Advanced Hepatocellular Carcinoma: The SEARCH trial

Discussant

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Disclosure slide

Speaker / Advisory role

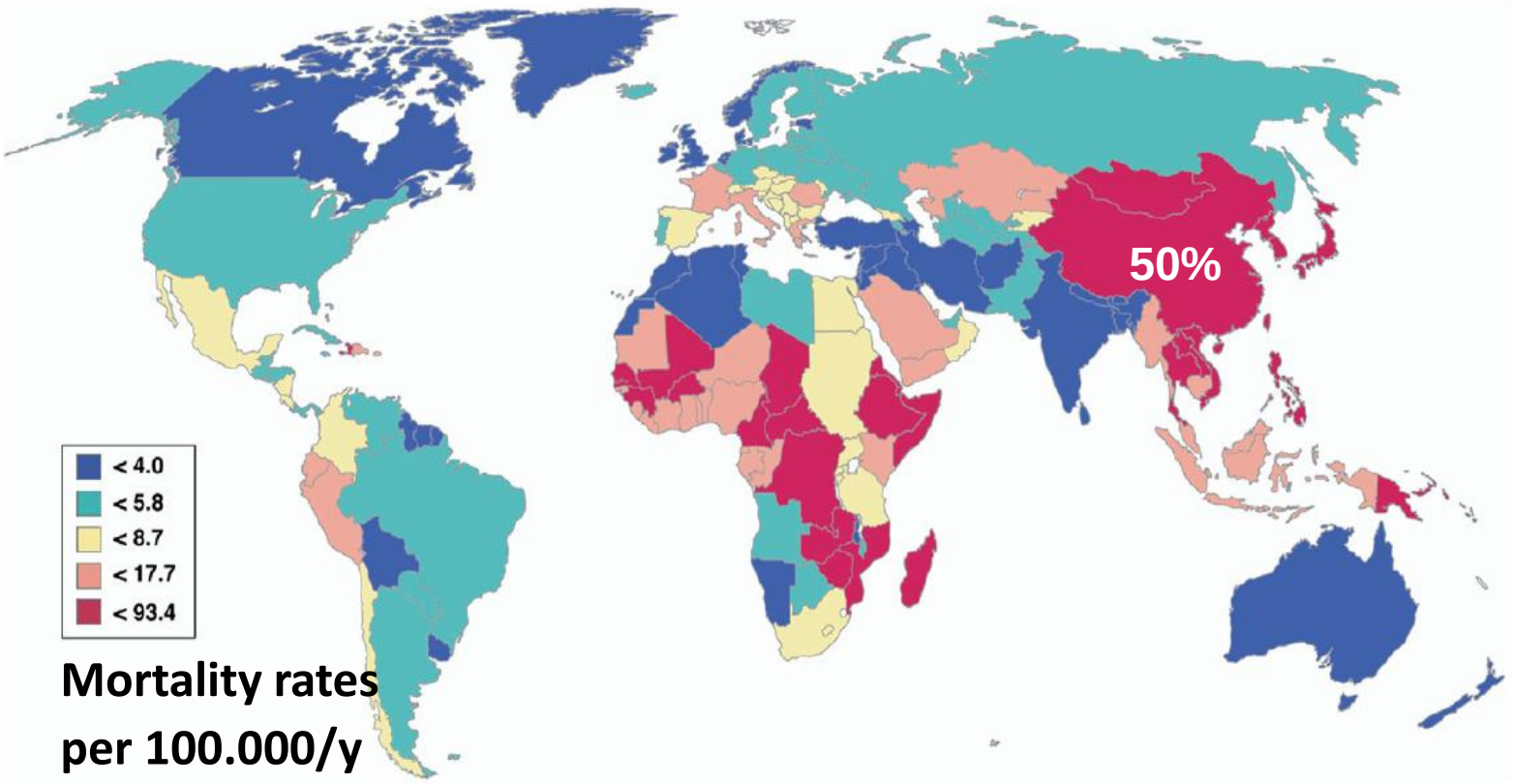
Bayer
Celgene
Clovis
Merck
Sanofi-Aventis

HCC

Major world health problem

- 90% of all primary liver cancers
- 3-7 % of all cancers worldwide
- 3rd cause of cancer-related deaths
- Incidence rising (in the US x2 in 15 years)

HCC – Mortality rates



Adapted from:

El-Serag HB, Rudolph KL: Gastroenterology 2007, 132: 2557

HCC

Well defined risk factors

- Hepatitis B (50%)
- Hepatitis C
- Alcoholic liver disease
- Hemochromatosis
- Aflatoxin, Vinyl chloride
- NASH
  (non-alcoholic steatohepatitis)

Clinical situation

- Most Patients (90%) suffer from liver cirrhosis
- HCC is the leading cause of death in liver cirrhosis

HCC- treatment overview

Early and intermediate stage tumors:

- resection, liver transplant, local ablation (potentially curative)
- Chemo- or radioembolization (mOS 20 months)

