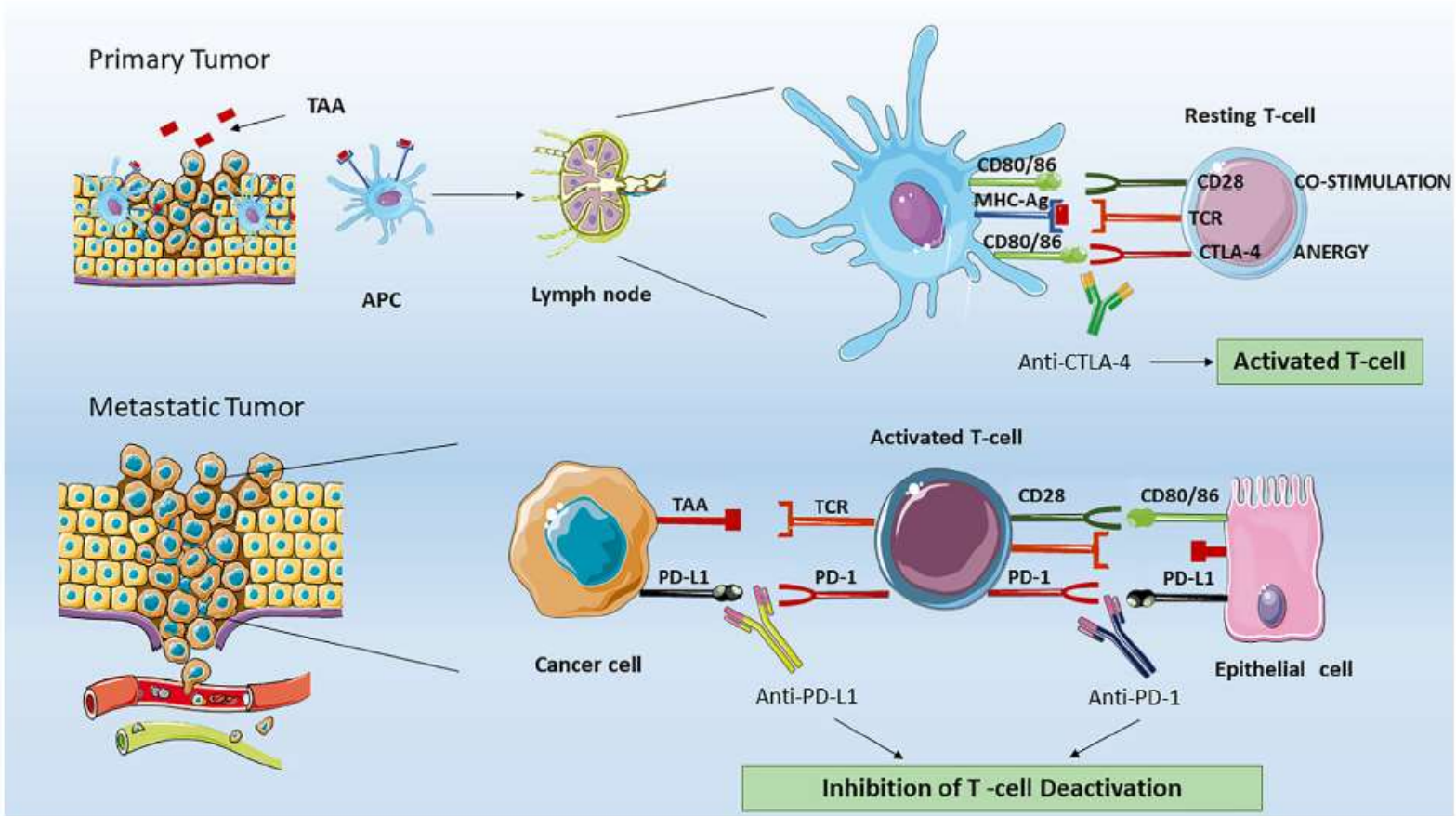
Immune checkpoint inhibitor (ICI) versus dual immune checkpoint inhibitor versus immune checkpoint inhibitor plus platinum compounds in metastatic NSCLC

Dr. Sanjay Rawal

- NSCLC constitutes 80-85% of lung cancer
- Advanced/metastatic disease is not amenable to surgery
- Cytotoxic chemotherapy, targeted therapy and immunotherapy are the available options for treatment in such cases.
- Immunotherapy has an important role in driver gene negative advanced NSCLS
- Anti-CTLA-4 and anti PD-1/PD-L1 agents are the mainstay of immunotherapy in NSCLC



Effect of immune check point inhibitors on T-lymphocytes

Front Immunol. 2020 Oct 8;11:574271

Immune check point inhibitors

CTLA-4	PD-1	PD-L1
Ipilimumab	Nivolumab	Atezolizumab
Tremelimumab	Pembrolizumab	Durvalumab
	Cemiplimab	Avelumab

ICIs represent different classes of monoclonal antibodies that interrupt the delivering of inhibitory signals to T cells, and reprogram adaptive immunity to participate to cancer elimination

CTLA-4-Cytotoxic T-Lymphocyte Antigen 4
PD-1- Programmed cell death protein 1
PD-L1- Programmed death ligand 1

Trials

PD-L1>50%

- KEYNOTE-024(Pembrolizumab)
- IMPOWER-110(Atezolizumab)
- EMPOWER-LUNG 1 (Cemiplimab)

PD-L1<50%

KEYNOTE-407(Pembro +CTx)

KEYNOTE-189(Pembro + CTx)

IMPOWER-150(ABCP)

IMPOWER-130(ACP)

CHECKMATE-9LA(Nivo+ Ipili +CTX)

CHECKMATE-227(Nivo +Ipili)

POSEIDON(Durval+Tremelimumab)

EMPOWER LUNG-3(Cemiplimab)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer

L. Gandhi, D. Rodríguez-Abreu, S. Gadgeel, E. Esteban, E. Felip, F. De Angelis, M. Domine, P. Clingan, M.J. Hochmair, S.F. Powell, S.Y.-S. Cheng, H.G. Bischoff, N. Peled, F. Grossi, R.R. Jennens, M. Reck, R. Hui, E.B. Garon, M. Boyer, B. Rubio-Viqueira, S. Novello, T. Kurata, J.E. Gray, J. Vida, Z. Wei, J. Yang, H. Raftopoulos, M.C. Pietanza, and M.C. Garassino, for the KEYNOTE-189 Investigators*

N Engl J Med. 2018 May 31;378(22):2078-2092

Study Design	Inclusion criteria	Intervention
Randomised, double blinded, phase 3 trial Intervention group(n=410) Placebo group(n= 206)	• Age >18 yrs • Pathologically confirmed metastatic NSCLC • ECOG performance status score 0 or 1 • At least one measurable lesion as per RECIST 1.1 • Provided a tumor sample for assessment of PD-L1 status	200 mg of pembrolizumab vs. saline placebo/Q3W x 35 cycles **Plus** 4 cycles of Cisplatin/Carboplatin(Q3W), followed by Pemetrexed every 3 weeks

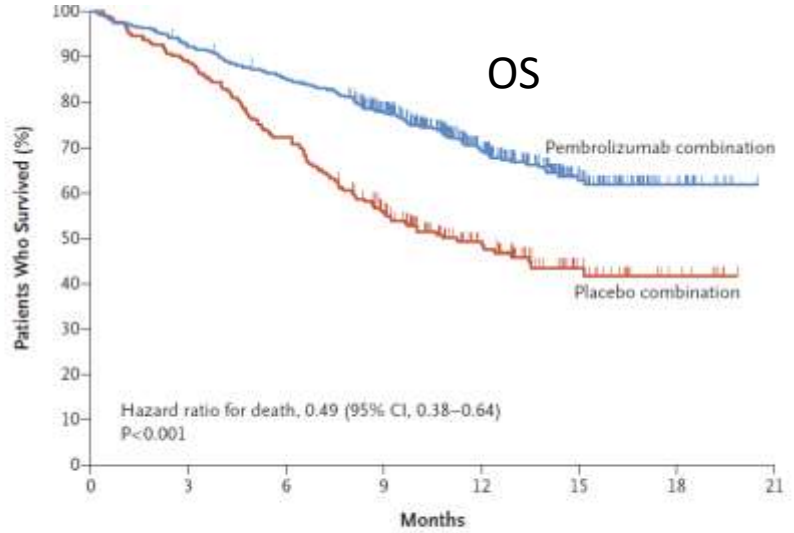
PFS- time from randomization to disease progression, as assessed by blinded, independent central radiologic review, or death from any cause, whichever occurred first

OS- time from randomization to death from any cause

RECIST- Response evaluation criteria in solid tumors

N Engl J Med. 2018 May 31;378(22):2078-2092

OS

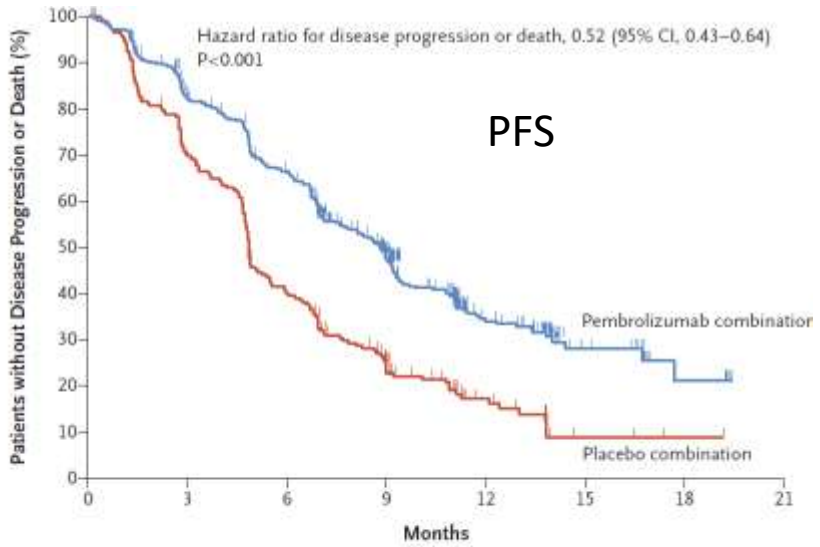


No. at Risk								
Pembrolizumab combination	410	377	347	278	163	71	18	0
Placebo combination	206	183	149	104	59	25	8	0

Median overall survival

- Pembrolizumab-combination group: not reached
- Placebo combination group: 11.3 months (95% CI, 8.7 to 15.1)

PFS



No. at Risk								
Pembrolizumab combination	410	322	256	149	60	17	5	0
Placebo combination	206	141	80	40	16	3	1	0

Progression free survival

- Pembrolizumab-combination group: 8.8 months(95% CI, 7.6 to 9.2)
- Placebo-combination: 4.9 months (95% CI, 4.7 to 5.5)

Estimated proportion of patients who were alive and progression-free at 12 months

- Pembrolizumab-combination group34.1% (95% CI, 28.8 to 39.5)
- Placebo-combination group 17.3% (95% CI, 12.0 to 23.5)

N Engl J Med. 2018 May 31;378(22):2078-2092

KEYNOTE-189 5-year update: First-line pembrolizumab + pemetrexed and platinum vs placebo + pemetrexed and platinum for metastatic nonsquamous NSCLC

	ITT N = 616	TPS ≥50% n = 202	TPS 1%–49% n = 186	TPS <1% n = 190
OS HR (95% CI)[a]	0.60 (0.50–0.72)	0.68 (0.49–0.96)	0.65 (0.46–0.90)	0.55 (0.39–0.76)
5-y OS rate[a],%	19.4 vs 11.3	29.6 vs 21.4	19.8 vs 7.7	9.6 vs 5.3
PFS HR (95%CI)[a,b]	0.50 (0.42–0.60)	0.35 (0.25–0.49)	0.57 (0.41–0.80)	0.67 (0.49–0.92)
ORR[b], %	48.3 vs 19.9	62.1 vs 25.7	50.0 vs 20.7	33.1 vs 14.3
Median DOR[a,b] mo (range)	12.7 (1.1+ to 68.3+) vs 7.1 (2.4 to 31.5)	15.3 (1.2+ to 68.3+) vs 7.1 (3.4 to 31.5)	13.6 (2.1+ to 67.6+) vs 7.6 (2.4 to 31.0+)	10.8 (1.1+ to 59.4+) vs 7.8 (4.1 to 28.3+)

Pembrolizumab + pemetrexed-platinum as first-line continued to show OS and PFS benefits with manageable toxicity as compared to placebo + pemetrexed-platinum irrespective of PD-L1 expression.

Ann Oncol., Volume 33, supplement 7, S992-S993, September 2022

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy for Squamous Non–Small-Cell Lung Cancer

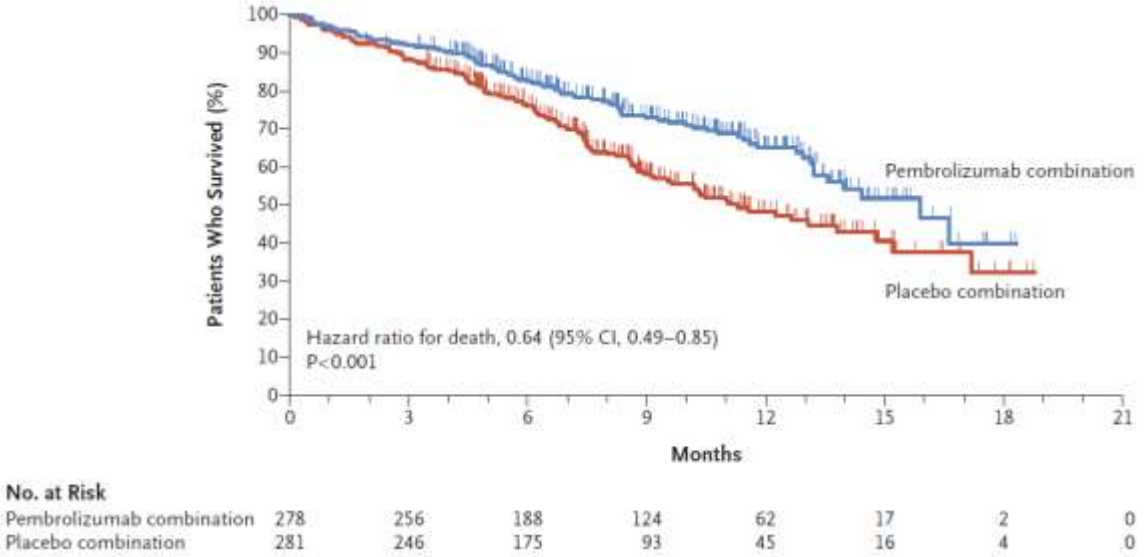
L. Paz-Ares, A. Luft, D. Vicente, A. Tafreshi, M. Gümüş, J. Mazières, B. Hermes, F. Çay Şenler, T. Csőszi, A. Fülöp, J. Rodríguez-Cid, J. Wilson, S. Sugawara, T. Kato, K.H. Lee, Y. Cheng, S. Novello, B. Halmos, X. Li, G.M. Lubiniecki, B. Piperdi, and D.M. Kowalski, for the KEYNOTE-407 Investigators*

N Engl J Med. 2018 Nov 22;379(21):2040-2051

Study Design	Inclusion criteria	Intervention
Randomised, double blinded, phase 3 trial Intervention group(n=278) Placebo group(n= 281)	• Age >18 yrs • Pathologically confirmed stage IV squamous NSCLC • received no previous systemic therapy for metastatic disease • ECOG performance status score 0 or 1 • At least one measurable lesion as per RECIST 1.1 • Provided a tumor sample for determination of PD-L1 status	200 mg of pembrolizumab vs. saline Q3W x 35 cycles **Plus** 4 cycles of Carboplatin & Paclitaxel(D1) or Nab-paclitaxel(D1,8,15) x Q3W

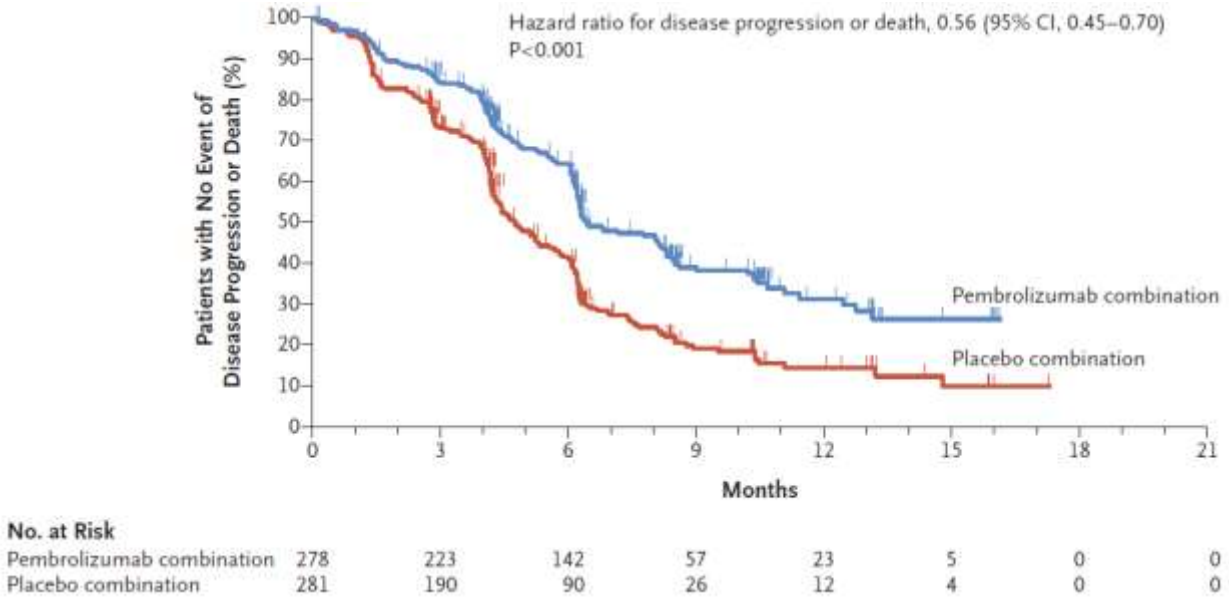
Primary end point: Overall survival and progression free survival

