Les traitements péri-opératoires des carcinomes bronchiques non à petites cellules

Virginie Westeel
Service de pneumologie
CHRU Besançon, France

Rationnel

- Destruction des micrométastases
- Réduction du risque de récidive (locorégionale, à distance)

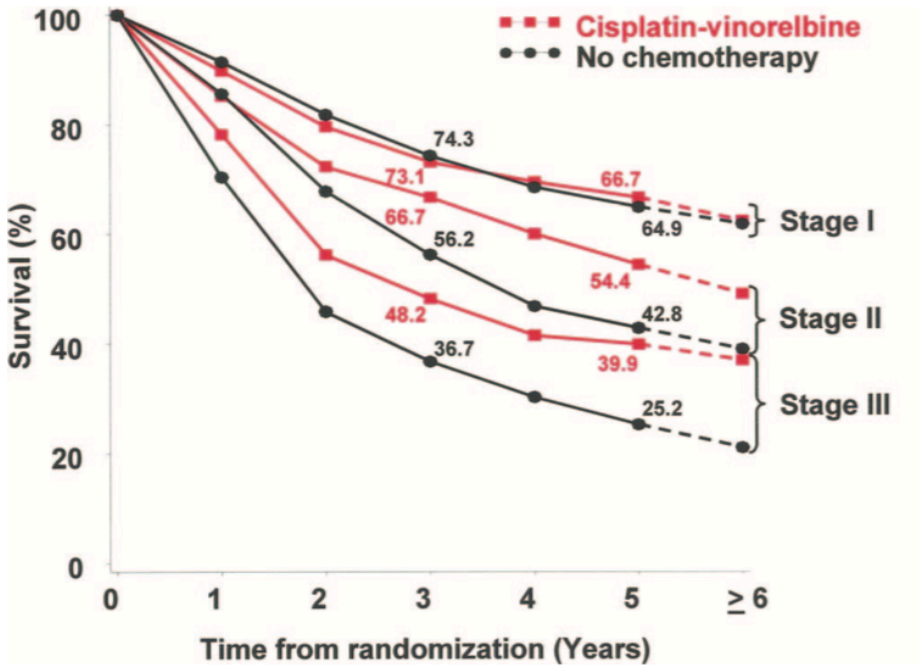


FIGURE 3. Overall survival curves by stage for the cisplatin-vinorelbine versus the observation (no chemotherapy) groups.

Douillard JY, J Thorac Oncol 2010; 5:220-8

Peri-operative Treatments in NSCLC

In wild-type NSCLC

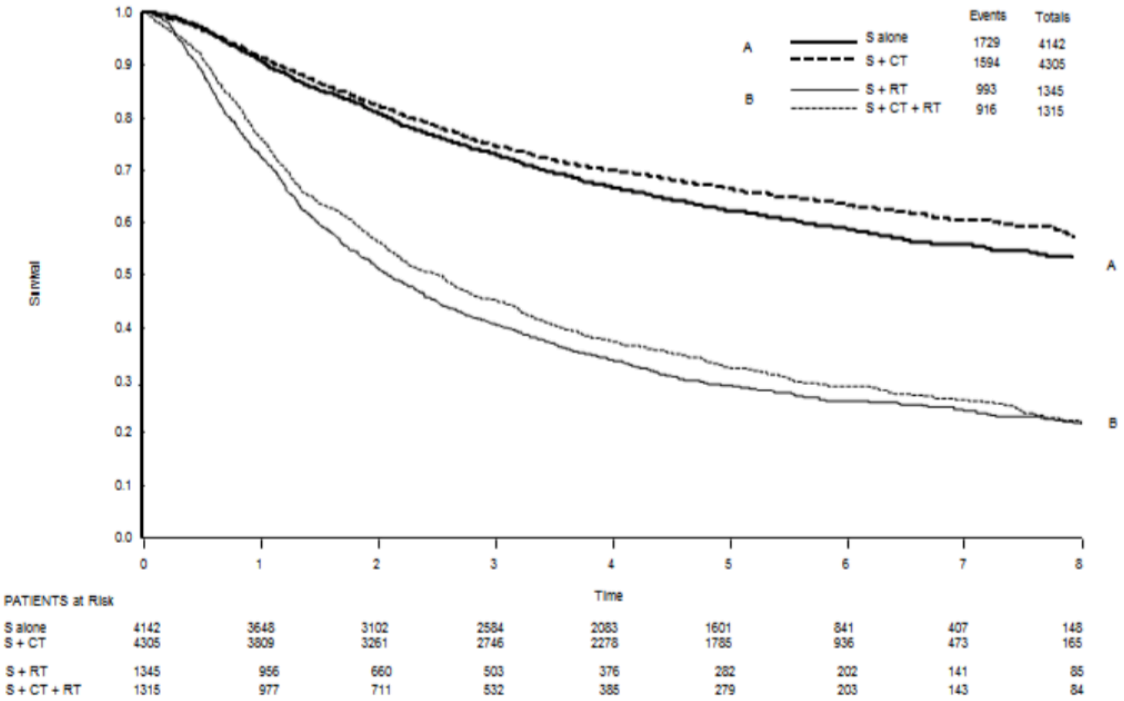
- Peri-operative chemotherapy
- Preoperative chemoradiation
- Perioperative targeted treatments
- Peri-operative immunotherapy

In EGFR mutated NSCLC

Postoperative radiotherapy

Adjuvant Chemotherapy: Survival Results 1 (IPD Meta-analysis)

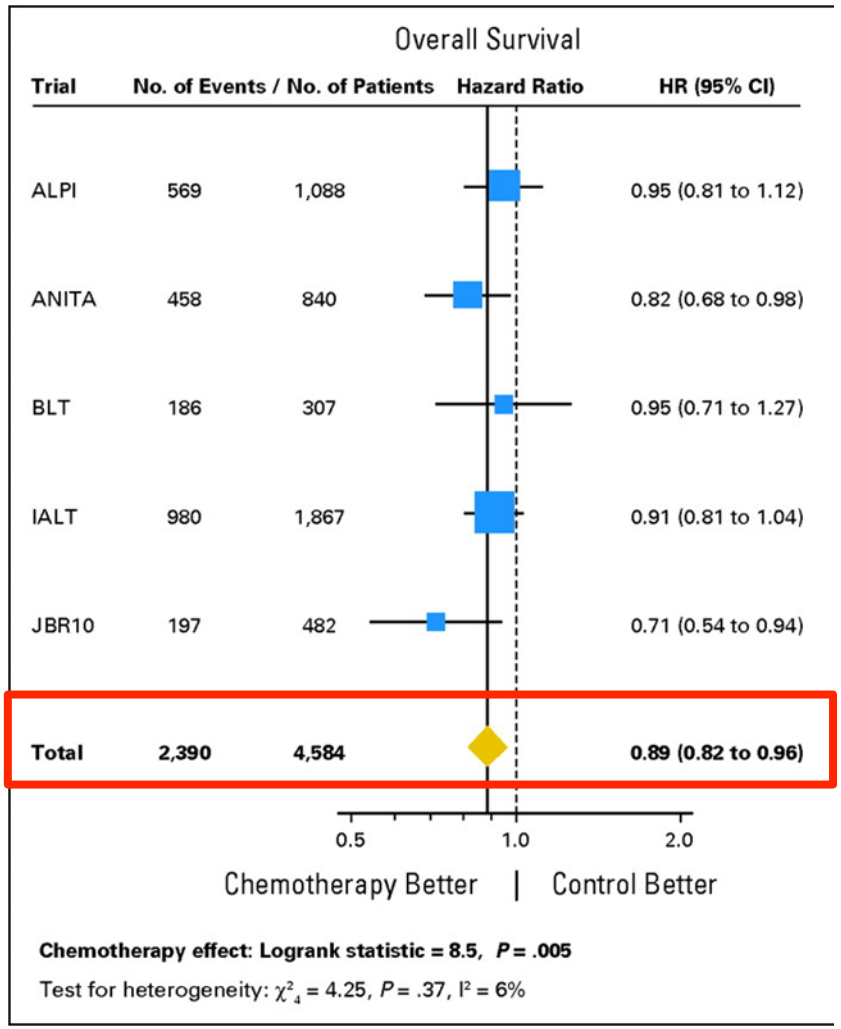
Figure 4. Simple (non-stratified Kaplan-Meier curves for trials of Surgery (S) and chemotherapy (CT) versus surgery alone and for trials of surgery and chemotherapy and radiotherapy (RT) versus surgery and radiotherapy.

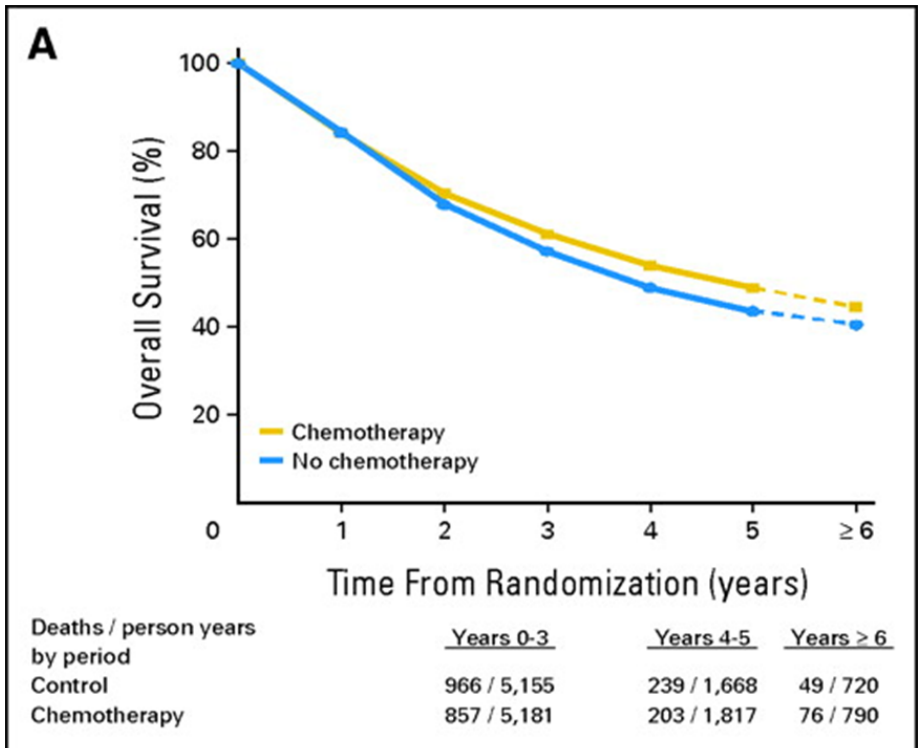


HR 0.86 (0.81 to 92); p< 0.0001

Burdett S, Cochrane Database of Systematic Reviews 2015, Issue 3. Art. No.: CD011430
NSCLC Meta-analysis Collaborative Group, Lancet 2010; 375:1267-77

The Cisplatin-based Adjuvant Chemotherapy Meta-analysis

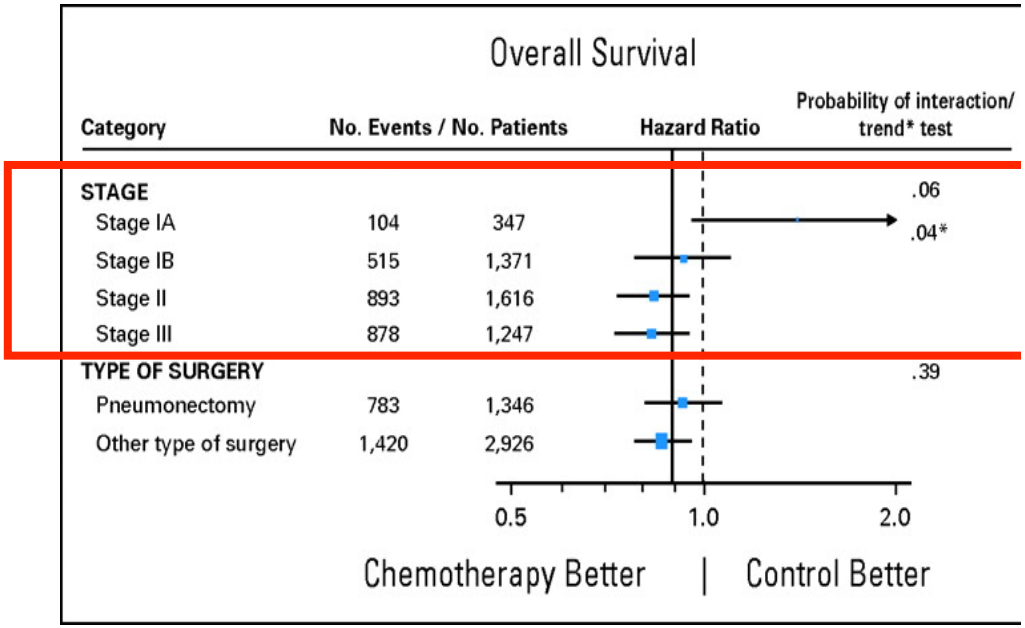




+5.4% at 5 yr

Pignon JP, J Clin Oncol 2008; 26:3552-9

Adjuvant Chemotherapy: Which Stages?



