

**Phase III, randomised, open-label,
first-line study of gefitinib vs
carboplatin / paclitaxel in clinically
selected patients with advanced non-
small-cell lung cancer (IPASS)**

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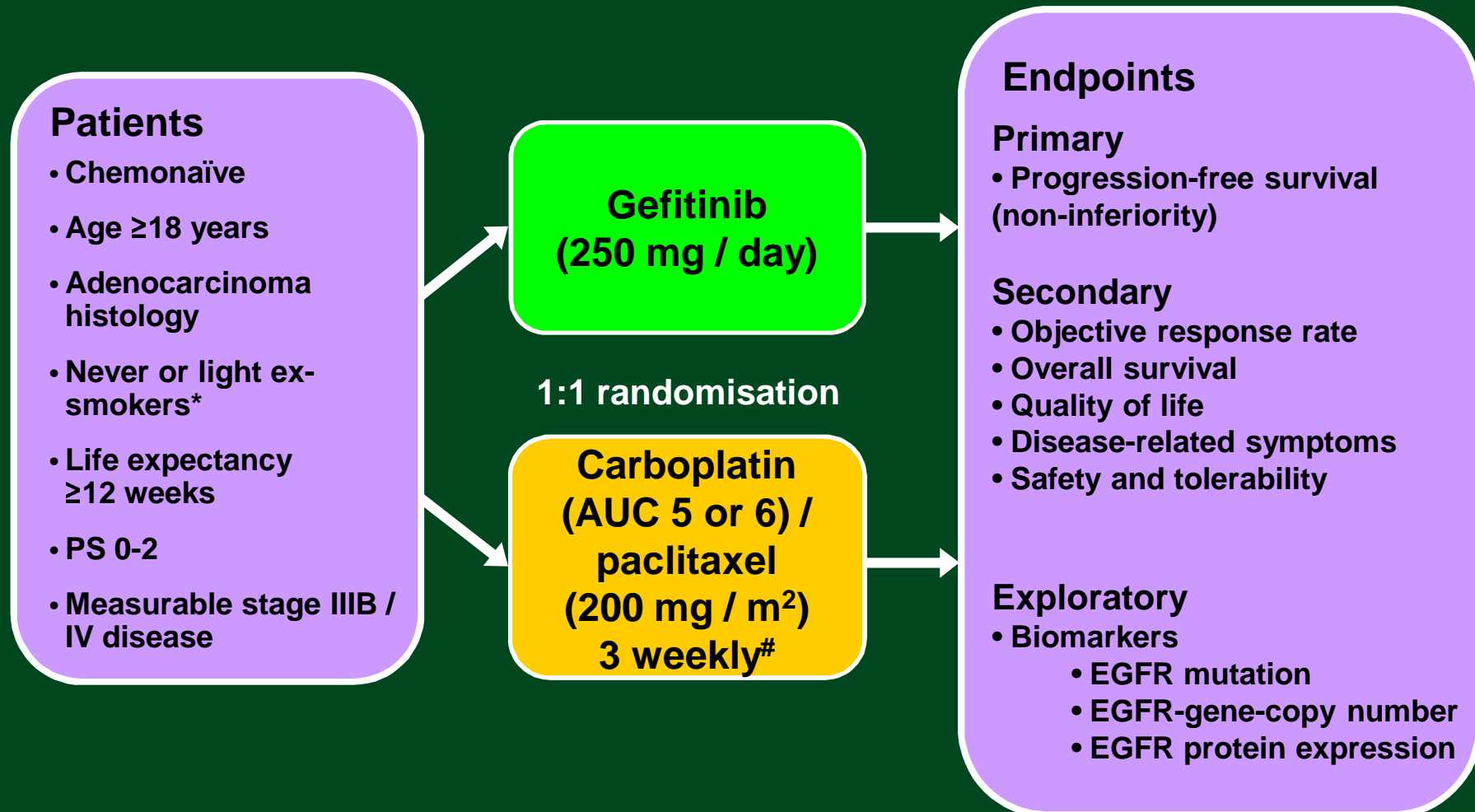
Background for IPASS (IRESSA Pan Asia Study)

- Multiple, non-comparative studies have demonstrated superior efficacy of EGFR TKIs in patients of Asian origin, never / light smokers and in patients with adenocarcinoma histology when compared to other patient groups¹⁻²
- A known higher incidence of EGFR mutation in patients with these characteristics makes analysis of efficacy by biomarker status particularly interesting³⁻⁵
- We hypothesised that a clinically selected group of patients with these characteristics treated with an EGFR TKI as first-line therapy would have efficacy at least as good as carboplatin / paclitaxel with benefits in tolerability and quality of life

EGFR TKI , epidermal growth factor receptor
tyrosine kinase inhibitor

¹ Mitsudomi and Yatabe 2007; ²Wu et al 2007;
³Paz-Ares et al 2006; ⁴Paez et al 2004;
⁵Lynch et al 2005

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

Statistical analysis

- **Primary analysis for progression-free survival**
 - to assess non-inferiority of gefitinib vs carboplatin / paclitaxel using a cox proportional hazard model
 - covariates included were gender, smoking history (never vs ex-smoker) and WHO performance status (0, 1 vs 2)
 - the pre-defined non-inferiority margin was a hazard ratio (HR) of 1.2
 - a total of 944 progression events needed for an 80% chance of concluding non-inferiority if gefitinib is truly non-inferior and a 2-sided 5% chance (significance level) of concluding non-inferiority in error
 - if non-inferiority accepted, same analysis used to assess potential superiority of gefitinib to carboplatin / paclitaxel in terms of progression-free survival

Study conduct

- **87 centres in 9 countries in Asia**
 - China, Hong Kong, Indonesia, Japan, Malaysia, Philippines, Singapore, Taiwan, Thailand
- **1217 patients randomised**
- **Randomisation period: March 2006 to October 2007**
- **Data cut-off: 14 April 2008**
 - 950 PFS events observed in ITT population (78% maturity)
- **Mean time on treatment**
 - gefitinib, 6.4 months
 - carboplatin / paclitaxel, 3.4 months (median number of cycles#: 6)
- **Final survival data (944 events) expected mid-2010**



#limited to a maximum of 6 cycles
PFS, progression-free survival; ITT, intent-to-treat

Demography (ITT population)

| | Gefitinib, % (N=609) | Carboplatin / paclitaxel, % (N=608) |
|----------------------------------|-------------------------|--|
| Age <65 years | 73 | 74 |
| Median age (range), years | 57 (24-84) | 57 (25-84) |
| Female ^a | 79 | 79 |
| WHO PS 0 / 1 / 2 ^a | 26 / 64 / 10 | 26 / 63 / 11 |
| Never smoker ^a | 94 | 94 |
| Light ex-smoker ^a | 6 | 6 |
| Mean smoking duration, years | 11.5 (N=38) | 14.5 (N=39) |
| Mean time since cessation, years | 24.6 (N=38) | 23.4 (N=39) |
| Metastatic disease | 75 | 76 |
| Time since diagnosis: <6 months | 96 | 94 |
| Chinese ethnicity ^b | 52 | 50 |
| Japanese ethnicity ^b | 19 | 20 |