N Engl J Med. 2018 Nov 22;379(21):2040-2051



Median overall survival

- Pembrolizumab-combination group: 15.9 months(95% CI,13.2 to NR)
- Placebo combination group: 11.3 months (95% CI, 9.5 to 14.8)



Progression free survival

- Pembrolizumab-combination group: 6.4 months (95% CI,6.2 to 8.3)
- Placebo combination group: 4.8 months (95% CI, 4.3 to 5.7)

N Engl J Med. 2018 Nov 22;379(21):2040-2051

Pembrolizumab Plus Chemotherapy in Squamous Non–Small-Cell Lung Cancer: 5-Year Update of the Phase III KEYNOTE-407 Study

Silvia Novello, MD, PhD[1]; Dariusz M. Kowalski, MD, PhD[2]; Alexander Luft, MD, PhD[3]; Mahmut Gümüş, MD[4]; David Vicente, MD[5]; Julien Mazières, MD, PhD[6]; Jeronimo Rodríguez-Cid, MD[7]; Ali Tafreshi, MD[8]; Ying Cheng, MD[9]; Ki Hyeong Lee, MD, PhD[10]; Alexander Golf, MD[11]; Shunichi Sugawara, MD, PhD[12]; Andrew G. Robinson, MD[13]; Balazs Halmos, MD[14]; Erin Jensen, MS[15]; Paul Schwarzenberger, MD[16]; M. Catherine Pietanza, MD[16]; and Luis Paz-Ares, MD, PhD[17]

	ITT(n=559)	TPS≥50%(n=146)	TPS 1%–49% (n=207)	TPS <1% (n=194)
OS HR(95% CI)	0.71(0.59 to 0.85)	0.68(0.47 to 0.97)	0.61(0.45 to 0.83	0.83(0.61 to 1.13)
5 yr OS rate%	18.4% vs. 9.7%	23.3% vs. 8.3	20.6% vs. 7.6%	10.7% vs. 13.1%
PFS HR(95% CI)	0.62(0.52 to 0.74)	0.48 (0.33 to 0.69)	0.60(0.45 to 0.81)	0.70(0.52 to 0.95)
ORR %	62.2% (56.2 to 68.0)	64.4 (52.3 to 75.3)	54.4 (44.3 to 64.2)	54.4 (44.3 to 64.2)
Median DOR mo (range)	9.0 (1.31+ to 61.51+)	10.4 (2.7 to 59.41+)	11.1 (1.31+ to 61.51+)	6.9 (1.41+ to 58.91+)

J Clin Oncol. 2023 Feb 3;JCO2201990

Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial

Howard West, Michael McCleod, Maen Hussein, Alessandro Morabito, Achim Rittmeyer, Henry J Conter, Hans-Georg Kopp, Davey Daniel, Steven McCune, Tarek Mekhail, Alona Zer, Niels Reinmuth, Ahad Sadiq, Alan Sandler, Wei Lin, Tania Ochi Lohmann, Venice Archer, Lijia Wang, Marcin Kowanetz, Federico Cappuzzo

Lancet Oncol 2019; 20: 924–37
Published Online
May 20, 2019
http://dx.doi.org/10.1016/S1470-2045(19)30167-6
See Comment page 889

Summary

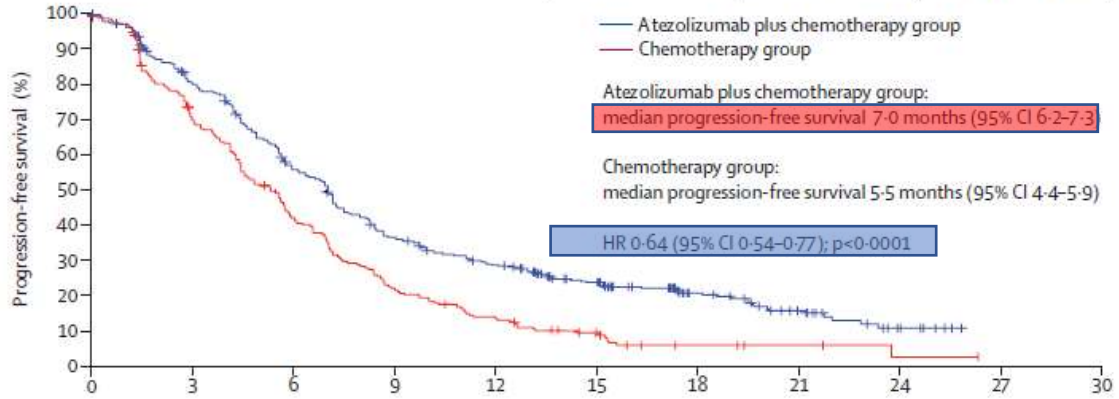
Background Atezolizumab (a monoclonal antibody against PD-L1), which restores anticancer immunity, improved overall survival in patients with previously treated non-small-cell lung cancer and also showed clinical benefit when combined with chemotherapy as first-line treatment of non-small-cell lung cancer. IMpower130 aimed to assess the efficacy and safety of atezolizumab plus chemotherapy versus chemotherapy alone as first-line therapy for non-squamous non-small-cell lung cancer.

Lancet Oncol. 2019 Jul;20(7):924-937

Study design	Inclusion criteria	Intervention
Multicentre, randomised, open-label, phase 3 Atezolizumab +chemotherapy group(n=483) Chemotherapy group(n=240)	• Age >18 yrs • Pathologically confirmed stage IV non squamous NSCLC • Received no previous systemic therapy for metastatic disease • ECOG performance status score 0 or 1 • Patients were required to have known PD-L1 tumour status	**Induction** : Atezolizumab 1200 mg Q3W in combination with chemotherapy (Carboplatin Q3W plus nab paclitaxel Q1W) (n=483) **or** Chemotherapy 4-6 cycles /Q3W (n=240) **Maintainence** : Atezolizumab plus chemotherapy group - 1200 mg intravenous atezolizumab Chemotherapy group: Best supportive care or pemetrexed switch

Lancet Oncol. 2019 Jul;20(7):924-937

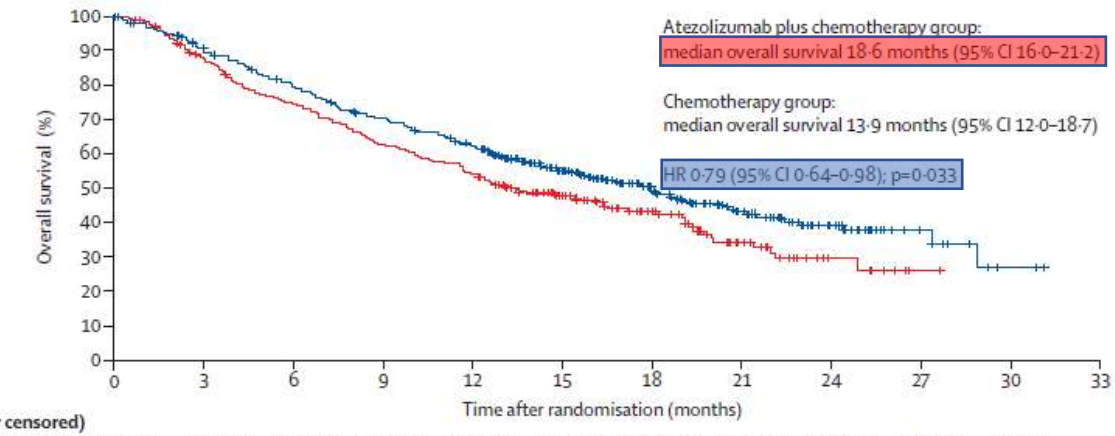
	Progression-free survival at 6 months	Progression-free survival at 12 months
Atezolizumab plus chemotherapy group	56·1% (95% CI 51·5–60·8)	29·1% (95% CI 24·8–33·4)
Chemotherapy group	42·5% (95% CI 35·9–49·1)	14·1% (95% CI 9·4–18·8)



Number at risk (number censored)

Atezolizumab plus chemotherapy group	451 (0)	351 (13)	242 (17)	157 (19)	119 (25)	78 (48)	41 (77)	23 (86)	7 (97)
Chemotherapy group	228 (0)	150 (13)	90 (14)	48 (14)	29 (15)	15 (21)	5 (26)	3 (28)	1 (29)

	Overall survival at 12 months	Overall survival at 24 months
Atezolizumab plus chemotherapy group	63·1% (95% CI 58·6–67·7)	39·6% (95% CI 33·6–45·7)
Chemotherapy group	55·5% (95% CI 48·9–62·2)	30·0% (95% CI 21·7–38·2)



Number at risk (number censored)

Atezolizumab plus chemotherapy group	451 (0)	400 (10)	351 (15)	305 (18)	268 (22)	194 (68)	129 (120)	75 (161)	40 (188)	12 (215)	4 (221)
Chemotherapy group	228 (0)	190 (12)	161 (13)	136 (13)	119 (13)	90 (28)	58 (52)	31 (70)	13 (85)	3 (94)	0 (0)

Lancet Oncol. 2019 Jul;20(7):924-937

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

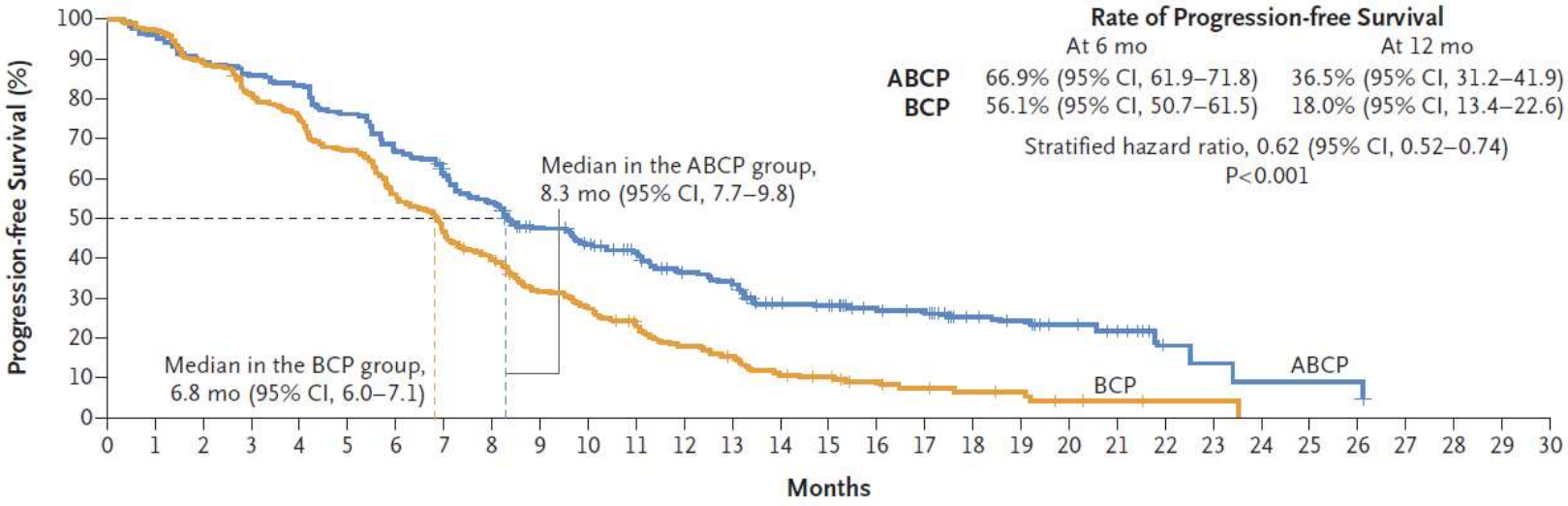
Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC

M.A. Socinski, R.M. Jotte, F. Cappuzzo, F. Orlandi, D. Stroyakovskiy, N. Nogami, D. Rodríguez-Abreu, D. Moro-Sibilot, C.A. Thomas, F. Barlesi, G. Finley, C. Kelsch, A. Lee, S. Coleman, Y. Deng, Y. Shen, M. Kowanetz, A. Lopez-Chavez, A. Sandler, and M. Reck, for the IMpower150 Study Group*

N Engl J Med. 2018 Jun 14;378(24):2288-2301

Study design	Inclusion criteria	Intervention
International, open-label, phase 3 study,	Stage IV or recurrent metastatic non squamous NSCLC ECOG performance status of 0 or 1 Tumor tissue available for biomarker testing Eligible to receive bevacizumab	Randomly assigned, in a 1:1:1 ratio, **ACP group(n=402)** - atezolizumab plus carboplatin plus paclitaxel, **ABCP group(n=400)** - atezolizumab plus bevacizumab plus carboplatin plus paclitaxel, or **BCP group(n=400)** - bevacizumab plus carboplatin plus paclitaxel Induction phase- 4-6/ 21 days cycle Maintainence phase : continued to receive atezolizumab, bevacizumab, or both until the occurrence of unmanageable toxic effects or disease progression

N Engl J Med. 2018 Jun 14;378(24):2288-2301

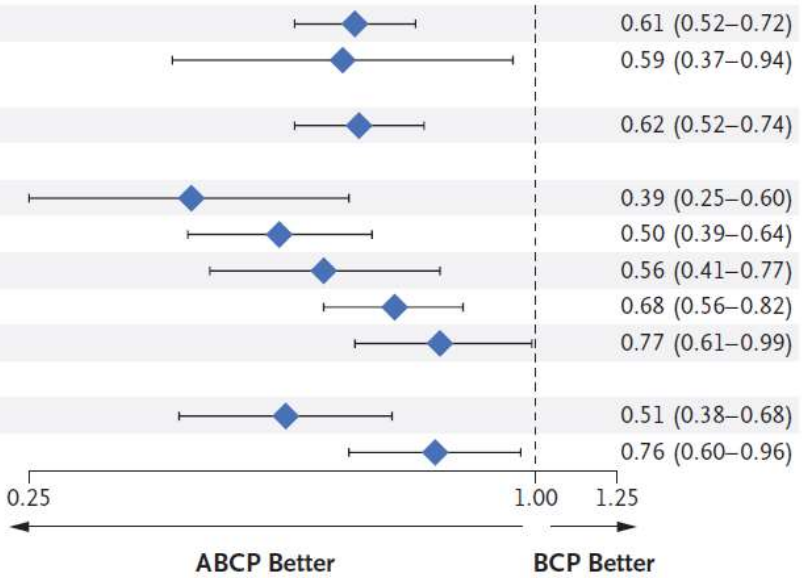


Kaplan–Meier estimates of progression-free survival

No. at Risk

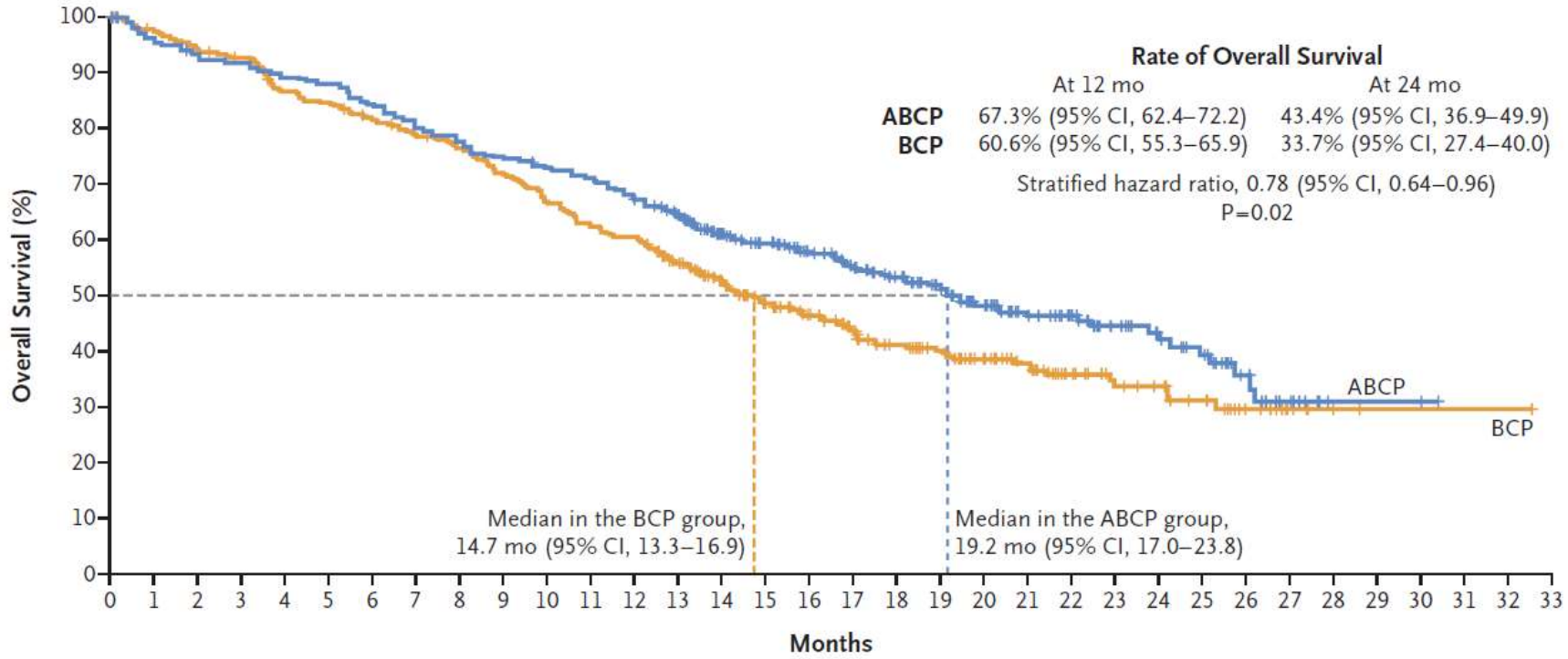
ABCP	356	332	311	298	290	265	232	210	186	151	124	111	87	77	58	55	42	39	27	24	16	12	4	3	2	2	2
BCP	336	321	292	261	243	215	179	147	125	91	69	55	39	32	21	18	12	9	7	6	3	2	1	1			

