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A double-blind, randomised, placebo-controlled phase III intergroup study of gefitinib in patients with advanced NSCLC, non-progressing after first line platinum-based chemotherapy (EORTC 08021/ILCP 01/03)

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ABSTRACT

Background: EORTC study 08021/ILCP 01/03 evaluated the role of consolidation gefitinib, an oral tyrosine kinase inhibitor (TKI), administered in patients with advanced non-small cell lung cancer (NSCLC), not progressing following standard 1st-line chemotherapy.

Methods: Patients with advanced NSCLC, not-progressing after four cycles of platinum-based chemotherapy, were randomised to receive either gefitinib 250 mg/d or matched placebo until progression or unacceptable toxicity. The primary end-point was overall survival (OS). Secondary end-points were progression-free survival (PFS) and toxicity. The study was powered to detect a 28% increase in OS from a median of 11–14.1 months (HR = 0.78) and planned to randomise 598 patients to observe 514 deaths.

Results: After inclusion of 173 patients, the trial was prematurely closed due to low accrual. Baseline characteristics for gefitinib ($n = 86$) and placebo ($n = 87$) arms were well balanced. After a median follow up of 41 months, the difference in median OS in the gefitinib and placebo arms was not statistically significant (10.9 and 9.4 months, HR 0.83 [95% confidence interval (95% CI) 0.60–1.15]; $p = 0.2$). The difference in median PFS significantly favoured gefitinib (4.1 and 2.9 months, HR = 0.61, [95% CI 0.45, 0.83]), $p = 0.0015$). Adverse events

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reported in more than 10% of patients were rash (47% with gefitinib versus 13% with placebo) and diarrhoea (34% with gefitinib versus13% with placebo).

Conclusions: Despite its premature closure, this trial confirms previous evidence that consolidation gefitinib is safe and improves PFS. However, no difference in OS was observed in this study (NCT00091156).

1. Introduction

Lung cancer is the most common cancer and the leading cause of cancer-related deaths in the United States of America.[1] In Europe, lung cancer accounted for 12% of approximately 3.2 million new cancer cases and 19.7% of cancer-related deaths.[2] More than 85% of lung cancer cases are classified as non-small cell lung cancer (NSCLC). The distressingly low cure rate for NSCLC, approximately 15% 5-year survival, can be attributed to the high rate of unresectable disease at presentation and the inability of systemic therapy to cure metastatic disease. It has become clear that for the latter group of patients, treatment with platinum-based chemotherapy confers a median survival benefit of 6–8 weeks when compared to the best supportive care alone or no chemotherapy.[3] In second line, the administration of single agent docetaxel and pemetrexed in selected patients has resulted in an improved outcome by increasing their 1 year survival by 10%.[4–6] However, many patients do not receive this salvage chemotherapy as they present with poor performance status (PS) and co-morbid conditions.[7,8] With the efficacy of chemotherapy plateauing, we need alternative treatment approaches to attain further improvements in outcome, such as the use of targeted agents and consolidation treatments.

As in many other solid tumours, NSCLC is often associated with the overexpression of the Epidermal Growth Factor Receptor (EGFR), which's activity is tightly regulated by the presence and identity of a ligand, its heterodimer composition, and the availability of phosphotyrosine-binding proteins.[9] Upon activation, EGFR activates two major pathways in solid tumours, the PI3K/AKT/mTOR pathway, and the RAS/RAF/MEK/MAPK pathway. These signalling pathways are important in tumour cell growth, local invasion, angiogenesis, protein translation and cell metabolism. Blocking of the EGFR pathway can be obtained either by a chimeric monoclonal antibody against the extracellular domain of EGFR e.g. cetuximab, or by orally active, reversible HER-1/EGFR TKIs, e.g. erlotinib and gefitinib. Four large randomised phase III studies of platinum based doublet chemotherapy regimens in combination with a TKI failed to show a survival benefit over the doublet chemotherapy alone as first line treatment in advanced NSCLC.[10–13] This was thought to be due to a presumed antagonism between TKI's and chemotherapy by blocking cells in the G1 phase of the cell cycle, and by their interference with platinum uptake into tumour cells, possibly by decreasing expression of membrane uptake transporters.[14,15] The PFS and OS curves of both INTACT-studies showed a crossing of the experimental over the placebo arm in favour of the former. In a landmark subgroup analysis of patients with adenocarcinoma who received more than 90 d of chemotherapy, a statistically significant improvement of OS was furthermore observed. As the oral TKI in both trials could be continued after the end of chemotherapy in non-progressing patients, both these findings could be considered the result of this, consolidation therapy.[11]

This hypothesis is further strengthened by the results of a placebo-controlled study in which single agent salvage erlotinib was shown to improve outcome in unselected NSCLC patients previously treated with platinum-based chemotherapy.[16]

Maintenance or consolidation chemotherapy aims at the prolongation of chemotherapy response with the administration of additional drugs at the end of a defined number of initial chemotherapy cycles.[17] Recent trials of maintenance chemotherapy given immediately after first-line treatment regimens have shown improvement in PFS and OS.[8]

These observations were the rationale to study the role of consolidation gefitinib in a placebo-controlled fashion, following first line palliative chemotherapy in non-progressive patients with advanced NSCLC.

