ESMO PRECEPTORSHIP ON

1st line chemotherapy for advanced NSCLC

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DISCLOSURES

Consulting, advisory role or lectures: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, Roche

Honoraria: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, Roche

Clinical trials research: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, Pfizer, Roche, Medimmun, Sanofi-Aventis, Taiho Pharma, Novocure, Daiichi Sankyo

Travel, Accommodations, Expenses: AstraZeneca, Roche, Novartis, prIME Oncology, Pfizer
Great Advances Have Been Made in Lung Cancer Therapy: Personalized Therapy in Advanced-Stage NSCLC

2000–2006
NSCLC

2006–2009
Treated according to histology

2010
Targeting EGFR

2011–2019...
Targeting an oncogenic driver

NSCLC

Nonsquamous

Squamous

Nonsquamous

Squamous

ALK, anaplastic lymphoma kinase; BRAF, B-Raf proto-oncogene, serine/threonine kinase; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; NSCLC, non-small-cell lung cancer
Chemotherapy first line NSCLC

- Chemotherapy benefit?
- How many agents?
- How many cycles?
- A best doublet?
- Cisplatin or carboplatin?
- Anti-EGFR association for SCC?
- Preferred treatment for NSCC?
- Addition of antiangiogenic?
- Maintenance benefit?
- For elderly patients?
- For PS2?
- And tomorrow…?
Survival in trials of supportive care vs supportive care plus chemotherapy

cisplatin based trials showed a benefit of chemotherapy: HR=0.73 (P<0.0001):

- A reduction in the risk of death of 27%

- Equivalent to an absolute improvement in survival of 10% at one year

Non-small Cell Lung Cancer Collaborative Group, BMJ 1995
Meta-analysis Chemo. vs BSC Overall Survival

2714 patients from 16 trials
-significant benefit of chemotherapy on survival (HR = 0.77, P < 0.0001)

Translating to an absolute improvement of 9% at 12 months

HR=0.77 [0.71-0.83]  

p=0.0001

NSCLC Meta-Analyses Collaborative Group, JCO 2008
Systemic therapy should be offered to all stage IV patients with PS 0–2 [I, A]

Levels of Evidence (LOE) and Grades of Recommendation (GOR)

<table>
<thead>
<tr>
<th>Levels of evidence</th>
<th>Grades of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Strong evidence for efficacy with a substantial clinical benefit, strongly recommended</td>
</tr>
<tr>
<td>II</td>
<td>Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended</td>
</tr>
<tr>
<td>III</td>
<td>Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional</td>
</tr>
<tr>
<td>IV</td>
<td>Moderate evidence against efficacy or for adverse outcome, generally not recommended</td>
</tr>
<tr>
<td>V</td>
<td>Strong evidence against efficacy or for adverse outcome, never recommended</td>
</tr>
</tbody>
</table>

D.Planchard et al, annals of onco 2018
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Response rate and survival with doublet vs single-agent regimens and triplet vs doublet regimens

<table>
<thead>
<tr>
<th></th>
<th>No. of Comparisons</th>
<th>No. of Patients</th>
<th>Ratio (95% Confidence Interval)</th>
<th>Treatment Effect</th>
<th>Heterogeneity</th>
<th>Absolute Benefit, %</th>
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</thead>
<tbody>
<tr>
<td><strong>Response rate†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2 vs 1 agents</td>
<td>33</td>
<td>7175</td>
<td>0.42 (0.37-0.47)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>13</td>
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<tr>
<td>3 vs 2 agents</td>
<td>35</td>
<td>4814</td>
<td>0.66 (0.58-0.75)</td>
<td>&lt;.001</td>
<td>.06</td>
<td>8</td>
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<tr>
<td><strong>1-Year survival‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 vs 1 agents</td>
<td>13</td>
<td>4125</td>
<td>0.80 (0.70-0.91)</td>
<td>&lt;.001</td>
<td>.03</td>
<td>5</td>
</tr>
<tr>
<td>3 vs 2 agents</td>
<td>10</td>
<td>2249</td>
<td>1.01 (0.85-1.21)</td>
<td>.88</td>
<td>.59</td>
<td>0</td>
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<tr>
<td><strong>Median survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 vs 1 agents</td>
<td>30</td>
<td>6022</td>
<td>0.83 (0.79-0.89)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>NA$</td>
</tr>
<tr>
<td>3 vs 2 agents</td>
<td>30</td>
<td>4550</td>
<td>1.00 (0.94-1.06)</td>
<td>.97</td>
<td>.04</td>
<td>NA$</td>
</tr>
</tbody>
</table>

