Targeting Angiogenesis in NSCLC

David Heigener
We met before!

Mexico 1986

Brazil 2014
Non-small-cell Lung Cancer

Worldwide, lung cancer is the **leading cause of cancer mortality** in males and the second-leading cause in females\(^1\)

\(\sim 85\%\) of lung cancers are of **NSCLC** histology\(^2\)

**Most NSCLC** cases (>75%) are diagnosed in **late stages** of disease (stage III or IV)\(^3\)

5-year **survival** rates are <15% across all stages of disease\(^4\)
ANGIOGENESIS: A HALLMARK OF CANCER

Anti-angiogenic therapy

- Regression of existing tumourvasculature
- Inhibition of new vessel growth
- No bone marrow suppression
- No cumulative toxicities

Improved efficacy in combination with a well-established safety profile
Angiogenesis and Tumor Growth

**ISOLATION OF A TUMOR FACTOR RESPONSIBLE FOR ANGIGENESIS**

By JUDAH FOLKMAN, M.D., EZIO MERLER, Ph.D., CHARLES ABERNATHY, M.D., and GRETCHEN WILLIAMS

*Journal of experimental Medicine* 1972; 133: 275-88

It appears that most solid tumors, whether they originate from a cell transformed by virus or carcinogen, or whether they begin as a metastatic implant, must exist early as a small population of cells dependent upon nutrients which diffuse from the extravascular space. Such a pinpoint colony eventually expands to a size where simple diffusion of nutrients (and wastes) is insufficient (Fig. 10). New capillaries are elicited and the tumor then enters a phase in which nutrients arrive by perfusion. It is possible that TAF is responsible for this final stage. It is tempting to suggest that tumor growth might be arrested at a very small size if the angiogenesis activity of this factor could be blocked. This would be analogous to the cessation of growth of bacterial colonies when their size exceeds the diffusion of nutrients. The indirect evidence from isolated perfused organs and from the work of Greene suggests that interruption of angiogenesis results in cessation of tumor growth at an early stage. Thus, the understanding of the mechanism of tumor angiogenesis has potential therapeutic importance.
Targets of Antiangiogenic Treatment

- VEGF Receptor Antibodies
- VEGF Receptor TKI
- Endothelial Cell Vehicles CD34^+ precursors
- Inhibitors of Invasion, MMPs
- Capillary Endothelial Cells
- Radioligands 125I-anti-endoglin
- Adhesion Molecule & Junctional Inhibitors anti-αvβ3, anti-VE-cadherin
- Antiangiogenic Gene Delivery Adenovirus, Retrovirus, Lentivirus, Liposomes, Naked DNA
- Signal Transduction Inhibitors & Proapoptotic Factors Tyrosine Kinase Inhibitors

Modified from Scappaticci, F. A. J Clin Oncol; 20:3906-3927 2002
Agenda

• Bevacizumab in First-Line Treatment of Lung Cancer
  – Combination with Chemotherapy
  – Combination with Erlotinib
• The Value of Maintenance
• Biomarkers for Angiogenesis
Paclitaxel–Carboplatin Alone or with Bevacizumab for Non–Small-Cell Lung Cancer

Alan Sandler, M.D., Robert Gray, Ph.D., Michael C. Perry, M.D., Julie Brahmer, M.D., Joan H. Schiller, M.D., Afshin Dowlati, M.D., Rogerio Lilienbaum, M.D., and David H. Johnson, M.D.

