



The effect of sorafenib on In-111 labeled bevacizumab uptake in patients with clear cell renal cell carcinoma

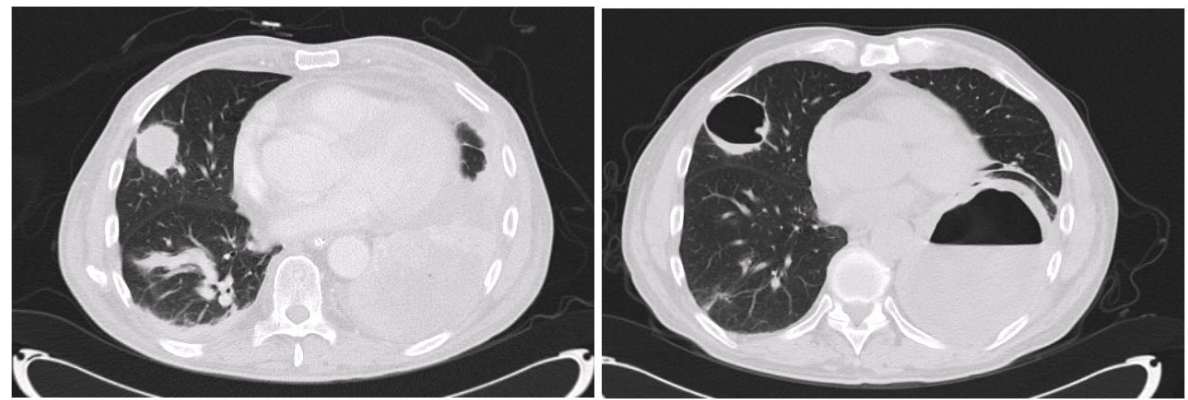
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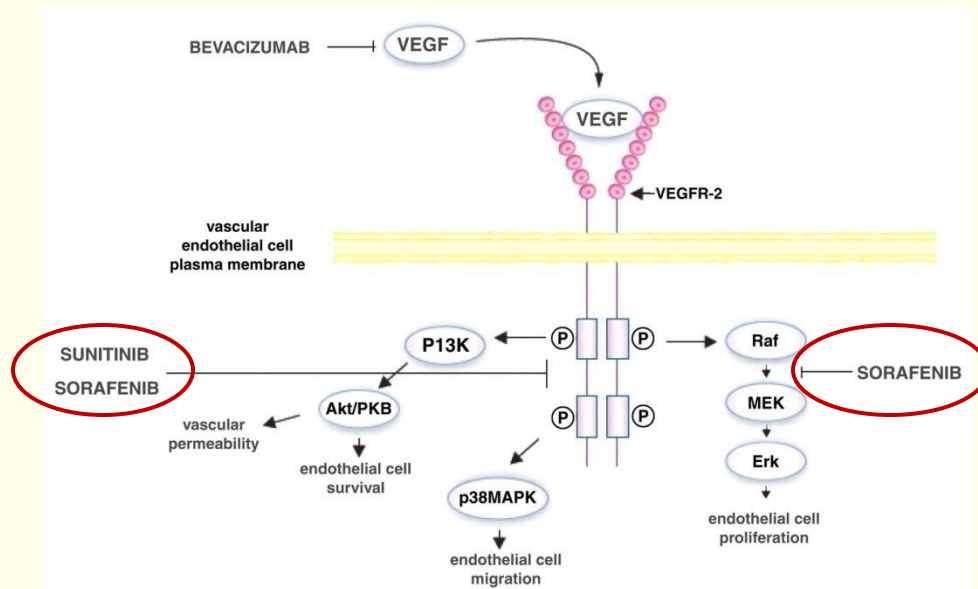
Background

- Angiogenesis inhibition as treatment strategy in mRCC
- Effective biomarkers of response are lacking
- Volumetric RECIST is insufficient



Sorafenib

- Sorafenib = tyrosine kinase inhibitor
- Targets: VEGFR2, VEGFR3, FLT-3, c-KIT, PDGFR, B-RAF, C-RAF
- Single agent treatment
PFS 3 → 6 months
OS 14.3 → 17.8 months
- Approved for mRCC
- Dose: 400 mg bid orally



