

## Phase II Trial of Sorafenib in Combination with Capecitabine in Patients with Hepatocellular Carcinoma: INST 08-20

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Disclosures of potential conflicts of interest may be found at the end of this article.

### TRIAL INFORMATION

- **ClinicalTrials.gov Identifier:** NCT01032850
- **Sponsor(s):** Bayer Healthcare
- **Principal Investigator(s):** Yehuda Patt
- **IRB Approved:** Yes

### LESSONS LEARNED

- There continues to be a lack of systemic options for advanced hepatocellular carcinoma (HCC); sorafenib and, very recently, regorafenib are the only approved options. There exists a potential to combine sorafenib with chemotherapeutic agents shown to be active in HCC, such as capecitabine, safely.
- Good tumor response was observed, with objective improvement in a few patients seldom seen by single agent sorafenib; however, because of the limited number of patients, meaningful conclusions on survival cannot be drawn.

### ABSTRACT

**Background.** Sorafenib is the currently approved first-line treatment for hepatocellular carcinoma (HCC). Capecitabine has antitumor activity in hepatobiliary cancers. The combination of the two, if tolerated, could possibly improve antitumor response, and survival.

**Methods.** Patients with advanced HCC ineligible for locoregional therapy, Eastern Cooperative Oncology Group performance status of  $\leq 2$ , Child-Pugh class A or B-7 cirrhosis, hemoglobin  $\geq 8.5$  g/dL, platelets  $\geq 50,000/\mu\text{L}$ , absolute neutrophil count (ANC)  $\geq 1,500$  cells/ $\mu\text{L}$ , and serum creatinine of  $\leq 2.0$  mg/dL were recruited. All subjects received a combination of sorafenib and capecitabine, on a 14-day 7-days on 7-days off schedule. The primary end point was safety and secondary end points were overall survival (OS) and disease control rate.

**Results.** A total of 15 out of 47 patients met inclusion criteria. Median age was 64 years (56–79) and 77% were male. With a median follow-up of 12 months, median OS was 12.7 months (95% confidence interval [CI], 8.5–23.4). Disease control rate was 77% (complete response 8%, partial response 8%, and stable disease 61%). Common adverse events were as follows: (a) thrombocytopenia (64%); (b) anemia (14%); (c) hypophosphatemia (21%); (d) hypomagnesemia (14%); (e) hyperbilirubinemia (21%); (f) increased aspartate transaminase (AST) (14%); (g) hand-foot syndrome (21%); and (h) deep vein thrombosis (21%).

**Conclusion.** At tolerable doses, the combination of sorafenib and capecitabine seems an active and safe palliative treatment

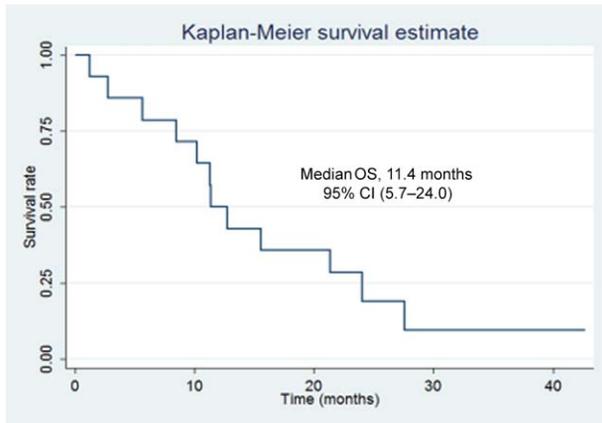
for HCC in class A and B-7 patients with cirrhosis. The small sample size does not allow comparison with single-agent sorafenib. *The Oncologist* 2017;22:1158–e116

### DISCUSSION

Sorafenib single agent continues to be the only U.S. Food and Drug Administration-approved systemic therapy for hepatocellular carcinoma (HCC) in 2017 since its approval almost 10 years ago. This study showed that the combination of sorafenib and capecitabine in patients with advanced HCC is an active and safe palliative regimen. The disease response rate observed in this study was higher than the outcomes reported by other studies using sorafenib as single agent [1, 2]. The small sample size did not allow determining if this observation translated into a better survival outcome as compared with single-agent sorafenib. Such a determination will require a randomized phase II trial.

