ASCO 2014: Lung Cancer Highlights

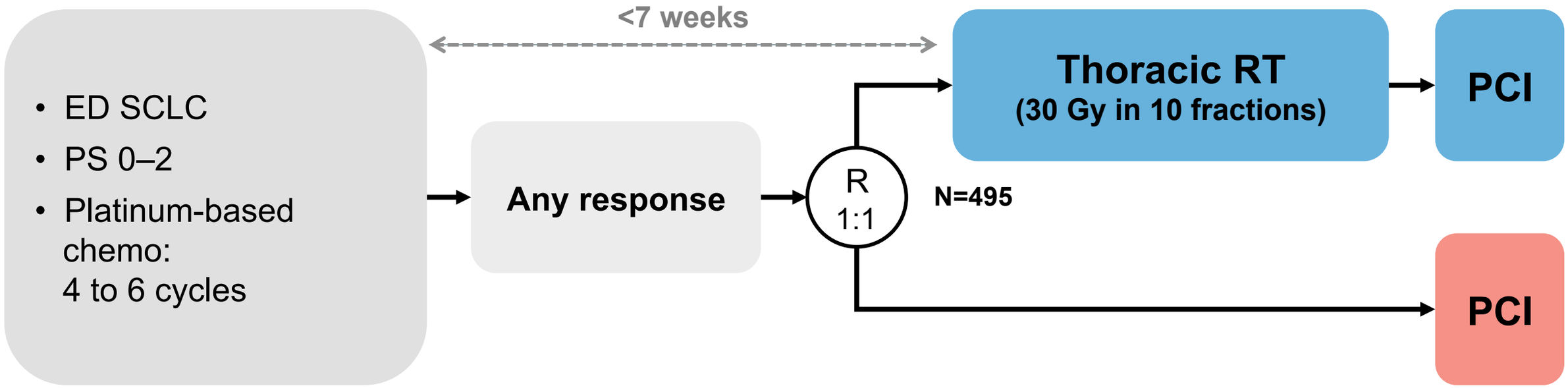
Paul Germonpré

How to improve outcome in ED SCLC?

- Thoracic radiotherapy (TRT)?
- Profylactic irradiation (PCI)?

Thoracic radiotherapy in extensive disease SCLC

Objective: to detect a 24% improvement in overall survival at 1 year (HR 0.76) with thoracic radiotherapy (TRT) in pts with extensive disease (ED) SCLC.



Primary endpoint: overall survivall (OS)

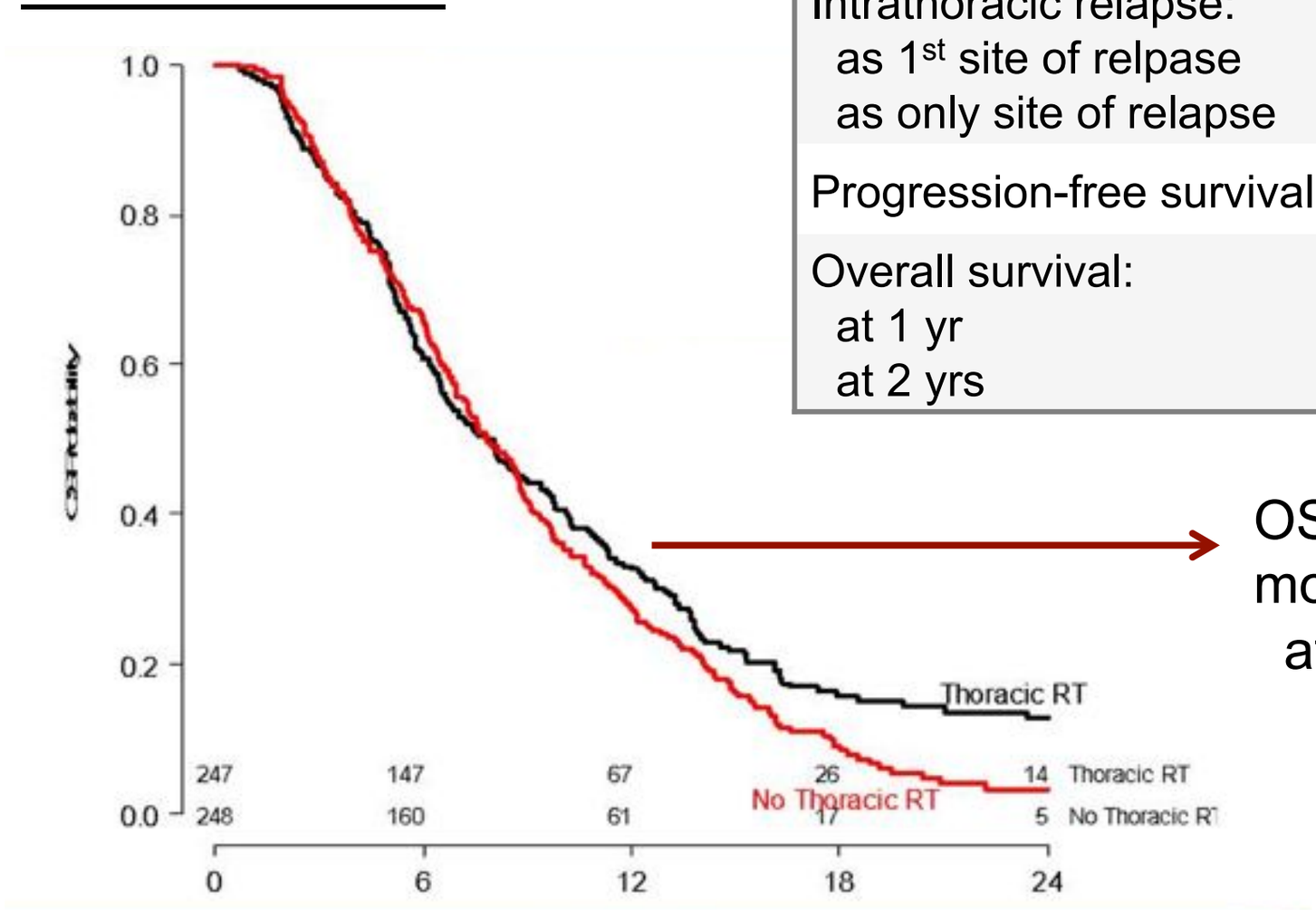
Imaging of the brain with CT/MRI was performed in only 46% of pts at initial staging and in 13% of pts after the chemotherapy!!

Slotman et al. *Annual Meeting ASCO 2014*: abstr 7502.

Thoracic radiotherapy in extensive disease SCLC

	TRT	No TRT	P-value
N	247	248	
Persistent intrathoracic disease following chemo	87 %	88 %	
Grade ≥3 toxicity	10.5 %	6.8 %	
Intrathoracic relapse:			
as 1st site of relpase	42 %	78 %	<0.001
as only site of relapse	20 %	46 %	< 0.001
Progression-free survival	HR 0.73		0.001
Overall survival:			
at 1 yr	33 %	28 %	NS
at 2 yrs	13 %	3 %	0.004

Overall survival:



OS-survival curves overlap during first 9 months and then diverged in favor of TRT:
at 1yr: HR 0.84 (NS)

Slotman et al. *Annual Meeting ASCO 2014*: abstr 7502.

Thoracic radiotherapy in extensive disease SCLC

Conclusion of the presenter:

- Thoracic radiotherapy improves intrathoracic control, progression-free survival and overall survival
- Thoracic radiotherapy should be offered in addition to profylactic cranial irradiation to all ED SCLC pts responding to initial chemotherapy

Slotman et al. *Annual Meeting ASCO 2014*: abstr 7502.

Thoracic radiotherapy in extensive disease SCLC

Conclusion of the presenter:

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- Thoracic radiotherapy should be offered in addition to profylactic cranial irradiation to all ED SCLC pts responding to initial chemotherapy

Do the Slotman trials (*NEJM* 2007, *357*: 664–672 and *Annual Meeting ASCO 201* abstr 7502) really allow us to recommend PCI and/or TRT to all ED SCLC pts???

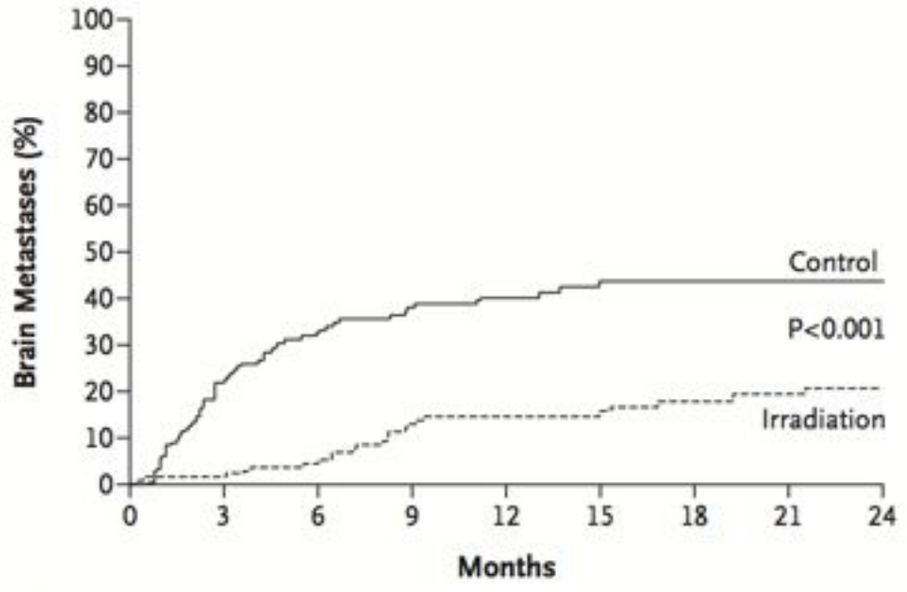
Slotman et al. *Annual Meeting ASCO 2014*: abstr 7502.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

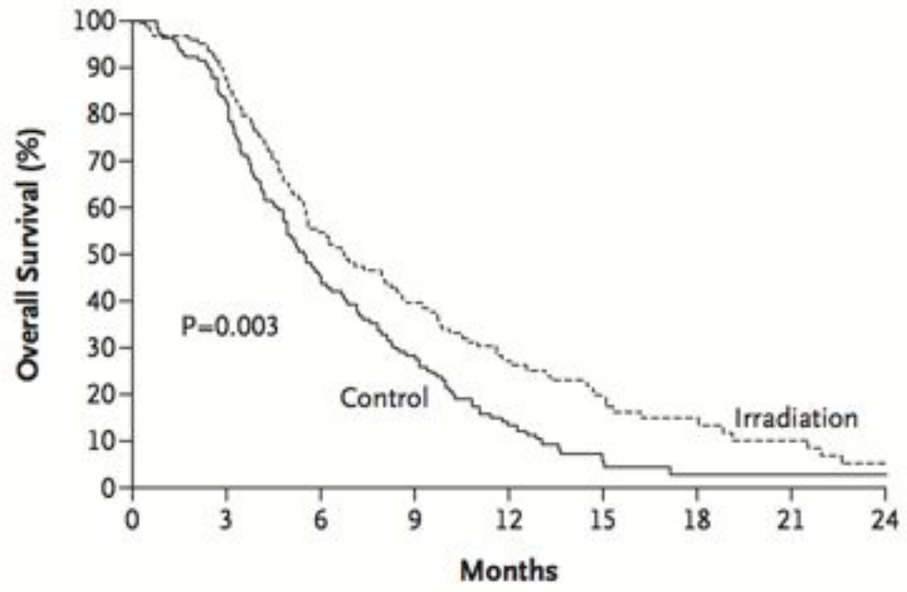
Prophylactic Cranial Irradiation in Extensive Small-Cell Lung Cancer

Ben Slotman, M.D., Ph.D., Corinne Faivre-Finn, M.D., Ph.D., Gijs Kramer, M.D.,*
Elaine Rankin, M.D., Michael Snee, D.M., Matthew Hatton, F.R.C.R.,
Pieter Postmus, M.D., Ph.D., Laurence Collette, Ph.D., Elena Musat, M.D.,
and Suresh Senan, Ph.D., F.R.C.R., for the EORTC Radiation Oncology Group
and Lung Cancer Group†



No. at Risk								
Control	143	94	48	29	11	2	1	1
Irradiation	143	119	66	38	24	16	10	5

Figure 1. Cumulative Incidence of Symptomatic Brain Metastases.



No. at Risk								
Control	143	115	58	36	15	3	2	1
Irradiation	143	119	67	44	26	17	11	6

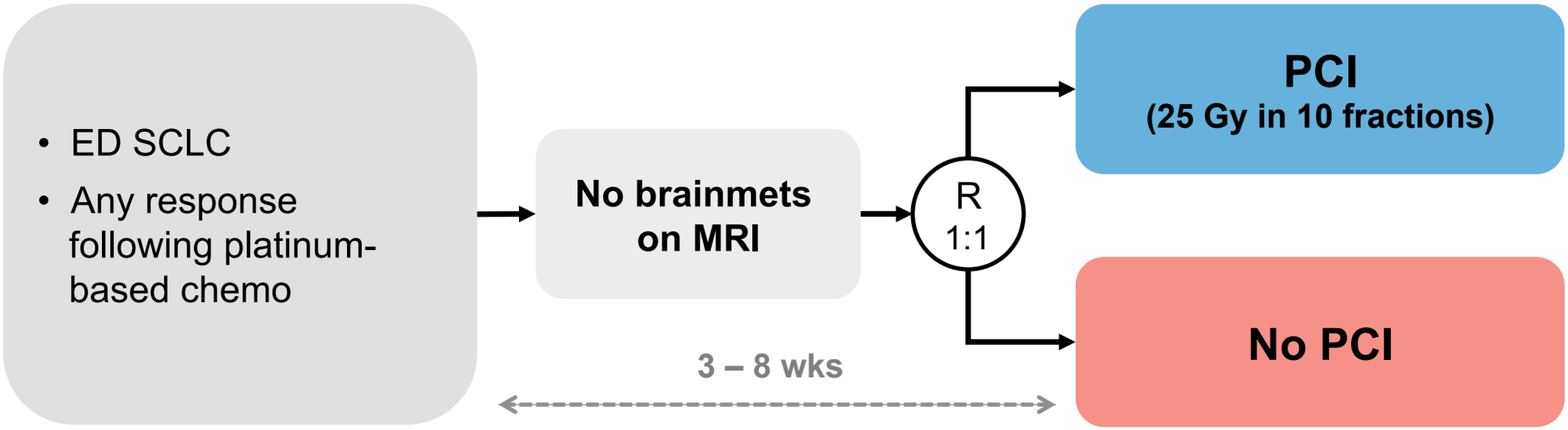
Figure 3. Overall Survival.

But: brain imaging was not part of standard staging and follow-up procedures, unless symptoms suggestive of brain metastases were present.

Slotman et al *N Engl J Med* 2007; 357: 664-672.

Profylactic cranial irradiation in ED SCLC:
no effect on overall survival (or even detrimental)

Objective: to detect a 25% improvement in overall survival (HR 0.75) with profylactic cranial irradiation (PCI) in pts with extensive disease (ED) SCLC.