WHO, World Health Organization

^a1 of the 3 stratification factors

^bnot the same as country of residence

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

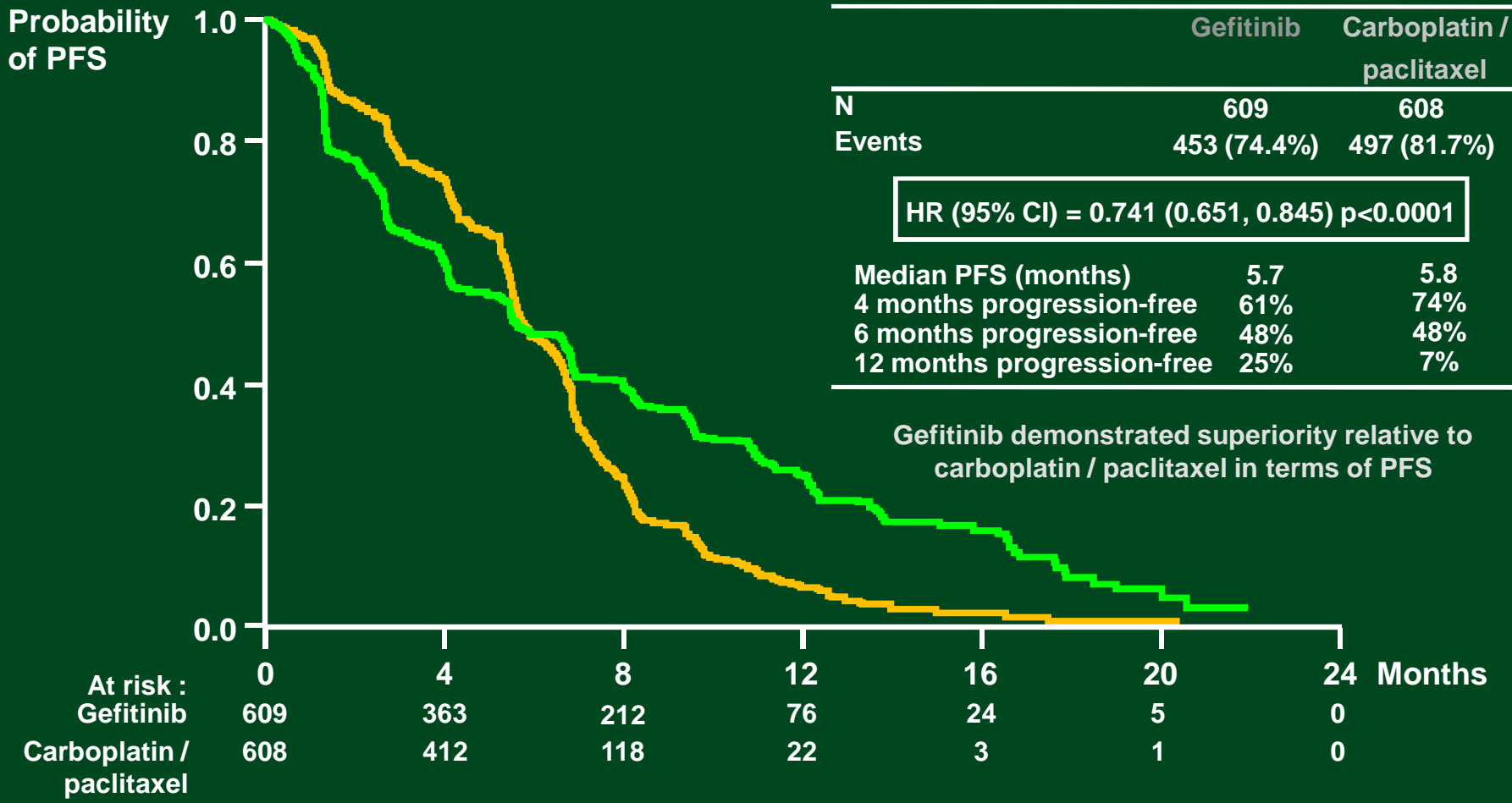
Gefitinib demonstrated superiority relative to carboplatin / paclitaxel in terms of PFS

Primary Cox analysis with covariates

HR <1 implies a lower risk of progression on gefitinib

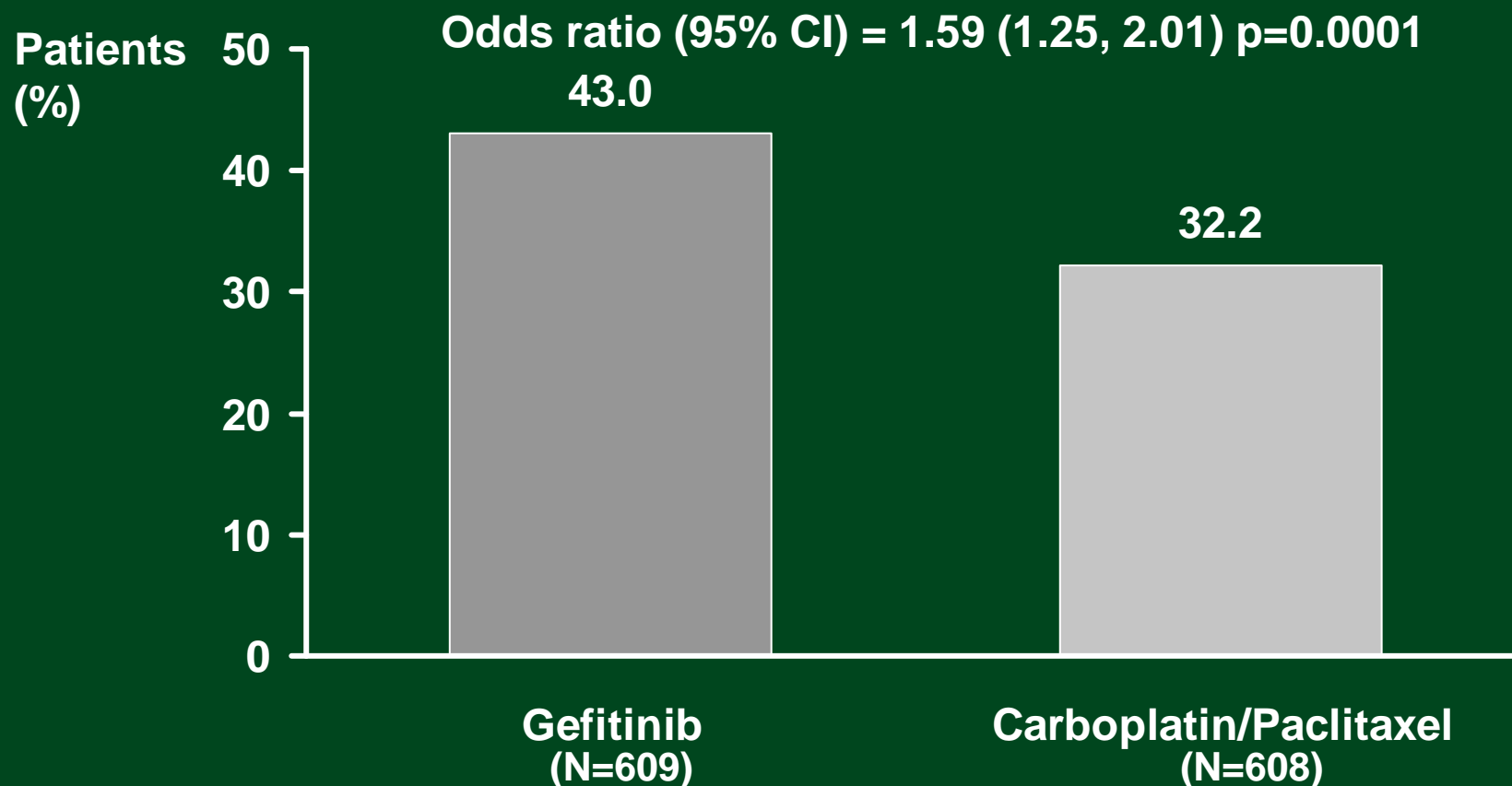
HR, hazard ratio; CI, confidence interval; PFS, progression-free survival

