ESMO – THE CHRISTIE PRECEPTORSHIP PROGRAMME

1st line chemotherapy for advanced NSCLC

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Head Dpt of Cancer Medicine
DISCLOSURE OF INTEREST

No personal financial disclosures

Institutional grants for clinical and translational research

AstraZeneca, BMS, Boehringer-Ingelheim, Lilly, Pfizer, Roche-Genentech, Sanofi-Aventis, Servier, Onxeo, OncoMed, Inivata, OSE Pharma, Loxo, Blueprint
PD-L1 ≥ 50%
Pembrolizumab [I, A]

Adapted from Novello – Ann Oncol 2016
OUTLINE

Annals of Oncology

2nd ESMO Consensus Conference on Lung Cancer: non-small-cell lung cancer first-line/second and further lines of treatment in advanced disease


1Thoracic Group, Department of Cancer Medicine, Gustave Roussy, Villejuif, France; 2Medicine Oncology, Roswell Park Cancer Institute, Buffalo, USA; 3The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; 4Aarhus University Hospital, Aarhus, Denmark; 5Aberdeen Royal Infirmary Anchor Unit, Aberdeen, UK; 6Hospital Universitario Virgen del Rocío, Sevilla, Spain; 7Department of Thoracic Oncology, Krankenhaus Grosshansdorf, Grosshansdorf, Germany; 8Department of Pulmonary Diseases, Vrije University Medical Centre (VUMC), Amsterdam, The Netherlands; 9Oncology Unit, Third Department of Medicine, Athens Chest Hospital Sotiria, Athens, Greece; 10Clinic of Oncology, University Hospital Zürich, Zürich, Switzerland; 11Medical Oncology, Vall D’Hebron University Hospital, Barcelona, Spain; 12Oncology Department, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland
## Level of Evidence (LOE) scale

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Evidence from at least one large randomized control trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity</td>
</tr>
<tr>
<td>II</td>
<td>Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity</td>
</tr>
<tr>
<td>III</td>
<td>Prospective cohort studies</td>
</tr>
<tr>
<td>IV</td>
<td>Retrospective cohort studies or case-control studies</td>
</tr>
<tr>
<td>V</td>
<td>Studies without control group, case reports, experts opinions</td>
</tr>
</tbody>
</table>

## Strength of recommendation (SOR) scale

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Strong evidence for efficacy with a substantial clinical benefit, strongly recommended</td>
</tr>
<tr>
<td>B</td>
<td>Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended</td>
</tr>
<tr>
<td>C</td>
<td>Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs,...), optional</td>
</tr>
<tr>
<td>D</td>
<td>Moderate evidence against efficacy or for adverse outcome, generally not recommended</td>
</tr>
<tr>
<td>E</td>
<td>Strong evidence against efficacy or for adverse outcome, never recommended</td>
</tr>
</tbody>
</table>
OUTLINE - 1st line: platinum based CT

- When to start?
- Cisplatin or carboplatin?
- A best doublet?
- How many cycles?
- For elderly patients?
- For PS2?
- Antiangiogenic?
- Other strategies
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

NSCLC Meta-Analyses Collaborative Group JCO 08
OUTLINE

1st line: platinum based CT

- When to start?
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- Antiangiogenic?
- Other strategies
Retrospective analysis of the British Columbia Cancer Registry

Immediate CT ≤ 8 weeks

- Referred to a medical oncologist n= 694
  - Immediate chemo n= 319 (46%)
  - Watch and wait n= 166 (24%)
  - Best supportive care n= 209 (30%)

- Patient choice (n=20)
  - No progression (n=13)
  - Asymptomatic (n=3)
  - Patient Moved (n=1)
  - Declining ECOG (n=36)
  - Patient died (n=35)
  - Asymptomatic (n=1)
  - Comorbid Illness (n=1)

FUI = 70 days

FUI = 25 days

Noonan, WCLC 2013
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%)
        - Still on watch and wait
          - n= 37 (22%)
    - Watch and wait
      - n= 166 (24%)
    - Best supportive care
      - n= 209 (30%)
      - Missed opportunity for chemo
        - n= 72 (43%)
      - Lost to follow-up
        - n= 7 (4%)

   Median Follow-up interval (FUI) = 22 days

FUI = 70 days
Patient choice (n=20)
No progression (n=13)
Asymptomatic (n=3)
Patient Moved (n=1)

