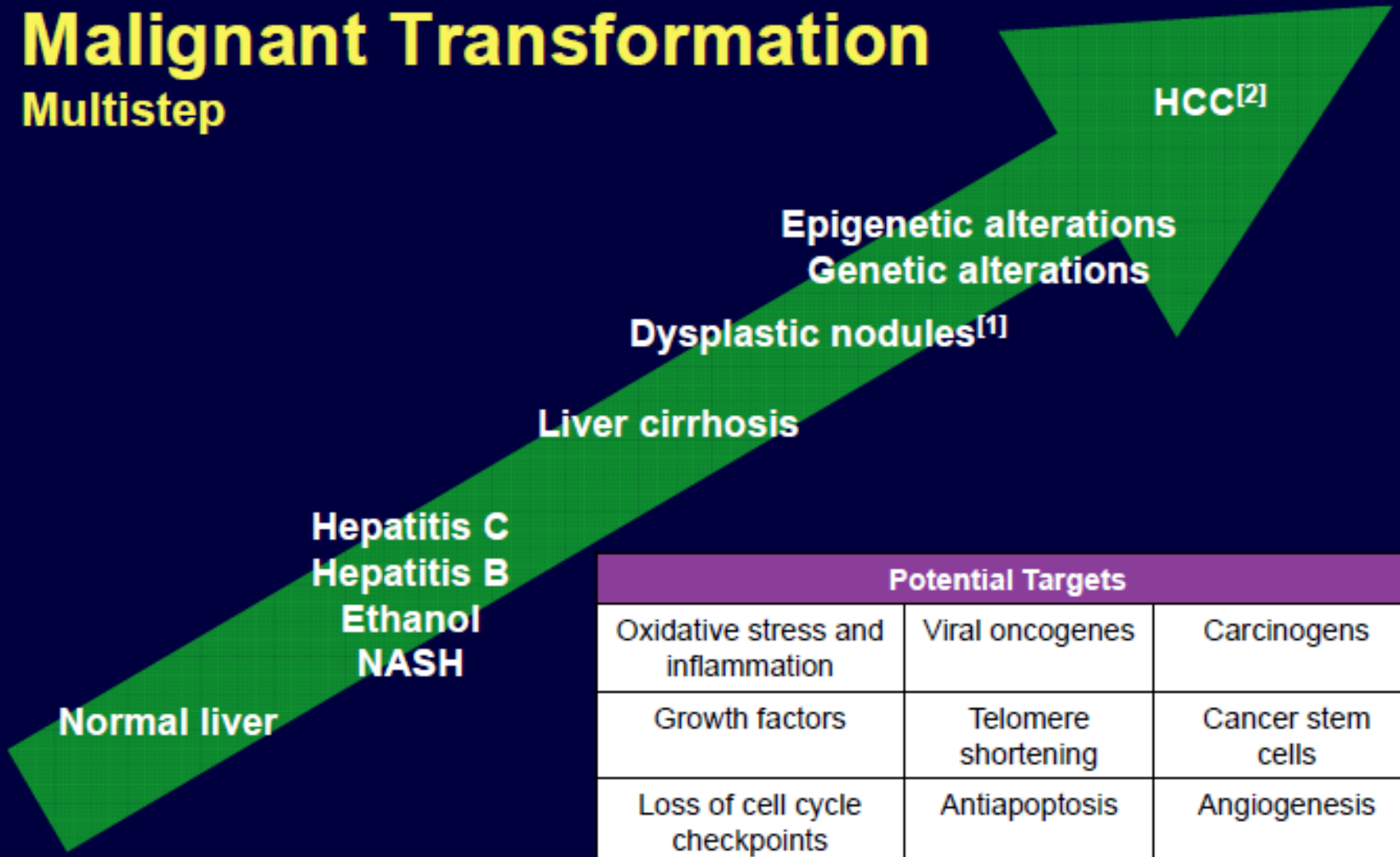
Malignant Transformation

Multistep



Potential Targets		
Oxidative stress and inflammation	Viral oncogenes	Carcinogens
Growth factors	Telomere shortening	Cancer stem cells
Loss of cell cycle checkpoints	Antiapoptosis	Angiogenesis

1. Tornillo L, et al. Lab Invest. 2002;82:547-553.
2. Verslype C, et al. AASLD 2007. Abstract 24.

Etiology of HCC

Distinct Geographic Distribution

Risk Factors	Europe and United States (%)		Japan (%)		Asia and Africa (%)	
	Estimate	Range	Estimate	Range	Estimate	Range
Hepatitis B virus	22	4~-58	20	18~-44	60	40~90
Hepatitis C virus	60	12~72	63	48~94	20	9~56
Alcohol	45	8~57	20	15~33	---	11~41
Tobacco	12	0~14	40	9~51	22	---
Oral contraceptives	---	10~50	**---**	**---**	8	---
Aflatoxin	Limited exposure		Limited exposure		Important exposure	
Other and emerging risk factors/cofactors	< 5	**---**	---	---	< 5	---

Bosch FX et al. Gastroenterology 2004;127:S5-16.

