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# Multimodality Therapy for NSCLC

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## Abstract

The standard therapy for patients with unresectable stage III non-small-cell lung cancer (NSCLC) is the combination of chemotherapy and radiotherapy. Although the concurrent use of both treatment modalities has been shown to be superior to sequential therapy, the role for additional chemotherapy, either as induction or as consolidation, remains unclear. Targeted therapy has met limited success in the treatment of unselected patients with stage III NSCLC. New studies using induction therapy with erlotinib or crizotinib for molecularly selected patients and consolidation therapy with checkpoint inhibitors are currently ongoing, and the results are eagerly awaited.

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## Keywords

Stage III NSCLC · Chemoradiotherapy · Molecularly targeted therapy · Immunotherapy

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## 1 Introduction

Lung cancer is both the most commonly diagnosed malignancy and cause of cancer death in the United States for men and women combined, with 240,000 new cases and 162,000 deaths estimated for the year 2015 [1]. Among patients with lung cancer, approximately 85 % have one of the non-small-cell lung cancer (NSCLC) histologies [2]. Stage III NSCLC was present in approximately 27 % of patients according to the sixth edition of the American Joint Commission on Cancer (AJCC) [3]. However, the proportion of stage III is currently lower due to the reclassification of the approximately 15–20 % of those with malignant pleural effusion to stage M1a in the seventh edition of AJCC [4, 5]. Stage III lung cancer is a heterogeneous disease, with several broad subgroups including T3N1 and selected cases of T4N0-1 which may be treated with surgery followed by adjuvant chemotherapy, T1-3N2 which is potentially resectable but usually treated with chemoradiation, and patients with invasive T4 or N3, which are unresectable and treated with chemoradiation [6].

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## 2 Chemoradiotherapy

### 2.1 Initial Studies with Chemoradiotherapy

The role of chemotherapy in the management of locally advanced NSCLC was established with the results of the Cancer and Leukemia Group B (CALGB) 8433 trial, which randomly assigned 155 patients with stage III NSCLC to sequential chemotherapy with cisplatin (100 mg/m<sup>2</sup> on days 1 and 29) and vinblastine (5 mg/m<sup>2</sup> weekly for 5 weeks) followed by radiotherapy with 60 Gy over six weeks, starting on day 50, or radiotherapy alone [7]. The response rate was 46 % for sequential chemoradiation and 35 % for radiation alone ( $p = 0.092$ ). The addition of chemotherapy significantly prolonged the median failure-free survival (PFS; 8.2 vs. 6.0 months;  $p = 0.041$ ), overall survival (OS; 13.8 vs. 9.7 months;  $p = 0.006$ ), and 3-year OS (23 % vs. 11 %) compared to radiation therapy alone. Chemo radiotherapy was more commonly associated with serious infection (7 % vs. 3 %) and significant weight loss (14 % vs. 6 %), but there were no treatment-related deaths in either arm.

Several trials have been conducted in an attempt to establish the optimal way to deliver chemotherapy and radiation. The Radiation Therapy Oncology Group

(RTOG) 9410 trial randomly assigned 610 patients to sequential cisplatin (100 mg/m<sup>2</sup> on days 1 and 29) and vinblastine (5 mg/m<sup>2</sup> weekly for 5 weeks) followed by radiotherapy 60 Gy starting on day 50, the same regimen with concurrent radiation starting on day 1, or concurrent radiation with 69.6 at 1.2 Gy twice daily beginning on day 1 with cisplatin (50 mg/m<sup>2</sup> on days 1, 8, 29, and 36) and oral etoposide (50 mg twice daily on days 1, 2, 5, and 6 for 10 weeks) [8]. The median OS for arms 1 to 3 was 14.6, 17.0, and 15.6 months. Concurrent chemoradiation conferred a slightly better 5-year survival rate compared to sequential chemoradiation (16 % vs. 10 %; hazard ratio [HR] 0.812; 95 % confidence interval [CI] 0.663–0.996; *p* = 0.046). Acute grade 3–5 adverse events, mostly esophagitis, mucositis, nausea, and vomiting, were more commonly seen in the concurrent therapy arms. Late toxicities were similar among the three groups.

