Lung cancer
Standard and beyond standard treatment
Topics

- Early stage non-small cell lung cancer
  - Adjuvant chemotherapy
- Metastatic non-small cell lung cancer
  - Palliative chemotherapy
  - Palliative care
Lung Cancer Facts:

• Non-small cell lung cancer (NSCLC) 70-80%
  – Most: Adenocarcinoma, Squamous carcinoma
  – Rare: large cell, large cell neuroendocrine carcinoma

• Small cell carcinoma 10-20%

• Risk factors: smoking is not the whole story
  – 10% “never smokers” (<100 cigarettes in a lifetime)

• Most cases incurable

• 40%: Stages I-IIIА potentially curable by surgery

• 60%: diagnosed at Stage IV
Suggested algorithm for locoregional lymph node staging

NSCLC

PET/CT-scan

- both CT and PET negative for mediastinal nodes and no central tumour or hilar N1 nodes
- CT or PET positive for mediastinal nodes or central tumour or hilar N1 nodes

- non-bulky mediastinal LN infiltration
  - EBUS/EUS
  - N0-N1
  - (2)
  - mediastinoscopy
    - N0-N1
    - N2-N3
  - upfront surgery

- bulky mediastinal LN infiltration
  - multimodality treatment

1 Category description according to CT (and PET) imaging as in ACCP staging document [Chest 143 Suppl 5:211S-250S, 2013], see text for more details.
2 A negative result of EBUS/EUS is usually confirmed by mediastinoscopy, as the latter has the highest negative predictive value.
PET has a complementary role to CT

- Detection of unexpected lymph node involvement or distant metastatic organ spread in 4-12% of stage I-III lung cancer.
- Determination of nature of some equivocal lesions on conventional CT imaging.
- Randomized trials demonstrated the utility of integrated PET-CT to significantly reduce futile thoracotomy rate or futile (chemo)radiotherapy rate.
Role of Adjuvant chemotherapy:
1995 Meta-Analysis Results

- 15% increase in the risk of death with alkylation agents
- 13% reduction in the risk of death with Platinum-based CT
- Absolute benefit for CT of 3% at 2 years and 5% at 5 years (HR: 0.87)

BMJ 311:899-909, 1995
### Post 1995 meta-analysis trials: results

<table>
<thead>
<tr>
<th>Study</th>
<th># Pts</th>
<th>Stage</th>
<th>CT</th>
<th>5YS gain</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALPI</td>
<td>1209</td>
<td>Ib-III</td>
<td>MVP</td>
<td>+1%</td>
<td>0.58</td>
</tr>
<tr>
<td>CALGB</td>
<td>344</td>
<td>Ib</td>
<td>CT</td>
<td>+2%</td>
<td>0.1</td>
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<tr>
<td>IALT</td>
<td>1868</td>
<td>Ib-III</td>
<td>PV/PE</td>
<td>+4%</td>
<td>0.03</td>
</tr>
<tr>
<td>NCIC</td>
<td>482</td>
<td>Ib-II</td>
<td>PV</td>
<td>+15%</td>
<td>0.02</td>
</tr>
<tr>
<td>ANITA</td>
<td>840</td>
<td>Ib-III</td>
<td>PV</td>
<td>+9%</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Lung Adjuvant Cisplatin Evaluation (LACE)

Overall survival by trial

- ALPI: 0.95 [0.81;1.12]
- ANITA: 0.82 [0.68;0.98]
- BLT: 1.00 [0.72;1.38]
- IALT: 0.91 [0.80;1.03]
- JBR10: 0.71 [0.54;0.94]
- Total: 0.89 [0.82;0.96]


