Sponsor: Sanofi **Drug substance(s):** Oxaliplatin	**Study Identifiers:** ChiCTR-OPC-15005865 **Study code:** OXALIL06932

Title of the study:

Prospective, Multicenter, Registry study of Oxaliplatin (Eloxatin®)/ Fluorouracil based regimen for Chinese patients with Locally Advanced or Metastatic Hepatocellular Carcinoma ineligible for curative resection and local treatment

Study Center(s):

25 Chinese sites

Study period:

Study initiation date [date first patient in (FPI)]: 01-Sep-2014

Study completion date [last patient completed/last patient out (LPO)]: 31-Oct-2023

Study Status: Terminated. low recruitment

Objectives:

Primary:

• To evaluate the safety profile of Eloxatin® /Fluorouracil-based regimen in patients with locally advanced or metastatic HCC who are not eligible for curative resection and local treatment in real-life practice.

Secondary:

• To evaluate the efficacy [Overall Survival (OS), progression-free survival (PFS), objective response rate (ORR) and disease control rate (DCR)] of Eloxatin® /fluorouracil-based regimen in these patients in real-life practice.

• To assess the duration, dose-intensity for the Eloxatin® /fluorouracil-based regimen in these patients in real-life practice.

Methodology:

This prospective, multicenter, registry assessed the safety and efficacy of systemic chemotherapy with Eloxatin® /fluorouracil based regimen in patients with locally advanced or metastatic hepatocellular carcinoma (HCC) who are not eligible for curative resection and local treatment.

In contrast to a randomized controlled clinical study, there are no imposed experimental intervention. The treatment is determined solely by the patient's physician.

The patients who were enrolled in the study were selected among patients for whom the physician decided to prescribe Eloxatin®/fluorouracil based regimen independently from study entry.

Participants (actual):

A total of 241 patients were enrolled in the study from 01/Sep/2014 to 17/Mar/2021 at 25 Chinese sites and 230 of them entered the treatment period with Eloxatin® / Fluorouracil.

All patients who entered the treatment period (n=230, 100%) discontinued treatment at some stage for the following reasons: disease relapse or recurrence (n=104), patient refusal to continue (n=39), adverse event (n=18), death (n=12), investigator decision (n=10), lost of follow-up (n=6), informed consent withdrawal (n=2), other causes (n=39).

After the last dose of chemotherapy, 204 out of 230 patients (88.7%) entered the followup period and 26 did not for the following reasons: 13 had died, 6 were lost of follow-up, 3 withdraw their consent, and 4 withdraw for other cause.

At the time of database lock (01/Mar/2023), 8 patients did not finish the clinical trial and 196 patients finished the clinical trial. Of these 196 patients, 165 patients had died, 26 patients were lost of follow-up, and 5 patients finished for another reason (1 patient did not receive further treatment; 1 patient refused follow-up; 2 patients refused treatment, and 1 patient withdrew from the trial due to tumor progression).

Of those 241 patients who were enrolled the study:

• 214 patients were analyzed in the FAS. Reasons for excluding 27 patients from the FAS were as follows: no visit to the center after treatment initiation (n=12), screening failure (n=11), Eloxatin not use (n=2), treated with Eloxatin only (n=2).

• 226 patients were analyzed in the SS. Reasons for excluding 15 patients from the SS analysis were as follows: screening failure (n=11), Eloxatin not use (n=2), Fluorouracil not combined with Eloxatin (n=2).

• 205 patients were analyzed in the EAS. Reasons for excluding 36 patients from the EAS analysis were as follows: no visit to the center after treatment initiation (n=13), screening failure (n=11), treatment regimen changed (n=6), eligibility criteria not met but treated with Eloxatin/Fluorouracil (n=3), Eloxatin not use (n=2), fluorouracil not combined with Eloxatin (n=1)

Study participant selection:

Eligibility criteria

Inclusion criteria:

• Male or female

• Aged 18 to 70 years old

• Patients with histologically or cytologically diagnosed HCC who are ineligible for curative resection and local treatment.