A meta-analysis of six randomized trial comparing concurrent to sequential chemoradiation in locally advanced NSCLC showed a significant improvement in median OS with the concurrent strategy (HR 0.84; 95 % CI 0.74–.95; *p* = 0.004) [9]. The absolute survival benefit was 5.7 % at 3 years, and 4.5 % at 5 years. Compared to the sequential strategy, concurrent chemoradiation was associated with increased grade 3–4 acute esophageal toxicity (18 % vs. 4 %; *p* <0.001).

## 2.2 Paclitaxel-Based Studies

The phase II Locally Advanced Multimodality Protocol (LAMP) study tested the regimen of paclitaxel and carboplatin combined with radiotherapy in stage III NSCLC [10]. A total of 276 patients were randomly assigned to sequential arm with two cycles of paclitaxel (200 mg/m<sup>2</sup>) and carboplatin (AUC = 6) followed by radiotherapy with 63 Gy, induction arm with two cycles of induction paclitaxel (200 mg/m<sup>2</sup>) and carboplatin (AUC = 6) followed by weekly paclitaxel (45 mg/m<sup>2</sup>) and carboplatin (AUC = 2) with concomitant radiotherapy 63 Gy, or consolidation arm with weekly paclitaxel (45 mg/m<sup>2</sup>) and carboplatin (AUC = 2) with concurrent RT 63 Gy followed by two cycles of consolidation paclitaxel (200 mg/m<sup>2</sup>) and carboplatin (AUC = 6). At a median follow-up of 39.6 months, the median OS of the sequential, induction, and consolidation arms was 13.0, 12.7, and 16.3 months, respectively. The 3-year survival rates were almost identical among the three arms (17 % for sequential, 15 % for induction, 17 % for consolidation). Median PFS and 1-year progression-free rates were, respectively, 9.0 months and 54 % for the sequential arm, 6.7 months and 46 % for the induction arm, and 8.7 months and 46 % for the consolidation arm. The consolidation arm was associated with increased rates of grade 3–4 esophagitis, lung toxicities, and myelosuppression.

The RTOG 0617 was a phase III study evaluating the role of high-dose versus standard-dose radiotherapy and the effect of additional cetuximab [11]. Patients with unresectable stage III NSCLC were randomly assigned to either standard-dose radiotherapy (60 Gy) with or without cetuximab, or high-dose radiotherapy (74 Gy)

with or without cetuximab. All patients received concurrent paclitaxel ( $45 \text{ mg/m}^2$ ) and carboplatin ( $\text{AUC} = 2$ ) with radiation followed by consolidation paclitaxel ( $200 \text{ mg/m}^2$ ) and carboplatin ( $\text{AUC} = 6$ ) for two cycles. For patients randomized to receive cetuximab, cetuximab was administered at  $400 \text{ mg/m}^2$  on day 1 followed by  $250 \text{ mg/m}^2$  weekly that continued through consolidation treatment. A total of 544 patients were enrolled. Standard-dose radiation was associated with improved median OS (28.7 vs. 20.3 months; HR 1.38; 95 % CI 1.09–1.76;  $p = 0.004$ ) compared to high-dose radiotherapy, with the latter causing increased rates of severe esophagitis (21 vs. 7, %;  $p < 0.0001$ ). The addition of cetuximab did not improve the median OS (25 vs. 24 months; HR 1.07; 95 % CI 0.84–1.35;  $p = 0.29$ ) or median PFS (median 10.8 vs. 10.7 months and 27.5 %; HR 0.99; 95 % CI 0.80–1.22;  $p = 0.89$ ) compared to chemotherapy alone. However, in a planned subset analysis, patients with over-expression of EGFR (H-score  $\geq 200$ ) had improved median OS with the use of cetuximab (42.0 vs. 21.2 months; HR 1.72; 95 % CI 1.04–2.84;  $p = 0.032$ ). Since the study did not suggest a survival benefit with high-dose radiotherapy or cetuximab in the overall population with stage III NSCLC, concurrent paclitaxel and carboplatin with standard-dose radiotherapy followed by two cycles of consolidation paclitaxel and carboplatin remains one of the standard treatments for unresectable stage III NSCLC.

