Systemisk behandling av lungekreft

Bjørn H. Grønberg

Professor, Institutt for klinisk og molekylær medisin, NTNU

Overlege, Kreftklinikken, St. Olavs Hospital

Thorax (1946), **1**, 1–25.

CARCINOMA OF THE BRONCHUS*

BY

A. TUDOR EDWARDS

X-ray therapy some years ago produced such general reactions as not to warrant submitting patients to the treatment, as so many were made more miserable than if left alone. In the last six years sufficient improvement has resulted to warrant the subjection of inoperable cases to this treatment with distinct hopes of amelioration of symptoms, disappearance of the radiological shadows in some cases, and prolongation of useful life. Nevertheless, I have yet to see a proven case of carcinoma of the bronchus cured by this measure for a period of three years, although a patient inoperable at thoracotomy five years ago still survives, having been treated for metastases on at least three occasions subsequent to the first course of treatment.

CONCLUSIONS

(1) Malignant disease of the lung appears to be increasing in incidence.

(2) A greater number are reaching the surgeon in an operable stage.

(3) The operative mortality has fallen from the neighbourhood of 50 per cent to 10 per cent or lower.

(4) Probably at the present time not more than 15 per cent of primary carcinomas of the lung are operable when first seen by a doctor.

(5) *X*-ray therapy carefully controlled will often ameliorate but never cure carcinoma of the bronchus.

(6) Pneumonectomy by modern technique offers the only hope of cure.

(7) Lobectomy or pneumonectomy is occasionally justifiable in the treatment of a solitary secondary malignant metastasis in the lung.

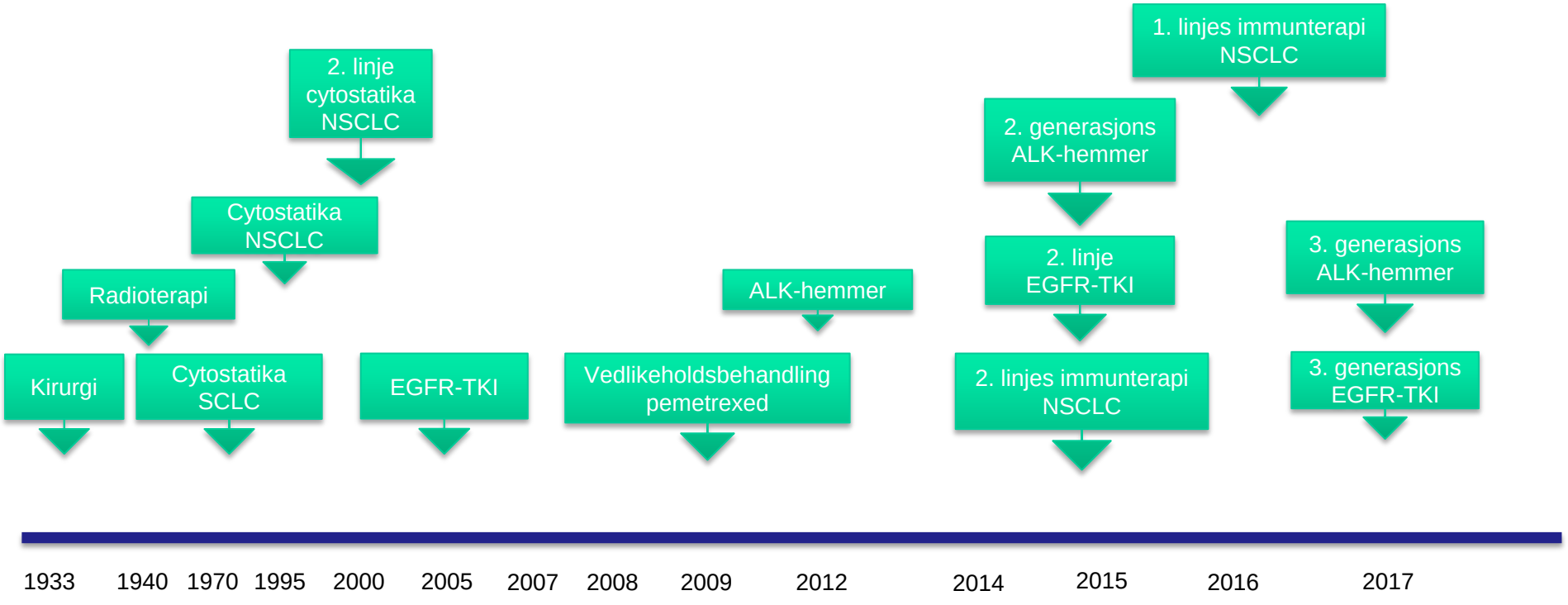
Alkylating Agents in Bronchogenic Carcinoma*

ROBERT A. GREEN, M.D., EDWARD HUMPHREY, M.D., HENRY CLOSE, M.D.
and MARY ELLEN PATNO, PH.D.

Ann Arbor, Michigan

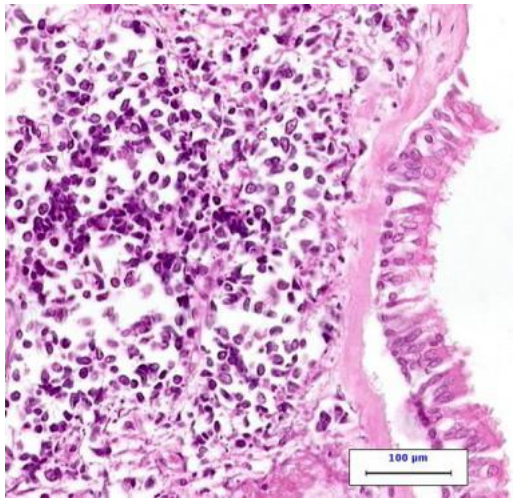
A large number of patients in a group of Veterans Administration Hospitals received a variety of alkylating agents in studies in which these agents were randomized with an inert compound. Intravenous cyclophosphamide, and possibly nitrogen mustard, had a slight favorable influence upon survival for all patients. A difference between the two agents was seen: patients with squamous cell carcinoma appeared to respond best to nitrogen mustard therapy and patients with small cell undifferentiated carcinoma to cyclophosphamide therapy, in fairly striking fashion. Over-all influences upon survival, however, were not remarkable.

Am J Med, 1969



Småcellet lungekreft (SCLC)	Ikke-småcellet lungekreft (NSCLC)
Ca. 15 %	> 80 %
•oat-cell carcinoma •combined small cell carcinoma	•plateepitelcarcinom •adenocarcinom •adenosquamøst carcinom •storcellet carcinom •udifferensiert carcinom
Høy følsomhet for cytostatika og stråling	Middels følsomme for cytostatika og stråling
	Viktige undergrupper skal ha targeted therapy

Småcellet lungekreft



Småcellet lungecancer

- Ca. 15 % av lungekrefttilfeller – *ca. 450 pr år i Norge*
- Meget kjemosensitiv - *RR 70-90%*
- Høy følsomhet for strålebehandling
- Majoriteten får tilbakefall innen et år
- Også pasienter med PS 3-4 bør tilbys behandling

Alkylating Agents in Bronchogenic Carcinoma*

ROBERT A. GREEN, M.D., EDWARD HUMPHREY, M.D., HENRY CLOSE, M.D. *and* MARY ELLEN PATNO, PH.D.
Ann Arbor, Michigan

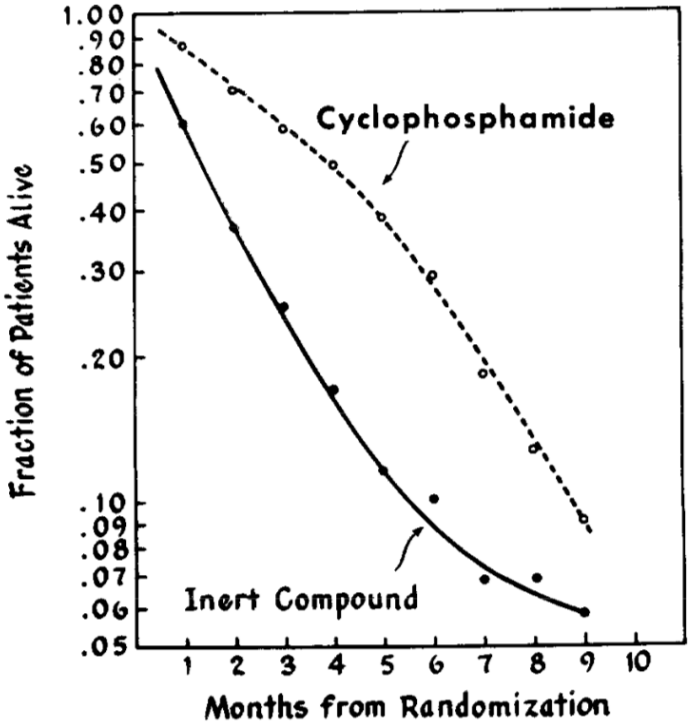
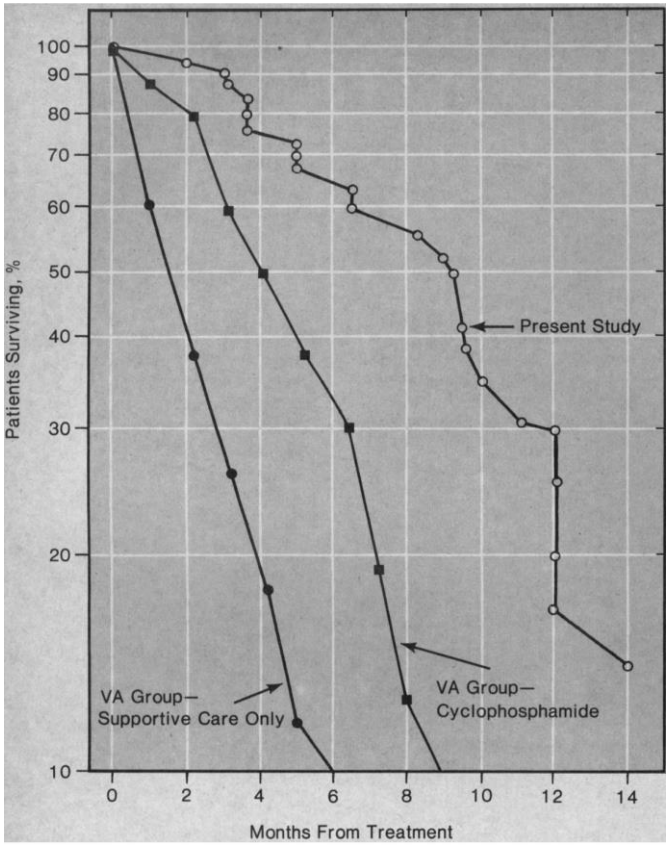


FIG. 2. Undifferentiated small cell carcinoma. Cyclophosphamide versus inert compound.

Am J Med, 1969

Improved Chemotherapy for Small-Cell Undifferentiated Lung Cancer

Lawrence H. Einhorn, MD; Will H. Fee, MD; Mark O. Farber, MD; Robert B. Livingston, MD; Jeffrey A. Gottlieb, MD



JAMA, 1976

Cisplatin and Etoposide Regimen Is Superior to Cyclophosphamide, Epirubicin, and Vincristine Regimen in Small-Cell Lung Cancer: Results From a Randomized Phase III Trial With 5 Years' Follow-Up

By Stein Sundstrøm, Roy M. Bremnes, Stein Kaasa, Ulf Aasebø, Reidulv Hatlevoll, Ragnar Dahle, Nils Boye, Mari Wang, Tor Vigander, Jan Vilsvik, Eva Skovlund, Einar Hannisdal, and Steinar Aamdal for the Norwegian Lung Cancer Study Group

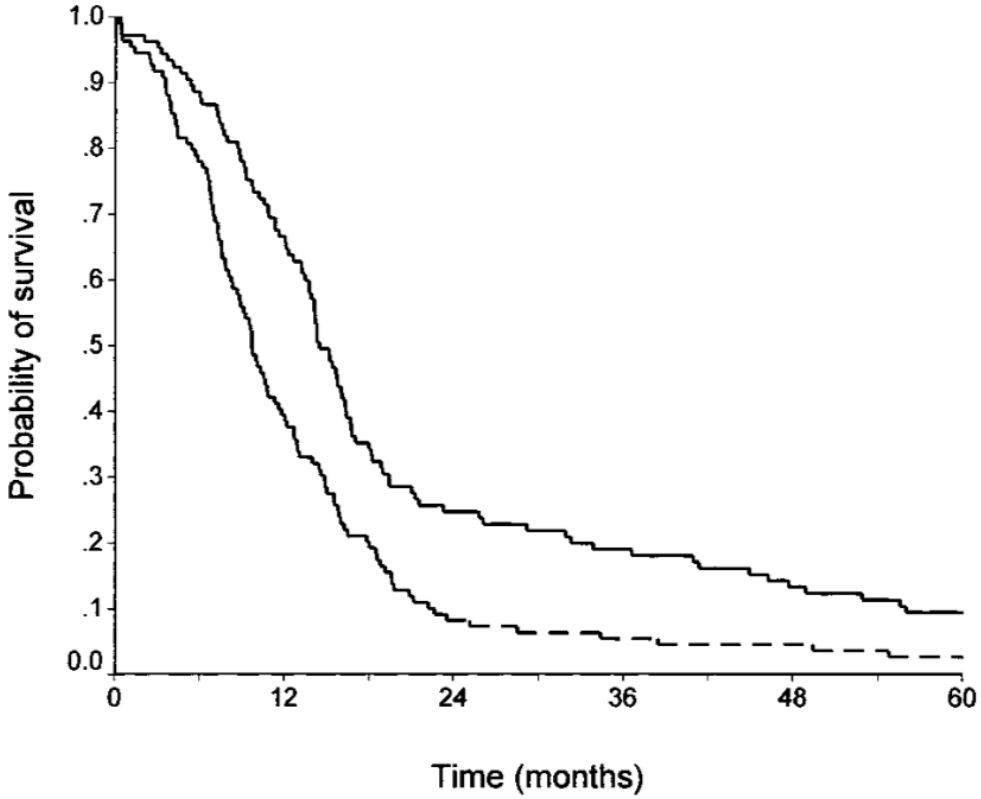
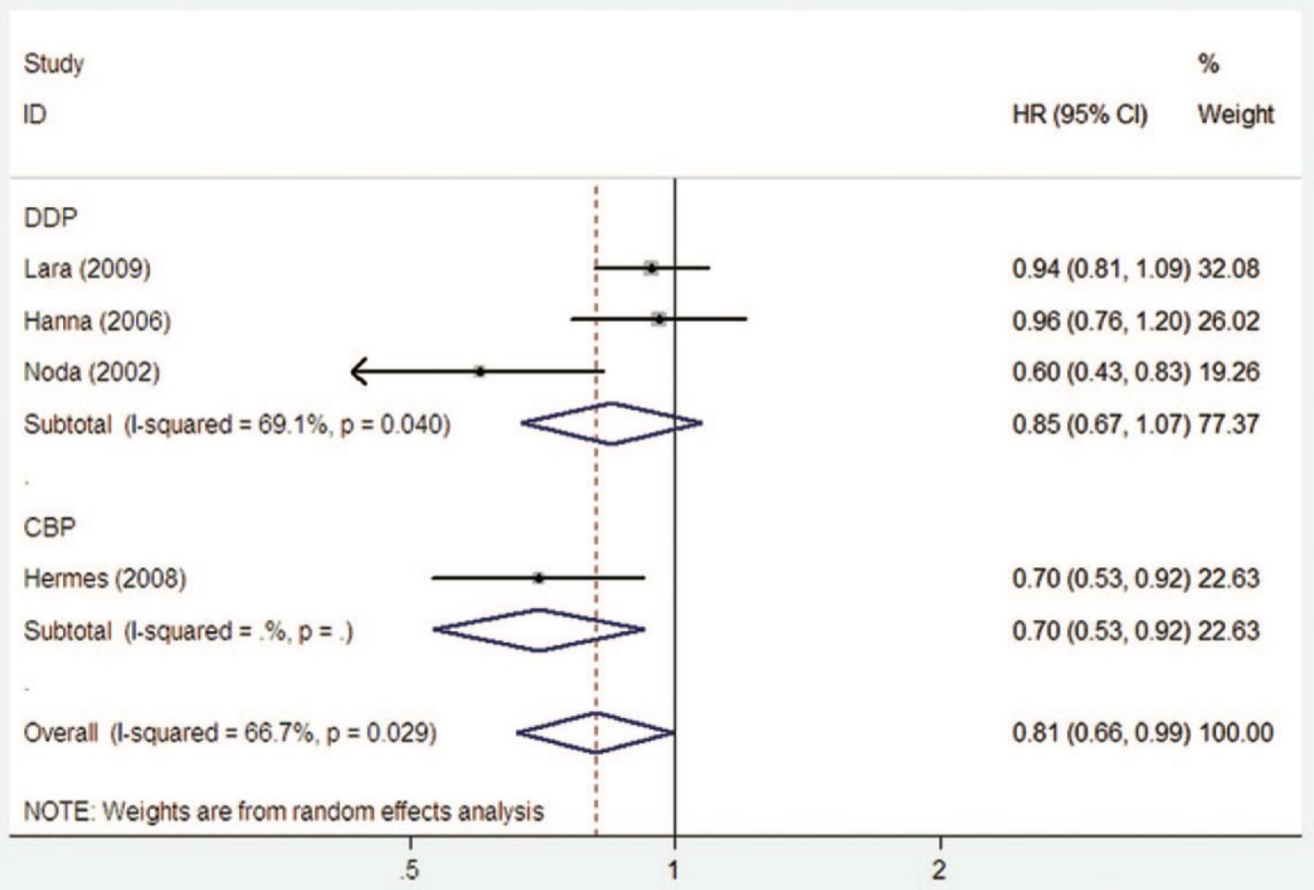


Fig 2. Overall survival of LD-SCLC patients (N = 214) according to treatment arm (*P* = .0001). CEV (dashed line), n = 109; EP (solid line), n = 105.

J Clin Oncol, 2002

A Meta-Analysis of Randomized Controlled Trials Comparing Irinotecan/Platinum with Etoposide/Platinum in Patients with Previously Untreated Extensive-Stage Small Cell Lung Cancer

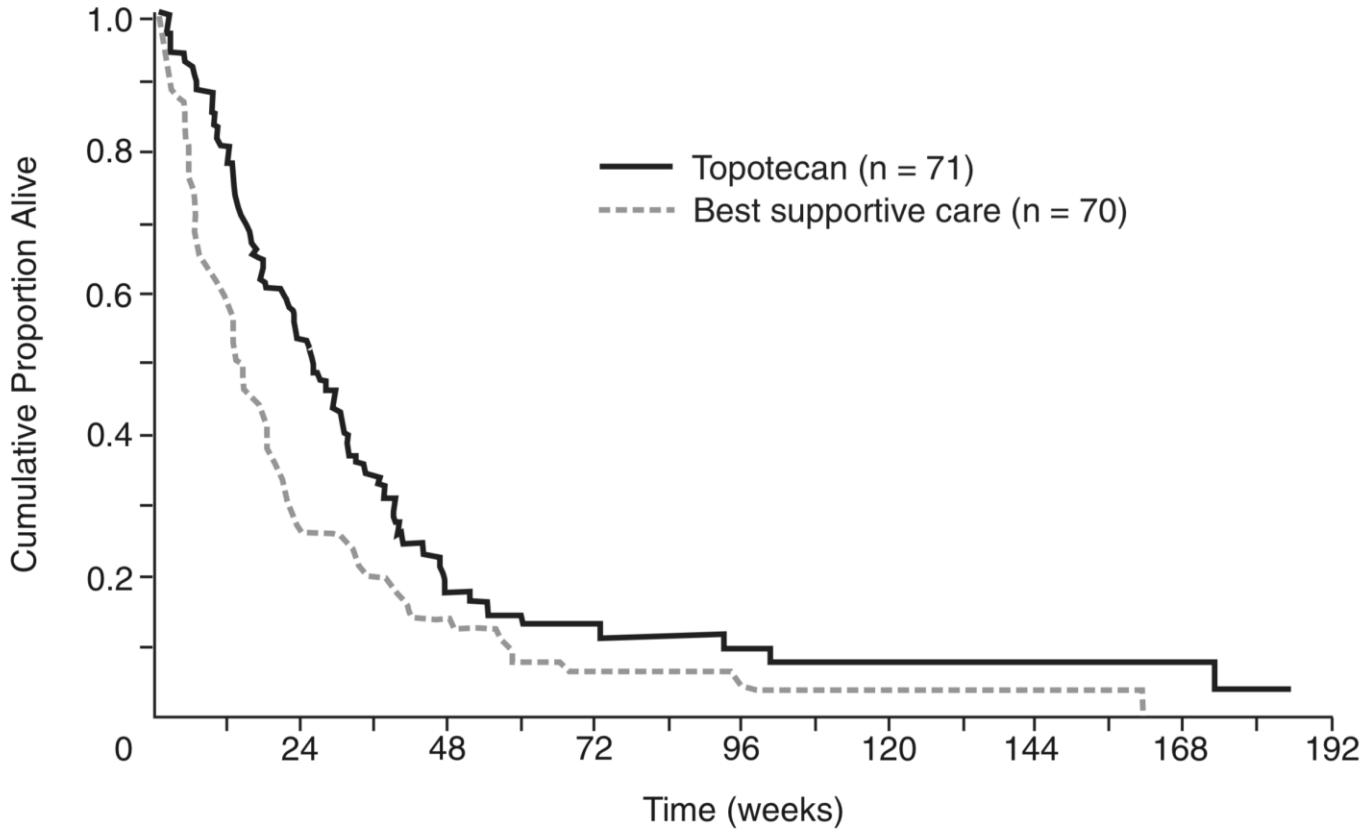
Jingwei Jiang, MM,† Xiaohua Liang, MD,*† Xinli Zhou, MD,*† Lizhen Huang, MS,‡ Ruofan Huang, MD,*† Zhaohui Chu, MM,*† and Qiong Zhan, MM*†*



J Thorac Oncol, 2010

Phase III Trial Comparing Supportive Care Alone With Supportive Care With Oral Topotecan in Patients With Relapsed Small-Cell Lung Cancer

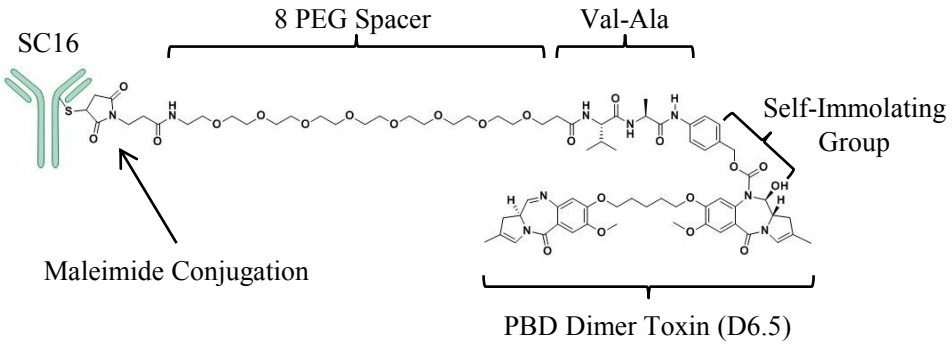
Mary E.R. O'Brien, Tudor-Eliade Ciuleanu, Hristo Tsekov, Yaroslav Shparyk, Branka Čučeviá, Gabor Juhasz, Nicholas Thatcher, Graham A. Ross, Graham C. Dane, and Theresa Crofts



