Biomolecular predictive factors of response: lights and shade

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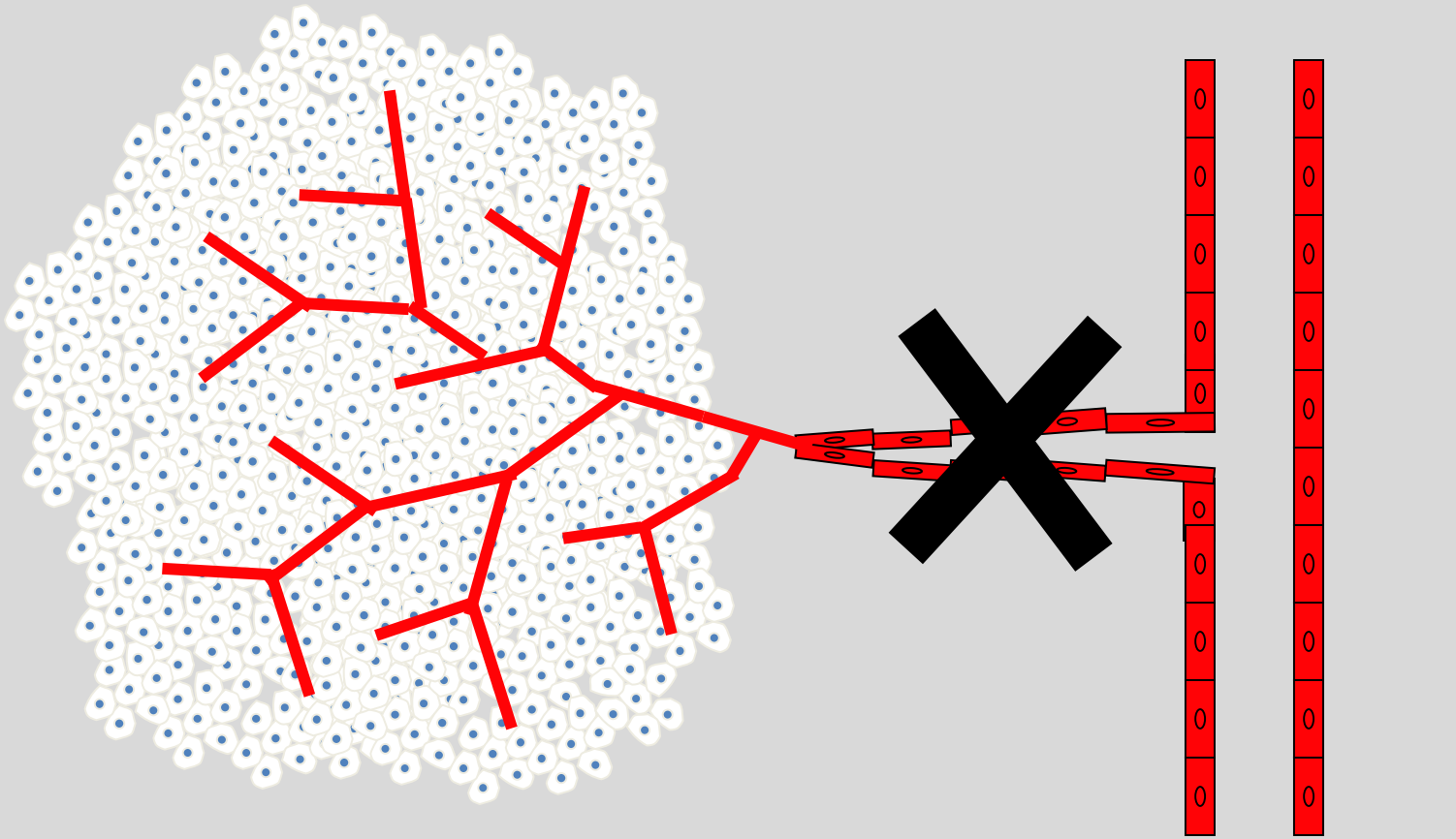
Università degli Studi di Trieste

What is anti-angiogenic therapy?

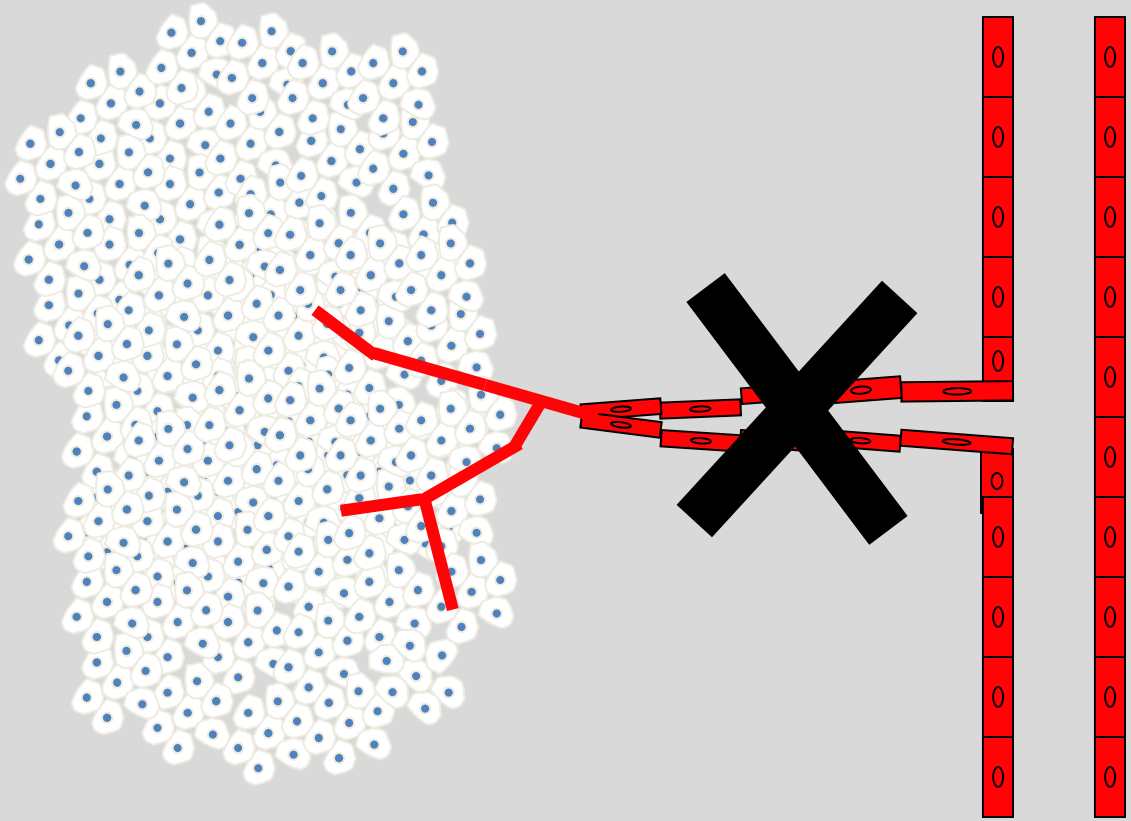
Anti-angiogenic therapy



Anti-angiogenic therapy

Tumour

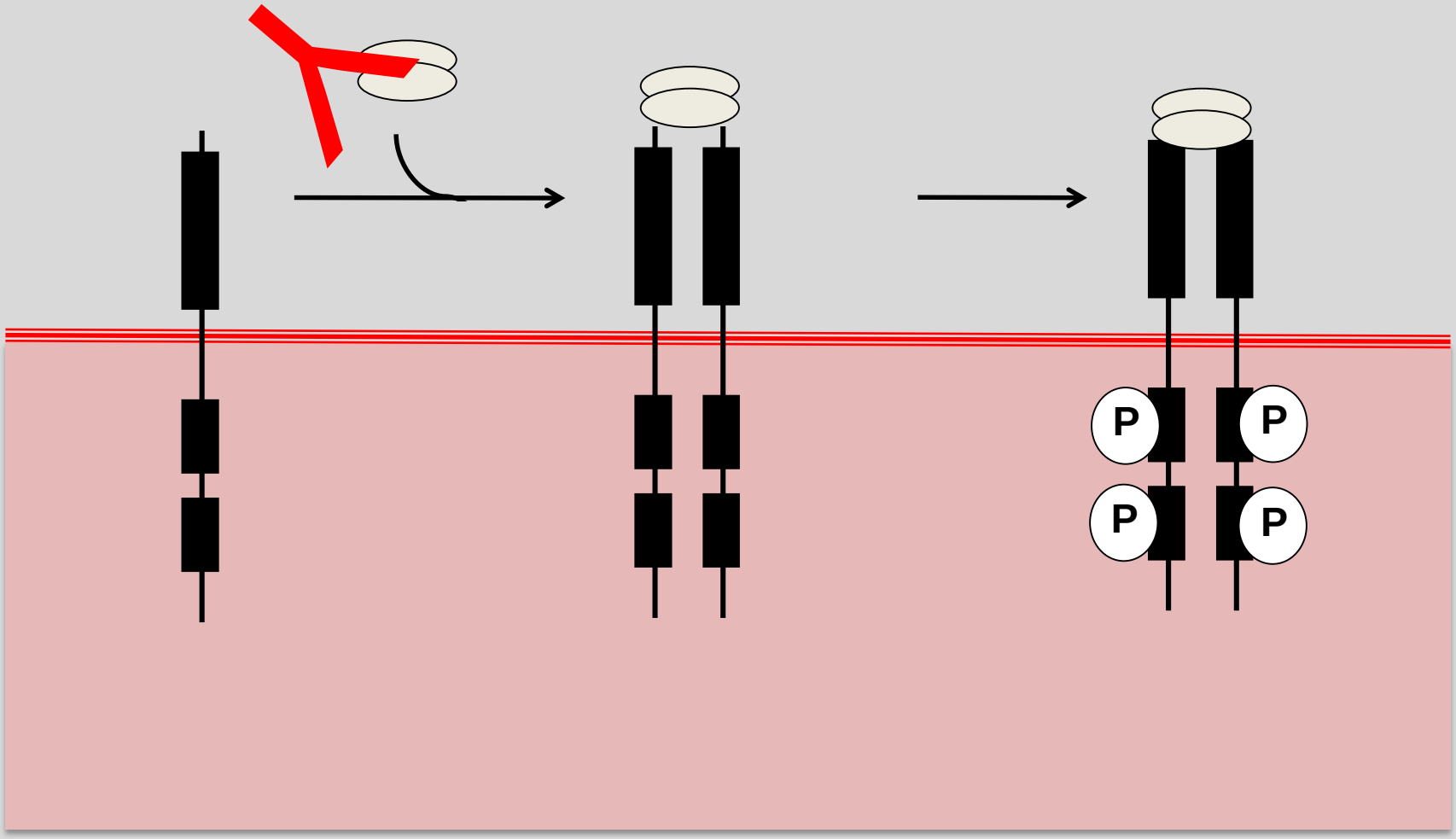
Blood vessel



How do we target angiogenesis?

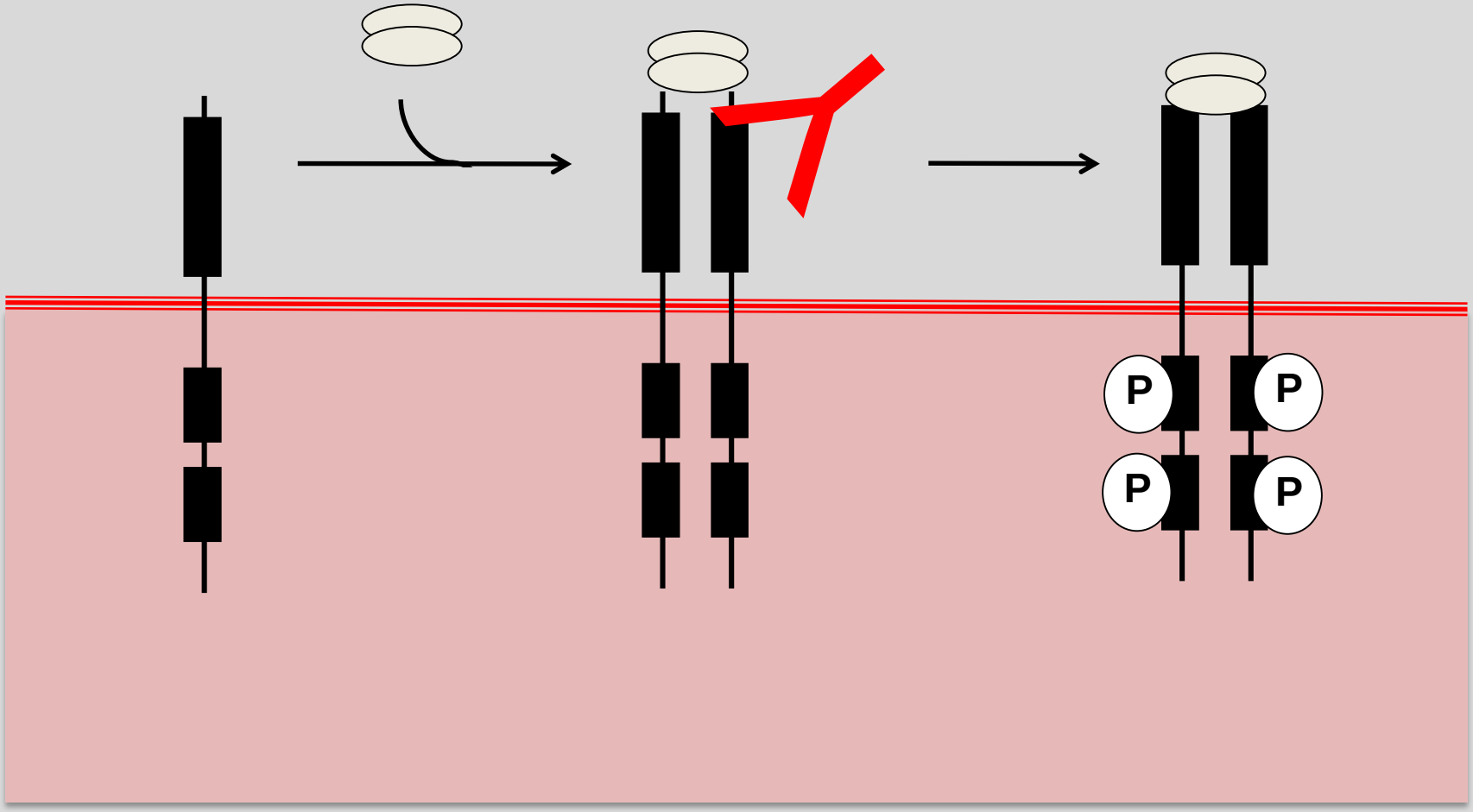
Inhibiting VEGF receptors

Bevacizumab (Avastin) *Genentech / Roche*
Aflibercept (Zaltrap) *Regeneron / Sanofi-Aventis*

