Tumor Hypoxia as a Target in Oncology?

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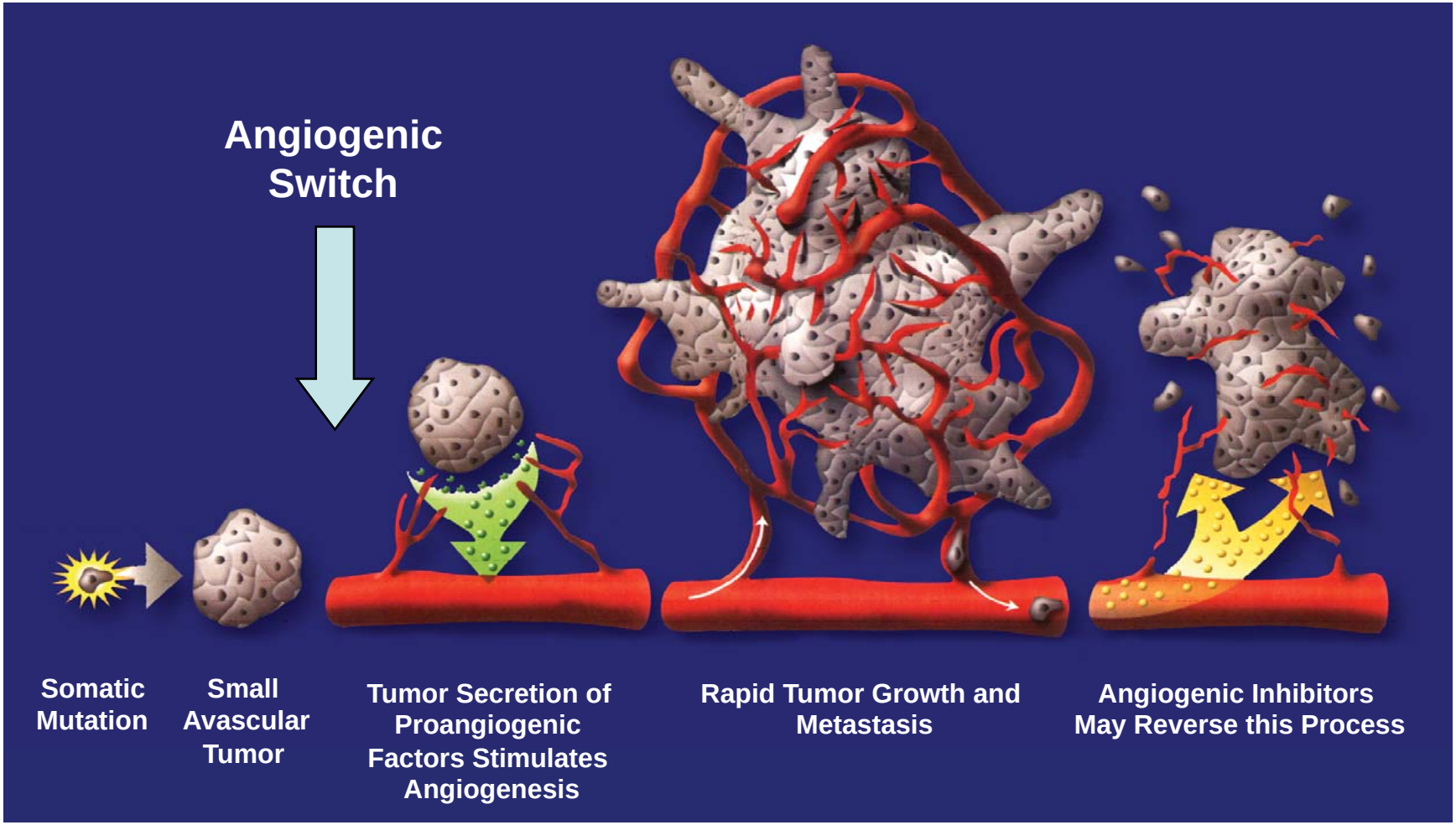
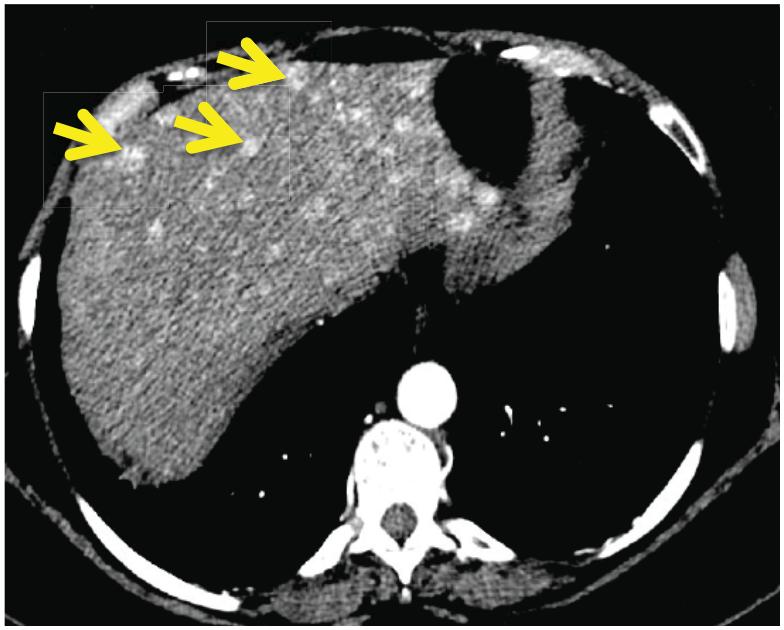
FOLKMAN: 1971

The story began with a simplistic but quite realistic cartoon on the role of tumor angiogenesis

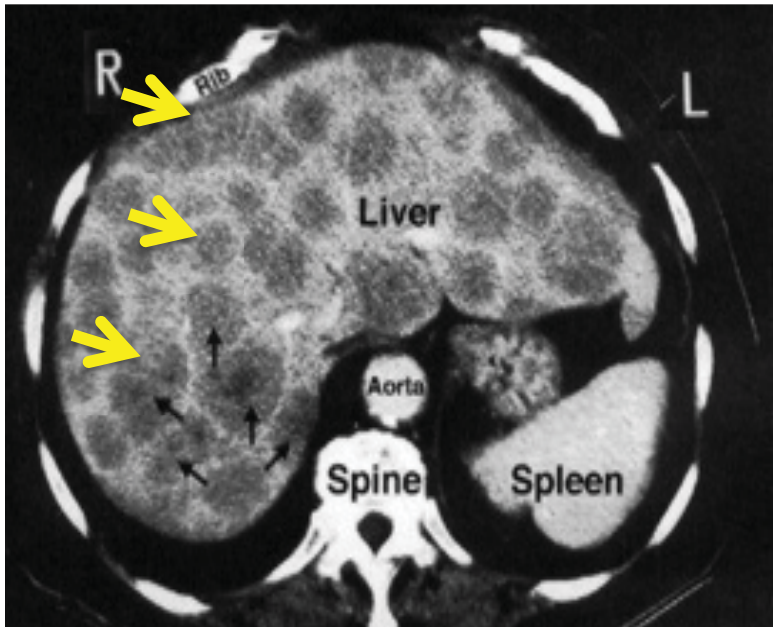


Most clinical observations fit with the Folkman theory although the process may have different patterns over time

Early metastatic liver implantation



Late development of liver metastasis

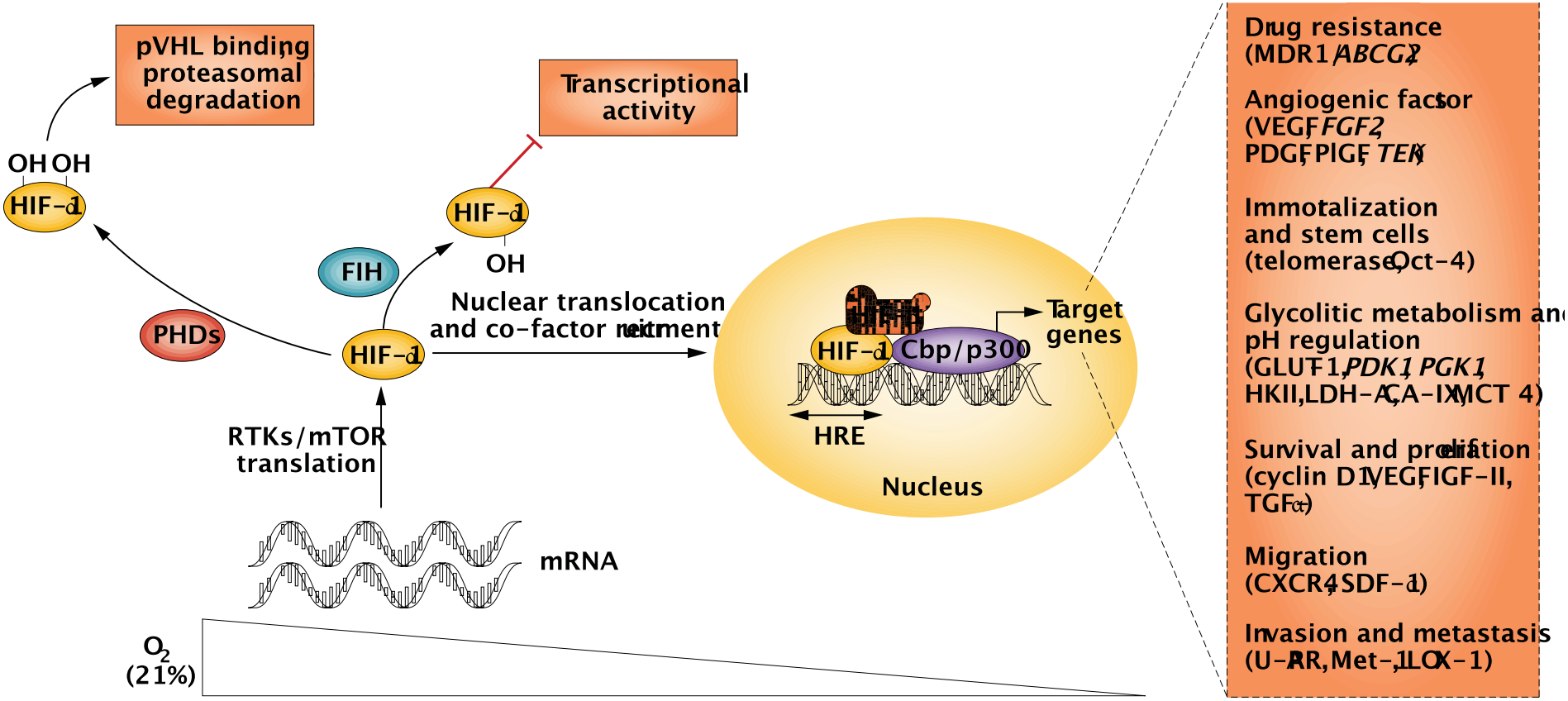


- Small tumor size
- Highly vascularized

Time

- Large tumor size
- Centrifuge expansion
- Well vascularized at the rim
- Necrotic/fibrotic at the center
- Reseeding of metastases

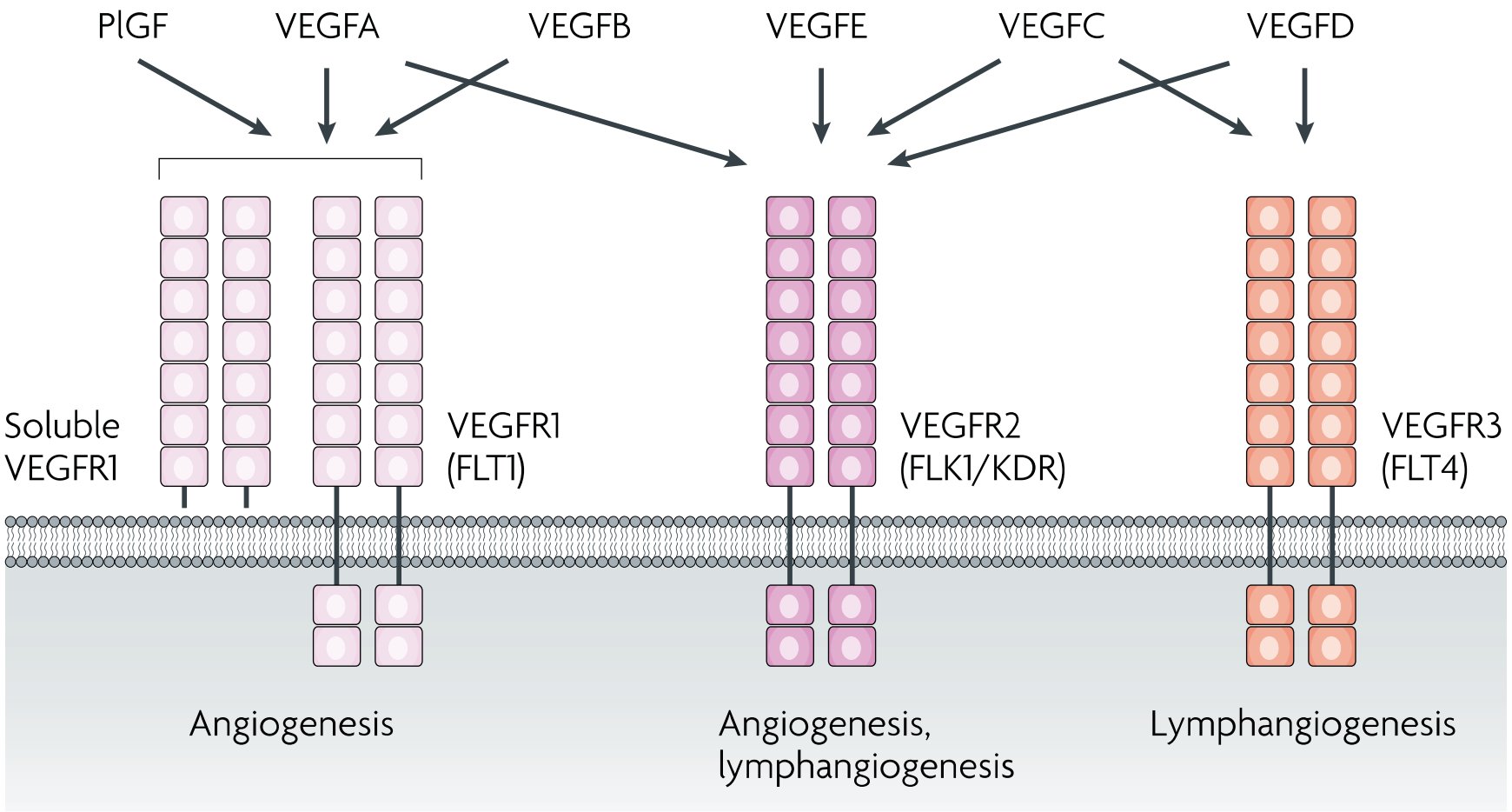
Regulation of HIF-related pathways under hypoxic conditions