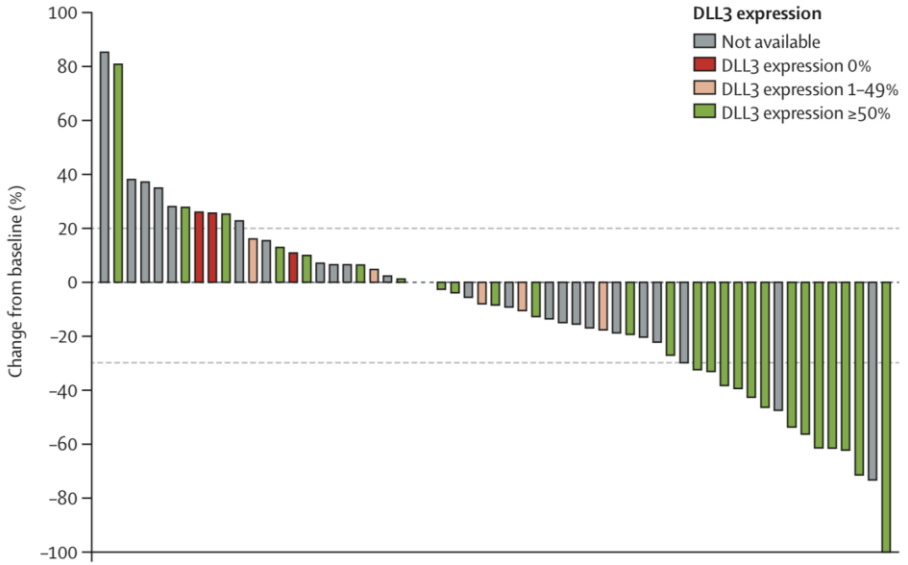
J Clin Oncol, 2006

Rovalpituzumab tesirine, a DLL3-targeted antibody-drug conjugate, in recurrent small-cell lung cancer: a first-in-human, first-in-class, open-label, phase 1 study

*Charles M Rudin, M Catherine Pietanza, Todd M Bauer, Neal Ready, Daniel Morgensztern, Bonnie S Glisson, Lauren A Byers, Melissa L Johnson, Howard A Burris III, Francisco Robert, Tae H Han, Sheila Bheddah, Noah Theiss, Sky Watson, Deepan Mathur, Bharathi Vennapusa, Hany Zayed, Satwant Lally, Donald K Strickland, Ramaswamy Govindan, Scott J Dylla, Stanford L Peng, David R Spigel, for the SCRX16-001 investigators**

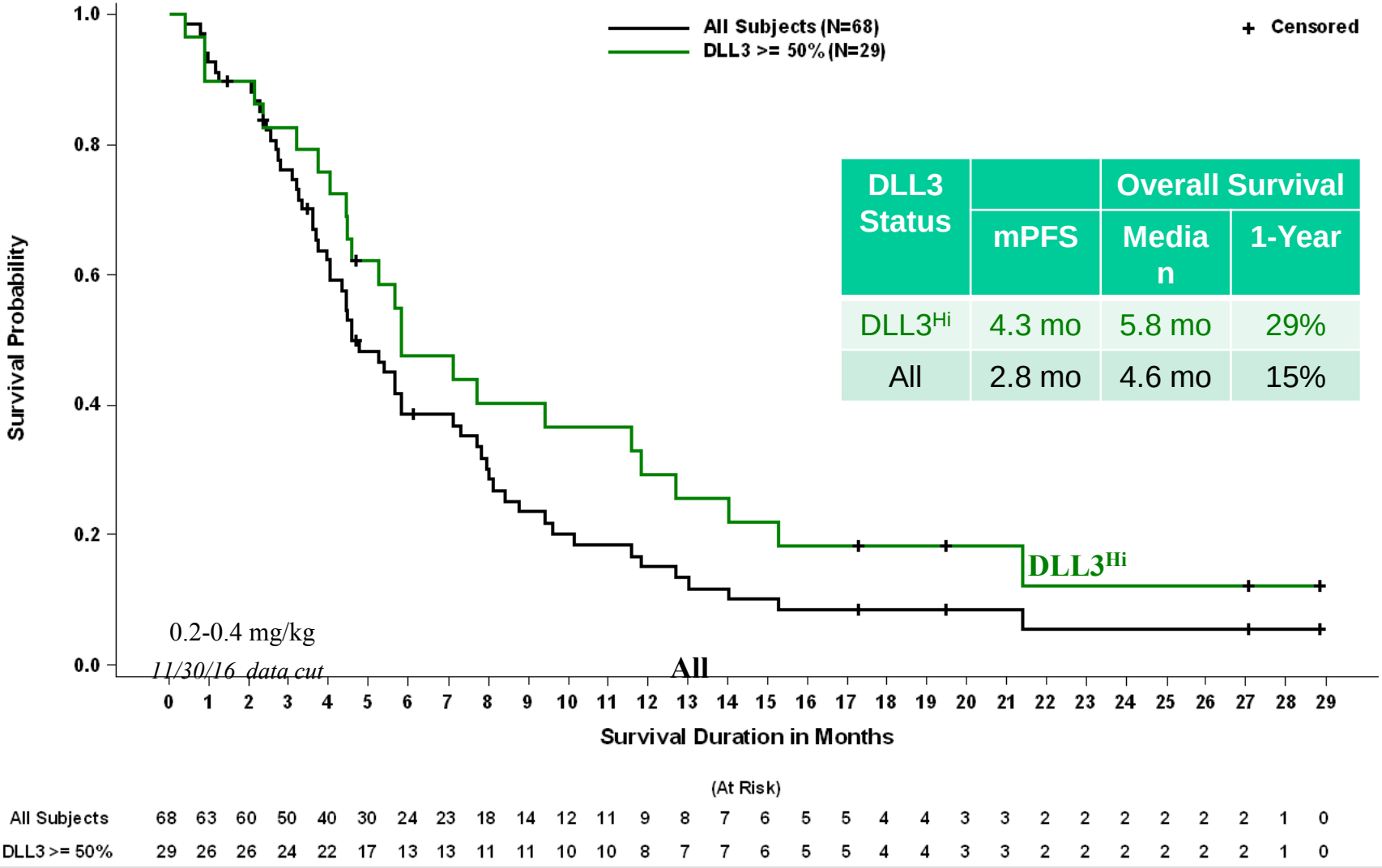


Cell cycle independent MOA; causes interstrand crosslinks



Lancet Oncol, 2016

SCLC Kaplan-Meier Overall Survival

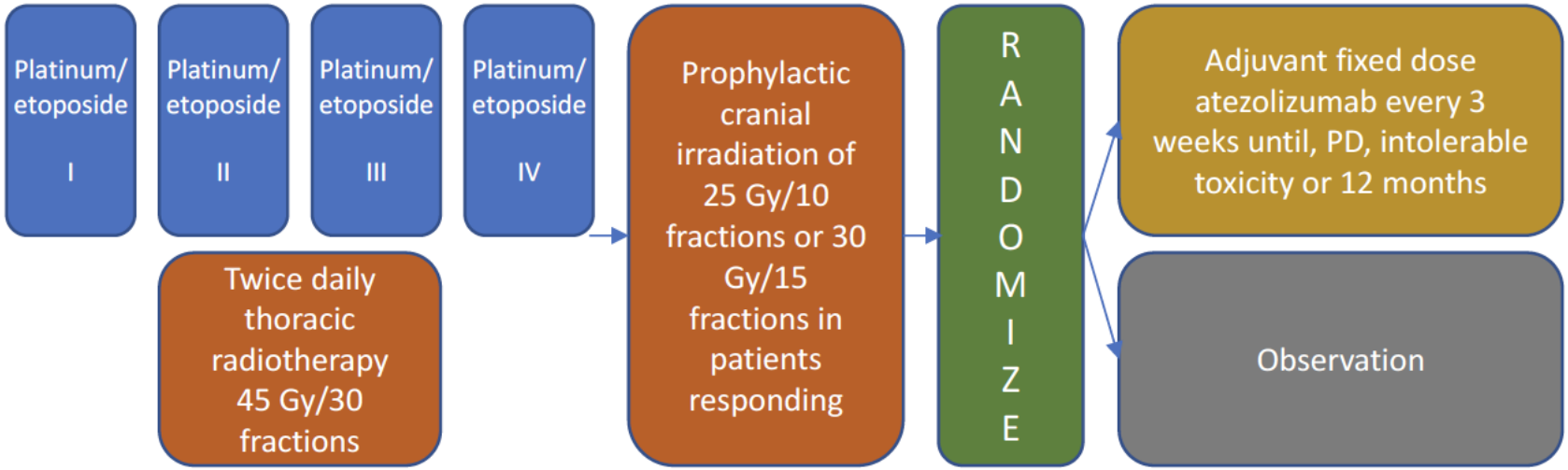


DLL3 Status		Overall Survival	
	mPFS	Median	1-Year
DLL3^{Hi}	4.3 mo	5.8 mo	29%
All	2.8 mo	4.6 mo	15%

Annet

- Bevacizumab er forsøkt, men har ikke vist overlevelsesgevinst
- Amrubicin har vist effekt, men ikke registrert
- Høydosebehandling evt. med stamcellestøtte gir lenger PFS, men mer toksisitet og ingen overlevelsesgevinst
- Lovende data på immunterapi, men ingen fase III data per i dag

ACHILES



Oppsummering

- Cisplatin/carboplatin + etoposide er standardregimet ved SCLC
- Platinum/irinotecan er likeverdig

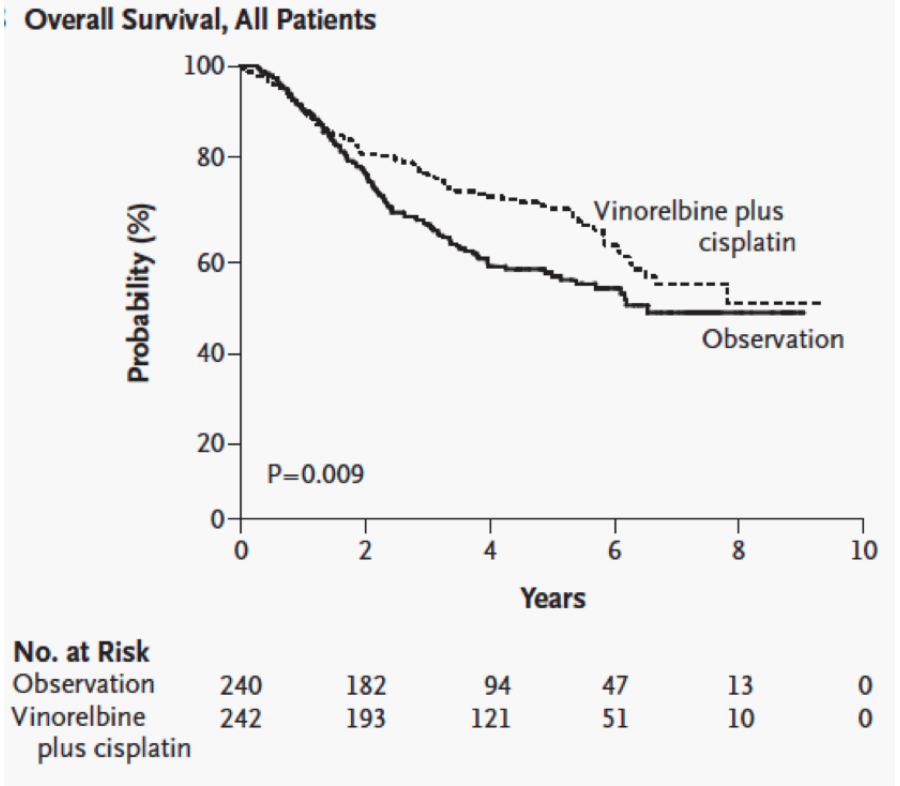
- Reinduksjon anbefales ved > (3-) 6 måneder fra siste behandlingsrunde til progresjon

- Aktuell 2. linjes behandling er platinum/irinotecan, ACO og topotecan

Ikke-småcellet lungekreft

Adjuvant cytostatika etter kirurgi

- Dokumentert overlevelsesgevinst i flere studier
- Anbefalt regime er cisplatin/vinorelbine, men andre platinum-dubletter som brukes ved metastatisk sykdom kan evt. Brukes
- Registerstudier viser like stor gevinst hos pasienter >70 år. Hos disse bør carboplatin og dosereduksjon vurderes.



NEJM 2005

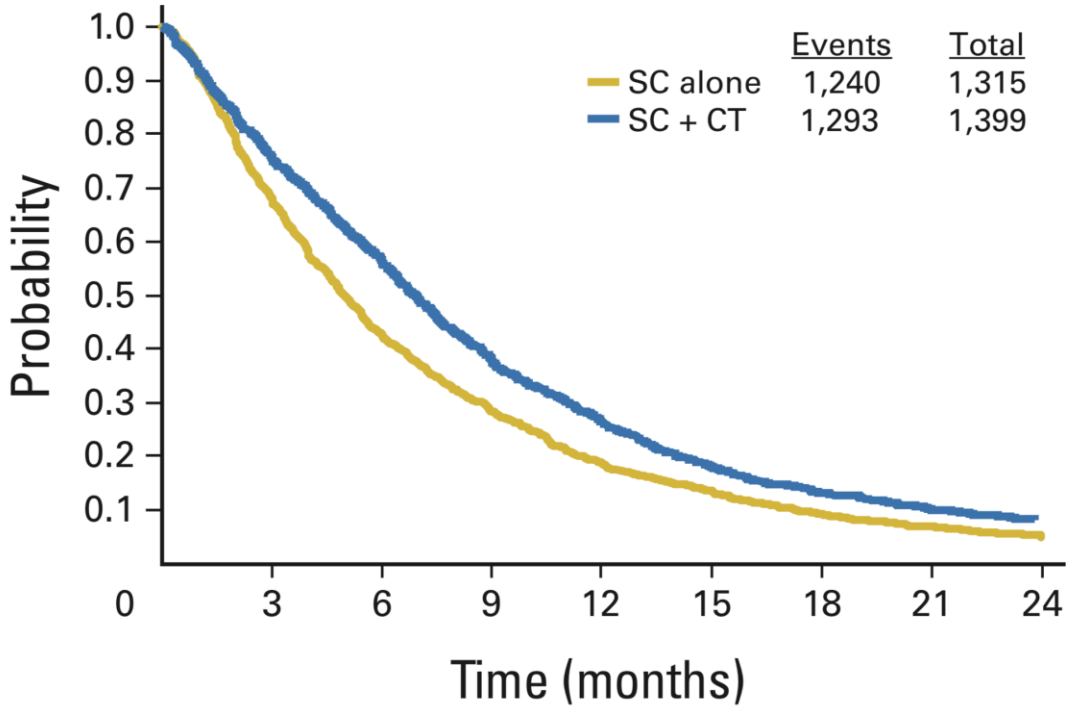
Konkomitant med radikal strålebehandling

- Mange regimer har vært brukt
- I Norge anbefales to kurer med cisplatin/etoposide
- I den danske NARLAL-studien gis platinum/vinorelbine PO

- Pasienter med stadium III som ikke er aktuelle for radikal strålebehandling kan vurderes for 4 kurer med carboplatin/vinorelbine + thoraxbestråling 2.8 Gy x 15 mellom 2. og 3. kur

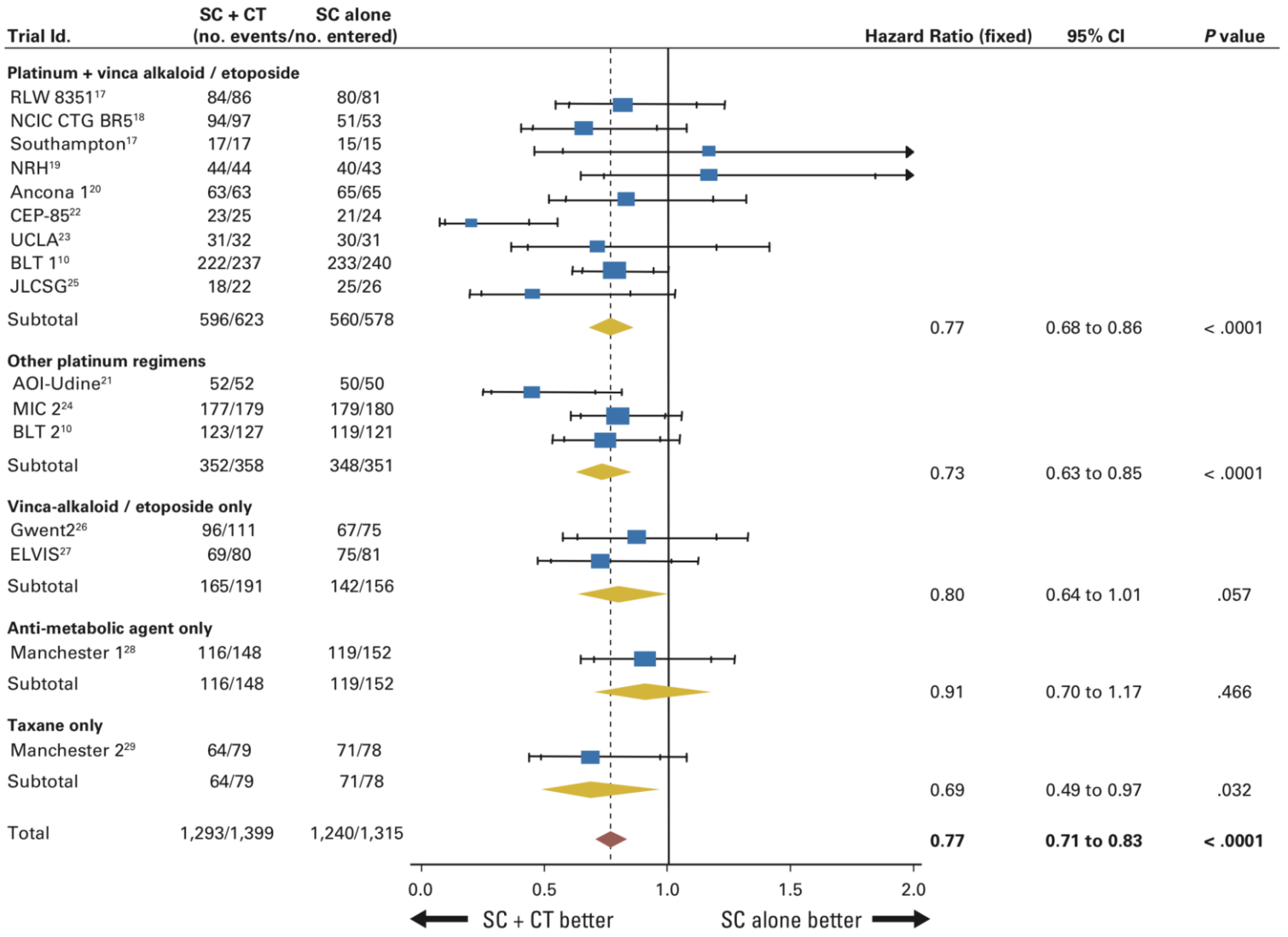
Chemotherapy in Addition to Supportive Care Improves Survival in Advanced Non–Small-Cell Lung Cancer: A Systematic Review and Meta-Analysis of Individual Patient Data From 16 Randomized Controlled Trials

NSCLC Meta-Analyses Collaborative Group



Patients at risk									
SC alone	1,315	884	552	363	231	161	107	77	55
SC + CT	1,399	1,052	779	519	349	233	165	115	91

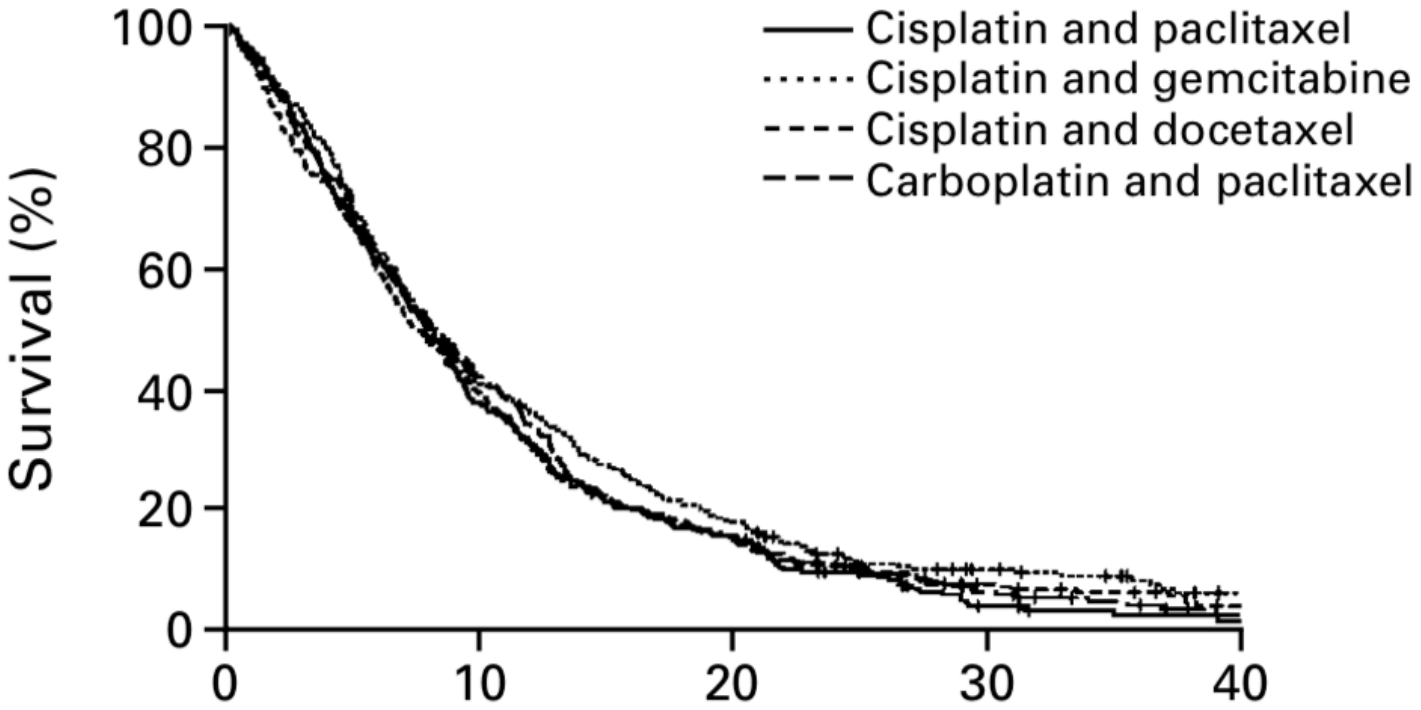
J Clin Oncol, 2008



Heterogeneity $P = .02$; $I^2 = 47$; interaction $P = .63$
(Sensitivity analysis excluding CEP-85 heterogeneity $P = .28$; $I^2 = 16$; interaction $P = .62$)

