TREATMENT OF ADVANCED NSCLC IN THE ELDERLY
An update

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Most cancer patients are aged >65 years

Proportion of patients aged >65 years with selected tumour (%)

Ovary: 46.3%
Breast: 48.2%
NHL: 51.2%
Corpus uteri: 55.4%
Leukaemia’s: 56.2%
Combined: 59.7%
Lung and bronchus: 62.7%
Rectum: 66%
Stomach: 68.5%
Urinary bladder: 69.9%
Pancreas: 71.8%
Colon: 73.8%
Prostate: 80.9%

More than 40% of lung cancer patients are over 70 years.

Cardiovascular/pulmonary comorbidities and lung cancer linked to tobacco smoking

DISEASE PREVALENCE IN THE ELDERLY

Population 65 years and older (%)

- Stroke: 7%
- Depression: 10%
- Alzheimer’s: 10%
- Diabetes: 13%
- Heart disease: 31%
- Hypertension: 40%
- Arthritis: 49%

Centers for Disease Control and Prevention/National Center for Health Statistics. Current Estimates from the National Health interview Survey 1995; Report 199
ORGAN FUNCTION DECLINES WITH AGE

Cardiovascular function
- Decreased elasticity of arterial system
- Loss of myocytes and atrial pacemaker cells
- Increased fibrosis of cardiac fibrous skeleton

Renal function
- Decreased renal blood flow
- Decreased glomerular filtration rate
- Decreased creatinine clearance

Hepatic function
- Reduced hepatic blood flow
- Decline in cytochrome P450 system

Bone marrow function
- Reduction of hematopoietic reserve

Renal and cardiac function key issues for cisplatin-based chemotherapy and related hydration

DOMAINS OF GERIATRIC ASSESSMENT
CHRONOLOGICAL VS. BIOLOGICAL AGE

Function
- Performance status (PS)
- Activities of daily living (ADL)
- Instrumental activities of daily living (IADL)
- Advanced activities of daily living (AADL)

Comorbidity
- Comorbidity scales (Charlon; CIRS)

QoL
- Disease-specific questionnaires

Cognition
- Folstein Minimental Status

Emotions
- Geriatric Depression Scale (GDS)

Social support network
Polypharmacy
Nutrition
A systematic review analysed 73 studies on geriatric assessment in cancer patient. The analysis showed that the assessment is feasible\(^1\).

A Phase 3 customised trial evaluating the impact of a CGA on decision making and treatments allocation did not show a superiority of this strategy in patients survival but slightly reduced treatment toxicity\(^2\).

There is limited evidence that it impacted treatment decision making.

Further research examining the effectiveness of geriatric assessment on treatment decision and outcome is needed.

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Treatment of Advanced Non–Small-Cell Lung Cancer in the Elderly: From Best Supportive Care to the Combination of Platin-Based Chemotherapy and Targeted Therapies

Cesare Gridelli, Division of Medical Oncology, “S.G. Moscati” Hospital, Avellino, Italy
Overall survival

Log-rank test: p=0.03
Cox model: p=0.02

Vinorelbine
MS = 6.5 months

Supportive care
MS = 4.8 months

EORTC LC-13: QoL analysis

Estimated effect of vinorelbine with 95% CI

Dyspnoea
Cough
Haemoptysis
Sore mouth
Swallowing trouble
Neuropathy
Hair loss
Pain in chest
Pain in shoulder
Pain elsewhere
Analgesics

A Phase 3 randomised trial comparing vinorelbine vs. docetaxel showed no statistically significant difference in terms of survival.

Response rate and progression-free survival were superior in docetaxel arm (22.9% and 7%; 5.4 and 3.1 months)

MILES STUDY

Vinorelbine
30 mg/m²
D1, D8

Gemcitabine
1200 mg/m²
D1, D8

Gemcitabine + Vinorelbine
NVB: 25 mg/m²
D1, D8
Gem: 1000 mg/m²
D1, D8

Overall survival

- Navelbine
- Gemcitabine
- Navelbine + Gemcitabine

Several retrospective analyses of elderly patients included in large Phase 3 randomised trial without upper limit age have been performed.

The analyses showed that platin-based chemotherapy is feasible in the elderly population with the same outcomes observed in their younger counterpart but with increased toxicity.

These analyses are at high risk of selection bias.
# Retrospective Analyses of Phase 3 Trials on Advanced NSCLC Elderly Patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Group</th>
<th>Trial No.</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Langer, 2000</td>
<td>ECOG</td>
<td>5592</td>
<td>PE vs. PTax vs. PTax+G-CSF</td>
</tr>
<tr>
<td>Kelly, 2001</td>
<td>SWOG</td>
<td>9308-9509</td>
<td>P vs. PV/PV vs. CbTax</td>
</tr>
<tr>
<td>Lilienbaum, 2002</td>
<td>CALGB</td>
<td>9730</td>
<td>Tax vs. CbTax</td>
</tr>
<tr>
<td>Langer, 2003</td>
<td>ECOG</td>
<td>1594</td>
<td>PTax vs. CbTax vs. PG vs. PTxt</td>
</tr>
<tr>
<td>Fossella, 2003</td>
<td>TAX</td>
<td>326</td>
<td>PV vs. PTxt vs. CbTxt</td>
</tr>
</tbody>
</table>
Several Phase 2 studies of cisplatin-based regimens using attenuated doses of drugs or special weekly schedules have been performed.

