Randomized phase III study of docetaxel versus docetaxel plus intercalated erlotinib in patients with relapsed non-squamous non-small cell lung carcinoma

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Background: Earlier preclinical and phase II research showed enhanced effect of docetaxel plus intercalated erlotinib. The NVALT-18 phase III study was designed to compare docetaxel with docetaxel plus intercalated erlotinib in relapsed metastasized non-squamous (NSQ) non-small cell lung cancer (NSCLC).

Methods: Patients with relapsed Epidermal Growth Factor Receptor (EGFR) wild type (WT) NSQ-NSCLC were randomized 1:1 to docetaxel 75 mg/m² intravenously on day 1 every 21 days (control), or docetaxel 75 mg/m² intravenously on day 1 plus erlotinib 150 mg/day orally on day 2 (experimental arm). Progression free survival (PFS) was the primary endpoint, secondary objectives were duration of response, overall survival (OS) and toxicity.

Results: Between October 2016 and April 2018 a total of 45 patients were randomized and received treatment in the control (N = 23) or experimental arm (N = 22), the study was stopped due to slow accrual. Median PFS was 4.0 months (95% CI: 1.5–7.1) versus 1.9 months (95% CI: 1.4–3.5), p = 0.01 respectively; adjusted hazard ratio (HR) 2.51 (95% CI: 1.16–5.43). Corresponding median OS was 10.6 months (95% CI: 7.0–8.6) versus 4.7 months (95% CI: 3.2–8.6), p = 0.004, with an adjusted HR of 3.67 (95% CI: 1.46–9.27). Toxicity was higher with combination therapy, with toxicity ≥ CTC grades 3 or 4 in 3N = 6 (26%) in the control arm and N = 17 (77%) in the experimental arm (p < 0.001), mainly consisting of gastrointestinal symptoms and leukopenia.

Conclusions: Our study shows detrimental effects of docetaxel plus intercalated erlotinib, and strongly discourages further exploration of this combination in clinical practice.

ARTICLE INFO

Keywords: Non-small-cell lung cancer Docetaxel Erlotinib

ABSTRACT

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Conclusions: Our study shows detrimental effects of docetaxel plus intercalated erlotinib, and strongly discourages further exploration of this combination in clinical practice.
1. Introduction

During the last decade the treatment paradigm for metastatic or locally advanced non-small cell lung carcinoma (NSCLC) has improved dramatically, with the introduction of immunotherapy with or without chemotherapy as first line regimen [1].

This poses a great challenge for patients progressing during or shortly after this first line of treatment. In those patients with non-squamous (NSQ) NSCLC treated with pemetrexed chemotherapy in first line, only docetaxel is left as the approved second line treatment [1].

Although erlotinib, a first generation Epidermal Growth Factor Receptor (EGFR) tyrosine kinase inhibitor (TKI), is approved for second or third line treatment, it is rarely used in the unselected population as the overall survival (OS) compared to placebo was limited and the efficacy is mainly driven by patients with activating EGFR driver mutations [1,2]. EGFR is a transmembrane tyrosine kinase protein receptor binding ligands of the EGF family, which activates several intracellular signaling cascades and is commonly expressed in NSCLC [3].

Preclinical models have shown that combination therapy of erlotinib and docetaxel with schedule dependent separation, results in additive apoptosis regardless of EGFR and Kirsten rat sarcoma viral oncogene homolog (KRAS) mutational status [4,5]. Several phase II studies have explored this combination hereafter [6-9].

In a previous randomized phase II study (NVALT-10), we showed improved OS in advanced relapsed NSQ-NSCLC patients treated with a combination of chemotherapy plus intercalated erlotinib compared to erlotinib monotherapy [10]. Pemetrexed was used as chemotherapy backbone in the non-squamous population and docetaxel in the squamous population. However, pemetrexed has moved to treatment in first line setting. Therefore the combination of the improved outcome shown in the NVALT-10 study and the pre-clinical evidence of additive effect of erlotinib and docetaxel led to the design of the NVALT-18 study.

