Combining targeted agents and hypo- and hyper-fractionated radiotherapy in NSCLC

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ABSTRACT

Radical radiotherapy remains the cornerstone of treatment for patients with unresectable locally advanced non small cell lung cancer (NSCLC) either as single modality treatment for poor performance status patients or with sequential or concomitant chemotherapy for good performance status patients. Advances in understanding of tumour molecular biology, targeted drug development and experiences of novel agents in the advanced disease setting have brought targeted agents into the NSCLC clinic. In parallel experience using modified accelerated fractionation schedules in locally advanced disease have demonstrated improved outcomes compared to conventional fractionation in the single modality and sequential chemo-radiotherapy settings. Early studies of targeted agents combined with (chemo-) radiotherapy in locally advanced disease in different clinical settings are discussed below and important areas for future studies are high-lighted.

KEYWORDS

Non small cell lung cancer (NSCLC); radical radiotherapy; modified fractionation; targeted agents

Introduction

Arguably one of the most important objectives for cancer researchers remains the reduction in the millions of years of healthy life lost to lung cancer worldwide each year [estimated at 24.5 million in 2008 (1)] with little impact made on the poor relative survival in recent years (2) and improvements in survival trailing behind other cancers (3). Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers. Approximately one third of these patients have early stage disease (stages I and II) at the time of presentation and are usually treated surgically, with radiotherapy being reserved for those who are medically inoperable. Another one third of patients present with advanced disease and radiotherapy is reserved for palliation of symptoms. The remainder of patients present with locally advanced disease (stage III) with the majority being unresectable and the mainstay of treatment is radical intent radiotherapy.

In good performance status patients, the addition of sequentially or concomitant platinum-based chemotherapy is considered as the standard of care in patients with locally advanced disease due to the associated improved outcome (4,5). Importantly, a meta-analysis of over 1,200 patients from six trials comparing concomitant to sequential chemo-radiotherapy reveals the concomitant approach is associated with lower loco-regional disease progression (absolute decrease of 6.1% at five years, from 35.0% to 28.9%) but similar distant disease progression (40.6% and 39.5%, respectively) compared to sequential (6). This suggests an important temporal relationship between the two treatment modalities. The consequent 4.5% increase in 5-year overall survival from 10.6% with sequential to 15.1% with concomitant chemotherapy highlights the opportunity for radio-sensitisation with systemic agents and the relevance of improved local disease control on long term outcome.

However, an estimated 60% of patients with locally advanced disease are not fit enough for concomitant chemo-radiotherapy due to poor performance status and co-morbidities (7). In addition to the less toxic alternative of sequential chemo-radiotherapy, radiotherapy dose escalation has been explored, given conventional doses achieve sub-optimal rates of local disease control with estimates of pathologically persistent tumour following treatment in 60% of patients (8). Tumour control probability modelling suggests that using conventional
fractionation (1.8 to 2 Gy daily), a dose of 84 Gy is required to achieve 50% probability of tumour control at three years (9), some 18-24 Gy higher than the standard dose radiotherapy. Unfortunately, preliminary clinical data from the RTOG 0617 randomised phase III trial of conventionally fractionated radiotherapy (with concurrent and consolidation platinum-based chemotherapy +/- cetuximab) comparing standard dose (60 Gy) to high dose (74 Gy) has revealed the conventionally fractionated high dose arm is associated with a higher rate of local disease progression (34% compared to 25%) and shorter median survival (19.5 months compared to 28.7 months) compared to standard dose (10). It is as yet unclear the reason for the detrimental effect of the higher dose arm, but the extended duration of treatment by dose escalating using conventionally fractionated may be an important factor.

The alternative strategy is to intensify radiotherapy dose using modified fractionation schedules and reduced overall length of the treatment course with the aim of reducing the effect of accelerated tumour cell repopulation during treatment (11,12). The number of fractions given each day can be increased from one to two or three with at least a 6-hour gap in-between (hyper-fractionation) or the number of daily fractions given can be decreased by increasing the dose per fraction (hypo-fractionation). Such schedules increase the biologically effective dose (BED) (13) delivered to the tumour. Experience with extreme hypo-fractionation in stereotactic ablative radiotherapy for early stage disease demonstrates that a BED of over 100 Gy (using a ratio of 10 for tumour linear to quadratic radio-sensitivity) is required to achieve local disease control rates in excess of 90% (14,15). A recent meta-analysis of over 2,000 patients, of which >80% had stage III disease, from eight trials comparing modified to conventional fractionation radiotherapy schedules reveals modified fractionation is associated with improved overall survival at five years (absolute increase of 2.5%, from 8.3% to 10.8%) compared to standard fractionation schedules and importantly, good compliance with the modified regimens (16). Additionally accelerated radiotherapy is associated with higher pathological complete resection rates than conventional fractionation in patients with stage III NSCLC treated with tri-modality therapy (17). The optimal modified fractionation schedule is yet to be clarified, however accelerated schedules to a total dose of 60-66 Gy are considered optimal for patients considered unsuitable for concomitant chemo-radiotherapy (18).