Interesting results and feasible toxicity profiles have been observed.

The results need to be confirmed in large Phase 3 randomised trials.
## CISPLATIN-BASED CHEMOTHERAPY WITH SPECIAL DOSES OR SCHEDULE

In advanced NSCLC elderly patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Drugs</th>
<th>Patients (n)</th>
<th>% OR</th>
<th>MS (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feliu, 2003</td>
<td>CDDP+GEM*</td>
<td>46</td>
<td>35</td>
<td>10.2</td>
</tr>
<tr>
<td>Lippe, 2000</td>
<td>CDDP+GEM**</td>
<td>15</td>
<td>40</td>
<td>-</td>
</tr>
<tr>
<td>Berardi, 2003</td>
<td>CDDP+GEM***</td>
<td>48</td>
<td>31.8</td>
<td>9</td>
</tr>
<tr>
<td>Mattioli, 2002</td>
<td>CDDP+VNR***</td>
<td>33</td>
<td>48</td>
<td>11</td>
</tr>
<tr>
<td>Ohe, 2004</td>
<td>CDDP+TXT***</td>
<td>33</td>
<td>52</td>
<td>15.8</td>
</tr>
<tr>
<td>Feliu, 2008</td>
<td>CDDP+TXT*</td>
<td>42</td>
<td>31</td>
<td>8.9</td>
</tr>
<tr>
<td>Gridelli, 2008a</td>
<td>CDDP+VNR# vs.</td>
<td>61</td>
<td>36</td>
<td>8.2</td>
</tr>
<tr>
<td></td>
<td>CDDP+GEM$</td>
<td>60</td>
<td>43</td>
<td>10.9</td>
</tr>
</tbody>
</table>

a. Phase 2 randomised trial; *CDDP 50 mg/m² q21; **CDDP 35 mg/m² weekly; ***CDDP 25 mg/m² weekly; #CDDP 40 mg/m² q21; CDDP 60 mg/m² q21.
CISPLATIN PLUS GEMCITABINE OR VINORELBINE
For elderly patients with advanced NSCLC: The MILES-2P Studies

ABSTRACT

Purpose
Two phase I/II trials were done to evaluate the feasibility of cisplatin combined with gemcitabine or vinorelbine in elderly patients with advanced non-small-cell lung cancer (NSCLC).

Patients and Methods
Patients with advanced NSCLC who were older than 70 years of age and who had a performance status of 0 to 1 were eligible. Cisplatin was given on day 1 (a starting dose of 50 mg/m² with increasing increments of 10 mg/m² at each level) and gemcitabine (1,000 mg/m²) or vinorelbine (25 mg/m²) on days 1 and 8. Cycles were repeated every 21 days. A two-stage flexible optimal design was applied in the phase II study, and unacceptable toxicity was the primary end point.

Results
Overall, 159 patients were enrolled: 38 in phase I and 121 in phase II studies. Cisplatin was feasible at 60 mg/m² with gemcitabine and at 40 mg/m² with vinorelbine. With the former combination, 50 of 60 (83.3%) patients were treated without unacceptable toxicity; objective responses were reported in 26 of 60 patients (43.5%; 95% CI, 30.6 to 56.8); median progression-free and overall survivals were 25.3 and 43.6 weeks, respectively. With the latter combination, 50 (82.0%) of 61 patients were treated without unacceptable toxicity; objective responses were reported in 22 of 61 patients (36.1%; 95% CI, 24.2 to 49.4); median progression-free and overall survivals were 21.1 and 33.1 weeks, respectively.

Conclusion
Both cisplatin (60 mg/m²) plus gemcitabine and cisplatin (40 mg/m²) plus vinorelbine are feasible and active in the treatment of elderly patients with advanced NSCLC. The former combination, which provides a higher dose of cisplatin, deserves comparison versus single-agent chemotherapy in this setting of patients.
## MILES-2: RESULTS

<table>
<thead>
<tr>
<th></th>
<th>CDDP 40 mg/m² + VIN</th>
<th>CDDP 60 mg/m² + GEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>61</td>
<td>60</td>
</tr>
<tr>
<td>Patients with unacceptable toxicity during cycles 1–3, n/N (%)</td>
<td>11/61 (18.1%)</td>
<td>10/60 (16.7%)</td>
</tr>
<tr>
<td>Response rate, %</td>
<td>36.1 (24.-%–49.4)</td>
<td>43.3 (30.%, 56.%)</td>
</tr>
<tr>
<td>Median PFS, weeks (95% CI)</td>
<td>21.1 (15.9, 28.4)</td>
<td>25.3 (22., 632.0)</td>
</tr>
<tr>
<td>Median OS, weeks (95% CI)</td>
<td>33.1 (23.1, 57.7)</td>
<td>43.6 (35.0, 56.3)</td>
</tr>
</tbody>
</table>
JCOG 0803/WJOG 4307L PHASE 3 TRIAL IN ADVANCED NSCLC ELDERLY PATIENTS

