Title: A Phase II Clinical Study of PD-1 Antibody SHR-1210 in Combination with Apatinib Mesylate or Chemotherapy in the Treatment of Advanced Primary Liver Cancer or Extrahepatic Cholangiocarcinoma
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A PHASE II CLINICAL STUDY OF PD-1 ANTIBODY SHR-1210 IN COMBINATION WITH APATINIB MESYLATE OR CHEMOTHERAPY IN THE TREATMENT OF ADVANCED PRIMARY LIVER CANCER OR EXTRAHEPATIC CHOLANGIOCARCINOMA

STATISTICAL ANALYSIS PLAN

(SAP)

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This SAP has been reviewed by the following personnel before being approved and effective.

Functional Role	Reviewer
[redacted]	[redacted]
[redacted]	[redacted]

ABBREVIATIONS

Term	Definition
CR	Complete response
DCR	Disease control rate
DoR	Duration of response
ECG	Electrocardiogram
FAS	Full analysis set
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PE	Physical examination
PFS	Progression-free survival
PR	Partial response
PKS	PK analysis set
SD	Stable disease
SS	Safety set
TEAE	Treatment-emergent adverse event
TRAE	Treatment-related treatment-emergent adverse event
TTR	Time to response
TTP	Time to progression

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1 REVISION

None. This version is drafted with reference to the protocol of SHR-1210-APTN-II-203-PLC (Version 2.0, 12 May, 2018).

2 INTRODUCTION

This study is a phase II clinical study evaluating PD-1 antibody SHR-1210 in combination with apatinib mesylate or chemotherapy in the treatment of advanced primary liver cancer or extrahepatic cholangiocarcinoma.

2.1 Study Design

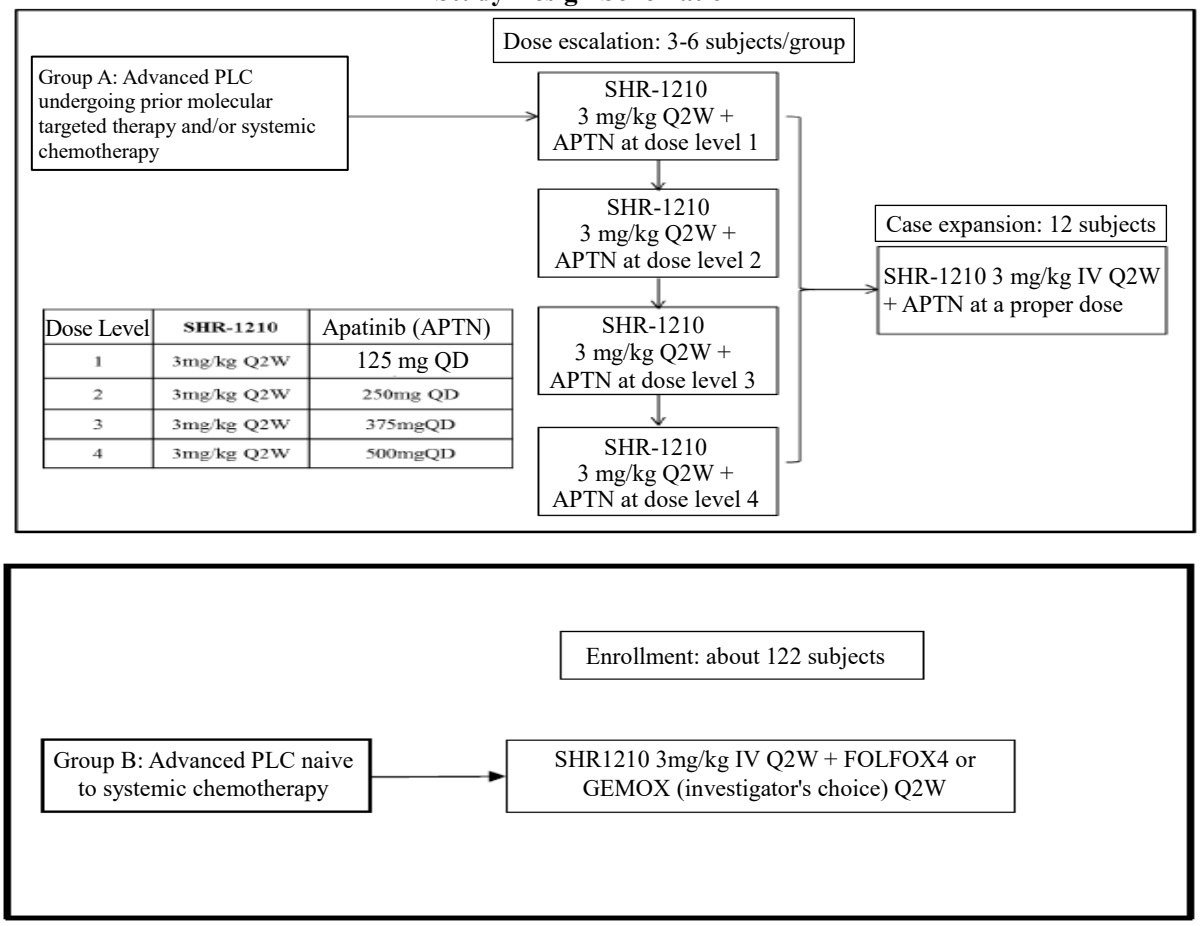
This study is an open-label phase II study, and 152 patients with advanced primary liver cancer or extrahepatic cholangiocarcinoma are intended to be enrolled. Subjects will be enrolled into treatment Group A or B based on whether they have received systemic treatment before.