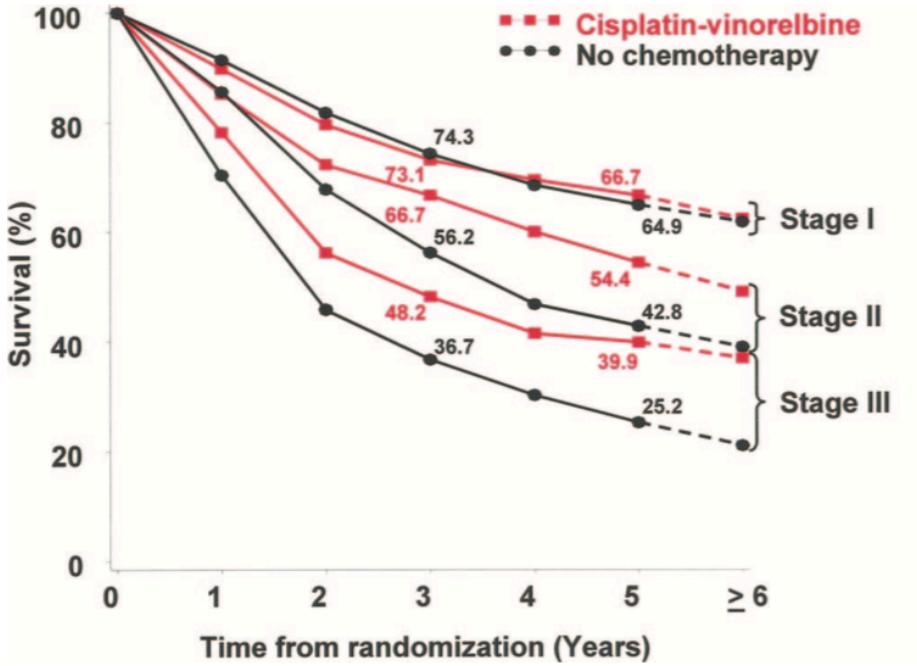
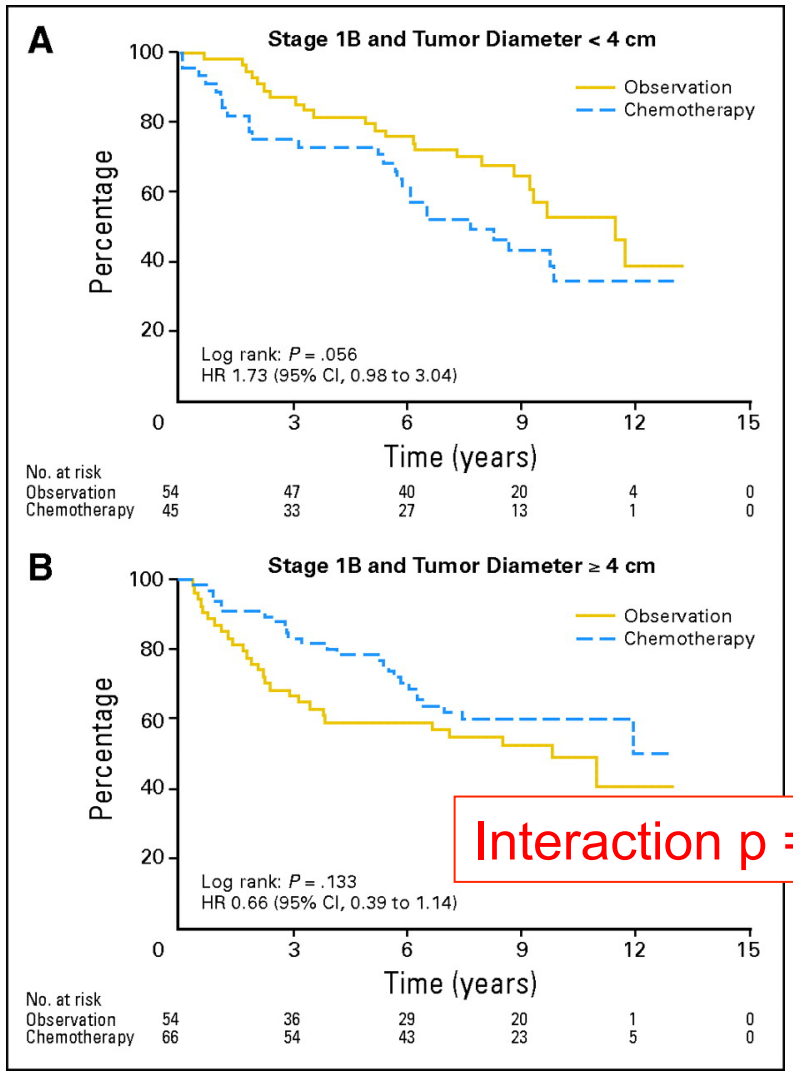


FIGURE 3. Overall survival curves by stage for the cisplatin-vinorelbine versus the observation (no chemotherapy) groups.

Pignon JP, J Clin Oncol 2008; 26:3552-9

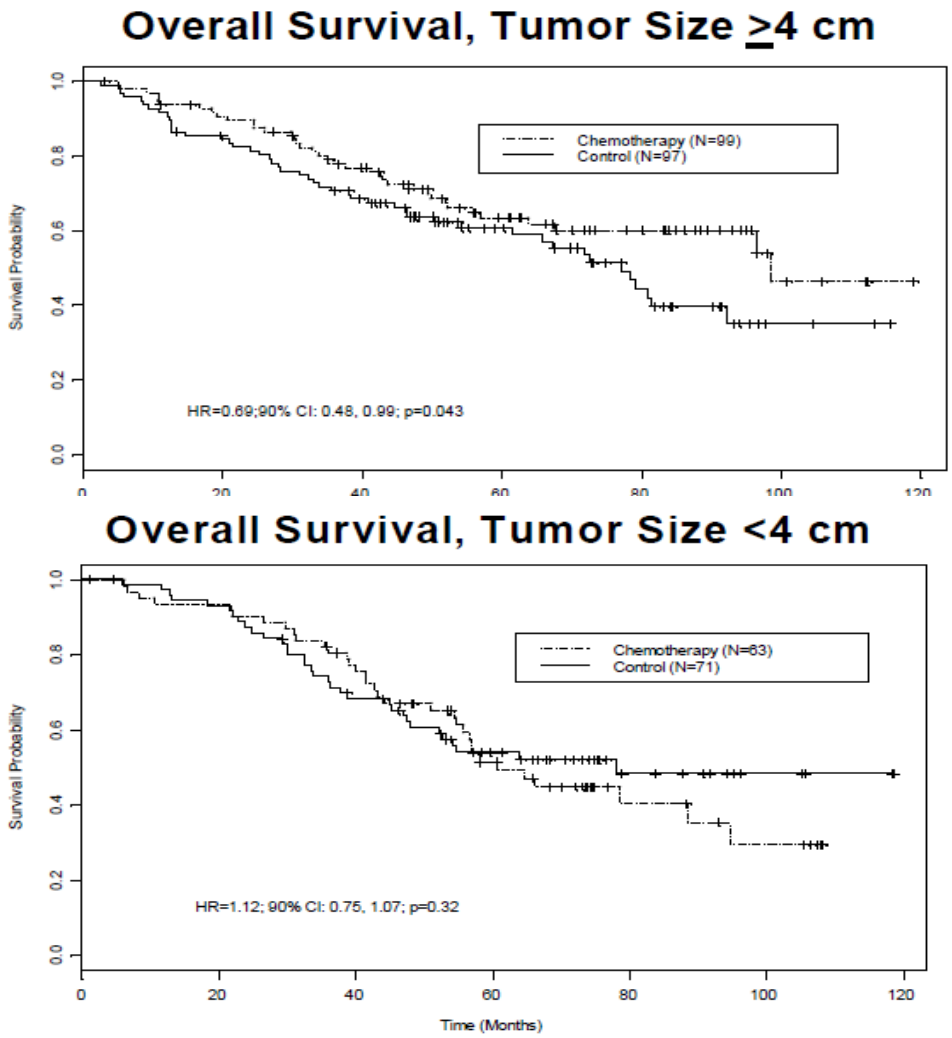
Douillard JY, J Thorac Oncol 2010; 5:220-8

Adjuvant Chemotherapy in Stage IB NSCLC



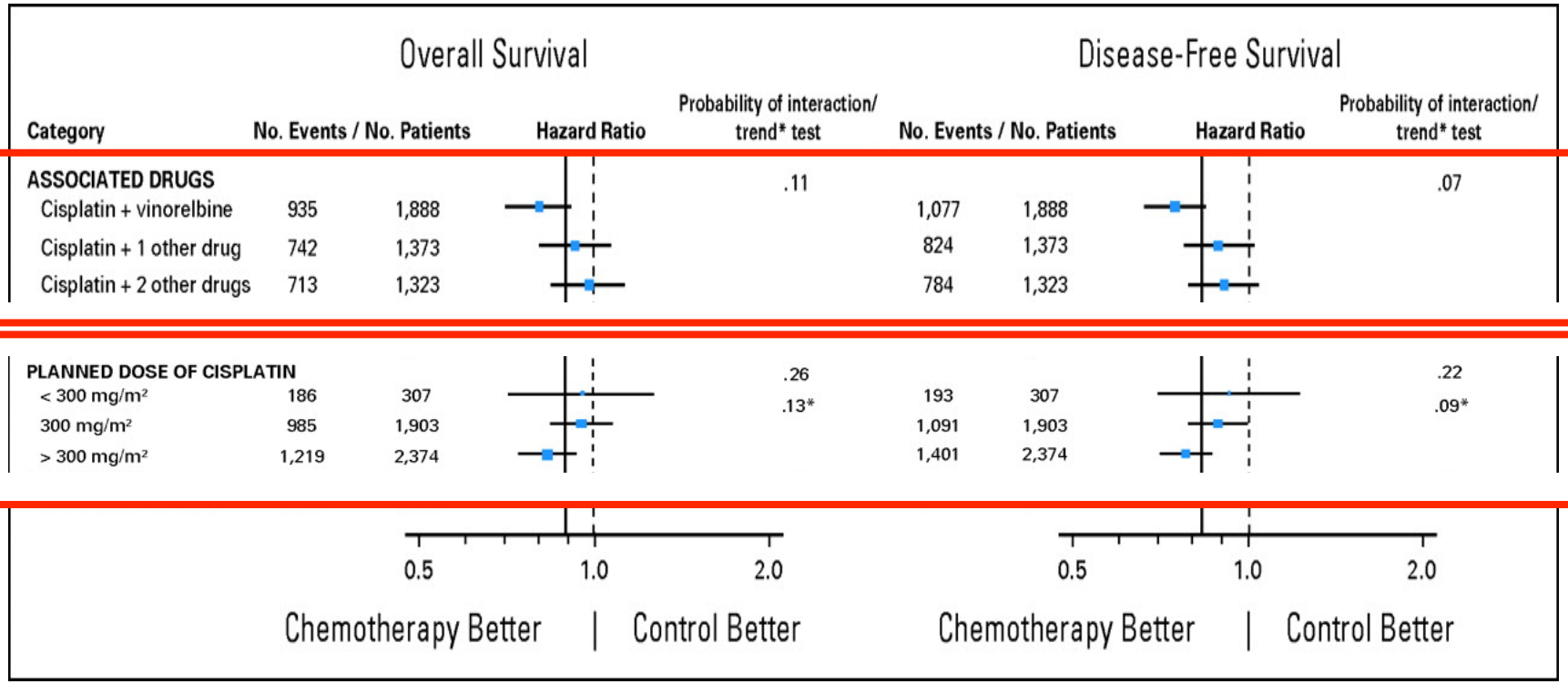
Butts et al. J Clin Oncol 2010; 28: 29

Interaction p = 0,02



Strauss, J Clin Oncol 2008; 26:5043

Adjuvant Chemotherapy: Which Drugs? Which Doses?



Pignon JP, J Clin Oncol 2008; 26:3552-9

Timing of Adjuvant Chemotherapy

- 12 473 pts
- US National cancer database

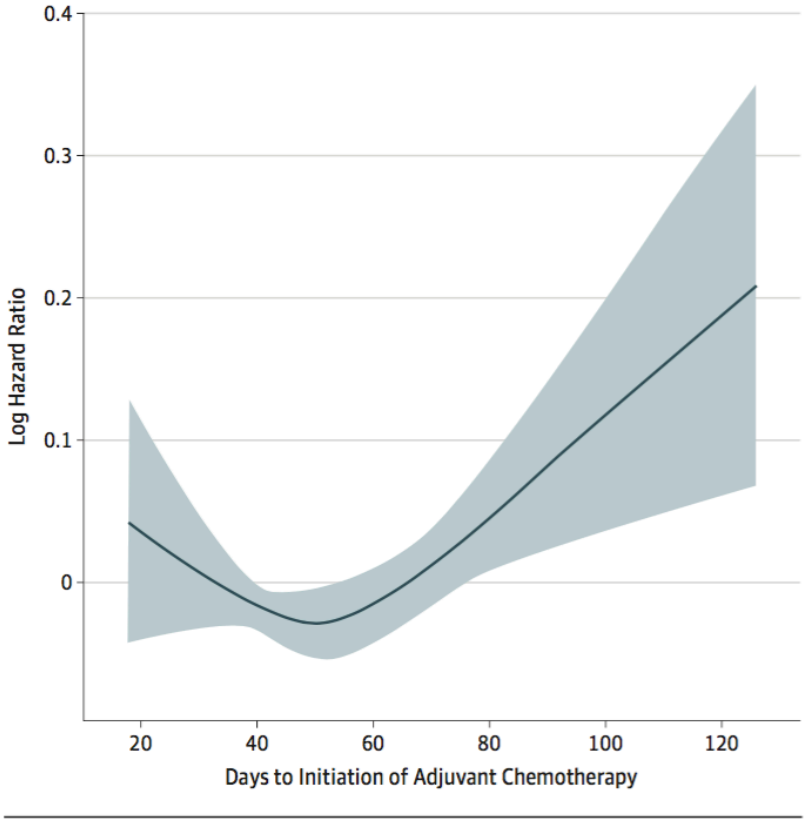
Table 2. Cox Proportional Hazards Model of Patients Who Underwent Adjuvant Chemotherapy

Covariate	No.	HR (95% CI)	*P* Value
Adjuvant chemotherapy timing			
Reference interval (39-56 d)	5137	[Reference]	
Earlier (<39 d)	3359	1.009 (0.944-1.080)	.79
Later (>56 d)	3977	1.037 (0.972-1.105)	.27

HR=0.664 (95%CI:0.623-0.707) p<0.001

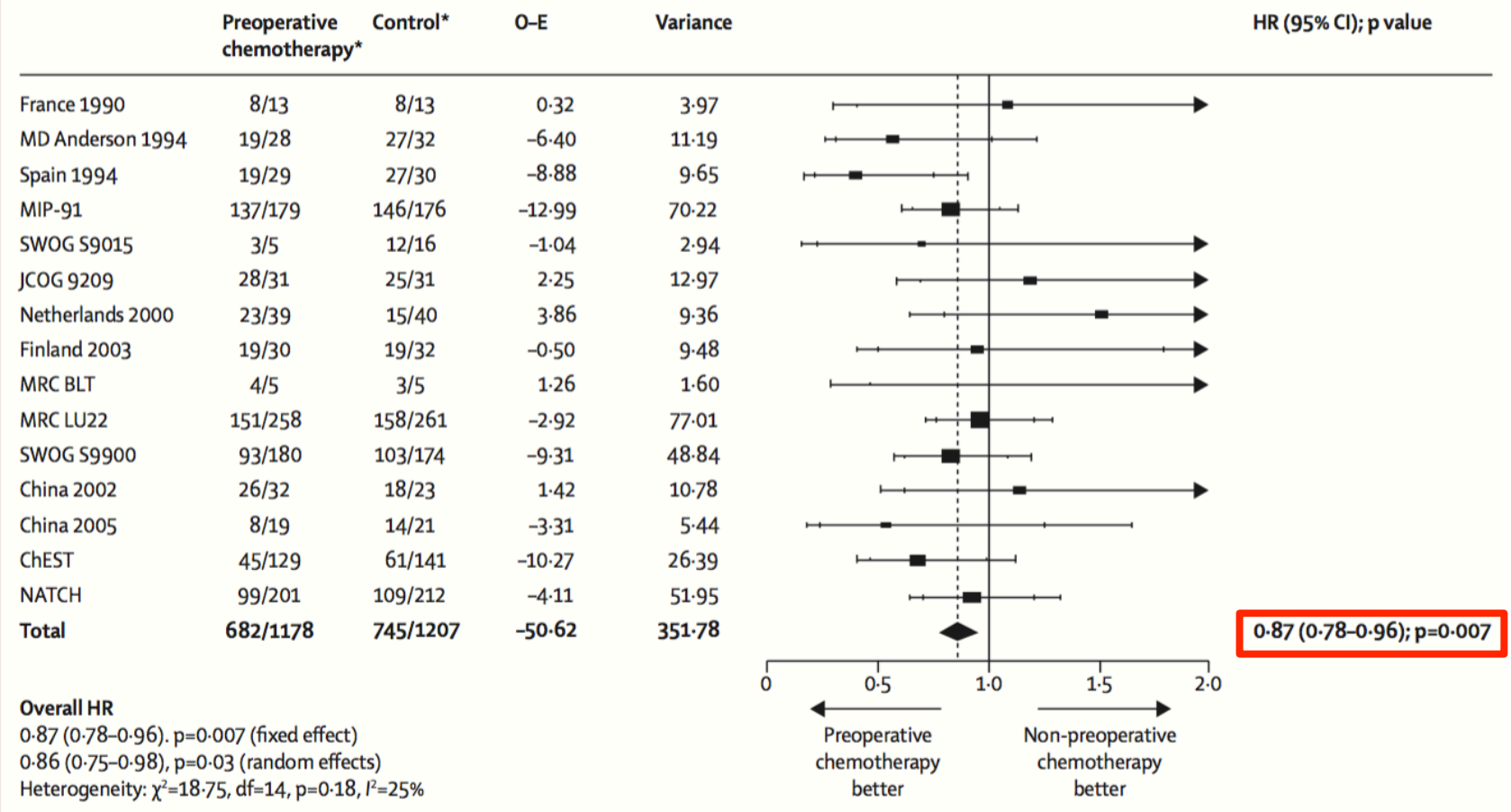
>56 days vs no chemotherapy

Figure 3. Restricted Cubic Spline Modeling of the Relationship Between Time to Initiation of Adjuvant Chemotherapy and Mortality Risk



