New molecular targeted agents in HCC

Andrew X. Zhu, MD, PhD

ESMO 16th World Congress on Gastrointestinal Cancer

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

HARVARD MEDICAL SCHOOL

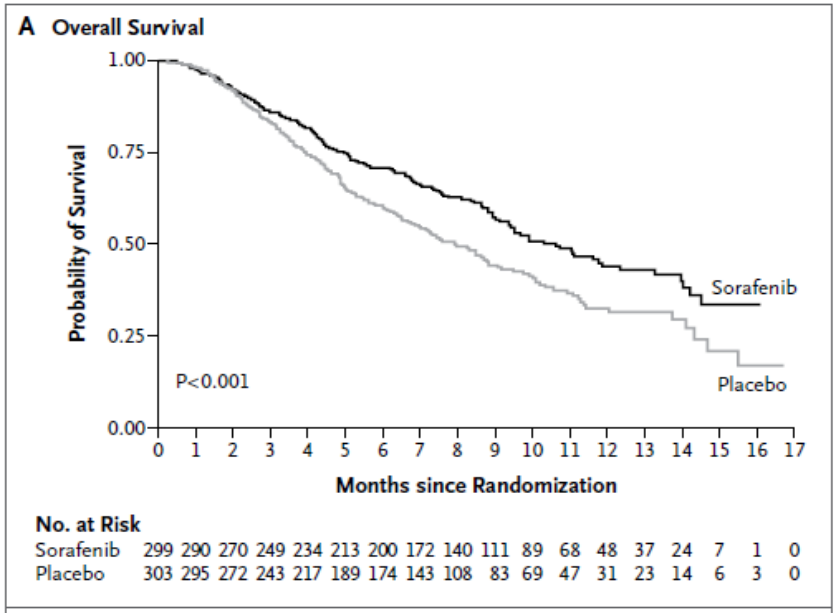
Group G: USA vs Germany 13:00 today

Discussion points

- Sorafenib in HCC-unanswered questions
- Ongoing trials-lessons learned from failed phase III studies
- Promising agents/strategies (my biased view)
- Future direction

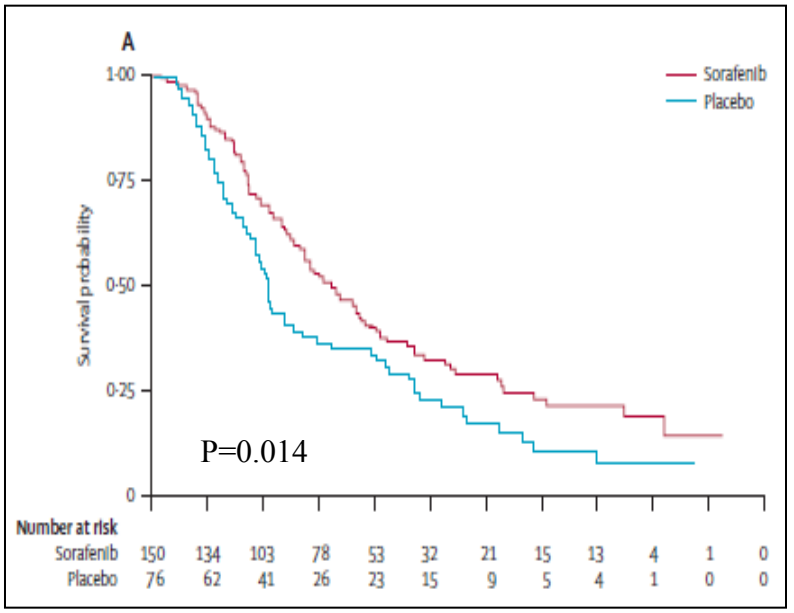
SHARP[1] vs Asia-Pacific Study[2]: Overall Survival

SHARP Trial



10.7 vs 7.9 mo
HR: 0.69 (0.55-0.87)

Asia-Pacific Trial



6.5 vs 4.2 mo
HR: 0.68 (0.50-0.93)

1. Llovet JM, et al. *N Engl J Med* 2008 359:378-90
2. Cheng AL, et al. *Lancet Oncology* 2009

Lessons from sorafenib development

- Modest efficacy in advanced HCC with Child A cirrhosis
- Toxicity management and dose adjustment are critical
- Outcomes vary depending on the etiology, geographic regions, and severity of underlying cirrhosis
- Mechanism of action of sorafenib that mediates clinical benefits and resistance remains unknown
- No validated predictive biomarkers for sorafenib in HCC

Biomarkers for Sorafenib

- **Tissue Biomarkers**
  - Nuclear pERK overexpression associated with prolonged TTP in phase 2 [1]
  - Tissue pERK staining was not associated with outcomes in phase 3[2]

1. Abou-Alfa GK, et al. J Clin Oncol. 2006;24:4293-4300. 2. Llovet JM, et al. N Engl J Med. 2008;359:378-390. 3. Llovet JM, et al. Clin Cancer Res. 2012;18:2290-2300. 4. Arao T, et al. Hepatology, 2013; 57(4):1407-15; Horwitz E at al, Cancer Discoery, 2014.

Biomarkers for Sorafenib

- **Tissue I**
  - Nuc
  - Tiss

2 [1]

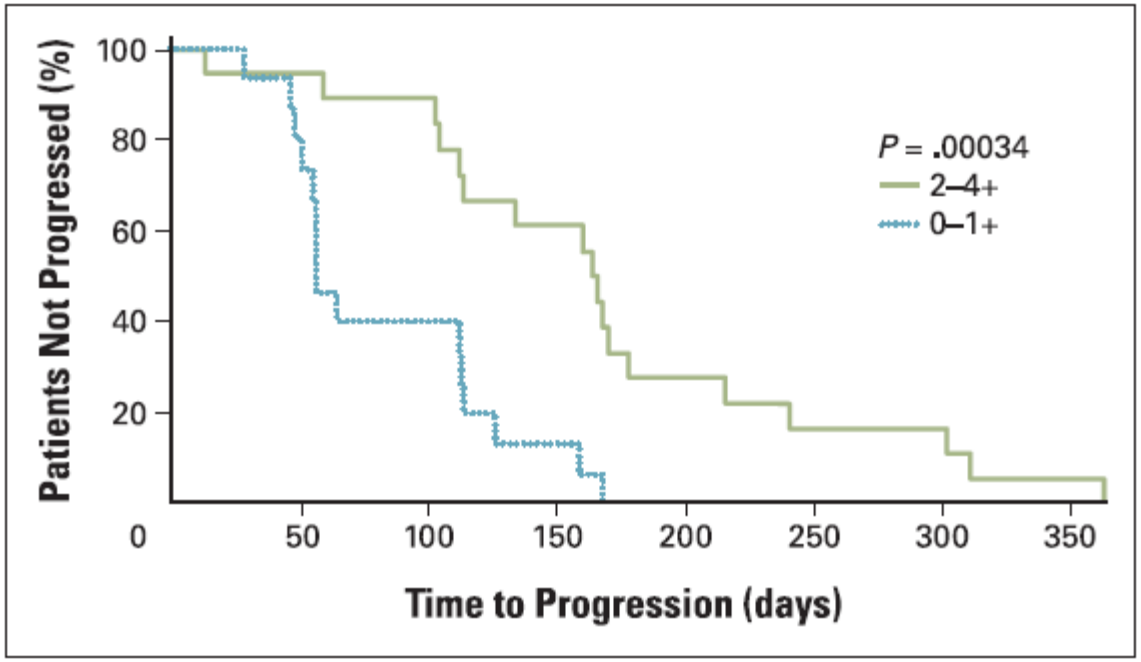


Fig 7. Percentage of patients not progressed plotted as a function of time to progression in patient tumors with a maximum phosphorylated extracellular signal regulated kinase staining intensity of either 0 and 1+ or 2+ through 4+ (n = 33).

1. Abou-Alfa GK, et al. J Clin Oncol. 2006;24:4293-4300. 2. Llovet JM, et al. N Engl J Med. 2008;359:378-390. 3. Llovet JM, et al. Clin Cancer Res. 2012;18:2290-2300. 4. Arao T, et al. Hepatology, 2013; 57(4):1407-15; Horwitz E at al, Cancer Discoery, 2014.

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  - High s-c-Kit and low HGF at baseline showed a trend towards improved OS[3]

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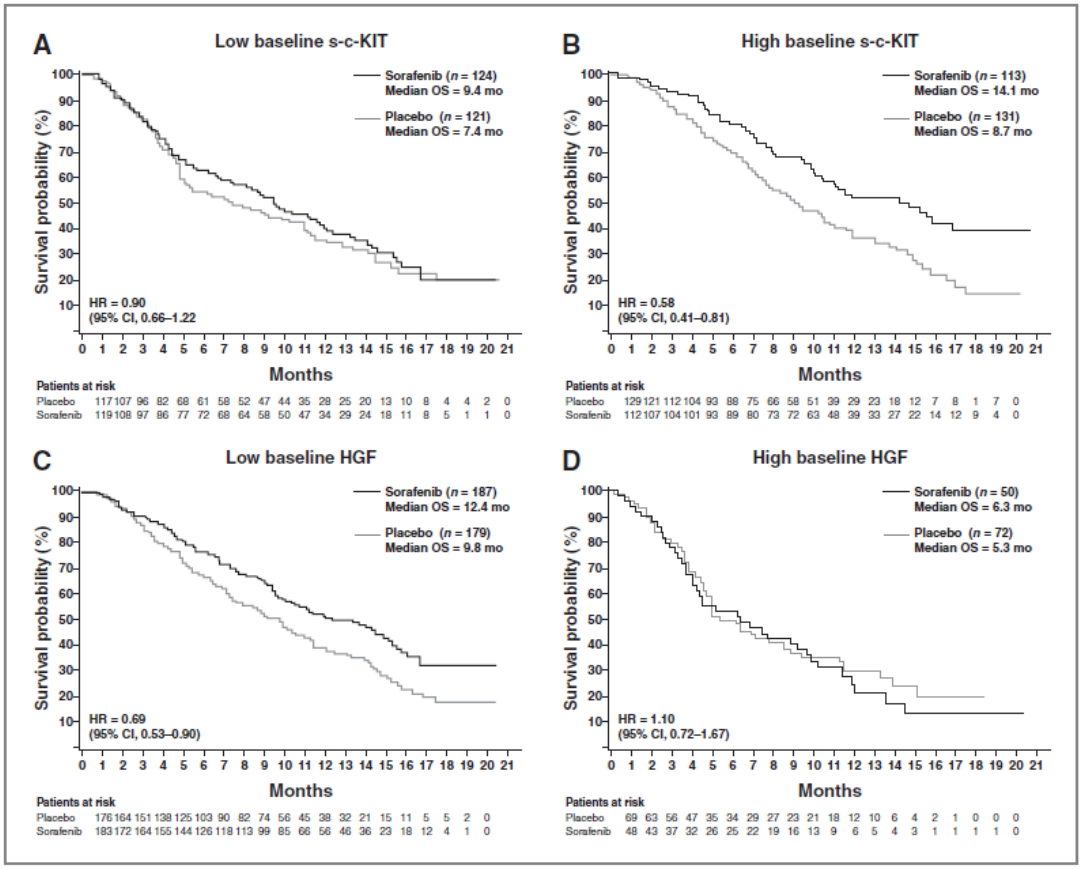

Figure 2. Analysis of baseline biomarkers as predictive factors for sorafenib benefit (OS). Low s-c-KIT (A) and high s-c-KIT (B), *P* value for biomarker treatment interaction = 0.081. C, low HGF and (D) high HGF, *P* value for biomarker treatment interaction = 0.073.

1. Abou-Alfa GK, et al. J Clin Oncol. 2006;24:4293-4300. 2. Llovet JM, et al. N Engl J Med. 2008;359:378-390. 3. Llovet JM, et al. Clin Cancer Res. 2012;18:2290-2300. 4. Arao T, et al. Hepatology, 2013; 57(4):1407-15; Horwitz E at al, Cancer Discoery, 2014.

