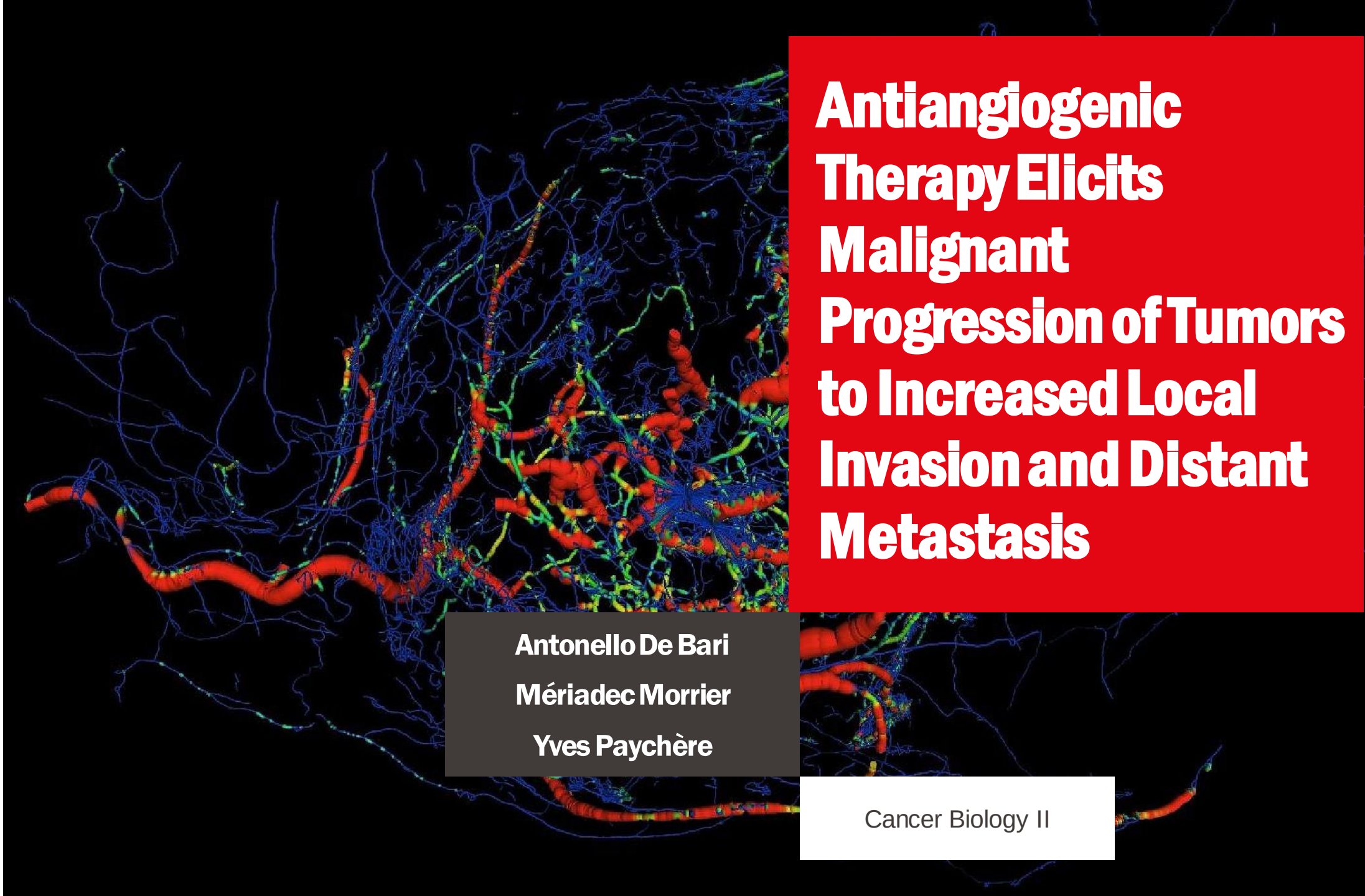
EPFL



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

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Cancer Biology II

Introduction and Methods

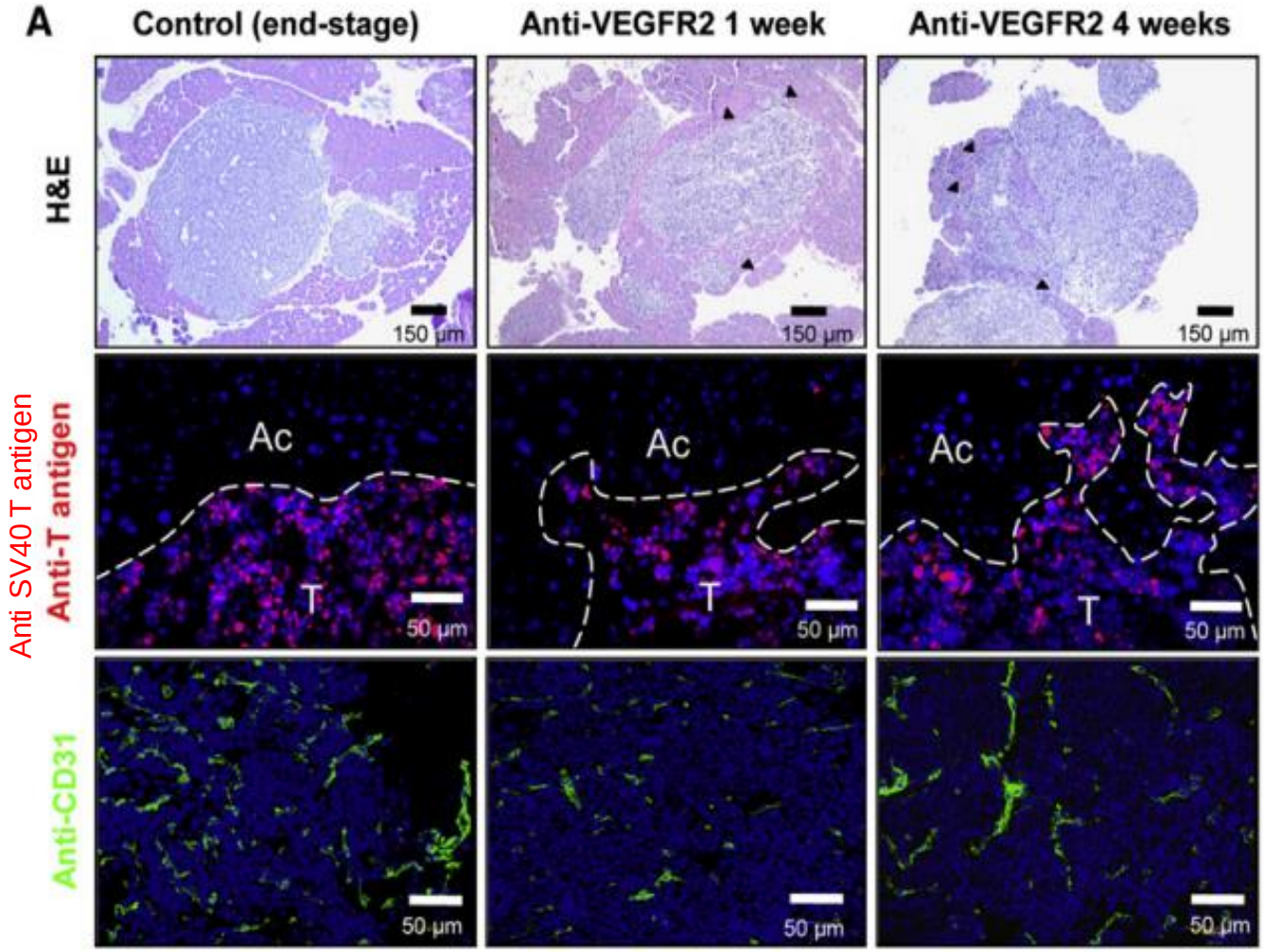
Key points

- Mouse model RIP1-Tag2: simian virus 40 large T-antigen (Tag) oncogene is expressed under the control of the rat insulin gene promoter (Rip), leading to β-cells carcinoma
- Tumor-bearing immunocompromised RIP1-Tag2 mice treated with DC101 (anti-mouse VEGFR2 antibody)