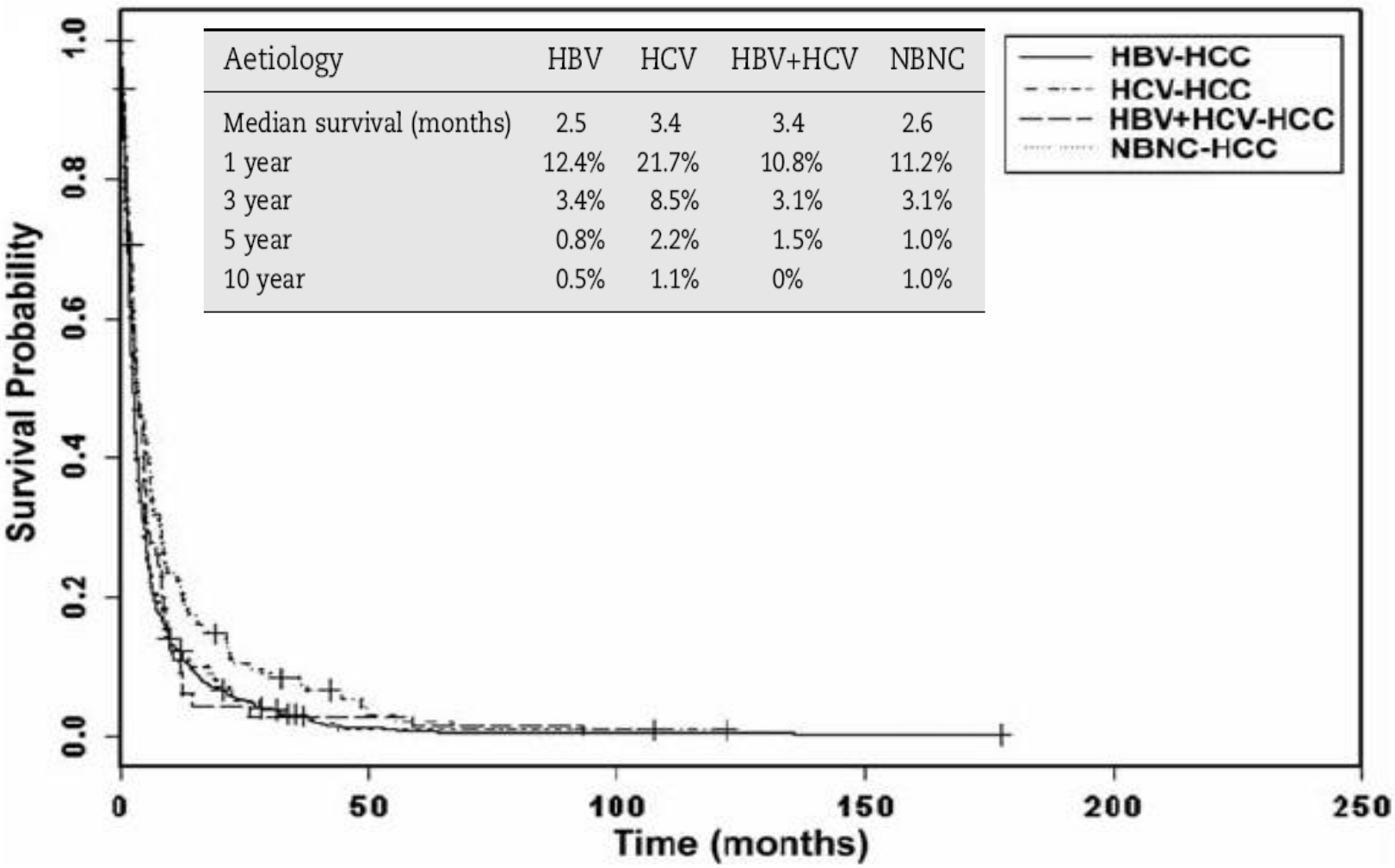
Incidence of HCC in Risk Groups

Subgroup	Incidence per Year (%)
All hepatitis B carriers > 40 yrs of age	0.2
Cirrhotic hepatitis B carriers	3-8
Hepatitis C cirrhosis	3-5
Stage 4 primary biliary cirrhosis	3-5
Alcoholic cirrhosis	?
Genetic hemochromatosis	?
Nonalcoholic steatohepatitis	?

Beasley RP, et al. Lancet. 1981;2:1129-1133. Koike K, et al. Oncology. 2002;62(suppl 1):29-37. Beasley RP. Hepatology. 1982;2(suppl):21S-26S. Fattovich G, et al. Gut. 1991;32:294-298. Manno M, et al. Gastroenterology. 2004;127:756-763. Hsu YS, et al. Hepatology. 2002;35:1522-1527. Fattovich G. J Hepatol 2003;39(suppl 1):S50-S58. Fattovich G, et al. Gastroenterology. 1997;112:463-472. Niederau C, et al. Hepatology. 1998;28:1687-1695. Niederau C, et al. N Engl J Med. 1996;334:1422-1427. Degos F, et al. Gut. 2000;47:131-136. Caballeria L, et al. Am J Gastroenterol. 2001;96:1160-1163.

Unsatisfactory Treatment Outcome for Advanced HCC Patients

Aetiology	HBV	HCV	HBV+HCV	NBNC
Median survival (months)	2.5	3.4	3.4	2.6
1 year	12.4%	21.7%	10.8%	11.2%
3 year	3.4%	8.5%	3.1%	3.1%
5 year	0.8%	2.2%	1.5%	1.0%
10 year	0.5%	1.1%	0%	1.0%



Chen CH et al. *Eur J Cancer* 2006;42:2524-9.

Systemic Treatment for HCC Before 2000

- Cytotoxic agents: few are active.
- Combination chemotherapy: not suitable for most HCC patients.
- Biologic agents, such as interferon, tamoxifen, somatostatin analog: not successful.

Exploring Molecular Targeted Therapy for Cancer

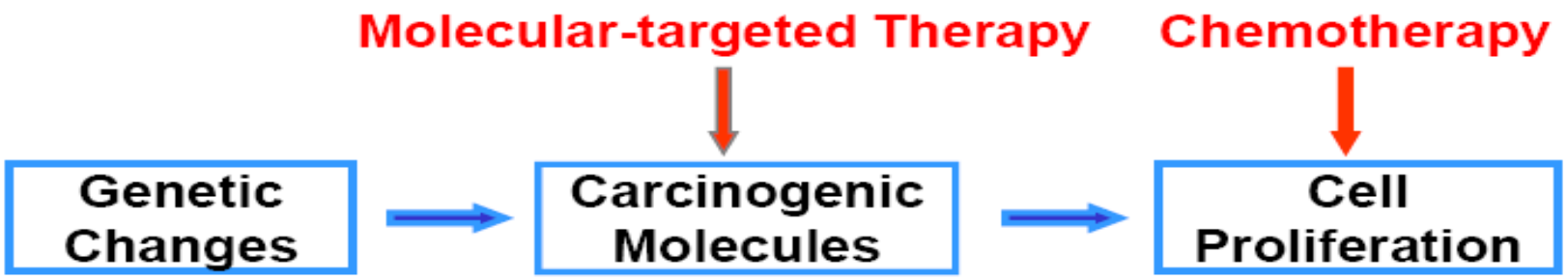


Table 1. Current status of selected targeted agents in NSCLC

Agent	Type	Targets	Phase
Bevacizumab	Ab	VEGF	FDA approved
VEGF trap	Fusion protein	VEGF	Phase II
PTK787/ZK222584 (Vatalanib)	TKI	VEGFR-1, VEGFR-2, PDGFR	Phase II
SU 11248 (Sunitinib)	TKI	VEGFR, PDGFR, Flt-3, c-kit	Phase II
BAY 43-9006 (Sorafenib)	TKI	VEGFR-2, PDGFR (and RAF*)	Phase III
ZD6474	TKI	VEGFR-2, VEGFR-3, EGFR	Phase III
Erlotinib	TKI	EGFR	EMEA and FDA approved
Gefitinib	TKI	EGFR	Phase III
Cetuximab	Ab	EGFR	Phase III
Trastuzumab	Ab	HER2	Phase II
HKI-272	TKI	EGFR, HER2	Phase II
CCI-779	Macrolide derivative	mTOR	Phase II
RAD001	Macrolide derivative	mTOR	Phase II
Bortezomib	boronic acid analogue	Proteasome	Phase II
AMG951	Portion of the native Apo2L/TRAIL	Death receptors DR4 and DR5	Phase Ib/II

