Paper 2: Anti-VEGF antibody therapy does not promote metastasis in genetically engineered mouse tumour models

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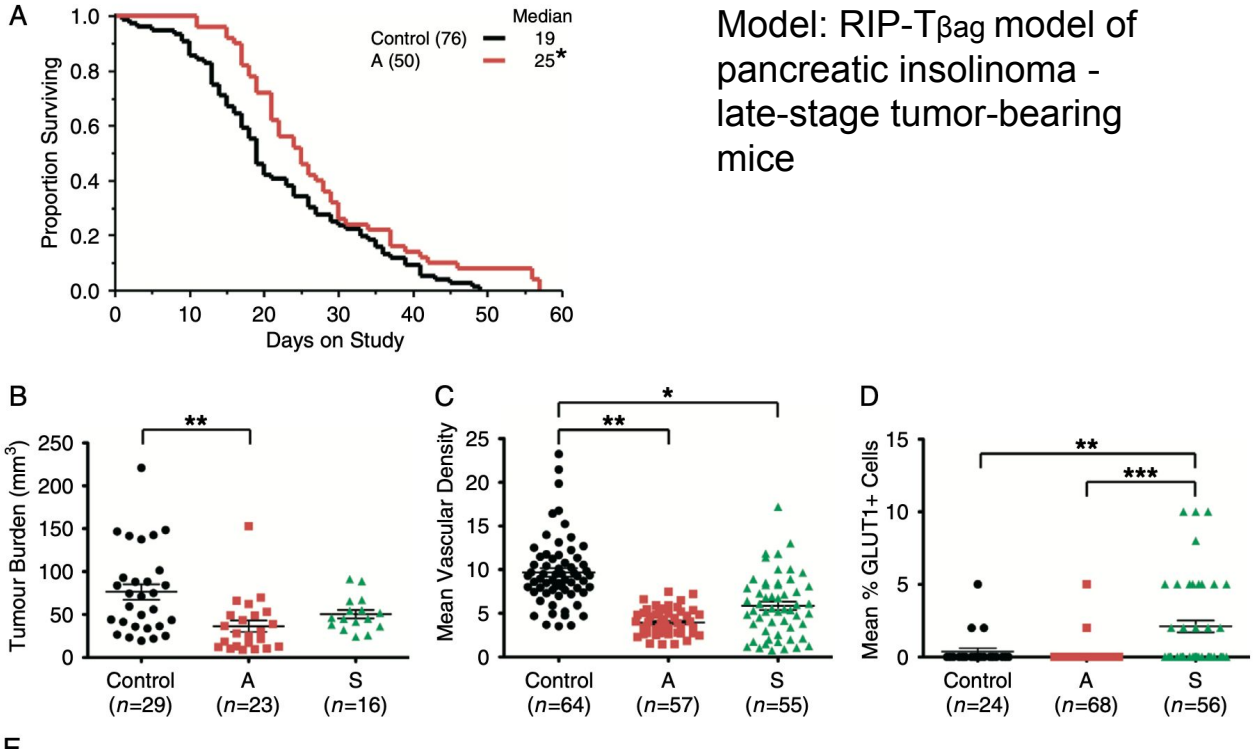
Introduction

- Some previous studies showed that short-term inhibition of VEGF or VEGFR enhanced tumor invasiveness and metastasis in preclinical models
- In this paper, the **long-term and short-term anti-VEGF monoclonal antibody treatment and its consequences on metastatic development** was studied in genetically engineered mouse tumor models of neuroendocrine and epithelial tumors.
- Results were compared to sunitinib treatment (small molecule multi-targeted receptor tyrosine kinase inhibitor)

Figure 1: Anti-VEGF therapy shows efficiency in the regression trial of pancreatic insolinoma model



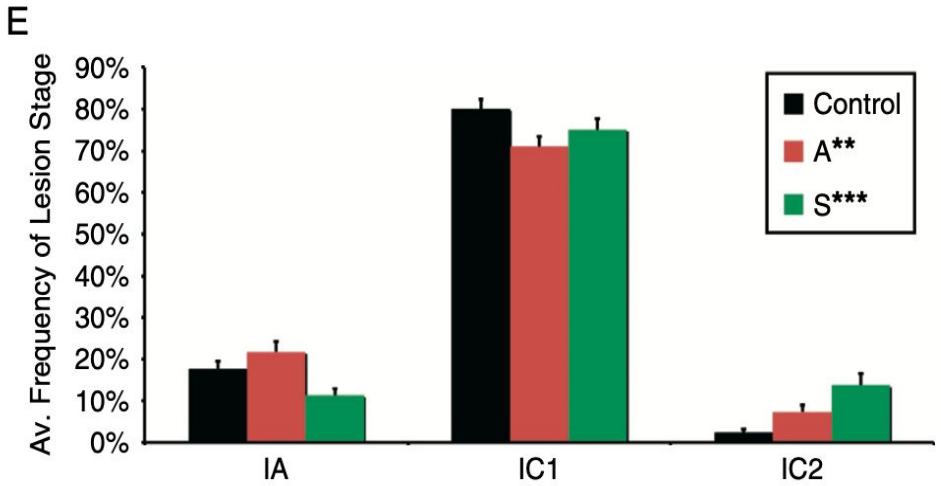
Model: RIP-Tβag model of pancreatic insolinoma - late-stage tumor-bearing mice