Oral capecitabine has been used as single agent in hepatobiliary cancers, with a median overall survival of 10 months in patients with HCC and well tolerated in cirrhotic patients [3]. Other investigators have explored different combinations with capecitabine, including platinum-based agents and other biological agents targeting vascular endothelial growth factor (VEGF) [4–6]. All of these studies have shown comparable results with similar treatment toxicity profile.

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**Figure 1.** Kaplan-Meier estimate of OS.  
Abbreviations: CI, confidence interval; OS, overall survival.

Similar to data reported in previous studies [1, 2, 7], 46% of our patients had been pretreated with locoregional treatments. Transarterial chemoembolization was the most commonly used locoregional modality prior to the beginning of systemic therapy in our population; this observation is consistent with data previously reported by other investigators and the current standard of care guidelines for the management of intermediate-stage, unresectable, and multifocal HCC [2, 8, 9].

There were two exceptional responders in this study: one patient had a complete response that lasted 14 months, and

**Table 1.** Treatment tolerance by dose levels

Dose level information	0	-1	-2	-3	-4
Capecitabine	850 mg/m <sup>2</sup> b.i.d.	700 mg/m <sup>2</sup> b.i.d.	600 mg/m <sup>2</sup> b.i.d.	500 mg/m <sup>2</sup> b.i.d.	500 mg/m <sup>2</sup> once daily
Sorafenib	400 mg b.i.d.	400 mg b.i.d.	400 mg b.i.d.	200 mg b.i.d.	200 mg b.i.d.
No. of cycles at dose level	14	18	21	12	4
% of cycles	20.2%	26.0%	30.4%	17.3%	5.7%

another patient had a very good partial response for a duration of 11 months; this patient died of complications from cirrhosis while his cancer was still under good control.

The observed rate of serious adverse events was similar to the results from other studies, supporting the published data regarding the safety of sorafenib in Child-Pugh B patients [7, 10-12]. Moreover, the addition of capecitabine, with dose adjustment as tolerated, did not seem to increase the rate of serious adverse events; there were no treatment-related deaths, and dosage adjustments were performed as necessary (Table 1).

**TRIAL INFORMATION**

Disease	Hepatocellular carcinoma
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	No designated number of regimens
Type of Study – 1	Phase II
Type of Study – 2	Single arm
Primary Endpoint	Safety
Primary Endpoint	Tolerability
Secondary Endpoint	Overall response rate
Secondary Endpoint	Disease control rate

**Additional Details of Endpoints or Study Design**

The primary analyses for study endpoints were descriptive, and thus the sample size was not based on power analysis or precision level of estimate, but based on empirical considerations according to historical studies.

Investigator’s Analysis	Active and should be pursued further
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**DRUG INFORMATION FOR PHASE II STUDY**

<b>Drug 1</b>	
Generic/Working name	Capecitabine
Trade name	Xeloda
Company name	Genentech
Drug type	Small molecule
Drug class	Antimetabolite
Dose	500-850 milligrams (mg) per square meter (m <sup>2</sup> )
Route	Oral (p.o.)
Schedule of administration	Capecitabine and sorafenib were administered b.i.d., 2 weeks on and 2 weeks off

<b>Drug 2</b>	
Generic/Working name	Sorafenib
Trade name	Nexavar
Company name	Bayer and Onyx Pharmaceuticals
Drug type	Small molecule
Drug class	Multi-targeted kinase inhibitor
Dose	200–400 mg per flat dose
Route	Oral (p.o.)
Schedule of administration	Capecitabine and sorafenib were administered b.i.d., 2 weeks on and 2 weeks off

#### PATIENT CHARACTERISTICS FOR PHASE II STUDY

Number of Patients, Male	65
Number of Patients, Female	3
Stage	Not collected
Age	Median (range): 65 (58–80)
Number of Prior Systemic Therapies	Median (range): 0 (0–2)
Performance Status: ECOG	0–7 1–5 2–1 3– Unknown—
Other	Complete baseline demographic and disease characteristics are presented in Table 2.

