FIRST-LINE TREATMENT of ADVANCED NON-SCLC in PATIENTS *WITHOUT* a DRIVER MUTATION

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What Are The Issues?

- Regimen (drugs) of choice.
  - Selection based on histology
- Number of drugs, 1 *vs* 2 *vs* 3.
- Is a platinum necessary?
- Cisplatin vs carboplatin
- Treatment of the elderly
- Addition of a Targeted Agent
- Chemotherapy or targeted agent
- Duration of treatment
  - Maintenance chemotherapy
  - Maintenance targeted agents

First-Line Chemotherapy Trials

- **ECOG 1594**
  - Gem/cis v Pac-24/cis v Pac-3/carbo v Doc/cis
- **SWOG 9509**
  - Pac-3/carbo v Vin/cis
- **TAX 326**
  - Doc/carbo or Doc/carbo v Doc/cis
- **Italian Study**
  - Gem/cis v Pac-3/carbo v Vin/cis
- **NO significant or meaningful differences**

First-Line Chemotherapy Trials

- **ECOG 1594**
  - Gem/cis v Pac-24/cis v Pac
- **SWOG 9509**
  - Pac-3/
- **TA**
  - D
- **Italia**
  - Gem
- **NO sig**

NO molecular testing done for any of these trials. Therefore, some patients with driver mutations may have been included.

/cis

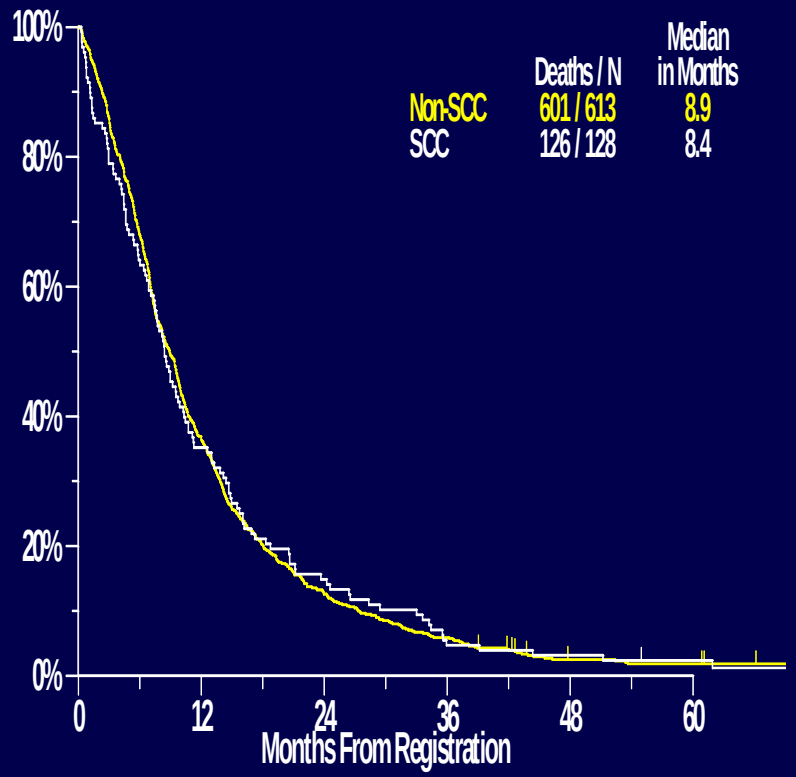
bo v Vin/cis

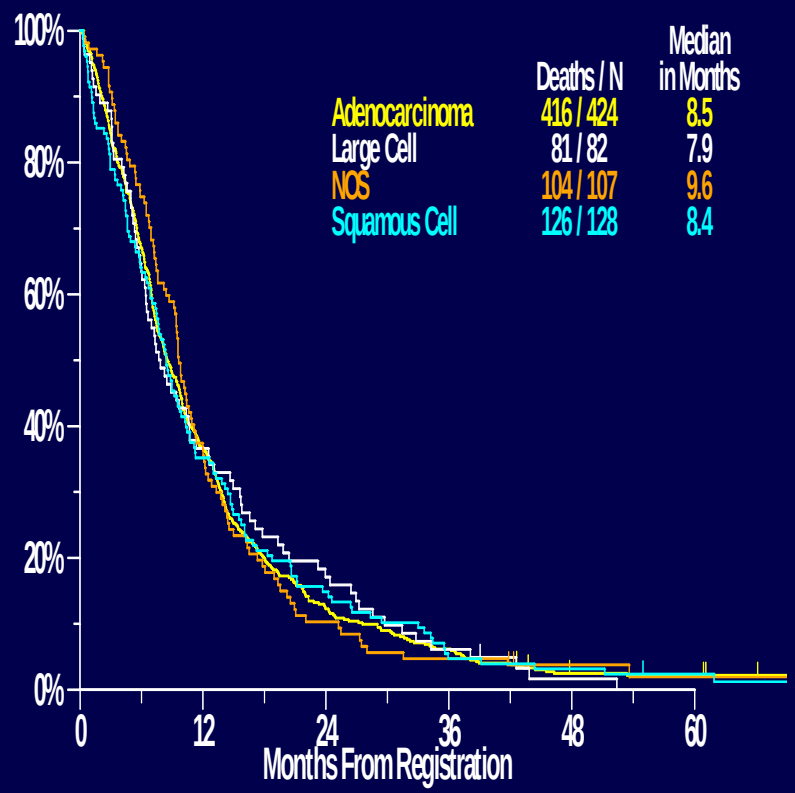
nificant or meaningful differences

Does Histology Matter????

Until recently, we did not think so.

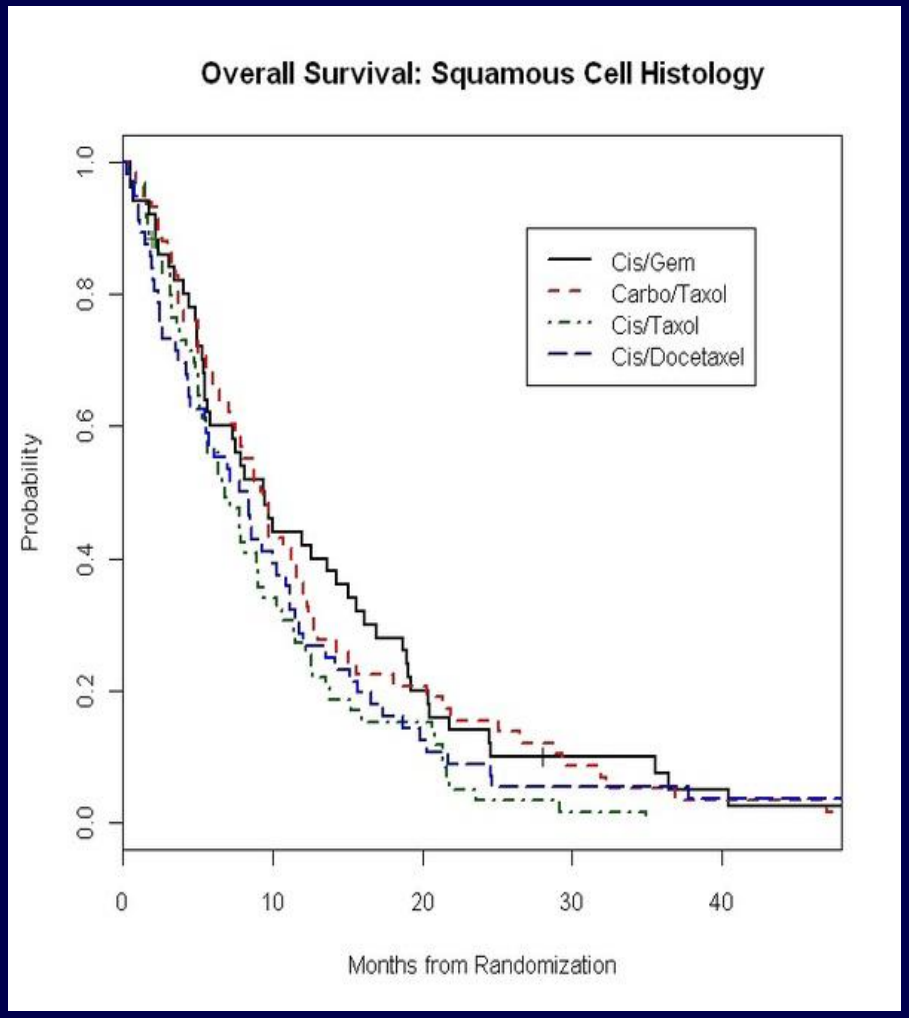
SWOG Tubulin-Targeting Agents Pooled Analyses: OS by Cell Type

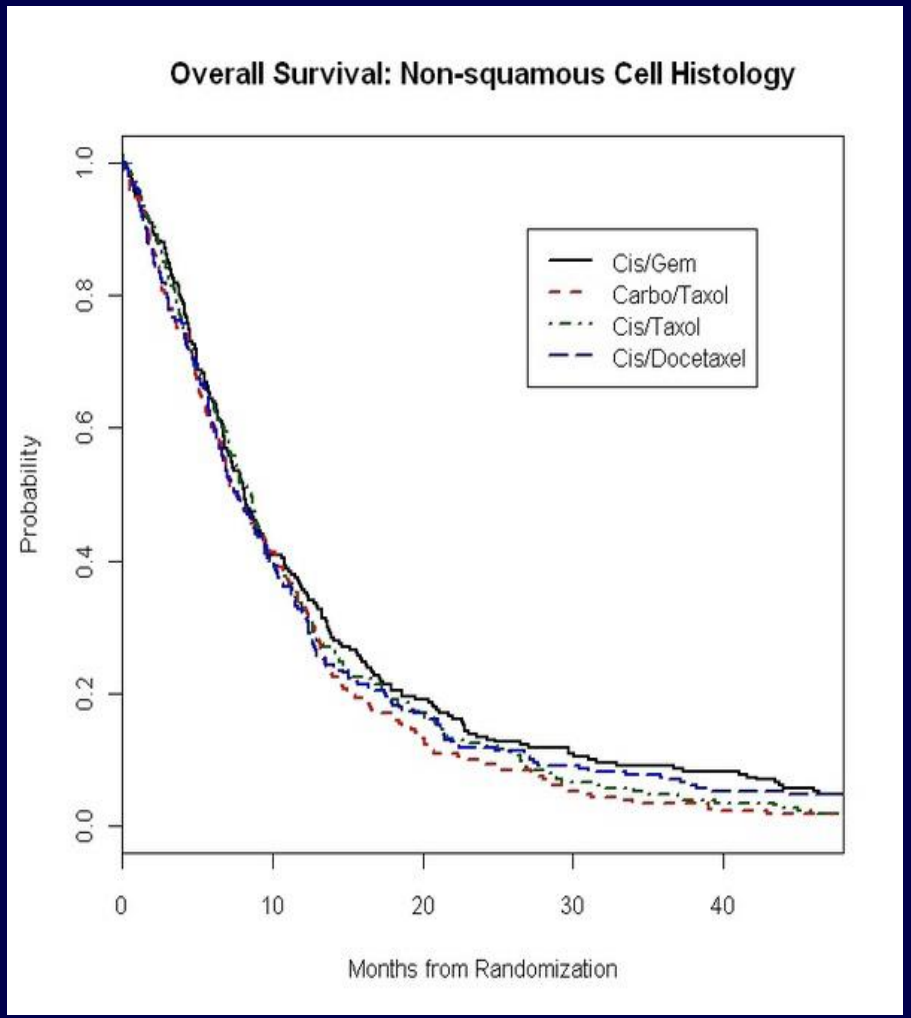




Chansky et al. Proc IASLC, San Francisco, 2009

Effect of Histology in ECOG 1594





Hoang et al Proc IASLC, San Francisco, 2009

Pem/Cis *vs* Gem/Cis in 1st-Line NSCLC

Randomization Factors

- Stage
- PS
- Gender
- Histo vs cyto dx
- Brain mets hx

R

Cisplatin 75 mg/m^2 day 1 plus
Pemetrexed 500 mg/m^2 day 1

Each cycle repeated q3weeks up to 6 cycles

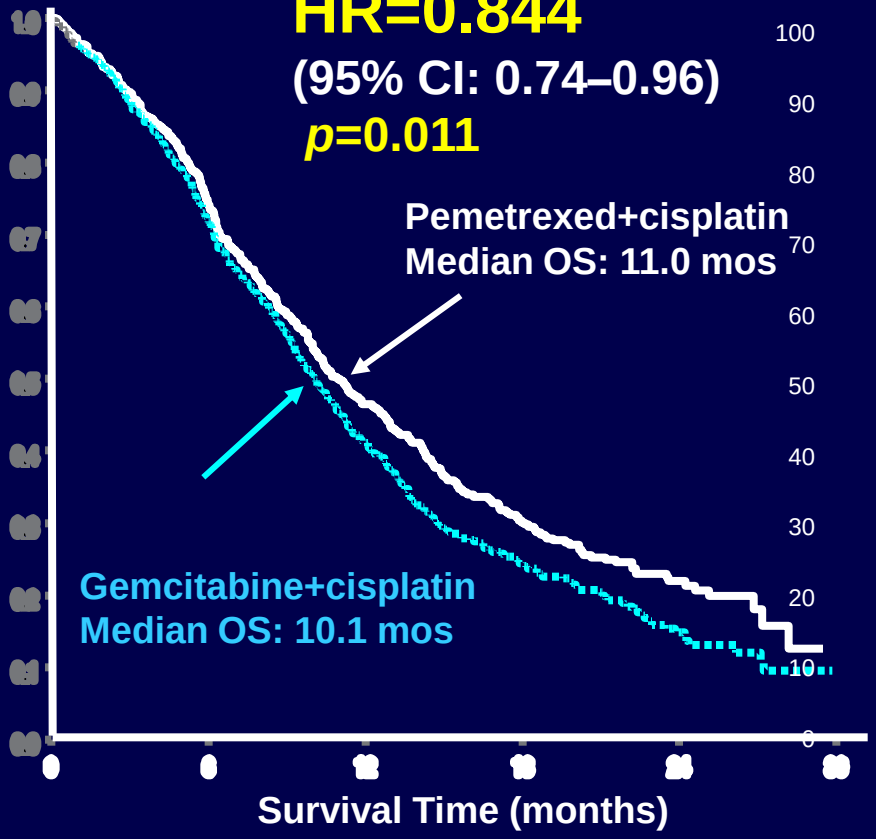
Cisplatin 75 mg/m^2 day 1 plus
Gemcitabine 1250 mg/m^2 days 1 & 8

Vitamin B_{12}, folate, and dexamethasone given in both arms

Analysis by Histology
(Qualtitive Interaction)

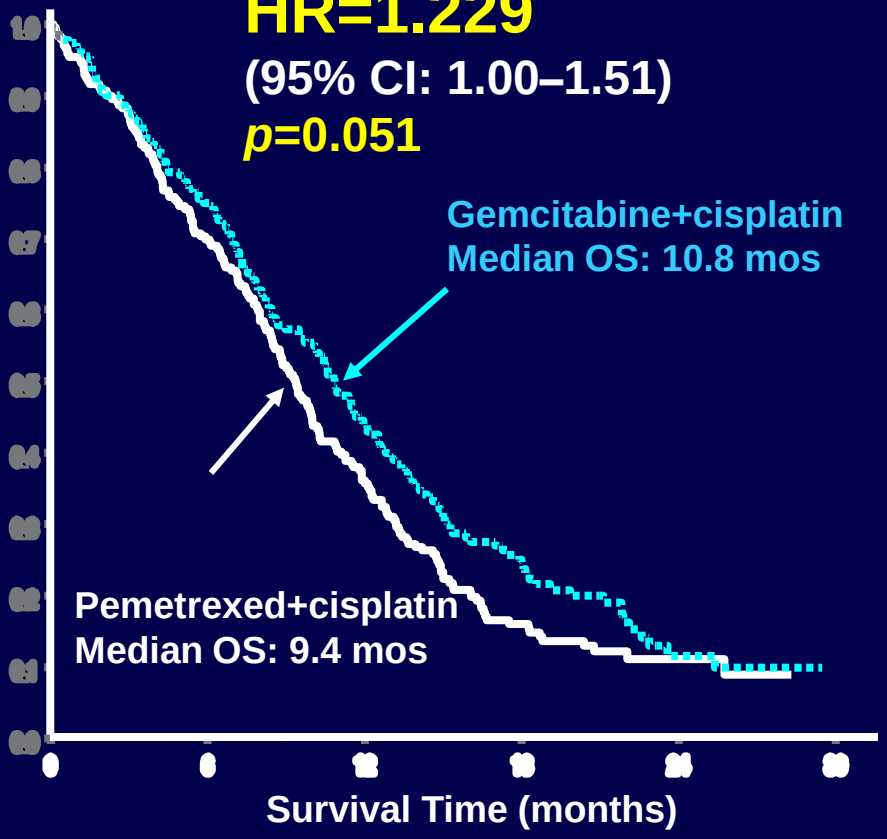
Nonsquamous* (n=1252)

HR=0.844
(95% CI: 0.74–0.96)
p=0.011



Squamous (n=473)

HR=1.229
(95% CI: 1.00–1.51)
p=0.051



* Nonsquamous=adenocarcinoma, large cell carcinoma, and other/indeterminate NSCLC histology

Scagliotti et al. J Clin Oncol 26: 3543, 2008

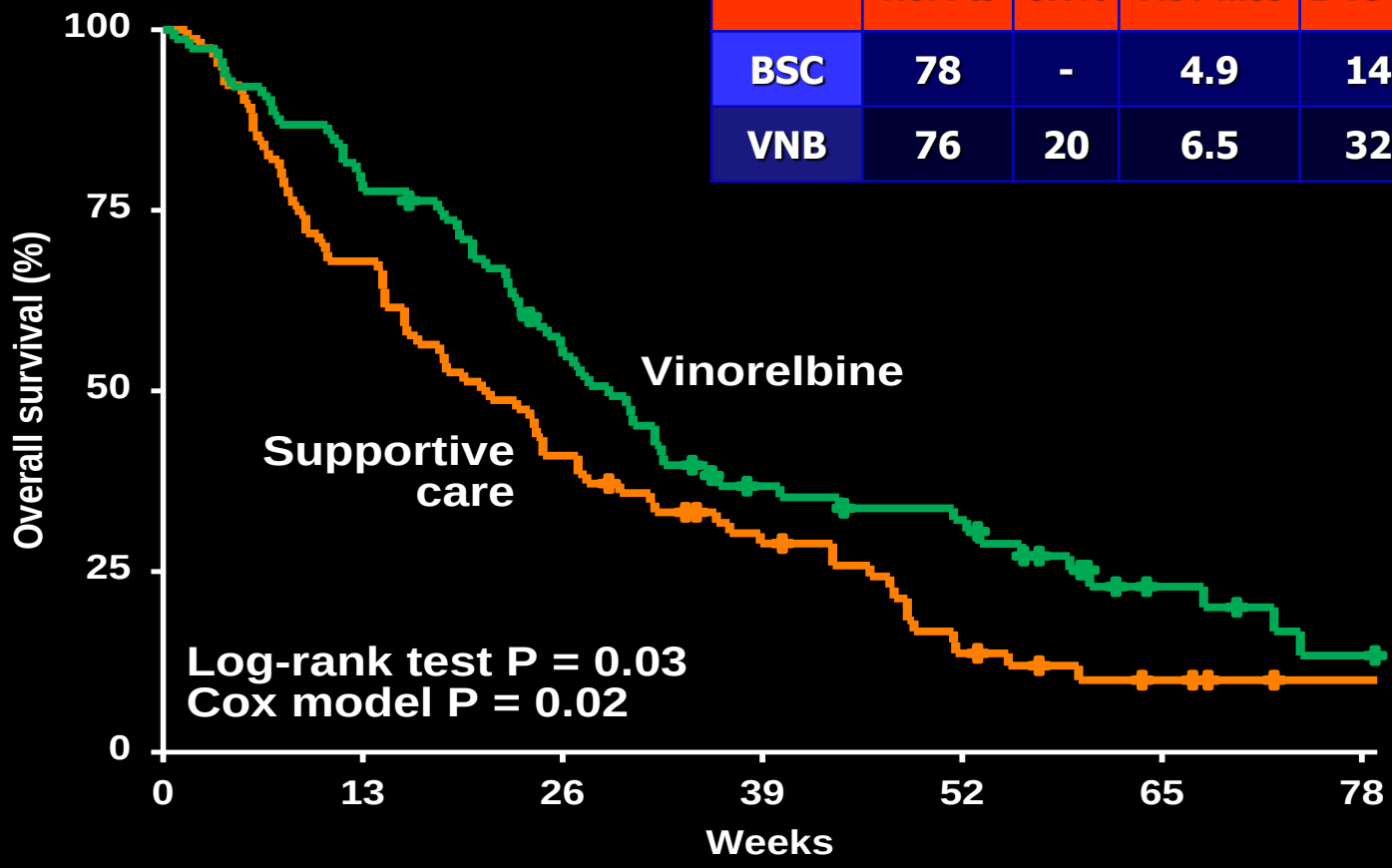
Treatment of the Elderly

Single agent chemotherapy

Combination chemotherapy

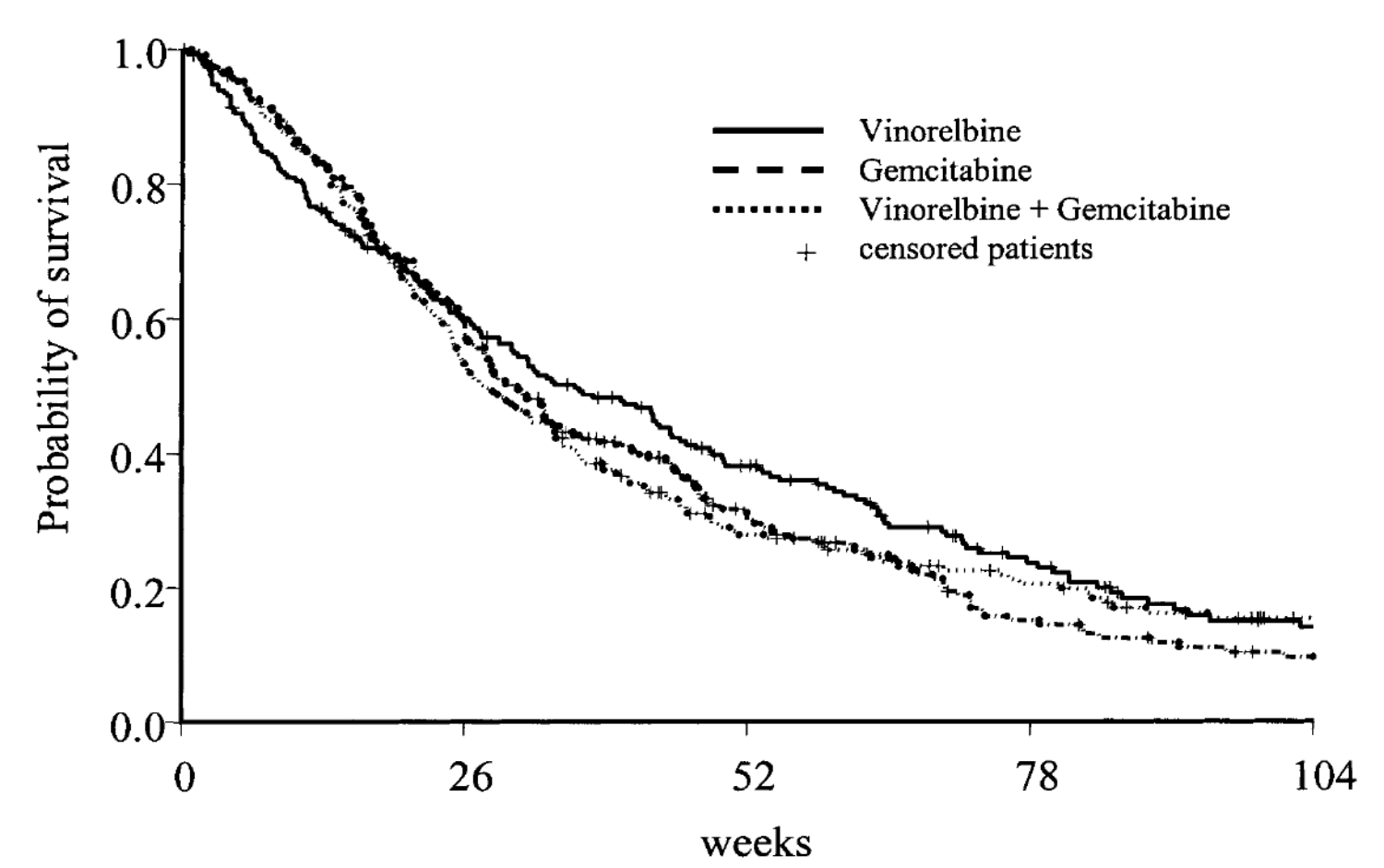
ELVIS Overall Survival

	No. Pts	0R%	MST mos	1-YS %
BSC	78	-	4.9	14
VNB	76	20	6.5	32



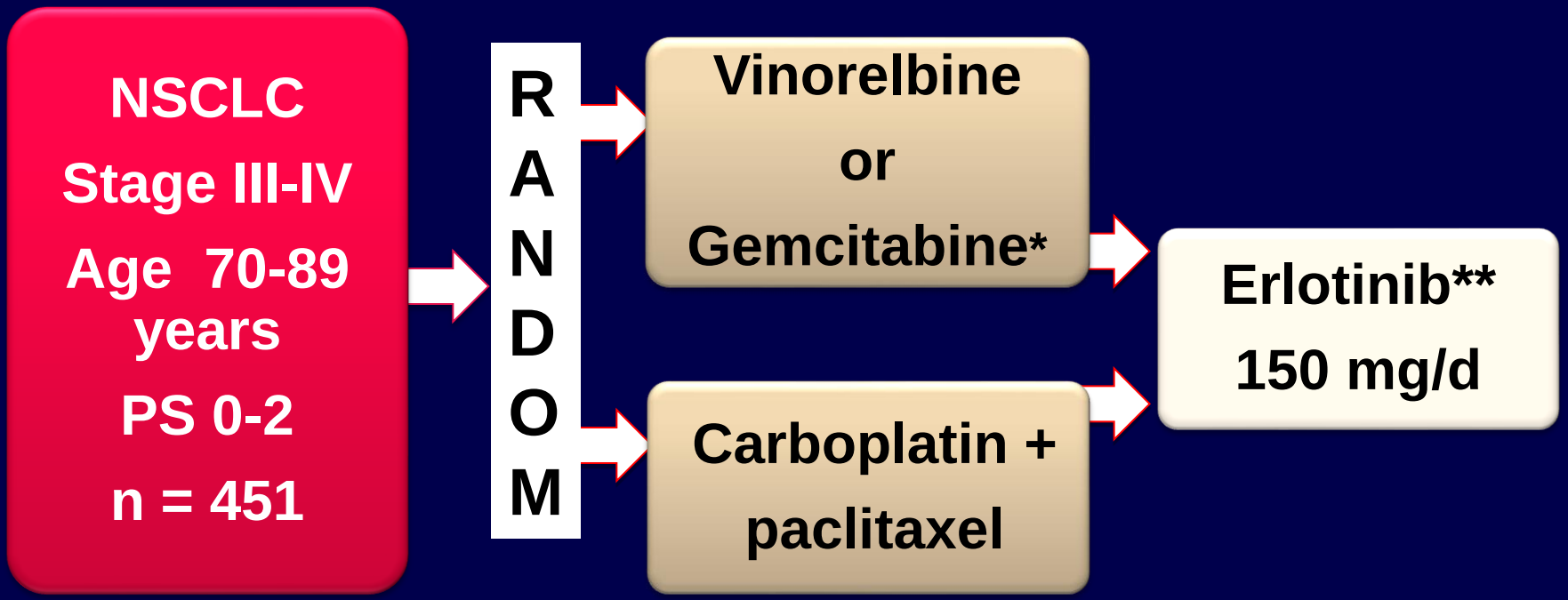
Journal of the National Cancer Institute, 1999

MILES Overall Survival



Journal of the National Cancer Institute, Vol. 95, No. 5, March 5, 2003

The Elderly
IFCT-0501 Study Schema



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
** In case of PD or excessive toxicity

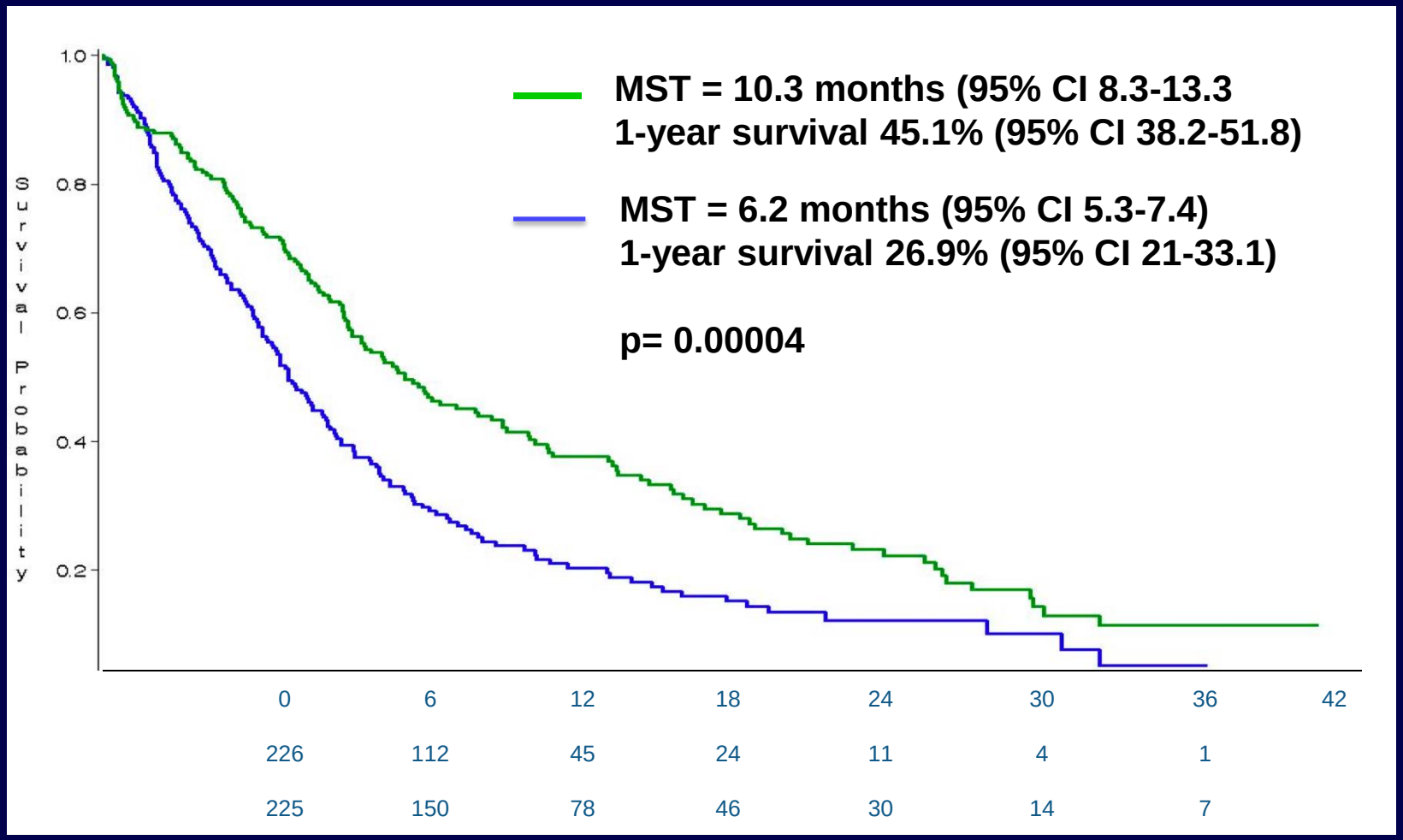
Chemotherapy Schedules

ARM A	V	V		V	V		V	V		V	V		V	V			
	G	G		G	G		G	G		G	G		G	G			
ARM B	C P	P	P		C P	P	P		C P	P	P		C P	P	P		
EVALUATION																	

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

Overall Survival (ITT)



