

*Inhibition of VEGF-C a
Novel Angiogenic and
Lymphangiogenic Molecule:
An Exciting New Paradigm
in the Treatment of Solid
Tumours*



WCC-2010

Presentation by Robert Klupacs

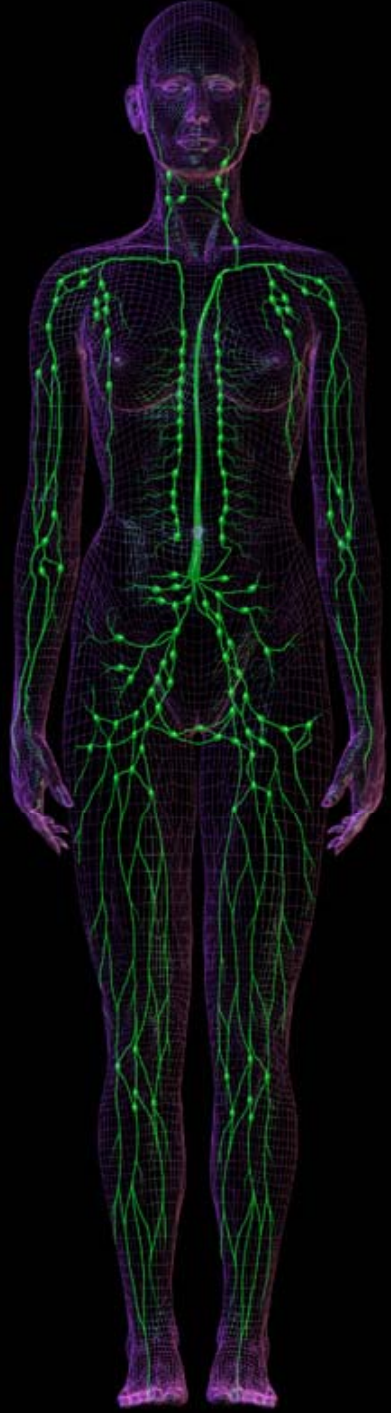
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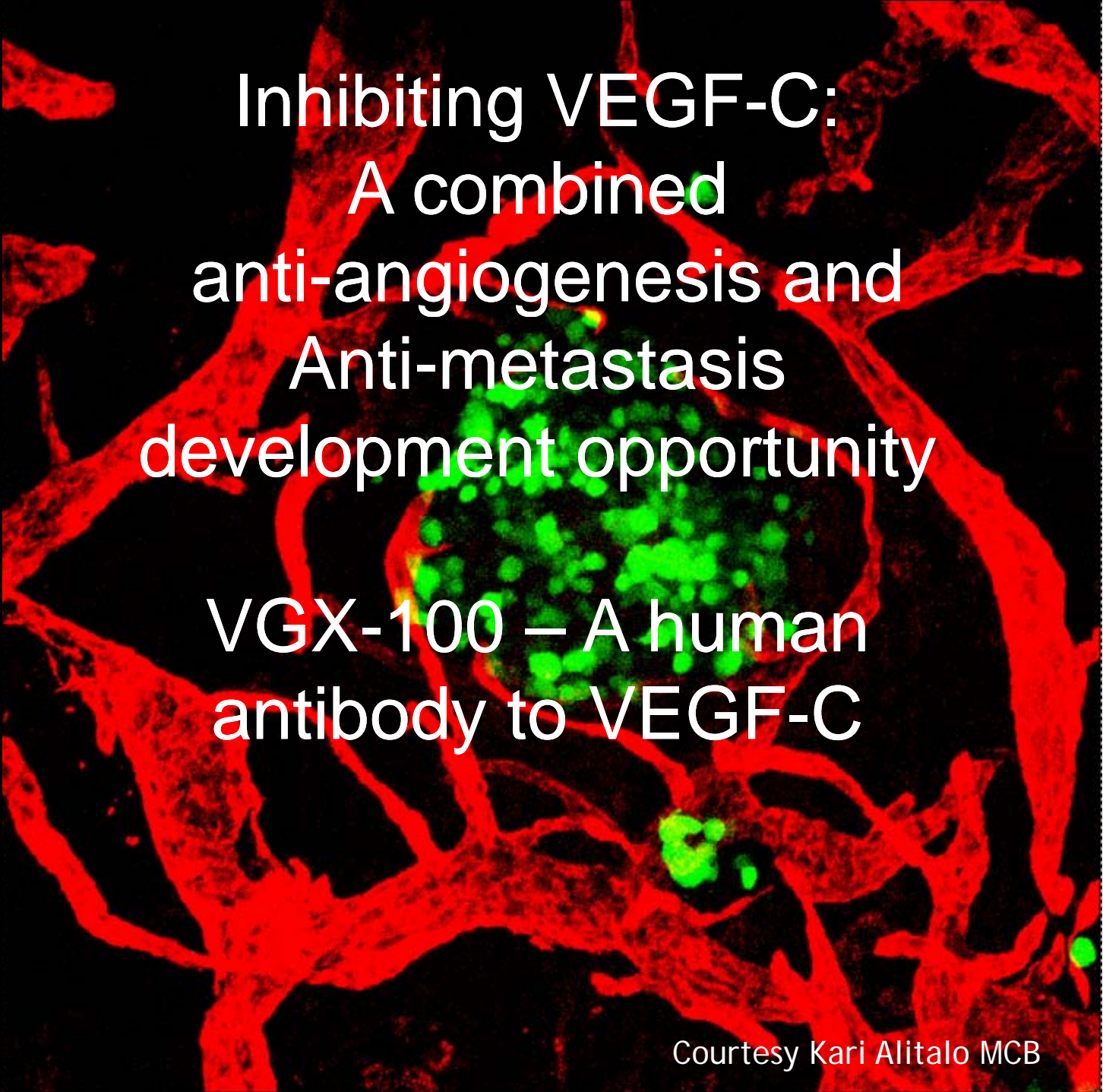
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Inhibiting VEGF-C:
A combined
anti-angiogenesis and
Anti-metastasis
development opportunity