#### PRIMARY ASSESSMENT METHOD FOR PHASE II STUDY

Assessment	47
Number of patients screened	47
Number of patients enrolled	15
Number of patients evaluable for toxicity	13
Number of patients evaluated for efficacy	13
Evaluation method	Response evaluation criteria in solid tumors (RECIST) 1.0
Response assessment CR	<i>n</i> = 1 (8%)
Response assessment PR	<i>n</i> = 1 (8%)
Response assessment SD	<i>n</i> = 8 (61%)
(Median) duration assessments OS	12.7 months, CI: 8.5–23.4

#### ADVERSE EVENTS: PHASE II STUDY

Name	All Dose Levels, All Cycles						All grades
	NC/NA	1	2	3	4	5	
Rash acneiform	92%	0%	0%	8%	0%	0%	8%
Alopecia	92%	0%	0%	8%	0%	0%	8%
Mucositis oral	92%	0%	0%	8%	0%	0%	8%
Skin and subcutaneous tissue disorders - Hand-foot syndrome	77%	0%	0%	23%	0%	0%	23%
Aspartate aminotransferase increased	85%	0%	0%	15%	0%	0%	15%
Blood bilirubin increased	77%	0%	0%	23%	0%	0%	23%
Hyponatremia	92%	0%	0%	8%	0%	0%	8%
Hypocalcemia	92%	0%	0%	8%	0%	0%	8%
Hypomagnesemia	85%	0%	0%	15%	0%	0%	15%
Hypophosphatemia	77%	0%	0%	23%	0%	0%	23%

Adverse events grade >3 at all dose levels, all cycles.

Abbreviation: NC/NA, no change from baseline/no adverse event.

## ASSESSMENT, ANALYSIS, AND DISCUSSION

## Completion

## Terminated Reason

## Investigator's Assessment

Study terminated before completion

Did not fully accrue

Active and should be pursued further

This study showed that the combination of sorafenib and capecitabine in patients with advanced hepatocellular carcinoma (HCC) is an active and safe palliative regimen. The disease response rate observed in this study was higher than the outcomes reported by other studies using sorafenib as single agent [1, 2]. The small sample size did not allow determining if this observation translated into a better survival outcome as compared with single-agent sorafenib. Such a determination will require a randomized phase II trial.

Oral capecitabine has been used as single agent in hepatobiliary cancers, with a median overall survival of 10 months in patients with HCC and well tolerated in cirrhotic patients [3]. Other investigators have explored different combinations with capecitabine, including platinum-based agents and other biological agents targeting vascular endothelial growth factor [4–6]. All of these studies have shown comparable results with similar treatment toxicity profile.

Similar to data reported in previous studies [1, 2, 7], 46% of our patients had been pretreated with locoregional treatments. Trans-arterial chemoembolization (TACE) was the most commonly used locoregional modality prior to the beginning of systemic therapy in our population; this observation is consistent with data previously reported by other investigators and the current standard of care guidelines for the management of intermediate-stage, unresectable, and multifocal HCC [2, 8, 9].

One patient had a prolonged complete response (CR) observed during the first 14 months since the beginning of the study regimen. The CR lasted for 11 months before disease progression (Figs. 2A, 2B, 3). Another patient on this trial experienced a good partial response and improvement in tumor

markers; however, this patient experienced worsening cirrhosis and died of complications of liver cirrhosis (Figs. 4A, 4B, 5).

Of note, this study population had a higher proportion of Child-Pugh class B; (B-7) patients compared with other studies (46% vs. 5% and 28% in the SHARP trial and GIDEON study, respectively), and similar prevalence of viral hepatitis infection and alcohol use in the HCC populations from North America analyzed in those same studies. The observed rate of serious adverse events was similar to the results from other studies, supporting the published data regarding the safety of sorafenib in Child-Pugh B patients [7, 10–12]. Moreover, the addition of capecitabine, with dose adjustment as tolerated, did not seem to increase the rate of serious adverse events.

Our study represents the first trial combining sorafenib and capecitabine in the management of advanced, unresectable HCC with findings supporting the activity and safety of this regimen. The small sample size does not allow comparison with single-agent sorafenib or capecitabine and/or in combination with other systemic treatments. Additional phase III data and studies of a larger scale will be necessary to determine if the combination of these two active agents might result in better survival outcomes when compared with the current standard of care.