Progression-free survival in ITT population



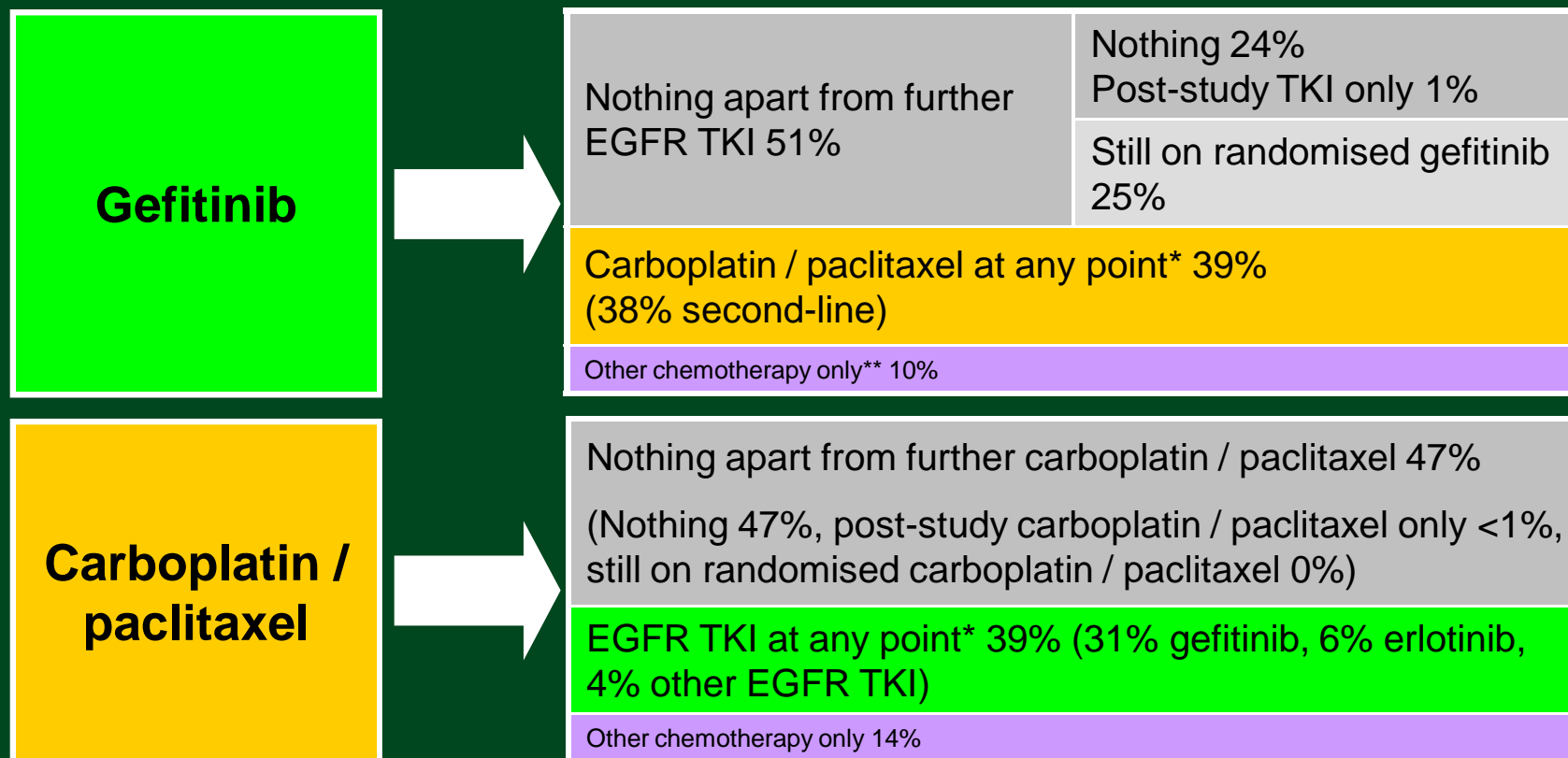
Primary Cox analysis with covariates
 HR <1 implies a lower risk of progression on gefitinib

Objective tumour response (RECIST) (ITT population)



Odds ratio >1 implies a greater chance of response on gefitinib
Odds ratio and p-value from logistic regression with covariates
RECIST, Response Evaluation Criteria In Solid Tumours

Post-discontinuation treatments (ITT population)

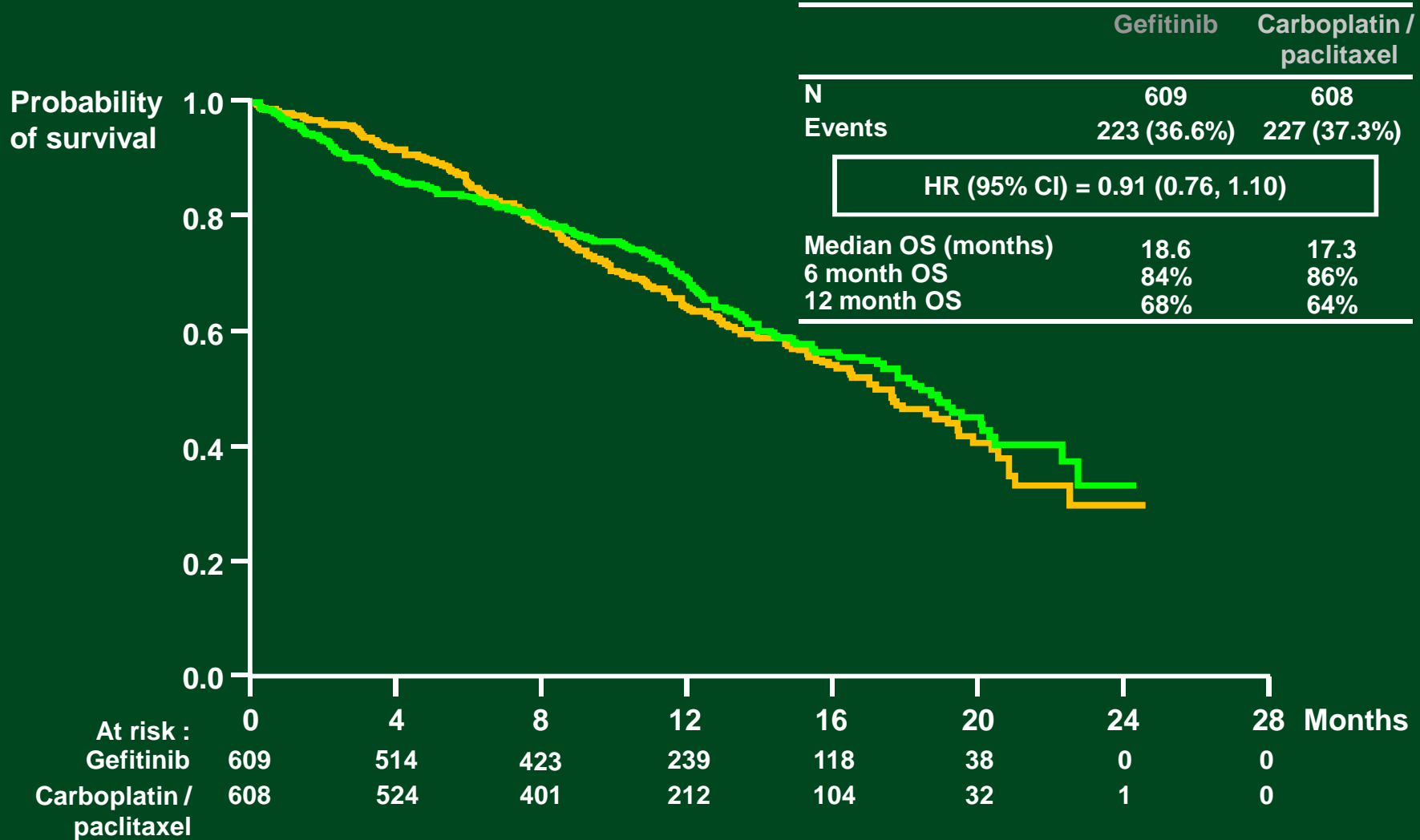


*Patients may have also received other chemotherapy and / or EGFR TKI during the study

