Anti-Angiogenesis Agents in NSCLC

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The Angiogenic Switch

Small tumor
• Nonvascular
• "Dormant"

Larger tumor
• Vascular
• Metastatic potential

Angiogenic
Switch

1-2 mm

VEGF-Vascular Endothelial Growth Factor

• Angiogenesis: essential for tumor growth > 2 to 3 mm³
• VEGF- most potent and specific angiogenesis factor
• VEGF levels correlate with prognosis in cancer (NSCLC)
• VEGF receptors (VEGFRs) on endothelial cells

VEGF: Targeted Approaches - Antibody

Adapted from Noonberg and Benz. Drugs. 2000;59:753.

Dvorak In Arch Allergy Immunol 107:233-5, 1995
Mattern Br J Cancer 73:931-4, 1996
Iwamoto J Thorac Cardiovasc Surg 115:1007-14, 1998
Bevacizumab in Adv NSCLC

- Phase III ECOG 4599
  - 878 patients: Carboplatin/Paclitaxel +/- Bevacizumab
  - PFS 6.2 vs 4.5 mo, response 35% vs 15%
  - MST 12.3 mo (10.3 mo control)

- Phase III AVAiL
  - 1043 patients: Cisplatin/Gemcitabine +/- Bevacizumab
  - PFS HR 0.75, p=0.003 at 7.5 mg/kg 0.85, p=0.046 at 15 mg/kg
  - RR 32% vs 20%
  - MST 13.6m (7.5); 13.4m (15); 13.1m (plac), NS

Special Populations

- Women
- Elderly
- Anti-coagulated
- Brain Metastases
- Squamous Histology

E4599 - Efficacy by Sex

<table>
<thead>
<tr>
<th></th>
<th>Male (HR)</th>
<th>Female (HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>0.69</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>p=0.003</td>
<td>P=0.80</td>
</tr>
<tr>
<td>PFS</td>
<td>0.53</td>
<td>0.68</td>
</tr>
<tr>
<td></td>
<td>P=&lt;0.0001</td>
<td>P=0.002</td>
</tr>
<tr>
<td>RR (%)</td>
<td>12.2 vs 23.5</td>
<td>7.4 vs 31.7</td>
</tr>
<tr>
<td></td>
<td>p=0.006</td>
<td>P&lt;0.0001</td>
</tr>
</tbody>
</table>

E4599: Age/Sex/Bevacizumab interaction

- Eligible patients from E4599 (N=850) were divided into male and female cohorts by treatment (-/+ BEV)
- Separated into age groups of < 60 or >/= 60 yo
- Survival calculated for each cohort
- Known prognostic factors such as performance status, weight loss, and stage were also compared for each sex/age cohort using two-sided Fisher’s exact tests
Age/Sex/Bevacizumab

Age 60 cut-point

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Bevacizumab</th>
<th>Median PFS</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 60 yo</td>
<td>Women - BEV</td>
<td>11.0 mo</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>Women + Bev</td>
<td>15.5 mo</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>Men - BEV</td>
<td>9.3 mo</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>Men + BEV</td>
<td>12.4 mo</td>
<td>73</td>
</tr>
<tr>
<td>&gt;= 60 yo</td>
<td></td>
<td>13.8 mo</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12.8 mo</td>
<td>122</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.5 mo</td>
<td>158</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11.0 mo</td>
<td>137</td>
</tr>
</tbody>
</table>

Wakelee IASLC 2008, abstr 131

Age/Sex/Bevacizumab

Elderly on E4599: Efficacy

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>PC</th>
<th>PCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly (70) n=224 (26% of trial)</td>
<td>17%</td>
<td>29%</td>
</tr>
<tr>
<td>Non-Elderly (&lt; 70)</td>
<td>14%</td>
<td>36%</td>
</tr>
</tbody>
</table>