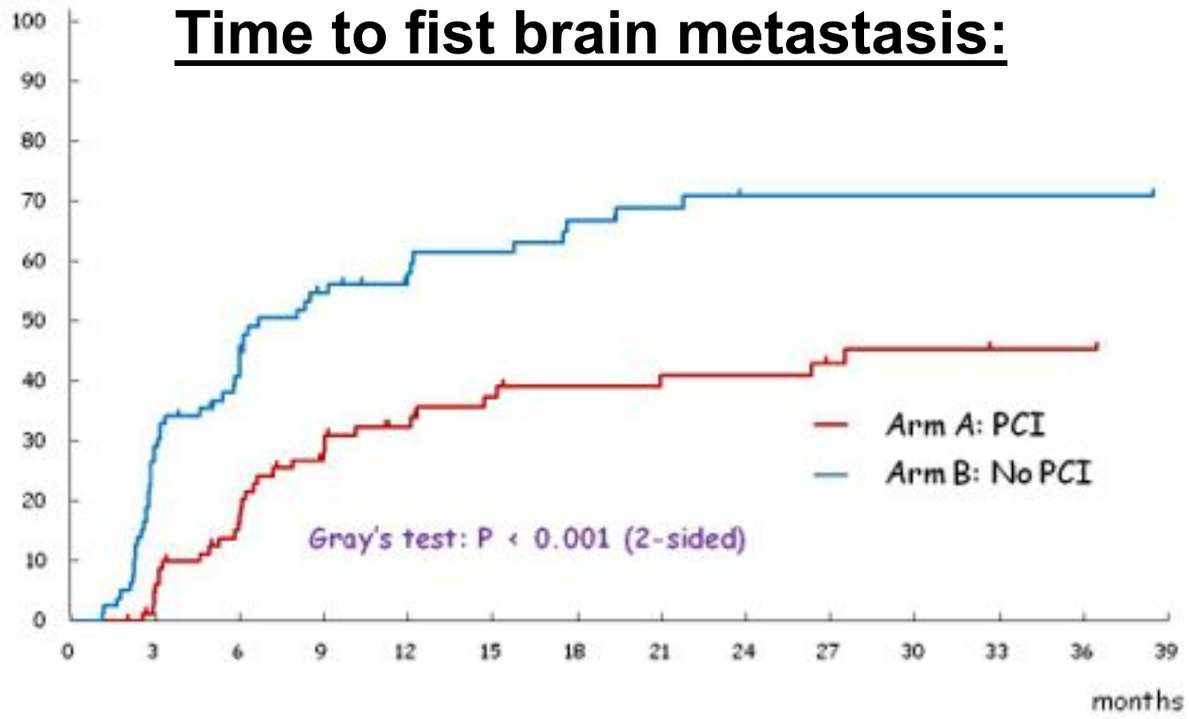
Primary endpoint: overall survivall (OS)

Trial stopped early following interim analysis due to futility !!

Seto et al. *Annual Meeting ASCO 2014*: abstr 7503.

Profylactic cranial irradiation in ED SCLC:
no effect on overall survival (or even detrimental)

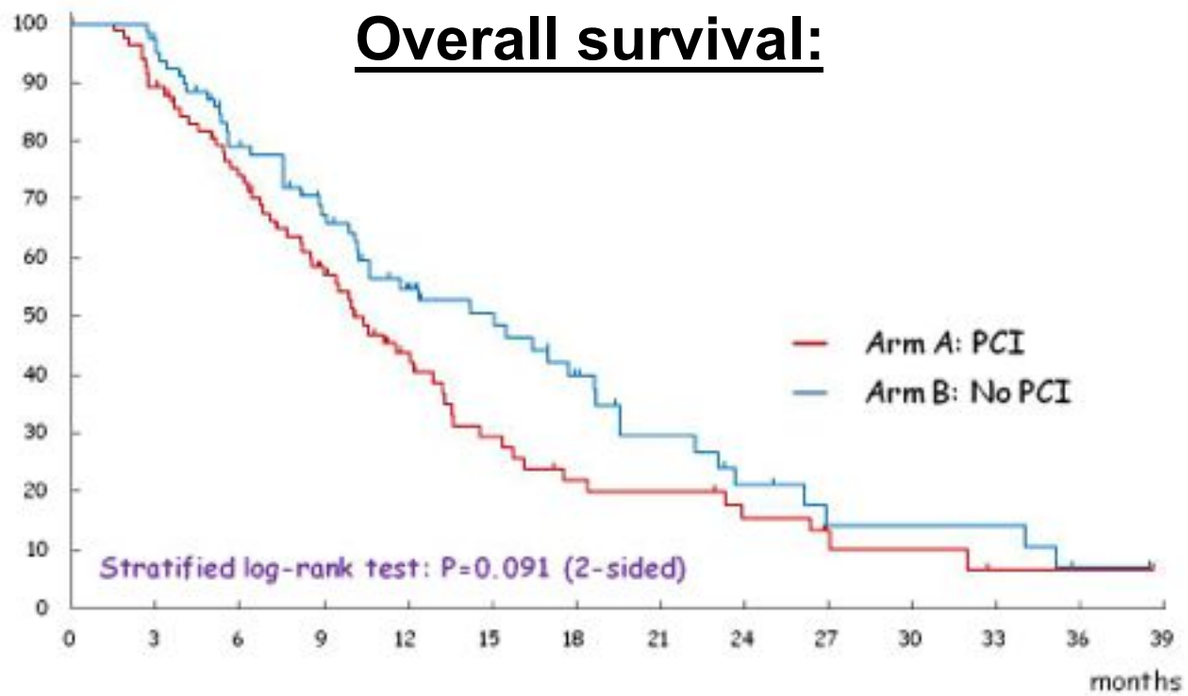
Time to fist brain metastasis:



	PCI	No PCI
N	84	79
Brain mets at 1 yr	32 % *	58%
PFS median	2.2 m	2.4 m
	HR 1.12 (*P* NS)	
OS median	10.1 m	15.1 m
	HR 1.38 (*P* 0.09)	

* P <0.001

Overall survival:



Seto et al. *Annual Meeting ASCO 2014*: abstr 7503.

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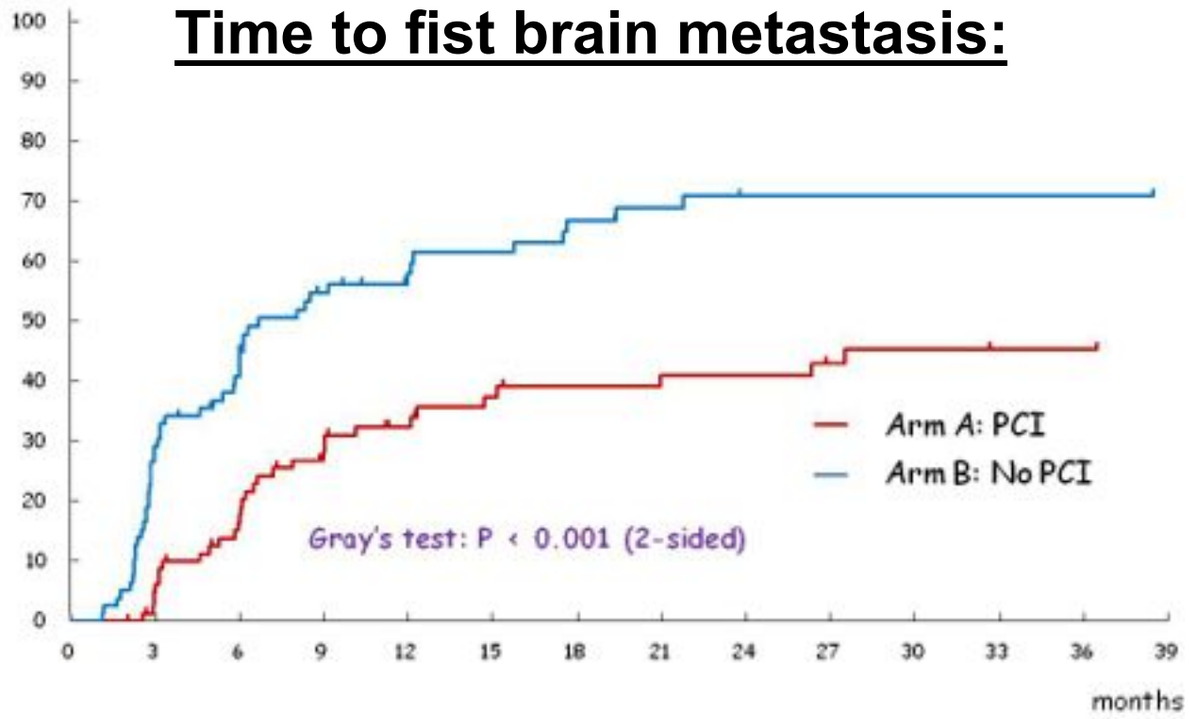

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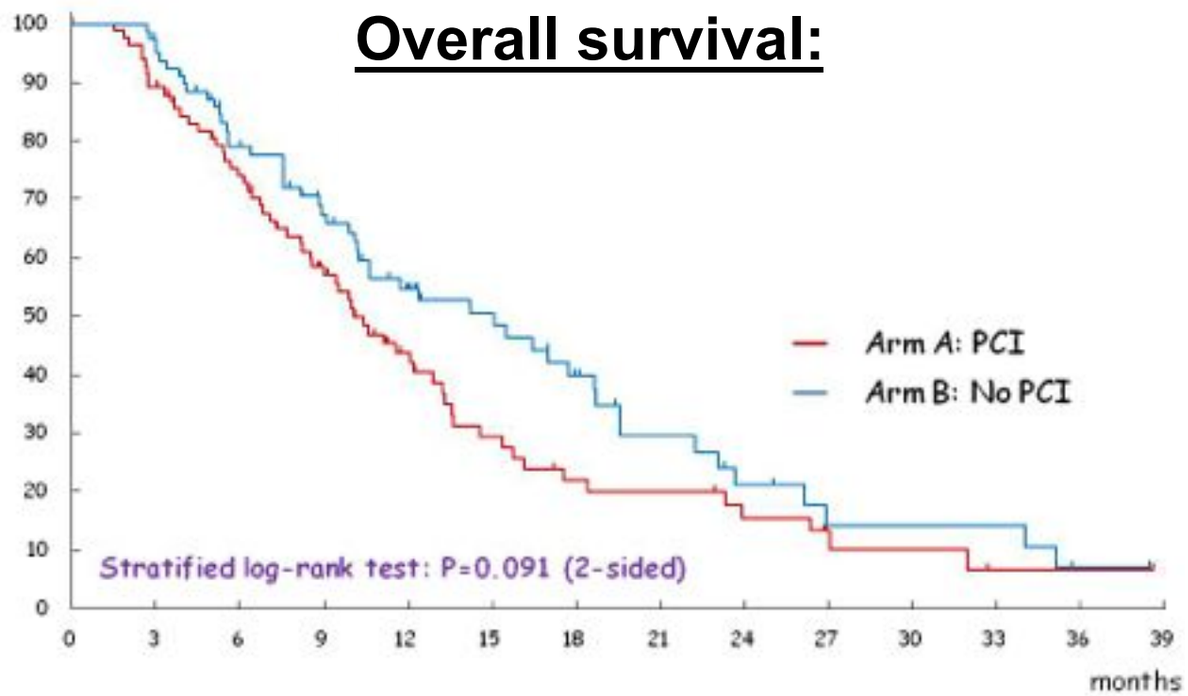


Profylactic cranial irradiation:

- has no effect on PFS
- does not improve OS in pts with confirmed absence of brainmets

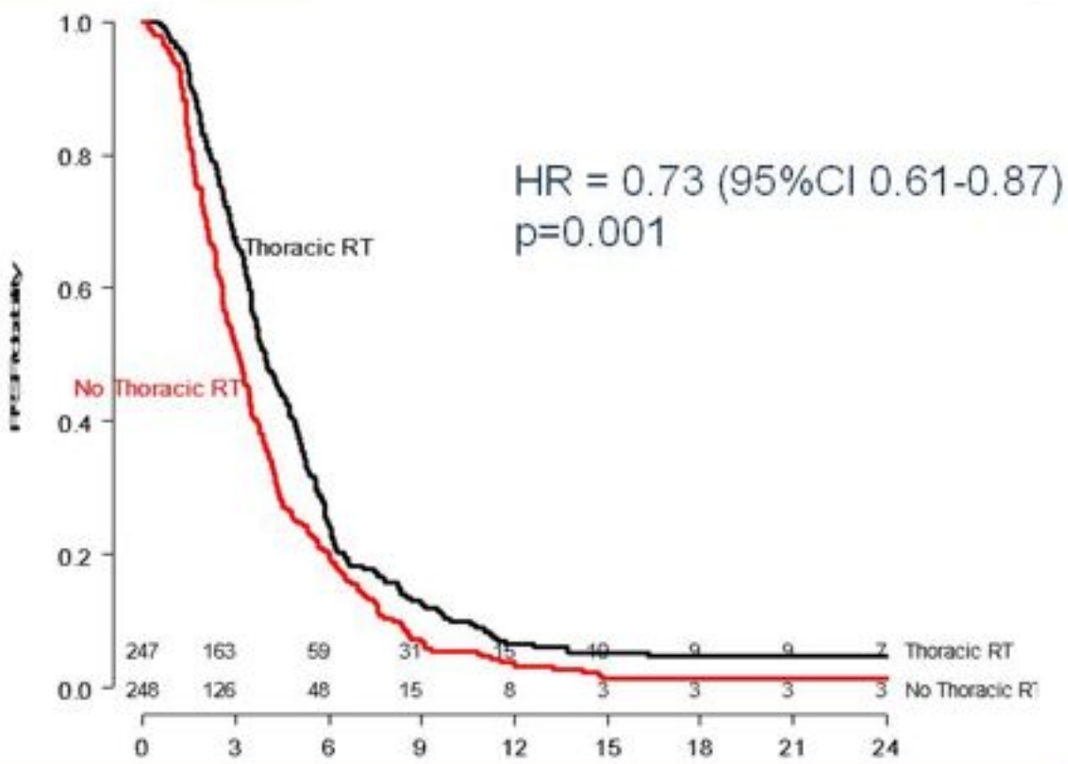
Seto et al. *Annual Meeting ASCO 2014*: abstr 7503.

Thoracic radiotherapy in extensive disease SCLC

	TRT	No TRT	P-value
Intrathoracic relapse: as 1st site of relpase as only site of relapse	 42 % 20 %	 78 % 46 %	 <0.001 < 0.001

The difference in intrathoracic controle does not result in a “clinically significant” difference in PFS

Progression-free survivall:



Slotman et al. *Annual Meeting ASCO 2014*: abstr 7502.

Role of Radiation Therapy in the Combined-Modality Treatment of Patients With Extensive Disease Small-Cell Lung Cancer: A Randomized Study

By Branislav Jeremic, Yuta Shibamoto, Nebojsa Nikolic, Biljana Milicic, Slobodan Milisavljevic, Aleksandar Dagovic, Jasna Aleksandrovic, and Gordana Radosavljevic-Asic

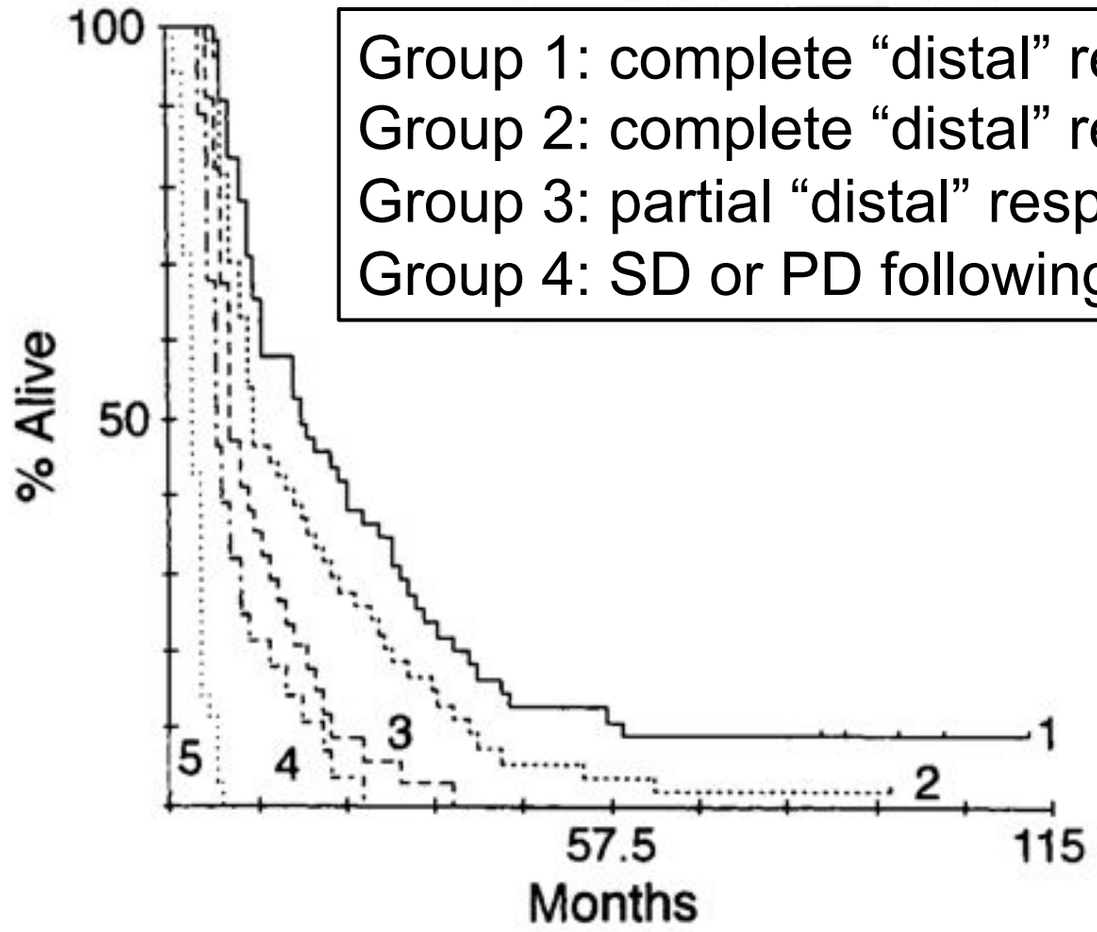


Fig 2. Overall survival in group 1 (——), group 2 (- - - -), group 3 (– – – –), group 4 (- · - · - · -), and group 5 (· · · · ·).