**1% also had EGFR TKI

Radiotherapy, surgery, medical procedures and other treatments excluded
EGFR TKI, EGFR tyrosine kinase inhibitor

Overall survival in ITT population (follow-up ongoing)



Cox analysis with covariates
 HR <1 implies a lower risk of death on gefitinib
 OS, overall survival

Adverse event summary

| n (%) | All AEs | | Treatment-related ^a | |
|-------------------------------|----------------------|--|--------------------------------|--|
| | Gefitinib (N=607) | Carboplatin / paclitaxel (N=589) | Gefitinib (N=607) | Carboplatin / paclitaxel (N=589) |
| AE | 580 (95.6) | 578 (98.1) | 538 (88.6) | 569 (96.6) |
| SAE | 99 (16.3) | 92 (15.6) | 21 (3.5) | 53 (9.0) |
| AE leading to death | 23 (3.8) | 16 (2.7) | 4 (0.7) | 3 (0.5) |
| AE leading to discontinuation | 42 (6.9) | 80 (13.9) | 24 (4.0) | 67 (11.4) |
| CTC Grade 3, 4 or 5 AE | 192 (31.6) | 368 (62.5) | 103 (17.0) | 334 (56.7) |
| ILD type AE | 16 (2.6) | 8 (1.4) | 8 (1.3) | 3 (0.5) |

^aInterpret with caution due to open-label study design

AE, adverse event; SAE, serious adverse event;

CTC, common toxicity criteria; ILD, interstitial lung disease

Haematological lab changes

| Lab parameter, n (%)# | Gefitinib (N=599) | Carboplatin / paclitaxel (N=577) |
|------------------------------|------------------------------|---|
| Neutropenia | 22 (3.7) | 387 (67.1) |
| Leukopenia | 9 (1.5) | 202 (35.0) |
| Anaemia | 13 (2.2) | 61 (10.6) |
| Thrombocytopenia | 6 (1.0) | 32 (5.5) |

#Lab parameter used was absolute neutrophil count, white blood cell count, haemoglobin or platelet count worsening from baseline to CTC grade 3/4; Calculations only include patients with a baseline and at least one post-baseline value for that lab parameter

Most common adverse events: >20% difference between treatments

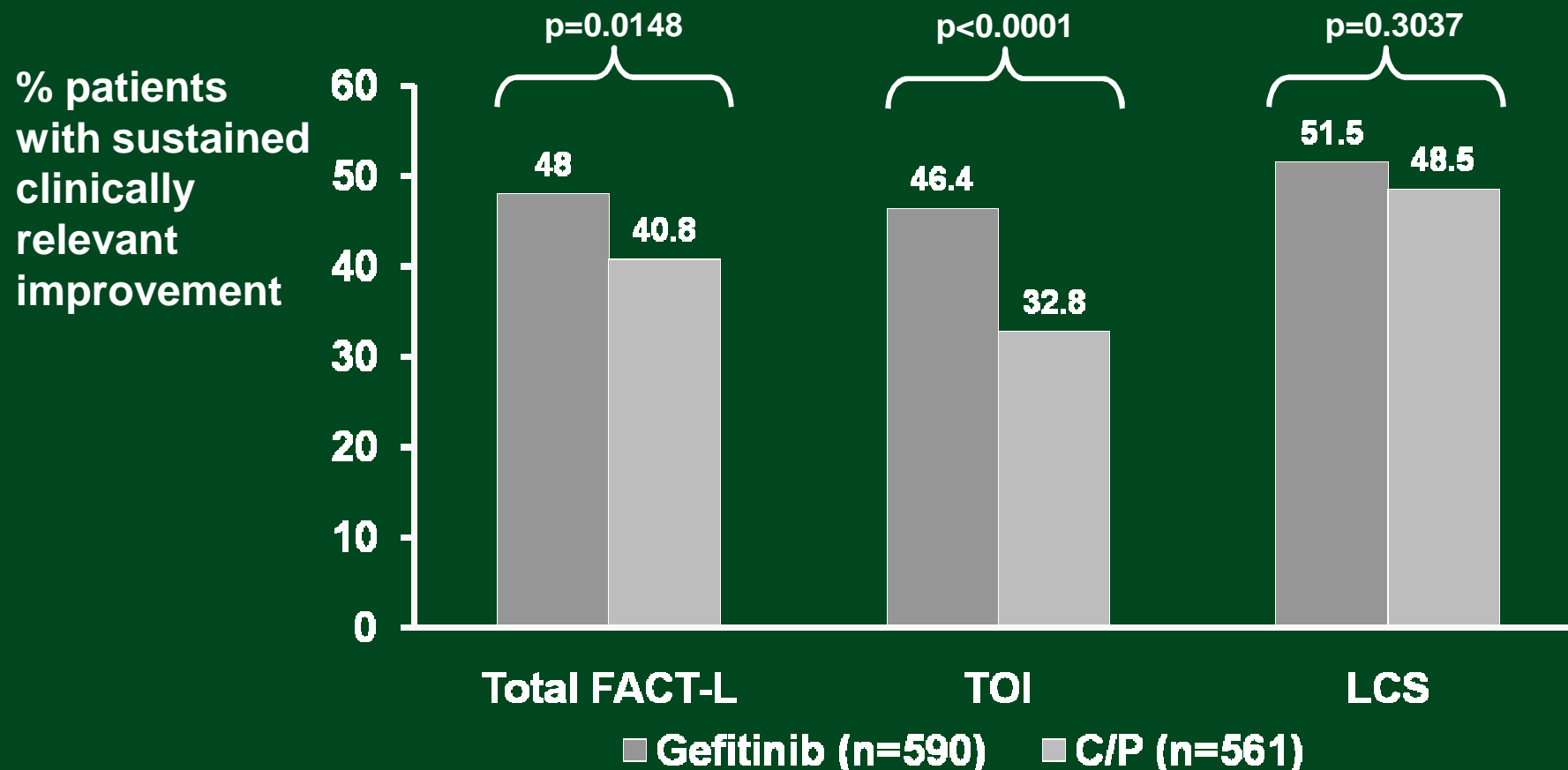
| AE, n (%) | Gefitinib | C / P | Gefitinib | C / P |
|----------------------|---------------------------|---------------------------|----------------------------|----------------------------|
| | All CTC grades (N=607) | All CTC grades (N=589) | CTC grade 3/4/5 (N=607) | CTC grade 3/4/5 (N=589) |
| Rash/Acne* | 402 (66.2) | 132 (22.4) | 19 (3.1) | 5 (0.8) |
| Neurotoxicity* | 66 (10.9) | 412 (69.9) | 2 (0.3) | 29 (4.9) |
| Diarrhoea | 283 (46.6) | 128 (21.7) | 23 (3.8) | 8 (1.4) |
| Alopecia | 67 (11.0) | 344 (58.4) | 0 | 0 |
| Anorexia* | 133 (21.9) | 251 (42.6) | 9 (1.5) | 16 (2.7) |
| Nausea | 101 (16.6) | 261 (44.3) | 2 (0.3) | 9 (1.5) |
| Asthenic conditions* | 102 (16.8) | 259 (44.0) | 2 (0.3) | 11 (1.9) |
| Vomiting | 78 (12.9) | 196 (33.3) | 1 (0.2) | 16 (2.7) |
| Myalgia | 47 (7.7) | 186 (31.6) | 3 (0.5) | 10 (1.7) |
| Dry skin | 145 (23.9) | 17 (2.9) | 0 | 0 |

