Community Oncology Alliance Conference

Lung Cancer: Next Steps in Incurable Disease

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Saturday, March 23, 2013
10:30 – 11:15AM
Orlando, FL

Lung Cancer: Next Steps in Incurable Disease

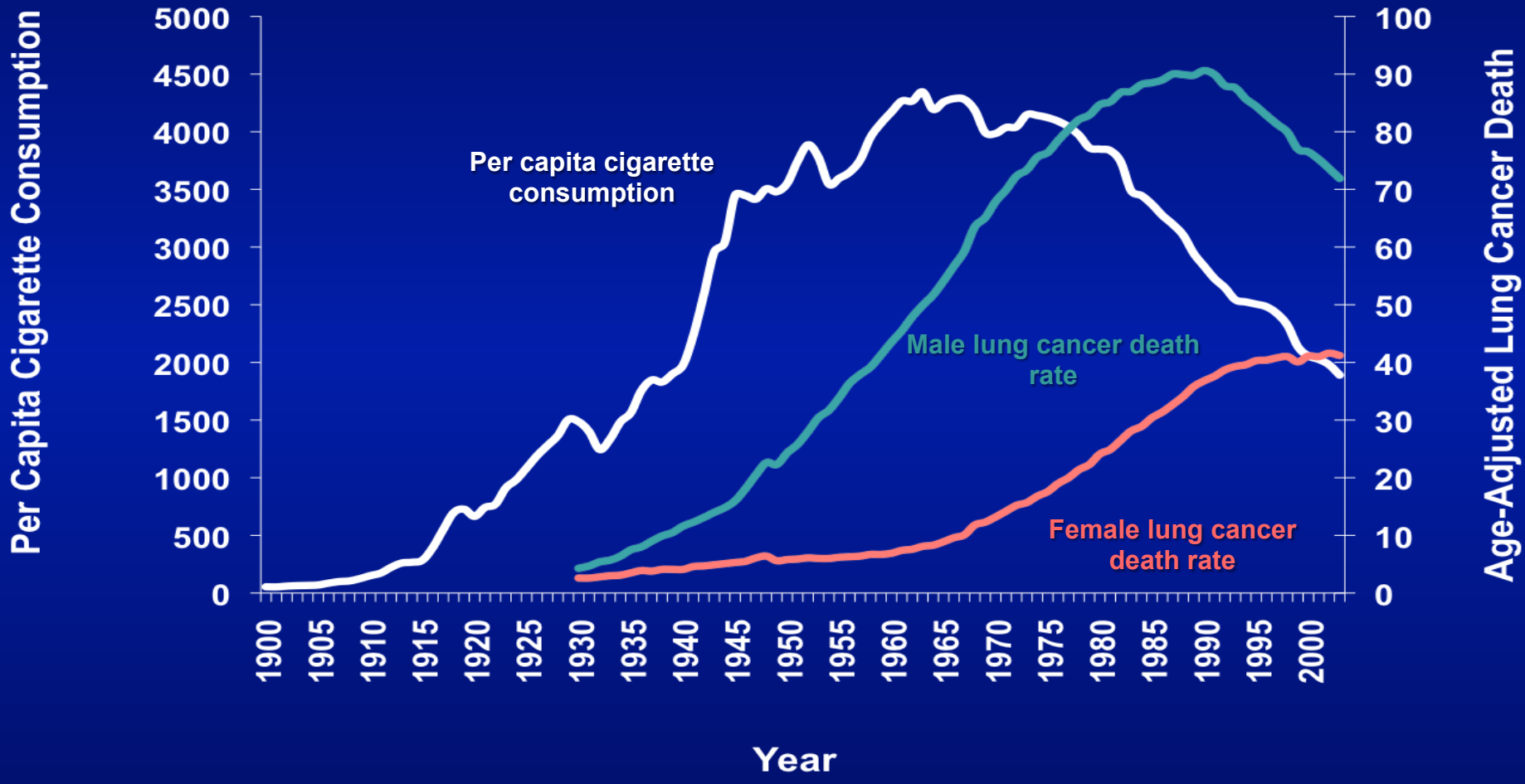
- A word on lung cancer screening
- How are we making progress in incurable disease?
  - More drugs
  - Getting the right drug to the right patient, and giving as much as you can (Maintenance therapy)
  - Better drugs
- Clinically relevant subgroups, 2013

Cancer in the United States

New Cases		Deaths	
Prostate	241,740	Lung	160,340
Breast	229,060	Colorectal	51,690
Lung	226,160	Breast	39,920
Colorectal	143,460	Prostate	28,170

Siegel, Cancer Statistics 2012, CA, 2012

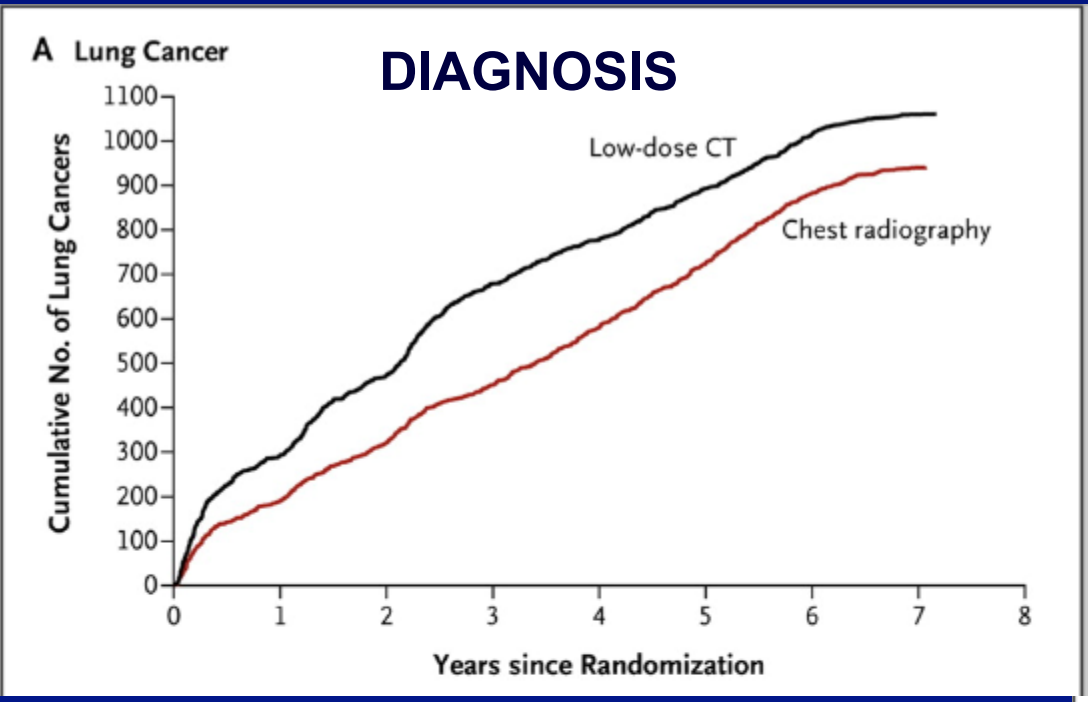
How to Reduce Lung Cancer Death: Stop Smoking!

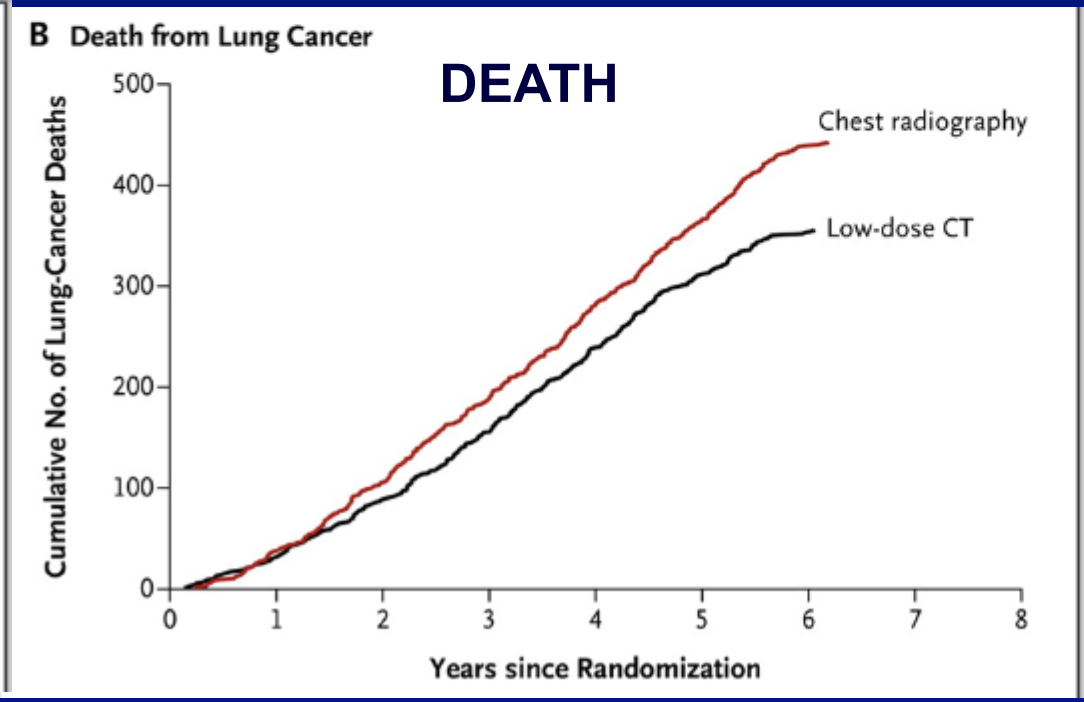


*Age-adjusted to 2000 US standard population.

Source: Death rates: US Mortality Public Use Tapes, 1960–2003, US Mortality Volumes, 1930–1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 2005. Cigarette consumption: US Department of Agriculture, 1900–2003.

How to Reduce Lung Cancer Death: LDCT Screen, Age 55-74, ≥ 30 pack-year



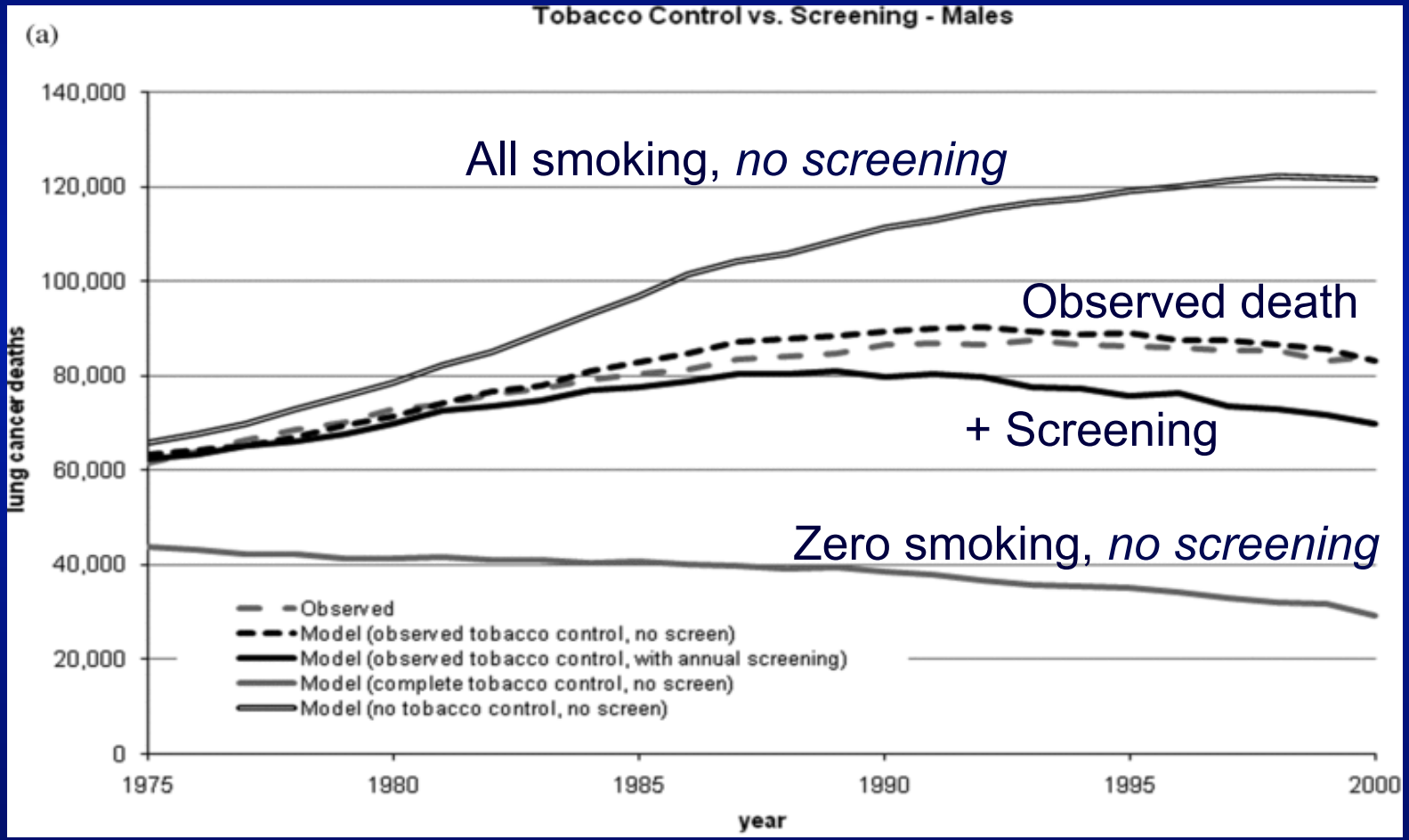


Lung Cancer Death Relative risk reduction: 20%, Absolute risk reduction: 0.33%

- Chance CT screening will save a life from lung cancer 1:300
- Chance CT screening will find a 4mm solid nodule 1:5
- Chance of death during evaluation of a benign nodule 1:2500

