ASCO 2007: an overview of highlighted Avastin trials in NSCLC

Phase III NSCLC

Subset analysis of ECOG 4599
Outcomes for elderly in advanced stage non–small cell lung cancer (NSCLC) patients (pts) treated with bevacizumab (B) in combination with carboplatin (C) and paclitaxel (P): Analysis of Eastern Cooperative Oncology Group (ECOG) 4599 study.

AVAiL Trial
Randomised, double-blind multicentre phase III study of bevacizumab in combination with cisplatin and gemcitabine in chemotherapy-naive patients with advanced or recurrent non-squamous non–small cell lung cancer (NSCLC): BO17704.

Lynch Discussion
Excerpt on bevacizumab — AVAiL vs. ECOG 4599

Analysis Across Trials
Bevacizumab: analysis of clinical benefit in females across trials in colorectal cancer and non–small cell lung cancer

Phase II NSCLC

• A phase II study of erlotinib (E) and bevacizumab (B) in patients (pts) with previously untreated stage IIIB/IV non–small cell lung cancer (NSCLC)

• Phase II trial of oxaliplatin, pemetrexed, and bevacizumab in previously-treated advanced non–small cell lung cancer (NSCLC)

• Pemetrexed and carboplatin plus bevacizumab as first-line therapy for advanced non-squamous non–small cell lung cancer (NSCLC): preliminary results

Malignant Mesothelioma

• Final analysis of a multi-center, double-blind, placebo-controlled, randomized phase II trial of gemcitabine/cisplatin (GC) plus bevacizumab (B) or placebo (P) in patients (pts) with malignant mesothelioma (MM)
Subset Analysis of ECOG 4599

Outcomes for elderly advanced stage non-small cell lung cancer (NSCLC) patients treated with bevacizumab (B) in combination with carboplatin (C) and paclitaxel (P): Analysis of Eastern Cooperative Oncology Group (ECOG) 4599 study.

Subset analysis of phase III trial of Avastin® in NSCLC (E4599): design

Elderly patients (≥70) account for approximately 50% of all lung cancer patients

**Objective of subset analysis of E4599**
Compare outcomes for paclitaxel and carboplatin combination (PC) chemotherapy and PC with bevacizumab in elderly patients enrolled in E4599

Eligible cases from E4599 = 850 (PC: n = 433, PCB: n = 417)
≥70 years: n = 224 (26%),
≥80 years: (1.6%)
Elderly median age: 74 years
Non-elderly median age: 63 years

AUC = area under the curve
Bv = bevacizumab
ECOG = Eastern Cooperative Oncology Group
NSCLC = non–small cell lung cancer
PC = paclitaxel/carboplatin
PCB = paclitaxel/carboplatin/bevacizumab
PS = performance status

Subset analysis of E4599: *efficacy of PCB vs. PC in elderly and non-elderly*

<table>
<thead>
<tr>
<th></th>
<th>Elderly (≥70)</th>
<th>Non-Elderly (&lt;70)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PC</td>
<td>PCB</td>
</tr>
<tr>
<td>CR + PR (%)</td>
<td>17</td>
<td>29</td>
</tr>
<tr>
<td>SD (%)</td>
<td>50</td>
<td>39</td>
</tr>
<tr>
<td>Median PFS (m)</td>
<td>4.9</td>
<td>5.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>p = 0.063</em></td>
</tr>
<tr>
<td>1-yr survival (%)</td>
<td>50</td>
<td>46</td>
</tr>
<tr>
<td>Survival (m)</td>
<td>12.1</td>
<td>11.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>p = 0.4</em></td>
</tr>
</tbody>
</table>

CR = complete response  PC = paclitaxel/carboplatin  
PCB = paclitaxel/carboplatin/bevacizumab  
PFS= progression-free survival  
PR = partial response  SD = stable disease

Subset analysis of E4599: summary

- Proportion of elderly patients in ECOG 4599 is the highest recorded among ECOG phase III trials.

- While there was an improvement with PCB in survival and PFS in the non-elderly cohort, there was no significant improvement noted in the elderly.

- PCB was associated with a higher degree of toxicity when compared to PC alone.

- The observations were limited by the post-hoc, retrospective nature of this analysis.

- The safety and efficacy of bevacizumab-chemotherapy combinations in elderly patients with NSCLC merits further investigation.