Population	No. of Patients (%)	Median Progression-free Survival (mo)		Hazard Ratio (95% CI)
		ABCP	BCP	
ITT population	800 (100)	8.3	6.8	0.61 (0.52–0.72)
Patients with *EGFR* or *ALK* genetic alternations	108 (14)	9.7	6.1	0.59 (0.37–0.94)
WT population	692 (87)	8.3	6.8	0.62 (0.52–0.74)
PD-L1 subgroups (in the WT population)				
TC3 or IC3	135 (20)	12.6	6.8	0.39 (0.25–0.60)
TC1/2/3 or IC1/2/3	354 (51)	11.0	6.8	0.50 (0.39–0.64)
TC1/2 or IC1/2	224 (32)	8.3	6.6	0.56 (0.41–0.77)
TC0/1/2 and IC0/1/2	557 (80)	8.0	6.8	0.68 (0.56–0.82)
TC0 and IC0	338 (49)	7.1	6.9	0.77 (0.61–0.99)
Teff subgroups (in the WT population)				
High gene-signature expression	284 (43)	11.3	6.8	0.51 (0.38–0.68)
Low gene-signature expression	374 (57)	7.3	7.0	0.76 (0.60–0.96)



Hazard ratios for disease progression or death in biomarker subgroups

N Engl J Med. 2018 Jun 14;378(24):2288-2301



No. at Risk

ABCP	359	339	328	323	314	310	296	284	273	264	256	250	235	218	188	167	147	133	119	103	84	66	57	41	34	28	16	9	2	2	2
BCP	337	326	315	308	287	280	268	255	247	233	216	203	196	174	152	129	115	101	87	77	66	56	40	32	29	22	13	6	3	1	1	1	1

Overall survival in the ABCP group and the BCP group

N Engl J Med. 2018 Jun 14;378(24):2288-2301

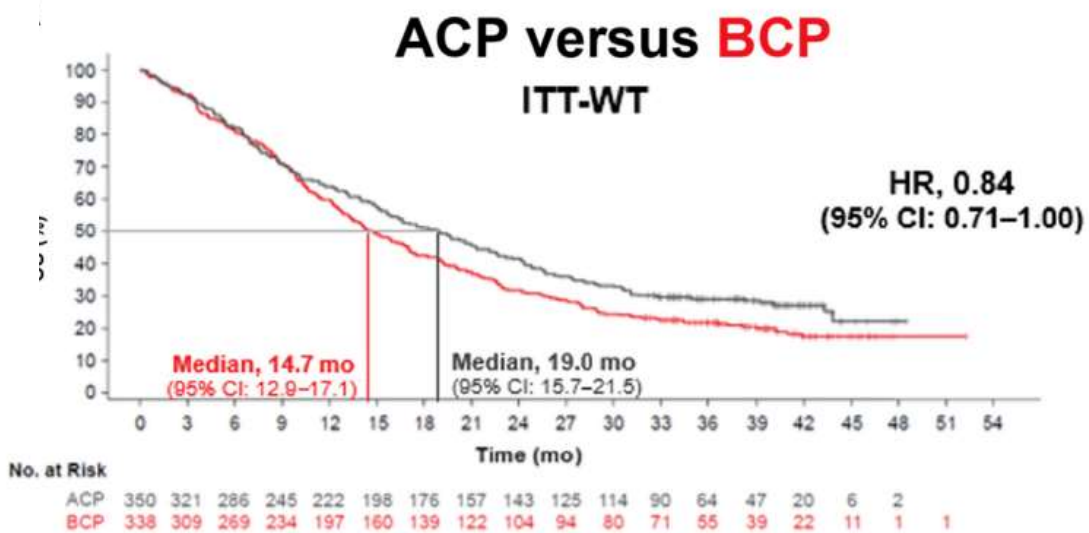
ORIGINAL ARTICLE

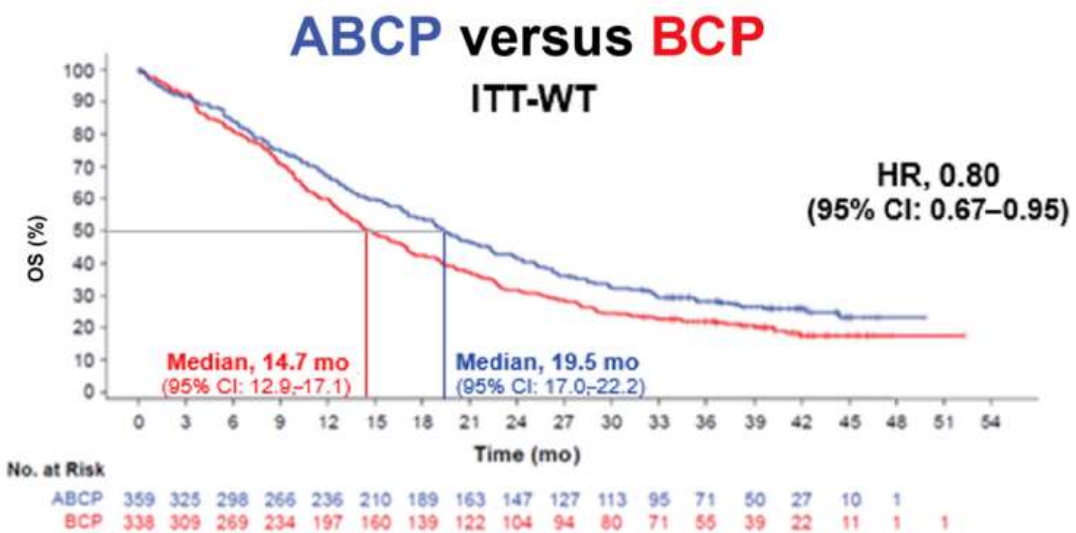
IASLC

IMpower150 Final Overall Survival Analyses for Atezolizumab Plus Bevacizumab and Chemotherapy in First-Line Metastatic Nonsquamous NSCLC

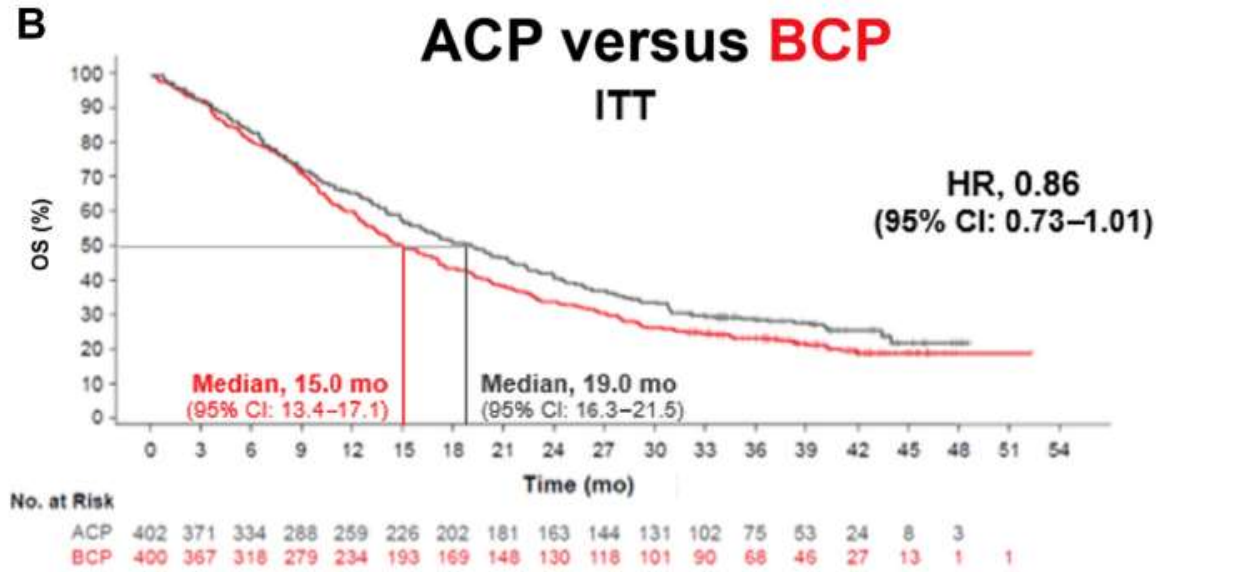
Mark A. Socinski, MD,[a,*] Makoto Nishio, MD,[b] Robert M. Jotte, MD, PhD,[c,d] Federico Cappuzzo, MD, PhD,[e] Francisco Orlandi, MD,[f] Daniil Stroyakovskiy, MD,[g] Naoyuki Nogami, MD, PhD,[h] Delvys Rodriguez-Abreu, MD,[i] Denis Moro-Sibilot, MD, MSc,[j] Christian A. Thomas, MD,[k] Fabrice Barlesi, MD, PhD,[l] Gene Finley, MD,[m] Shengchun Kong, PhD,[n] Anthony Lee, PharmD,[n] Shelley Coleman, RN,[n] Wei Zou, PhD,[n] Mark McCleland, PhD,[n,o] Geetha Shankar, PhD,[n,p] Martin Reck, MD, PhD[q]

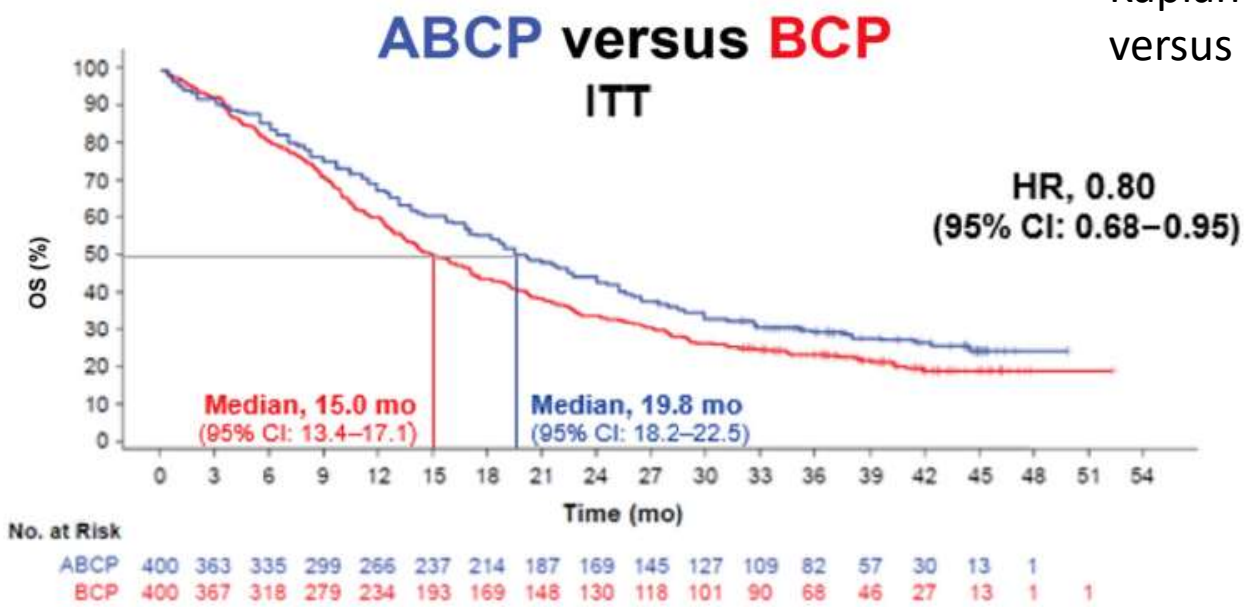
Kaplan-Meier analyses of OS : ACP or ABCP versus BCP in the ITT-WT populations





J Thorac Oncol. 2021 Nov;16(11):1909-1924





Kaplan-Meier analyses of OS : ACP or ABCP versus BCP in the ITT populations

J Thorac Oncol. 2021 Nov;16(11):1909-1924

The NEW ENGLAND JOURNAL of MEDICINE

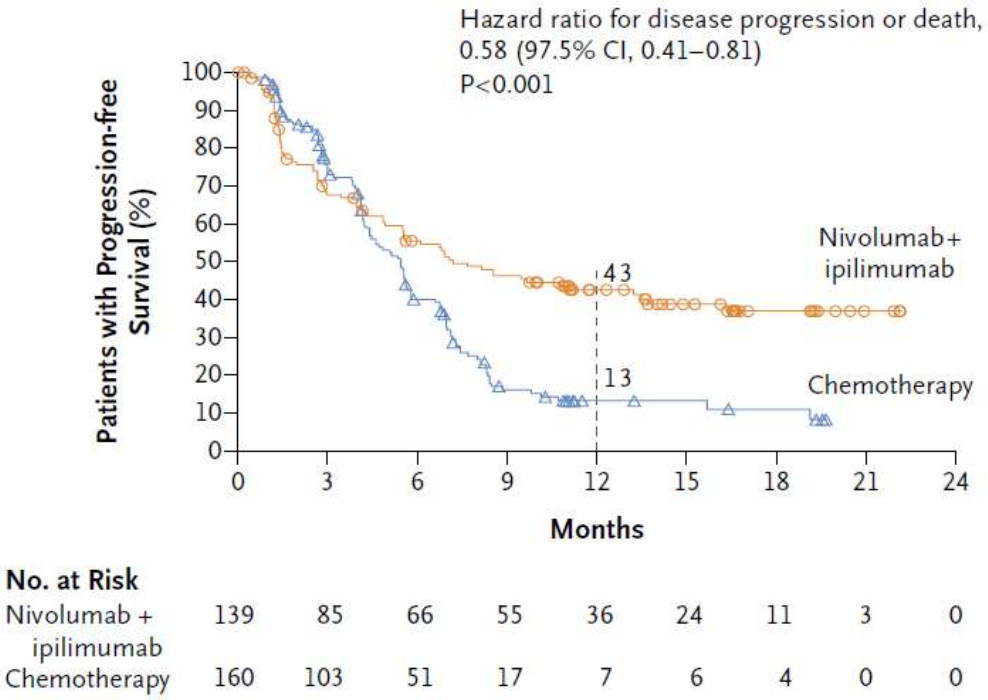
ORIGINAL ARTICLE

Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden

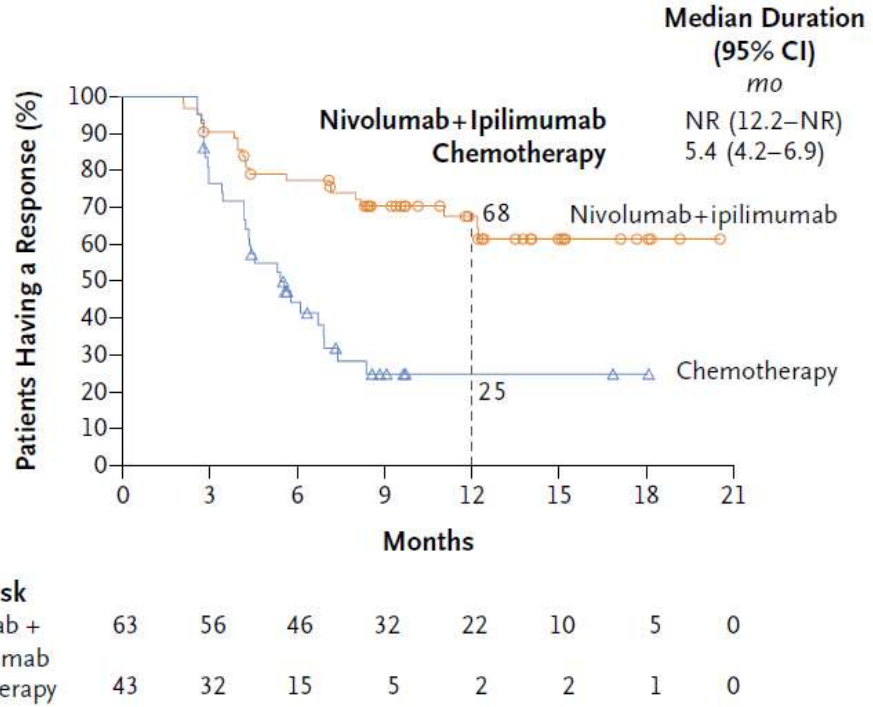
M.D. Hellmann, T.-E. Ciuleanu, A. Pluzanski, J.S. Lee, G.A. Otterson, C. Audigier-Valette, E. Minenza, H. Linardou, S. Burgers, P. Salman, H. Borghaei, S.S. Ramalingam, J. Brahmer, M. Reck, K.J. O'Byrne, W.J. Geese, G. Green, H. Chang, J. Szustakowski, P. Bhagavatheeswaran, D. Healey, Y. Fu, F. Nathan, and L. Paz-Ares

Study design	Inclusion criteria	Intervention
Multi-part, phase 3, randomized trial	• Histologically confirmed squamous or non squamous stage IV or recurrent NSCLC • ECOG performance status 0 or 1 • No previous systemic anticancer therapy as primary therapy for advanced or metastatic disease	**PD-L1 at least 1%:** • Nivolumab (3 mg/kg Q2W) plus Ipilimumab (1 mg/Kg Q6W)(n=396), • Platinum doublet chemotherapy based on tumor histologic type Q3W x 4 cycles(n=396), • Nivolumab (240 mg Q2w)(n=397) PD-L1 less than 1%: • Nivolumab (3 mg/Kg Q2W) plus ipilimumab (1 mg/kg Q6W) (n=187) • Platinum doublet chemotherapy(based on tumor histologic type Q3W x 4 cycles (n=177) or • Nivolumab (360 mg) plus platinum doublet chemotherapy based on tumor histologic type Q3W x 4 Cycles, (n=186)

