KLINISCHE RATIONALE FÜR DEN EINSATZ DER ERSTEN ZIELGERICHTETEN MONOTHERAPIE BEI NSCLC IN DER 1ST LINE

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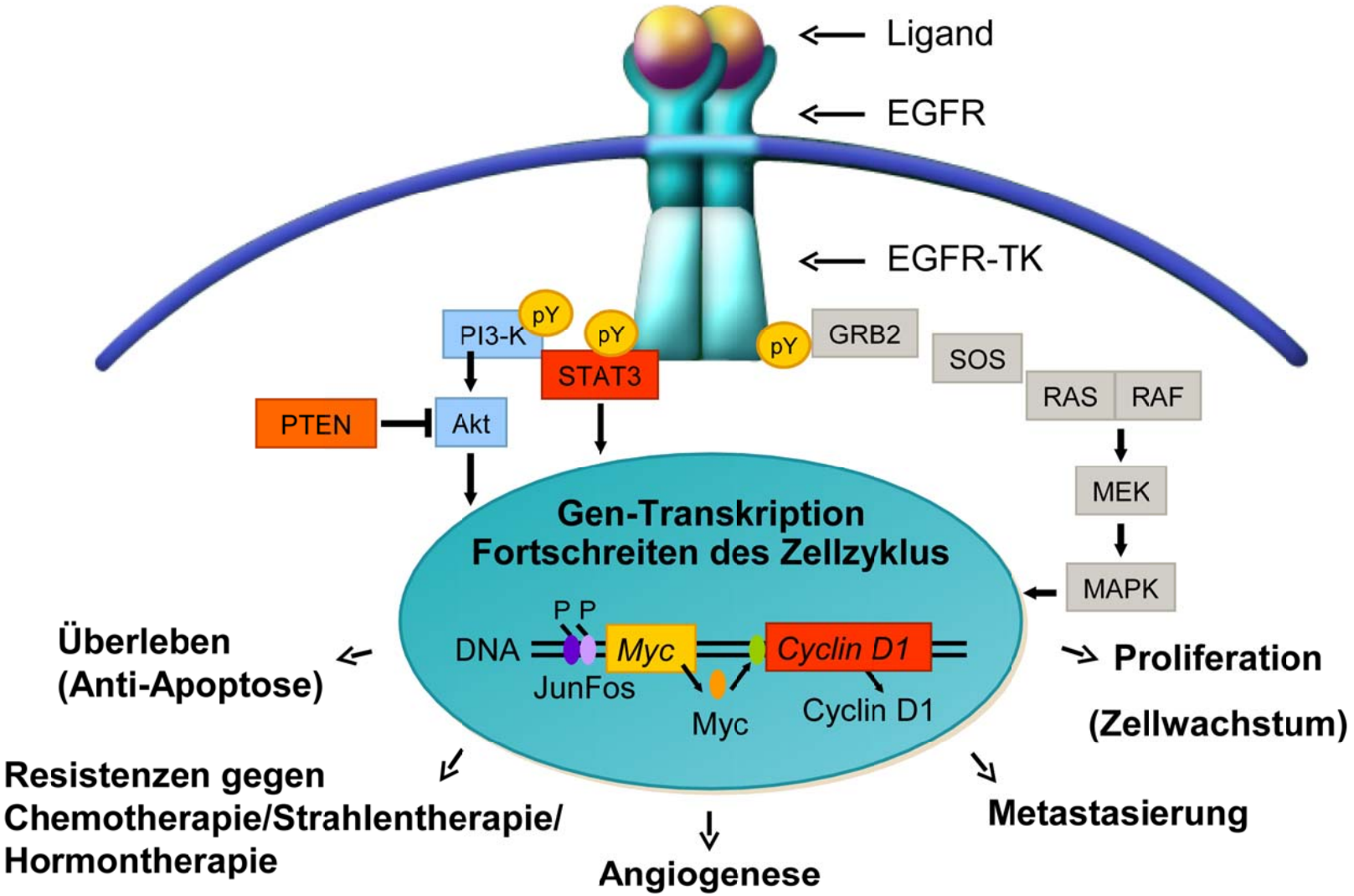
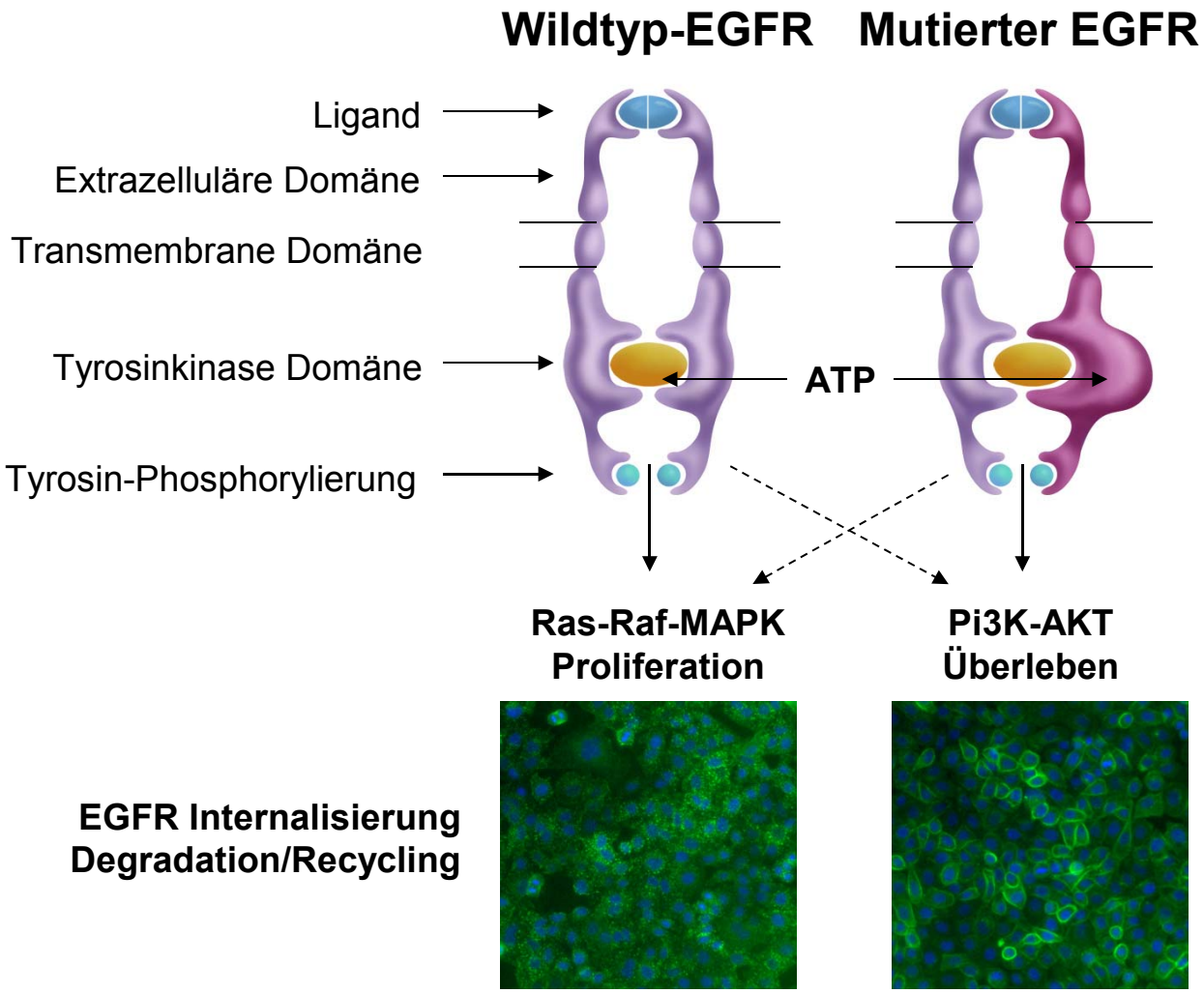
Die Aktivierung von EGFR: Zentraler Faktor bei der Tumorentwicklung



