Predictive Models for Chemo- and Radiotherapy

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Disclosures

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Brain metastases (BM) development after chemoradiation for stage III Non-Small Cell Lung Cancer: does the type of chemotherapy matter?

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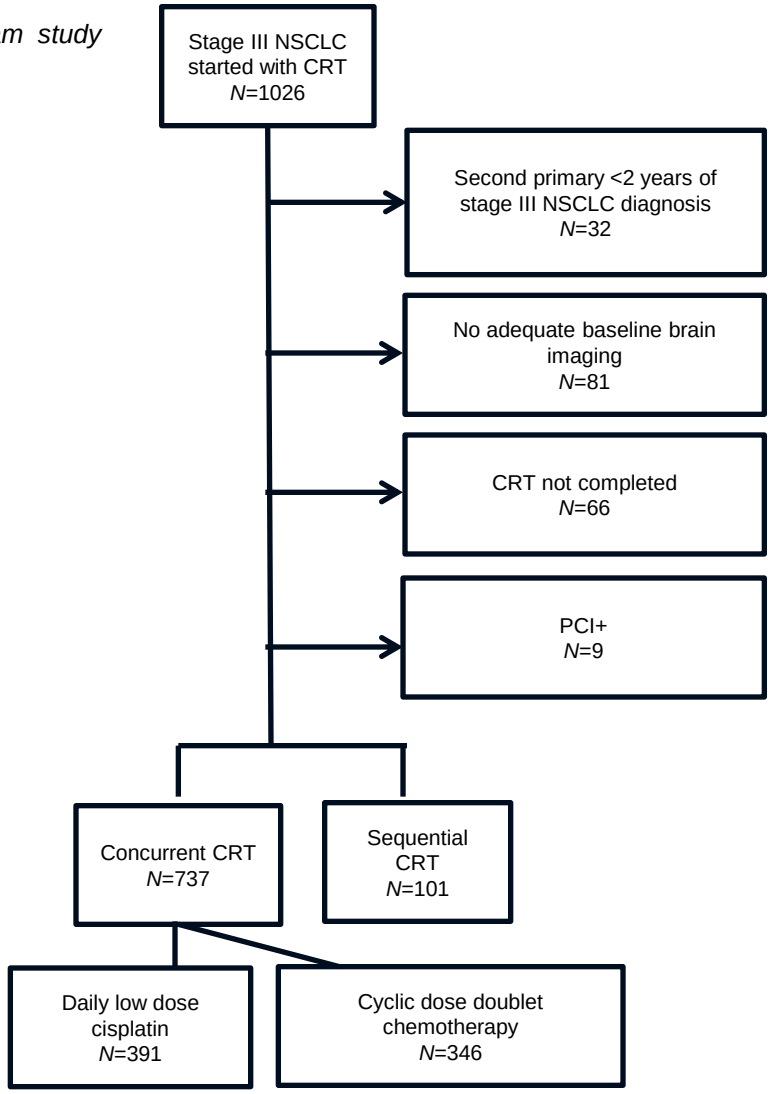
Consort diagram study inclusion



Retrospective multicenter study

- Jan 1st 2006 - June 30th 2014
- Last date of FU June 30th 2015

Included

- ^{18}FDG-PET staged stage III NSCLC pts who completed CRT
- Baseline CT/MRI brain without BM

Primary endpoints

- For different chemotherapy regimens:
  - BM development within 1st year of stage III NSCLC diagnosis;
  - BM as only site of first relapse

Maastricht UMC+ | azM | Maastricht University

Results

Percentage brain metastases development < 1 year

	BM <1 year of NSCLC diagnosis *N* (%)	***p*-value**	**BM as only site of first relapse *N* (%)**	***p*- value**
Patients (*N*)	88/838 (11)		39/838 (5)	
CRT				
- Sequential	10/101 (10)	0.834	4/101 (4)	0.724
- Concurrent	78/737 (11)		35/737 (5)	
Concurrent CRT				
- Doublet CTx	37/346 (11)	0.927	14/346 (4)	0.399
- Daily LD cis	41/391 (11)		21/391 (5)	

***Abbrevations: LD; low dose, cis; cisplatin*.**

Logistic regression analysis

Only concurrent chemoradiation patients (*N*=737)		
	OR (95% CI)	*p*-value
All brain relapses <1 year		
Gender (female vs male)	1.01 (0.67-1.51)	0.974
Age (continuous, older vs younger)	0.98 (0.96-0.99)	**0.037**
T-stage (T3-4 vs T0-2)	1.18 (0.78-1.77)	0.431
N-stage (N2-3 vs N0-1)	1.88 (0.90-3.93)	0.095
Treatment regimen (LD cis vs cyclic doublet)	0.96 (0.65-1.41)	0.819
Histology (SQCC vs AdC)	0.19 (0.10-0.36)	**<0.001**
Histology (NOS vs AdC)	0.73 (0.47-1.12)	0.153

Abbrevations: LD: low dose; cis: cisplatin; SQCC; squamous cell carcinoma, AdC; adenocarcinoma, NOS; not otherwise specified.

Results

- No differences in BM diagnosis < 1 year, as first site of relapse irrespective of
  - Concurrent versus sequential
- Within concurrent group:
  - Daily low dose cisplatin (N=391) versus cyclic dose taxane based (N=69) or non-taxane based Ctx (N=277)
  - Daily low dose cisplatin (N=391) versus cisplatin/etoposide (N=188), cisplatin/vinorelbin (N=65), weekly cisplatin/docetaxel (N=60)

Conclusions

- **11% of pts developed BM <1 year after stage III diagnosis despite no suspect brain imaging at initial diagnosis**
- **Results not dependent on type of chemotherapy regimen used within CRT treatment**

<u>Possible explanations and future directions:</u>

- **Microscopic BM present at initial diagnosis and ineffective Ctx due to inadequate blood-brain barrier (BBB) penetration**
- **BM development after CRT due to seeding of extracranial metastases**
- **Future: risk stratification tool & regular FU for high risk patients or PCI / BBB penetrating agents**

Cancer Science
Japanese Cancer Association JCA
Open Access

Impact of *KRAS* mutation on response and outcome of patients with stage III non-squamous non-small cell lung cancer

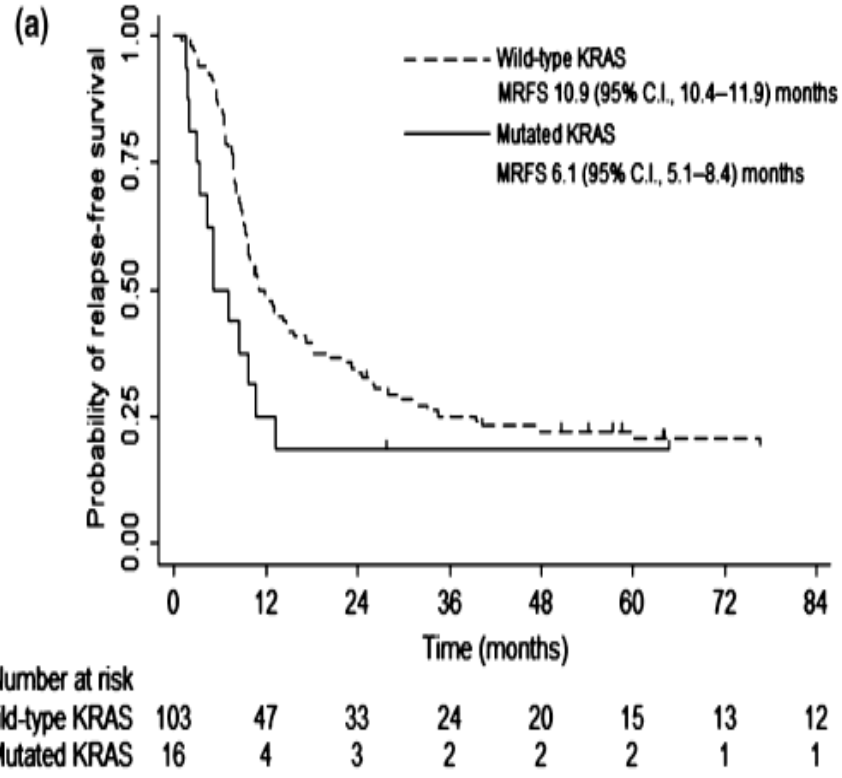
Shigehiro Yagishita,[1,2] Hidehito Horinouchi,[1,3] Kuniko S. Sunami,[1,3,5] Shintaro Kanda,[1] Yutaka Fujiwara,[1] Hiroshi Nokihara,[1] Noboru Yamamoto,[1] Minako Sumi,[4] Kouya Shiraishi,[5] Takashi Kohno,[5] Koh Furuta,[6] Koji Tsuta,[7] Tomohide Tamura[1] and Yuichiro Ohe[1,3]

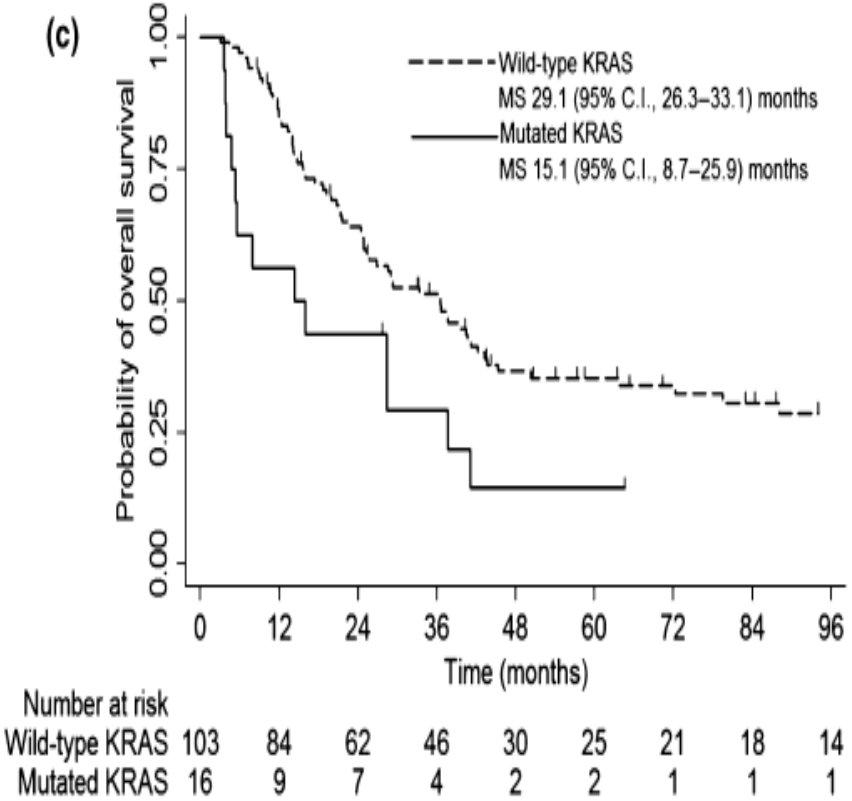
[1]Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo; [2]Department of Respiratory Medicine, Juntendo University Graduate School of Medicine, Tokyo; [3]Advanced Clinical Research of Cancer, Juntendo University Graduate School of Medicine, Tokyo; [4]Department of Radiation Oncology, National Cancer Center Hospital, Tokyo; [5]Division of Genome Biology, National Cancer Center Research Institute, Tokyo; Departments of [6] Clinical Laboratories, Tokyo; [7]Pathology, National Cancer Center Hospital, Tokyo, Japan

Overall results

- 119 patients were included in the analysis
- KRAS mutations were found at a frequency of 13%
- Patients with KRAS mutations had a shorter median relapse-free survival (6.1 vs 10.9 months) and a lower response rate (63% vs 81%)
- As for the first relapse site, patients with KRAS mutations had fewer local relapses (8% vs 23%) and more brain metastases (46% vs 12%)
- After disease progression, patients with KRAS mutations had a significantly shorter median survival post-progression (2.5 vs 7.3 months, P = 0.028) and median overall survival (15.1 vs 29.1 months, P = 0.022)

Median Relapse Free and Overall Survival





Brain metastases after definitive concurrent chemoradiotherapy in patients with stage III lung adenocarcinoma: carcinoembryonic antigen as a potential predictive factor

Horinouchi H et al. Cancer Sci. 2012 Apr;103(4):756-9. doi: 10.1111/j1349-7006.2012.02217.x.