With the recent increase in understanding of the molecular biology of NSCLC and experience of the use of targeted agents in the advanced disease setting, a number of published studies report on combining targeted agents into radical treatment schedules for locally advanced disease, from addition to concomitant chemo-radiotherapy in good performance status patients to combination with radiotherapy alone in elderly or poor performance status patients. Published studies in the various clinical settings are discussed below.

**Molecular biology of NSCLC and epidermal growth factor receptor (EGFR) inhibitors**

EGFR is one of a family of four structurally similar tyrosine kinase-associated receptors which comprise the human epidermal growth factor receptor (HER) family. EGFR (HER1 or ERBB1) was the first to be described in humans, and identified to be a protein comprising an extracellular ligand-binding domains, trans-membrane domain and an intracellular tyrosine kinase domain (19). Each receptor must homo- or hetero-dimerise to activate the intrinsic kinase activity and phosphorylate tyrosine residues on the C-terminal tail, activating intracellular signalling pathways. Epidermal growth factor expression has long been regarded as a poor prognostic factor in NSCLC, suggesting its potential as a therapeutic target (20,21).

Since then, a number of small molecule reversible and more recently irreversible EGFR tyrosine kinase motif inhibitors (TKIs) have been developed, with gefitinib and erlotinib both demonstrating modest activity in EGFR wild-type advanced NSCLC (22,23), leading to licensing for erlotinib. The discovery of constitutionally activating somatic EGFR mutations mapping to the kinase domain in 2004 (24,25) changed drug development strategies, with gefitinib, erlotinib and afatinib now licensed for EGFR TKI naïve advanced NSCLC, with an overwhelming consistent evidence from eight randomized trials demonstrating their superior efficacy over chemotherapy in advanced NSCLC. In this setting, toxicities of EGFR TKIs are more manageable than chemotherapy, and toxic fatalities rare usually at up to 3%. Moreover, there seems to be no obvious difference in proportion of grade 3-5 toxicities between the three agents. The most significant serious adverse event reported in EGFR-TKI development was initially pneumonitis. However, with greater experience of use of these agents in the advanced disease setting, rates of grade 3-5 pneumonitis are routinely observed at up to 3% of most trial series, with no clear differences between the agents, but a possible geographical distribution, with increased events reported from East Asian series (26). Whether this reflects pharmacogenomic differences or differing clinical diagnostic interpretation remains unresolved.

Unlike the success of the EGFR-TKIs, targeting through antibody inhibition has proven more problematic in advanced NSCLC. Whilst preclinical models demonstrated the activity of anti-EGFR monoclonal antibodies (MABs) against several carcinoma cell lines, with synergistic activity in combination with
EGFR inhibitors with conventional fractionation radical radiotherapy alone

In the clinical setting, subsequent to the encouraging improved outcomes with minimal additional toxicity in locally advanced head and neck cancer patients treated with radical radiotherapy combined with cetuximab compared to radiotherapy alone (46), similar studies have been carried out in patients with locally advanced NSCLC. Given the patient population offered radiotherapy alone tend to be elderly and/or with poor performance status, the N0422 phase II single arm study of radical radiotherapy (60 Gy) combined with concomitant cetuximab is interesting (47) (Table 1). The cohort of 57 patients with stage III NSCLC who were considered unfit for combined chemo-radiotherapy included either patients aged 65 years or older with an ECOG performance status of 0-1 or patients of any age with a performance status of 2. Fifty patients (86%) completed the entire treatment and there were no treatment related deaths. Grade 3/4 toxicities were experienced by 31 (54%) patients, with the most common side effects being fatigue (9%) and dyspnoea (9%). The median survival of the cohort was 15.1 (95% CI: 31.1-19.3) months. Of note, patients in this study were not staged with positron emission tomography (PET) scans and outdated radiotherapy techniques were used. A similar smaller single arm phase II study, the Near trial, treated 30 patients with stage III NSCLC, who were considered unfit for or who had refused combined chemo-radiotherapy, with radical radiotherapy (66 Gy) combined with concomitant cetuximab followed by maintenance cetuximab (48) (Table 1). The median age of this cohort was younger at 71 years and all patients had a Karnofsky performance status of ≥70%, however, the median survival was encouraging at 19.6 (95% CI: 11.5-24.7) months. Treatment completion rate and grade 3/4 toxicity rates were similar at 90% (27 patients) and 40% (12 patients), respectively, with the most common side effect being pneumonia (10%). There were however three deaths (myocardial infarction, bacterial endocarditis related sepsis, pulmonary embolus following deep vein thrombosis) reported as unlikely related to the treatment. Both studies included elective nodal irradiation up to 40-50 Gy, however in contrast to the first study, patients in the Near trial were staged with PET scans and modern radiotherapy techniques were used, including intensity modulated radiotherapy (IMRT) and cone beam CT image guided delivery. It is also noted that while the median percentage of normal lung planned to receive 20 Gy (V20) in this cohort of patients was 26%, the range extended up to 60% and therefore included patients at high risk for pulmonary complications due to the radiotherapy (51). Given the skin toxicity rates associated with cetuximab, there is interest in newer EGFR MAbs that demonstrate a lower incidence of skin complications, with phase I studies of nimotuzumab in the palliative radiotherapy setting for NSCLC patients demonstrating feasibility and tolerance (52,53).