Salazar MC, JAMA Oncol 2017

Neo-adjuvant Chemotherapy: Survival Results 1 (IPD Meta-analysis)



	Preoperative chemotherapy*	Control*	O–E	Variance	HR (95% CI); p value
France 1990	8/13	8/13	0·32	3·97	
MD Anderson 1994	19/28	27/32	−6·40	11·19	
Spain 1994	19/29	27/30	−8·88	9·65	
MIP-91	137/179	146/176	−12·99	70·22	
SWOG S9015	3/5	12/16	−1·04	2·94	
JCOG 9209	28/31	25/31	2·25	12·97	
Netherlands 2000	23/39	15/40	3·86	9·36	
Finland 2003	19/30	19/32	−0·50	9·48	
MRC BLT	4/5	3/5	1·26	1·60	
MRC LU22	151/258	158/261	−2·92	77·01	
SWOG S9900	93/180	103/174	−9·31	48·84	
China 2002	26/32	18/23	1·42	10·78	
China 2005	8/19	14/21	−3·31	5·44	
ChEST	45/129	61/141	−10·27	26·39	
NATCH	99/201	109/212	−4·11	51·95	
Total	**682/1178**	**745/1207**	**−50·62**	**351·78**	**0·87 (0·78–0·96); p=0·007**

Overall HR
0·87 (0·78–0·96). p=0·007 (fixed effect)
0·86 (0·75–0·98), p=0·03 (random effects)
Heterogeneity: χ^2=18·75, df=14, p=0·18, I^2=25%

NSCLC Meta-analysis Collaborative Group, Lancet 2014; 383:1561-71

Neo-adjuvant Chemotherapy: Survival Results 2

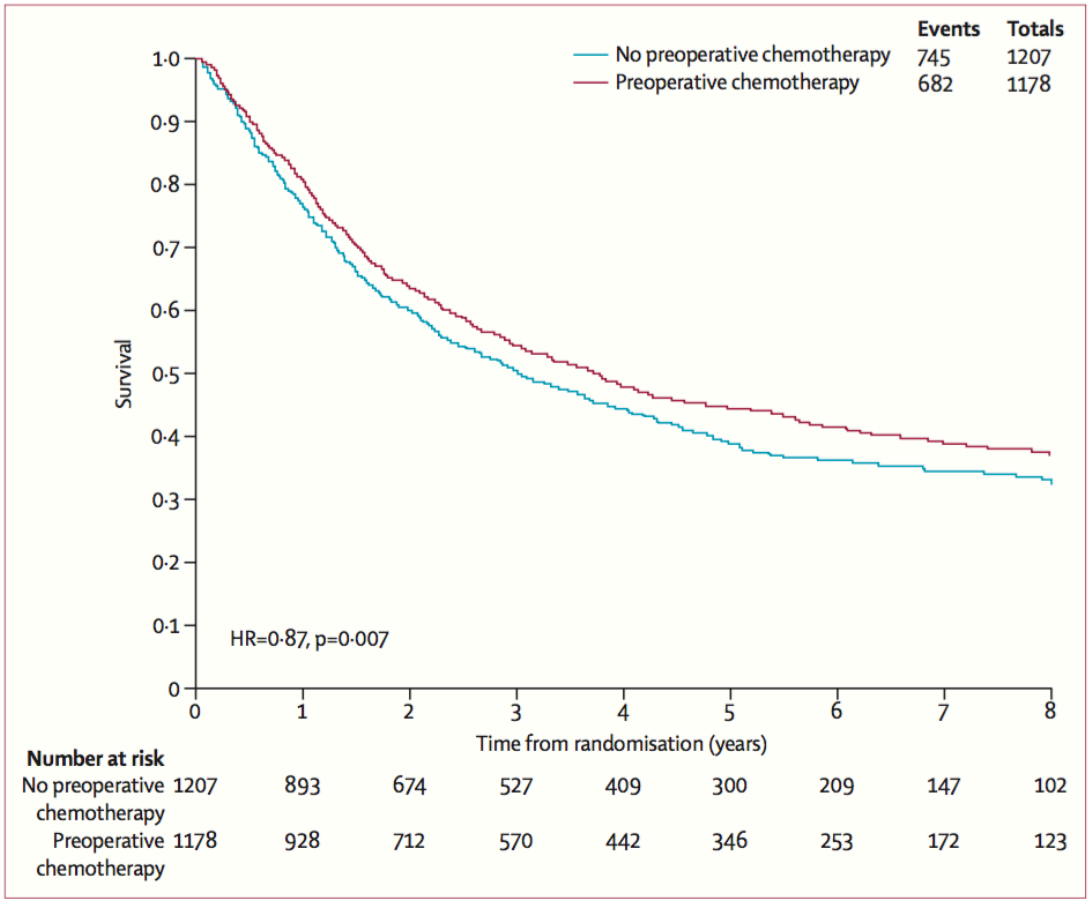
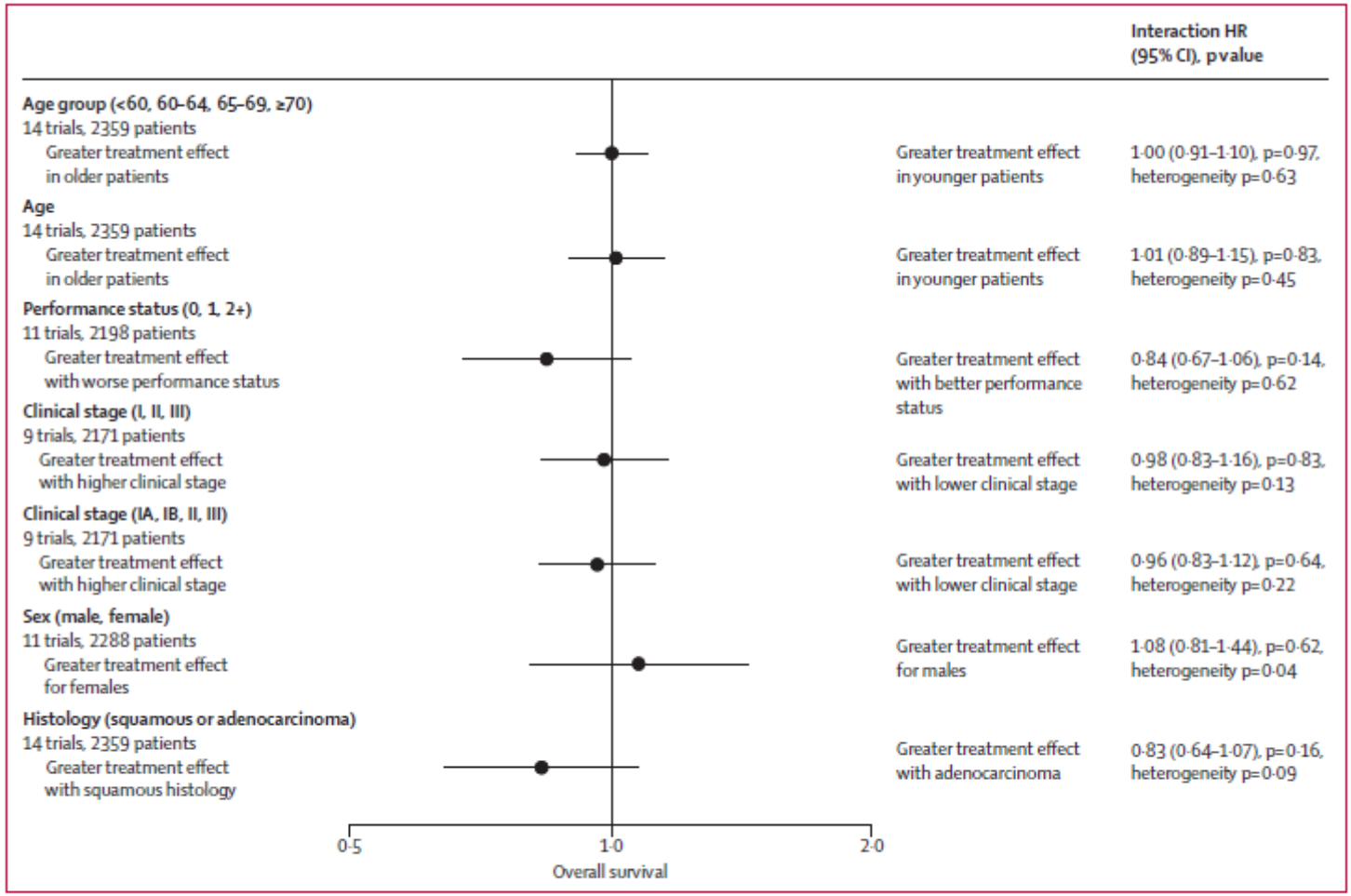


Figure 2: **Kaplan-Meier curves (non-stratified) of the effect of preoperative chemotherapy on time to survival**

- 13% reduction in the relative risk of death
- + 5% at 5 years

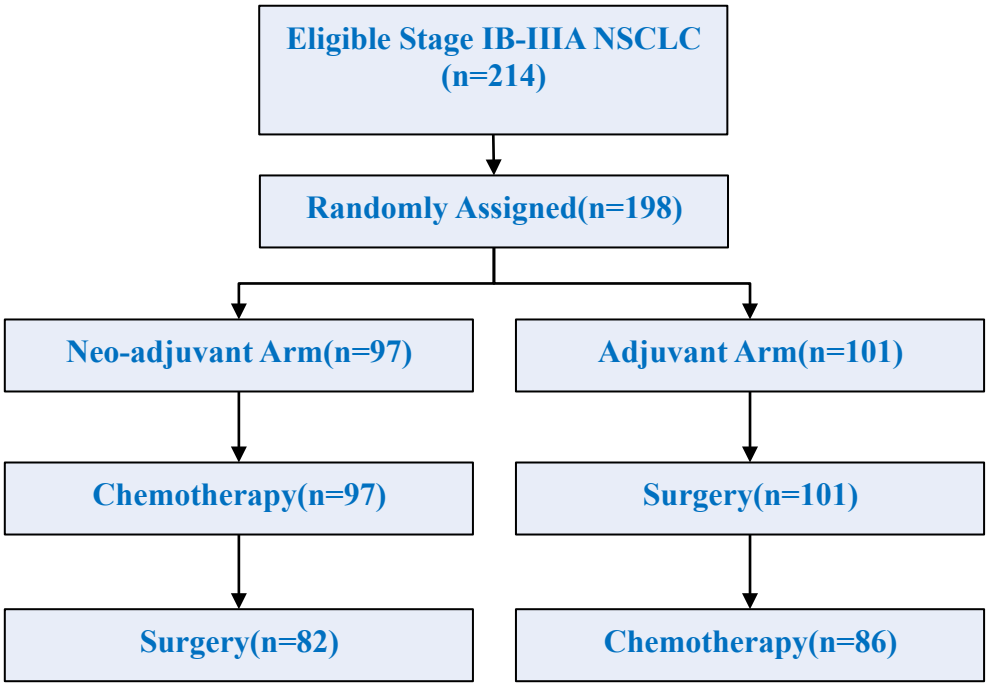
NSCLC Meta-analysis Collaborative Group, Lancet 2014; 383:1561-71

Who should receive Neoadjuvant Chemotherapy?



NSCLC Meta-analysis Collaborative Group, Lancet 2014; 383:1561-71

Adjuvant vs Neoadjuvant



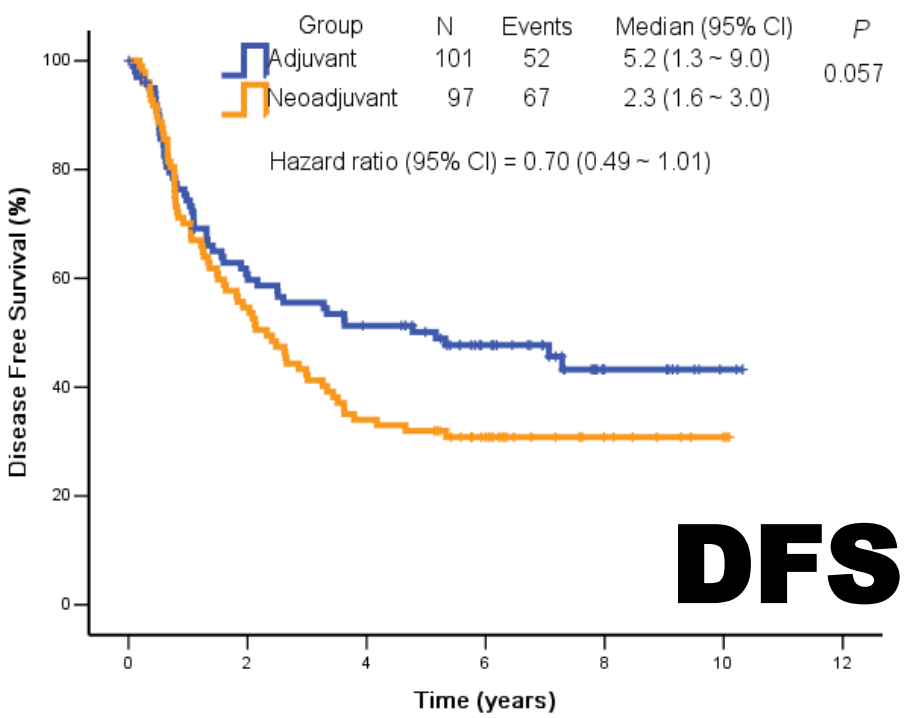
Stop for slow accrual

- **Multi-center phase 3 trial**
- **Mar. 2006 ~ May 2011**
- **Stratification:** Gender, Center, Stage (IB *vs.* II *vs.* IIIA), Pathology (adeno *vs*. non-adeno)
- **Objectives:**