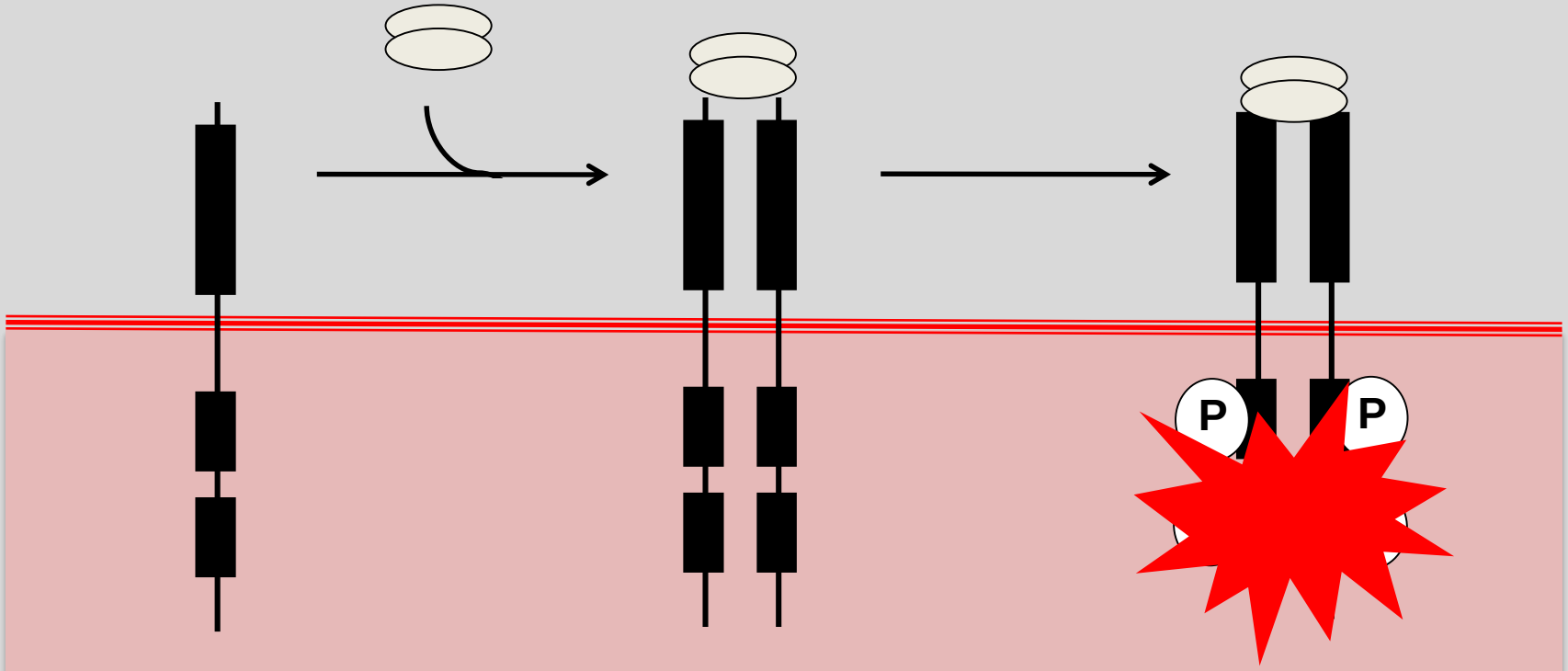


Inhibiting VEGF receptors

Ramucirumab (IMC-1121B)
Imclone Systems / Eli Lilly



Inhibiting VEGF receptors



Sunitinib (Sutent) *Pfizer*
Pazopanib (Votrient) *GlaxoSmithKline*

What results can be seen in patients?

Clinical translation of angiogenesis inhibitors

- Extensive laboratory studies have demonstrated that these drugs can suppress tumour growth by inhibiting angiogenesis
- In patients, angiogenesis inhibitors have been tested:

  1. Neoadjuvant setting *(prior to surgery for primary disease)*

  2. Adjuvant setting *(after surgery for primary disease)*

  3. Metastatic setting (*advanced stage disease)*
- **Best results have been observed in advanced disease:**

  e.g. sunitinib in metastatic renal cancer

  e.g. bevacizumab in metastatic colorectal cancer

  e.g. aflibercept in metastatic colorectal cancer
- But, less successful in other cancers e.g. *metastatic breast cancer*

How can we predict who will respond?

VEGF-pathway inhibition (sunitinib) in metastatic renal cancer

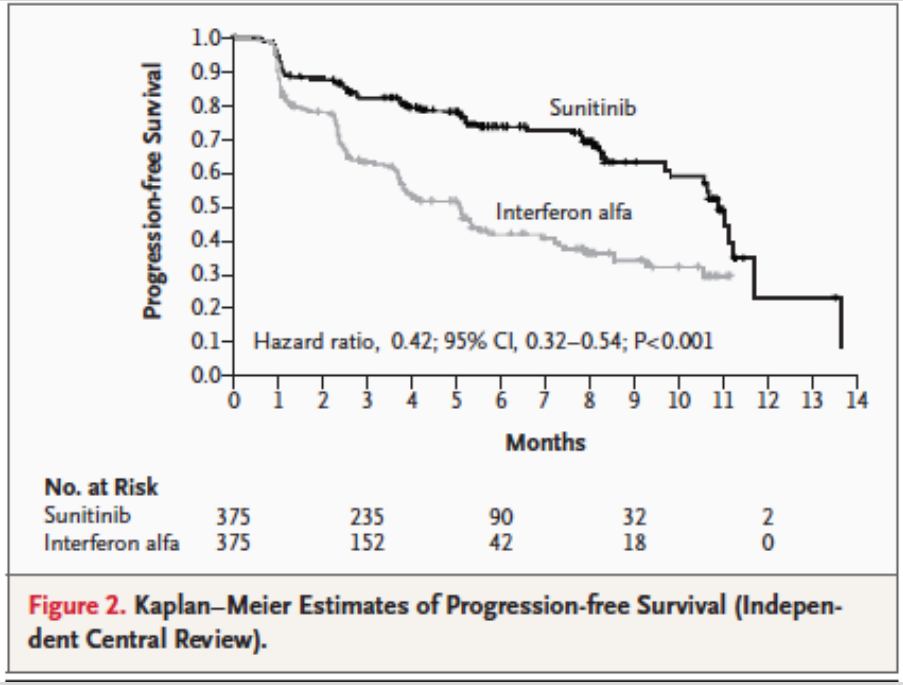
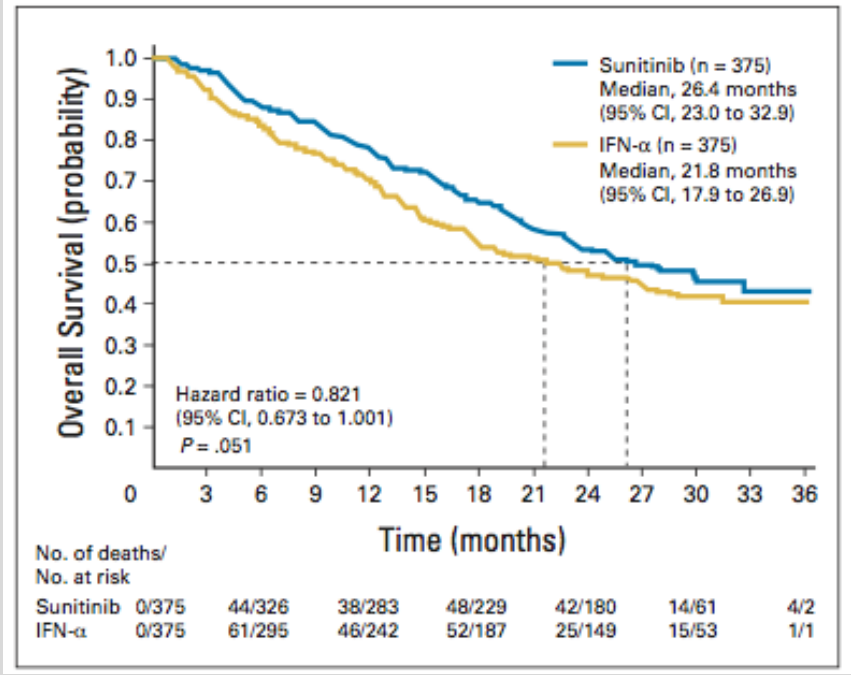


Figure 2. Kaplan–Meier Estimates of Progression-free Survival (Independent Central Review).