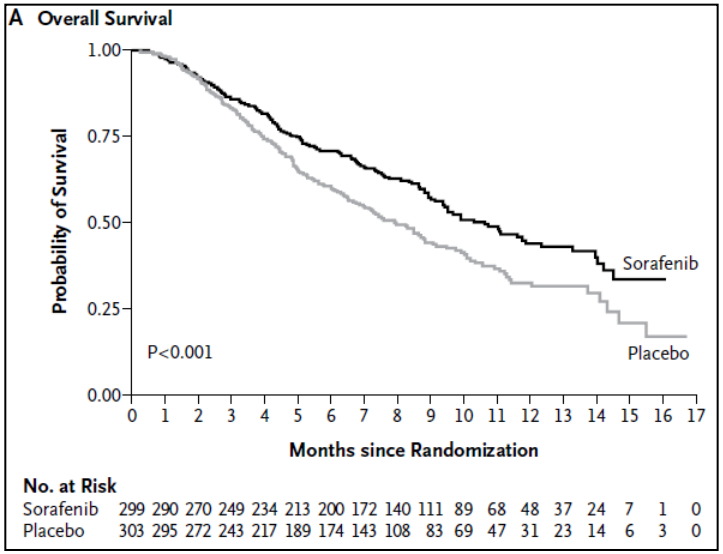
Advanced tumors (BCLC C: portal invasion, N1, M1):

- No confirmed survival benefit in phase III trials e.g. for
  - chemotherapy
  - tamoxifen
  - immunotherapy
- 2008: Two positive trials for sorafenib

EASL-EORTC Clinical Practice Guideline
Eur J Cancer 2012; 48: 599
J Hepatol 2012; 56: 908

Sorafenib in advanced HCC

- **SHARP trial** (Llovet et al., NEJM 359:378, 2008)
  N = 602, sorafenib vs. placebo



10.7 vs. 7.9 months
(HR 0.69, 95% CI 0.55-0.87)

- **Asia-Pacific trial** (Cheng et al. Lancet Oncol 10:25, 2009)
  N = 271, 2:1 sorafenib vs. Placebo
  median OS **6.5 vs. 4.2 months** (HR 0.68, 95% CI 0.50-0.93)

SEARCH
A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial of Sorafenib plus Erlotinib in Patients with Hepatocellular Carcinoma (HCC)

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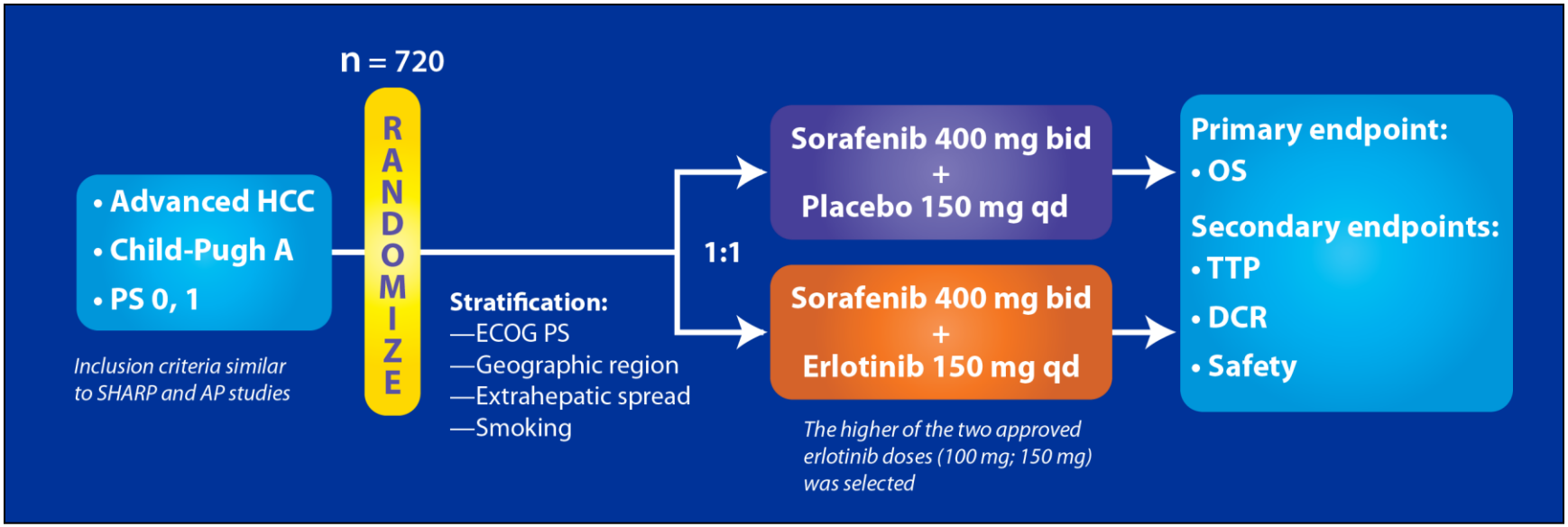
SEARCH: Trial summary



