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Prediction of toxicity in concurrent chemoradiation for non-small cell lung cancer

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Publication date

2014

Document Version

Final published version

[Link to publication](#)

Citation for published version (APA):

Uijterlinde, W. I. (2014). *Prediction of toxicity in concurrent chemoradiation for non-small cell lung cancer*. [Thesis, externally prepared, Universiteit van Amsterdam].

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Chapter 4

Additional weekly Cetuximab to concurrent chemo radiotherapy in locally advanced non-small cell lung carcinoma: efficacy and safety outcomes of a randomized, multi-center phase II study investigating

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Radiotherapy and Oncology. 2014;1:126-31

Abstract

Background: Modest benefits from concurrent chemoradiotherapy in patients with locally advanced NSCLC warrant further clinical investigations to identify more effective treatment regimens. Cetuximab, a monoclonal antibody against the epidermal growth factor receptor has shown activity in NSCLC. We report on the safety and efficacy of the combination of daily dose Cisplatin and concurrent radiotherapy with or without weekly Cetuximab.

Patients and Methods: Patients received high dose accelerated radiotherapy (66 Gy in 24 fractions) and concurrent daily Cisplatin (6 mg/m²) without (Arm A) or with (Arm B) weekly Cetuximab (400 mg/m² loading dose one week prior to radiotherapy followed by weekly 250 mg/m²). The primary endpoint of the trial was objective local control rate (OLCR) determined at 6-8 weeks after treatment. Toxicity was reported as well.

Results: Between February 2009 and May 2011, 102 patients were randomized. Median follow up was 29 months. The OLCR was 84% in Arm A and 92% in Arm B (p=0.36). The one-year local progression free interval (LPFI) and overall survival (OS) were 69 and 82% for Arm A and 73 and 71% for Arm B, respectively (LPFI p=0.39; OS p=0.99). Toxicity compared equally between both groups.

Conclusion: The addition of Cetuximab to radiotherapy and concurrent Cisplatin did not improve disease control in patients with locally advanced NSCLC but increased treatment related toxicity

Introduction

Non small-cell lung carcinoma (NSCLC) remains the leading cause of cancer-related mortality. About 35% of patients present with locally advanced disease. Despite improvement in irradiation techniques and the addition of concurrent chemotherapy, the treatment outcome of locally advanced NSCLC needs to be improved. The 5-years (yr) overall survival (OS) rate of this group of patients is only 15-20%. Two meta-analyses have shown that the absolute benefit in 3- and 5-yr OS of concurrent chemoradiotherapy (CRT) over the sequential approach was 5.7 and 4.5%, respectively(1;2). Cisplatin-based chemotherapy remains the standard of care in CRT (3). Single-agent Cisplatin administered concurrent to the radiotherapy revealed comparable efficacy with platinum doublet concurrent schedules and has the advantage of improved tolerability, which makes it possible to treat a larger proportion of patients (1;4-7).

The epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein that is over-expressed in many solid tumors including NSCLC. Cetuximab is a chimeric IgG1 monoclonal antibody that specifically binds to the EGFR. This results in internalization of the receptor, thereby preventing the ligands EGF and TGF- α from interacting with the receptors and effectively blocking ligand-induced EGFR phosphorylation(8;9). In addition, Cetuximab has been found to enhance the effects of chemotherapy and radiotherapy in an experimental system (10). In locally advanced squamous cell carcinoma of the head and neck, the addition of Cetuximab to high dose radiotherapy resulted in a significant increase in locoregional control and overall survival (11). In advanced stage NSCLC, Cetuximab has been shown to be beneficial in a sub-population of patients when combined with the platinum double Cisplatin and Vinorelbine (12;13). An advantageous effect of the addition of Cetuximab to the treatment of locally advanced NSCLC was hypothesized and the combination of Cetuximab with daily dose Cisplatin and high dose accelerated radiotherapy was shown to be feasible (14). Here we report the outcome of a randomized multicenter phase 2 trial (<http://trialregister.nl>. Trial ID: NTR2230).

Material and Methods

Study design

In this prospective multicenter open-label randomized phase 2 trial patients with inoperable locally advanced NSCLC received standard CRT consisting of daily Cisplatin and radiotherapy with or without weekly Cetuximab. Written informed consent was obtained from each patient. The study was approved by the local independent ethics committee and was designed in accordance with the International Conference on Harmonization and Good Clinical Practice, and the Declaration of Helsinki.

