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Sponsor/company:	sanofi-aventis	**ClinicalTrials.gov Identifier:**	NCT00559455
		Study Code:	OXALI_L_02859
Generic drug name:	oxaliplatin	**Date:**	18 May 2011

Title of the study:	Phase II Study of Oxaliplatin + 5-FluoroUracil/Leucovorin (Eloxatin+5-FU/LV) in Patients With Unresectable Hepatocellular Carcinoma (OXALI_L_02859 – HCC phII)		
Investigator(s):	JunSuk Kim, Korea University Guro Hospital		
Study center(s):	7 centers in Korea		
Publications (reference):	none		
Study period: Date first patient/subject enrolled: 28-Sep-2007 Date last patient/subject completed: 28-Jan-2010		**Phase of development:** Phase II	
Objectives:	-Primary objective: To determine the Tumor Response Rate of patients with hepatocellular carcinoma treated with the combination chemotherapy of Eloxatin+5-FU/LV -Secondary objectives: To evaluate progression free survival, overall survival, safety and tolerability of patients with hepatocellular carcinoma treated with the combination chemotherapy of Eloxatin+5-FU/LV		
Methodology:	multi-center, single arm, open-label study		
Number of patients/subjects:	Planned: 37	Enrolled: 38	Treated: 38
Evaluated:	Efficacy analysis (in the ITT population): 38		Safety: 38
Diagnosis and criteria for inclusion:	-Diagnosis: Histologically, cytologically or clinically diagnosed unresectable hepatocellular carcinoma -Main inclusion criteria: 1) Signed informed consent before the treatment 2) people between 18 and 75 years old 3) Histologically, cytologically or clinically diagnosed (in patient with cirrhosis, Alpha-Fetoprotein/AFP≧400μg/L and morphological evidence [contrast Computed Tomography/CT/ Magnetic Resonance Imaging/MRI] of hypervascular liver tumor, and elevated AFP level due other reasons [germ cell carcinoma, progressive chronic hepatitis, pregnancy, etc] can be excluded) unresectable hepatocellular carcinoma, ineligible or if the patient does not consent to receive local invasive treatment (chemo-embolism,		

	ablation, etc.). However, if existing HBV or HCV or Cirrhosis and diagnosed as HCC through more than 2 morphological evidence including CT or MRI despite AFP<400 μg/L, it would be allowed. 4) At least one measurable lesion (on conventional CT: ≧2cm, on spiral CT or MRI ≧1cm) but the lesion which was treated interventionally or locally can't be a measurable lesion. 5) Patients with unresectable lesions 6) Have not received palliative systemic chemotherapy. If the patient received previous systemic chemotherapy as adjuvant treatment or radiation therapy to the non-target lesions, it would be allowed. 7) The period of Washout of prior chemotherapy must be greater than 4 weeks. 8) World Health Organization performance status: 0 to 2 (Karnofsky Performance Score/KPS: ≧70) 9) Life expectancy: greater than 3 months 10) Patients must have adequate organ and marrow function as defined below: Absolute neutrophil count ≧1,500/μl Platelets ≧75,000/μl Asparagine AminoTransferase/AST, Alanine AminoTransferase/ALT ≦2.5XUNL (upper normal limit); Total Bilirubin/TB ≦ 1.5XUNL, INR≦1.5 , Creatinine ≦1.5XULN, Child stage A or B (However, if AST,ALT<5XULN and TB is normal, it would be allowed.)
Investigational product: Dose: Administration:	Oxaliplatin: 50mg/vial 5-Fluorouracil:250mg/vial , 500mg/vial Leucovorin: 15mg/vial or ample, 30mg/ample, 50mg/vial or ample, 100mg/vial or ample OXA： 85mg/m², 2 hours IV infusion, D1; LV 200mg/ m², D1&D2 5-FU IV bolus 400mg/ m², 2hrs D1; 5-FU 22 hrs continuous IV infusion 600mg/ m², D1 and 2; Every 2 weeks Intravenous
Duration of treatment: Treatment was repeated every 2 weeks as 1 cycle until disease progression, intolerable toxicities, death, withdrawal consent by patient, lost to follow up. Expected treatment duration was approximately 12 weeks (about 6 cycles.)	**Duration of observation:** every 6 weeks until death or study termination.
Reference therapy:	NA
Criteria for evaluation:	
Efficacy:	Primary efficacy variable: For response rate, objective responses (Complete Response/CR and Partial Response/PR) for measurable disease were assessed by investigators according to Response Evaluation Criteria in Solid Tumors/RECIST criteria. Secondary efficacy variables: Progression Free Survival(PFS) and Overall Survival(OS) PFS is defined as the interval between registration date and documentation of progression or death due to any cause.