The current NVALT-18 study (NCT02775006) was designed to investigate the efficacy of docetaxel with intercalated erlotinib compared to standard docetaxel monotherapy in patients with relapsed (EGFR and Anaplastic Lymphoma Kinase (ALK) wild type (WT)) NSQ-NSCLC. The study was ended prematurely due to slow accrual.

2. Material and methods

2.1. Study design

The NVALT-18 study is a prospective multicenter randomized open label phase III trial (NCT02775006). The protocol (see Supplementary data) was reviewed and approved by the Netherlands Cancer Institute (Antoni van Leeuwenhoek) medical ethical committee, written informed consent was obtained from all patients before randomization. Patients were followed until death or loss to follow up.

2.2. Study population

Patients were recruited at 12 sites in The Netherlands (Supplementary Fig. S1) between October 2016 and April 2018. Eligibility criteria included relapse of non-squamous cell (EGFR and ALK WT) NSCLC after platinum-based chemotherapy and/or checkpoint inhibitor, WHO performance status 0-1, adequate organ function and measurable disease according to Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1) [11]. Presence of brain metastases was allowed provided cranial irradiation was completed more than 4 weeks before inclusion and steroid treatment had been stopped for at least 2 weeks before study inclusion. More details on in- and exclusion criteria are available in the Supplementary Data.

Patients were stratified for WHO performance score (0 versus 1), previous immunotherapy (yes versus no) and treatment free interval after platinum-based therapy (<6 months versus greater than 6 months) and randomized by a centralized computer randomization system (TENALEA) to open-label treatment.

2.3. Study treatment

Patients were randomized 1:1 to the control arm (A): docetaxel 75 mg/m² administered intravenously on day 1 every 21 days, or the experimental arm (B): docetaxel 75 mg/m² on day 1 administered intravenously plus erlotinib 150 mg/day on day 2–16 orally every 21 days. Treatment was continued until progression of disease, unacceptable toxicity or patient refusal.

2.4. Assessments

Patients were assessed before each cycle of treatment. Computed tomography of the chest and upper abdomen was scheduled every 6 weeks during treatment, and response was evaluated by RECIST v1.1 [11].

All adverse events (AE) equal to or exceeding Common Toxicity Criteria (CTC) version 4.03 grade 3, interstitial lung disease of any degree and all Serious Adverse Events (SAEs) were reported. The primary outcome measure was PFS, defined as the time from randomization to progression or death. Secondary endpoints were response rate, duration of response, OS (defined as time from randomization to death), and toxicity.

2.5. Statistical analysis

The intended number of inclusions was 230 with a preplanned interim analysis at 80 events.

Assuming a median time-to-event of 3 months in the control group and a hazard ratio (HR) of 0.67 in favor of combination therapy, performing the final analysis after observing 198 events would yield 80% power to show combination therapy superior at either analysis at a two-sided overall confidence level of 95%.

The (asymmetric) stopping boundaries for the interim analysis were based on the spending function of Hwang-Shih-DeCani with gamma = -4 for both alpha and beta spending. With a single interim at 80 events this corresponds to stopping for efficacy when the observed HR is below 0.52 and stopping for futility when the observed HR is above 1.09.

Both PFS and OS were estimated by the Kaplan-Meier method and compared between arms by the log-rank test and by means of Cox proportional hazard models (R version 3.6, R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patient characteristics

Between October 2016 and April 2018 a total of 45 patients were randomized and received treatment in the control arm (N = 23) or the experimental arm (N = 22). The study terminated prematurely due to slow accrual. As docetaxel shifted from second to third line treatment after approval of second line immune checkpoint inhibitors the study was amended on 22nd February 2016 to allow inclusion of patients who were pretreated with second line immunotherapy. Nevertheless this had negative impact on our expected inclusion rate and in practice also on the number of available patients, as less patients receive treatment in a subsequent therapy line as the disease progresses in time. Baseline characteristics are displayed in Table 1 and Supplementary Table S1. Thirty patients (67%), 15 patients in each arm, were pretreated with second line immunotherapy. At time of database lock on16th May 2019 the median follow up was 16 months (95% confidence interval (CI) 11.5 – NR).
Table 1

