Debate on stage III NSCLC: The role of systemic therapy

Rolf Stahel
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Stage III disease: The problem of heterogeneity, the risk of distant metastases

T3/T4 disease

N2/N3 disease

Risk of distant mets and local relapse > 60%
2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III NSCLC: Incidental stage IIIA(N2)

If, despite adequate mediastinal staging procedures, N2 disease is only documented intraoperatively, surgery should be followed by adjuvant chemotherapy [I, A]. In case of complete resection, addition of postoperative radiotherapy is not routinely recommended, but may be an option following individual risk assessment [V, C]

Eberhard, Ann Oncol 2015
Lung Adjuvant Cisplatin Evaluation
Chemotherapy vs control

<table>
<thead>
<tr>
<th>Category</th>
<th>No. Deaths / No. Entered</th>
<th>Hazard ratio (Chemotherapy / Control)</th>
<th>HR</th>
<th>[95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA</td>
<td>102 / 347</td>
<td>1.41 [0.96;2.09]</td>
<td></td>
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<tr>
<td>Stage IB</td>
<td>509 / 1371</td>
<td>0.92 [0.78;1.10]</td>
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<tr>
<td>Stage II</td>
<td>880 / 1616</td>
<td>0.83 [0.73;0.95]</td>
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<tr>
<td>Stage III</td>
<td>865 / 1247</td>
<td>0.83 [0.73;0.95]</td>
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</tr>
</tbody>
</table>

Test for trend: p = 0.051

CT may be detrimental for stage IA, but stage IA patients were generally not given the potentially best combination cisplatin+vinorelbine (13% of stage IA patients versus ~43% for other stages)

Pignon, ASCO 2006, JCO 2008
CALGB 9633: adjuvant carboplatin/paclitaxel in stage IB

Tumor $\geq$ 4 cm
Tumor $<$ 4 cm

Strauss, JCO 2008
7507: Randomized phase III trial of customized adjuvant chemotherapy (CT) according to BRCA-1 expression levels in patients with node positive resected non-small cell lung cancer (NSCLS) SCAT: A Spanish Lung Cancer Group trial (Eudract:2007-000067-15; NCTgov: 00478699) – Massuti B et al

**Study objective**
- To investigate the role of BRCA1 as a differential regulator in the response of patients with NSCLC to cisplatin and antimicrotubule agents

**Control group**
- Docetaxel 75 mg/m² + cisplatin 75 mg/m² D1 (n=108)

**Experimental groups**
- Low BRCA1: Gemcitabine 1250 mg/m² D1, 8 + cisplatin 75 mg/m² D1 (n=110)
- Intermediate BRCA1: Docetaxel 75 mg/m² + cisplatin 75 mg/m² D1 (n=127)
- High BRCA1: Docetaxel 75 mg/m² D1 (n=110)

**Key patient inclusion criteria**
- Stage II and III post-surgery NSCLC
- R0
- pN1/pN2 (n=500)

**Primary endpoint**
- OS

**Secondary endpoints**
- DFS, toxicity, recurrence pattern

**Stratification**
- N1 vs. N2
- Age ≤65 vs. >65 years
- Non-squamous vs. squamous
- Lobectomy vs. pneumonectomy

Key results

- No significant difference was seen in OS (HR=0.86) between the experimental and control groups.
- Treatment according to BRCA1 levels did not improve OS.
Adjuvant gefitinib in (unselected) resected NSCLC

OAS all patients

OAS EGFR mut patients

Goss, JCO 2013
7501: A randomized, double-blind phase 3 trial of adjuvant erlotinib (E) versus placebo (P) following complete tumor resection with or without adjuvant chemotherapy in patients (pts) with stage IB-IIIA EGFR positive (IHC/FISH) non-small cell lung cancer (NSCLC): RADIANT results – Kelly K et al

• **Study objective**
  – To evaluate adjuvant erlotinib vs placebo following complete tumour resection in patients with stage IB–IIIA NSCLC and *EGFR* FISH+ or *EGFR* IHC+

