Current Challenges in Systemic Therapy for Hepatocellular Carcinoma

APASL STC, 23, Nov., 2013, Cebu

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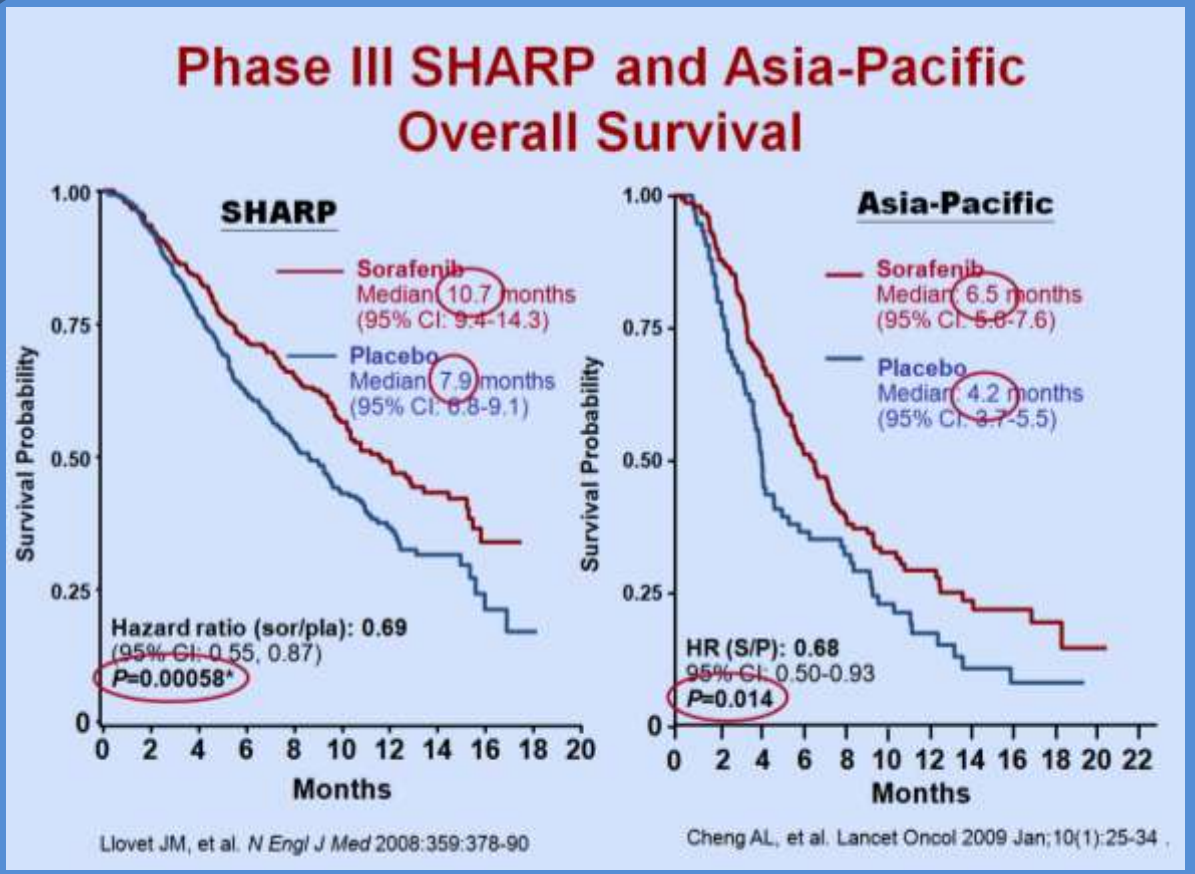
6 Years On - - -

- Results of SHARP was presented in June 2007. Sora
  2007) a
- Up to 70
  tested in r
  succeede



Drug Deve… for HCC (…

Multi-targeted …

sorafenib, sur…
linifanib, bri…

Phase III Trial of Linifanib vs Sorafenib in Patients with Advanced HCC

- 1035 p'ts randomized
- Median OS: 9.1 m (L) vs 9.8 m (S)
- Secondary end points (TTP and ORR) favored L, safety favored S.

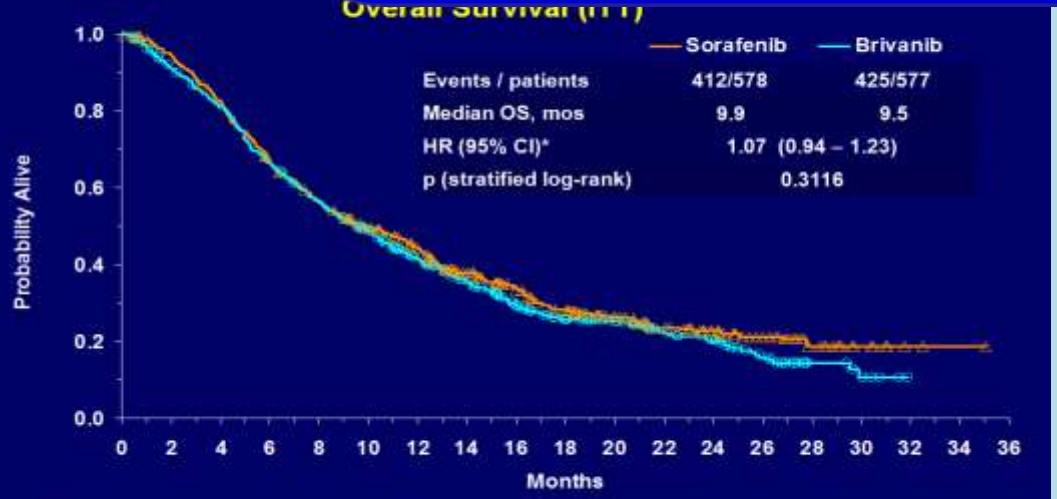
Cainap C et al Proc ASCO 2012, #249

Phase III, …

	Briva… (n = 2…
Median OS	9.4 m…
Median TTP*	4.2 m…
DCR*	71.2…
ORR*	11.5…

CI, confidence interval; HR…
*Modified RECIST for HCC
‡Cochran-Mantel-Haenszel…

Phase III, …



*HR (95% CI) for per-protocol population (575 patients in each arm) was 1.06 (0.93-1.22)

BMS Highly Confidential - Not for Distribution

Johnson P et al. J Clin Oncol. 2013 Oct 1;31(28):3517-24

…% CI: 7.4–9.2)
…% CI: 8.9–11.4)
…1.50)
…0 35 40
…val; HR: hazard ratio
…oc ASCO 2011, #4000

Two Groups of Front-runners

EOLVE-1 (Phase III, Placebo-controlled, 2nd-line) failed to meet its primary end point (OS)

3. mTOR inhibitors

Drug Development for HCC (2010-2013)