N Engl J Med. 2018 May 31;378(22):2093-2104



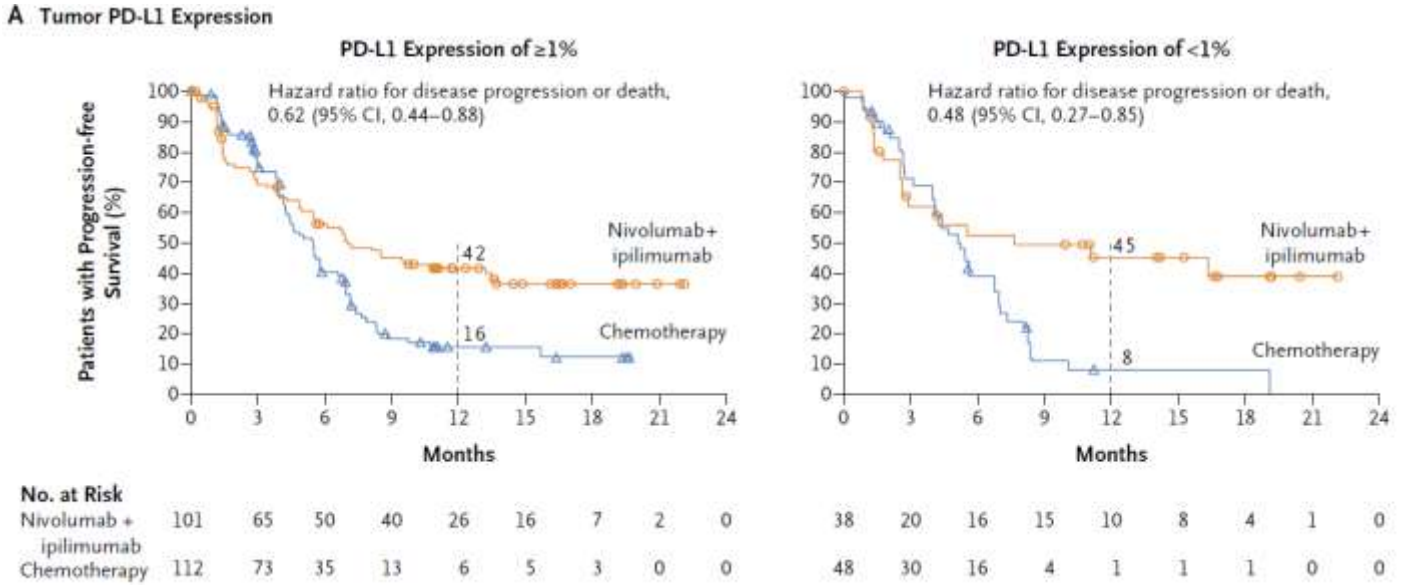
Progression free survival



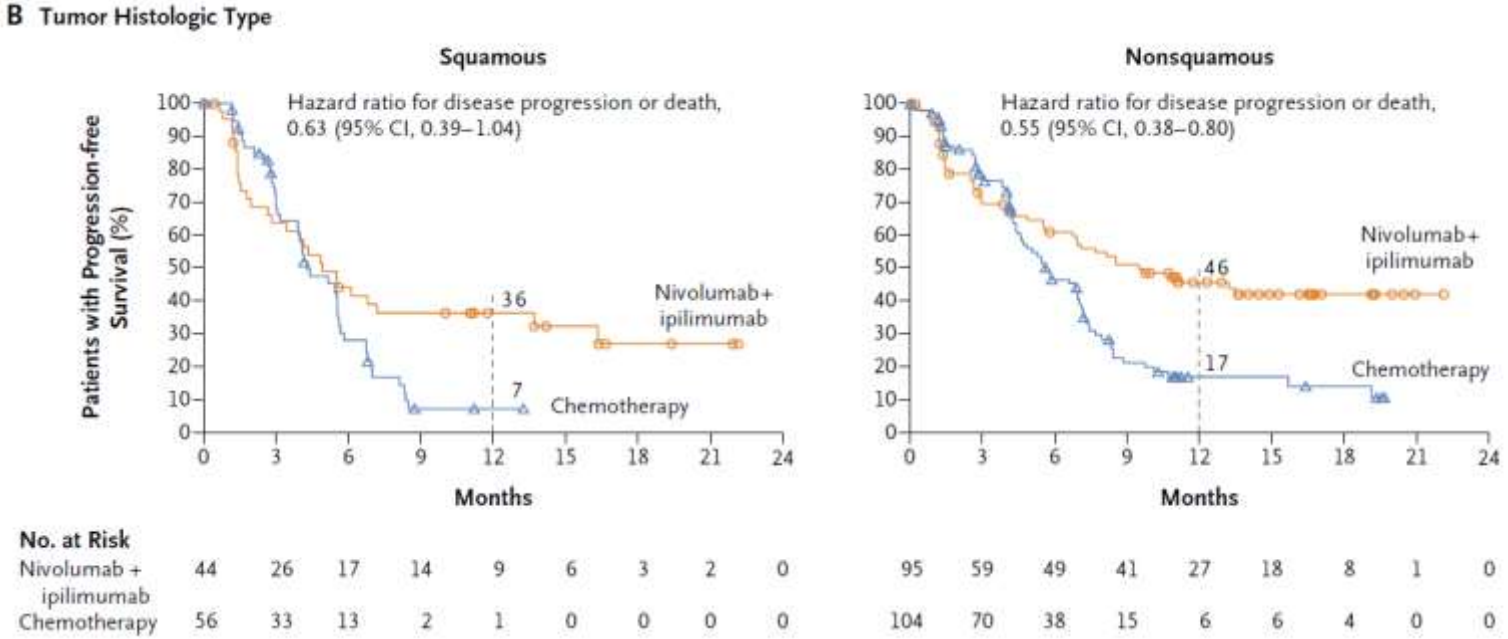
Duration of response

Efficacy of Nivolumab plus Ipilimumab versus chemotherapy in patients with a high tumor mutational burden

N Engl J Med. 2018 May 31;378(22):2093-2104



Progression-free survival among patients with a high tumor mutational burden according to tumor PD-L1 expression



Progression-free survival among patients with a high tumor mutational burden according to histologic type

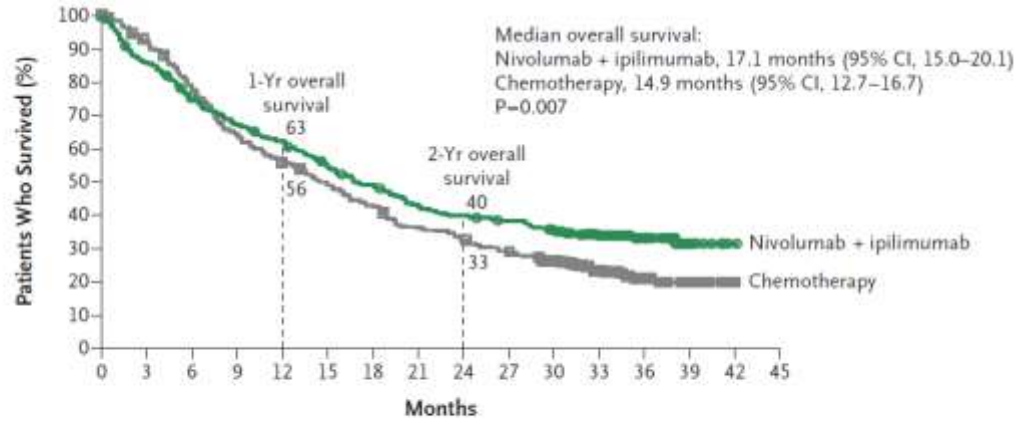
N Engl J Med. 2018 May 31;378(22):2093-2104

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab plus Ipilimumab in Advanced Non–Small-Cell Lung Cancer

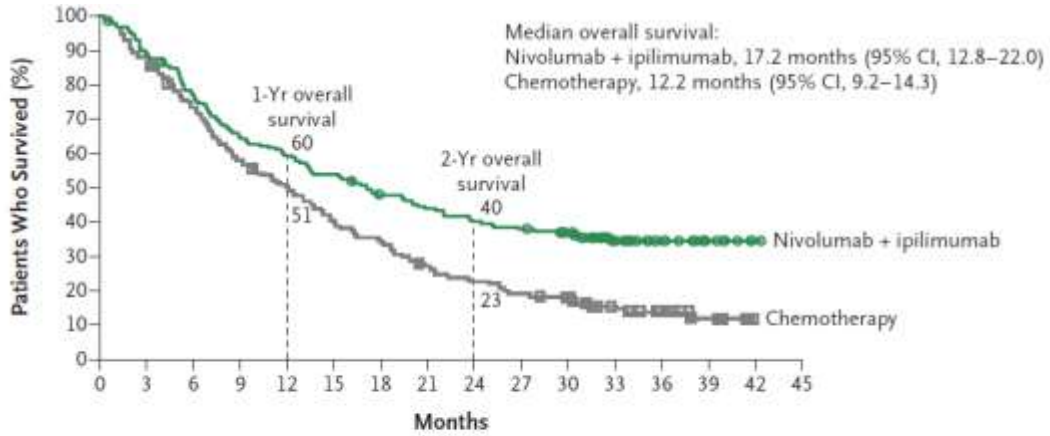
M.D. Hellmann, L. Paz-Ares, R. Bernabe Caro, B. Zurawski, S.-W. Kim, E. Carcereny Costa, K. Park, A. Alexandru, L. Lupinacci, E. de la Mora Jimenez, H. Sakai, I. Albert, A. Vergnenegre, S. Peters, K. Syrigos, F. Barlesi, M. Reck, H. Borghaei, J.R. Brahmer, K.J. O'Byrne, W.J. Geese, P. Bhagavatheeswaran, S.K. Rabindran, R.S. Kasinathan, F.E. Nathan, and S.S. Ramalingam



No. at Risk

Nivolumab + ipilimumab	396	341	295	264	244	212	190	165	153	145	129	91	41	9	1	0
Chemotherapy	397	358	306	250	218	190	166	141	126	112	93	57	22	6	1	0

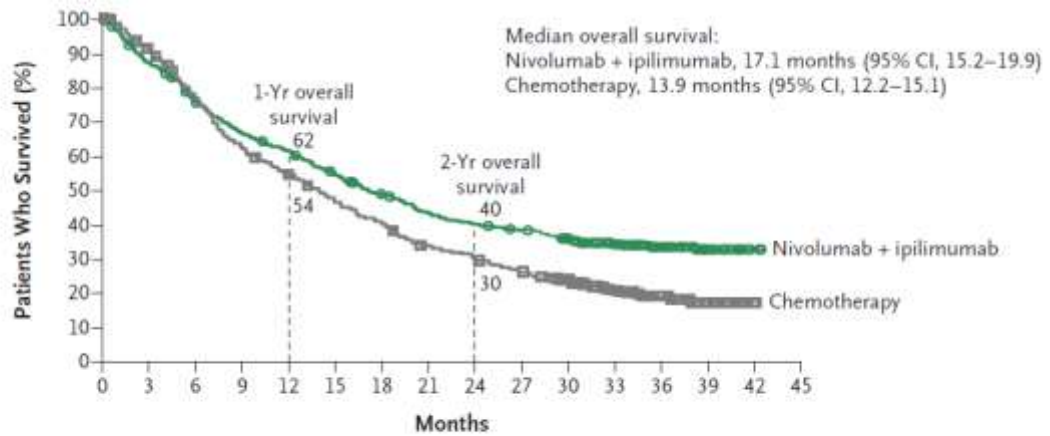
Overall survival in patients with a PD-L1 expression level of 1%or more



No. at Risk

Nivolumab + ipilimumab	187	165	142	120	110	100	87	80	73	69	59	34	19	8	2	0
Chemotherapy	186	164	135	107	92	74	62	49	41	35	29	19	12	5	0	0

Overall survival in patients with a PD-L1 expression level of <1%



No. at Risk

Nivolumab + ipilimumab	583	506	437	384	354	312	277	245	226	214	188	125	60	17	3	0
Chemotherapy	583	522	441	357	310	264	228	190	167	147	122	76	34	11	1	0

Overall survival in all patients

N Engl J Med. 2019 Nov 21;381(21):2020-2031

Five-Year Survival Outcomes With Nivolumab Plus Ipilimumab Versus Chemotherapy as First-Line Treatment for Metastatic Non–Small-Cell Lung Cancer in CheckMate 227

Julie R. Brahmer, MD[1]; Jong-Seok Lee, MD, PhD[2]; Tudor-Eliade Ciuleanu, MD, PhD[3]; Reyes Bernabe Caro, MD, PhD[4]; Makoto Nishio, MD, PhD[5]; Laszlo Urban, MD[6]; Clarisse Audigier-Valette, MD[7]; Lorena Lupinacci, MD[8]; Randeep Sangha, MD[9]; Adam Pluzanski, MD, PhD[10]; Jacobus Burgers, MD, PhD[11]; Mauricio Mahave, MD[12]; Samreen Ahmed, MD[13]; Adam J. Schoenfeld, MD[14]; Luis G. Paz-Ares, MD, PhD[15]; Martin Reck, MD, PhD[16]; Hossein Borghaei, DO, MS[17]; Kenneth J. O'Byrne, MD, PhD[18]; Ravi G. Gupta, MD[19]; Judith Bushong, BS[19]; Li Li, MS, DPH[19]; Steven I. Blum, MBA[19]; Laura J. Eccles, PhD[19]; and Suresh S. Ramalingam, MD[20]

- **5-year OS rates-**

  Nivolumab plus Ipilimumab vs. chemotherapy: 24% vs. 14% (PD-L1 ≥1%)

  Nivolumab plus Ipilimumab vs. chemotherapy: 19% vs.7% (PD-L1 ≤1%).

- **Duration of response(median)** –

  Nivolumab plus Ipilimumab vs. chemotherapy: 24.5 vs. 6.7 months(PD-L1 ≥1%)

  Nivolumab plus Ipilimumab vs. chemotherapy: 19.4 vs. 4.8 months(PD-L1 ≤1%).

- Patient surviving 5 years 66%(PD-L1 ≥1%) and 64%(PD-L1 ≤1%) were off Nivolumab and Ipilumab without initiating subsequent systemic anticancer treatment by 5 year time point
- Survival benefit continued after Nivolumab plus Ipilimumab discontinuation because of treatment-related adverse events, with a 5-year OS rate of 39% (combined PD-L1 ≥1% and ≤1% populations)

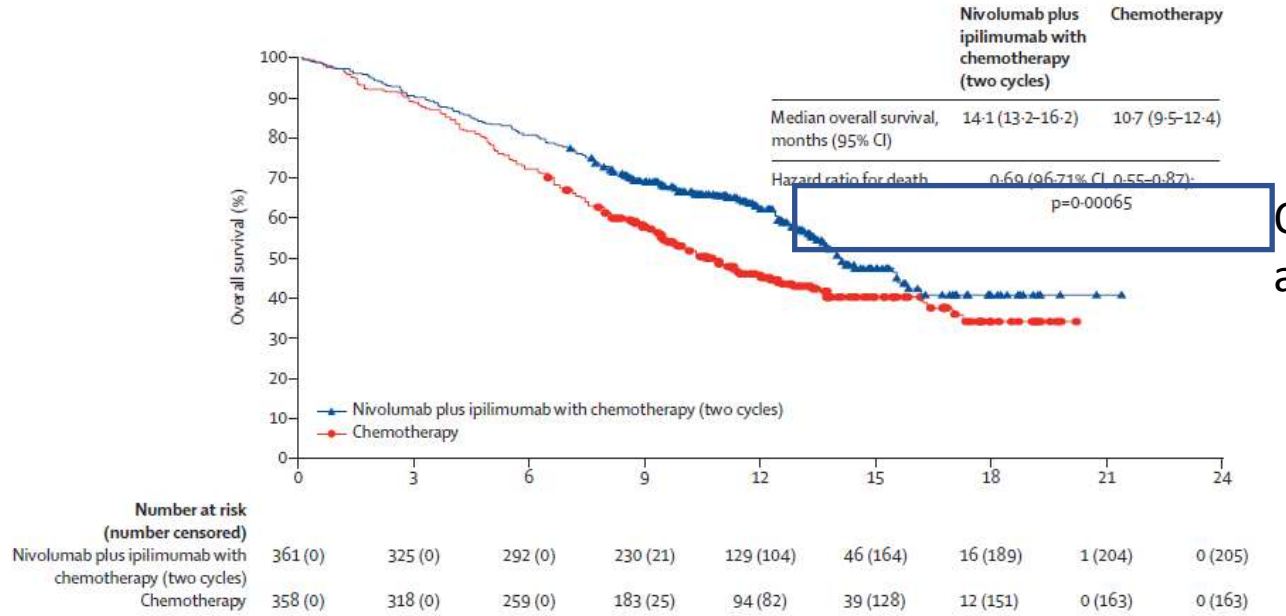
J Clin Oncol. 2022 Oct 12;101200JCO2201503