5 trials, 4584 patients

(ALPI, BLT, IALT, JBR 10, ANITA)
3.9% survival advantage at 3 years

5.3% survival advantage at 5 years

HR = 0.8995 CI (0.82-0.96) P = 0.005

The benefit of adjuvant treatment in several other cancers in adults

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Stage</th>
<th>Reference</th>
<th>5-years (%)</th>
<th>10-years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>Early (Chemo)</td>
<td>EBCTCG, Lancet 1992</td>
<td>3.2</td>
<td>6.3</td>
</tr>
<tr>
<td>Breast</td>
<td>Early (Tamoxifen)</td>
<td>EBCTCG, Lancet 1992</td>
<td>3.6</td>
<td>6.2</td>
</tr>
<tr>
<td>Ovarian</td>
<td>Early (Platinum)</td>
<td>Trimbos JB, JNCI 2003</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>Colorectal</td>
<td>Dukes B,C (5-FU + LV)</td>
<td>IMPACT, Lancet 1995</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Lung</td>
<td>Stage I-IIIA</td>
<td>Pignon JP, et al. JCO 2008</td>
<td>5</td>
<td>-</td>
</tr>
</tbody>
</table>
LACE Analysis by Stage

Adjuvant chemo has greatest benefit for stage II and III and is detrimental for stage IA patients.
### Stage IB T Size Analysis

<table>
<thead>
<tr>
<th></th>
<th>T 3 - 4 cm</th>
<th></th>
<th>T ≥ 4 cm</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR OS</td>
<td>p</td>
<td>HR OS</td>
<td>p</td>
</tr>
<tr>
<td>CALGB 9633</td>
<td>1.02</td>
<td>0.51</td>
<td>0.66</td>
<td>0.04</td>
</tr>
<tr>
<td>JBR.10</td>
<td>1.73</td>
<td>0.07</td>
<td>0.66</td>
<td>0.13</td>
</tr>
<tr>
<td>No Chemo Benefit</td>
<td></td>
<td></td>
<td>Potential Chemo Benefit</td>
<td></td>
</tr>
</tbody>
</table>

#### Figures:

**C**

CALGB Stage IB and Tumor Diameter ≥ 4 cm

- Chemotherapy (N = 99)
- Control (N = 97)

**B**

JBR.10 Stage IB and Tumor Diameter ≥ 4 cm

- Observation
- Chemotherapy

---

*7th edition of TNM staging*

*Tumors > 5 - 7 cm are Stage IIA*

*Tumors > 7 cm are Stage IIB*
Long Term Adjuvant Benefit

- IALT -yes at 5 yrs, no at 8 yrs
- ANITA -yes at 6.3 years
- JBR.10 yes at 5 yrs, YES at > 9 yrs
- All show benefit in stage II+
- Stage IB benefit? Overall NO:
  - Yes if >4cm in CALGB 9633
  - Probably if >4cm in JBR.10
IALT: DFS at 8 years

Le Chevalier, ASCO 2008
IALT: OS at 8 years

Chemotherapy: 578 deaths
- 495 deaths before 5 years
- 83 deaths after 5 years

Control: 590 deaths
- 534 deaths before 5 years
- 56 deaths after 5 years

HR = 0.91 [0.81-1.02]
p = 0.10

Le Chevalier, ASCO 2008
Cause of death

Non-lung cancer mortality

HR: 1.34
p=0.06

Local recurrence rate

p=0.002

Distant metastases rate

p=0.02

Second malignancies

p=0.54

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Non-Cancer Related Mortality with Adjuvant Chemotherapy

Conclusion

• Cisplatin-based adjuvant chemotherapy improves the cure rate for patients with Stage II-IIIA NSCLC with a PS of 0-1.

• No role for adjuvant chemotherapy in patients with a tumor size <3 cm (Stage IA).

• Controversial role for adjuvant chemotherapy in patients with a tumor size of >4 cm with subset analyses suggesting a benefit.

• Non-cancer mortality may be increased in patients receiving chemotherapy.
**N2-N3**

**Diagram: Treatment Algorithm for Locoregional Non-Small-Cell Lung Cancer**

- **Imaging:**
  - CT-Scan

- **Invasive LN Result:**
  - Not required if negative LNs on PET

- **Category of N2:**
  - Surgery: unforeseen N2

- **Therapeutic Approach:**
  - Adjuvant chemotherapy (radiotherapy)

- **N2LN Result:**
  - N1-N2
  - N0-N1

- **Dedicated Multidisciplinary Assessment:**
  - Potentially resectable N2

- **Non-Surgical Multimodality Treatment:**
  - Surgical multimodality treatment

- **Not Required:**
  - Unresectable N2

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*Figure 2. Suggested algorithm for treatment in patients with locoregional non-small-cell lung cancer, based on imaging, invasive lymph node staging tests and multidisciplinary assessment.*

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1 Category description according to CT imaging as in ACCP staging document [Chest 143 Suppl 5:211S-250S, 2013], see text for more details.