Subjects in Group A will receive treatment of SHR-1210 in combination with apatinib mesylate (APTN) for exploring the optimal dose first. The objective is to determine the optimal dose of SHR-1210 combined with APTN in patients with advanced primary liver cancer. After the determination of the optimal dose of the combined medication, the dose expansion stage will be proceeded for collecting sufficient safety data of immunotherapy combined with targeted therapy.

Subjects in Group B will receive treatment of SHR-1210 in combination with the FOLFOX4 or GEMOX regimen. The objective is to explore the safety and tolerability of the immunotherapy combined with systemic chemotherapy.

This study will consist of a screening period, a treatment period, and a follow-up period. The study treatment will continue until progressive disease, intolerable toxicity, or subject withdrawal. Every 4-week is a treatment cycle.

Study Design Schematic



Up to 158 subjects are intended to be enrolled in this study (Group A + Group B).

Subjects in Group A will be given dose level 1 as the starting dose. The subjects will be enrolled in the group in sequence (see Table 1) from low dose to high dose to explore the optimal dose. The first cycle (28 days) of continuous administration is the tolerability observation period. After the tolerability observation period, if none of the 3 subjects experienced clinically significant toxicity, study of the next dose group may be initiated. If 1 of the 3 subjects developed clinically significant toxicity, another 3 subjects will be enrolled. If no clinically significant toxicity is observed in the later-enrolled 3 subjects, study of the next dose group may be initiated. If ≥ 1 of the 3 later-enrolled subjects developed clinically significant toxicity again, the dose exploration will be terminated. The dose prior to the current one is the tolerable dose.

Also, the Bayesian logistic regression model (BLRM) will be used as an auxiliary analysis to help explore the probability of clinically significant toxicity at different doses.

Finally, the optimal dose level for case extension is determined through dose exploration, with 8-12 subjects enrolled, to collect sufficient safety data for the combination therapy.

Table 1. Dose levels for Group A.

Dose Level	SHR-1210	Apatinib (APTN)	Number of Enrolled Subjects
1	3 mg/kg Q2W	125 mg QD	3-6
2	3 mg/kg Q2W	250 mg QD	3-6
3	3 mg/kg Q2W	375 mg QD	3-6
4	3 mg/kg Q2W	500 mg QD	3-6

A regimen will be selected by the investigator for the subjects in Group B according to Table 2. Six (6) subjects are first enrolled to receive treatment at dose level 1. If the proportion of subjects showing clinically significant toxicity in the 6 subjects is < 0.33, more subjects will be enrolled to receive treatment at the same dose level until a total of about 122 subjects.

Table 2. Dose levels for Group B.

<table>
<tr><th>Dose Level</th><th>SHR-1210</th><th>FOLFOX4</th><th>Number of Enrolled Subjects</th></tr>
<tr><td rowspan="3">1</td><td rowspan="3">3 mg/kg
Q2W</td><td>D1: Oxaliplatin (OXA) 85 mg/m^2 (2-h infusion) + levoleucovorin (LV) 200 mg/m^2 (2-h infusion), followed by fluorouracil 400 mg/m^2 (bolus injection), and fluorouracil 600 mg/m^2 (22-h infusion)
D2: Levoleucovorin (LV) 200 mg/m^2 (2-h infusion), followed by fluorouracil 400 mg/m^2 (bolus injection), and fluorouracil 600 mg/m^2 (22-h infusion)
Q2W</td><td rowspan="3">Approximately 122 subjects</td></tr>
<tr><td>GEMOX</td></tr>
<tr><td>D1: Gemcitabine 800 mg/m^2 (80-min infusion)
D2: Oxaliplatin (OXA) 85 mg/m^2 (2-h infusion)
Q2W</td></tr>
</table>

During the study period, imaging tumor assessments are performed every 8 weeks (±7 days) until progressive disease or the subject's initiation of other anti-tumor treatments.

2.2 Study Objectives

2.2.1 Primary objective

To evaluate the safety and tolerability of PD-1 antibody SHR-1210 in combination with apatinib mesylate or FOLFOX4 or GEMOX regimen in the treatment of advanced primary liver cancer or extrahepatic cholangiocarcinoma.

2.2.2 Secondary objective

To preliminarily observe the efficacy of PD-1 antibody SHR-1210 in combination with apatinib mesylate or FOLFOX or GEMOX regimen in the treatment of advanced primary liver cancer or extrahepatic cholangiocarcinoma.

2.3 Sample Size

The sample size of Group A will depend on the number of dose groups and the decision made by the clinical department based on some results in the trial. According to the trial data of Group A, 6-12 subjects will be enrolled in the tolerable dose group for the extension study. Approximately 24-36 subjects need to be enrolled.

The sample size of the cholangiocarcinoma population in Group B is calculated as follows:

With reference to previous study results, an unacceptable ORR of 6%, an expected ORR of 15%, a two-sided alpha of 0.05, and a power of 80% are assumed. The Simon two-stage minimax design is adopted. Forty-five (45) subjects are enrolled in the first stage. If at least 3 subjects show response, then proceed to the second stage. Thirty-seven (37) subjects are enrolled in the second stage. A total of 82 subjects will finally be enrolled. If 10 or more subjects show response, then proceed to the next step of the study. Considering a proportion of non-evaluable efficacy of 10%, approximately 92 subjects with cholangiocarcinoma must be enrolled and treated.