<table>
<thead>
<tr>
<th></th>
<th>Control arm (A): Docetaxel monotherapy (N = 23)</th>
<th>Experimental arm (B): Docetaxel + erlotinib (N = 22)</th>
<th>All (N = 45)</th>
</tr>
</thead>
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</tr>
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<td>11 (50)</td>
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</tr>
<tr>
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<td>Former</td>
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</tr>
<tr>
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</tr>
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<td>19 (86)</td>
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</tr>
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<td>22 (100)</td>
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<tr>
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<td>15 (68)</td>
</tr>
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<td>7 (32)</td>
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<td>of systemic treatment chemotherapy + ICI</td>
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<td>0</td>
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<td>15 (33)</td>
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<tr>
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<td>SD</td>
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<td>9 (41)</td>
</tr>
<tr>
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<td>7 (30)</td>
<td>10 (45)</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>2 (9)</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

WHO PS: World Health Organization Performance Score, NOS; not otherwise specified, LCNEC; large cell neuro-endocrine carcinoma, ICI; immune checkpoint inhibitor, CR; complete response, PR; partial response, SD; stable disease, PD; progressive disease.

3.2. Progression free survival

At final analysis all patients had developed disease progression. In the docetaxel monotherapy control arm (A) median PFS was 4 months (95% CI: 1.5–7.1 months). In the experimental docetaxel with intercalated erlotinib arm (B) median PFS was 1.9 months (95% CI 1.4–3.5 months), adjusted hazard ratio (HR) 2.51 (95% CI: 1.16–5.43), p = 0.01 (Fig. 1A).

3.3. Statistical evaluation primary endpoint

Although the data refute the Null hypothesis (in the opposite direction from what was expected at the beginning of the trial) the decision to stop the trial was made before looking at the data and hence independent of this outcome. Simulations show that had we continued the trial to the point of the first preplanned interim analysis, the study would in all probability have been stopped at that time. Under assumption of the Null hypothesis (but given the results in the first 45 patients) the probability of crossing the stopping-for-futility boundary at the first interim analysis is 76%. Under the assumption that OS in the subsequent patients would follow the same distributions (in each arm) as seen in the first 45 patients, this probably would even be over 99%.

3.4. Tumor response

Objective response rate (best confirmed response complete or partial response) was 13% (N = 3) in the control arm (A) and 9% (N = 2) in the erlotinib plus docetaxel experimental arm (B), see Table 1. Durations of the tumor responses for these 3 patients in arm A were 14, 19 and 40 weeks, and in arm B 8 and 25 weeks, respectively.

3.5. Overall survival

Median OS from randomization was 10.6 months (95% CI: 7.0–8.6 months) in the control arm and only 4.7 months (95% CI: 3.2–8.6 months) in the experimental arm, adjusted HR 3.67 (95% CI: 1.46–9.27), p = 0.004, see Fig. 1B. The one year survival rate was 43% (95% CI: 26%–74%) in the control monotherapy arm and 14% (95% CI: 5%–39%) in the experimental arm.

3.6. Toxicity

In the control arm 6 patients (26%) experienced toxicity ≥ CTCAE grade 3 compared to 17 patients (77%) in the experimental arm (p = 0.0009), mainly consisting of gastrointestinal symptoms and leukopenia. There were no CTCAE grade 5 AEs reported in this study.

There was one case of possible pneumonitis in a patient with pulmonary infection in the control arm (A) grade 3, treated with intravenously cefuroxime and prednisolone. The patient had a full recovery.

Toxicity is summarized in Table 2.

3.7. Treatment delivery

The median number of docetaxel courses was 2 (range 1 – 21) in the full study cohort: median 3 (range 1 – 21) in the control arm and median 2 (range 1 – 10) in the experimental arm. Patients received more than 6 cycles of therapy in 5 cases (22%) in the control arm and 2 cases (9%) in the experimental arm.

In 26 courses in 16 patients administration of docetaxel was modified, i.e., reduced or delayed. A total of 16 modifications was due to adverse events; 4 events in N = 4 in the control arm and 12 events in N = 9 in the experimental arm. In 3 patients (control arm N = 1, experimental arm N = 2) an AE led to discontinuation of docetaxel treatment without progression of disease at that time point.