### 2.3 Etoposide-Based Studies

The phase II Southwest Oncology Group (SWOG) 9019 trial evaluated the regimen of cisplatin and etoposide with radiotherapy [12]. Patients with stage III NSCLC were treated with cisplatin ( $50 \text{ mg/m}^2$  on days 1, 8, 29, and 36) and etoposide ( $50 \text{ mg/m}^2/\text{day}$  on days 1–5, and 29–33) along with concurrent radiation 45 Gy. In the absence of disease progression, patients then received further radiotherapy to a total dose of 61 Gy with 2 additional cycles of cisplatin and etoposide. The median OS for the 50 enrolled patients was 15 months, with 3-year OS and 5-year OS of 17 and 15 %, respectively. Major adverse events include neutropenia (grade 4 in 32 %), anemia (grade 3–4 in 28 %), esophagitis (grade 3–4 in 20 %), and respiratory infection (grade 3–4 in 8 %). This study established the role of cisplatin and etoposide with concurrent radiotherapy as one of the standard treatments for locally advanced NSCLC.

In the phase II SWOG 9504 study, patients with stage IIIB NSCLC received the same chemoradiation regimen used in SWOG 1909, with two cycles of consolidation docetaxel ( $75 \text{ mg/m}^2$ ) 4–6 weeks after completion of chemoradiation in the absence of tumor progression [13]. The response rates, median PFS, and median OS for the 83 patients accrued were 67 %, 16 months, and 26 months, respectively. The 3-year survival was 37 %. Neutropenia (74 %), infection (21 %), and esophagitis (17 %) were the most common severe adverse events. Four patients died of treatment-related toxicities, two from pneumonitis and two from infection.

## 2.4 Pemetrexed-Based Studies

The phase II CALGB 30407 study examined the role of concurrent chemoradiation with pemetrexed and carboplatin with or without cetuximab in patients with stage III NSCLC [14]. Patients were randomly assigned to four cycles of pemetrexed ( $500 \text{ mg/m}^2$ ) and carboplatin ( $\text{AUC} = 5$ ) with concomitant radiation 70 Gy or the same chemoradiation regimen with the addition of cetuximab ( $400 \text{ mg/m}^2$  loading dose followed by  $250 \text{ mg/m}^2$  weekly for 12 weeks). All patients received four cycles of consolidation pemetrexed ( $500 \text{ mg/m}^2$ ). Among the 101 enrolled, 65 % had non-squamous histologies. The median OS for patients treated with and without cetuximab was 25.2 and 21.2 months, respectively. Toxicities were similar between the two treatment arms. Common grade 3 and greater adverse events include myelosuppression, esophagitis, dysphagia, pneumonitis, dehydration, nausea, and vomiting. This study demonstrated the feasibility of concurrent chemoradiation with carboplatin and pemetrexed, with no benefits from the addition of cetuximab.

Choy and colleagues compared cisplatin to carboplatin during pemetrexed-based chemoradiation regimen in a phase II trial [15]. When the study first opened, patients with squamous cell histology were eligible. After the preferential efficacy of pemetrexed in non-squamous histology was revealed in a phase III study [16], the protocol was amended in 2008 to exclude squamous cell histology. A total of 98 patients with unresectable stage III NSCLC were randomly assigned to receive pemetrexed ( $500 \text{ mg/m}^2$ ) in combination with carboplatin ( $\text{AUC} = 5$ ) or cisplatin ( $75 \text{ mg/m}^2$ ). Concurrent radiotherapy was delivered to a total dose of 64 to 68 Gy. Patients also received three cycles of consolidation pemetrexed. The cisplatin arm was associated with increased median OS (27 vs. 18.7 months), 2-year OS (58.4 % vs. 45.4 %), and median PFS (13.1 vs. 8.8 months). Due to the small sample size and study design, the comparison between the two regimens was not performed. Nevertheless, both regimens were considered active and well tolerated. Dehydration was the most common grade 3–4 non-hematologic toxicity in both arms (6.5 % in the carboplatin arm and 9.6 % in the cisplatin arm). Esophagitis was experienced in 4.3 % in the carboplatin group and 5.7 % in the cisplatin group. The carboplatin arm had more severe hematologic adverse events compared to the cisplatin arm (anemia 10.9 % vs. 7.7 %; febrile neutropenia 4.3 % versus 0 %; thrombocytopenia 8.6 % vs. 5.7 %, respectively).

## 2.5 Comparison of Chemotherapy Regimens

The two most commonly used chemotherapy regimens in combination with radiotherapy in stage III NSCLC are cisplatin plus etoposide and carboplatin plus paclitaxel. In a small study conducted by Dr. Wang and colleagues, 65 patients with stage III NSCLC were randomized to cisplatin plus etoposide or carboplatin plus paclitaxel during concurrent radiotherapy with 60 Gy [17]. Cisplatin and etoposide was associated with increased median OS (20.2 vs. 13.5 months) and 3-year OS (33.1 vs. 13 %,  $p = 0.04$ ).

