Anti-Angiogenic Therapy Overview of Current Strategies and Results

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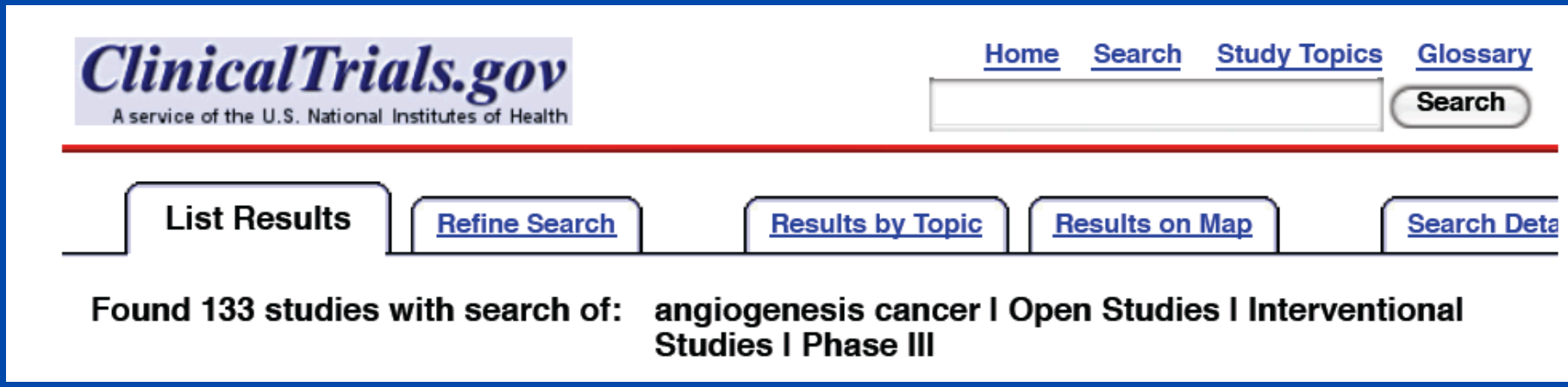
Disclosures

- 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)

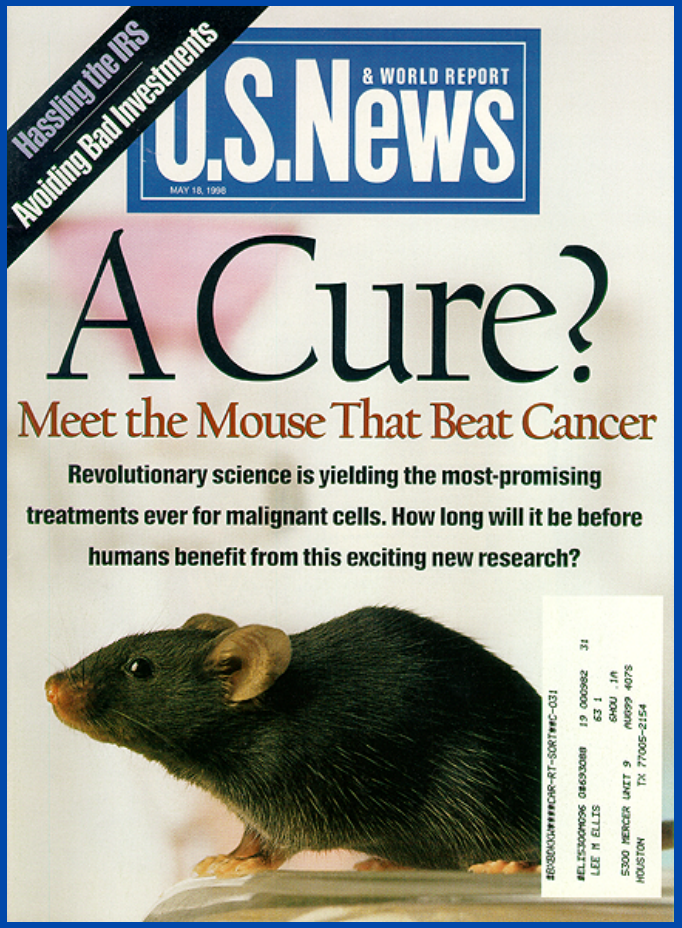
Ang/Tie-2 inhibitors (AMG-386, Phase III Ovarian)