Quoix et al. Proc ASCO, 2010

Maintenance Chemotherapy

Continuing First-Line Induction Chemotherapy Doublet

No survival benefit

More toxicity

Worse QOL

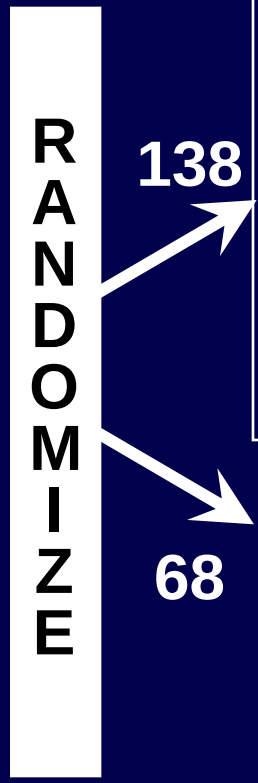
Maintenance Chemotherapy

Continuing *Same* First-Line Single Agent Induction Chemotherapy *Without the Platinum Analogue*

Advanced NSCLC
Gemcitabine Maintenance Therapy

Stage IV NSCLC (n=352)

CR / PR / SD after cisplatin + gemcitabine (n=206)



138

Maintenance gemcitabine 1250 mg/m^2 day 1, 8 Q3W plus BSC

(No cisplatin)

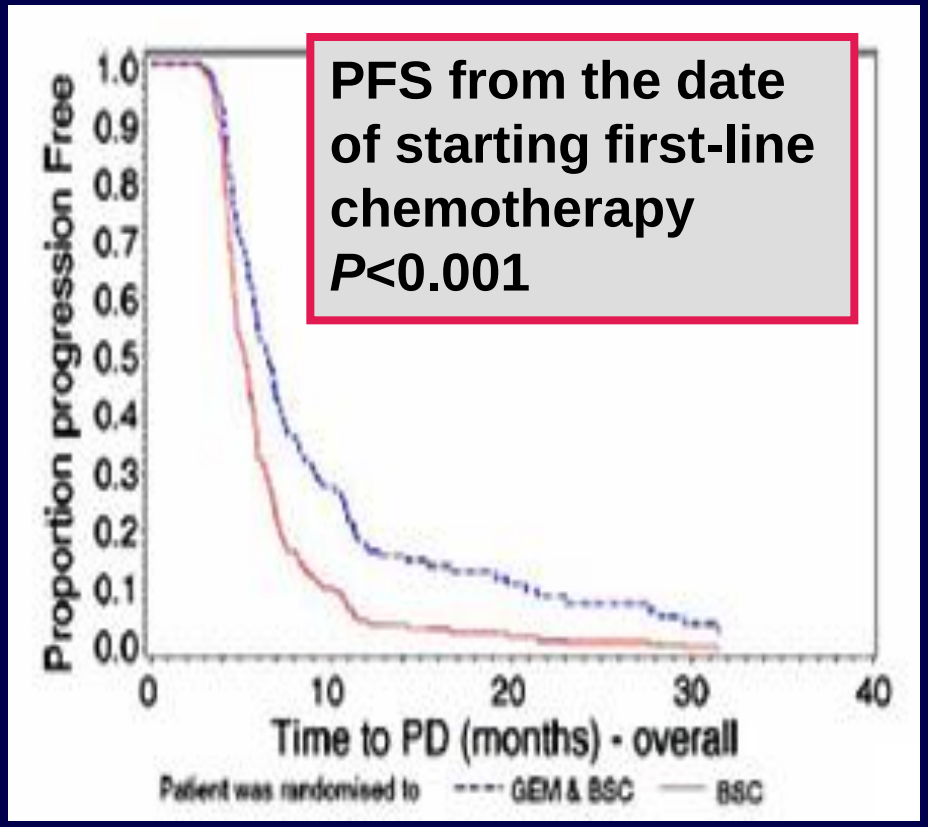
68

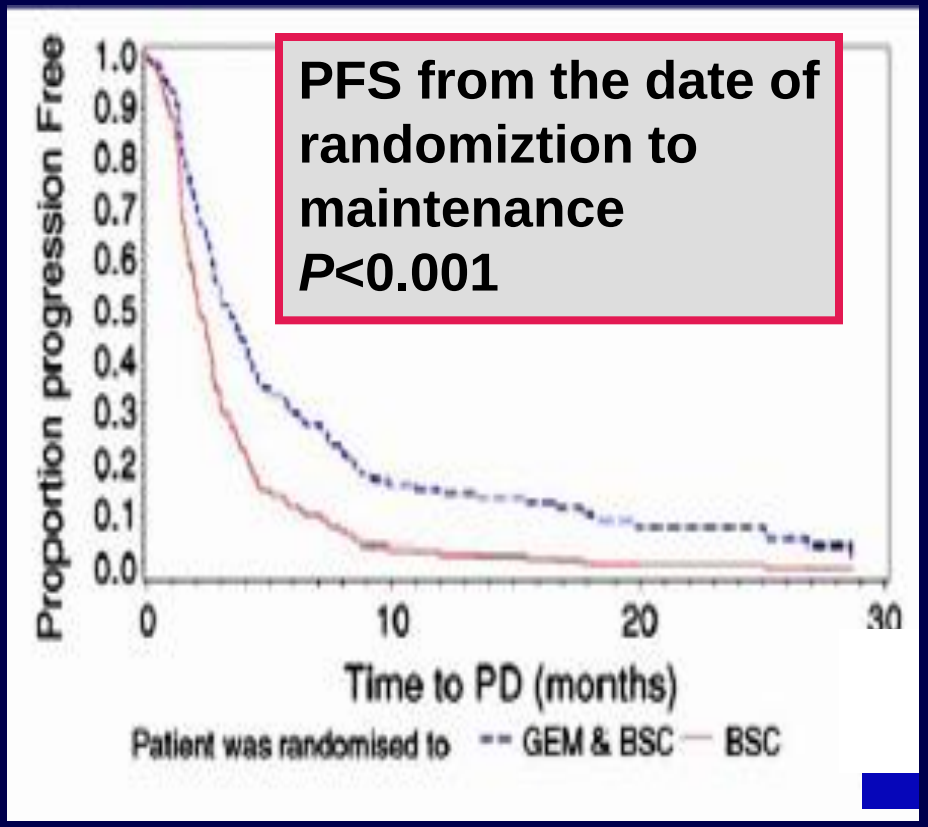
BSC only

Primary endpoint: median time to progression

Brodowicz et al, Lung Cancer 2006; 52: 155-163

Advanced NSCLC
Gemcitabine Maintenance Therapy

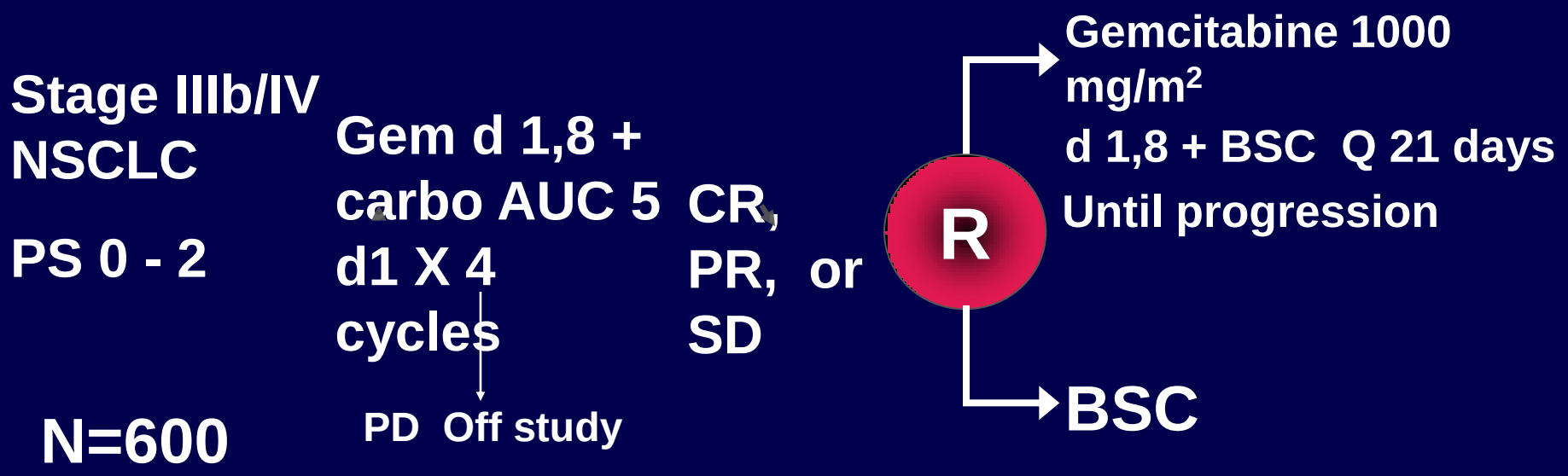




Overall survival: 13.0 mos *vs* 11.0 mos, p=0.19

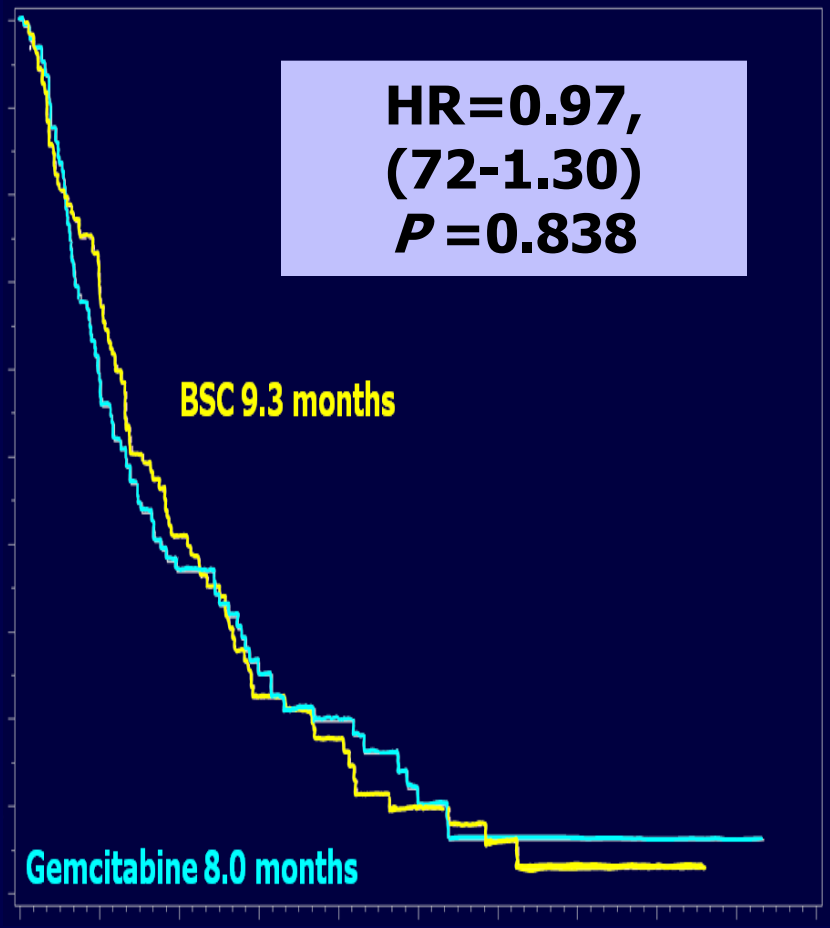
Brodowicz et al, Lung Cancer 2006; 52: 155-163

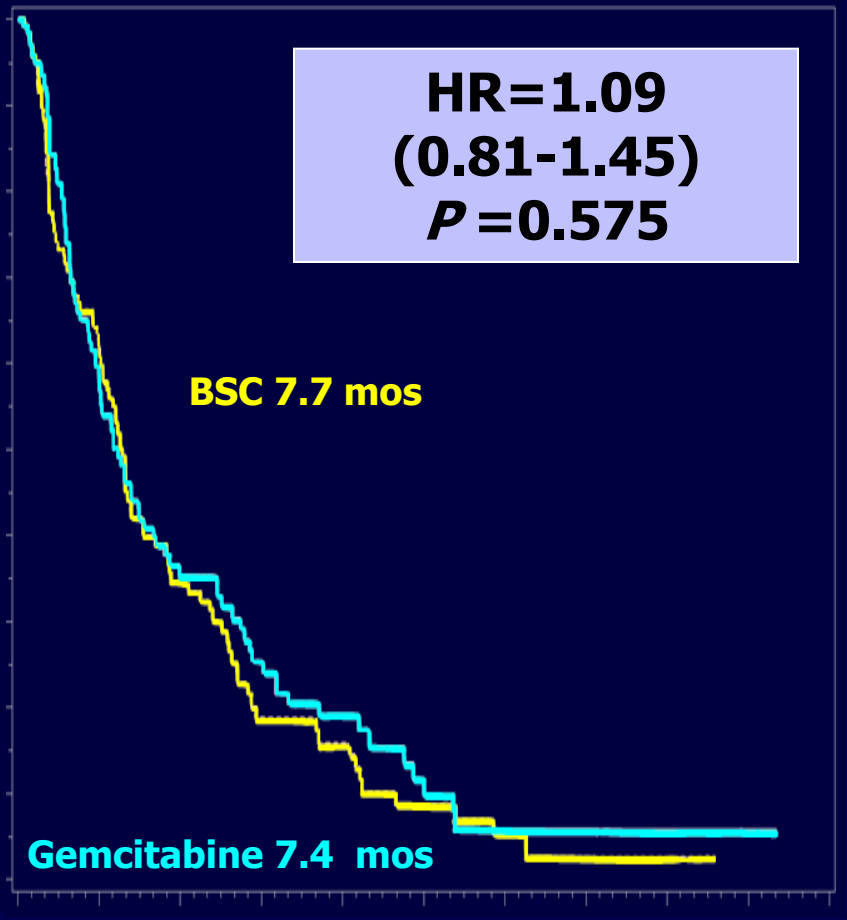
POI-01-003-050: Maintenance Gemcitabine After 1st-Line Therapy in Advanced NSCLC



Primary endpoint: OVERALL Survival

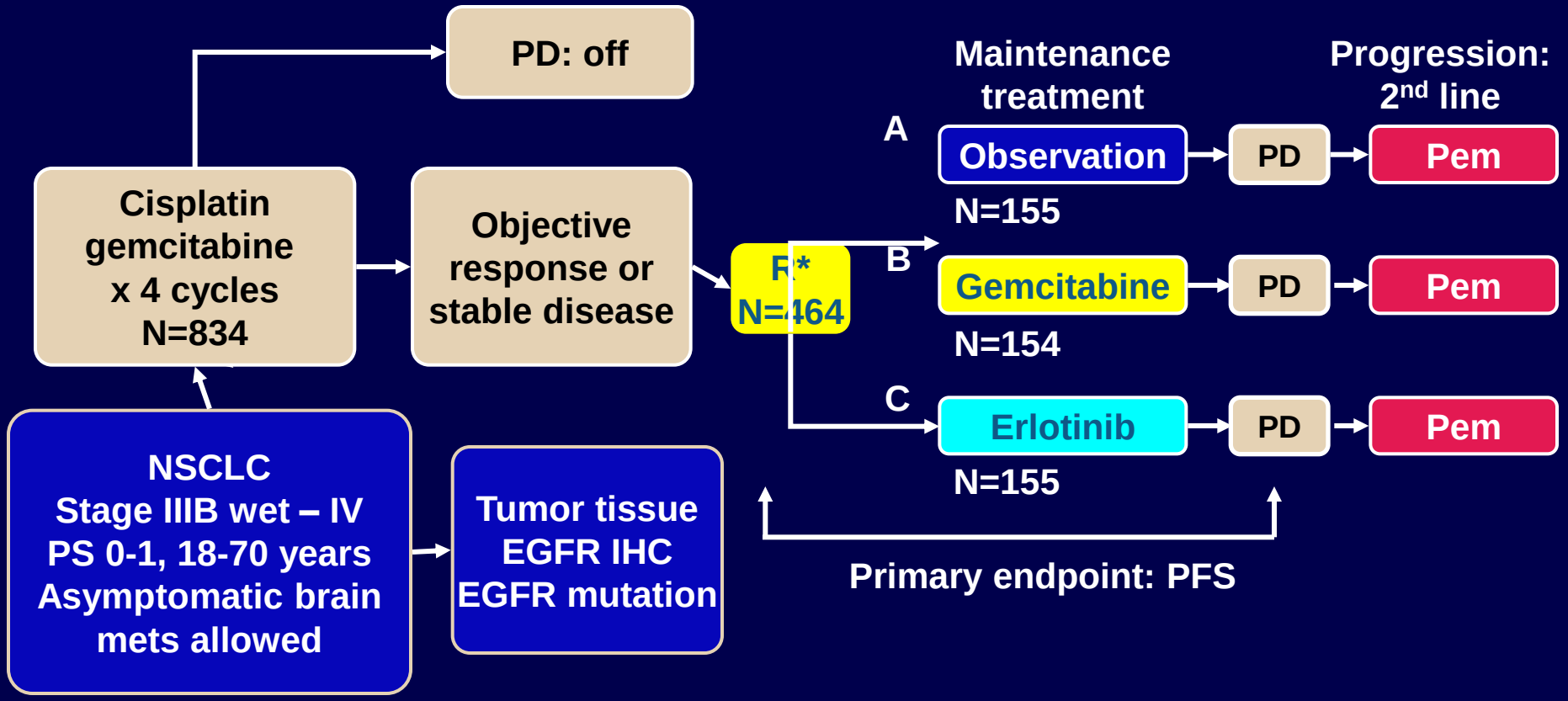
Progression-Free & Overall Survival





Belani et al. Proc ASCO, 2010

IFCT-GFPC 0502 Study Design



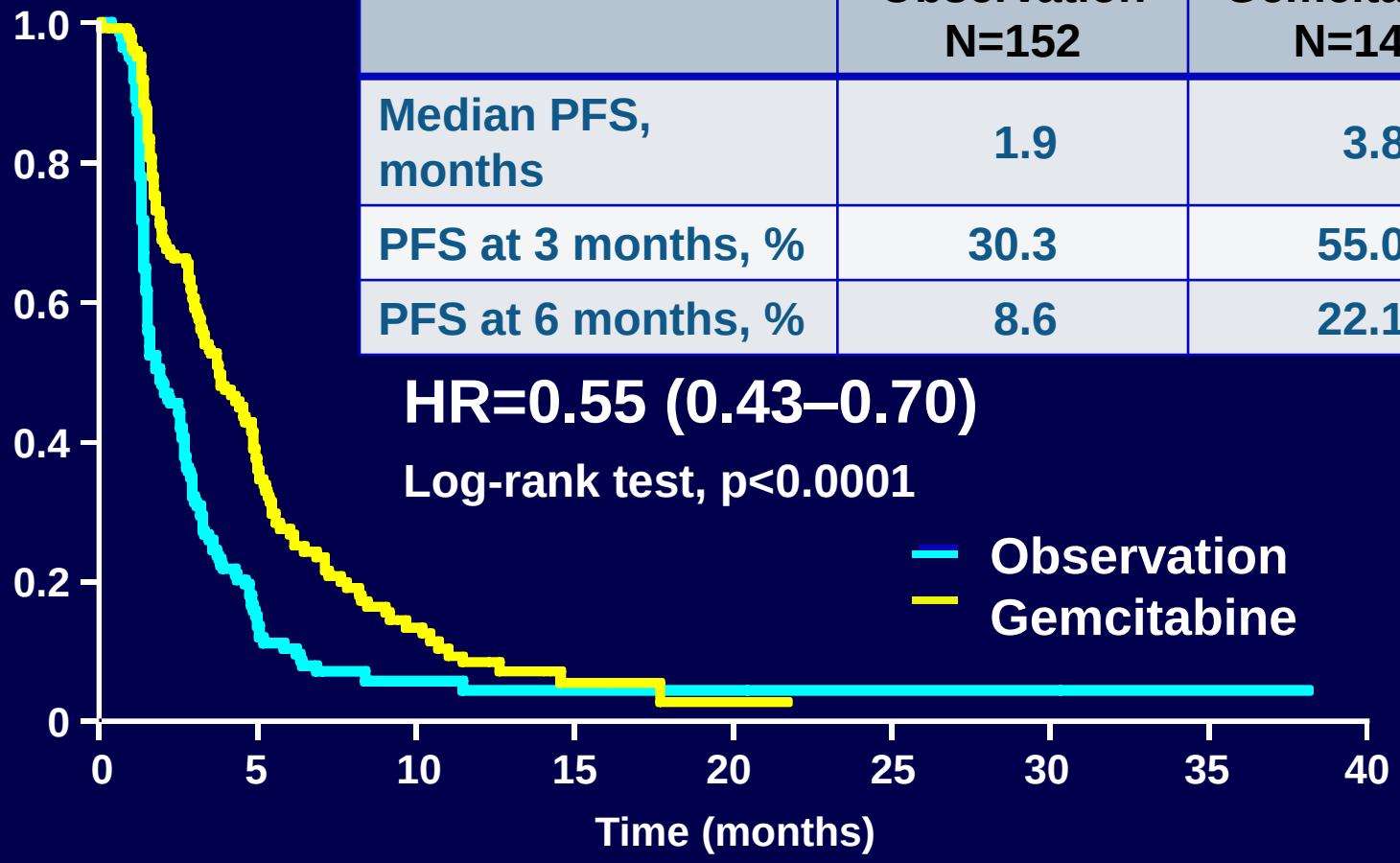
Induction chemo: cisplatin 80 mg/m^2 d1 + gemcitabine 1,250 mg/m^2 d1, d8

Arm B: gemcitabine 1,250 mg/m^2 d1, d8 Q 3 wks

Arm C: erlotinib 150 mg PO daily

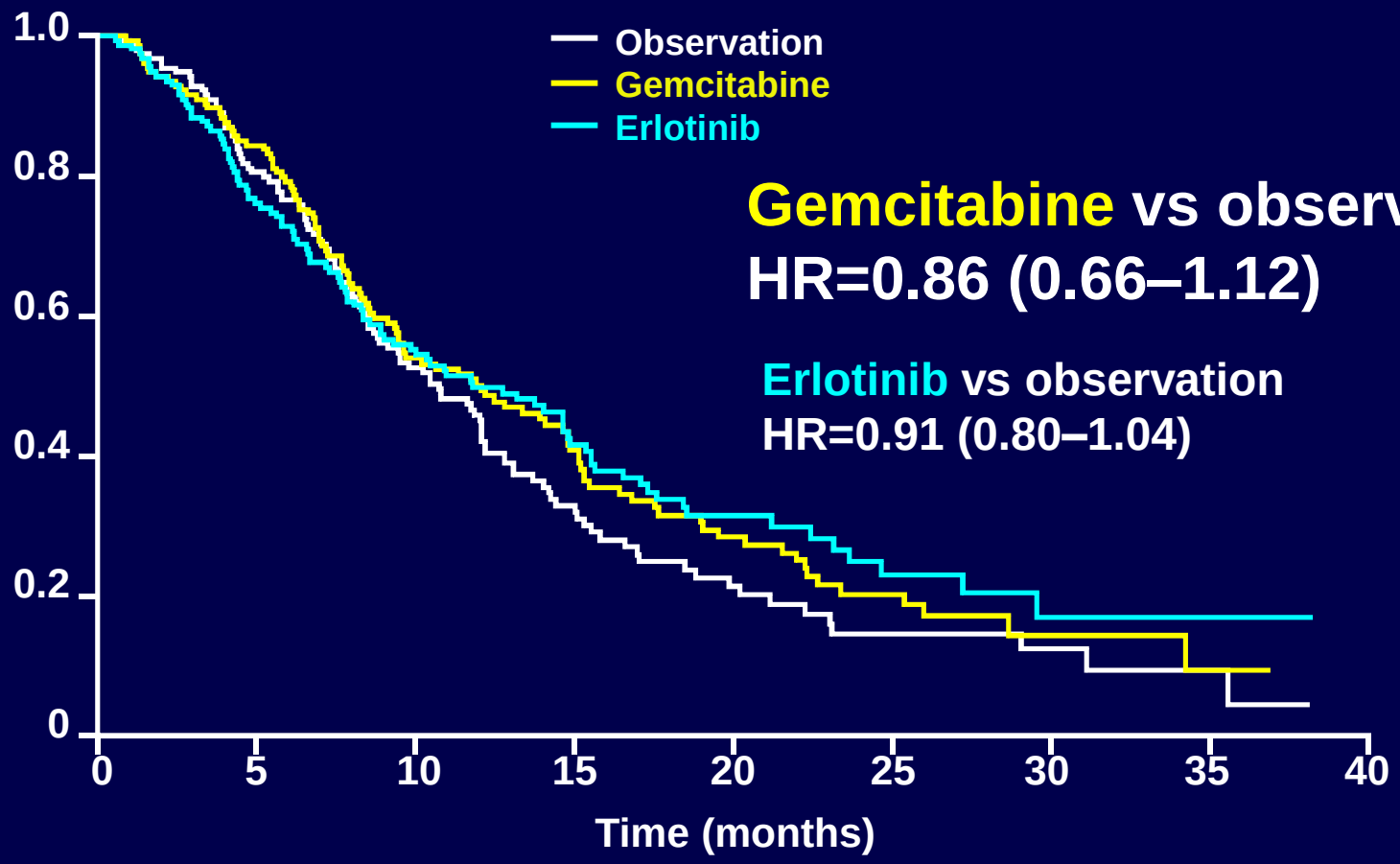
PFS by Independent Review Gemcitabine *vs* Observation

	Observation N=152	Gemcitabine N=149
Median PFS, months	1.9	3.8
PFS at 3 months, %	30.3	55.0
PFS at 6 months, %	8.6	22.1



Perol et al. Proc ASCO, 2010

Overall Survival

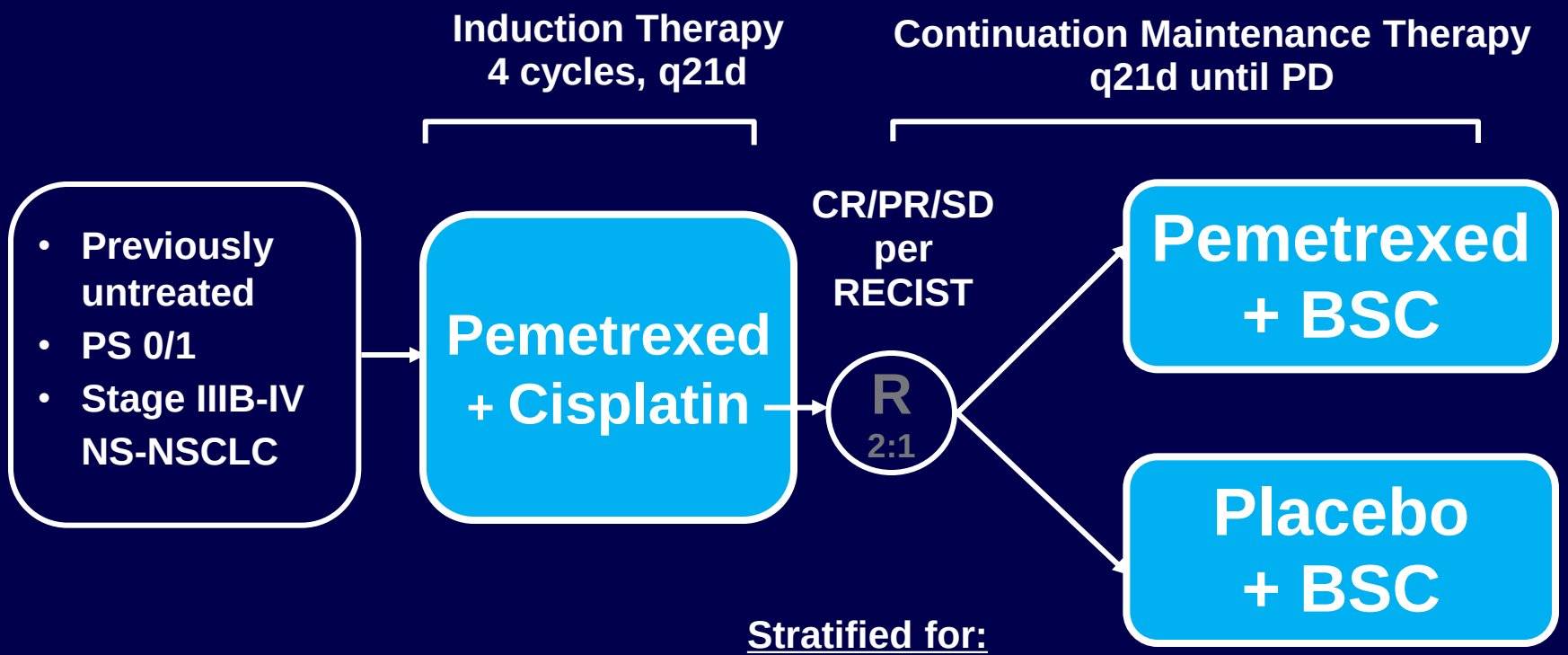


Median follow-up: 21.6 months

324 deaths / 464 randomized patients (69.6%)