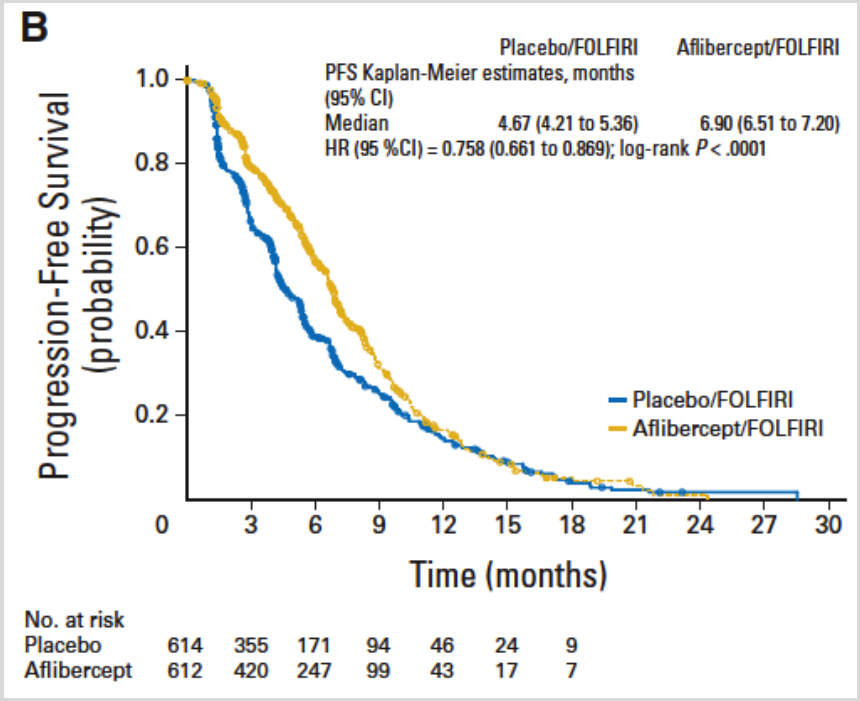
PFS extended by ~6 months

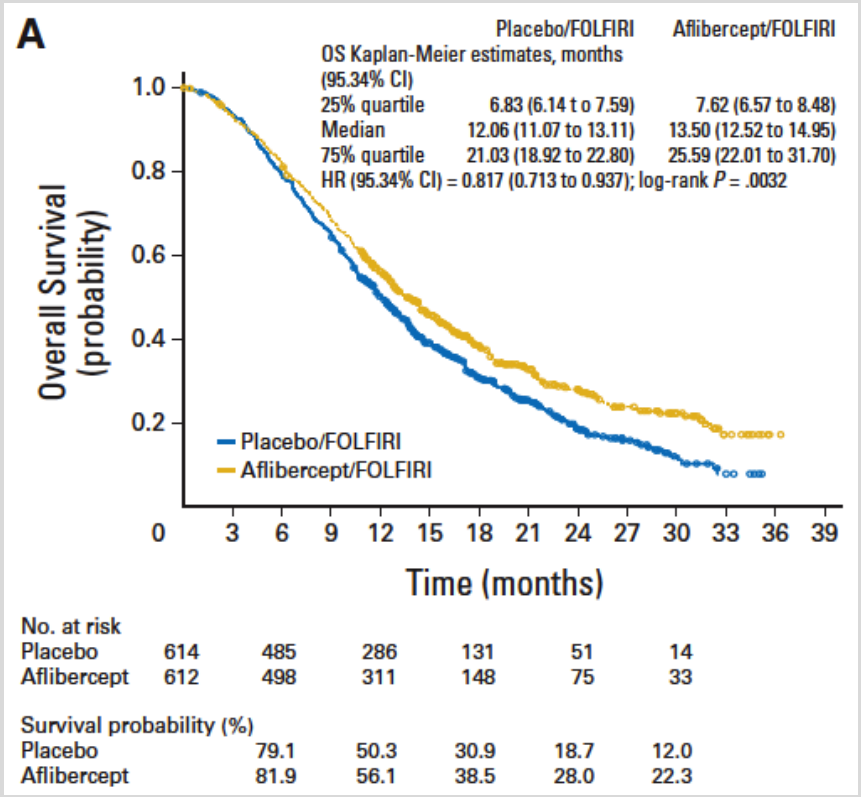


Unstratified, OS extended by ~6 months
Stratified, OS extended by ~14 months

Motzer *et al.*, NEJM 2007, Motzer *et al.*, JCO 2009

VEGF-pathway inhibition (aflibercept) in metastatic colorectal cancer





PFS extended by ~2.2 months

OS extended by ~1.5 months

Van Cutsem JCO 2012

VEGF-pathway inhibition (bevacizumab) in metastatic breast cancer

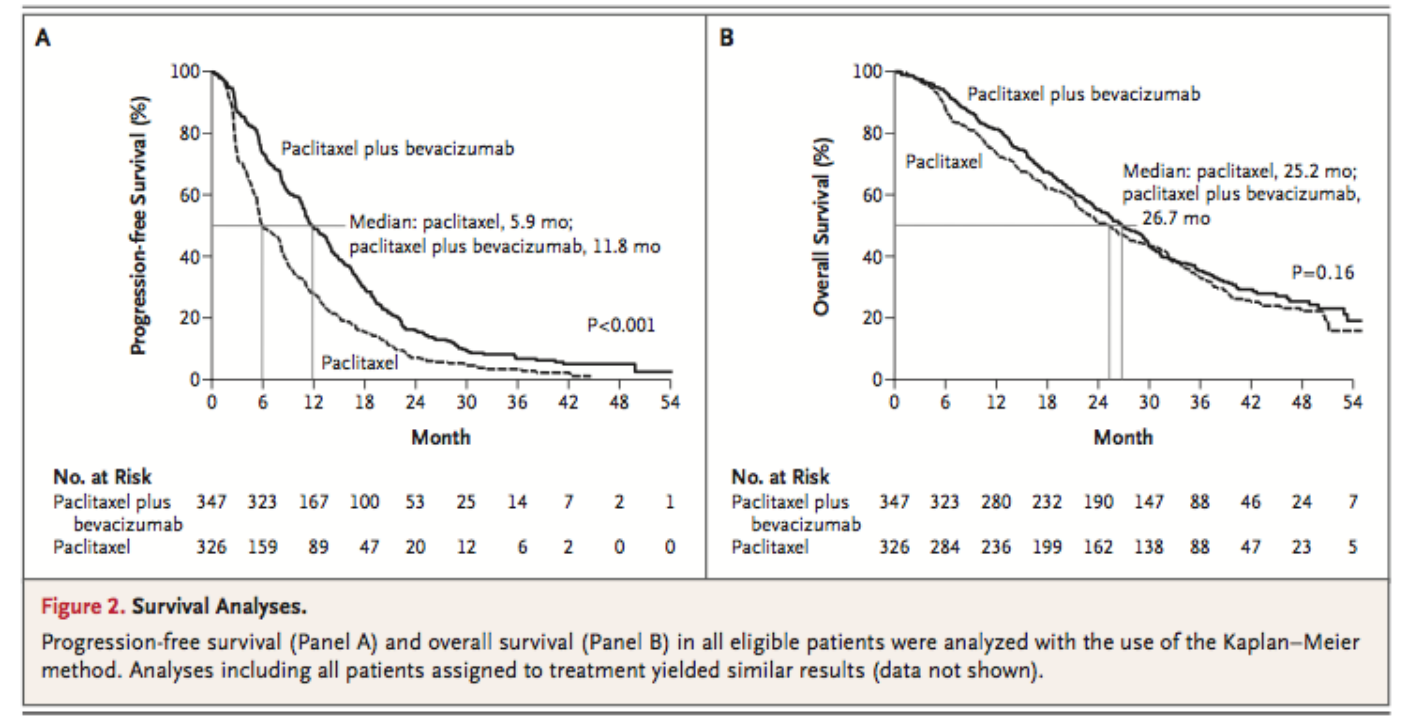


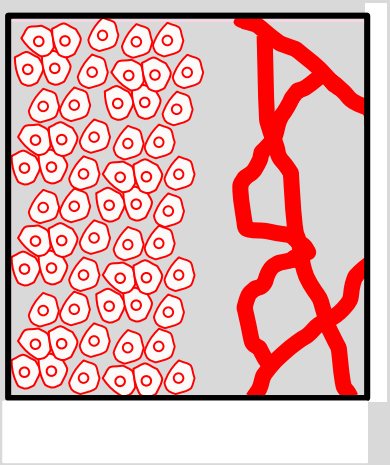
Figure 2. Survival Analyses.

Progression-free survival (Panel A) and overall survival (Panel B) in all eligible patients were analyzed with the use of the Kaplan–Meier method. Analyses including all patients assigned to treatment yielded similar results (data not shown).

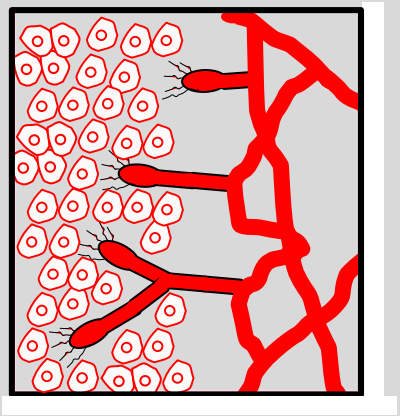
PFS extended by ~6 months Effect on OS not significant

Miller *et al.*, NEJM 2007

Targeting the tumour vasculature



Sprouting angiogenesis



Conventional anti-angiogenic drugs target sprouting angiogenesis by inhibiting VEGF signalling

- **Aflibercept**
- *colorectal*

- **Regorafenib**
- *colorectal*

- **Bevacizumab**
- *cervical, colorectal, lung, ovarian*

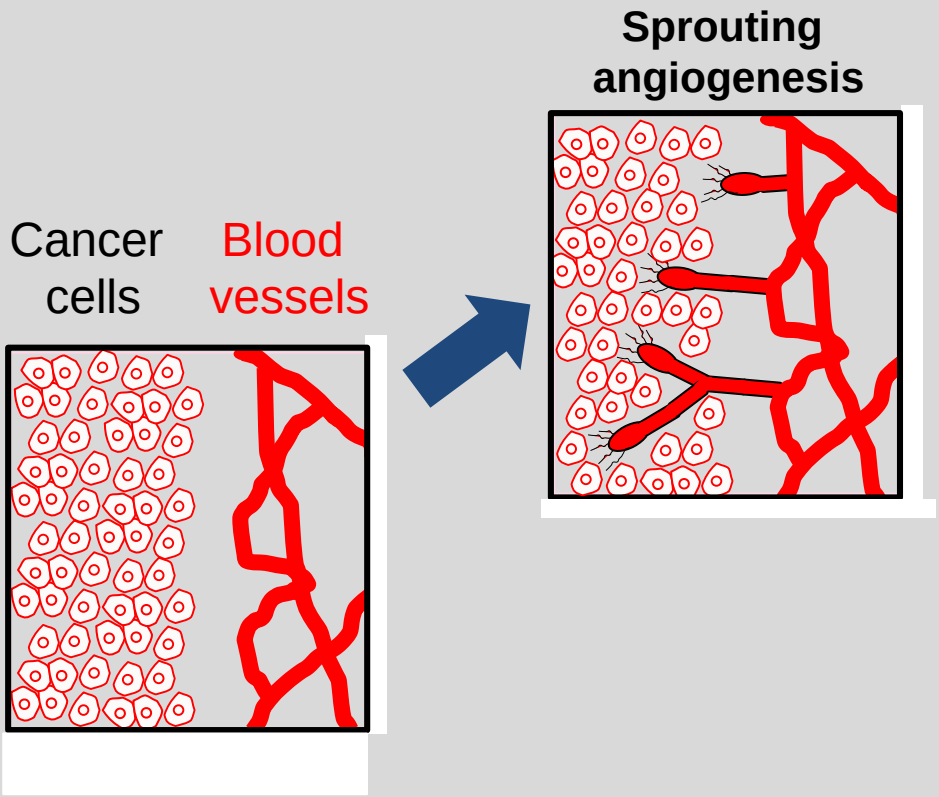
- **Sunitinib, Pazopanib**
- *renal*

- **Sorafenib**
- *hepatocellular*
- *carcinoma*

Ramuciramab
gastric

But, the benefit in terms of extending progression free survival and overall survival is modest, measured only in terms of months

Targeting the tumour vasculature

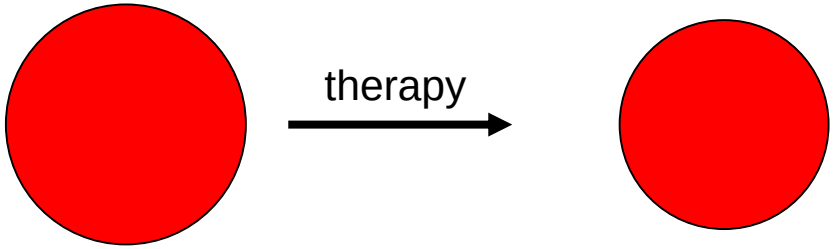


Also, anti-angiogenic drugs have failed to demonstrate a benefit in:

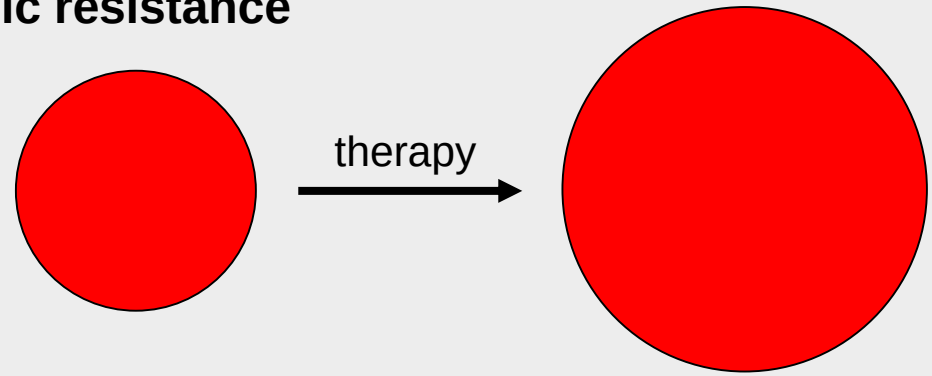
- ***Breast cancer***
- *Glioblastoma*
- *Melanoma*
- *Pancreatic cancer*
- *Prostate cancer*

Response and resistance to therapy

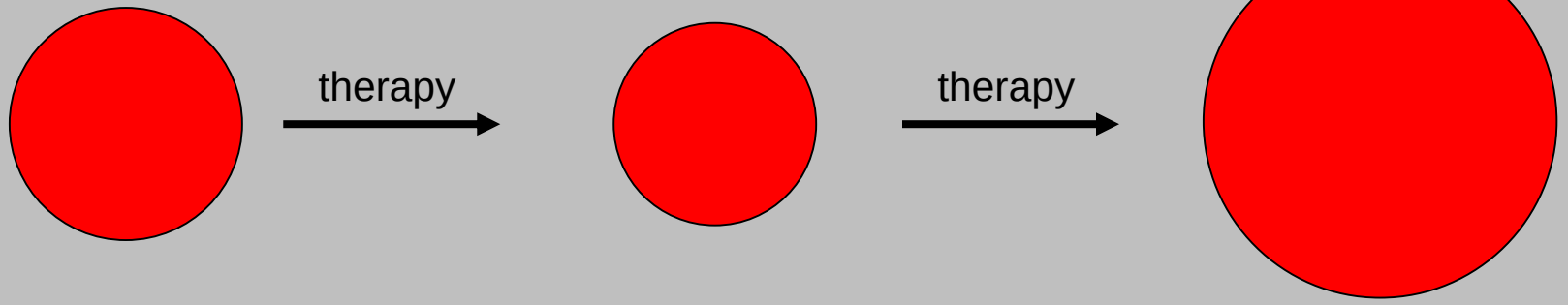
Response



Intrinsic resistance



Aquired resistance



How does resistance to therapy happen?

Proposed mechanisms of resistance

- Upregulation of alternative pro-angiogenic signals

  e.g. FGF2 (basic FGF), PLGF, IL8, HGF, Bv8, angiopoetins, Delta-Notch

- Compensatory host responses

  e.g. infiltration by myeloid cells, fibroblasts or endothelial progenitor cells (EPCs)

- Novel angiogenesis mechanisms

  e.g. co-option of existing blood vessels, vessel intususception

- Endothelial resistance

  e.g. vessel maturation (including pericyte recruitment), e.g. transformed ECs

- Adaptation of tumour cells

  e.g. altered metabolism e.g. autophagy e.g. tumour agression

- Pharmacology

Thus identifying predictive biomarker would be important
But biomarkers for anti-angiogenic therapy are elusive
MORE SHADE THEN LIGHTS

Circulating biomarkers
e.g. levels of circulating VEGF?

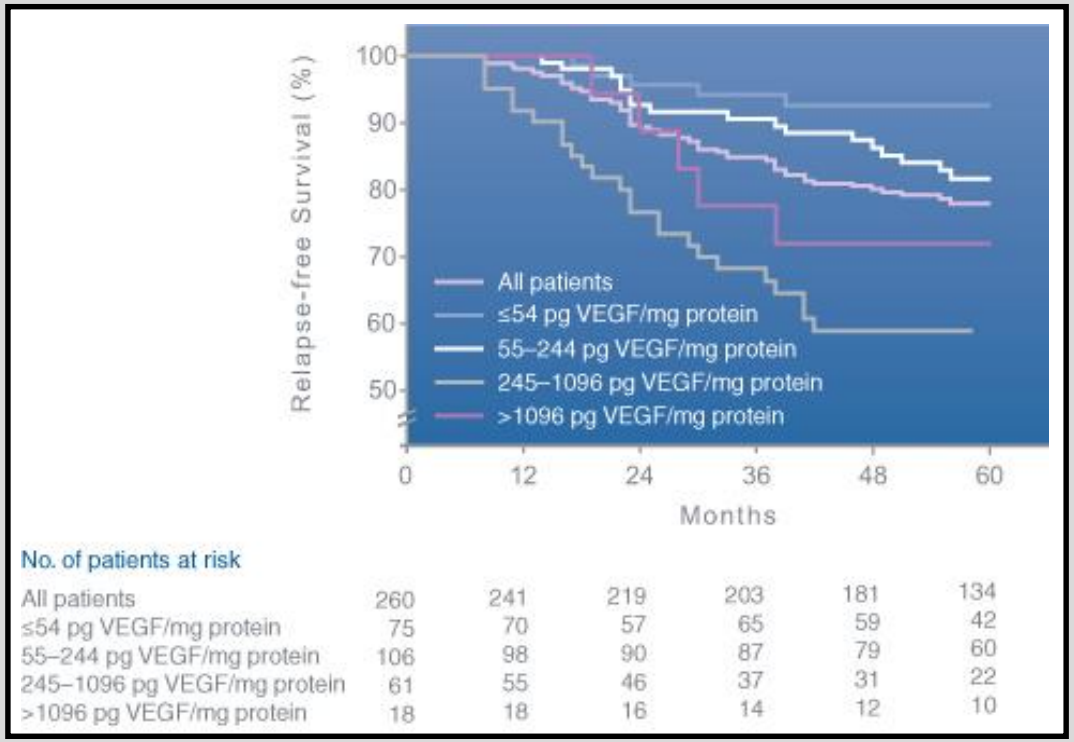
Polymorphisms in the VEGF pathway
e.g. VEGF-2578AA and VEGF-1154AA