Overall results

- In total, 116 patients were identified with a median (range) age of 57 (35-74) years
- Of these, 86 (74%) were men, all patients had platinum-based chemotherapy, and 100 (86%) received a total dose of 60 Gy in 30 fractions as definitive thoracic radiotherapy
- 95 patients had disease progression or recurrence
  - 19 (16%) developed brain metastases as the sole site of initial recurrence
  - 43 (37%) patients developed brain metastases at some time during follow-up
- Time to brain metastases was associated with the pretreatment carcinoembryonic antigen (CEA) value, with a hazard ratio = 2.64 (C.I. 1.39-5.02; P = 0.003)

PCI in operable stage III NSCLC treated with neoadjuvant chemoRt

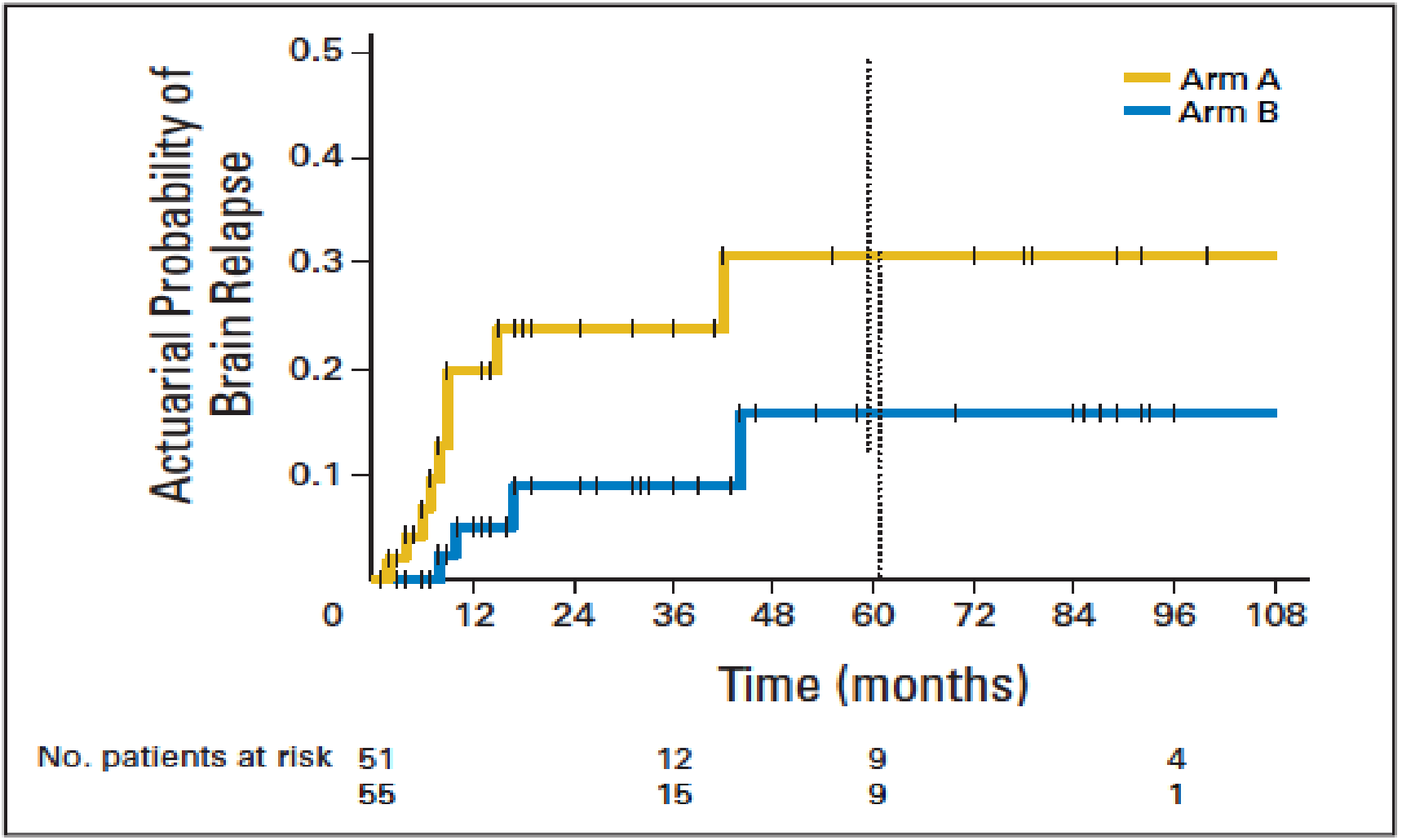
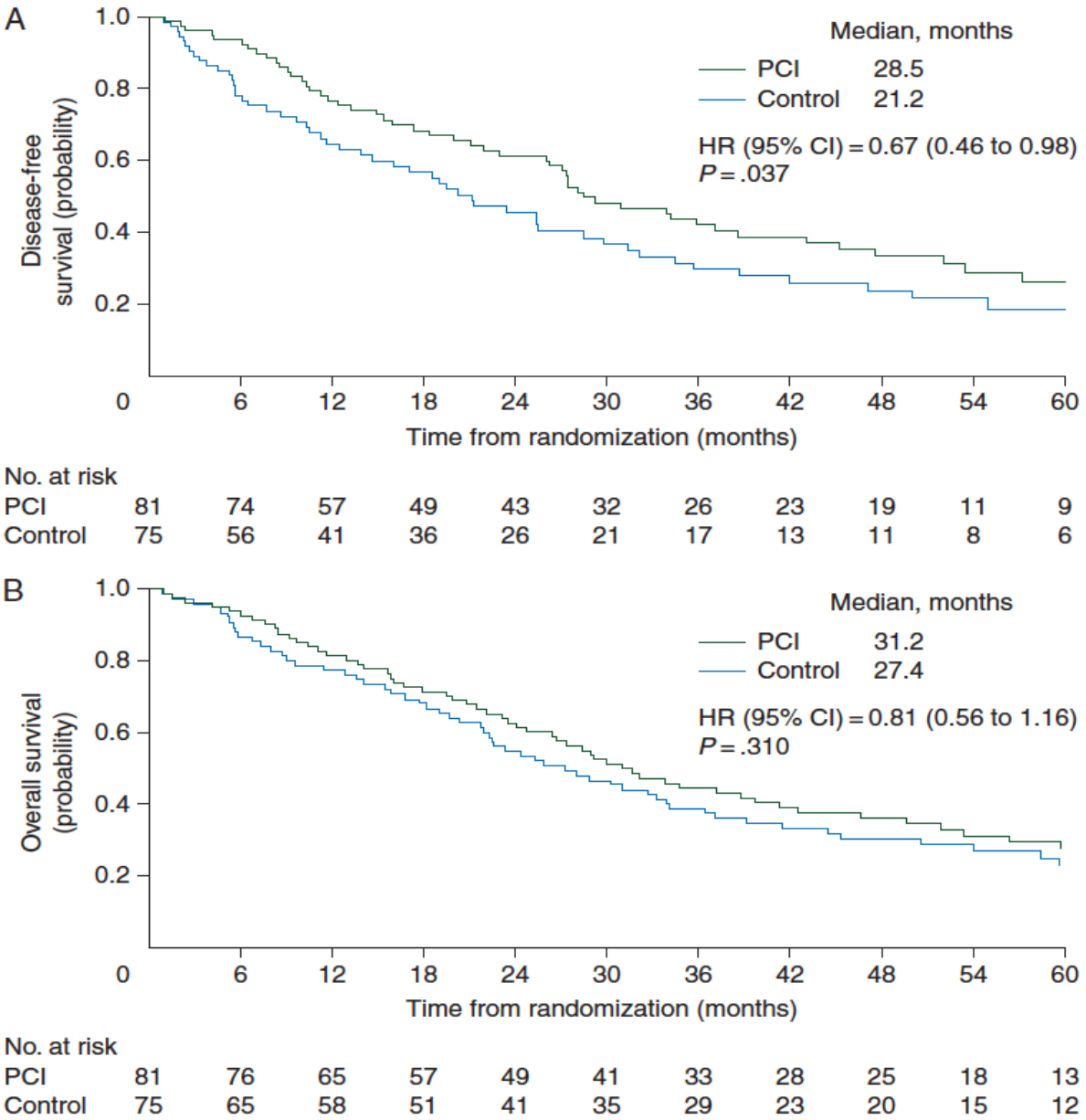


Fig 1. Actuarial probabilities of brain relapse at first site of failure by intent-to-treat analysis.

Pottgen C et al, JCO 2007

Results

- PCI significantly reduced the probability of brain metastases as first site of failure (7.8% at 5 years v 34.7%; P = .02)
- the overall brain relapse rate was reduced comparably (9.1% at 5 years v 27.2%; P = .04)
- A slightly reduced neurocognitive performance in comparison with the age-matched normal population was found for patients in both treatment groups.



Li N et al, Ann Oncol. 2015 Mar;26(3):504-9. doi: 10.1093/annonc/mdu567

Prophylactic Cranial Irradiation for Patients With Locally Advanced Non-Small-Cell Lung Cancer at High Risk for Brain Metastases

- **A seer database analysis of 17852 patients showed no evidence of an overall survival benefit for PCI in this setting**

Park HS, Decker RH, Wilson LD, Yu JB. Clin **Lung Cancer**. 2015 Jul;16(4):292-7

Bevacizumab and pemetrexed versus pemetrexed alone as maintenance therapy for patients with advanced nonsquamous NSCLC:

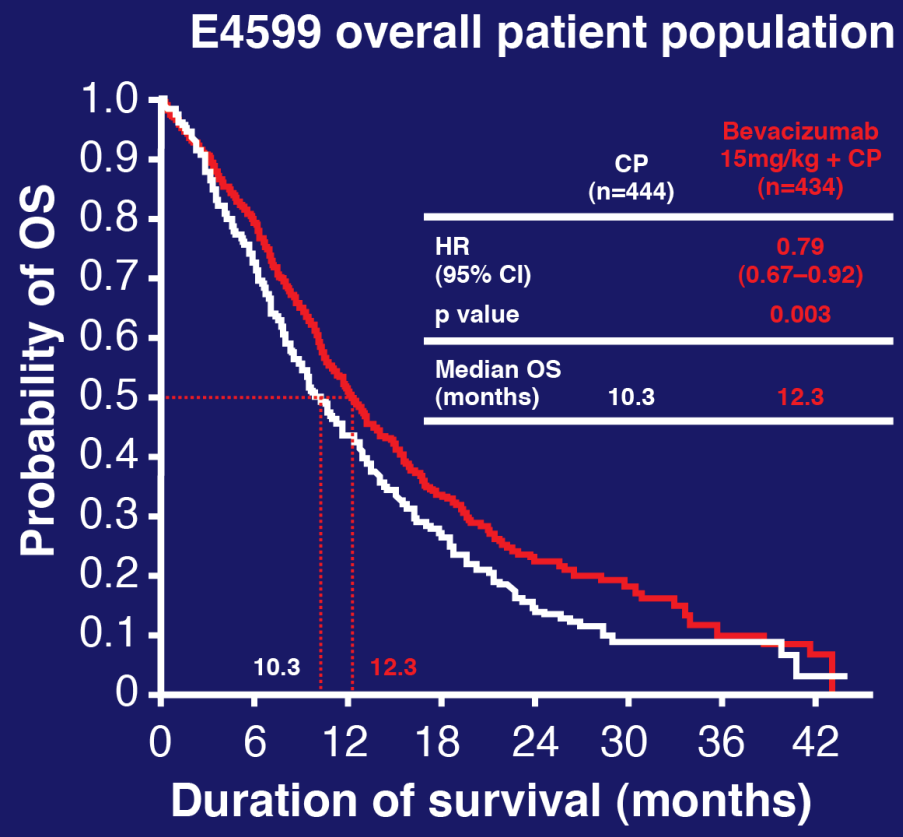
Results of the expanded SAKK19/09 trial

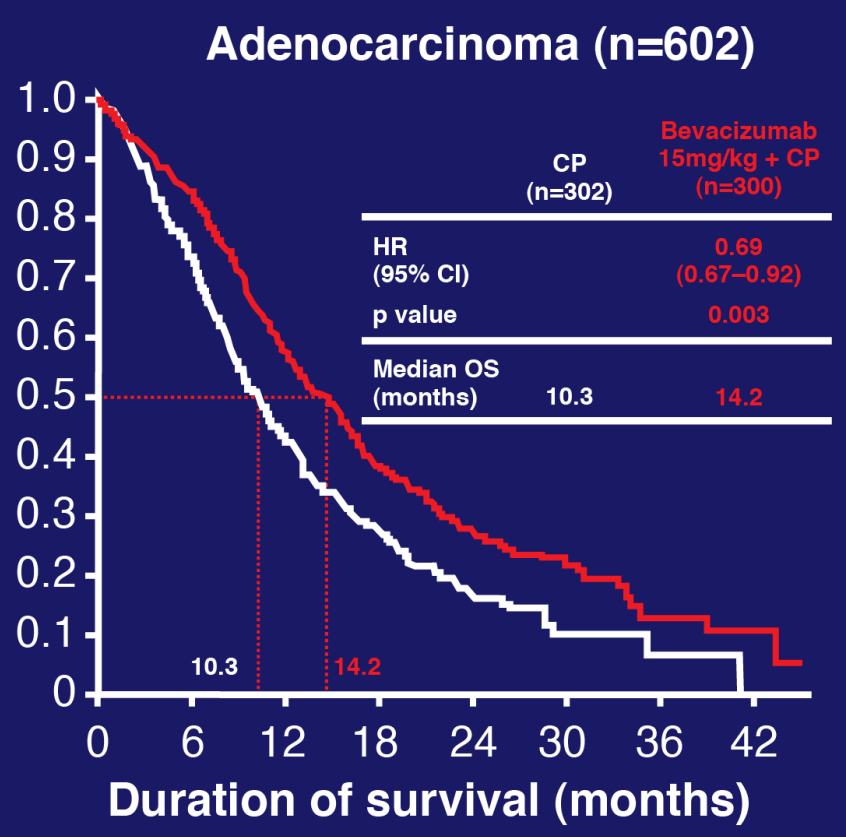
Gautschi O, Li Q, Matter-Walstra K, Betticher D, Früh M, Rauch D, Pless M, Froesch P, Mach N, Ochsenbein AF; on behalf of the SAKK