Perol et al. Proc ASCO, 2010

PARAMOUNT: Study Design

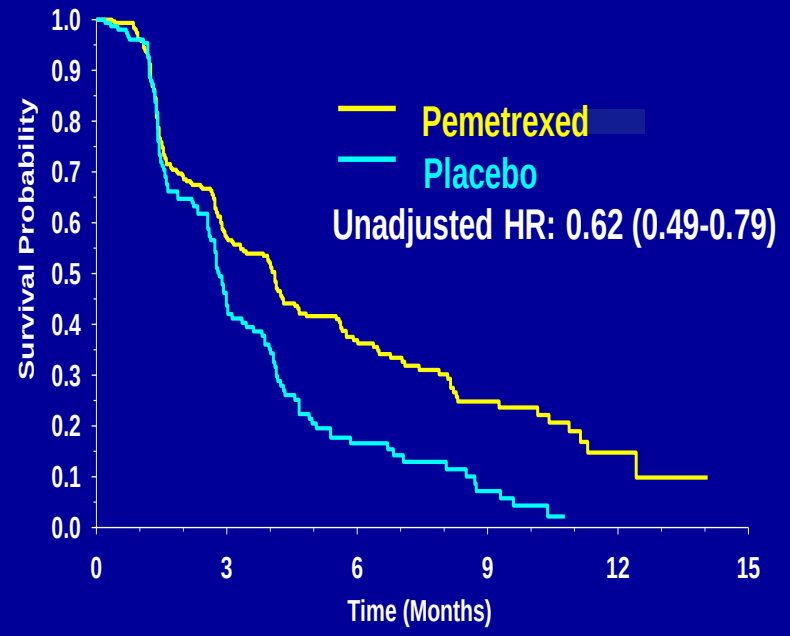


Stratified for:

- PS (0 vs 1)
- Disease stage (IIIB vs IV) prior to induction
- Response to induction (CR/PR vs SD)

PARAMOUNT: PFS from Randomization

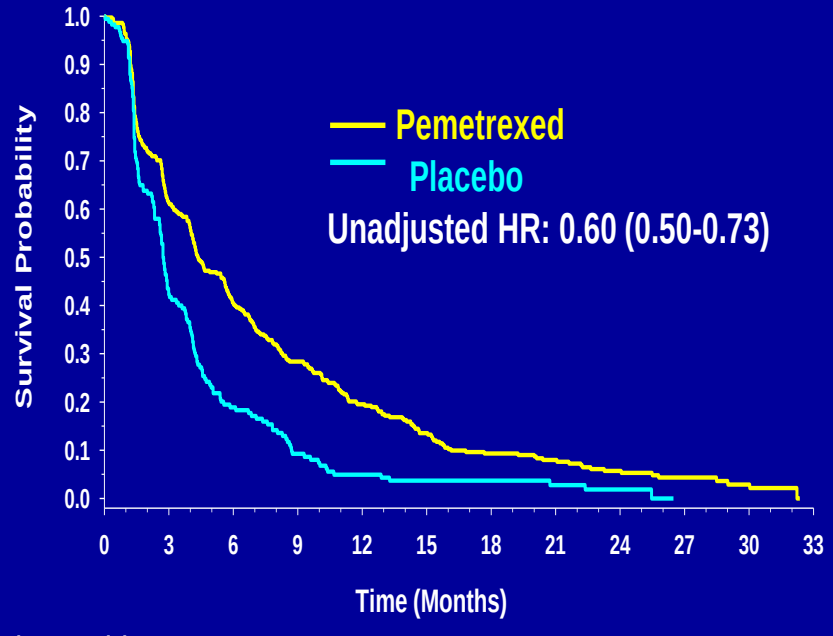
PFS: Primary Efficacy Endpoint



Patients at Risk

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

PFS: Reassessed at Time of Final OS



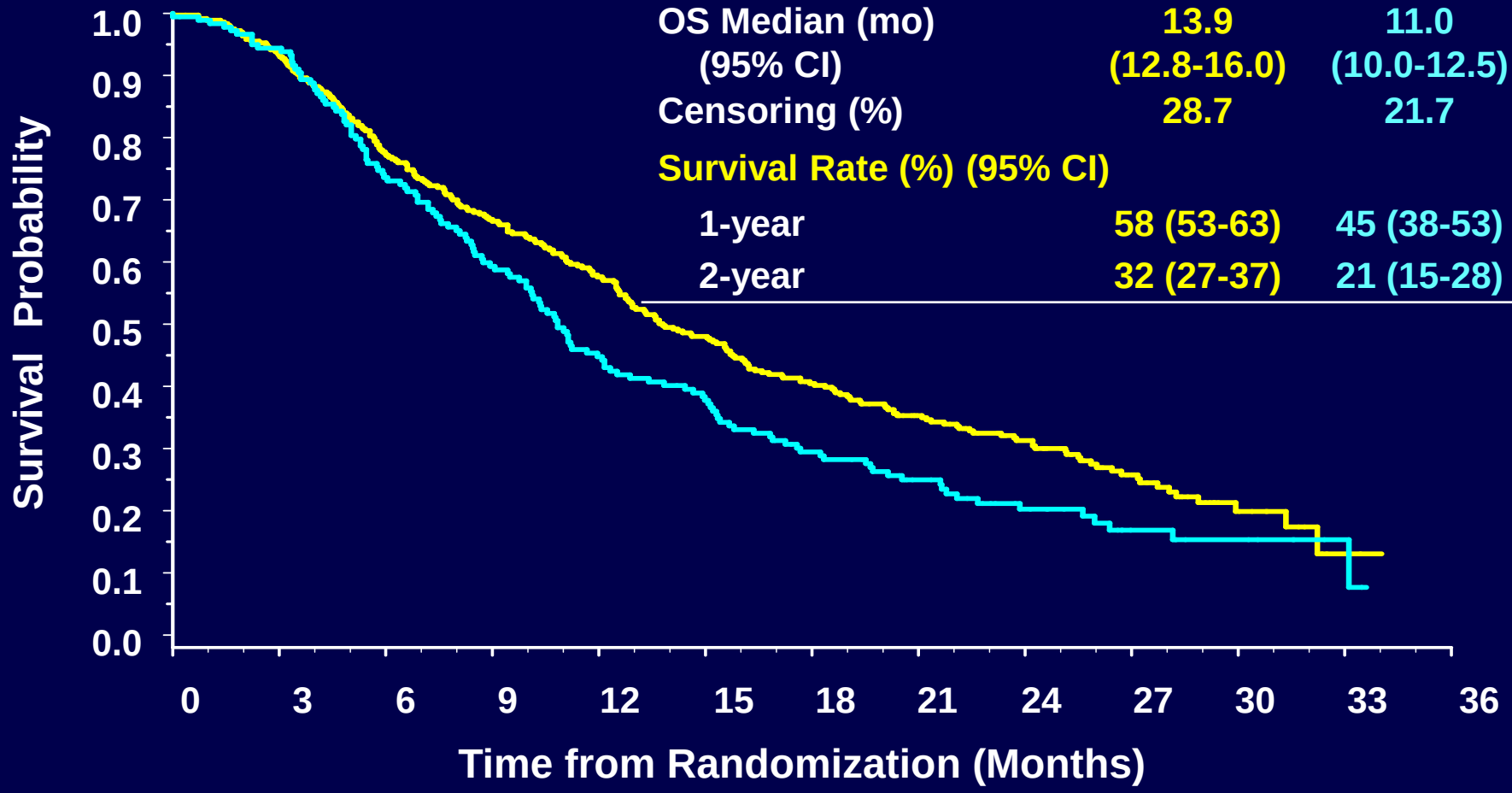
Patients at Risk

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

Pas Ares et al. Proc ASCO, 2012

PARAMOUNT: Final OS from Randomization

	Pem	Placebo
OS Median (mo)	13.9	11.0
(95% CI)	(12.8-16.0)	(10.0-12.5)
Censoring (%)	28.7	21.7
Survival Rate (%) (95% CI)		
1-year	58 (53-63)	45 (38-53)
2-year	32 (27-37)	21 (15-28)

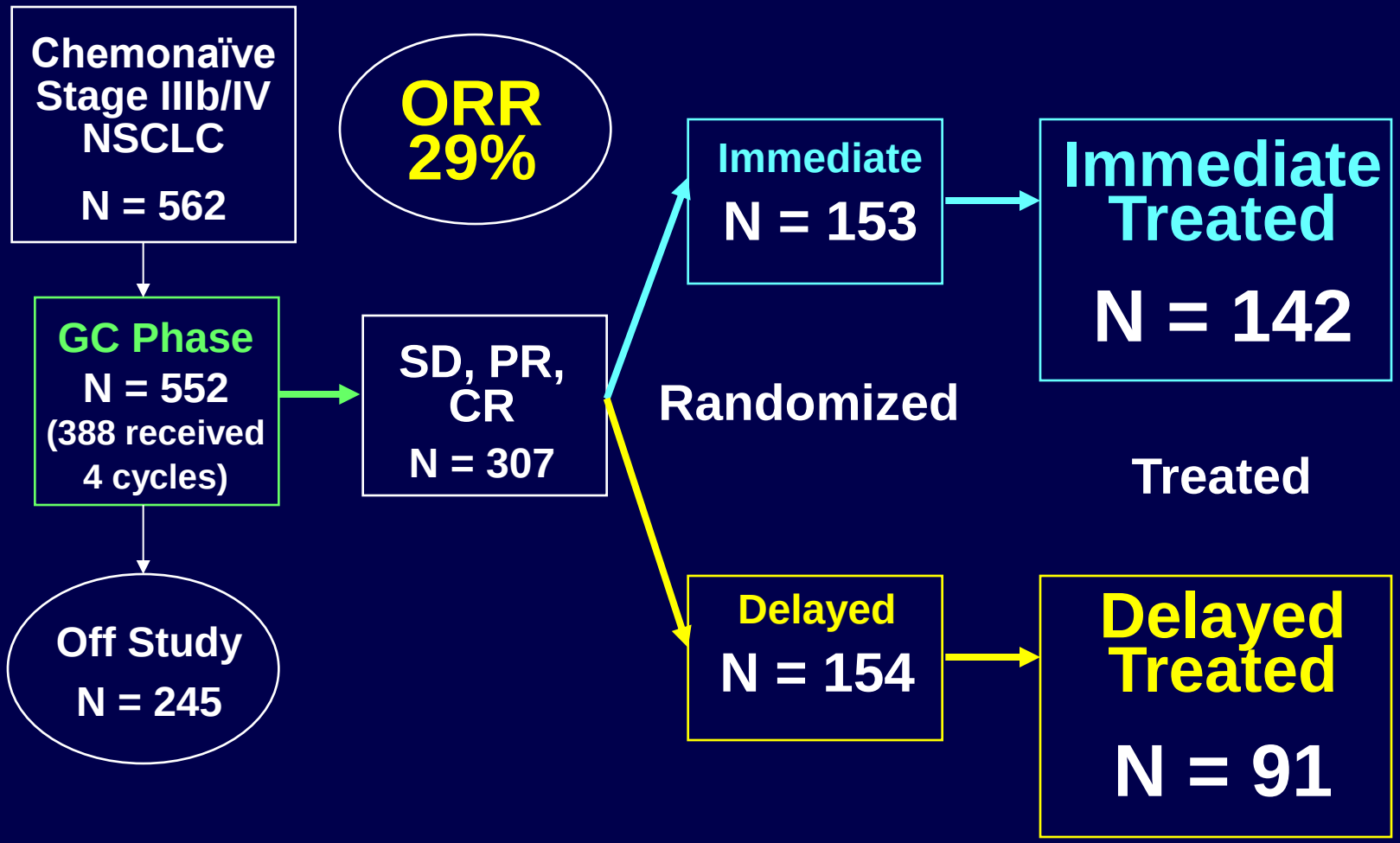


Pas Ares et al. Proc ASCO, 2012

Maintenance Chemotherapy

Switching to a *New* Chemotherapy Agent in Responding and Stable Patients (Usually a Single Agent)

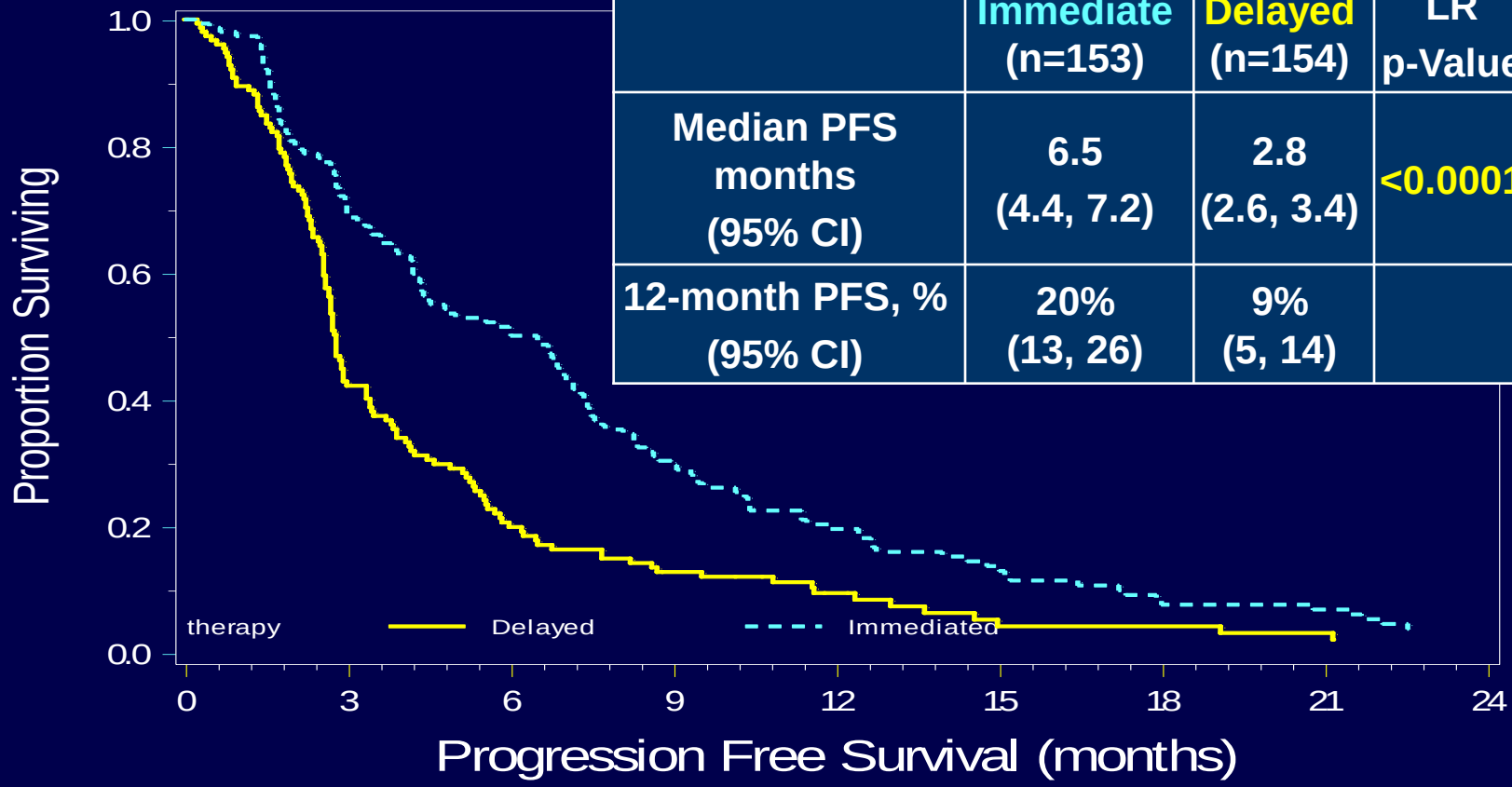
Immediate *versus* Delayed Docetaxel



Fidias et al. J Clin Oncol 27: 591, 2009

Progression-Free Survival
Total Randomized Population

	Immediate (n=153)	Delayed (n=154)	LR p-Value
Median PFS months (95% CI)	6.5 (4.4, 7.2)	2.8 (2.6, 3.4)	<0.0001
12-month PFS, % (95% CI)	20% (13, 26)	9% (5, 14)	

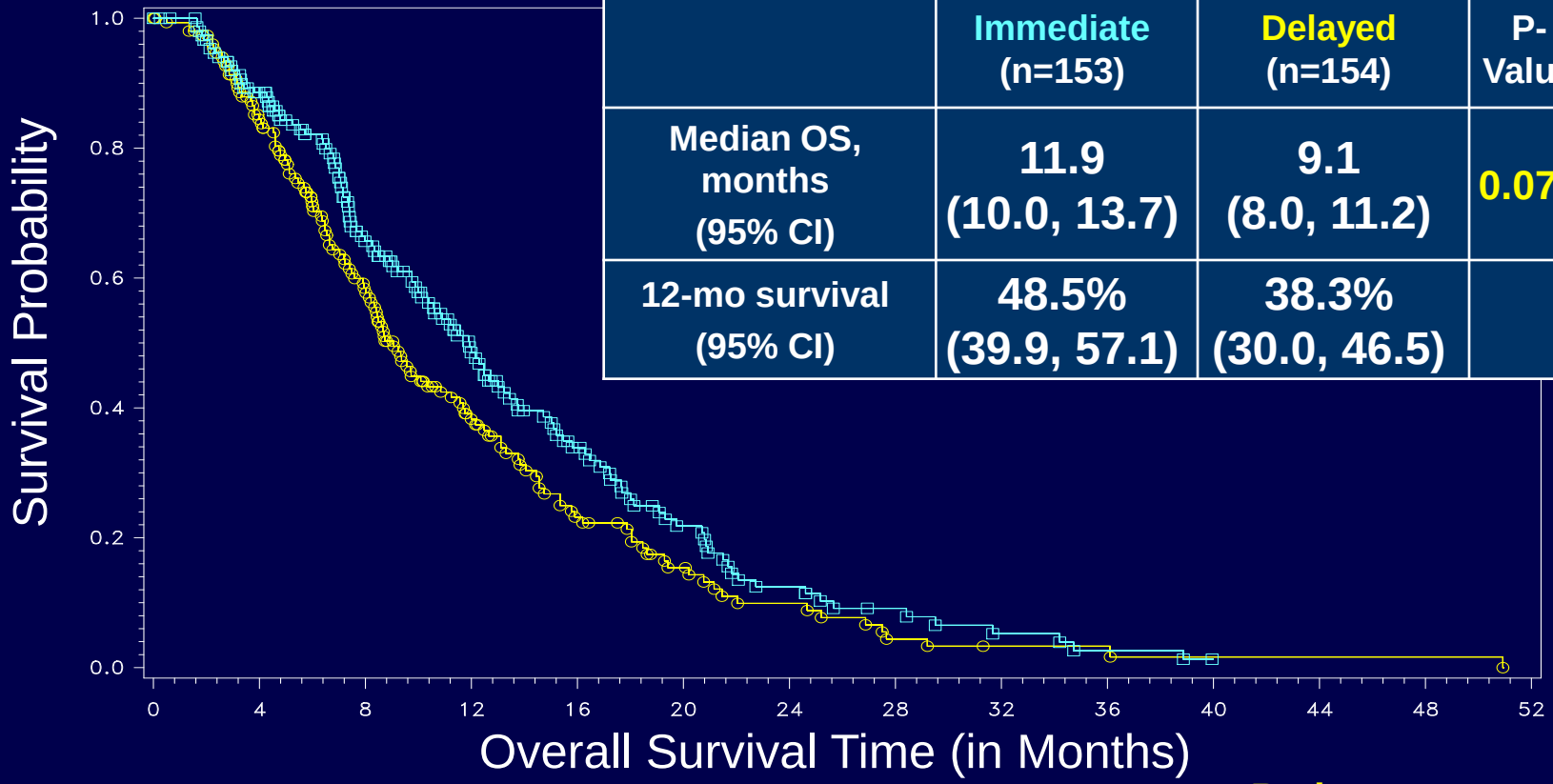


I:	153	72	27	11	5
D	154	28	10	4	2

Patients at Risk

Fidias et al. J Clin Oncol 27: 591, 2009

Overall Survival



	Immediate (n=153)	Delayed (n=154)	P-Value
Median OS, months (95% CI)	11.9 (10.0, 13.7)	9.1 (8.0, 11.2)	0.071
12-mo survival (95% CI)	48.5% (39.9, 57.1)	38.3% (30.0, 46.5)	

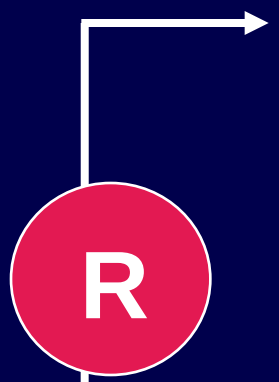
I:	153	111	56	27	12	5	2	Patients at Risk
D:	154	98	45	22	9	3	2	

Under-powered for survival benefit

Fidias et al. J Clin Oncol 27: 591, 2009

JMEN: Phase III Study of Maintenance Pemetrexed after Standard First-Line Therapy in Advanced NSCLC

- Stage IIIB or IV NSCLC who has not progressed after 4 cycles of a standard chemotherapy



Pemetrexed 500 day 1

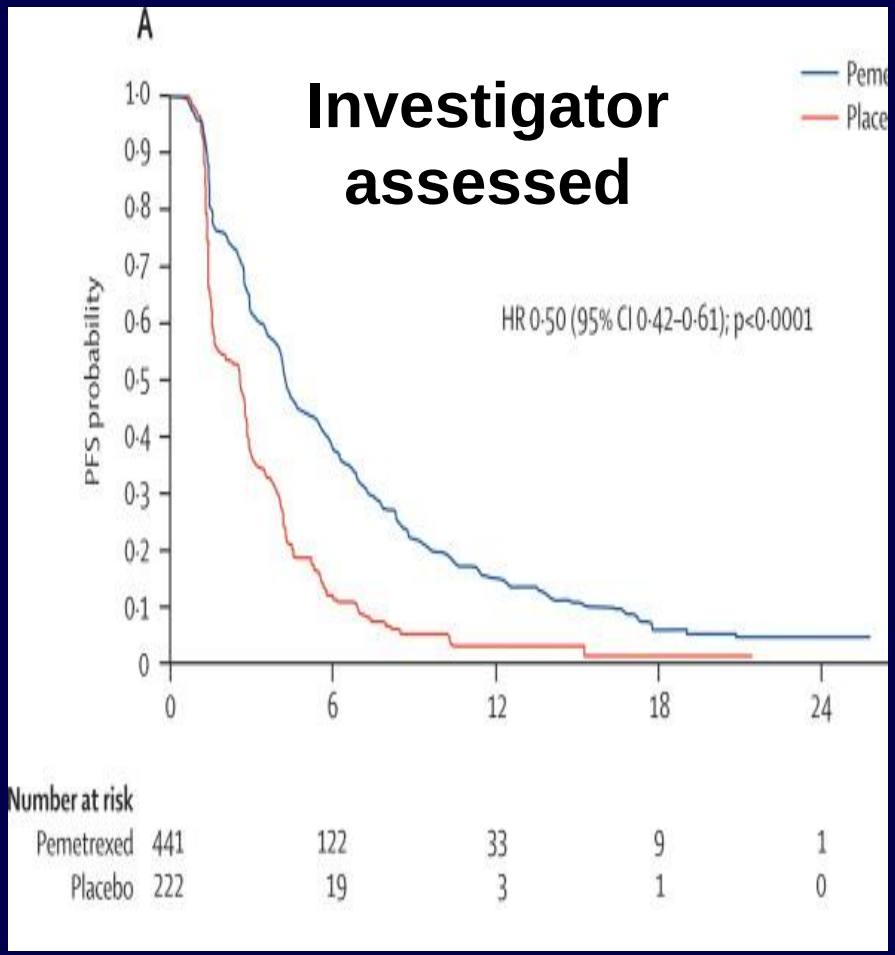
N = 660 Patients

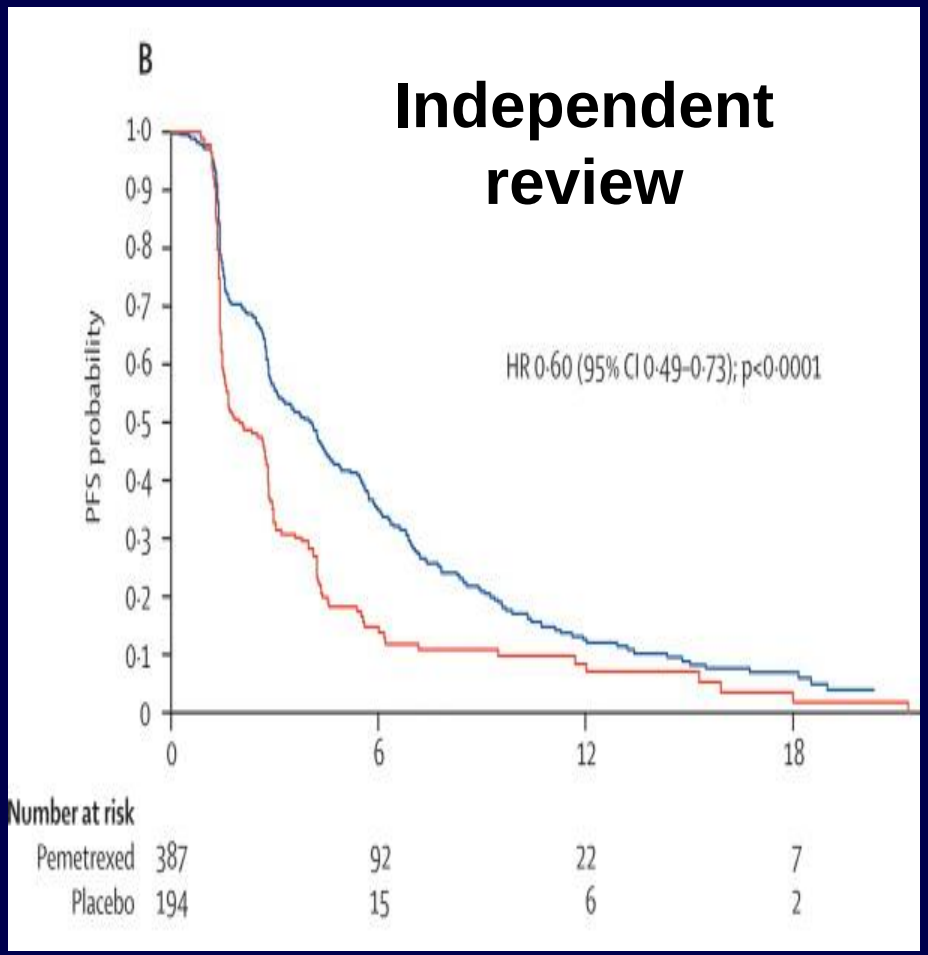
Placebo + day 1

Primary objective: PFS, Superiority design

Secondary objectives: RR, OS, TTPD, TWQ (Time to Worsening QOL), QOL based on LCSS