ECOG = Eastern Cooperative Oncology Group
NSCLC = non–small cell lung cancer   PC = paclitaxel/carboplatin
PCB = paclitaxel/carboplatin/bevacizumab   PFS = progression-free survival

AVAiL Trial

Randomised, double-blind multicentre phase III study of bevacizumab in combination with cisplatin and gemcitabine in chemotherapy-naïve patients with advanced or recurrent non-squamous non-small cell lung cancer (NSCLC): BO17704

AVAiL trial: study design

- **Primary endpoint**: PFS
- **Secondary endpoints**: Overall survival; response rates; duration of response; safety
- Cisplatin 80 mg/m² IV on day 1 and gemcitabine 1,250 mg/m² on day 1 + day 8 (3-weekly)
- Avastin 7.5 mg/kg or 15 mg/kg or placebo IV on day 1 (3-weekly)
- Avastin or placebo continued after chemotherapy until progressive disease
- Stratification factors: disease stage, ECOG PS, region, gender
- Entry criteria: no brain metastases, no squamous cell carcinoma, no hemoptysis
- Tumour assessment every three cycles

CG = cisplatin/gemcitabine; ECOG = Eastern Cooperative Oncology Group
IV = intravenous; NSCLC = non–small cell lung cancer
PD = progressive disease
PFS = progression-free survival; PS = performance status
AVAiL trial: PFS: primary analysis (intent-to-treat) of Avastin 7.5 mg/kg versus pooled placebo

**Graph:**
- **X-axis:** Time (months) from 0 to 18
- **Y-axis:** Possibility of PFS ranging from 0 to 1.0
- Two curves:
  - **Green** for Placebo + CG (n = 347)
  - **Blue** for Avastin 7.5 mg/kg + CG (n = 345)

**Table:**
<table>
<thead>
<tr>
<th></th>
<th>Placebo + CG (n = 347)</th>
<th>Avastin 7.5 mg/kg + CG (n = 345)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>-</td>
<td>0.75</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.62, 0.91)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>-</td>
<td>0.0026</td>
</tr>
</tbody>
</table>

**Legend:**
- CG = cisplatin/gemcitabine; CI = confidence interval
- HR = hazard ratio; PFS = progression-free survival

**AVAiL trial: PFS: primary analysis (intent-to-treat) of Avastin 15 mg/kg versus pooled placebo**

![Graph showing progression-free survival (PFS) over time for Avastin 15 mg/kg + CG compared to placebo + CG.](image)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Placebo + CG (n = 347)</th>
<th>Avastin 15 mg/kg + CG (n = 351)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>0.82 (0.68, 0.98)</td>
</tr>
<tr>
<td>3</td>
<td>0.8</td>
<td>0.85 (0.71, 1.00)</td>
</tr>
<tr>
<td>6</td>
<td>0.6</td>
<td>0.89 (0.73, 1.07)</td>
</tr>
<tr>
<td>9</td>
<td>0.4</td>
<td>0.93 (0.76, 1.12)</td>
</tr>
<tr>
<td>12</td>
<td>0.2</td>
<td>0.97 (0.79, 1.19)</td>
</tr>
<tr>
<td>15</td>
<td>0.1</td>
<td>1.00 (0.82, 1.22)</td>
</tr>
<tr>
<td>18</td>
<td>0.0</td>
<td>1.00 (0.83, 1.21)</td>
</tr>
</tbody>
</table>

**HR** = hazard ratio  
**CI** = confidence interval  
**PFS** = progression-free survival

### AVAiL trial: summary of efficacy

<table>
<thead>
<tr>
<th></th>
<th>Placebo + CG (n = 324)</th>
<th>Avastin 7.5 mg/kg + CG (n = 323)</th>
<th>Avastin 15 mg/kg + CG (n = 332)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate (%)</td>
<td>20</td>
<td>34, <em>p</em> &lt;0.0001</td>
<td>30, <em>p</em> = 0.0017</td>
</tr>
<tr>
<td>Median duration of response (months)</td>
<td>4.7, (4.6, 5.6)</td>
<td>6.1, (5.1, 7.0)</td>
<td>6.1, (5.0, 6.6)</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>6.1</td>
<td>6.7</td>
<td>6.5</td>
</tr>
<tr>
<td>Overall survival</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

- The protocol-specified number of events required for the fully powered survival analysis has not been reached.