In the experimental arm the erlotinib administration was modified in 13 out of 22 patients. In 4 patients the daily dose was reduced to 100 mg and in 1 patient further reduced to 50 mg because of non-hematological AEs. The intercalated scheme was stopped earlier or interrupted in 9 patients; twice because of a hematological AE, in 7 patients because of a non-hematological AE and once on request of the patient. In 4 patients a cycle was postponed, once on request of the patient, otherwise because of adverse events.
and intercalated erlotinib therapy is superior to docetaxel monotherapy II NVALT-10 study [4,5,10]. However, the data reported here suggest the was based on data from preclinical research and the results of the phase-4. Discussion

Toxicity (related to treatment).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Adverse events (grade 3 &amp;-4)</th>
<th>Control arm (A), N = 23 (%)</th>
<th>Experimental arm (B), N = 22 (%)</th>
<th>All (N = 45, (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological</td>
<td>Leukopenia</td>
<td>3 (13)</td>
<td>5 (23)</td>
<td>8 (18)</td>
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<tr>
<td></td>
<td>Neutropenia</td>
<td>1 (4)</td>
<td>2 (9)</td>
<td>3 (7)</td>
</tr>
<tr>
<td></td>
<td>Febrile neutropenia</td>
<td>1 (4)</td>
<td>4 (18)</td>
<td>5 (11)</td>
</tr>
<tr>
<td></td>
<td>Leukocytosis</td>
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<td>1 (5)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>General</td>
<td>Malaise</td>
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<td>1 (5)</td>
<td>1 (2)</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
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<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td></td>
<td>Weight loss</td>
<td>1 (4)</td>
<td>1 (5)</td>
<td>2 (4)</td>
</tr>
<tr>
<td></td>
<td>Pain</td>
<td>0</td>
<td>2 (9)</td>
<td>2 (4)</td>
</tr>
<tr>
<td></td>
<td>Syncope</td>
<td>0</td>
<td>1 (5)</td>
<td>1 (2)</td>
</tr>
<tr>
<td></td>
<td>Infection</td>
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<td>1 (5)</td>
<td>1 (2)</td>
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<td></td>
<td>Sepsis</td>
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<td>2 (4)</td>
</tr>
<tr>
<td>Gastrointestinal disorder</td>
<td>Abdominal pain</td>
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<td>1 (2)</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
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<td>2 (9)</td>
<td>2 (4)</td>
</tr>
<tr>
<td></td>
<td>Dysphagia</td>
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<td>1 (2)</td>
</tr>
<tr>
<td></td>
<td>Oral mucositis</td>
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<td>2 (9)</td>
<td>2 (4)</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>0</td>
<td>1 (5)</td>
<td>1 (2)</td>
</tr>
<tr>
<td></td>
<td>Bilirubin increased</td>
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<td>1 (5)</td>
<td>1 (2)</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>0</td>
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<td>1 (2)</td>
</tr>
<tr>
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<td>Respiratory failure</td>
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<td>1 (2)</td>
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<td>Dyspnea</td>
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<td>Other</td>
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<td>Pruritus</td>
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<td>1 (5)</td>
<td>1 (2)</td>
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</table>

4. Discussion

Our hypothesis that a schedule dependent combination of docetaxel and intercalated erlotinib therapy is superior to docetaxel monotherapy was based on data from preclinical research and the results of the phase II NVALT-10 study [4,5,10]. However, the data reported here suggest the contrary as the primary endpoint (PFS) was significantly shorter in the experimental arm than in the control arm. In addition, the secondary endpoint OS was significantly shortened in the experimental arm. Meanwhile toxicity was worse in the combination arm.