FUI = 25 days
Declining ECOG (n=36)
Patient died (n=35)
Asymptomatic (n=1)
Comorbid Illness (n=1)

Noonan, WCLC 2013
Overall Survival of Upfront CT versus WW Populations

Log-rank p-value < 0.0001

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hazard Ratio for death (95% CI)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Upfront CT</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>WW-chemo</td>
<td>1.02 (0.74-1.40)</td>
<td>0.93</td>
</tr>
<tr>
<td>WW-missed</td>
<td>2.23 (1.69-2.94)</td>
<td>&lt;0.0001</td>
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</table>

CPH Model Covariates:

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Hazard Ratio for death (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (%)</td>
<td>Male 1.00, Female 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>0-1 1.00, 2-4 1.40 (1.13-1.74)</td>
<td>0.002</td>
</tr>
</tbody>
</table>
OUTLINE
1st line: platinum based CT

- When to start?
- Cisplatin or carboplatin?
- A best doublet?
- How many cycles?
- For elderly patients?
- For PS2?
- Antiangiogenic?
- Other strategies

**Recommendation:**
The administration of first-line chemotherapy should be offered at diagnosis to asymptomatic patients with metastatic NSCLC. (B, III)
OUTLINE

1st line: platinum based CT

- When to start?
- Cisplatin or carboplatin?
- A best doublet?
- How many cycles?
- For elderly patients?
- For PS2?
- Antiangiogenic ?
- Other strategies
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

Survival benefit for 3rd generation combo

Ardizzoni JNCI 2007
### Cisplatin: dose

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dose (mg/m²)</th>
<th>Administration Schedule</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin/Vinorelbine</td>
<td>100</td>
<td>day 1/25 days 1, 8, 15, 22 every 4 weeks</td>
<td>[Fossella 2003 (28)]</td>
</tr>
<tr>
<td>Cisplatin/Vinorelbine</td>
<td>80</td>
<td>day 8/30 days 1 and 8</td>
<td>[Georgoulias 2005 (79)]</td>
</tr>
<tr>
<td>Cisplatin/Paclitaxel</td>
<td>75</td>
<td>day 2/135 (24 hour) day 1 every 3 weeks</td>
<td>[Schiller 2002 (55)]</td>
</tr>
<tr>
<td>Cisplatin/Docetaxel</td>
<td>75</td>
<td>day 1/75 day 1 every 3 weeks</td>
<td>[Fossella 2003 (28)]</td>
</tr>
<tr>
<td>Cisplatin/Docetaxel</td>
<td>75</td>
<td>day 1/75 day 1 every 3 weeks</td>
<td>[Schiller 2002 (55)]</td>
</tr>
<tr>
<td>Cisplatin/Gemcitabine</td>
<td>100</td>
<td>day 1/1000 days 1, 8, 15 every 4 weeks</td>
<td>[Schiller 2002 (55)]</td>
</tr>
</tbody>
</table>
OUTLINE

1st line: platinum based CT

- When to start?
- Cisplatin or carboplatin?
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- How many cycles?
- For elderly?
- For PS2?
- Antiangiogenic?
- Other strategies

Recommendations:
- Cisplatin should be used in fit patients with PS 0–1 who have adequate organ function. (B, I)
- Cisplatin at ≥ 75 mg/m² q3wks should be used with 3rd-generation drugs. (B, V)
OUTLINE

1st line: platinum based CT

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- Other strategies
### Platinum-based Doublets for NSCLC

**North American Experience (SWOG + ECOG)**

<table>
<thead>
<tr>
<th></th>
<th>SWOG</th>
<th>ECOG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>RO</td>
</tr>
<tr>
<td>Cisplatine + Vinorelbine</td>
<td>207</td>
<td>27%</td>
</tr>
<tr>
<td>Paclitaxel + Carboplatine</td>
<td>201</td>
<td>27%</td>
</tr>
<tr>
<td>Paclitaxel + Carboplatine</td>
<td>299</td>
<td>15%</td>
</tr>
<tr>
<td>Docetaxel + Cisplatine</td>
<td>304</td>
<td>17%</td>
</tr>
</tbody>
</table>

Source: Kelly et al., JCO 01.; Schiller et al., NEJM 02
Platinum-based Doublets for NSCLC

