Molecular Biology of Hepatocellular Carcinoma and Targeted Therapies

First International Course on Translational Hepatology:
Focus on HCV Disease
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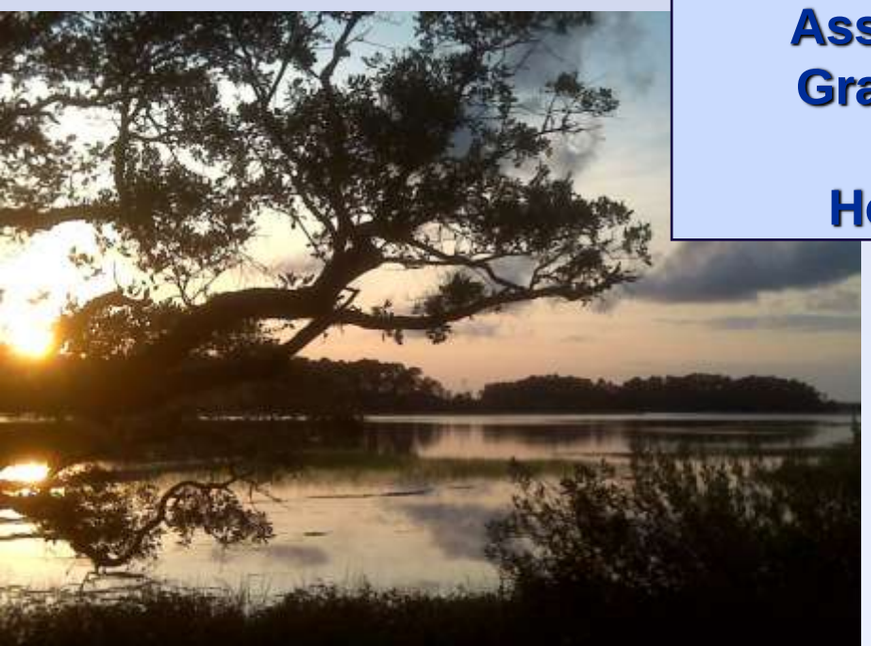

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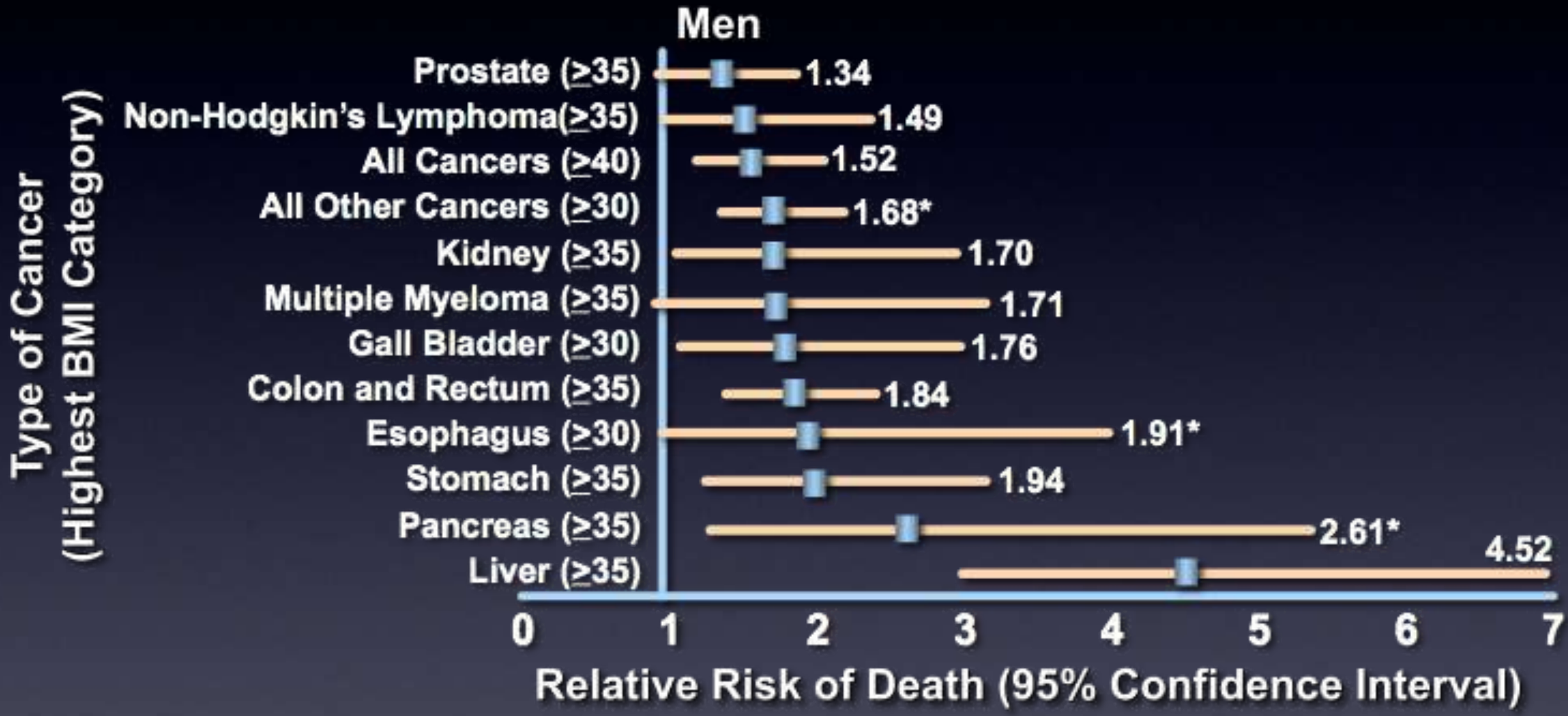
Hepatocellular Carcinoma (HCC) is a Challenging Cancer

- **HCC is a complex malignancy:**
  - Multiple etiologies:
    - HBV, HCV, alcohol, fatty liver,
    - hemochromatosis, alpha-1 anti-trypsin deficiency, other metabolic diseases,
    - exogenous hormones, autoimmune hepatitis, aflatoxin-B exposure.
  - Inflammatory environment of cirrhotic liver contributes to carcinogenesis.
- ***HCC is predicted to increase 4-fold in the U.S.***
- **Why is HCC Incidence Increasing?**
  - Rising incidence of cirrhosis from multiple causes.
  - Large pool of *>4,000,000 HCV+ individuals* who acquired HCV prior to identification & screening, plus *38,000 new cases annually.*
  - Increasing prevalence of obesity, fatty liver (non-alcoholic fatty liver disease, NAFLD).
  - Improved survival for patients with cirrhosis.

Obesity and Liver Cancer

Calle, et al, NEJM 2003

Mortality from Cancer in Obese US Men (n=900,053)

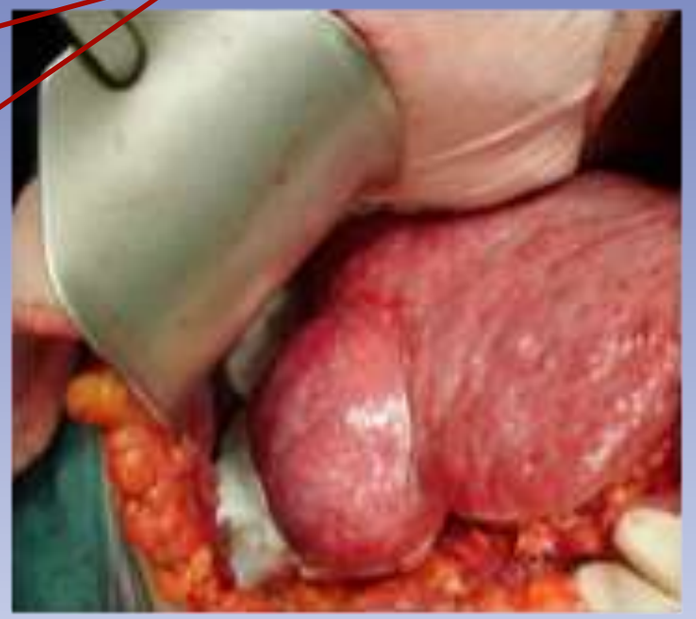


Calle EE, & et al, N Engl J Med 2003

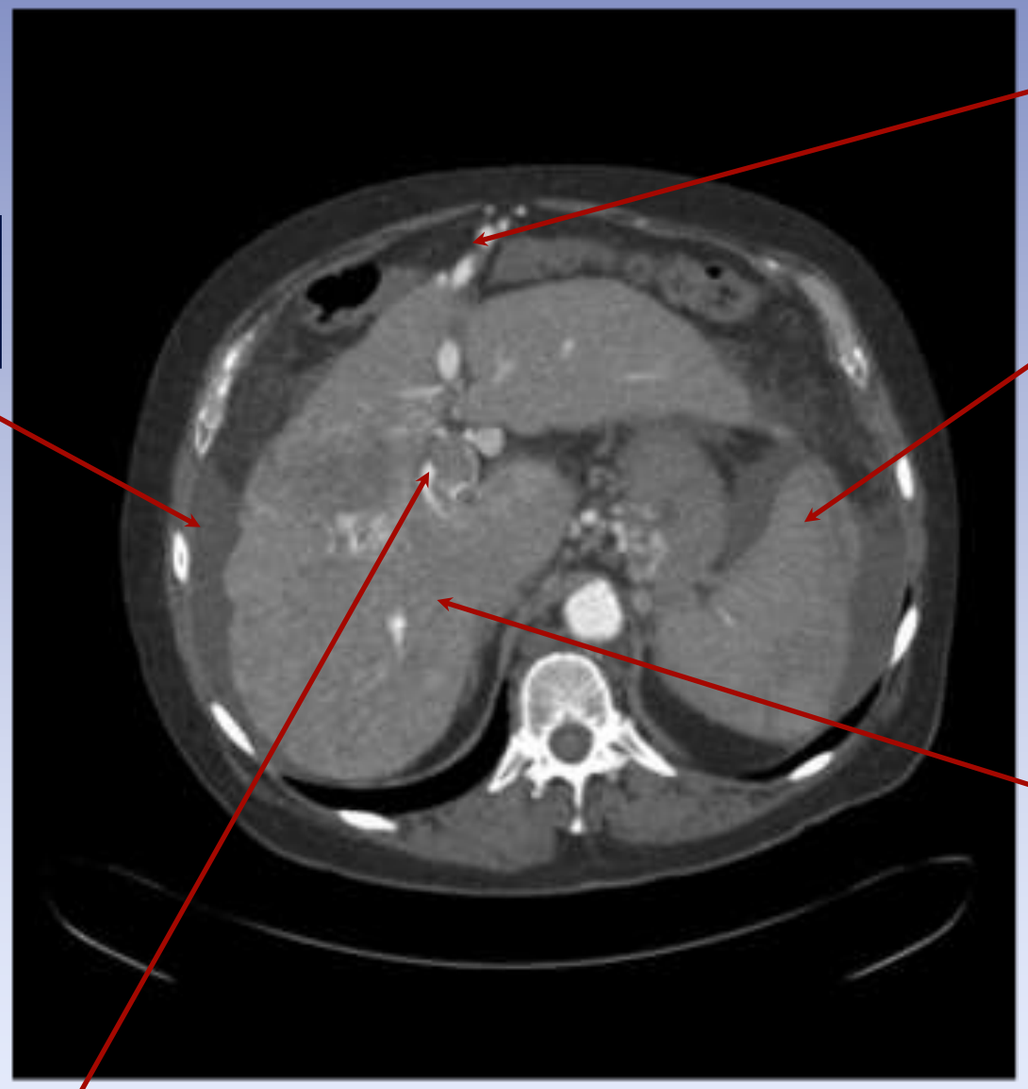
HCC is unique - one patient, two diseases:

Consequences of cirrhosis:

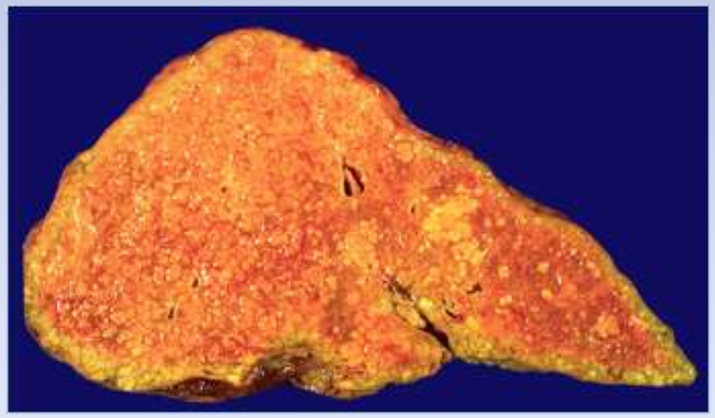
Portal hypertension leads to splenomegaly, varices.



