بسم الله الرحمن الرحيم

# Randomized, Multicenter, Open-Label Study of FOLFOX4 Versus Doxo As Palliative Chemotherapy in Patients With Advanced HCC From Asia (EACH Study)

(Published ahead of print on August 26, 2013 JCO)

Ahmed Nofal, MD

Medical Oncology Assistant Consultant

# Introduction

HCC is the 3rd most common cancer in Asia because of the very high prevalence of the main etiologic factors including: chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. The annual incidence of HCC in China alone contributes to 55% of global HCC cases.

# *Introduction (continued)*

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

## *Introduction (continued)*

HCC is known to be highly refractory to conventional chemotherapy because of its heterogeneity and multiple etiologies. Before the advent of Sorafenib, which is the current standard of care in this group of patients, there was no standard systemic drug or treatment regimen had shown an obvious survival benefit in HCC

## *Introduction (continued)*

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.

## *Introduction (continued)*

In a phase II study of the FOLFOX4 regimen in Chinese patients with HCC, median OS was 12.4 months, mean TTP was 2.0 months, and the RR was 18.2%. Together with the acceptable safety profile, these data warranted further investigation. Hence, the EACH 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 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 were randomly assigned to receive FOLFOX4 or DOX in a ratio of one to one. 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. Previous treatment with chemotherapeutic agents or anticancer herbal treatments had to have been completed 4 weeks before random assignment. Previous adjuvant chemotherapy had to have been completed 12 months before random assignment.

# Patient Eligibility: Inclusion criteria

Inclusion criteria were as follows: Karnofsky performance score 70; life expectancy 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.

# Patient Eligibility: Exclusion criteria

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 non-target lesion); CNS metastasis; and other serious illness or medical condition.

# Treatment

Patients received either FOLFOX4 (OXA 85 mg/m2 intravenously [IV] on day 1; LV 200 mg/m2 IV from hour 0 to 2 on days 1 and 2; and FU 400 mg/m2 IV bolus at hour 2, then 600mg/m2 over 22 hours on days 1 and 2, once every 2 weeks) or DOX (50 mg/m2 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 Analysis

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

# *Efficacy and Safety Analysis (Continued)*

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.

# Statistical Analysis

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.

## *Statistical Analysis (continued)*

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 Fisher's exact test.

# 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 (Fig. 1).
- Patient demographics and baseline disease characteristics were well matched between the study groups (Fig. 2).
- 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.

