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Randomized, Multicenter, Open-Label Study of Oxaliplatin Plus Fluorouracil/Leucovorin Versus Doxorubicin As Palliative Chemotherapy in Patients With Advanced Hepatocellular Carcinoma From Asia

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ABSTRACT

Purpose
To determine whether FOLFOX4 (infusional fluorouracil, leucovorin, and oxaliplatin) administered as palliative chemotherapy to patients with advanced hepatocellular carcinoma (HCC) provides a survival benefit and efficacy versus doxorubicin.

Patients and Methods
This multicenter, open-label, randomized, phase III study in mainland China, Taiwan, Korea, and Thailand involved 371 patients age 18 to 75 years who had locally advanced or metastatic HCC and were ineligible for curative resection or local treatment. They were randomly assigned at a ratio of one to one to receive either FOLFOX4 (n = 184) or doxorubicin (n = 187). The primary end point was overall survival (OS); secondary end points included progression-free survival (PFS), response rate (RR) by RECIST (version 1.0), and safety.

Results
At the prespecified final analysis, median OS was 6.40 months with FOLFOX4 (95% CI, 5.30 to 7.03) and 4.97 months with doxorubicin (95% CI, 4.23 to 6.03; $P = .07$; hazard ratio [HR], 0.80; 95% CI, 0.63 to 1.02). Median PFS was 2.93 months with FOLFOX4 (95% CI, 2.43 to 3.53), and 1.77 months with doxorubicin (95% CI, 1.63 to 2.30; $P < .001$; HR, 0.62; 95% CI, 0.49 to 0.79). RR was 8.15% with FOLFOX4 and 2.67% with doxorubicin ($P = .02$). On continued follow-up, the trend toward increased OS with FOLFOX4 was maintained ($P = .04$; HR, 0.79; 95% CI, 0.63 to 0.99). Toxicity was consistent with previous experiences with FOLFOX4; proportions of grade 3 to 4 adverse events were similar between treatments.

Conclusion
Although the study did not meet its primary end point, the trend toward improved OS with FOLFOX4, along with increased PFS and RR, suggests that this regimen may confer some benefit to Asian patients, but an OS benefit cannot be concluded from these data.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the third most common cancer in Asia because of the high prevalence of its main etiologic agents: chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections.[1,2] The annual incidence of HCC in China alone contributes to 55% of global HCC cases.[1]

A large proportion of Asian patients with HCC present with locally advanced or metastatic disease, at which point they are ineligible for curative treatments.[3] Their prognosis is poor, with a median survival time of 3 to 4 months with supportive care.[4,5] Consequently, there is a significant unmet medical need for treatments for advanced HCC, both in Asia and worldwide.

HCC is known to be highly refractory to conventional systemic chemotherapy because of its heterogeneity and multiple etiologies.[6] Before the advent of the molecular-targeted agent sorafenib,[5,7] which has subsequently become the standard of care, no standard systemic drug or treatment regimen had shown an obvious survival benefit in HCC.[8,9]

At the time this study was designed, sorafenib was still undergoing clinical studies and had not been approved for use, and no systemic chemotherapy regimen had been definitively recommended as the standard for treating HCC. Clinical activity of several regimens containing oxaliplatin (OXA) in advanced HCC had been demonstrated in phase II studies.[10,11] In a phase II study of the FOLFOX4 (infusional fluorouracil [FU], leucovorin [LV], and OXA) regimen in Chinese patients with HCC, median overall survival (OS) was 12.4 months, mean time to progression was 2.0 months, and the response rate (RR) was 18.2%.[12,13] Together with the acceptable safety profile, these data warranted further investigation. Hence, the EACH (Oxaliplatin [Eloxatin] Plus FOLFOX4 Compared With Single-Agent Doxorubicin [Adriamycin] As Palliative Chemotherapy in Advanced Hepatocellular Carcinoma Patients) study was carried out to determine whether palliative chemotherapy with FOLFOX4, administered to patients with advanced HCC in Asia who were ineligible for curative resection or local treatment, could provide a survival benefit and greater efficacy compared with doxorubicin (DOX).

PATIENTS AND METHODS

Study Design

EACH was a prospective, international, multicenter, open-label, randomized, phase III study of FOLFOX4 versus DOX in patients with advanced HCC. Eligible patients enrolled by the investigators received a patient number and were randomly assigned to receive FOLFOX4 or DOX in a ratio of one to one. Random assignment, which was centralized, was generated by a statistician from the Virginia Contract Research Organization via an interactive voice randomization system. The study protocol was approved by the institutional review boards (IRBs) and/or independent ethics committees (IECs) of the participating institutions.

Patient Eligibility

Eligible patients were age 18 to 75 years; had histologically, cytologically, or clinically diagnosed unresectable HCC; and were ineligible for local invasive treatment. Clinically diagnosed patients had to have: (1) evidence of HBV or HCV with hepatic cirrhosis; (2) α-fetoprotein levels $\geq$ 400 μg/L; and (3) morphologic evidence of hypervascular liver tumor. Patients had to have at least one measurable lesion according to RECIST (version 1.0; $\geq$ 2 cm on computed tomography [CT]; $\geq$ 1 cm on spiral CT or magnetic resonance imaging).[14] Lesions that had undergone previous interventional or local therapy were not considered measurable lesions.

Previous treatment with chemotherapeutic agents or anticancer herbal treatments had to have been completed $\geq$ 4 weeks before random assignment. Previous adjuvant chemotherapy had to have been completed $>$ 12 months before random assignment.