Speaker

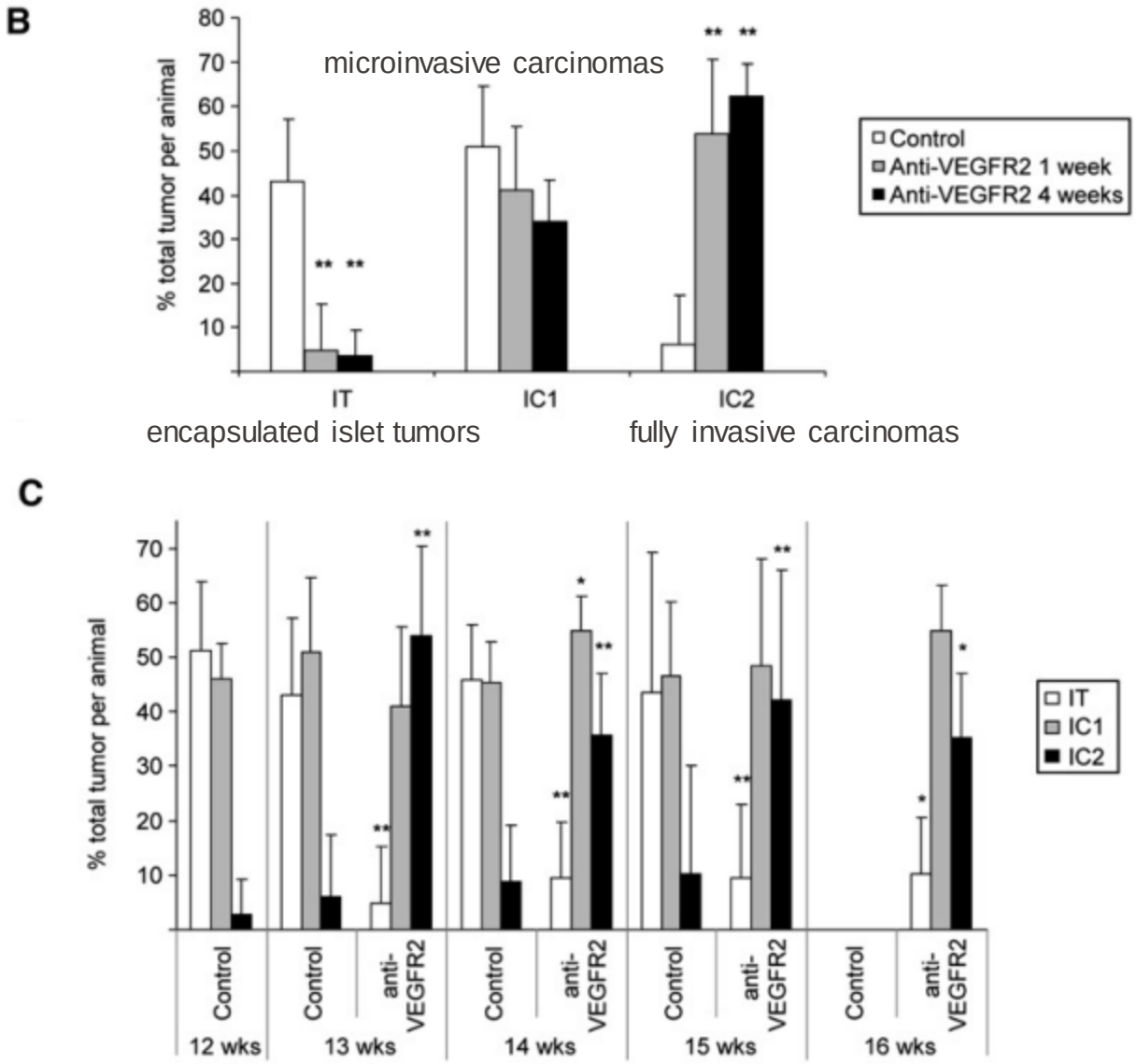
Results

Increased Invasive Phenotype after AntiVEGFR2 Therapy



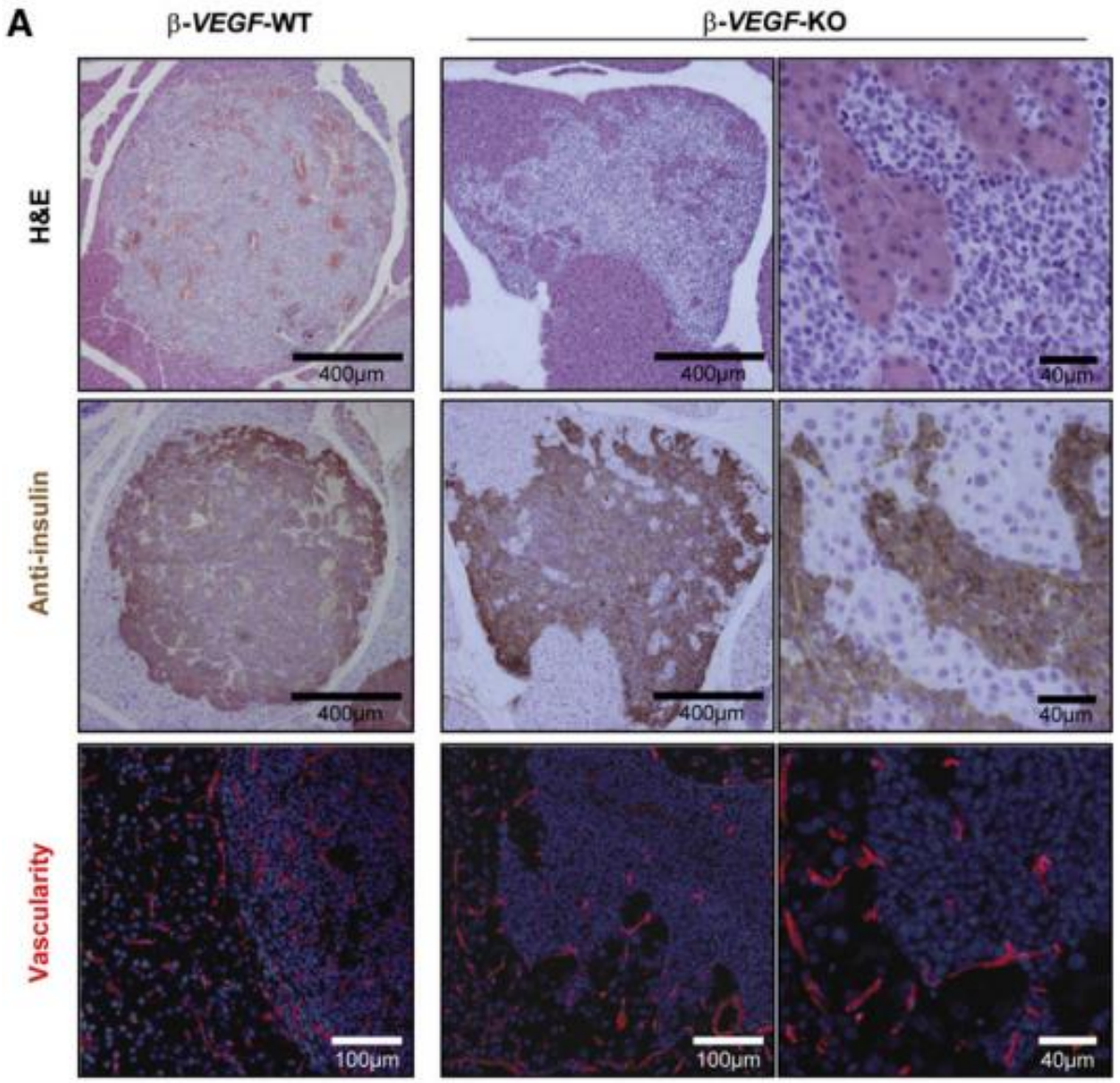
- Prominent invasive front in the treated mouse (black arrows)
- Control more encapsulated

Increased Invasive Phenotype after AntiVEGFR2 Therapy