CR+PR

Median PFS

Median survival

In Elderly: Significant increases in neutropenia, GIB, proteinuria, related deaths (6.3% vs 2.6%, p=08)

Wakelee IASLC 2008, abstr 131

Wakelee IASLC 2008, abstr 131

Anti-coagulation

On AVAIIL:
- Concomitant administration of heparin derivatives or warfarin does lead to increased risk of grade 1 epistaxis
- No increase in grade 3-5 bleeding events (but only 58 total patients of over 650 treated with bevacizumab on study)

On ARIES (observational phase IV)
- 91 pts (of 1014) on anticoagulation
- Grade 3-5 bleeding in 3/91 vs 23/923
- No Pulm hemorrhage on anticoagulation
- 1 CNS hemorrhage (of 91)
- No GI hemorrhage

Ramalingam JCO 2008, 26:60

Leigh 8th Intl Lung Cancer Congress: Maui June 2007, Spigel IASLC 2008, abs 141
Brain Metastases
ASCO 2008

<table>
<thead>
<tr>
<th>Study</th>
<th>Abstr</th>
<th># pts with BrM</th>
<th>CNS Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>E4599 / AVAIL</td>
<td>Archer A# 8114</td>
<td>0</td>
<td>24 – BrM at progression</td>
</tr>
<tr>
<td>(-) BrM at enrollment, 1086 pts received Bevacizumab</td>
<td></td>
<td>6 (1- new BrM, 5 – w/o BrM)</td>
<td></td>
</tr>
<tr>
<td>ATLAS (phase III)</td>
<td>Akerley A# 8043</td>
<td>26</td>
<td>Treated BrM (WBRT)</td>
</tr>
<tr>
<td>Carbo/Taxol + Bev + Bev +/- Erlot maintenance</td>
<td></td>
<td>1 (G2), post-progression after 14 cycles of Bev</td>
<td></td>
</tr>
<tr>
<td>PASSPORT (phase II)</td>
<td>Akerley A# 8043</td>
<td>65</td>
<td>Treated BrM (RS, NS, WBRT)</td>
</tr>
<tr>
<td>(1st or 2nd line Chemo + Bev)</td>
<td></td>
<td>(-)</td>
<td></td>
</tr>
<tr>
<td>ARIES (OCS)</td>
<td>Lynch A# 8077</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Bev in 1st line setting, 1031 pts</td>
<td></td>
<td>(-)</td>
<td></td>
</tr>
<tr>
<td>SAIL (OCS)</td>
<td>Dansin A# 6085</td>
<td>0 known</td>
<td>12 new symptomatic BrM</td>
</tr>
<tr>
<td>Bev in 1st line setting, 1699 pts No screening for asympt BrM</td>
<td></td>
<td>3, none had BrM</td>
<td></td>
</tr>
</tbody>
</table>

Squamous Cell Histology

- Several trials halted due to bleeding and concern of TE fistula after radiation (based on small cell experience)
- All had used radiation to “stabilize tumor”
- BRIDGE trial- phase II- stage IIIB/IV Squamous NSCLC
- 2 cycles carboplatin/paclitaxel → Chemo + Bev (15 mg/kg)
  - N=47, 31 got Bevacizumab
  - Excluded: prior hemoptysis, cavitation, into vessel
  - 4 had prior lung radiation (mostly remote)
  - Median 5 cycles of bevacizumab (85 days)
  - 1 Gr 5 pulmonary hemorrhage, 1 Gr 1 PH, no other bleeding

ATLAS allowed for peripheral squamous NSCLC

ECOG 1505
Adj Chemo+/- Bevacizumab

**ELIGIBLE:**
Resected IB-IIIA
> Lobectomy
No prior chemo
No planned XRT
No h/o CVA/TIA
No ATE w/in 1 yr

**STRATIFIED:**
- Stage (IB (≥4cm), II, IIIA-N2, IIIA-T3N1)
- Histology (Squam vs other)
- Gender
- Chemo regimen

**RANDOMIZE**

- Chemotherapy X 4 cycles
- Chemotherapy X 4 cycles Plus Bevacizumab X 1 year

- Investigator Choice of 4 chemo regimens
  - Cis/Vinorelbine, Cis/Docetaxel, Cis/Gemcitabine, Cis/Pemetrexed