First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial

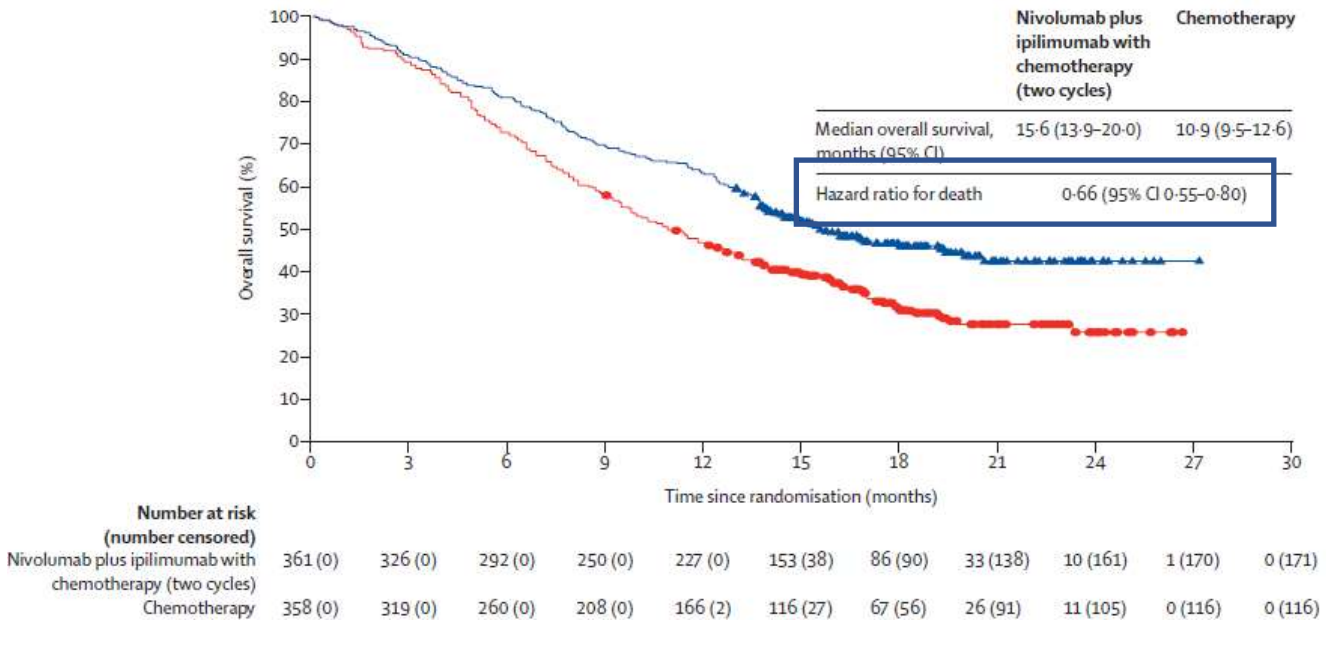
Luis Paz-Ares, Tudor-Eliade Ciuleanu, Manuel Cobo, Michael Schenker, Bogdan Zurawski, Juliana Menezes, Eduardo Richardet, Jaafar Bennouna, Enriqueta Felip, Oscar Juan-Vidal, Aurelia Alexandru, Hiroshi Sakai, Alejo Lingua, Pamela Salman, Pierre-Jean Souquet, Pedro De Marchi, Claudio Martin, Maurice Pérol, Arnaud Scherpereel, Shun Lu, Thomas John, David P Carbone, Stephanie Meadows-Shropshire, Shruti Agrawal, Abderrahim Oukessou, Jinchun Yan, Martin Reck

Study design	Inclusion criteria	Intervention
International, randomised, open-label phase 3 trial	• Age >18 yrs • Histologically confirmed squamous or non-squamous stage IV or recurrent NSCLC • Received no previous systemic therapy for metastatic disease • ECOG performance status score 0 or 1 • Provided a tumor sample for determination of PD-L1 status • have a life expectancy of at least 3 months	Nivolumab(n=361) 360 mg i.v. Q3W, followed by Ipiliumab 1mg/kg i.v. Q6W plus histology-based platinum doublet chemotherapy (i.v. Q3W x 2 cycles) or Chemotherapy(n=358) alone (i.v. Q3W x 4 cycles)

Lancet Oncol. 2021 Feb;22(2):198-211



Overall survival in all randomly assigned patients at interim analysis



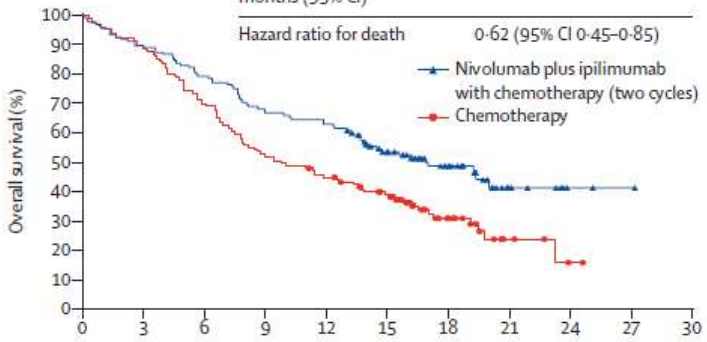
Overall survival in all randomly assigned patients at interim analysis with longer follow-up

Lancet Oncol. 2021 Feb;22(2):198-211

Overall survival in patients with tumour PD-L1 expression

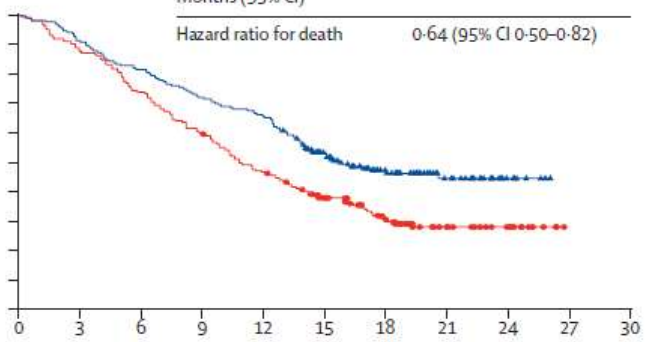
≤ 1%

	Nivolumab plus ipilimumab with chemotherapy (two cycles)	Chemotherapy
Median overall survival, months (95% CI)	16·8 (13·7–NR)	9·8 (7·7–13·7)
Hazard ratio for death	0·62 (95% CI 0·45–0·85)	



≥1%

	Nivolumab plus ipilimumab with chemotherapy (two cycles)	Chemotherapy
Median overall survival, months (95% CI)	15·8 (13·8–NR)	10·9 (9·5–13·2)
Hazard ratio for death	0·64 (95% CI 0·50–0·82)	

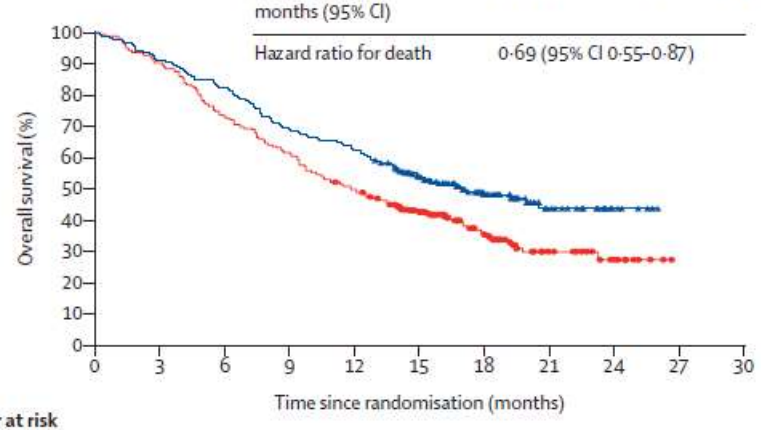


Number at risk (number censored)																						
Nivolumab plus ipilimumab with chemotherapy (two cycles)	135 (0)	120 (0)	107 (0)	90 (0)	85 (0)	53 (20)	31 (38)	8 (58)	2 (64)	1 (65)	0 (66)	203 (0)	185 (0)	166 (0)	147 (0)	133 (0)	92 (17)	52 (48)	25 (73)	8 (90)	0 (98)	0 (98)
Chemotherapy	129 (0)	116 (0)	90 (0)	68 (0)	57 (1)	43 (8)	19 (25)	5 (36)	1 (39)	0 (40)	0 (40)	204 (0)	179 (0)	151 (0)	122 (0)	95 (1)	64 (15)	42 (26)	19 (46)	10 (55)	0 (65)	0 (65)

Overall survival in patients with tumour histology

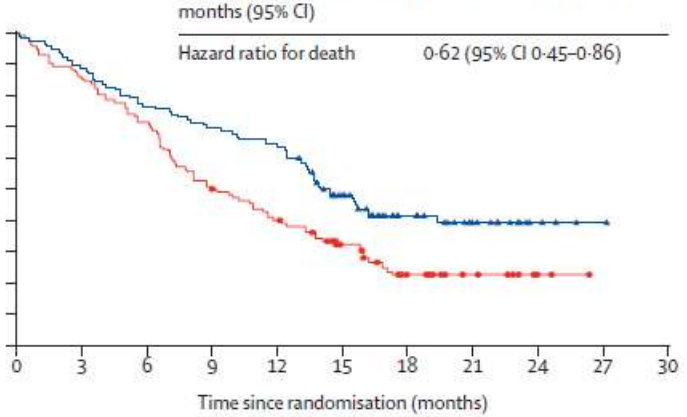
Non-squamous

	Nivolumab plus ipilimumab with chemotherapy (two cycles)	Chemotherapy
Median overall survival, months (95% CI)	17·0 (14·0–NR)	11·9 (9·9–14·1)
Hazard ratio for death	0·69 (95% CI 0·55–0·87)	



Squamous

	Nivolumab plus ipilimumab with chemotherapy (two cycles)	Chemotherapy
Median overall survival, months (95% CI)	14·5 (13·1–19·4)	9·1 (7·2–11·6)
Hazard ratio for death	0·62 (95% CI 0·45–0·86)	



Number at risk (number censored)																						
Nivolumab plus ipilimumab with chemotherapy (two cycles)	246 (0)	224 (0)	204 (0)	170 (0)	154 (0)	107 (28)	62 (64)	20 (102)	6 (116)	0 (122)	0 (122)	115 (0)	102 (0)	88 (0)	80 (0)	73 (0)	46 (10)	24 (26)	13 (36)	4 (45)	1 (48)	0 (49)
Chemotherapy	246 (0)	223 (0)	180 (0)	152 (0)	122 (1)	87 (19)	53 (41)	18 (70)	9 (78)	0 (87)	0 (87)	112 (0)	96 (0)	80 (0)	56 (0)	44 (1)	29 (8)	14 (15)	8 (21)	2 (27)	0 (29)	0 (29)

Lancet Oncol. 2021 Feb;22(2):198-211

LBA9026 **Poster Session**

First-line (1L) nivolumab (NIVO) + ipilimumab (IPI) + 2 cycles of chemotherapy (chemo) versus chemo alone (4 cycles) in patients (pts) with metastatic non–small cell lung cancer (NSCLC): 3-year update from CheckMate 9LA.

Summary of efficacy outcomes by PD-L1 expression.

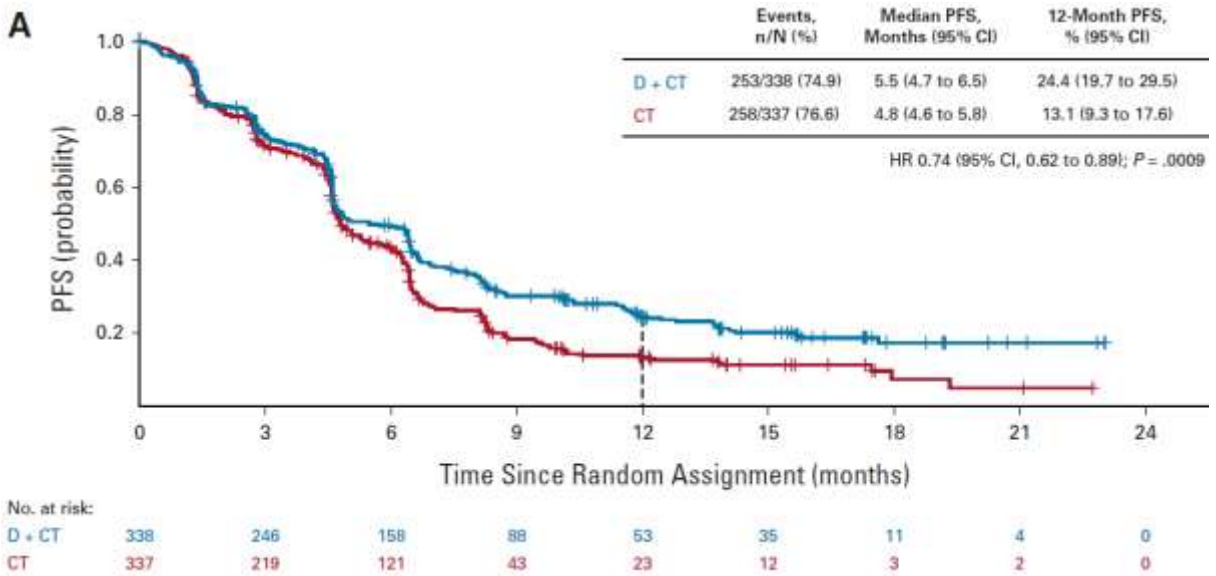
	PD-L1 < 1% NIVO + IPI + chemo (n = 135)	PD-L1 < 1% Chemo (n = 129)	PD-L1 ≥ 1% NIVO + IPI + chemo (n = 204)	PD-L1 ≥ 1% Chemo (n = 204)	All randomized NIVO + IPI + chemo (n = 361)	All randomized Chemo (n = 358)
Median OS, mo	17.7	9.8	15.8	10.9	15.8	11.0
OS HR (95% CI) vs chemo	0.67 (0.51–0.88)	–	0.74 (0.60–0.93)	–	0.74 (0.62–0.87)	–
3-y OS rate, %	25	15	28	19	27	19
3-y PFS rate, %	17	3	12	6	13	5
ORR, n (%)	43 (32)	26 (20)	86 (42)	56 (28)	137 (38)	90 (25)
Median DOR, mo	17.5	4.3	11.3	5.6	12.4	5.6
Responders with ongoing response ≥ 3 y, %	37	0	18	17	23	14

Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non–Small-Cell Lung Cancer: The Phase III POSEIDON Study

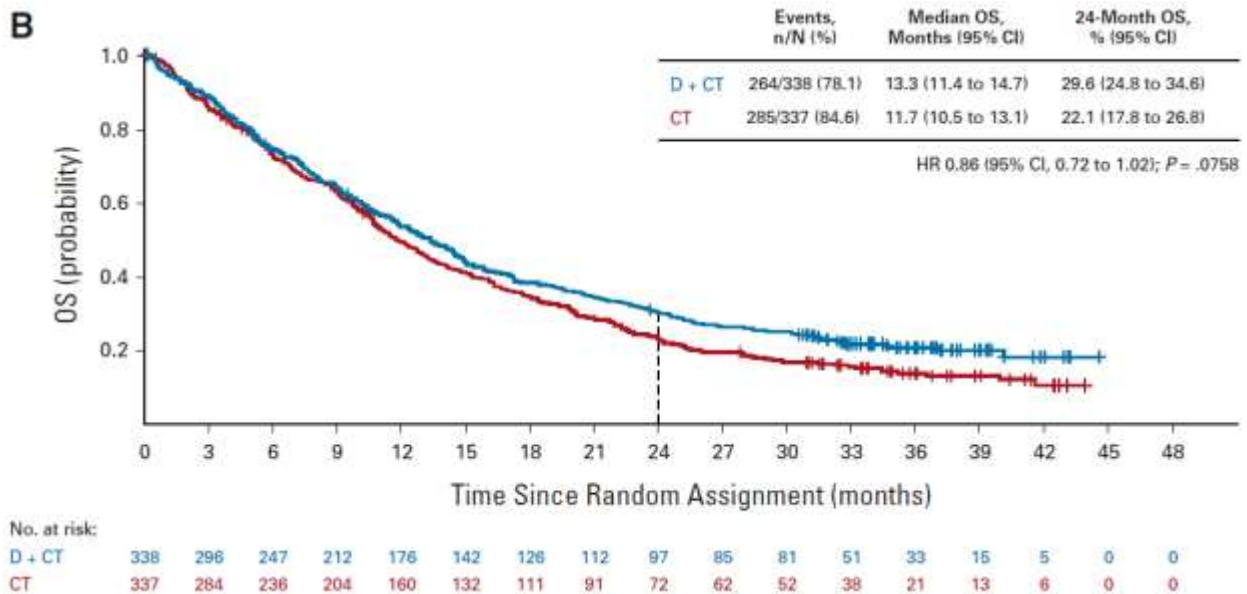
Melissa L. Johnson, MD[1]; Byoung Chul Cho, MD, PhD[2]; Alexander Luft, MD[3]; Jorge Alatorre-Alexander, MD[4]; Sarayut Lucien Geater, MD[5]; Konstantin Laktionov, MD[6]; Sang-We Kim, MD, PhD[7]; Grygorii Ursol, MD[8]; Maen Hussein, MD[9]; Farah Louise Lim, MBBS, MRCP[10]; Cheng-Ta Yang, MD[11]; Luiz Henrique Araujo, MD, PhD[12]; Haruhiro Saito, MD, PhD[13]; Niels Reinmuth, MD, PhD[14]; Xiaojin Shi, MD[15]; Lynne Poole, MSc[16]; Solange Peters, MD, PhD[17]; Edward B. Garon, MD[18]; and Tony Mok, MD[19] for the POSEIDON investigators

Study design	Inclusion criteria	Intervention
Phase3, global, randomized, open label study with three arm design	• Age >18 yrs with NSCLC • Received no previous systemic therapy for metastatic disease • ECOG performance status score 0 or 1 • Had measurable disease as per RECIST • No sensitizing EGFR mutations or ALK rearrangements and PD-L1 expression status	• Tremelimumab 75mg + Durvalumab 1,500 mg + chemotherapy for up to four 21-day cycles, followed by durvalumab 1,500 mg Q4W until disease progression (PD), with one additional tremelimumab dose after chemotherapy at week 16/cycle 6 (fifth dose). (n= 338) • Durvalumab 1,500 mg + chemotherapy for up to four 21-day cycles, followed by durvalumab 1,500 mg Q4W until PD. (n= 338) • Chemotherapy for up to six 21-day cycles.(n=337)