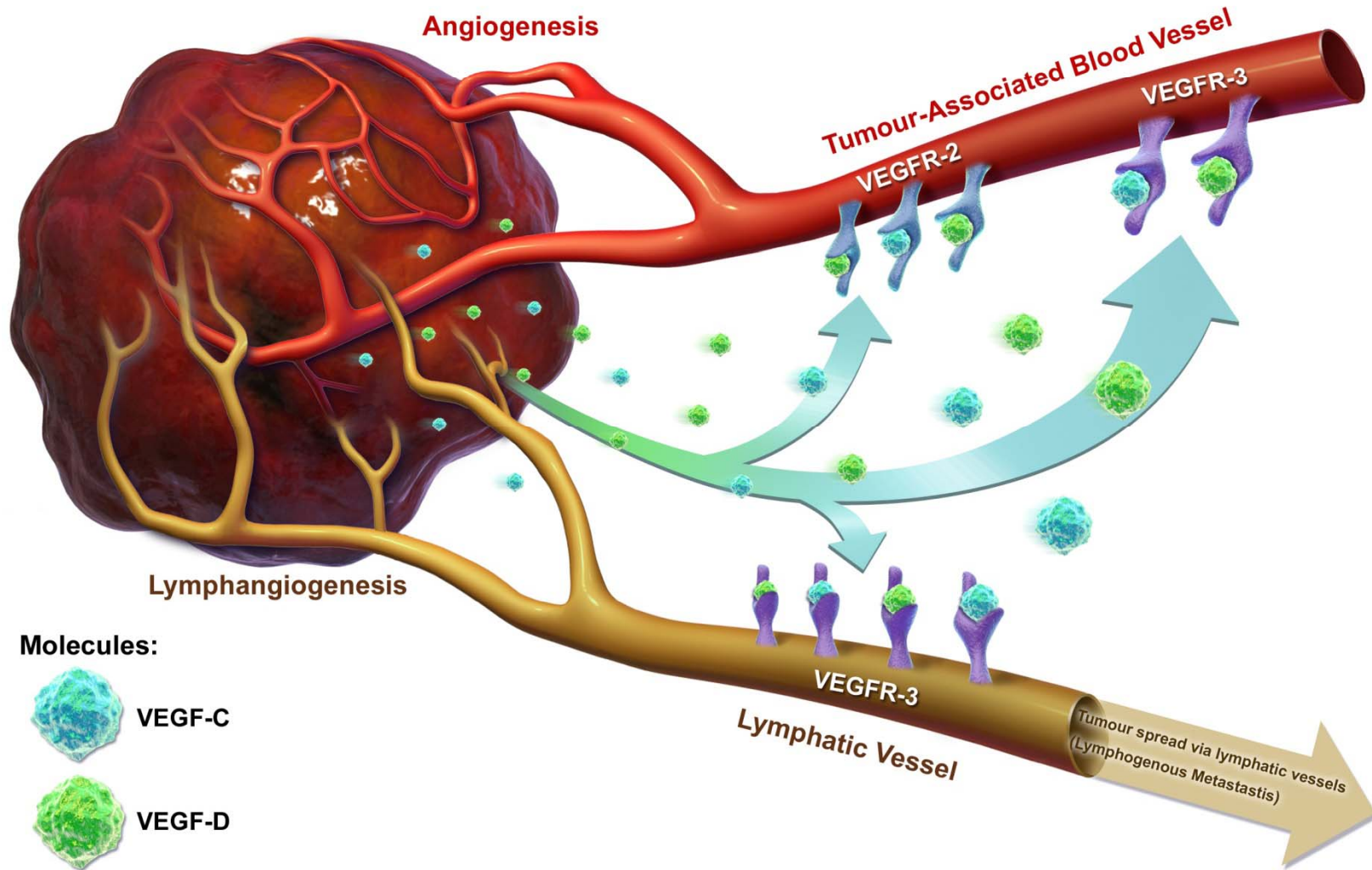
VGX-100 – A human
antibody to VEGF-C

Courtesy Kari Alitalo MCB

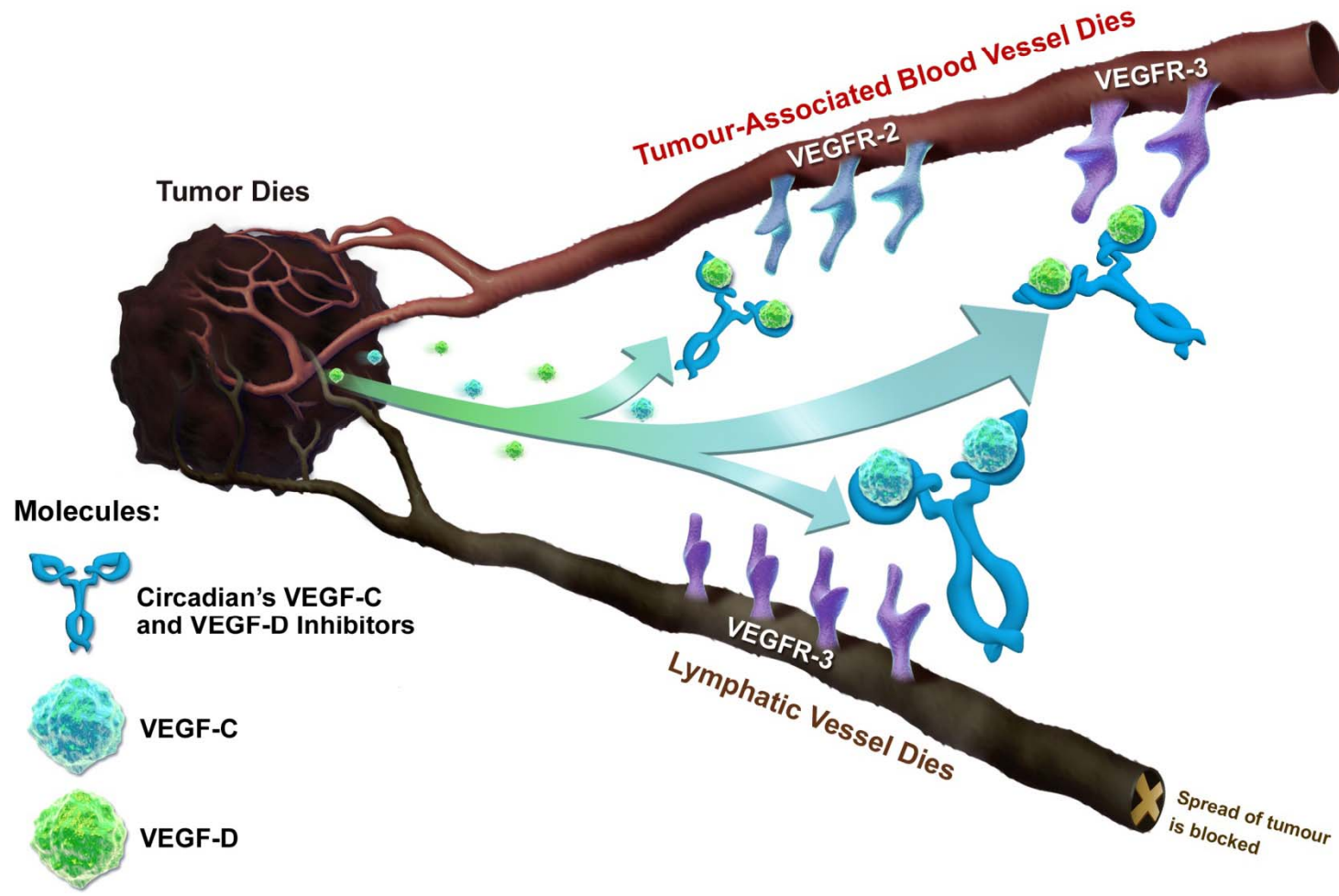
Improving anti-angiogenesis: A major commercial opportunity

- Avastin®: Humanised Antibody to VEGF-A
- Sold by Genentech/Roche
- Approved for 5 tumour types
- 2009 Sales - \$US5.7B
- Effective but not across the board
 - Not all patients respond to therapy (30-50% response rate)
 - 25-50% of responders become “resistant” within 12 to 18 months
 - Potential reasons:
 - Tumour growth due to factors other than VEGF-A; and/or
 - Other angiogenic factors being turned on when VEGF-A blocked (i.e. VEGF-C, VEGF-D)