No survival benefit observed for three-agent over two-agent regimens

Delbaldo.C et al, JAMA 2004
Should chemotherapy combinations for advanced NSCLC be platinum-based?

statistically significant reduction (equal to 22%) in the risk of death at 1 year for platinum over non-platinum combinations, without induction of unacceptable increase in toxicity

Pujol JL et al, cancer 2006
Platinum-based doublets are recommended in all patients with no contraindications to platinum compounds [I, A]
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Two Versus Four Additional Cycles (Phase III)

Study confirms **non inferiority of OS** with four cycles compared with six cycles of chemotherapy for the first-line treatment of advanced NSCLC

Joon Oh Park et al, JCO 2007
Meta-analysis of individual patient data: Six versus fewer planned cycles of first-line platinum-based CT for NSCLC

Six cycles of first-line platinum-based CT did not improve OS compared with three or four courses

Antonio Rossi et al, lancet onco 2014
Therefore, **four cycles of platinum-based doublets** followed by less toxic maintenance monotherapy [I, A], or four cycles in patients not suitable for maintenance monotherapy [I, A], up to a maximum of six [IV, B], are currently recommended.
Chemotherapy first line NSCLC

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Several platinum-based regimens with third-generation cytotoxics (paclitaxel, gemcitabine, docetaxel, vinorelbine) have shown comparable efficacy.
nab-PC regimen have a significantly higher ORR compared with paclitaxel/carboplatin, and less neurotoxicity

- Higher ORR than PC (33% v 25%, 1.313; P=.005) and in patients with squamous (41% v 24%; P<.001)
- Significantly less grade ≥3 neuropathy, neutropenia, arthralgia, and myalgia

Mark A. Socinski et al, JCO 2012
Platinum-based doublets are the recommended ChT option in all stage IV NSCLC patients with no contraindications to platinum compounds [I, A]

The nab-PC regimen could be considered a chemotherapeutic option in advanced NSCLC patients, particularly in patients with greater risk of neurotoxicity, preexisting hypersensitivity to paclitaxel or contraindications for standard paclitaxel premedication [I, B]
Chemotherapy first line NSCLC

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Meta-analysis suggests that cisplatin-based chemotherapy is slightly superior to carboplatin-based chemotherapy

Nine trials that included a total of 2968 patients

**Response**
- CIS 30%
- CARBO 24%
**HR = 1.37 (IC 95% = 1.16-1.61)**
P <0.001

**Survival**
**HR = 1.07 (IC 95% = 0.99 to 1.15)**
P = 0.100

- Carboplatin associated with a non–statistically significant increase in the hazard of mortality
- With third-generation CT, carboplatin-based chemotherapy associated with a statistically significant increase in mortality

- Cisplatin-based chemotherapy: more severe nausea and vomiting and nephrotoxicity
- Carboplatin-based chemotherapy: severe thrombocytopenia

Ardizzoni JNCI 2007
Meta-analysis including 10 trials with 3973 patients: could not demonstrate any difference between carboplatin-based and cisplatin based ChT in OS

No difference between carboplatin and cisplatin-based chemotherapy in OS (HR= 1.00; 95% CI, 0.51-1.97)

- **Cisplatin** caused more nausea or vomiting, or both (RR:0.46; 95% CI 0.32-0.67)
- **and carboplatin** caused more thrombocytopenia (RR: 2.00; 95% CI 1.37-2.91) and neurotoxicity (RR: 1.55; 95% CI 1.06-2.27)

de Castria TB et al, Cochrane library 2013
Any platinum-based doublets with a third-generation agent including gemcitabine, vinorelbine or taxanes can be used.
Chemotherapy first line NSCLC

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Necitumumab, monoclonal antibody against EGFR, did not demonstrate a significant impact in first-line treatment NSCC when added to cisplatin/pemetrexed (INSPIRE Trial)