*Grouped term (sum of several preferred terms)

Ordered by decreasing frequency in overall population; Difference in overall incidence is >20% greater on gefitinib; Difference in overall incidence is > 20% greater on C / P

C / P, carboplatin / paclitaxel

Quality of life and symptom improvement rates (EFQ population)

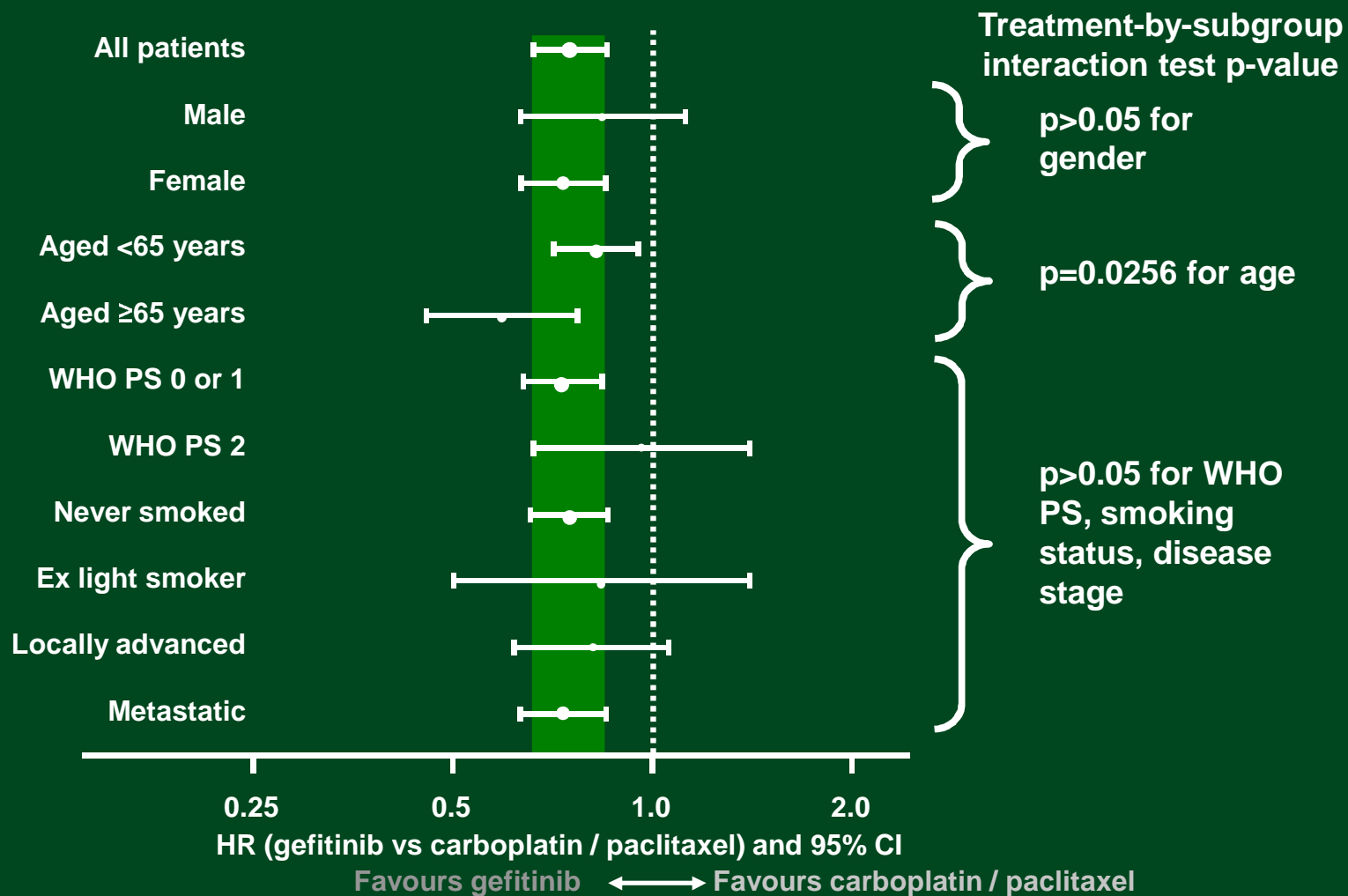


p-values from logistic regression with covariates

Clinically relevant improvement pre-defined as 6-point improvement for FACT-L and TOI; 2-point improvement for LCS, maintained for at least 21 days

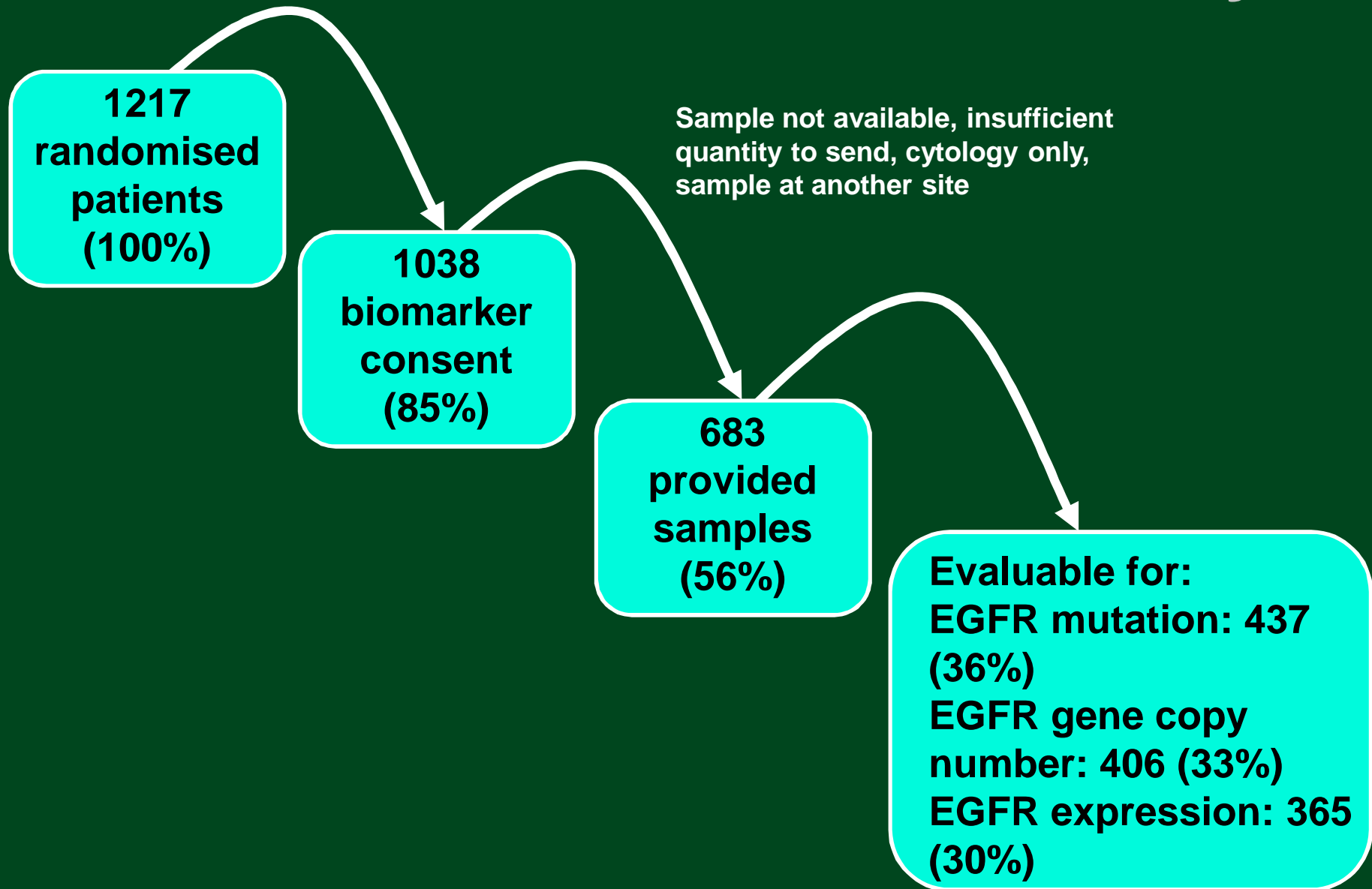
EFQ, evaluable for quality of life; FACT-L, Functional Assessment of Cancer Therapy-Lung; TOI, Trial Outcome Index; LCS, Lung Cancer Subscale