COMPARISON OF FOUR CHEMOTHERAPY REGIMENS FOR ADVANCED NON–SMALL-CELL LUNG CANCER

JOAN H. SCHILLER, M.D., DAVID HARRINGTON, PH.D., CHANDRA P. BELANI, M.D., COREY LANGER, M.D., ALAN SANDLER, M.D., JAMES KROOK, M.D., JUNMING ZHU, PH.D., AND DAVID H. JOHNSON, M.D., FOR THE EASTERN COOPERATIVE ONCOLOGY GROUP



NEJM, 2002

Palliative chemotherapy beyond three courses conveys no survival or consistent quality-of-life benefits in advanced non-small-cell lung cancer

C von Plessen[*,1], B Bergman[2,8], O Andresen[1,9], RM Bremnes[3], S Sundstrøm[4], M Gilleryd[2,8], R Stephens[5], J Vilsvik[6], U Aasebø[7] and S Sörenson[1,10], for the Norwegian Lung Cancer Study Group

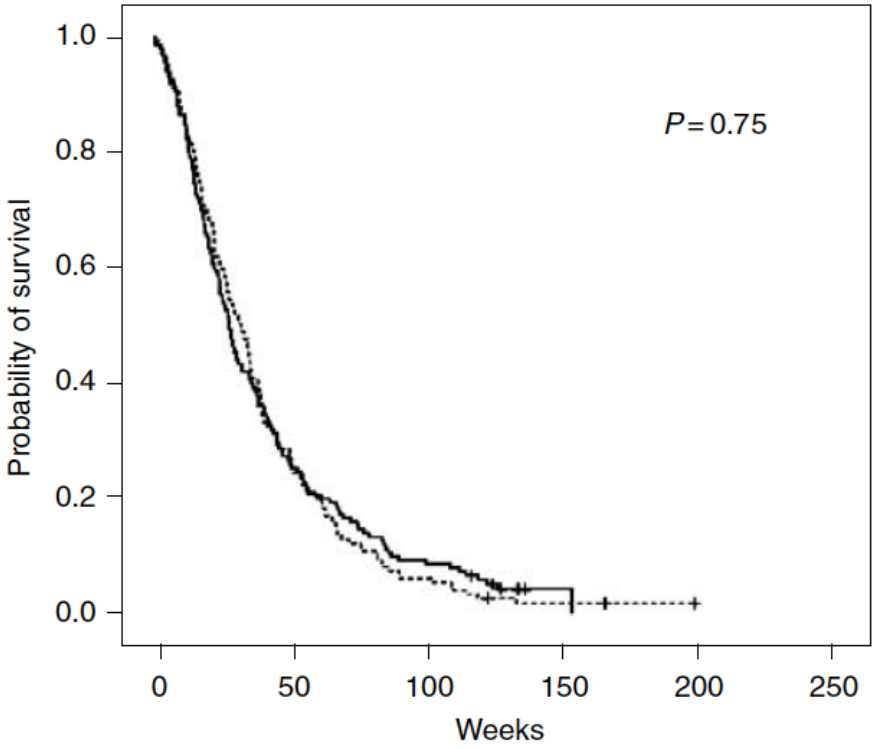


Figure 3 Overall survival by treatment group: C3 (randomised to receive three courses) marked with solid line and C6 (randomised to receive six courses) with dotted line. *P*-value refers to a log-rank test.

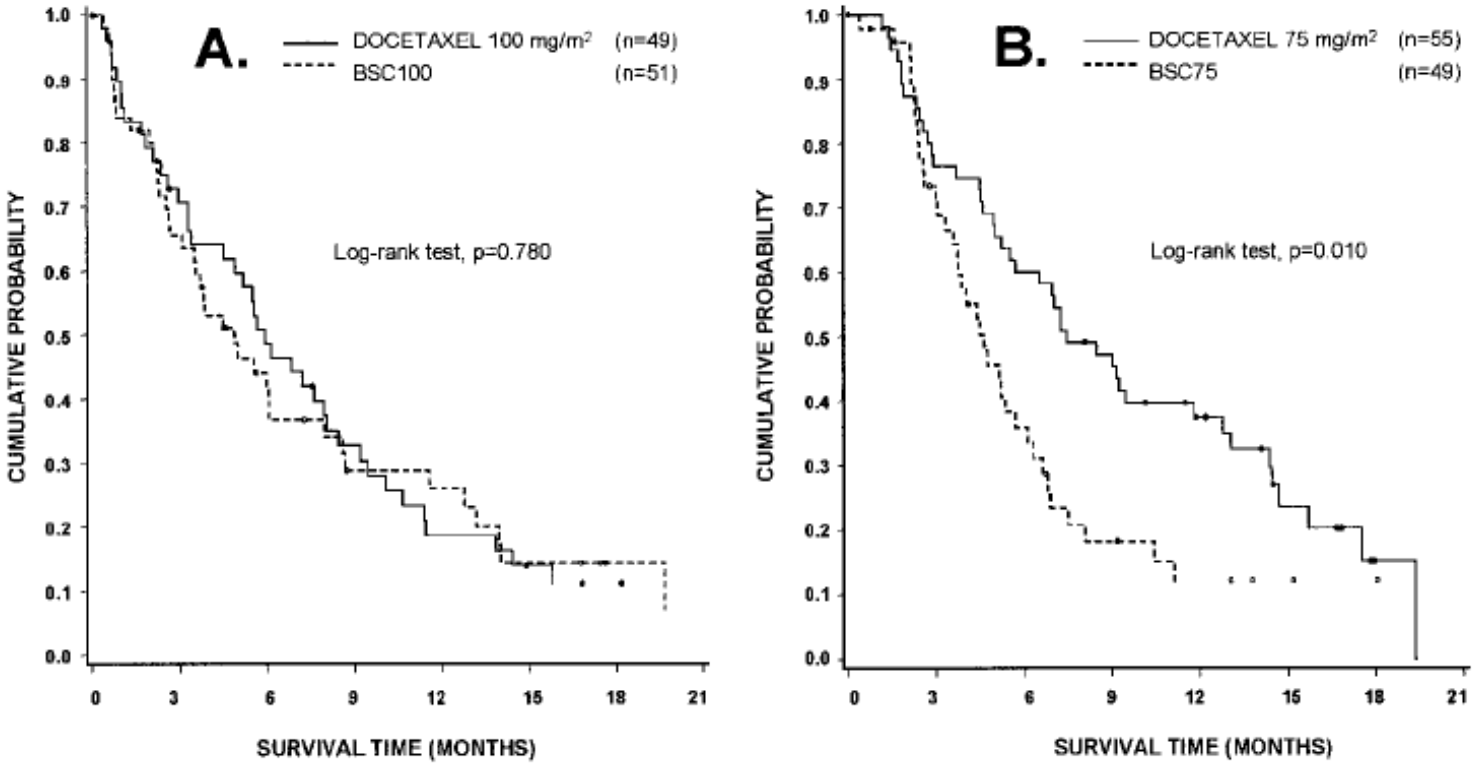
Br J Cancer, 2002

ST. OLAVS HOSPITAL
UNIVERSITETSSYKEHUSET I TRONDHEIM

NTNU
Kunnskap for en bedre verden

Prospective Randomized Trial of Docetaxel Versus Best Supportive Care in Patients With Non–Small-Cell Lung Cancer Previously Treated With Platinum-Based Chemotherapy

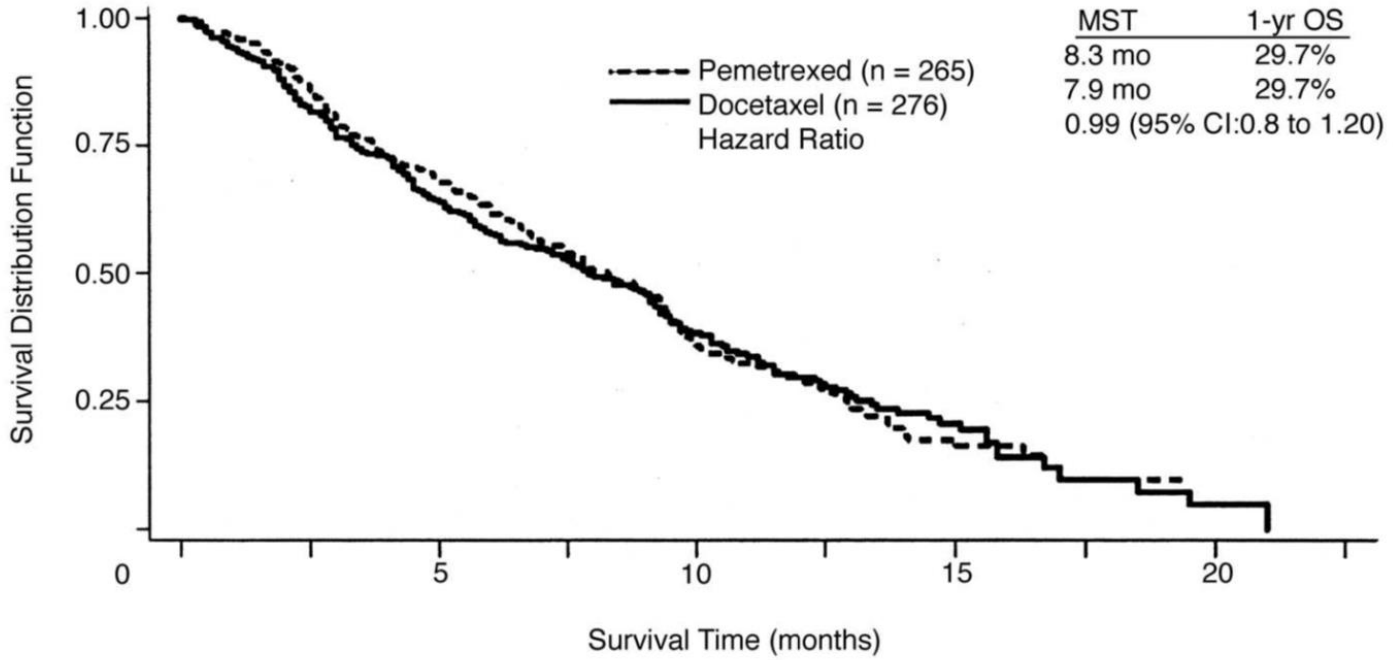
By Frances A. Shepherd, Janet Dancey, Rodryg Ramlau, Karin Mattson, Richard Gralla, Mark O'Rourke, Nathan Levitan, Laurent Gressot, Mark Vincent, Ronald Burkes, Susan Coughlin, Yong Kim, and Jocelyne Berille



J Clin Oncol, 2000

Randomized Phase III Trial of Pemetrexed Versus Docetaxel in Patients With Non–Small-Cell Lung Cancer Previously Treated With Chemotherapy

Nasser Hanna, Frances A. Shepherd, Frank V. Fossella, Jose R. Pereira, Filippo De Marinis, Joachim von Pawel, Ulrich Gatzemeier, Thomas Chang Yao Tsao, Miklos Pless, Thomas Muller, Hong-Liang Lim, Christopher Desch, Klara Szondy, Radj Gervais, Shaharyar, Christian Manegold, Sofia Paul, Paolo Paoletti, Lawrence Einhorn, and Paul A. Bunn Jr.

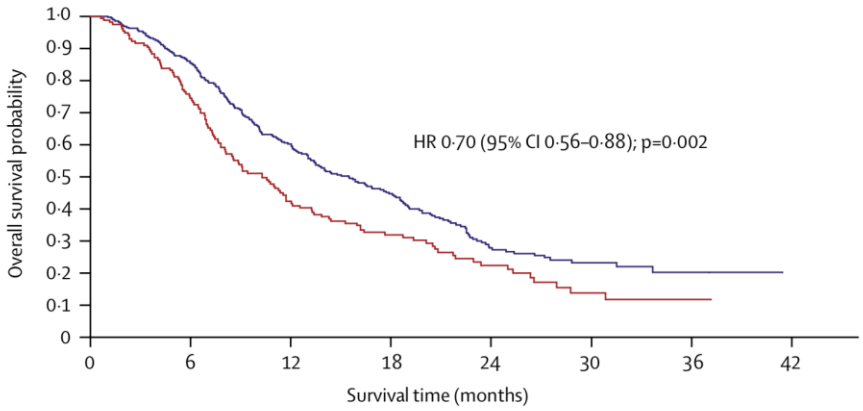


Pts At Risk					
Pemetrexed	283	189	78	16	0
Docetaxel	288	177	78	19	1

J Clin Oncol, 2004

Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study

Tudor Ciuleanu, Thomas Brodowicz, Christoph Zielinski, Joo Hang Kim, Maciej Krzakowski, Eckart Laack, Yi-Long Wu, Isabel Bover, Stephen Begbie, Valentina Tzekova, Branka Cucevic, Jose Rodrigues Pereira, Sung Hyun Yang, Jayaprakash Madhavan, Katherine P Sugarman, Patrick Peterson, William J John, Kurt Krejcy, Chandra P Belani



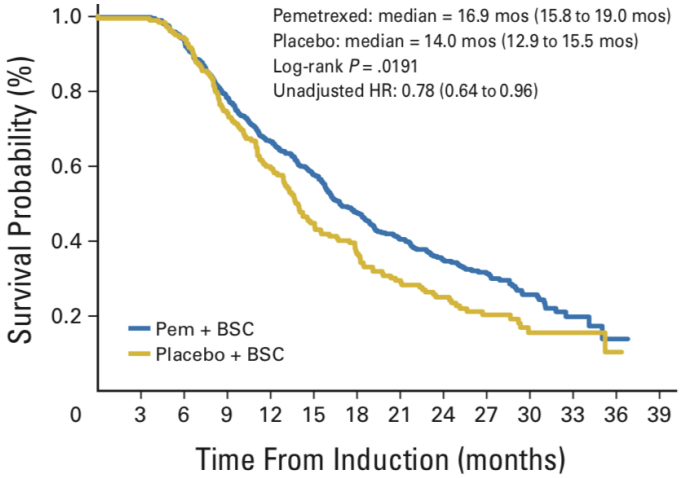
Number at risk

Pemetrexed	325	265	178	117	51	25	9	0
Placebo	156	112	63	42	20	7	3	0

Lancet, 2009

PARAMOUNT: Final Overall Survival Results of the Phase III Study of Maintenance Pemetrexed Versus Placebo Immediately After Induction Treatment With Pemetrexed Plus Cisplatin for Advanced Nonsquamous Non–Small-Cell Lung Cancer

Luis G. Paz-Ares, Filippo de Marinis, Mircea Dediu, Michael Thomas, Jean-Louis Pujol, Paolo Bidoli, Olivier Molinier, Tarini Prasad Sahoo, Eckart Laack, Martin Reck, Jesús Corral, Symantha Melemed, William John, Nadia Chouaki, Annamaria H. Zimmermann, Carla Visseren-Grul, and Cesare Gridelli



No. at risk

Pem + BSC	359	335	276	234	200	164	138	106	77	42	15	2	0
Placebo + BSC	180	168	132	103	78	63	49	35	23	12	8	3	0

J Clin Oncol, 2013

Oppsummering cytostatika

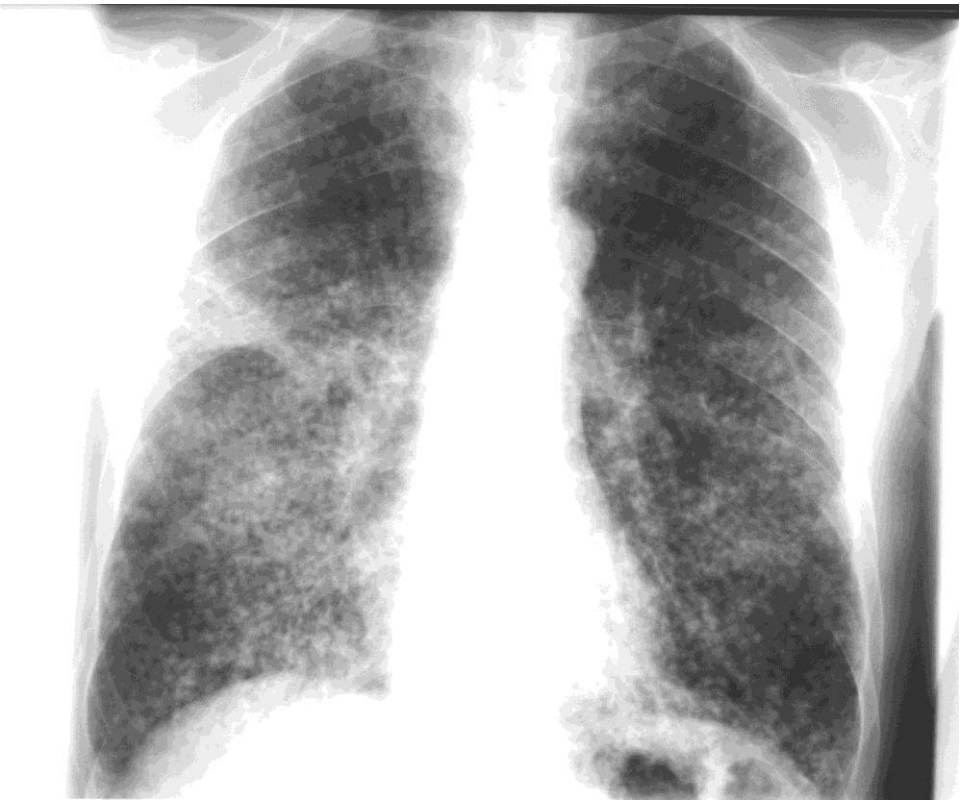
- Carboplatin/vinorelbine er standard regime ved avansert NSCLC
- Vinorelbine kan evt. Gis PO dag 8, sannsynligvis uten kontroll hematologi

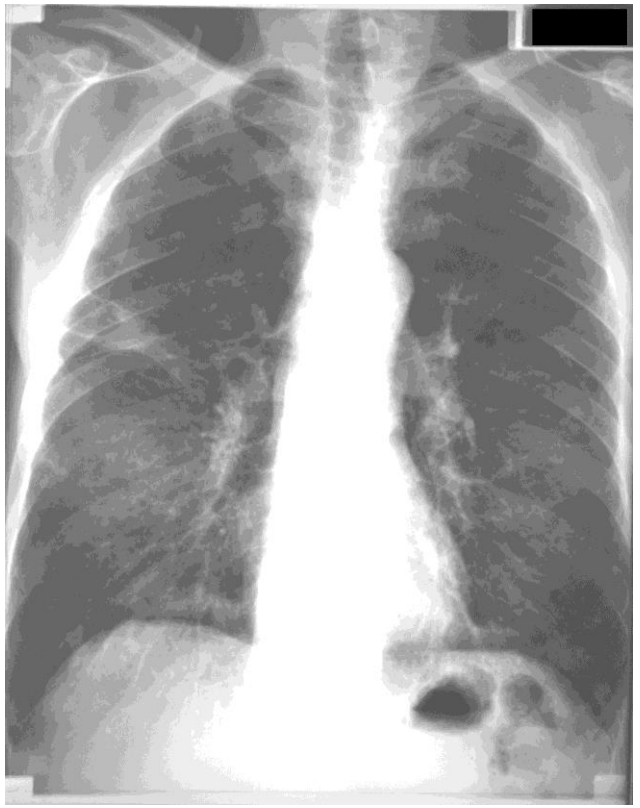
- Vedlikeholdsbehandling med pemetrexed vurderes hos pasienter med non-squamous histologi, som ikke progredierer på induksjonsbehandling og har PS 0-1 *(PD-L1?)*

- Reinduksjonsbehandling kan vurderes dersom det er mer enn (3-) 6 måneder etter forrige behandlingsrunde

- Pemetrexed anbefales som 2. linjes behandling ved non-squamous histologi
- Docetaxel anbefales som 2. linjes behandling ved plateepitelcarcinom

Case report

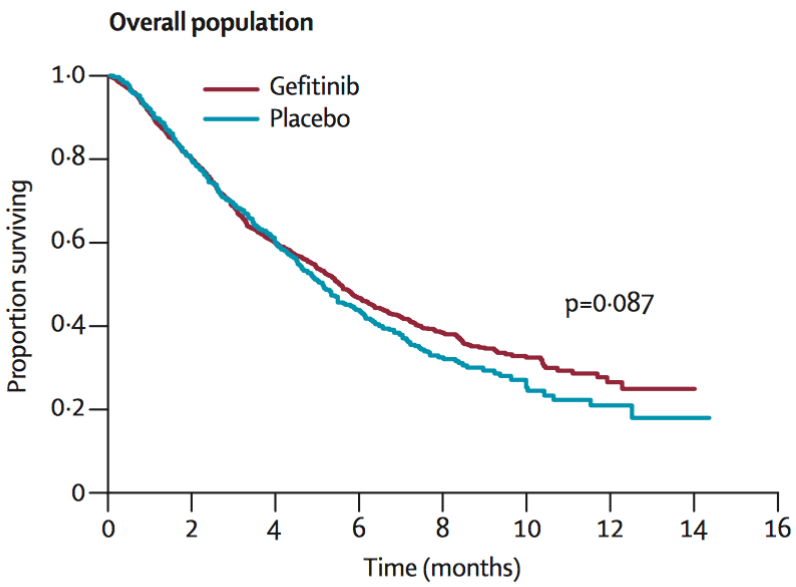




- 73 år gammel mann som hadde fått all tilgjengelig behandling, ingen respons på 1. eller 2. linjes cytostatika
- Carcinomatose i lungene, O2-trengende og mer enn 100 hjernemetastaser

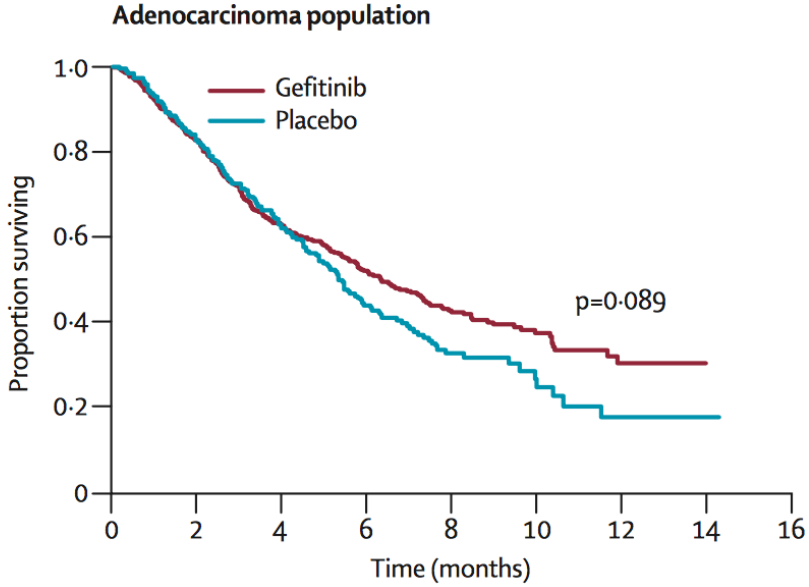
Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer)