- Age >70 years
- IIIB-IV NSCLC
- PS 0–1

Weekly docetaxel
- DOC 60 mg/m²
- Day 1
- Every 3 weeks

Weekly CDDP + docetaxel
- CDDP 25 mg/m²
- DOC 20 mg/m²
- Day 1, 8, 15
- Every 4 weeks

### JCOG 0803/WJOG 4307L
STOPPED AT FIRST PLANNED INTERIM ANALYSIS

<table>
<thead>
<tr>
<th></th>
<th>Taxotere</th>
<th>CDDP + Taxotere</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>137</td>
<td>139</td>
</tr>
<tr>
<td>Toxic deaths, n</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>17.3</td>
<td>13.3</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.55 (0.976, 2.485)</td>
<td></td>
</tr>
<tr>
<td>Probability CDDP + TXT superior to TXT at final analysis, %</td>
<td>0.966</td>
<td>–</td>
</tr>
</tbody>
</table>
**IFCT TRIAL: STUDY SCHEME**

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

- **Vinorelbine or Gemcitabine**
- **Carboplatin + Paclitaxel**

- **Erlotinib** 150 mg/d

*Choice of the centre at the beginning of the study; **In case of PD or excessive toxicity; ^CBDCA AUC 6 d1;Taxol 90 mg/m² d1-8-15/q28.*

## RESPONSE RATE

<table>
<thead>
<tr>
<th></th>
<th>Single Agent Arm A (n=211)</th>
<th>Doublet Arm B (n=210)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>23 (10.9%)</td>
<td>61 (29.05%)</td>
<td>&lt;10⁻⁵</td>
</tr>
<tr>
<td>ST</td>
<td>96 (45.5%)</td>
<td>81 (38.57%)</td>
<td>0.18</td>
</tr>
<tr>
<td>DCR (PR + ST)</td>
<td>119 (56.4%)</td>
<td>142 (67.62%)</td>
<td>0.02</td>
</tr>
<tr>
<td>PD</td>
<td>46 (21.8%)</td>
<td>15 (7.14%)</td>
<td>&lt;10⁻⁴</td>
</tr>
<tr>
<td>Not reported</td>
<td>15 (7.11%)</td>
<td>20 (9.53%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Withdrawal before 1st evaluation*</td>
<td>31 (14.7%)</td>
<td>33 (15.7%)</td>
<td>0.88</td>
</tr>
</tbody>
</table>

OVERALL SURVIVAL

Survival probability

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

- **Doublet**
  - MST = 6.2 months (95% CI 5.3–7.4)
  - 1-year survival 26.9% (95% CI 21–33.1)
  - \( p = 0.00004 \)

### Haematological Toxicity

<table>
<thead>
<tr>
<th>Grade 3–4, n(%)</th>
<th>Arm A Single agent</th>
<th>Arm B Doublet</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gem n=149</td>
<td>VNR n=61</td>
<td>All n=210</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>7 (4.7)</td>
<td>23 (37.7)</td>
<td>30 (14.3)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0 (0)</td>
<td>6 (9.84)</td>
<td>6 (2.9)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>3 (2.01)</td>
<td>6 (9.84)</td>
<td>9 (4.3%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2 (1.34)</td>
<td>0 (0)</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

## NON-HAEMATOLOGICAL TOXICITY

<table>
<thead>
<tr>
<th>Grade 3–4, n (%)</th>
<th>Arm A Single agent</th>
<th>Arm B Doublet</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gem n=149</td>
<td>VNR n=61</td>
<td>All n=210</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>9 (6.04)</td>
<td>4 (6.56)</td>
<td>13 (6.2)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2 (1.34)</td>
<td>0 (0)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>1 (0.67)</td>
<td>1 (1.64)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (0.67)</td>
<td>0 (0)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3 (2.01)</td>
<td>1 (1.64)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Reduced general condition</td>
<td>1 (0.67)</td>
<td>2 (3.28)</td>
<td>3 (1.5)</td>
</tr>
</tbody>
</table>

