Systemic treatment of metastatic NSCLC: How do we define progression and what is to be done?

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ESMO 2014

Maastricht UMC+

academisch ziekenhuis Maastricht azM

Maastricht University

DISCLOSURES

Consultation fee

- Roche
- Eli Lilly
- Pfizer
- Astra Zeneca
- Amgen
- BMS

Systemic treatment of metastatic NSCLC: How do we define progression and what is to be done?

Response Evaluation Criteria in Solid Tumours: RECIST 1.1

Eisenhauer, EJC 2009

Systemic treatment of metastatic NSCLC: How do we define progression and what is to be done?

ESMO guideline 2014

Annals of Oncology 2014

Systemic treatment of metastatic NSCLC: How do we define progression and what is to be done?

Response Evaluation Criteria in Solid Tumours: RECIST 1.1

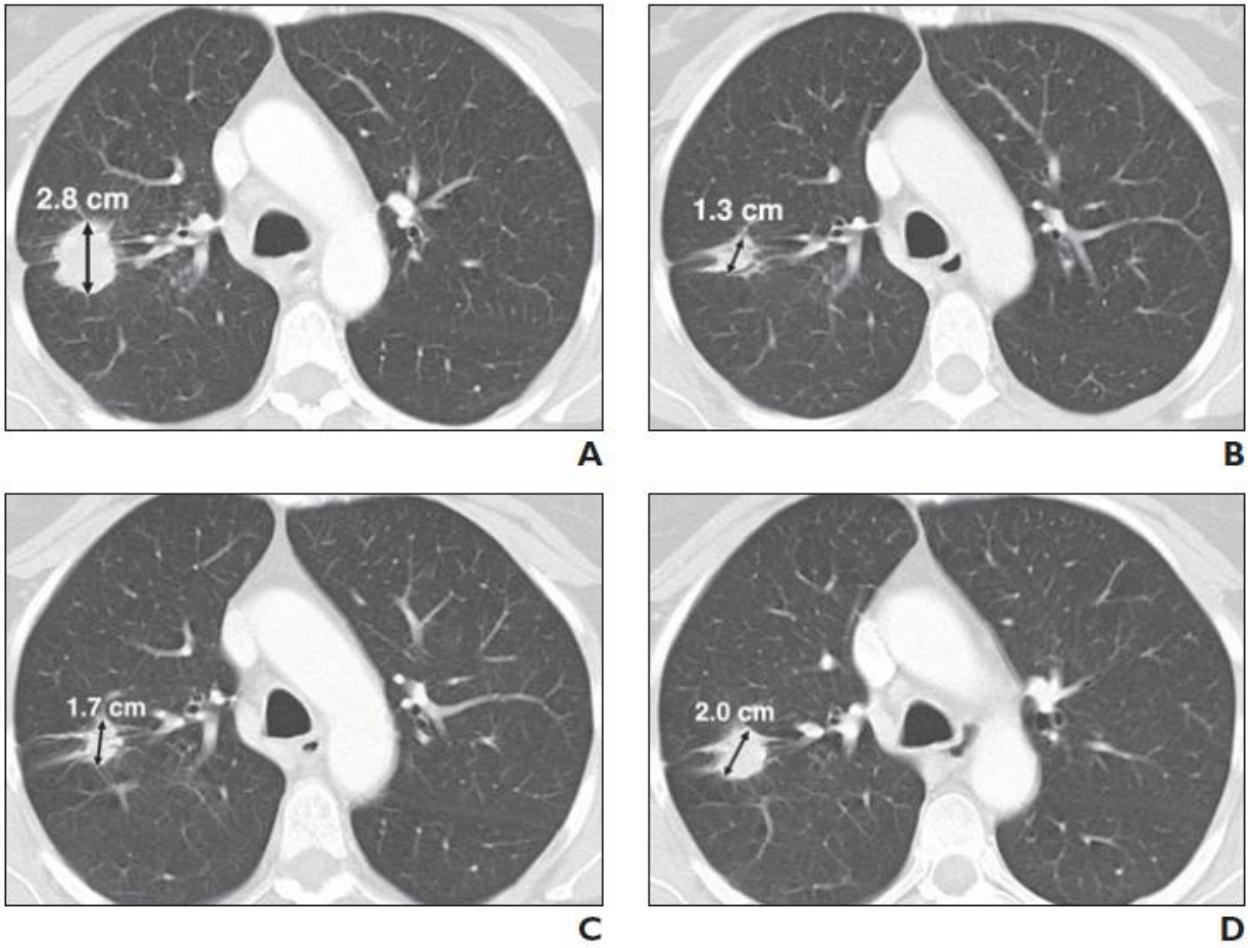
1981: WHO-criteria	focus tumor response: **CLINICAL TRIALS**
2000: RECIST	minimum size
	number of lesions (10)
	unidimensional
2009: RECIST 1.1	less lesions (5, 2 per organ)
	non-measurable disease: PD overall disease
	FDG-PET/MRI
	assessment of LN

Eisenhauer, EJC 2009

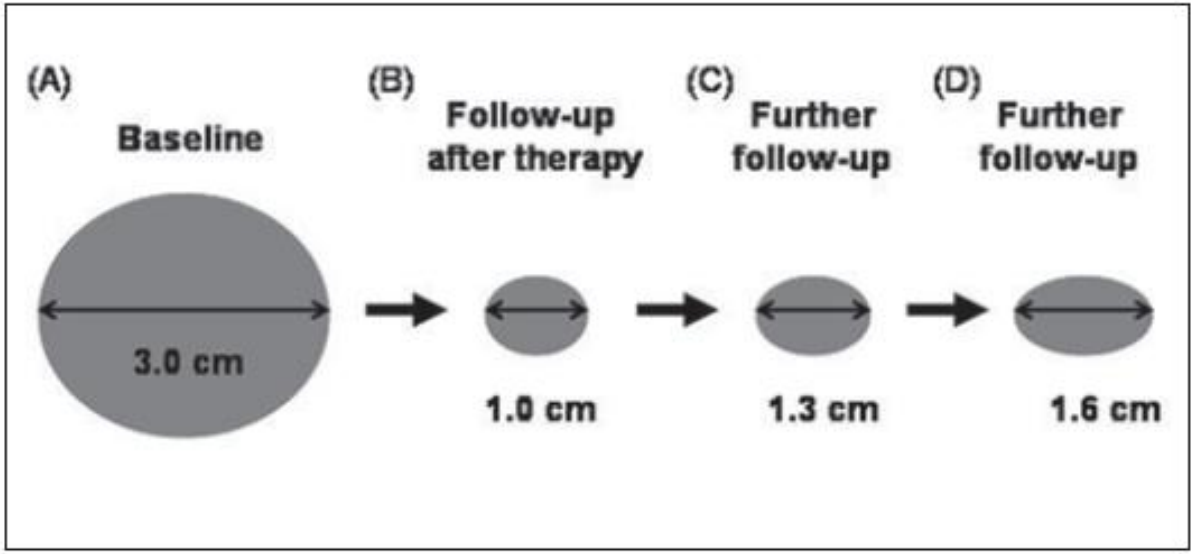
Progressive Disease: RECIST 1.1

- At least 20% increase in sum of diameters target lesions AND > 5 mm increase
- New lesions
- “unequivocal” progression non- target lesions