Besse B et al. *Ann Oncol* 2007;18 Suppl 9:ix135

Complex Genetic Aberrations in HCC

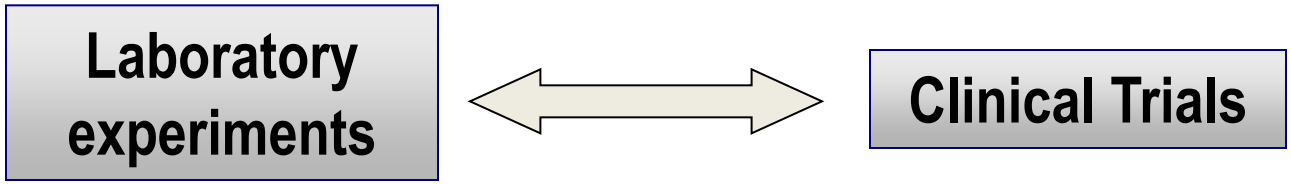
Nearly every carcinogenic pathway is altered to some degree in HCC…

- **Growth factors and receptors**
  EGFR, HGFR, IGF axis, TGF-β family, FRGR
- **Intracellular signaling pathways**
  MAPK/MEK, PI3K/Akt/mTOR, Hedgehog, PKC, Wnt/β-Catenin
- **Cell cycle control**
  Cyclin A, Cyclin B1, Cyclin D1, Cyclin E
- **Oncogenes**
  Ras, Myc, Met, Aurora-A
- **Tumor suppressors**
  p53, p16, p21, p27, Rb, E-Cadherin
- **Apoptosis**
  Fas/Fas ligand
- **Extracellular matrix**
  MMPs, Integrins

Thomas MB et al. *J Clin Oncol* 2005;23:2892-9..

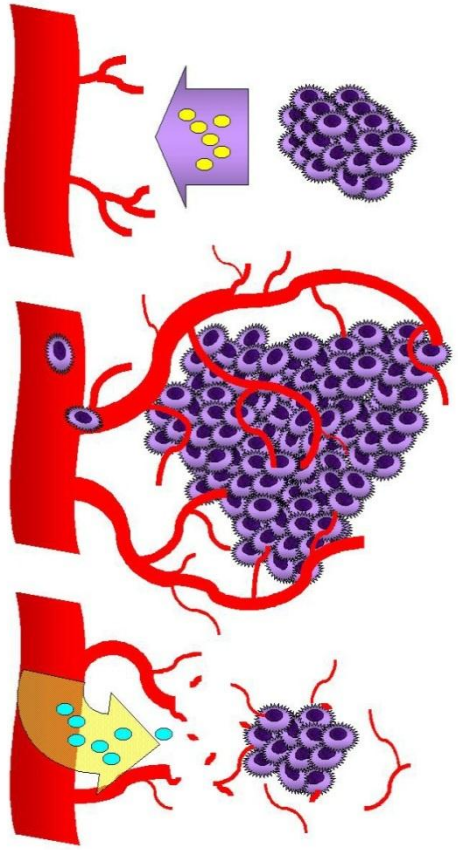
Targeted Therapy for HCC
Integration of Basic and Clinical Research

- Better understanding the pathogenesis of HCC
  → better preclinical validation of the targets
  → develop new strategies or new drugs



- Clinical research
  → look for the molecular basis
  → design new strategies or new drugs

Anti-angiogenesis Therapy in Advanced HCC



- Mostly a hypervascular tumor
- Expression of pro-angiogenic factors (VEGF, FGF, MMP) in tumor and stromal cells
- Circulating angiogenic factors in patients with HCC

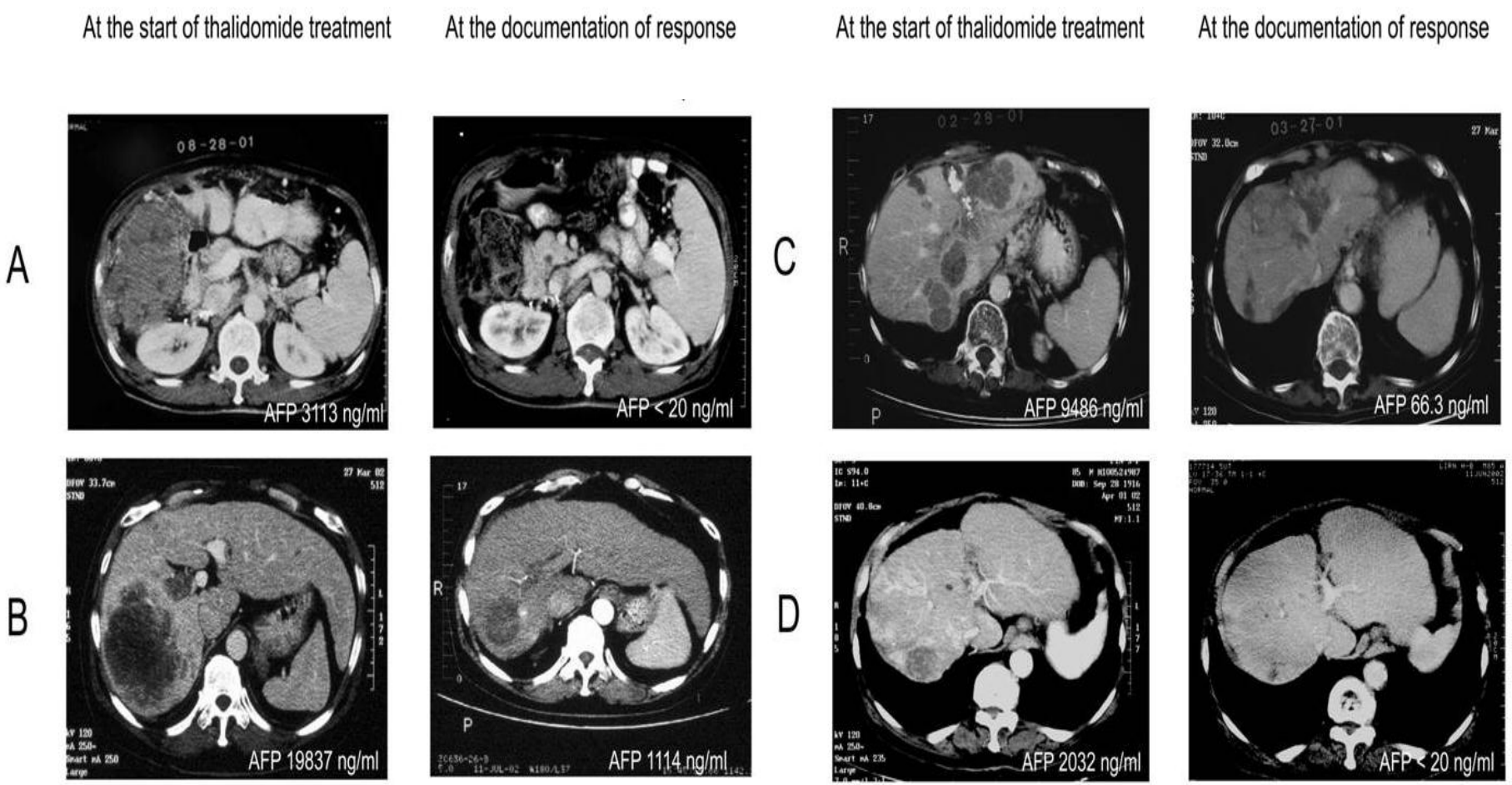
Anti-angiogenesis Therapy in Advanced HCC: thalidomide