*North American Experience (SWOG + ECOG)*

![Graph showing survival by treatment group for stage IV NSCLC patients. The graph compares survival rates for different treatment regimens, including Cis/Paclitaxel, Cis/Gemcitabine, Cis/Docetaxel, and Carbo/Paclitaxel.](image)
## Histological classification of NSCLC

<table>
<thead>
<tr>
<th>Classification</th>
<th>Characteristics¹</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-squamous</strong></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma (AC)</td>
<td>• Malignant epithelial tumors with glandular differentiation</td>
</tr>
<tr>
<td>(30–50%)*</td>
<td>• IASLC classification of invasive AC:²</td>
</tr>
<tr>
<td></td>
<td>• Lepidic, acinar, papillary, micropapillary, or solid pattern predominant</td>
</tr>
<tr>
<td></td>
<td>• Variants: invasive mucinous AC, colloid, fetal, and enteric</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>• Involves large cells (subtypes are giant cell, clear cell) with large nuclei</td>
</tr>
<tr>
<td>10%*</td>
<td>• No evidence of squamous or glandular differentiation</td>
</tr>
<tr>
<td><strong>Squamous</strong></td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>• Involves cells of the squamous epithelium</td>
</tr>
<tr>
<td>30%†</td>
<td>• Two variants of clinicopathologic significance³</td>
</tr>
<tr>
<td></td>
<td>• Papillary variant</td>
</tr>
<tr>
<td></td>
<td>• Basaloid variant</td>
</tr>
</tbody>
</table>

*Image from www.surgical-pathology.com; †Image from http://www.lmp.ualberta.ca/resources/pathoimages/PC-S.htm; ³Other less common subtypes of non-squamous NSCLC include adenosquamous carcinoma and sarcomatoid carcinoma.³

Pemetrexed vs gemcitabine (+CDDP)

- Pemetrexed 500 mg/m² j 1
- Cisplatin 75 mg/m² j 1

- Adenocarcinoma + LCC → pemetrexed better

- SCC → Gemcitabine better
Pemetrexed vs gemcitabine (+CDDP)

- **Post-treatment**
  - 56.1% of gem/cis
    - Pem 13.4%
    - Gem 8.6%
    - Docetaxel 27.6%
    - EGFR TKI 22.5%
  - 52.6% of pem/cis
    - Pem 3.5%
    - Gem 16.7%
    - Docetaxel 25.4%
    - EGFR TKI 24.9%

Only 13.4% pts crossed over to pemetrexed!
Pemetrexed vs placebo after 4 cycles pemetrexed/cisplatin

**PFS**
- Pemetrexed: median = 4.4 mos (4.1 to 5.7 mos)
- Placebo: median = 2.8 mos (2.6 to 3.0 mos)
- Log-rank $P < .001$
- Unadjusted HR: 0.60 (0.50 to 0.73)

**OS**
- Pemetrexed: median = 13.9 mos (12.8 to 16.0 mos)
- Placebo: median = 11.0 mos (10.0 to 12.5 mos)
- Log-rank $P = 0.0195$
- Unadjusted HR: 0.78 (0.64 to 0.96)

**OS maintenance pemetrexed: 13.9 months**
Adjusted HR*, [CI 95%] 0.98 [0.85-1.14], P=0.81
OUTLINE
1st line: platinum based CT

- When to start?
- Cisplatin or carboplatin?
- A best doublet?
- How many cycles?
- For elderly patients?
- For PS2?
- Antiangiogenic?
- Other strategies

Recommendation:
There is no single platinum-based doublet standard chemotherapy. Pemetrexed-based doublets are restricted to non-squamous NSCLC. (A, I)
OUTLINE

1st line: platinum based CT

- When to start?
- Cisplatin or carboplatin?
- A best doublet?
- How many cycles?
- For elderly patients?
- For PS2?
- Antiangiogenic?
- Other strategies
Optimal duration of chemotherapy

First line registration trials

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

PFS: 4 vs 6 cycles of cisplatin-based CT

<table>
<thead>
<tr>
<th>MST (mo)</th>
<th>6-cycle</th>
<th>4-cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6.2 (5.7-6.7)</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
3-4 cycles vs. More