For the population with hepatocellular carcinoma in Group B, 20-30 subjects are intended to be enrolled for evaluating the safety of combination therapy and preliminarily evaluating the efficacy. Approximately 122 subjects are to be enrolled in Group B.

3 STATISTICAL HYPOTHESIS AND DECISION RULE

For the sample size calculation of the cholangiocarcinoma population in Group B of this study, the adaptive Simon two-stage design is adopted. If at least 3 subjects in Stage I (45 subjects enrolled) show response, the study will proceed to Stage II. If the minimum number of subjects showing response (3 subjects with response) is observed before the enrollment of Stage I is completed, the enrollment of Stage II can be started immediately after the completion of the

Stage I enrollment without delay. If the minimum number of subjects showing response (3 subjects with response) is not observed after the enrollment of Stage I is completed, enrollment must be delayed until the conditions for continuing the enrollment are met. In the Stage II, 37 subjects are enrolled, reaching a total enrollment of 82 subjects. If 10 or more subjects show response, the efficacy of the investigational subject supports the next step of the study.

4 STUDY ENDPOINTS

4.1 Efficacy Endpoints

- Objective response rate (ORR) assessed by the investigator based on RECIST 1.1, including the proportion of complete response (CR) and partial response (PR)
- Duration of response (DoR) assessed by the investigator based on RECIST 1.1
- Disease control rate (DCR) assessed by the investigator based on RECIST 1.1
- Progression-free survival (PFS) assessed by the investigator based on RECIST 1.1
- Time to response (TTR) assessed by the investigator based on RECIST 1.1
- Time to progression (TTP) assessed by the investigator based on RECIST 1.1
- Overall survival (OS)

4.1.1 Objective response rate (ORR)

ORR: Defined as the proportion of all subjects whose best overall response (BOR) is assessed to be complete response (CR) or partial response (PR) according to RECIST 1.1 criteria. CR or PR must be confirmed at least 4 weeks (28 days) after the initial assessment. BOR refers to the best response assessed by the investigator, i.e., the best response recorded from the date of first dose to the objective documentation of progressive disease as per the RECIST v1.1 criteria or to the start of a new anti-cancer treatment (whichever comes first).

4.1.2 Disease control rate (DCR)

DCR: Defined as the percentage of subjects with CR, PR, and stable disease (SD) for greater than or equal to 6 weeks in the analysis set based on RECIST 1.1. BOR of CR or PR must be confirmed at least 4 weeks (28 days) after the initial assessment.

4.1.3 Duration of response (DoR)

DoR: Defined as the time from the date of first recorded tumor objective response (CR, PR, assessed based on RECIST 1.1) to the date of first recorded objective tumor progression (assessed based on RECIST 1.1) or the date of death due to any cause, whichever occurs first, in subjects with a BOR of CR and PR.

4.1.4 Progression-free survival (PFS)

PFS: Defined as the time from the date of the first dose to the date of first recorded tumor progression (assessed based on RECIST 1.1) or the date of death due to any cause, whichever occurs first.

Censoring rules:

- If there is no baseline tumor measurement or there is baseline tumor measurement but with missing tumor evaluation after baseline, censoring will be based on the date of the first dose.
- If the subject does not have progressive disease or die prior to end of study/analysis cutoff date/dropout and has not received new anti-cancer treatment, censoring will be based on the date of the last valid efficacy evaluation.
- If a new anti-cancer treatment has been initiated before progressive disease or death, censoring will be based on the date of the last valid efficacy evaluation prior to the new anti-cancer treatment.
- For death or progressive disease occurring after two or more scheduled visits (two scheduled visits refer to 16 weeks) are missing, censoring will be based on the date of last valid efficacy assessment carried out prior to death or progressive disease.
- For death or progressive disease with the absence of two scheduled visits after the first dose, censoring will be based on the date of the first dose.

4.1.5 Time to response (TTR)

TTR: Defined as the time from the date of the first dose to the date of first recorded tumor response (assessed based on RECIST 1.1) in subjects whose BOR is CR or PR.

4.1.6 Time to progression (TTP)

TTP: Defined as the time from the date of the first dose to the date of radiographic progression (assessed by the investigator based on RECIST 1.1).

Censoring rules:

- If there is no baseline tumor measurement or there is baseline tumor measurement but with missing tumor evaluation after baseline, censoring will be based on the date of the first dose.

- If the subject does not have progressive disease prior to end of study/analysis cutoff date/dropout and has not received new anti-cancer treatment, censoring will be based on the date of the last valid efficacy evaluation.
- If a new anti-cancer treatment has been initiated before progressive disease, censoring will be based on the date of the last efficacy evaluation prior to the new anti-cancer treatment.
- If death occurs before progressive disease, censoring will be based on the date of the last valid efficacy evaluation prior to death.
- For progressive disease occurring after two or more scheduled visits (two scheduled visits refer to 16 weeks) are missing, censoring will be based on the date of last valid efficacy assessment carried out prior to progressive disease.
- For progressive disease with the absence of two scheduled visits after the first dose, censoring will be based on the date of the first dose.