11.3 vs 11.5 m (HR 1.01; p=0.96)

5.6 vs 5.6 months

Luis Paz-Ares et al, Lancet onco 2015
However, outcomes were different when necitumumab was combined with different ChT regimens in SCC (SQUIRE Trial)

Nick Thatcher et al, lancet onco 2015

11.5 vs 9.9 months
Addition of necitumumab to gemcitabine–cisplatin significantly prolonged OS in the subpopulation of pts with EGFR-expressing sq-NSCLC (SQUIRE)

Large majority of these patients (95%) had tumor samples expressing EGFR protein; only 5% had tumors without detectable EGFR protein

L. Paz-Ares et al, annals of onco 2016
EGFR FISH might predict for additional benefit

Overall Survival in EGFR FISH Positive* Patients

<table>
<thead>
<tr>
<th></th>
<th>GC+N</th>
<th>GC</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>111</td>
<td>97</td>
</tr>
<tr>
<td>Unstratified HR (95% CI)</td>
<td>0.70 (0.52, 0.96)</td>
<td></td>
</tr>
<tr>
<td>Median, months (95% CI)</td>
<td>12.6 (11.5, 15.9)</td>
<td>9.2 (7.2, 12.1)</td>
</tr>
</tbody>
</table>

Amplification = 7%
High polysomy = 30%

Tumor samples were available with valid FISH results obtained for 51% of ITT population

Boyle et al. IASLC WCLC 2015
FLEX trial showed that OS is prolonged with the EGFR targeted antibody cetuximab added to chemotherapy

Immunohistochemical evidence of EGFR expression in at least one positively stained tumour cell

PFS, not different (HR 0.943, 0.825–1.077; p=0.39), median 4.8 months in both groups

Robert Pirker et al, lancet 2009
Based on these results, due to the limited clinical improvement, the addition of necitumumab to cisplatin and gemcitabine has not been adopted as a standard in Europe for advanced SCC and its use should be carefully evaluated [I, C; ESMO-MCBS v1.1 score: 1].

Same for cetuximab

Therefore, platinum-based doublets with the addition of a third-generation cytotoxic agent (gemcitabine, vinorelbine, taxanes) are recommended in advanced SCC patients without major comorbidities and PS 0–2 [I, A]

D.Planchard et al, annals of onco 2018
Stage IV SCC

4-6 cycles
Platinum–based ChT:
- Cisplatin/gemcitabine [I, A]
- Cisplatin/docetaxel [I, A]
- Cisplatin/paclitaxel [I, A]
- Cisplatin/incorrect [I, A]
- Carboplatin/gemcitabine [I, A]
- Carboplatin/docetaxel [I, A]
- Carboplatin/paclitaxel [I, A]
- Carboplatin/incorrect [I, A]
- Carboplatin/nab-P [I, B]

D. Planchard et al, annals of onco 2018
Chemotherapy first line NSCLC

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- And tomorrow…?
Pemetrexed-based combination ChT represents a therapeutic option,

Pemetrexed use should be restricted to NSCC in any line of treatment in advanced disease [II, A]

Giorgio Vittorio Scagliotti et al, JCO 2008
Meta-analysis showed a slight but significant survival benefit compared with gemcitabine- or docetaxel-based combinations.
Any platinum-based doublets with a third-generation agent including gemcitabine, vinorelbine or taxanes can be used in NSCC

Pemetrexed-based combination ChT represents a therapeutic option,

Pemetrexed use should be restricted to NSCC in any line of treatment in advanced disease [II, A]

The combination of carboplatin with pemetrexed can be an option in patients with a contraindication to cisplatin [II, B]
Chemotherapy first line NSCLC

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- Anti-EGFR association for SCC ?
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- **Addition of antiangiogenic ?**
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- And tomorrow…?
Bevacizumab improves OS when combined with paclitaxel/carboplatin regimens in patients with NSCC and PS 0–1

Hazard ratio, 0.66
P<0.001

Hazard ratio, 0.79
P=0.003

6.2 vs 4.5m

12.3 vs 10.3m

Alan Sandler et al, NEJM 2006
Phase III Study of First-Line Carboplatin/Paclitaxel Plus Bevacizumab or Placebo in Chinese Patients (BEYOND)