## DISCLOSURES

**Cristhiam Rojas-Hernandez:** Daichii Sankyo (RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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FIGURES AND TABLES

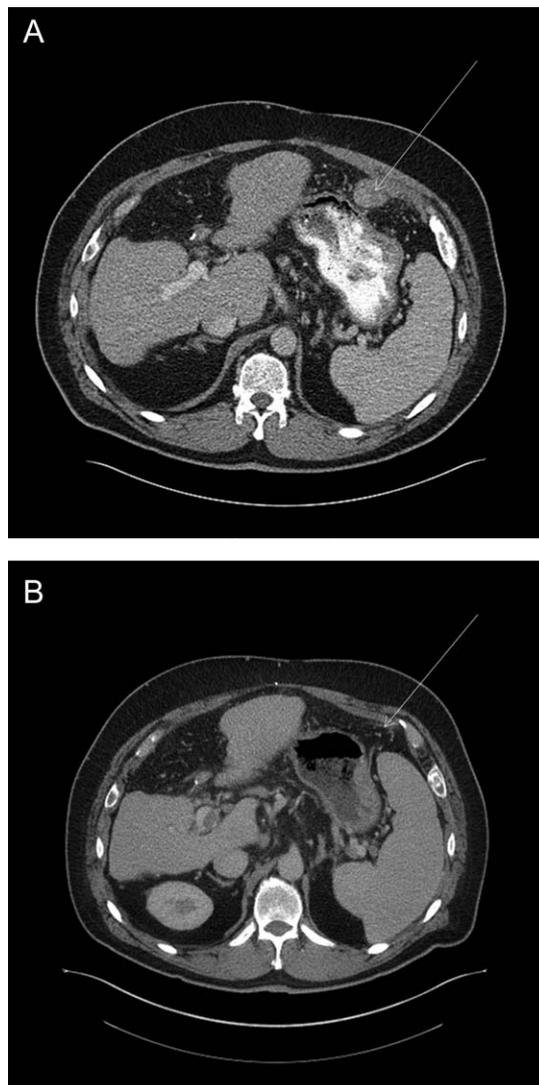


Figure 2. Patient 1. Pre-treatment (A) and post-treatment (B) computed tomography scan with a complete response.

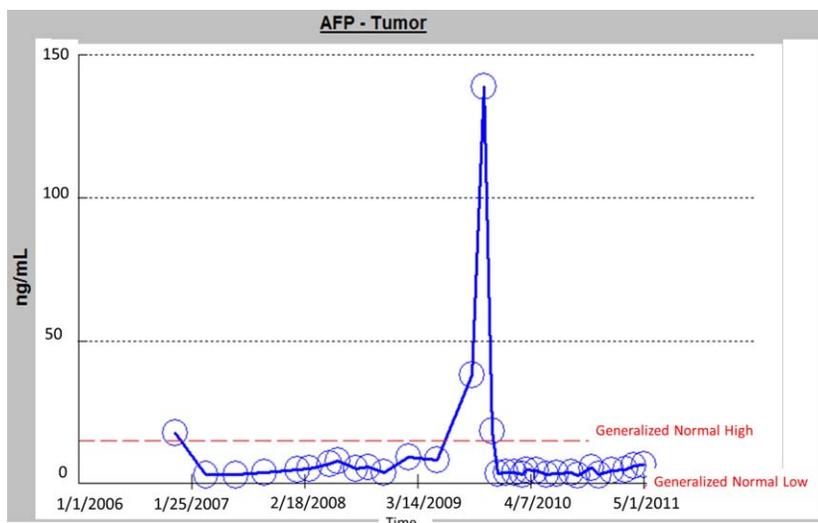
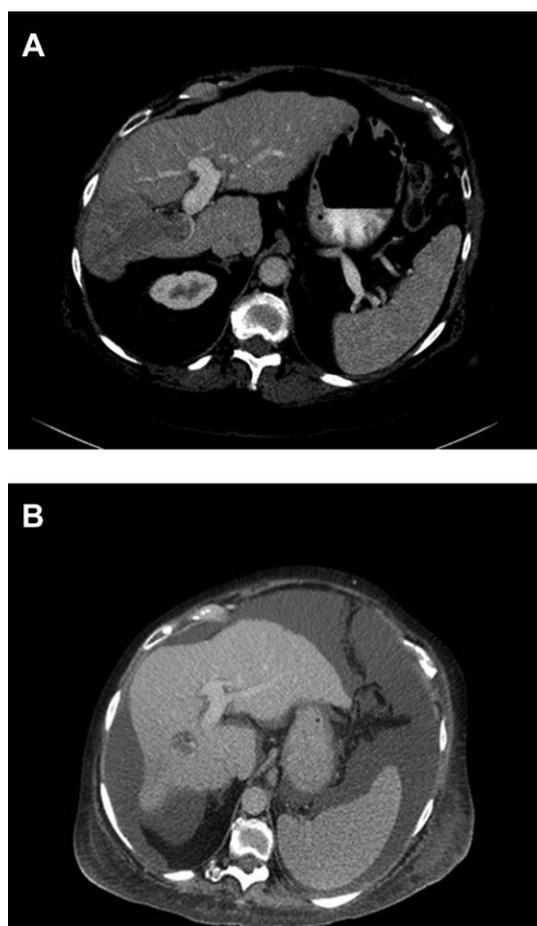
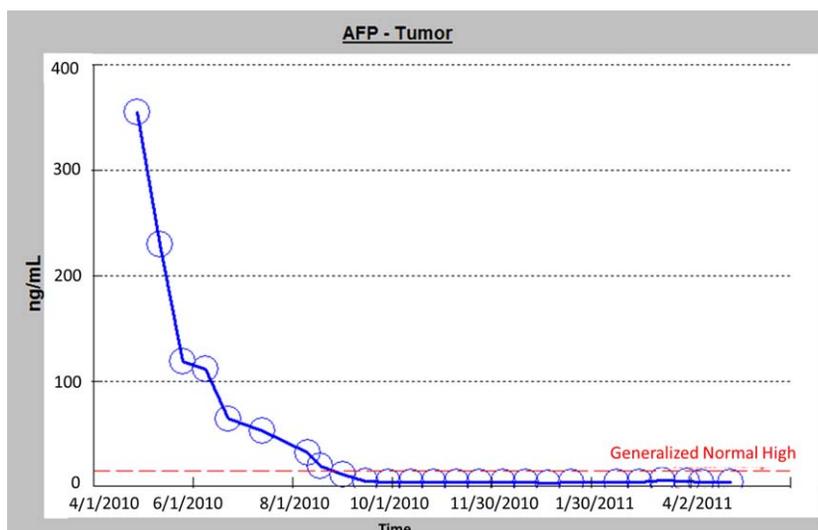