2 See text for factors involved in the choice between non-surgical and surgical multimodality treatment.
Advanced NSCLC

NCCN Guidelines Version 1.2015
Non-Small Cell Lung Cancer

SYSTEMIC THERAPY FOR METASTATIC DISEASE

HISTOLOGIC SUBTYPE

TESTING RESULTS

- Adenocarcinoma
- Large Cell
- NSCLC not otherwise specified (NOS)

- Squamous cell carcinoma

- EGFR mutation testing\(^3\) (category 1)\(^3\)
- ALK testing (category 1)\(^3\)
- EGFR and ALK testing should be conducted as part of multiplex/nest generation sequencing\(^{hh}\)

- Consider EGFR mutation and ALK testing\(^3\) especially in never smokers or small biopsy specimens, or mixed histology\(^{b}\)
- EGFR and ALK testing should be conducted as part of multiplex/nest generation sequencing\(^{hh}\)

- Sensitizing EGFR mutation positive
- ALK positive
- Both sensitizing EGFR mutation and ALK are negative or unknown\(^{kk}\)

- Sensitizing EGFR mutation positive
- ALK positive
- Both sensitizing EGFR mutation and ALK are negative or unknown\(^{kk}\)

- See First-Line Therapy (NSCL-17)
- See First-Line Therapy (NSCL-18)
- See First-Line Therapy (NSCL-19)
- See First-Line Therapy (NSCL-17)
- See First-Line Therapy (NSCL-16)
- See First-Line Therapy (NSCL-20)

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\(^{a}\)See Principles of Pathologic Review (NSCL-A).
\(^{c}\)The NCCN NSCLC Guidelines Panel strongly endorses broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. See Emerging Targeted Agents for Patients With Genetic Alterations (NSCL-H).
\(^{d}\)In patients with squamous cell carcinoma, the observed incidence of EGFR mutations is 2.7% with a confidence that the true incidence of mutations is less than 3.6%. This frequency of EGFR mutations does not justify routine testing of all tumor specimens. Forbes SA, Bharama G, Bamford S, et al. The catalogue of somatic mutations in cancer (COSMIS). Curr Protoc Hum Genet 2008:chapter 10:unit 10.11.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Adenocarcinoma and Squamous Cell Carcinoma are Different

- Smoking association
- Metastasis potential
- Genetic alterations EGFR:
  Adeno 40-50%
  Sq CC < 5%, others
- Pharmacogenomics
- Different Tx outcome

(Lin PY, et al. Lung Cancer 2009)
Lung Cancer Mutation Consortium
Analysis of Lung Adenocarcinomas

Driver mutations found in 60% (252/422) of tumours completely tested

Impact of Molecularly Targeted Therapy in Patients with Oncogenic Driver Mutation

![Graph showing survival probability over years with different treatment groups: No targeted therapy, Targeted therapy, No driver. Log-rank P < .001.](image)

*JAMA. 2014;311(19):1998-2006*
"Oncogene-addicted" vs. "non-addicted"

NSCLC

"Oncogene-addicted" NSCLC:
- Fulfill preclinical criteria of oncogene addiction
- Long-term responses in the clinical trials
- Targeted therapies preferably used in the first-line setting
- Monotherapy more common than combination therapies w/cytotoxics

"Non-oncogene addicted" NSCLC:
- No proof of single abnormality driving tumor proliferation
- Targeted therapies much less effective, usually targeting mechanisms of progression, used in the second/third-line setting and in combination w/cytotoxics
“Oncogene-addicted” NSCLC

Type of molecular alteration

Driver mutations:
- EGFR
- HER2
- KRAS
- NRAS
- BRAF
- MEK1
- DDR2 (?)
- PIK3CA (?)