Hypertension
e.g. increase in hypertension is surrogate for benefit

Imaging
e.g. features beyond change in size

VEGF as a prognostic and predictive factor in breast cancer

The VEGF ligand is correlated with poor survival in

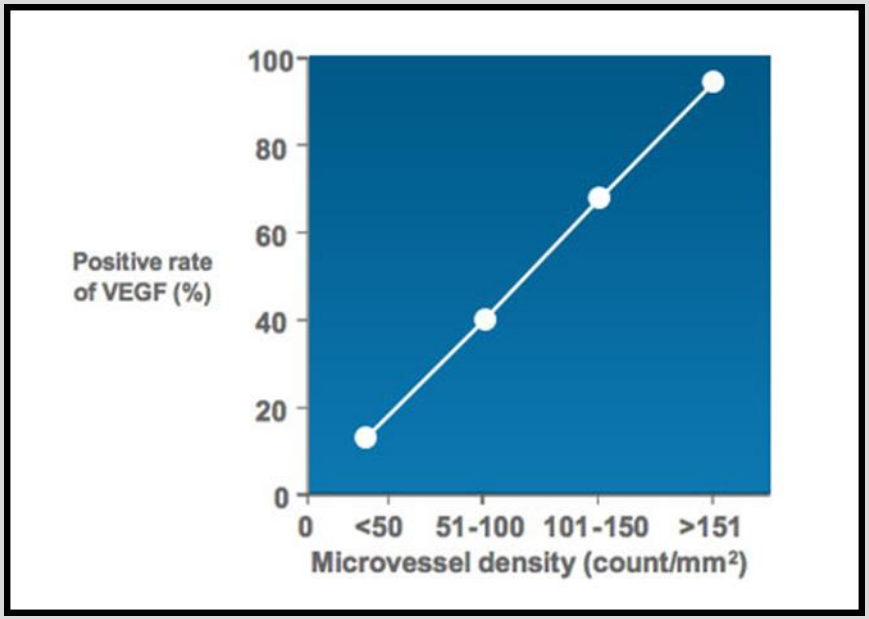


Gasparini G, Toi M, Gion M, et al. Prognostic significance of vascular endothelial growth factor protein in node-negative breast carcinoma. *J Natl Cancer Inst.* 1997;89(2):139-147. Adapted by permission of Oxford University Press.

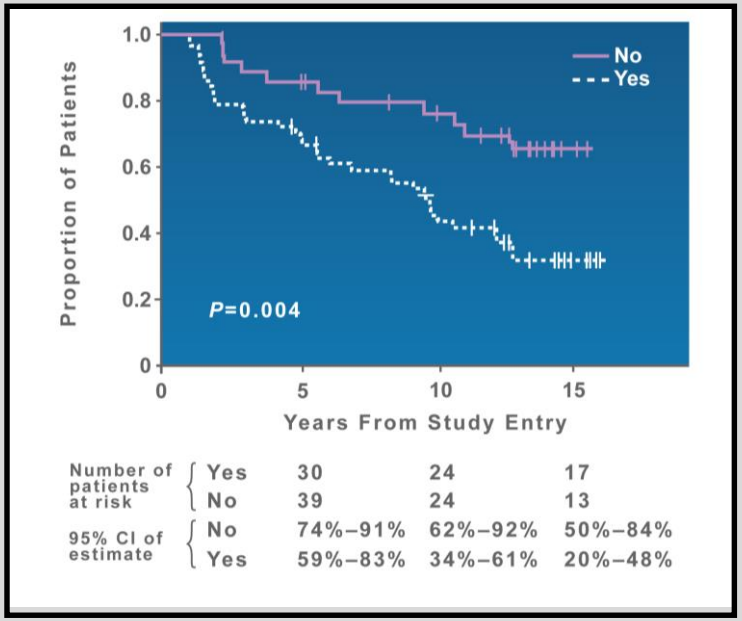
- VEGF expression negatively correlates with relapse-free and overall survival[1]
- Large prospective clinical studies are needed to better clarify the prognostic role of VEGF in breast cancer

Reference: 1. Gasparini G, Toi M, Gion M, et al. *J Natl Cancer Inst.* 1997;89:139-147.

The VEGF ligand and microvessel density are associated with poor prognosis in breast cancer



Adapted from Toi 1995. Reproduced with permission from *Breast Cancer Research and Treatment.*



Guidi AJ, Berry DA, Broadwater G, et al. Association of angiogenesis in lymph node metastases with outcome of breast cancer. *J Natl Cancer Inst.* 2000;92(6):486-492. Adapted by permission of Oxford University Press.

- VEGF expression correlates with microvessel density in breast cancer[1,2]
- Presence of microvascular “hot spots” is associated with poor disease-free and overall survival[3]

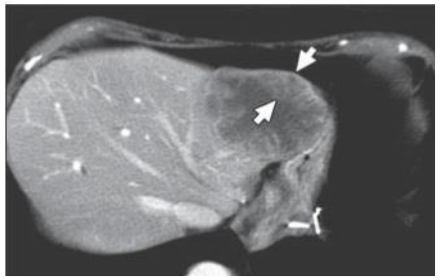
References: 1. Toi M, Inada K, Suzuki H, Tominaga T. *Breast Cancer Res Treat.* 1995;36:193-204. **2.** Guidi AJ, Schnitt SJ, Fischer L, et al. *Cancer.* 1997;80:1945-1953. **3.** Guidi AJ, Berry DA, Broadwater G, et al. *J Natl Cancer Inst.* 2000;92:486-492.

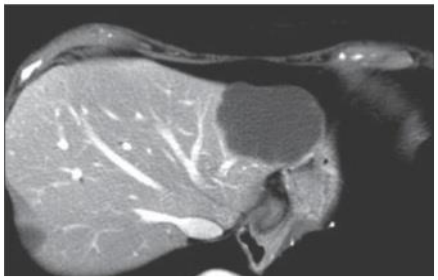
Morphological changes predict outcome

Pre-treat scan

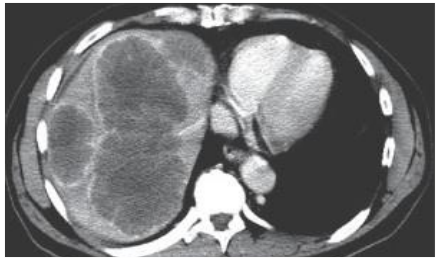
Post-treat scan

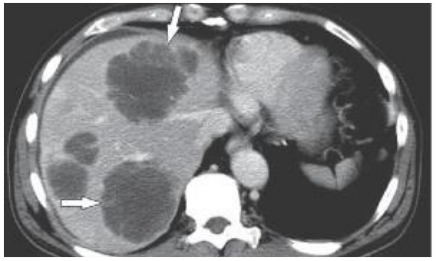
Optimal response



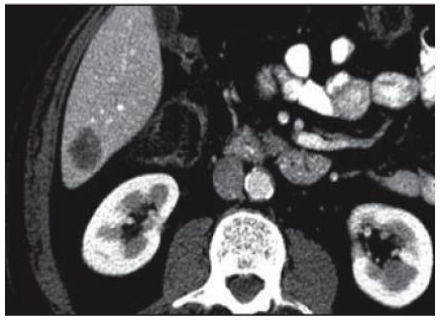


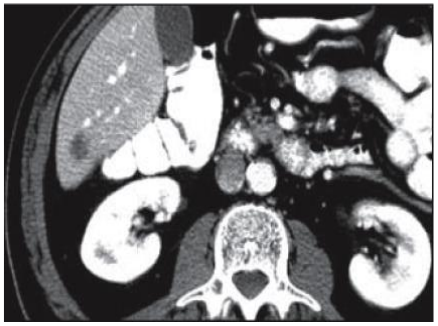
Partial response



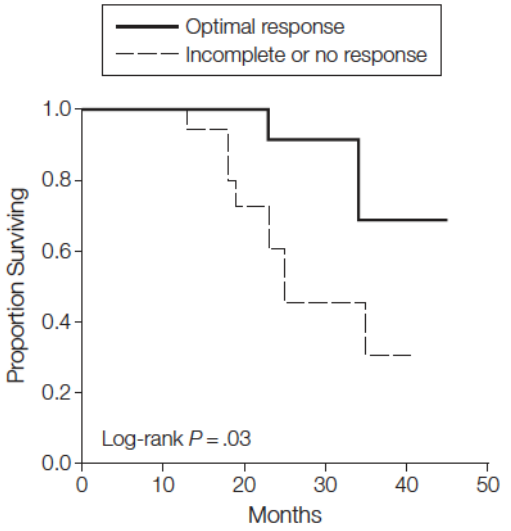


Absent response

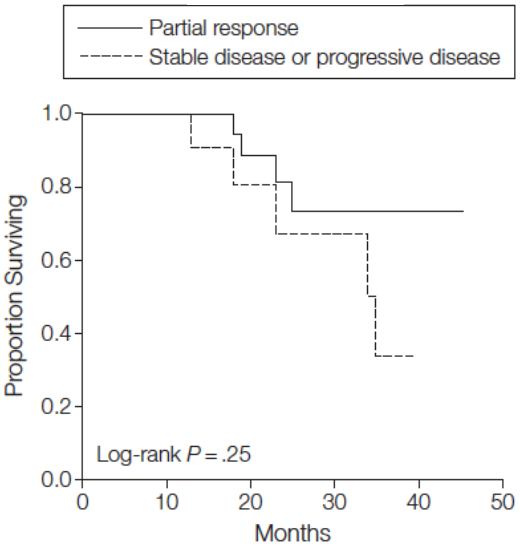




Morphology



RECIST



Boonsirikamchai et al AJR 2011
Chun et al JAMA 2009

Proposed mechanisms of resistance

- Upregulation of alternative pro-angiogenic signals

  e.g. FGF2 (basic FGF), PLGF, IL8, HGF, Bv8, Angiopoetins, Delta-Notch

- Compensatory host responses

  e.g. infiltration by myeloid cells, fibroblasts or endothelial progenitor cells (EPCs)

- Novel angiogenesis mechanisms

  e.g. co-option of existing blood vessels, e.g. vessel intususception

- Endothelial resistance

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- Adaptation of tumour cells

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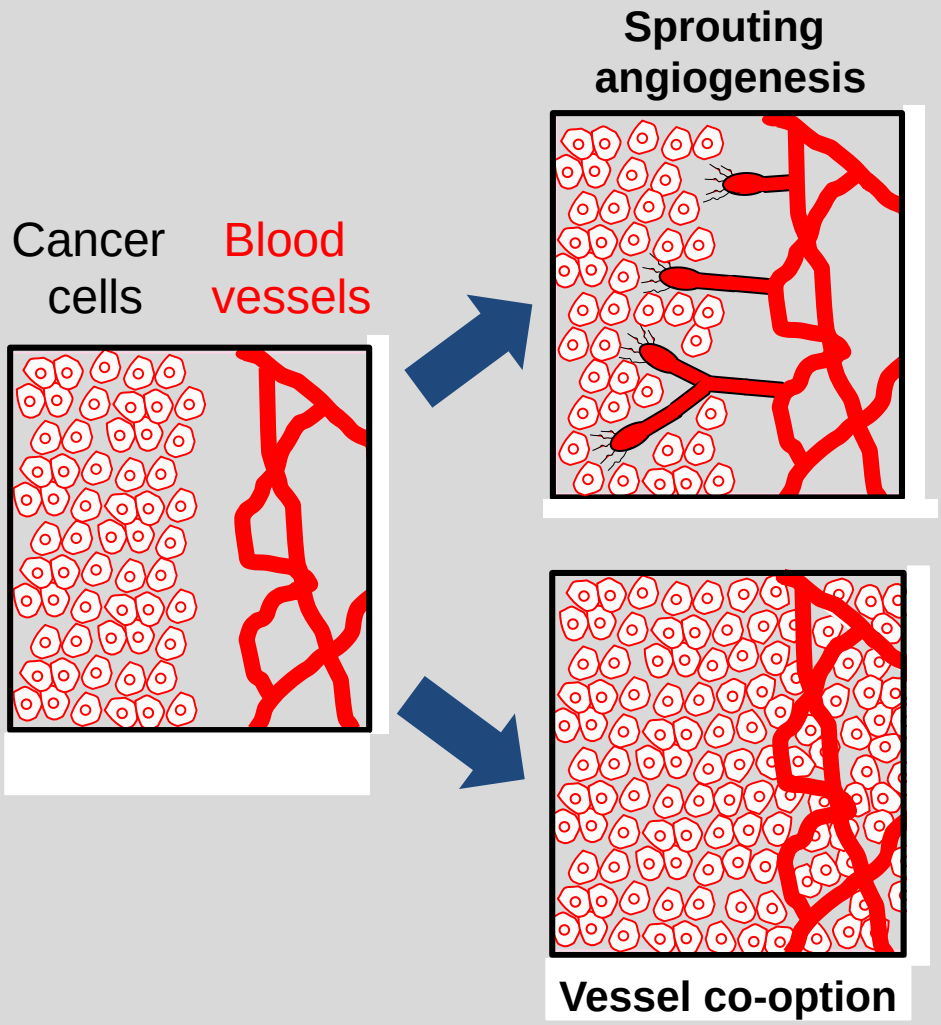
- Pharmacology