Inclusion criteria were as follows: Karnofsky performance score $\geq$ 70; life expectancy $\geq$ 3 months; Barcelona Clinic liver cancer (BCLC) stage B or C disease; Child-Pugh stage A or B disease; and adequate organ and marrow function, with neutrophil count $\geq 1.5 \times 10^9$/L, platelet count $\geq 75 \times 10^9$/L, AST or ALT $< 2.5\times$ upper limit of normal (ULN), total bilirubin $< 1.5 \times$ ULN, international normalized ratio < 1.5, and normal baseline left ventricular ejection fraction $\geq$ lower limit of normal for the institution. Patients with AST and ALT $< 5\times$ ULN could be recruited if total bilirubin was in the normal range. Patients had to provide signed informed consent to participate.

Key exclusion criteria included: documented allergy to platinum compounds or other study drugs; any previous OXA or DOX treatment, except adjuvant treatment $>$ 12 months before random assignment; previous liver transplantation; concomitant use of any other anticancer therapy, including interferon alfa and herbal medicine approved by the local authority to be used as anticancer medicine (except palliative radiotherapy to a nontarget lesion); CNS metastasis; and other serious illness or medical condition.

Treatment

Patients received either FOLFOX4 (OXA 85 mg/m^2 intravenously [IV] on day 1; LV 200 mg/m^2 IV from hour 0 to 2 on days 1 and 2; and FU 400

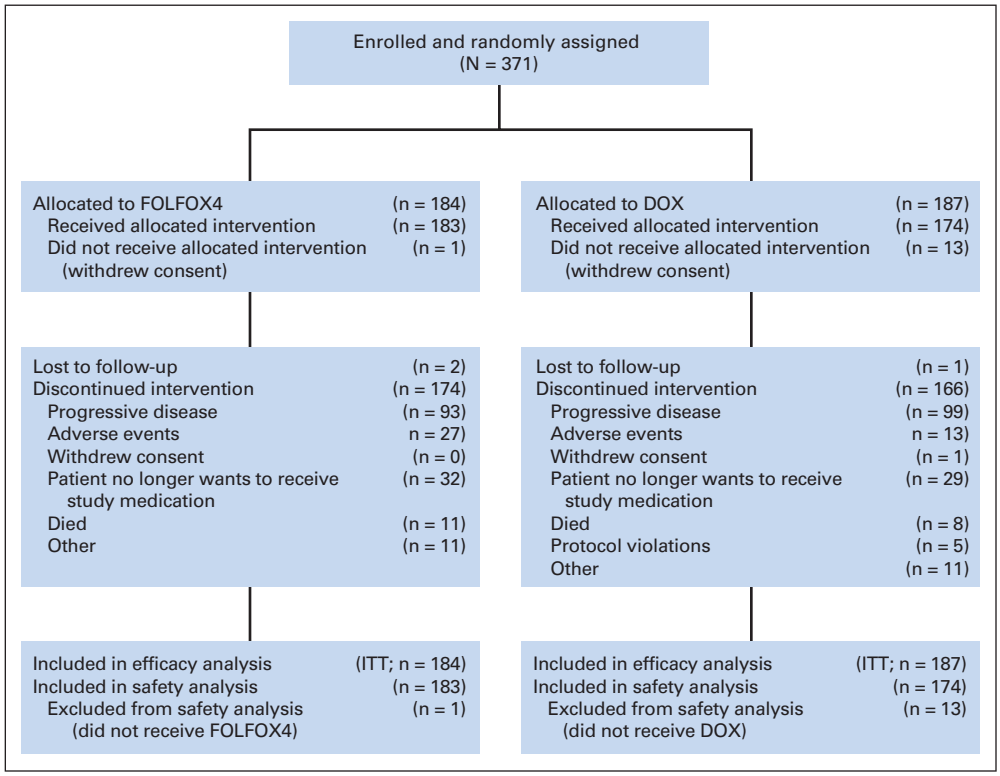

Fig 1. Flow diagram of patient disposition. DOX, doxorubicin; FOLFOX4, infusional fluorouracil, leucovorin, and oxaliplatin.

mg/m^2 IV bolus at hour 2, then 600 mg/m^2 over 22 hours on days 1 and 2, once every 2 weeks) or DOX (50 mg/m^2 IV, once every 3 weeks). Treatment was continued until disease progression, intolerable toxicity, or eligibility for surgical resection (ie, treatment phase). The follow-up phase began once a patient terminated the treatment phase.

Efficacy and Safety Analyses

Tumor evaluation via CT or magnetic resonance imaging scans using RECIST (version 1.0) was performed within 2 weeks before random assignment, every 6 weeks ± 1 week during the study treatment phase, and every 2 months ± 1 week during the follow-up phase at the patients' respective medical centers. All objective responses had to be confirmed via the same imaging method at least 4 weeks after their first observation. Physical, clinical, and laboratory examinations were performed at baseline, at the start of each chemotherapy cycle during the treatment phase, and at follow-up visits every 2 months. Patients were monitored for cardiac toxicity associated with DOX via ultracardiosonography and ECGs at baseline and as clinically indicated.

The primary end point was an intent-to-treat (ITT) analysis of OS with FOLFOX4 compared with single-agent DOX. OS was defined as the interval between the date of random assignment and date of death. Secondary end points included the efficacy of the two treatments with regard to progression-free survival (PFS; defined as the interval between random assignment and progression or death resulting from any cause), RR (according to RECIST 1.0), and secondary resection rate. Disease control rate (DCR) was also evaluated.

All randomly assigned patients were included in the ITT analysis of efficacy. Patients who were evaluable for safety had to have received at least one dose of study medication. Patients were observed every 2 months until death or until their final follow-up visit.

Prespecified interim analyses were carried out after 85 and 166 events (deaths) were observed. The prespecified final analysis was conducted on May 31, 2009, after 266 events had occurred (death event rate of approximately 71% of the final 371 patient cases). To further evaluate and confirm the reliability and robustness of the trend observed at the prespecified analysis using more matured OS data, the IRBs and IECs suggested that patients be continuously monitored via routine survival follow-up visits according to a schedule similar to that planned in the protocol. It was also suggested that one additional post hoc analysis (ie, follow-up analysis) be conducted after additional sufficient death events had occurred. Before conducting any post hoc analysis as suggested by the IRBs and IECs, the sponsor prospectively decided, based on the estimated event rate of progress, that the data cutoff date for this additional post hoc analysis should occur approximately 7 months after the final analysis, after 80% of events had occurred. The post hoc analysis was therefore conducted on December 31, 2009, after 305 events had occurred (death event rate of 82% of the final 371 patient cases). Presented here are the efficacy data from the prespecified final and post hoc follow-up analyses and the safety data from the prespecified final analysis.