878 Patients with metastatic or recurrent non–squamous-cell, non–small-cell lung cancer enrolled

444 Assigned to paclitaxel and carboplatin alone

434 Assigned to paclitaxel and carboplatin plus bevacizumab
Overall Survival: 12.3 Versus 10.3 Months

Hazard ratio, 0.79
P = 0.003

BPC group (305 events in 417 patients)

PC group (344 events in 433 patients)
Progression-free Survival 6.2 Versus 4.5 Months

- BPC group
  - 374 events in 417 patients
- PC group
  - 405 events in 433 patients

Hazard ratio, 0.66
P < 0.001
<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Paclitaxel–Carboplatin Group (N=440)</th>
<th>Paclitaxel–Carboplatin–Bevacizumab Group (N=427)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
<td>Grade 5</td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>2 (0.5)</td>
<td>1 (0.2)</td>
<td></td>
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<tr>
<td>Proteinuria</td>
<td></td>
<td></td>
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<tr>
<td>Bleeding events (all)</td>
<td>3 (0.7)</td>
<td></td>
<td></td>
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<tr>
<td>Central nervous system hemorrhage</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Epistaxis</td>
<td>1 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematemesis</td>
<td>1 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1 (0.2)</td>
<td></td>
<td></td>
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<tr>
<td>Melena or gastrointestinal bleeding</td>
<td>1 (0.2)</td>
<td></td>
<td></td>
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<tr>
<td>Other hemorrhage</td>
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</tbody>
</table>
ECOG 4599 + AVAIL: Response

Ansprechrate (%)

- Placebo + CG (n=324) 20%
- Bevacizumab 15mg/kg + CG (n=332) 30%
- Bevacizumab 7.5mg/kg + CG (n=323) 34%

- P<0.001
- P=0.0023
- P<0.0001

The Value of Response

Pre Bevacizumab

Under Bevacizumab
BEYOND: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase III Study of First-Line Carboplatin/Paclitaxel Plus Bevacizumab or Placebo in Chinese Patients With Advanced or Recurrent Nonsquamous Non–Small-Cell Lung Cancer

Caicun Zhou, Yi-Long Wu, Gongyan Chen, Xiaoqing Liu, Yunzhong Zhu, Shun Lu, Jifeng Feng, Jianxing He, Baohui Han, Jie Wang, Guoliang Jiang, Chunhong Hu, Hao Zhang, Gang Cheng, Xiangqun Song, You Lu, Hongming Pan, Wenjuan Zheng, and Anny-Yue Yin
By Beyond-Trial: Design

Phase III (double-blinded, multi-centre) study

Locally advanced, metastatic or recurrent NSCLC (stage IIIB, IV) first-line n=270

- Primary endpoint
  - PFS

- Secondary endpoints
  - ORR
  - OS
  - DoR and safety
  - PFS with bev to 3rd PD

Zhou et al.; J Clin Oncol 2015
Beyond: PFS

Randomly assigned treatment
- PI + CP
- B + CP

Median PFS 6.5 vs 9.2 months
HR, 0.40; 95% CI, 0.29 to 0.54
P < .001

<table>
<thead>
<tr>
<th>Time of Study (month)</th>
<th>No. at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PI + CP</td>
</tr>
<tr>
<td>0</td>
<td>138</td>
</tr>
<tr>
<td>6</td>
<td>63</td>
</tr>
<tr>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
</tr>
</tbody>
</table>
Overall Survival

Randomly assigned treatment
- PI + CP
- B + CP

Median OS 17.7 vs 24.3 months
HR, 0.68; 95% CI, 0.50 to 0.93
P = .0154

No. at risk
- PI + CP: 138, 122, 89, 64, 50, 9, 0
- B + CP: 138, 128, 102, 83, 64, 18, 0

Zhou et al.; J Clin Oncol 2015
Efficacy of Bevacizumab in First-line Treatment Of Non-squamous NSCLC: Meta-Analysis of Data from RCTs

For AVF0757g trial, direction of OS HR unknown; worst scenario chosen.
Tolerability of Bevacizumab in first-line treatment of non-squamous NSCLC: Meta-Analysis of data from RCTs