NLST, NEJM 2011

How to Reduce Lung Cancer Death: Smoking Cessation More Effective than LDCT



Risk Analysis
pages S117-S124, 7 AUG 2012 DOI: 10.1111/j.1539-6924.2011.01652.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1539-6924.2011.01652.x/full#f3

Smoking Kills

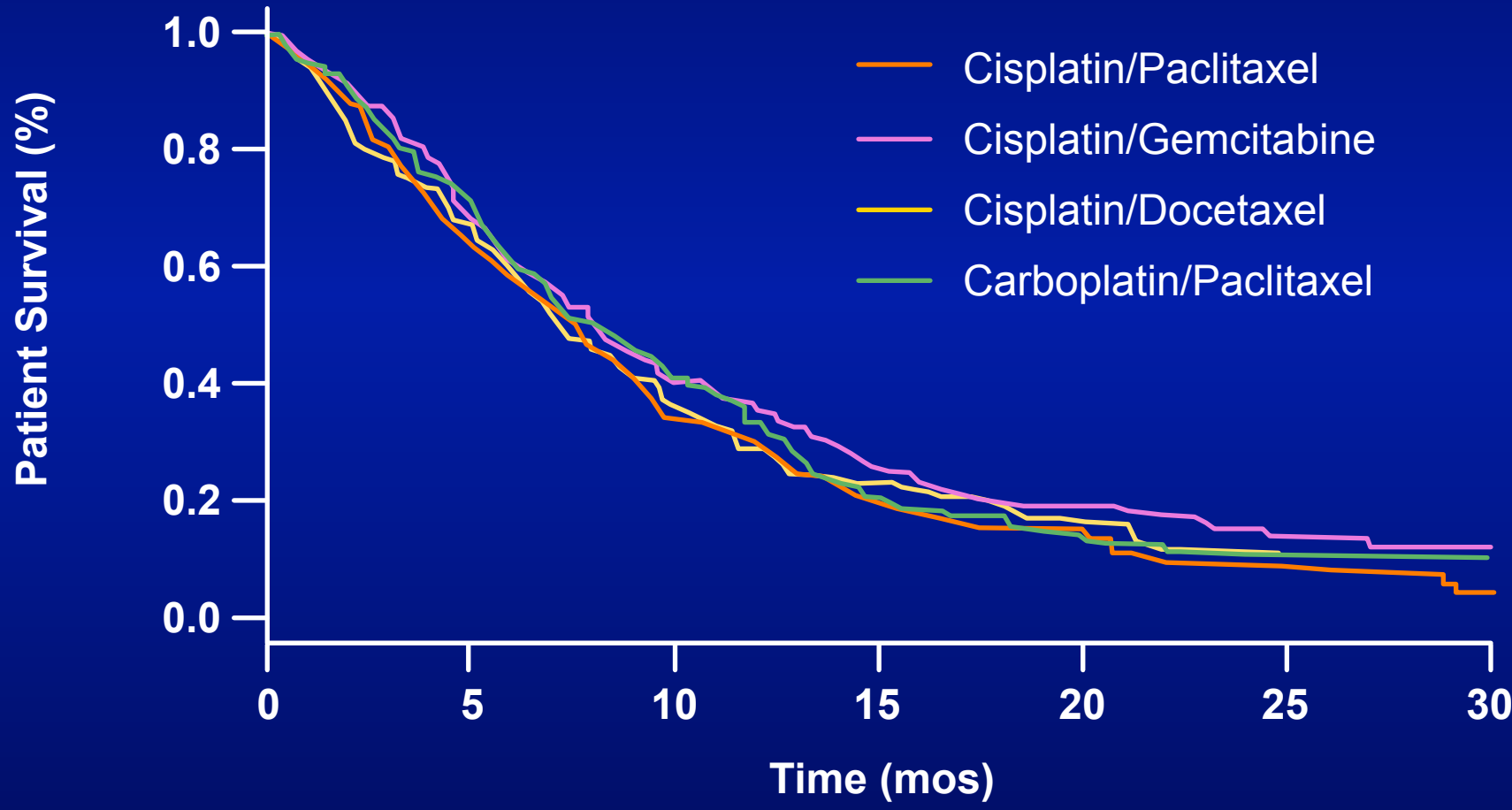
CT Screening Saves Lives

Chemotherapy for Stage IV NSCLC

Survival	No Chemo	Best Cytotoxic Chemo
MST (mo)	4	10
1-year (%)	10	40
2-year (%)	1	15

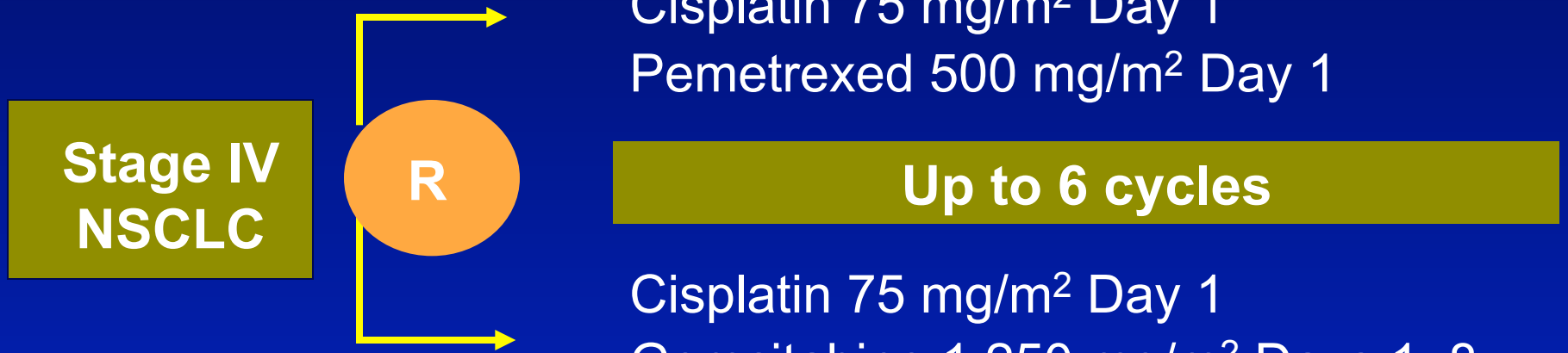
NSCLC Meta-Analyses Collaborative Group, J Clin Oncol. 2008; 26(28): 4617–25
Scagliotti, J Clin Oncol. 2008 Jul 20;26(21):3543-51

What is the best Cytotoxic Chemotherapy for Stage IV NSCLC?



Schiller et al, NEJM 2002

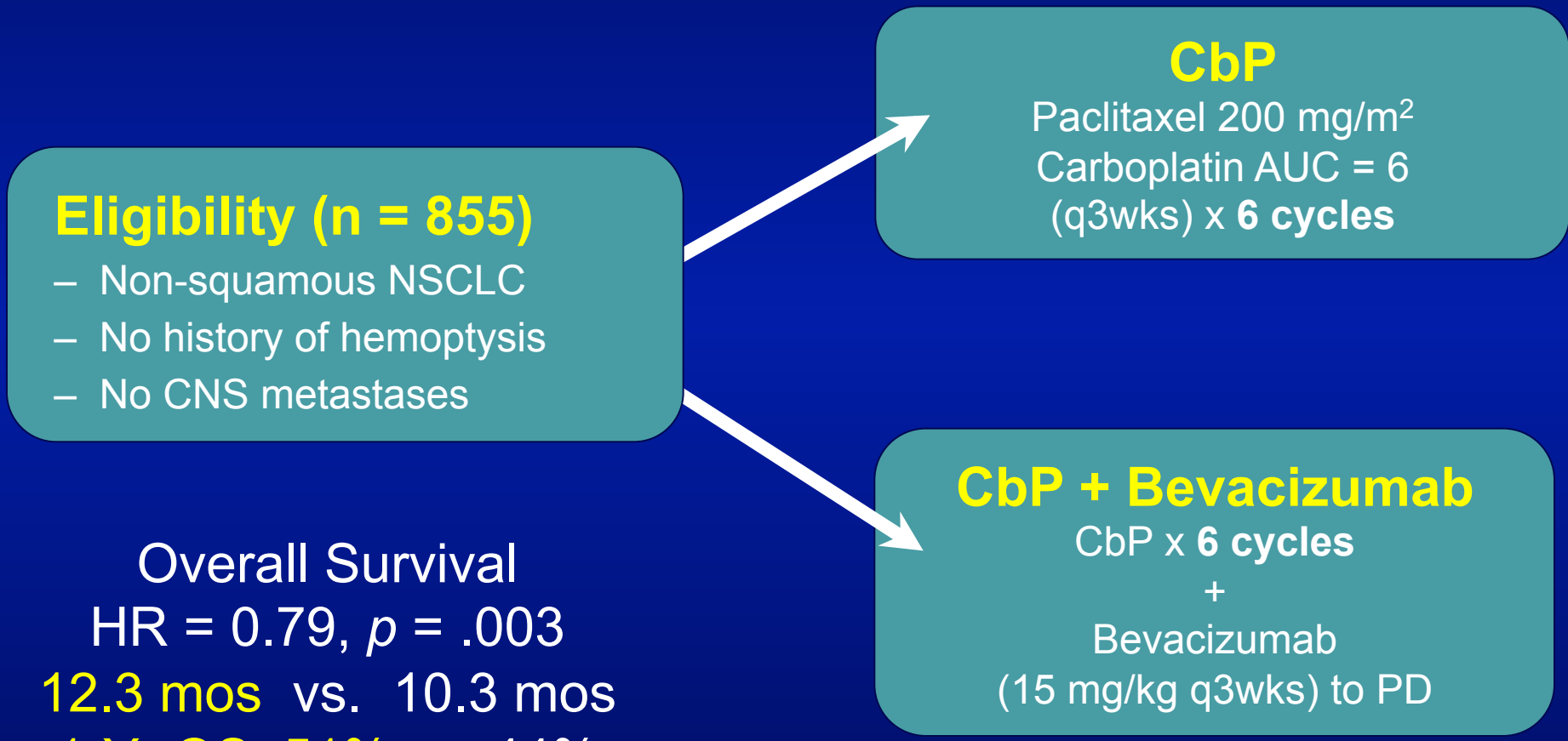
Gemcitabine / Cis vs. Pemetrexed / Cis



Results	Pemetrexed/Cisplatin	Gemcitabine/Cisplatin	
No. patients	862	863	
Median survival (mos)	10.3	10.3	
Non-squamous	11.8	10.4	HR 0.81
Squamous	9.4	10.8	HR 1.23

Scagliotti et al, 2008.

Bevacizumab in Non-Squamous NSCLC



Overall Survival
HR = 0.79, *p* = .003
12.3 mos vs. 10.3 mos
1-Yr OS: 51% vs. 44%
ORR: 35% vs. 15%

Sandler et al, NEJM 2006.

