Targeted therapies: Promises, successes, failures.
Vienna September 2012
Disclaimer

• I apologise (profusely) if I fail to mention:-
  – your favourite tumour type
  – your favourite anti-angiogenic agent
  – your favourite trial
  – your favourite clinical investigator (especially if it is you)
  – your favourite pharmaceutical company (especially if you are employed by one)
In the absence of vascularisation, solid tumours remain dormant and 2–3 mm in size, with size being limited by the ability of oxygen and nutrients to diffuse into the tumour.


Transplanted mouse tumours associated with microvasculature


The hype

Folkman ‘will cure cancer within two years’

James Watson, Nobel Laureate
Some post-hoc rationalisation

Anti-VEGF reduces interstitial fluid pressure, increases vessel density, and increases drug delivery.

Anti-VEGF antibody ‘normalises’ tumour vasculature

Pre-clinical studies of anti-VEGF therapy: ↑ delivery of chemotherapy

H33342 = tumour perfusion marker
*p<0.05 vs placebo

Rapid Decrease in Delivery of Chemotherapy to Tumors after Anti-VEGF Therapy: Implications for Scheduling of Anti-Angiogenic Drugs

Perfusion

Net rate of influx of $[^{11}\text{C}]$docetaxel

Van der Veldt et al, Cancer Cell (2012) 21:82-91
Expression of VEGF in ~6,500 tissue specimens (GeneLogic/Affymetrix®)

Overexpression of VEGF in human tissue
RCC Sunitinib vs. IFN-α: PFS by Independent Central Review

HR = 0.538
95% CI (0.439, 0.658)
P < 0.00001

ORR 47% vs 12%, p < 0.001


HR = hazard ratio.
ICON-7: carbo-taxol±bevacizumab OS update

ITT population

FIGO stage III suboptimal & Stage IV with debulking

<table>
<thead>
<tr>
<th>High-risk subgroup</th>
<th>CP (n=234)</th>
<th>CP+Bev (n=231)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths, n (%)</td>
<td>109 (47)</td>
<td>79 (34)</td>
</tr>
<tr>
<td>Median, months</td>
<td>28.8</td>
<td>36.6</td>
</tr>
<tr>
<td>Log-rank test</td>
<td>p=0.002</td>
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</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.64 (0.48–0.85)</td>
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<tr>
<td>1-year OS rate (%)</td>
<td>86</td>
<td>92</td>
</tr>
</tbody>
</table>
Bevacizumab in platinum-resistant recurrent ovarian cancer

Events, n (%)
- CT (n=182): 166 (91%)
- BEV + CT (n=179): 135 (75%)

Median PFS, months (95% CI)
- CT (n=182): 3.4 (2.2–3.7)
- BEV + CT (n=179): 6.7 (5.7–7.9)

HR (unadjusted) (95% CI)
- Log-rank p-value (2-sided, unadjusted)
  - CT (n=182): 0.48 (0.38–0.60)
  - BEV + CT (n=179): <0.001

Response rate (RECIST and/or CA125)
- CT (n=182): 12.6%
- BEV + CT (n=179): 30.9%

Pujade-Lauraine et al ASCO 2012
Recurrent Glioblastoma
Bevacizumab as a Single-Agent and in Combination