Faivre et al. *Targeted Oncol* 2012;7:127−133

Rapisarda et al. *Nat Reviews* 2012;9:378−390

The VEGF/VEGFR axes have captured the attention of the scientific and medical community for now more than 10 years



Molecular basis for sunitinib efficacy and future clinical development

Sandrine Faivre, George Demetri‡, William Sargent§ and Eric Raymond**

HIF pathway addicted tumor types

Tumor types	Trial outcomes using antiangiogenic agents
Renal cell carcinoma VHL, VEGFR, mTOR	Sunitinib, temsirolimus, sorafenib, everolimus, axitinib, pazopanib, bevacizumab
Neuroendocrine tumors VHL, VEGFR, MEN, mTOR	
Pancreatic	Sunitinib, everolimus, bevacizumab?
Mid-gut	Everolimus? sunitinib?
Primary liver tumors VEGFR, mTOR	
Hepatocarcinoma	Sorafenib (other VEGFR inhibitors have activity but are not more effective or are more toxic)
Cholangiocarcinoma	Sunitinib?
Squamous cell carcinoma VEGFR, mTOR	Trial failures due to the development of on-target toxicity: bleeding, cavitations, necrosis, …)
Lung, Head & Neck	*Bevacizumab, sunitinib, sorafenib*

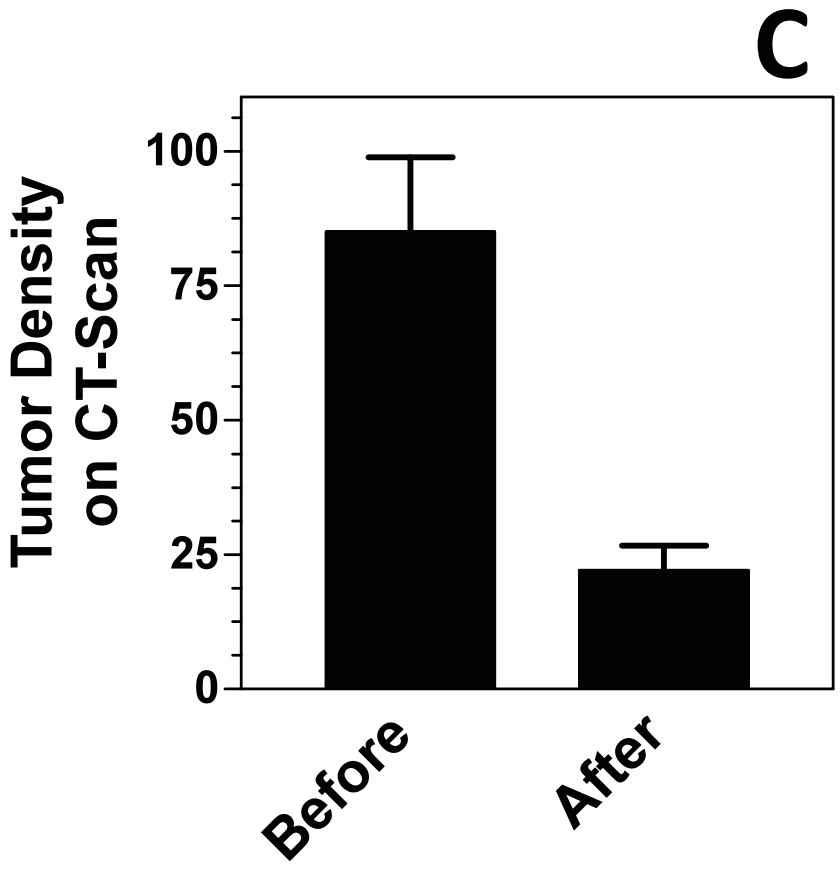
What can we learn from typical examples

VEGF/VEGFR-ADDICTED TUMORS

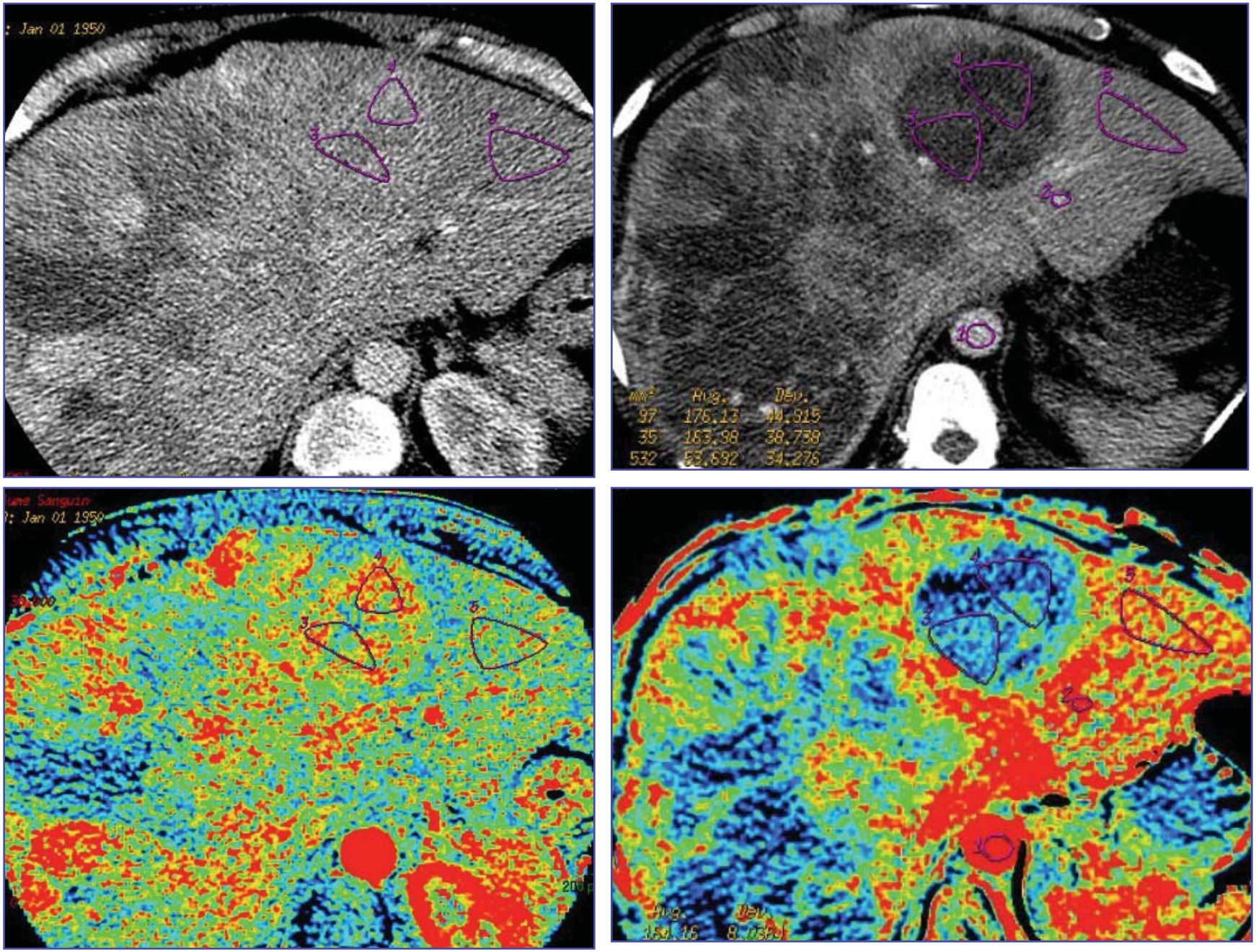
Dramatic tumor responses can rapidly be obtained using VEGFR-targeted agents

Emergence of resistance will emerge in most patients, the pattern of tumor progression in the clinic being very similar from one tumor type to another

