SESSION 3: ADVANCED NSCLC

1st-line Chemotherapy for Advanced disease

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Chief Medical Officer (CMO)
ESMO
Lugano CH
Chemotherapy for Advanced NSCLC. Improves survival

- Cisplatin-based
  HR 0.73 OS (+10% at 1 year)
- Long term Alkylation agent: HR 1.26 detrimental
- Trial heterogeneity p<.0001

11 Randomized Trials in Advanced NSCLC of Chemotherapy versus BSC
Meta-analyzed by the MRC and NSCLC Collaborative Group 1995

1970-1985: 11 trials, 1190 patients

DATA CONFIRMED IN 2004
BIG LUNG TRIAL

725 patients, stage III and IV, 54% Squamous, randomized to CT or BSC

**Table 2  Choice of chemotherapy regimen**

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>NoC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV</td>
<td>16 (4%)</td>
<td>18 (5%)</td>
</tr>
<tr>
<td>MIC</td>
<td>127 (35%)</td>
<td>121 (34%)</td>
</tr>
<tr>
<td>MVP</td>
<td>153 (42%)</td>
<td>151 (42%)</td>
</tr>
<tr>
<td>NP</td>
<td>68 (19%)</td>
<td>71 (20%)</td>
</tr>
</tbody>
</table>

C, chemotherapy; NoC, no chemotherapy. For details of chemotherapy regimens, see text.

- Survival Benefit: HR 0.77 p=0.0006
  mOS 8 vs 5.7m
- Benefit in all subgroups:
  - Age
  - Histology
  - PS
  - CT regimen
  - Gender
- No difference in QoL
- Cost effective

1ST-LINE CHEMOTHERAPY TRIALS
of Platinum-based Doublets with 3rd generation drugs

- ECOG 1594
  - Gem/cis v Pac-24/cis v Pac-3/carbo v Doc/cis
- SWOG 9509
  - Pac-3/carbo v Vin/cis
- TAX 326
  - Doc/carbo or Doc/cis v Vin/cis
- Italian Study
  - Gem/cis v Pac-3/carbo v Vin/cis
- JMDB
  - Gem/cis v pemetrexed/cis
- NO significant or meaningful differences
TRIALS OF THIRD GENERATION AGENTS

ECOG 1594

SWOG 9509

Italian Study

Vin/Cis  
Gem/Cis  
Pac/Cbp

Survival (%)
0  10  20  30  40  50  60  70  80  90  100

Time (months)
0  6  12  18  24  30  36  42  48  54  60

P = .044 by non-parametric covariate-adjusted log-rank test

Survival (%)
0  0.1  0.2  0.3  0.4  0.5  0.6  0.7  0.8  0.9  1.0

Survival Time in months (mos)
0  6  12  18  24  30  36  42  48  54  60

Cis/Paclitaxel  
Cis/Gemcitabine  
Cis/Docetaxel  
Carbo/Paclitaxel

ESMO
No useful biomarker has been identified to target a given chemotherapy drug.

All the trials performed with chemotherapy were done before the era of mutation and gene alteration identification.

Histology may be considered.
Until 2008-2010
  - Histology was not a matter in the choice for a chemotherapy regimen

Analysis of Pemetrexed-Cisplatin vs. Gemcitabine-Cisplatin (JMDB trial) showed differences in outcome
EFFECT OF HISTOLOGY ECOG 1594

Overall Survival: Squamous Cell Histology

Overall Survival: Non-squamous Cell Histology

Hoang et al Proc IASLC, San Francisco, 2009
SWOG POOLED ANALYSIS OF ANTI-MICRO-TUBULIN AGENTS in 4 randomized trials 1146 patients
JMDB: PEM/CIS VS GEM/CIS IN 1ST LINE NSCLC

ITT all histologies (1725 NSCLC)

cisplatin/pemetrexed; CG, cisplatin/gemcitabine

PEM/CIS VS GEM/CIS IN 1st LINE NSCLC OS ACCORDING TO HISTOLOGY (SQ VS. NSQ)