- Anti-VEGF shows a benefit in OS (vs CTRL)
- Anti-VEGF and sunitinib show decrease in tumor burden and mean vascular density
- sunitinib shows increase in tumor hypoxia (GLUT1+ percentage)

A: anti-VEGF
S: sunitinib

Figure 1: Evaluation of tumor invasion

IA: benign adenomas
IC1: micro-invasive carcinoma
IC2: macro-invasive carcinoma



A: anti-VEGF
S: sunitinib

- Anti-VEGF shows small significant change in frequency of IA, IC1 and IC2
- sunitiniib shows a clear shift in the tumor stage and grade

Figure 1: Anti-VEGF does not increase metastasis in the lymph node and liver

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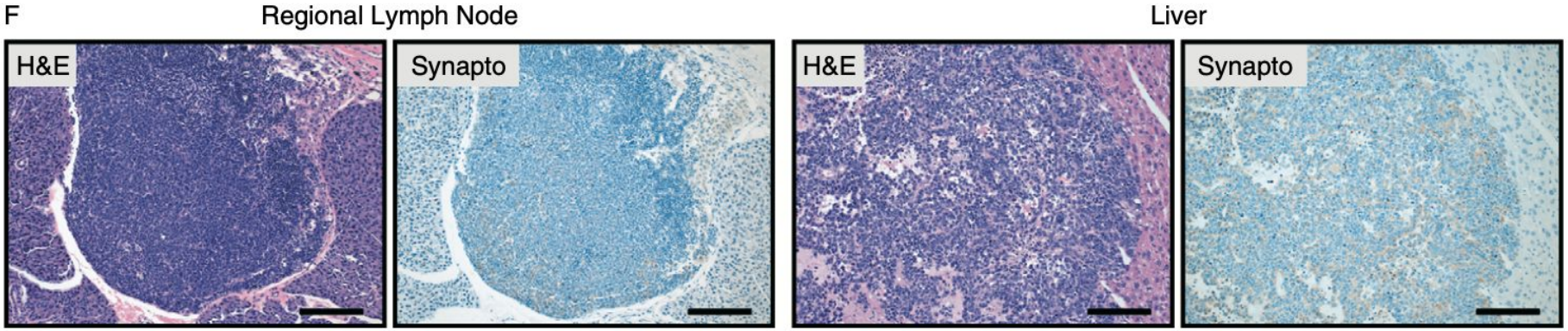

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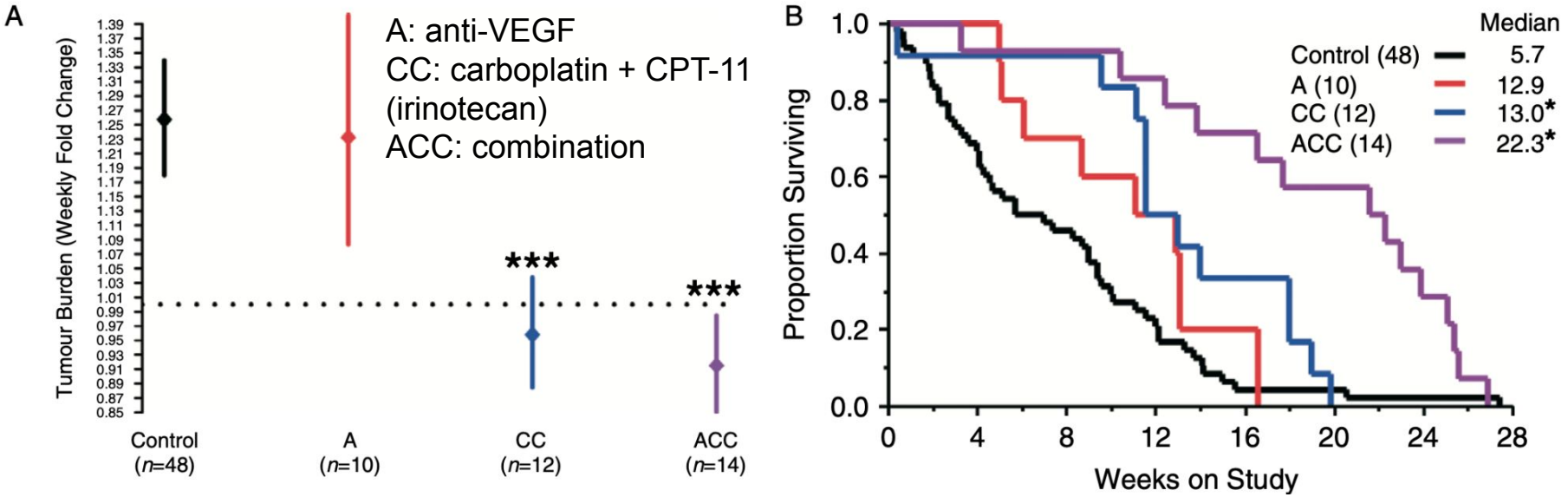
Treatment	SCLC, short-term (14d): # of Positive Mice / Total # Examined				
	Regional Lymph Node Metastases	Liver Metastases		Metastases to Additional Sites* (Macro &/or Micro)	Total # Mice with any Confirmed Mets (Macro &/or Micro)
	Macro	Macro	Micro		
Control	1/12	0/12	1/5	0/12	2/12
Anti-VEGF	2/10	0/10	0/3	0/10	2/10