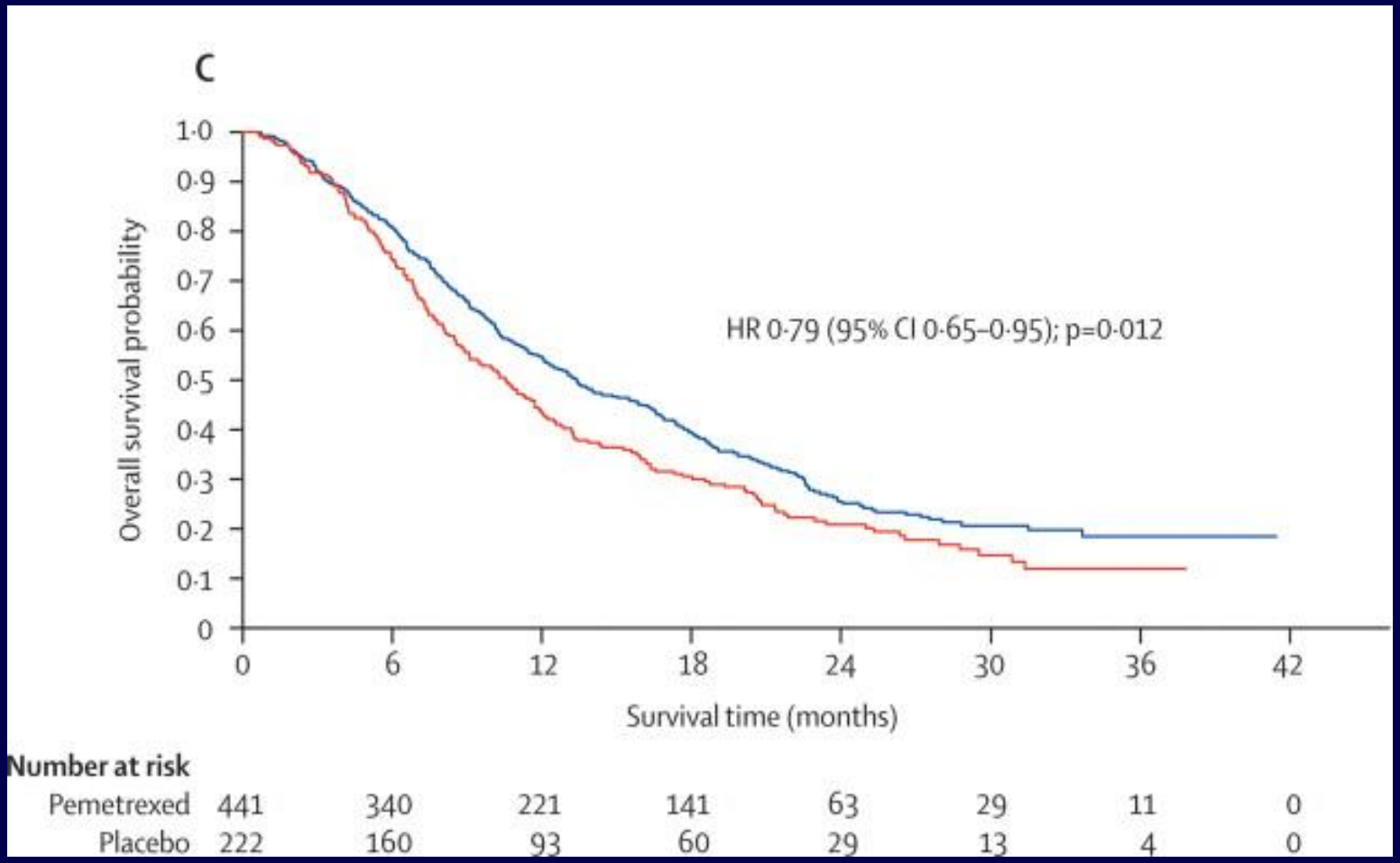
JMEN: PFS





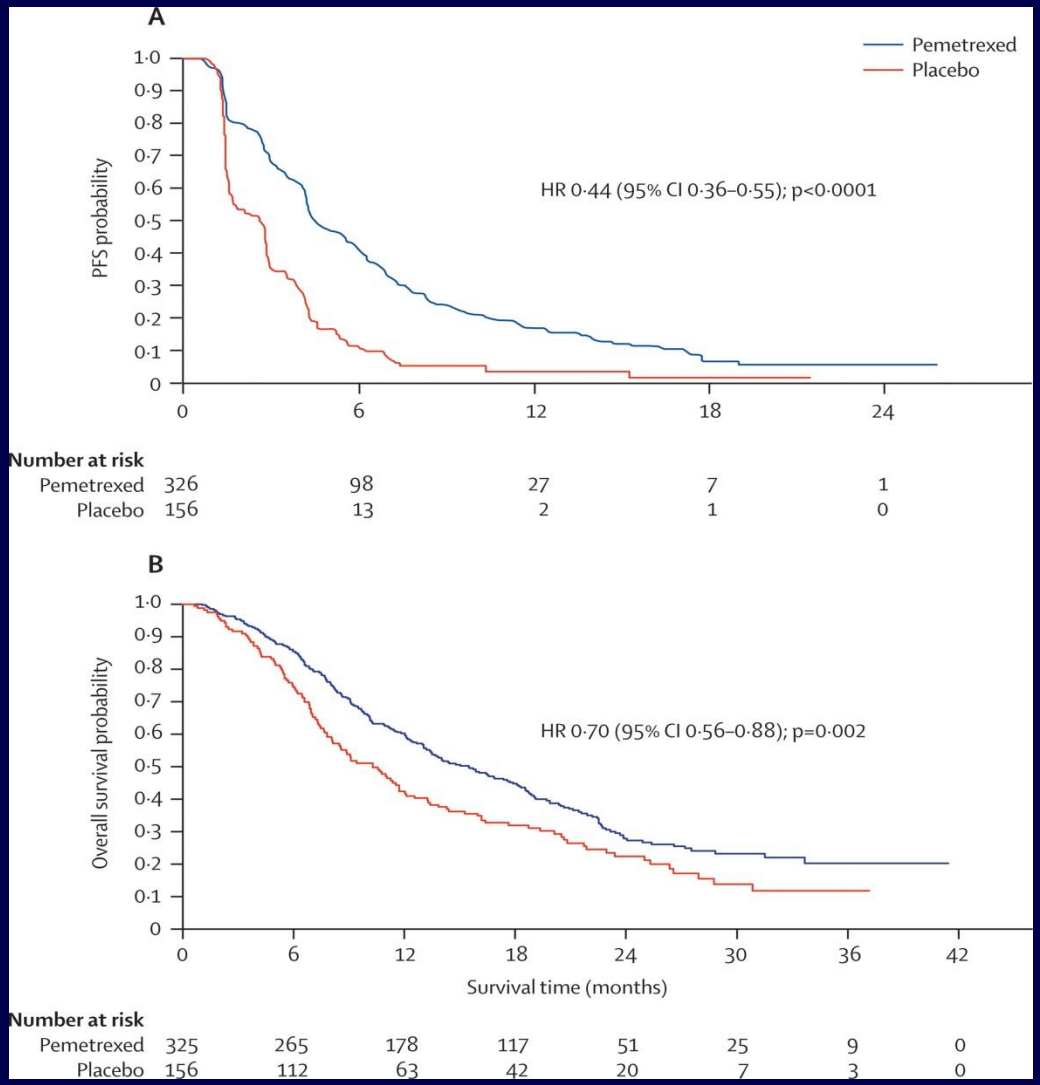
Ciulaneau et al. Lancet, 2009

JMEN: Overall Survival



Ciulaneau et al. Lancet, 2009

Non-Squamous Subset



PFS and OS in the *non-squamous sub-set*

PFS HR 0.44, p<0.0001

OS HR 0.70, p=0.002

Ciulanu et al. Lancet, 2009

JMEN Efficacy by Histology

	Med OS* months		p-value HR	Med PFS* months		p-value HR	CR+PR+SD %		p-value
	Pem	Placebo		Pem	Placebo		Pem	Placebo	
Nonsquamous n=481	15.5	10.3	0.002 0.7 (0.56-0.88)	4.5	2.6	<0.0001 0.44 (0.36-0.55)	58	33	<0.0001
Adeno n=328	16.8	11.5	0.026 0.73 (0.56- 0.96)	4.6	2.7	<0.0001 0.51 (0.38- 0.68)	61.0	33.0	<0.0001
Large Cell n=20	8.4	7.9	0.964 0.98 (0.36- 2.65)	4.5	1.5	0.125 0.40 (0.12- 1.29)	46	33	0.670
Other n=133	11.3	7.7	0.025 0.61 (0.40- 0.94)	4.1	1.6	0.025 0.61 (0.40- 0.94)	51	32	0.041
Squamous n=182	9.9	10.8	0.678 1.07 (0.77- 1.50)	2.4	2.5	0.896 1.03 (0.71-1.49)	35	35	>0.999

*** Treatment-by-histology interaction tests significant for OS and PFS.**

Addition of Targeted Agents to First-Line Chemotherapy Doublets

Bevacizumab

Cetuximab

Denosumab

To date everything else has been disastrous!!!

ECOG 4599: Phase III Trial of Bevacizumab in Non-squamous NSCLC

Eligibility

- **Non-squamous NSCLC**
- **No History of Hemoptysis**
- **No CNS Metastases**

Stratification Variables

- RT vs no RT
- Stage IIIB or IV vs recurrent
- Weight loss <5% vs ≥5%
- Measurable vs nonmeasurable

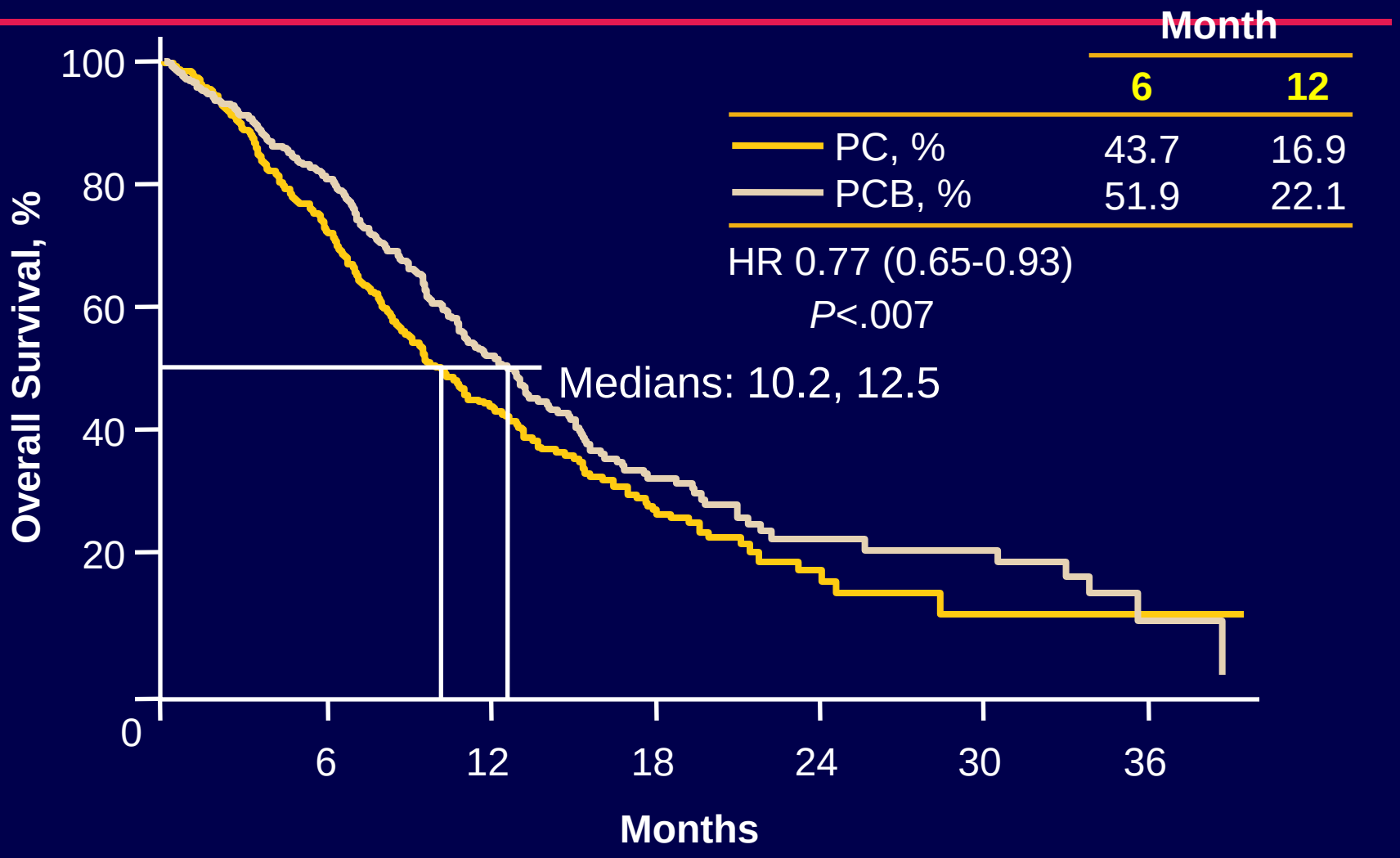
PC

Paclitaxel 200 mg/m²
Carboplatin AUC=6
(every 3 weeks) x
6 Cycles*

PCB

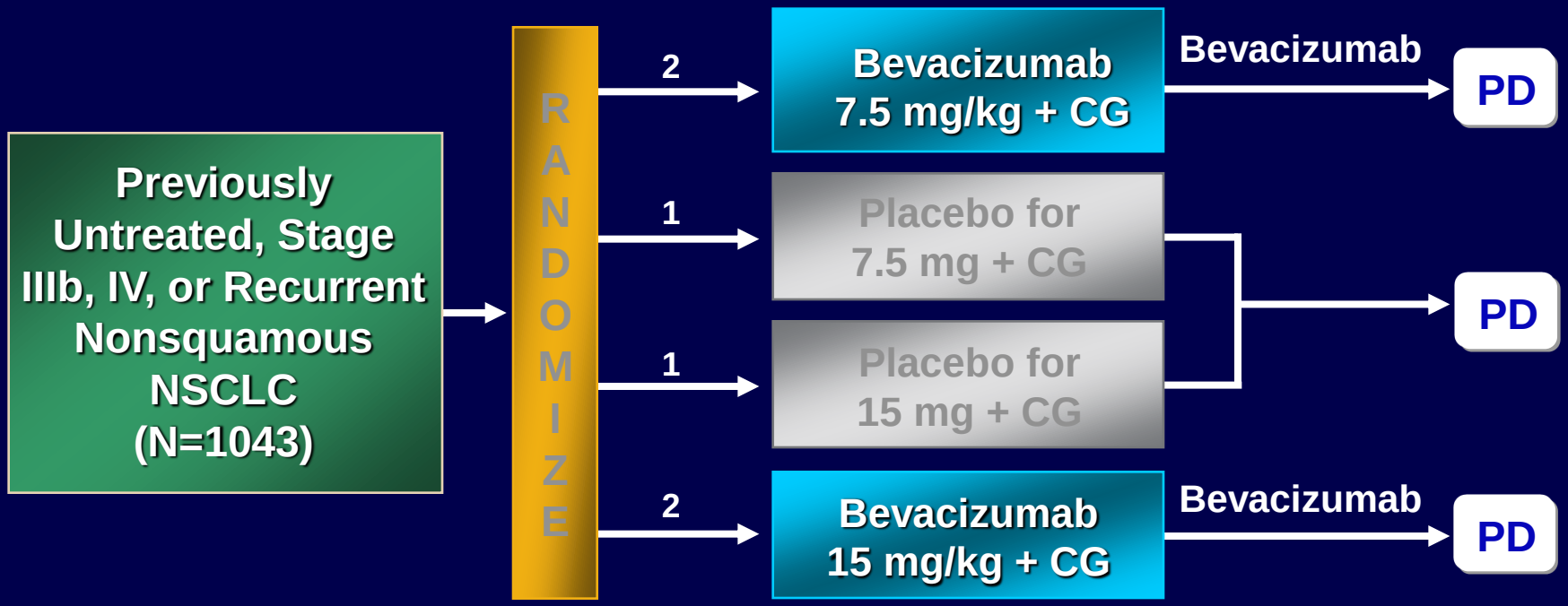
PC x 6 Cycles
+
Bevacizumab
(15 mg/kg every
3 weeks) to PD

ECOG 4599: Overall Survival by Treatment



Sandler AB et al. NEJM, 2006

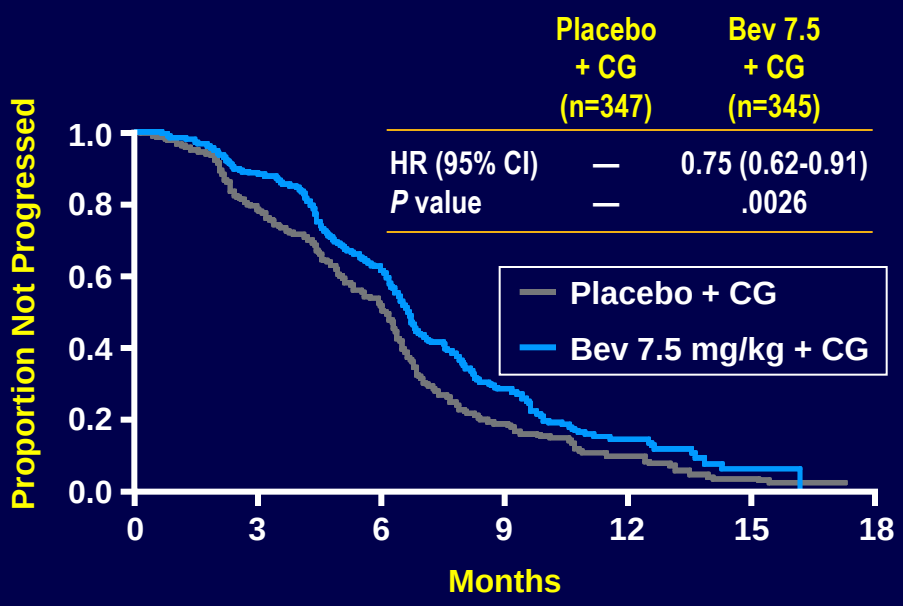
First-Line Cisplatin & Gemcitabine +/- Bevacizumab in Advanced NSCLC (AVAiL)



- Cisplatin 80 mg/m2 IV Day 1 + Gemcitabine 1250 mg/m2 on Day 1, 8 (q 3 weeks)
- Bevacizumab 7.5 mg/kg or 15 mg/kg or Placebo IV Day 1 (q 3 weeks)

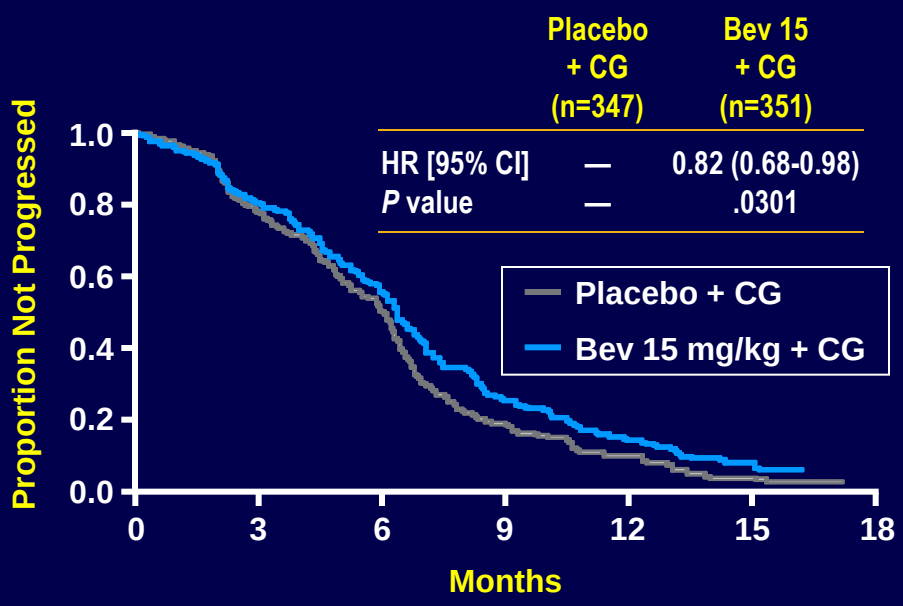
AVAiL: Progression-Free Survival

Primary Analysis (intent-to-treat) of Bevacizumab 7.5 mg/kg Versus Pooled Placebo



No. at Risk							
Placebo + CG	347	228	122	36	12	3	0
Bev 7.5 + CG	345	251	150	52	18	3	0

Primary Analysis (intent-to-treat) of Bevacizumab 15 mg/kg Versus Pooled Placebo

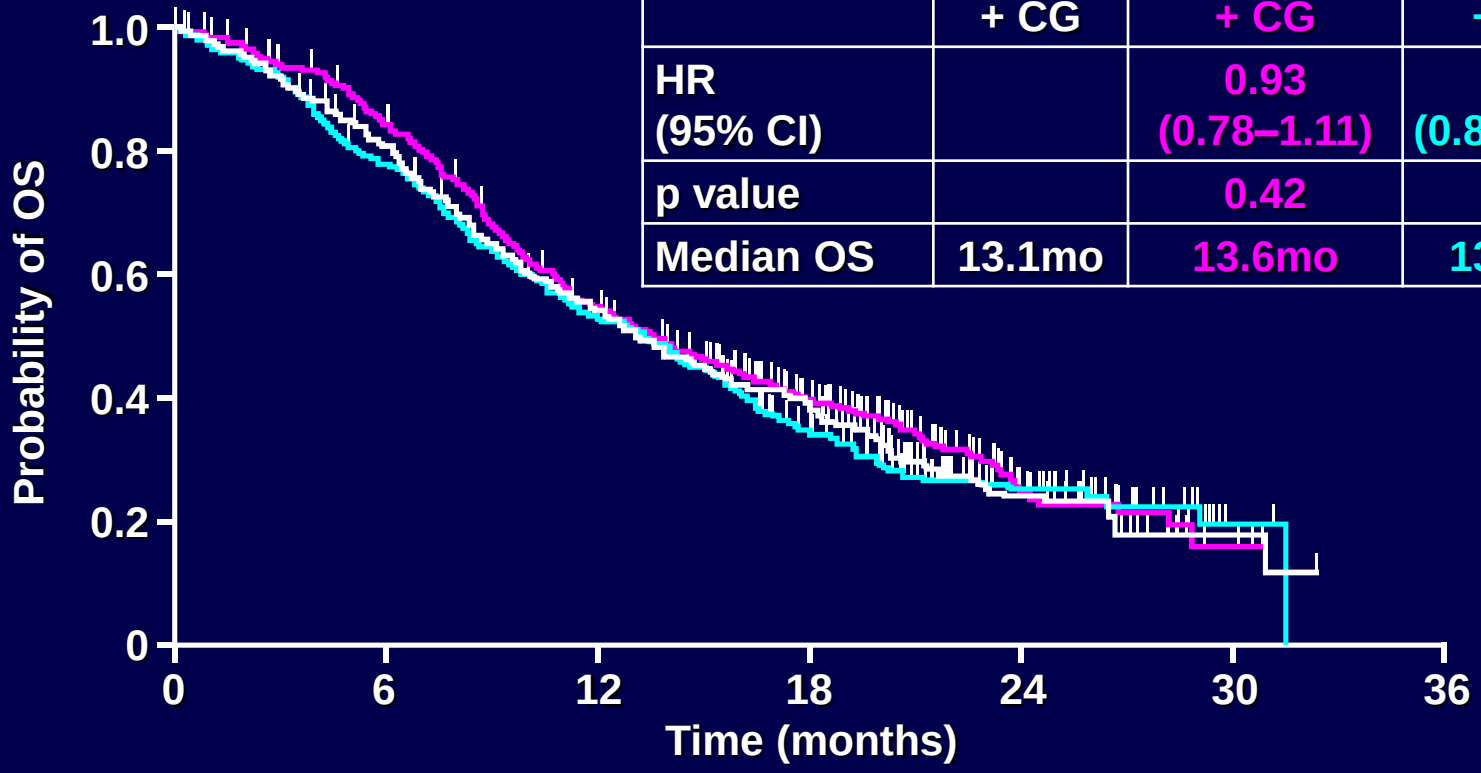


No. at Risk							
Placebo + CG	347	228	122	36	12	3	0
Bev 15 + CG	351	238	148	46	16	5	0

Adapted with permission from Manegold C et al. Presented at: American Society of Clinical Oncology Annual Meeting. June 1-5, 2007. Abstract LBA7514.

AVAiL: Overall Survival

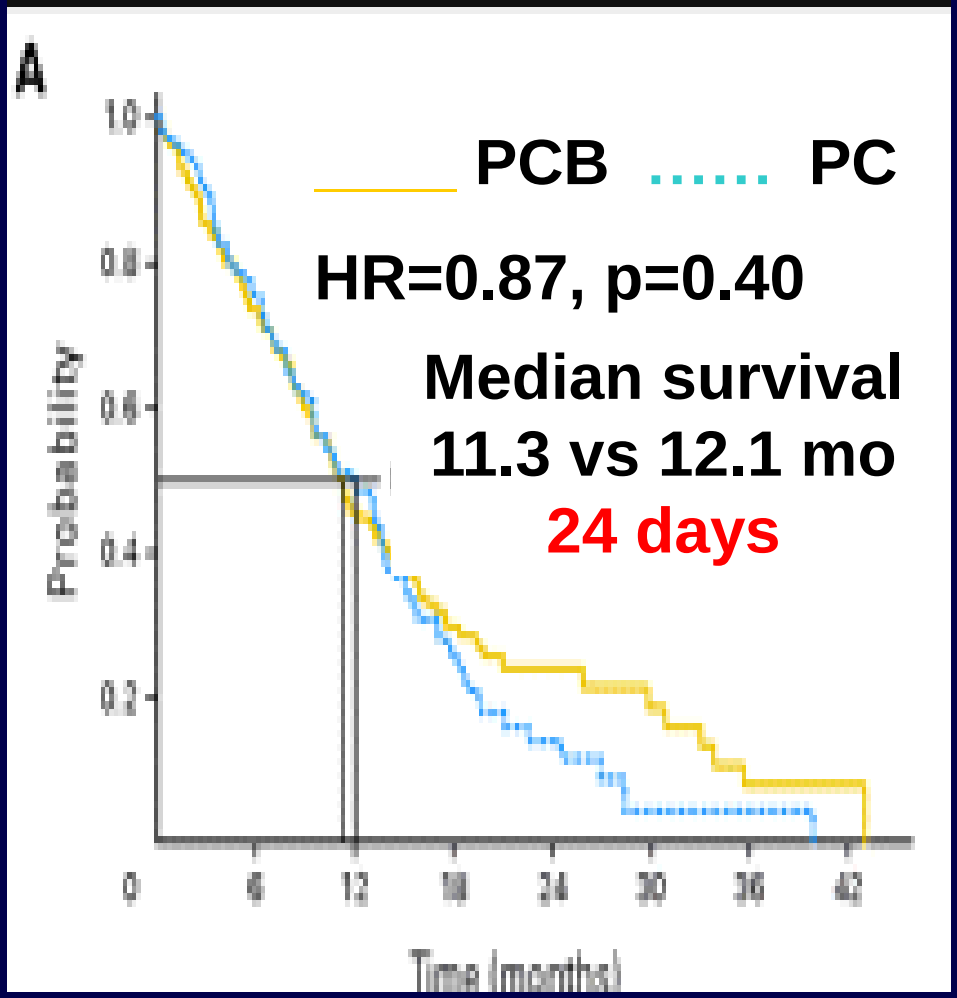
	Placebo + CG	Bev 7.5mg/kg + CG	Bev 15mg/kg + CG
HR (95% CI)		0.93 (0.78–1.11)	1.03 (0.86–1.23)
p value		0.42	0.76
Median OS	13.1mo	13.6mo	13.4mo



No. at risk							
Placebo + CG	347	272	182	100	36	3	0
Bev 7.5mg/kg + CG	345	286	182	107	34	3	0
Bev 15mg/kg + CG	351	264	177	92	33	2	0

***ITT (intent-to-treat) population**

ECOG 4599: Effect of Age

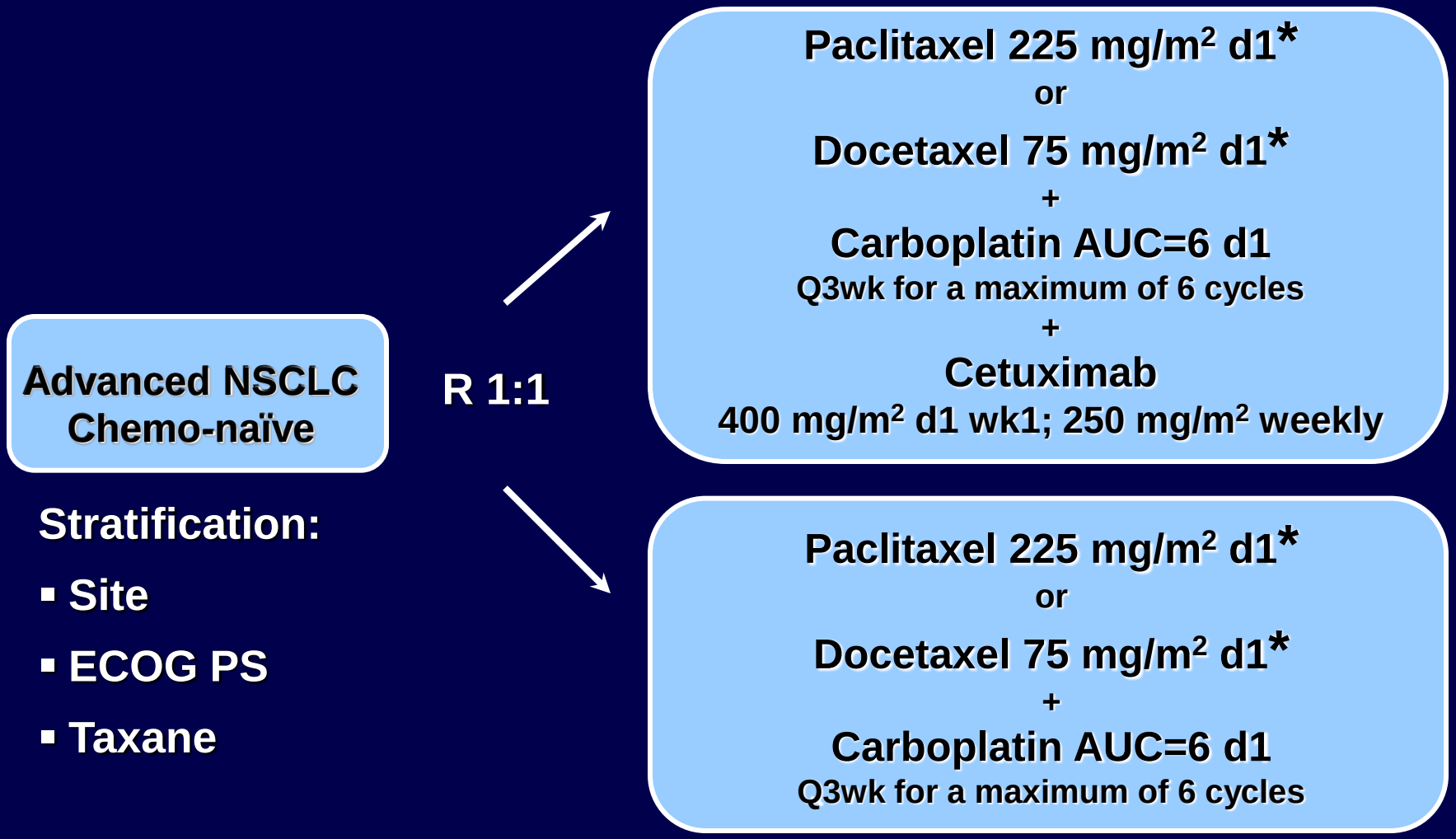


- Febrile neutropenia
  0.9 vs 6.2%, p=0.03
- Hypertension
  0.9 vs 6.2%, p=0.03
- Hemorrhage
  1.7 vs 7.9%, p=0.03
- Proteinuria
  0 vs 7.9%, p=0.002