Ascites



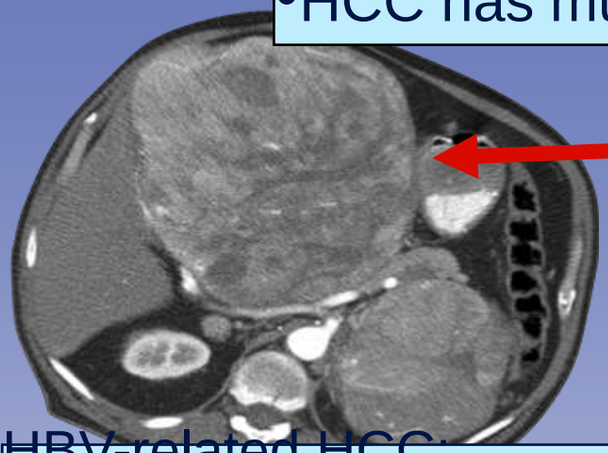
Diffuse nodular, fatty liver



Main portal vein thrombus

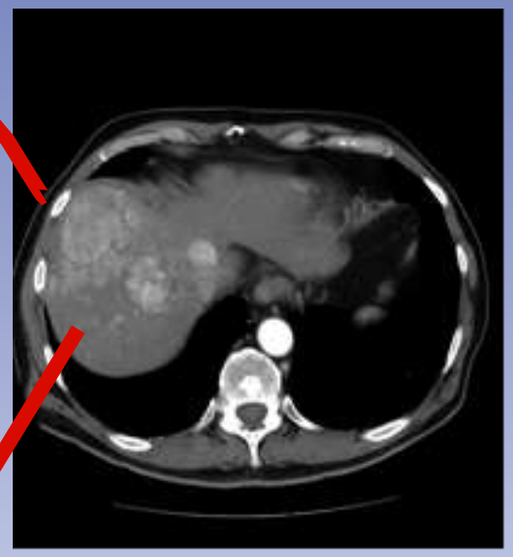
HCC is unique - one patient, two diseases:

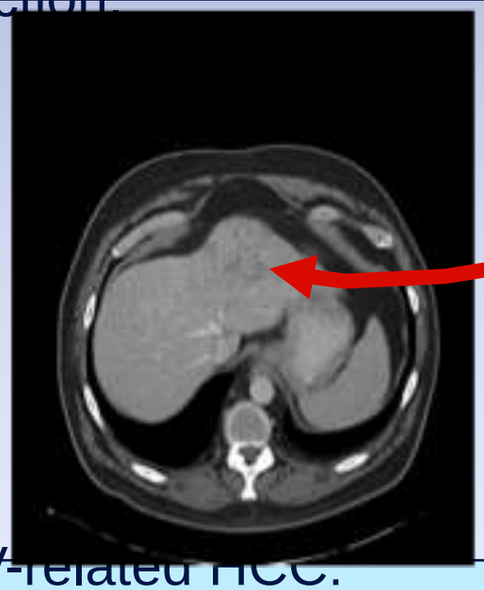
- HCC has multiple underlying etiologies > yields a molecularly complex tumor:



HBV-related HCC:

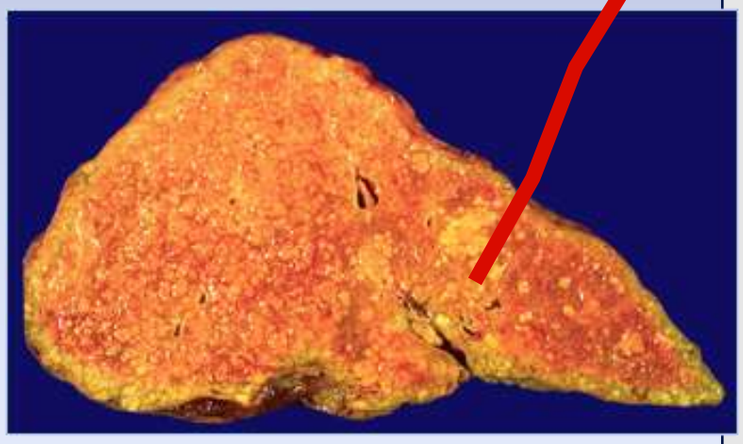
- <50% develop in cirrhosis.
- Typically form large dominant masses with tumor capsule.
- Young patients, normal hepatic function.





HCV-related HCC:

- >90% in cirrhosis.
- Diffuse, infiltrative, multifocal HCC.
- Older patients, mild-severe hepatic dysfunction.



- Cirrhosis = “field defect” - entire liver is a premalignant lesion
- High recurrence rates after resection, locoregional therapy
- Cirrhosis > portal HTN > thrombocytopenia > impaired synthetic function >GIB risk.
- Co-morbidities of cirrhosis complicate clinical trial design for new chemotherapeutic agents, patient recruitment.

Current HCC Treatment Algorithm

Liver Transplantation

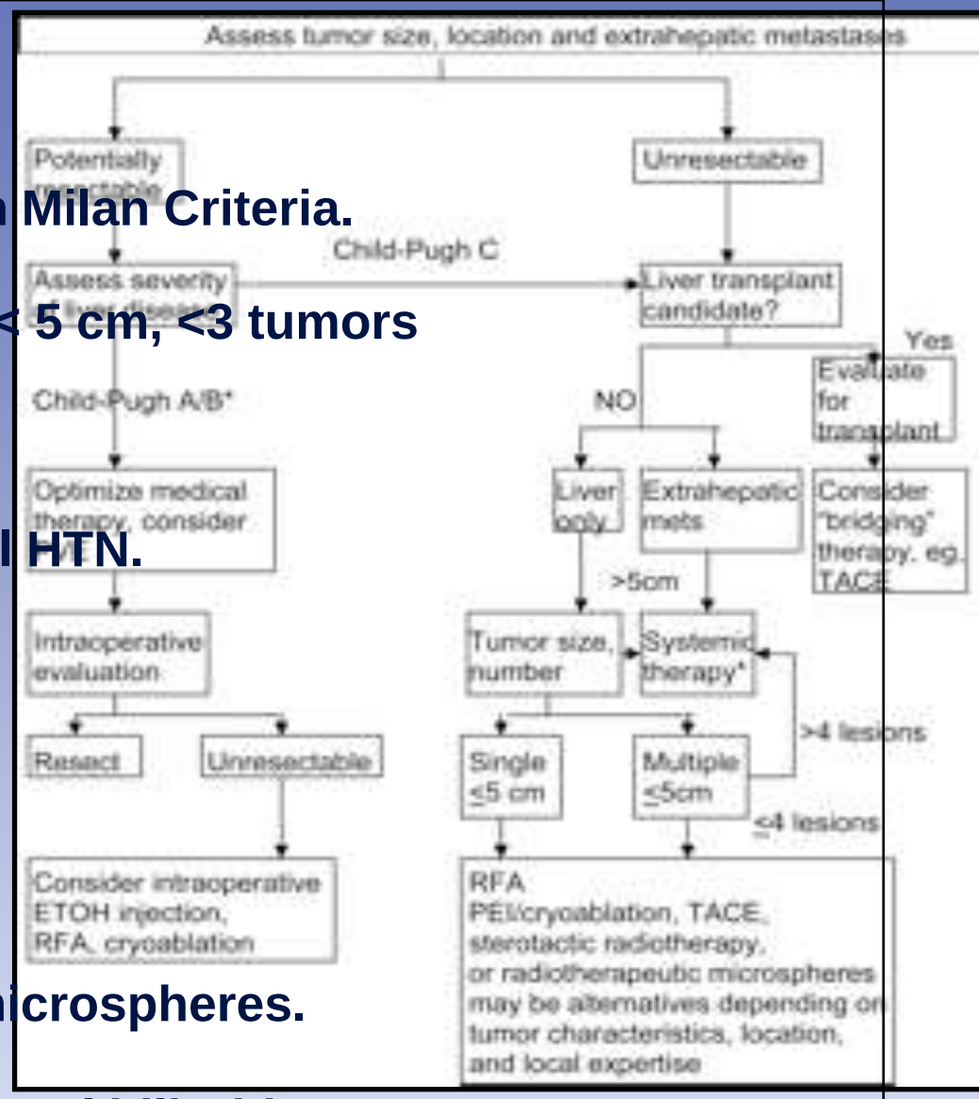
- **Current 5 year survival 65-75% for patients transplanted within Milan Criteria.**
- **No extrahepatic disease, no gross vascular invasion, 1 tumor < 5 cm, <3 tumors**

Hepatic resection

- **Few patients eligible due to cirrhosis; contraindicated in portal HTN.**
- **Recurrence rate 50% at 18 months.**

Regional therapy - field is rapidly evolving

- **Trans-arterial selective delivery of embolic material +/-:**
- **cytotoxic agent, drug-eluting beads, yttrium90-embedded microspheres.**
- **Level 1 evidence of benefit only for solitary tumors < 8 cm, normal bilirubin.**
- **Contraindicated when bilirubin >3, main PVT.**
- ***Advanced HCC >75% of patients:***
- **Median survival 6-8 months**
- **Sorafenib improves median survival from 7.9 to 10.7 months , but with chronic side effects.**



Systemic chemotherapy for patients with advanced HCC

- HCC is a highly chemotherapy-resistant tumor.
- Hepatocytes and HCC cells produce over express multi-drug resistance (mdr1) gene > produce cellular efflux pumps.
- Numerous classes of conventional cytotoxic drugs have been studied in HCC:
  - Anthracyclines
  - Taxanes
  - Anti-metabolites
  - interferons
  - cell cycle inhibitors

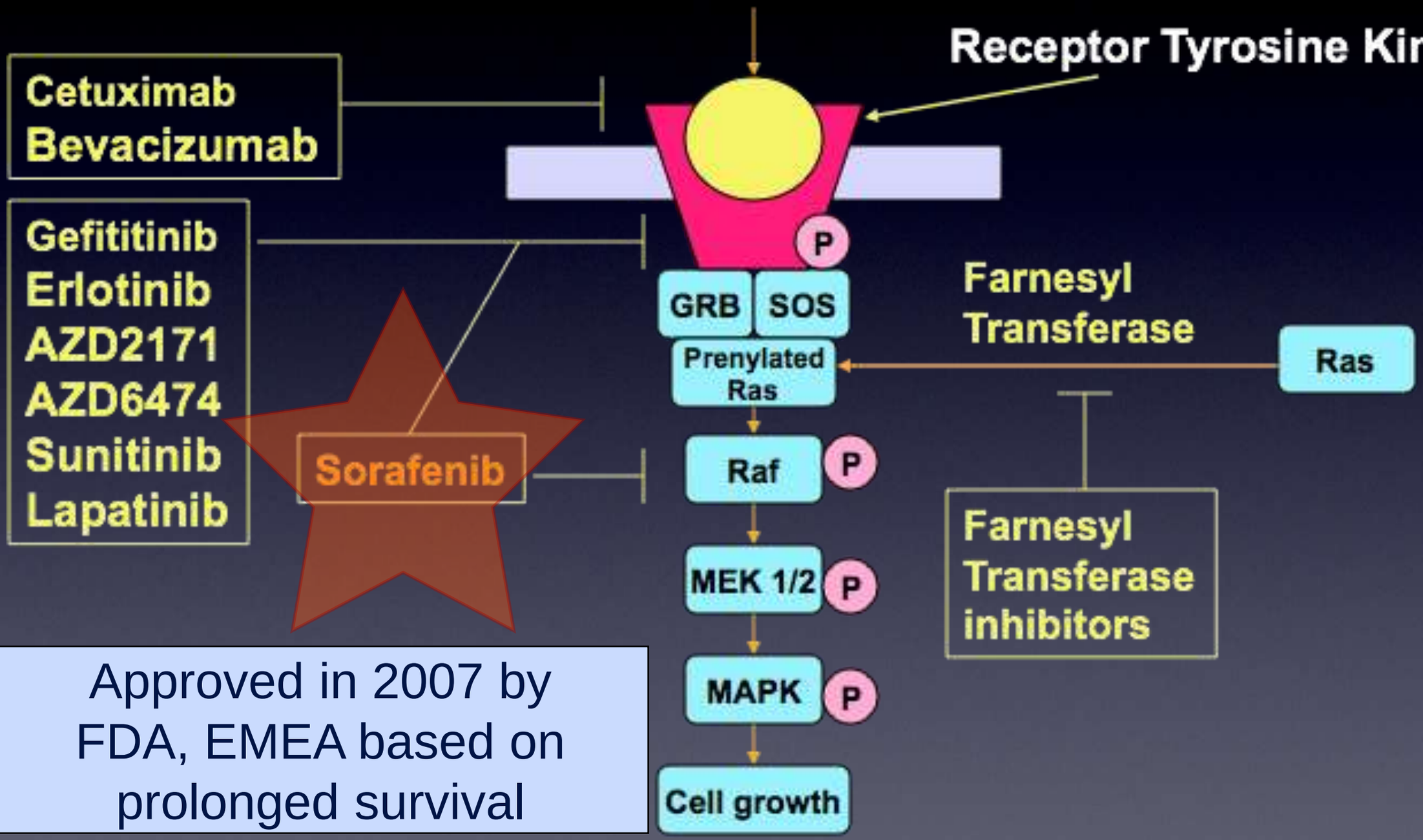
Despite 30 years of clinical trials of numerous chemotherapy agents, no drug or combination showed patient benefit.