CG = cisplatin/gemcitabine  
CI = confidence interval  
PFS = progression-free survival

AVAiL trial: safety

<table>
<thead>
<tr>
<th>Safety summary of all treated patients (%)</th>
<th>Placebo + CG (n = 327)</th>
<th>Avastin 7.5 mg/kg + CG (n = 330)</th>
<th>Avastin 15 mg/kg + CG (n = 329)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade 3–5 AEs</td>
<td>75</td>
<td>76</td>
<td>81</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>35</td>
<td>35</td>
<td>44</td>
</tr>
<tr>
<td>AEs leading to death</td>
<td>4</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severe (grade ≥3) AEs with ≥2% difference between Avastin arms and placebo arm (%)</th>
<th>Placebo + CG (n = 327)</th>
<th>Avastin 7.5 mg/kg + CG (n = 330)</th>
<th>Avastin 15 mg/kg + CG (n = 329)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>32</td>
<td>40</td>
<td>36</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>23</td>
<td>27</td>
<td>23</td>
</tr>
<tr>
<td>Anemia</td>
<td>14</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Asthenia</td>
<td>3</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>&lt;1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pulmonary hemorrhage n (%)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary hemorrhage (grade ≥3)</td>
<td>2 (0.6)</td>
<td>5 (1.5)</td>
<td>3 (0.9)</td>
</tr>
</tbody>
</table>

AE = adverse event  CG = cisplatin/gemcitabine

AVAiL trial: summary

- This is the second randomized phase III trial to show benefit from Avastin therapy in advanced NSCLC in terms of progression-free survival and response rate.

- Similar benefit was seen with both Avastin doses vs. control.

- Overall survival data are pending.

- Avastin in combination with cisplatin/gemcitabine was well tolerated, no new safety signals were observed, and incidence of severe hemoptysis/pulmonary hemorrhage 1.5%.

NSCLC = non–small cell lung cancer

Lynch Discussion

Excerpt on bevacizumab in NSCLC — with perspective on AVAiL and ECOG 4599 trials

Presented: Saturday, June 2, 2007

ECOG = Eastern Cooperative Oncology Group
NSCLC = non–small cell lung cancer
Lynch: *questions for bevacizumab*

1. Does bevacizumab improve outcomes in NSCLC?
2. Does it matter which chemotherapy is combined with bevacizumab?
3. Is there a gender difference in terms of benefit from bevacizumab in NSCLC?
4. Is bevacizumab safe for patients excluded from E4599?
   - Brain mets
   - Anticoagulation
   - Squamous cell patients
5. Is there value to maintenance bevacizumab?
6. Does the dose of bevacizumab matter (7.5 mg/kg vs. 15 mg/kg)?

NSCLC = non–small cell lung cancer
Lynch: AVAiL trial

- Key statistical issues
  - Randomized trial powered for PFS
  - Not powered for OS
  - Not designated to compare the two bevacizumab arms to each other, but rather only to the control (non-bevacizumab arm)

- Entry criteria similar to E4599 (no brain mets, no squamous cell carcinoma, no hemoptysis)

- Three notable differences:
  - Therapeutic anti-coagulation allowed during trial (not at entry)
  - Patients with “dry” 3B not eligible
  - Patients assessed every 3 cycles, not 2 cycles

OS = overall survival
PFS = progression-free survival
Lynch: *efficacy – AVAiL vs. E4599*

<table>
<thead>
<tr>
<th></th>
<th>CG</th>
<th>CG 7.5</th>
<th>CG 15</th>
<th>PC</th>
<th>PC 15</th>
</tr>
</thead>
<tbody>
<tr>
<td># Patients</td>
<td>347</td>
<td>345</td>
<td>351</td>
<td>433</td>
<td>417</td>
</tr>
<tr>
<td>RR</td>
<td>20%</td>
<td>34%*</td>
<td>30%*</td>
<td>15%</td>
<td>35%*</td>
</tr>
<tr>
<td>PFS</td>
<td>6.1</td>
<td>6.7*</td>
<td>6.5*</td>
<td>4.5</td>
<td>6.3*</td>
</tr>
<tr>
<td>OS</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>10.3</td>
<td>12.3*</td>
</tr>
</tbody>
</table>

* p <0.05

CG = cisplatin/gemcitabine
OS = overall survival
PC = paclitaxel/carboplatin
PFS = progression-free survival
RR = response rate
Lynch: PFS endpoint - AVAiL vs. E4599

