Maintenance chemotherapy: A treatment opportunity or a new standard of care?

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Sevilla

Maintenance in advanced NSCLC: treating before disease progression until progression or intolerance

Traditional approach
First-line treatment
Platinum doublet chemotherapy
(4–6 cycles)

Break from treatment
2nd/3rd line treatment

Diagnosis CR/PR/SD PD PD

Increased time to PD

Maintenance approach
Maintenance therapy

Diagnosis CR/PR/SD PD PD
Maintenance treatment – Types

- **Continuation therapy**: Prolonged platinum doublet chemotherapy
- **Continuation Maintenance**: Continuation of non-platinum agent used in doublet chemotherapy
  - e.g. paclitaxel, gemcitabine, pemetrexed
- **Switch Maintenance**: Introduction of a new cytotoxic agent
  - e.g. docetaxel, pemetrexed, erlotinib
- **Targeted Maintenance**: Triplet induction therapy followed of maintenance with the same targeted agent
  - e.g. bevacizumab (EGOC 4599), cetuximab (Flex)

Switch Maintenance With Docetaxel

Chemotherapy-naive patients with stage IIIB/IV NSCLC (N = 566)

Immediate Docetaxel (n = 153)

Delayed Docetaxel* (n = 156)

*Initiated at first evidence of progressive disease

- Primary endpoint: OS
- Other endpoints: PFS, ORR, safety, QOL


Docetaxel Switch Maintenance: PFS

 Patients at Risk, n
 Delayed 156  59   28  18   13                        6                        1
 Immediate 153 106  72   42   26                       5                        2

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

Docetaxel Switch Maintenance: OS

![Graph showing the probability of OS over time for delayed and immediate maintenance with Docetaxel, showing a HR of 0.84 (95% CI: 0.65–1.08) and p<0.0853.]

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


JMEN Study Design

- Double-blind, multicenter, placebo-controlled, phase III trial
  - Randomized 2:1 according to sex, PS, stage, best response, nonplatinum drug, brain metastases

Patients with stage IIIIB/IV NSCLC, ECOG PS 0-1, 4 prior cycles of gem, doc, or tax + cis or carb, with CR, PR, or SD

![Flowchart showing the study design with two treatment arms: Pemetrexed 500 mg/m² (d1,q21d) + BSC (n = 441)* and Placebo (d1,q21d) + BSC (n = 222)*.]

- Primary endpoint: PFS

*B12, folate, and dexamethasone given in both arms

Cielanu et al., Lancet 2010
Maintenance pemetrexed (JMEN):

**PFS and OS**

**PFS**

- Pemetrexed: 4.0 months
- Placebo: 2.0 months

**OS**

- Pemetrexed: 13.4 months
- Placebo: 10.6 months

**HR = 0.599**

(95% CI: 0.49–0.73)

*p < 0.00001*

**HR = 0.79**

(95% CI: 0.65–0.95)

*p = 0.012*

Cielanu et al., Lancet 2010

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**Overall Survival by Histology**

**Non-squamous (n=401)**

- HR = 0.70
- (95% CI: 0.56–0.86)
- *p = 0.003*

**Squamous (n=182)**

- HR = 1.07
- (95% CI: 0.49–1.73)
- *p = 0.678*

Cielanu et al., Lancet 2010
SATURN: Erlotinib maintenance

Chemonaive advanced NSCLC (n=1,949) → 4 cycles of 1st-line platinum-based doublet → Non-PD (n=889)

Erlotinib 150mg/day → PD
Non-PD (n=889) → Placebo → PD

Mandatory tumour sampling

Co-primary endpoints
- PFS in all patients
- PFS in patients with EGFR IHC+ tumours

Secondary endpoints
- OS in all patients and those with EGFR IHC+ tumours, OS and PFS in EGFR IHC– tumours; biomarker analyses; safety; time to symptom progression; quality of life (QoL)

