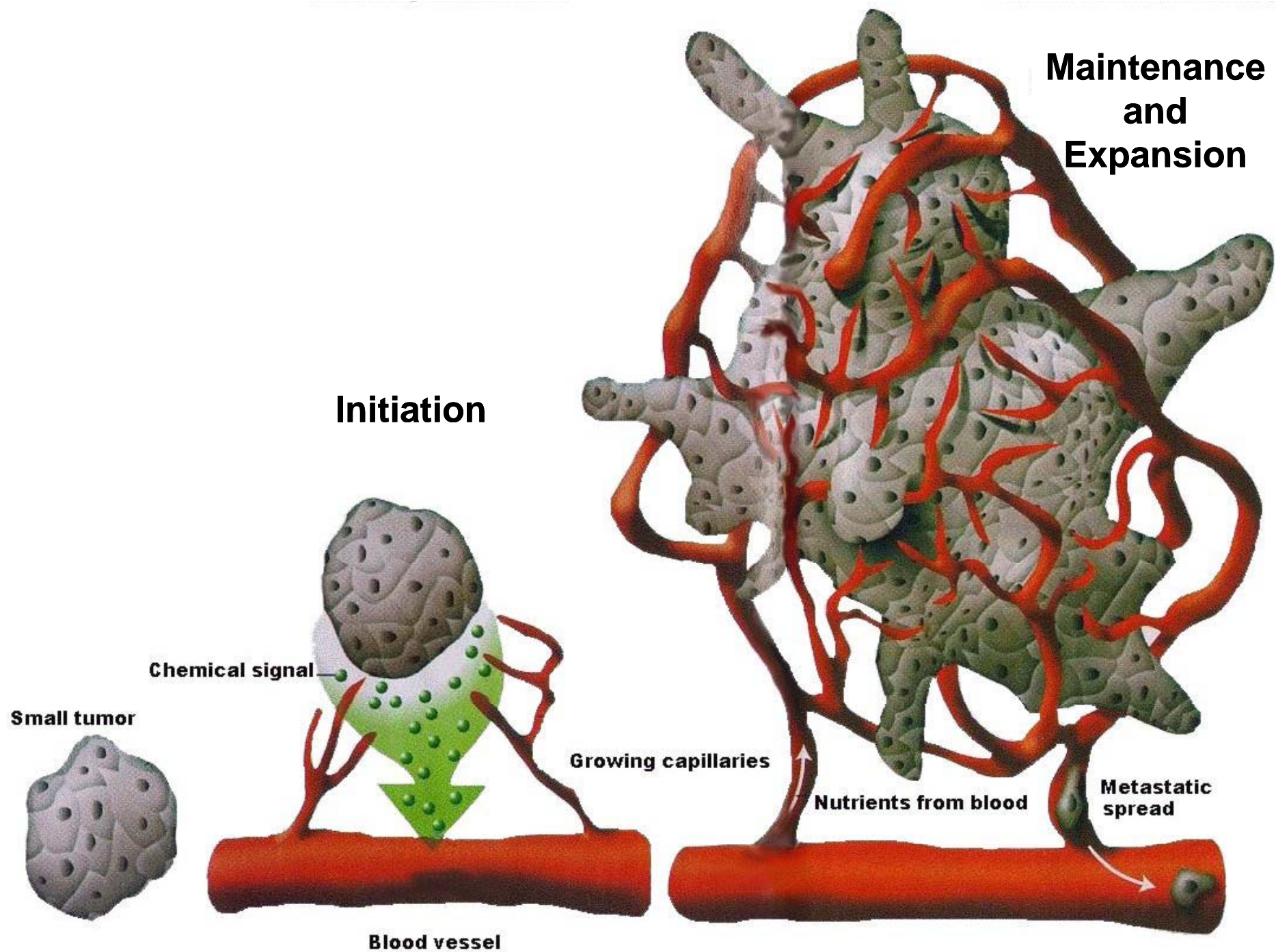


Vascular Disruption and Antiangiogenesis

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University of Florida

Why Do Cancer Therapies Fail?

- Both *local recurrences* and *distant metastases* are significantly affected by tumor progression and tumor pathophysiology.
- These factors are critically impacted by the initiation and maintenance/expansion of a *tumor blood vessel network*.