Progression in small lesions



Nishino, am j rad 2010



Nishino, am j rad 2010

Clinical cases

Promising drug

Patient looks happy, holiday plans

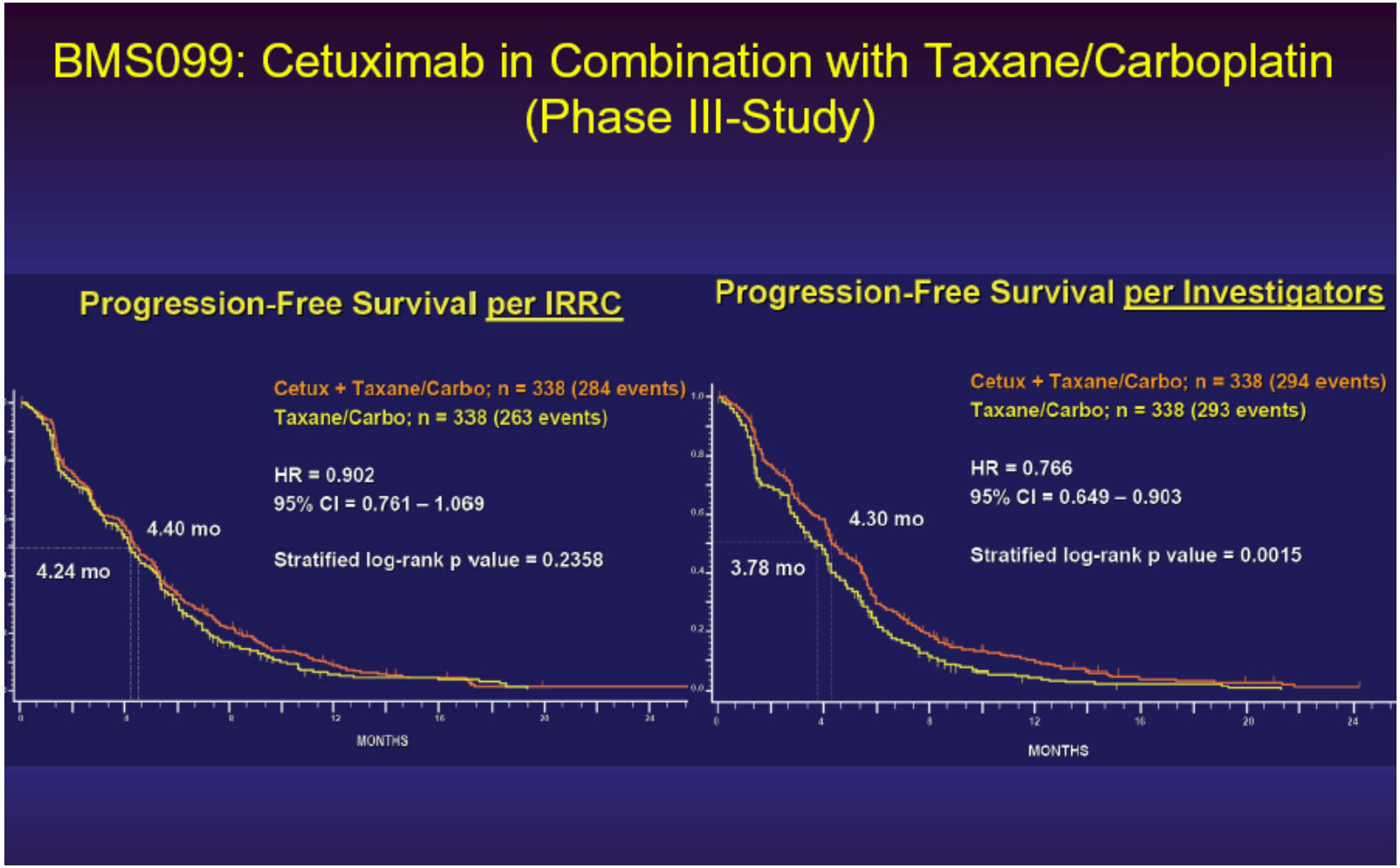
RECIST 1.1: 21%↑

Drug with side effects

Doubt about effectiveness

RECIST 1.1: 19%↑

Recist RECIST?

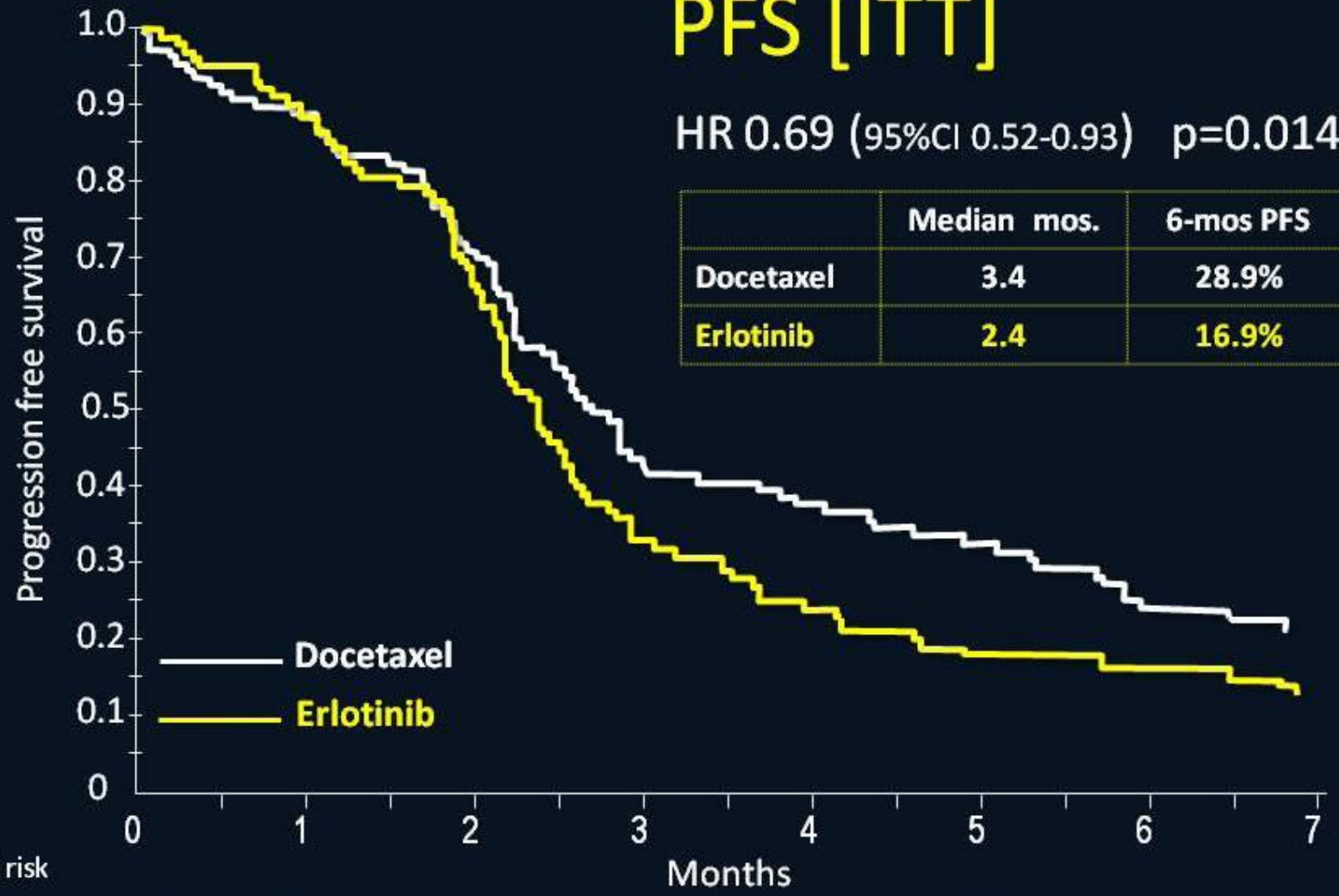


Lynch JCO 2010

PFS [ITT]

HR 0.69 (95%CI 0.52-0.93) p=0.014

	Median mos.	6-mos PFS
Docetaxel	3.4	28.9%
Erlotinib	2.4	16.9%



Patients at risk

Docetaxel	110	95	74	43	37	30	22	19
Erlotinib	109	90	67	33	24	18	16	11

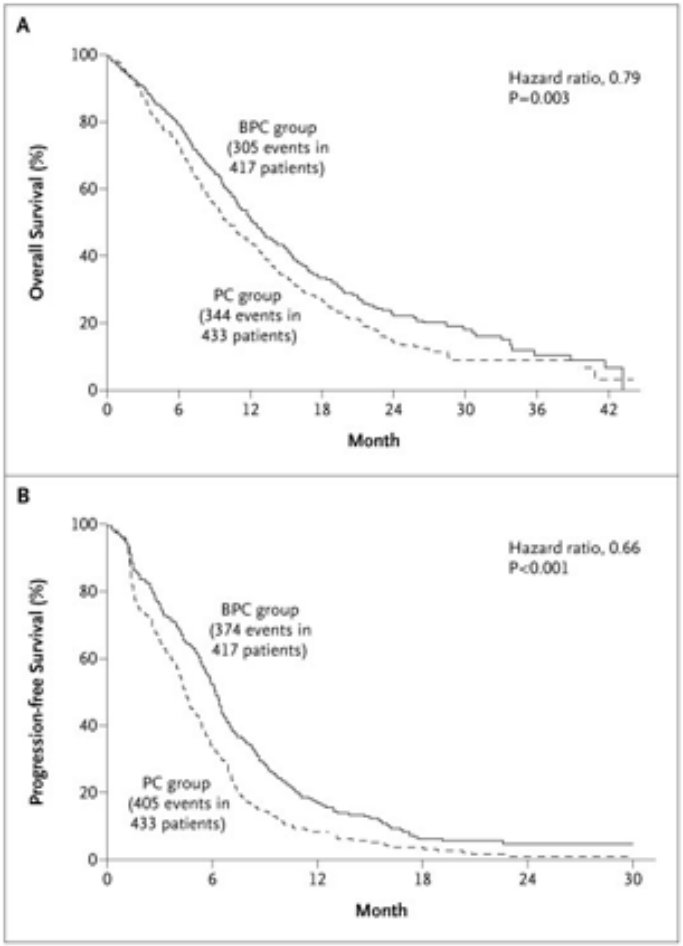
Components of progression

Reason to stop follow-up of target lesion measurements lly exclusive).

