Maintenance therapy in advanced non-small cell lung cancer.

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Evolution of front line therapy in NSCLC – unselected pts

• 1970’s – 1980’s: Treatment until progression

• 1990’s: Treatment limited to 6–8 courses

• 2000’s: 3–4 courses of platinum-based therapy.
  – Provided 2nd-line therapy is considered

• 2010: 4–6 courses of platinum-based therapy + maintenance
Strategies for post Platinum therapy

- First-line platinum doublet ± bevacizumab
- CR/PR or SD
- Maintenance → PD → 2nd line
- Break (‘Watch and wait strategy’)
- PD → 2nd line

Platinum therapy

Post-platinum therapy
Concepts of Maintenance

"Switch" Maintenance

1st-line: Platin-based Combination
CR, PR, SD
4 cycles
Maintenance Monotherapy with new compound
Progression
Second Line Treatment
JMEN (Pemetrexed)\textsuperscript{1}
SATURN (Erlotinib)\textsuperscript{2}

"Continuation" Maintenance

1st-line: Pemetrexed/Cisplatin
Pemetrexed/Cisplatin/Bev
CR, PR, SD
4 cycles
Maintenance Pemetrexed or Pemetrexed/Bev
Progression
Second Line Treatment
PARAMOUNT\textsuperscript{3}
AVAPERL\textsuperscript{4}

Selection of patients with good prognosis
Endpoints:
- Quality of Life
- Symptom Control
- Tolerability
Gemcitabine vs placebo in NSCLC

Primary endpoint:
1. Time to progression

Secondary endpoints:
1. ORR
2. Response duration
3. Overall survival
4. Toxicity
5. Symptom control
Gemcitabine vs Placebo in NSCLC

Progression free survival through study period (left) and maintenance phase (right)
# Gemcitabine vs placebo in NSCLC

<table>
<thead>
<tr>
<th></th>
<th>BSC</th>
<th>Gem-BSC</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TTP, overall</strong></td>
<td>5.0 (4.5–5.7)</td>
<td>6.6 (5.9–7.2)</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>TTP, maintenance</strong></td>
<td>2.0 (1.6–2.6)</td>
<td>3.6 (2.8–4.1)</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>OS</strong></td>
<td>11 (9.7–13.5)</td>
<td>13 (11.0–16.7)</td>
<td>0.195</td>
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Immediate vs delayed docetaxel (Phase III)
Docetaxel Switch Maintenance: PFS

- Median PFS delayed vs immediate: 2.7 vs 5.7 mos ($P = .0001$)

**Patients at Risk, n**

<table>
<thead>
<tr>
<th></th>
<th>Delayed</th>
<th>Immediate</th>
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<tr>
<td>Mos</td>
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<tr>
<td>48</td>
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</tr>
</tbody>
</table>

**HR** = 0.71 (95% CI: 0.55–0.92) $p<0.0001$

Docetaxel Switch Maintenance: OS

- **Median OS delayed vs immediate**: 9.7 vs 12.3 mos ($P = .0853$)
- **1-yr survival delayed vs immediate**: 43.5% vs 51.1%

Pem/BSC vs placebo/BSC in NSCLC: Study design

- Stage IIIB/IV NSCLC
- PS 0/1
- 4 prior cycles of gem, doc, or tax + cis or carb, with CR, PR, or SD (NO PEMETREXED)

Randomization factors:
- gender
- PS
- stage
- best tumor response to induction
- non-platinum induction drug
- brain mets

Primary Endpoint = PFS

Pemetrexed 500 mg/m$^2$ (d1,q21d) + BSC (N=441)*

Placebo (d1, q21d) + BSC (N=222)*

* $B_{12}$, folate, and dexamethasone given in both arms

Ciuleanu, et al. Presented at: Annual Meeting of the American Society of Clinical Oncology, June 2, 2008; Chicago, IL.
Ciuleanu, et al. Presented at: Annual Meeting of the American Society of Clinical Oncology, June 2, 2008; Chicago, IL.
Maintenance pemetrexed (JMEN):

Overall Survival by Histology

Non-squamous (n=481)

HR = 0.70 (95% CI: 0.56-0.88)

P = 0.002

Squamous (n=182)

HR = 1.07 (95% CI: 0.49–1.73)

P = 0.678

Cielanu et al., Lancet 2010
Switch Maintenance: Pemetrexed Response after induction therapy

Non squamous NSCLC

Induction response CR/PR

Induction response SD

Second Line Pemetrexed after Maintenance Gemcitabine or Erlotinib. IFCT-GFPC 0502