Targeting VEGF can improve survival

E4599: 1st line paclitaxel/carboplatin +/- bevacizumab in nonsquamous

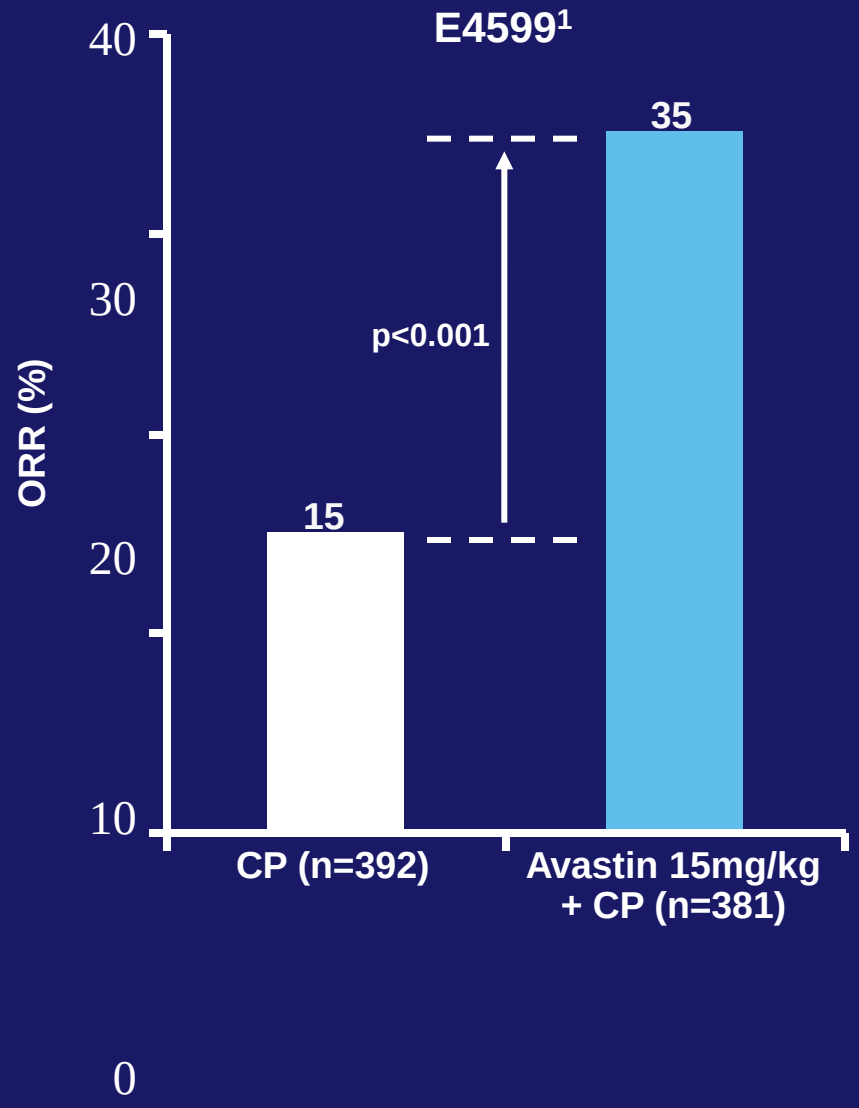
E4599: adenocarcinoma subset

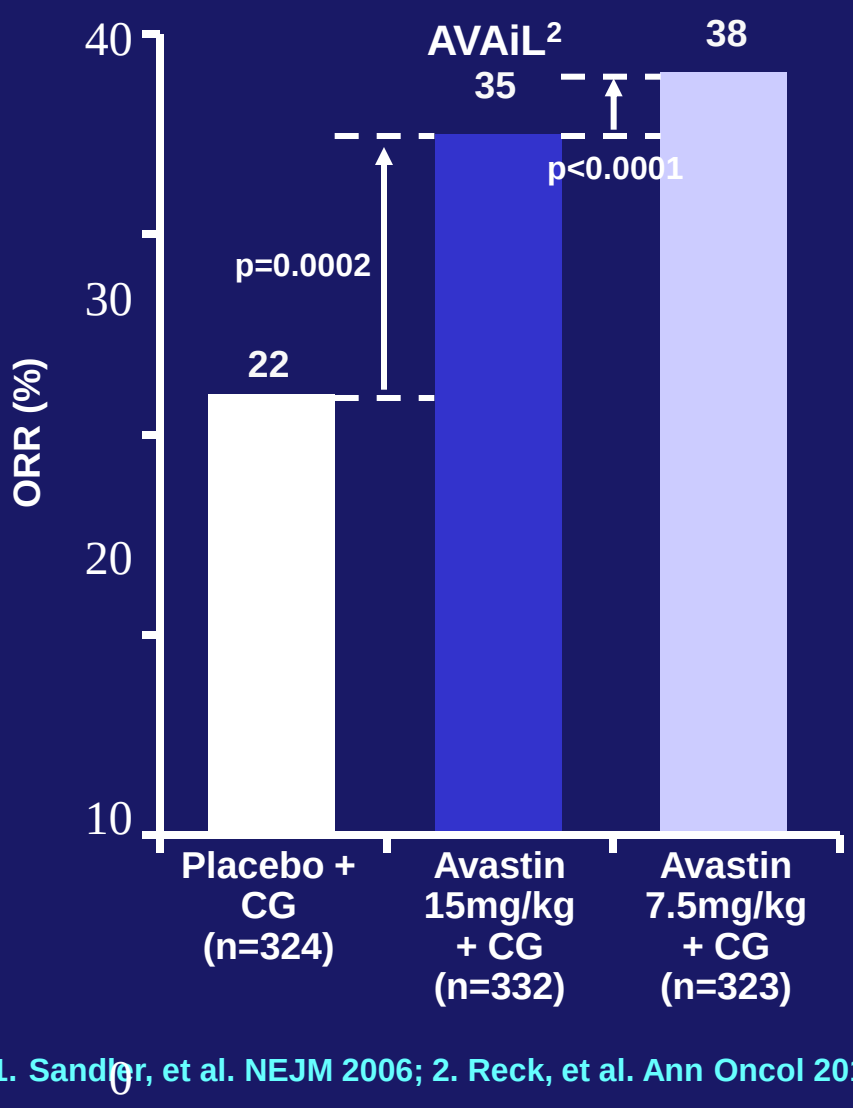




Sandler, et al. N Engl J Med 2006; Sandler, et al. J Thorac Oncol 2010.

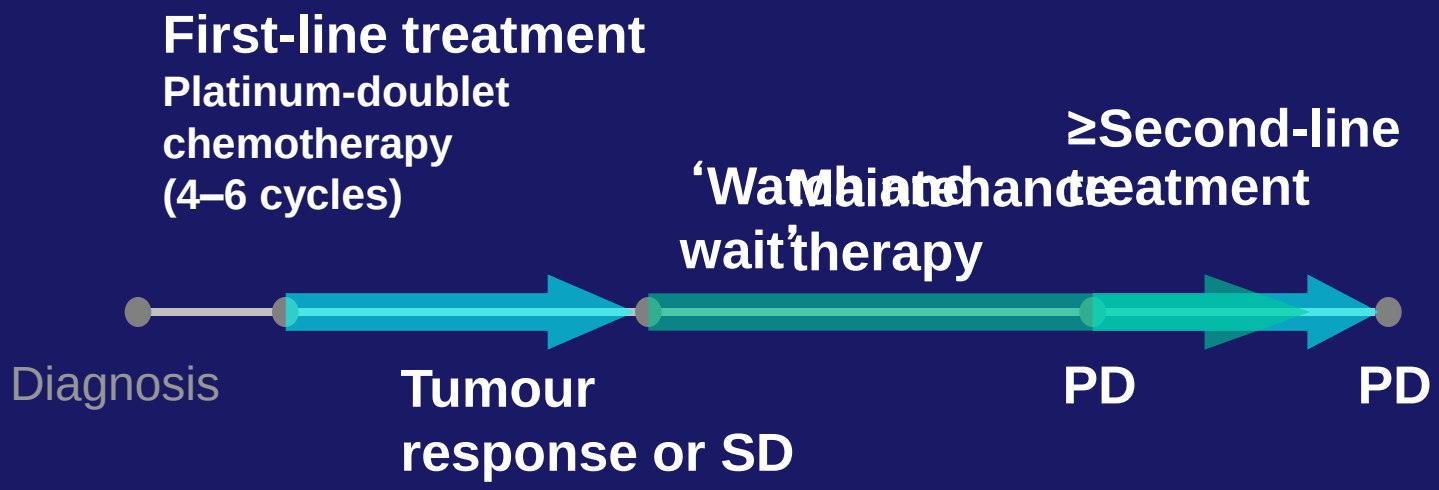
Bevacizumab and Chemotherapy: Consistent increase in ORR