<table>
<thead>
<tr>
<th>BV Dose (mg/kg)</th>
<th>Chemotherapy</th>
<th>Study Design</th>
<th>Number of Patients</th>
<th>CR/PR (%)</th>
<th>PFS, Median (wk)</th>
<th>PFS-6 (%)</th>
<th>OS, Median (wk)</th>
<th>Reference</th>
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<tbody>
<tr>
<td>10</td>
<td>Carboplatin + cetuximab</td>
<td>Retrospective 6 series</td>
<td>83</td>
<td>19</td>
<td>22</td>
<td>30</td>
<td>Francesconi et al.71</td>
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<td>Etoposide</td>
<td>Phase II</td>
<td>27</td>
<td>23</td>
<td>18</td>
<td>45</td>
<td>46</td>
<td>Reardon et al.72</td>
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<td>10</td>
<td>Irinotecan</td>
<td>Phase II</td>
<td>23</td>
<td>61</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>Vredenburgh et al.10</td>
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<td>10</td>
<td>Irinotecan</td>
<td>Phase II</td>
<td>35</td>
<td>57</td>
<td>24</td>
<td>46</td>
<td>42</td>
<td>Vredenburgh et al.11</td>
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<tr>
<td>10</td>
<td>Irinotecan</td>
<td>Phase II</td>
<td>82</td>
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<td>35</td>
<td>Friedman et al.8</td>
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<tr>
<td>10</td>
<td>Irinotecan</td>
<td>Retrospective 37 series</td>
<td>68</td>
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<td>46</td>
<td>Zuniga et al.74</td>
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<tr>
<td></td>
<td>Irinotecan</td>
<td>Retrospective 27 series</td>
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<td>20</td>
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<td>Kang et al.73</td>
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<td>5</td>
<td>Irinotecan</td>
<td>Retrospective 20 series</td>
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<td>19</td>
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<td>28</td>
<td>Bokstein et al.76</td>
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<tr>
<td>5 or 10</td>
<td>Irinotecan</td>
<td>Retrospective 13 series</td>
<td>77</td>
<td>24</td>
<td>NR</td>
<td>27</td>
<td>Ali et al.75</td>
<td></td>
</tr>
</tbody>
</table>

led to rapid approval for bevacizumab in Glioma by FDA May 2009
Breast Cancer: Bevacizumab and chemotherapy: PFS

**E2100 (IRF assessment)**

- Paclitaxel (n=354)
- Bevacizumab + paclitaxel (n=368)

HR=0.48* (0.39–0.61) p<0.0001

**RIBBON-1: taxane/anthracycline cohort**

- Placebo + taxane/anthracycline (n=207)
- Bevacizumab + taxane/anthracycline (n=415)

HR=0.64* (0.52–0.80) p<0.0001

**AVADO**

- Placebo + docetaxel (n=241)
- Bevacizumab 15mg/kg q3w + docetaxel (n=247)

HR=0.67* (0.54–0.83) p=0.0002†

**RIBBON-1: capecitabine cohort**

- Placebo + capecitabine (n=206)
- Bevacizumab + capecitabine (n=409)

HR=0.69* (0.56–0.84) p=0.0002

*Stratified and censored for non-protocol therapy before disease progression
†p value is exploratory; IRF = independent review facility

Bevacizumab in MBC: overall survival

<table>
<thead>
<tr>
<th></th>
<th>Non-bevacizumab (n=1,008)</th>
<th>Bevacizumab (n=1,439)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, months</td>
<td>26.4</td>
<td>26.7</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.97 (0.86–1.08)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p=0.56</td>
<td></td>
</tr>
<tr>
<td>1-year OS rate, %</td>
<td>77</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>p=0.003</td>
<td></td>
</tr>
</tbody>
</table>

**Graph:**
- OS estimate vs. time (months)
- Green line: Non-bevacizumab
- Pink line: Bevacizumab

**Number at risk:**
- Non-bevacizumab: 1008, 892, 746, 621, 426, 178, 51, 19, 8
- Bevacizumab: 1439, 1333, 1127, 916, 591, 204, 55, 23, 5

O'Shaughnessy, et al. ASCO 2010
FDA Commissioner announces Avastin decision 
Drug not shown to be safe and effective in breast cancer patients

FDA Commissioner announces Avastin decision Drug not shown to be safe and effective in breast cancer patients.

FDA Commissioner Margaret A. Hamburg, M.D., said today she is revoking the agency’s approval of the breast cancer indication for Avastin (bevacizumab) after concluding that the drug has not been shown to be safe and effective for that use.

Avastin’s risks include severe high blood pressure; bleeding and hemorrhaging; heart attack or heart failure; and the development of perforations in different parts of the body such as the nose, stomach, and intestines.
Taxane ± bevacizumab: Overall Survival
(taxane-pretreated hormone receptor-negative population)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median (months)</th>
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</thead>
<tbody>
<tr>
<td>Bevacizumab + taxane</td>
<td>25.6</td>
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<tr>
<td>(n=69)</td>
<td></td>
</tr>
<tr>
<td>Taxane alone (n=52)</td>
<td>15.0</td>
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</tbody>
</table>

Hazard ratio (stratified only by study) = 0.61
(95% CI 0.40–0.94)

p=0.0247

AVAB00092e October 2010

Miles et al. Ann Oncol 2010; Suppl
Anti-VEGF therapy in the adjuvant setting?