- Progression-Free Survival: Median PFS 6.5 vs 9.2 months, HR 0.40; 95% CI 0.29 to 0.54, P < .001
- Overall Survival: Median OS 17.7 vs 24.3 months, HR 0.68; 95% CI 0.50 to 0.93, P = .0154

Caicun Zhou et al, JCO 2015
AVAIL Trial (Bev + CisP and Gemcitabine): The PFS benefit did not translate into a significant OS benefit

- **ITT**
  - Placebo + CG: (n = 347)
  - Bevacizumab 7.5 mg/kg + CG: (n = 345)
  - Bevacizumab 15 mg/kg + CG: (n = 351)
- **Number of deaths**
  - Placebo + CG: 240
  - Bevacizumab 7.5 mg/kg + CG: 233
  - Bevacizumab 15 mg/kg + CG: 242
- **Median time to event, months (95% CI)**
  - Placebo + CG: 13.1 (11.8–15.2)
  - Bevacizumab 7.5 mg/kg + CG: 13.6 (11.8–15.8)
  - Bevacizumab 15 mg/kg + CG: 13.4 (11.1–15.1)
- **P value**
  - Placebo + CG: P = 0.420
  - Bevacizumab 7.5 mg/kg + CG: P = 0.93 (0.78–1.11)
  - Bevacizumab 15 mg/kg + CG: P = 1.03 (0.86–1.23)
- **HR versus placebo (95% CI)**
  - Placebo + CG: 0.75 (0.62 to 0.91)
  - Bevacizumab 7.5 mg/kg + CG: 0.93 (0.78–1.11)
  - Bevacizumab 15 mg/kg + CG: 1.03 (0.86–1.23)

**PP**

- **Number of deaths**
  - Placebo + CG: 202
  - Bevacizumab 7.5 mg/kg + CG: 207
  - Bevacizumab 15 mg/kg + CG: 194
- **Median time to event, months (95% CI)**
  - Placebo + CG: 13.7 (12.2–16.2)
  - Bevacizumab 7.5 mg/kg + CG: 14.1 (12.3–16.9)
  - Bevacizumab 15 mg/kg + CG: 14.5 (13.3–16.3)
- **P value**
  - Placebo + CG: P = 0.553
  - Bevacizumab 7.5 mg/kg + CG: P = 0.94 (0.78–1.14)
  - Bevacizumab 15 mg/kg + CG: P = 0.97 (0.80–1.18)

**14.5 vs 14.1 vs 13.7m**

Martin Reck et al, annals of onco 2010  
Martin Reck et al, JCO 2009
Meta-analysis of randomised, phase II/III trials adding bevacizumab to platinum-based chemotherapy as first-line

<table>
<thead>
<tr>
<th>Category</th>
<th>Dose 7.5 mg/kg</th>
<th>Dose 15 mg/kg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial</td>
<td>Bevacizumab</td>
<td>Control</td>
<td>O-E</td>
</tr>
<tr>
<td>AVF-0757g 7.5</td>
<td>18/32</td>
<td>17/32</td>
<td>0.8</td>
</tr>
<tr>
<td>AVAIL 7.5</td>
<td>233/345</td>
<td>240/347</td>
<td>-7.5</td>
</tr>
<tr>
<td>Subtotal</td>
<td>251/377</td>
<td>257/379</td>
<td>-6.8</td>
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<tr>
<td>AVF-0757g 15</td>
<td>16/34</td>
<td>17/32</td>
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<tr>
<td>ECOG 4599</td>
<td>335/434</td>
<td>363/444</td>
<td>-38.5</td>
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<tr>
<td>AVAIL 15</td>
<td>242/351</td>
<td>240/347</td>
<td>1.7</td>
</tr>
<tr>
<td>JO19907</td>
<td>66/117</td>
<td>33/58</td>
<td>-0.2</td>
</tr>
<tr>
<td>Subtotal</td>
<td>659/936</td>
<td>653/881</td>
<td>-36.0</td>
</tr>
<tr>
<td>Total</td>
<td>910/1313</td>
<td>910/1260</td>
<td>-42.7</td>
</tr>
</tbody>
</table>

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

Soria JC et al, annals of onco 2013
BRAIN study demonstrates encouraging efficacy and acceptable safety of bevacizumab with first-line paclitaxel and carboplatin in patients asymptomatic, untreated brain metastases

Besse. B et al, CCR 2015
AvaALL phase III: BVZ beyond PD

**Primary endpoint:** OS

**OS**
11.8 vs 10.2 months

**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
Bevacizumab improves OS when combined with paclitaxel/carboplatin regimens in patients with NSCC and PS 0–1 and, therefore, may be offered in the absence of contraindications in eligible patients with advanced NSCC [I, A].