# Fig. 1: Flow diagram of patient disposition

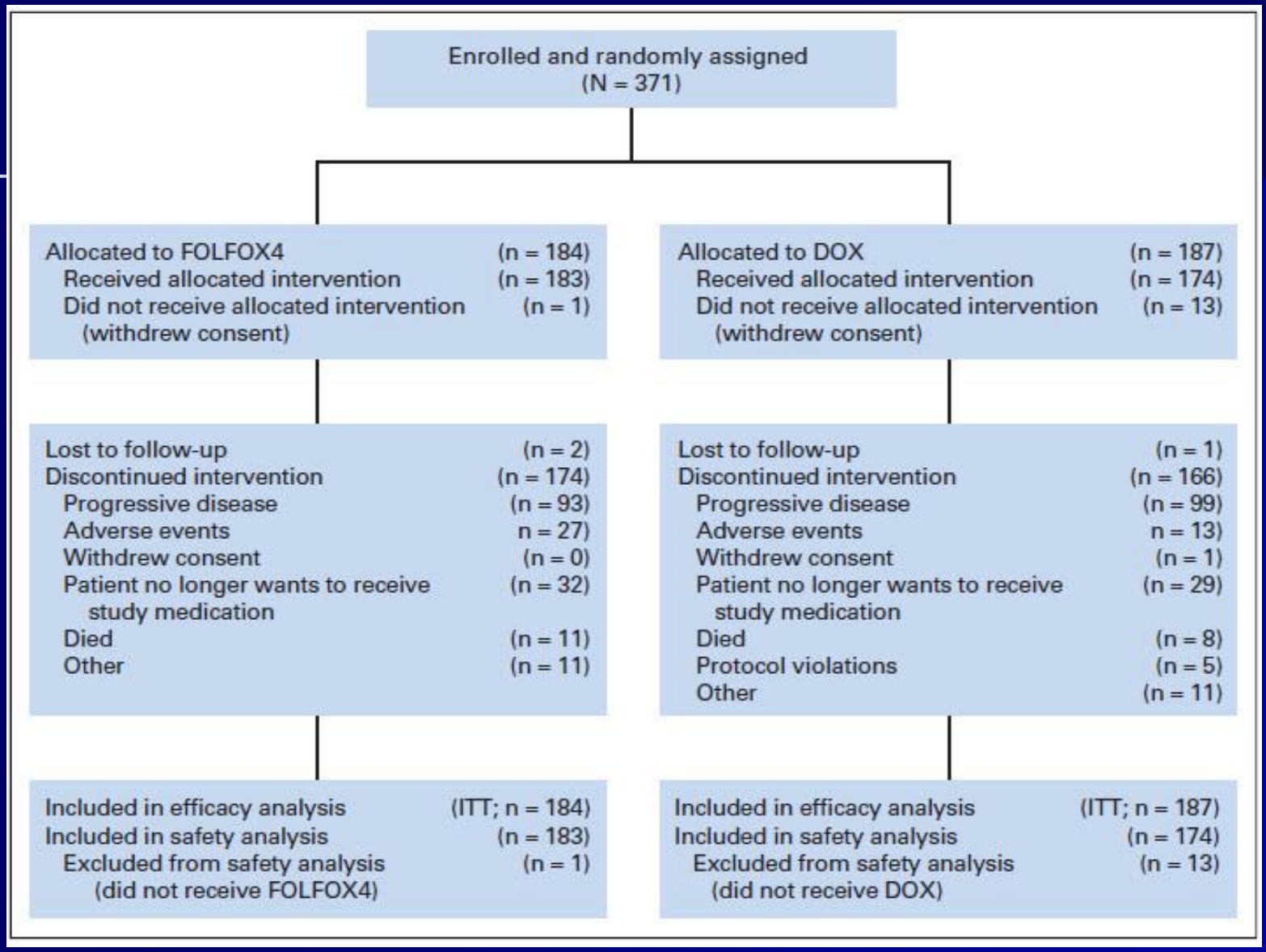

Fig. 2: Baseline patient demographics and clinical characteristics in ITT population

**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 | | 9.84 | |
| 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, infant to treat; RFA, radiofrequency ablation; SD, standard deviation; TACE, transarterial chemoembolization; TAE, transarterial embolization.

*American Joint Committee on Cancer staging.

# 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).

# *Efficacy (continued)*

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 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.

