MADRID 2014 ESMO congress

Systemic treatment of metastatic NSCLC

Non-oncogenic addicted NSCLC patients: What is the best approach?

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Thoracic Oncology Unit

GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

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OUTLINE

Annals of Oncology

2nd ESMO Consensus Conference on Lung Cancer: non-small-cell lung cancer first-line/second and further lines of treatment in advanced disease

B. Besse[1*], A. Adjei[2], P. Baas[3], P. Meldgaard[4], M. Nicolson[5], L. Paz-Ares[6], M. Reck[7], E. F. Smit[8], K. Syrigos[9], R. Stahel[10], E. Felip[11], S. Peters[12] & Panel Members[†]

[1]Thoracic Group, Department of Cancer Medicine, Gustave Roussy, Villejuif, France; [2]Medicine Oncology, Roswell Park Cancer Institute, Buffalo, USA; [3]The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; [4]Aarhus University Hospital, Aarhus, Denmark; [5]Aberdeen Royal Infirmary Anchor Unit, Aberdeen, UK; [6]Hospital Universitario Virgen del Rocio, Sevilla, Spain; [7]Department of Thoracic Oncology, Krankenhaus Grosshansdorf, Grosshansdorf, Germany; [8]Department of Pulmonary Diseases, Vrije University Medical Centre (VUMC), Amsterdam, The Netherlands; [9]Oncology Unit, Third Department of Medicine, Athens Chest Hospital Sotiria, Athens, Greece; [10]Clinic of Oncology, University Hospital Zürich, Zürich, Switzerland; [11]Medical Oncology, Vall D'Hebron University Hospital, Barcelona, Spain; [12]Oncology Department, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland

Level of Evidence (LOE) scale

I	Evidence from at least one large randomized control trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, experts opinions

Strength of recommendation (SOR) scale

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs,..), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

OUTLINE -1

1st line: platinum based CT

- When to start?
- Cisplatin or carboplatin?
- A best doublet?
- How many cycles?
- For elderly patients?
- For PS2?
- Antiangiogenic ?

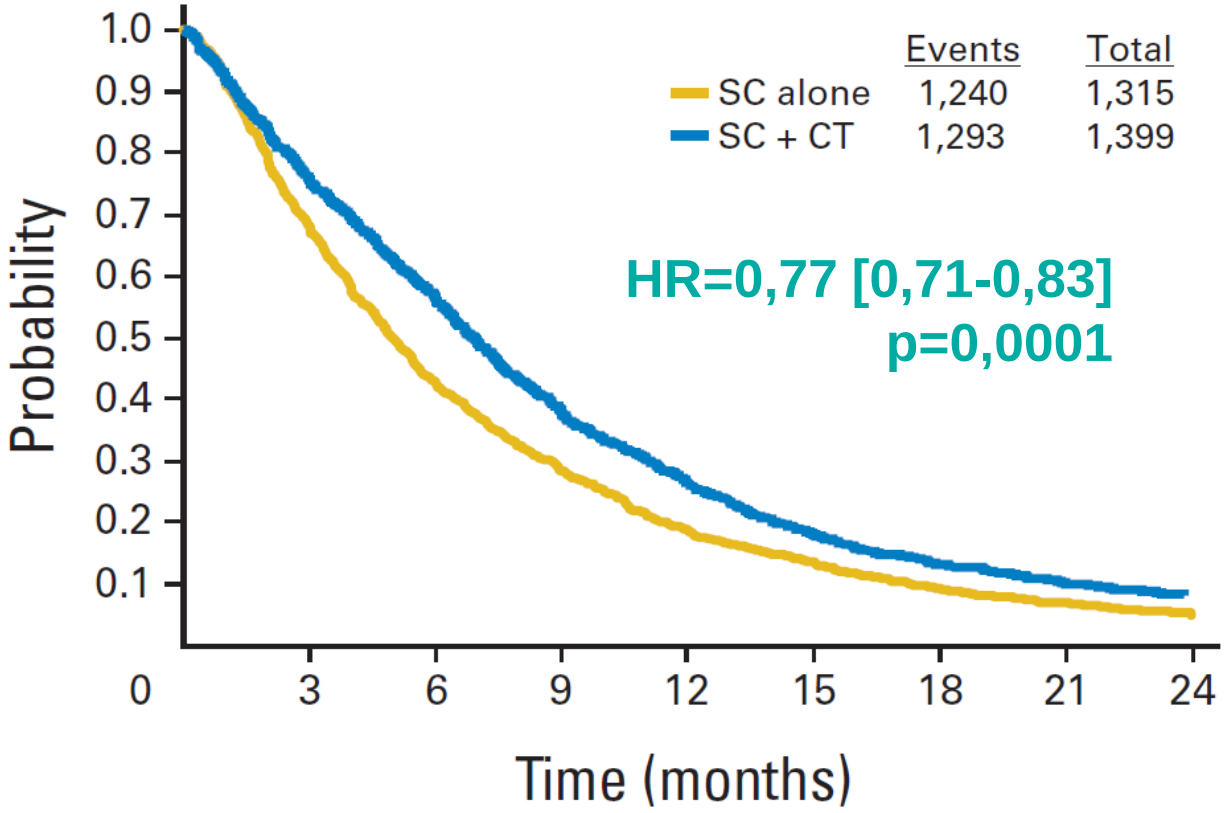
OUTLINE -2

Beyond 1st line

- Switch maintenance
- Continuation maintenance
- Which pts for 2nd/3rd line?
- Best 2nd/3rd line?
- Beyond second line?
- Re-challenge platinum?

Meta-analysis Chemo. vs BSC Overall Survival

- N=2714
- 16 trials
- 9 with platin.
- 1 yr absolute benefit : 9% (20% to 29%).



Patients at risk									
SC alone	1,315	884	552	363	231	161	107	77	55
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NSCLC Meta-Analyses Collaborative Group JCO 08

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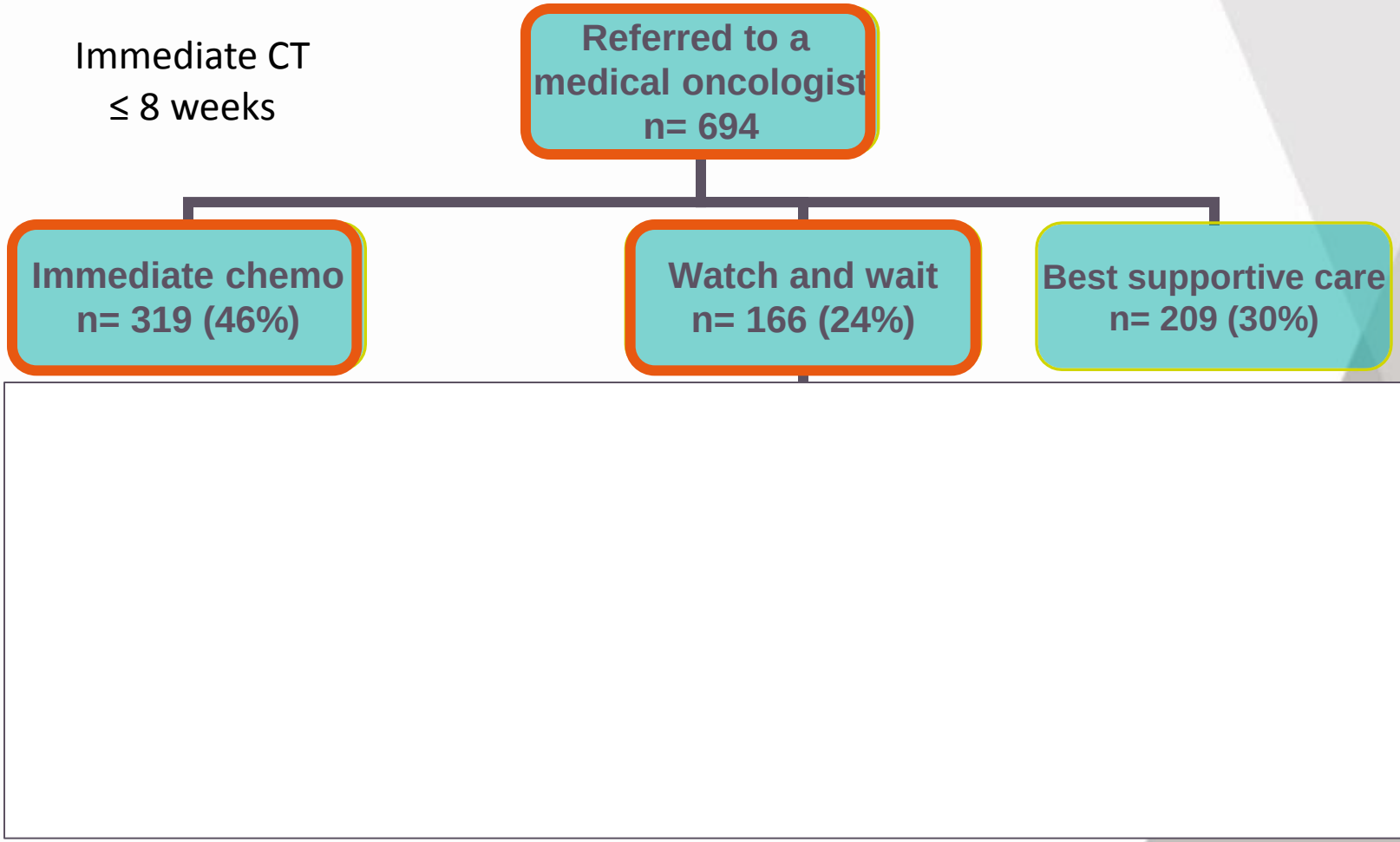
Retrospective analysis of the British Columbia Cancer Registry

Immediate CT
≤ 8 weeks



Noonan, WCLC 2013

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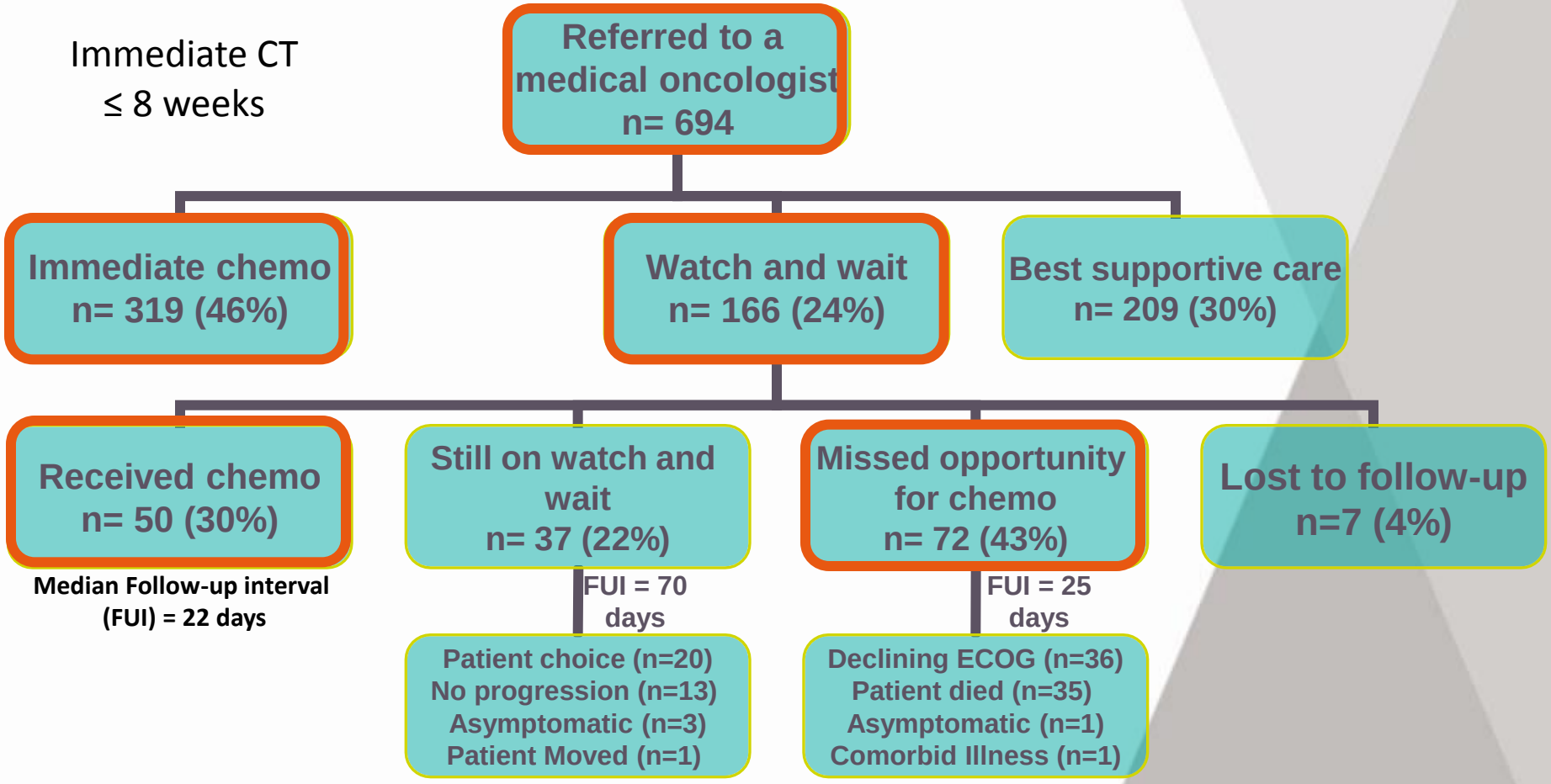
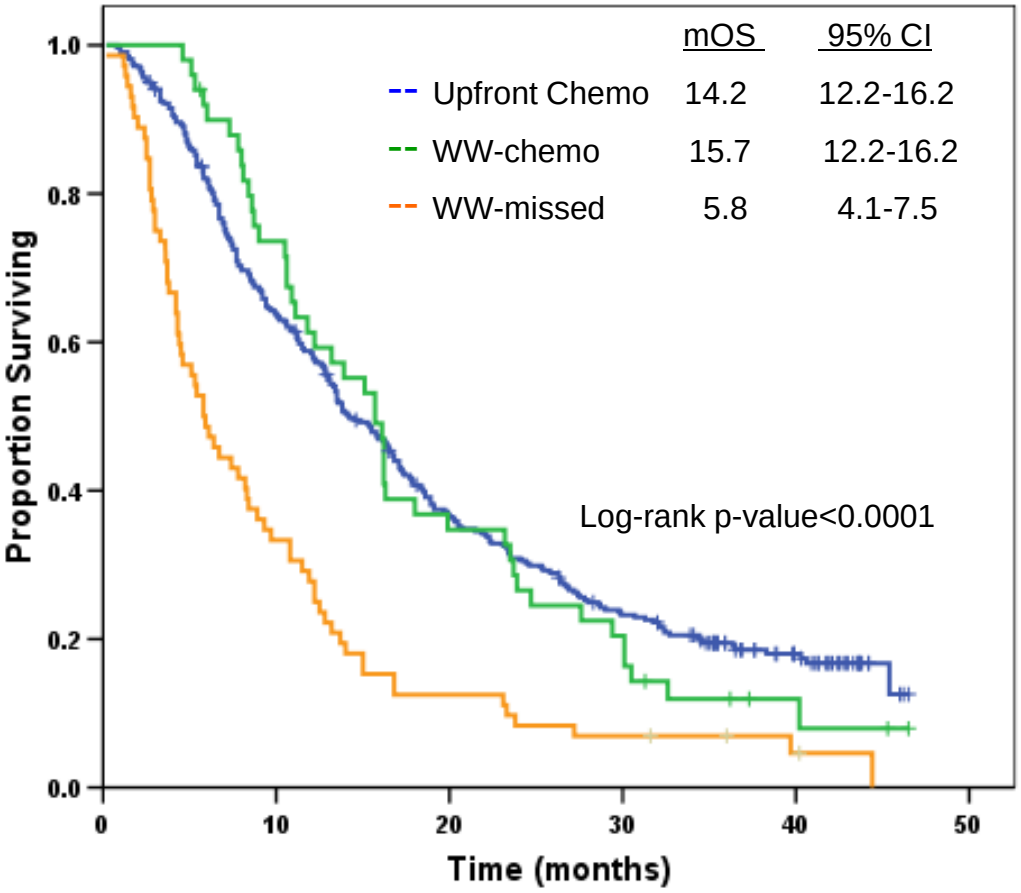


Noonan, WCLC 2013

Overall Survival of Upfront CT versus WW Populations



CPH Model Covariates:	Hazard Ratio for death (95% CI)	p-value
Sex (%)		
Male	1.00	
Female	0.86 (0.70-1.06)	0.16
Age	0.99 (0.98-1.00)	0.24
ECOG PS		
0-1	1.00	
2-4	1.40 (1.13-1.74)	0.002
Treatment		
Upfront CT	1.00	
WW-chemo	1.02 (0.74-1.40)	0.93
WW-missed	2.23 (1.69-2.94)	<0.0001

Noonan, WCLC 2013

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- Antiangiogenic ?

Recommendation:

The administration of first-line chemotherapy should be offered at diagnosis to asymptomatic patients with metastatic NSCLC. (B, III)

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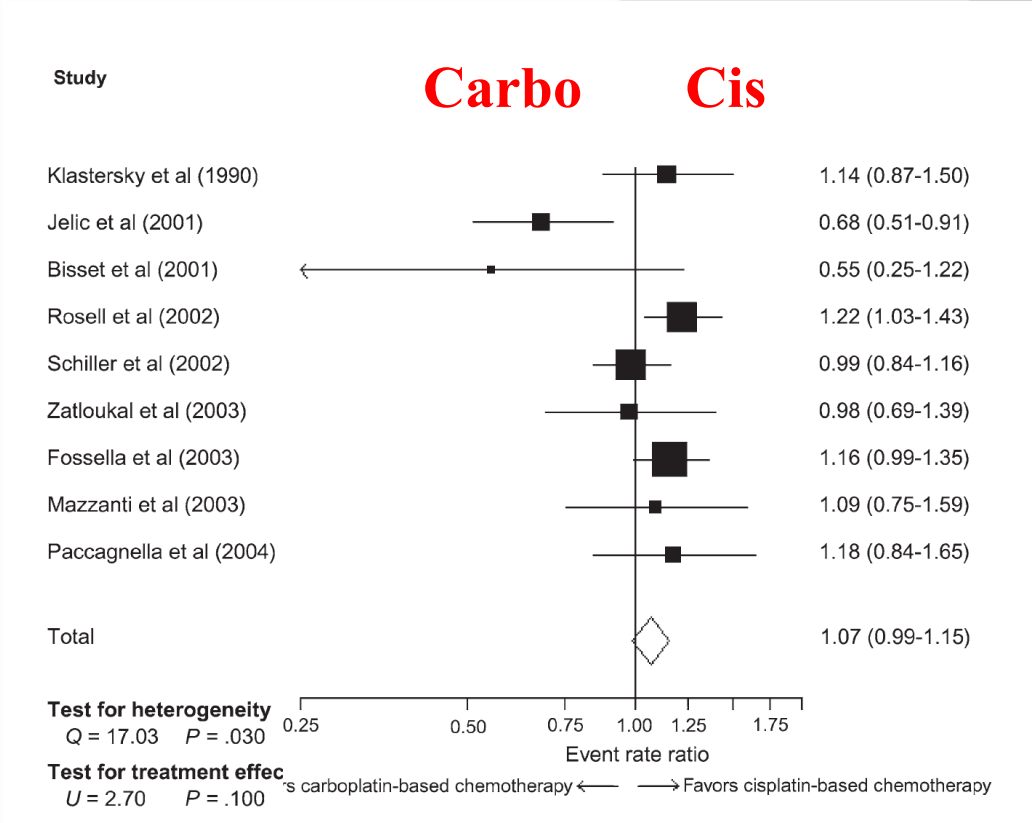
Cisplatin or carboplatin ?

