
Systemic Therapy in HCC?

Something is really new this year!

Difficulties

- HCC is not a single disease entity
 - Hep C induced HCC may differ from Hep B or aflatoxin or alcoholic cirrhosis
 - There seems to be variability in the rapidity of its progression
- HCC comes in the setting of cirrhosis in most cases
 - Making treatment more complex as we are dealing with two diseases
 - And we have issues of drug metabolism

Systemic Therapy Choices

- Chemotherapy
- Hormonal Therapy
- “Immune” Therapy (interferon)
- Targeted Therapy

Chemotherapy

- Doxorubicin
 - Arguably the most effective chemotherapy agent
 - Hepatically metabolized
 - Elevated bilirubin makes doxorubicin too toxic
 - Application is limited
 - Response rates vary (10-26%)
 - Meta-analysis
 - Two RCTs exist
 - Doxorubicin vs tamoxifen
 - Doxorubicin vs placebo
 - Efficacy is questionable in terms of survival

Chemotherapy

- 5-FU (capecitabine)
 - The other “standard” drug
 - Safer in liver failure/cirrhosis
 - Ubiquitously metabolized
 - I could not find a randomized trial of 5-FU vs placebo

Combined Chemotherapy

- PIAF
 - Platinum, interferon, adriamycin (doxorubicin), 5-FU
 - In phase II trials had RRs approaching 40%
- Phase III trial in 188 patients: PIAF vs doxorubicin
 - RR was 20% vs 10%, respectively
 - Survivals were 8.7 vs 6.8 months (p, 0.83)
 - HR = 0.98

Platinums

- Although PIAF was not too effective, it is clear that platinums add to the efficacy of other drugs in a variety of diseases.
- Response rates seem to increase when platinums are used though the effect does not clearly translate to survival benefit

Hormonal Therapy

- Estrogen has been implicated in the etiology of HCC
- Estrogen receptors have been found on liver cells, benign hepatic lesions and hepatomas
- Tamoxifen, an antiestrogen (mostly), has had variable impact on RCTs

Tamoxifen Randomized trials

- 12 RCTs and 4 meta-analyses
 - 4 positive trials
 - 8 negative trials
 - 2 positive meta-analyses
 - 2 negative meta-analyses
- 2 largest trials were negative
 - Barbare, et al JCO 2005 (420 pts)
 - Suggested the subset with good hepatic function did get survival benefit
 - CLIP trial Lancet, 1998 (477 pts)

Other Hormonal Treatments

- Androgen receptors have also been found on HCC
 - Not as many randomized trials, but
 - All trials of anti-androgens (LHRH antagonists, flutamide) are negative
- Megesterol
 - Apparently progesterone receptors also exist
 - One phase II looked promising
 - I'm unaware of any phase III trials

Somatostatin Analogues

- Rationale:
 - HCC cells have demonstrated somatostatin receptors
 - Somatostatin can inhibit growth of cells in vitro
- Results of trials
 - RCTs have had conflicting results in terms of survival
 - May have some QOL benefit that needs further exploration

Interferon

- This has intriguing issues
 - Interferons have anti-tumor activity, though limited
 - Interferon also has anti-HCV and anti-HBV properties
- In RCTs
 - In HBV patients there was survival benefit
 - In HCV patients there was no survival benefit
 - Were the diseases different or is this an effect of small trials?

Standard Therapy Conclusions

- There is probably some limited activity from many of the old therapies
 - Chemo: doxorubicin and 5-FU
 - Hormones: tamoxifen, octreotide
 - Immune therapy: interferon
- However, these agents each work with a subset of patients and we have not spent any effort dissecting this issue out

Can targeted therapies save
the day?

Angiogenesis

- HCC is highly vascular
- HCC overexpresses VEGF (and this may confer a poor prognosis)
- HCC may have VEGF receptors itself
- In pre-clinical trials
 - VEGF inhibitors have inhibited HCC growth
 - PTK 787 inhibited both angiogenesis and inhibited tumor growth through an angiogenesis-independent effect

Trials With Targeted Therapies in HCC: Sunitinib

Trial/Dose	Patients	Endpoints	Outcome	Significant AEs
Phase 2 (Zhu et al)/ 37.5 mg/day 4w on/2 w off	Locally advanced, unresectable, or metastatic HCC (N=26)	1°: PFS 2°: Safety, ORR, duration of response, OS	Median PFS = 4.1 months; Median OS = 11.6 months; ORR = 3.9%	Grade 3/4 (%) AEs: neutropenia (12%), lymphopenia (12%), thrombocytopenia (12%), SGOT (23%), SGPT (12%)
Phase 2 (Faivre et al)/ 50 mg/day 4w on/2w off	Unresectable HCC (N=37)	1°: ORR 2°: Clinical benefit rate, duration of response, OS	Median OS = 45 weeks; Median TTP = 21 weeks; ORR = 2.7%	Grade 3/4 (%) AEs: thrombocytopenia (35%), neutropenia (24%), anemia (19%), leukopenia (11%); 4 deaths

Zhu AX et al. Presented at: 43rd ASCO Annual Meeting; June 1-5, 2007; Chicago, IL. (Abstract 4637);

Faivre SJ et al. Presented at: 43rd ASCO Annual Meeting; June 1-5, 2007; Chicago, IL. (Abstract 3546).