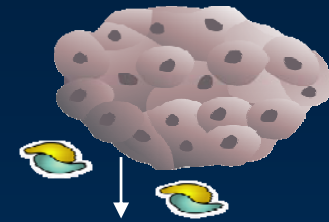


Vascular Disruption and Antiangiogenesis

Hypoxia and acidity are inducers of angiogenic signaling

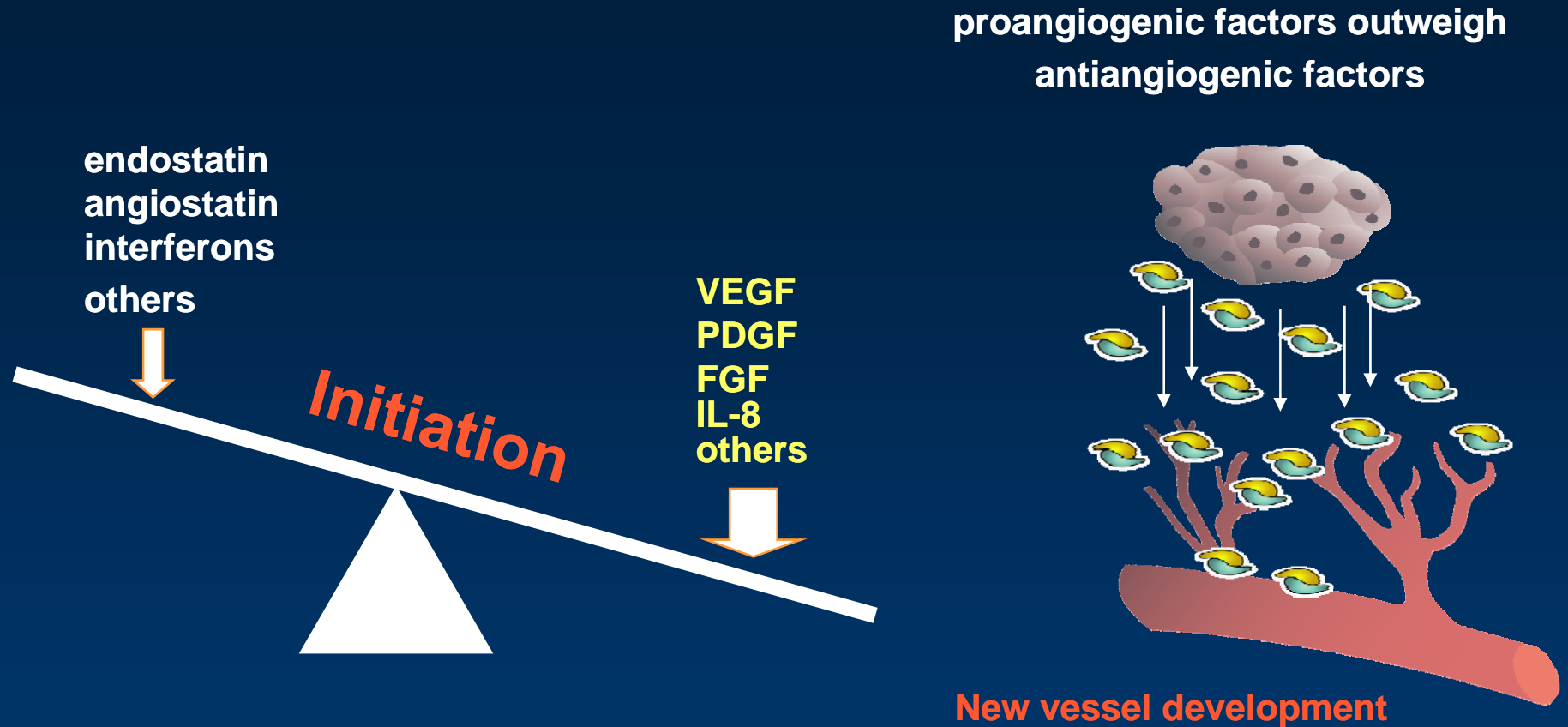
endostatin
angiostatin
interferons
others

