

Lung Cancer – state of the art

First-line chemotherapy and second-line chemotherapy

Wilfried Ernst Erich Eberhardt

*Department of Medical Oncology ,
University Hospital Essen ,
University Duisburg-Essen,
wilfried.eberhardt@uni-duisburg-essen.de*

Conflict of interest statement - WEE Eberhardt

1. CEO function or other direct job relationships

none

2. Advisor function

advisory board function

Astra Zeneca, Roche, Eli Lilly, Novartis, Pfizer, BayerSchering, Sanofiaventis, Boehringer Ingelheim, BMS, GSK, Amgen

3. stocks

none

4. honoraria

for lectures

Pierre Fabre, MerckSerono, Astra Zeneca, Roche, Eli Lilly, Novartis, Pfizer, BayerSchering, SanofiAventis, OSI, BMS, GSK, Boehringer Ingelheim, Synthon

5. research funding

study research grant

Eli Lilly

6. scientific evidence

none

7. other financial relations

none

FIGURE 1 Ten Leading Cancer Types for the Estimated New Cancer Cases and Deaths, by Sex, United States, 2008

Estimated New Cases*

			Males	Females			
Prostate	186,320	25%			Breast	182,460	26%
Lung & bronchus	114,690	15%			Lung & bronchus	100,330	14%
Colon & rectum	77,250	10%			Colon & rectum	71,560	10%
Urinary bladder	51,230	7%			Uterine corpus	40,100	6%
Non-Hodgkin lymphoma	35,450	5%			Non-Hodgkin lymphoma	30,670	4%
Melanoma of the skin	34,950	5%			Thyroid	28,410	4%
Kidney & renal pelvis	33,130	4%			Melanoma of the skin	27,530	4%
Oral cavity & pharynx	25,310	3%			Ovary	21,650	3%
Leukemia	25,180	3%			Kidney & renal pelvis	21,260	3%
Pancreas	18,770	3%			Leukemia	19,090	3%
All Sites	745,180	100%			All Sites	692,000	100%

Estimated Deaths

			Males	Females			
Lung & bronchus	90,810	31%			Lung & bronchus	71,030	26%
Prostate	28,660	10%			Breast	40,480	15%
Colon & rectum	24,260	8%			Colon & rectum	25,700	9%
Pancreas	17,500	6%			Pancreas	16,790	6%
Liver & intrahepatic bile duct	12,570	4%			Ovary	15,520	6%
Leukemia	12,460	4%			Non-Hodgkin lymphoma	9,370	3%
Esophagus	11,250	4%			Leukemia	9,250	3%
Urinary bladder	9,950	3%			Uterine corpus	7,470	3%
Non-Hodgkin lymphoma	9,790	3%			Liver & intrahepatic bile duct	5,840	2%
Kidney & renal pelvis	8,100	3%			Brain & other nervous system	5,650	2%
All Sites	294,120	100%	All Sites		271,530	100%	

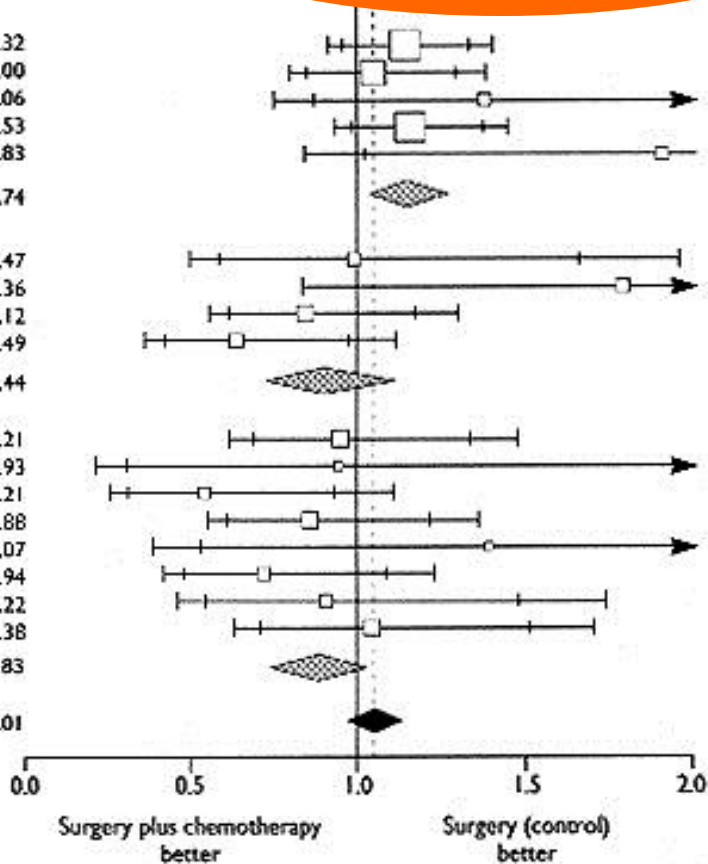
From Jemal, A. et al.
CA Cancer J Clin 2008;58:71-96.

Chemotherapy in Stage IIIB/IV - CTx vs BSC -

Results of trials of surgery versus surgery plus chemotherapy (test for heterogeneity $\chi^2_{\text{HetT}}=28.98$, $\text{df}=16$, $P=0.02$; test for interaction $\chi^2_{\text{HetB}}=10.97$, $\text{df}=2$, $P=0.004$, $\chi^2_{\text{HetW}}=18.01$, $\text{df}=14$, $P=0.21$)
(see tables for references to trials).

Trial	No of events/ No of patients entered		Observed - expected deaths	Variance
	Surgery plus chemotherapy	Surgery		
Long term alkylating agents:				
MRC LUO2	415/428	209/215	18.22	143.32
VASAG	251/291	128/152	4.50	86.00
EORTC 08741	38/71	36/75	5.82	18.06
VASOG 5	292/424	261/417	20.63	137.53
WPL 7351	25/36	15/36	6.36	9.83
Subtotal	1021/1250	649/895	55.53	394.74
Other drugs:				
OLCSG 1a	30/163	28/158	-0.09	14.47
OLCSG 1b	27/41	21/42	6.59	11.36
SGACLC ACTLC I	70/154	75/152	-6.10	36.12
WJSG 2 (2 and 3)	38/108	49/100	-9.79	21.49
Subtotal	165/466	173/452	-9.39	83.44
Cisplatin based:				
LCSG 801	66/140	71/143	-1.81	34.21
OLCSG 1c	5/12	7/16	-0.19	2.93
FLCSG I	20/54	30/56	-7.79	12.21
SGACLC ACTLC2	64/165	68/167	-4.80	32.88
IPCR Chiba	11/15	7/14	1.33	4.07
WJSG 2 (1 and 3)	44/115	49/100	-7.66	22.94
LCSG 853	29/94	32/94	-1.65	15.22
JLCSG	59/111	52/98	0.98	27.38
Subtotal	298/706	316/688	-21.58	151.83
Total	1484/2422	1138/2035	24.57	630.01

1995



British Medical Journal Publishing Group et al. BMJ
1995;311:899-909

Chemotherapy in Stage IIIB/IV - CTx vs BSC -

Mitomycin, Ifosfamide, and Cisplatin in Unresectable Non-Small-Cell Lung Cancer: Effects on Survival and Quality of Life

By M.H. Cullen, L.J. Billingham, C.M. Woodroffe, A.D. Chetiyawardana, N.H. Gower, R. Joshi, D.R. Ferry, R.M. Rudd, S.G. Spiro, J.E. Cook, C. Trask, E. Bessell, C.K. Connolly, J. Tobias, and R.L. Souhami