*LNs, Kidney, Ovary, Heart

Model: RIP-Tβag model of pancreatic insolinoma - late-stage tumor-bearing mice

Figure 2: Efficiency of treatments in SCLC model

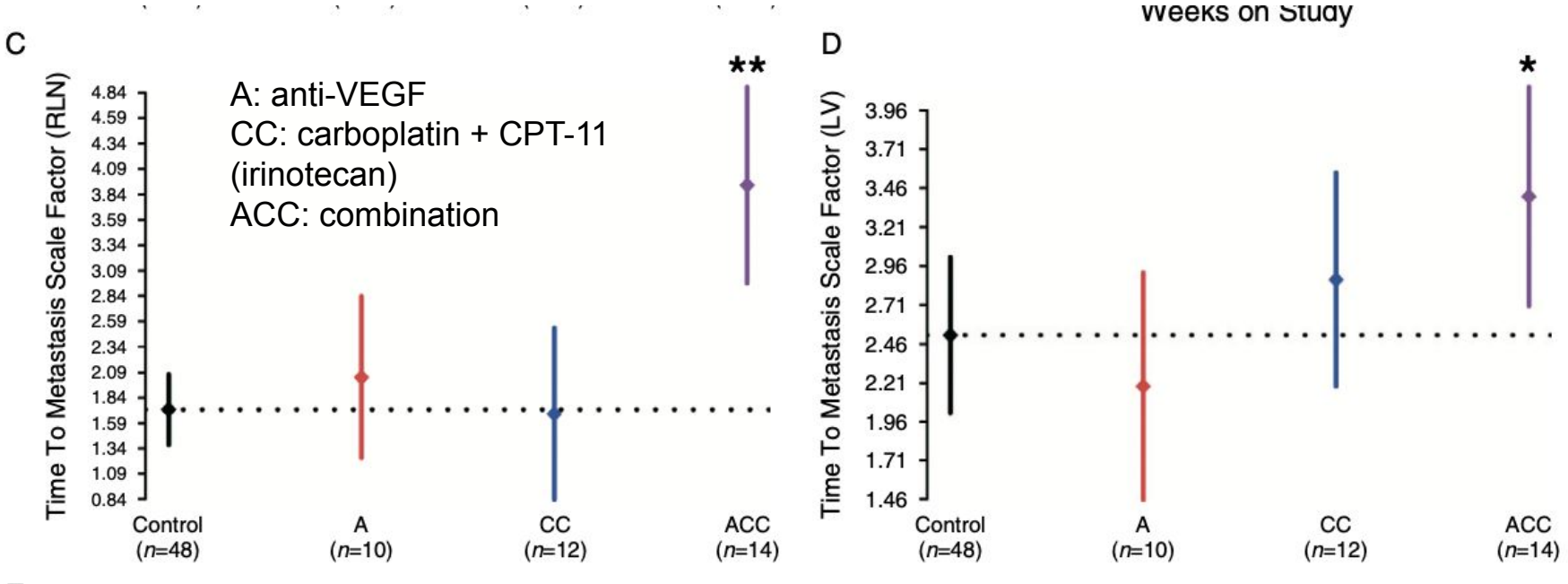
Model: Small cell lung cancer driven by *Rb* and *p53* tumour suppressor inactivation



- Only chemotherapy shows a significant growth inhibition
- Both chemotherapy and combination treatment show benefit in OS

Figure 2: Impact of treatment on metastases

Model: Small cell lung cancer driven by *Rb* and *p53* tumour suppressor inactivation