SEARCH: Rationale

- Sorafenib inhibits PDGFRβ, VEGFRs, c-Raf, B-Raf kinases
- Erlotinib inhibits EGFR, may thus be synergistic

Erlotinib

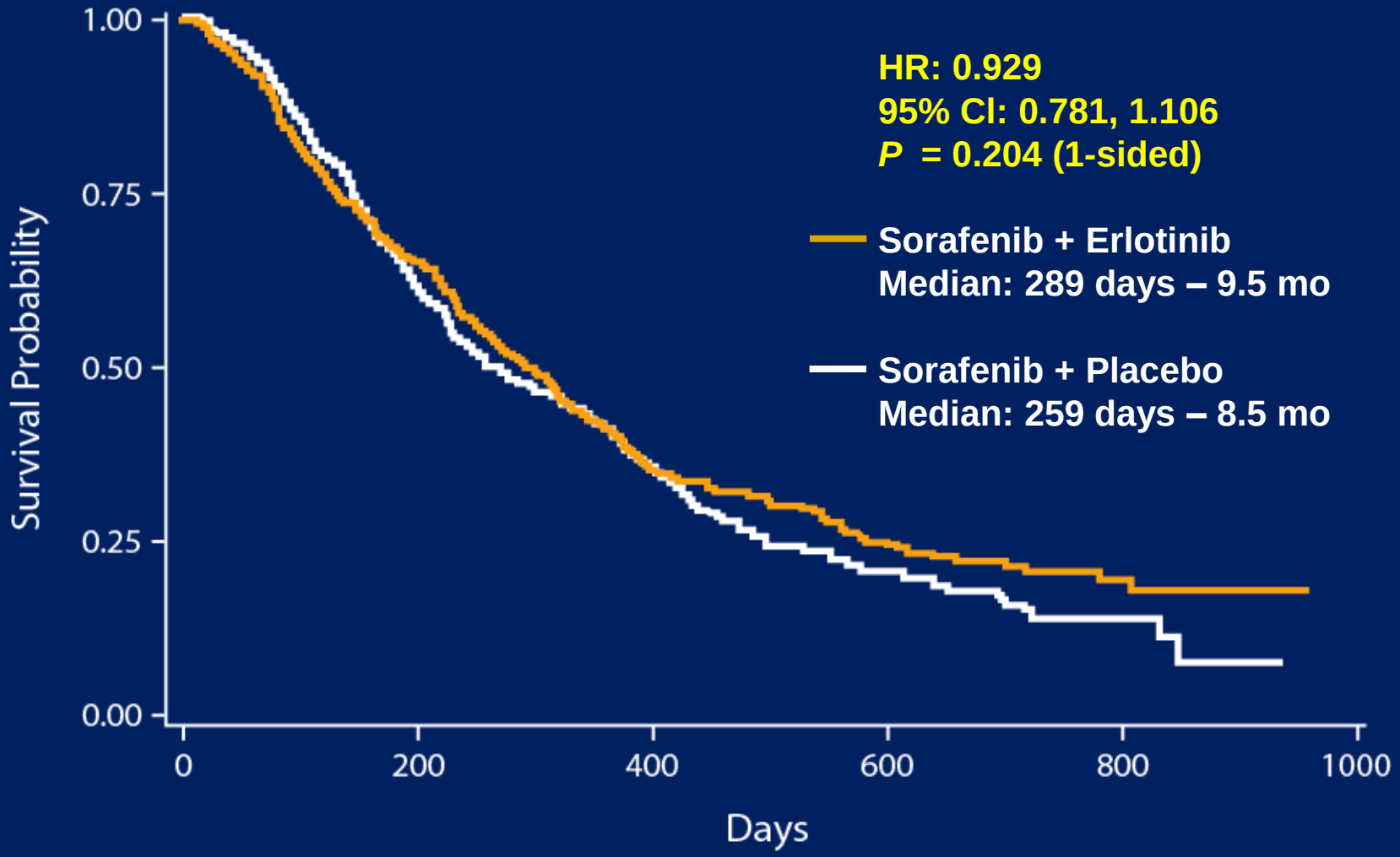
- EGFR is overexpressed in hepatic fibrosis, early HCC
- The ligands EGF and TGFβ are mitogenic for hepatocytes
- EGF expression has been demonstrated in HCC cell lines
- Two single agent phase II trials with encouraging results
  - mOS 10.75 months and 13 months
  - no correlation with EGFR expression (68% and 52%)

Yamaguchi K et al. J Surg Oncol 1995, 58: 240
Philip AP et al. J Clin Oncol 2005, 27: 6657
Thomas MB et al. Cancer 2007, 110: 1059