Statistical Analyses

The efficacy parameters of OS and PFS were compared between the two treatment arms in the ITT population using a stratified log-rank test procedure at overall 5% significance level. Stratification factors were patients' countries, BCLC stage, and disease status, as specified at the time of random assignment. The survival curves were estimated using the Kaplan-Meier method. Medians and corresponding 95% CIs were also provided by treatment arm. Significance levels were calculated using a group sequential approach, with efficacy boundaries based on an O'Brien-Fleming alpha spending function that took into account two interim analyses of OS.

RR was compared between the two treatments using the Cochran-Mantel-Haenszel test stratified by country, BCLC stage, and disease status at the time of random assignment. RR, DCR, and secondary resection rates were also compared between the two treatment arms using the χ^2 test or Fisher's exact test.

For analysis of safety data, adverse events (AEs), hematologic toxicity, general physical examinations, special examinations, and laboratory data were described and analyzed for the safety population.

Table 1. Baseline Patient Demographics and Clinical Characteristics in ITT Population

Characteristic	FOLFOX4 (n = 184) No.	FOLFOX4 (n = 184) %	DOX (n = 187) No.	DOX (n = 187) %
Age, years				
Mean		49.53		49.30
SD		10.77		10.80
Sex				
Male	166	90.22	163	87.17
Female	18	9.78	24	12.83
Weight, kg				
Mean		61.45		62.98
SD		9.24		9.94
HBV infection	171	92.93	168	89.84
HCV infection	9	4.97	16	8.60
Liver cirrhosis	102	55.74	100	53.48
Duration of disease, years				
Mean		0.66		0.66
SD		1.57		1.57
Disease status				
Tumor confined to liver	80	43.48	75	40.11
Metastatic disease	104	56.52	112	59.89
Child-Pugh stage				
A	163	88.59	163	87.17
B	21	11.41	24	12.83
BCLC stage				
B	39	21.20	35	18.72
C	145	78.80	152	81.28
Primary tumor stage*				
T0	1	0.54	2	1.07
T1	16	8.70	12	6.42
T2	16	8.70	24	12.83
T3	123	66.85	118	63.10
T4	20	10.87	20	10.70
TX	8	4.35	11	5.88
Regional lymph node stage*				
N0	127	69.02	130	69.52
N1	46	25.00	41	21.93
NX	11	5.98	16	8.56
Distant metastasis stage*				
M0	80	43.48	74	39.57
M1	104	56.52	112	59.89
MX	0	0.00	1	0.53
Disease stage*				
I	8	4.35	2	1.07
II	7	3.80	11	5.88
IIIA	51	27.72	51	27.27
IIIB	6	3.26	2	1.07
IIIC	8	4.35	9	4.81
Surgery	48	26.09	50	26.74
Radiotherapy	12	6.52	18	9.63
Chemotherapy				
Previously treated	38	20.65	56	29.95
Naive	146	79.35	171	70.05
Local treatment to target lesion				
TACE/TAE	65	35.33	70	37.43
Ethanol injection	10	5.43	10	5.35
RFA	9	4.89	13	6.95
Other	5	2.72	8	4.28

Abbreviations: BCLC, Barcelona Clinic liver cancer; DOX, doxorubicin; FOLFOX4, infusional fluorouracil, leucovorin, and oxaliplatin; HBV, hepatitis B virus; HCV, hepatitis C virus; ITT, intent to treat; RFA, radiofrequency ablation; SD, standard deviation; TACE, transarterial chemoembolization; TAE, transarterial embolization.

*American Joint Committee on Cancer staging.

The sample size was calculated as follows: when the sample size in each group was at least 200, or the total number of events was > 249, a 5% significance level two-sided log-rank test for equality of survival curves had an 80% power to detect the difference between 43% OS with FOLFOX4 and 30% OS with DOX at 1 year, with a constant hazard ratio (HR) of 0.70.

RESULTS

Patient Characteristics and Treatment

Between March 15, 2007, and May 31, 2009, 371 patients were randomly assigned to receive either FOLFOX4 (n = 184) or DOX (n = 187) at 38 centers in four Asian countries (ITT population; Fig 1). Seventy percent of patients were recruited in mainland China, 5% in Taiwan, 14% in Korea, and 11% in Thailand (Appendix Table A1, online only). Of these, 14 patients did not take the study medication (FOLFOX4, n = 1; DOX, n = 13) and were therefore excluded from the safety analysis. The last patient's final follow-up visit took place on May 14, 2011.

Patient demographics and baseline disease characteristics were well matched between the study groups (Table 1). The most common prior local therapy was transarterial chemoembolization (TACE), and the mean number of cycles (± standard deviation [SD]) of TACE/transarterial embolization received was 2.77 ± 2.20 cycles in the FOLFOX4 arm and 3.46 ± 2.78 cycles in the DOX arm ($P = .11$).

The median number of treatment cycles received was four (range, one to 18 cycles) for FOLFOX4 and two (range, one to 14 cycles) for DOX. The average percentage of projected dose-intensity (± SD) was 84.89% ± 11.94% and 93.01% ± 8.46% in the FOLFOX4 and DOX arms, respectively.