Studies of erlotinib and gefitinib in combination with radical radiotherapy alone in locally advanced NSCLC have raised concerns about pulmonary toxicity. In particular, a phase II study from Japan (49) (Table 1) on good performance status patients with a median age of 54 years was closed early due to toxicity concerns. Of the nine patients with stage III NSCLC recruited to the study, seven received gefitinib concurrently with thoracic radiotherapy (60 Gy). Three dimensional (3D) conformal planning was used and all plans had a lung V20≤35%. Despite this, two of these patients experienced acute pulmonary toxicity (grade 1 and 3) after approximately 30 Gy had been delivered. In contrast, another phase II study from China (50) (Table 1)
Table 1. Published studies of EGFR inhibitors with conventional fractionation radical radiotherapy alone.

<table>
<thead>
<tr>
<th>Ref</th>
<th>Patients</th>
<th>Disease</th>
<th>Induction</th>
<th>Target dose/ fractionation</th>
<th>RT planning/delivery</th>
<th>Concomitant</th>
<th>Consolidation/ maintenance</th>
<th>Compliance/toxicity</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(47) Ph II</td>
<td>Number: 57; Age: 77 [60-87]; M/F: 60/40; PS: 22/57/21</td>
<td>Path: 38/43/19; Stage: 0/59/41/0; PET: N</td>
<td>–</td>
<td>60 Gy 30#; Once daily; ENI to 44 Gy</td>
<td>Planning: 2D; Verification: IGRT N</td>
<td>Cetuximab</td>
<td>–</td>
<td>Compliance 86% overall; G3/4 54%; Overall G5 0%; Oesoph G3/4 7%; Pulmon G3/4 9%;</td>
<td>15.1</td>
</tr>
<tr>
<td>(48) Ph II</td>
<td>Number: 30; Age: 71 [57-82]; M/F: 77/23; PS: (Karnofsky ≥70%)</td>
<td>Path: 33/57/10; Stage: 6/57/37/0; PET: Y</td>
<td>–</td>
<td>66 Gy 33#; Once daily; ENI to 40-50 Gy</td>
<td>Planning: 4D IMRT; PTV: 254 [46-529]; Lung V_{20} 26% [15-60]; Verification: IGRT Y</td>
<td>Cetuximab Cetuximab</td>
<td>Compliance 90% overall; G3/4 40%; Overall G5 10%; Oesoph G3/4 3%; Pulmon G3/4 23%;</td>
<td>19.6</td>
<td></td>
</tr>
<tr>
<td>(49) Ph I</td>
<td>Number: 9; Age: 63 [56-71]; M/F: 89/11; PS: (All 0-1)</td>
<td>Path: 72/14/14; Stage: 0/55/44/0; PET: N</td>
<td>–</td>
<td>60 Gy 30#; Once daily; ENI to 40 Gy</td>
<td>Planning: 3D; Lung V_{20} All ≤35%; Verification: IGRT N</td>
<td>Gefitinib</td>
<td>–</td>
<td>Compliance 44% overall; G3/4 44%; Overall G5 0%; Oesoph G3/4 0%; Pulmon G3/4 11%;</td>
<td>–</td>
</tr>
<tr>
<td>(50) Ph I</td>
<td>Number: 26; Age: 56 [30-84]; M/F: 42/58; PS: 4/85/11</td>
<td>Path: 73/15/12; 54% prior systemic chemotherapy</td>
<td>‘Individualised’ GTV 70 Gy 30#; PTV 50 Gy 30#; Once daily; ± SABR to 1-3 metastatic sites</td>
<td>Planning: 3DCRT/IMRT; GTV: 56 [5-420]; Lung V_{20} 14% [3-28]; Verification: IGRT Y</td>
<td>Gefitinib or Erlotinib 69% maintenance median 7.3 months</td>
<td>Compliance 96% overall; G3/4 NR; Overall G5 0%; Oesoph G3/4 4%; Pulmon G3/4 4%;</td>
<td>21.8</td>
<td></td>
<td></td>
</tr>
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</table>

