., Martin Steins, M.D., Marina C. Garassino, M.D., Joachim G. Aerts, M.D., Manuel Domine, M.D., Luis Paz-Ares, M.D., Martin Reck, M.D., Christine Baudelet, Ph.D., Christopher T. Harbison, Ph.D., Brian Lestini, M.D., Ph.D., and David R. Spigel, M.D.

N ENGL J MED 373;2 NEJM.ORG JULY 9, 2015

- Gerandomiseerde open label, fase III studie
- Stadium IIIB/IV plaveiselcelcarcinoom, progressie na 1e lijn
- ECOG 0-1
- 2 armen (1:1 randomisatie): nivo 3 mg/kg q2w, docetaxel 75 mg/m2 q3w
- Primaire uitkomst: OS
- PD-L1 expressie werd retrospectief geëvalueerd

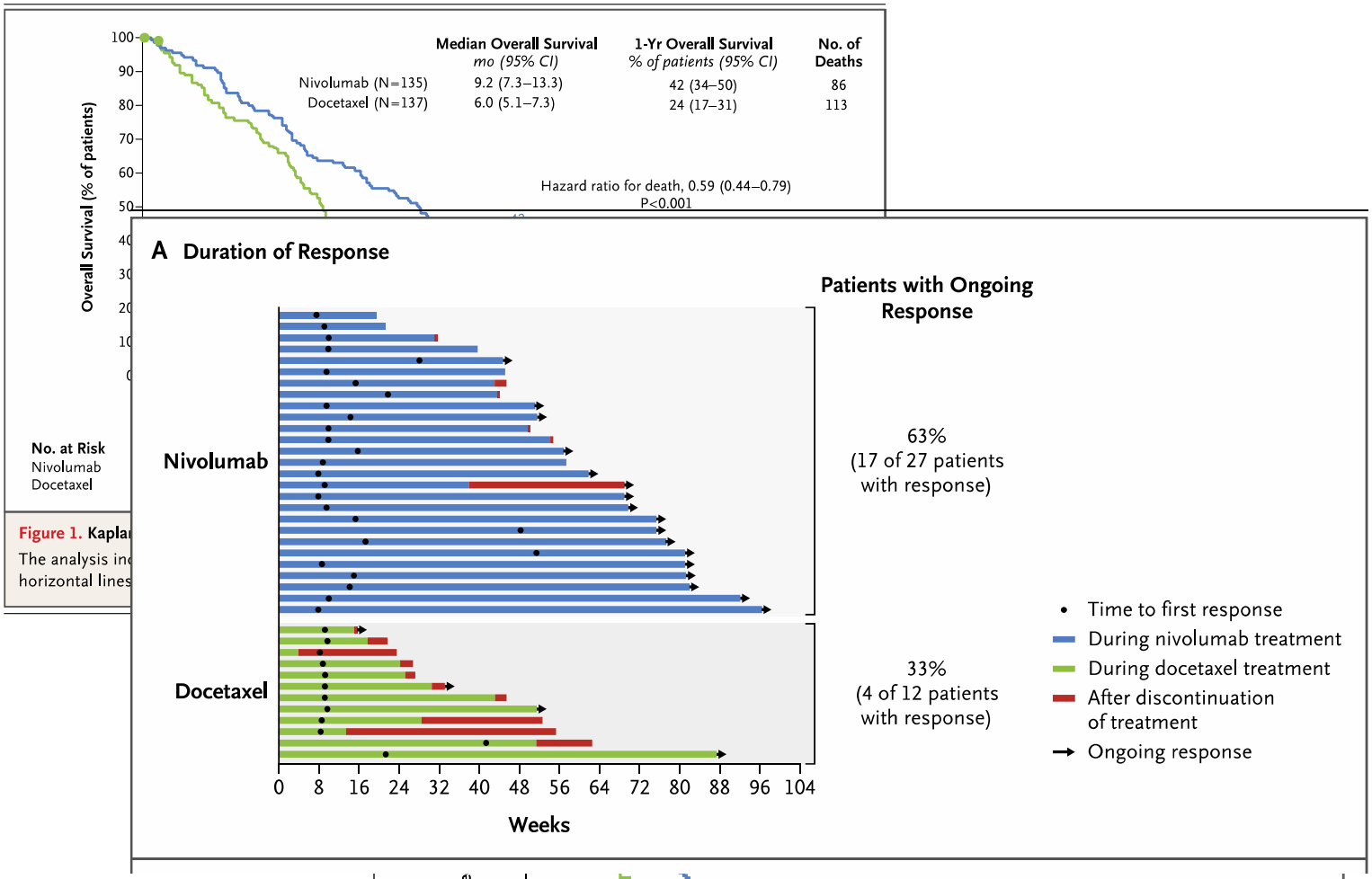
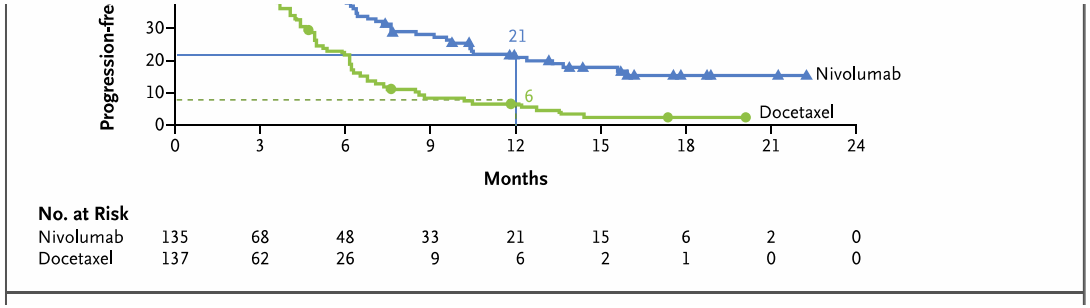
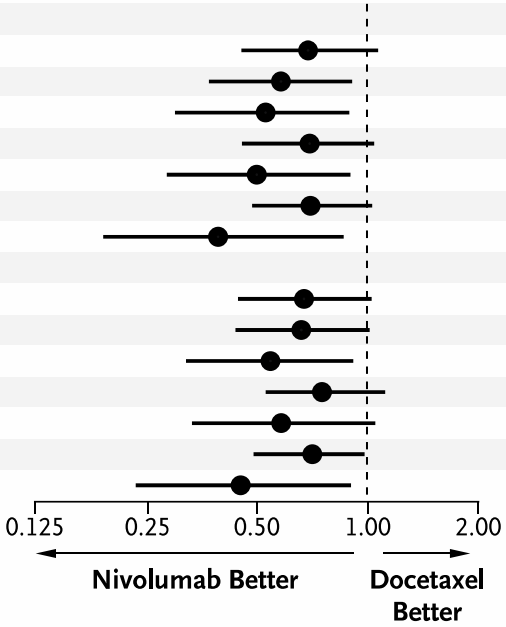


Figure 1. Kaplan
The analysis in
horizontal lines



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 057

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer

H. Borghaei, L. Paz-Ares, L. Horn, D.R. Spigel, M. Steins, N.E. Ready, L.Q. Chow, E.E. Vokes, E. Felip, E. Holgado, F. Barlesi, M. Kohlhäufl, O. Arrieta, M.A. Burgio, J. Fayette, H. Lena, E. Poddubskaya, D.E. Gerber, S.N. Gettinger, C.M. Rudin, N. Rizvi, L. Crinò, G.R. Blumenschein, Jr., S.J. Antonia, C. Dorange, C.T. Harbison, F. Graf Finckenstein, and J.R. Brahmer

This article was published on September 27, 2015, at NEJM.org.

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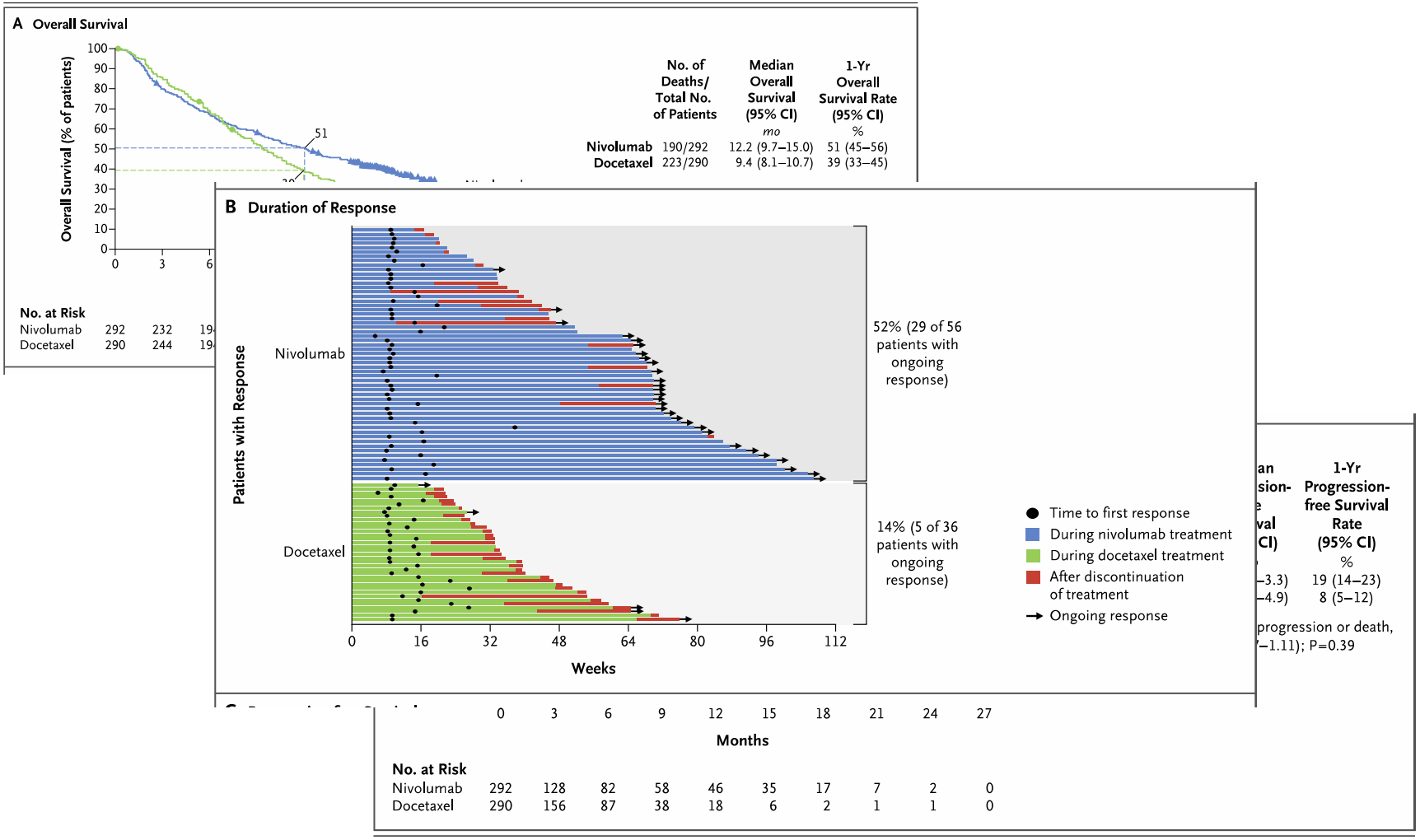
- Gerandomiserde open label, fase III studie
- Stadium IIIB/IV niet-plaveiselcelcarcinoom, progressie na 1e lijn
- ECOG 0-1
- 2 armen (1:1 randomisatie): nivo 3 mg/kg q2w, docetaxel 75 mg/m2 q3w
- Primaire uitkomst: OS
- PD-L1 expressie werd retrospectief geëvalueerd


A Overall Survival
Overall Survival (% of patients)
100
90
80
70
60
50
40
30
20
10
0
51
0
3
No. at Risk
Nivolumab 292 232
Docetaxel 290 244
No. of Deaths/ Total No. of Patients
Median Overall Survival (95% CI)
mo
1-Yr Overall Survival Rate (95% CI)
%
Nivolumab 190/292 12.2 (9.7–15.0) 51 (45–56)
Docetaxel 223/290 9.4 (8.1–10.7) 39 (33–45)
B Duration of Response
Patients with Response
Nivolumab
Docetaxel
52% (29 of 56 patients with ongoing response)
14% (5 of 36 patients with ongoing response)
0
16
32
48
64
80
96
112
Weeks
Time to first response
During nivolumab treatment
During docetaxel treatment
After discontinuation of treatment
Ongoing response
1-Yr Progression-free Survival Rate (95% CI)
%
19 (14–23)
8 (5–12)
progression or death,
P=0.39
0 3 6 9 12 15 18 21 24 27
Months
No. at Risk
Nivolumab 292 128 82 58 46 35 17 7 2 0
Docetaxel 290 156 87 38 18 6 2 1 1 0

Keynote 010

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

www.thelancet.com **Vol 387 April 9, 2016**

- Open label, fase II / III studie
- Stadium IV, zowel plaveiselcel als niet-plaveiselcelcarcinoom, progressie na 1e lijn
- ECOG 0-1
- PD-L1 expressie ≥ 1%
- 3 armen (1:1:1 randomisatie): pembro 2 mg/kg q3w, pembro 10 mg/kg q3w, docetaxel 75 mg/m2 q3w
- Primaire uitkomst: OS en PFS in zowel gehele populatie als in populatie met PD-L1 expressie > 50%

	All patients			Patients with tumour proportion score ≥50%		
	Pembrolizumab 2 mg/kg (n=344)	Pembrolizumab 10 mg/kg (n=346)	Docetaxel (n=343)	Pembrolizumab 2 mg/kg (n=139)	Pembrolizumab 10 mg/kg (n=151)	Docetaxel (n=152)
Age (years)	63·0 (56·0–69·0)	63·0 (56·0–69·0)	62·0 (56·0–69·0)	62·0 (56·0–69·0)	64·0 (58·0–70·0)	60·0 (54·0–69·5)
Men	212 (62%)	213 (62%)	209 (61%)	81 (58%)	89 (59%)	93 (61%)
Race						
White	246 (72%)	250 (72%)	251 (73%)	102 (73%)	111 (74%)	117 (77%)
Asian	73 (21%)	72 (21%)	72 (21%)	27 (19%)	28 (19%)	29 (19%)
Black or African American	13 (4%)	8 (2%)	7 (2%)	5 (4%)	5 (3%)	1 (1%)
Other	5 (1%)	5 (1%)	2 (1%)	2 (1%)	0 (0%)	1 (1%)
Unknown	7 (2%)	11 (3%)	11 (3%)	3 (2%)	7 (5%)	4 (3%)
Region						
East Asia	64 (19%)	64 (18%)	62 (18%)	21 (15%)	25 (17%)	26 (17%)
Not east Asia	280 (81%)	282 (82%)	281 (82%)	118 (85%)	126 (83%)	126 (83%)
ECOG performance status*						
0	112 (33%)	120 (35%)	116 (34%)	47 (34%)	47 (31%)	49 (32%)
1	229 (67%)	225 (65%)	224 (65%)	91 (65%)	104 (69%)	102 (67%)
2	3 (1%)	1 (<1%)	1 (<1%)	1 (1%)	0 (0%)	1 (1%)
3	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Unknown	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Histology						
Squamous	76 (22%)	80 (23%)	66 (19%)	29 (21%)	41 (27%)	26 (17%)
Non-squamous	240 (70%)	244 (71%)	240 (70%)	95 (68%)	98 (65%)	111 (73%)
Other	9 (3%)	6 (2%)	10 (3%)	4 (3%)	5 (3%)	5 (3%)
Unknown	19 (6%)	16 (5%)	27 (8%)	11 (8%)	7 (5%)	10 (7%)
PD-L1 TPS						
≥50%	139 (40%)	151 (44%)	152 (44%)	139 (100%)	151 (100%)	152 (100%)
1–49%	205 (60%)	195 (56%)	191 (56%)	0 (0%)	0 (0%)	0 (0%)
Smoking status						
Former or current	279 (81%)	285 (82%)	269 (78%)	112 (81%)	122 (81%)	113 (74%)
Never	63 (18%)	60 (17%)	67 (20%)	26 (19%)	29 (19%)	34 (22%)
Unknown	2 (1%)	1 (<1%)	7 (2%)	1 (1%)	0 (0%)	5 (3%)
Stable brain metastases	56 (16%)	48 (14%)	48 (14%)	32 (23%)	23 (15%)	23 (15%)
EGFR status						
Wild-type	293 (85%)	288 (83%)	294 (86%)	119 (86%)	127 (84%)	131 (86%)
Mutant	28 (8%)	32 (9%)	26 (8%)	8 (6%)	13 (9%)	12 (8%)
Unknown	23 (7%)	26 (8%)	23 (7%)	12 (9%)	11 (7%)	9 (6%)
ALK translocation						
No	307 (89%)	305 (88%)	310 (90%)	120 (86%)	131 (87%)	137 (90%)
Yes	2 (1%)	4 (1%)	2 (1%)	2 (1%)	2 (1%)	1 (1%)
Unknown	35 (10%)	37 (11%)	31 (9%)	17 (12%)	18 (12%)	14 (9%)
Previous systemic therapies						
Adjuvant	6 (2%)	7 (2%)	3 (1%)	2 (1%)	4 (3%)	3 (2%)
Neo-adjuvant	1 (<1%)	1 (<1%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)

(Table 1 continues on next page)