Cappuzzo, et al. WCLC 2009

PFS: Erlotinib versus placebo (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Erlotinib (n=437)</th>
<th>Placebo (n=447)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS at 12 weeks (%)</td>
<td>53</td>
<td>40</td>
</tr>
<tr>
<td>PFS at 24 weeks (%)</td>
<td>31</td>
<td>17</td>
</tr>
</tbody>
</table>

HR=0.71 (0.62–0.82)
Log-rank p<0.0001

Cappuzzo, et al. WCLC 2009
**OS: Erlotinib versus placebo (ITT)**

- Erlotinib (n=438)
- Placebo (n=451)

OS probability

HR=0.81 (0.70–0.95)

Log-rank p=0.0088

**Time (months)**

0 3 6 9 12 15 18 21 24 27 30 33 36

**OS: Erlotinib versus placebo (ITT)**

Cappuzzo, et al. WCLC 2009

**IFCT-GFPC 0502: Gemcitabine vs Erlotinib vs Observation as Maintenance**

- Patients without disease progression randomized 1:1:1
- Chemotherapy-naive patients with stage IIIB/IV NSCLC (N = 834)
- Patients stratified by sex, histology, smoking status, treatment center, and response/stabilization following first-line therapy
- Primary endpoint: PFS
- Other endpoints: OS, safety, symptom control, effect of EGFR status

### 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>Median PFS, mos</td>
<td>3.8</td>
<td>2.9</td>
<td>1.9</td>
</tr>
<tr>
<td>▪ HR vs observation</td>
<td>0.55 (0.43-0.70)</td>
<td>0.82 (0.73-0.93)</td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ P value</td>
<td>&lt; .0001</td>
<td>.002</td>
<td></td>
</tr>
<tr>
<td>Median OS*, mos</td>
<td>12.1</td>
<td>11.8</td>
<td>10.7</td>
</tr>
<tr>
<td>▪ HR vs observation</td>
<td>0.86 (0.66-1.12)</td>
<td>0.91 (0.80-1.04)</td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ P value</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>


### Maintenance treatment – Types

- **Continuation therapy:** Prolonged platinum doublet chemotherapy
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Advanced NSCLC: Gemcitabine Maintenance Therapy

Chemotherapy-naive patients with stage IIIB/IV NSCLC and CR / PR / SD after cisplatin + gemcitabine (N = 206)

- Primary endpoint: PFS

Maintenance gemcitabine 1250 mg/m² Days 1, 8 Q3W plus BSC (n = 138)

BSC only (n = 68)


Advanced NSCLC: Gemcitabine Maintenance Therapy – PFS

- OS: 13.0 mos vs 11.0 mos, P = .195

PFS from the date of starting first-line

PFS from the date of randomization

HR=0.69 (95% CI: 0.56–0.86) p<0.001

IFCT-GFPC 0502: Gemcitabine vs Erlotinib vs Observation as Maintenance

Patients without disease progression randomized 1:1:1

Chemotherapy-naive patients with stage IIIIB/IV NSCLC (N = 834)

- Patients stratified by sex, histology, smoking status, treatment center, and response/stabilization following first-line therapy
- Primary endpoint: PFS
- Other endpoints: OS, safety, symptom control, effect of EGFR status

Perol M et al. ASCO 2010: Abstract 7507

Gemcitabine or Erlotinib

IFCT-GFPC 0502: Results

- Patients who received 2nd-line pemetrexed: 73% (Obs), 55% (Gem), and 60% (Erl)
- Grade 3-4 treatment-related AEs were more common in Gem (27%) and Erl (14%) than in Obs (2%)

Perol M et al, J Clin Oncol 28:154, 2010 (suppl; abstr 7507)
**Pemetrexed Maintenance v Placebo in Nonsquamous NSCLC: Phase III Study**

Chemotherapy-naive patients with stage IIIIB/IV nonsquamous NSCLC (N = 900 planned)