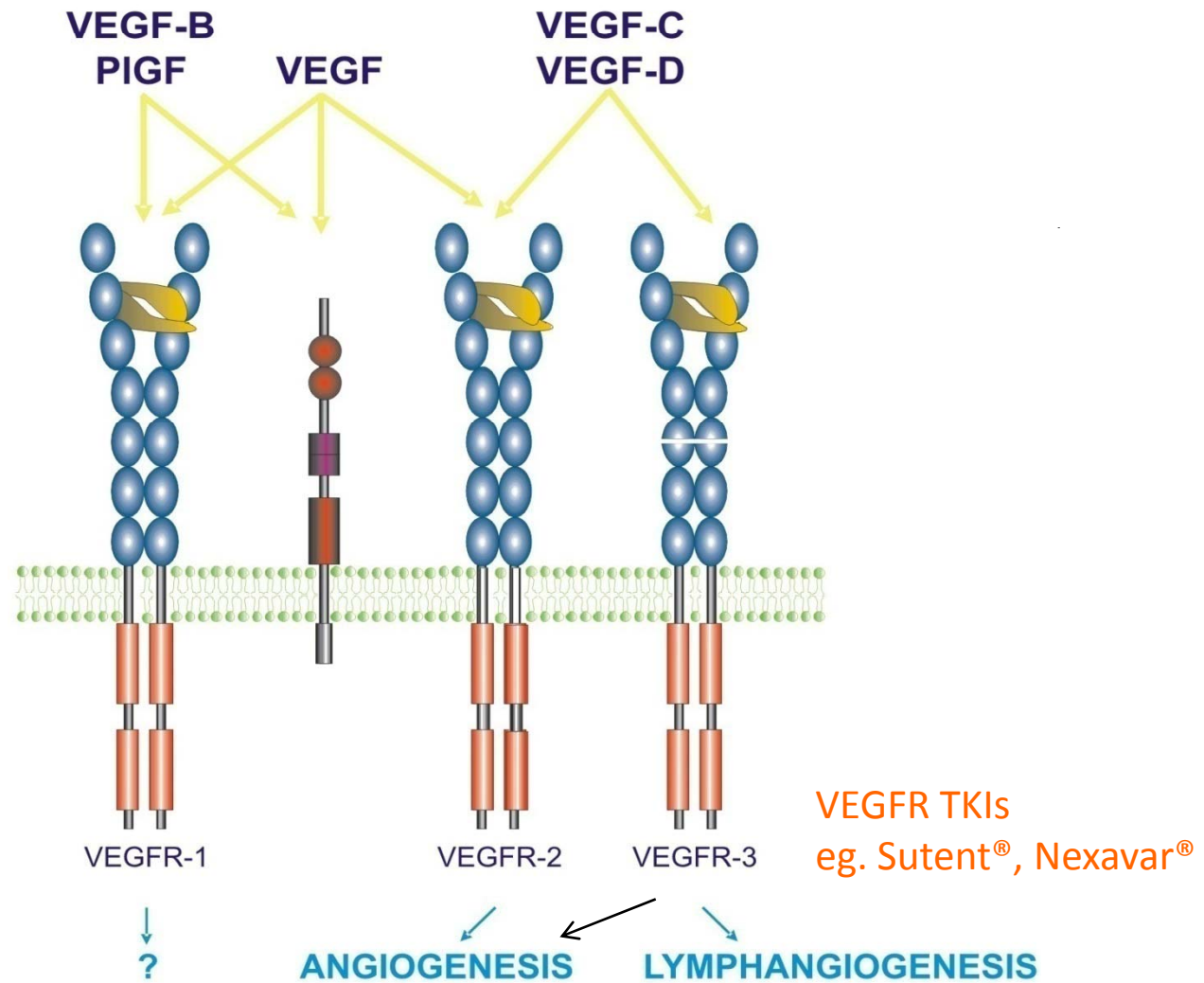
Concept-Inhibiting Tumour Growth & Spread



Concept-Inhibiting Tumour Growth & Spread



Angiogenesis & Lymphangiogenesis

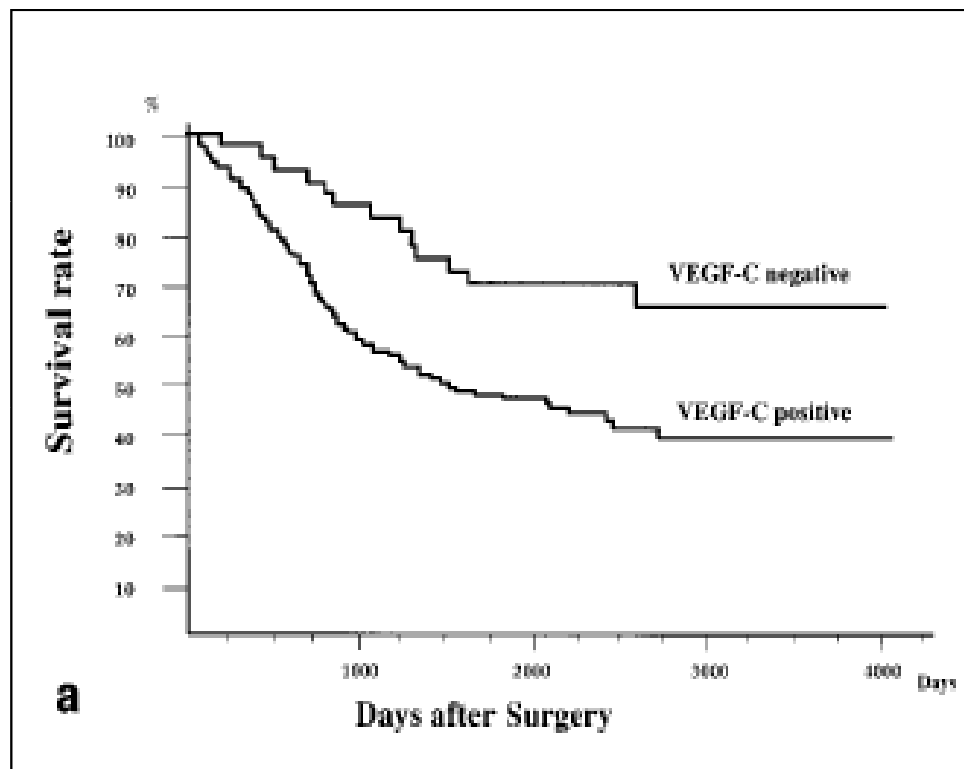




VEGF-C

- Linked to disease outcome in a number of tumour types
- Known to be alternate angiogenic ligand for VEGF-A
- Blockade in animal models has significant anti-tumour effects

Poor prognosis for Non Small Cell Lung Cancer patients expressing VEGF-C



180 NSCLCs

5yr survival rates for patients:

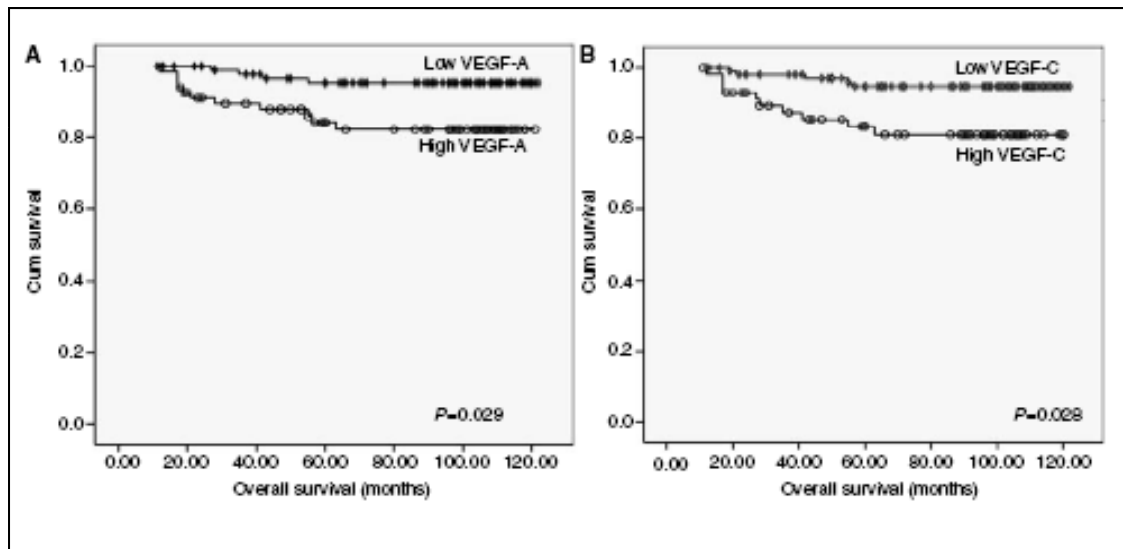
VEGF-C positive: 47%

VEGF-C negative: 70%

VEGF-C and VEGFR-3 correlated with:

- Decreased survival
- Pts with positive staining for both had poorest prognosis

Poor survival of breast cancer patients with high VEGF and VEGF-C levels



117 invasive breast cancer

VEGF-C correlated with:

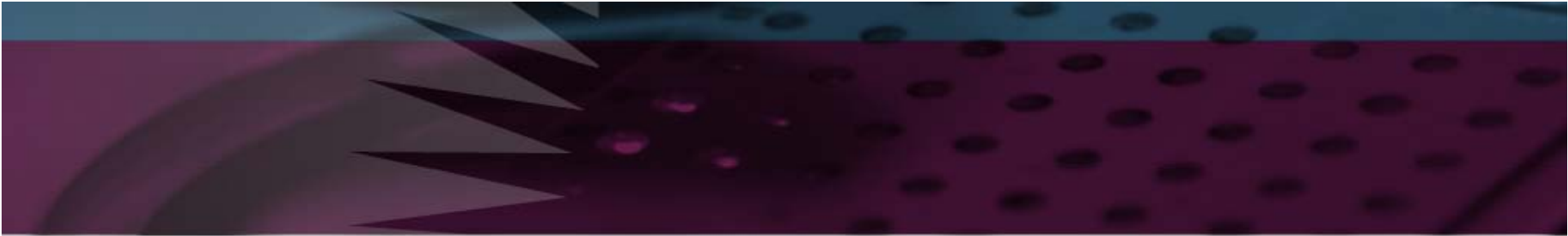
- LVD
- LN Metastases
- Decreased OS

Pts with high VEGF-C & VEGF levels have worst prognosis



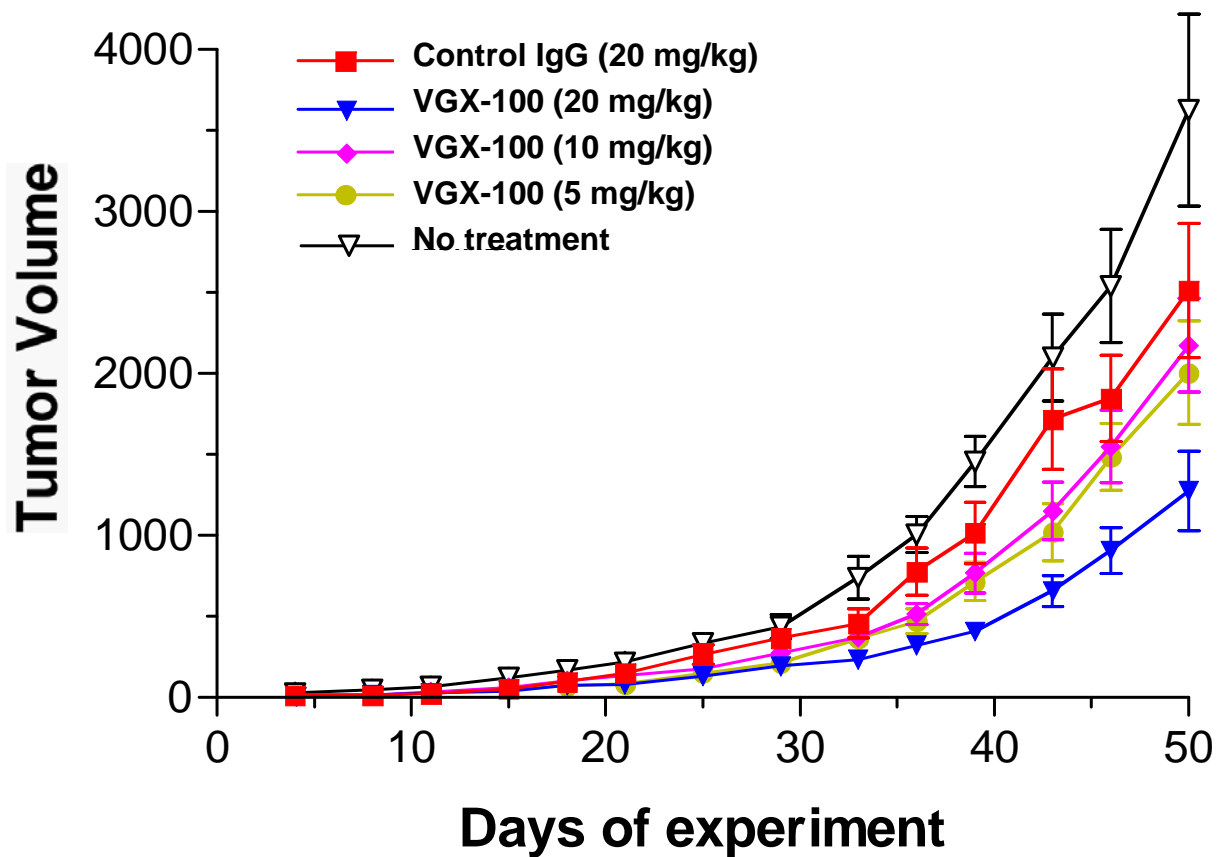
VGX-100

- VGX-100 is a human IgG1 (lambda) VEGF-C neutralising antibody
- VGX-100 neutralises all forms of VEGF-C (full-length, partially processed and mature)
- VGX-100 binds mature VEGF-C with high affinity (KD=1.8 nM)
- VGX-100 neutralises mouse and human VEGF-C (utility in mouse and human tumor models)