In a retrospective analysis using the Department of Veterans Affairs Central Cancer Registry, 1,842 patients treated with either cisplatin plus etoposide or carboplatin plus paclitaxel with concomitant radiation from 2001 to 2010 were identified [18]. Cisplatin plus etoposide was used in 27 % of patients and was associated with increased median OS in univariable analysis (17.3 vs. 14.6 months, HR 0.88; 95 % CI 0.79–.98,  $p = 0.02$ ). Nevertheless, since the population of patients receiving cisplatin plus etoposide had a higher proportion of overall favorable features such as younger age, less weight loss, and better comorbidity scores, a propensity score-match data set was performed. With this analysis, the improvement in OS from cisplatin plus etoposide did not reach statistical significance (HR 0.97; 95 % CI 0.85–1.10). The rates of hospitalization (2.4 vs. 1.7;  $p < 0.001$ ), outpatient visits (17.6 vs. 12.6;  $p < 0.001$ ), infections (47.3 vs. 39.4 %;  $p = 0.002$ ), acute kidney disease/dehydration (30.5 % vs. 21.2 %;  $p < 0.001$ ), and mucositis plus esophagitis (18.6 % vs. 14.4 %;  $p = 0.0246$ ) were increased in the cisplatin plus etoposide regimen compared to carboplatin plus paclitaxel.

The PROCLAIM study is a phase III trial comparing cisplatin plus pemetrexed to cisplatin plus etoposide during concurrent chemoradiotherapy [19]. Patients with stage III NSCLC were randomly assigned to receive three cycles of cisplatin (75 mg/m<sup>2</sup>) and pemetrexed (500 mg/m<sup>2</sup>) every 3 weeks or cisplatin (50 mg/m<sup>2</sup> on days 1, 8, 29, and 36) plus etoposide (50 mg/m<sup>2</sup> on days 1–5 and 29–33) during concurrent radiotherapy with 66 Gy. After concomitant chemoradiation, patients received further consolidation chemotherapy with four cycles of pemetrexed in the cisplatin plus pemetrexed arm or a choice of 3 regimens in the cisplatin plus etoposide arm. The cisplatin plus pemetrexed was associated with a numerically superior response rate (36 % vs. 33 %,  $p = 0.458$ ), median PFS (11.4 vs. 9.8 months; HR 0.86; 95 % CI 0.71–1.04), and median OS (26.8 vs. 25.0 months; HR 0.98; 95 % CI 0.79–1.20;  $p = 0.831$ ), although none reached statistical significance. The pemetrexed arm was associated with decreased rates of severe neutropenia (24.4 % vs. 44.5 %) and esophagitis (15.5 % vs. 20.6 %). This study demonstrated that cisplatin plus pemetrexed with concurrent radiotherapy was as effective as cisplatin plus etoposide, but with a better safety profile.

## 2.6 Consolidation Chemotherapy

Although several studies include the use of consolidation chemotherapy, its role in the management of patients with unresectable stage III NSCLC remains undefined (Table 1).

In the HOG/USO study, the chemoradiation followed by consolidation docetaxel, as used in the SWOG 9504 regimen, was compared to chemoradiation alone [20]. Although the planned accrual was for 259 patients, the trial was closed early, after enrollment of 203 patients, when an interim analysis suggested evidence of futility. Compared to observation, the docetaxel arm was associated with similar median OS (21.2 vs. 23.2 months,  $p = 0.883$ ) and 3-year OS (27.1 % vs. 26.1 %). Consolidation docetaxel was associated with increased rates of febrile neutropenia

**Table 1** Clinical trials of consolidation chemotherapy for stage III NSCLC

Trial	Year	Study arms	Median OS (months)	Survival rate
HOG/USO <sup>20</sup>	2008	Cis/Etop + RT - > Obs versus Cis/Etop + RT - > Doc	23.2 versus 21.2 ( <i>p</i> = 0.08)	(3-yr) 26.1 % versus 27.1 %
GILT <sup>21</sup>	2012	Cis/Vin + RT - > Obs versus Cis/Vin + RT - > Cis/Vin	18.5 versus 20.8 ( <i>p</i> = 0.87)	(4-yr) 21.4 % versus 25.3 %
KCSG-LU05-04 <sup>22</sup>	2015	Cis/Doc + RT - > Obs versus Cis/Doc + RT - > Cis/Doc	20.6 versus 21.8 ( <i>p</i> = 0.44)	NA