4.1.7 Overall survival (OS)

OS: Defined as the time from the date of the first dose to death due to any cause. If death does not occur, censoring will be based on the subject's last survival date.

If the subject's death has not been obtained by the analysis cutoff date, the latest complete date of the following data (including but not limited to) will be used as the last survival date:

- All dates of examinations and evaluations of the subjects (tumor response evaluation, blood tests (laboratory), vital signs, physical examination, ECOG PS, pregnancy test, urinalysis, routine stool test, etc.)
- Start and end dates of previous and concomitant medications/concomitant non-drug treatments
- The date of knowing the survival status on the survival follow-up page
- The start and end dates of new anti-tumor treatment after the discontinuation of study treatment
- The start and end dates of AEs
- The start and end dates of study treatment
- The date on the end of study page

Only the date of actual examinations can be used to derive the last survival date. The dates of examinations and evaluations carried out after the cutoff date will not be used to derive the last survival date.

4.1.8 6-, 9-, and 12-month survival rates (6/9/12-month OS%)

6-, 9-, and 12-month survival rates: Defined as the survival rates at 6/9/12 months from the date of the first dose. The 6-, 9-, and 12-month survival rates will be estimated using the Kaplan-Meier method.

4.2 Safety Endpoints

Incidence and severity of adverse events (AEs) and serious adverse events (SAEs). Safety data including the following will be collected and summarized according to the study protocol:

- Adverse events
- Laboratory tests
- Vital signs
- ECOG PS
- ECG
- Physical examination

4.2.1 Adverse events

Including any AE occurring after signing the informed consent form (ICF) and being enrolled in the study.

The following AEs will be collected as adverse events of special interest (AESIs) as per the study protocol:

- Grade ≥ 3 infusion reaction
- Grade ≥ 2 diarrhea/colitis, uveitis, and interstitial pneumonitis
- Other Grade ≥ 3 immune-related AEs
- Any possible hepatic enzyme abnormalities
- Grade 4 amylase or lipase increased

The following analyses will be conducted subsequently:

- Grade ≥ 3 infusion reaction
- Grade ≥ 2 diarrhea/colitis, uveitis, and interstitial pneumonitis
- Grade ≥ 3 immune-related AE
- Any possible hepatic enzyme abnormalities (see the table below)
- Grade 4 amylase or lipase increased

Hepatic enzyme abnormalities:

<table>
<tr><td>Baseline Period</td><td colspan="2">Normal (AST/ALT and TBIL)</td><td colspan="2">Abnormal (AST/ALT/TBIL)</td></tr>
<tr><td rowspan="2">Treatment Period</td><td>ALT ≥ 3 × ULN</td><td>AST ≥ 3 × ULN</td><td>ALT ≥ 8 × ULN</td><td>AST ≥ 8 × ULN</td></tr>
<tr><td colspan="2">Meet one of the two criteria above, with TBIL ≥ 2 × ULN and ALP ≤ 2 × ULN without hemolysis</td><td colspan="2">Meet one of the two criteria above, with TBIL ≥ 3 × ULN or increase ≥ 1 × baseline value</td></tr>
</table>

4.2.2 Laboratory test

Laboratory test results including hematology, clinical chemistry, blood lipase, blood amylase, blood electrolytes, blood coagulation function, alpha-fetoprotein, urinalysis, stool routine, thyroid function, and virological tests will be collected at the visit time points specified in the study protocol.

4.2.3 Vital signs

Vital signs including body temperature, heart rate, respiratory rate, diastolic blood pressure, and systolic blood pressure will be collected at time points predetermined in the study protocol.

4.2.4 Electrocardiogram (ECG)

Heart rate, PR, QT, QTc, QRS, and QTcF will be collected at time points predetermined in the study protocol.

4.2.5 Physical examination

Physical examinations include general condition, head and face, skin, lymph nodes, eyes, ears, nose, throat, oral cavity, respiratory system, cardiovascular system, abdomen, reproductive-urinary system, musculoskeletal system, nervous system, mental state, and other evaluations. These data will be collected at protocol-specified visits/time points.

4.2.6 Other safety endpoints

None.

4.3 Pharmacokinetic Endpoints

None. Not involved in this study.

4.4 Pharmacodynamic Endpoints

None. Not involved in this study.

4.5 Other Endpoints

None.

5 STATISTICAL ANALYSIS

5.1 General Considerations

5.1.1 Analysis sets

The following analysis sets/populations will be defined for statistical analysis:

- **Full analysis set (FAS)**
  It is defined as all eligible subjects who have used the investigational drug after enrollment. The FAS is the primary analysis set for the efficacy analysis of this study.
- **Safety analysis set (SS)**

  It is defined as all enrolled subjects who have received the study drugs at least once and have post-administration safety evaluation data.

5.1.2 General rules and analysis

Baseline

Unless otherwise stated, the "baseline" in this study is defined as the last non-missing measurement value obtained prior to the first use of the investigational drug, including the measurements taken on the day of and prior to the first dose.

Study days

The day of the first dose is defined as the start day of the study. Then, based on the start day of the study, the number of days of study corresponding to test or event is calculated by the following formula:

- Study days = examination date - start date of the study, if the date of an examination/event is before the start date of study;
- Study days = examination date - start date of the study + 1, if the date of an examination/event is on or after the start day of study.

