Novel Molecular Therapies In Hepatocarcinoma

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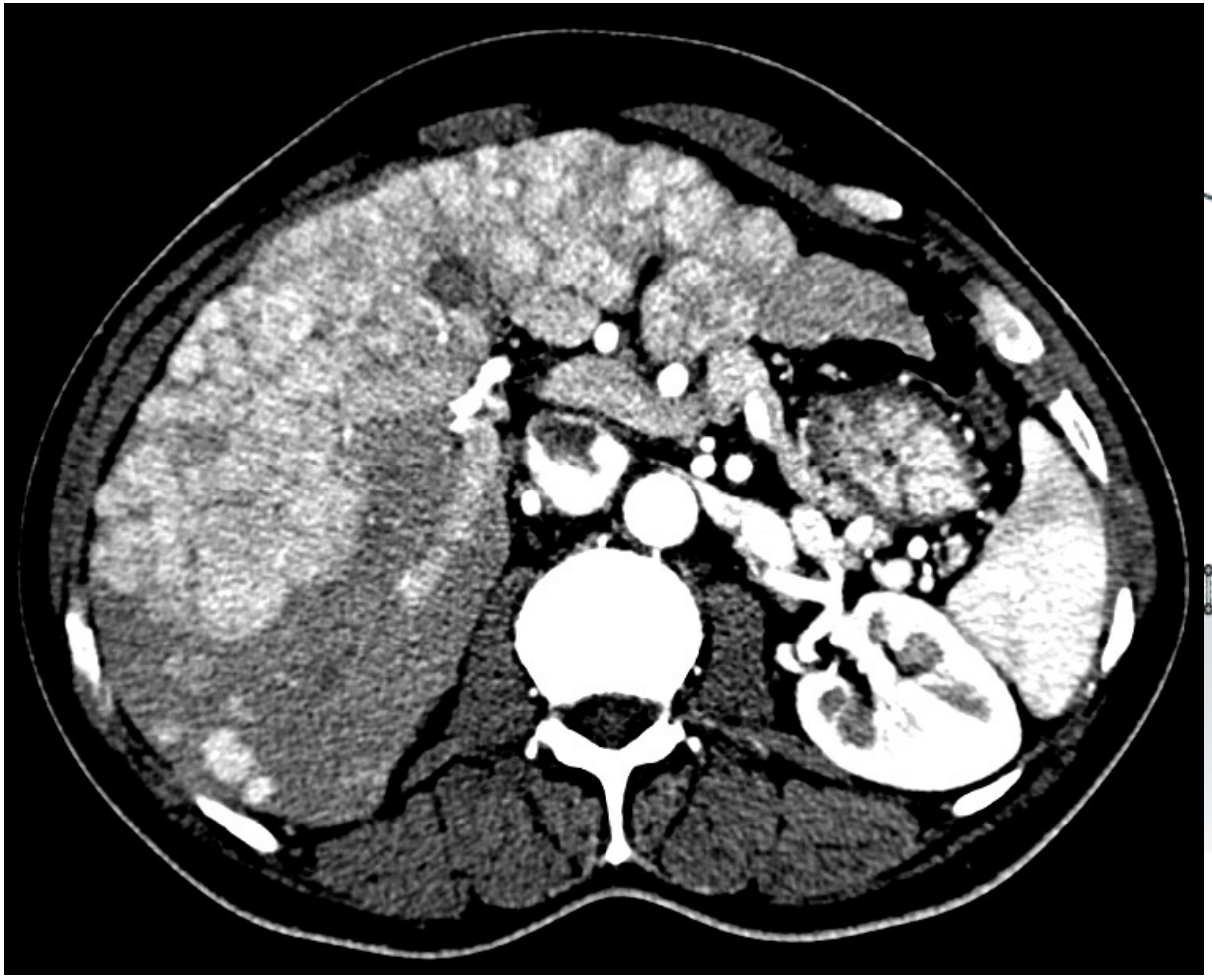
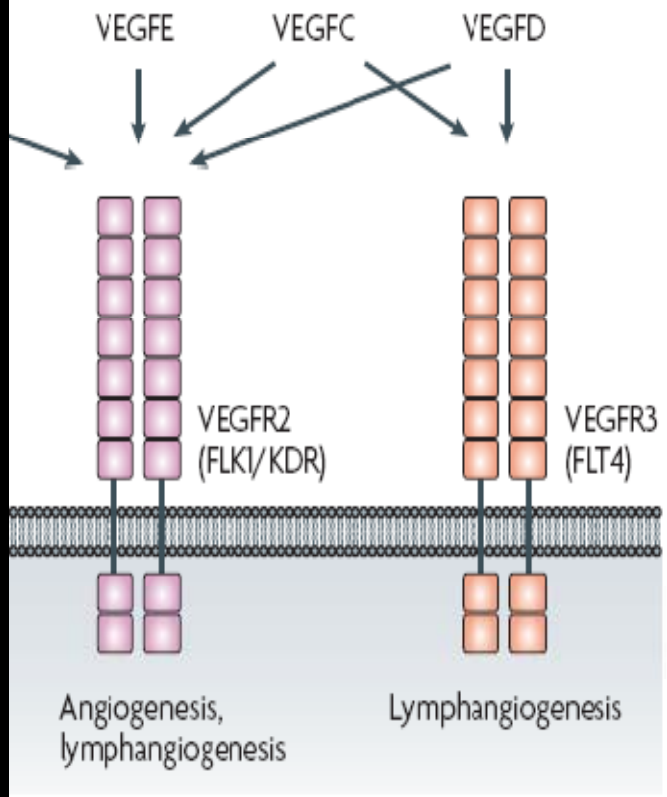
HCC is a highly vascular tumor sensitive to antiangiogenic therapy





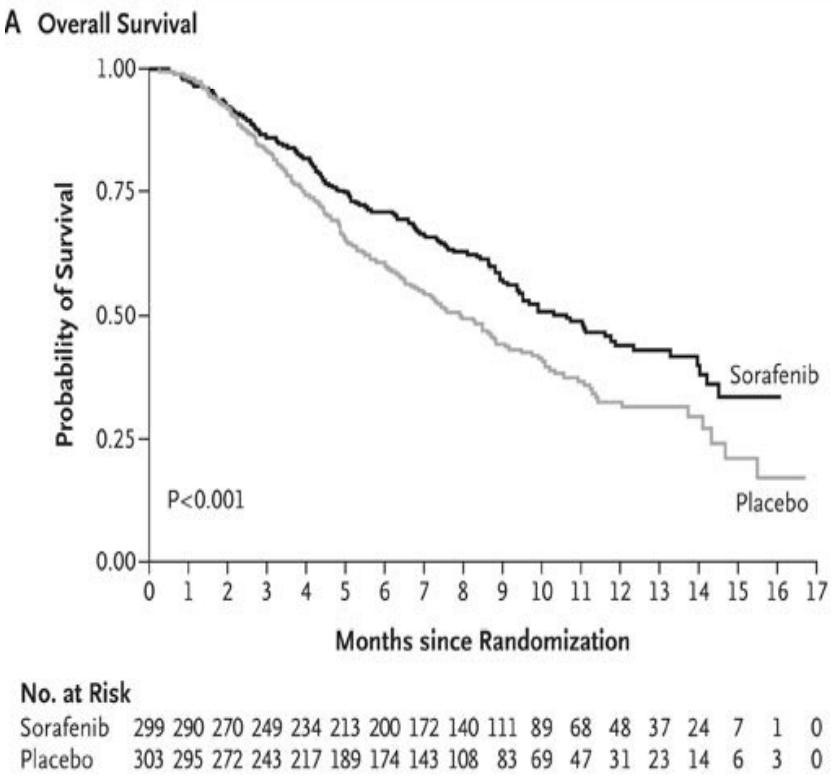
Molecular basis for sunitinib efficacy and future clinical development

NATURE REVIEWS | DRUG DISCOVERY

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

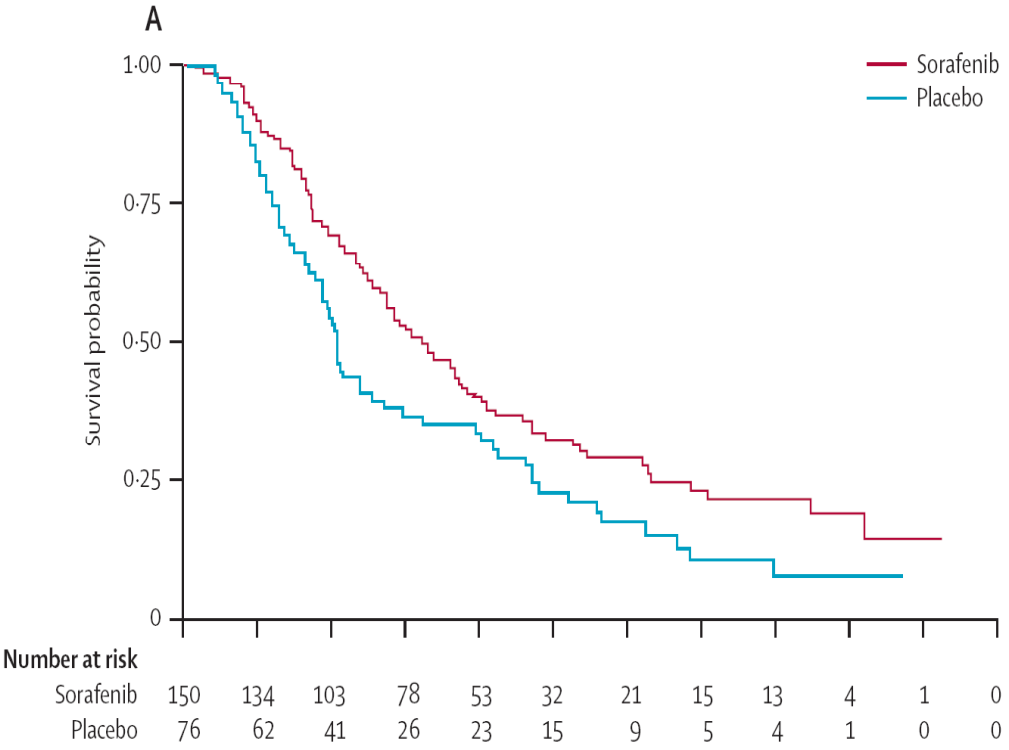
Sorafenib is a Consolidated Therapy in Advanced HCC throught 2 Randomized Phase III Trials