Ongoing Studies With Bevacizumab-Based Regimen

Regimen	Study	No. of Patients	Response Rate (%)	Median PFS/TTP (months)	PFS at 6 Months (%)	Median Survival (months)
Single agent	Schwartz et al.	25	PR=8 SD=72	6.5	NR	NR
	Malka et al.	30	PR=12.5 SD=54	NR	NR	NR
+ Chemotherapy	Zhu et al.	30	PR=17 SD=53	4.6	56	10.7
	Sun et al.	30	PR=13.3 SD=76.7	4.5	NR	10.6
	Hsu et al.	25	ORR=16 DCR=60	4.1	34	10.7
+ Erlotinib	Thomas et al.	44	DCR=50	9 (n=34)	75 (at 4 months)	19 (n=34)

Results from studies adapted from presentations at ASCO Annual Meeting; June 1-5, 2007; Chicago, IL.

Summary of Recent Phase II Studies With EGFR Inhibitors in HCC

Study	Regimen	No. of Patients	RR (%)	Median PFS/TTP (months)	PFS at 6 Months (%)	Median Survival (months)
Philip et al.	Erlotinib	38	9	3.2	32	13
Thomas et al.	Erlotinib	40	0	3.1	28	6.3
O'Dwyer et al.	Gefitinib	31	3	2.8	NR	6.5
Ramanathan et al.	Lapatinib	30	5	2.3	NR	6.2
Zhu et al.	Cetuximab	30	0	1.36	3	9.6
Gruenwald et al.	Cetuximab	32	0	1.87	NR	NR
Louafi et al.	Cetuximab -GEMOX	43	23	NR	NR	NR

Table communicated by Dr. Andrew Zhu, Harvard Medical School, unpublished.

EGFr

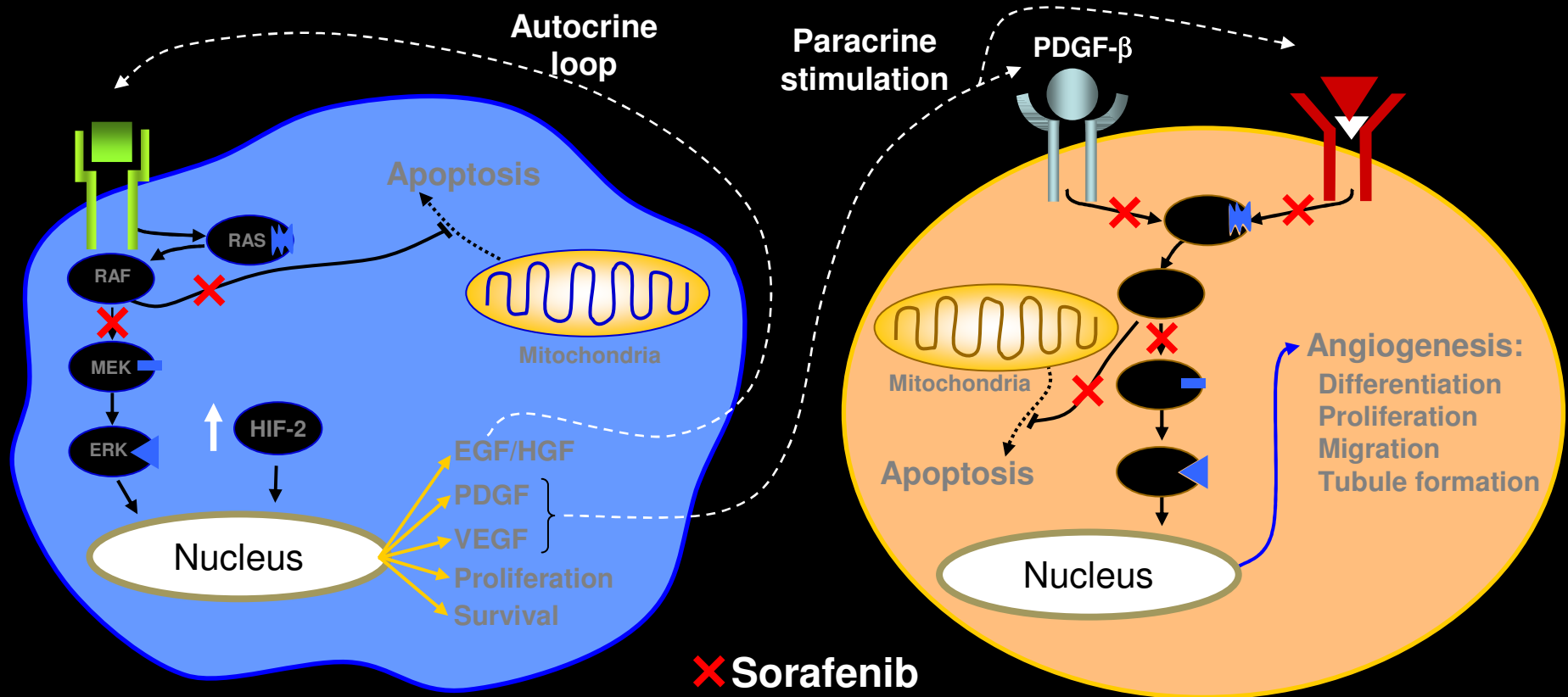
- Overexpressed in a variety of tumor types including HCC
 - Response rates to erlotinib <10%
 - Response rate to lapatinib <10%
 - Response rate to cetuximab 0%