General analysis

Unless otherwise specified, the following descriptive statistics will be summarized by the type of variables:

- Measurement data will be summarized using mean, standard deviation, median, maximum, and minimum.
- Count data are summarized using frequency and percentage.
- For time-to-event data, Kaplan-Meier method will be used to estimate the survival function and median time to event onset, and a survival curve will be plotted.

Number of decimal places

Unless otherwise specified, number of decimal places in the analysis report will be determined as per the following rules:

- The decimal places of the minimum and maximum will remain the same as that of raw data to be acquired; there should be one additional decimal place for the mean and median, and 2 additional decimal places for standard deviation, up to 4 decimal places.
- The percentage will be rounded to 1 decimal place. If the frequency is 0, the percentage is not displayed.
- The 95% CI, if being a decimal, will retain at least 2 decimal places and at most 4 decimal places. *P* values less than 0.0001 will be presented as "< 0.0001".
- Time to event (in months) will be rounded to one decimal place.

Analysis software

All statistical analyses will be conducted using SAS® 9.4 or above.

5.1.3 Derived variables

Time to first pathological diagnosis (months) = (date of enrollment - date of first pathological diagnosis + 1)/30.4375;

Time from last treatment to enrollment (months) = (date of enrollment - last date of any previous anti-tumor treatment + 1)/30.4375.

Duration of exposure to SHR-1210 (days) = date of last dose + 14 - date of first dose;

Duration of exposure to SHR-1210 (months) = (date of last dose + 14 - date of first dose)/30.4375;

Duration of exposure to APTN (days) = date of last dose - date of first dose + 1;

Duration of exposure to APTN (months) = (date of last dose - date of first dose + 1)/30.4375;

The FOLFOX4 regimen contains oxaliplatin (OXA), levulinic acid calcium (LV), and fluorouracil:

Duration of exposure to FOLFOX4 regimen (days) = date of last dose - date of first dose + x, where x = 14 if the last dose is given on D1 or x = 13 if on D2;

Duration of exposure to FOLFOX4 regimen (months) = (date of last dose - date of first dose + x)/30.4375, where x = 14 if the last dose is given on D1 or x = 13 if on D2;

The GEMOX regimen contains gemcitabine and oxaliplatin (OXA):
Duration of drug exposure to GEMOX regimen (days) = date of last dose - date of first dose + x, where x = 14 if the last dose is given on D1 or x = 13 if on D2;

Duration of exposure to GEMOX regimen (months) = (date of last dose - date of first dose + x)/30.4375, where x = 14 if the last dose is given on D1 or x = 13 if on D2;

Relative dose intensity (%) = actual drug exposure/planned drug exposure ×100%;

Dose intensity = cumulative dose/duration of drug exposure.

5.1.4 Covariates and subgroups

Subgroup variables involved in the statistical analysis of this trial:

- Gender (male vs. female)
- Age (< 65 years old vs. ≥ 65 years old)
- Baseline BMI (< 25 kg/m^2 vs. ≥ 25 kg/m^2)
- ECOG (0 vs. 1);
- Alpha-fetoprotein level at baseline (< 400 ng/mL vs. ≥ 400 ng/mL)
- BCLC stage (B vs. C)
- Child-Pugh score (Class A vs. Class B)
- Median diameter of the largest target lesion (< 30 mm vs. ≥ 30 mm)
- Diameter of single lesion in the liver (< 70 mm vs. ≥ 70 mm)
- Presence of portal invasion (yes vs. no)
- Presence of extrahepatic metastasis (yes vs. no)

5.1.5 Analysis window

Data obtained from post-baseline visits will be summarized by protocol visits shown in eCRF. There is no need to consider whether the visit window specified by the protocol has been exceeded.

In the analysis carried out by visits, the statistical analysis will be performed according to the planned time points in the protocol, i.e., the time points of unscheduled visits do not need to be shown.

5.1.6 Missing data

If the missing date and month needs to be imputed, they will be imputed in accordance with the imputation rules of Hengrui date-type data. Time-to-event data will be right-censored if no event is recorded. The judgment of censoring and the calculation of censored time are presented in the corresponding sections. Other missing data are not handled. Apart from exceptional circumstances, the following imputing rules apply to the missing dates of safety data events.

Completely missing dates will not be imputed. If the day is missing but the year and month of the event onset are the same as those of study treatment, then the missing day is imputed with the day of first dose of study treatment, otherwise it is imputed with the first day of that month; if the day of the end date is missing but the year and month of the event onset are the same as those of end date of study treatment, then it is imputed with the day when the study treatment is ended, otherwise it is imputed with the last day of that month.

If both month and day of an event onset date are missing but its year is the same as that of study treatment, then they are imputed with the month and day of starting study treatment, otherwise, they are imputed with 1 Jan.

All imputed dates must be before the date of withdrawal of informed consent form, loss to follow-up, and death.

5.1.7 Cutoff rule

Data as of 31 Mar., 2021 are planned to be cutoff. See the instructions for data cutoff for details.

5.2 Study Subjects

5.2.1 Disposition of subjects

The number of screened subjects, number of enrolled subjects, number and percentage of treated subjects, number and percentage of subjects in the analysis sets (including the FAS and SS), number of subjects who discontinue study/treatment, and number and percentage of corresponding subjects to the reasons for discontinuation.

5.2.2 Demographics

Age, gender, ethnicity, height, weight, and body mass index of the subjects will be summarized using descriptive statistics. A detailed list will be provided.