*Nick Thatcher, Alex Chang, Purvish Parikh, José Rodrigues Pereira, Tudor Ciuleanu, Joachim von Pawel, Sumitra Thongprasert, Eng Huat Tan, Kristine Pemberton, Venice Archer, Kevin Carroll**



Number at risk

Gefitinib	1129	901	588	325	175	76	19
Placebo	563	446	289	160	77	28	12



Number at risk

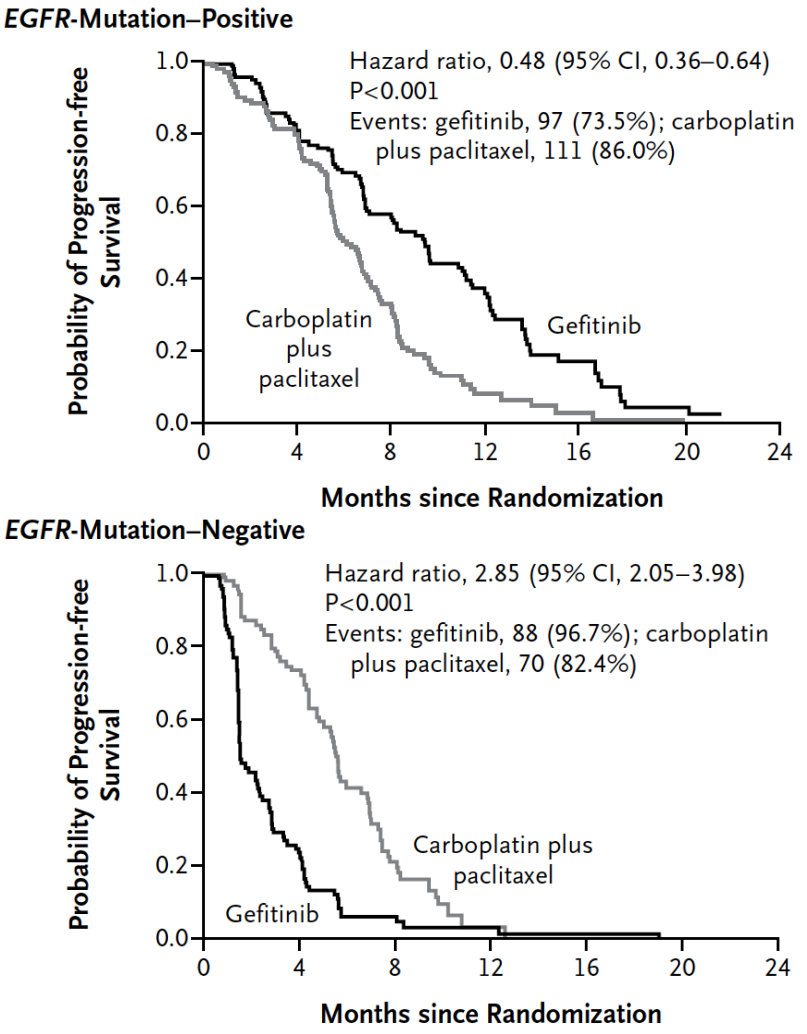
Gefitinib	541	446	303	184	106	52	13
Placebo	271	223	143	78	39	14	5

Lancet, 2005

Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma

Tony S. Mok, M.D., Yi-Long Wu, M.D., F.A.C.S., Sumitra Thongprasert, M.D., Chih-Hsin Yang, M.D., Ph.D., Da-Tong Chu, M.D., Nagahiro Saijo, M.D., Ph.D., Patrapim Sunpaweravong, M.D., Baohui Han, M.D., Benjamin Margono, M.D., Ph.D., F.C.C.P., Yukito Ichinose, M.D., Yutaka Nishiwaki, M.D., Ph.D., Yuichiro Ohe, M.D., Ph.D., Jin-Ji Yang, M.D., Busyamas Chewaskulyong, M.D., Haiyi Jiang, M.D., Emma L. Duffield, M.Sc., Claire L. Watkins, M.Sc., Alison A. Armour, F.R.C.R., and Masahiro Fukuoka, M.D., Ph.D.

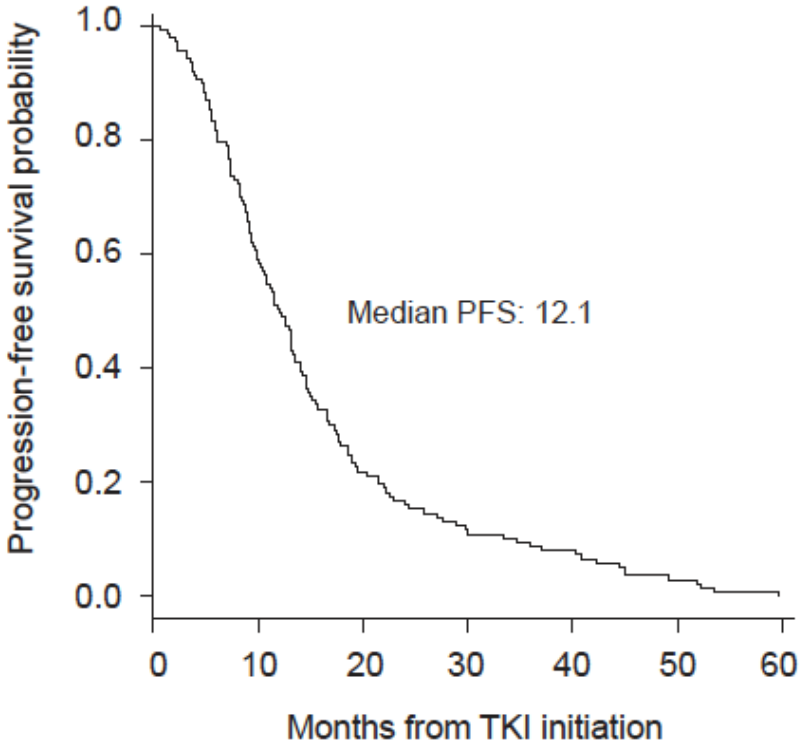
- Tidlige studier viste at kvinner, ikke-røykende, sør-øst asiater hadde bedre respons enn andre
- Senere studier viste at det først og fremst er pasienter med EGFR-mutasjoner som responderer
- Nevnte subgrupper har oftere EGFR-mutasjoner
- Alle pasienter med non-squamous histologi testes rutinemessig for EGFR-mutasjoner i Norge
- Tre aktuelle medikament til første-linjes behandling: gefitinib, erlotinib og afatinib

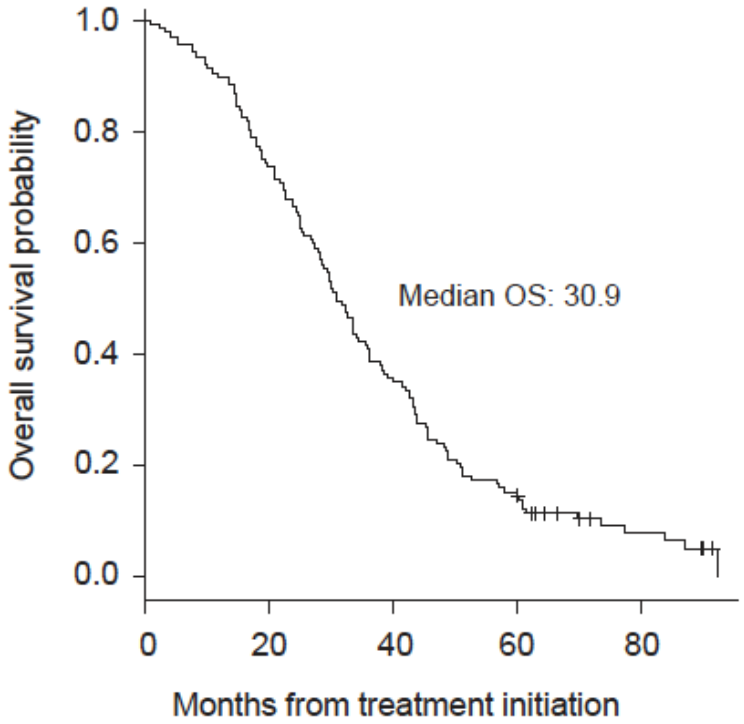


NEJM, 2009

Five-Year Survival in *EGFR*-Mutant Metastatic Lung Adenocarcinoma Treated with EGFR-TKIs

Jessica J. Lin, MD,[a,b] Stephanie Cardarella, MD,[a,c] Christine A. Lydon, BA,[a] Suzanne E. Dahlberg, PhD,[d] David M. Jackman, MD,[a,b,e] Pasi A. Jänne, MD, PhD, Bruce E. Johnson, MD[a,b,e,*]



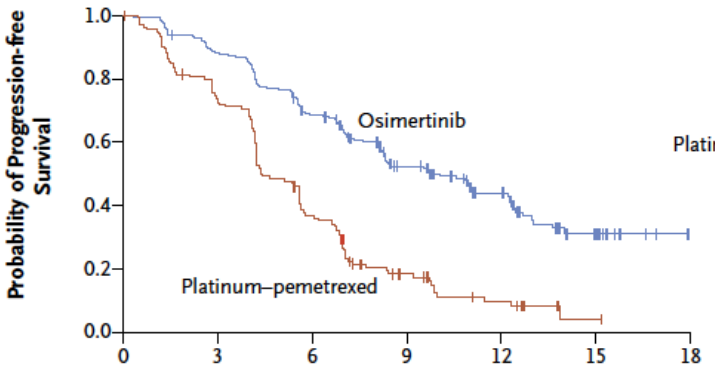


J Thor Oncol, 2015

Osimertinib or Platinum–Pemetrexed in *EGFR* T790M–Positive Lung Cancer

T.S. Mok, Y.-L. Wu, M.-J. Ahn, M.C. Garassino, H.R. Kim, S.S. Ramalingam, F.A. Shepherd, Y. He, H. Akamatsu, W.S.M.E. Theelen, C.K. Lee, M. Sebastian, A. Templeton, H. Mann, M. Marotti, S. Ghiorghiu, and V.A. Papadimitrakopoulou, for the AURA3 Investigators*

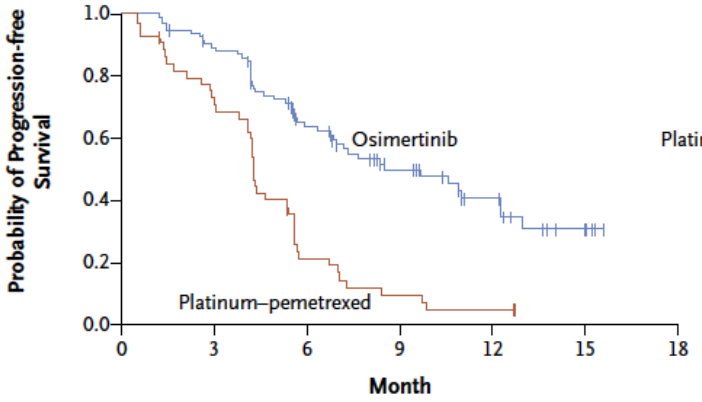
A Patients in Intention-to-Treat Population



	No. of Patients	Median Progression-free Survival
		mo (95% CI)
Osimertinib	279	10.1 (8.3–12.3)
Platinum–pemetrexed	140	4.4 (4.2–5.6)

Hazard ratio for disease progression or death, 0.30 (95% CI, 0.23–0.41)
P<0.001

B Patients with CNS Metastases



	No. of Patients	Median Progression-free Survival
		mo (95% CI)
Osimertinib	93	8.5 (6.8–12.3)
Platinum–pemetrexed	51	4.2 (4.1–5.4)

Hazard ratio for disease progression or death, 0.32 (95% CI, 0.21–0.49)

N Engl J Med, 2016

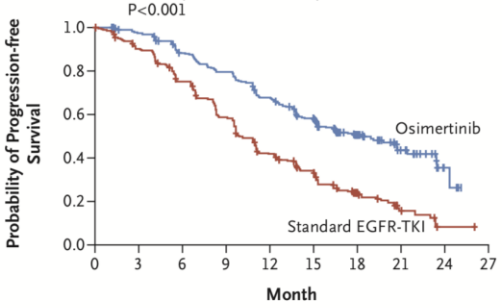
Osimertinib in Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

J.-C. Soria, Y. Ohe, J. Vansteenkiste, T. Reungwetwattana, B. Chewaskulyong, K.H. Lee, A. Dechaphunkul, F. Imamura, N. Nogami, T. Kurata, I. Okamoto, C. Zhou, B.C. Cho, Y. Cheng, E.K. Cho, P.J. Voon, D. Planchard, W.-C. Su, J.E. Gray, S.-M. Lee, R. Hodge, M. Marotti, Y. Rukazenkov, and S.S. Ramalingam, for the FLAURA Investigators*

A Progression-free Survival in Full Analysis Set

	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Osimertinib	279	18.9 (15.2–21.4)
Standard EGFR-TKI	277	10.2 (9.6–11.1)

Hazard ratio for disease progression or death, 0.46 (95% CI, 0.37–0.57)
P<0.001



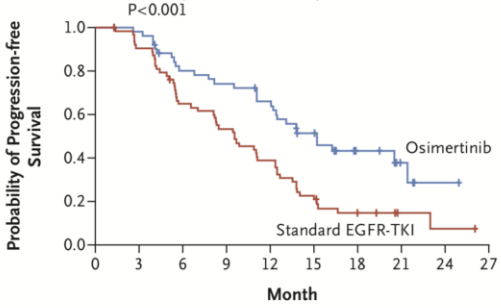
No. at Risk

Osimertinib	279	262	233	210	178	139	71	26	4	0
Standard EGFR-TKI	277	239	197	152	107	78	37	10	2	0

B Progression-free Survival in Patients with CNS Metastases

	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Osimertinib	53	15.2 (12.1–21.4)
Standard EGFR-TKI	63	9.6 (7.0–12.4)

Hazard ratio for disease progression or death, 0.47 (95% CI, 0.30–0.74)
P<0.001



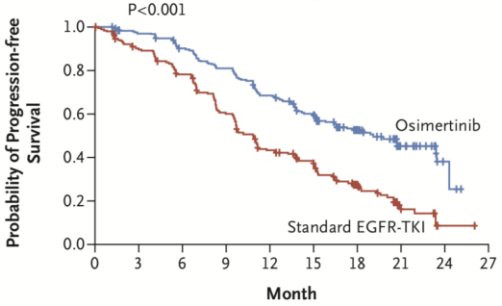
No. at Risk

Osimertinib	53	51	40	37	32	22	9	4	1	0
Standard EGFR-TKI	63	57	40	33	24	13	6	2	1	0

C Progression-free Survival in Patients without CNS Metastases

	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Osimertinib	226	19.1 (15.2–23.5)
Standard EGFR-TKI	214	10.9 (9.6–12.3)

Hazard ratio for disease progression or death, 0.46 (95% CI, 0.36–0.59)
P<0.001



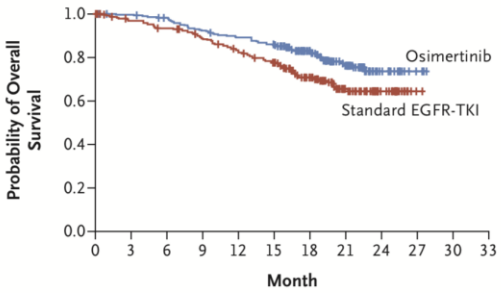
No. at Risk

Osimertinib	226	211	193	173	146	117	62	22	3	0
Standard EGFR-TKI	214	182	157	119	83	65	31	8	1	0

D Overall Survival

	No. of Patients	Median Overall Survival (95% CI)
		mo
Osimertinib	279	NC (NC–NC)
Standard EGFR-TKI	277	NC (NC–NC)

Hazard ratio for death, 0.63 (95% CI, 0.45–0.88)
P=0.007



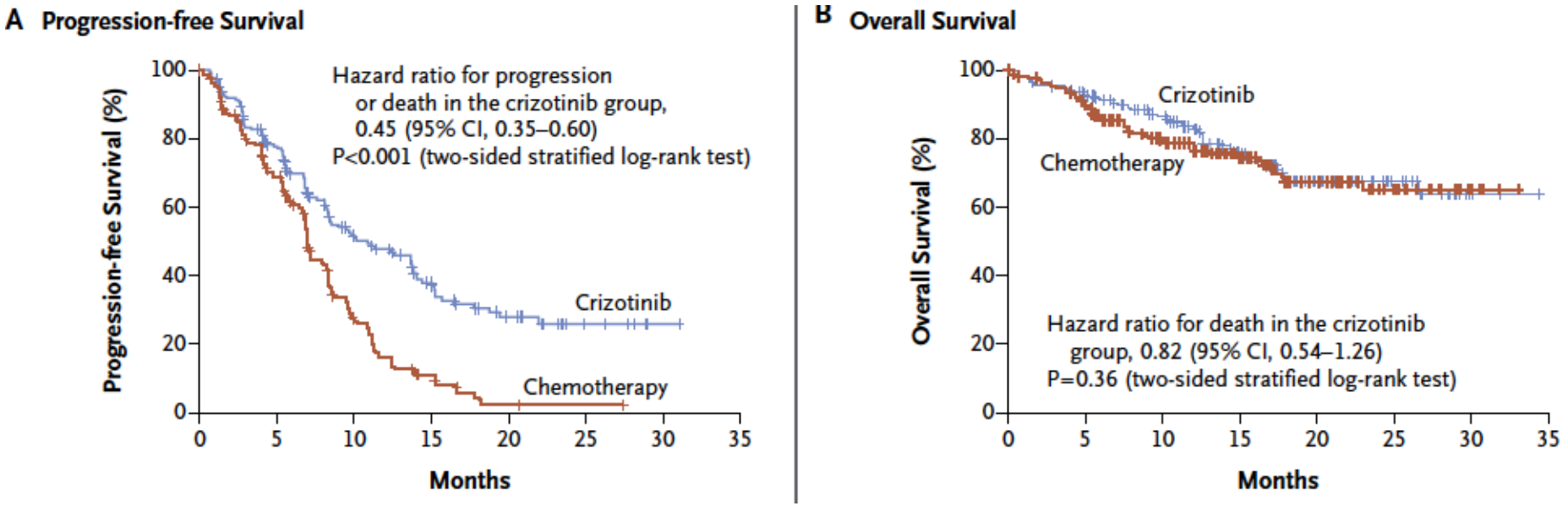
No. at Risk

Osimertinib	279	276	269	253	243	232	154	87	29	4	0	0
Standard EGFR-TKI	277	263	252	237	218	200	126	64	24	1	0	0

N Engl J Med, 2017

First-Line Crizotinib versus Chemotherapy in *ALK*-Positive Lung Cancer

Benjamin J. Solomon, M.B., B.S., Ph.D., Tony Mok, M.D., Dong-Wan Kim, M.D., Ph.D., Yi-Long Wu, M.D., Kazuhiko Nakagawa, M.D., Ph.D., Tarek Mekhail, M.D., Enriqueta Felip, M.D., Ph.D., Federico Cappuzzo, M.D., Jolanda Paolini, B.Sc., Tiziana Usari, B.Sc., Shrividya Iyer, Ph.D., Arlene Reisman, M.P.H., Keith D. Wilner, Ph.D., Jennifer Tursi, M.Sc., and Fiona Blackhall, M.D., Ph.D., for the PROFILE 1014 Investigators*

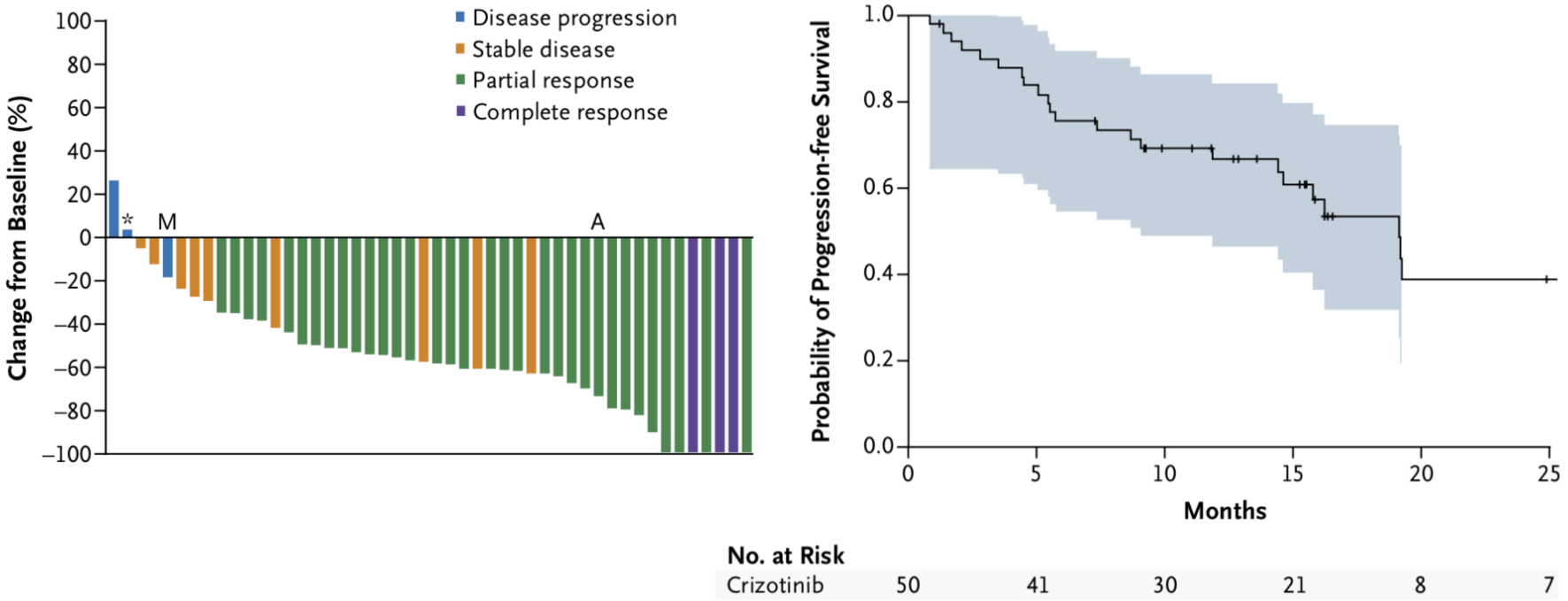


N Engl J Med, 2013

Crizotinib in *ROS1*-Rearranged Non–Small-Cell Lung Cancer

Alice T. Shaw, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Yung-Jue Bang, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Benjamin J. Solomon, M.B., B.S., Ph.D., Ravi Salgia, M.D., Ph.D., Gregory J. Riely, M.D., Ph.D., Marileila Varella-Garcia, Ph.D., Geoffrey I. Shapiro, M.D., Ph.D., Daniel B. Costa, M.D., Ph.D., Robert C. Doebele, M.D., Ph.D., Long Phi Le, M.D., Ph.D., Zongli Zheng, Ph.D., Weiwei Tan, Ph.D., Patricia Stephenson, Sc.D., S. Martin Shreeve, M.D., Ph.D., Lesley M. Tye, Ph.D., James G. Christensen, Ph.D., Keith D. Wilner, Ph.D., Jeffrey W. Clark, M.D., and A. John Iafrate, M.D., Ph.D.