- In other words, relatively poor, but about the same as everything else

Sorafenib Targets Both EGFR Pathway (sort of) and Angiogenesis

Tumor cell

Vascular cell



Phase III SHARP Trial: Study Design

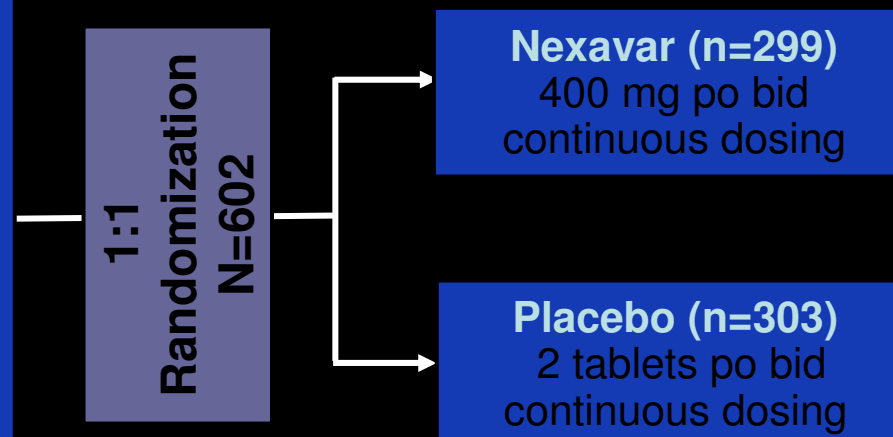
- 1^o endpoints: OS, time to symptomatic progression (FHSI8-TSP)
- 2^o endpoints: Time to progression, disease control rate, safety

Eligibility Criteria

- HCC verified by histology
- Child-Pugh class A
- ECOG PS 0-2
- No prior systemic anticancer treatment
 - Prior hormonal therapy allowed
- Prior surgical or locoregional treatments allowed
- Measurable disease

Stratification

- Macroscopic vascular invasion and/or extrahepatic spread
- ECOG PS
- Geographical region



- Treatment continued until radiographic and symptomatic progression or any adverse event requiring withdrawal
- Treatment cycle defined as 6 weeks

ECOG PS=Eastern Cooperative Oncology Group performance status.

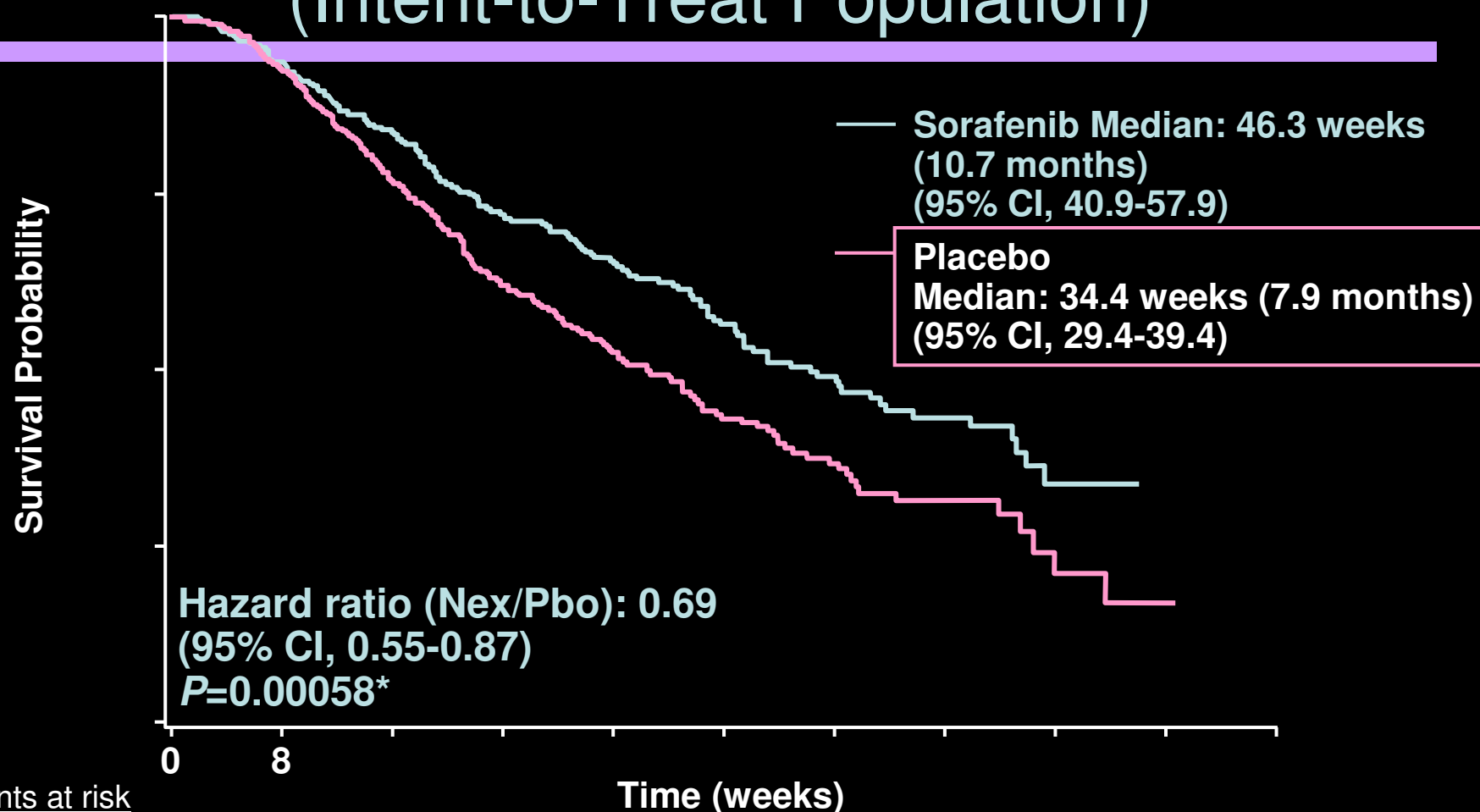
Llovet JM et al. Presented at: 2007 ASCO Annual Meeting; June 1-5, 2007; Chicago, IL.