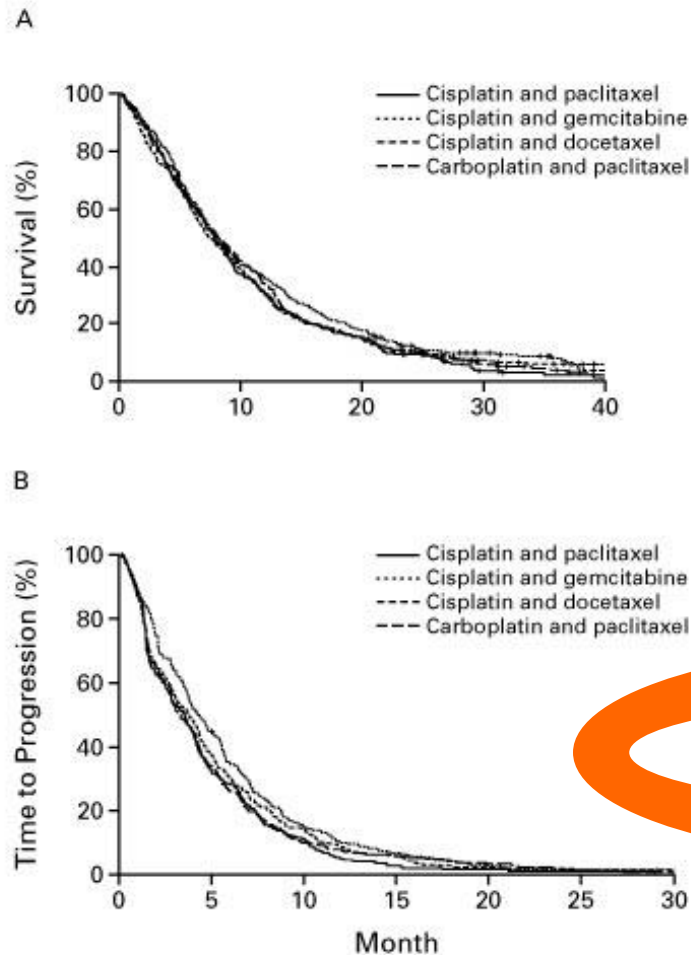
J Clin Oncol 17:3188-3194. © 1999

CTx vs BSC : Improvement in OS but more to that improvement in Quality of life in comparison to BSC where a decrease in QoL was expected

1999

Chemotherapy in Stage IIIB/IV - modern combinations comparable -

Kaplan-Meier Estimates of Overall Survival (Panel A) and the Time to Progression of Disease (Panel B) in the Study Patients, According to the Assigned Treatment



2002

Chemotherapy in Stage IIIB/IV - Cis vs Carbo -

CISCA META ANALYSIS

2007

Response and Survival

	CIS	CARBO	p
RR (%)	33	26	<0.001
Overall Survival (Monate)	9.1	8.4	0.101
1-year survival (%)	37	34	NA

CISCA-Subgroup-Analysis: Survival

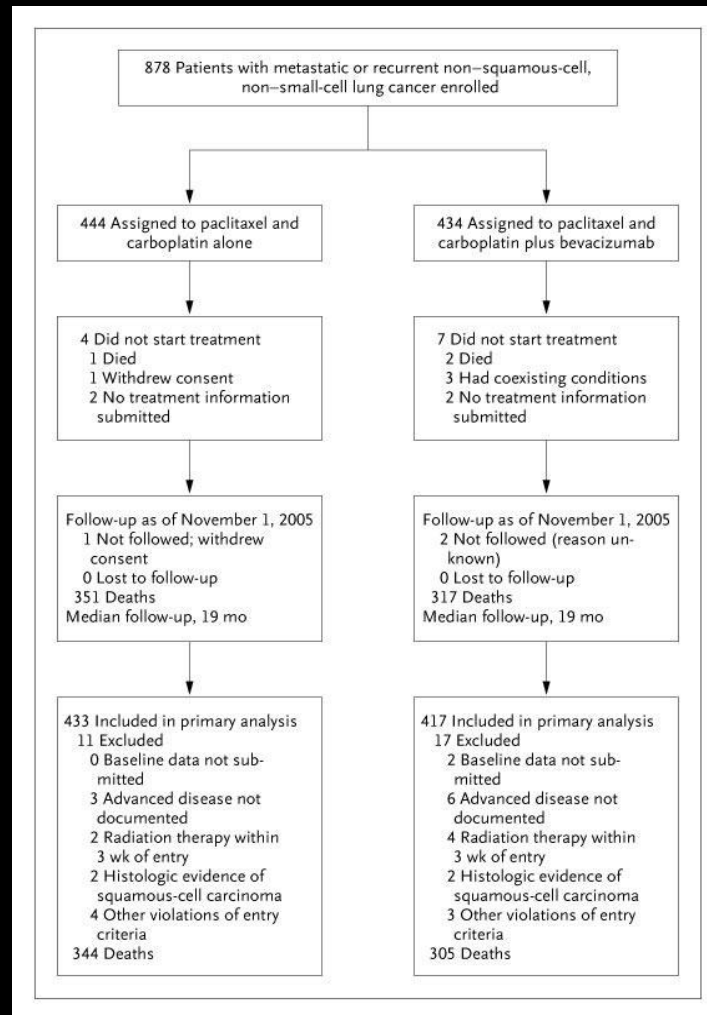
2007

Subgroups	HR	95 % CI	p
Non-Squamous-cell Ca	1,12	1,01–1,23	0,026
Squamous-cell Ca	0,97	0,85–1,10	0,586
Second-generation-CT	0,94	0,80–1,11	0,467
Third-generation-CT	1,11	1,01–1,21	0,028

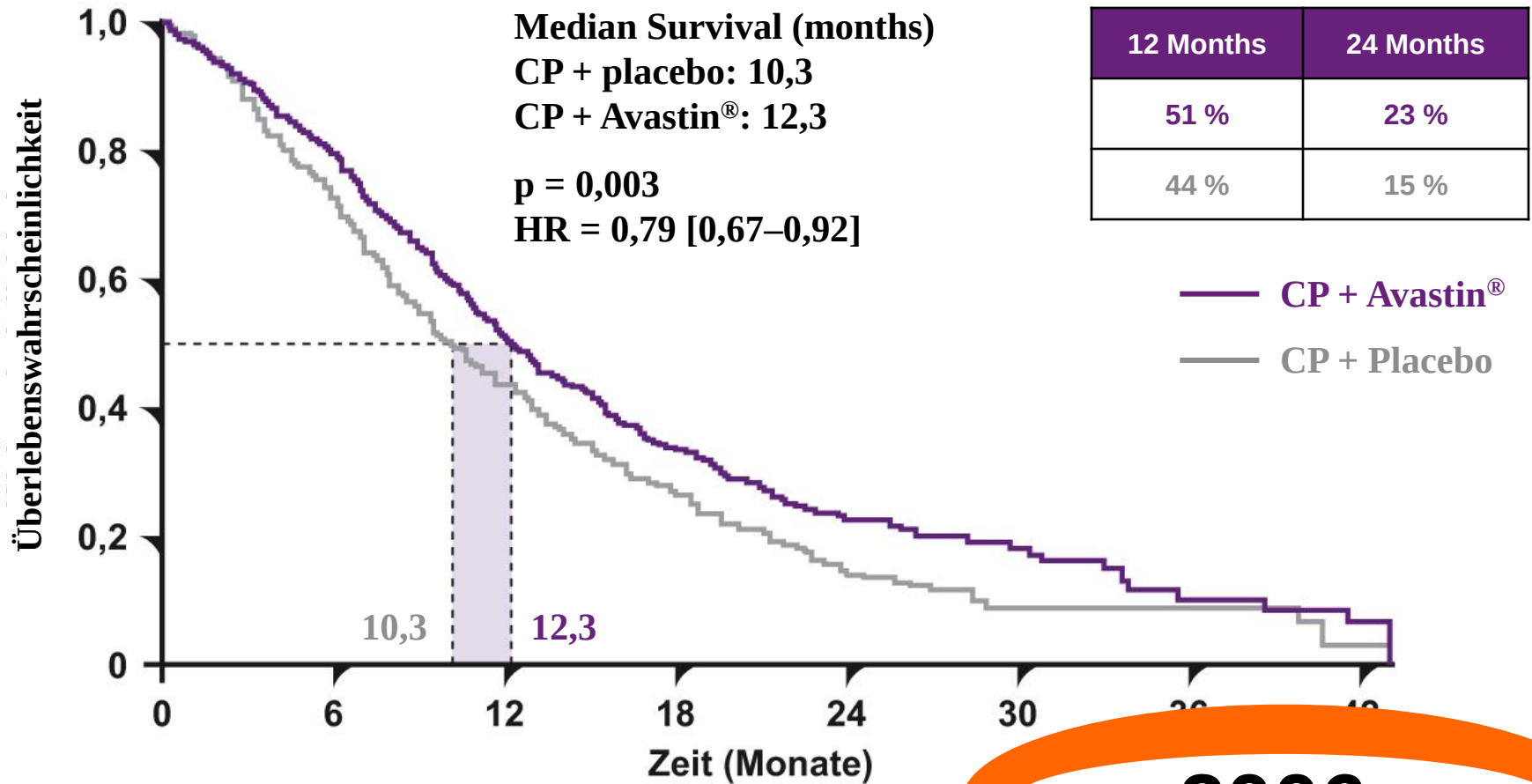
- patients with non-squamous cell carcinoma showed a significant survival benefit with cisplatin combinations
- Patients with a third-generation cisplatinum combination showed a significant survival benefit

Chemotherapy in Stage IIIB/IV - any progress ? -

Enrollment, Randomization, and Follow-up of Patients in the Study.