Negative Randomized Chemotherapy Clinical Trials in HCC

Study	Regimen	Phase	N	RR%	MS (mos)
Yeo JNCI 2005	*PIAF vs adriamycin	III	94/94	20.9 vs 10.5	8.6 vs 6.83
Posey et al ASCO 2005	TI38067 vs adriamycin	II/III	169/170	NA	5.7 vs 5.6
Gish et al JCO 2007	Nolatrexed vs doxorubucin	II	37/17	0	4.9 vs 3.7
Mok et al JCO	Nolatrexed vs doxorubicin	III	444	1.4 vs 4.0	5.5 vs 8 (p=.0068)
Barbare	Tamoxifen vs BSC	II	210/210	NA	4.8 vs 4.0
Dollinger et al ASCO 2008	Thymosin vs placebo	III	65/68	NA	5.0 vs 5.2
SUN 1170	Sunitinib vs sorafenib	III		NA	Trial closed at 1st interim analysis

TARGETED THERAPY FOR HCC

The Dawn of a New Era



Approved in 2007 by FDA, EMEA based on prolonged survival

Recent Trials of Molecular-Targeted Agents in HCC

Regimen	Phase	Sample size	RR%	PFS/TTP	Median survival (months)	Reference
Sorafenib	2	137	2.2		9.3	Abou Alfa et al JCO 2006
Sorafenib vs placebo ("SHARP" trial)	3	602	2.3	5.5 (T)	10.7 (vs 7.9 placebo, p=0.00058)	Llovet et al NEJM 2008
Sorafenib vs placebo	3	150/76		TTP 2.8 vs 1.4 PFS 2.8 vs 1.4	6.2 (vs 4.1 placebo)	Cheng et al Lancet Oncology 2009
Sorafenib + doxorubicin vs doxorubicin + placebo	RII	47/49	4/2	8.6/4.8 (T)	13.7/6.5	Abou Alfa et al
Bevacizumab	2	46	13	6.9 (P)	12.4	Seigel et al JCO 2008
Sirolimus	2	21	4.7		6.5	Rizell et al 2008
Erlotinib	2	38	9	3.2 (P)	13	Philip et al JCO 2005
Erlotinib	2	40	0	6.3 (P)	10.75	Thomas et al Cancer 2007
Cetuximab	2	32	0	1.4	9.6	Zhu et al Cancer 2007
Gefitinib	2	31	3	2.8 (P)	6.5	O'Dwyer et al ASCO 2006
Sunitinb	2	34	2.9	3.9	9.8	Zhu et al JCO 2009
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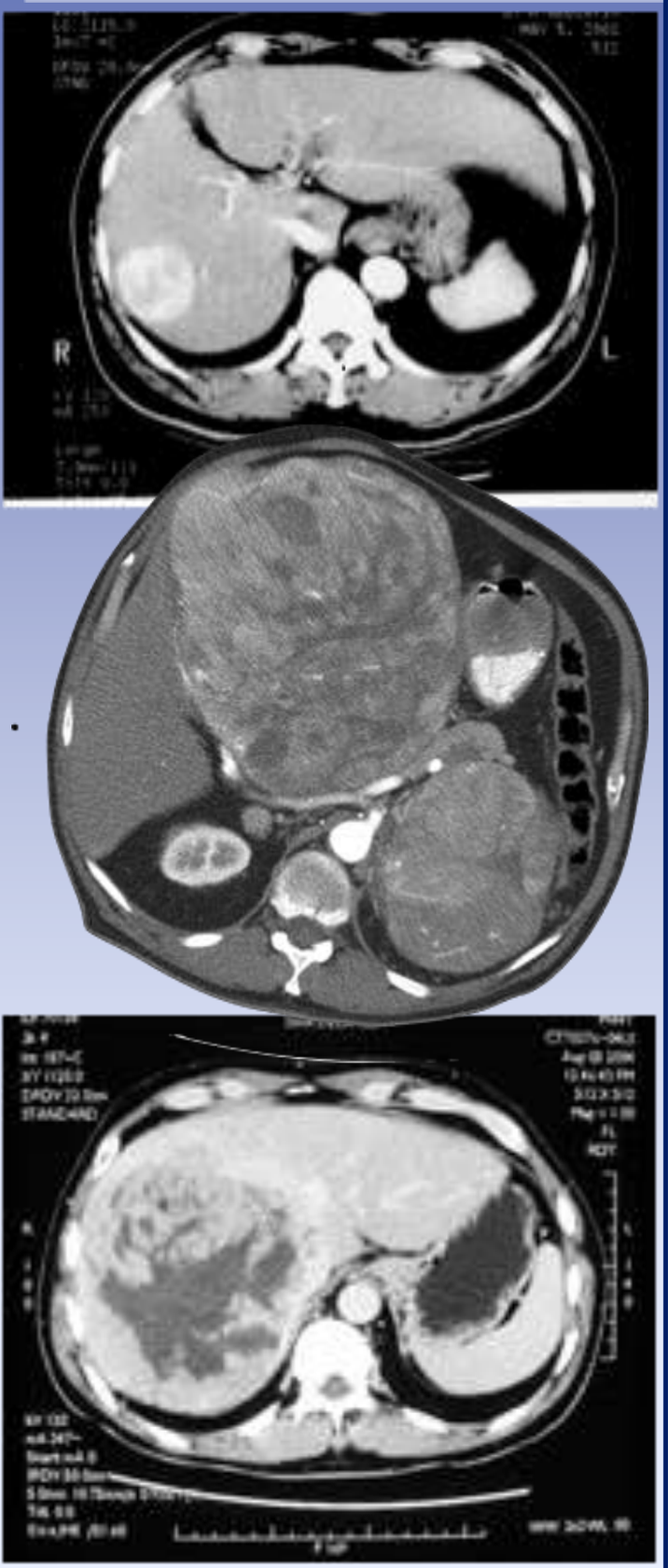
Bevacizumab + erlotonib	2	40	25	9.0 (T)	15.65	Thomas et al JCO 2009
Bevacizumab + erlotonib	2	59	27.5		No prior Tx: 15.0 (n=44) Prior sorafenib: 8.2 (n=7) Prior other Tx" 17.9 (n=8)	Kaseb, Garrett-Meyer, Thomas et al 2011 (in press)

Linking Targeted Agents* to Molecular Targets in Cancer: *What is the Evidence?*

Agent	Target	Tumor type	Effect	Target Validation
Trastuzumab Lapatinib	HER2 receptor HER1-2 heterodimers	Her2-overexpressing breast cancer	Improves survival Decreases recurrence as adjuvant therapy	yes
Bevacizumab	mAB binds serum VEGF A ligand	Metastatic colorectal, lung, breast cancers	Improves survival, TTP in metastatic colon, lung, breast cancers	no
Cetuximab (EGFR mAb)	Extra-cellular domain EGFR	Irinotecan-refractory colorectal cancer	Improves survival, TTP in metastatic colon	Kras mutants do not benefit from EGFR mAb
Gefitinib Erlotinib (EGFR TKI)	Intracellular phosphorylation site	non-small cell lung pancreatic	Improves survival NSCLA, 2nd line Improves PFS in pancreatic ca by <2 wks	EGFR mutations in minority of patients predict benefit
Sorafenib	Raf-ras pathway VEGF	RCC, HCC	Improves survival,TTP	no
Sunitinib	Raf-ras pathway VEGF	GIST RCC	Improves survival,TTP	no
Bortezomib	mTOR	Myeloma	Improves survival decreases transfusions	no
Imatinib	C-kit	GIST CML	Improves RR, survival Decreases recurrence	yes

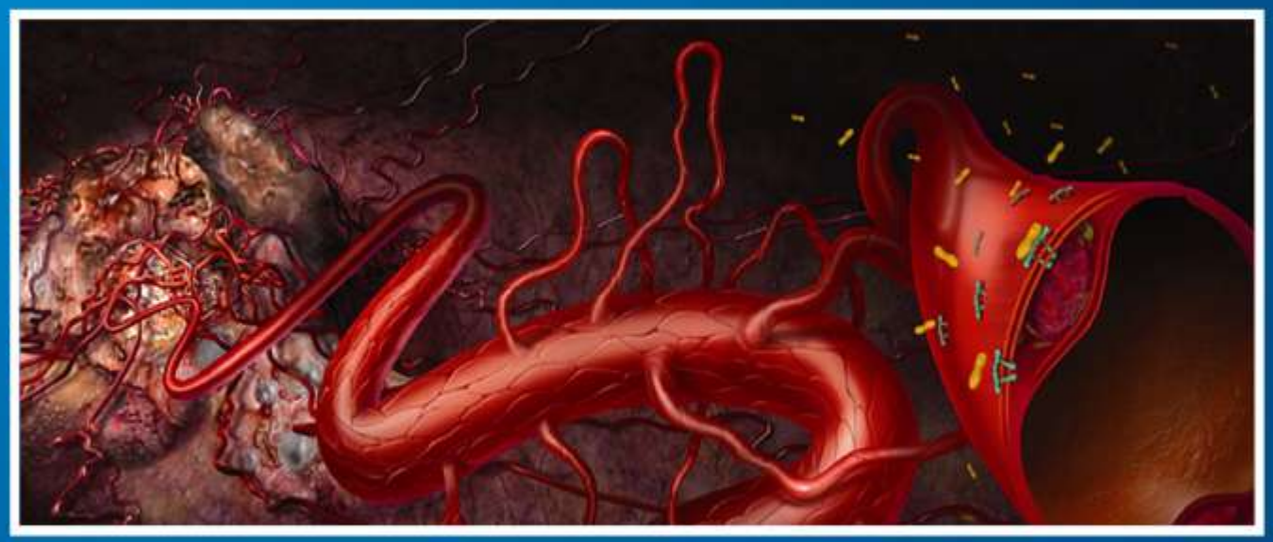
Evidence for the Critical Role of Angiogenesis in HCC:



- HCC are highly vascularized, propensity for vascular invasion
- Growth factors EGF, TGFβ, HGF, VEGF all involved in normal liver regeneration
- Increased growth factors expression seen in chronic hepatitis, cirrhosis, dysplastic nodules, HCC cell lines and tissue
- VEGF over-expression and increased microvessel density (MVD) common in HCC
- VEGF gene is transcribed, expressed and VEGF secreted by HCC
- High VEGF expression in HCC measured by immunohistochemistry (IHC) tissue significantly associated with:
  - increased arterialization
  - poorer tumor differentiation
  - high proliferative index
  - poor tumor encapsulation

Angiogenesis in HCC Progression

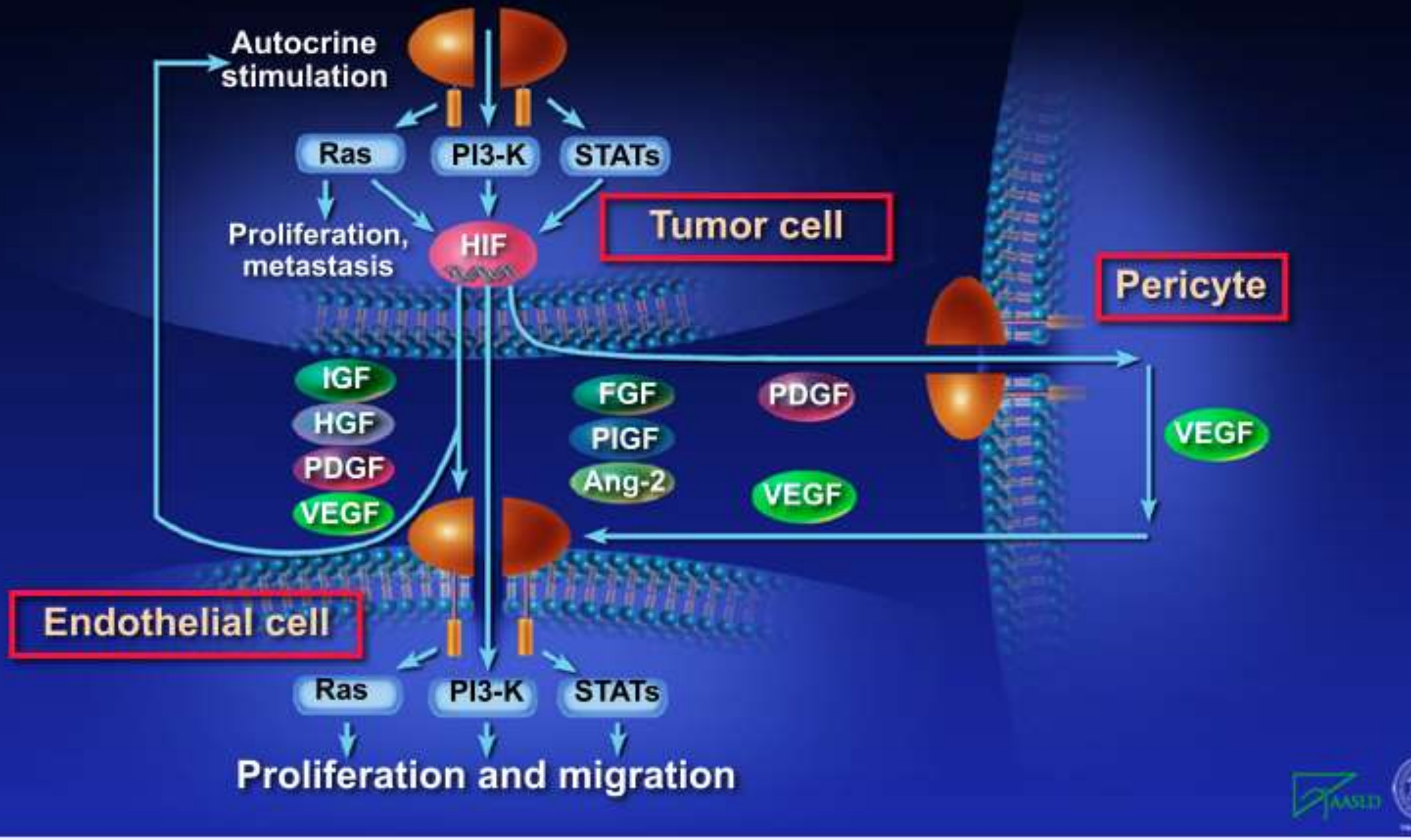
- Angiogenic factors implicated in HCC include
  - VEGFs (vascular endothelial growth factors)
  - PDGFs (platelet-derived growth factors)
  - PlGF (placental growth factor)
  - TGF-α, TGF-β (transforming growth factors-alpha, -beta)
  - bFGF (basic fibroblast growth factor)
  - EGF (epidermal growth factor)
  - HGF (hepatocyte growth factor)
  - ANGs (angiopoietins)
  - IL-4, IL-8 (interleukins-4, -8)