Median OS: 10.7 vs 7.9 months
p<0.001



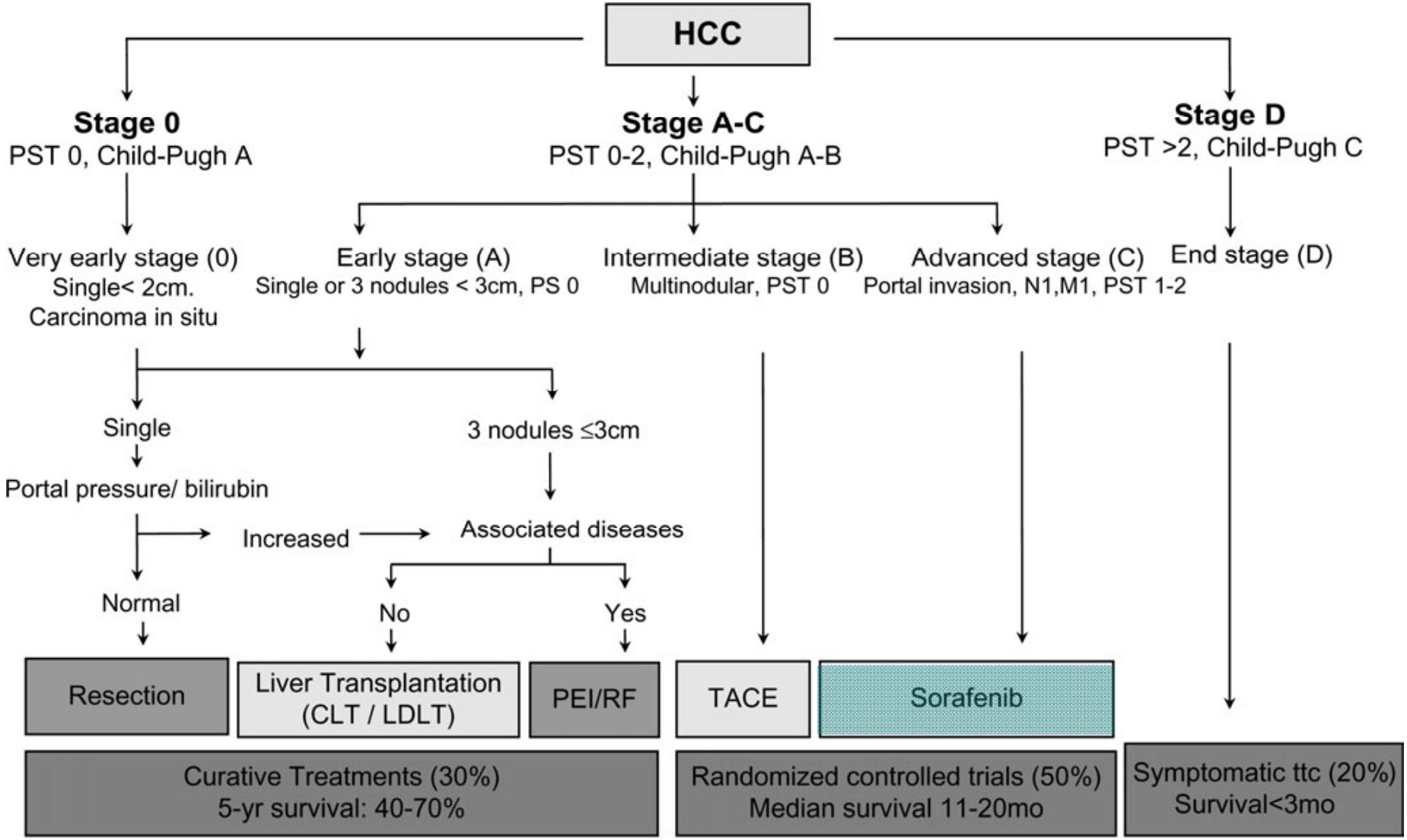
Llovet JM et al, N Engl J Med 2008

Median OS: 6.5 vs 4.2 months
p=0.014



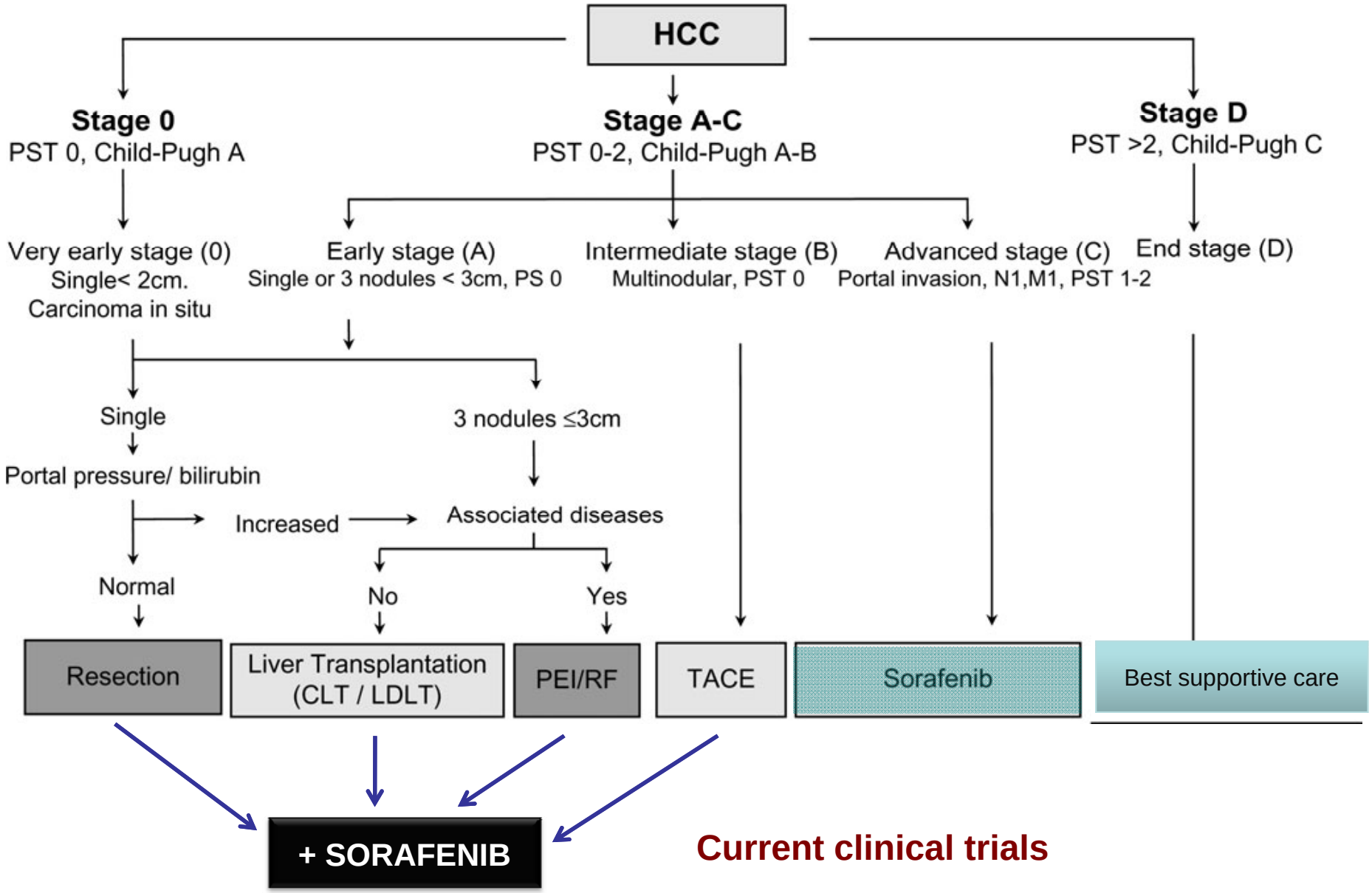
Cheng AL et al, Lancet Oncol 2009

BCLC Staging and Treatment Strategy



Llovet JM et al, J Natl Cancer Inst 2008

BCLC Staging and Treatment Strategy



Current clinical trials

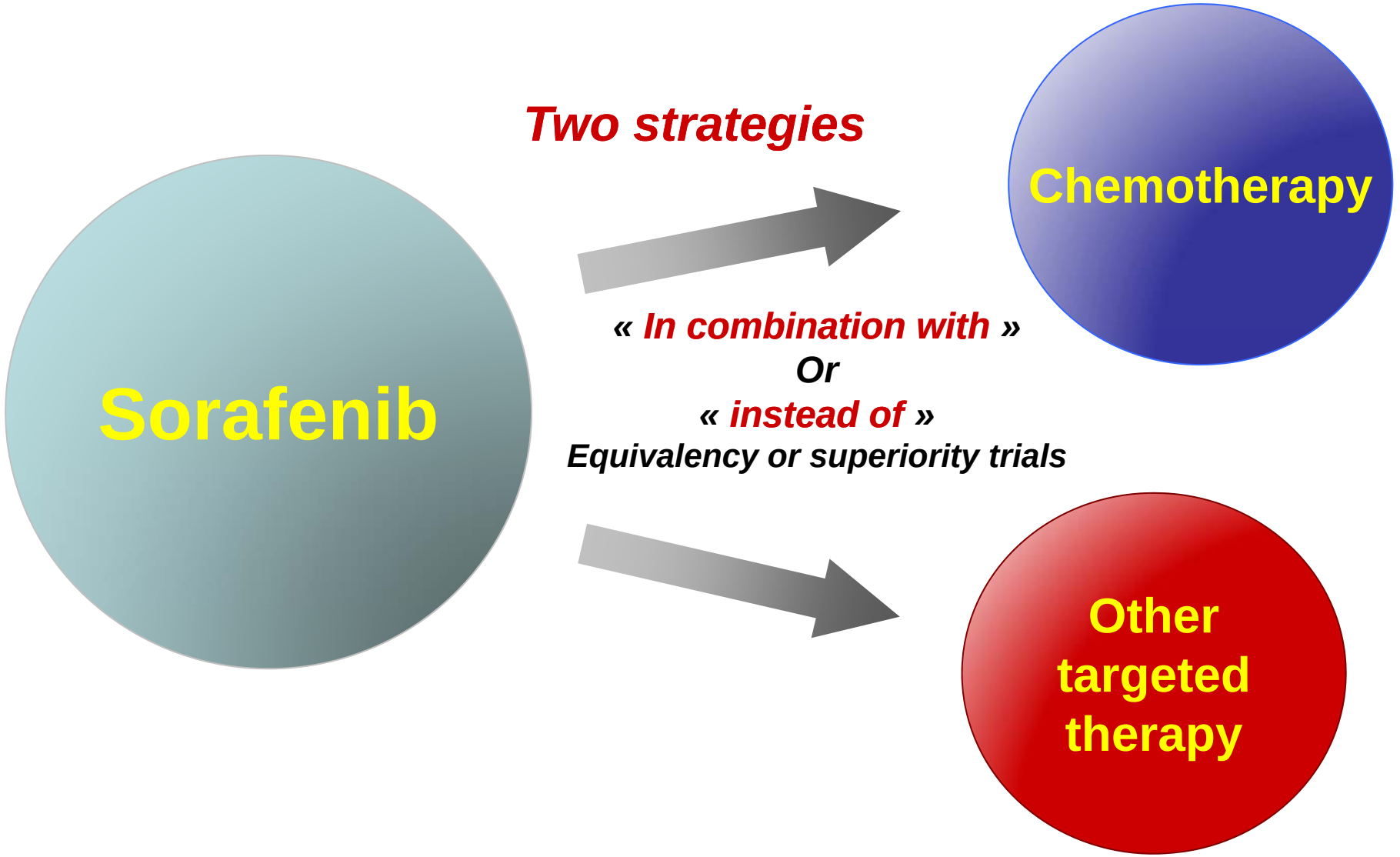
Current limitations of sorafenib in HCC

- **Although extended by sorafenib, PFS and overall survival remain limited**
  - **Secondary resistance may eventually occur after several weeks of drug exposure**
  - **Resistance may be counteracted by increasing the doses in some patients who tolerate well sorafenib**
  - **Stopping treatment may be sometimes associated with an accelerated growth (flair up) of the tumor**
- **No other option is currently available for patients with poor tolerance or primary resistance to sorafenib**

Activity of selected targeted agents in the treatment of HCC

Agent	n	Response rate %	Median TTP/PFS months	Median OS months	Study
Sorafenib	137	2	4.2	9.2	Abou-Alfa, 2006
Sorafenib vs placebo	602	2 vs1	5.2 vs 2.8	10.7 vs 7.9	Llovet, 2008
Sorafenib vs placebo	226	NR	2.8 vs 1.4	6.5 vs 4.2	Cheng, 2009
Sorafenib + dox vs placebo + dox	96	4 vs 2	8.6 vs 4.8	13.7 vs 6.5	Abou-Alfa, 2008
Bevacizumab	46	13	6.9 (PFS)	12.4	Siegel, 2008
Bevacizumab + erlotinib	40	25	9.0 (PFS)	15.7	Thomas, 2009
Erlotinib	38	8	3.2	13	Philip, 2005
Erlotinib	40	3	6.5	10.8	Thomas 2007
Cetuximab	30	0	1.4 (PFS)	9.6	Zhu, 2007
Sunitinib	37	3	NR	8.0	Faivre, 2007
Sunitinib	34	3	4.0 (PFS)	9.9	Zhu, 2007
Sirolimus	14	40	100% PFS @ 16wks	NR	Decaens, 2009
Brivanib	96	NR	NR	BR	Raoul, 2009