Group 1: complete "distal" response following chemo → consolidation RT
Group 2: complete "distal" response following chemo → no consolidation RT
Group 3: partial "distal" response following chemo → consolidation RT
Group 4: SD or PD following chemo → supportive care

Results: **For 206 assessable patients, the median survival time (MST) was 9 months and the 5-year survival rate was 3.4%. Patients in group 1 had significantly better survival rates than those in group 2 (MST, 17 *v* 11 months; 5-year survival rate, 9.1% *v* 3.7%, respectively; *P* = .041). Local control was also better in group 1, but the difference was only marginally not significant (*P* = .062). There was no difference in distant metastasis-free survival between groups 1 and 2. Acute high-grade toxicity was higher in group 2 than in group 1.**

Jeremic et al *J Clin Oncol* 1999; 17: 2092-2099.

Thoracic radiotherapy in extensive disease SCLC

	TRT	No TRT	P-value
Intrathoracic relapse: as 1st site of relpase as only site of relapse	 42 % 20 %	 78 % 46 %	 <0.001 < 0.001

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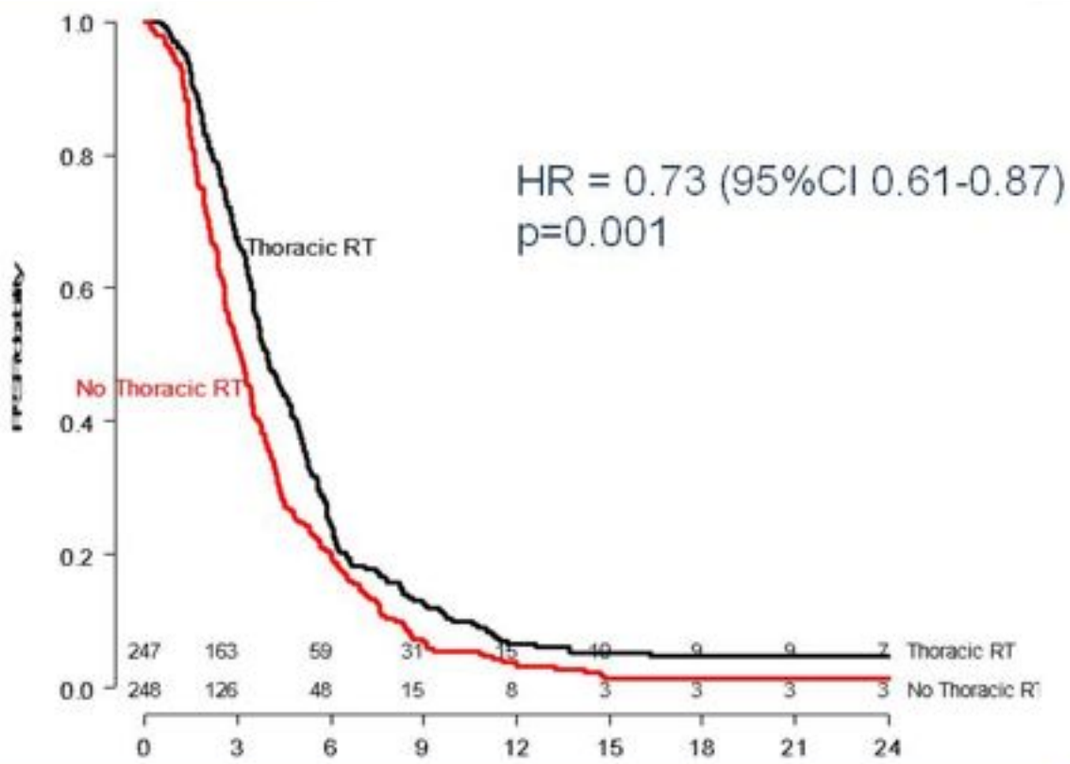


Personal conclusion: thoracic radiotherapy **could** be offered to ED SCLC pts achieving a “complete extrathoracic response”

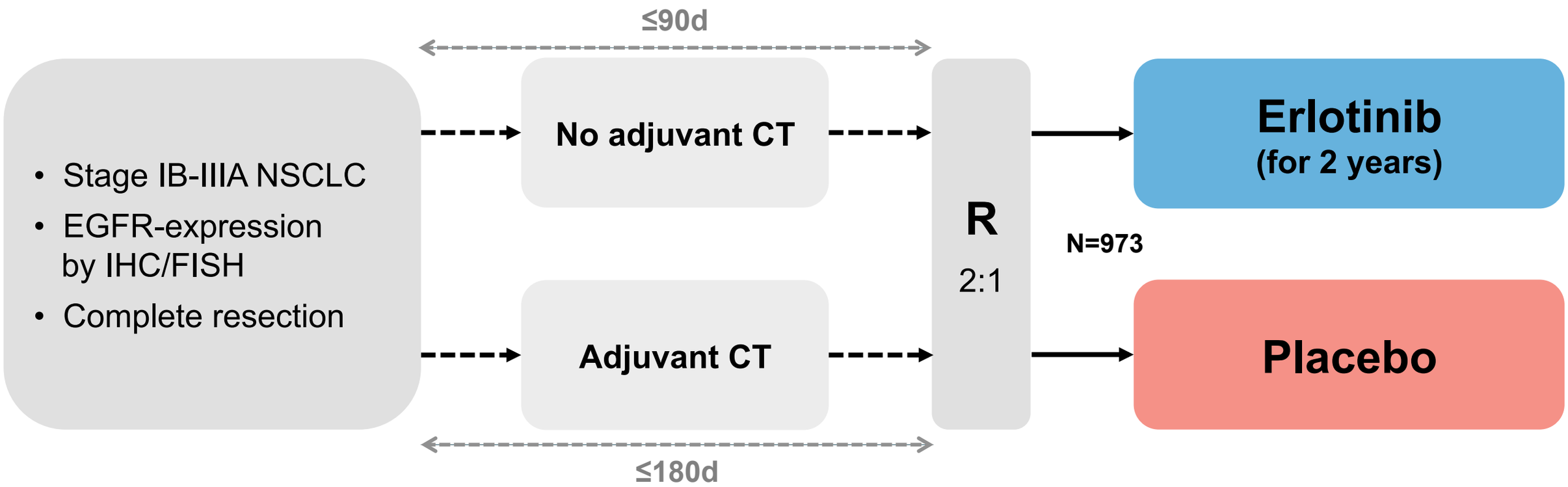
Slotman et al. *Annual Meeting ASCO 2014*: abstr 7502.

How to improve outcome in stage I-III NSCLC?

- Adjuvant erlotinib?
- Consolidation chemotherapy following CRT?
- “To cut” and/or “to burn”?
- Postoperative radiotherapy?
- Treatment in academic centers?

RADIANT: adjuvant erlotinib in stage IB-IIIA NSCLC

Objective: to detect if erlotinib prolongs disease-free survival (DFS) in completely resected stage IB-IIIA EGFR-expressing (IHC/FISH) NSCLC.

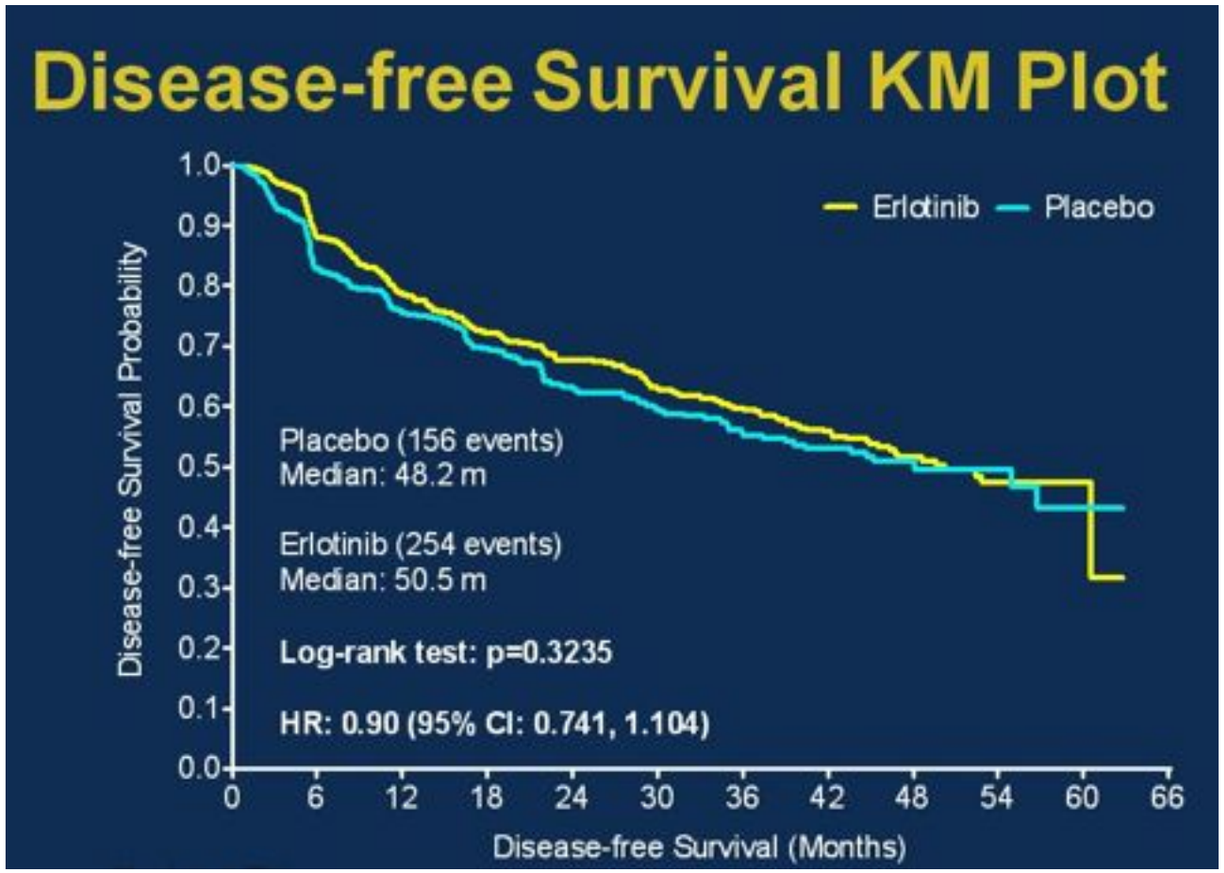


Primary endpoint: disease-free survivall (DFS)
Secondary endpoint: OS; DFS and OS in *EGFR* mut^{+} subgroup

Statistics: hierarchical testing procedure → if 1ary endpoint not met, then all 2ary endpoint deemed non-significant (regardless of p-value).

Kelly et al. *Annual Meeting ASCO 2014*: abstr 7501; Shepherd et al. *Annual Meeting ASCO 2014*: abstr 7513.

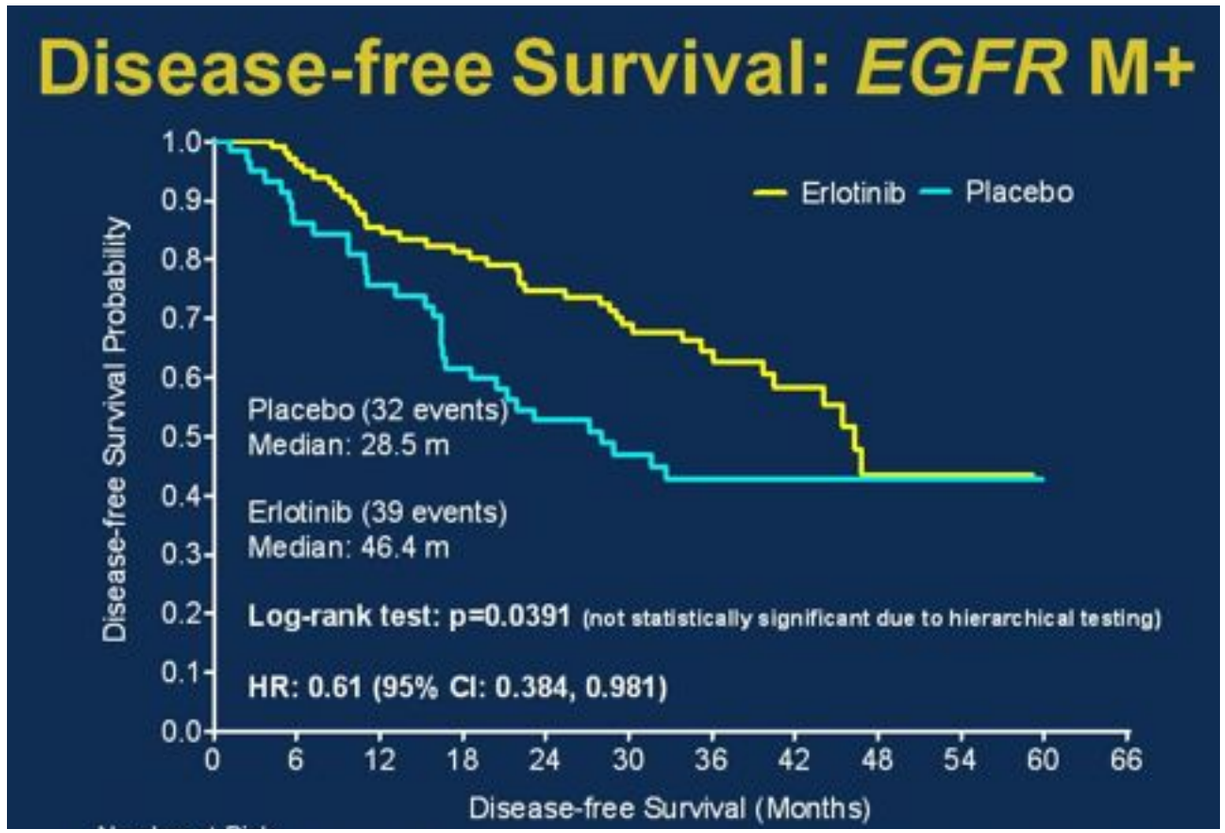
RADIANT: adjuvant erlotinib in stage IB-IIIA NSCLC



All pts	Erlotinib	Placebo
N	623	350
EGFR mut +	16.4 %	16.7 %
Prior adjuvant chemo	51 %	57 %
DFS median	48.2 m	50.5 m
	HR 0.90 (*P* 0.90)	
OS median	NR	NR
	HR 1.13 (*P* 0.3750)	

Kelly et al. *Annual Meeting ASCO 2014*: abstr 7501; Shepherd et al. *Annual Meeting ASCO 2014*: abstr 7513.