<table>
<thead>
<tr>
<th></th>
<th>AVAiL 7.5</th>
<th>AVAiL 15</th>
<th>E4599 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>0.75</td>
<td>0.82</td>
<td>0.66</td>
</tr>
<tr>
<td>(p)-value</td>
<td>0.0026</td>
<td>0.0301</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HR = hazard ratio  
PFS = progression-free survival
Lynch: *toxicity – AVAiL vs. E4599*

<table>
<thead>
<tr>
<th></th>
<th>CG</th>
<th>CG 7.5</th>
<th>CG 15</th>
<th>PC</th>
<th>PC 15</th>
</tr>
</thead>
<tbody>
<tr>
<td># Patients</td>
<td>347</td>
<td>345</td>
<td>351</td>
<td>433</td>
<td>417</td>
</tr>
<tr>
<td>3/4 pmn</td>
<td>32%</td>
<td>40%</td>
<td>36%</td>
<td>16.8%*</td>
<td>25.5%*</td>
</tr>
<tr>
<td>3/4 plts</td>
<td>23%</td>
<td>27%</td>
<td>23%</td>
<td>0.2%*</td>
<td>1.6%*</td>
</tr>
<tr>
<td>3/4/5 hemoptysis</td>
<td>0.6%</td>
<td>1.5%</td>
<td>0.9%</td>
<td>0.2%</td>
<td>1.9%</td>
</tr>
<tr>
<td>3/4 bleeding</td>
<td>2%</td>
<td>4%</td>
<td>4%</td>
<td>0.7%</td>
<td>4.4%</td>
</tr>
<tr>
<td>3/4 htn</td>
<td>2%</td>
<td>6%</td>
<td>9%</td>
<td>0.7%</td>
<td>7%</td>
</tr>
</tbody>
</table>

* Grade 4 only

CG = cisplatin/gemcitabine
PC = paclitaxel/carboplatin
htn = hypertension  pmn = neutropenia  plts = thrombocytopenia
Lynch: does bevacizumab improve outcomes in NSCLC?

- Benefit of bevacizumab in advanced NSCLC is independent of which chemotherapy is used:
  - paclitaxel/carboplatin
  - cisplatin/gemcitabine

- Safety data should be available soon to support the combination of bevacizumab with platinum-based regimens containing docetaxel, pemetrexed, and vinorelbine.

NSCLC = non–small cell lung cancer
Lynch: *does it matter which chemotherapy is combined with bevacizumab?*

- AVAiL clearly supports the findings of E4599: prolongation of PFS and response rate in eligible patients with NSCLC.

- HR 0.75 and 0.82 slightly higher than 0.66 may be due to:
  - Subtle differences in patient populations
  - Assessment every 3 cycles rather than 2 cycles
  - Use of cisplatin-containing regimen

*HR = hazard ratio
NSCLC = non–small cell lung cancer
PFS = progression-free survival*
Lynch: is there a gender difference in terms of benefit from bevacizumab in NSCLC?

- ECOG 4599 showed improved RR, PFS, and OS in men.

- No impact on OS for women in E4599, despite better RR and PFS

- AVAiL confirms improved RR and PFS in women with use of bevacizumab

- While not answered yet in AVAiL, at this point there is no rationale for withholding bevacizumab for eligible women with NSCLC

ECOG = Eastern Cooperative Oncology Group
NSCLC = non–small cell lung cancer
OS = overall survival
PFS = progression-free survival
RR = response rate
Lynch: *is bevacizumab safe for patients excluded from E4599?*

- AVAiL does not tell us anything about patients with brain metastases or squamous cell carcinoma.

- AVAiL data suggest that pulmonary bleeding is not increased in the following patients:
  - Central tumours
  - Patients requiring full dose anti-coagulation (FDAC) during therapy

- Treatment of patients requiring FDAC should be done with caution and careful monitoring
Lynch: *is there value to maintenance bevacizumab?*

- Of patients in AVAiL >70% received maintenance bevacizumab compared to <10% of control patients
- Both E4599 and AVAiL employed strategy of maintenance therapy
- Prolongation of PFS and OS only seen in schemes using maintenance
- Clearly important question for future trials, but until data emerge to the contrary, maintenance should be given unless progressive disease or toxicity intervenes

**OS** = overall survival  
**PFS** = progression-free survival
Lynch: what does AVAiL tell us about dose?

- Both doses (7.5 mg/kg and 15 mg/kg) of bevacizumab prolonged PFS and RR when combined with cisplatin and gemcitabine.