Genomic rearrangements:
- ALK
- ROS1
- RET
- NTRK1
- MYB-NFIB
- CRTC1-MAML2

Amplifications and high copy numbers:
- MET
- EGFR (?)
- FGFR1 (?)
- MYC (?)

cAMP, cyclic adenosine monophosphate; CRTC1, cAMP response element binding protein-regulated transcription coactivator 1; DDR2, discoidin domain-containing receptor 2; FGFR1, fibroblast growth factor receptor 1; NFIB, nuclear factor 1 B-type; MAML2, mastermind-like protein 2.
“Oncogene-addicted” NSCLC

Role of molecular target

Growth factor receptors:
- EGFR
- HER2
- ALK
- ROS1
- NTRK1
- RET
- MET
- FGFR1
- DDR2

Cytoplasmic proteins:
- KRAS
- BRAF
- PIK3CA
- MEK1

Transcription factors:
- MYB-NFIB
- CRTC1-MAML2
Systemic treatment of Non-oncogene addicted NSCLC

- When to started
- Cisplatin or carboplatin
- A best doublet
- How many cycles
- For elderly patients
- For PS2
- 2\textsuperscript{nd}/3\textsuperscript{rd} line chemotherapy
- Palliative care
Meta-analysis Chemo. VS BSC Overall survival

N=2714
16 trials
9 with platin.
1 yr absolute benefit : 9%
(20% to 29%).

HR=0.77 [0.71-0.83]
p=0.0001


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When to started
Retrospective analysis of the British Columbia Cancer Registry

Immediate CT ≤ 8 weeks

- Referred to a medical oncologist n= 694
  - Immediate chemo n= 319 (46%)
    - Received chemo n= 50 (30%)
      - Median Follow-up interval (FUI) = 22 days
    - Still on watch and wait n= 37 (22%)
      - FUI = 70 days
        - Patient choice (n=20)
        - No progression (n=13)
        - Asymptomatic (n=3)
        - Patient Moved (n=1)
  - Watch and wait n= 166 (24%)
  - Best supportive care n= 209 (30%)
    - Missed opportunity for chemo n= 72 (43%)
      - FUI = 25 days
        - Declining ECOG (n=36)
        - Patient died (n=35)
        - Asymptomatic (n=1)
        - Comorbid Illness (n=1)
    - Lost to follow-up n= 7 (4%)
Overall Survival of Upfront CT versus WW Populations

<table>
<thead>
<tr>
<th>CPH Model Covariates:</th>
<th>Hazard Ratio for death (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.00</td>
<td>0.16</td>
</tr>
<tr>
<td>Female</td>
<td>0.86 (0.70-1.06)</td>
<td>0.16</td>
</tr>
<tr>
<td>Age</td>
<td>0.99 (0.98-1.00)</td>
<td>0.24</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>1.00</td>
<td>0.002</td>
</tr>
<tr>
<td>2-4</td>
<td>1.40 (1.13-1.74)</td>
<td>0.002</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upfront CT</td>
<td>1.00</td>
<td>0.93</td>
</tr>
<tr>
<td>WW-chemo</td>
<td>1.02 (0.74-1.40)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>WW-missed</td>
<td>2.23 (1.69-2.94)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Log-rank p-value < 0.0001
Recommendation:
The administration of first-line chemotherapy should be offered at diagnosis to asymptomatic patients with metastatic NSCLC. (B, III)
Cisplatin or carboplatin
**CISCA**

**Response**
CIS 30%
CARBO 24%
OR = 1.37
IC 95% = 1.16-1.61
P < .001

**Survival**
HR = 1.07
IC 95% = 0.99 to 1.15
P = .100
A best doublet
# Platinum-based Doublets for NSCLC

**SWOG**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>RO</th>
<th>MS (m)</th>
<th>S 1 an</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatine + Vinorelbine</td>
<td>207</td>
<td>27%</td>
<td>8</td>
<td>33%</td>
</tr>
<tr>
<td>Paclitaxel + Carboplatine</td>
<td>201</td>
<td>27%</td>
<td>8</td>
<td>36%</td>
</tr>
</tbody>
</table>