Age, height, weight, body mass index, sum of diameters of baseline target lesions, and other measurement data will be summarized using the number (n) of evaluable subjects, mean, standard deviation (SD), median, minimum (Min), maximum (Max) and other descriptive statistics.

Gender, ethnicity, etiology (hepatitis B and non-hepatitis B), ECOG PS, BCLC stage, Child-Pugh score, AFP level, presence of invasion to large vessels, presence of extrahepatic metastasis, diameter of single lesion in the liver, and other categorical variables will be summarized using descriptive statistics by the number and percentage of evaluable subjects to the corresponding total number of subjects. Hepatitis B is defined as follows: Surface antigen positive or HBV-DNA positive at baseline.

Age will be calculated with the number of full years between date of birth and signing date of the informed consent form.

Course of disease (months) = (date of first dose – date of first pathological diagnosis + 1)/30.4375.

The BMI calculation formula is: BMI (kg/m^2) = baseline weight (kg)/baseline body height (m^2).

5.2.3 Medical history

Medical history will be coded by system organ class (SOC) and preferred term (PT) in the ICH Medical Dictionary for Regulatory Activities (MedDRA) v23.1. History of allergy, tumor diagnosis, history of chemotherapy, history of targeted therapy, history of radiotherapy, cancer surgery history, medical history, local tumor treatment history, etc. of the subjects will be described accordingly by group.

All medical history will be listed.

5.2.4 Prior therapy and concomitant medication

Prior medications are defined as drugs whose use has been completed before the first dose of the investigational drug during the treatment period. Concomitant medications are defined as drugs that are used after the first dose of the investigational drug, or drugs that are used before the first dose of the investigational drug but are continued to be used during the treatment period.

Prior therapies and concomitant medications are not subjected to medical coding. All prior concomitant medication, concomitant medication, and concomitant non-drug therapy will be listed.

5.2.5 Protocol deviations

Prior to database locking, data of all subjects will be checked for important protocol deviations, if any. All potential important protocol deviations will be reviewed and evaluated by the investigator and the sponsor.

Protocol deviations will be summarized and described by group (each dose level in Group A (apatinib 125 mg group, 250 mg group, 375 mg group, and 500 mg group), different tumor types and treatment regimens in Group B, and different locations and treatment regimens of cholangiocarcinoma in Group B). Protocol deviations will also be listed in detail by subject.

5.3 Efficacy Analysis

The efficacy analysis for this study includes the data assessed by the investigator per RECIST 1.1. The evaluation data will be based on the following endpoints: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and not evaluable (NE). All efficacy analysis will be based on the FAS by treatment group (Group A and Group B), dose level in Group A (apatinib 125 mg group, 250 mg group, 375 mg group, and 500 mg group), different tumor types and treatment regimens in Group B, and different locations and treatment regimens of cholangiocarcinoma in Group B.

5.3.1 Efficacy analyses

5.3.1.1 Objective response rate (ORR)

ORR is defined in Section 4.1.1.

The ORR of each group will be calculated and the corresponding 95% confidence intervals (CIs) will be estimated using the Clopper-Pearson method. The best response of each dose group will be summarized using descriptive statistics.

If response evaluation data of one subject are missing or unknown, then the subject is not evaluable (NE) and will be included in the denominator for percentage calculation.

5.3.1.2 Disease control rate (DCR)

DCR is defined in Section 4.1.2.

Disease control rate (DCR) will be analyzed with method similar to that of objective response rate. DCR will be point estimated and the 95% CI will be calculated using the Clopper-Pearson method.

5.3.1.3 Duration of response (DoR)

DoR is defined in Section 4.1.3.

DoR will be analyzed based on subjects with confirmed CR or PR. The censoring rules are the same as those for PFS. DoR (months) will be calculated using the following formula: (DoR event date/censoring date – first date of CR/PR + 1)/30.4375.

The median DoR (mDoR) will be estimated using the Kaplan-Meier method. The two-sided 95% CI of the median duration will be estimated using the Brookmeyer Crowley method. The survival curve will be plotted.

In addition, descriptive statistics such as the number of subjects, minimum, and maximum will be used to summarize the DoR data. If the maximum value is censored data, it will be displayed in the form of "xx+". The number and percentage of subjects with DoR of at least 6/9/12 months will be calculated.

5.3.1.4 Time to response (TTR)

TTR is defined in Section 4.1.5.

TTR (months) will be calculated using the following formula: (TTR event date – date of first dose + 1)/30.4375.

TTR (months) will be described using the mean, standard deviation, median, maximum, and minimum by population.

5.3.1.5 Progression-free survival (PFS)

PFS is defined in Section 4.1.4.

PFS (months) will be calculated using the following formula: (PFS event date/censoring date – date of first dose + 1)/30.4375.

KM method will be used to analyze PFS, and the median time (month) of PFS will be calculated. The two-sided 95% CI of the median duration will be estimated using the Brookmeyer Crowley method. The PFS curve will be plotted. The 6-, 9-, and 12-month PFS rates will be estimated using the Kaplan-Meier method. The 95% CI of the corresponding survival rate will be calculated using the log (-log) transformation (based on normal approximation) with back transformation to CIs on the untransformed scale.

In addition, the number and percentage of subjects experiencing PFS events, and the number and percentage of censored subjects will be calculated and categorized based on the reason for censoring.

5.3.1.6 Time to progression (TTP)

TTP is defined in Section 4.1.6.