Chemotherapy for Stage IV NSCLC

Survival	No Chemo	Cyto-toxic chemo	Carbo + taxol + bev	Pem + cis for non-squamous
MST (mo)	6	10	12	12
1-year (%)	10	40	50	50
2-year (%)	1	15	20	20

NSCLC Meta-Analyses Collaborative Group, J Clin Oncol. 2008; 26(28): 4617–25
Scagliotti, J Clin Oncol. 2008 Jul 20;26(21):3543-51
Sandler, NEJM 2006

Cetuximab for Stage IV NSCLC

Advanced stage NSCLC
EGFR IHC 1 +
No prior Rx
No brain mets
N=1125

RANDOMIZE

Cisplatin 80 mg/m^2 Day 1
Vinorelbine 25 mg/m^2 Days 1, 8
Cetuximab 225–400 mg/m^2 x 1 → 250 mg/m^2/wk

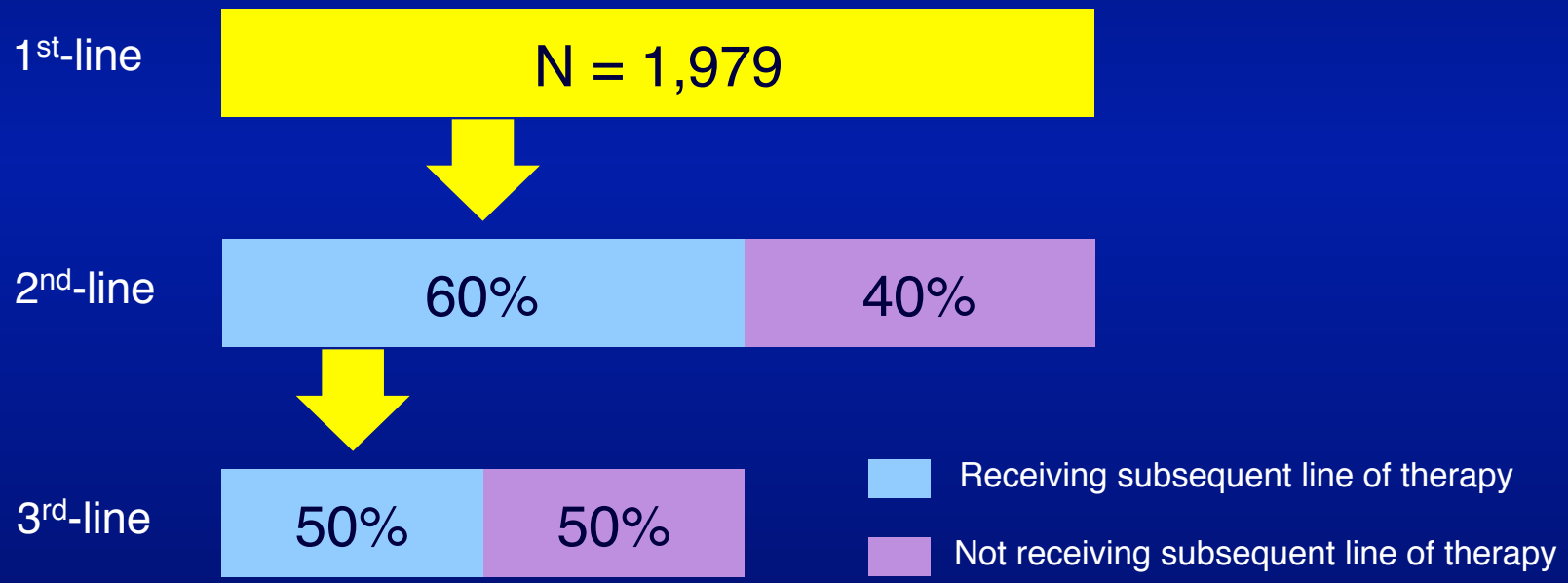
Cisplatin 80 mg/m^2 Day 1
Vinorelbine 25 mg/m^2 Days 1, 8
1 cycle = 3 wks

Overall Survival
HR = 0.87, p = .044
11.3 mos vs. 10.1 mos
ORR: 36% vs. 29%

Pirker R et al. *Lancet.* 2009;373:1525-1531.

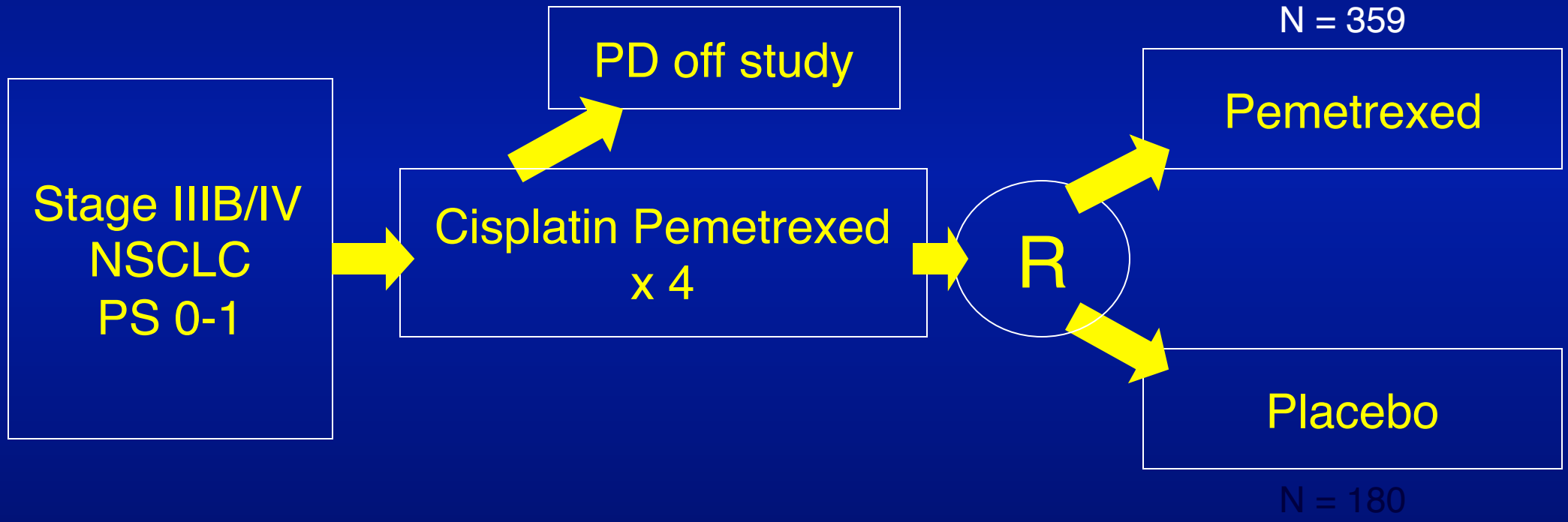
Why Is Maintenance Therapy Important?

Observed "second-line" Treatment Rates



IntrinsiQ longitudinal data. 2005-2007
Average pts sampled per year: 1st-line (1,979), 2nd-line (1,182), 3rd-line (679).

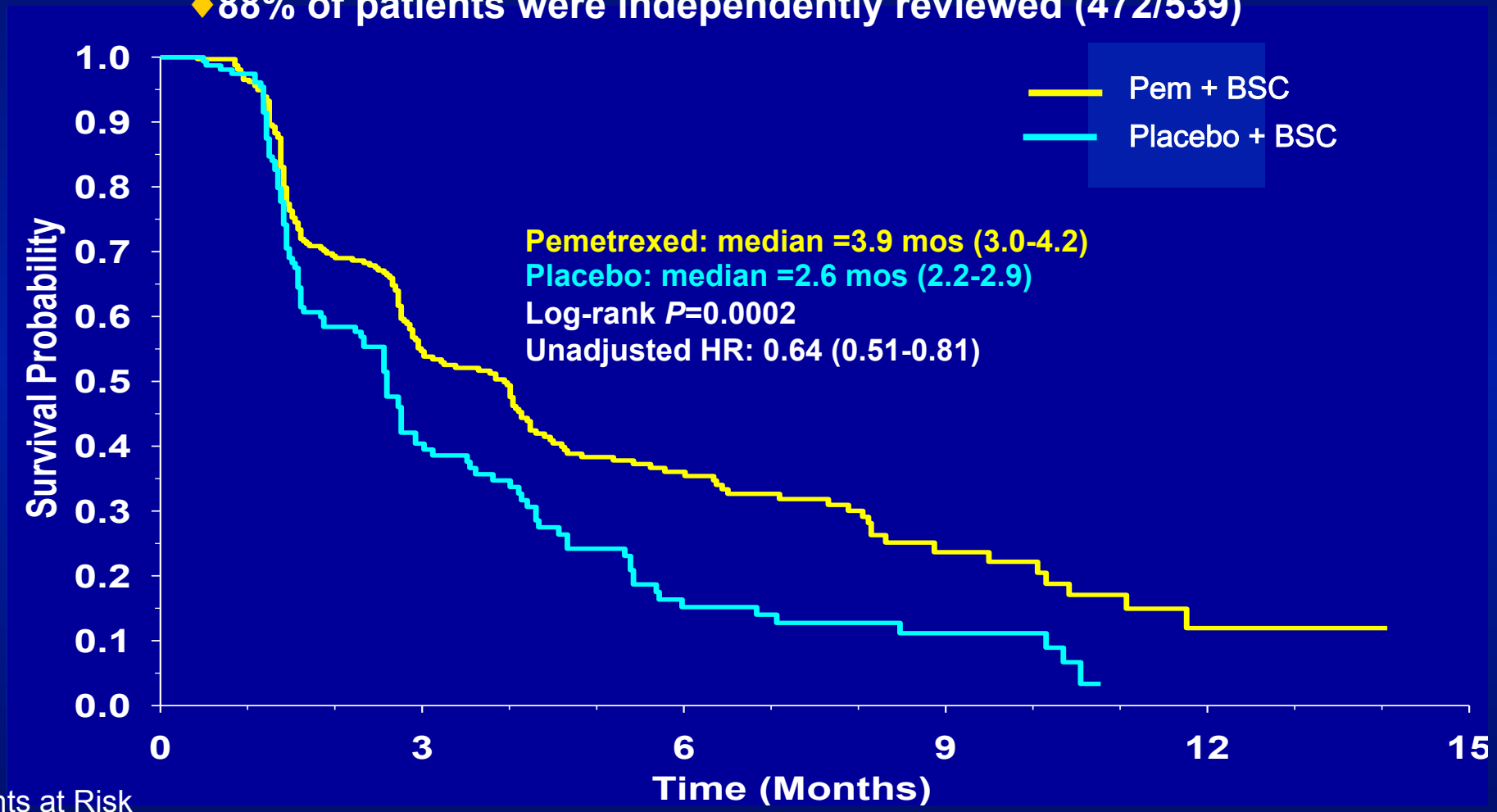
"Continuation" Maintenance
PARAMOUNT



Paz Ares, Lancet Oncology 13, 2012

PARAMOUNT: PFS (from Maintenance)

- 88% of patients were independently reviewed (472/539)