Nonsquamous=adenocarcinoma, large cell carcinoma, and other/indeterminate NSCLC histology

SURVIVAL HAZARD RATIOS (CISPLATIN/PEMETREXED VS. CISPLATIN/GEMCITABINE) in groups according to baseline characteristics.
Based on the JMDB trial:
- Pemetrexed is no longer recommended in Squamous
- Gemcitabine may be used in both Sq and NSq

Most frequent used regimen in 1st-line:
- Squamous: Gem-Cis
- Non-Squamous: Pem-Cis
- All other regimen showed no difference
  ✓ Including Paclitaxel-Carboplatin
POINTBREAK: STUDY DESIGN
NON-SQUAMOUS NSCLC 1ST LINE

- Randomized, open-label, phase III superiority study conducted in US
- Pemetrexed 500 mg/m2; Carboplatin AUC 6; Bevacizumab 15 mg/kg
- Paclitaxel 200 mg/m2; Carboplatin AUC 6; Bevacizumab 15 mg/kg

**Inclusion:**
- No prior systemic therapy for lung cancer
- PS 0/1
- Stage IIIB-IV NS-NSCLC
- Stable tx’r brain mets

**Exclusion:**
- Peripheral neuropathy ≥ Gr 1
- Uncontrolled pleural effusions

**Induction Phase**
q21d, 4 cycles

- Pemetrexed (folic acid & vitamin B₁₂) + Carboplatin + Bevacizumab
- Paclitaxel + Carboplatin + Bevacizumab

**Maintenance Phase**
q21d until PD

- Pemetrexed (folic acid & vitamin B₁₂) + Bevacizumab
- Bevacizumab

**Stratified for:**
PS (0 vs 1); sex (M vs F); disease stage (IIIB vs IV); measurable vs nonmeasurable disease
OS FROM RANDOM ASSIGNMENT FOR:
(A) the intent-to-treat (ITT) population
(B) the maintenance population

![Graph A: ITT Population]

![Graph B: Maintenance Population]
**CIS- OR CARBO-PLATIN?**

- Carboplatin:
  - Introduced in clinical trials in 1981
  - Easier to use
  - Different toxicity profile

- 2 meta-analysis have addressed the question.
CIS- VS. CARBO-PLATIN META-ANALYSIS
Hotta at al JCO 2004 22 3852

- 8 trials, 2948 pts, all trials until Dec. 2001
  - Done on published data
  - Including 2nd and 3rd generation drugs:
    ✓ Etoposide, Mitomycin, Vindesine, Vinblastine
    ✓ Paclitaxel, Gemcitabine, Docetaxel

- Advantage for Cisplatin on RR:
  - Odd Ratio: 1.36 (1.15-1.61) p<0.001 overall
  - Odd Ratio: 1.38 (1.14-1.67) p<0.001 for 3rd generation drugs
CIS- VS. CARBO-PLATIN META-ANALYSIS
Hotta at al JCO 2004 22 3852

Outcome according to Overall Survival:

**ALL ELIGIBLE TRIALS**

HR 1.05
0.907-1.216
P=0.515

**3rd GENERATION DRUGS**

HR 1.106
0.1005-1.218
P=0.039
CIS- VS. CARBO-PLATIN META-ANALYSIS
Ardizzoni A et al JNCI 2007 99 847

- 9 trials, 2968 pts,
  - Done on Individual Patients Data
  - Including 2nd and 3rd generation drugs:
    ✓ Etoposide, Mitomycin, Vindesine, Vinblastine
    ✓ Tirapazamine, Paclitaxel, Gemcitabine, Docetaxel

- Advantage for Cisplatin on RR: (30 vs. 24%)
  - Odd Ratio: 1.37 (1.16-1.61) p<0.001 overall
CIS- VS. CARBO-PLATIN META-ANALYSIS
Ardizzoni A et al JNCI 2007 99 847