Anti-Angiogenesis Special Populations: Summary

- Younger Women have increased benefit from Bevacizumab (? Estrogen interaction)
- Caution with elderly patients - ongoing trials
- Hemoptysis remains an issue, but anti-coagulation can be considered cautiously
- Trials in pts with treated brain mets show probably safety
- Squamous histology still a major bleeding risk, though BRIDGE encouraging, radiation potentially harmful
- Adjuvant trial E1505 stratifies by sex, no age cut-point, allows for anti-coagulation and any histology
VEGF: Targeted Approaches - TKI

**Tyrosine kinase inhibitors**

Adapted from Noonberg and Benz. *Drugs.* 2000;59:753.

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**VEGFR TKIs and Toxicity**

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZD6474-Vandetanib</td>
<td>Diarrhea, rash, hypertension (mild), proteinuria, ↑ QTc interval</td>
</tr>
<tr>
<td>AZD2171-Cediranib</td>
<td>Fatigue, nausea/vomiting, diarrhea</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Diarrhea, fatigue, pancreatitis, hypertension, hand/foot syndrome</td>
</tr>
<tr>
<td>SU-11248 Sunitinib</td>
<td>Asthenia, rash, skin discoloration (yellow), hair depigmentation, neutropenia, hypertension, diarrhea, nausea/vomiting, anorexia, arthralgia, rare epistaxis/hemoptysis</td>
</tr>
<tr>
<td>AG-013736 Axitinib</td>
<td>Fatigue, Hypertension, transaminisitis, seizure, stomatitis, diarrhea, nausea/vomiting, anorexia, arthrogryphosis, rare epistaxis/hemoptysis</td>
</tr>
<tr>
<td>PTK787-Vatalanib</td>
<td>Fatigue, nausea/vomiting, dizziness, ataxia, transaminisitis</td>
</tr>
<tr>
<td>GW786034 Pazopanib</td>
<td>Fatigue, hypertension, transaminisitis, proteinuria, diarrhea, nausea/vomiting, anorexia, arthrogryphosis, rare epistaxis/hemoptysis</td>
</tr>
<tr>
<td>AMG-706-Motesanib</td>
<td>Hypertension, diarrhea, thrombosis, fatigue, cholecystitis</td>
</tr>
<tr>
<td>BIBF1120</td>
<td>Nausea/vomiting, diarrhea, fatigue, abdominal pain, transaminisitis</td>
</tr>
<tr>
<td>ABT-869</td>
<td>Hypertension, proteinuria, fatigue, rash, nausea, anorexia, diarrhea</td>
</tr>
</tbody>
</table>

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**Phase III trials of Vandetanib in advanced NSCLC**

**Overview**

<table>
<thead>
<tr>
<th>Study name</th>
<th>Abstract</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZODIAC</td>
<td>CRA8003</td>
</tr>
<tr>
<td>ZEAL</td>
<td>TREND in PFS</td>
</tr>
<tr>
<td>ZEST</td>
<td>8009</td>
</tr>
<tr>
<td>ZEPHYR</td>
<td>PENDING</td>
</tr>
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</table>