Median age of lung cancer patients is >70

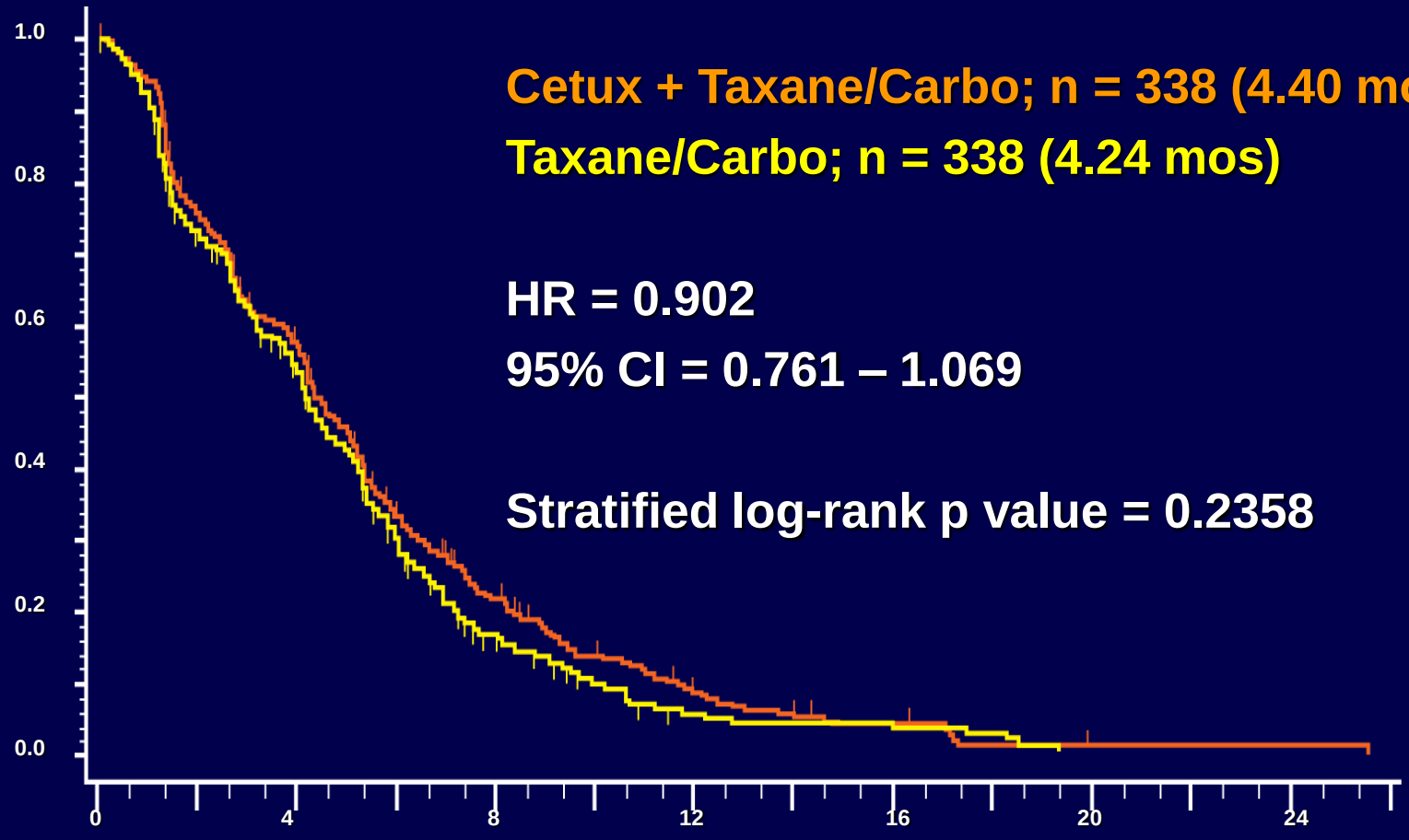
Ramalingham et al. J Clin Oncol 26: 60, 2008

BMS 099 Treatment Schema



* Choice of taxane per individual patient, by investigator

BMS 099 Progression-Free Survival *Per IRRC*



Cetux + Taxane/Carbo; n = 338 (4.40 mos)

Taxane/Carbo; n = 338 (4.24 mos)

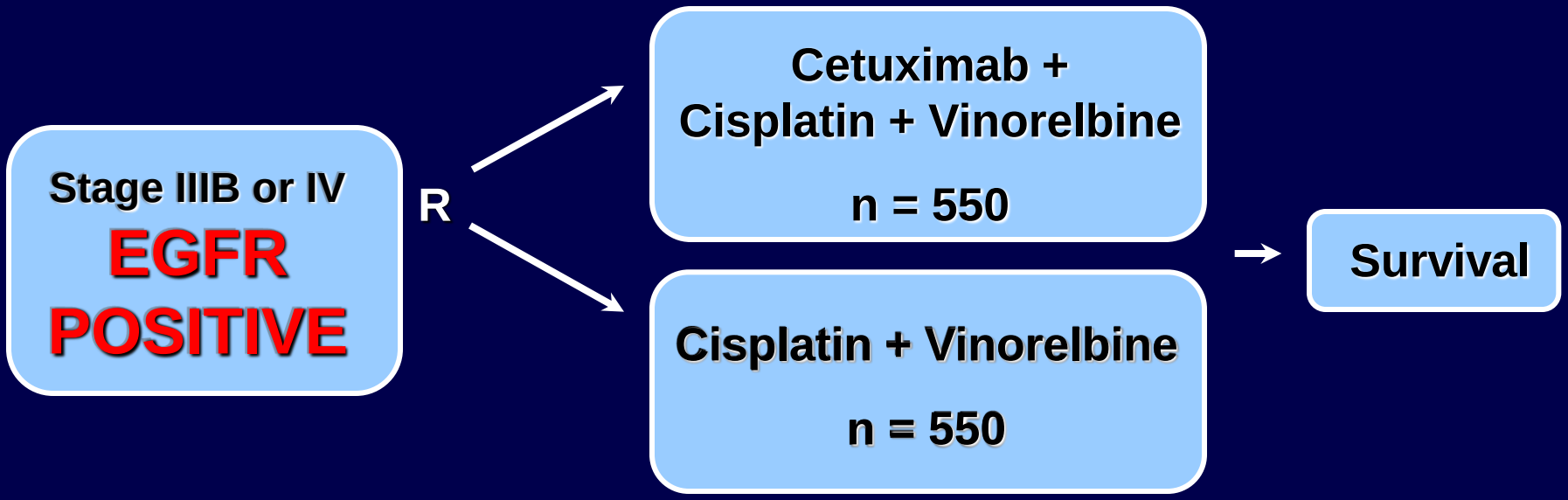
HR = 0.902

95% CI = 0.761 – 1.069

Stratified log-rank p value = 0.2358

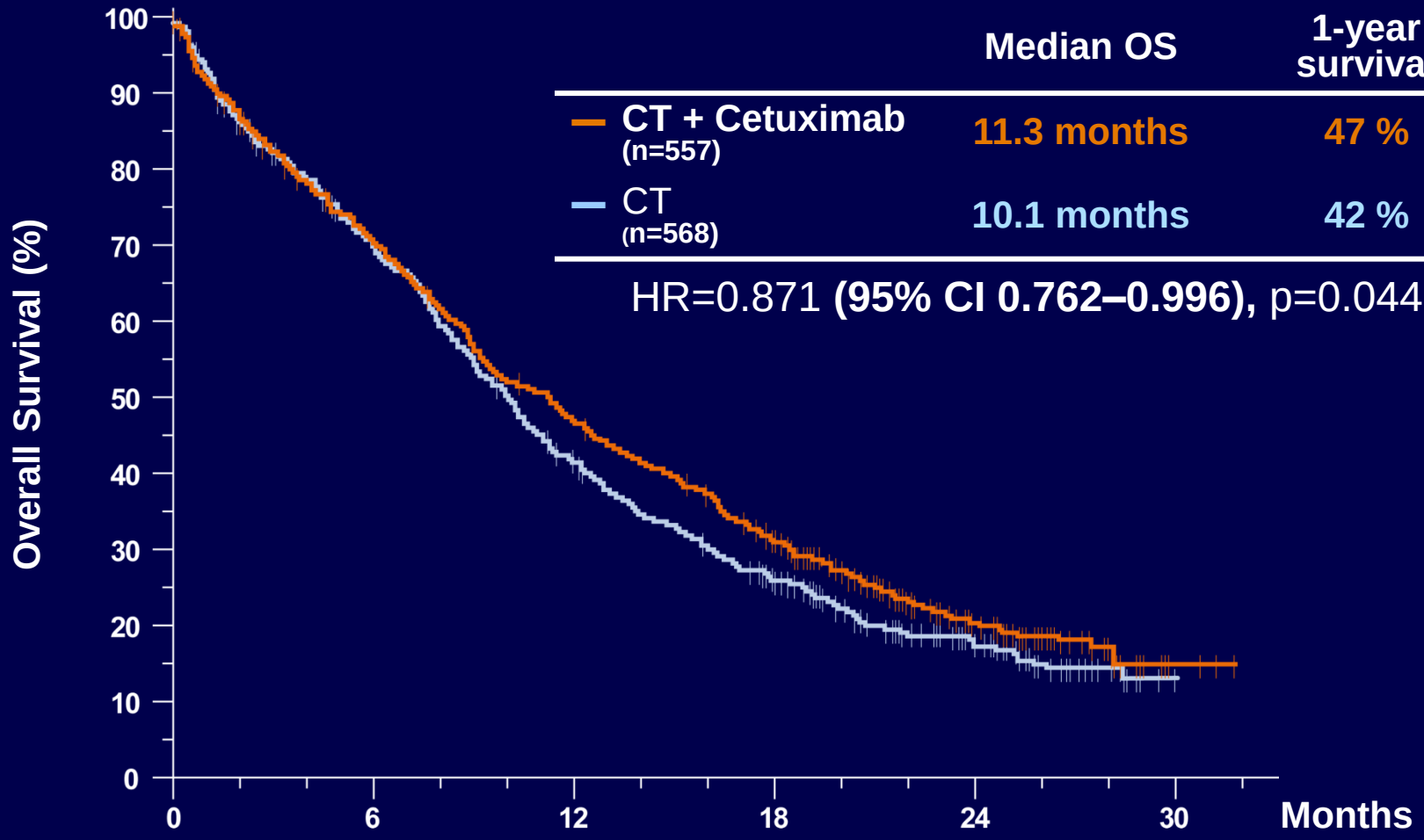
Lynch, J Clin Oncol, 2010

FLEX



- **Eligibility Criteria:** EGFR-expressing, advanced stage NSCLC; No prior CT
- **Primary Endpoint:** Median overall survival (845 events needed)
- **Secondary Endpoints:** Survival rate (1 and 2 y), PFS rate (6 and 12 mo), response rate, safety, QoL
- **Sample Size:** 1100 in 170 centers in EU, Latin America, Asia

FLEX Overall Survival

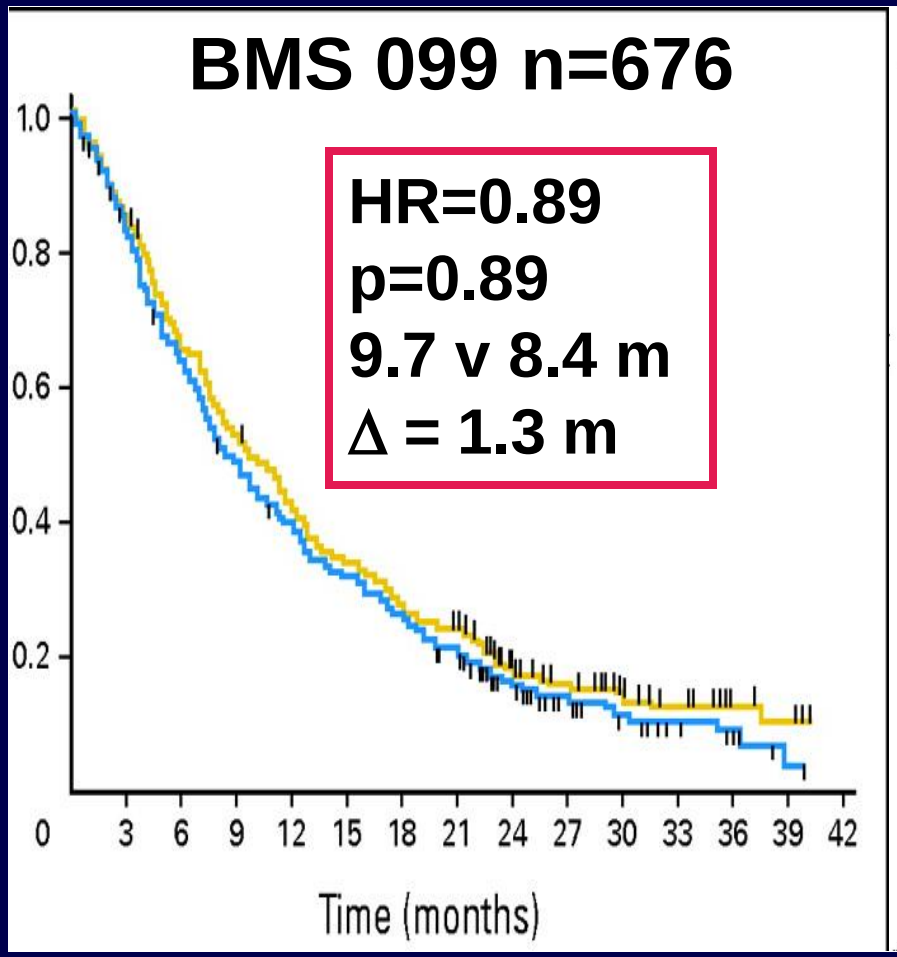


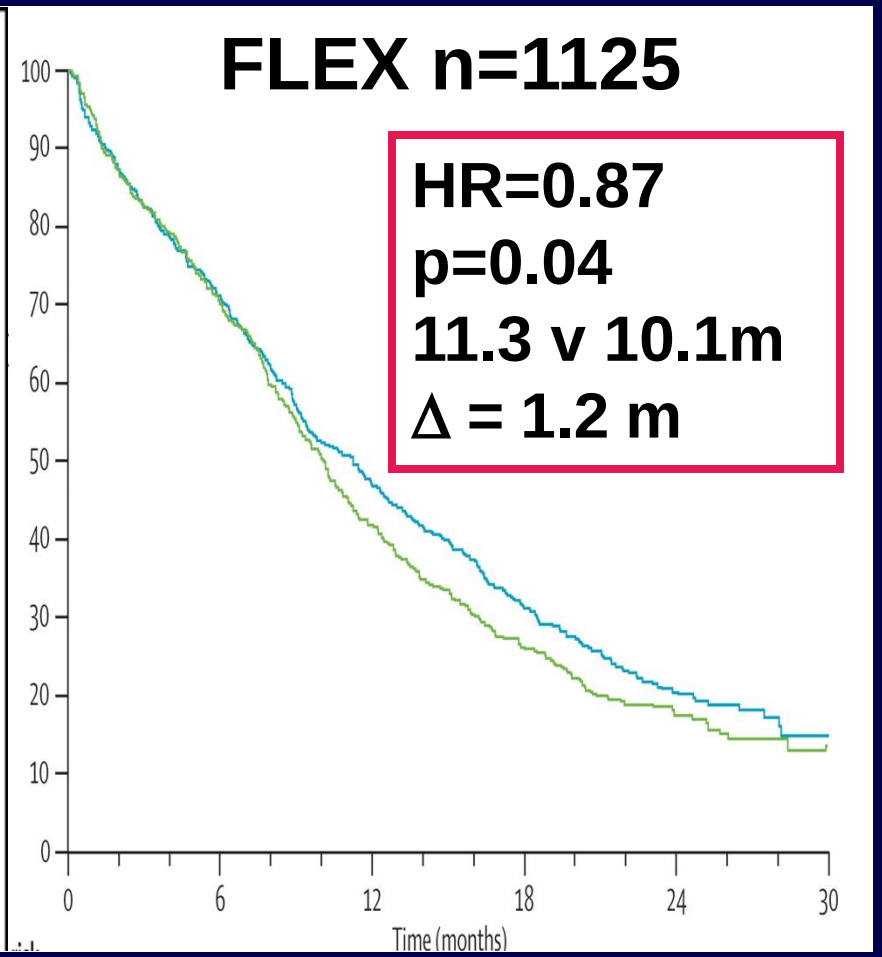
	Median OS	1-year survival
CT + Cetuximab (n=557)	11.3 months	47 %
CT (n=568)	10.1 months	42 %

HR=0.871 **(95% CI 0.762–0.996),** p=0.044

Pirker et al Lancet, 2009

Does Size Matter??





Lynch *et al*
J Clin Oncol 2010

Pirker *et al*
Lancet 2009

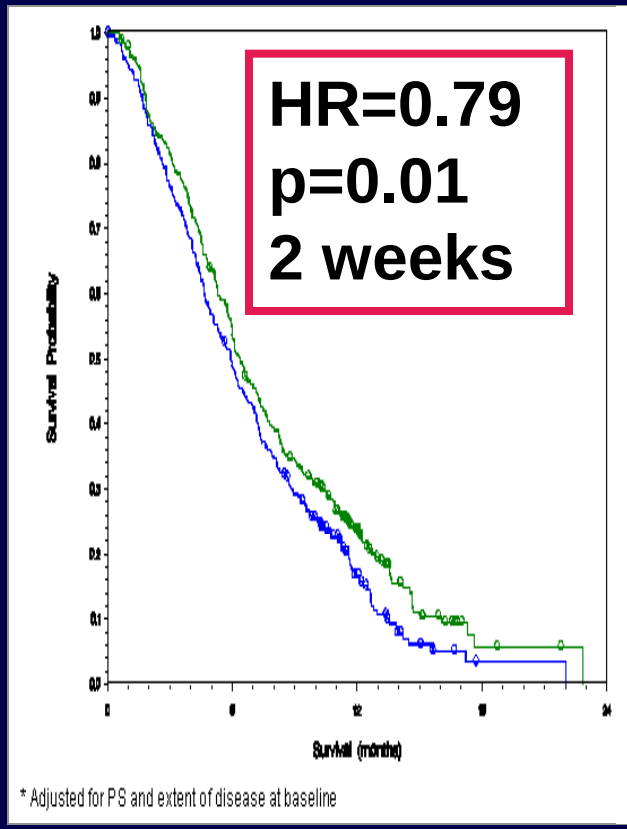
Summary of Cetuximab Trials

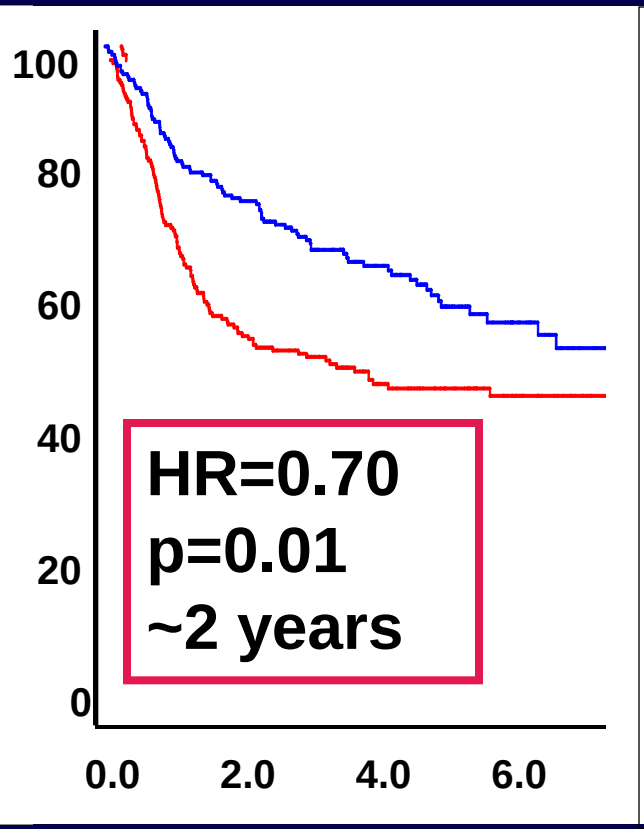
	LUCAS		BMS-099		BMS-100		FLEX*	P
ORR								9%
PFS								.8
0S Median								0.1
1-Year	32%	26%	??	??	50%	36%	47%	24%

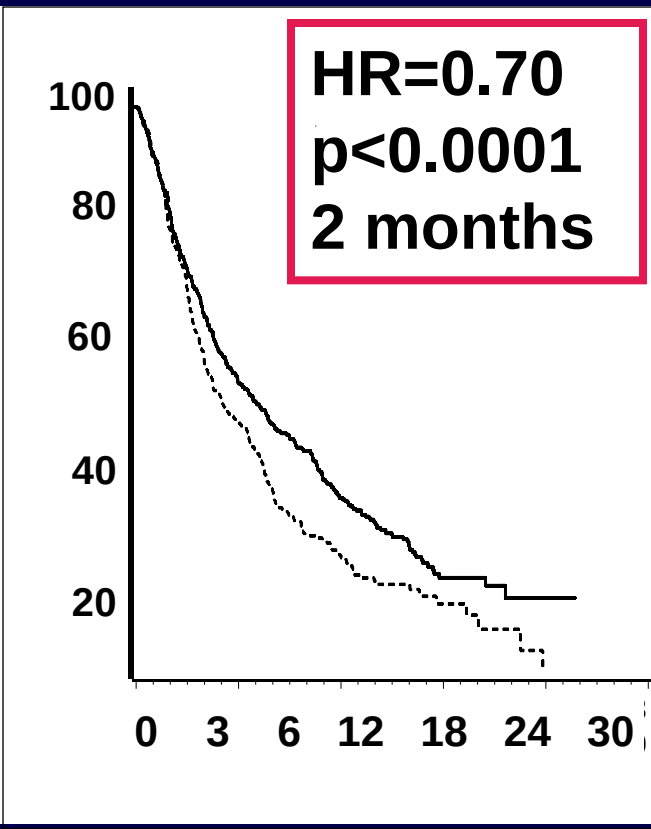
Cetuximab not approved for lung cancer in any jurisdiction

* Required EGFR IHC positivity

Statistically Significant *versus* Clinically Significant or *Relevant*





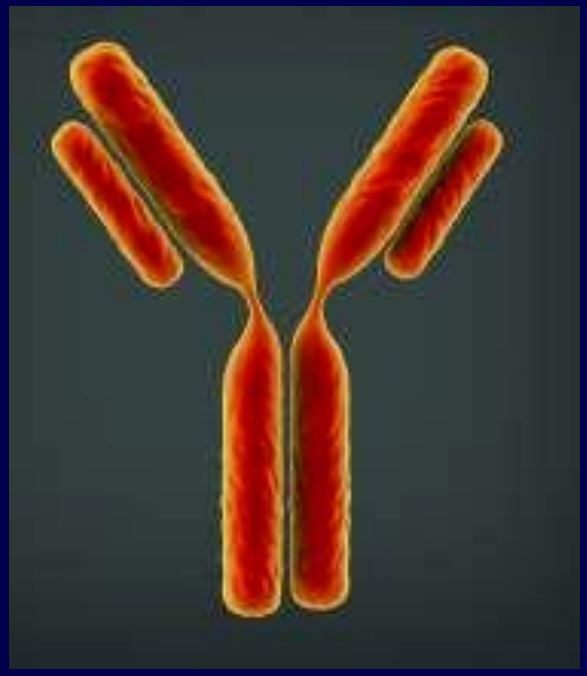


PA.3
Moore *et al*
J Clin Oncol 2007

BR.10
Winton *et al*
NEJM 2005

BR.21
Shepherd *et al*
NEJM 2005

Denosumab



- Fully human monoclonal antibody
  - Lower risk of allergic reactions
  - Stable PK profile
- High affinity for **RANK ligand**
  - $K_d = 3 \times 10^{-12}$ M
- By binding RANKL, RANK receptor activation and downstream signaling are inhibited
- Does not bind to TNFα, TNFß, TRAIL, or CD40L

Bekker PJ, et al. J Bone Miner Res. 2004;19:1059-1066.

Boyle WJ, et al. Nature. 2003;423:337-342.

Amgen, data on file

Study 244: Lung Cancer Subgroup

Key Inclusion

Adults with lung cancer and bone metastases

Key Exclusion

Current or prior intravenous bisphosphonate administration

1:1

Denosumab 120 mg SC and Placebo IV* Q4W (N = 411)

Zoledronic Acid 4 mg IV* and Placebo SC Q4W (N = 400)

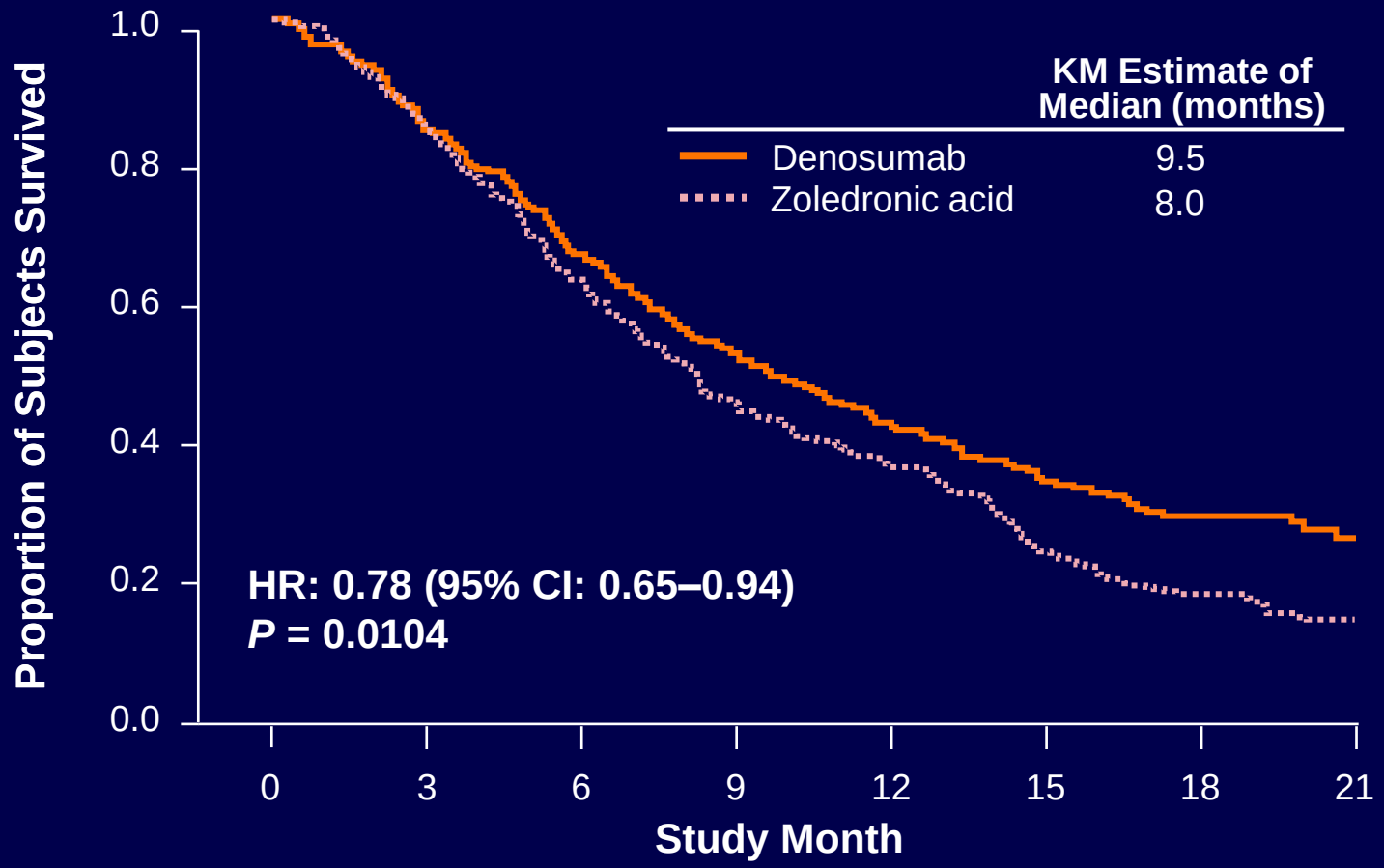
Daily supplementation with Calcium (500 mg) and Vitamin D (400 IU) strongly recommended

Lung Cancer Type, n (%)	Zoledronic Acid	Denosumab	Total
NSCLC	352 (88)	350 (85)	702 (100)
Adenocarcinoma	211 (60)	189 (54)	400 (57)
Squamous Cell	75 (21)	88 (25)	163 (23)
Other	66 (19)	73 (21)	139 (20)
SCLC	48 (12)	61 (15)	109 (100)

*IV product dose adjusted for baseline creatinine clearance and subsequent dose intervals determined by serum creatinine (per Zometa® label)

Scagliotti G, et al. 3rd European Lung Cancer Conference. 2012

Post Hoc Analysis: OS - NSCLC



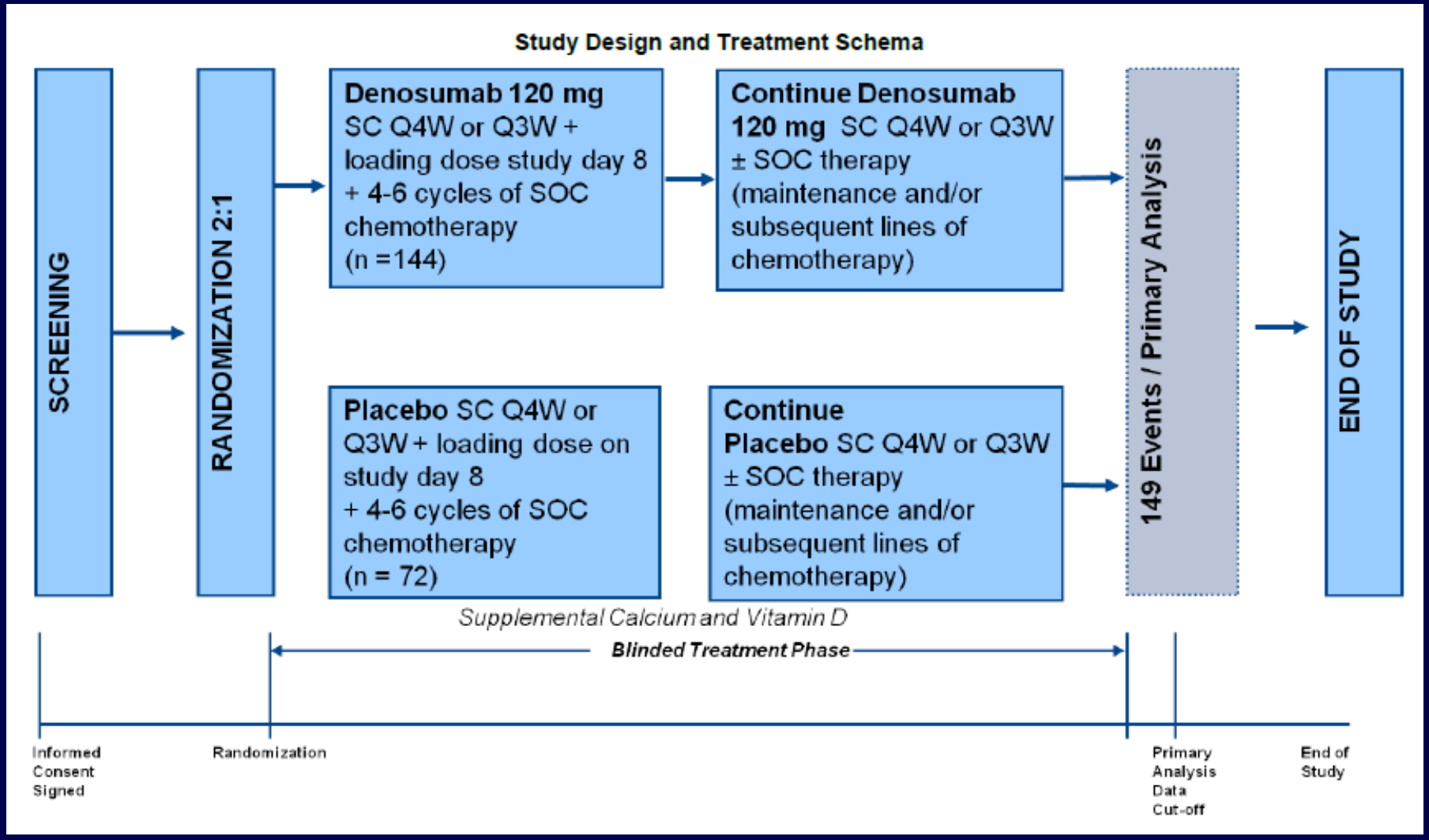
Subjects at Risk:

Zoledronic acid	352	275	185	123	91	40	23	12
Denosumab 350	278	203	148	110	66	39	24	

Scagliotti G, et al. 3rd European Lung Cancer Conference. April 2012; Abstract and Oral Presentation

.