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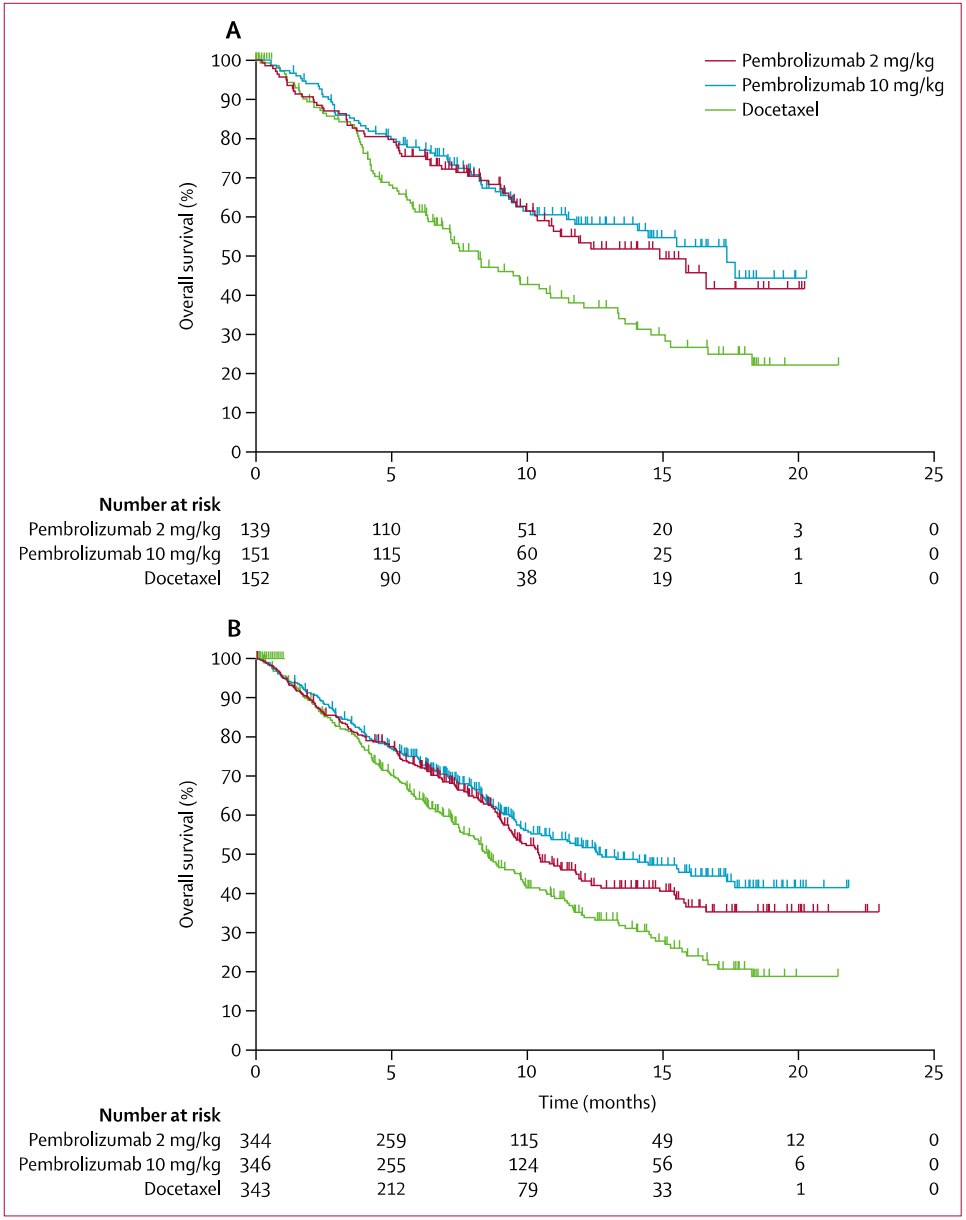

Figure 2: **Kaplan-Meier analysis of overall survival**
(A) For patients with a PD-L1 tumour proportion score of 50% or greater. (B) For all patients.

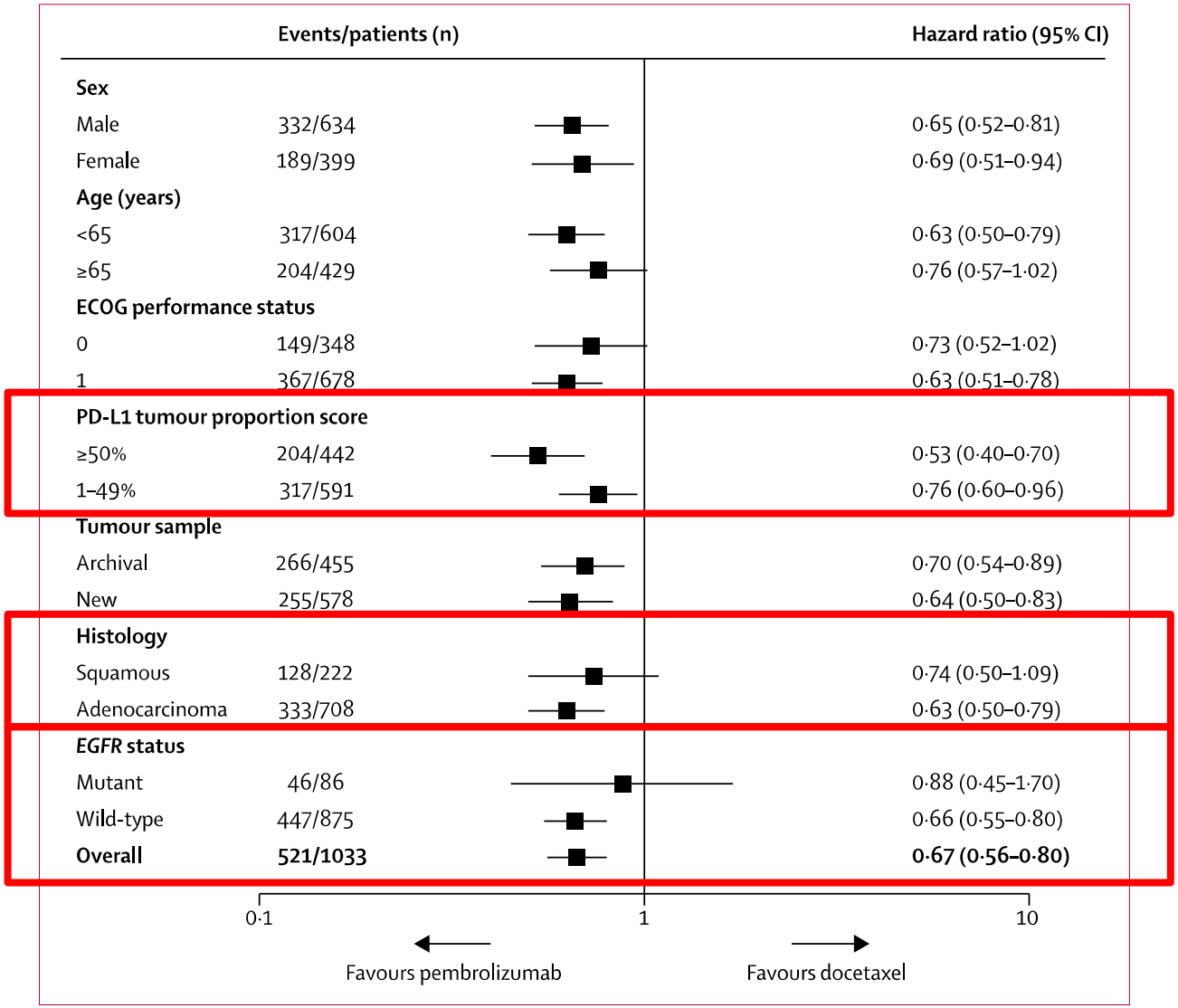

Figure 3: **Subgroup analysis of overall survival**
Shows the comparison of the pooled pembrolizumab doses versus docetaxel. ECOG=Eastern Cooperative Oncology Group.

POPLAR

Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial

*Louis Fehrenbacher, Alexander Spira, Marcus Ballinger, Marcin Kowanetz, Johan Vansteenkiste, Julien Mazieres, Keunchil Park, David Smith, Angel Artal-Cortes, Conrad Lewanski, Fadi Braiteh, Daniel Waterkamp, Pei He, Wei Zou, Daniel S Chen, Jing Yi, Alan Sandler, Achim Rittmeyer, for the POPLAR Study Group**

- Open label, fase II studie
- Stadium IV, zowel plaveiselcel als niet-plaveiselcelcarcinoom, progressie na 1e lijn
- ECOG 0-1
- Stratificatie voor tumor infilterende immuun cel status
- 2 armen (1:1 randomisatie): atezo 1200 mg q3w - docetaxel 75 mg/m2 q3w
- Primaire uitkomst: OS

	Atezolizumab (n=144)	Docetaxel (n=143)
Age (years)	62 (42–82)	62 (36–84)
Sex		
Male	93 (65%)	76 (53%)
Female	51 (35%)	67 (47%)
Tobacco use history		
Never	27 (19%)	29 (20%)
Current	25 (17%)	21 (15%)
Previous	92 (64%)	93 (65%)
Pathology or histology		
Non-squamous	95 (66%)	95 (66%)
Squamous	49 (34%)	48 (34%)
ECOG performance status*		
0	46 (32%)	45 (32%)
1	96 (68%)	97 (68%)
PD-L1 tumour-infiltrating immune cell expression level		
0	62 (43%)	63 (44%)
1	53 (37%)	54 (38%)
2	19 (13%)	18 (13%)
3	10 (7%)	8 (6%)
PD-L1 tumour cell expression level		
0	96 (67%)	82 (57%)
1	19 (13%)	21 (15%)
2	14 (10%)	25 (18%)
3	15 (10%)	15 (11%)
Number of previous therapies in the locally advanced or metastatic setting		
1	93 (65%)	96 (67%)
2	51 (35%)	47 (33%)
EGFR mutation†		
Thr790Met	1 (1%)	0
Positive	10 (12%)	8 (10%)
Negative	72 (87%)	75 (90%)
EMLA-ALK translocation‡		
Yes	0	3 (5%)
No	61 (100%)	55 (95%)
KRAS mutation§		
Yes	14 (33%)	13 (43%)
No	28 (67%)	17 (57%)

Data are median (range) or n (%). ECOG=Eastern Cooperative Oncology Group. PD-L1=programmed death ligand 1.*Of 142 patients in each group. †Of 83 patients in each group with known *EGFR* mutation status. ‡Of 61 patients in the atezolizumab group and 58 in the docetaxel group with known *EMLA-ALK* translocation status. §Of 42 patients in the atezolizumab group and 30 in the docetaxel group with known *KRAS* mutation status.

Table 1: **Baseline characteristics of the intention-to-treat population**

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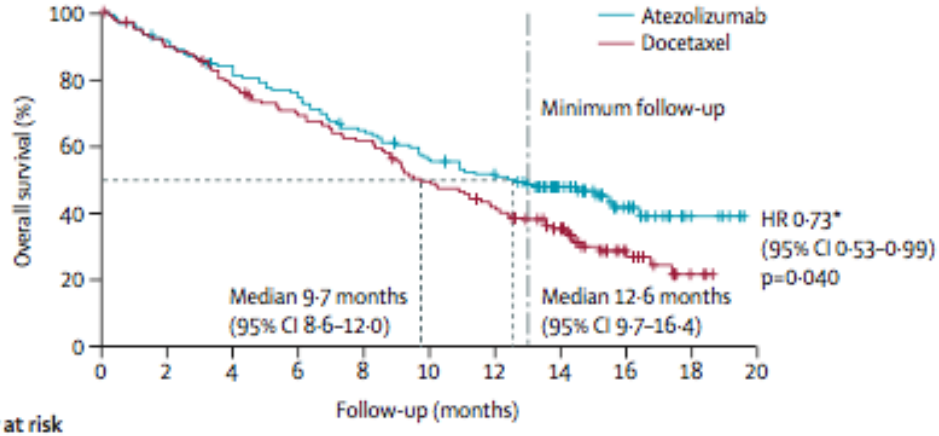
A Intention to treat

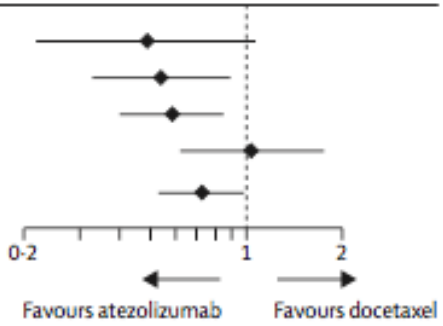


Number at risk

Atezolizumab	144	131	117	106	90	78	69	42	20	7	0
Docetaxel	143	123	106	92	82	65	54	39	17	3	0

B

	n (%)	HR*	95% CI	p value	Median overall survival (months [95% CI])	
					Atezolizumab (n=144)	Docetaxel (n=143)
TC3 or IC3	47 (16%)	0·49	0·22–1·07	0·068	15·5 (9·8–NE)	11·1 (6·7–14·4)
TC2/3 or IC2/3	105 (37%)	0·54	0·33–0·89	0·014	15·1 (8·4–NE)	7·4 (6·0–12·5)
TC1/2/3 or IC1/2/3	195 (68%)	0·59	0·40–0·85	0·005	15·5 (11·0–NE)	9·2 (7·3–12·8)
TC0 and IC0	92 (32%)	1·04	0·62–1·75	0·871	9·7 (6·7–12·0)	9·7 (8·6–12·0)
Intention to treat	287	0·73	0·53–0·99	0·040	12·6 (9·7–16·4)	9·7 (8·6–12·0)



OAK

Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial

*Achim Rittmeyer, Fabrice Barlesi, Daniel Waterkamp, Keunchil Park, Fortunato Ciardiello, Joachim von Pawel, Shirish M Gadgeel, Toyoaki Hida, Dariusz M Kowalski, Manuel Cobo Dols, Diego L Cortinovis, Joseph Leach, Jonathan Polikoff, Carlos Barrios, Fairooz Kabbinavar, Osvaldo Arén Frontera, Filippo De Marinis, Hande Turna, Jong-Seok Lee, Marcus Ballinger, Marcin Kowanetz, Pei He, Daniel S Chen, Alan Sandler, David R Gandara, for the OAK Study Group**

Published **Online**

December 12, 2016

- Open label, fase III studie
- Stadium IIIB/IV, zowel plaveiselcel als niet-plaveiselcelcarcinoom, progressie na 1e lijn
- ECOG 0-1
- 2 armen (1:1 randomisatie): atezo 1200 mg q3w - docetaxel 75 mg/m2 q3w
- Primaire uitkomst: OS (in eerste 850 pten)

	Atezolizumab (n=425)	Docetaxel (n=425)	Overall (N=850)
Age (years)			
Median (range)	63·0 (33·0–82·0)	64·0 (34·0–85·0)	64·0 (33·0–85·0)
Age ≥65 years	190 (45%)	207 (49%)	397 (47%)
Sex			
Male	261 (61%)	259 (61%)	520 (61%)
Female	164 (39%)	166 (39%)	330 (39%)
Race			
White	302 (71%)	296 (70%)	598 (70%)
Asian	85 (20%)	95 (22%)	180 (21%)
Black	5 (1%)	11 (3%)	16 (2%)
Other*	13 (3%)	9 (2%)	22 (3%)
Unknown	20 (5%)	14 (3%)	34 (4%)
ECOG performance status			
0	155 (36%)	160 (38%)	315 (37%)
1	270 (64%)	265 (62%)	535 (63%)
Tobacco use history			
Never	84 (20%)	72 (17%)	156 (18%)
Current	59 (14%)	67 (16%)	126 (15%)
Previous	282 (66%)	286 (67%)	568 (67%)
***EGFR* mutation**			
Positive	42 (10%)	43 (10%)	85 (10%)
Negative	318 (75%)	310 (73%)	628 (74%)
Unknown	65 (15%)	72 (17%)	137 (16%)
***EML4-ALK* translocation**			
Positive	2 (<1%)	0	2 (<1%)
Negative	223 (52%)	201 (47%)	424 (50%)
Unknown	200 (47%)	224 (53%)	424 (50%)
***KRAS* mutation**			
Positive	26 (6%)	33 (8%)	59 (7%)
Negative	99 (23%)	104 (24%)	203 (24%)
Unknown	300 (71%)	288 (68%)	588 (69%)
Histology			
Non-squamous	313 (74%)	315 (74%)	628 (74%)
Squamous	112 (26%)	110 (26%)	222 (26%)
PD-L1 subgroups			
TC3 or IC3	72 (17%)	65 (15%)	137 (16%)
TC2/3 or IC2/3	129 (30%)	136 (32%)	265 (31%)
TC1/2/3 or IC1/2/3†	241 (57%)	222 (52%)	463 (54%)
TC0 and IC0	180 (42%)	199 (47%)	379 (45%)
Number of previous therapies in the locally advanced or metastatic setting			
1	320 (75%)	320 (75%)	640 (75%)
2	105 (25%)	105 (25%)	210 (25%)

Data are median (range) and n (%), unless otherwise indicated. ECOG=Eastern Cooperative Oncology Group. IC=tumour-infiltrating immune cell. PD-L1=programmed death-ligand 1. TC=tumour cell. *Other includes American Indian, Alaska native, Hawaiian native, other Pacific Islander, other, and multiple. †Tumour tissue for eight patients was not evaluable for TC1/2/3 or IC1/2/3.