Phase III SHARP Trial: Baseline Patient Characteristics

Characteristics	Sorafenib (n=299)	Placebo (n=303)
Age (median, yr)	65	66
Male (%)	87	87
Region (%)		
Europe	88	87
N. America	9	10
Other	3	3
Etiology (%)		
Viral hepatitis C	29	27
Viral hepatitis B	19	18
Alcohol	26	26
Other	26	29
Child-Pugh (%)		
A	95	98
B	5	2



Phase III SHARP Trial: Overall Survival (Intent-to-Treat Population)



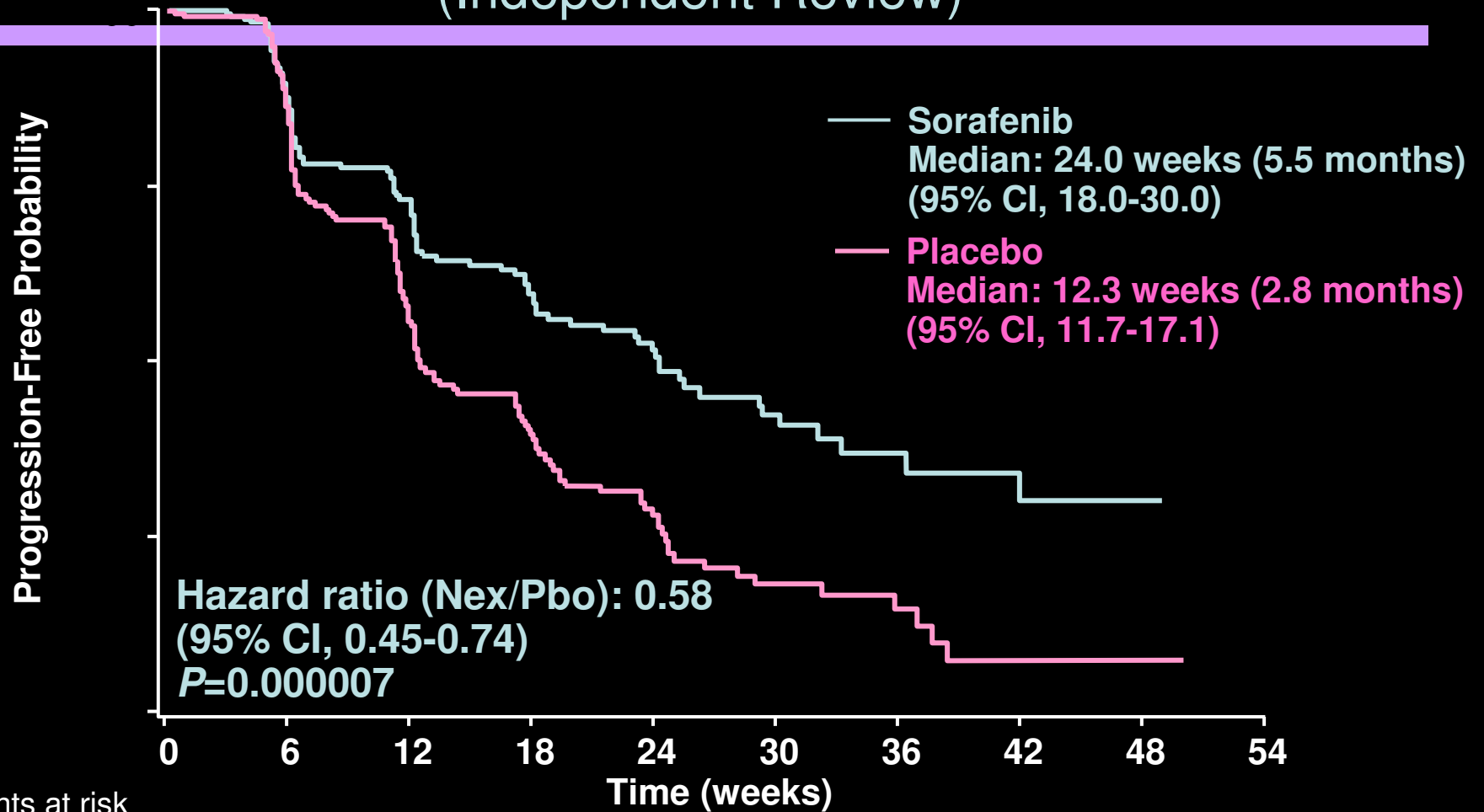
Patients at risk

	0	8								
Sorafenib:	299	274	241	205	161	108	67	38	12	0
Placebo:	303	276	224	179	126	78	47	25	7	0