Current trial designs in first line therapy in hepatocellular carcinoma

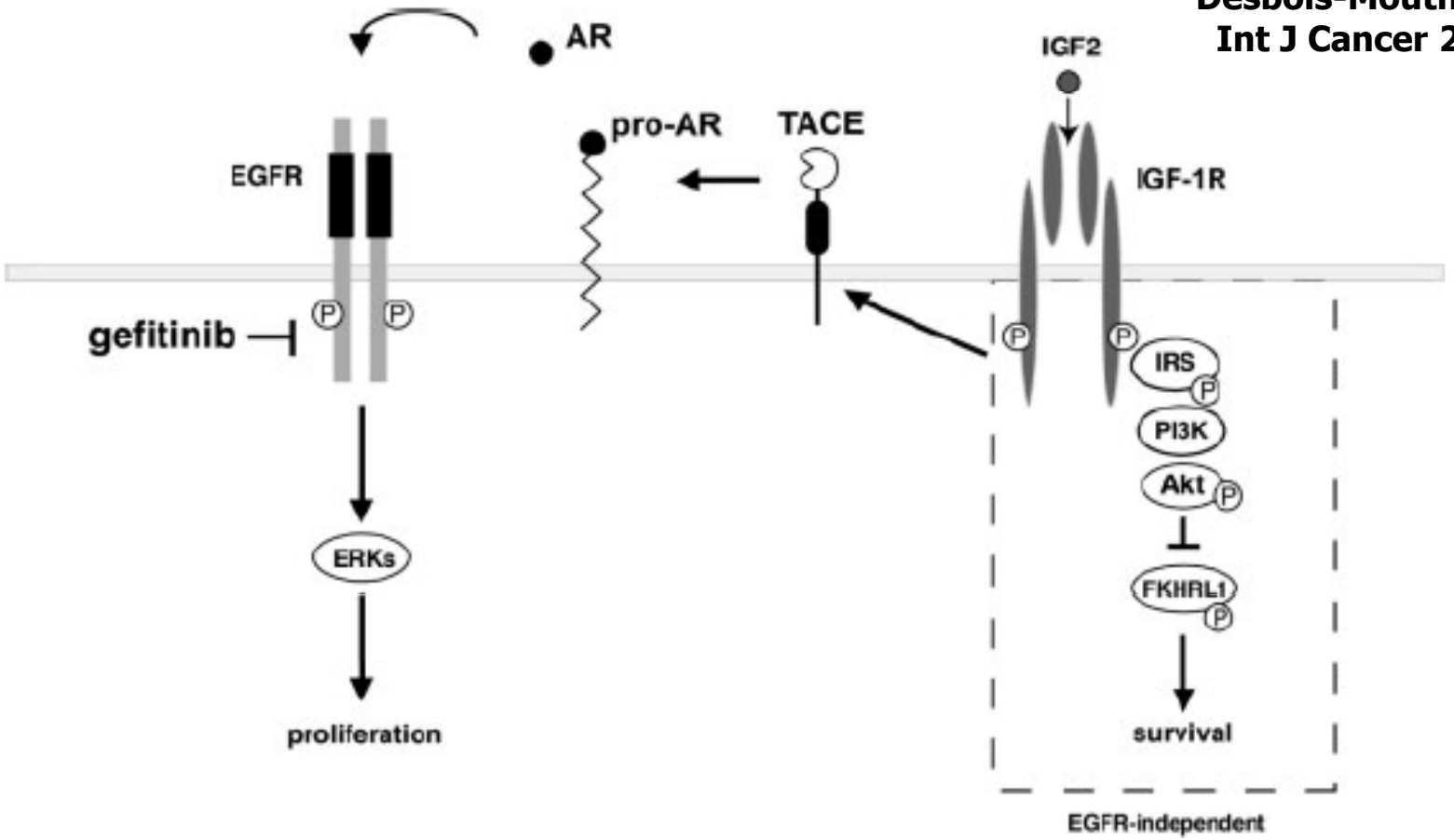


Combining sorafenib with the potential best candidates

- **With EGFR inhibitors**
  - **SEARCH :** Erlotinib plus sorafenib vs sorafenib
- **With chemotherapy**
  - **GONEX :** GEMOX plus sorafenib vs sorafenib
  - **CALGB-NCI :** DOXO plus sorafenib vs sorafenib

Potential for other combinations: EGFR and IGF2/IGF-1R cooperate for proliferation and survival in HCC

Desbois-Mouthon C, Int J Cancer 2006



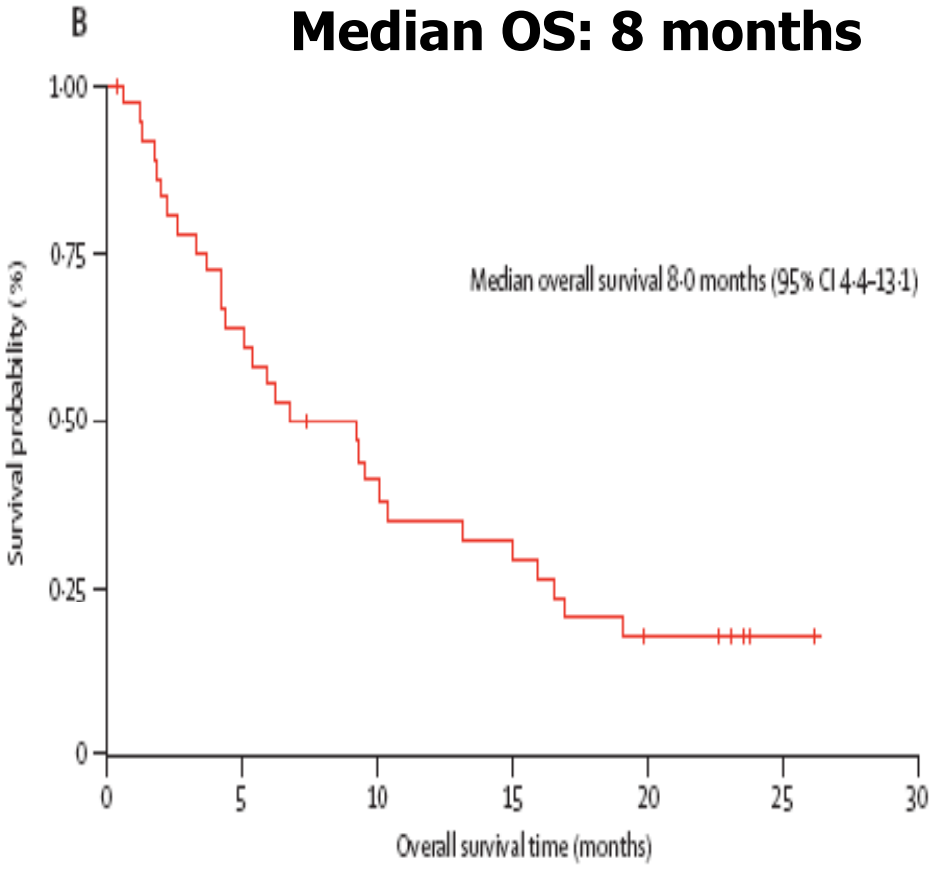
Several phase I/II trials are currently exploring these combinations

www.ClinicalTrial.gov

Other targeted therapies trying beating up sorafenib in first line

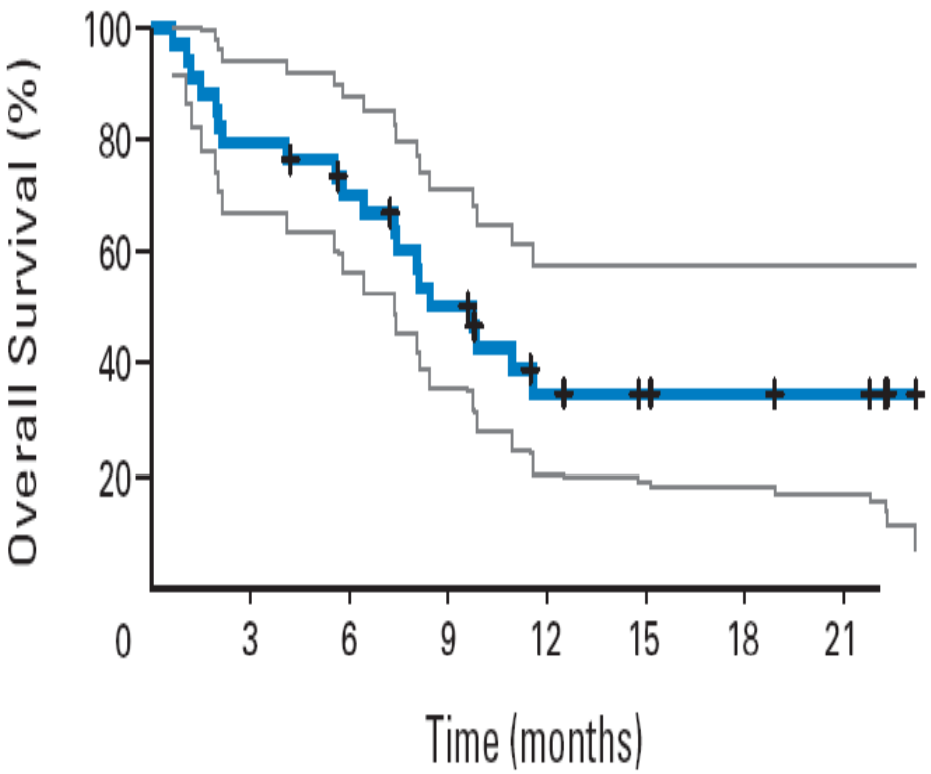
Phase II studies of sunitinib in CHC

Median OS: 8 months



Faivre S et al, Lancet Oncol, 2009

Median OS: 9.8 months



Zhu AX et al, J Clin Oncol, 2009

Brivanib in HCC patients failing prior antiangiogenic therapy - 2nd-line

- **Phase II in 46 patients with unresectable locally advanced or metastatic HCC who had failed:**
  - **Sorafenib**
  - **Thalidomide**
  - **(sunitinib or bevacizumab)**
- **Disease control rate : 46%**
- **Median (investigator-assessed) TTP: 2.7 months**
- **Median OS 9.8 months**

Raoul ASCO 2009; Finn ASCO GI 2009

Linifanib (ABT-869): Phase II trial in advanced HCC patients

- Potent and selective oral inhibitor of VEGF and PDGF RTKIs
- 44 patients treated until PD, ≥1 prior systemic therapy and at least 1 measurable lesion

Endpoint	Child Pugh A n=38 (95%CI)	Child-Pugh B n=6 (95%CI)	All pts n=44 (95%CI)
Progression-free 16wks - %	34.2 (19.6, 51.4)	16.7 (0.4, 64.1)	31.8 (18.6, 47.6)
Overall response rate - %	7.9 (1.7, 21.4)	0	6.8 (1.4, 18.7)
Time to progression* (TTP) - months	5.4 (3.6, 14.1)	3.7 (0.7, NR	3.7 (3.6, 7.3)
TTP radiographic *- months	5.4 (3.6, NR)	NR (3.7, NR)	5.4 (3.6, NR)
Overall survival* - months	10.4 (8.4, 14.9)	2.5 (1.1, 4.5)	9.7 (6.3, 12.2)
*Estimated median			

- 1 death possibly related to Lanifanib (intracranial hemorrhage, Day 111, C-P B pt

Toh H et al. ASCO 2010; abstract #4038

Other multitarget tyrosine kinase inhibitors

- **Sunitinib** – Pfizer – phase III trial – Terminated
  - VEGFR/PDGFR
  - Primary endpoint OS
- **Brivanib** – BMS – Phase III trial – Ongoing
  - VEGFR/FGFR
  - Primary endpoint OS
- **Linifanib** – Abbott – Phase III trial - Ongoing
  - VEGFR/PDGFR
  - Primary endpoint OS

Hypoxia-dependent VEGF expression present at baseline may be further enhanced during VEGFR therapy