<table>
<thead>
<tr>
<th>Category</th>
<th>% Grade ≥3 toxicity</th>
<th>Odds ratio</th>
<th>OR [95% CI]</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria</td>
<td>N = 3(^1) 2.4%</td>
<td>4.81</td>
<td>2.28; 10.1</td>
<td>F(^2) = 0% P = 0.55</td>
</tr>
<tr>
<td>Hypertension</td>
<td>N = 4 8.1%</td>
<td>3.69</td>
<td>2.49; 5.47</td>
<td>F(^2) = 16% P = 0.31</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>N = 4 8.2%</td>
<td>1.03</td>
<td>0.74; 1.43</td>
<td>F(^2) = 36% P = 0.20</td>
</tr>
<tr>
<td>Haemorrhagic events</td>
<td>N = 4 4.6%</td>
<td>2.67</td>
<td>1.63; 4.39</td>
<td>F(^2) = 0% P = 0.84</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>N = 4 4.6%</td>
<td>0.84</td>
<td>0.57; 1.23</td>
<td>F(^2) = 0% P = 0.71</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>N = 4 40.7%</td>
<td>1.53</td>
<td>1.25; 1.87</td>
<td>F(^2) = 0% P = 0.67</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>N = 3(^1) 3.5%</td>
<td>1.72</td>
<td>1.01; 2.95</td>
<td>F(^2) = 0% P = 0.50</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>N = 3(^2) 24.1%</td>
<td>1.17</td>
<td>0.88; 1.55</td>
<td>F(^2) = 0% P = 0.59</td>
</tr>
<tr>
<td>Anaemia</td>
<td>N = 3(^2) 11.5%</td>
<td>0.92</td>
<td>0.64; 1.33</td>
<td>F(^2) = 0% P = 0.54</td>
</tr>
</tbody>
</table>

\(^1\)Without AVF-0757g trial
\(^2\)Without ECOG 4599 trial

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Preclinical Effect of Bevacizumab and Erlotinib

- Mouse Model with EGFR-mut Xenograft

* p < 0.01; ** p < 0.05; *** p < 0.001.

1. Li et al. Cancer Chemo Pharmacol 2014
Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): an open-label, randomised, multicentre, phase 2 study


154 assessed for eligibility and randomised

77 randomly assigned to receive erlotinib plus bevacizumab combination

- 2 withdrew before treatment started

- 75 received erlotinib plus bevacizumab
  - 55 discontinued erlotinib
  - 12 adverse events
  - 37 insufficient efficacy
  - 6 other reasons
  - 63 discontinued bevacizumab
  - 31 adverse events
  - 26 insufficient efficacy
  - 6 other reasons

77 randomly assigned to receive erlotinib alone

- 66 discontinued erlotinib
  - 14 adverse events
  - 50 insufficient efficacy
  - 1 death
  - 1 other reasons
Progression-free survival

- **Erlotinib plus bevacizumab group**
  - Median: 16.0 months (95% CI: 13.9-18.1; 46 events)

- **Erlotinib alone group**
  - Median: 9.7 months (95% CI: 5.7-11.1; 57 events)

Number at risk:
- Erlotinib plus bevacizumab group: 75, 72, 69, 64, 60, 53, 49, 43, 38, 30, 20, 13, 8, 4, 4, 0
- Erlotinib alone group: 77, 66, 57, 44, 39, 29, 24, 21, 18, 12, 10, 5, 2, 1, 0

HR 0.54 (95% CI 0.36-0.79)
Overall survival (immature, no stats!)

Seto et al.; Lancet Oncol, 2014
## Jo25567-Study: Safety

<table>
<thead>
<tr>
<th></th>
<th>Bevacizumab + Erlotinib (n = 75)</th>
<th>Erlotinib (n = 77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade-3/4-AEs, n (%)</td>
<td>68 (91)**</td>
<td>41 (53)</td>
</tr>
<tr>
<td>Erlotinib-Duration of Tx (median), Days</td>
<td>431 (21–837)</td>
<td>254 (18–829)</td>
</tr>
<tr>
<td>Bevacizumab-Duration of Tx (median), Days</td>
<td>325 (1–815)</td>
<td>–</td>
</tr>
<tr>
<td>Bevacizumab-Discontinuation due to AE, %</td>
<td>41</td>
<td>–</td>
</tr>
<tr>
<td>Erlotinib-Discontinuation due to AE, %</td>
<td>16</td>
<td>18</td>
</tr>
</tbody>
</table>