Denosumab 20120249 Study Schema



EGFR Inhibitors or Chemotherapy as First-Line Monotherapy in Unselected Patients

TORCH Trial

Patient population
- NSCLC
- Age >18 and <70
- PS 0-1
- Stage IIIb-IV

Phase II analysis of activity: *after XX patients have been assigned Erlotinib*

900 patients planned as phase III sample size: *669 events required to demonstrate non-inferiority in survival*

RANDOM

Erlotinib → **Chemotherapy**

Chemotherapy → **Erlotinib**

First-line treatment

Second-line treatment (after PD)

Stratification
- histology
- smoking status
- gender
- centre
- PS
- stage

Chemotherapy
- Cisplatin, 80 mg/m^2, day 1
- Gemcitabine, 1200 mg/m^2, day 1 and 8
- every 3 weeks, for 6 cycles

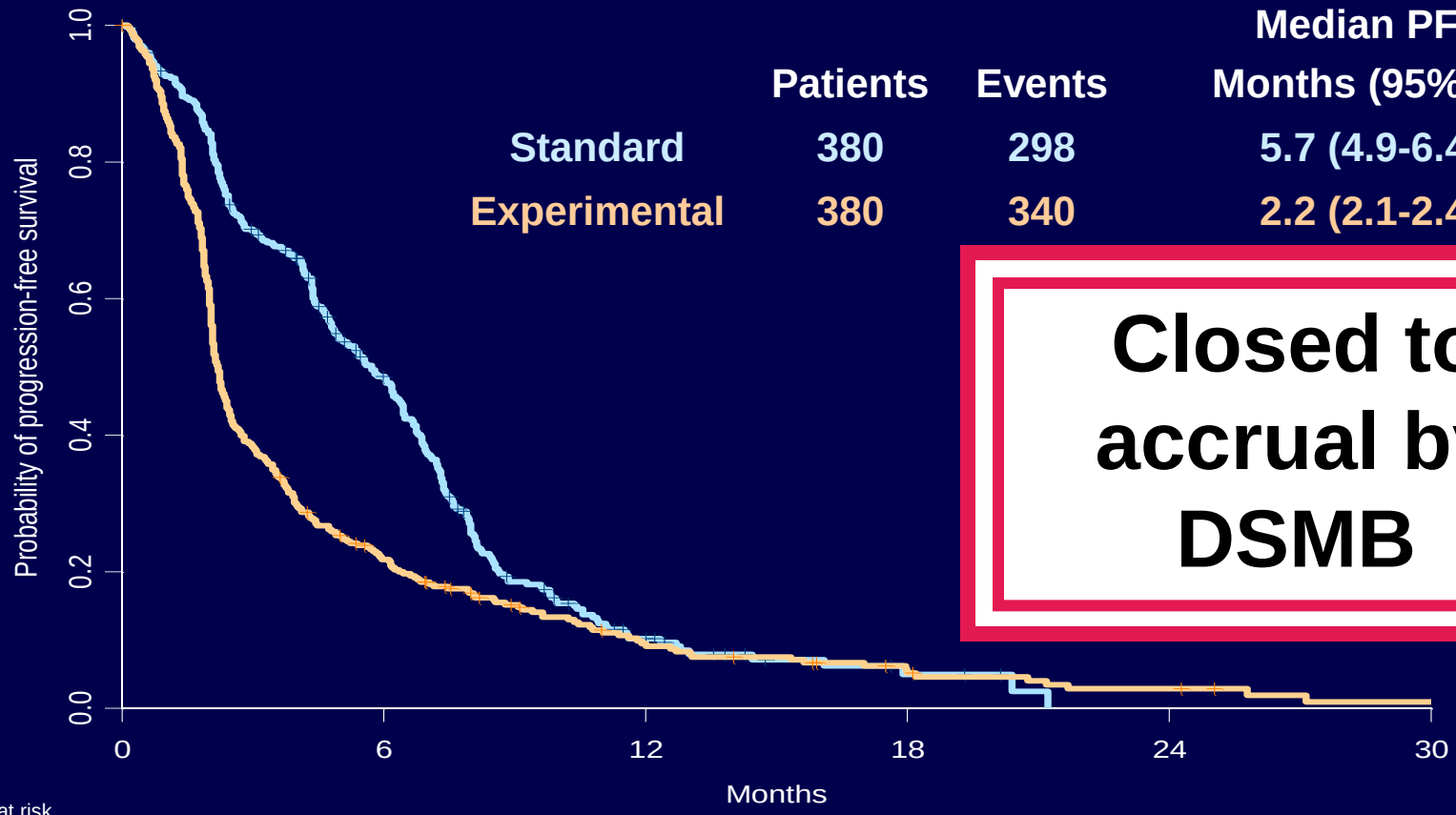
Erlotinib
- 150 mg/die p.o.
- until progression

Response

	Standard arm (n=380)		Experimental arm (n=380)	
Objective response	**121 (32%)**		**70 (18%)**	
	Cis+Gem	**Erlotinib**	**Erlotinib**	**Cis+Gem**
CR 1st line	**3 (1%)**		**1 (<1%)**	
PR 1st line	**103 (27%)**		**36 (9%)**	
CR 2nd line		**1 (<1%)**		**2 (1%)**
PR 2nd line		**23 (6%)**		**33 (9%)**
No response	**259 (68%)**		**310 (82%)**	
SD	**124 (33%)**		**110 (29%)**	
PD	**64 (17%)**		**101 (27%)**	
NE or missing	**71 (19%)**		**99 (26%)**	

*Intention to treat analysis: total response rate (Objective response *vs.* no response) p= 0.0001

Progression-free Survival
(1st line treatment)



	Patients	Events	Median PFS Months (95% CI)
Standard	380	298	5.7 (4.9-6.4)
Experimental	380	340	2.2 (2.1-2.4)

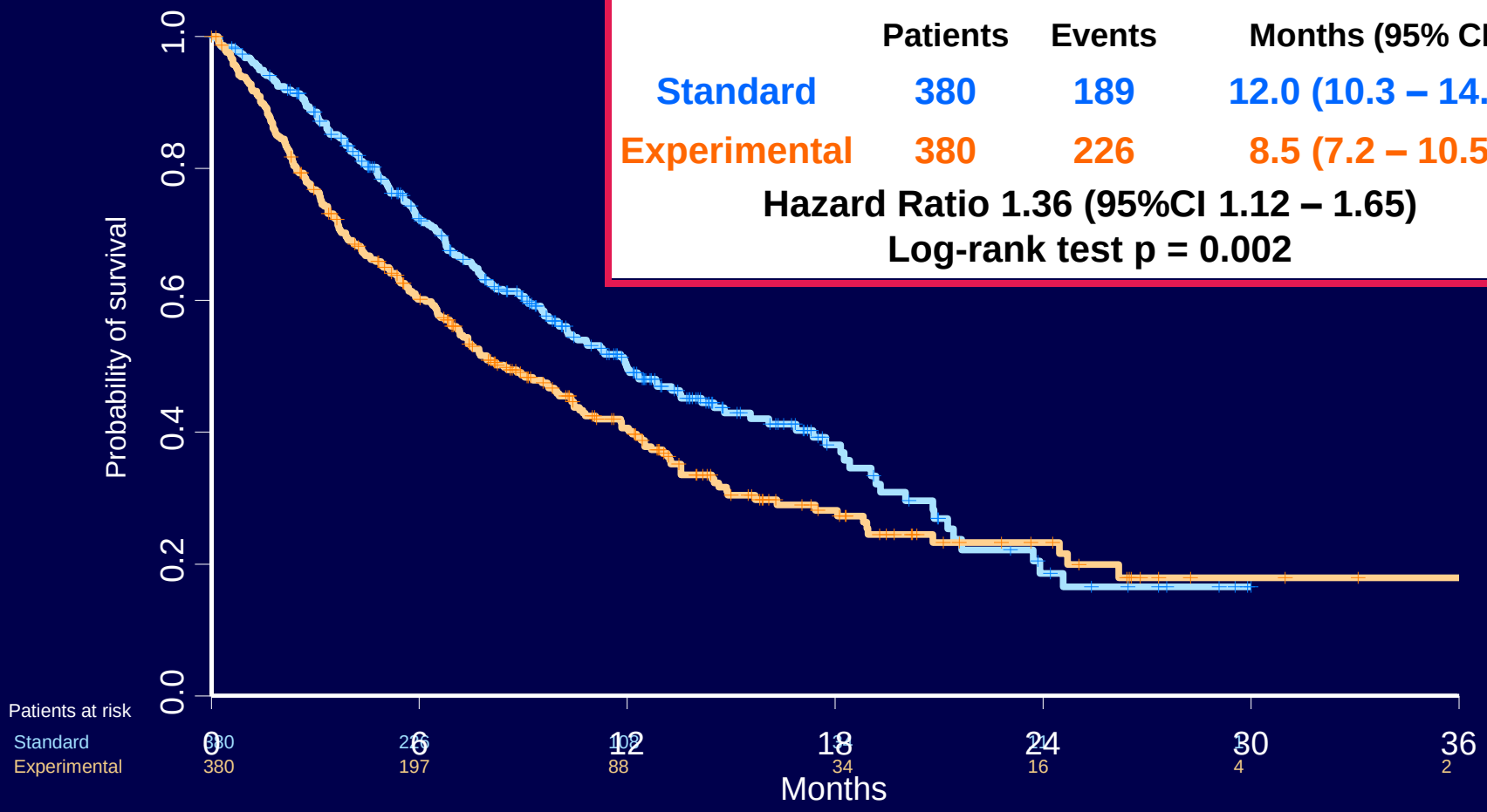
Closed to accrual by DSMB

Gridelli et al. Proc ASCO, 2010

Updated Overall Survival
(May 2010, median follow-up 12.9 months)

	Patients	Events	Median OS Months (95% CI)
Standard	380	189	12.0 (10.3 – 14.8)
Experimental	380	226	8.5 (7.2 – 10.5)

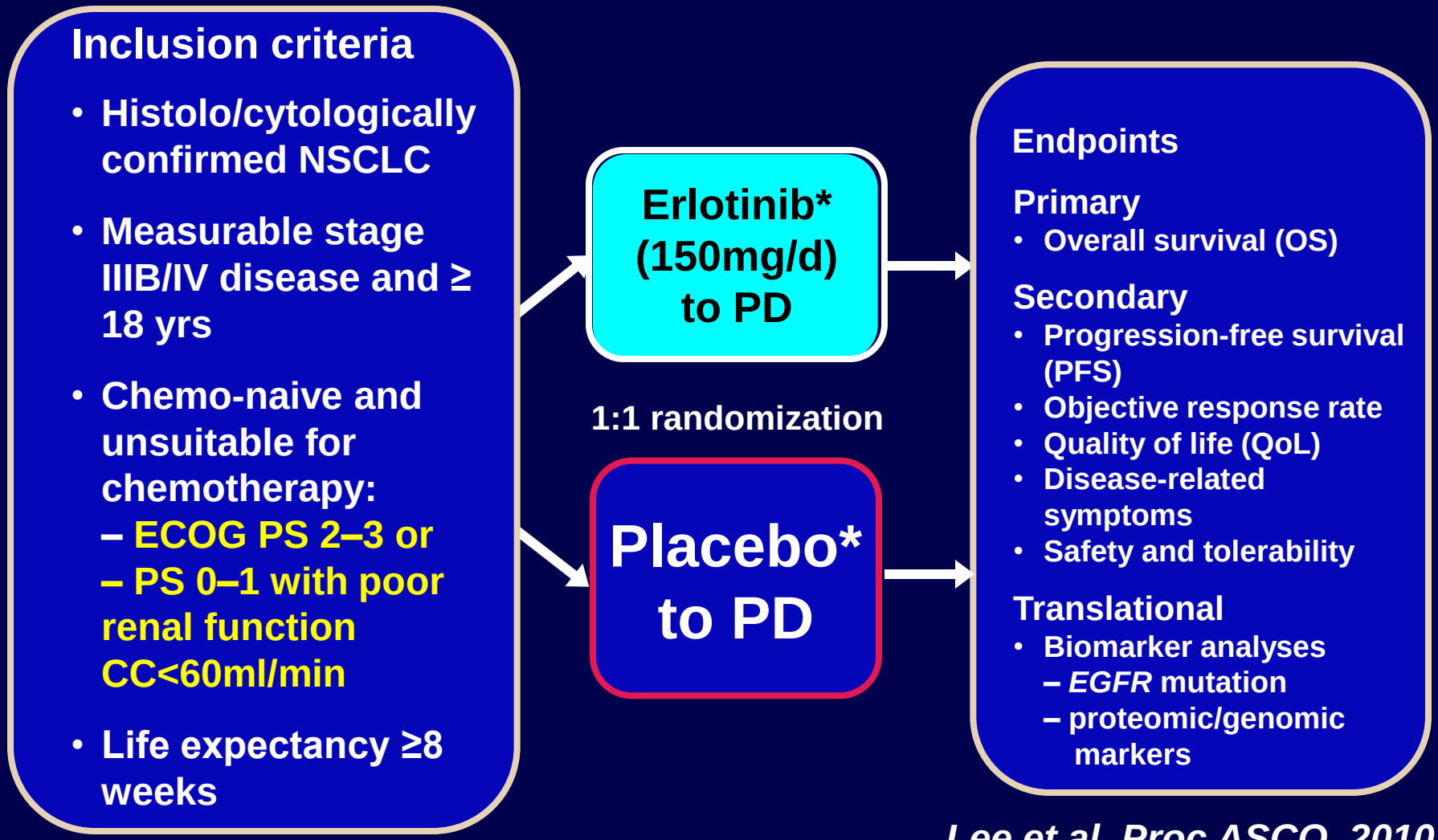
Hazard Ratio 1.36 (95%CI 1.12 – 1.65)
Log-rank test p = 0.002



First-Line Treatment with Single-Agent EGFR Inhibitors *or* Chemotherapy

Clinical Selection
The “Kinder, Gentler” studies

TOPICAL Study Design



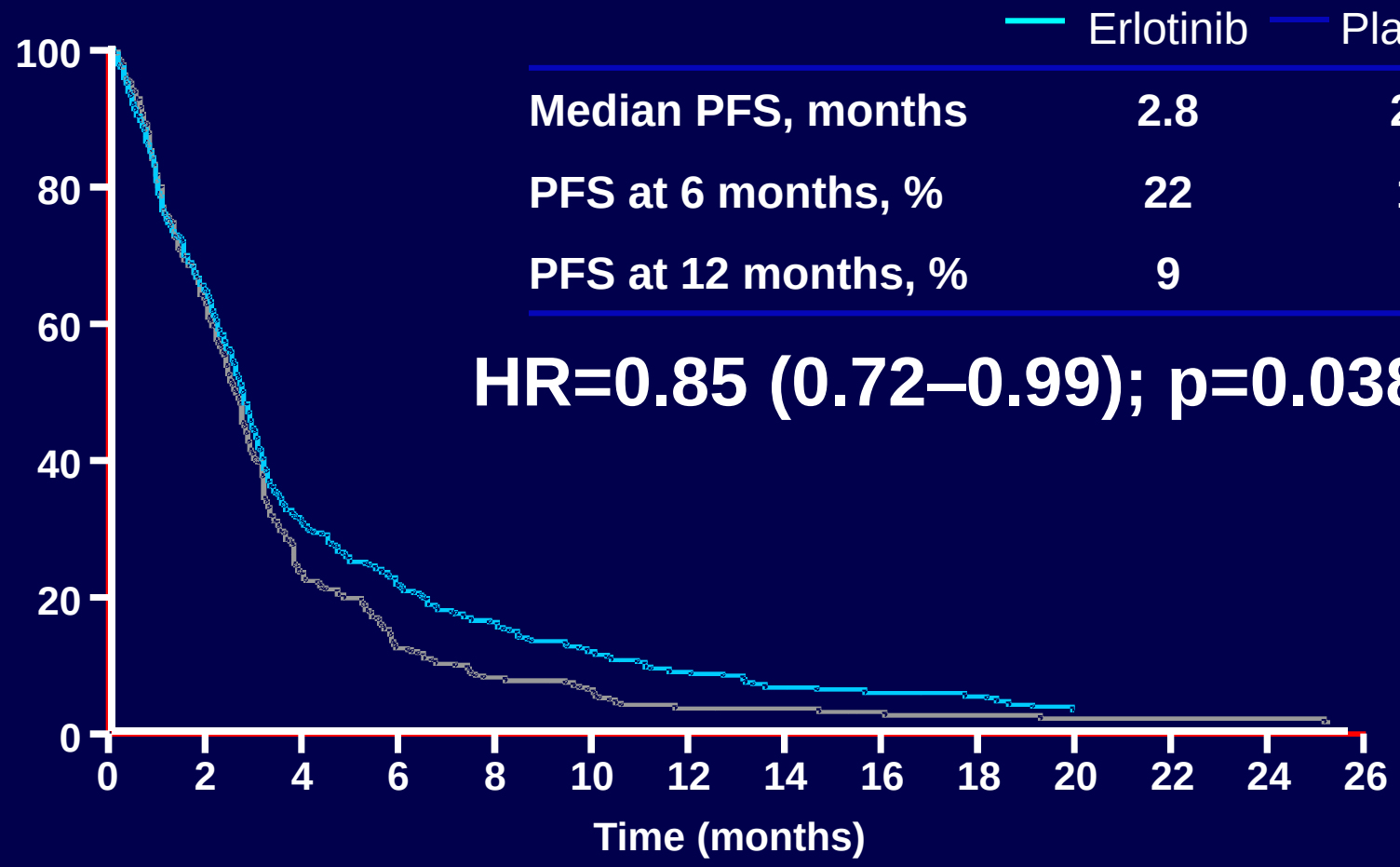
Lee et al, Proc ASCO, 2010

Baseline Characteristics

	Erlotinib (n=350)	Placebo (n=320)
Age, median (range), years	77.4 (42–91)	77.2 (45–91)
Male / female, %	61 / 39	61 / 39
Stage IIIB / IV, %	36 / 64	33 / 67
ECOG PS 0–1 / 2 / 3, %	16 / 55 / 29	16 / 56 / 28
Adenocarcinoma / squamous / large cell / other, %	38 / 38 / 4 / 20	38 / 40 / 5 / 17
Caucasian / Asian / other, %	96 / 2 / 2	98 / 1 / 1
Current / ex- / never smoker, %	36 / 59 / 5	37 / 57 / 6
Pack-years (current/ex-smoker), median (range)	40 (1–220)	38 (1–130)
Median time since cessation (ex-smoker), years	18	17

Lee et al, Proc ASCO, 2010

Progression-free Survival

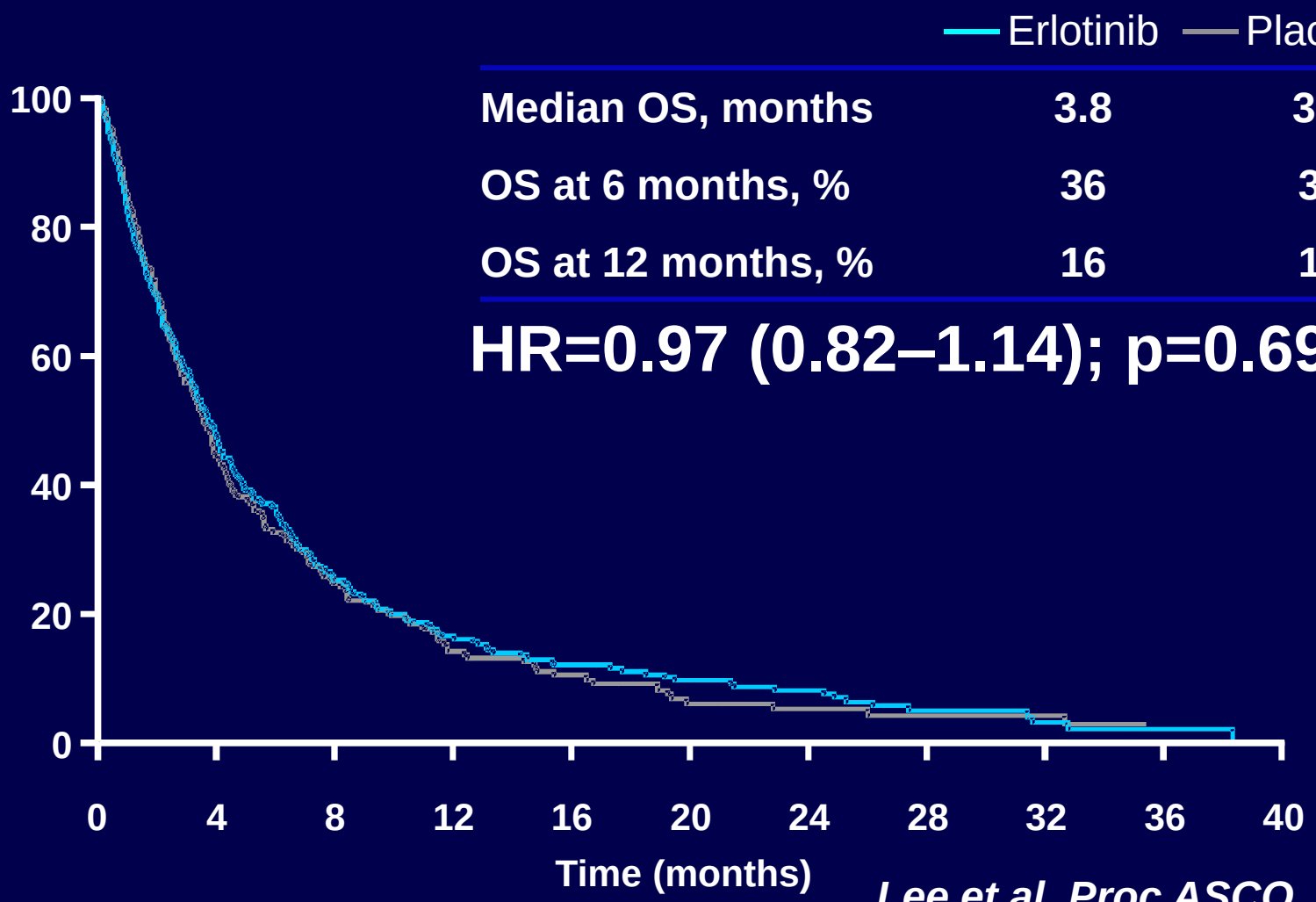


	Erlotinib	Placebo
Median PFS, months	2.8	2.7
PFS at 6 months, %	22	13
PFS at 12 months, %	9	4

HR=0.85 (0.72–0.99); p=0.038

Lee et al, Proc ASCO, 2010

Overall Survival

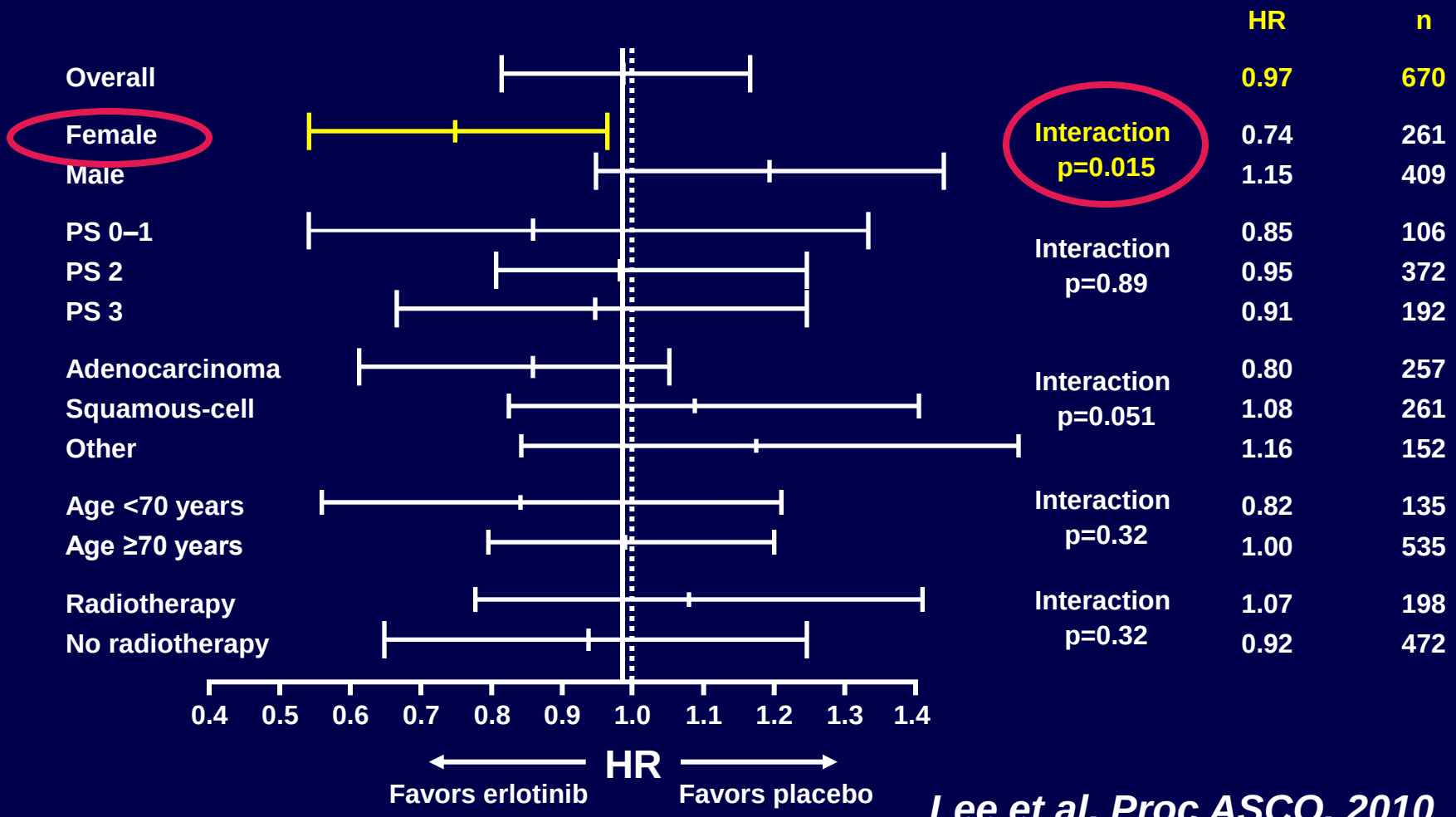


	Erlotinib	Placebo
Median OS, months	3.8	3.6
OS at 6 months, %	36	33
OS at 12 months, %	16	14