Progression-free survival in pre-planned clinical subgroups (ITT population)

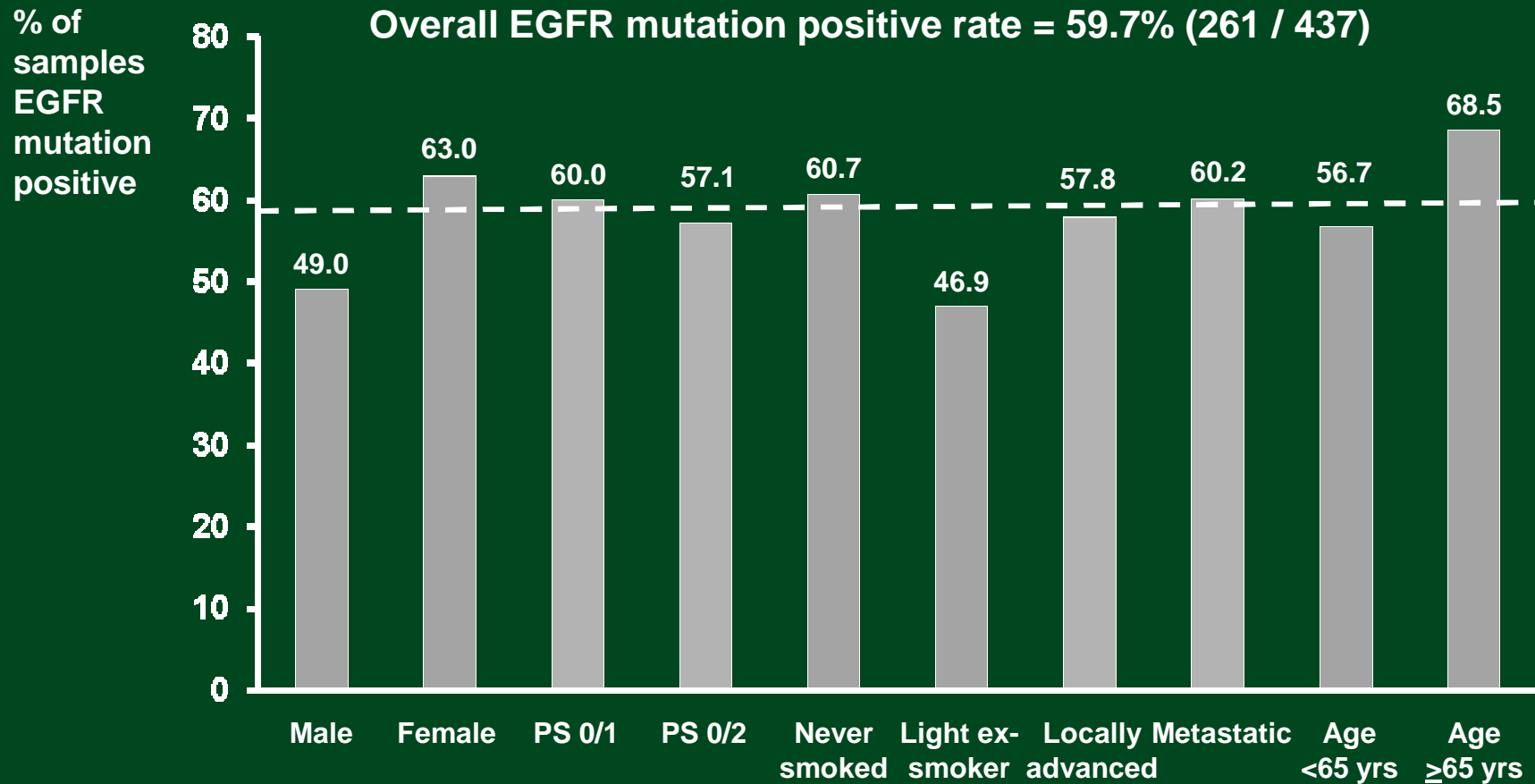


Cox analysis with covariates

Attrition rates in biomarker analysis



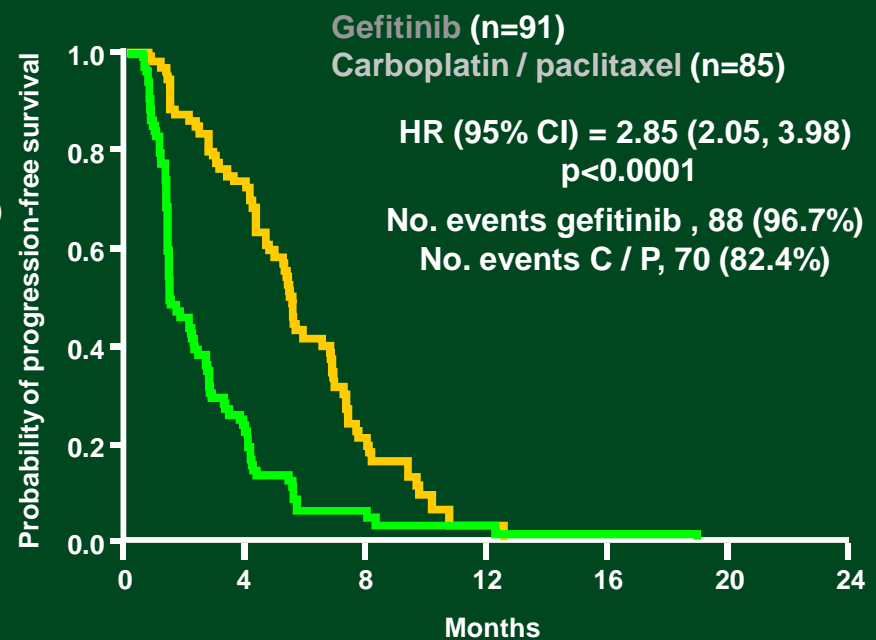
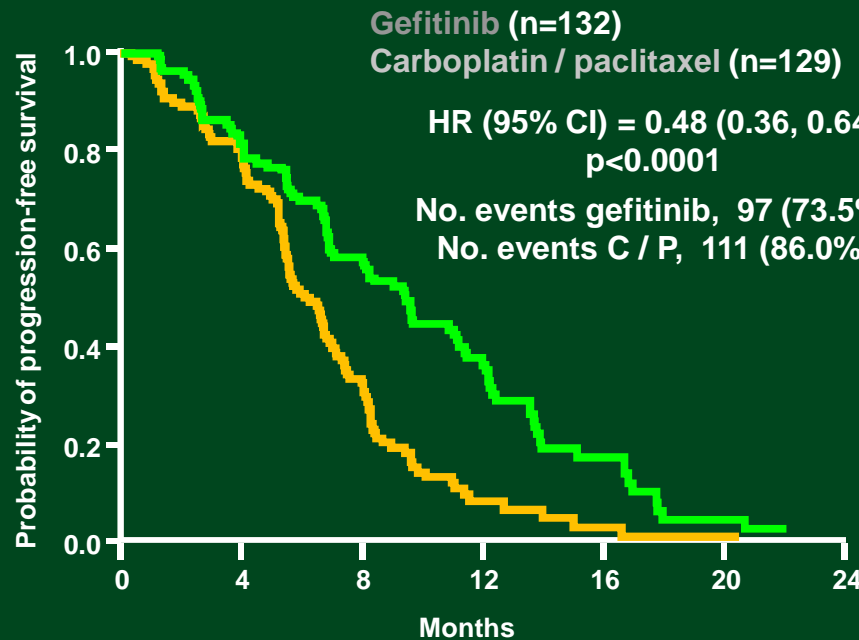
EGFR mutation positive status and clinical characteristics