FGFR inhibitors

anti-angiogenic TKI

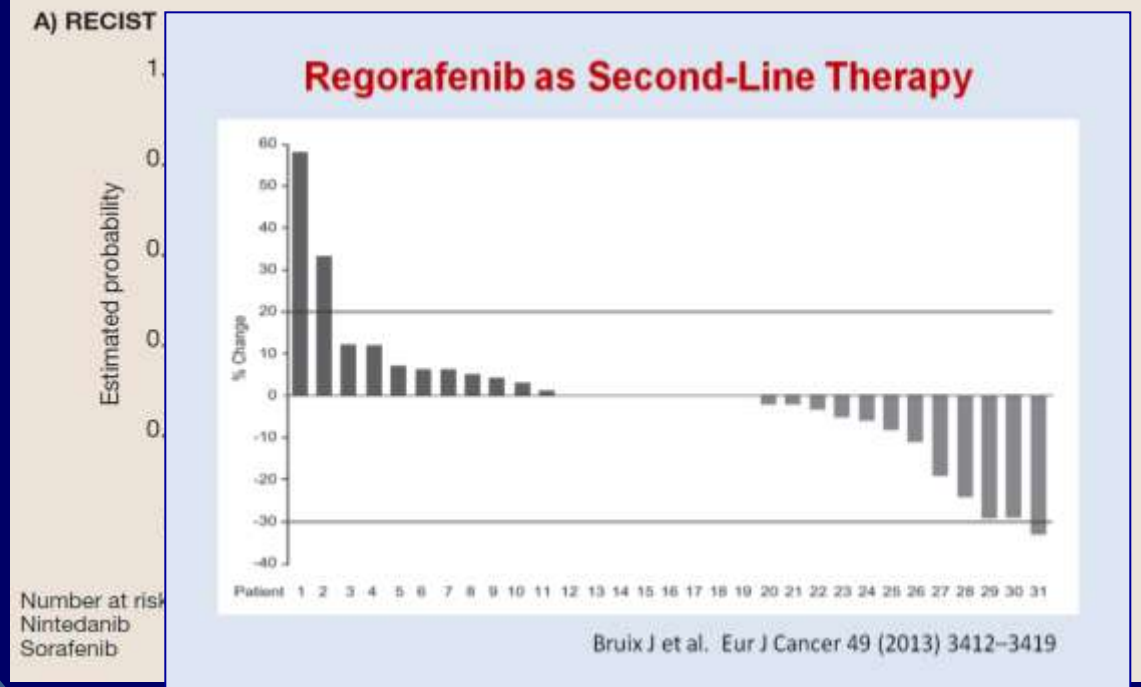
sorafenib, sunitinib, vandetanib, linifanib, brivanib, nintedanib, dovitinib, orantinib, lenvatini

Phase

Novel cat

mTORi, M PI3K/Akt inhibitors anti-PD1, A3 adenc

Randomized Phase II Study of Nintedanib vs Sorafenib

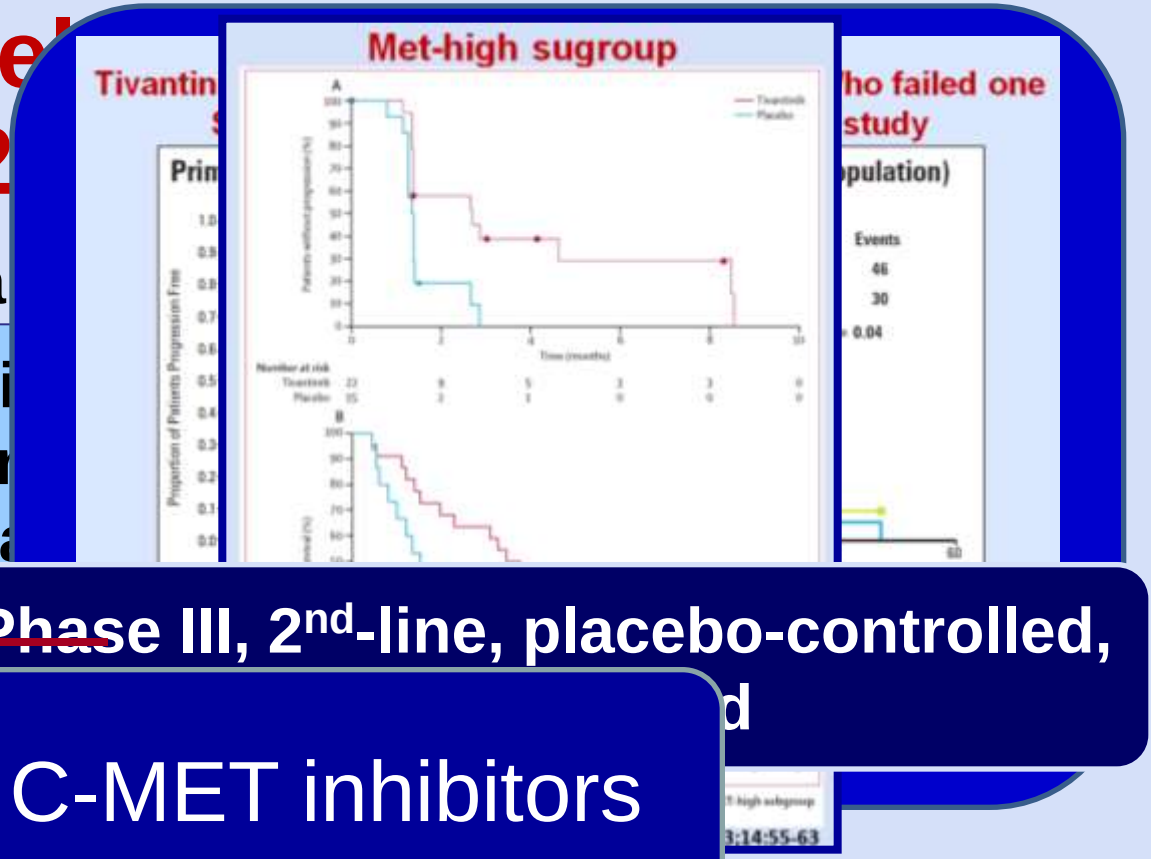


Yen CJ et al ECCO/ESMO 2013

Drug Deve
(2

Multi-targeted a

sorafenib, suni
linifanib, brivar
orantinib, lenva
apatinib, for



Phase III, 2nd-line, placebo-controlled,
d

Phase III, 2nd
cont

C-MET inhibitors

- ≦1 systemic Tx (51% sorafenib)
- Cabozantinib 100 mg/day x12 wks, lead-in.
- 2/36 PR (RR=5%, DCR=68%) at lead-in.
- One more PR after randomization.

Verslype C et al Proc. ASCO 2012;#4007

Why MTT fails in RCT ?

- Fails to target on driver mutations.

Identification of New Targets for HCC by New Geneneration Sequencing and Massive Cell Lines Screening/Molecular Correlation

- Wnt/β-Catenin
- JAK/STAT
- FGF19/FGFR4
- HER-3

Why MTT fails in RCT ?

- Fails to enrich a group of patients who would benefit more.