Reason	Breast cancer ($n = 1$	Lung cancer ($n = 1853$)	Colorectal cancer ($n = 734$)	Total ($n = 3728$)
Occurrence of a new lesion	507 (44%)	530 (29%)	309 (42%)	1346 (36%)
Non-target progressive disease	280 (25%)	505 (27%)	247 (34%)	1032 (28%)
Death	4 (0.4%)	1 (0.1%)	0	5 (0.1%)
Lost to follow-up[‡]	28 (2.5%)	8 (0.4%)	3 (0.4%)	39 (1.1%)
Progression of target lesions[§]	437 (38%)	961 (52%)	417 (57%)	1815 (49%)
End of follow-up[†]	320 (28%)	552 (30%)	197 (27%)	1069 (29%)

Litiere, EJC, 2014

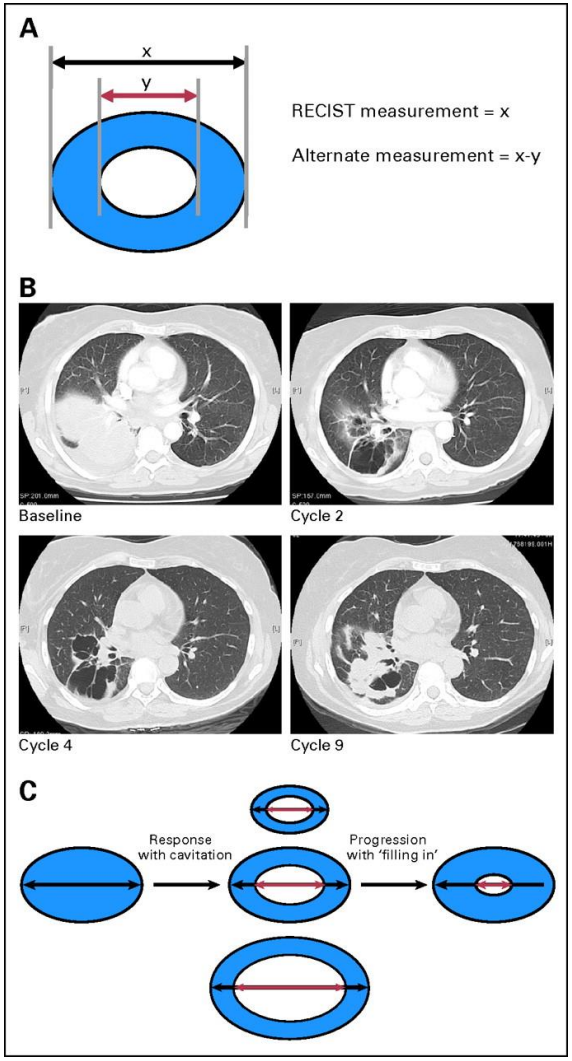
Carboplatin-paclitaxel-bevacizumab



Sandler, NEJM, 2006

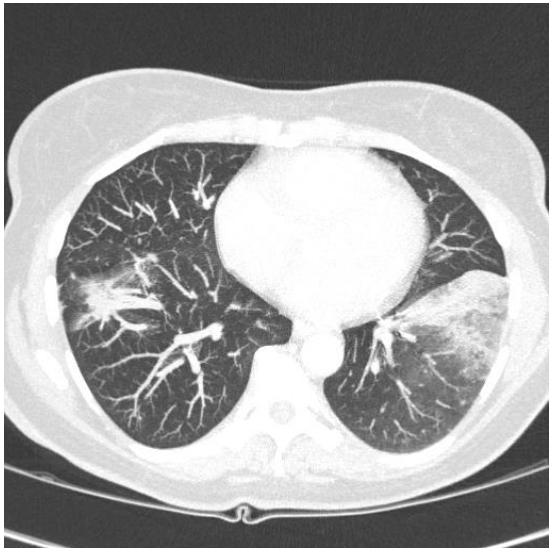
Carboplatin-paclitaxel-bevacizumab

target lesion measurement by Response Evaluation Criteria in Solid Tumors (RECIST) and alternate methods.