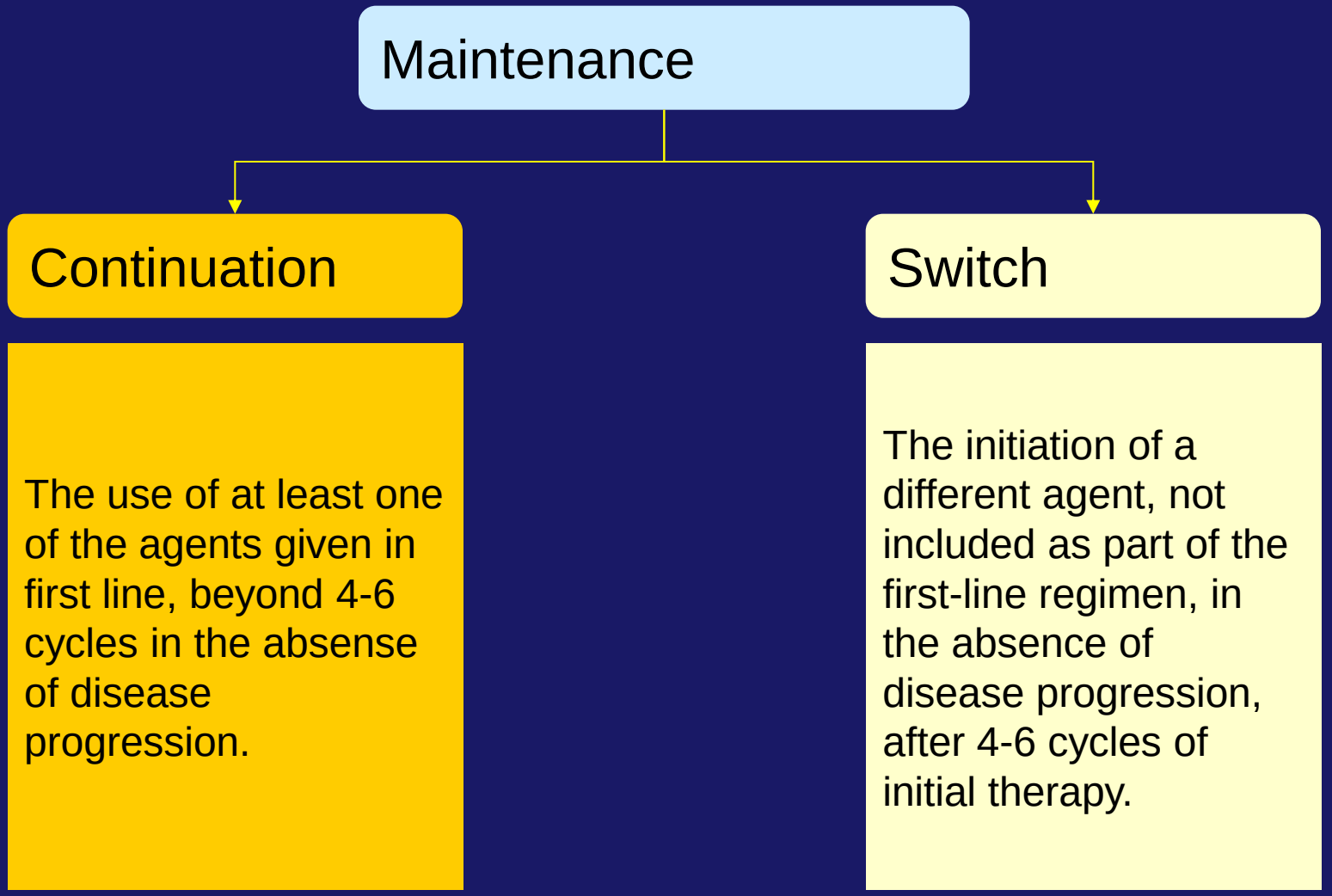


1. Sandler, et al. NEJM 2006; 2. Reck, et al. Ann Oncol 2010

Historical approach to NSCLC

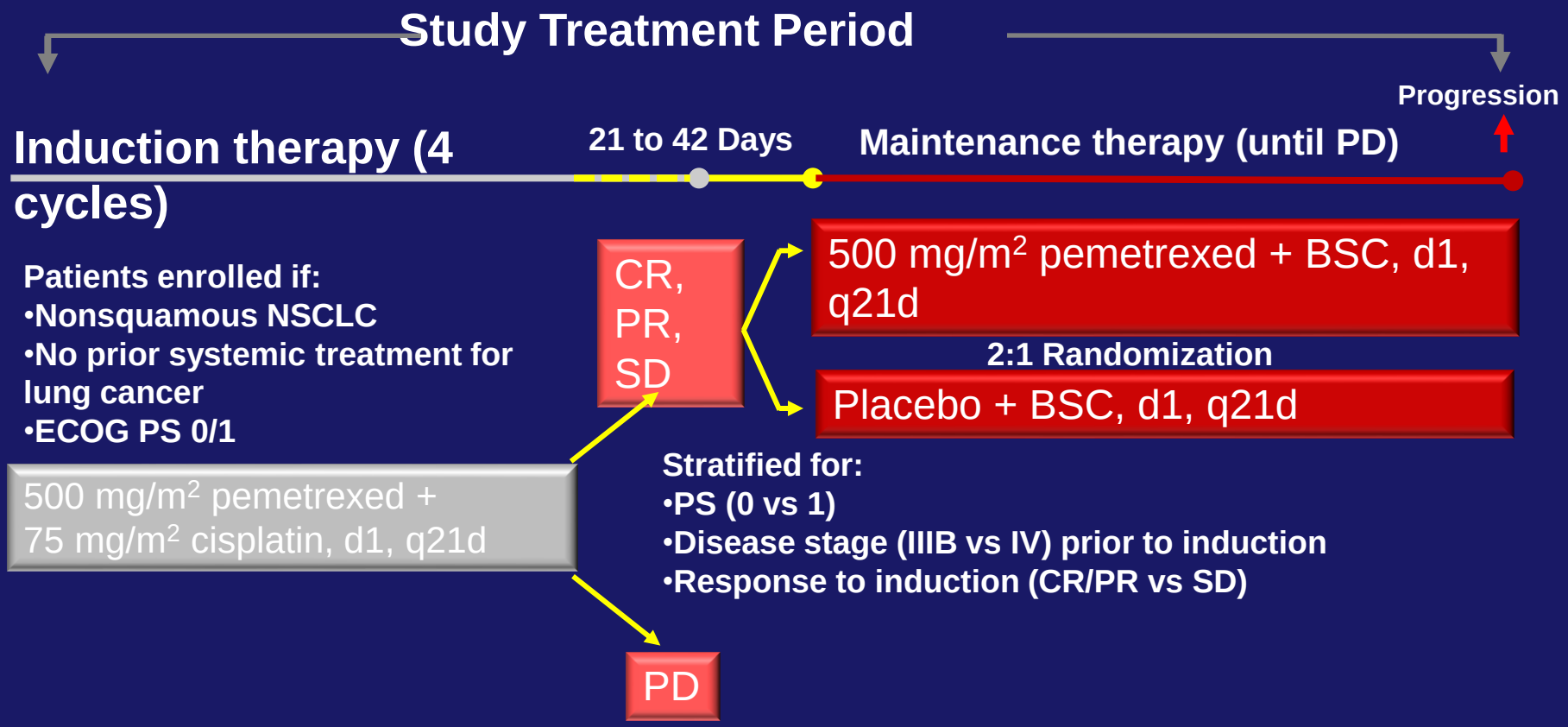


Maintenance therapy: Classification and Definition



NCCN Guidelines Version 3.2011 Non-Small Cell Lung Cancer: NSCL-F 2/3.

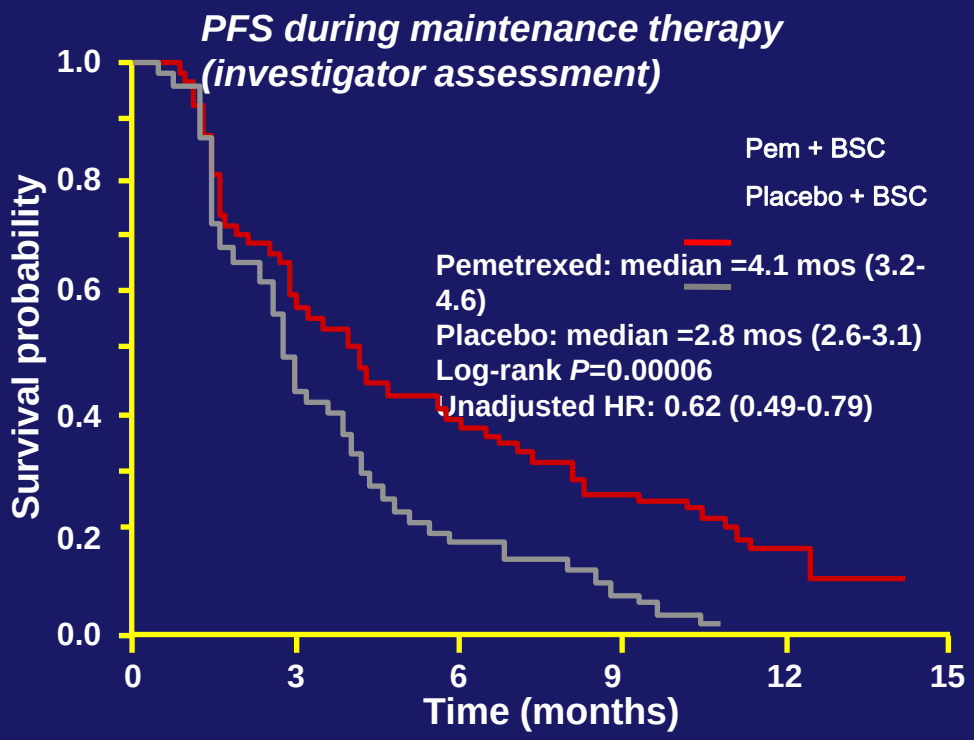
PARAMOUNT: study design



- Randomized, placebo-controlled, double-blind, phase III study
- Folic acid and vitamin B12 administered to both arms
- Objectives: primary : PFS; secondary: OS, RR, PRO, resource utilization, AEs

Paz-Ares et al. J Clin Oncol 29: 2011; (suppl; abstr CRA7510)

PARAMOUNT: efficacy



PFS	Pemetrexed (n=359)	Placebo (n=180)
Investigator-assessed events	184 (51%)	118 (66%)
Progression events	173 (94%)	113 (96%)
Deaths	11 (6%)	5 (4%)

PFS (investigator assessment)

- PFS in all subgroups (stage, induction response, pre-randomization PS, smoking status, age, sex histology) favoured pemetrexed treatment
- PFS from induction: 6.90 (pemetrexed) vs 5.59 months (placebo), HR 0.59 (0.47-0.74), p<0.0001

PFS during maintenance therapy (independent assessment):

- 88% patients independently reviewed
- Median PFS: 3.9 (pemetrexed) vs 2.6 months (placebo), HR 0.64 (0.51-0.81), p=0.0002

Response to maintenance therapy (independent assessment):

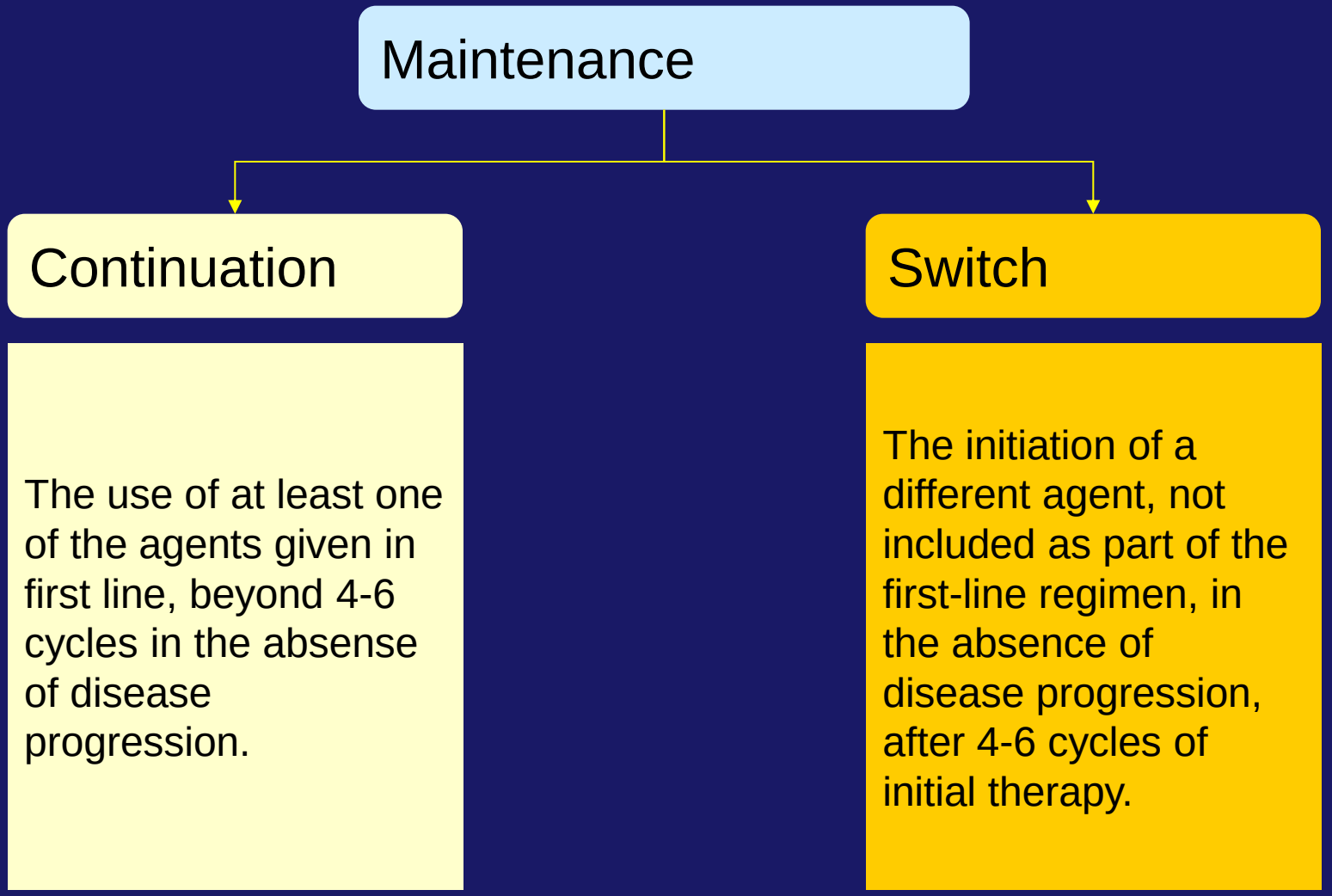
- RR: 2.8% (pemetrexed) vs 0.6% (placebo), p=0.176
- DCR: 71.8% (pemetrexed) vs 59.6% (placebo), p=0.009

PRO:

- No statistical differences in EQ-5D index score or visual analogue scale observed between treatment groups

Paz-Ares et al. J Clin Oncol 29: 2011; (suppl; abstr CRA7510)

Maintenance therapy: Classification and Definition



NCCN Guidelines Version 3.2011 Non-Small Cell Lung Cancer: NSCL-F 2/3.