***Table* 1: Baseline characteristics of the intention-to-treat primary population**

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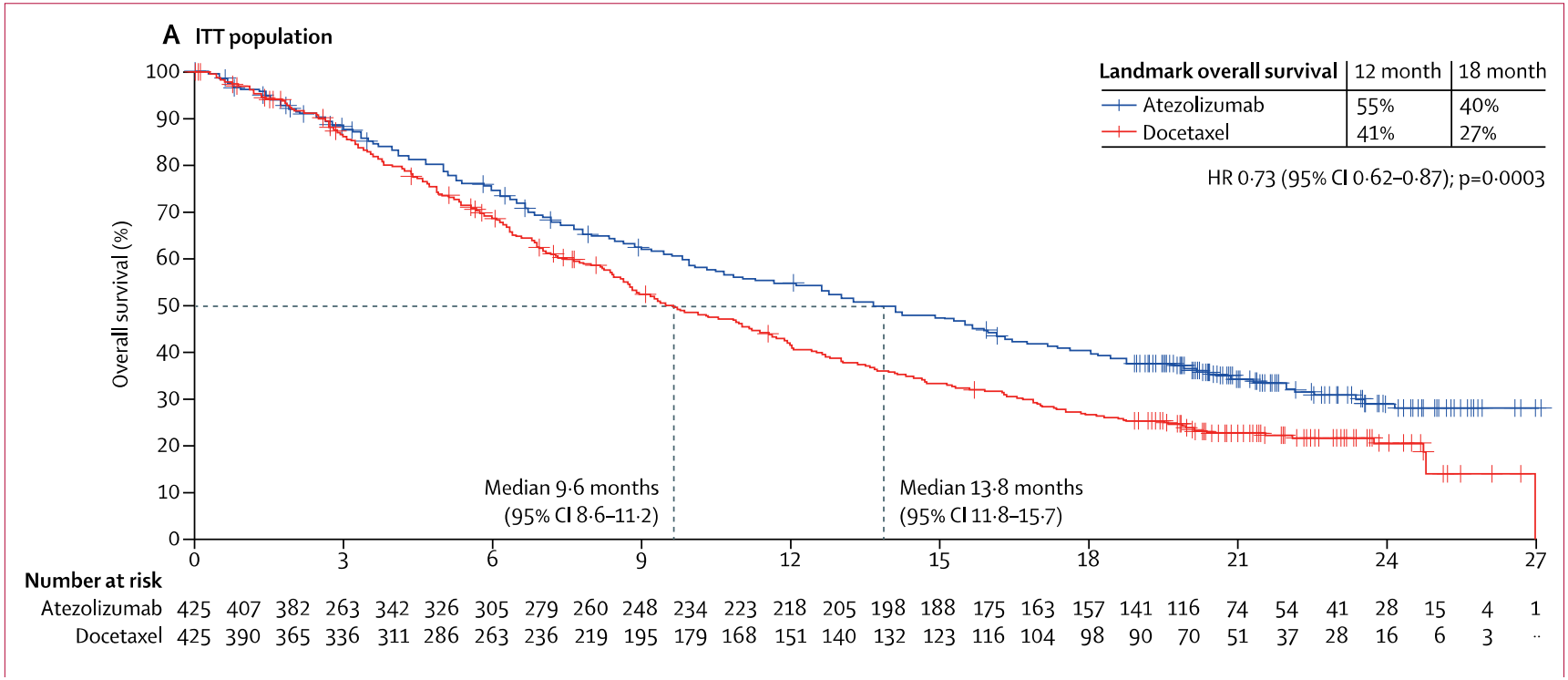
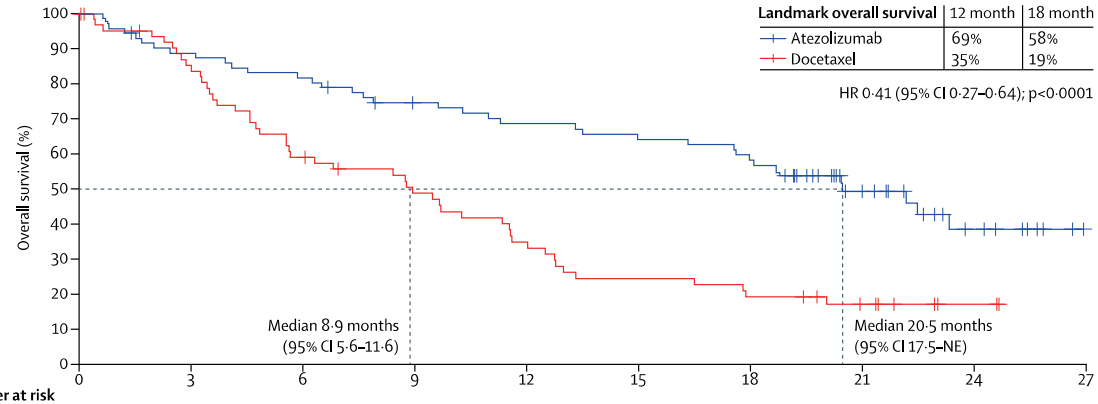

A ITT population
Overall survival (%)
100
90
80
70
60
50
40
30
20
10
0
Landmark overall survival | 12 month | 18 month
Atezolizumab | 55% | 40%
Docetaxel | 41% | 27%
HR 0·73 (95% CI 0·62–0·87); p=0·0003
Median 9·6 months
(95% CI 8·6–11·2)
Median 13·8 months
(95% CI 11·8–15·7)
0 3 6 9 12 15 18 21 24 27
Number at risk
Atezolizumab 425 407 382 263 342 326 305 279 260 248 234 223 218 205 198 188 175 163 157 141 116 74 54 41 28 15 4 1
Docetaxel 425 390 365 336 311 286 263 236 219 195 179 168 151 140 132 123 116 104 98 90 70 51 37 28 16 6 3 ..

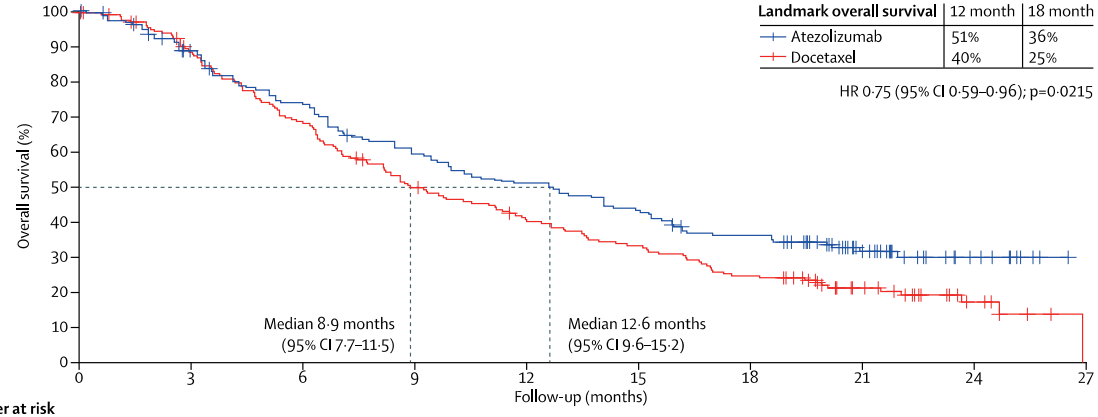
D TC3 or IC3 population



Number at risk

Atezolizumab	72	69	65	63	61	59	58	55	51	50	49	47	46	46	44	43	43	42	39	34	28	19	16	11	8	6	2
Docetaxel	65	59	57	51	45	40	36	32	32	28	25	24	20	15	14	14	14	13	11	11	9	7	4	3	2	..	..

E TC0 and IC0 population

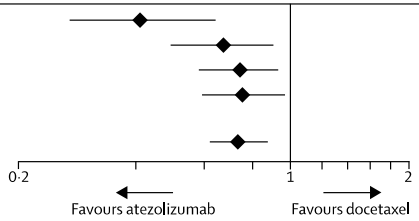


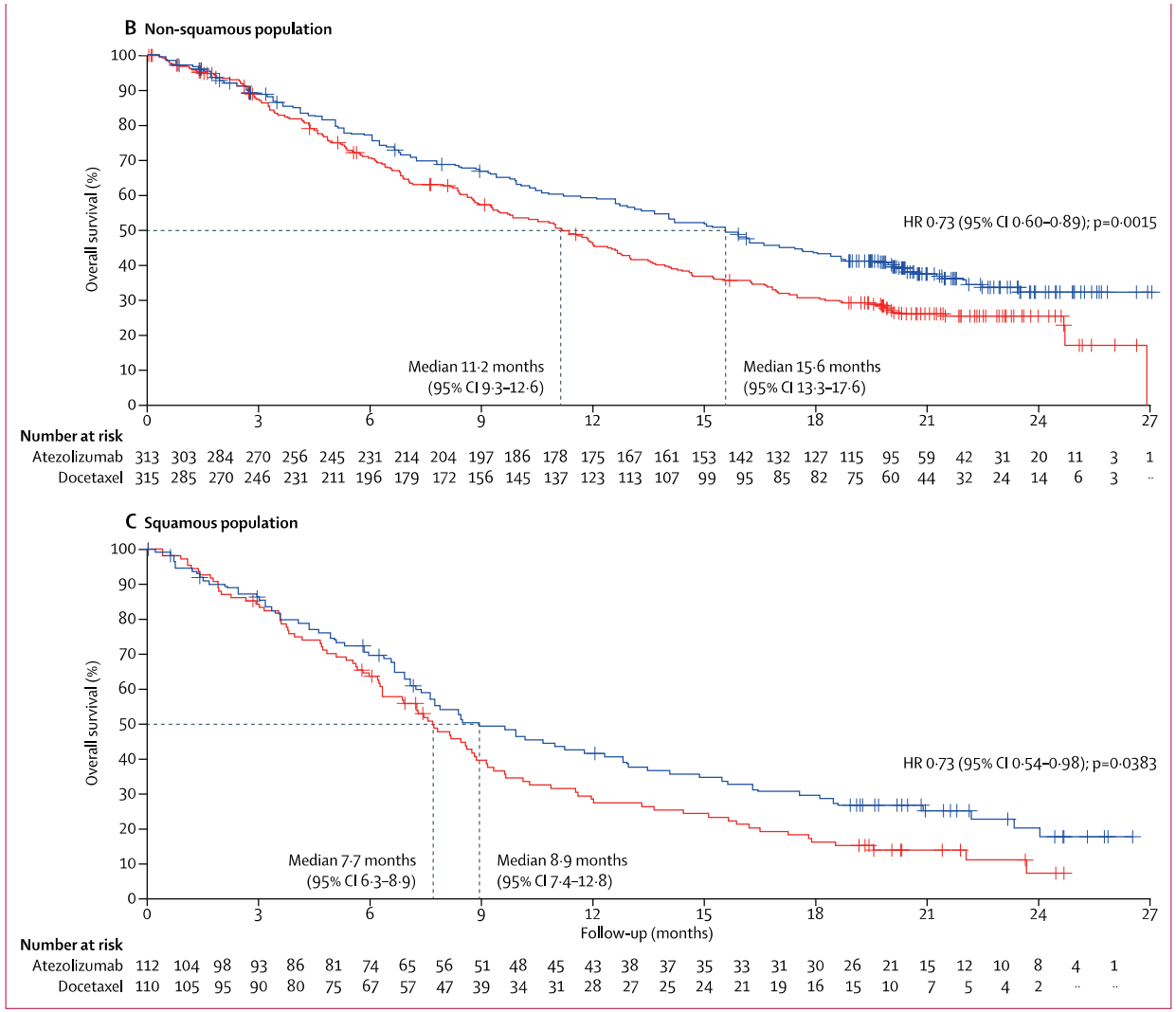
Number at risk

Atezolizumab	180	173	163	152	139	132	125	112	106	100	93	88	86	81	79	73	64	59	59	53	45	27	17	13	9	5	1
Docetaxel	199	187	177	161	147	135	124	110	101	89	82	79	70	66	60	58	54	45	43	39	29	23	19	13	8	3	2

F

	n (%)	Median overall survival (months)		HR (95% CI)
		Atezolizumab	Docetaxel	
TC3 or IC3	137 (16)	20·5	8·9	0·41 (0·27–0·64)
TC2/3 or IC2/3	265 (31)	16·3	10·8	0·67 (0·49–0·90)
TC1/2/3 or IC1/2/3	463 (54)	15·7	10·3	0·74 (0·58–0·93)
TC0 and IC0	379 (45)	12·6	8·9	0·75 (0·59–0·96)
ITT	850 (100)	13·8	9·6	0·73 (0·62–0·87)




B Non-squamous population
Overall survival (%)
HR 0·73 (95% CI 0·60–0·89); p=0·0015
Median 11·2 months
(95% CI 9·3–12·6)
Median 15·6 months
(95% CI 13·3–17·6)
Number at risk
Atezolizumab 313 303 284 270 256 245 231 214 204 197 186 178 175 167 161 153 142 132 127 115 95 59 42 31 20 11 3 1
Docetaxel 315 285 270 246 231 211 196 179 172 156 145 137 123 113 107 99 95 85 82 75 60 44 32 24 14 6 3 ..
C Squamous population
Overall survival (%)
HR 0·73 (95% CI 0·54–0·98); p=0·0383
Median 7·7 months
(95% CI 6·3–8·9)
Median 8·9 months
(95% CI 7·4–12·8)
Follow-up (months)
Number at risk
Atezolizumab 112 104 98 93 86 81 74 65 56 51 48 45 43 38 37 35 33 31 30 26 21 15 12 10 8 4 1
Docetaxel 110 105 95 90 80 75 67 57 47 39 34 31 28 27 25 24 21 19 16 15 10 7 5 4 2 .. ..

Wat was de situatie voor ESMO / WCLC?

1e lijn stadium IV

Keynote 024

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 10, 2016 VOL. 375 NO. 19

Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer

Martin Reck, M.D., Ph.D., Delvys Rodríguez-Abreu, M.D., Andrew G. Robinson, M.D., Rina Hui, M.B., B.S., Ph.D., Tibor Csőszi, M.D., Andrea Fülöp, M.D., Maya Gottfried, M.D., Nir Peled, M.D., Ph.D., Ali Tafreshi, M.D., Sinead Cuffe, M.D., Mary O'Brien, M.D., Suman Rao, M.D., Katsuyuki Hotta, M.D., Ph.D., Melanie A. Leiby, Ph.D., Gregory M. Lubiniecki, M.D., Yue Shentu, Ph.D., Reshma Rangwala, M.D., Ph.D., and Julie R. Brahmer, M.D., for the KEYNOTE-024 Investigators*

- Chemo naief, stadium IV
- PD-L1 ≥ 50%
- Geen EGFR / ALK
- Randomisatie (1:1): pembrolizumab 200 mg / 3 weken – platinum doublet
- Cross-over naar pembro na progressie toegestaan
- Primaire uitkomst: PFS
- Secundaire uitkomst: OS, Respons Rate en safety

Table 1. Baseline Demographic and Disease Characteristics of Patients in the Intention-to-Treat Population.*

Characteristic	Pembrolizumab Group (N = 154)	Chemotherapy Group (N = 151)
Age — yr		
Median	64.5	66.0
Range	33–90	38–85
Male sex — no. (%)	92 (59.7)	95 (62.9)
Region of enrollment — no. (%)		
East Asia	21 (13.6)	19 (12.6)
Non–East Asia	133 (86.4)	132 (87.4)
ECOG performance-status score — no. (%)†		
0	54 (35.1)	53 (35.1)
1	99 (64.3)	98 (64.9)
Smoking status — no. (%)		
Current	34 (22.1)	31 (20.5)
Former	115 (74.7)	101 (66.9)
Never	5 (3.2)	19 (12.6)
Histology — no. (%)		
Squamous	29 (18.8)	27 (17.9)
Nonsquamous	125 (81.2)	124 (82.1)
Brain metastases — no. (%)	18 (11.7)	10 (6.6)
Previous systemic neoadjuvant therapy — no. (%)	3 (1.9)	1 (0.7)
Previous systemic adjuvant therapy — no. (%)	6 (3.9)	3 (2.0)