TTP (months) will be calculated using the following formula: (TTP event date/censoring date – date of first dose + 1)/30.4375.

The Kaplan-Meier method will be used to analyze TTP, calculate the median time (months) of TTP and corresponding two-sided 95% CI, and plot the survival curves.

In addition, the number and percentage of subjects experiencing TTP events, and the number and percentage of censored subjects will be calculated and categorized based on the reason for censoring.

5.3.1.7 Overall survival (OS)

OS is defined in Section 4.1.7.

OS (months) will be calculated using the following formula: (OS event date/censoring date – date of first dose + 1)/30.4375.

The median OS (mOS) will be analyzed using the Kaplan-Meier method. The two-sided 95% CI of the median duration will be estimated using the Brookmeyer Crowley method. The survival curve will be plotted. The follow-up times (months) will be described using the number of subjects, maximum, and minimum. If the maximum is censored data, it will be presented in the form of "xx+".

At the same time, the number and percentage of OS events as well as the censoring number and percentage are calculated and classified according to the reason of censoring.

5.3.1.8 6-, 9-, and 12-month survival rates (6/9/12-month OS%)

See section 4.1.8 for the definition of 6-, 9-, and 12-month survival rates.

The Kaplan-Meier method will be used to calculate the 6-, 9-, and 12-month survival rates and calculate the 95% CI (using the log (-log) transformation (based on normal approximation) with back transformation to CIs on the untransformed scale).

5.3.2 Exploratory analysis

No exploratory analysis is involved.

5.3.3 Subgroup analysis

The efficacy endpoint of investigator-assessed ORR will undergo the following subgroup analysis based on the FAS, for descriptive analysis only.

- Gender (male vs. female)
- Age (< 65 years old vs. ≥ 65 years old)
- Baseline BMI (< 25 kg/m^2 vs. ≥ 25 kg/m^2)
- ECOG (0 vs. 1)
- Alpha-fetoprotein level at baseline (< 400 ng/mL vs. ≥ 400 ng/mL)
- Child-Pugh score (Class A vs. Class B)
- Median diameter of the largest target lesion (< 30 mm vs. ≥ 30 mm)
- Diameter of single lesion in the liver (< 70 mm vs. ≥ 70 mm)
- Presence of portal invasion (yes vs. no)
- Presence of extrahepatic metastasis (yes vs. no)

5.3.4 Other analysis

Based on the FAS, the sum of post-baseline target lesion diameter values against the change value of baseline best efficacy will be plotted (i.e. waterfall plot).

Based on the FAS, the pool plots of objective response will be drawn.

Based on the FAS, the classifications of subsequent anti-tumor treatments (chemotherapy, targeted therapy, radiotherapy, surgery, traditional Chinese medicine, and others) after progressive disease will be summarized and listed.

Based on the SS, the ORR will be summarized according to the presence or absence of capillary endothelial proliferation (RCEP). The inter-group differences in ORR between the two populations will be tested. And the *P* value will be calculated using the Fisher Exact probability method.

5.4 Safety Analysis

All safety analyses will be conducted based on the SS.

5.4.1 Extent of exposure

The duration of drug exposure, cumulative dose, dose intensity, and other information regarding the use of the investigational drug SHR-1210, apatinib mesylate, FOLFOX4 regimen, and GEMOX regimen will be summarized by group and drug. Derived variables are defined in Section 5.1.3.

5.4.2 Adverse events

All adverse events (AEs) will be coded according to MedDRA v23.1 and graded using NCI CTCAE v4.0.3. For the same SOC and/or PT, multiple occurrences of the same event in one subject will be counted only once. For the same AE reported in one subject multiple times but varying in CTCAE grade, the worst grade episode will be enumerated. AE analysis will mainly focus on treatment emergent adverse events (TEAE), i.e., AEs that occur on the day of the first study dose (combination of SHR-1210 and apatinib or combination of SHR-1210 and FOLFOX4/GEMOX) or thereafter.

This study is a trial on combined medication. For drug-related adverse events, the correlation with the combined drugs must also be considered. Treatment-related includes "definitely related", "possibly related", and "indeterminable". For Group A, treatment-related is defined as "SHR-1210-related" or "APTN-related". For Group B, treatment-related is defined as "SHR-1210-related" or "combination chemotherapy-related" (i.e., "FOLFOX4 related"/ "GEMOX-related"). If the relationship between an AE and the study drug is missing, the AE will be considered as a treatment-related AE.

The incidences of AEs will be sorted from high to low based on their corresponding SOC, and the incidences of AEs under each SOC will be sorted from high to low based on their PT. If the incidence of ≥ 2 PT is equal, the AEs will be sorted alphabetically. Refer to the notes below each chart of Mock-Up Shell for details.