Bevacizumab might therefore be considered with platinum-based regimens beyond paclitaxel/carboplatin in the absence of contraindications [II, B].

Treatment with bevacizumab has also shown encouraging efficacy and acceptable safety in patients with NSCC and asymptomatic, untreated brain metastases.

D. Planchard et al, Annals of Oncology 2018
Stage IV NSCC: Molecular tests negative (ALK/BRAF/EGFR/ROS1)

4-6 cycles
Platinum-based ChT:
- Cisplatin/gemcitabine [I, A]
- Cisplatin/docetaxel [I, A]
- Cisplatin/paclitaxel [I, A]
- Cisplatin/vinorelbine [I, A]
- Carboplatin/gemcitabine [I, A]
- Carboplatin/docetaxel [I, A]
- Carboplatin/paclitaxel [I, A]
- Carboplatin/vinorelbine [I, A]
- Cisplatin/pemetrexed [II, A]
- Carboplatin/pemetrexed [II, B]
- Carboplatin/nab-P [I, B]

+- bevacizumab [I, A with carboplatin/paclitaxel, otherwise III, B]

D. Planchard et al, Annals of Oncology 2018
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PARAMOUNT: Study Design

Induction Therapy
4 cycles, q21d

Continuation Maintenance Therapy
q21d until PD

Pemetrexed + Cisplatin

Pemetrexed + BSC

Placebo + BSC

CR/PR/SD per RECIST

R 2:1

Stratified for:
- PS (0 vs 1)
- Disease stage (IIIB vs IV) prior to induction
- Response to induction (CR/PR vs SD)

Primary endpoint: PFS

• Previously untreated
• PS 0/1
• Stage IIIB-IV NS-NSCLC
Continuation maintenance with pemetrexed is an effective and well tolerated treatment option for patients with advanced non-squamous NSCLC (PARAMOUNT trial)

Luis G. Paz-Ares et al, JCO 2013 and lancet onco 2012
AVAPERL: trial design*

Randomised, open-label, phase III study

Dose of bevacizumab = 7.5mg/kg; dose of pemetrexed = 500mg/m$^2$; dose of cisplatin = 75mg/m$^2$

RECIST-related endpoints measured from the pre-induction phase

Stratification factors
- Gender
- Smoking status
- Response at randomisation

Previously untreated stage IIIB–IV non-squamous NSCLC n=376

Bevacizumab + pemetrexed + cisplatin‡

First-line induction 4 cycles, q3w

Continuation maintenance q3w until PD

CR/PR/SD per RECIST§§

Follow-up

Bevacizumab n=125

Bevacizumab + pemetrexed n=128


‡Randomised, open-label, phase III study

§§§§

Dose of bevacizumab = 7.5mg/kg; dose of pemetrexed = 500mg/m$^2$; dose of cisplatin = 75mg/m$^2$

§§§§

RECIST-related endpoints measured from the pre-induction phase
Bevacizumab plus pemetrexed maintenance associated with a significant PFS benefit compared with bevacizumab alone (AVAPERL)

7.4 vs 3.7 mos

Barlesi F et al, JCO 2013
No benefit on overall survival (Updated survival analysis of AVAPERL trial)

Barlesi F et al, annals of onco 2014

19.8 vs 15.9m (HR: 0.88)
POINTBREAK: phase III trial of bevacizumab with pemetrexed

Previously untreated, stage IIIB or IV, non-squamous NSCLC, treated CNS mets, PS 0–1 (n=939)

Primary endpoint
OS

Secondary endpoints
ORR and DCR
PFS and TTP
safety and QoL

OS did not improve with the PemCBev regimen compared with the PacCBev regimen, although PFS was significantly improved with PemCBev.