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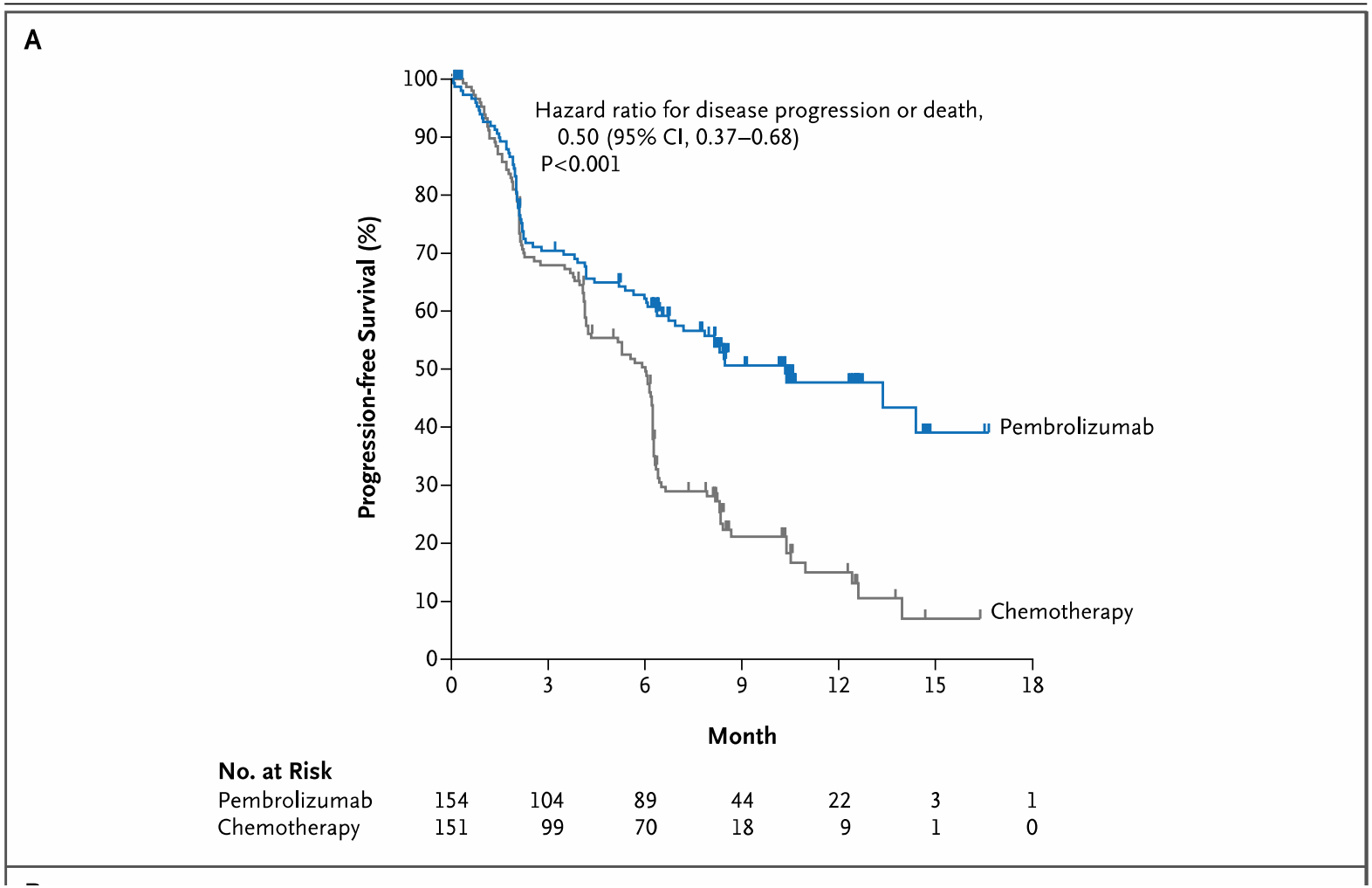
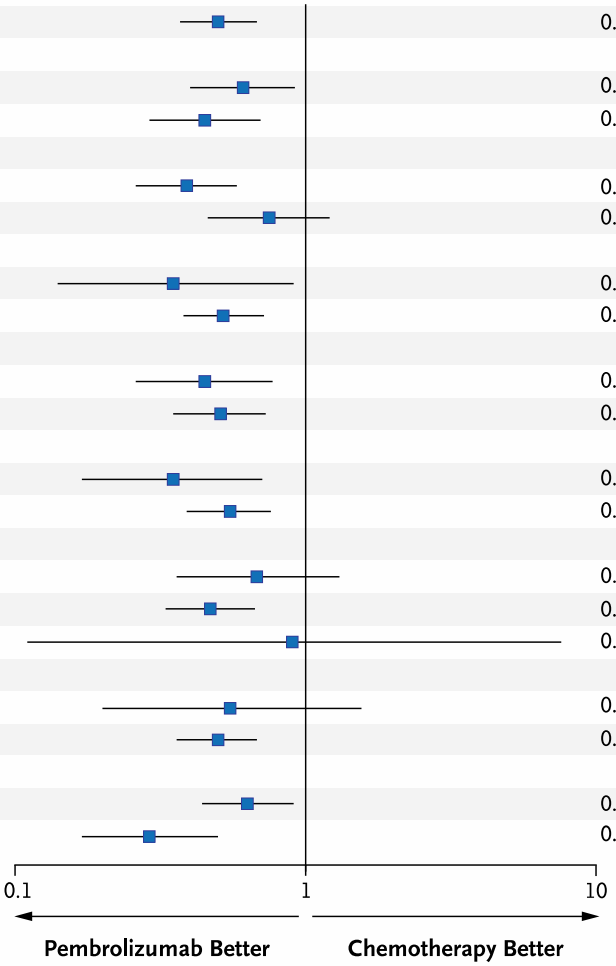
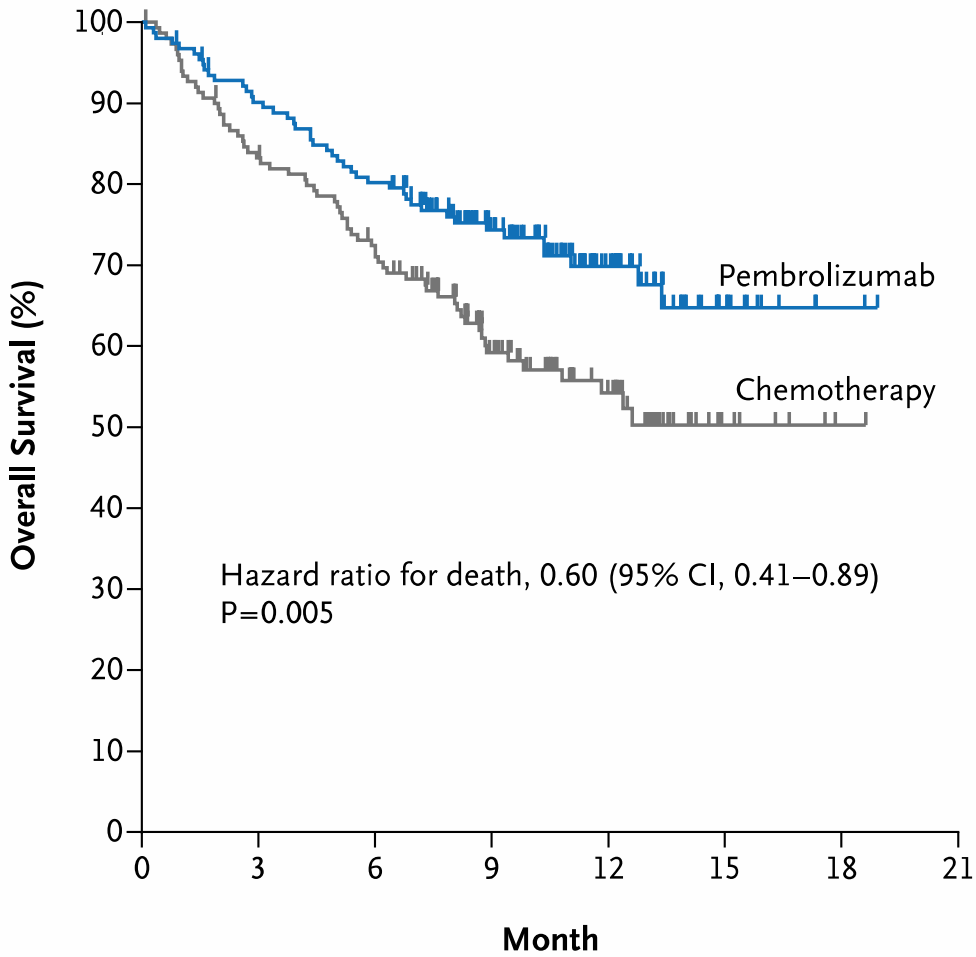

A
Hazard ratio for disease progression or death,
0.50 (95% CI, 0.37–0.68)
P<0.001
Progression-free Survival (%)
100
90
80
70
60
50
40
30
20
10
0
Pembrolizumab
Chemotherapy
0
3
6
9
12
15
18
Month
No. at Risk
Pembrolizumab 154 104 89 44 22 3 1
Chemotherapy 151 99 70 18 9 1 0

B

Subgroup	No. of Events/ No. of Patients	Hazard Ratio for Disease Progression or Death (95% CI)
Overall	189/305	0.50 (0.37–0.68)
Age		
<65 yr	91/141	0.61 (0.40–0.92)
≥65 yr	98/164	0.45 (0.29–0.70)
Sex		
Male	116/187	0.39 (0.26–0.58)
Female	73/118	0.75 (0.46–1.21)
Region of enrollment		
East Asia	21/40	0.35 (0.14–0.91)
Non–East Asia	168/265	0.52 (0.38–0.72)
ECOG performance-status score		
0	59/107	0.45 (0.26–0.77)
1	129/197	0.51 (0.35–0.73)
Histologic type		
Squamous	37/56	0.35 (0.17–0.71)
Nonsquamous	152/249	0.55 (0.39–0.76)
Smoking status		
Current	44/65	0.68 (0.36–1.31)
Former	133/216	0.47 (0.33–0.67)
Never	12/24	0.90 (0.11–7.59)
Brain metastases at baseline		
Yes	17/28	0.55 (0.20–1.56)
No	172/277	0.50 (0.36–0.68)
Platinum-based chemotherapy regimen		
Included pemetrexed	120/199	0.63 (0.44–0.91)
Did not include pemetrexed	69/106	0.29 (0.17–0.50)





No. at Risk

Pembrolizumab	154	136	121	82	39	11	2	0
Chemotherapy	151	123	106	64	34	7	1	0

Table 2. Summary of Response in the Intention-to-Treat Population.*

Variable	Pembrolizumab Group (N = 154)	Chemotherapy Group (N = 151)
Objective response†		
No. of patients	69	42
% (95% CI)	44.8 (36.8 to 53.0)	27.8 (20.8 to 35.7)
Time to response — mo‡		
Median	2.2	2.2
Range	1.4 to 8.2	1.8 to 12.2
Duration of response — mo‡§		
Median	NR	6.3
Range	1.9+ to 14.5+	2.1+ to 12.6+

Keynote 021

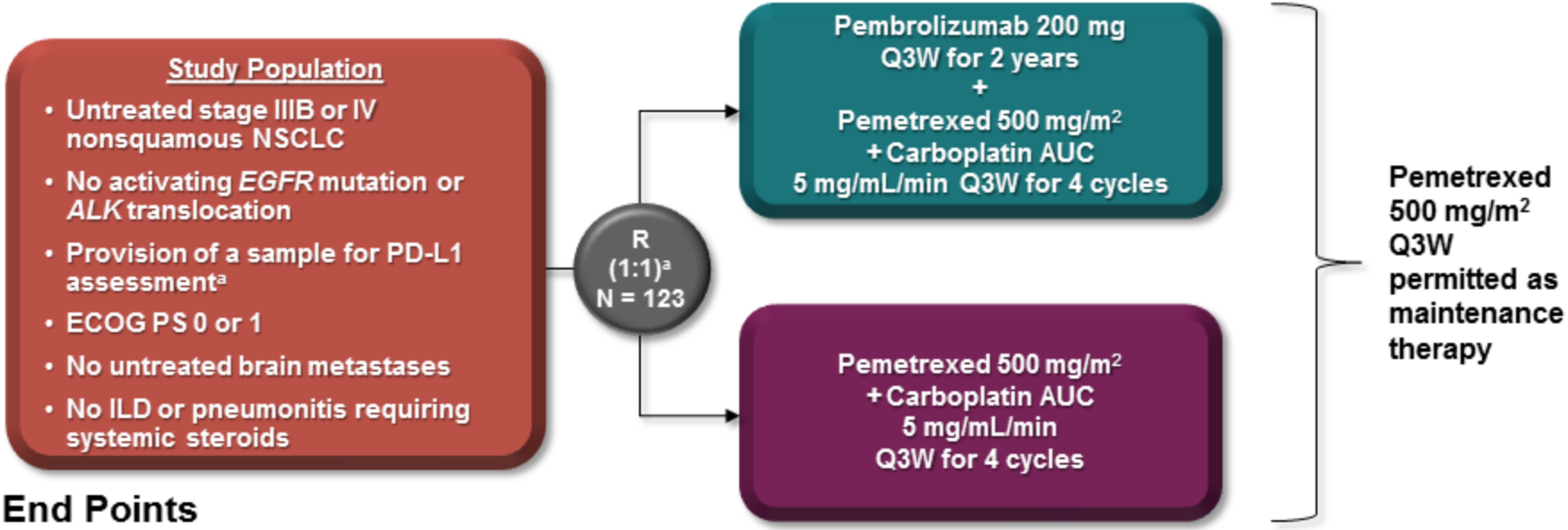
Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study

*Corey J Langer, Shirish M Gadgeel, Hossein Borghaei, Vassiliki A Papadimitrakopoulou, Amita Patnaik, Steven F Powell, Ryan D Gentzler, Renato G Martins, James P Stevenson, Shadia I Jalal, Amit Panwalkar, James Chih-Hsin Yang, Matthew Gubens, Lecia V Sequist, Mark M Awad, Joseph Fiore, Yang Ge, Harry Raftopoulos, Leena Gandhi, for the KEYNOTE-021 investigators**

Lancet Oncol 2016;
17: 1497–508

Published **Online**
October 9, 2016

KEYNOTE-021 Cohort G



End Points

- Primary: ORR (RECIST v1.1 per blinded, independent central review)
- Key secondary: PFS
- Other secondary: OS, safety, relationship between antitumor activity and PD-L1 TPS
- No alpha allocated for updated analysis; all *P* values are nominal (one-sided $P < 0.025$)

[a]Randomization was stratified by PD-L1 TPS <1% vs ≥1%.

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	Pembrolizumab plus chemotherapy (N=60)	Chemotherapy (N=63)
Age, years	62·5 (54–70)	63·2 (58–70)
Sex		
Male	22 (37%)	26 (41%)
Female	38 (63%)	37 (59%)
Ethnic origin		
White	49 (82%)	58 (92%)
Asian	5 (8%)	5 (8%)
Black or African American	4 (7%)	0
Other*	2 (3%)	0
ECOG performance status†		
0	24 (40%)	29 (46%)
1	35 (58%)	34 (54%)
Tumour histology		
Adenocarcinoma	58 (97%)	55 (87%)
NSCLC not otherwise specified	2 (3%)	7 (11%)
Large cell carcinoma	0	1 (2%)
Disease stage		
IIIA	0	1 (2%)
IIIB	1 (2%)	2 (3%)
IV	59 (98%)	60 (95%)
Smoking status		
Current or former smoker	45 (75%)	54 (86%)
Never smoker	15 (25%)	9 (14%)
Stable brain metastases	9 (15%)	6 (10%)
PD-L1 TPS		
<1%	21 (35%)	23 (37%)
1–49%	19 (32%)	23 (37%)
≥50%	20 (33)	17 (27%)
Previous systemic (neo)adjuvant therapy	4 (7%)	5 (8%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. NSCLC=non-small-cell lung cancer. TPS=tumour proportion score. *Other ethnic origins in the pembrolizumab plus chemotherapy group included one patient (2%) who was American Indian or Alaska Native and one patient (2%) who did not define their ethnic origin. †One patient (2%) in the pembrolizumab plus chemotherapy group had an ECOG performance status of 2; this patient did not receive study treatment.

Table 1: **Baseline demographics and disease characteristics in the intention-to-treat population**

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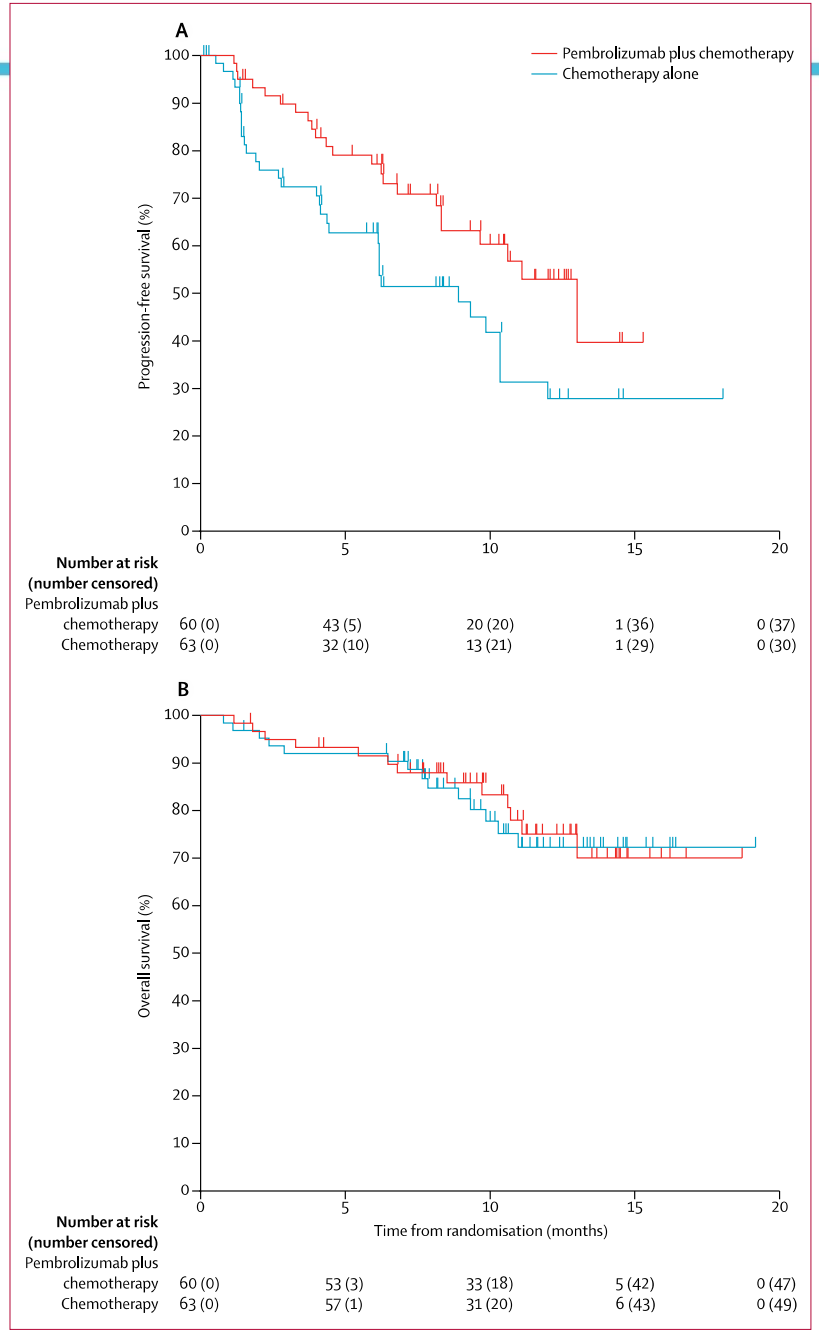

Figure 3: **Kaplan-Meier estimates of progression-free survival (A) and overall survival (B)**
Progression-free survival assessed per Response Evaluation Criteria In Solid Tumors version 1.1 by masked, independent central radiology review in the intention-to-treat population.