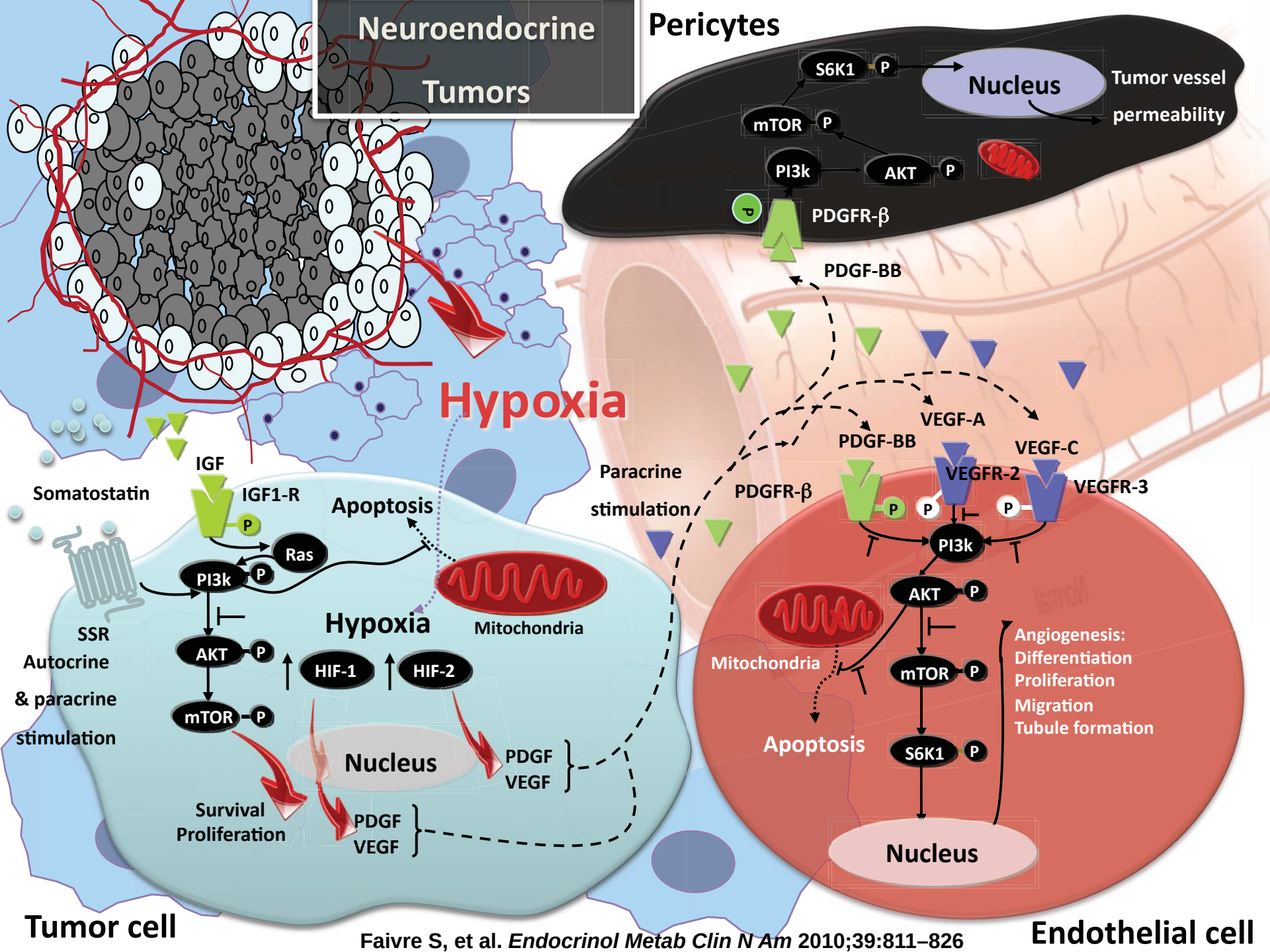
Sunitinib in Hepatocellular Carcinoma



Faivre S et al, J Clin Oncol 2010

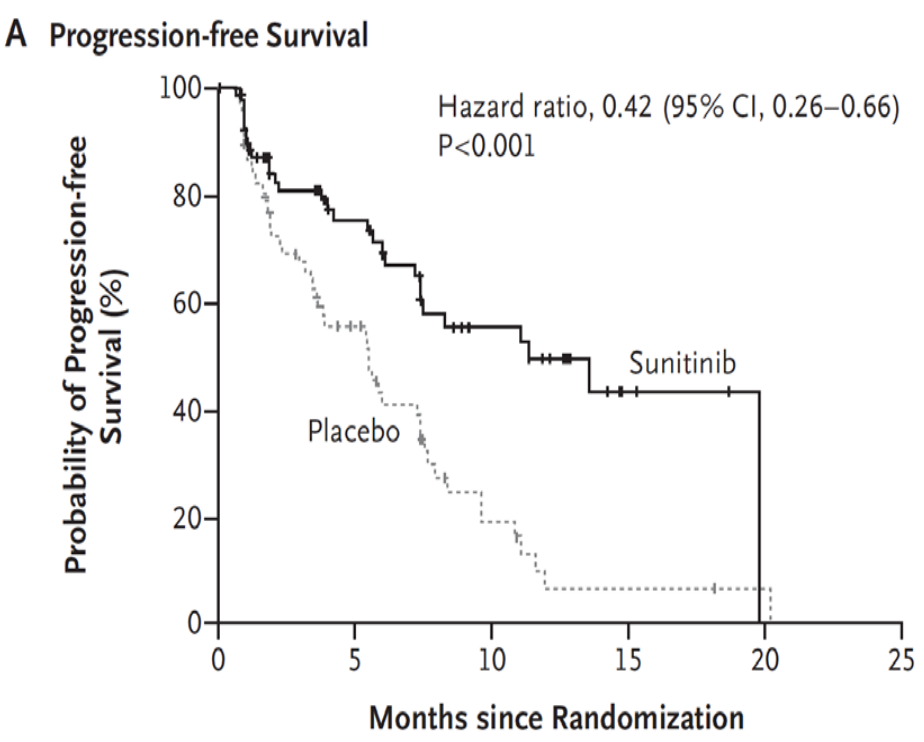


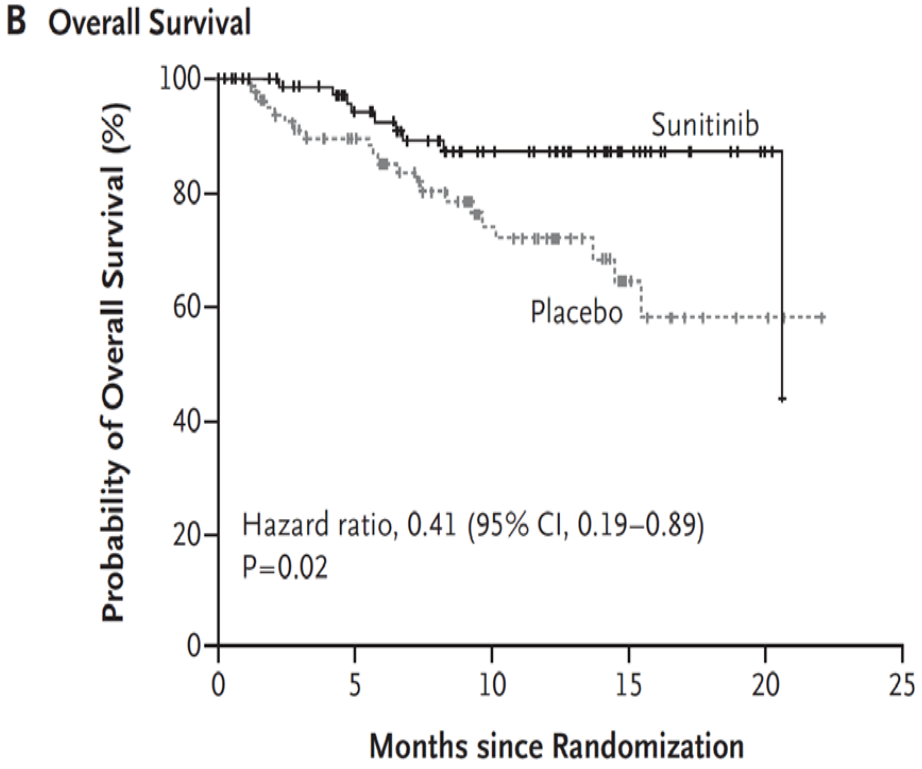
Faivre S. et al. Clin Cancer Res. 2011



Faivre S, et al. *Endocrinol Metab Clin N Am* 2010;39:811–826

Pancreatic neuroendocrine tumors are addicted to HIF/VEGFR driven angiogenesis: PFS (primary endpoint)





Raymond E, et al. *N Engl J Med* 2011;364:501−513

Radiological Response Evaluation: Partial Response (by RECIST) and Major Hypodensity after Treatment

Baseline

- **Heterogeneous hypervascular lesions**

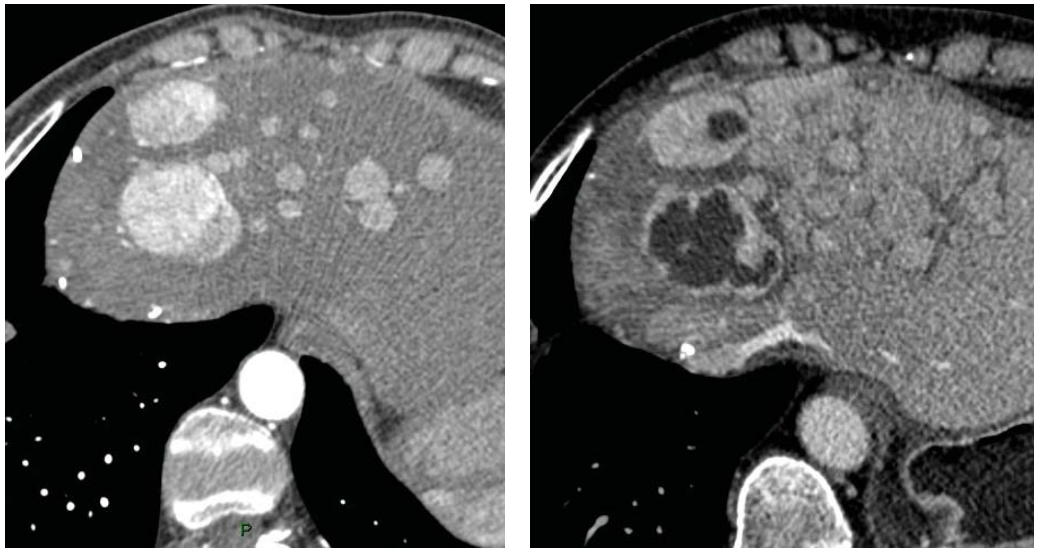
After Cycle 6

- **Decrease in size + induction of hypodensity suggesting necrosis in target lesions**

Sandrine Faivre, Beaujon, Study A6181111

Radiological scan assessment must integrate RECIST criteria, but also density modifications (Choi criteria)