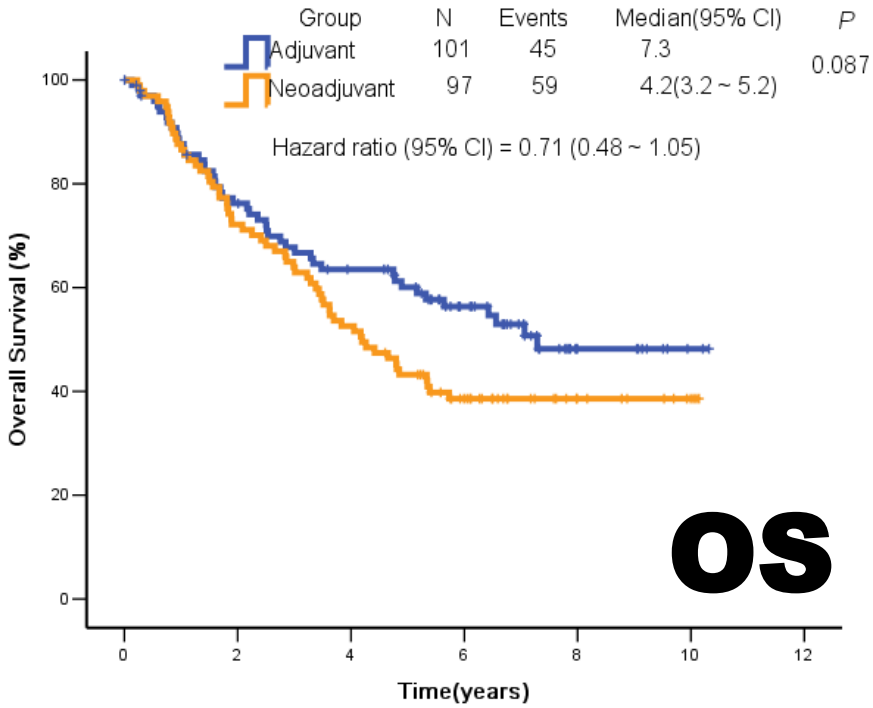
  -Primary endpoint: 3-yr DFS
  -Secondary endpoints: safety; 5-yr OS

Yang X, WCLC 2016; 0A09.03

Adjuvant vs Neoadjuvant



DFS



OS

NO. at Risk

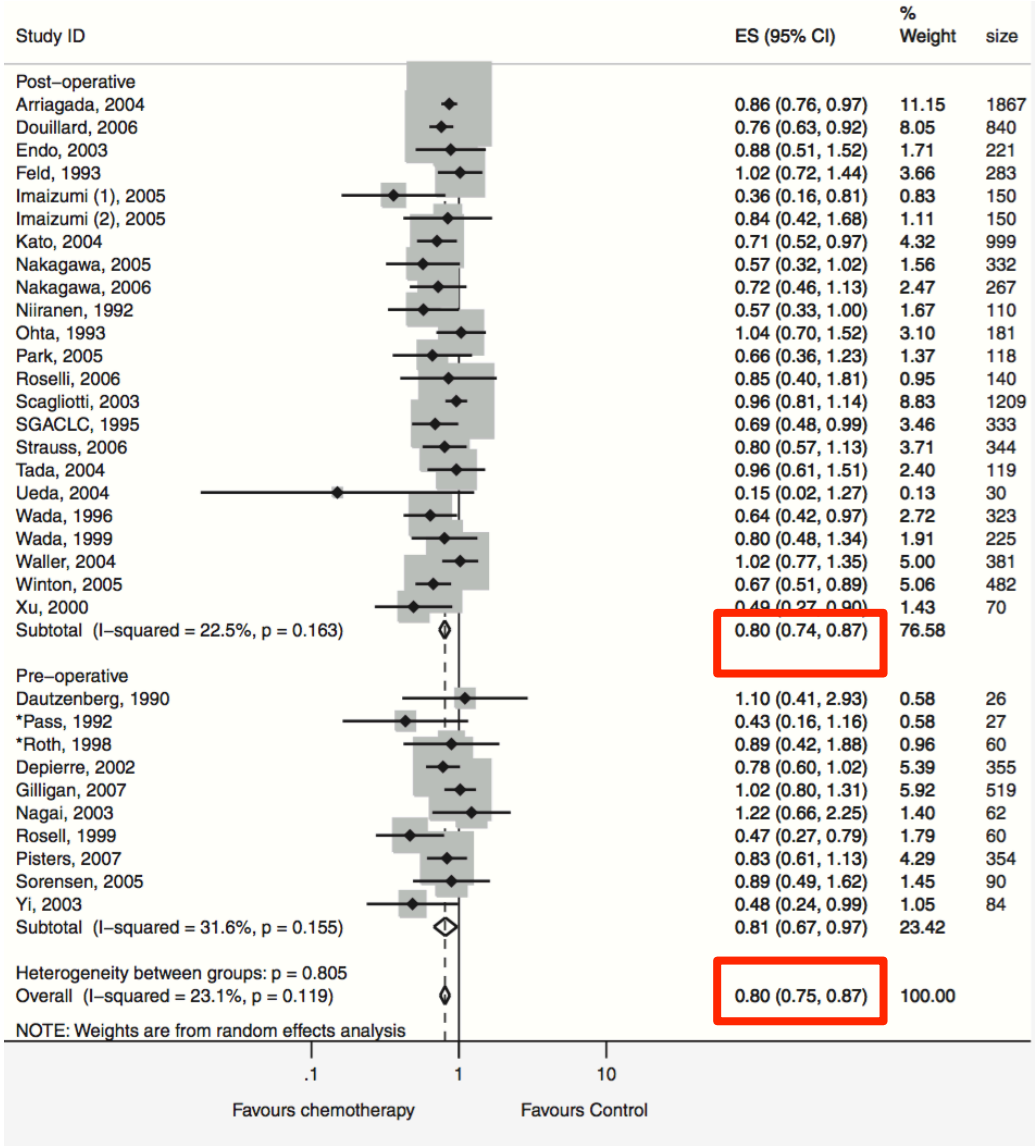
Adjuvant	101	63	54	51	49	49	49
Neoadj.	97	53	33	30	30	30	30

NO. at Risk

Adjuvant	101	78	66	60	56	56	56
Neoadj.	97	70	51	38	38	38	38

Yang X, WCLC 2016; 0A09.03

Adjuvant vs Neoadjuvant: a Meta-analysis

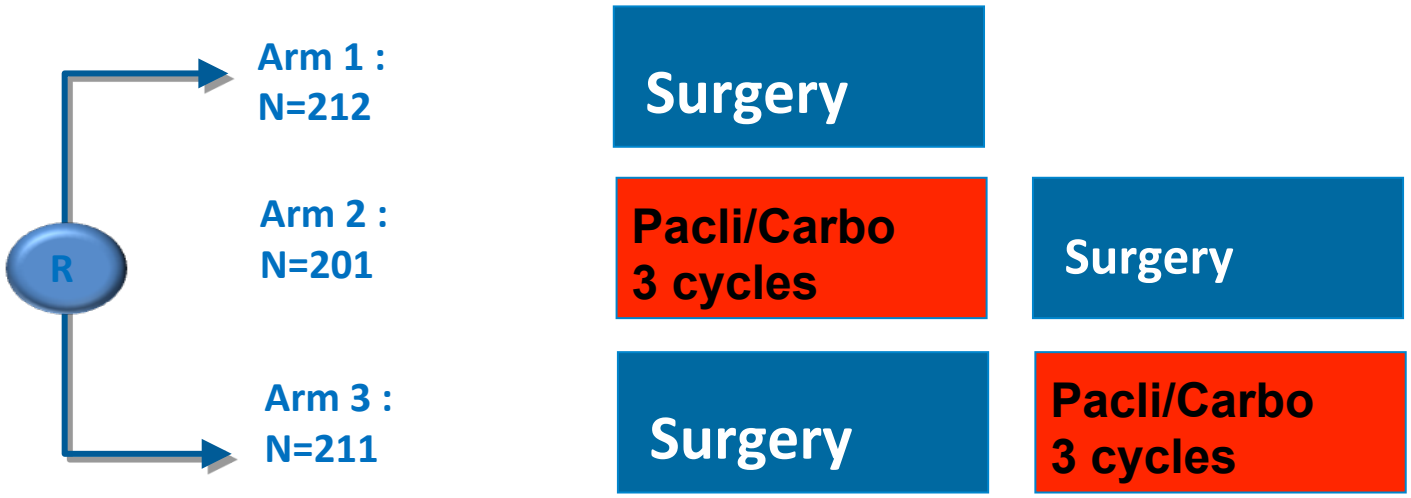


Lim E,
J Thorac Oncol
2009;
4:1380-8

Adjuvant or Neoadjuvant?

Phase III

624 patients
IA (>2 cm),
IB, II, T3N1



Paclitaxel 200 mg/m² + carboplatin AUC 6 q3wk

Main objective: PFS at 5 yr chemotherapy vs surgery

Felip E, J Clin Oncol 2010; 28:3138-3145

Adjuvant or Neoadjuvant? Compliance

Trials	At least 1 cycle	2 cycles	3 cycles	4 cycles
ALPI	90%	ND	69%	NA
IALT	92%	ND	ND	ND
ANITA	90%	72%	61%	50%
JBR10	95.5%	64%	55%	45%
NATCH adj	66%	ND	61%	NA
Depierre	98%	90%	NA	NA
NATCH neoadj	97%	ND	90%	NA
Gilligan	96%	89%	96%	NA
SWOG 9900	ND	ND	79%	NA

Peri-operative Treatments in NSCLC

In wild-type NSCLC

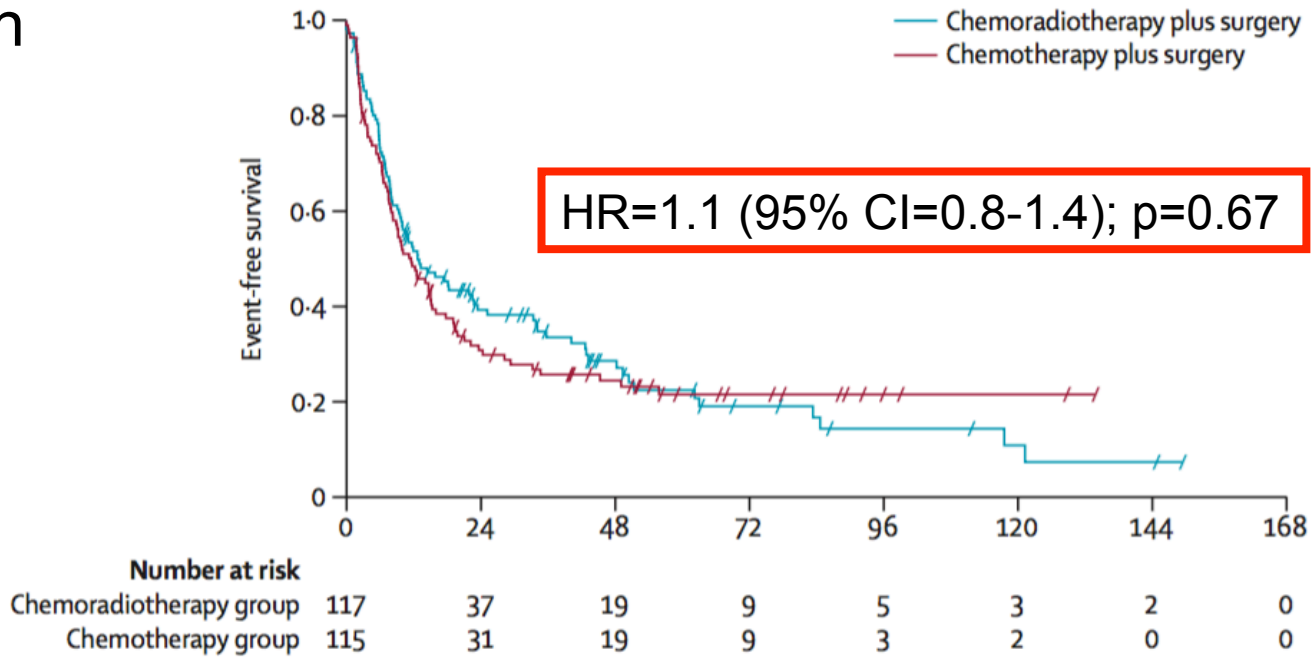
- Peri-operative chemotherapy
- Preoperative chemoradiation
- Perioperative targeted treatments
- Peri-operative immunotherapy

In EGFR mutated NSCLC

Postoperative radiotherapy

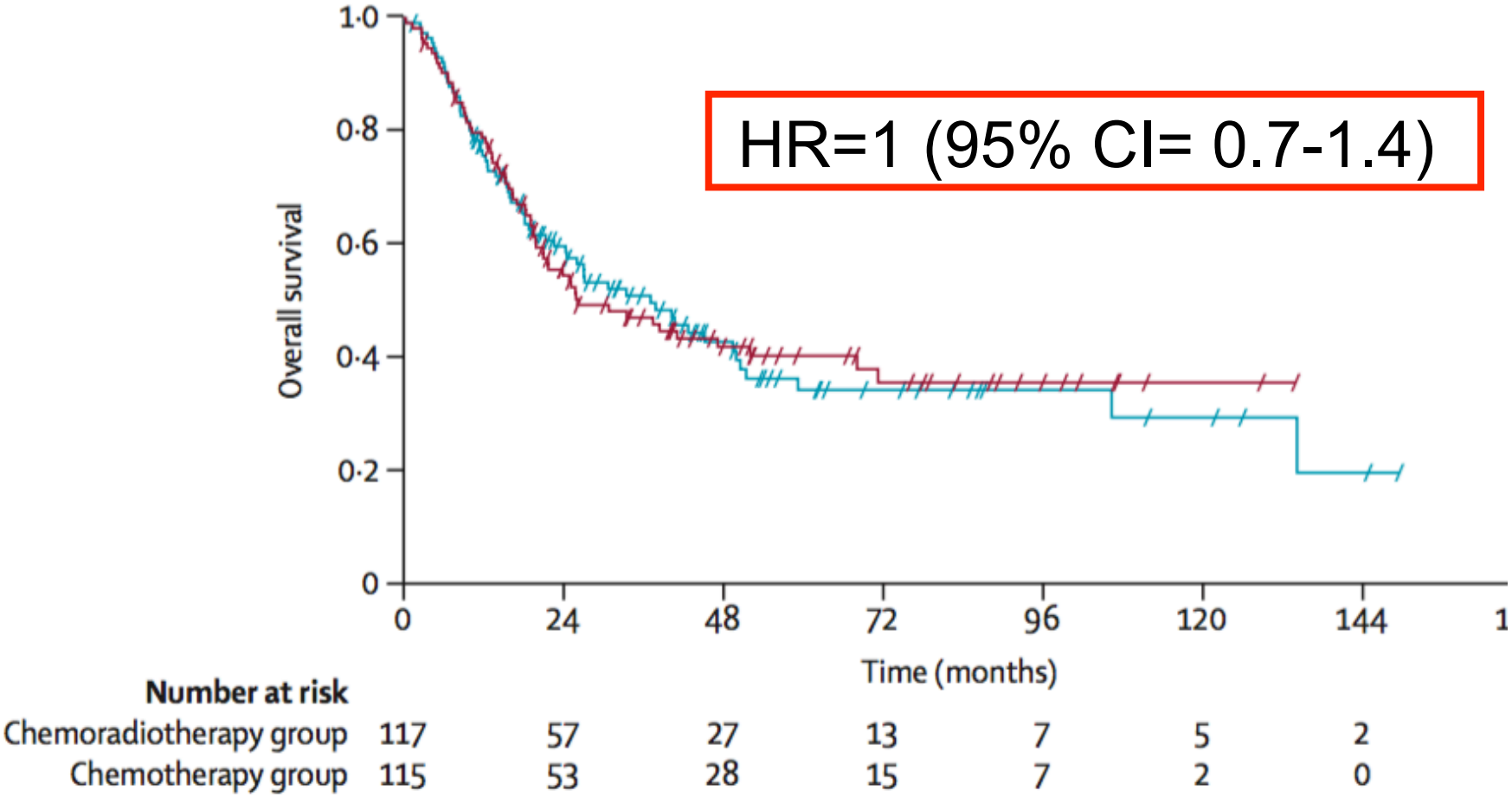
Preoperative Chemoradiation for Stage IIIA N2