CISCA

Response
CIS 30 %
CARBO 24%
OR = 1.37
IC 95% = 1.16-1.61
P <.001

Survival
HR = 1.07
IC 95% = 0.99 to 1.15
P = .100



Survival benefit for 3rd generation combo

Ardizzoni JNCI 2007

Cisplatin: dose

Regimen Dose (mg/m^2) and Administration Schedule [Reference]
Cisplatin/Vinorelbine 100 day 1/25 days 1, 8, 15, 22 every 4 weeks [Fossella 2003 (28)]
Cisplatin/Vinorelbine 80 day 8/30 days 1 and 8 [Georgoulias 2005 (79)]
Cisplatin/Paclitaxel 75 day 2/135 (24 hour) day 1 every 3 weeks [Schiller 2002 (55)]
Cisplatin/Docetaxel 75 day 1/75 day 1 every 3 weeks [Fossella 2003 (28)]
Cisplatin/Docetaxel 75 day 1/75 day 1 every 3 weeks [Schiller 2002 (55)]
Cisplatin/Gemcitabine 100 day 1/1000 days 1, 8, 15 every 4 weeks [Schiller 2002 (55)]

Goffin, JTO 2010

OUTLINE -1

1st line: platinum based CT

- When to start?
- Cisplatin or carboplatin?
- A best d
- How ma
- For elde
- For PS2
- Antiangi

Recommendations:

- Cisplatin should be used in fit patients with PS 0–1 who have adequate organ function. (B, I)

- Cisplatin at ≥ 75 mg/m² q3wks should be used with 3rd-generation drugs. (B, V)

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Platinum-based Doublets for NSCLC

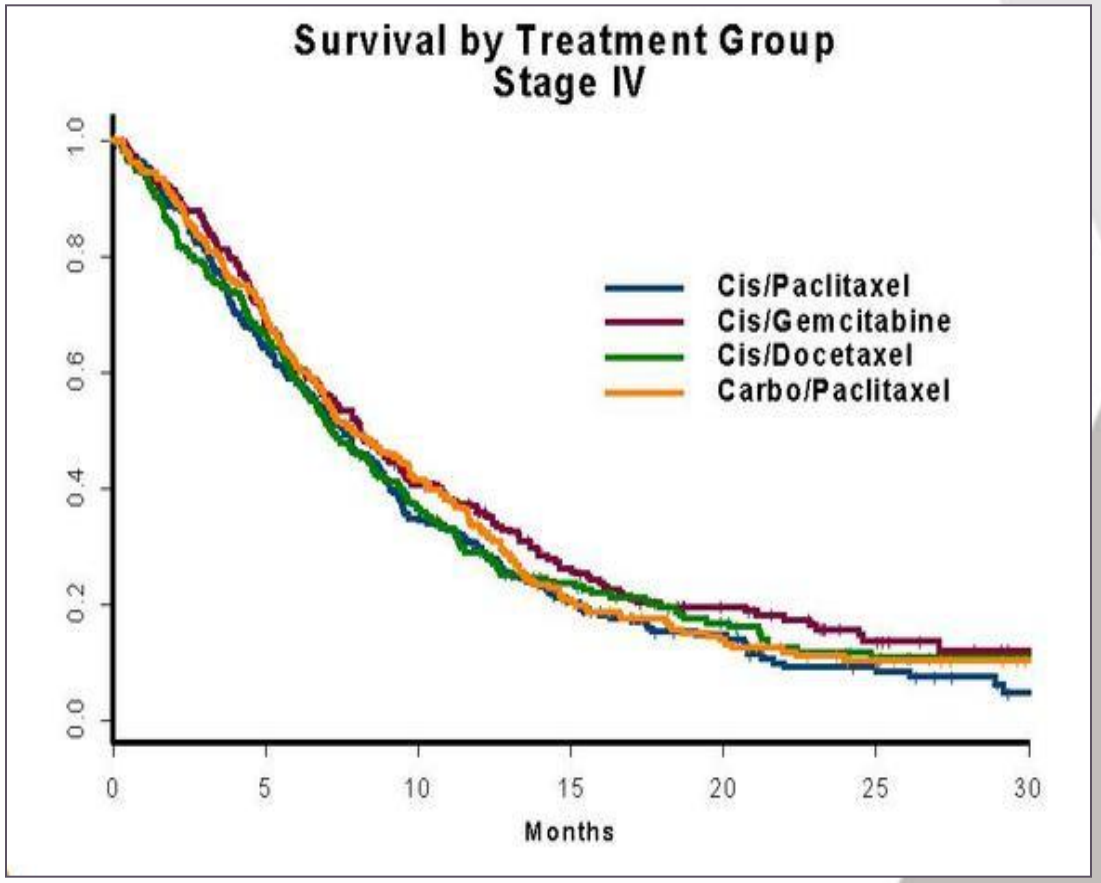
North American Experience (SWOG + ECOG)

	n	RO	MS (m)	S 1 an
SWOG				
Cisplatine + Vinorelbine	207	27%	8	33%
Paclitaxel + Carboplatine	201	27%	8	36%
ECOG				
Paclitaxel + Carboplatine	299	15%	8	34%
Gemcitabine + Cisplatine	301	21%	8	36%
Paclitaxel + Cisplatine	303	21%	8	31%
Docetaxel + Cisplatine	304	17%	7.5	31%

Kelly et al., JCO 01,; Schiller et. al., NEJM 02

Platinum-based Doublets for NSCLC

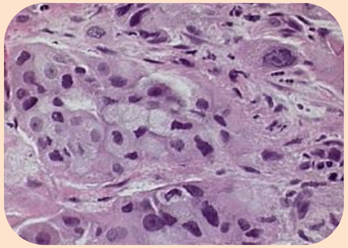
North American Experience (SWOG + ECOG)

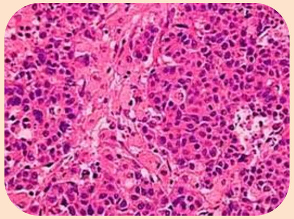


Schiller et. al., NEJM 02

Histological classification of NSCLC

	Classification		Characteristics[1]

Non-squamous[‡]	**Adenocarcinoma (AC) 30–50%***		• Malignant epithelial tumors with glandular differentiation
			• IASLC classification of invasive AC:[2]
			  • Lepidic, acinar, papillary, micropapillary, or solid pattern predominant
			  • Variants: invasive mucinous AC, colloid, fetal, and enteric

	Large cell carcinoma 10%*		• Involves large cells (subtypes are giant cell, clear cell) with large nuclei • No evidence of squamous or glandular differentiation

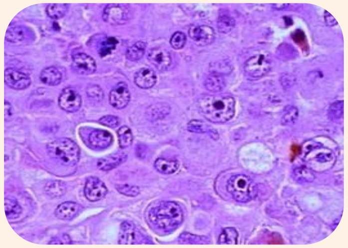
Squamous	**Squamous cell carcinoma 30%†**		• Involves cells of the squamous epithelium
			• Two variants of clinicopathologic significance[3]
			  • Papillary variant
			  • Basaloid variant

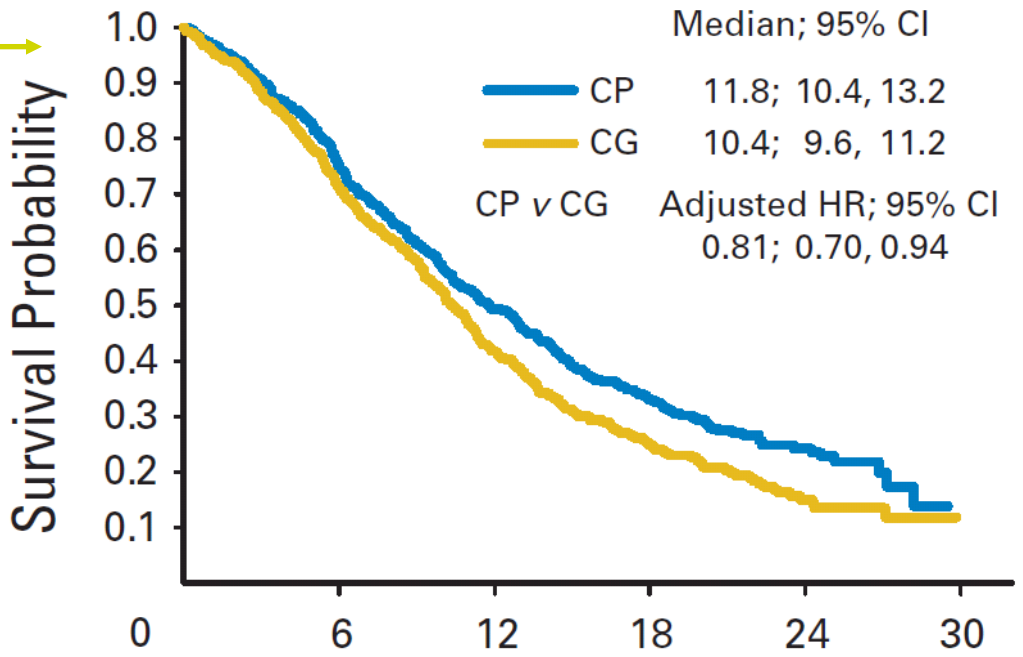
*Image from www.surgical-pathology.com; †Image from http://www.lmp.ualberta.ca/resources/pathoimages/PC-S.htm;
‡Other less common subtypes of non-squamous NSCLC include adenosquamous carcinoma and sarcomatoid carcinoma.[3]

1. Langer CJ, *et al. J Clin Oncol* 2010;28:5311–5320; 2. Travis WD, *et al. J Thorac Oncol* 2011;4:244–285; 3. WHO 2004.

Pemetrexed vs gemcitabine (+CDDP)

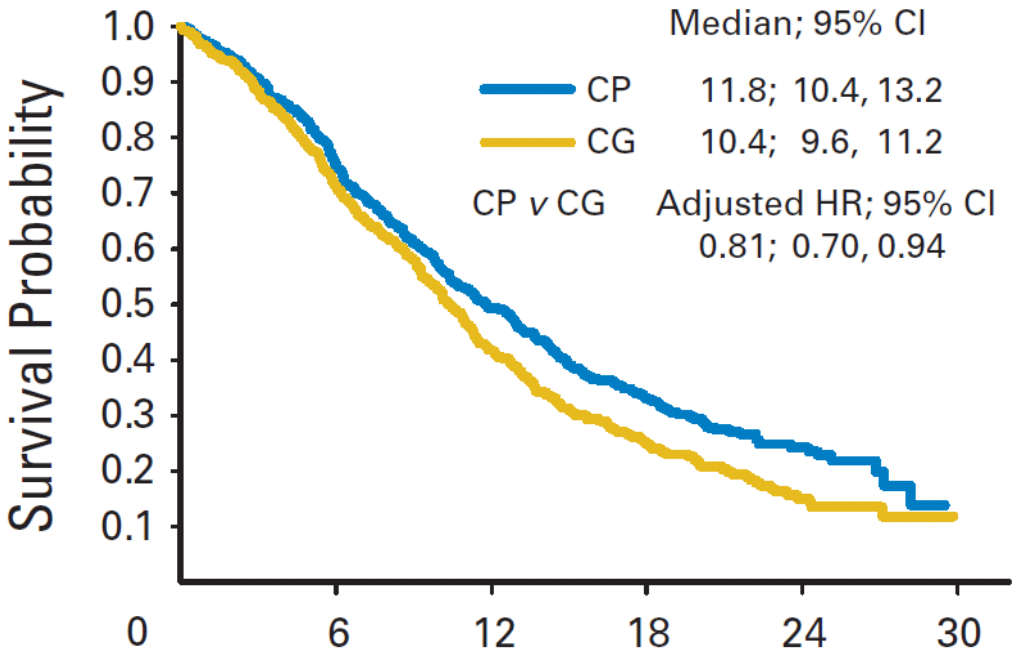
- **Pemetrexed** **500 mg/m²** **j 1**
- **Cisplatin** **75 mg/m²** **j 1**

- **Adenocarcinoma + LCC → pemetrexed better**
- **SCC → Gemcitabine better**



Scagliotti JCO 2008

Pemetrexed vs gemcitabine (+CDDP)



Only 13.4% pts crossed over to pemetrexed!

- **Post-treatment**
- **56.1% of gem/cis**
  - Pem 13.4%
  - Gem 8.6%
  - Docetaxel 27.6%
  - EGFR TKI 22.5%
- **52.6% of pem/cis**
  - Pem 3.5%
  - Gem 16.7%
  - Docetaxel 25.4%
  - EGFR TKI 24.9%

OUTLINE -1

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- A best doublet?
- How many cycles?
- For elderly patients?
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- Antiangiogenic ?

Recommendation:

There is no single platinum-based doublet standard chemotherapy. Pemetrexed-based doublets are restricted to non-squamous NSCLC. (A, I)

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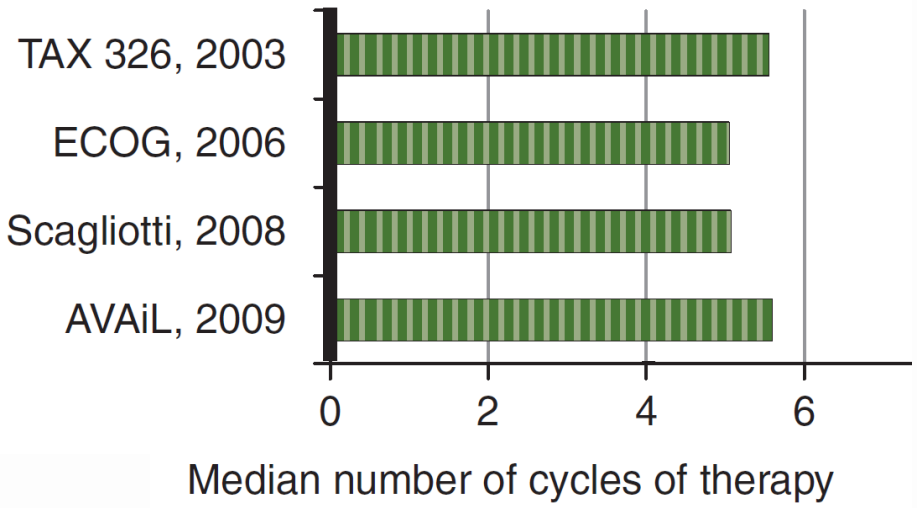
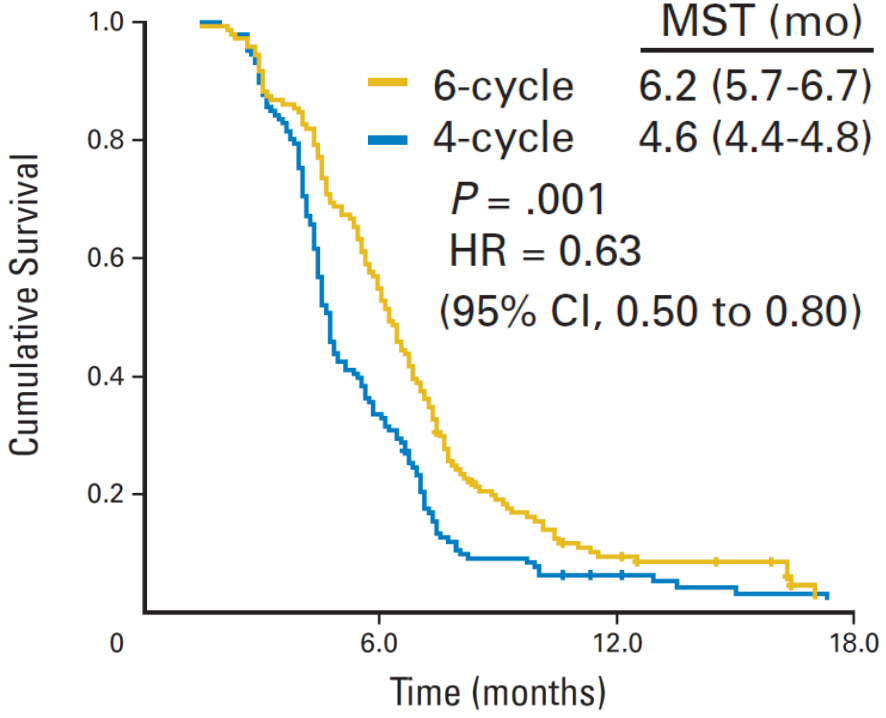
Optimal duration of chemotherapy

First line registration trials



Docetaxel ; TAX 326
Bevacizumab ; ECOG, AVAIL
Pemetrexed ; Scagliotti

PFS: 4 vs 6 cycles of cisplatin-based CT

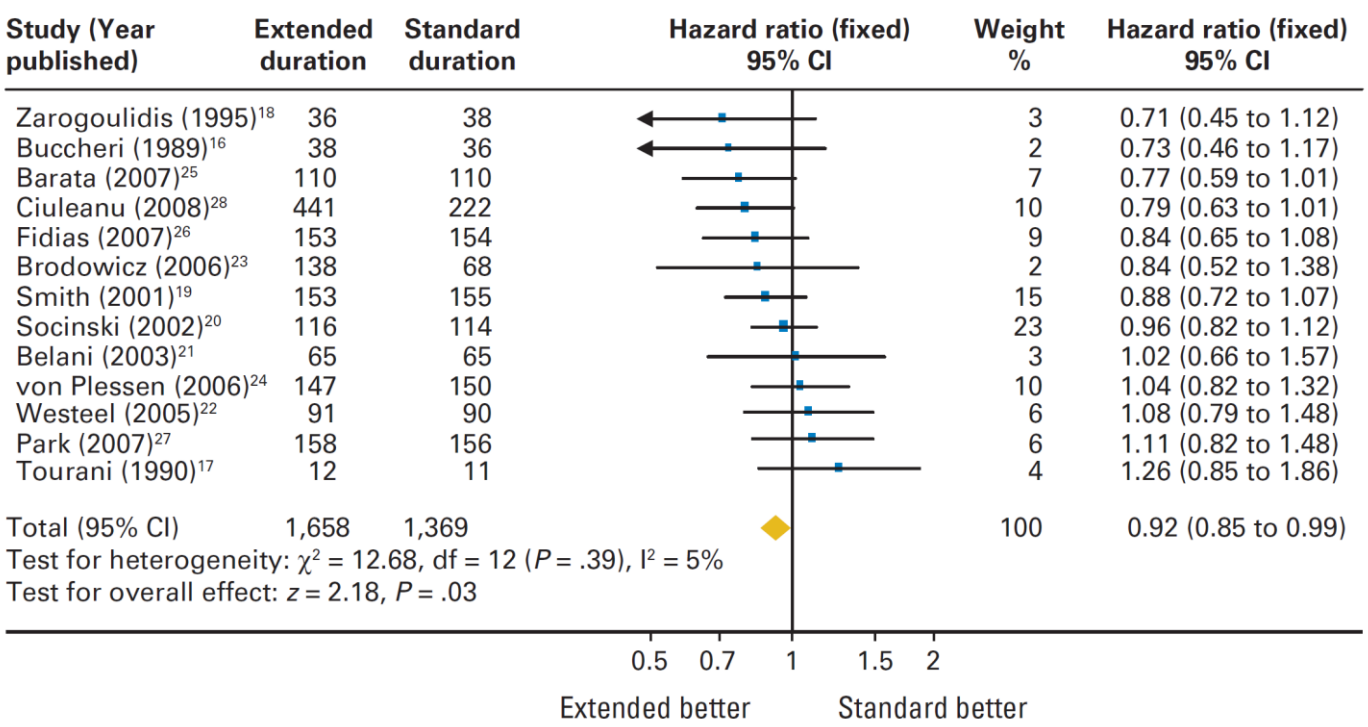


Non progressive Patients after 2 cycles

Polo, Ann Oncol 13 - Park *et al* JCO 07

3-4 cycles vs. More

Overall survival



Study (Year published)	Extended duration	Standard duration	Weight %	Hazard ratio (fixed) 95% CI
Zarogoulidis (1995)[18]	36	38	3	0.71 (0.45 to 1.12)
Buccheri (1989)[16]	38	36	2	0.73 (0.46 to 1.17)
Barata (2007)[25]	110	110	7	0.77 (0.59 to 1.01)
Ciuleanu (2008)[28]	441	222	10	0.79 (0.63 to 1.01)
Fidias (2007)[26]	153	154	9	0.84 (0.65 to 1.08)
Brodowicz (2006)[23]	138	68	2	0.84 (0.52 to 1.38)
Smith (2001)[19]	153	155	15	0.88 (0.72 to 1.07)
Socinski (2002)[20]	116	114	23	0.96 (0.82 to 1.12)
Belani (2003)[21]	65	65	3	1.02 (0.66 to 1.57)
von Plessen (2006)[24]	147	150	10	1.04 (0.82 to 1.32)
Westeel (2005)[22]	91	90	6	1.08 (0.79 to 1.48)
Park (2007)[27]	158	156	6	1.11 (0.82 to 1.48)
Tourani (1990)[17]	12	11	4	1.26 (0.85 to 1.86)
Total (95% CI)	1,658	1,369	100	0.92 (0.85 to 0.99)

Test for heterogeneity: $\chi^2 = 12.68$, df = 12 ($P = .39$), $I^2 = 5\%$

Test for overall effect: $z = 2.18$, $P = .03$

PFS; HR = 0.75; 95% CI, 0.69 to 0.81; *P* =0.00001

OS ; HR = 0.92; 95% CI, 0.86 to 0.99; *P* =0.03).