**Key patient inclusion criteria**
- Complete resected NSCLC
- Stage IB–IIIA
- *EGFR* IHC+/FISH+
- ECOG PS 0–2 (n=973)

**Primary endpoint**
- Disease-free survival (FAS)

**Secondary endpoints**
- OS (FAS)
- Disease-free survival and OS (*EGFR* M+ subset)

Stratification
- Histology, stage, prior adjuvant CT, *EGFR* FISH status, smoking status, country

**R 2:1**

- Erlotinib 150 mg/day (n=623)
- Placebo (n=350)

FAS, full analysis set

Kelly et al. J Clin Oncol 2014; 32 (suppl 5; abstr 7501)
RADIENT

**DFS**
- Placebo (156 events) Median: 48.2 m
- Erlotinib (254 events) Median: 50.5 m

Log-rank test: p = 0.3235
HR: 0.90 (95% CI: 0.741, 1.104)

**OS**
- Placebo (35 events) Median: not reached
- Erlotinib (112 events) Median: not reached

Log-rank test: p = 0.3350
HR: 1.13 (95% CI: 0.881, 1.448)

Kelly, ASCO 2014
RADIENT: Sufficient duration of therapy?

GIST: Adjuvant imatinib for 3 years  
Breast Cancer: Adjuvant tamoxifen for 5 or 10 years

5 year survival rate 92% vs 81.7%  
(HR 0.45 95%CI 0.22-0.89, p=0.02)

Joenssu, JAMA 2013; Davies, Lancet 2013
Ongoing trials

- USA: Intergroup ECOG 1505: Bevacizumab added to adjuvant chemotherapy
- NCI/Cooperative Group Trials: ALCHEMIST
  - Adjuvant erlotinib vs placebo for EGFR mutant NSCLC (n=410)
  - Adjuvant crizotinib vs placebo for ALK positive NSCLC (n=336)
- Japan: WJOG6410L (IMPACT)
  - Stage II-III: surgery -> cisplatin/vinorelbine vs gefitinib (n=230)
- China: CTONG1104 (ADJUVANT) - recruited
  - Stage II-IIIA: surgery -> cisplatin/vinorelbine vs gefitinib (n=220)
1173O: MAGRIT, a double-blind, randomized, placebo-controlled phase III study to assess the efficacy of the recMAGE-A3 + AS15 cancer immunotherapeutic as adjuvant therapy in patients with resected MAGE-A3-positive non-small cell lung cancer (NSCLC) – Vansteenkiste JF et al

- **Key results**
  - Median DFS was not significantly different between MAGE-A3 CI and placebo (60.5 vs. 57.9 months; HR 1.024, 95% CI 0.89, 1.18; p=0.7379)

  ![DFS graph](image-url)

  - **MAGE-A3 CI** (597 events)
    - Median: 60.5 (95% CI 57.2, –)
  - **Placebo** (298 events)
    - Median: 57.9 (95% CI 55.7, –)
  - p*= 0.7379
  - HR 1.02 (95% CI 0.89, 1.18)

  *Likelihood ratio test from Cox regression model stratified by chemotherapy and adjusted for baseline variables used as minimisation factors

PEARLS: Phase III trial of adjuvant pembrolizumab in stages IB-III
Risk modifications by other parameters

FIGURE 1. Overall survival of the study population according to the presence/absence of microscopic vascular invasion. MST, mean survival time.

Ruffini, JTO 2011; Higgins, JTO 2012
Adjuvant chemotherapy of resected NSCLC

• Cisplatin based chemotherapy is the standard
• It should be administered in stage II-III A
• It must be evaluated in stage IB (>4 cm recommended)
• Usual criteria used in trials were
  • < 75 yrs
  • < 2 months after surgery
  • PS 0-1
  • No post-operative complications
• Carboplatin-based chemotherapy is on option if cisplatin is counter-indicated
Adjuvant chemotherapy of resected NSCLC