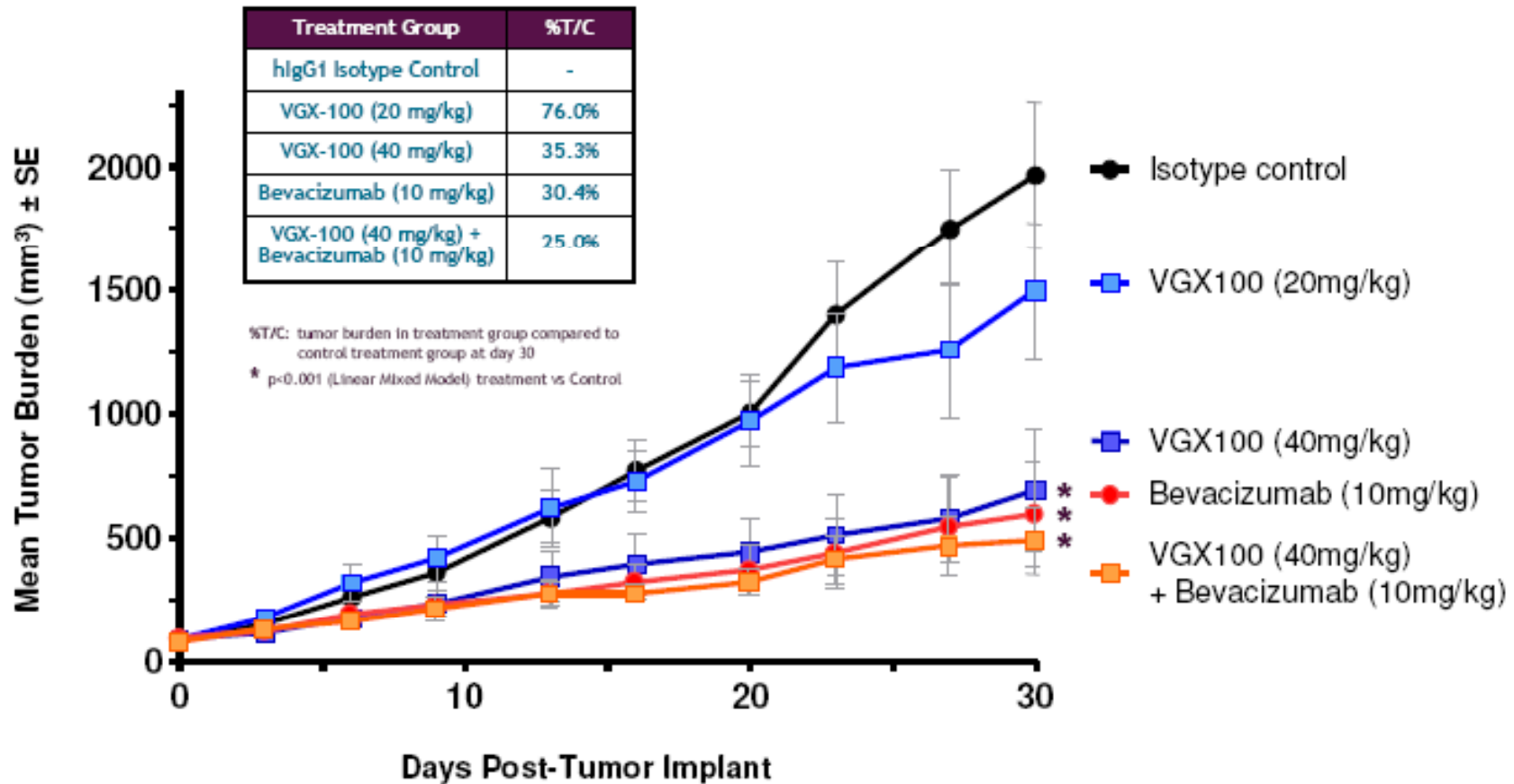


In Vivo Data
Effective in:
Breast
Pancreatic
Glioblastoma
Prostate
Colorectal

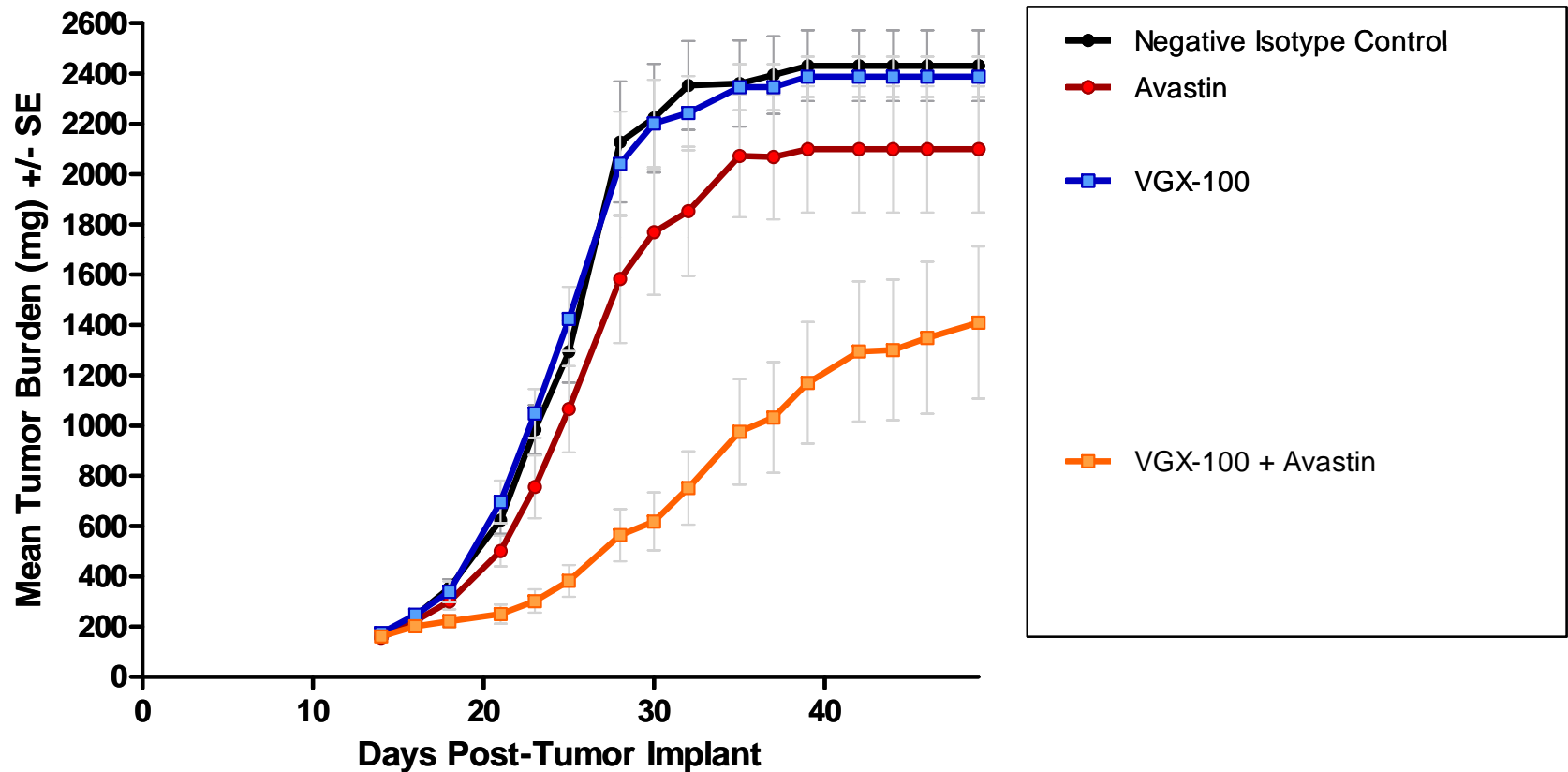
Dose-dependent inhibition of MDA-MB-231 breast cancer xenografts



VGX-100 is active as a monotherapy in KP4 human pancreatic tumor xenografts



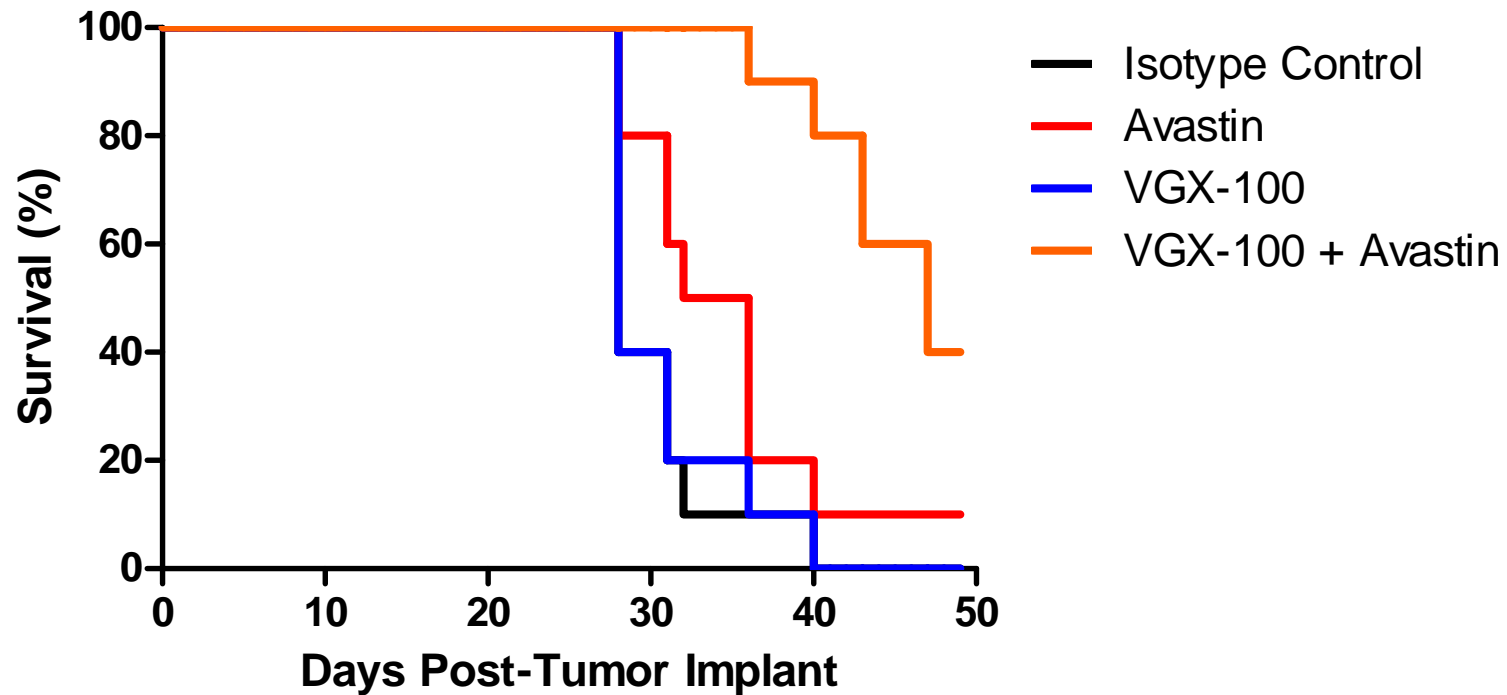
VGX-100 is active in combination with Avastin in U87MG human glioblastoma xenografts