Abbreviations: Ref, Reference; Ph, phase; Number, number of patients; Age, median age of patients in years [range]; M/F, percentage of males to females; PS, percentage of patients with performance status of 0/1/2; Path, percentage of patients with histological adenocarcinoma/squamous cell carcinoma/other subtypes of NSCLC; Stage, percentage of patients with stage II/IIIA/IIIB/IV disease; PET Y/N, Yes or No to mandatory use of PET for staging; ENI, elective nodal irradiation; 2D, 2 dimensional; 3D, 3 dimensional; 4D, 4 dimensional; CRT, conformal radiotherapy; IMRT, intensity modulated radiotherapy; IGRT Y/N, Yes or No to use of image-guided radiotherapy delivery; GTV/PTV, gross or planning target volume median in cm$^3$ [range]; Lung V_{20}, median percentage of total lung volume receiving at least 20 Gy [range]; Toxicity G3/4/S, rates of grades of toxicity; NR, not reported; Oesoph, oesophageal; Pulmon, pulmonary; DLT, dose limiting toxicity; Medial survival, overall median survival in months.
studied 26 patients with stage III or IV disease, treated with 'individualised' radical radiotherapy in combination with either erlotinib or gefitinib. The patients were a heterogeneous group with only 5 (19%) patients having stage III disease. The 21 (81%) patients with stage IV disease had up to three organs treated with stereotactic ablative radiotherapy in addition to radical thoracic radiotherapy given concurrently with the EGFR tyrosine kinase inhibitor. However, treatment was completed as planned in 96% of patients and grade 3/4 pulmonary toxicity rates were acceptable at 4%. The whole cohort had a promising median survival of 21.8 (95% CI: 8.5-35.1) months. Additional toxicity concerns with erlotinib, published in abstract only, come from a small phase I/II Canadian study of erlotinib given concurrently with radical radiotherapy (60 Gy) in poor risk patients with PS 2 or weight loss >5% (54). This study was terminated early due to grade 3-5 pulmonary toxicity in two of five patients.

**EGFR inhibitors with conventional fractionation sequential chemo-radiotherapy**

An early phase I study demonstrated the safety of combining cetuximab with radical radiotherapy (64 Gy) following induction platinum-based chemotherapy in 12 patients with stage III NSCLC (55) (Table 2). One patient died of bronchopneumonia during treatment and two others experienced grade 3 toxicity (a fatigue and a pneumonitis). All patients radiotherapy plans had a lung $V_{20} < 30\%$ (median 22%).

Subsequently a single arm phase II study, the Satellite trial, treated 71 patients with stage III NSCLC using a combination of cetuximab and radical radiotherapy (68 Gy) following induction chemotherapy (56) (Table 2). The patients were of good performance status [0-1] with a relatively low median age of 62 years, however 37% had significant weight loss prior to treatment, a documented poor prognostic factor (60, 61). Interestingly, this study omitted elective nodal irradiation, yet despite this PTV volumes up to 1,543 cm$^3$ (median 586 cm$^3$) were treated and lung $V_{20}$ parameters up to 54% (median 33%) were documented. Importantly, the study reports high compliance rates, low severe toxicity and a median overall survival of 17 (95% CI: 14-0-23.0) months in the whole cohort and a median survival of 24 months in the patients with $<5\%$ weight loss prior to treatment. Impact on health related quality of life with the combination also appears reasonable (62). Of note, the one patient with grade 5 toxicity developed pneumonitis soon after treatment and had a lung $V_{20}$ of 41%, higher than the recommended QUANTEC constraint of 35% (51). Recently a further phase II study of 40 patients with stage II NSCLC reported on experience of cetuximab with concurrent radiotherapy (73.5 Gy) followed by cetuximab and consolidation chemotherapy with paclitaxel and carboplatin (57) (Table 2). The radiotherapy volumes and normal tissue constraints are not reported however one patient died from pneumonitis after 56 Gy of radiotherapy. Overall median survival was 19.4 (95% CI: 15.4-26) months and interestingly no oesophageal toxicity > grade 2 was observed.

Again concerns over pulmonary toxicity have been raised in studies of EGFR TKIs in combination with radical radiotherapy given sequentially with systemic chemotherapy. A Japanese phase II study, JCOG 0402 trial, in 38 good performance status patients with stage III NSCLC and median age of 60 years received gefitinib concurrently with radical radiotherapy (60 Gy) following two cycles of platinum-based induction chemotherapy (58) (Table 2). Compliance with completing the planned concomitant phase of treatment was low at 63% and a patient (3%) developed grade 3 pneumonitis. However, a promising median survival rate of 28.5 (95% CI: 22.5-38.2) months was reported. The CALEB 30106 phase II study evaluated the addition of gefitinib concurrently with radical sequential or concomitant chemo-radiotherapy to patients with stage III NSCLC, based on initial assessment of prognostic factors (59). Patients considered as 'poor risk' in the study were those with a PS of 2 and/or weight loss of $\geq$5%. These patients were treated similarly to in the Japanese study, with two cycles of platinum-based chemotherapy followed by gefitinib given concurrently with radical radiotherapy (66 Gy). The grade 3/4 pulmonary toxicity rate was 10% with grade 5 pulmonary toxicity rate of 5%. The median survival was 19 (95% CI: 9.9-28.4) months. In both studies PET staging was not mandated and 2D radiotherapy planning was permitted with comparable elective nodal irradiation included to 40-44 Gy. An additional confounding factor for the studies is that in both protocols patients were additionally offered maintenance gefitinib. These studies were designed prior to the reporting of the randomised phase III SWOG S0023 trial of concurrent chemo-radiotherapy and consolidation docetaxel with or without maintenance gefitinib in stage III NSCLC, demonstrating inferior survival for the maintenance gefitinib arm (63).