The wrong context?
Adjuvant study in colorectal cancer
NSABP C-08 mFF6 ± bevacizumab

3yDFS

mFF6+B
291  77.4  HR = 0.89

mFF6
312  75.5  p    = 0.15

Allegra et al, JCO (2011) 29: 11-16
Adjuvant study in colorectal cancer
NSABP C-08 mFF6 ± bevacizumab

DFS at 1 Yr
HR 0.60
p 0.0004

Event-free at 1 Yr
HR 1.07
p 0.48

Allegra et al, JCO (2011) 29: 11-16
Angiogenesis:
is this a linear or stochastic behaviour?

1 year of anti-angiogenic therapy
E5103 & Beatrice & BETH

Adapted from EBCTCG. Lancet 1998;352:930-942
<table>
<thead>
<tr>
<th>Assumptions 20-40 yrs ago</th>
<th>Assumptions 2002-2010</th>
<th>What we know from clinical trial results (in 2012)</th>
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<tr>
<td>Angio inhibition would induce dormancy in all tumor types</td>
<td>Angio inhibition would provide <em>benefit</em> across tumor types</td>
<td>Benefit is tumor dependent and context dependent (+/- chemo)</td>
</tr>
</tbody>
</table>
Angiogenesis: -multiple (non-mutating) factors -multiple targets

- Extracellular: VEGF, IL8, FGF, PDGF, Ang (HGF, heparanase)
- Membrane: RTK, Integrins, Cadherins, V-CAM, ephrin
- Intracellular: notch, mutations and receptor mutants
Inhibition of Angiopoetin1-2/Tie-2 axis

- HER2 negative
- 1st-line MBC
- Measurable/evaluable
- n=220

AMG386 (10mg/kg) QW
paclitaxel 90mg/sq.m QW (3on/1off)
bevacizumab (10mg/kg Q2W)

AMG386 (3mg/kg) QW
paclitaxel 90mg/sq.m QW (3on/1off)
bevacizumab (10mg/kg Q2W)

AMG386 placebo QW
paclitaxel 90mg/sq.m QW (3on/1off)
bevacizumab (10mg/kg Q2W)

AMG386 open label (10mg/kg QW)
paclitaxel 90mg/sq.m QW (3on/1off)

Dieras et al. ASCO 2011
The future?
Multikinase VEGFR inhibitors

<table>
<thead>
<tr>
<th></th>
<th>VEGFR</th>
<th>KIT</th>
<th>PDGFR</th>
<th>FGF</th>
<th>RET</th>
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<th>RAF</th>
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<td>Pazopanib</td>
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<td>Vandetanib</td>
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<td>Sorafenib</td>
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<td>Other angiogenic factors are important and may contribute to resistance</td>
<td>Dual targeting of bypass pathways have not led to major advances</td>
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</tbody>
</table>
Angiogenic factors increased by VEGF inhibition

Multiple circulating proangiogenic factors induced by sunitinib malate are tumor-independent and correlate with antitumor efficacy

Mediators of escape/rebound e.g., VEGF, FGF, PIGF, SDF1-α
Does inhibiting the VEGF pathway make things worse?

Anti-VEGFR2, SU10944, sunitinib, tumor VEGF KO

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

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 Casanovas1,*

1Translational Research Laboratory, Catalan Institute of Oncology, IDIBELL, 08907 L’Hospitalet de Llobregat, Spain
2Department of Biochemistry & Biophysics, Diabetes Center, and Helen Diller Family Comprehensive Cancer Center
3Department of Neurosurgery and Helen Diller Family Comprehensive Cancer Center
University of California, San Francisco, San Francisco, CA 94143, USA
4Department of Biochemistry, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka 537-8511, Japan
5Department de Ciències Fisiològiques II, Universitat de Barcelona, IDIBELL, 08907 L’Hospitalet de Llobregat, Spain
6These authors contributed equally to this work
*Correspondence: dh@ucsf.edu (D.H.), ocasanovas@iconcologia.net (O.C.)
DOI 10.1016/j.ccr.2009.01.027

