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original article

A randomized phase II study comparing erlotinib versus erlotinib with alternating chemotherapy in relapsed non-small-cell lung cancer patients: the NVALT-10 study[†]

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Background: Epidermal growth factor receptor tyrosine kinase inhibitors (TKIs) administered concurrently with chemotherapy did not improve outcome in non-small-cell lung cancer (NSCLC). However, in preclinical models and early phase noncomparative studies, pharmacodynamic separation of chemotherapy and TKIs did show a synergistic effect.
Patients and methods: A randomized phase II study was carried out in patients with advanced NSCLC who had progressed on or following first-line chemotherapy. Erlotinib 150 mg daily (monotherapy) or erlotinib 150 mg during 15 days intercalated with four 21-day cycles docetaxel for squamous (SQ) or pemetrexed for nonsquamous (NSQ) patients was administered (combination therapy). After completion of chemotherapy, erlotinib was continued daily. Primary end point was progression-free survival (PFS).
Results: Two hundred and thirty-one patients were randomized, 115 in the monotherapy arm and 116 in the combination arm. The adjusted hazard ratio for PFS was 0.76 [95% confidence interval (CI) 0.58–1.02; $P = 0.06$], for overall survival (OS) 0.67 (95% CI 0.49–0.91; $P = 0.01$) favoring the combination arm. This improvement was primarily observed in NSQ subgroup. Common Toxicity Criteria grade 3+ toxic effect occurred in 20% versus 56%, rash in 7% versus 15% and febrile neutropenia in 0% versus 6% in monotherapy and combination therapy, respectively.
Conclusions: PFS was not significantly different between the arms. OS was significantly improved in the combination arm, an effect restricted to NSQ histology.
Study Registration number: NCT00835471.
Key words: NSCLC, second line, intercalated, erlotinib

introduction

For patients with advanced non-small-cell lung cancer (NSCLC) who fail first-line platinum-based chemotherapy, several treatment options are available. Based on phase III clinical trials and meta-analysis, single-agent pemetrexed or docetaxel or the first-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) erlotinib are

recommended by national and international guidelines. One way to improve therapeutic outcome may be to combine different cytotoxic agents. The NVALT-7 study showed that the carboplatin and pemetrexed combination was associated with superior progression-free survival (PFS) compared with treatment with single-agent pemetrexed in second-line NSCLC patients [1]. Subsequently, the use of pemetrexed became restricted to patients with nonsquamous (NSQ) histology. Recently, a joint analysis of NVALT-7 and an identical Italian trial revealed that the survival benefit of carboplatin–pemetrexed was restricted to squamous (SQ) cell histology, suggesting no improvement in survival of the doublet over pemetrexed alone for other histologies [2].

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Another option to improve outcome may be to combine EGFR-TKIs and cytotoxic chemotherapy. Although front-line phase III studies testing this concept in advanced NSCLC patients were negative [3, 4], pharmacodynamic separation of chemotherapy, and EGFR-TKIs were synergistic in preclinical models and early exploratory studies [5–10].

Therefore, we designed a study in patients who failed previous cytotoxic treatment to compare PFS between erlotinib and intercalating erlotinib with pemetrexed for NSQ cell lung cancer or docetaxel in SQ cell lung cancer. In addition, quantitative and qualitative toxic effects of each regimen, response rates, and overall survival (OS) were characterized.

methods and patients

This is a randomized open-label phase II study carried out in patients with pathologically confirmed locally advanced or metastatic NSCLC who had progressed on or following first-line platinum-based chemotherapy. Other inclusion criteria were at least one unidimensionally measurable lesion meeting Response Evaluation Criteria In Solid Tumors (RECIST) 1.0, ECOG Performance Status (PS) 0–2, age ≥18 years, and adequate bone marrow reserve and hepatic and renal function. Further details on inclusion criteria are provided in supplementary data, available at *Annals of Oncology* online.