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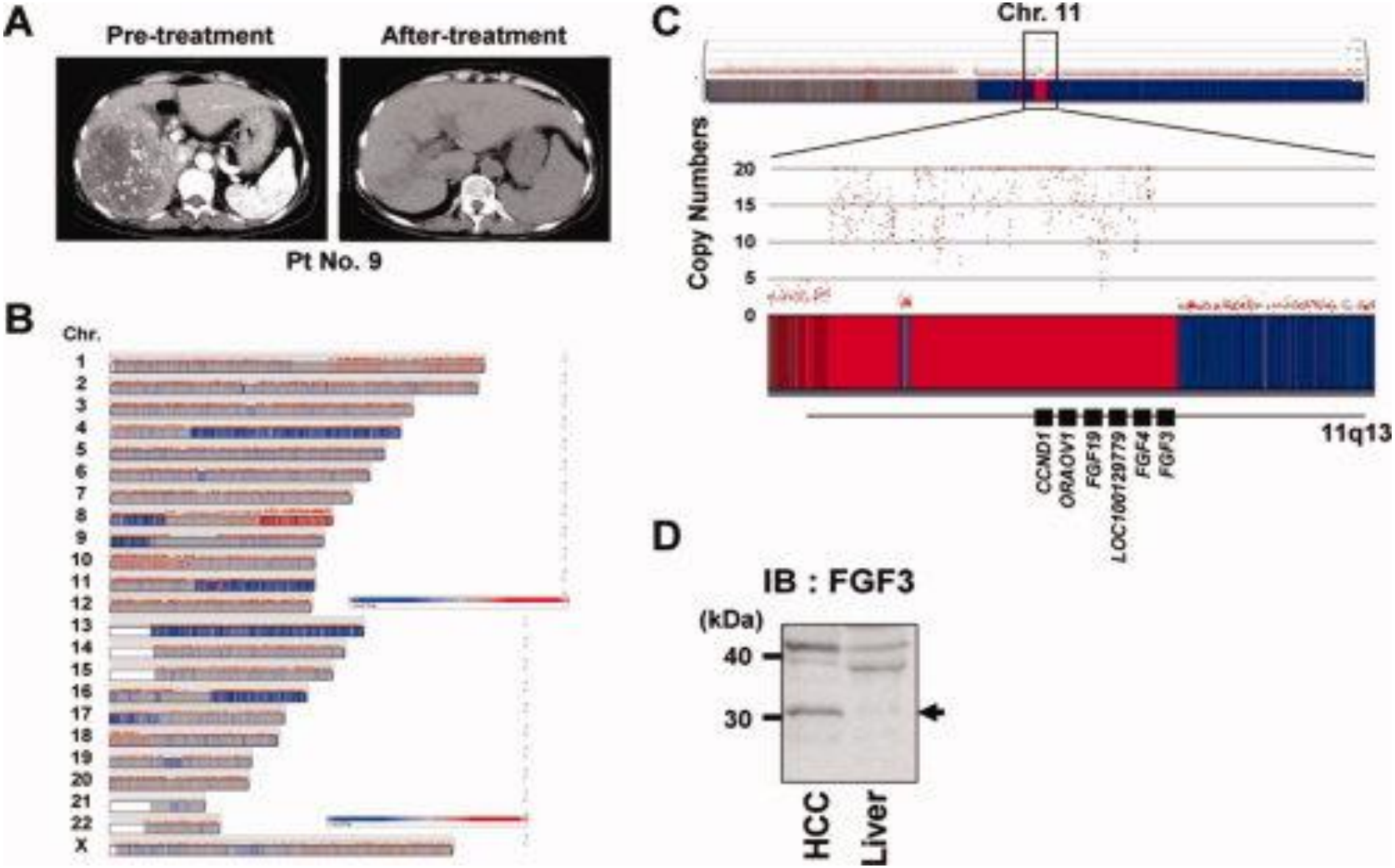
- **Genomic Biomarkers**
  - FGF3/FGF4 and VEGF A amplification predicted response in small number of HCC patients [4, 5]

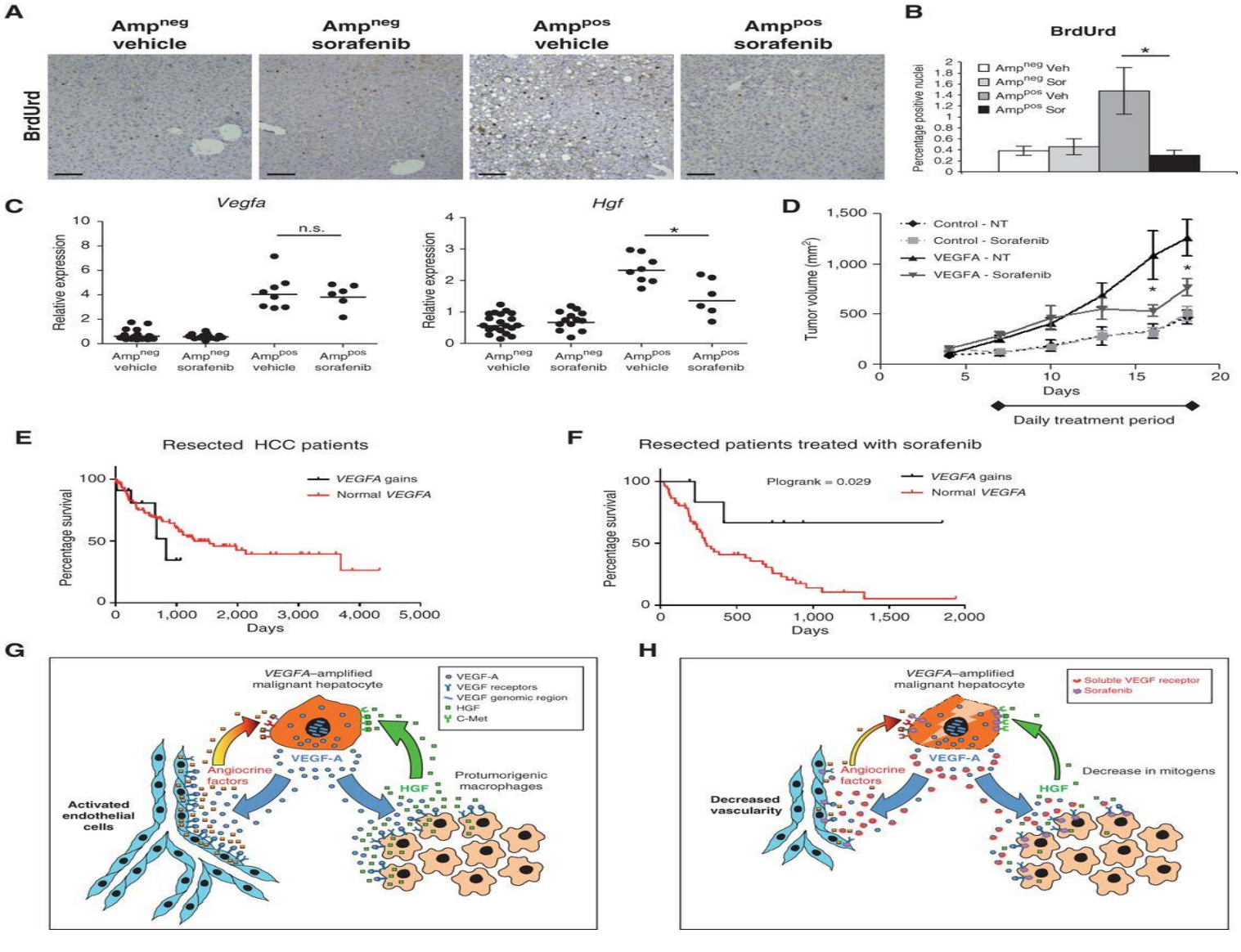
1. Abou-Alfa GK, et al. J Clin Oncol. 2006;24:4293-4300. 2. Llovet JM, et al. N Engl J Med. 2008;359:378-390. 3. Llovet JM, et al. Clin Cancer Res. 2012;18:2290-2300. 4. Arao T, et al. Hepatology, 2013; 57(4):1407-15; Horwitz E at al, Cancer Discoery, 2014.

FGF3/FGF4 amplification predicting sorafenib sensitivity



Arao et al, Hepatology 2013

VEGFA-Amplified HCCs Are Highly Sensitive to Sorafenib



Horwitz et al, Cancer Discov, 2014

Failed Phase III Trials in Advanced HCC

Arms	Principle Targets of Experimental Drug	# of Patients	Median overall survival
First Line			
Sunitinib vs. SOR[1]	VEGFR, PDGFRa/b, c-KIT, FLT3, and RET	n=1074	8.1 vs. 10 months, HR 1.31 (1.13-1.52), p = 0.0019
Brivanib vs. SOR[2] (BRISK-FL)	VEGFR, FGFR	n=1155	9.5 vs. 9.9 months, HR 1.07 (0.94-1.23), p = 0.3116
Linifanib vs. SOR[3]	VEGFR, PDGFR	n=1035	9.1 vs. 9.8 months, HR 1.046 (0.896-1.221), p= 0.1785
Erlotinib/SOR vs. Placebo/SOR[4] (SEARCH)	EGFR	n=720	9.5 vs. 8.5 months, HR 0.929 (0.781-1.106), p = 0.204
Second Line			
Brivanib vs. BSC[5] (BRISK-APS)	VEGFR, FGFR	n=395	9.4 vs. 8.2 months, HR 0.89 (0.69-1.15), p = 0.3307
Everolimus vs. BSC[6] (EVOLVE-1)	mTOR	n=546	7.6 vs. 7.3 months. HR 1.05 (0.86-1.27), p=0.675

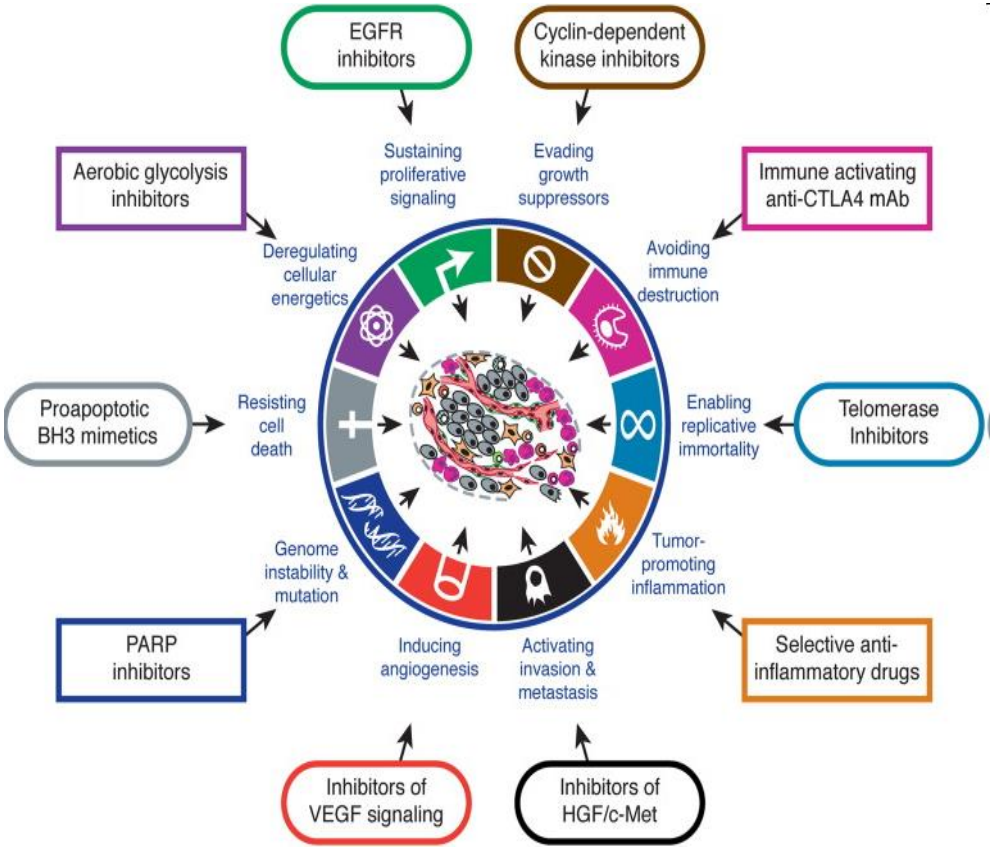
SOR = Sorafenib; BSC = Best Supportive Care; OS = Overall Survival; HR = Hazard Ratio