2. Methods

EORTC 08021/ILCP 01/03 was a double blind placebo-controlled randomised phase 3 trial designed to study the effect of gefitinib consolidation therapy on outcome in patients non-progressing after receiving first line platinum doublet chemotherapy. Patients with histologically or cytologically confirmed stage IIIB or IV NSCLC (according to the UICC 6th staging system), who were; not amenable to local therapy, non-progressing after prior platinum based chemotherapy (2–6 cycles), and without unacceptable toxicity, were randomised at the end of induction therapy (no later than 3 weeks after the last disease evaluation) to receive either a daily gefitinib tablet of 250 mg or a matched daily placebo tablet. Further eligibility criteria included: age older than 18 years, WHO PS of two or less, and adequate renal, hepatic and haematological functions. Patients with brain metastasis were also eligible, provided the latter were asymptomatic after cranial irradiation. The main exclusion criteria were previous anti-EGFR therapy, symptomatic brain metastasis, other malignancies, pregnancy or breast-feeding and interstitial pulmonary disease. Ethics committee approval was obtained in all centres before the activation of the trial and written informed consent for every participant, before inclusion, was mandatory. Treatment started within 1 week of randomisation and patients were treated until disease progression, excessive toxicity, patient refusal or clinical decision.

Patients who had smoked less than 100 cigarettes in their lifetime were classified as 'never smokers', those having