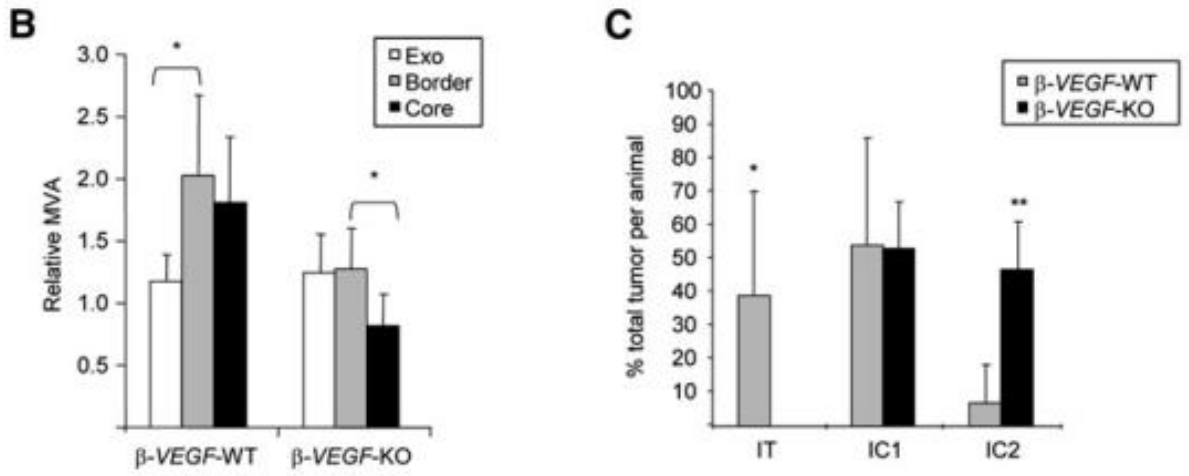
- Longer anti-VEGFR2 treatment leads to increased tumor invasiveness
- 1-week anti-VEGFR2-treated animals maintained for an additional 1, 2, or 3 weeks without treatment
- More invasive phenotype is maintained after the end of the treatment
- But all controls died before 16w