Plasma Biomarkers as Predictors of Outcome in Patients with Advanced Hepatocellualr Carcinoma

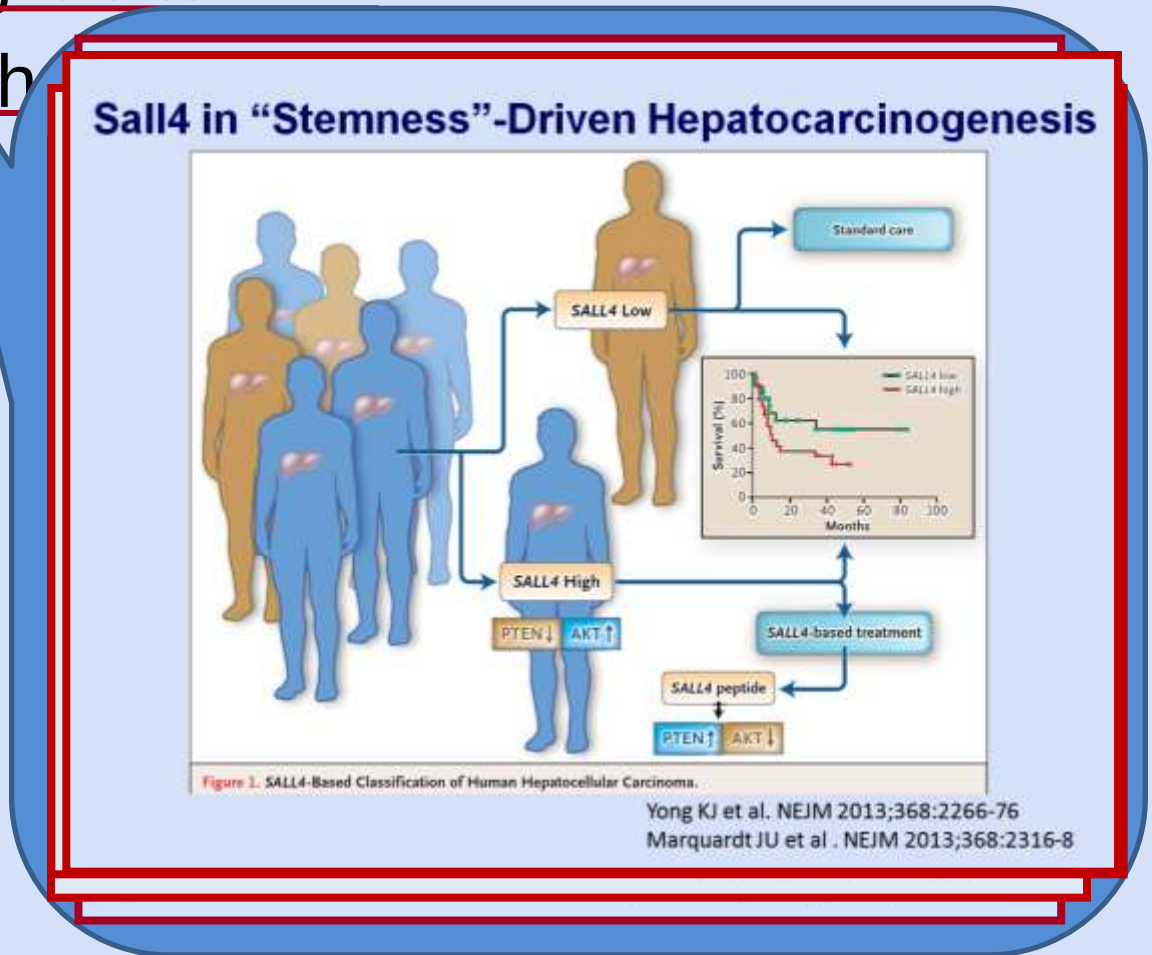
- Low baseline Ang 2 and VEGF
  - Predict better survival.
- High s-c-KIT and low HGF
  - Trend toward better survival under sorafenib Tx.

Llovet J et al, Clin Cancer Res 2012 Feb. 28

Facing the Challenges

Beyond driver mutations

- Targeting CSC/EMT
- Immun th
- Oncolyt
- Targetin

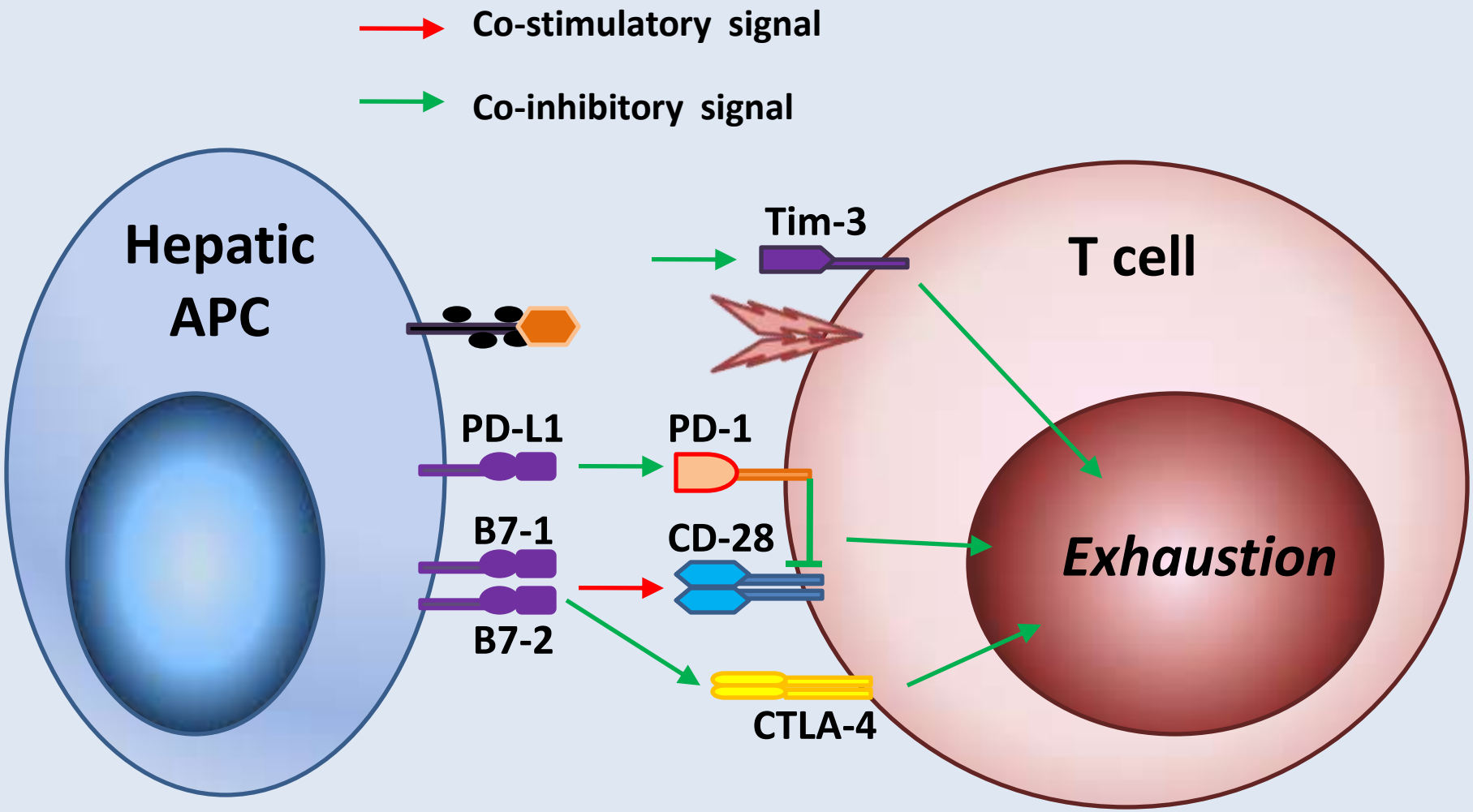


Recent Advancements of Cancer Immunotherapy

-- Implication on HCC drug development

- Reactivation of exhausted T cells by releasing immune check-points
- Chimeric-antigen receptor T cells (CART)