Efficacy

At both the first and second interim analyses, the median OS was greater with FOLFOX4 than with DOX (Figs 2A and 2B; $P = .01$; HR, 0.56; 95% CI, 0.35 to 0.89; and $P = .02$; HR, 0.69; 95% CI, 0.50 to 0.94, respectively). At the prespecified final analysis, the median OS in the ITT population was 6.40 months with FOLFOX4 (95% CI, 5.30 to 7.03) compared with 4.97 months with DOX (95% CI, 4.23 to 6.03). A trend toward increased survival with FOLFOX4 was observed (Fig 2C; $P = .07$; HR, 0.80; 95% CI, 0.63 to 1.02). At the follow-up analysis 7 months later, this trend toward increased survival with FOLFOX4 was

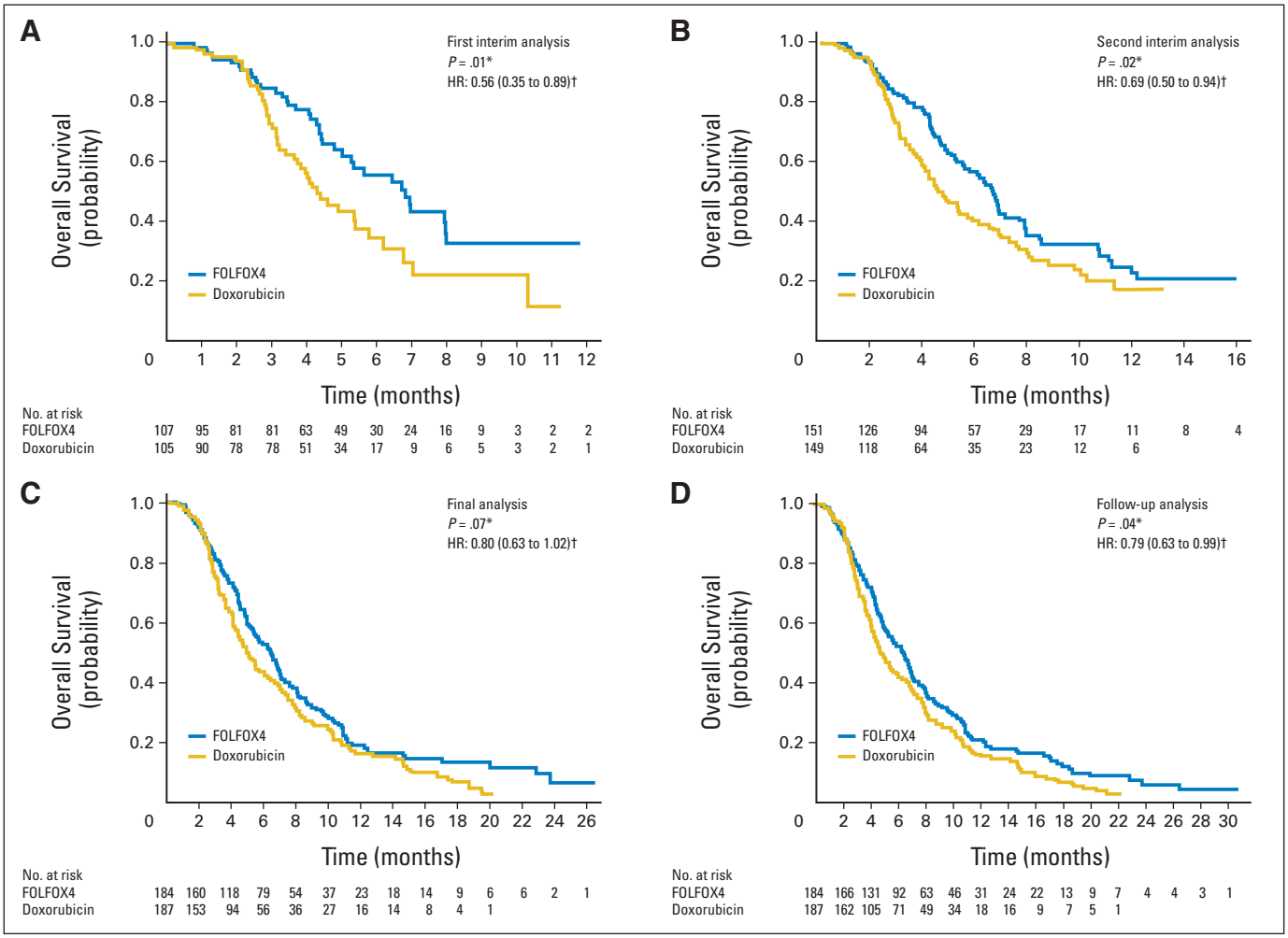

Fig 2. Kaplan-Meier curves showing median overall survival in the intent-to-treat population at (A) first interim, (B) second interim, (C) final, and (D) follow-up analyses. (*) Stratified log-rank test. (†) Hazard ratio (HR) was obtained from Cox model, stratified by country, Barcelona Clinic liver cancer stage, and disease status. FOLFOX4, infusional fluorouracil, leucovorin, and oxaliplatin.