J Clin Oncol. 2022 Nov 3;JCO2200975

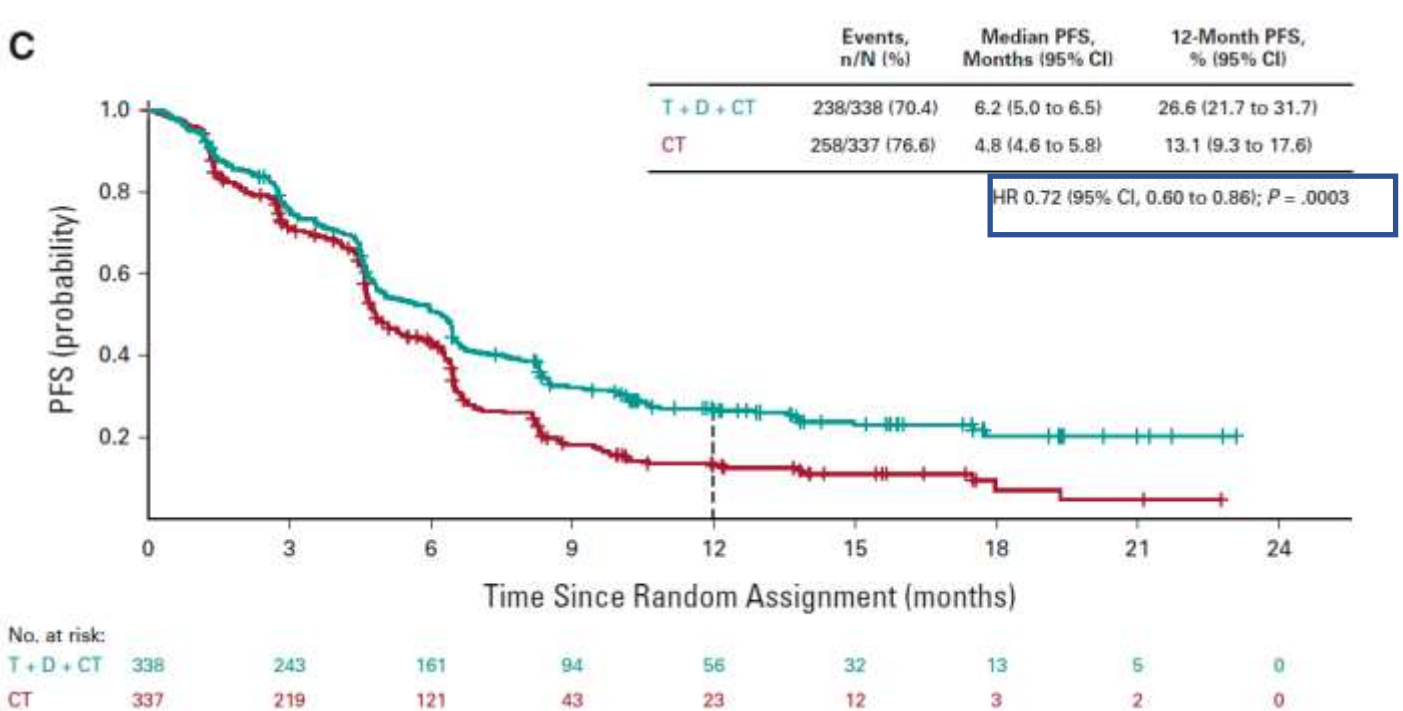


PFS with D+ CT vs. CT

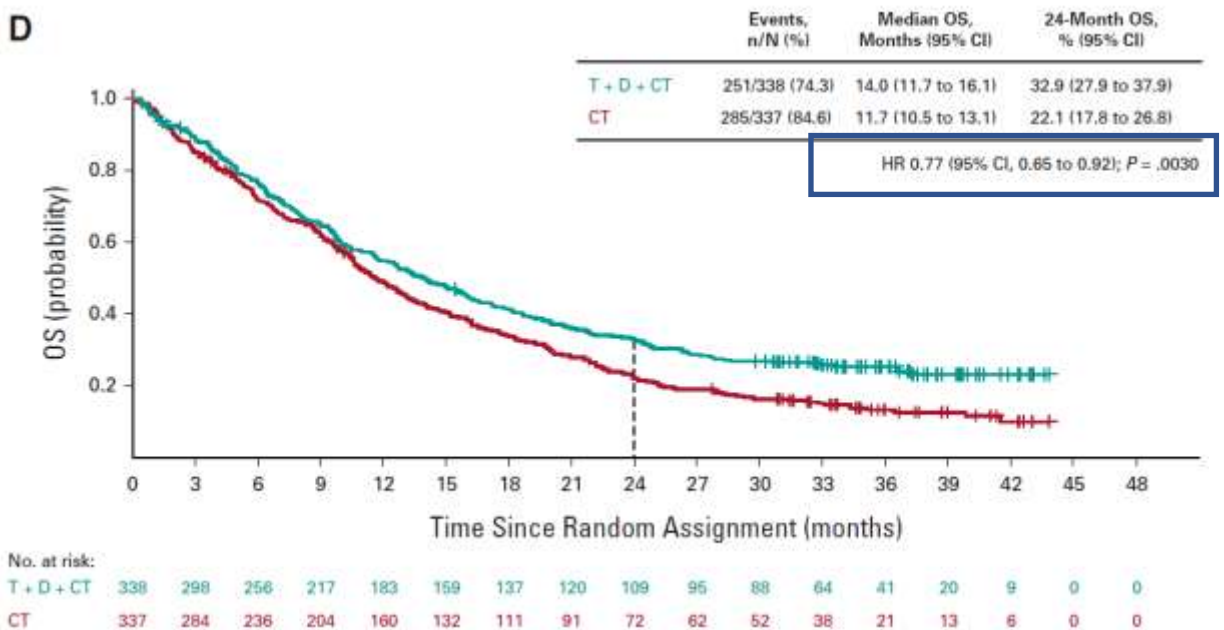


OS with D+ CT vs. CT

J Clin Oncol. 2022 Nov 3;JCO2200975



PFS with T+ D+ CT vs. CT



OS with T+ D+ CT vs. CT

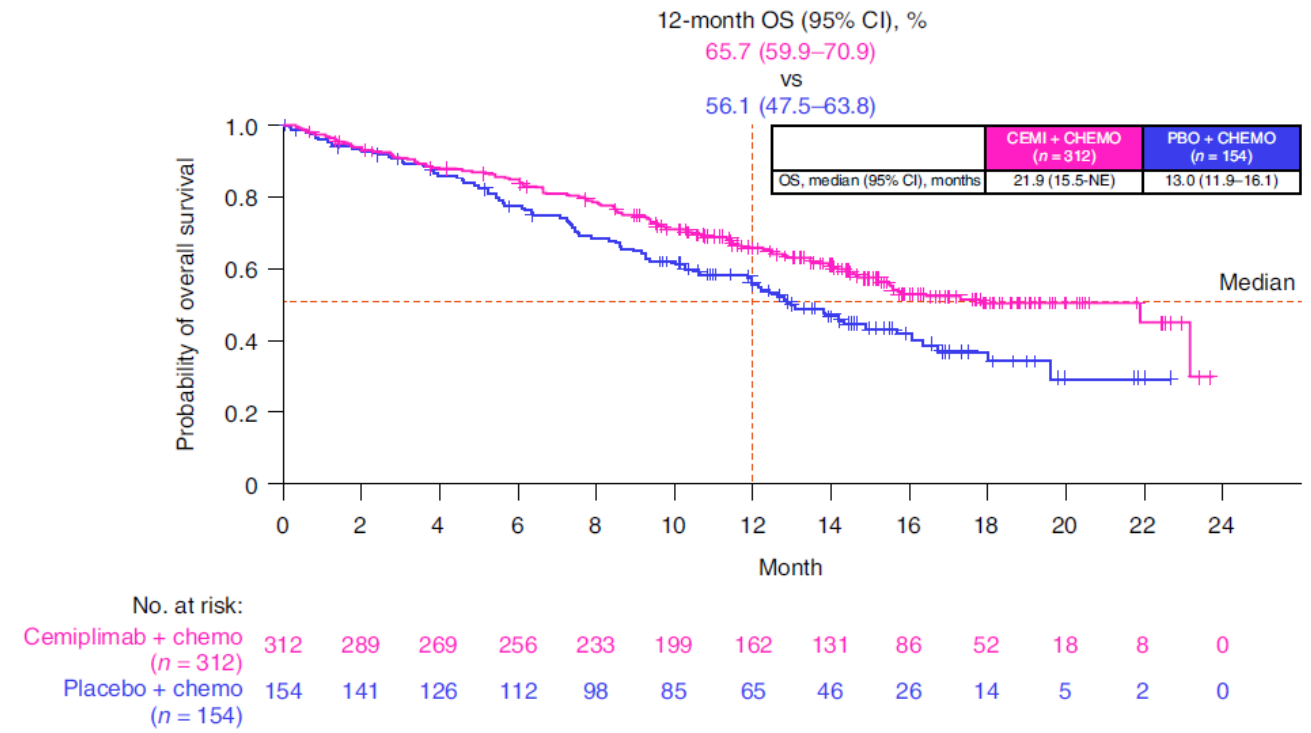
J Clin Oncol. 2022 Nov 3;JCO2200975

Cemiplimab plus chemotherapy versus chemotherapy alone in non-small cell lung cancer: a randomized, controlled, double-blind phase 3 trial

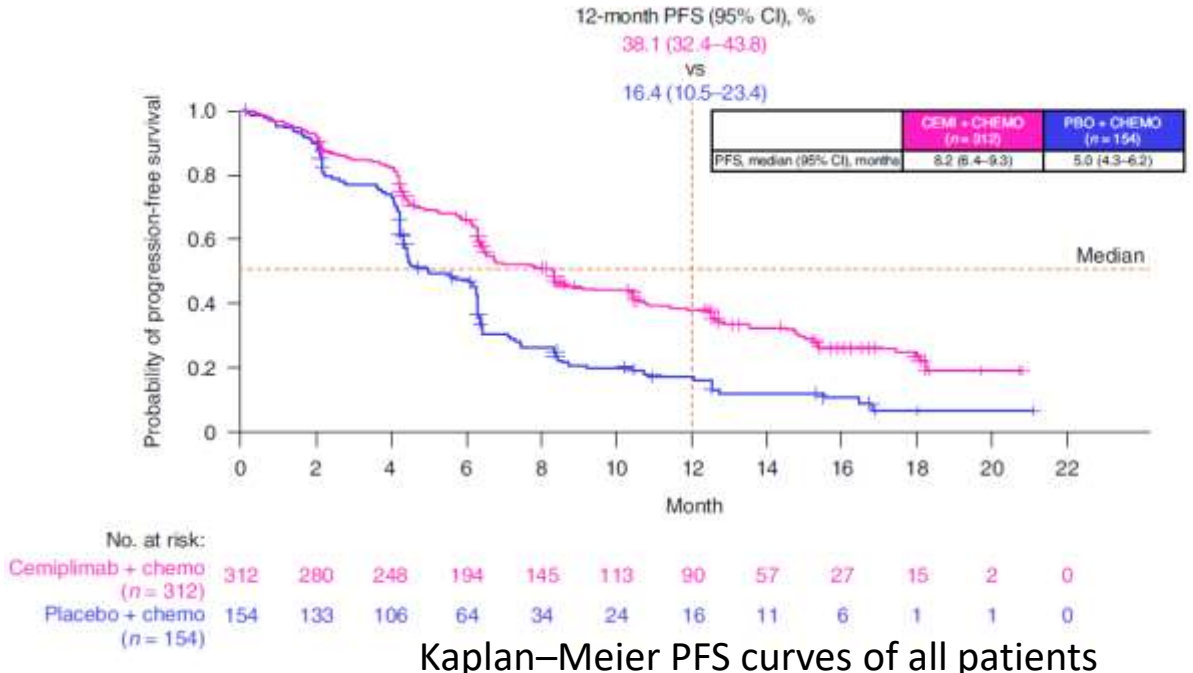
Miranda Gogishvili[1], Tamar Melkadze[2], Tamta Makharadze[3], Davit Giorgadze[4], Mikhail Dvorkin[5], Konstantin Penkov[6], Konstantin Laktionov[7], Gia Nemsadze[8], Marina Nechaeva[9], Irina Rozhkova[10], Ewa Kalinka[11], Christian Gessner[12,13], Brizio Moreno-Jaime[14], Rodolfo Passalacqua[15], Siyu Li[16], Kristina McGuire[16], Manika Kaul[16], Anne Paccaly[16], Ruben G. W. Quek[16], Bo Gao[16], Frank Seebach[16], David M. Weinreich[16], George D. Yancopoulos[16], Israel Lowy[16], Giuseppe Gullo[16] and Petra Rietschel[16]

Study design	Inclusion criteria	Intervention
Randomized, controlled, double-blind phase 3 trial	NSCLC (metastatic or unresectable locally advanced disease not suitable for definitive chemoradiation), with either squamous or non-squamous histology and any level of PD-L1 expression	Cemiplimab + chemotherapy(n=312) vs. Placebo +chemotherapy(n=154)

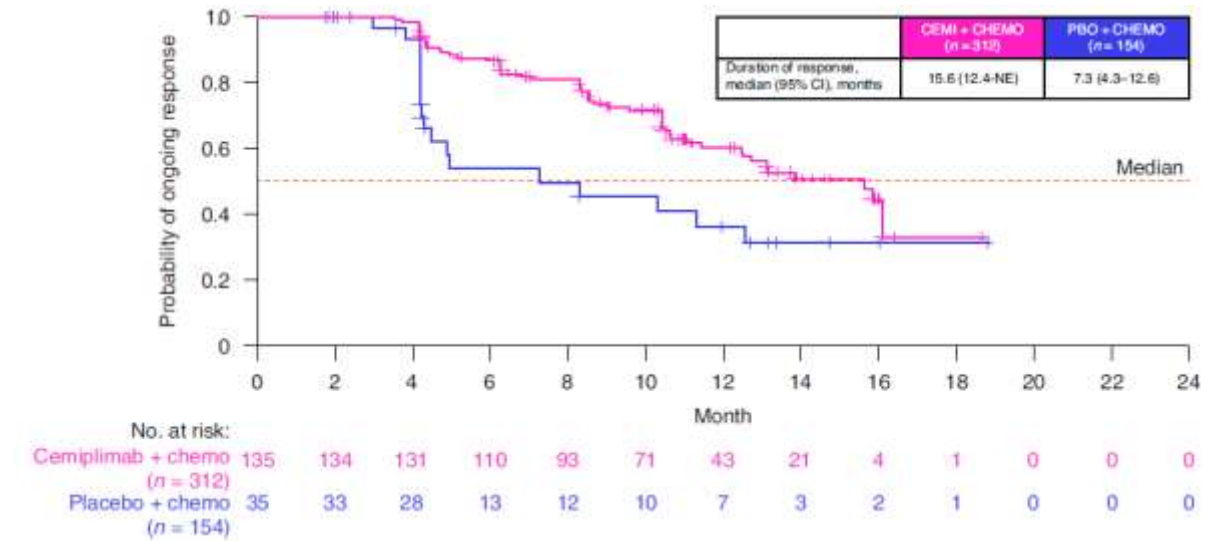
Nat Med. 2022 Nov;28(11):2374-2380



Kaplan–Meier OS curves of all patients



Kaplan–Meier PFS curves of all patients



Kaplan–Meier curves of DOR in all patients

Nat Med. 2022 Nov;28(11):2374-2380

The NEW ENGLAND JOURNAL of MEDICINE

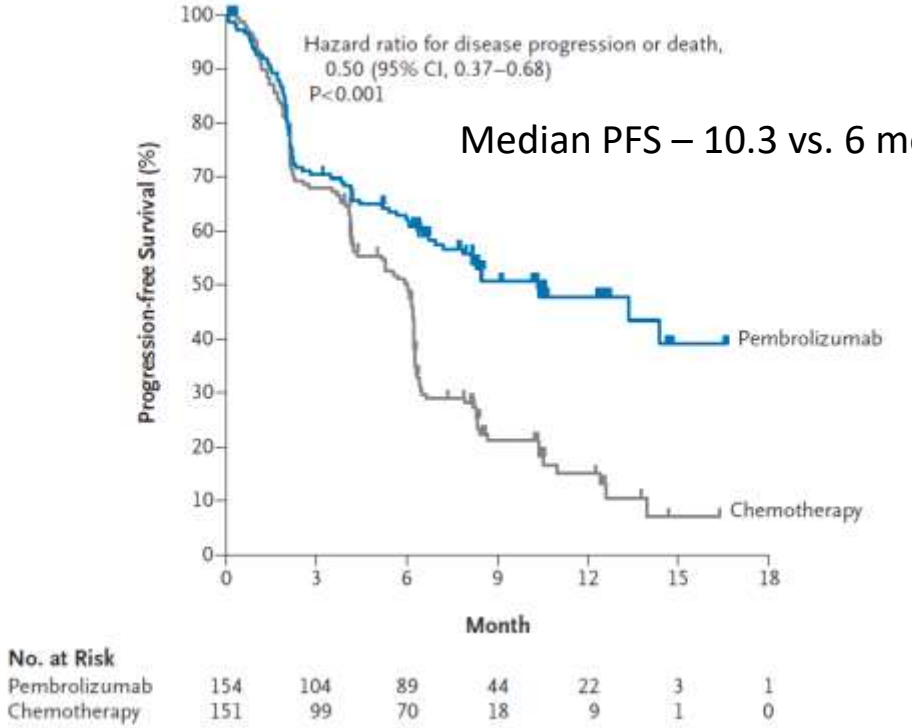
ESTABLISHED IN 1812 NOVEMBER 10, 2016 VOL. 375 NO. 19

