New Directions in Angiogenesis

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Objectives

- Review of angiogenesis in non-small cell lung cancer (NSCLC)
- Summarize clinical data with VEGF and VEGFR inhibitors to date in NSCLC
- Discuss examples of newer agents/targets
Angiogenesis: a hallmark of cancer

The switch:

- **On**
- **Off**

Activators
- aFGF
- bFGF
- VEGF
- PDGF
- LPA
- SDF-1
- PIGF
- EGF

Inhibitors
- Thrombospondin-1
- 16 kD Prolactin
- Interferon α/β
- Platelet factor-4
- Angiostatin
- Endostatin, Canstatin
- Tumstatin

Many Agents Previously Tested

- MMPIs
- Thalidomide
- Squalamine
- NSAIDs
- Interferons
- Endostatin
- Vascular disrupting agents – ASA404, combrestatin

VEGF, VEGFR inhibitors
Agents targeting the VEGF pathway

- Anti-VEGF ligand Antibodies (Bevacizumab)
- Soluble VEGFRs (Aflibercept)
- Anti-VEGF Receptor Antibodies (Ramucirumab)
- Small-molecule VEGFR inhibitors (BIBF 1120*, cediranib, sunitinib, sorafenib, vandetanib, vatalanib, motesanib, axitinib, pazopanib, linifanib)

*This compound is an investigational agent. Its efficacy and safety have not been established.

Adapted from Podark K, Anderson KC. Blood. 2005;105:1383–95
Targeting angiogenesis/VEGF can improve survival

E4599: 1st line paclitaxel/carboplatin +/- bevacizumab in nonsquamous

E4599: adenocarcinoma subset

### Combination studies with VEGF/R inhibitors plus chemotherapy or EGFR TKIs in NSCLC

#### Chemotherapy +/- VEGF/R inhibitor

<table>
<thead>
<tr>
<th>Agent</th>
<th>RR</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab + PCb</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bevacizumab + GC</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Afibercept + Doc</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Sorafenib + PCb</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sorafenib + GC*</td>
<td>NR</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Sorafenib + Pem</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Motesanib + PCb*</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Vandetanib + Pem</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vandetanib + Doc</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Cediranib + PCb</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

#### Erlotinib +/- VEGF/R Inhibitor

<table>
<thead>
<tr>
<th>Agent</th>
<th>RR</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Bevacizumab 2nd Ln</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Bevacizumab Maint</td>
<td>NR</td>
<td>+</td>
<td>–</td>
</tr>
</tbody>
</table>

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*In non-squamous patients; PCb=paclitaxel/carboplatin; GC=gemcitabine/cisplatin; Doc=docetaxel; Pem=pemetrexed; 2\(\text{nd}\) Ln=second line; Maint=maintenance.

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Ongoing trials

• Adjuvant setting
  • E1505 – cisplatin-based doublet +/- bevacizumab x 1 yr
  • Pazopanib in stage 1

• First line
  • Platinum doublet +/- ramucirumab
  • Platinum doublet +/- VEGFR TKIs axitinib, ABT-869 (nonsquamous)

• Maintenance
  • Randomized trials of VEGFR TKIs sunitinib, pazopanib
  • AVAPERL1: Bevacizumab +/- Pemetrexed
  • ECOG 5508: Bevacizumab vs. Pemetrexed vs. Combination

• Second line
  • LUME-Lung 1 – docetaxel +/- BIBF 1120*
  • Docetaxel +/- ramucirumab
  • NCIC CTG IND 196: Erlotinib +/- foretinib (VEGFR, MET TKI)

*This compound is an investigational agent. Its efficacy and safety have not been established.
Future Directions of Angiogenesis Inhibition in NSCLC

- Anti-VEGFR2 MAb - Ramucirumab (1121B)
- Anti-EGFL7 (MEGF0444A)
- Human Anti-PDGFRα Monoclonal Antibody (IMC-3G3)
Anti-VEGFR2 MAb
Ramucirumab (1121B)
1121B NSCLC Studies

• 1\textsuperscript{st} line (platinum doublets with 1121B)
  – Phase 2 single arm 1\textsuperscript{st} line Cb paclitaxel study CP12-0708 – completed (PI: Camidge)

  – Phase 2 randomized open label 1\textsuperscript{st} line PltGem PltPem study CP12-0917 – ongoing (PI: Bonomi, Camidge)

• 2\textsuperscript{nd} line (Docetaxel with 1121B)
  – Phase 3 randomized double blind study (JVBA or CP12-1027) – ongoing (PI: Garon, Perol)
First Line NSCLC (CP12-0708) Study

Study Design

Primary endpoint: PFS rate at 6 months
Secondary endpoints: ORR, duration of response, OS, OS at 1 year, safety
Sites: US + UK