OS 3r generation vs old; (HR=0.70 interaction *v* 0.92 interaction; *P* =0.003).

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Recommendation:

- 4 cycles of chemotherapy is standard. (A, I)

- Continuation of a doublet regimen beyond 4 cycles may be considered in selected, non progressing pts (C, I)

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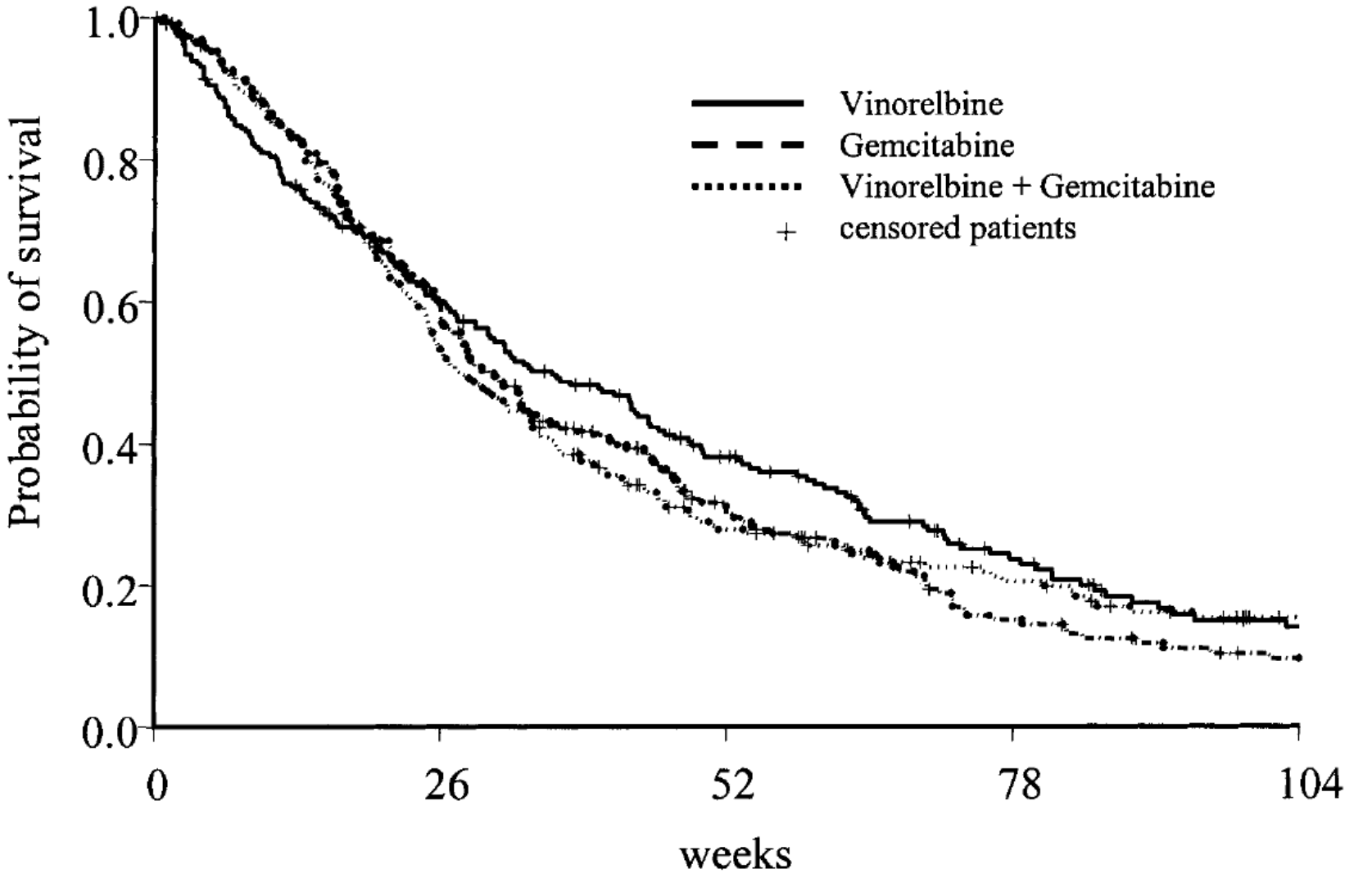
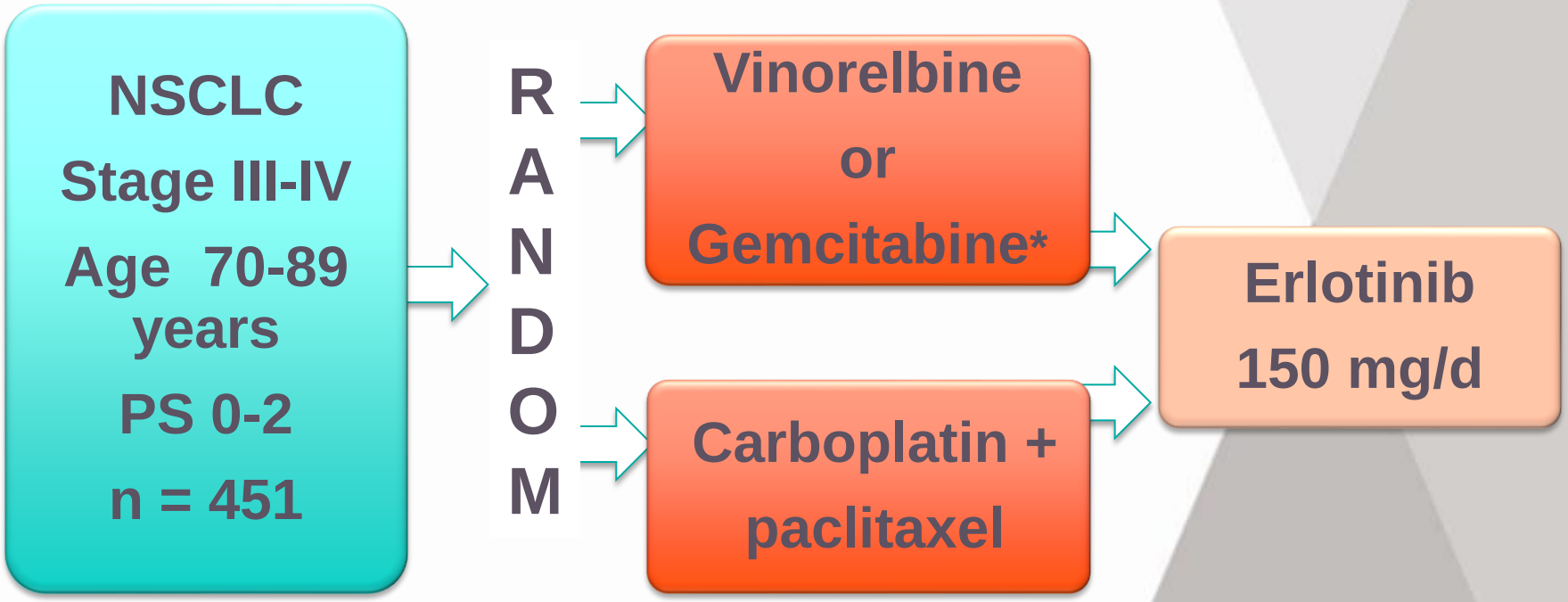
Miles Study: Results



Gridelli J Natl Cancer Inst. 2003

Weekly paclitaxel combined with monthly carboplatin versus single agent therapy in patients aged 70 to 89 : IFCT-0501



Phase III study
Stratification by centre, PS 0-1 vs. 2, age ≤80 vs. >80 and stage III vs. IV

*Choice of the center at the beginning of the study

Quoix, ASCO 2010

First-line Treatment

ARM A	V	V		V	V		V	V		V	V		V	V				
	G	G		G	G		G	G		G	G		G	G				
WEEKS	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
ARM B	CP	P	P		CP	P	P		CP	P	P		CP	P	P			
EVALUATION						■						■						■

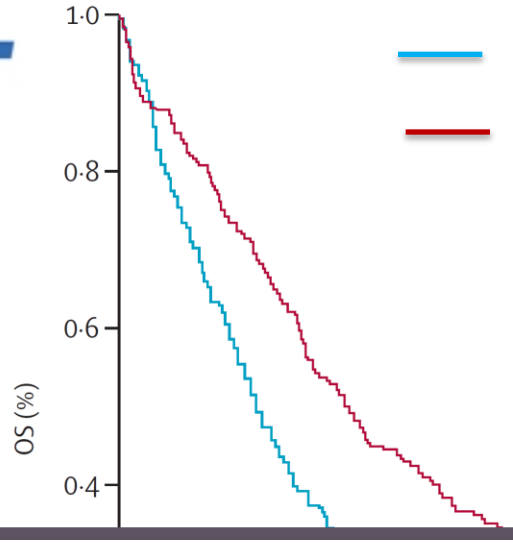
IFCT

V : Vinorelbine : 30 mg/m^2
G : Gemcitabine : 1150 mg/m^2
C : Carboplatin : AUC 6
P : Paclitaxel : 90 mg/m^2

} Choice of the center

Quoix, ASCO 2010

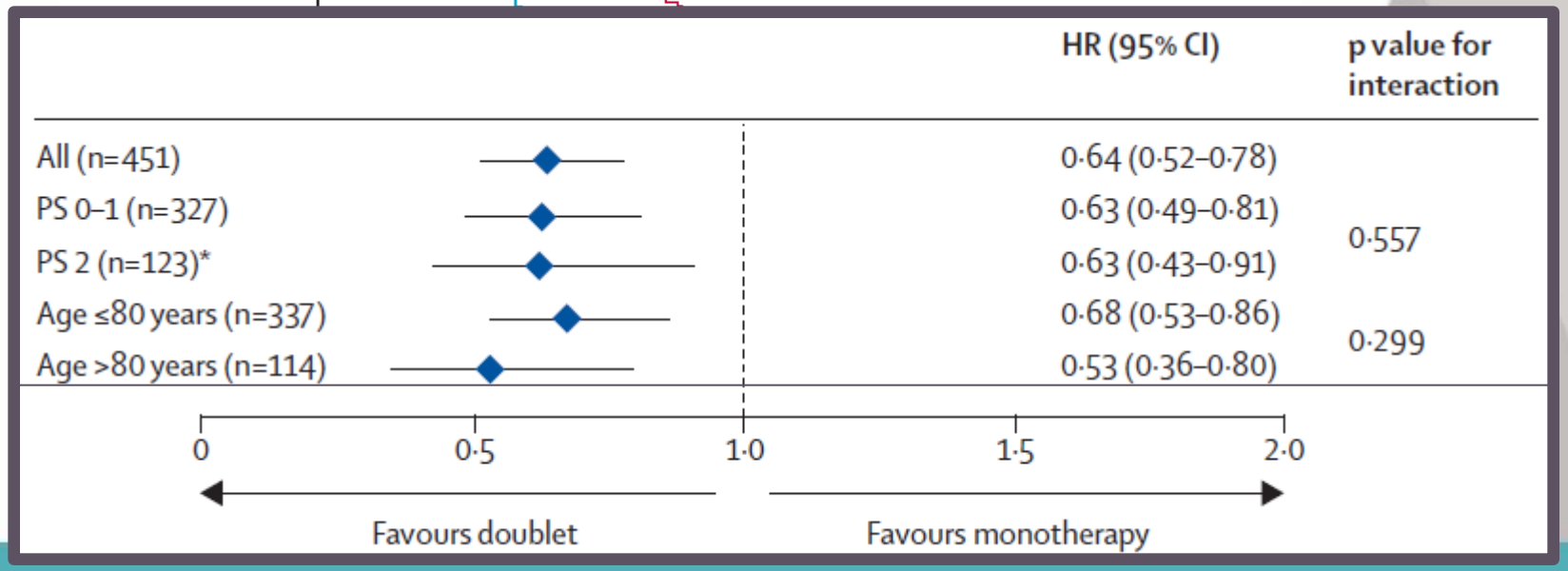
Overall survival (Primary Objective)



MST = 10.3 months (95% CI 8.3-12.6)

MST = 6.2 months (95% CI 5.3-7.3)

HR= 0.64 (0.52-0.78); p= 0.00004



Quoix, The Lancet 2011

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Recommendation:

- Platinum-based chemotherapy is preferred in fit elderly patients with PS 0–1 and adequate organ function.

- Single-agent third-generation drugs are preferred in unfit elderly patients. (B, I)

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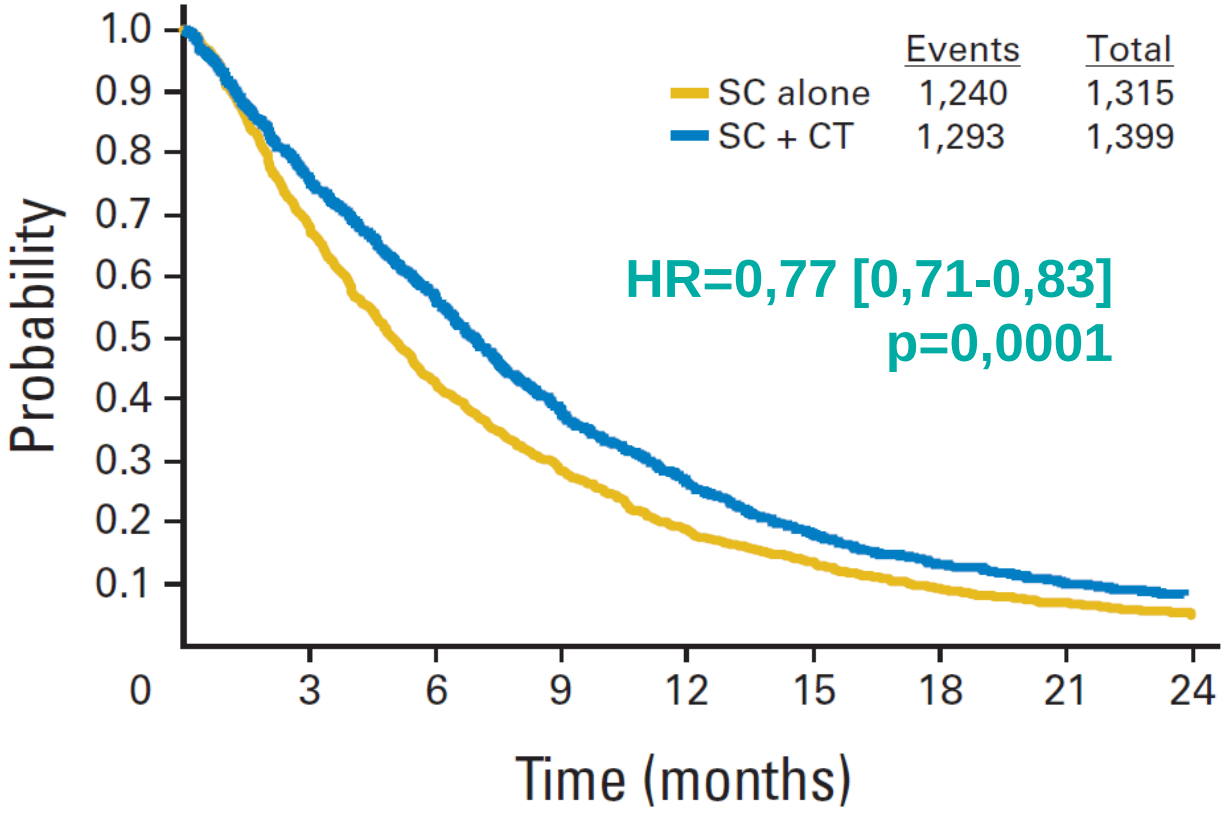

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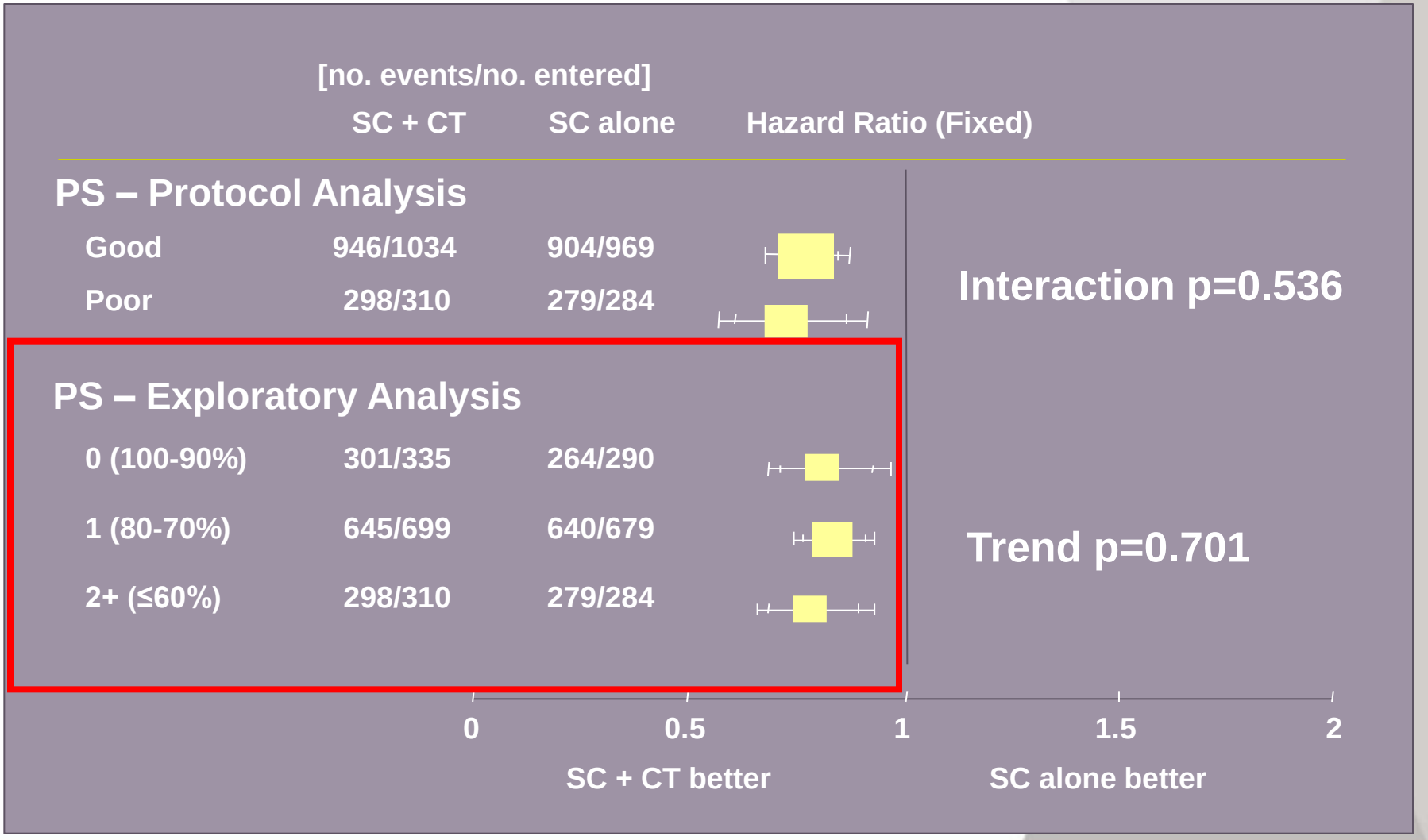
NSCLC Meta-Analyses Collaborative Group JCO 08