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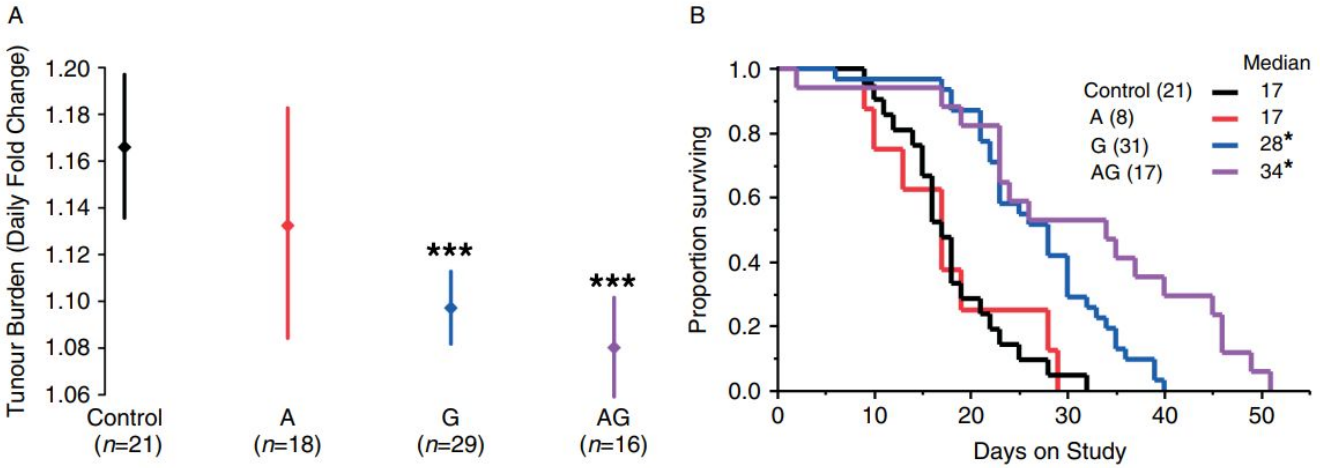
Only the combination treatment shows a statistically significant increase in the time to metastasis scale factor

Figure 3a & 3b - Anti-VEGF effects in GEMM of PDAC

Model: Kras mutant model of pancreatic ductal adenocarcinoma (PDAC)



- A: anti-VEGF treatment
- G: gemcitabine (chemotherapy)
- AG: combination of gemcitabine and anti-VEGF
- Chemotherapy and combination therapy display slower tumor growth and higher survival rates