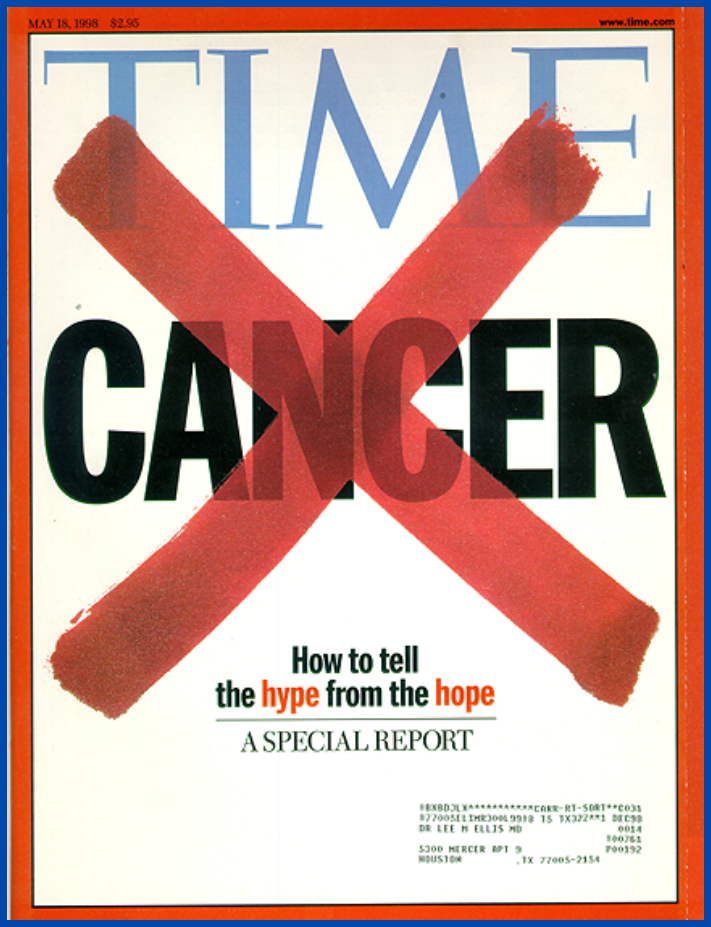
Endostar: NSCLC Phase III (China)

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

Parameter	1990s	2011
Tumor Response	Induce tumor dormancy in all tumors	Tumor and Context Dependent - true responses (RCC) - minimal impact as single agent in other solid tumors (NETs?) –Maximum benefit obtained when combined with CTX (when there is benefit)
Toxicity	No toxicity -specific for "activated" tumor vasculature	HTN Arterio-thromboembolic events Bowel perforations Hemorrhage Proteinuria
Resistance	No resistance to therapy	Tumors DO become resistant and progress after initial response
Predictive Markers	????	NONE

A Report Card in 2011

How Have We Done?

Summary of Progression Free Survival (PFS) and Response Rates (RR) with VEGF-Targeted Therapies

Cancer Type	How Utilized or Studied	Increase PFS Over Standard Care Δ	Increase RR Δ	FDA Approval
Renal Cell Ca	Single agent	3-6 months	8-30%	Y
NET	Single agent	6 months	9%	Pending
GBM (Phase 2)	Single agent	1-2 months	15-20%	Y
HCC	Single agent	1.4-3 months	2%	Y
CRC	+ Chemo	0-4 months	0-10%	Y
NSCLC	+ Chemo	0-2 months	3-15%	Y
Breast Cancer	+ Chemo	1-6 months	10-22%	Withdrawn
Gastric	+ Chemo	1.4 months*	9%	N
Prostate	+ Chemo	2.4 months*	11%	N
Pancreas	+ Chemo	0-1 month*	0-1%	N
Melanoma	+ Chemo	0-1.4	1-9%	N
Ovarian	After chemo/ Bev	1.7-4 months	?	Pending

* 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

Cancer Cell 2008

Marta Pàez-Ribes,[1,6] Elizabeth Allen,[2,6] James Hudock,[3] Takaaki Takeda,[4] Hiroaki Okuyama,[4] Francesc Viñals,[1,5] Masahiro Inoue,[4] Gabriele Bergers,[3] Douglas Hanahan,[2,*] and Oriol Casanovas[1,*]

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

John M.L. Ebos,[1,2] Christina R. Lee,[1] William Cruz-Munoz,[1] Georg A. Bjarnason,[3] James G. Christensen,[4] and Robert S. Kerbel[1,2,*]

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

Summary of Progression Free Survival (PFS) and Response Rates (RR) with VEGF-Targeted Therapies

Cancer Type	How Utilized or Studied	Increase PFS Over Standard Care Δ	Increase RR Δ	HR	FDA Approval (For best results)
Renal Cell Ca	Single agent	3-6 months	8-30%	0.42-0.63	Y
NET	Single agent	6 months	9%	0.42	Pending
GBM (Phase 2)	Single agent	1-2 months	15-20%	0.75-0.76	Y
HCC	Single agent	1.4-3 months	2%	0.68-0.69	Y
CRC	+ Chemo	0-4 months	0-10%	0.54-0.83	Y
NSCLC	+ Chemo	0-2 months	3-15%	0.66-0.85	Y
Breast Cancer	+ Chemo	1-6 months	10-22%	0.60-0.86	Withdrawn
Gastric	+ Chemo	1.4 months*	9%	0.8	N
Prostate	+ Chemo	2.4 months*	11%	0.77	N
Pancreas	+ Chemo	0-1 month*	0-1%	0.73-1.00	N
Melanoma	+ Chemo	0-1.4	1-9%	0.78-0.91	N
Ovarian	After chemo/ Bev	1.7-4 months	?	0.65-0.79	Pending