	Patients who were lost to follow-up or who received other anti-cancer therapy before progression were censored. OS is defined as the interval between registration date and documentation of death due to any cause. Patients who weren't observed the death were censored at the date when the last survival confirmed.
Safety:	Safety data was collected as following: Adverse Events, hematological toxicity, general physical examination (weight, BSA, vital signs, physical examination, neurological examination, and Karnofsky performance status), special examination (chest X-ray, ECG), and laboratory data. Adverse event and toxicity were evaluated on the basis of National Cancer Institute-Common Terminology Criteria for Adverse Events / NCI-CTCAE v.3.0. The highest grade among toxicities above was summarized patients and cycles
Statistical methods:	Analysis population: Intent-to-treat (ITT) population includes all registered patients who received at least one dose of study treatment. Per protocol (PP) population includes all registered patients among ITT population who didn't have any major protocol violation. Efficacy analyses were conducted in ITT and PP population and safety analyses was conducted in safety population who received at least one dose of study treatment. And the response rate is defined as the number of patients whose tumor is diagnosed as CR or PR divided by the total number of patients with measurable tumor. The response rate was estimated and corresponding 95% one-sided CI was provided. Progression free survival and overall survival was estimated using Kaplan-Meier method. And it was provided 25%, 50%, 75% survival time of PFS and OS. If applicable, 95% CI was provided. Adverse events were summarized into hematological toxicities and non-hematological toxicities. Adverse events were coded using NCI-CTCAE v.3.0 and analyzed using the worst NCI CTC grade. Adverse events were summarized using frequency and percentage by system organ class and preferred term.

Summary of Results:

38 patients had been registered and treated FOLFOX 4 regimen from September 2007 to May 2009. They were histologically or clinically diagnosed as unresectable hepatocellular carcinoma. Men were 35(92.11%) among 38 and median age was 55.84±8.10 at baseline. And the mean duration of hepatocellular carcinoma was 0.61 years [range 0-9.38 years].

At baseline, 30(78.95%) had stage IV and 38(100%) were chemotherapy naive. The median cycle number of study medication administration was 4 cycles (range 1-17).

Main results of efficacy and safety are same as below.

Efficacy results

The statistical result of the primary efficacy variable, response rate, is estimated as the number of patients whose tumor is diagnosed as CR or PR divided the total number of patients with measurable tumor. One patient was not included in the primary efficacy analysis because the patient's tumor wasn't assessed.
In ITT population, the response rate was 16.22% (PR: 6/37patients). It is higher than 10% clinically significant response rate, but it didn't demonstrate the hypothesis statistically that the objective response rate is over than 25%.
In PP population, the response rate was 11.473% (PR: 4/35 patients)

Response rate in ITT population

Response	N=37 Patients (%)
Response rate [95% one-sided CI]	6(16.22%) [7.31, 29.52]
Complete response (CR)	0(0.00%)
Partial response (PR)	6(16.22%)
Stable disease (SD)	18(48.65%)
Progressive disease (PD)	13(35.14%)
Not evaluable (NE)	0(0.00%)

PFS was defined as the time interval from registration to documentation of progression or death due to any cause, whichever comes first. In the absence of confirmation of death, follow up loss or receiving other anticancer therapy before progression, the patients were censored at the last date patient is know to be alive or at the last tumor assessment date before tumor progression was confirmed.