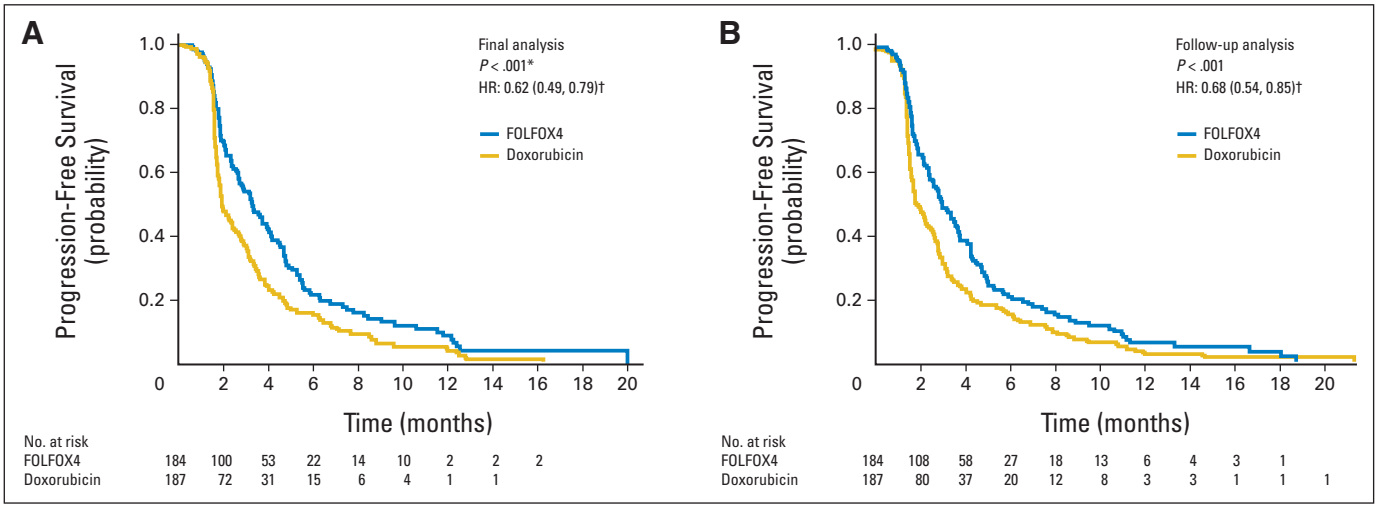

Fig 3. Kaplan-Meier curves showing median progression-free survival in the intent-to-treat population at (A) final and (B) follow-up analyses. (*) Stratified log-rank test. (†) Hazard ratio (HR) was obtained from Cox model, stratified by country, Barcelona Clinic liver cancer stage, and disease status. FOLFOX4, infusional fluorouracil, leucovorin, and oxaliplatin.

maintained (Fig 2D; $P = .04$; HR, 0.79; 95% CI, 0.63 to 0.99). Median OS was 6.47 months (95% CI, 5.33 to 7.03) with FOLFOX4 and 4.90 months (95% CI, 4.2 to 6.03) with DOX.

The median PFS in the ITT population at the prespecified final analysis was 2.93 months (95% CI, 2.43 to 3.53) with FOLFOX4, which was longer than that with DOX (1.77 months; 95% CI, 1.63 to 2.30; $P < .001$; HR, 0.62; 95% CI, 0.49 to 0.79; Fig 3A). The statistically significant improvement in median PFS with FOLFOX4 was maintained at the follow-up analysis (Fig 3B; $P < .001$; HR, 0.68; 95% CI, 0.54 to 0.85).

The RR and DCR observed in the FOLFOX4 arm at the prespecified final analysis were greater than those observed with DOX (Table 2; $P = .02$ and $P < .001$, respectively); these improved RRs in the FOLFOX4 arm were consistently maintained at the follow-up analysis (Table 2). Only one patient (in the FOLFOX4 arm) underwent secondary resection.

Safety

No statistically significant differences between treatments was seen for the overall number of patients who reported AEs, the number of patients reporting AEs of grade ≥ 3 severity, serious AEs, deaths, or discontinuations (Table 3). The most common treatment-related nonhematologic AEs reported in the FOLFOX4 study arm were nausea, AST elevation, and anorexia (Table 3), whereas alopecia, AST elevation, and nausea were the AEs most commonly reported in the DOX arm. No differences in cardiac toxicity were observed between the two treatment arms. α-fetoprotein levels changed from normal to

Table 2. Disease Response in ITT Population at Prespecified Final and Follow-Up Analyses

	Final Analysis					Follow-Up Analysis				
	FOLFOX4 (n = 184)		DOX (n = 187)			FOLFOX4 (n = 184)		DOX (n = 187)		
Parameter	No.	%	No.	%	*P**	No.	%	No.	%	*P**
RR†	15	8.15	5	2.67	.02	16	8.70	5	2.67	.01
95% CI	4.63 to 13.09		0.87 to 6.13			5.05 to 13.74		0.36 to 6.13		
DCR‡	96	52.17	59	31.55	< .001	98	53.26	61	32.62	< .001
95% CI	45.78 to 60.64		25.96 to 39.84			45.78 to 60.64		25.96 to 39.84		
CR§	0	0.00	0	0.00		0	0.00	0	0.00	
PR§	15	8.15	5	2.67		16	8.70	5	2.67	
SD§	81	44.02	54	28.88		82	44.57	56	29.95	
PD§	54	29.35	76	40.64		54	29.35	76	40.64	
Not evaluable	34	18.48	52	27.81		32	17.39	50	26.74	

Abbreviations: CR, complete response; DCR, disease control rate; DOX, doxorubicin; FOLFOX4, infusional fluorouracil, leucovorin, and oxaliplatin; PD, progressive disease; PR, partial response; RR, response rate; SD, stable disease.
*Cochran-Mantel-Haenszel test.
†Defined as CR plus PR.
‡Defined post hoc as CR plus PR plus SD.
§*P* values not determined for individual parameters.

Table 3. Treatment-Emergent AEs in Safety Population

Summary of Safety Events	FOLFOX4 (n = 183) No.	FOLFOX4 (n = 183) %	DOX (n = 174) No.	DOX (n = 174) %	P
Any AE	173	94.54	159	91.38	.24
AE grade ≥ 3	102	55.74	79	45.40	.05
Any SAE	34	18.58	27	15.52	.44
Death resulting from SAE	11	6.01	9	5.17	.73
Discontinuation	42	22.95	30	17.24	.18