12.6 versus 13.4 months; HR 1.00; P=0.949
IFCT-GFPC 0502 study design
Maintenance Gemcitabine or Erlotinib

**Observation**

- **IFCT-GFPC 0502 study design**
- **Maintenance Gemcitabine or Erlotinib**

**Progression:**
- 2nd line

**Primary endpoint:** PFS

**Cisplatin gemcitabine**
- N=834
- x 4 cycles
- N=464
- NSCLC
- Stage IIIB wet – IV
- PS 0-1
- 18-70 years
- Asymptomatic brain mets allowed

**Objective response or stable disease**

- PD: off

**Stratification factors:**
- gender
- histology: adenocarcinoma vs other histology
- smoking status: non-smokers vs current/former smokers
- center
- response vs stabilization to induction chemotherapy

**Maintenance treatment**

- Observation
  - N=155
  - PD
  - Pemetrexed

- Gemcitabine
  - N=154
  - PD
  - Pemetrexed

- Erlotinib
  - N=155
  - PD
  - Pemetrexed

**Tumor tissue**
- EGFR IHC
- EGFR mutation

**Objective response or stable disease**

*Stratification factors:
Continuation maintenance with gemcitabine significantly reduces disease progression with a non-significant OS improvement in pts treated with four cycles of cisplatin/gemcitabine.

3.8 vs 1.9 months

Perol. M et al, JCO 2012
Decision-making about maintenance therapy must take into account histology, residual toxicity after first-line ChT, response to platinum doublet, PS and patient preference.

Continuing pemetrexed following completion of four cycles of first-line cisplatin/pemetrexed ChT is, therefore, recommended in patients with NSCC, in the absence of progression after first-line ChT and upon recovery from toxicities from the previous treatment [I, A].

Continuation maintenance with gemcitabine significantly reduces disease progression with a non-significant OS improvement in patients with advanced NSCLC treated with four cycles of cisplatin/gemcitabine as first-line ChT [I, C].

D. Planchard et al, annals of onco 2018
Stage IV NSCC: Molecular tests negative (ALK/BRAF/EGFR/ROSI)

4-6 cycles
Platinum-based ChT:
- Cisplatin/gemcitabine [I, A]
- Cisplatin/docetaxel [I, A]
- Cisplatin/paclitaxel [I, A]
- Cisplatin/vinorelbine [I, A]
- Carboplatin/gemcitabine [I, A]
- Carboplatin/docetaxel [I, A]
- Carboplatin/paclitaxel [I, A]
- Carboplatin/vinorelbine [I, A]
- Cisplatin/pemetrexed [II, A]
- Carboplatin/pemetrexed [II, B]
- Carboplatin/nab-P [II, B]
+/- bevacizumab [I, A with carboplatin/paclitaxel, otherwise III, B]

Partial response or stable disease

Maintenance treatment:
- Pemetrexed (continuation) [I, A]
- Gemcitabine (continuation) [I, B]
- Pemetrexed (switch) [I, B]
+/- bevacizumab (if given before)
Chemotherapy first line NSCLC

- Chemotherapy benefit?
- How many agents?
- How many cycles?
- A best doublet?
- Cisplatin or carboplatin?
- Anti-EGFR association for SCC?
- Preferred treatment for NSCC?
- Addition of antiangiogenic?
- Maintenance benefit?
- For elderly patients?
- For PS2?
- And tomorrow...?
Elderly patients

In the early 2000s, based on several phase III trials, single-agent ChT over BSC was established as the standard of care for first-line therapy of advanced NSCLC patients aged > 70 years.

Overall survival not statistically significantly improved

Shinzoh Kudoh et al, JCO 2006
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

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

Vinorelbine or Gemcitabine*
Carboplatin + paclitaxel

Erlotinib 150 mg/d

*Choice of the center at the beginning of the study

Elisabeth Quoix et al, lancet 2011
First-line Treatment

| WEEKS | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 |
|-------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|
| ARM A | V | V | V | V | V | V | V | V | V | V  | V  | V  | V  | V  | V  | V  | V  | V  |
|       | G | G | G | G | G | G | G | G | G | G  | G  | G  | G  | G  | G  | G  | G  | G  |
| ARM B | C | P | P | C | P | P | C | P | P | C  | P  | P  | C  | P  | P  | C  | P  | P  |

**EVALUATION**

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

Choice of the center

Elisabeth Quoix et al, lancet 2011
Platinum-based doublet chemotherapy associated with survival benefits compared with vinorelbine or gemcitabine in elderly pts

mPFS 6.0 vs 2.8 m, HR: 0.51
mOS 10.3 vs 6.2 mo (HR 0.64, p<0.0001)

Toxic effects more frequent in the doublet chemotherapy (most frequent, decreased neutrophil count (48.4% vs 28 12.4%; asthenia 10.3% vs 5.8%).