**EGFR inhibitors with conventional fractionation concomitant chemo-radiotherapy**

The addition of cetuximab to concomitant chemo-radiotherapy has also been studied in patients with locally advanced NSCLC. The phase II RTOG 0324 study treated 87 good performance status patients radical radiotherapy (63 Gy) and concomitant and consolidation carboplatin, paclitaxel and cetuximab (64)
Table 2. Published studies of EGFR inhibitors with conventional fractionation radical sequential chemo-radiotherapy.

<table>
<thead>
<tr>
<th>Ref</th>
<th>Patients</th>
<th>Disease</th>
<th>Induction</th>
<th>Target dose/fractionation</th>
<th>RT planning/delivery</th>
<th>Concomitant maintenance</th>
<th>Consolidation/maintenance</th>
<th>Compliance/toxicity</th>
<th>Median survival (months)</th>
</tr>
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<tr>
<td><strong>(55) Ph I</strong></td>
<td>Number: 12;</td>
<td>Path: 33/50/17; ≤4 cycles</td>
<td>64 Gy 32#;</td>
<td>Planning: 3D;</td>
<td>Cetuximab</td>
<td>–</td>
<td>Compliance 75%;</td>
<td>Overall G3/4 17%;</td>
<td>–</td>
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<tr>
<td>Age: 68 [58-76];</td>
<td>Stage: 40/60;</td>
<td>platinum</td>
<td>Once daily;</td>
<td>Verification: IGRT N;</td>
<td></td>
<td></td>
<td>Overall G5 8%;</td>
<td>Oesoph G3/4 0%;</td>
<td>Pulmon G3/4 8%</td>
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<tr>
<td>M/F: 74/25;</td>
<td>PET: N</td>
<td>doublet</td>
<td>ENI to 50 Gy</td>
<td>Lung V20: 22% [14-29]</td>
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<tr>
<td>PS: 42/58/0</td>
<td>&gt;5% wt lo: 37%</td>
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| **(56) Ph II**| Number: 71; | Path: 49/39/12; 2 cycles | 68 Gy 34#; | Planning: 3D; | Cetuximab | – | Compliance 82%; | Overall G3/4 NR; | 17.0 |
| Age: 62 [42-81]; | Stage: 37/63; | cisplatin | Once daily; | Verification: IGRT N; | | | Overall G5 1%; | Oesoph G3/4 1%; | Pulmon G3/4 4% |
| M/F: 50/50; | PET: N | docetaxel | No ENI | GTV: 91 [9-499]; | | | | |
| PS: 62/38/0 | >5% wt lo: 37% | | | PTV: 586 [135-1,543]; | | | | |
| Lung V20: 33% [12-54] | | | | | | | | |

| **(57) Ph II**| Number: 40; | Path: 37/27/35; | 73.5 Gy 35#; | Planning: 2D/3D; | Cetuximab | Paclitaxel carboplatin | Compliance 84%; | Overall G3/4 NR; | 19.4 |
| Age: 67 [40-82]; | Stage: 32/64; | | | | | cetuximab | Overall G5 3%; | Oesoph G3/4 0%; | Pulmon G3/4 11% |
| M/F: 65/35; | PET: N | | | | | | | | |
| PS: All 0-1 | >5% wt lo: 37% | | | | | | | | |

| **(58) Ph I/II**| Number: 38; | Path: 97/0/3; | 2 cycles | Planning: 2D/3D; | Gefitinib | Gefitinib | Compliance 63%/24%; | Overall G3/4 NR; | 28.5 |
| Age: 60 [30-69]; | Stage: 58/42; | cisplatin | 60 Gy 30#; | Verification: IGRT N | | | Overall G5 0%; | Oesoph G3/4 0%; | Pulmon G3/4 3% |
| M/F: 37/63; | PET: N | vinorelbine | Once daily; | | Gefitinib | Gefitinib | | | |
| PS: 76/24/0; | >5% wt lo: 5% | ENI to 40 Gy | No ENI | | | | | | |

| **(59) Ph II**‘Poor risk’ arm; | Number: 21; | Path: 32/48/20; | 2 cycles | Planning: 2D/3D; | Gefitinib | Gefitinib | Compliance NR; | Overall G3/4 71%; | 19.0 |
| Number: 21; | Stage: 43/57; | carboplatin | 66 Gy 33#; | Verification: IGRT N | Gefitinib | Gefitinib | Overall G5 5%; | Oesoph G3/4 19%; | Pulmon G3/4 10% |
| Age: 68 [41-82]; | Stage: 43/57; | PET: N | 66 Gy 33#; | | Gefitinib | Gefitinib | | | |
| M/F: 76/24; | Paclitaxel | Once daily; | ENI to 44 Gy | | | | | | |
| PS: 0/62/38; | >5% wt lo: ≥62% | | | | | | | | |