## DEATHS

<table>
<thead>
<tr>
<th>n, (%)</th>
<th>Arm A single agent (n=168)</th>
<th>Arm B doublet (n=143)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxic deaths</td>
<td>3 (1.83)</td>
<td>9 (6.62)</td>
<td>0.035</td>
</tr>
<tr>
<td>Cancer</td>
<td>149 (90.90)</td>
<td>112 (82.40)</td>
<td></td>
</tr>
<tr>
<td>Intercurrent disease</td>
<td>8 (4.88)</td>
<td>14 (10.30)</td>
<td></td>
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<tr>
<td>Unknown</td>
<td>4 (2.44)</td>
<td>1 (0.74)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>
“In clinical practice, particularly in patients with metastatic disease, frequent diagnosis is performed by fine needle aspiration biopsy (FNAB) that produces a general cytological NSCLC diagnosis. When possible, we should always try to obtain a tumour sample tissue for a subtype of histological diagnosis, even using more invasive approaches. In a future era of treatments guided by molecular biomarkers, this will be mandatory, though waiting to obtain a molecular characterisation of circulating tumour cells that may provide a non-invasive strategy. However, to date, we need a sure diagnosis in order to administer a well-tolerated and optimal treatment to our patients.”
NON-SQUAMOUS NSCLC: CIS/PEM
PRE-PLANNED SUBSET ANALYSIS
OS: cis/pem vs. cis/gem (Phase 3)

Phase 3 PC vs. GC Trial: Study Design

1st line treatment for advanced NSCLC

- Pemetrexed 500 mg/m² + Cisplatin 75 mg/m²
- Gemcitabine 1250 mg/m² d1, 8 + Cisplatin 75 mg/m²

Q3 weeks x 6 cycles

N=1725

Primary endpoint: OS (non-inferiority)
Secondary endpoints: RR, response duration, PFS, TTP, TTF, Tox

Pemetrexed therapy in elderly patients with good performance status: Analysis of two Phase 3 trials of patients with nonsquamous NSCLC

Study Treatment Period

Induction Therapy (4 cycles) 21 to 42 Days
Maintenance Therapy (Until PD)

Patients enrolled if:
- Nonsquamous NSCLC
- No prior systemic treatment for lung cancer
- ECOG PS 0/1

CR, PR, SD

500 mg/m² Pemetrexed + 75 mg/m² Cisplatin, d1, q21d

500 mg/m² Pemetrexed + BSC, d1, q21d

2:1 Randomisation

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

- Folic acid and vitamin B12 administered to both arms

Progression

Primary objective: PFS
Secondary objectives: OS, RR, QoL, resource utilisation and AEs

The efficacy and safety of pemetrexed treatment was evaluated in elderly patients with nonsquamous NSCLC and PS 0-1. Data from two large randomised studies were retrospectively analysed for patients <65 years, ≥65 years, and <70 years, ≥70 years. Safety and efficacy were similar between older and younger groups. Pemetrexed (first-line treatment combined with cisplatin or as a maintenance therapy) is a viable treatment option for these patients

MILES 3 (all histologies)

- **Gemcitabine**
  - GEM 1200 mg/m² d1, 8, q21

- **Gemcitabine + Cisplatin**
  - GEM 1000 mg/m² d1, 8, q21
  - CIS 60 mg/m² d1, q21

MILES 4 (non-squamous only)

- **Gemcitabine**
  - GEM 1200 mg/m² d1, 8, q21

- **Gemcitabine + Cisplatin**
  - GEM 1000 mg/m² d1, 8, q21
  - CIS 60 mg/m² d1, q21

- **Pemetrexed**
  - PEM 500 mg/m² d1, q21

- **Pemetrexed + Cisplatin**
  - PEM 500 mg/m² d1, 8, q21
  - CIS 60 mg/m² d1, q21
# Cisplatin-Based First-Line Treatment of Elderly Patients With Advanced Non–Small-Cell Lung Cancer: Joint Analysis of MILES-3 and MILES-4 Phase III Trials

Cesare Gridelli, Alessandro Morabito, Luigi Cavaiana, Andrea Luciani, Paolo Maione, Laura Bonanno, Virginia Filippazzi, Silvana Leo, Saverio Cintieri, Fortunato Cardillo, Marco Angelo Burgio, Domenico Bilancia, Diego Cortinovis, Francesco Rosetti, Roberto Bianco, Vittorio Gribia, Fabrizio Artioli, Roberto Bordonaro, Vittorio Fregoni, Manlio Mencoboni, Fabrizio Nelli, Ferdinando Ricardi, Giuditta di Isernia, Raffaele Costanzo, Giansanto Rocco, Gennaro Daniele, Simona Signorillo, Maria Carmela Piccirillo, Ciro Gallo, and Francesco Perrone

<table>
<thead>
<tr>
<th></th>
<th>Monotherapy</th>
<th>Platinum-doublet</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible, n/N</td>
<td>260/268</td>
<td>246/263</td>
<td></td>
</tr>
<tr>
<td>Responders (CR+PR), n (%) (95% CI)</td>
<td>22 (8.5) (5.4, 12.5)</td>
<td>38 (15.5) (11.2, 20.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>CR</td>
<td>1 (0.4)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>21 (8.1)</td>
<td>38 (15.5)</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>63 (24.2)</td>
<td>61 (24.8)</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>175 (65.3)</td>
<td>147 (55.9)</td>
<td></td>
</tr>
</tbody>
</table>

*Mantel-Haenszel estimate controlling for trial, histotype and non-platinum companion drug.