*O'Brien-Fleming threshold for statistical significance was $P=0.0077$.

Llovet JM et al. Presented at: 2007 ASCO Annual Meeting; June 1-5, 2007; Chicago, IL.

Phase III SHARP Trial: Time to Tumor Progression (Independent Review)



Patients at risk

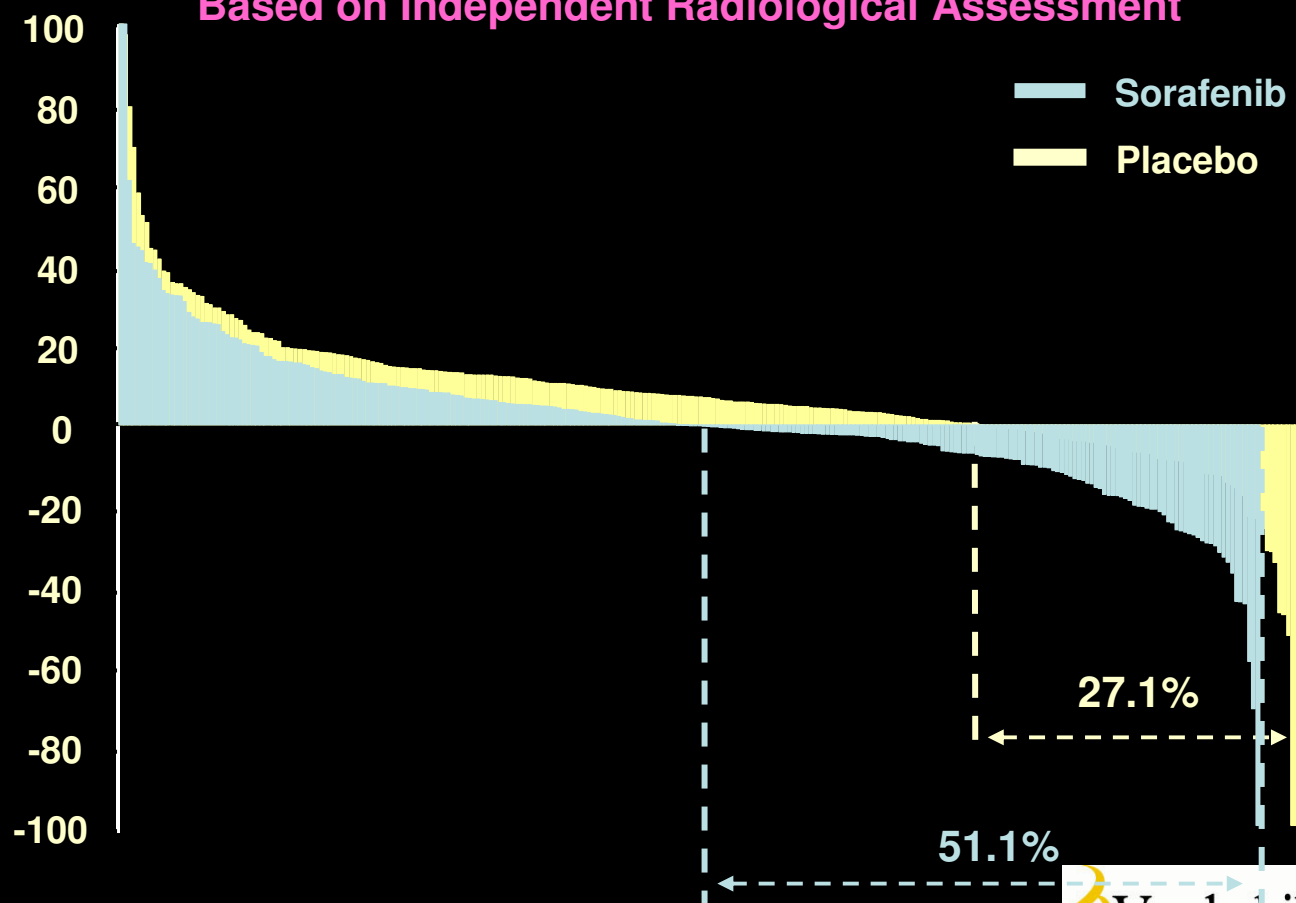
	0	6	12	18	24	30	36	42	48	54
Sorafenib:	299	196	126	80	50	28	14	8	2	
Placebo:	303	192	101	57	31	12	8	2		

Llovet JM et al. Presented at: 2007 ASCO Annual Meeting; June 1-5, 2007; Chicago, IL.
Data on file. Bayer HealthCare.