• Or patients with clinically diagnosed HCC who are ineligible for curative resection or local treatment. Clinically diagnosed patients should fulfil the following criteria (1+2+3(b) or 1+3(a)):

1) Evidence of HBV or HCV with hepatic cirrhosis;

2) Alpha-fetoprotein (AFP) levels ≥400 μg/L; or AFP levels ≥200 μg/L lasting for 2 months;

3) Morphological evidence of hypervascular liver tumour.

a) If the nodule diameter is greater than 2cm, either CT or MRI evaluation is needed.

b) If the nodule diameter is 1 to 2cm, both CT and MRI evaluation are needed

• Or patients with histologically or cytologically or clinically diagnosed HCC who are not willing to accept resection and local treatment.

• Physician's intention to treat with Eloxatin® and fluorouracil based systemic chemotherapy

• Signed informed consent form (ICF) prior to study entry

Exclusion criteria:

• Patients who are receiving any other study treatment or experimental medical treatment within 30 days prior to study entry.

• Documented allergy to platinum compound.

• Pregnant or lactating women or women of childbearing potential without proper contraceptive methods.

Study products:

The prescription of therapies was under the only responsibility of the patient's physician.

Patients enrolled in the study were selected among those patients for whom the physician had decided to prescribe Eloxatin® /fluorouracil-based regimen, independently from study entry.

The physician was referred to the latest package insert (PI) of Eloxatin® in China for any information on treatment prescribed.

Duration of observation:

Every patient should be followed till death, or patient's withdrawal or 12 months after the last eligible patients' enrollment, whichever comes first.

Criteria for evaluation:

Primary Analysis:

Percentages of patients with drug-related high-grade (Grade 3 and higher) liver toxicity.

Secondary Analyses:

Safety:

•The severity of AEs was evaluated according to NCI CTCAE 4.0.

Efficacy:

•Overall Survival (OS) defined as the duration from the informed consent signature to death from any cause.

• Progression Free Survival (PFS) defined as the duration from the informed consent signature to disease progression or death from any cause.

•Objective Response Rate (ORR) defined as percentage of patients with complete response (CR) and partial response (PR) per RECIST 1.1.

•Disease Control Rate (DCR) defined as percentage of patients with CR, PR or stable disease (SD).Treatment Exposure: Cycles, actual dose-intensity and relative dose intensity.

Clinical Laboratory Evaluations.

Statistical methods:

General Statistical Methodologies:

Descriptive statistics were provided:

•For continuous variables: number of cases, minimum, median, maximum, mean and standard deviation

•For categorical variables: number of cases, frequencies and percentages per group

Exploratory analyses were done using two-sided tests at the 0.05 significance level unless specifically stated otherwise.

Specific Statistical Methods:

(1) Patient Disposition:

•The number of patients included in the study

•The number of patients with treatment discontinuation and reasons for treatment discontinuation

•The number of patients entering the follow-up period

•The number of deaths

•The number of dropouts

•The number of patients still alive at the end of study

2) Demographics and Other Baseline Characteristics

•Demographics and others;

•HCC characteristics at baseline;

•Prior treatments for HCC;

•Clinical examination.

Since chronic infection with hepatitis B virus (HBV) remains the overwhelming cause of HCC in China [3], with a prevalence of hepatitis B of nearly 10% in the general population, the following subgroups were described:

• Etiology of HCC (HBV vs. Others). HCC was considered related to HBV infection if HbsAg and HBV-DNA were both positive.

• Prior Treatment (Yes vs. No). Prior Treatment for HCC was defined as having received any of the following treatments: Surgery, Prior systemic chemotherapy, Local treatment for target lesions and Sorafenib.

All relevant Information related to other prior treatment (such as dose, unit, route of administration), as well as disease history (except for HBV infection, HCV infection and hepatic cirrhosis) were also listed by patient.

Primary Analysis:

Percentages of patients with drug-related high-grade (Grade 3 and higher) liver toxicity (i.e. AST, ALT and/or bilirubin elevation), and corresponding 95% Clopper-Pearson confidence intervals were calculated by subgroup and overall.

This primary analysis was conducted on the following populations:

• The Full Analysis Set (FAS), defined as all patients who have visited the investigational site at least once after the Eloxatin® / Fluorouracil start, no matter changing treatment regimen or not.

• The Safety Set (SS), defined asregistered participants who received Eloxatin® /Fluorouracil at least once, no matter changing treatment regimen or not.