Cisplatin-Based First-Line Treatment of Elderly Patients With Advanced Non–Small-Cell Lung Cancer: Joint Analysis of MILES-3 and MILES-4 Phase III Trials

Cesare Gridelli, Alessandro Morabito, Luigi Cavanna, Andrea Luciani, Paolo Maione, Laura Bonanno, Virgilio Filippazzi, Silvana Leo, Saverio Cintieri, Fortunato Ciardiello, Marco Angelo Burgio, Domenico Bilancia, Diego Cortinovis, Francesco Rosetti, Roberto Bianco, Vittorio Gelbisa, Fabrizio Arrioli, Roberto Bordone, Vittorio Fregoni, Manlio Mencoboni, Fabrizio Nelli, Ferdinando Ricardi, Giuditta di Isernia, Raffaele Costanzo, Gaetano Rocco, Gennaro Daniele, Simona Signorillo, Maria Carmela Piccirillo, Ciro Gallo, and Francesco Perrone

![Graphs showing overall survival and progression-free survival](image-url)
CONCLUSIONS

Although improving PFS and response rate, addition of cisplatin to single-agent chemotherapy failed to significantly prolong the overall survival of elderly patients with advanced NSCLC.

Severe haematological toxicity, fatigue and anorexia were worse with cisplatin-based chemotherapy.
IFCT-1201 MODEL TRIAL
Randomised, comparative Phase 3 trial

- Histological or cytological diagnosis of NSCLC
- With Stage IIIIB unresectable and non-irradiable or Stage IV
- Without EGFR/ALK mutations (or unknown)
- Measurable disease (RECIST 1.1)
- Age ≥70 years and <90 years
- MMS >23
- PS 0-2

Induction
Weekly paclitaxel
Monthly carboplatine x4 cycles

R 1:1
Responding or stabilised pts

Arm A – Follow-up
Non-squamous
Pemetrexed
Squamous
Gemcitabine

Arm B – Maintenance
Carboplatine: AUC 6 D1=D29
Paclitaxel: 90 mg/m^2, D1=D8=D22
Gemcitabine 1150 mg/m^2 D1=D8=D22
Pemetrexed 500 mg/m^2 D1=D22

Quoix E, et al. Abstract #3420. Presented at ESMO 2018. Reproduced with permission from Dr E Quoix
EFFICACY: OS/PFS OF THE 328 RANDOMISED PATIENTS (AFTER INDUCTION)

Median OS, 95% CI:
14.1 [12.0-17.0], events = 134, censored = 32
14.0 [10.9-16.9], events = 125, censored = 37
ρ=0.72

HR (not adjusted) = 0.96 [0.75-1.22]; ρ=0.72
HR (adjusted) = 0.91 [0.71-1.16]; ρ=0.45

Median PFS, 95% CI:
2.7 [2.6-3.1], events = 160, censored = 6
5.7 [4.8-7.1], events = 135, censored = 27
ρ<0.001

HR (not adjusted) = 0.52 [0.41-0.66]; ρ<0.001
HR (adjusted) = 0.51 [0.40-0.64]; ρ<0.001

Data cut-off: July 01, 2018
Database export: August 20, 2018

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OUTCOMES FOR ELDERLY A-NSCLC PTS (28%)

Treated with bevacizumab + carboplatin and paclitaxel:
Retrospective analysis of ECOG 4599 Trial

**Conclusion:** In elderly NSCLC patients, PCB was associated with a higher degree of toxicity, but no obvious improvement in survival compared with PC. Data from this unplanned, retrospective analysis justify prospective evaluation of the therapeutic index of PCB regimen in elderly patients.
ISOLATING THE ROLE OF BEVACIZUMAB IN ELDERLY PATIENTS

With previously untreated nonsquamous non-small-cell lung cancer

Secondary analyses of the ECOG 4599 and PointBreak Trials

Median OS in patients <75 years was 13.4 months with PC + Bev vs. 10.2 months with PC (HR, 0.78; 95% CI: 0.68, 0.89)

Median OS in patients ≥75 years was 9.6 months with PC + Bev vs. 13.0 months with PC (HR, 1.05; 95% CI, 0.70–1.57)
PHASE 2 STUDY OF FIRST-LINE GEFITINIB IN ELDERLY PATIENTS

With advanced NSCLC harbouring EGFR mutation

Thirty-one elderly patients over 75 years affected by advanced NSCLC harbouring an activating EGFR mutation received first-line gefitinib

The treatment was well tolerated and showed similar results compared with younger patients included in Phase 3 randomised trials

Response rate: 74%; PFS:12.1 mos; OS: 33.8 mos

OSIMERTINIB IN ELDERLY PATIENTS
With epidermal growth factor receptor T790M-Positive Non-Small-Cell Lung Cancer who progressed during prior treatment: A Phase 2 Trial