Wells A Int J Biochem Cell Biol 1999; 31: 637-643
Baselga J et al. Signal 2000; 1: 12-21

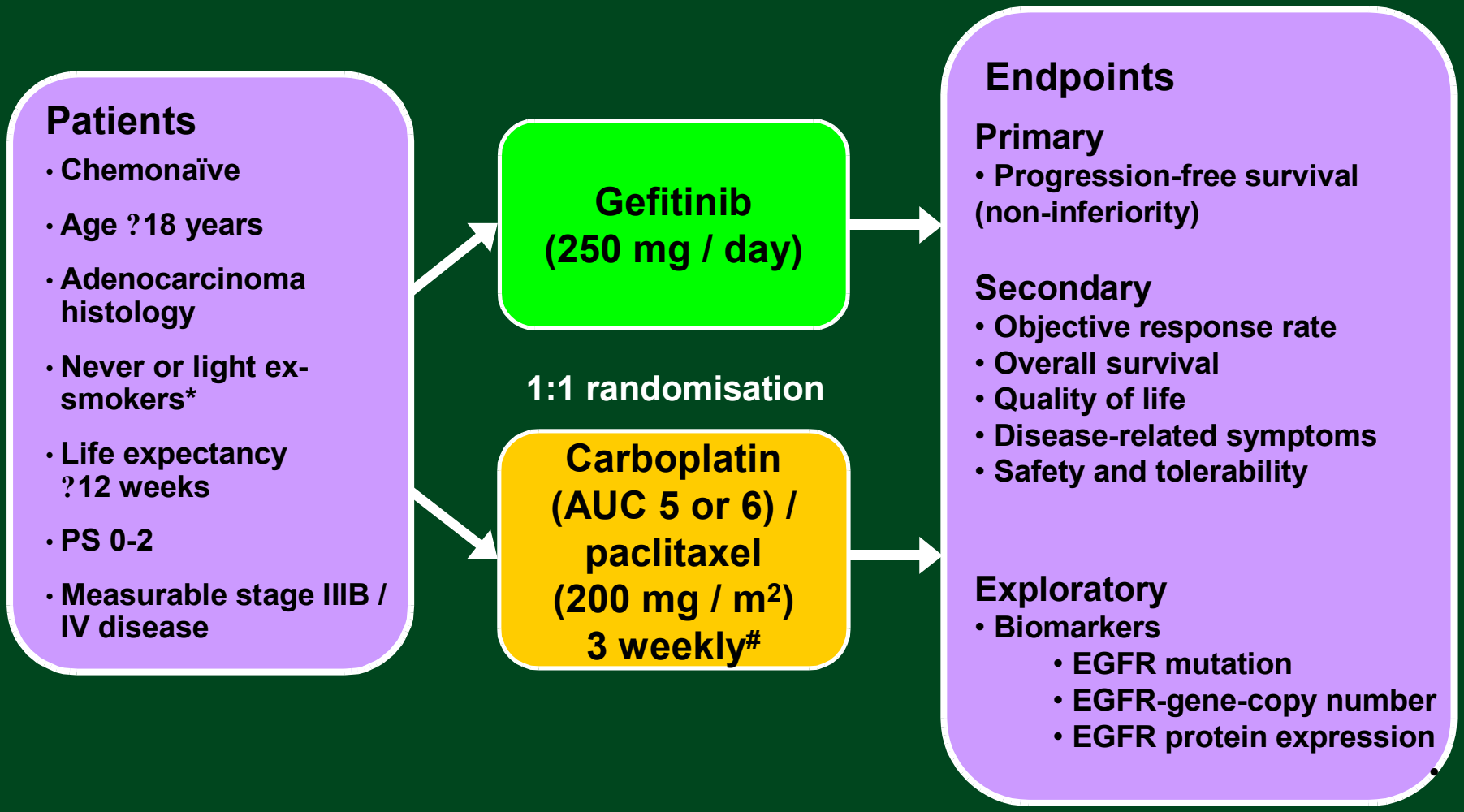
Mutation bewirkt konformative Änderung und zunehmende Aktivierung



