A Randomized Phase II Open Label Multi-Institution Study of the Combination of Bevacizumab (B) and Erlotinib (E) Compared to Sorafenib (S) in the First-Line Treatment of Patients (pts) With Advanced Hepatocellular Carcinoma (HCC)

Abstract 337

Thomas MB, Garett-Mayer E, Anis M, Anderton K, Benz T, Adelman A, Brisendine A, Duddalwar V, Weiss G, Siegel A, Bendell J, Baron A, El-Khoueiry A

Background

- HCC is the 3nd leading cause of cancer death worldwide, and one of the most rapidly increasing cancers in the United States and other Western countries.
- Most HCCs arise in the setting of liver cirrhosis from varied causes, including viral hepatitis infection, obesity and metabolic syndrome leading to hepatic steatosis, excessive alcohol consumption, and hemochromatosis.
- Most patients present with advanced disease that is not amenable to liver transplantation, surgical resection or liver-directed therapies, and thus require systemic therapy.
- Sorafenib, a multi-targeted tyrosine kinase inhibitor (TKI) has shown prolonged time-to-progression (5.5 vs 2.8 months) and overall survival (10.7 vs 7.9 months) in the SHARP trial, and is the only approved anti-cancer drug for HCC.

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Background

- HCC is a heterogeneous tumor with complex molecular carcinogenesis. Increased growth factor expression, including epidermal (EGF), hepatocyte (HGF), transforming (TGF), and vascular endothelial (VEGF) have been implicated in progression from normal liver to cirrhosis, dysplastic nodules (DN), to overt HCC. HCCs are hypervascular tumors and increased serum and tumor expression of VEGF and VEGF are poor prognostic features.

- Bevacizumab (B) is a mAb that binds circulating ligand of the transmembrane VEGF receptor; Erlotinib (E) is a TKI that inhibits EGFR signal transduction.

- Published single-arm trial data suggest clinical benefit from B+E in HCC.

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Study Design & Objectives

- This was an open-label randomized phase II, multi-institution, investigator-initiated study to investigate the combination of B+E and S as first-line treatment for patients with advanced HCC. Sample size of 90 evaluable patients.
- **Primary endpoint:** Estimate the HR for OS of B+E vs. S with its 95% confidence interval. A difference in OS favoring the B+E arm with a HR of 0.67 was expected and of interest, based on median OS for B+E and S of 15 and 10.7 months seen in previous trials.
- **Secondary endpoints:** Event-free survival (EFS), toxicity, and overall response rate (RR).
- Key Eligibility Criteria: Advanced HCC not amenable to transplant, resection, or liver-directed therapy; ECOG PS 0-2, Childs-Pugh A-B7, CLIP score ≤5, no prior systemic therapy, platelets ≥75,000/mm^3, total bilirubin up to 2.0 X ULN, transaminases up to 5 X ULN.

- **Treatment Plan:**
  - Patients were randomized 1:1 to receive S 400 mg orally twice daily, continuously, or B 10 mg/kg IV every 14 days and E 150 mg orally daily.
  - Treatment cycles were 28 days, restaging every 2 cycles by Investigator-assessed RR per RECIST 1.1 and subsequent independent radiologic review.

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Study Results

A total of 95 patients were registered, 43 pts in the S arm and 47 pts in the B+E arm
Pts who received at least 1 dose of study drug(s) and were evaluable

	Sorafenib (N = 43)	B+E (N = 47)	*P* value
Age	Median: 61 years Range: 44-81	Median: 61 years Range: 43-82	0.72
ECOG N(%)			0.44
0	17(40)	15(32)	
1	25(58)	32(68)	
2	1(2)	0	
Childs-Pugh M(%)			0.36
A	39(91)	39(83)	
B7	4(9%)	8(17)	
CLIP score N(%)			0.95
0	4(9)	7(15)	
1	10(23)	10(21)	
2	17(40)	17(36)	
3	7(16)	7(15)	
4-5	5(11)	6(13)	