- Survival data are immature and study is not powered for OS.

- Both doses were associated with acceptable rates of serious toxicity, and it is reasonable to continue trials with either dose.

OS = overall survival  
PFS = progression-free survival  
RR = response rate
**Lynch: what is the optimal dose for bevacizumab?**

- AVAiL is preliminary and we need OS data

- However:
  - AVAiL provides a strong rationale for 7.5 in terms of response rate, toxicity, and PFS
  - IFL data from colon cancer strongly support 7.5 for survival

- Unless there is a “surprise” in the AVAiL survival data — 7.5 is the dose going forward

- Burden of proof is on those who favour 15 mg/kg to demonstrate that it is more effective

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**Definitions:**
- IFL = irinotecan, 5-FU bolus, leucovorin
- OS = overall survival
- PFS = progression-free survival
Lynch: *bevacizumab conclusions*

Bevacizumab is clear standard of care in eligible first-line NSCLC

- Dose of 7.5 mg/kg likely going forward
- Bevacizumab should be given until progression
- FDAC with caution

FDAC = full dose anti-coagulation
NSCLC = non–small cell lung cancer
Benefit in Females

Bevacizumab: Analysis of clinical benefit in females across trials in colorectal cancer and non-small cell lung cancer

### Benefit in females: duration of survival

<table>
<thead>
<tr>
<th>Bevacizumab</th>
<th>Females (n)</th>
<th>Control median mos</th>
<th>Bv median mos</th>
<th>HR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E4599</td>
<td>387</td>
<td>13.1</td>
<td>13.3</td>
<td>0.98</td>
<td>(0.77–1.25)</td>
</tr>
<tr>
<td>Ph III – NSCLC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OSI2950g</td>
<td>55</td>
<td>6.9</td>
<td>16.4</td>
<td>0.34</td>
<td>(0.16–0.72)</td>
</tr>
<tr>
<td>Ph II – NSCLC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVF2192g</td>
<td>97</td>
<td>12.5</td>
<td>16.6</td>
<td>0.83</td>
<td>(0.51–1.34)</td>
</tr>
<tr>
<td>Ph II – mCRC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVF2107g</td>
<td>328</td>
<td>15.7</td>
<td>18.7</td>
<td>0.73</td>
<td>(0.54–0.99)</td>
</tr>
<tr>
<td>Ph III – mCRC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E3200</td>
<td>227</td>
<td>10.3</td>
<td>12.9</td>
<td>0.73</td>
<td>(0.55–0.98)</td>
</tr>
<tr>
<td>Ph III – mCRC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bv = bevacizumab  
CI = confidence interval  
HR = hazard ratio  
mCRC = metastatic colorectal cancer  
NSCLC = non–small cell lung cancer  

**Benefit in females: progression-free survival**

<table>
<thead>
<tr>
<th>Bevacizumab Trial</th>
<th>Females (n)</th>
<th>Control median mos</th>
<th>Bv median mos</th>
<th>HR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E4599 Ph III – NSCLC</td>
<td>387</td>
<td>5.3</td>
<td>6.2</td>
<td>0.71</td>
<td>(0.57–0.88)</td>
</tr>
<tr>
<td>OSI2950g Ph II – NSCLC</td>
<td>55</td>
<td>2.8</td>
<td>5.6</td>
<td>0.32</td>
<td>(0.15–0.69)</td>
</tr>
<tr>
<td>AVF2192g Ph II – mCRC</td>
<td>97</td>
<td>5.8</td>
<td>7.0</td>
<td>0.72</td>
<td>(0.43–1.20)</td>
</tr>
<tr>
<td>AVF2107g Ph III – mCRC</td>
<td>328</td>
<td>5.6</td>
<td>9.2</td>
<td>0.60</td>
<td>(0.46–0.78)</td>
</tr>
<tr>
<td>E3200 Ph III – mCRC</td>
<td>227</td>
<td>4.2</td>
<td>7.2</td>
<td>0.61</td>
<td>(0.46–0.81)</td>
</tr>
</tbody>
</table>

Bv = bevacizumab  
CI = confidence interval  
HR = hazard ratio  
mCRC = metastatic colorectal cancer  
NSCLC = non–small cell lung cancer  

Benefit in females: conclusion

- Improved overall survival, progression-free survival, and tumour response was observed in females with bevacizumab plus chemotherapy, compared to chemotherapy-alone, in all trials in mCRC and refractory advanced NSCLC patients — with the only exception being improved overall survival in women for study E4599.