1. Semela D, Dufour J-F. *J Hepatol*. 2004;41:864-880. **2.** Folkman J. *Curr Mol Med*. 2003;3:643-651.

HCC Pathogenesis

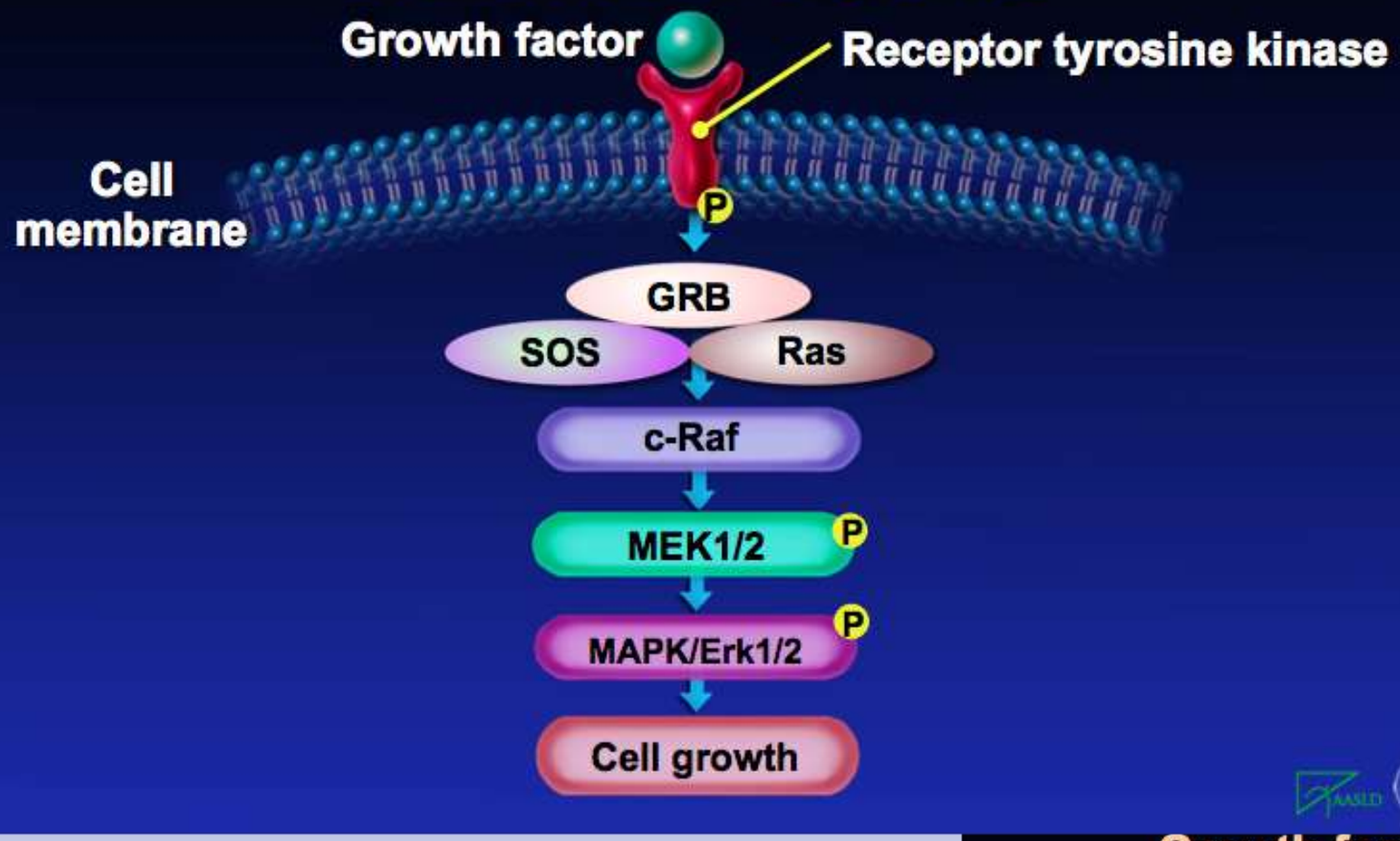
Angiogenic Signaling in Cancer

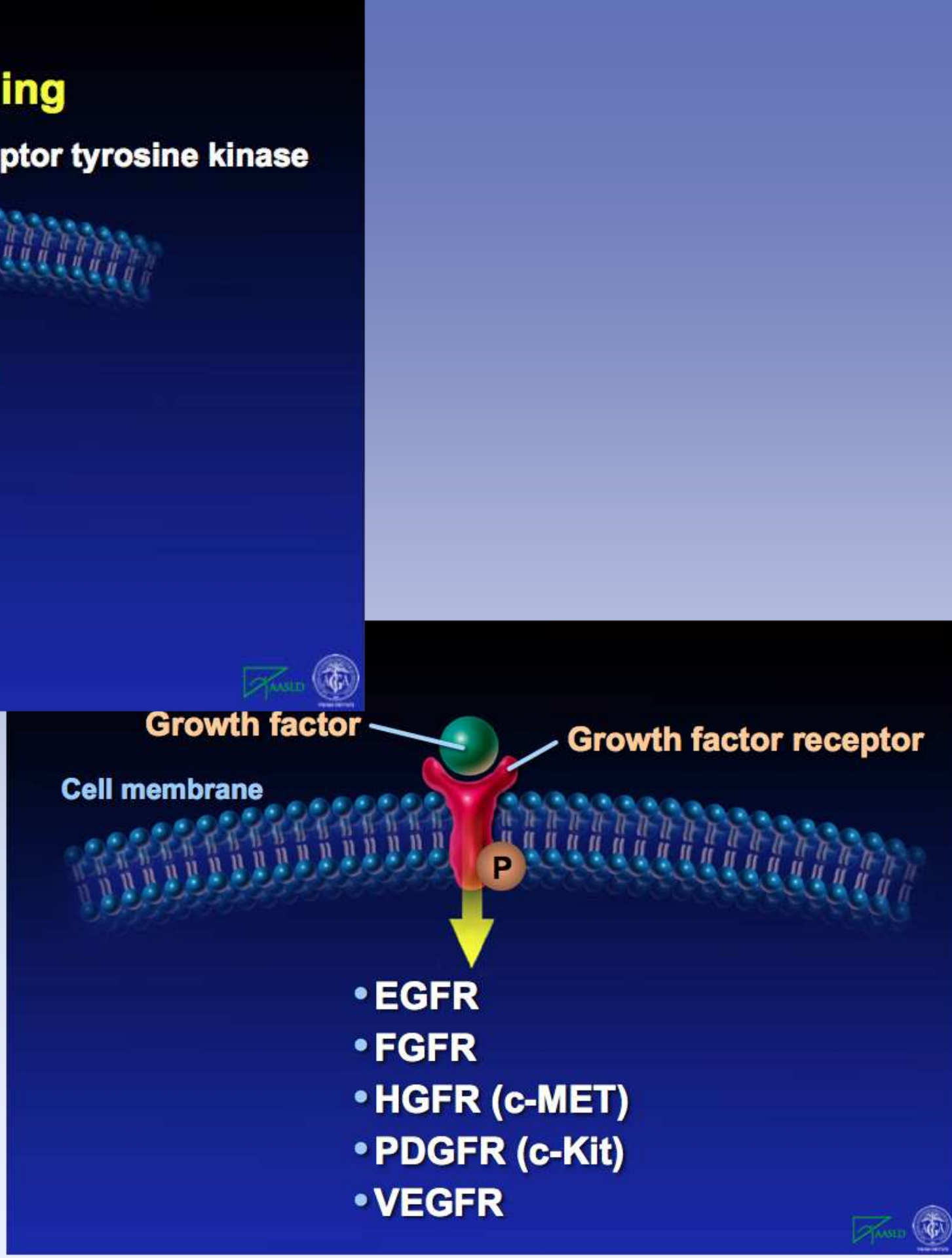


Factor	Role in hepatocellular carcinoma
HGF (hepatocyte growth factor)	Known pro-angiogenic growth factor, acts via c-met. Common in hepatocyte regeneration; predicts poor prognosis.
EGF (epidermal growth factor receptor)	Known mitogen in multiple tumor types; Increases HCC proliferations in multiple cell line. EGF over-expression common in chronic hepatitis, cirrhosis and HCC (40-80%).
FGF (fibroblast growth factor receptor)	Upregulates DNA synthesis. Mitogenic for hepatocytes, potent inducer of angiogenesis. Interacts with EGFR; Frequent in hepatitis, cirrhosis, HCC; not in normal liver
IGF (insulin-like growth factor) family	Common in fetal liver; declines after birth; highly prevalent in HCC IGF pro-carcinogenic in many tumor types. May be link between fatty liver and HCC. Preclinical data shows anti-IGF-1 tyrosine kinase inhibitors induce growth inhibition, apoptosis, cell cycle arrest in HCC cell lines.
PDGF (platelet-derived growth factor)	An angiogenic molecule promotes endothelial cell migration. May be potent stimulator of angiogenesis in HCC.

HCC Pathogenesis

Growth Factor Signaling





TARGETED THERAPY FOR HCC
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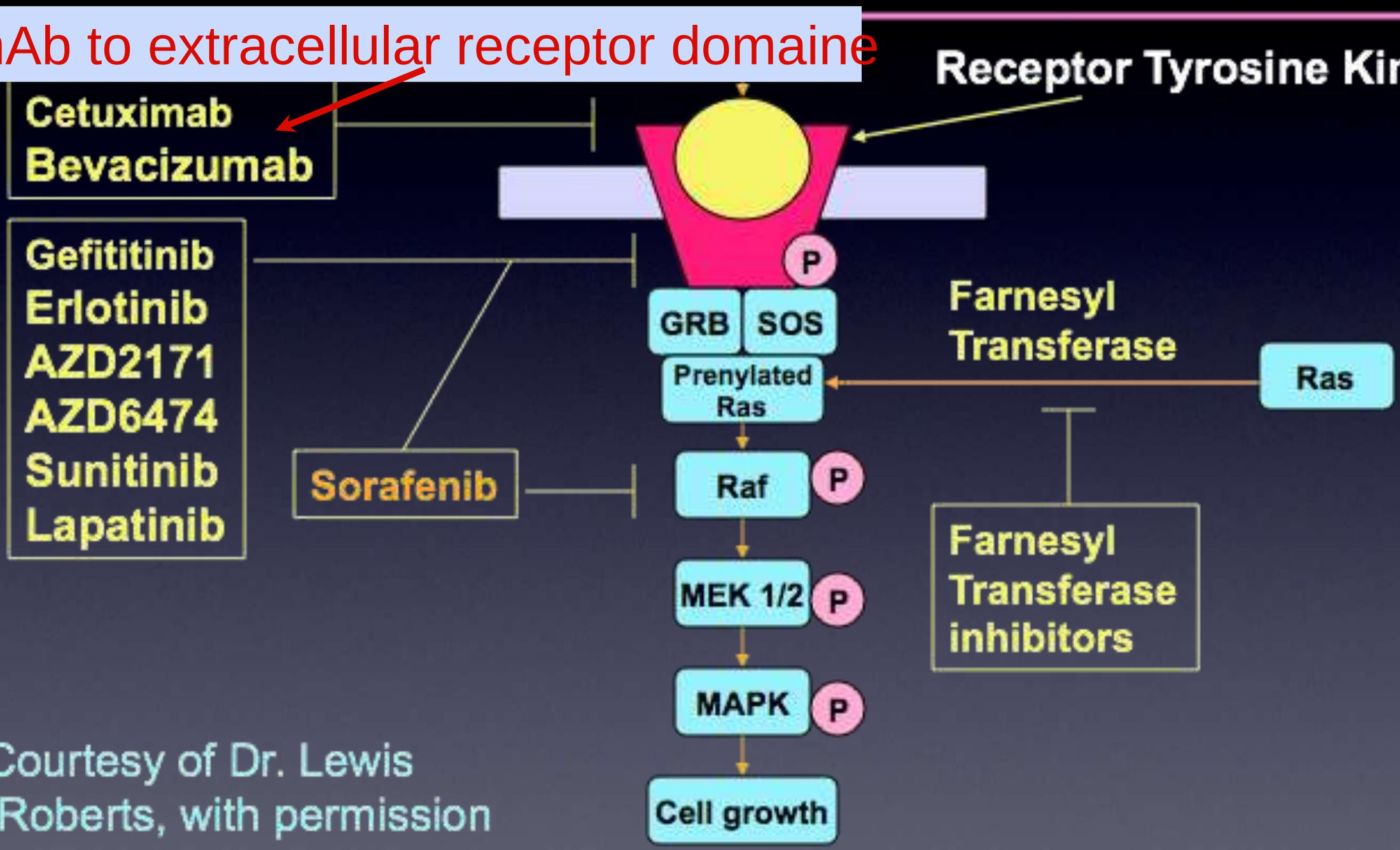

Courtesy of Dr. Lewis Roberts, with permission

Recent Trials of Molecular-Targeted Agents in HCC

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Phase II trial of bevacizumab and erlotinib in HCC

- **Trial based on:**
  - Importance of VEGF and EGF in HCC carcinogenesis.
  - Improved survival of bevacizumab, erlotinib in multiple other tumor types.

- **Single-arm, open label trial of B+E in unresectable HCC**
  - Bevacizumab (humanized mAb against VEGF-A ligand)
  - Erlotonib (oral tyrosine kinase inhibitor TKI binds EGF)

- **Primary Endpoint progression-free survival at 16 weeks therapy >50%**
  - Based on “historical controls” from small Phase II trials (pre-SHARP trial results)
  - Goal: identify meaningful “biologic signal” of drug activity
  - Evaluate safety of dual targeted agents in HCC.