- 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

- 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 when patients subsequently receive the experimental therapy off study
  - The controversy in breast cancer
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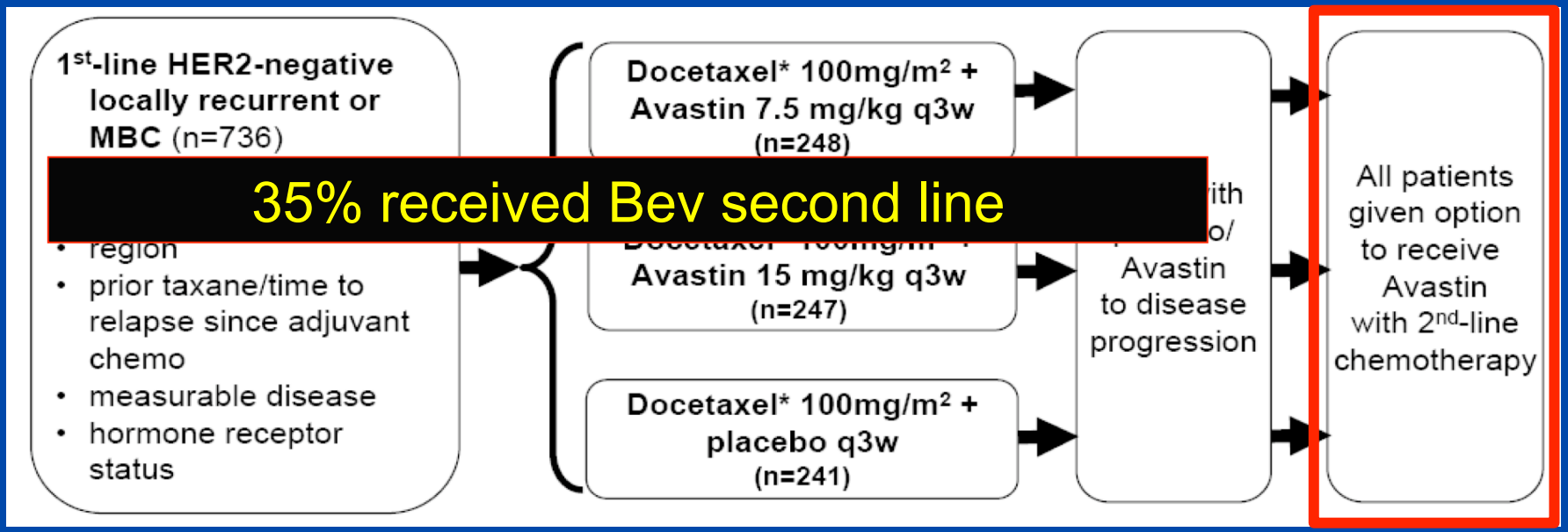
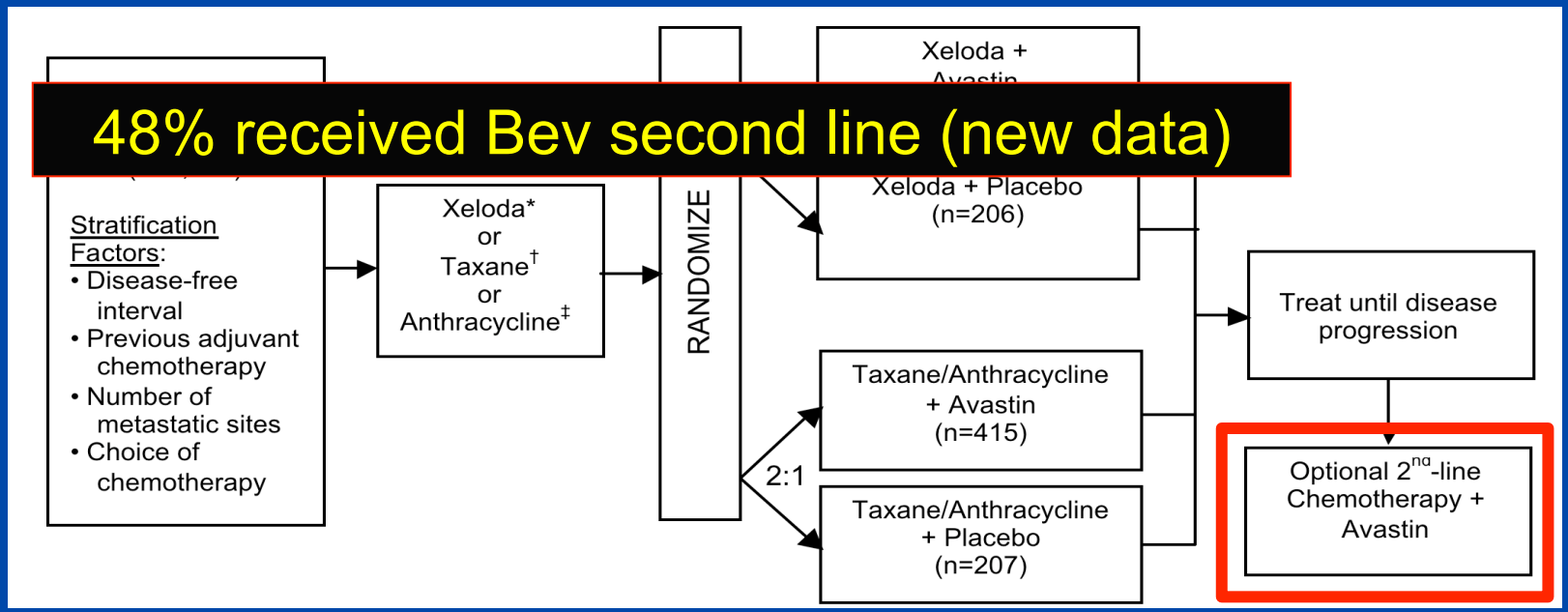
AVADO Study Design