In ITT population, patients with progression disease or death were 81.58%(31/38 patients) and the other 7 patients (18.42%) were censored. Among patients of 35 in the PP population, 30 patients (85.71%) experienced progression disease or death. The others of 5 patients(14.29%) were censored.

Progression free survival was estimated using Kaplan-Meier method, the medical PFS in ITT population was 3.10 months (95% CI: 2.37, 4.53), 75% PFS time was 1.93 months (95% CI: 1.43, 2.63) and 25% PFS time was 5.87 months (95% CI: 3.20, 11.10). In PP population, median PFS was 3.00 months (95% CI: 2.03, 3.80) and 75% PFS time was 1.83 (95% CI: 1.33, 2.535) and 25% PFS time was 5.7 months (95% CI: 3.13, 10.87). The PFS curves of the ITT and PP population were almost same.

Overall survival was defined as the time between registration and death due to any cause. In the absence of confirmation of death, the patients was censored at the last date patient is know to be alive.

In ITT population, observed death was 52.63% (20/38 patients) and the others of 18 patients (47.37%) were censored. In PP population, 20 patients (57.14%) of total 35 patients was death and 15 patients (42.86%) was censored.

Median survival time which was estimated using Kaplan-Meier was 11.97 months (95% CI: 5.53, 24.50) and 75% survival time was 4.17 months (95% CI: 2.53, 7.87) in ITT population. In PP population, the medical survival time was 12.20 months (95% CI: 6.07, -) and 75% survival time was 4.77 months (95%CI: 2.63, 7.87). 25% survival time was unable to be estimated because survival rates at the final follow-up time were over than 25% in both of the ITT and the PP population. And the survival curves between ITT and PP population was almost same.

The objective response rate was 16.22% (PR: 6patients) in ITT and 11.43% (PR: 4 patients) in PP population.

Safety results:

The safety population was 38 patients who received at least one dose of the study medication. Adverse events were summarized into hematological toxicities and non-hematological toxicities.

For the non-hematological toxicities, at least one adverse event was reported for 38 patients. Adverse events considered to be possibly related to treatment (ADR) were reported in 35 patients (92.11%). Non-hematological toxicities with over grade 3 was reported in 52.63% and SAE occurred in 36.84% of patients. One death was observed after receiving study treatment. Twelve patients (31.58%) discontined study medication permanently and among them, ADR were reported in 9 patients.

Adverse events	AE No. of patients N=38	ADR No. of pateints N=38
Patients with AEs	38(100.00%)	35(92.11%)
Patients with AEs of Grade ≥ 3	20(52.63%)	8(21.05%)
Patients with SAEs	14(36.84%)	3(7.89%)
Patients who died due to AEs	1(2.63%)	0(0.00%)
Patients discontinued due to AEs	12(31.58%)	9(23.68%)

Leucocytopenia, anemia, thrombocytopenia and neutropenia, which are major hematological toxicity, were reported in most of patients. Leucocytopenia was reported in 6 patients (15.79%) and anemia in 2 pateints (5.26%), thrombocytopenia in 4 patients (10.53%), and neutropenia in 12 patients (31.58%) for AE with grade 3.

Hematological Toxicities	Grade	No. of patients(%) N=38	No. of cycle(%) N=210
Leucocytopenia	1	11(28.95%)	49(23.33%)
	2	12(31.58%)	44(20.95%)
	3	6(15.79%)	16(7.62%)
	4	0(0.00%)	0(0.00%)
Anemia	1	11(28.95%)	52(24.76%)

		2	5(13.16%)	26(12.38%)
		3	2(5.26%)	3(1.43%)
		4	0(0.00%)	0(0.00%)
	Thrombocytopenia	1	13(34.21%)	66(31.43%)
		2	11(28.95%)	41(19.52%)
		3	4(10.53%)	12(5.71%)
		4	0(0.00%)	0(0.00%)
	Neutropenia	1	3(7.89%)	32(15.24%)
		2	8(21.05%)	26(12.38%)
		3	12(31.58%)	45(21.43%)
		4	6(15.79%)	6(2.86%)
Date of report:	13-Apr-2011			