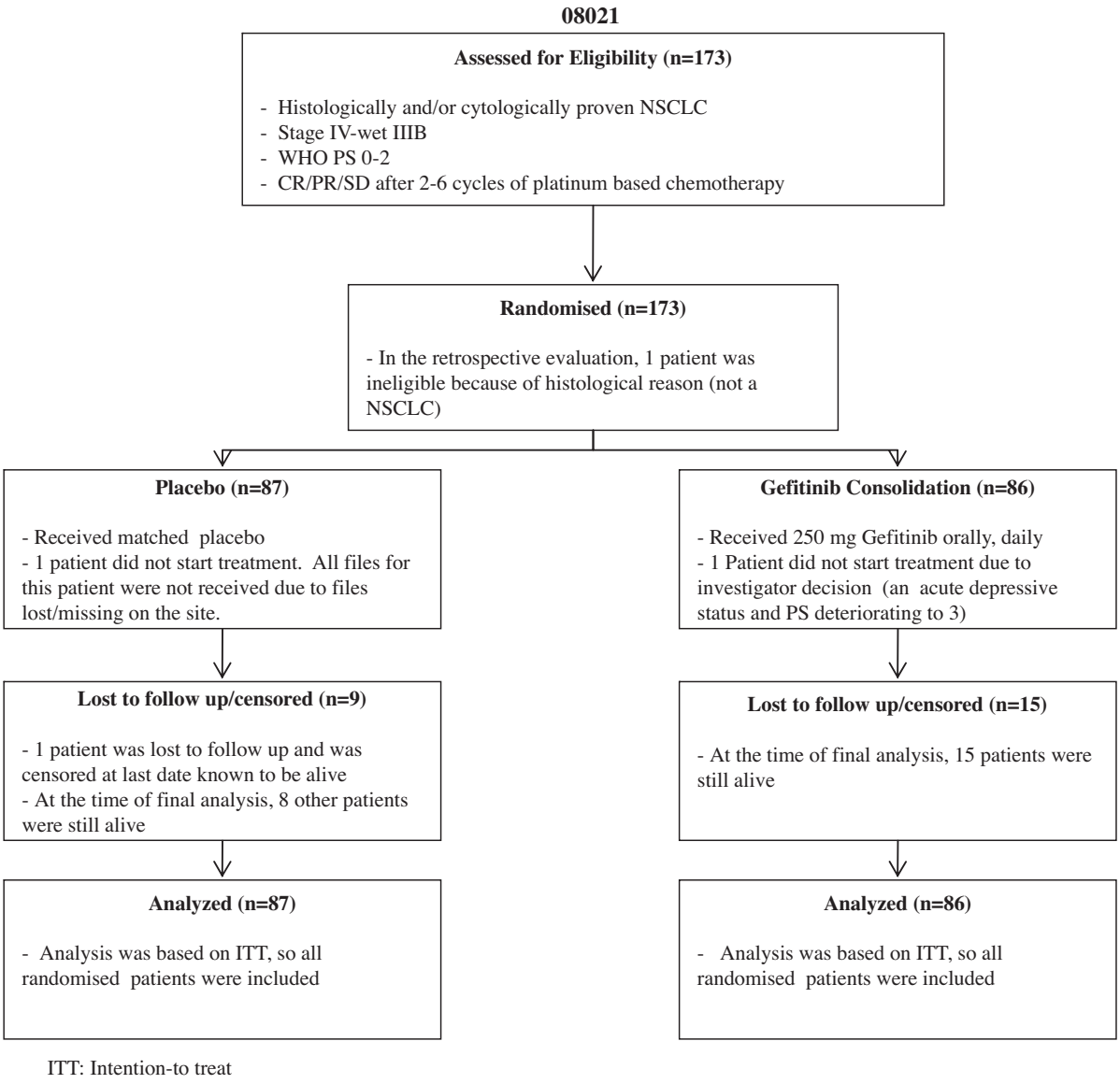

Fig. 1 – Study design and patient flow.

smoked 100 or more cigarettes but who had not smoked within the last year were designated as 'former smokers'. Tumour assessments according to Response Evaluation Criteria In Solid Tumours (RECIST v 1.0)[18] were performed using spiral CT-scan at completion of chemotherapy and at 6 weeks intervals until 12 months, every 3 months until 24 months and then every 6 months until progressive disease (PD). Disease control is defined as response or no change after receiving investigational therapy. Adverse events were reported following the National Cancer Institute Common Terminology Criteria (NCI-CTCAE) version 2.0. After disease progression, further treatment was left at the investigator's discretion. Unblinding was allowed only if the investigator needed this information to decide on further therapy.

EORTC 08021/ILCP 01/03 used a centralised double blind random assignment of patients carried out using the minimisation technique with stratification by initial stage (IIIB versus IV), PS at the end of chemotherapy (0–1 versus 2), best response obtained (stable disease (SD) versus partial response (PR)/complete response (CR)) and institution. The primary end-point was OS, secondary end-points included PFS and safety. Analysis of OS and PFS was conducted on the intention-to treat population and estimated from the time of randomisation using the Kaplan–Meier method. Comparisons between treatment arms were made by employing log-rank tests adjusted for the stratification factors except institution. In the PFS analysis, an event was defined as any disease progression (defined by RECIST v 1.0)[18] or death, whichever occurred first. Patients who were still alive without progression were censored at the time of last follow-up. Assuming a median survival of 11 months in the control group, an increase of 28% in median survival (to 14 months) for all patients in the experimental arm was considered clinically worthwhile. In order to detect such a benefit (hazard ratio = 0.78) with 80% power using a 2-sided 0.05 alpha level test, a total of 514 events was required. Additional subgroup analyses for the treatment effect on OS and PFS by

smoking status and disease stage at diagnosis, WHO PS and best response to induction chemotherapy at randomisation were predefined. Furthermore, it was planned to analyse OS and PFS according to EGFR-expression by immunohistochemistry (IHC). Tumour tissue for EGFR IHC was not initially mandatory for inclusion. EGFR IHC positive staining was defined as any staining of tumour cell membranes above the background level. A 10% cut off point was used to indicate EGFR positive status. This trial was registered at www.clinicaltrials.gov (NCT00091156).

3. Results

Starting in May 2004, 24 institutions included 173 patients of whom 86 received gefitinib and 87 placebos. The study underwent two major scientific amendments. In May 2006, after accrual of 100 patients, an attempt was made to include patients with the highest chance of responding and, therefore, the possibility of a smaller sample size. At the time selection was based on high EGFR staining by IHC. In December 2007, after accrual of 166 patients, an unplanned interim analysis for futility was prompted by the negative results of the SWOG 0023 trial, in which consolidation gefitinib was shown to have a deleterious effect on survival of selected patients with stage III NSCLC treated with chemoradiotherapy and adjuvant docetaxel.[19] Subsequently, restriction of accrual to high EGFR expression by IHC was discontinued to revive accrual, which had declined after the implementation of the selection and the reporting of the ISEL results (20). The trial was closed in July 2009, due to persistently low accrual despite several attempts to stimulate interest.