Switch Maintenance: Overview of Chemotherapy Clinical Trials

Efficacy Summary

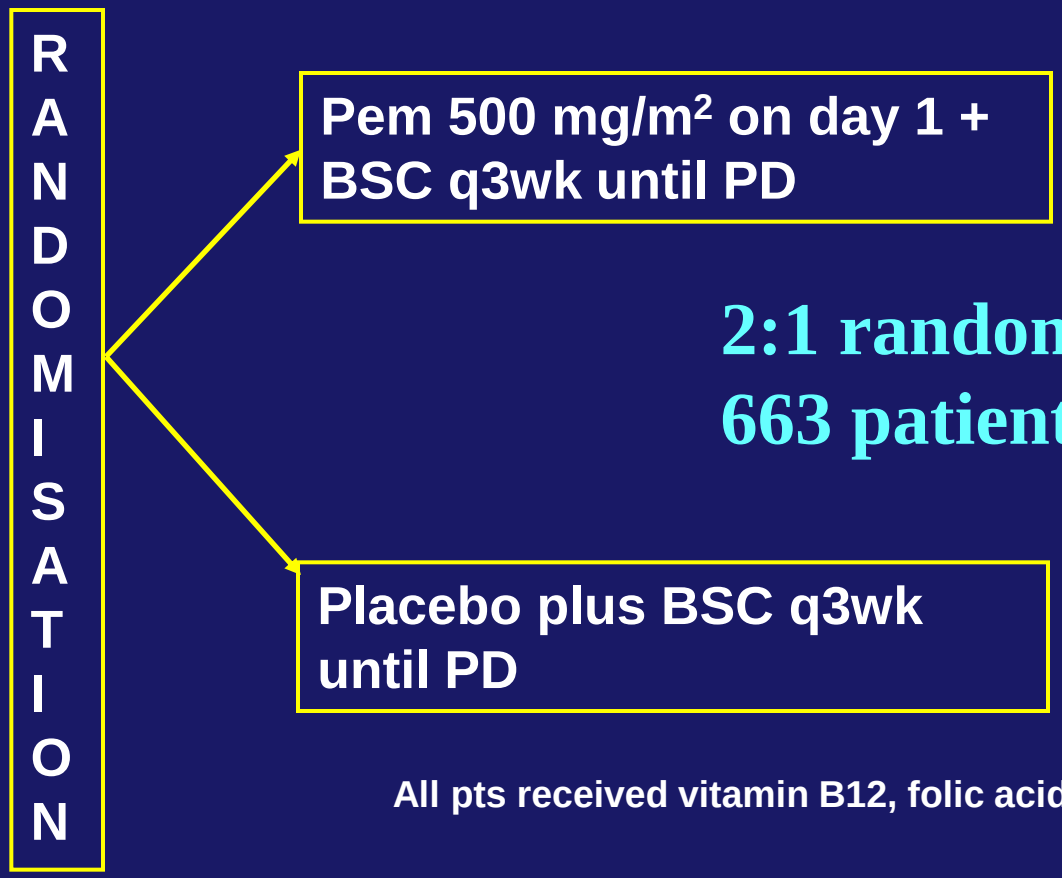
Study	Maintenance	Median TTP/PFS	Median OS
Westeel 2005[1]	Vinorelbine 25mg/m^2/w ×6m vs. Observation	5m vs. 3m (p=0.11)	12.3m vs. 12.3m (p=0.48)
Fidias 2008[2]	Immediate docetaxel 75mg/m^2 q3w×6 cycles) vs. delayed docetaxel 75mg/m^2 q3w at first PD	5.7m vs. 2.7m (p<0.001)	12.3m vs. 9.7m (p=0.0853)
Ciuleanu 2009[2]	ALIMTA® 500mg/m^2 q3w+BSC vs. BSC	4.0m vs. 2.0m (p<0.001)	13.4m vs. 10.6m (p=0.012)

1. Westeel V, et al. J Natl Cancer Inst 2005;97:499-506.
2. Fidias P and Novello S. J Clin Oncol 2010; 28:5116-5123.

NSCLC: Maintenance treatment

Maintenance Pem plus BSC vs placebo plus BSC

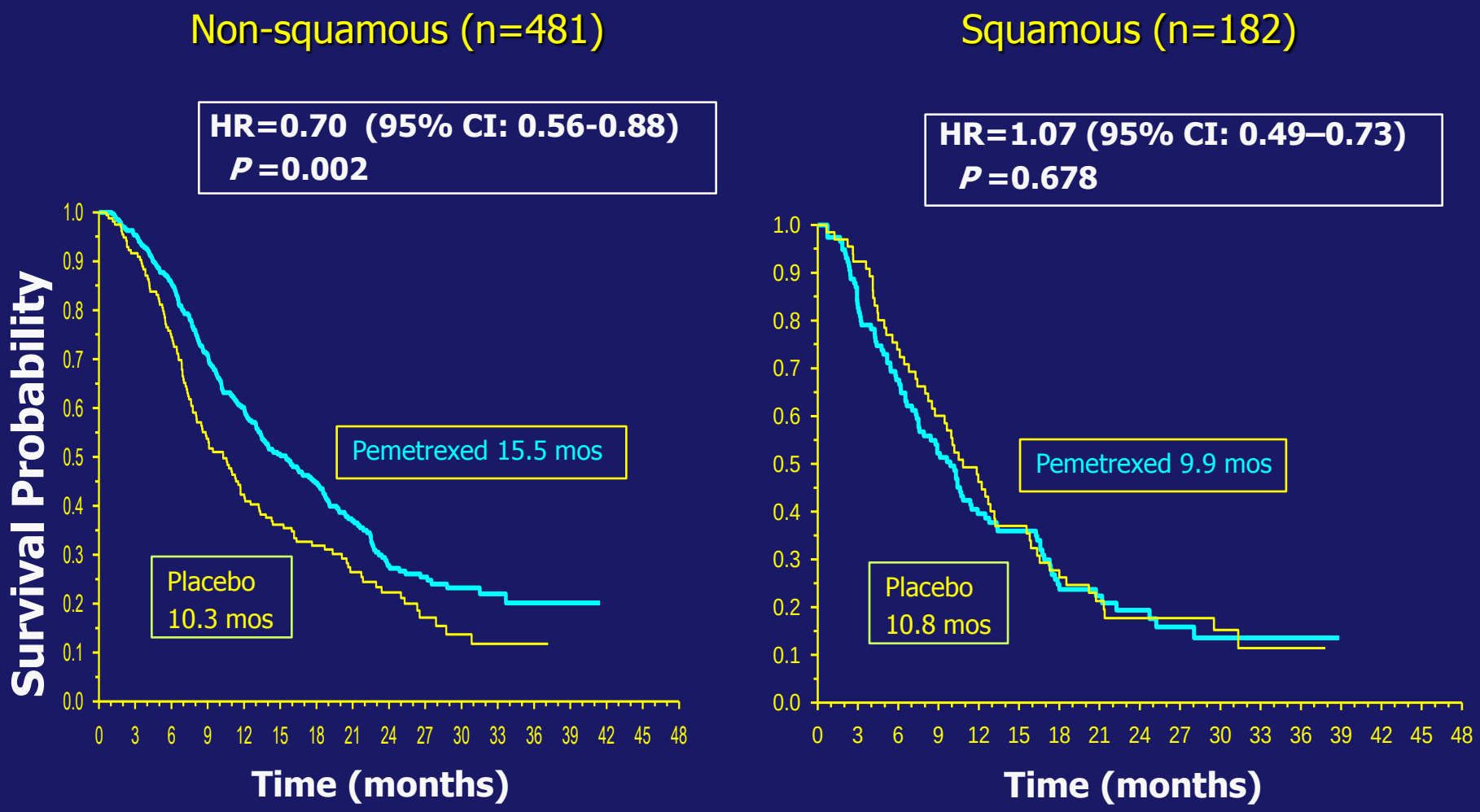
- **Design**



2:1 randomisation
663 patients randomised

All pts received vitamin B12, folic acid and dexamethasone

Overall Survival by Histology

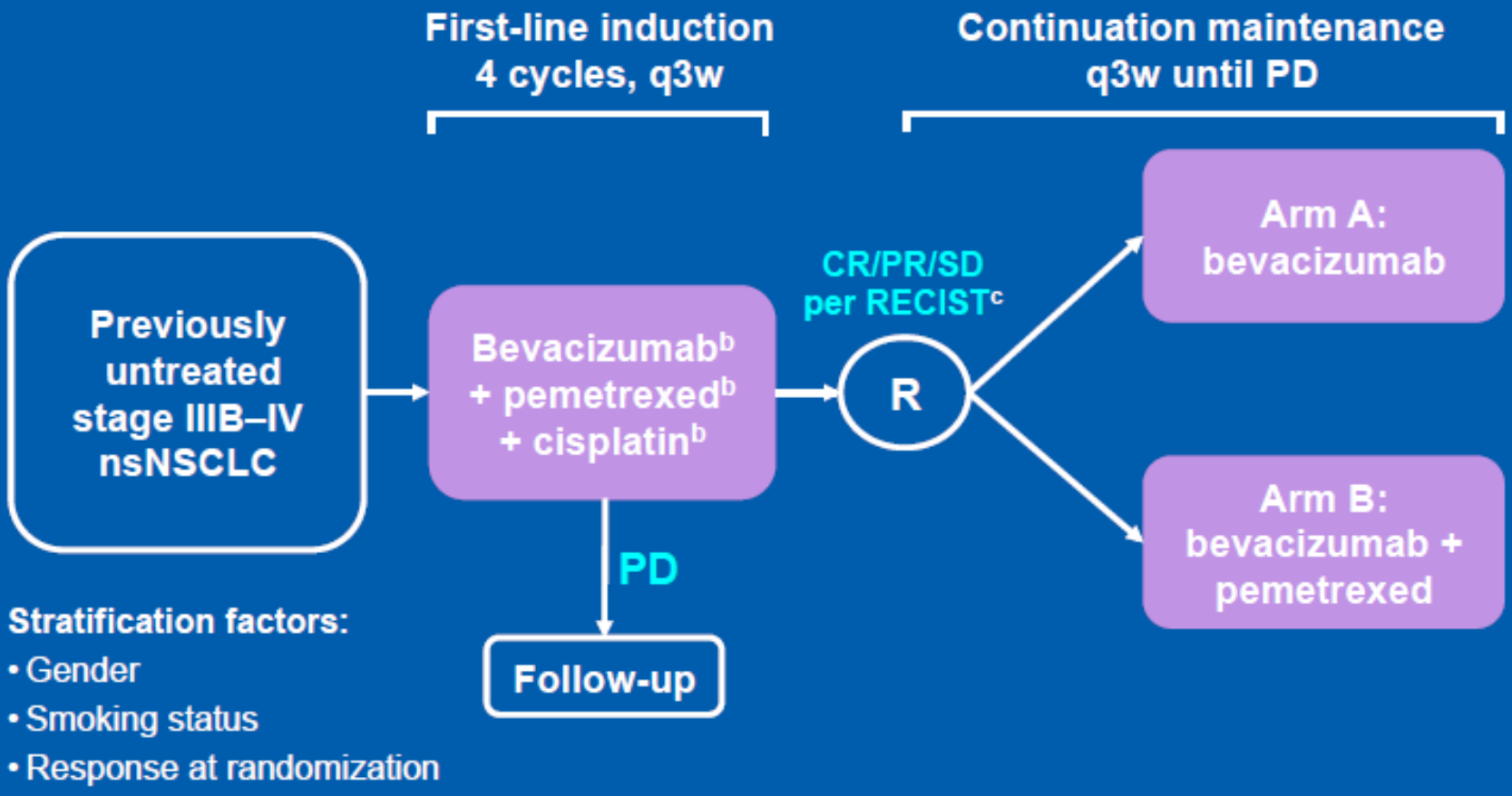


PRONOUNCE: randomized, open-label, phase III study of first-line pemetrexed + carboplatin followed by maintenance pemetrexed versus paclitaxel + carboplatin + bevacizumab followed by maintenance bevacizumab in patients with advanced nonsquamous non-small-cell lung cancer

- PFS, OS, ORR, or DCR did not differ significantly between the arms

Zinner Rg et al, J Thorac Oncol. 2015 Jan;10(1):134-42.