<table>
<thead>
<tr>
<th>Primary assessment method</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title</td>
<td></td>
</tr>
<tr>
<td>Number of patients enrolled</td>
<td>36</td>
</tr>
<tr>
<td>Number of patients evaluable for toxicity</td>
<td>36</td>
</tr>
<tr>
<td>Number of patients evaluated for efficacy</td>
<td>36</td>
</tr>
<tr>
<td>Evaluation method</td>
<td></td>
</tr>
<tr>
<td>Response Assessment CR</td>
<td>n=1</td>
</tr>
<tr>
<td>Response Assessment PR</td>
<td>n=20</td>
</tr>
<tr>
<td>Response Assessment SD</td>
<td>n=14</td>
</tr>
<tr>
<td>Response Assessment PD</td>
<td>n=1</td>
</tr>
<tr>
<td>Response Assessment OTHER</td>
<td>n=0</td>
</tr>
</tbody>
</table>

Lessons learned
- Non-small-cell lung cancer (NSCLC) represents 85% of lung cancer in elderly patients.
- In the present study performed in the 36 elderly subjects with epidermal growth factor receptor (EGFR) T790M mutation-positive NSCLC, osimertinib 80 mg demonstrated statistically significant improvement in the objective response rate, which was comparable to those in the nonelderly population.
- Osimertinib appears to be an effective and safe treatment option in elderly patients with advanced NSCLC with EGFR mutation; further research in larger scale is warranted.

PHASE 3 STUDY OF FIRST-LINE OSIMERTINIB VS. GEFITINIB OR ERLOTINIB

Final analysis: Overall survival

PHASE 3 STUDY OF FIRST-LINE
OSIMERTINIB VS. GEFTINIB OR ERLOTINIB

In EGFR positive NSCLC: Confirmed efficacy and no safety concerns in the elderly

Overall survival across subgroups

**PHASE 3 STUDY OF FIRST-LINE CRIZOTINIB VS. CISPLATIN+PEMETREXED**

In ALK positive NSCLC: Confirmed efficacy and no safety concerns in the elderly

**Progression-free survival, according to subgroups**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crizotinib vs. chemotherapy</td>
<td>343</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤65 yr</td>
<td>35</td>
<td>0.45 (0.35–0.60)</td>
</tr>
<tr>
<td>&gt;65 yr</td>
<td>308</td>
<td>0.37 (0.17–0.77)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker or former smoker</td>
<td>125</td>
<td>0.53 (0.36–0.76)</td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>218</td>
<td>0.33 (0.12–0.63)</td>
</tr>
<tr>
<td>Time since diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 yr</td>
<td>35</td>
<td>0.44 (0.30–0.65)</td>
</tr>
<tr>
<td>&lt;1 yr</td>
<td>288</td>
<td>0.44 (0.30–0.65)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>324</td>
<td>0.43 (0.29–0.68)</td>
</tr>
<tr>
<td>0 or 1</td>
<td></td>
<td>0.27 (0.16–0.45)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>322</td>
<td>0.41 (0.28–0.61)</td>
</tr>
<tr>
<td>No</td>
<td>21</td>
<td>0.49 (0.27–0.86)</td>
</tr>
<tr>
<td>Type of disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic</td>
<td>336</td>
<td>0.48 (0.37–0.63)</td>
</tr>
<tr>
<td>Locally advanced</td>
<td>7</td>
<td>0.54 (0.37–0.79)</td>
</tr>
<tr>
<td>Brain metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>92</td>
<td>0.57 (0.35–0.93)</td>
</tr>
<tr>
<td>No</td>
<td>251</td>
<td>0.44 (0.24–0.73)</td>
</tr>
</tbody>
</table>

PHASE 3 STUDY OF FIRST-LINE ALECTINIB VS. CRIZOTINIB

In ALK positive NSCLC: Confirmed efficacy and no safety concerns in the elderly for the new standard alectinib

Progression-free survival

Subgroup analysis

“While there are no elderly-specific trials, this review attempts to look at the current available data from a geriatric oncology perspective. We reviewed data from Phase III studies that led to newly approved indications of checkpoint inhibitors in NSCLC, melanoma, and renal cell cancer. Data were reviewed with respect to response, survival, and toxicity according to three groups: <65 years, 65–75 years, and >75 years. Current literature does not allow one to draw definite conclusions regarding the role of immune checkpoint inhibitors in older adults. However, they may offer a potentially less toxic but equally efficacious treatment option for the senior adult oncology patient.”
INNATE IMMUNOSENESCENCE

Neutrophils in the aged
Preserved
- Number (in healthy elderly)
- Adherence
- TLR expression

Reduced
- Chemotaxis
- Phagocytosis
- Superoxide production
- Molecules recruitment into lipid raft
- Signal transduction
- Apoptosis