SEARCH: Statistics

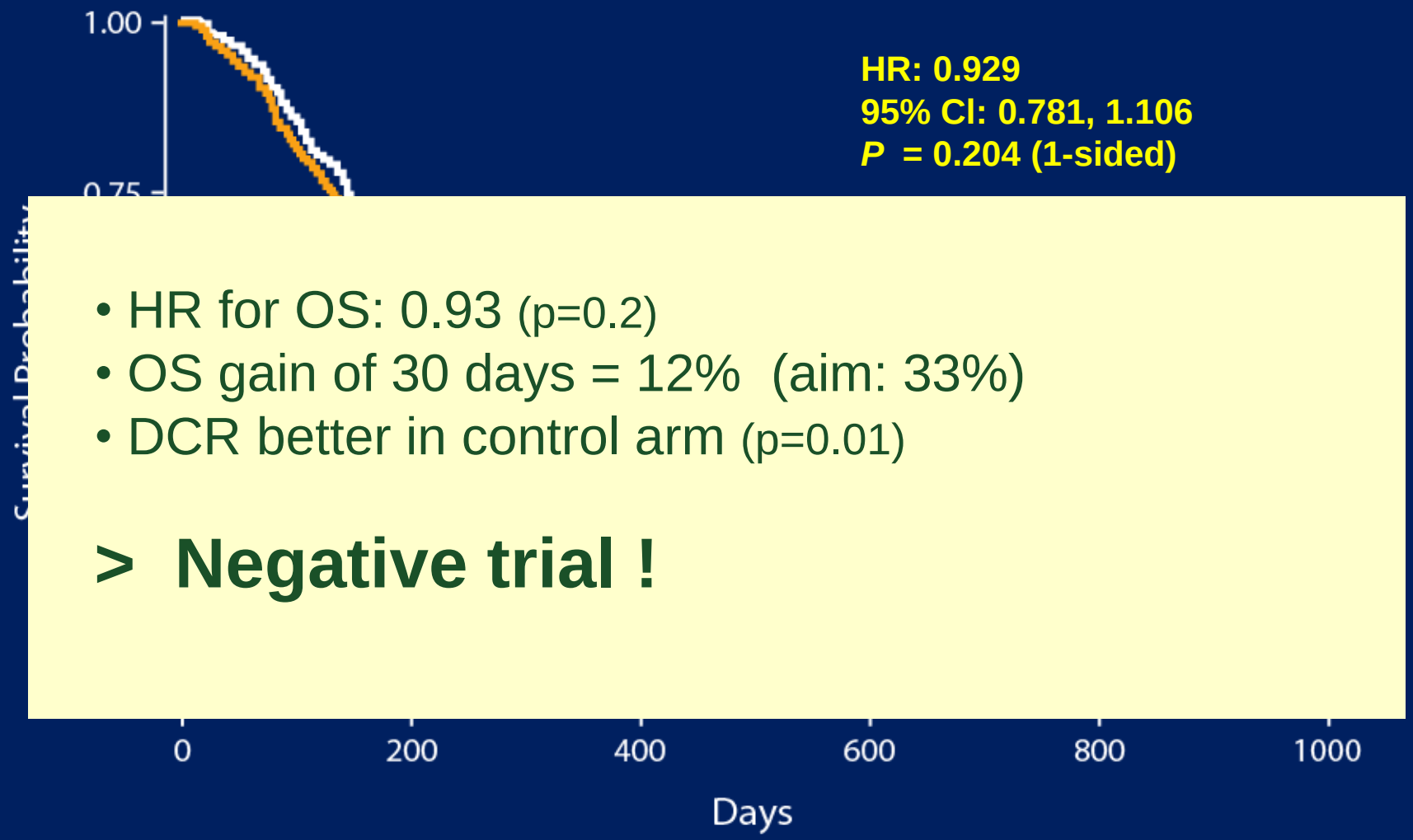
- N=720 pts with advanced HCC
- Primary end point:
  33% increase in median OS
  521 events (90% power, α one-sided 0.025)
- Current Analysis:
  Database lock 7th June 2012
  523 deaths (72.6% of 720 pts)

Overall Survival*



*ITT Population

Overall Survival*



HR: 0.929
95% CI: 0.781, 1.106
***P* = 0.204 (1-sided)**

- HR for OS: 0.93 (p=0.2)
- OS gain of 30 days = 12% (aim: 33%)
- DCR better in control arm (p=0.01)

> Negative trial !

*ITT Population

Obvious Reasons ?

- Backbone Sorafenib > well supported
  - 2 phase III trials
- Rationale > can be defended
- Trial Design > solid
  - standard dose of inhibitors
  - sufficiently powered two arm phase III
  - completed in time with expected event number
  - aim 33 % probably too enthusiastic (SHARP 36%)
- Patient population > standard
- Toxicity > fairly similar in both arms

Can we leave it there ?