- NSCLC wet IIIB or IV
- All histologies
- No prior CT
- No blood vessel involvement or tumor cavitation
- Treated brain mets allowed
- Age ≥ 18
- ECOG ≤ 1

Ramucirumab 10 mg/kg + Paclitaxel 200 mg/m² + Carboplatin AUC 6 q3w up to 6 cycles (CT)

Ramucirumab until
- PD
- unacceptable toxicity
- withdrawal of consent

N = 40
Gender:
Male 35%
Female 65%

Performance Status:
ECOG 0 38%
ECOG 1 62%

Histology:
Adenocarcinoma 97%
Adenocarcinoma with focal squamous 3%
CP12-0708: Preliminary Safety Results N=35
Related Events

<table>
<thead>
<tr>
<th>Most Common AEs</th>
<th>All Grades N (%)</th>
<th>Grade 3 N (%)</th>
<th>Grade 4 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>6 (17.1)</td>
<td>1 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>3 (8.6)</td>
<td>2 (5.7)</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4 (11.4)</td>
<td>2 (5.7)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4 (11.4)</td>
<td>2 (5.7)</td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2 (5.7)</td>
<td></td>
<td>2 (5.7)</td>
</tr>
</tbody>
</table>

- 11% (4) of pts had CNS metastases at study entry, there were no CNS hemorrhages during treatment with ramucirumab
- No deaths were reported for pts on-study or within 30 days of last dose of ramucirumab
- 1 patient with partial squamous histology enrolled, 3 cycles of treatment already received, no hemoptysis, no pulmonary bleeding.
CP12-0708: Preliminary Efficacy Results

• Preliminary PFS in the ITT population is 5.78 months
• Preliminary PFS rate at 6 months is 49%

Clinical Benefit

<table>
<thead>
<tr>
<th>Clinical Benefit</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
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<td>3%</td>
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<tr>
<td>PR</td>
<td>14</td>
<td>48%</td>
</tr>
<tr>
<td>ORR</td>
<td>15</td>
<td>52%</td>
</tr>
<tr>
<td>ORR&lt;sup&gt;b&lt;/sup&gt;</td>
<td>17&lt;sup&gt;b&lt;/sup&gt;</td>
<td>59%</td>
</tr>
<tr>
<td>SD&lt;sup&gt;b&lt;/sup&gt;</td>
<td>13&lt;sup&gt;b&lt;/sup&gt;</td>
<td>45%</td>
</tr>
<tr>
<td>PD</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td>DCR</td>
<td>28</td>
<td>97%</td>
</tr>
</tbody>
</table>

<sup>a</sup>: RECIST 1.0
<sup>b</sup>: includes 2 pts with >30% reduction sumLD; confirmatory scans pending
n=280 patients
• 1st line NSCLC
• Stage IV
• all histologies
• ECOG ≤ 2

Stratification Factor
• histology
Randomization
• treatment group

Primary endpoint:
• PFS

1st LINE INDUCTION
4 – 6 cycles

ARM A:
Pemetrexed + Carbo OR Cisplatin

ARM B:
1121B + Pemetrexed + Carbo OR Cisplatin

ARM C:
Gemcitabine + Carbo OR Cisplatin

ARM D:
1121B + Gemcitabine + Carbo OR Cisplatin

MAINTENANCE

ARM A:
Pemetrexed

ARM B:
Pemetrexed + 1121B

ARM D:
1121B

Treatment untill:
• PD
• unacceptable toxicity
• consent withdrawal
I4T-MC-JVBA: Study Design

Stratification Factors:
- ECOG PS
- Gender
- Prior maintenance therapy
- Geographic region

Primary endpoint:
- Overall survival (events: N= 869)

N = 1242

R 1:1

Arm A:
- Docetaxel 75mg/m² q3w
- Ramucirumab 10mg/kg q3w

Arm B:
- Docetaxel 75mg/m² q3w
- Placebo 10mg/kg q3w

Treatment until:
- PD
- Unacceptable toxicity
- Consent withdrawal

• NSCLC stage IV progressing during/after prior platinum-based-CT ± maintenance therapy
• Prior Bev therapy allowed
• All histologies
• ECOG ≤ 1
Anti-EGFL7 (MEGF0444A)
Anti-EGFL7 (MEGF0444A)

Target: EGFL7
- Extracellular matrix protein
- Tumor enriched
- Supports endothelial cell survival - particularly under stress

MEGF0444A
- Humanized monoclonal anti-EGFL7 Ab
- Tumor-selective
- Antivascular/antiangiogenic activity
- Inhibits tumor vascular regrowth following antiVEGF tx