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

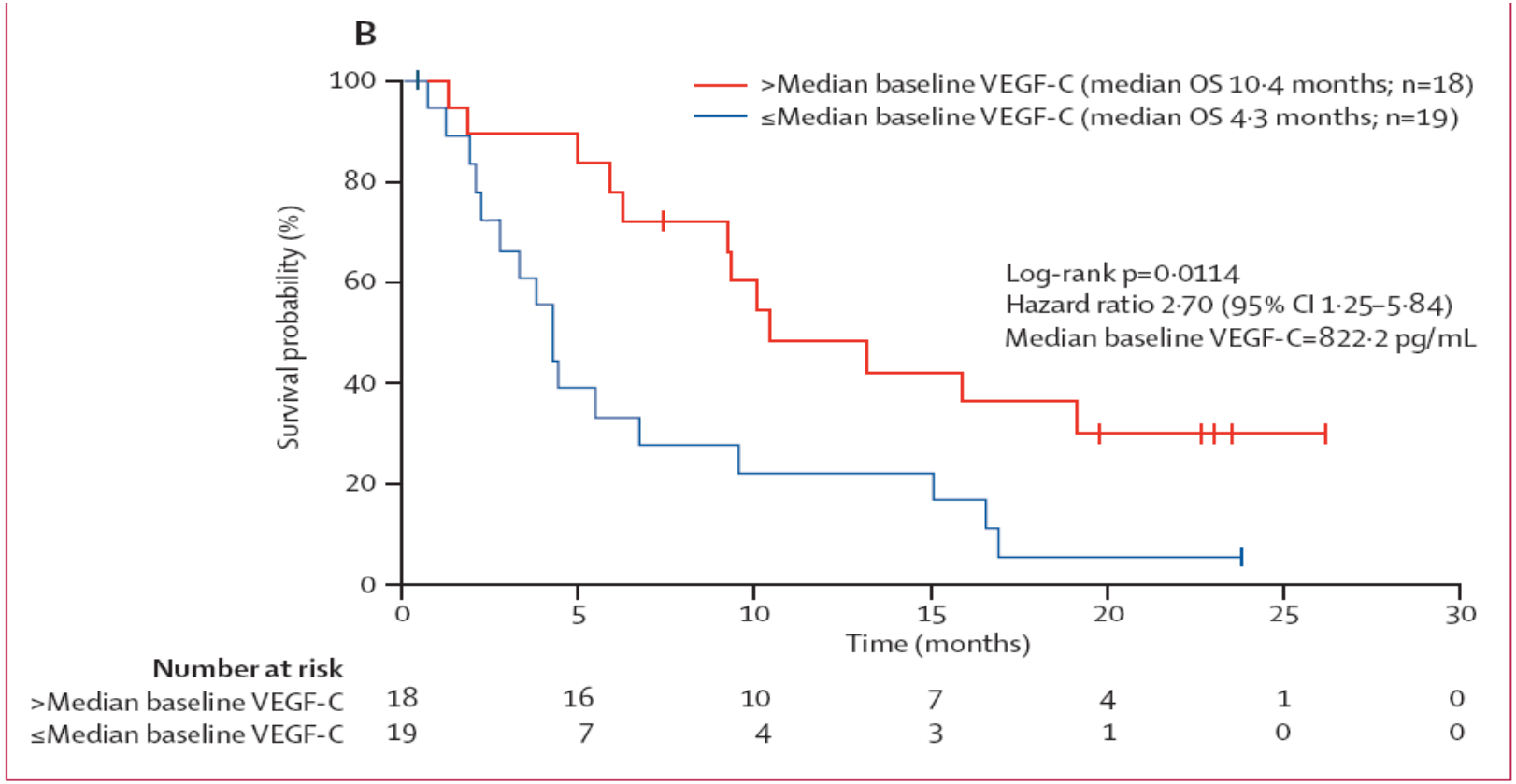
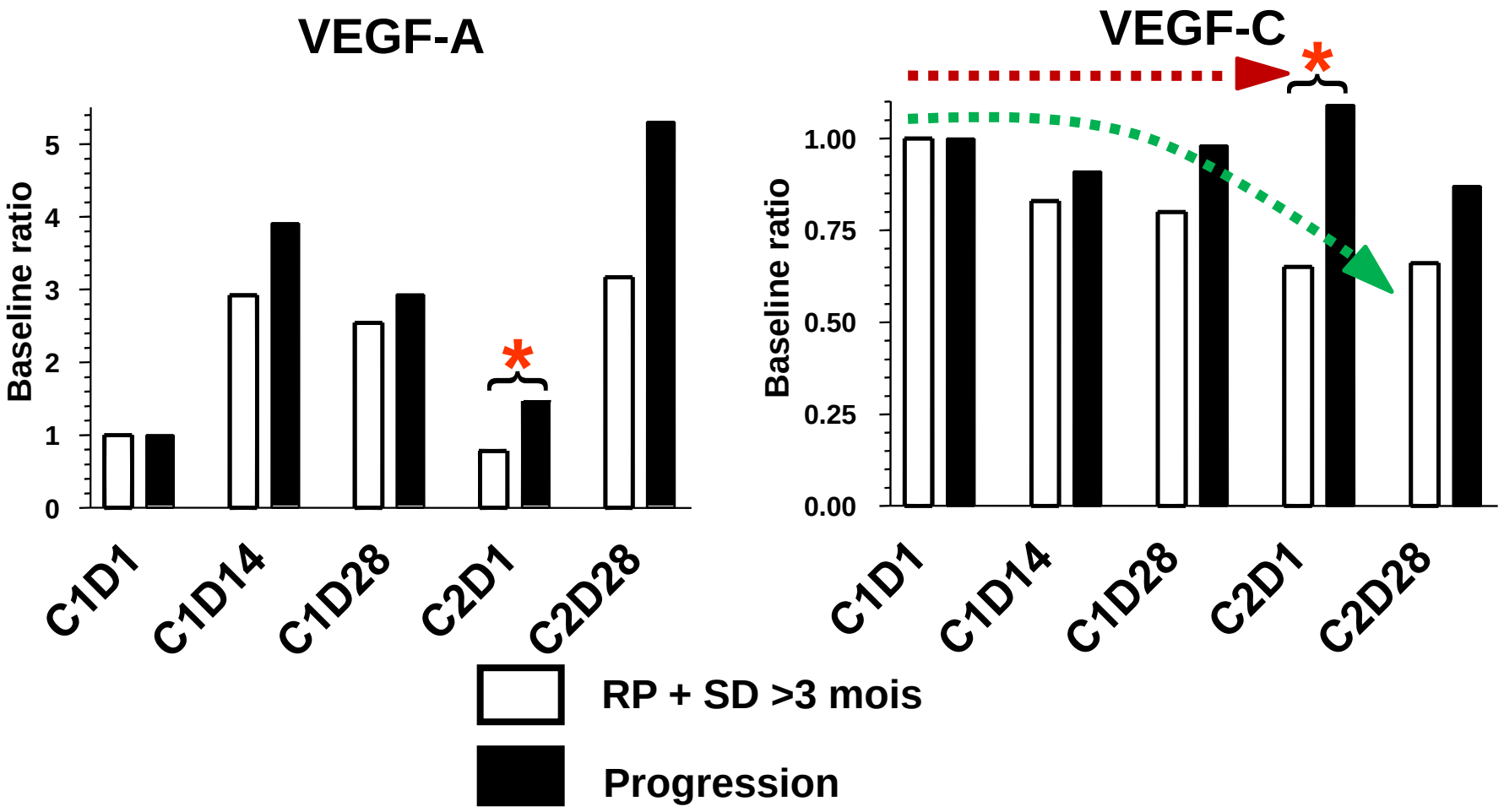


Figure 3: **Predictive value of vascular endothelial growth factor (VEGF) C in patients with advanced hepatocellular carcinoma treated with sunitinib**

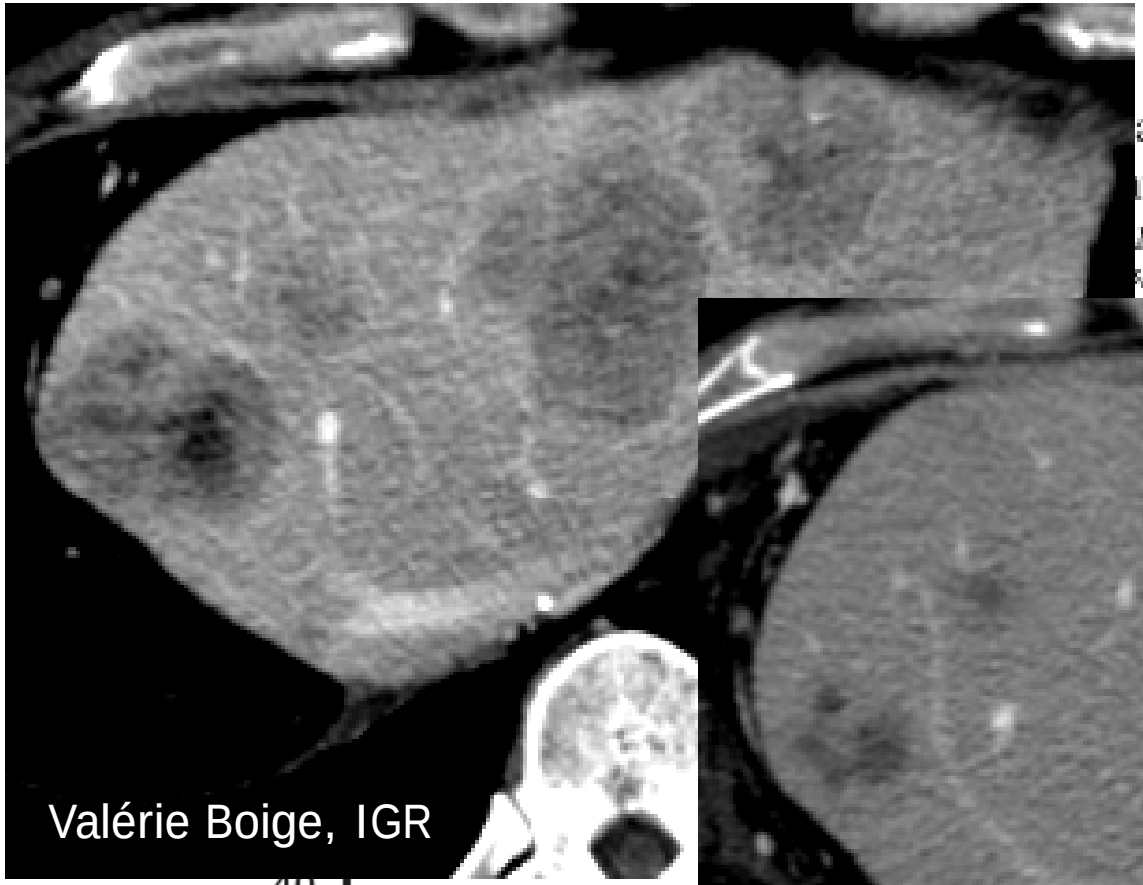
Lancet Oncol 2009; 10: 794–800

Changes from baseline VEGF levels in patients treated with sunitinib



*Significance assessed by Wilcoxon rank-sum test with two-sided P-value <0.05; PR = partial response; SD = stable disease; C = cycle; D = day

Bevacizumab in HCC



al and Biologic Effects of
tocellular Carcinoma

lec Goldenberg, Jennifer J. Knox, Hden Chen,
, Madhu Mazumdar, Elizabeta Papa,

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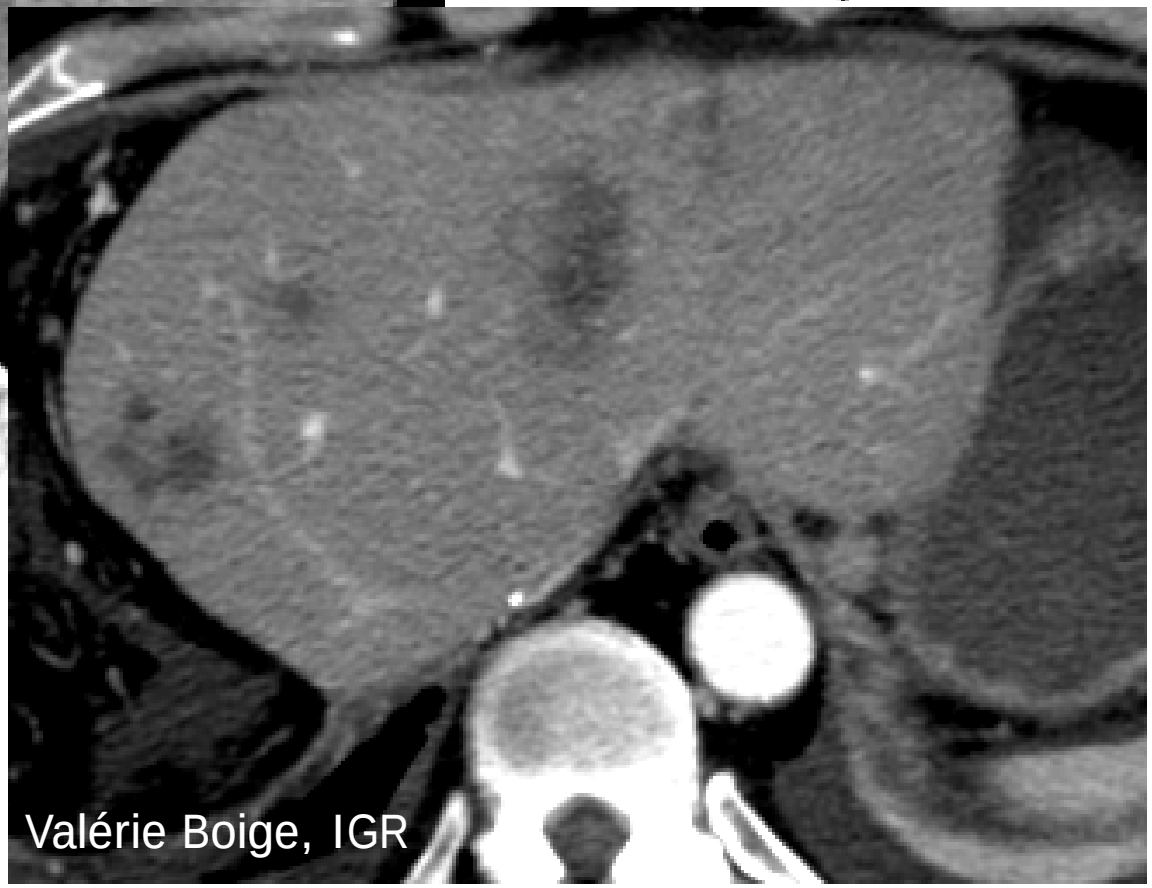


Resistance to first line treatment with sorafenib leads to educated guess for second line proposals