Adverse events were coded using the MedDRA dictionary (version 17.0) that provides the primary system organ class and preferred term information.

Secondary Analyses:

(1) Safety

The following analysis were conducted on the safety set:

•Incidence and severity of all adverse events (AEs)

•Incidence of treatment-emergent adverse events (TEAEs)

•Incidence of drug-related TEAEs

•Incidence of drug-related AEs

•Incidence of serious AEs (SAEs)

•Incidence of AEs leading to treatment discontinuation

•Incidence of AEs leading to early study withdrawals

•Incidence of AEs leading to dose adjustment

•Incidence of Unexpected Adverse Drug Reaction (ADR)

The severity of AEs was evaluated according to NCI CTCAE 4.0. The TEAE observation period was defined as the time from first dose of treatment up to 30 days after the last dose of treatment. Unexpected Adverse Drug Reaction (ADR) was defined as any related AE which was not listed in the latest version package insert of Eloxatin® in China.

The aforementioned incidences and corresponding 95% confidence intervals (via Clopper- Pearson's exact method) were calculated by subgroup and overall.

AEs were summarized by system organ class (SOC) and preferred term (PT). Each patient was counted only once within a system organ class or a preferred term by using the adverse events with the highest severity within each category. SOC and PT were both sorted alphabetically. AEs were summarized by severity of AE and subgroup.

Finally, all information pertaining to AEs noted during the study was listed by patient, detailing verbatim given by the investigator, preferred term, system organ class, date of onset, date of resolution, severity, and relationship to treatment. The profile of death was listed by patient too.

(2) Efficacy

The efficacy analysis was conducted on EAS population:

• The efficacy analysis set (EAS) is defined as registered participants who met the eligibility criteria and have visited the investigational site at least once after administration, whose treatment regimen cannot be changed during the study. When the efficacy endpoint(s) can't be derived from raw data for some patients, sensitivity analysis would be conducted after excluding these patients from efficacy analysis set.

The following efficacy endpoints were analysed on the Efficacy Analysis Set (EAS) (defined as all registered participants who met the eligibility criteria and visited the investigational site at least once after Eloxatin® / Fluorouracil initiation:

•Overall Survival (OS) defined as the duration from the informed consent signature to death from any cause

•Progression Free Survival (PFS) defined as the duration from the informed consent signature to disease progression or death from any cause

•Objective Response Rate (ORR) defined as percentage of patients with complete response (CR) and partial response (PR) per RECIST 1.1

•Disease Control Rate (DCR) defined as percentage of patients with CR, PR or stable disease (SD).

For the analysis of time-to-event data, the Kaplan-Meier method was employed to estimate median OS and PFS and corresponding 95% confidence intervals and to obtain the curves for OS and PFS, respectively. Subgroup analysis based on etiology of HCC (HBV vs. Others) and Prior Treatment (Yes vs. No) was performed too.

ORR and DCR with corresponding 95% CI were calculated by subgroup and overall.

(3) Treatment Exposure

Cycles, actual dose-intensity and relative dose intensity were calculated and summarized using descriptive statistics by subgroup and overall.

•Actual Dose Intensity (ADI) (mg/m^2 /week) = cumulative dose (mg/m^2)/ chemotherapy duration (weeks)

•Relative Dose Intensity (RDI) = actual dose intensity (mg/m^2/week)/ planned dose intensity (mg/m^2/week)

(4) Clinical Laboratory Evaluations

The clinical laboratory evaluations were as follows:

•Hematology test

•Blood Chemistry Test

•PT and INR

•AFP

For quantitative parameters, the value at the visit was summarized by mean, standard deviation, minimum, median and maximum by subgroup and overall, whereas for qualitative parameters, the frequency table by visit was provided by subgroup and overall.

Shift tables were used to show changes from baseline between normal, no clinically significant abnormal (NCSA) findings and clinically significant abnormal (CSA) findings by subgroup.

All information relevant to clinical laboratory evaluation was listed by patient.

(5) Other Evaluations Related to Safety

Other evaluations related to safety included:

•Weight, Body surface area

•Vital sign, Physical examination

•ECOG performance status

Shift tables of vital sign, physical examination and ECOG performance status was adopted to show changes from baseline between normal, NCSA and CSA findings by subgroup.