Targeting the tumour vasculature



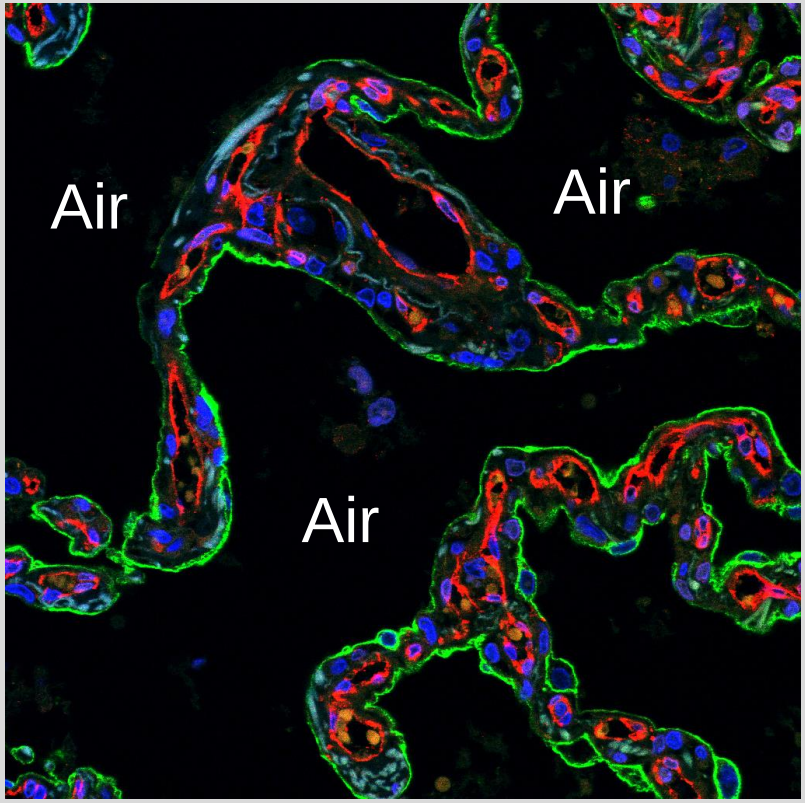
Cancer cells incorporate pre-existing blood vessels from surrounding tissue

Prevalent in primary tumours of highly vascular organs e.g. lungs, liver, brain

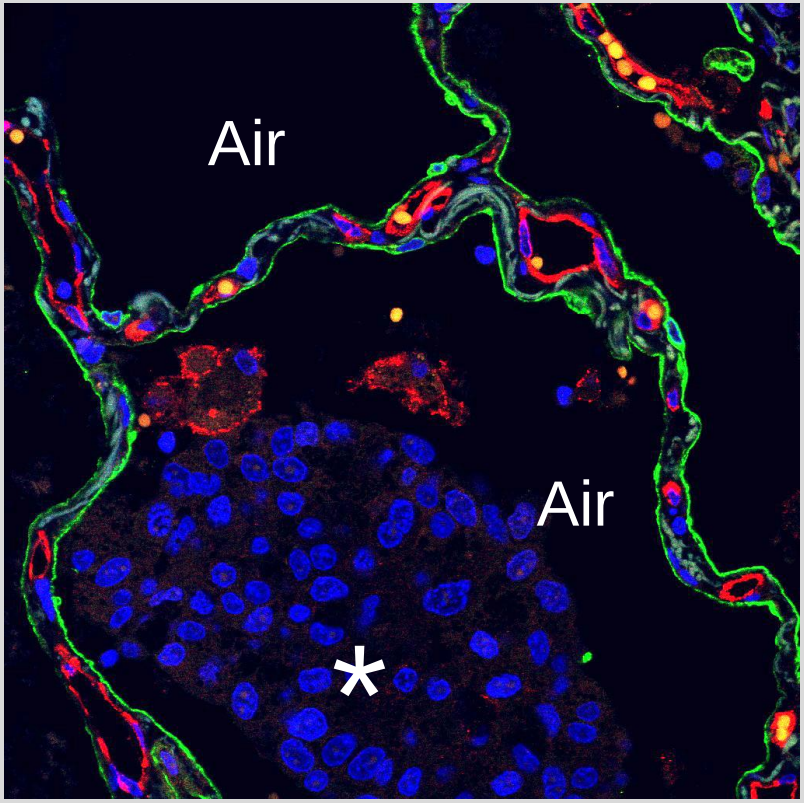
Prevalent in metastases to highly vascular organs e.g. lungs, liver, brain

The vessel co-option process in human breast cancer lung metastases

Normal human lung



Invasion of alveolar air spaces by breast cancer cells



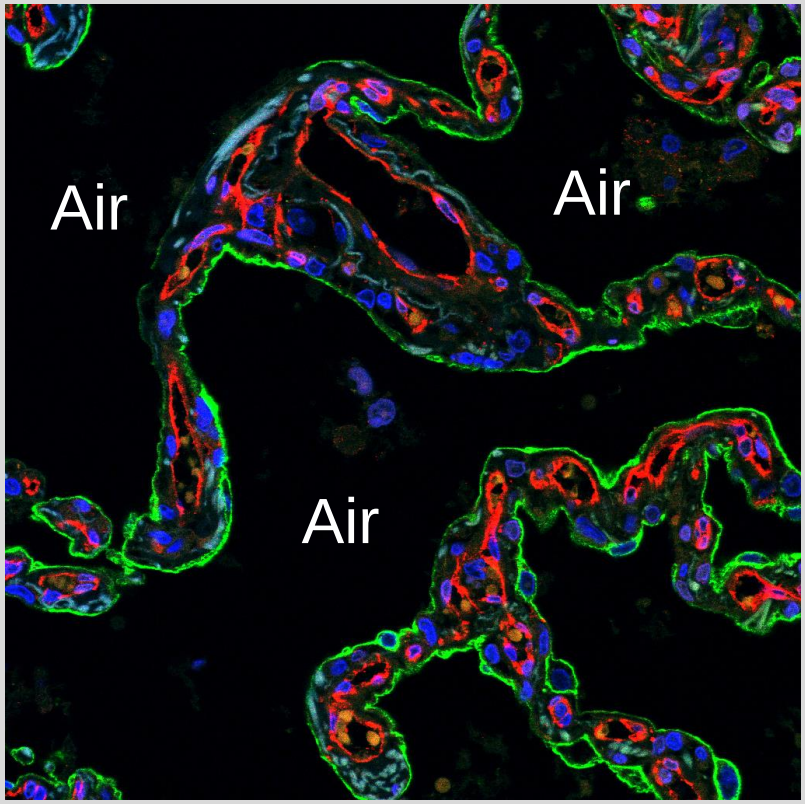
Blood vessels (CD31)

Alveolar epithelium (CK7)

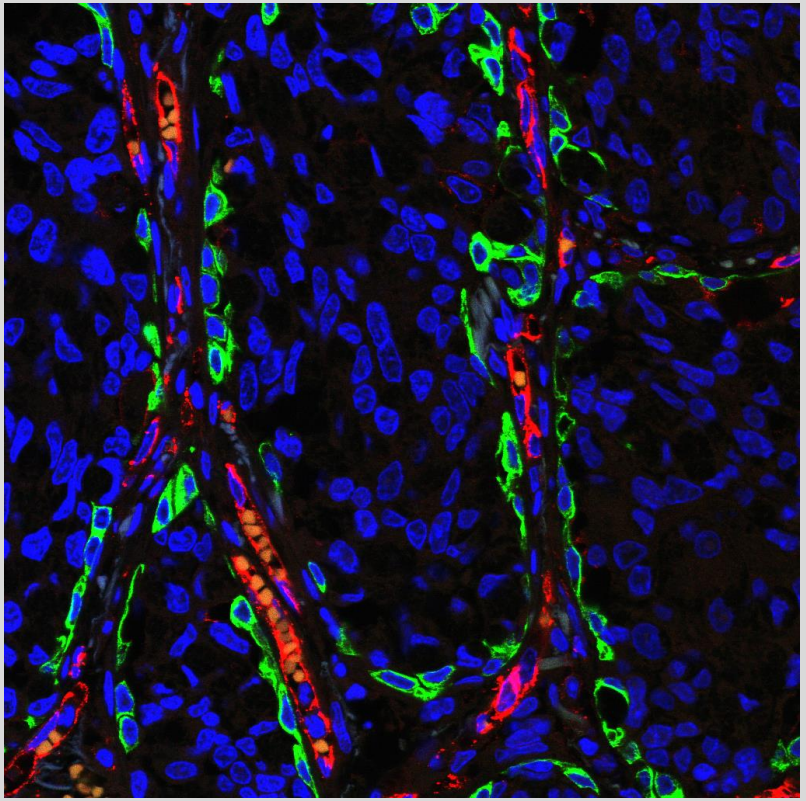
Bridgeman *et al,* J Pathol 2016

The vessel co-option process in human breast cancer lung metastases

Normal human lung



Complete filling of air spaces & alveolar capillaries co-opted



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The vessel co-option process in human breast cancer lung metastases

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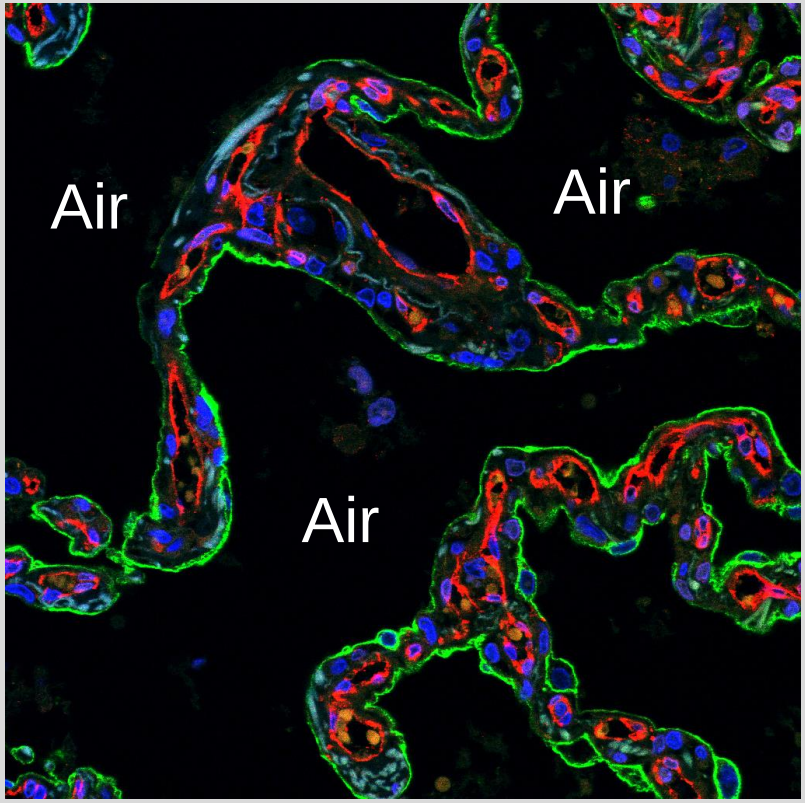
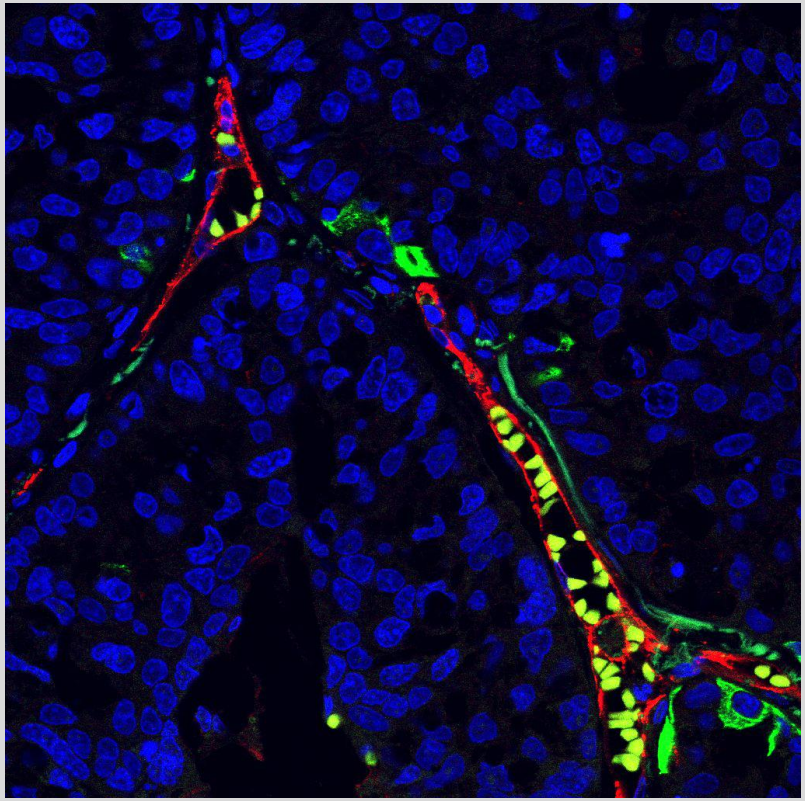


Loss of epithelium from co-opted vessels



Blood vessels (CD31)

Alveolar epithelium (CK7)

Bridgeman *et al,* J Pathol 2016

Which growth patterns predominate in human metastaes?