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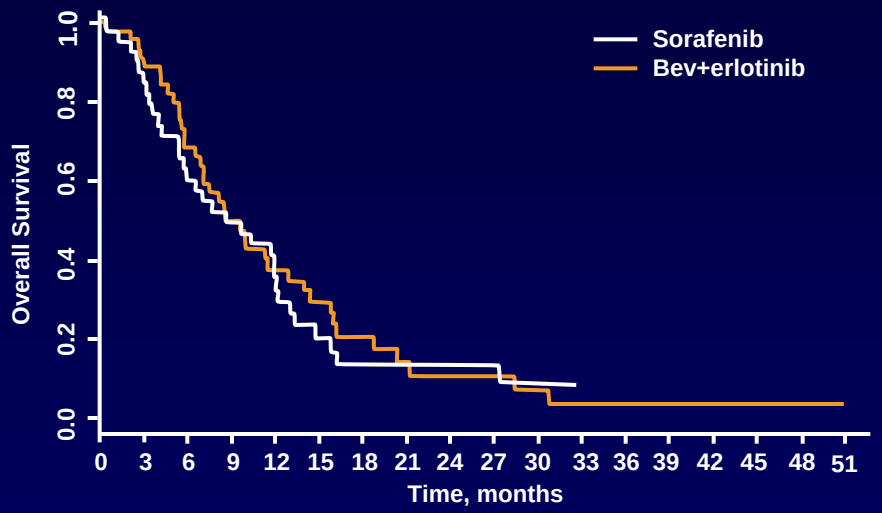
Study Efficacy: Overall Survival

Overall survival by treatment arm, all patients
HR = 0.92 (95% CI 0.57-1.47), favoring B+E vs sorafenib

	Sorafenib (N = 43)	B+E (N = 47)
Median survival	8.6 months (95% CI: 5.7-12.2 months)	8.6 months (95% CI: 7.0-13.9 months)
12 months survival	35% (95% CI: 22%-55%)	37% (95% CI: 25%-55%)



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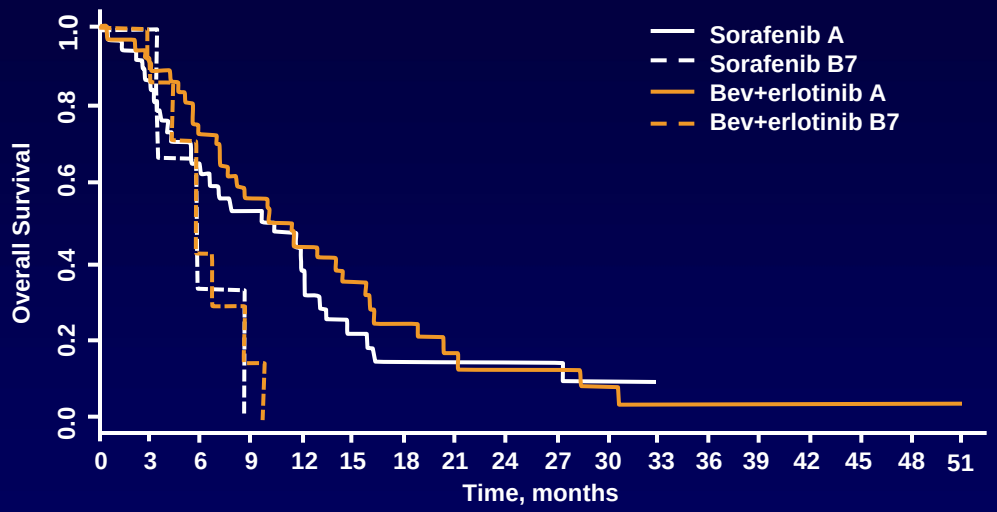
Study Efficacy: Overall Survival

Overall survival by treatment arm <u>for patients who are Childs-Pugh A</u>
***P* = .55 based on a logrank test**