Prior treatment with pemetrexed in NSQ or docetaxel in SQ was allowed if the time between the end of first-line treatment and recurrence of the disease was at least 9 weeks. All patients provided written informed consent according to the local medical ethical committee rules.

treatment

After stratification for ECOG-PS (0–1 versus 2), response to prior treatment (complete and partial response versus stable or progressive disease), treatment-free interval after platinum-based therapy (<6 versus >6 months) and histology (SQ versus NSQ), patients were centrally randomized to receive either erlotinib monotherapy 150 mg daily or erlotinib 150 mg daily from day 2 to day 16 every 21 days in combination with chemotherapy on day 1. Erlotinib was administered daily at the same time each day on an outpatient basis, at least 1 h before or 2 h after the ingestion of any food or other medication. The patients kept a preprinted diary for monitoring their medication usage. For the SQ docetaxel 75 mg/m^2 and for NSQ pemetrexed 500 mg/m^2 was administered for 4 cycles on a 3-weekly basis. After completion of chemotherapy, erlotinib was continued daily until intolerable toxic effect or progressive disease was observed.

To preclude any bias, all patients received supplemental vitamin B$_{12}$ 1000 μm once every 6–9 weeks and folic acid 0.5 mg daily during the whole study treatment.

Treatment after disease progression was at the discretion of the treating physician.

assessments

Patients were evaluated at baseline with a complete medical history and physical examination, routine hematology and biochemistry, and computed tomography scans of chest and upper abdomen. Clinical evaluation, routine hematology, and biochemistry were required every 3 weeks before each cycle in both arms. Computed tomography of chest and upper abdomen were repeated every two cycles of chemotherapy and every 6 weeks during erlotinib treatment.

Objective response was determined by using RECIST (version 1.0). Toxic effect was scored according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTC-AE) version 3.

erlotinib concentrations

In a subgroup of patients in the intermittent combination schedule, a plasma sample for pharmacokinetics analysis was drawn on day 22 just before chemotherapy (or alternatively at start of cycle 3 or 4). See supplementary Data, available at *Annals of Oncology* online [11].

outcomes

The primary end point was PFS, defined as the time from randomization to the first evidence of tumor progression or death, when it occurred before disease progression. Secondary end points included OS, tumor response, and toxic effect. OS duration was defined as the time between randomization and death. No central review of tumor response was carried out.

statistical considerations

sample size calculation. A median PFS in NSCLC patients treated with second-line erlotinib was assumed to be ∼3 months [3]. To detect a decrease of the hazard of tumor progression in the combined arm of 33% [hazard ratio (HR) = 0.67] with the log-rank test (alpha = 0.05, two sided) and with 80% power, a total of 230 patients needed to be included (115 in each arm) and patients followed until a total of 190 had progressed.

statistical methods. All patients were analyzed on an intent-to-treat principle. Log-rank tests and multivariate Cox regression were used to compare end points. Tests were stratified by factors used for stratification at randomization. The Efron approximation was used to handle ties and the proportional hazards assumption was assessed via scaled Schoenfeld residuals. The Kaplan–Meier technique was used for survival curves and to calculate 1-year survival estimates using the log–log confidence interval (CI) method. A subgroup analysis was preplanned to estimate treatment effect within the SQ and NSQ subgroups. Toxic effect and tumor response were compared using Fisher exact tests. Dose intensity was calculated as (dose given/time given)/(dose planned/time planned).

The study was registered at clinical trials NCT00835471.

results

From March 2009 to December 2011, 231 patients were enrolled on the study. At the time of analysis, the median follow-up for all patients was 19 months (95% CI 15–26 months). A total of 178 (77%) patients had died, predominantly (*n* = 159) as a result of disease progression. Four (2%) patients never started treatment (two in each arm), one due to death, two due to clinical progression, and one patient refusal.

patient characteristics

All patient characteristics were well balanced and summarized in Table 1. Median time off platinum treatment was 10 weeks (range 1–93 weeks) in the monotherapy arm and 9.8 weeks (range 3–39 weeks) in the combination arm. Most patients in both SQ and NSQ were treated with gemcitabine cisplatin as first-line treatment. Fifteen percent of the patients in the second-line pemetrexed combination subgroup received pemetrexed platinum treatment as first-line treatment and median time off treatment was 7.5 months (range 3–20 months). In the monotherapy arm, this percentage was 19%. In the docetaxel combination arm, docetaxel platinum as first-line treatment was given to one (1%) patient 5 months before randomization, compared with four (3%) in the monotherapy arm median 18 months (range 12–42 months). In 60 (26%)