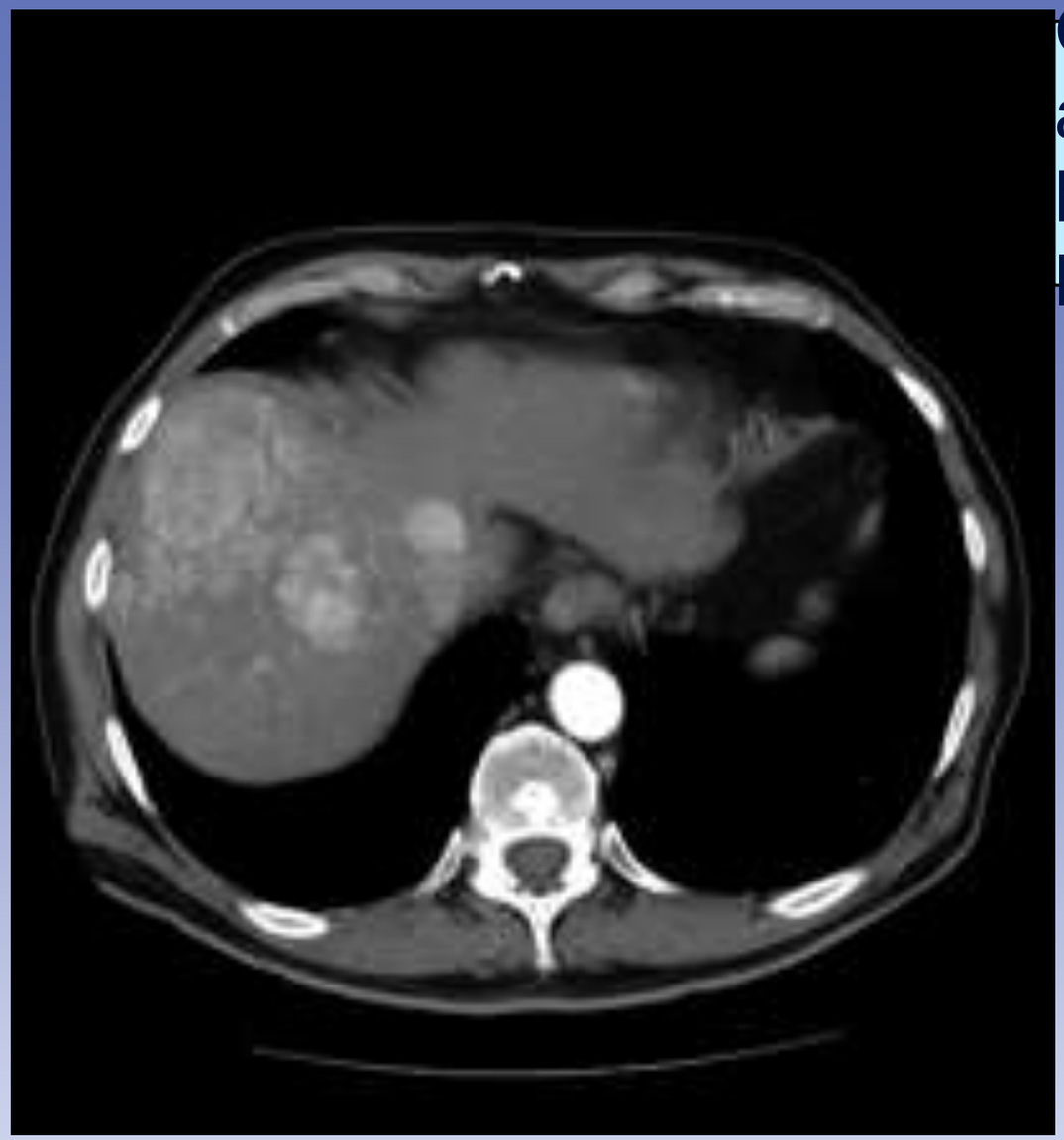
- **Eligibility criteria:**
  - One prior systemic therapy allowed; unlimited regional treatments
  - Performance Status 0-2
  - Childs-Pugh A, B; bilirubin <2, transaminases ≤ 5 XULN, platelets ≥ 60,000
  - Portal vein thrombus allowed
  - No fibrolamellar HCC
  - Prior variceal bleeding allowed if >3 months.

Summary of Survival Data: ITT Analysis

Prior treatment history	PFS in months Median (95% CI)	OS in months Median (95% CI)
No prior treatment (n=44)	8.8 (5.5, 10.1)	15.6 (9.5, 19.5)
Prior treatment with sorafenib (n=8)	7.9 (4.2, 13.3)	13.3 (4.2, 22.3)
Prior treatment with other systemic therapy (n=6)	6.6 (1.9, 11.0)	14.4 (1.9, Inf*)

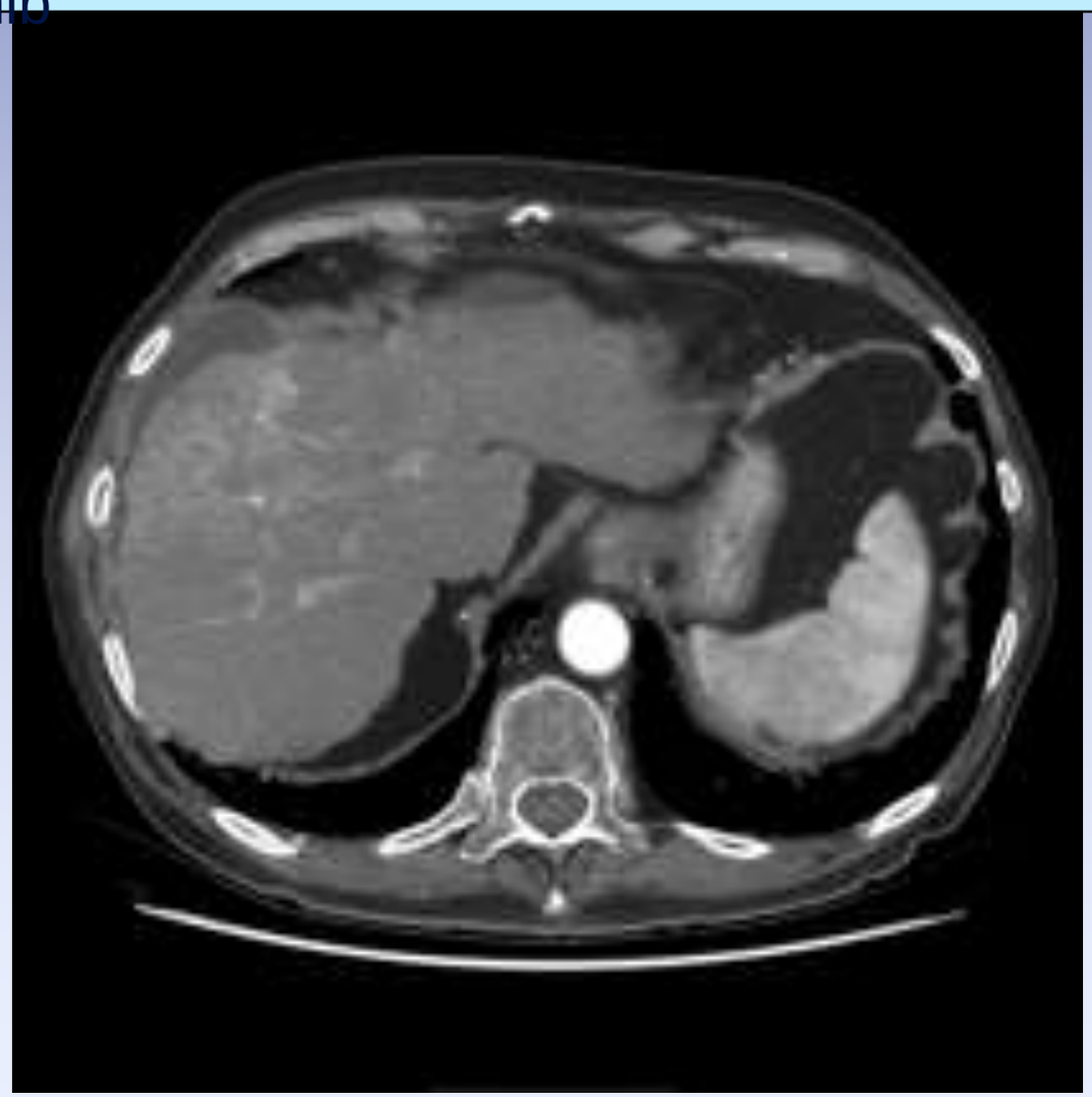
*Upper limit is infinite because of the small number of patients with prior treatment with regimens not including sorafenib

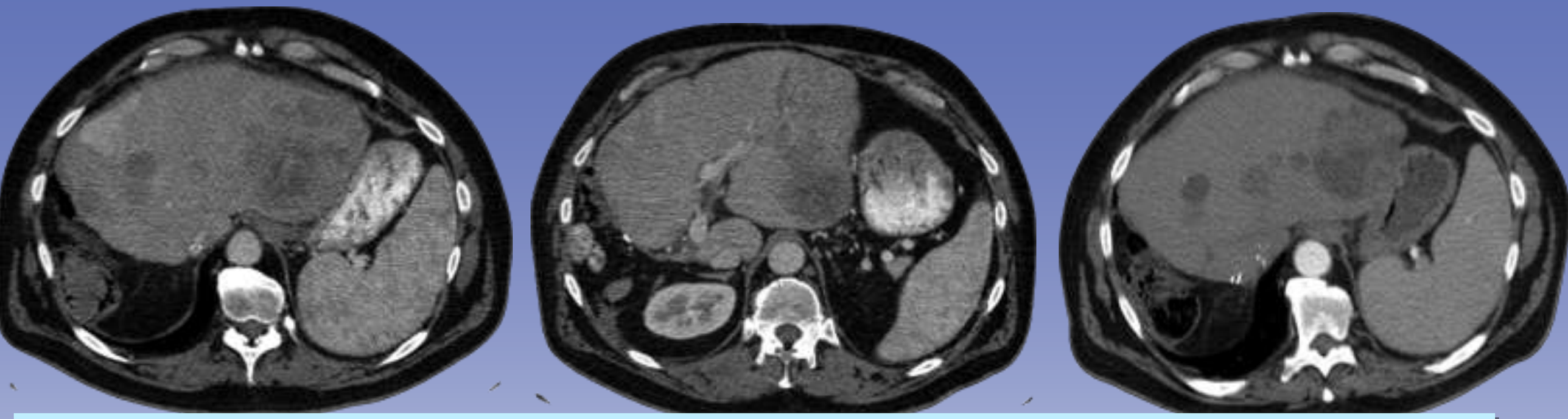
Radiographic evidence of tumor responses in HCC patients treated with **bevacizumab** and **erlotinib**



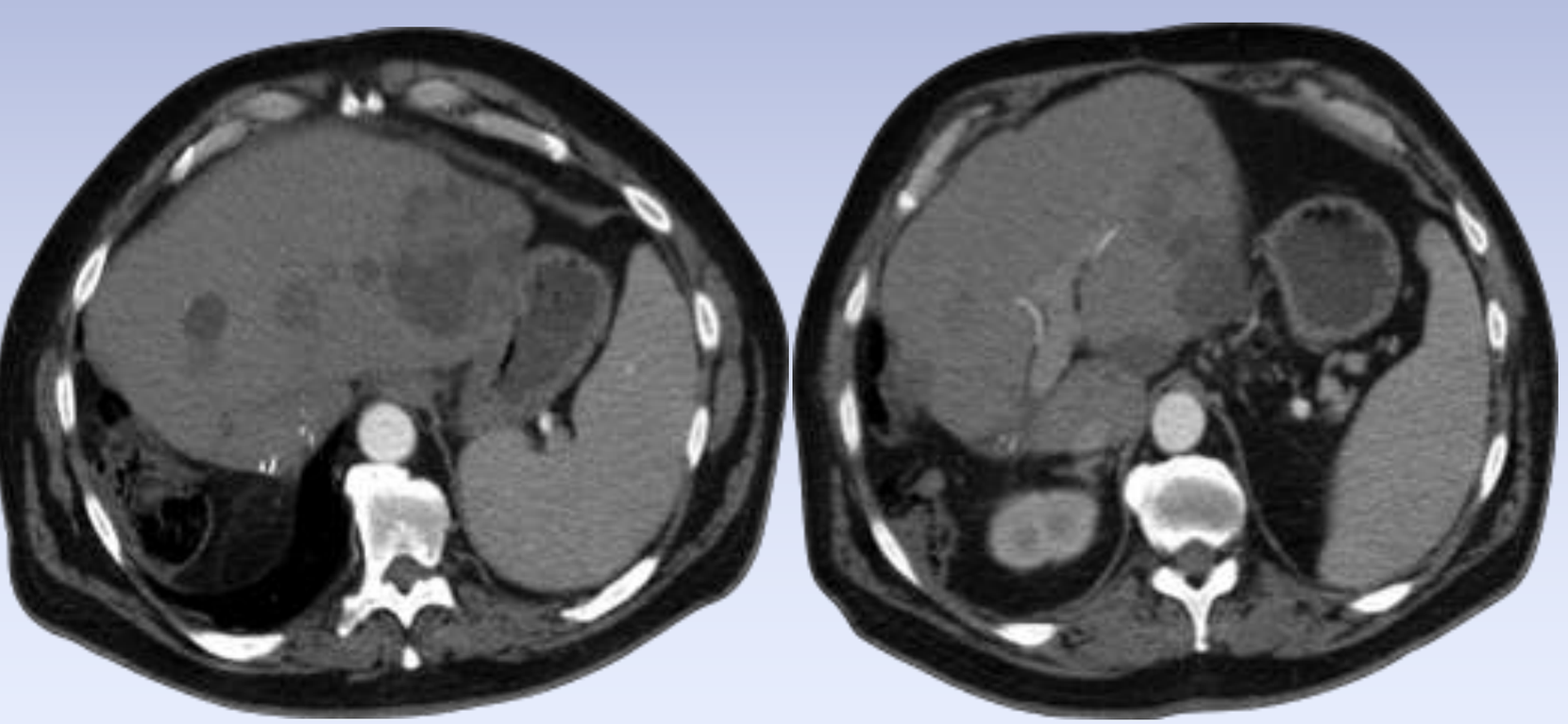
Computed tomography of the abdomen of a 76 year old man with multi-focal hypervascular HCC in right lobe liver,baseline.