- Evidence suggests a clinical benefit with bevacizumab in females with advanced non-squamous NSCLC.

mCRC = metastatic colorectal cancer
NSCLC = non–small cell lung cancer
Avastin plus Tarceva

A phase II study of erlotinib (E) and bevacizumab (B) in patients (pts) with previously untreated stage IIIb/IV non-small cell lung cancer (NSCLC)

With erlotinib: objective & results

- Determine rate of non-progression in 46 patients with advanced NSCLC after 6 weeks of treatment with erlotinib, 150 mg daily, and bevacizumab, 15 mg/kg every 3 weeks.

- The combination was well tolerated with a rate of non-progression at 6 weeks of 71% and an overall tumour response rate of 20%.

- Median overall survival was 7.9 months, and median progression-free survival was 5.7 months.

- To date 22 patients are still in survival follow-up and 17 are without progression.

- Most common treatment-related adverse events were skin rash (64%) and diarrhea (53%).
With erlotinib: *safety*

<table>
<thead>
<tr>
<th>Most common adverse events</th>
<th>All grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>29 (64%)</td>
<td>11 (24%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24 (53%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>13 (29%)</td>
<td></td>
</tr>
<tr>
<td>Pruritis</td>
<td>6 (13%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (9%)</td>
<td></td>
</tr>
<tr>
<td>Mucositis</td>
<td>4 (9%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>4 (9%)</td>
<td></td>
</tr>
<tr>
<td>Muscle pain</td>
<td>4 (9%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (9%)</td>
<td></td>
</tr>
<tr>
<td>Thrombosis/embolism</td>
<td>3 (7%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>3 (7%)</td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>2 (4%)</td>
<td></td>
</tr>
<tr>
<td>Colon perforation</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Elevated liver enzymes</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1 (2%)</td>
<td></td>
</tr>
</tbody>
</table>

Avastin with Oxaliplatin & Pemetrexed

Phase II trial of oxaliplatin, pemetrexed, and bevacizumab in previously-treated advanced non-small cell lung cancer (NSCLC)

With oxaliplatin & pemetrexed: design & efficacy

- Single-agent chemotherapy is standard for third-line and second-line therapy of NSCLC. Combination chemotherapy has to date not proven to be superior — often adding additional toxicity without additional efficacy.

- Of the 34 evaluable patients for tumour response, 0 had CR, 9 (27%) had PR, 15 (44%) had SD, and 10 (29%) had PD.

Non-squamous NSCLC (n = 36)
Brain mets
ECOG PS 0 or 1
Prior chemotherapy

Pemetrexed 500 mg/m²
Oxaliplatin 120 mg/m²
Bevacizumab 15 mg/kg
Q 21 days x 6 cycles

CR = complete response
ECOG = Eastern Cooperative Oncology Group
NSCLC = non–small cell lung cancer
PD = progressive disease
PR = partial response
PS = performance status
SD = stable disease
With oxaliplatin & pemetrexed: PFS and OS

- Data for PFS and OS are preliminary
- Estimated median PFS is 5.7 months (95% CI 4.1 – 7.6 mos)
- Estimated median OS is 15.0 months (95% CI 7.4 – 20.7 mos)

CI = confidence interval
OS = overall survival
PFS = progression-free survival
## With oxaliplatin & pemetrexed: safety

<table>
<thead>
<tr>
<th>Serious Adverse Events</th>
<th>Grade III</th>
<th>Grade IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hgb</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Platelets</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Infectious colitis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Wheeze/bronchospasm</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Face pain</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

With oxaliplatin & pemetrexed:

**Conclusion**

These data suggest that the combination of pemetrexed, oxaliplatin, and pemetrexed is tolerable and has a promising response rate.