1. Cheng et al, *JCO*, 2013; 2. Johnson, et al, *JCO*, 2013; 3. Cainap et al, GI ASCO 2012;
4. Zhu, et al, ESMO 2012; 5. Llovet et al, *JCO*, 2013; 6. Zhu et al *JCO*, 2014

Lessons from failed phase III trials

- Phase II data need to be more robust for efficacy assessment
- Surrogate endpoints (ORR, TTP, and PFS) have limitations
- Safety and tolerability of the tested agents/regimens are important
- Clinical and biological heterogeneity of HCC impact the performance of targeted therapies in HCC
- Patient resource utilization is high

Therapeutic targeting of the hallmarks of cancer and ongoing HCC trials



Hanahan and Weinberg, Cell, 2011

Zhu AX Am Soc Clin Oncol Educ Book. 2012

Single Agent Studies
Antiangiogenic agents Sunitinib, brivanib, bevacizumab, ramucirumab, TSU-68, linifanib, cediranib, pazopanib, lenvatinib, lenalidomide, and axitinib **Epidermal growth factor receptor inhibitors** Erlotinib, gefitinib, lapatinib, cetuximab **mTOR inhibitors** Everolimus, temsirolimus, sirolimus, CC-223 **c-Met inhibitors** Tivantinib, cabozantinib, foretinib, MetMab, INC-280, LY2875358 **MEK inhibitors** Selumetinib (AZD6244), Refametinib **Histone deacetylase inhibitor** Belinostat, resminostat **HSP-90 inhibitor** Ganetespib (STA-9090) **Oncolytic Virus** JX-594 **Immune-based therapy** Tremelimumab, PD-1 and PD-L1 inhibitors
Combination Studies
With Sorafenib: Everolimus, AZD6244, Bevacizumab, Temsirolimus, Vorinostat, GC33, OSI-906, OMP-4F28 **Without Sorafenib** Bevacizumab + Erlotinib

Antiangiogenic agents in HCC

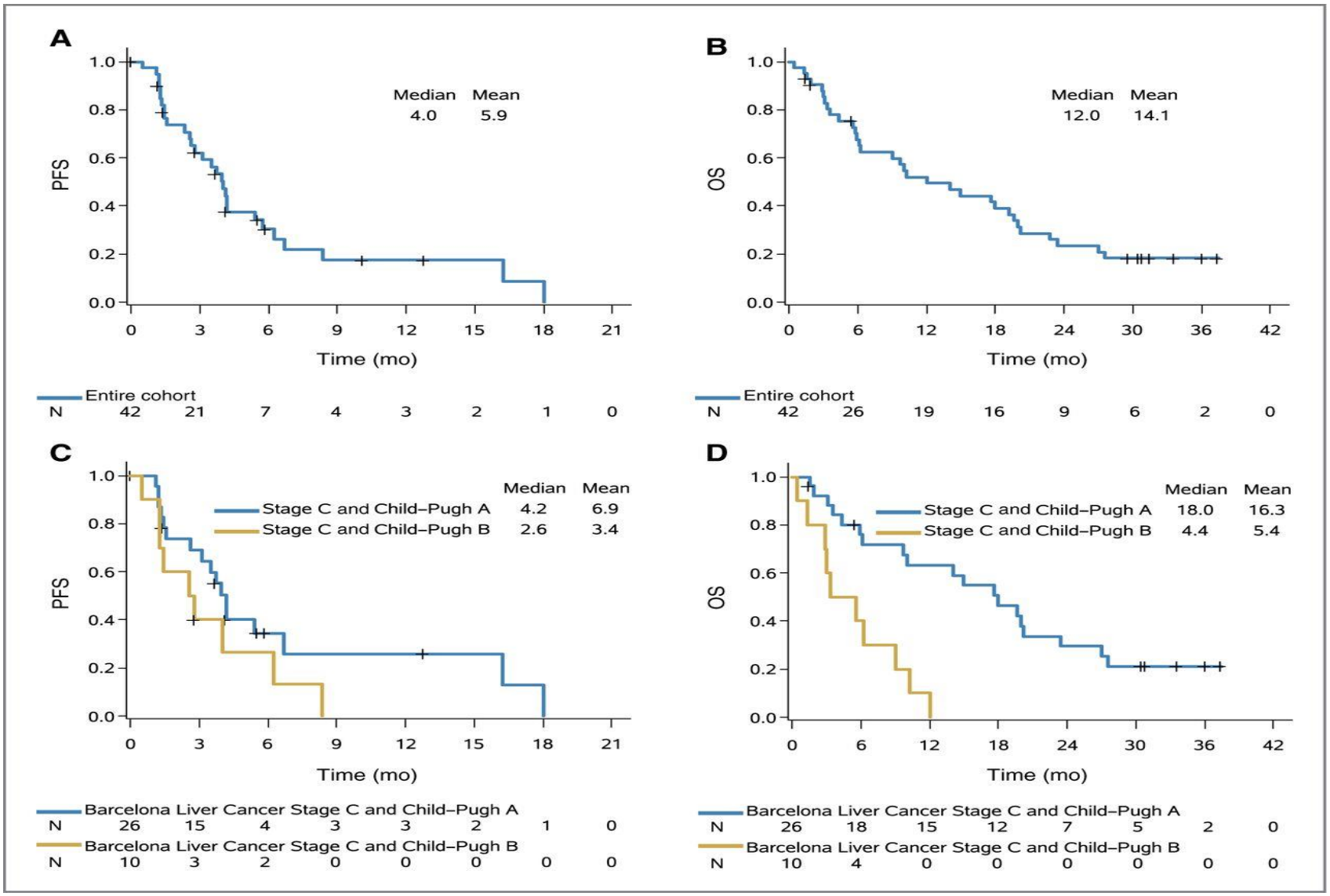
- Ramucirumab
  - Recombinant human monoclonal antibody against VEGFR-2
  - Efficacy: RR 10%, PFS 4.0 months, OS 12.0 months
  - Grade 3-4 AEs: hypertension (12%), fatigue (5%), GI bleeding (5%)

- Levantinib
  - Small molecule inhibitor of VEGFR1-3, FGFR1-4, RET, KIT, PDGFRβ
  - Efficacy: 37% RR per mRECIST; 24% RR per RECIST1.1; median TTP (investigator assessment) of 12.8 months and OS of 18.7 months
  - High incidence of hypertension, anorexia, proteinuria, HFSR, fatigue, and thrombocytopenia

- Combining VEGFR inhibitors with other antiangiogenic inhibitors: sorafenib plus dalantercept, sorafenib plus Ang 2 inhibitors, sorafenib plus bevacizumab etc

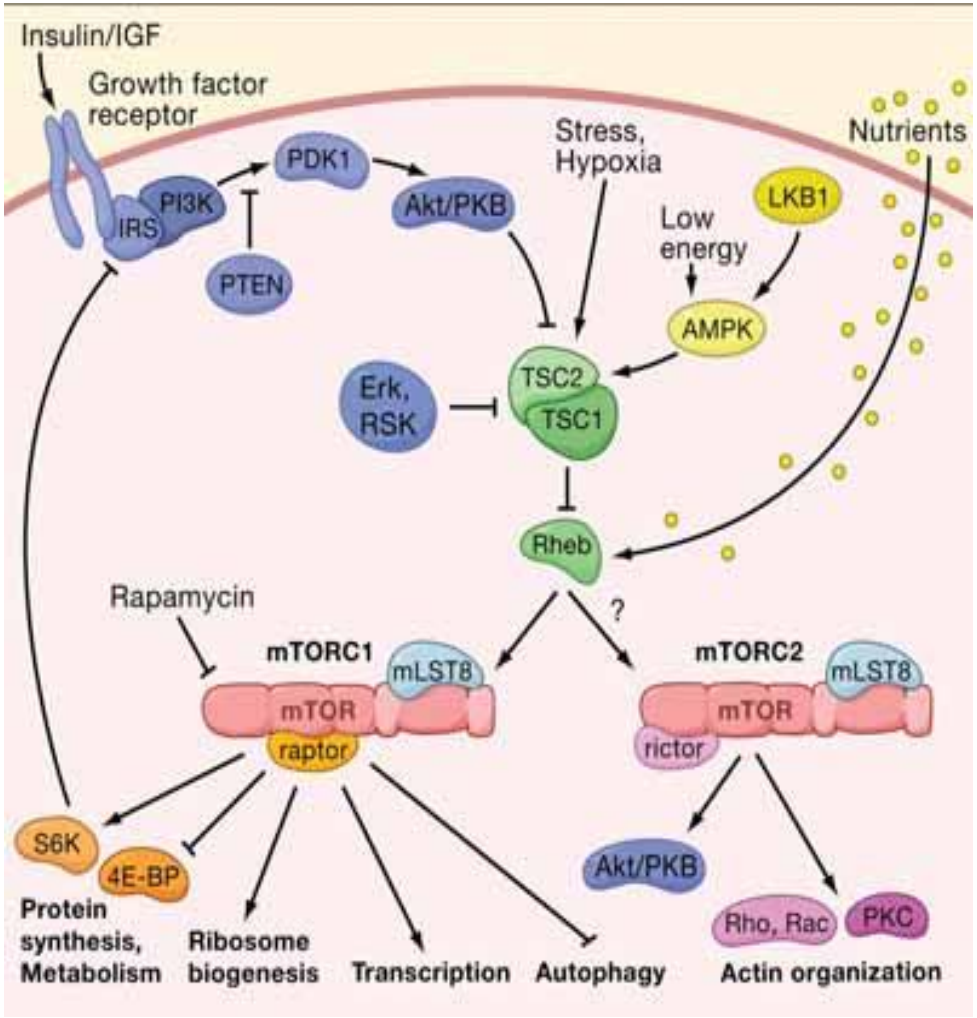
Zhu AX et al. Clin Cancer Res , 2013; Kudo M et al, ILCA, 2013

Phase II study of Ramucirumab in advanced HCC



Zhu AX et al. Clin Cancer Res , 2013

Targeting mTOR in HCC



- Intracellular serine/threonine kinase in the PI3K/Akt pathway
- mTOR activation in involved in HCC
- First generation mTOR inhibitors (rapologs): everolimus, temsirolimus, sirolimus
- Combining sorafenib with either everolimus or temsirolimus
- Novel mTOR inhibitors under development

1. Harris and Lawrence. *Sci STKE*. 2003;(212):re15.
2. Villanueva et al, *Gastroenterology*. 2008
3. Zhu et al, *Cancer*, 2011
4. Shiah et al, *Aliment Pharmacol Ther*. 2013
5. Finn et al, *Hepatology*, 2013
6. Kelley et al, *Ann Oncol*, 2013
7. Wullschleger et al. *Cell*. 2006

Phase I study of everolimus in combination with sorafenib in advanced HCC

- Eligibility: advanced HCC, ECOG 0-1, Child A
- 30 patients enrolled (everolimus 2.5/5 mg, 16/14)
- DLTs: grade 3 AST (1), grade 3-4 thrombocytopenia (5), hyperbilirubinemia (1)
- MTD: everolimus 2.5 mg daily and sorafenib 400 mg bid
- TTP: 3.5/3.6 months in the 2.5/5.0 mg groups respectively
- Median TTP and OS in the 2.5-mg cohort were 4.5 months and 7.4 months, respectively, and 1.8 months and 11.7 months, respectively, in the 5.0-mg cohort

Finn R et al. J Hepatol. 2013 Dec;59(6):1271-7.