Progression-free survival in EGFR mutation positive and negative patients

EGFR mutation positive

EGFR mutation negative



At risk :

| | | | | | | | |
|-----------|-----|-----|----|----|----|---|---|
| Gefitinib | 132 | 108 | 71 | 31 | 11 | 3 | 0 |
| C / P | 129 | 103 | 37 | 7 | 2 | 1 | 0 |

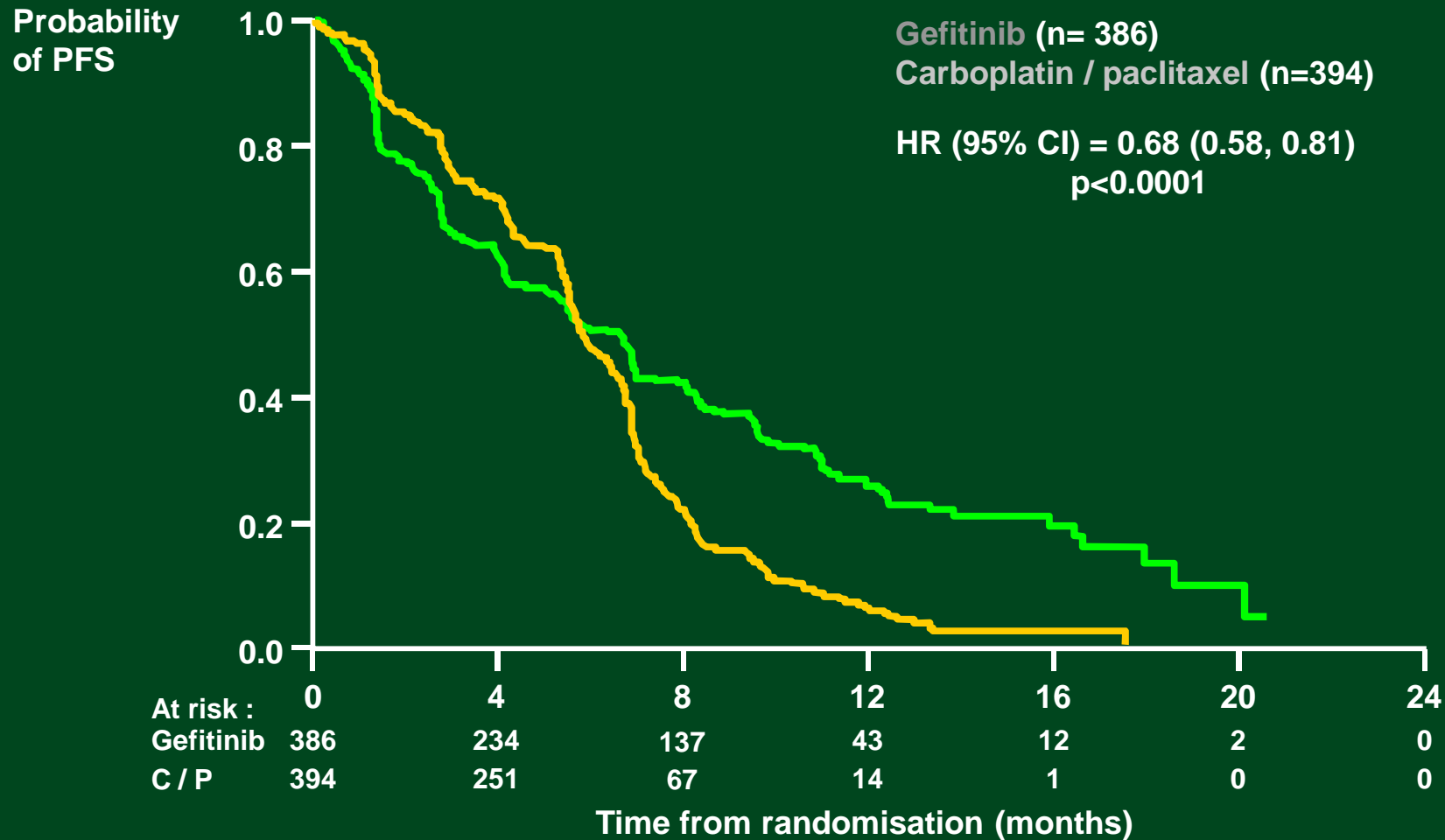
| | | | | | | | |
|-----------|----|----|----|---|---|---|---|
| Gefitinib | 91 | 21 | 4 | 2 | 1 | 0 | 0 |
| C / P | 85 | 58 | 14 | 1 | 0 | 0 | 0 |