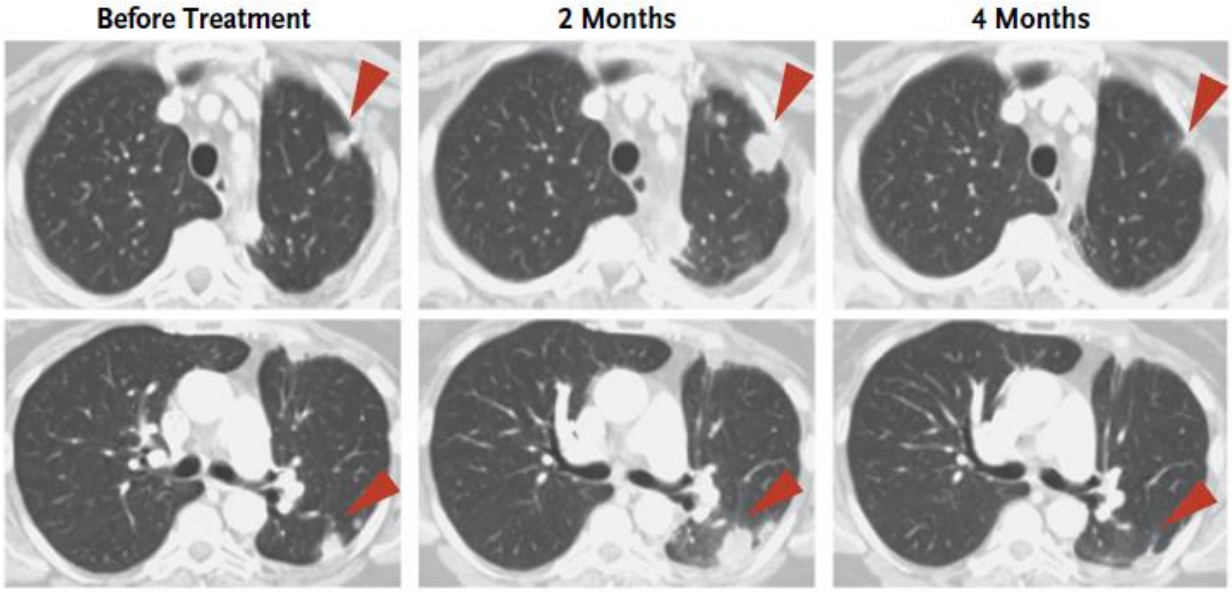
Crabb S J et al. JCO 2009;27:404-410

KRAS+ NSCLC, sorafenib-metformine



Immune related response

D Patient with Non–Small-Cell Lung Cancer

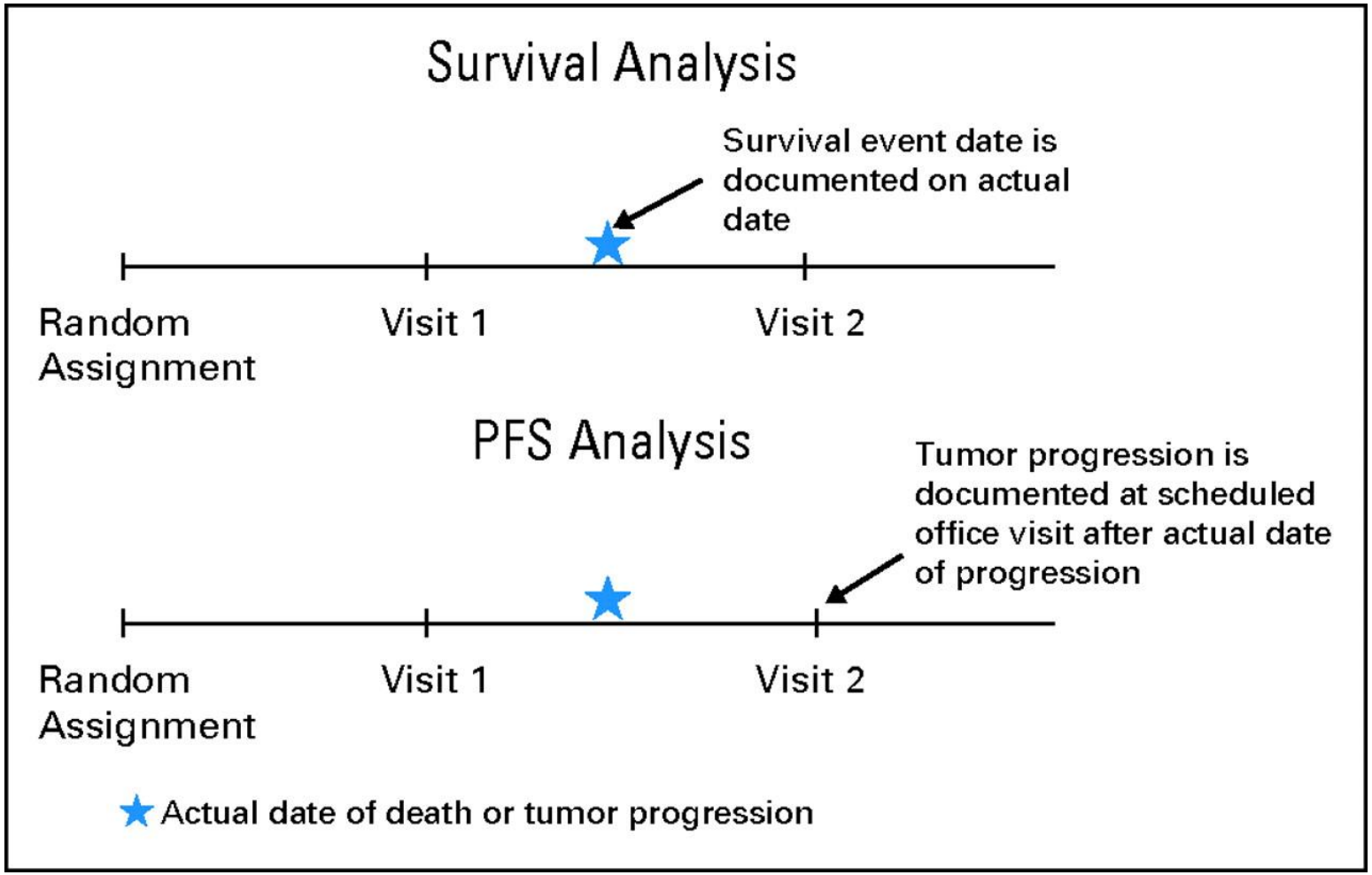


Topalian, NEJM 2012

Frequency of response assessment

RECIST 1.1: every 6-8 weeks

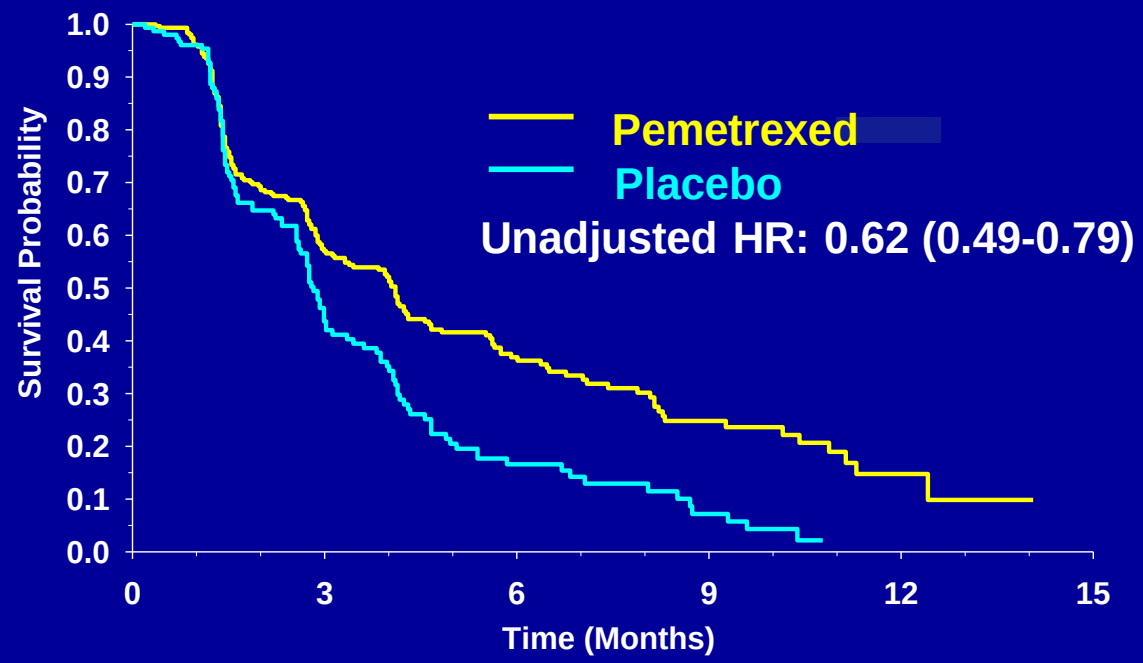
Soft versus hard endpoint



Bhattacharya, JCO 2009

40% of pts progressive 6 weeks after first line treatment

PFS: Primary Efficacy Endpoint



Patients at Risk

Pem + BSC	359	132	57	21	4	0
Plac+ BSC	180	52	15	5	0	0

Paz Ares, paramount

Median PFS ~ 6 months

REVEL

Time since previous therapy		
<9 months	400 (64%)	374 (60%)
≥9 months	226 (36%)	251 (40%)
Missing	2 (<1%)	0

INTEREST

Time from diagnosis to randomisation (months)		
<6	191 (26·1%)	201 (27·4%)
6–12	280 (38·2%)	274 (37·4%)
>12	260 (35·5%)	258 (35·2%)
Unknown	2 (0·3%)	0

Kim, Lancet, 2008; Garon Lancet 2014

Progression in daily practice

To achieve 'unequivocal progression' there must be an *overall* level of substantial worsening in non-target disease that is of a magnitude that, even in the presence of SD or PR in target disease, the treating physician would feel it important to change therapy. Examples of unequivocal progression are

1Eisenhauer, EJC 2009

Systemic treatment of metastatic NSCLC: How do we define progression and what is to be done?

Which patients should receive second and third line treatment?

Recommendation 16: second- or third-line therapy should be offered to patients with PS 0–1 who present with signs of disease progression (radiological and/or clinical) after first- or second-line therapy.

Strength of recommendation: A

Level of evidence: I

PARMAMOUNT discontinuation treatment

	Pemetrexed (N=359) %*	Placebo (N=180) %*
Patients Receiving Post Discontinuation Therapy	64	72
Erlotinib	40	43
Docetaxel†	32	43
Gemcitabine	10	8
Vinorelbine	8	6
Investigational drug	6	4
Carboplatin	5	4
Paclitaxel	3	3
Pemetrexed	2	4
Cisplatin	1	2