Sorafenib with or without everolimus in patients with unresectable HCC: A randomized multicenter phase II trial (SAKK 77/08 and SASL 29)

- Unresectable or metastatic HCC, Child-Pugh A/B7
- S 800 mg alone or S 800 mg + E 5 mg
- primary endpoint was progression free survival at 12 weeks
- 106 pts were randomized: 46 pts received S and 60 pts S+E (93 pts are evaluable for the primary endpoint, 105 pts for the safety analysis)
- PFS12 rate was 70% in S (95% CI: 54-83) and 68% in S+E (95% CI: 53-81)
- Response rate was 0% in S arm and 10% in S+E arm
- Median PFS was 6.6 vs. 5.7, median TTP was 7.6 vs. 6.3, and median OS 10 vs. 12 months in the S vs. S+E arm
- Grade 3 and 4 adverse events occurred in 72% (S) and in 86% (S+E)

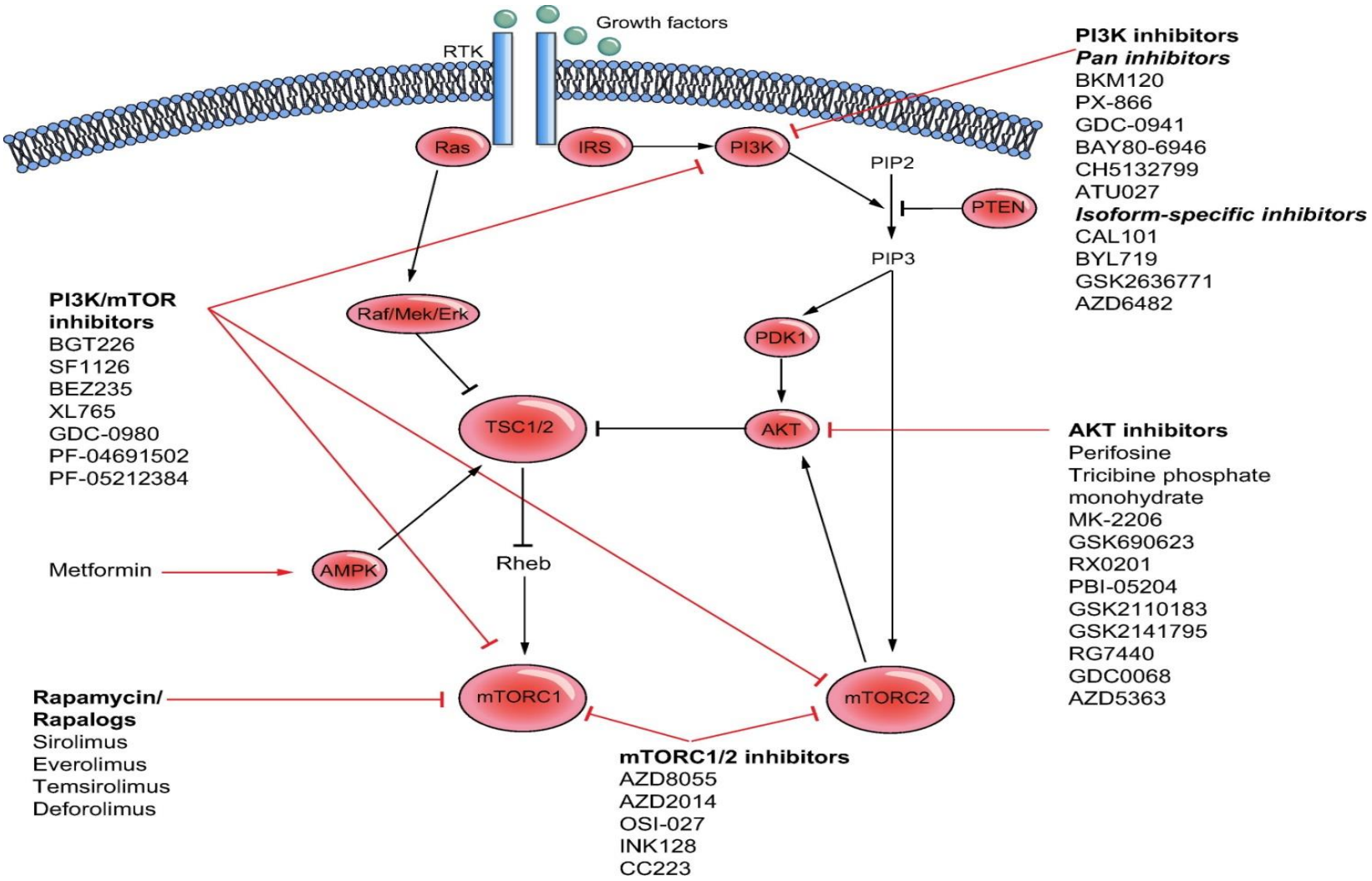
Koeberle et al, J Clin Oncol 32:5s, 2014 (suppl; abstr 4099)

Temsirolimus combined with sorafenib in HCC: a phase I study

- Eligibility:, incurable HCC and Child Pugh score ≤B7
- 25 patients enrolled
- DLTs: grade 3 HFSR and grade 3 thrombocytopenia
- MTD: temsirolimus 10 mg weekly plus sorafenib 200 mg twice daily
- Two patients (8%) had a confirmed PR; 15 (60%) had stable disease (SD). AFP declined ≥50% in 60% assessable patients.

Kelley RK et al. Ann Oncol. 2013 Jul;24(7):1900-7.

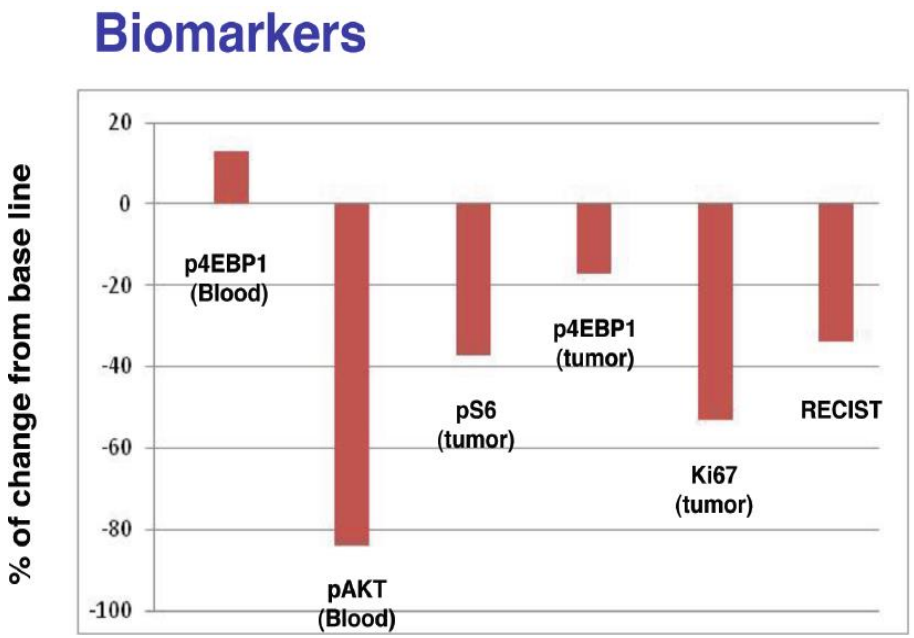
Agents targeting the mTOR signaling pathway

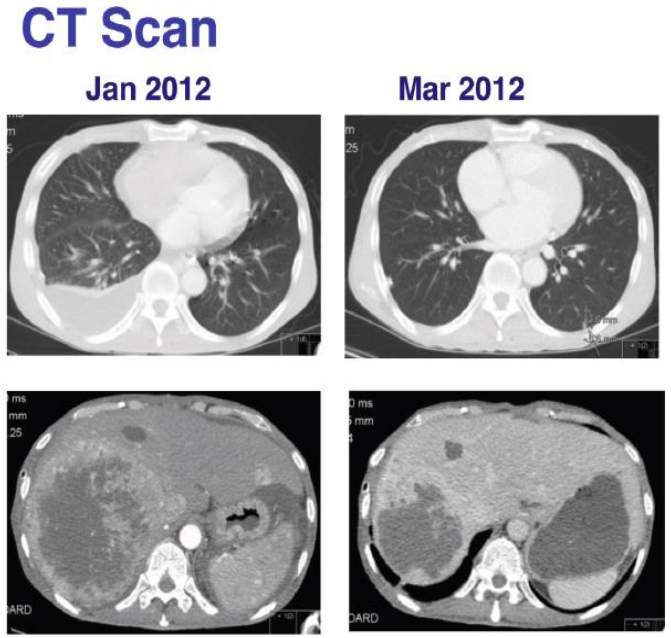


Matter MS et al, J Hepatol. 2014

Phase 1 Expansion Trial of an Oral TORC1/TORC2 Inhibitor (CC-223) in Advanced Solid Tumors

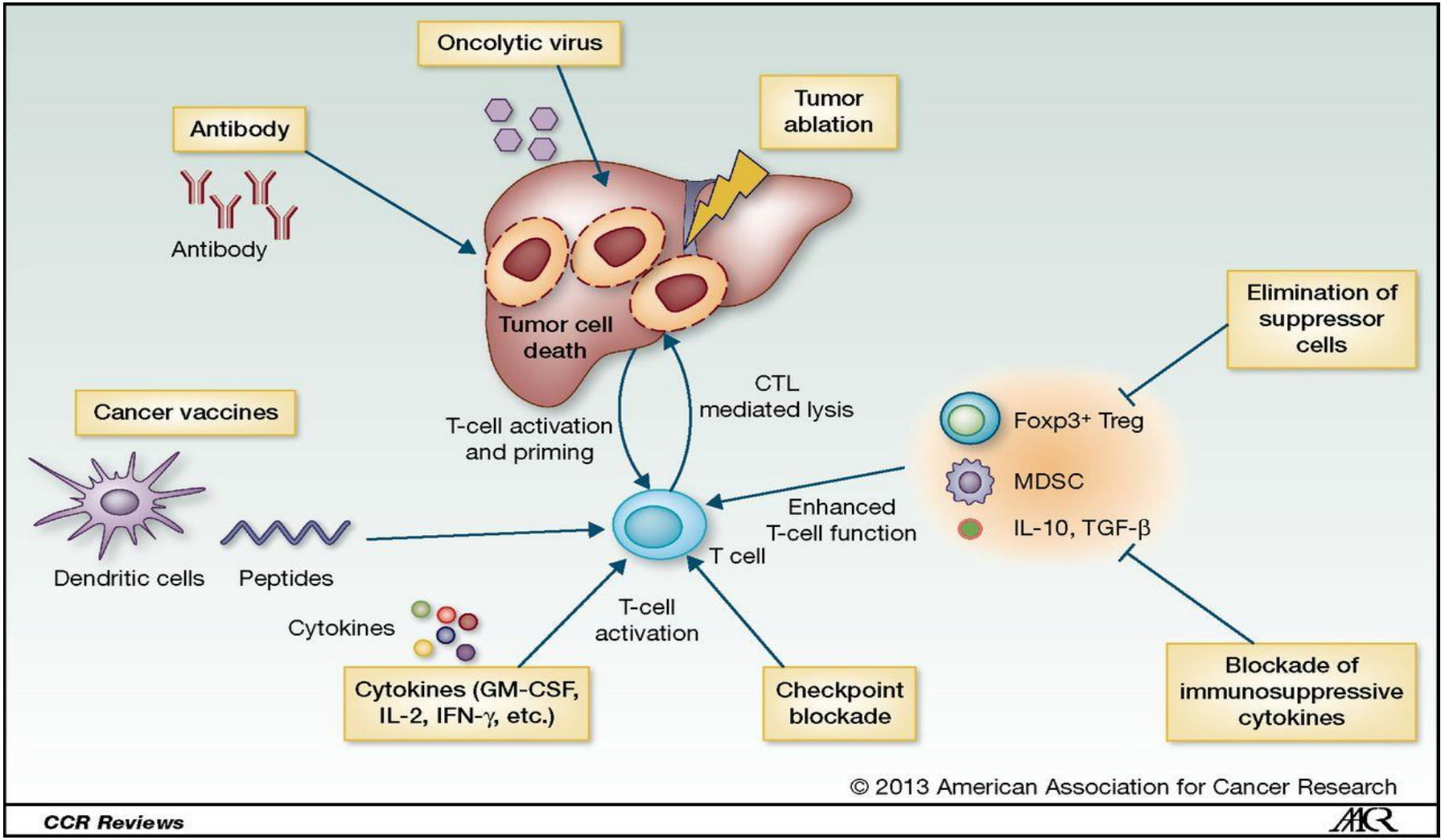
- Evidence of TORC1 & TORC2 pathway inhibition
- MTD 45 mg once daily but RP2D was 30 mg daily
- CC-223 has comparable toxicities to other drugs targeting this pathway
- DLT: hyperglycemia (30 mg), rash (45 mg), fatigue & mucositis (60 mg)
- HCC cohort: 27 patients enrolled: 3 PR (11%), 9 SD (33%)





