Current standards and practice changing studies in stages I-III NSCLC

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Disclosures

Consultant or Advisory Role in the last two years
I have received honoraria as a consultant at advisory boards from Abbvie, AstraZeneca, Boehringer Ingelheim, MSD, Pfizer, Roche and Takeda.

Speaker Honoraria in the last two years
I have received honoraria as a speaker from Astra Zeneca, Boehringer Ingelheim, Lilly, MSD and Roche.

DMC in the last two years
Roche and Takeda

Financial Support of ETOP trials (president and scientific chair)
AstraZeneca, BMS, Boehringer Ingelheim, Genentech, MSD, Roche, and Pfizer.
Adjuvant therapy for surgically resected NSCLC

- Adjuvant ChT should be offered to patients with resected stage II and III NSCLC [I, A] and can be considered in patients with resected stage IB disease and a primary tumour >4cm [II,B].

- For adjuvant ChT, a two-drug combination with cisplatin is preferable [I, A]. In randomised studies, the attempted cumulative cis-platin dose was up to 300 mg/m2, delivered in three to four cycles. The most frequently studied regimen is cisplatin–vinorelbine.

- At the present time, the choice of adjuvant therapy should not be guided by molecular analyses [IV, B].
## Adjuvant phase III clinical trials in NSCLC

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Primary endpoint</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab After Surgery and Chemotherapy in Treating Patients With Stage IB-IIIA Non-small Cell Lung Cancer (ANVIL)</td>
<td>Phase III IB-IIIA DFS OS</td>
<td>714</td>
</tr>
<tr>
<td>Study of Pembrolizumab (MK-3475) vs Placebo for Participants With Non-small Cell Lung Cancer After Resection With or Without Standard Adjuvant Therapy (MK-3475-091/KEYNOTE-091) (PEARLS)</td>
<td>Phase III IB-IIIA DFS</td>
<td>1400</td>
</tr>
<tr>
<td>A Phase III, Open-Label, Randomized Study to Investigate the Efficacy and Safety of Atezolizumab (Anti-PD-L1 Antibody) Compared With Best Supportive Care Following Adjuvant Cisplatin-Based Chemotherapy in Patients With Completely Resected Stage IB-IIIA Non-Small Cell Lung Cancer (IMpower 010)</td>
<td>Phase III IB-III DFS</td>
<td>1127</td>
</tr>
<tr>
<td>Double Blind Placebo Controlled Controlled Study of Adjuvant MEDI4736 In Completely Resected NSCLC</td>
<td>Phase III IB-III DFS in PD-L1 positive</td>
<td>1100</td>
</tr>
</tbody>
</table>
Treatment recommendation for locoregional NSCLC

- No enlarged LNs and peripheral tumour
  - Imaging CT Scan
  - No enlarged N2 nodes but central tumour or hilar LNs
    - Enlarged discrete N2 LNs
      - Category of N2
        - Surgery: unforeseen N2
          - Adjuvant chemotherapy (radiotherapy)

- Extensive mediastinal N2 infiltration
  - Invasive LN Result
    - Not required if negative LNs on PET
      - N0-N1
        - Potentially resectable N2
          - Dedicated multidisciplinary assessment
            - Surgical multimodality treatment
          - Non-surgical multimodality treatment
        - Unresectable N2
          - Not required

Postmus, Ann Oncol 2017
• All patients planned for definitive stage III NSCLC treatment should undergo a diagnostic contrast-enhanced CT scan of the chest and upper abdomen followed by a PET or a combined PET-CT with a CT technique with adequately high resolution for initial staging purposes [I, A] in order to rule out detectable extrathoracic, extracranial metastasis, and to assess potential mediastinal lymph node involvement, ideally within 4 weeks before the start of treatment [III, B]

• Single PET-positive distant lesions need pathological confirmation [V, B]