Decreased tumor vascularity, partial tumorresponse after 6 months bevcizumab and erlotinib

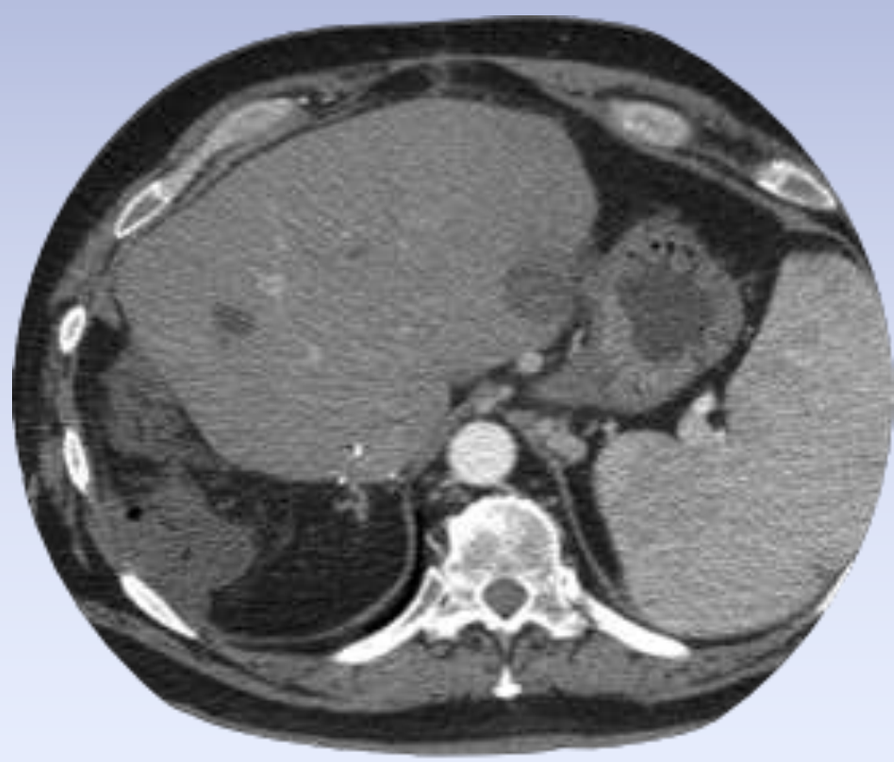




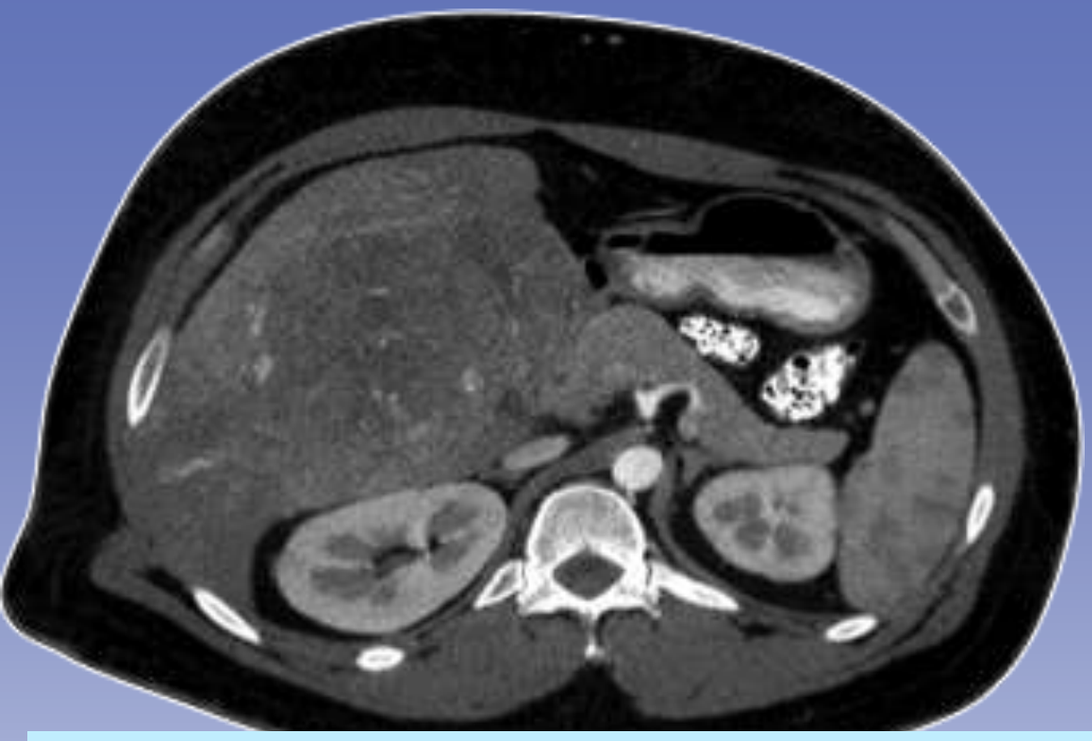
62 yo man with multifocal recurrent HCC, PVT 4 mos after extended rt hepatectomy
Baseline alpha-fetoprotein (AFP) 214,046