Macrophages in the aged
Preserved
- Number (altered subsets)

Reduced
- Chemotaxis
- Phagocytosis
- Superoxide production
- Signal transduction
- Apoptosis
- TLR expression and function
- MHC class II expression
- Cytokine production

Increased
- PGE2 production

Dendritic cells in the aged

pDC:
- Decreased IFN-α/β production
- Decreased antigen presentation

mDC:
- Decreased TLR-mediated signaling
- Decreased antigen presentation
- Decreased chemotaxis and endocytosis

CHECKMATE 057 (NCT01673867) STUDY DESIGN

- Stage IIIb/IV non-SQ NSCLC
- Pretreatment (archival or recent) tumour samples required for PD-L1
- ECOG PS 0–1
- Failed 1 prior platinum doublet
- Prior maintenance therapy allowed
- Prior TKI therapy allowed for known ALK translocation or EGFR mutation

N=582

- Nivolumab
  - 3 mg/kg IV q2w until PD or unacceptable toxicity
  - n=292

- Docetaxel
  - 75 mg/m² IV q3w until PD or unacceptable toxicity
  - n=290

Patients stratified by prior maintenance therapy and line of therapy (second- vs third-line)

Primary endpoint
- OS

Additional endpoints
- ORR
- PFS
- Safety
- Efficacy by tumour PD-L1 expression
- Quality of life (LCSS)

PD-L1 expression measured using the Dako/BMS automated IHC assay
- Fully validated with analytical performance having met all predetermined acceptance criteria for sensitivity, specificity, precision, and robustness

**Footnotes:**

- Maintenance therapy included pemetrexed, bevacizumab, or erlotinib (not considered a separate line of therapy).
- Per RECIST v1.1 criteria as determined by the investigator.

OVERALL SURVIVAL

### Treatment Effect on OS in Predefined Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>Unstratified HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>582</td>
<td>0.75 (0.62, 0.91)</td>
</tr>
<tr>
<td><strong>Age categorisation (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>339</td>
<td>0.81 (0.62, 1.04)</td>
</tr>
<tr>
<td>≥65 and &lt;75</td>
<td>200</td>
<td>0.63 (0.45, 0.89)</td>
</tr>
<tr>
<td>≥75</td>
<td>43</td>
<td>0.90 (0.43, 1.87)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>319</td>
<td>0.73 (0.56, 0.96)</td>
</tr>
<tr>
<td>Female</td>
<td>263</td>
<td>0.78 (0.58, 1.04)</td>
</tr>
<tr>
<td><strong>Baseline ECOG PS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>179</td>
<td>0.64 (0.44, 0.93)</td>
</tr>
<tr>
<td>≥1</td>
<td>402</td>
<td>0.80 (0.63, 1.00)</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current/former smoker</td>
<td>458</td>
<td>0.70 (0.56, 0.86)</td>
</tr>
<tr>
<td>Never smoked</td>
<td>118</td>
<td>1.02 (0.64, 1.61)</td>
</tr>
<tr>
<td><strong>EGFR mutation status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>82</td>
<td>1.18 (0.69, 2.00)</td>
</tr>
<tr>
<td>Not detected</td>
<td>340</td>
<td>0.66 (0.51, 0.86)</td>
</tr>
<tr>
<td>Not reported</td>
<td>160</td>
<td>0.74 (0.51, 1.06)</td>
</tr>
</tbody>
</table>
FDA SUBSET ANALYSIS OF THE SAFETY OF NIVOLUMAB
In elderly patients with advanced cancers

Adverse events by age in patients treated with nivolumab

<table>
<thead>
<tr>
<th></th>
<th>Patients &lt;65 yrs (n=616), n (%)</th>
<th>Patients ≥65 yrs (n=414), n (%)</th>
<th>Patients ≥70 yrs (n=212), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1–2 adverse events</td>
<td>584 (94.8)</td>
<td>394 (95.2)</td>
<td>202 (95.3)</td>
</tr>
<tr>
<td>Grade 3–5 adverse events</td>
<td>360 (58.4)</td>
<td>259 (62.6)</td>
<td>152 (71.7)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>313 (50.8)</td>
<td>242 (58.5)</td>
<td>123 (58.0)</td>
</tr>
<tr>
<td>All adverse events leading to discontinuation</td>
<td>89 (14.4)</td>
<td>71 (17.1)</td>
<td>42 (19.8)</td>
</tr>
<tr>
<td>AEs requiring treatment with immune modulating medication</td>
<td>256 (41.5)</td>
<td>196 (47.3)</td>
<td>110 (51.9)</td>
</tr>
</tbody>
</table>

Select irAEs where immune modulating medication was initiated

<table>
<thead>
<tr>
<th></th>
<th>Patients &lt;65 yrs, n (%)</th>
<th>Patients ≥65 yrs, n (%)</th>
<th>Patients ≥70 yrs, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea/colitis</td>
<td>15 (2.4)</td>
<td>17 (4.1)</td>
<td>11 (5.2)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>23 (3.7)</td>
<td>8 (1.9)</td>
<td>5 (2.4)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>8 (1.3)</td>
<td>3 (0.7)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Nephritis and renal dysfunction</td>
<td>6 (1.0)</td>
<td>8 (1.9)</td>
<td>7 (3.3)</td>
</tr>
<tr>
<td>Rash</td>
<td>47 (7.6)</td>
<td>34 (8.2)</td>
<td>22 (10.4)</td>
</tr>
</tbody>
</table>

irAEs, immune-related adverse events.