Survival by Patient Subgroup

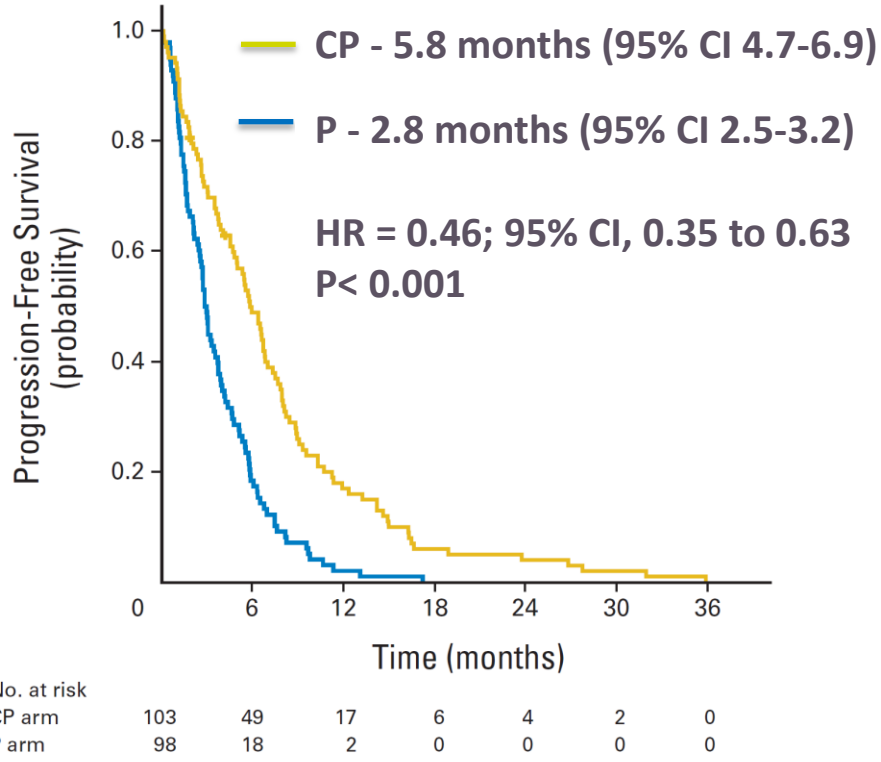


NSCLC Meta-Analyses Collaborative Group JCO 08

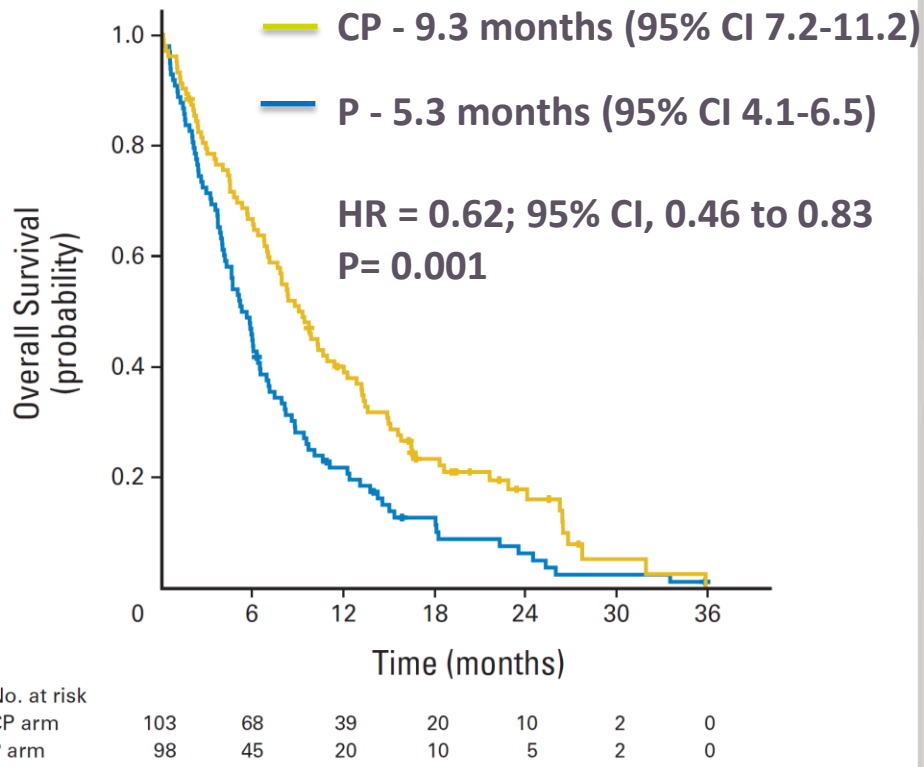
Pemetrexed vs. Pemetrexed-carboplatin in PS2 pts

MADRID 2014 ESMO congress

PFS



OS (Primary endpoint)



4 cycles, n=201

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Recommendation:

Platin-based combinations are preferred over single-agent chemotherapy. (B, I)

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- How many cycles?
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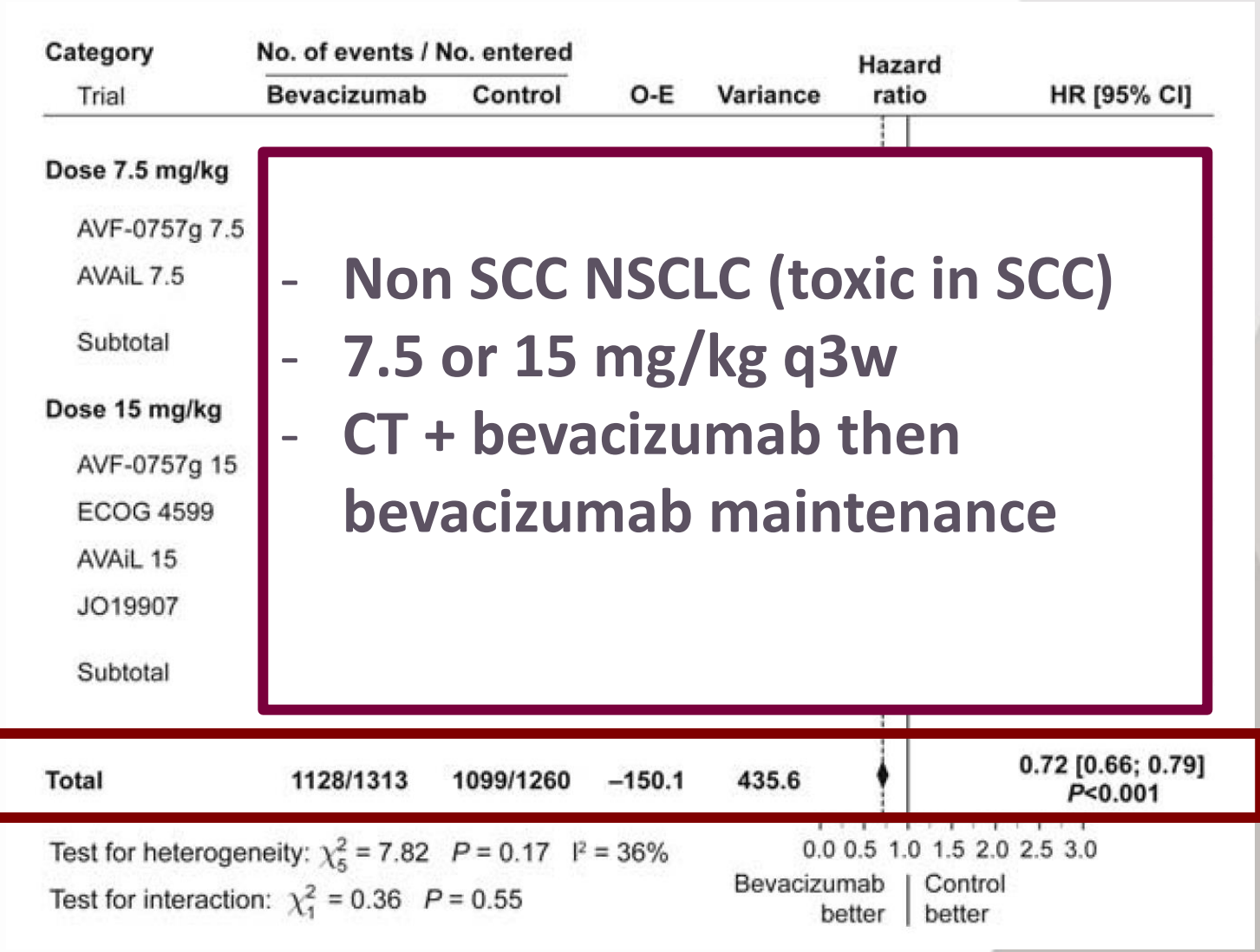
- For PS2?
- **Anti-angiogenic ?**

Bevacizumab
Pooled Analysis for PFS



- Non SCC NSCLC (toxic in SCC)
- 7.5 or 15 mg/kg q3w
- CT + bevacizumab then bevacizumab maintenance

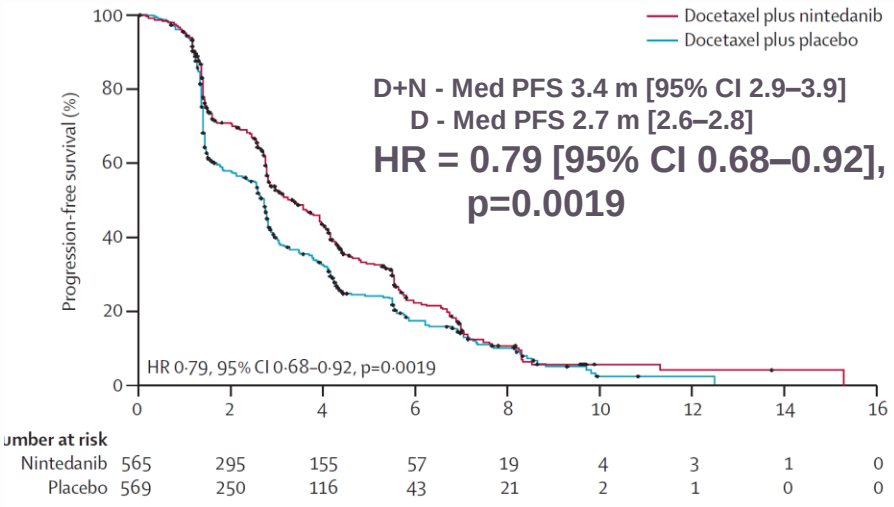
Negative phase III trials in NSCLC with anti-angiogenic agents (2000-2012)

Compound	Mechanism of action	N° trials	N	End Point
Thalidomide	Anti-angiogenic	2	1267	OS
Cediranib	VEGFR TKI	2	602	OS
Vandetanib	Multikinase TKI	3	2698	PFS/OS
AE-941	Anti-angiogenic	1	379	OS
Sorafenib	Multikinase TKI	2	1830	OS
Motesanib	Multikinase TKI	1	1090	OS
Sunitinib	Multikinase TKI	1	960	OS
Aflibercet	VEGF/PlGF	1	913	OS
Total		11	9739	

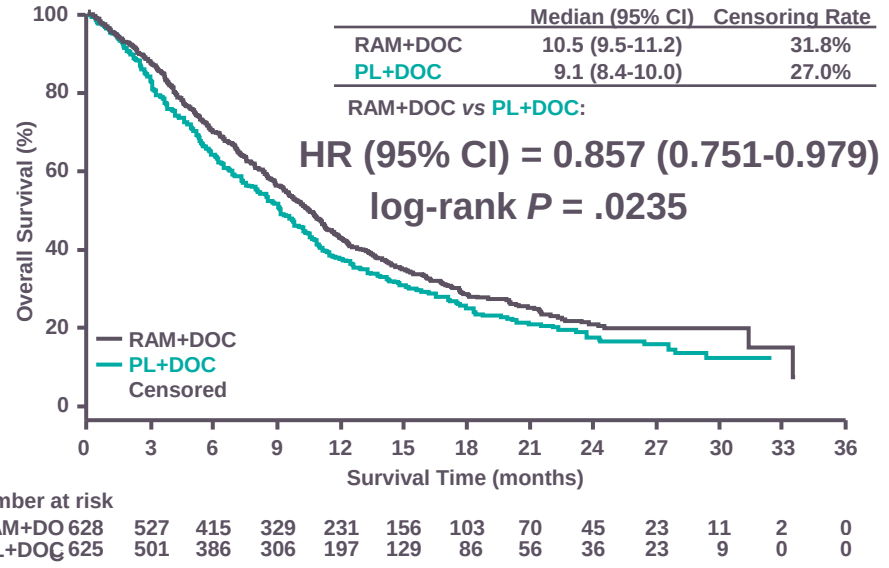
Anti-angiogenic agents in 2nd line?

MADRID 2014 ESMO congress

PFS - Docetaxel +/- nindetanib (VEGFR TKI)



OS - Docetaxel +/- ramucirumab (VEGFR2 Ab)



OS benefit in adenocarcinoma
PFS benefit in refractory pts (HR= 0.67 (0.43-1.04,p=0.0725).

OS benefit in SCC and non SCC

Perol ASCO 14, Reck Lancet Oncol 14

1st line metastatic NSCLC

Treatment options

Gemcitabine	1250 mg/m²	d 1, 8	q3w
Cisplatin	80 mg/m²	d 1	

All histologies

Vinorelbine	25 mg/m²	d 1, 8, 15, 22	
Cisplatin	100 mg/m²	d 1	d1=d28

Historical design, all histologies

Pemetrexed	500 mg/m²	d1	
Cisplatin	75 mg/m²	d1	d1=d21

Non squamous NSCLC

+/- bevacizumab if non SCC.
7,5 mg/kg or 15 mg/kg d1=d21

1st line metastatic NSCLC

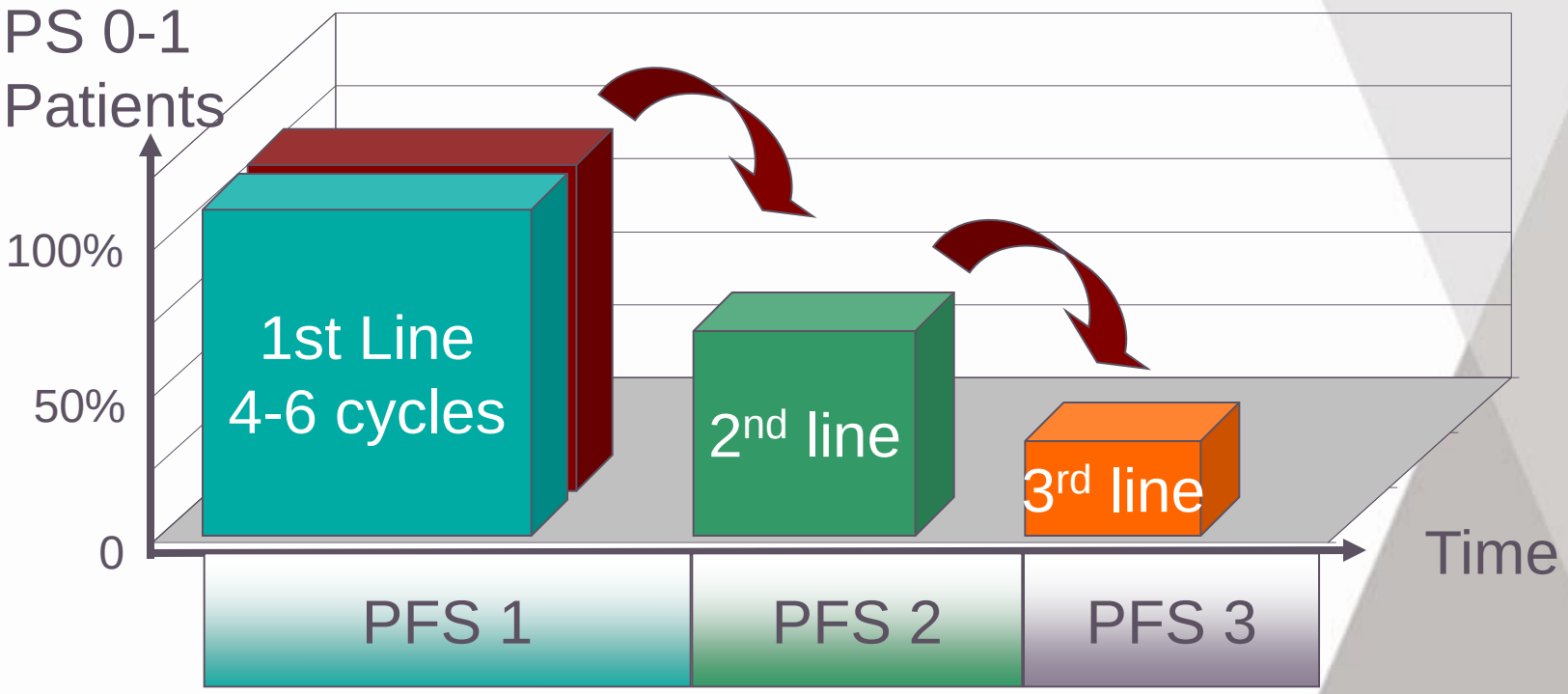
Treatment options

Docetaxel	75 mg/m²	d 1	d1=d21
Cisplatin	75 mg/m²	d 1	
Paclitaxel	135 mg/m²(24 h)	d 1	d1=d21
Cisplatin	75 mg/m²	d 2	
Paclitaxel	225 mg/m²(3 h)	d 1	d1=d21
Carboplatin	AUC 6	d 1	