Patient Population

Patients presenting with a histologically or cytologically confirmed diagnosis of NSCLC, stage III (6th version, TNM staging) disease, without malignant pleural effusion were eligible for this study. Also patients with stage II disease, that were inoperable because of poor lung function or co-morbidities were included. 18-Fluorodeoxyglucose-positron emission tomography and computed tomography scans (FDG PET/CT) were used as a staging tool and were performed within 6 weeks prior to the start of treatment. Brain metastases were excluded using magnetic resonance imaging (MRI). If indicated and possible, non-invasive procedures such as endoscopic ultrasound were performed to assess mediastinal nodal involvement. The highest nodal level was confirmed. Inclusion criteria included WHO (ECOG) performance status 0-1, aged 18 years or older, and adequate hematological, renal and hepatic functions. Exclusion criteria were: other known active malignancies, previous radiotherapy to the ipsilateral chest, serious cardio-vascular diseases within the last 6 months (myocardial infarction, uncontrolled angina, decompensated heart failure), uncontrolled hypertension, pregnancy, previous treatment with EGFR-targeted drugs or monoclonal antibodies and symptomatic peripheral neuropathy (Common toxicity criteria for adverse events, version 2, grade ≥ 2).

Treatment

The treatment scheme has been described elsewhere. Briefly, the loading dose of Cetuximab was 400 mg/m² intravenously (iv), followed by a weekly dose of 250 mg/m² iv, administered for a total of 6 administrations. Radiotherapy and Cisplatin started one week after the Cetuximab loading dose. Daily Cisplatin

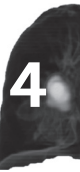
was given from the first radiotherapy fraction onwards for a total of 24 fractions, five times per week over a period of 32 days. Radiotherapy consisted of a high dose accelerated regimen (66 Gy in 24 fractions). The Cisplatin dose was 6 mg/m² given 1-1.5 hour before radiotherapy as an intravenous infusion given as a push (+/- 10 ml).

Radiotherapy treatment planning was performed using 3D conformal radiotherapy or intensity-modulated radiotherapy (IMRT) using a 4-dimensional treatment planning CT-scan. The involved irradiation fields encompassed the primary tumor and pathological lymph nodes on the FDG-PET scan. The Gross Tumor Volume (GTV) and normal structures were delineated according to a formalized protocol, and the delineations were approved during a multidisciplinary meeting. The GTV was expanded to a planned target volume (PTV) using a 12 mm margin + $\frac{1}{4}$ of the tumor peak-to-peak amplitude, the GTV lymph nodes with a uniform 12 mm margin. All treatment plans were optimized to have 99% of the PTV volume receiving at least 95% of the prescribed dose, with maxima of 115% allowed. The following organ constraints were taken into account: Spinal cord dose \leq 50 Gy (EQD2); Esophagus: V35 <65%; Heart \leq 40 Gy and \leq 50 Gy to 2/3 and \leq 66 Gy to 1/3; Mean Lung Dose < 20 Gy. Radiation was given using cone beam CT guidance. All patients were treated with photon beams of 10 MV. The PTV was irradiated with 2.75 Gy per fraction. The dose was specified according to the ICRU 50 guidelines, using advanced tissue inhomogeneity corrections.

Patient Evaluation

Physical examination and laboratory tests were performed twice weekly during treatment followed by 2-weekly controls until recovery. Regular follow up consisted of a 3-monthly visit and included physical examination and radiologic evaluation consisting of an alternating Chest X ray and a CT scan of the thorax during 5 consecutive years.

The tumor and lymph nodes were measured at onset of therapy and response was evaluated according to Response Evaluation Criteria In Solid Tumors (RECIST 1.1) (15). Best overall treatment response (complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) was assessed 6-8 and 24 weeks after the end of treatment using CT-scan. The patients were reviewed in our multidisciplinary meeting with the response at 6 to 8 weeks. This early response assessment was used because some patients



were considered candidate for additional surgery (in case of downstaging of the mediastinum).

Assessment of safety

Toxicity was scored at baseline, weekly during treatment and 3, 10, 18, 28 and 59 weeks after treatment using the Common Toxicity Criteria of adverse events (CTCAE) version 3.0. Acute toxicity was defined as that occurring during weeks 1-12 and late toxicity defined as toxicities that occur thereafter.