- Possible mechanisms:
  - Inhibitor of VEGF- and bFGF-induced angiogenesis
  - Inhibitor of TNF-α synthesis
  - Free radical production
  - Immune modulation

A Clinical Trial of Thalidomide in Advanced HCC

- 53 Men, 15 women, median age 62.1 years
- HBsAg (+): 37 (54.4%), anti-HCV (+): 24 (35.3%)
- Thalidomide 100 mg b.i.d, p.o.
  dose escalation in 100-mg steps
- One CR and 3 PR, RR = 6.3%
  Another 6 patients had > 50% reduction of α-FP
  20 SD, 39 PD
- All response occurred with thalidomide 200-300 mg/day

Hsu C et al. *Oncology* 2003;65:242-9.



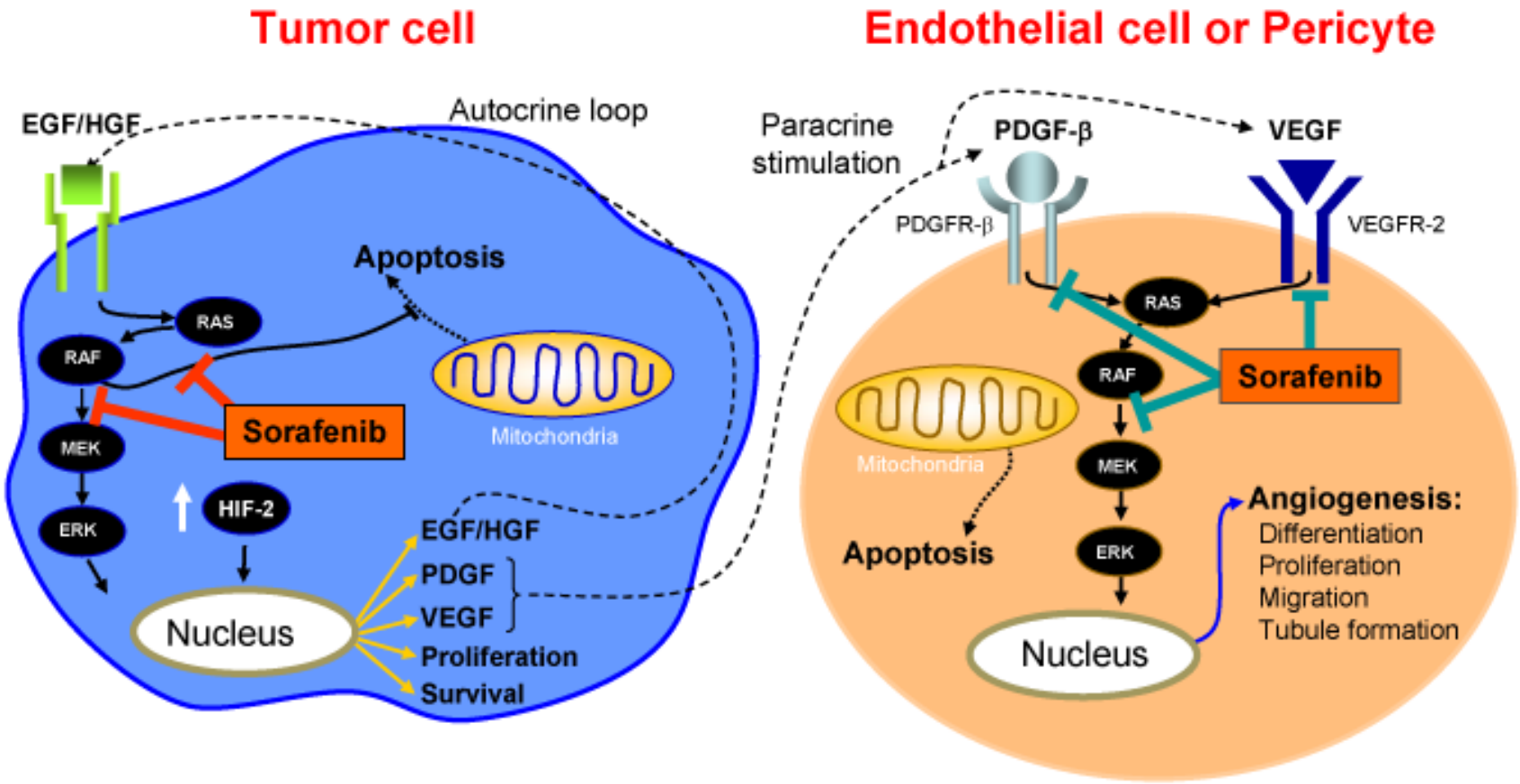
Hsu C et al. *Oncology* 2003;65:242-9.