RECIST stability, CHOI response



Dreyer C, et al
ESMO 2012, Poster #1163P

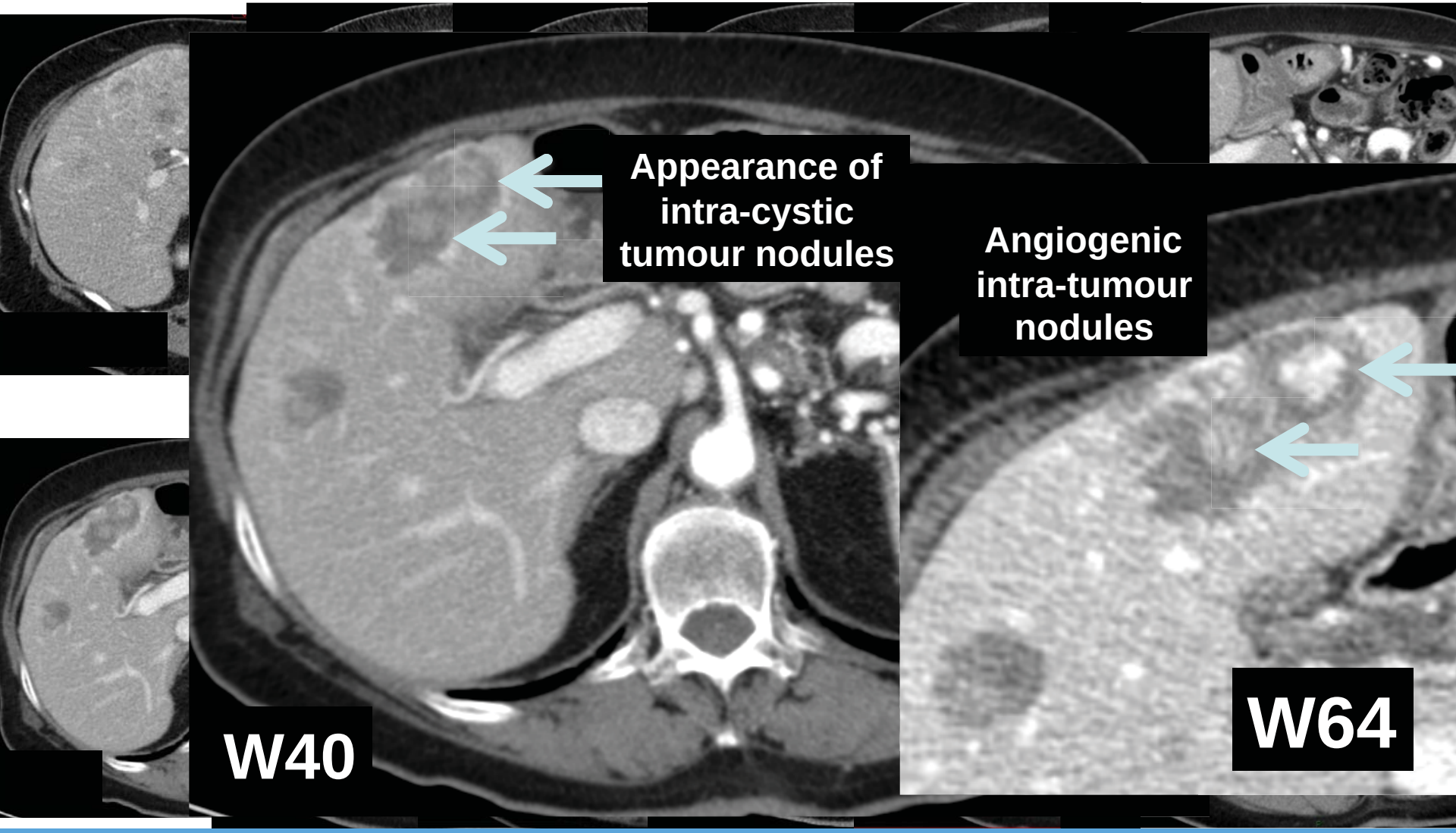
RECIST criteria

	Sunitinib (n=12)	Everolimus (n=10)
PR	1	1
SD	11	7
PD	0	2

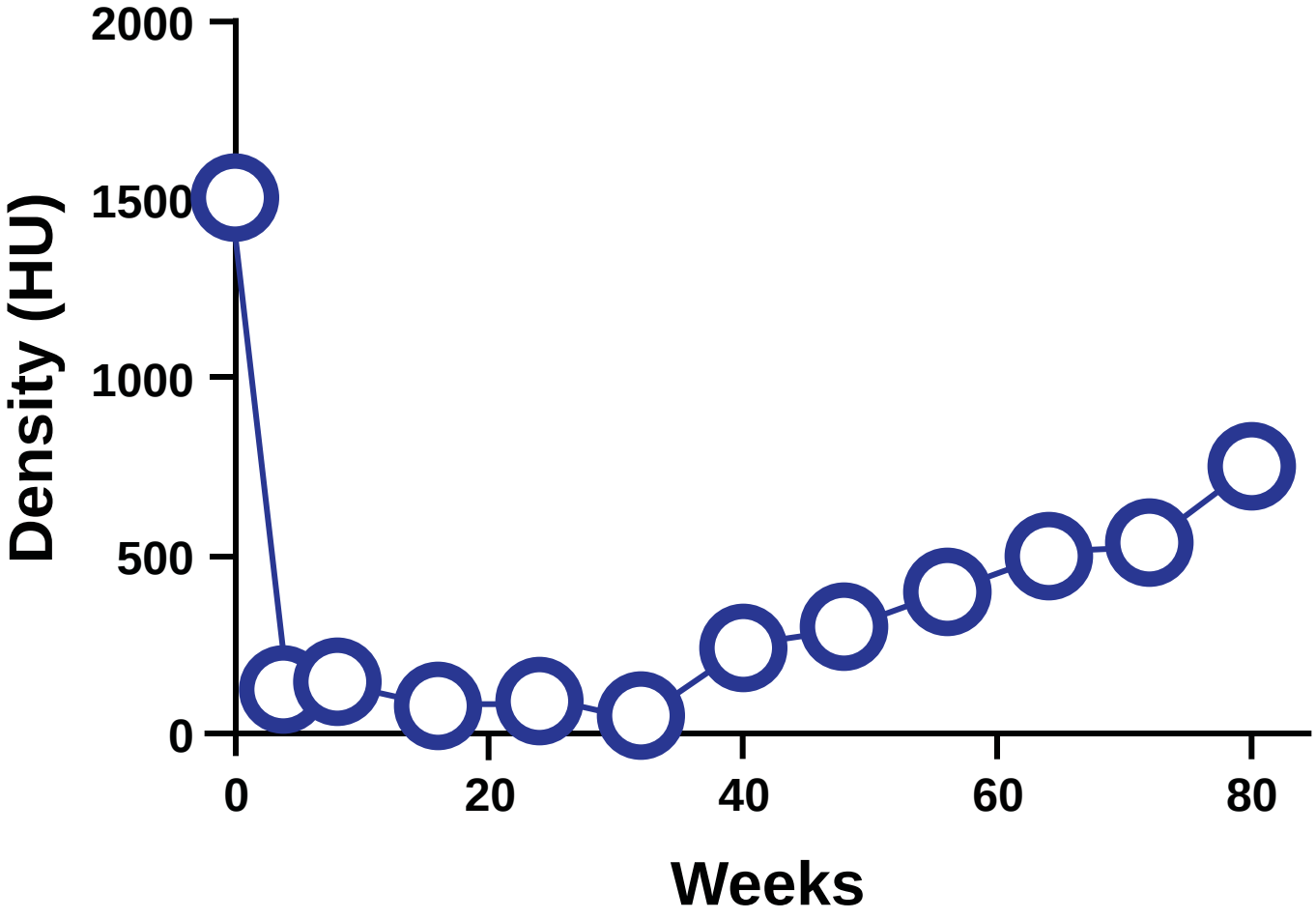
CHOI criteria

	Sunitinib (n=12)	Everolimus (n=10)
PR	9	2
SD	3	5
PD	0	3

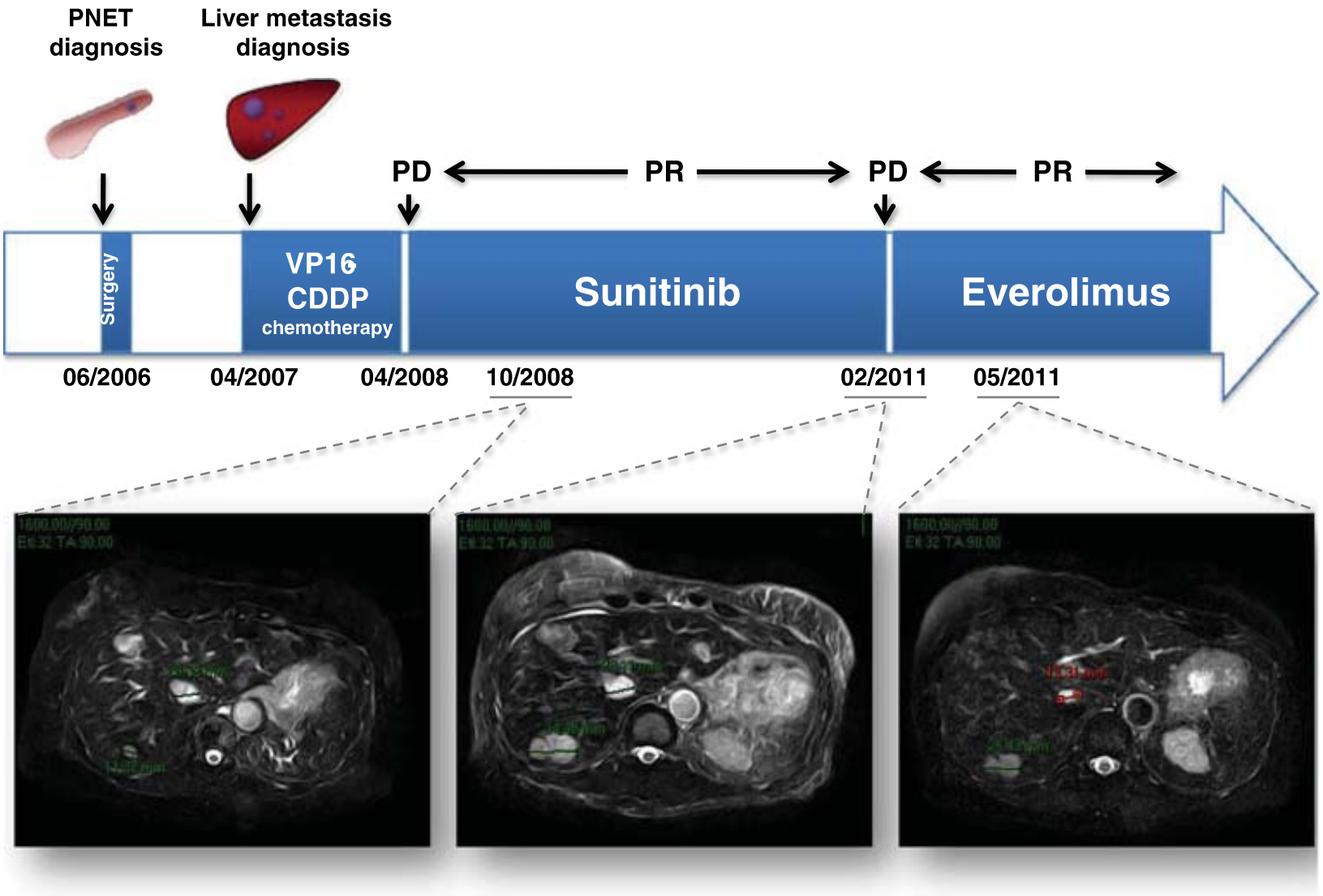
Taking a closer look at target lesions under sunitinib…



Changes in tumour density over time under treatment with sunitinib

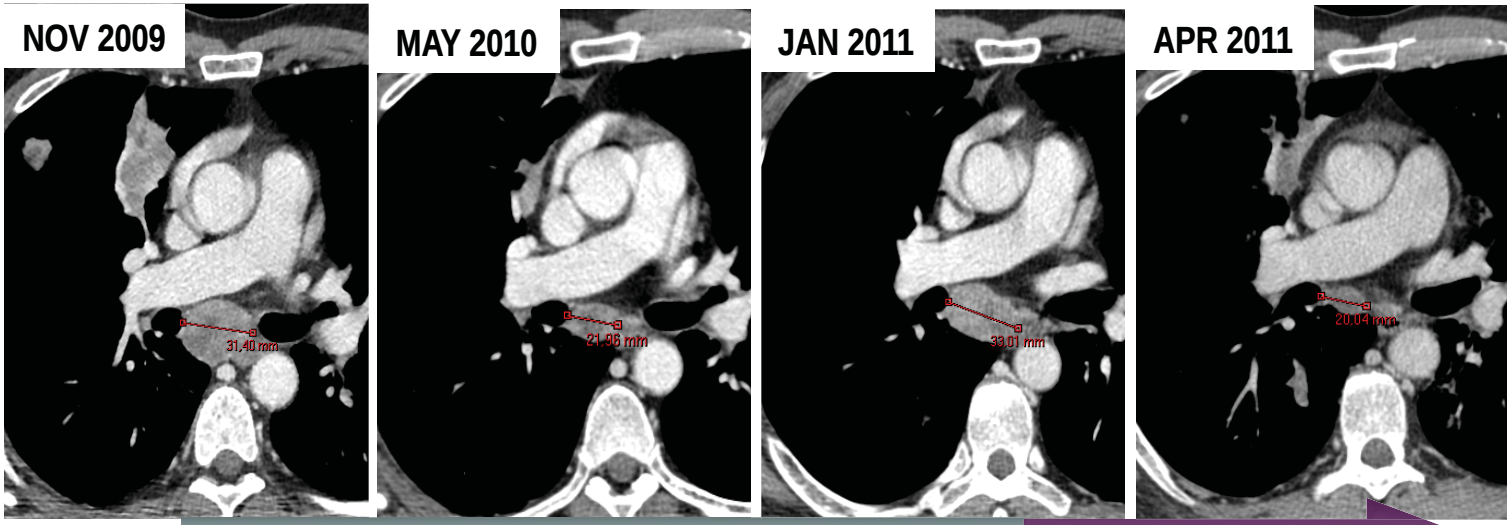


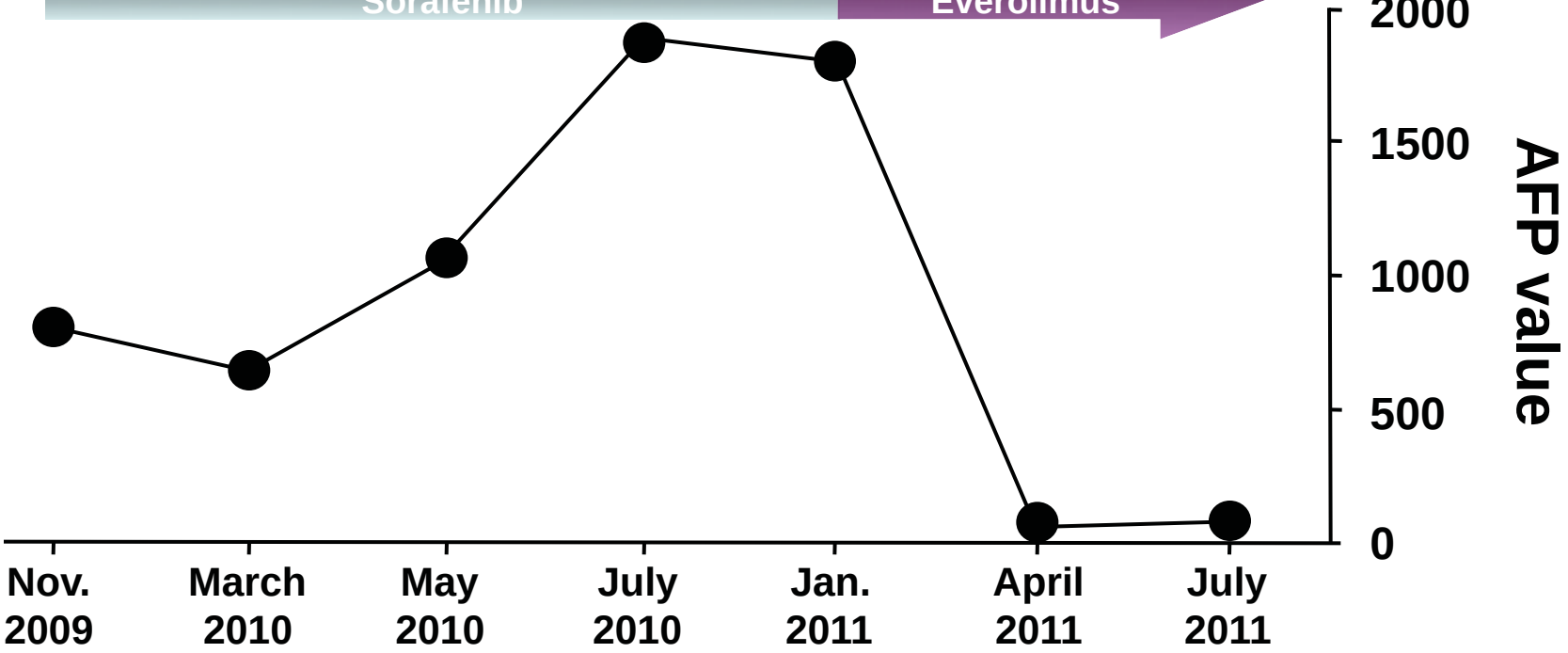
A case study of sequencing targeted agents



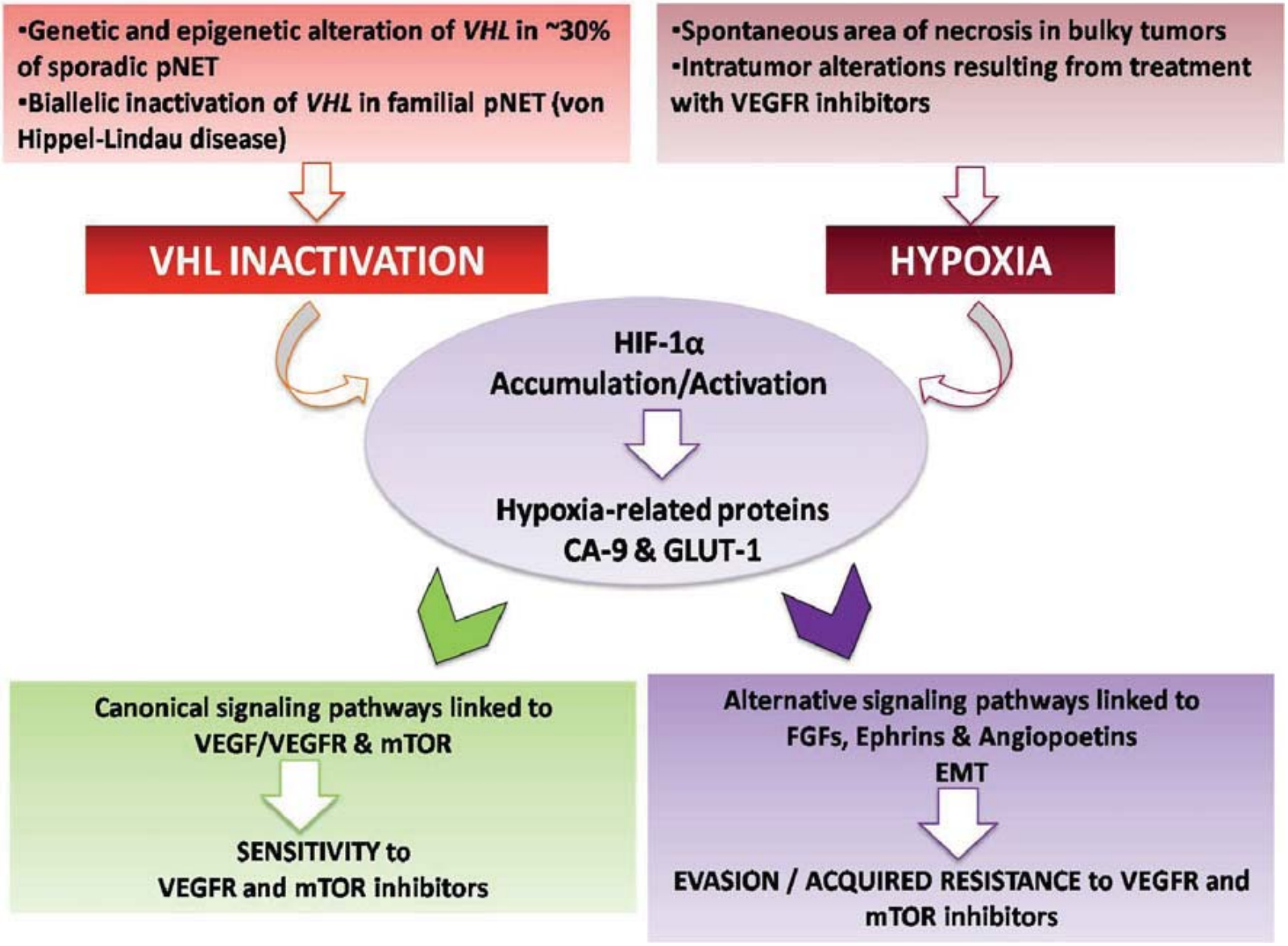
Tijeras-Raballand A, et al. Targ Oncol 2012;7:173–181