EGFR Internalisierung
Degradation/Recycling

EGFR-Signale länger an der Zellmembran→ erhöhte Rezeptoraktivität

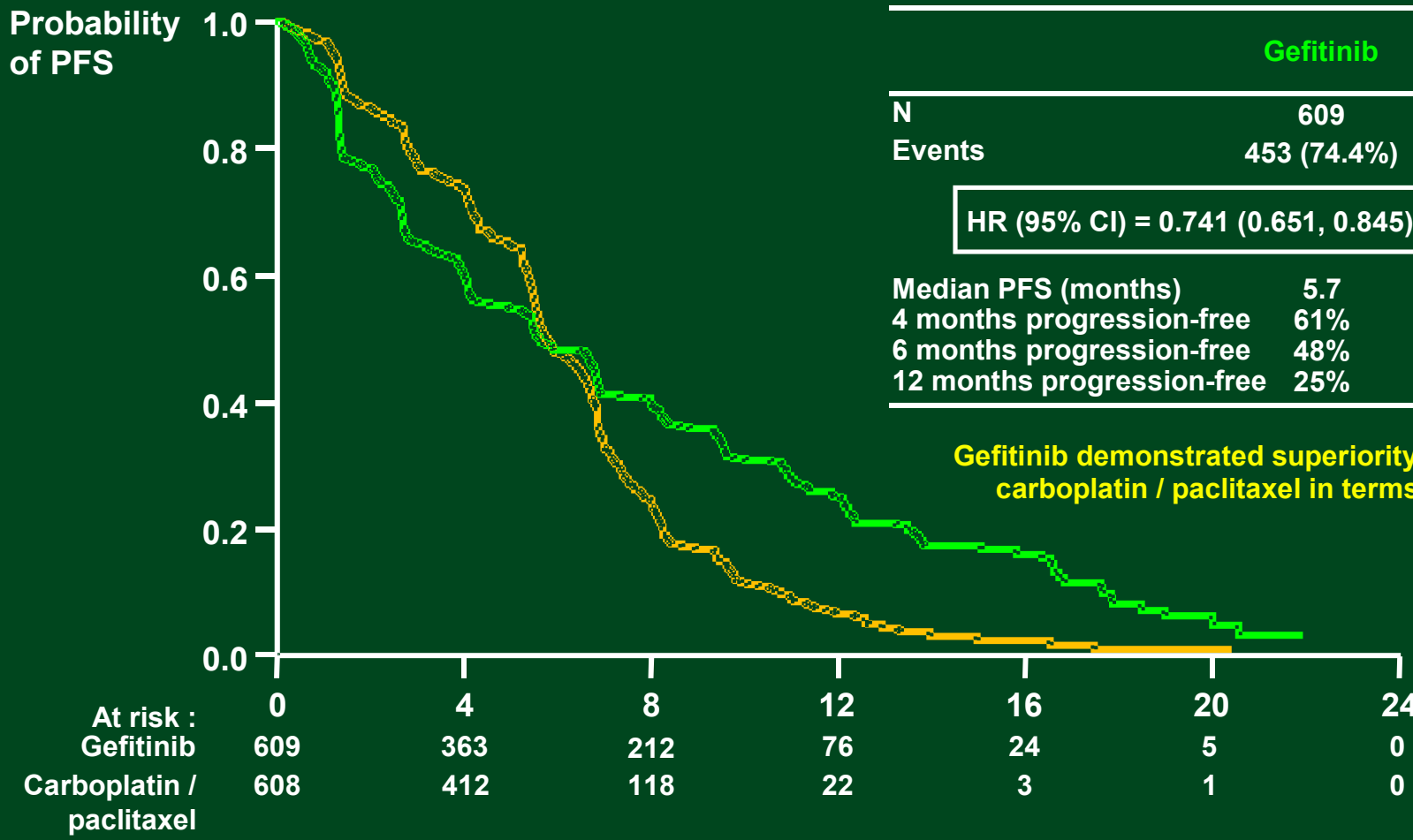
Study design



*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, NEJM 2009

Progression-free survival in ITT population



	Gefitinib	Carboplatin / paclitaxel
N	609	608
Events	453 (74.4%)	497 (81.7%)

HR (95% CI) = 0.741 (0.651, 0.845) p<0.0001

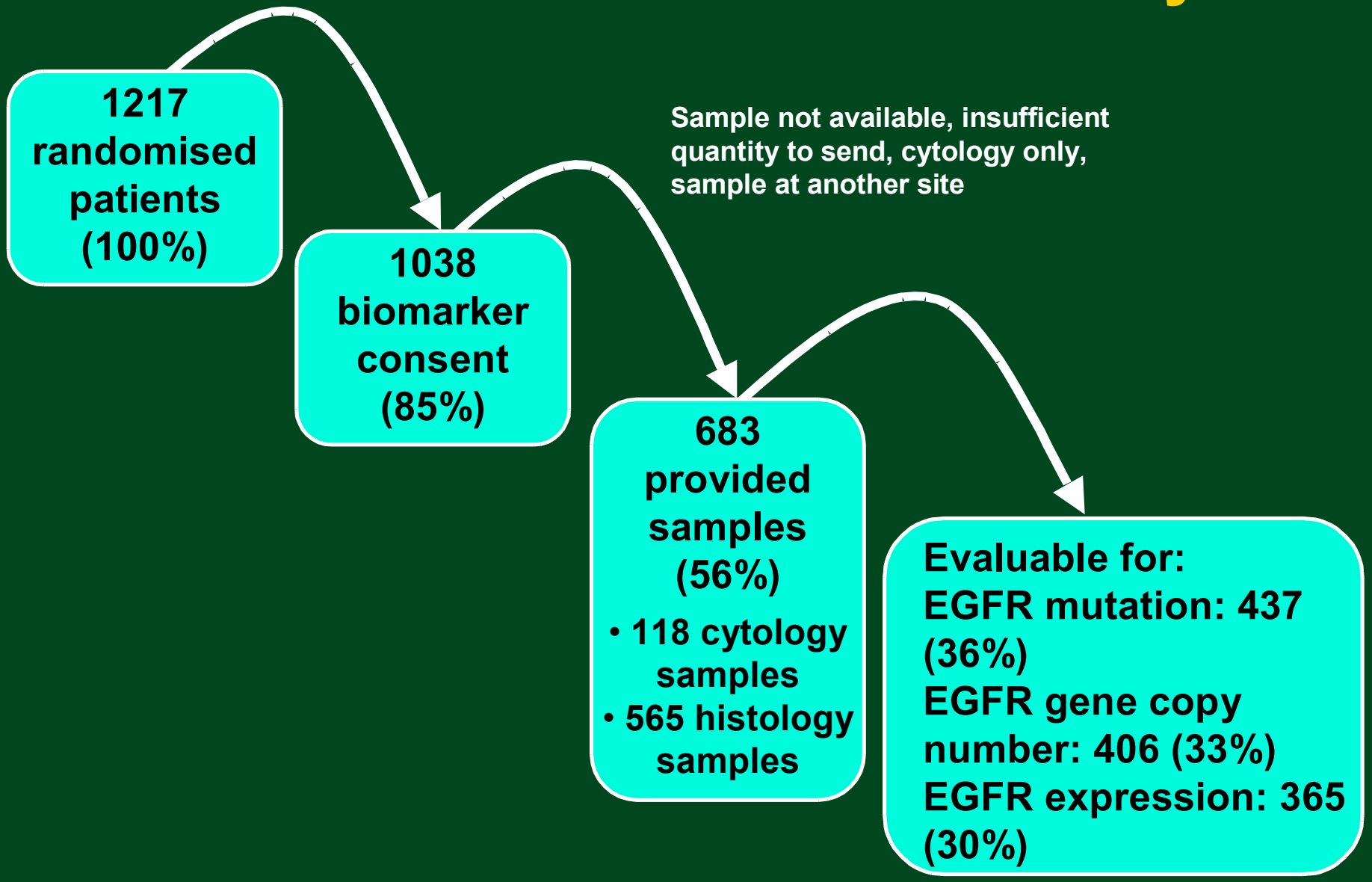
Median PFS (months)	5.7	5.8
4 months progression-free	61%	74%
6 months progression-free	48%	48%
12 months progression-free	25%	7%