AVAPERL trial design[a]



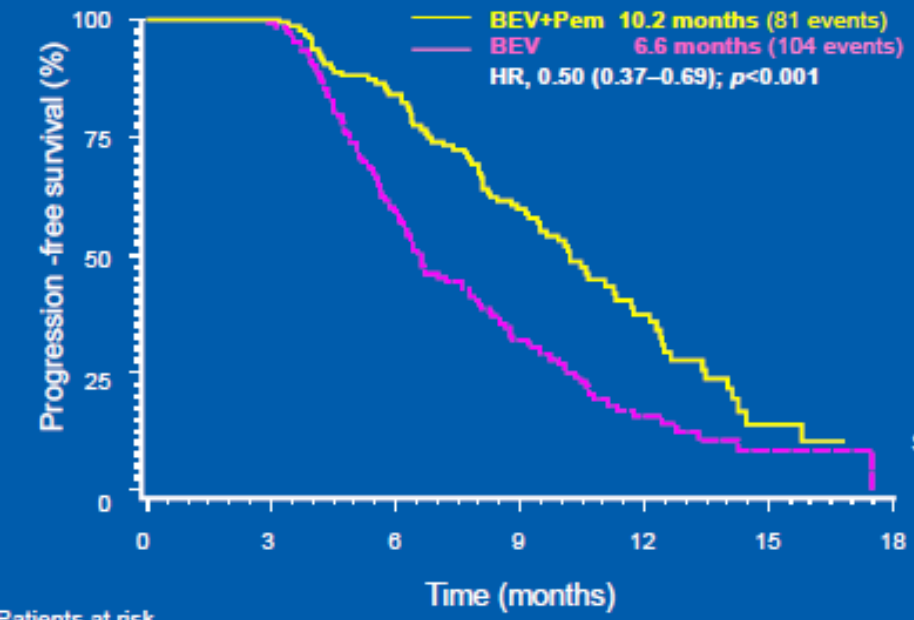
nsNSCLC, nonsquamous non–small cell lung cancer

[a]Randomized, open-label, phase III study; [b]Dose of bevacizumab = 7.5 mg/kg; dose of pemetrexed = 500 mg/m^2; dose of cisplatin = 75 mg/m^2. RECIST-related end points measured from the preinduction phase

Barseli et al. EJC: 2011; (suppl; abstr 34LBA)

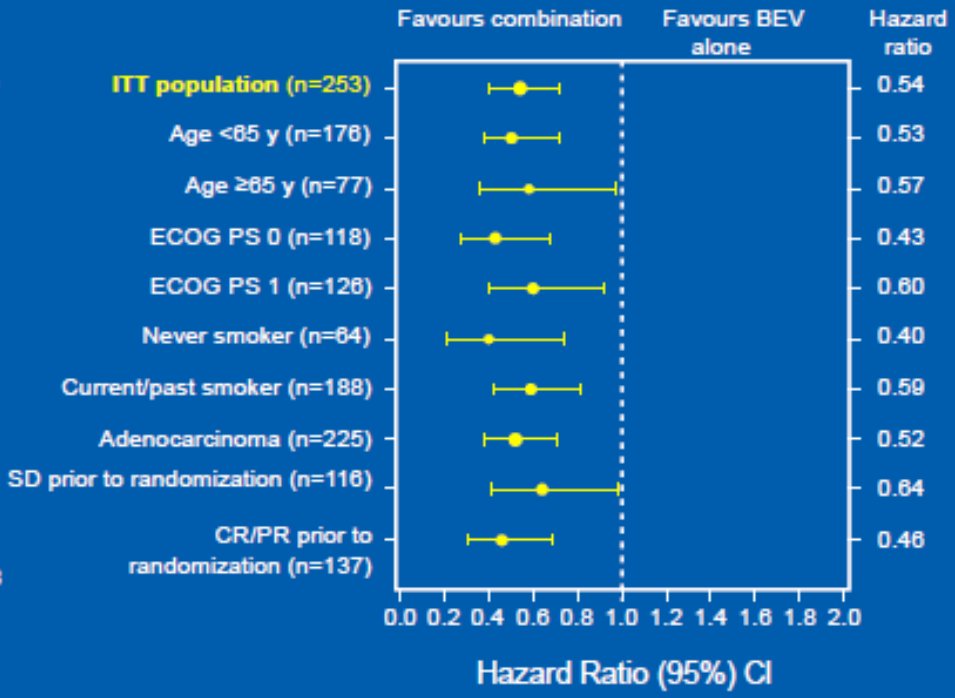
Key results

PFS from induction[a]



[a] Randomized patients, intent-to-treat population

PFS subgroup analysis

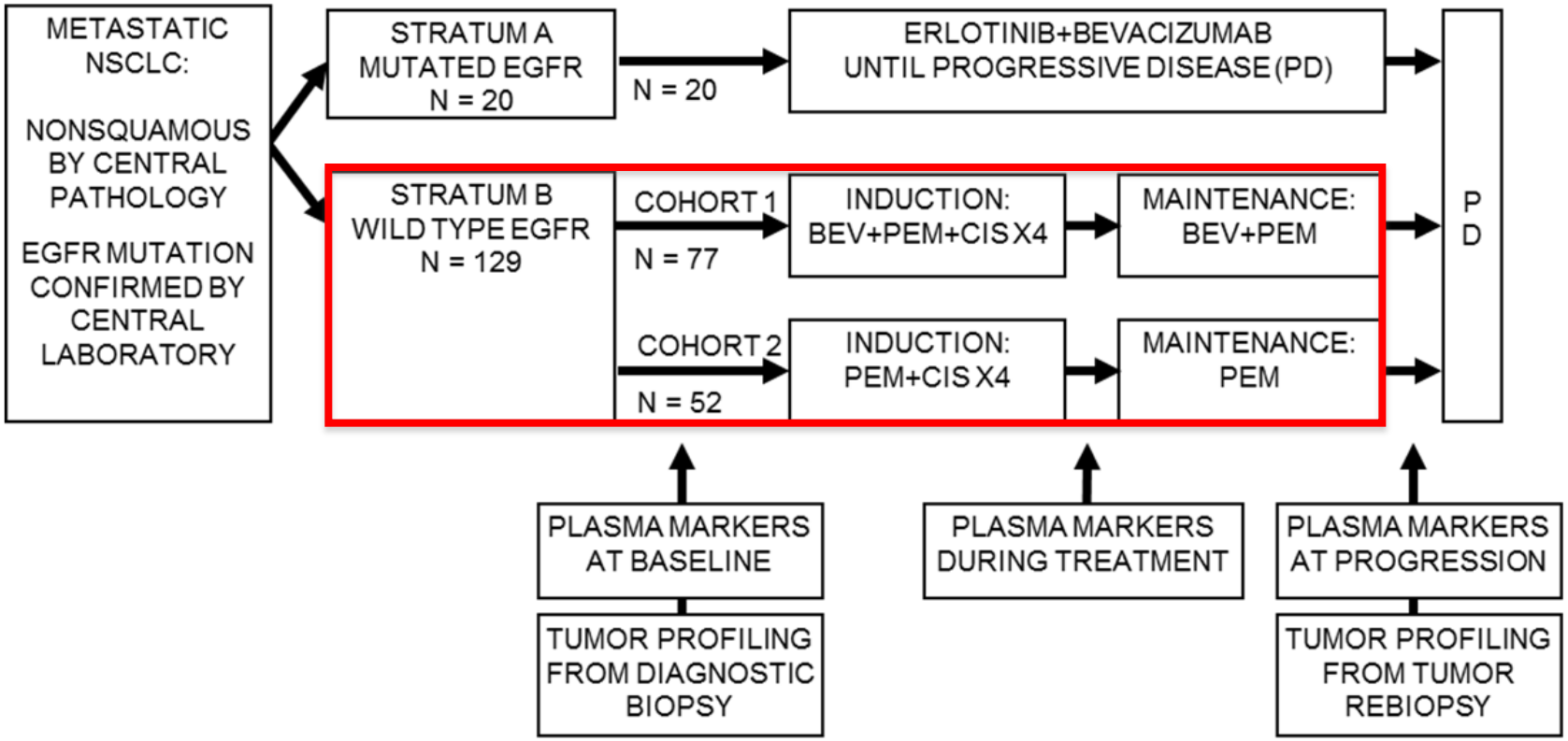


Pem + BEV maintenance treatment was associated with a marked increase in PFS over BEV alone

Positive effect on PFS was observed in all subgroups studied

Barseli et al. EJC: 2011; (suppl; abstr 34LBA)

SAKK 19/09 Trial Overview



SAKK
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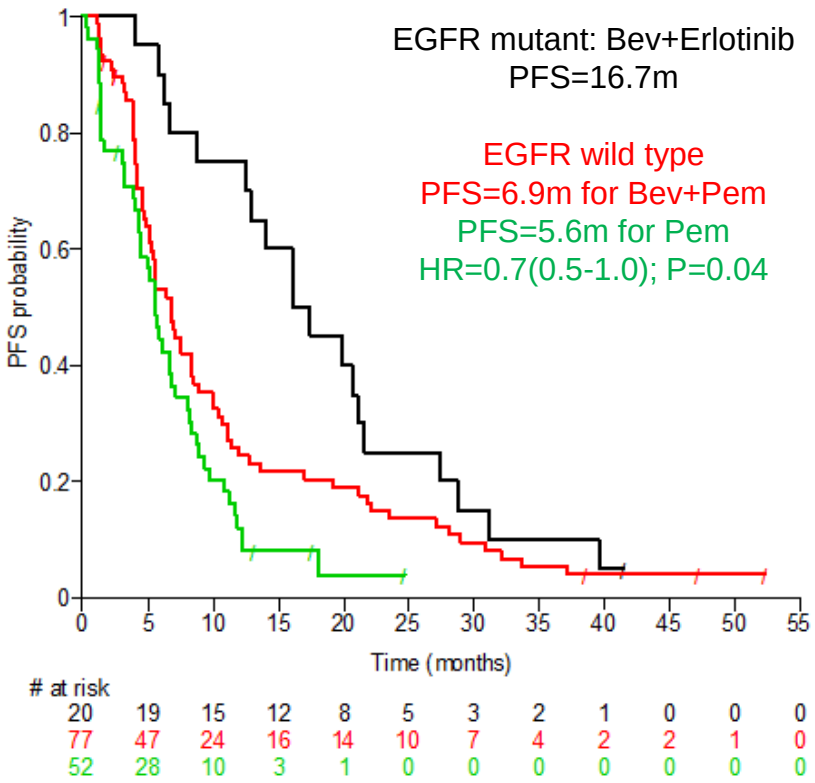
Aims and Methods

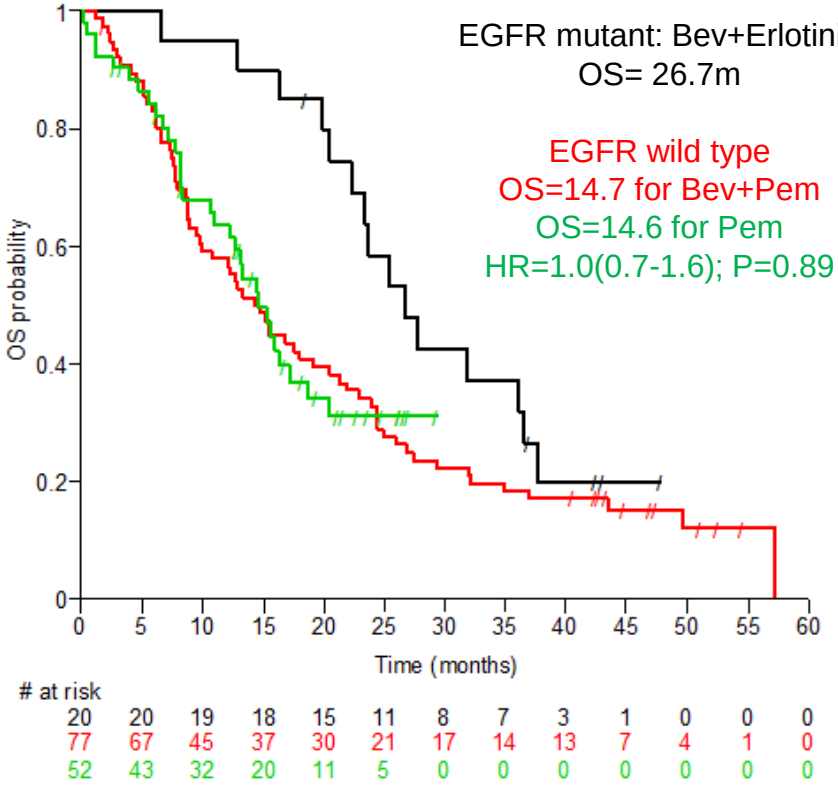
- Efficacy analysis of new cohort 2 (Pem alone)
- Comparison with updated cohort 1 (Bev+Pem; Gautschi, Clin Lung Cancer 2015)
- Identical population, Pem dose and follow up
- Primary endpoint: PFS by RECIST1.1
- Further outcomes of interest: survival, response, adverse effects, treatment costs