Abbreviations: Ref, reference; Ph, phase; Number, number of patients; Age, median age of patients in years (range); M/F, percentage of males to females; PS, percentage of patients with performance status of 0/1/2; >5% wt lo, percentage of patients with >5% weight loss; Path, percentage of patients with histological adenocarcinoma/squamous cell carcinoma/other subtypes of NSCLC; Stage, percentage of patients with stage IIIA/IIIB disease; PET Y/N, Yes or No to mandatory use of PET for staging; ENI, elective nodal irradiation; 2D, 2 dimensional; 3D, 3 dimensional; 4D, 4 dimensional; CRT, conformal radiotherapy; IMRT, intensity modulated radiotherapy; IGRT Y/N, Yes or No to use of image-guided radiotherapy delivery; GTV/PTV, gross or planning target volume median in cm³ (range); Lung V20, median percentage of total lung volume receiving at least 20 Gy (range); Toxicity G3/4/5, rates of grades of toxicity; NR, not reported; Oesoph, oesophageal; Pulmon, pulmonary; DLT, dose limiting toxicity; Median survival, overall median survival in months.
Table 3. Published studies of EGFR inhibitors with conventional fractionation radical concomittant chemo-radiotherapy.

<table>
<thead>
<tr>
<th>Ref</th>
<th>Patients</th>
<th>Disease</th>
<th>Induction</th>
<th>Target dose/fractionation</th>
<th>RT planning/delivery</th>
<th>Concomitant</th>
<th>Consolidation/maintenance</th>
<th>Compliance/toxicity</th>
<th>Median survival (months)</th>
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</thead>
<tbody>
<tr>
<td>(64) Ph II</td>
<td>Number: 87; Path: NR; Age: 64 [42-85]; M/F: 57/43; PS: 47/53/0; &gt;5% wt lo: 0%</td>
<td>Number: 87;</td>
<td>Path: NR</td>
<td>63 Gy 35#; Planning: 3D;</td>
<td>Carboplatin/paclitaxel weekly + Cetuximab</td>
<td>2 cycles</td>
<td>Carboplatin/paclitaxel + Cetuximab</td>
<td>Compliance 68%; NH G3/4 68%; Overall G5 7%; Oesoph G3/4 7%; Pulmon G3/4 9%</td>
<td>22.7</td>
</tr>
<tr>
<td>(65) Ph II</td>
<td>Arm A Number: 48; Arm B Number: 53; M/F: 56/44; PS: 58/42/0; Path: 46/35/19; Stage: 60/38</td>
<td>Arm A Path: NR</td>
<td>70 Gy 35#; Planning: 3D/4D;</td>
<td>Carboplatin/Pemetrexed Arm A; Carboplatin/Pemetrexed + Cetuximab Arm B</td>
<td>≤4 cycles</td>
<td>Pemetrexed</td>
<td>Arm A Compliance: 54%; NH G3/4 52%; Overall G5 4%; Arm B</td>
<td>21.2</td>
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<tr>
<td>(59) Ph II</td>
<td>‘Good risk’ arm Number: 39; Path: NR; Age: 64 [44-82]; M/F: 72/28; PS: 46/54/0; &gt;5% wt lo: 0%</td>
<td>2 cycles carboplatin/paclitaxel/irinotecan</td>
<td>66 Gy 33#; Planning: 2D/3D;</td>
<td>Carboplatin/paclitaxel/gefitinib</td>
<td>Gefitinib</td>
<td>Compliance NR; Overall G3/4 86%; Overall G5 5%; Oesoph G3/4 31%; Pulmon G3/4 11%</td>
<td>13.0</td>
<td></td>
<td></td>
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<tr>
<td>(66) Ph II</td>
<td>Number: 23; Path: NR; Age: 62 [44-82]; M/F: 48/52; PS: 60/40/0; &gt;5% wt lo: 17%</td>
<td>2 cycles carboplatin/paclitaxel</td>
<td>74 Gy 37#; Planning: 2D/3D;</td>
<td>Carboplatin/paclitaxel/gefitinib</td>
<td>—</td>
<td>Compliance 86%; Overall G5 0%; Oesoph G3/4 5%; Pulmon G3/4 10%</td>
<td>16.0</td>
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## Table 3 (continued)