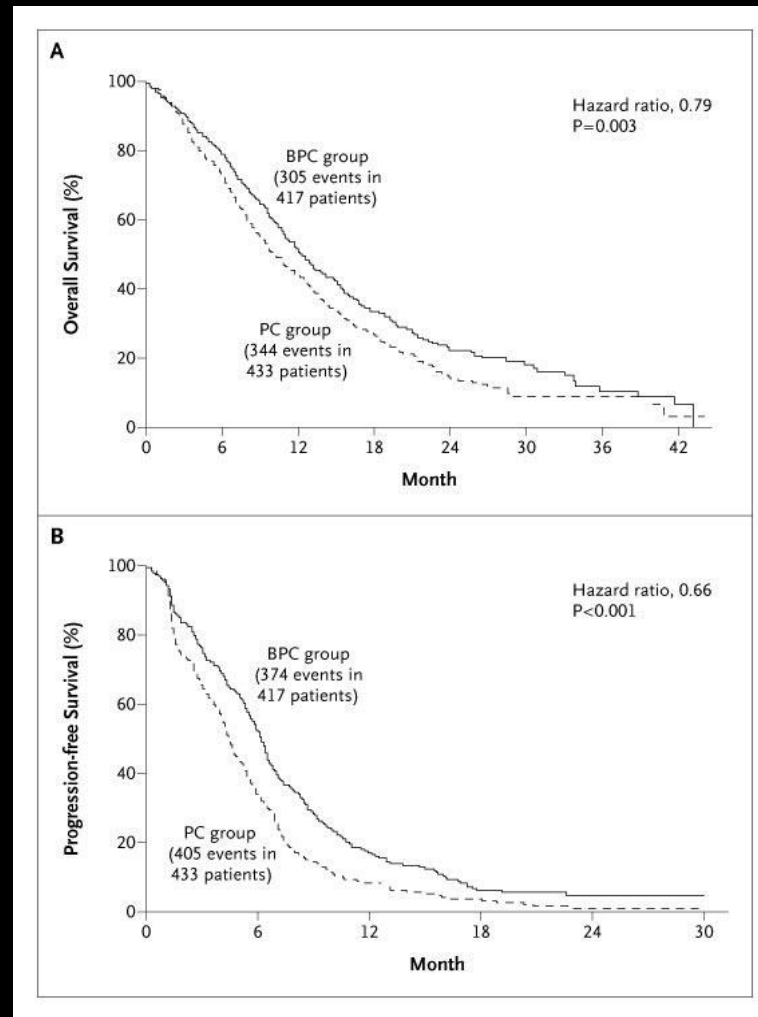


Phase-III E4599 ECOG: Overall survival

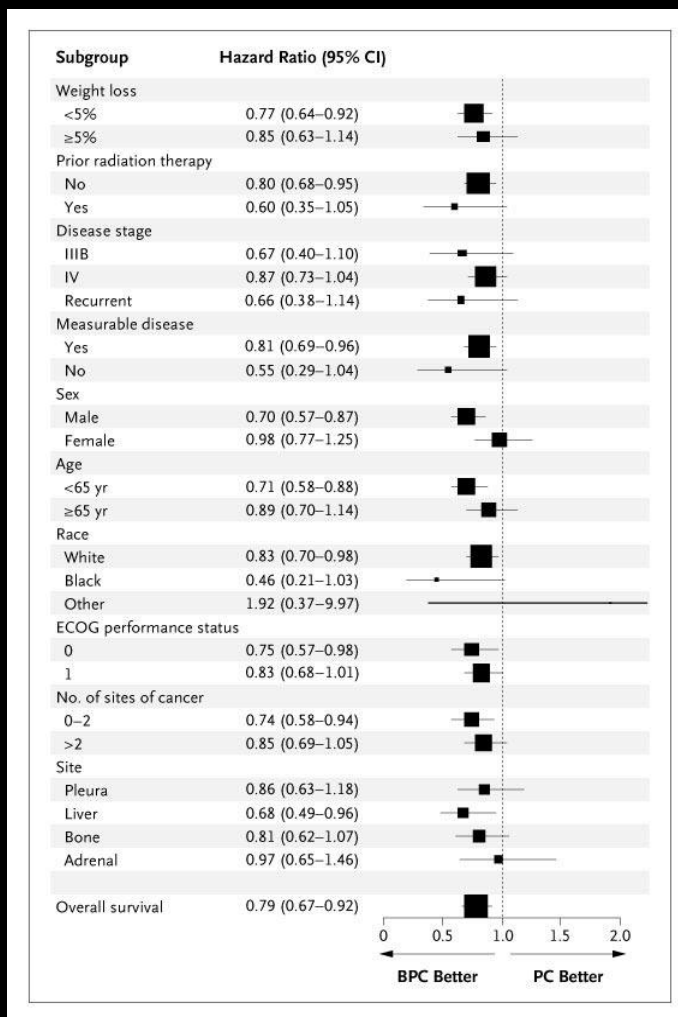


2006

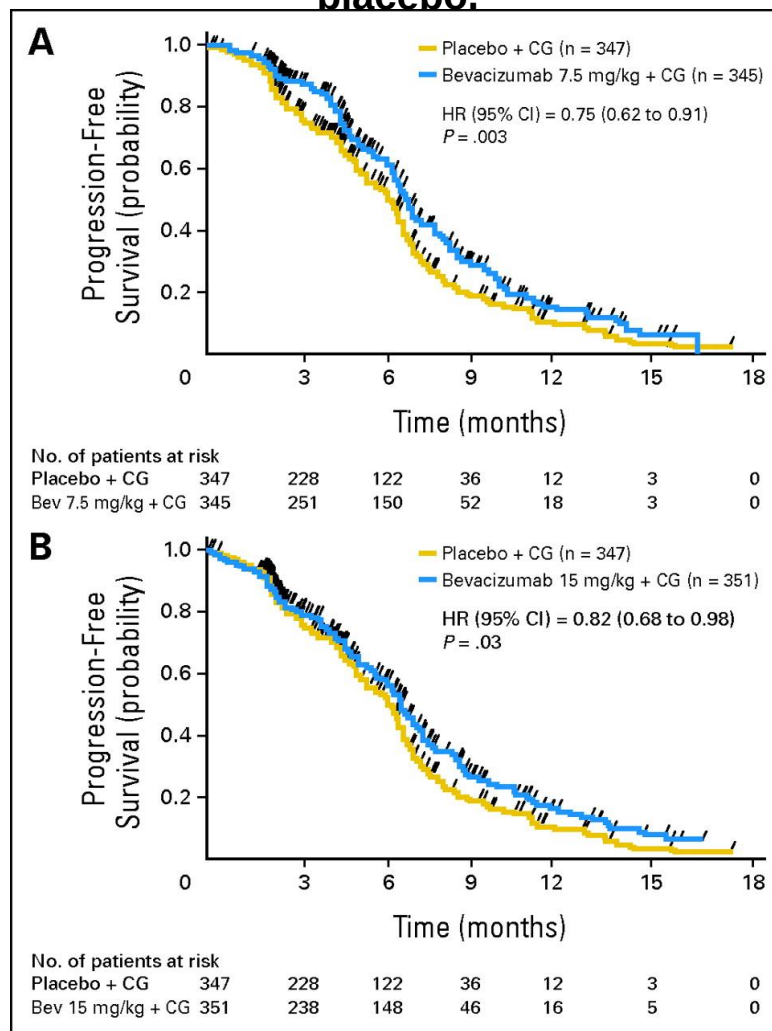
Kaplan–Meier Estimates of Overall Survival (Panel A) and Progression-free Survival (Panel B).