T cell dysfunction in chronic hepatitis and HCC



Modified from Watanabe T, et al. *J Viral Hepat* 2010

Nivolumab (anti-PD1) plus Ipilimumab (anti-CTLA4) in Advanced Melanoma

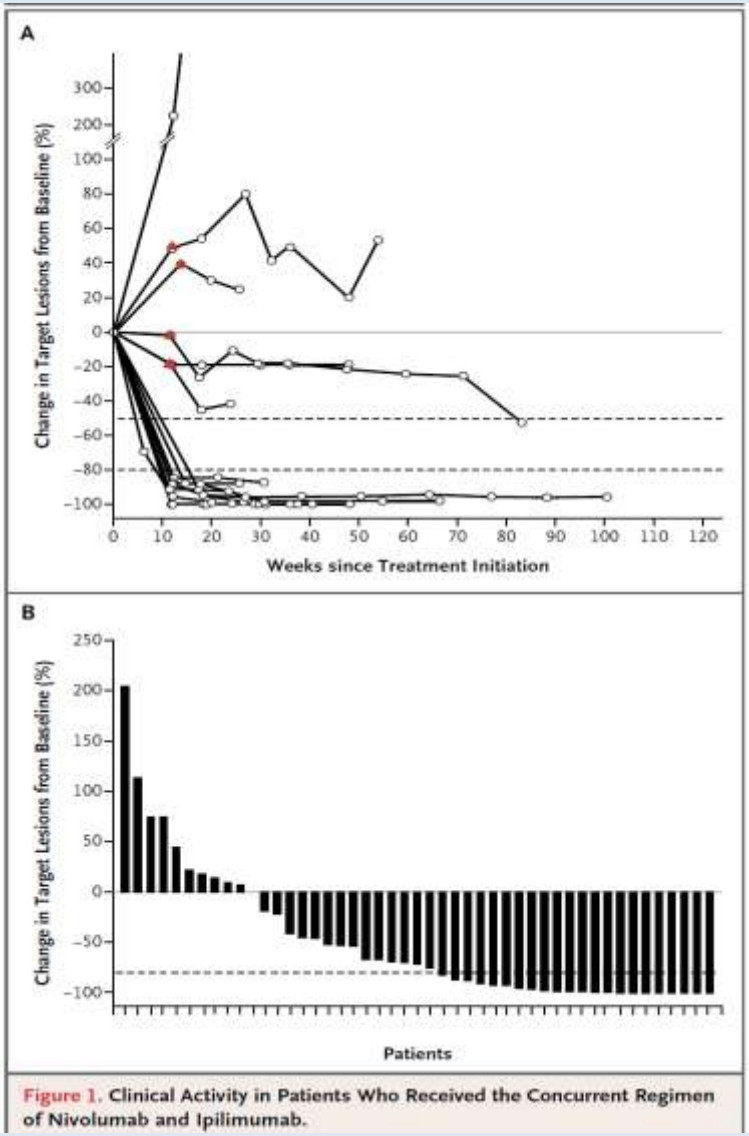


Figure 1. Clinical Activity in Patients Who Received the Concurrent Regimen of Nivolumab and Ipilimumab.

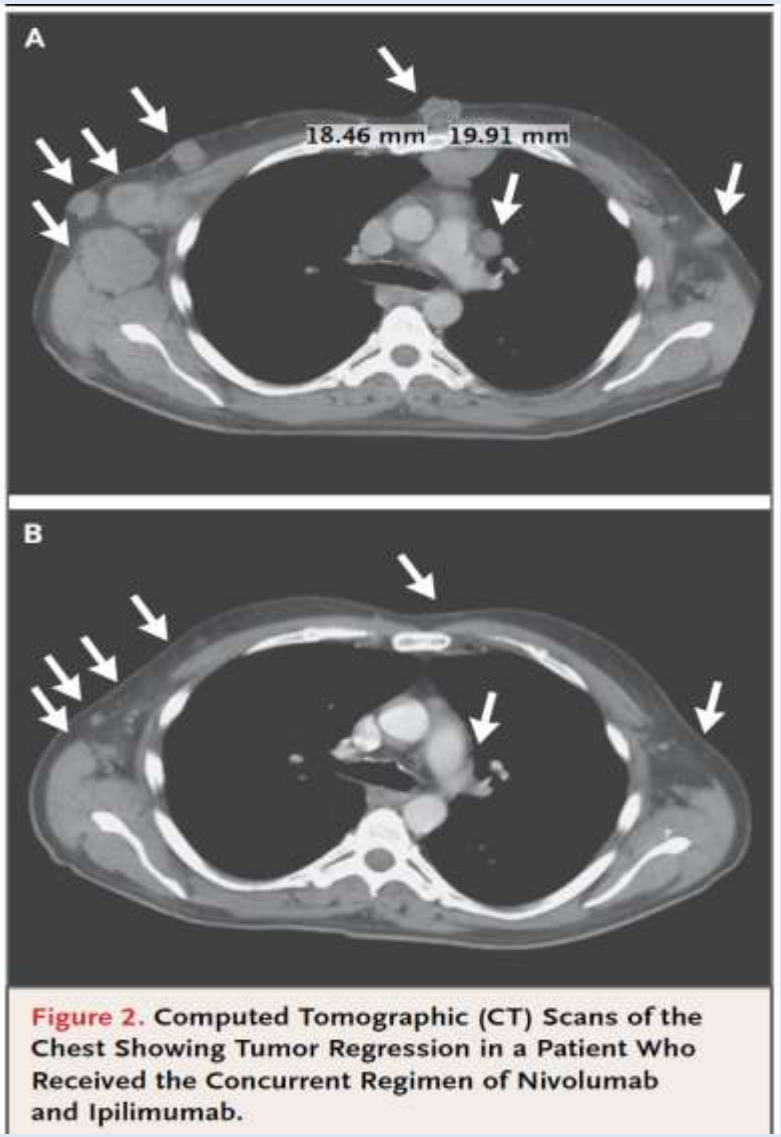


Figure 2. Computed Tomographic (CT) Scans of the Chest Showing Tumor Regression in a Patient Who Received the Concurrent Regimen of Nivolumab and Ipilimumab.

Jedd D et al. NEJM Jun 2, 2013

A Phase I Dose Escalation Study to Investigate the Safety, Immunoregulatory Activity, Pharmacokinetic, and Preliminary Antitumor Activity of Anti-Programmed-Death-1 (PD-1) (BMS-936558) in Advanced HCC in Subjects with or without chronic viral hepatitis

Clinical Trials. Gov (2013)