An antagonistic phenomenon could be anticipated when the two drugs are given concomitantly as cell cycle arrest in G1 due to the cytostatic effect of the EGFR-TKI might prevent the cytotoxic effect of docetaxel in the S and G2/M phase [4,5]. However, in vitro exploration of dose scheduling showed an additional effect of cell proliferation-inhibition and apoptosis when erlotinib was administered after docetaxel [4,5]. An intercalated scheme of chemotherapy on day 1 with EGFR-TKI on day 2-16 in a 21 day cycle was therefore proposed as an optimal trial design. In a phase I/II trial the intercalated scheme of docetaxel and erlotinib was feasible and tolerable [6]. However, reports of phase II trials show opposite results. One trial showed no additional effect of the combination therapy in 147 randomized patients [7]. On the other hand, another study reported improved PFS, OS and disease control rate in the combination arm in 68 randomized patients [8]. Another phase II study conducted in male patients with squamous NSCLC was ended prematurely and showed no improvement in PFS at 6 months [9]. The most important differences between these studies and our study are the continuation treatment (erlotinib versus docetaxel plus intercalated erlotinib) and the difference in mutational status. While patients in the NVALT-18 were *EGFR-WT*, the other studies contained high levels of unknown mutational status which could explain the higher response rates and better outcomes. This is supported by the plasma analysis on a phase I/II trial where activating *EGFR* mutations detected in plasma were significantly associated with better outcomes [12].

Another single arm phase I/II trial included *EGFR-WT* patients and showed no improved overall response rate for the docetaxel and erlotinib combination [13]. The clinical trials on docetaxel with intercalated erlotinib are summarized in Table 3.

An important difference between cell line experiments and clinical trials in patients is the recurrence of drug administration in cycles. Whereas cell lines typically only receive 1 cycle of ‘therapy’ before measurements, patients are treated with several cycles of treatment. Possibly the remaining circulating erlotinib still has an antagonistic effect on the cytotoxic action of docetaxel after the first cycle. In the NVALT-10 study, erlotinib concentrations were measured in a subgroup of patients on day 22 prior to chemotherapy administration (and after 5 days of erlotinib interruption) [10]. Although the plasma levels of erlotinib did not reach therapeutic levels, the drug was still detectable in 12 out of 25 patients with a mean concentration of 79 ng/mL (SD 120 ng/mL) [10]. Enduring detection of erlotinib concentrations in tissue specimens after resection in a neoadjuvant setting up to 13 days after the last administration was reported earlier [14]. The mean lung tumor tissue erlotinib levels were 149 ng/g (SD 153 ng/g) after a mean of 7 days (SD 4.9 days) between last erlotinib intake and surgery. We hypothesize that erlotinib could still have activity in the intracellular compartment diminishing the cytotoxic effect of the chemotherapy after the 5 day washout period in our study, and a longer washout period could be necessary to overcome the antagonistic effect. Unfortunately we were unable to collect adequate samples for a preplanned pharmacokinetic analysis.

More adverse events equal to or exceeding CTC grade 3 were
reported in the docetaxel plus erlotinib arm. In addition, an earlier study reported a clinically relevant pharmacokinetic interaction between docetaxel and the TKI pazopanib, leading to a more than 50% increased systemic exposure to docetaxel [15]. Although we did not measure docetaxel concentrations in the NVALT-18 study, we cannot rule out that docetaxel levels increased due to erlotinib leading to more toxicity in the combination arm.

A limitation of our study was the open label design and lack of a double-blind experiment in this setting. Furthermore we did not include our prespecified sample size (as described in the study protocol in supplementary data).

Table 3
Clinical trials on docetaxel with intercalated erlotinib.