**Induction CT:**
- Cisplatin 80mg/m² day 1
- Gemcitabine 1,250mg/m² day 1, day 8

**Arm B:**
- Gemcitabine: 1,250mg/m² day 1, day 8/3 weeks

**Arm C:**
- Erlotinib 150mg daily

**Stratification factors**
- Gender
- Histology: adenocarcinoma versus other histology
- Smoking status: non-smokers versus current/former smokers
- Centre
- Response versus stabilisation to induction CT
### IFCT-GFPC 0502: Treatment Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Gemcitabine (n = 149)</th>
<th>Erlotinib (n = 153)</th>
<th>Observation (n = 152)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median PFS, mos</strong></td>
<td>3.8</td>
<td>2.9</td>
<td>1.9</td>
</tr>
<tr>
<td><strong>HR vs observation (95% CI)</strong></td>
<td>0.55 (0.43-0.70)</td>
<td>0.82 (0.73-0.93)</td>
<td></td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>&lt; .0001</td>
<td>.002</td>
<td></td>
</tr>
<tr>
<td><em><em>Median OS</em>, mos</em>*</td>
<td>12.1</td>
<td>11.8</td>
<td>10.7</td>
</tr>
<tr>
<td><strong>HR vs observation (95% CI)</strong></td>
<td>0.86 (0.66-1.12)</td>
<td>0.91 (0.80-1.04)</td>
<td></td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

**IFCT-GFPC 0502: Treatment Outcomes**

![Table of Treatment Outcomes](image)

- **Factors**
- **Observation** (n) | **Gemcitabine** (n) | **HR** | **95% CI**
- **SD** | 73 | 73 | 1.13 | 0.79 | 1.62
- **OR** | 82 | 81 | 0.72 | 0.51 | 1.04
- **Adenocarcinoma** | 102 | 102 | 0.98 | 0.72 | 1.35
- **Non adenocarcinoma** | 53 | 52 | 0.79 | 0.51 | 1.21
- **Smoker** | 142 | 136 | 0.88 | 0.67 | 1.15
- **Non-smoker** | 12 | 17 | 0.96 | 0.41 | 2.27
- **Male** | 113 | 113 | 0.84 | 0.62 | 1.12
- **Female** | 42 | 41 | 1.12 | 0.66 | 1.90
- **Pemetrexed** | 130 | 114 | 0.78 | 0.58 | 1.04
- **No pemetrexed** | 25 | 40 | 1.30 | 0.71 | 2.36
- **PS 0** | 68 | 61 | 0.65 | 0.44 | 0.97
- **PS 1** | 81 | 82 | 0.97 | 0.68 | 1.37
- **PS ≥2** | 5 | 9 | 2.10 | 0.56 | 7.83
- **All** | 155 | 154 | 0.89 | 0.69 | 1.15

Perol M. Poster presented at ESMO 2010: PD370
Concepts of Maintenance

"Switch“ Maintenance

1st-line: Platin-based Combination

CR, PR, SD

4 cykles

Maintenance Monotherapy with new compound

until Progression

Progression

Second Line Treatment

JMEN (Pemetrexed)$^1$

SATURN (Erlotinib)$^2$

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1st-line: Pemetrexed/Cisplatin

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Maintenance Pemetrexed or Pemetrexed/Bev

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Progression

Second Line Treatment

PARAMOUNT$^3$

AVAPERL$^4$

Selection of patients with good prognosis

Endpoints:

- Quality of Life
- Symptom Control
- Tolerability
Primary endpoint: Progression free survival

Inclusion criteria
- Non-squamous NSCLC
- Stage IIIB/IV
- Chemonaïve
- ECOG PS 0-1 (n=939)

Stratification:
- PS (0 vs. 1)
- Stage (IIIB vs. IV) before induction
- Response after induction (CR/PR vs. SD)

Supplementation with Folic acid and Vitamin B12 in both arms

Pemetrexed 500 mg/m² iv q21d

Cisplatin
75 mg/m² iv q21d

CR, PR, SD

Pemetrexed 500 mg/m² iv q21d
n=359

Placebo
n=180

PS, propensity score; CR, complete response: vollständiges Ansprechen; PR, partial response: teilweises Ansprechen; SD, stable disease: Krankheitsstabilisierung; PD, progressive disease: progressiver Krankheitsverlauf
PARAMOUNT: Progression free survival