Case Study: objective response with everolimus after progression with sorafenib in advanced HCC



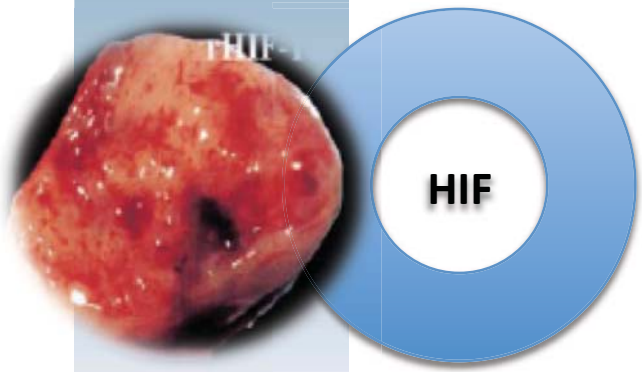


HIF-1 activation plays an important role in the activation of VEGF/ VEGFR & mTOR and angiogenesis in neuroendocrine tumors



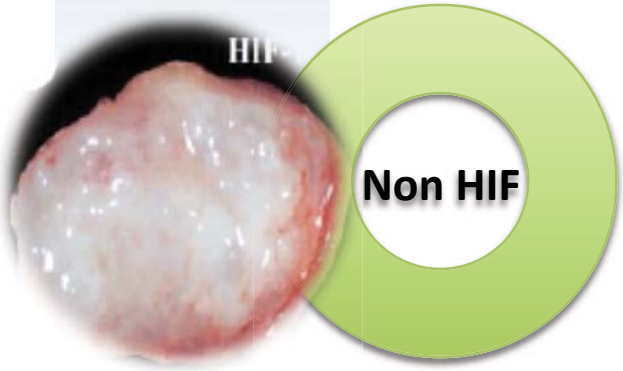
Tijeras-Raballand A, Neuzillet C, Couvelard A, *et al.* Target Oncol. 2012

Two forms of angiogenesis



HIF-driven angiogenesis

In HIF(+) xerograft, tumors bleed profusely and severely

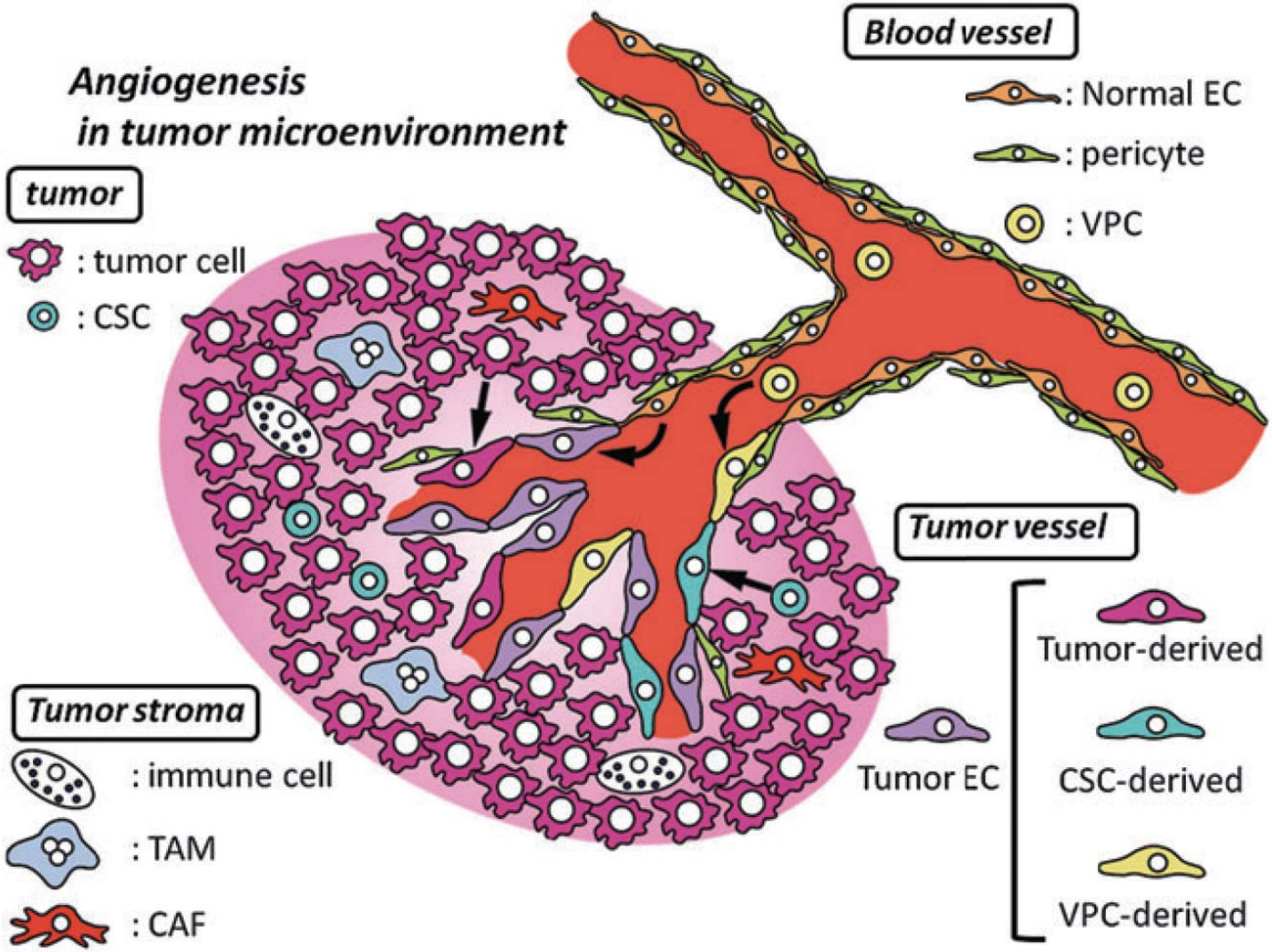


HIF-independent angiogenesis

HIF(-) xerograft vasculature is more uniform, with few but large vessel and display more avascular areas

Nature 1998;394:485-90

Multiple cellular systems and interactions have been identified in tumor angiogenesis



Adapted from Hida K. et al, *Pathology International 2011; 61: 630–637*

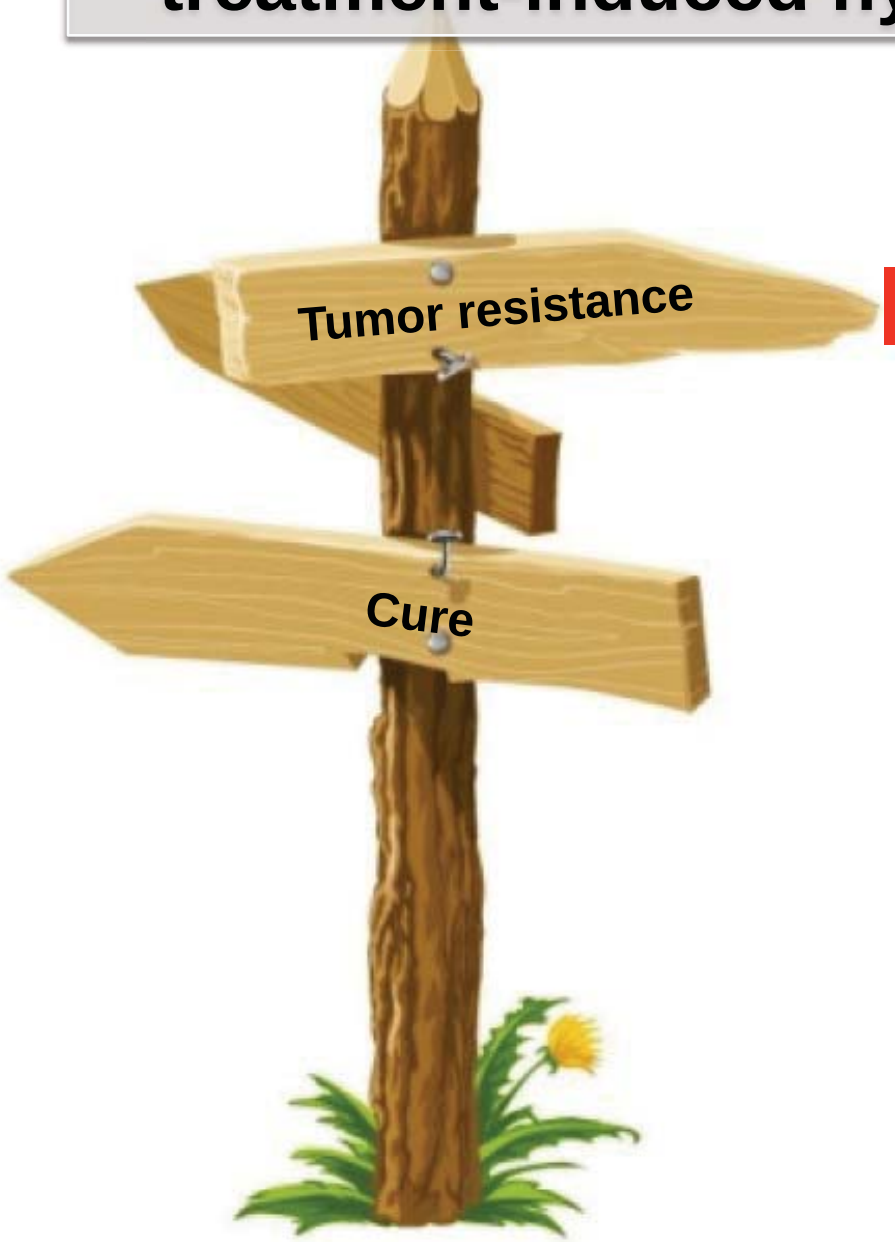
What can we learn from other tumor types?

Pathways underlying tumor resistance

Acquired resistance is constantly occurring over time upon VEGFR-I exposure

Tumor plasticity might involve several mechanisms yielding survival and increased invasiveness