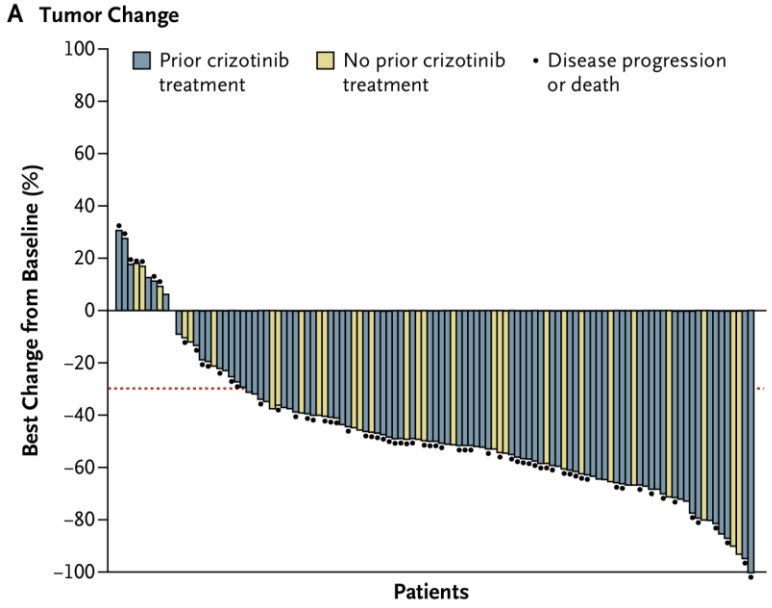
A Best Response

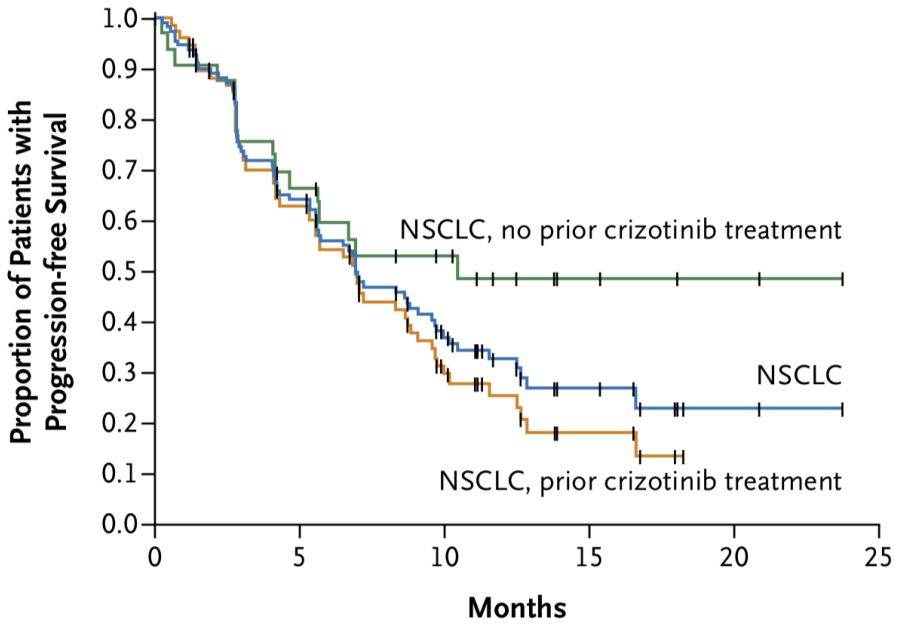


N Engl J Med, 2014

Ceritinib in *ALK*-Rearranged Non–Small-Cell Lung Cancer

Alice T. Shaw, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., Ranee Mehra, M.D., Daniel S.W. Tan, M.B., B.S., Enriqueta Felip, M.D., Ph.D., Laura Q.M. Chow, M.D., D. Ross Camidge, M.D., Ph.D., Johan Vansteenkiste, M.D., Ph.D., Sunil Sharma, M.D., Tommaso De Pas, M.D., Gregory J. Riely, M.D., Ph.D., Benjamin J. Solomon, M.B., B.S., Ph.D., Juergen Wolf, M.D., Ph.D., Michael Thomas, M.D., Martin Schuler, M.D., Geoffrey Liu, M.D., Armando Santoro, M.D., Yvonne Y. Lau, Ph.D., Meredith Goldwasser, Sc.D., Anthony L. Boral, M.D., Ph.D., and Jeffrey A. Engelman, M.D., Ph.D.





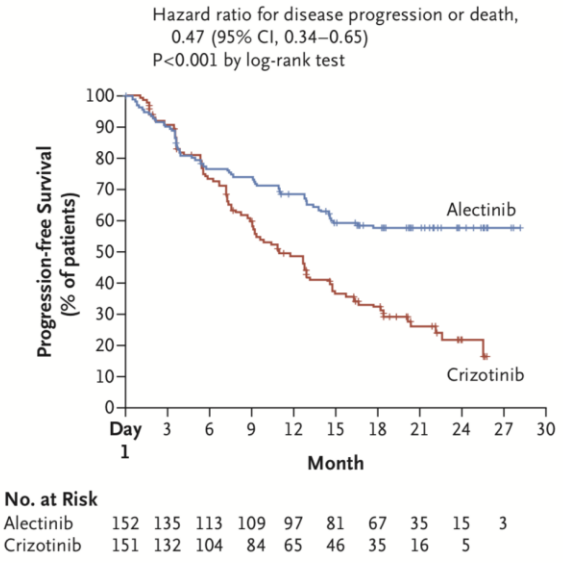
No. at Risk

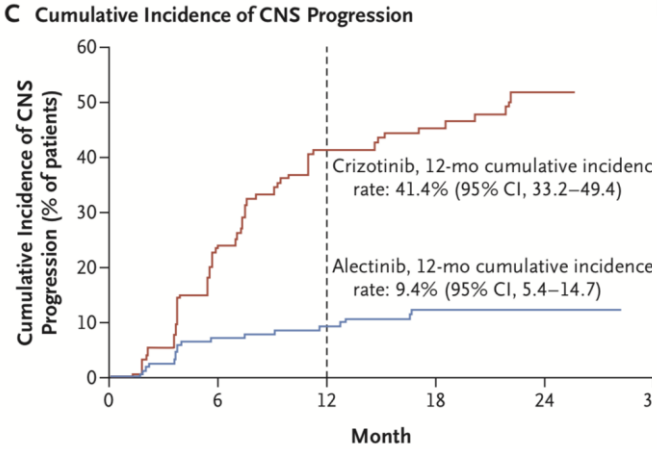
NSCLC, no prior crizotinib treatment	34	21	13	4	2	0
NSCLC	114	66	30	9	2	0
NSCLC, prior crizotinib treatment	80	45	17	5	0	

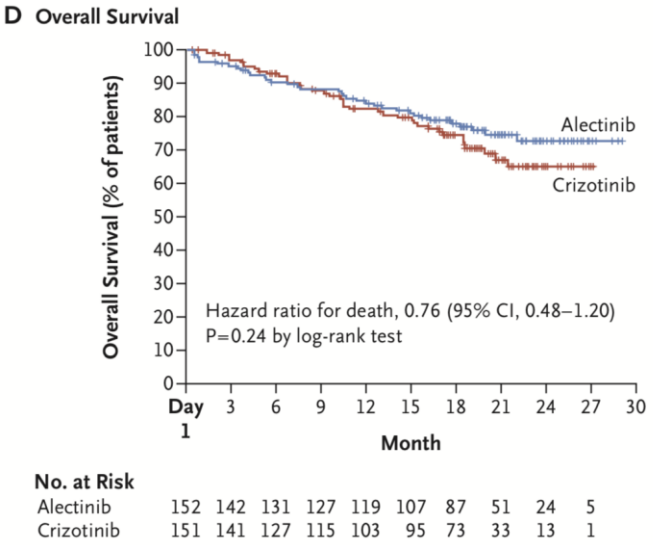
N Engl J Med, 2014

Alectinib versus Crizotinib in Untreated *ALK*-Positive Non–Small-Cell Lung Cancer

Solange Peters, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Alice T. Shaw, M.D., Ph.D., Shirish Gadgeel, M.D., Jin S. Ahn, M.D., Dong-Wan Kim, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Maurice Pérol, M.D., Rafal Dziadziuszko, M.D., Rafael Rosell, M.D., Ph.D., Ali Zeaiter, M.D., Emmanuel Mitry, M.D., Ph.D., Sophie Golding, M.Sc., Bogdana Balas, M.D., Johannes Noe, Ph.D., Peter N. Morcos, Pharm.D., and Tony Mok, M.D., for the ALEX Trial Investigators*





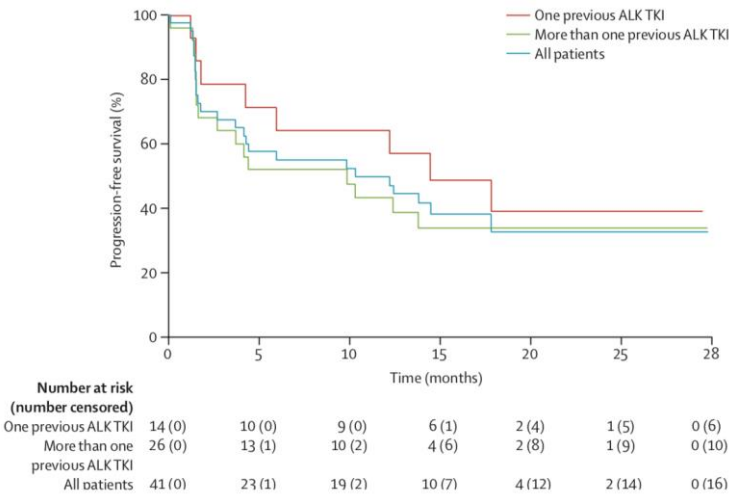


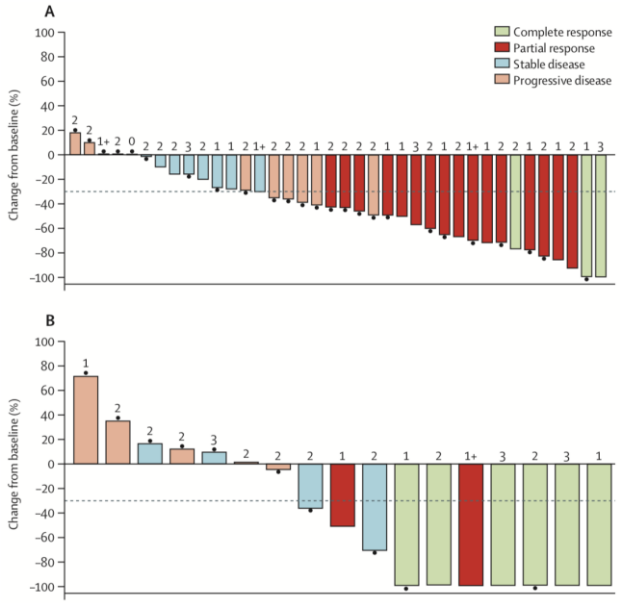
N Engl J Med, 2017

Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial

AliceTShaw,EnriquetaFelip,ToddMBauer,BenjaminBesse,AlejandroNavarro,SophiePostel-Vinay,JustinFGainor,MelissaJohnson, Jorg Dietrich, Leonard P James, Jill S Clancy, Joseph Chen, Jean-François Martini, Antonello Abbattista, Benjamin J Solomon

	Patients (n=54)
Age, years	
Mean (SD)	52 (13)
Median (IQR)	50 (43–58)
Sex	
Male	22 (41%)
Female	32 (59%)
Race*	
White	42 (78%)
Asian	7 (13%)
Other	5 (9%)
Histology	
Adenocarcinoma	51 (94%)
Other	3 (6%)
ECOG performance status†	
0	20 (38%)
1	31 (58%)
>1	2 (4%)
Brain metastases	
Present	39 (72%)
Absent	15 (28%)
ALK and ROS1 status	
ALK-positive	41 (76%)
ROS1-positive	12 (22%)
Unconfirmed‡	1 (2%)
Previous ALK or ROS1 TKI	
None	6 (11%)
One	20 (37%)
Two or more	28 (52%)

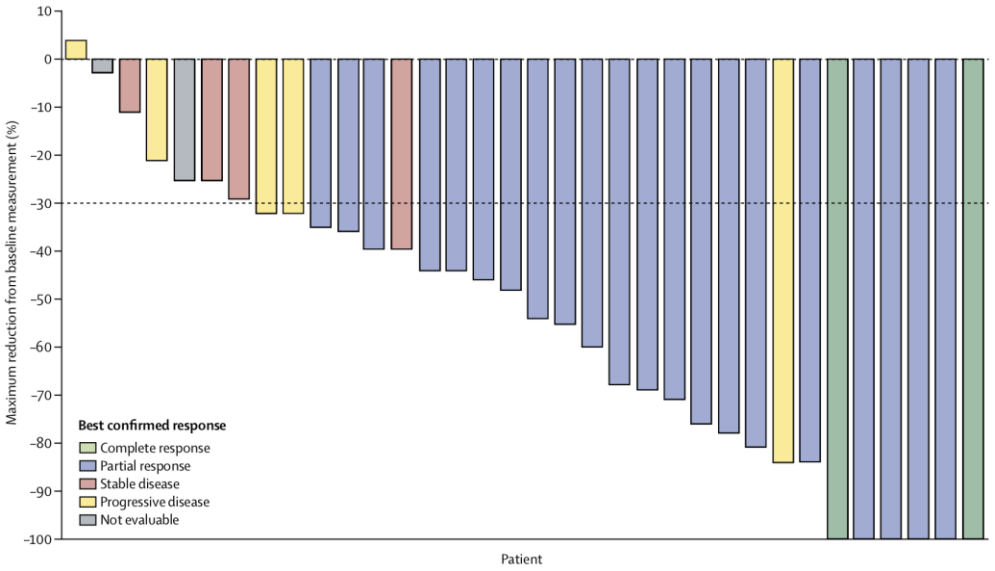


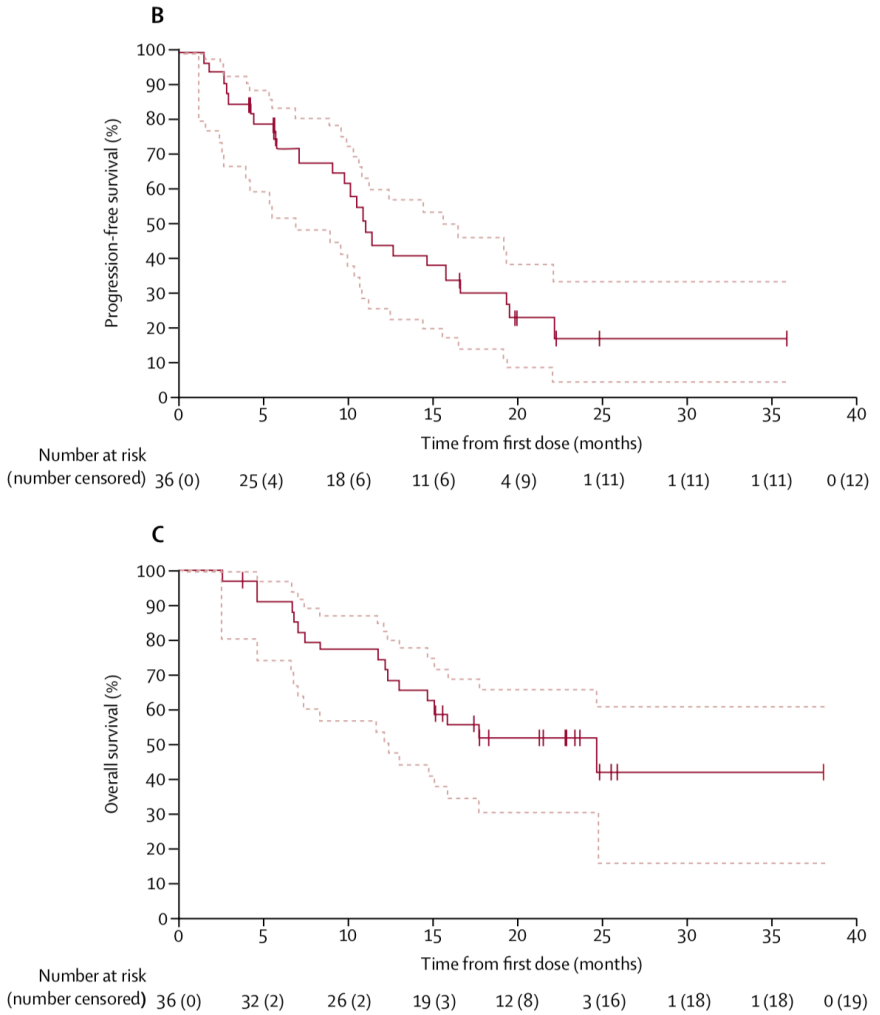


Lancet Oncol, 2017

Dabrafenib plus trametinib in patients with previously untreated *BRAF*^{V600E}-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial

David Planchard, Egbert F Smit, Harry J M Groen, Julien Mazieres, Benjamin Besse, Åslaug Helland, Vanessa Giannone, Anthony M D'Amelio Jr, Pingkuan Zhang, Bijoyesh Mookerjee, Bruce E Johnson





Lancet Oncol, 2017

Oppsummering målrettet behandling

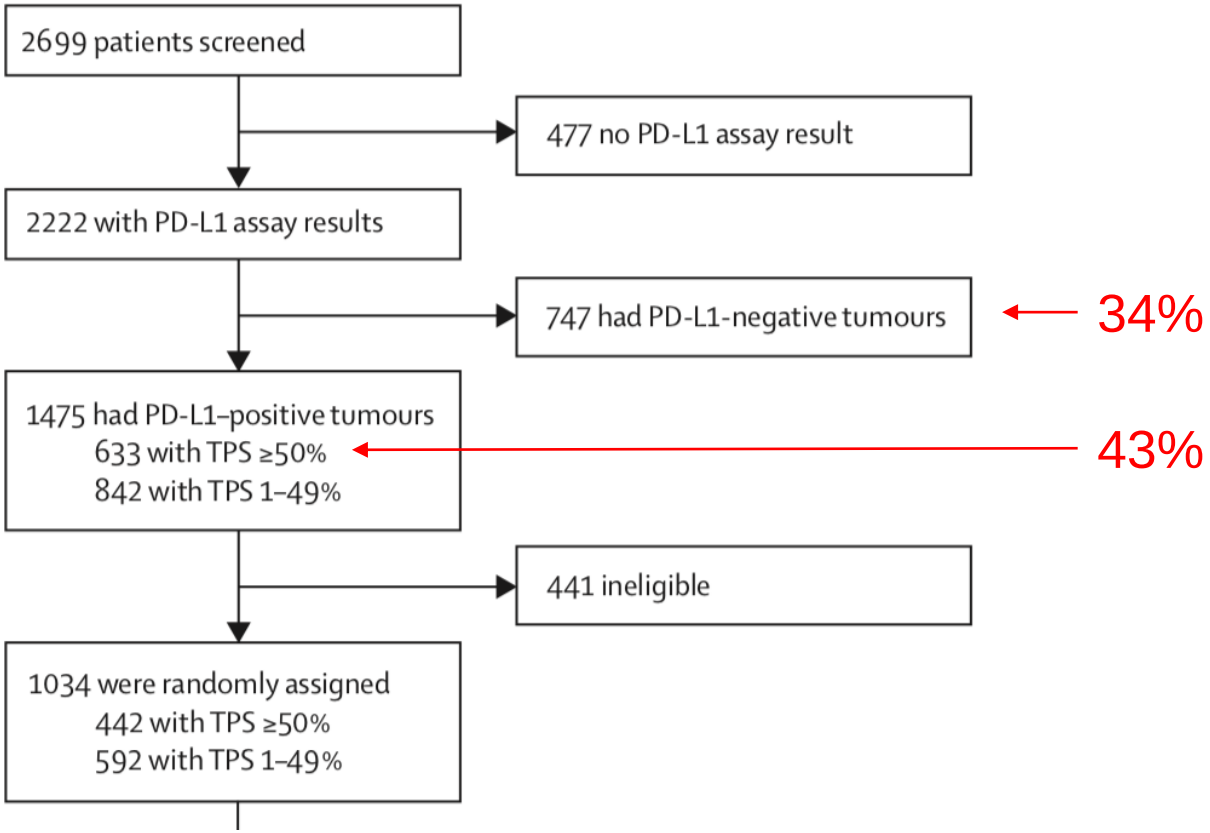
- Gefitinib/erlotinib/afatinib gis som første-linjes behandling ved avansert NSCLC og påviste sensitiviserende EGFR-mutasjon
- Osimertinib er ikke akseptert til bruk som 2. linjes behandling av Beslutningsforum

- Crizotinib gis som første-linjes behandling ved avansert NSCLC og påviste sensitiviserende EGFR-mutasjon
- Crizotinib ved ROS1 translokasjon er til vurdering
- Ceritinib og alectinib er til vurdering hos Beslutningsforum

- Dabrafenib og trametinib er til vurdering hos Beslutningsforum

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

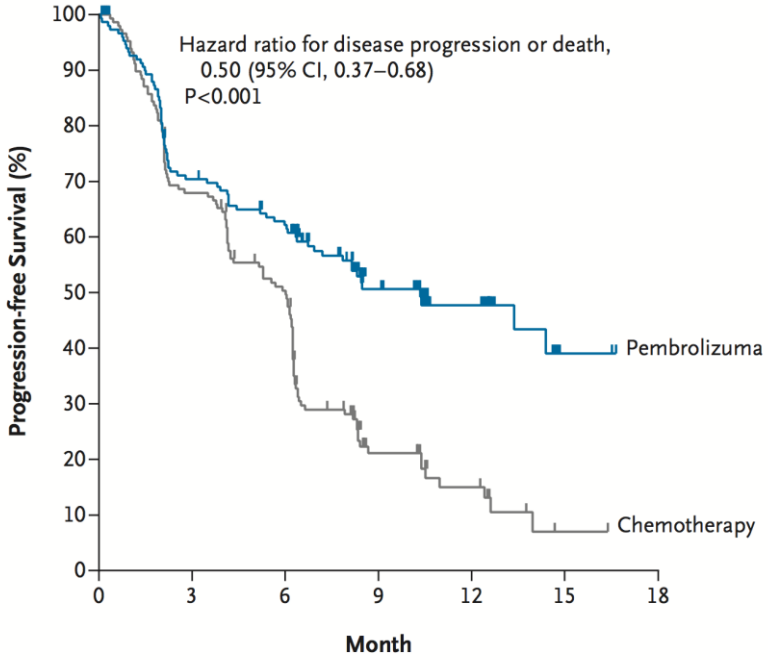
Roy S Herbst, Paul Baas, Dong-Wan Kim, Enriqueta Felip, José L Pérez-Gracia, Ji-Youn Han, Julian Molina, Joo-Hang Kim, Catherine Dubos Arvis, Myung-Ju Ahn, Margarita Majem, Mary J Fidler, Gilberto de Castro Jr, Marcelo Garrido, Gregory M Lubiniecki, Yue Shentu, Ellie Im, Marisa Dolled-Filhart, Edward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