Hazard Ratios for Death, According to the Subgroup Analysis.

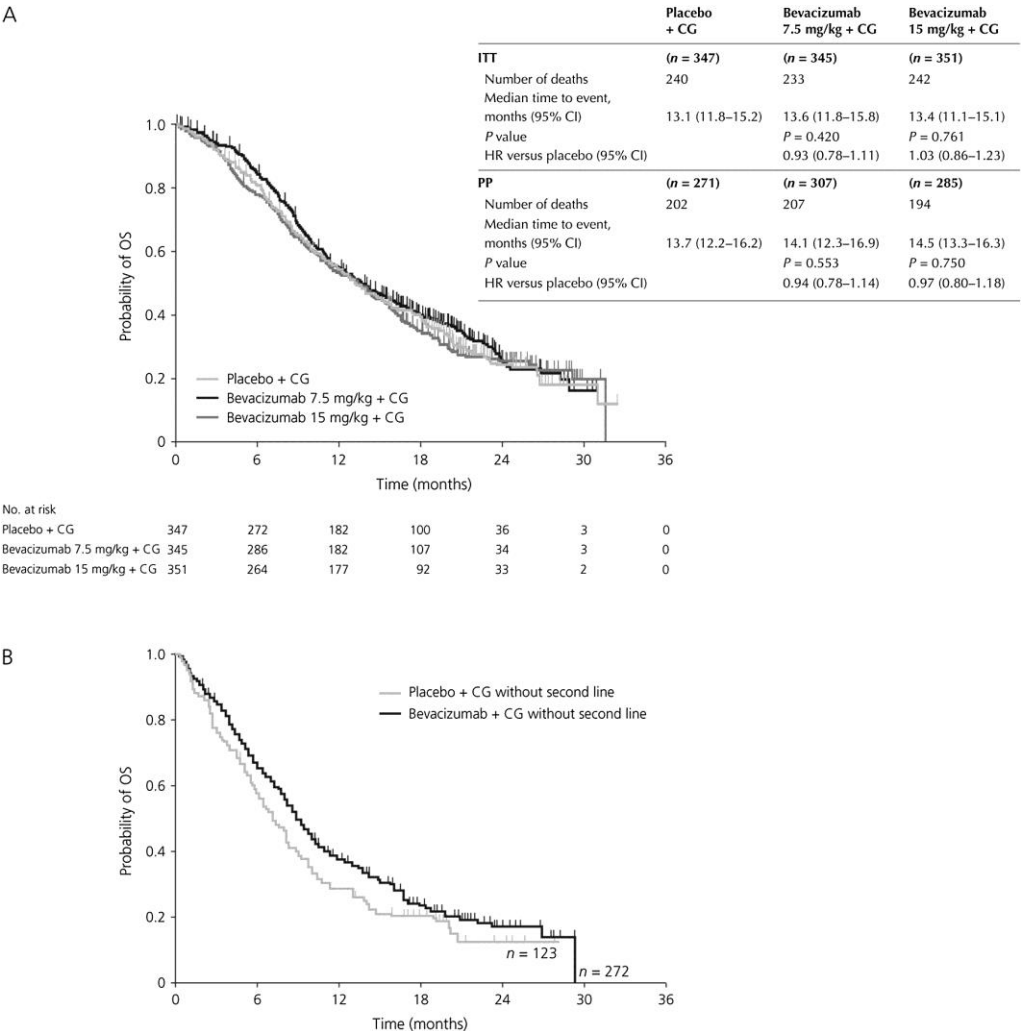


Plot of Kaplan-Meier estimates for progression-free survival (intent-to-treat population) for the (A) 7.5 mg/kg bevacizumab (Bev) arm and (B) 15 mg/kg bevacizumab arm compared with placebo.



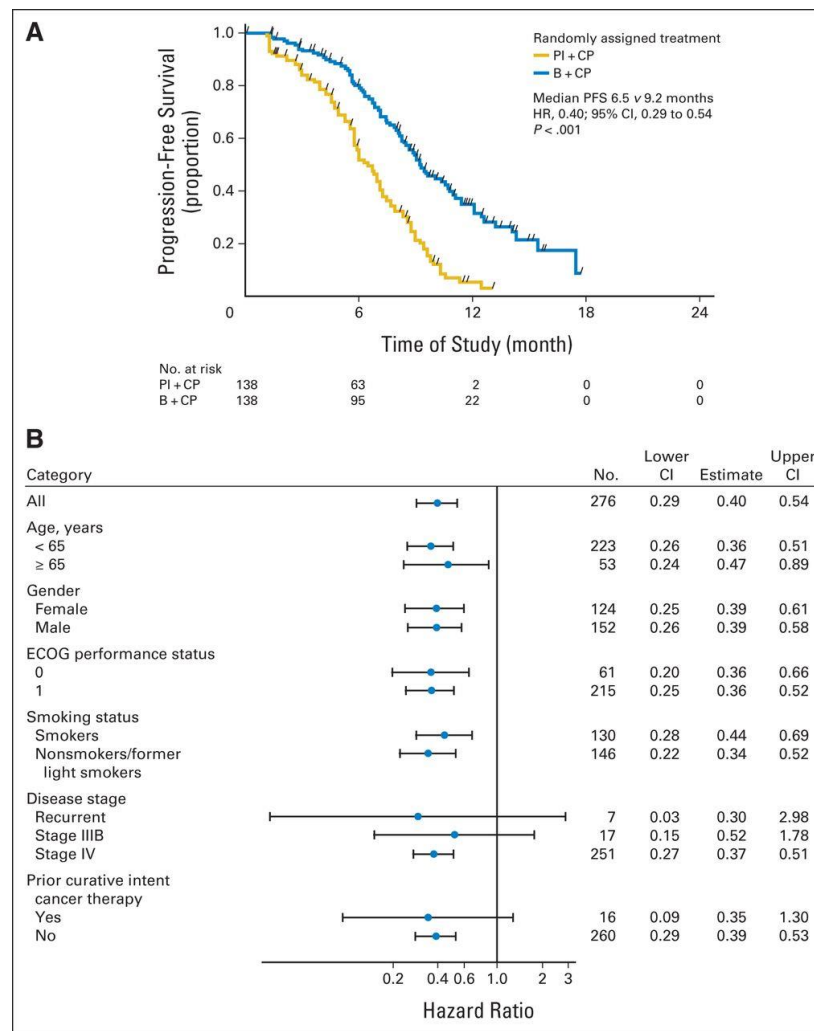
Martin Reck et al. JCO 2009;27:1227-1234

Plots of Kaplan–Meier estimates for OS (ITT population) for the bevacizumab 7.5 mg/kg group and the bevacizumab 15 mg/kg group relative to placebo, together with time to event data for the OS analysis in the ITT and PP populations (A) and for the subgroup of patients who did not receive poststudy therapy (B).