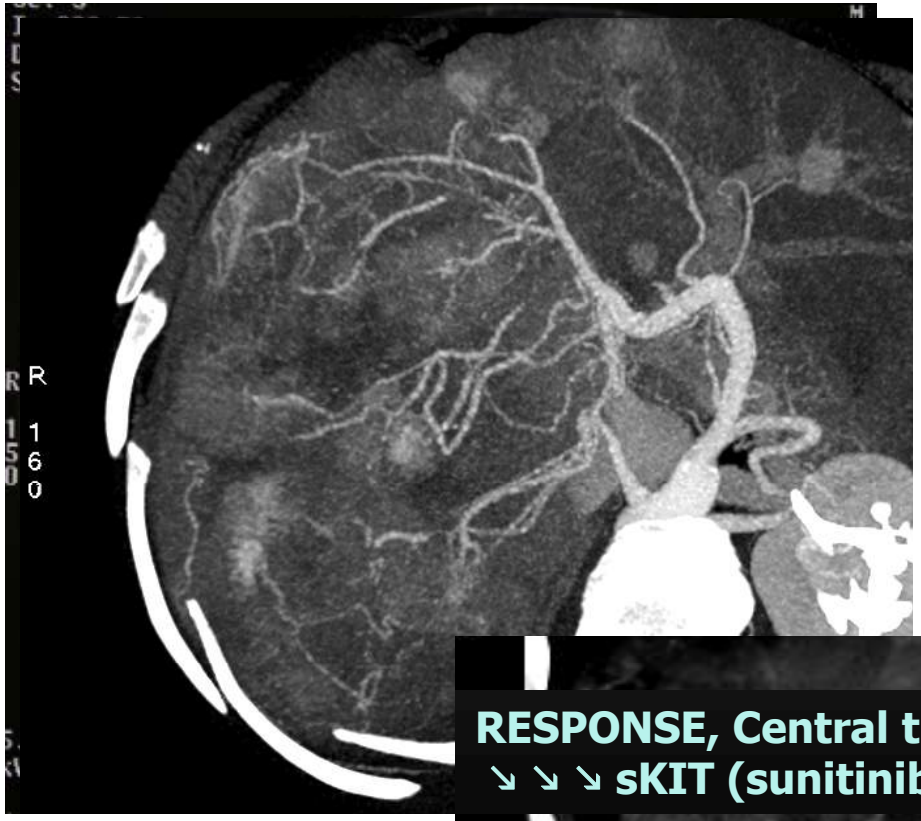
Two large second line randomize trials

- Everolimus (RAD001) *versus* placebo
  - Rational: inhibiting mTOR acitvation
  - Novartis
  - 531patients
  - Overall survival

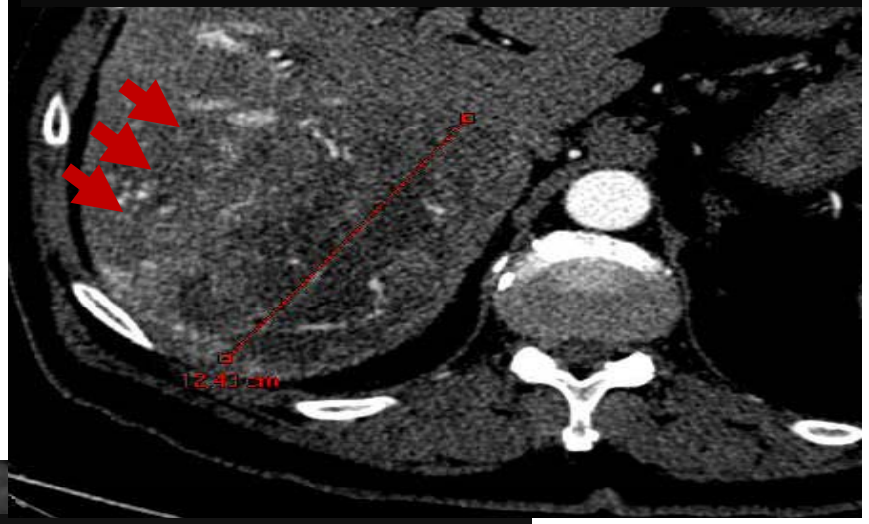
- Brivanib *versus* placebo
  - Rational: inhibiting FGFR
  - BMS
  - 340 patients
  - Overall survival

Other agents and combinations under investigation

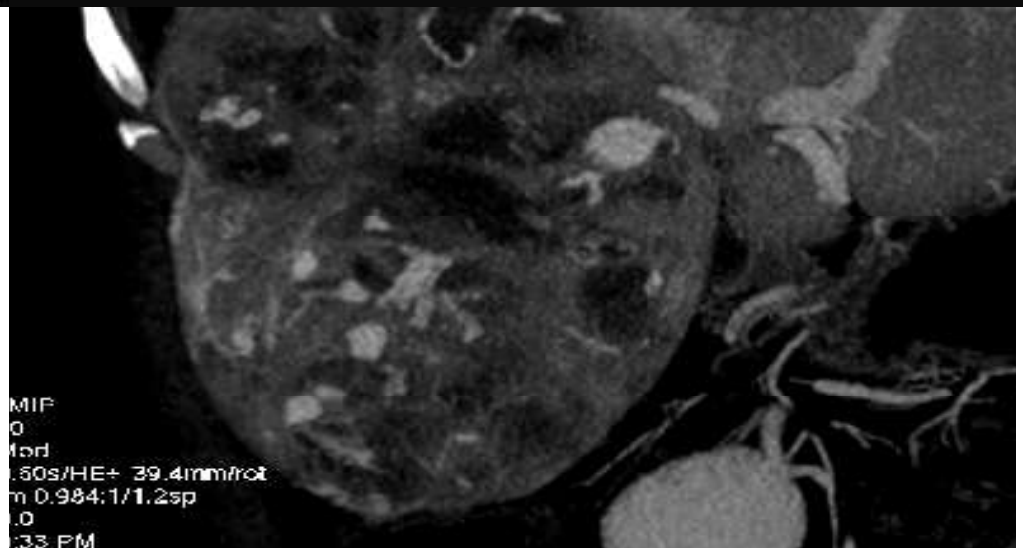
- **Maputumumab + sorafenib**
- **Octreotide**
- **OSI single-agent**
- **Tegafur + sorafenib**
- **SECOX- Cape + oxaliplatin + sorafenib 1st-line**
- **5-FU + sorafenib 1st-line**
- **LBH 589 + sorafenib**
- **SIR spheres + sorafenib**
- **MEK inhibitors**

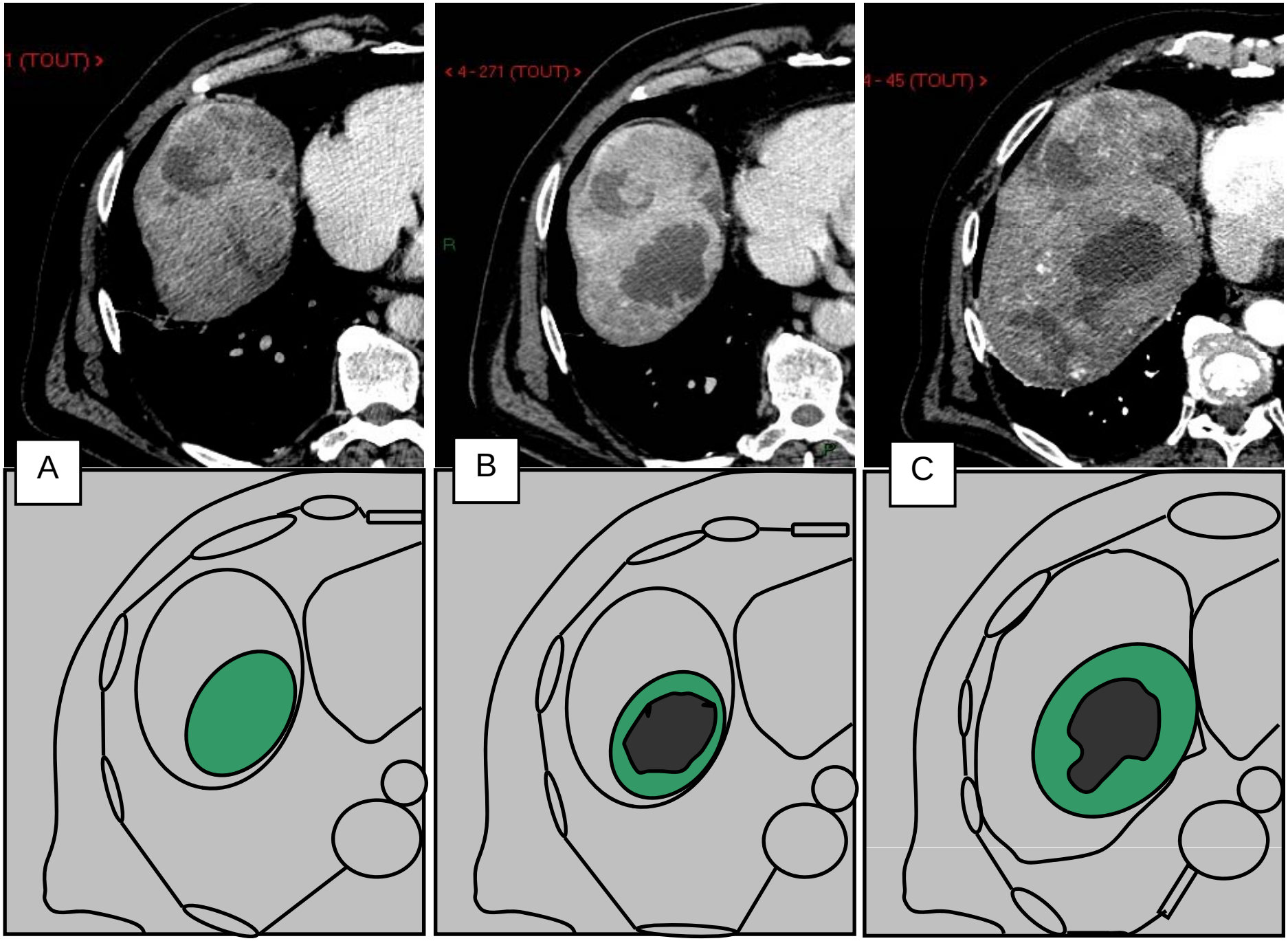


RESISTANCE, No Necrosis
↗ sKIT, ↗ AFP, ↗ SDF1 (sunitinib)
Limited decrease in HGF (sorafenib)

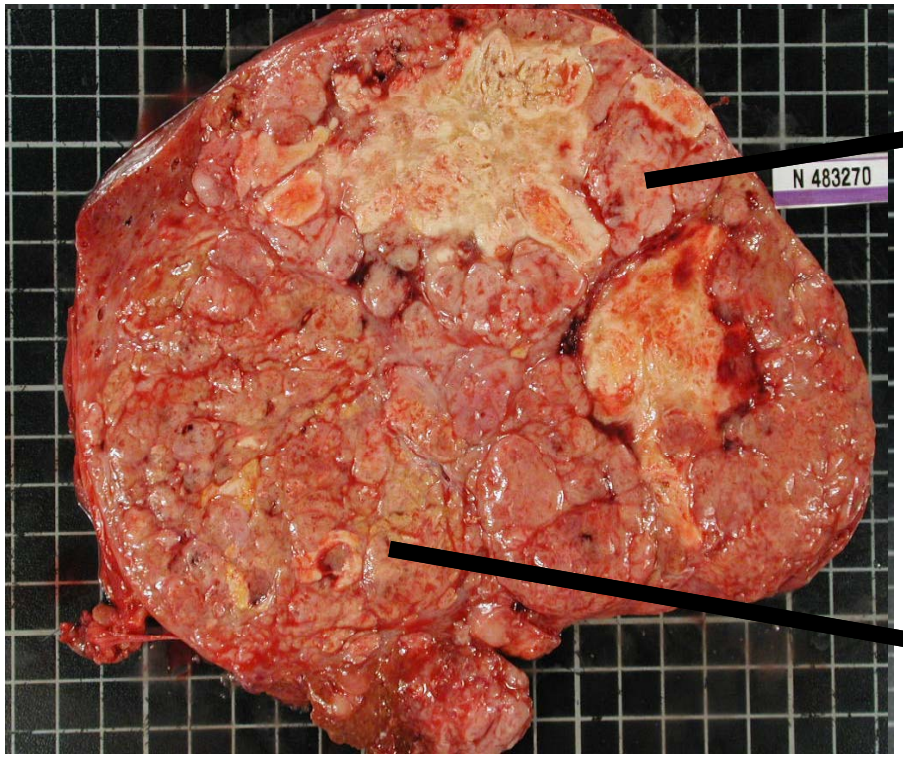


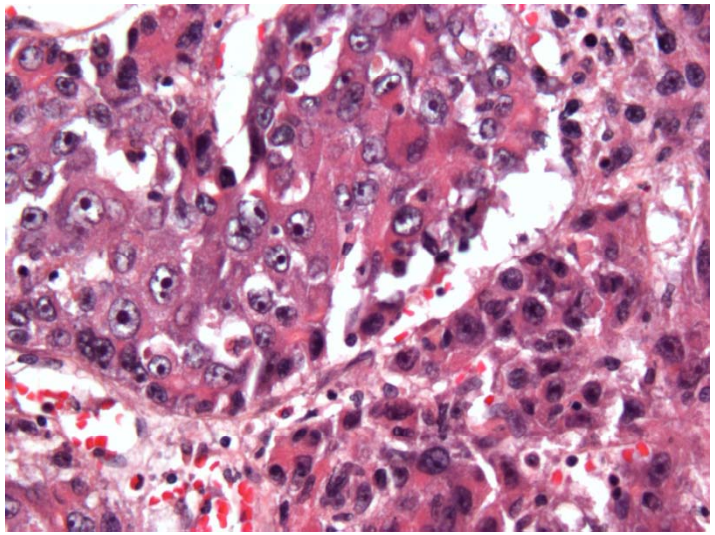
RESPONSE, Central tumor necrosis
↘ ↘ ↘ sKIT (sunitinib), ↘ ↘ ↘ HGF (sorafenib)