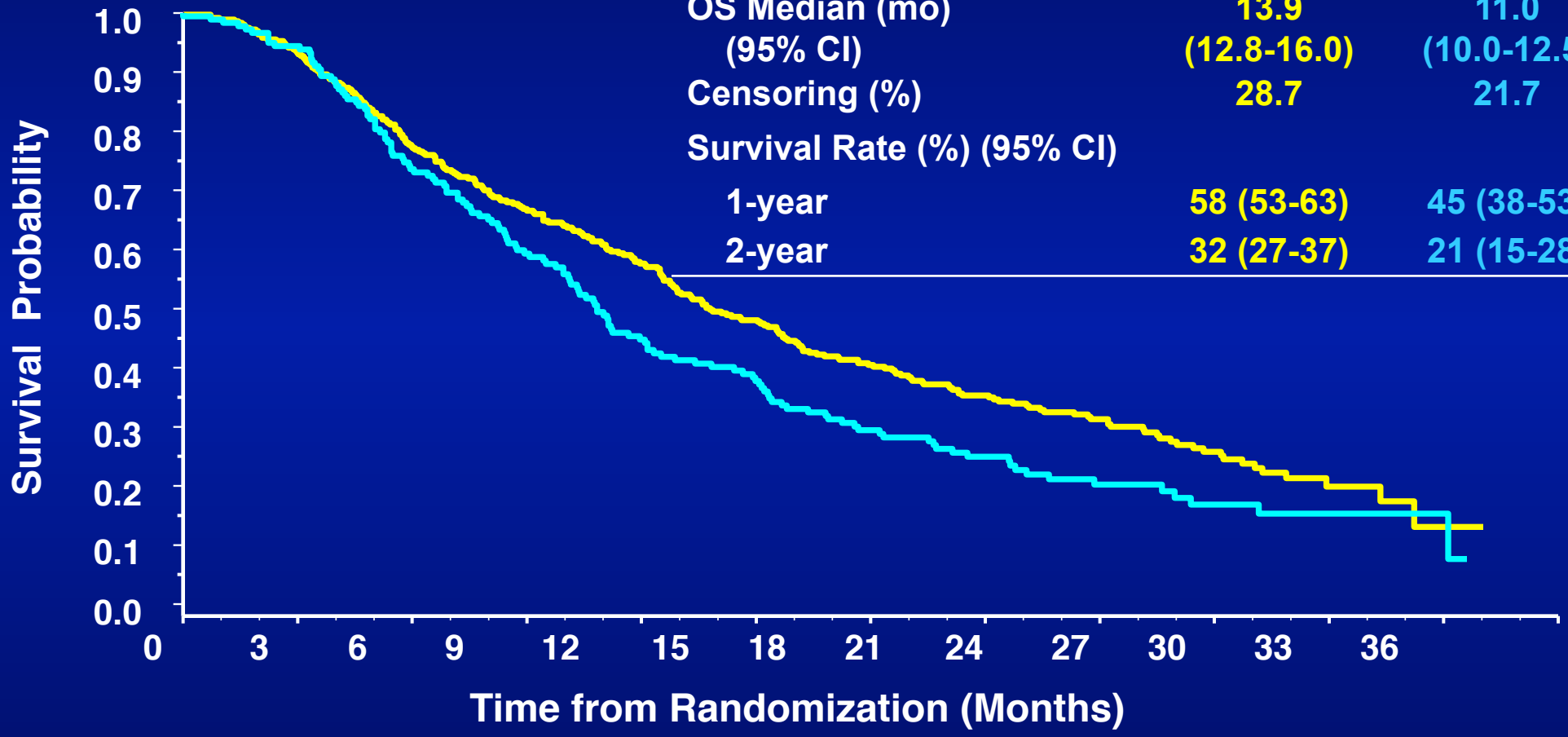


Patients at Risk

Pem + BSC	N=316	128	56	16	4	0
Placebo + BSC	N=156	44	13	7	0	0

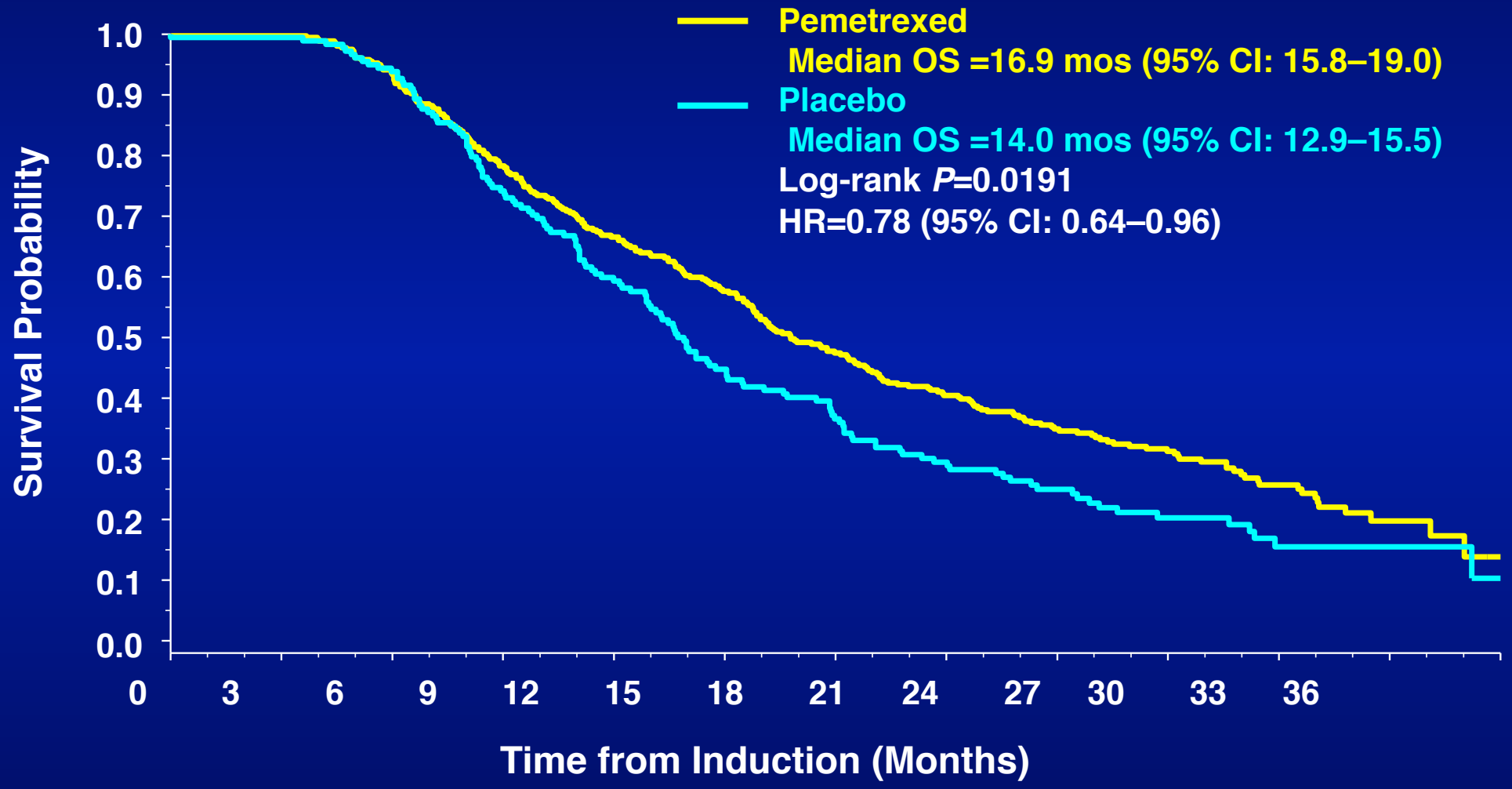
PARAMOUNT: OS (from Maintenance)

	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)



Paz Ares, Lancet Oncology 13, 2012

PARAMOUNT: OS (from Induction)

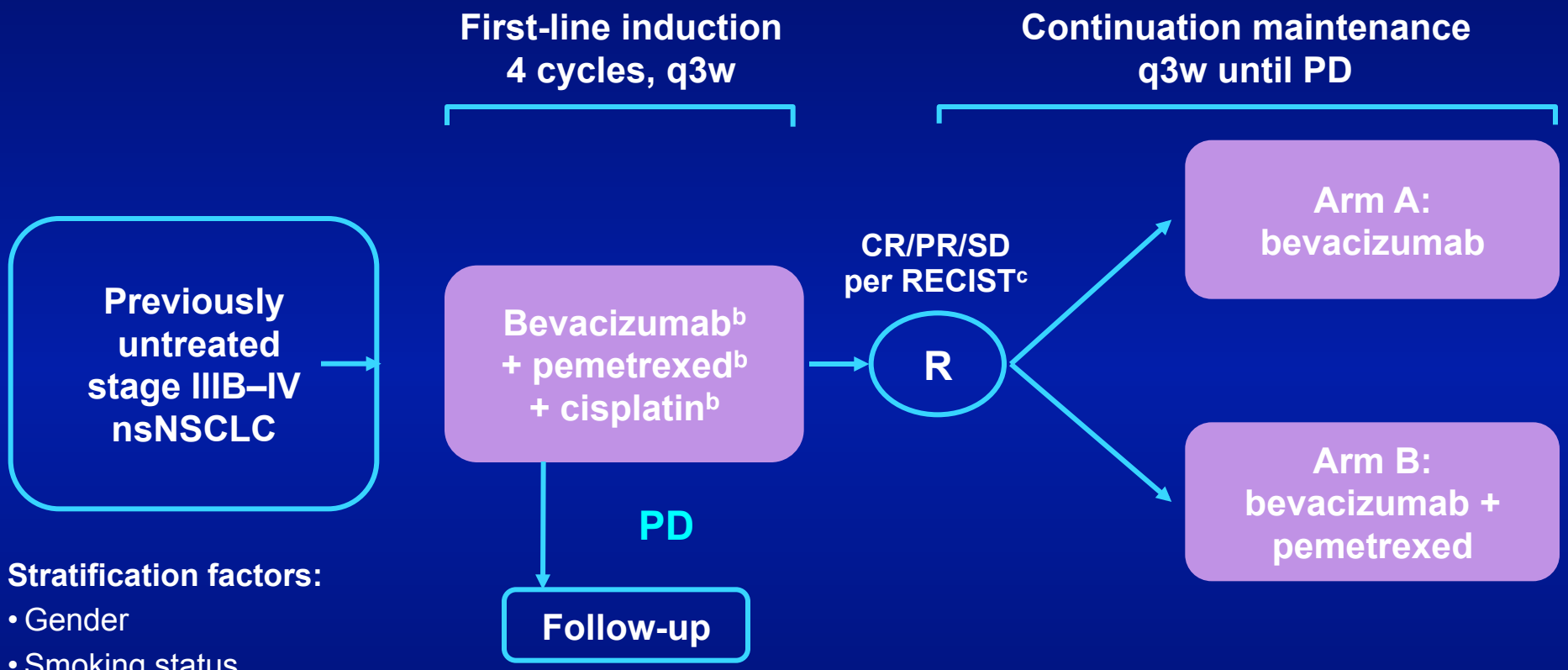


Paz Ares, Lancet Oncology 13, 2012

PARAMOUNT: 2nd line therapy

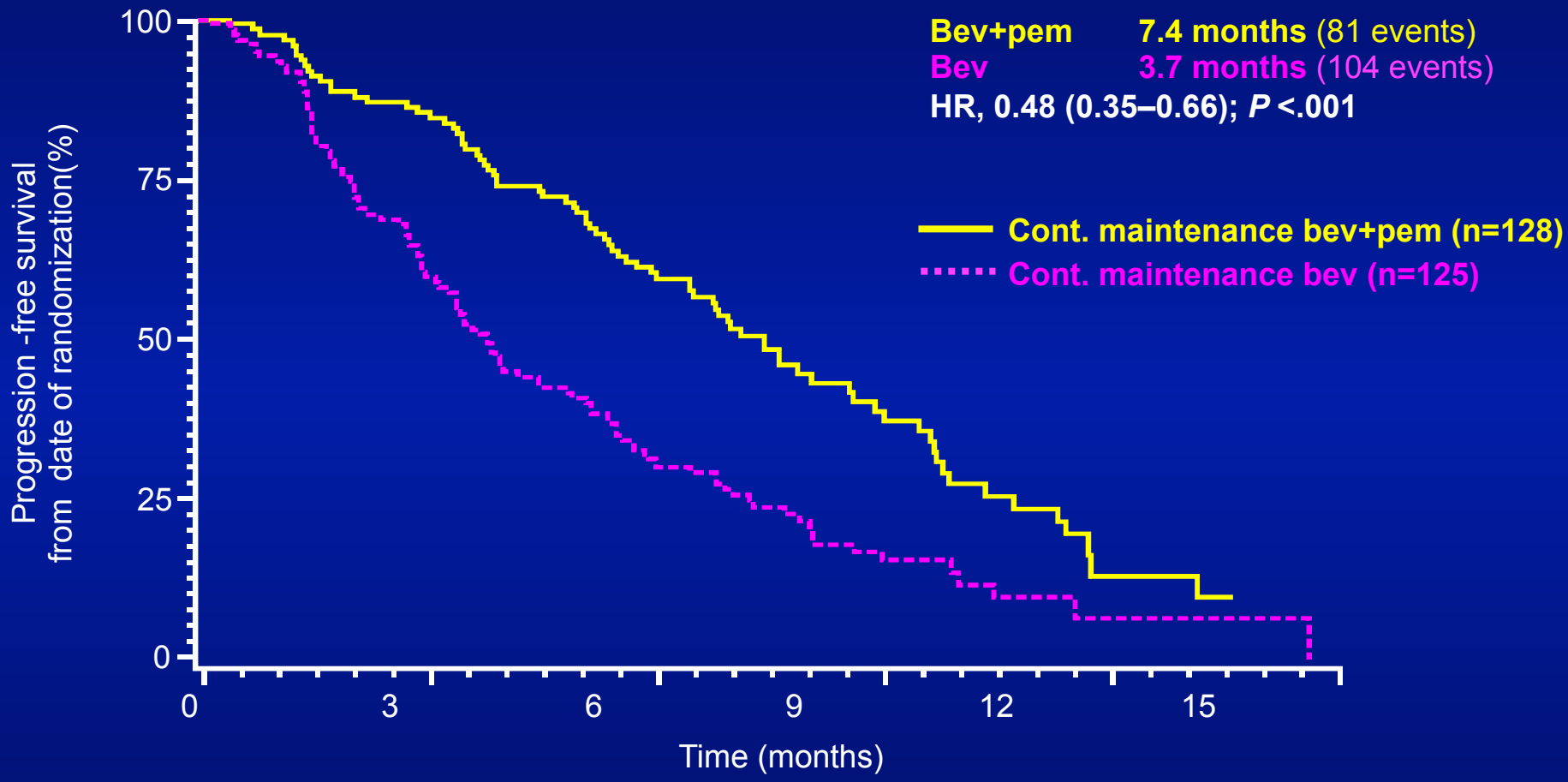
	Continuation Maintenance	Placebo
Any	58%	64%
Erlotinib	31%	37%
Docetaxel	29%	35%
Gemcitabine	8%	3%
Vinorelbine	4%	2%
Bevacizumab	2%	<1%
Cisplatin	2%	<1%
Other	12%	8%