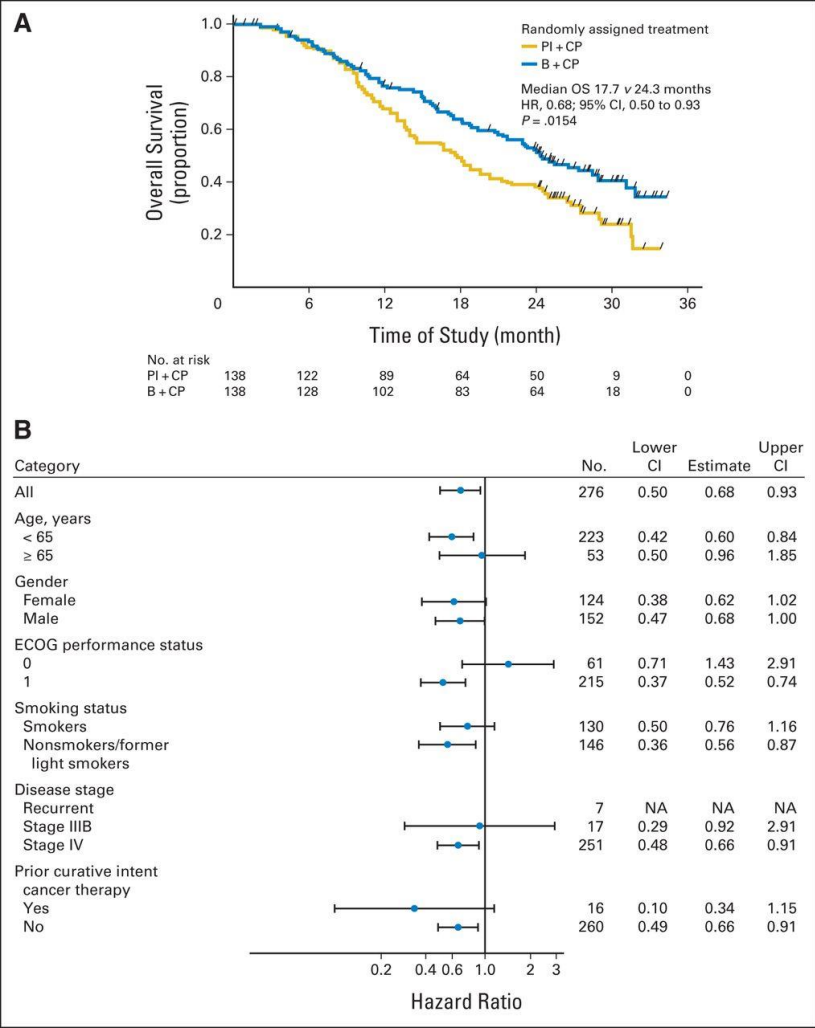
M. Reck et al. Ann Oncol 2010;21:1804-1809

(A) Kaplan-Meier curve of progression-free survival (PFS) in the intent-to-treat population.



Caicun Zhou et al. JCO 2015;33:2197-2204

(A) Kaplan-Meier curve of overall survival (OS) in the intent-to-treat population (data cutoff April 30, 2014).

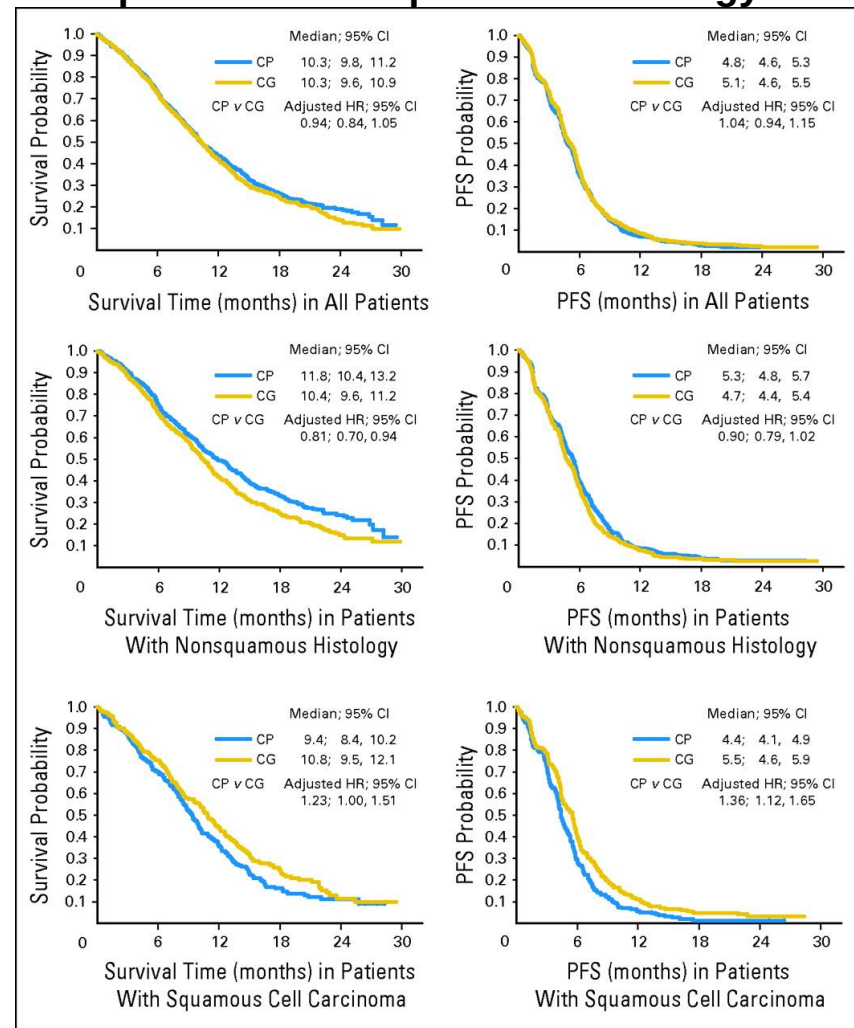


Caicun Zhou et al. JCO 2015;33:2197-2204

1st line chemotherapy

- NSQCC: Chemotherapy + Bev
- Signal is clear: Benefit in RR, PFS and OS with inclusion of Bev

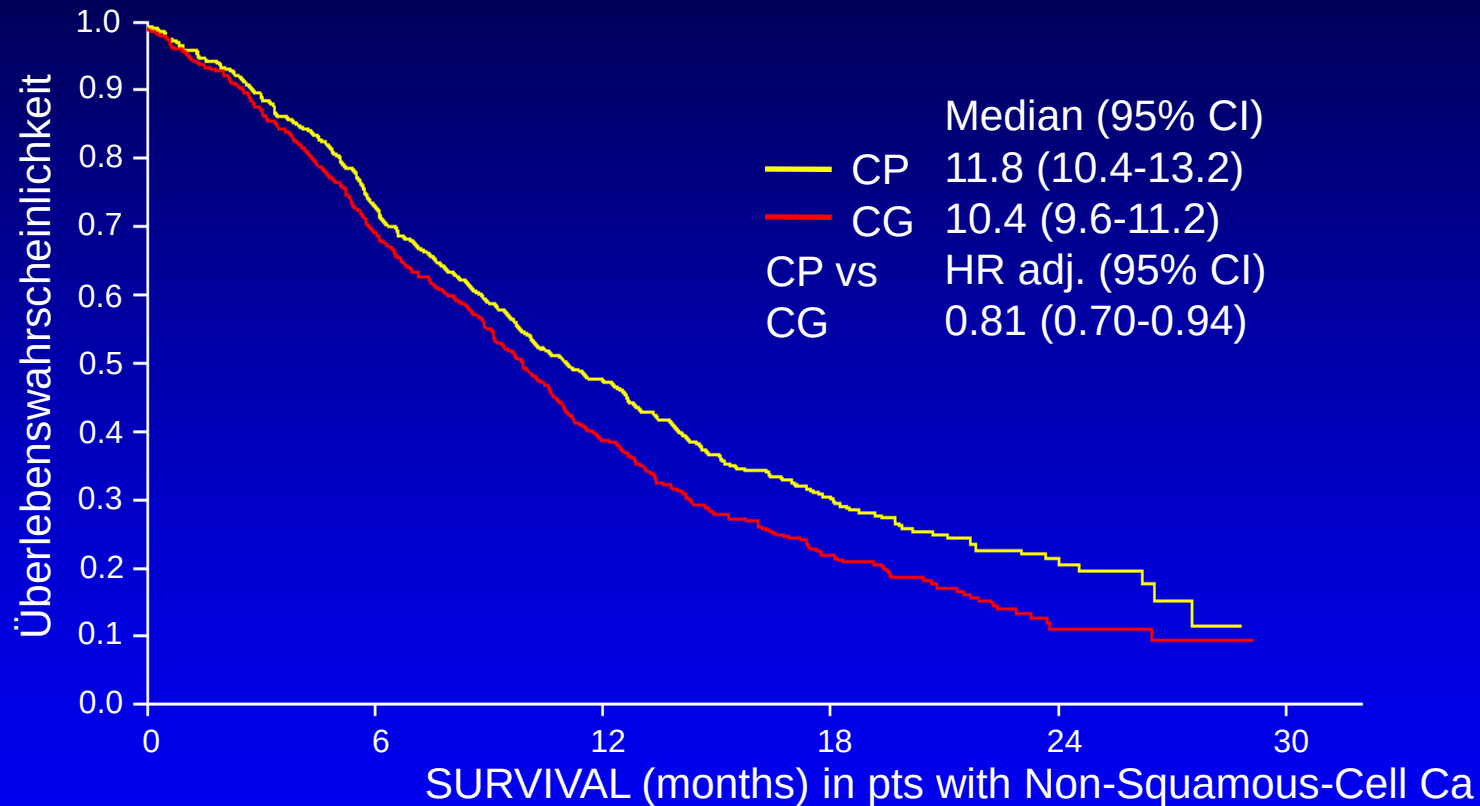
Kaplan-Meier overall survival and progression-free survival (PFS) curves for the entire population, patients with nonsquamous histology (adenocarcinoma plus large cell), and patients with squamous histology.