Chimeric Antigen Receptors (CAR)-modif

In Girl's Last Hope, Altered Immune Cells Beat Leukemia

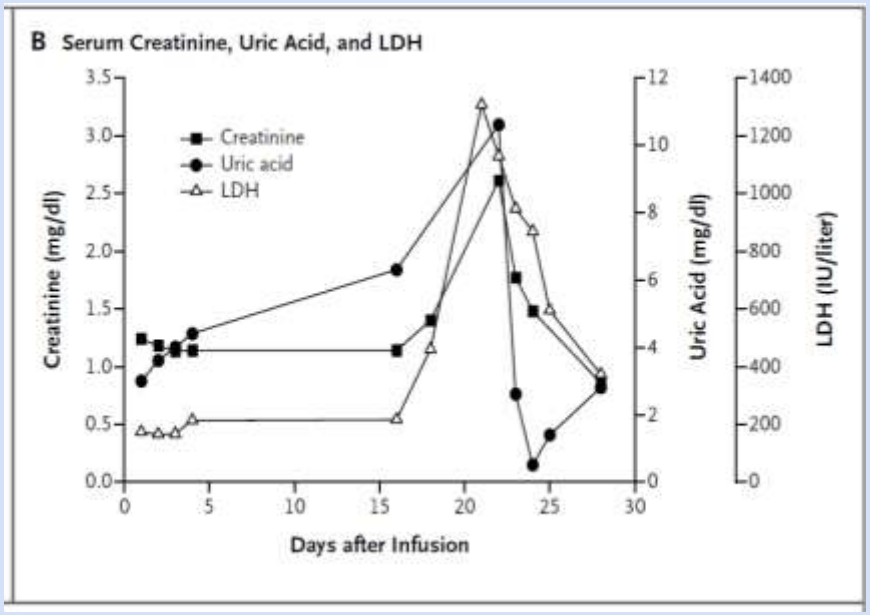
Jeff Swensen for The New York Times

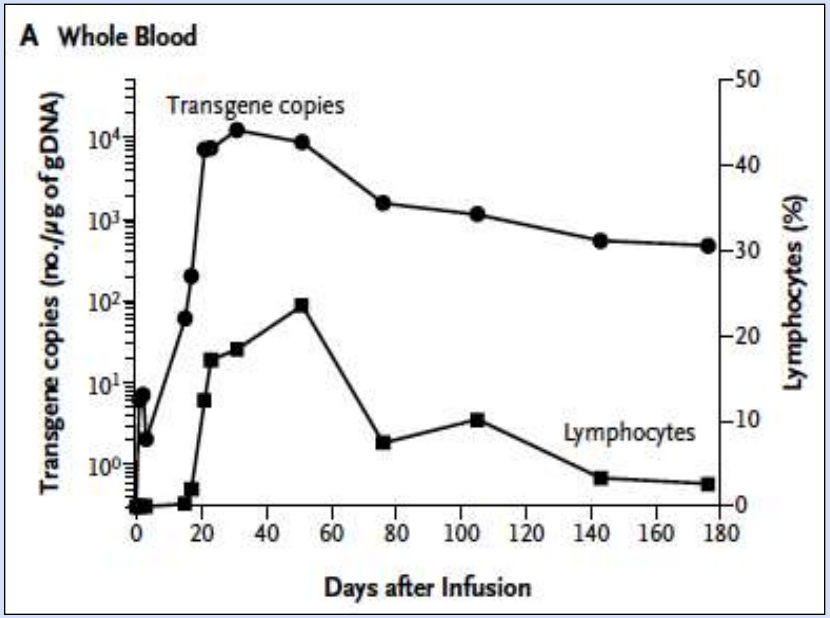
Emma Whitehead, with her mother, Kari. Last spring, Emma was near death from acute lymphoblastic leukemia but is now in remission after an experimental treatment at the Children's Hospital of Philadelphia. More Photos »

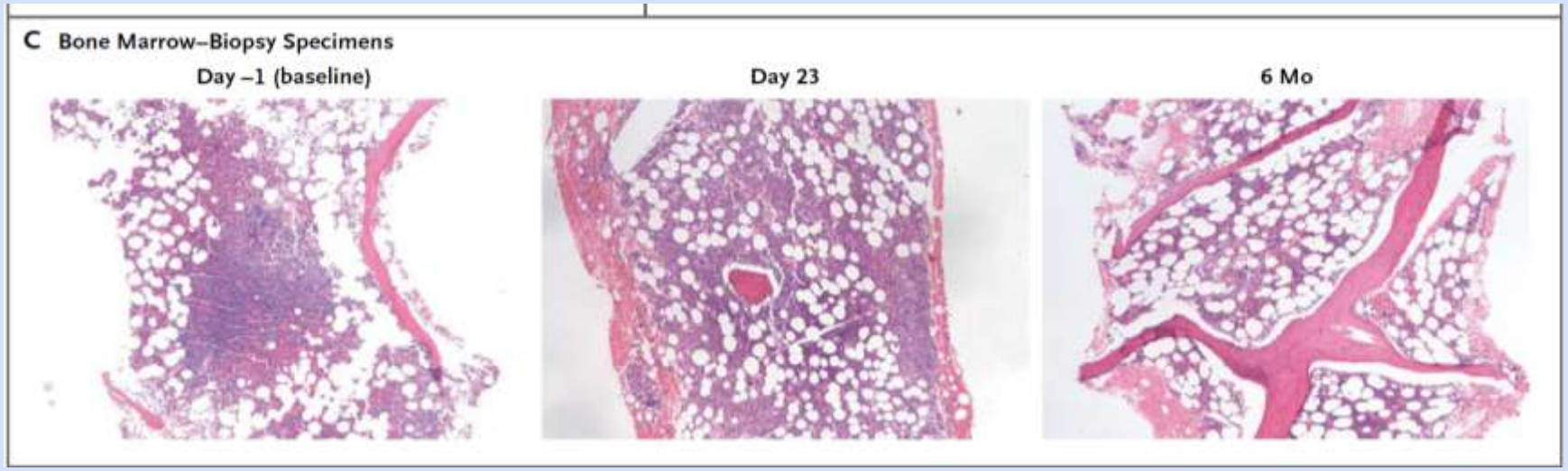
By DENISE GRADY
Published: December 9, 2012 | 381 Comments

Essand M & Loskog ASI. J Int Med 2013;273:166-181

CAR–Modified T Cells in CLL



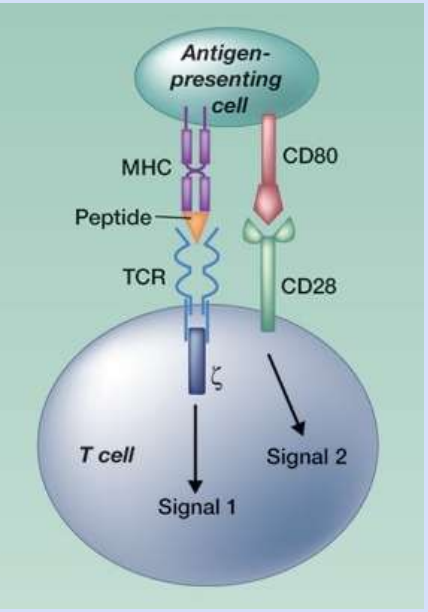




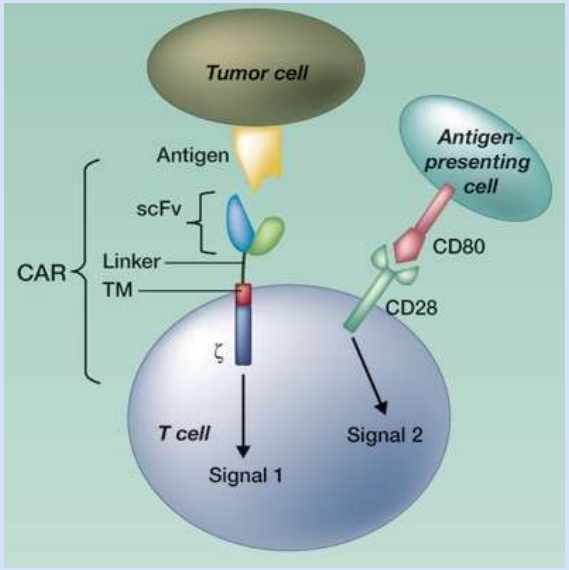
David L et al. N Engl J Med 2011;365:725-33

T cells and Chimeric Antigen Receptors (CARs)