RADIANT: adjuvant erlotinib in stage IB-IIIA NSCLC



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Prior adjuvant chemo	51 %	57 %
DFS median	48.2 m	50.5 m
	HR 0.90 (*P* 0.90)	
OS median	NR	NR
	HR 1.13 (*P* 0.3750)	

EGFR mut+	Erlotinib	Placebo
DFS median	46.4 m	28.5 m
	HR 0.61 (*P* 0.04)	
OS median	NR	NR
	HR 1.09 (*P* 0.8)	

Conclusion:

- Adjuvant erlotinib does not prolong disease-free survival in resected early stage *EGFR*-expressing NSCLC

Kelly et al. *Annual Meeting ASCO 2014*: abstr 7501; Shepherd et al. *Annual Meeting ASCO 2014*: abstr 7513.

Phase III Study of Cisplatin, Etoposide, and Concurrent Chest Radiation With or Without Consolidation Docetaxel in Patients With Inoperable Stage III Non–Small-Cell Lung Cancer: The Hoosier Oncology Group and U.S. Oncology

Nasser Hanna, Marcus Neubauer, Constantin Yiannoutsos, Ronald McGarry, James Arseneau, Rafat Ansari, Craig Reynolds, Ramaswamy Govindan, Anton Melnyk, William Fisher, Donald Richards, Daniel Bruetman, Thomas Anderson, Naveed Chowhan, Sreenivasa Nattam, Prasad Mantravadi, Cynthia Johnson, Tim Breen, Angela White, and Lawrence Einhorn

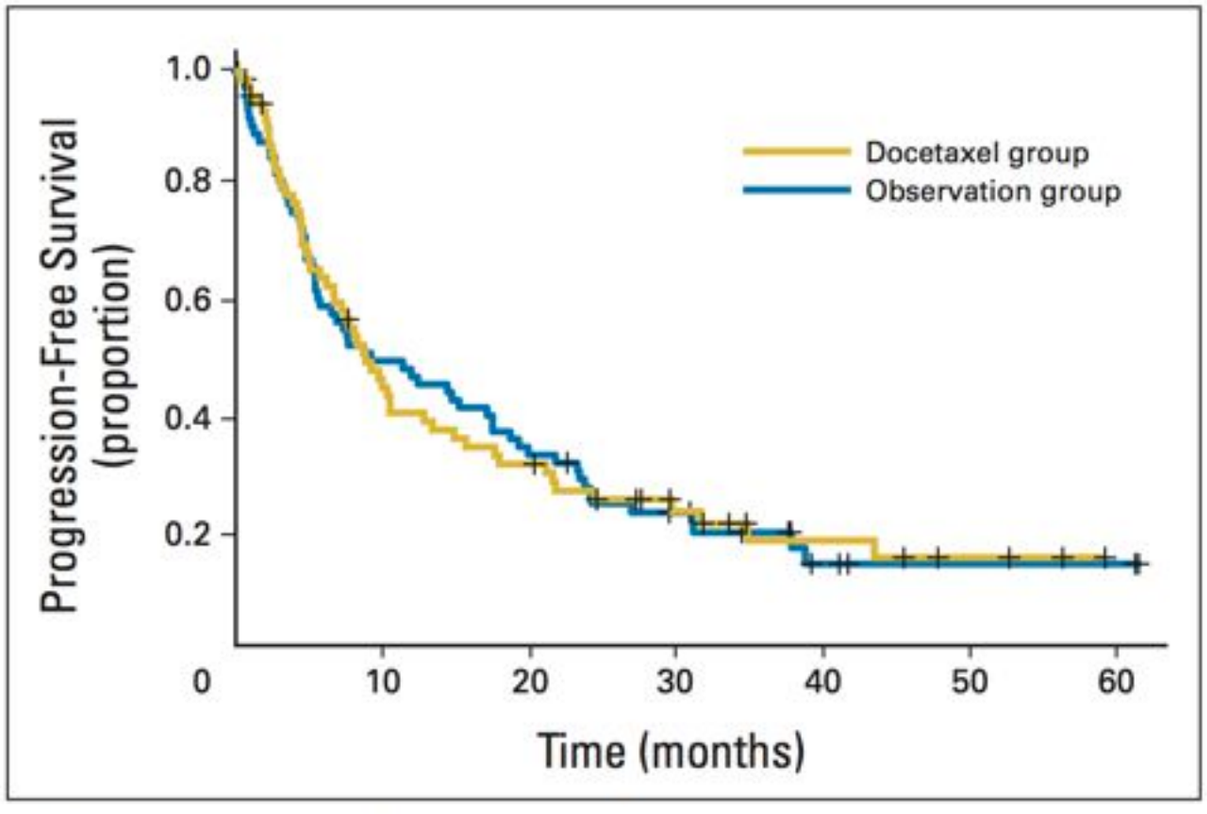


Fig 4. Progression-free survival comparison of the two randomly assigned arms.

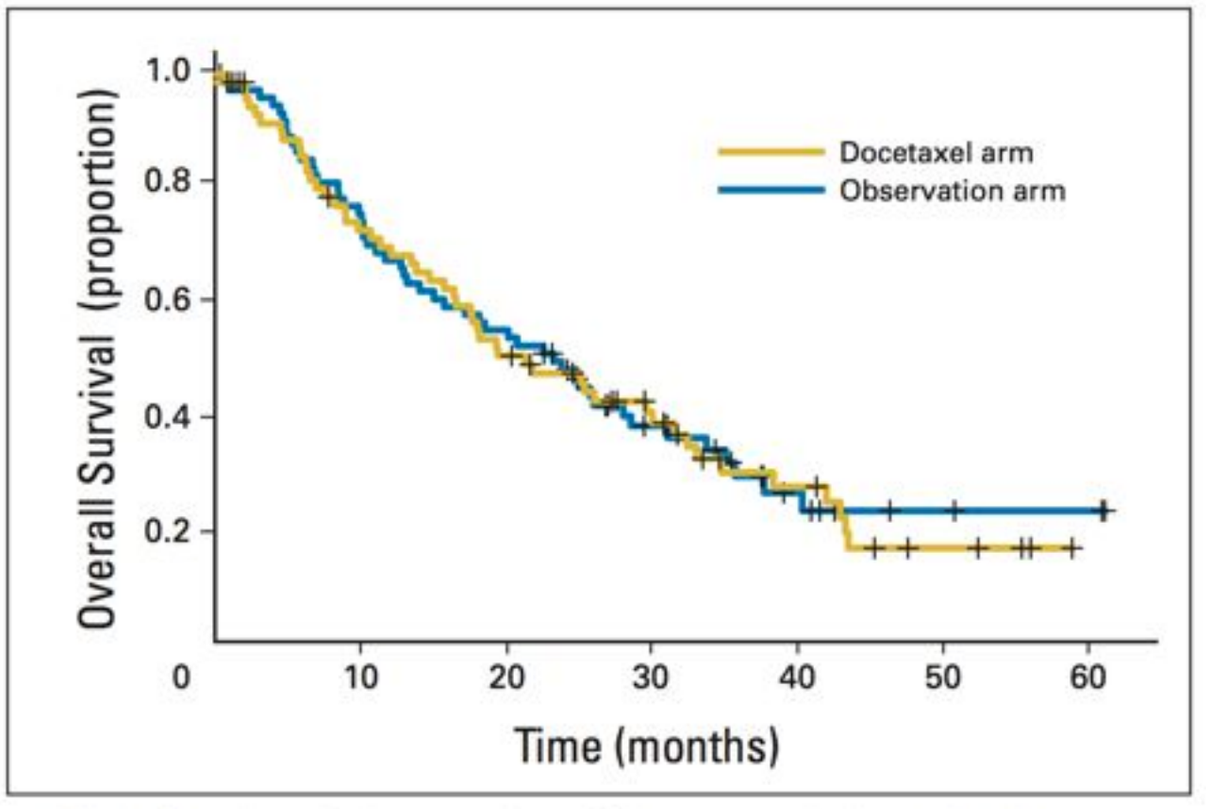
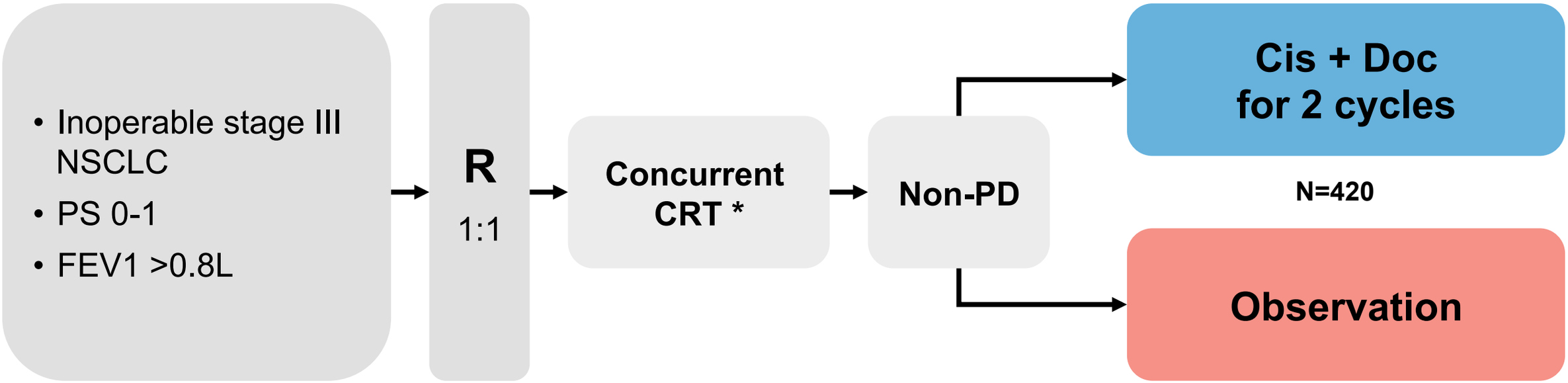


Fig 3. Overall survival comparison of the two randomly assigned arms.

Consolidation chemotherapy after concurrent chemoradiation for inoperable stage III NSCLC

Objective: to evaluate if consolidation chemotherapy after concurrent chemoradiotherapy (CRT) prolongs progression-free survival (PFS) in inoperable stage III NSCLC.



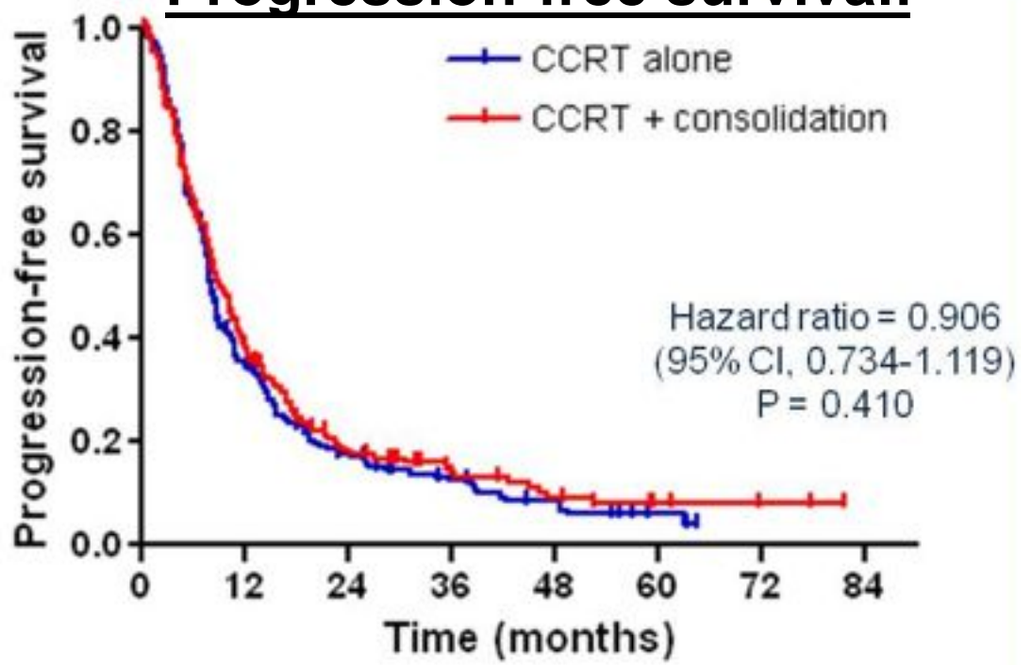
Primary endpoint: progression-free survivall (PFS)

** 66 Gy in 6.5 weeks with weekly cis+doc (20mg/m² each)*

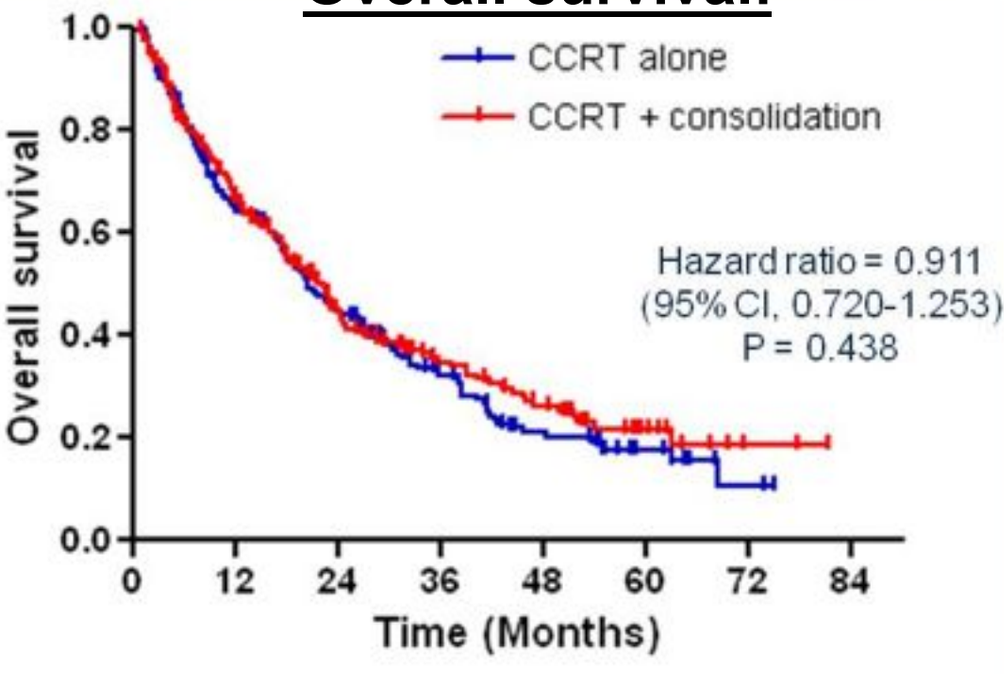
Park et al. *Annual Meeting ASCO 2014*: abstr 7500.