ESMO consensus guideline 2014

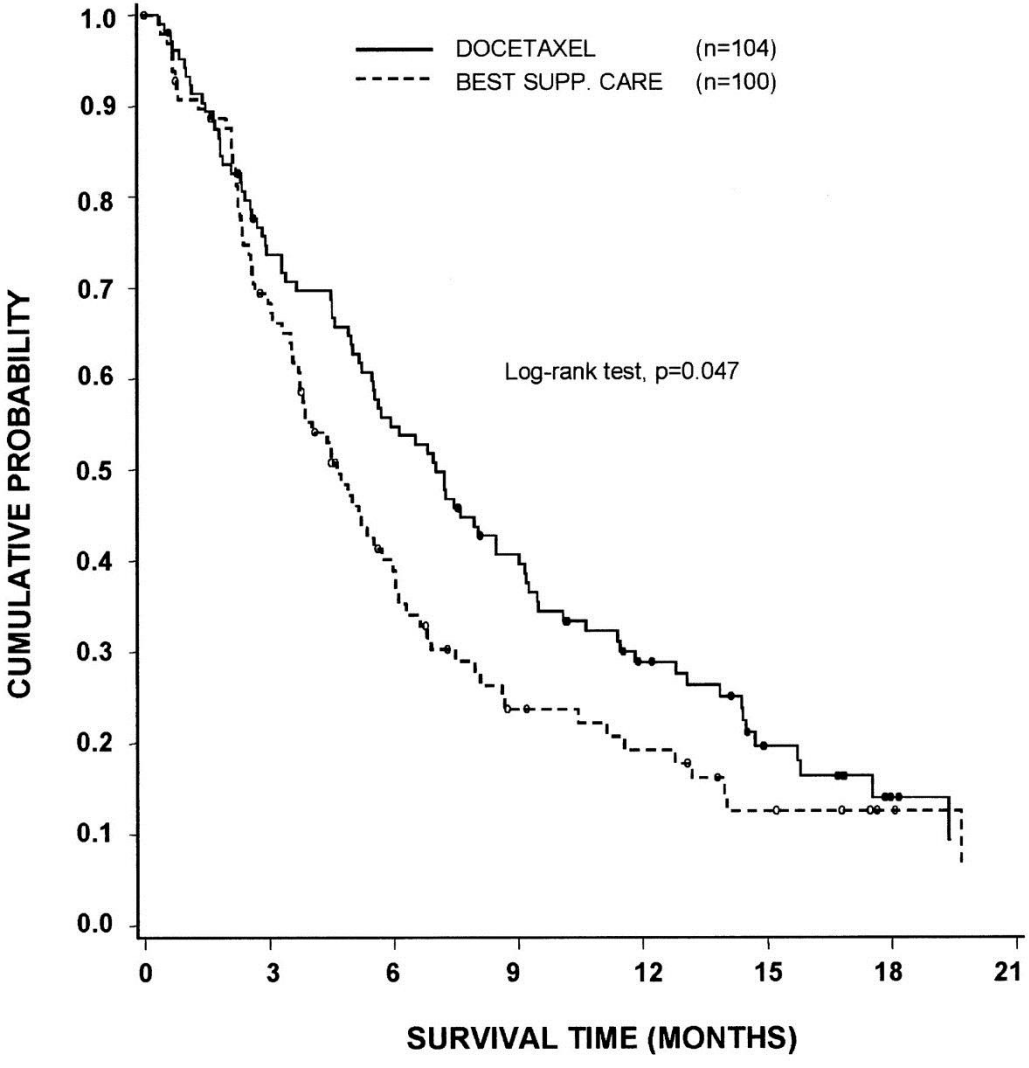
Recommendation 12: in advanced NSCLC patients treated with first-line cisplatin-doublet chemotherapy, there is no proven role for re-challenge with platinum compounds.
Strength of recommendation: D
Level of evidence: II

Annals Oncology, 2014

What kind of chemotherapy should be offered in second line?

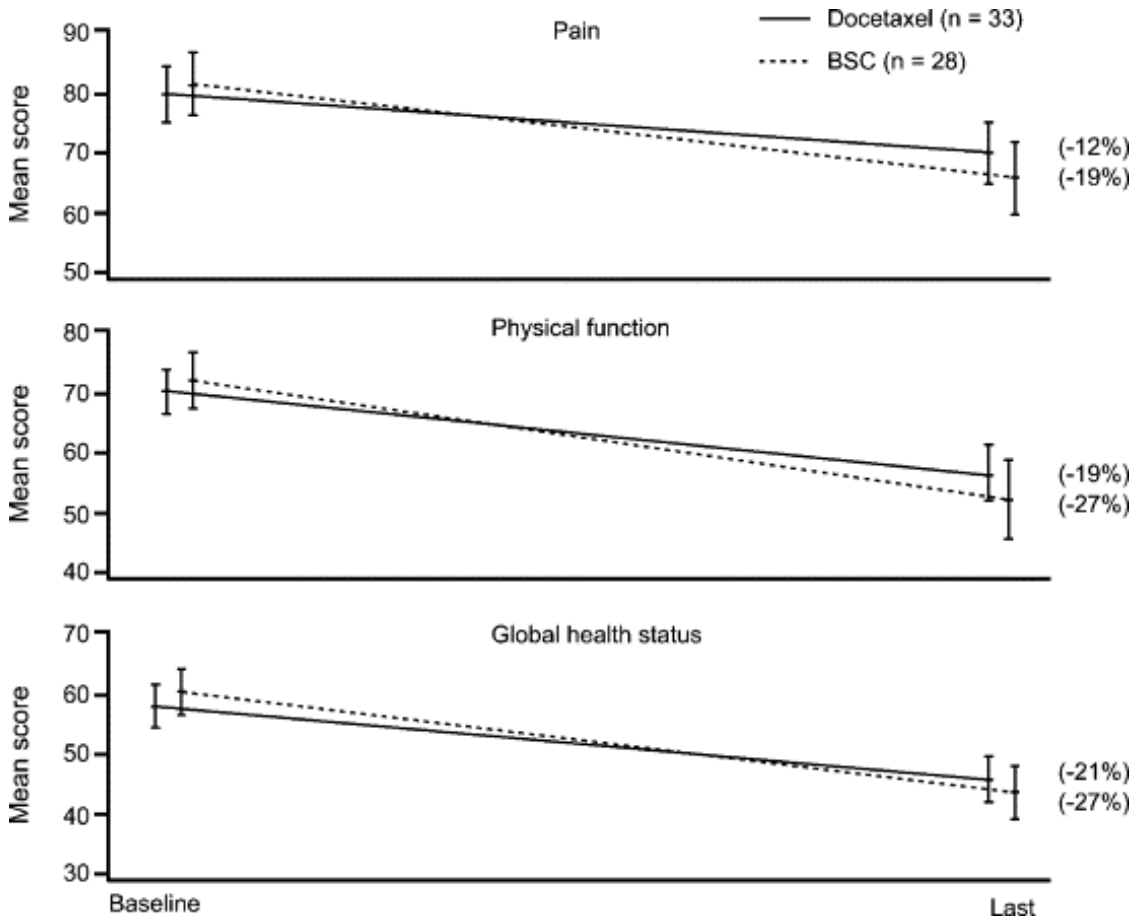
Recommendation 17: chemotherapy can be offered to patients who have a PS 0–1. Regardless of the WT status of the tumour a choice between docetaxel, pemetrexed or erlotinib can be made. For fit patients, chemotherapy may be more effective than erlotinib.
Strength of recommendation: B
Level of evidence: I

Docetaxel > BSC



Shepherd F A et al. JCO 2000;18:2095-2103

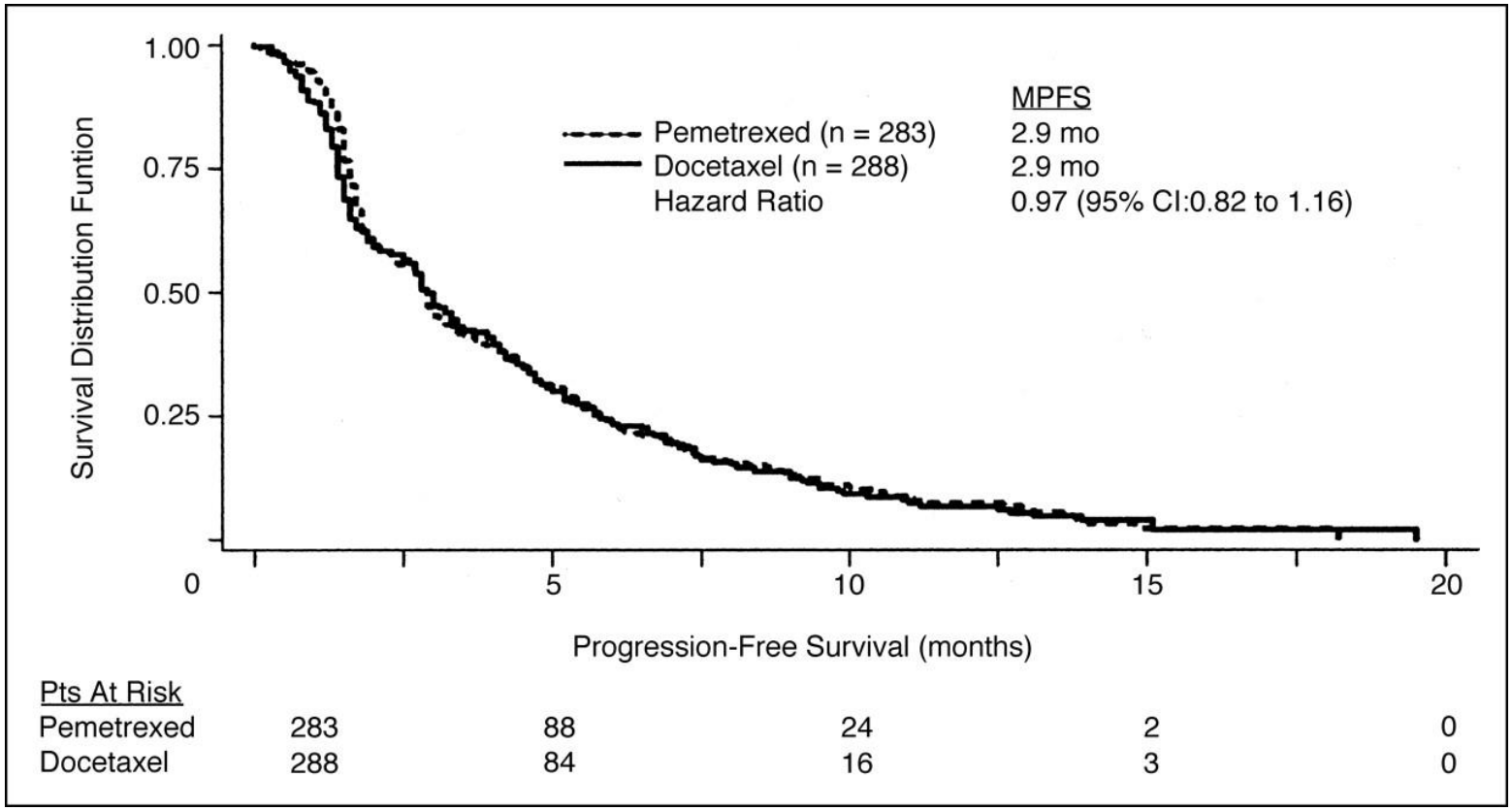
Quality of life assessment of second-line docetaxel versus best supportive care



Mean QLQ-C30 scores at baseline and at last assessment.