Phase III SHARP Trial: Maximum Percent Reduction in Tumor Measurement

% Change in Target Lesion From Baseline to Smallest Tumor Size Post-Baseline
Based on Independent Radiological Assessment



Data on file, Bayer HealthCare.

Phase III SHARP Trial: Best Response by RECIST (Independent Review)

	Sorafenib N=299 %	Placebo N=303 %
Overall response		
Complete response	0	0
Partial response	2.3	0.7
Stable disease	71	67
Progressive disease	18	24
Progression-free rate at 4 mo	62	42
Duration of treatment (median, weeks)	23	19
FHSI8-TSP rate*	68	66

*FHSI8-TSP rate between-group difference, $P=0.77$.

Llovet JM et al. Presented at: 2007 ASCO Annual Meeting; June 1-5, 2007; Chicago, IL.



Phase III SHARP Trial: Overview of Safety Events

	Nexavar N=297	Placebo N=302
Treatment-emergent serious adverse events (SAEs, %)	52	54
Drug-related treatment-emergent SAEs (%)	14	9
Adverse event leading to permanent discontinuation of study medication (%)	32	35

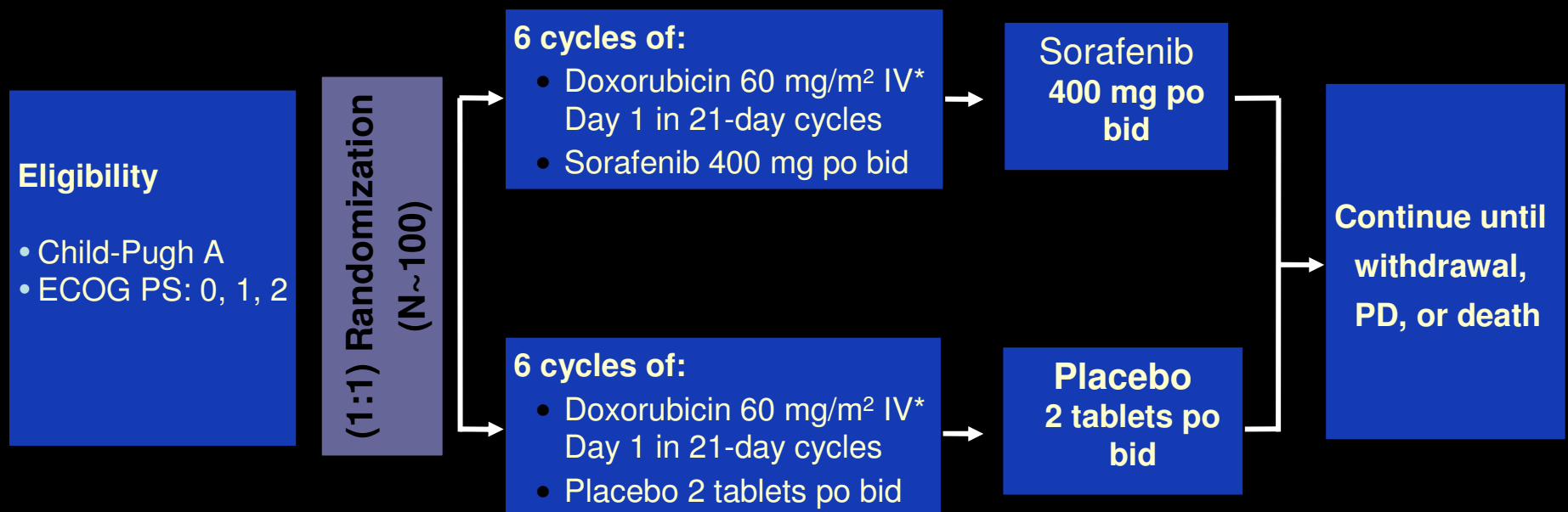
Data on file. Bayer HealthCare.

Llovet JM et al. Presented at: 2007 ASCO Annual Meeting; June 1-5, 2007; Chicago, IL.



Sorafenib in HCC: Phase II Doxorubicin ± Sorafenib

- 1^o endpoint: TTP
- 2^o endpoints: OS, overall disease control rate, QoL



*At physician discretion, doxorubicin was allowed up to a maximum accumulated dose of 450 mg/m².