<table>
<thead>
<tr>
<th>Ref</th>
<th>Patients</th>
<th>Disease</th>
<th>Induction</th>
<th>Target dose/fractionation</th>
<th>RT planning/delivery</th>
<th>Concomitant</th>
<th>Consolidation/maintenance</th>
<th>Compliance/toxicity</th>
<th>Median survival (months)</th>
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<tbody>
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<td>(67) Ph I</td>
<td>Number: 16; Age: 64 [43-79]; M/F: 56/44; PS: 6/94/0</td>
<td>—</td>
<td>70 Gy 35#</td>
<td>Planning: 3D; Verification: IGRT N</td>
<td>Gefitinib + Dose-escalating docetaxel</td>
<td>2 cycles Docetaxel + Gefitinib</td>
<td>Compliance 88%; Overall G5 19%; Oesoph G3/4 19%; Pulmon G3/4 6%</td>
<td>21.0</td>
<td></td>
</tr>
<tr>
<td>(68) Ph I</td>
<td>Step 1 Number: 5; Stage: NR; PET: ‘optimal’</td>
<td>Variable</td>
<td>63 Gy 34#</td>
<td>Planning: 3D; Verification: IGRT N</td>
<td>Step 1 gefitinib Step 2 Cisplatin + Gefitinib</td>
<td>Gefitinib</td>
<td>Step 1 Overall G5 0%; Oesoph G3/4 0%; Pulmon G3/4 0%; Step 2 Overall G5 0%; Oesoph G3/4 22%; Pulmon G3/4 11%</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>(69) Ph I</td>
<td>Arm A Number: 17</td>
<td>Arm B Carcetobilin paclitaxel</td>
<td>66 Gy 33#</td>
<td>Planning: 2D/3D; Verification: IGRT N</td>
<td>Arm A Cisplatin etoposide erlotinib; Arm B carboplatin paclitaxel erlotinib</td>
<td>Arm A docetaxel</td>
<td>Arm A Overall G5 0%; Oesoph G3/4 18%; Pulmon G3/4 6%</td>
<td>Arm A 10.2</td>
<td></td>
</tr>
<tr>
<td>Arms A+B</td>
<td>Age: 63 [39-78]; M/F: 59/41; PS: 71/29</td>
<td>PET: N</td>
<td>ENI to 44 Gy</td>
<td>ENI to 40 Gy</td>
<td>ENI to 40 Gy</td>
<td>ENI to 40 Gy</td>
<td>ENI to 40 Gy</td>
<td>ENI to 40 Gy</td>
<td>ENI to 40 Gy</td>
</tr>
</tbody>
</table>

Abbreviations: Ref, reference; Ph, phase; Number, number of patients; Age, median age of patients in years (range); M/F, percentage of males to females; PS, percentage of patients with performance status of 0/1/2; >5% wt lo, percentage of patients with >5% weight loss; Path, percentage of patients with histological adenocarcinoma/squamous cell carcinoma/other subtypes of NSCLC; Stage, percentage of patients with stage IIIA/IIIB disease; PET Y/N, Yes or No to mandatory use of PET for staging; ENI, elective nodal irradiation; 2D, 2 dimensional; 3D, 3 dimensional; 4D, 4 dimensional; CRT, conformal radiotherapy; IMRT, intensity modulated radiotherapy; IGRT Y/N, Yes or No to use of image-guided radiotherapy delivery; GTV/PTV, gross or planning target volume median in cm³ (range); Lung V20, median percentage of total lung volume receiving at least 20 Gy (range); Toxicity G3/4/5, rates of grades of toxicity; NR, not reported; NH, non-haematological toxicity; Oesoph, oesophageal; Pulmon, pulmonary; DLT, dose limiting toxicity; Media survival, overall median survival in months.
(Table 3). The majority of patients were staged with PET and all had 3D conformal radiotherapy. Compliance with treatment was 68% and grade 3/4 toxicity rates were acceptable, however there were six deaths (7%) considered as related to the treatment and at least three of these were pulmonary in nature. The median survival was encouraging at 22.7 (95% CI: 15.3-30.4) months. Another phase II study in 101 good performance status patients with locally advanced NSCLC compared high-dose radical radiotherapy (70 Gy) given with concomitant carboplatin and pemetrexed chemotherapy with or without cetuximab, followed by maintenance pemetrexed. PET staging was mandated and 3D or 4D radiotherapy was used without elective nodal irradiation. Compliance was similarly just over 50% in both arms with acceptable grade 3/4 toxicity rates. There were two (4%) patients with grade 5 toxicities in the arm without cetuximab and three (6%) patients in the cetuximab arm, all pulmonary related. The median survival rates were 21.2 and 25.2 months in the non-cetuximab versus cetuximab arms, respectively. The patients were highly selected which may account in part for the higher than anticipated median survival in the non-cetuximab arm. It is important to note this study was designed before lack of efficacy of pemetrexed in squamous histology was known (70). Also there is concern about the effect of the high-dose of radiotherapy used in this study, given in standard 2 Gy daily fractions, due to the recent preliminary results from the subsequent phase III RTOG 0617 study. The RTOG 0617 trial treated 544 patients with locally advanced NSCLC using radical radiotherapy with concomitant carboplatin and paclitaxel chemotherapy followed by consolidation chemotherapy and randomised patients in a 2×2 factorial design between an escalated dose of 74 Gy compared to 60 Gy in 2 Gy daily fractions and between concomitant cetuximab or not. The initial results of the radiotherapy dose analyses demonstrated a worse prognosis in the high-dose compared to standard-dose radiotherapy arm (10), with an 18-month overall survival of 53.9% versus 66.9%, respectively. Recently, the initial results of the cetuximab analyses were also presented (10) and unfortunately no significant difference was observed in median survival or 18 month overall survival between the cetuximab and non-cetuximab arms (23.1 versus 23.5 months and 60.8% versus 60.2%, respectively). The addition of cetuximab was however associated with increase toxicity compared to the non-cetuximab arm (≥ grade 3 non-haematological 70.5% versus 50.7% and ≥ grade 4 35.8% versus 28.2%, respectively).