Tumor plasticity in response to treatment-induced hypoxia and necrosis



YES

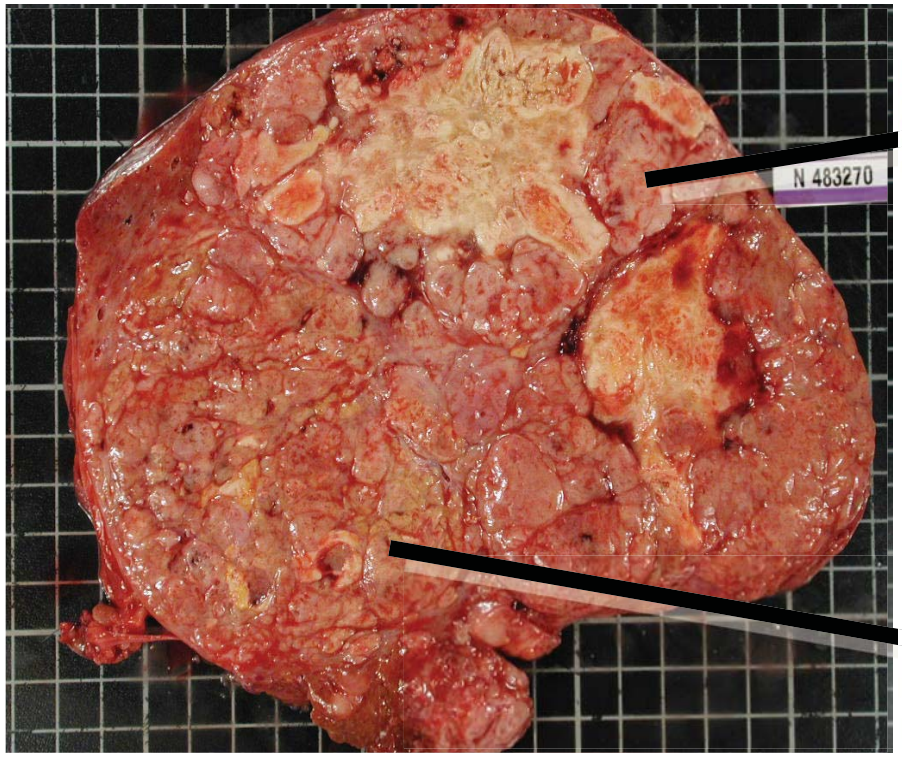
NO

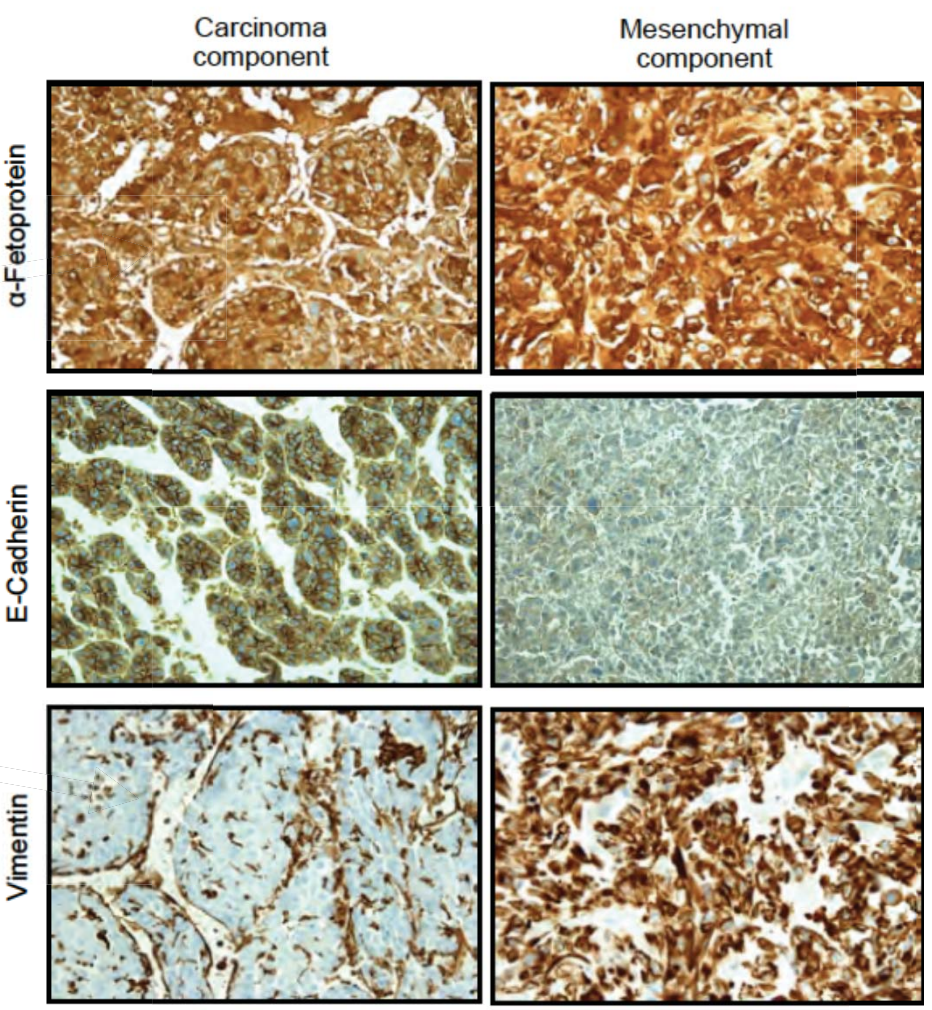
In the presence of VEGFR inhibitors both cancer cells and angiogenic cells will have to adapt to novel hypoxic conditions and anaerobic glucose metabolism

Endothelial cells will ‘switch’ again for other angiogenic factors

Cancer cells will adopt a more agressive phenotype by activating EMT

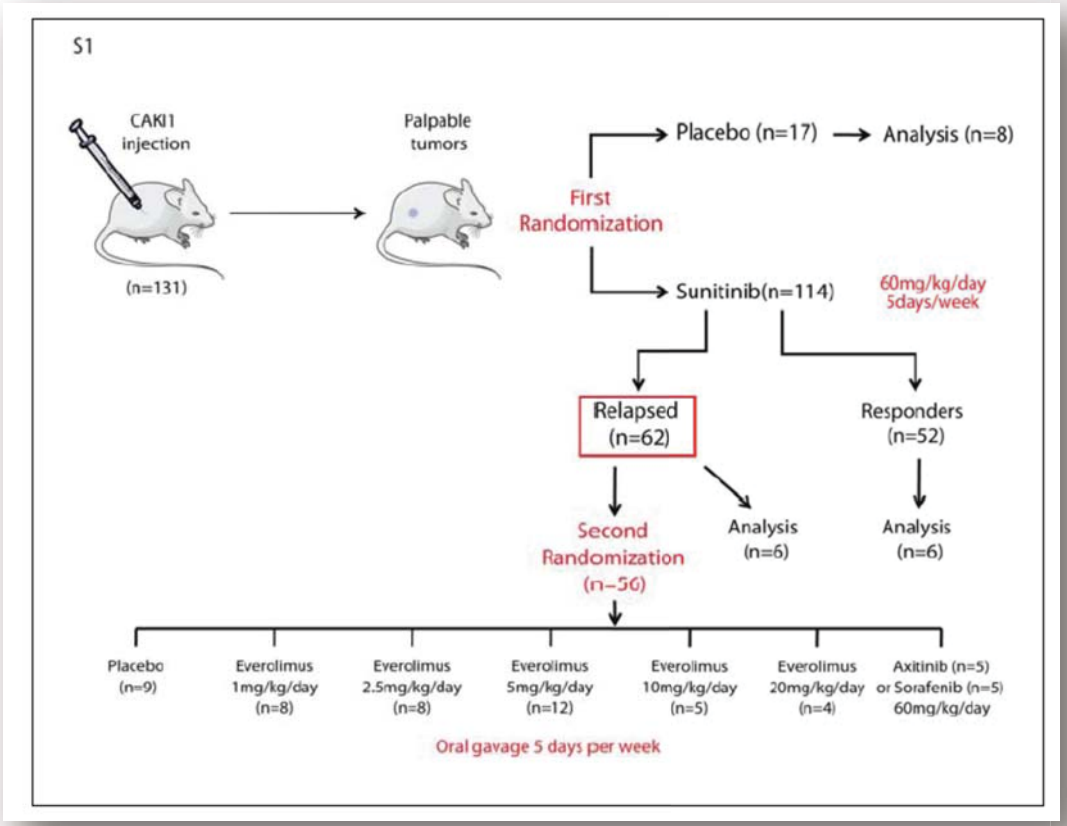
Examination of a HCC tumor at the time of resistance to sunitinib

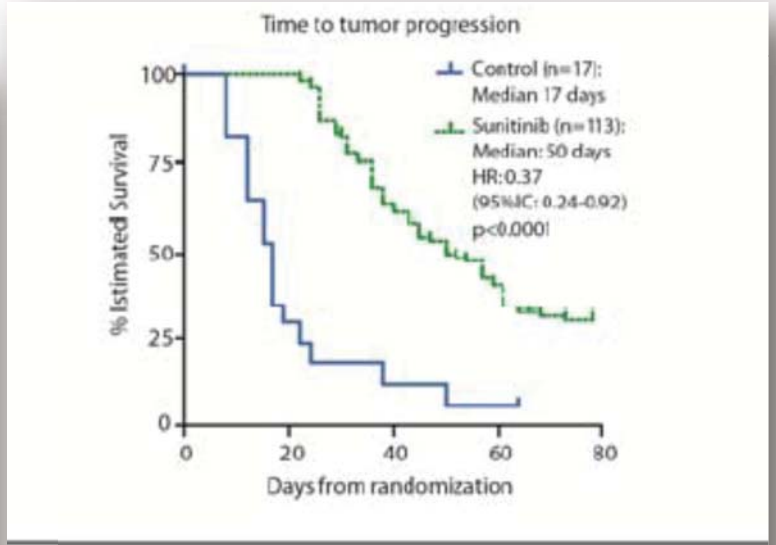


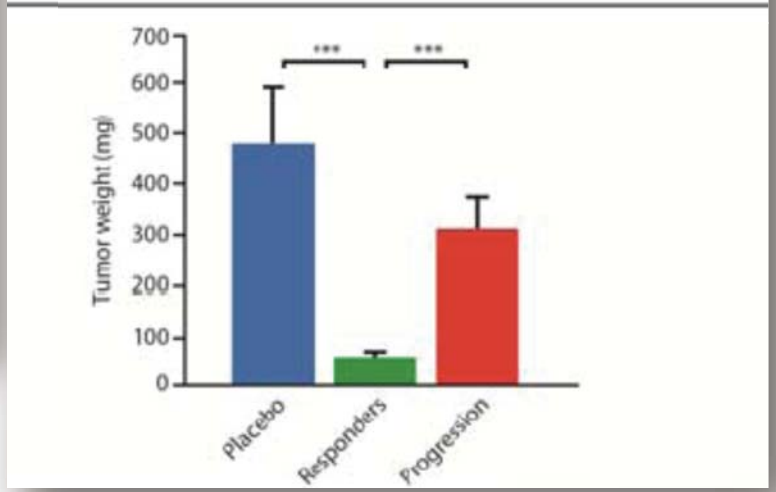


Marijon H et al. J. Hepatol 2011

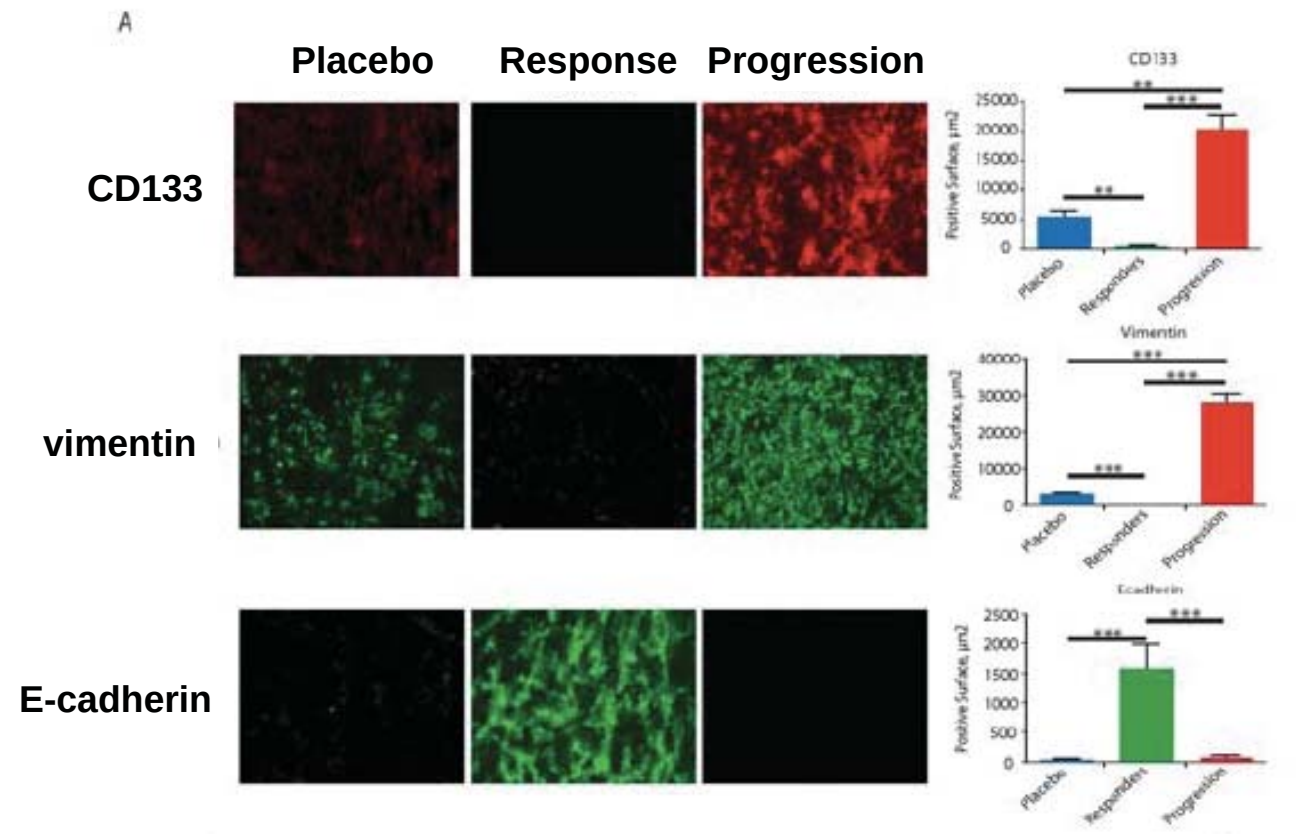
CLINICAL TRIAL IN MICE

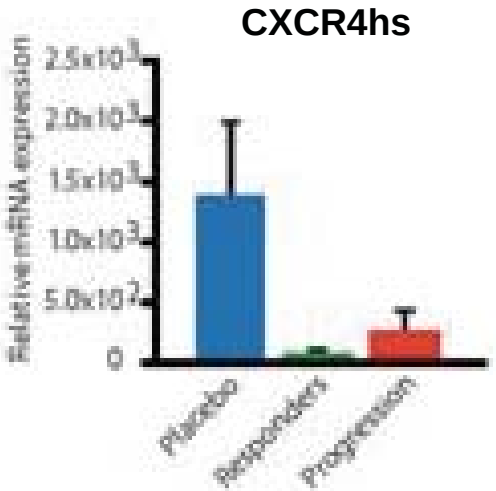


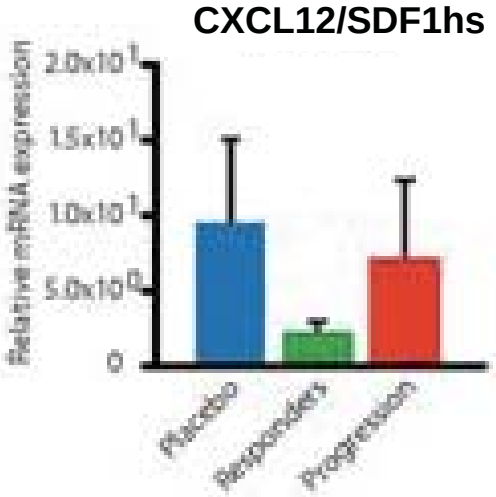




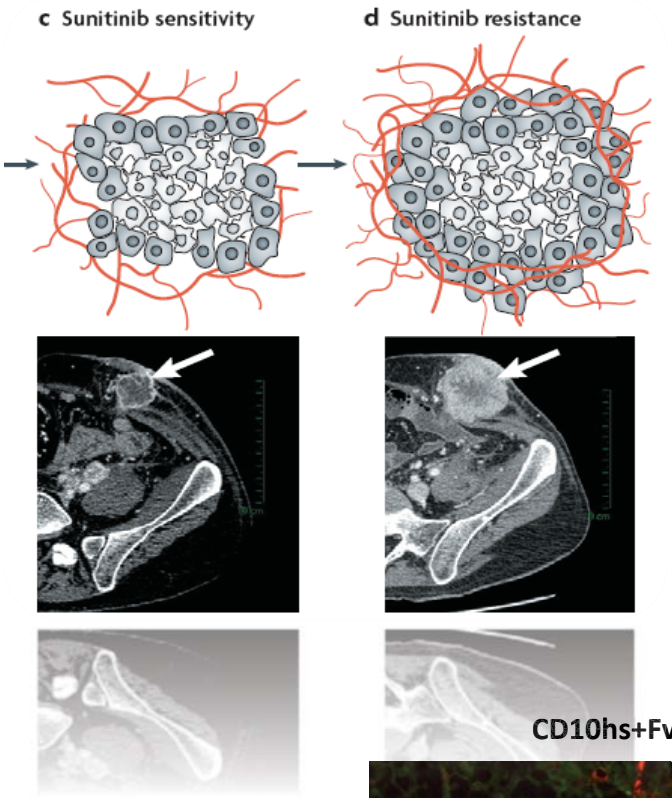
Renal tumors that progress under sunitinib contains more stem cells and mesenchymal cells