Alveolar (vessel co-option)

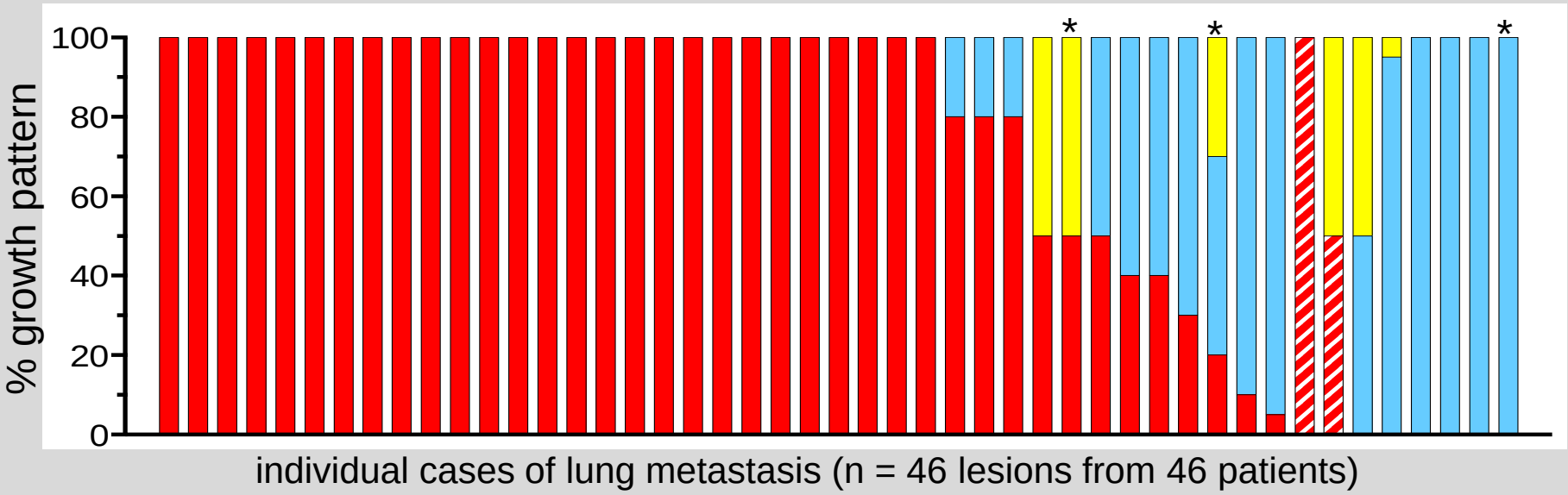
Interstitial (vessel co-option)

Perivascular cuffing (vessel co-option)

Pushing (angiogenesis)

Bridgeman *et al,* J Pathol 2016

Vessel co-option occurs in >90% of human breast cancer lung metastases examined



Alveolar (vessel co-option)

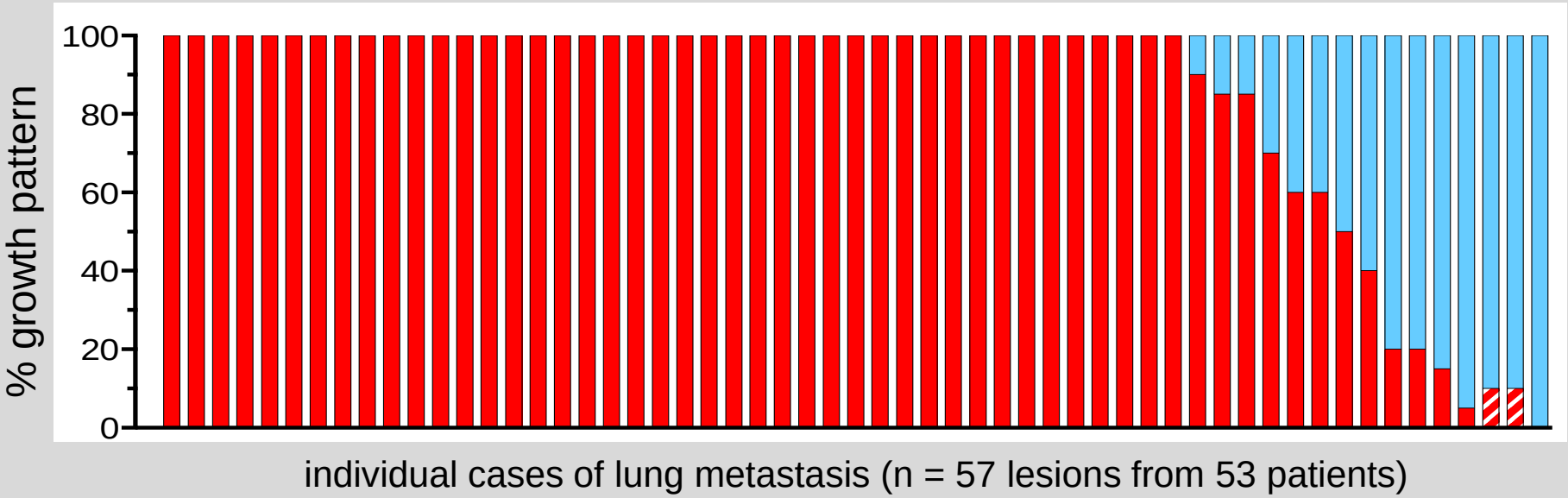
Interstitial (vessel co-option)

Perivascular cuffing (vessel co-option)

Pushing (angiogenesis)

Bridgeman *et al,* J Pathol 2016

Vessel co-option occurs in >90% of human colorectal cancer lung metastases examined



Alveolar (vessel co-option)

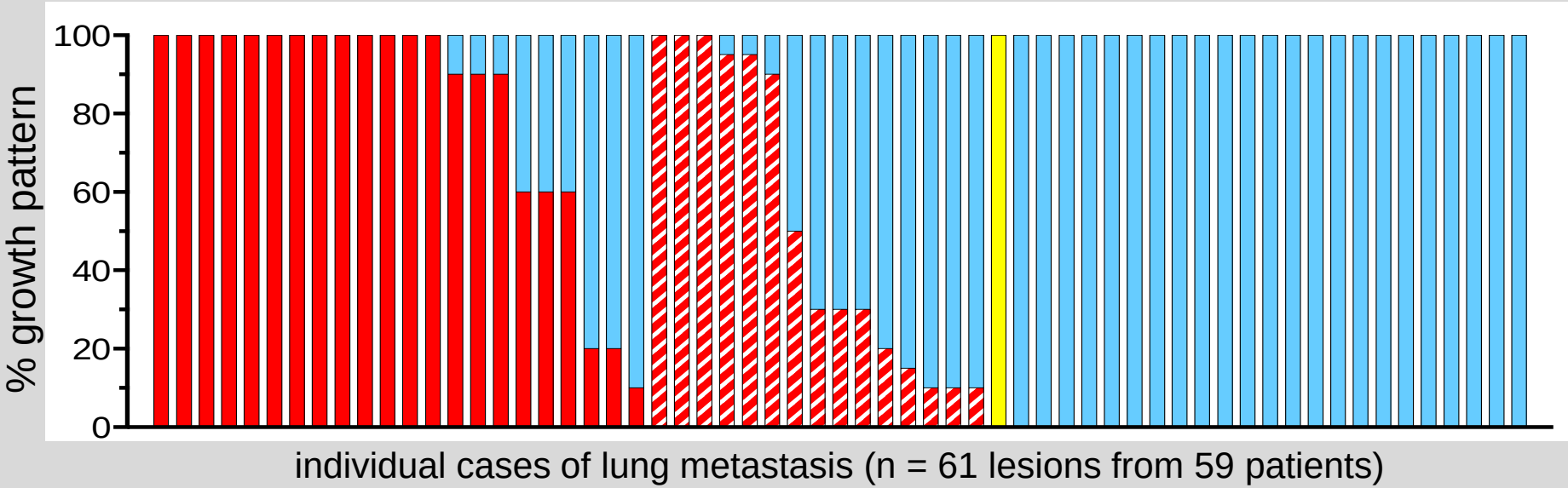
Interstitial (vessel co-option)

Perivascular cuffing (vessel co-option)

Pushing (angiogenesis)

Bridgeman *et al,* J Pathol 2016

Vessel co-option occurs in ~60% of human renal cancer lung metastases examined



Alveolar (vessel co-option)

Interstitial (vessel co-option)

Perivascular cuffing (vessel co-option)

Pushing (angiogenesis)

Bridgeman *et al,* J Pathol 2016

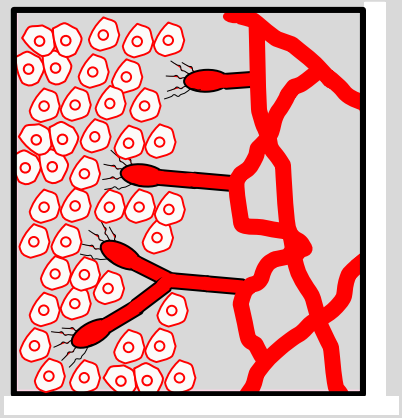
Anti-angiogenic drugs were designed to target angiogenesis

…but they were not designed to target vessel co-option

Vessel co-option could be a mechanism of both innate resistance and acquired resistance

Pushing growth pattern

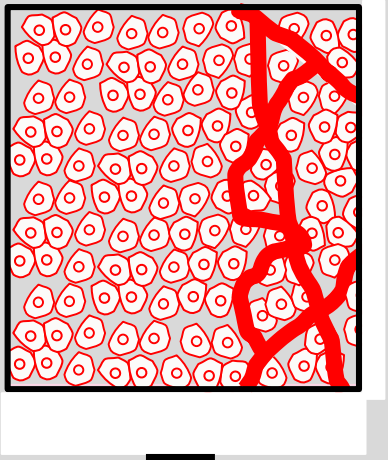
Sprouting angiogenesis



Responsive to anti-angiogenic drug

Alveolar growth pattern

Vessel co-option



Resistant to anti-angiogenic drug

nature medicine

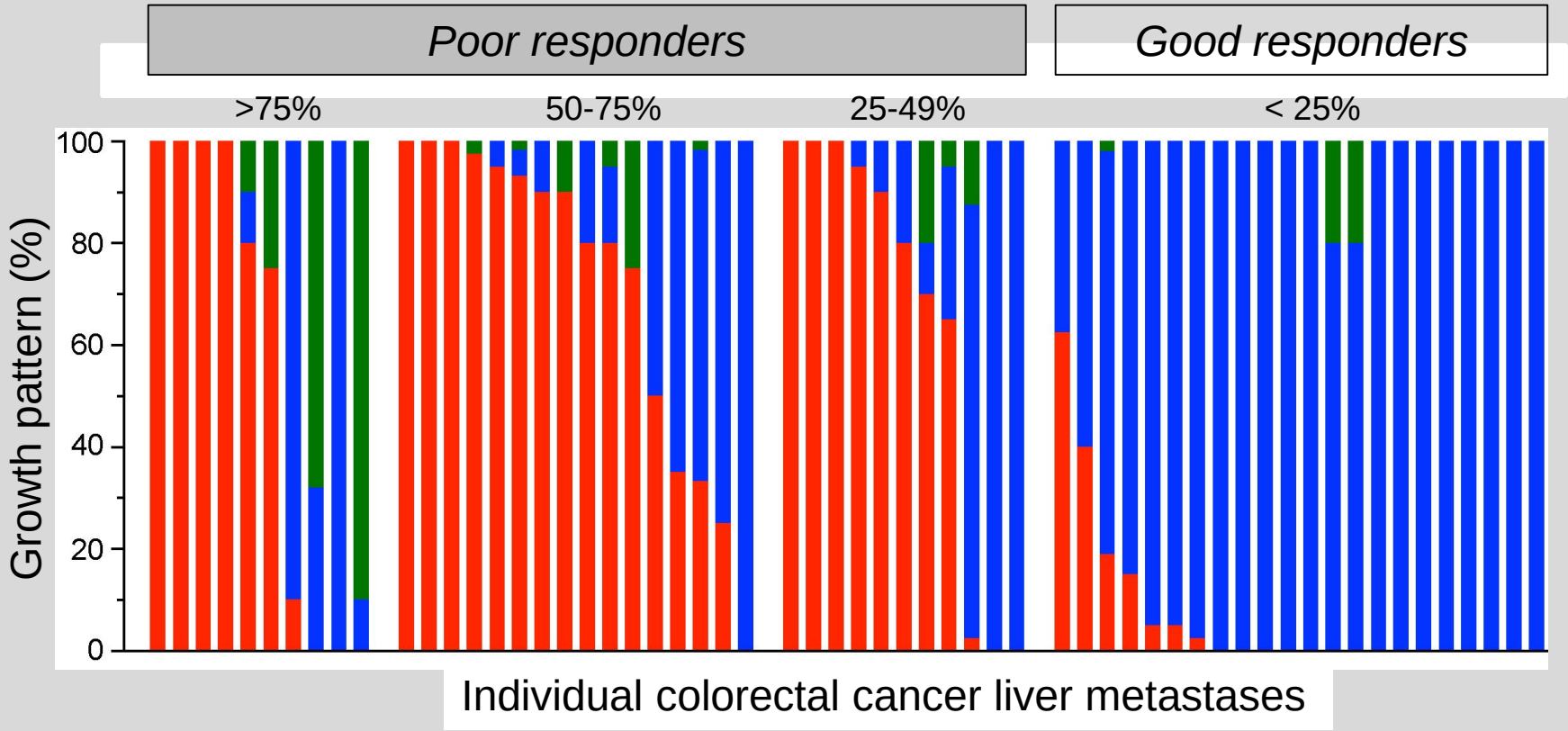
Vessel co-option mediates resistance to anti-angiogenic therapy in liver metastases

Sophia Frentzas[1,2,11], Eve Simoneau[3,11], Victoria L Bridgeman[1,11], Peter B Vermeulen[1,4,11], Shane Foo[1,11], Eleftherios Kostaras[1], Mark R Nathan[1], Andrew Wotherspoon[2], Zu-hua Gao[3], Yu Shi[3], Gert Van den Eynden[4], Frances Daley[5], Clare Peckitt[2], Xianming Tan[6], Ayat Salman[3], Anthoula Lazaris[3], Patrycja Gazinska[7], Tracy J Berg[1], Zak Eltahir[2], Laila Ritsma[8], Jacco van Rheenen[8], Alla Khashper[3], Gina Brown[2], Hanna Nyström[4,9], Malin Sund[9], Steven Van Laere[4], Evelyne Loyer[10], Luc Dirix[4], David Cunningham[2,12], Peter Metrakos[3,12] & Andrew R Reynolds[1,12]

Growth patterns correlate with pathological response

Replacement (vessel co-option)
Desmoplastic (angiogenesis)
Pushing (angiogenesis)

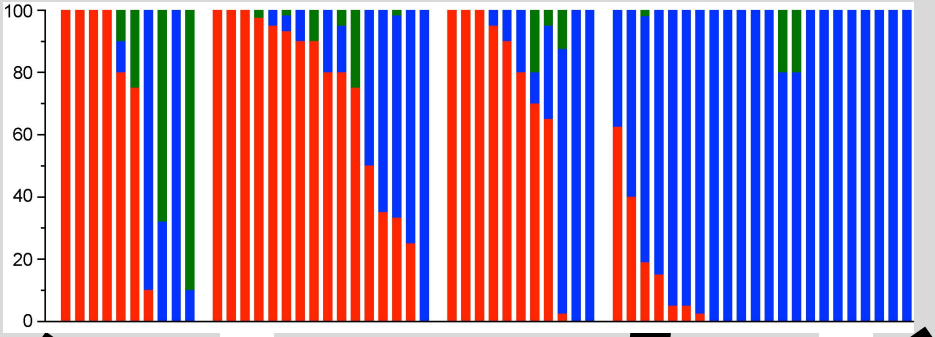
$P < 0.0001$
(chi-squared test)