Outcome according to Overall Survival:

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yrs.</td>
<td>2037</td>
</tr>
<tr>
<td>≥65 yrs.</td>
<td>930</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
</tr>
<tr>
<td>IIIIB</td>
<td>941</td>
</tr>
<tr>
<td>IV</td>
<td>2025</td>
</tr>
<tr>
<td><strong>PS</strong></td>
<td></td>
</tr>
<tr>
<td>0 - 1</td>
<td>2558</td>
</tr>
<tr>
<td>2</td>
<td>401</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>1139</td>
</tr>
<tr>
<td>Non-squamous</td>
<td>1821</td>
</tr>
<tr>
<td><strong>Drugs generation</strong></td>
<td></td>
</tr>
<tr>
<td>Second-</td>
<td>638</td>
</tr>
<tr>
<td>Third-</td>
<td>2330</td>
</tr>
</tbody>
</table>

- **OVERALL POPULATION**
  HR 1.07 (0.99-1.15)
  P=0.10

- **SQUAMOUS** HR 0.97
- **NON-SQUAMOUS** HR 1.12

- **3rd GENERATION DRUGS**
  HR 1.11 (1.01-1.21)

Favors carboplatin-based chemotherapy ←  Favors cisplatin-based chemotherapy
Outcome according to Overall Survival:

<table>
<thead>
<tr>
<th>Grade 3/4</th>
<th>OR Cis vs. Carbo (value &gt; 1 favor Cis)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets</td>
<td>2.27 (1.71-3.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>0.96</td>
<td>ns</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0.95</td>
<td>ns</td>
</tr>
<tr>
<td>Anemia</td>
<td>1.10</td>
<td>ns</td>
</tr>
<tr>
<td>Nausea/ Vomiting</td>
<td>0.42 (0.33-0.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal</td>
<td>0.37 (0.15-0.88)</td>
<td>=0.018</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>0.96 (0.75-1.23)</td>
<td>ns</td>
</tr>
</tbody>
</table>
1ST-LINE CHEMOTHERAPY IN NSCLC

Contribution of targeted agents:

- **Anti-angiogenic:**
  - Bevacizumab (Approved)

- **Anti-EGFR MoAbs**
  - Necitumumab (Approved EMA/CHMP 15/12/2015)
  - Cetuximab (not approved)
BEVACIZUMAB IN NSCLC: ECOG 4599 STUDY DESIGN

- Eligibility:
  - Non-squamous
  - Non hemoptysis
  - No CNS metastases
- Stratification variables
  - RT vs no RT
  - Stage IIIB or IV vs recurrent
  - WT loss <5% vs ≥5%
  - Measurable vs non-measurable

Randomized

Paclitaxel 200 mg/m²
Carboplatin AUC=6
q 3 weeks x 6 cycles

PC x 6 cycles +
Bevacizumab 15 mg/Kg
q 3 wks to PD

Sandler A, NEJM 2006
ECOG 4599:
Response Rate

- CP (n=392) - Overall response rate: 15%
- Avastin + CP (n=381) - Overall response rate: 35%

Statistical difference: 20% (p<0.001)
ECOG 4599:
OS and PFS

<table>
<thead>
<tr>
<th></th>
<th>6 Mo</th>
<th>12 Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC, %</td>
<td>43.7</td>
<td>16.9</td>
</tr>
<tr>
<td>PCB, %</td>
<td>51.9</td>
<td>22.1</td>
</tr>
<tr>
<td>HR 0.79 (0.65-0.93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>P</em> &lt; .003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medians: 10.2 vs. 12.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>6 Mo</th>
<th>12 Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC, %</td>
<td>6.2</td>
<td>4.5</td>
</tr>
<tr>
<td>PCB, %</td>
<td>16.9</td>
<td>22.1</td>
</tr>
<tr>
<td>HR 0.66 (0.57-0.77)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>P</em> &lt; .001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medians: 6.2 vs. 4.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Kaplan–Meier Estimates of Overall Survival (Panel A) and Progression-free Survival (Panel B).
BPC denotes paclitaxel and carboplatin plus bevacizumab, and PC paclitaxel and carboplatin alone.
ECOG 4599:
Effect of Age (58% patients < 65 y old)
Cut-of value > 70y