*Cis* cisplatin; *Etop* etoposide; *RT* radiotherapy; *Obs*, observation; *Doc* docetaxel; *Vin* vinorelbine

and grade 3–5 pneumonitis (9.6 % vs. 1.4 %). Five percent of patients in the docetaxel arm died of grade 5 toxicities.

The phase III GILT study examined the role of consolidation cisplatin and oral vinorelbine after concurrent chemoradiotherapy [21]. Patients received two cycles of oral vinorelbine (50 mg/m<sup>2</sup> on days 1, 8, and 15) and cisplatin (20 mg/m<sup>2</sup> on days 1–4) every 4 weeks with concomitant radiotherapy at 66 Gy. Patients without disease progression were further randomized to two cycles of consolidation therapy with oral vinorelbine (60–80 mg/m<sup>2</sup> on days 1 and 8) and cisplatin (80 mg/m<sup>2</sup> on day 1) every 3 weeks versus observation. A total of 279 patients were enrolled. The overall response rate of chemoradiation was 60.7 %. Consolidation chemotherapy did not improve median PFS (6.4 vs. 5.5 months, *p* = 0.63) or median OS (20.8 vs. 18.5 months, *p* = 0.87). The 4-year survival rates were 25.3 and 21.4 % for the consolidation and the observation arm, respectively. Concurrent chemoradiation caused esophagitis in 8.6 %, nausea in 5.0 %, fatigue in 3.3 %, and pneumonia/pneumonitis in 2.6 %. Neutropenia and anemia were the most common severe hematologic toxicities (neutropenia in 11.2 % and anemia in 3.2 %). Consolidation chemotherapy caused more neutropenia (11.7 % vs. 5.7 %), anemia (3.5 % vs. 1.1 %), nausea (4.7 % vs. 2.9 %), and fatigue (2.3 % vs. 1.0 %) compared to observation.

The KCSG-LU05-04 trial was a phase III study examining the efficacy of consolidation cisplatin plus docetaxel following concurrent chemoradiation with the same regimen [22]. Concurrent chemoradiation entailed weekly cisplatin (20 mg/m<sup>2</sup>) and docetaxel (20 mg/m<sup>2</sup>) for 6 weeks with 66 Gy of radiotherapy. Consolidation docetaxel was given at 35 mg/m<sup>2</sup> on days 1 and 8 every 3 weeks for three cycles. A total of 437 patients in Korea, China, and Taiwan were randomly assigned to concurrent chemoradiation alone versus chemoradiation followed by consolidation docetaxel. Although numerically superior, the improvement in median PFS (9.1 vs. 8.1 months, HR 0.91; 95 % CI 0.73–1.12; *p* = 0.36) and median OS (20.6 vs. 21.8 months; HR 0.91; 95 % CI 0.72–1.25; *p* = 0.44) did not reach statistical significance. The most common grade 3–4 toxicities in the

chemoradiotherapy phase were esophagitis (9.5 %), infection (6.4 %), anorexia (4.0 %), and anemia (5.4 %). Consolidation chemotherapy induced more neutropenia (6.9% vs. 2.9 %), febrile neutropenia (1.8% vs. 0 %), fatigue (4.6 versus 0 %), and anorexia (3.5 versus 1.2 %) compared to observation.

In a pooled analysis including 3,479 patients from 41 studies, consolidation chemotherapy did not prolong median OS compared to observation alone (19.0 vs. 17.9 months; HR 0.94; 95 % CI 0.81–1.09;  $p = 0.40$ ) [23]. The 3-year survival rates were also similar between the consolidation and the observation group (27.0 % vs. 24.8 %). Grade 3–5 neutropenia, esophagitis, pneumonitis, and treatment-related deaths were similar in the two study groups.

With the lack of established benefit from consolidation chemotherapy in 3 randomized Clinical trials and a pooled analysis, the American Society for Radiation Oncology (ASTRO) guideline recommended against routine use of consolidation chemotherapy after concurrent chemoradiation [24]. However, patients who did not receive full doses of systemic chemotherapy during radiotherapy can be considered for consolidation chemotherapy.