Sample size

The primary endpoint of the trial was objective local control rate (OLCR) defined as the rate of subjects with local CR, PR or SD at week 6-8 after treatment. For the standard treatment arm (Arm A), an OLCR of 60% was expected. It was hypothesized that the OLCR in the Cetuximab arm (Arm B) would reach 85%. With the estimated response and 102 patients randomized (51 in each Arm), a 2-sided test ($\alpha=0.05$) would provide at least 80% power to detect a difference in OLCR of 25%.

Pathology

Histological and cytological specimens of available cases were centrally reviewed and EGFR immunohistochemistry was performed using the Roche / Ventana 5B7 EGFR antibody. H-scores for staining intensity were assessed.

Statistical methods

Differences in the occurrence of adverse events and treatment reductions were tested using Fisher exact tests. OLCR was defined as the absence of local progression. Preferably, local progression as shown during radiological follow up was confirmed by histopathological examination. In the absence of tumor tissue, a confirmed radiological progression or a single observation of progression was accepted as loss of disease control. Similarly objective control rate (OCR) was defined as the absence of progression, while response rate (RR) was defined as either partial or complete best overall response. OLCR, OCR and response rate RR were compared using the Fisher exact tests and confidence intervals for proportions were calculated using the normal approximation. OS was calculated as time from randomization until death from any cause. Local progression free interval (LPMI) was calculated as time from randomization until

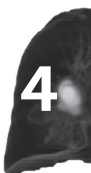
local progression. Patients alive at last contact were censored for OS, and those who were alive and local disease-free at last contact or death were censored at this date for LPFI. In addition patients who received surgery for any reason were censored at the date of surgery. Surgical interventions were discussed during a multidisciplinary meeting and were deemed relevant in case of suspected improvement of local disease control. Survival outcomes were compared using log-rank tests, and, for LPFI and OS, the interaction between treatment and histology was assessed using Cox proportional hazards regression. The proportional hazards assumption was assessed using Schoenfeld residuals. Survival curves are presented using the Kaplan-Meier method. Median follow up was assessed as the median time from randomization until last contact, with events being patients alive at last contact.

EGFR H-scores were considered elevated for values ≥ 200 (13). The association between EGFR status (normal vs. elevated) and histology (squamous vs. non-squamous) was assessed using a Fisher exact test, and the association between these factors and both LPFI and OS was assessed using multivariable Cox regression models.

The analysis was performed using the R software v 3.0.1 using the survival package for the time-to-event analyses (16;17).

Results

Between February 2009 and May 2011, 102 patients were randomized (51 patients in each Arm) (Figure 1 and Table 1). The median age was 63 years (range: 29-80) and 69% were male. Baseline NSCLC staging was: II (8%), IIIa (51%), and IIIb (41%). Median follow up was 29 months. Twenty-one patients had a surgical procedure within weeks 8 and 12 post-completion of the concurrent CRT, 10 in Arm A and 11 in Arm B (16 lobectomy, 2 pneumonectomy, 2 lymph node dissections and 1 debulking). Another 5 patients had a procedure between 16 and 35 weeks after end of concurrent CRT, 3 in Arm A and 2 in Arm B (3 lobectomy, 1 radio frequent ablation, 1 metastasectomy). All surgeries were performed after the week 6-8 tumor assessment of the primary endpoint.