Main Results



EGFR mutant: Bev+Erlotinib
PFS=16.7m

EGFR wild type
PFS=6.9m for Bev+Pem
PFS=5.6m for Pem
HR=0.7(0.5-1.0); P=0.04



EGFR mutant: Bev+Erlotinib
OS= 26.7m

EGFR wild type
OS=14.7 for Bev+Pem
OS=14.6 for Pem
HR=1.0(0.7-1.6); P=0.89

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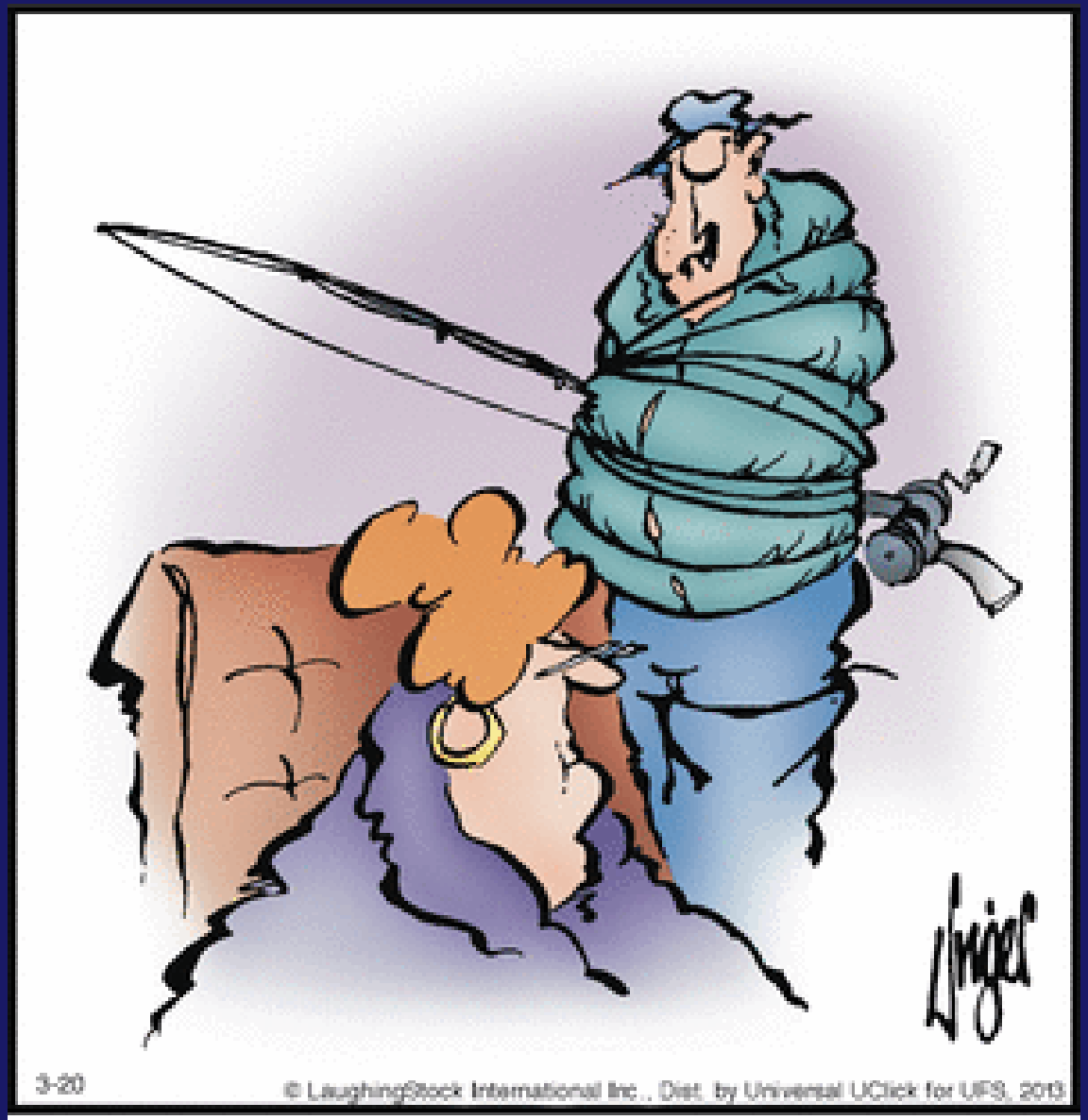
Conclusions

- Maintenance therapy with Bev+Pem increased PFS, but not OS, compared with Pem alone
- Treatment costs per month were $10,226 with Bev+Pem and $6,251 with Pem alone
- Translational research is ongoing, using rebiopsies at progression
- The ongoing ECOG 5508 phase III trial compares Bev versus Pem versus Bev+Pem (OS as primary endpoint)



"I hooked a real big one but it kept swimming around the boat."

nab-Paclitaxel + Carboplatin (*nab*-P/C) in Advanced Non-small Cell Lung Cancer (NSCLC): Outcomes in Elderly Patients (pts) With Squamous (SCC) Histology

Cesare Gridelli, Tianlei Chen, Amy Ko, Mary O'Brien, Teng Jin Ong, Mark A. Socinski, Pieter E. Postmus

Gridelli C, et al. Poster presented at ELCC 2016 [Poster FPN 216PD].

Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial.

Quoix E et al, Lancet. 2011 Sep 17;378(9796):1079-88. doi: 10.1016/S

Overall results

- 226 enrolled patients were randomly assigned monotherapy and 225 doublet chemotherapy
- Median age was 77 years and median follow-up was 30.3 months (range 8.6-45.2)
- Median overall survival was 10.3 months for doublet chemotherapy and 6.2 months for monotherapy (hazard ratio 0.64, 95% CI 0.52-0.78; p<0.0001)
  - 1-year survival was 44.5% (95% CI 37.9-50.9) and 25.4% (19.9-31.3), respectively
  - Toxic effects were more frequent in the doublet chemotherapy group than in the monotherapy group (most frequent, decreased neutrophil count (108 [48.4%] vs 28 [12.4%]; asthenia 23 [10.3%] vs 13 [5.8%])

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Weekly *nab*-Paclitaxel in Combination With Carboplatin Versus Solvent-Based Paclitaxel Plus Carboplatin as First-Line Therapy in Patients With Advanced Non–Small-Cell Lung Cancer: Final Results of a Phase III Trial

Mark A. Socinski, Igor Bondarenko, Nina A. Karaseva, Anatoly M. Makhson, Igor Vynnychenko, Isamu Okamoto, Jeremy K. Hon, Vera Hirsh, Paul Bhar, Hui Zhang, Jose L. Iglesias, and Markus F. Renschler

Overall response rate: Primary end-point of the study

Table 2. Response Rates for the Intent-to-Treat Population and Histologic Subset Based on Independent Radiologic Assessment

Response Rates	*nab*-PC			sb-PC			Response Rate Ratio*	95% CI	*P*†
	No.	%	95% CI	No.	%	95% CI			
	n = 521			n = 531					
Intent-to-treat									
Overall response	170	33	28.6 to 36.7	132	25	21.2 to 28.5	1.313	1.082 to 1.593	.005
Complete response	0			1	< 1				
Partial response	170	33		131	25				
Stable disease‡	104	20		128	24				
Progressive disease	83	16		84	16				
	n = 229			n = 221					
Squamous subset									
Overall response	94	41	34.7 to 47.4	54	24	18.8 to 30.1	1.680	1.271 to 2.221	< .001
	n = 292			n = 310					
Nonsquamous subset									
Overall response	76	26	21.0 to 31.1	78	25	20.3 to 30.0	1.034	0.788 to 1.358	.808

NOTE: The Hommel procedure was used to adjust for the three comparisons related to tumor response (overall populations and two histology subgroups).[22] The treatment and histology interaction was based on logistic regression.

Abbreviations: nab-PC, 130-nm albumin-bound paclitaxel + carboplatin; sb-PC, solvent-based paclitaxel + carboplatin.

*95% CIs for response rate ratios are calculated according to the asymptotic 95% CI of the relative risk of *nab*-PC to sb-PC.

†*P* values are based on the χ^2 test.

‡Stable disease was defined as ≥ 16 weeks.

Annals of Oncology 24: 314–321, 2013
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Safety and efficacy of weekly *nab*®-paclitaxel in combination with carboplatin as first-line therapy in elderly patients with advanced non-small-cell lung cancer

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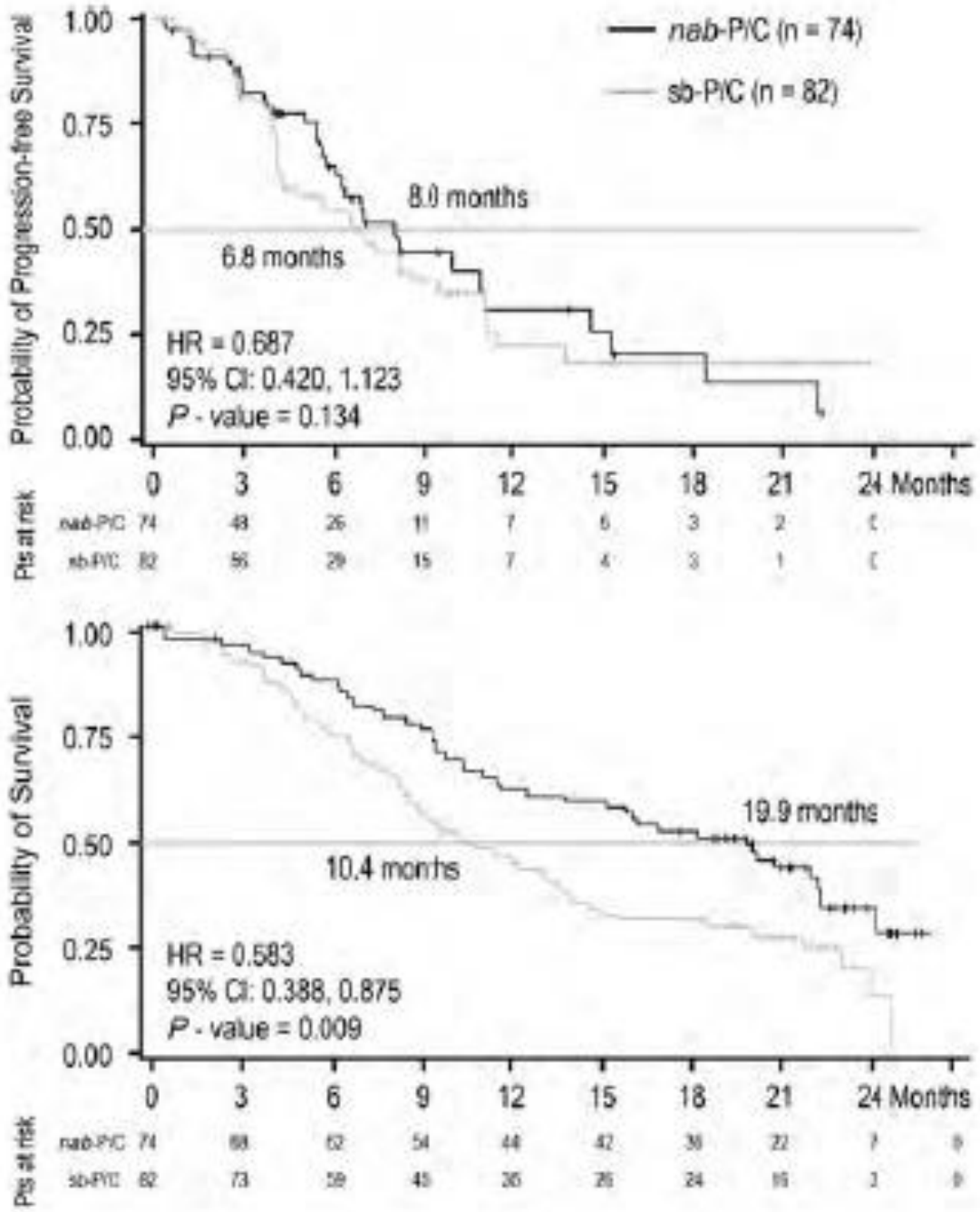

Kaplan–Meier curves in the elderly population:

(a)PFS (top) with 8.0 and 6.8 median months in the nab-P/C versus sb-P/C arms, respectively

(b) OS (bottom) with 19.9 and 10.4 median months in the nab-P/C versus sb-P/C arms, respectively

nab-P/C, 130-nm albumin-bound paclitaxel + carboplatin; sb-P/C, solvent-based paclitaxel + carboplatin

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Survival, quality-adjusted survival, and other clinical end points in older advanced non-small-cell lung cancer patients treated with albumin-bound paclitaxel

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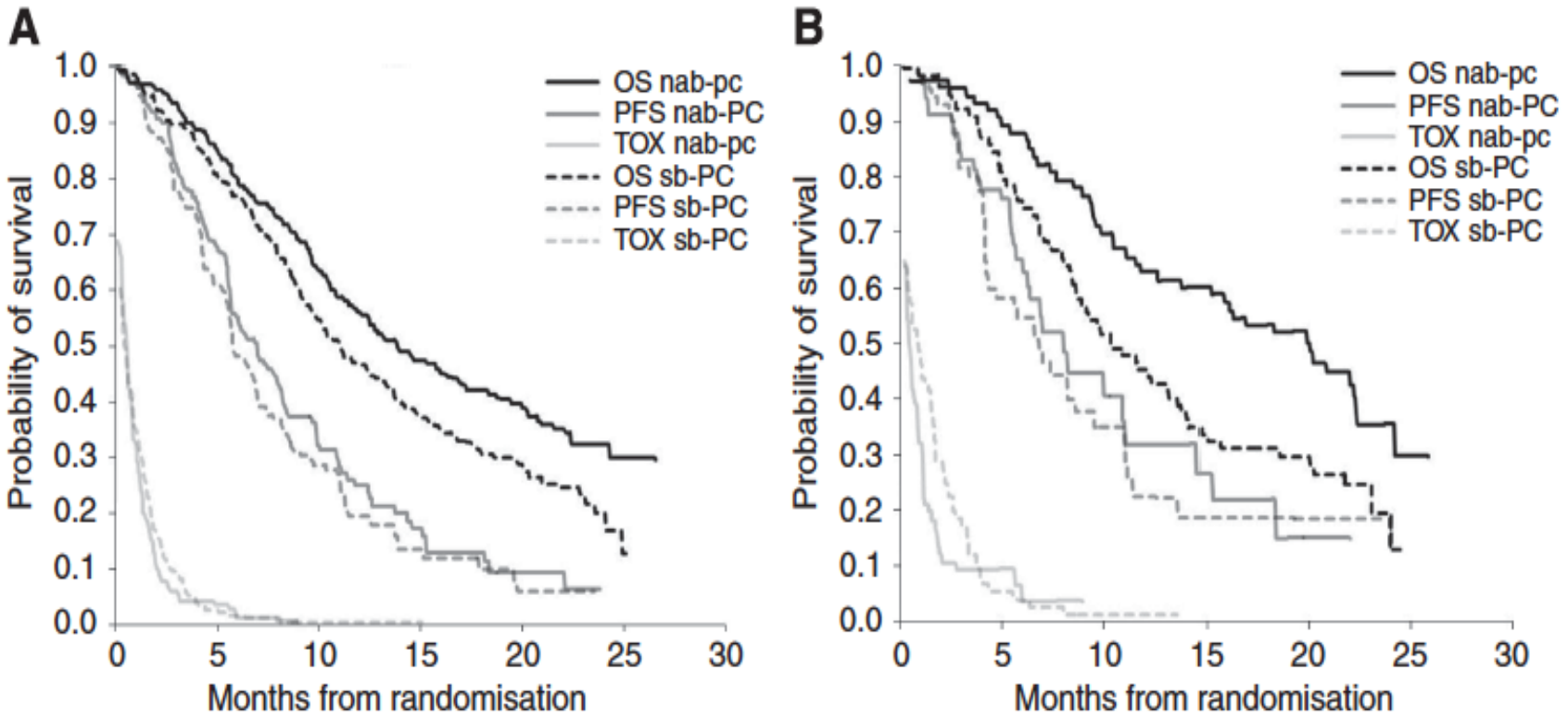
Overall results