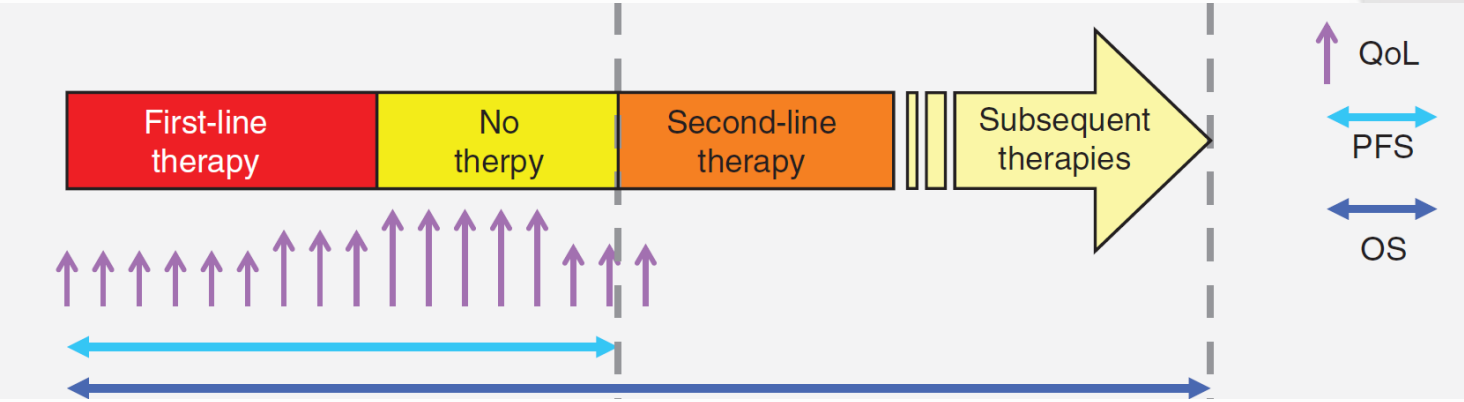
All histologies, induce alopecia

+/- bevacizumab if non SCC.
7,5 mg/kg or 15 mg/kg d1=d21

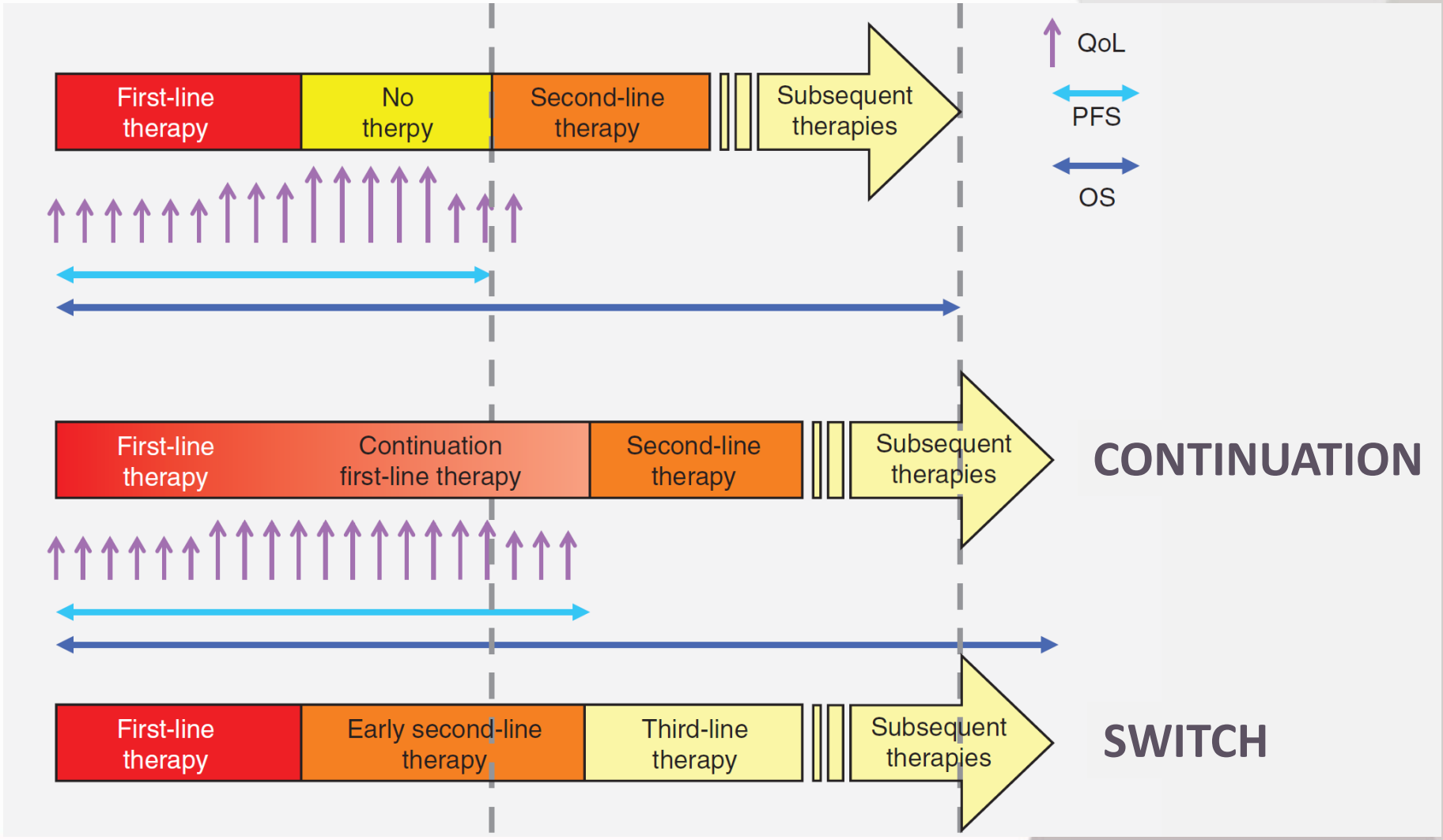
The historical managment



Each new line : 30% patients lost

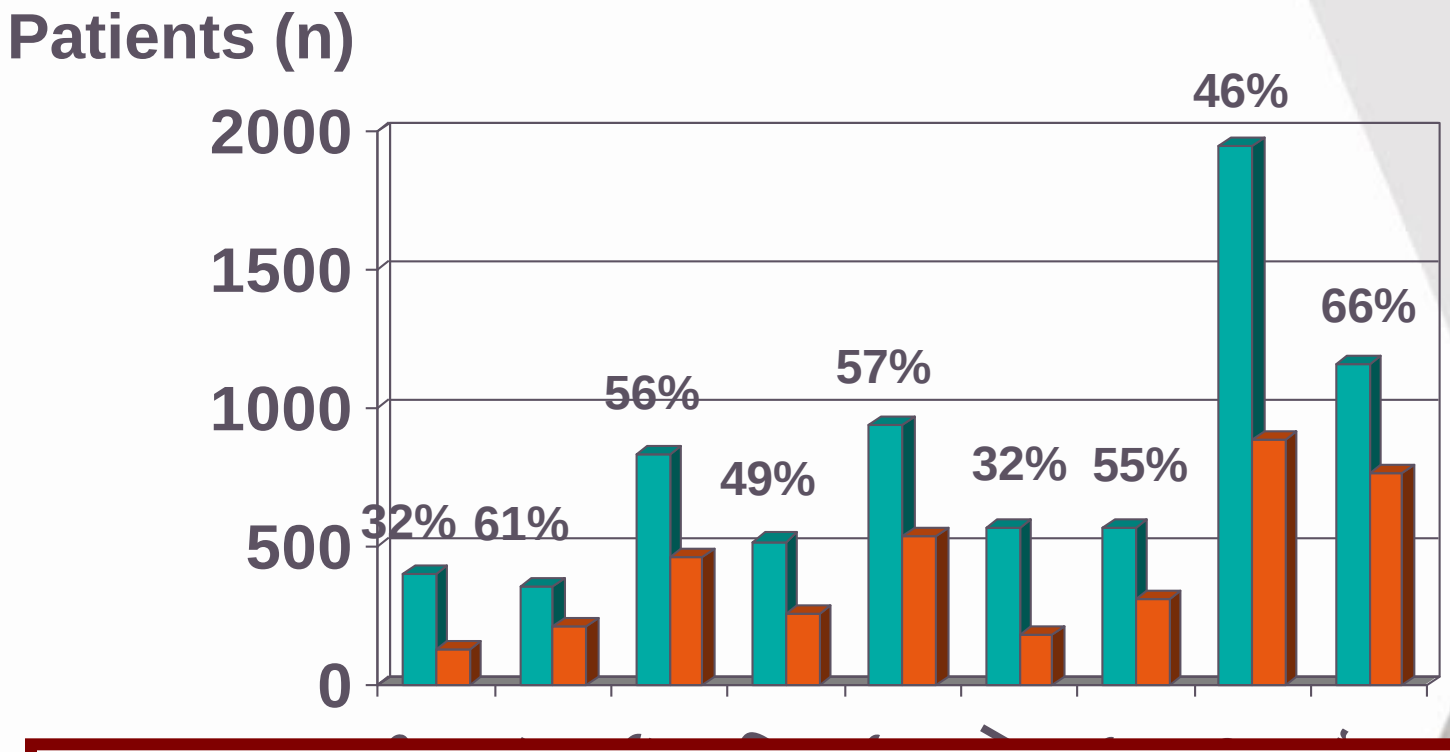


Polo, Ann Oncol



Polo, Ann Oncol

100% of the pts get maintenance ?



- Only 4 cycles with a platinum compound
- Only non progressive patients (50%) get maintenance

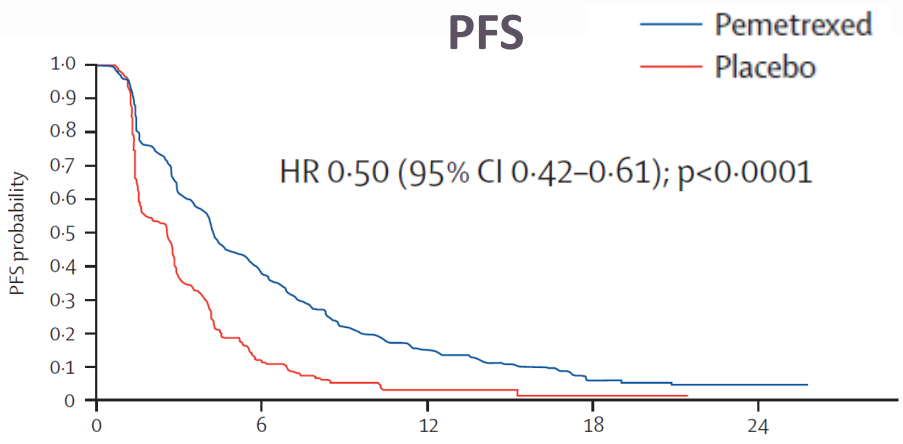
Belani, 2003, Westeel, 2005; Brodowicz, 2006 Fidias, 2009Miller, 2009Belani, 2010, Cappuzzo, 2010, Gaafar, 2010, Perol E, 2010

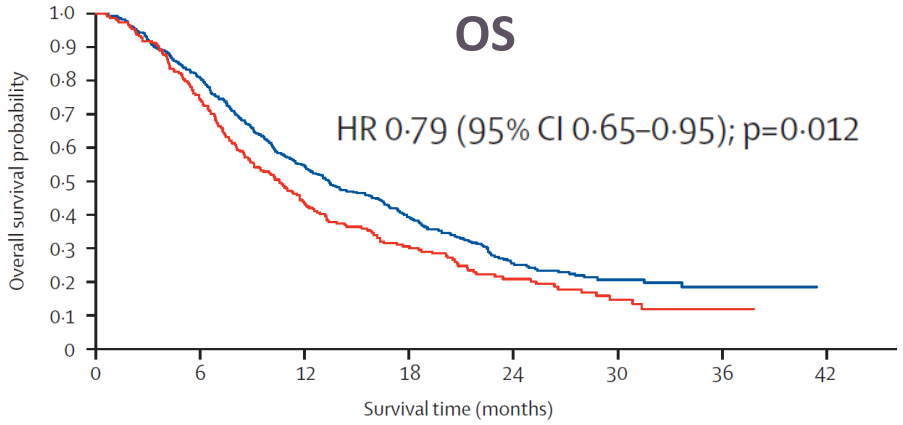
OUTLINE -2
beyond 1st line

- **Switch maintenance**
- Continuation maintenance
- Which pts for 2nd/3rd line?
- Best 2nd/3rd line?
- Beyond second line?
- Re-challenge platinum?

Switch Maintenance

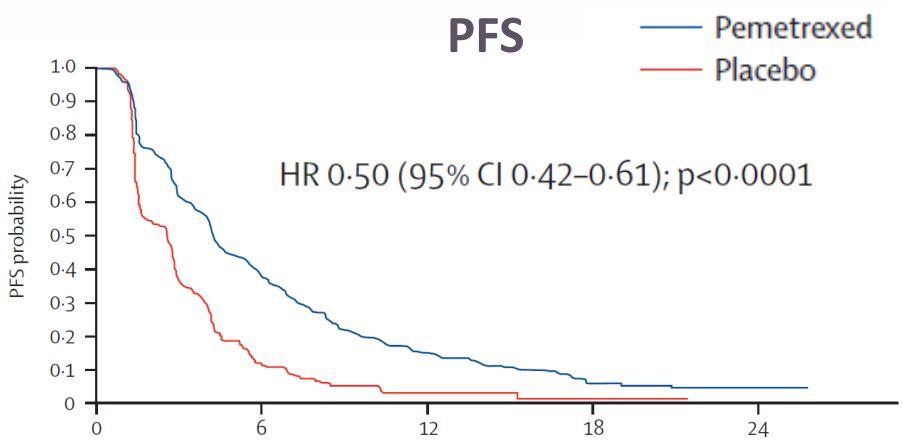
Pemetrexed vs placebo
Induction CT without pemetrexed

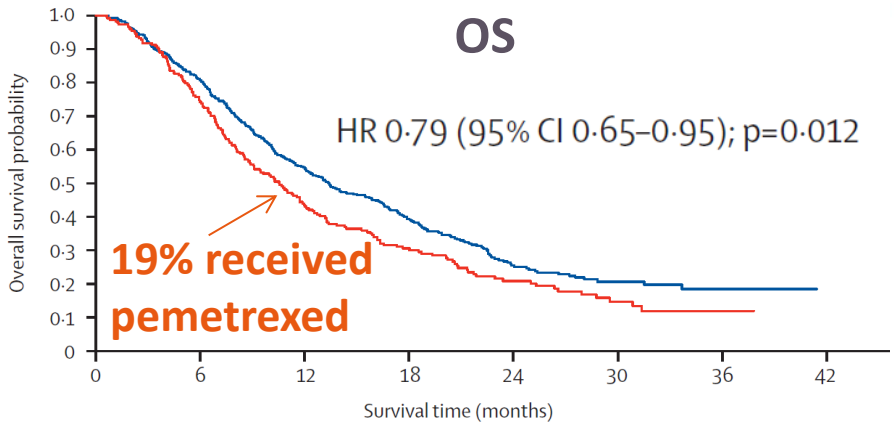




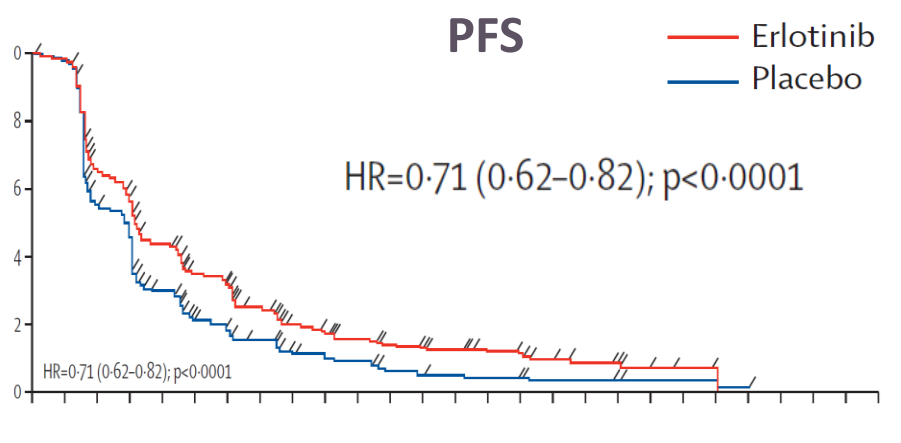
Switch Maintenance

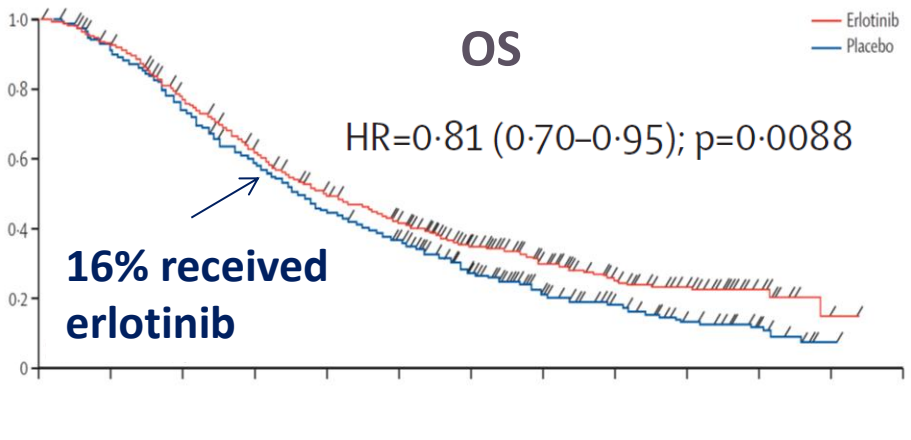
Pemetrexed vs placebo
Induction CT without pemetrexed





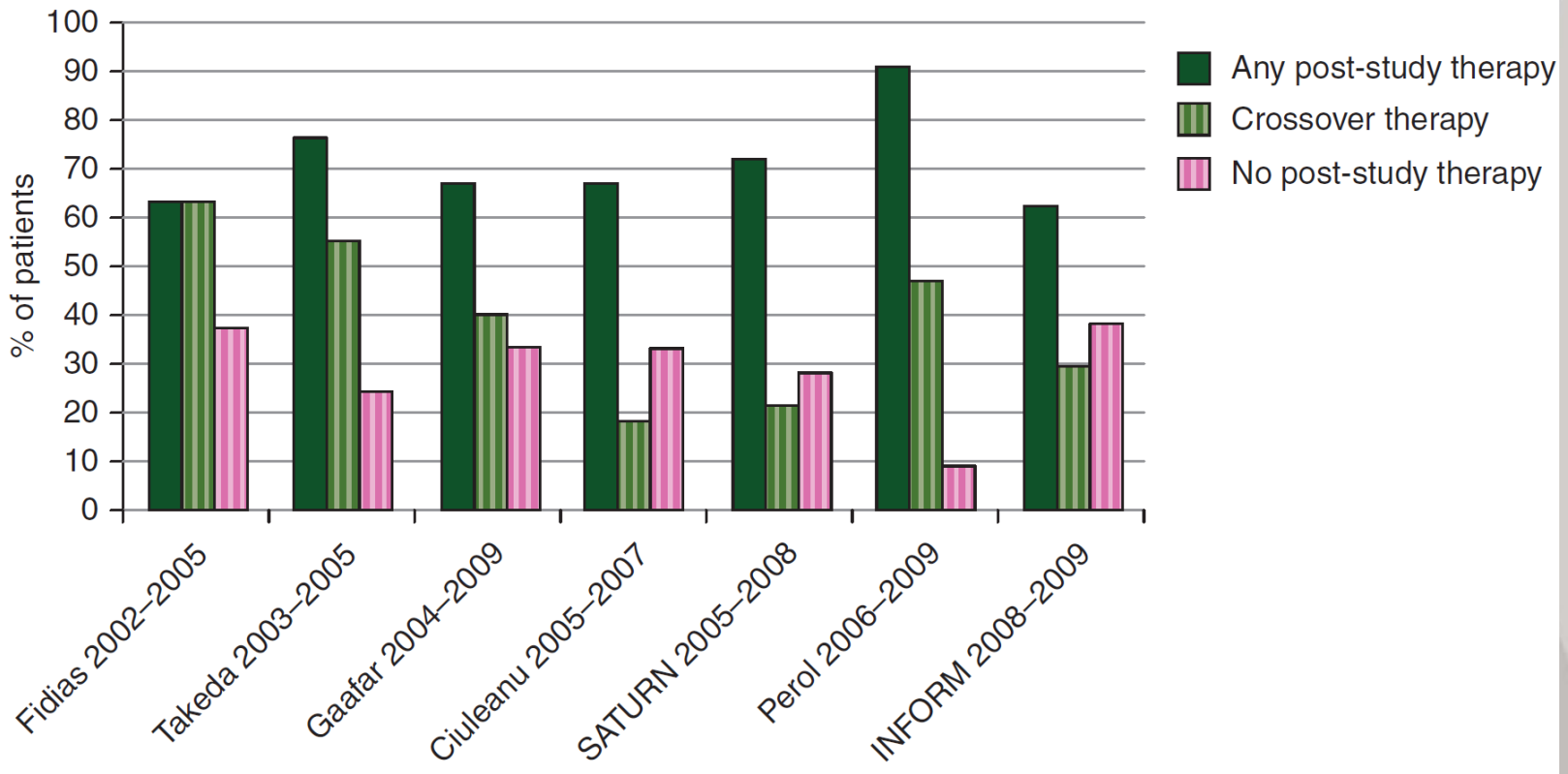
Erlotinib vs placebo





Cappuzzo Lancet Oncol 2010, Cileanu Lancet 2009

Cross-over



Polo, Ann Oncol 13

Switch Maintenance vs response to 1st line chemotherapy

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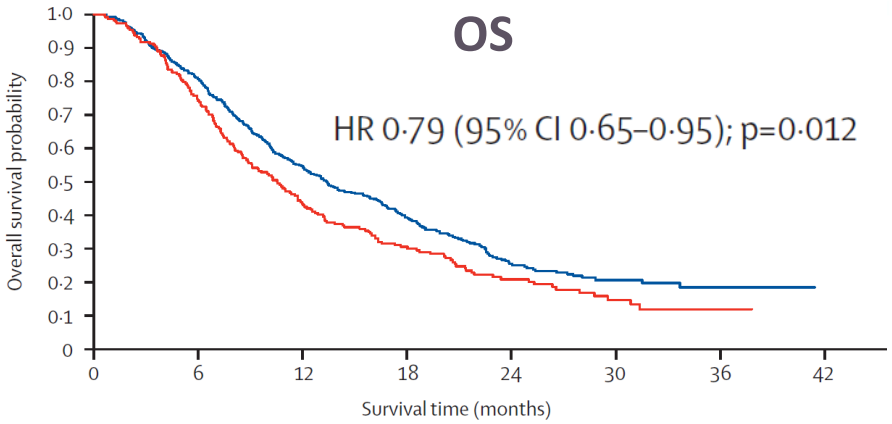
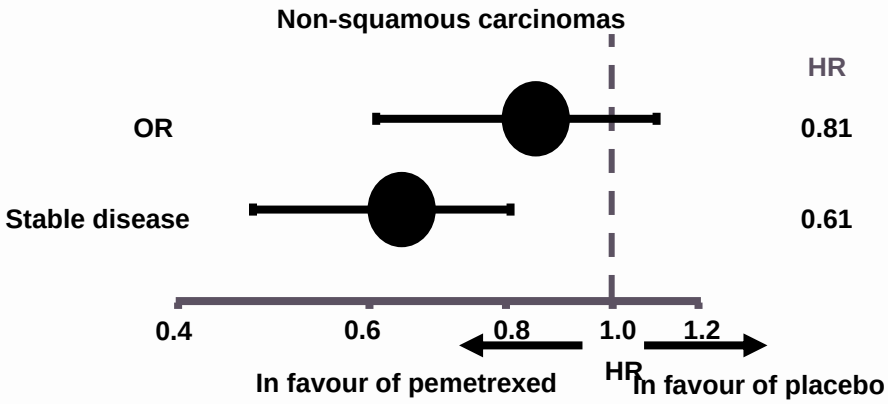
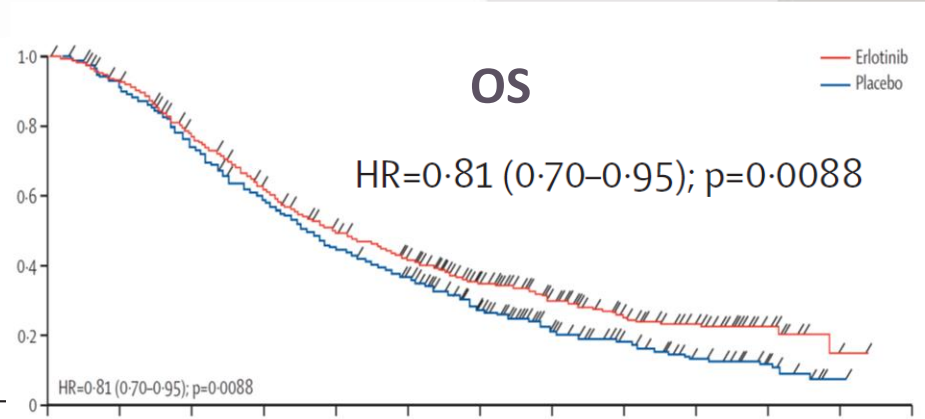
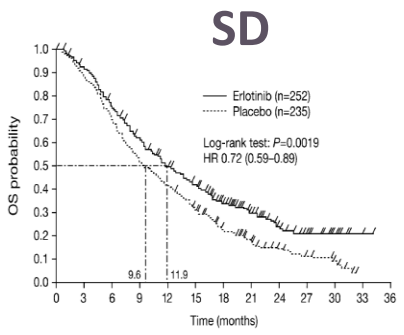
Pemetrexed vs placebo
Induction CT without pemetrexed