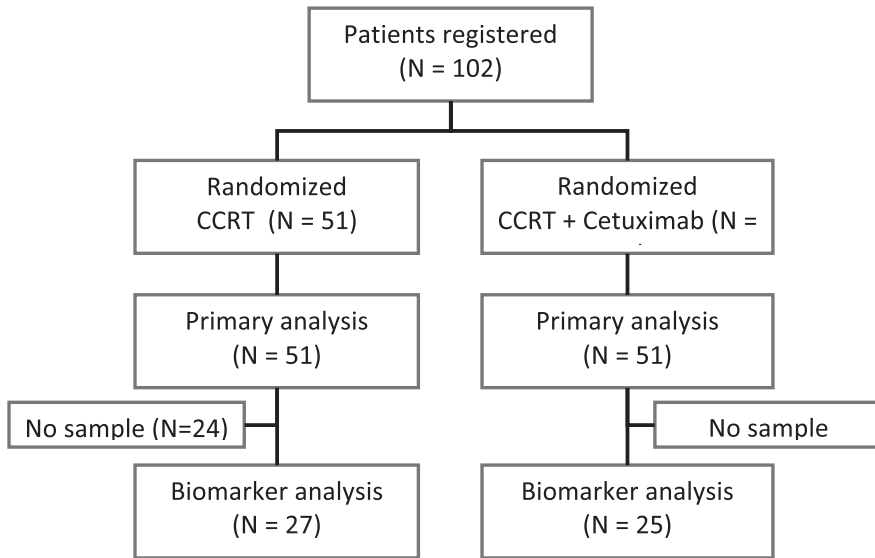


Figure 1. CONSORT Diagram

Table 1. Patient characteristics

	CRT	CRT + Cetuximab
	N=51	N=51
Age (yrs)*	63 (37-78)	62 (29-80)
Female / Male	29% / 71%	33% / 67%
Ethnic origin (Asian/non-Asian)	2%/98%	6%/94%
Staging		
-IIa/b	4%	12%
-IIIa	54%	47%
-IIIb	41%	41%
Histology		
-Adeno	32%	33%
-Large cell	28%	24%
-Squamous	38%	41%
-Other	2%	2%
Smoking history		
-Never	3%	3%

	CRT	CRT + Cetuximab
	N=51	N=51
-Former	49%	37%
-Current	49%	61%
PS 0/1/2	42%/56%/2%	39%/61%/0%
FEV1 (%)*	87% (39%-151%)	77% (40%-121%)
GTV (cm3)*	107 (25-907)	120 (5-460)
PTV (cm3)*	547 (66-1766)	451 (49-1855)
MLD*	16 (4.1-22.7)	15.7 (7.0-20.0)
SUVmax*	13.7 (6.3-35.9)	10.9 (6.2-31.8)

*Median and range are given; CRT= chemoradiotherapy; PS=performance score (WHO); GTV=gross tumor volume; PTV= planning target volume; MLD = mean lung dose; SUV= standard uptake value

A proportion of patients was unable to complete protocol treatment. Intention-to-treat analysis showed that 42 patients (82%) received all cycles of Cetuximab. Six percent received less than 2 cycles. For the entire cohort, 82% received full dose Cisplatin and 10% received 3 weeks or less. Full dose Cisplatin was delivered to 65% vs. 80% of patients for the standard versus the experimental arm *respectively* (p=0.12). Full dose radiotherapy was delivered to 84% vs. 88% of patients for the standard versus the experimental arm *respectively* (p=0.77). In total eleven percent of the population were unable to complete protocol treatment due to toxicity.

Safety

Grade ≥ 3 acute toxicities for the most common side effects of standard versus experimental arm: anorexia (6% vs. 22%), dysphagia (15% vs. 23%) and fatigue (16% vs. 18%). Acneiform rash grade ≥ 3 (8%) and pneumonia (6%) were encountered in the experimental arm only. Overall, more patients experienced toxicity grade ≥ 3 in the experimental arm (65% vs. 45%; p=0.03). However regarding the specific toxicity frequencies, only anorexia was significantly different between the two treatment groups. (p=0.04) (Table 2).

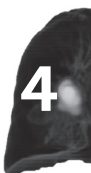


Table 2. Best overall response assessment after concurrent chemoradiotherapy with or without Cetuximab

	CRT	CRT + Cetuximab
	N=51	N=51
CR	3 (6%)	1 (2%)
PR	27 (53%)	26 (51%)
SD	11 (22%)	15 (29%)
PD	5 (10%)	6 (12%)
NE	5 (10%)	3 (6%)

CRT= chemoradiotherapy; CR=complete response; PR=partial response; PD=progressive disease; SD=stable disease; NE=non-evaluated. The best overall response was assessed 6 to 8 and 24 weeks after the end of treatment using CT scan.

One patient was hospitalized in the first week of treatment, due to a pulmonary infection with staphylococcus aureus after an endobronchial stenting procedure. One patient presented with fever and interstitial nodules after the 3rd administration of Cetuximab, in the 2nd week of treatment. He continued treatment after 2 weeks and presented again in the 6th week of treatment with an infectious pneumonia with increased C-reactive protein (CRP) responding to antibiotics. A third patient was hospitalized after his second Cetuximab (first Cisplatin) administration with fever and dyspnoea. CT chest showed alveolar consolidations and interstitial nodules interpreted as pulmonary metastases. The patient discontinued Cisplatin and Cetuximab. Two patients (4%) in the experimental arm died due to neutropenic sepsis one week after treatment and this was reported to be definitely related to the treatment.