DUIDELIJKHEID OVER VOORSCHRIJFBELEID NIVOLUMAB EN PEMBROLIZUMAB

NVALT-advies voor immunotherapie bij NSCLC

Sinds de goedkeuring door de EMA van nivolumab voor de indicatie van tweedelijns behandeling van het niet-kleincellig longcarcinoom is het behandelalgoritme van deze ziekte vrijwel continu aan verandering onderhevig. Recentelijk is ook pembrolizumab door de EMA goedgekeurd. De NVALT beschrijft in deze publicatie de plaats van beide middelen in het huidige behandelarsenaal.

De NVMO-commissie BOM oordeelde eind 2015 dat nivolumab een plaats heeft in de Nederlandse behandelsetting bij de tweedelijns behandeling van gevorderd plaveiselcelcarcinoom van de long (CheckMate 017-studie) en oordeelde een jaar later dat nivolumab tevens een plaats heeft in de tweedelijns behandeling van het niet-plaveiselcelcarcinoom van de long (CheckMate 057-studie).[1, 2] In dit nummer van *Medische Oncologie* publiceert de commissie BOM twee adviezen over pembrolizumab bij niet-kleincellig longcarcinoom (zie adviezen op pagina's 51 en 57).

Eerste en tweede lijn

Pembrolizumab is, net als nivolumab, een PD-1-remmer. In de tweedelijns setting is pembrolizumab getest bij patiënten met een niet-kleincellig longcarcinoom met PD-L1-expressie (*tumor proportion score* [TPS] ≥ 1 procent) (KEYNOTE 010), waarbij echter alleen de resultaten voor de door de EMA geregistreerde dosering van 2 mg/kg bij patiënten met TPS ≥ 50 procent voldoen aan de PASKWIL-criteria voor een positief advies. In de eerstelijns setting is pembrolizumab alleen getest in een groep patiënten met niet-kleincellig longcarcinoom met hoge PD-L1-expressie (TPS ≥ 50 procent) (KEYNOTE 024) en voldoen de resultaten van deze studie aan de PASKWIL-criteria voor een positief advies. Het is overigens opvallend dat in deze studie een nog niet eerder onderzochte (absolute) dosis van 200 mg werd gebruikt. Op basis van de resultaten van de KEYNOTE 024-studie heeft de EMA pembrolizumab ook voor deze eerstelijns indicatie geregistreerd bij patiënten met TPS ≥ 50 procent. Wanneer al deze gegevens worden beoordeeld, betekent dit dat er enerzijds een positief advies is voor behandeling met nivolumab van patiënten met niet-kleincellig longcarcinoom in de tweede lijn in een voor PD-L1-expressie ongeselecteerde populatie, en dat er anderzijds een positief advies is voor behandeling met pembrolizumab in de eerste lijn of tweede lijn in een geselecteerde populatie van patiënten met niet-kleincellig longcarcinoom met hoge PD-L1-expressie (TPS ≥ 50 procent), hetgeen ongeveer 30 procent van de totale populatie is.

Behoefte selectie patiënten

Gezien het feit dat in de voor PD-L1 ongeselecteerde populatie van patiënten met niet-kleincellig longcarcinoom slechts 20 tot 30 procent van de patiënten langdurig voordeel heeft van behandeling met immunotherapie, is er behoefte aan selectie van patiënten. Er werpen zich nu diverse vragen op:

1. Is PD-L1-expressie, gezien de wisselende predictieve waarde, wel een goede biomarker voor selectie van patiënten met niet-kleincellig longcarcinoom voor behandeling met nivolumab?
2. Welke afkapwaarde moet dan worden gekozen?
3. Met welk antilichaam of welke test kan de PD-L1-expressie het best worden bepaald?

Deze laatste vraag is waarschijnlijk het makkelijkst te beantwoorden omdat de pathologen in Nederland bezig zijn de immunohistochemische bepaling van PD-L1 te implementeren. Het lijkt dat de antilichamen 28-8 en 22C3 dezelfde resultaten geven, maar het is niet bekend of de predictieve waarde van beide antilichamen vergelijkbaar is voor pembrolizumab en nivolumab. Belangrijk blijft echter de vraag of er wel moet gaan worden getest, omdat er tenslotte reeds een positief advies is voor de ongeselecteerde groep patiënten.

Advies beroepsgroep

Het advies van de NVALT is:

1. om patiënten met een gemetastaseerd niet- kleincellig longcarcinoom zonder activerende EGFR-mutatie of ALK-translocatie en een hoge PD-L1-expressie (TPS ≥ 50 procent) gemeten met 22C3 IHC (Dako) in de eerste lijn te behandelen met pembrolizumab 200 mg per 3 weken;
2. om patiënten met een gevorderd of gemetastaseerd niet-kleincellig longcarcinoom zonder activerende EGFR-mutatie of ALK-translocatie en progressie van ziekte na eerdere platinumbevattende chemotherapie in de tweede lijn te behandelen met nivolumab 3 mg/kg iedere 2 weken; bij patiënten met een hoge PD-L1-expressie (TPS ≥ 50 procent) wordt dan gekozen voor pembrolizumab 2 mg/kg per 3 weken. Dit geldt voor zowel het adenocarcinoom als het plaveiselcelcarcinoom. Data voor patiënten die in de eerste lijn zijn behandeld met immunotherapie ontbreken;
3. in overweging nemende dat in de CheckMate 057-studie PD-L1-expressie predictieve waarde heeft en dat er behoefte is aan een methode om patiënten met een niet-plaveiselcelcarcinoom van de long te selecteren die geen voordeel lijken te hebben van behandeling, om terughoudend te zijn met nivolumab voor patiënten zonder PD-L1-expressie (< 1 procent). ←

Referenties

[1] Kerst JM, Eskens FALM, Beerepoot LV, et al; NVMO-commissie BOM. Nivolumab bij gevorderd plaveiselcelcarcinoom van de long. Med Oncol 2015;18(6):37-40.

[2] Eskens FALM, Wymenga ANM, Beerepoot LV, et al; NVMO-commissie BOM. Nivolumab bij gevorderd niet-plaveiselcelcarcinoom van de long. Med Oncol 2016;19(6):35-8.

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Advies beroepsgroep

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2. om patiënten met een gevorderd of gemetastaseerd niet-kleincellig longcarcinoom zonder activerende EGFR-mutatie of ALK-translocatie en progressie van ziekte na eerdere platinumbevattende chemotherapie in de tweede lijn te behandelen met nivolumab 3 mg/kg iedere 2 weken; bij patiënten met een hoge PD-L1-expressie (TPS ≥ 50 procent) wordt dan gekozen voor pembrolizumab 2 mg/kg per 3 weken. Dit geldt voor zowel het adenocarcinoom als het plaveiselcelcarcinoom. Data voor patiënten die in de eerste lijn zijn behandeld met immunotherapie ontbreken;
3. in overweging nemende dat in de CheckMate 057-studie PD-L1-expressie predictieve waarde heeft en dat er behoefte is aan een methode om patiënten met een niet-plaveiselcel-carcinoom van de long te selecteren die geen voordeel lijken te hebben van behandeling, om terughoudend te zijn met nivo-lumab voor patiënten zonder PD-L1-expressie (< 1 procent). ←

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Wat is de situatie na ESMO / WCLC?

ESMO / WCLC

2e lijn stadium IV

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

IASLC 18TH WORLD CONFERENCE ON LUNG CANCER
October 15–18, 2017 | Yokohama, Japan
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Long-term survival in atezolizumab-treated patients with 2L+ NSCLC from the Phase III randomized OAK study

Miyako Satouchi,[1] Louis Fehrenbacher,[2] Manuel Cobo Dols,[3] Ji-Youn Han,[4] Joachim von Pawel,[5] Rodolfo Bordoni,[6] Toyoaki Hida,[7] Keunchil Park,[8] Denis Moro-Sibilot,[9] Paul Conkling,[10] Christina Matheny,[11] Wei Yu,[11] Pei He,[11] Marcin Kowanetz,[11] Mayank Gandhi,[11] Marcus Ballinger,[11] Alan Sandler,[11] David Gandara[12]

[1]Hyogo Cancer Center, Akashi, Japan; [2]Kaiser Permanente Medical Center, Vallejo, CA, USA; [3]Hospital Regional Universitario Carlos Haya, Málaga, Spain; [4]National Cancer Center, Goyang, Korea; [5]Asklepios-Fachkliniken München-Gauting, Gauting, Germany; [6]Georgia Cancer Specialists and Northside Hospital Cancer Institute, Atlanta, GA, USA; [7]Aichi Cancer Center Hospital, Nagoya, Japan; [8]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [9]Hôpital Albert Michallon, La Tronche, France; [10]US Oncology Research, Virginia Oncology Associates, Norfolk, VA, USA; [11]Genentech, Inc., South San Francisco, CA, USA; [12]UC Davis Comprehensive Cancer Center, Sacramento, CA, USA

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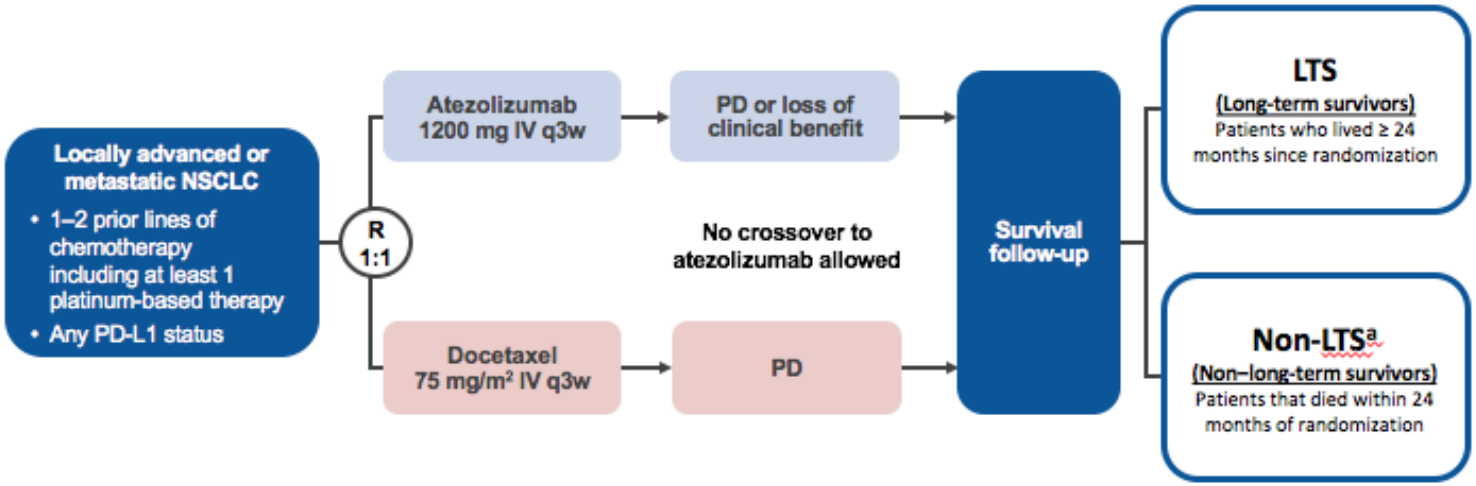
OAK: Phase III study of atezolizumab vs docetaxel in 2L/3L NSCLC



- **Primary endpoint (first 850 enrolled patients):** OS in the ITT population (ITT850)
- **Data cutoff:** 23 January, 2017; **Minimum follow-up:** 26 months

[a] Patients censored prior to 24 months were excluded from this analysis.
NCT02008227.

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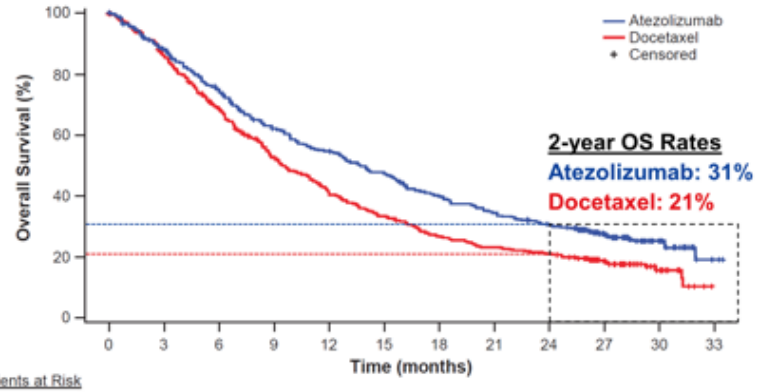
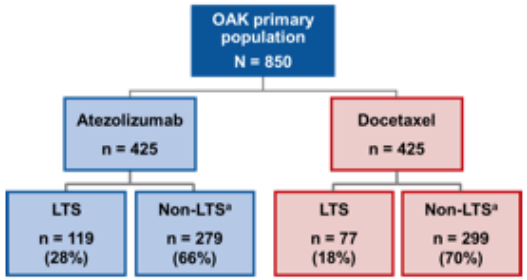
Landmark 2-year overall survival in OAK

Overall survival (OS) in ITT850



No. of Patients at Risk

Atezolizumab	425	363	305	248	218	188	157	136	119	71	27	2
Docetaxel	425	336	263	195	151	123	98	85	77	43	13	



LTS, long-term survivors.
[a] 27 atezolizumab- and 49 docetaxel-arm patients were censored prior to 24 months and excluded from this analysis.
Data cutoff: 23 January, 2017.

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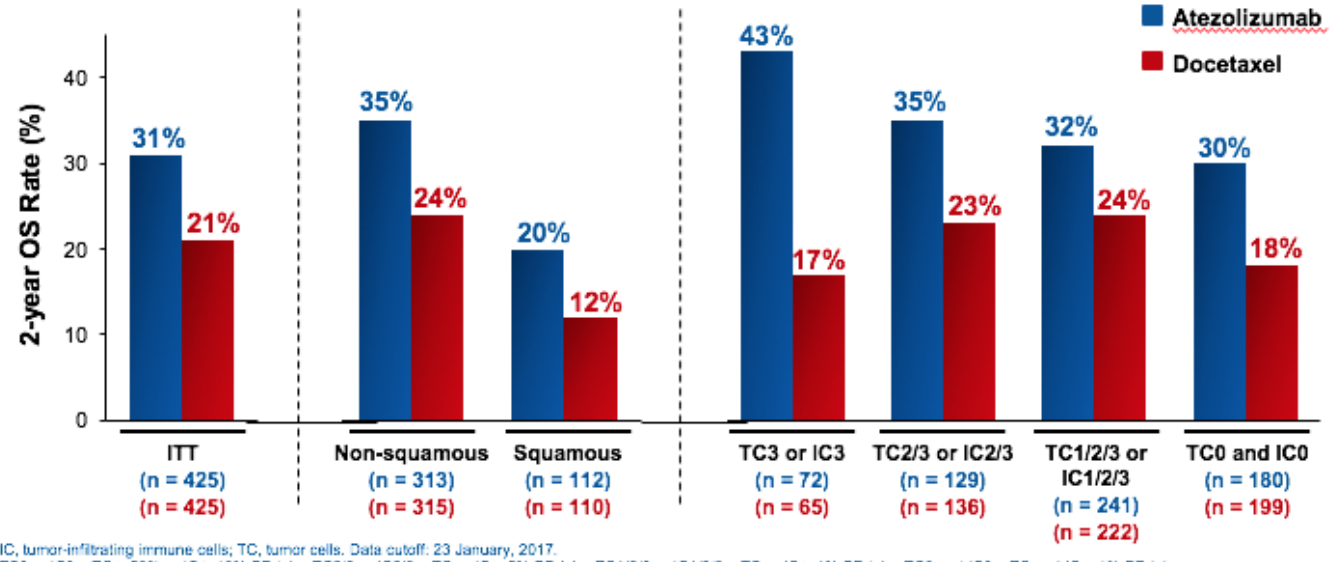
Long-term survival benefit by histology and PD-L1 expression subgroups



IC, tumor-infiltrating immune cells; TC, tumor cells. Data cutoff: 23 January, 2017.
TC3 or IC3 = TC ≥ 50% or IC ≥ 10% PD-L1+; TC2/3 or IC2/3 = TC or IC ≥ 5% PD-L1+; TC1/2/3 or IC1/2/3 = TC or IC ≥ 1% PD-L1+; TC0 and IC0 = TC and IC < 1% PD-L1+.