**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>0.71 (0.45 to 1.12)</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>0.73 (0.46 to 1.17)</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>0.77 (0.59 to 1.01)</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>0.79 (0.63 to 1.01)</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>0.84 (0.65 to 1.08)</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>0.84 (0.52 to 1.38)</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>0.88 (0.72 to 1.07)</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>0.96 (0.82 to 1.12)</td>
</tr>
<tr>
<td>Belani (2003)</td>
<td>96</td>
<td>65</td>
<td>1.02 (0.66 to 1.57)</td>
<td>3</td>
<td>1.02 (0.66 to 1.57)</td>
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<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>1.04 (0.82 to 1.32)</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>1.08 (0.79 to 1.48)</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>1.11 (0.82 to 1.48)</td>
</tr>
<tr>
<td>Tourani (1990)</td>
<td>12</td>
<td>11</td>
<td>1.26 (0.85 to 1.86)</td>
<td>4</td>
<td>1.26 (0.85 to 1.86)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1,658</td>
<td>1,369</td>
<td>0.92 (0.85 to 0.99)</td>
<td>100</td>
<td>0.92 (0.85 to 0.99)</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; \( P =0.003 \).**
Pemetrexed vs placebo after 4 cycles pemetrexed/cisplatin

**PFS**

- Pemetrexed: median = 4.4 mos (4.1 to 5.7 mos)
- Placebo: median = 2.8 mos (2.6 to 3.0 mos)
- Log-rank $P < .001$
- Unadjusted HR: 0.60 (0.50 to 0.73)

**OS**

- Pemetrexed: median = 13.9 mos (12.8 to 16.0 mos)
- Placebo: median = 11.0 mos (10.0 to 12.5 mos)
- Log-rank $P = .0195$
- Unadjusted HR: 0.78 (0.64 to 0.96)

**OS maintenance pemetrexed: 13.9 months**

Paz-Ares JCO 2013
Strategy made in Pharmas

Control ARM

- 6X GEM CIS
- 4X PEM CIS

Exp ARM

- 6X PEM CIS
- 4X PEM CIS then PEM
1st line: platinum based CT

- When to start?
- Cisplatin or carboplatin?
- A best doublet?
- How many cycles?
- For elderly patients?
- For PS2?
- Antiangiogenic?

**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)
OUTLINE

1st line: platinum based CT

- When to start?
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- A best doublet?
- How many cycles?
- For elderly patients?
- For PS2?
- Antiangiogenic?
- Other strategies
Miles Study: Results

![Survival probability graph showing different treatment outcomes over weeks.]

- **Vinorelbine**
- **Gemcitabine**
- **Vinorelbine + Gemcitabine**
- **Censored patients**

Gridelli J Natl Cancer Inst. 2003
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

Random

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

*Choice of the center at the beginning of the study

Quoix, ASCO 2010
## First-line Treatment

<table>
<thead>
<tr>
<th>ARM A</th>
<th>Weeks</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>V</td>
<td>V</td>
<td></td>
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<td>V</td>
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<table>
<thead>
<tr>
<th>ARM B</th>
<th>Weeks</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>P</td>
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<td>P</td>
<td></td>
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<tr>
<td>P</td>
<td>P</td>
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</tbody>
</table>

### Choice of the center

- **V**: Vinorelbine: 30 mg/m²
- **G**: Gemcitabine: 1150 mg/m²
- **C**: Carboplatin: AUC 6
- **P**: Paclitaxel: 90 mg/m²

Quoix, ASCO 2010
Overall survival (Primary Objective)

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

Quoix, The Lancet 2011
1st line: platinum based CT

- When to start?
- Cisplatin or carboplatin?
- A best doublet?
- How many cycles?
- For elderly patients?
- For PS2?
- Antiangiogenic?