VEGF
PDGF
FGF
IL-8
others



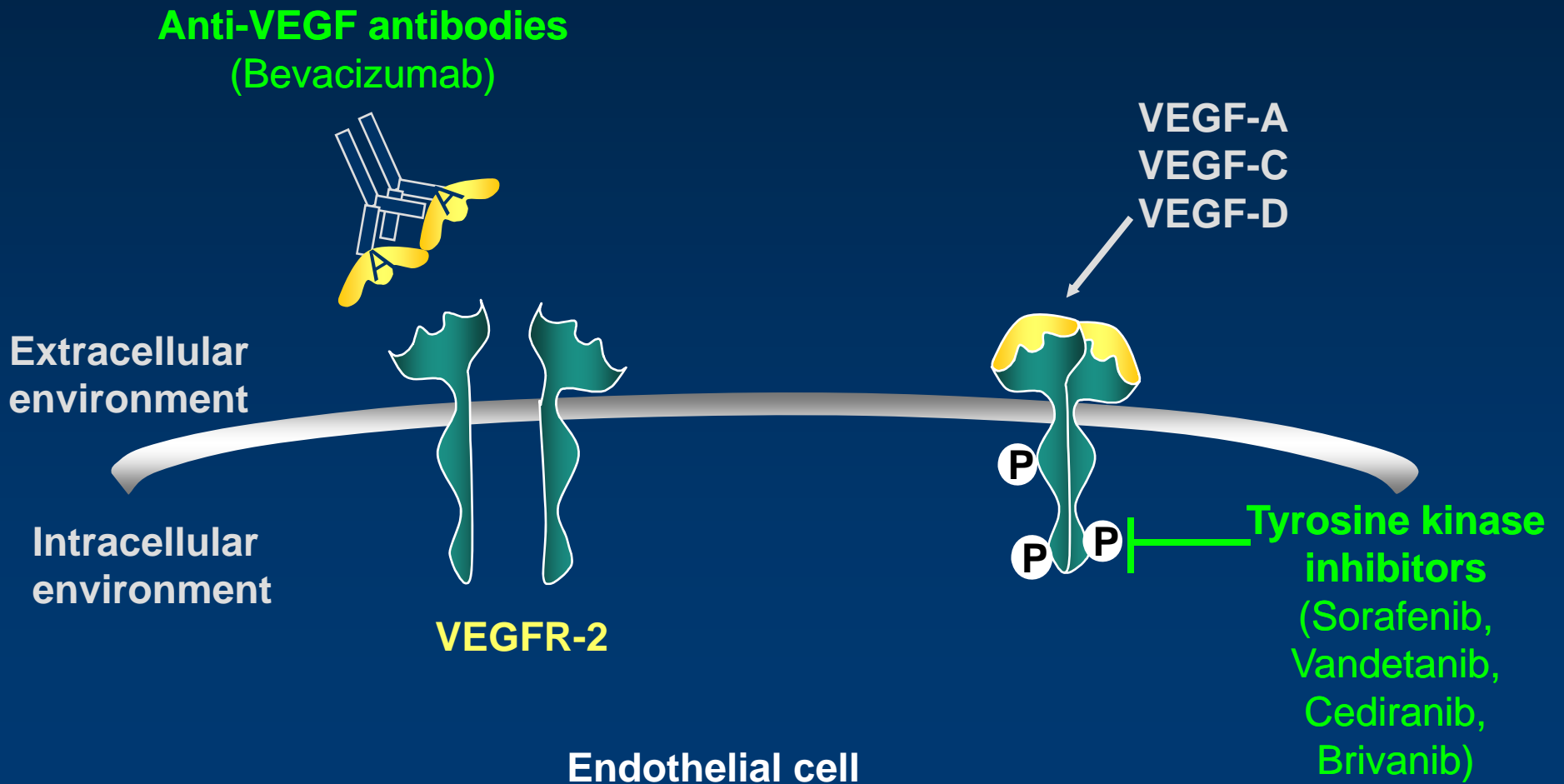
Balance

Vascular Disruption and Antiangiogenesis



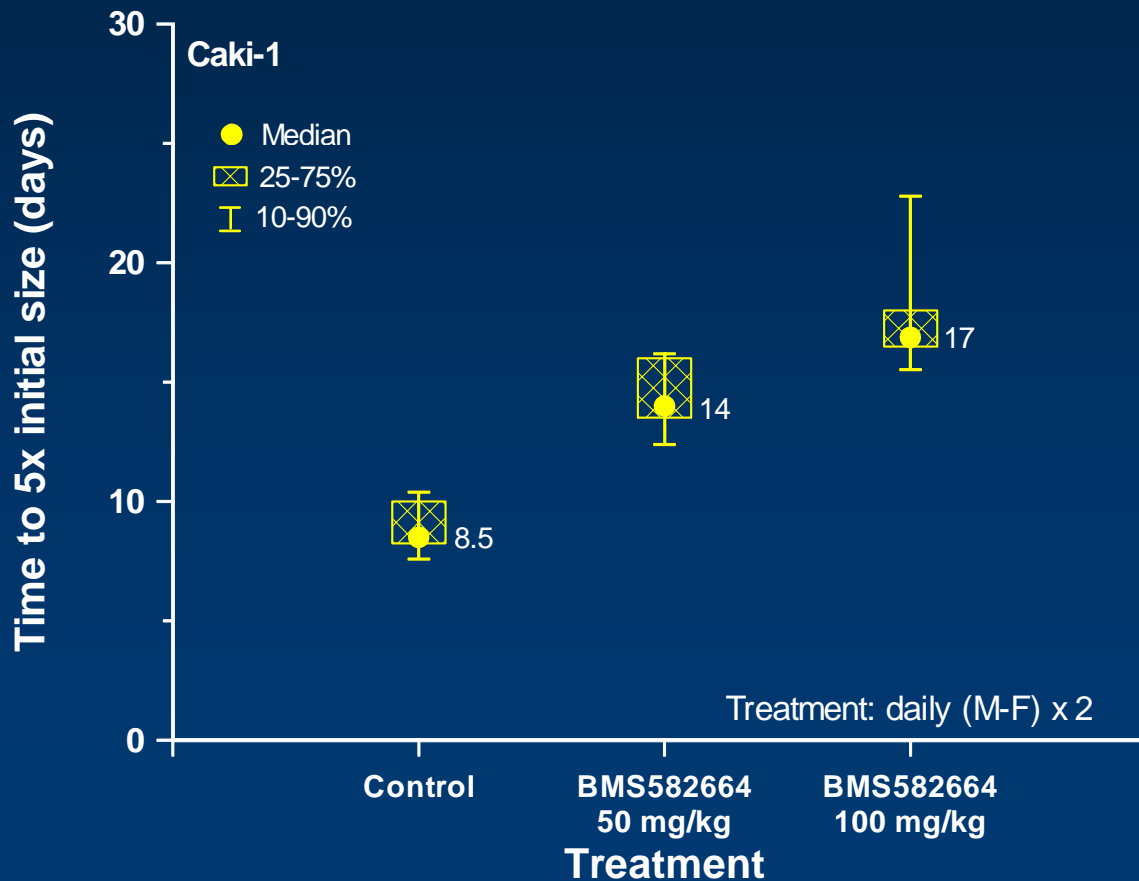
- VEGF is considered the most powerful proangiogenic factor in tumors
 - Associated with tumor growth rate, vessel density, metastases

Inhibition of VEGF signaling



Vascular Disruption and Antiangiogenesis

- Inhibitors of VEGF-associated signaling demonstrate antitumor efficacy in a wide variety of rodent tumor models and human tumor xenografts including renal, colorectal, KS, and sarcoma.



Vascular Disruption and Antiangiogenesis

- But – anti-angiogenic therapy efficacy in solid tumors has been modest – and – such therapies are unlikely to eliminate the entire tumor cell population on their own.

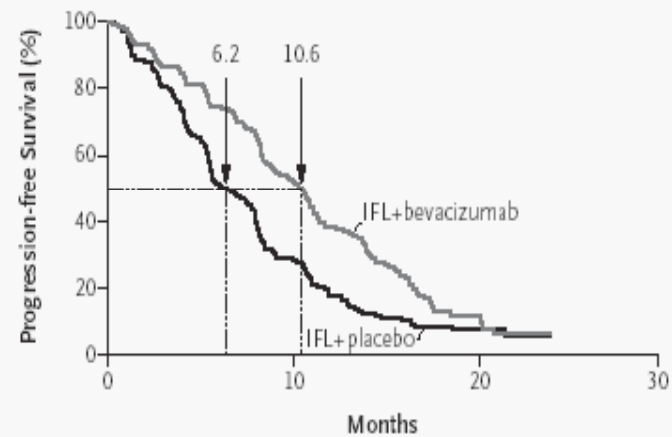
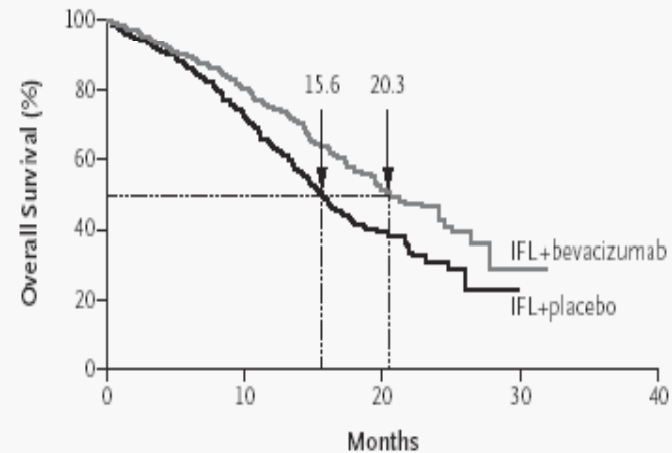
The **NEW ENGLAND**
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Bevacizumab plus Irinotecan, Fluorouracil, and Leucovorin
for Metastatic Colorectal Cancer