Varga A et al, ASCO 2013

Immune-based approaches in HCC



Greten TF et al, *Clin Cancer Res*, 2013

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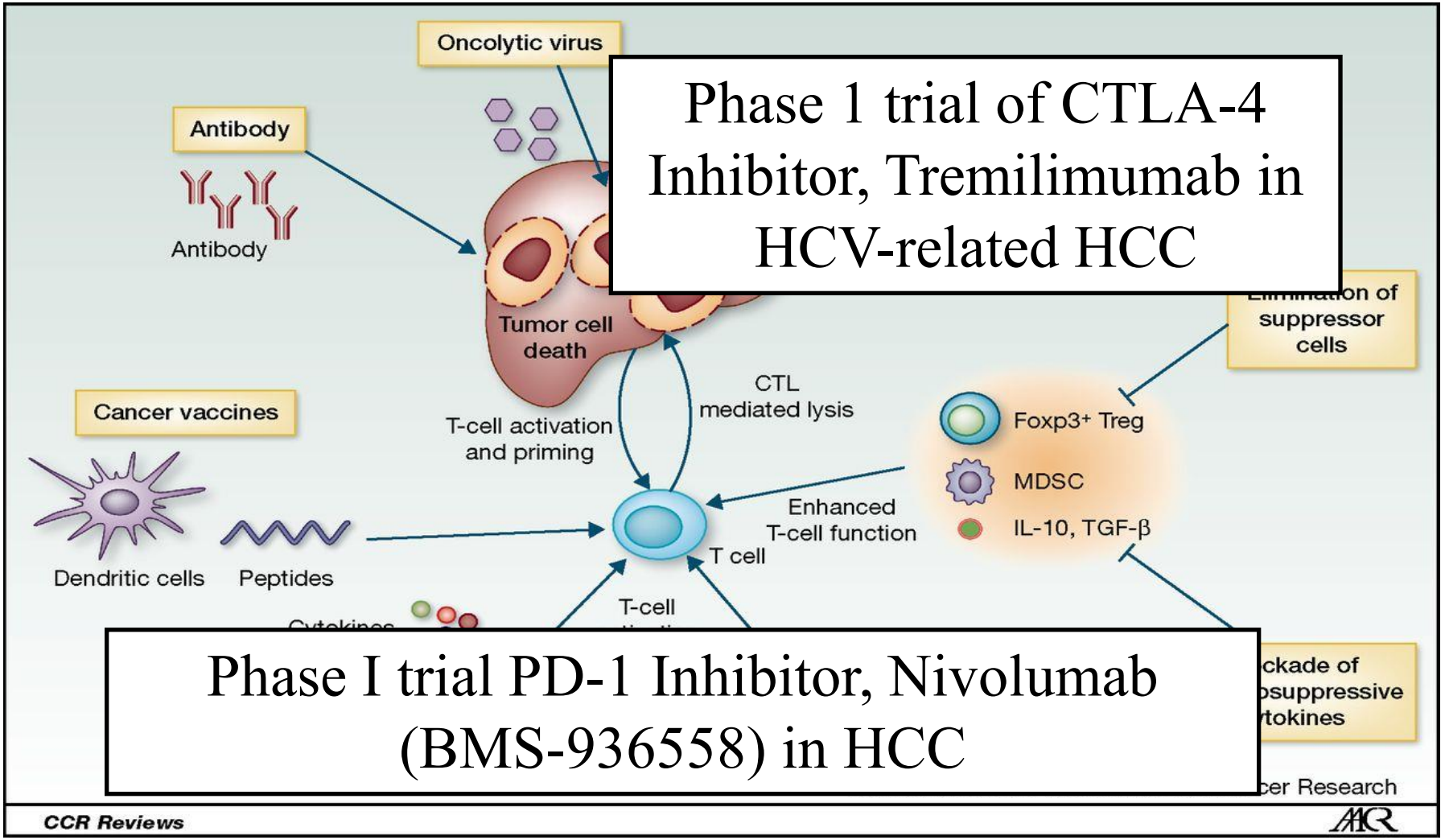
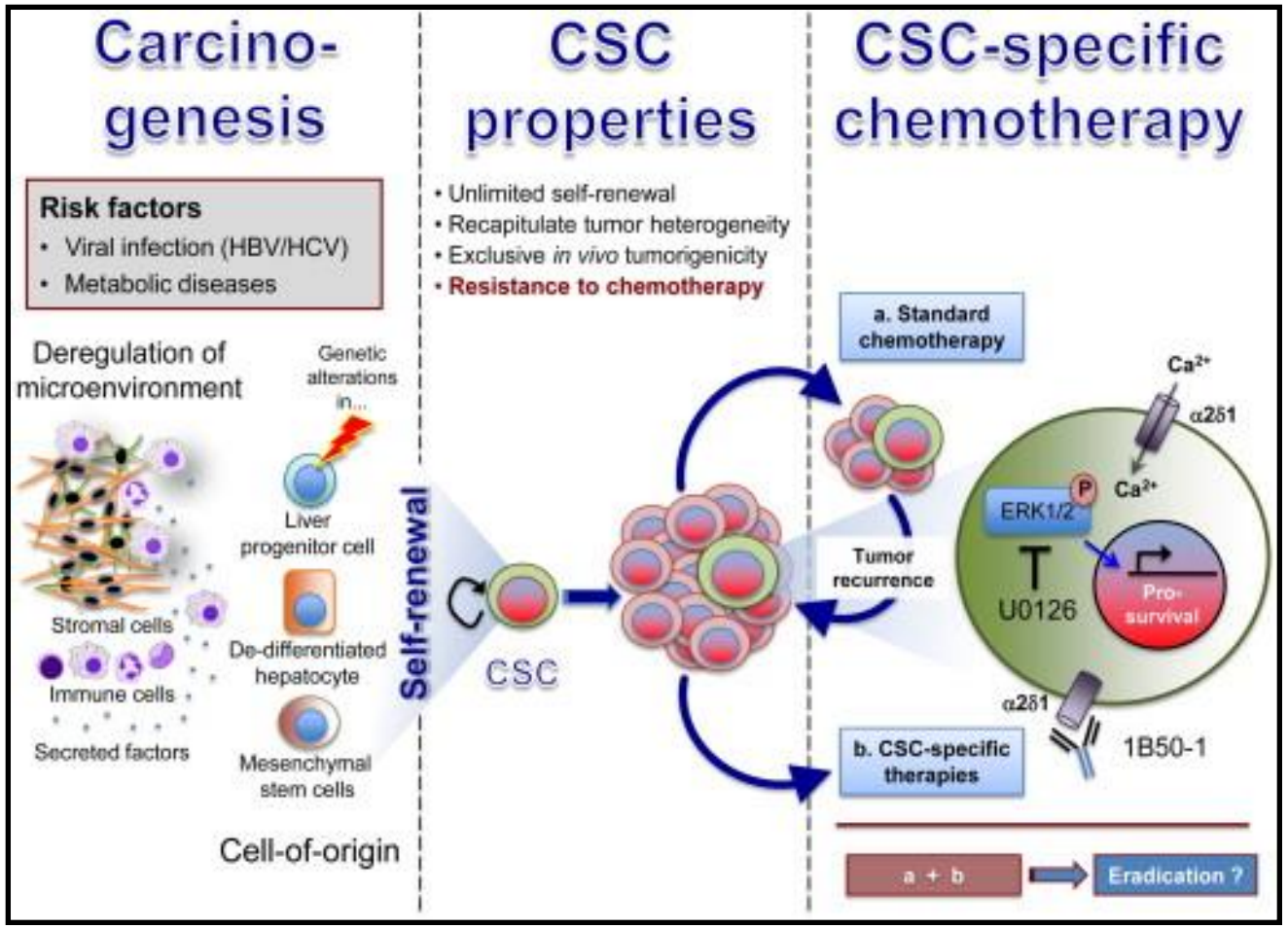


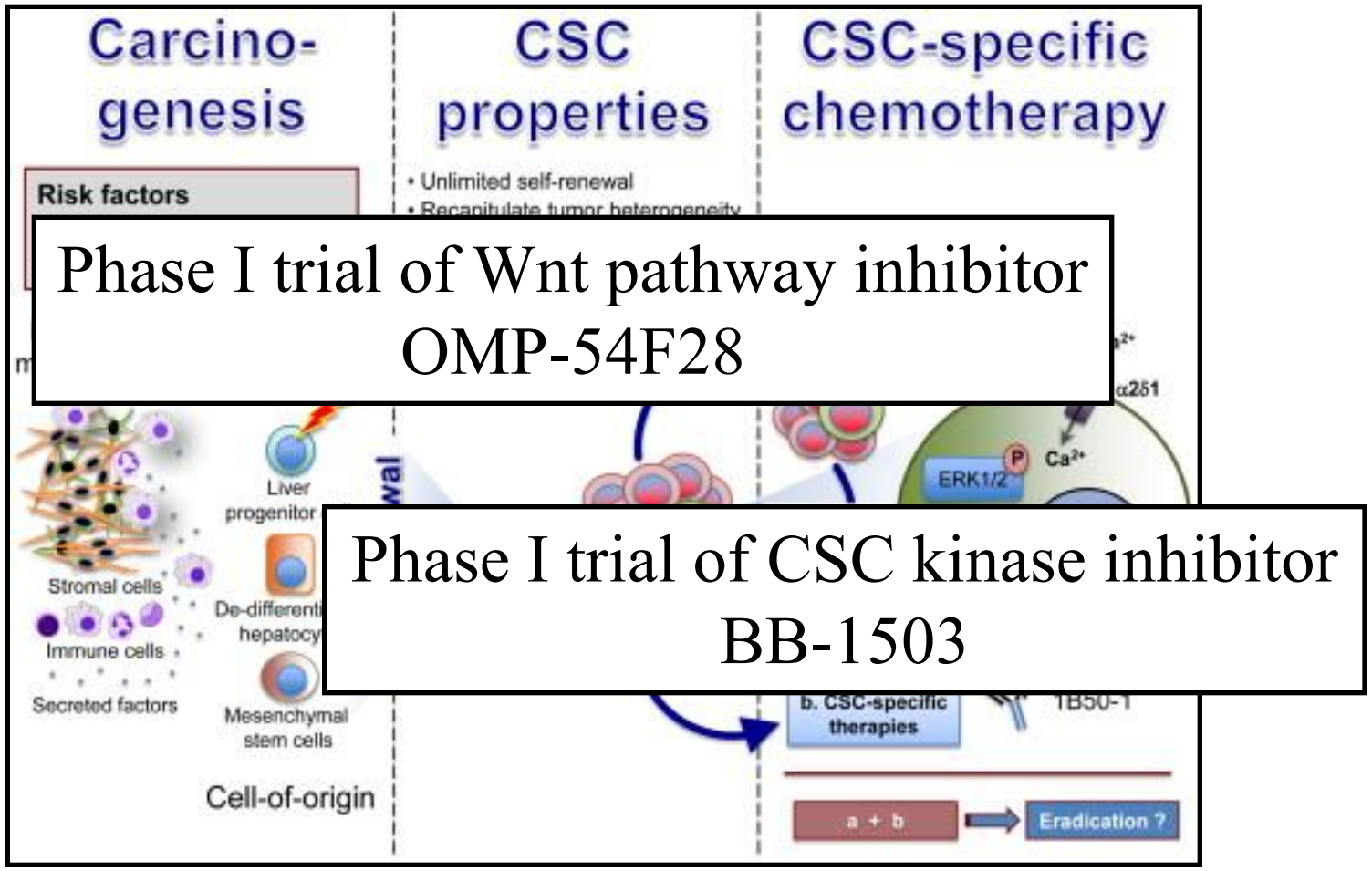
Greten TF et al, *Clin Cancer Res*, 2013