PFS: Primary Efficacy Endpoint

PFS: Reassessed at Time of Final OS

Patients at Risk

 Paramount: Overall survival

PARAMOUNT: OS; Subgroup analysis

- All randomized patients (n=539)
  - Stage IV (n=490)
  - Stage IIIb (n=49)
- Response after induction CR/PR (n=234)
- Response after Induction SD (n=285)
- PS 1 before randomisation (n=363)
- PS 0 before randomisation (n=173)
- Neversmoker (n=117)
- Smoker (n=418)
- Male (n=313)
- Female (n=226)
- Age <70 (n=447)
- Age ≥70 (n=92)
- Age <65 (n=350)
- Age ≥65 (n=189)
- Other histology (n=32)
- Large cell histology (n=36)
- Adenocarcinoma (n=471)

Hazards Ratio (95% KI)

- Pemetrexed
- Placebo

Probability of survival

- Hazards Ratio
  - All randomized patients, Stage IV, Stage IIIb, Response after induction CR/PR, Response after Induction SD, PS 1, PS 0, Neversmoker, Smoker, Male, Female, Age <70, Age ≥70, Age <65, Age ≥65, Other histology, Large cell histology, Adenocarcinoma


CR, complete response: vollständiges Ansprechen; PR, partial response: teilweises Ansprechen; SD, stable disease: Krankheitsstabilisierung; PS, propensity score
QoL Study in Paramount

EQ-5D UK population-based index score

EQ-5D VAS

Mean Score (Scale -0.59 to +1.00)

Mean Rating (Scale 0 to 100)

Top of bar = mean value at that cycle for pemetrexed

Top of bar = mean value at that cycle for placebo

Mean value at baseline (Cycle 0)

Mean change from baseline

N = 265 132 241 129* 160 83 149 66 108 48 98 36

N = 266 126 239 127* 162 81 147 65 107 48 98 36

* Indicates significance
## Efficacy: PFS & OS

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Maintenance drug</th>
<th>PFS HR (95% CI)</th>
<th>OS HR (95% CI)</th>
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<tbody>
<tr>
<td><strong>Switch Maintenance</strong></td>
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<tr>
<td>Westeel et al.</td>
<td>181</td>
<td>Vinorelbine</td>
<td>0.77 (0.55-1.07)</td>
<td>1.08 (0.79-1.48)</td>
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<tr>
<td>Fidias et al.</td>
<td>309</td>
<td>Docetaxel</td>
<td>0.71 (0.55-0.92)</td>
<td>0.84 (0.65-1.08)</td>
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<tr>
<td>Capuzzo</td>
<td>889</td>
<td>Erlotinib</td>
<td>0.71 (0.62–0.82)</td>
<td>0.81 (0.70-0.95)</td>
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<tr>
<td>Ciuleanu et al.</td>
<td>663</td>
<td>Pemetrexed</td>
<td>0.60 (0.49-0.73)</td>
<td>0.79 (0.65-0.95)</td>
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<tr>
<td><strong>Continuation Maintenance</strong></td>
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<tr>
<td>Paz-Ares et al</td>
<td>539</td>
<td>Pemetrexed</td>
<td>0.62 (0.49-0.79)</td>
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<tr>
<td>Brodowicz et al.</td>
<td>206</td>
<td>Gemcitabine</td>
<td>0.69 (0.56-0.86)</td>
<td>0.84 (0.52-1.30)</td>
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<tr>
<td>Belani et al.</td>
<td>255</td>
<td>Gemcitabine</td>
<td>1.09 (0.81-1.45)</td>
<td>0.97 (0.72-1.30)</td>
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<tr>
<td>Perol et al.</td>
<td>309</td>
<td>Gemcitabine</td>
<td>0.56 (0.44-0.72)</td>
<td>0.89 (0.67-1.15)</td>
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<tr>
<td>Trial</td>
<td>N</td>
<td>Maintenance Drug</td>
<td>QoL &amp; Symptom Control</td>
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<tr>
<td><strong>Switch Chemotherapy Maintenance</strong></td>
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<tr>
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<td>Fidias et al.</td>
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<td>Erlotinib</td>
<td>Better pain control</td>
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<td>Cielanu et al.</td>
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<td>Pemetrexed</td>
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<td>Pemetrexed</td>
<td>No detrimental effect</td>
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</tbody>
</table>
Antibody maintenance
E4599: study design

- Primary endpoint
  - overall survival (OS)

- Secondary endpoints
  - objective response rate
  - progression-free survival (PFS)
  - duration of response
  - safety

Previously untreated stage IIIB, IV or recurrent predominantly non-squamous NSCLC (n=878)

- CP q3w x6 (n=444)
- Bevacizumab (15mg/kg) + CP q3w x6 (n=434)

*No crossover permitted*

E4599

Bevacizumab 15mg/kg + CP (n=444)

HR (95% CI) 0.79 (0.67–0.92)

p value 0.003

Median OS (months) 10.3 12.3


CP=carboplatin/paclitaxel
Pemetrexed or Bevacizumab maintenance?