**ECOG**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>RO</th>
<th>MS (m)</th>
<th>S 1 an</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel + Carboplatine</td>
<td>299</td>
<td>15%</td>
<td>8</td>
<td>34%</td>
</tr>
<tr>
<td>Gemcitabine + Cisplatine</td>
<td>301</td>
<td>21%</td>
<td>8</td>
<td>36%</td>
</tr>
<tr>
<td>Paclitaxel + Cisplatine</td>
<td>303</td>
<td>21%</td>
<td>8</td>
<td>31%</td>
</tr>
<tr>
<td>Docetaxel + Cisplatine</td>
<td>304</td>
<td>17%</td>
<td>7.5</td>
<td>31%</td>
</tr>
</tbody>
</table>
Platinum-based Doublets for NSCLC
<table>
<thead>
<tr>
<th>Classification</th>
<th>Characteristics</th>
</tr>
</thead>
</table>
| **Adenocarcinoma (AC) 30–50%** | • Malignant epithelial tumors with glandular differentiation  
  • IASLC classification of invasive AC:  
    • Lepidic, acinar, papillary, micropapillary, or solid pattern predominant  
    • Variants: invasive mucinous AC, colloid, fetal, and enteric |
| **Large cell carcinoma 10%** | • Involves large cells (subtypes are giant cell, clear cell) with large nuclei  
  • No evidence of squamous or glandular differentiation |
| **Squamous cell carcinoma 30%** | • Involves cells of the squamous epithelium  
  • Two variants of clinicopathologic significance  
    • Papillary variant  
    • Basaloid variant |
Pemetrexed vs gemcitabine (+CDDP)

- Pemetrexed: 500 mg/m²
- Cisplatin: 75 mg/m²

- Adenocarcinoma + LCC → pemetrexed better
- SCC → Gemcitabine better

Survival Probability

Median; 95% CI
- CP: 11.8; 10.4, 13.2
- CG: 10.4; 9.6, 11.2
- CP vs CG: Adjusted HR; 95% CI
  0.81; 0.70, 0.94
A best doublet

Recommendation:
There is no single platinum-based doublet standard chemotherapy. Pemetrexed-based doublets are restricted to non-squamous NSCLC. (A, I)
How many cycles
First line registration trials

- TAX 326, 2003
- ECOG, 2006
- Scagliotti, 2008
- AVAiL, 2009

Median number of cycles of therapy

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PFS: 4 vs 6 cycles of cisplatin-based CT

<table>
<thead>
<tr>
<th></th>
<th>MST (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-cycle</td>
<td>6.2 (5.7-6.7)</td>
</tr>
<tr>
<td>4-cycle</td>
<td>4.6 (4.4-4.8)</td>
</tr>
</tbody>
</table>

\[
P = .001 \\
HR = 0.63 \\
(95\% CI, 0.50 to 0.80)
\]

Non progressive Patients after 2 cycles

Docetaxel; TAX 326
Bevacizumab; ECOG, AVAIL
Pemetrexed; Scagliotti
### Overall survival

<table>
<thead>
<tr>
<th>Study (Year published)</th>
<th>Extended duration</th>
<th>Standard duration</th>
<th>Hazard ratio (fixed) 95% CI</th>
<th>Weight %</th>
<th>Hazard ratio (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zarogoulidis (1995)</td>
<td>36</td>
<td>38</td>
<td>0.71 (0.45 to 1.12)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Buccheri (1989)</td>
<td>38</td>
<td>36</td>
<td>0.73 (0.46 to 1.17)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Barata (2007)</td>
<td>110</td>
<td>110</td>
<td>0.77 (0.59 to 1.01)</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Ciuleanu (2008)</td>
<td>441</td>
<td>222</td>
<td>0.79 (0.63 to 1.01)</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Fidias (2007)</td>
<td>153</td>
<td>154</td>
<td>0.84 (0.65 to 1.08)</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Brodowicz (2006)</td>
<td>138</td>
<td>68</td>
<td>0.84 (0.52 to 1.38)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Smith (2001)</td>
<td>153</td>
<td>155</td>
<td>0.88 (0.72 to 1.07)</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Socinski (2002)</td>
<td>116</td>
<td>114</td>
<td>0.96 (0.82 to 1.12)</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Belani (2003)</td>
<td>65</td>
<td>65</td>
<td>1.02 (0.66 to 1.57)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>von Plessen (2006)</td>
<td>147</td>
<td>150</td>
<td>1.04 (0.82 to 1.32)</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Westeel (2005)</td>
<td>91</td>
<td>90</td>
<td>1.08 (0.79 to 1.48)</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Park (2007)</td>
<td>158</td>
<td>156</td>
<td>1.11 (0.82 to 1.48)</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Tournai (1990)</td>
<td>12</td>
<td>11</td>
<td>1.26 (0.85 to 1.86)</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>1,658</td>
<td>1,369</td>
<td>0.92 (0.85 to 0.99)</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 12.68$, df = 12 ($P = .39$), $I^2 = 5\%$