Rini et al. JCO 2005;23:1028



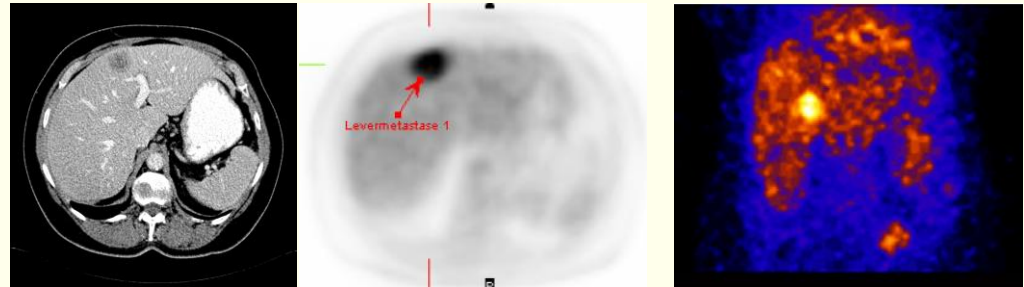
Neoadjuvant sorafenib study

- Aim:
 - To evaluate the effect of neoadjuvant sorafenib treatment on uptake of ^{111}In -bevacizumab in RCC

In-111-bevacizumab scintigraphy

- Bevacizumab is a monoclonal antibody (mAb) against VEGF (vascular endothelial growth factor)

- Scintigraphic imaging with ^{111}In -bevacizumab



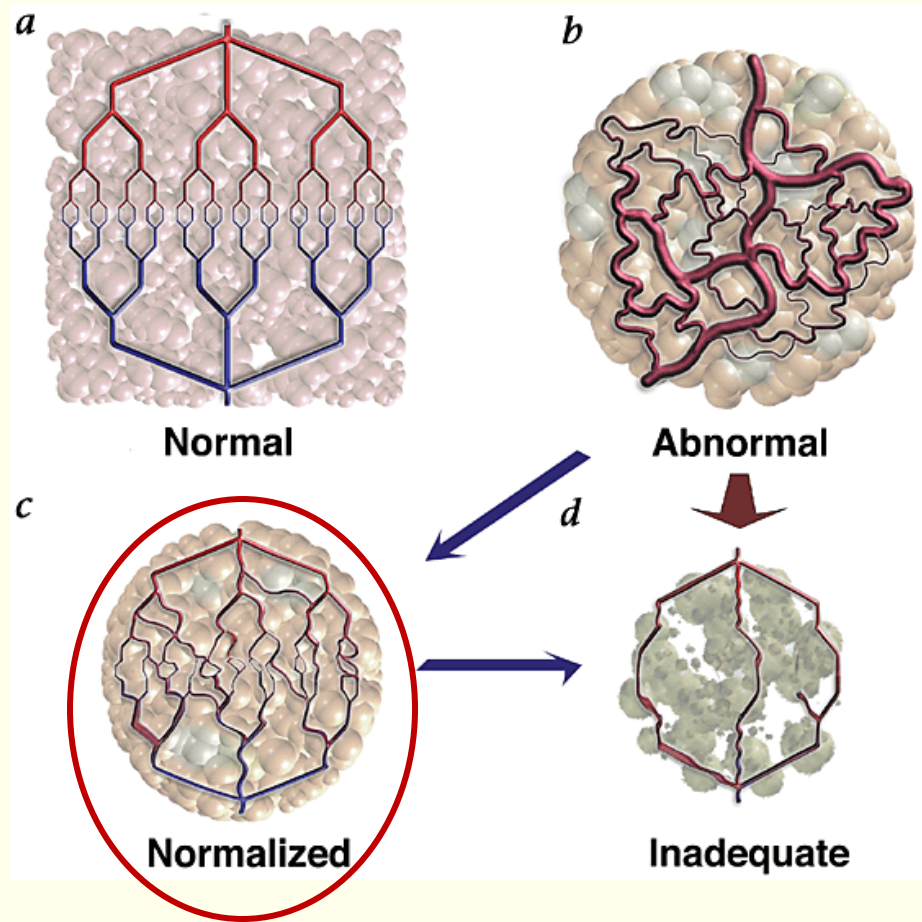
Adapted from: Stollman et al. Int J Cancer 2008

- Penetration and accumulation of mAbs in solid tumors is limited due to:
 - High interstitial fluid pressure (IFP)
 - Abnormal tumor vessels

What is the influence of sorafenib on uptake?

