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Prescribing decisions should be made based on the approved package insert in the country of prescription

Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00471965
Generic drug name:	Oxaliplatin	**Study Code:**	OXALI_L_00858
		Date:	17 September 2010

Title of the study:	Oxaliplatin (Eloxatin®) + 5FU/LV (FOLFOX4) compared with single-agent doxorubicin (Adriamycin) as palliative Chemotherapy in advanced Hepatocellular carcinoma patients ineligible for curative resection or local treatment （EACH study）		
Investigator(s):	Professor Shukui Qin, Nanjing Bayi Hospital, No.34, 34 Biao, Yang Gongjing, Nanjing, Jiangsu Province, P.R. China		
Study center(s):	38 centers with 103 investigators in mainland China, Korea, Taiwan and Thailand		
Publications (reference):	ASCO 2010 Abstract #4008 (oral presentation on 7 June 2010): Phase III study of oxaliplatin+5-fluorouracil/leucovorin (FOLFOX4) versus doxorubicin as palliative systemic chemotherapy in advanced HCC in Asian patients. Qin S, Bai Y, Ye S, Fan J, Lim HY, Cho JY, Thongprasert S, Chao Y, Rau K, Sun Y.		
Study period: Date first patient enrolled: 14 March 2007 Cut-off date for final analysis: 31 May 2009 2nd cut-off date for continued follow-up: 31 December 2009		**Phase of development:** Phase III	
Objectives:	Primary endpoint: overall survival (OS) Secondary endpoints: progression-free survival (PFS)*, response rate (RR), secondary resection rate, quality of life (QoL) and safety		
Methodology:	Multicenter, open-label, randomized, prospective Phase III study		
Number of patients/subjects:	Planned: 440	Randomized: 371	Treated: 357
Evaluated:	Efficacy analysis (in the ITT population): 371	Safety: 357	Pharmacokinetics: Not applicable

Diagnosis and criteria for inclusion:	1. Histologically, cytologically or clinically diagnosed unresectable hepatocellular carcinoma patients, ineligible for, or unwilling to consent to receive local invasive treatment (chemo-embolism, ablation, etc.) 2. At least one measurable lesion 3. Cancer treatment-naïve patients (except for surgery) or patients who progressed after previous interventional or local therapy 4. Karnofsky performance status ≥70 and life expectancy greater than 3 months, Barcelona Clinic liver cancer Stage B/C 5. Patients must have adequate organ and marrow function
Investigational product:	Oxaliplatin (Eloxatin®) combined with 5-fluorouracil/leucovorin (FOLFOX4 regimen)
Dose:	Oxaliplatin 85 mg/m^2, intravenous, Day 1 5-fluorouracil 400 mg/m^2 intravenous bolus, Days 1, 2 5-fluorouracil 600 mg/m^2 continuous infusion 22 h, Days 1, 2 Leucovorin 200 mg/m^2, intravenous, Days 1, 2
Administration:	Intravenous

Duration of treatment: FOLFOX4 regimen was repeated every 2 weeks as a cycle. Doxorubicin was repeated every 3 weeks as a cycle. All patients were treated until progressive disease, intolerable toxicity, patient withdrawal of consent, loss to follow-up, when patients became eligible for surgical resection or death.	**Duration of observation:** Patients were followed up every 2 months until death was observed or until the study was terminated.

Reference therapy:	Doxorubicin
Dose:	50 mg/m^2 intravenous on Day 1
Administration:	Intravenous
Criteria for evaluation:	
Efficacy: Or Pharmacodynamics:	OS: time from randomization to death due to any cause. PFS: time from randomization to progression or death due to any cause. **NOTE:** Time to tumor progression (TTP) in the clinical study protocol was defined as time from randomization to progression or death due to any cause, which is the same as the commonly used definition of PFS. In this study report PFS is used instead of TTP. RR: Response Evaluation Criteria in Solid Tumors 1.0. QoL: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire version 3.0
Safety:	National Cancer Institute Common Terminology Criteria for Adverse Events 3.0.
Pharmacokinetics:	Not applicable
Pharmacokinetic sampling times and bioanalytical methods:	Not applicable