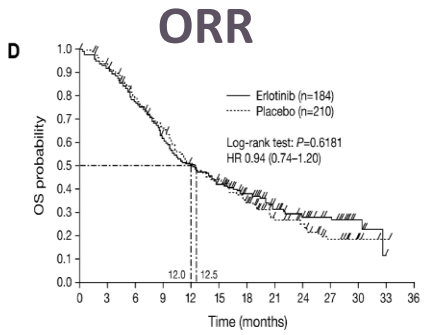




Erlotinib vs placebo







HR=0.72 (0.59-0.89) **HR=0.94 (0.74-1.20)**

Cileanu Lancet 09, Cappuzzo Lancet Oncol 10, Belani, ASCO 09, Coudert Ann Oncol 11

OUTLINE -2
beyond 1st line

- **Switch maintenance**

Recommendations:

Switch maintenance with pemetrexed may be offered to patients with advanced non-squamous carcinoma who are not treated with pemetrexed first-line treatment. (B,II)

Switch maintenance with erlotinib is a treatment option for patients with advanced NSCLC who have stable disease after first-line platin-based chemotherapy. (B,IV)

IFCT-GFPC 0502

Cisplatin gemcitabine x 4 cycles N=834

Objective response or stable disease

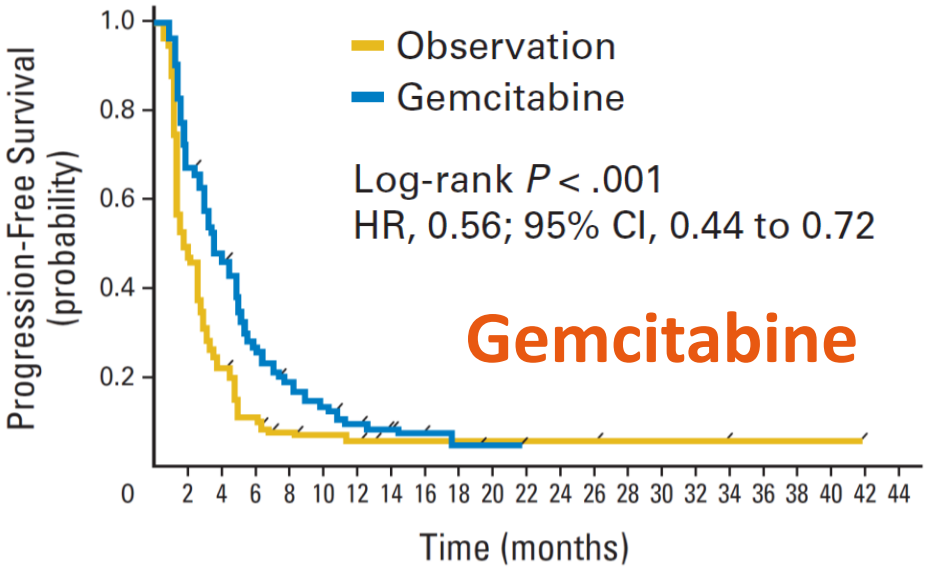
R* N=464

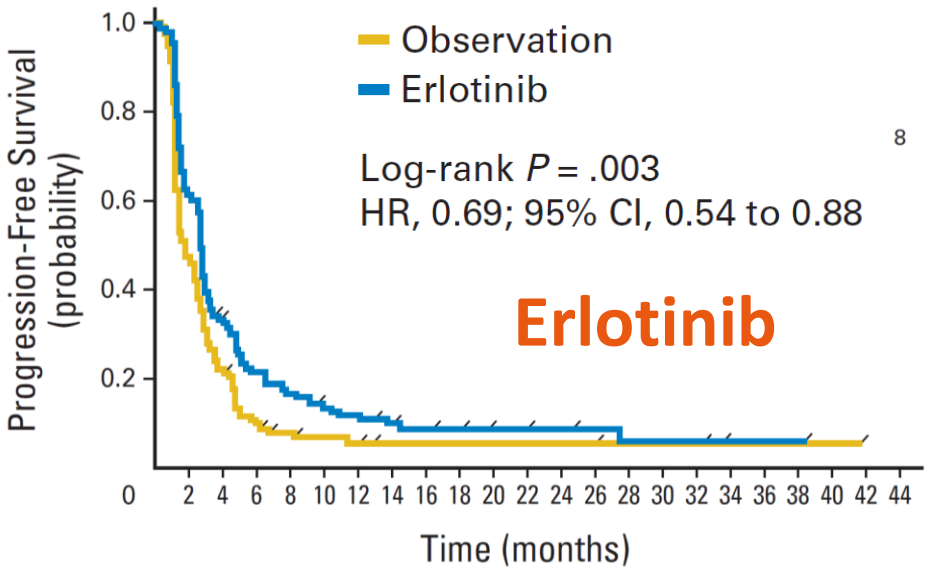
A Observation N=155

B Gemcitabine N=154

C Erlotinib N=155

Primary endpoint: PFS





OUTLINE -2
beyond 1st line

- Switch maintenance
- **Continuation maintenance**
- Which pts for 2nd/3rd line?
- Best 2nd/3rd line?
- Beyond second line?
- Re-challenge platinum?

Pemetrexed vs placebo after 4 cycles pemetrexed/cisplatin

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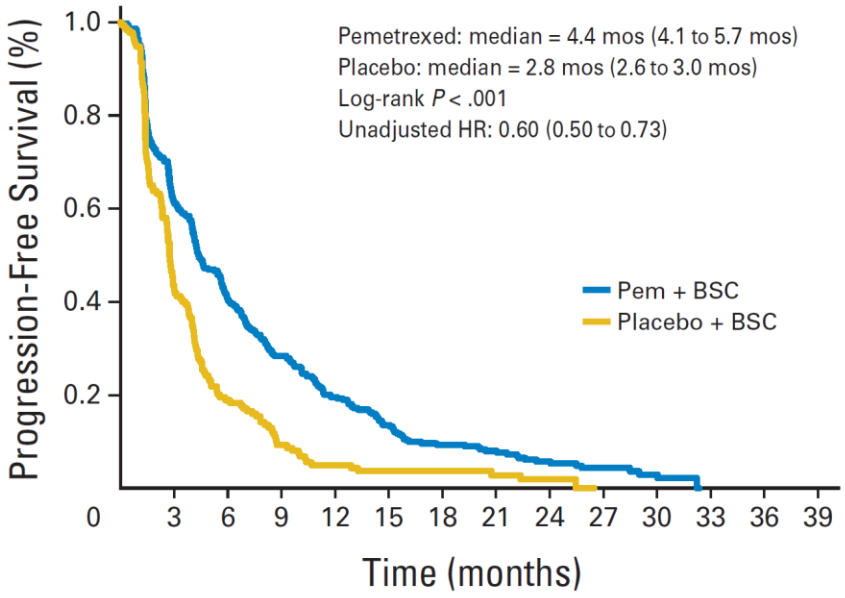
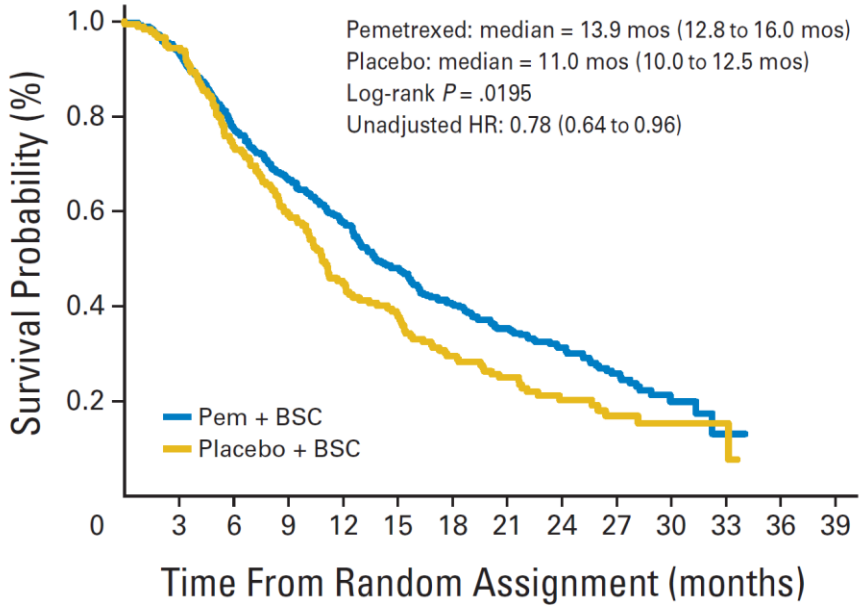
PFS



No. at risk

Pem + BSC	359	215	139	97	67	47	32	22	16	10	5	0
Placebo + BSC	180	75	33	16	9	7	6	4	2	0	0	0

OS



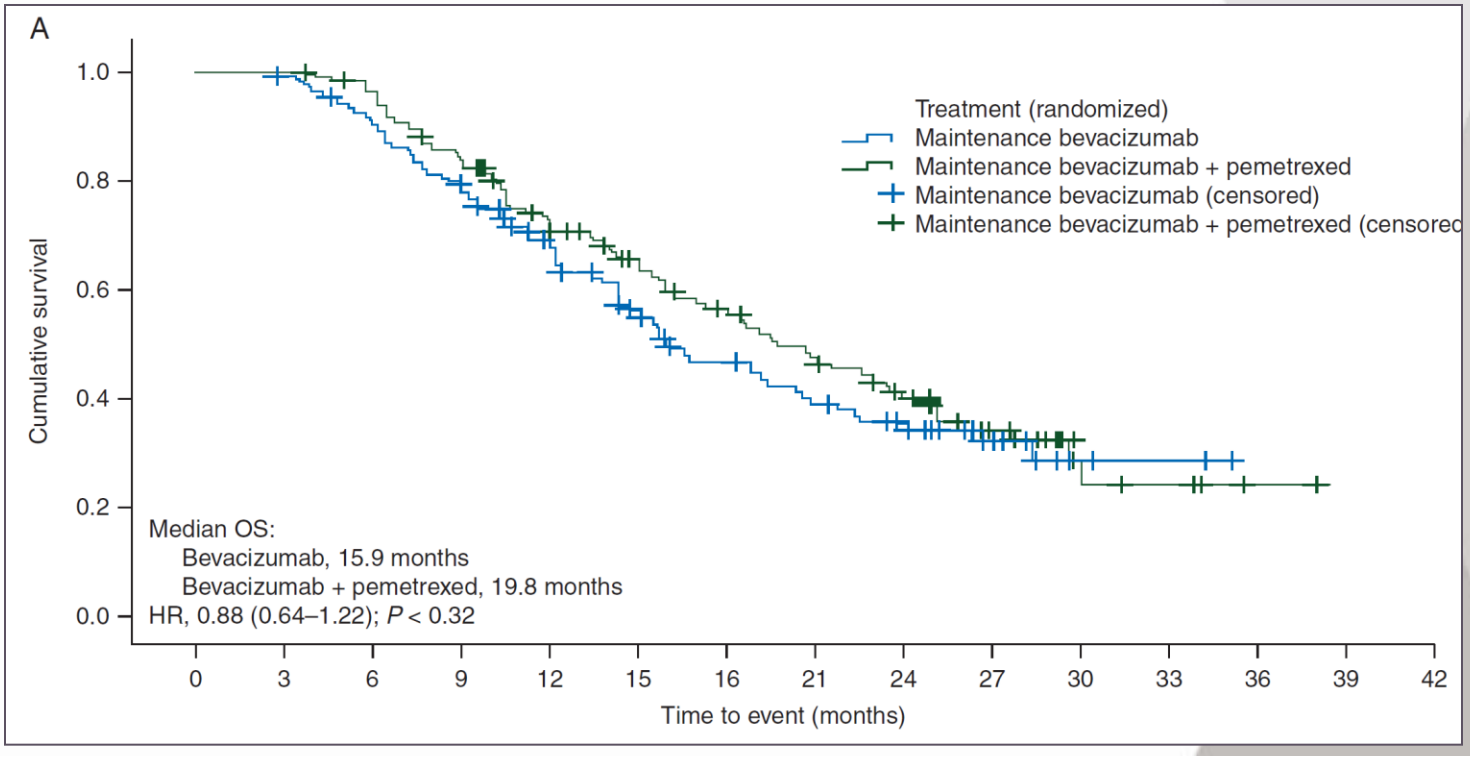
No. at risk

Pem + BSC	359	333	272	235	200	166	138	105	79	43	15	2	0
Placebo + BSC	180	169	131	103	78	65	49	35	23	12	8	3	0

OS maintenance pemetrexed: 13.9 months

Paz-Ares JCO 2013

Pemetrexed + bevacizumab vs bevacizumab after 4 cycles pemetrexed/cisplatin/bevacizumab



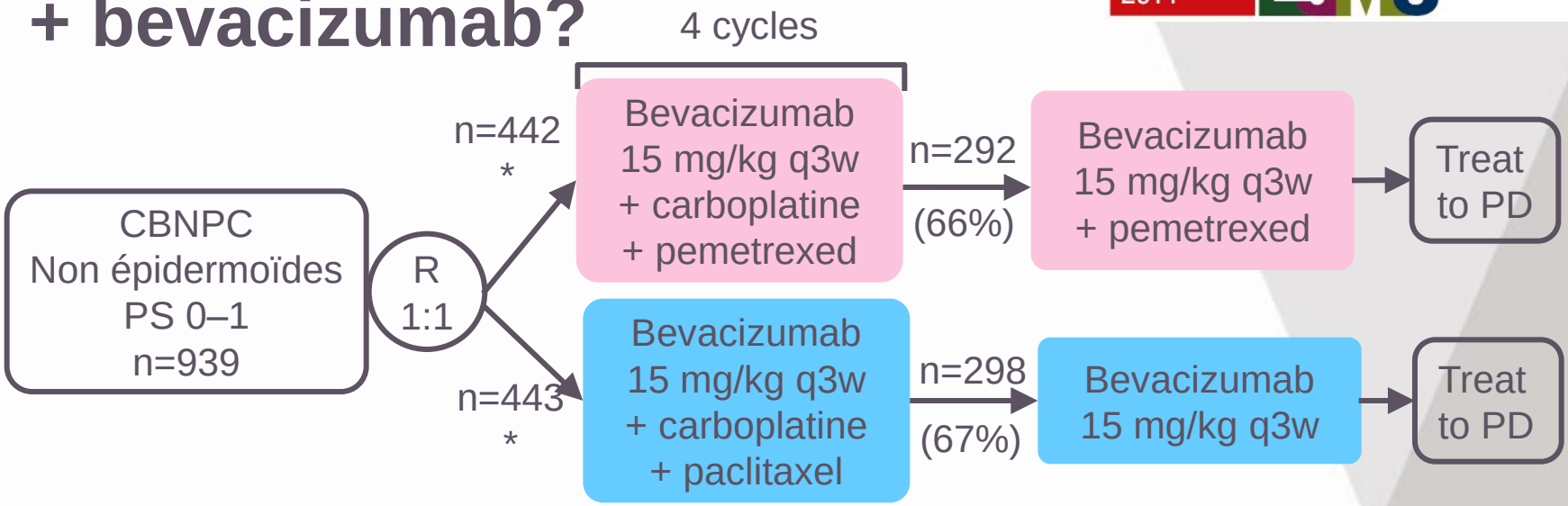
AVAPERL

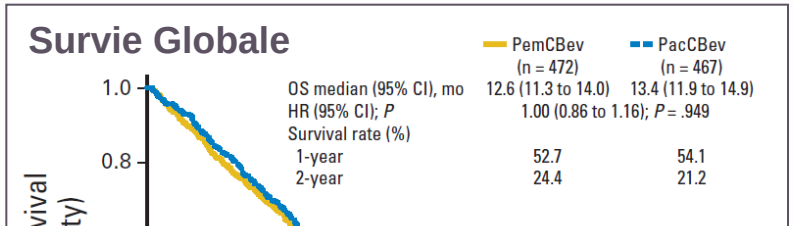
OS maintenance pemetrexed/bevacizumab: 19.8 months

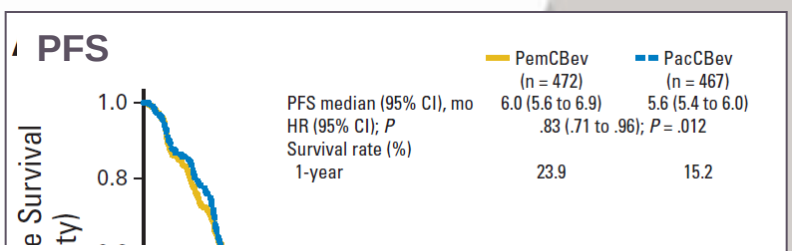
Barlesi Ann Oncol 2014

Maintenance pemetrexed + bevacizumab?

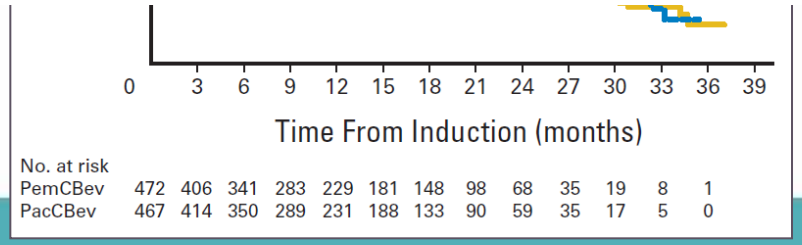
MADRID 2014 ESMO congress

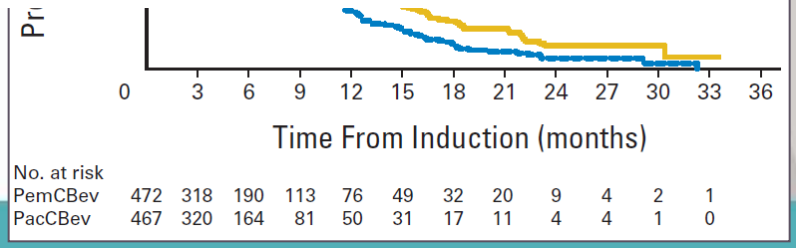






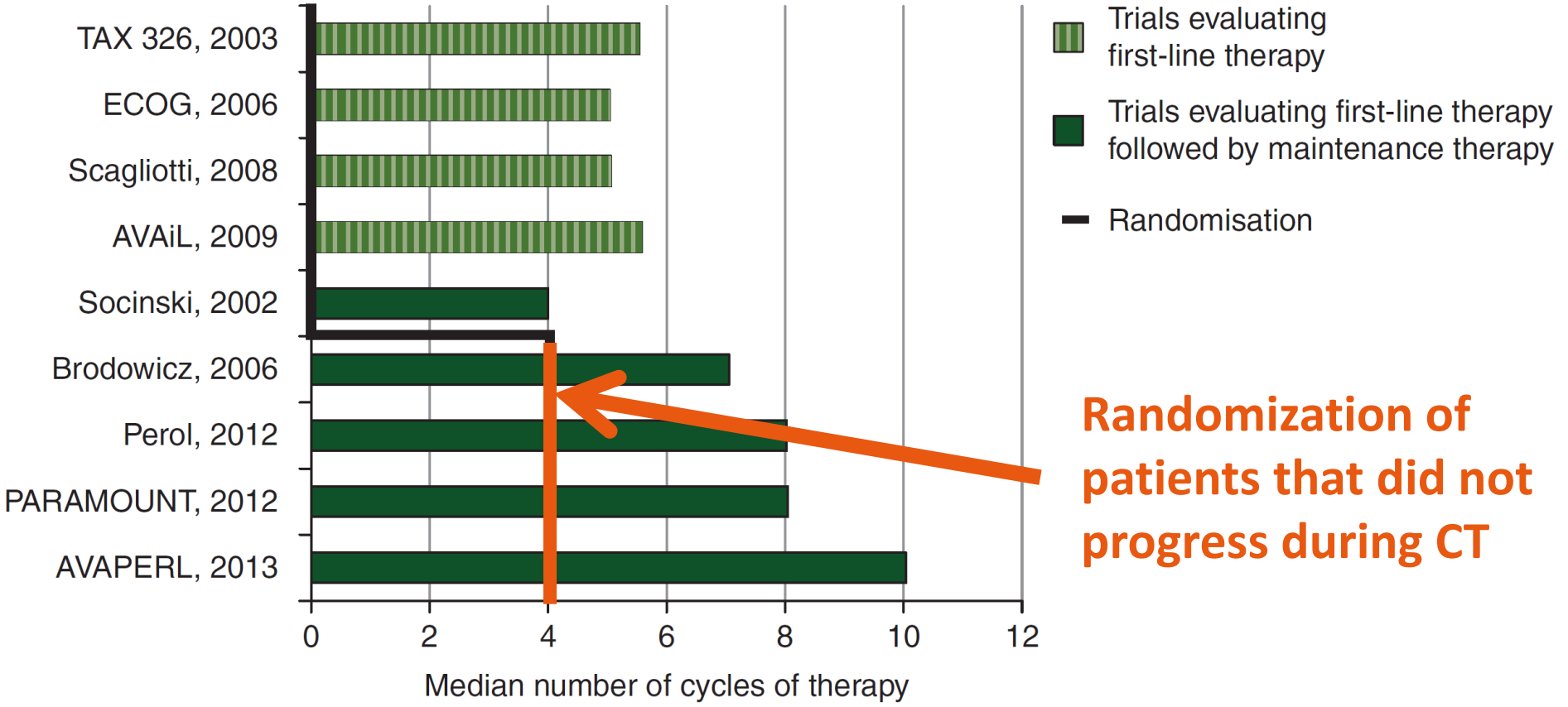
OS maintenance pemetrexed/bevacizumab: 12.6 months
Vs 19.8 months in AVAPERL





Patel JCO 2013

Mind the randomization!