- Sorafenib
 - Reduces microvessel density
 - Reduces IFP
 - Normalizes tumor vasculature

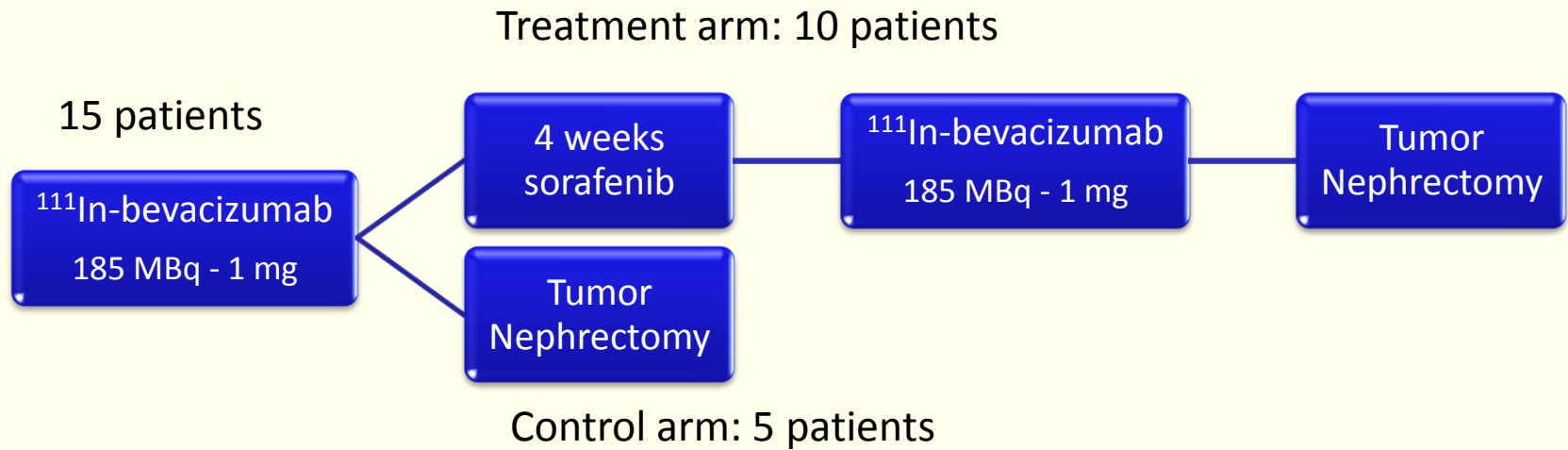
- Hypothesis:
 - IFP↓ and normalization of tumor blood vessels → higher uptake of mAbs in ccRCC?



Jain RK, Nature Medicine, 2001; vol 7, 987-989



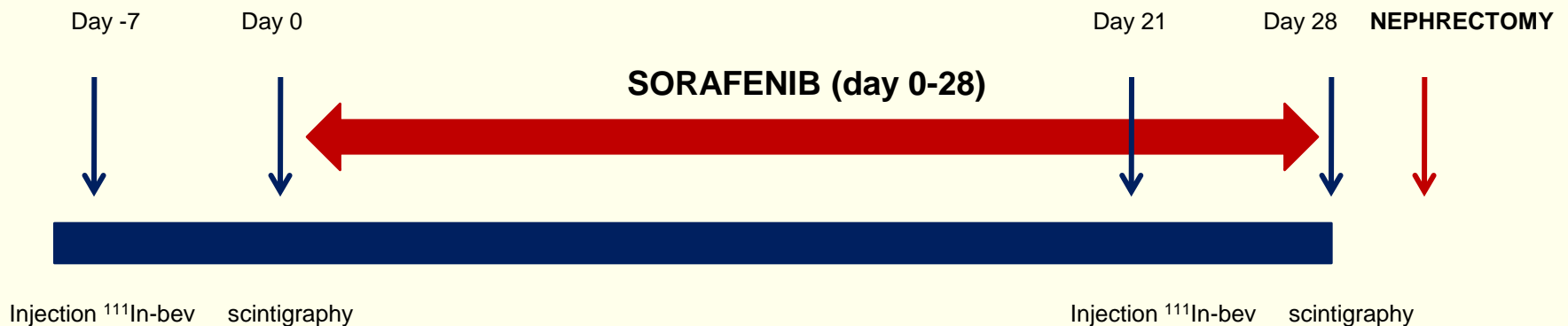
Study flow chart





^{111}In Indium-bevacizumab scintigraphy

- 1 mg DTPA-conjugated bevacizumab labeled with 100 MBq ^{111}In Indium iv
- Whole body scan after 7 days
- After nephrectomy: radioactivity was counted in a 1 cm slice