Table 1. Patient characteristics

	Monotherapy (N = 115)	Combination (N = 116)	All (N = 231)
Gender			
Male	75 (65%)	73 (63%)	148 (64%)
Female	40 (35%)	43 (37%)	83 (36%)
Age (years)			
Median (range)	64.0 (38–81)	62.5 (40–82)	63.0 (38–82)
PS			
0	39 (34%)	49 (42%)	88 (38%)
1	67 (58%)	57 (49%)	124 (54%)
2	9 (8%)	9 (8%)	18 (8%)
3		1 (0.9%)	1 (0.4%)
Smoking			
Never	7 (6%)	9 (8%)	16 (7%)
Present	35 (30%)	29 (25%)	64 (28%)
Past	63 (55%)	68 (59%)	131 (57%)
Unknown	10 (9%)	10 (9%)	20 (9%)
Histology			
Adeno	50 (43%)	50 (43%)	100 (43%)
Large-cell	15 (13%)	22 (19%)	37 (16%)
Squamous-cell	40 (35%)	34 (29%)	74 (32%)
Undifferentiated	2 (2%)	2 (2%)	4 (2%)
Bronchoalveolar		1 (0.9%)	1 (0.4%)
Plavelsel	1 (0.9%)		1 (0.4%)
Other	2[a] (2%)	1[b] (1%)	3 (1%)
Unknown	5 (4%)	6 (5%)	11 (5%)
Stage			
Ib	1 (0.9%)		1 (0.4%)
IIIb	28 (24%)	22 (19%)	50 (22%)
IV	86 (75%)	94 (81%)	180 (78%)

[a]One adeno + neuroendocrine and one squamous + adeno carcinoma.
[b]One large-cell neuroendocrine carcinoma.

patients, EGFR mutation testing was carried out before initiation of first-line therapy. Three (5%) patients were EGFR mutation positive, and all the three were randomized to the monotherapy arm.

PFS and OS

Median PFS was 4.9 months (95% CI 4.2–6.3 months) for patients treated with erlotinib monotherapy and 6.1 months (95% CI 4.7–7.9 months) for the combination arm (Figure 1, Table 2). The adjusted log-rank test for PFS for all patients ($P = 0.06$; unadjusted $P = 0.11$) and the adjusted Cox proportional HR being 0.76 (95% CI 0.58–1.02) were not different between both arms but showed a trend in favor of the combination arm.

Although the histology interaction did not reach statistical significance ($P = 0.49$), the trend for an increase in PFS in the combination arm was observed to be larger in the NSQ subgroup (adjusted HR = 0.72; 95% CI 0.51–1.02; $P = 0.06$; unadjusted $P = 0.05$) than in the SQ subgroup (adjusted HR = 0.92; 95% CI 0.56–1.52; $P = 0.73$), Figure 1. For patients treated with monotherapy erlotinib, PFS and OS for patients with SQ histology compared with NSQ histology was not statistically significantly different (PFS: HR = 1.27, 95% CI 0.82–1.95, $P = 0.42$; OS: HR = 1.32, 95% CI 0.84–2.08, $P = 0.28$).

OS showed an improvement for the combination arm. Median OS was 5.5 months (95% CI 4.5–8.5 months) versus 7.8 months (95% CI 6.5–10.8 months) for monotherapy versus combination therapy, respectively (adjusted log-rank, $P = 0.01$; HR = 0.67, 95% CI 0.49–0.91), Figure 1. This improvement was restricted to NSQ patients. There was no evidence of failure of proportional hazards for either PFS or OS.