Randomization of patients that did not progress during CT

Polo, Ann Oncol 13 - Park *et al* JCO 07

OUTLINE -2
beyond 1st line

- Switch maintenance
- **Continuation maintenance**
- Which pts fo
- Best 2nd/3rd
- Beyond sec
- Re-challeng

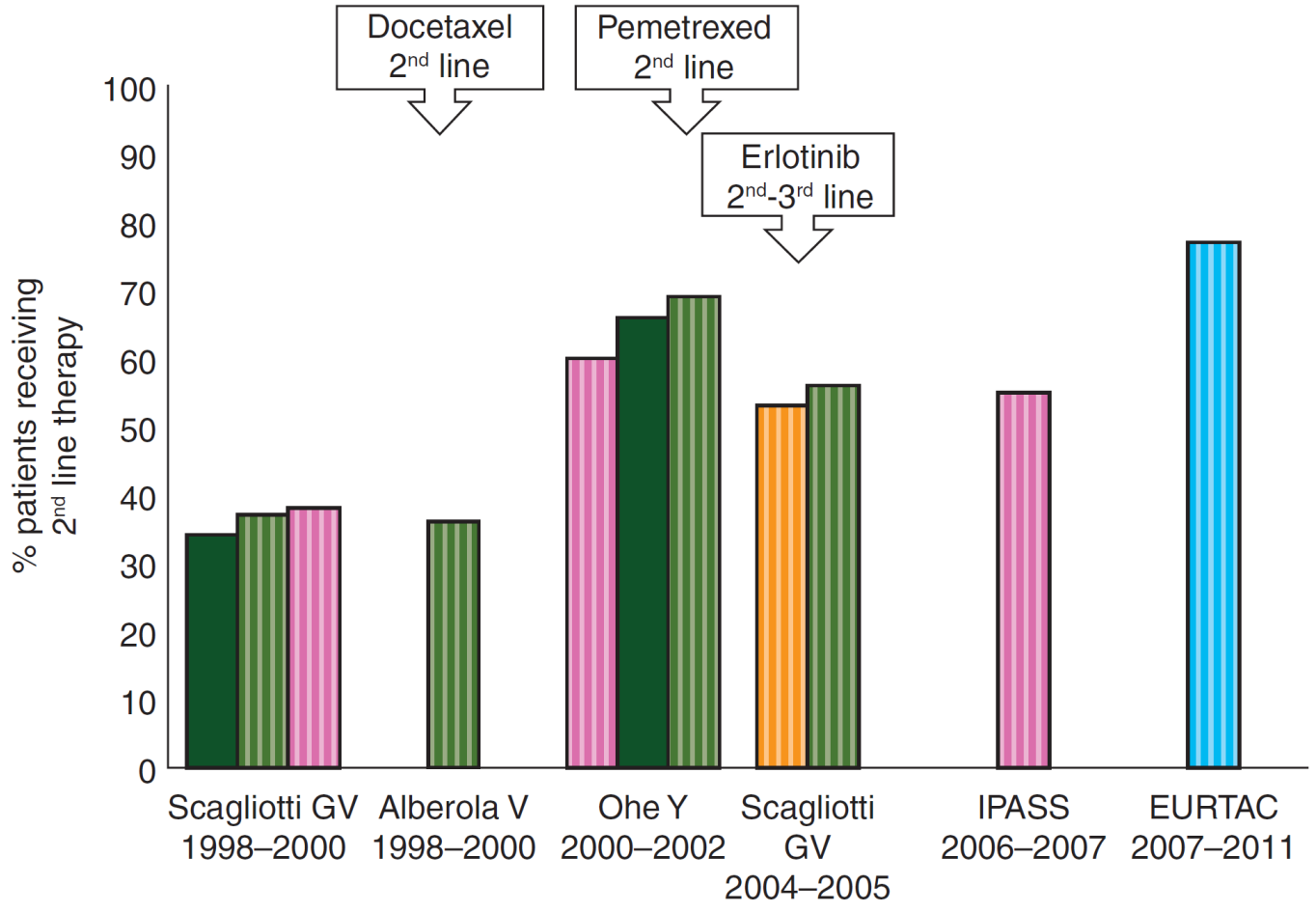
Recommendation:

Continuation maintenance treatment with pemetrexed may be offered to patients with advanced non-squamous NSCLC not progressing after first-line pemetrexed- cisplatin therapy. (A,I)

OUTLINE -2
beyond 1st line

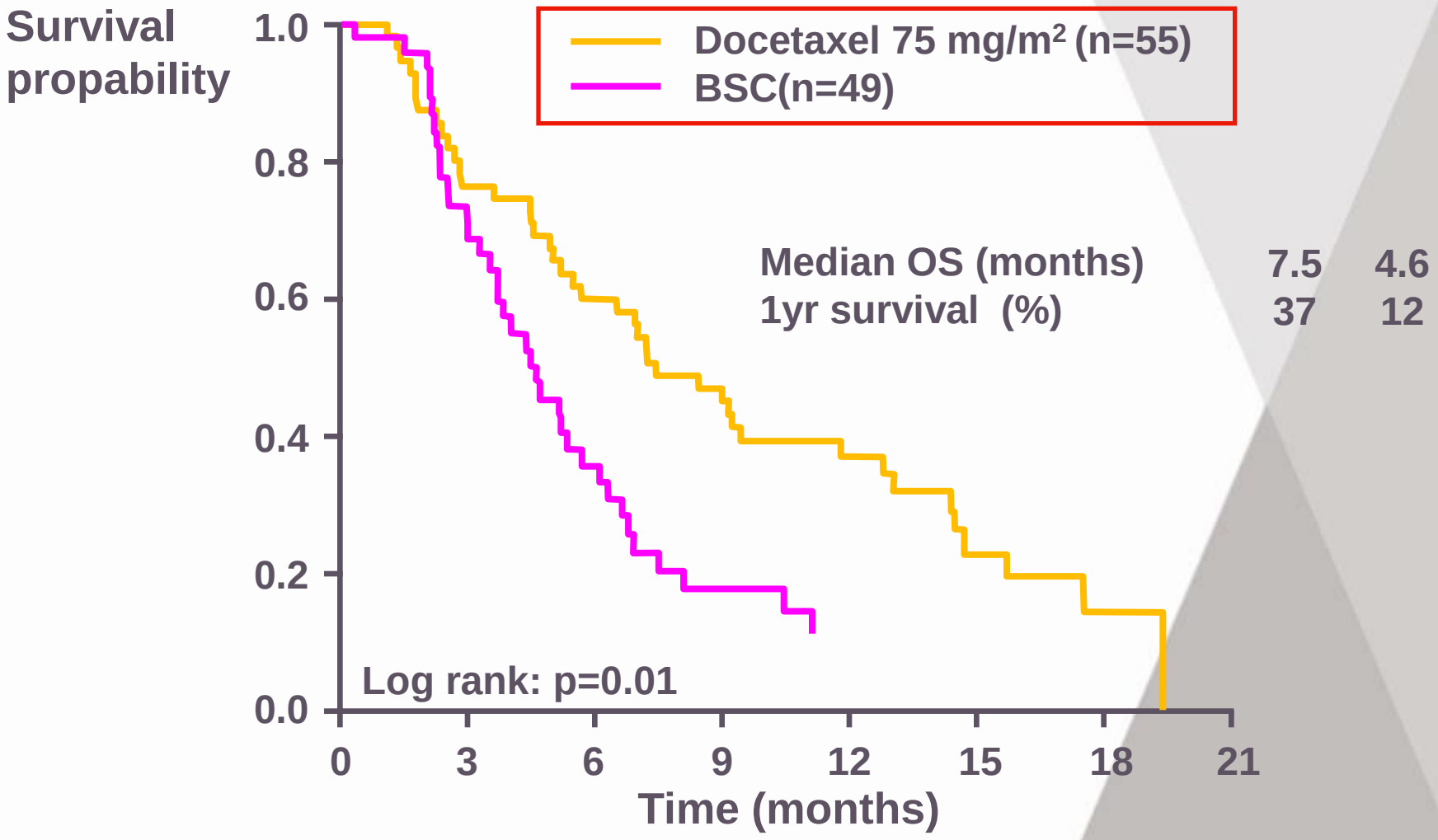
- Switch maintenance
- Continuation maintenance
- **Which pts for 2nd/3rd line?**
- Best 2nd/3rd line?
- Beyond second line?
- Re-challenge platinum?

Second line uptake



Polo, Ann Oncol

Docetaxel – 2000

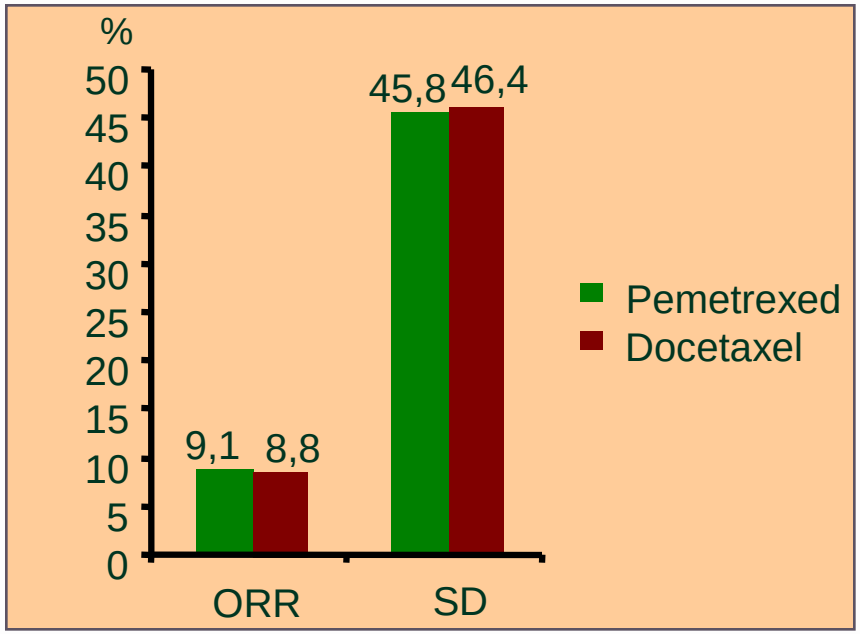


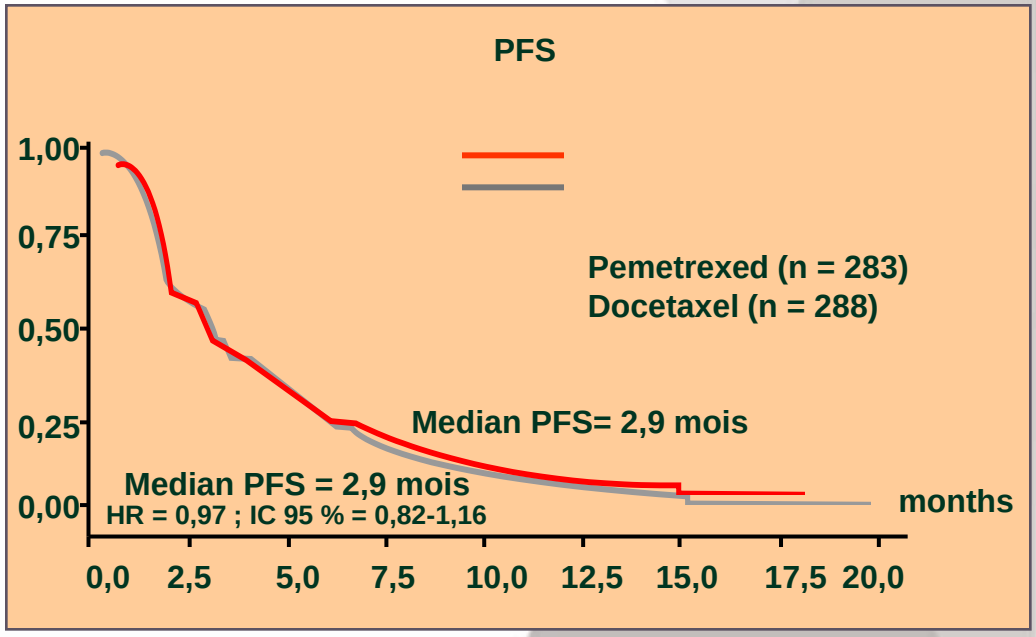
Shepherd FA et al. J Clin Oncol 2000;18:2095-103

Pemetrexed – A.M.M. 2003

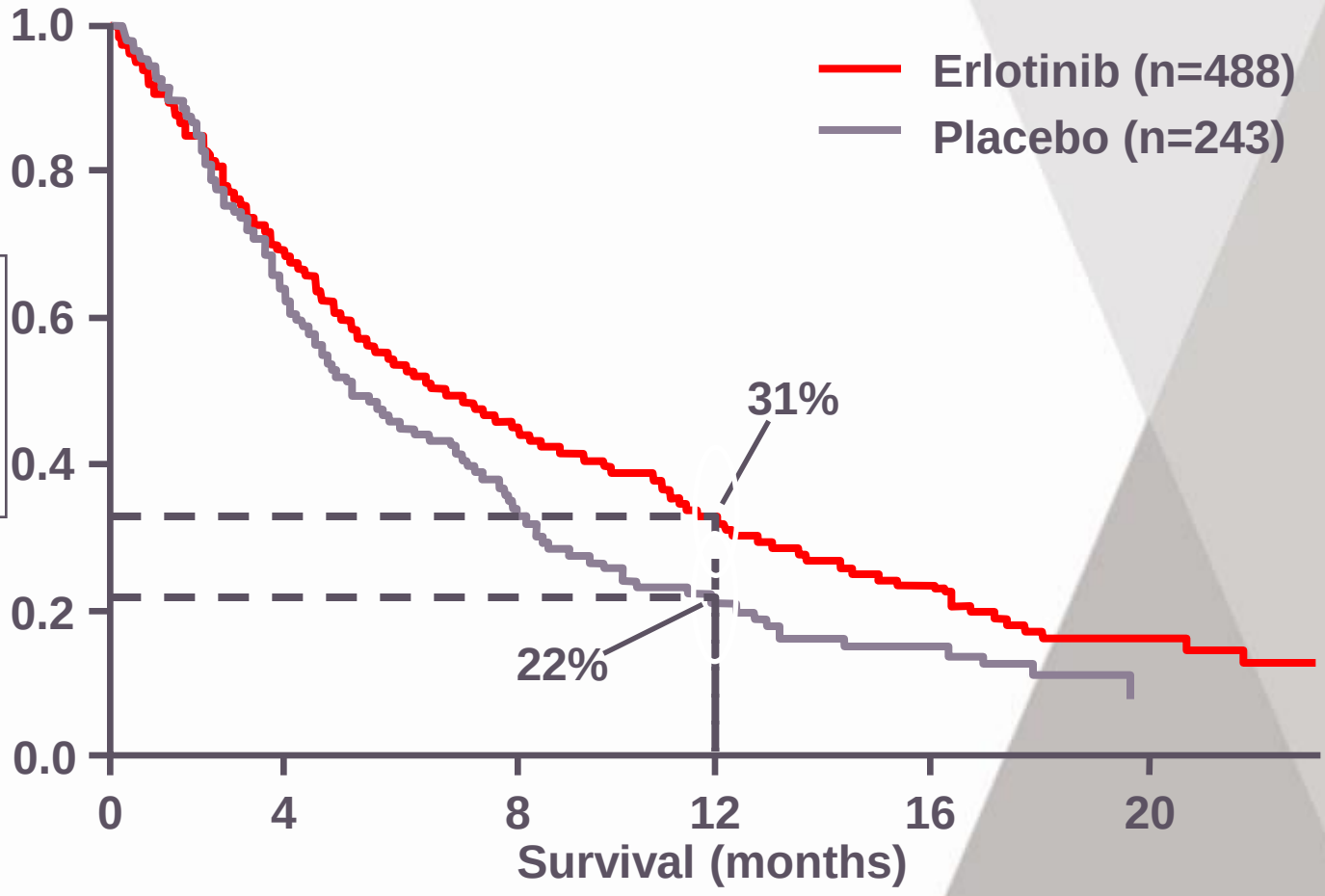
R → docetaxel 75 mg/m² q3w

R → pemetrexed 500 mg/m² q3w
+ Vit.B12 and folates





Erlotinib –2005



No selection on EGFR!

Shepherd et al NEJM 05

OUTLINE -2
beyond 1st line

- Switch maintenance
- Continuation maintenance
- **Which pts for 2nd/3rd line?**
- Best 2nd/3rd line?
- Beyond second line?
- Re-challenge platinum?

Recommendation:

2nd or 3rd-line therapy should be offered to patients with PS 0–1 who present with signs of disease progression (radiological and/or clinical) after 1st- or 2nd-line therapy.

OUTLINE -2
beyond 1st line

- Switch maintenance
- Continuation maintenance
- Which pts for 2nd/3rd line?
- **Best 2nd/3rd line?**
- Beyond second line?
- Re-challenge platinum?

2nd line for advanced NSCLC

A best choice ?

Docetaxel : 75 mg/m² - d1 = d21
ORR : 9% - PFS : 2,9 m

But if paclitaxel is given first line ?