35% received Bev second line

RIBBON-1 Study Design



48% received Bev second line (new data)

VEGF-Targeted Therapies: A Report Card

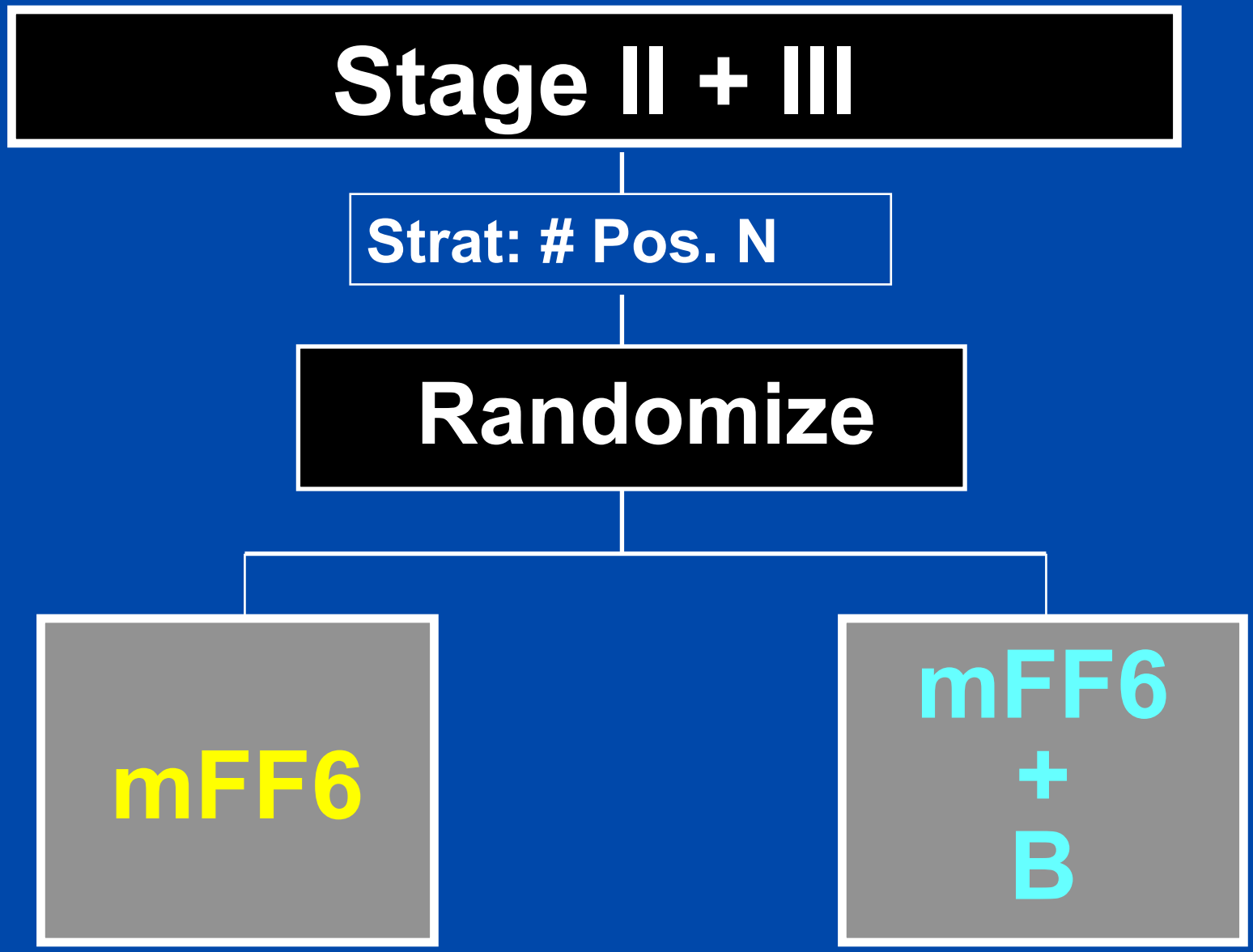
Cancer Type	How Utilized or Studied	Increase PFS Over Standard Care Δ	Increase RR Δ	HR	FDA Approval	Grade
Renal Cell Ca	Single agent	3-6 months	8-30%	0.42-0.63	Y	B+
NET	Single agent	6 months	9%	0.42	Pending	B+
GBM (Phase 2)	Single agent	1-2 months	15-20%	0.75-0.76	Y	B-
HCC	Single agent	1.4-3 months	2%	0.68-0.69	Y	B-
CRC	+ Chemo	0-4 months	0-10%	0.54-0,83	Y	C+
NSCLC	+ Chemo	0-2 months	3-15%	0.66-0.85	Y	C
Breast Cancer	+ Chemo	1-6 months	10-22%	0.60-0.86	Withdrawn	B
Gastric	+ Chemo	1.4 months*	9%	0.8	N	C-
Prostate	+ Chemo	2.4 months*	11%	0.77	N	E
Pancreas	+ Chemo	0-1 month*	0-1%	0.73-1.00	N	F-
Melanoma	+ Chemo	0-1.4	1-9%	0.78-0.91	N	E
Ovarian	After chemo/Bev	1.7-4 months	?	0.65-0.79	Pending	B+