Hurvitz et al, 2004

- 811 untreated metastatic colorectal cancer patients
- randomized to IFL +/- bevacizumab
- Primary endpoint = overall survival
- Secondary endpoint = progression free survival, response rate



No. at Risk

IFL+bevacizumab	402	269	143	36	6	0
IFL+placebo	411	225	73	17	8	0

Vascular Disruption and Antiangiogenesis

Target the
angiogenesis
process

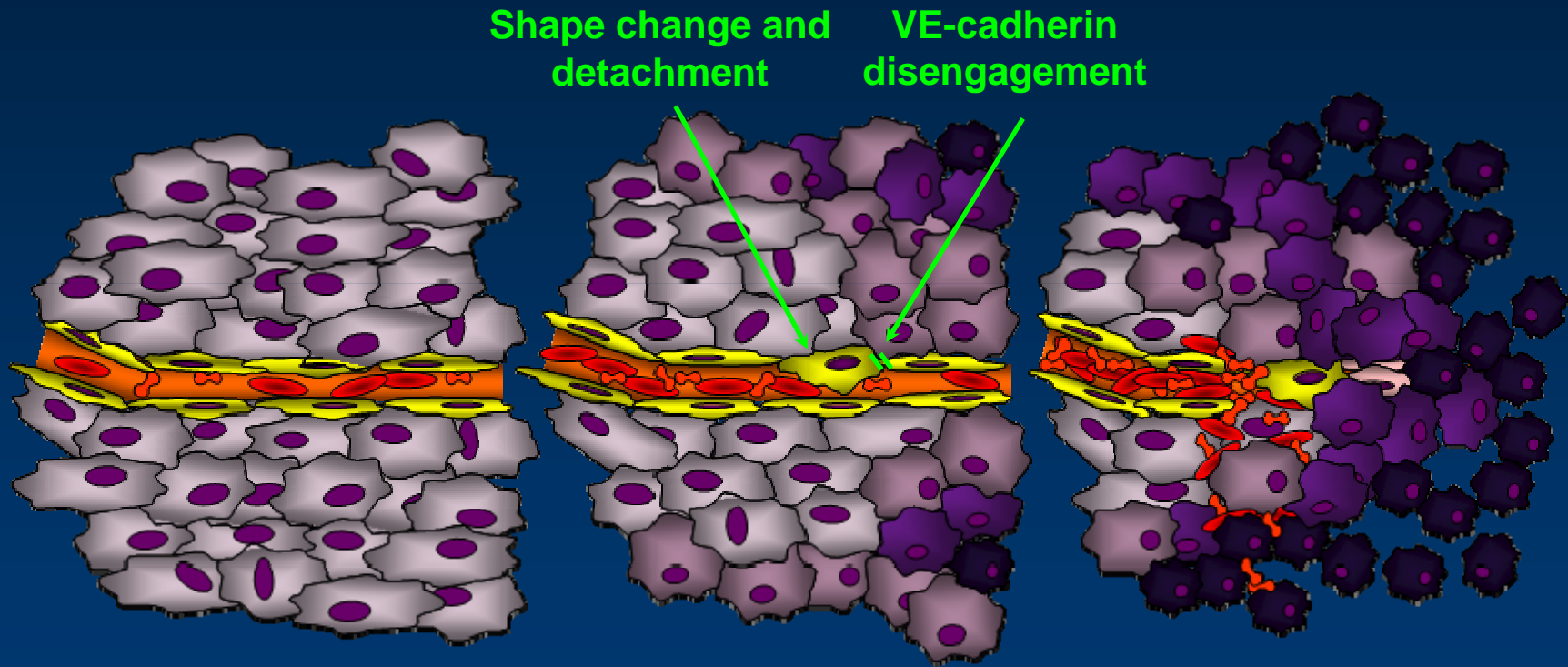
Target the
existing vessel
network



- Biologic based
- Small molecule drugs
 - short-lived tubulin depolymerizing agents