Adapted from Edelman ASCO 2009
**ZODIAC vs. ZEAL**

<table>
<thead>
<tr>
<th>Agent</th>
<th>ZODIAC</th>
<th>ZEAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>Z (694)</td>
<td>P (697)</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>Z (256)</td>
<td>P (278)</td>
</tr>
<tr>
<td>RR</td>
<td>17%*</td>
<td>10%</td>
</tr>
<tr>
<td>PFS HR</td>
<td>.79*</td>
<td>.86</td>
</tr>
<tr>
<td>PFS</td>
<td>4.0m*</td>
<td>3.2m</td>
</tr>
<tr>
<td>OS</td>
<td>10.6m</td>
<td>10.0m</td>
</tr>
<tr>
<td>OS HR</td>
<td>.91</td>
<td>.86</td>
</tr>
<tr>
<td>PFS HR</td>
<td>.79*</td>
<td>.86</td>
</tr>
<tr>
<td>OS</td>
<td>10.6m</td>
<td>10.0m</td>
</tr>
<tr>
<td>OS HR</td>
<td>.91</td>
<td>.86</td>
</tr>
</tbody>
</table>

* p-value < .05

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**Cediranib BR.24: Interim Analysis Jan 2008**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Cediranib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>IN</td>
<td>12%</td>
<td>5%</td>
</tr>
<tr>
<td>PD</td>
<td>5%</td>
<td>16%</td>
</tr>
<tr>
<td>PR</td>
<td>41%</td>
<td>19%</td>
</tr>
<tr>
<td>SD</td>
<td>40%</td>
<td>56%</td>
</tr>
</tbody>
</table>

- CR + PR: 41 vs 20 % p = 0.006
- PFS met the criteria to proceed to phase III, HR 0.77
- Reported fatal serious adverse events (any causality): 11.5 % vs 2 % (p = 0.002)

BR.24 Closed
BR.29 opened with Cediranib at 20 mg qd

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**VEGFR TKIs Sorafenib**

- **BAY43-9006 Sorafenib**
  - RPh II ECOG 2501 (400 mg bid): few responses, PFS +1.6 mo, p.009 and OS benefit +2.9 mo, NS (Schiller ASCO 2008) to be updated at WCLC
  - Ph II 51 pts no RR but many SD (Gatzemeier ASCO 2006)
  - Randomized phase III trial of sorafenib vs placebo as 3rd/4th line therapy ongoing
  - Ph III carbo/paclitaxel +/- sorafenib - no benefit, + harm in Squamous (ESCAPE study)

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**Sorafenib: E2501 Schema**

- Ph II ECOG 2501 (400 mg bid): few responses, PFS +1.6 mo, p.009 and OS benefit +2.9 mo, NS (Schiller ASCO 2008) to be updated at WCLC
- Ph II 51 pts no RR but many SD (Gatzemeier ASCO 2006)
- Randomized phase III trial of sorafenib vs placebo as 3rd/4th line therapy ongoing
- Ph III carbo/paclitaxel +/- sorafenib - no benefit, + harm in Squamous (ESCAPE study)
Sorafenib: E2501
PFS: Step 2 cohort

- **Initial Treatment**
  - Bay 43-9006: 51
  - Placebo: 32

- **Total**
  - 83

- **Median**
  - Bay 43-9006: 3.6 months (2.3-4.7)
  - Placebo: 2.0 months (1.8-2.3)

- **Log Rank Test; p=0.009**

- **HR**
  - 2.16 (95% CI: 1.21, 3.86)

Sorafenib Placebo

PFS measured from randomization; 12 pts censored at drug switching date

Schiller PASCO 2008

Other VEGFR TKIs

<table>
<thead>
<tr>
<th>VEGFR TKI</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>AG013736 Axitinib</td>
<td>9% single agent RR in 32 pts 2nd+ line adv NSCLC at 5 mg bid, MST 14.6 mo (Schiller ASCO 07), ongoing phase III trial</td>
</tr>
<tr>
<td>PTK787 Vatalanib</td>
<td>1250 mg qd or bid (500mg am/750 mg pm) 3/112 deaths (2 bleeds, 1 PE); 7% RR (4/57) w/ bid (Gauler ASCO 2007)</td>
</tr>
<tr>
<td>GW786034 Pazopanib</td>
<td>Some tumor shrinkage in 30/35 pts in neo-adjuvant study (Altorki IASLC 2008), biologic correlates</td>
</tr>
<tr>
<td>ABT-869</td>
<td>Phase I-NSCLC 2/8 PR (Steinberg IASLC 2008), ongoing trials Phase II -NSCLC 7% RR; mPFS ~110 days (Tan ASCO 2009)</td>
</tr>
<tr>
<td>BIBF1120</td>
<td>2nd or 3rd line 1/74 PR, 46% SD (von Pawel ASCO 2007) + Pem 3/20 PR (Hanna IASLC 2007) +carbo/paclitaxel 7/77 PR (Camidge IASLC 2007)</td>
</tr>
</tbody>
</table>