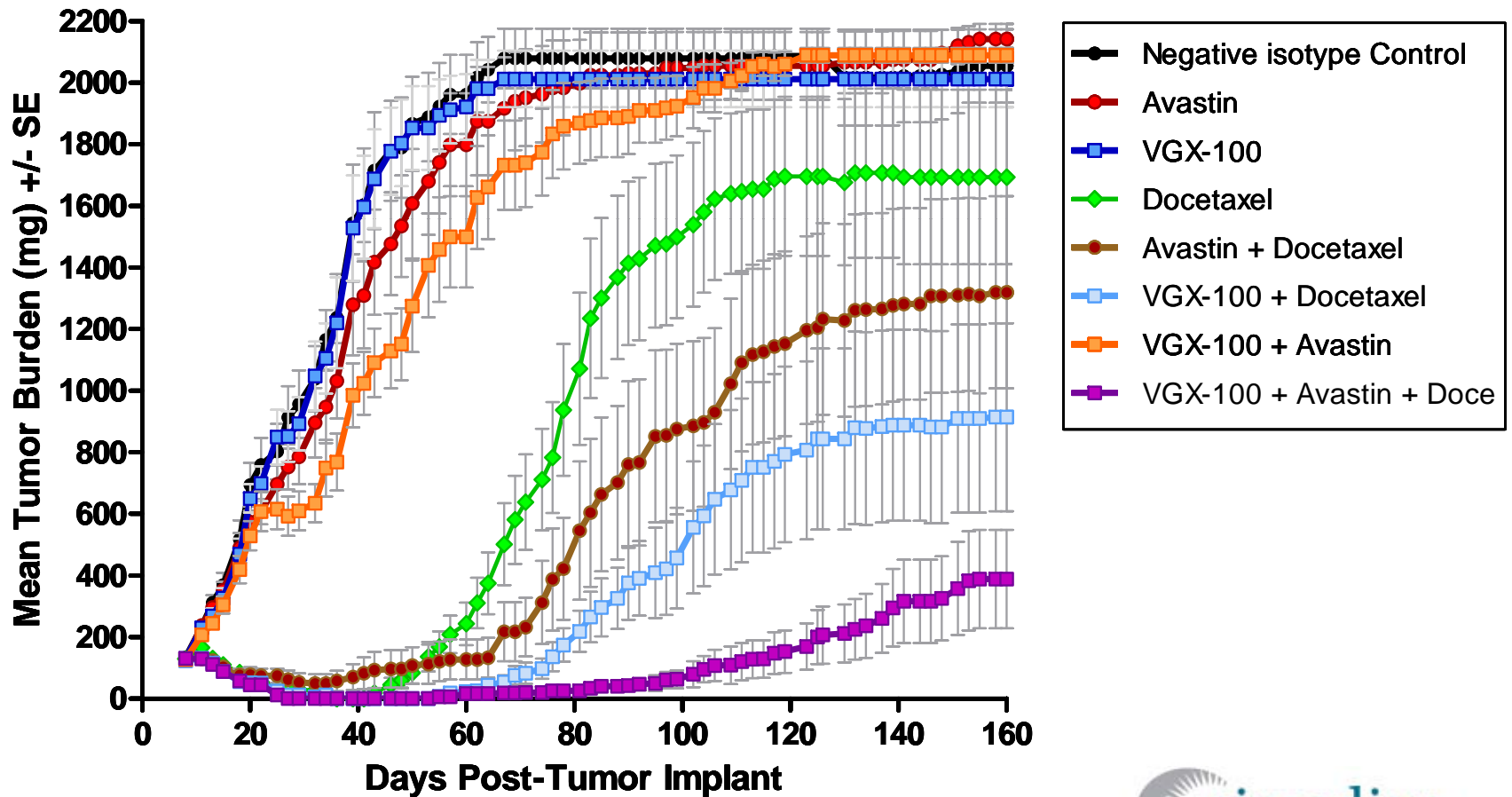
At Day 49, VGX-100 + Avastin reduces tumor burden by:

- 42% compared to control IgG
- 33% compared to single-agent Avastin.

Combination treatment VGX-100 + Avastin Extends Survival in U87MG model



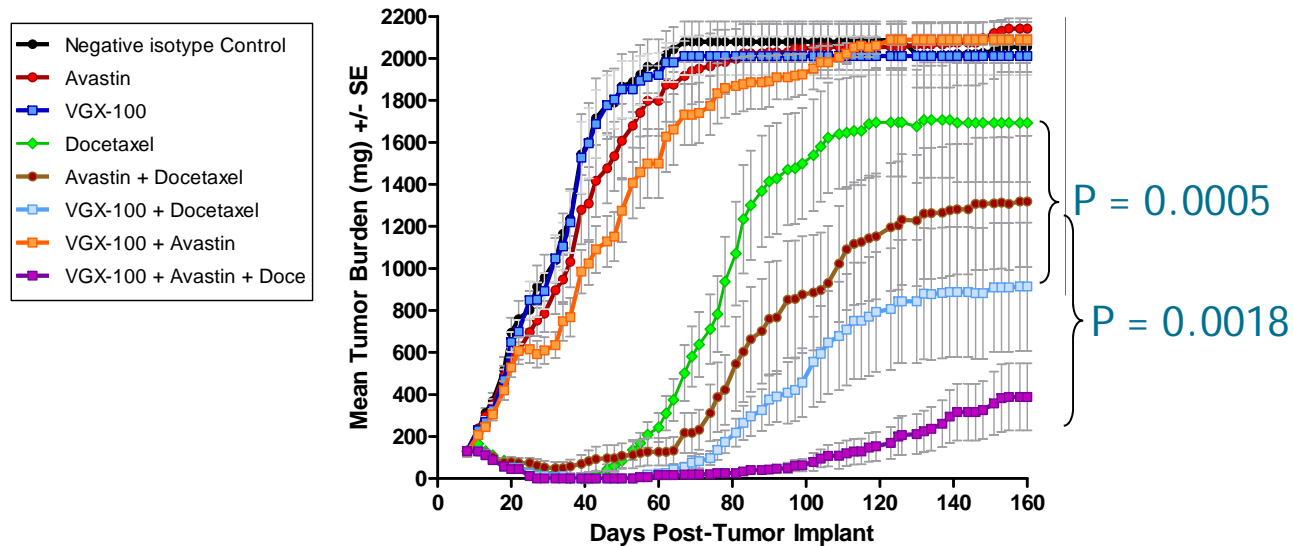
VGX-100 single-agent & combination therapy in PC-3 prostate cancer xenografts



Docetaxel: Weekly IV at 10 mg/kg for 3 weeks. Vehicle: 10% EtOH, 10% Tween 20, 80% water.