One patient in the erlotinib group died by drowning, and a potential association with the study drug was confirmed.
Putting in to perspective: afatinib vs erlotinib/bevacizumab in japanese pts w/o brain mets *

<table>
<thead>
<tr>
<th>JO25567</th>
<th>PFS (Months)</th>
<th>ORR [%]</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Frequent</td>
<td>Del19</td>
</tr>
<tr>
<td></td>
<td>Mutations</td>
<td></td>
</tr>
<tr>
<td>Erlotinib +</td>
<td>16,0&lt;sup&gt;1&lt;/sup&gt;</td>
<td>18,0&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bevacizumab (n=75)</td>
<td>HR 0,54</td>
<td>HR 0,41</td>
</tr>
<tr>
<td></td>
<td>signifikant</td>
<td>signifikant</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>LUX-Lung 3</th>
<th>PFS (Months)</th>
<th>ORR [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib,</td>
<td>16,4&lt;sup&gt;2&lt;/sup&gt;</td>
<td>19,2&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Subpopulation</td>
<td>HR 0,26</td>
<td>HR 0,14</td>
</tr>
<tr>
<td>Japanese pts*</td>
<td>significant</td>
<td>significant</td>
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<td>(n=61)</td>
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</table>

* Post-hoc-Subgruppenanalyse der LUX-Lung 3-Studie

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  – Combination with Chemotherapy
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• The Value of Maintenance
• Biomarkers for Angiogenesis
Incorporation of Bevacizumab in the Primary Treatment of Ovarian Cancer

Robert A. Burger, M.D., Mark F. Brady, Ph.D., Michael A. Bookman, M.D.,
Gini F. Fleming, M.D., Bradley J. Monk, M.D., Helen Huang, M.S.,
Robert S. Mannel, M.D., Howard D. Homesley, M.D., Jeffrey Fowler, M.D.,
Benjamin E. Greer, M.D., Matthew Boente, M.D., Michael J. Birrer, M.D., Ph.D.,
and Sharon X. Liang, M.D., for the Gynecologic Oncology Group*

1873 Patients were enrolled and underwent randomization

- 625 Were assigned to control therapy:
- 625 Were assigned to bevacizumab-initiation therapy:
- 623 Were assigned to bevacizumab-throughout therapy:
Progression-free Survival

Proportion with Progression-free Survival

Months since Randomization

No. at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
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<th>30</th>
<th>32</th>
<th>34</th>
<th>36</th>
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</thead>
<tbody>
<tr>
<td>Control</td>
<td>625</td>
<td>535</td>
<td>283</td>
<td>169</td>
<td>133</td>
<td>78</td>
<td>49</td>
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</tr>
<tr>
<td>Bev initiation</td>
<td>625</td>
<td>552</td>
<td>319</td>
<td>190</td>
<td>121</td>
<td>67</td>
<td>40</td>
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<tr>
<td>Bev throughout</td>
<td>623</td>
<td>559</td>
<td>386</td>
<td>256</td>
<td>162</td>
<td>97</td>
<td>56</td>
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</table>
Overall Survival

![Image showing survival rates for different treatment groups over months since randomization, with a table showing the number of patients at risk at different time points for each group.]
E4599: retrospective analyses of non-progressors on study 21 days after cycle 6

<table>
<thead>
<tr>
<th></th>
<th>Median OS, months</th>
<th>CP non-progressors (n=134)</th>
<th>Bev + CP non-progressors (n=217)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postinduction*</td>
<td></td>
<td>11.4</td>
<td>12.8</td>
</tr>
<tr>
<td></td>
<td>HR (adjusted)=0.75</td>
<td></td>
<td>p=0.03</td>
</tr>
<tr>
<td>Overall‡</td>
<td></td>
<td>15.8</td>
<td>17.0</td>
</tr>
</tbody>
</table>