Giorgio Vittorio Scagliotti et al. JCO 2008;26:3543-3551

Cis/Pem vs Cis/Gem in 1st-line-treatment of NSCLC

OS: Adenocarcinoma versus Large cell carcinoma



Patients ALIVE

CP 512	369	235	109	36	0
CG 488	334	188	80	21	0

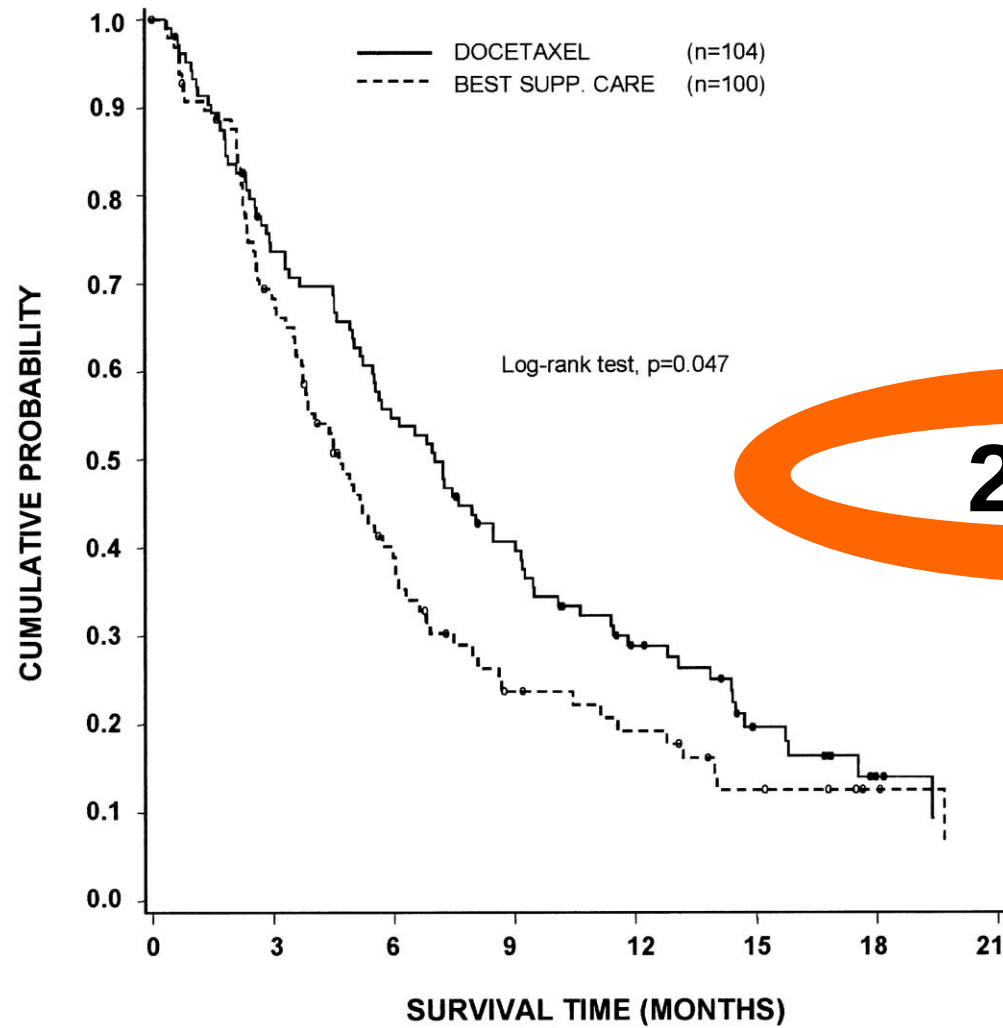
24
Scagliotti GV et al, Presented at 12th World Conference on Lung Cancer: Sept 5, 2007; Seoul, Korea.

1st line chemotherapy

- NSQCC: Chemotherapy + Bev
- NSQCC: Cisplatin + Pemetrexed
- SCC: Cisplatin + Gem, Cis + Pac, Cis + Nav, Cis + Doce

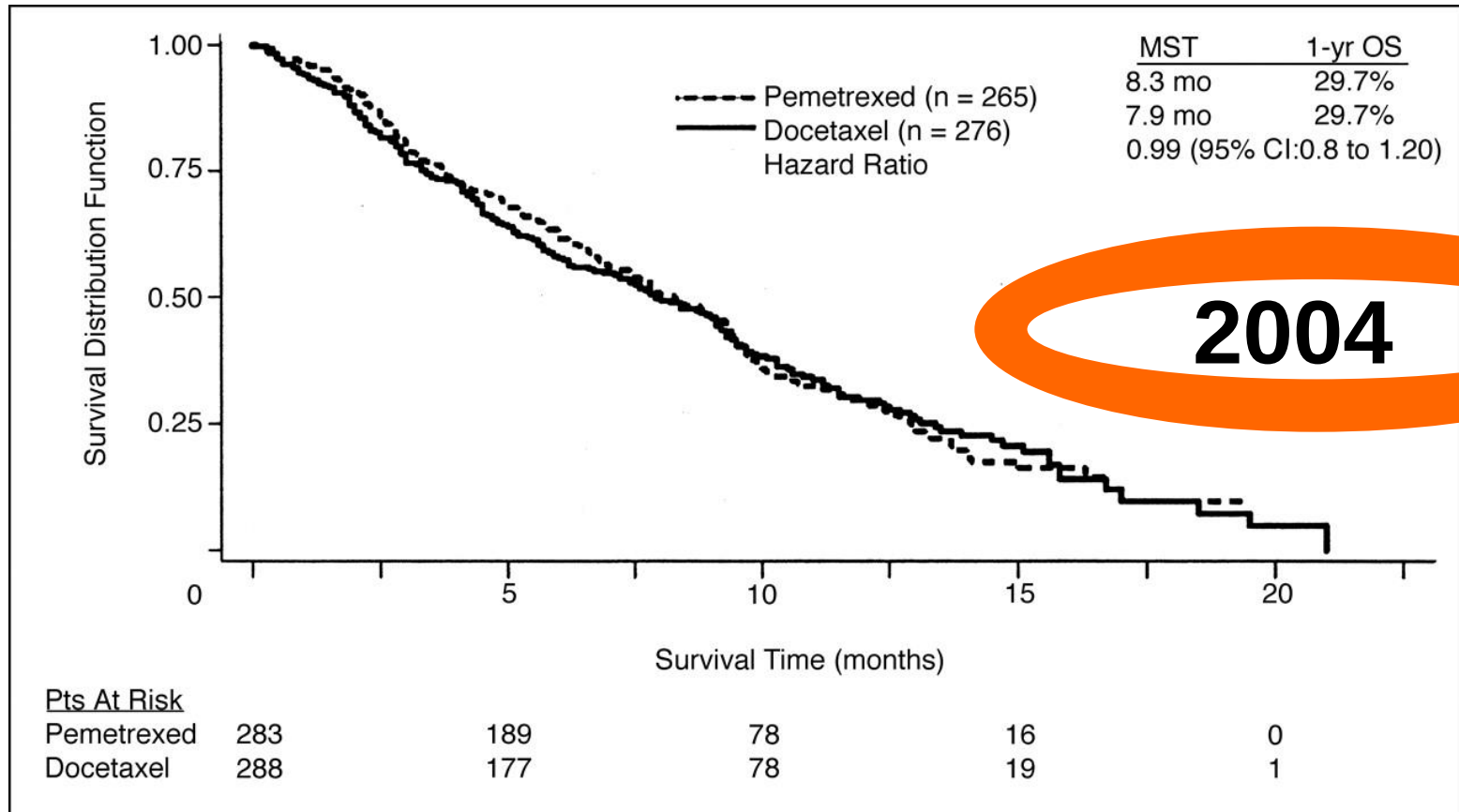
Chemotherapy in Stage IIIB/IV - Second-line-CTx -