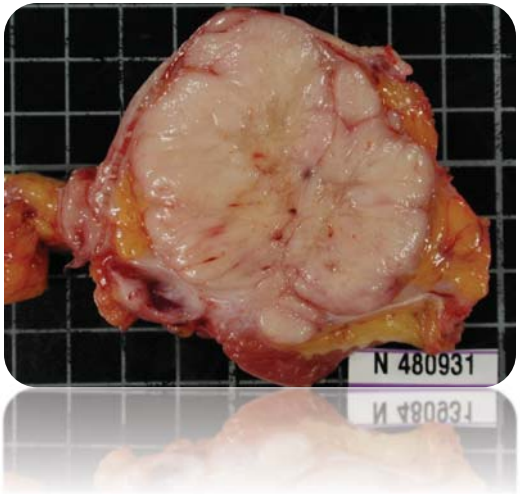


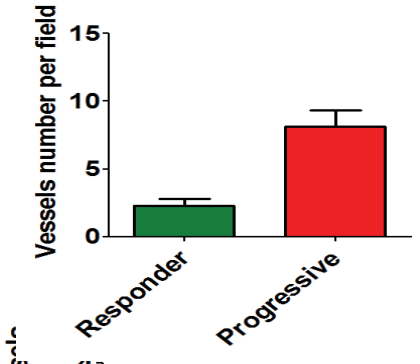


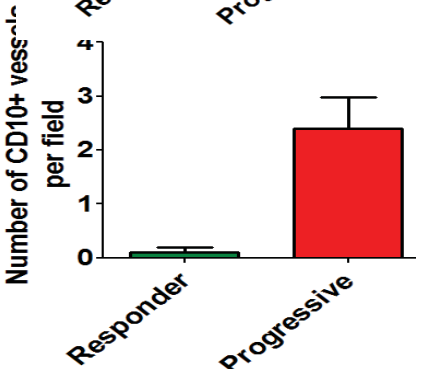


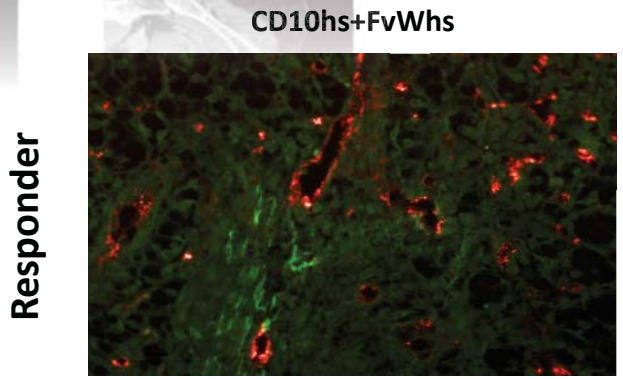
Vascular mimicry may occur in renal carcinomas from patients who progress under sunitinib therapy

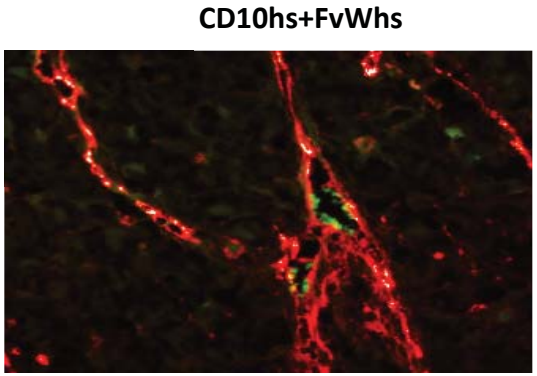




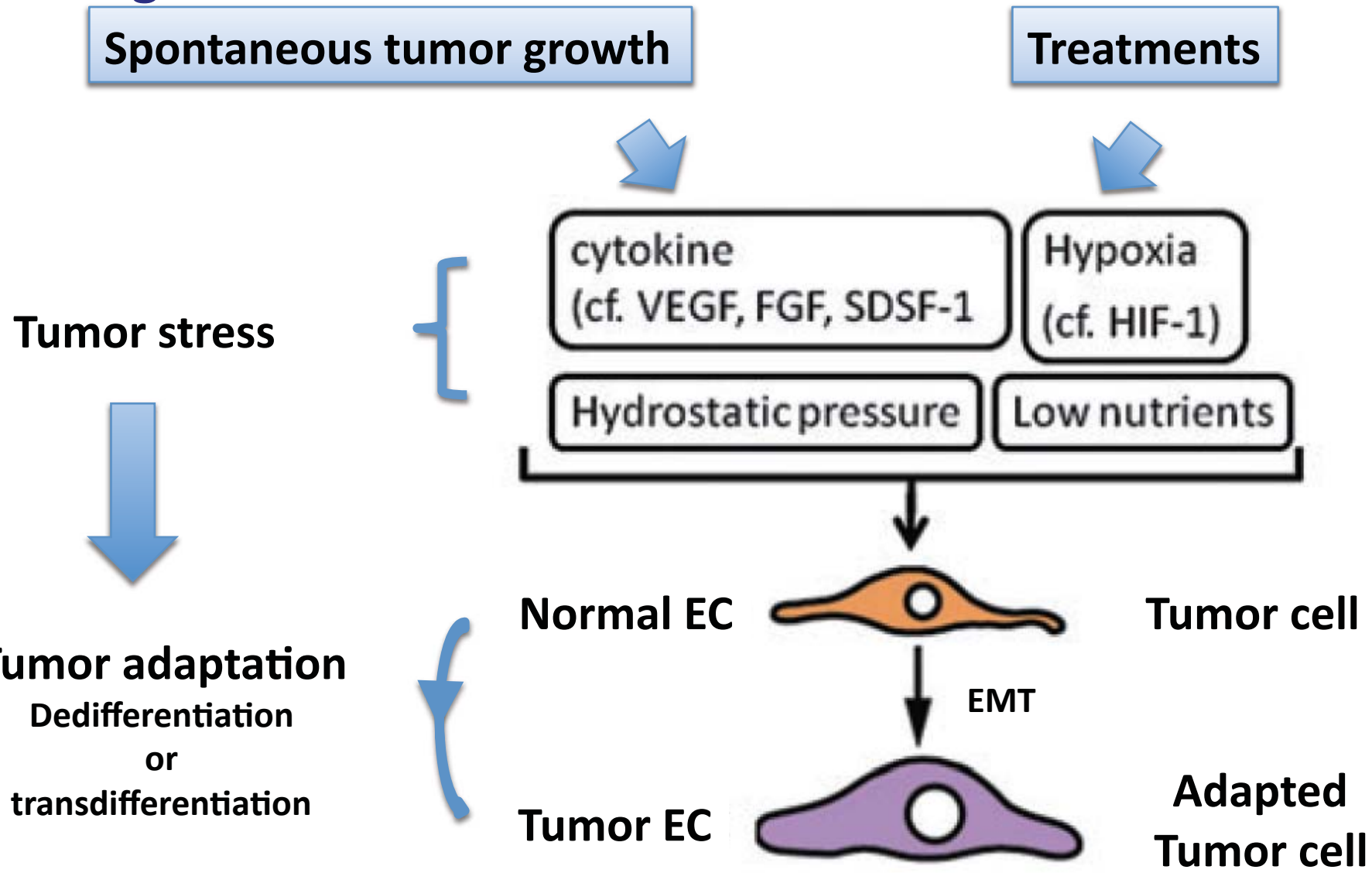








Changes in the stroma and tumor cells as a result of tumor growth and treatment-induced tumor insults



Adapted from Hida K. et al, *Pathology International 2011; 61: 630–637*

Sorafenib-tolerant HCC cells display an SDF-1/MIF- dependent invasive phenotype that can be inhibited by CXCR4 inhibitors

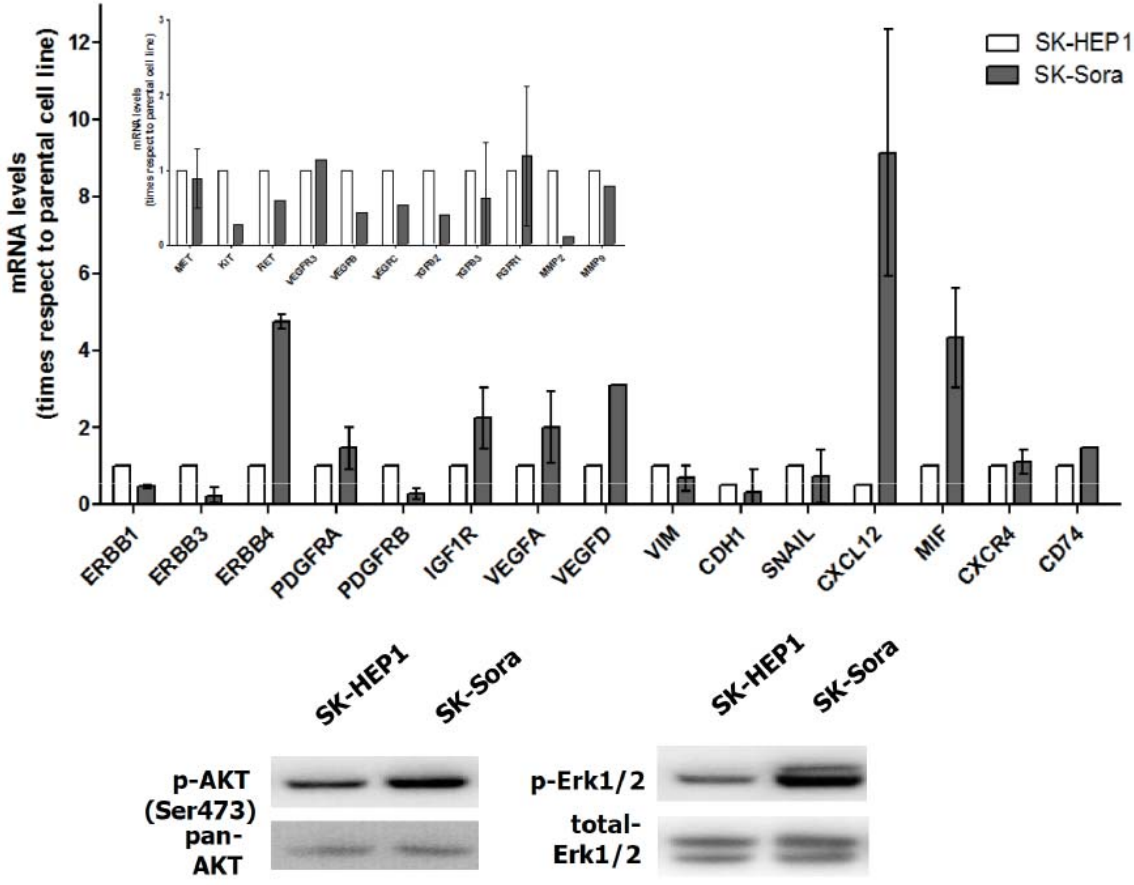
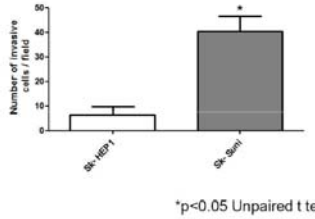