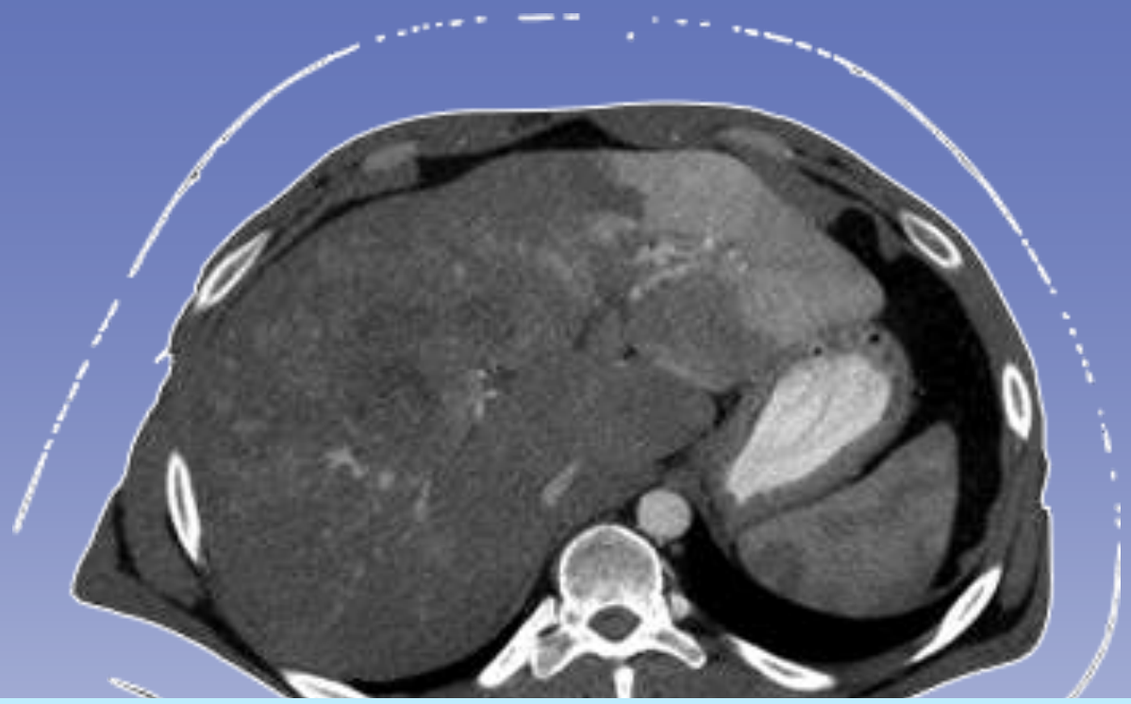


After 16 weeks B+E, partial response, AFP 287

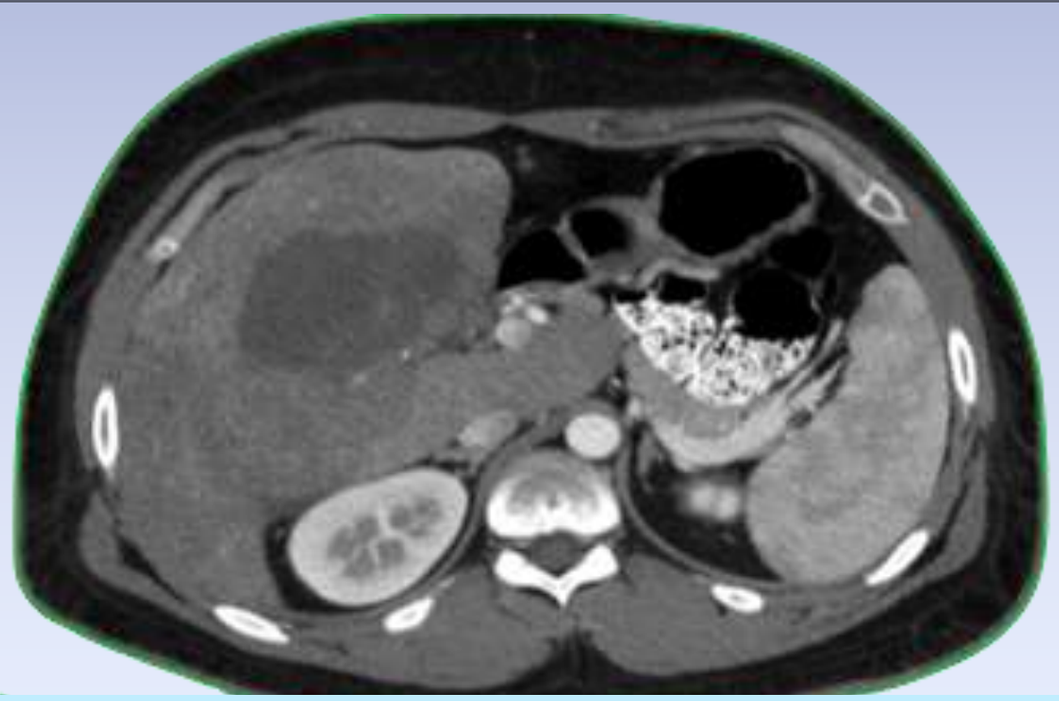


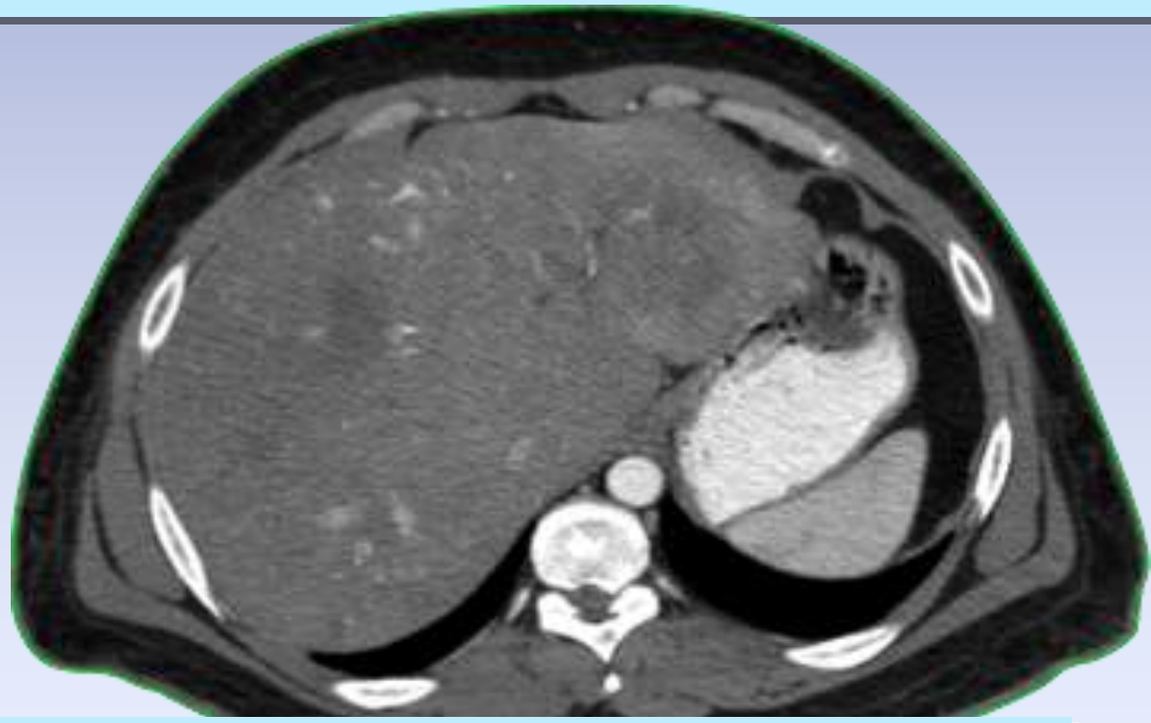
Sustained PR after 10 mos



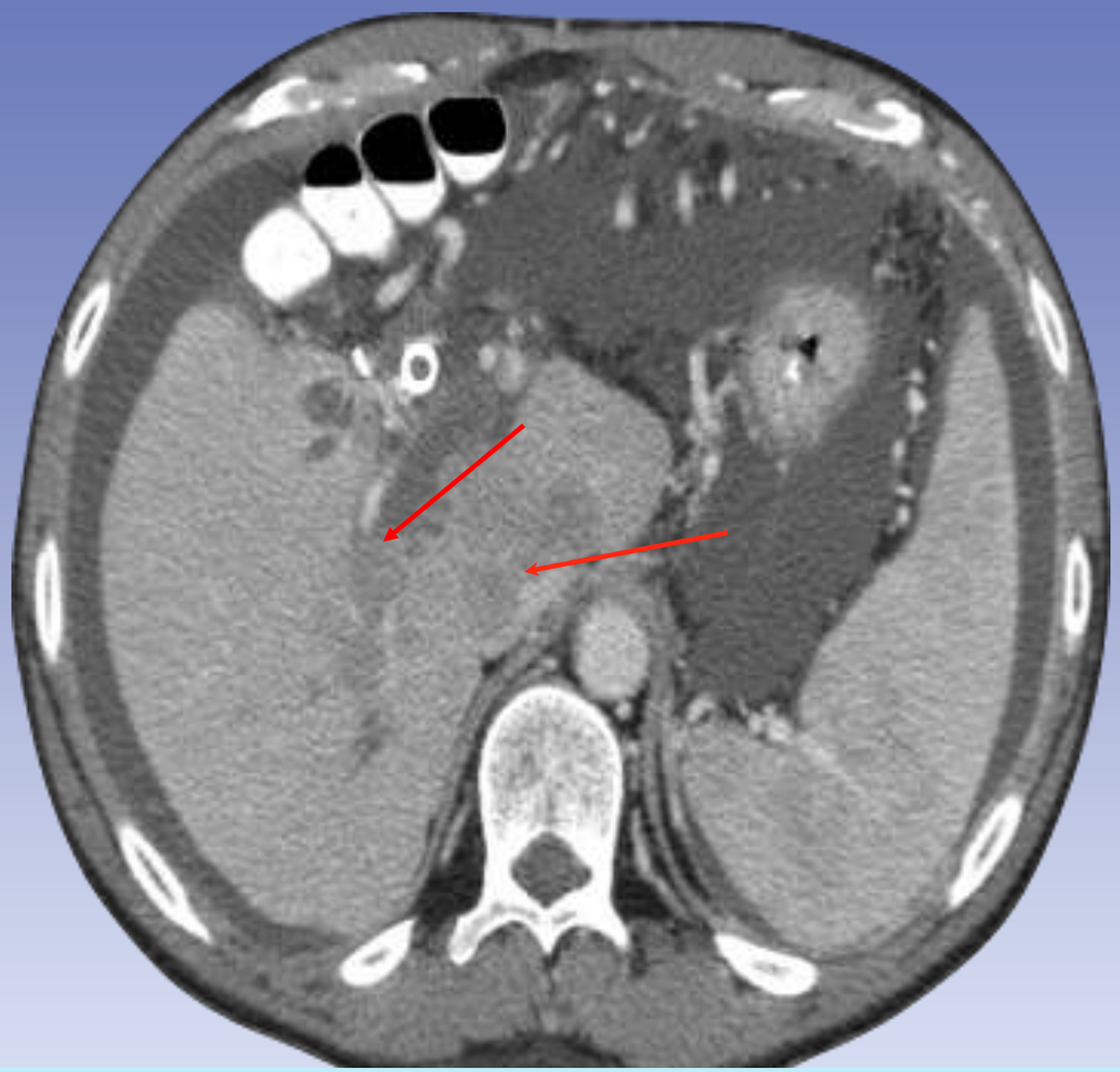


29 yo man with cirrhosis, metabolic syndrome, massive HCC. Baseline, AFP 70,000

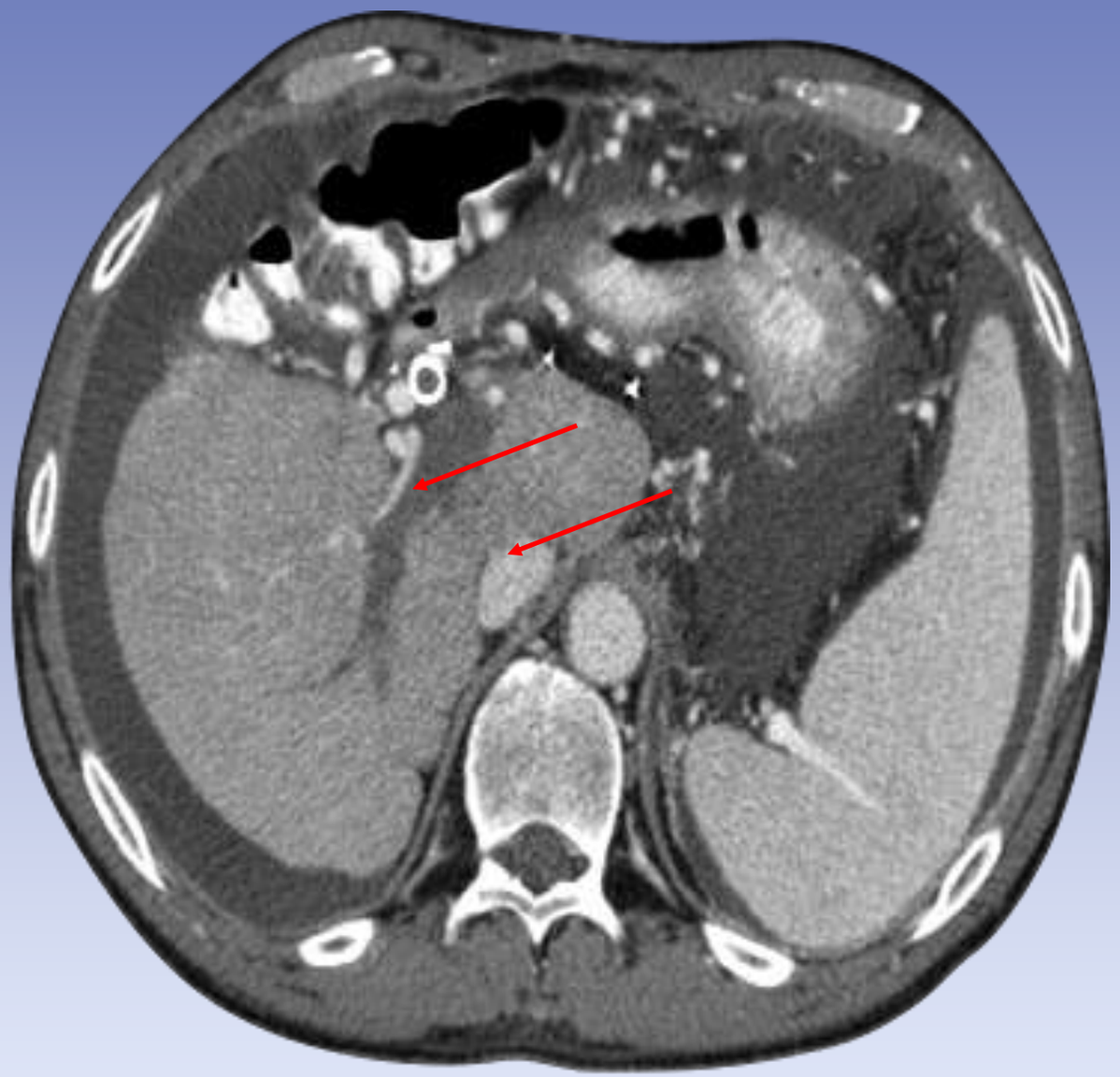




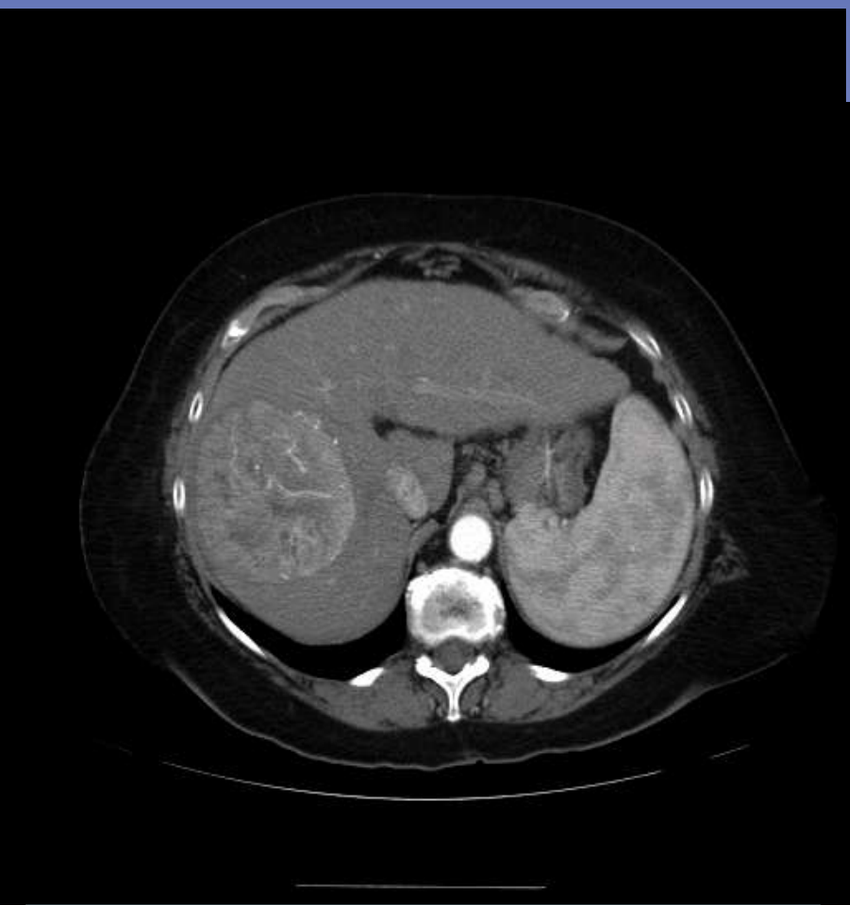
Restaging CT after 16 weeks bevacizumab +erlotinib decreased tumor vascularity, AFP 30,000

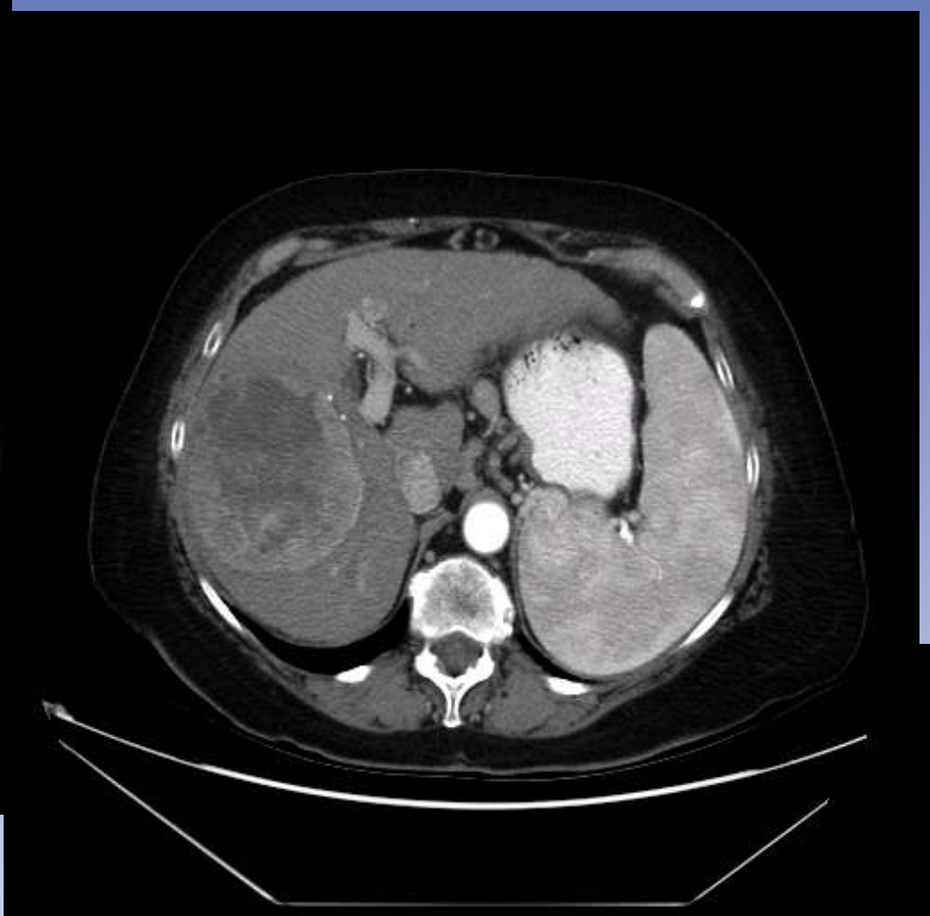


50 yo man with recurrent HCC in right portal vein (tumor thrombus) and adjacent liver. Tumor effacing IVC. Baseline AFP 2,073



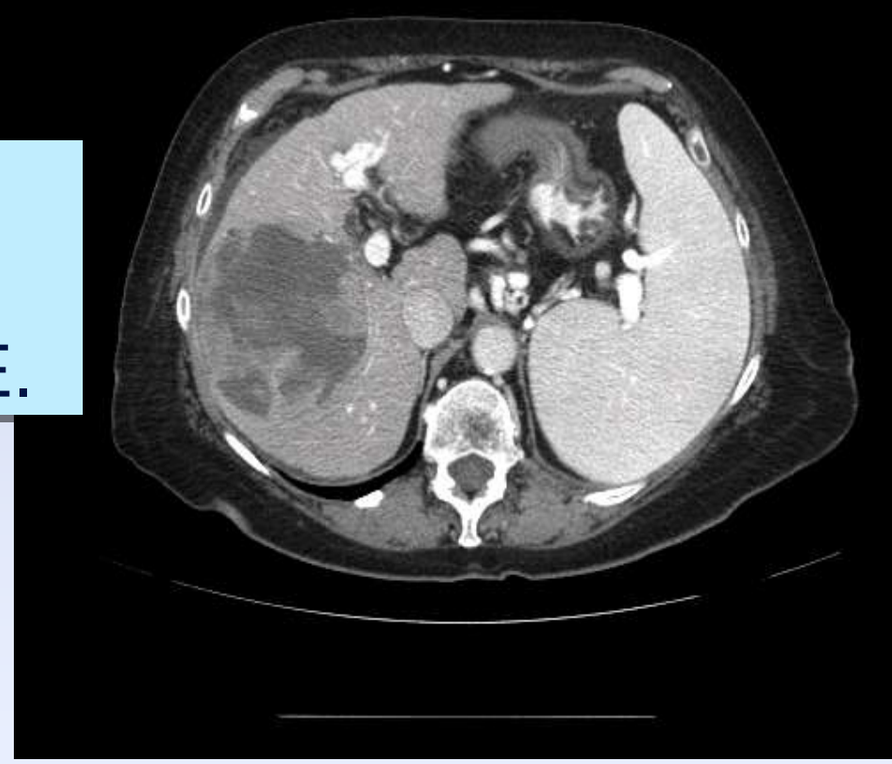
PR after 8 weeks B+E, improved IVC flow. AFP 482