Adjuvant Therapy

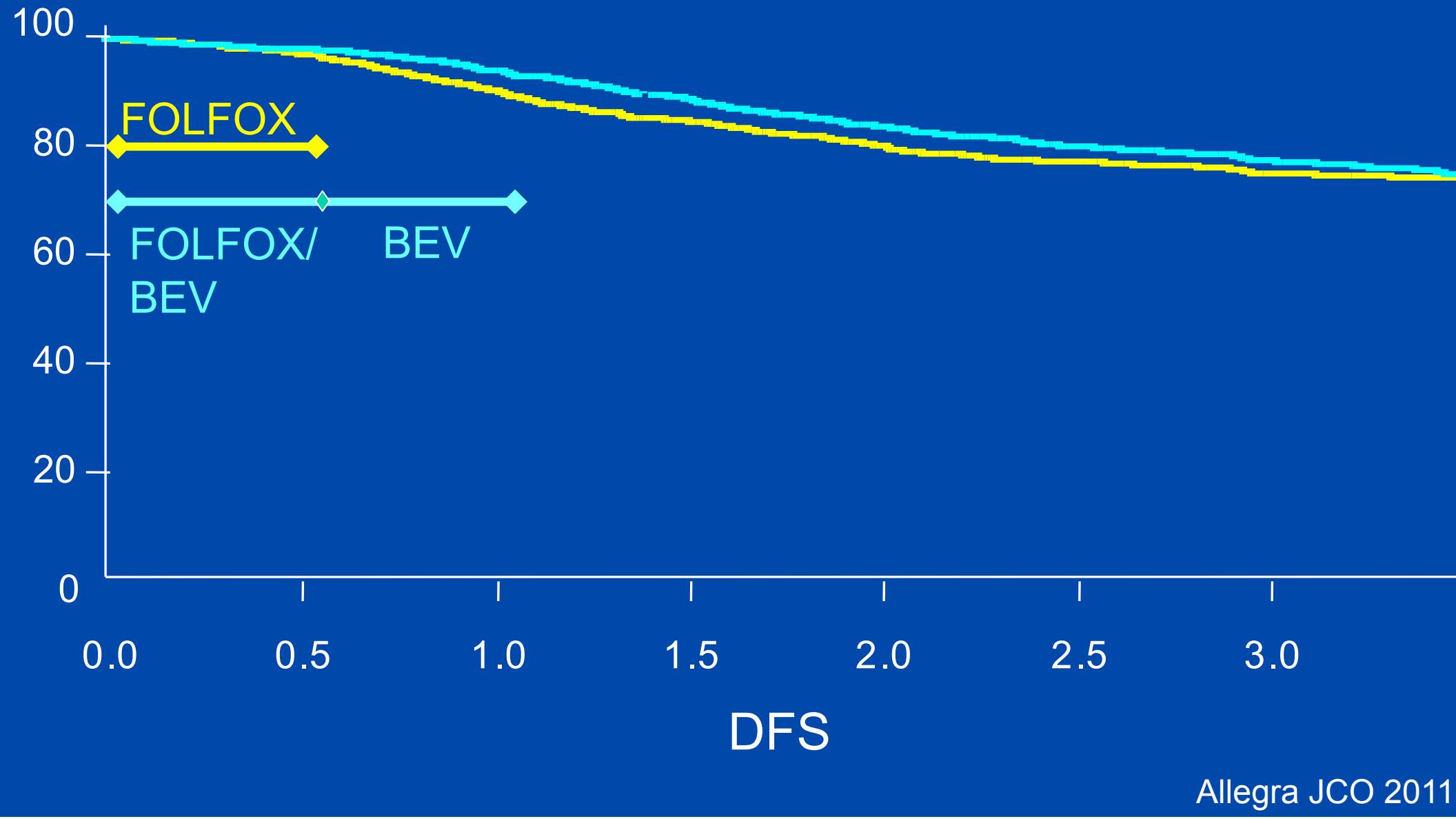
Adjuvant Therapy in CRC and Cure

- 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



A Snapshot of C08



Allegra JCO 2011

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

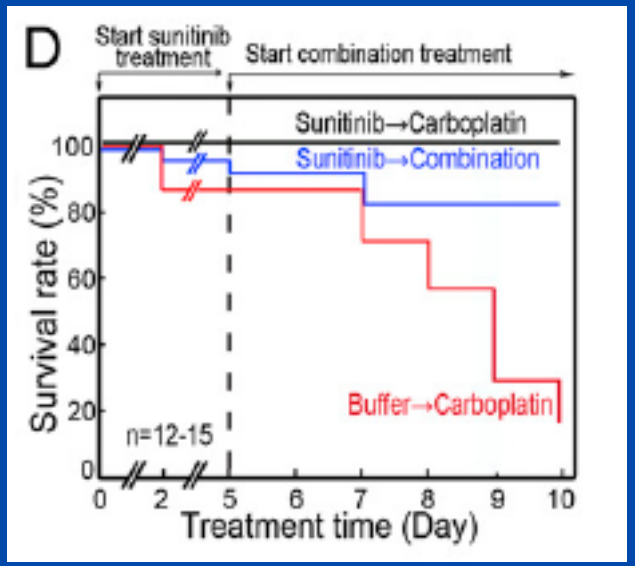
- Two negative trials
  - No reason to think that "tweaking the regimen" (longer duration) will provide lasting benefit
  - Another example that "more is not better"
- We must re-focus on cytotoxic therapies rather than cytostatic therapies in the adjuvant setting in CRC (failure of NO147, 2010)
- An 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