The design and patient flow is shown in Fig. 1. The baseline characteristics were well balanced between the 2 groups (Table 1). A total of 69 patients (40%) had an objective response while 104 patients (60%) had SD after a median of 4 cycles of chemotherapy prior to randomisation. Prior chemotherapy was cisplatin-based in 39 patients (45%) in the gefitinib arm and 49 patients (56%) in the placebo arm, and carboplatin-based for 46 (54%) patients in the gefitinib arm versus 38 patients (44%) in the placebo arm. Smoking status was current versus former smokers in 25 versus 42 (29% versus 49%) in the gefitinib arm and 23 versus 42 (26% versus

Table 1 – Baseline patient characteristics.

	Treatment		Total (N = 173)
	Placebo (N = 87) N (%)	Gefitinib (N = 86) N (%)	N (%)
Age			
Median	62.0	61.0	61.0
Range	28.0–76.0	36.0–80.0	28.0–80.0
Gender			
Male	66 (76)	67 (78)	133 (77)
Female	21 (24)	19 (22)	40 (23)
Clinical stage			
IIIB	13 (15)	16 (19)	29 (17)
IV	74 (85)	70 (81)	144 (83)
Performance status			
0	30 (35)	31 (36)	61 (35)
1	53 (61)	49 (57)	102 (59)
2	4 (5)	6 (7)	10 (6)
Prior platinum chemotherapy[a]			
Cisplatin-based	49 (56)	39 (45)	88 (51)
Carboplatin-based	38 (44)	46 (55)	84 (49)
Cis/carbo-platin based	0 (0)	1 (1)	1 (1)
Response to chemotherapy			
Complete/partial response	35 (40)	34 (40)	69 (40)
Stable disease	52 (60)	52 (61)	104 (60)
Histological type			
Squamous	19 (22)	15 (17)	34 (20)
Adenocarcinoma	40 (46)	49 (57)	89 (51)
Undifferentiated	15 (17)	13 (15)	28 (16)
Large cell carcinoma	13 (15)	9 (11)	22 (13)
Smoking status			
Non-smoker[b]	20 (23)	18 (21)	38 (22)
Current smoker	23 (26)	25 (29)	48 (28)
Former smoker	42 (48)	42 (49)	84 (49)
Missing	2 (2)	1 (1)	3 (2)

[a] Median number of chemotherapy cycles is 4 in both groups.
[b] Non-smoker is defined as a patient who had never smoked more than 100 cigarettes; percentages are rounded to the nearest digit.

Table 2 – Best Overall Response during consolidation treatment according to patients' response to prior chemotherapy.

	Treatment		Total (N = 69)
	Placebo (N = 35) N (%)	Gefitinib (N = 34) N (%)	N (%)
Patients with CR/PR to prior chemotherapy			
Best overall response			
CR	0 (0.0)	2 (5.9)	2 (2.9)
PR	1 (2.9)	1 (2.9)	2 (2.9)
NC	19 (54.3)	24 (70.6)	43 (62.3)
PD	14 (40.0)	7 (20.6)	21 (30.4)
Not assessed	1 (2.9)	0 (0.0)	1 (1.4)
	Treatment		Total (N = 104)
	Placebo (N = 52) N (%)	Gefitinib (N = 52) N (%)	N (%)
Patients with SD to prior chemotherapy			
Best overall response			
CR	0 (0.0)	1 (1.9)	1 (1.0)
PR	0 (0.0)	6 (11.5)	6 (5.8)
NC	37 (71.2)	34 (65.4)	71 (68.3)
PD	14 (26.9)	8 (15.4)	22 (21.2)
Not assessed	0 (0.0)	2 (3.8)	2 (1.9)
Missing	1 (1.9)	1 (1.9)	2 (1.9)

CR = Complete response.
PR = Partial response.
NC = No change.
PD = Progressive disease.