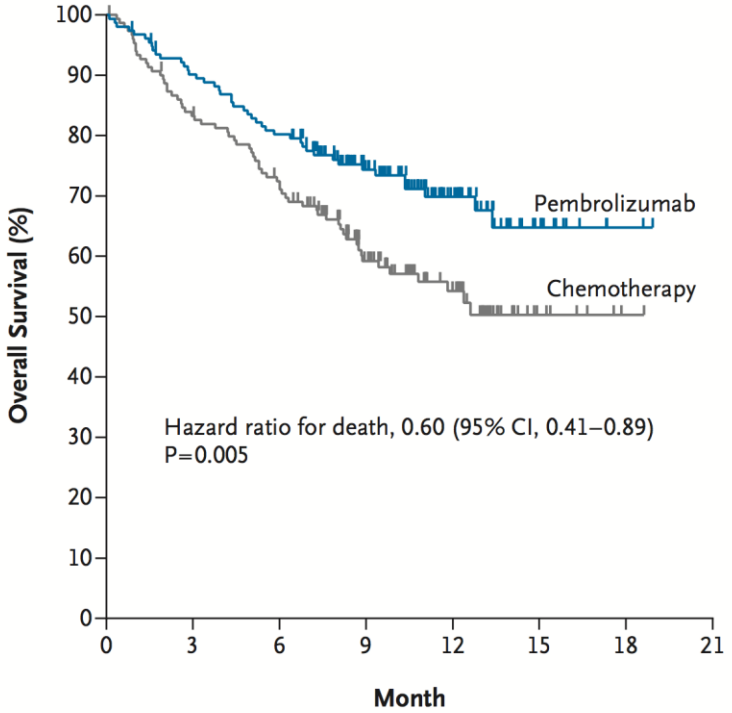
Lancet, 2016

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*



No. at Risk							
Pembrolizumab	154	104	89	44	22	3	1
Chemotherapy	151	99	70	18	9	1	0

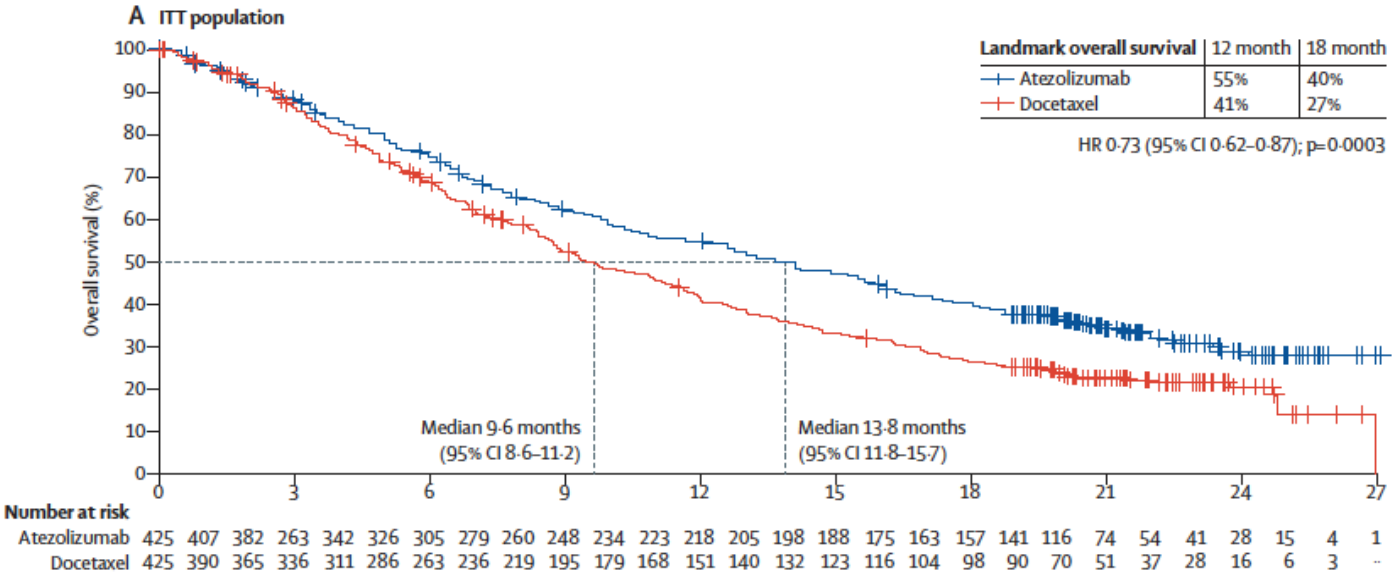


No. at Risk								
Pembrolizumab	154	136	121	82	39	11	2	0
Chemotherapy	151	123	106	64	34	7	1	0

NEJM, 2016

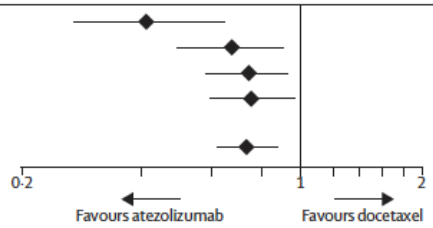
Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial

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, Oswaldo 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*



F

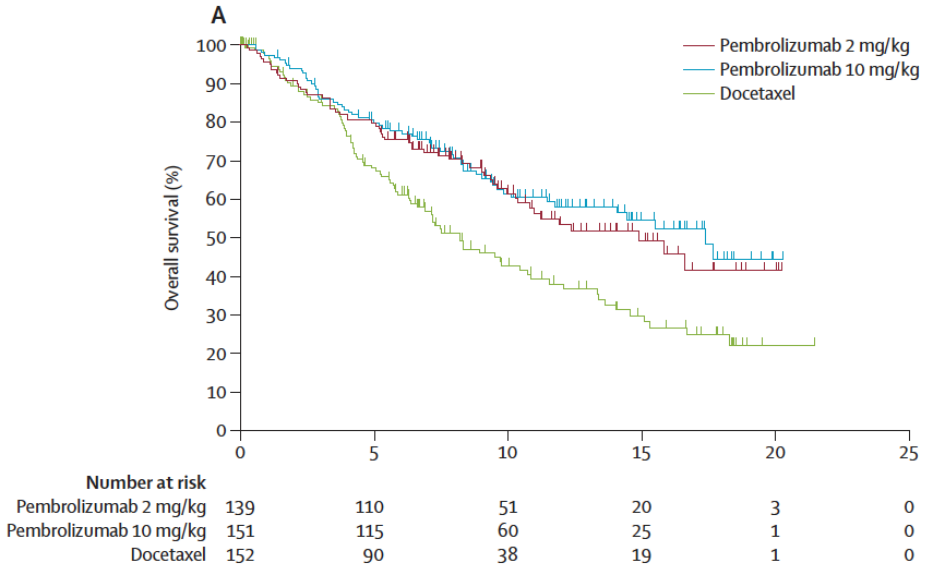
	n (%)	Median overall survival (months)		HR (95% CI)
		Atezolizumab	Docetaxel	
TC3 or IC3	137 (16)	20·5	8·9	0·41 (0·27–0·64)
TC2/3 or IC2/3	265 (31)	16·3	10·8	0·67 (0·49–0·90)
TC1/2/3 or IC1/2/3	463 (54)	15·7	10·3	0·74 (0·58–0·93)
TC0 and IC0	379 (45)	12·6	8·9	0·75 (0·59–0·96)
ITT	850 (100)	13·8	9·6	0·73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



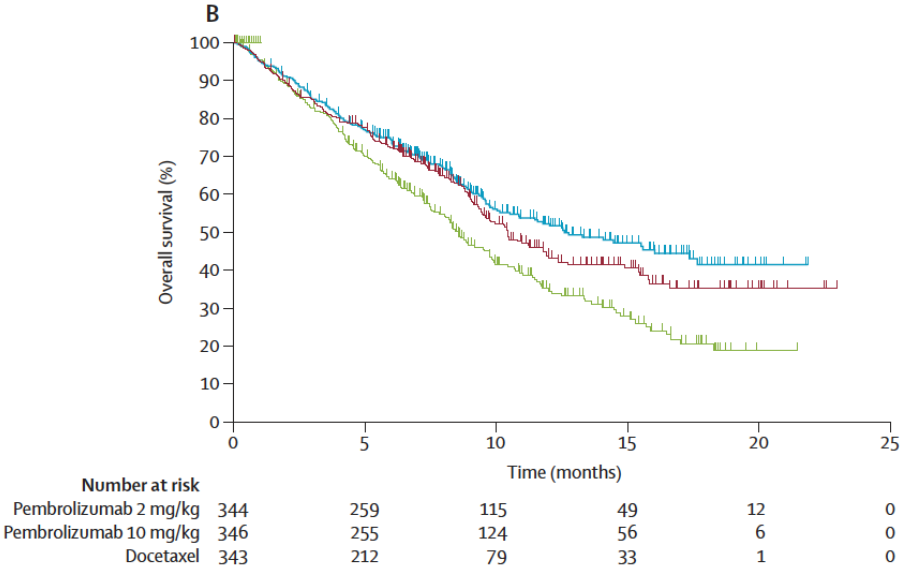
NEJM, 2017

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



50-100% PD-L1 positive

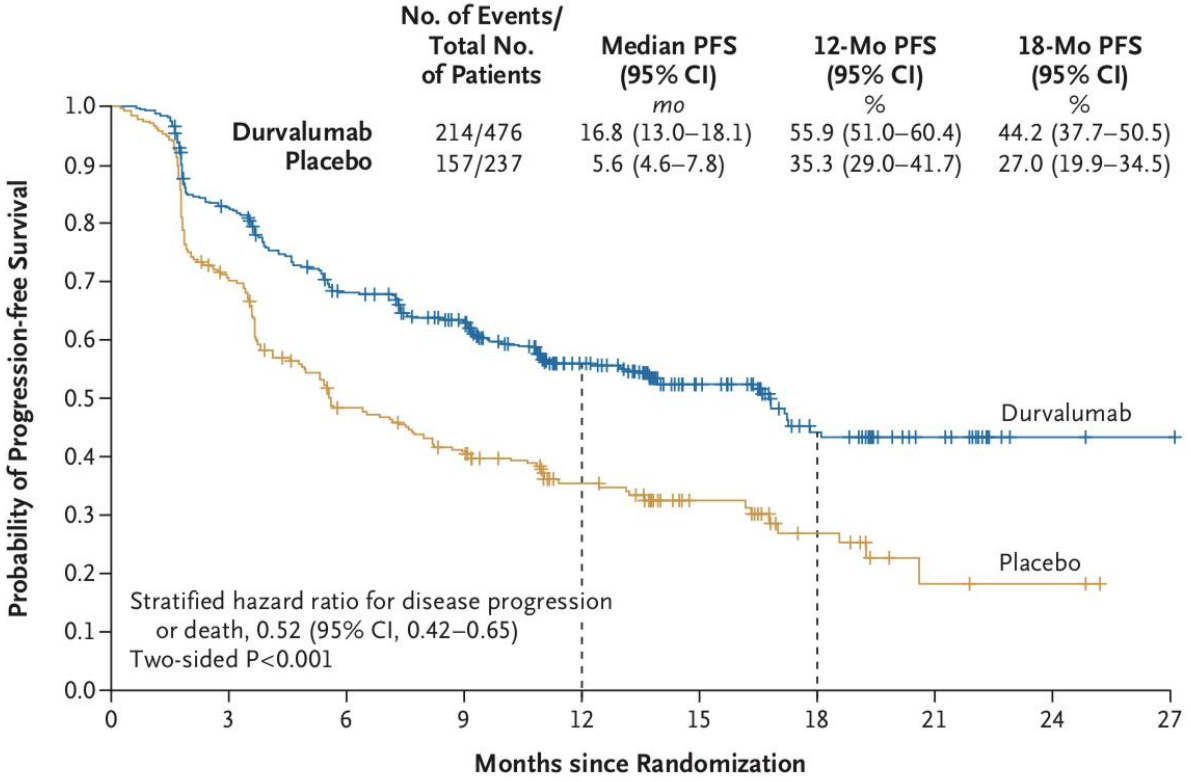


Alle pasienter

NEJM, 2015

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*



NEJM, 2017

AACR American Association for Cancer Research
ANNUAL MEETING 2017 WASHINGTON, DC

Five-Year Follow-up From the CA209-003 Study of Nivolumab in Previously Treated Advanced Non-Small Cell Lung Cancer: Clinical Characteristics of Long-term Survivors

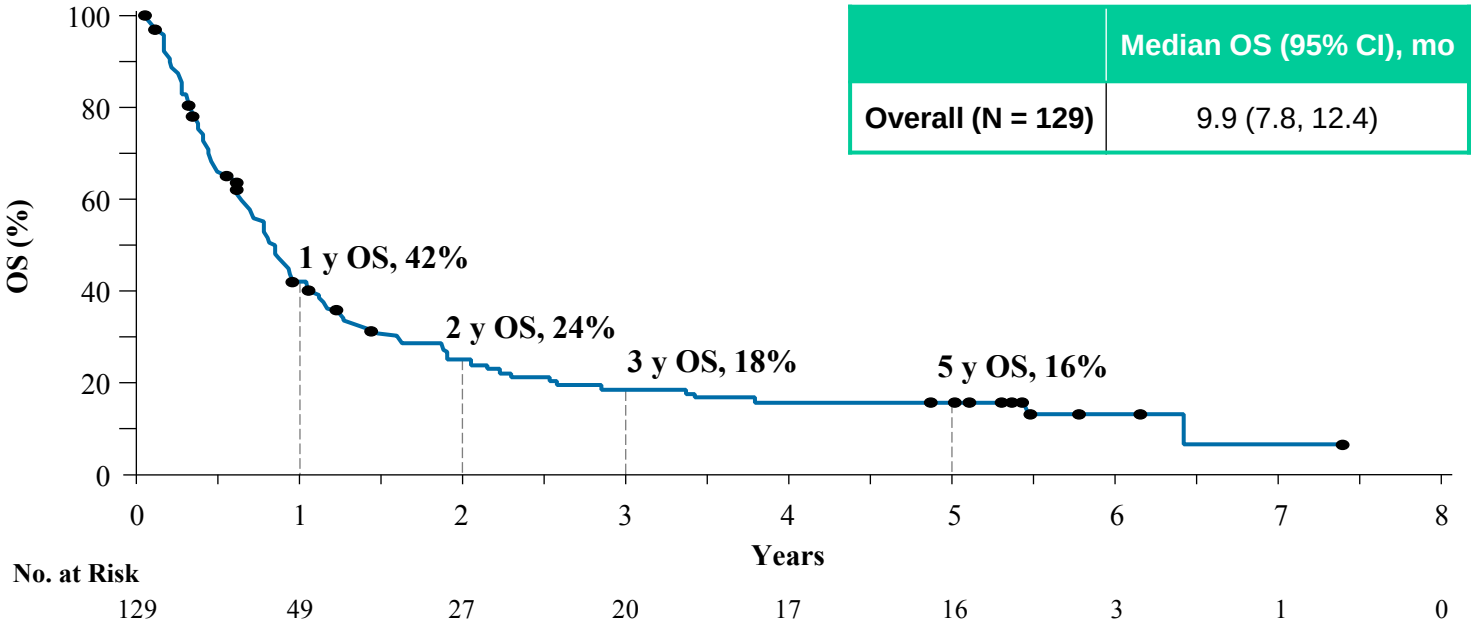
Julie Brahmer,[1] Leora Horn,[2] David Jackman,[3] David Spigel,[4] Scott Antonia,[5] Matthew Hellmann,[6] John Powderly,[7] Rebecca Heist,[8] Lecia Sequist,[8] David C. Smith,[9] Philip Leming,[10] William J. Geese,[11] Dennis Yoon,[11] Ang Li,[11] Scott Gettinger[12]

[1]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [2]Vanderbilt University Medical Center, Nashville, TN, USA; [3]Dana-Farber Cancer Institute, Boston, MA, USA; [4]Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN, USA; [5]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; [6]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [7]Carolina BioOncology Institute, Huntersville, NC, USA: [8]Massachusetts General Hospital, Boston, MA, USA; [9]University of Michigan, Ann Arbor, MI, USA; [10]The Christ Hospital Cancer Center, Cincinnati, OH, USA; [11]Bristol-Myers Squibb, Princeton, NJ, USA; [12]Yale Cancer Center, New Haven, CT, USA

IONO17NP01745-01

5-Year Estimates of OS[a]

CA209-003 5-Year Update: Phase 1 Nivolumab in Advanced NSCLC

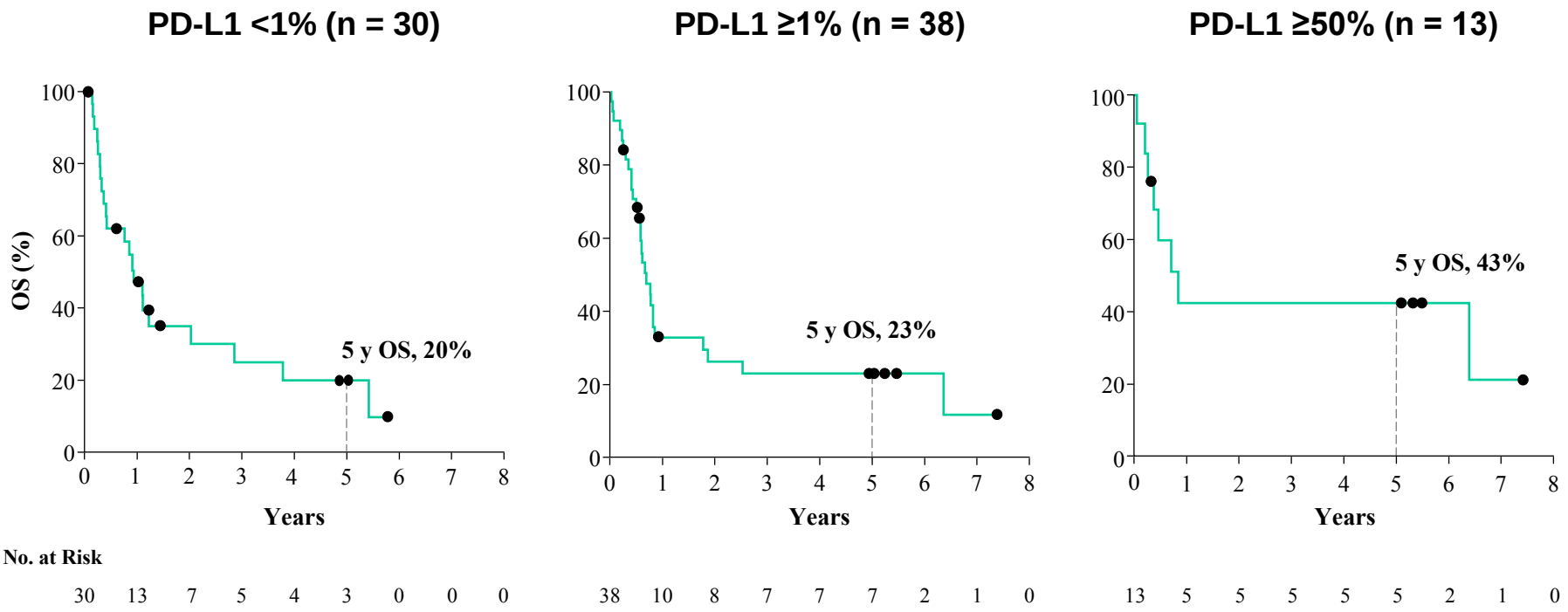


	Median OS (95% CI), mo
Overall (N = 129)	9.9 (7.8, 12.4)

[a]There were 3 deaths between 3 and 5 years, all due to disease progression; 1 surviving patient was censored for OS prior to 5 years (OS: 58.2+ months)

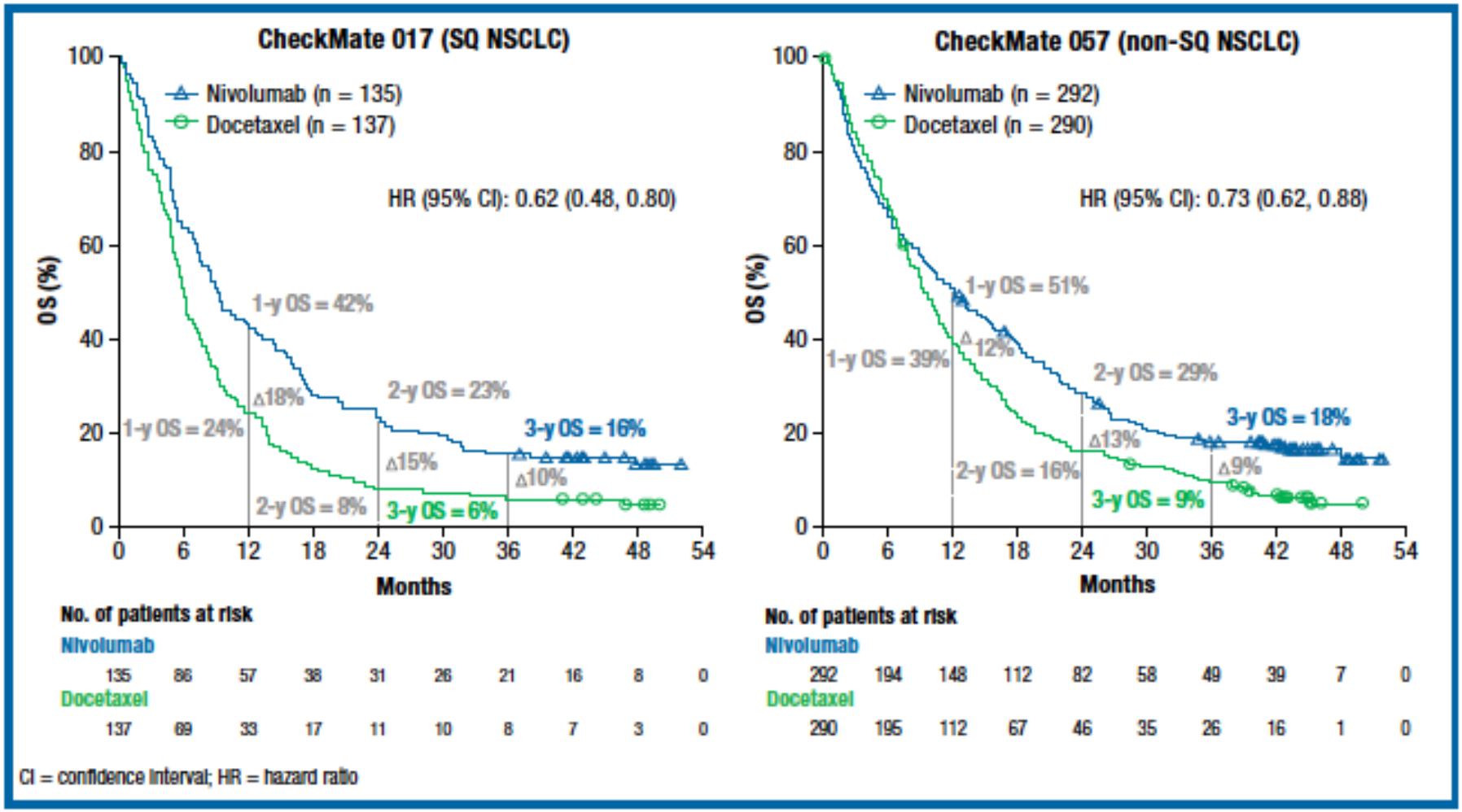
5-Year Estimates of OS by PD-L1 Status[a]