Antiangiogenic agents significantly improve survival in tumor-bearing mice by increasing tolerance to chemotherapy-induced toxicity

Danfang Zhang[a,b], Eva-Maria E. Hedlund[a], Sharon Lim[a], Fang Chen[a], Yin Zhang[a], Baocun Sun[b], and Yihai Cao[a,1]



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

Could Our Models Be Wrong?

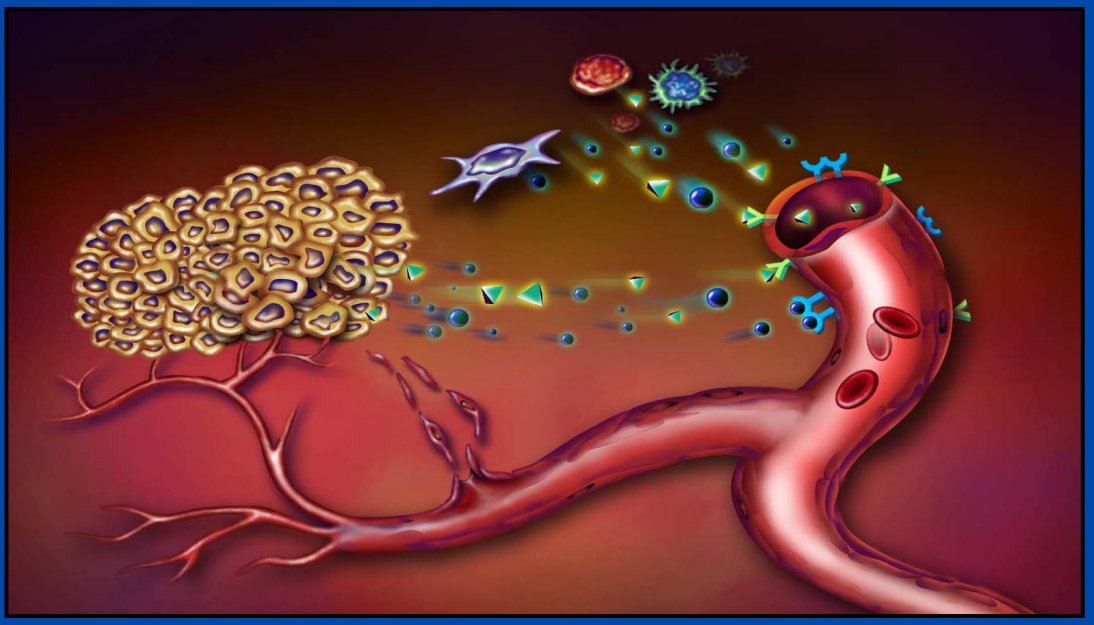
- Preclinical modeling is based on “sprouting angiogenesis”, but in humans, the role of blood vessels in mediating tumor growth is much more complicated