- **OS in the control arm (S) of SEARCH is less than in SHARP (8.5 vs. 10.7 months)**

- Sorafenib/Erlotinib
  - Trend for better OS
  - More Responses (p 0.051)
- Sorafenib/Placebo
  - Better disease control (p 0.01)

SEARCH: Patient characteristics

	SEARCH (S ± Erlot) N=720	SHARP (S vs. Placebo) N=602	Asia/Pacific (S vs. Placebo) N=226
Age	61y	65y	51y
Male	81%	87%	86%
Europe/Americas vs. Asia	75/25	100/--	--/100
ECOG PS 0/1/2	61/39	54/38/8	26/68/5
Child Pugh A	97	95	97
BCLC Stage B/C	15/85	18/82	4/96
Hepatitis B/C	35/27	18/28	74/9
Prior Embolization (TACE)	29%	48%	
Surgery	8%	19%	
OS Sorafenib arm	8.5	10.7	6.5

Llovet et al. NEJM 2008, 359: 378

Cheng et al. Lancet Oncol 2009, 10: 25

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SEARCH: efficacy?

	Sorafenib + Placebo	Sorafenib + Erlotinib	p
Response rate	4%	7%	0.051
Overall survival	8.5 mo	9.5 mo	0.2
Time to progression	4.0 mo	3.2 mo	0.9
Disease control rate (CR + PR + SD)	53 %	44%	0.01

SEARCH: toxicity and treatment

	Sorafenib + Placebo	Sorafenib + Erlotinib
SAEs		
Treatment emergent	194	210
Deaths during first 30 days tx	9	15
Deaths up to 30 days after tx	65	76
Selected AEs (all grade)		
Rash	40%	52%
Anorexia	37%	43%
Diarrhea	59%	76%
Study drug administration		
Daily dose	95%	96%
Interruptions	80%	83%
Median Tx duration	4.0 months	2.8 months

Toxicity and DFS ?

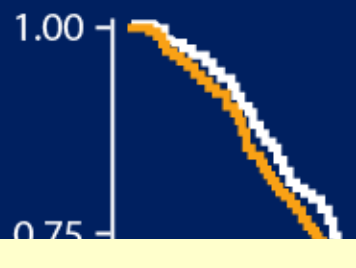
- Number of reported AEs are slightly higher in the experimental arm
- Treatment duration is shorter

> Increased toxicity per time period !!

> Impact on disease control rate likely:

- no tumor measurements at end of study;
- in case of termination for toxicity, the date of the previous measurement was used for definition of confirmed DC

Overall Survival*



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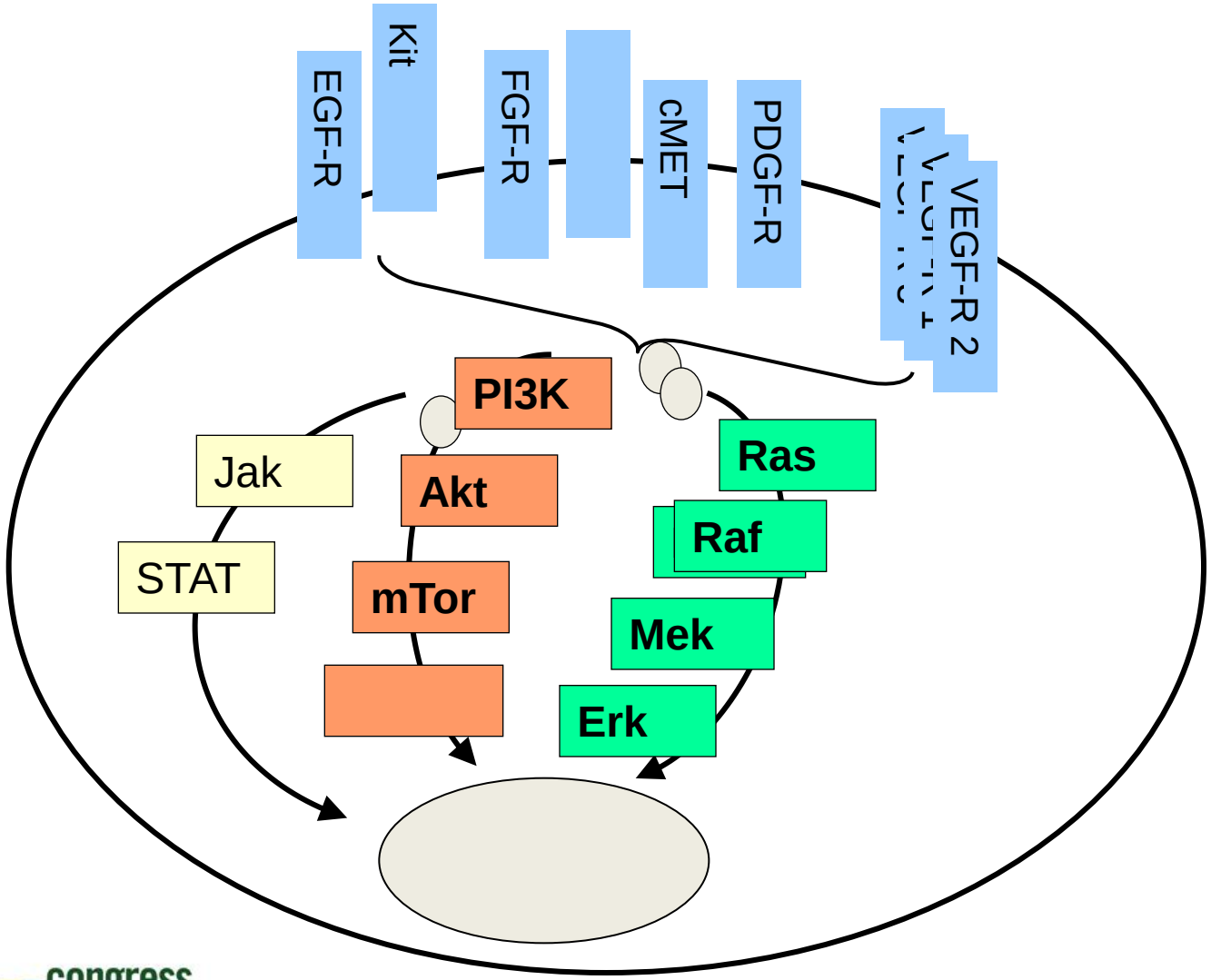
- HR for OS: 0.93 (p=0.2)
- OS gain of 30 days = 12% (aim: 33%)
- RR improved with Erlotinib (p = 0.051)