Many Others in Development
Motesanib (AMG706)
BMS690514, OSI930, CP547,632

VEGFR TKIs Sunitinib

- **SU11248 Sunitinib**
  - Intermittent - 10% single agent RR in 63 pts with 3 hemorrhagic deaths - (Socinski ASCO 06, JCO 2009)
  - Continuous - 37.5 mg qd 1 PR in 45 pts 2nd/3rd line adv NSCLC, MST 37 wks (Brahmer ASCO 2007)
  - In pts with treated brain metastases was safe and effective (Novello ASCO 2008, abs 8077)
  - Combo trials with Pem, carbo/tax, gem/cis and erlotinib (Plll) ongoing
  - CALGB planned trial of maintenance sunitinib vs/+ pemetrexed

VEGFR-TKI Summary

- Vandetanib promising in combination with 2nd line chemotherapy
  - Improved PFS with docetaxel
  - Improved LC symptoms with both docetaxel and pemetrexed
  - Equivalent to erlotinib
  - Placebo results awaited
- Cediranib with 1st line chemo promising (BR.24)
- Sorafenib single agent promising results, didn’t pair well with carbo/taxol
- Multiple ongoing trials with sunitinib, axitinib, vatalanib, pazopanib, motesanib, ABT869, BIBF1120, others
Other Anti-Angiogenesis Agents in Development in NSCLC

- Aflibercept (VEGF-TRAP)
  - Fusion protein of extracellular domains of VEGFR1 + 2 + IgG Fc
    - Ongoing phase I/III Cisplatin/Pemetrexed/Aflibercept
    - Ongoing phase III Docetaxel + Aflibercept/Placebo

- Ramucirumab (IMC-1121B)
  - Anti-VEGFR2 IgG1 monoclonal antibody
    - Ongoing phase II Carboplatin/paclitaxel/Ramucirumab

- CDP-791
  - Anti-VEGFR2 mAb
    - Completed carbo/paclitaxel/CDP-791 - no data available

Other Anti-Angiogenesis Agents in Development in NSCLC

- Adnectin (CT-322)
  - Fibronectin based small protein that blocks VEGFR2/VEGF interaction, phase I completed

- Rh-Endostatin
  - Endogenous collagen XVIII fragment with anti-angiogenic properties, which reduces the expression of VEGF
  - Ongoing chemotherapy combination trials

- Vascular disrupting agents (VDAs)
  - Not anti-angiogenesis drugs, but destructive of tumor vasculature directly
    - Multiple in development (CA4P, ABT-751, ZD6126)
    - ASA-404 promising RPhII data now in phase III NSCLC trials
      - Carboplatin/paclitaxel + ASA404/Placebo
      - Docetaxel +ASA404/Placebo

Anti-Angiogenesis in NSCLC: Conclusions

- Expansion of use to excluded patient populations
  - Younger women, some elderly, anti-coagulated, brain metastases, select squamous, adjuvant trial

- Exciting new drugs in development - VEGFR-TKIs
  - Encouraging results with sunitinib, sorafenib, vandetanib, cediranib others

- Novel agents in development - VDAs, other antibodies

- Predictive and prognostic markers are in development to help guide patient selection
  - ICAM, VEGF levels, VEGF polymorphisms, C/AFs..