Non-small lung cancer (CA209057 and CA209017)
Advanced renal cell cancer (CA209025)
Melanoma (CA209066)
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In elderly patients with advanced cancers

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<tr>
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<td>1 (0.5)</td>
</tr>
<tr>
<td>Nephritis and renal dysfunction</td>
<td>6 (1.0)</td>
<td>8 (1.9)</td>
<td>7 (3.3)</td>
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irAEs, immune-related adverse events

Non-small lung cancer (CA209057 and CA209017)
Advanced renal cell cancer (CA209025)
Melanoma (CA209066)
To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.


Key endpoints
- Primary: PFS (RECIST v1.1 per blinded, independent central review)
- Secondary: OS, ORR, safety
- Exploratory: DOR

*To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met. Reck M, et al. New Engl J Med 2016;375(19):1823–33.
PEMBROLIZUMAB VS. CHEMOTHERAPY FOR PD-L1–POSITIVE NON–SMALL-CELL LUNG CANCER

TREATMENT EFFECT ON OS IN PREDEFINED SUBGROUPS

Safety and efficacy of pembrolizumab monotherapy in elderly patients with PD-L1-positive advanced non-small-cell lung cancer: Pooled analysis from the KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042 studies

Kaname Nosaki, Hideo Saka, Yukio Hosomi, Paul Baas, Gilberto de Castro Jr., Martin Reck, Yi-Lung Wu, Julie R. Brahmer, Enriqueta Felip, Takeshi Sawada, Kazuo Noguchi, Shi Rong Han, Bilal Pipedd, Debra A. Rush, Gilberto Lopes
Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer


Overall survival

Subgroup analysis of overall survival

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Events/No. of Patients</th>
<th>Hazard Ratio for Death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>133/112</td>
<td>0.43 (0.31–0.61)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>102/104</td>
<td>0.64 (0.43–0.95)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>143/163</td>
<td>0.70 (0.50–0.99)</td>
</tr>
<tr>
<td>Female</td>
<td>92/233</td>
<td>0.29 (0.19–0.44)</td>
</tr>
<tr>
<td>ECOG performance status score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>74/266</td>
<td>0.44 (0.28–0.71)</td>
</tr>
<tr>
<td>1</td>
<td>159/346</td>
<td>0.53 (0.39–0.71)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current or former</td>
<td>211/543</td>
<td>0.54 (0.41–0.71)</td>
</tr>
<tr>
<td>Never</td>
<td>24/73</td>
<td>0.23 (0.10–0.54)</td>
</tr>
<tr>
<td>Brain metastases at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>51/108</td>
<td>0.36 (0.20–0.62)</td>
</tr>
<tr>
<td>No</td>
<td>184/508</td>
<td>0.53 (0.39–0.71)</td>
</tr>
<tr>
<td>PD-L1 tumor proportion score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1%</td>
<td>84/190</td>
<td>0.59 (0.38–0.92)</td>
</tr>
<tr>
<td>≥2%</td>
<td>135/388</td>
<td>0.47 (0.34–0.66)</td>
</tr>
<tr>
<td>1–49%</td>
<td>65/186</td>
<td>0.55 (0.34–0.90)</td>
</tr>
<tr>
<td>≥50%</td>
<td>70/192</td>
<td>0.42 (0.26–0.68)</td>
</tr>
<tr>
<td>Platinum-based drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carboplatin</td>
<td>176/445</td>
<td>0.52 (0.39–0.71)</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>59/171</td>
<td>0.41 (0.24–0.69)</td>
</tr>
</tbody>
</table>
CONCLUSIONS

- Treatment of advanced NSCLC in the elderly is a challenging and emerging issue
- No agreement on the definition of “elderly” (65 – 70 – 75 years?)
- “Biological" age rather than "chronological" age should guide medical decision
- Geriatric assessment welcome, but to date, no easy tools available and limited evidence that it impacts treatment decision making
- Very few specifically designed Phase 3 trials
- Role of carboplatin-based chemotherapy needs to be confirmed with more feasible regimens
- Role of cisplatin-based chemotherapy needs to be confirmed with more feasible regimens
- Confirmed efficacy and no toxicity concerns for targeted therapies
- Confirmed efficacy and no toxicity concerns for immunotherapy (even when combined with chemotherapy)
- Very few data on chemotherapy in octogenarians
THANK YOU!