- **Primary endpoint:** PFS
- **Other endpoints:** OS, ORR, patient-reported outcomes, resource utilization, toxicity

**PARAMOUNT: Patient Disposition**

- **400 Patients Not Randomized**
  - 217 Progressive Disease
  - 62 Adverse Event
  - 56 Death
  - 29 Study Disease
  - 15 AE
  - 11 Drug-Related AE
  - 1 Procedure-Related AE
  - 65 Other Reasons

- **1022 Patients Screened**
- **939 Patients Enrolled**
  - **539 Patients Randomized** (2:1 Randomization)
  - **548 Patients Eligible for Maint**
    - 8 Discontinued Pt Decision
    - 1 Discontinued Phys Decision

- **Induction Phase**
  - **Pemetrexed Arm N=359**
  - **Placebo Arm N=180**

- **Maintenance Phase**
  - **136 (38%) Patients on Pemetrexed Maintenance at Data Cut Off**
  - **43 (24%) Patients on Placebo at Data Cut Off**
**PARAMOUNT: Investigator Assessed PFS (from Maintenance)**

Survival Probability vs. Time (Months)

- **Pemetrexed:** median = 4.1 mos (3.2-4.6)
- **Placebo:** median = 2.8 mos (2.6-3.1)
- Log-rank \( P = 0.00006 \)
- Unadjusted HR: 0.62 (0.49-0.79)

**Patients at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Pem + BSC</th>
<th>Placebo + BSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>359</td>
<td>180</td>
</tr>
<tr>
<td>132</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>57</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

** PARAMOUNT: Subgroup PFS Hazard Ratios**

- **All Randomized Patients (N=539)**
- **Stage IV (n=489)**
- **Stage III (n=50)**
- **Induction Response CR/PR (n=242)**
- **Induction Response SD (n=280)**
- **Pre-randomization PS 1 (n=366)**
- **Pre-randomization PS 0 (n=170)**
- **Non-smoker (n=116)**
- **Smoker (n=419)**
- **Male (n=313)**
- **Female (n=226)**
- **Age ≥ 70 (n=92)**
- **Age 65-69 (n=97)**
- **Age < 65 (n=350)**
- **Other Histologic Diagnosis (n=32)**
- **Large Cell Carcinoma (n=36)**
- **Adenocarcinoma (n=471)**

- CR/PR 4.1 2.6
- SD 4.1 3.0
- **P= 0.67**
- **P= 0.53**
- **P= 0.41**

- **P= 0.70**
- **P= 0.64**
- **P= 0.39**

**Favors Pemetrexed**

**Favors Placebo**

- PFS results were internally consistent; benefit was seen across all subgroups
- CR/PR and SD subgroups benefited from pemetrexed maintenance (median PFS = 4.1 mos for both)
**PARAMOUNT: Independently Reviewed PFS (from Maintenance)**

- 88% of patients were independently reviewed (472/539)

- Pemetrexed: median = 3.9 mos (3.0-4.2)
- Placebo: median = 2.6 mos (2.2-2.9)
- Log-rank $P=0.0002$
- Unadjusted HR: 0.64 (0.51-0.81)

**PARAMOUNT: Investigator Assessed PFS (from Induction)**

- Pem: median = 6.90 (6.2-7.5)
- Placebo: median = 5.59 (5.5-6.0)
- Log Rank $P<0.00001$
- Unadjusted HR: 0.59 (0.47-0.74)
# Paramount Induction vs JMDB