HR=0.97 (0.82–1.14); p=0.69

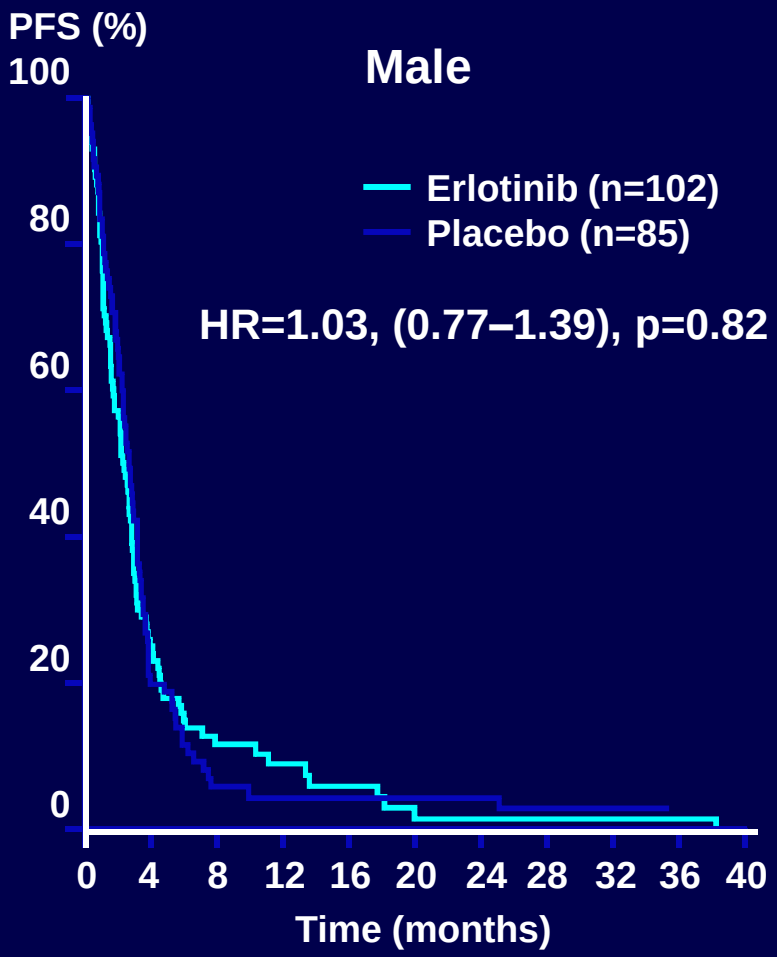
Lee et al, Proc ASCO, 2010

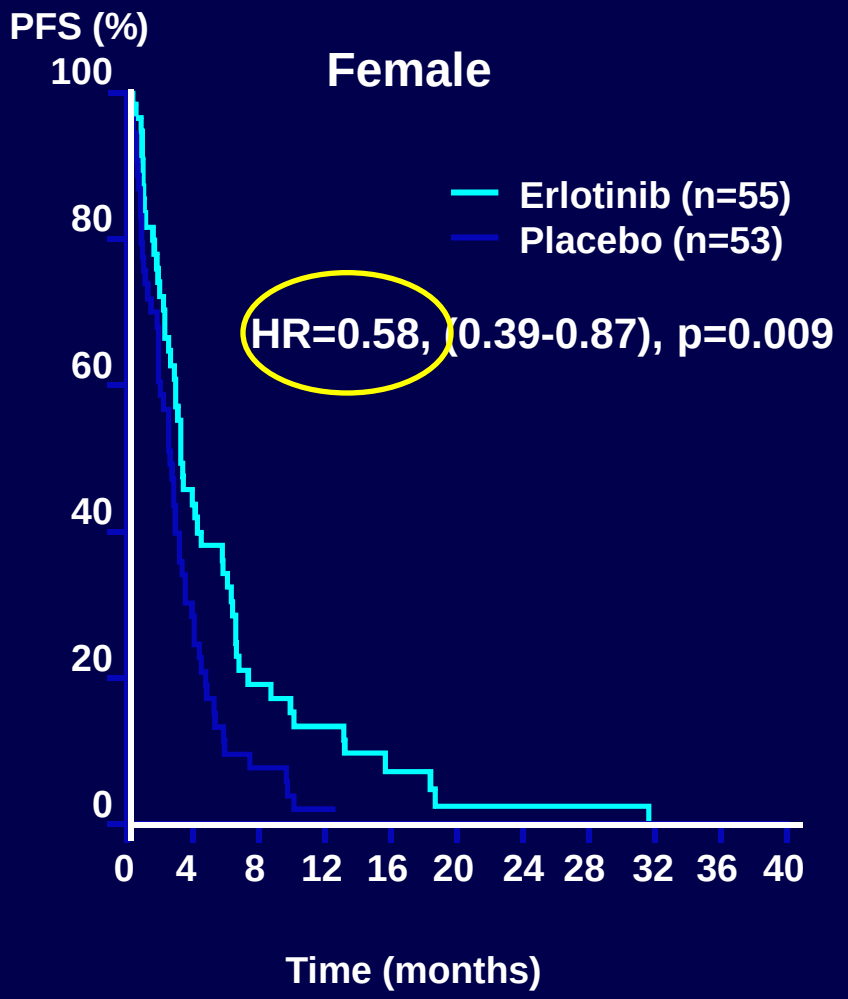
OS: Preplanned Subgroups



Lee et al, Proc ASCO, 2010

PFS: Wild-type *EGFR* by Sex





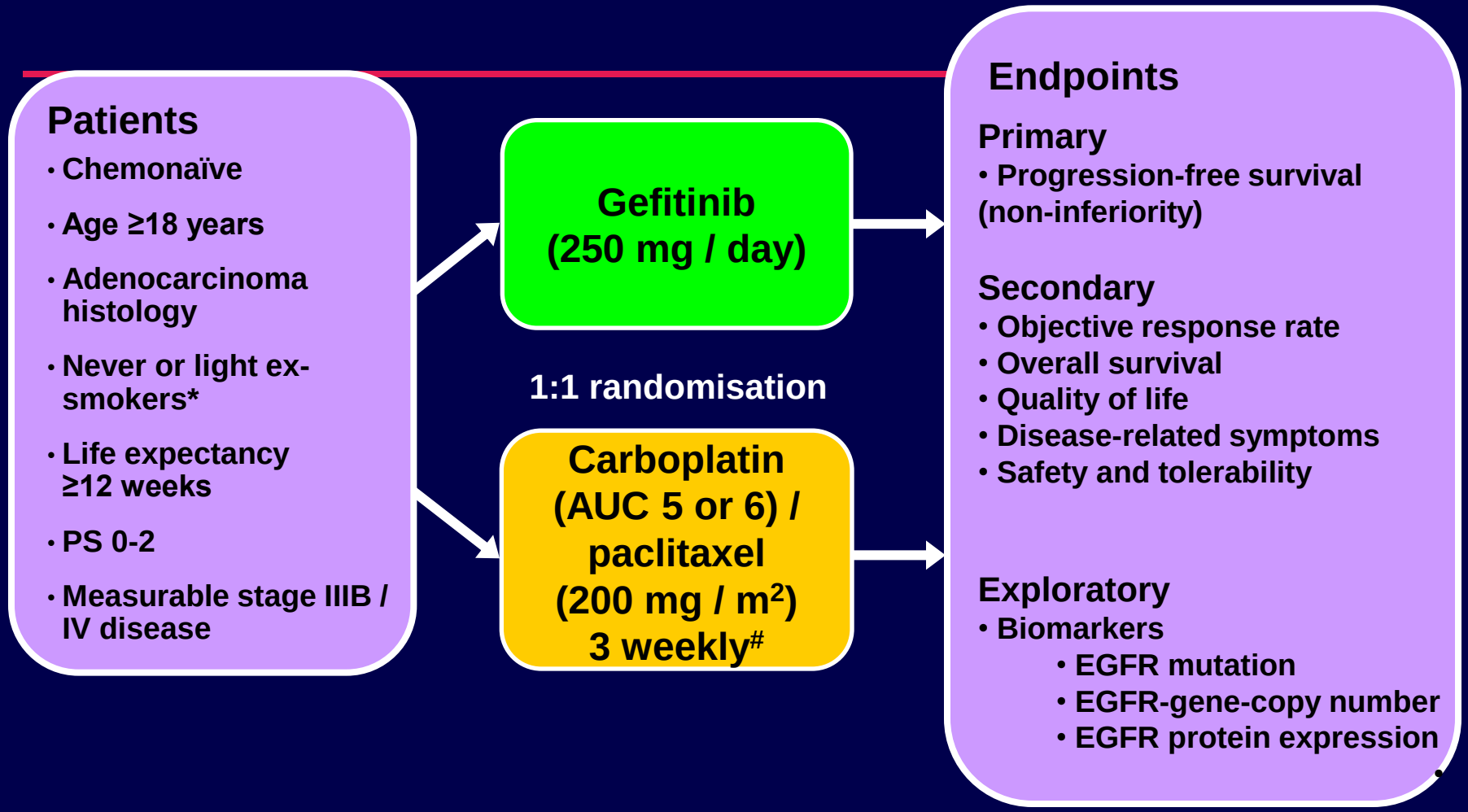
Lee et al, Proc ASCO, 2010

First-Line Treatment with Single-Agent EGFR Inhibitors in *Selected* Patient Populations

Clinically Selected Patients

IPASS
First Signal

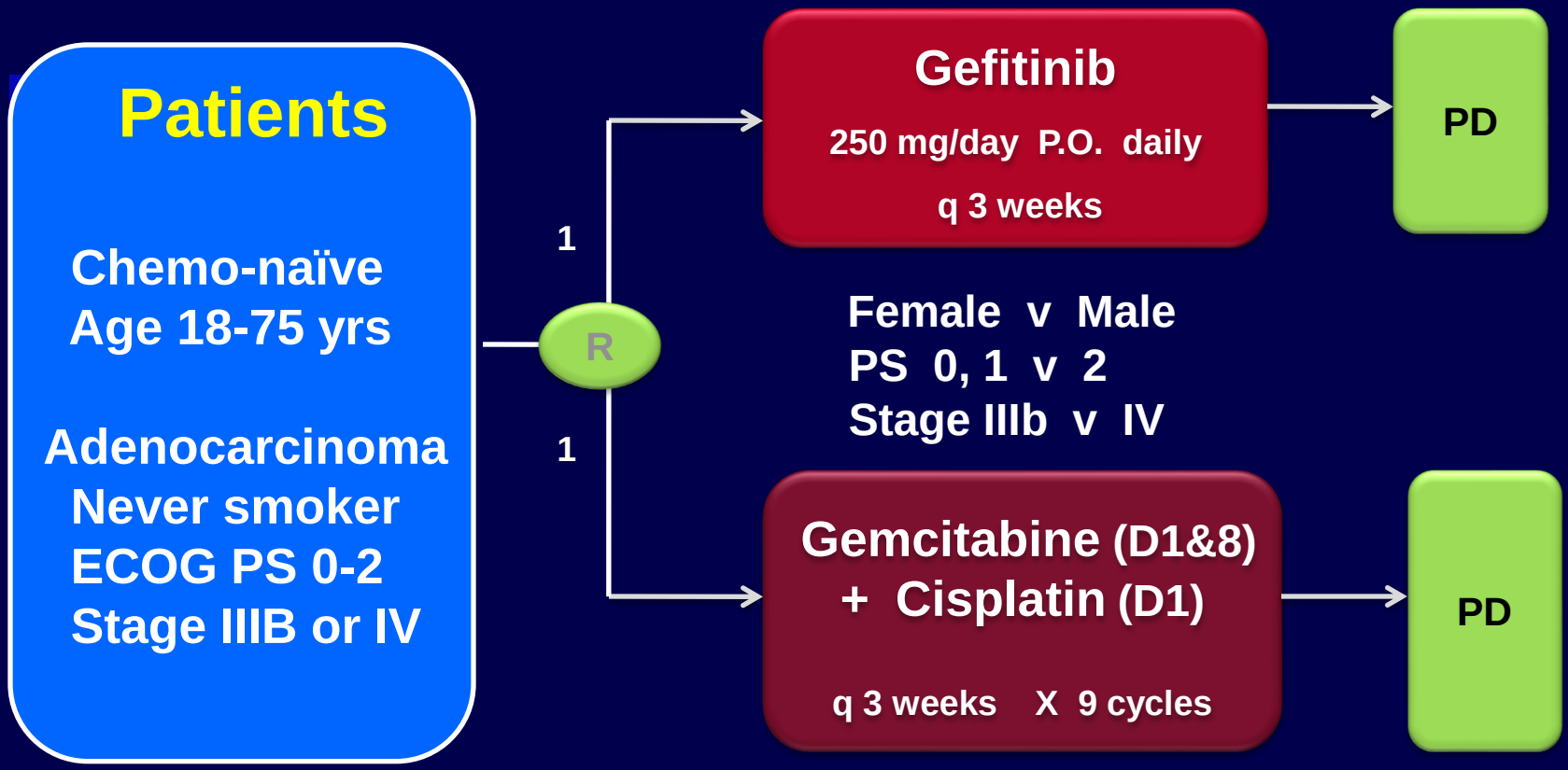
IPASS Study Design



*Never smokers, <100 cigarettes in lifetime; light ex-smokers, stopped ≥15 years ago and smoked ≤10 pack years; #limited to a maximum of 6 cycles
Carboplatin / paclitaxel was offered to gefitinib patients upon progression
PS, performance status; EGFR, epidermal growth factor receptor

Mok et al ESMO LBA 2, 2008

First-SIGNAL: Study Design

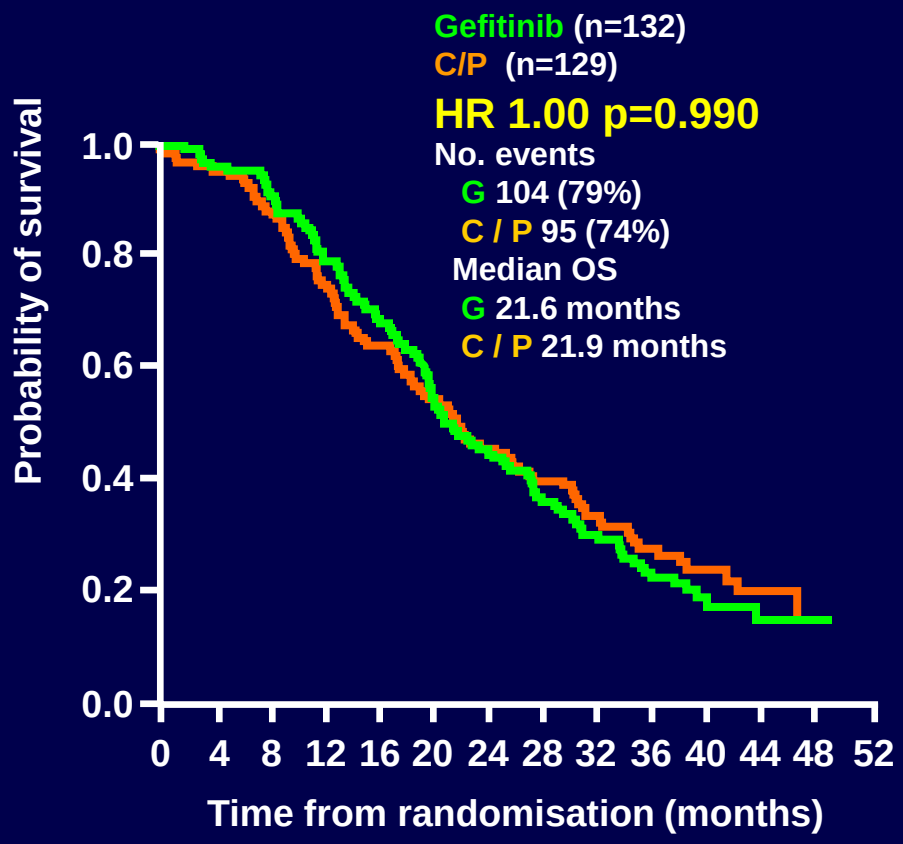


D= day; q3wks = every 3 weeks; PD = progressive disease
Gemcitabine 1,250mg/m^2 (D1&8) ; Cisplatin 75mg/m^2 (D1)

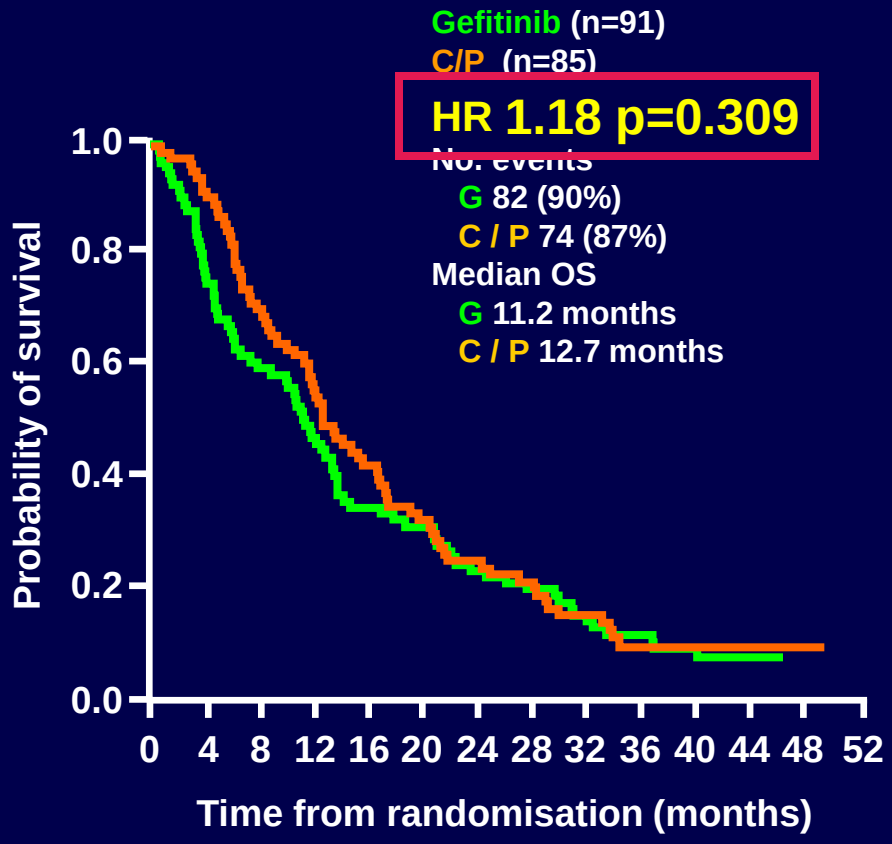
Lee et al. Proc IASLC, 2009

IPASS: 2010 OS by *EGFR* mutation status

EGFR mutation +



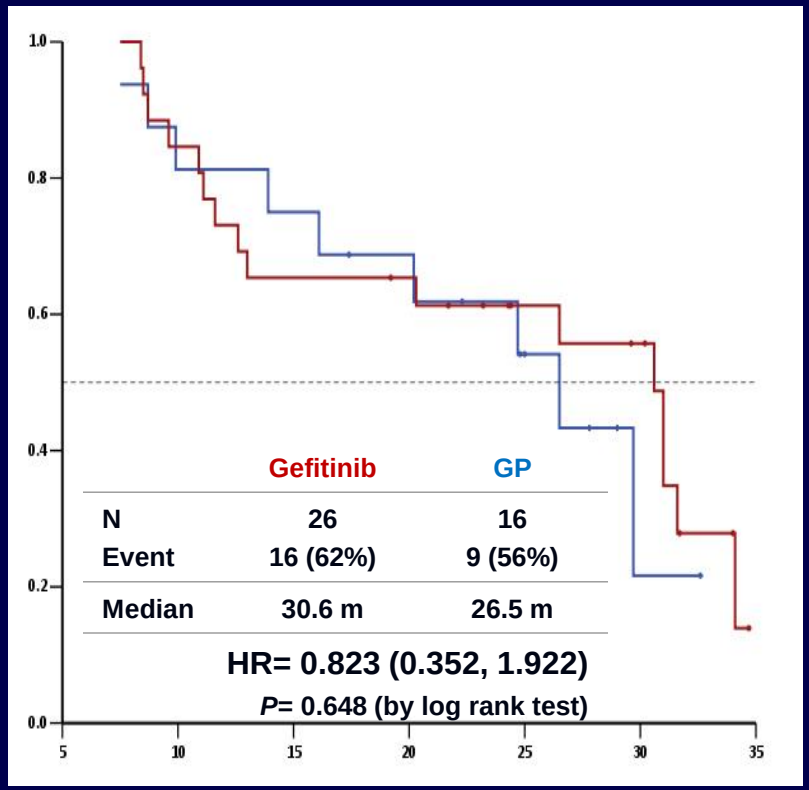
EGFR mutation -



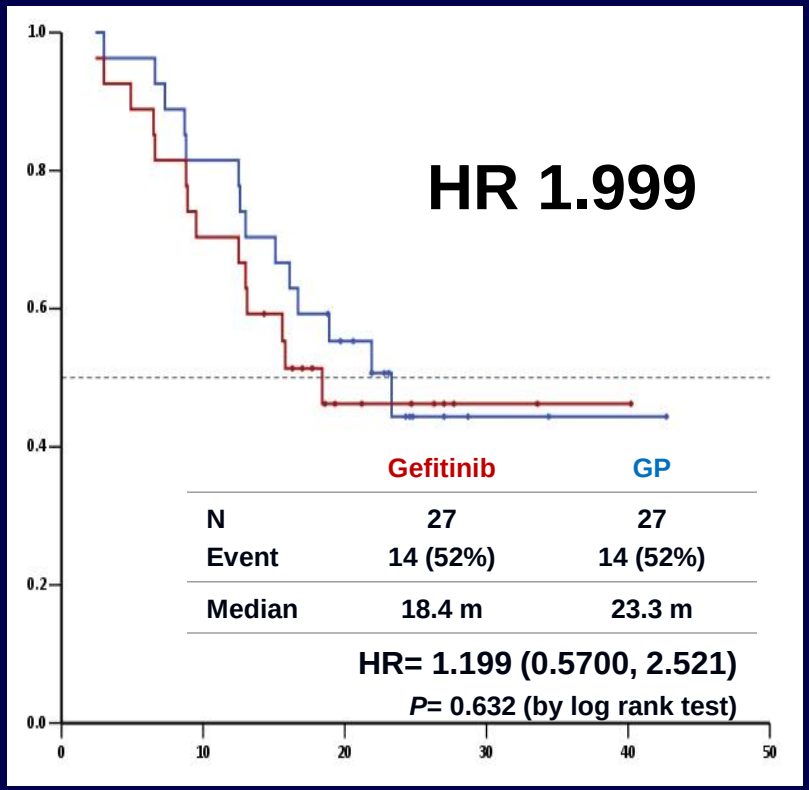
Yang CH et al. ESMO 2010

First-SIGNAL Overall Survival by *EGFR* Mutation Status

EGFR mutation Positive
Gefitinib vs. GP



EGFR mutation Negative
Gefitinib vs. GP



Lee et al. Proc IASLC WCLC, 2009

My Interpretation

- For first-line treatment, I do *NOT* think we should be selecting patients for EGFR therapy based on clinical characteristics
  - OS (immature) IPASS HR 1.2
  - OS First-SIGNAL HR 1.2
- We should NOT be willing to accept a 20% *increase in the risk of death*
- This may not be the case in second (including maintenance) or third-line therapy where patients with both *EGFR* WT and mutant tumors appear to benefit from EGFR TKI therapy

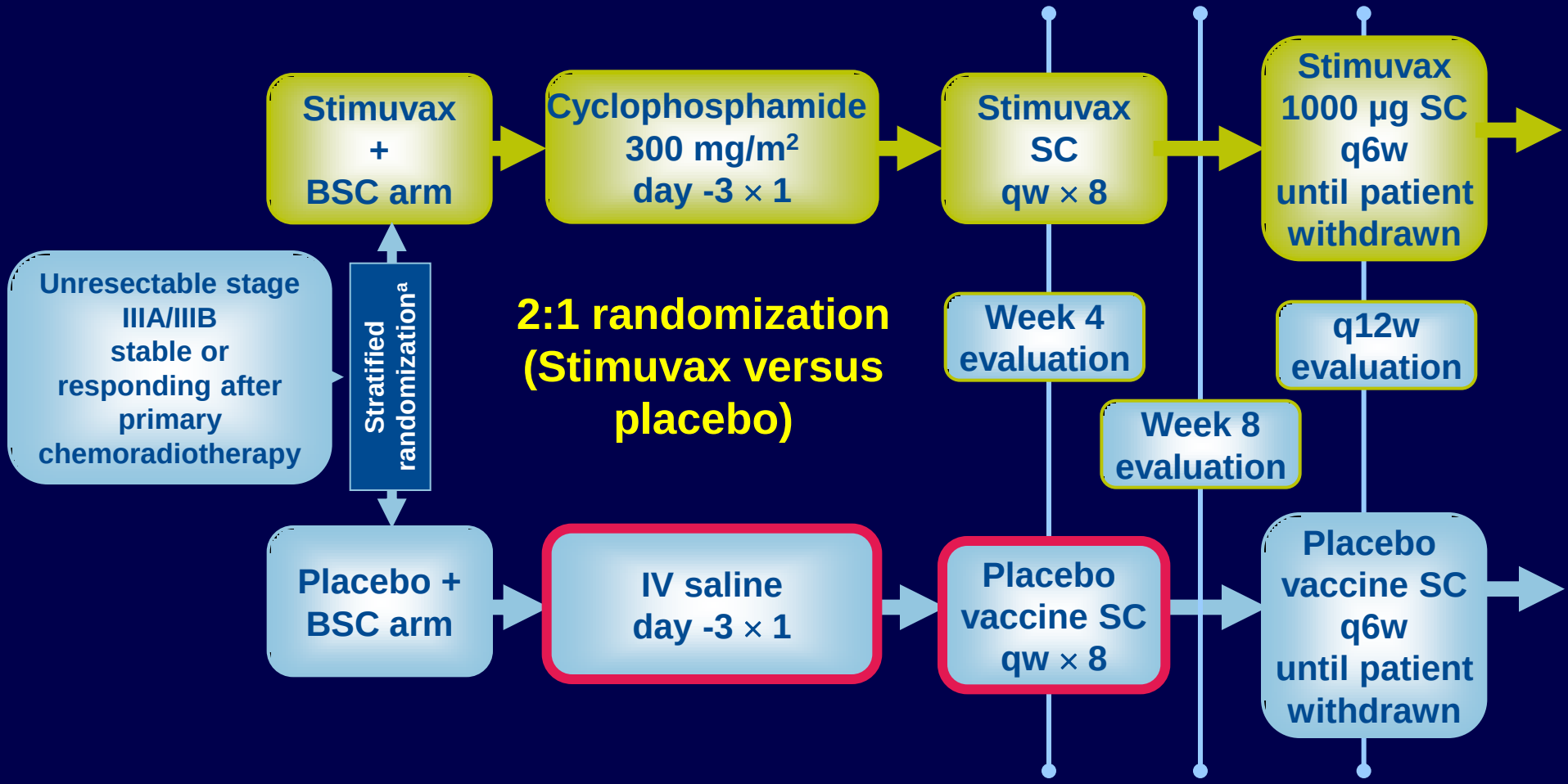
Well, You Might Say……

- You have not told us anything new
- What do we have to look forward to for patients without driver mutations???

Immunotherapy

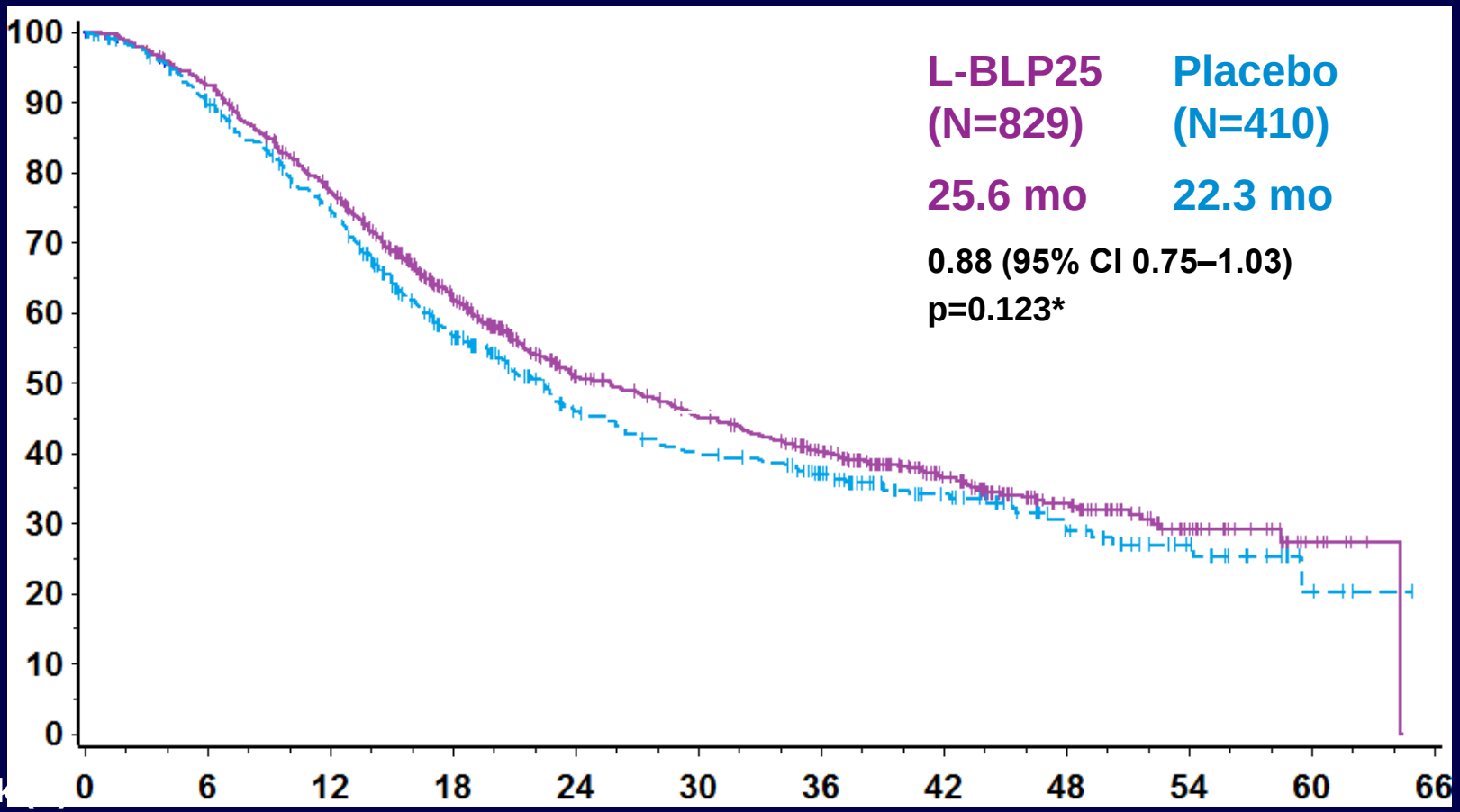
Vaccines
Immunomodulation

START Trial
Treatment and Evaluations



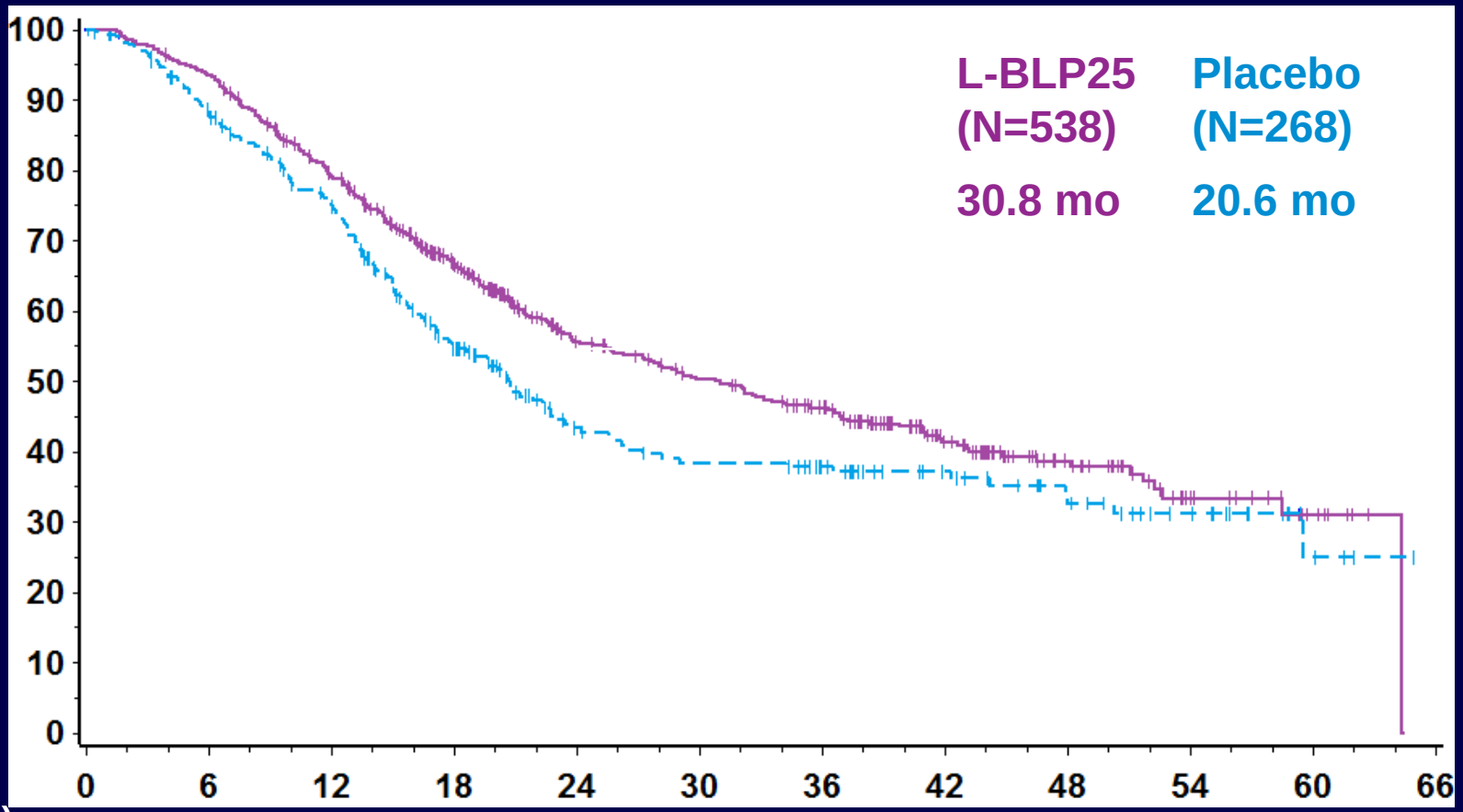
www.clinicaltrials.gov/ct2/show/NCT00409188