- Multicenter phase III
- Pathologically proven stage IIIAN2
- 1:1 randomisation
- Cisplatin docetaxel
- +/- sequential RT
  (44 Gy / 22 F / 3 wk)
- Primary endpoint: event-free survival



M PLess, Lancet 2015; 386:1049-56

Preoperative Chemoradiation for Stage IIIA N2



M PLess, Lancet 2015; 386:1049-56

Peri-operative Treatments in NSCLC

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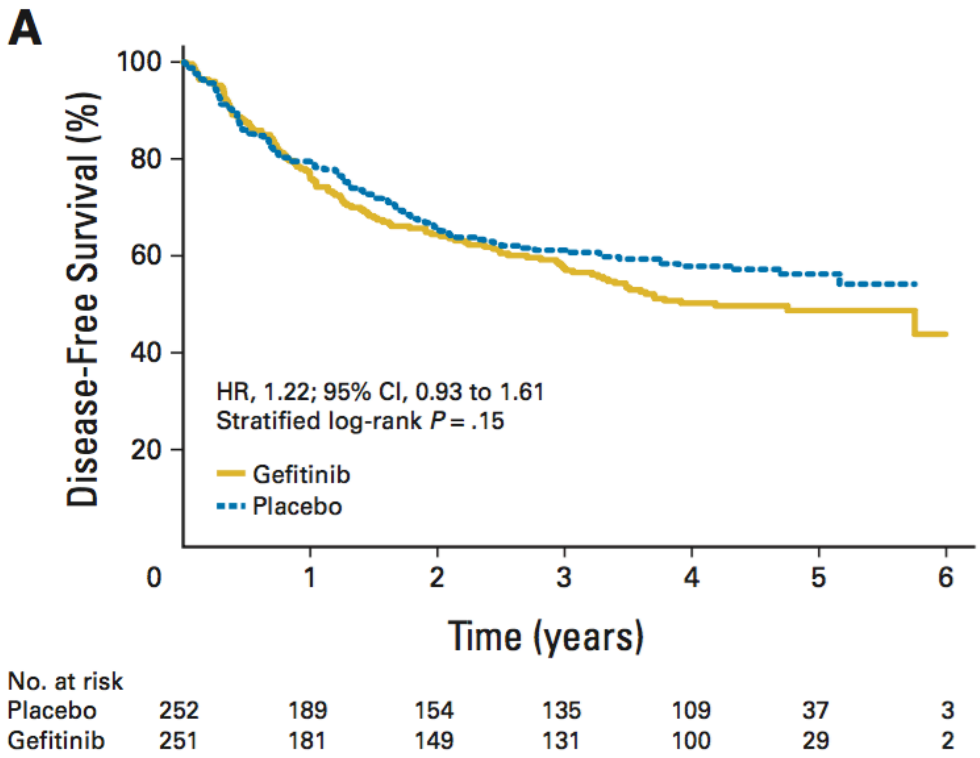
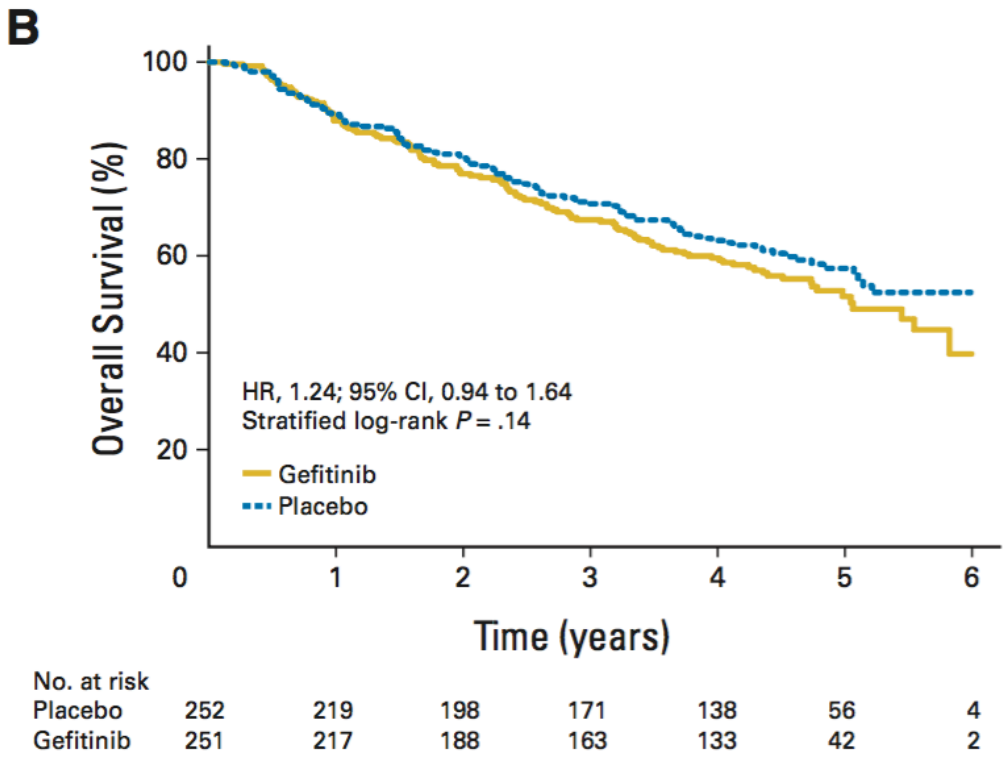
- Preoperative chemoradiation
- Perioperative targeted treatments
- Peri-operative immunotherapy

In EGFR mutated NSCLC

Postoperative radiotherapy

Adjuvant Gefitinib in All-comers (BR19)



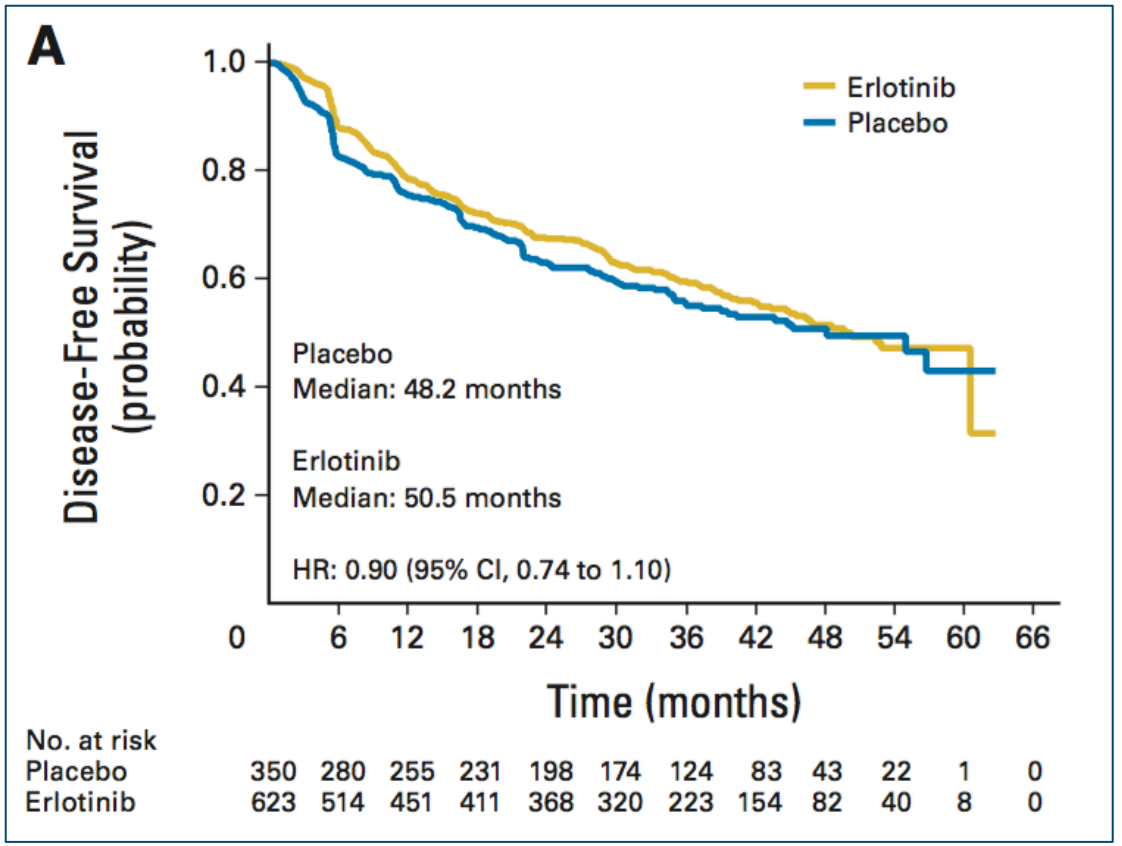


Stage IB, II, IIIA completely resected Trial prematurely closed
After adjuvant chemotherapy, Gefitinib x 2 yr *vs* placebo

Goss G, J Clin Oncol 2013; 31:3320-26

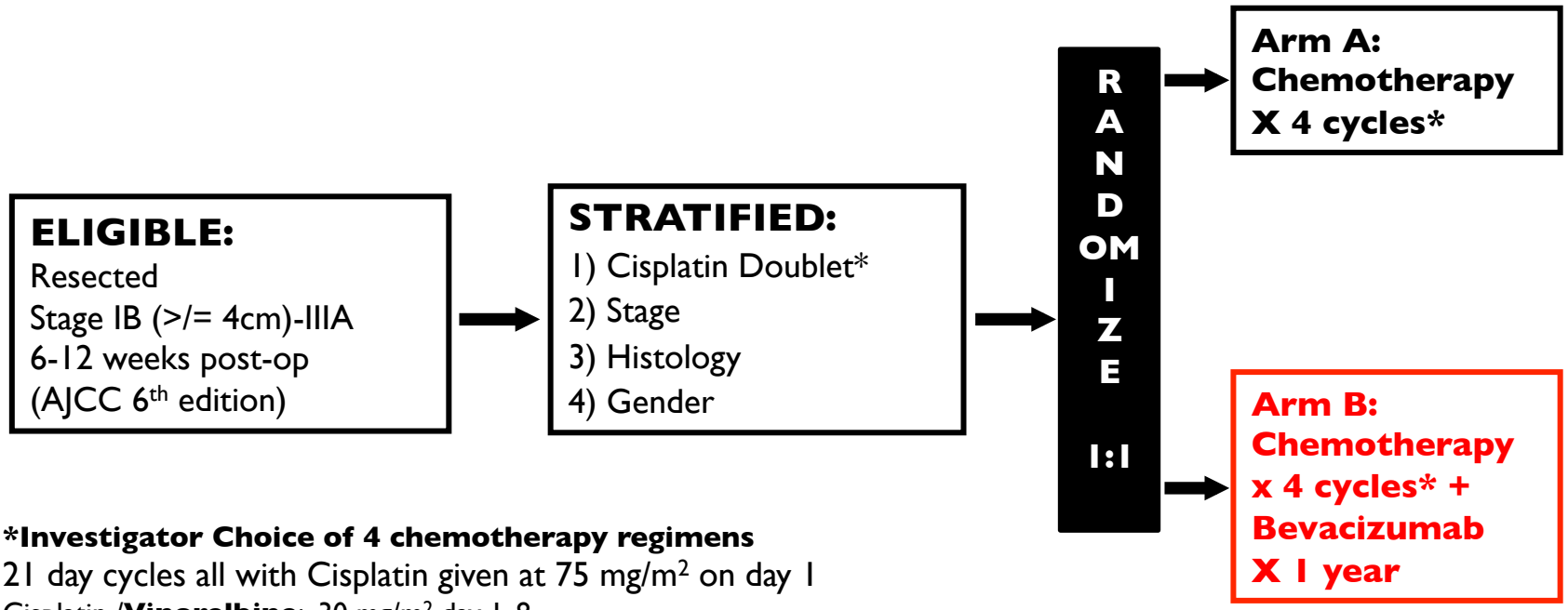
RADIANT: Adjuvant Erlotinib in All-comers

- Primary endpoint: DFS
- Phase III trial
- Adjuvant erlotinib (2 yr) *vs* placebo
- pStage IB-IIIA
- OS: HR=1.09 (95%CI=0.545-2.161) p=.815