Consolidation chemotherapy after concurrent chemoradiation for inoperable stage III NSCLC

Progression-free survival:



Overall survival:



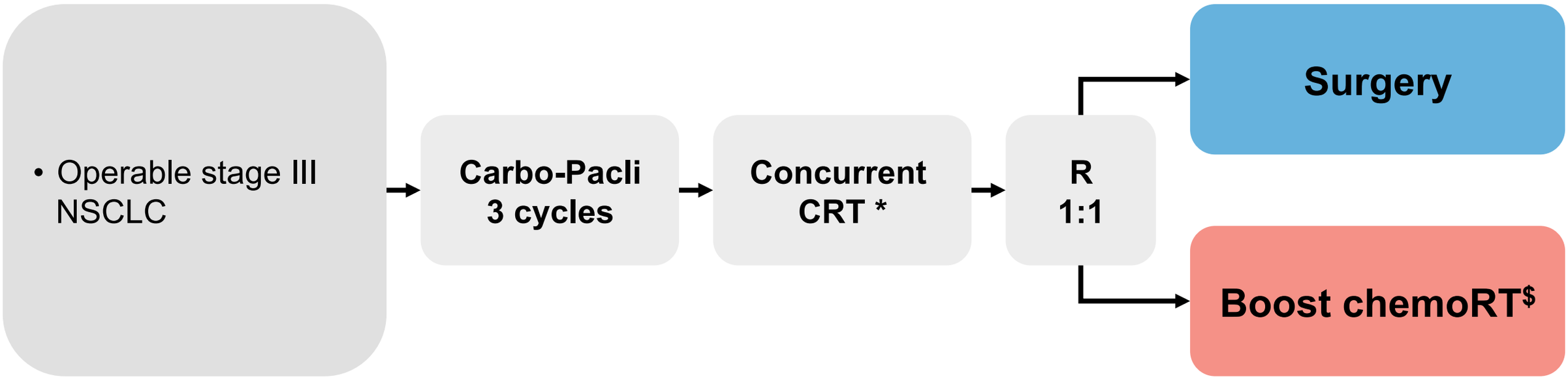
	Cons CT	Obs
N	209	211
Stage IIIA/IIIB	19% / 81%	25% / 75%
PFS median	9.1 m	8.1 m
	HR 0.906	(*P* 0.410)
OS median	21.8 m	20.6 m
	HR 0.911	(*P* 0.438)
Distant failure	30 %	27 %

Conclusion:

- Consolidation chemo following concurrent chemoradioation for stage III NSCLC does not improve survival

Park et al. *Annual Meeting ASCO 2014*: abstr 7500.

Operable stage III NSCLC: surgery *vs* definitve RT



N=246 ----------► **N=161**

Despite fact that the trial was run in “high volume centers”, the trial was closed after 8 years due to slow accrual!!!

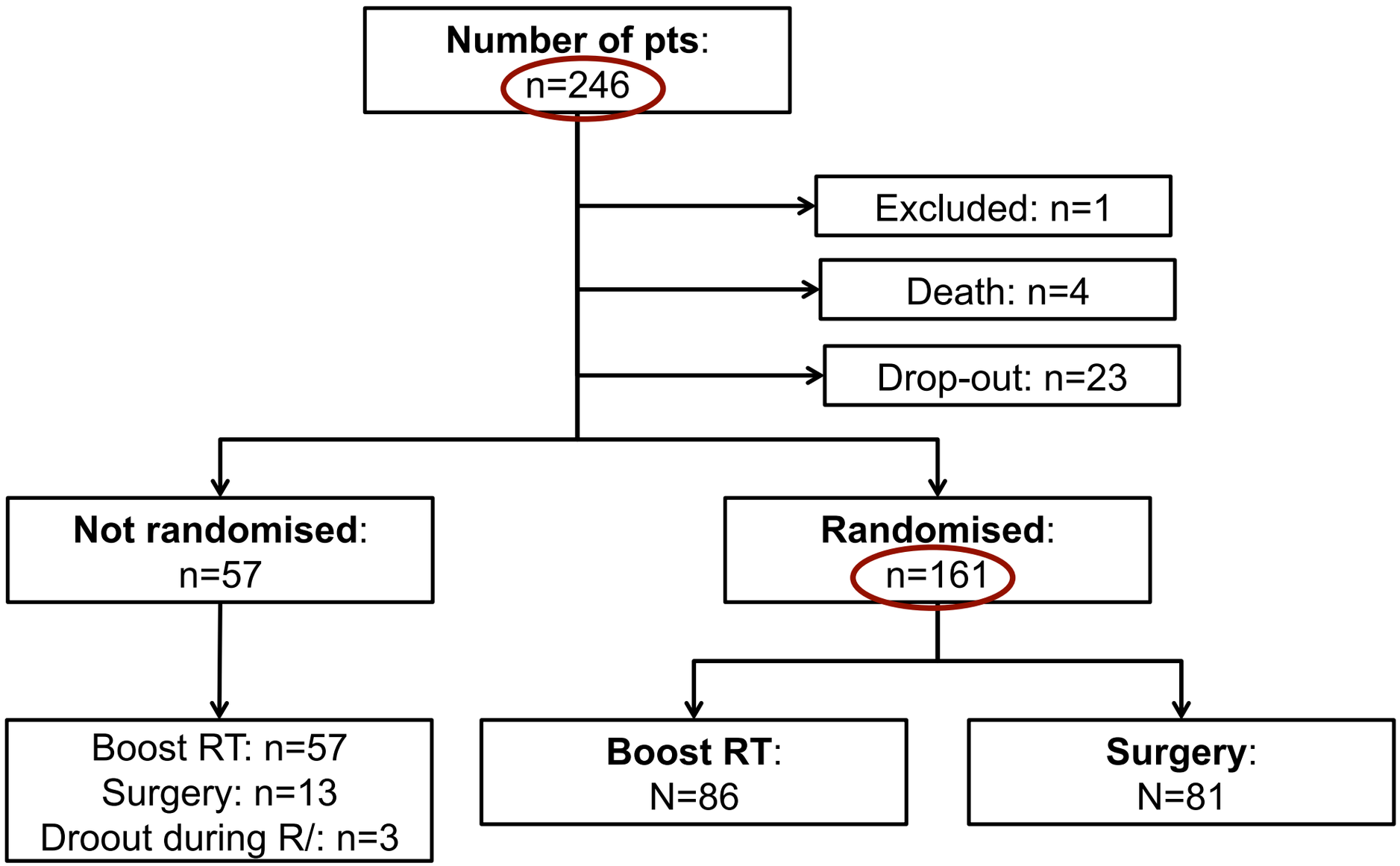
Primary endpoint: overall survival (OS)

** RT 45Gy (15x 1.5Gy bid) with weekly cis+VRB*

$ RT 20Gy (10x 2Gy od) with weekly cis+VRB

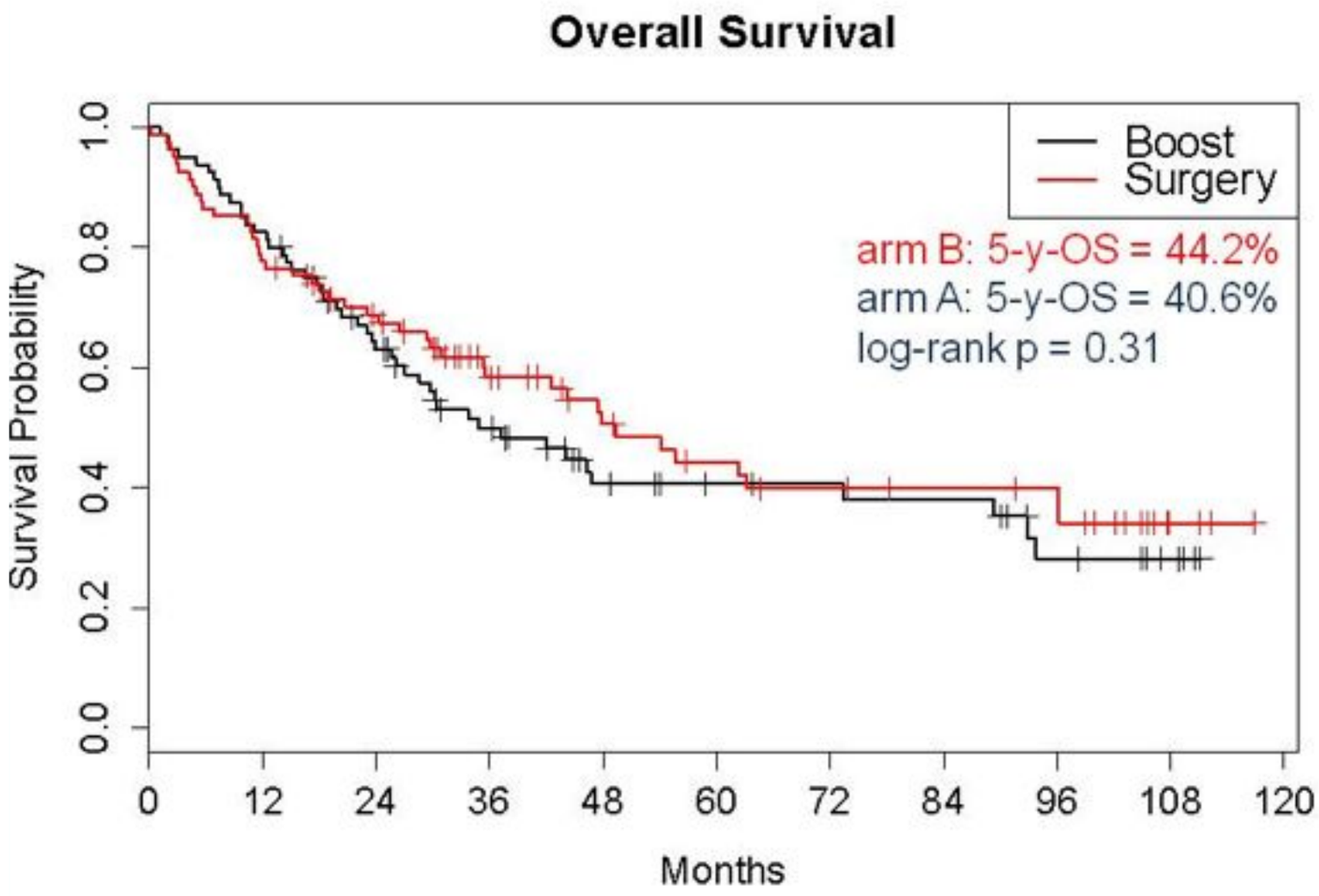
Eberhardt et al. *Annual Meeting ASCO 2014*: abstr 7510.

Operable stage III NSCLC: surgery *vs* definitve RT



Eberhardt et al. *Annual Meeting ASCO 2014*: abstr 7510.

Operable stage III NSCLC: surgery *vs* definitve RT



- Long-term OS was excellent with both treatment arms.
- Both options are acceptable and should be discussed with individual pts.
- However the real question is: how representative are the patients enrolled in this trial for the vast majority of stage III NSCLC pts???

Eberhardt et al. *Annual Meeting ASCO 2014*: abstr 7510.

Postoperative radiotherpay (PORT) for pN2 NSCLC treated with adjuvant chemotherapy

- Objective: to investigate the impact of modern PORT (≥45 Gy) on overall survival for N2 NSCLC treated with surgery and chemotherapy
- Method: data obtained from National Cancer Database

Figure 2- Unadjusted OS

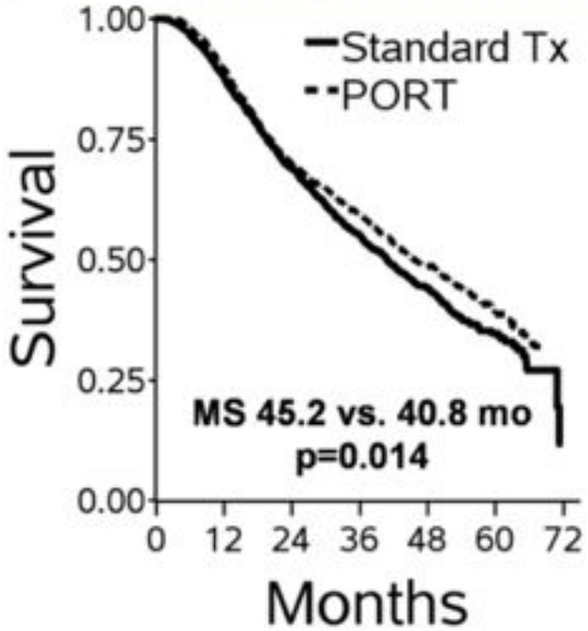
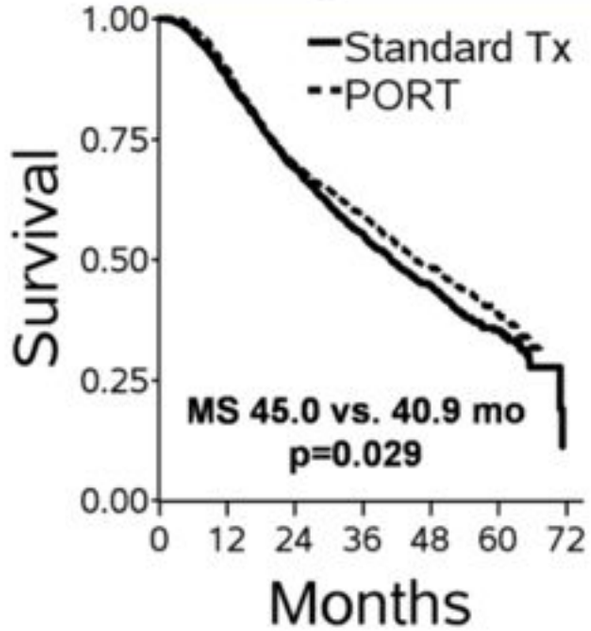


Figure 3- IP Adjusted OS



Multivariate analysis	HR
PORT vs no PORT	0.888
Age	1.017
Tumor size	1.008
Lobectomy vs sub-lobec	0.581
Male vs female	1.379
Urban vs non-urban	0.827
Charlson 2 vs 0	1.283

- Authors conclusions:
  - Modern PORT appears to confer an additional 5% survival advantage beyond what is achieved with adjuvant chemotherapy alone.

Robinson et al. *Annual Meeting ASCO 2014*: abstr 7509.

Operable stage III NSCLC: does institution matter?

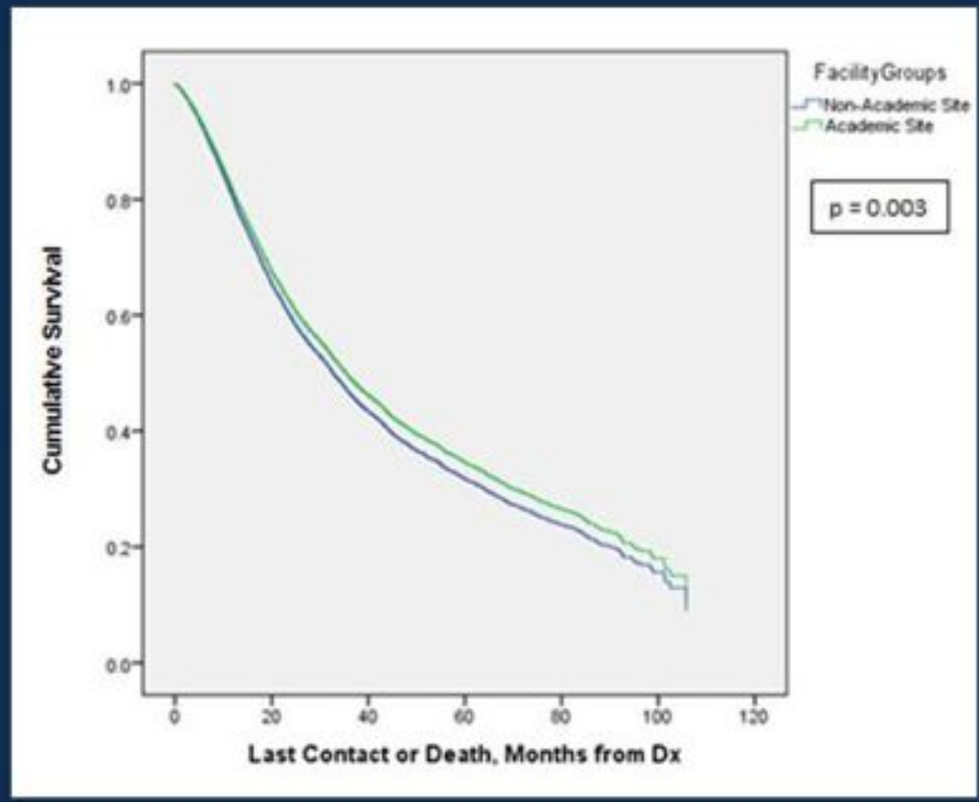
- Objective: to identify differences in clinical stage IIIA NSCLC pts undergoing pulmonary resection in academic *vs* non-academic centers
- Method: data obtained from National Cancer Database
- In academic centers:
  - More induction chemotherapy (50% *vs* 41%)
  - More lobectomy versus sub-lobar resections (70% *vs* 68%)
  - Lower 30-day mortality rate (3.3% *vs* 4.5%)
  - Increased median survival (34 m *vs* 29 m)
- In non-academic centers:
  - More likely to receive PORT (28% vs 22%)
- Authors conclusions:
  - Pts undergoing surgery at academic center have improved long-term survival. Possible reasons include increased use of induction chemotherapy.