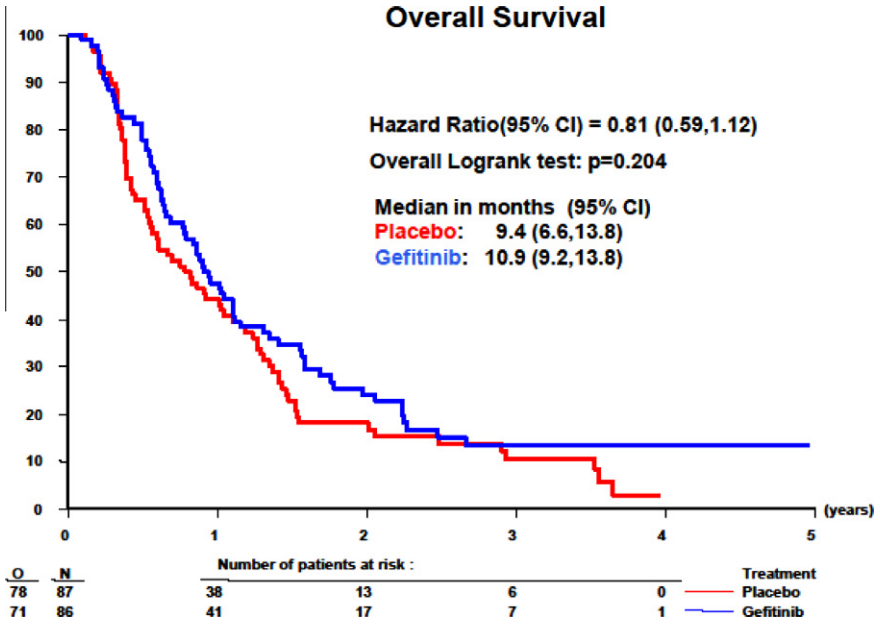

Fig. 2 – Overall survival in the gefitinib and placebo groups.

48%) in the placebo arm, and non-smokers in 18 (21%) patients in the gefitinib arm versus 20 (23%) in the placebo arm. No pemetrexed or bevacizumab was given with the chemotherapy regimens in either group.

Two patients (one in each group) did not receive their allocated treatment. The majority of patients studied did not require a treatment interruption (80% versus 91% in gefitinib arm versus placebo arm). The median treatment duration in the gefitinib arm was 115 d (23–1261) and 85 d (7–1076) for the placebo arm, respectively. The median duration of treatment interruptions was 10 d (1–44) and 5 d (1–75) in the gefitinib and placebo arms, respectively. Interruptions due to toxicity were reported in 10 patients (12%) in the gefitinib arm versus 1 patient (1%) in the placebo arm.

A further objective response was reported in 10 patients (12%) in the gefitinib arm versus 1 patient (1%) in the placebo

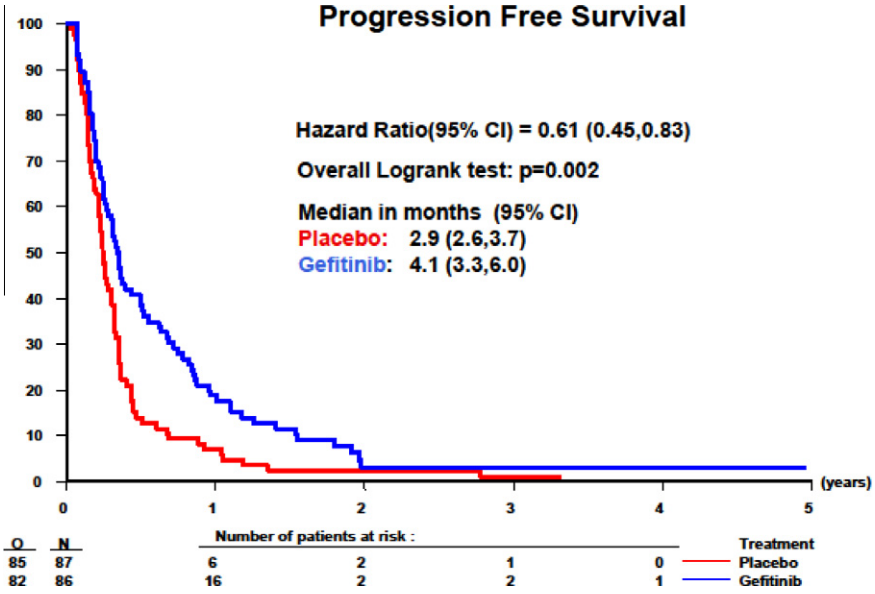

Fig. 3 – Progression free survival in the gefitinib and placebo groups.

arm ($p = 0.004$), whilst disease control was achieved in 68 patients (79%) in gefitinib arm compared to 57 patients (66%) in the placebo arm ($p = 0.07$) (Table 2). The most common cause of death was disease progression, which occurred in 66 patients (77%) in the gefitinib arm versus 72 patients (83%) in the placebo arm. Other causes of death include (number of patients), indistinguishable PD and toxicity (0 versus 1), cardiovascular disease (0 versus 1), other (1 versus 1) and unknown (4 versus 3) in gefitinib and placebo arms respectively. After a median follow up of 41 months, a median OS of 10.9 months was observed in the gefitinib arm versus 9.4 months in the placebo arm (HR of 0.83 with 95% CI 0.60–1.15, $p = 0.2$) (Fig. 2). Median PFS was 4.1 and 2.9 months for the gefitinib and placebo arms, respectively (HR 0.61, 95% CI 0.45–0.83, $p = 0.0015$) (Fig. 3).