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IASLC 18TH WORLD CONFERENCE ON LUNG CANCER

October 15–18, 2017 | Yokohama, Japan

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3-year survival and duration of response in randomized Phase II study of atezolizumab vs docetaxel in 2L/3L NSCLC (POPLAR)

Keunchil Park,[1] Conrad Lewanski,[2] Shirish Gadgeel,[3] Louis Fehrenbacher,[4] Julien Mazières,[5] Achim Rittmeyer,[6] Ji-Youn Han,[7] Angel Artal-Cortes,[8] Fadi Braiteh,[9] Mayank Gandhi,[10] Wei Yu,[10] Christina Matheny,[10] Pei He,[10] Alan Sandler,[10] Marcus Ballinger,[10] Johan Vansteenkiste[11]

[1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [2]Charing Cross Hospital, London, UK; [3]University of Michigan, Ann Arbor, MI, USA; [4]Kaiser Permanente Medical Center, Vallejo, CA, USA; [5]Toulouse University Hospital, Toulouse, France; [6]Lungenfachklinik Immenhausen, Immenhausen, Germany; [7]National Cancer Center, Goyang, Korea; [8]Hospital Universitario Miguel Servet, Zaragoza, Spain; [9]Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; [10]Genentech, Inc., South San Francisco, CA, USA; [11]University Hospitals KU Leuven, Leuven, Belgium

Park, et al. WCLC 2017

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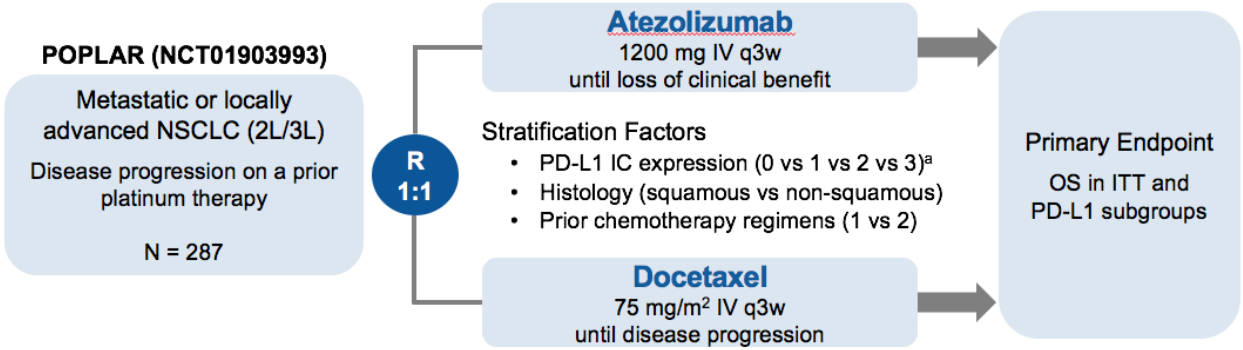
POPLAR: a randomized Phase II study of atezolizumab vs docetaxel in NSCLC

- Atezolizumab (anti–PD-L1) has demonstrated OS benefit over docetaxel (HR, 0.73 [95% CI: 0.53, 0.99]) in a randomized Phase II study, POPLAR, in patients with advanced NSCLC[1]
  - This benefit has been confirmed in the randomized Phase III study OAK[2]

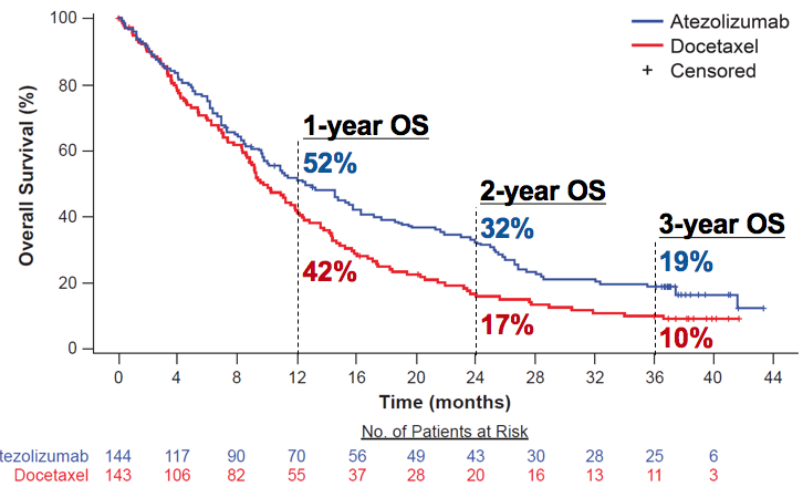


- This presentation describes survival results from POPLAR after a minimum of 3 years follow-up
  - **Data cutoff:** 7 April 2017; **Median follow-up:** 38 months

IC, tumor-infiltrating immune cells. [a] Tumors were prospectively evaluated for PD-L1 expression using the VENTANA SP142 IHC assay.

References: 1. Fehrenbacher L, et al. *Lancet*, 2016. **2.** Rittmeyer A, et al. *Lancet*, 2017.

Landmark overall survival and duration of response in POPLAR



+ denotes a censored value.
Data cutoff: 7 April, 2017

- Improved OS with atezolizumab vs docetaxel was observed at 1, 2 and 3 years
- ORR with both atezolizumab and docetaxel was 15%
- Median duration of response:
  - Atezolizumab: 22.3 mo (range 2.9 to 38.7+)
  - Docetaxel: 7.2 mo (range, 1.5+ to 15.4)
- Treatment-related Grade 3-4 AEs:
  - Atezolizumab: 14%
  - Docetaxel: 40%

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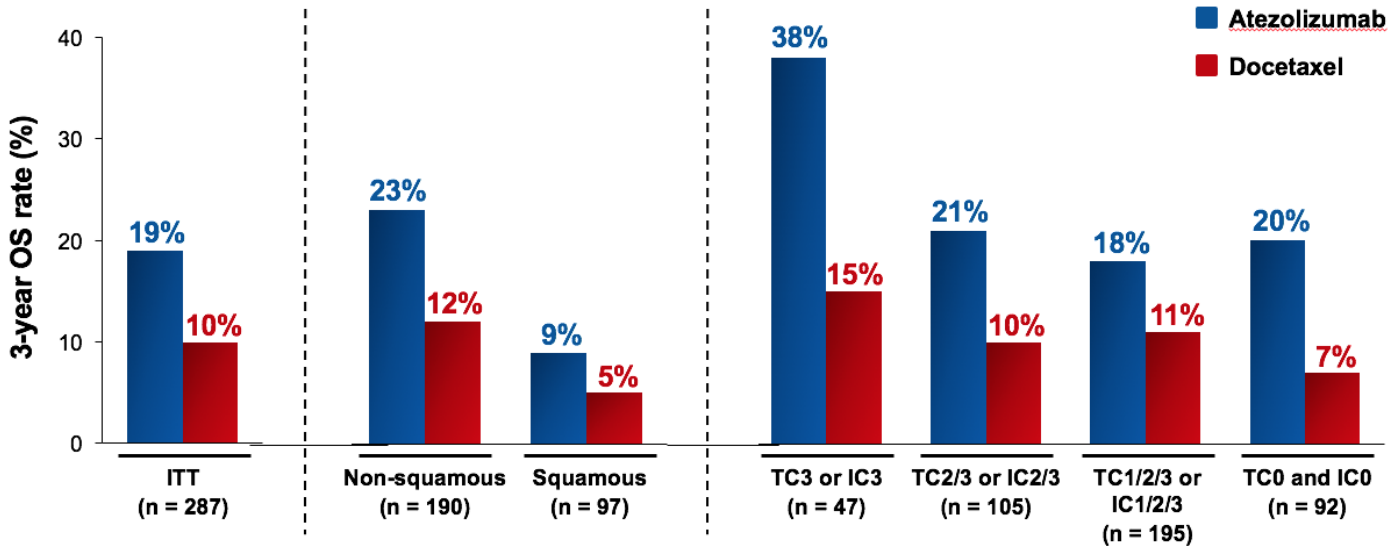
3-year overall survival with atezolizumab vs docetaxel by histology and PD-L1 expression subgroups



IC, tumor-infiltrating immune cells; TC, tumor cells. Data cutoff: 7 April, 2017.
TC3 or IC3 = TC ≥ 50% or IC ≥ 10% PD-L1+; TC2/3 or IC2/3 = TC or IC ≥ 5% PD-L1+; TC1/2/3 or IC1/2/3 = TC or IC ≥ 1% PD-L1+; TC0 and IC0 = TC and IC < 1% PD-L1+.

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IFCT

IFCT-1502 CLINIVO: Real-life experience with nivolumab in patients with advanced NSCLC

Olivier MOLINIER, Clarisse AUDIGIER-VALETTE, Jacques CADRANEL, Isabelle MONNET, José HUREAUX, Werner HILGERS, Eric FAUCHON, Elisabeth FABRE, Benjamin BESSE, Philippe BRUN, Daniel COËTMEUR, Elisabeth QUOIX, Pierre MOURLANETTE, Fabrice BARLESI, Stéphanie BORDENAVE-CAFFRE, Thomas EGENOD, Pascale MISSY, Franck MORIN, Denis MORO-SIBILOT, Nicolas GIRARD

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9371 - N. Girard et al.
IFCT-1502 CLINIVO: Real-life experience with nivolumab in 600 patients (pts) with advanced Non-Small Cell Lung Cancer (NSCLC).

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Methods

- This analysis included 902 patients with stage IIIB/IV NSCLC who received ≥1 dose of nivolumab 3mg/kg q2w through the French EAP.

- Data were collected from patients medical records by IFCT research staff at each site of the study.

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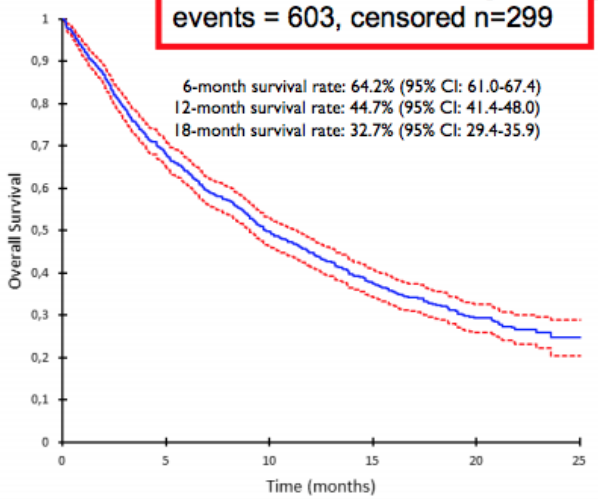
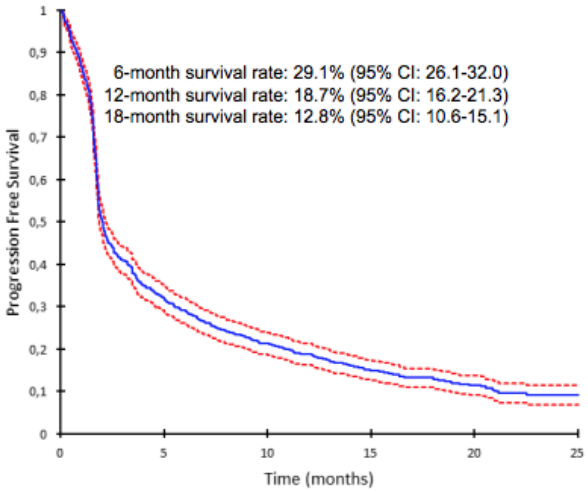
Efficacy of nivolumab: survival

Median OS, 95% CI: 9.9 [9.1-11.3]
events = 603, censored n=299





9371 - N

IFCT-1502 CLINIVO: Real-life experience with nivolumab in 600 patients (pts) with advanced Non-Small Cell Lung Cancer (NSCLC).

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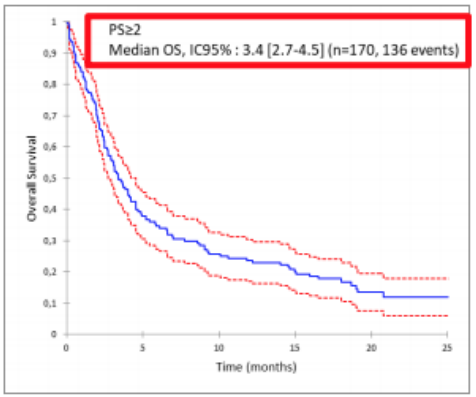
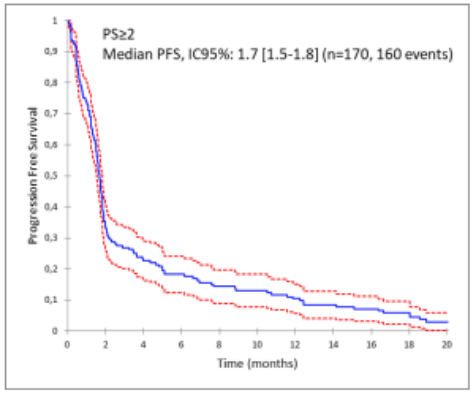
Efficacy of nivolumab: PS≥2 patients

Best response %, 95%CI	Total (n=121)	
Objective response	12%	[6.5%-18.3%]
Stable Disease	31%	[23.1%-39.7%]
Disease Control	44%	[35.0%-52.6%]
Progression	56%	[47.4%-65.0%]





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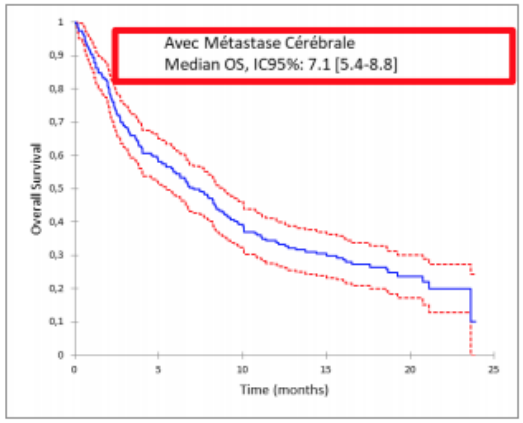
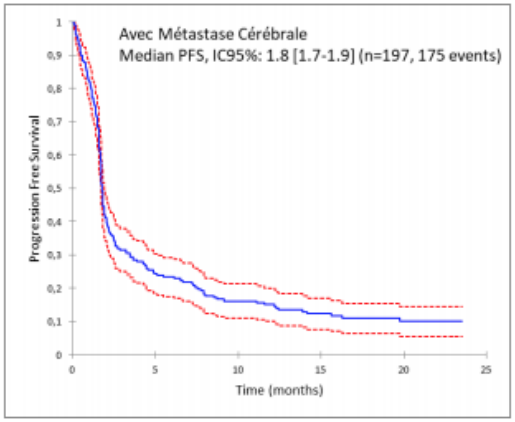
Efficacy of nivolumab: patients with brain metastases

Best response %, 95%CI	Total (n=159)	
Objective response	16%	[10.1%-21.4%]
Stable	33%	[26.0%-40.7%]
Disease Control	49%	[41.3%-56.8%]
Progression	51%	[43.2%-58.7%]





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IFCT-1502 CLINIVO: Real-life experience with nivolumab in 600 patients (pts) with advanced Non-Small Cell Lung Cancer (NSCLC).

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Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-based Chemotherapy for Advanced NSCLC With PD-L1 TPS ≥50%

Julie R. Brahmer,[1] Delvys Rodríguez-Abreu,[2] Andrew G. Robinson,[3] Rina Hui,[4] Tibor Csőszi,[5] Andrea Fülöp,[6] Maya Gottfried,[7] Nir Peled,[8] Ali Tafreshi,[9] Sinead Cuffe,[10] Mary O'Brien,[11] Suman Rao,[12] Katsuyuki Hotta,[13] Antonio Riccio,[14] Jing Yang,[14] M. Catherine Pietanza,[14] Martin Reck[15]

[1]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [2]Hospital Universitario Insular de Gran Canaria, Las Palmas, Spain; [3]Cancer Centre of Southeastern Ontario at Kingston General Hospital, Kingston, ON, Canada; [4]Westmead Hospital and the University of Sydney, Sydney, NSW, Australia; [5]Jász-Nagykun-Szolnok County Hospital, Szolnok, Hungary; [6]Országos Korányi TBC és Pulmonológiai Intézet, Budapest, Hungary; [7]Meir Medical Center, Kfar-Saba, Israel; [8]Davidoff Cancer Center, Tel Aviv University, Petah Tikva, Israel; [9]Southern Medical Day Care Centre, Wollongong, NSW, Australia; [10]St. James's Hospital and Cancer Trials Ireland (formerly ICORG – All Ireland Cooperative Oncology Research Group), Dublin, Ireland; [11]The Royal Marsden Hospital, Sutton, Surrey, UK; [12]MedStar Franklin Square Hospital, Baltimore, MD, USA; [13]Okayama University Hospital, Okayama, Japan; [14]Merck & Co., Inc., Kenilworth, NJ, USA; [15]Lung Clinic Grosshansdorf, Airway Research Center North (ARCN), member of the German Center for Lung Research (DZL), Grosshansdorf, Germany.