Targeting Cancer Stem Cells in HCC



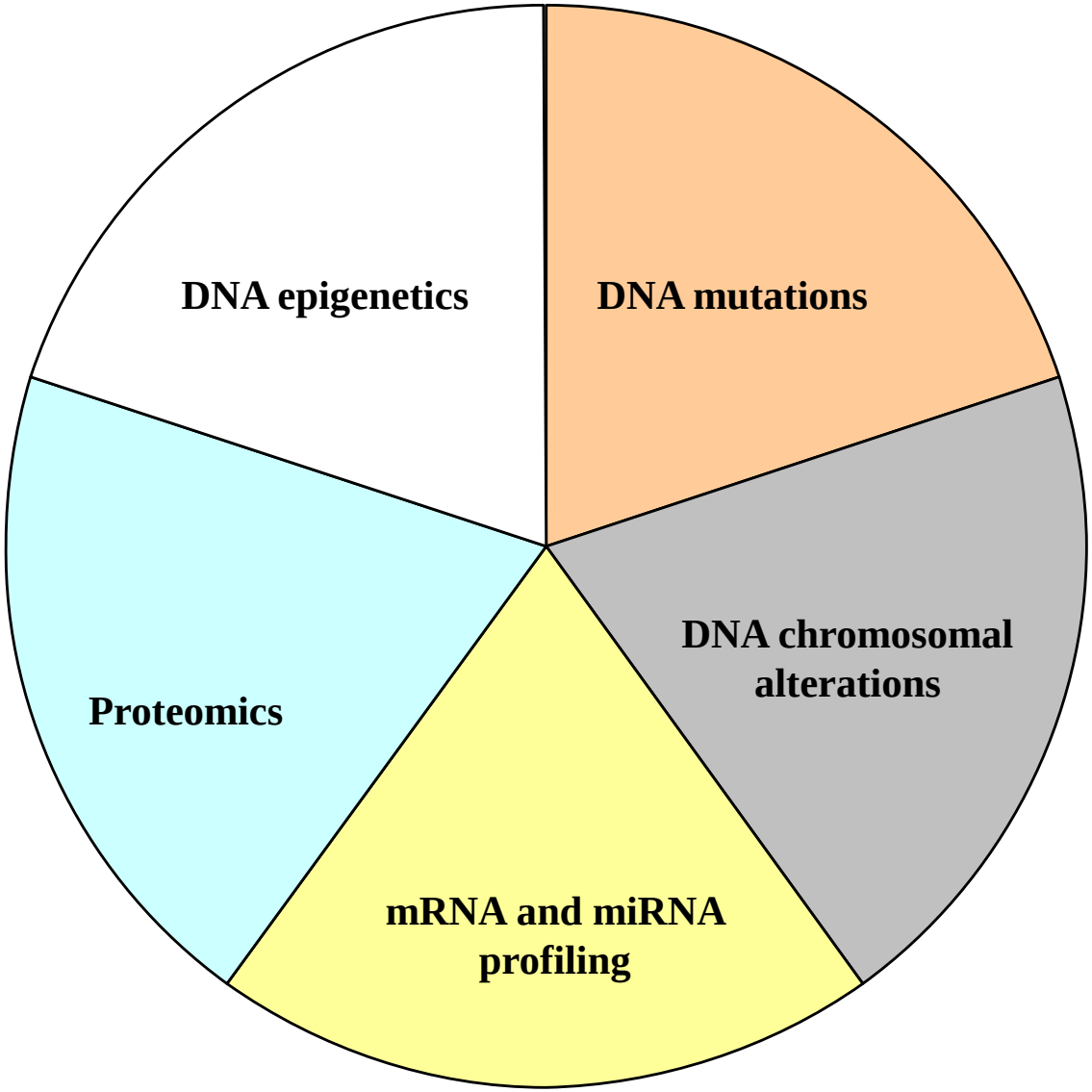
Sainz and Heeschen, Cancer Cell, 2013

Targeting Cancer Stem Cells in HCC

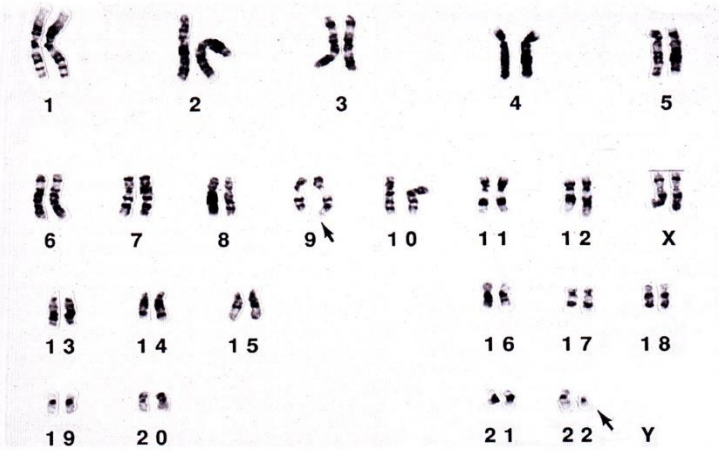


Sainz and Heeschen, Cancer Cell, 2013

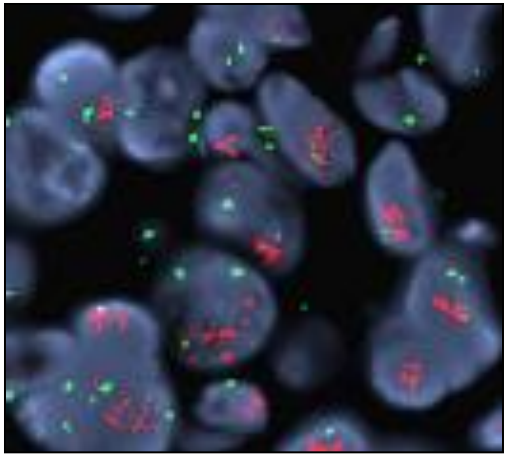
Can genomic medicine guide therapy in HCC?



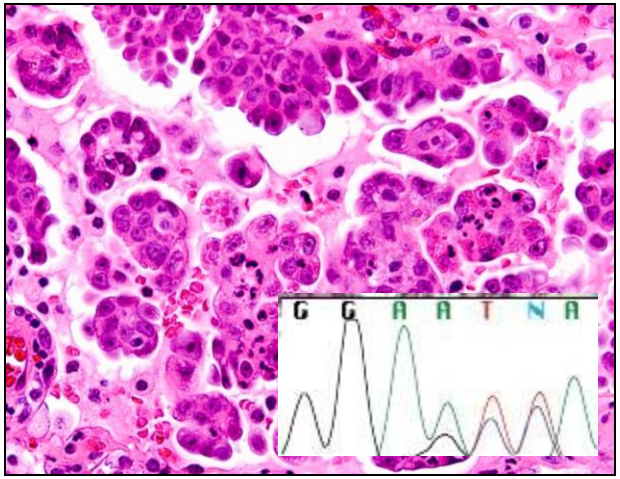
BCR-ABL Imatinib
100% CML



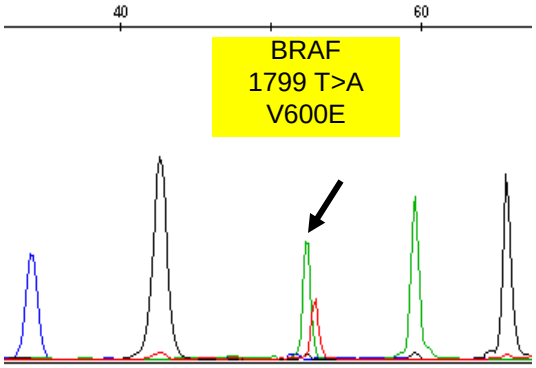
HER2 Trastuzumab
20-30% IDC



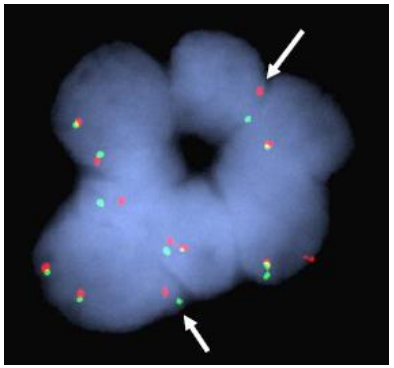
EGFR Erlotinib/ Gefitinib
20% Lung adenocarcinomas