- Perivascular tracks persist along vessels damaged by antiangio tx

Sprouting Vessel  Regressed Vessel
- EGFL7
- Empty tracks

Untreated Tumor  Anti-VEGF  Treated Tumor

GEMM: Kras^{G12D} and p53^{-/-}

- Surviving Fraction
- Weeks on Treatment
- Control MAb
- Anti-VEGF
- Anti-EGFL7 + Anti-VEGF
Anti-EGFL7 Phase 1 Program

Standard 3+3 dose escalation
Pts with advanced solid tumors
Bevacizumab-type exclusion criteria

Phase Ia: single agent
- No DLTs, no new safety signals
- No single agent activity (consistent with MOA)

Phase Ib: combination
- No DLTs and no exacerbation of bev-associated adverse events
- PK supports flat dosing and dosing q2w and q3w
- Circulating progenitor cells (CPCs): decrease with anti-EGFL7.5 mg/kg q2w + bev
- DCE-MRI: decrease in $K_{\text{trans}}$ at 5 mg/kg q2w

Phase Ia
- single agent
  - 0.3 mg/kg
  - 1 mg/kg
  - 3 mg/kg
  - 7.5 mg/kg
  - 15 mg/kg
- Expansion Cohort
  - 3 mg/kg and 15 mg/kg

Phase Ib
- Arm A + bevacizumab
  - 2 mg/kg
  - 5 mg/kg
  - 10 mg/kg
- Arm B + bevacizumab / paclitaxel
  - 2 mg/kg
  - 5 mg/kg
  - 10 mg/kg
- Expansion Cohorts
  - 5 and 10 mg/kg
  - Flat & rapid dose
  - RCC
  - Tumor biopsy
Time on Study and Best Response
Arm B (anti-EGFL7 + bev + paclitaxel)

Data as of 9 Jan 2012.

* Unconfirmed.
NILE (MEF4984g): NSCLC 1st-Line aEGFL7

- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, DoR, safety/tolerability, PK, QoL
- Exploratory endpoints: Diagnostic biomarker hypotheses
- 12 pt safety run-in
- Stratification factors: ECOG PS, gender, adjuvant chemotherapy
- Key inclusions: measurable disease, > 12 months from adjuvant chemo/XRT
- Key exclusions: squamous histology, hemoptysis, CNS mets, therapeutic anticoagulation, significant cardiovascular disease

Previously untreated, inoperable/recurrent/metastatic non-squamous NSCLC

N = 100

R

6 cycles

aEGFL7 (600 mg IV Q3 wk) + bevacizumab + carboplatin + paclitaxel

placebo + bevacizumab + carboplatin + paclitaxel

placebo + bevacizumab

Treat to PD

Treat to PD
Anti-EGFL7 MEGF0444A
Summary

• Anti-EGFL7 (MEGF0444A) appears safe in combination with bevacizumab with or without paclitaxel
  - No DLTs or new safety signals observed
  - No significant exacerbation of bev-associated toxicities
• PK and PD biomarkers support Phase II dose / schedule
• Antitumor activity observed, including 2 PRs in Arm A (+ bev) and 6 PRs in Arm B (+bev/paclitaxel) in Phase Ib
• NILE: > 23 pts enrolled
  • No related SAEs, formal interim safety analysis pending

Preclinical and Phase I data provide strong rationale for ongoing Phase II studies combining anti-EGFL7 with standard of care chemo/bevacizumab in first-line mCRC and mNSCLC
Importance of targeting alternative pathways such as FGF and PDGFR

- After blockade of VEGF pathway, there is compensatory upregulation of FGF, PDGFR, EGFR, others
- Additional blockade of FGF, PDGFR suppresses angiogenesis

FGF(R)=fibroblast growth factor (receptor); PDGF(R)=platelet-derived growth factor (receptor); VEGF(R)=vascular growth factor (receptor).
Randomized phase II study of human anti-platelet-derived growth factor receptor alpha (PDGFRα) monoclonal antibody (IMC-3G3) with paclitaxel/carboplatin (P/C) or P/C alone in first-line treatment of stage IIIb/IV NSCLC

- Paclitaxel $200 \text{ mg/m}^2 + \text{ carboplatin } AUC=6 +/-. \text{ IMC-3G3 } 15 \text{ mg/kg on Days 1 and 8 of each 21 day cycle}$

- IMC is continued as maintenance in patients w/o PD

- $N = 136 \text{ patients}$

- Recently closed to accrual
Conclusions

• Angiogenesis and VEGF/R remain important targets in NSCLC, with single agent and combination activity

• Results range from practice-changing survival gain in one trial (E4599: bevacizumab/paclitaxel/carboplatin) to consistent PFS gains without OS benefit in most trials

• Future efforts being directed toward other angiogenic targets