Phase II Trials of Anti-angiogenic Agents in Advanced HCC

Author	Patients Evaluable	Treatment	Response Rate	Main Toxicity
Hsu	63	Thalidomide 200-600 mg/d	6.3 % 1CR, 3PR, 20SD	Lethargy
Patt	32	Thalidomide 400-1,200 mg/d	3.1 % 1PR, 1MR, 10SD	Somnolence
Lin	26	Thalidomide 200-600 mg/d	3.8 % 1CR, 2SD	Somnolence
Chiou	42	Thalidomide 50-200 mg/d	5.0 % 2PR, 9SD	Skin, Dizziness
Schwartz	46	Bevacizumab 5 or 10 mg/kg/2w	13.0 % 6PR, 30SD	Bleeding
Abou-Alfa	137	Sorafenib 400 mg bid	2.2 % 3PR, 8MR, 46SD	Lethargy
Faivre	37	Sunitinib 50 mg/d x 4w	2.7 % 1PR, 13SD	Bleeding
Raoul	45	Brivanib 800 mg/d	11.1 % 5PR, 16SD	Fatigue

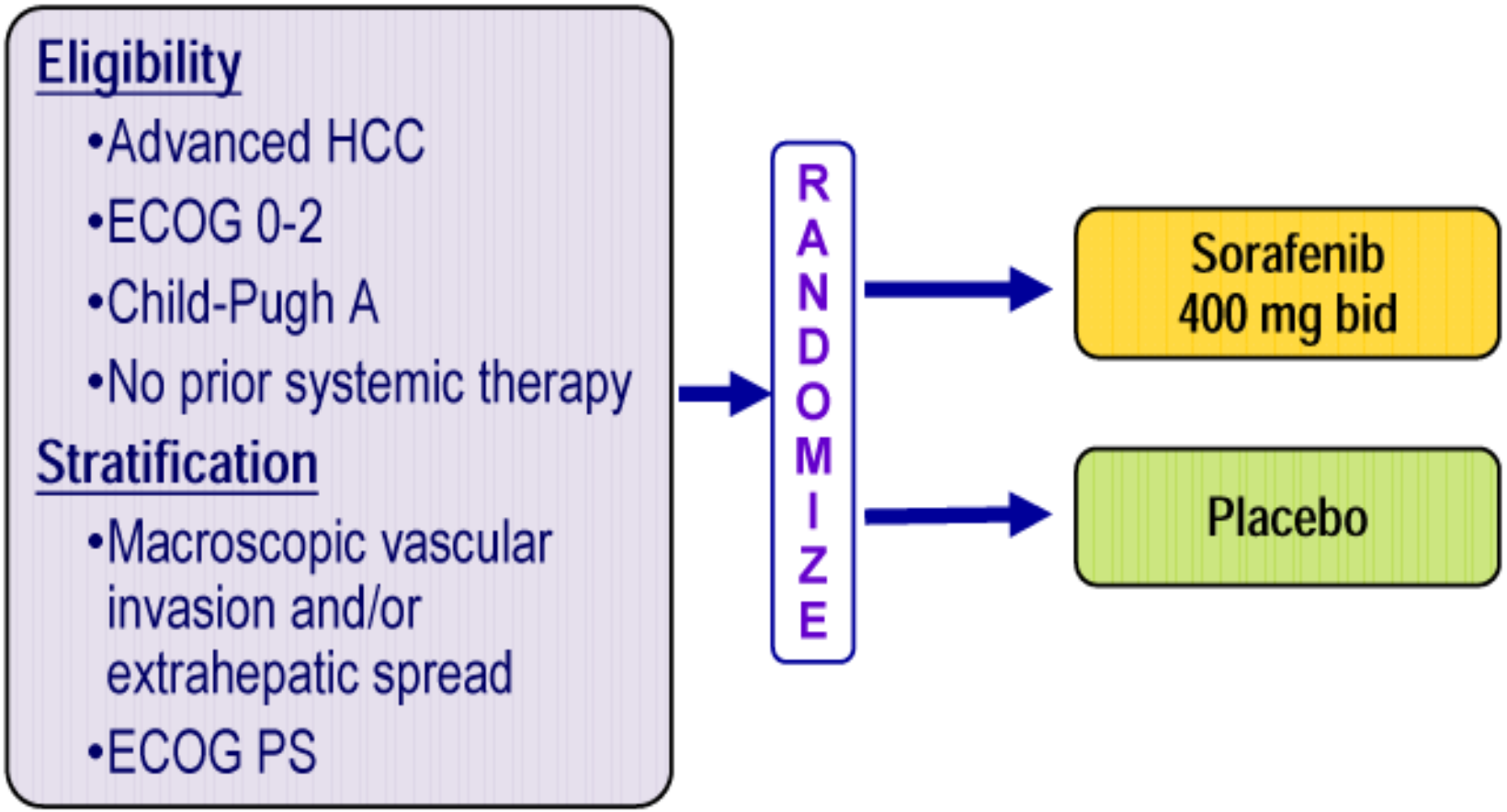
Hsu C et al. Oncology 2003;65:242-9.
Lin AY et al. Cancer 2005;103:119-25.
Abou-Alfa GK et al. J Clin Oncol 2006:24;4293-300
Faivre S et al. Lancet Oncol 2009:10;794-800.
Patt YZ et al. Cancer 2005;103:749-55.
Schwartz JD et al. J Clin Oncol 2008:26;2992-8.
Chiou HE et al. World J Gastroenterol 2006;12:6955-60.
Raoul L et al. J Clin Oncol 27:15s, 2009 (abstr 4577)

Sorafenib Targets Both Tumor-Cell Proliferation and Angiogenesis



Wilhelm S et al. *Cancer Res* 2004;64:7099-109.