Treatment by subgroup interaction test, p < 0.0001

ITT population

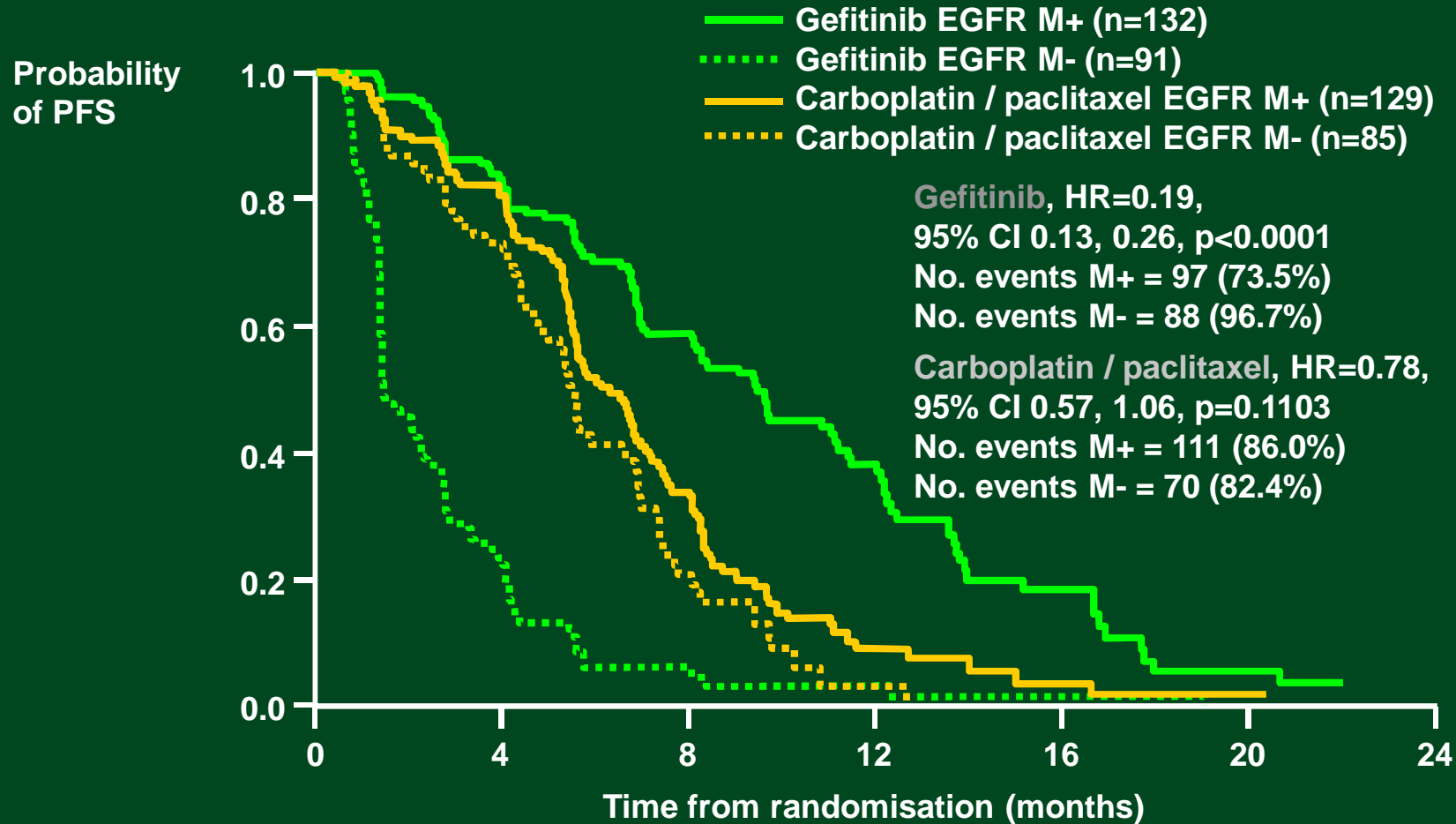
Cox analysis with covariates

Progression-free survival in EGFR mutation status unknown patients



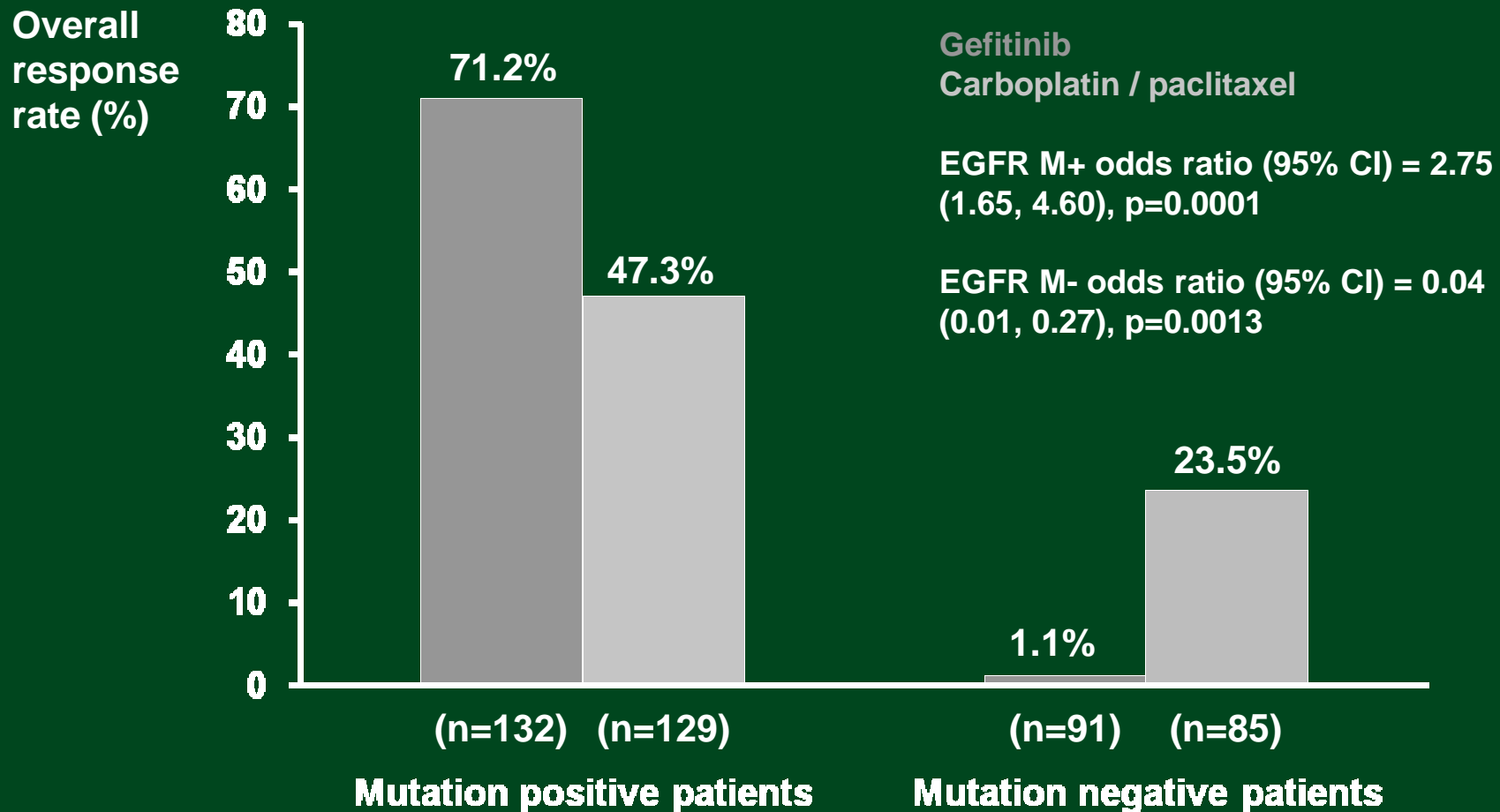
ITT population
Cox analysis with covariates

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

Objective response rate in EGFR mutation positive and negative patients



Odds ratio >1 implies greater chance of response on gefitinib

Conclusions (1)

- **The study exceeded its primary objective and demonstrated superiority of gefitinib relative to carboplatin / paclitaxel in terms of PFS**
 - however, the effect was not constant over time, initially favouring carboplatin / paclitaxel and then favouring gefitinib, potentially driven by differences in PFS outcomes for patients with EGFR mutation positive (gefitinib benefit) and negative (carboplatin / paclitaxel benefit) tumours
 - EGFR mutation status was a strong predictive biomarker for the effect of gefitinib compared to carboplatin / paclitaxel
- **Objective response rate was superior for gefitinib compared to carboplatin / paclitaxel**
- **Overall survival was similar for both treatments (survival follow-up is ongoing and survival may be influenced by subsequent treatments)**

Conclusions (2)

- **Gefitinib had a more favourable tolerability profile than carboplatin / paclitaxel**
- **QoL improvement rates were significantly greater with gefitinib than carboplatin / paclitaxel**
- **Disease-related symptom improvement rates were similar for gefitinib and carboplatin / paclitaxel**
- **Gefitinib can be considered an important therapy for first-line treatment of locally advanced or metastatic NSCLC patients with adenocarcinoma who have never smoked or are light ex-smokers**

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