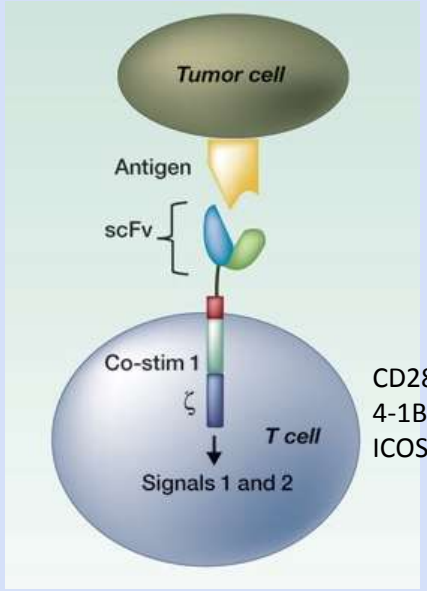
T cell receptor signaling



1st CAR signaling

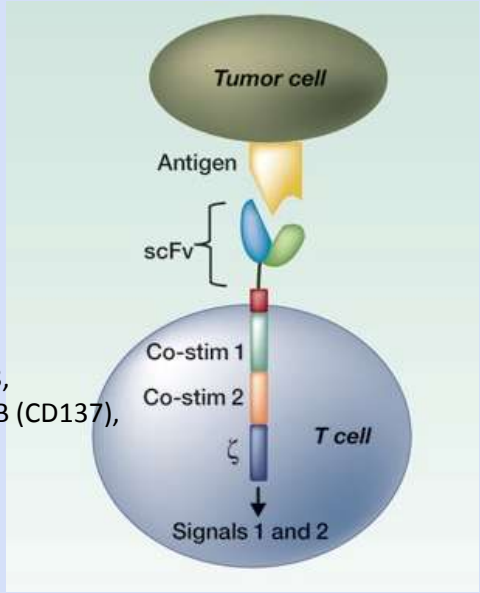


2nd CAR signaling



CD28,
4-1BB (CD137),
ICOS

3rd CAR signaling



"Living drugs"
Not HLA-restricted.
More cytotoxic , potent and persistent

scFv: single-chain variable fragment

Target antigen	Associated malignancy
α-Folate receptor	Ovarian cancer
CAIX	Renal cell carcinoma
CD19	B-cell malignancies (B-NHL, B-CLL, B-ALL…)
CD20	B-cell Lymphomas
CD30	Hodgkin lymphoma
CD33	AML
CD44v7/8	Cervical carcinoma
CEA	Breast cancer, Colorectal cancer
EGP-2	Multiple malignancies
EGP-40	
erb-B2	
erb-B 2,3,4	
FBP	
Fetal acethylcholine recep	
GD2	
GD3	
Her2/neu	astoma
IL-13R-a2	
KDR	Tumor neovasculature
k-light chain	B-cell malignancies
LeY	Carcinomas
L1 cell adhesion molecule	Neuroblastoma
MAGE-A1	Melanoma
Murine CMV infected cells	Murine CMV
MUC1	Breast, Ovary
NKG2D ligands	Various tumors
Oncofetal antigen (h5T4)	Various tumors
PSCA	Prostate carcinoma
PSMA	Prostate/tumor vasculature
TAA targeted by mAb IgE	Various tumors
TAG-72	Adenocarcinomas
VEGF-R2	Tumor neovasculature

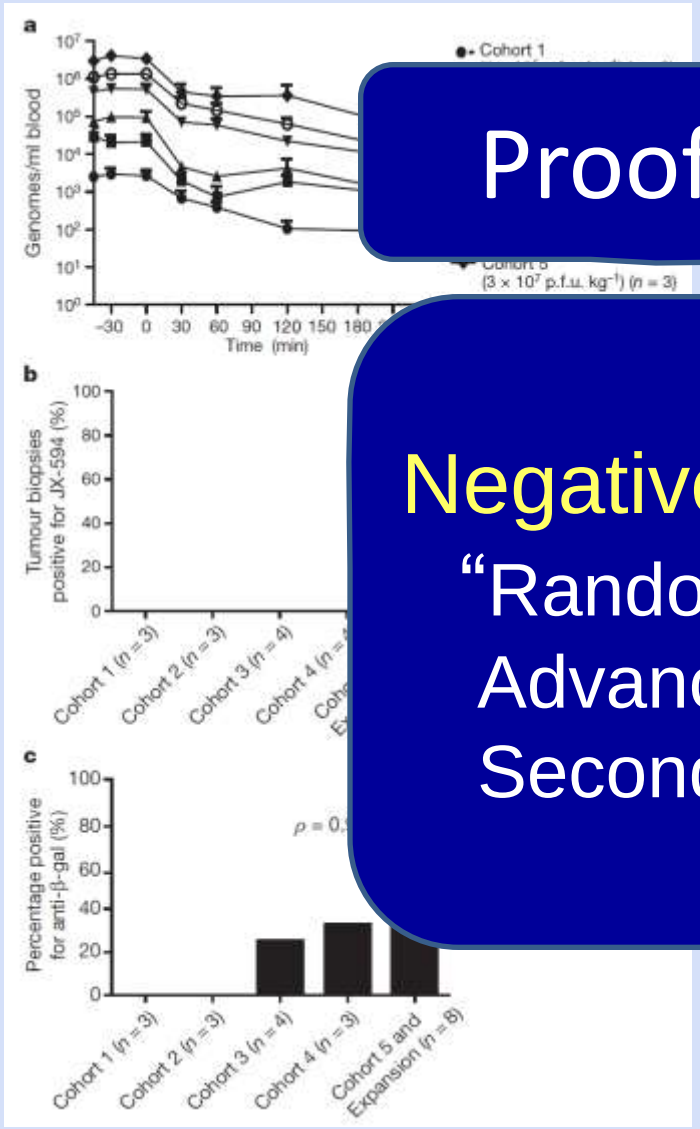
Will the CART come to HCC ?