Late toxicities (≥ 3 months after treatment) grade ≥ 3 were primarily pulmonary toxicity (4% vs. 0%) and esophagus toxicity (8% vs. 6%). Late pulmonary toxicity grade 3 was observed in week 13 in one patient with contra-lateral pneumonia and in one patient who had previously suffered from a post-obstructive pneumonia following the placement of an endobronchial stent. Regarding late esophagus toxicity, 5 patients suffered from mucositis during week 14; and 2 patients suffered from stenosis during weeks 31-53 requiring dilatation.

Efficacy

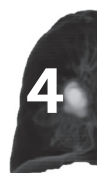
The OLCR was 84% (95% CI: 74%-94%) in Arm A (= Standard concurrent CRT) and 92% (95% CI: 85%-100%) in Arm B (Cetuximab Arm) (95% CI: -5%-20%; Fisher $p=0.36$). The OCR was 80% (95% CI: 69%-91%) in Arm A and 82% (95% CI: 72%-93%) in Arm B (Fisher $p=1.00$). Radiological analysis showed comparable results for both treatment arms with a partial or complete response of 59% (95% CI: 45%-72%) in Arm A and 53% (95% CI: 39%-67%) in Arm B ($p=0.69$) (Table 3).

Table 3. Acute Toxicity Grade³ 3 (CTCAE V3.0) of concurrent chemoradiotherapy with or without additional Cetuximab

	Concurrent CRT (Cisplatin) %	Concurrent CRT (Cisplatin + Cetuximab) %	p-value*
Total Grade ³ 3 acute toxicity	45%	65	0.03
Acne like rash	-	8	ns
Anorexia	6	22	0.04
Dysphagia	15	23	ns
Fatigue	16	18	ns
Nausea	6	4	ns
Vomiting	-	2	ns
Pain	2	10	ns
Cough	-	2	ns
Pneumonia	-	6	ns
Anaemia	2	2	ns
Leukopenia	11	8	ns
Neutropenia	6	8	ns
Thrombocytopenia	6	8	ns

The 1- and 2-year LPFI rate was 69% (95% CI: 55%-87%) and 54% (95% CI: 39%-75%) respectively for Arm A, while in Arm B the 1- and 2-year PFS rate was 73% (95% CI: 59%-91%) and 61% (95% CI: 46%-83%), respectively (Figure 2A). The OS rate after one and two years was 82% (95% CI: 72%-93%) and 58% (95% CI: 45%-74%), respectively for the Arm A. In Arm B the 1- and 2-year OS rate was 71% (95% CI 59%-84%) and 62% (95% CI 50%-77%), respectively (Figure 2B). Log-rank tests for both LPFI and OS did not show significant differences between treatment Arms (LPFI HR=0.71, 95%CI 0.33-1.54, $p=0.39$; OS HR=1.00, 95%CI 0.57-1.77, $p=0.99$).

Within 6 months following randomization, 13 patients (13%) showed disease progression: 6 in Arm A and 7 in Arm B. In all cases PD was due to the occurrence



of distant metastases, 3 patients also showed local progression. At the time of reporting, 48 patients (47%) had died, 40 (39%) were alive and disease free and 14 (14%) were alive with progressive disease. In total 52 (51%) patients had experienced progression of which 14 (27%) were local or locoregional, 22 (42%) distant and 14 (27%) were both local and distant (another 2 patients had PD type unreported at death). Thirty-four (71%) deaths had shown disease progression whereas in 14 patients other causes were reported of which 2 were CRT related (1 sepsis, 1 radiation pneumonitis) and 2 were consequences of additional surgery (1 pulmonary embolism and 1 massive bleeding). Four patients died due to comorbidities and in 6 patients the cause of death was unreported.