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### 3 Molecularly Targeted Therapy

Several targeted drugs used in advanced stage NSCLC have been tried in patients with locally advanced disease. Bevacizumab, a monoclonal antibody against vascular endothelial growth factor receptor (VEGFR), is an approved therapy for patients with advanced non-squamous NSCLC [25]. The use of bevacizumab during chemoradiation, however, was associated with increased risk of bleeding and development of trachea–esophageal fistula [26]. Due to the severe toxicities, bevacizumab is no longer being investigated during chemoradiotherapy.

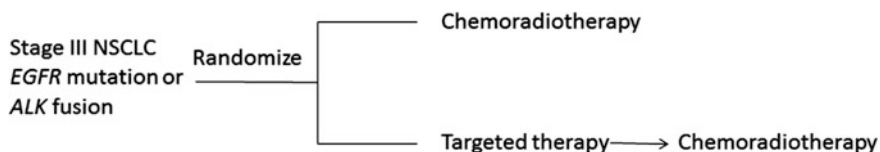
The epidermal growth factor receptor has been studied in patients with stage III NSCLC with trial including both the monoclonal antibody cetuximab and the tyrosine kinase inhibitors gefitinib and erlotinib. In the NEAR trial, 30 patients who were unfit or unwilling to receive chemoradiation received weekly cetuximab during radiotherapy followed by 13 weeks of consolidation [27]. The treatment was well tolerated, and the outcomes including median OS of 19.5 months and 2-year OS of 34.9 % are comparable to those obtained from standard chemoradiation. Using a similar design except for the consolidation cetuximab, the N0422 study showed a median OS of 15.1 months in 57 patients with stage III NSCLC who were elderly or had poor performance status [28]. The Swedish Lung Cancer Group trial examined the role of concurrent weekly cetuximab in combination with thoracic radiation therapy (68 Gy over 7 weeks), following 2 cycles of induction chemotherapy with cisplatin and docetaxel [29]. The clinical benefit rate at 12 months was 30 % and median OS was 17 months. Grade 3 esophagitis was seen in 1.4 % and grade 3 skin toxicity in 4.2 %. Ramalingam and colleagues conducted a multicenter single-arm phase II trial in which 40 patients with unresectable IIIA or IIIB NSCLC were treated with thoracic radiotherapy to a dose of 73.5 Gy in 35 fractions over 7 weeks in combination with weekly cetuximab, which was



continued during consolidation therapy with carboplatin and paclitaxel for a maximum of 26 doses [30]. The median OS, primary endpoint of the study, was 19.4 months. Cetuximab addition to chest radiation and consolidation chemotherapy was well tolerated with 3 patients experiencing a grade 3 rash. No grade 3 or 4 esophagitis was observed. EGFR gene copy number by fluorescence in situ hybridization (FISH) was not predictive of outcomes in this study. The safety of cetuximab in combination with definitive chemoradiation in NSCLC has also been demonstrated by the Radiation Therapy Oncology Group (RTOG) 0324 and Cancer and Leukemia Group B (CALGB) 30407 trials, where toxicities observed in the arms with combined chemotherapy and cetuximab were comparable to those with chemotherapy alone [14, 31].

The Southwest Oncology Group (SWOG) S0023 trial was designed to evaluate whether the addition of gefitinib maintenance therapy improved overall survival following concurrent chemoradiation with cisplatin and etoposide followed by three cycles of consolidation docetaxel [32]. A total of 243 molecularly unselected patients with stage III NSCLC were randomized to receive gefitinib or placebo following concurrent chemoradiation with cisplatin and etoposide and consolidation docetaxel. Although gefitinib was well tolerated, survival was worse in the gefitinib arm, predominantly due to tumor progression. The Japanese Cooperative Oncology Group (JCOG) 0402 study examined the role of induction chemotherapy followed by gefitinib and concurrent thoracic radiation in patients with unresectable adenocarcinoma, selected by light or never smoking status only, and did not meet predefined criteria for feasibility due to increased toxicity mostly with grade 3 and 4 liver enzyme elevations [33]. In a phase II study including 46 unselected patients with stage III NSCLC treated with erlotinib 150 mg daily during standard chemoradiation with weekly carboplatin plus paclitaxel followed by two cycles of consolidation with chemotherapy alone, the median and 5-year OS were encouraging at 36.5 months and 39.5 %, respectively [34]. Of note, there were 4 patients with *EGFR* mutation and 5 patients with unknown *EGFR* status in the study, precluding the evaluation of the effects of this mutation in the outcome.