<table>
<thead>
<tr>
<th></th>
<th>Paramount Induction</th>
<th>JMDB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median number of induction cycles</td>
<td>4 cycles then pemetrexed maintenance</td>
<td>1st-line treatment with 6 cycles</td>
</tr>
<tr>
<td><strong>Response:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response Rate (CR/PR)</td>
<td>30.1%</td>
<td>28.6%</td>
</tr>
<tr>
<td>Disease control rates (CR/PR/SD)</td>
<td>74.5%</td>
<td>63.8%</td>
</tr>
<tr>
<td><strong>Toxicity:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory toxicities</td>
<td>13.7%</td>
<td>21.4%</td>
</tr>
<tr>
<td>Nonlaboratory toxicities</td>
<td>14.8%</td>
<td>21.9%</td>
</tr>
<tr>
<td>Possible treatment-related deaths</td>
<td>1.2%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>14.2%</td>
<td>16.4%</td>
</tr>
<tr>
<td>Supportive care</td>
<td>almost the same</td>
<td></td>
</tr>
</tbody>
</table>

Supportive care almost the same:
- More colony-stimulating factors in Paramount
- More anti-emetics use in JMDB

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# Paramount: Post-discontinuation therapy (PDT-eligible patients)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Pemetrexed (N=200) n (%)</th>
<th>Placebo (N=122) n (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with PDT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug Name:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erlotinib</td>
<td>62 (31)</td>
<td>45 (37)</td>
<td>0.329</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>58 (29)</td>
<td>43 (35)</td>
<td>0.266</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>15 (8)</td>
<td>4 (3)</td>
<td>0.147</td>
</tr>
<tr>
<td>Investigational drug</td>
<td>10 (5)</td>
<td>4 (3)</td>
<td>0.580</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>8 (4)</td>
<td>2 (2)</td>
<td>0.329</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>3 (2)</td>
<td>1 (0.8)</td>
<td>1.00</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>3 (2)</td>
<td>1 (0.8)</td>
<td>1.00</td>
</tr>
<tr>
<td>Other</td>
<td>13 (7)</td>
<td>6 (5)</td>
<td></td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>2 (1.0)</td>
<td>1 (0.8)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**PARAMOUNT: Health-related Quality of Life Assessment (EQ-5D)**

- EQ-5D is a health-status questionnaire consisting of two parts:
  - Index score generated from five descriptive questions (relating to mobility, self-care, activities, discomfort, anxiety)
  - Visual analog scale: patients rate their present health
- Administered at:
  - Baseline (before induction)
  - Day 1 of each cycle of induction or maintenance therapy (prior to treatment)
  - 30-day post-discontinuation visit
- Compliance at all time points during maintenance phase was >80%
- No statistical differences in EQ-5D index score or visual analog scale were observed between treatment arms.

**PARAMOUNT: CTCAEs Grade 3/4 Drug-related Toxicities (Randomized Patients)**

<table>
<thead>
<tr>
<th>Grade 3/4 Event</th>
<th>Pemetrexed N=359 (%)</th>
<th>Placebo N=180 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue*</td>
<td>4.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Anemia*</td>
<td>4.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>3.6</td>
<td>0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>1.7</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>0.3</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.3</td>
<td>0</td>
</tr>
<tr>
<td>Neuropathy-sensory</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Mucositis/stomatitis</td>
<td>0.3</td>
<td>0</td>
</tr>
<tr>
<td>ALT (SGPT)</td>
<td>0.3</td>
<td>0</td>
</tr>
</tbody>
</table>

*Statistically significant between arms (Fisher’s exact test P≤0.05)
AVAPEARL1 Trial
Pemetrexed Maintenance v Bevacizumab in Nonsquamous NSCLC: Phase III Study

Chemotherapy-naive patients with stage IIIB/IV nonsquamous NSCLC
(N = 360 planned)

- Primary endpoint: PFS
- Other endpoints: OS, ORR, QoL, toxicity

Patients without disease progression randomized 1:1

Pemetrexed/Cisplatin/Bevacizumab for 4 cycles
Bevacizumab

Pemetrexed + Bevacizumab

Clinicaltrials.gov.