Vascular Disrupting Agents

elicit a tumor cell death cascade due to prolonged ischemia



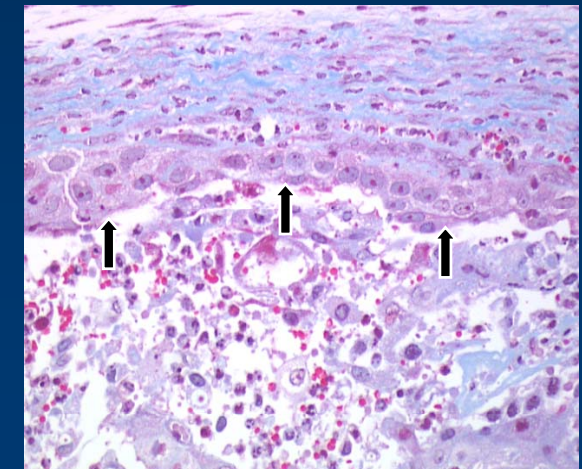
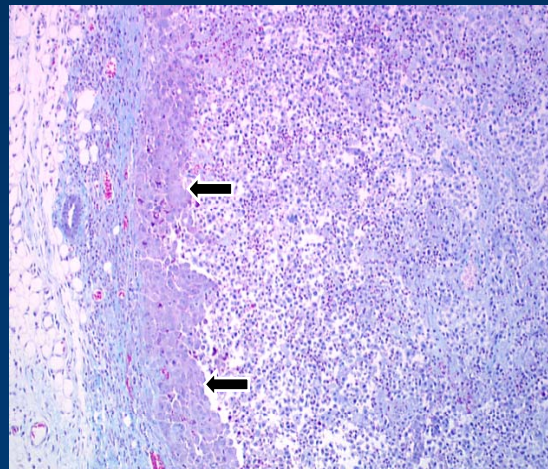
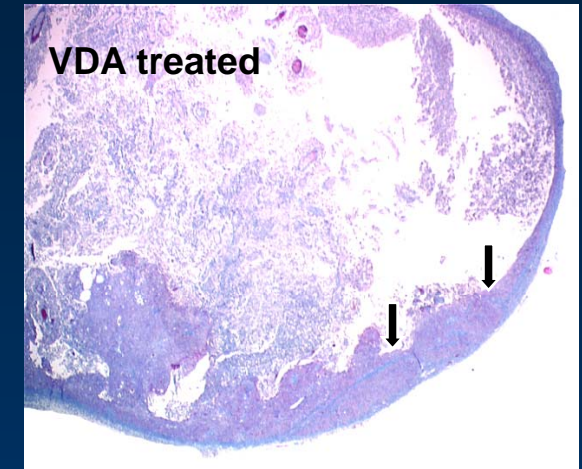
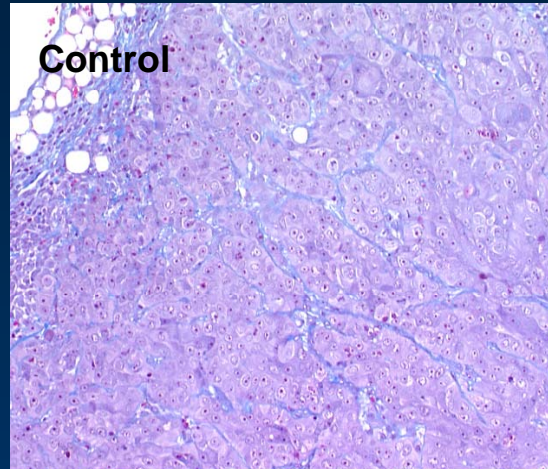
Tumor neovasculation

Damage to established vessel

Vessel occlusion and tumor necrosis

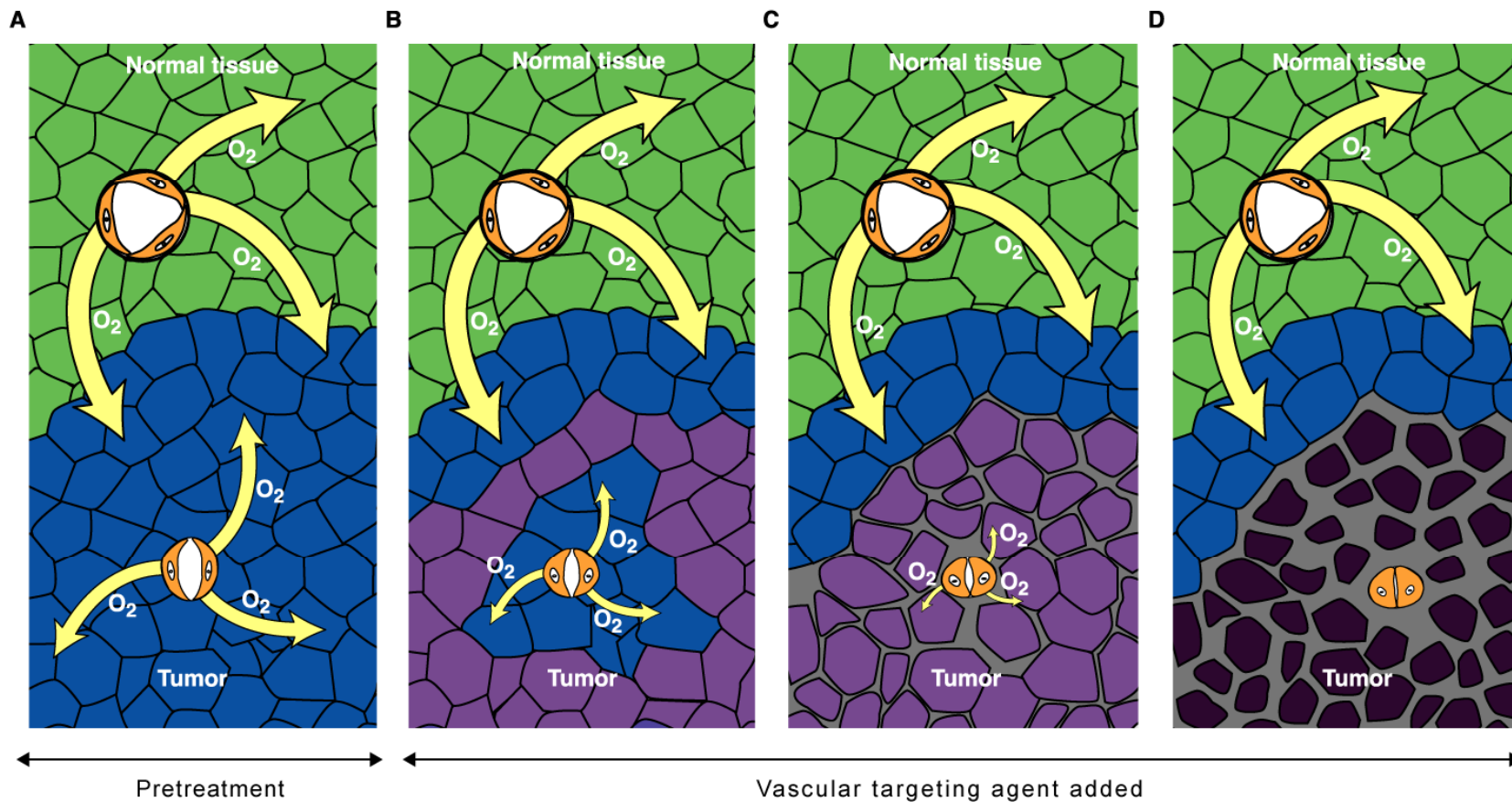
VDA Treatment Efficacy

- Vascular disrupting agents effectively eliminate large areas of solid tumors.
- Particularly areas typically resistant to conventional anti-cancer therapies.