Kelly K, J Clin Oncol 2015; 33:4007-14

Adjuvant Bevacizumab



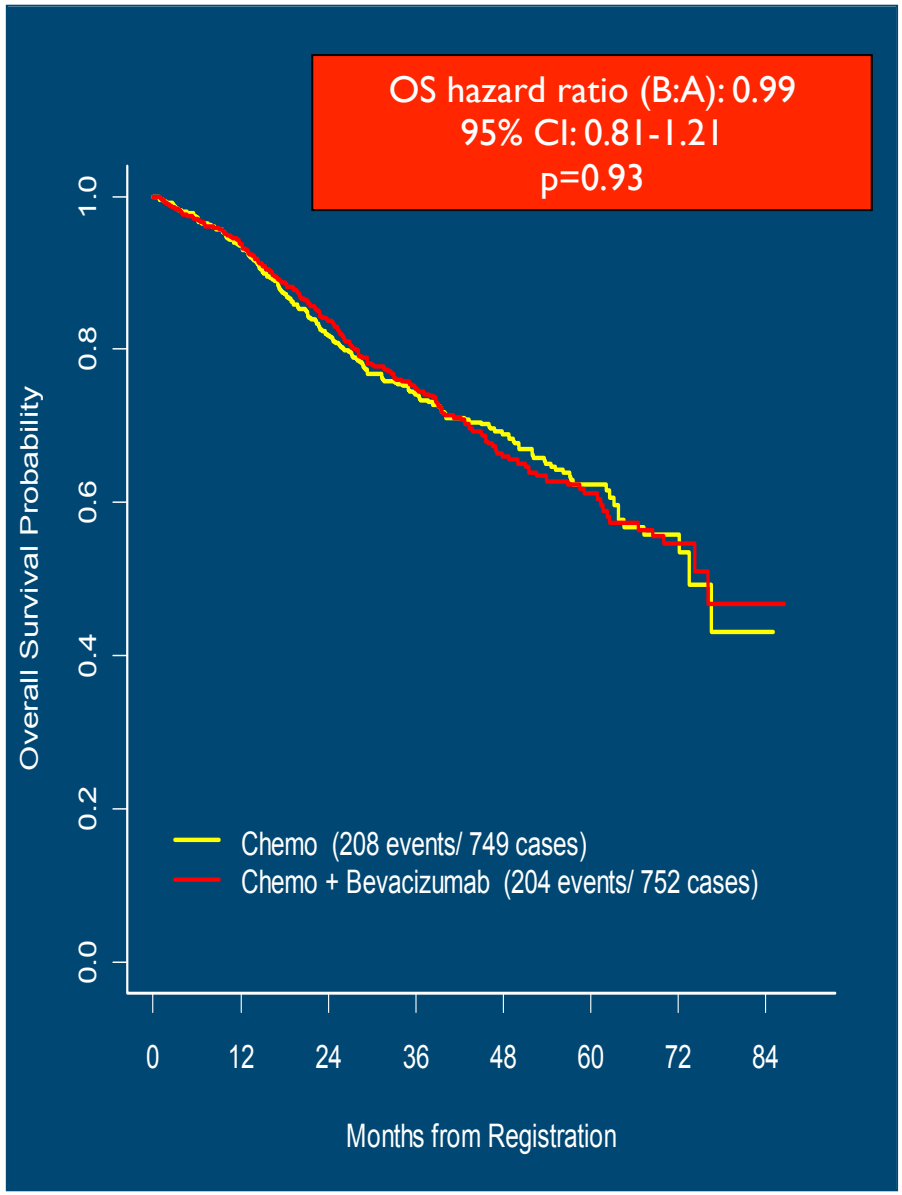
***Investigator Choice of 4 chemotherapy regimens**
21 day cycles all with Cisplatin given at 75 mg/m^2 on day 1
Cisplatin /**Vinorelbine**: 30 mg/m^2 day 1, 8
Cisplatin /**Docetaxel** 75 mg/m^2 day 1
Cisplatin /**Gemcitabine** 1200 mg/m^2 day 1,8
Cisplatin /**Pemetrexed** 500 mg/m^2 day 1 (2009 amendment)

Bevacizumab 15 mg/kg IV q 3 weeks for up to 1 year

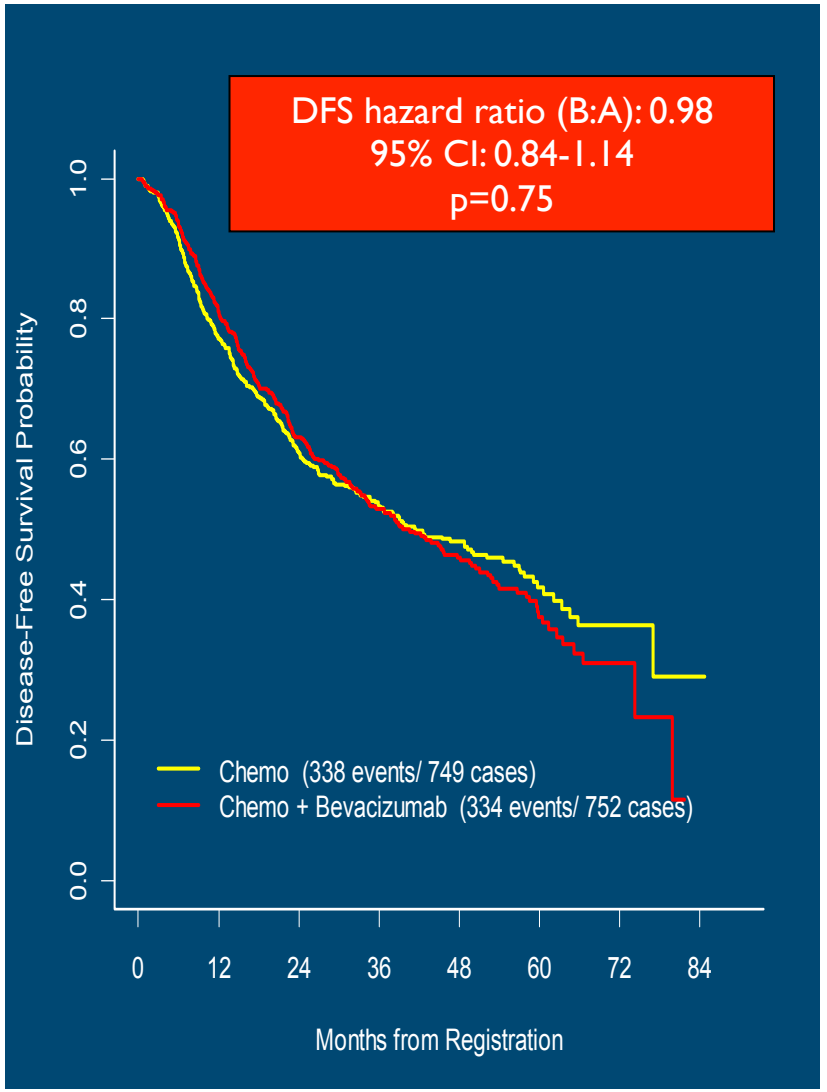
Primary endpoint: Overall survival

Wakelee H, WCLC 2015: Plen 04-03

Adjuvant Bevacizumab: Overall Survival



Disease Free Survival



Wakelee H, WCLC 2015: Plen 04-03

Peri-operative Treatments in NSCLC

In wild-type NSCLC

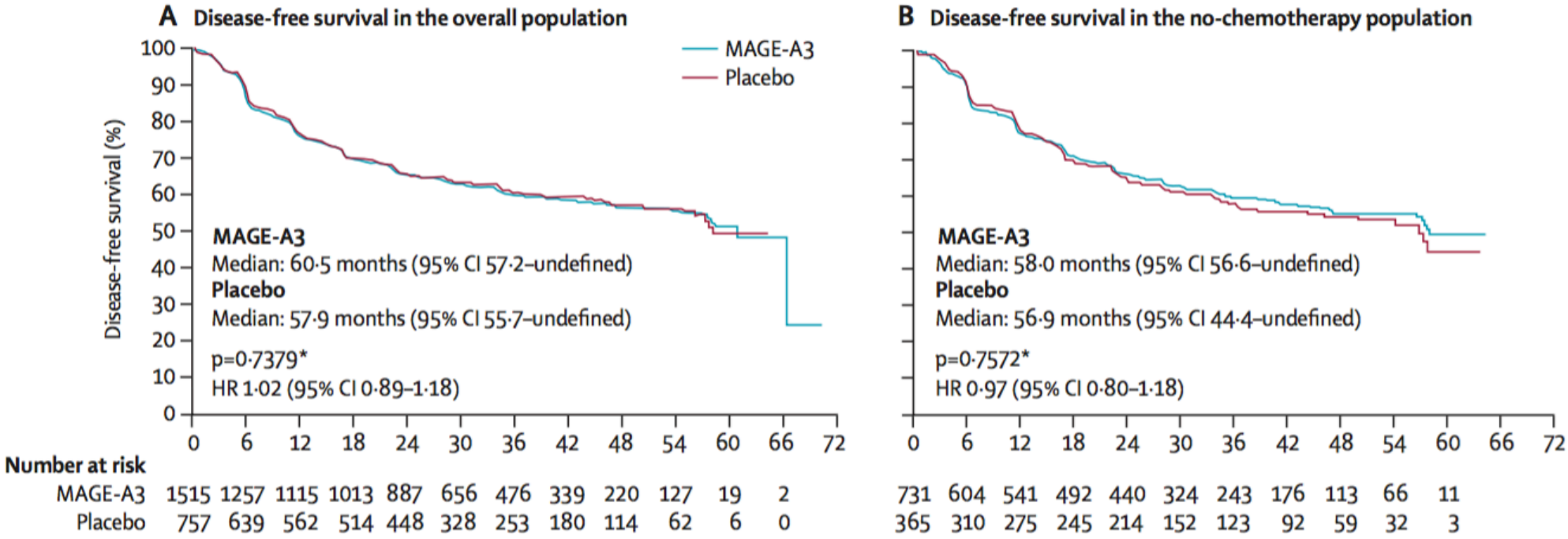
- Peri-operative chemotherapy
- Preoperative chemoradiation
- Perioperative targeted treatments
- Peri-operative immunotherapy

In EGFR mutated NSCLC

Postoperative radiotherapy

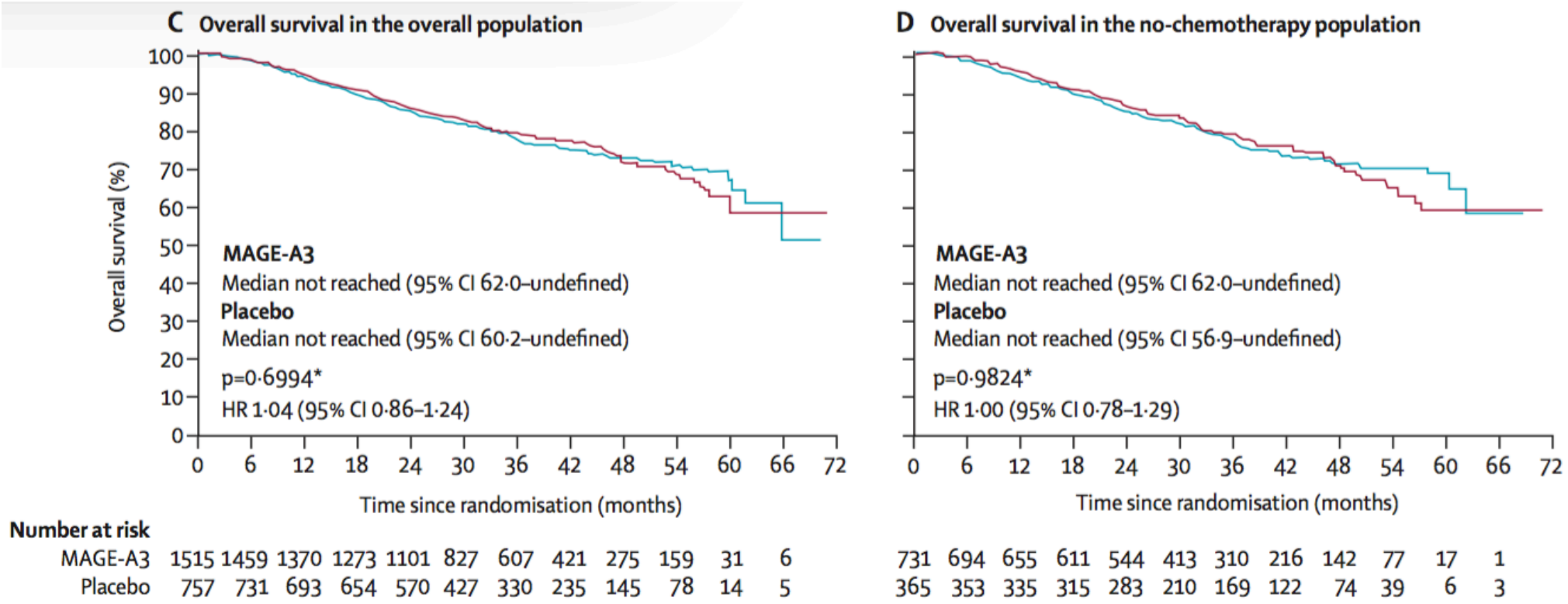
MAGE A-3 Vaccine in MAGE A-3+ NSCLC: DFS

- Resected stage I, II, IIIA NSCLC - 13 intramuscular injections in 27 months - Primary endpoint: DFS



Vansteenkiste J, Lancet Oncol 2016; 17:822-35

MAGE A-3 vaccine in MAGE A-3+ NSCLC: Overall Survival



Vansteenkiste J, Lancet Oncol 2016; 17:822-35

Neoadjuvant Nivolumab

- 18 pts with resectable stage I–IIIA NSCLC (22 ASCO)
- Nivolumab 3 mg/kg D-28&14, prior to surgery
- Responses:
  - 7 major pathologic responses (<10% residual tumour)
  - 1 complete pathologic response, 13 stable disease
  - ASCO: 10% responses, 43% major pathologic responses
- 1 Grade 3–4 adverse event
- No delay in surgery in any patient
- Increased T cell infiltrate in responders

Forde P, ESMO 2016 LBA41_PR / Chaft JE, ASCO 2017 Abstract 8508

Ongoing Phase III trials of Adjuvant Checkpoint Inhibitors

Drug/Trial	Description	Stages entered	Description	Primary Endpoint
Nivolumab ALCHEMIST/ANVIL	US NCI, observation as control,	IB (4cm) – IIIA, after adj chemo and/or radiation	Phase 3 Allows PD-L1+ and PD-L1 -	OS/DFS
Atezoliumab Impower010	Global, placebo controlled,	IB (4cm) – IIIA, after adj chemo	Phase 3 Allows PD-L1+ / -	DFS
MEDI4736	Global, placebo controlled	IB (4cm) – IIIA, after adj chemo	Phase 3 Allows PD-L1+ / -	DFS
Pembrolizumab Keynote-091	ETOP/EORTC, placebo controlled	IB (4cm) – IIIA, after adj chemo	Phase 3 Allows PD-L1+ / -	DFS

Peri-operative Treatments in NSCLC

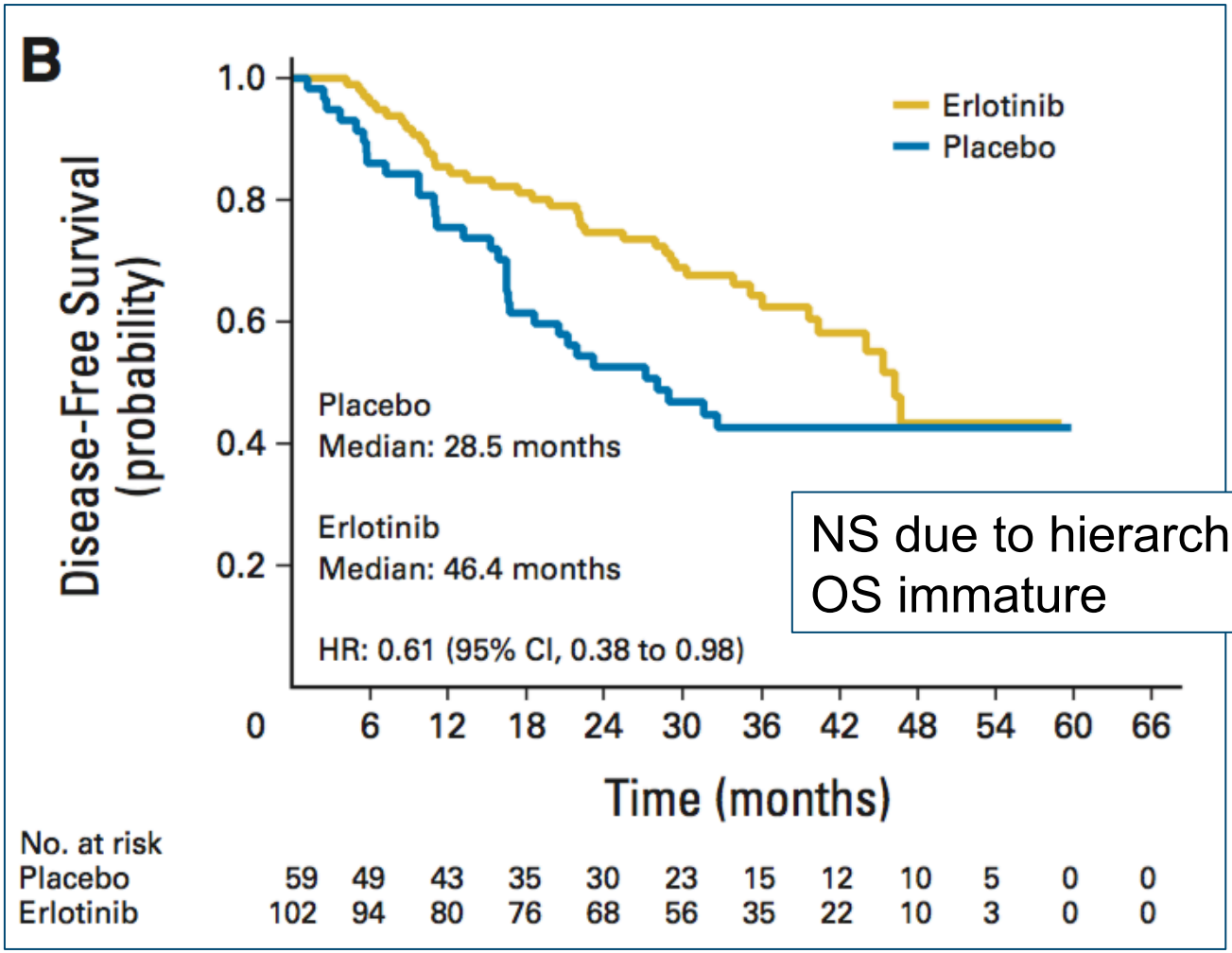
In wild-type NSCLC

- Peri-operative chemotherapy
- Preoperative chemoradiation
- Perioperative targeted treatments
- Peri-operative immunotherapy
- Postoperative mediastinal radiotherapy