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)
OUTLINE

1st line: platinum based CT

- When to start?
- Cisplatin or carboplatin?
- A best doublet?
- How many cycles?
- For elderly patients?
- For PS2?
- Antiangiogenic?
- Other strategies
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
Survival by Patient Subgroup

<table>
<thead>
<tr>
<th></th>
<th>SC + CT</th>
<th>SC alone</th>
<th>Hazard Ratio (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS – Protocol Analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<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></td>
</tr>
<tr>
<td>PS – Exploratory Analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<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>

Interaction p=0.536
Trend p=0.701

[NSCLC Meta-Analyses Collaborative Group JCO 08]
Pemetrexed vs. Pemetrexed-carboplatin in PS2 pts

**PFS**
- CP - 5.8 months (95% CI 4.7-6.9)
- P - 2.8 months (95% CI 2.5-3.2)
- HR = 0.46; 95% CI, 0.35 to 0.63
  - P< 0.001

**OS (Primary endpoint)**
- CP - 9.3 months (95% CI 7.2-11.2)
- P - 5.3 months (95% CI 4.1-6.5)
- HR = 0.62; 95% CI, 0.46 to 0.83
  - P= 0.001

4 cycles, n=201
OUTLINE

1st line: platinum based CT

- When to start?
- Cisplatin or carboplatin?
- A best doublet?
- How many cycles?
- For elderly patients?
- For PS2?
- Antiangiogenic?
- Other strategies

Recommendation:
Platin-based combinations are preferred over single-agent chemotherapy. (B, I)
OUTLINE

1st line: platinum based CT

- When to start?
- Cisplatin or carboplatin?
- A best doublet?
- How many cycles?
- For elderly patients?
- For PS2?
- Anti-angiogenic?
- Other strategies
Bevacizumab

- Non squamous NSCLC
- Chemo Naive Stage IIIB-IV
- ECOG PS 0–1
- INR <1.5
- No history of bleeding or TEE
- No brain mets

Sandler NEJM 2006
Paclitaxel – Carboplatin - Bevacizumab

**Population**
Non squamous NSCLC
Chemo Naive Stage IIIB-IV

**Paclitaxel (200mg/m², d1)**
+ **Carboplatin (AUC 6, J1)**
  
  d1=d21

6 cycles

444 patients

**Paclitaxel (200mg/m², d1)**
+ **Carboplatin (AUC 6, d1)**
+ **Bevacizumab (15mg/kg, d1)**
  
  d1=d21

6 cycles + maintenance bvz

434 patients

Sandler NEJM 2006
Paclitaxel – Carboplatine - Bevacizumab

OS

Median: 12.5 mo vs 10.2 mo

<table>
<thead>
<tr>
<th></th>
<th>12 mo</th>
<th>24 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCB</td>
<td>51.9%</td>
<td>22.1%</td>
</tr>
<tr>
<td>PC</td>
<td>43.7%</td>
<td>16.9%</td>
</tr>
</tbody>
</table>

HR: 0.77 (0.65-0.93)  p=0.007
Bevacizumab  
Pooled Analysis for PFS

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of events / No. entered</th>
<th>Hazard ratio</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bevacizumab</td>
<td>Control</td>
<td>O-E</td>
</tr>
<tr>
<td>Dose 7.5 mg/kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVF-0757g 7.5</td>
<td>1128/1313</td>
<td>1099/1260</td>
<td>-150.1</td>
</tr>
<tr>
<td>AVAiL 7.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose 15 mg/kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVF-0757g 15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG 4599</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVAiL 15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JO19907</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1128/1313</td>
<td>1099/1260</td>
<td>-150.1</td>
</tr>
</tbody>
</table>

- Non SCC NSCLC (toxic in SCC)
- 7.5 or 15 mg/kg q3w
- CT + bevacizumab then bevacizumab maintenance
AVAiL: Ph III Cis/Gem +/- Bevacizumab

+/- bevacizumab 7.5 mg/kg

- Placebo + CG (n = 347)
- Bevacizumab 7.5 mg/kg + CG (n = 345)

HR (95% CI) = 0.75 (0.62 to 0.91)
P = .003

+/- bevacizumab 15 mg/kg

- Placebo + CG (n = 347)
- Bevacizumab 15 mg/kg + CG (n = 351)

HR (95% CI) = 0.82 (0.68 to 0.98)
P = .03

No formal comparison of the doses
But does dose matter?
BO21015 (ABIGAIL)

Previously untreated, stage IIIB, IV non-squamous NSCLC (n=300)
Stratified by stage, gender, PS, chemotherapy

- Bevacizumab 7.5mg/kg q3w + up to six 21-day cycles of CG or CP (n=150)
- Bevacizumab 15mg/kg q3w + up to six 21-day cycles of CG or CP (n=150)