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Patient population</th>
<th>EGFR Status</th>
<th>Arms</th>
<th>Cycles</th>
<th>Maintenance</th>
<th>N−</th>
<th>ORR</th>
<th>PFS (months)</th>
<th>OS (months)</th>
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<tr>
<td>Sangha et al, 2011 [8]</td>
<td>I/II</td>
<td>Solid tumors/NSCLC, any treatment line</td>
<td>unknown</td>
<td>IA docetaxel 70–75 mg/m2 every 21 days, erlotinib day 2,9 and 16 (600–1000 mg)</td>
<td>6</td>
<td>E</td>
<td>17 (10 NSCLC)</td>
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<td>NA</td>
<td>NA</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td>IB docetaxel 70–75 mg/m2 every 21 days, erlotinib days 2–16 (150–300 mg)</td>
<td>6</td>
<td>E</td>
<td>25 (12 NSCLC)</td>
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<td>Auliac et al, 2014 [9]</td>
<td>II</td>
<td>NSCLC, second line</td>
<td>WT 68%, unknown 32%</td>
<td>C docetaxel 75 mg/m2 every 21 days</td>
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<td>8.3</td>
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<td></td>
<td></td>
<td></td>
<td>WT 66%, unknown 34%</td>
<td>E docetaxel 75 mg/m2 every 21 days, erlotinib 150 mg days 2–16 (150–300 mg)</td>
<td>6</td>
<td>E</td>
<td>39</td>
<td>28.20%</td>
<td>4.1</td>
<td>18.2</td>
</tr>
<tr>
<td>Juan et al, 2015 [10]</td>
<td>II</td>
<td>NSCLC, second line</td>
<td>M 3%, WT 14%, unknown 83%</td>
<td>C erlotinib 150 mg/d continuously</td>
<td>NA</td>
<td>E</td>
<td>35</td>
<td>9%</td>
<td>2.1</td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>WT 3%, unknown 97%</td>
<td>E docetaxel 75 mg/m2 every 21 days, erlotinib 150 mg days 2–16</td>
<td>4</td>
<td>E</td>
<td>33</td>
<td>3%</td>
<td>3.0</td>
<td>7.5</td>
</tr>
<tr>
<td>Gridelli et al, 2016 [11]</td>
<td>II</td>
<td>Male SQ-NSCLC, second line</td>
<td>unknown</td>
<td>C erlotinib 150 mg/d continuously</td>
<td>NA</td>
<td>E</td>
<td>36</td>
<td>2.8%</td>
<td>2.3</td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>E docetaxel 75 mg/m2 every 21 days, erlotinib 150 mg days 2–16</td>
<td>4</td>
<td>E</td>
<td>38</td>
<td>8.1%</td>
<td>2.8</td>
<td>8.9</td>
</tr>
<tr>
<td>Kimura et al, 2019 [13]</td>
<td>I/II</td>
<td>NSCLC, second line, EGFR-WT</td>
<td>WT</td>
<td>I docetaxel 60 mg/m2 every 21 days, erlotinib 150 mg days 2–16</td>
<td>NA</td>
<td>DE</td>
<td>12</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>II docetaxel 60 mg/m2 every 21 days, erlotinib 150 mg days 2–16</td>
<td>NA</td>
<td>DE</td>
<td>46</td>
<td>17.10%</td>
<td>3.5</td>
<td>11.3</td>
</tr>
<tr>
<td>Steendam et al, 2021</td>
<td>III</td>
<td>NSQ-NSCLC, second (or &gt; ) line, EGFR/ALK WT</td>
<td>WT</td>
<td>C docetaxel 75 mg/m2 every 21 days</td>
<td>NA</td>
<td>D</td>
<td>23</td>
<td>13%</td>
<td>4.0</td>
<td>10.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>E docetaxel 75 mg/m2 every 21 days, erlotinib 150 mg days 2–16</td>
<td>NA</td>
<td>D</td>
<td>22</td>
<td>9%</td>
<td>1.9</td>
<td>4.7</td>
</tr>
</tbody>
</table>

NSCLC, non-small cell lung cancer; SQ, squamous; NSQ, non-squamous; EGFR, Epidermal Growth Factor Receptor; WT, wild-type; M, mutated; N, number; E, experimental; E-I/E-II, experimental phase I/II; C, control; D, docetaxel; E, erlotinib; DE, docetaxel plus intercalated erlotinib; ORR, objective response rate; PFS, progression free survival; OS, overall survival; NA, not applicable.

5. Conclusion

These data strongly discourage the clinical use or the further investigation of the docetaxel plus intercalated erlotinib regimen in (EGFR and ALK WT) NSQ-NSCLC. Whether these data may be extrapolated to other EGFR-TKIs and/or other taxanes is currently unknown, but caution on adverse outcomes is strongly advised.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank all patients and their families, and all the colleagues at the participating centers for their contributions to the NVALT-18 trial.

Funding

This work was supported by The Dutch Cancer Society (Grant number EMCR-2015-8059). The funding source had no involvement in the conduct of the research or the preparation of the article.

Disclosures

CS reports advisory board honorarium from Boehringer Ingelheim, grants (to institution) from AstraZeneca, other (hospitality/symposium) from Roche and Lilly, outside the submitted work. SK reports personal fees from Roche, outside the submitted work. HG reports fees (to...
Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2021.08.002.

References