Study Schema of SHARP and AP Studies

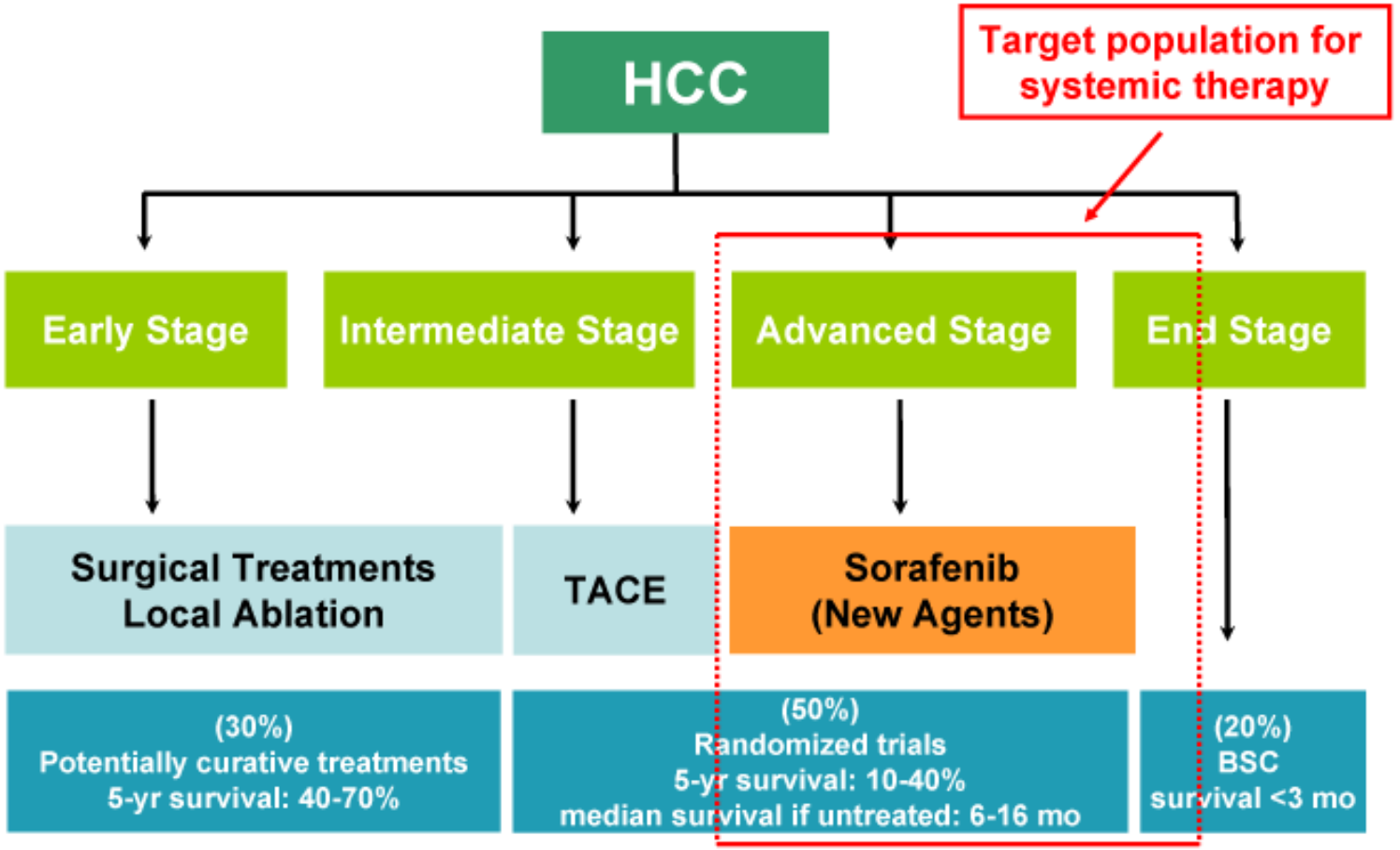


Phase III sorafenib studies of Advanced HCC: SHARP Vs. Asia-Pacific Study

	SHARP Study			Asia-Pacific Study		
	Sorafenib (N=299)	Placebo (N=303)	Hazard Ratio (95%CI)	Sorafenib (N=150)	Placebo (N=76)	Hazard Ratio (95%CI)
Overall survival (M)			0.69 (0.55-0.87)			0.68 (0.50-0.93)
Median	**10.7**	**7.9**		**6.5**	**4.2**	
Time to progression (M)			0.58 (0.45-0.74)			0.57 (0.42-0.79)
Median	**5.5**	**2.8**		**2.8**	**1.4**	
Level of response (%)						
CR+PR	0+2	0+1		0+3	0+1	
SD	71	67		54	28	
Disease control rate (%)	43	32		35	16	

Llovet JM et al. *N Engl J Med* 2008;359:378-90.
Cheng AL et al. *Lancet Oncol* 2009;10:25-34.

HCC Treatment Schedule



Llovet JM et al. *Hepatology* 2008;48:1312-27.

Molecular Targeted Therapy for HCC

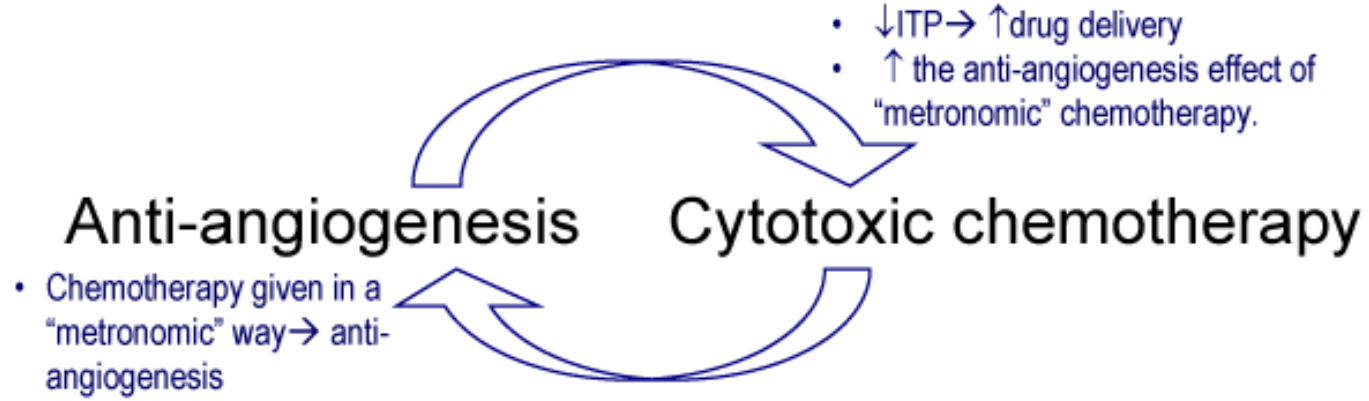
- Anti-angiogenesis
- EGFR tyrosine kinase inhibitors
- Combination of anti-angiogenesis and chemotherapy (conventional or metronomic)
- Novel targets and combination of targeted agents