Figure 3. Corresponding alphafeto-protein (AFP) curve for patient 1. Corresponding to pre-treatment (Fig. 2A) and post-treatment (Fig. 2B) computed tomography scan with a complete response. Abbreviation: AFP, alphafeto-protein.



**Figure 4.** Patient 2. Pre-treatment (A) and post-treatment (B) partial response on computed tomography scan.



**Figure 5.** Corresponding AFP curve for patient 2. Corresponding to pre-treatment (Fig. 4A) and post-treatment (Fig. 4B) partial response on computed tomography scan.

Abbreviation: AFP, alphafeto-protein.

**Table 2.** Baseline demographic and disease characteristics

Demographic and disease characteristics	n (%)
Median age, years (range)	65 (58–80)
Male	10 (77%)
Female	3 (33%)
ECOG Performance Status	
0	7 (54%)
1	5 (38%)
2	1 (8%)
AJCC TNM Staging	
IIIA	2 (15%)
IIIB	1 (8%)
IVA	2 (15%)
IVB	8 (62%)
Prior therapies, median (range)	0 (0–2)
None	7 (54%)
TACE	4 (31%)
TACE plus sorafenib	2 (15%)
Cause of disease	
Viral hepatitis C only	7 (54%)
Viral hepatitis B only	1 (8%)
Viral hepatitis C & B	2 (15%)
Alcohol only	2 (15%)
Alcohol and viral hepatitis	4 (31%)
Child-Pugh class	
A	7 (54)
B-7	6 (46)
Bilirubin mg/dL, median (range)	1.0 (0.5–2.0)
Albumin g/dL, median (range)	3.6 (2.7–4.1)
Platelet count $\times 10^3/\mu\text{L}$ , median (range)	136 (54–356)
INR, median (range)	1.15 (1.04–1.62)
Alpha-fetoprotein ng/mL, median (range)	436 (3.6–36,300)

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; INR, international normalized ratio; TACE, trans-arterial chemoembolization; TNM, TNM classification of malignant tumors.

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