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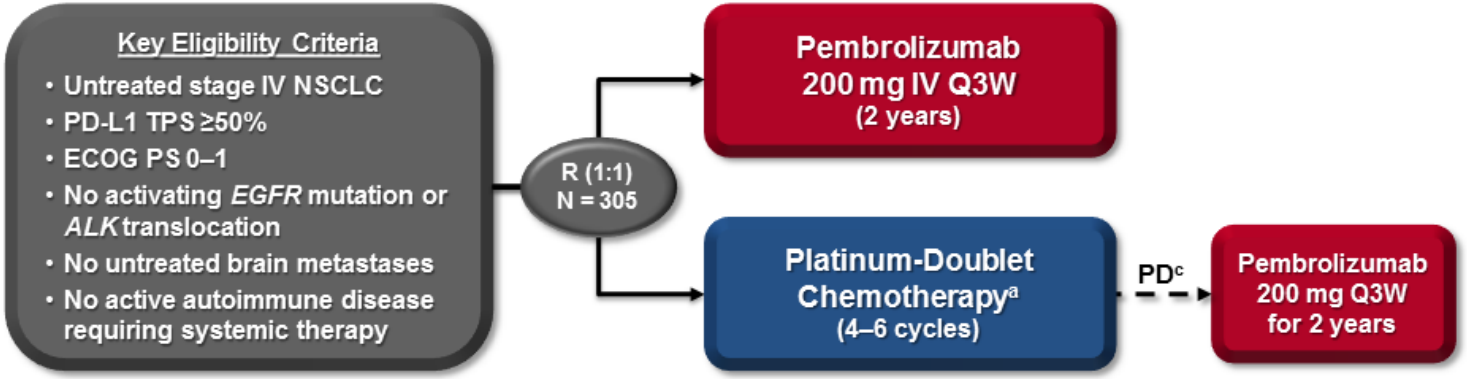
KEYNOTE-024 Study Design (NCT02142738)



- Pemetrexed + carboplatin[b]
- Pemetrexed + cisplatin[b]
- Paclitaxel + carboplatin
- Gemcitabine + carboplatin
- Gemcitabine + cisplatin

End Points

Primary:	PFS (RECIST v1.1, blinded independent central review)
Key secondary:	OS
Secondary:	ORR, safety
Exploratory:	DOR

[a]Optional pemetrexed maintenance therapy for nonsquamous disease. [b]Permitted for nonsquamous disease only.
[c]Prior to the DMC recommendation and amendment 6, which permitted those in the chemotherapy arm to be offered pembrolizumab (based on interim analysis 2 data), patients were eligible for crossover when PD was confirmed by blinded, independent central radiology review.

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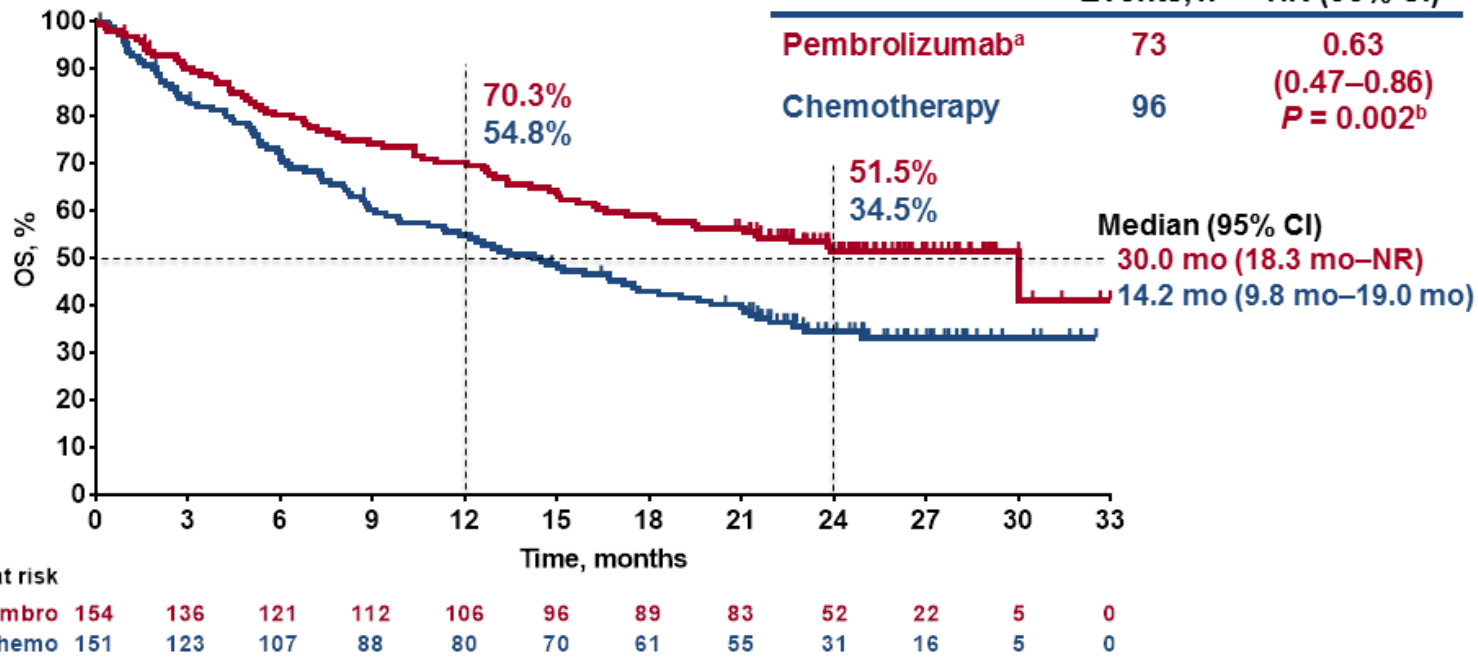
Overall Survival: Updated Analysis



[a]Effective crossover rate from chemotherapy to anti-PD-L1 therapy, 62.3% (82 patients crossed over to pembrolizumab during the study and 12 received anti-PD-L1 therapy outside of crossover). [b]Nominal *P* value. NR, not reached.
Data cutoff: July 10, 2017.

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Pemetrexed-Carboplatin plus Pembrolizumab as First-Line Therapy for Advanced Nonsquamous NSCLC: KEYNOTE-021 Cohort G Update

Hossein Borghaei,[1] Corey J. Langer,[2] Shirish Gadgeel,[3] Vassiliki A. Papadimitrakopoulou,[4] Amita Patnaik,[5] Steven F. Powell,[6] Ryan D. Gentzler,[7] Renato G. Martins,[8] James P. Stevenson,[9] Shadia I. Jalal,[10] Amit Panwalkar,[11] James Chih-Hsin Yang,[12] Matthew Gubens,[13] Lecia V. Sequist,[14] Mark M. Awad,[15] Joseph Fiore,[16] Sanatan Saraf,[16] Harry Raftopoulos,[16*] Leena Gandhi[15]

[1]Fox Chase Cancer Center, Philadelphia, PA, USA; [2]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [3]Karmanos Cancer Institute/Wayne State University, Detroit, MI, USA; [4]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [5]Laura and Isaac Perlmutter Cancer Center, NYU Langone Medical Center, New York, NY, USA; [6]Sanford Health, Sioux Falls, SD, USA; [7]University of Virginia, Charlottesville, VA, USA; [8]Seattle Cancer Care Alliance, Seattle, WA, USA; [9]Cleveland Clinic, Cleveland, OH, USA; [10]Indiana University School of Medicine, Indianapolis, IN, USA; [11]Sanford Roger Maris Cancer Center, Fargo, ND, USA; [12]National Taiwan University Hospital, Taipei, Taiwan; [13]University of California San Francisco, San Francisco, CA, USA; [14]Massachusetts General Hospital, Boston, MA, USA; [15]Dana-Farber Cancer Institute, Boston, MA, USA; [16]Merck & Co., Inc., Kenilworth, NJ, USA *Previous employee

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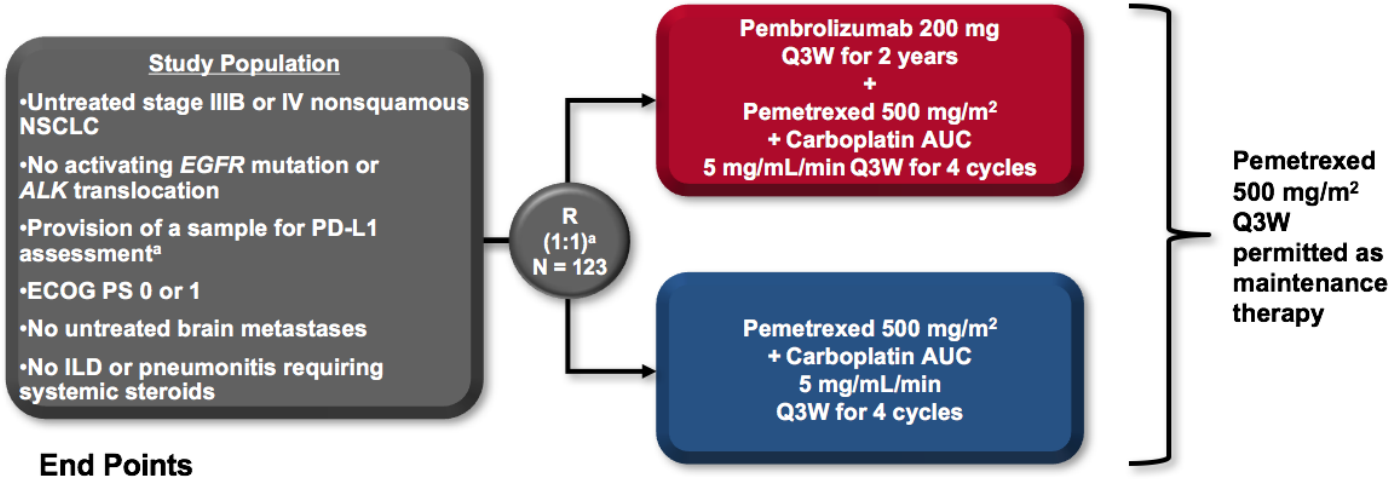
KEYNOTE-021 Cohort G

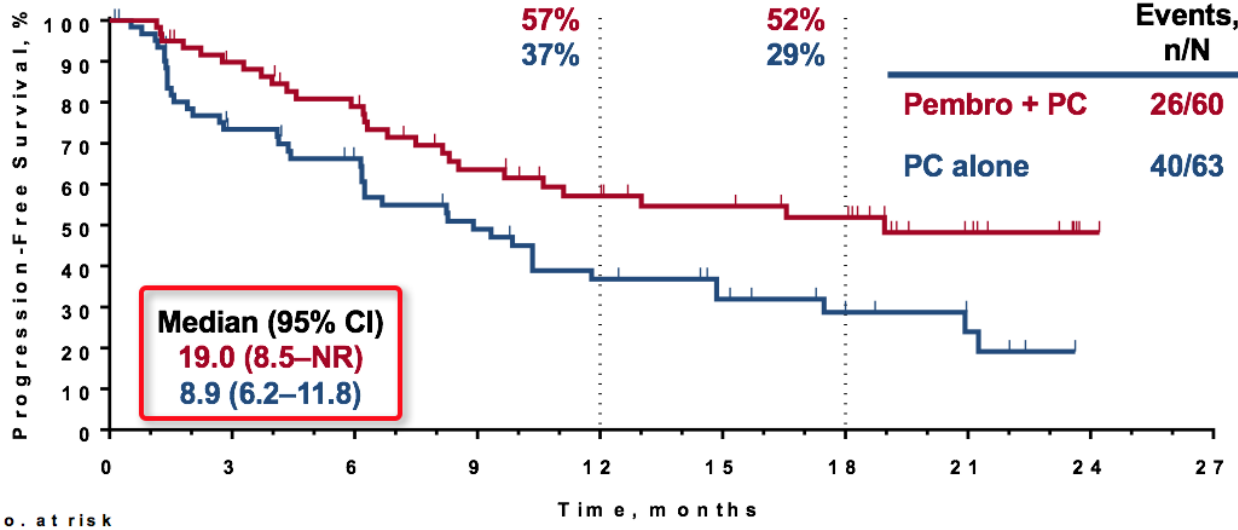


End Points

- Primary: ORR (RECIST v1.1 per blinded, independent central review)
- Key secondary: PFS
- Other secondary: OS, safety, relationship between antitumor activity and PD-L1 TPS
- No alpha allocated for updated analysis; all *P* values are nominal (one-sided $P < 0.025$)

[a]Randomization was stratified by PD-L1 TPS <1% vs ≥1%.

Progression-Free Survival
(RECIST v1.1 by Blinded, Independent Central Review)



	Events, n/N	HR (95% CI)
Pembro + PC	26/60	0.54 (0.33–0.88) $P = 0.0067^a$
PC alone	40/63	

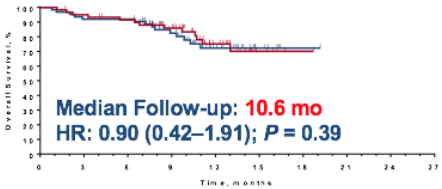
No. at risk

60	51	43	32	24	22	17	9	1	0
63	42	35	25	18	13	8	5	1	0

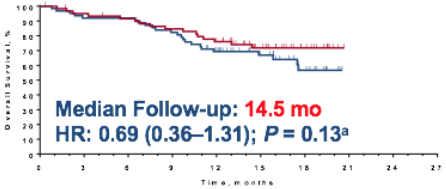
[a]P value is descriptive (one-sided P < 0.025).
Data cut-off: May 31, 2017.

Overall Survival

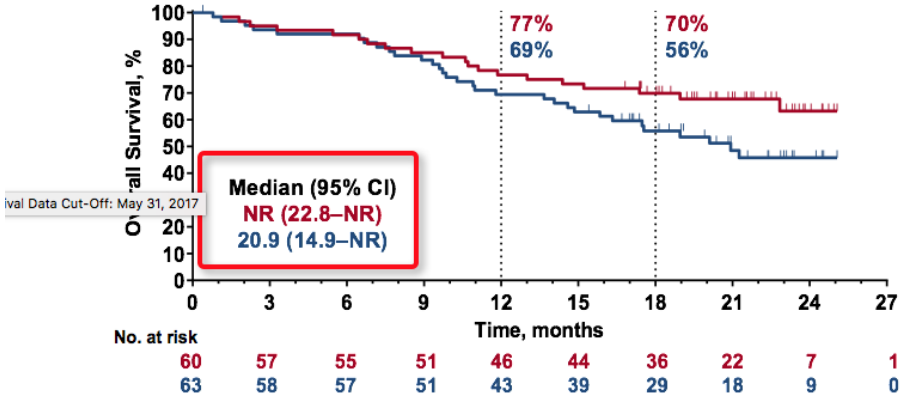
Data Cut-off: August 8, 2016[1]



Data Cut-off: December 31, 2016[2]



Data Cut-off: May 31, 2017



Median Follow-Up: 18.7 mo

	Events, n/N	HR (95% CI)
Pembro + PC	20/60[b]	0.59 (0.34–1.05)
PC alone	31/63[b]	*P* = 0.03[a]

1. Langer CJ, et al. Lancet Oncol. 2016;17(11):1497-1508. 2. Papadimitrakopoulou VA, et al. 2017. J Clin Oncol. 35(suppl): abstract 9094.
[a]P value is descriptive (one-sided P < 0.025). [b]24 additional deaths since primary analysis (pembro + PC, n = 7; PC alone, n = 17).

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PACIFIC: A DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE III STUDY OF DURVALUMAB AFTER CHEMORADIATION THERAPY IN PATIENTS WITH STAGE III, LOCALLY ADVANCED, UNRESECTABLE NSCLC

Luis Paz-Ares[1], Augusto Villegas[2], Davey Daniel[3], David Vicente[4], Shuji Murakami[5], Rina Hui[6], Takashi Yokoi[7], Alberto Chiappori[8], Ki Hyeong Lee[9], Maike de Wit[10], Byoung Chul Cho[11], Maryam Bourhaba[12], Xavier Quantin[13], Takaaki Tokito[14], Tarek Mekhail[15], David Planchard[16], Haiyi Jiang[17], Yifan Huang[17], Phillip A. Dennis[17], Mustafa Özgüroğlu[18]

[1]Hospital Universitario 12 de Octubre, CiberOnc, Universidad Complutense and CNIO, Madrid, Spain; [2]Cancer Specialists of North Florida, Jacksonville, FL, USA; [3]Tennessee Oncology, Chattanooga, TN, and Sarah Cannon Research Institute, Nashville, TN, USA; [4]Hospital Universitario Virgen Macarena, Seville, Spain; [5]Kanagawa Cancer Center, Yokohama, Japan; [6]Westmead Hospital and the University of Sydney, Sydney, NSW, Australia; [7]Kansai Medical University Hospital, Hirakata, Japan; [8]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA; [9]Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju, Korea; [10]Vivantes Klinikum Neukoelln, Berlin, Germany; [11]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea; [12]Centre Hospitalier Universitaire de Liège, Liège, Belgium; [13]CHU Montpellier and ICM Val d'Aurelle, Montpellier, France; [14]Kurume University Hospital, Kurume, Japan; [15]Florida Hospital Cancer Institute, Orlando, FL, USA; [16]Gustave Roussy, Villejuif, France; [17]AstraZeneca, Gaithersburg, MD, USA; [18]Istanbul University Cerrahpasa School of Medicine, Istanbul, Turkey

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Acknowledgement: Dr. Scott J. Antonia of H. Lee Moffitt Cancer Center and Research Institute is the lead author for this study; Dr. Paz-Ares is presenting on his behalf

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Yokoi, A. Chiappori, K.H. Lee, M. de Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.-C. Kim, C.S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. de Castro Carpeño, C. Wadsworth, G. Melillo, H. Jiang, Y. Huang, P.A. Dennis, and M. Özgüroğlu, for the PACIFIC Investigators*

This article was published on September 8, 2017, at NEJM.org.