**Primary endpoint**
- PFS without Grade 4 AE (G4PFS)

**Secondary endpoints**
- PFS, OS, RR, DCR
- Safety and tolerability

**Induction phase**
4 cycles, q3w
- Pem 500 mg/m² + Cb AUC6 (n=182)
- Pac 200 mg/m² + Cb AUC6 + Bev 15 mg/kg (n=179*)

**Maintenance treatment**
q3w
- Pem 500 mg/m² (n=98)
- Bev 15 mg/kg (n=95)

**Stratification**
- PS (0 vs. 1); sex (M vs. F); disease stage (M1a vs. M1b)

**Key patient inclusion criteria**
- No prior systemic treatment
- ECOG PS 0-1
- Stable IIIB-IV non-squamous NSCLC
- Stable treated brain mets (n=361)

Zinner et al. J Clin Oncol 31, 2013 (suppl; abstr LBA8003)
Primary Endpoint: G4PFS (ITT)

- **Pem+Cb:** median G4PFS = 3.9 mo
- **Pac+Cb+Bev:** median G4PFS = 2.9 mo

Log-rank p value = 0.176
HR (90% CI) = 0.85 (0.70–1.04)

<table>
<thead>
<tr>
<th>Number of G4PFS events</th>
<th>Pem+Cb (n=152)</th>
<th>Pac+Cb+Bev (n=144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G4 AE</td>
<td>24.3%</td>
<td>44.4%</td>
</tr>
<tr>
<td>PD</td>
<td>62.5%</td>
<td>47.2%</td>
</tr>
<tr>
<td>Death</td>
<td>13.2%</td>
<td>8.3%</td>
</tr>
</tbody>
</table>

Patients at Risk
- **Pem+Cb** 182 87 44 26 14 7 5 3 1 0
- **Pac+Cb+Bev** 179 75 33 17 9 3 0 0 0 0

Zinner et al. J Clin Oncol 31, 2013 (suppl; abstr LBA8003)
Primary Endpoint: Progression free survival

Inclusion criteria:
• Non-squamous NSCLC
• Stage IIIb/IV
• No prior treatment
  n=414

Stratification:
• gender
• smoker vs never smoker
• CR/PR vs. SD

Maintenance with Bevacizumab ± Pemetrexed (AVAPERL):
Randomised, open phase III trial

Start of induction treatment
Induction therapy (4 cycles)
Maintenance therapy until PD)
Progression

Pemetrexed
500 mg/m² iv q21d
Cisplatin
75 mg/m² iv q21d
Bevacizumab
7,5 mg/kg iv q21d
n=253
CR, PR, SD
n=125

Pemetrexed
500 mg/m² iv q21d
Bevacizumab
7,5 mg/kg iv q21d
n=128

Bevacizumab
7,5 mg/kg iv q21d
n=376

AVAPERL: PFS from randomisation

Therapx | PFS (Months) | n
---|---|---
Bev + Pem | 7,4 (81 Events) | 128
Bev | 3,7 (104 Events) | 125
HR | 0,48 (0,35–0,66); p<0,001 |

Maintenance Bev + Pem (n=128)
Maintenance Bev (n=125)

AVAPERL: Overall survival

Median OS:
Bevacizumab, 15.9 months
Bevacizumab + pemetrexed, 19.8 months
HR, 0.88 (0.64–1.22); P < 0.32

POINTBREAK phase III trial

Bevacizumab 15 mg/kg q3w + carboplatin + pemetrexed
4 cycles

Bevacizumab 15 mg/kg q3w + carboplatin + paclitaxel

Bevacizumab 15 mg/kg q3w

Treat to PD

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

R 1:1

n=442*

n=443*

n=292
(66%)

n=298
(67%)

- Primary endpoint
  - OS

- Secondary endpoints
  - ORR and DCR
  - PFS and TTP
  - safety and QoL

Pl: J Patel

*Patient numbers excluding those not treated

Patel, et al. IASLC 2012 (Chicago)
POINTBREAK: OS (primary endpoint) – ITT population