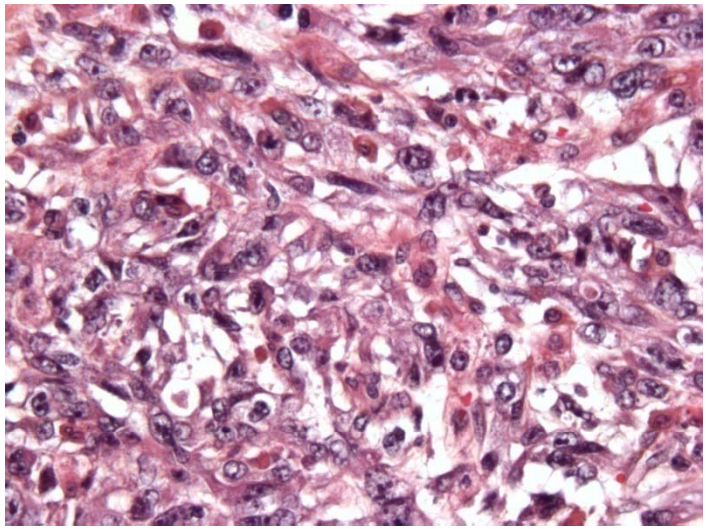



A
B
C

Pathological examination of the tumor at the time of resistance to sunitinib

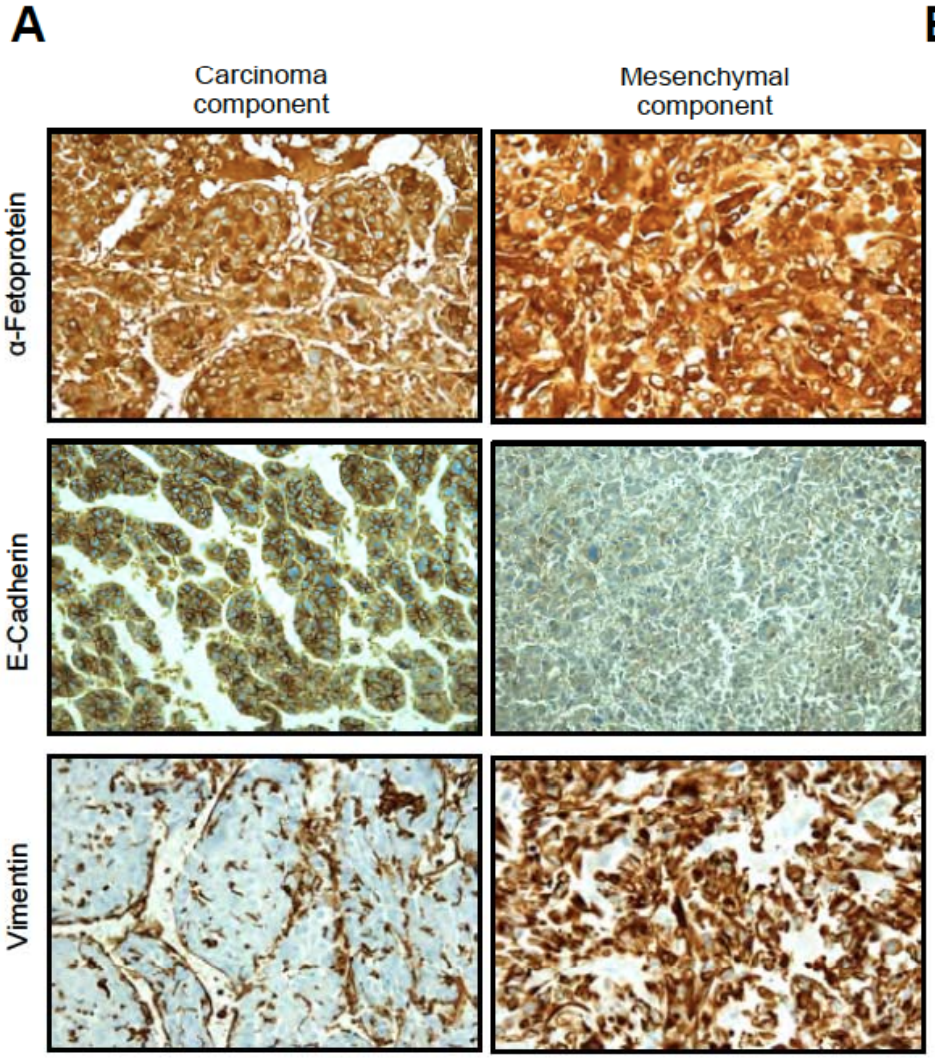


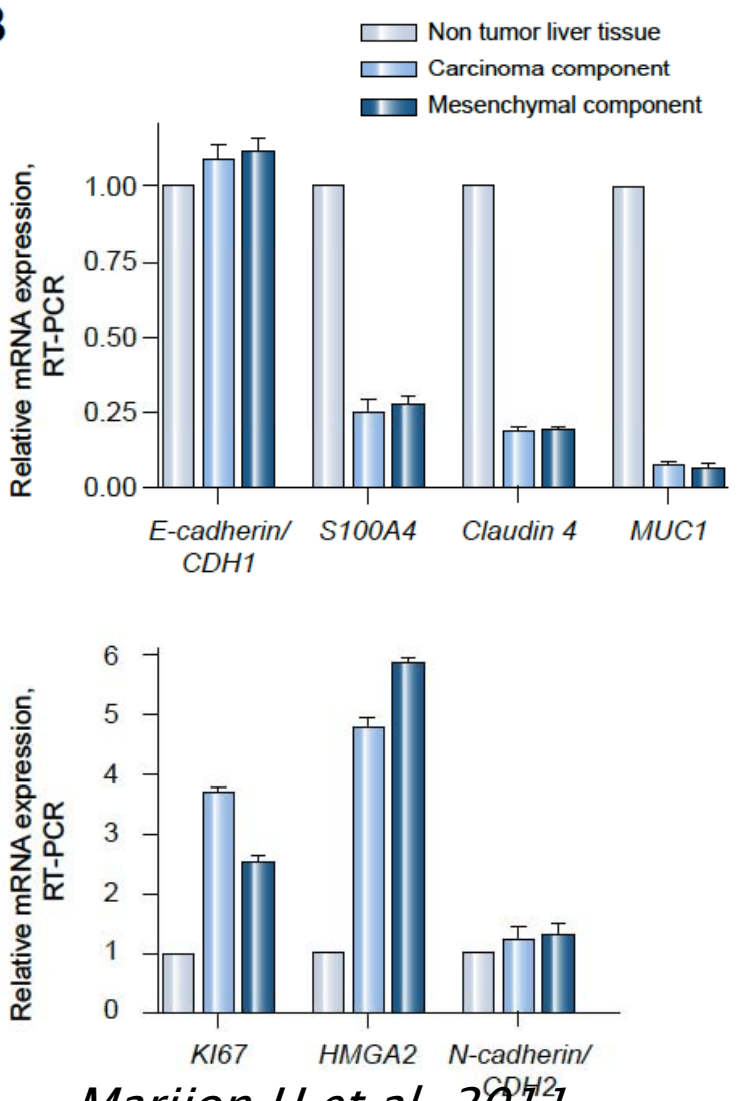




Marijon H et al. 2011

Resistance to sunitinib is associated with changes that suggested mesenchymal transition