Gefitinib demonstrated superiority relative to carboplatin / paclitaxel in terms of PFS

Primary Cox analysis with covariates
HR <1 implies a lower risk of progression on gefitinib

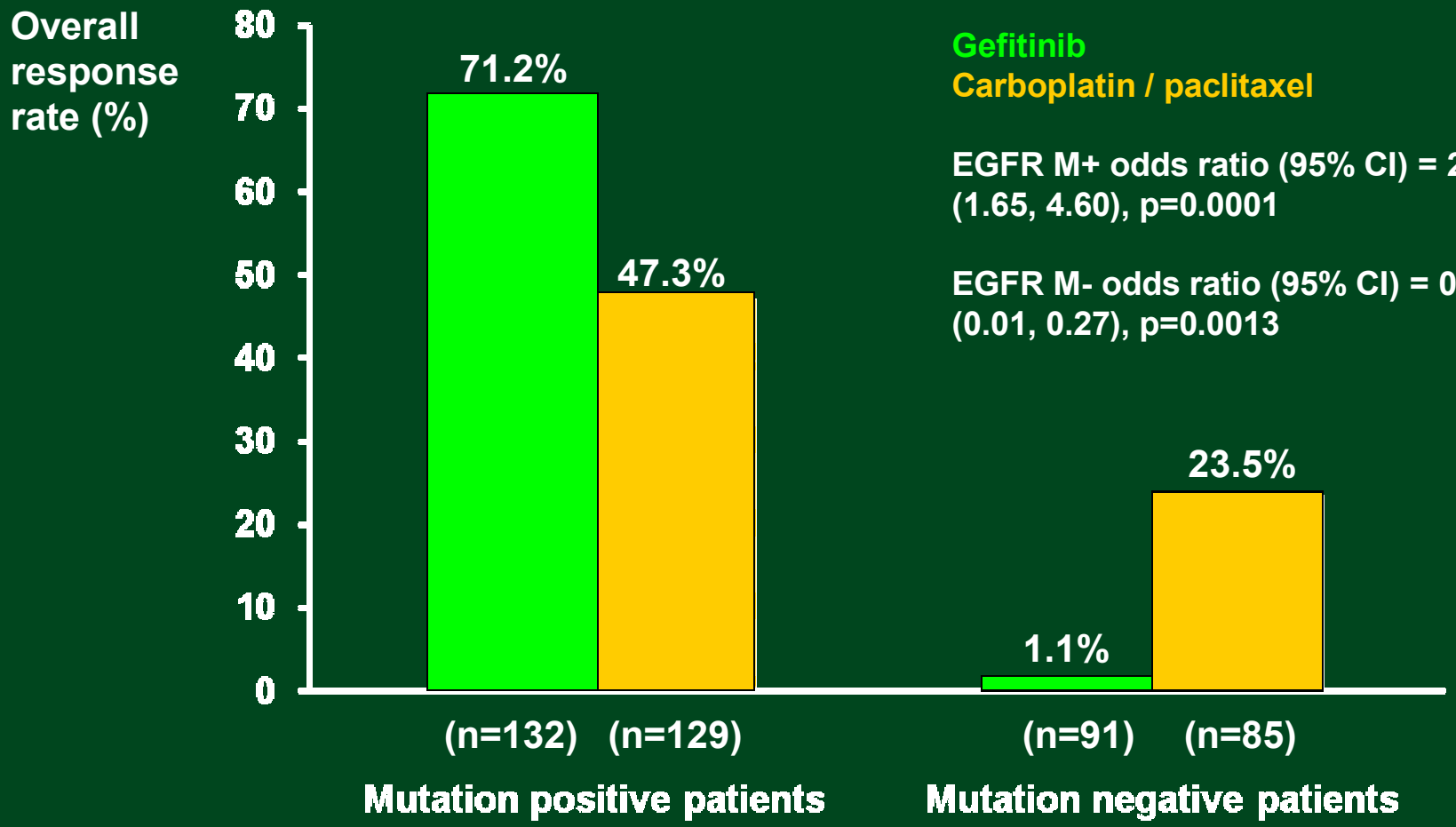
Mok et al, NEJM 2009

Attrition rates in biomarker analysis



Mok et al, NEJM 2009

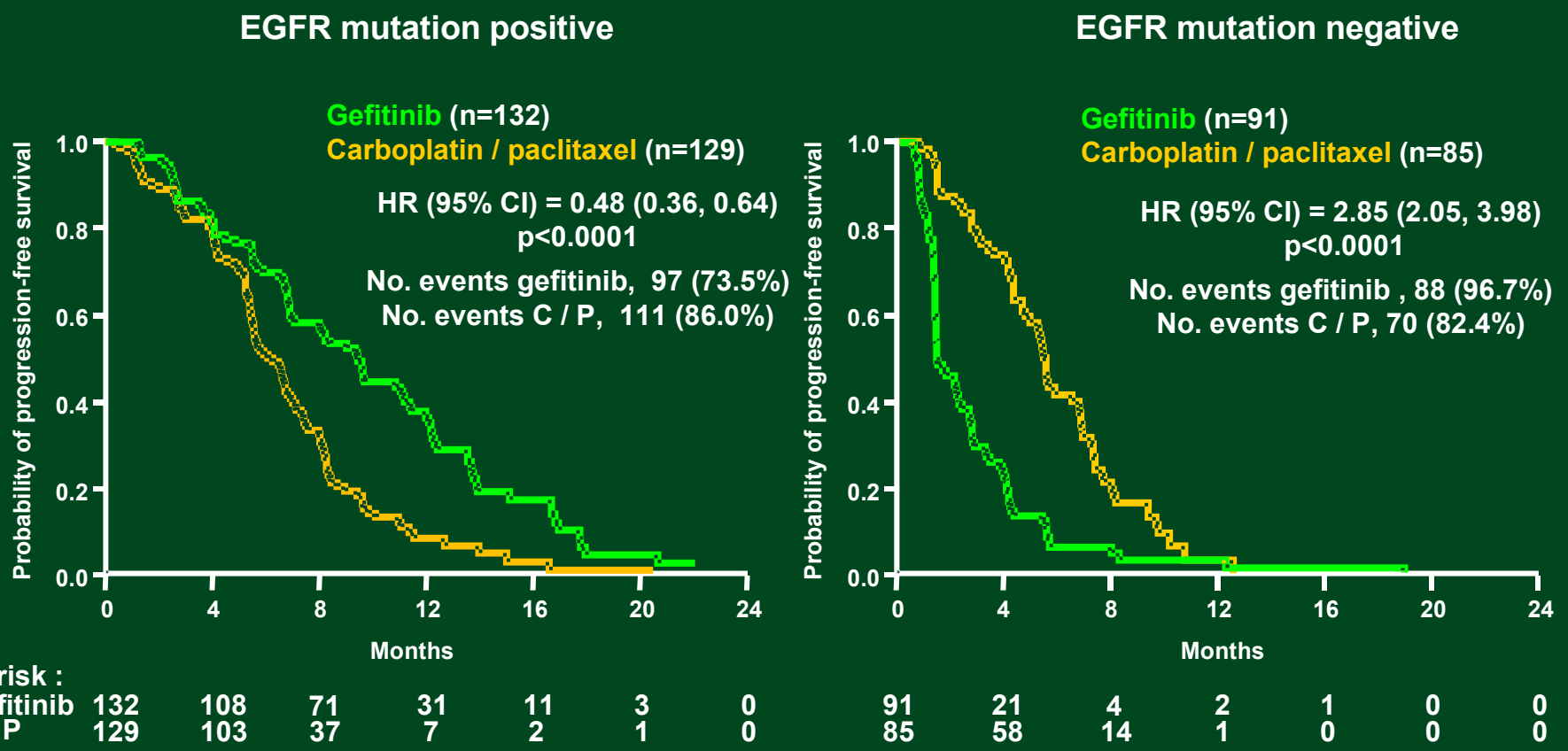
Objective response rate in EGFR mutation positive and negative patients