- Grade 3-5 CP vs CPB
  0.9 vs 6.2%, p=0.03
- Febrile neutropenia
  0.9 vs 6.2%, p=0.03
- Hypertension
  0.9 vs 6.2%, p=0.03
- Hemorrhage
  1.7 vs 7.9%, p=0.03
- Proteinuria
  0 vs 7.9%, p=0.002

Median age of lung cancer patients is >70

GEMCITABINE-CISPLATIN+/- BEVACIZUMAB IN NSCLC:

A Phase III Trial

Two-stage design
- Initially, 210 patients will be randomised to one of the three arms (1:1:1)
- following assessment, 1:1 randomisation continues to the CG-alone plus one CG + Avastin arm
- no crossover allowed

- Previously untreated, stage IIIb, IV or recurrent NSCLC (n=830)

- Cisplatin 80mg/m2 i.v. every 3 weeks; gemcitabine 1,250mg/m2 days 1 and 8 every 3 weeks
- Primary endpoint: PFS
- Secondary endpoints include OS and response rate

CG alone × 6

Bevacizumab 7.5mg/kg every 3 weeks + CG × 6

Bevacizumab 15mg/kg every 3 weeks + CG × 6

PD

PD
Primary Analysis (intent-to-treat) of Bevacizumab 7.5 mg/kg Versus Pooled Placebo

<table>
<thead>
<tr>
<th>Months</th>
<th>Placebo + CG (n=347)</th>
<th>Bev 7.5 + CG (n=345)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>0.75 (0.62-0.91)</td>
</tr>
<tr>
<td>6</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>0.0</td>
<td></td>
</tr>
</tbody>
</table>

Proportion Not Progressed

HR (95% CI) — 0.75 (0.62-0.91)

P value — .0026

6.7 vs. 6.1 m

Primary Analysis (intent-to-treat) of Bevacizumab 15 mg/kg Versus Pooled Placebo

<table>
<thead>
<tr>
<th>Months</th>
<th>Placebo + CG (n=347)</th>
<th>Bev 15 + CG (n=351)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>0.82 (0.68-0.98)</td>
</tr>
<tr>
<td>6</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>0.0</td>
<td></td>
</tr>
</tbody>
</table>

Proportion Not Progressed

HR [95% CI] — 0.82 (0.68-0.98)

P value — .0301

No. at Risk

<table>
<thead>
<tr>
<th>Placebo + CG</th>
<th>Bev 7.5 + CG</th>
<th>Placebo + CG</th>
<th>Bev 15 + CG</th>
</tr>
</thead>
<tbody>
<tr>
<td>347</td>
<td>345</td>
<td>347</td>
<td>351</td>
</tr>
<tr>
<td>228</td>
<td>251</td>
<td>228</td>
<td>238</td>
</tr>
<tr>
<td>122</td>
<td>150</td>
<td>122</td>
<td>148</td>
</tr>
<tr>
<td>36</td>
<td>52</td>
<td>36</td>
<td>46</td>
</tr>
<tr>
<td>12</td>
<td>18</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Reck M: J Clin Oncol 2009; 27: 1227-34
AVAiL: Overall Survival (2nd End-point)

![Graph showing overall survival probabilities over time for Placebo + CG, Bev 7.5mg/kg + CG, and Bev 15mg/kg + CG.]