	Sorafenib (N = 39)	B+E (N = 39)
Median survival	10.26 months (95% CI: 5.9-13.0 months)	11.4 months (95% CI: 7.5-16.0 months)
12 months survival	38% (95% CI: 25%-59%)	44% (95% CI: 31%-64%)



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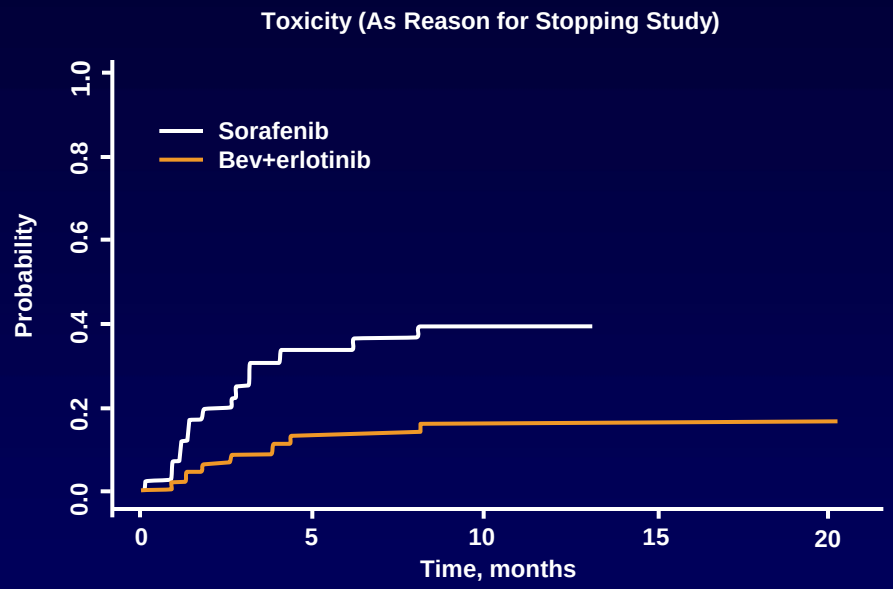
Study Results: Safety & Tolerability
Adverse Events (AE)

Adverse events – sorafenib		
AE Type	**Grade 3**	**Grade 4**
Fatigue	7	
Hyponatremia	6	
Pain	5	
Hand-foot skin reaction	4	
AST increase	4	
Hypertension	2	1

Adverse events – B+E		
AE Type	**Grade 3**	**Grade 4**
Pain	6	1
Rash	6	
Hemorrhage	3	1
Diarrhea	4	
AST increase	4	
Alk phos incr	4	



A competing risks analysis showed toxicity as a reason for stopping study treatment to be higher in th S arm.
HR for toxicity: 0.35 (*P* = .019)

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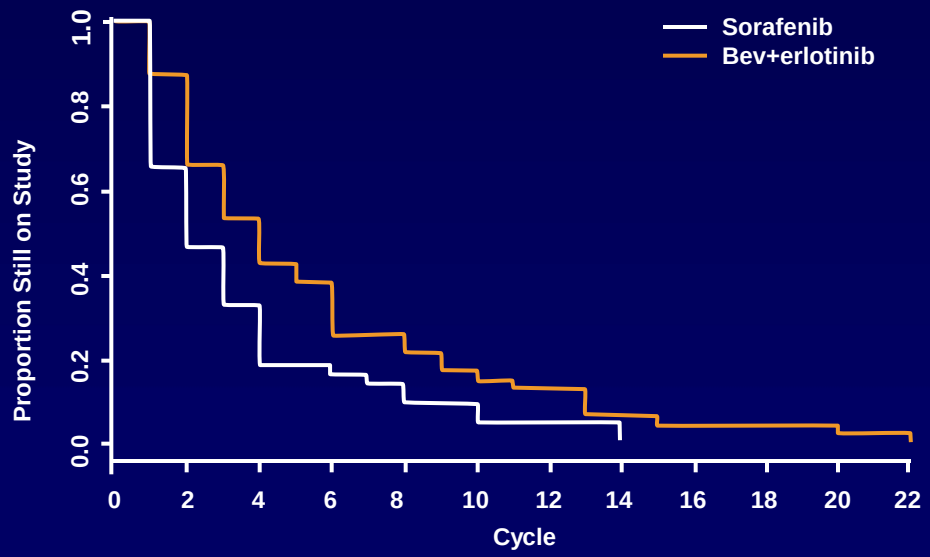
Study Results: Safety & Tolerability