Figure 3c & 3d - RLN and liver metastases

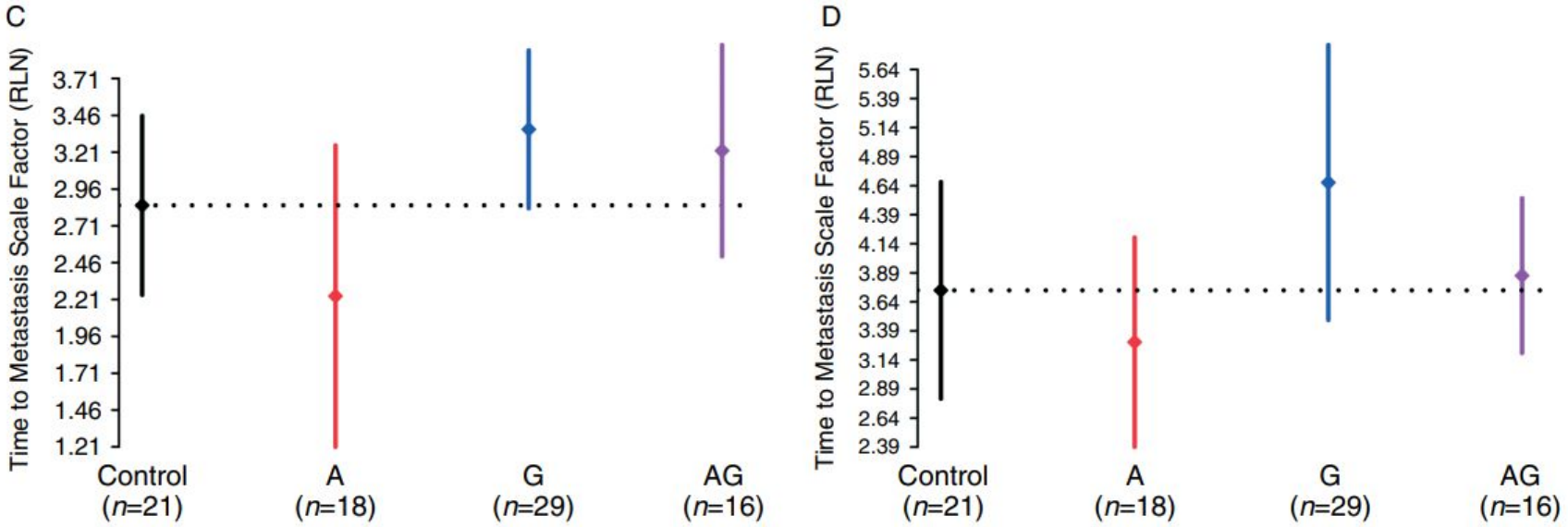


Figure 3e, 3f

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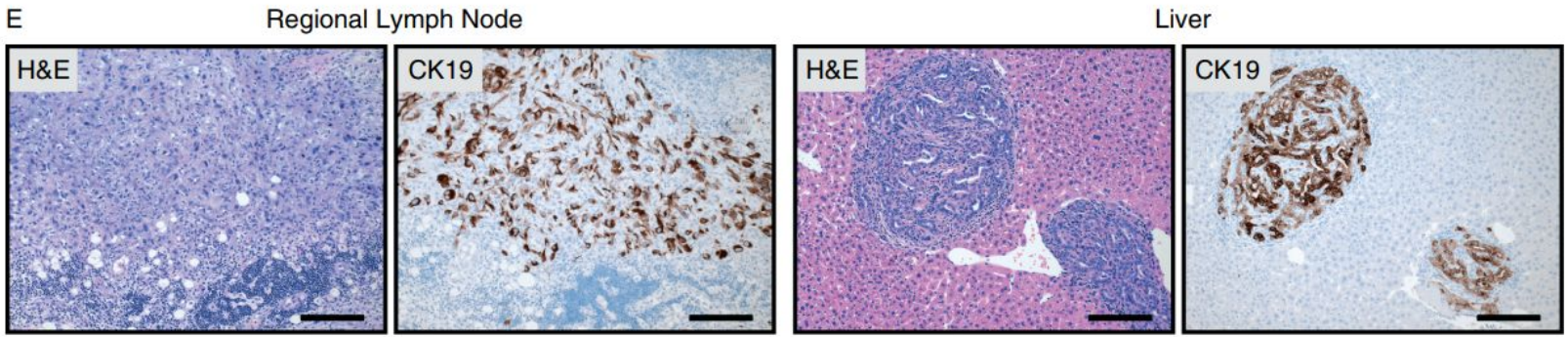

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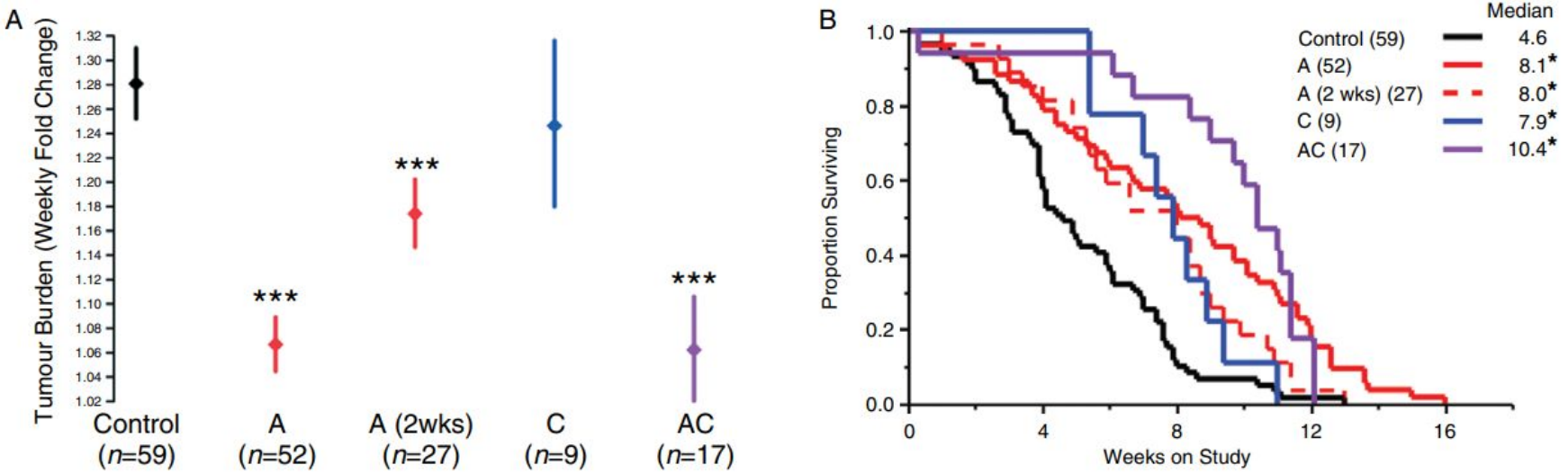
Treatment	PDAC, short-term (7d): # of Positive Mice / Total # Examined		
	Regional Lymph Node Metastases	Liver Metastases	Total # Mice with any Confirmed Met
Control	0/9	0/9	0/9
Anti-VEGF	1/4	0/4	1/4
Gemcitabine	1/7	1/7	2/7
Anti-VEGF+Gemcitabine	0/4	0/4	0/4