Primary endpoint:
exploration of correlation between candidate biomarkers and overall response rate to chemotherapy plus bevacizumab

Carboplatin/Gemcitabine (CG) or Carboplatin/Paclitaxel (CP)
Chemotherapy regimen was not randomly allocated but was chosen by the Investigator

Mok – J Thorac Oncol 2014
Only LOW baseline plasma VEGF-A correlated with PFS (p=0.002) and OS (p=0.004)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>n</th>
<th>Median PFS (months)</th>
<th>6-month PFS rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bev 15 mg/kg + CP</td>
<td>62</td>
<td>7.1</td>
<td>68</td>
</tr>
<tr>
<td>Bev 7.5 mg/kg + CP</td>
<td>66</td>
<td>6.3</td>
<td>52</td>
</tr>
<tr>
<td>Bev 15 mg/kg + CG</td>
<td>87</td>
<td>6.1</td>
<td>51</td>
</tr>
<tr>
<td>Bev 7.5 mg/kg + CG</td>
<td>88</td>
<td>6.8</td>
<td>63</td>
</tr>
</tbody>
</table>

7.5 mg/kg vs. 15 mg/kg, **HR 1.01**, 95% CI: 0.78-1.31

~60% of patients received CG
BRAIN: phase II trial of bevacizumab in patients with CNS metastases

Stage IV non-squamous NSCLC with untreated asymptomatic brain metastases (n=66)

Bevacizumab 15 mg/kg q3w + paclitaxel + carboplatin

6 cycles

n=66

Summary of response rates for primary tumours and metastases (% and 95% CI; n=67) for Pac + Carbo + Bev → Bev

First-line Pac + Carbo + Bev → Bev (n=67)

Median PFS/OS (months)

PFS: 6.7
OS: 16.0
AvaALL phase III: BVZ beyond PD

Primary endpoint: OS

Bev + platinum doublet therapy followed by Bev maintenance in advanced non-squamous NSCLC (N=485)

Investigator choice of SOC

Bev (7.5mg/kg or 15mg/kg i.v. q3w) + SOC1

Bev + SOC2

Bev + SOC3

No crossover allowed

1:1

PD1

SOC1

SOC2

SOC3

PD2

PD3

Bev + SOC
Median OS 11.86 months (95% CI: 10.22–13.67)

SOC
Median OS 10.22 months (95% CI: 8.61–11.93)

HR 0.84 (90% CI: 0.71–1.00)

p=0.1044

Courtesy of J. Remon

Bennouna – ASCO 2017
### Negative phase III trials in NSCLC with anti-angiogenic agents (2000-2012)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mechanism of action</th>
<th>N° trials</th>
<th>N</th>
<th>End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide</td>
<td>Anti-angiogenic</td>
<td>2</td>
<td>1267</td>
<td>OS</td>
</tr>
<tr>
<td>Cediranib</td>
<td>VEGFR TKI</td>
<td>2</td>
<td>602</td>
<td>OS</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>Multikinase TKI</td>
<td>3</td>
<td>2698</td>
<td>PFS/OS</td>
</tr>
<tr>
<td>AE-941</td>
<td>Anti-angiogenic</td>
<td>1</td>
<td>379</td>
<td>OS</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Multikinase TKI</td>
<td>2</td>
<td>1830</td>
<td>OS</td>
</tr>
<tr>
<td>Motesanib</td>
<td>Multikinase TKI</td>
<td>1</td>
<td>1090</td>
<td>OS</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Multikinase TKI</td>
<td>1</td>
<td>960</td>
<td>OS</td>
</tr>
<tr>
<td>Aflibercet</td>
<td>VEGF/PIGF</td>
<td>1</td>
<td>913</td>
<td>OS</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>11</strong></td>
<td><strong>9739</strong></td>
<td></td>
</tr>
</tbody>
</table>
OUTLINE

1st line: platinum based CT

• When to start?
• Cisplatin or carboplatin?
• A best doublet?
• How many cycles?
• For elderly patients?
• For PS2?
• Anti-angiogenic?
• Other strategies
Cetuximab, meta-analysis

Cetuximab + CT improved OS (HR 0.88, p=0.009) PFS (HR 0.90, p=0.045) and RR (ORR 1.46, p< 0.001)

Greatest survival benefit in Squamous (HR 0.77, 95% CI 0.64–0.93)