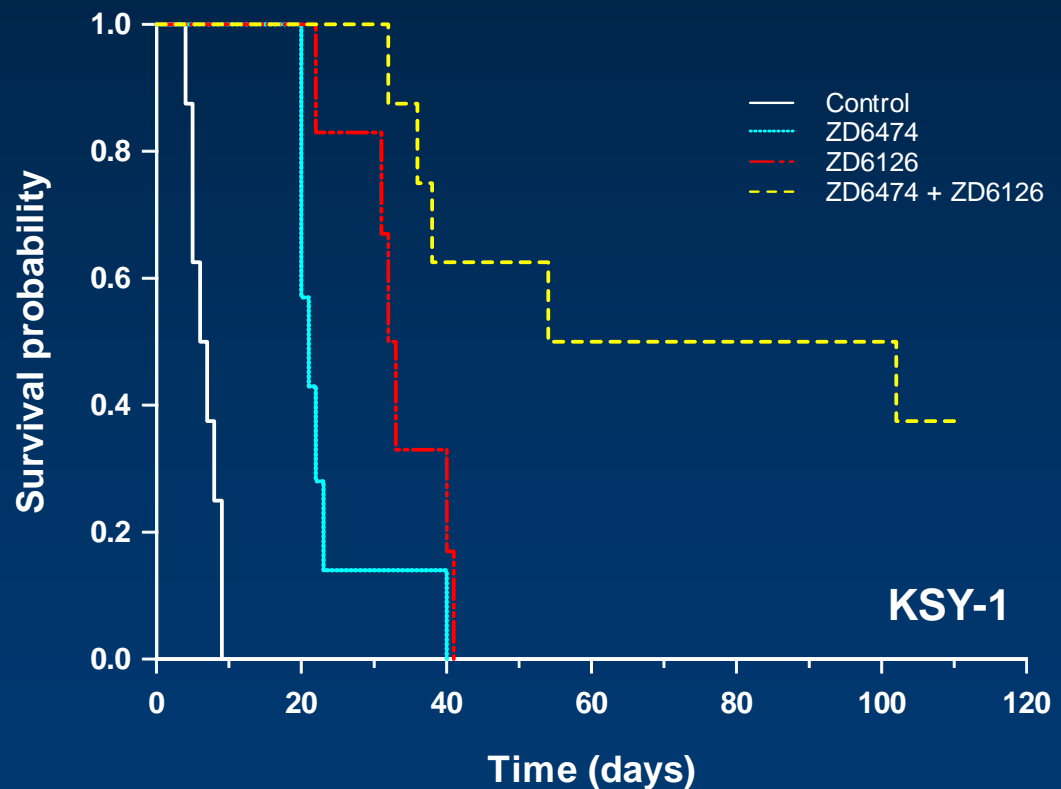
Vascular Disruption and Antiangiogenesis

- But – cells surviving at the tumor periphery aggressively promote neovascularization – and – such therapies are unlikely to eliminate the entire tumor cell population on their own.