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

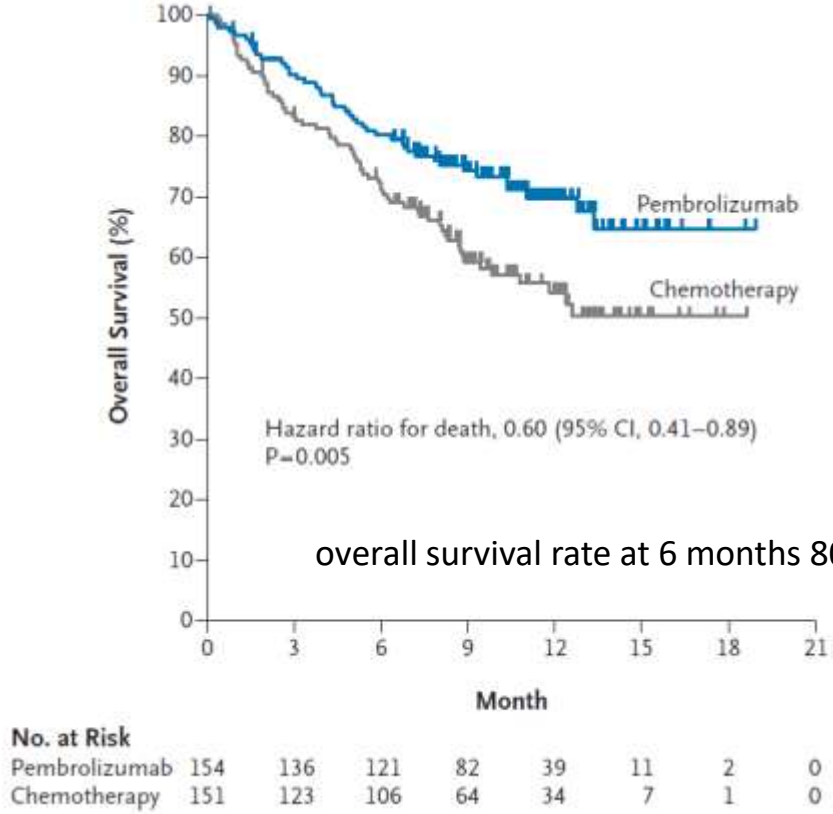
Martin Reck, M.D., Ph.D., Delvys Rodríguez-Abreu, M.D., Andrew G. Robinson, M.D., Rina Hui, M.B., B.S., Ph.D., Tibor Csőszi, M.D., Andrea Fülöp, M.D., Maya Gottfried, M.D., Nir Peled, M.D., Ph.D., Ali Tafreshi, M.D., Sinead Cuffe, M.D., Mary O'Brien, M.D., Suman Rao, M.D., Katsuyuki Hotta, M.D., Ph.D., 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*

Study design	Inclusion criteria	Intervention
International, randomized, open-label,phase 3	• Age >18 yrs • Histologically or cytologically confirmed stage IV NSCLC with no sensitizing EGFR mutations or ALK translocation • Undergone no previous systemic therapy for metastatic disease • ECOG performance status score 0 or 1 • At least one measurable lesion as per RECIST 1.1 • A life expectancy of at least 3 months • PD-L1 tumor proportion score of ≥50%	Patients randomized in a 1:1 ratio, to receive treatment with either Pembrolizumab (200 mg i.v. Q3W) for 35 cycles (n=154) or 4 to 6 cycles of any one of the following platinum based chemotherapy(n=151): • carboplatin plus pemetrexed, • cisplatin plus pemetrexed, • carboplatin plus gemcitabine, • cisplatin plus gemcitabine, or • carboplatin plus paclitaxel

N Engl J Med. 2016 Nov 10;375(19):1823-1833



Median PFS – 10.3 vs. 6 months



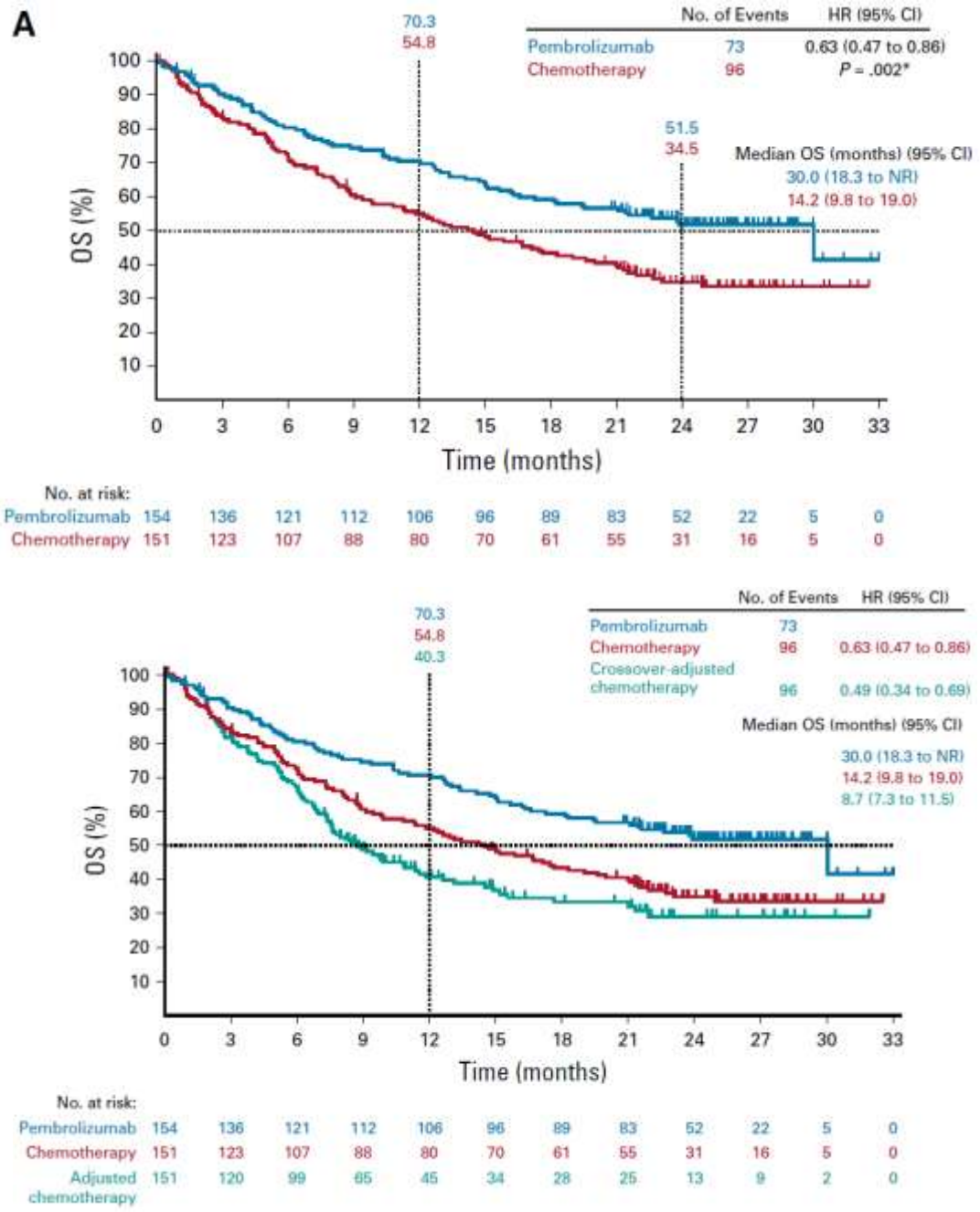
overall survival rate at 6 months 80.2% vs. 72.4 %

- Response rate was higher in the pembrolizumab group than in the chemotherapy group (44.8% vs. 27.8%)
- Median duration of response was longer (not reached [range, 1.9+ to 14.5+ months] vs. 6.3 months [range, 2.1+ to 12.6+])
- Treatment-related adverse events of any grade were less frequent (occurring in 73.4% vs. 90.0% of patients), as were grade 3, 4, or 5 treatment-related adverse events (26.6% vs. 53.3%)

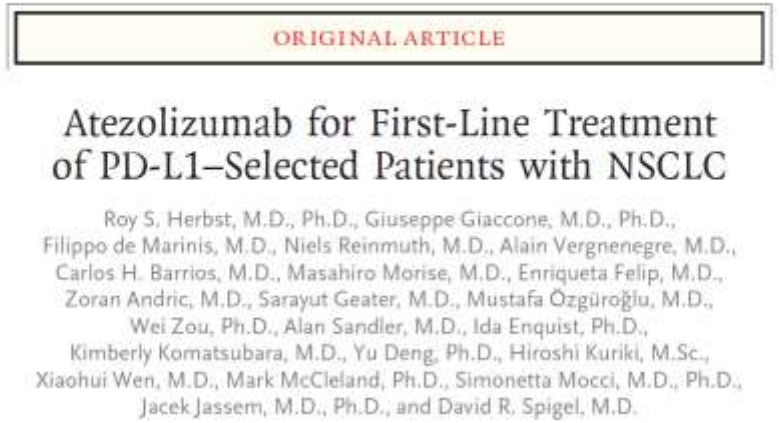
N Engl J Med. 2016 Nov 10;375(19):1823-1833

Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater

Martin Reck, MD, PhD[1]; Delvys Rodríguez-Abreu, MD[2]; Andrew G. Robinson, MD[3]; Rina Hui, MBBS, PhD[4]; Tibor Csőszi, MD[5]; Andrea Fülöp, MD[6]; Maya Gottfried, MD[7]; Nir Peled, MD, PhD[8]; Ali Tafreshi, MD[9]; Sinead Cuffe, MD[10]; Mary O'Brien, MD[11]; Suman Rao, MD[12]; Katsuyuki Hotta, MD, PhD[13]; Kristel Vandormael, MSc[14]; Antonio Riccio, PhD[15]; Jing Yang, PhD[15]; M. Catherine Pietanza, MD[15]; and Julie R. Brahmer, MD[16]



J Clin Oncol. 2019 Mar 1;37(7):537-546


ORIGINAL ARTICLE

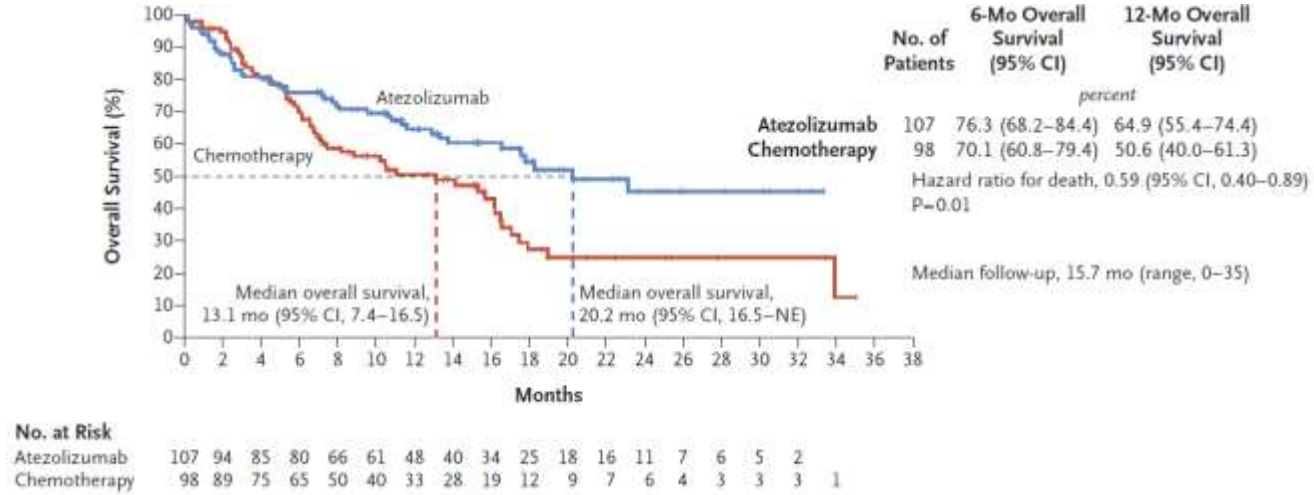
Atezolizumab for First-Line Treatment of PD-L1–Selected Patients with NSCLC

Roy S. Herbst, M.D., Ph.D., Giuseppe Giaccone, M.D., Ph.D., Filippo de Marinis, M.D., Niels Reinmuth, M.D., Alain Vergnenegre, M.D., Carlos H. Barrios, M.D., Masahiro Morise, M.D., Enriqueta Felip, M.D., Zoran Andric, M.D., Sarayut Geater, M.D., Mustafa Özgüroğlu, M.D., Wei Zou, Ph.D., Alan Sandler, M.D., Ida Enquist, Ph.D., Kimberly Komatsubara, M.D., Yu Deng, Ph.D., Hiroshi Kuriki, M.Sc., Xiaohui Wen, M.D., Mark McCleland, Ph.D., Simonetta Mocci, M.D., Ph.D., Jacek Jassem, M.D., Ph.D., and David R. Spigel, M.D.

Study design	Inclusion criteria	Intervention
Randomized, open-label, phase 3 trial	• Age >18 yrs • Histologically or cytologically confirmed stage IV NSCLC • Undergone no previous systemic therapy for metastatic disease • ECOG performance status score 0 or 1 • At least one measurable lesion as per RECIST 1.1 • PD-L1 expression on at least 1% of tumor cells or tumor infiltrating immune cells covering at least 1% of the tumor area as determined by the SP142 assay was required	Atezolizumab (1200 mg i.v.) or platinum-based chemotherapy (4 or 6 cycles) Q3W. (n=285) Chemotherapy group (n=287): **Nonsquamous NSCLC**: cisplatin (75 mg/m^2) or carboplatin (AUC,6) in addition to pemetrexed (500 mg/m^2) **Squamous NSCLC**: Cisplatin (75 mg/m^2) **plus** Gemcitabine (1250 mg/m^2) or carboplatin (AUC, 5) **plus** gemcitabine (1000 mg/m^2)i.v.

N Engl J Med. 2020 Oct 1;383(14):1328-1339

High expression of PD-L1

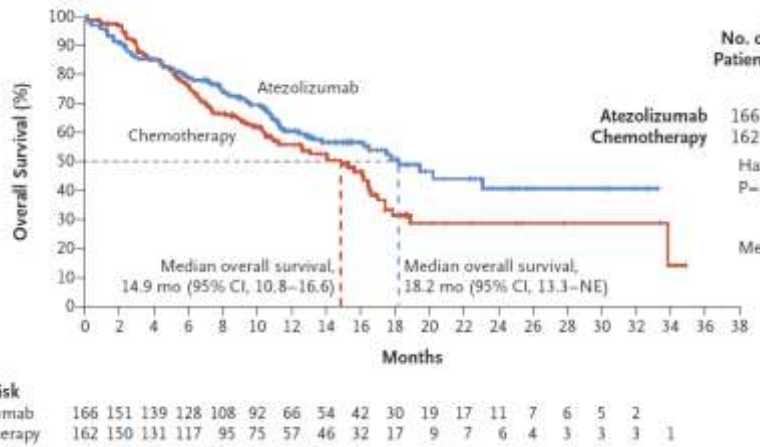


	No. of Patients	6-Mo Overall Survival (95% CI)	12-Mo Overall Survival (95% CI)
		percent	
Atezolizumab	107	76.3 (68.2–84.4)	64.9 (55.4–74.4)
Chemotherapy	98	70.1 (60.8–79.4)	50.6 (40.0–61.3)

Hazard ratio for death, 0.59 (95% CI, 0.40–0.89)
P=0.01

Median follow-up, 15.7 mo (range, 0–35)

High or intermediate expression of PD-L1

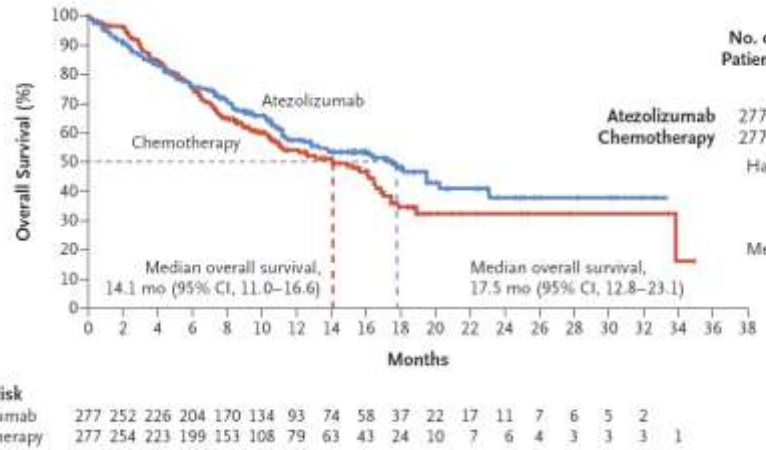


	No. of Patients	6-Mo Overall Survival (95% CI)	12-Mo Overall Survival (95% CI)
		percent	
Atezolizumab	166	79.3 (73.1–85.5)	60.7 (52.6–68.7)
Chemotherapy	162	76.1 (69.3–82.8)	56.0 (47.7–64.3)

Hazard ratio for death, 0.72 (95% CI, 0.52–0.99)
P=0.04

Median follow-up, 15.2 mo (range, 0–35)

Any expression of PD-L1



	No. of Patients	6-Mo Overall Survival (95% CI)	12-Mo Overall Survival (95% CI)
		percent	
Atezolizumab	277	76.2 (71.1–81.3)	57.6 (51.2–64.0)
Chemotherapy	277	75.7 (70.5–80.9)	54.3 (47.7–60.8)

Hazard ratio for death, 0.83 (95% CI, 0.65–1.07)

Median follow-up, 13.4 mo (range, 0–35)

Kaplan–Meier estimates of overall survival among the patients whose tumors were wild-type with respect to EGFR mutations or ALK translocations