MIR1219

VGX-100 in PC-3 prostate cancer xenografts: Statistical Analysis of Tumor Burden



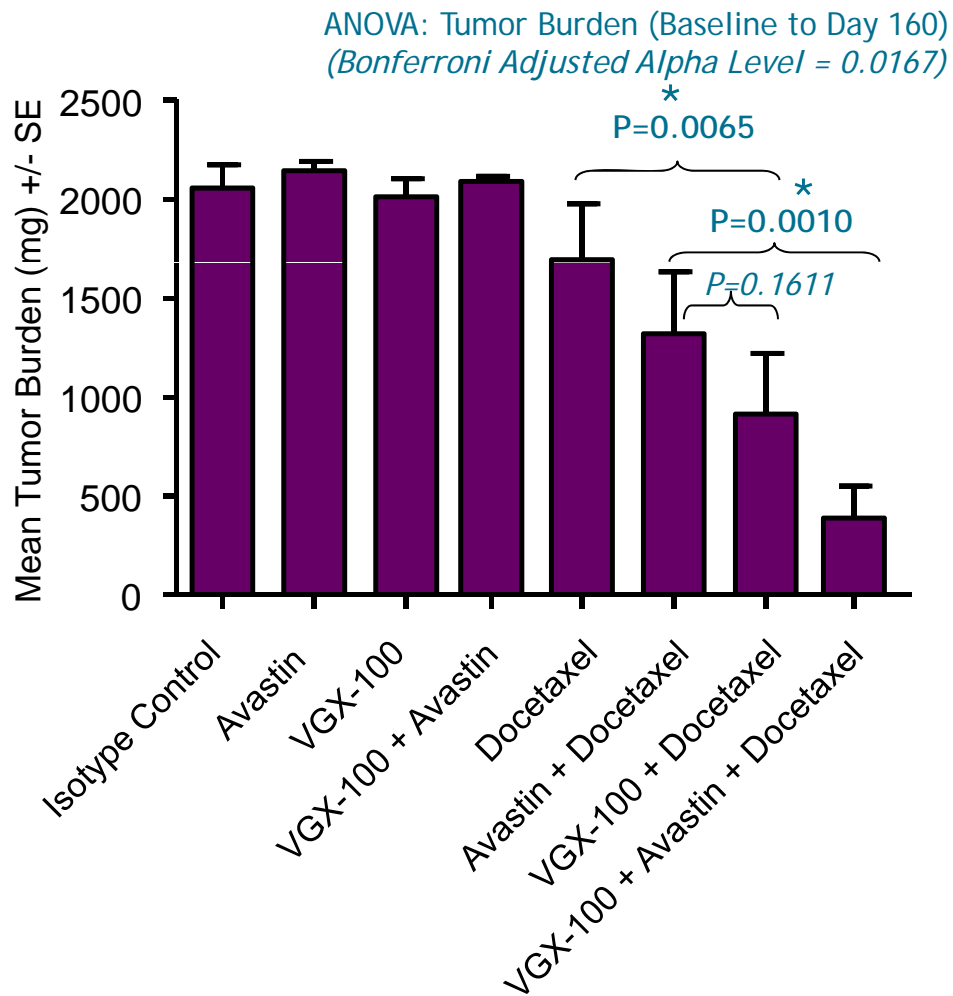
ANOVA examining Area Under the Curve (tumor burden over time):

Key Comparison	P-value
VGX-100 + Docetaxel vs Docetaxel Alone	0.0005
VGX-100 + Docetaxel vs Avastin + Docetaxel	0.1491
VGX-100 + Avastin + Docetaxel vs Avastin + Docetaxel	0.0018

Bonferroni Adjusted Alpha Level = 0.0167

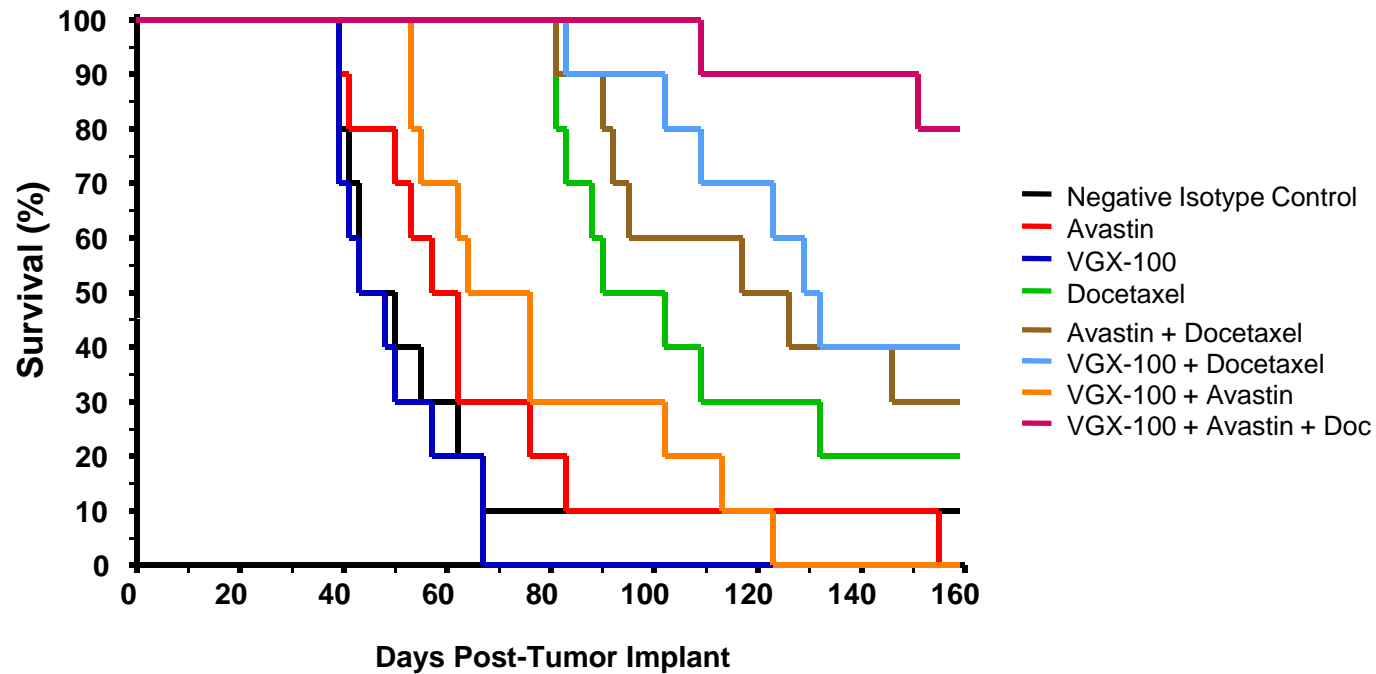


PC-3 tumor weight at day 160



Treatment Group	%T/C (D160)
hIgG1 Isotype Control	-
Bevacizumab	104.2%
VGX-100	97.9%
VGX-100 + Avastin	101.7%
Docetaxel	82.4%
Avastin + Docetaxel	64.2% Inhibition: 35.8%
VGX-100 + Docetaxel	44.5% Inhibition: 55.5%
VGX-100 + Avastin + Docetaxel	Inhibition: 83.4% 16.6%

VGX-100 in combination with docetaxel and Avastin enhances survival



Log-Rank Test: Survival Data

Key Comparison	P-value
VGX-100 + Docetaxel vs Docetaxel Alone	0.1658
VGX-100 + Docetaxel vs Avastin + Docetaxel	0.5604
VGX-100 + Avastin + Docetaxel vs Avastin + Docetaxel	0.0161

Bonferroni Adjusted Alpha Level = 0.0167

VGX-100 in combination with docetaxel and Avastin enhances survival

Treatment Group	Avg. Survival (days)	%CR	%PR	%TFS
hIgG1 Isotype Control	59.9	0	0	0
Avastin	67.8	0	0	0
VGX-100	49	0	0	0
Docetaxel	108.6	100	0	20
Avastin + Docetaxel	122.7	70	0	0
VGX-100 + Docetaxel	131.8	100	0	20
VGX-100 + Avastin	77.7	0	0	0
VGX-100 + Avastin + Docetaxel	154	100	0	40

CR: Complete Regression. Tumor burden reduced to an immeasurable volume at any point after the first treatment.