Pemetrexed : 500 mg/m² - d1 = d21
ORR : 9% - PFS : 2,9 m

Non SCC only

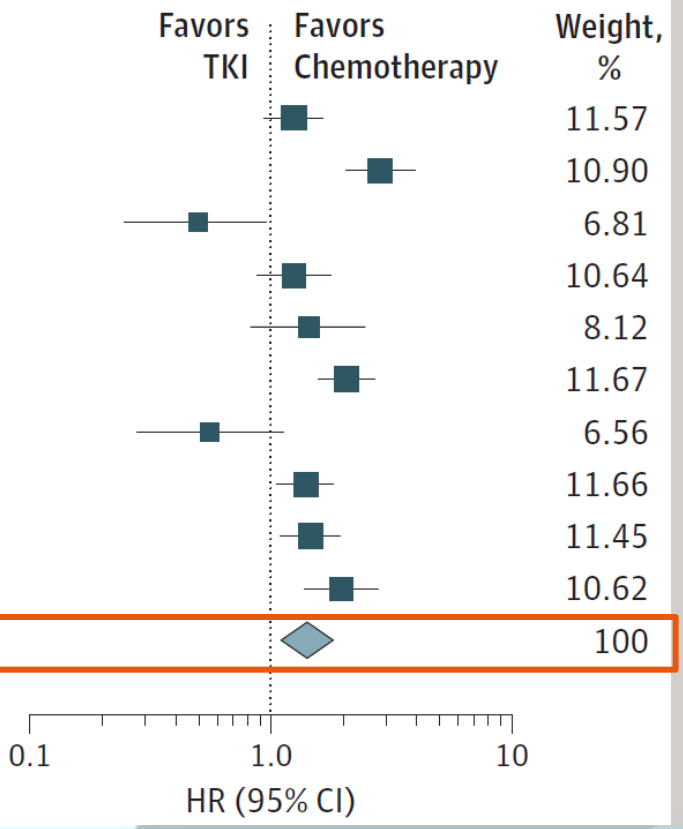
Erlotinib : 150 mg/d
ORR : 9% - PFS : 2,2 m

All histology

EGFR wt tumors
Chemotherapy vs EGFR TKI

Progression Free Survival

Source	No. of Patients With WT *EGFR* TKI	No. of Patients With WT *EGFR* Chemotherapy	Progression-Free Survival, HR (95% CI)	Weight, %
INTEREST,[12,27] 2008 and 2010	106	123	1.24 (0.94-1.64)	11.57
IPASS,[5,28] 2009 and 2011	91	85	2.85 (2.05-3.98)	10.90
ML20322,[29] 2012	21	15	0.50 (0.25-0.97)	6.81
TITAN,[13] 2012	75	74	1.25 (0.88-1.78)	10.64
First-SIGNAL,[30] 2012	27	27	1.42 (0.82-2.47)	8.12
TORCH,[14] 2012	119	117	2.07 (1.58-2.71)	11.67
KCSG-LU08-01,[31] 2012	18	20	0.56 (0.28-1.13)	6.56
TAILOR,[15] 2013	109	110	1.39 (1.06-1.82)	11.66
DELTA,[33] 2013	109	90	1.45 (1.09-1.94)	11.45
CTONG-0806,[34] 2013	81	76	1.96 (1.37-2.78)	10.62
Overall: $I^2 = 79.1\%$; $P < .001$	756	737	1.41 (1.10-1.81)	100

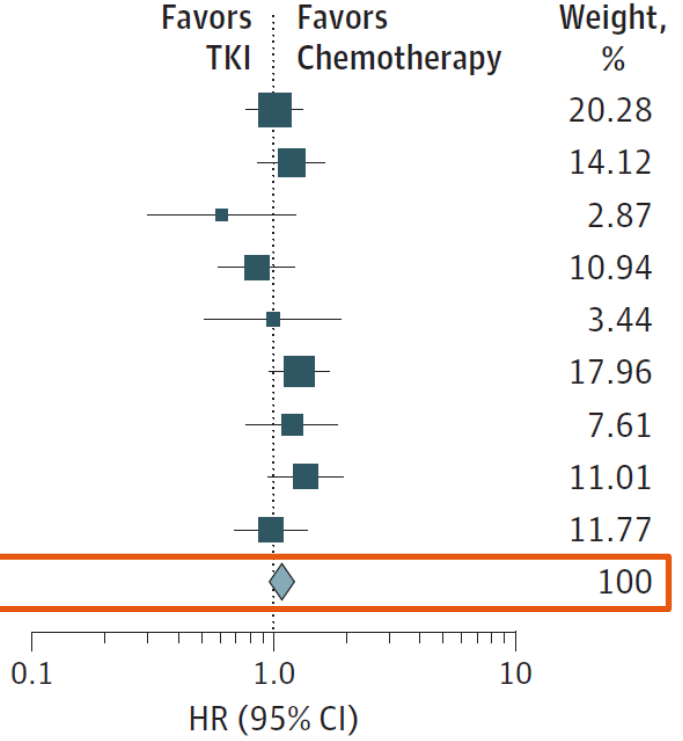


Not on Individual patient's data

EGFR wt tumors
Chemotherapy vs EGFR TKI

Overall Survival

Source	No. of Patients With WT *EGFR* TKI	No. of Patients With WT *EGFR* Chemotherapy	HR (95% CI)	Weight, %
INTEREST,[12,27] 2008 and 2010	119	134	1.02 (0.78-1.33)	20.28
IPASS,[5,28] 2009 and 2011	91	85	1.18 (0.86-1.63)	14.12
ML20322,[29] 2012	21	15	0.62 (0.30-1.24)	2.87
TITAN,[13] 2012	75	74	0.85 (0.59-1.22)	10.94
First-SIGNAL,[30] 2012	27	27	1.00 (0.52-1.91)	3.44
TORCH,[14] 2012	119	117	1.29 (0.97-1.71)	17.96
CT/06.05,[32] 2013	55	57	1.19 (0.77-1.84)	7.61
TAILOR,[15] 2013	109	110	1.28 (0.95-1.96)	11.01
DELTA,[33] 2013	109	90	0.98 (0.69-1.39)	11.77
Overall: $I^2 = 0\%$; $P = .496$	725	709	1.08 (0.96-1.22)	100



Not on Individual patient's data

OUTLINE -2
beyond 1st line

- Switch maintenanc
- Continuation maint
- Which pts for 2nd/3r
- **Best 2nd/3rd line?**
- Beyond second lin
- Re-challenge platin

Recommendation:

Chemotherapy can be offered to patients who have a PS 0–1. Regardless of the EGFR status of the tumour a choice between docetaxel, pemetrexed or erlotinib can be made. For fit patients, chemotherapy may be more effective than erlotinib. (B,I)

OUTLINE -2
beyond 1st line

- Switch maintenance
- Continuation maintenance
- Which pts for 2nd/3rd line?
- Best 2nd/3rd line?
- **Beyond second line?**
- Re-challenge platinum?

Long survivor?

Literature series on long-term survivors with advanced NSCLC.

Study (year)	LTS	$N_{LTSpatients}$	Stage	Predictive factors	Remarks
Okamoto et al. [3]	>2 years	17 of 222	IV	PS, adenocarcinoma, surgery, lower *N*-stage	19 patients surgery
Satoh et al. [4]	>2 years	14 of 109	Advanced	PS, EGFR-TKI	
Kaira et al. [5]	>5 year	10 of 124	Advanced	PS, adenocarcinoma, EGFR-TKI	2 resections of solitary brain mets
Dujon et al. [6]	>2 years	23 of 169	Advanced	PS, comorbidity, response, EGFR-TKI	
Giroux Leprieur et al. [7]	>2 years	39 of 245	Advanced	PS, response, surgery, *N* of lines, treatment-free interval	Resectable patients
This series	>2 years	31 vs. 34	Advanced	(PS), (gender), response, *N* of lines, treatment-free interval	

LTS: definition of long-term survival; $N_{LTS\ patients}$: number of long-term survivors; *N*-stage: lymph node stage; PS: performance status; EGFR-TKI: epidermal growth factor tyrosine kinase inhibitor; mets: metastases; *N* of lines: number of metastatic treatment lines.

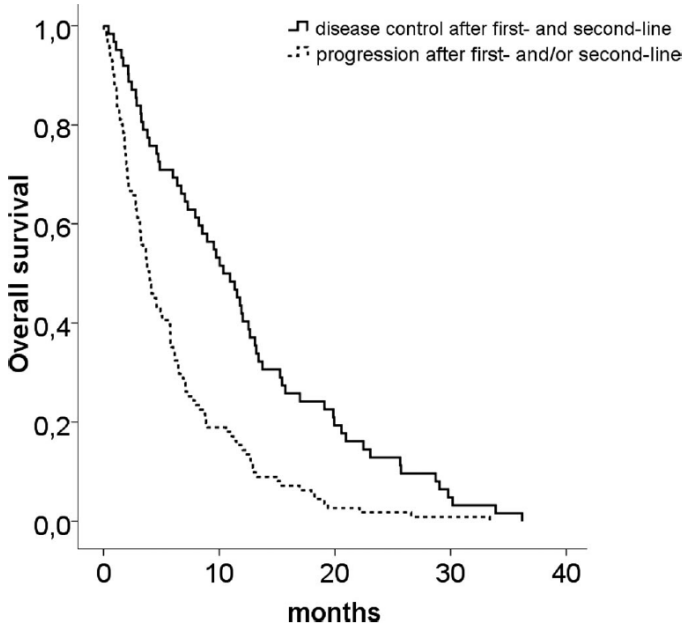
French retrospective study

173/1292 pts received a 3rd line

Disease control after 2 lines matters

OS = 10.3 m vs 4.0 m

HR=0.45 (0.32-0.62)



Van Damne Lung Cancer 2013, Girard JTO 06

OUTLINE -2
beyond 1st line

- Switch maintenance
- Continuation maintenance
- Which pts for 2nd/3rd line?
- Best 2nd/3rd line?
- **Beyond second line?**
- Re-challenge platinum?

Recommendation:
Selected patients may benefit from third line or fourth-line systemic treatment. (C,II)

OUTLINE -2
beyond 1st line

- Switch maintenance
- Continuation maintenance
- Which pts for 2nd/3rd line?
- Best 2nd/3rd line?
- Beyond second line?
- **Re-challenge platinum?**

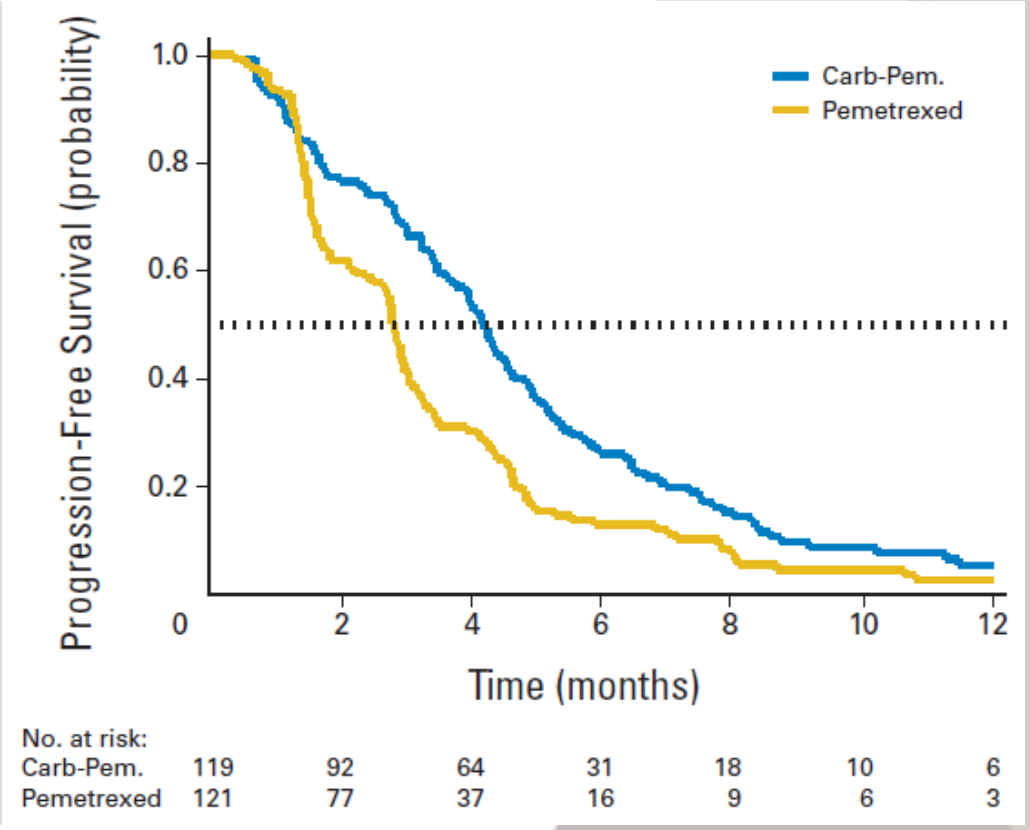
Platinum again in second line?

- Pemetrexed vs. pemetrexed-carboplatin
- N=240
- ORR : 7 vs 17%
- PFS med :
  2,8 vs 4,6 m

ADK : 2,9 vs 4,3 m

SCC : 2,6 vs 3,5 m

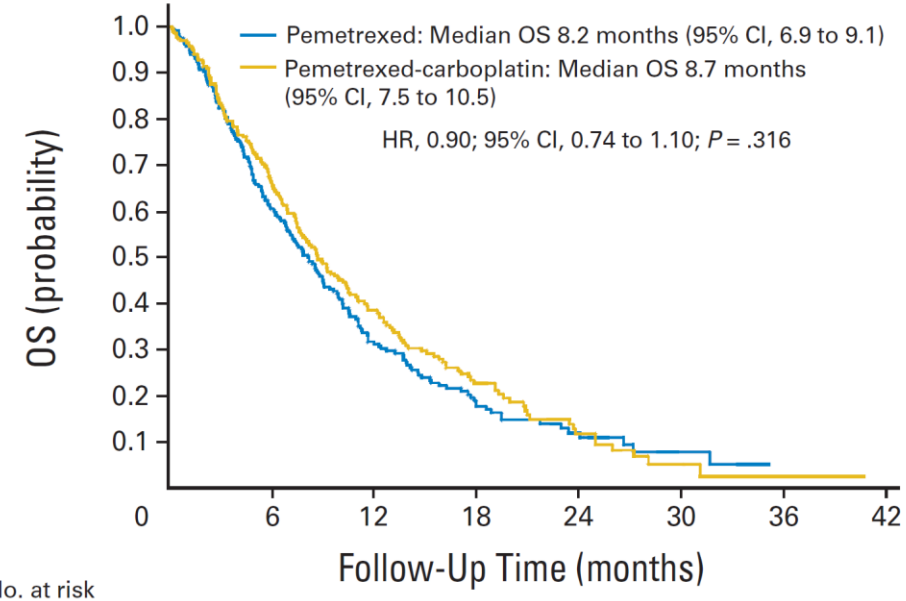
- OS med
  7,6 vs 8 m
  HR=0,85 [0,63- 1,2]

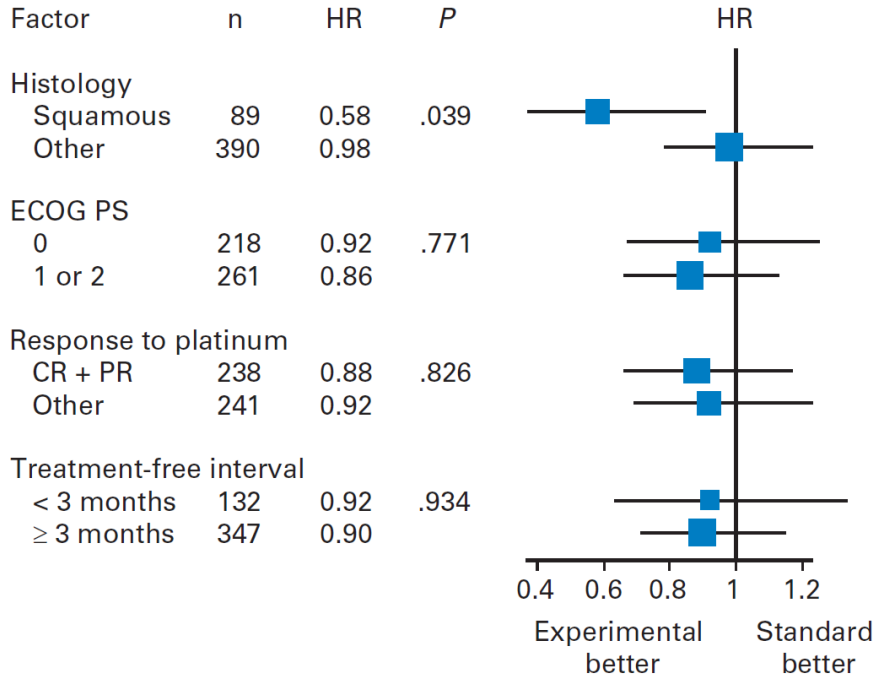


25% SCC – better OS if free interval > 6 months

Pem. vs Pem. + carbo
Pooled analysis - OS

GOIRC 02-2006 & NVALT 7





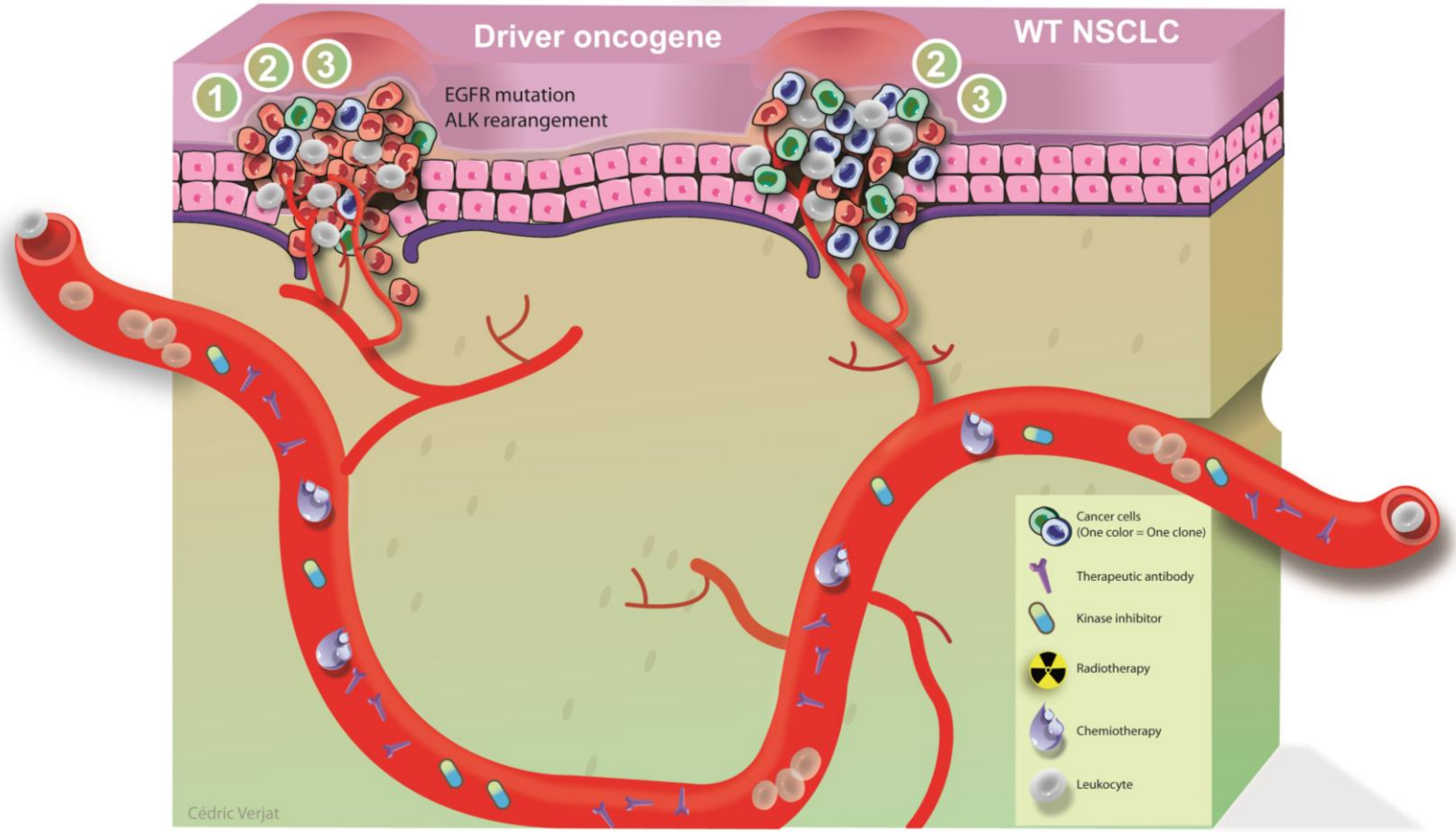
OUTLINE -2
beyond 1st line

- Switch maintenance
- Continuation maintenance
- Which pts for 2nd/3rd line?
- Best 2nd/3rd line?
- Beyond second line?
- **Re-challenge platinum?**

Recommendation:

In advanced NSCLC patients treated with first-line cisplatin-doublet chemotherapy, there is no proven role for re-challenge with platinum compounds. (D,II)


Wed,Jul 02,2008 PM03:01:06
Camera02


Driver oncogene
WT NSCLC
1
2
3
2
3
EGFR mutation
ALK rearangement
Cancer cells
(One color = One clone)
Therapeutic antibody
Kinase inhibitor
Radiotherapy
Chemiotherapy
Leukocyte
Cédric Verjat

NSCLC stage IV, PS 0 or 1

P2/old

Non Squamous cell carc.

SCC

EGFR and ALK wt

Fit?

Eligible for bevacizumab

Non eligibles for bevacizumab

Yes

No

CDDP (carboP if CI)

+ Gemcitabine, taxanes ou vinorelbine
or pemetrexed if non-SCC
+/- bevacizumab in non-SCC

Single agent

Docetaxel ou erlotinib

Pemetrexed