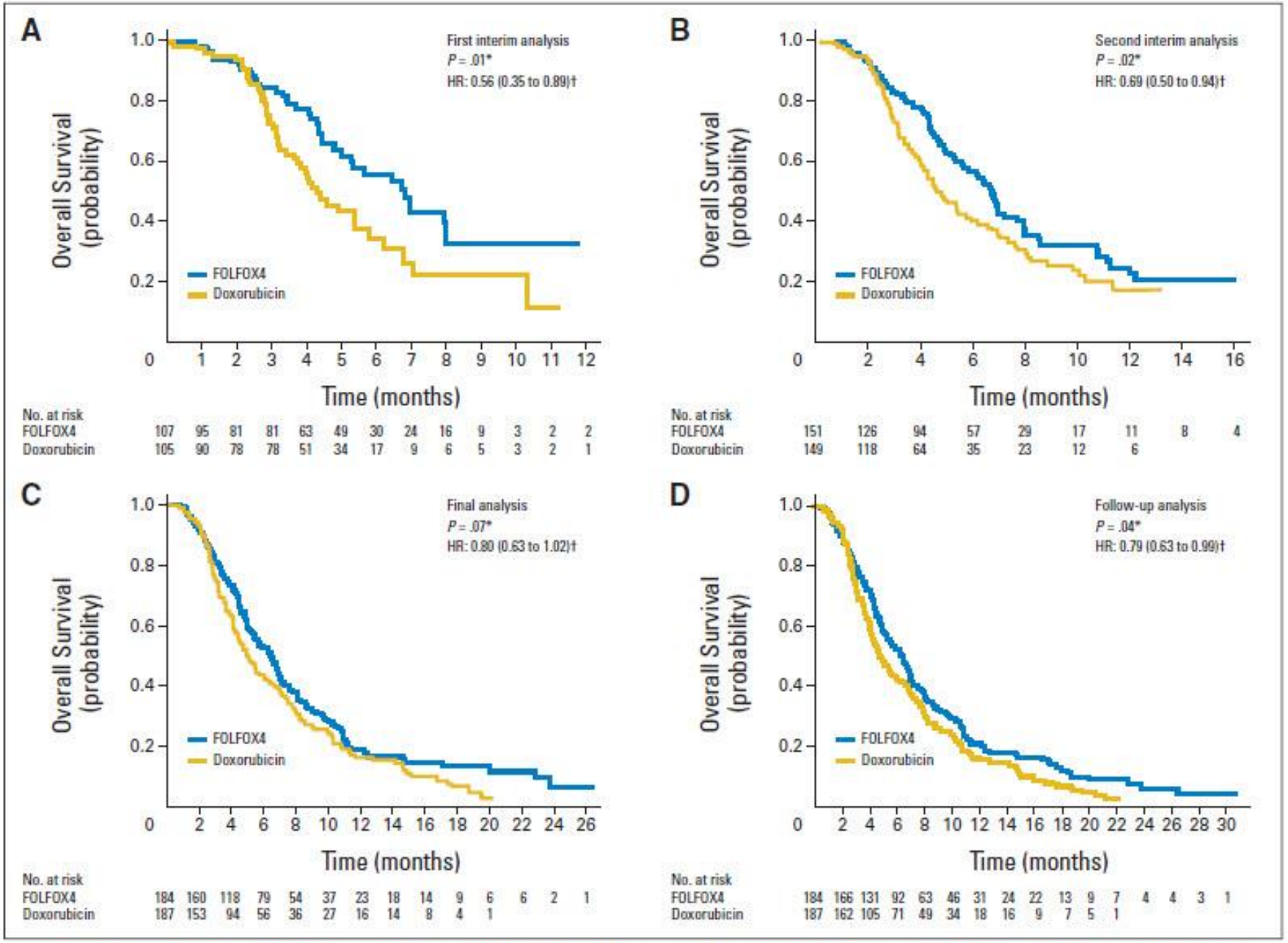


**Fig 2.** Kaplan-Meier curves showing median overall survival in the intent-to-treat population at (A) first interim, (B) second interim, (C) final, and (D) follow-up analyses. (*) Stratified log-rank test. (†) Hazard ratio (HR) was obtained from Cox model, stratified by country, Barcelona Clinic liver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

## *Efficacy (continued)*

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).