Increased Tumor Invasion after Tumor-Specific Vegf-A Deletion



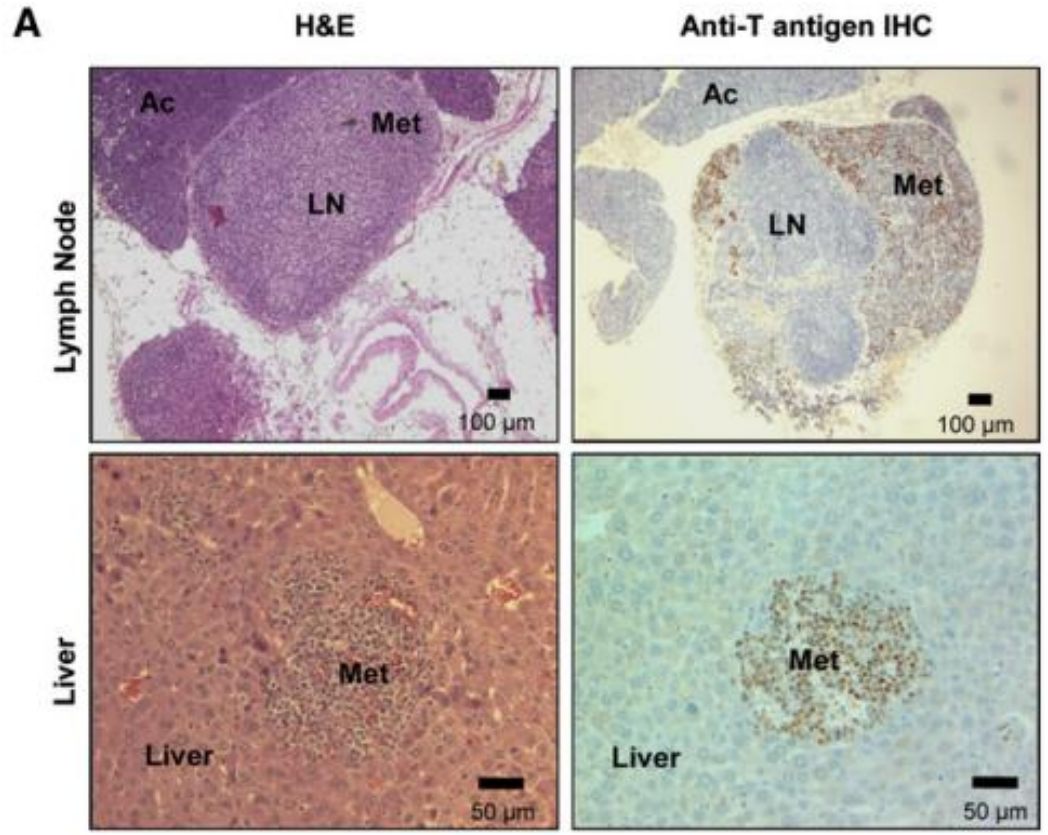
- RIP1-Tag2/ Cre;Vegf-A$^{fl/fl}$ mice (b-VEGF-KO)
- the borders are much more irregular, and the tumor is more invasive than wt
- Less blood vessels than wt

Increased Tumor Invasion after Tumor-Specific Vegf-A Deletion



- Same micro vessels area at the invasive front similar to wt exocrine tissue (MVA)
- Possible co-option of vessels
- Higher grades in Vegf-A KO mouse

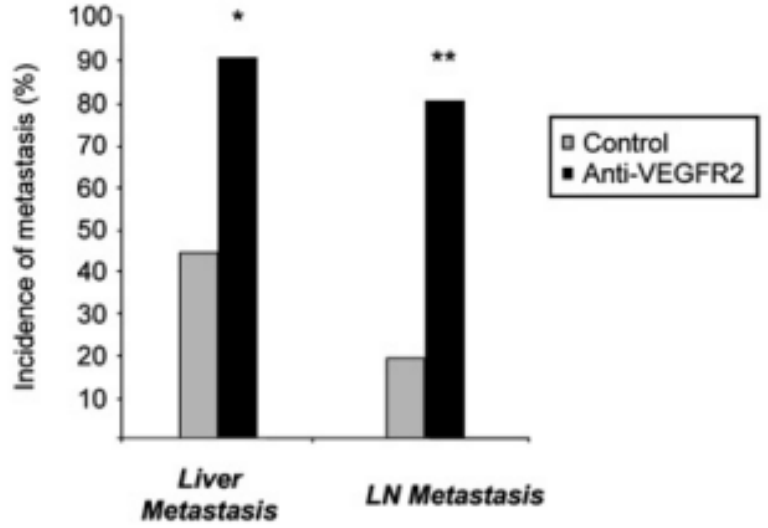
Increased Incidence of Lymph Node and Liver Metastasis in Anti-VEGFR2-Treated Animals



- Switch to immunocompetent mouse
- Presence of tumor metastases determine with H&E staining and Anti-SV40 T antigen immuno staining

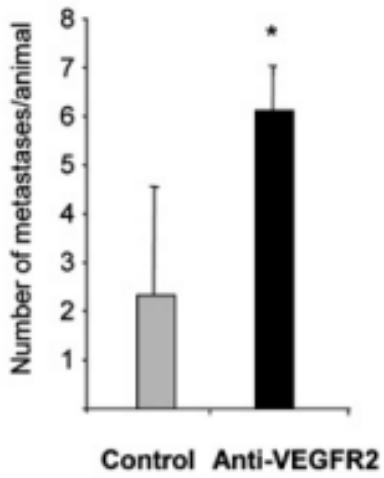
Increased Incidence of Lymph Node and Liver Metastasis in Anti-VEGFR2-Treated Animals