Samson et al. *Annual Meeting ASCO 2014*: abstr 7512.

Operable stage III NSCLC: does institution matter?

Patient and treatment variables	Hazard ratio (HR) with 95% CI
Age	1.02 (1.02-1.03)*
Male gender	1.21 (1.15-1.27)*
Charlson-Deyo comorbidity score 1	1.12 (1.06-1.18)*
Charlson-Deyo comorbidity score 2	1.34 (1.23-1.46)*
Pre-operative radiation therapy	1.21 (1.14-1.28)*
Pre-operative chemotherapy	0.66 (0.62-0.70)*
Treatment at academic facility	0.93 (0.88-0.97)*
Lobectomy	0.72 (0.67-0.77)*
Pneumonectomy	1.02 (0.93-1.12)

Hazard ratios for mortality based on patient and treatment variables.
* Indicates $p < 0.05$.



Overall survival for patients receiving pulmonary resection at academic and non-academic centers.

Is the survival difference due to the difference in institution or to the difference in patient-population in the different institutions? The latter seems not unlikely!

Samson et al. *Annual Meeting ASCO 2014*: abstr 7512.

How to improve outcome in stage IV NSCLC?

- Afatinib for common *EGFR* mut^{+} NSCLC?
- Crizotinib for *ALK*-FISH^{+} NSCLC?
- Necitumumab for squamous NSCLC?
- Ramucirumab in 2nd line treatment?

Phase III trials of 1st line EGFR-TKI *vs* chemo in *EGFR* mutation positive NSCLC

Trial	N	Ethnicity	EGFR-TKI	Chemotherapy
IPASS (subgroup)	261	asian	Gefitinib	Cis + Doc (6x)
WJTOG3405	172	asian	Gefitinib	Cis + Doc (6x)
NEJ002	228	asian	Gefitinib	Carbo + Pacli (6x)
OPTIMAL	165	asian	Erlotinib	Carbo + Gemci (4x)
EURTAC	174	caucasian	Erlotinib	Cis/Carbo + Doc/Gemci (4x)
LUX-Lung 3	345	mixed	Afatinib	Cis + Pem (6x)
LUX-Lung 6	364	asian	Afatinib	Cis + Gemci (6x)

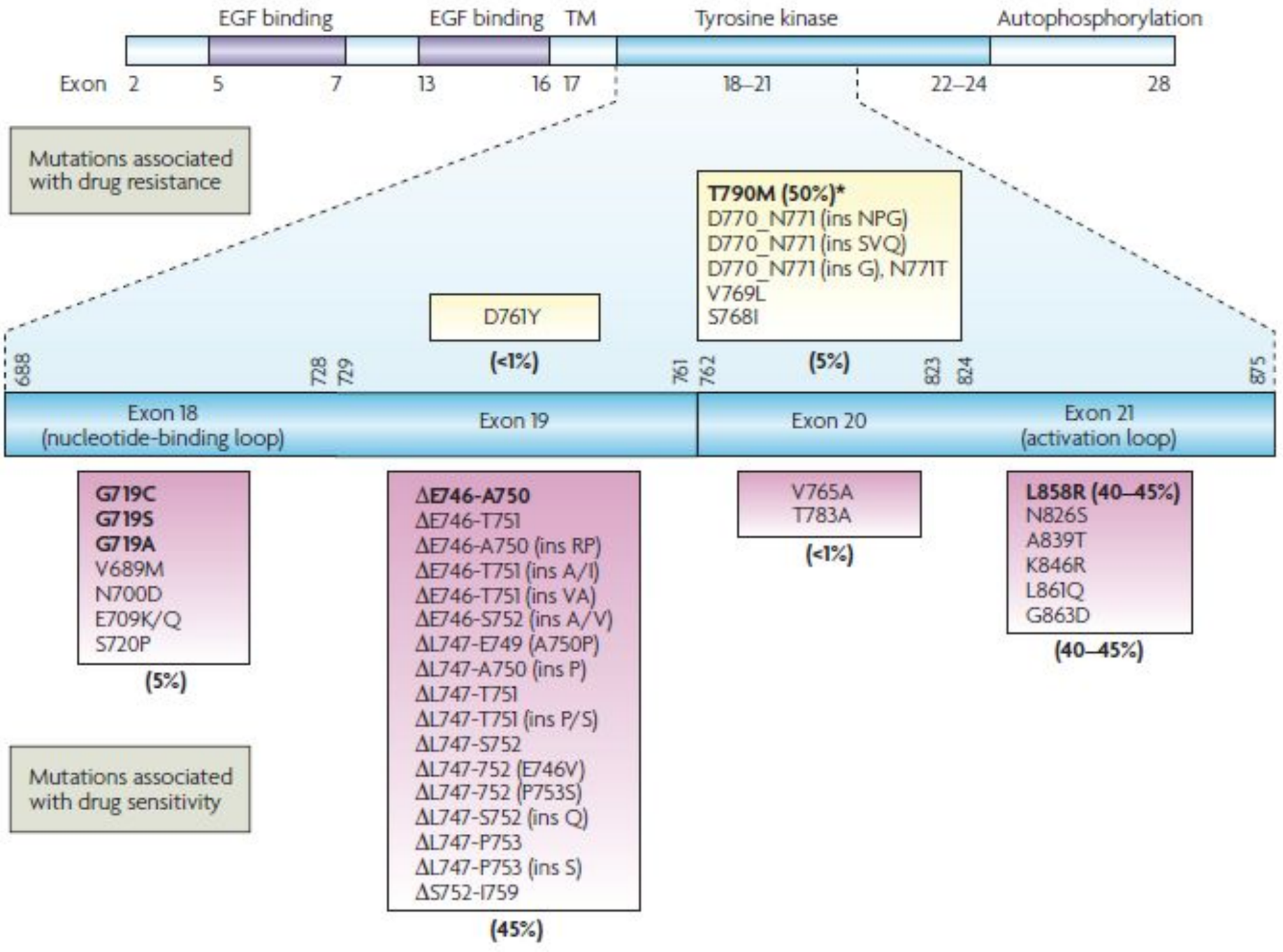
Trial	*EGFR* mutations	PFS (m)	HR PFS	HR OS
IPASS (subgroup)	19Del/L858R + other (8%)	9.6 *vs* 6.3	0.48	1.00
WJTOG3405	19Del/L858R	9.2 *vs* 6.3	0.49	1.25
NEJ002	19Del/L858R + other (6%)	10.8 *vs* 5.4	0.30	0.89
OPTIMAL	19Del/L858R	14.7 *vs* 4.6	0.16	1.04
EURTAC	19Del/L858R	9.7 *vs* 5.2	0.37	0.93
Lux-Lung 3	19Del/L858R + other (11%)	11.1 *vs* 6.9	0.58	0.88
Lux-Lung 6	19Del/L858R + other (11%)	11.0 *vs* 5.6	0.28	0.93

EGFR-TKIs in 1st line treatment: clinical grade ≥3 toxicities

	Afatinib [1,2]	**Gefitinib** [3,4,5]	**Erlotinib** [6,7]
Diarrhea	5 – 14 %	1 – 4 %	1 – 5 %
Rash or acne	14 – 16 %	2 – 5%	2 – 13 %
Stomatitis or mucositis	5 – 9 %	0 – 0.2 %	0 – 1 %
Paronychia	11 – 33 %	0.3 – 1%	0 %

1. Sequist et al *J Clin Oncol* 2013; 31:3327-3334.
2. Wu et al *Lancet Oncol* 2014; 15: 213–22.
3. Mok et al *N Engl J Med* 2009;361:947-57.
4. Maemondo et al *N Engl J Med* 2010;362:2380-8.
5. Mitsudomi et al *Lancet Oncol* 2010;11:121-128.
6. Zhou et al *Lancet Oncol* 2011; 12: 735-742.
7. Rossel et al *Lancet Oncol* 2012; 13: 239-246.

"*EGFR* mutation": different mutations have different sensitivities to EGFR-TKIs



OS in NSCLC with common *EGFR*-mutations: afatinib *versus* chemotherapy

- Treatment naïve stage IIIB/IV adenocarcinoma of the lung
- Presence of *EGFR* mutation in the tumor tissue
- ECOG PS 0 or 1

R
2:1

Stratification by EGFR mutation type and by race

Afatinib
40 mg orally once daily

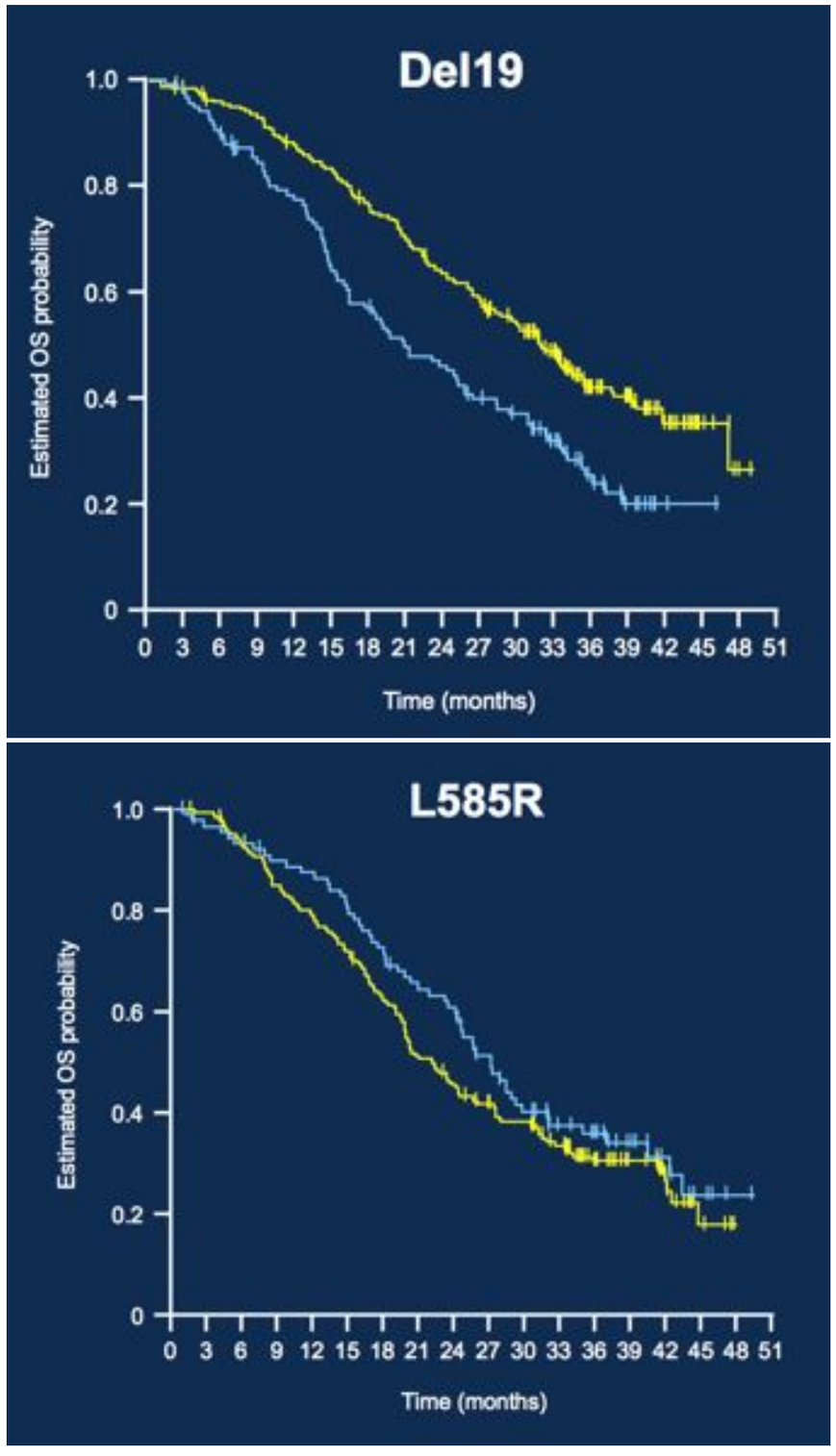
LUX-Lung 3[1]:
Cisplatin + pemetrexed
up to 6 cycles

LUX-Lung 6[2]:
Cisplatin + gemcitabine
up to 6 cycles

- Primary endpoint: PFS (independent review)
- **Pre-planned subgroup analysis of patients with common mutations**
- **Exploratory analysis of combined OS data stratified by study and EGFR mutation type**

1. Sequist et al. *J Clin Oncol*. 2013;31:3327; 2. Wu et al. *Lancet Oncol*. 2014;15:213.

OS in NSCLC with common *EGFR*-mutations: afatinib *versus* chemotherapy



	Afatinib	Chemo
Del19 and L585R	419 pts	212 pts
OSmedian	27.3 m	24.3 m
	HR 0.81 (*P* 0.037)	
Subsequent chemo	58 %	37 %
Subsequent EGFR-TKI	31 %	66 %
Del19	236 pts	119 pts
OS median	31.7 m	20.7 m
	HR 0.59 (*P* 0.0001)	
L585R	183 pts	93 pts
OS median	22.1 m	26.9 m
	HR 1.25 (*P* 0.160)	

Yang et al. *Annual Meeting ASCO 2014*: abstr 8004.