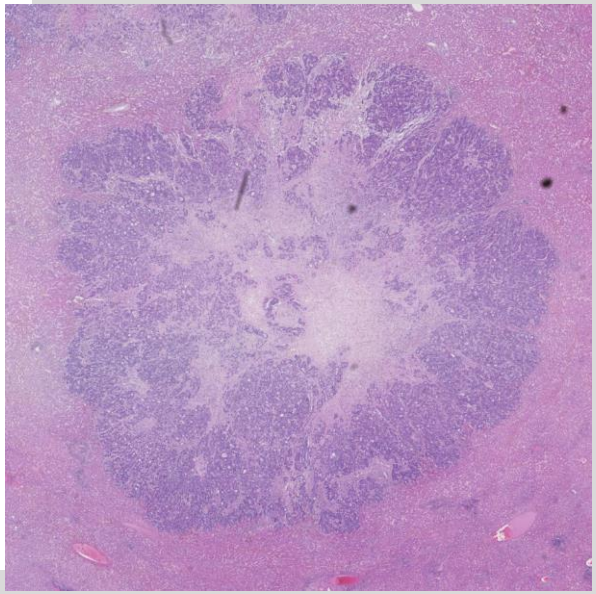


59 lesions from 33 patients receiving 4-12 cycles of bev-chemo prior to liver resection

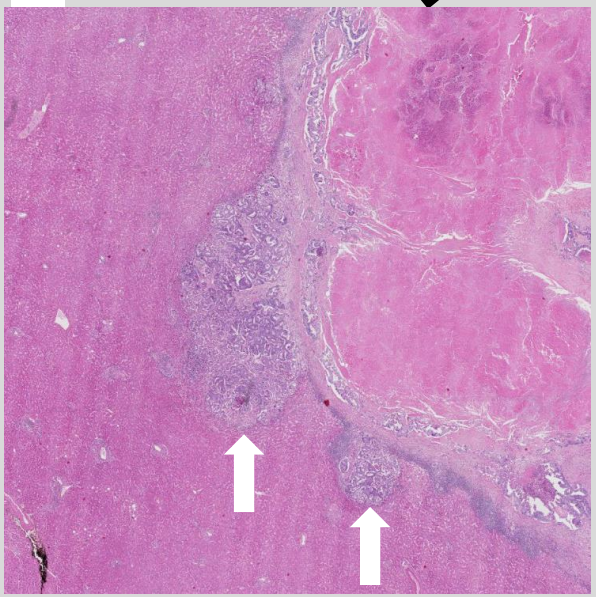
Frentzas *et al,* Nature Medicine, 2016

Growth patterns correlate with pathological response

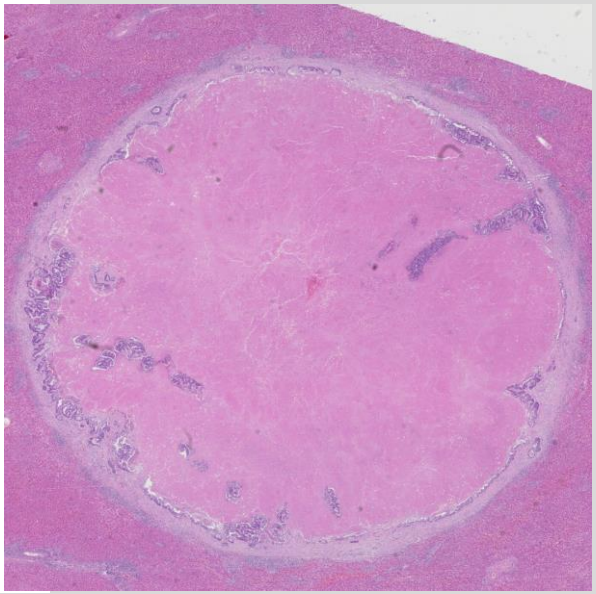




>75% viable tumour
100% replacement



<25% viable tumour
80% desmoplastic
20% replacement

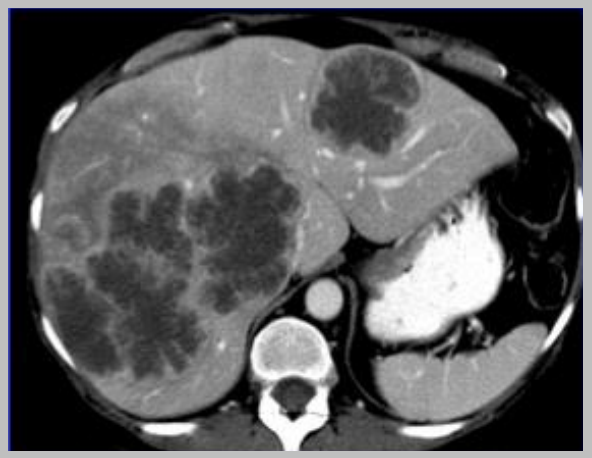


<25% viable tumour
100% desmoplastic

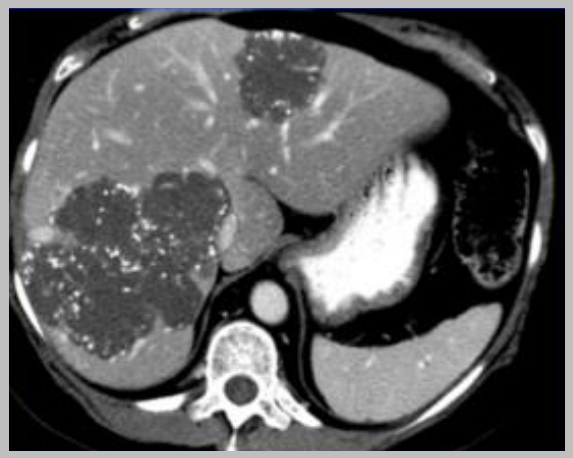
Frentzas *et al,* Nature Medicine, 2016

Progression of disease in CRC liver metastasis patients treated with bevacizumab

‘New lesions’ can appear after treatment initiation

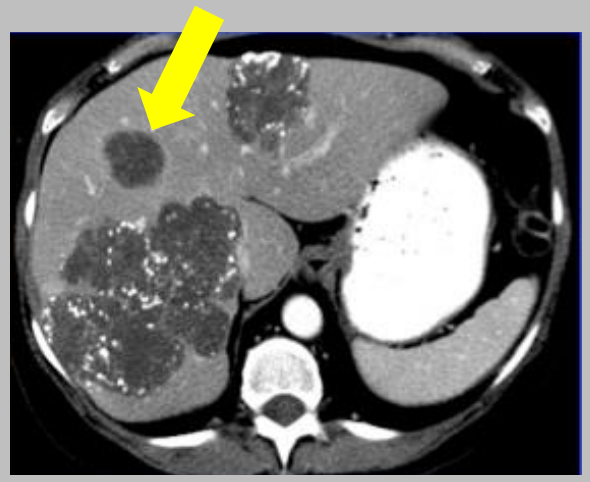


pre-treatment



chemo+bev

26 months

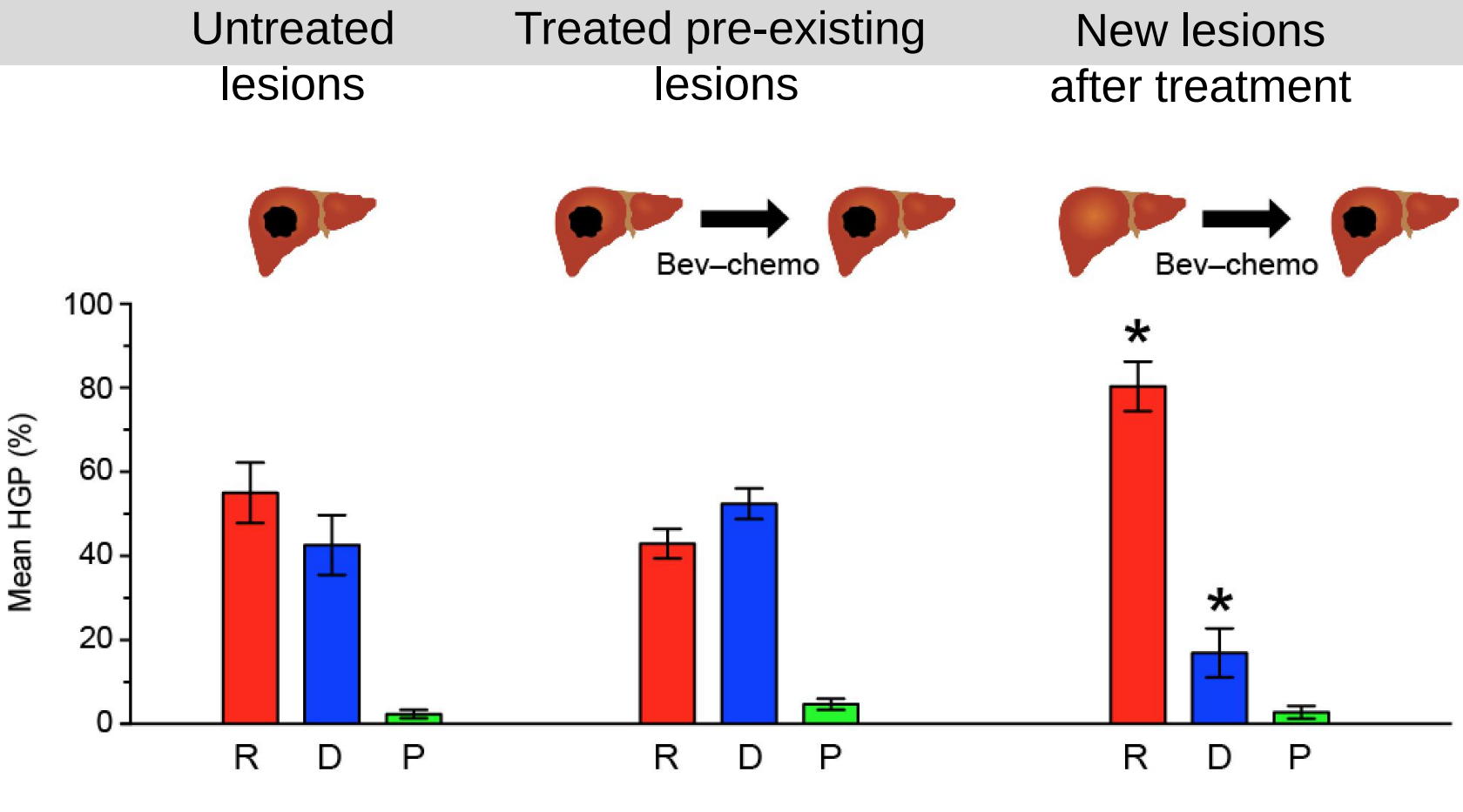


chemo+bev

28 months

Data from Evelyne Loyer (MD Anderson)

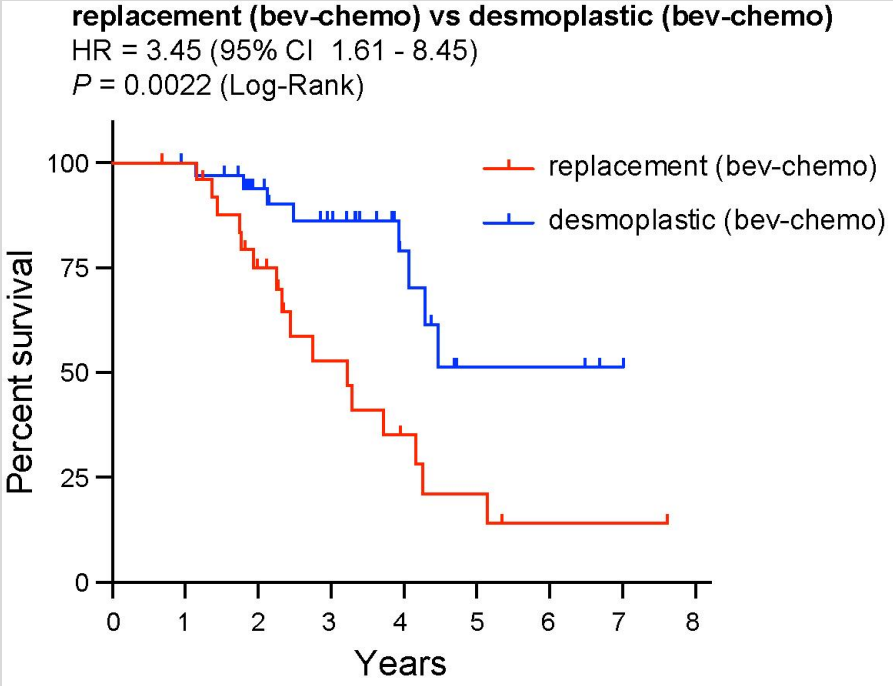
Progression on treatment is associated with increased prevalence of the replacement pattern (vessel co-option)