Sunitinib, Sorafenib, SU10944

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. Kerbel1,2,*

1Molecular and Cellular Biology Research, Sunnybrook Health Sciences Centre, Toronto, ON M4N 3M5, Canada
2Department of Medical Biophysics, University of Toronto, Toronto, ON M5G 2M9, Canada
3Sunnybrook Odette Cancer Centre, Toronto, ON M5G 2M9, Canada
4Pfizer Global Research and Development, La Jolla Labs, La Jolla, CA 92121, USA
*Correspondence: robert.kerbel@sunnybrook.ca
DOI 10.1016/j.ccr.2009.01.021
Rebound: increased invasiveness and metastatic potential when TKI is withdrawn

- In genetically engineered mice with pancreatic neuroendocrine tumours, withdrawing sunitinib after limited-duration therapy and with tumours still responding resulted in
  - increased proportion of invasive tumour versus control
  - significant increase in number of liver metastases

*p<0.05; **p<0.01 versus controls

Time from bevacizumab discontinuation due to AEs to progressive disease/death: pooled dataset

Studies included in the analysis: AVOREN, AViTA, AVADO, NO16966; analysis includes 596 out of a total of 4205 patients

Number remaining:
- Placebo: 234, 67, 24, 11, 3, 0
- Bevacizumab: 362, 102, 28, 11, 2, 0

Miles et al. JCO. 2011 29:83-88
Tumour invasion after treatment of glioblastoma with bevacizumab

3/12 bev decreased enhancement & oedema

8/12 bev non-enhancing FLAIR changes

2/12 post bev increase non-enhancing & enhancing tumour

increases in IGFBP2, CA9, MMP2 by IHC

Bevacizumab improves quality of life in patients with recurrent glioma

Reduced steroid requirement

Improved Independent Living Scores

Bevacizumab beyond progression in patients with mCRC

Overall survival

Unstratified HR: 0.81 (95% CI: 0.69–0.94)  
p=0.0062 (log-rank test)

Arnold et al ASCO 2012
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<td>Other angiogenic factors are important and may contribute to resistance</td>
<td>Dual targeting of bypass pathways have not led to major advances</td>
</tr>
<tr>
<td>Resistance would not occur</td>
<td>Resistance is inevitable</td>
<td>Continuation of therapy may be of some benefit</td>
</tr>
<tr>
<td>Did not consider consequences of withdrawal</td>
<td>Preclinical and anecdotes- Withdraw may lead to “flare”</td>
<td>No hard data to support that withdrawal leads to “flare”</td>
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<tr>
<td>Did not consider consequences of induction of hypoxia</td>
<td>VEGF inhibitors may increase tumor aggressiveness</td>
<td>In GBM, VEGF inhibitors may increase invasion and metastasis, but patients may still benefit from therapy</td>
</tr>
</tbody>
</table>
Candidate biomarkers of response and resistance to antiangiogenic therapy

Do all patients benefit a bit, or do a few benefit a lot?

Conventional criteria (patient, tumour, pre-Rx characteristics)

<table>
<thead>
<tr>
<th></th>
<th>Baseline biomarkers</th>
<th>Dynamic biomarkers</th>
<th>Escape biomarkers</th>
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</thead>
<tbody>
<tr>
<td><strong>Physiological:</strong></td>
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<tr>
<td></td>
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<td>Hypertension</td>
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<tr>
<td><strong>Gene level:</strong></td>
<td>VEGF or IL-8 genotype</td>
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<tr>
<td><strong>Imaging:</strong></td>
<td>Vascular MRI parameters (K\text{\text{trans}}, CBV)</td>
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<tr>
<td><strong>Circulating:</strong></td>
<td>ICAM1, LDH or VEGF(?)</td>
<td>Collagen IV</td>
<td>SDF1\alpha, IL-6 or bFGF CPCs</td>
</tr>
</tbody>
</table>

Jain R K et al. (2009) Biomarkers of response and resistance to antiangiogenic therapy

*Nat Rev Clin Oncol* doi:10.1038/nrclinonc.2009.63
DCE-MRI as biomarker of response to VEGF inhibition: baseline $K_{\text{trans}}$ (RCC)


Hahn, O.M., Yang, C., Medved, M., Karczmar, G., Kistner, E., Karrison, T., Manchen, E. Mitchell, M., Ratain, M.J., Stadler, W.M.
Summary of plasma VEGF-A findings across tumour types