BRAF V600E PLX4032
50-60% Melanoma



ALK Crizotinib
3-5% Lung adenocarcinoma



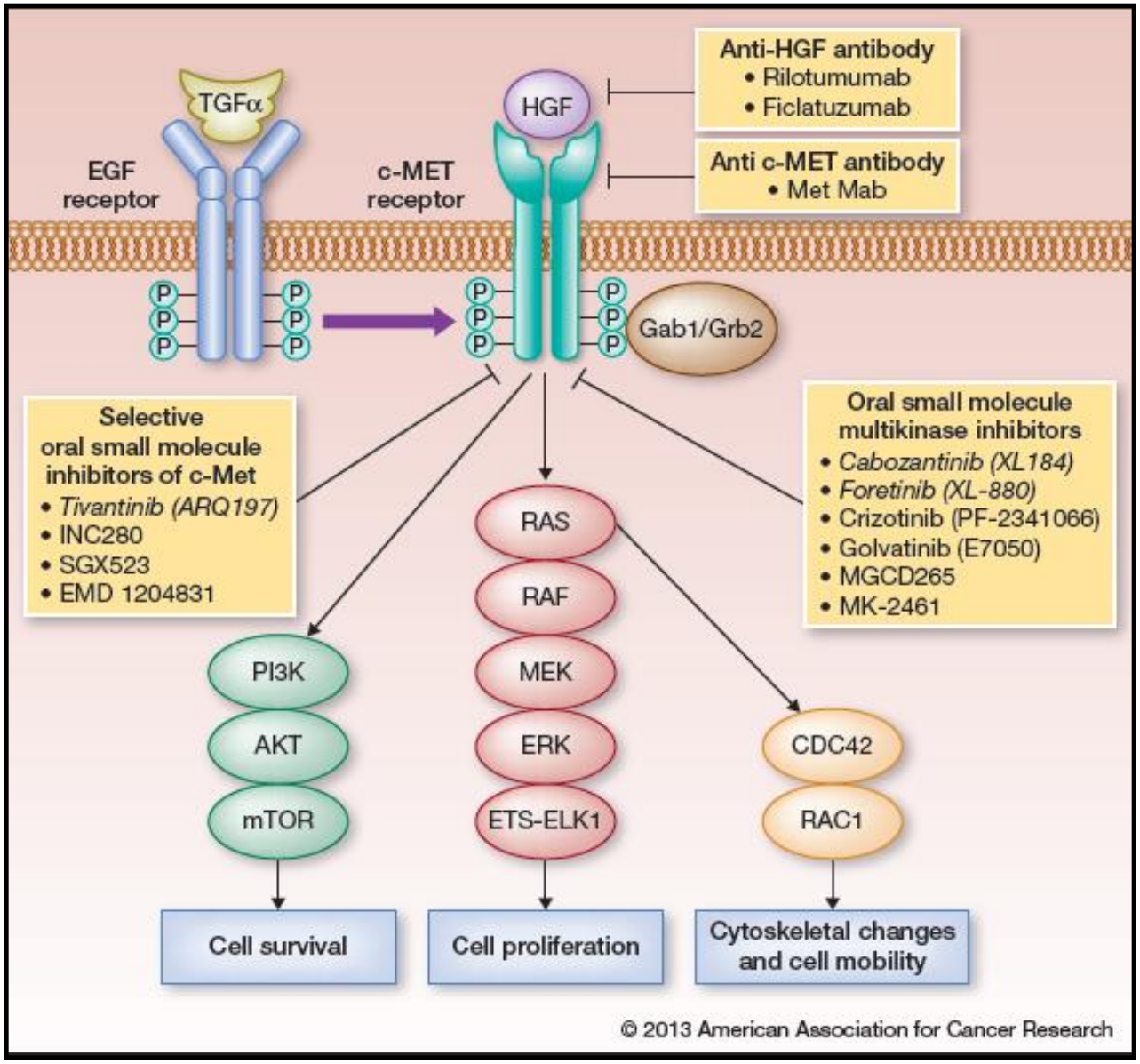
Courtesy of Dr. Iafrate

HCC trials based on oncogenic loops and molecular signatures

- c-MET overexpression
- Glypican 3: randomized phase II study with GC33, a recombinant humanized antibody against glypican-3
- RAS mutations: two stage phase II trial with refametinib in combination with sorafenib in patients with RAS mutation positive advanced HCC (5%)
- FGF19 amplification (5-10%): FGFR4 inhibitors
- VEGFA amplification (7-11%): VEGF/R inhibitors

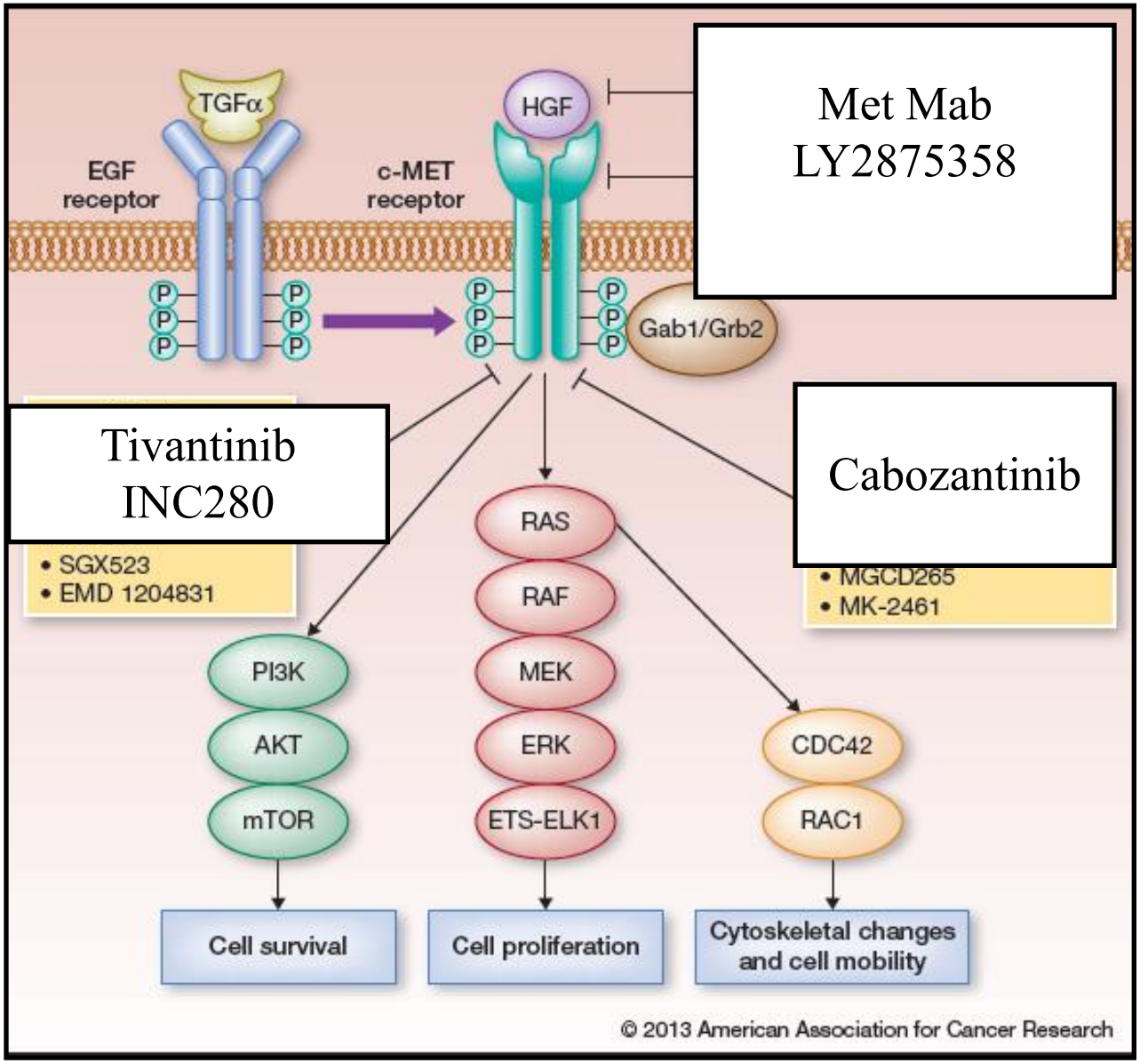
Zhu AX et al, Clin Cancer Res, 2013; Choo SP et al, J Clin Oncol 30, 2012 (suppl; abstr 4100); Sawey ET et al, Cancer Cell, 2011; Chiang DY et al, Cancer Res 2008

Targeting the HGF/c-MET Pathway



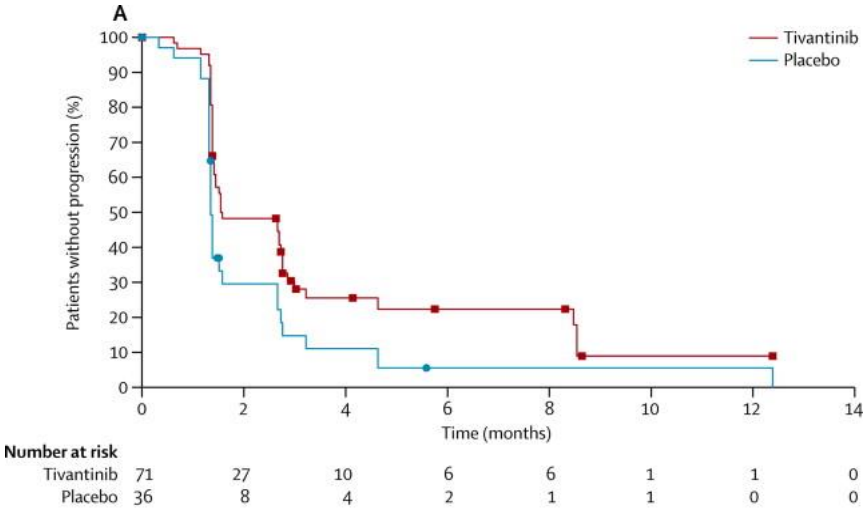
Goyal L, Muzumdar MD, Zhu AX., *Clin Cancer Res.* 2013

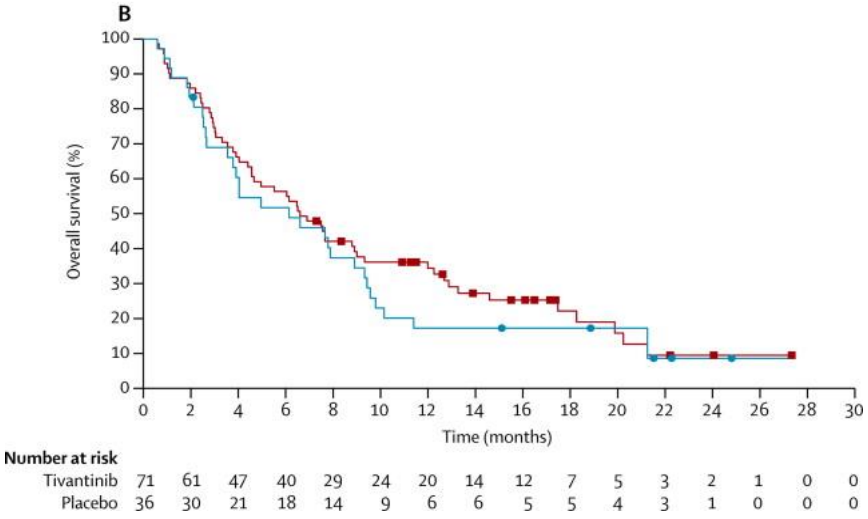
Targeting the HGF/c-MET Pathway

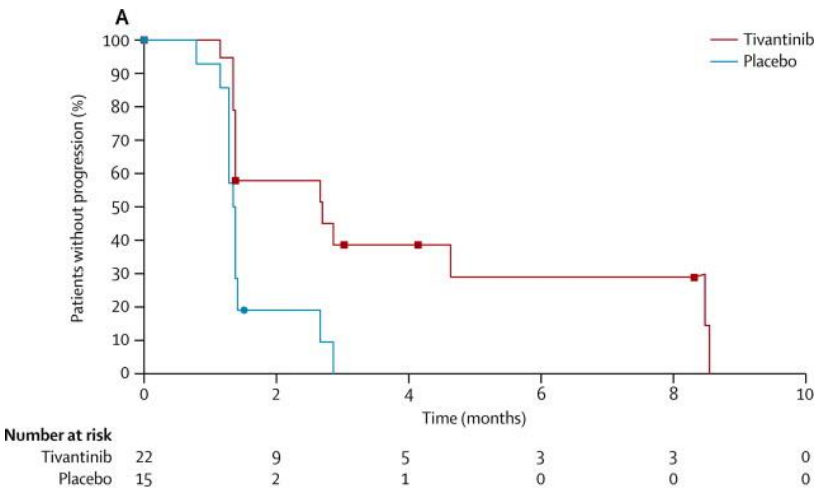


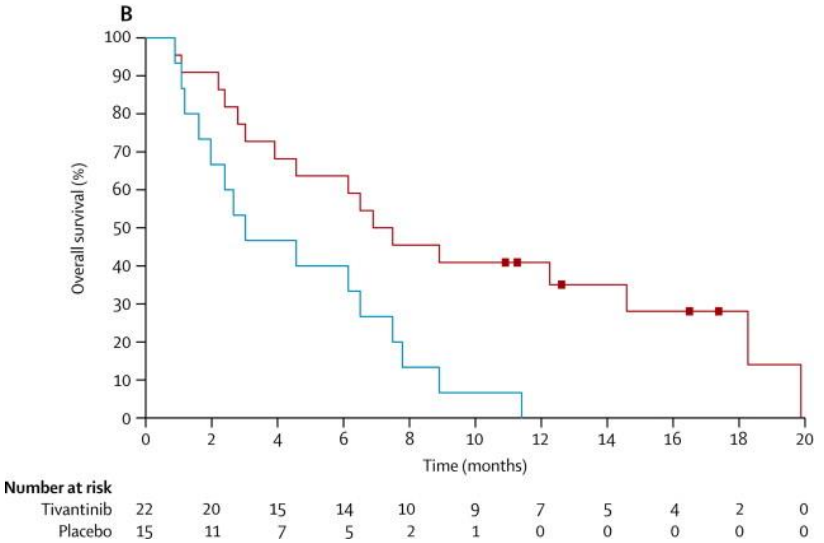
Goyal L, Muzumdar MD, Zhu AX., *Clin Cancer Res.* 2013