Elisabeth Quoix et al, lancet 2011
The treatment effect for doublet chemotherapy was consistent across all subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR (95% CI)</th>
<th>p value for interaction</th>
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</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>
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<tr>
<td>PS 2 (n=123)*</td>
<td>0.63 (0.43–0.91)</td>
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<tr>
<td>Age ≤80 years (n=337)</td>
<td>0.68 (0.53–0.86)</td>
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<tr>
<td>Age &gt;80 years (n=114)</td>
<td>0.53 (0.36–0.80)</td>
<td>0.299</td>
</tr>
</tbody>
</table>

Elisabeth Quoix et al, Lancet 2011
Cisplatin or carboplatine: does it matter? Yes!
The Miles 3 and Miles 4 trials

PS 0-1
>70 years, median age 75
52 pts aged 80 and over (9.8%)
70% non-squamous
79% males
Advanced NSCLC

R

Pem or Gem
n = 268

Pem or Gem +
cisplatin 60 mg/m²
n = 263

Gridelli C J Clin Oncol 2018;36:2585-92
Addition of cisplatin to single-agent chemotherapy does not significantly prolong overall survival

- ORR: 15.5% (95%CI 11.2-20.6), cisplatin arm
- ORR: 8.5% (95%CI 5.4-12.5), monotherapy arm

Significantly more frequent and more severe hematologic, neurologic toxicity, mucositis, nausea and vomiting

Cisplatin too toxic for elderly compared to carboplatine!

Gridelli C J Clin Oncol 2018;36:2585-92
Benefit of Bevacizumab in elderly ...? No benefit, observed for bevacizumab-eligible patients who were 75 years or above

Pooled analysis of 2 phase III studies (E4599 and PointBreak):
A: overall survival of the pts aged <75
B: overall survival of the pts aged ≥ 75 years

8% grade 5 events in pts ≥ 75 years treated with Beva versus 2% for those treated with CT alone

Systematic review identified platinum-based combination ChT as the preferred option for patients > 70 years of age with PS 0–2. Addition of platinum agents resulted in improvement in OS (HR: 0.76), PFS (HR: 0.76) and ORR (RR: 1.57) compared with non-platinum containing therapy. Carboplatin associated with an OS benefit (HR: 0.67) whereas cisplatin was not (HR: 0.91)
Carboplatin-based doublet ChT is recommended in eligible elderly patients with PS 0–2 and with adequate organ function [I, A]

For those patients not eligible for doublet ChT, single-agent ChT remains the standard of care [I, B]
Chemotherapy first line NSCLC

- Chemotherapy benefit?
- How many agents?
- How many cycles?
- A best doublet?
- Cisplatin or carboplatin?
- Anti-EGFR association for SCC?
- Preferred treatment for NSCC?
- Addition of antiangiogenic?
- Maintenance benefit?
- For elderly patients?
- For PS2?
Combination chemotherapy with Carbo+Pem significantly improves survival in pts with ECOG PS of 2

2.8 vs 5.8 months (HR: 0.46; P<.001)
5.3 vs 9.3 months (HR: 0.62; P=.001)

Anemia (grade 3, 3.9%; grade 4, 11.7%) and neutropenia (grade 3, 1%; grade 4, 6.8%) more frequent with CP. Four treatment-related deaths in the CP arm.