	All AEs				Grade 3 to 4 AEs			
	FOLFOX4 (n = 183)		DOX (n = 174)		FOLFOX4 (n = 183)		DOX (n = 174)	
Individual AEs	No.	%	No.	%	No.	%	No.	%
Hematologic								
Neutropenia	126	68.85	87	50.00	56	30.60	40	22.99
Leukocytopenia	108	59.02	70	40.23	16	8.74	17	9.78
Thrombocytopenia	111	60.66	51	29.31	14	7.65	11	6.32
Anemia	79	43.17	79	45.40	9	4.91	14	8.04
Nonhematologic								
Nausea	75	40.98	48	27.59	0	0.00	0	0.00
AST	58	31.69	50	28.74	22	11.96	21	12.07
Anorexia	49	26.78	36	20.69	2	1.09	0	0.00
Vomiting	41	22.40	29	16.67	2	1.09	0	0.00
ALT	40	21.86	32	18.39	7	3.82	6	3.45
Bilirubin	37	20.22	27	15.52	7	3.82	9	5.17
Fatigue	32	17.49	17	9.77	2	1.09	1	0.57
Diarrhea	29	15.85	18	10.34	4	2.17	3	1.72
Sensory neuropathy	28	15.30	1	0.57	1	0.54	0	0.00
Alopecia	15	8.20	76	43.68	1	0.54	9	5.17
Allergy	8	4.37	1	0.57	2	1.09	0	0.00
Febrile neutropenia	7	3.82	6	3.44	3	1.63	6	3.44

Abbreviations: AE, adverse event; DOX, doxorubicin; FOLFOX4, infusional fluorouracil, leucovorin, and oxaliplatin; SAE, serious AE.

abnormal in 1.63% of patients receiving FOLFOX4 and 2.67% of patients receiving DOX.

DISCUSSION

To our knowledge, the EACH study is the first large, international, multicenter phase III study of systemic chemotherapy and of the FOLFOX4 regimen in advanced HCC. Although the primary end point of OS benefit with FOLFOX4 did not reach statistical significance at the prespecified end point, FOLFOX4 showed increased OS compared with DOX throughout the study; this was maintained on continued follow-up 7 months later.

Efficacy was demonstrated at the prespecified final analysis, when FOLFOX4 treatment was associated with increased median PFS, RR, and DCR versus DOX; these statistically significant efficacy outcomes with FOLFOX4 were also maintained at follow-up. Hence, FOLFOX4 may offer some clinical benefit to patients with advanced, inoperable HCC, although an OS benefit could not be concluded from these data.

Toxicity in this study was consistent with previous experience with FOLFOX4 for metastatic colorectal cancer in Asian[12,15] and Western[16] patients. Although high toxicity was previously reported with a regimen of floxuridine, leucovorin, DOX, and cisplatin in patients with HBV and HCV,[17] the proportions of AEs reported at grade 3 to 4 severity in this study were similar between treatments, despite the high proportion of patients (> 90%) who had hepatitis; AEs could be well managed.

The open-label design was a study limitation, but it was unavoidable because the regimens had different appearances and were administered differently, and it was felt to be unethical to subject the patients to the additional dummy IV infusions and extra hospital visits that would have been required for a blinded protocol. At the time this study was designed, DOX had become a default standard of treatment, and sorafenib was not yet available. Furthermore, DOX had served as a control agent for several comparative trials of single agents and combination regimens.[18-21] Therefore, it seemed reasonable to use DOX as the control agent for this study. Clinical studies with single-agent DOX have involved dosages of 40 to 75 mg/m^2.[22,23] The subtherapeutic dose of 50 mg/m^2 every 3 weeks was chosen for safety reasons, because Asian patients with advanced HCC frequently have HBV and liver cirrhosis with impaired liver function, and DOX toxicity can be high; a drug-related mortality rate of 25% was reported with doses of DOX 60 to 75 mg/m^2 in Asian patients.[23] Another Asian study, published shortly before the EACH study was designed, showed a drug-related mortality rate of 3% in those treated with DOX 60 mg/m^2.[20]

Another study limitation was that statistical significance was not achieved for the primary end point (ie, OS) at the prespecified final analysis. However, compared with DOX, increased OS was observed with FOLFOX4 at all analysis time points throughout the study, including the post hoc follow-up analysis conducted 7 months after the prespecified end point. Moreover, prespecified subgroup analyses showed that statistically significant OS benefits with FOLFOX4 were achieved in those with metastatic disease (data not shown; $P = .03$); chemotherapy is generally less effective in localized HCC.[24] A third limitation was that the RR was determined from CT scans by the investigators rather than by central review, and radiologists were not blinded to patients' treatment.

In 2007, sorafenib was the first systemic therapy to prolong survival in patients with advanced HCC,[7] and it has subsequently become the new reference standard for systemic treatment of patients with advanced HCC. However, in pivotal phase III studies, the survival benefits of sorafenib were more modest in Asian[5] than in Western[7] patients, and the objective RRs were low (2% to 3%), with no complete responses observed. When the OS data of the EACH study are viewed in comparison with those of the SHARP (Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol)[7] and the Asia Pacific[5] studies of sorafenib, it should be taken into account that the EACH study patients were more heavily pretreated at baseline, and a greater proportion had poor prognostic factors. In the EACH study, 25% of patients had received prior chemotherapy versus < 1% in SHARP, and 36% had received a mean of three TACE cycles versus 29% in SHARP (number of cycles was not specified). Pretreatment was not described for the Asia Pacific sorafenib study,[5] but in the EACH study, more patients had HBV (91% *v* 73% in the Asia Pacific study), and fewer were Child-Pugh A (88% *v* 97%). In a retrospective comparison of sorafenib versus cytotoxic chemotherapy in Korean patients with advanced HCC, the efficacy of conventional chemotherapy was not inferior to that of sorafenib.[25] A phase II study in a HBV-endemic Asian population showed that patients with extrahepatic disease were significantly less likely to benefit from single-agent sorafenib.[26] By contrast, in the EACH study, statistically significant

survival benefits were seen with FOLFOX4 in patients who had metastatic disease.