• For patients with operable N2 disease, pathological staging of the mediastinum is advised [III, C]
All patients planned for curative stage III NSCLC treatment should receive brain imaging for initial staging [III, B]. **Contrast-enhanced brain MRI** is the preferred method for staging of the brain in stage III disease [III, A]. If it is not possible to perform MRI, dedicated contrast-enhanced brain CT scan is advised [III, B].
• If single station N2 disease can be demonstrated by preoperative pathological nodal analysis, resection followed by adjuvant ChT, induction ChT followed by surgery or induction CRT followed by surgery are options. If induction ChT alone is given preoperatively, PORT is not standard treatment, but may be an option based on critical evaluation of locoregional relapse risks [IV,C].

• In multistation N2 or N3, concurrent definitive CRT is preferred [I,A]. An experienced multidisciplinary team is of paramount importance in any complex multimodality treatment strategy decision, including the role of surgery in these cases [IV,C].

By Katherine M.W. Pisters, Mark G. Kris, Richard J. Gralla, Muhammed B. Zaman, Robert T. Heelan, and Nael Martini

Conclusion: We have observed pathologic complete responses in approximately 12% of advanced NSCLC patients treated with preoperative MVP chemotherapy. These pathologically determined responses were seen only in patients with major objective responses clinically. Pathologic complete response predicts excellent survival and functional level and should be considered a major end point in the evaluation of preoperative chemotherapy programs.

Mediastinal lymph node clearance after docetaxel-cisplatin neoadjuvant chemotherapy is prognostic of survival in patients with stage IIIA pN2 non-small-cell lung cancer: a multicenter phase II trial

- The median EFS and OS were 14.8 months (range, 2.4 to 53.4) and 33 months (range, 2.4 to 53.4), respectively.
- Local relapse occurred in 27% of patients with tumor resection, with distant metastases in 37%. 
- Multivariate analyses identified mediastinal clearance (hazard ratio, 0.22; P = .0003) and complete resection (hazard ratio, 0.26; P = .0006) as strongly prognostic factors for increased survival.
SAKK trials on neoadjuvant therapy of stage III NSCLC

SAKK 16/00 (*Pless, Lancet 2015*): Hypothesis: Neoadjuvant chemo-radiotherapy could increase nodal downstaging and R0 resection rate, resulting in an improved local control, event-free survival and overall survival.
Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial (SAKK 16/00): Event-free survival

The SAKK study failed to show benefit by adding relatively low doses of RT (45 Gy) to ChT.

Pless, Lancet 2015
Multimodal treatment in operable Stage III NSCLC: A pooled analysis on long-term Results of three SAKK trials (SAKK 16/96, 16/00, 16/01)

5- and 10-year survival:
Stage IIIA: 41% and 29%
Stage IIIB: 35% and 27%
Multimodal treatment in operable Stage III NSCLC: A pooled analysis on long-term Results of three SAKK trials (SAKK 16/96, 16/00, 16/01)

The most frequent location of relapse was distant failure in 53%, but first site of relapse was locoregional in 33%, whereas 14% had both locoregional and distant failure
Phase III study of surgery versus definitive concurrent chemo-radiotherapy boost in patients with resectable Stage IIIA(N2) and selected IIIB NSCLC after induction chemotherapy and concurrent Chemoradiotherapy (ESPATUE).

The ESPATUE trial confirmed that CRT (45 Gy) followed by surgery, is as good as CRT with definitive RT (65–71 Gy) given as a boost in the last week of CRT.
Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data
Neoadjuvant PD-1 blockade in resectable lung cancer with two infusions of nivolumab 2 weeks apart: Major pathological response

63yo M, ex-smoker, adeno, PD-L1 2%+, <10% viable tumor at resection

% pathological regression:
10 out of 45 patients (22% [95% CI: 11%, 37%]) without an EGFR or ALK genetic alteration treated with neoadjuvant atezolizumab had a MPR

- There was no observable correlation between pathologic and radiographic responses
Neoadjuvant nivolumab or nivolumab plus ipilimumab for resectable NSCLC: Clinical and correlative results from the NEOSTAR study