"Continuation" Maintenance AVAPERL



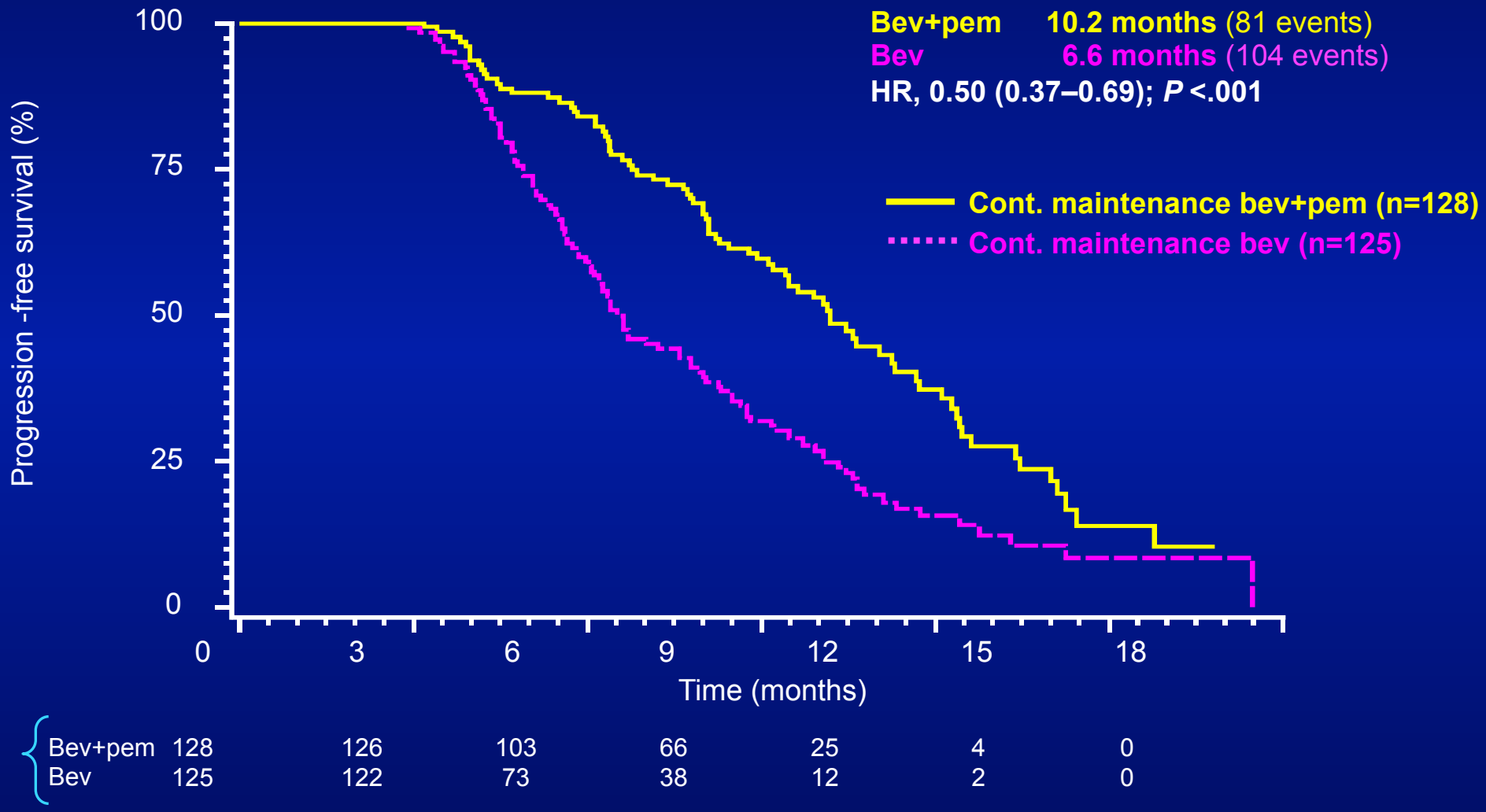
Barlesi F, *Eur J Cancer.* 2011;47(suppl 2). Abstract LBA34

AVAPERL: PFS (from Maintenance)



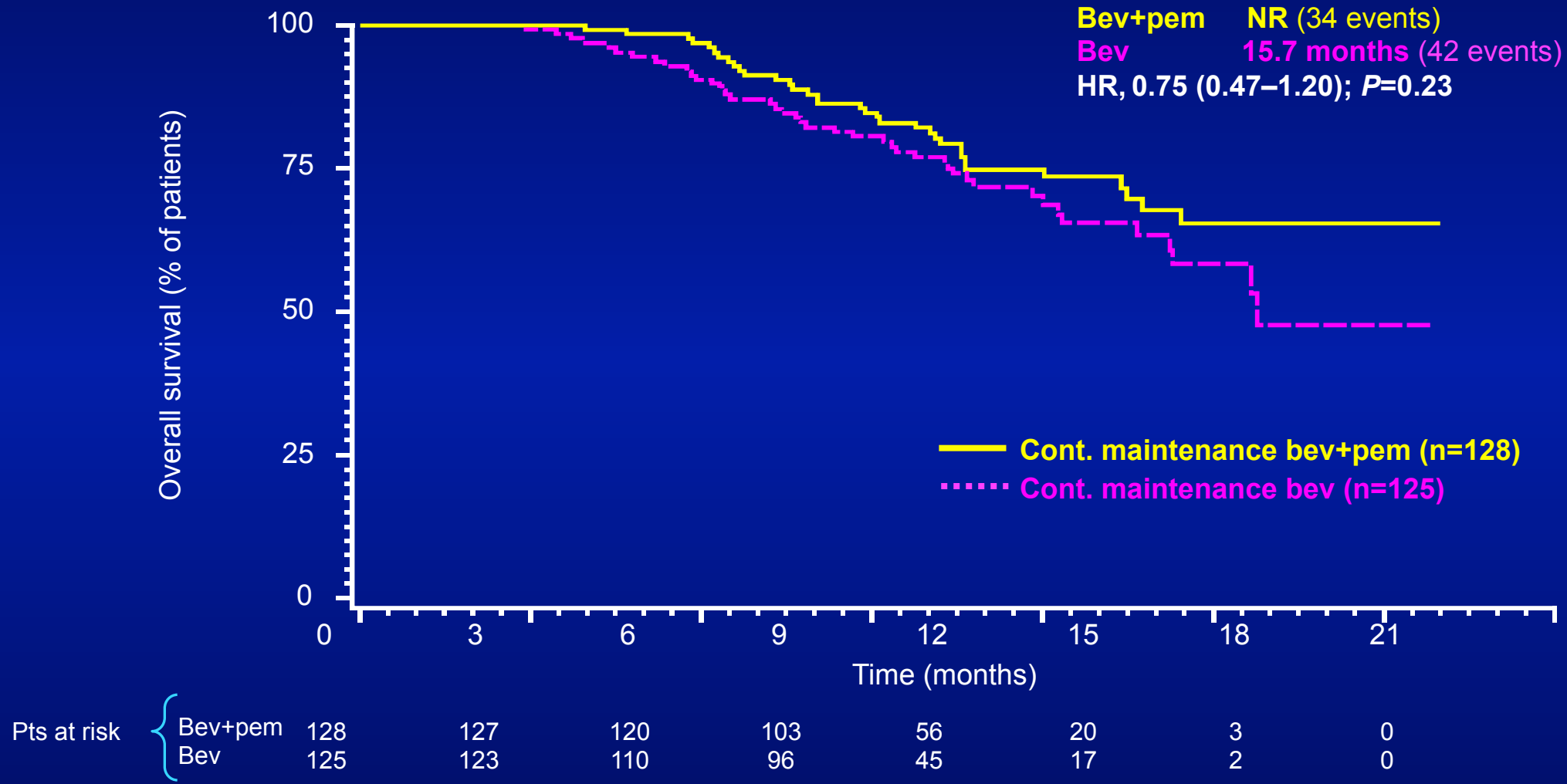
Barlesi F, *Eur J Cancer.* 2011;47(suppl 2). Abstract LBA34

AVAPERL: PFS (from Induction)



Barlesi F, *Eur J Cancer.* 2011;47(suppl 2). Abstract LBA34

AVAPERL: OS (from Induction)



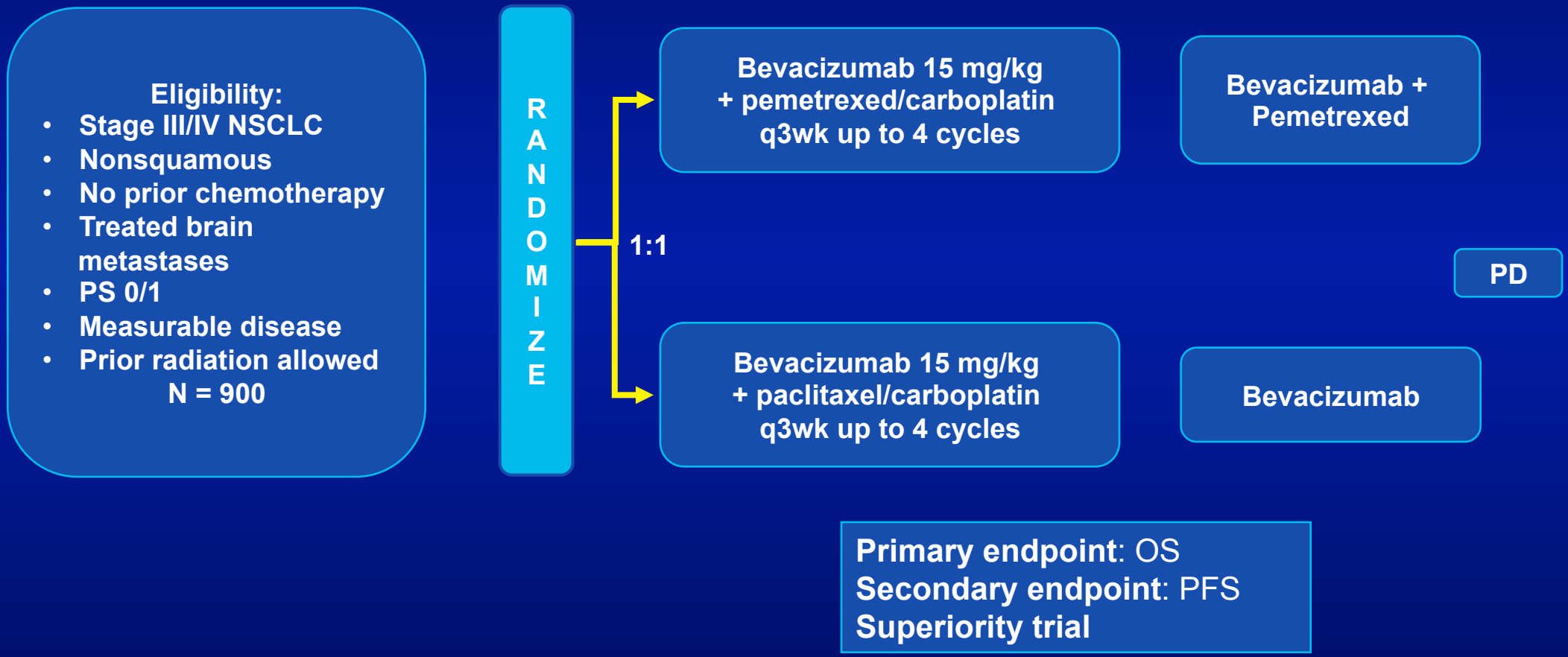
Barlesi F, *Eur J Cancer.* 2011;47(suppl 2). Abstract LBA34

Chemotherapy for Stage IV NSCLC

Survival	No Chemo	Cyto-toxic chemo	Carbo + taxol + bev	Pem + cis non-squam	"4 cycles" + maint.
MST (mo)	6	10	12	12	17
1-year (%)	10	40	50	50	70
2-year (%)	1	15	20	20	40

NSCLC Meta-Analyses Collaborative Group, J Clin Oncol. 2008; 26(28): 4617–25
Scagliotti, J Clin Oncol. 2008 Jul 20;26(21):3543-51
Sandler, NEJM 2006
Paz Ares, Lancet Oncology 13, 2012
Barlesi F, *Eur J Cancer.* 2011;47(suppl 2). Abstract LBA34

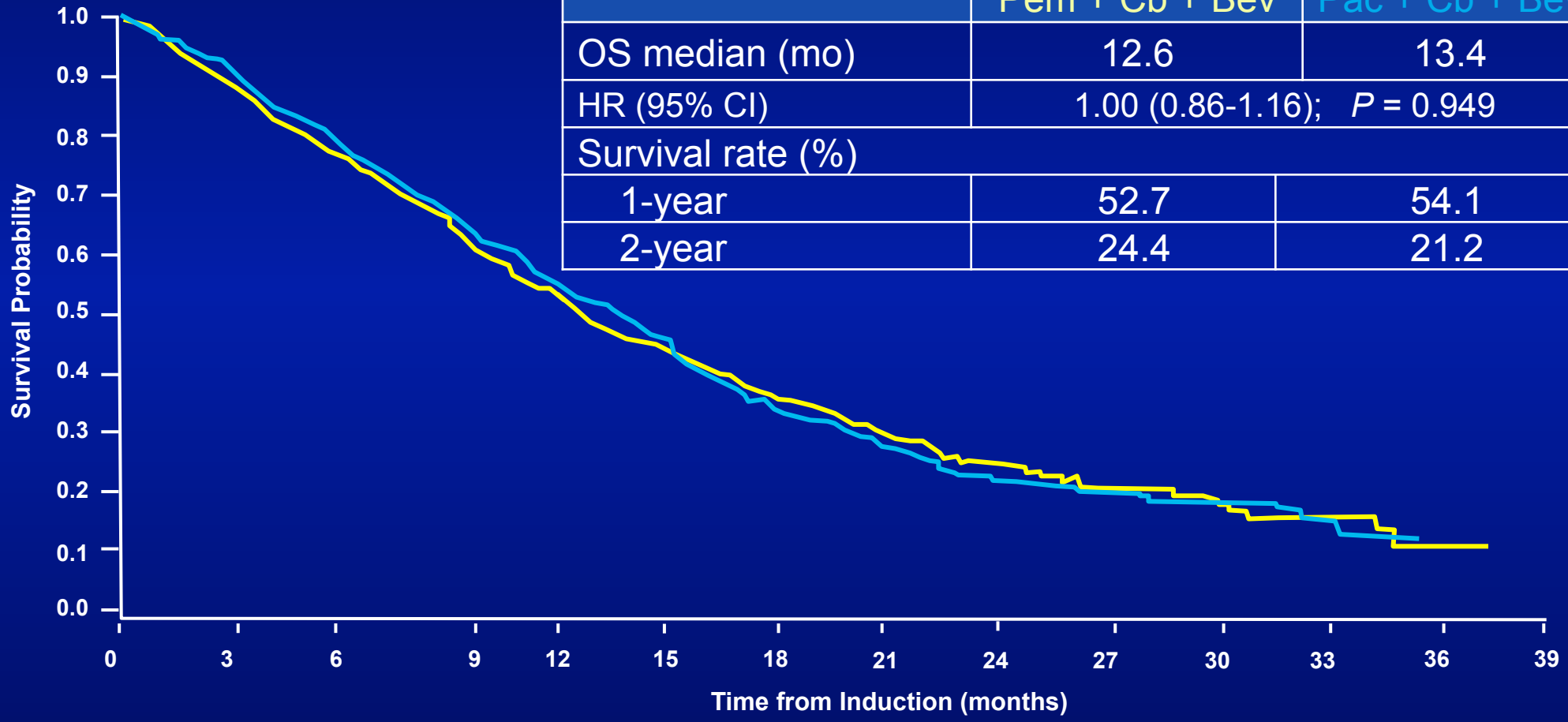
Putting it all together: POINTBREAK Study



US National Institutes of Health. Available at: http://www.clinicaltrials.gov/ct2/show/NCT00762034. Accessed November 19, 2012.