Tivantinib vs placebo for second-line treatment of advanced HCC: randomized phase II study



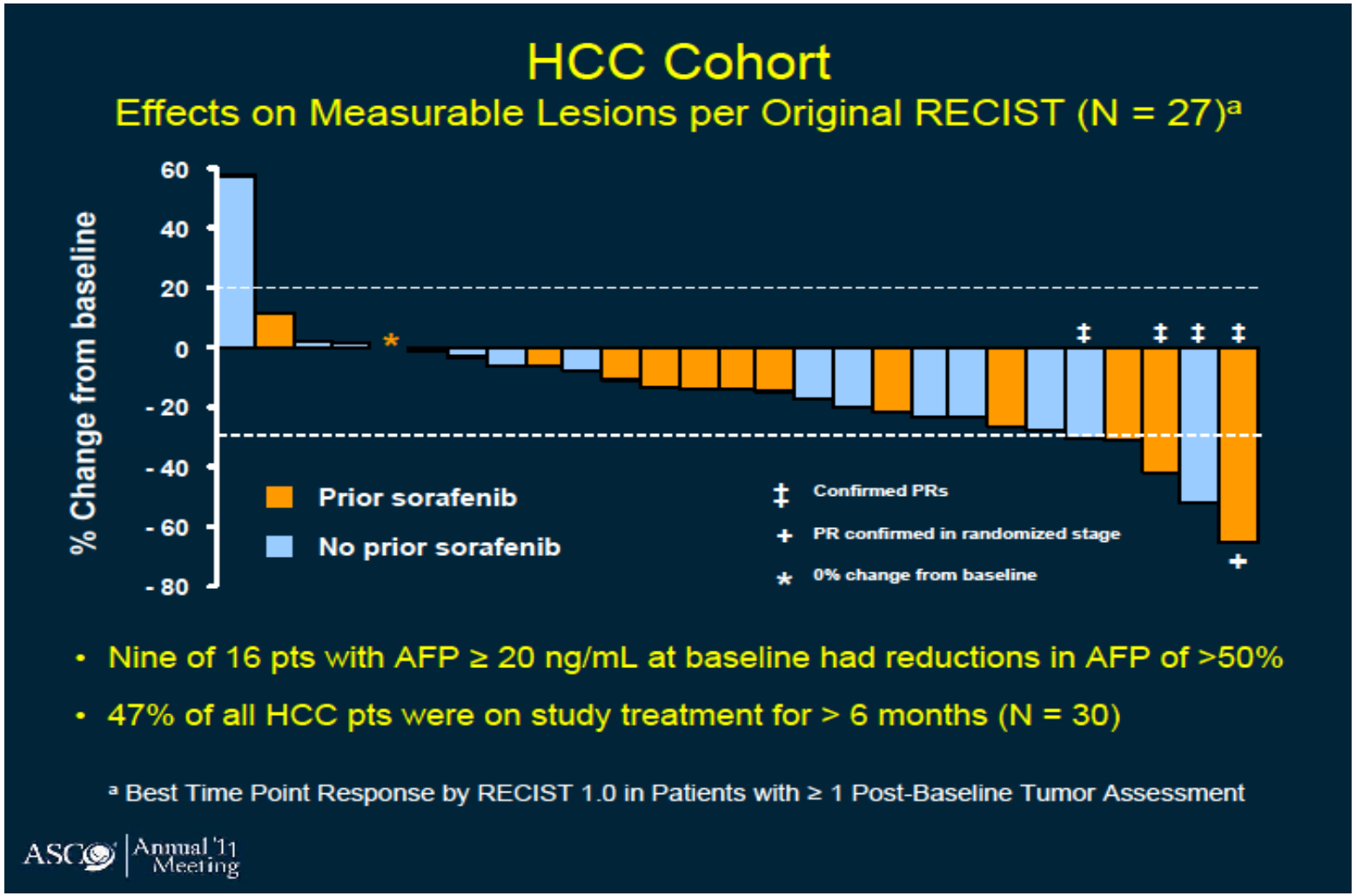






Santoro A et al, Lancet Oncol 14:55-63, 2013

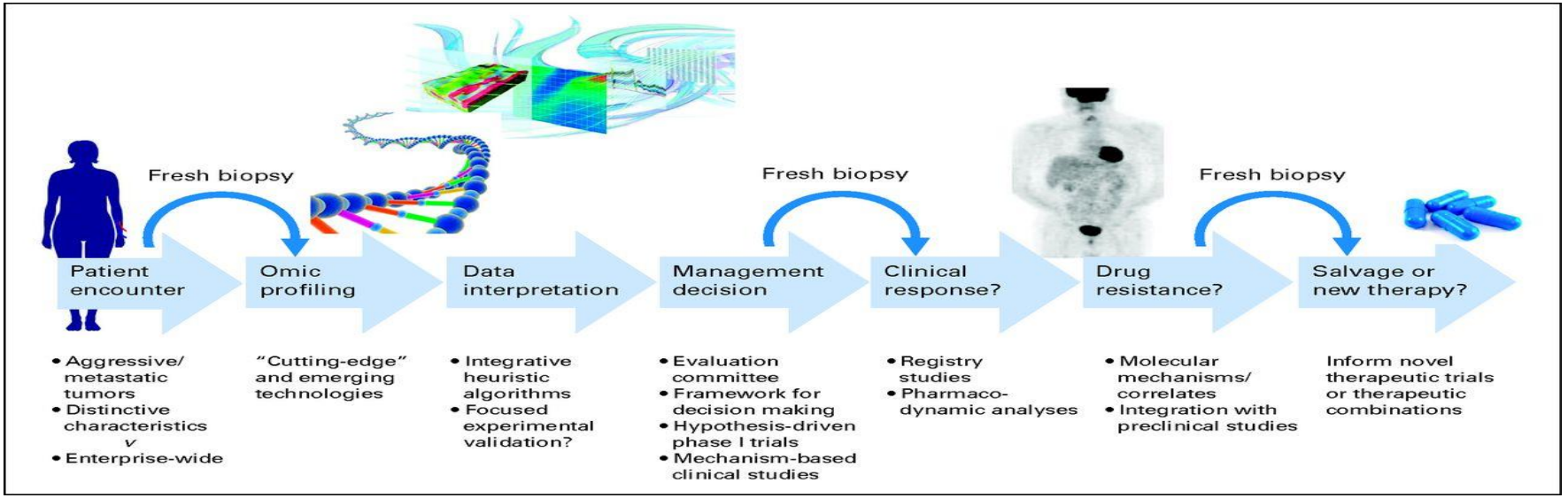
Cabozantinib in HCC Cohort

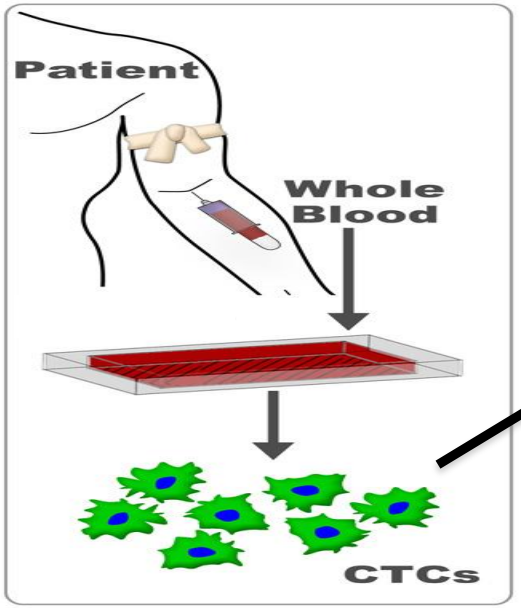


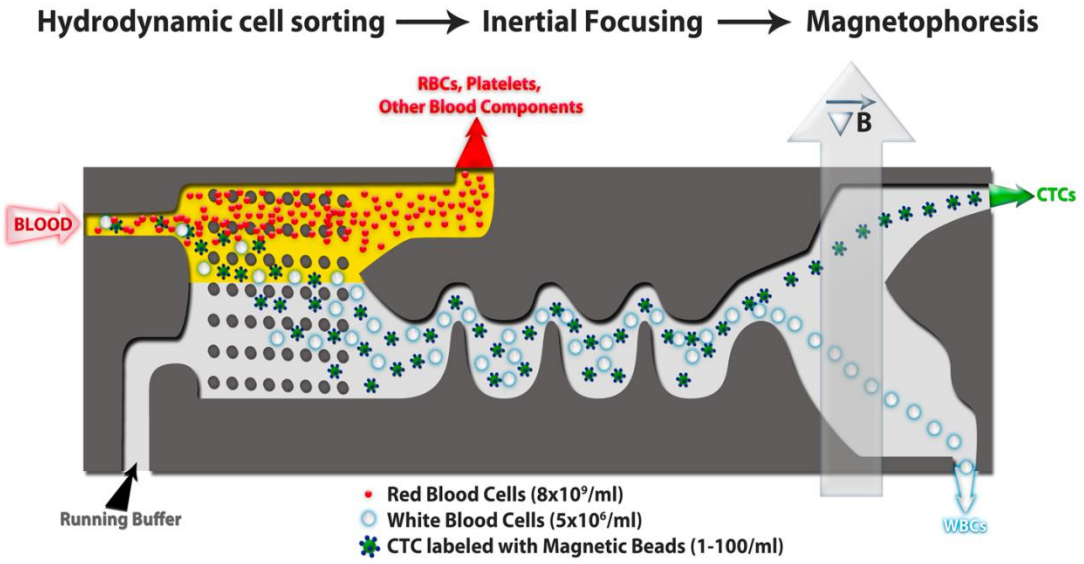
Updated (41 patients): PFS 4.4 m, OS 15.1 m

Gordon MS et al, ASCO 2011
Verslype C et al, ASCO 2012

The importance of tissue acquisition and CTC







Garraway LA, JCO, 2013; Courtesy of Dr. R Oklu

Ongoing phase III trials in advanced HCC

First line

- Sorafenib/Doxorubicin vs. Sorafenib/placebo (CALGB80802)
- Lenvatinib vs. sorafenib

Targeting advanced HCC with vascular invasion: combining sorafenib with local-regional therapy

- Sorafenib +/- SBRT (RTOG 1112)
- Sorafenib +/- TACE
- Sorafenib vs. Y90

Second line

- ADI-PEG 20 vs. BSC
- Tivantinib vs. BSC
- Regorafenib vs. BSC
- Cabozantinib vs. BSC

Unselected population

Lack of adequate randomized phase II data

High risk for failure

Conclusions and Future Perspectives

- Sorafenib remains the only systemic agent approved for the treatment of HCC
- Angiogenesis pathway is important in hepatocarcinogenesis. Despite the negative data of several VEGFR TKI, phase III trial with lenvatinib is ongoing
- The early experience for c-Met/HGF and mTOR inhibitors are intriguing
- We need to explore other novel agents with unique mechanism of action in HCC (immune based therapy, stem cell inhibitors etc)
- Identification of relevant predictive markers and applying molecular classification are important in predicting response and enriching the population in future HCC trial design-proof of concept trials needed