CA209-003 5-Year Update: Phase 1 Nivolumab in Advanced NSCLC



[a]PD-L1 status was not evaluable in 61 (47%) of 129 patients; the estimated 5-y OS rate in patients with unknown PD-L1 status was 10%

Figure 2. OS (3 years' minimum follow-up)



CI = confidence interval; HR = hazard ratio

CheckMate 153: Randomized Results of Continuous vs 1-Year Fixed-Duration Nivolumab in Patients With Advanced Non-Small Cell Lung Cancer

David R. Spigel,[1]* Mihael McCleod,[2]* Maen A. Hussein,[3]* David M. Waterhouse,[4]* Lawrence Einhorn,[5] Leora Horn,[6] Ben Creelan,[7] Sunil Babu,[8]* Natasha B. Leighl,[9] Felix Couture,[10] Jason Chandler,[11]* Glenwood Goss,[12] George Keogh,[13]* Edward B. Garon,[14]* Kenneth B. Blankstein,[15]* Davey B. Daniel,[16]* Mohamed Mohamed,[17]* Ang Li,[18] Nivedita Aanur,[18] Robert Jotte[19]*

[1]Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN, USA; [2]Florida Cancer Specialists, Cape Coral, FL, USA; [3]Florida Cancer Specialists, Leesburg, FL, USA; [4]OHC (Oncology Hematology Care, Inc), Cincinnati, OH, USA; [5]Indiana University, Indianapolis, IN, USA; [6]Vanderbilt University Medical Center, Nashville, TN, USA; [7]Moffitt Cancer Center, Tampa, FL, USA; [8]Fort Wayne Medical Oncology and Hematology, Fort Wayne, IN, USA; [9]The Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; [10]CISSS Chaudiéere-Appalaches, Levis, QC, Canada; [11]West Cancer Center, Memphis, TN, USA; [12]The Ottawa Hospital, University of Ottawa, Ottawa, ON, Canada; [13]Charleston Hematology Oncology Associates, Charleston, SC, USA; [14]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [15]Hunterdon Healthcare, Flemington, NJ, USA; [16]Tennessee Oncology, Chattanooga, TN, USA; [17]Cone Health Cancer Center at Wesley Long, Greensboro, NC, USA; [18]Bristol-Myers Squibb, Princeton, NJ, USA; [19]The US Oncology Network/Rocky Mountain Cancer Centers, Denver, CO, USA

*Immuno-Oncology Integrated Community Oncology Network (IO ICON) member

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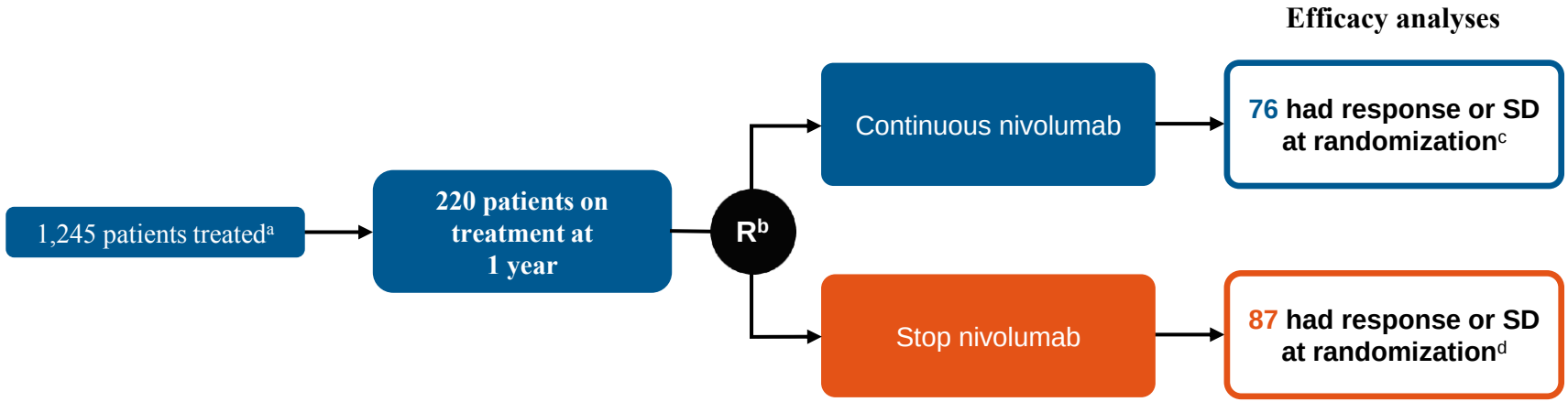
CheckMate 153: Continuous vs 1-Year Nivolumab

Patient Flow and Analysis Populations



[a]Main US cohort; 1,025 patients discontinued prior to 1 year due to progression, death, study withdrawal, toxicity, or other reasons;
[b]All 220 patients continuing on treatment at 1 year were randomized regardless of response status; 57 of these 220 patients had PD and were randomized as allowed per protocol; safety analyses were based on all 220 patients, 107 in the continuous arm and 113 in the stop arm; [c]8 patients discontinued treatment due to patient request or withdrawal of consent; [d]12 patients discontinued treatment due to patient request or withdrawal of consent

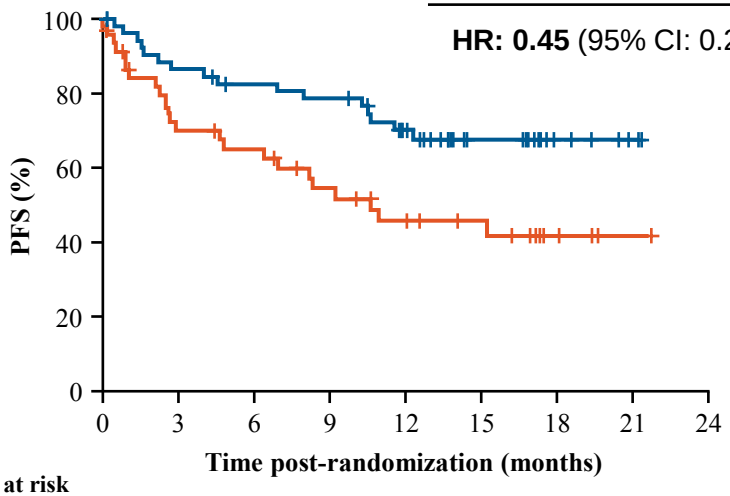
CheckMate 153: Continuous vs 1-Year Nivolumab

PFS From Randomization by Response Status[a]

CR/PR

	Median, months (95% CI)
Continuous tx	NR (NR)
1-year tx[b,c]	10.6 (4.8, NA)

HR: 0.45 (95% CI: 0.24, 0.85)

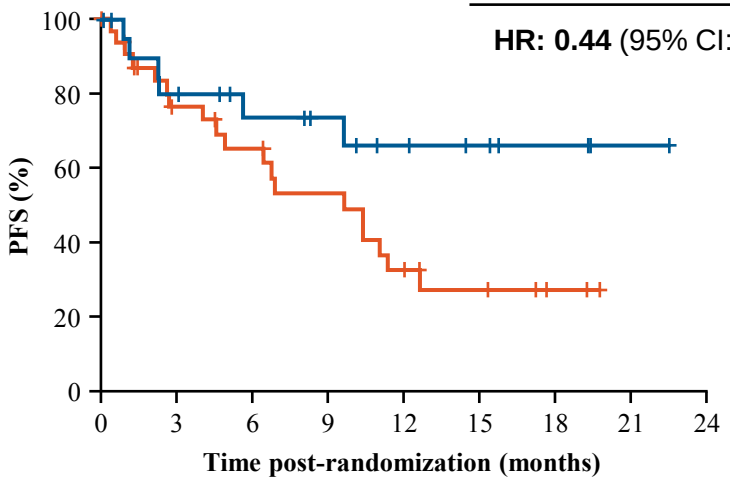


No. at risk									
Continuous tx	53	45	41	39	28	17	7	2	0
1-year tx	49	29	26	20	14	11	3	1	0

SD

	Median, months (95% CI)
Continuous tx	NR (5.6, NA)
1-year tx[b]	9.6 (4.5, 12.6)

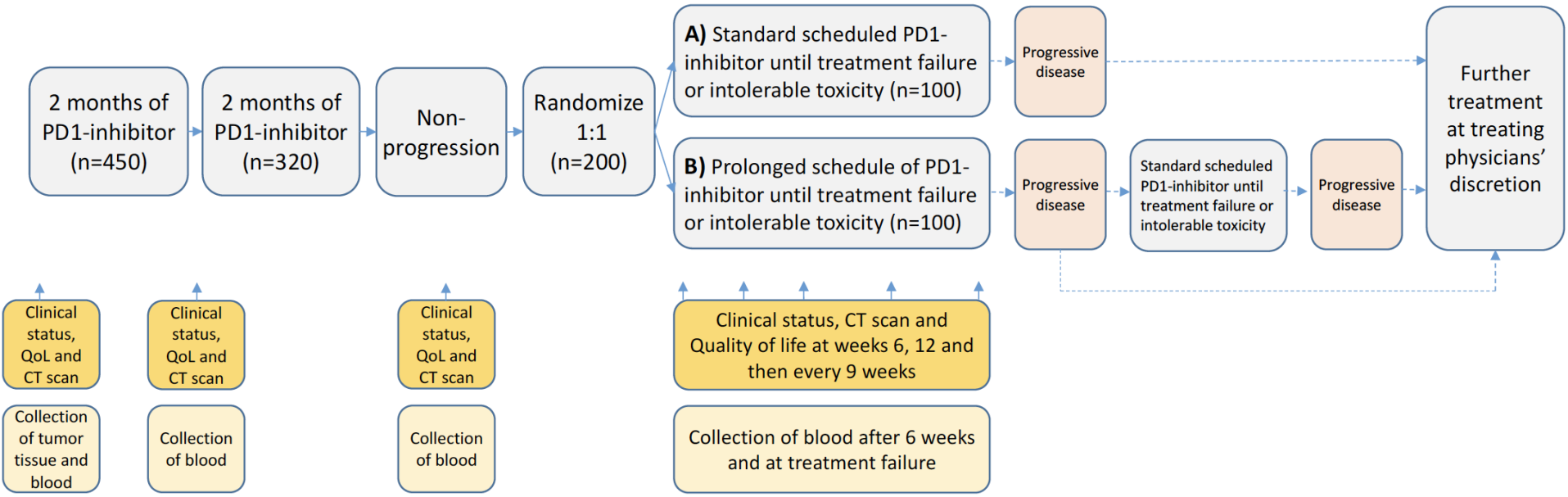
HR: 0.44 (95% CI: 0.17, 1.09)



Continuous tx	23	15	12	10	7	5	3	1	0
1-year tx	38	21	17	13	7	5	2	0	0

[a]Best overall response prior to randomization; minimum/median follow-up time post-randomization, 10.0/14.9 months; [b]With optional retreatment allowed at PD; [c]Two patients who stopped treatment had CR prior to randomization; both patients lost CR (6 and 13 months after stopping treatment) with progression due to new lesions; NA = not available

SALSA



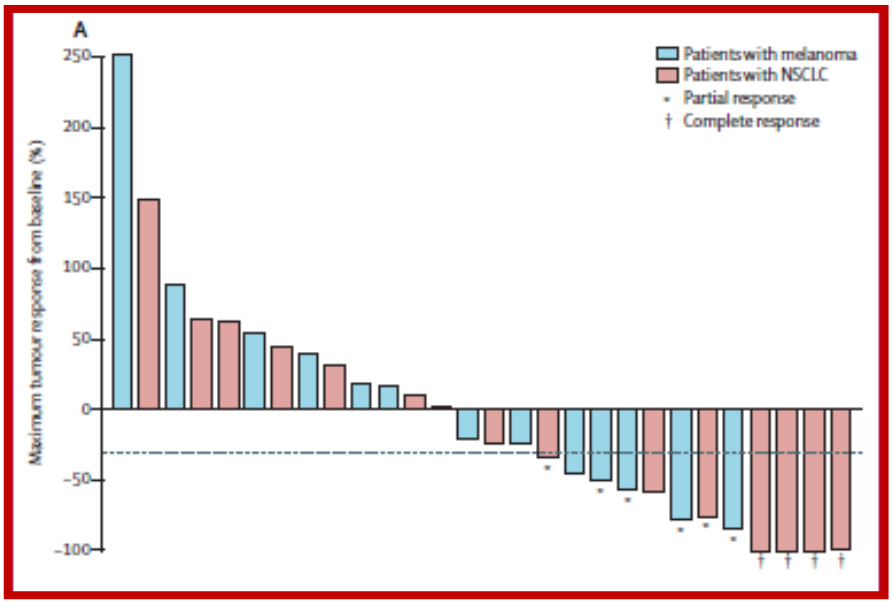
Immunotherapy and brain metastases – phase II study of pembrolizumab

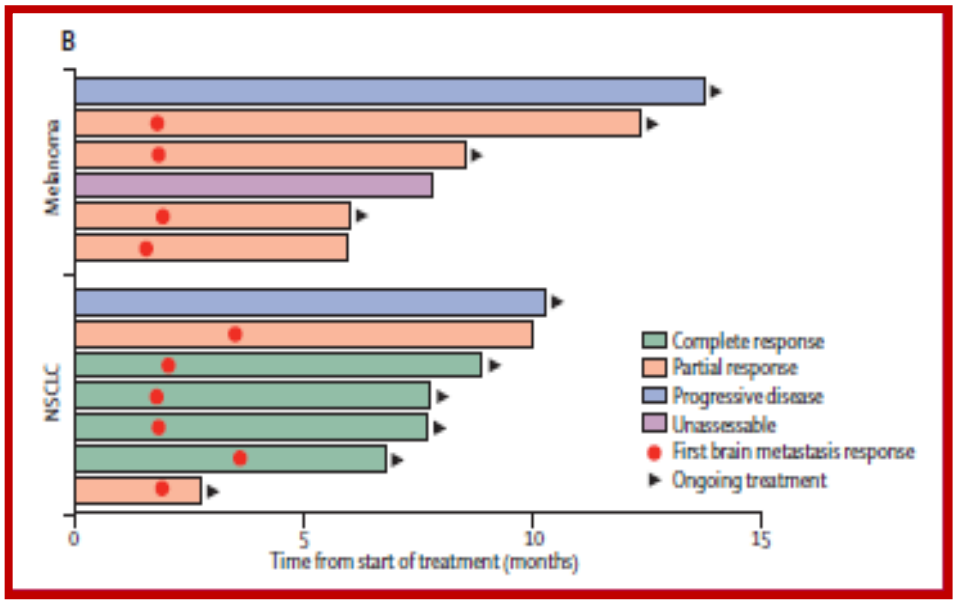
Key Eligibility:
- Advanced NSCLC or melanoma
- At least 1 untreated or progressive brain metastasis 5-20mm
- No neurologic symptoms or steroid requirement
- PS 0-1
- PD-L1 expression after the most recent systemic therapy

→ Pembrolizumab 10mg/kg q2 weeks

→ Brain metastasis PD → Consider radiation or surgery to progressing lesions

→ Brain metastasis CR, PR, or SD → Continue pembrolizumab if systemic control achieved

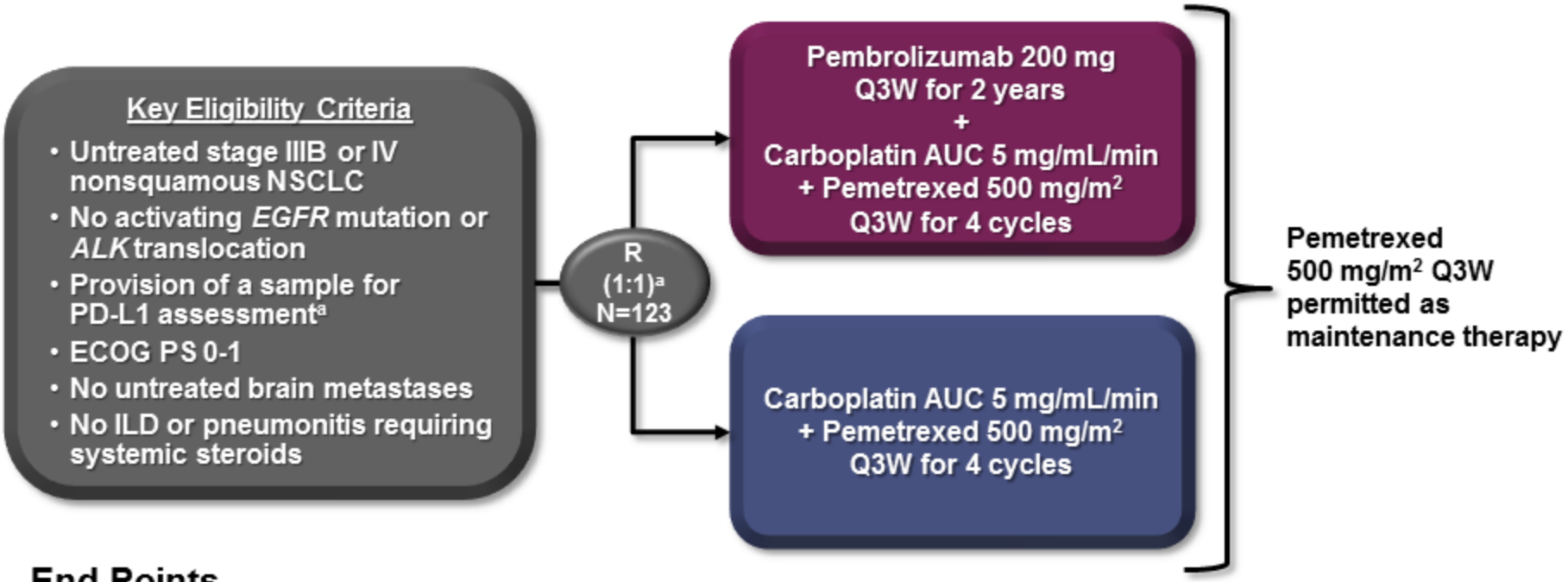




Goldberg SB, et al. *Lancet Oncol*. 2016;17:976-983.

CJ Langer. ESMO 2016.

KEYNOTE-021 Cohort G



End Points

Primary: ORR (RECIST v1.1 per blinded, independent central review)

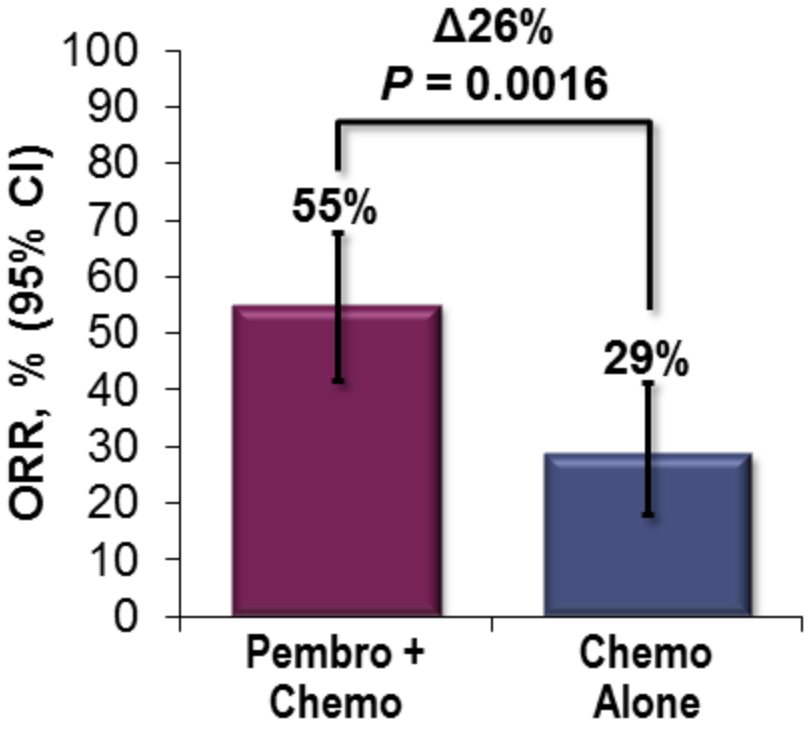
Key secondary: PFS

Other secondary: OS, safety, relationship between antitumor activity and PD-L1 TPS

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

CJ Langer. ESMO 2016.