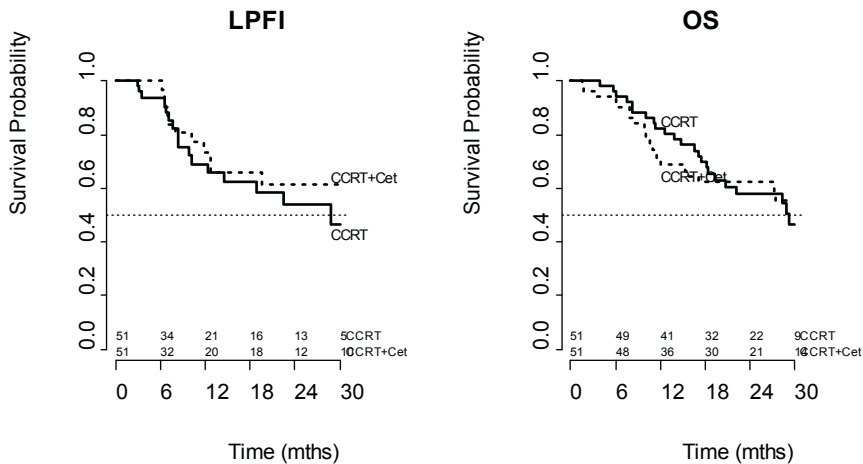


Figure 2. Local progression free interval (a) and overall survival (b) in patients treated with CCRT and CCRT with Cetuximab.

Analysis biopsies and H-scores

Samples were available from 52 patients, 27 (53%) in Arm A and 25 (49%) in Arm B (Figure 1). EGFR expression was elevated (with an immunohistochemistry score ≥ 200) in 29 patients, 12 in Arm A and 17 in Arm B. There was a trend for more squamous patients to have elevated EGFR status (68% vs. 42%; $p=0.09$). There was no evidence of a predictive interaction for OS between either EGFR or histology and treatment (EGFR: $p=0.53$; histology: $p=0.74$), nor was there

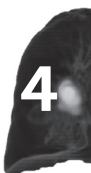
evidence of prognostic value of EGFR status ($p=0.82$). However, squamous cell patients had a significantly worse OS than non-squamous patients ($HR=1.85$, $95\%CI$ 1.04-3.29, $p=0.04$).

Discussion

This study showed that the addition of weekly Cetuximab to radiotherapy and concurrent daily dose Cisplatin did not improve outcome. This study showed that the addition of weekly Cetuximab to high-dose radiotherapy concurrent with daily dose Cisplatin was feasible in a large group of patients with locally advanced NSCLC although more grade ≥ 3 toxicities were observed.

Several studies have been performed to assess the safety and efficacy of Cetuximab in locally advanced NSCLC (Table 4). In a small, single arm phase II trial Cetuximab combined with radiotherapy (30x2Gy) (18) showed promising effects in fragile elderly patients with a median PFS of 7.2 months. In a single arm phase II Swedish NSCLC trial Cetuximab was added to RT after 2 cycles of induction chemotherapy (19). The regimen was feasible and fairly active with a median OS time of 17.1 months. However, in controlled trials there is no evidence of an improved treatment efficacy of the Cetuximab arms. In the randomized phase II trial by the Cancer and Leukemia group B (CALGB) (trial 30407), 101 patients were treated with Pemetrexed, Carboplatin, and radiotherapy (30x2Gy) with or without Cetuximab (20). The median failure free and the 18-month OS rate in the Cetuximab arm were not different from the control arm. Our present trial confirms these findings and does not suggest that Cetuximab improves the efficacy of concurrent CRT in an unselected patient cohort.

The concurrent treatment regimen with chemotherapy and Cetuximab is feasible but challenging. Blumenschein et al. reported on safety of Cetuximab concurrent with chemo radiotherapy in the Radiation Therapy Oncology Group (RTOG) 0324 phase 2 trial (21). Besides the haematological toxicity, the safety profile between this trial and the current trial is comparable. However, not only grade ≥ 3 non-haematological toxicity, but also the number of grade 5 toxicities seems to be lower for the single agent low dose Cisplatin concurrent radiotherapy regimen and this is consistent with the recent systematic review by Koning et al (6). The safety profile of single agent Cetuximab and RT without



concurrent chemotherapy is better tolerated (18;20;22). Acute toxicity grade 3 was seen in only 10-37% of the study population. However, this increased tolerance seems to go at the cost of decreased efficacy.

Despite the fact that 6% of the patients within the current trial treated with additional Cetuximab experienced a grade ≥ 3 pulmonary events, only one event could be attributed directly to the treatment. The other pulmonary problems were either infections or disease progression and were not related to the Cetuximab administration. Late esophagus toxicity was seen in 8% of the patients, which was not significantly different from the population not treated with additional Cetuximab.