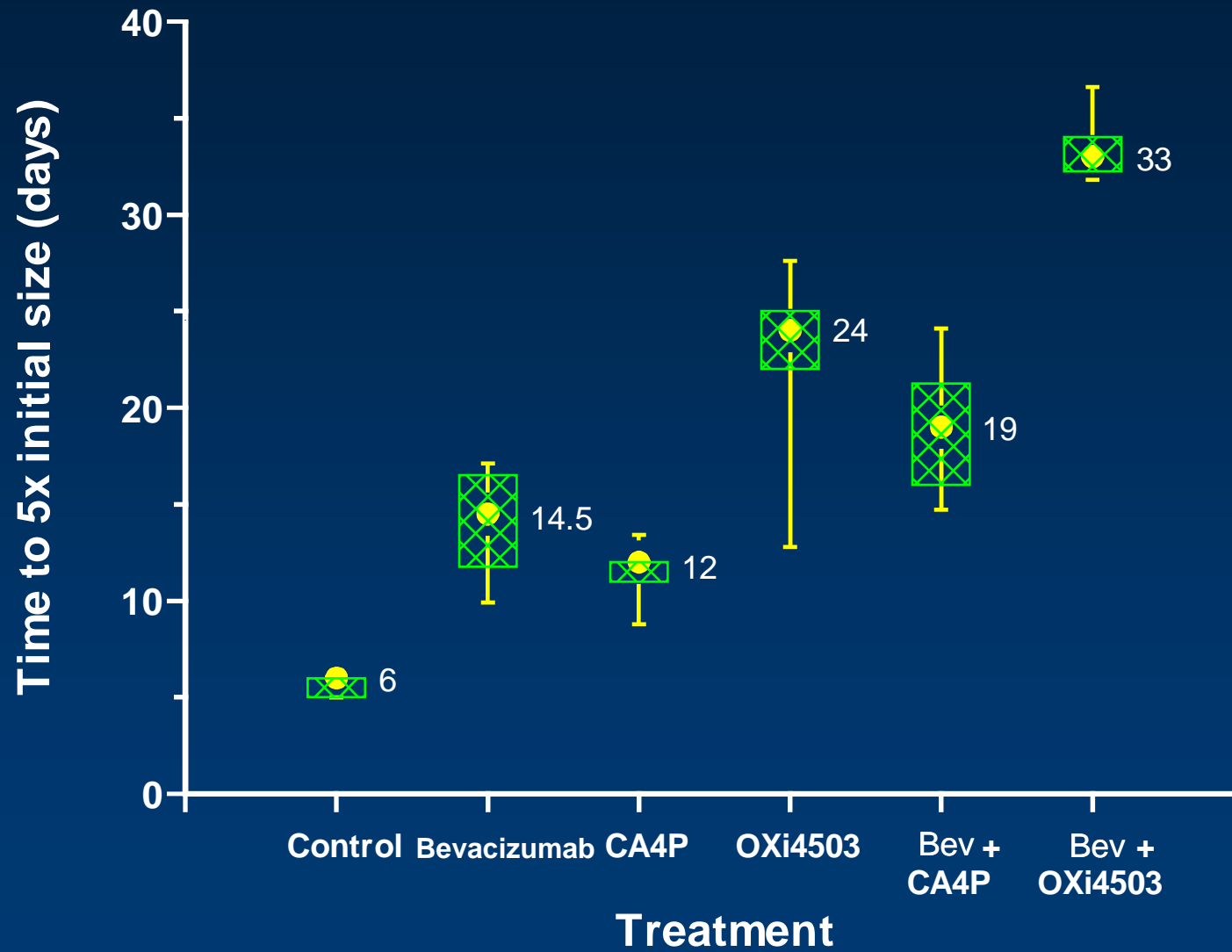


Combining Vessel Directed Strategies

- VDAs effectively eliminate large areas of tumors
- Cells surviving VDA treatment aggressively promote neovascularization
- VDAs plus AIs provide more effective tumor therapy than either treatment alone



Vascular Disruption and Antiangiogenesis



Conclusion

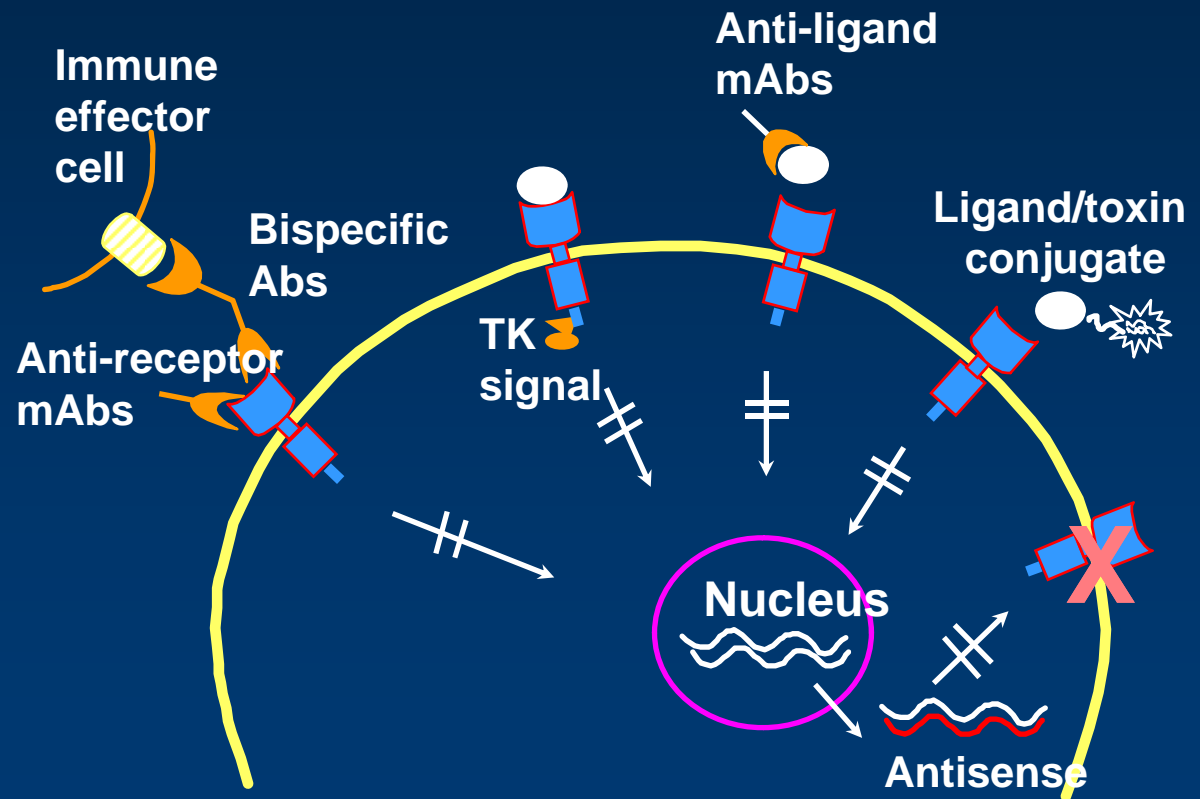
- Therapeutic strategies relying on single biologic agent targeting approaches may be beneficial but their ultimate impact on treatment efficacy is likely to be limited.
- AIs and VDAs can modify conventional anti-cancer therapy – but better cytotoxics are needed.
- The application of combined *Biologic Targeting Strategies* needs to be considered.