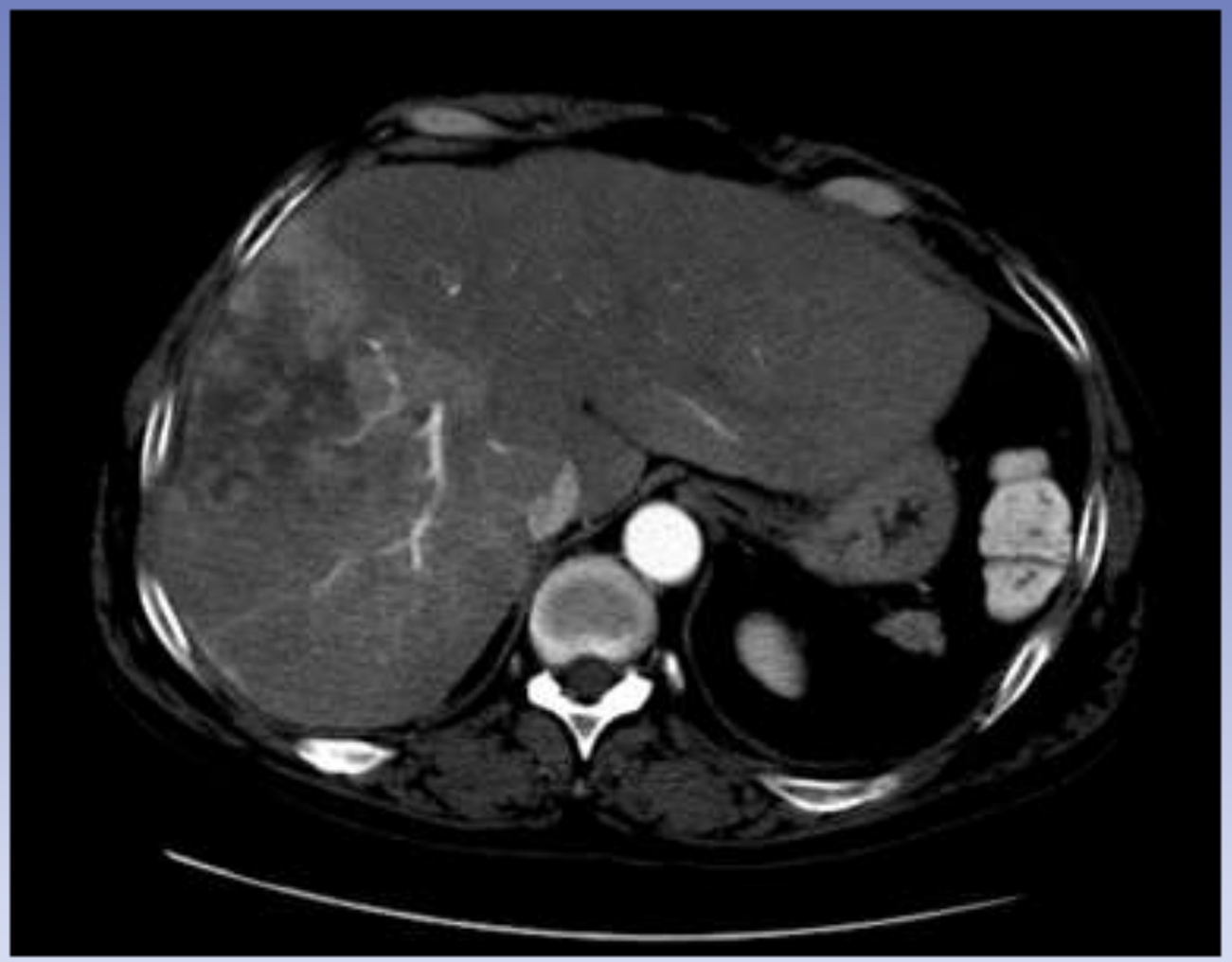


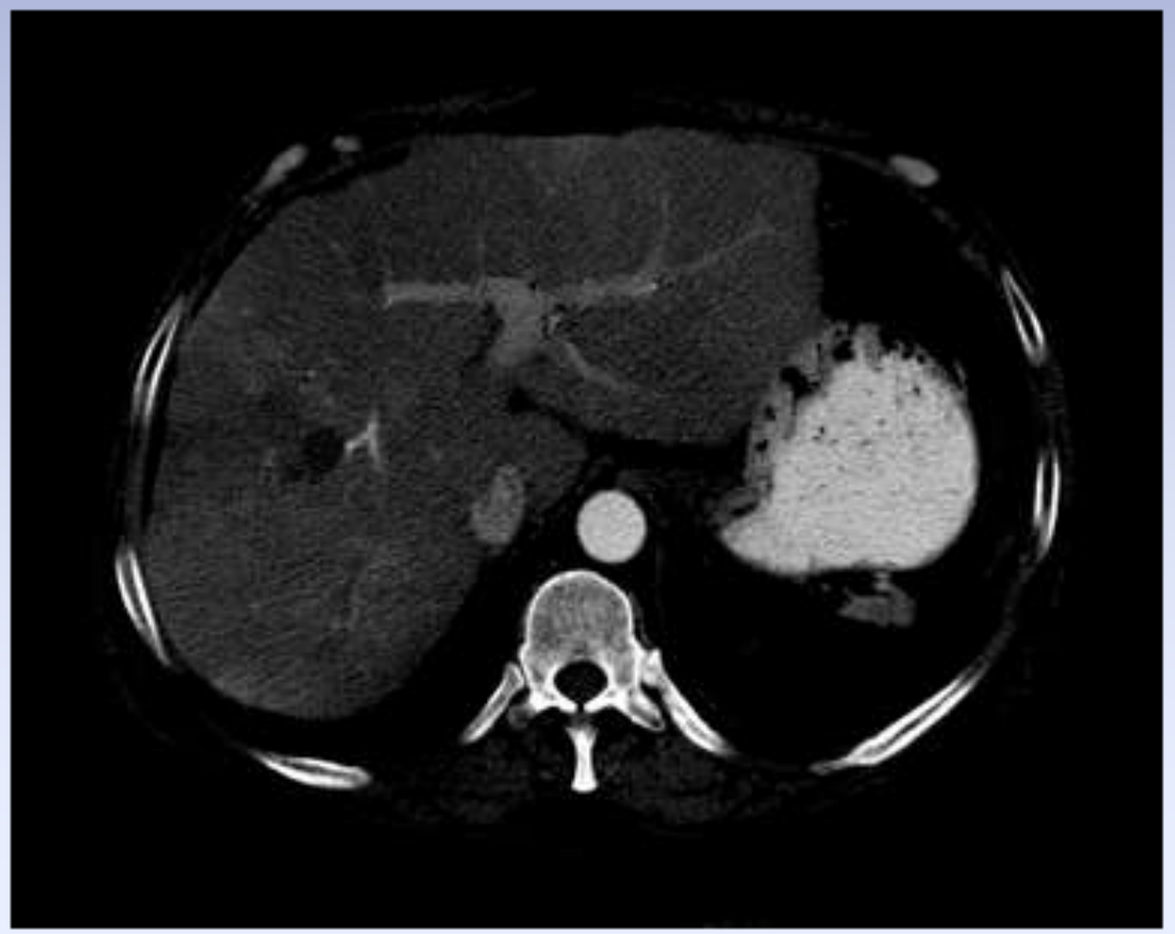
63 year old woman with hypervascular HCC, right lobe. Significant portal HTN precluded resection.

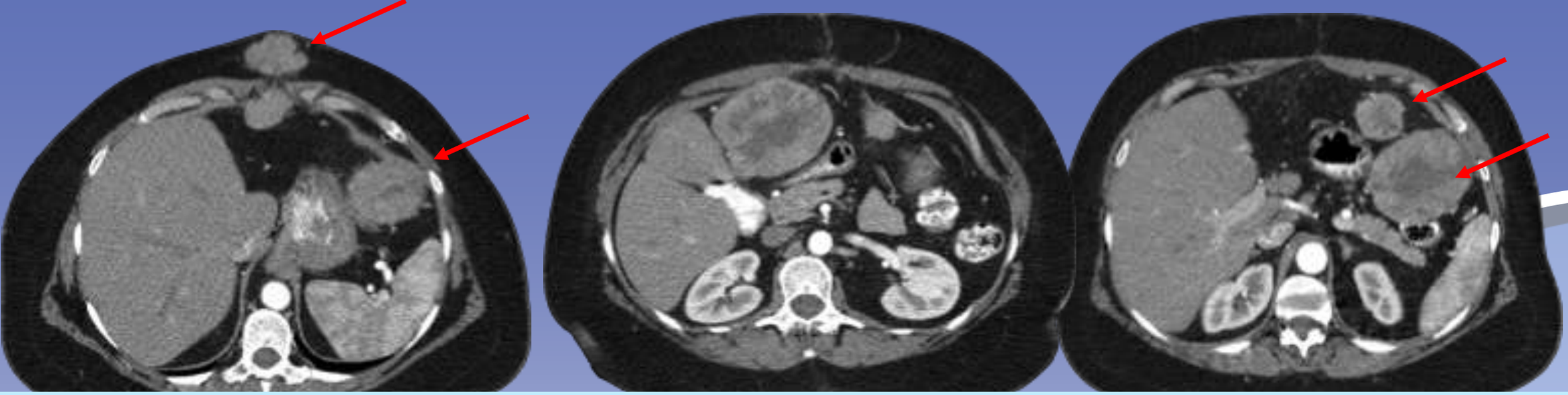
Decreased tumor vascularity after 8, 16 weeks treatment with B+E.



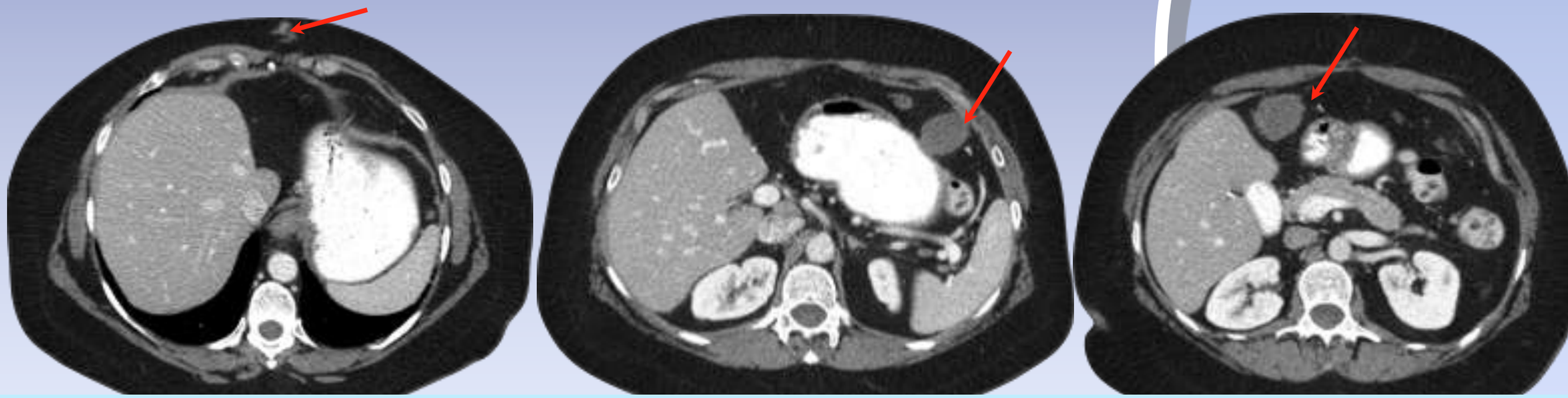
Radiographic Evidence of Tumor Response to B+E in Second-Line Setting After Progression on Sorafenib







48 yo woman presented with ruptured 9 cm HCC 8/05, underwent primary resection. Developed recurrent multiple abdominal implants 3/06; failed 5FU/IFN



Patient treated with B+E off-protocol; significant radiographic response after 6 mos. 2/07 underwent resection of prior incision, port sites, residual implants. No tumor detected in any specimen=pCR. Free of disease June 2008

Thomas et al Journal of Surgical Oncology Oct 2007

An exciting time in hepatocellular carcinoma...

- **SHARP trial established sorafenib as standard of care systemic therapy for advanced disease patients**

- **Explosion of interest and clinical research in HCC-**
  - **156 actively recruiting, phase II or III interventional trials in HCC listed on www.clinicaltrials.gov**
  - **Broad international recruitment**
  - **Multiple trials for each stage of disease**

- **Numerous targeted agents are now in clinical trials**

- .....However - are the “right” agents being studied?

Current Randomized Trials in HCC

Regimen	Study Phase	Rationale
Sorafenib vs Sunitinib	**III**	**OS Sorafenib 10.7 months Ph III** **OS Sunitinib 8-9.8 months in 2 Ph II** **Closed at 1st interim analysis for futility**
Sorafenib vs Erlotinib + Sorafenib	**III**	**OS Sorafenib 10.7 months Ph III**
Sorafenib vs Bevacizumab+Erlotinib	**Randomized Ph II**	**OS Sorafenib 10.7 months Ph III** **TTP 5.5. vs 2.8 months** **Response rate 28%** **OS B+E 15.6 months (n=58)** **TTP 8.8 months**
Sorafenib vs Brivinib	**III**	**OS Sorafenib 10.7 months Ph III** **OS 10 months Ph II**
Sorafenib vs doxorubicin+sorafenib	**III**	**OS Sorafenib 10.7 mos Ph III** **OS Dox+S 13.8 mos Randomized Ph II**
Sorafenib vs ABT869	**RII**	**OS Sorafenib 10.7 mos Ph III** **OS 9.7 months Ph II**

Molecular Biology of Hepatocellular Carcinoma and Targeted Therapies

Conclusions:

- HCC is a highly molecularly complex tumor...
- ...Yet a single agent sorafenib, that targets ras-raf-signaling pathway is the first chemotherapy agent to improve patient survival.
- The prominent role of growth factor dysregulation in HCC provides opportunities to develop potent, combination targeted therapy strategies.
- It is essential to develop *molecular characterization systems* of all stages and etiologies of HCC.

Molto grazie

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