AEs will be summarized using descriptive statistics according to Hengrui's Statistical Analysis Reporting Standards, including but not limited to:

- Overview of adverse events (all-cause and treatment-related)
- Summary of AEs by SOC, PT, and CTCAE grade
- Summary of AEs by SOC and PT (all grades and CTCAE Grade ≥ 3)
- Summary of AEs with an incidence of ≥ 5% by SOC and PT
- Summary of SAEs by SOC, PT, and CTCAE grade
- Summary of SAEs by SOC and PT (all grades and CTCAE Grade ≥ 3)
- Summary of SAEs with an incidence of ≥ 5% by SOC and PT

  Summary of treatment-related AEs by SOC and PT (all grades and CTCAE Grade ≥ 3)
- Summary of treatment-related AE by SOC, PT, and CTCAE grade
- Summary of treatment-related AEs with an incidence of ≥ 5% by SOC and PT
- Summary of AESIs including reactive capillary endothelial proliferation, Grade ≥ 3 infusion reaction, Grade ≥ 2 interstitial pneumonia, Grade ≥ 3 immune-related adverse event, and hepatic enzyme abnormal by SOC and PT
- Summary of immune-related adverse event by SOC and PT
- Summary of AEs resulting in study withdrawal by SOC and PT
- Summary of AEs resulting in treatment withdrawal by SOC and PT
- Summary of treatment-related AEs resulting in treatment withdrawal by SOC and PT
- Summary of AEs resulting in death by SOC and PT
- Summary of treatment-related AEs resulting in death by SOC and PT

All collected AEs will be listed. SAEs, AESIs, treatment-related AEs, AEs resulting in study withdrawal, and AEs resulting in death will be listed, respectively.

Clinically significant toxicities will be summarized and listed by frequency and percentage.

Subjects who have at least one reactive capillary endothelial proliferation, subjects who have at least one cutaneous reactive capillary endothelial proliferation, and subjects who have at least one non-cutaneous reactive capillary endothelial proliferation, and their corresponding outcomes will be summarized and listed using frequency and percentage by dose groups in Group A and different tumor types or different locations in Group B.

5.4.3 Laboratory evaluations

The baseline is defined as the last measurement before the first dose. Data will be summarized using descriptive statistics according to Hengrui Statistical Analysis Reporting Standards, including but not limited to:

- Incidence of abnormal measurements and parameters.

Listings of abnormal laboratory findings will be provided.

5.4.4 Vital signs

The examination items for vital signs include: weight (kg), body temperature (℃), heart rate (beat/min), respiratory rate (resp/min), diastolic blood pressure (mmHg), and systolic blood pressure (mmHg).

Vital signs data will also be reported in listing.

5.4.5 Electrocardiogram (ECG)

The examination items for ECG include: heart rate (beat/min), PR interval (ms), QT interval (ms), QTC (ms), QRS (ms), and QTcF (ms).

The most significant decrease in ECG results from baseline in each group will be classified and summarized per the following criteria: change < 30 ms, 30 ms ≤ change ≤ 60 ms, and change > 60 ms.

ECG data will be reported in listing.

5.4.6 Physical examination

Physical examination data will be reported in listing.

5.4.7 Other safety measures

The number and percentage of subjects who have at least one reactive capillary endothelial proliferation, the number and percentage of subjects who have at least one cutaneous reactive capillary endothelial proliferation, and the number and percentage of subjects who have at least one non-cutaneous reactive capillary endothelial proliferation will be summarized based on the SS. In addition, the time from dose interruption to recovery/resolution will be calculated based on subjects with multiple events that all recovered/resolved, or with events that recovered with sequelae/resolved with sequelae. The date of recovery/resolution is based on the latest date of multiple events that all recovered/resolved, or events that recovered with sequelae/resolved with sequelae.

- If the date of the last dose is less than the date of recovery/solution, the time from dose interruption to recovery/resolution refers to the date of recovery/solution - the date of last dose + 1;
- If the date of the last dose is greater than the date of recovery/solution, the time from dose interruption to recovery/resolution refers to the date of recovery/solution - the date of last dose;

In addition, the time from dose interruption to remission is calculated based on subjects with multiple events that all remitted.

- If the date of the last dose is less than the date of remission, the time from dose interruption to remission refers to the date of remission - the date of last dose + 1;
- If the date of the last dose is greater than the date of remission, the time from dose interruption to remission refers to the date of remission - the date of last dose;

The time from dose interruption to recovery/resolution, the time from dose interruption to remission, and other measurement data will be summarized using descriptive statistics such as the number of subjects (n), mean, standard deviation (SD), median, minimum (Min), and maximum (Max).

5.5 Pharmacokinetic Analysis

This trial does not involve PK analysis.

5.6 Pharmacodynamics Analysis

This trial does not involve PD analysis.

5.7 Other Analysis

This trial does not involve other analyses.

6 INTERIM ANALYSIS

This trial does not involve interim analysis.

7 REFERENCES

1. Simon R (1989). Controlled Clinical Trials 10: 1-10.

2. NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

See http://evs.nci.nih.gov/ftp1/CTCAE/About.html.

8 APPENDIX

Appendix 1. Best overall response (BOR) with CR and PR to be confirmed

Table 1. Best overall response when confirmation of CR and PR required

Overall Response at First Time Point	Overall Response at Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD (provided minimum criteria for SD duration met, otherwise, PD)
CR	PD	SD (provided minimum criteria for SD duration met, otherwise, PD)
CR	NE	SD (provided minimum criteria for SD duration met, otherwise, NE)
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD (provided minimum criteria for SD duration met, otherwise, PD)
PR	NE	SD (provided minimum criteria for SD duration met, otherwise, NE)
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable.
[a]: If a CR is truly met at first time point, then efficacy of any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, will still be evaluated as PD at that point (since disease will reappear after CR). Best response will depend on whether minimum duration for SD is met. However, sometimes CR may be claimed when subsequent scans suggest small lesions are likely still present and in fact the subject has PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.