Summary:

Demographics and other baseline characteristics:

In the FAS (n=214), median age was 52.0 years (range 25-73) and most patients were males (n=190, 90.0%). Overall, 194 patients (90.7%) reported HBV infection history and 5 (2.3%) had HCV infection history. The etiology of HCC was attributed to HBV in 55 patients (all were HbsAg and HBV-DNA positive) and to another cause in 139 patients. In addition, 163 patients (76.2%) had Hepatic Cirrhosis history.

The majority of patients were diagnosed with stage IVB disease (63.1%), 88.5% were classified Child-Pugh A and 79.2% BCLC stage C. 183 patients (85.5%) were ECOG 0- 1, 7 patients (3.3%) were ECOG 2 at baseline. Most patients had a tumor of the right lobe (57.0%) and most common metastatic site was lung (57.6%).

A total of 169 patients (79.0%) received prior treatment for HCC, mainly local treatment for target lesions (65.0%), followed by surgery (49.1%). Furthermore, 49 patients (22.9%) were prescribed prior Sorafenib. Compared to patients who received a prior treatment for HCC, those who were treatment naïve had more T3-T4 tumors (100% vs. 26.0%) and more bilateral tumors (31.1% vs. 13.6%).

At baseline, 44 patients (20.8%) had clinically significant abnormalities of physical examination and 4 patients (1.9%) had clinically significant abnormalities of vital signs. Clinically significant ECG and chest X-ray abnormalities were reported for 10 patients (6.1%) and 21 patients (37.5%), respectively.

Comparable baseline characteristics were observed for the SS and EAS populations.

Primary Analysis:

The primary endpoint of the study was the proportion of drug-related high-grade (Grade 3 and higher) liver toxicity in FAS and SS populations.

In the FAS population (n=214), 5 patients (2.3%) (95%CI: 0.763, 5.368) experienced drug-related high-grade liver toxicity.

The proportions by subgroups were as follows:

• 3 patients (5.5%) with HCC related to HBV infection developed high-grade liver toxicities versus 2 patients (1.3%) with HCC related to other etiologies.

• 4 patients (2.4%) with prior treatment for HCC developed high-grade liver toxicities versus 1 patient (2.2%) with no prior treatment for HCC.

In the SS population (n=226), 5 patients (2.2%) (95%CI: 0.722, 5.087) developed drugrelated high-grade liver toxicity. Results by subgroups were as follows:

• 3 HBV patients (5.3%) developed drug-related high-grade liver toxicity versus 2 non-HBV patients (1.2%).

• 4 patients (2.2%) with prior treatment for HCC developed high-grade liver toxicities versus 1 patient (2.1%) with no prior treatment for HCC.

Secondary Analyses:

1. Safety analyses in SS population

An overview of adverse events (AEs) reported during the study is provided in the table below.

	Safety Set (n=226)
N patients (%) with an AE from any cause	203 (89.8%)
N patients (%) with TEAEs	202 (89.4%)
N patients (%) with grade ≥ 3 TEAEs	90 (39.8%)
N patients (%) with drug-related TEAEs	176 (77.9%)
N patients (%) with grade ≥ 3 drug-related TEAEs	56 (24.8%)
N patients (%) with SAEs	38 (16.8%)
N patients (%) with AEs leading to death	14 (6.2%)
N patients (%) with AEs leading to treatment discontinuation	28 (12.4%)
N patients (%) with AEs leading to dose adjustment	19 (8.4%)

203 patients (89.8%) experienced a total of 1734 AEs while on treatment or during the follow-up period, 202 patients (89.4%) experienced 1654 treatment-emergent adverse events (TEAEs) and 176 patients (77.9%) reported 1055 drug-related TEAEs. There were 175 patients (77.4%) with 1040 TEAEs related to oxaliplatin, 170 patients (75.2%) with 990 fluorouracil related TEAEs, 108 patients (47.8%) with 631 LV related TEAEs and 0 unexpected drug related TEAE.

38 patients (16.8%) experienced 48 SAEs, including 14 patients 6.2%) with SAEs resulting in death and 12 patients (5.3%) who experienced 18 drug-related SAEs.