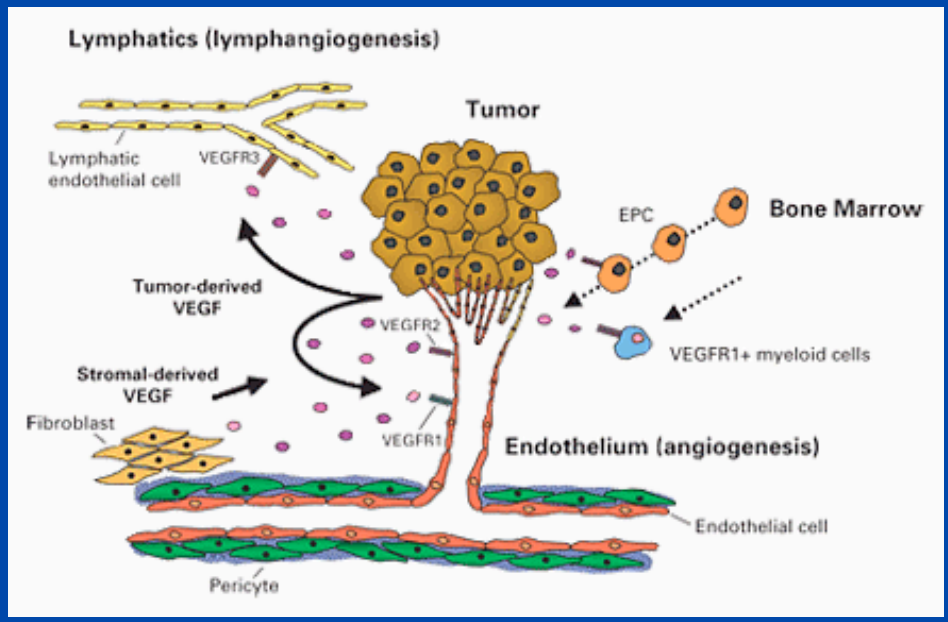
Challenge Existing Paradigms

- 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



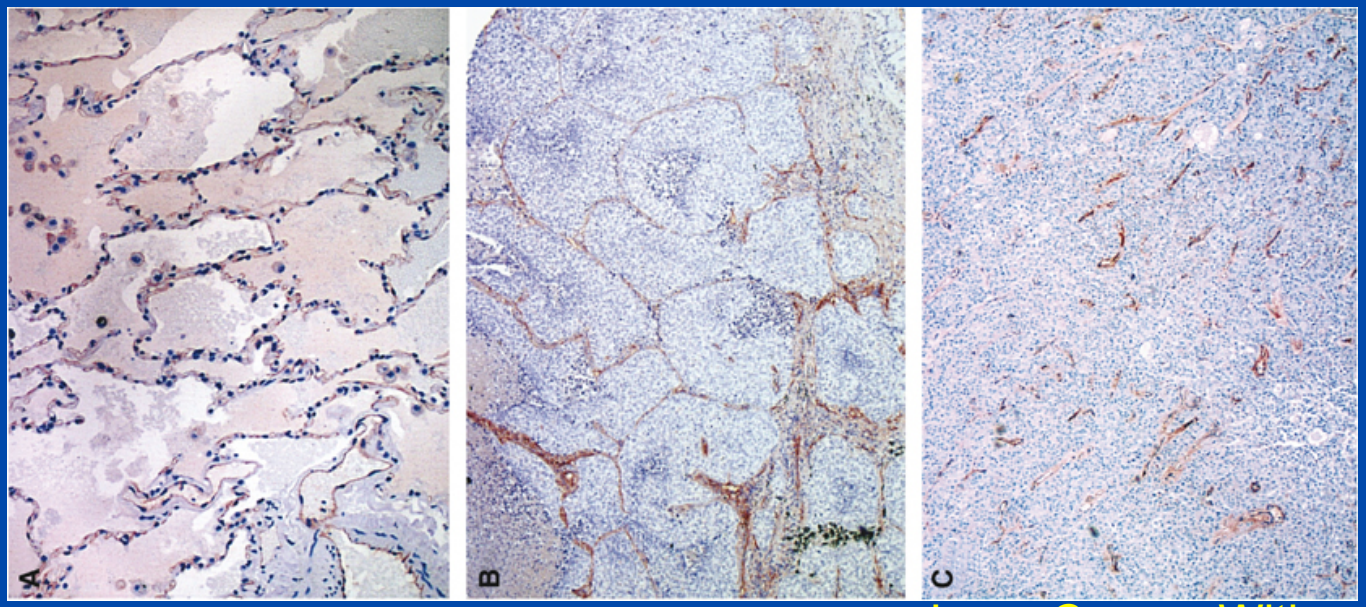


*Holash et al. Science 2009

Is nonangiogenesis a novel pathway for cancer progression? A study using 3-dimensional tumour reconstructions

British Journal of Cancer (2006) 94, 1176–1179

O Adighibe[1,5], K Micklem[2], L Campo[2], M Ferguson[2], A Harris[3], R Pozos[4], K Gatter[2] and F Pezzella[*,2]



H&E Normal

Lung Cancer With Preserved Alveolar Architecture

Lung Cancer With Destroyed Alveolar Architecture

- In highly vascularized organs, tumor cells may coopt the vasculature
  - Alveolar architecture is maintained in tumors growing in the lung

Different Growth Patterns of Non-Small Cell Lung Cancer Represent Distinct Biologic Subtypes

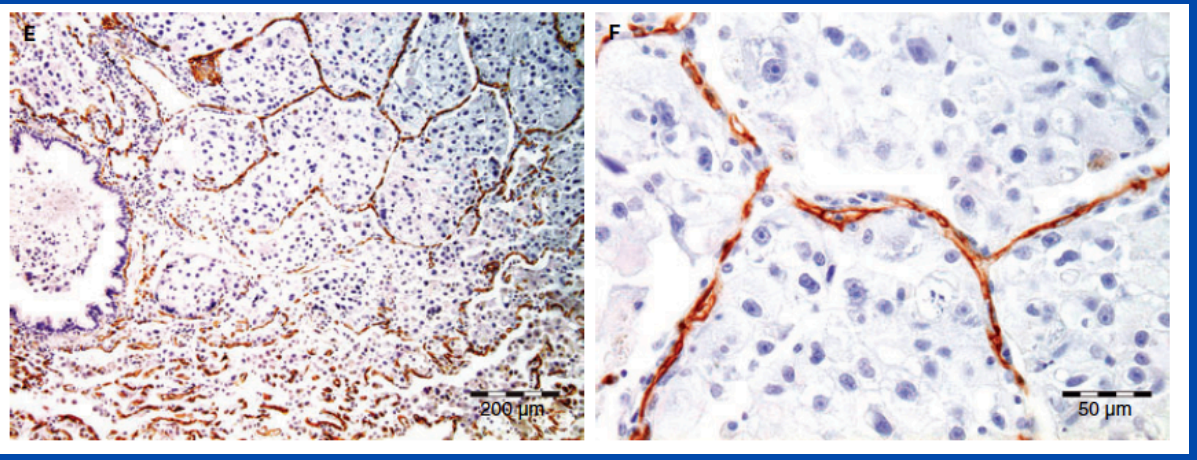
Peyman Sardari Nia, MD, Cecile Colpaert, MD, PhD, Peter Vermeulen, MD, PhD, Joost Weyler, MD, PhD, Francesco Pezzella, MD, PhD, Paul Van Schil, MD, PhD, and Eric Van Marck, MD, PhD