START Primary Endpoint: Overall Survival



Butts et al. Proc ASCO, 2013

Overall Survival: Concurrent Chemo/RT

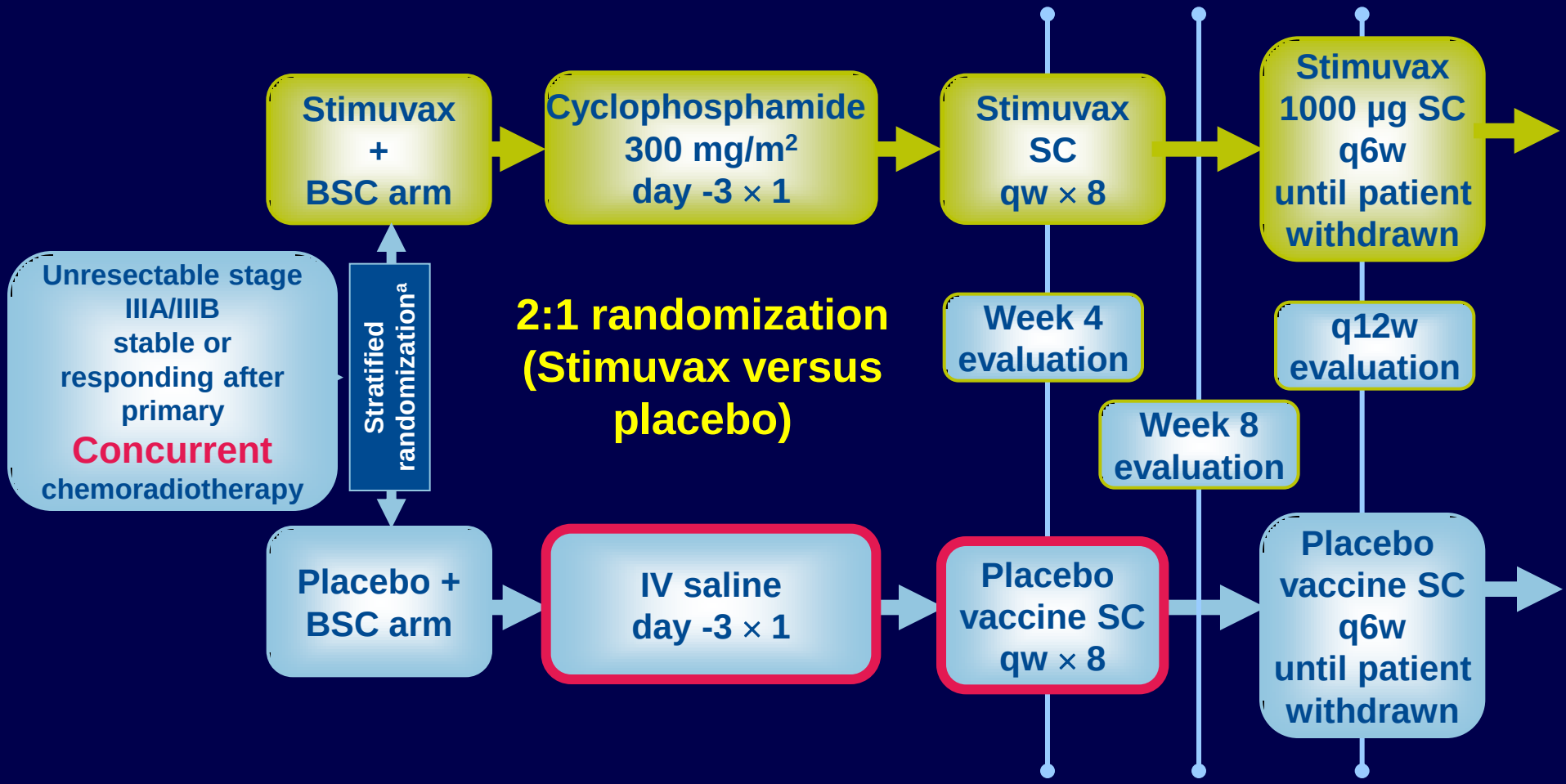


At risk (N)												
Placebo	268	227	186	118	73	62	54	40	26	16	4	0
L-BLP25	538	499	412	295	205	176	147	89	51	24	7	0

Months

Butts et al. *Lancet Oncol*, 2013

START-2 Trial
Treatment and Evaluations

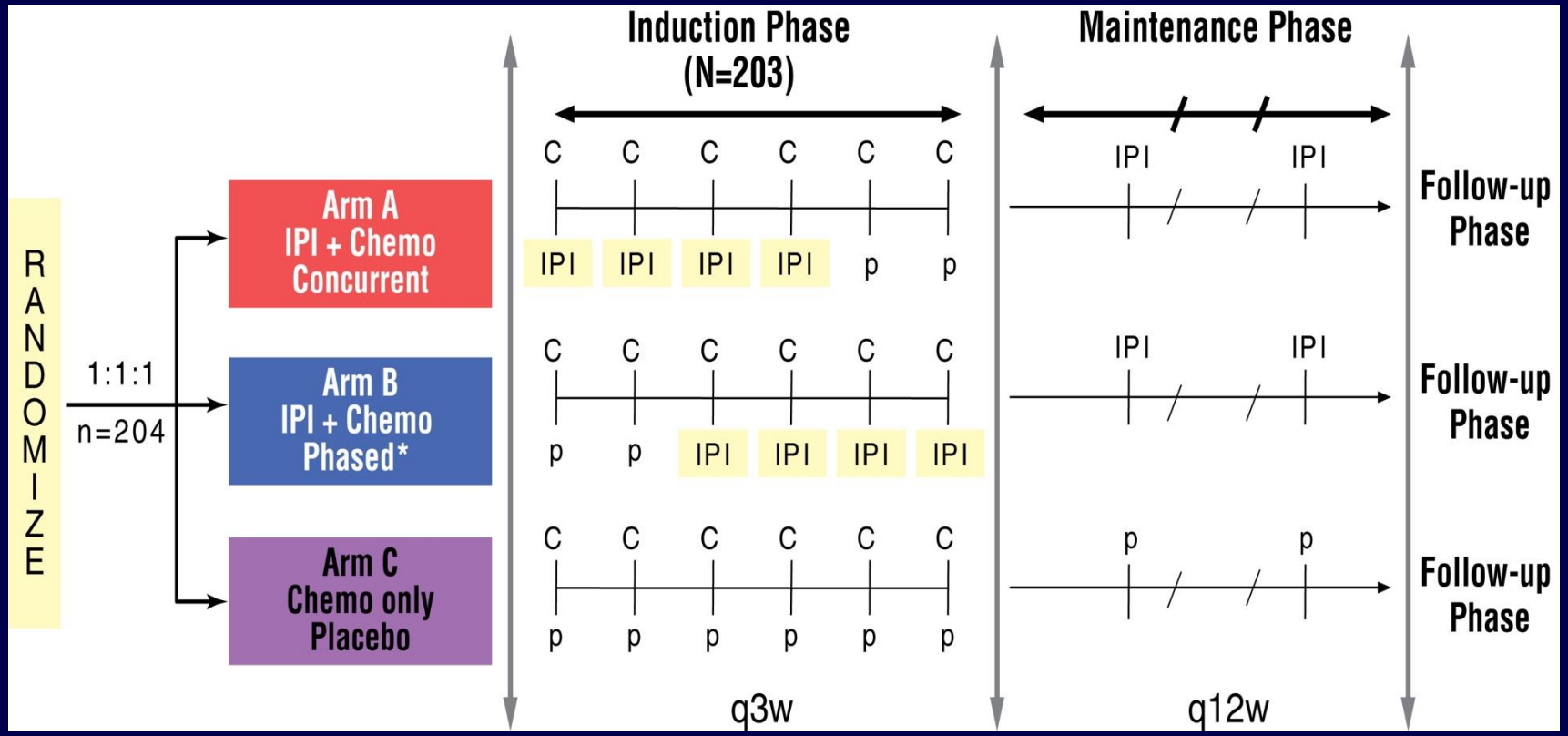


www.clinicaltrials.gov/ct2/show/NCT00409188

Ipilimumab

Anti-CTLA-4 monoclonal antibody

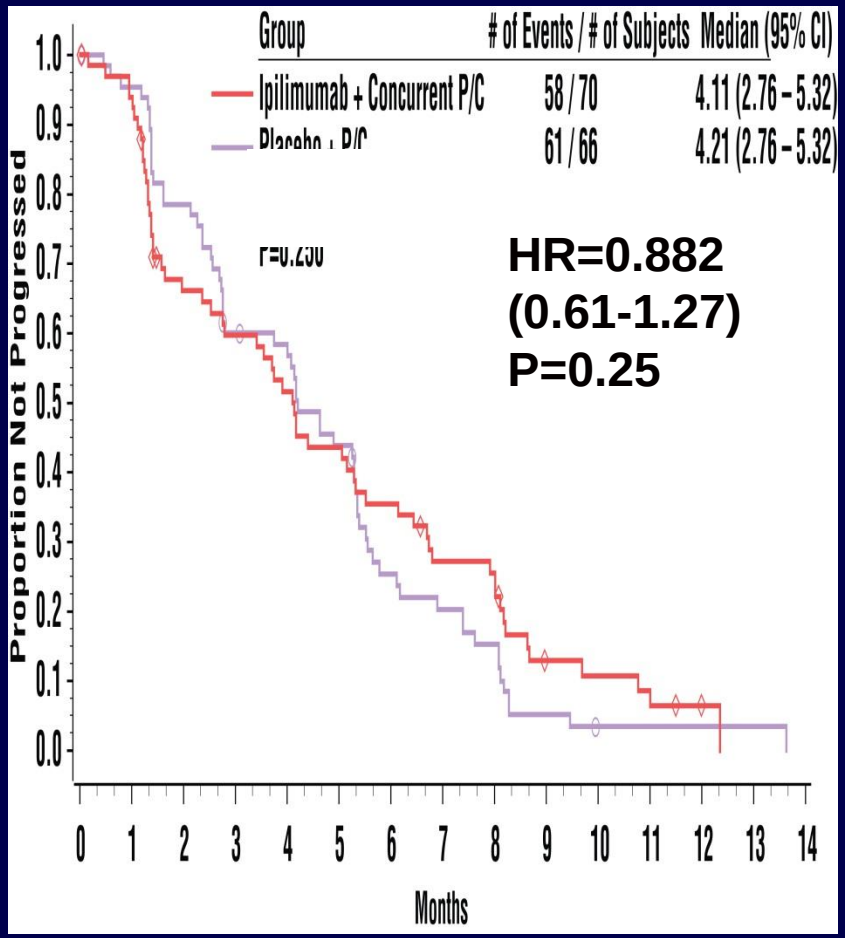
Trial CA184-041 Study Design



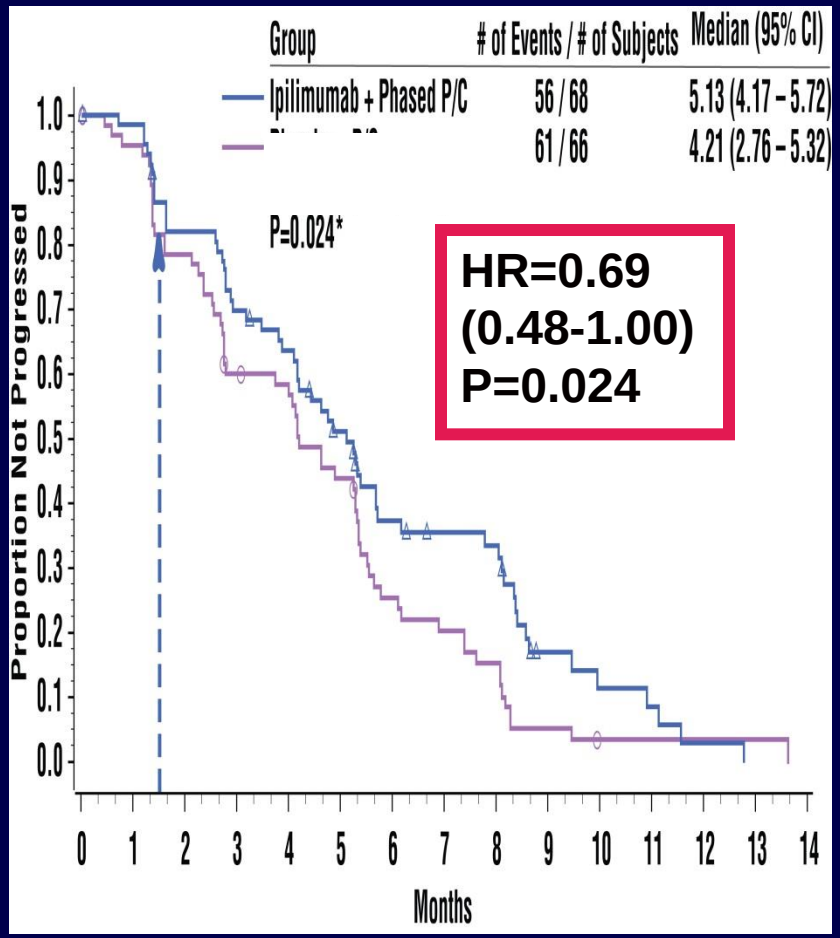
Chemo: Paclitaxel (175 mg/m^2)/Carboplatin (AUC=6) IV
C: chemotherapy doublet
IPI: Ipilimumab (10 mg IV)
p: Placebo
Note: Steroids were given as premedication

Ipilimumab in NON-SCLC: Overall Survival by Arm

Concurrent schedule



Phased schedule

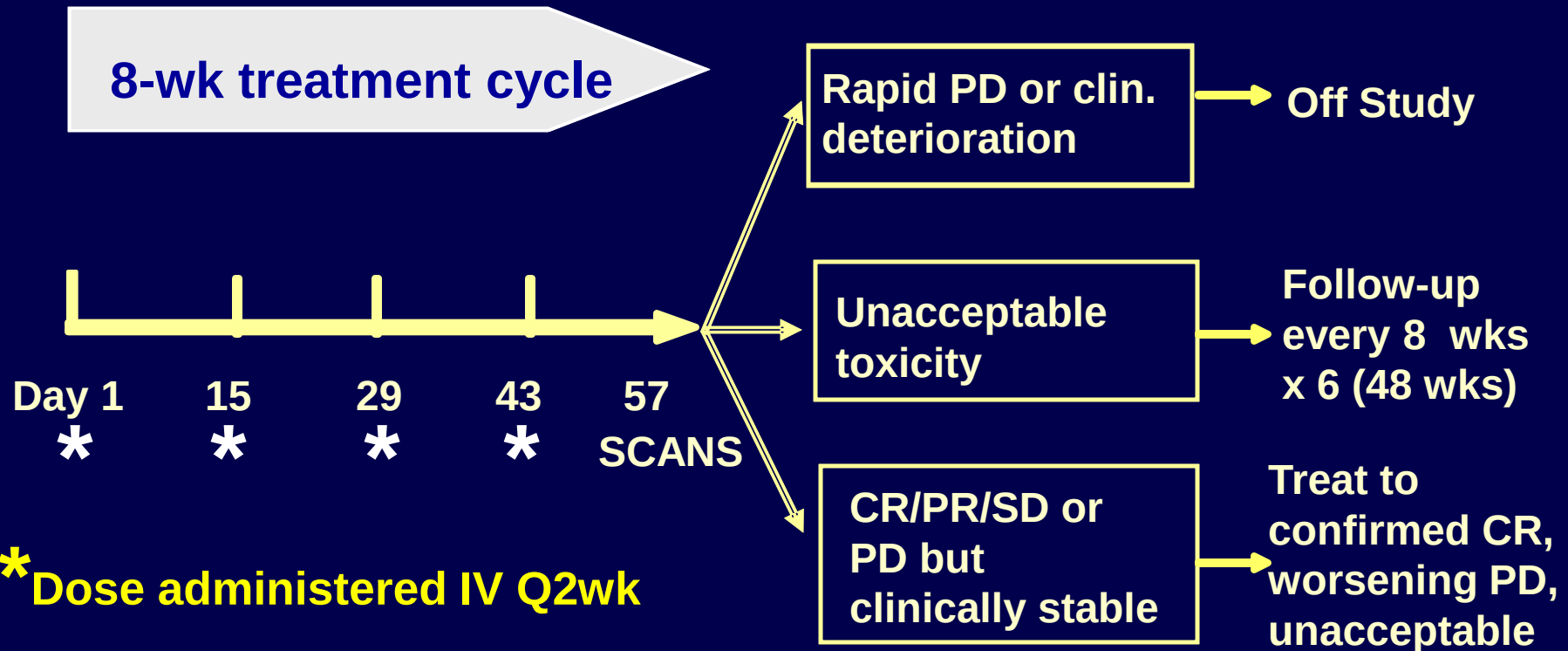


Lynch et al. IASLC, Chicago, 2010

Anti-PD-1 Monoclonal Antibodies

BMS-936558 (MDX-1106/ONO-4538)
MK-3475

BMS-936558 Study Design: Phase I Multi-dose Regimen



*Dose administered IV Q2wk

Doses tested for NSCLC: 1, 3, 10 mg/kg

Eligibility: Advanced MEL, RCC, NSCLC, CRC, or CRPC with PD after 1-5 systemic therapies

Brahmer et al. Proc ASCO, 2012

Clinical Activity of BMS-936558 in NSCLC

Pop	Dose (mg/kg)	Pts n	ORR n (%)	Duration of Response (mo)	SD ≥24 wk n (%)	PFSR at 24 wk (%)
ALL NSCLC	**1-10**	**76**	**14 (18%)**	**1.9+ - 30.8+**	**5 (7%)**	**26%**
NSCLC	1	18	1 (6)	9.2+	1 (6)	16
	3	19	6 (32)	1.9+ to 30.8+	2 (11)	41
	10	39	7 (18)	3.7 to 14.8+	2 (5)	24

- ORR was assessed using modified RECIST v1.0
- 3 NSCLC patients had a persistent reduction in baseline target lesions in the presence of new lesions but were not classified as responders for the ORR calculation

Brahmer et al. Proc ASCO, 2012

BMS CA209 012 Study Design

Arm A n=6 or 12
Gemcitabine 1250 mg/M²
Cisplatin 75 mg/ M²
BMS-936558 Dosing per arm

Arm B n=6 or 12
Pemetrexed 500 mg/M²
Cisplatin 75 mg/ M²
BMS-936558 Dosing per arm

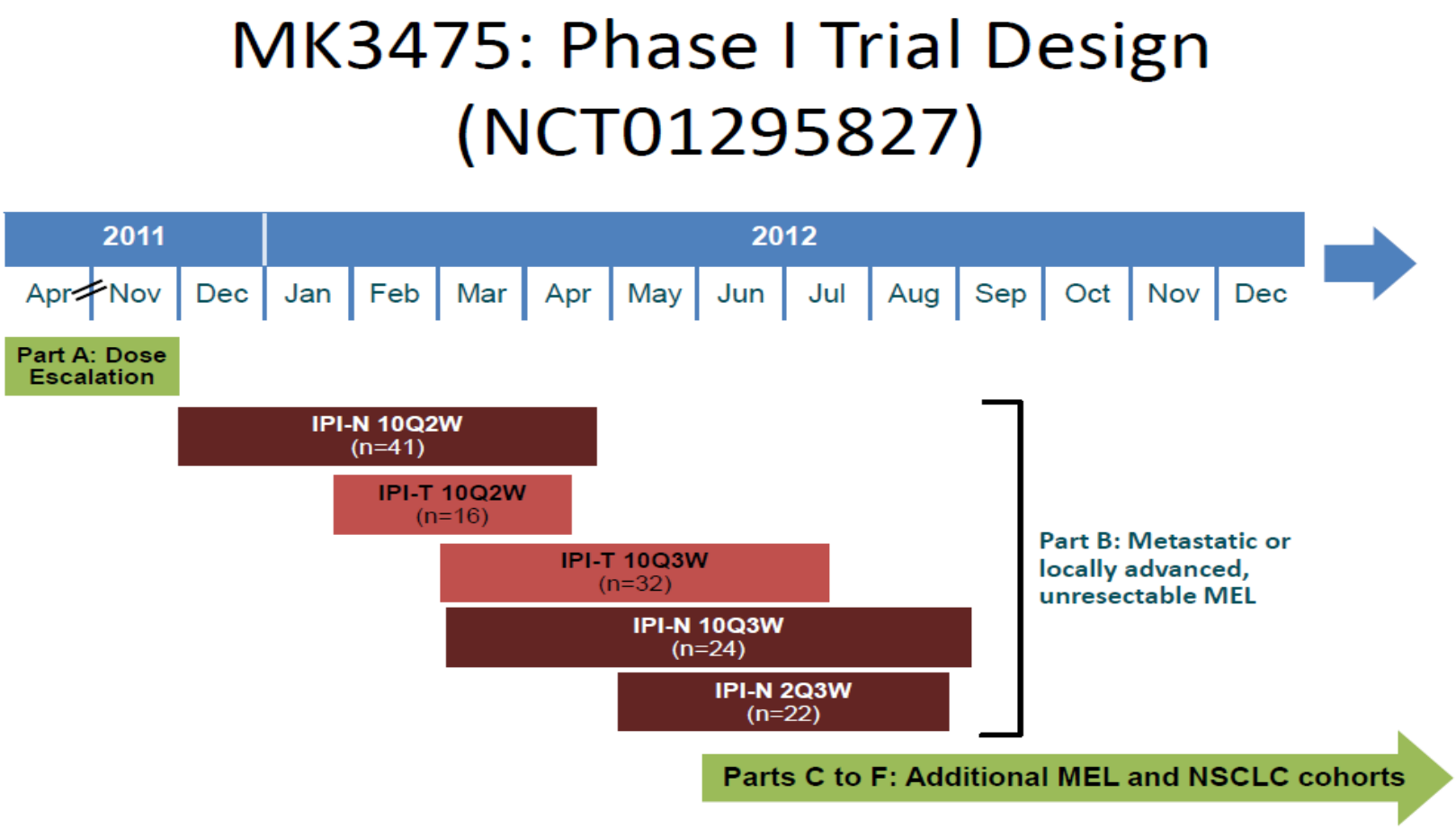
Arm C n=6 or 12
Paclitaxel 200 mg/M²
Carboplatin AUC 6
BMS-936558 Dosing per arm

Arm D n=6 or 12
Bevacizumab (15 mg/kg)
BMS-936558 (5 mg/kg, q 21 days)

Arm E n=6 or 12
Erlotinib (150 mg PO, Daily)
BMS-936558 (3 mg/kg, q 14 days)

Arm F n=6 or 12
BMS-936558 (3 mg/kg, q 14 days)

MK-3475 Phase I Trial



IPI-N=ipilimumab-naive; IPI-T=ipilimumab-pretreated; MEL=melanoma; NSCLC=non–small cell lung cancer.

Ribas A et al. 2013 ASCO Annual Meeting Proceedings. Abstract 9009.

MK-3475 in Non-SCLC

Subgroup	irRC, Investigator Review			RECIST v1.1, Independent Review			Median OS, wk (95% CI)
	N	ORR, n (%) [95% CI]	Median PFS, wk (95% CI)	N	ORR,* (%), [95% CI]	Median PFS, wk (95% CI)	
All	38	9 (24%) [11%, 40%]	9.1 (8.3, 17.4)	33	7 (21%) [9%, 39%]	9.7 (7.6, 17)	51 (14, NR)
Non-squamous	31	7 (23%) [10%, 41%]	9.1 (8.3, 17.0)	26	4 (16%) [4%, 35%]	10.3 (7.6, 17)	35 (14, NR)
Squamous	6	2 (33%) [4%, 78%]	23.5 (2.7, NR)	6	2 (33%) [4%, 78%]	15.2 (1.4, NR)	NR (2.7, NR)
Patients with measurable disease on baseline imaging and an evaluable tumor specimen for PD-L1							
Score ≥ potential cut point	9	6 (67%) [30%, 93%]	—	7	4 (57%) [18%, 90%]	—	—
Score < potential cut point	24	1 (4%) [0%, 21%]	—	22	2 (9%) [1%, 29%]	—	—

*Response rate per RECIST v1.1 is based on those patients who had ≥1 measurable lesion at baseline per central review. All responses were confirmed except for 2. One patient withdrew consent for treatment, unrelated to toxicity, after the first imaging assessment, and 1 patient had a confirmatory scan of PR at day 27.

Garon et al. Proc WCLC, 2013

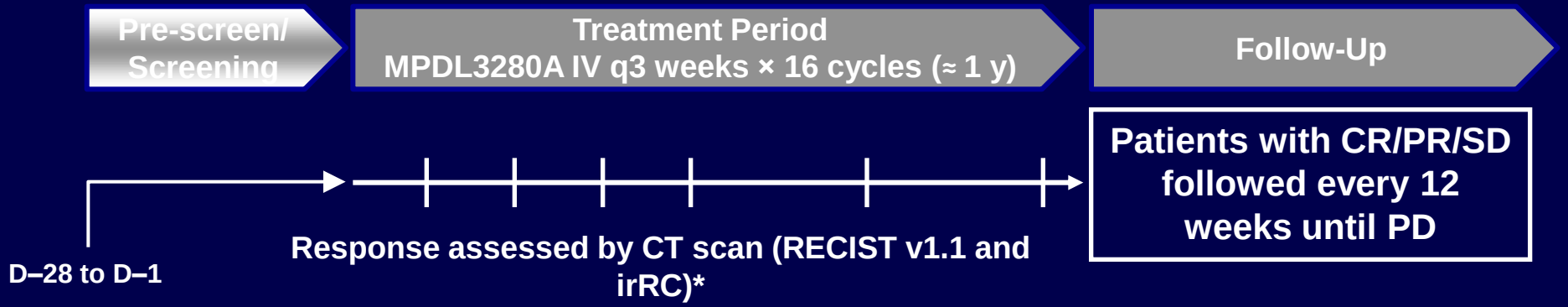
PD-1 or PD-L1???

MPDL3280A: Phase Ia Objectives and Schema

Population: patients with incurable or metastatic solid tumor
Diagnostic: multi-modality biomarkers, including PD-L1, being evaluated

Primary Objectives

- **Evaluate safety and tolerability of MPDL3280A**
- **Determine the MTD and identify recommended Phase II dose**



Key Eligibility Criteria

- Measurable disease per RECIST v1.1
- ECOG PS 0 or 1

MPDL3280A Phase Ia: Response *Investigator Assessed*

	Single Agent RECIST 1.1 Response Rate (ORR[a])	SD of 24 Weeks or Longer	24-Week PFS Rate
Overall population (N = 175)	**21%**	19%	42%
NSCLC (n = 53)	**23%**	17%	45%
Nonsquamous (n = 42)	**21%**	17%	44%
Squamous (n = 11)	**27%**	18%	46%

[a] ORR includes investigator-assessed unconfirmed and confirmed PR.
Six patients who did not have a post-baseline scan were included as non-responders.
Patients first dosed at 1-20 mg/kg by Oct 1, 2012; data cutoff Apr 30, 2013.

Soria et al, ESMO 2013

MPDL3280A Phase Ia: Best Response by PD-L1 IHC Status - NSCLC

Diagnostic Population[a] (n = 53)	ORR[b] % (n/n)	PD Rate % (n/n)
IHC 3	83% (5/6)	17% (1/6)
IHC 2 and 3	46% (6/13)	23% (3/13)
IHC 1/2/3	31% (8/26)	38% (10/26)
All Patients[c]	23% (12/53)	40% (21/53)

[a] IHC 3: ≥ 10% tumor immune cells positive for PD-L1 (IC+); IHC 2 and 3: ≥ 5% tumor immune cells positive for PD-L1 (IC+); IHC 1/2/3: ≥ 1% tumor immune cells positive for PD-L1 (IC+); IHC 0/1/2/3: all patients with evaluable PD-L1 tumor IC status.
[b] ORR includes investigator-assessed unconfirmed and confirmed PR.
[c] All patients includes patients with IHC 0/1/2/3 and 7 patients have an unknown diagnostic status.
Patients first dosed at 1-20 mg/kg by Oct 1, 2012; data cutoff Apr 30, 2013.

Soria et al, ESMO 2013

Summary

- Not much new with respect to chemotherapy
- Addition of targeted therapy has been disappointing
- Vaccine therapy trials, for the most part have been disappointing as well, although tecemotide may have a role in Stage III NSCLC
- Immune modulation appears interesting, but beware the “promising Phase II syndrome”. Results of Phase III trials are some years away.