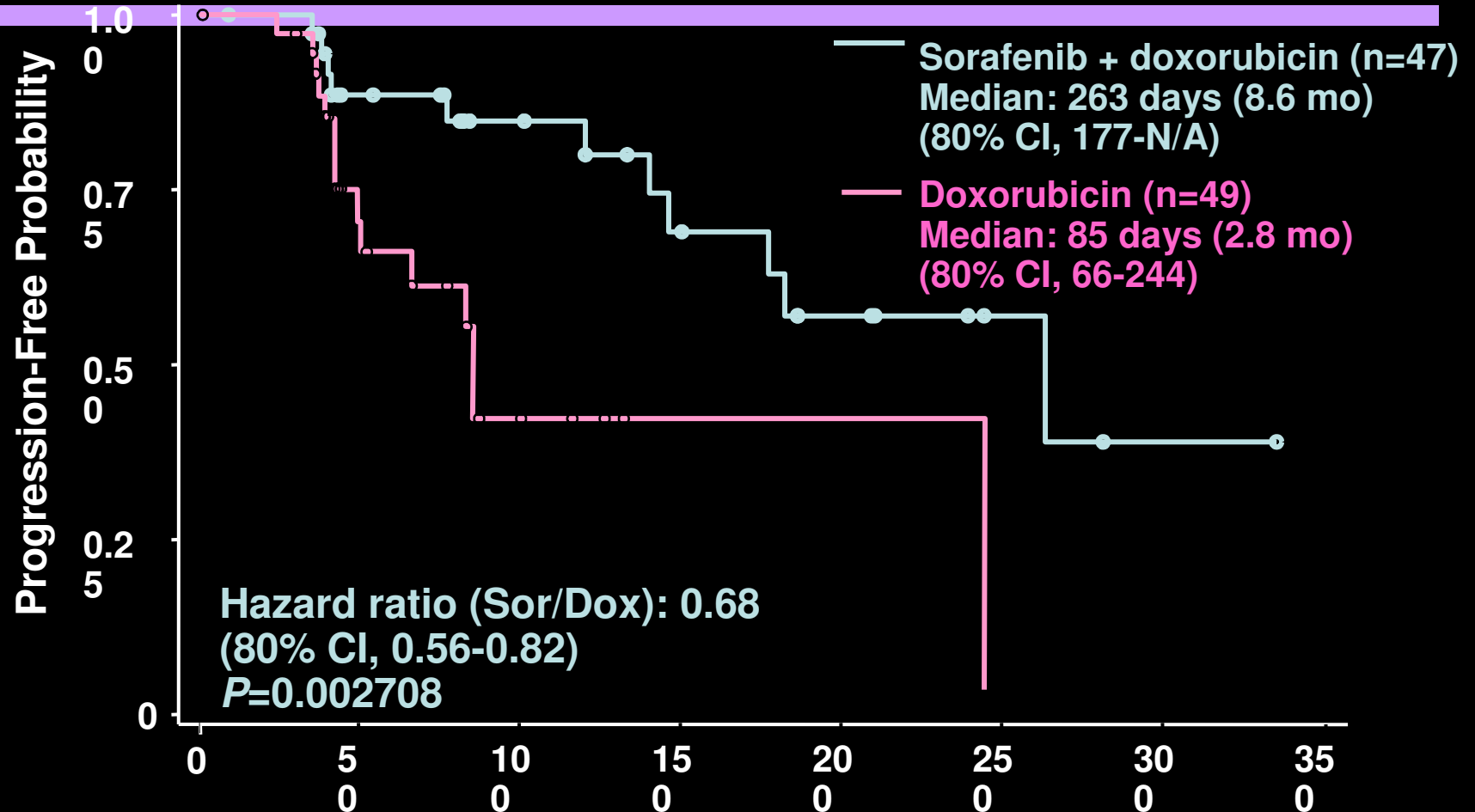
QoL=quality of life.

Abou-Alfa, et al ECCO, 2007

Sorafenib in HCC: Doxorubicin ± Sorafenib—Interim Analysis

- Independent DSMB performed an interim analysis in January 2007
- In this preliminary analysis, TTP and OS in the Sorafenib + doxorubicin arm appeared to be encouraging
- Per the external DSMB recommendation, the trial has been unblinded, and remaining patients on the control arm have been crossed over to doxorubicin + sorfenib