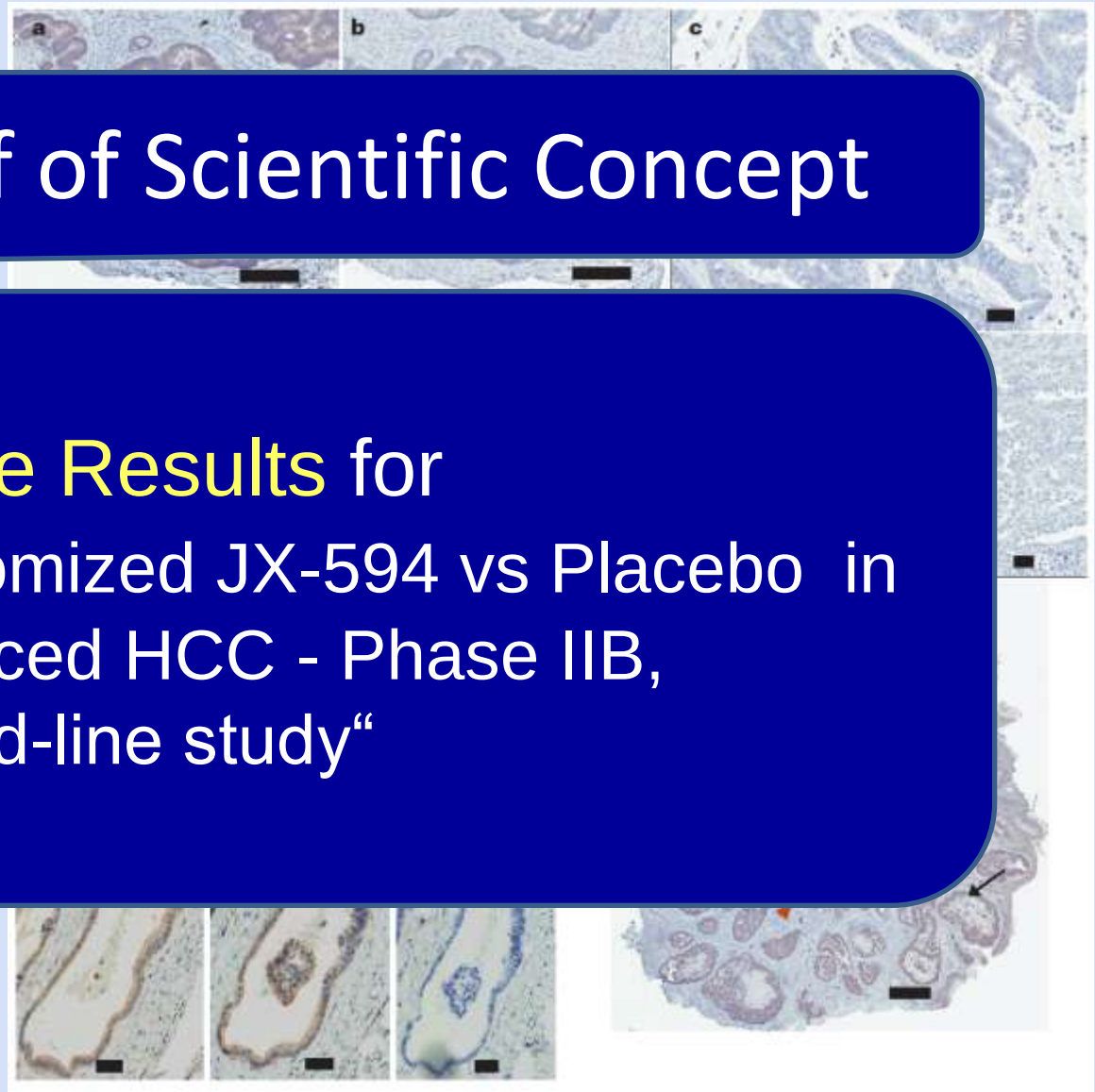
Facing the Challenges

Beyond driver mutations

- Targeting CSC/EMT
- Immunotherapy
- Oncolytic virotherapy
- Targeting “non-oncogene addiction”

Intravenous delivery of a multi-mechanistic cancer-targeted oncolytic poxvirus in humans





Proof of Scientific Concept

Negative Results for

"Randomized JX-594 vs Placebo in Advanced HCC - Phase IIB, Second-line study"

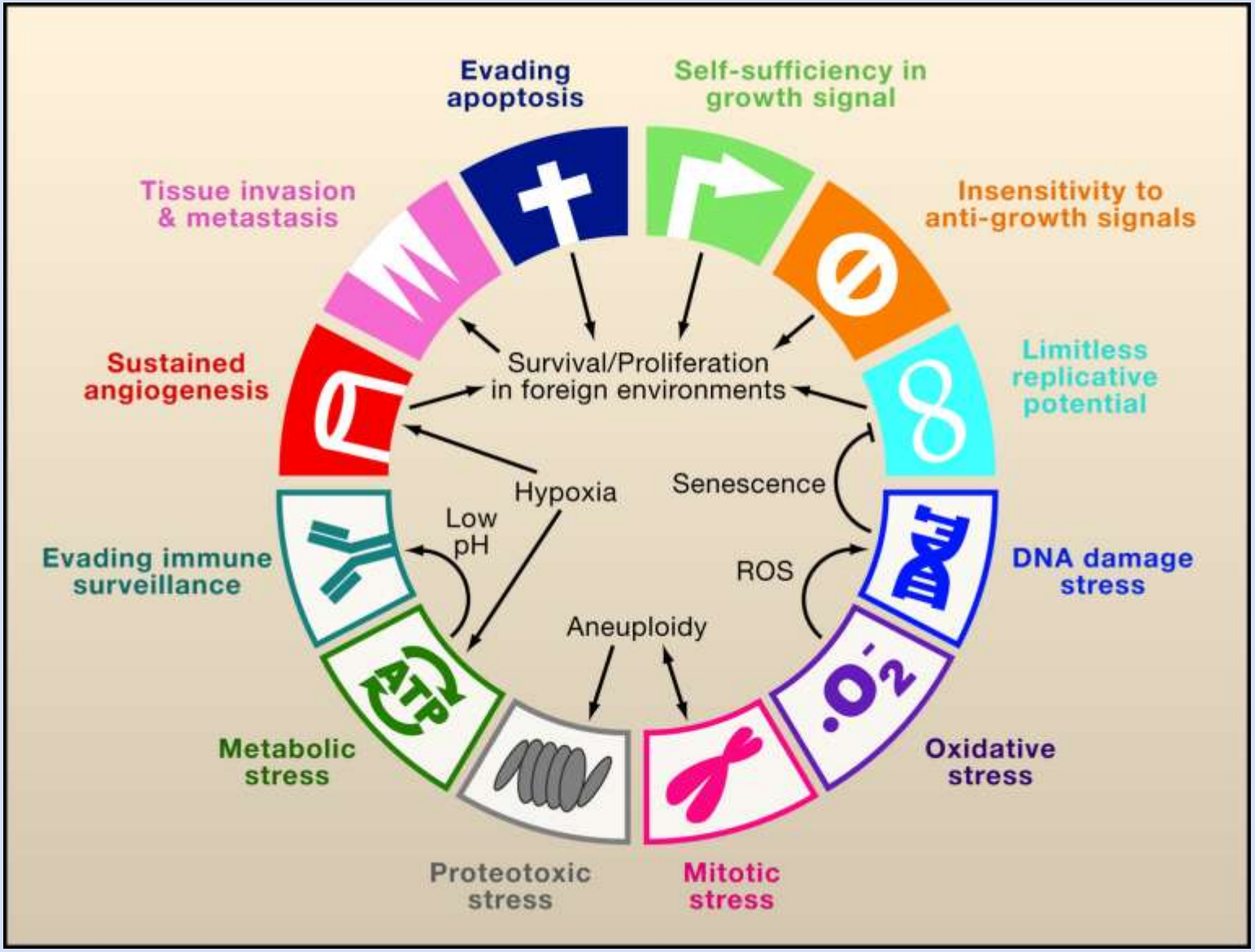
Breitbach CJ, et al. Nature 2011;477:100-104