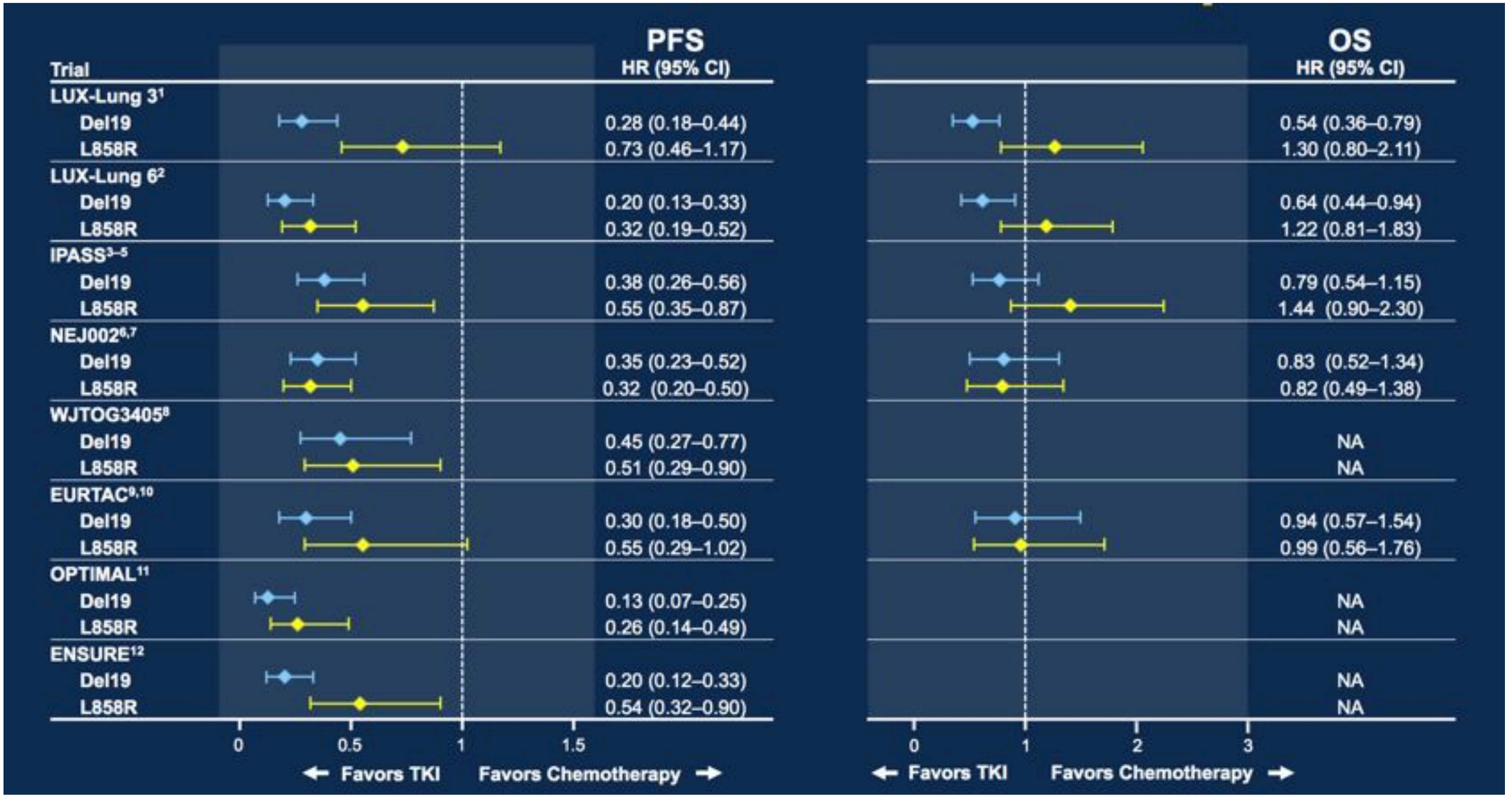
OS in NSCLC with common *EGFR*-mutations: afatinib *versus* chemotherapy

Conclusion of the presenter:

- First-line afatinib significantly improved OS vs chemotherapy in *EGFR* Del19 patients in two randomized trials
  - LUX-Lung 3: median 33.3 vs 21.1 months, HR=0.54, p=0.0015
  - LUX-Lung 6: median 31.4 vs 18.4 months, HR=0.64, p=0.0229
- No significant difference in OS of patients with L858R mutations, individually or in exploratory combined analysis
- Del19 and L858R patients are two distinct populations and should be studied separately in the future
- First-line afatinib should be the standard of care for EGFR Del19 patients and remains a treatment option for EGFR L858R patients

Yang et al. *Annual Meeting ASCO 2014*: abstr 8004.

Survival with different EGFR-TKI in NSCLC with “common” Del19 and L858R *EGFR*-mutations



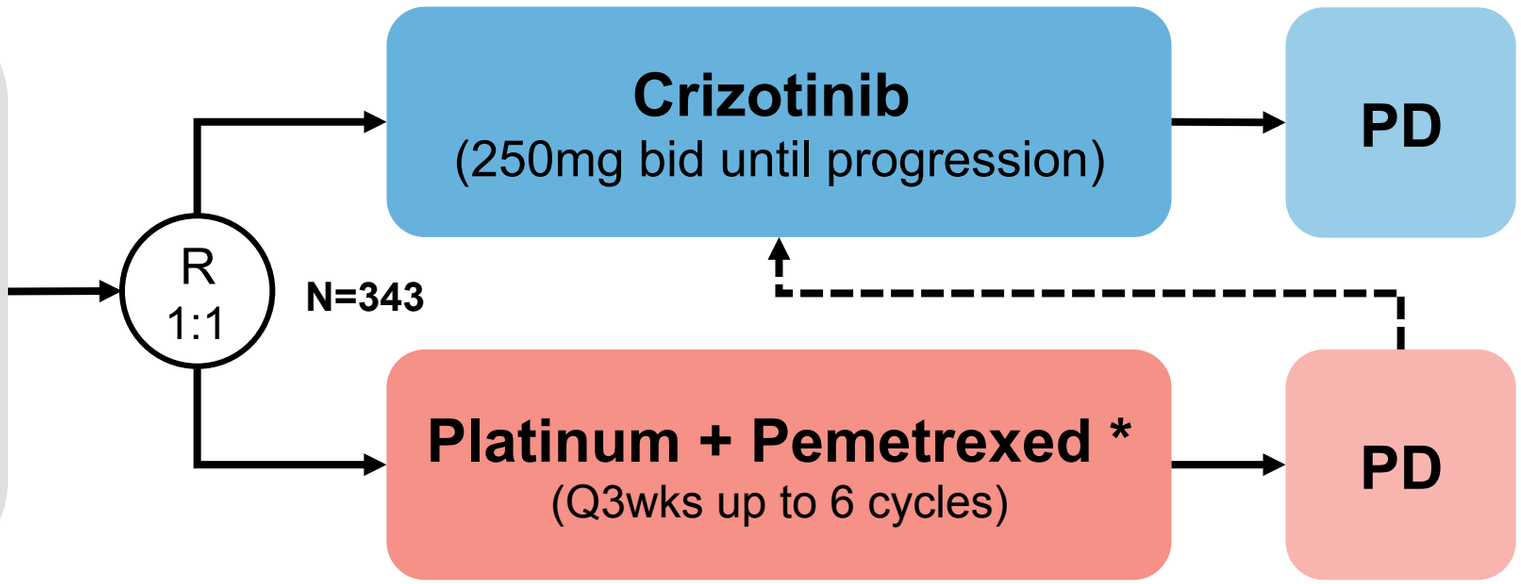
Personal conclusion:
first-line afatinib **could** be the standard of care for *EGFR* Del19 muts

1. Sequist et al. *J Clin Oncol*. 2013;31:3327; 2. Wu et al. *Lancet Oncol*. 2014;15:213; 3. Mok et al. *N Engl J Med*. 2009;361:947; 4. Fukuoka et al. *J Clin Oncol*. 2011;29:2866; 5. Yang et al. *Eur J of Cancer*. 2011 (suppl1;S633); 6. Maemondo et al. *N Engl J Med*. 2010;362:2380; 7. Inoue et al. *Ann Oncol*. 2013;24:54; 8. Mitsudomi et al. *Lancet Oncol.* 2010;11:121; 9. Rosell et al. *Lancet Oncol*. 2012;13:239; 10. TARCEVA® (erlotinib) prescribing information, 2013; 11. Zhou et al. *Lancet Oncol.* 2011;12:735; 12. Wu et al. *J Thorac Oncol*. 2013;8:suppl 2 (P1.11-021).

1st line crizotinib *vs* chemotherapy in *ALK*+ NSCLC

Objective: to compare the efficacy and safety of crizotinib with that of pemetrexed–platinum in patients with previously untreated advanced non-squamous *ALK*-positive NSCLC.

- ALK-FISH positive non-squamous advanced NSCLC
- Treatment naïve
- PS 0-2



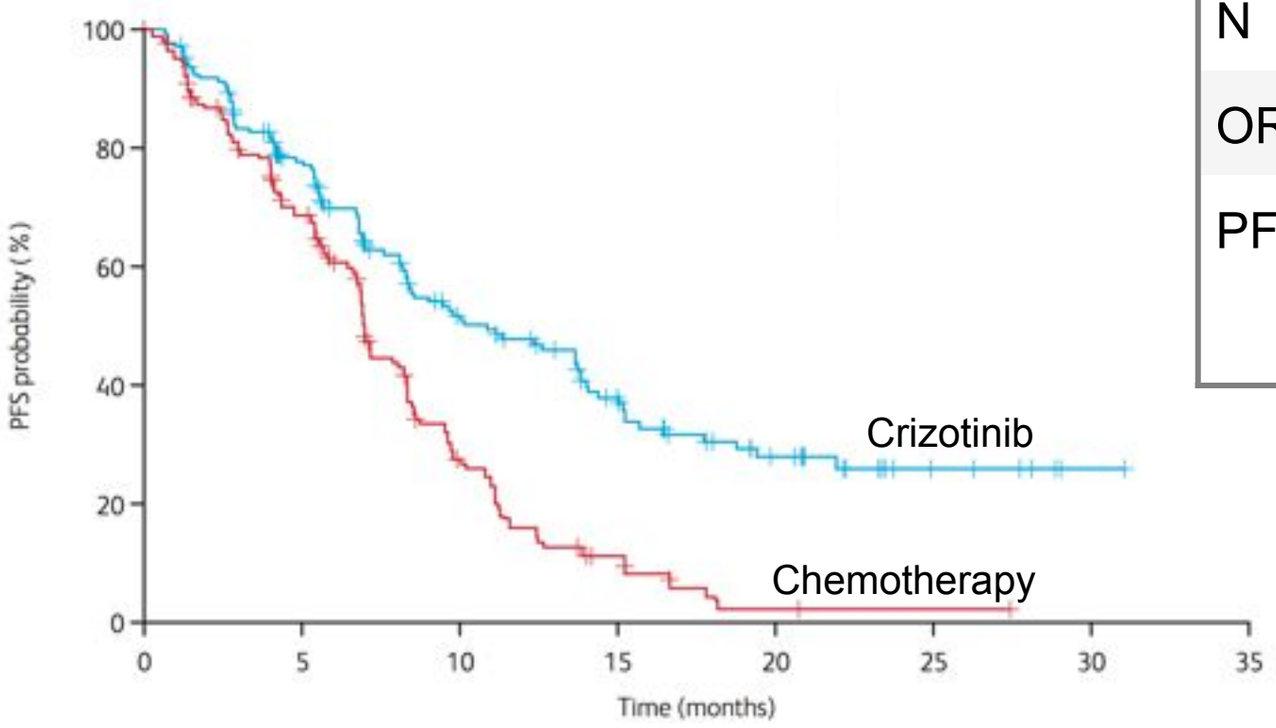
Primary endpoint: progression-free survivall (PFS)

* Pemetrexed 500 mg/m^2 + Cisplatin 75 mg/m^2 or Carboplatin AUC 5-6 on d1

Mok et al. *Annual Meeting ASCO 2014*: abstr 8002.

1st line crizotinib *vs* chemotherapy in *ALK*+ NSCLC

Progression-free survival:



	Crizot	Chemo
N	172	171
ORR	74%	45%
PFS median	10.9 m	7.0 m
	HR 0.45	(*P* 0.<0.0001)

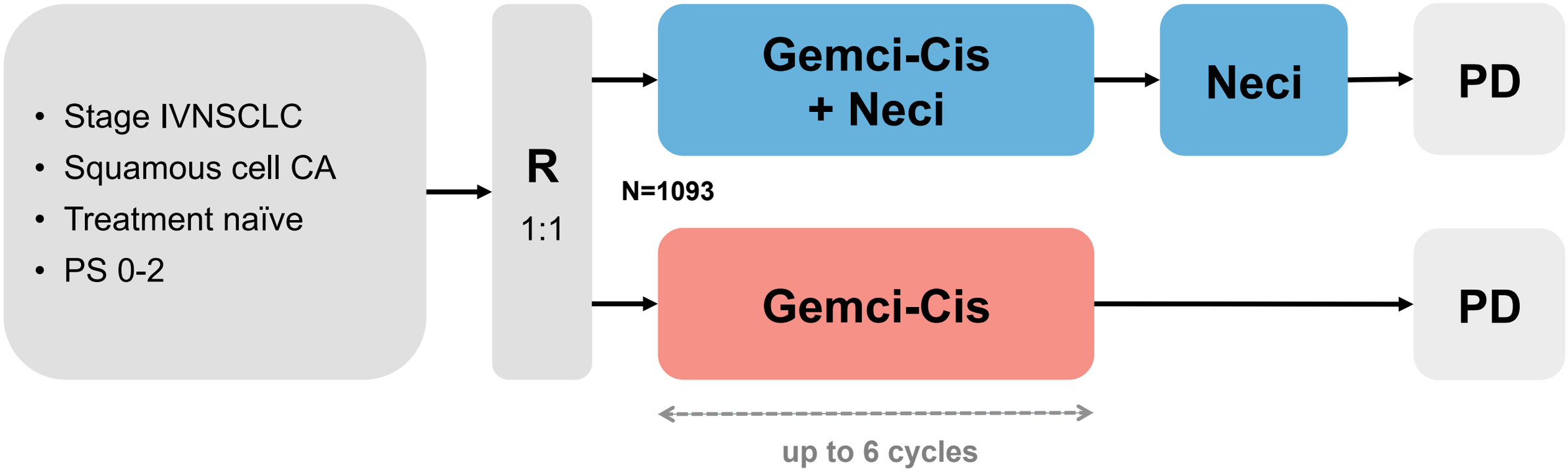
Conclusion:

- 1st-line crizotinib treatment resulted in statistically significant and clinically meaningful improvements in response rate and PFS and ORR as compared with platinum-based chemotherapy and had an acceptable safety profile.

Mok et al. *Annual Meeting ASCO 2014*: abstr 8002.

SQUIRE: necitumumab in squamous cell NSCLC

Necitumumab: monoclonal human IgG1 anti-EGFR antibody.



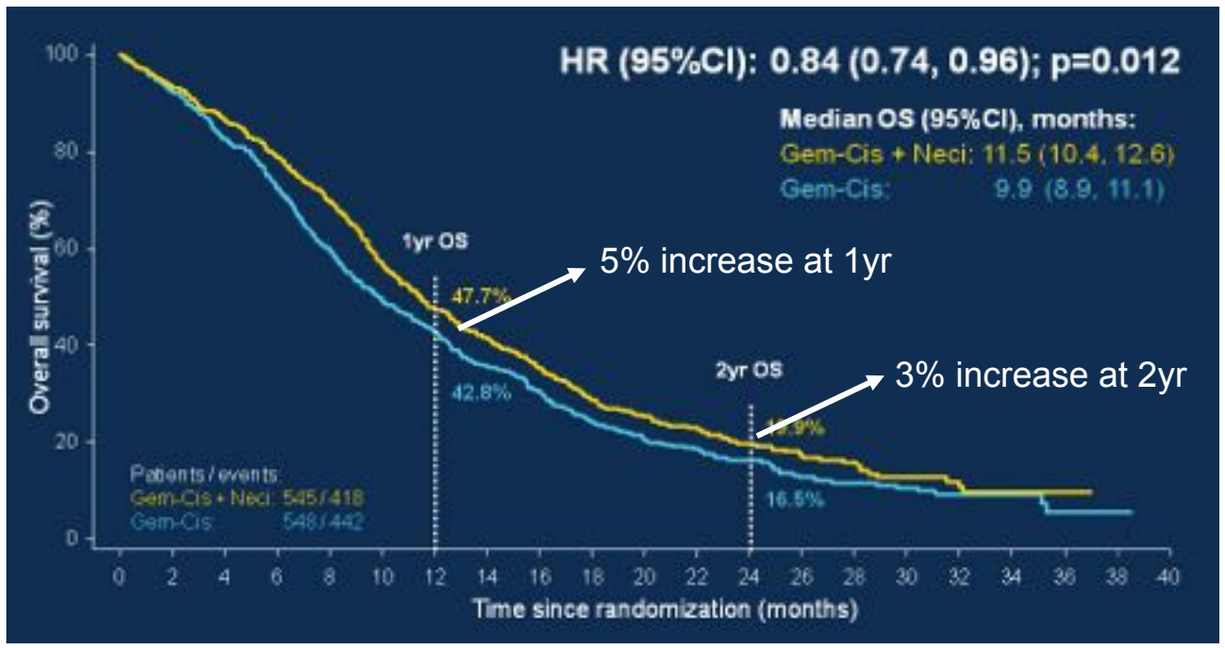
Primary endpoint: overall survivall (OS)