Subgroup analysis by predefined clinical characteristics showed no significant differences in OS (Fig. 4A), but a significant benefit in PFS of gefitinib over placebo in all subgroups except patients with PS 2, although the analysis was done on a small number of patients. Analysis of the post-study treatment showed that in the gefitinib arm, seven cases received erlotinib and six cases continued on gefitinib versus 27 cases receiving erlotinib and eight gefitinib in the placebo arm. Salvage chemotherapy was administered to 21 patients (24%) and 23 patients (26%) of the G- and P-groups, respectively

The result of EGFR IHC was available in 42 cases of whom 31 tested positive (74%) and 11 negative (26%). Baseline characteristic were imbalanced between arms with regard to EGFR IHC and the small number of patients/events in these two arms precluded further comprehensive analysis of the translational end-point.

Withdrawal due to adverse events (AE) occured in 8% versus 5% of patients in the gefitinib and placebo arms, respectively. AEs reported in more than 10% of patients were rash (47% versus 13%) and diarrhoea (34% versus 13%) in the gefitinib and placebo arms respectively (Table 3). Grade 3–4 haematological toxicities in the gefitinib and placebo arms were neutropenia (1.2% versus 0%), thrombocytopenia (1.2% versus 0%) and anaemia (2.3% versus 0%) (Table 4). Most frequent grade 3–4 non-haematological toxicities included fatigue (4.7% versus 1.2%), rash (2.4% versus 0%) and changes in transaminases (9.4% versus 1.2%) in the gefitinib and placebo arms, respectively (Table 3).

4. Discussion

EORTC 08021/ILCP 01/03 shows that a consolidation treatment with gefitinib following first line platinum-based chemotherapy in patients with advanced NSCLC results in a highly significant improvement in PFS. This improvement was observed in all clinical subgroups of patients, except in patients with PS 2 at randomisation. Although there was no significant improvement of the primary end-point OS, the observed HR trend was in favour of consolidation gefitinib. As the study was stopped early, it could not reach the required number of events to adequately assess OS The results of EORTC 08021/ILCP 01/03 are aligned with those of SATURN, a similar trial in which consolidation erlotinib was given following first line palliative chemotherapy. Patients were also unselected for baseline EGFR protein expression status and improvement, although confined to patients with SD after chemotherapy,[21] was seen in both PFS and OS. In our trial, the observed imbalance in post-treatment TKI administration in favour of the placebo arm might have contributed to the lack of OS benefit.

Randomised trials using consolidation chemotherapy have consistently shown an improvement in PFS at the cost of increased toxicity. Improvements in OS have only been reported when the consolidation regimen was different from the induction regimen, or important differences in post-discontinuation treatment were present.[17,22] Subgroup analyses by best response to induction chemotherapy have not been reported. Taken together, these results suggest that the observed effect of maintenance treatment is due to a delay of progression by the earlier introduction of salvage therapy.