• Valid predictive biomarkers remain yet to be defined
• Which platin-based combination to be used remains open to interpretation
• Place of targeted agents remains to be further defined
  • First results for EGFR TKI disappointing, but there are ongoing trials
  • Await results for bevacizumab (discouraging in other cancers)
• Immune checkpoint inhibitors will be explored
  • LINC: MEDI4737 for one year (RIII, IFCT-1401I, BR31, NVALT-24)
  • PEARLS: Pembrolizumab for one year (RIII, EORTC, ETOP)
Possible strategies include several options: induction chemotherapy followed by surgery, induction chemoradiotherapy followed by surgery, or concurrent definitive chemoradiotherapy[I, A]. No recommendation can yet be made; however, an experienced multidisciplinary team is of paramount importance in any complex multimodality treatment strategy decision. If induction chemotherapy alone is given preoperatively, postoperative radiotherapy is not standard treatment but may be an option based on critical evaluation of loco-regional relapse risks [IV, C]
Neoadjuvant chemotherapy followed by surgery: the two small landmark trials

Roth: CTX/VP/CDDP x 3
mOS 21 vs 14 months (p=0.048)
3y OS 43% vs 19%

Rosell: MiViP x 3
mOS 22 vs 10 months (p=0.005)

Roth et al., J Natl Cancer Inst 1994; 86:673-680

Rosetl et al. Lung Cancer 1999; 26: 7–14
Meta-analysis of induction chemotherapy in NSCLC all stages

<table>
<thead>
<tr>
<th>References</th>
<th>Recruitment</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roth et al.</td>
<td>1987–1993</td>
<td>IIIa</td>
</tr>
<tr>
<td>Rosell et al.</td>
<td>1989–1991</td>
<td>IIIa</td>
</tr>
<tr>
<td>Zhou et al.</td>
<td>1990–2001</td>
<td>III</td>
</tr>
<tr>
<td>Liao et al.</td>
<td>1995–1997</td>
<td>I–IIla</td>
</tr>
<tr>
<td>Li et al.</td>
<td>1990–1995</td>
<td>III</td>
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<tr>
<td>JCOG</td>
<td>1993–1998</td>
<td>IIIa</td>
</tr>
<tr>
<td>Yao et al.</td>
<td>1990–2002</td>
<td>III</td>
</tr>
<tr>
<td>Sorensen et al.</td>
<td>1998–2004</td>
<td>Ib–IIla</td>
</tr>
<tr>
<td>S9900</td>
<td>1999–2004</td>
<td>Ib–IIla</td>
</tr>
<tr>
<td>MRC LU22</td>
<td>1997–2005</td>
<td>I–III</td>
</tr>
<tr>
<td>Ch.E.S.T.</td>
<td>2000–2004</td>
<td>Ib–IIla</td>
</tr>
</tbody>
</table>

Song et al. (expanded from Burdett et al. JTO 2006), J Thor Oncol 2010; 5:510-516
SAKK 16/96: 3 cycles of neoadjuvant cisplatin/docetaxel in stage IIIA(N2): The importance of complete resection

Overall survival

- Complete resection
- Incomplete resection
- All

p<0.0001
SAKK 16/00 (IIIA/N2 NSCLC): Trial design

**Primary endpoint: event free survival**

**Chemotherapy:**
- Cisplatin 100 mg/m² d1 x 3 cycles q3
- Docetaxel 85 mg/m² d1 x 3 cycles q3w + G-CSF

**Radiotherapy:**
- 3 weeks after last chemotherapy
- 44 Gy in 22 fractions in 3 weeks
  - accelerated concomitant boost

**Surgery:**
- 3-4 weeks after completion of chemotherapy or radiotherapy

Pless, ASCO 2014
SAKK 16/00 (IIIA/N2 NSCLC): Event-free survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median EFS (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>RT</td>
<td>13.1 (9.9, 23.5)</td>
</tr>
<tr>
<td>no RT</td>
<td>11.8 (8.4, 15.2)</td>
</tr>
</tbody>
</table>

HR = 1.1 (95% CI: 0.8-1.4)  p = 0.665

Pless, ASCO 2014
What about selected surgical stages III: Erlotinib in M+?