Courtesy of J. Remon

Pujol - Lung Cancer 2014
SQUIRE trial: Necitumumab in Squamous

First-line Stage IV Squamous NSCLC<sup>3,4</sup>
ECOG PS 0-2

Neci + Gem-Cis q3w (N=545)
Necitumumab 800 mg D1, D8
Gemcitabine 1250 mg/m², D1, D8
Cisplatin 75 mg/m², D1

Maximum of 6 cycles

Neci q3w
800 mg D1, D8

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

Primary Endpoint: OS

Randomization 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)
SQUIRE trial: Necitumumab in Squamous

1y OS: 43%
2y OS: 20%

1y OS: 48%
2y OS: 17%

Courtesy of J. Remon

GUSTAVE ROUSSY
THÈME DU DIAPORAMA

Thatcher - Lancet Oncol 2015
Nab-paclitaxel in NSCLC

First-line Stage IV ECOG PS 0-2

N=1052

EndPoint: ORR

Nab-Paclitaxel 100 mg/m² QW CBDCA (AUC=6) Q3W

Maximum of 6 cycles

Paclitaxel 100 mg/m² QW CBDCA (AUC=6) Q3W

Socinski – JCO 2012 * Socinski – Ann Oncol 2013

Courtesy of J.Remon

Favors nab-PC
New standard?

<table>
<thead>
<tr>
<th></th>
<th>Nab-Paclitaxel</th>
<th>Nab-Paclitaxel Carboplatin</th>
<th>Paclitaxel CBDCA</th>
<th>Necitumumab Cis/Gem</th>
<th>Placebo Cis/Gem</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N (Squamous)</strong></td>
<td>229</td>
<td>221</td>
<td>545</td>
<td>548</td>
<td></td>
</tr>
<tr>
<td><strong>ORR (%)</strong></td>
<td>41</td>
<td>24*</td>
<td>31</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td><strong>PFS (mo)</strong></td>
<td>5.6</td>
<td>5.7</td>
<td>5.7</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td><strong>OS (mo)</strong></td>
<td>10.7</td>
<td>9.5</td>
<td>11.5</td>
<td>9.9*</td>
<td></td>
</tr>
<tr>
<td><strong>G3-5 AE (%)</strong></td>
<td>70</td>
<td>68</td>
<td>72</td>
<td>62</td>
<td></td>
</tr>
</tbody>
</table>

* Statistically significant


Courtesy of J. Remon
First-Line IO + CT

**Ph. II Pem. Carbo.**

+/- PEMBROLIZUMAB

KEYNOTE 021

- Progression-Free Survival (%)
  - HR: 0.54 (0.33–0.88)
  - \( P = 0.0067 \)

**Ph. III Pacli. Carbo. Bev.**

+/- ATEZOLIZUMAB

IMPOWER 150

- Progression-Free Survival (%)
  - HR: 0.617 (95% CI: 0.517, 0.737)
  - \( P < 0.0001 \)

**Press release - Jan, 16th 2018**

Ph. III KEYNOTE 189

Positive for PFS and OS

All comers


Reck M, et al. ESMO IO Meeting 2017
### 1st line metastatic NSCLC

**Treatment options**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Dose (mg/m²)</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td>1250</td>
<td>d 1, 8</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>80</td>
<td>d 1</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>25</td>
<td>d 1, 8, 15, 22</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>100</td>
<td>d 1, d1=d28</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>500</td>
<td>d1</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>75</td>
<td>d1, d1=d21</td>
</tr>
</tbody>
</table>

*All histologies*

*Historical design, all histologies*

*Non squamous NSCLC*

+/- bevacizumab if non SCC.
7.5 mg/kg or 15 mg/kg d1=d21
1st line metastatic NSCLC

**Treatment options**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>75 mg/m²</td>
<td>d 1</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>75 mg/m²</td>
<td>d 1</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>135 mg/m² (24 h)</td>
<td>d 1</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>75 mg/m²</td>
<td>d 2</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>225 mg/m² (3 h)</td>
<td>d 1</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>AUC 6</td>
<td>d 1</td>
</tr>
</tbody>
</table>

All histologies, induce alopecia

+/- bevacizumab if non SCC.
7.5 mg/kg or 15 mg/kg d1=d21
WE NEED NEW CHEMO!