Odds ratio >1 implies greater chance of response on gefitinib

Mok et al, NEJM 2009

Progression-free survival in EGFR mutation positive and negative patients



At risk :							
Gefitinib	132	108	71	31	11	3	0
C / P	129	103	37	7	2	1	0

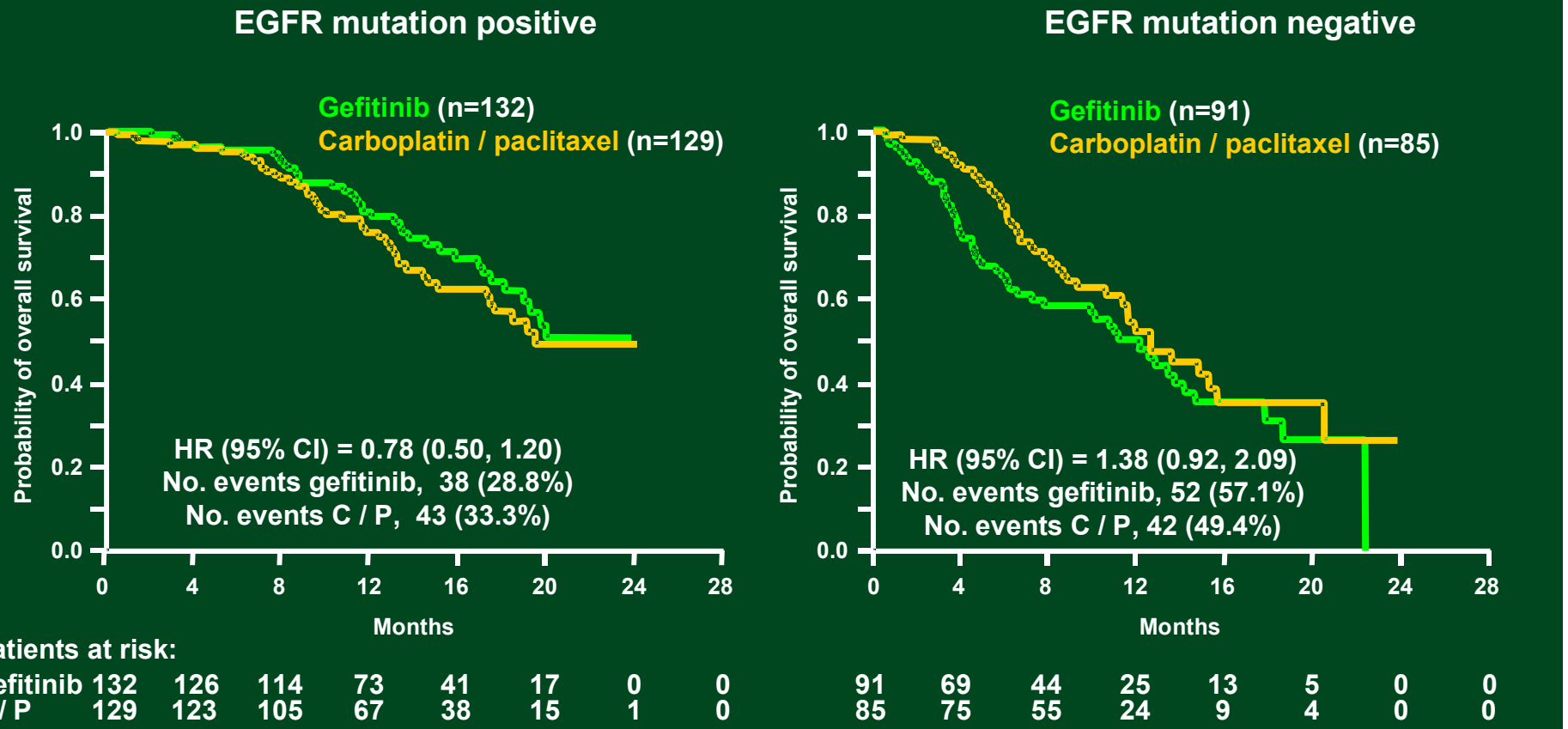
91	21	4	2	1	0	0
85	58	14	1	0	0	0

Treatment by subgroup interaction test, p<0.0001

ITT population
Cox analysis with covariates

Mok et al, NEJM 2009

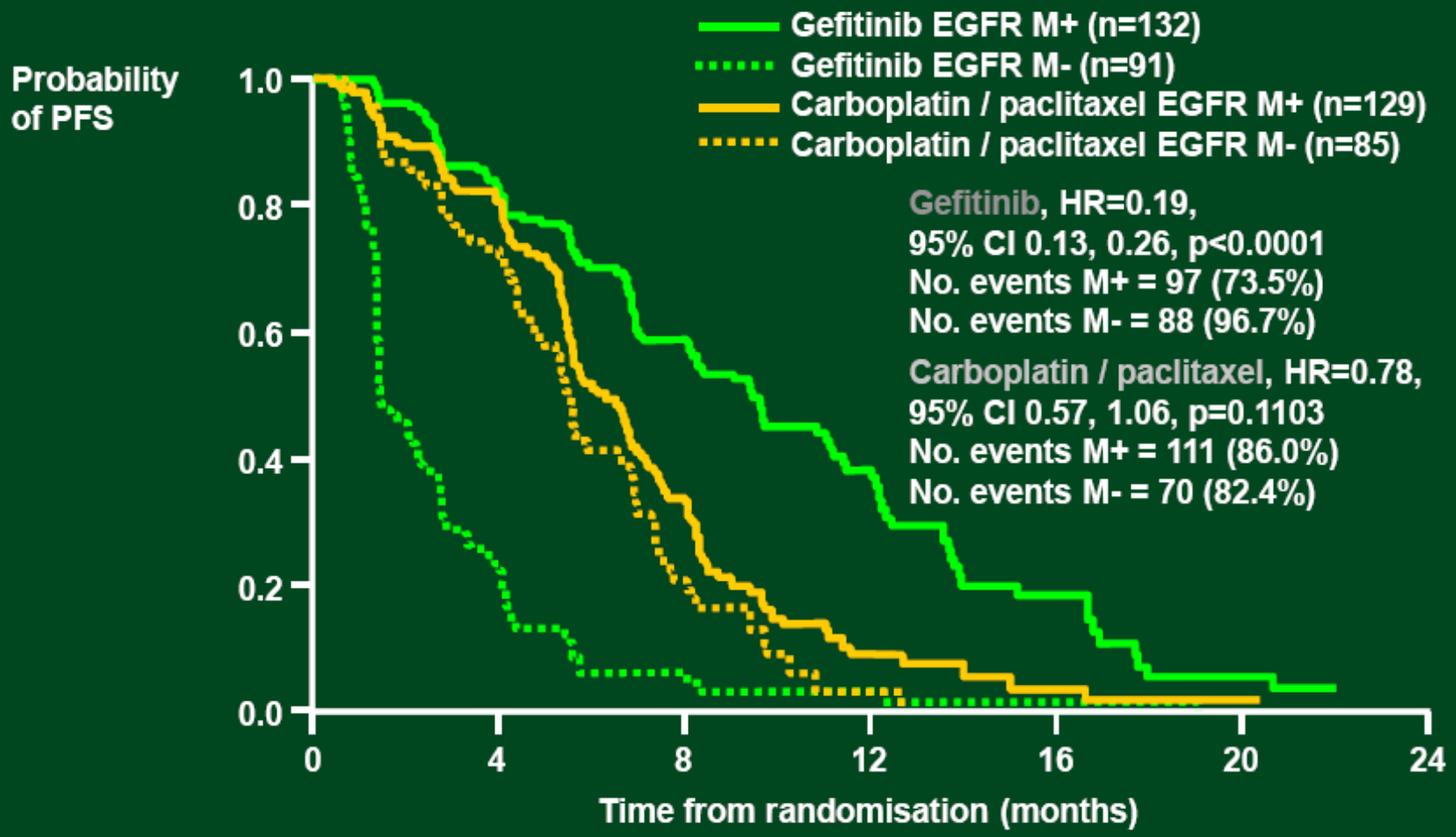
Overall survival in EGFR mutation positive and negative patients



Cox analysis with covariates
HR <1 implies a lower risk of death on gefitinib
ITT population
Post-hoc analysis of overall survival by EGFR mutation status