- Erlotinib in neoadjuvant setting in patients with stage IIIA, N2-positive NSCLC (Korea, completed)
- Erlotinib as neoadjuvant treatment in patients with stage IIIA N2 NSCLC with activating EGFR mutation (ML25444, China, ongoing)
- Erlotinib before surgery in stage III NSCLC patients who have EGFR positive tumors (EVENT, US, ongoing)
- Erlotinib versus gemcitabine/cisplatin as neoadjuvant treatment in NSCLC, a phase II randomized trial (EMERGING, China, ongoing)
- Erlotinib versus docetaxel and cisplatin as neoadjuvant therapy in stage III NSCLC patients, a phase II randomized trial (Oncology, Taiwan, ongoing)
Concurrent chemoradiotherapy is the treatment of choice in patients evaluated as unresectable in stage IIIA and IIIB [I, A]. If concurrent chemoradiotherapy is not possible – for any reason - sequential approaches of induction chemotherapy followed by definitive radiotherapy represent a valid and effective alternative [I, A].
Most comparative studies of concurrent chemoradiotherapy versus sequential administration were using cisplatin + etoposide or cisplatin + vinca alkaloid (typically: cisplatin + vinorelbine). There are no comparative phase III trials using the paclitaxel/carboplatin regimen. When delivered perioperatively, cisplatin-based combinations are considered the treatment of choice, in the absence of contraindications [I, A].

In the stage III disease with chemoradiotherapy strategy, 2-4 cycles of concomitant chemotherapy should be delivered [I, A]. There is no evidence for induction or consolidation chemotherapy.
Individual patient data meta-analysis: sequential vs concurrent chemo-radiotherapy

A

Percent

Time Since Random Assignment (years)

HR = 0.84 (95%CI, 0.74 to 0.95)
P = .004

Aupérin, JCO 2010
Induction vs concurrent CT-RT: OS

RTOG trial 9410: Cisplatin-vinblastin before or current with radiotherapy

Arm 1 (sequential) vs Arm 2 (concurrent): 17.0 vs 14.6 months (HR 0.81, 0.66-0.99)

Acute grade 3 toxicity > in concurrent arm, but late toxicity rates were similar!

Curran, JNCI 2011
Chemoradiotherapy: No evidence for advantage with induction or consolidation chemotherapy in stage III

Carboplatin-paclitaxel induction followed by chemoradiotherapy

Concurrent PE chemo-radiotherapy followed by docetaxel

Vokes, JCO 2007

Hanna, JCO 2008
Gefitinib after local radical radiotherapy

Kelly, JCO 2010
Which chemotherapy? Chemotherapy followed by chemoradiotherapy

Agents
- NVB - CDD
- TXL - CDD
- GEM - CDD

1 year Surv.
- 65%
- 62%
- 68%

Vokes, JCO 2002
The median survival time and 5-year survival rates were 20.5, 19.8, and 22.0 months and 17.5%, 17.8%, and 19.8% in arms A, B, and C, respectively. The incidences of grade 3 to 4 neutropenia, febrile neutropenia, and gastrointestinal disorder were significantly higher in arm A than in arm B or C (P < .001).

Cave: noninferiority of OS was not demonstrated in the present study (numbers? power?, outcomes?)
Daily cisplatin

### Table 1. Three Regimens for Treating Non–Small-Cell Lung Cancer.

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>1ST COURSE*</th>
<th>REST PERIOD</th>
<th>2ND COURSE*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DAY 1</td>
<td>DAY 8</td>
<td>DAY 15</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>x x x x</td>
<td>x x x x</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy + cisplatin,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 mg/m² weekly</td>
<td>↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy + cisplatin,</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>6 mg/m² daily</td>
<td>↑ ↑ ↑ ↑ ↑</td>
<td>↑ ↑ ↑ ↑ ↑</td>
<td>↑ ↑ ↑ ↑ ↑</td>
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</tbody>
</table>

![Graph showing survival rates](image)

The four-year point denotes survival as of May 1991, for which P = 0.054 overall. Kaplan–Meier analysis showed that for the comparison of group 2 with group 1, P = 0.36; group 3 with group 1, P = 0.009; group 2 with group 3, P = 0.20; and group 1 with groups 2 and 3, P = 0.04. RT denotes radiotherapy.