In EGFR mutated NSCLC

Postoperative radiotherapy

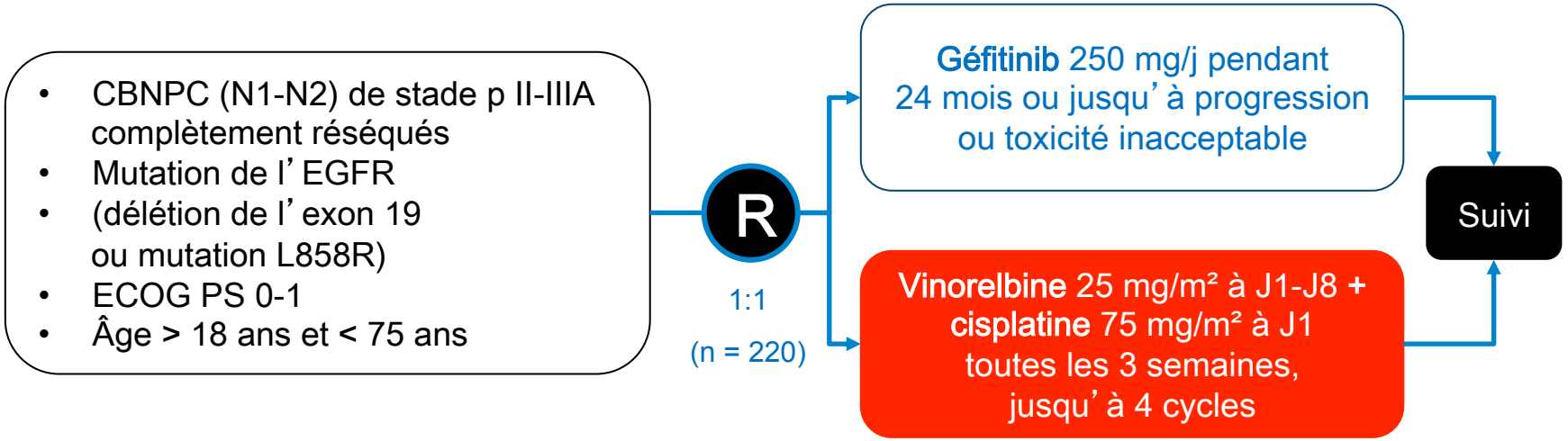
Erlotinib in EGFRmut in RADIANT



NS due to hierarchical testing
OS immature

Kelly K, J Clin Oncol 2015; 33:4007-14

Géfitinib *vs* vinorelbine + cisplatine en adjuvant chez les patients EGFR muté opérés

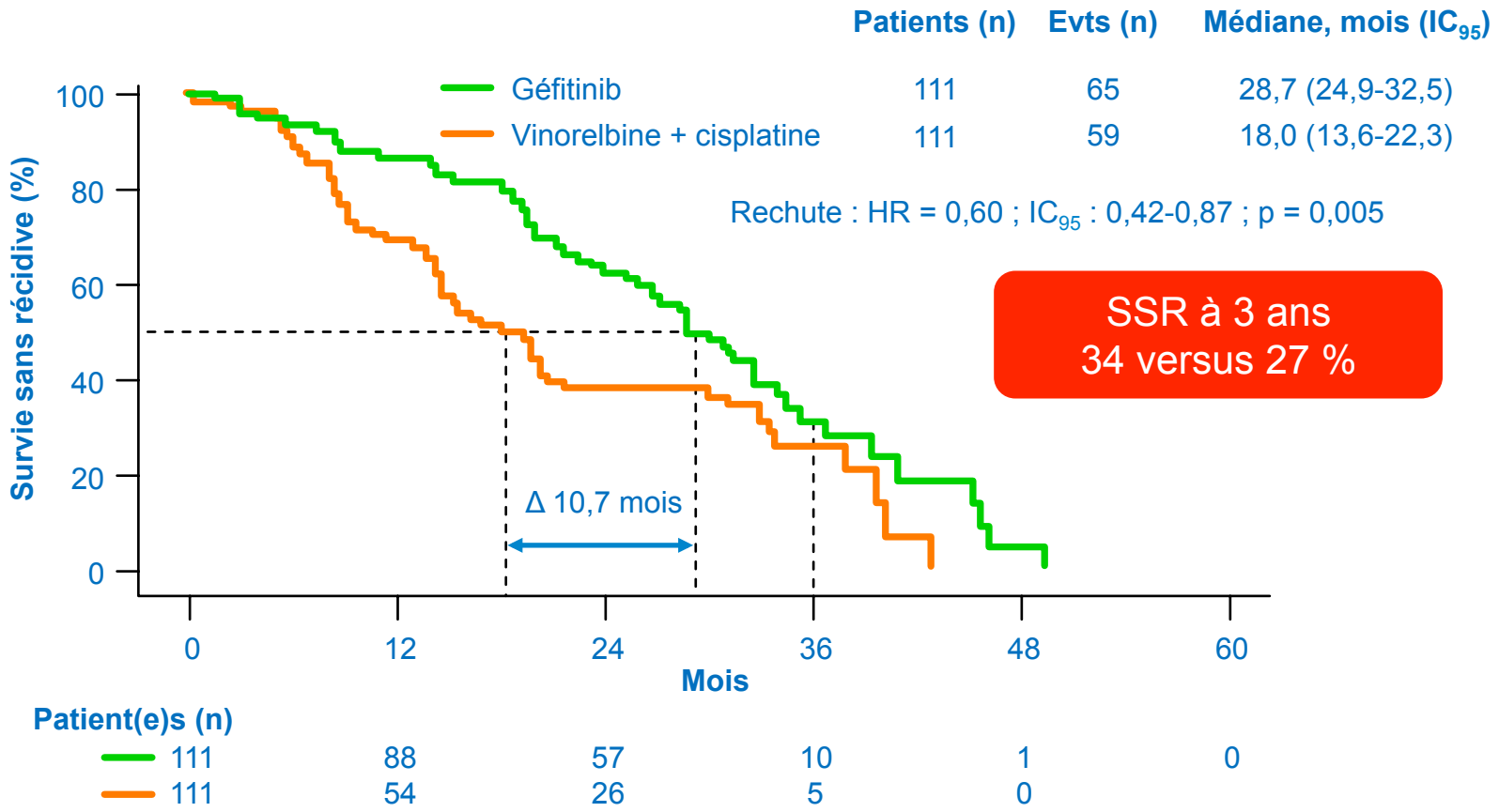


- Facteurs de stratification
  - Mutation de l'EGFR
  - Stade N
- Évaluation de l'efficacité
  - Toutes les 12 semaines

- Critère principal
  - SSR
- Critères secondaires
  - Taux de SSR à 3 et 5 ans, SG, taux de SG à 5 ans, tolérance, QdV (FACT-L, LCSS, TOI), analyses exploratoires des biomarqueurs

Congrès américain d'oncologie 2017 - D'après Wu Y et al., abstr. 8500, actualisé

Géfitinib *vs* vinorelbine + cisplatine en adjuvant chez les patients EGFR muté opérés: résultats



Congrès américain d'oncologie 2017 - D'après Wu Y et al., abstr. 8500, actualisé

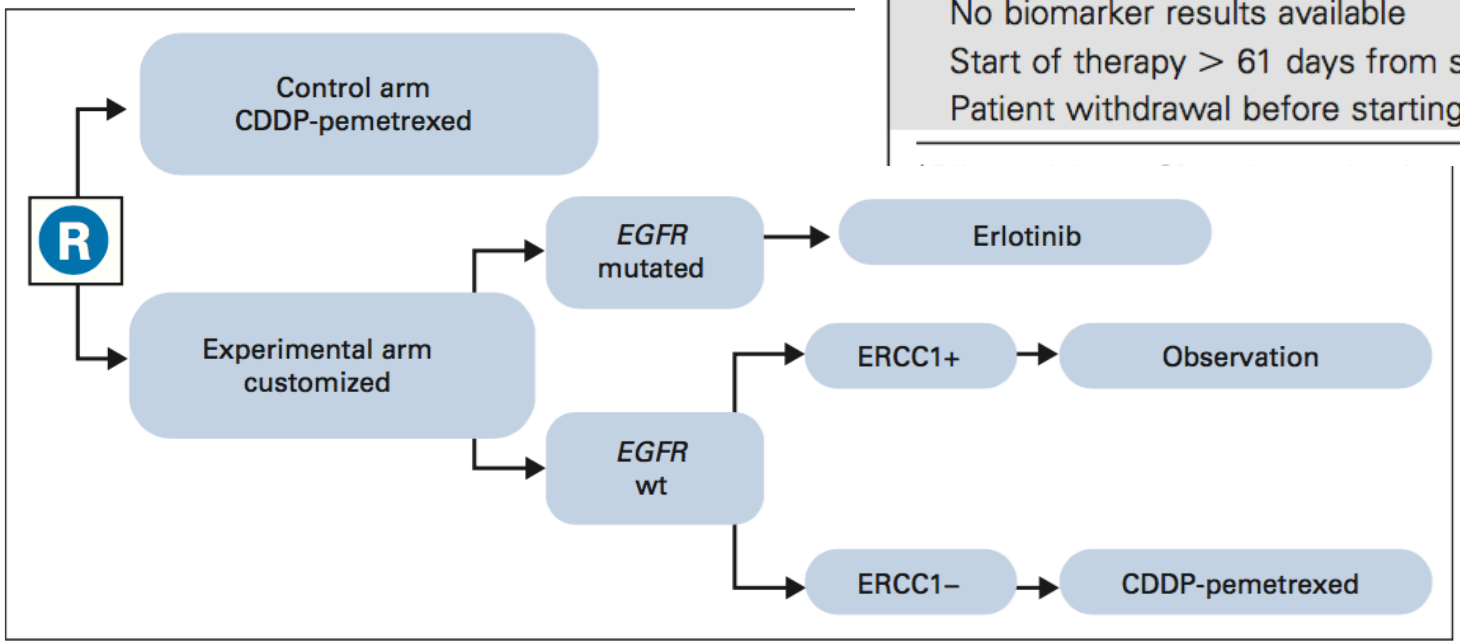
Ongoing EGFR TKI Adjuvant Trials in EGFRmut patients

Trial	Country	EGFR TKI	Control	EGFR TKI duration
ALCHEMIST	USA	Erlotinib Crizotinib (for ALK+)	Placebo	2 yr
IMPACT WJOG 6401L	Japan	gefitinib	Cisplatin vinorelbine x4	2 yr
NCT02125240 without adjuvant chemo	China	Icotinib	Placebo	6-12 months
NCT01996098 (after 4 cycles of adjuvant platinum-based chemo)	China	Icotinib	observation	6-12 months

TASTE

Table 2. Primary End Point

Primary Efficacy Parameter	Total Patients (N = 150) No.	%
Success	120	80.0
90% CI, %*	74.6 to 85.4	
95% CI, %	73.6 to 86.4	
Failure†	30	20.0
Reasons for failure		
No biomarker results available	8	
Start of therapy > 61 days from surgery	17	
Patient withdrawal before starting treatment	5	



Wislez M, J Clin Oncol 2014; 32:1256-61

Peri-operative Treatments in NSCLC

In wild-type NSCLC

- Peri-operative chemotherapy
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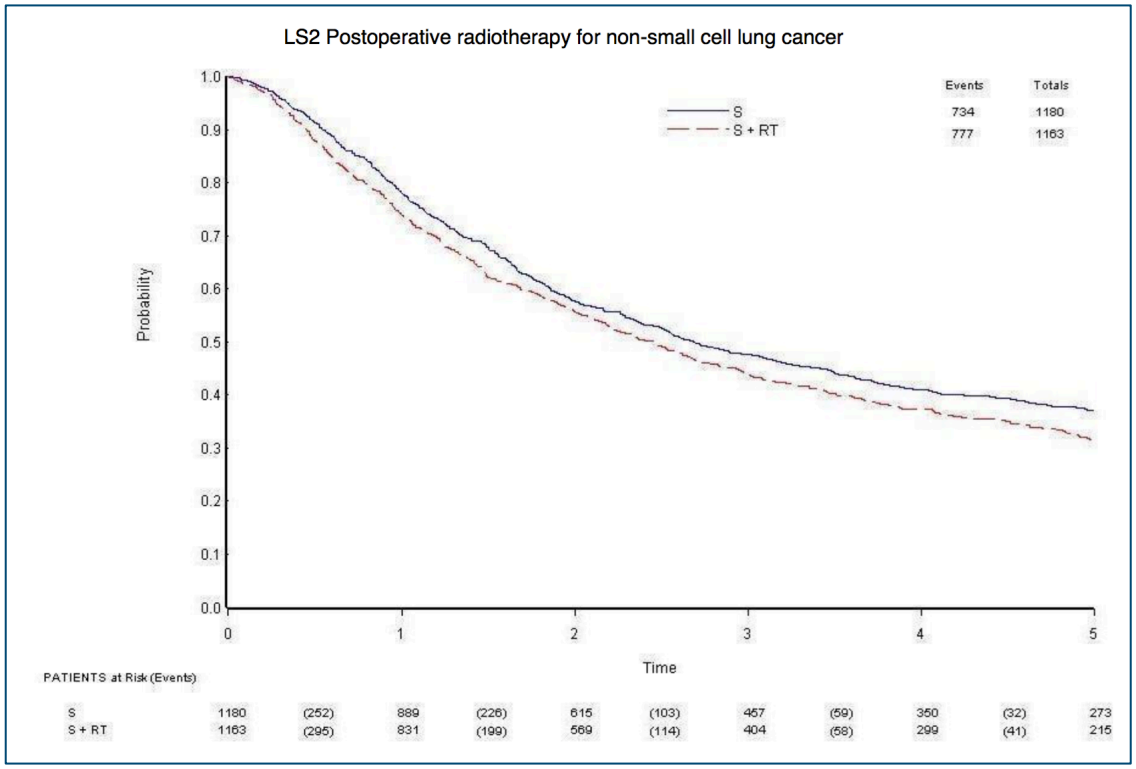
- Perioperative targeted treatments
- Peri-operative immunotherapy
- Postoperative mediastinal radiotherapy