Mok et al, NEJM 2009

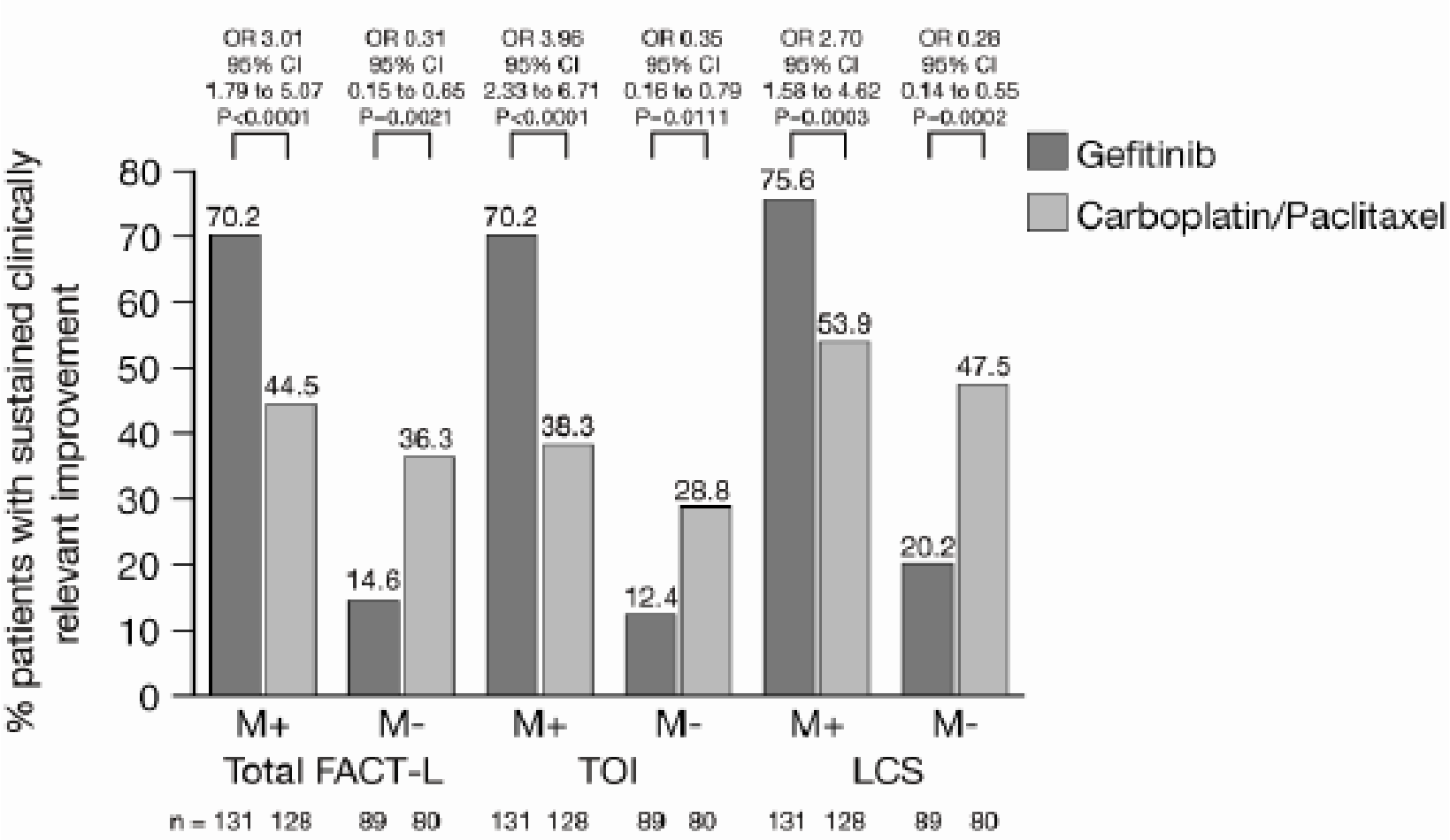
Comparison of PFS by mutation status within treatment arms



Hazard ratio <1 implies a lower risk of progression in the M+ group than in the M- group
M+, mutation positive; M-, mutation negative