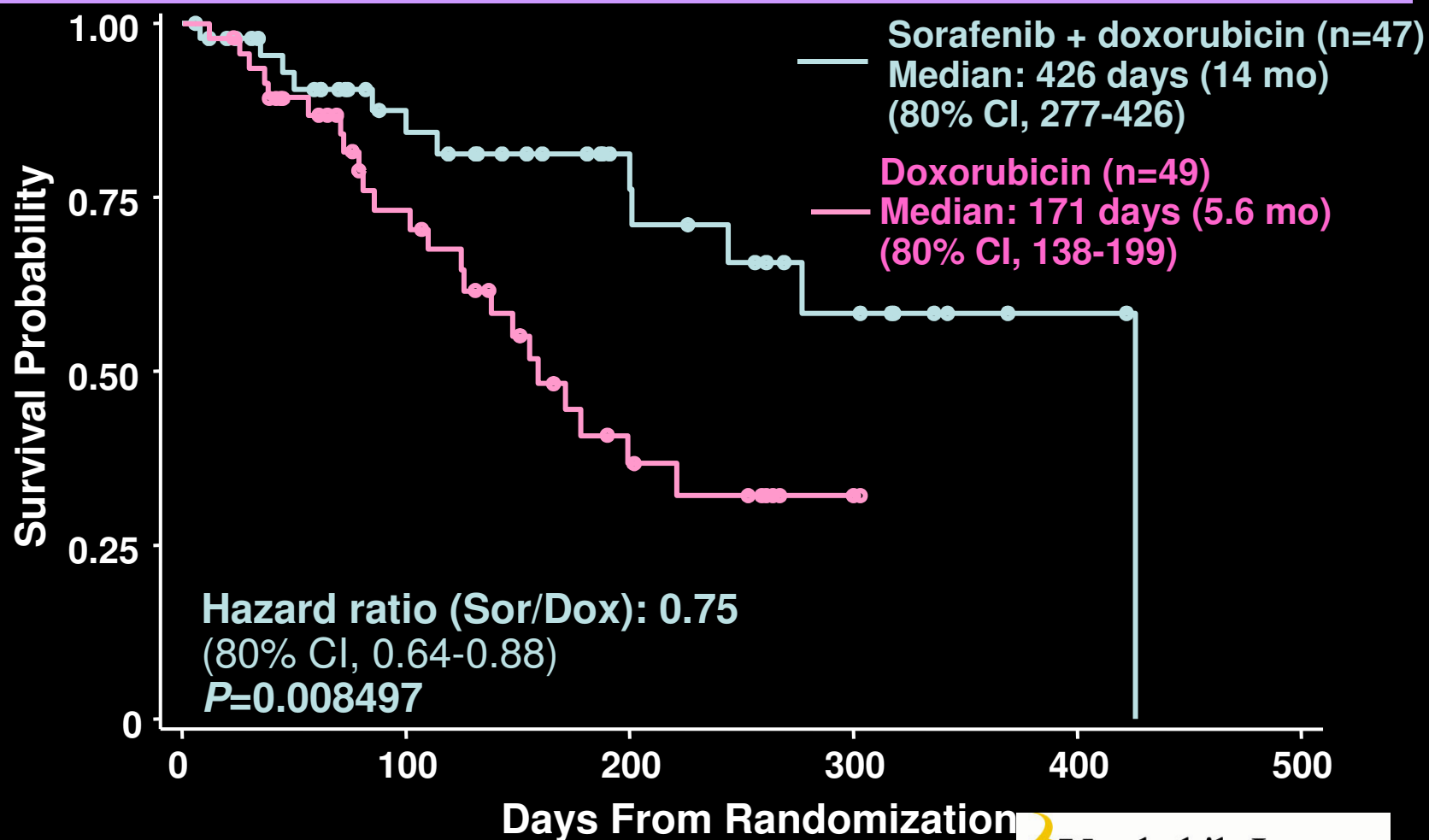
Phase II Doxorubicin ± Sorafenib— Time to Progression



October 2006 data cut off. Based on independent tumor assessment and actual visit date.

Abou-Alfa, et al ECCO, 2007

Nexavar in HCC: Phase II Doxorubicin ± Nexavar— Overall Survival



October 2006 data cut off.
Abou-Alfa, ECCO 2007

Phase II Doxorubicin ± Sorafenib— Best Response by RECIST (Independent Review)

	Sorafenib +		Doxorubicin	
	Doxorubicin N=47		N=49	
	n	(%)	n	(%)
Overall response				
Complete response	0	(0)	1	(2)
Partial response	2	(4)	0	(0)
Stable disease	31	(66)	24	(49)
Progressive disease	4	(9)	11	(22)
Not assessable	10	(21)	13	(27)
Disease control rate	24	(51)	9	(18)

October 2006 data cut off.
Abou-Alfa, et al. ECCO, 2007.

NF Kappa B

- NF Kappa B is activated in most forms of liver injury
 - Both Hep B and Hep C induced HCC may have origins in NF kappa B activation
 - There are no pure NF kappa B inhibitors in testing now, but
 - Bortezomib inhibits proteasome degradation of I kappa B, the inhibitor of NF kappa B
 - Bortezomib was more active than doxorubicin in F4 HCC models
 - And additive with doxorubicin in HCC while synergistic in lymphoma

NF kappa B

- Bortezomib single agent in 20 German pts produced 7 stable diseases
- 2nd study is ongoing at Mayo clinic
- Bortezomib + doxorubicin is being studied in HCC in ECOG
 - Correlatives in serum should help us better understand how this works

HCC Conclusions

- Chemotherapy and other systemic therapies have had limited efficacy
 - We need to better understand in whom they can help
 - We may be able to utilize them more wisely
 - For now, should mostly be done on clinical trials
- With sorafenib, we have a first positive trial
 - A new standard regimen
 - Never compared to doxorubicin
 - Limited data in Child's B
 - There are hints that other similar agents may have activity
- Last, but not least, is RECIST relevant in this (or any other) disease