In the FLEX trial, high EGFR expression was shown to favorably predict the outcome with a Cetuximab containing treatment regimens in advanced stage NSCLC (13). The number of available biopsies in the current study was too low to definitively answer the question of the predictive value of EGFR expression in the Cetuximab containing radiation schedule. Despite this limitation our data do not suggest that a high expression predict a favorable outcome. These contrasting results might be explained by the phenomenon that radiation can induce EGFR expression as was shown in *in vivo models*, using squamous carcinoma cell lines, as well as *in vivo* in normal epithelial cells (23;24). Therefore, the EGFR expression at onset of the therapy might not represent the actual EGFR expression during treatment.

Several trials in locally advanced NSCLC revealed the better efficacy results of concurrent CRT regimens in recent years (20;25-28). The results of the current trial are no exception and were especially impressive because they were achieved with single agent Cisplatin only. The improvement can be explained in part by staging procedures as the FDG-PET / CT scan and MRI of the brain have led to a refined patient selection. Also improved irradiation techniques might have resulted in the better outcome. Daily Cisplatin concurrent CRT has remained an effective and competitive regimen (29;30). There has been controversy regarding the efficacy of single agent Cisplatin in stage III disease. It seems counterintuitive to treat patients with presumably microscopically disseminated disease without high dose platinum doublets. Although no randomized trials have been performed to compare single agent Cisplatin with doublets, the current results indicate that single agent CCRT is an acceptable and potent treatment regimen.

The daily dose regimen provides us with a treatment regimen that can be used for the majority of patients with locally advanced stage disease because of its favorable toxicity profile (6;7). Also patients with stage II that are not operable and are no candidates for stereotactic treatment might benefit from this regimen because of the favorable local control in comparison to radiotherapy alone.

Phase III trials with more effective regimens are warranted but the phase II data do not suggest that the addition of more modern chemotherapeutics will dramatically increase the efficacy of concurrent CRT (20). Recent advances in stage IV disease have mainly come from molecular-profile directed therapy (31-33). Alas, combining targeted agents with high dose irradiation proved to be challenging (34-36). More effective regimens and better selection tools are still awaited for this patient group.

There are some limitations of our study. First of all the backbone concurrent CRT is not a generally used regimen. The results however, cannot be translated directly to other concurrent regimen but are in concordance with other Cetuximab radiotherapy trials. Second, a fairly high proportion of patients were operated after concurrent CRT. The two arms were well balanced but it might have influenced the outcome. Third, the OLRC was determined early following concurrent CRT. Usually, response is assessed about 12 weeks following treatment. Although the early response measurement was practical due to potential surgical options, response at later time points would have been preferred. Fourth, the size of the current trial is relatively modest. A small difference in the efficacy might have been missed.

In conclusion, the addition of weekly Cetuximab to chemoradiotherapy, using accelerated radiotherapy, in patients with locally advanced NSCLC did not improve treatment outcome while increasing treatment related toxicity.

Acknowledgement

This trial was supported by an unrestricted grant from Merck Serono.



Table 4. Phase II and III trials on Cetuximab and radiotherapy in locally advanced NSCLC

	Chemotherapy regimen	RT (Total dose + no. Fractions)	Patient selection & number	OS (months)	2-yrs OS	Ref.
N0422	Concurrent Cetuximab	60Gy, 30fx	Stage III (57)	15.1	22%	¹
Near	Concurrent Cetuximab followed by maintenance Cetuximab	66Gy, 33fx	Stage II/III (1/29)	19.5	35%	²
Satellite	Induction Docetaxel and Cisplatin (x2) followed by Concurrent Cetuximab	68Gy, 34fx	Stage III (75)	17	37%	³
RTOG 0324	Concurrent Cetuximab, Carboplatin, and Paclitaxel followed by Consolidation Carboplatin and Paclitaxel	65Gy, 35fx	Stage III (87)	22.7	49%	⁴
CALGB 30407	Concurrent Carboplatin, Pemetrexed, +/- Cetuximab, followed by Consolidation Pemetrexed (x4)	70Gy, 35fx	Stage III (101)	(S) 22.4 (C) 22.2	(S) 54%* (C) 58%*	⁵
RTOG 0617	Concurrent weekly Carboplatin, Paclitaxel chemotherapy, +/- Cetuximab followed by consolidation chemotherapy ± Cetuximab (x2)	(LD) 60Gy (30x) vs. (HD) 74Gy (37fx)	Stage III (417)	(LD) 21.7 (HD) 20.7	n.a.	⁶

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