Confirmed Objective Response Rate
(RECIST v1.1 by Blinded, Independent Central Review)



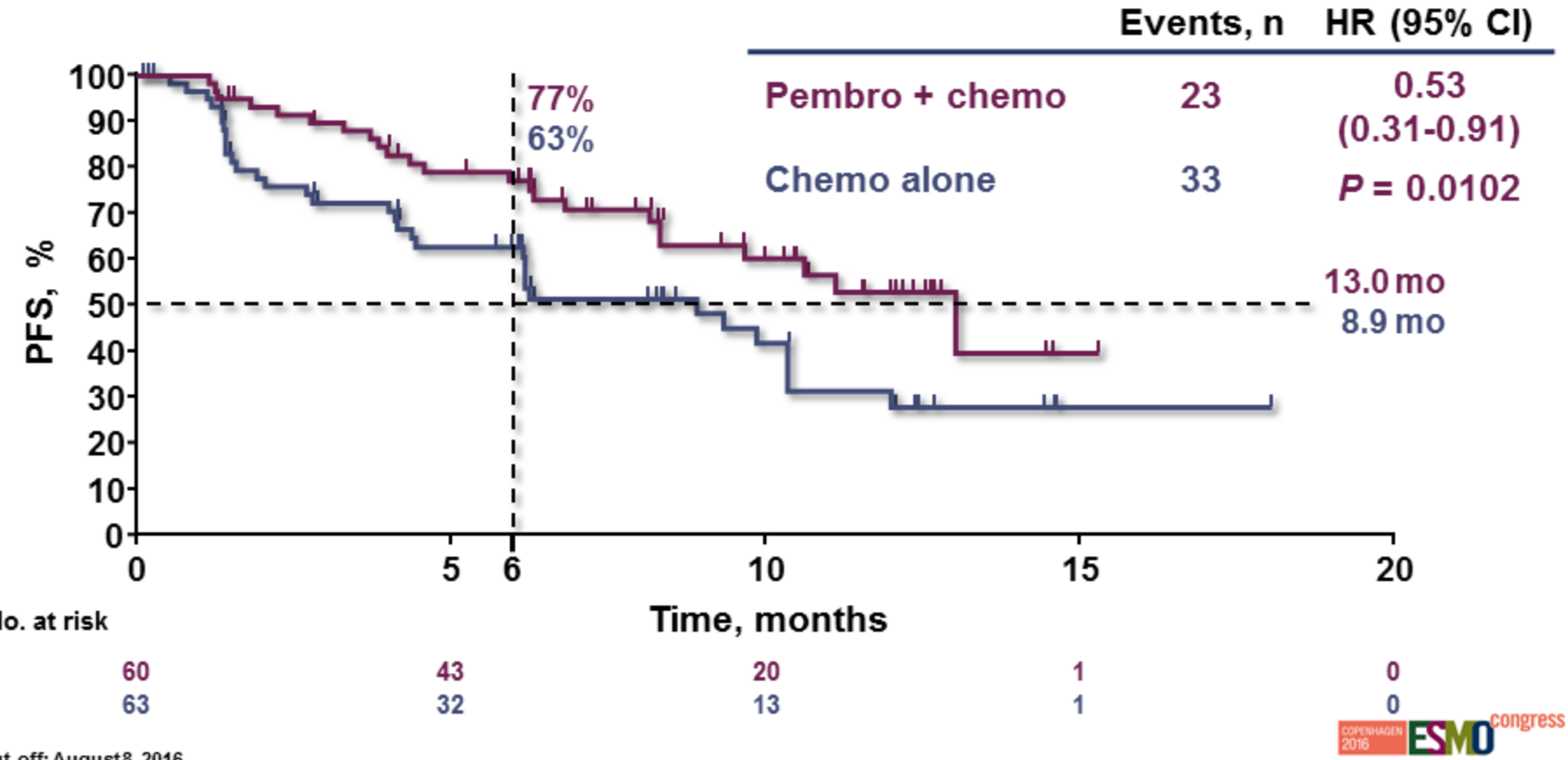
	Pembro + Chemo Responders n = 33	Chemo Alone Responders n = 18
TTR, mo median (range)	1.5 (1.2-12.3)	2.7 (1.1-4.7)
DOR, mo median (range)	NR (1.4+-13.0+)	NR (1.4+-15.2+)
Ongoing response,[a] n (%)	29 (88)	14 (78)

Data cut-off: August 8, 2016.

DOR = duration of response; TTR = time to response.
[a]Alive without subsequent disease progression.

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

CJ Langer. ESMO 2016.



Data cut-off: August 8, 2016.

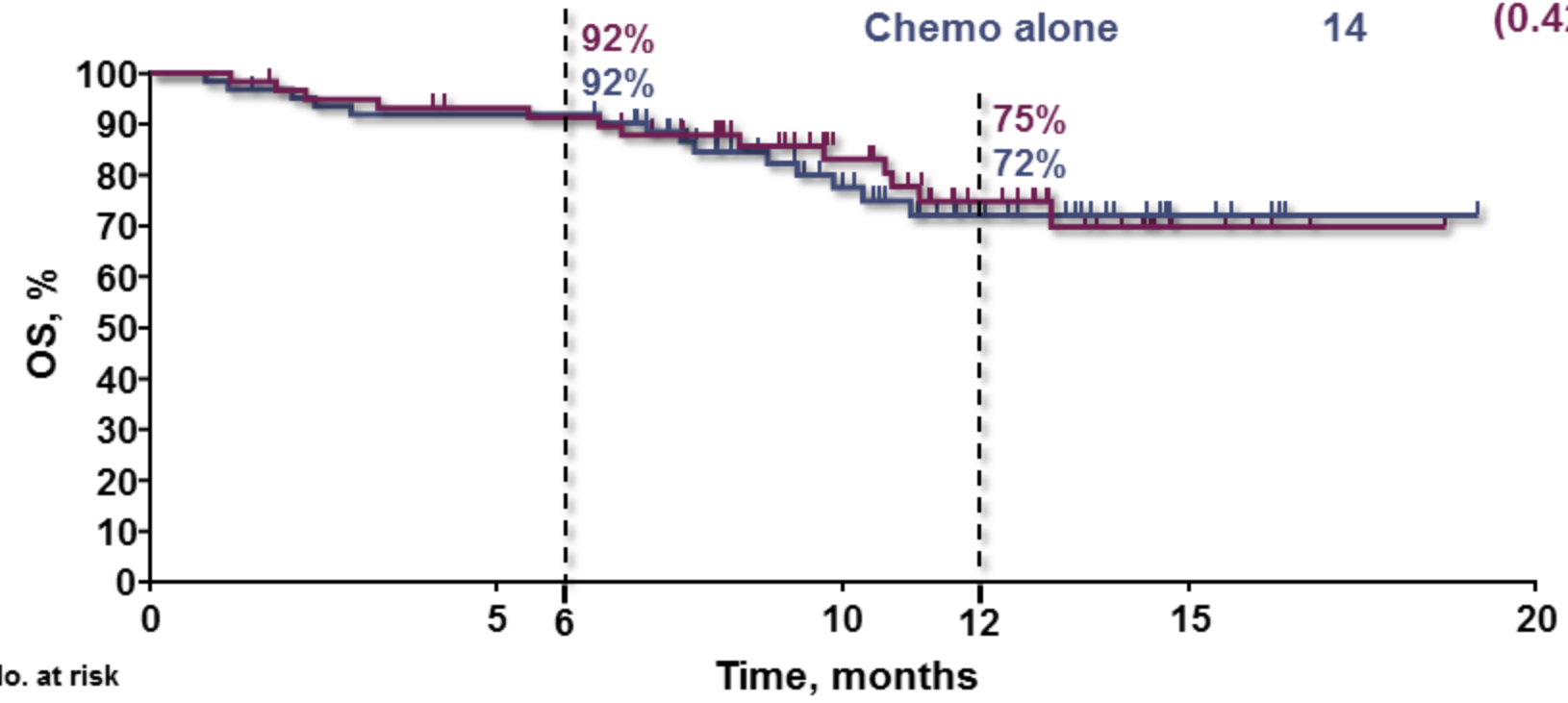
ST. OLAVS HOSPITAL
UNIVERSITETSSYKEHUSET I TRONDHEIM

NTNU
Kunnskap for en bedre verden

CJ Langer. ESMO 2016.

Overall Survival

	Events, n	HR (95% CI)
Pembro + chemo	13	0.90 (0.42-1.91)
Chemo alone	14	



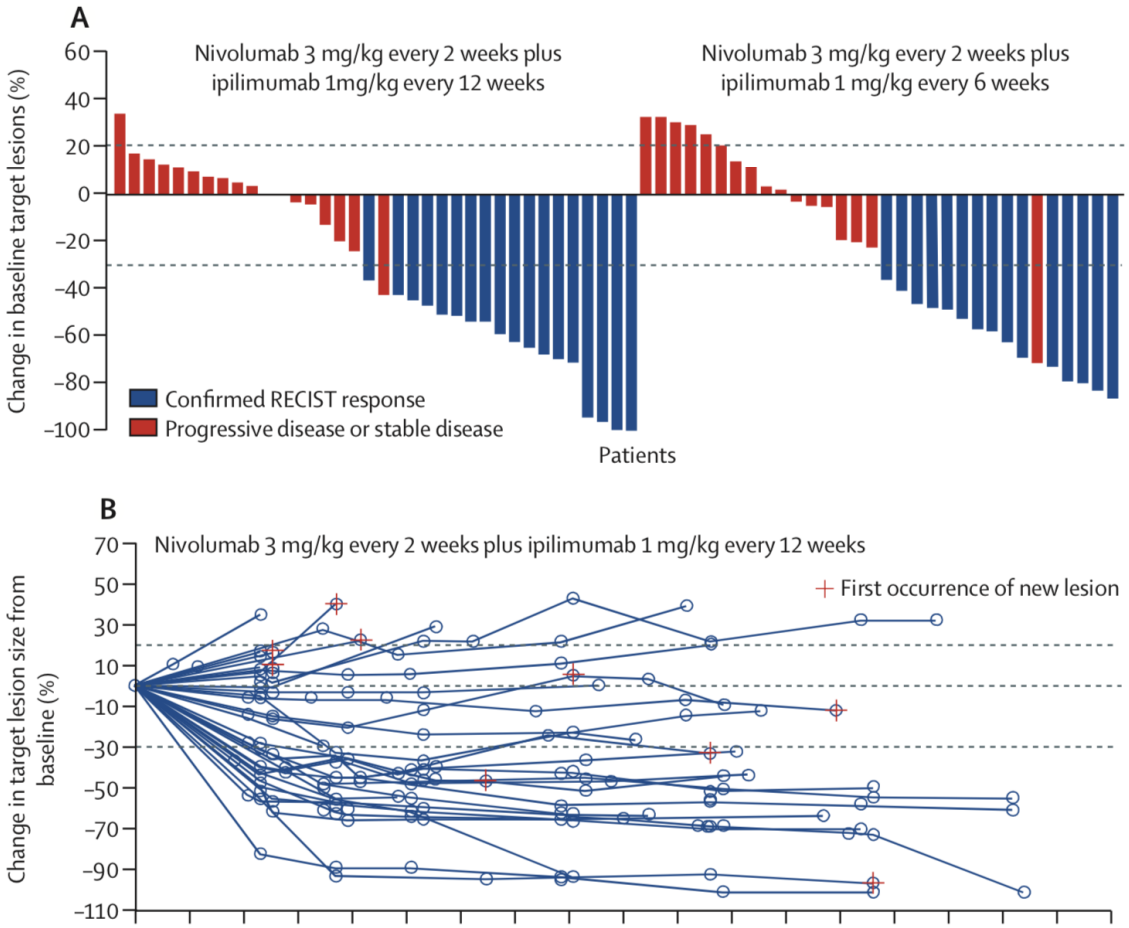
No. at risk

60	53	33	5	0
63	57	31	6	0

Data cut-off: August 8, 2016.

Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study

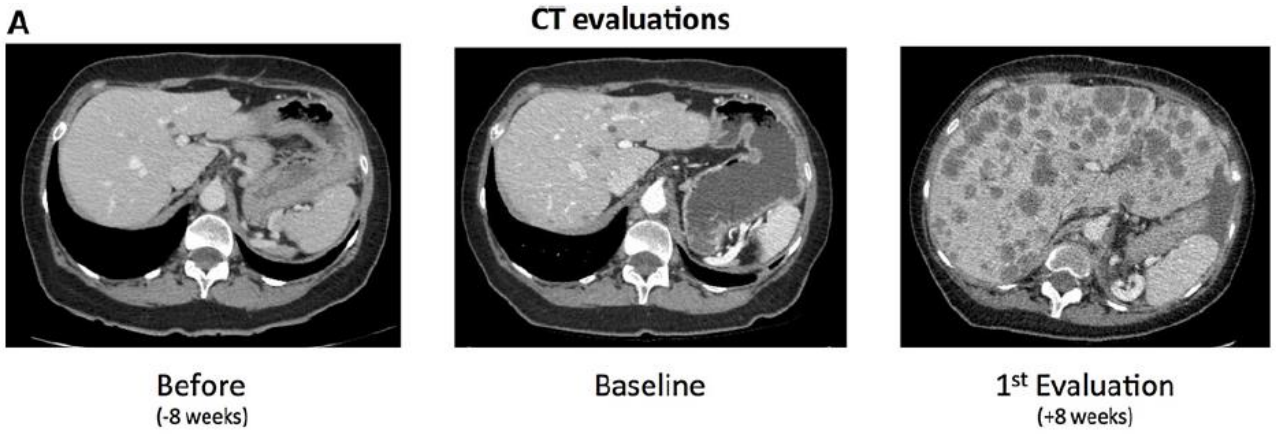
Matthew D Hellmann, Naiyer A Rizvi, Jonathan W Goldman, Scott N Gettinger, Hossein Borghaei, Julie R Brahmer, Neal E Ready, David E Gerber, Laura Q Chow, Rosalyn A Juergens, Frances A Shepherd, Scott A Laurie, William J Geese, Shruti Agrawal, Tina C Young, Xuemei Li, Scott J Antonia



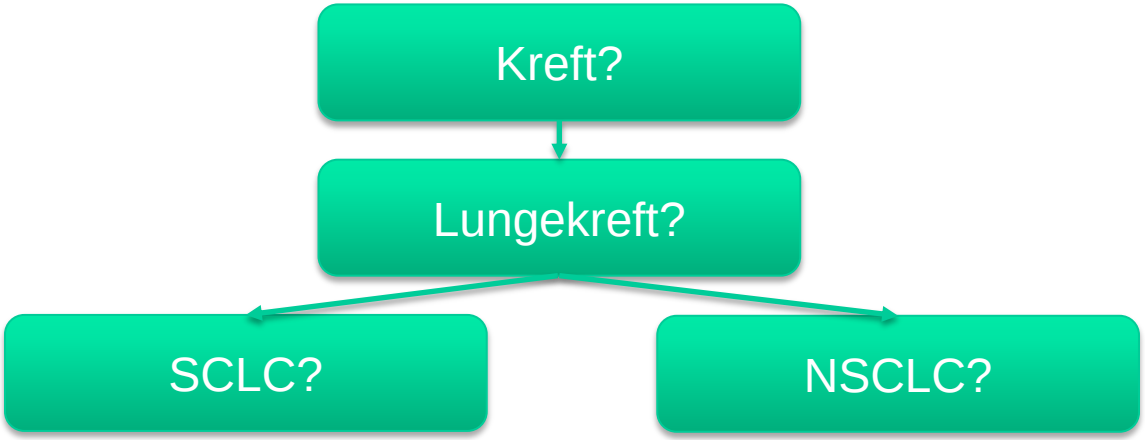
Lancet Oncol, 2016

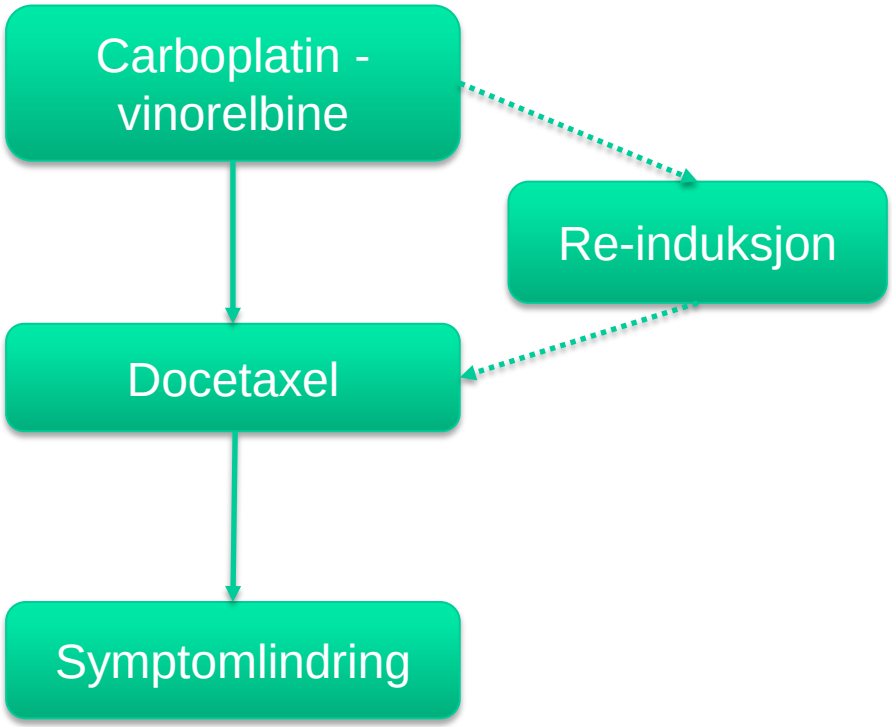
Hyperprogressive Disease Is a New Pattern of Progression in Cancer Patients Treated by Anti-PD-1/PD-L1

Stéphane Champiat[1,2], Laurent Dercle[3], Samy Ammari[4], Christophe Massard[1], Antoine Hollebecque[1], Sophie Postel-Vinay[1,2], Nathalie Chaput[5,6,7,8], Alexander Eggermont[9], Aurélien Marabelle[1,10], Jean-Charles Soria[1,2], and Charles Ferté[1,11,12]

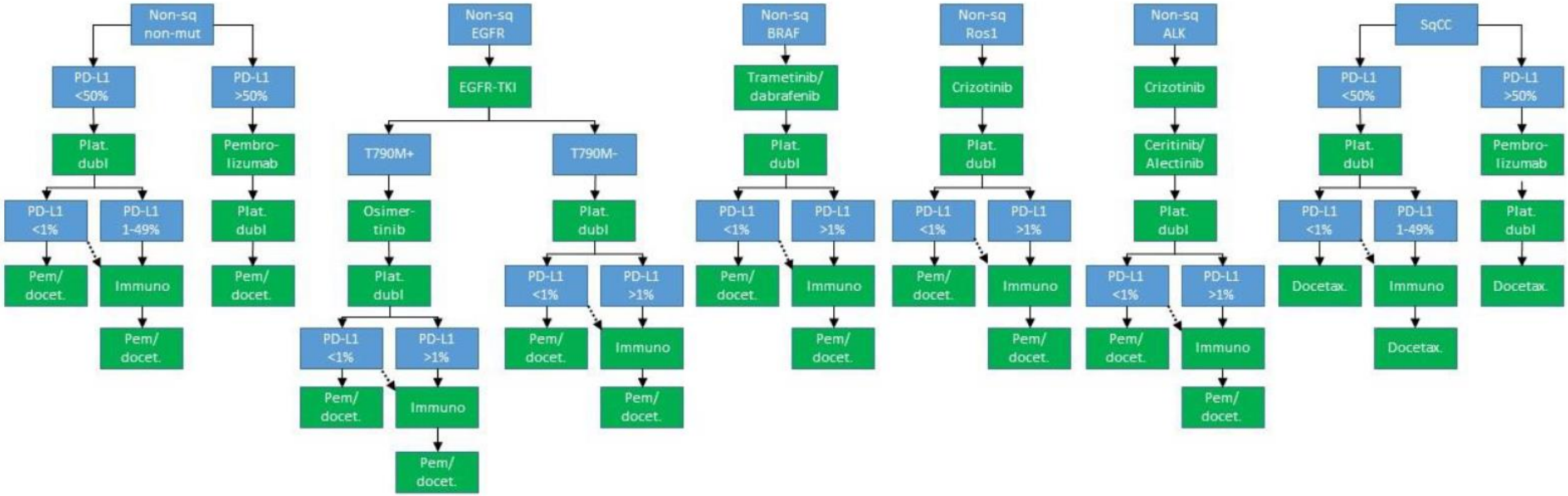


Clin Cancer Res 2016





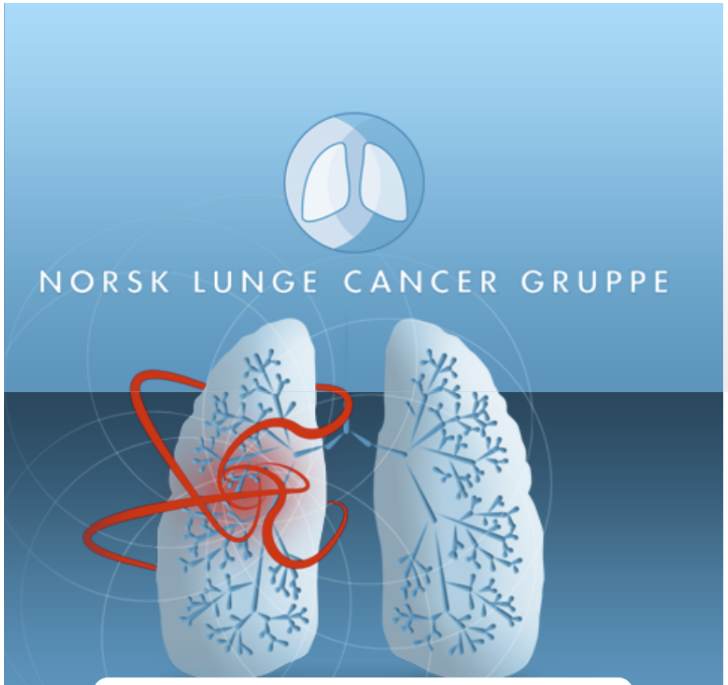
Oppdatert behandlingsalgoritme, avansert NSCLC



Vurdèr alltid inklusjon i kliniske studier!

Oppsummering immunterapi

- Pembrolizumab monoterapi er førstevalg som førstelinjesbehandling ved avansert NSCLC og PD-L1 uttrykk på 50% eller mer
- Immunterapi med nivolumab, pembrolizumab eller atezolizumab er godkjent som 2+ linjes behandling ved avansert NSCLC ved PD-L1 uttrykk på 1% eller mer
- Lovende data på immunterapi etter radiokjemoterapi ved stadium III NSCLC
- Fase III data på kombinasjonsbehandling med immunterapi og cytostatika kommer i 2018



Velkommen!

Hovedinnholdet på nettsidene til NLCG er handlings-programmet, men her ligger også annen nyttig informasjon for lungekreft-interesserte leger, pasienter, pårørende og andre. Ansvarlig for sidene er Styret i Norsk lungekreftgruppe (se link til høyre).
Vi håper internettsidene gir den informasjonen man forventer å finne, men forslag til endringer er selvsagt svært velkomne!

Søk

Nyheter

- TREM-studien med tredjegenerasjons EGFR-hemmer for pasienter som progredierer på EGFR-TKI er nå åpna, info er lagt ut her (11.08.15)
- I slutten av august arrangerer ETOP (sammenslutning av europeiske lungekreftgrupper som NLCG) et workshop som dekker hele lungekreftfeltet, og ser ut til å være et meget godt møte. NLCG er medlem i ETOP, og møtet er derfor gratis for den som melder seg via NLCG før 15. juni, og reise vil bli dekket (19.5.15).
- Handlingsprogrammet er nå revidert, og inneholder retningslinjer for utredning og behandling av lungekreft, mesoteliom og thymom (11.5.15)
- BI Lung cancer research award skal også i år deles ut på Onkologisk forum. Prisen er på inntil 40.000 kroner, og går til årets beste poster/vitenskapelige innlegg innen lungekreftfeltet. Se her for søknadsskjema og ytterligere informasjon - søknadsfrist 20. oktober (12.04.15).
- Det ligger nå en link til en smart kalkulator for beregning av volumdoblings-tid som er nyttig i vurdering av benign/malign lesjon under linkesamlinga vår (10.4.15)
- Norsk lungekreftgruppe i samarbeid med Kreftforeningens nasjonale kompetansemiljø for lungekreft inviterer til tverrfaglig nasjonalt møte om lungekreft ved Radiumhospitalet, 22. mai. Hold av datoen! (20.2.15)