<table>
<thead>
<tr>
<th></th>
<th>Placebo + CG</th>
<th>Bev 7.5mg/kg + CG</th>
<th>Bev 15mg/kg + CG</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI)</td>
<td>0.93 (0.78–1.11)</td>
<td>1.03 (0.86–1.23)</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.42</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>Median OS</td>
<td>13.1mo</td>
<td>13.6mo</td>
<td>13.4mo</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Placebo + CG</th>
<th>Bev 7.5mg/kg + CG</th>
<th>Bev 15mg/kg + CG</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo + CG</td>
<td>347</td>
<td>272</td>
<td>182</td>
</tr>
<tr>
<td>Bev 7.5mg/kg + CG</td>
<td>345</td>
<td>286</td>
<td>182</td>
</tr>
<tr>
<td>Bev 15mg/kg + CG</td>
<td>351</td>
<td>264</td>
<td>177</td>
</tr>
</tbody>
</table>

Reck M: J Clin Oncol 2009; 27: 1227-34
CONTRIBUTION OF BEVACIZUMAB IN 1ST-LINE NSCLC

- ECOG: a positive trial
  - On OS, PFS and RR
  - Patients highly selected (histo, CV risk factor, no proximal tumors)
  - No benefit over 65y
  - No benefit in women

- AVAIL:
  - Benefit on PFS at 7.5 mg/kg (6.7 vs.6.1m [+18d])
  - No benefit on OS
  - Patients highly selected
  - No age or gender effect

- Overall modest benefit, not constant

- Scored as 2 in the ESMO-MCBS (not worth it)
Forest plots of HR for (A) OS and (B) PFS from four randomised trials of bevacizumab (7.5 mg/kg or 15 mg/kg) added to standard chemotherapy in 1st-line NSCLC.

A  

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of 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>Dose 7.5 mg/kg</td>
<td>Bevacizumab: 18/32, Control: 17/32</td>
<td>0.8</td>
<td>6.6</td>
<td>1.13 [0.52; 2.42]</td>
<td></td>
</tr>
<tr>
<td>AVF-0757g 7.5</td>
<td>AVAIL 7.5</td>
<td></td>
<td></td>
<td>0.92 [0.75; 1.13]</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>251/377, 257/397</td>
<td>−6.8</td>
<td>97.0</td>
<td>0.93 [0.76; 1.14]</td>
<td></td>
</tr>
<tr>
<td>Dose 15 mg/kg</td>
<td>Bevacizumab: 16/34, Control: 17/32</td>
<td>1.0</td>
<td>6.2</td>
<td>1.18 [0.54; 2.59]</td>
<td></td>
</tr>
<tr>
<td>AVF-0757g 15</td>
<td>ECOG 4599: 335/434, 363/444</td>
<td>−38.5</td>
<td>172.5</td>
<td>0.80 [0.69; 0.93]</td>
<td></td>
</tr>
<tr>
<td>AVAIL 15</td>
<td>AVAIL 15</td>
<td>242/351, 240/347</td>
<td>−0.2</td>
<td>22.0</td>
<td>0.99 [0.65; 1.50]</td>
</tr>
<tr>
<td>JO19907</td>
<td>66/117, 33/58</td>
<td>−36.0</td>
<td>288.8</td>
<td>0.66 [0.42; 1.02]</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>659/936, 653/881</td>
<td>−36.0</td>
<td>288.8</td>
<td>0.80 [0.56; 1.11]</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>910/1313, 910/1260</td>
<td>−42.7</td>
<td>385.8</td>
<td>0.90 [0.81; 0.99]</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 4.78$, $P = 0.44$, $I^2 = 0%$
Test for interaction: $\chi^2 = 0.22$, $P = 0.64$