Ann Thorac Surg 2008;

Histopathology 2007, **51**, 354–361. DOI: 10.1111/j.1365-2559.2007.02800.x

Distinct angiogenic and non-angiogenic growth patterns of lung metastases from renal cell carcinoma

P Sardari Nia, J Hendriks, G Friedel,[1] P Van Schil & E Van Marck[2]



British Journal of Cancer (2004) 90, 1429 – 1436

www.bjcancer.com

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 Stessels[1,2], G Van den Eynden[1,2], I Van der Auwera[1,2], R Salgado[1,2], E Van den Heuvel[1,2], AL Harris[3], DG Jackson[4], CG Colpaert[1,2], EA Van Marck[1,2], LY Dirix[1,2] and PB Vermeulen[*,1,2]

[1]Translational Cancer Research Group Antwerp, Department of Pathology, University Hospital, University of Antwerp, Edegem, Belgium; [2]Translational Cancer Research Group Antwerp, Departments of Pathology and Oncology, General Hospital Sint-Augustinus, Wilrijk, Belgium; [3]Molecular Oncology Laboratory, Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Headington, Oxford, UK; [4]MRC 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-Vitiani[1]*, Roberto Pallini[2]*, Mauro Biffoni[1], Matilde Todaro[3], Gloria Invernici[4], Tonia Cenci[5], Giulio Maira[2], Eugenio Agostino Parati[4], Giorgio Stassi[3,6], Luigi Maria Larocca[5] & Ruggero De Maria[1,7]

Glioblastoma stem-like cells give rise to tumour endothelium

Rong Wang[1,2,3], Kalyani Chadalavada[4], Jennifer Wilshire[5], Urszula Kowalik[1], Koos E. Hovinga[1,6], Adam Geber[1], Boris Fligelman[1], Margaret Leversha[4], Cameron Brennan[1,3,7] & Viviane Tabar[1,2,3]

Our Success is Best in the Most Angiogenic Tumors

(where a tumor mass was created that was larger than the original organ)

Cancer Type	How Utilized or Studied	Increase PFS Over Standard Care Δ	Increase RR Δ	HR	FDA Approval
Renal Cell Ca	Single agent	3-6 months	8-30%	0.42-0.63	Y
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Ovarian	After chemo/ Bev	1.7-4 months	?	0.65-0.79	Pending

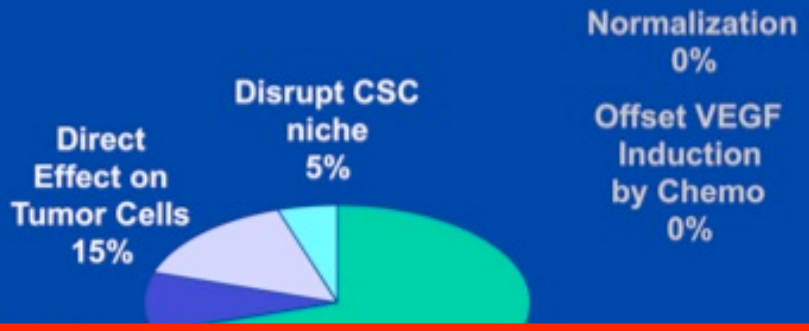
With Such Varied Results With VEGF-Targeted Therapies, There Must be Multiple Mechanisms of Action of This Class of Drugs

Proposed Mechanisms of Action of Anti-VEGF Rx

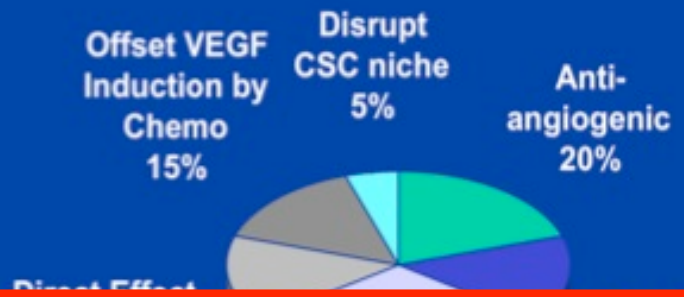
- Anti-angiogenic
- “Normalization” of the vasculature with improved delivery of chemo and O_2
- Direct effect on tumour cells
- Vascular “constriction”
- Offset effects of stress
- Immune function
- Disruption of the CSC niche

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?

Anti-Angiogenesis 2011

- 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 in different tumor types
- "Me Too" drugs are unlikely to advance the field

Thank You For Your Attention!