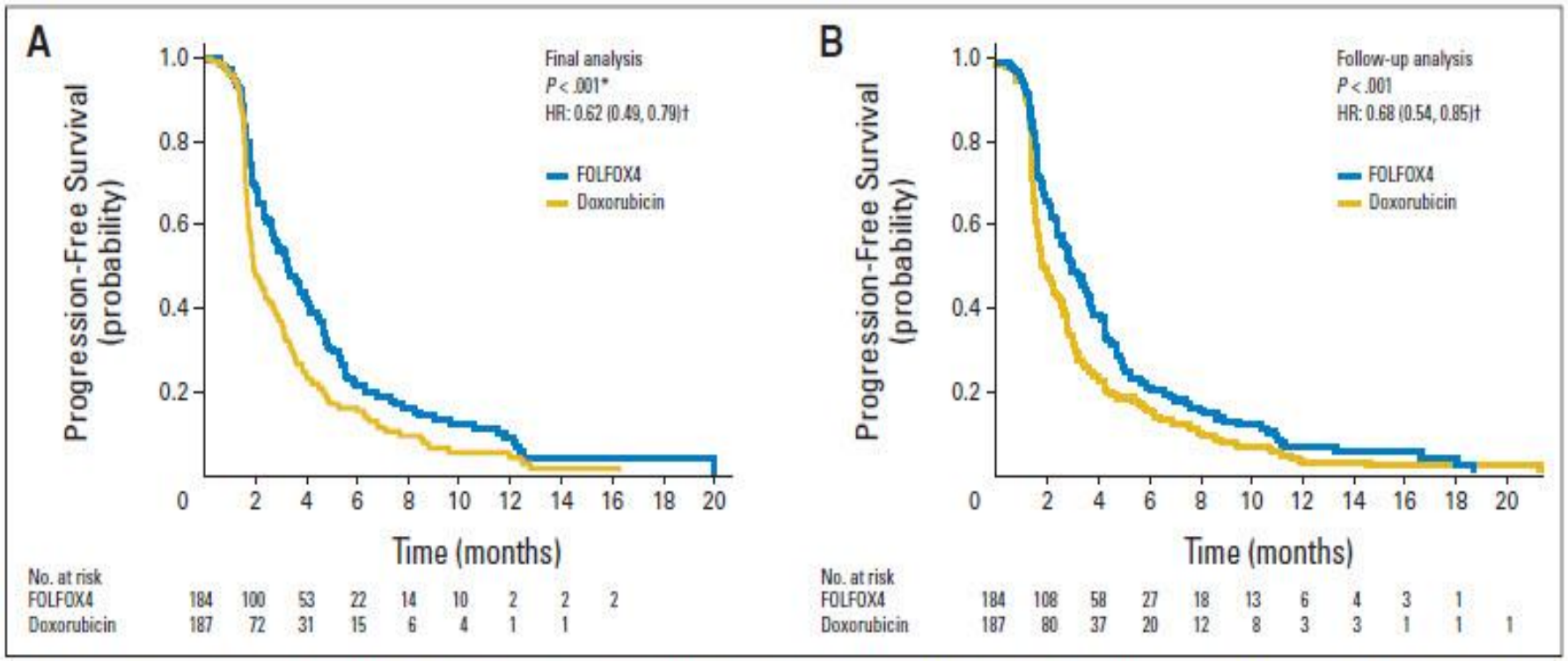


**Fig 3.** Kaplan-Meier curves showing median progression-free survival in the intent-to-treat population at (A) final and (B) follow-up analyses. (*) Stratified log-rank test. (†) Hazard ratio (HR) was obtained from Cox model, stratified by country, Barcelona Clinic liver cancer stage, and disease status.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

## *Efficacy (continued)*

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).

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

| Parameter | Final Analysis | | | | | Follow-Up Analysis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | FOLFOX4 (n = 184) | | DOX (n = 187) | | | FOLFOX4 (n = 184) | | DOX (n = 187) | | |
| | 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.

# 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. The most common treatment-related nonhematologic AEs reported in the **FOLFOX4 study arm** were nausea, AST elevation, and anorexia, 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.

**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.

# Discussion

the EACH study is the first large, international, multicenter phase III study of systemic chemotherapy and of the FOLFOX4 regimen in advanced HCC.

## *Discussion (continued)*

At the prespecified final analysis, **FOLFOX4 treatment** was associated with increased median PFS, RR, and DCR versus DOX; these statistically significant efficacy outcomes 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.

## *Discussion (continued)*

**Toxicity** in this study was consistent with previous experience with FOLFOX4 for mCRC in Asian and Western patients. The proportions of AEs reported at grade 3 to 4 severity in this study were similar between treatments.

## *Discussion (continued)*

At the time this study was designed, **DOX** had become a default standard of treatment, and sorafenib was not yet available. In 2007, **sorafenib** was the first systemic therapy to prolong survival in patients with advanced HCC, 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 than in Western patients, and the objective RRs were low (2% to 3%), with no complete responses observed.

## *Discussion (continued)*

When the OS data of the **EACH** study are viewed in comparison with those of the **SHARP** (Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol) and the **Asia Pacific 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.

## *Discussion (continued)*

The **tolerability** of sorafenib in Asian patients may also be of concern because of the high incidence of hand-foot-skin reaction. 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.

# *Discussion (continued)*

**Study limitations:**

1. The open-label design, but it was unavoidable because the regimens had different appearances and were administered differently.
2. Statistical significance was not achieved for the primary end point (OS) at the prespecified final analysis. However, compared with DOX, increased OS was observed with FOLFOX4 at all analysis time points throughout the study.
3. RR was determined from CT scans by the investigators rather than by central review, and radiologists were not blinded to patients' treatment.

## *Discussion (continued)*

**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.

# Thank You