AVAPERL: PFS from randomization

Bev+pem 7.4 months (81 events)
Bev 3.7 months (104 events)
HR, 0.48 (0.35–0.66); P < .001

AVAPERL: PFS from randomization

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Pts at risk</th>
<th>Bev+pem (n=128)</th>
<th>Bev (n=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>128</td>
<td>125</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
<td>104</td>
<td>73</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>67</td>
<td>36</td>
</tr>
<tr>
<td>9</td>
<td>25</td>
<td>25</td>
<td>13</td>
</tr>
<tr>
<td>12</td>
<td>100</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>15</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Bev, bevacizumab; cont., continuation; HR, hazard ratio; ITT, intent to treat; pem, pemetrexed; pts, patients.

Barlesi et al., ESMO 2011

* Median follow-up time in ITT population (excluding induction): 8.28 months (bev+pem arm), 7.95 months (bev arm)
### 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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Switch Maintenance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
</tr>
<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>
</tr>
<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>
</tr>
<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>
</tr>
</tbody>
</table>

| **Continuation Maintenance** |     |                  |                 |                |
| Paz-Ares et al  | 539 | Pemetrexed       | 0.62 (0.49-0.79) | NA             |
| Brodowicz et al.| 206 | Gemcitabine      | 0.69 (0.56-0.86) | 0.84 (0.52-1.30) |
| Belani et al.   | 255 | Gemcitabine      | 1.09 (0.81-1.45) | 0.97 (0.72-1.30) |
| Perol et al.    | 309 | Gemcitabine      | 0.56 (0.44-0.72) | 0.89 (0.67-1.15) |

### Efficacy: QOL

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Maintenance drug</th>
<th>QoL &amp; Symptom Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Switch Chemotherapy Maintenance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Westeel et al.</td>
<td>181</td>
<td>Vinorelbine</td>
<td>NR</td>
</tr>
<tr>
<td>Fidias et al.</td>
<td>309</td>
<td>Docetaxel</td>
<td>No differences</td>
</tr>
<tr>
<td>Capuzzo</td>
<td>889</td>
<td>Erlotinib</td>
<td>Better pain control</td>
</tr>
<tr>
<td>Ciuleanu et al.</td>
<td>663</td>
<td>Pemetrexed</td>
<td>Better pain and hemoptisis control</td>
</tr>
</tbody>
</table>

| **Continuation Chemotherapy Maintenance** |     |                  |                       |
| Paz-Ares et al | 539 | Pemetrexed       | No detrimental effect |
| Brodowicz et al.| 206 | Gemcitabine      | NR                    |
| Belani et al.  | 255 | Gemcitabine      | NR                    |
| Perol et al.   | 309 | Gemcitabine      | NR                    |
Toxicity: Grade III-IV Events

<table>
<thead>
<tr>
<th>Agent</th>
<th>Neutropenia</th>
<th>Fatigue</th>
<th>Rash</th>
<th>Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel^</td>
<td>28%</td>
<td>10%</td>
<td>NR</td>
<td>1%</td>
</tr>
<tr>
<td>Pemetrexed†</td>
<td>3%</td>
<td>5%</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>0%</td>
<td>2%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Erlotinib*</td>
<td>0%</td>
<td>&lt;1%</td>
<td>6%</td>
<td>2%</td>
</tr>
</tbody>
</table>

^No Grade 4
†All patients received decadron and anti-emetics; 28% had Grade 3/4 thrombocytopenia
‡10% received on RBC transfusion; 6% received ago and 4% were hospitalized for Grade 3/4 toxicity; all patients received oral decadron, anti-emetics, B12 injections and daily folic acid supplementation

Consistent PFS and OS results in JMEN & Saturn studies: Greater benefit in patients with SD versus CR/PR

Belani CP, et al. ASCO 2009 (Abs. CRA0011)
### PARAMOUNT: Subgroup PFS Hazard Ratios