We sought to determine whether the effect of treatment on PFS or OS differed between patients known EGFR wild-type and unknown EGFR status in NSQ. The interaction estimates were nonsignificant, indicating that there is no detectable difference between treatment effects between the two cohorts (included in supplementary data, available at *Annals of Oncology* online)

1-year survival rate for all patients was 30% (95% CI 24–27), for monotherapy 22% (95% CI 15–32), and 38% (95% CI 30–48) for patients allocated to combination therapy.

treatment delivery

In the erlotinib monotherapy, arm treatment was halted before disease progression due to adverse events in 9%, death in 9%, and patient refusal 5%. In the combination arm, treatment was discontinued before disease progression in 10% due to patient refusal (9% NSQ, 11% SQ), 17% due to adverse events (11% NSQ, 26% SQ), and 7% due to death. Forty-seven percent of patients in the combination arm received the total planned treatment of four cycles of chemotherapy. Additional data are presented in Suplementary Data, available at *Annals of Oncology* online.

toxic effect

Toxic effect exceeding CTCAE grade 2 was significantly increased in the combination arm 55% versus 19% in the monotherapy arm ($P < 0.0001$; supplementary table, available at *Annals of Oncology* online). Hematological toxic effect was observed in the combination arm only, with febrile neutropenia in 6% of patients; 4% in the pemetrexed treated cohort and 10% in the docetaxel treated cohort. Toxic deaths were not observed in this study.

response to treatment

Response to treatment is presented in Table 2. Significantly more patients in the combination arm experienced disease control (response or stable disease) as best overall response than in the monotherapy arm [62 (54%) versus 43 (39%), $P = 0.03$].

erlotinib concentrations

Samples from 25 patients (21%) were available for analysis. In all of these patients, the concentrations were below 500 ng/ml, the serum level required for adequate tyrosine kinase inhibition. Thirteen samples had erlotinib concentrations below the lower detection limit of 2 ng/ml. The other 12 samples had a mean concentration of 79 ng/ml (SD 120 ng/ml).

post discontinuation therapy

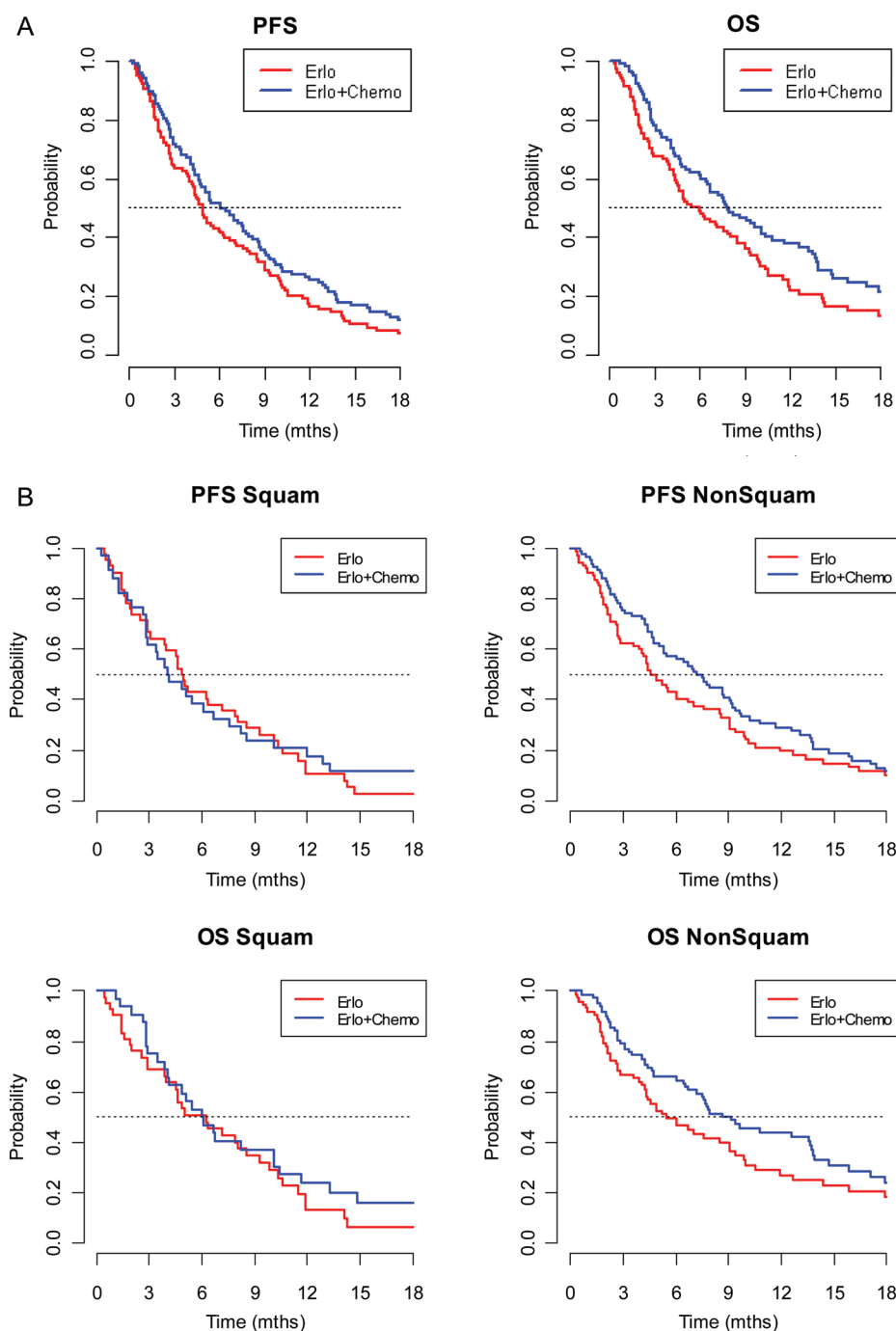Ninety-three (40%) of patients received third-line cytotoxic therapy, 48 (42%) in the monotherapy, and 45 (39%) in the