The tolerability of sorafenib in Asian patients may also be of concern because of the high incidence of hand-foot-skin reaction; all-grade events have been reported in 21% to 73% of Asian patients.[5,27-30] An increased risk of all-grade bleeding events compared with placebo or control was also reported in a meta-analysis of sorafenib and sunitinib clinical studies in HCC.[31] Although sorafenib has been approved for the treatment of advanced HCC, it is not yet widely used in Asia, mainly because of cost, and lower doses are often used to improve tolerability.[28]

Nevertheless, because HCC is a heterogeneous disease with complex molecular and genetic pathogeneses, and so many key carcinogenic pathways play pivotal roles in its development and metastasis, future treatment options will most likely involve a regimen that combines a molecular-targeted therapy, like sorafenib, with systemic chemotherapy like OXA. A phase II study of sorafenib combined with OXA and capecitabine (SECOX) in Hong Kong patients with advanced HCC showed promising results: median TTP was 7.1 months, and median OS was 10.2 months, although 73% of patients reported hand-foot-skin reaction.[30]

In conclusion, patients with advanced HCC have a poor prognosis, with a median survival time of 6 to 9 months in Western countries and only 3 to 4 months with supportive care in East Asian countries.[5,28] These differences in survival are attributable to regional differences between etiologic factors, staging, clinical manifestation, and management strategy.[3,24,28] Because of the limited efficacy, expense, and unresolved issues regarding the optimal use of sorafenib in Asians, and because the majority of advanced HCC cases are seen in these populations, there remains a substantial unmet need for more-effective treatment options. Although this study did not meet its primary end point, and an OS benefit cannot be concluded from these data, the data presented here do show that FOLFOX4 may confer some benefit to Asian patients with advanced, inoperable HCC and may provide another useful treatment option. The observed absolute increase in OS of 1.47 months with FOLFOX4 was not insignificant in Asian patients whose prognosis for survival was only 3 to 4 months. The findings from this study, along with the body of evidence supporting OXA use, has led to FOLFOX4 being included in the Chinese national clinical practice guidelines for treatment of primary liver cancer as one of the systemic chemotherapy options for advanced HCC.[32]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Yuen MF, Hou JL, Chutaputti A: Hepatocellular carcinoma in the Asia Pacific region. J Gastroenterol Hepatol 24:346-353, 2009
2. Jemal A, Bray F, Center MM, et al: Global cancer statistics. CA Cancer J Clin 61:69-90, 2011
3. Yang T, Lu JH, Wu MC: Hepatocellular carcinoma in China. Student BMJ 18:c1026, 2010
4. Chow PK, Tai BC, Tan CK, et al: High-dose tamoxifen in the treatment of inoperable hepatocellular carcinoma: A multicenter randomized controlled trial. Hepatology 36:1221-1226, 2002
5. Cheng AL, Kang YK, Chen Z, et al: Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 10:25-34, 2009
6. Zhu AX: Systemic therapy of advanced hepatocellular carcinoma: How hopeful should we be? Oncologist 11:790-800, 2006
7. Llovet JM, Ricci S, Mazzaferro V, et al: Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359:378-390, 2008
8. Nowak AK, Chow PK, Findlay M: Systemic therapy for advanced hepatocellular carcinoma: A review. Eur J Cancer 40:1474-1484, 2004
9. Thomas MB, Zhu AX: Hepatocellular carcinoma: The need for progress. J Clin Oncol 23:2892-2899, 2005
10. Yen Y, Lim DW, Chung V, et al: Phase II study of oxaliplatin in patients with unresectable, metastatic, or recurrent hepatocellular cancer: A California Cancer Consortium Trial. Am J Clin Oncol 31: 317-322, 2008
11. Louafi S, Boige V, Ducreux M, et al: Gemcitabine plus oxaliplatin (GEMOX) in patients with advanced hepatocellular carcinoma (HCC): Results of a phase II study. Cancer 109:1384-1390, 2007
12. Qin S, Wang YJ, Wu Q, et al: Phase II study of oxaliplatin + 5-fluorouracil/leucovorin in patients with unresectable hepatocellular carcinoma. Presented at the ASCO Gastrointestinal Cancers Symposium, Orlando, FL, January 19-21, 2007 (abstr 151)
13. Qin SK, Cao MR, Qian J, et al: Clinical study of FOLFOX regimen for the patients with advanced hepatocellular carcinoma [in Chinese]. Chin Clin Oncol 10:58-60, 2005
14. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors: European Organisation for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205-216, 2000
15. Fuse N, Doi T, Ohtsu A, et al: Feasibility of oxaliplatin and infusional fluorouracil/leucovorin (FOLFOX4) for Japanese patients with unresectable metastatic colorectal cancer. Jpn J Clin Oncol 37: 434-439, 2007
16. Goldberg RM, Tabah-Fisch I, Bleiberg H, et al: Pooled analysis of safety and efficacy of oxaliplatin plus fluorouracil/leucovorin administered bimonthly in elderly patients with colorectal cancer. J Clin Oncol 24:4085-4091, 2006
17. Patt YZ, Charnsangavej C, Yoffe B, et al: Hepatic arterial infusion of floxuridine, leucovorin, doxorubicin, and cisplatin for hepatocellular carcinoma: Effects of hepatitis B and C viral infection on drug toxicity and patient survival. J Clin Oncol 12: 1204-1211, 1994
18. Llovet JM, Burroughs A, Bruix J: Hepatocellular carcinoma. Lancet 362:1907-1917, 2003
19. Rampone B, Schiavone B, Martino A, et al: Current management strategy of hepatocellular

carcinoma. World J Gastroenterol 15:3210-3216, 2009

20. Yeo W, Mok TS, Zee B, et al: A randomized phase III study of doxorubicin versus cisplatin/interferon alpha-2b/doxorubicin/fluorouracil (PIAF) combination chemotherapy for unresectable hepatocellular carcinoma. J Natl Cancer Inst 97:1532-1538, 2005