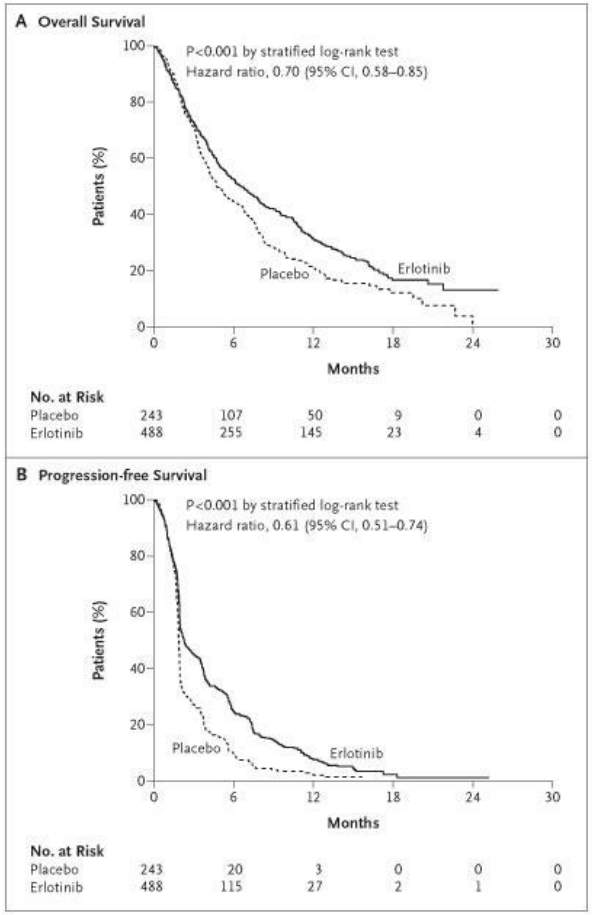
Dancey, Lung Cancer, Volume 43, Issue 2, 2004, 1