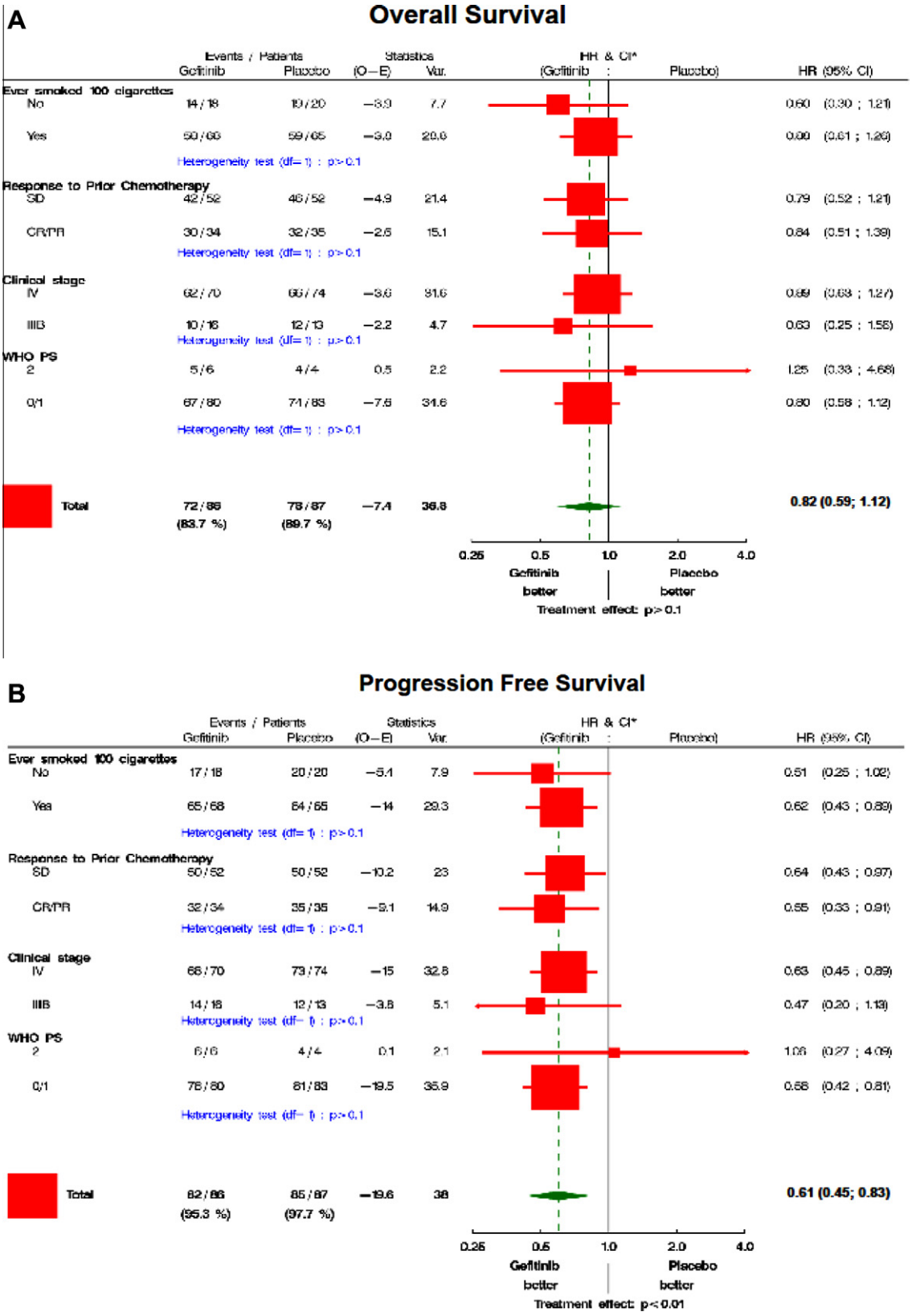

Fig. 4 – Forest plots of overall survival (A) progression free survival (B) according to different clinical characteristics.

Clinicians who support the maintenance approach advocate that such a strategy increases the chances of actually receiving a salvage treatment, as more than 50% of advanced NSCLC patients are at risk of never receiving second line chemotherapy because of poor PS. However, it is unclear whether this undertreatment also applies to oral EGFR TKIs, which are

Table 3 – Treatment related non-haematological grade 3 and 4 adverse events.

	Treatment		Total (N = 171)
	Placebo(N = 86) N (%)	Gefitinib (N = 85) N (%)	N (%)
Cardiovascular/general			
Grade 3	2 (2.3)	0 (0.0)	2 (1.2)
Grade 4	1 (1.2)	0 (0.0)	1 (0.6)
Fatigue (lethargy, malaise, asthenia)			
Grade 3	1 (1.2)	4 (4.7)	5 (2.9)
Rash/desquamation			
Grade 3	0 (0.0)	1 (1.2)	1 (0.6)
Grade 4	0 (0.0)	1 (1.2)	1 (0.6)
Dermatology/skin			
Grade 3	0 (0.0)	1 (1.2)	1 (0.6)
Anorexia			
Grade 3	1 (1.2)	0 (0.0)	1 (0.6)
Diarrhoea			
Grade 3	0 (0.0)	1 (1.2)	1 (0.6)
Vomiting			
Grade 3	0 (0.0)	1 (1.2)	1 (0.6)
Gastrointestinal			
Grade 3	1 (1.2)	0 (0.0)	1 (0.6)
Hepatic-other			
Grade 3	0 (0.0)	7 (8.2)	7 (4.1)
Grade 4	1 (1.2)	1 (1.2)	2 (1.2)
Infection without neutropenia			
Grade 3	1 (1.2)	1 (1.2)	2 (1.2)
Dizziness/lightheadedness			
Grade 3	1 (1.2)	0 (0.0)	1 (0.6)
Neurology			
Grade 3	3 (3.5)	0 (0.0)	3 (1.8)
Pain			
Grade 3	6 (7.0)	4 (4.7)	10 (5.8)
Cough			
Grade 3	3 (3.5)	1 (1.2)	4 (2.3)
Dyspnoea			
Grade 3	5 (5.8)	4 (4.7)	9 (5.3)
Grade 4	1 (1.2)	0 (0.0)	1 (0.6)
Pulmonary			
Grade 3	1 (1.2)	0 (0.0)	1 (0.6)
Renal/genitourinary			
Grade 3	0 (0.0)	2 (2.4)	2 (1.2)
Grade 4	0 (0.0)	1 (1.2)	1 (0.6)
Other toxicity			
Grade 3	3 (3.5)	4 (4.7)	7 (4.1)
Grade 4	1 (1.2)	3 (3.5)	4 (2.3)

Table 4 – Treatment related haematological/biochemical grade 3 and 4 adverse events.