- DCR better in control arm ??

> Negative trial ?!
> Rationale ??

*ITT

HCC


EGF-R
Kit
FGF-R
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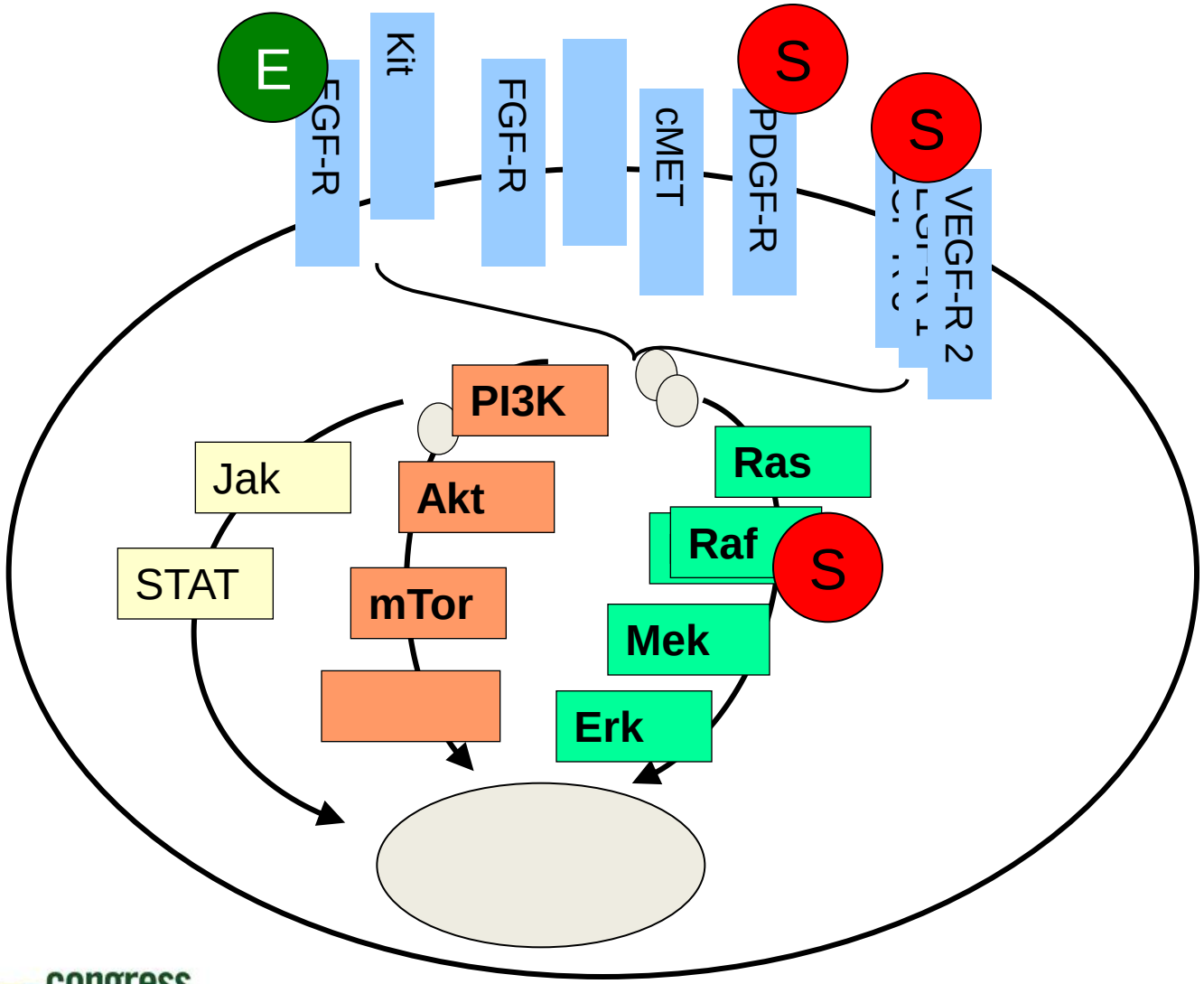
PDGF-R
VEGF-R 2
PI3K
Jak
Akt
Ras
Raf
STAT
mTor
Mek
Erk