* Cisplatin 75 mg/m^2 D1; Gemcitabine 1250 mg/m^2 D1,D8; Necitumumab 800 mg D1,D8

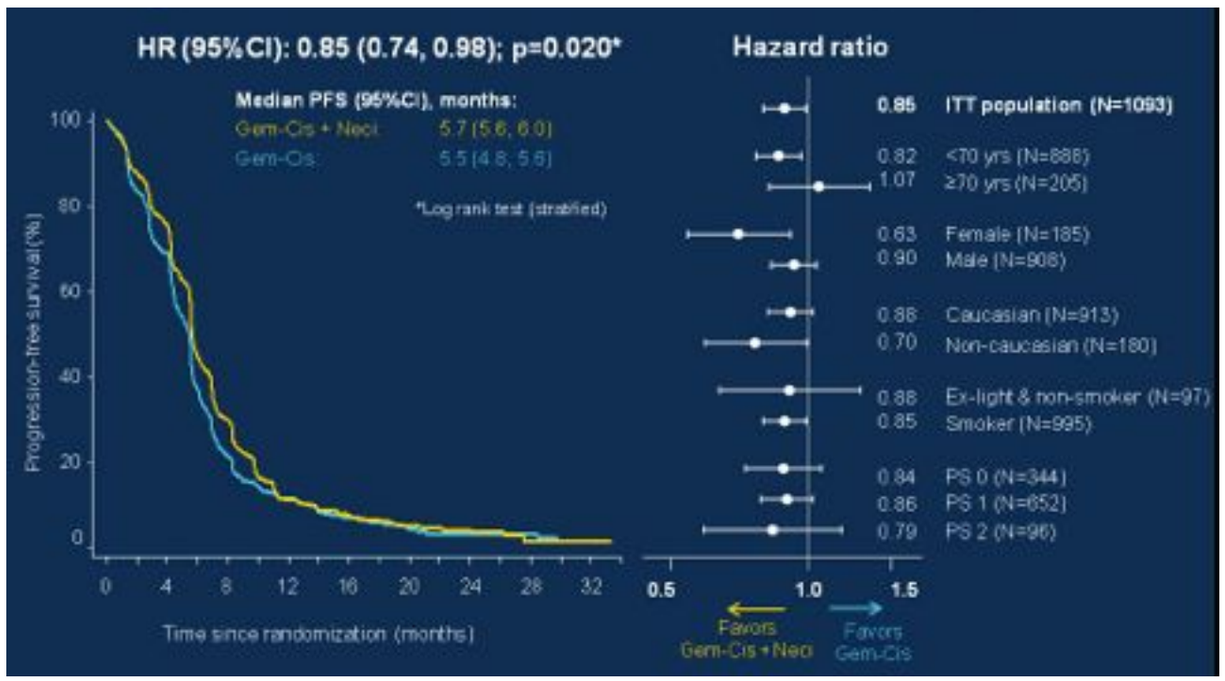
Thatcher et al. *Annual Meeting ASCO 2014*: abstr 8008.

SQUIRE: necitumumab in squamous cell NSCLC

Overall survival:



Progression-free survival:



	GC + Neci	GC
N	545 pts	548pts
ORR	31% *	29%
PFS median	5.7 m	5.5 m
	HR 0.85 (*P* 0.020)	
OS median	11.5 m	9.9 m
	HR 0.84 (*P* 0.012)	
Post-study R/	47%	45%
Grade ≥3 AE	72%	62%

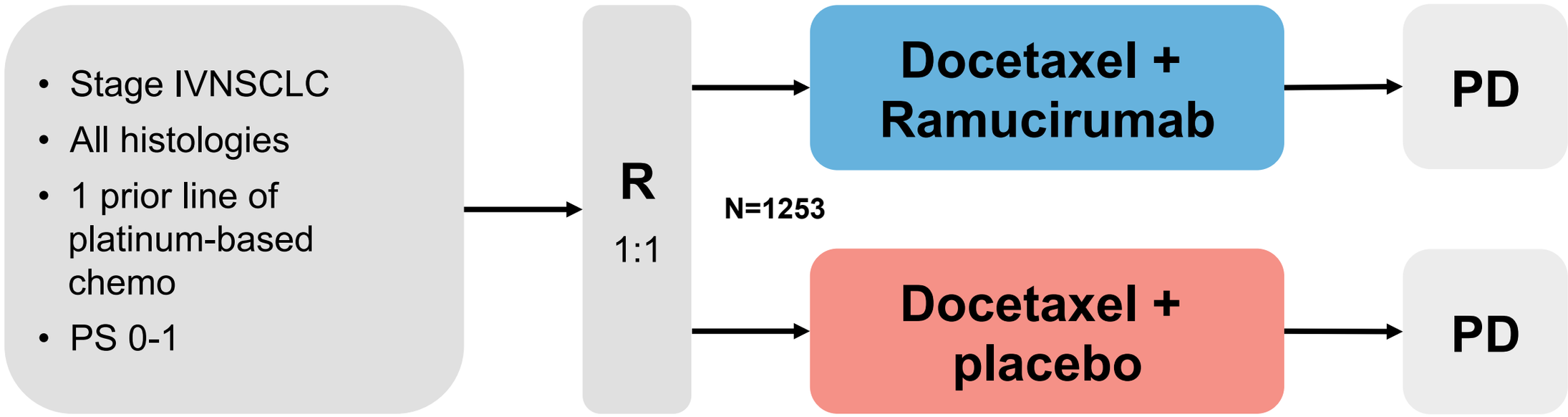
Conclusion:

- Study mets its 1ary endpoint (OS)
- Acceptable toxicity profile
- EGFR IHC H-score not predictive

Thatcher et al. *Annual Meeting ASCO 2014*: abstr 8008.

REVEL: ramucirumab in 2nd line treatment

Ramucirumab: monoclonal human IgG1 anti-VEGFR-2 antibody.

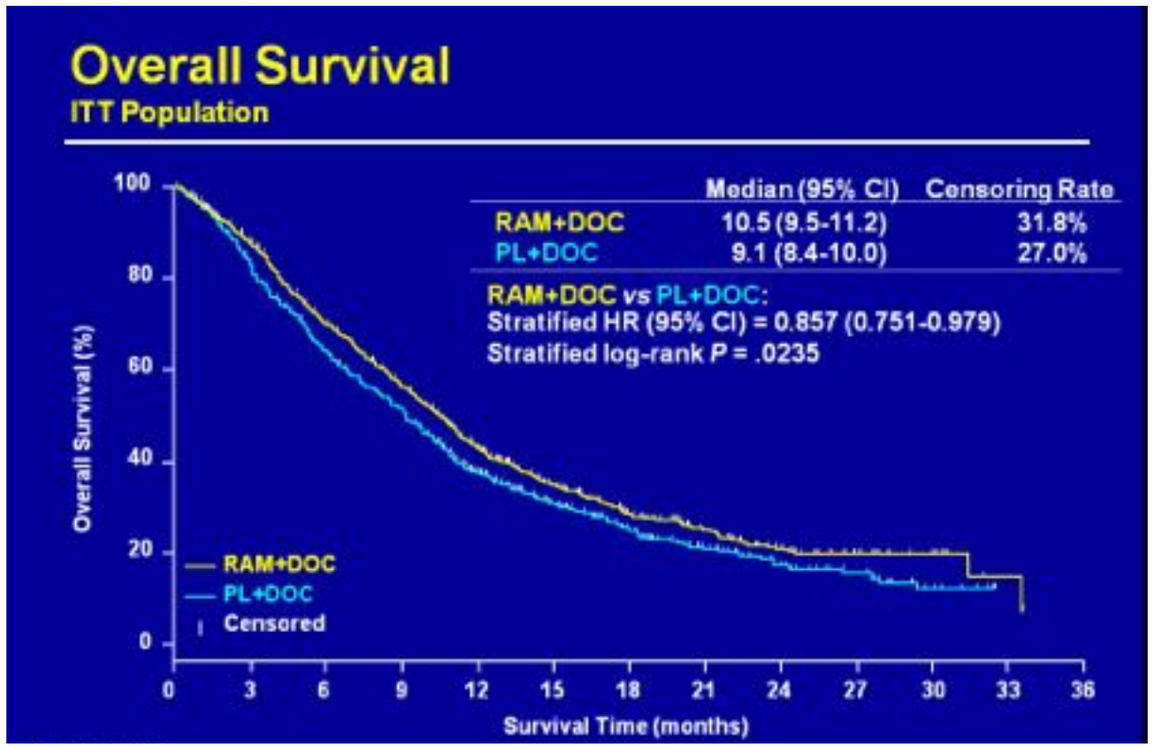


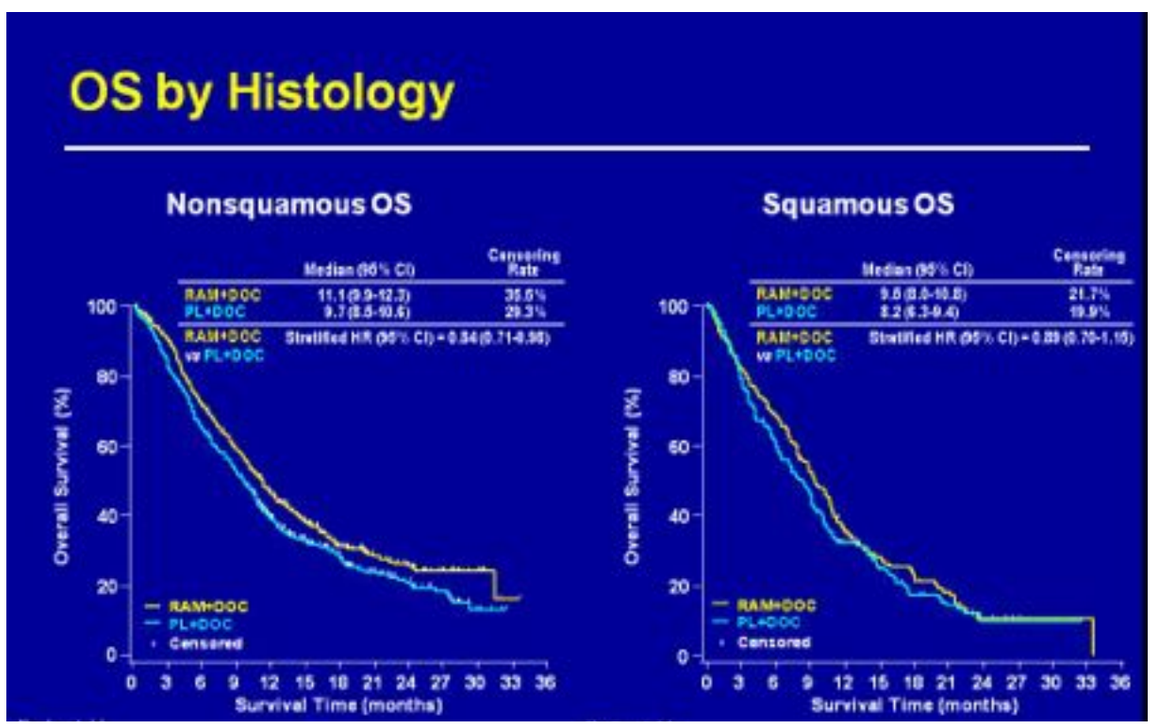
Primary endpoint: overall survivall (OS)

* Docetaxel 75 mg/m^2 D1; Ramucirumab 10 mg/kg D1 every 3 weeks

Pérol et al. *Annual Meeting ASCO 2014*: abstr 8006.

REVEL: ramucirumab in 2nd line treatment





	D + Ramu	D
N	628 pts	625 pts
ORR	23% *	14%
PFS median	4.5 m	3.0 m
	HR 0.762 (*P* <0.0001)	
OS median	10.5 m	9.1 m
	HR 0.857 (*P* 0.024)	
Post-study R/	45%	48%
Febrile neutro	16%	10%

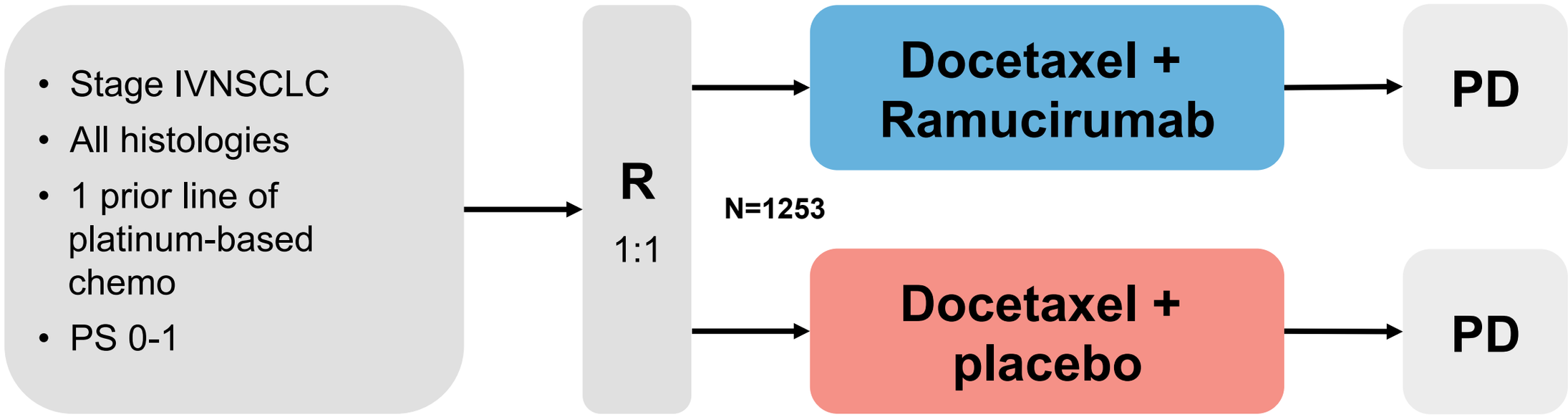
Conclusion:

- Study mets its 1ary endpoint (OS)
- PFS and OS improvements observend across all subgroups

Pérol et al. *Annual Meeting ASCO 2014*: abstr 8006.

REVEL: ramucirumab in 2nd line treatment

Ramucirumab: monoclonal human IgG1 anti-VEGFR-2 antibody.



Primary endpoint: overall survivall (OS)

* Docetaxel 75 mg/m^2 D1; Ramucirumab 10 mg/kg D1 every 3 weeks

Pérol et al. *Annual Meeting ASCO 2014*: abstr 8006.

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

			Primary End Point		Secondary End Point	
Cancer Type	Patient Population	Current Baseline Median OS (months)	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

Ellis et al *J Clin Oncol* 2014; 32: 1277-1280.

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	Median OS	OS HR	1yr OS	Median PFS
Recommended target	**+ 2.5-4 m**	**0.76 – 0.80**	**+ 8-9%**	**+ 3-4 m**
1st line afatinib common muts	+ 3 m	0.81	+ *~2%*	
1st line afatinib Del19 muts	+ 11 m	0.59	+ *~10%*	
1st line crizotinib				+ 3.9 m
Necimumab in squamous CA	+ 1.6 m	0.84	+ 5%	+ 0.2 m
Ramucirumab in 2nd line	+ 1.6 m	0.86	+ *~5%*	+ 1.5 m

Ellis et al *J Clin Oncol* 2014; 32: 1277-1280.

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	Median OS	OS HR	1yr OS	Median PFS
Recommended target	**+ 2.5-4 m**	**0.76 – 0.80**	**+ 8-9%**	**+ 3-4 m**
1st line afatinib common muts	+ 3 m	0.81	+ *~2%*	
1st line afatinib Del19 muts	+ 11 m	0.59	+ *~10%*	
1st line crizotinib				+ 3.9 m
Necimumab in squamous CA	+ 1.6 m	0.84	+ 5%	+ 0.2 m
Ramucirumab in 2nd line	+ 1.6 m	0.86	+ *~5%*	+ 1.5 m

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