comparison of survival of all patients treated with docetaxel and all BSC patients



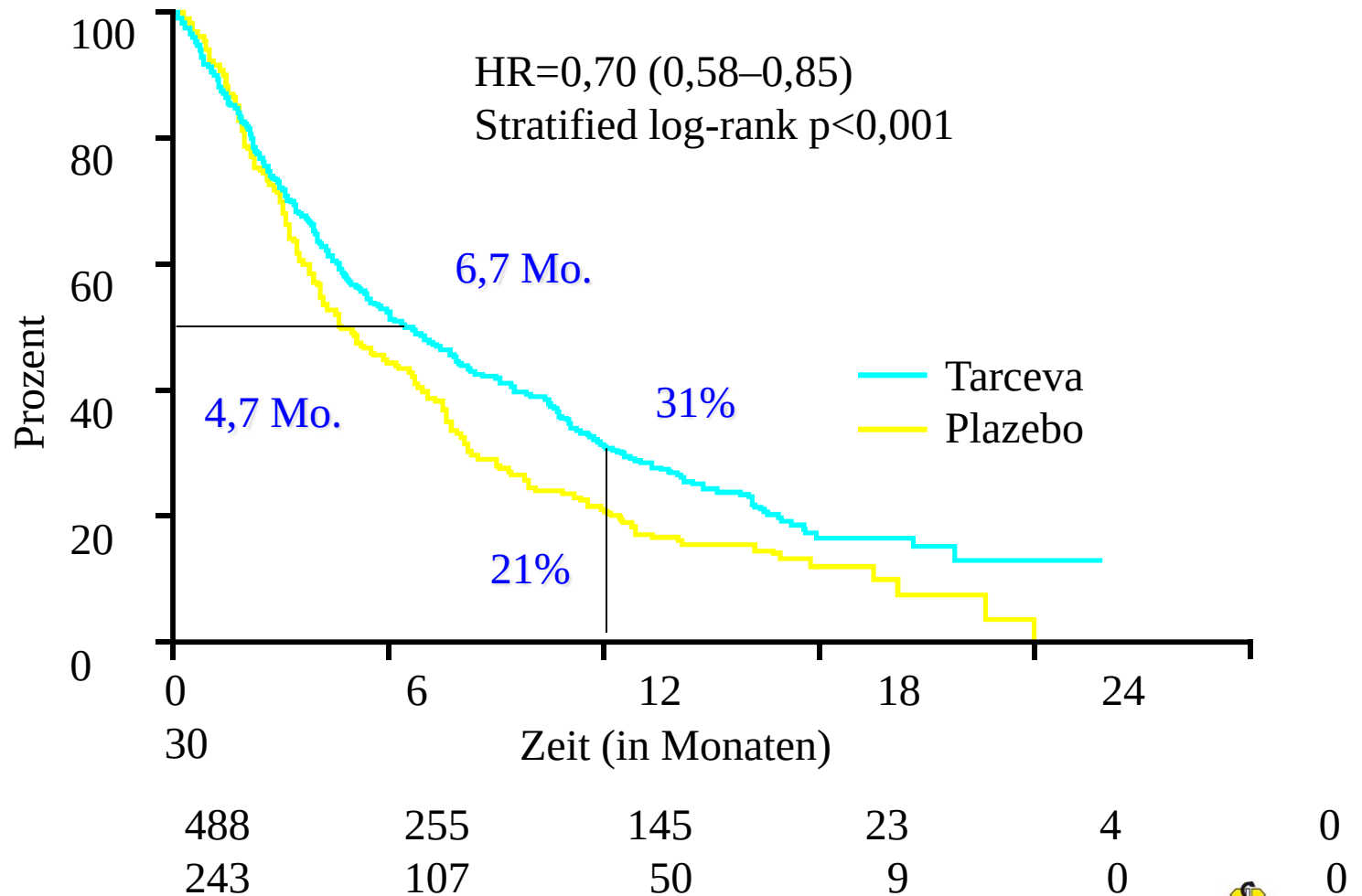
Shepherd, F. A. et al. J Clin Oncol; 18:2095-2103 2000

overall survival: pemetrexed versus docetaxel



Hanna, N. et al. J Clin Oncol; 22:1589-1597 2004

BR.21: Overall survival



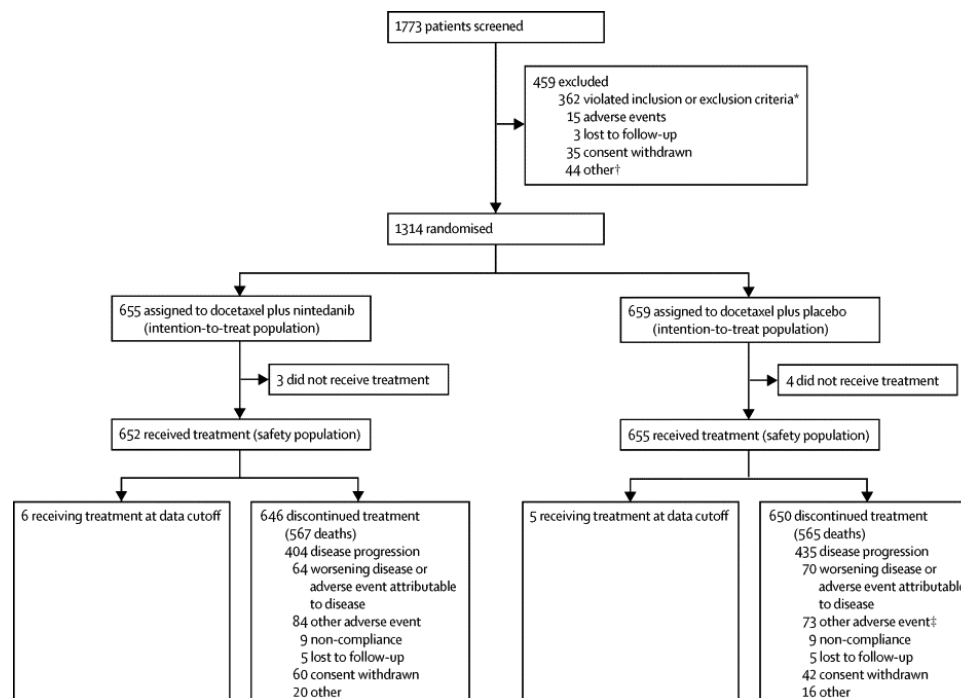


Figure 1 Trial profile *151 (41·7%) patients had active brain metastases; 82 (22·7%) had radiographic evidence of a cavitary or necrotic tumour, or a centrally located tumour, or both; 64 (17·7%) did not have at least one measurable lesion; 26 (7·2%) had ...