Number of cycles of treatment and severe adverse events (SAEs): The plot below shows the time on treatment (ie, the number of cycles). Sorafenib patients discontinued treatment sooner than the B+E patients. Out of the 43 patients in the sorafenib arm, 15 (35%) received only one cycle of treatment. In the B+E arm, six out of 47 received only one cycle (13%).

The difference in curves is significant (*P* = .02) by a logrank test.



	Sorafenib (N = 43)	B+E (N = 47)
Number of cycles initiated per arm	150	261
Median number of cycles initiated	2	4
Total number of SAEs in treatment arm	21	30
SAE rate per cycle of treatment* (ie, Number of SAEs in treatment arm divided by number of cycles	21/150 = 0.14	30/261 = 0.11

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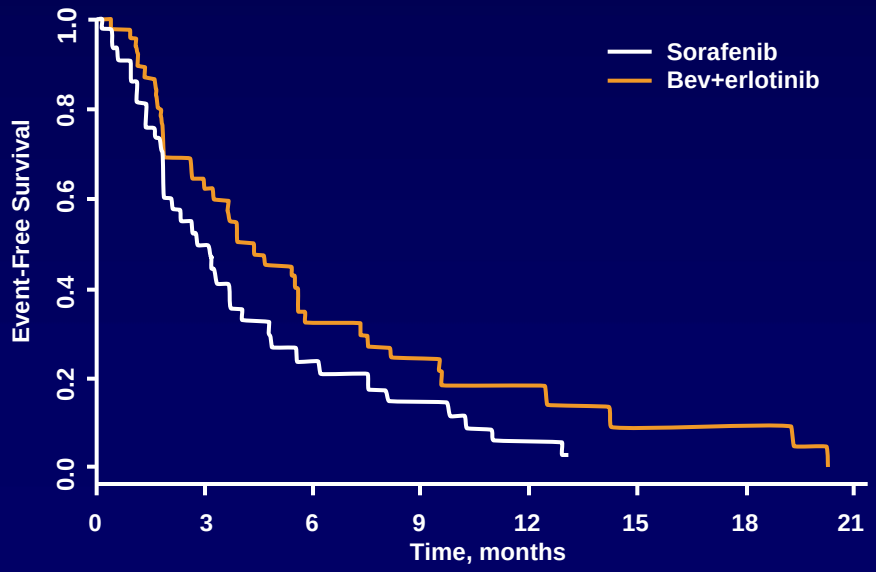
Study Efficacy: EFS

EFS: Defined as the time to treatment discontinuation due to progression, death, toxicity or other serious clinical events requiring treatment discontinuation

- B+E (N = 47); median EFS = 4.37 (95% CI: 2.99-7.36)
- S (N = 43); median EFS = 2.76 (95% CI: 1.84-4.80)
- HR = 0.67 (95% CI: 0.42, 1.07), *P* value = .09
- RR %: B+E 15% (95% CI: 6.2%-28%)
  S 9% (95% CI: 2.6%-22%)



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Conclusions

- This is the largest randomized, investigator-initiated first-line interventional clinical trial in HCC ever completed in the United States.
- Although the study did not meet its primary endpoint, the combination of bevacizumab and erlotinib shows clinically meaningful anti-tumor activity in advanced HCC patients, with overall survival similar to that of sorafenib.
- B+E is better tolerated than sorafenib based on the HR for toxicity and EFS.

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