Results – Targeting and IHC

Control arm (n=5), mean(range)

Pathology	Volume (cm ³)	%ID/g	Targeting	VEGF-A staining	CD-31 staining
ccRCC (5x)	247 (13-622)	0.012 (0.002-0.028)	High (5x)	++ (+ - +++)	++ (+ - +++)

Treatment arm (n=10), mean(range)

	Pathology	Volume (cm ³)	%ID/g	Change in targeting	VEGF-A staining	CD-31 staining
Before Sorafenib	ccRCC (9x) oncocytoma (1x)	416 (3.7 -1450)	0.019 (0.002-0.057)	-60% (+1.4 - -90%) (p=0.011)	++ (+ - +++)	+/- (neg - +++)
After Sorafenib			0.007 (0.001-0.029)			

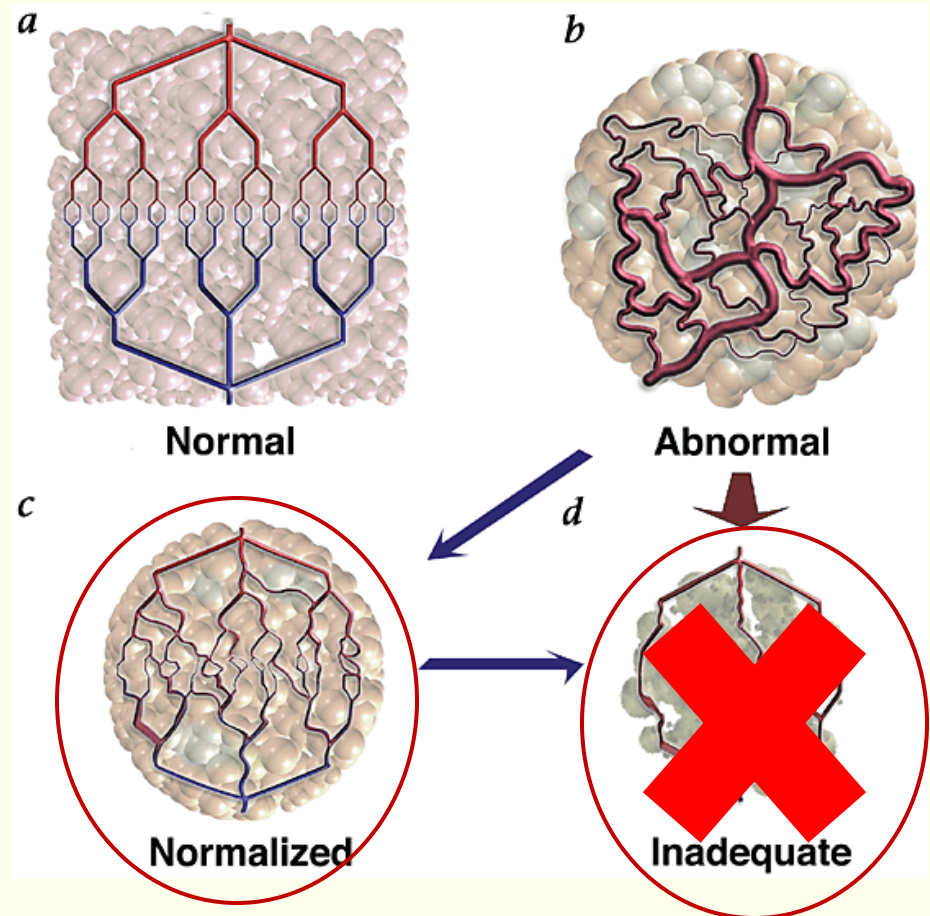


Conclusions

- High tumor uptake of ^{111}In -bevacizumab in ccRCC
- Decreased tumor uptake after neoadjuvant treatment with sorafenib
- Decreased uptake is the result of damaged tumor vasculature, VEGF expression remained intact.
- ^{111}In -bevacizumab scintigraphy can be interesting for the evaluation of treatment effect of angiogenesis inhibitors in ccRCC

Future

- Optimization of time window:
effect of 1 week treatment with sorafenib?
- Combination therapy based on vessel normalization:
enhanced delivery of a second agent?





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