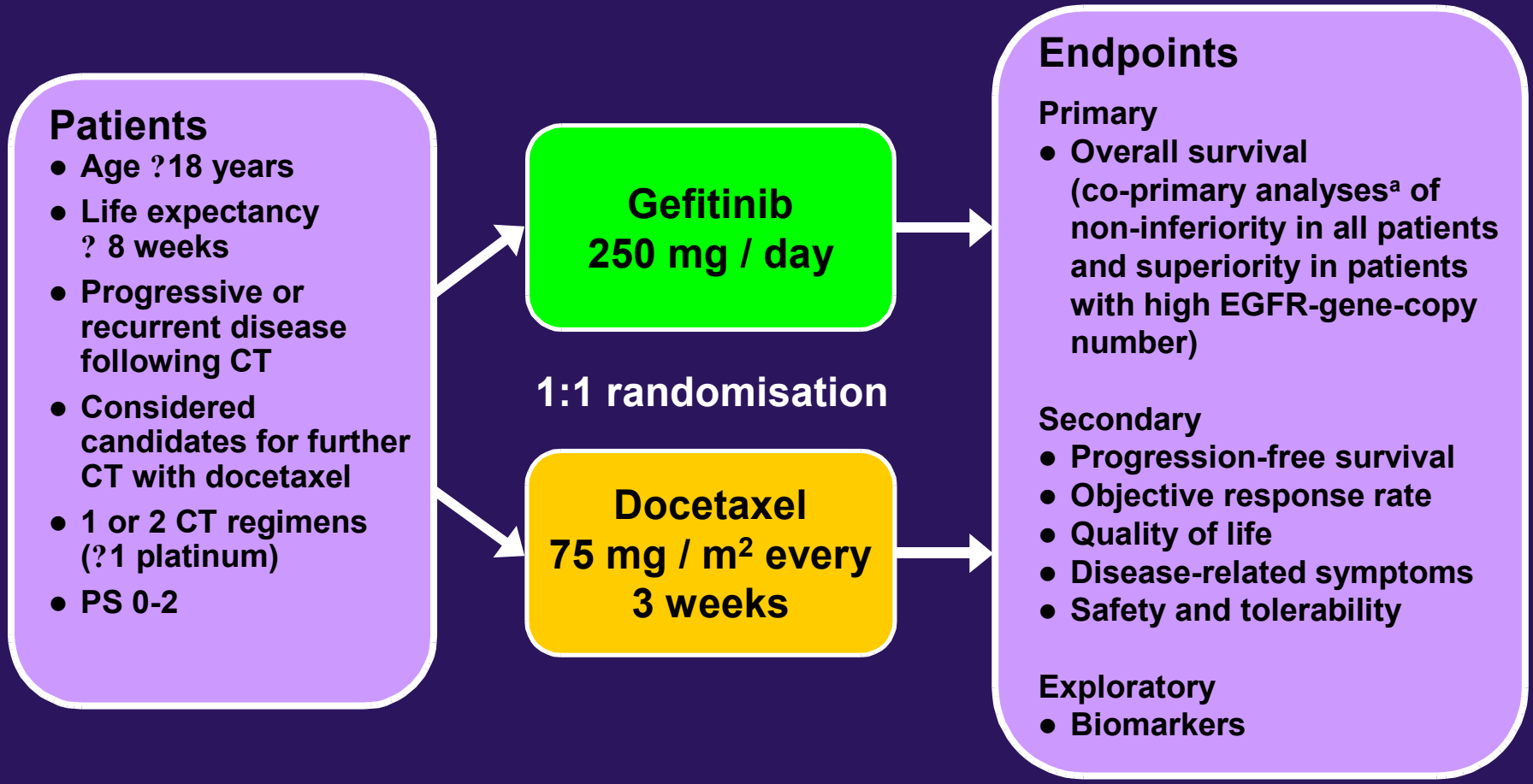
Mok et al, NEJM 2009

IPASS: Lebensqualität und Symptomatik



Supplement to: Mok et al, NEJM 2009

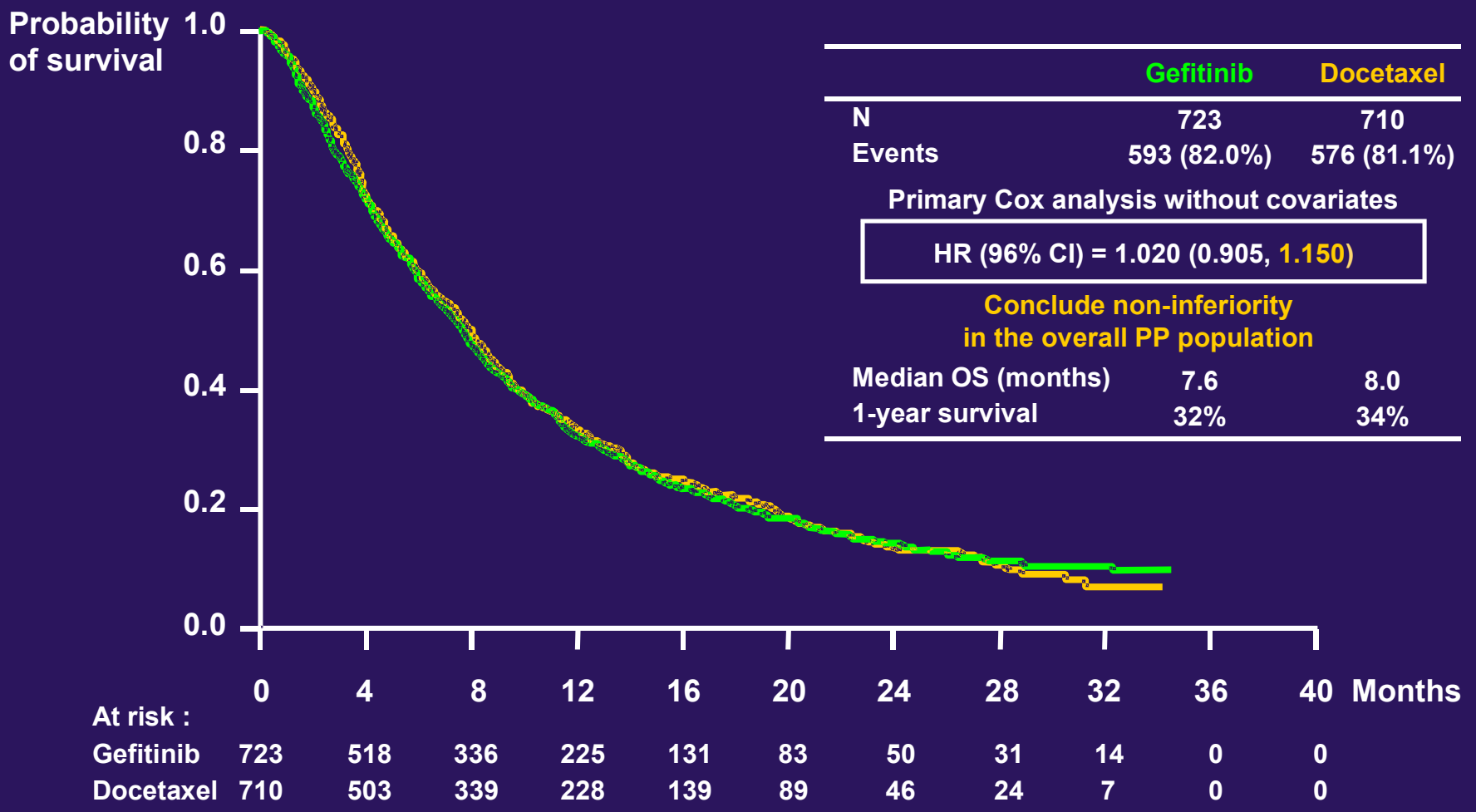
INTEREST study design



[a]Modified Hochberg procedure applied to control for multiple testing
CT, chemotherapy; PS, performance status

Kim et al. Lancet 2008

Overall survival



	Gefitinib	Docetaxel
N	723	710
Events	593 (82.0%)	576 (81.1%)

Primary Cox analysis without covariates

HR (96% CI) = 1.020 (0.905, 1.150)

Conclude non-inferiority in the overall PP population

Median OS (months)	7.6	8.0
1-year survival	32%	34%

At risk :											
Gefitinib	723	518	336	225	131	83	50	31	14	0	0
Docetaxel	710	503	339	228	139	89	46	24	7	0	0

Per-protocol (PP) population

Pre-specified NI limit in HR terms (translates to ≥50% effect retention [Rothmann 2003]) = 1.154

NI, non-inferiority; HR, hazard ratio; OS, overall survival

Kim et al. Lancet 2008

INTEREST: Subgruppenanalyse bei vortherapierten EGFR mutierten NSCLC

Population	N	Objektive Ansprechrate und 95 % KI für Unterschiede zwischen den Behandlungen[a]	Progressionsfreies Überleben[ab]	Primärer Endpunkt Gesamtüberleben[ab]