	Treatment		Total (N = 171)
	Placebo (N = 86) N (%)	Gefitinib (N = 85) N (%)	N (%)
Absolute neutrophil count			
Grade 3	0 (0.0)	1 (1.2)	1 (0.6)
Platelets			
Grade 3	0 (0.0)	1 (1.2)	1 (0.6)
Haemoglobin			
Grade 3	2 (2.3)	0 (0.0)	2 (1.2)
Bilirubin			
Grade 3	1 (1.2)	1 (1.2)	2 (1.2)
Hypernatraemia			
Grade 3	0 (0.0)	1 (1.2)	1 (0.6)
Grade 4	1 (1.2)	0 (0.0)	1 (0.6)
Hyponatraemia			
Grade 3	7 (8.1)	7 (8.2)	14 (8.2)
Hyperkalaemia			
Grade 3	0 (0.0)	1 (1.2)	1 (0.6)
Hypokalaemia			
Grade 3	1 (1.2)	1 (1.2)	2 (1.2)
Hypercalcaemia			
Grade 3	1 (1.2)	0 (0.0)	1 (0.6)
Hypocalcaemia			
Grade 4	1 (1.2)	2 (2.4)	3 (1.8)
Alkaline phosphatase			
Grade 3	0 (0.0)	1 (1.2)	1 (0.6)
SGPT, ALAT			
Grade 3	0 (0.0)	7 (8.2)	7 (4.1)
Grade 4	1 (1.2)	2 (2.4)	3 (1.8)
SGOT, ASAT			
Grade 3	1 (1.2)	7 (8.2)	8 (4.7)

typically also prescribed to PS 2-3 patients, a subgroup of candidates for salvage chemotherapy. Surveillance after 1st line chemotherapy, including appropriate imaging, would pick up early asymptomatic progression, avoiding undertreatment while allowing most patients a treatment break of at least 6–8 weeks in order to recover from the residual toxicity of chemotherapy. Contrary to the SATURN data, we did not observe a differential effect in PFS or OS according to the stratification factor 'best response to first-line chemotherapy'. This effect could either be fortuitous in the former trial, or likely due to the lack of power in our trial. Given the discrepancy it is not clear if response to first-line therapy is important or not in the outcome of maintenance therapy.

It is uncertain whether the observed effect of maintenance treatment on outcome is restricted to EGFR TKIs. Several trials have shown the equivalence of TKI with either second-line docetaxel or pemetrexed,[23] suggesting a similar single agent activity in unselected patients. Maintenance pemetrexed has been shown to improve outcome with a similar magnitude as erlotinib.[8] Trials comparing consolidation TKI versus chemotherapy are presently lacking. Toxicity and mortality will be key issues in this setting. Maintenance gefitinib was well tolerated in this trial and did not result in any unexpected toxicity or treatment interruptions.

This trial did not succeed in identifying predictive biomarkers, to enable a better selection of patients for maintenance treatment, due to the low number of patients who had evaluable samples. The reported effect of maintenance erlotinib on OS and PFS was highest in, but not restricted to,

patients carrying an activating mutation in the EGFR gene. These data are in line with the results of trials exploring the role of single agent TKI in first-[24,25] and second-line[16,20] treatment and suggest that TKI maintenance treatment should be considered an option for any patient with an EGFR activating mutation with advanced NSCLC following first-line chemotherapy. Treatment selection in EGFR-wild type patients is more difficult. It can be advocated that decisions on maintenance TKI should not solely be based on variables such as response to first-line chemotherapy or EGFR activating mutational status, but that factors, such as residual toxicity, avoidance of new toxicity and patients' wishes regarding a treatment break should also be taken into consideration. The latter suggestion is supported by the observation that gefitinib did not appear to improve PFS in PS 2 patients in this trial.

In conclusion, despite its premature closure, this trial supports previous evidence that maintenance treatment with a TKI improves PFS while inferring acceptable toxicity.

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Clinical trials

This study was registered in ClinicalTrials.gov with number NCT00091156 and presented at the 46th ASCO Annual Meeting (Chicago, June, 2010) and the 35th ESMO meeting (Milan, October 2010).

Conflict of interest statement

None declared.

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