POINTBREAK: OS

	Pem + Cb + Bev	Pac + Cb + Bev
OS median (mo)	12.6	13.4
HR (95% CI)	1.00 (0.86-1.16); *P* = 0.949	
Survival rate (%)		
1-year	52.7	54.1
2-year	24.4	21.2

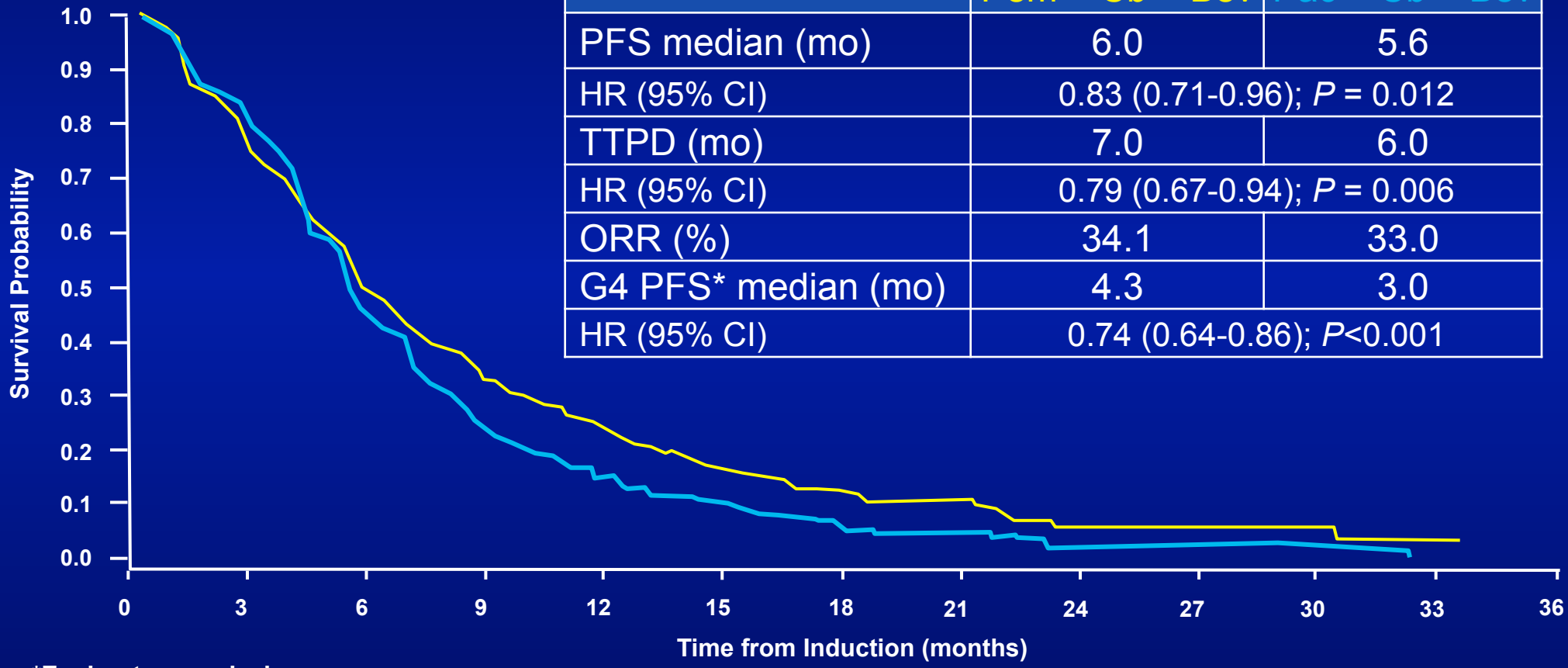


Censoring rate for Pem + Cb + Bev was 27.8%; for Pac + Cb + Bev was 27.2%.

Patel J et al. 2012 Multidisciplinary Symposium in Thoracic Oncology. Abstract LBDL1.

POINTBREAK: PFS

	Pem + Cb + Bev	Pac + Cb + Bev
PFS median (mo)	6.0	5.6
HR (95% CI)	0.83 (0.71-0.96); *P* = 0.012	
TTPD (mo)	7.0	6.0
HR (95% CI)	0.79 (0.67-0.94); *P* = 0.006	
ORR (%)	34.1	33.0
G4 PFS* median (mo)	4.3	3.0
HR (95% CI)	0.74 (0.64-0.86); *P*<0.001	



*Exploratory analysis.
ORR = overall response rate; PFS = progression-free survival; TTPD = time to disease progression.
Censoring rate for Pem + Cb + Bev was 26.9%; for Pac + Cb + Bev was 23.3%.
Patel J et al. 2012 Multidisciplinary Symposium in Thoracic Oncology. Abstract LBDL1.

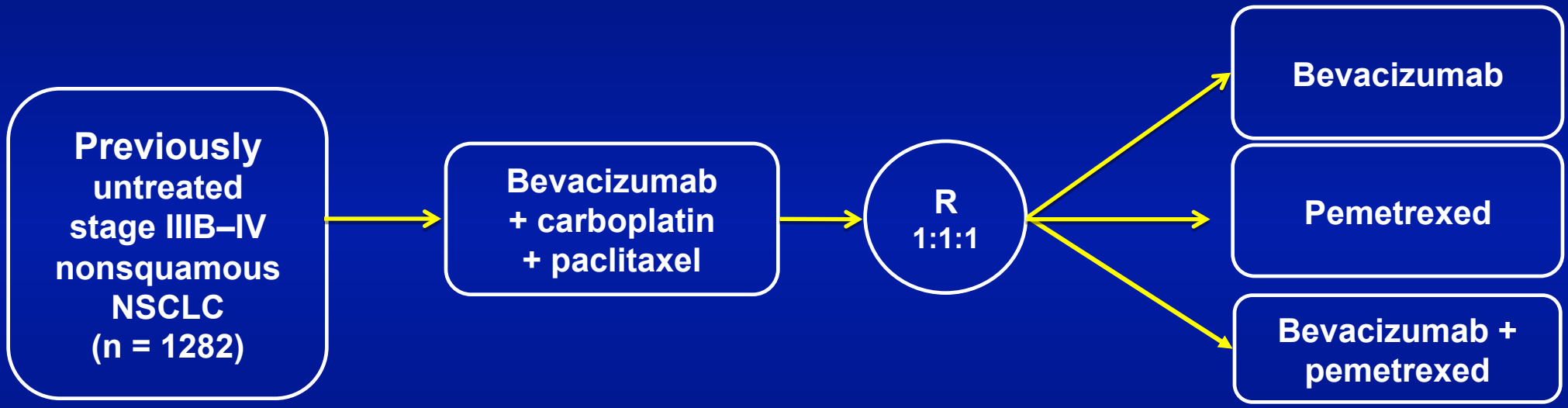
Putting it all together

- The key is to figure out which drug to give to which patient.
- Once you are on an effective drug, stay on it as tolerated. (Most patients are unable to tolerate more than 6 cycles of platinum, or taxanes.)
- Finding the right drug is more important than the concept of “maintenance” therapy

What about “switch” maintenance?

Drug	N	PFS	OS
Docetaxel v. delay	309	5.7 2.7	12.3 9.7
Pemetrexed v. placebo	663	4.0 2.0	13.4 10.6
Erlotinib v. placebo	889	12 wks 11 wks	12.0 11.0
Erlotinib + bevacizumab v. bevacizumab	768	4.8 3.7	15.9 13.9

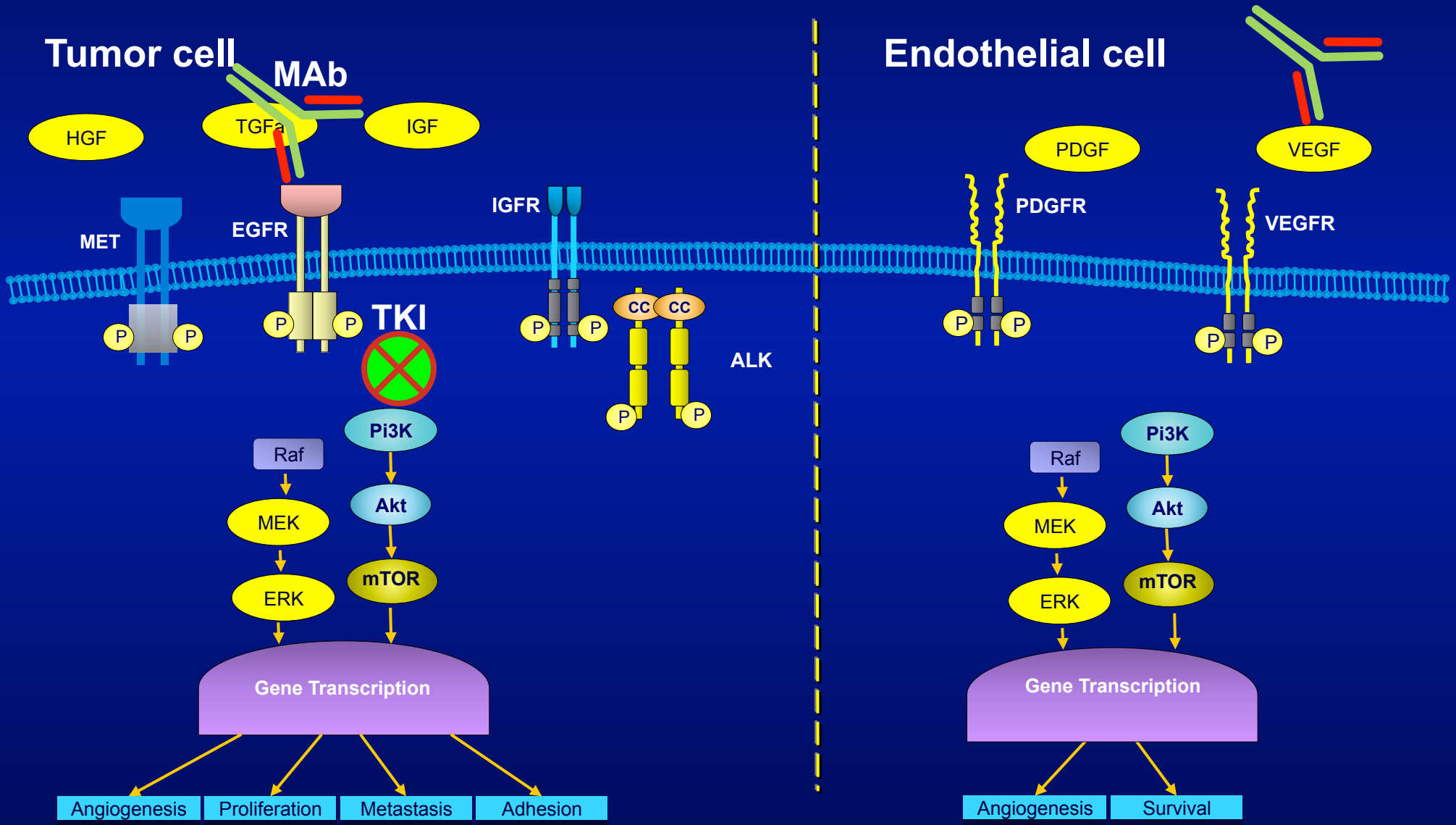
ECOG-5508



Primary endpoint: OS

ClinicalTrials.gov. Available at: http://clinicaltrials.gov/ct2/show/NCT01107626. Accessed 30 January 2013.