Phase II Trials of EGFR Inhibitors in HCC

Author	Pts	Treatment	Response rate	Toxicity
Philip	38	Erlotinib 150mg/d	9 % 3PR, 12SD	Skin Diarrhea
Thomas	40	Erlotinib 150 mg/d	0 % 17SD	GI, Skin Liver
Vergote	17	Gefitinib 500 mg/d	0 % 5SD	Diarrhea N/V
O'Dwyer	31	Gefitinib 250 mg/d	3.2 % 1PR, 7SD	Diarrhea BM, Skin
Gruenwald	15	Cetuximab 400mg/m^2 → 250mg/m^2	0 % 2SD	Skin
Zhu	30	Cetuximab 400mg/m^2 → 250mg/m^2	0 % 5SD	Skin Diarrhea
Ramanathan	40	Lapatinib 1500 mg/d	5 % 2PR, 13SD	Fatigue

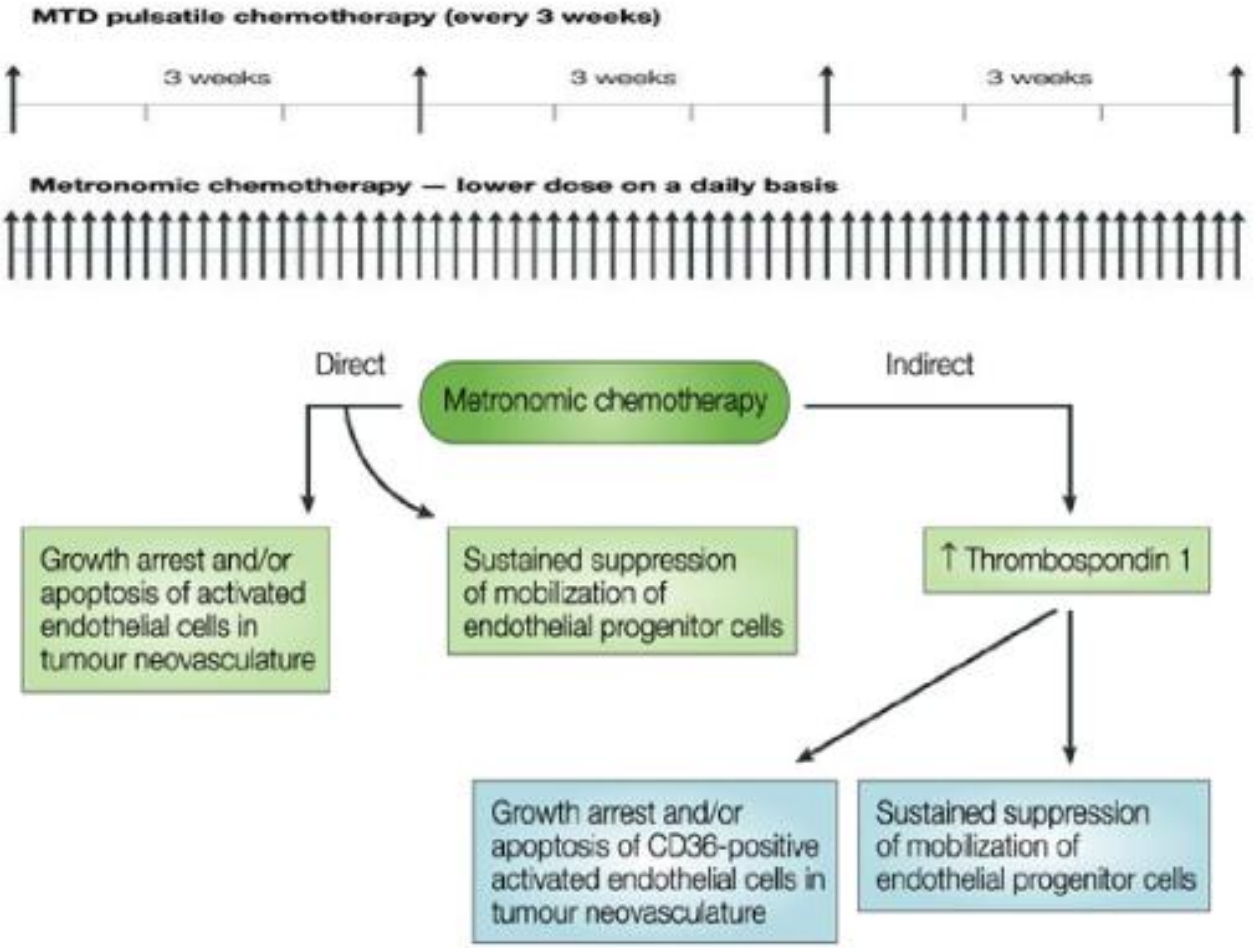
Philip PA et al. J Clin Oncol. 2005;23(27):6657-63.
Vergote IB et al. Proc Am Soc Clin Oncol 2005 (Abstr 3162
Gruenwald V et al. Proc Am Soc Clin Oncol 2006(Abstr 14079)
Ramanathan RK, et al. Cancer Chemother Pharmacol 2009:64;777-83.
Thomas MB et al. Cancer 2007:110;1059-66.
O'Dwyer et al. Proc Am Soc Clin Oncol 2006 (Abstr 4143)
Zhu AX et al. Cancer 2007:110;581-9.

Further Improvement of Anti-angiogenesis Approach



Colorectal cancer			
Avastin (5 mg/kg)	+	IFL	↑survival
Avastin (5 mg/kg)	+	5-FU/LV	↑survival
Breast cancer			
Avastin (15mg/kg)		Capecitabine	↑response; no survival benefit
NSCLC			
Avastin (15mg/kg)		Carbo/Taxol	↑survival

Metronomic Chemotherapy



Kerbel RS et al. *Nature Reviews Cancer* 2004;4:423-36.

Combination of Metronomic Chemotherapy with Anti-angiogenic Agents – NTUH clinical trials

- Xeloda + Avastin (XA)
- UFUR + Thalidomide (UT)
- UFUR + Sorafenib (US)

Oral 5-FU Preparations for Advanced HCC

	Capecitabine	UFT
Patient No.	37	28
Dosage	1000 mg/m^2, BID, d1-14/21 days	400 mg, BID Continuously
Efficacy		
RR (%)	11	18
SD (%)	11	Not reported
Toxicity		
Grade ¾	PLT ↓ (8%)	0
All grades	HFS, WBC ↓	GI

Patt YZ et al. *Cancer* 2004;101:578-86.
Ishikawa T et al. *J Gastroenterol Hepatol* 2001;16:452-9.