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Trial</th>
<th>Prognostic</th>
<th>Potentially predictive</th>
<th>Sample buffer</th>
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<td></td>
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<td>PFS</td>
<td>OS</td>
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<tr>
<td>mBC</td>
<td>AVADO</td>
<td>✓</td>
<td>✓</td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>mBC</td>
<td>AVEREL</td>
<td>✓</td>
<td>?</td>
<td>?</td>
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<td>AVAGAST</td>
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<td>mPaC</td>
<td>AViTA</td>
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<td>✓</td>
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<td>mCRC</td>
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<td>X</td>
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<tr>
<td>NSCLC</td>
<td>AVAiL</td>
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<td>✓</td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>RCC</td>
<td>AVOREN</td>
<td>✓</td>
<td>✓</td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Sample buffer: EDTA, Citrate

<sup>a</sup>Result might have been confounded by crossover

Jayson et al. EMCC 2011; Gianni et al. SABCS 2011
### Docetaxel ± bevacizumab (AVADO)

**PFS according to VEGF-A quartiles**

<table>
<thead>
<tr>
<th>VEGF-A quartile (pg/mL)</th>
<th>No. of patients</th>
<th>No. of events</th>
<th>Median PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bevacizumab 15 mg/kg + docetaxel</td>
<td>Placebo + docetaxel</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>1st</td>
<td>71</td>
<td>43</td>
<td>8.6</td>
</tr>
<tr>
<td>2nd</td>
<td>68</td>
<td>43</td>
<td>8.5</td>
</tr>
<tr>
<td>3rd</td>
<td>65</td>
<td>43</td>
<td>8.4</td>
</tr>
<tr>
<td>4th</td>
<td>61</td>
<td>36</td>
<td>10.3</td>
</tr>
</tbody>
</table>

Miles DW, et al. Cancer Res 2010;70(24 Suppl.):558 (abstract P2-16-04)
MERiDiAN (GO25632): Study Design

Previously untreated MBC (n=480)

28-day cycle:
Paclitaxel 90mg/m² d1, 8 and 15
Bevacizumab 10mg/kg d1 and 15

Paclitaxel

Paclitaxel + Bev 10mg/kg q2w

Stratify:
- Plasma VEGF-A level (low, high)
- Adjuvant chemotherapy (yes, no)
- ER and/or PR (positive, negative)
- Regions (Asia, N America, Europe)
<table>
<thead>
<tr>
<th>Assumptions 20-40 yrs ago</th>
<th>Assumptions 2002-2010</th>
<th>What we know from clinical trial results (in 2012)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angio inhibition would induce dormancy in all tumor types</td>
<td>Angio inhibition would provide <em>benefit</em> across tumor types</td>
<td>Benefit is tumor dependent and context dependent (+/- chemo)</td>
</tr>
<tr>
<td>Little discussion of multiplicity of angiogenic factors</td>
<td>Other angiogenic factors are important and may contribute to resistance</td>
<td>Dual targeting of bypass pathways have not led to major advances</td>
</tr>
<tr>
<td>Resistance would not occur</td>
<td>Resistance is inevitable</td>
<td>Continuation of therapy may be of some benefit</td>
</tr>
<tr>
<td>Did not consider consequences of withdrawal</td>
<td>Preclinical and anecdotes- Withdraw may lead to “flare”</td>
<td>No hard data to support that withdrawal leads to “flare”</td>
</tr>
<tr>
<td>Did not consider consequences of induction of hypoxia</td>
<td>VEGF inhibitors may increase tumor aggressiveness</td>
<td>In GBM, VEGF inhibitors may increase invasion and metastasis, but patients may still benefit from therapy</td>
</tr>
<tr>
<td>Did not think about biomarkers</td>
<td>Biomarkers are elusive</td>
<td>Maybe? Need validation, sometimes complex</td>
</tr>
</tbody>
</table>
Angiogenesis therapies in the clinic – a two-edged sword?

• Promises
  – a non-mutating target on which most cancers seem to depend
  – a complex multi-factorial process

• Successes
  – improved outcome in several tumour types
  – clinical benefits are tumour AND context dependent

• Failures (largely our own)
  – agents developed along the lines of cytotoxic drugs
  – negligible collection of relevant information in trials
  – failure to understand the underlying mechanisms
  – implications for scheduling, biomarkers
Angiogenesis therapies in the clinic a two-edged sword?

We can do a lot better than this.

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