In EGFR mutated NSCLC

Postoperative radiotherapy

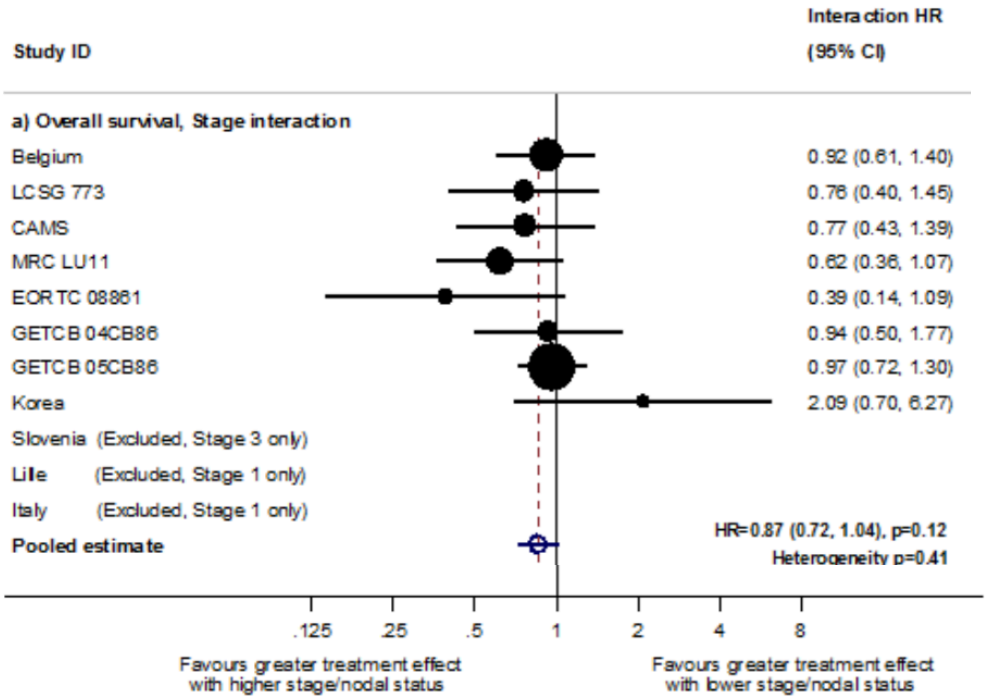
Postoperative Radiotherapy: the Updated Meta-analysis

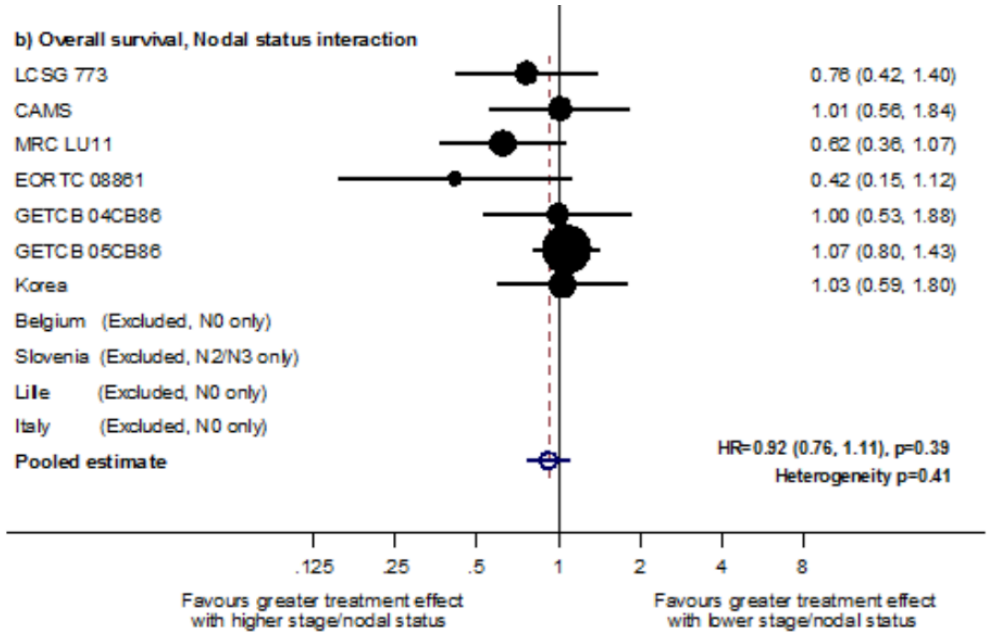
- IPD meta-analysis
- 11 trials / 2343 pts
- HR=1.18
- 18% relative increase in risk of death
- Absolute detriment: 5% at 2 yr (95% CI=2-9%)
- reducing survival from 58 to 53%.



Cochrane Database Syst Rev. 2016 Oct 11;10:CD002142

Postoperative Radiotherapy for N2?





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Postoperative Radiotherapy

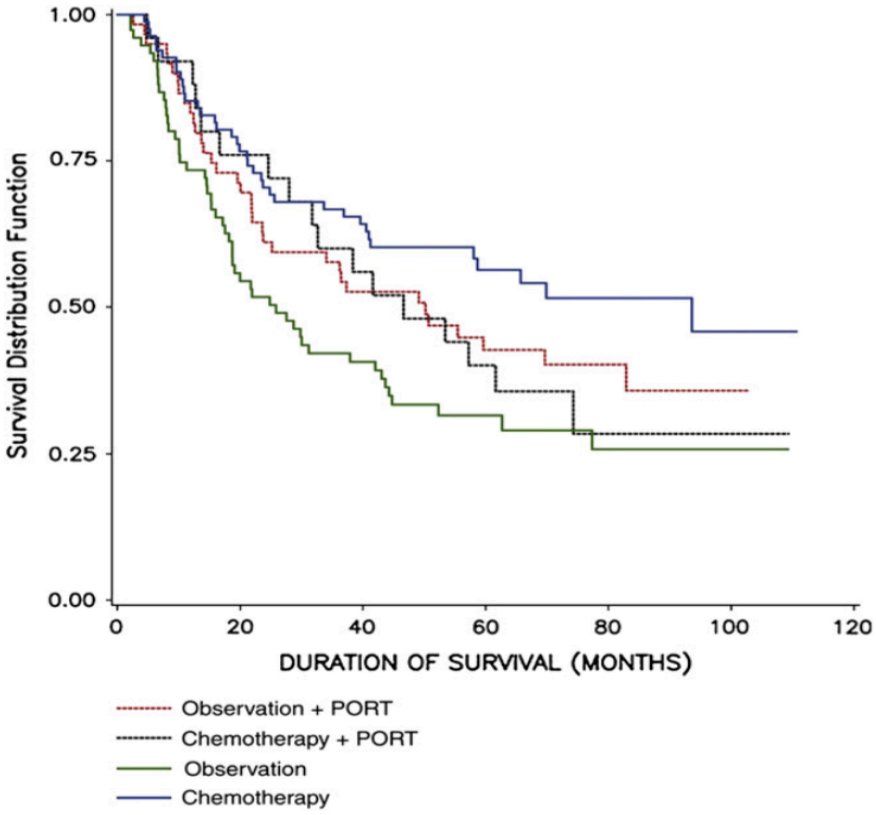

Fig. 2. Overall survival according to treatment received in the pN1 patients in the Adjuvant Navelbine International Trialist Association (ANITA) trial.

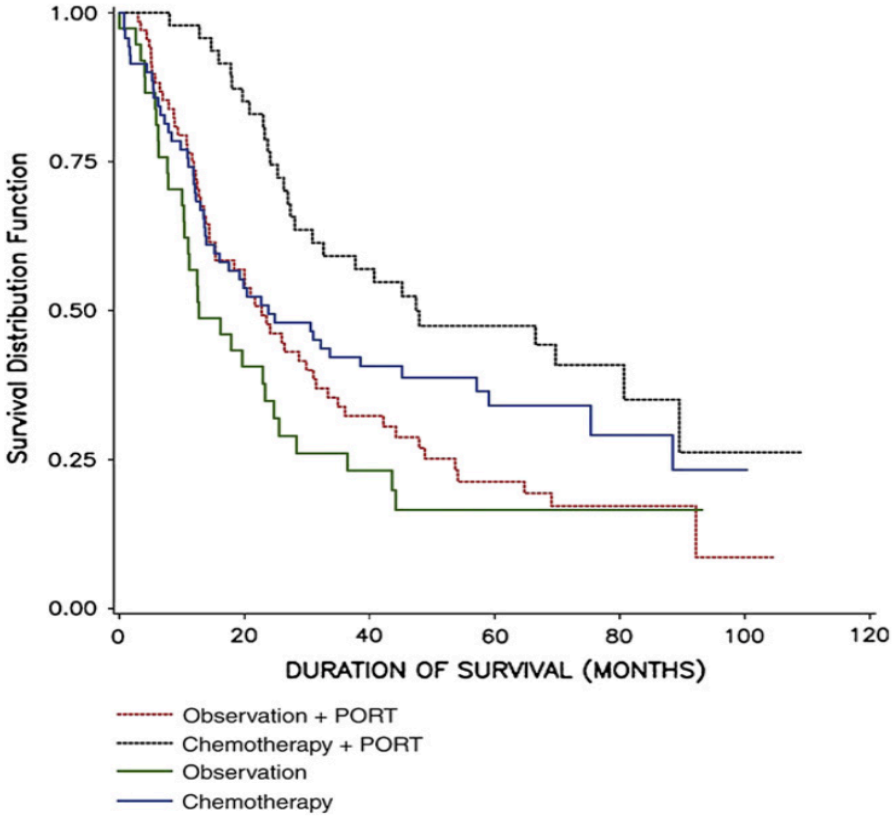

Fig. 3. Overall survival according to treatment received in the pN2 patients in the Adjuvant Navelbine International Trialist Association (ANITA) trial.

Douillard JY, Int. J. Radiation Oncology Biol. Phys. 2008; 72:695–701

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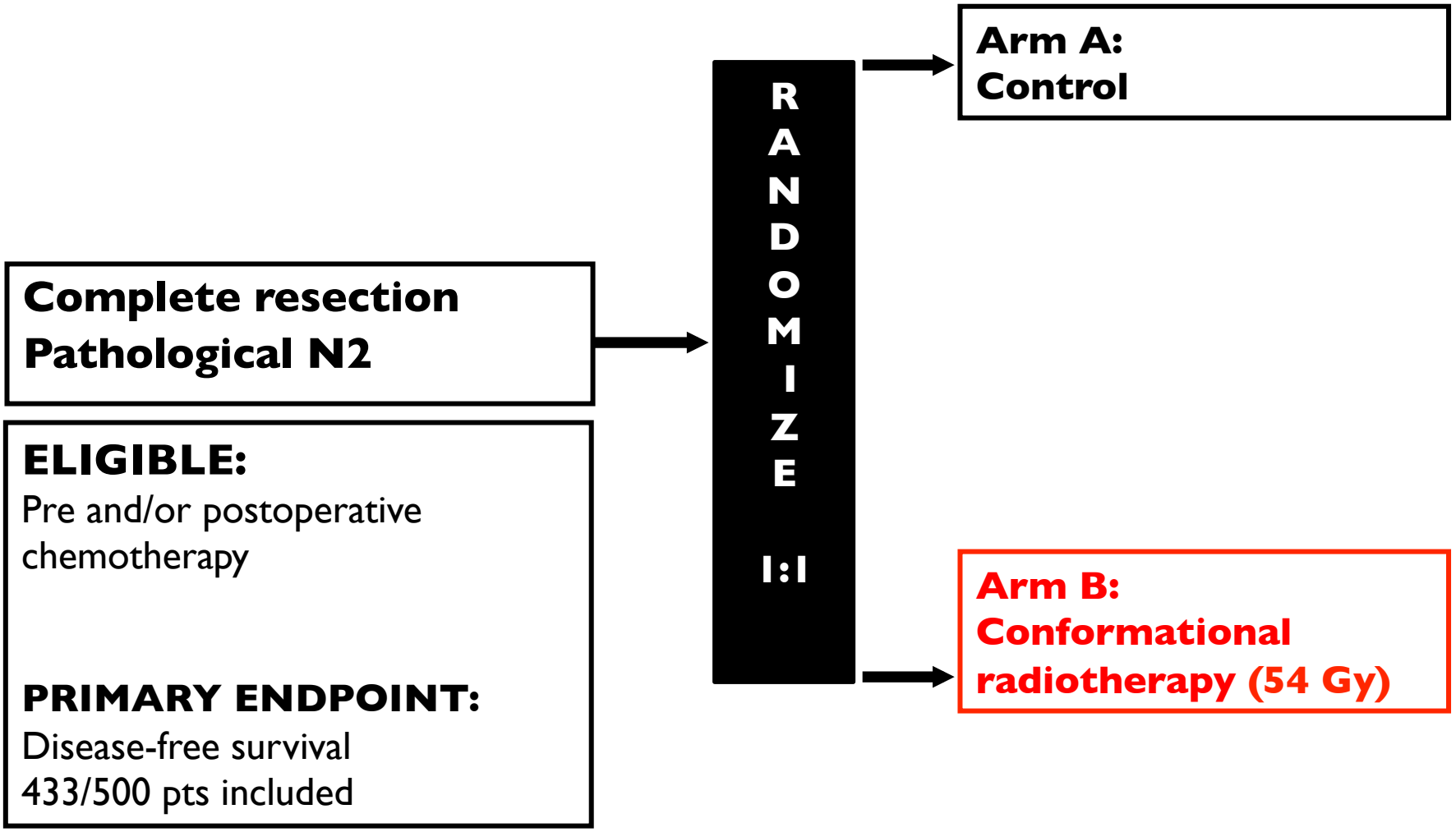

Conclusions: Perioperative chemotherapy

- Neo- and adjuvant chemotherapy increase survival in resectable NSCLC: +5% at 5 years
- Adjuvant chemotherapy:
  - stage II-III, IB ≥4cm
  - Best evidence for cisplatin-vinorelbine
  - cisplatin≥300 mg/m^2
- Preoperative radiotherapy does not add to preoperative chemotherapy in stage IIIA N2
- Postoperative radiotherapy for N2?

Conclusions: New Treatments

- **No indication** for targeted therapies in wild-type EGFR
- Interest of EGFR and ALK TKIs to be demonstrated in EGFRmut/ALK+ NSCLC
- Interest of immune checkpoint inhibitors to be demonstrated