Molecular Targets for New Drugs



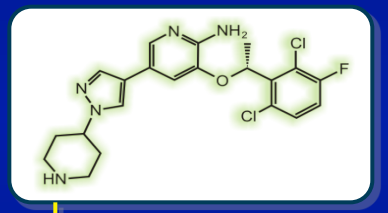
1st-line EGFR TKI for *EGFR* mutation

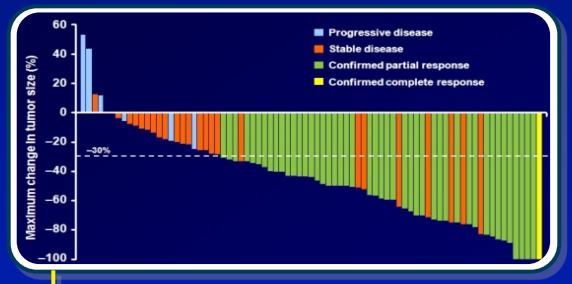
Study	Drugs	ORR	PFS	OS
IPASS Yang, ESMO 2010	gefitinib vs. carbo + paclitaxel	**71%** 47%	N=261 **HR 0.48** P<.0001	HR 1.00 P=0.990
First-SIGNAL Lee, IASLC 2009	gefitinib vs. cis + gemcitabine	**85%** 37%	N=42 **HR 0.62** P=.084	HR 0.82 P=.648
WJTOG 3405 Tsurutani ESMO 2009	gefitinib vs. cis + docetaxel	**62%** 32%	N=172 **HR 0.49** P<.001	Not reported
NEJ 002 Maemondo NEJM 2010	gefitinib vs. carbo + paclitaxel	**74%** 31%	N=228 **HR 0.30** P<.001	HR NS P=0.31
OPTIMAL Zhou, ESMO 2010	erlotinib vs. carbo + gemcitabine	**83%** 36%	N=154 **HR 0.16** P<.0001	Not reported
LUX-Lung 3 ASCO, 2012	afatinib vs. cis + pemetrexed	**56%** 23%	N=345 **HR 0.58** P=.0004	Not reported

Crizotinib

Identification of the transforming *EML4–ALK* fusion gene in non-small-cell lung cancer

Manabu Soda[1,2], Young Lim Choi[1], Munehiro Enomoto[1,2], Shuji Takada[1], Yoshihiro Yamashita[1], Shunpei Ishikawa[5], Shin-ichiro Fujiwara[1], Hideki Watanabe[1], Kentaro Kurashina[1], Hisashi Hatanaka[1], Masashi Bando[2], Shoji Ohno[2], Yuichi Ishikawa[6], Hiroyuki Aburatani[5,7], Toshiro Niki[3], Yasunori Sohara[4], Yukihiko Sugiyama[2] & Hiroyuki Mano[1,7]





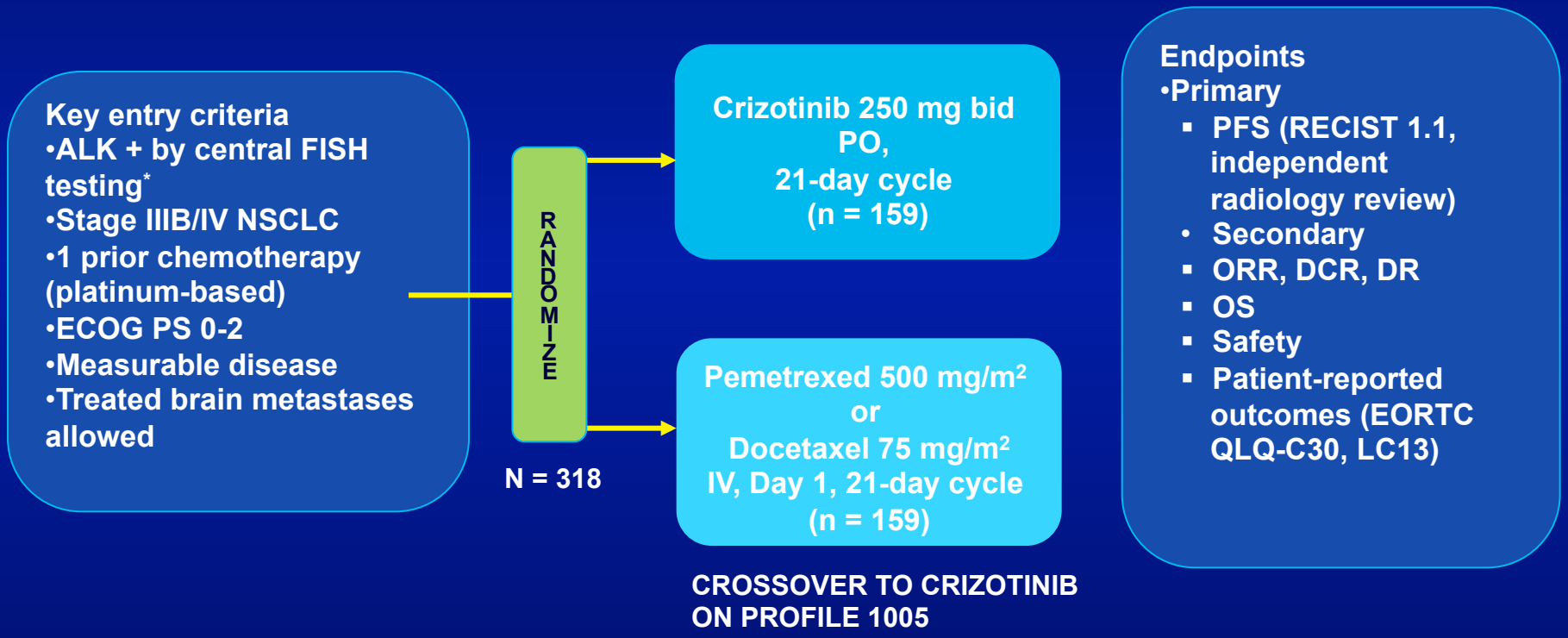
2005	2006	2007	2008	2009	2010	2011	2012
Lead compound identified	Clinical testing begins	Discovery of EML4-ALK fusion gene[1]	First clinical responses observed in ALK+ tumors	Phase 3 lung cancer trial initiated	ASCO plenary of expanded ALK+ cohort[2]	FDA approval	EMA approval

Rapid timeline from compound identification, target discovery, and clinical results

1. Soda M et al. *Nature.* 2007;448:561-566.
2. Bang JY et al. ASCO 2010 Annual Meeting. Abstract 3.

Crizotinib Phase III

Study Design



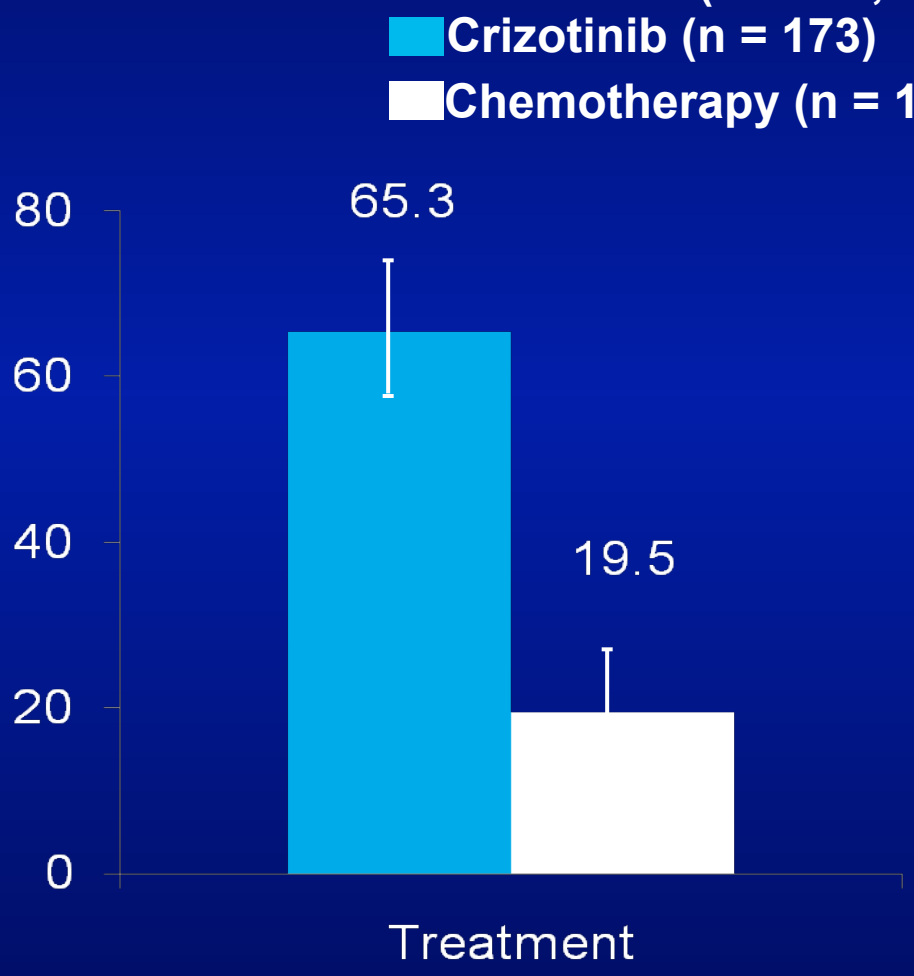
PROFILE 1007:NCT00932893

*ALK status determined using standard ALK break-apart FISH assay.
Stratification factors: ECOG PS (0/1 vs 2), brain metastases (present/absent), and prior EGFR TKI (yes/no).

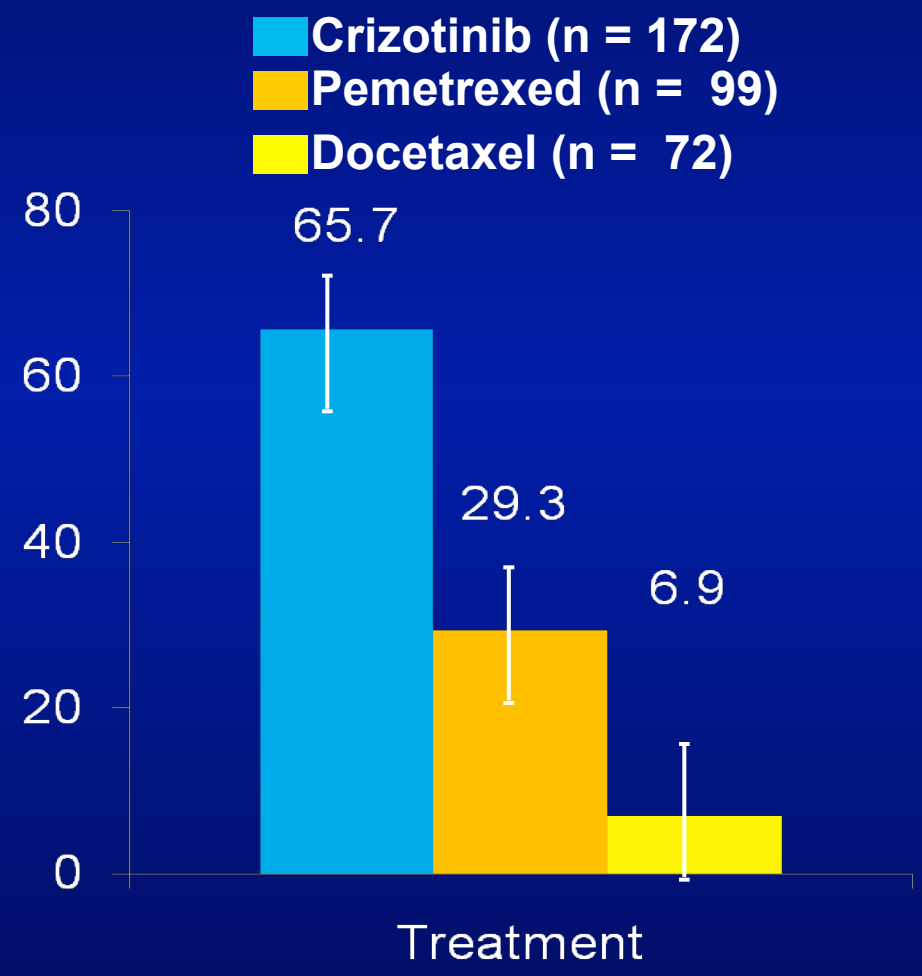
Shaw AT et al. ESMO 2012. Abstract LBA-1.