A

Figure 1. Kaplan–Meier curves of progression-free (PFS) [HR 0.76; 95% confidence interval (CI) 0.58–1.02; $P = 0.06$] and overall survival (OS) (HR 0.67; 95% CI 0.49–0.91; $P = 0.01$) for all patients (A) and divided by histology (B). Squam, squamous cell histology; NonSquam, non-squamous histology; erlo, erlotinib.)

combination arm. Most often, patients were treated with pemetrexed (35% monotherapy, 31% combination arm).

discussion

This is the first randomized study investigating the role of combining chemotherapy and intercalated erlotinib versus erlotinib alone in Caucasian patients with recurrent, platinum-pretreated NSCLC. Although a trend in favor of the combination was observed, the primary end point PFS was not met

(HR = 0.76, $P = 0.06$). A preplanned subgroup analysis showed that the trend for an increase in PFS was primarily in patients with NSQ treated with pemetrexed–erlotinib. In these patients, PFS increased from 4.9 to 7.2 months (HR = 0.72, $P = 0.06$), whereas the docetaxel-treated patients with SQ did not show a difference. Significantly more patients in the combination arm experienced disease control (response or stable disease) as best overall response than in the monotherapy arm ($P = 0.03$)

The drawbacks of PFS measured by the local investigator are well recognized. The secondary end point OS was significantly

Table 2. Efficacy

	All patients		Squamous		Non-squamous	
	Monotherapy N = 115	Combination N = 116	Monotherapy N = 42	Combination N = 34	Monotherapy N = 73	Combination N = 82
BoR						
PR*	8 (7%)	15 (13%)	1 (2%)	2 (6%)	7 (10%)	13 (16%)
SD	37 (32%)	47 (41%)	17 (40%)	12 (34%)	20 (27%)	35 (43%)
PD	58 (50%)	36 (31%)	19 (45%)	11 (32%)	39 (53%)	25 (30%)
NE	12 (10%)	18 (16%)	5 (12%)	9 (26%)	7 (10%)	9 (11%)
PFS (months)						
Median	4.9	6.1	4.9	4.1	4.9	7.2
95% CI	(4.2–6.3)	(4.7–7.9)	(3.8–8.0)	(2.9–7.6)	(3.9–7.6)	(5.3–9.3)
OS (months)						
Median	5.5	7.8	6.2	6.1	5.5	9.1
95% CI	(4.5–8.5)	(6.5–10.8)	(4.5–9.8)	(4.1–10.4)	(4.3–9.4)	(7.2–13.8)

*Confirmed.
NE details presented in supplementary Data, available at *Annals of Oncology* online.

prolonged in the combination arm and this beneficial effect was again restricted to the patients with NSQ.