Test for overall effect: $z = 2.18$, $P = .03$

**PFS; HR = 0.75; 95% CI, 0.69 to 0.81; $P = 0.00001$**

**OS; HR = 0.92; 95% CI, 0.86 to 0.99; $P = 0.03$.**

**OS 3r generation vs old; (HR=0.70 interaction v 0.92 interaction; $P = 0.003$).**
How many cycles

Recommendation:
- 4 cycles of chemotherapy is standard. (A, I)
- Continuation of a doublet regimen beyond 4 cycles may be considered in selected, non-progressing pts (C, I)
For elderly patients
# Chemotherapy in Elderly Patients with Advanced NSCLC

<table>
<thead>
<tr>
<th>Author</th>
<th>Regimen</th>
<th>N</th>
<th>Response</th>
<th>MS (mo)</th>
<th>1 YR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gridelli*</td>
<td>Vinorelbine</td>
<td>78</td>
<td>20%</td>
<td>6.5</td>
<td>32%*</td>
</tr>
<tr>
<td></td>
<td>BSC</td>
<td>76</td>
<td>--</td>
<td>4.9</td>
<td>14%</td>
</tr>
<tr>
<td>Frasci‡</td>
<td>Gemcitabine + Vinorelbine</td>
<td>76</td>
<td>22%</td>
<td>7</td>
<td>30%*</td>
</tr>
<tr>
<td></td>
<td>Vinorelbine</td>
<td>76</td>
<td>15%</td>
<td>4.5</td>
<td>13%</td>
</tr>
<tr>
<td>Gridelliφ</td>
<td>Vinorelbine</td>
<td>233</td>
<td>18.4%</td>
<td>8.8</td>
<td>41%</td>
</tr>
<tr>
<td></td>
<td>Gemcitabine</td>
<td>233</td>
<td>17.3%</td>
<td>6.6</td>
<td>26%</td>
</tr>
<tr>
<td></td>
<td>Gemcitabine + Vinorelbine</td>
<td>237</td>
<td>20%</td>
<td>7.6</td>
<td>31%</td>
</tr>
</tbody>
</table>

‡Frasci et al, Proc ASCO 2000, 19:A1895

*p < 0.05
Weekly paclitaxel combined with monthly carboplatin versus single agent therapy in patients aged 70 to 89: IFCT-0501

- NSCLC
- Stage III-IV
- Age 70-89 years
- PS 0-2
- n = 451

Randomization:
- Vinorelbine or Gemcitabine*
- Carboplatin + paclitaxel
- Erlotinib 150 mg/d

Phase III study
Stratification by centre, PS 0-1 vs. 2, age ≤80 vs. >80 and stage III vs. IV
Weekly paclitaxel combined with monthly carboplatin versus single agent therapy in patients aged 70 to 89: IFCT-0501

- MST = 10.3 months (95% CI 8.3-12.6)
- MST = 6.2 months (95% CI 5.3-7.3)

HR = 0.64 (0.52-0.78); p = 0.00004

Phase III study
Stratification by centre, PS 0-1 vs. 2, age ≤80 vs. >80 and stage III vs. IV
<table>
<thead>
<tr>
<th>Group</th>
<th>HR (95% CI)</th>
<th>p value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n=451)</td>
<td>0.64 (0.52–0.78)</td>
<td></td>
</tr>
<tr>
<td>PS 0–1 (n=327)</td>
<td>0.63 (0.49–0.81)</td>
<td>0.557</td>
</tr>
<tr>
<td>PS 2 (n=123)*</td>
<td>0.63 (0.43–0.91)</td>
<td></td>
</tr>
<tr>
<td>Age ≤80 years (n=337)</td>
<td>0.68 (0.53–0.86)</td>
<td>0.299</td>
</tr>
<tr>
<td>Age &gt;80 years (n=114)</td>
<td>0.53 (0.36–0.80)</td>
<td></td>
</tr>
</tbody>
</table>
For elderly patients