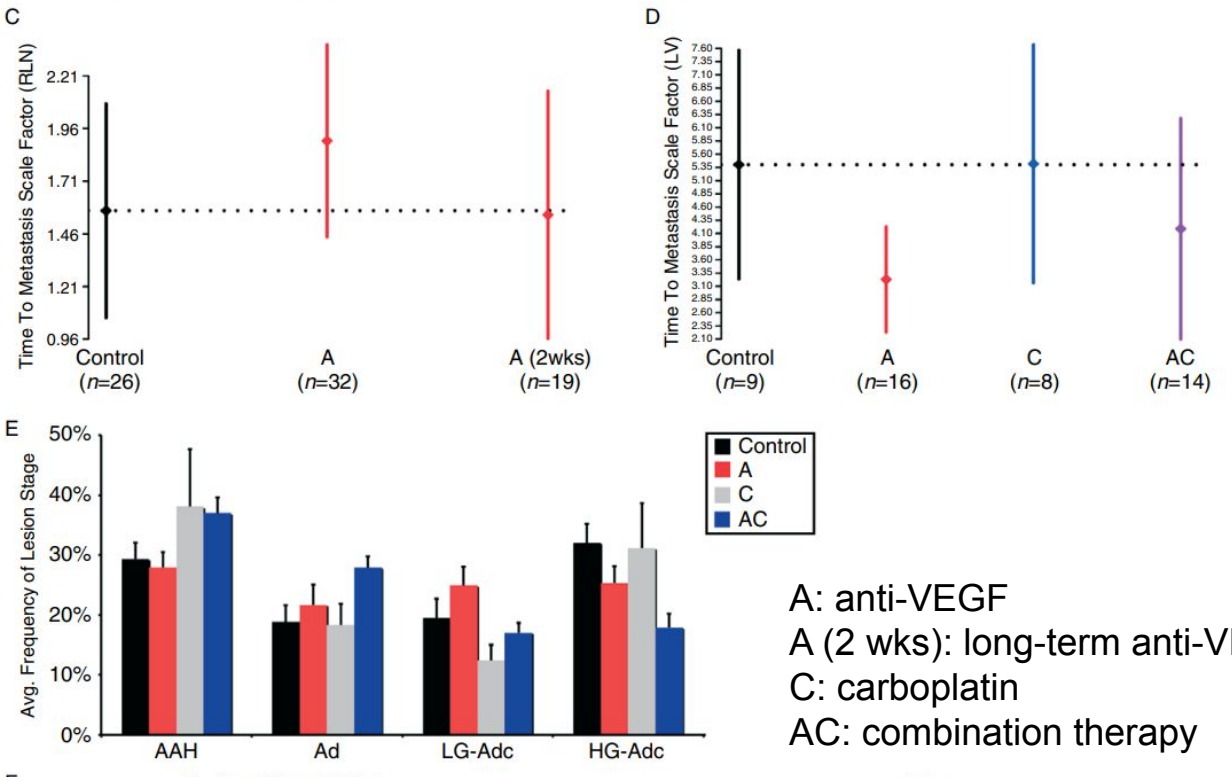
Figure 4a & 4b

Model: Kras and p53 mutant model of non-small cell lung carcinoma (NSCLC)



A: anti-VEGF
A (2 wks): long-term anti-VEGF
C: carboplatin
AC: combination therapy

Figure 4c, 4d & 4e



A: anti-VEGF
A (2 wks): long-term anti-VEGF
C: carboplatin
AC: combination therapy

Figure 4f & 4g

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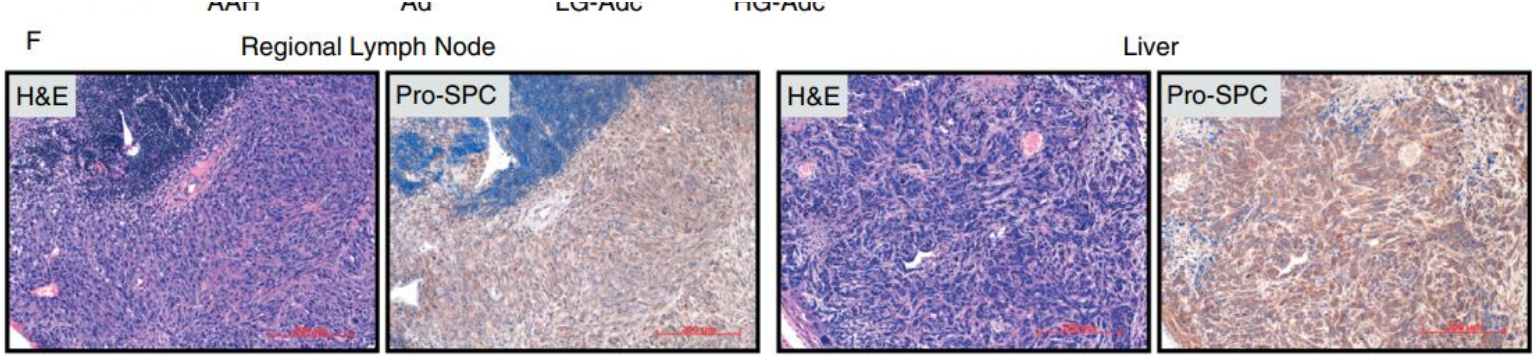