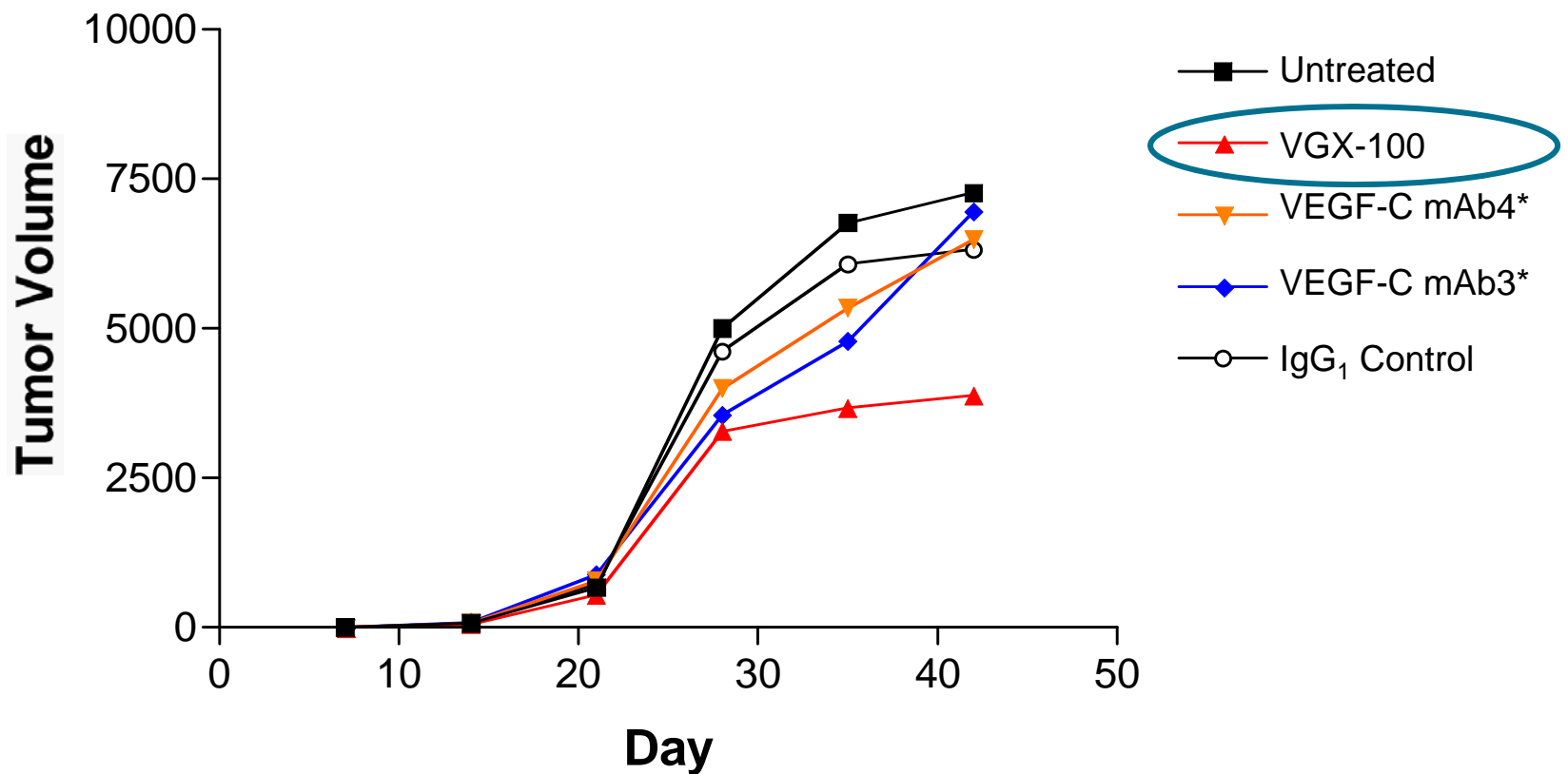
PR: Partial Regression. Tumor burden decreases to less than half of the tumor burden at first treatment.

TFS: Tumor Free Survivor. Tumor burden is immeasurable at termination of experiment (day 160).



Slower growth of orthotopic PC-3 tumors treated with VGX-100

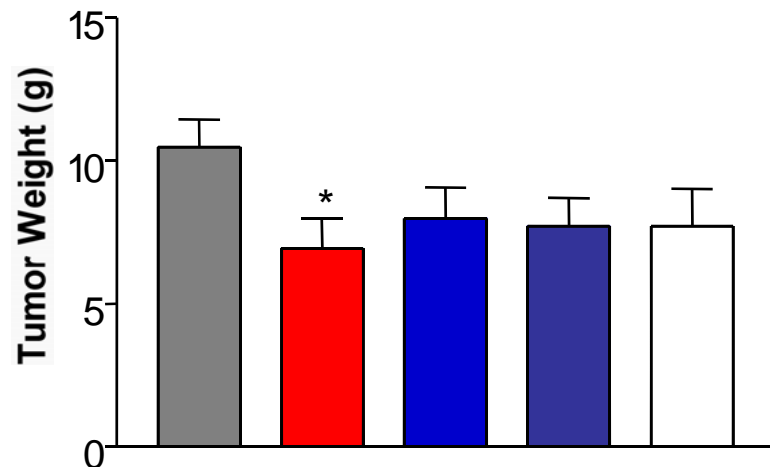
PC-3 Growth rate



▪ Dosing: 20 mg/kg every 7d.

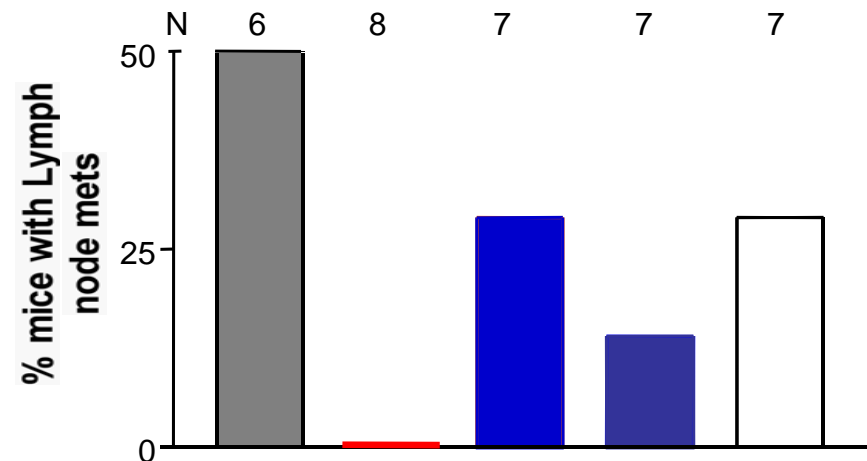
VGX-100 inhibits PC-3 tumor growth and metastasis

Day 47 PC-3 Tumor Weights



* P<0.05

Lymph Node Metastatic Frequency



Legend:

- Untreated
- VGX-100
- VEGF-C mAb4**
- VEGF-C mAb3**
- IgG1 Control

VGX-100

- VEGF-C Blockade a major role in improving anti-angiogenic therapy
- Increasing understanding of value of target
- Animal studies extremely encouraging
- Clinical trials H1 2011