Recommendation:
- Platinum-based chemotherapy is preferred in fit elderly patients with PS 0–1 and adequate organ function.
- Single-agent third-generation drugs are preferred in unfit elderly patients. (B, I)
For PS2
Meta-analysis Chemo. vs BSC Overall Survival

- N=2714
- 16 trials
- 9 with platin.
- 1 yr absolute benefit: 9% (20% to 29%).

P-values:

HR=0.77 [0.71-0.83]  
p=0.0001
### PS – Protocol Analysis

<table>
<thead>
<tr>
<th></th>
<th>SC + CT</th>
<th>SC alone</th>
<th>Hazard Ratio (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>946/1034</td>
<td>904/969</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>298/310</td>
<td>279/284</td>
<td>Interaction p=0.536</td>
</tr>
</tbody>
</table>

### PS – Exploratory Analysis

<table>
<thead>
<tr>
<th></th>
<th>SC + CT</th>
<th>SC alone</th>
<th>Trend p=0.701</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (100-90%)</td>
<td>301/335</td>
<td>264/290</td>
<td></td>
</tr>
<tr>
<td>1 (80-70%)</td>
<td>645/699</td>
<td>640/679</td>
<td></td>
</tr>
<tr>
<td>2+ (≤60%)</td>
<td>298/310</td>
<td>279/284</td>
<td></td>
</tr>
</tbody>
</table>
For PS2

**Recommendation:**
Platin-based combinations are preferred over single-agent chemotherapy.
(B, I)
2nd/3rd line chemotherapy
Survival probability

- **Docetaxel 75 mg/m² (n=55)**
- **BSC (n=49)**

**Median OS (months):**
- Docetaxel: 7.5
- BSC: 4.6

**1yr survival (%):**
- Docetaxel: 37
- BSC: 12

**Log rank: p=0.01**
docetaxel 75 mg/m² q3w
pemetrexed 500 mg/m² q3w
+ Vit.B12 and folates

ORR

SD

45.8

46.4

9.1

8.8

Median PFS = 2.9 mois
HR = 0.97 ; IC 95% = 0.82-1.16
Survival probability

No selection on EGFR!

Erlotinib (n=488)
Placebo (n=243)
**Recommendation:**

2\textsuperscript{nd} or 3\textsuperscript{rd}-line therapy should be offered to patients with PS 0–1 who present with signs of disease progression (radiological and/or clinical) after 1\textsuperscript{st}- or 2\textsuperscript{nd}-line therapy.

2\textsuperscript{nd}/3\textsuperscript{rd} line chemotherapy
Palliative care
Early Palliative Care for Patients with Metastatic Non-Small-Cell Lung Cancer

Jennifer S. Temel, M.D., Joseph A. Greer, Ph.D., Alona Muzikansky, M.A.,
Emily R. Gallagher, R.N., Sonal Admane, M.B., B.S., M.P.H.,
Vicki A. Jackson, M.D., M.P.H., Constance M. Dahlin, A.P.N.,
Craig D. Blinderman, M.D., Juliet Jacobsen, M.D., William F. Pirl, M.D., M.P.H.,
J. Andrew Billings, M.D., and Thomas J. Lynch, M.D.

ABSTRACT
150 patients with newly diagnosed metastatic NSCLC

Baseline Data Collection

Randomized

Early palliative care integrated with standard oncology care

Meet with palliative care within 3 weeks of signing consent and \textit{at least} monthly thereafter

Standard oncology care

Meet with palliative care only when \textit{requested} by patient, family or oncology clinician.