Pemetrexed = docetaxel



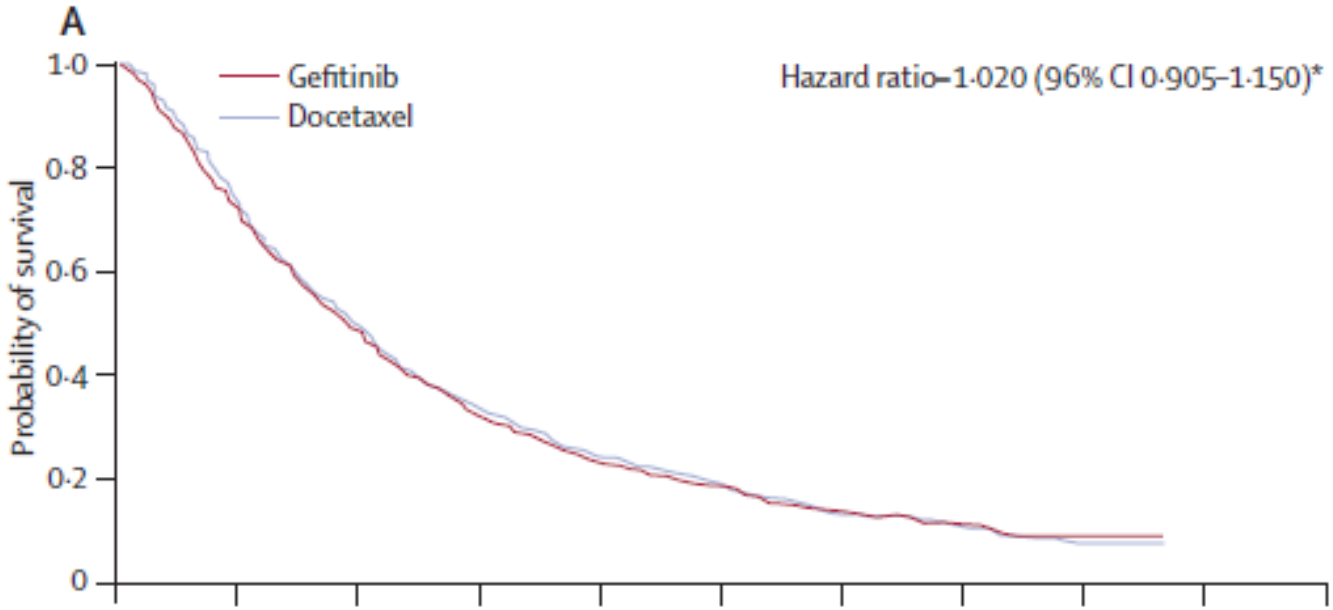
Hanna N et al. JCO 2004;22:1589-1597

ERLOTINIB > BSC



Shepherd FA et al. N Engl J Med 2005;353:123-132

Gefitinib = docetaxel

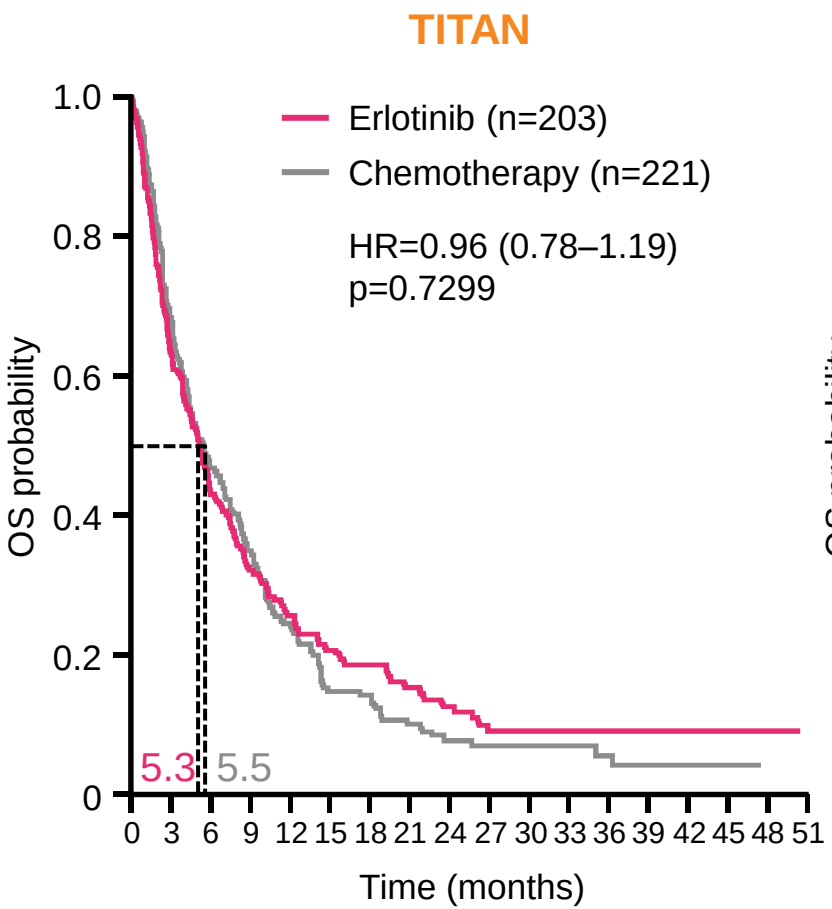


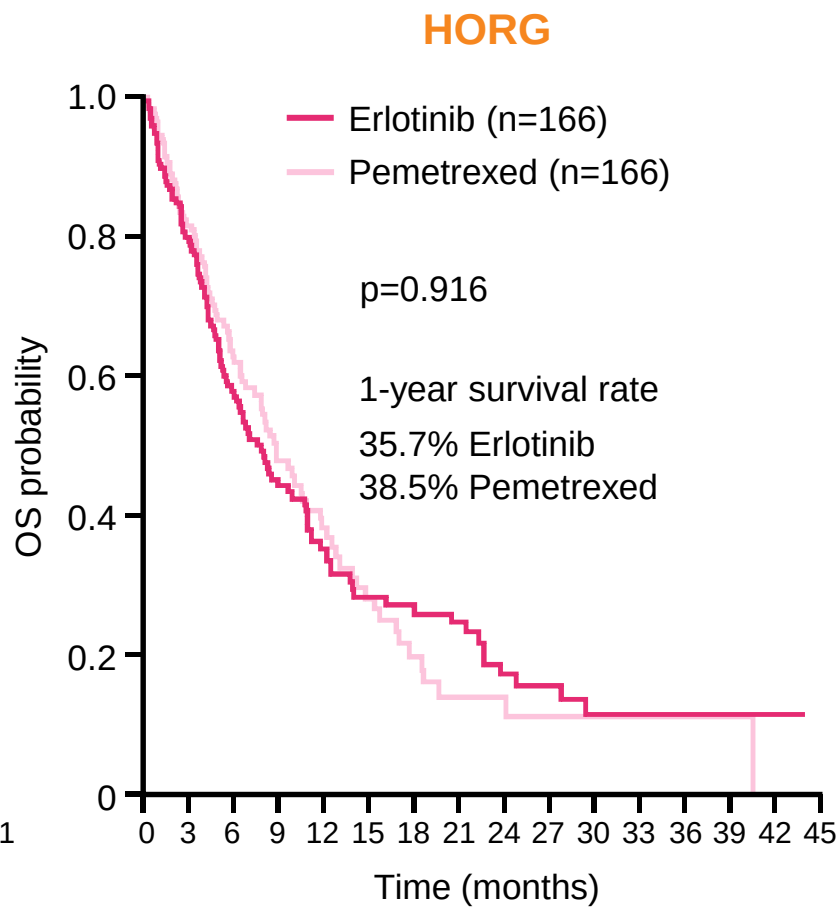
Number at risk

Gefitinib	723	518	336	225	131	83	50	31	14	0	0
Docetaxel	710	503	339	228	139	89	46	24	7	0	0

Kim, Lancet, 2008

Comparable second-line OS with erlotinib vs chemotherapy in overall populations





1. Ciuleanu, et al. Lancet Oncol 2012; 2. Vamvakas, et al. ASCO 2010

approved second line agents

Docetaxel

Erlotinib

Pemetrexed

Tailor: primary endpoint OS

TAILOR Study Design

- Advanced/recurrent
- Previous platinum based doublet
- EGFR wild-type
- KRAS determined
- ECOG PS 0-2

R → 1:1

DOCETAXEL
75 mg/m2 iv day 1,21 OR
35 mg/m2 iv day 1,8,15,28

ERLOTINIB
150 mg po, daily

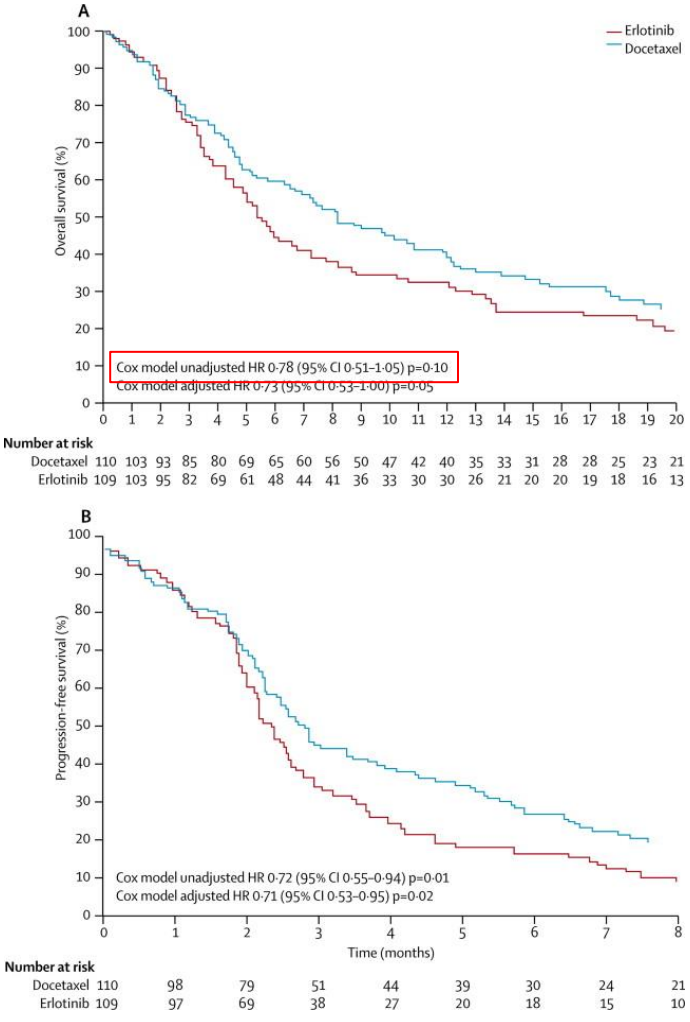
CROSS OVER NOT ALLOWED

STRATIFICATION
minimization approach
- centre
- recurrent/progressed
- type of prior chemotherapy regimen (pem vs gem vs vnb)
- ECOG-PS (0-1 vs 2)
- adequacy of tissue sample (optimal vs suboptimal)

TAILOR

ASCO Annual Meeting

Erlotinib vs Docetaxel in WT NSCLC



Garassino ,The Lancet Oncology, Volume 14, Issue 10, 2013, 981 - 988

approved second line agents

Docetaxel = comparator

Erlotinib = tailor?

Pemetrexed = first line option

Nintedanib

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

Martin Reck, Rolf Kaiser, Anders Mellemgaard, Jean-Yves Douillard, Sergey Orlov, Maciej Krzakowski, Joachim von Pawel, Maya Gottfried, Igor Bondarenko, Meilin Liao, Claudia-Nanette Gann, José Barrueco, Birgit Gaschler-Markefski, Silvia Novello, for the LUME-Lung 1 Study Group

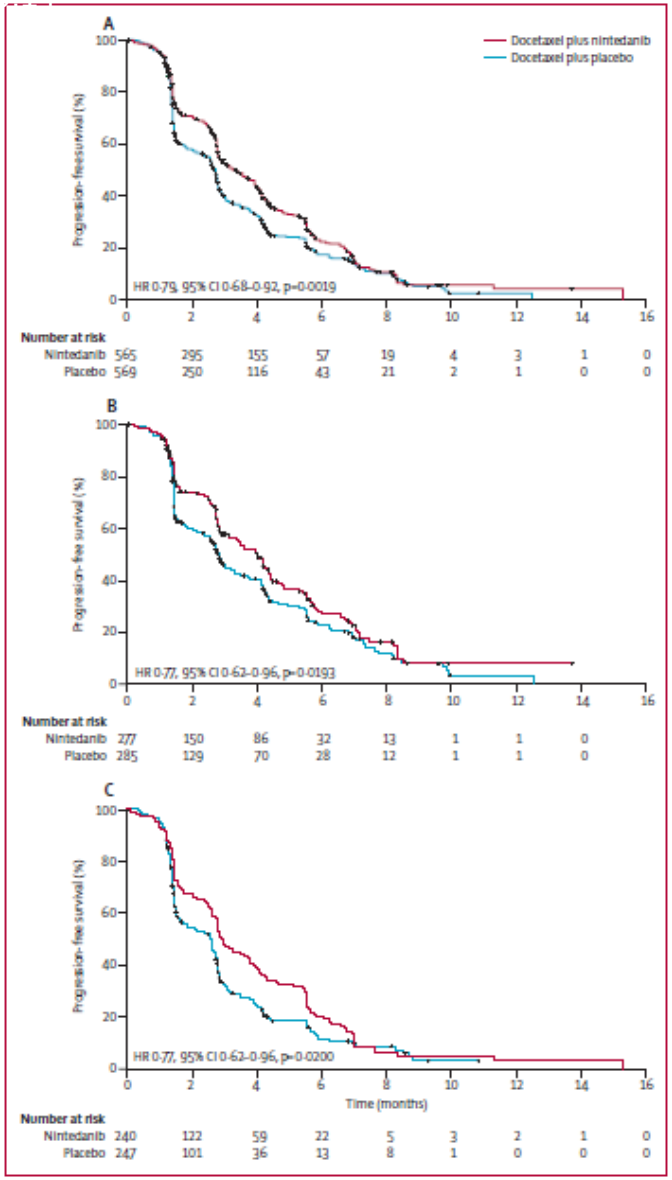


Figure 2: Kaplan-Meier curves for progression-free survival by central independent review at the time of primary analysis
(A) Total population. (B) Patients with adenocarcinoma histology. (C) Patients with squamous-cell carcinoma histology. Patients without documented disease progression or death were censored at the last tumour assessment. HR=hazard ratio.