B



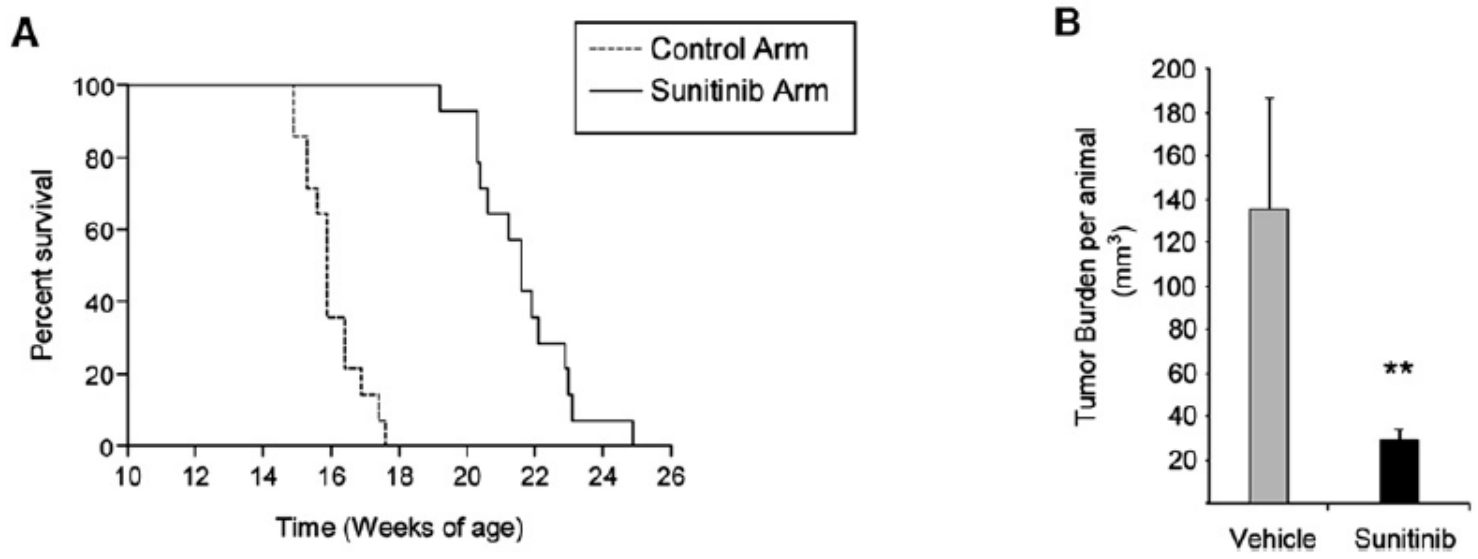
Treatment:	Yes	No		Yes	No	
Anti-VEGFR2	9 (90%)	1 (10%)	10	8 (80%)	2 (20%)	10
Control	7 (44%)	9 (56%)	16	3 (19%)	13 (81%)	16
	16	10	26	11	15	26
	χ^2, $p < 0.05$			χ^2, $p < 0.01$		

C



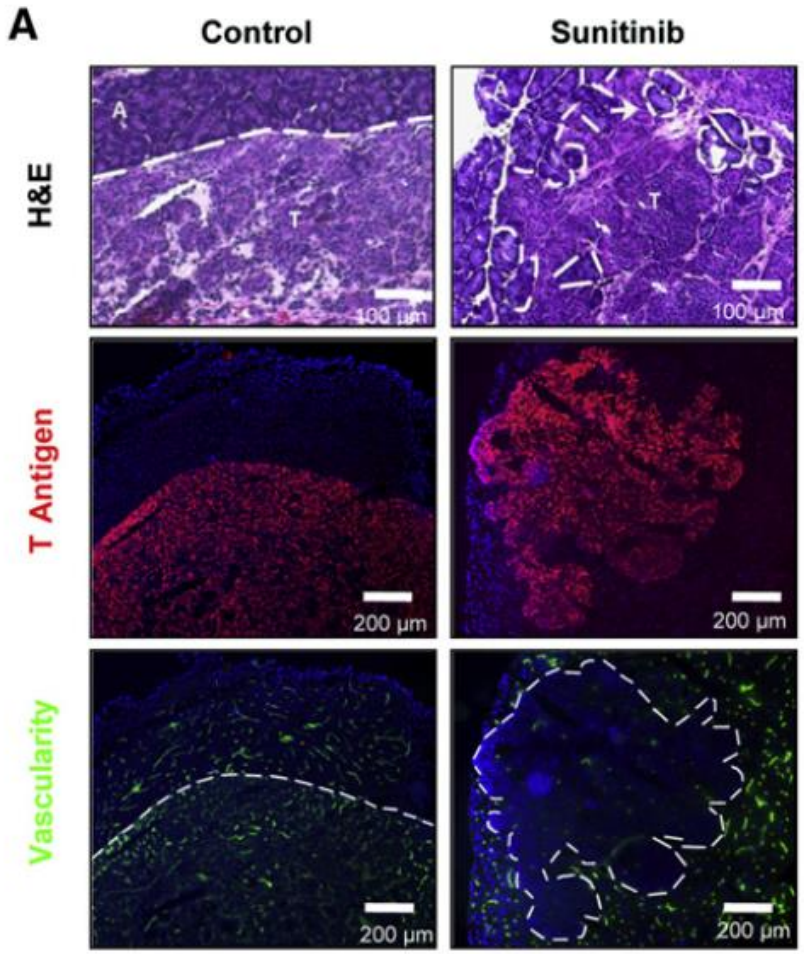
- more metastases in mouse treated

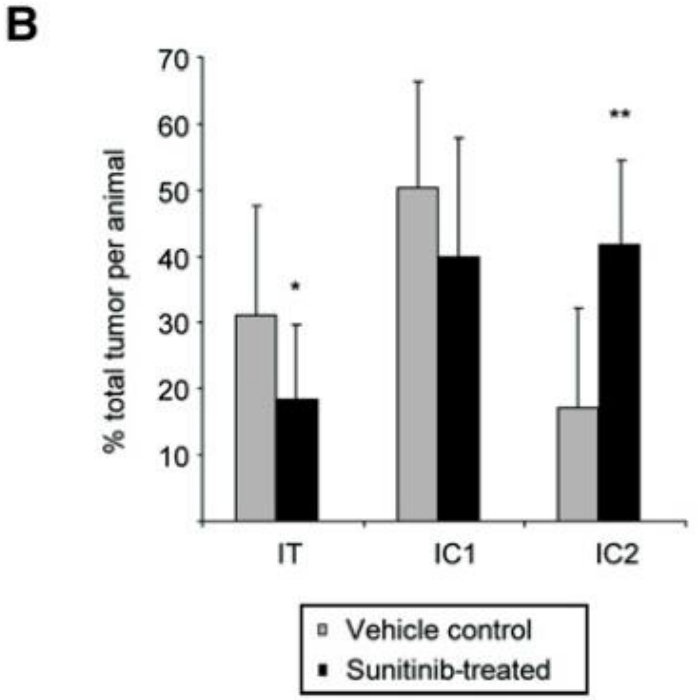
Combined anti-VEGFR2 + anti-PDGFR therapies have a strong anti-tumor effect



- Sunitinib induces better survival and decreases tumor burden after 5 weeks of treatments
- Are there also unwanted side effects ?