Martin Reck , Rolf Kaiser , Anders Møller , Jean-Yves Douillard , Sergey Orlov , Maciej Krzakowski , Joachim ...

Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial

The Lancet Oncology, Volume 15, Issue 2, 2014, 143 - 155

[http://dx.doi.org/10.1016/S1470-2045\(13\)70586-2](http://dx.doi.org/10.1016/S1470-2045(13)70586-2)

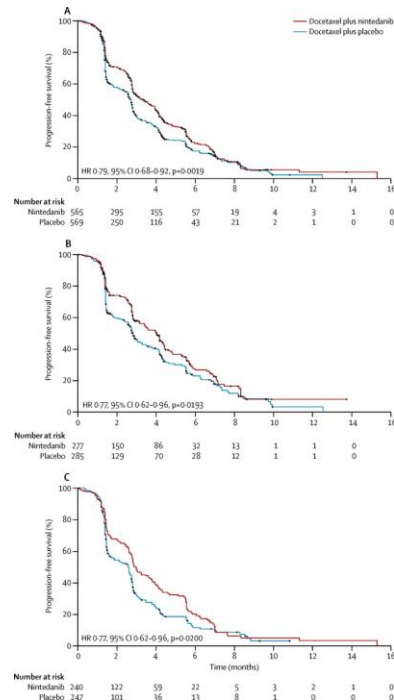


Figure 2 Kaplan-Meier curves for progression-free survival by central independent review at the time of primary analysis (A) Total population. (B) Patients with adenocarcinoma histology. (C) Patients with squamous-cell carcinoma histology. Patients without...

Martin Reck , Rolf Kaiser , Anders Møller , Jean-Yves Douillard , Sergey Orlov , Maciej Krzakowski , Joachim ...

Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial

The Lancet Oncology, Volume 15, Issue 2, 2014, 143 - 155

[http://dx.doi.org/10.1016/S1470-2045\(13\)70586-2](http://dx.doi.org/10.1016/S1470-2045(13)70586-2)

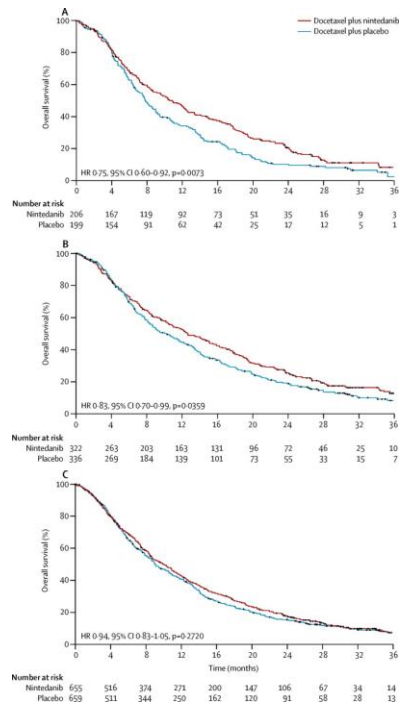


Figure 3 Kaplan-Meier curves for overall survival at the time of final analysis (A) Patients with adenocarcinoma histology and time since start of first-line therapy of less than 9 months. (B) All patients with adenocarcinoma histology. (C) Total population...

Martin Reck , Rolf Kaiser , Anders Møller , Jean-Yves Douillard , Sergey Orlov , Maciej Krzakowski , Joachim ...

Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial

The Lancet Oncology, Volume 15, Issue 2, 2014, 143 - 155

[http://dx.doi.org/10.1016/S1470-2045\(13\)70586-2](http://dx.doi.org/10.1016/S1470-2045(13)70586-2)

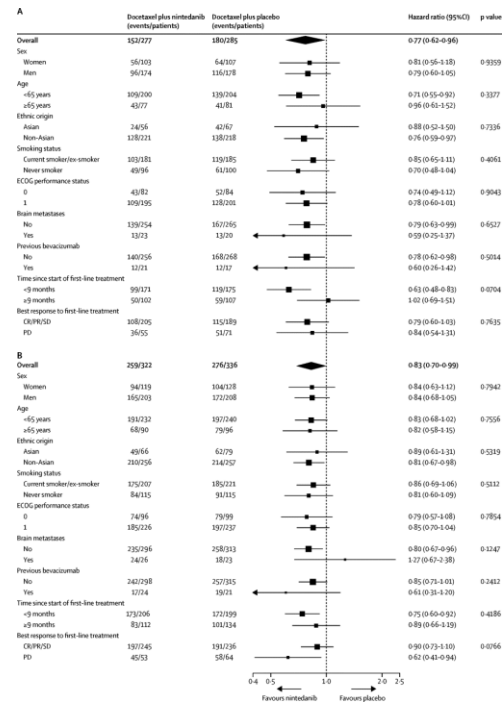


Figure 4 Effect of treatment on survival in subgroups by baseline characteristics in patients with adenocarcinoma histology (A) Progression-free survival at time of primary analysis. (B) Overall survival at time of final analysis. Bubble size represents n...

Martin Reck , Rolf Kaiser , Anders Møller , Jean-Yves Douillard , Sergey Orlov , Maciej Krzakowski , Joachim ...

Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial

The Lancet Oncology, Volume 15, Issue 2, 2014, 143 - 155

[http://dx.doi.org/10.1016/S1470-2045\(13\)70586-2](http://dx.doi.org/10.1016/S1470-2045(13)70586-2)

2nd line chemotherapy

- Single agent therapy
- Randomized phase-III for docetaxel, pemetrexed and erlotinib !
- Randomized phase-III for Doce + nintedanib !

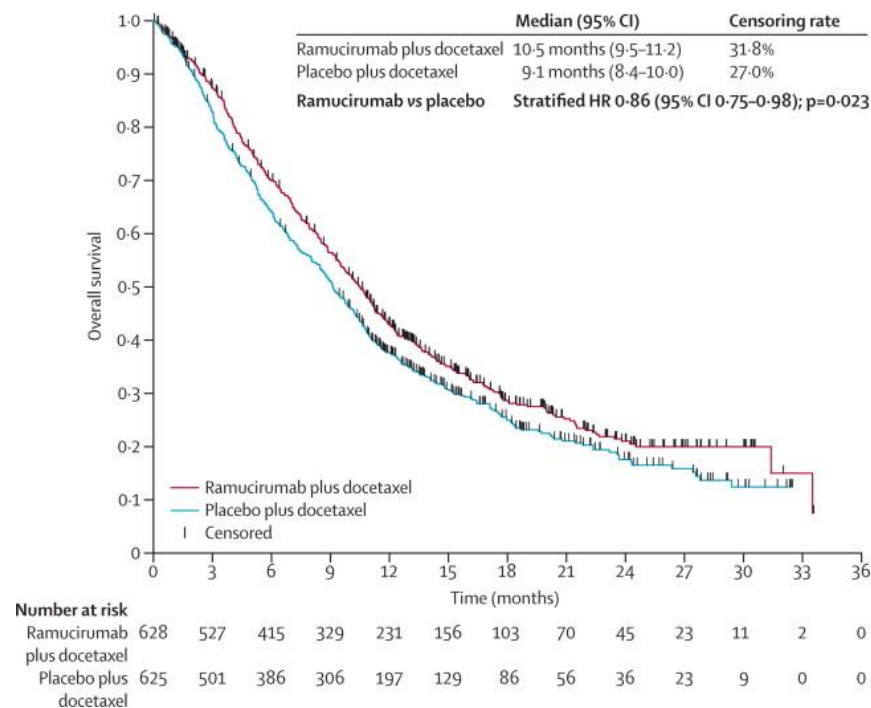


Figure 2 Kaplan-Meier estimates of overall survival in the intention-to-treat population HR=hazard ratio.

Edward B Garon , Tudor-Eliade Ciuleanu , Oscar Arrieta , Kumar Prabhash , Konstantinos N Syrigos , Tuncay Goksel ,...

Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial

The Lancet, Volume 384, Issue 9944, 2014, 665 - 673

[http://dx.doi.org/10.1016/S0140-6736\(14\)60845-X](http://dx.doi.org/10.1016/S0140-6736(14)60845-X)