Anti-Angiogenic Therapy
Overview of Current Strategies and Results

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UT MD Anderson Cancer Center
Houston, Texas, USA

TAT, Paris, 2011
Disclosures

• Honorarium for consulting:
  – Genentech/Roche, AVEO, BMS
Overview of Current Strategies and Results

• **Current State of Clinical Efficacy in the Clinic**
  – Successes? Failures? Or Both?

• **Rethinking Our Models**

  • I will focus my discussion on Phase III data
    • We only have data on VEGF-targeted agents in the Phase III setting.
    • Findings from earlier phase clinical trials have **not** always translated into confirmation in Phase III studies.
    • Other anti-angiogenic approaches will be discussed by other speakers in this session.
  
  • I will challenge existing paradigms to stimulate discussion.
Other anti-angiogenic agents in late phase clinical trials

Integrin antagonists (Cilengitide, Phase III CNS)
Ang/Tie-2 inhibitors (AMG-386, Phase III Ovarian)
Endostar: NSCLC Phase III (China)

VEGF TKIs that also target other mediators
- Tie-2
- FGFRs
- (PDGFRs, c-Kit, Ret, others)
Anti-angiogenic Therapy: A Cure for Cancer or Hype?????
## Concepts of Anti-angiogenic (-VEGF) Therapy: Then and Now

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1990s</th>
<th>2011</th>
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<tbody>
<tr>
<td>Tumor Response</td>
<td>Induce tumor dormancy in all tumors</td>
<td>Tumor and Context Dependent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- true responses (RCC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- minimal impact as single agent in other solid tumors (NETs?)</td>
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<tr>
<td></td>
<td></td>
<td>- Maximum benefit obtained when combined with CTX (when there is benefit)</td>
</tr>
<tr>
<td>Toxicity</td>
<td>No toxicity - specific for “activated”</td>
<td>HTN</td>
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<tr>
<td></td>
<td>tumor vasculature</td>
<td>Arterio-thromboembolic events</td>
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<td></td>
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<td>Bowel perforations</td>
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<td>Hemorrhage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Proteinuria</td>
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<tr>
<td>Resistance</td>
<td>No resistance to therapy</td>
<td>Tumors <strong>DO</strong> become resistant and progress after initial response</td>
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<td>Predictive Markers</td>
<td>????</td>
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A Report Card in 2011

How Have We Done?
## Summary of Progression Free Survival (PFS) and Response Rates (RR) with VEGF-Targeted Therapies

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* Although PFS is improved, primary endpoint of overall survival not met
The Pendulum Effect and Anti-angiogenic Therapy

“Angio Bashing” Due to the Lack of OS Benefit and Interpretation of Preclinical Studies

2004-2005

2011
The Cause of Angio-Bashing

Few Studies Showing OS Benefit

Antiangiogenic Therapy Elicits Malignant Progression of Tumors to Increased Local Invasion and Distant Metastasis

Accelerated Metastasis after Short-Term Treatment with a Potent Inhibitor of Tumor Angiogenesis

News & Events
FDA NEWS RELEASE
For Immediate Release: Dec. 16, 2010
Media Inquiries: Erica Jefferson, 301-796-4988, erica.jefferson@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA begins process to remove breast cancer indication from Avastin label
Drug not shown to be safe and effective in breast cancer patients
I am the first to say that we are not aggressive enough and not creative enough. We need to shoot higher.

**ASCO GI Talk 2010**

**We Need to Do Better!**

We Must Be More Creative!!

“Me too” drugs and trials are unlikely to significantly advance the field

It is time to move new approaches forward!!

Defining our goal:
To **SIGNIFICANTLY** improve overall survival
But...Have We Done As Poorly As The Press And “Angio-bashers” Make It Seem?
Caveats for Interpretation of Clinical Trials

- Median PFS can be misleading
  - The hazard ratio takes into account the entire curve, and is not just a snapshot in time

- Overall survival cannot be assessed when crossover is allowed or patients subsequently receive the experimental therapy off study
  - The controversy in breast cancer
    - AVADO and RIBBON-1
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- Although PFS is improved, the primary endpoint of overall survival was not met
- Not all negative studies are included, as PIs do not rush to publish negative studies
Caveats for Interpretation of Clinical Trials

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• Overall survival cannot be assessed when crossover is allowed, or when patients subsequently receive the experimental therapy off study
  – The controversy in breast cancer
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35% received Bev second line

48% received Bev second line (new data)
# VEGF-Targeted Therapies: A Report Card

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Adjuvant Therapy
Adjuvant Therapy in CRC and Cure

- The goal of adjuvant therapy in CRC is CURE (OS)
  - DFS is not really meaningful without an improvement in overall survival in asymptomatic patients
  - DFS is a surrogate for OS for chemotherapy regimens
    - Sargent, et al. End points for colon cancer adjuvant trials: observations and recommendations based on individual patient data from 20,898 patients enrolled onto 18 randomized trials from the ACCENT Group. JCO. 2007
- But
  - NSABP C-08/AVANT taught us that early DFS cannot be used as a surrogate for DFS (OS) after discontinuation of the drug for regimens where Bev is administered for a finite period of time
NSABP C-08

Stage II + III

Strat: # Pos. N

Randomize

mFF6

mFF6 + B

Wolmark ASCO 2009
A Snapshot of C08

DFS

FOLFOX

FOLFOX/BEV

BEV

DFS

Allegra JCO 2011
Adjuvant Anti-Angiogenic Therapy in CRC (and other cancers)

• Two negative trials
  – No reason to think that “tweaking the regimen” (longer duration) will provide lasting benefit
  – Another example that “more is not better”

• We must re-focus on cytotoxic therapies rather than cytostatic therapies in the adjuvant setting in CRC (failure of NO147, 2010)

• An interim analysis should be done on all trials with VEGF-targeted agents where there is minimal single agent activity (Breast, Lung)
  – I think the most promising diseases for adjuvant therapy are those where we observe single agent responses (RCC)
We Need to REFINE VEGF-Targeted Therapy, Not Abandon It

- Biomarkers, Biomarkers, Biomarkers
- Duration of therapy
  - Through multiple lines of therapy?
    - Studies in RCC with different agents
    - BRITE and ARIES registries with Bev in CRC
  - Sequential?
    - First or second line?
      - Chemo can induce the target…we tend to see better results in second line therapy (E3200)
      - Fan et al. MCT 2008
What Have We Learned So Far?