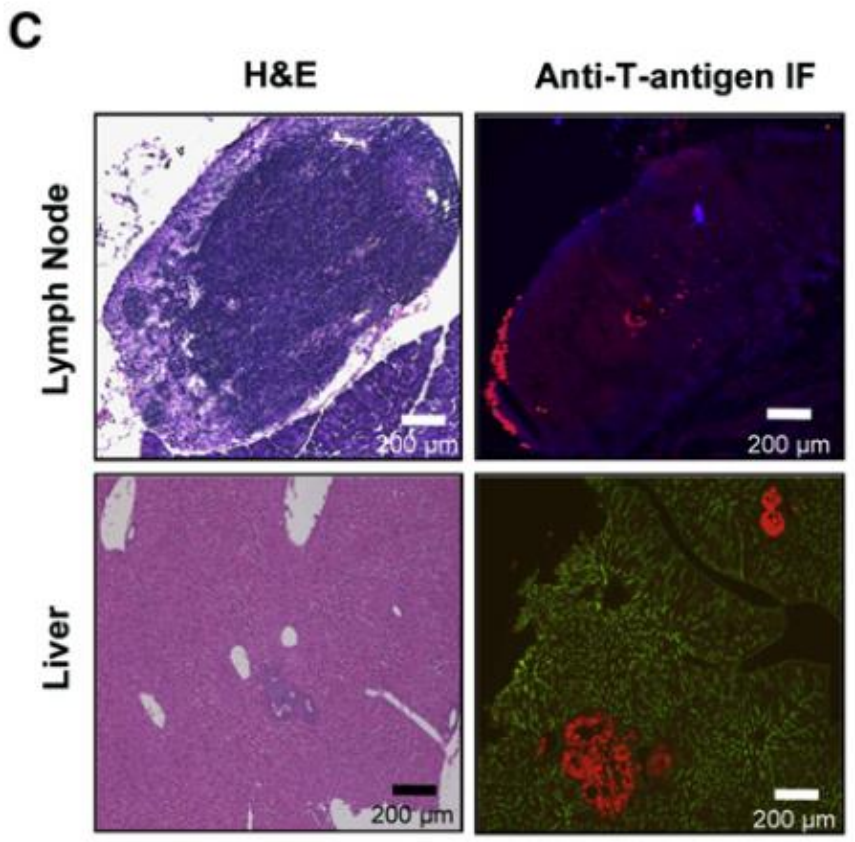
In parallel to its anti-angiogenic activity, sunitinib increases invasiveness

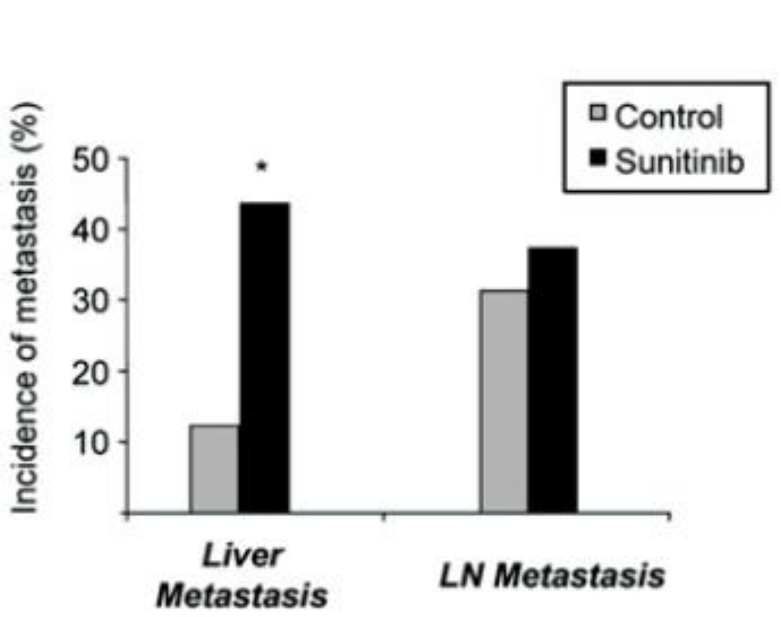




- More invasive tumors in animals treated for 5 weeks
- Some tumors malignant to a "rarely seen degree".

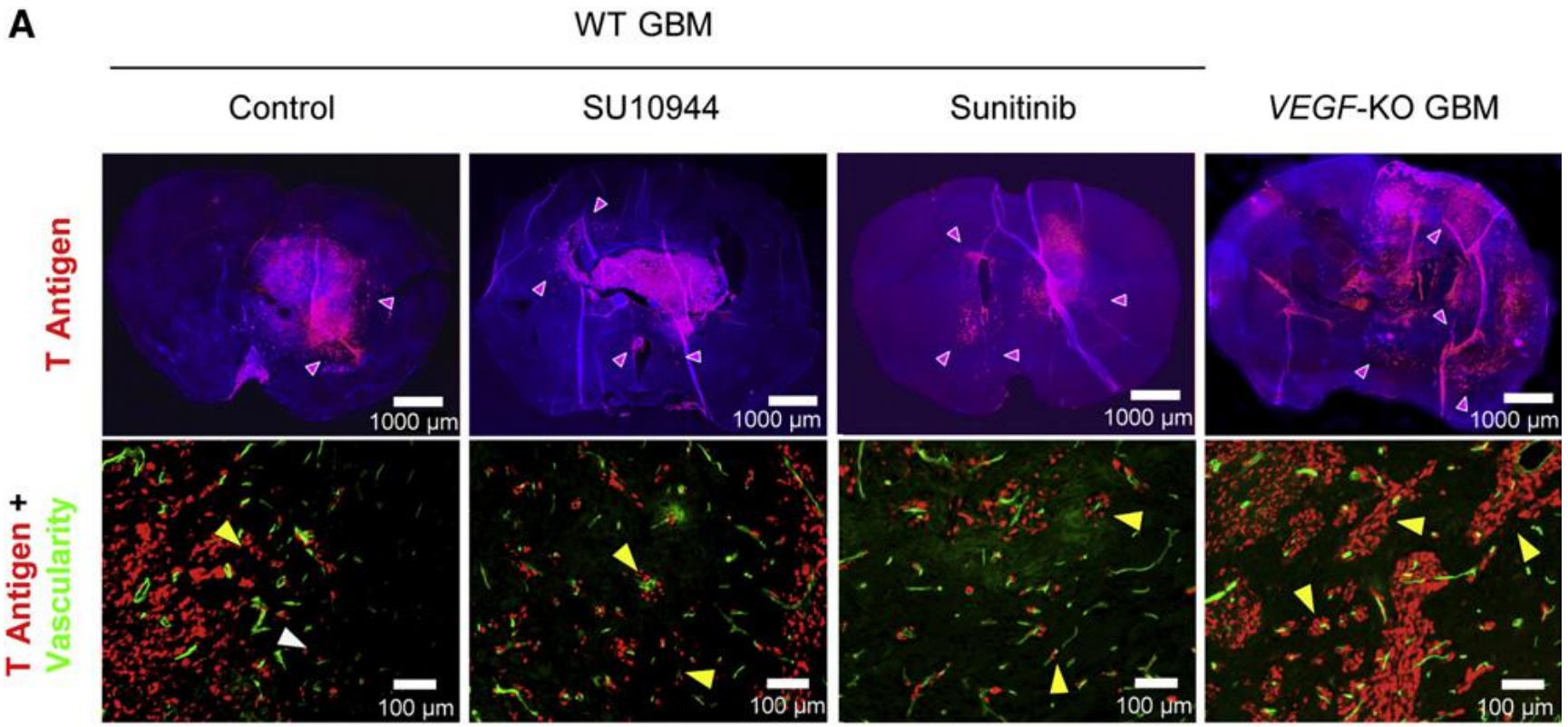
Sunitinib also triggers distant metastases