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PACIFIC: Study Design

Phase III, Randomized, Double-blind, Placebo-controlled, Multicenter, International Study

- Patients with stage III, locally advanced, unresectable NSCLC who have not progressed following definitive platinum-based cCRT (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- Estimated life expectancy of ≥12 weeks
- Archived tissue was collected

All-comers population

1–42 days post-cCRT

R

2:1 randomization, stratified by age, sex, and smoking history
N=713

Durvalumab
10 mg/kg q2w for up to 12 months
N=476

Placebo
10 mg/kg q2w for up to 12 months
N=237

Co-primary endpoints

- PFS by BICR using RECIST v1.1*
- OS

Key secondary endpoints

- ORR (per BICR)
- DoR (per BICR)
- Safety and tolerability
- PROs

*Defined as the time from randomization (which occurred up to 6 weeks post-cCRT) to the first documented event of tumor progression or death in the absence of progression.
ClinicalTrials.gov number: NCT02125461 BICR, blinded independent central review; cCRT, concurrent chemoradiation therapy; DoR, duration of response; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PROs, patient-reported outcomes; PS, performance status; q2w, every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization

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Table 1. Baseline Characteristics, Stratification Factors, and Prior Therapy in the Intention-to-Treat Population.*

Characteristic	Durvalumab (N=476)	Placebo (N=237)	Total (N=713)
Age — yr			
Median	64	64	64
Range	31–84	23–90	23–90
Sex — no. (%)			
Male	334 (70.2)	166 (70.0)	500 (70.1)
Female	142 (29.8)	71 (30.0)	213 (29.9)
Race — no. (%)†			
White	337 (70.8)	157 (66.2)	494 (69.3)
Black	12 (2.5)	2 (0.8)	14 (2.0)
Asian	120 (25.2)	72 (30.4)	192 (26.9)
Disease stage — no. (%)			
IIIA	252 (52.9)	125 (52.7)	377 (52.9)
IIIB	212 (44.5)	107 (45.1)	319 (44.7)
Other‡	12 (2.5)	5 (2.1)	17 (2.4)
WHO performance-status score — no. (%)§			
0	234 (49.2)	114 (48.1)	348 (48.8)
1	240 (50.4)	122 (51.5)	362 (50.8)
Tumor histologic type — no. (%)			
Squamous	224 (47.1)	102 (43.0)	326 (45.7)
Nonsquamous	252 (52.9)	135 (57.0)	387 (54.3)
Smoking status — no. (%)			
Current smoker	79 (16.6)	38 (16.0)	117 (16.4)
Former smoker	354 (74.4)	178 (75.1)	532 (74.6)
Never smoked	43 (9.0)	21 (8.9)	64 (9.0)
Previous radiotherapy — no. (%)¶			
<54 Gy	3 (0.6)	0	3 (0.4)
≥54 to ≤66 Gy	442 (92.9)	217 (91.6)	659 (92.4)
>66 to ≤74 Gy	30 (6.3)	19 (8.0)	49 (6.9)
Previous chemotherapy — no. (%)‖			
Induction	123 (25.8)	68 (28.7)	191 (26.8)
Concurrent with radiation therapy	475 (99.8)	236 (99.6)	711 (99.7)
Best response to previous chemoradiotherapy — no. (%)			
Complete response	9 (1.9)	7 (3.0)	16 (2.2)
Partial response	232 (48.7)	111 (46.8)	343 (48.1)
Stable disease	222 (46.6)	114 (48.1)	336 (47.1)

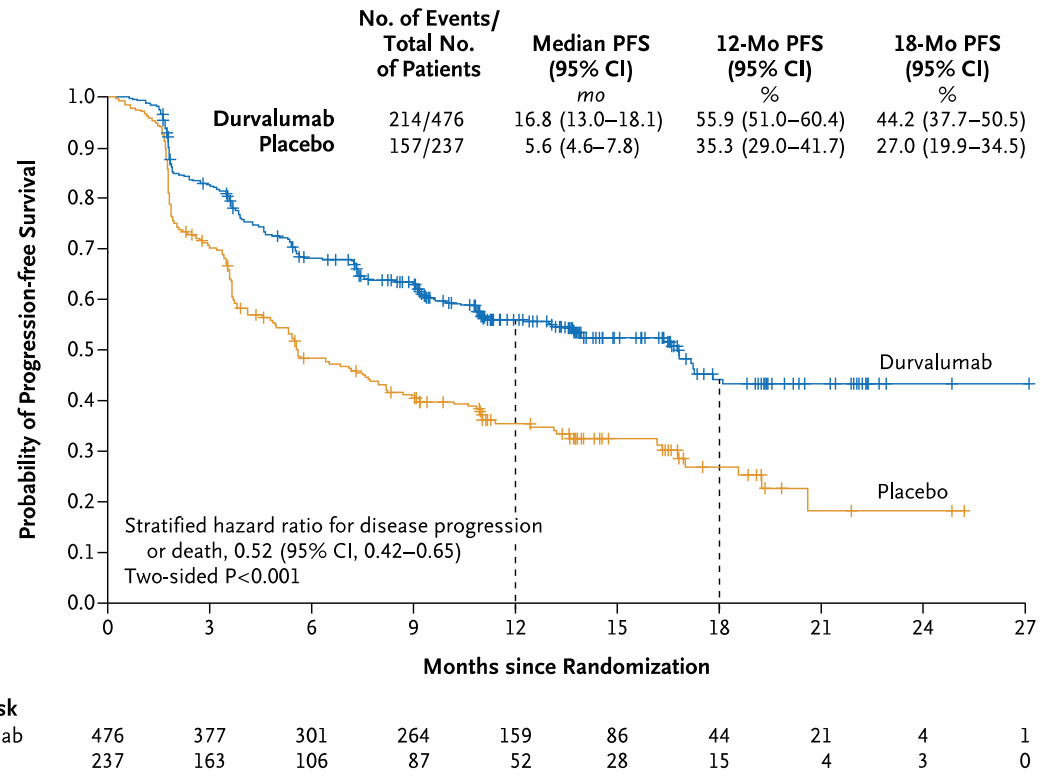

Figure 1. Progression-free Survival in the Intention-to-Treat Population.

Shown are Kaplan–Meier curves for progression-free survival (PFS), defined according to the Response Evaluation Criteria in Solid Tumors, version 1.1, and assessed by means of blinded independent central review. Tick marks indicate censored observations, and vertical lines indicate the times of landmark PFS analyses. The intention-to-treat population included all patients who underwent randomization.

Subgroup	Durvalumab	Placebo	Unstratified Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients		
All patients	476	237	0.55 (0.45–0.68)
Sex			
Male	334	166	0.56 (0.44–0.71)
Female	142	71	0.54 (0.37–0.79)
Age at randomization			
<65 yr	261	130	0.43 (0.32–0.57)
≥65 yr	215	107	0.74 (0.54–1.01)
Smoking status			
Smoker	433	216	0.59 (0.47–0.73)
Nonsmoker	43	21	0.29 (0.15–0.57)
NSCLC disease stage			
IIIA	252	125	0.53 (0.40–0.71)
IIIB	212	107	0.59 (0.44–0.80)
Tumor histologic type			
Squamous	224	102	0.68 (0.50–0.92)
Nonsquamous	252	135	0.45 (0.33–0.59)
Best response			
Complete response	9	7	—
Partial response	232	111	0.55 (0.41–0.75)
Stable disease	222	114	0.55 (0.41–0.74)
PD-L1 status			
≥25%	115	44	0.41 (0.26–0.65)
<25%	187	105	0.59 (0.43–0.82)
Unknown	174	88	0.59 (0.42–0.83)
EGFR mutation			
Positive	29	14	0.76 (0.35–1.64)
Negative	315	165	0.47 (0.36–0.60)
Unknown	132	58	0.79 (0.52–1.20)

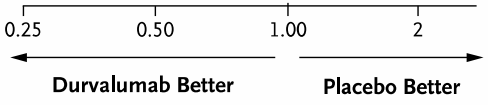

Figure 2. Subgroup Analysis of Prognostic Factors for Progression-free Survival in the Intention-to-Treat Population.

Progression-free survival was defined according to RECIST, version 1.1, and assessed by means of blinded independent central review. The hazard ratio and 95% confidence interval were not calculated for the complete response because this subgroup had less than 20 events. EGFR denotes epidermal growth factor receptor, and PD-L1 programmed death ligand 1.

Table 2. Antitumor Activity in the Intention-to-Treat Population.*

Variable	Durvalumab (N=443)†	Placebo (N=213)†	Treatment Effect‡	P Value
Objective response				
No. of patients with response	126	34		
% of patients (95% CI)	28.4 (24.3–32.9)	16.0 (11.3–21.6)	1.78 (1.27–2.51)	<0.001
Best overall response — no. (%)§				
Complete response	6 (1.4)	1 (0.5)		
Partial response	120 (27.1)	33 (15.5)		
Stable disease	233 (52.6)	119 (55.9)		
Progressive disease	73 (16.5)	59 (27.7)		
Could not be evaluated	10 (2.3)	1 (0.5)		
Duration of response — mo				
Median	NR	13.8	0.43	
95% CI		6.0–NR	0.22–0.84	
Ongoing response at data cutoff point — %¶				
At 12 mo	72.8	56.1		
At 18 mo	72.8	46.8		

Patient-Reported Outcomes With Durvalumab After Chemoradiation in Locally Advanced, Unresectable NSCLC: Data From PACIFIC

Rina Hui[1], Mustafa Özgüroğlu[2], Davey Daniel[3], David Vicente[4], Shuji Murakami[5], Takashi Yokoi[6], Alberto Chiappori[7], Ki Hyeong Lee[8], Maike de Wit[9], Byoung Chul Cho[10], Jhanelle E. Gray[7], Anna Rydén[11], Louis Viviers[12], Lynne Poole[13], Phillip A. Dennis[14], Scott J. Antonia[7]

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Presented by: Dr Rina Hui

IASLC 2017

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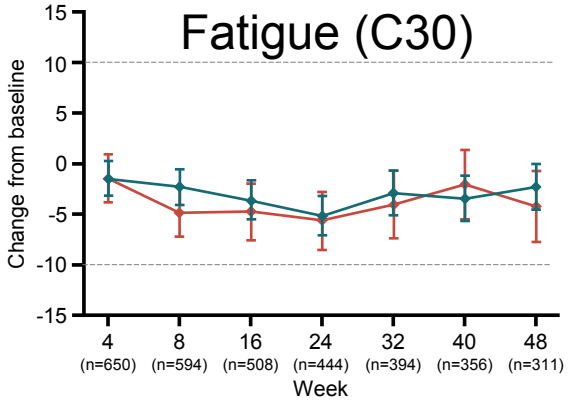
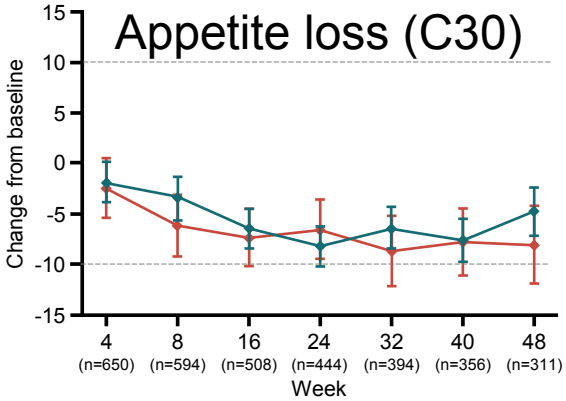
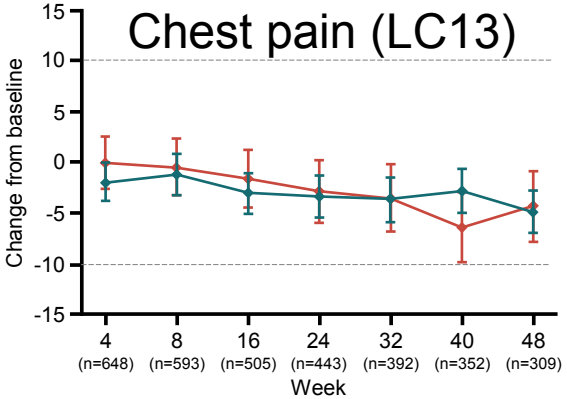
No Changes from Baseline: Key Symptoms

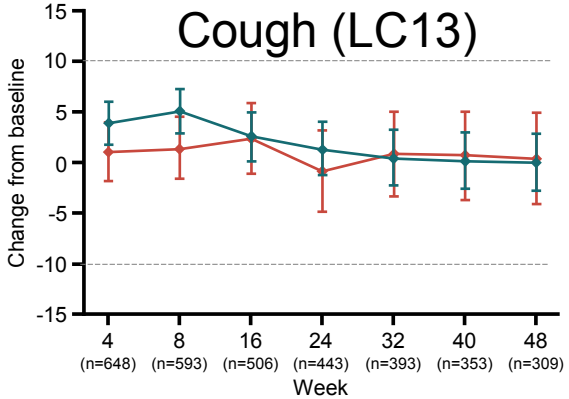
- Key symptoms scores remained stable throughout the study, with both durvalumab and placebo
- No significant differences between arms in changes from baseline for key symptoms

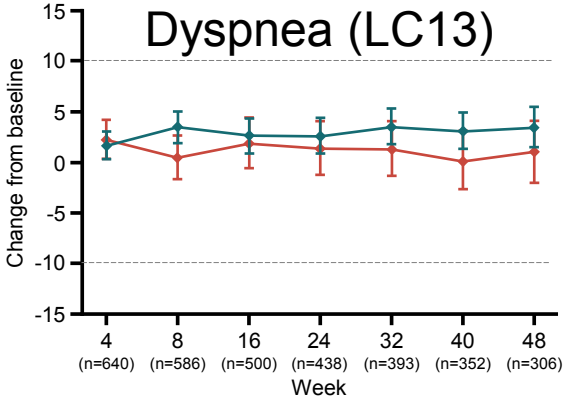
Durvalumab Placebo







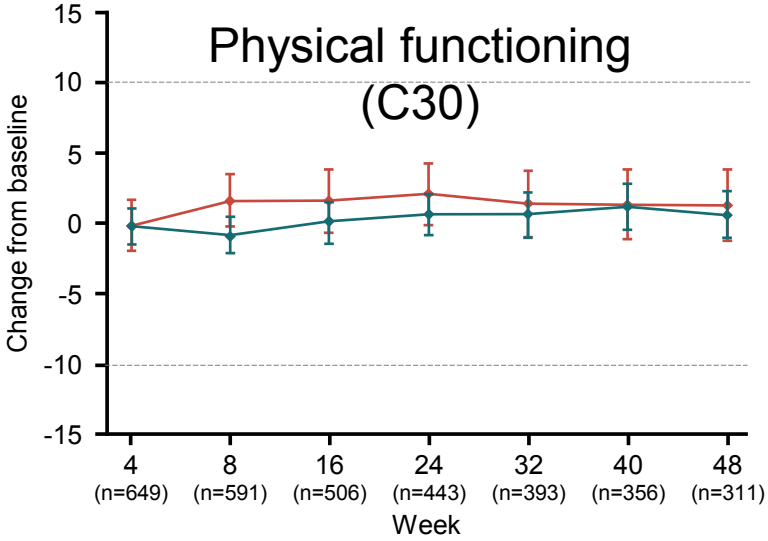


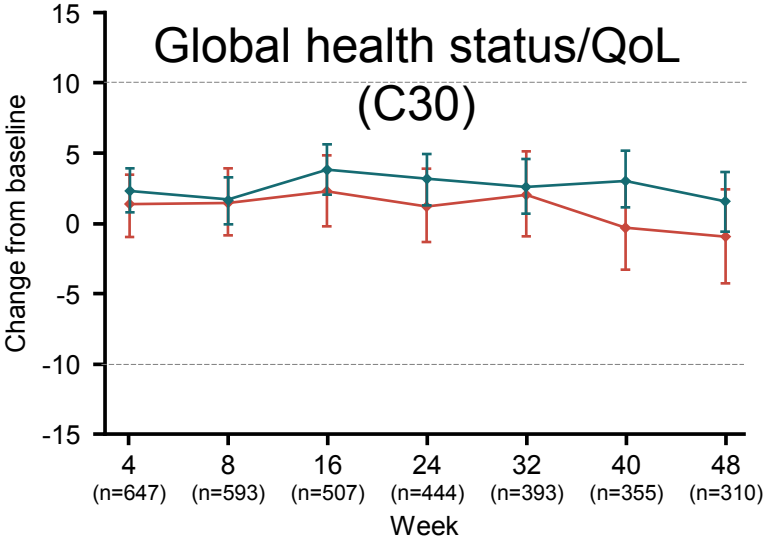


catharina ziekenhuis

No Changes from Baseline: Functioning and Global Health Status

- Functioning and global health status scores remained stable throughout the study
- No significant differences between arms in changes from baseline





Durvalumab Placebo

QoL, quality of life

Huidige / toekomstige situatie?

Huidige / toekomstige situatie?

Stadium III (na concurrent chemoradiatie):
Durvalumab (EAP)

1e lijn Stadium IV:
Plaveiselcelcarcinoom + niet-plaveiselcelcarcinoom
PD-L1 expressie ≥ 50% ➔ pembrolizumab
PD-L1 expressie < 50% ➔ chemotherapie

2e lijn Stadium IV:
Plaveiselcel carcinoom:
PD-L1 expressie ≥ 50% ➔ pembrolizumab (of nivolumab)
PD-L1 expressie < 50% ➔ nivolumab

Non-plaveiselcel carcinoom:
PD-L1 expressie ≥ 1% ➔ pembrolizumab (of nivolumab)
PD-L1 expressie < 1% ➔ nivolumab (?) of atezolizumab

Wat brengt de toekomst?

Rol van immunotherapie van stadium I / II?

Combinatie van immunotherapie met andere middelen?