21. Abou-Alfa GK, Johnson P, Knox JJ, et al: Doxorubicin plus sorafenib vs doxorubicin alone in patients with advanced hepatocellular carcinoma: A randomized trial. JAMA 304:2154-2160, 2010

22. Burroughs A, Hochhauser D, Meyer T: Systemic treatment and liver transplantation for hepatocellular carcinoma: Two ends of the therapeutic spectrum. Lancet Oncol 5:409-418, 2004

23. Lai CL, Wu PC, Chan GC, et al: Doxorubicin versus no antitumor therapy in inoperable hepatocellular carcinoma: A prospective randomized trial. Cancer 62:479-483, 1988

24. Hsu C, Shen YC, Cheng CC, et al: Geographic difference in survival outcome for advanced hepatocellular carcinoma: Implications on future clinical trial design. Contemp Clin Trials 31:55-61, 2010

25. Lee S, Yoon S, Shin S, et al: Sorafenib versus cytotoxic chemotherapy for patients with advanced hepatocellular carcinoma: A retrospective, single-institution study. Presented at the ASCO Gastrointestinal Cancers Symposium, San Francisco, CA, January 20-22, 2011 (abstr 339)

26. Yau T, Chan P, Ng KK, et al: Phase 2 open-label study of single-agent sorafenib in treating advanced hepatocellular carcinoma in a hepatitis B-endemic Asian population: Presence of lung metastasis predicts poor response. Cancer 115:428-436, 2009

27. Lee HC: Systemic chemotherapy of hepatocellular carcinoma: Korean experience. Oncology 75:114-118, 2008 (suppl 1)

28. Chen PJ, Furuse J, Han KH, et al: Issues and controversies of hepatocellular carcinoma-targeted therapy clinical trials in Asia: Experts' opinion. Liver Int 30:1427-1438, 2010

29. Cheng A, Kang Y, Lin D, et al: Phase III trial of sunitinib (Su) versus sorafenib (So) in advanced hepatocellular carcinoma (HCC). J Clin Oncol 29: 2011 (suppl; abstr 4000)

30. Yau TCP, Cheung FY, Lee AS, et al: Phase II trial of sorafenib with capecitabine and oxaliplatin (SECOX) in patients with locally advanced or metastatic hepatocellular carcinoma. Presented at the Joint ECCO 15 and 34th ESMO Multidisciplinary Congress, Berlin, Germany, September 20-24, 2009

31. Je Y, Schutz FA, Choueiri TK: Risk of bleeding with vascular endothelial growth factor receptor tyrosine-kinase inhibitors sunitinib and sorafenib: A systematic review and meta-analysis of clinical trials. Lancet Oncol 10:967-974, 2009

32. Chinese Ministry of Health: Diagnosis and Treatment Guideline of Primary Liver Cancer (ed 2011). Beijing, China, Chinese Ministry of Health, September 30, 2011

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Appendix

Table A1. Patients Recruited by Country and Center

Country/Center	FOLFOX4 (n = 184)		DOX (n = 187)	
	No.	%	No.	%
China	129	70.11	130	69.52
Cancer Institute and Hospital Chinese Academy of Medical Sciences	2	1.09	2	1.07
Nanjing Bayi Hospital	13	7.07	13	6.95
Beijing Cancer Hospital	4	2.17	6	3.21
Beijing People's Hospital	1	0.54	1	0.53
Heilongjiang Provincial Cancer Hospital	19	10.33	11	5.88
First Affiliate Hospital of China Medical University	5	2.72	4	2.14
Jiangsu Provincial Cancer Hospital	4	2.17	2	1.07
First Affiliate Hospital of Suzhou University Medical College	6	3.26	3	1.60
Fuzhou General Hospital	6	3.26	3	1.60
Affiliate Hospital of Qingdao University Medical College	3	1.63	3	1.60
Zhongshan Hospital Fudan University	4	2.17	8	4.28
Liver Cancer Institute of Fudan University	6	3.26	10	5.35
Affiliate Hospital of Nantong University	2	1.09	0	0.00
Southwest Hospital	8	4.35	7	3.74
Tangdu Hospital of Fourth Military Medical University	4	2.17	11	5.88
Wuhan Union Hospital	5	2.72	6	3.21
Sun Yat-Sen University Cancer Center	10	5.43	6	3.21
First Affiliate Hospital of Sun Yat-Sen University	12	6.52	6	3.21
Second Affiliate Hospital of Sun Yat-Sen University	2	1.09	3	1.60
Guangdong Provincial People's Hospital	5	2.72	5	2.67
Southern Medical University Southern Hospital	1	0.54	1	0.53
Jilin Provincial Cancer Hospital	6	3.26	15	8.02
Nantong Cancer Hospital	1	0.54	4	2.14
Korea	25	13.59	27	14.44
Kyungpook National University Hospital	1	0.54	0	0.00
Seoul National University Bundang Hospital	4	2.17	2	1.07
Samsung Medical Center	5	2.72	9	4.81
Seoul Bohun Hospital	7	3.80	5	2.67
Youngdong Severance Hospital	5	2.72	7	3.74
Yeungnam University Medical Center	2	1.09	2	1.07
Chung-Ang University Hospital	1	0.54	2	1.07
Thailand	19	10.33	21	11.23
Chiang Mai University	7	3.80	3	1.60
Chulalongkorn Hospital	0	0.00	2	1.07
Khon Kaen University	10	5.43	10	5.35
Phramongkutklao Hospital	1	0.54	5	2.67
Ramathibodi Hospital	1	0.54	0	0.00
Rajavithi Hospital	0	0.00	1	0.53
Taiwan	11	5.98	9	4.81
Linkou Chang-Gung Memorial Hospital	6	3.26	4	2.14
Kaohsiung Chang-Gung Memorial Hospital	5	2.72	5	2.67

Abbreviations: DOX, doxorubicin; FOLFOX4, infusional fluorouracil, leucovorin, and oxaliplatin.