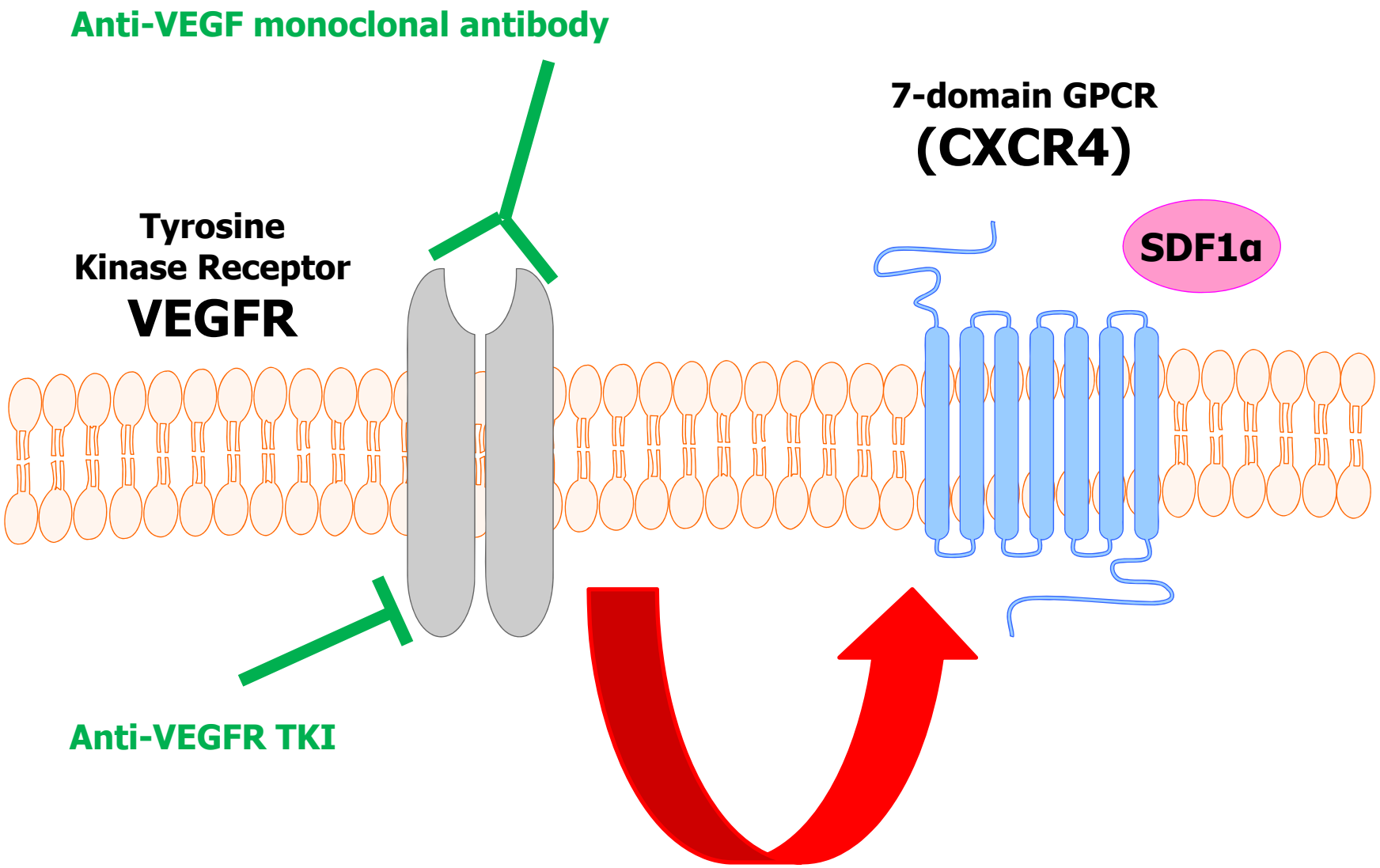




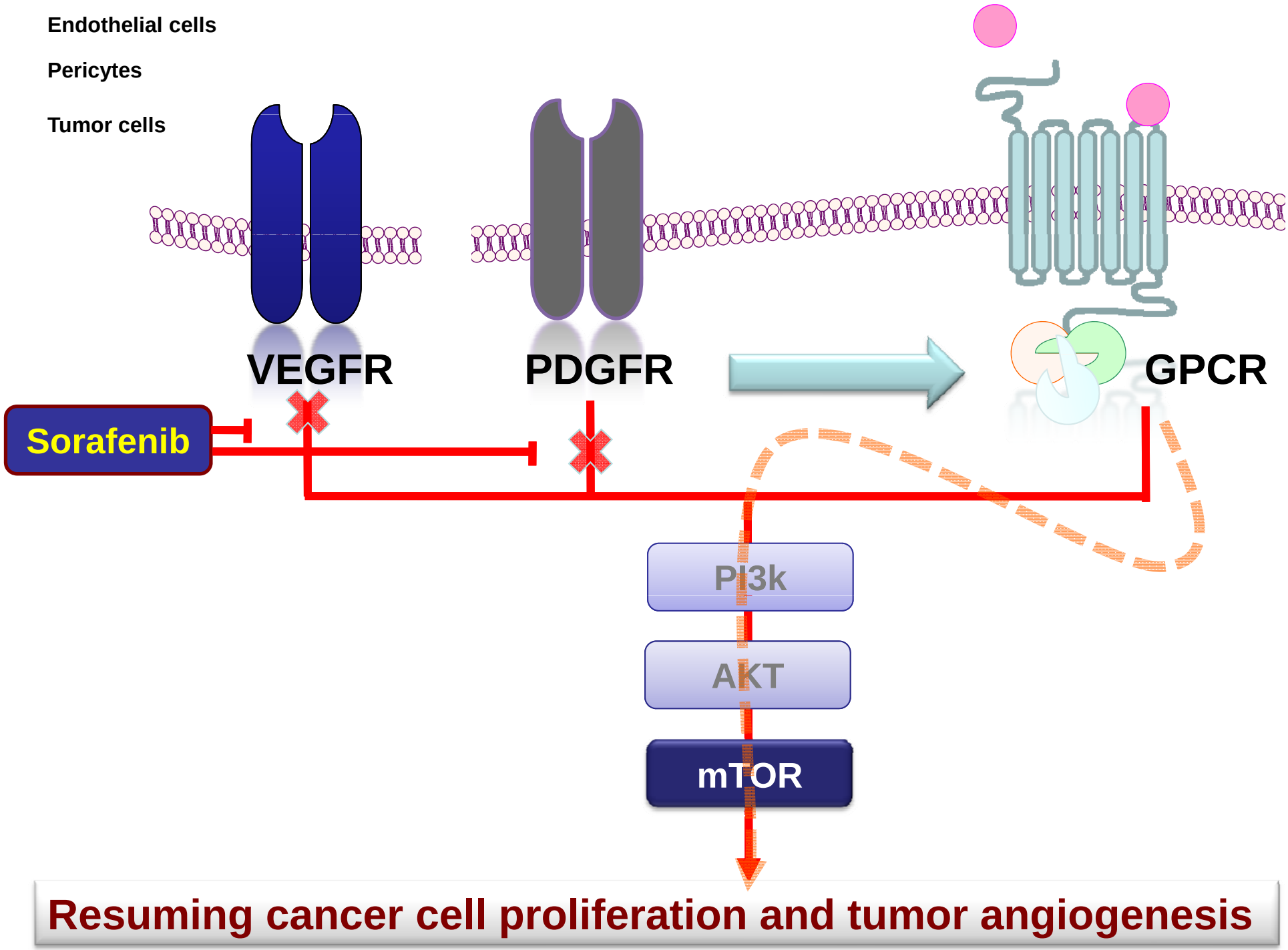
Marijon H et al. 2011

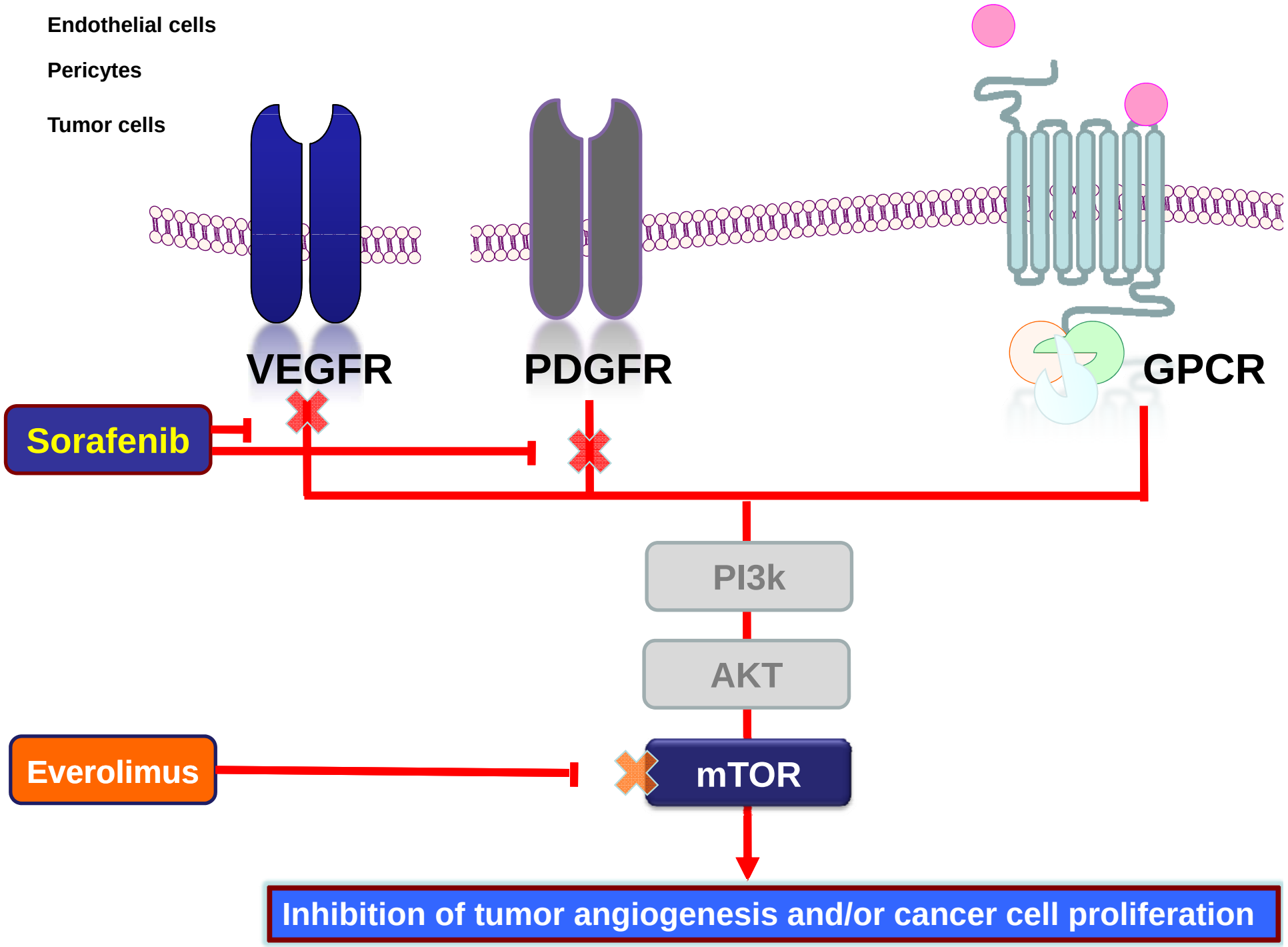
« Patients with more elevated AFP, IL-6, soluble c-KIT, SDF1, sVEGFR1, and CPCs at any time point during sunitinib treatment were associated with higher hazard of immediate progression or mortality (*P <.05)"*

Zhu AX et al. J Clin Oncol 2009, 27: 3027

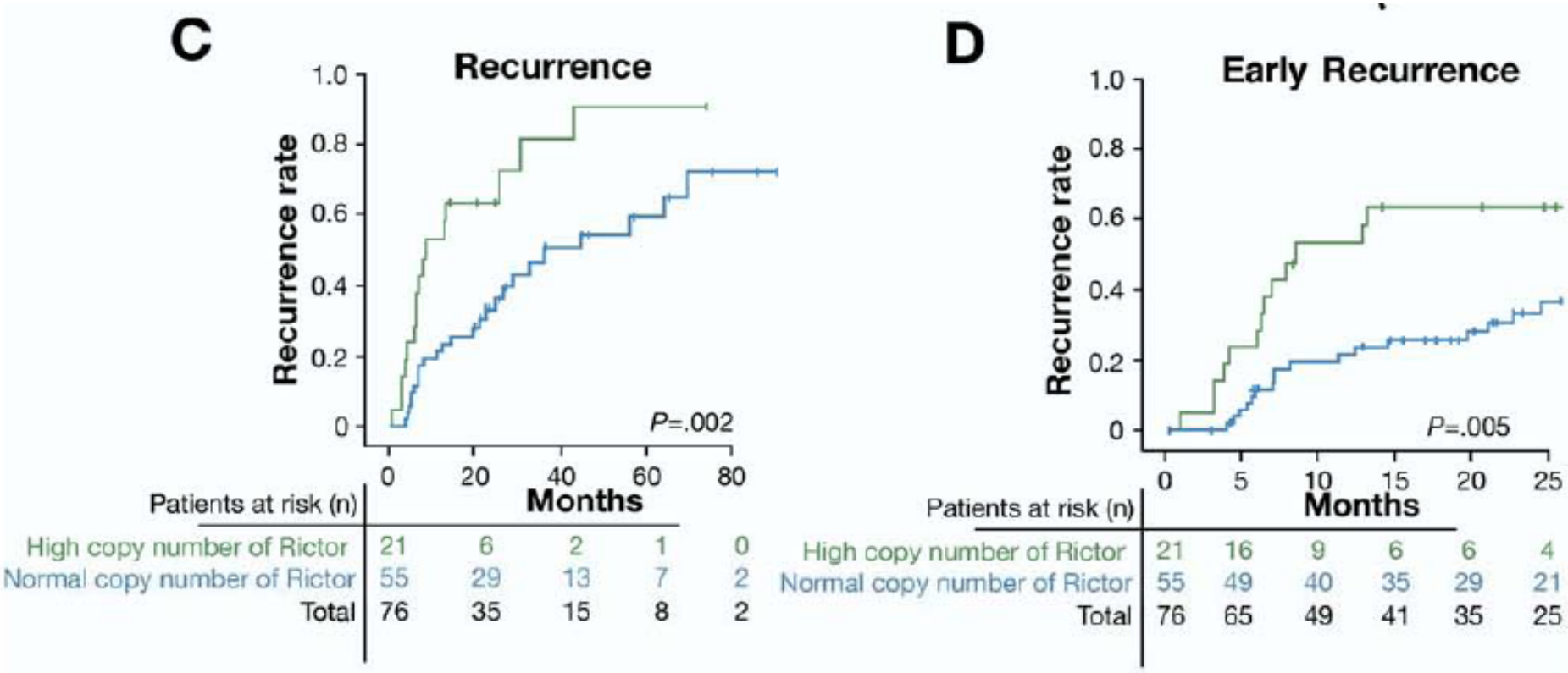


Acquired resistance to VEGF/VEGFR inhibitors involving SDF1α/CXRC4 alternative signalling pathways


Endothelial cells
Pericytes
Tumor cells
VEGFR
PDGFR
GPCR
Sorafenib
PI3k
AKT
mTOR
Resuming cancer cell proliferation and tumor angiogenesis

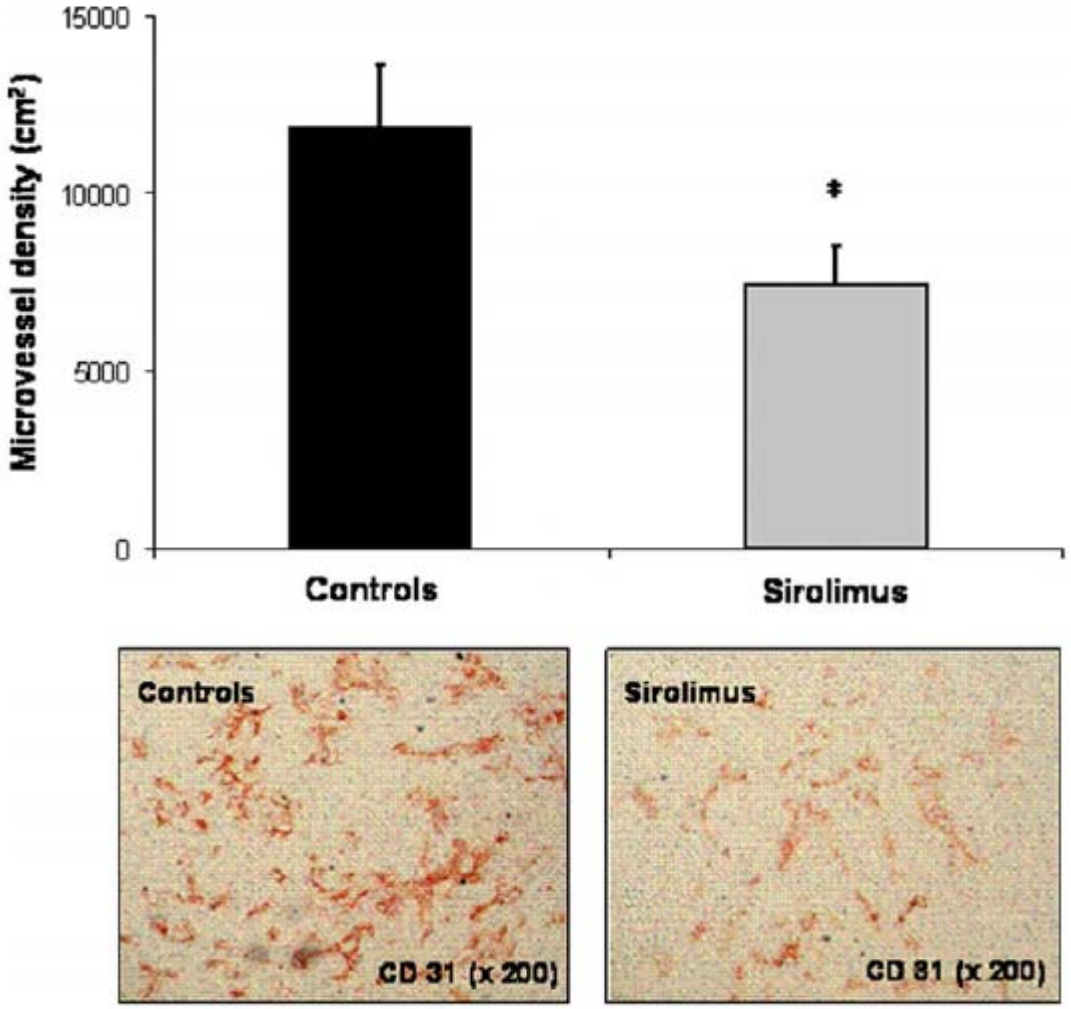

Endothelial cells
Pericytes
Tumor cells
VEGFR
PDGFR
GPCR
Sorafenib
PI3k
AKT
Everolimus
mTOR
Inhibition of tumor angiogenesis and/or cancer cell proliferation