Phase I studies of erlotinib and gefitinib given with concomitant chemo-radiotherapy for locally advanced disease have demonstrated feasibility of the combination with both standard (68,69) and high-dose (66,67) conventionally fractionated radiotherapy, although the associated median survivals reported in these studies have been disappointing (~12-16 months) (Table 3). Again confounding factors are noted including for example, lack of PET staging and use of maintenance gefitinib (63) in some studies. In addition, the CALEB 30106 phase II study discussed above in relation to combination of gefitinib given with sequential chemoradiotherapy, treated the ‘good-risk’ patients, defined as PS 0-1 with <5% weight loss, with two cycles of induction carboplatin and paclitaxel chemotherapy followed by concomitant gefitinib and chemo-radiotherapy to 66 Gy in standard fractionation, followed by maintenance gefitinib. The median overall survival was poor at 13 (95% CI: 8.5-17.2) months and worse than the median survival of 19 (95% CI: 9.9-28.4) months observed in the ‘poor-risk’ patients treated sequentially.

Considerable pre-clinical rationale exists to combine other targeted therapeutics with radiotherapy. The phosphoinositol 3-kinase (PI3K)/Akt/mTOR pathway is transforming for some NSCLC and a number of inhibitors of components of this pathway are in development for advanced NSCLC. Some of these have been shown to be radio-sensitizers in non-NSCLC models (71). Perhaps the best investigated includes abrogation of the tumour microvasculature by vascular disrupting agents (e.g., ZD6126) or anti-angiogenic agents (e.g., bevacizumab). VEGF is known to be upregulated by irradiation and VEGF inhibition is associated with increased tumour control after irradiation in pre-clinical models (72). However, early phase studies have raised toxicity concerns about combinations of agents targeting tumour vasculature or angiogenesis with radiotherapy in NSCLC patients (73) whereas early phase studies of radiotherapy combined with agents targeting tumour cell proliferation and survival pathways demonstrate feasibility (74,75). A recent review highlights the number of pre-clinical and ongoing early phase clinical studies assessing targeting agents in NSCLC patients (76). With the rapidly expanding availability of novel targeted agents and growing experience of these agents in the advanced disease setting, careful consideration of the optimal agents to combine with radiation and study design remains paramount to maximise therapeutic gain and avoid undue toxicity. Guidelines have been published to provide a framework for assessment of novel radio-sensitizers in the pre-clinical and early phase clinical setting (77). Of the different exploitable mechanisms (78) by which a drug may interact with radiotherapy to improve the therapeutic ratio, it may be that NSCLC patients identified as harbouring
Given the initial results from the phase III RTOG 0617 study, there does not appear to be a role for the additional of cetuximab in combination with standard dose concurrent chemo-radiotherapy using conventional fractionation. Interestingly, no significant interaction between the radiotherapy dose and the addition of cetuximab were observed. The question remains as to whether cetuximab can be safely added to modified fractionation schedule chemo-radiotherapy and whether this provides any benefit.

**Additional considerations**

When considering the total dose of radiation prescribed for a given schedule, it is important to consider that locally advanced NSCLC encompasses a heterogenous population of individuals with differing volume, location and extent of disease. Recently the concept of isotoxic dose escalation was introduced, moving away from a fixed radiotherapy dose prescription for all patients to a tailored prescription based on the surrounding normal tissue dose constraints, predicting a certain acceptable probability of toxicity (81). Use of this approach in modified fractionation radiotherapy with sequential or concomitant chemotherapy demonstrates promising results the in phase II setting (82-84). The study of the addition of targeted agents to isotoxic dose escalated accelerated radiotherapy schedules is an interesting area of ongoing research.

For trial design, patient selection remains important and patients need to be optimally staged and stratified based on prognostic variables to ensure the results are repeatable in the wider patient population. State-of-the-art radiotherapy techniques for planning and delivery, including IMRT and image-guided radiotherapy (IGRT), stand to optimise the therapeutic window. Detailed reporting of radiotherapy planning and delivery parameters will reduce the heterogeneity in studies discussed above and permit optimal comparison between studies and reproducibility of outcomes.

Further work is required to improve understanding of the mechanisms of response and toxicity using targeted agents with radiation and to assess for early predictors of response and toxicity, particularly with respect to fraction-size sensitivity with the increasing use of altered fractionation radiotherapy schedules.

**Conclusions**

Advances in the molecular understanding of NSCLC have accelerated in recent years and the era of personalised medicine in systemic treatment, particularly in advanced disease, has become a reality. At the same time, advances in technology and imaging have led to improvements in patient selection and in accuracy of radical radiotherapy planning and delivery for locally advanced NSCLC. The combination of individualised biological optimisation using novel targeted agents with physical optimisation using state-of-the-art radical (chemo-) radiotherapy, including accelerated-fractionation schedules and individualised radiotherapy dose-prescriptions, stands to improve outcomes in the heterogeneous population of patients with unresectable locally advanced NSCLC.

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