Current Development

Beyond driver mutations

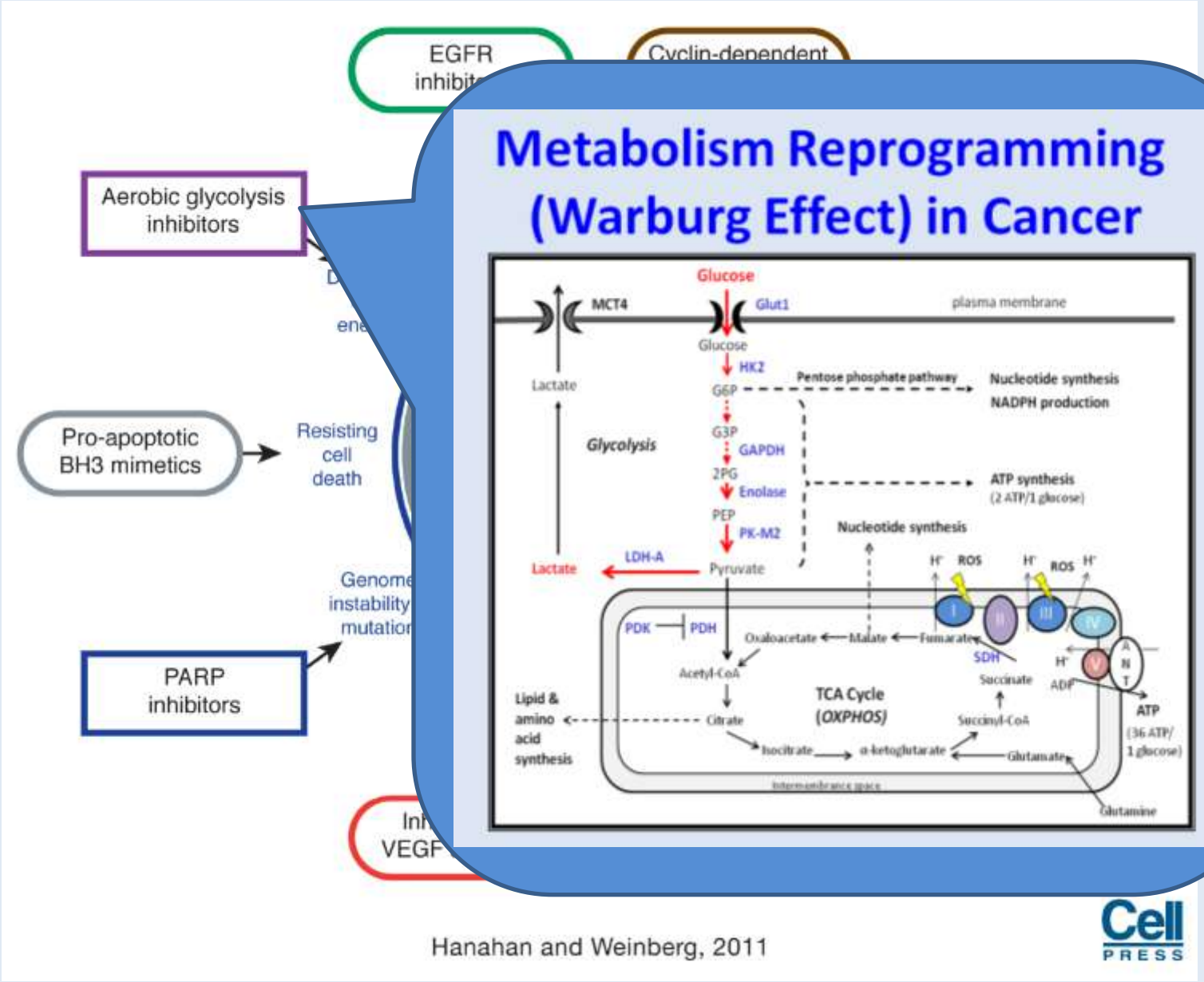
- Targeting CSC/EMT
- Immunotherapy
- Oncolytic virotherapy
- Targeting “non-oncogene addiction”

The Hallmarks of Cancer (modified by Luo J et al)



Luo J, et al. Cell 2009;136:823-830

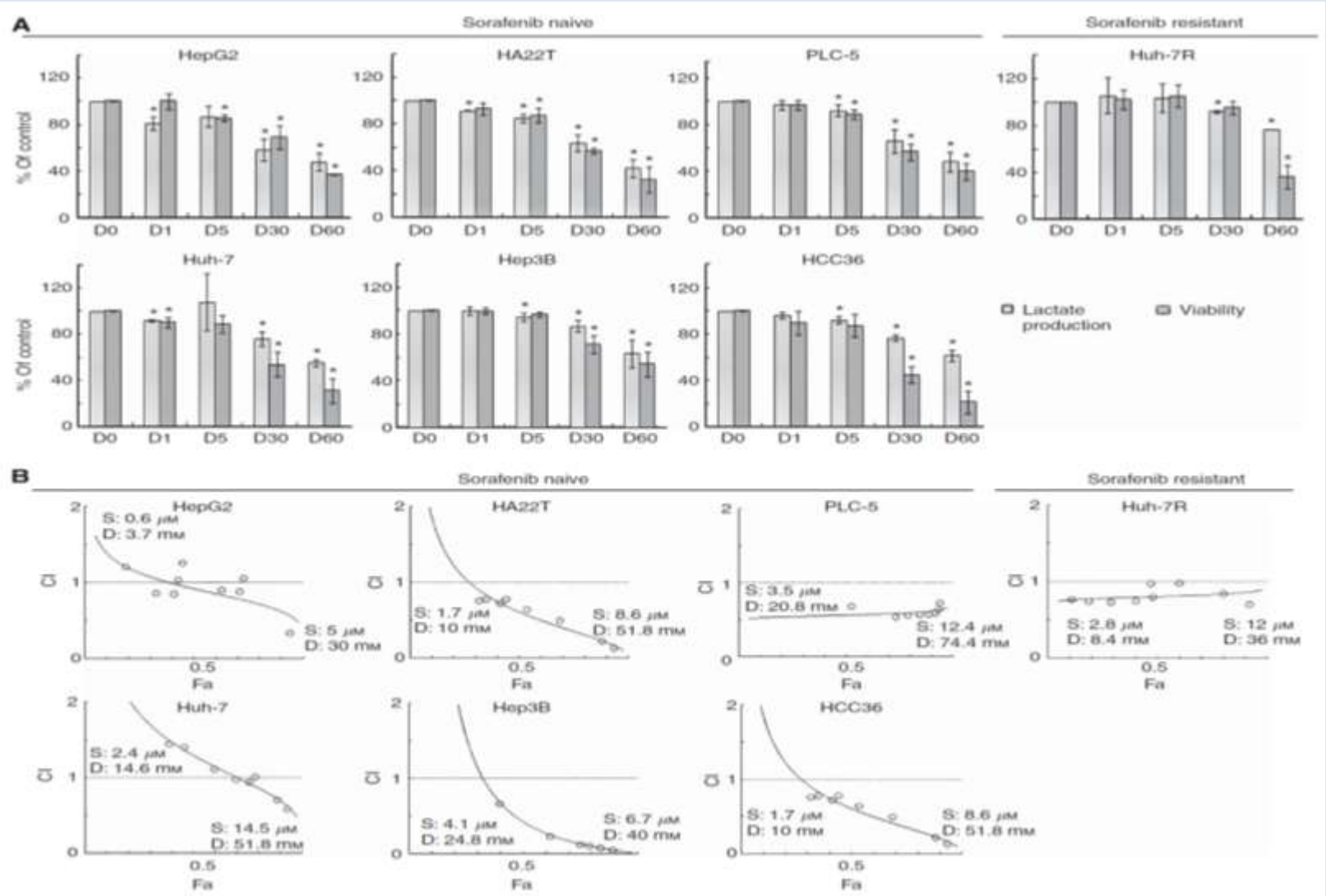
Therapeutic Targeting of the Hallmarks of Cancer



Hanahan and Weinberg, 2011

Cell PRESS

Activating Oxidative Phosphorylation by a PDK inhibitor Overcomes Sorafenib Resistance of HCC



Shen YC et al. Br J Cancer (2013) 108, 72–81

CONCLUSIONS

- **The field failed to find a new drug for HCC in the past 6 years.**
- **NGS and "encyclopedia" cell lines analyses help identify new targets e.g. Wnt/B-catenin, JAK/STAT, FGF19/FGFR4, Neuregulin/Her-3, for drug development.**
- **Research on new-modality Tx. Includes CSC/EMT, immunotherapy, oncolytic virotherapy, and metabolism-targeted therapy is on the horizon.**