- Among patients aged ⩾60 years (N=546), nab-PC (N=265) significantly increased ORR and prolonged OS, despite a non-significant improvement in PFS, vs sb-PC (N=281).
- Nab-PC improved QoL
  - less neuropathy, arthralgia, and myalgia
  - more anaemia and thrombocytopenia
- Nab-PC yielded significant Q-TWiST (quality adjusted time without symptoms or toxicity) benefits (11.1 vs 9.8 months; 95% CI of gain: 0.2-2.6), with a relative Q-TWiST gain of 10.8% (6.4% to 15.1% in threshold analysis)
- In the ⩾70 years age group, nab-PC showed
  - similar, non-significant, ORR, PFS, and Q-TWiST benefits
  - significantly improved OS and QoL.



Partitioned survival plots (A) in patients > 60 years and (B) in patients > 70 years.

Efficacy Summary in Patients With SCC NSCLC by Age

Outcome by Age	≥ 70 Years		≥ 65 Years		≥ 60 Years	
	***nab*-P/C n = 35**	**P/C n = 30**	***nab*-P/C n = 67**	**P/C n = 70**	***nab*-P/C n = 106**	**P/C n = 110**
Overall Response Rate, %	46	20	46	26	45	25
Ratio of ORR (95% CI) *P* value	2.286 (1.025 - 5.095) 0.029		1.799 (1.120 - 8.892) 0.012		1.845 (1.251 - 2.721) 0.001	
Median Overall Survival, months	16.9	8.6	13.9	9.4	11.8	9.5
Hazard ratio (95% CI) *P* value	0.50 (0.275 - 0.896) 0.018		0.62 (0.411 - 0.928) 0.019		0.70 (0.510 - 0.961) 0.027	
Median Progression-Free Survival, months	5.7	5.7	5.7	5.7	5.7	5.7
Hazard ratio (95% CI) *P* value	0.68 (0.347 - 1.339) 0.267		0.70 (0.443 - 1.102) 0.120		0.71 (0.499 - 1.014) 0.058	

- ORR and OS outcomes were significantly better with *nab*-P/C vs P/C across all ages, including pts ≥ 70 years of age

nab-P/C, *nab*-paclitaxel/carboplatin; P/C, paclitaxel/carboplatin; SCC, squamous cell carcinoma.

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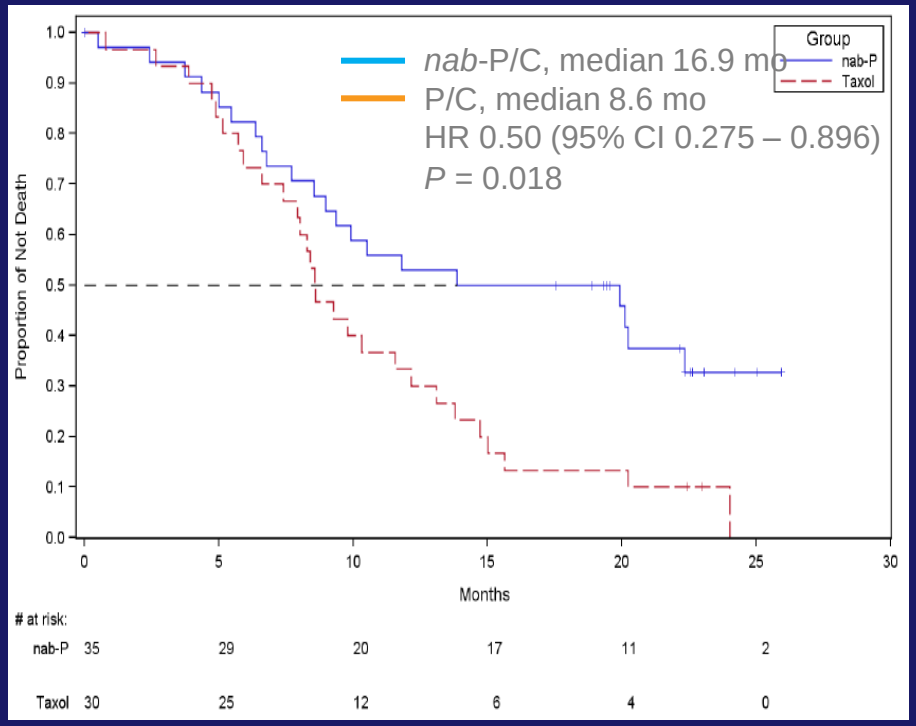
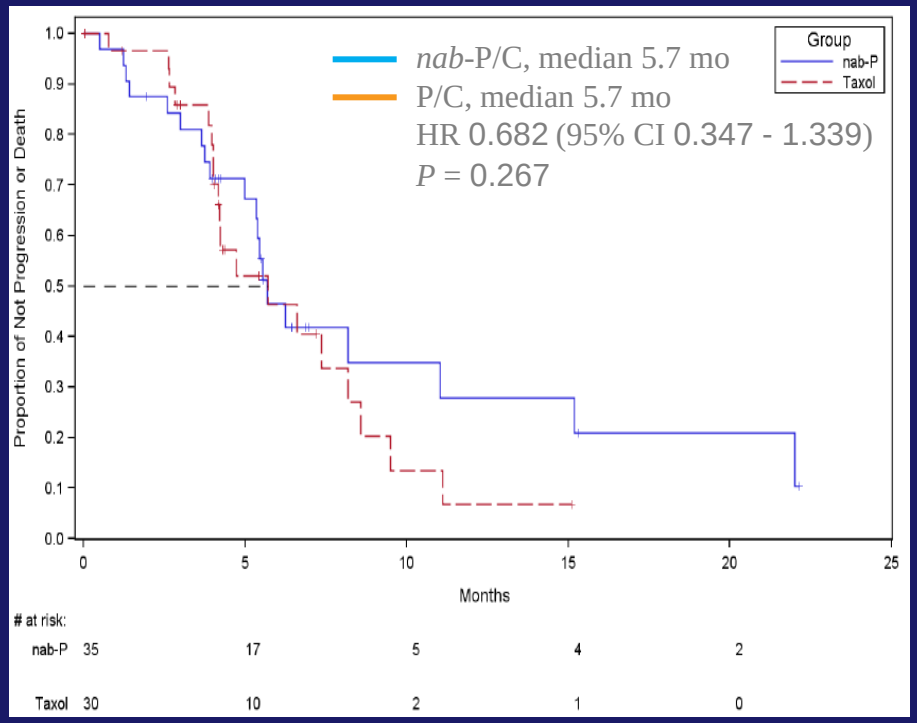
Survival in Patients ≥ 70 Years of Age With SCC

Overall Survival



Progression-Free Survival



- *nab*-P/C vs P/C treatment resulted in less grade 3/4 neutropenia (50% vs 63%) but more grade 3/4 thrombocytopenia (21% vs 10%) and anemia (21% vs 7%); this trend was observed in the phase III trial ITT population as well as the individual elderly and SCC subsets

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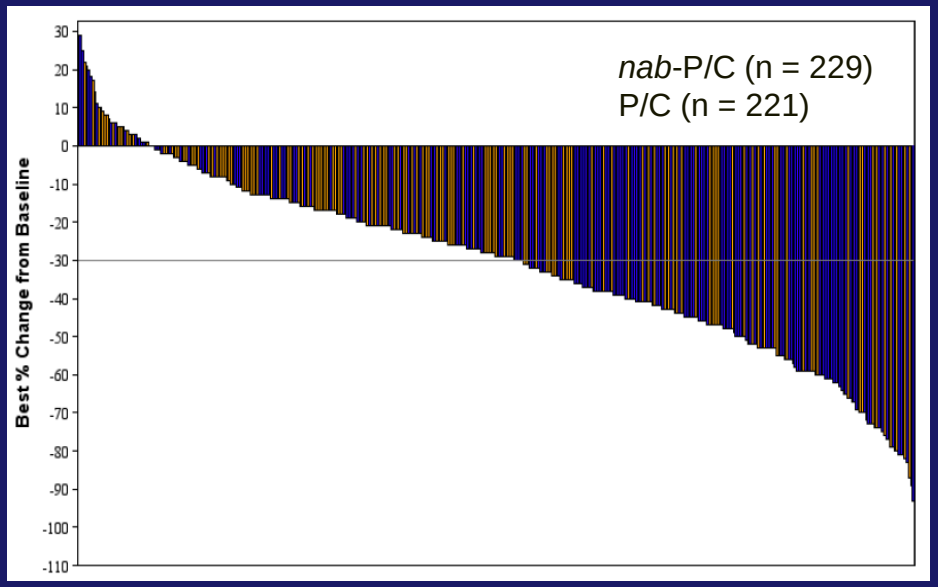
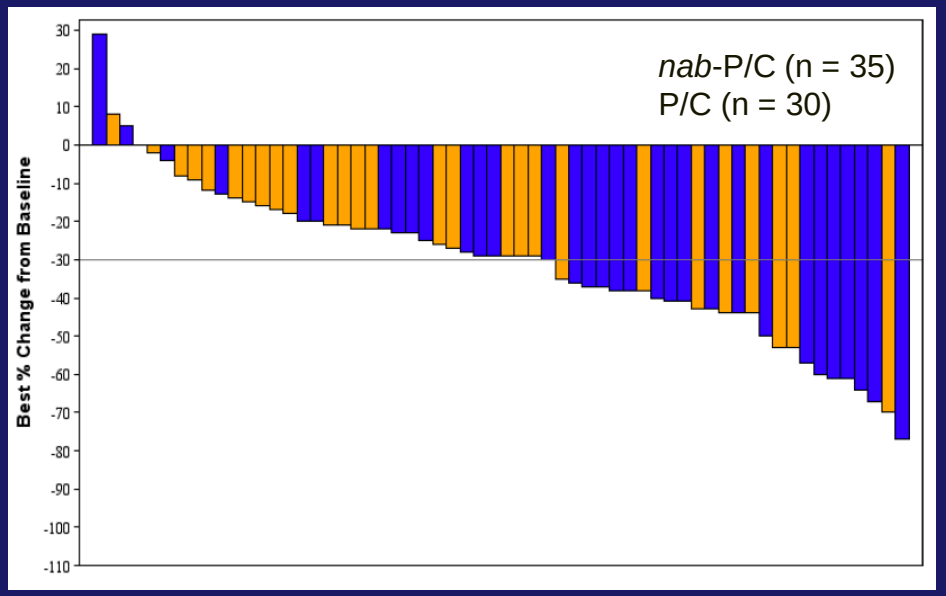
Best Change from Baseline in Target Lesions

Patients with SCC



Patients ≥ 70 Years of Age with SCC



- More pts with SCC, including those ≥ 70 years of age, treated with *nab*-P/C vs P/C had greater decreases from baseline in total length of target lesions

Conclusion: Treatment with *nab*-P/C vs P/C resulted in significant improvements in ORR and OS in patients ≥ 70 years of age with SCC; similar findings were observed in other age groups

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Conclusions

- No firmly established predictor for development of brain metastases post chemoradiotherapy yet defined
  - KRAS and CEA promising but require further evaluation
  - Prophylactic cranial irradiation reduces relapse from brain metastases but overall survival benefit unproven
- Bevacizumab does not appear to add significantly to pemetrexed in the maintenance treatment of non-squamous NSCLC
- Nap-paclitaxel may have a role in selected elderly patients with NSCLC, both non-squamous and squamous