High copy number of Rictor seems to be an important pronostic factor in HCC

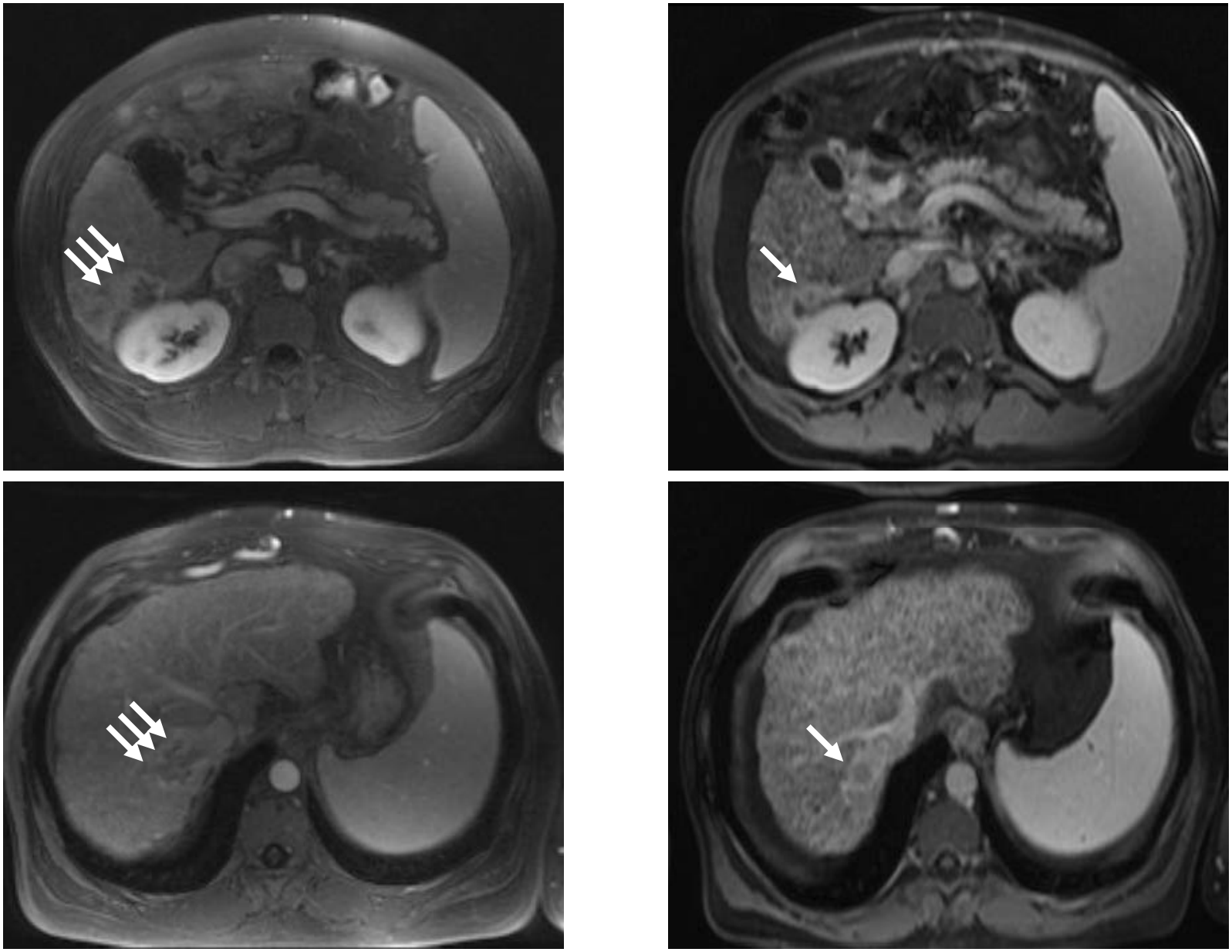


Villanueva A et al, Gastroenterology 2008

Rapamycin blocks tumor growth and angiogenesis in HCC mouse xenografts



Semela D et al, J Hepatol, 2008

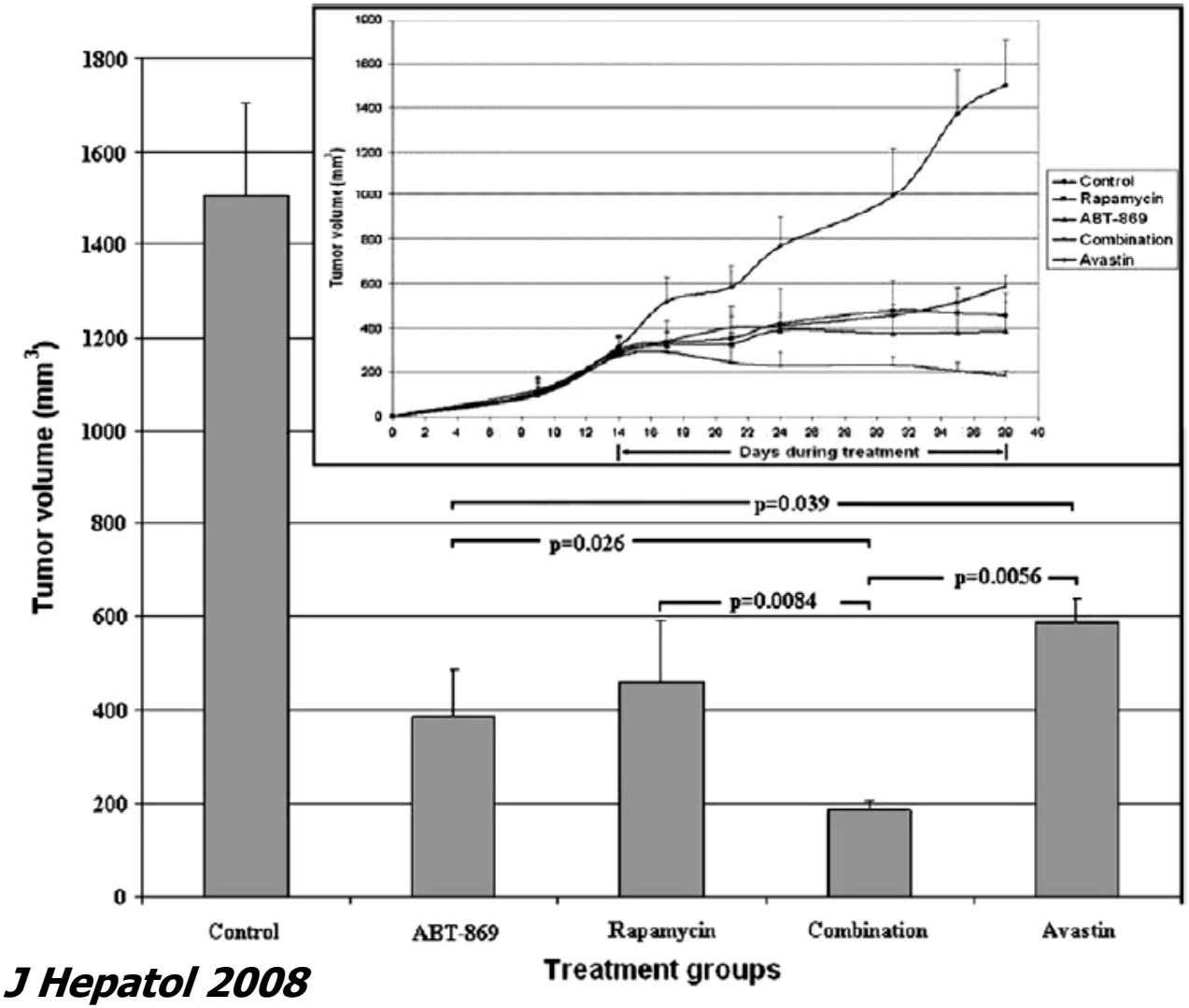


Baseline, sum of diameters : 60 mm

After 2 months, sum of diameters : 37 mm

Courtesy of Dr Thomas Decaens, Henri Mondor Hospital, France

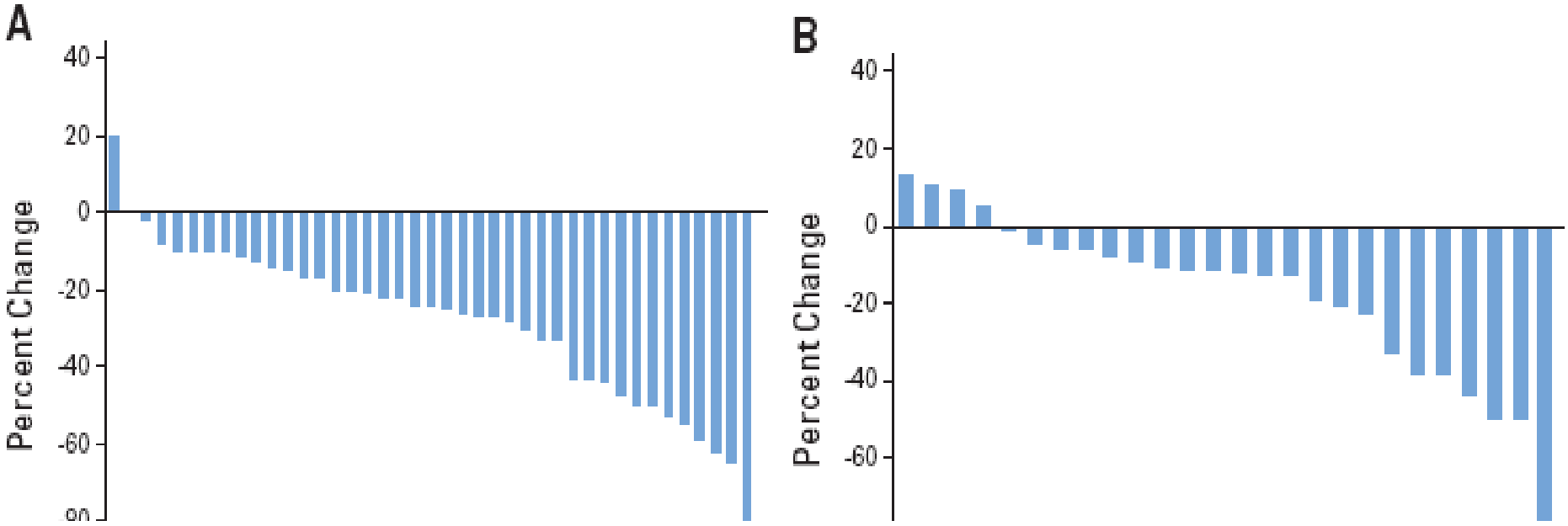
Rapamycin potentiates the effects of VEGF/VEGFR inhibitors in SK-Hep1 mouse xenografts



Jasinghe VJ et al. J Hepatol 2008

Phase II Trial of Bevacizumab and Everolimus in Patients With Advanced Renal Cell Carcinoma

John D. Hainsworth, David R. Spigel, Howard A. Burris III, David Waterhouse, Bobby L. Clark, and Robert Whorf



Bevacizumab/everolimus is active and well tolerated in the treatment of advanced clear cell renal cancer, either as first-line treatment or after treatment with sunitinib and/or sorafenib.

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CONCLUSIONS

- **First line trials**
  - **Either investigate the effect of sorafenib-based combinations (with cytotoxic and targeted agents)**
  - **Or challenge sorafenib with novel drugs (with similar mechanisms of action)**

- **Second line trials**
  - **Potentially more potent VEGFR/PDGFR inhibitors and mTOR inhibitors are currently considered**
  - **Should take into account the potential progression of cirrhosis i.e. select drugs with favorable safety profile**
  - **Are primarily based on a rational developed based on understanding resistance to sorafenib**

- **Access to tumor tissue (biopsy, surgical specimen) may contribute to comprehensively select targeted therapies for future trials and provide individualized therapeutics**

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