- **Eligibility**
  - NSCLC Stage I-IIIA N2 single station (AJCC77)
  - Contralateral 2 and/or 4 node eval to exclude N3
  - Surgical candidate
  - ECOG PS 0-1

- **Stratification**
  - Stage

- **EVALUATION**
  - CT, PET/CT Tumor (Archival/fresh)
  - Blood, Stool

- **BIOMARKERS**
  - CT, PET/CT Blood, Stool
  - Tumor Uninvolved lung

**Arm A:** Nivolumab 3 mg/kg D1,15,29

**Arm B:** Nivolumab 3 mg/kg D1,15,28 + Ipilimumab 1 mg/kg D1

**Surgery** (within 3-6 weeks after last dose)

**Primary endpoint:** ≤ 10% viable tumor (MPR)

**Overall ITT**

<table>
<thead>
<tr>
<th></th>
<th>Resected + not resected*</th>
<th>Total n = 44</th>
<th>N n = 23</th>
<th>NI n = 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPR + pCR</td>
<td>11 (25%)</td>
<td>4 (17%)</td>
<td>7 (33%)</td>
<td></td>
</tr>
<tr>
<td>0% viable tumor (pCR)</td>
<td>8 (18%)</td>
<td>2 (9%)</td>
<td>6 (29%)</td>
<td></td>
</tr>
<tr>
<td>1-10% viable tumor</td>
<td>3 (7%)</td>
<td>2 (9%)</td>
<td>1 (5%)</td>
<td></td>
</tr>
</tbody>
</table>

Pre-specified trial efficacy boundary: ≥ 6 MPRs

Cascone, ASCO 2019
Neoadjuvant atezolizumab in resectable NSCLC (NSCLC): Interim analysis and biomarker data from a multicenter study (LCMC3)
NEO-adjuvant chemo-immunotherapy for the treatment of STAGE IIIA resectable NSCLC: A phase II multicenter exploratory study—Final data of patients who underwent surgical assessment

Clinical response after Neoadjuvant treatment (ITT)

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (CR)</td>
<td>3 (6.5%)</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>33 (72%)</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>8 (17.5%)</td>
</tr>
</tbody>
</table>

Table 2. Radiological response (n=46).

Pathological response after Neoadjuvant treatment

<table>
<thead>
<tr>
<th>Response Type</th>
<th>N (%)</th>
<th>95% IC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major pathological resp. (MPR)</td>
<td>35 (85.36%)</td>
<td>71-95%</td>
</tr>
<tr>
<td>Complete pathological resp.</td>
<td>25 (71.4%)</td>
<td>54-87%</td>
</tr>
<tr>
<td>Partial response</td>
<td>6 (14.6%)</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 3. Pathological response (n=41). MPR was defined as <10% and include CPR.
Pathological response after neoadjuvant chemotherapy in resectable NSCLC: proposal for the use of major pathological response as a surrogate endpoint

Panel 2: Proposals

- Major pathological response, defined as less than 10% residual tumour after neoadjuvant therapy, should be adopted as an outcome measurement in non-small-cell lung cancers.
- Methods for assessment of the degree of pathological response should adhere to those described by Pataer and colleagues.
- Future neoadjuvant clinical trials integrating prospective assessment of pathological response should be prioritised for resectable NSCLCs.
- Major pathological response could ultimately be an acceptable endpoint for accelerated regulatory approval, but trials should still be designed to investigate overall survival to validate the initial findings and comprehensively assess the toxic effects.
## Chemo-radiotherapy

Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced NSCLC:

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. Deaths / No. Entered</th>
<th>O-E</th>
<th>Variance</th>
<th>Hazard Ratio</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 8831</td>
<td>45/46/39/45</td>
<td>2.4</td>
<td>20.9</td>
<td></td>
<td>1.12 (0.73 to 1.72)</td>
</tr>
<tr>
<td>WJLGC</td>
<td>131/156/142/158</td>
<td>-16.8</td>
<td>67.3</td>
<td></td>
<td>0.78 (0.61 to 0.99)</td>
</tr>
<tr>
<td>RTOG 9410</td>
<td>180/204/189/203</td>
<td>-20.5</td>
<td>91.1</td>
<td></td>
<td>0.80 (0.65 to 0.98)</td>
</tr>
<tr>
<td>GMMA Ankara 95</td>
<td>15/15/15/15</td>
<td>-1.0</td>
<td>7.0</td>
<td></td>
<td>0.87 (0.41 to 1.82)</td>
</tr>
<tr>
<td>GLOT-GFPC NPC</td>
<td>87/102/96/103</td>
<td>-9.9</td>
<td>45.0</td>
<td></td>
<td>0.80 (0.60 to 1.07)</td>
</tr>
<tr>
<td>EORTC 08972</td>
<td>63/60/66/78</td>
<td>-0.5</td>
<td>31.9</td>
<td></td>
<td>0.98 (0.69 to 1.39)</td>
</tr>
<tr>
<td>Total</td>
<td>521/603/547/602</td>
<td>-46.4</td>
<td>263.1</td>
<td></td>
<td>0.84 (0.74 to 0.95)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 3.24, P = .08, I^2 = 0\%$

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Auprin, JCO 2010
Chemo-radiotherapy: No evidence for advantage with induction or consolidation chemotherapy in stage III

Carboplatin-paclitaxel induction followed by chemo-radiotherapy

Concurrent PE chemo-radiotherapy followed by docetaxel consolidation

Vokes, JCO 2007

Hanna, JCO 2008
Randomized phase III comparison of standard-dose versus high-dose chemo-radiotherapy ± cetuximab for stage III NSCLC

One-sided log-rank p=0.0042
Median PFS 11 months
One-sided log-rank, p=0.2938

*Carboplatin and paclitaxel
OS results of the phase III PROCLAIM trial: Pemetrexed, cisplatin or etoposide, cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced NSCLC

Survival probability

Time from randomisation (months)

1.0
0.8
0.6
0.4
0.2
0

Survival probability

Time from randomisation (months)

2-yr OS
3-yr OS

Pem-CIS
Eto-Cis

Etoposide + cisplatin: 25.0 (22.2, 29.8)
Pemetrexed + cisplatin: 26.8 (20.4, 30.9)

Median PFS 10 and 11 months
PACIFIC: Consolidation durvalumab for 1 year after chemo-radiotherapy of stage III NSCLC

- Phase 3, randomized, double-blind, placebo-controlled, multicenter, global study (28 countries)\(^1\)\(^-\)\(^3\)

\[\text{Patients with locally advanced unresectable NSCLC (Stage III) in a consolidation setting (N=702)}\]

Absence of progression following at least 2 cycles of platinum-based chemotherapy concomitant with radiation therapy

- **Primary endpoints**\(^3\)
  - PFS, OS

- **Secondary endpoints**\(^1\)
  - ORR, DoR, DSR
  - Safety/tolerability
  - PK, immunogenicity, QoL

\[\text{Arm 1 (n=468): Durvalumab i.v. 10 mg/kg q2w for up to 12 months} \]

\[\text{Arm 2 (n=234): Placebo i.v. q2w} \]

713 pts with stage III NSCLC after chemo-radiotherapy

2:1 durvalumab 10 mg/kg Q2w for 12 months or placebo

\(27|\text{Paz-Ares, ESMO 2017; Antonia, NEJM 2017}\)
PACIFIC: Consolidation durvalumab for 1 year after chemo-radiotherapy of stage III NSCLC: Progression-free survival

Median PFS from start of therapy @ 20 months

Paz-Ares, ESMO 2017; Antonia, NEJM 2017
Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC

<table>
<thead>
<tr>
<th>Durvalumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Events/ Total No. of Patients</td>
<td>183/476</td>
</tr>
<tr>
<td>Median Overall Survival (95% CI)</td>
<td>NR (34.7–NR)</td>
</tr>
<tr>
<td>12-Mo Overall Survival Rate (95% CI)</td>
<td>83.1 (79.4–86.2)</td>
</tr>
<tr>
<td>24-Mo Overall Survival Rate (95% CI)</td>
<td>66.3 (61.7–70.4)</td>
</tr>
</tbody>
</table>

Stratified hazard ratio for death, 0.68 (99.73% CI, 0.47–0.997)
Two-sided P=0.0025

Antonia, NEJM 2018
Exploratory analyses of overall survival in PACIFIC

**OS by PD-L1 TC ≥1%**

<table>
<thead>
<tr>
<th></th>
<th>No. events / No. patients (%)</th>
<th>Median OS (95% CI), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durvalumab, ≥1%</td>
<td>70/212 (33.0)</td>
<td>NR (NR, NR)</td>
</tr>
<tr>
<td>Placebo, ≥1%</td>
<td>45/91 (49.5)</td>
<td>29.1 (17.7 NR)</td>
</tr>
</tbody>
</table>

≥1% OS HR 0.53 (95% CI, 0.36, 0.77)

**OS by PD-L1 TC <1%**

<table>
<thead>
<tr>
<th></th>
<th>No. events / No. patients (%)</th>
<th>Median OS (95% CI), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durvalumab, &lt;1%</td>
<td>41/80 (45.6)</td>
<td>NR (20.8, NR)</td>
</tr>
<tr>
<td>Placebo, &lt;1%</td>
<td>19/68 (32.8)</td>
<td>NR (27.3, NR)</td>
</tr>
</tbody>
</table>

<1% OS HR 1.36 (95% CI, 0.79, 2.34)

Faivre-Finn, ESMO 2018
Exploratory analyses of overall survival in PACIFIC

<table>
<thead>
<tr>
<th></th>
<th>PFS (BICR)</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>No. of events / No. of patients (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Durvalumab</td>
</tr>
<tr>
<td>ITT¹,²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from last radiotherapy to randomisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;14 days</td>
<td></td>
<td>214/476 (45.0)</td>
</tr>
<tr>
<td>≥14 days</td>
<td></td>
<td>164/356 (46.1)</td>
</tr>
</tbody>
</table>

Faivre-Finn, ESMO 2018
NICOLAS – A phase II trial evaluating the safety and efficacy of the addition of concurrent anti-PD-1 nivolumab to standard first-line chemotherapy and radiotherapy in locally advanced stage IIIA/B NSCLC (Amendment 2)

**Primary Endpoint:**
Grade ≥3 pneumonitis

**Key secondary endpoint:**
1-year PFS

**Sample Size:**
43 patients → extended to 78 patients under amendment 2

**Countries:**
Belgium, Germany, Netherland, Spain, Switzerland
Safety evaluation of nivolumab added concurrently to radiotherapy in a standard first line chemo-radiotherapy regimen in stage III non-small cell lung cancer—The ETOP NICOLAS trial

Pneumonitis in 34 (42.5%):
- Grade 1: 7
- Grade 2: 19
- Grade 3: 8
- No association with V20 lung dose
Summary on systemic treatment as part of multimodality therapy of earlier stages of NSCLC

- After curative resection, 4 cycles of adjuvant cisplatin-based chemotherapy remain as standard of care in stages II and III disease
- Immune checkpoint inhibition and targeted approaches remain investigational
- Major pathological responses have been observed using neoadjuvant immune checkpoint inhibition alone or in combination. However, MPR is not approved a surrogate endpoint for survival and we have to wait for survival data from randomized phase III trials to make a final judgment
- Durvalumab consolidation has become the standard of care after chemoradiotherapy of stage III disease. Ongoing trials are investigation the optimal timing of immunotherapy.