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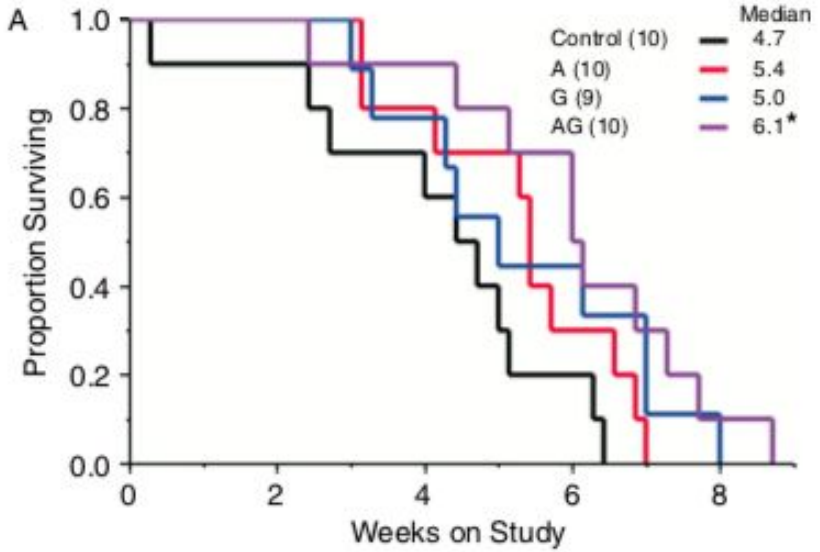
Treatment	NSCLC, short-term (14d): # of Positive Mice / Total # Examined					
	Regional Lymph Node Metastases		Liver Metastases		Metastases to Additional sites* (Macro &/or Micro)	Total # Mice with any Confirmed Mets (Macro &/or Micro)
	Macro	Micro	Macro	Micro		
Control	1/16	0/9	0/16	0/7	0/16	1/16
Anti-VEGF	0/18	0/10	0/18	1/3	0/18	1/18
Carboplatin	0/8	0/7	0/8	0/3	0/8	0/8
Anti-VEGF+Carboplatin	0/10	0/8	0/10	0/10	0/10	0/10

*LNs, Epicardium, Kidney, Rib Cage, Heart

Figure 5A - anti-VEGF treatment in PDAC mice model

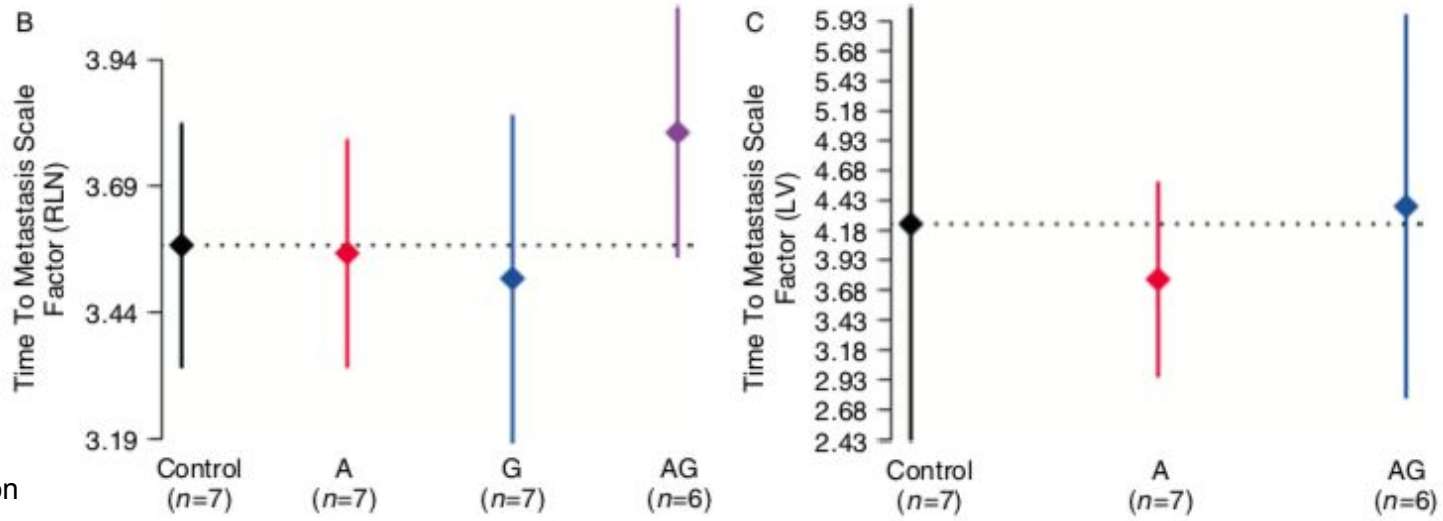
- series of prevention experiments → can anti-VEGF therapy impact early-stage disease?
- Contrast to late-stage treatment: anti-VEGF monotherapy results in insignificant OS benefit, but combination has significant OS benefit



A = anti-VEGF
G = gemcitabine
AG = combination

Figure 5B & C - anti-VEGF treatment in PDAC mice model doesn't show increase in time to metastasis

- assessment of the metastatic incidence in the RLNs and LV:
  - no significant differences in the probability of observing micro-metastases
  - trend towards an increase in the time required to detect RLN metastases in the combination group

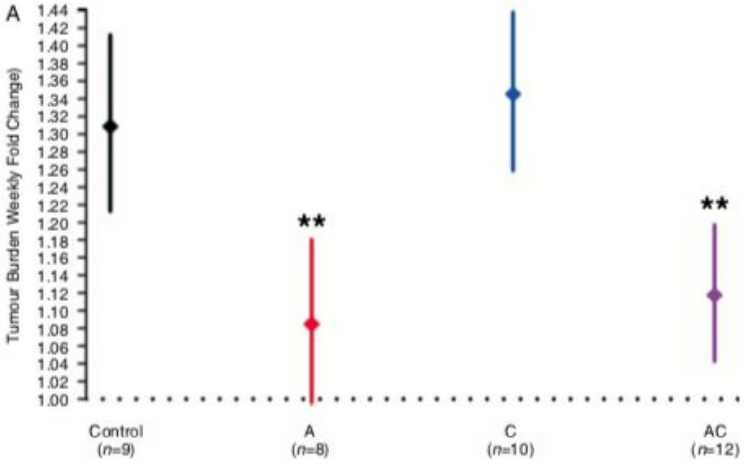


A = anti-VEGF
G = gemcitabine
AG = combination

Figure 6A - anti-VEGF treatment in NSCLC mice model shows decrease in tumor burden

- Anti-VEGF mono- and combination therapy with carboplatin: inhibition of tumour growth.
- Carboplatin alone did not impact tumour growth in either the prevention or regression (Figure 4A) setting.