*Calculated from the landmark date +21 days
‡Calculated from start of induction treatment

Sandler, et al. WCLC 2011
AvaALL: phase IIIb study of bevacizumab continued beyond progression in NSCLC

- Primary endpoint: OS
- Secondary endpoints: PFS, safety, QoL and biomarker analysis
- Actively recruiting patients

Stage IIIB/IV non-squamous NSCLC treated with platinum-doublet (4–6 cycles) + bevacizumab PLUS ≥ 2 cycles of bevacizumab maintenance

Primary endpoint: OS

Randomise 1:1

SOC2* + bevacizumab
SOC3‡ + bevacizumab
SOC4 ± bevacizumab

*SOC2: labelled agents for second-line treatment of NSCLC
‡SOC3 and beyond: choice of labelled agents is the investigator’s choice

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Retrospective analysis of bevacizumab-induced hypertension and clinical outcome in patients with colorectal cancer and lung cancer

Aya Nakaya¹, Takayasu Kurata¹, Takashi Yokoi¹, Shigeyoshi Iwamoto², Yoshitaro Torii¹, Yuichi Katashiba¹, Makoto Ogata¹, Madoka Hamada², Masanori Kon² & Shosaku Nomura¹

¹First Department of Internal Medicine, Kansai Medical University, Osaka, Japan
²Department of Surgery, Kansai Medical University, Osaka, Japan
OS in Lung Cancer: High Blood Pressure (HBP (+)) versus Normotensive (HBP (-))

Median OS
- HBP(+) : 43.0 m
- HBP(-) : 26.3 m

$P = 0.00451$
A Correlative Biomarker Analysis of the Combination of Bevacizumab and Carboplatin-Based Chemotherapy for Advanced Nonsquamous Non–Small-Cell Lung Cancer

Results of the Phase II Randomized ABIGAIL Study (BO21015)

Tony Mok, MD,* Vera Gorbunova, MD,† Erzsebet Juhasz, MD,‡ Barna Szima, MD,§ Olga Burdaeva, MD,∥ Sergey Orlov, MD, PhD,¶ Chong-Jen Yu, MD, PhD,‖ Venice Archer, MD,# Magalie Hilton, MSc,** Paul Delmar, PhD,** Celine Pallaud, PhD,** and Martin Reck, MD, PhD††
Serum-Biomarkers Evaluated:

- bFGF
- E-selectin
- ICAM
- PI GF
- VEGF-A
- VEGFR-1
- VEGFR-2
Survival as a Function of Serum-VEGF-A Level
Hypertension and VEGF A are prognostic but presumably not predictive (but control Arm is lacking in both trials).

Other possible Candidate:

TSFT

(see in next Presentation)
Translational research: Optimising treatment in patients without oncogenic alteration

I

Retrospective identification of patients with available tissue

Completely resected adenocarcinoma Stage I, II

Deep phenotyping

Relapse (local/distant) within 1 year

Without relapse ≥1 year

Morphological markers
Vessel density, patterns of vessel growth, types of vascularisation

Tissue-based markers
VEGFR 1–3, FGF, PDGF, ICAM-1, CD34, C 105, FAP, K167

Infiltration of immune cells

Oncogenic alterations
EGFR, ALK, KRAS, BRAF, RET

II

Clinical validation in clinical cohort with available biomaterials receiving nintedanib plus docetaxel

Specific profile of vessels addicted to fast-progressing tumours

...to find the one who makes the difference...

Reck M, Reinmuth N, Kugler C, Olchers T, Sonnek J, Watermann I, Ammerpohl O,
Goldmann T, Thomas M, Huber RM, Klingmüller U, Stiewe H, Golpon H
Thank you for the Attention!

May 2015: Barcelona – Munich 3:0

like him.