Figure 3.2. Molecular and biochemical characterization of SK-Sora



*p<0.05 Unpaired t test

Figure 2.3. Invasive phenotype of SK-Suni

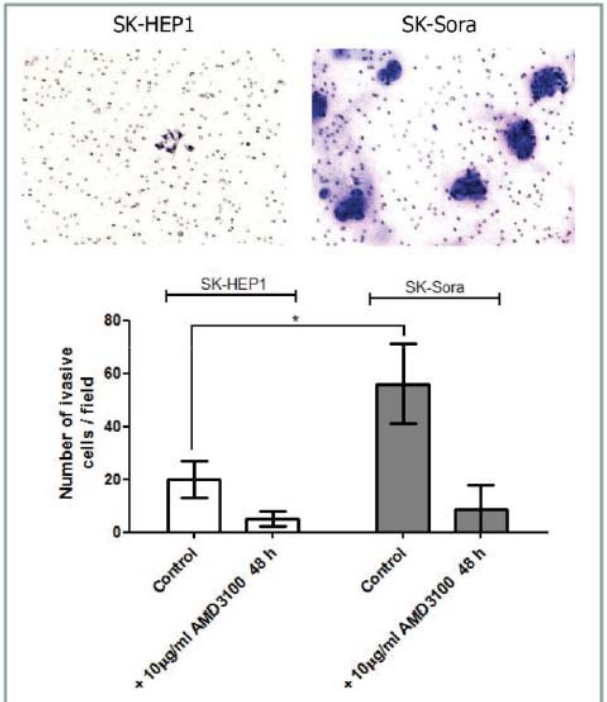
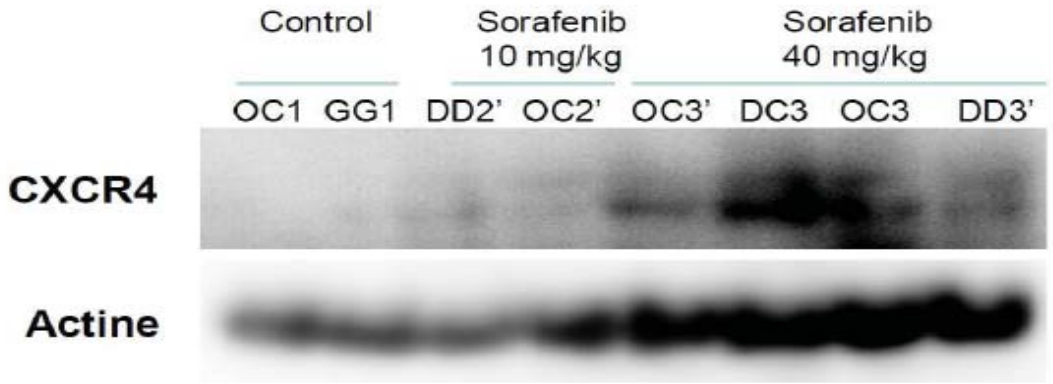
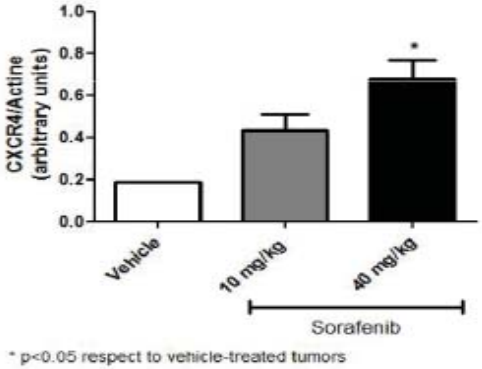


Figure 3.3. Invasive phenotype of SK-Sora

Emergence of resistance to sorafenib increases CXCR4 expression

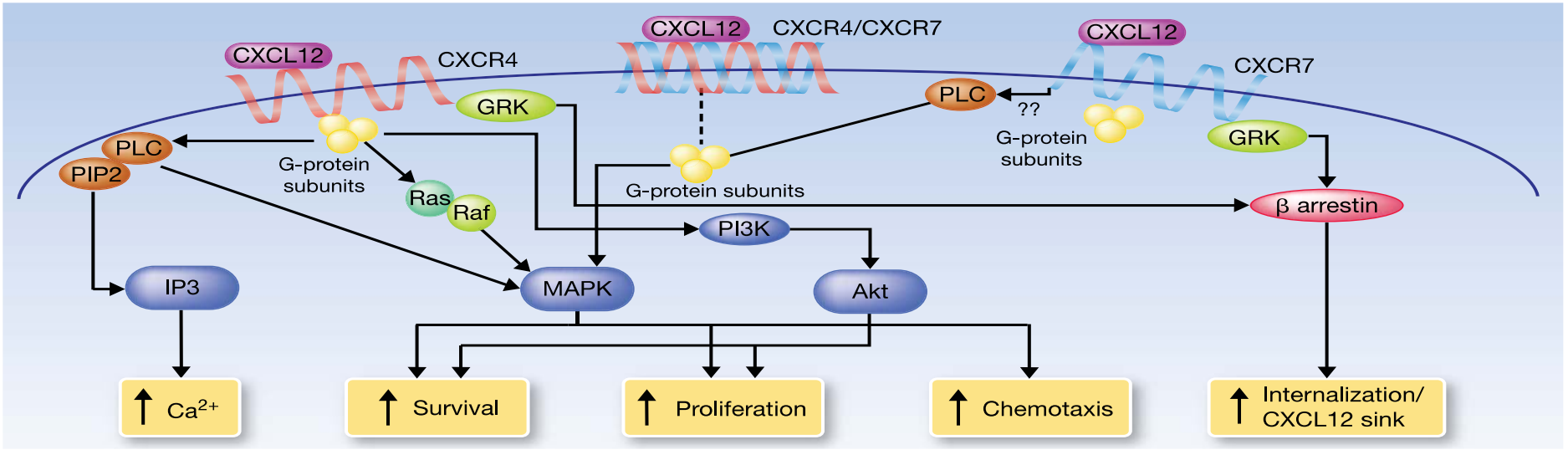




CXCR4 expression is increased in SK-HEP1 xenografts implanted in mice and treated with sorafenib (40 mg/kg/day) for 25 days

Riveiro ME et al, ILCA 2011

Following TK inhibition, other types of receptors are involved in tumor signaling: Chemokines receptors (CXCR)



CXCR4 & CXCR7 are 7-transmembrane, G protein-coupled receptors

Clinical challenge for new drugs

Tumor pattern in first line

- ✓ Primary angiogenic switch
- ✓ Cancer cell proliferation
- ✓ Primary tumor fibrosis
- ➔ VEGFR/PDGFR, mTOR

Angiogenesis inhibitors

Tumor pattern at disease progression

- ✓ Second angiogenic switch
- ✓ Cancer cell migration
- ✓ Healing fibrosis
- ➔ HGF/MET, TGFb/TGFbR, SDF-1/CXCR4

Safety and efficacy of sunitinib in patients with advanced hepatocellular carcinoma: an open-label, multicentre, phase II study

Sandrine Faivre, Eric Raymond, Eveline Boucher, Jean Douillard, Ho Y Lim, Jun S Kim, Magaly Zappa, Silvana Lanzalone, Xun Lin, Samuel DePrimo, Charles Harmon, Ana Ruiz-Garcia, Maria J Lechuga, Ann Lii Cheng

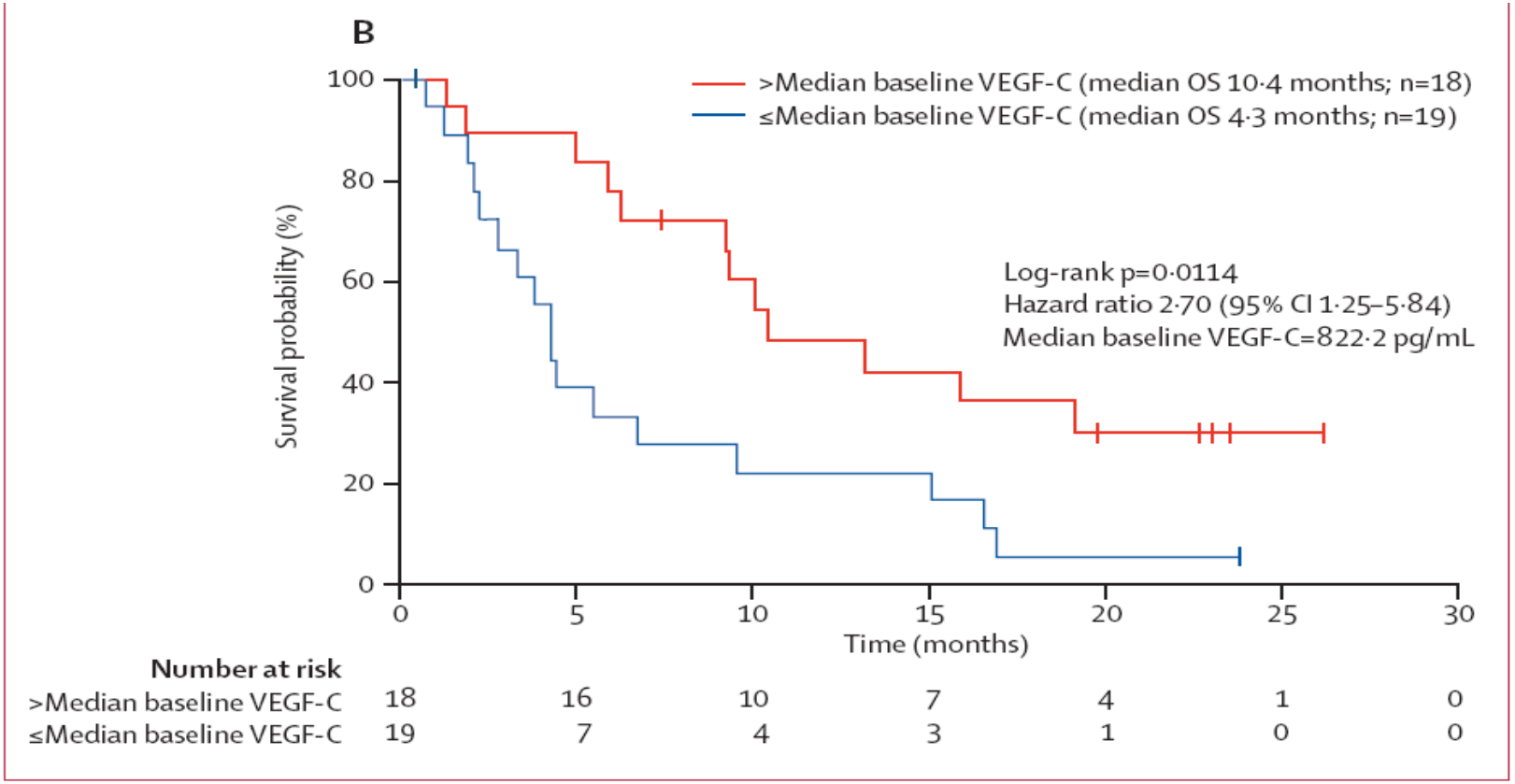
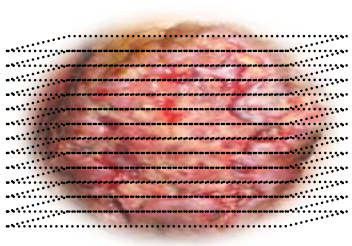


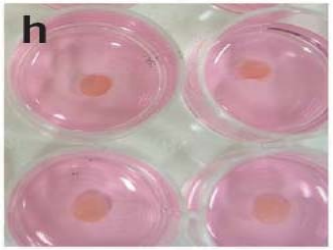
Figure 3: **Predictive value of vascular endothelial growth factor (VEGF) C in patients with advanced hepatocellular carcinoma treated with sunitinib**

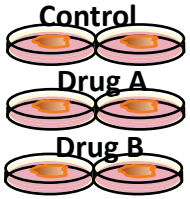
Lancet Oncol 2009; 10: 794–800

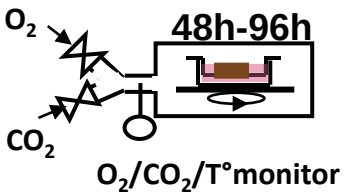
TIPCAN – HCC: TIssue Profiling in CANcer

***Ex Vivo* Tissue Culture Model**



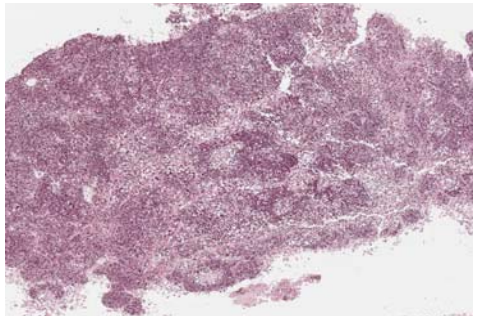




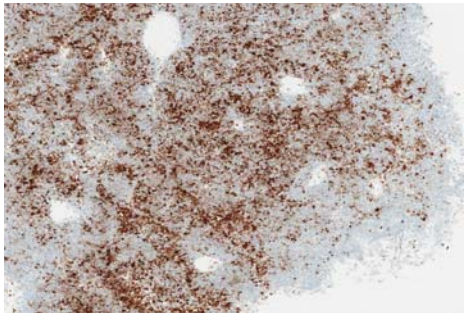


HCC slice culture

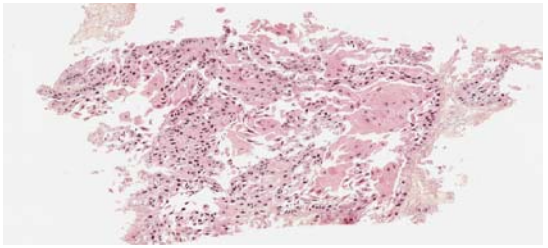
+ Drug 24h (HES)



+ Drug 24h (caspase 3)



Tumor biopsy slice



Tijeras-Raballand ILCA 2013, Rebours V Plos one 2013

Conclusions

- **Important progresses were made in the last 15 years in VEGF/VEGFR-addicted (HIF-dependent) tumors using VEGFR/PDGFR and mTOR inhibitors**
- **Albeit their potent effects, above drugs may induce tumor stress and/or tissue injury that ignites adaptive plasticity in tumors such as EMT**
- **Although likely to be present in most tumors, little is known about other forms of HIF-independent tumor angiogenesis**
- **Implementing translational research using modern tools of molecular biology (paired biopsies, blood biomarkers, ex-vivo TIPCAN) will contribute to better knowledge toward individualized therapeutics**