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Pemetrexed</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Randomized Patients (N=539)</td>
<td>0.62</td>
<td>0.65</td>
</tr>
<tr>
<td>Stage IV (n=489)</td>
<td>0.62</td>
<td>0.65</td>
</tr>
<tr>
<td>Stage III (n=50)</td>
<td>0.66</td>
<td>0.74</td>
</tr>
<tr>
<td>Induction Response CR/PR (n=342)</td>
<td>0.48</td>
<td>0.50</td>
</tr>
<tr>
<td>Induction Response SD (n=389)</td>
<td>0.74</td>
<td>0.74</td>
</tr>
<tr>
<td>Pre-randomization PS 0 (n=175)</td>
<td>0.67</td>
<td>0.70</td>
</tr>
<tr>
<td>Non-smoker (n=116)</td>
<td>0.61</td>
<td>0.70</td>
</tr>
<tr>
<td>Smoker (n=419)</td>
<td>0.41</td>
<td>0.70</td>
</tr>
<tr>
<td>Male (n=313)</td>
<td>0.39</td>
<td>0.70</td>
</tr>
<tr>
<td>Female (n=226)</td>
<td>0.53</td>
<td>0.70</td>
</tr>
<tr>
<td>Age ≥70 (n=92)</td>
<td>0.62</td>
<td>0.70</td>
</tr>
<tr>
<td>Age 65-69 (n=97)</td>
<td>0.60</td>
<td>0.70</td>
</tr>
<tr>
<td>Age &lt;65 (n=350)</td>
<td>0.60</td>
<td>0.70</td>
</tr>
<tr>
<td>Other Histologic Diagnosis (n=32)</td>
<td>0.64</td>
<td>0.70</td>
</tr>
<tr>
<td>Large Cell Carcinoma (n=36)</td>
<td>0.39</td>
<td>0.70</td>
</tr>
<tr>
<td>Adenocarcinoma (n=471)</td>
<td>0.60</td>
<td>0.70</td>
</tr>
</tbody>
</table>

- PFS results were internally consistent; benefit was seen across all subgroups
- CR/PR and SD subgroups benefited from pemetrexed maintenance (median PFS=4.1 mos for both)

Paz-Ares et al. ASCO 2011; abstr CRA7510
Ongoing Clinical Trials
ECOG 5508

Paclitaxel
Carboplatin
Bevacizumab
N=1236

Nonprogressors
N=864

Bevacizumab
Bevacizumab
Pemetrexed
Pemetrexed

Primary endpoint: Overall Survival

Ongoing Clinical Trials
POINTBREAK STUDY

Primary Endpoint: OS

Arm A: 450 patients
- Induction therapy:
  up to four 21-day cycles
  Patients with CR, PR, or SD
  After induction therapy
  Continue on to maintenance therapy
- Maintenance therapy:
  until PD or treatment discontinuation
  Patients with PD:
  follow up q50d until death
  Patients without PD:
  follow up q2w until PD;
  thereafter, follow up q50d until death

Arm B: 450 patients
- Paclitaxel
  200 mg/m² IV q21d
  Carboplatin
  AUC 6 IV q21d
  Bevacizumab
  15 mg/kg IV q21d

- Pemetrexed
  500 mg/m² IV q21d
  Bevacizumab
  15 mg/kg IV q21d

Determination of eligibility

Post-discontinuation follow-up
Summary

- Advanced NSCLC is a rapidly progressing disease, with only a short window of opportunity for therapeutic intervention
- First-line platinum doublet chemotherapy is stopped after 4–6 cycles because of cumulative toxicity and limited incremental benefit
- Up to 50% of patients receive no further therapy due to rapid worsening of symptoms and performance status
- Maintenance by chemotherapy with pemetrexed offers the possibility of continued active treatment to delay disease progression and symptom deterioration
  - Continuation maintenance represents true maintenance. Available data with pemetrexed are relevant and promising
  - Data on switch maintenance are robust
  - Further studies are ongoing