B  

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of events / No. entered</th>
<th>O-E</th>
<th>Variance</th>
<th>Hazard ratio</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose 7.5 mg/kg</td>
<td>Bevacizumab: 29/32, Control: 27/32</td>
<td>−2.4</td>
<td>8.9</td>
<td>0.76 [0.39; 1.47]</td>
<td></td>
</tr>
<tr>
<td>AVF-0757g 7.5</td>
<td>AVAIL 7.5</td>
<td>311/345, 324/347</td>
<td>−35.2</td>
<td>122.3</td>
<td>0.75 [0.63; 0.90]</td>
</tr>
<tr>
<td>Subtotal</td>
<td>340/377, 351/379</td>
<td>−37.6</td>
<td>131.1</td>
<td>0.75 [0.63; 0.89]</td>
<td></td>
</tr>
<tr>
<td>Dose 15 mg/kg</td>
<td>Bevacizumab: 29/34, 27/32</td>
<td>−5.5</td>
<td>8.5</td>
<td>0.52 [0.27; 1.02]</td>
<td></td>
</tr>
<tr>
<td>AVF-0757g 15</td>
<td>ECOG 4599: 341/434, 348/444</td>
<td>−70.2</td>
<td>167.8</td>
<td>0.66 [0.57; 0.77]</td>
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</tr>
<tr>
<td>AVAIL 15</td>
<td>AVAIL 15</td>
<td>324/351, 324/347</td>
<td>−18.9</td>
<td>116.3</td>
<td>0.65 [0.71; 1.02]</td>
</tr>
<tr>
<td>JO19907</td>
<td>94/117, 49/58</td>
<td>−17.8</td>
<td>29.8</td>
<td>0.55 [0.38; 0.79]</td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>768/936, 748/881</td>
<td>−112.5</td>
<td>322.5</td>
<td>0.71 [0.63; 0.79]</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1128/1313, 1099/1260</td>
<td>−150.1</td>
<td>435.6</td>
<td>0.72 [0.66; 0.79]</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 7.82$, $P = 0.17$, $I^2 = 36%$
Test for interaction: $\chi^2 = 0.36$, $P = 0.55$
ANTI-EGFR TRIALS

- BMS-099: taxane/carboplatin +/- cetuximab
- FLEX: vinorelbine/cisplatin +/- cetuximab in EGFR IHC +ve cases only
- SQUIRE: gemcitabine/cisplatin +/- necitumumab in Squamous cancer
OS SIGNIFICANCE?

BMS 099: TAXANE CARBO+/-Cetuximab
All histology, no EGFR expression required

FLEX: Vinorelbine Cisplatin+/-Cetuximab
All histology, EGFR IHC +

Lynch et al
J Clin Oncol 2010

Pirker et al
Lancet 2009
FLEX SURVIVAL:
high EGFR expression (H score > 200)
Squamous cell carcinoma (N=144)
Screening
Entry criteria:
Stage IV squamous NSCLC
ECOG PS 0-2

1

R

Gem-Cis + Neci q3w (N= 545)
Necitumumab (800 mg D1, D8)

Maximum of 6 cycles

PR
CR
SD

Neci q3w (800 mg D1, D8)

PD
PD

Gem-Cis q3w (N = 548)
Gemcitabine (1250 mg/m², D1, D8)
Cisplatin (75 mg/m², D1)

Randomization (R) stratified by: ECOG PS (0-1 vs. 2) and geographic region (North America, Europe and Australia; vs. South America, South Africa and India; vs. Eastern Asia)

- Patient selection not based on EGFR protein expression
- Radiographic tumour assessment (investigator read): at baseline and every 6 weeks until PD
- Mandatory tissue collection
- Primary End Point: OS

PRIMARY OUTCOME: OVERALL SURVIVAL (ITT)

HR (95%CI): 0.84 (0.74, 0.96); p=0.012

Median OS (95%CI), months:
Gem-Cis + Neci: 11.5 (10.4, 12.6)
Gem-Cis: 9.9 (8.9, 11.1)

Follow-up time (median): Gem-Cis + Neci: 25.2 months; Gem-Cis: 24.8 months

Scored as 1 in the ESMO MCBS (not worth it)