### No. at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>Year</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>114</td>
<td>51</td>
</tr>
<tr>
<td>Group 2</td>
<td>110</td>
<td>45</td>
</tr>
<tr>
<td>Group 3</td>
<td>107</td>
<td>54</td>
</tr>
</tbody>
</table>
Daily carboplatin

Patients >70 years with unresectable stage III NSCLC treated with 60 Gy with or without concurrent low-dose carboplatin [30 mg/m² per day, 5 days a week for 20 days

Atagi, Lancet Oncol 2012
Cisplatin/etoposide versus carboplatin/ paclitaxel with concurrent radiotherapy for stage III NSCLC: VHA data

Santana-Davila, JCO 2014
7506: Final overall survival (OS) results of the phase III PROCLAIM trial: Pemetrexed (Pem), cisplatin (Cis) or etoposide (Eto), Cis plus thoracic radiation therapy (TRT) followed by consolidation cytotoxic chemotherapy (CTX) in locally advanced nonsquamous non-small cell lung cancer (nsNSCLC) – Senan S et al

Study objective
• To evaluate the efficacy and safety of pemetrexed + cisplatin vs. etoposide + cisplatin plus thoracic radiation therapy (TRT) followed by consolidation cytotoxic chemotherapy in locally advanced nsNSCLC

Key patient inclusion criteria
• Stage IIIA-IIIB unresectable nsNSCLC
• Measurable tumour lesion
• No prior chemo
• ECOG PS 0/1 (n=598)

Primary endpoint
• OS

Secondary endpoints
• PFS, ORR, safety

*Investigator’s choice of: etoposide 50 mg/m² D1–5 q4w + cisplatin 50 mg/m² D1, 8 q4w; vinorelbine 30 mg/m² IV D1, 8 q3w + cisplatin 75 mg/m² IV D1 q3w; or paclitaxel 200 mg/m² IV q3w + carboplatin AUC6 IV q3w.

Key results

- OS in the pemetrexed + cisplatin treatment arm was not statistically different to survival in the etoposide + cisplatin arm (HR 0.98 [95%CI 0.79, 1.20]; p=0.831).

Median OS (95%CI), months
- Pemetrexed + cisplatin: 26.8 (20.4, 30.9)
- Etoposide + cisplatin: 25.0 (22.2, 29.8)

HR (95%CI) 0.98 (0.79, 1.20)
Log-rank p=0.831

Key results

- PFS trended in favour of pemetrexed + cisplatin, but did not reach statistical significance (11.4 vs. 9.8 months, respectively; HR 0.86 [95%CI 0.71, 1.04]; p=0.130)
- ORR was similar between groups (35.9% with pemetrexed + cisplatin; 33.0% with etoposide + cisplatin (p=0.458)
- DCR was higher with pemetrexed + cisplatin (80.7% vs. 70.7%; p=0.004)
- The pemetrexed + cisplatin arm had a significantly lower incidence of overall drug-related grade 3/4 AEs
  - Any Grade 3–5 AE: 67.8% vs. 79.4% (p=0.001)
  - Grade 3/4 neutropenia/granulocytopenia: 24.4% vs. 44.5% of patients (p<0.05)
  - Grade 3/4 pneumonitis: 1.8% vs. 2.6%
  - Grade 3/4 esophagitis: 15.5% vs 20.6%

Conclusion

- OS was similar for the pemetrexed + cisplatin arm vs. the control arm, but pemetrexed + cisplatin did have a better safety profile than etoposide + cisplatin in patients with nsNSCLC

DCR, disease control rate (CR+PR+SD)
Randomized phase III comparison of standard-dose versus high-dose chemo-radiotherapy ± cetuximab for stage III NSCLC