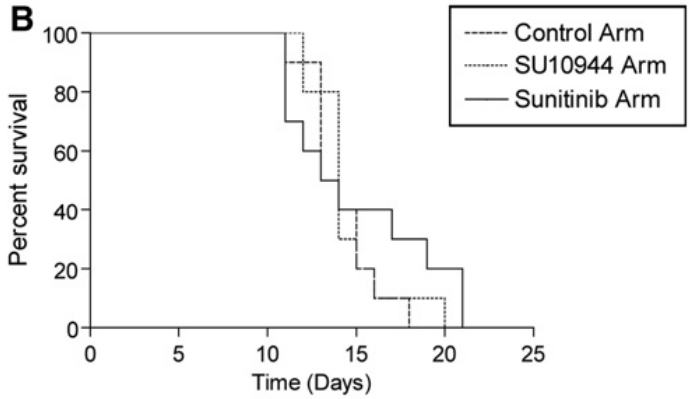
- Sunitinib treatment increased the number of cases of liver metastases
- No particular effect on LN metastases

VEGF Inhibitors also evoke increased invasiveness in orthotopic glioblastoma

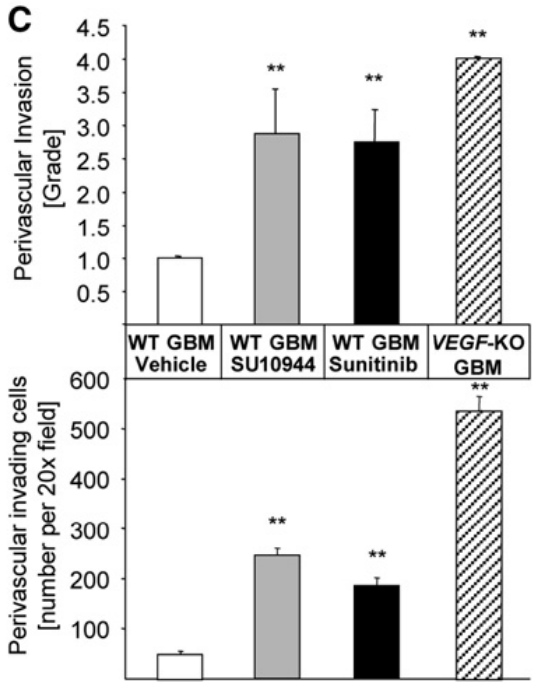


- Thinner tumor vasculature than in control
- Treated GBMs are more invasive and predominantly migrate along blood vessels