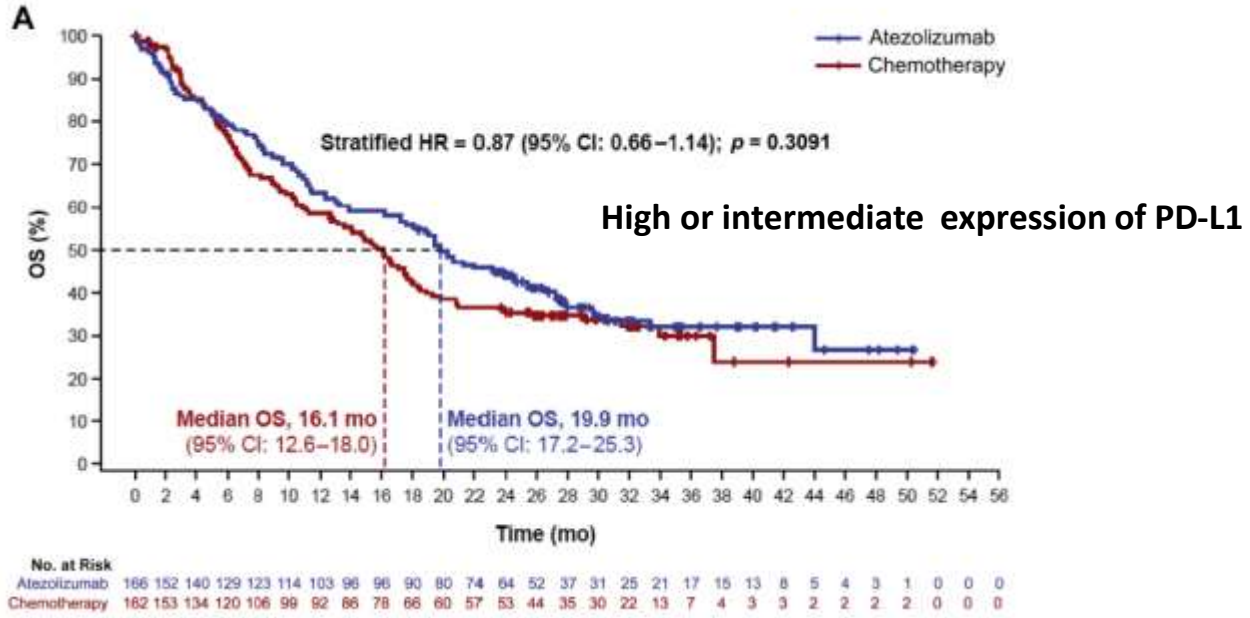
Lancet. 2021 Feb 13;397(10274):592-604

ORIGINAL ARTICLE

IASLC

Updated Overall Survival Analysis From IMpower110: Atezolizumab Versus Platinum-Based Chemotherapy in Treatment-Naive Programmed Death-Ligand 1-Selected NSCLC

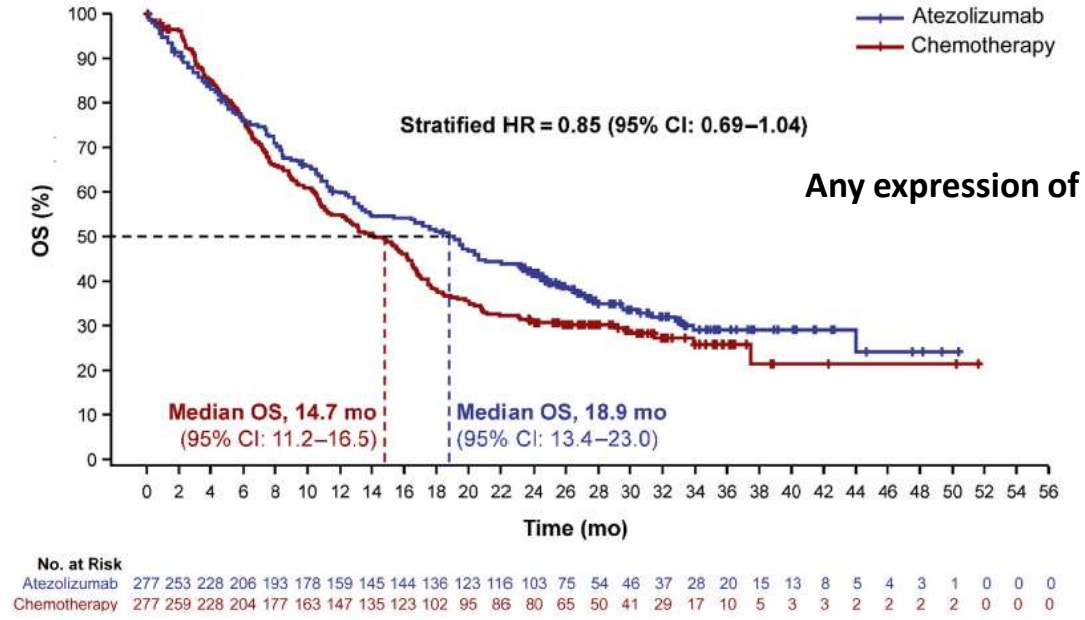
Jacek Jassem, MD, PhD,[a] Filippo de Marinis, MD,[b] Giuseppe Giaccone, MD, PhD,[c] Alain Vergnenegre, MD,[d] Carlos H. Barrios, MD,[e] Masahiro Morise, MD,[f] Enriqueta Felip, MD,[g] Cristina Oprean, MD,[h] Young-Chul Kim, MD, PhD,[i] Zoran Andric, MD,[j] Simonetta Mocci, MD, PhD,[k] Ida Enquist, PhD,[k] Kimberly Komatsubara, MD,[k] Mark McCleland, PhD,[k] Hiroshi Kuriki, MSc,[k] Monette Villalobos, MBA, MSc, BSN,[k] See Phan, MD,[k] David R. Spigel, MD,[l] Roy S. Herbst, MD, PhD[m,*]



High or intermediate expression of PD-L1

Exploratory updated OS analysis in the high PD-L1 expression WT group-Atezolizumab versus chemotherapy

- Stratified HR = 0.76, 95% CI: 0.54–1.09
- Median= 20.2 versus 14.7 months



Any expression of PD-L1

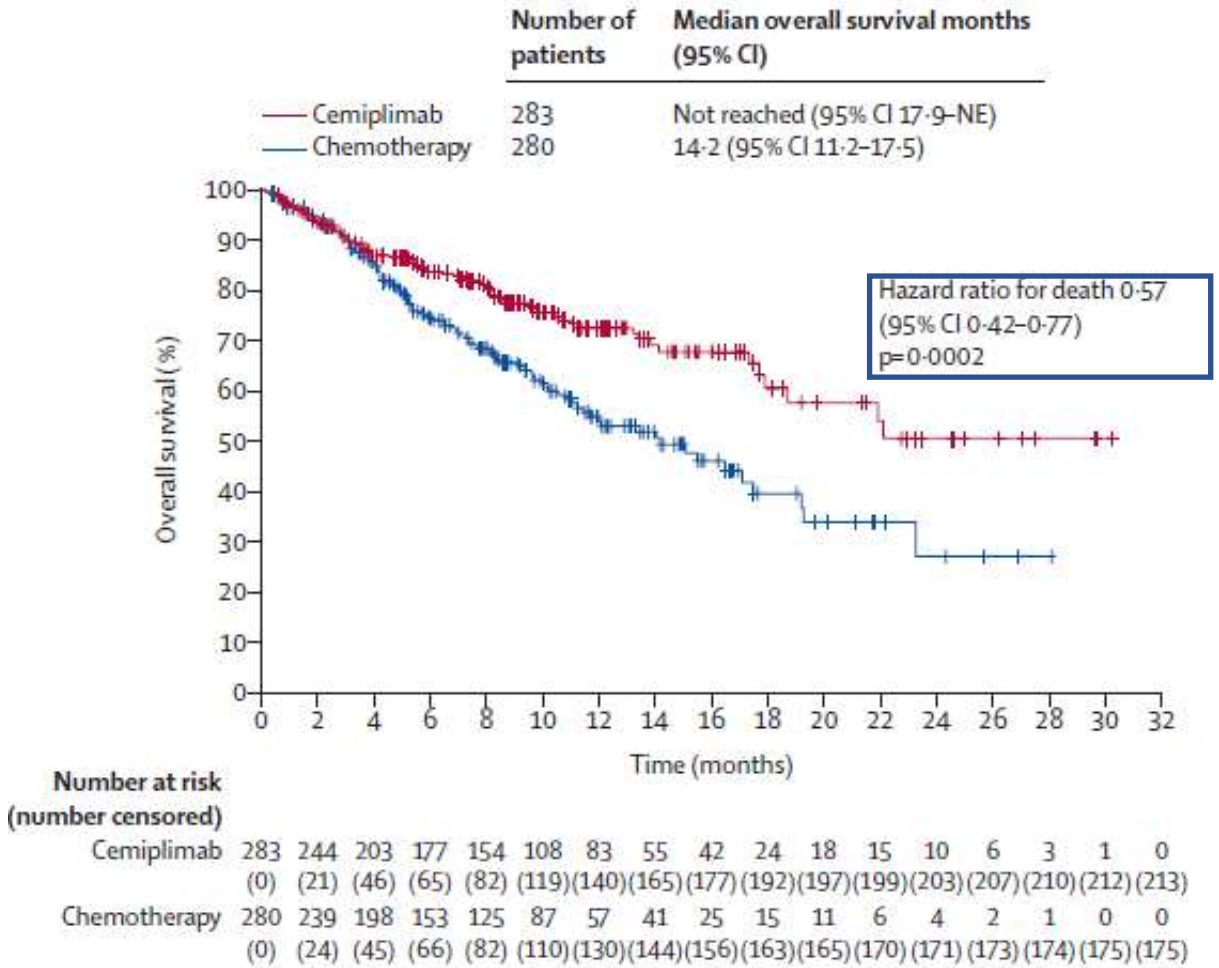
J Thorac Oncol. 2021 Nov;16(11):1872-1882

Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial

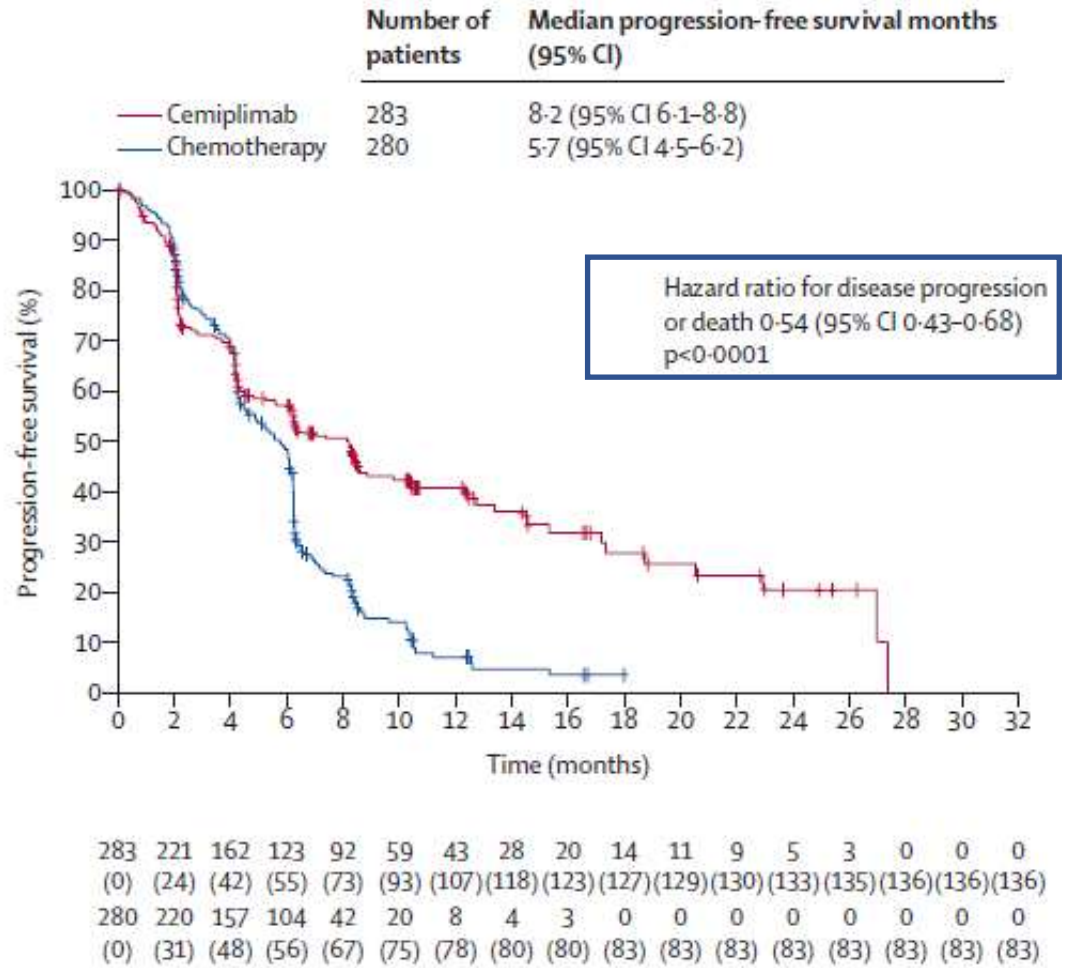
Ahmet Sezer, Saadettin Kilickap, Mahmut Gümüş, Igor Bondarenko, Mustafa Özgüroğlu, Miranda Gogishvili, Haci M Turk, Irfan Cicin, Dmitry Bentsion, Oleg Gladkov, Philip Clingan, Virote Sriuranpong, Naiyer Rizvi, Bo Gao, Siyu Li, Sue Lee, Kristina McGuire, Chieh-I Chen, Tamta Makharadze, Semra Paydas, Marina Nechaeva, Frank Seebach, David M Weinreich, George D Yancopoulos, Giuseppe Gullo, Israel Lowy, Petra Rietschel

Study design	Inclusion criteria	Intervention
Multicentre, open-label, global, phase 3, randomized, controlled trial	• Age >18 yrs • Histologically or cytologically confirmed stage IIIB or IIIC or stage IV squamous or non-squamous non-small-cell lung cancer with PD-L1 expressed in at least 50% of tumour cells • ECOG performance status score 0 or 1 • Adequate organ and bone marrow function • At least one measurable lesion as per RECIST 1.1	Cemiplimab (n=280) 350 mg i.v over a period of 30 min Q3w (for up to 108 weeks, up to 36 treatment cycles) or Four to six cycles of investigator's choice of platinum-doublet chemotherapy(n=283)

Lancet. 2021 Feb 13;397(10274):592-604



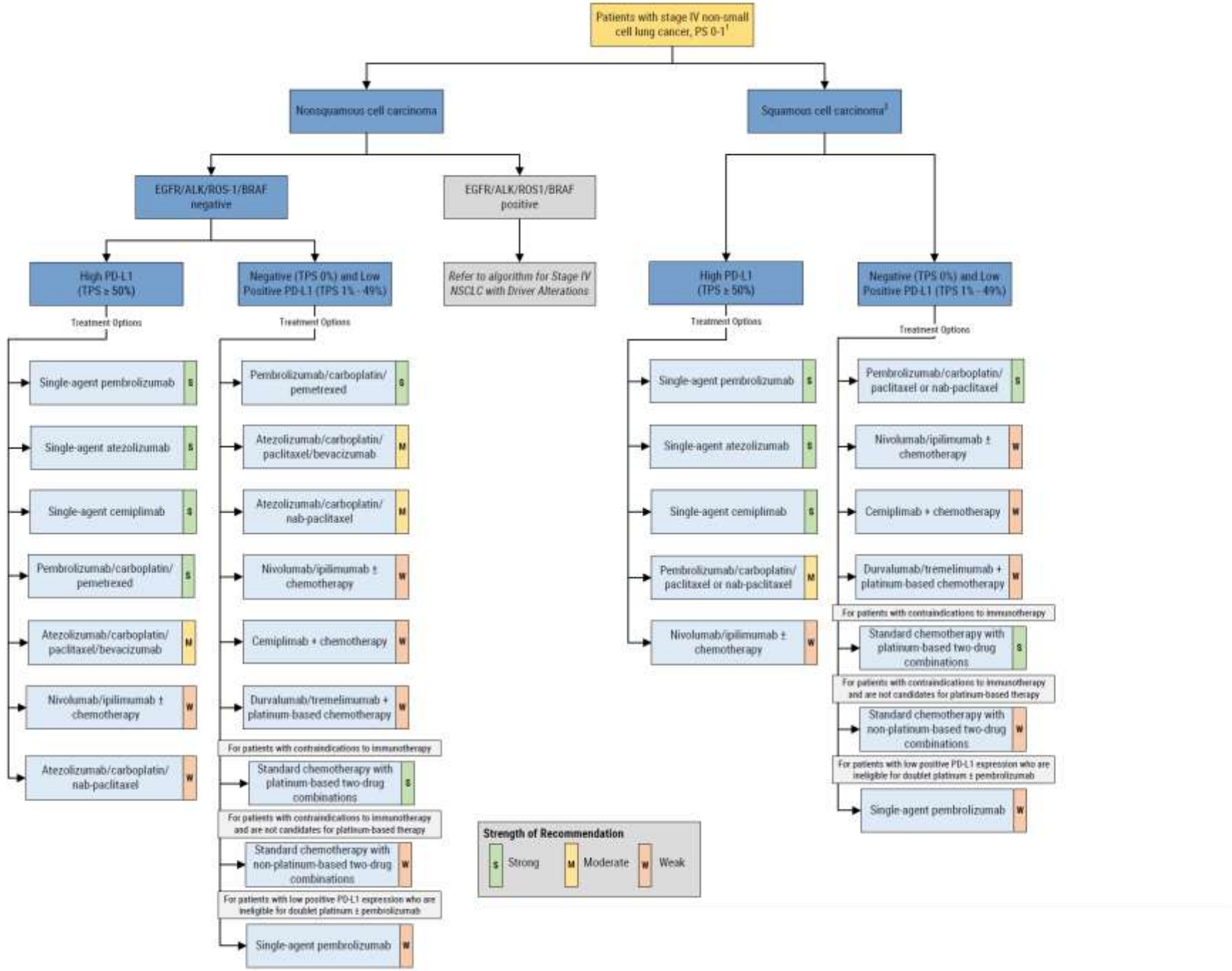
Overall survival in the PD-L1 50% population



Progression-free survival in the PD-L1 50% population

Objective response rate – Cemiplimab(39%) vs. chemotherapy(20%)
Median duration of response – cemiplimab(16·7 months; 95% CI 12·5–22·8) vs. chemotherapy 6·0 months; 95% CI 4·3–6·5)

Lancet. 2021 Feb 13;397(10274):592-604



ASCO Guidelines- First line treatment options for patients with stage IV NSCLC without driver alterations

China innovative lung cancer drugs

PD-1 mAb

- Camrelizumab
- Sintilimab
- Tislelizumab

PD-L1 mAb

- Sugemalimab