REVEL: Study Design

- Stage IV NSCLC after one platinum-based chemo +/- maintenance
- Prior Bev allowed
- All histologies
- PS 0 or 1

1:1

RANDOMIZE

Ramucirumab 10 mg/kg + Docetaxel 75 mg/m² q3wks N=628

Placebo + Docetaxel 75 mg/m² q3wks N=625

Treatment until disease progression or unacceptable toxicity

Stratification factors:
- ECOG PS 0 *vs* 1
- Gender
- Prior maintenance
- East-Asia vs. ROW

Primary endpoint: **Overall Survival**

Secondary endpoints:
PFS, ORR, safety, patient-reported outcomes

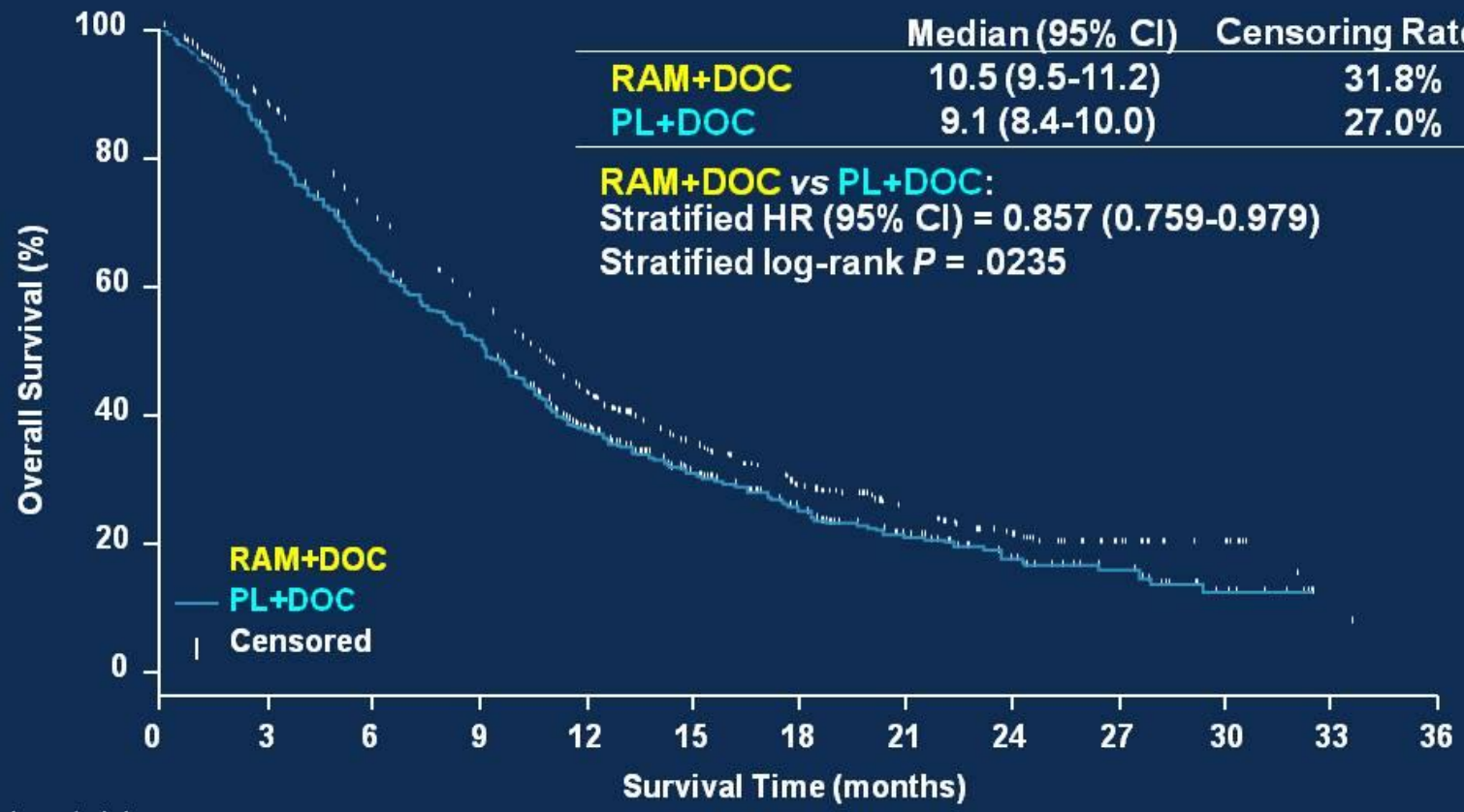
Abbreviations: Bev=bevacizumab; ECOG PS=Eastern Cooperative Oncology Group performance status; ORR=objective response rate; PFS=progression-free survival; ROW=rest of the world; q3wks=every 3 weeks.

Abstract 8006 Presented Maurice Perol

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Overall Survival

ITT Population



	Median (95% CI)	Censoring Rate
RAM+DOC	10.5 (9.5-11.2)	31.8%
PL+DOC	9.1 (8.4-10.0)	27.0%

RAM+DOC *vs* PL+DOC:
Stratified HR (95% CI) = 0.857 (0.759-0.979)
Stratified log-rank *P* = .0235

Number at risk

RAM+DOC	628	527	415	329	231	156	103	70	45	23	11	[illegible]
PL+DOC	625	501	386	306	197	129	86	56	36	23	9	[illegible]

Abstract 8006: Presented Maurice Perol

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Second line treatment

	endpoint	comparator	HR OS	HR PFS
Docetaxel	OS	placebo	7 mnts	10.6 wks
Erlotinib	OS	placebo	0.70	0.61
Nintedanib	PFS	docetaxel	0.94	0.79
Ramucirumab	OS	docetaxel	0.86	0.76

American Society of Clinical Oncology Perspective: Raising the Bar for Clinical Trials by Defining Clinically Meaningful Outcomes

Lee M. Ellis, David S. Bernstein, Emile E. Voest, Jordan D. Berlin, Daniel Sargent, Patricia Cortazar, Elizabeth Garrett-Mayer, Roy S. Herbst, Rogerio C. Lilenbaum, Camelia Sima, Alan P. Venook, Mithat Gonen, Richard L. Schilsky, Neal J. Meropol, and Lowell E. Schnipper

Table 1.

Summary of Recommended Targets for Meaningful Clinical Trial Goals

Cancer Type	Patient Population	Current Baseline Median OS (months)	Primary End Point		Secondary End Point	
			Improvement Over Current OS That Would Be Clinically Meaningful (months)	Target HRs	Improvement in 1-Year Survival Rate (%)*	Improvement in PFS (months)
Pancreatic cancer	FOLFIRINOX-eligible patients	10 to 11[19]	4 to 5	0.67 to 0.69	48 → 63	4 to 5
Pancreatic cancer	Gemcitabine or gemcitabine/nab-paclitaxel–eligible patients	8 to 9[20,21]	3 to 4	0.6 to 0.75	35 → 50	3 to 4
Lung cancer	Nonsquamous cell carcinoma	13[22]	3.25 to 4	0.76 to 0.8	53 → 61	4
Lung cancer	Squamous cell carcinoma	10[23]	2.5 to 3	0.77 to 0.8	44 → 53	3
Breast cancer	Metastatic triple negative, previously untreated for metastatic disease	18[24,25]	4.5 to 6	0.75 to 0.8	63 → 71	4
Colon cancer	Disease progression with all prior therapies (or not a candidate for standard second- or third-line options)	4 to 6[26]	3 to 5	0.67 to 0.67	25 → 35	3 to 5

JCO, 2014

Systemic treatment of metastatic NSCLC: How do we define progression and what is to be done?

Defining progression = important as 2th line treatment improves outcome

Defining progression = not simple in daily practice

“clinical progression”

New second line treatment options needed

Controversy

Parachute approach to evidence based medicine

Malcolm Potts, Ndola Prata, Julia Walsh, Amy Grossman

Waiting for the results of randomised trials of public health interventions can cost hundreds of lives, especially in poor countries with great need and potential to benefit. If the science is good, we should act before the trials are done

PHOTOS.COM

Sometimes it's best just to jump in

BMJ 2006