Crizotinib Phase III

ORR ratio 3.4 (95% CI, 2.5-4.7); *P*<0.0001

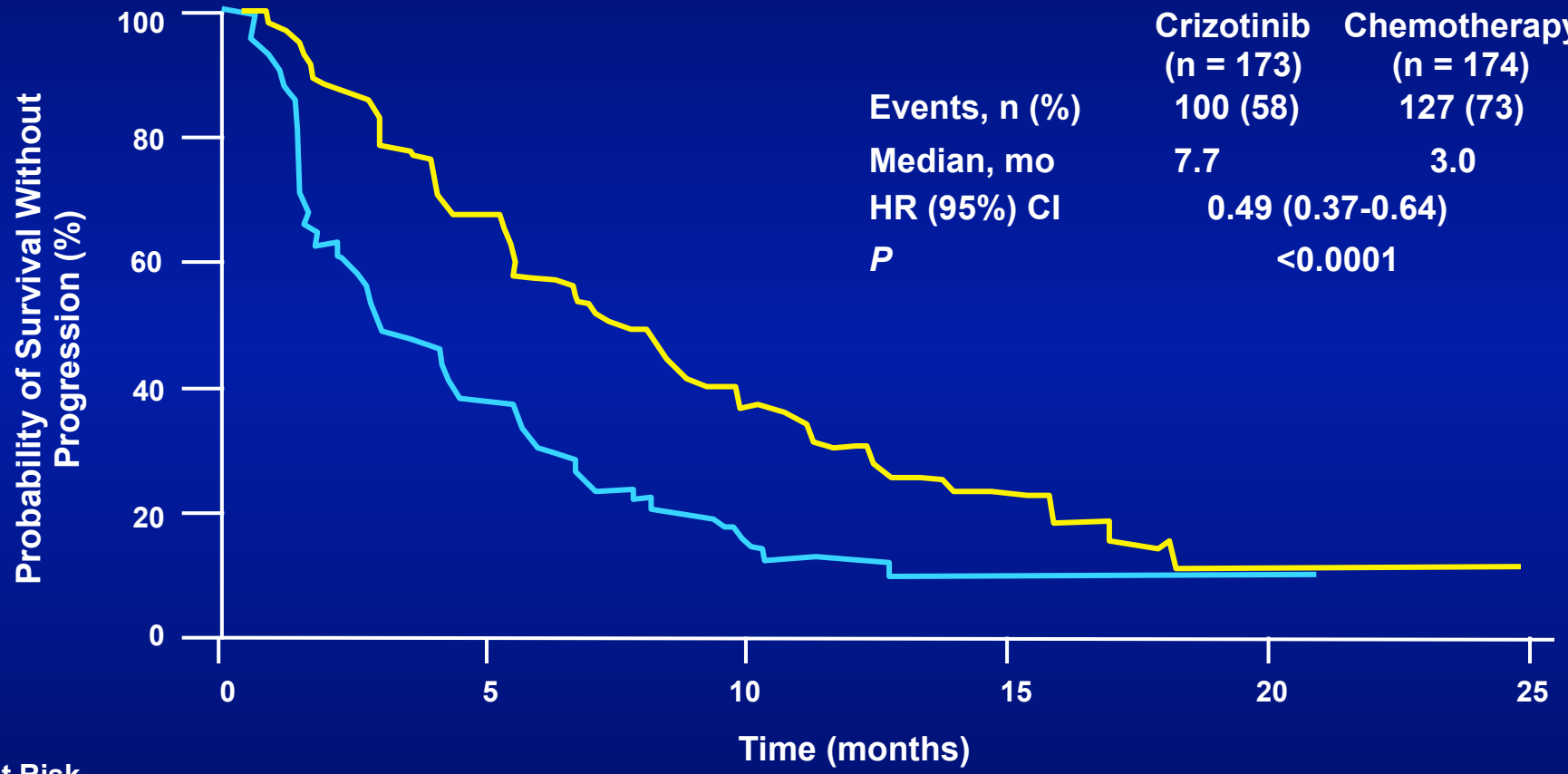


Shaw AT et al. ESMO 2012. Abstract LBA-1.



Shaw AT et al. ESMO 2012. Abstract LBA-1.

Crizotinib Phase III

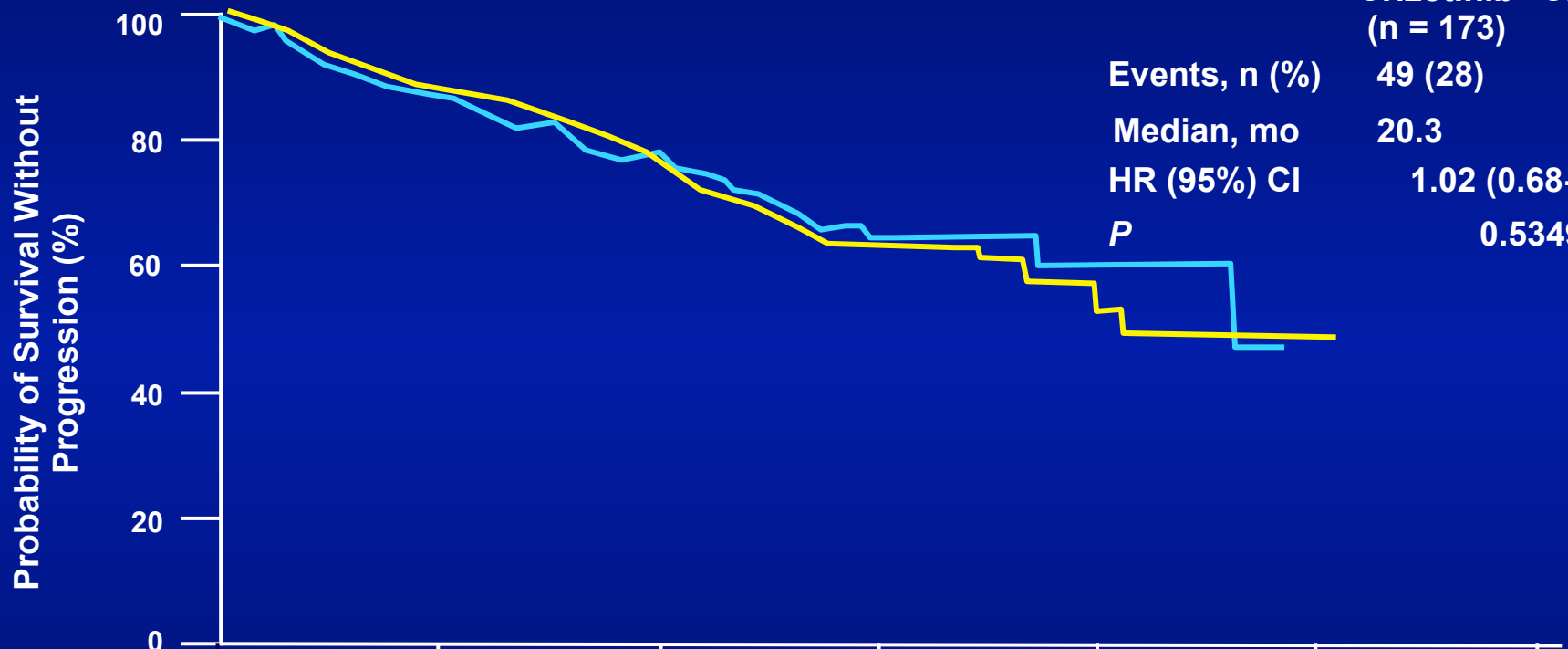


	Crizotinib (n = 173)	Chemotherapy (n = 174)
Events, n (%)	100 (58)	127 (73)
Median, mo	7.7	3.0
HR (95% CI	0.49 (0.37-0.64)	
P	<0.0001	

No. at Risk						
Crizotinib	173	93	38	11	2	0
Chemotherapy	174	49	15	4	1	0

Shaw AT et al. ESMO 2012. Abstract LBA-1.

Crizotinib Phase III



	Crizotinib (n = 173)	Chemotherapy* (n = 174)
Events, n (%)	49 (28)	47 (23)
Median, mo	20.3	22.8
HR (95% CI	1.02 (0.68-1.54)†	
P	0.5349	

No. at Risk							
Crizotinib	173	129	82	37	11	1	0
Chemotherapy	174	129	84	34	10	0	

*111 patients crossed over to crizotinib outside PROFILE 1007.
†HR adjusted for crossover using rank-preserving structural failure time method: 0.83 (0.36-1.35).

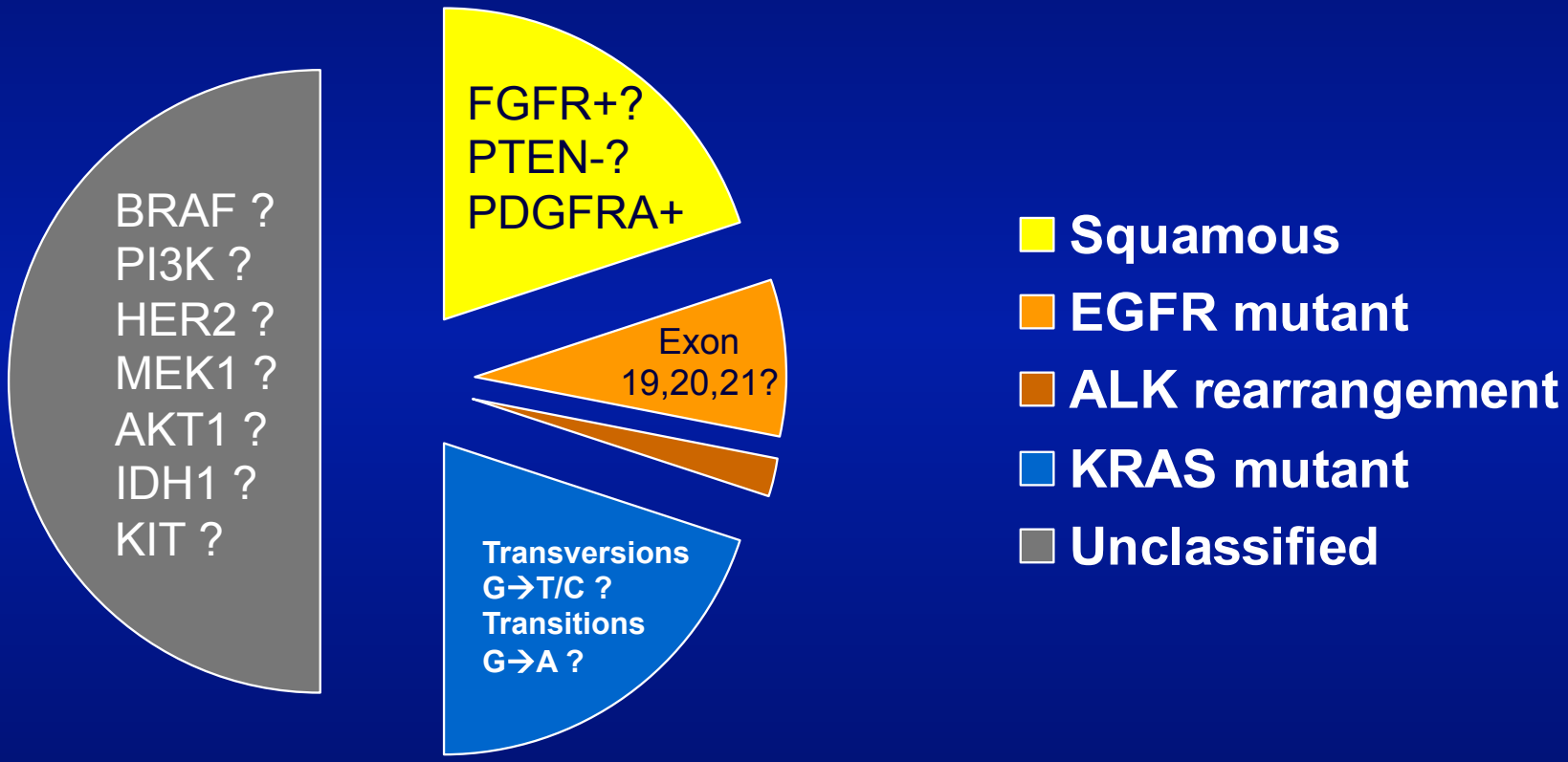
Shaw AT et al. ESMO 2012. Abstract LBA-1.

Chemotherapy for Stage IV NSCLC

Survival	No Chemo	Cyto-toxic chemo	Carbo + taxol + bev	Pem + cis non-squam	"4 cycles" + maint.	EGFR TKI for EGFR mutant	ALK TKI for ALK trans
MST (mo)	6	10	12	12	17	24	24
1-year (%)	10	40	50	50	70	80	80
2-year (%)	1	15	20	20	40	50	50

NSCLC Meta-Analyses Collaborative Group, J Clin Oncol. 2008; 26(28): 4617–25
Scagliotti, J Clin Oncol. 2008 Jul 20;26(21):3543-51
Sandler, NEJM 2006
Paz Ares, Lancet Oncology 13, 2012
Barlesi F, *Eur J Cancer.* 2011;47(suppl 2). Abstract LBA34
Mok, NEJM 2008
Shaw, Lancet Oncology 2012; 12(11):1004-12.

Stage IV NSCLC: Clinically Relevant Subgroups, 2013



Chemotherapy for Extensive Stage Small Cell Lung Cancer

Survival	No Chemo	Best Cytotoxic chemo
MST (mo)	3	10
1-year (%)	1	35
2-year (%)	0	8

Hanna, J Clin Oncol 24:2038, 2006

“Don’t smoke cigarettes !”

Lung Cancer: Next Steps in Incurable Disease

- A word on lung cancer screening
- How are we making progress in incurable disease?
  - More drugs
  - Getting the right drug to the right patient, and giving as much as you can (Maintenance therapy)
  - Better drugs
- Clinically relevant subgroups, 2013