A = anti-VEGF
C = carboplatine
AC = combination



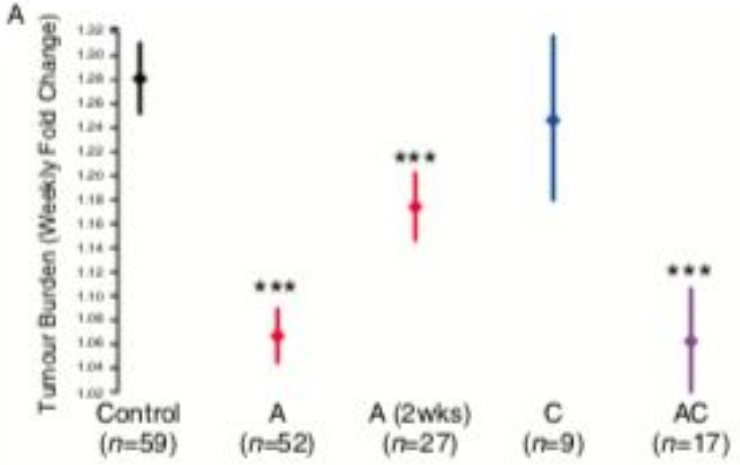


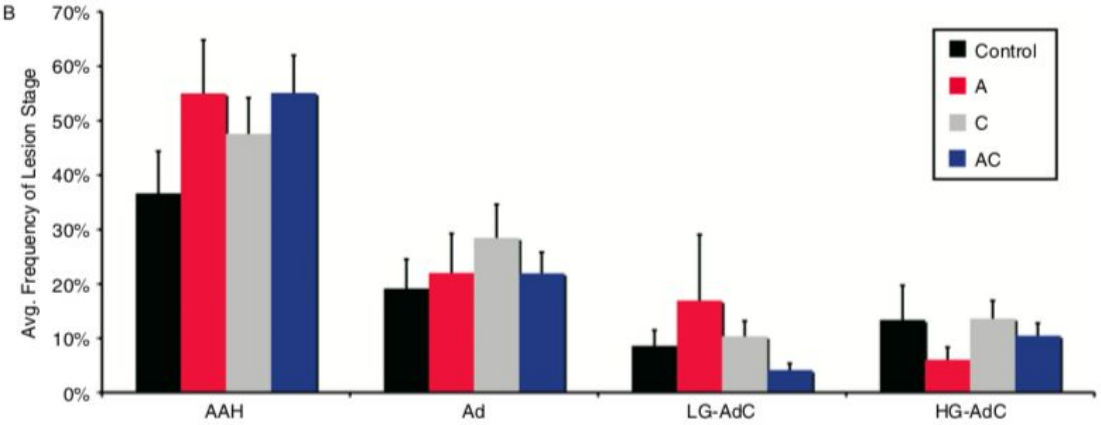
Fig. 4A

Figure 6B & C - anti-VEGF treatment in NSCLC mice model

- in anti-VEGF treated mice:
  - reduced numbers of lung lesions per mouse
  - decreased frequency of HG-AdC (high grade adenocarcinoma)
  - increased frequency of earlier-stage AAH
- Rare lesions in the RLNs and LV and no significant differences between any of the groups.

A = anti-VEGF
C = carboplatine
AC = combination

B



C

Treatment	NSCLC, long-term (Prevention): # of Positive Mice / Total # Examined					
	Regional Lymph Node Metastases		Liver Metastases		Metastases to Additional Sites* (Macro &/or Micro)	Total # Mice with any Confirmed Mets (Macro &/or Micro)
	Macro	Micro	Macro	Micro		
Control	1/9	0/9	0/9	0/7	2/9	2/9
Anti-VEGF	0/8	0/8	0/8	0/7	0/8	0/8
Carboplatin	0/10	0/10	0/10	0/10	1/10	1/10
Anti-VEGF+Carboplatin	0/12	0/12	0/12	0/10	1/12	1/12

*LNs, Epicardium, Kidney, Rib Cage, Heart

Results

- Anti-VEGF therapy decreased tumor burden and increased overall survival, either as a single agent or in combination with chemotherapy
- Neither short nor long-term exposure to anti-VEGF seemed to alter incidence of metastasis in the mouse tumor models
- Sunitinib treatment increases metastasis in pancreatic neuroendocrine tumors, as previously shown by other studies