Statistical methods:	Population for efficacy analysis: Intent-To-Treat (ITT) population, evaluable population (EP, for secondary analysis of OS). Population for safety analysis: safety population, according to treatment actually received. The patients in one arm were not allowed to be crossed over to the other arm throughout the study. OS and PFS were compared between the two treatment arms, using a log-rank test procedure at overall 5% significance level, stratified by factors as specified at the time of randomization: countries, Barcelona Clinic Liver Cancer (BCLC) staging and disease status. The survival curves were estimated using Kaplan–Meier estimates. Median and corresponding 95% confidence intervals were provided by treatment arms. RR and secondary resection rate were compared between the two treatment arms using Cochran-Mantel-Haenzel test stratified by country, BCLC stage and disease status. Differences between treatment arms in the QoL were analyzed by repeated measures ANOVA or two-group t-test/ Wilcoxon signed rank test. Adverse events (AE) differences between groups were assessed by chi-square test.
Summary:	From March 2007 to May 2009, 371 eligible patients with histologically, cytologically or clinically diagnosed unresectable HCC (88.7% male, median age 50 years [range 18–75 years], mean duration of disease 0.75±1.54 years [range 0–14.96 years]) were randomized to receive FOLFOX4 (n=184) or doxorubicin (n=187). At baseline, 58.22% had metastatic disease and 74.66% were chemotherapy naïve. The median cycle number of study medication administration was four cycles (range 1–18) of FOLFOX4 and two cycles (range 1–14) of doxorubicin. There were two cut-off dates for efficacy analysis: 31 May 2009 and 31 December 2009. At the cut-off date for final analysis (266 deaths, which occurred on 31 May 2009), OS in the ITT population was analysed. PFS, RR and QoL were also analysed in the ITT population. 249 was protocol pre-specified number of events for final analysis. However, at this cut-off date on 31 May 2009, 266 events were eventually reported. Subgroup analysis including in the Chinese population was performed as protocol pre-specified. Safety was evaluated in whole safety population and in the Chinese safety population. At the second cut-off date (305 deaths, which occurred on 31 December 2009), the post-hoc continued follow-up for OS in the ITT population and in the Chinese (ITT) population were triggered.

Efficacy results: or Pharmacodynamic results:	For analysis on OS, there were two pre-specified interim analyses, final analysis and analysis at the 2nd cut off date with continued follow-up. OS analysis in the ITT population

		FOLFOX4	Doxorubicin	Hazard ratio, 95% CI	p-value
Deaths, n/N (%)	1st interim analysis	38/107 (35.5)	47/105 (44.8)	0.560 (0.354, 0.885)	0.0119
	2nd interim analysis	82/151 (54.3)	84/149 (56.4)	0.686 (0.498, 0.944)	0.0202
	Final analysis	136/184 (73.9)	130/187 (69.5)	0.797 (0.625, 1.017)	0.0695
	Continued follow up analysis	154/184 (83.7)	151/187 (80.8)	0.785 (0.626, 0.985)	0.0425

OS Analysis in the Chinese (ITT) population

		FOLFOX4	Doxorubicin	Hazard ratio, 95% CI	p-value
Deaths, n/N (%)	Final analysis	100/140 (71.4)	97/139 (69.8)	0.736 (0.554, 0.977)	0.0302
	Continued follow up analysis	117/140 (83.6)	114/139 (82.0)	0.754 (0.580, 0.980)	0.0281

At the cut-off date for final analysis (31 May 2009), OS in the ITT population was close to statistical significance between the FOLFOX4 and doxorubicin arms in favor of FOLFOX4 with 20.3% risk reduction in death (p= 0.0695). After 7 months continued followed up (31 Dec 2009), it has reached p=0.0425 for OS.

In the Chinese population, treatment with FOLFOX4 had a significant improvement in median OS at both cut off date, p=0.032 and 0.0281 respectively.

The reduced risk in death is supported by consistent results on anti-tumor activities of PFS and RR.

<table>
<tr><td>Safety results:</td><td>Safety data observed in this study was consistent with previous experiences of FOLFOX4 and doxorubicin with no new adverse drug reaction detected. There were no significant differences between the study arms in the number of patients who reported all grades of AEs or AEs with severity of ≥Grade 3. Similarly, there were no significant differences between the study arms in terms of discontinuation rate or number of deaths due to serious AEs (SAEs). The incidence of Grade 3/4 AEs considered to be possibly related to treatment was also similar between the two treatment arms. FOLFOX4 tended to have higher adverse events on neutropenia, leukocytopenia and thrombocytopenia compared with doxorubicin, although these effects were of Grade 2 or lower.

In the study, death is the variable for both efficacy and safety. There was no statistically significant difference in the number of deaths due to SAEs between the FOLFOX4 and doxorubicin arms.
<table>
<tr><th></th><th>FOLFOX4 (n=183)</th><th>Doxorubicin (n=174)</th><th>p-value</th></tr>
<tr><td>Adverse events, n (%)</td><td>173 (94.54)</td><td>159 (91.38)</td><td>0.2428</td></tr>
<tr><td>Adverse events ≥ Grade 3, n (%)</td><td>102 (55.74)</td><td>79 (45.40)</td><td>0.0509</td></tr>
<tr><td>Serious adverse events, n (%)</td><td>34 (18.58)</td><td>27 (15.52)</td><td>0.4423</td></tr>
<tr><td>Deaths, n (%)</td><td>11 (6.01)</td><td>9 (5.17)</td><td>0.7306</td></tr>
<tr><td>Discontinuations, n (%)</td><td>42 (22.95)</td><td>30 (17.24)</td><td>0.1790</td></tr>
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<tr><td>Pharmacokinetic results:</td><td>Not applicable</td></tr>
<tr><td>Date of report:</td><td>27-August-2010</td></tr>
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