• The efficacy of VEGF-targeted therapy is
  – Tumor specific
  – Context specific (with or without chemo)
  – Agent specific (TKIs ≠ MoABs)
  – The effects of VEGF inhibition as adjuvant therapy is distinct from that in advanced stage disease (CRC)

• This is not a simple field to understand
  – You cannot make broad generalizations regarding drugs, tumor types, or stage of tumors
Overview of Current Strategies and Results

- Current State of Clinical Efficacy in the Clinic
  - Successes? Failures? Or Both?
- Rethinking Our Models
  - Sprouting angiogenesis?
  - Angiocrine signaling (next year if invited back)
For Angiogenesis, “One Size” Does NOT Fit All

Standard size in Texas
Could Our Models Be Wrong?

• Preclinical modeling is based on “sprouting angiogenesis”, but in humans, the role of blood vessels in mediating tumor growth is much more complicated
Challenge Existing Paradigms

• In vascular organs, where metastasis occurs (liver, lung, brain), why do we need angiogenesis?
• Is it possible that some tumors do NOT require new blood vessels, but rely totally on existing blood vessels?
  – Heresy!
“Sprouting Angiogenesis”
Tumor Cells Do Not Float in Free Space in Zero Gravity

• Tumor cells develop in organs where they then initially coop* vessels prior to (if) initiating angiogenesis

*Holash et al. Science 2009
In highly vascularized organs, tumor cells may coopt the vasculature
- Alveolar architecture is maintained in tumors growing in the lung
Distinct angiogenic and non-angiogenic growth patterns of lung metastases from renal cell carcinoma

P Sardari Nia, J Hendriks, G Friedel, P Van Schil & E Van Marck

Breast adenocarcinoma liver metastases, in contrast to colorectal cancer liver metastases, display a non-angiogenic growth pattern that preserves the stroma and lacks hypoxia

F Steenbeek1,2, G Van den Eynden1,2, J Van der Auwer1,2, R Salgado1,2, E Van den Heuvel1,3, AL Harris1, DG Jackson1, CG Golpaert1,2, EA Van Marck1,2, LY Dirix1,2 and PB Vermeulen1,2

1 Translational Cancer Research Group Antwerp, Department of Pathology, University Hospital, University of Antwerp, Edegem, Belgium; 2Translational Cancer Research Group Antwerp, Department of Pathology and Oncology, General Hospital Sint-Augustinus, Wilrijk, Belgium; 3Molecular Oncology Laboratory, Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Headington, Oxford, UK; *WIR, Human Immunology Unit, Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Headington, Oxford, UK.
Tumour vascularization via endothelial differentiation of glioblastoma stem-like cells

Lucia Ricci-Vitiani1*, Roberto Pallini2*, Mauro Biffoni1, Matilde Todaro3, Gloria Invernici4, Tonia Cenci5, Giulio Maira2, Eugenio Agostino Parati4, Giorgio Stassi3,6, Luigi Maria Larocca5 & Ruggero De Maria1,7

Glioblastoma stem-like cells give rise to tumour endothelium

Rong Wang1,2,3, Kalyani Chadalavada4, Jennifer Wilshire5, Urszula Kowalik1, Koos E. Hovinga1,6, Adam Geber1, Boris Fligelman1, Margaret Leversha4, Cameron Brennan1,3,7 & Viviane Tabar1,2,3

9 DECEMBER 2010 | VOL 468 | NATURE | 829
Our Success is Best in the Most Angiogenic Tumors
(where a tumor mass was created that was larger than the original organ)

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With Such Varied Results With VEGF-Targeted Therapies, There Must be Multiple Mechanisms of Action of This Class of Drugs
Proposed Mechanisms of Action of Anti-VEGF Rx

- Anti-angiogenic
- “Normalization” of the vasculature with improved delivery of chemo and O$_2$
- Direct effect on tumour cells
- Vascular “constriction”
- Offset effects of stress
- Immune function
- Disruption of the CSC niche
Anti-VEGF Therapy: My Theory on Different Mechanisms of Action in Different Tumor Systems

Renal Cell Carcinoma
(single agent activity)

Colon Carcinoma
(only active with chemo)

Clinical Implications

We have not successfully developed combination AA Therapy.

Combination therapy may need to take into consideration the MOA of VEGF inhibition in particular tumor types.

For RCC----Anti-endothelial cell therapy? (Tie-2, others)
For CRC---- HIF inhibitors?
We have some successes, and some failures
- It is not appropriate to evaluate an entire field with a single “grade”

Understanding the role of the tumor vasculature in different tumors in different sites will aid in selecting patients for therapy
- Biomarker studies must be individualized for each tumor type

One size does not fill all for angiogenesis, and mechanisms of action of angiogenesis inhibition in different tumor types

“Me Too” drugs are unlikely to advance the field
Thank You For Your Attention!