AEs leading to discontinuation occurred in 28 patients (12.4%) and AEs leading to dose modifications occurred in 19 patient (8.4%)

The incidence of patients with Grade 3 and higher TEAEs was 39.8% (90 patients, 212 events), the incidence of patients with Grade 3 and higher drug-related TEAEs was 24.8% (56 patients, 124 events). There were 55 patients (24.3%) reported 123 Grade 3 and higher TEAEs related to oxaliplatin, 54 patients (23.9%) reported 117 Grade 3 and higher TEAEs related to Fluorouracil, 30 patients (13.3%) reported 75 Grade 3 and higher TEAEs related to LV.

Most frequently reported Grade 3 and higher TEAEs were neutrophil count decreased (28 patients (12.4%), 41 events), white blood cell count decreased (23 patients (10.2%), 39 events). Most frequently reported Grade 3 and higher drug-related TEAEs were neutrophil count decreased (28 patients (12.4%), 40 events), white blood cell count decreased (21 patients (9.3%), 34 events).

Most frequently reported AEs were white blood cell count decreased (89 patients (39.4%)), platelet count decreased (78 patients (34.5%)), neutrophil count decreased (70 patients (31%)), Aspartate aminotransferase increased (60 patients (26.5%)), and nausea (49 patients (21.7%)).

The incidence of patients with mild (Grade 1) AEs was 16.4% (37 patients, 987 events) and the incidence of moderate (Grade 2) events was 32.3% (73 patients, 523 events). Severe (Grade 3) AEs occurred in 74 patients (32.7%, 201 events) and life-threatening (Grade 4) AEs occurred in 8 patients (3.5%, 12 events). Fatal (Grade 5) adverse events were reported for 11 patients (4.9%, 11 events).

2. Efficacy

Over a median follow-up duration of 65.5 months (95% CI: 47.0, 73.8), 167 patients died with a median overall survival of 9.1 months (95%CI: 6.8, 10.3). At 6 and 12 months, 57.1% and 31.7% of patients were still alive. Median OS was slightly lower in patients with no prior treatment (6 vs 9 months in those with prior HCC treatment) possibly reflecting the fact that these patients

had more T3-T4 and bilateral primary tumors. Median OS was also slightly lower in patients with HBV-related HCC (6 vs 10 months).

The median PFS was 3.9 months (95% CI: 3.0, 4.7). At 6 months, 34.1% of patients had not progressed. Median PFS was 4.0 months in patients with prior HCC treatment and 2.5 months in those who were treatment naïve. PFS was comparable in patients with HCC related to HBV (median 3 months) and those with HCC related to another cause (median 4 months).

Objective response rate (ORR) was 3.9% (95% CI: 1.7, 7.5) and disease control rate was 30.2% (95% CI 24.0-37.0). Seven patients (3.4%) had a partial response, 1 patient (0.5%) had a complete response and 54 patients (26.3%) had a stable disease. ORR was 4.4% in patients with prior HCC treatment and 2.2% in those who were treatment naïve with DCRs of 26.9% and 24.4%, respectively. ORR was 1.9% in patients with HCC related to HBV and 4.6% in those with HCC related to another cause, with DCRs of 24.4% and 27.2%, respectively.

3. Treatment Exposure

In SS, 226 patients received an average of 3.4 cycles of treatment (range: 1-13 cycles), with a mean actual dose intensity (ADI) of 31.34 mg/m^2 /week (range: 9.1- 57.5mg/m^2 /week) and a mean relative dose intensity (RDI) of 0.72 (range: 0.2-1.2). Treatment exposure was not influenced by the etiology of HCC (HBV or other cause) and prior treatment for HCC (yes or no).

4. Clinical Laboratory Evaluations

The abnormal significant test results with high frequency were decrease of white blood cell count, neutrophil count, red blood cell count, platelet count, and increase of bilirubin, ALT, AST. In some patients, ALT, AST, and AFP turned back to normal along with the treatment.

5. Other Evaluations Related to Safety

Other evaluations including weight, body surface area, vital sign, physical examination, and ECOG performance score remained at the same level in the majority of patients.

Issue date: 23-Sep-2024