<table>
<thead>
<tr>
<th>RT Technique</th>
<th>Concurrent Treatment</th>
<th>Consolidation Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 3D-CRT</td>
<td>Arm A: Concurrent chemotherapy*</td>
<td>Arm A: Consolidation chemotherapy*</td>
</tr>
<tr>
<td>2. IMRT</td>
<td>RT to 60 Gy, 5 x per wk for 6 wks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arm B: Concurrent chemotherapy*</td>
<td>Arm B: Consolidation chemotherapy*</td>
</tr>
<tr>
<td></td>
<td>RT to 74 Gy, 5 x per wk for 7.5 wks</td>
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</tr>
<tr>
<td></td>
<td>Arm C: Concurrent chemotherapy* and Cetuximab</td>
<td>Arm C: Consolidation chemotherapy* and Cetuximab</td>
</tr>
<tr>
<td></td>
<td>RT to 60 Gy, 5 x per wk for 6 wks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arm D: Concurrent chemotherapy* and Cetuximab</td>
<td>Arm D: Consolidation chemotherapy* and Cetuximab</td>
</tr>
<tr>
<td></td>
<td>RT to 74 Gy, 5 x per wk for 7.5 wks</td>
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</tbody>
</table>

*Carboplatin and paclitaxel
Randomized phase III comparison of standard-dose versus high-dose chemo-radiotherapy ± cetuximab for stage III NSCLC

(A) One-sided log-rank, \( p=0.0042 \).

(B) One-sided log-rank, \( p=0.2938 \).

*Bradley, Lancet Oncology 2015*
EGFR TKI and radiotherapy in EGFR mutated NSCLC (RTOG 1210/Alliance 31101)

Co-Principal Investigators’
Alliance: Ramaswamy Govindan, MD
RTOG: Hak Choy, MD

Eligibility Criteria
• Non-squamous NSCLC
• Unresectable stage IIIA or IIIB disease;
• Presence of mutations in EGFR TK or EML4-ALK translocation
• Absence of T790M mutation in the EGFR TK domain;
• PS $\leq$ 1
• Determined to be a candidate for concurrent chemoradiation
Individualized Combined Modality Therapy for Stage III For EGFR / ALK driven tumours
RTOG 1210/Alliance 31101

Stratification

Mutation Type
1. EGFR
2. ALK

Weight Loss (in prior 6 mos.)
1. ≤ 5%
2. > 5%

ALK Translocation Cohort

Arm 1: Erlotinib, 150 mg/day
for 12 weeks

Crizotinib, 250 mg/bid, 12 wks

Concurrent chemotherapy and radiation, 64 Gy

Arm 2: Concurrent Chemotherapy and radiation, 64 Gy

Chemotherapy regimen:
Cisplatin and etoposide or Paclitaxel and carboplatin
Other ongoing EGFR TKI + radiotherapy phase II trials in EGFR M+ Stage III

• A randomized phase II to evaluate the efficacy and safety of erlotinib versus etoposide plus cisplatin With concurrent RT (China, primary endpoint PFS)

• A randomized phase II study of induction CT or erlotinib followed by concurrent CT-RT (Korea, primary endpoint RR)

• A phase II trial of RT combined with gefitinib (China, primary endpoint RR)
START: A phase III study of L-BLP25 cancer immunotherapy for unresectable stage III non-small cell lung cancer after sequential or concurrent chemoradiation
NICOLAS: A feasibility trial evaluating anti-PD1 nivolumab consolidation after standard first line chemotherapy and radiotherapy in locally advanced stage IIIA7B NSCLC

Screening, eligibility and enrolment

Stage IIIA / B NSCLC
Investigator’s choice

Whole body FDG PET-CT

Standard treatment

chemo cycle 1
chemo cycle 2
chemo cycle 3

Radiotherapy
66Gy, 33 fractions

Radiotherapy
66Gy, 24fractions

CT after Radioth.

Trial treatment

Anti PD-1 consolidation:
nivolumab 10mg/kg every 2 weeks

Year 1: CT every 8 weeks
Year 2: CT every 12 weeks

Chemotherapy: Cisplatin (or Carboplatin) doublet

PE: Grade ≥3 pneumonitis free rate; N = 43 pts
Systemic therapy and radiotherapy

- There is no standard regimen/schedule for concomitant chemoradiotherapy
- Cisplatin doublet is proven to be beneficial, but there is also evidence for the activity of carboplatin combinations
- Choices of chemotherapy is based on expected toxicity
- Targeted agents remain investigational
- The role of immunotherapy is under investigation