Temel, ASCO 2010, #7509
Study Rationale

Current Care Model

"curative" or "life-prolonging" treatment

symptom control and palliative care

At time of diagnosis

Death

Proposed Care Model

"curative" or "life-prolonging" treatment

symptom control and palliative care

At time of diagnosis

Death

Temel, ASCO 2010, #7509

www.iom.edu
Effect of Early PC on 12-week Psychological Distress

![Bar chart showing the comparison between Standard Care and Early Palliative Care for Depression, Major Depressive Disorder, and Anxiety with p-values of 0.01, 0.04, and 0.66 respectively.](chart)
Change in QOL from Baseline to 12 Weeks

FACT-Lung

Mean change Early Palliative Care = + 4.2
Mean change Standard Care = - 0.4
\( p = 0.09 \)

FACT- Lung TOI

Mean change Early Palliative Care = + 2.3
Mean change Standard Care = - 2.3
\( p = 0.04 \)
# Quality of EOL Care and Resource Utilization

**ASCO Quality Measures**

1. No hospice
2. Enrolled in hospice ≤ 3 days before death
3. Chemotherapy within 14 days of death (DOD)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Standard Care</th>
<th>Early Palliative Care</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggressive EOL Care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No hospice</td>
<td>30 (54)</td>
<td>16 (33)</td>
<td>0.05</td>
</tr>
<tr>
<td>Hospice ≤ 3 days</td>
<td>22 (39)</td>
<td>15 (31)</td>
<td></td>
</tr>
<tr>
<td>Chemo within 14 DOD</td>
<td>5 (15)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 (24)</td>
<td>7 (18)</td>
<td></td>
</tr>
<tr>
<td>Hospital/ER Admissions within 30 DOD</td>
<td>31 (55)</td>
<td>19 (39)</td>
<td>0.12</td>
</tr>
<tr>
<td>Days on hospice</td>
<td>4 (0-269)</td>
<td>11 (0-117)</td>
<td>0.09</td>
</tr>
<tr>
<td>Documented Resuscitation Preference</td>
<td>11 (28)</td>
<td>18 (53)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

105 deaths at time of data analysis with data on chemotherapy within 14 DOD available on 90 patients

---

Temel, ASCO 2010, #7509
Survival Analysis

Median Survival
- Early palliative care: 11.6 mo
- Standard care: 8.9 mo

Controlling for age, gender and PS, adjusted HR=0.59 (0.40-0.88), p=0.01

Temel, ASCO 2010, #7509
Dying of cancer, he says in video that goes viral...

RICHARD TEO

“Everyone knows they’re going to die, but nobody believes it. If we did, we would do things differently”

www.richardteo.com

‘Only when we learn how to die then we learn how to live’
- Dr Richard Teo
เราถูกสอนมาให้เป็นผู้ให้บริการสาธารณสุข เป็นมืออาชีพ แต่ทั้งหมดทั้งทั้งหมด เรายังไม่รู้อยู่ดีว่าคนใช้รู้สึกจริงๆ เช่นไร ผมไม่ได้ให้ขอให้พวกคุณเข้าอกเข้าใจคนใช้อายุลึกซึ้งอะไรมากมาย ผมไม่คิดว่านั้นจะทำให้เราเป็นมืออาชีพอรอก แต่จริงๆ แล้วเราได้พยายามที่จะเข้าใจความเจ็บปวดของพวกเขาหรือยัง? พวกเราส่วนใหญ่คงจะไม่ได้เป็นอย่างนั้น ไม่เป็นไร เพราะแค่เราย้ายตัวอยู่และที่ที่พักจะบอกพวกคุณคือ จงพยายามเอาใจเข้ามาใส่ใจเรา (put yourself in your patient’s shoes)
เมื่อผมเผชิญหน้ากับความตาย ผมได้ลอกคราบตัวเองออกทั่วหมด เหลือไว้เพียงสิ่งที่สำคัญที่สุดเท่านั้น ที่น่าจำกัดคือ เมื่อเราเรียนรู้ว่า เราจะตายอย่างไร นั่นแหละเรื่องจริงจะเรียนรู้ว่าเราจะมีชีวิตอย่างไร  ผมรู้ว่ามันออกจะเคร่งเครียดไปหน่อยสำหรับเซ้าวันนี้ แต่ นั่นคือความจริงครับ นี่คือสิ่งที่ผมได้ประสบมา