PFS in the monotherapy arm was equal in both SQ and NSQ, confirming the earlier observations. The intermittent dosing schedule of erlotinib is designed to overcome the potential antagonism between cytotoxic chemotherapy and EGFR TKIs. In second-line treatment, both docetaxel and pemetrexed have been investigated. Recently, comparative studies, although only published in abstract form, with this intercalated dosing schedule were found to be positive [12, 13]. To the best of our knowledge, no studies comparing docetaxel or pemetrexed and intermitted erlotinib with single-agent erlotinib in second-line treatment of NSCLC are available in the current literature.

The increased efficacy of combining these drugs is thought to be mediated by a number of mechanisms not solely related to the genetic signature of the tumor cells. In cell line experiments, pemetrexed was found to increase EGFR phosphorylation and reduce Akt phosphorylation (sensitizing tumor cells to erlotinib), while erlotinib was found to reduce thymidylate synthase expression and activity, which in turn may sensitize tumor cells to pemetrexed [7]. Docetaxel and EGFR inhibition combinations were found to increase the antiproliferative and cytotoxic effect of the individual drugs in cancer cell lines and tumor models [14].

Erlotinib concentrations were below 500 ng/ml, the level required for adequate tyrosine kinase inhibition [15]. The wash-out period therefore appears adequate, but does not exclude an interaction at the intracellular level.

Several drawbacks in the design of the study must be noted. First, EGFR mutation testing was not mandatory at entry into the study. In 26% of the total patient population, EGFR mutation testing was carried out. Excluding the patients with SQ-cell carcinoma, in whom EGFR mutation is seldom found, the fraction of patients tested is 33%. Three mutation-positive patients who were not pretreated with EGFR-TKI were entered into the trial and randomized to the monotherapy arm. As patients were not selected for the trial based on criteria to enrich for EGFR mutation positivity, we hypothesize that the prevalence of EGFR mutation in NSQ group will be comparable

with the general prevalence in the Dutch population of about 10%–15% in a NSQ population.

Second, the number of chemotherapy cycles is limited to four. To optimize the synergistic effect, it can be hypothesized that chemotherapy should be continued beyond four cycles. The study reported by van Pawel et al. compared pemetrexed versus pemetrexed and intermittent erlotinib in patients with NSQ histology in a randomized phase II study. In their study, pemetrexed in both arms was continued until disease progression. Their study was positive for PFS and OS in favor of the combination arm.

Third, at the time of study, design information concerning maintenance treatment with pemetrexed was not available. Therefore, patients were treated with standard first-line chemotherapy without maintenance pemetrexed treatment.

The data of our study suggest no additional value of adding docetaxel to erlotinib in SQ-cell carcinoma patients. What is not resolved in this study is whether this lack in synergy is a chemotherapy related, histology or mutation-related, or pharmacodynamic-related phenomenon.

The toxic effect profiles support a synergistic effect of pemetrexed and erlotinib but not for docetaxel and erlotinib. In 26% of patients on pemetrexed–erlotinib combination therapy, a dose reduction of erlotinib was required compared with 6% of patients in the docetaxel combination arm. However, to substantiate any pharmacological interaction, detailed pharmacokinetic studies should be carried out. As no dose escalations were allowed, this increased number of dose reductions may have influenced efficacy.

In conclusion, although this study, comparing monotherapy with combination chemotherapy and erlotinib, in patients with both SQ and NSQ was just negative for its primary end point (PFS), a significant prolongation of OS was found. This improvement appears restricted to the NSQ patients in whom erlotinib was combined with pemetrexed. Combination therapy intercalated chemotherapy and erlotinib should be further investigated preferably with cytotoxic chemotherapy treatment being continued beyond four cycles.

disclosure

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