HCC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PDGF-R
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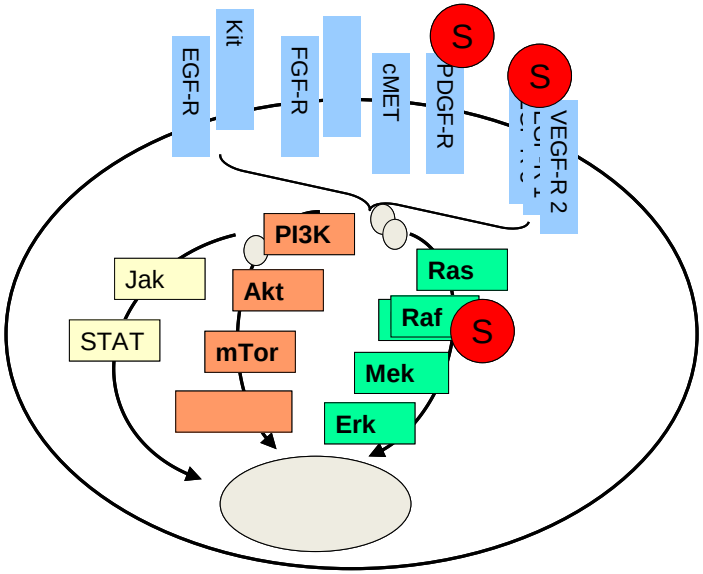
VEGF-R 2
PI3K
Jak
Akt
Ras
Raf
S
STAT
mTor
Mek
Erk

HCC

- Highly vascularized tumor
- Dependent on angiogenesis
- Gene signature as in liver regeneration
- Develops in cirrhotic liver
  - loss of liver mass
  - Macroenvironment of growth factor activity
  - mainly angiogenic factors
  - mesenchymal stimulation through HGF/met
  - less expression of EGF

Sorafenib

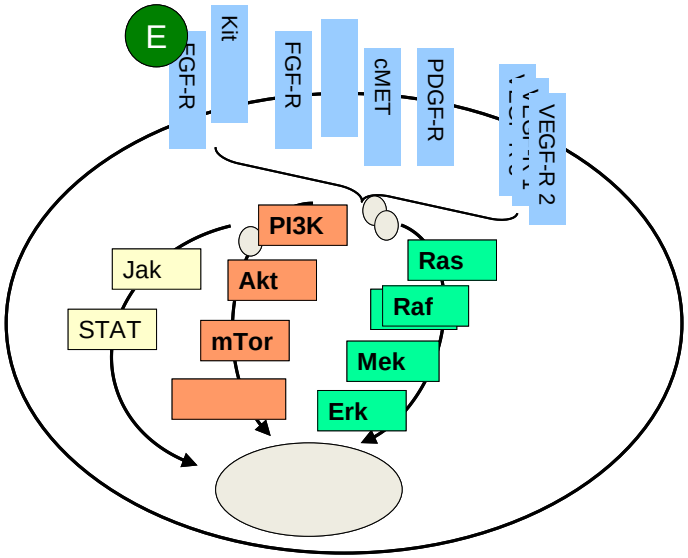


Triple action (at least)

- Inhibits angiogenesis through the VEGFR/PDGFR
- Inhibits met-stimulated epithelial-mesenchymal transition through Raf
- Decreases paracrine secretion of HIF-1α / VEGF

Nagai T et al. Mol Cancer Ther 2011; 10: 169
Liu L et al. Clin Cancer Res 2012 epub