TREATMENT OF THE ELDERLY

- Single agent therapy
- Combination chemotherapy
TREATMENT OF THE ELDERLY

ELVIS

randomized trial
- Elderly 70 and older
- All histologies
- 1st line

- Administered
  Day 1 and 8
  Q 3 weeks

Vinorelbine 30mg/m2 (n=80)

vs

Best Supportive Care (n=81)

Primary end-point OS and QoL
ELVIS: STUDY DESIGN

Overall survival (%)

Log-rank test P = 0.03
Cox model P = 0.02

Vinorelbine
Supportive care

Weeks
0 13 26 39 52 65 78

No. Pts | 0R% | MST mos | 1-YS %
--- | --- | --- | ---
BSC | 78 | - | 4.9 | 14
VNB | 76 | 20 | 6.5 | 32
Phase III randomized trial

- Elderly 70 and older
- All histologies
- 1st line

- Administered
  Day 1 and 8
  Q 3 weeks

  → Vinorelbine 30mg/m2  (n=233)
  → Gemcitabine 1200mg/m2  (n=233)
  → Gem 1000mg/m2+Vino 25mg/m2  (n=232)

Primary end-point OS
MILES: Gemcitabine v Vinorelbine v Gem/Vin

Primary End-point not met: Vino vs Doublet HR 1.17
Gem vs doublet HR 1.06
More toxicity in the combination arm
IFCT-0501 ELDERLY TRIAL

Single agent vs Doublet

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

Random

Vinorelbine or Gemcitabine*
Carboplatin + paclitaxel

Erlotinib**
150 mg/d

Stratification by centre, PS 0-1 vs. 2, age ≤80 vs. >80 and stage III vs. IV

*Choice of the center at the beginning of the study
** In case of PD or excessive toxicity
IFCT-0501 ELDERLY TRIAL

Single agent vs Doublet in Elderly (70-89y)
All histologies

- Primary end-point OS

MST = 10.3 months (95% CI 8.3-13.3)
1-year survival 45.1% (95% CI 38.2-51.8)

MST = 6.2 months (95% CI 5.3-7.4)
1-year survival 26.9% (95% CI 21-33.1)

p= 0.00004

Quoix et al. Lancet 378, 1079, 2011
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.,

Figure 3. Kaplan–Meier Estimates of Survival According to Study Group.

Figure 2. Twelve-Week Outcomes of Assessments of Mood.
Reco 1: the administration of first-line chemotherapy should be offered at diagnosis to asymptomatic patients with metastatic NSCLC.

Strength of recommendation: B   Level of evidence: II

Reco 2: cisplatin should be used in fit patients with performance status (PS) 0–1 who have adequate organ function.

Strength of recommendation: B   Level of evidence: I

Reco 3: cisplatin at 75 mg/m2 q3wks should be used with third-generation drugs.

Strength of recommendation: B   Level of evidence: V

Reco 11: 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.

Strength of recommendation: B   Level of evidence: I
Reco 4: there is no single platinum-based doublet standard chemotherapy. Pemetrexed-based doublets are restricted to non-squamous NSCLC.  
Strength of recommendation: A  Level of evidence: I  
MCBS for Pemetrexed: 4

Reco 5: four cycles of chemotherapy is standard.  
Strength of recommendation: A  Level of evidence: I

Reco 6: continuation of a doublet regimen beyond 4 cycles may be considered in selected, non-progressing patients  
Strength of recommendation: C  Level of evidence: I

Reco 7: when platinum-based chemotherapy is indicated, a combination with bevacizumab is a treatment option in eligible patients with non-squamous NSCLC. In this case, carboplatin/paclitaxel is the preferred combination.  
Strength of recommendation: I  Level of evidence: A  
MCBS for Bevacizumab: 2
A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS)