Patient Characteristics at Baseline

	XA	UT	US
Patients No	45	43	53
Median age	54	55	47
Male	89%	95%	89%
KPS <90	20%	24%	25%
HCV	18%	16%	25%
AFP ≧400	71%	71%	47%
CLIP ≧4	24%	37%	9%
Prior local tx	24%	72%	47%

Efficacy and Adverse Effects

	XA	UT	US
Dosage	X: 800 mg/m^2, BID, d1-14 A: 7.5 mg/kg, d1, q21d	U: 125 mg/m^2, BID T: 100 mg, BID	U: 125 mg/m^2, BID S: 400 mg, BID
Efficacy			
CR+PR	9%	9%	6%
SD	43%	23%	51%
Survival (m)			
OS	5.9	4.6	7.4
PFS	2.7	1.9	3.7
Toxicity			
Grade 3/4	↑ AST (16%)	Unremarkable	Fatigue (15%)
All grades	Skin, GI, Hematology	Somnolence	Skin, GI, Hematology

Approved Targeted Molecular Therapies With Possible Efficacy in HCC

- Dasatinib: CML
- Bevacizumab: breast cancer, NSCLC, CRC
- Erlotinib: NSCLC, pancreatic cancer
- Sunitinib: RCC, GIST
- Lapatinib: breast cancer
- Bortezomib: myeloma, mantle cell lymphoma
- Sorafenib: RCC, HCC
- Temsirolimus: RCC

Exploring Molecular Targets for HCC (I)

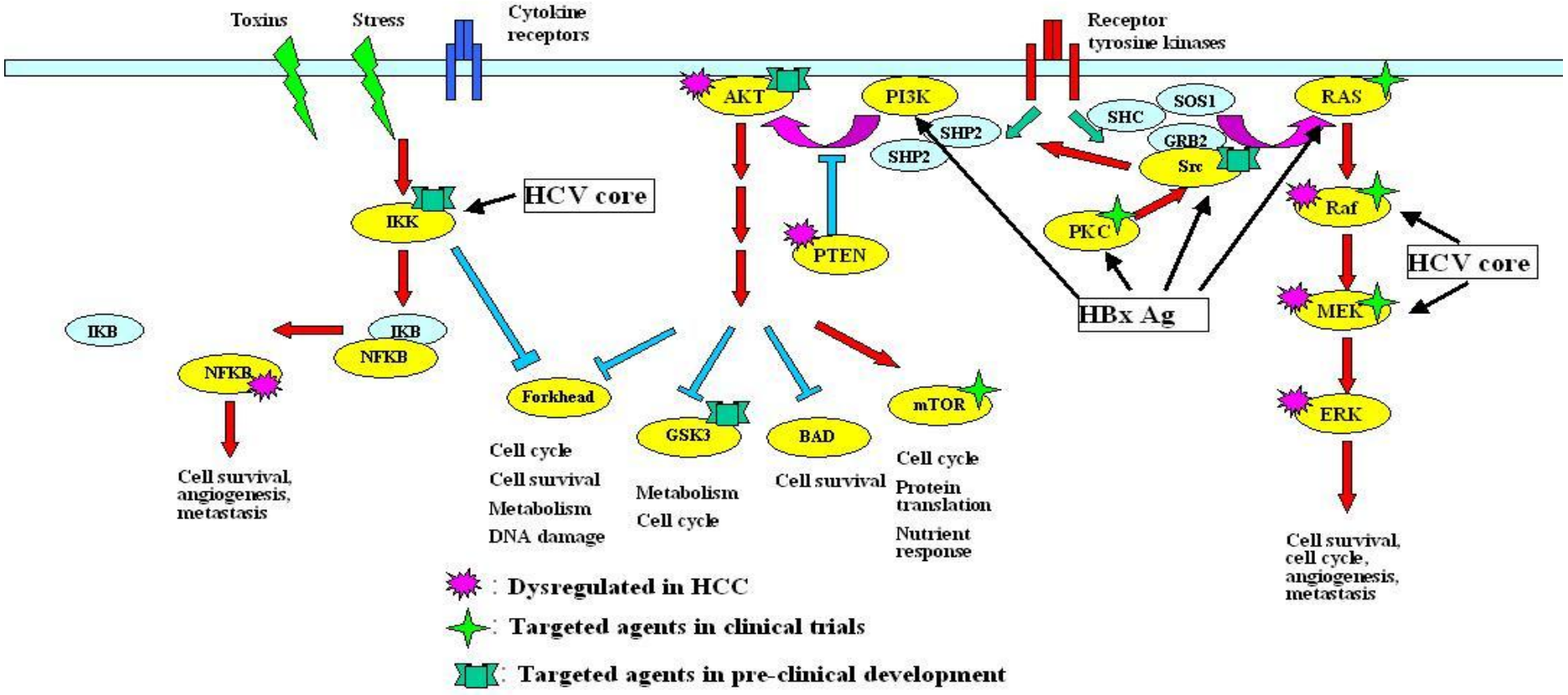
Tumor *vs.* Non-tumor with cDNA Microarray

Author	Differentially-Expressed Genes	Consistent Genes In ≧ 2 Studies
Okabe	335	Cyclin G1, cdc28 protein kinase 1, MMP 11, Forkhead box M1, MAPK3 (Erk1), CD34, Leukemia-associated phosphoprotein p18
Xu	2,253	Cyclin G1, cdc28 protein kinase 1, MAPK3 (Erk1)
Chen	1,640	Forkhead box M1, CD34, Leukemia-associated phosphoprotein p18
Delpuech	44	Cyclin G1, cdc28 protein kinase 2, MMP 14

Okabe H et al. *Cancer Res* 2001;61:2129-37.
Chen X et al. *Mol Biol Cell* 2002;13:1929-39.
Xu XR et al. *PNAS* 2001;98:15089-94.
Delpuech O et al. *Oncogene* 2002;21:2926-37.

Exploring Molecular Targets for HCC (II)

Viral Proteins and Signal Transduction Pathways



Exploring Novel Targeting Agents and Combination Strategies

Aurora kinase inhibitors, IGFR inhibitors, MEK inhibitors, m-TOR inhibitors, PI3K inhibitors, PDK inhibitors, HDAC inhibitors, proteosome inhibitors, multi-target inhibitors, anti-DR5 antibody……

Combined (EGFR + Src) inhibition
Combined (Raf + MEK) inhibition
Combined (proteosome + PI3K) inhibition
……

Summary and Perspective

1. Single-agent antiangiogenesis therapy has modest activity (2-13% RR).
2. Sorafenib has become the reference drug.
3. Combination of anti-angiogenesis with metronomic chemotherapy appears useful.
4. EGFR TK inhibitor, erlotinib, has modest activity (0-9% RR).
5. Novel targets and combination of targeted agents are under investigation.