VEGF Inhibitors also evoke increased invasiveness in orthotopic glioblastoma



- Sunitinib treatment produced a survival advantage

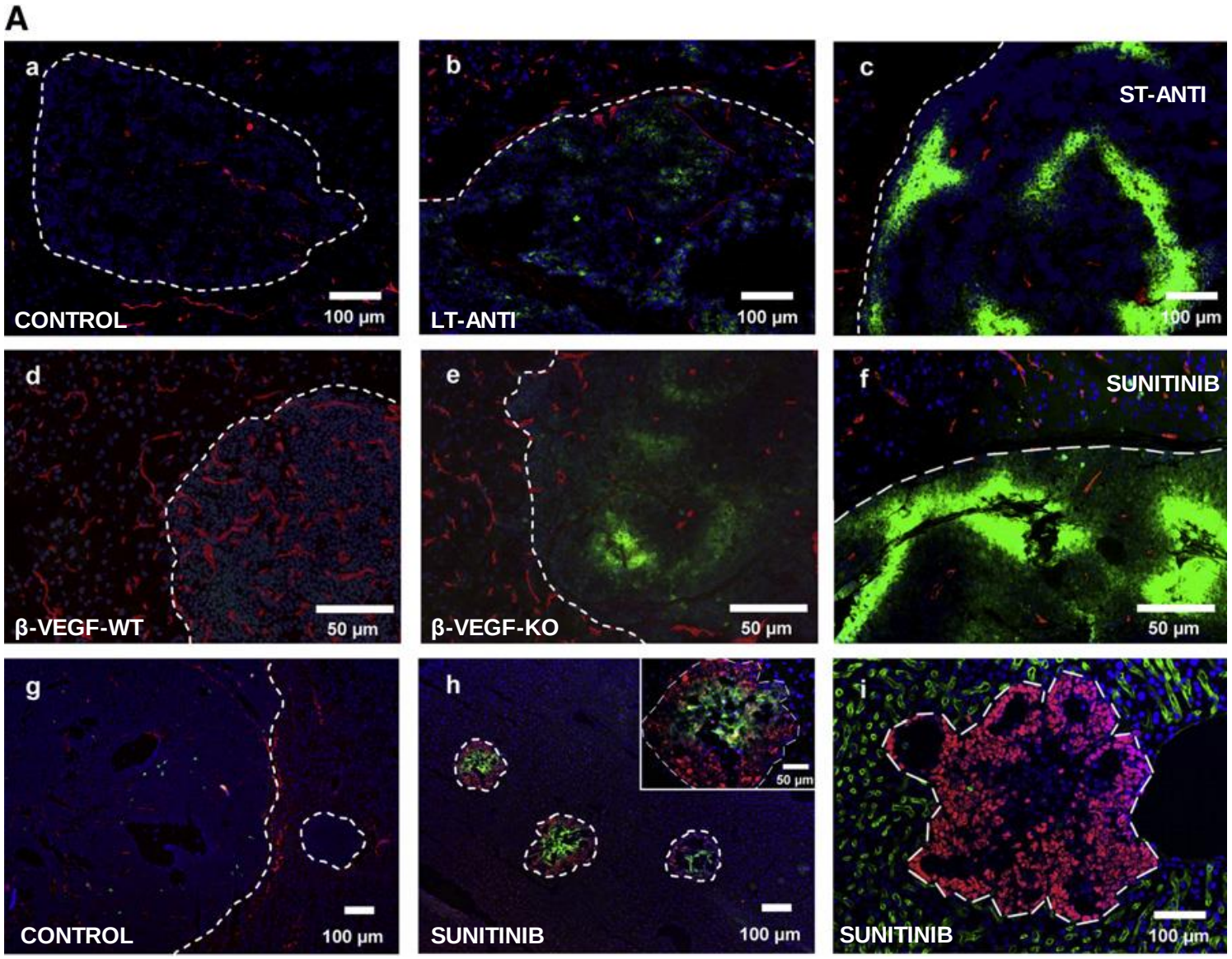


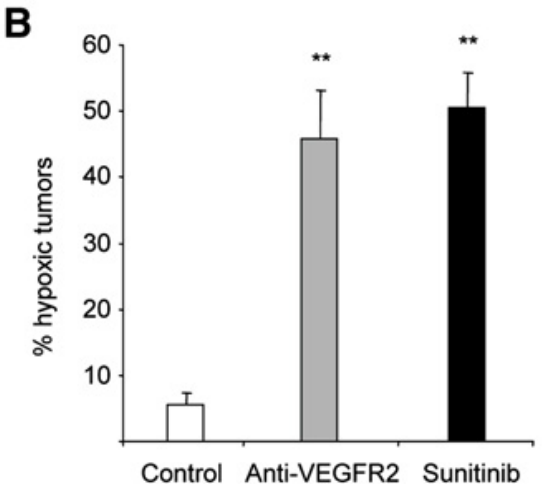
- All treated GBMs show increase in perivascular infiltration
- More pronounced with VEGF-KO mice

Differences could be explained by complete lack of VEGF before tumor formation in VEGF-KO

Hypoxia is implicated in the adaptive response

Pancreas



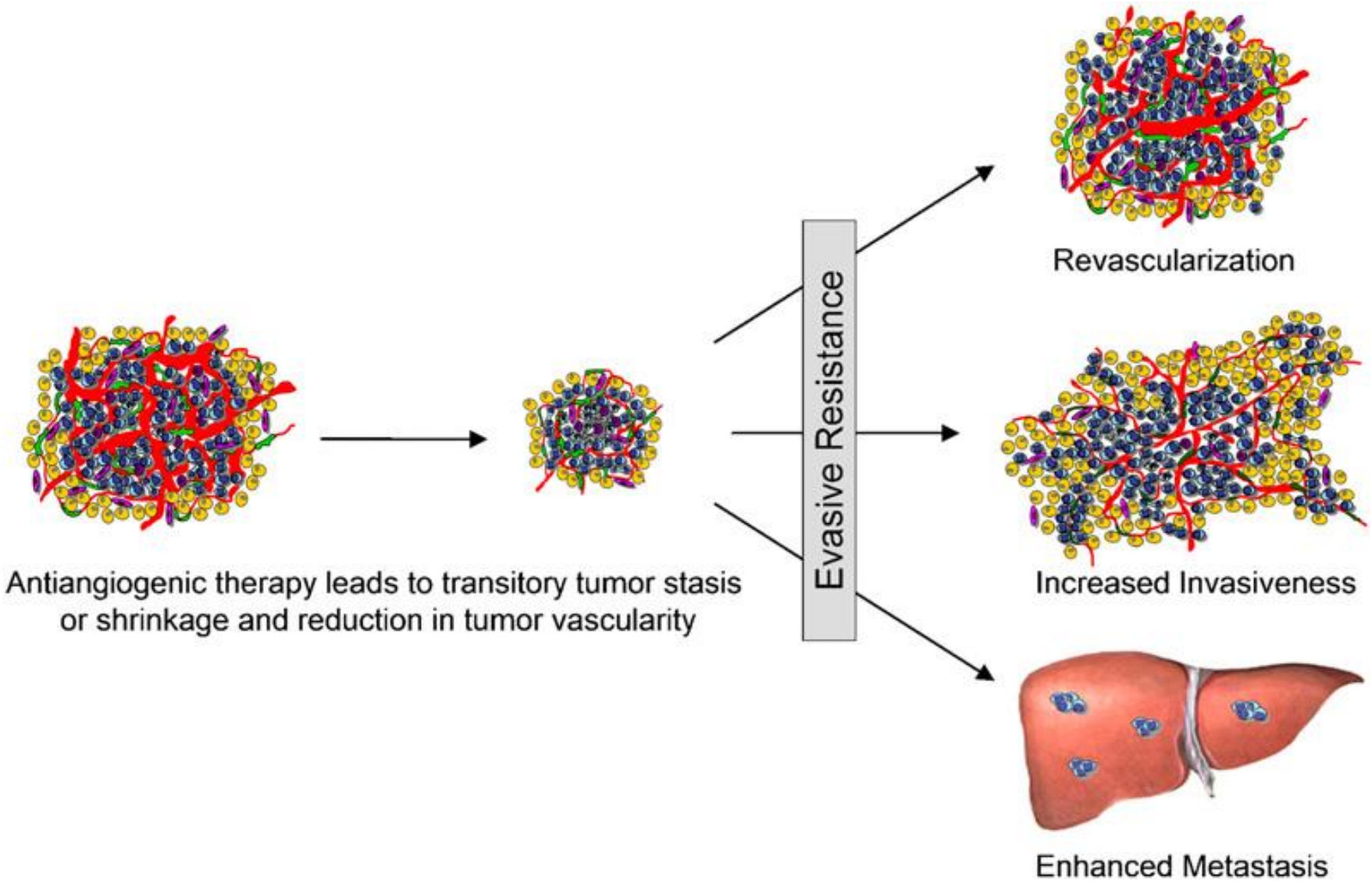


Pimonidazole

CD31+

Liver

Summary


Revascularization
Evasive Resistance
Increased Invasiveness
Antiangiogenic therapy leads to transitory tumor stasis
or shrinkage and reduction in tumor vascularity
Enhanced Metastasis

Thank You for your attention