Frentzas *et al,* Nature Medicine, 2016

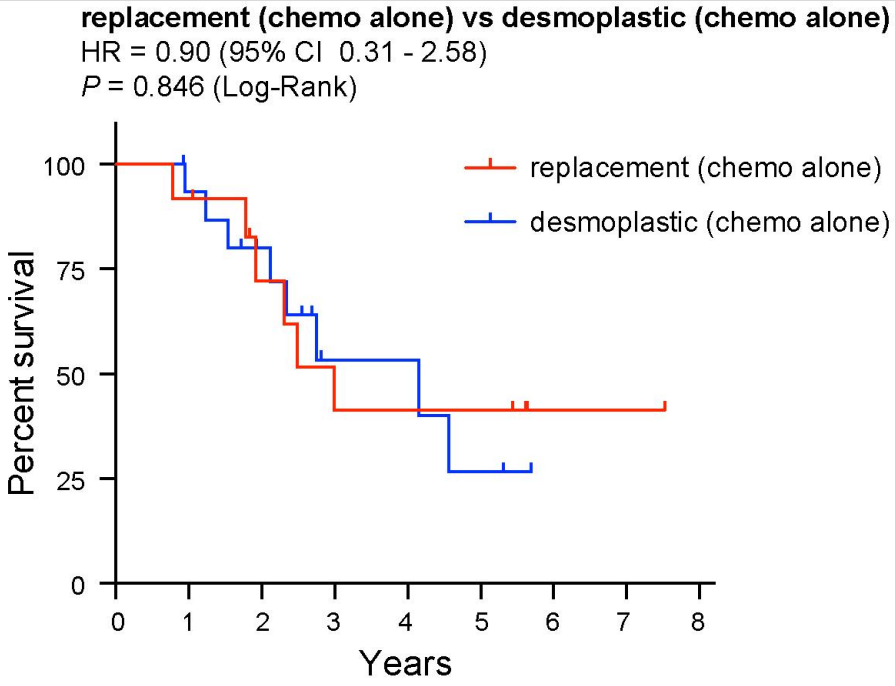
Patients with vessel co-option achieve less clinical benefit from bevacizumab

Bevacizumab and chemotherapy



n = 61 patients (bevacizumab-chemotherapy group)

Chemotherapy only

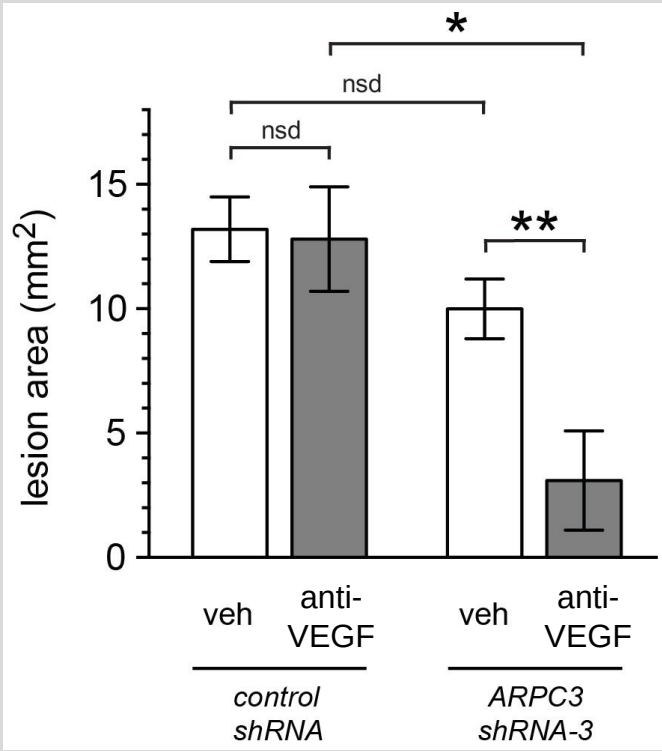


n = 29 patients (chemotherapy-only group)

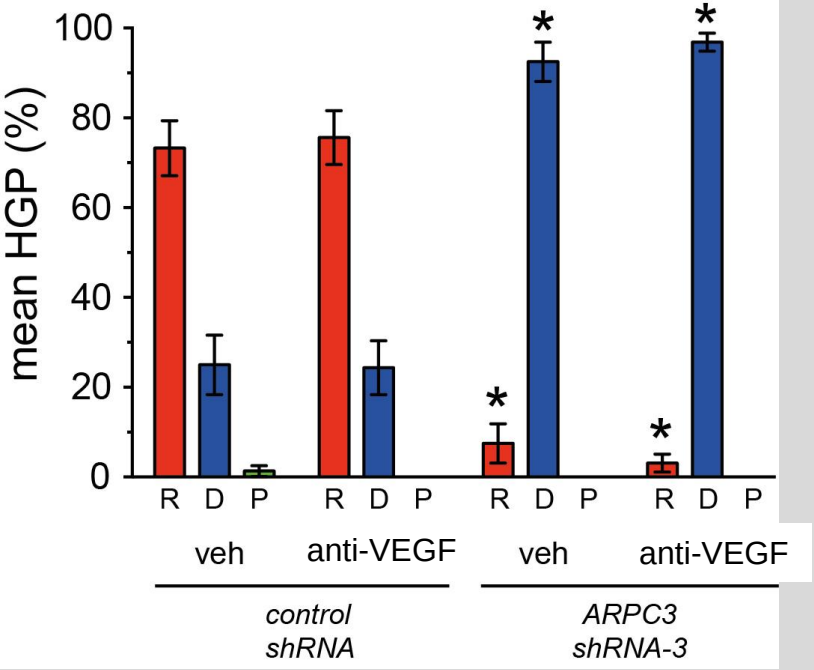
Frentzas *et al,* Nature Medicine, 2016

Suppressing vessel co-option improves the response to anti-angiogenic therapy

Tumour burden



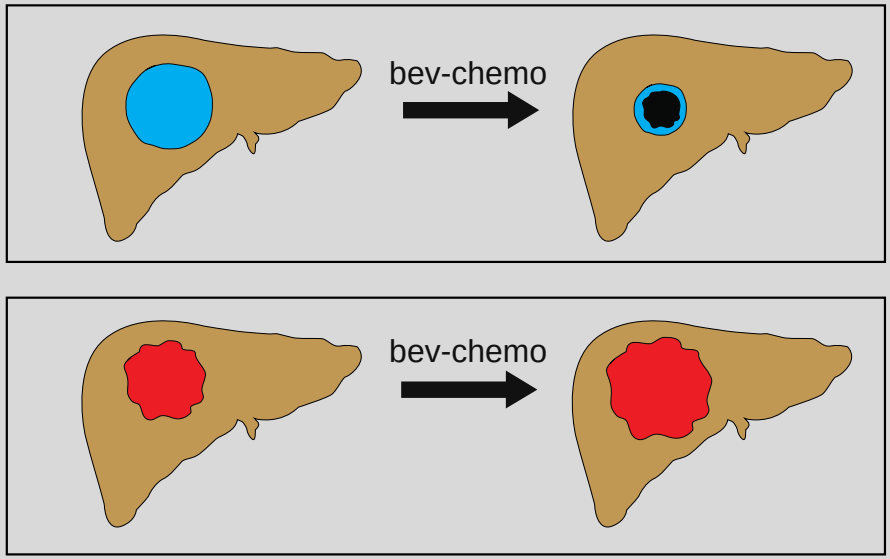
Growth pattern



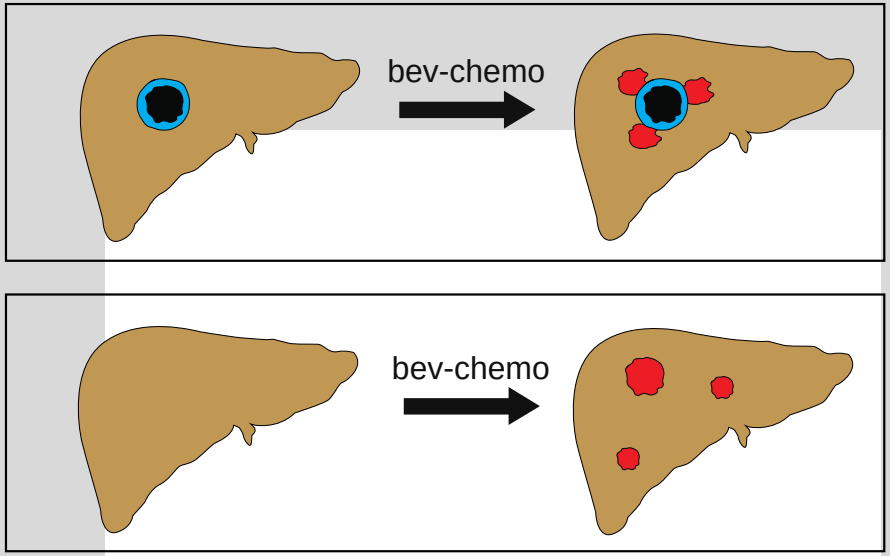
Frentzas *et al,* Nature Medicine, 2016

Role of the growth patterns in response & resistance to treatment

Innate resistance



Acquired resistance



Viable replacement growth pattern

Viable desmoplastic growth pattern

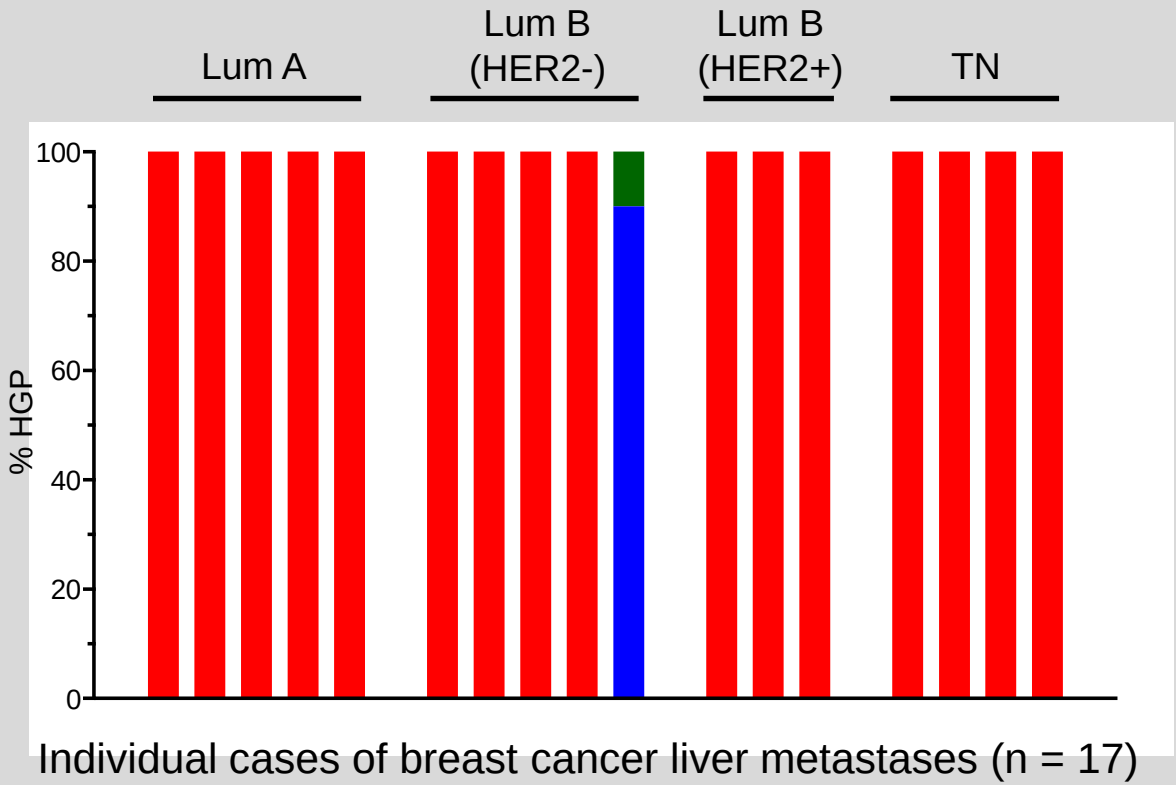
Infarct-like necrosis

Replacement growth pattern (vessel co-option) predominates in human breast cancer liver metastases

Replacement (vessel co-option)

Desmoplastic (angiogenesis)

Pushing (angiogenesis)

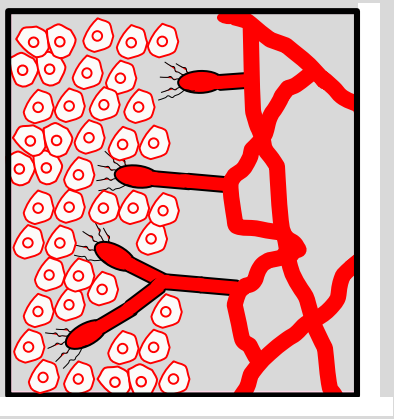


Frentzas *et al,* Nature Medicine, 2016

A reversible switch from angiogenesis to vessel co-option?

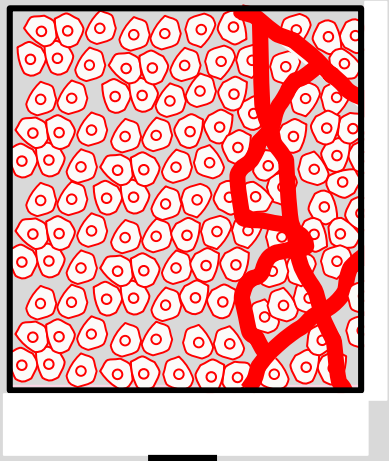
Increased cancer cell motility?

Sprouting angiogenesis



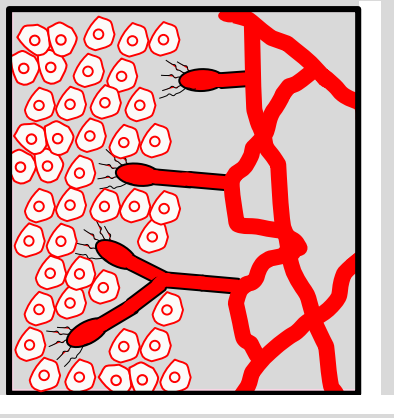
Treatment

Vessel co-option



Discontinue treatment

Sprouting angiogenesis



Responsive to anti-angiogenic drug

Resistant to anti-angiogenic drug

Regain responsiveness to anti-angiogenic drug?

Summary

Blood vessels are required for tumour growth

Anti-angiogenic therapy targets these vessels

VEGF-targeted agents are effective in patients

Predictive markers are elusive

Mechanisms of resistance are poorly understood

Understanding resistance (important for biomarkers and improved strategies for therapy

Conclusions

Cancers can utilise angiogenesis or vessel co-option

There is spatial and temporal plasticity in these mechanisms

Vessel co-option is associated with resistance to conventional anti-angiogenic drugs

Stratifying tumours as ‘angiogenic’ or ‘vessel co-opting’ might be used as a predictive biomarker for anti-angiogenic drugs

New therapies which can target both angiogenesis and vessel co-option are warranted