Erlotinib

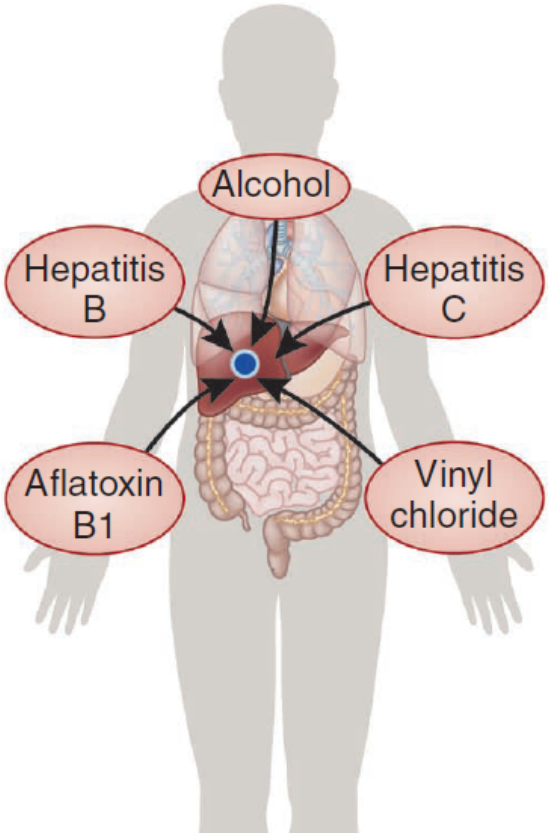


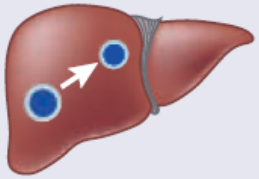
Action in HCC ?

- Erlotinib induces VEGF mRNA, thus stimulating endothelial cell migration and vascular sprouting
- Erlotinib downregulates ERK phosphorylation without effect on cell viability
  (in contrast to Sorafenib, which inhibits both)
- But: Erlotinib is effective in some Sorafenib-resistant cell lines

Ezzoukhry Z et al. Int J Cancer; 2012 epub
Sieghart et al. J Hepatol 2012; 57: 592

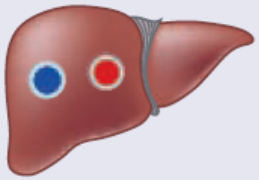
HCC are highly heterogeneous





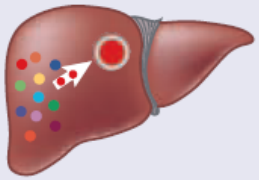
PVTT

- Intrahepatic metastasis from primary HCC
- Largely overlapping mutations, with a few newly acquired alterations



MCT

- Distinct individual mutations; independent tumorigenesis
- Same overall mutation spectrum; same mutagenic background



Random versus clonal HBV integration

- Numerous random, low-frequency integrations in non-tumor cells
- Clonal, high-abundance integrations in tumor cells

Zhang Z. Nature Genetics 2012, 10: 1075

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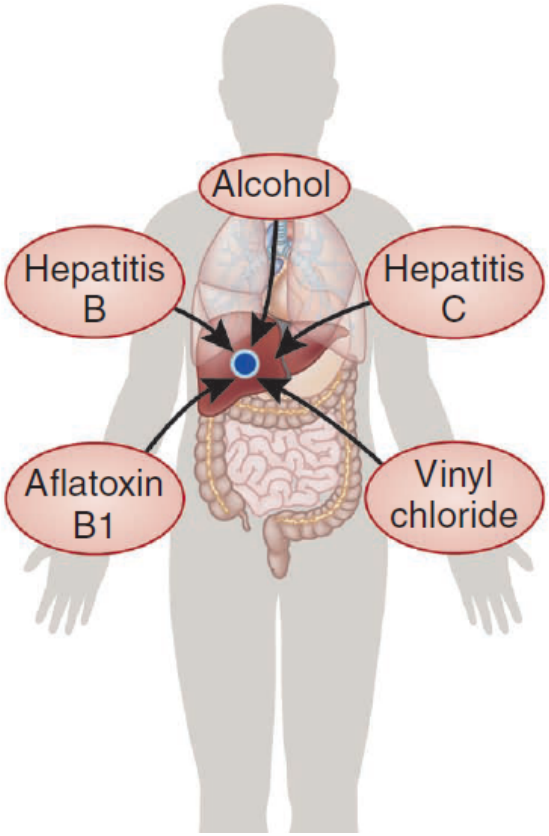

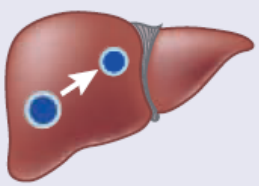

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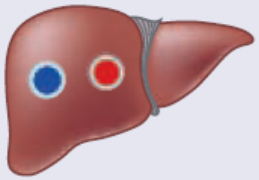

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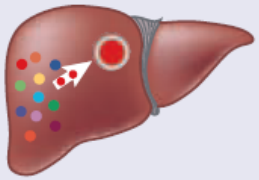

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Summary

- The combination of Sorafenib/Erlotinib as compared to Sorafenib/Placebo did not significantly improve overall survival in a mixed population of HCC
- Erlotinib treatment increased the toxicity in the experimental arm which likely influenced the statistical evaluation of TTP and DCR
- Subgroups of HCC may profit from Erlotinib treatment

Conclusion

- Sorafenib remains the standard treatment for advanced HCC
- Combinations with less toxicity needed
- Subgroup analysis necessary
  - Hep B vs. Hep C vs. other causes
  - extention of disease (local vs. metastatic?)
  - EGFR copy number, mutation
  - EGFR downstream target (Ras, Raf)
  - VEGFR and Ligands
  - HGF/met
  - Epiregulin/Amphiregulin