HR = 1.00 (0.86–1.16)  
p = 0.949

Patel, et al. IASLC 2012 (Chicago)
### FLEX Study design

**NSCLC wet IIIb/IV EGFR-expressing**

- **Chemotherapy + Cetuximab**

  - **Chemotherapy**
  - **Cetuximab**

  - Maintenance: Cetuximab until PD or intolerable toxicity

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**Chemotherapy (CT)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>80 mg/m² day 1</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>25 (30) mg/m² days 1, 8</td>
</tr>
<tr>
<td></td>
<td>Every 3 weeks, up to 6 cycles</td>
</tr>
</tbody>
</table>

**Cetuximab**

- Initial dose 400 mg/m²
- Then 250 mg/m² weekly

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*ASCO Annual '08 Meeting*
FLEX Overall survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS</th>
<th>1-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT + Cetuximab</td>
<td>11.3 months</td>
<td>47%</td>
</tr>
<tr>
<td>CT</td>
<td>10.1 months</td>
<td>42%</td>
</tr>
</tbody>
</table>

HR=0.871 (95% CI 0.762-0.996), p=0.044

p-value = stratified log-rank test (2-sided)
SQUIRE: Study Design

Population
First-Line
Stage IV squamous NSCLC
ECOG PS 0-2

NECI + Gem-Cis q3w (N=545)
Maximum of 6 cycles

CR PR PD

NECI q3w

PD

Gem-Cis q3w (N=548)

PD

Primary Objective: Overall survival
Secondary Objectives: PFS, ORR, safety, QoL
Exploratory Objective: EGFR protein expression (IHC, DAKO PharmDx)
SQUIRE: G/C + Neci vs G/C in Stage IV SqCLC

1093 pts
- First-line stage IV SqCLC
- ECOG PS 0-2

G/C (1250 mg/m²; 75 mg/m²) + Neci 800 mg d 1,8 (n = 545)

G/C (n = 548)

Maximum of 6 cycles

<table>
<thead>
<tr>
<th></th>
<th>G/C + Neci</th>
<th>G/C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stratified HR (95% CI)</td>
<td>0.84 (0.74-0.96)</td>
<td>.01</td>
</tr>
<tr>
<td>Stratified P value (log-rank)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median OS, mos (95% CI)</td>
<td>11.5 (10.4-12.6)</td>
<td>9.9 (8.9-11.1)</td>
</tr>
</tbody>
</table>

Evolution of front line therapy in NSCLC – selected pts

• 2005 – 2016: molecular selected patients

• continue treatment until progression:
  – EGFR
  – Alk
  – ROS1
  – B-RAF
Maintenance in Lung Cancer
“Oncogene Addicted”

Erlotinib in EGFR m+ NSCLC
EURTAC Trial

Rosell R et al., Lancet Oncol 2012
Evolution of front line therapy in NSCLC – selected pts

- 2005 – 2016: molecular selected patients continue treatment until progression

- 2016: PD-L1 positive (>50%) continue pembrolizumab
Key Eligibility Criteria
- Untreated stage IV NSCLC
- PD-L1 TPS ≥50%
- ECOG PS 0-1
- No activating EGFR mutation or ALK translocation
- No untreated brain metastases
- No active autoimmune disease requiring systemic therapy

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

Pembrolizumab
200 mg IV Q3W (2 years)

R (1:1) N = 305

Platinum-Doublt Chemotherapy
(4-6 cycles)
Progression-Free Survival

Assessed per RECIST v1.1 by blinded, independent central review. Data cut-off: May 9, 2016.
Overall Survival

Data cut-off: May 9, 2016.

No. at risk

<table>
<thead>
<tr>
<th>Time, months</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
<th>21</th>
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</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>154</td>
<td>136</td>
<td>121</td>
<td>82</td>
<td>62</td>
<td>11</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Chemo</td>
<td>151</td>
<td>123</td>
<td>106</td>
<td>64</td>
<td>34</td>
<td>7</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

OS, %

- Pembro: 80% at 6 months, 72% at 12 months
- Chemo: 70% at 6 months, 54% at 12 months

HR (95% CI): 0.60 (0.41-0.89) P = 0.005
Evolution of front line therapy in NSCLC – mutation status unknown

• Platin based chemotherapy
  – Maintenance?
Continuation Gefitinib when EGFR mut status is unknown

Yang et al. J.Thor. Oncol. 2015
Continuation Gefitinib when EGFR mut status is unknown

Yang et al. J.Thor. Oncol. 2015
Guidelines

• Maintenance therapy recommended by
  – ESMO
  – ASCO
Conclusions

• Both switch and continuation maintenance chemotherapy prolong PFS and OS

• Antibody maintenance prolong PFS and OS (?)

• Small molecule offered untill PD.