The RTOG 1306 is a phase II study evaluating the role of targeted agents in molecularly selected patients with locally advanced NSCLC. In this study, patients with stage III *EGFR*-mutant lung cancer and *ALK*-positive NSCLC will be



**Fig. 1** RTOG 1306 schema *Targeted therapy Erlotinib* for EGFR mutation or crizotinib for *ALK* fusion for 12 weeks. If CT scan after 6 weeks of targeted therapy does not show *PR*, patients should proceed directly to chemoradiation *Chemotherapy* cisplatin plus etoposide or carboplatin plus paclitaxel *Radiation* 60 Gy in 30 fractions with intensity-modulated radiation therapy (IMRT) or 3D conformal radiation therapy (3D-CRT)

randomized to 12 weeks of induction erlotinib (*EGFR*-mutant) or crizotinib (*ALK*-positive) followed by chemoradiation, or chemoradiation alone (Fig. 1) [35].

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## 4 Immunotherapy

In patients with stage III disease, the largest experience with immunotherapy is with tecemotide (liposomal BLP25), a peptide-based vaccine consisting of synthetic mucin 1 (MUC-1) lipopeptide combined with the adjuvant monophosphoryl lipid A and three lipids forming a liposomal product. In a phase II study, 171 patients with stage IIIB or IV NSCLC who had no tumor progression after the initial therapy were randomized to tecemotide 100 µg weekly for 8 weeks followed by maintenance every 6 weeks until tumor progression or observation [36]. Although there was no benefit from the vaccine in the study population, a post hoc analysis showed increased median (not reached vs. 13.3 months) and 2-year OS (60 % vs. 36.7 %) in the tecemotide group. The encouraging results in patients with stage III NSCLC led to the START trial, a phase III study where 1,513 patients were randomized to receive tecemotide versus placebo following definitive chemoradiation [37]. Although tecemotide was not associated with improved median OS in the entire patient population (25.6 vs. 22.3 months, HR 0.88, 95 % CI 0.75–1.03,  $p = 0.12$ ), it improved median OS in a subset analysis of patients treated with concurrent chemoradiation (30.8 vs. 20.6 months; HR 0.78; 95 % CI 0.64–0.95,  $p = 0.01$ ). In the updated analysis with a median follow-up of 58 months, the addition of tecemotide was associated with increased median OS in patients treated with concurrent chemoradiation (29.8 vs. 20.8 months, HR 0.81; 95 % CI 0.68–0.98,  $p = 0.026$ ) but not in those treated with sequential therapy (20.7 vs. 25.5 months, HR 1.04; 95 % CI 0.82–1.31,  $p = 0.76$ ) [38]. Soluble MUC and antinuclear antibodies were associated with improved survival in patients treated with tecemotide. Two large randomized studies testing tecemotide in patients treated with concurrent chemoradiation, START2 and INSPIRE, were discontinued after the results from the EMR 63325-009 study, which showed no benefit from the addition of tecemotide to chemoradiation.

Checkpoint inhibitors represent a promising new approach to the treatment of NSCLC, with nivolumab and pembrolizumab approved for patients with previously treated advanced stage NSCLC [39–41]. The role of immune checkpoint inhibitors in patients with locally advanced NSCLC is currently being investigated. Both anti-programmed death 1 (PD-1) and anti-programmed death cell ligand 1 (PDL-1) antibodies are being investigated as consolidation therapy after standard chemoradiation for patients with stage III NSCLC [42].

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## 5 Conclusions

The cure rates for patients with locally advanced NSCLC remain suboptimal with standard chemoradiation. There are several acceptable chemotherapy regimens to be used during concurrent radiotherapy, and the escalation of the radiation dose is

not associated with improved outcomes. Consolidation chemotherapy, although commonly used, has not shown improvement in survival compared to chemoradiation alone and should be considered only in selected cases. The role for targeted therapy in molecularly selected patients is currently being evaluated in this potentially curative patient population, although its applicability is limited by the low probability of patients harboring targetable driver gene abnormalities. There are ongoing studies testing consolidation therapy with checkpoint inhibitors, and the results are eagerly awaited.

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