Single Pathway

- Multiple intervention points

- Combinations targeting

- Ligand
- Receptor
- TK signal
- Message



Single Pathway Targeting Concerns

- **The complexity of neovascularization pathways implies that disrupting only a single aspect of angiogenesis probably will not suffice.**
- **Multiple RTKs are co-activated in tumors and redundant inputs drive and maintain downstream signaling, thereby limiting the efficacy of therapies targeting single RTKs.**

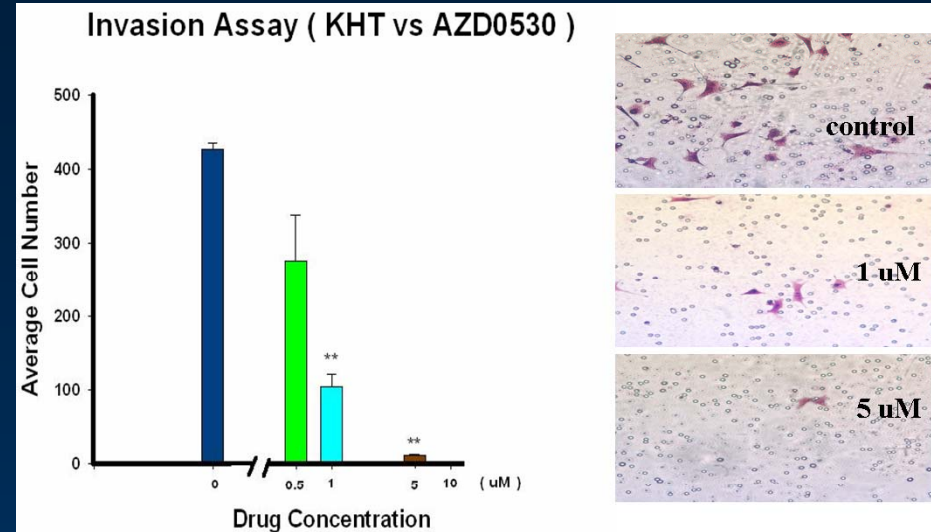
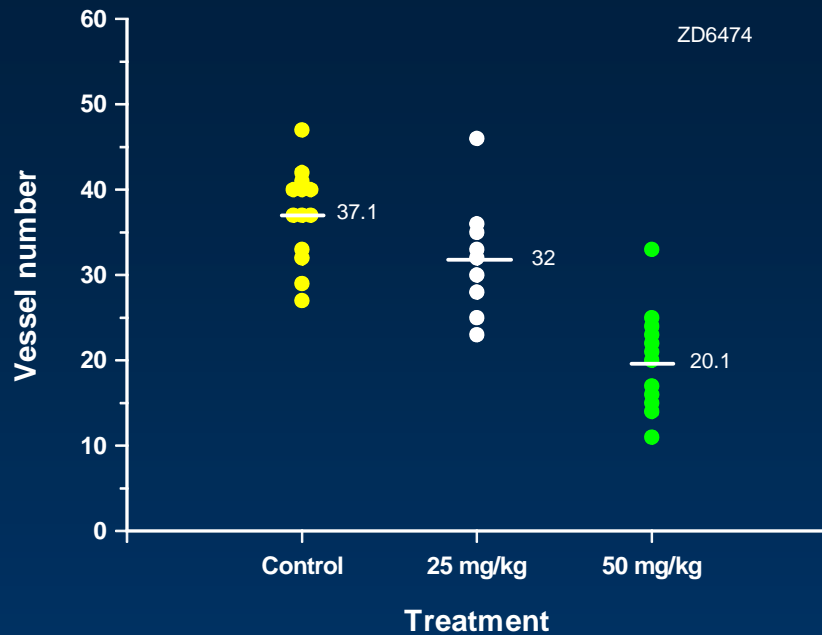
Multiple Pathway Targeting

- **Possible Strategies**
 - **Single molecule affecting several pathways**
 - **Sunitinib (PDGF, VEGF, other RTKs)**
 - **Sorafenib (Raf, PDGF, VEGF, cKit)**
 - **Vandetanib (VEGF, EGF)**
 - **Individual agents for individual pathways**

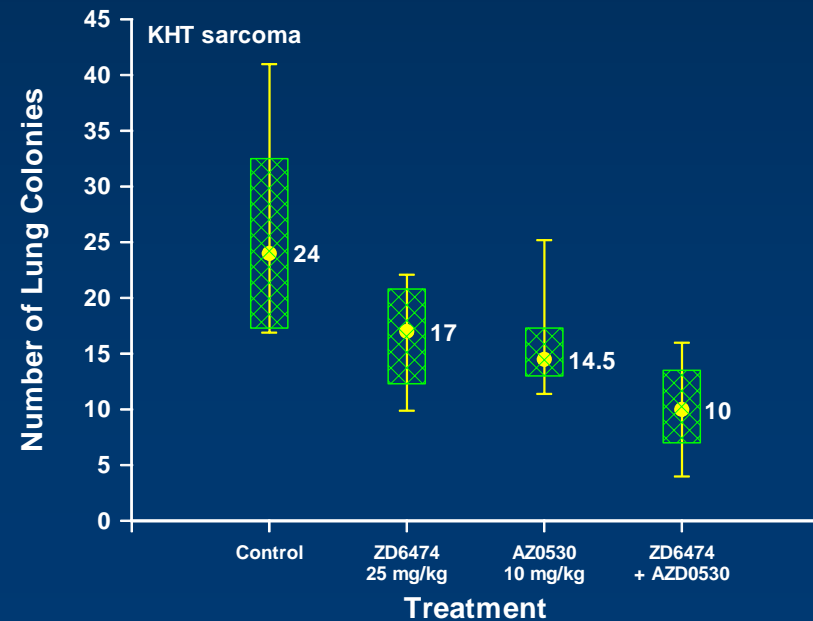
Targeting Functionally Related Pathways

- **Progression**
 - Proliferation (EGF – Cetuximab, TKIs; mTOR – RAD001, Temsirolimus)
 - Vasculature (VDAs, AIs)
- **Metastases**
 - Angiogenesis (VEGF – various TKI ‘nibs’)
 - Invasion (Src – AZD0530, Dasatinib)

Vascular Disruption and Antiangiogenesis



- Combining strategies that target angiogenesis and cell invasion may inhibit metastases formation.



Conclusions

- Future therapeutic strategies should seek to develop “combination biologic therapy” targeting multiple intervention points and/or functionally related pathways.
- **And** – to apply such combinations of biologic agents in conjunction with conventional anticancer treatments.