With Pemetrexed & Carboplatin

Pemetrexed and carboplatin plus bevacizumab for advanced non-squamous non-small cell lung cancer (NSCLC): Preliminary results

With pemetrexed & carboplatin: design & efficacy

- Pemetrexed in combination with carboplatin has shown to have promising activity and toxicity profile in advanced NSCLC

- Bevacizumab was added to this regimen to evaluate the toxicities and estimate median TTP

AUC = area under the curve
CR = complete response
ECOG = Eastern Cooperative Oncology Group
NSCLC = non–small cell lung cancer
PD = progressive disease
PR = partial response
PS = performance status
SD = stable disease
TTP = time to tumour progression

With pemetrexed & carboplatin: overall survival

Overall Survival

Overall Survival ($N_{\text{nn}} = 40$ pts)

With pemetrexed & carboplatin: \textit{safety}

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>DVT</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Diverticulitis</td>
<td>3</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Diverticulitis</td>
<td>4</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Infection</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Infection</td>
<td>4</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
With pemetrexed & carboplatin: *conclusion*

- Recruitment is still continuing for this study
- Treatment with pemetrexed and carboplatin plus bevacizumab in patients with advanced non-squamous NSCLC is promising with an acceptable toxicity profile
- Of the 39 evaluable patients there has been a response rate (CR + PR) of 59% (21 patients) (95% CI 38% - 70%)
- Patients with a prior history of diverticulitis should be excluded until the relationship between diverticulitis and this regimen is explored further
- Maintenance pemetrexed and bevacizumab appears to favourably increase time to progression

CI = confidence interval; CR = complete response
NSCLC = non–small cell lung cancer
PR = partial response
Malignant Mesothelioma

Final analysis of a multi-center, double-blind, placebo-controlled, randomized phase II trial of gemcitabine/cisplatin (GC) plus bevacizumab (B) or placebo (P) in patients (pts) with malignant mesothelioma (MM)

Malignant mesothelioma: VEGF

- In vitro VEGF (vascular endothelial growth factor) increases proliferation of MM.
- In mesothelioma patients, the highest VEGF levels of any solid tumour are observed.
- There is an inverse correlation between VEGF levels and survival.
- Several VEGF inhibitors have demonstrated modest single-agent activity in phase II trials.

MM = malignant mesothelioma
VEGF = vascular endothelial growth factor
Malignant mesothelioma: phase II study

**design**

- **Primary endpoint:** progression-free survival (PFS)
- **Secondary endpoints:** overall survival; response rates; toxicity
- **Correlative:** measure plasma VEGF as a predictor of outcome
- Avastin or placebo continued after chemotherapy until progressive disease
- Entry criteria: ECOG PS 0–1
- CT scans every two cycles

**Previously untreated malignant mesothelioma (MM) ECOG PS 0-1 (n = 108)**

- Gemcitabine 1,250 mg/m², D1, D8
- Cisplatin 75 mg/m², D1
- Avastin 15 mg/kg, D1
  - 3-weekly
  - 6 cycles

- Placebo 15 mg/kg, D1
  - 3-weekly

- Gemcitabine 1,250 mg/m², D1, D8
- Cisplatin 75 mg/m², D1
- Placebo 15 mg/kg, D1
  - 3-weekly

ECOG = Eastern Cooperative Oncology Group
PD = progressive disease
PS = performance status
VEGF = vascular endothelial growth factor
Malignant mesothelioma: *PFS and OS*

<table>
<thead>
<tr>
<th>Table 1: Progression-free and overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>CGB</strong></td>
</tr>
<tr>
<td>Median progression-free survival</td>
</tr>
<tr>
<td>(95% CI)</td>
</tr>
<tr>
<td>1-year PFS</td>
</tr>
<tr>
<td>Median overall survival</td>
</tr>
<tr>
<td>(95% CI)</td>
</tr>
<tr>
<td>1-year OS</td>
</tr>
</tbody>
</table>

*Adjusted for stratification factors (PS and histology)*

CI = confidence interval; CGB = cisplatin/gemcitabine/bevacizumab
CGP = cisplatin/gemcitabine/placebo; HR = hazard ratio; OS = overall survival;
PFS = progression-free survival; PS = performance status
Malignant mesothelioma: OS for VEGF ≤ median

Overall survival by treatment: VEGF ≤ median

OS = overall survival
VEGF = vascular endothelial growth factor

Malignant mesothelioma: conclusion

- The addition of bevacizumab to gemcitabine and cisplatin did not yield statistically significant differences in progression-free survival, overall survival, response, or grade 3/4 toxicity.
- Pre-treatment, lower VEGF levels correlated with better outcome.
- Bevacizumab-treated patients with low baseline VEGF levels had longer PFS and OS.

OS = overall survival
PFS = progression-free survival
VEGF = vascular endothelial growth factor