N. I. Cherry*, R. Sullivan², U. Dafni³, J. M. Kerst⁴, A. Sobrero⁵, C. Zielinski⁶, E. G. E. de Vries⁷ & M. J. Piccart⁸,⁹

ESMO-MCBS: NSCLC Metastatic disease 1st line

<table>
<thead>
<tr>
<th>Worst</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Best</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cisplatin</strong> pemetrexed versus cisplatin gemcitabine</td>
<td>First-line stage IIIb or IV (non-squamous)</td>
<td>OS (non-inferiority)</td>
<td>10.4 months</td>
<td>1.4 months</td>
<td>0.81 (0.70-0.94)</td>
<td>Less grade 3 + toxicity, neutropenia, anemia, thrombocytopenia</td>
</tr>
<tr>
<td><strong>Paclitaxel</strong>/carboplatin and bevacizumab</td>
<td>First-line stage IIIb or IV, non-squamous</td>
<td>OS</td>
<td>10.3 months</td>
<td>2.0 months</td>
<td>0.79 (0.67-0.92)</td>
<td></td>
</tr>
<tr>
<td><strong>OsGemcit</strong> of necitumumab</td>
<td>1st line treatment of patients with metastatic squamous non-small cell lung cancer.</td>
<td>OS</td>
<td>9.9 months</td>
<td>1.6 months</td>
<td>0.84 (0.74-0.96)</td>
<td></td>
</tr>
</tbody>
</table>

[78]
NSCLC 1st LINE CHEMOTHERAPY

Is it for all patients in practice?

- Treatment efficacy based on data from clinical trials
  - Selection bias (age, co-morbidity, biological selection, access to specialized centres...)

- In clinical practice, other parameters interfere
  - Patients choice, accessibility to treatment centres, insurance...
  - The whole population of m+NSCLC is not treated
NSCLC 1ST LINE CHEMOTHERAPY

Is it for all patients in practice?

- Treatment efficacy based on data from clinical trials
  - Selection bias (age, co-morbidity, biological selection…)

- In clinical practice, other parameters interfere
  - Patients choice, accessibility to treatment centers, insurance…
  - The whole population of m+NSCLC is not treated
Treatment/no treatment distribution from the US National Cancer Data base by advanced stages 1998-2012

C

Stage IIIB (N=136,603)

D

Stage IV (N=424,265)
(B) Trends in number of patients in each treatment group for stage IV.

(B) Overall survival in stage IV undergoing chemotherapy versus no treatment after propensity score matching of 19,046 patient pairs (log-rank test $p < 0.0001$)
NSCLC 1\textsuperscript{st} LINE CHEMOTHERAPY

Is it for all patients in practice?

- Despite improved supportive care, tolerance and side-effect management
- Reason for not receiving treatment
  - Older age, female gender, non-white race, high Charlson score
  - Low income, no insurance, low education,
  - Rural location and access to specialized care centres
  - Practice pattern of referring physicians
NSCLC 1\textsuperscript{st} LINE TREATMENT

Chemotherapy in the future

- 20\% of patients with driver mutations
- High rate of “no treatment” patients
- Low development rate of cytotoxic new drugs
- Emergence of immunotherapy in 1st line
  - High Magnitude of clinical benefit (MCBS 4)
  - Better tolerance profile

<table>
<thead>
<tr>
<th>pembrolizumab vs platinum-based chemotherapy</th>
<th>KEYNOTE -24</th>
<th>1st line Metastatic and advanced NSCLC with PD-L1 &gt;50%, EGFR and ALK-WT</th>
<th>PFS</th>
<th>6 months</th>
<th>4.3 months</th>
<th>0.50 (0.37 - 0.68)</th>
<th>5 months' survival</th>
<th>72.4%*</th>
<th>gain 7.8%*</th>
<th>0.60 (0.41-0.83)</th>
<th>Reduced</th>
<th>4</th>
<th>4</th>
</tr>
</thead>
</table>

- Long lasting effect
- Ease of administration
- But cost to be considered in many countries