Mauro Zukin et al, JCO 2013
Platinum-based doublets are superior to single-agent therapy in the 1st line treatment of PS2

significant increase in patients treated with platinum-based combination: grade 3–4 anemia (OR: 2.743), grade 3–4 neutropenia (OR: 7.239); grade 3–4 thrombocytopenia (OR: 12.881)
Therefore, **platinum-based (preferably carboplatin) doublets** should be considered in eligible PS 2 patients [I, A]

**Single-agent ChT** with gemcitabine, vinorelbine, docetaxel [I, B] or pemetrexed (restricted to NSCC) [II, B] is an alternative treatment option.

D. Planchard et al, *annals of onco* 2018
Poor PS (3–4) patients should be offered BSC in the absence of documented sensitising alterations such as EGFR mutations, ALK or ROS1 rearrangements or BRAF V600 mutation [III, B]
Chemotherapy first line NSCLC

- Chemotherapy benefit?
- How many agents?
- How many cycles?
- A best doublet?
- Cisplatin or carboplatin?
- Anti-EGFR association for SCC?
- Preferred treatment for NSCC?
- Addition of antiangiogenic?
- Maintenance benefit?
- For elderly patients?
- For PS2?
- And tomorrow…?
Treatment regimens evaluated in first-line NSCLC immunotherapy studies

Pablo Martinez et al, CCR 2019
Non-Squamous NSCLC

**KN-189**
- Pembrolizumab
- Carbo/Cisplatin + Pemetrexed

**Impower 150**
- Atezolizumab
- Carboplatin<sup>e</sup> + Paclitaxel + Bevacizumab<sup>e</sup>

**Impower 132**
- Atezolizumab
- Carboplatin or cisplatin + pemetrexed
- 4 or 6 cycles

**Impower 130**
- Atezolizumab
- Carboplatin + nab paclitaxel (CnP)

<table>
<thead>
<tr>
<th></th>
<th>OS</th>
<th>PFS</th>
<th>OS</th>
<th>PFS</th>
<th>OS</th>
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<tbody>
<tr>
<td>KN-189</td>
<td>X (HR: 0.49)</td>
<td>X (HR: 0.52)</td>
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<tr>
<td>Impower 150</td>
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<td>X (HR: 0.61)</td>
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<tr>
<td>Impower 132</td>
<td>- (HR: 0.81)</td>
<td>X (HR: 0.60)</td>
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<tr>
<td>Impower 130</td>
<td>X (HR: 0.79)</td>
<td>X (HR: 0.64)</td>
<td></td>
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</tbody>
</table>
**Pembrolizumab** in combination with pemetrexed and a platinum-based ChT should be considered a standard option in metastatic non-squamous NSCLC [I, A]

**Combination of atezolizumab and bevacizumab** with carboplatin and paclitaxel is a therapeutic option in patients with PS 0-1 with metastatic nonsquamous NSCLC, in the absence of contraindications to use of immunotherapy [I, A; not EMA-approved]

**Atezolizumab** in combination with pemetrexed and a platinum-based ChT is a therapeutic option in metastatic non-squamous NSCLC [I, B; not EMA-approved]
Squamous NSCLC

**KN-407**
- Pembrolizumab
- Carbo/Cisplatin + Pemetrexed

  - **OS**: X (HR:0.64)
  - **PFS**: X (HR:0.56)

**Impower 131**
- Atezolizumab
- Carboplatin + nab paclitaxel (CnP)

  - **OS**: - (HR:0.96)
  - **PFS**: X (HR:0.71)
Combination of pembrolizumab and carboplatin with paclitaxel or nab-P is a standard choice in patients with metastatic squamous NSCLC
[I, A; not EMA approved]

The use of atezolizumab with nab-PC today represents an option in patients with metastatic squamous NSCLC
[I, B; not EMA-approved]

D. Planchard et al, Annals of Onco 2018
Adding Carboplatin and Pemetrexed to gefitinib for first line EGFR-mutated NSCLC (NEJ009)

Stratified by sex, stage, type of EGFR mutation, and smoking history

A. Nakamura et al, ASCO 2018
Adding Carboplatine and Pemetrexed to gefitinib significantly improves PFS and OS

Gefitinib combined with carboP and pemetrexed may be an effective treatment option for first line of EGFR-mutated NSCLC

A.Nakamura et al, ASCO 2018
Addition of carboplatin and pemetrexed to gefitinib represents a first-line option in patients with EGFR-mutated tumours [I, B; not EMA-approved]
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THANK YOU

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