Gesamt	1466	9,1 % vs. 7,6 % [-1,5 %; 4,5 %]	HR 1,04 [0,93; 1,18] 2,2 m vs. 2,7 m p = 0,4658	HR 1,020 [0,905; 1,150][c] 7,6 m vs. 8,0 m p = 0,7332
EGFR-mutations-positiv	44	42,1 % vs. 21,1 % [-8,2 %; 46,0 %]	HR 0,16 [0,05; 0,49] 7,0 m vs. 4,1 m p = 0,0012	HR 0,83 [0,41; 1,67] 14,2 m vs. 16,6 m p = 0,6043
EGFR-mutations-negativ	253	6,6 % vs. 9,8 % [-10,5 %; 4,4 %]	HR 1,24 [0,94; 1,64] 1,7 m vs. 2,6 m p = 0,1353	HR 1,02 [0,78; 1,33] 6,4 m vs. 6,0 m p = 0,9131

IRESSA Fachinformation, Stand 06/2009

Zusammenfassung

- Das Vorliegen einer EGFR Mutation ist ein starker prädiktiver Faktor für die Wirksamkeit von Iressa versus Carboplatin/Paclitaxel

- In der 1st line Therapie der NSCLC-Patienten mit positiven EGFR-Mutationsstatus zeigt Iressa:

  - eine signifikant höhere Ansprechrate (71,2% vs 47,3%; p = 0,0001)
  - ein signifikant längeres progressionsfreies Überleben (9,5 Monate vs 6,3 Monate; p < 0, 0001)

- Herausforderung für die Praxis: histologische Probe

Mit Iressa steht erstmals eine tatsächlich zielgerichtete Therapie in allen Therapielinien zur Verfügung, die in der Erstlinientherapie eine bessere Alternative zur bisherigen Chemotherapie bietet