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Global Assessment of Predictive Biomarkers in Malian BCLC Stage C Hepatocellular Carcinoma Patients under Mono or Combination Immune Checkpoint Inhibitors Treatment: A Proposed Research Protocol

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ABSTRACT

Background: *According to the Barcelona Clinic Liver Cancer (BCLC) staging system, only the advanced stage (stage C) hepatocellular carcinoma (HCC) patient is eligible for systemic treatments. In addition to sorafenib and lenvatinib that represent the standard-of-care options in the first-line treatment, the multikinase inhibitors regorafenib and cabozantinib or ramucirumab, the anti-vascular-endothelial growth factor-2 (VEGF-R2) in the second-line setting but their poor tolerability have brought out the need for new therapeutic strategies, the immune checkpoint inhibitors (ICIs) might represent the most important novelty and the future perspective also in the field of HCC. Therefore, the need to identify predictive biomarkers to select those patients who might actually benefit from ICIs-based treatment is urgently a challenge. Our central hypothesis is that the global assessment of predictive biomarkers could help patient-specific choices for ICIs treatment by developing simplified therapeutic algorithms and novel prognostic index for efficient HCC management. The primary aim of this work will be to globally assess predictive biomarkers in Malian patients with BCLC stage C HCC undergoing treatment with ICIs in mono or in combination.*

Method/Design: *To assess hematogical, biochemical, immunohistological, epigenetical, genetical and neoantigenic predictive biomarkers in Malian BCLC stage C HCC cohort, we are going to conduct a national and multi-centre cohort study with prospective data collection during the study period between January 1, 2024 to December 31, 2026. All consented patient with BCLC stage C HCC treated with sorafenib or ICIs in first line or second line therapy during a study period will be included. Potential participants will be screened for eligibility criteria and after obtaining well-informed written consent. The participants will be distributed in 1: 1 manner into experimental group/group A (ICIs mono or combination therapy with first or second line) and control group/group B (Sorafenib in first line).*

Discussion: *This cohort study will the potential to make an important contribution to increase the knowledge on predictive biomarkers associated to clinical responses outcomes, immune-related adverse events and others evolutionary outcomes in-patient with HCC under ICIs treatment.*

Keywords
Research protocol, Predictive biomarkers, Immune checkpoint inhibitors, Hepatic carcinoma cancer, Africa.

Background
Primary liver cancer is the sixth most commonly diagnosed cancer and the third leading cause of cancer death worldwide in 2020, with approximately 906,000 new cases and 830,000 deaths [1]. Primary liver cancer includes hepatocellular carcinoma (HCC) (comprising 75%-85% of cases) and intrahepatic cholangiocarcinoma (10%-15%), as well as other rare types [1]. The main risk factors for HCC are chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), aflatoxin-contaminated foods, heavy alcohol intake, excess body weight, type 2 diabetes, and smoking [2]. In Mali, in 2020, liver cancer is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death, with an estimated 727 new cases and 684 deaths [3,4].

Regarding diagnostic and therapeutic strategy of HCC, the Barcelona Clinic Liver Cancer (BCLC) is the one of more staging systems used. It consist five stages for the disease: patients with early HCC (stage 0/A) who are candidates for curative-intent radical therapies such as resection, liver transplantation and ablation; patients with multinodular tumours (stage B, intermediate) and candidate to local treatment, such as chemoembolization; those in advanced stage (stage C), eligible for systemic treatments and patients in terminal stage (stage D) for whom palliative cares are recommended [5].

In addition to tyrosine kinase inhibitors, multikinase inhibitors and anti-vascular-endothelial growth factor-2 (VEGF-R2), the systemic management of HCC has been revolutionized by the advent of immune checkpoint inhibitors (ICIs), a therapeutic class of monoclonal antibodies that blocks the immune checkpoints. These are co-inhibitory molecules physiologically expressed in different cells types, such as natural killer cells, dendritic cells, tumor-associated macrophages, monocytes and myeloid-derived suppressor cells (MDSCs)—including B and T cells, and that mantains self-tolerance. ICIs act by applying a break that prevent the activation of these cells, limiting tissue damage. The main immune checkpoint receptors are CTLA-4, PD-1, TIM-3, BTLA, VISTA, LAG-3 and OX-40. In this field, two classes of ICIs are currently being tested as mono or combination therapies: CTLA-4 (tremelimumab and ipilimumab) and PD-1/PD-L1 inhibitors (anti-PD-1: nivolumab, pembrolizumab, tislelizumab, camrelizumab and sintilimab; anti PD-L1: atezolizumab and durvalumab) [6-9]. Additionally, the authorization was recent in the majority of cases, even though, we have a very few data (or no one in some cases) regarding the phase IV, as well as real life data from the every-day clinical practice [9].

Indeed, Numerous studies on predictive biomarkers in various cancers treatment with ICIs such immune cell infiltration, peripheral blood analyses, PD-L1 overexpression, copy number alterations, neoantigen clonality, mutational landscape, mismatch-repair deficiency, transcription factors, and miRNA were performed [9-16].

Despite, literature data on predictive biomarkers in patients with advanced HCC under ICIs remain insufficient to propose a patient-specific choice for ICIs treatment and even to develop simplified therapeutic algorithms and novel prognostic index for efficient HCC management.

Although, the biotherapy is progressively invited in the therapeutic arsenal of inflammatory diseases, especially HCC in Africa and particularly in Mali where global assessment of hematogical, biochemical, immunohistological, epigenetical, genetical and neoantigenic predictive biomarkers associated to therapeutic efficacy, ICIs toxicities, and others evolutionary (partial remission, progression-free survival, overall survival, relapsed cases, and deaths) outcomes in HCC patient constitute almost a virgin ground.

Thus, a global assessment of predictive biomarkers in patients with advanced HCC under ICIs compared to those under empirical sorafenib 200 mg therapy could allow the identification of relevant predictive biomarkers associated with therapeutic efficacy and immune-related adverse events (irAEs), and the development of a simplified therapeutic algorithms and novel prognostic index helping in patient selection and decision making by distinguishing responders and non-responders.

In Mali, none study has assesses predictive biomarkers especially from patients with advanced HCC on ICIs. Here, there are some laboratories skills with high training specialist for hematological, biochemical, immunohistochemical tests but genetic and epigenetic approaches knowing some difficulties. In order to assess overall predictive biomarkers, such project can helping for determine the prevalence of patients with advanced HCC on ICIs, relevant predictive associated to therapeutic response and irAEs, built Malian robust oncology team and further Cancer training and research center in perspective.

The primary aim of this work will be to globally assess predictive biomarkers in Malian patients with BCLC stage C HCC undergoing treatment with immune checkpoint inhibitors in mono or in combination. The specific aims will be: i. to describe sociodemographic aspects of a study population; ii. to determine the clinical presentation of a study population; iii. to class our HCC patients according to the Barcelona Clinic Liver Cancer staging system; iv. to describe therapeutic and follow up aspects of a study population; v. to identify predictive biomarkers associated to clinical responses; vi. to identify predictive biomarkers associated to irAEs; vii. to put in place a biobank for adequate investigation.

Method

Setting/location

The Hemato-oncology and internal medicine department at the University Hospital Center of the Point G and oncology department at the Hospital Luxembourg Mother and child Hospital will serve as the place of recruitment of patients. These hospitals treat cancer cases in Mali. The anatomopathology department at the University Hospital Center of the Point G will conduct immunohistochemical examination especially HCC diagnosis. Hematological and biomedical laboratory unit of Univesity Clinical Research Center (UCRC), well-epuiped with well-trained biologist, will serve to carry out hematological and biochemical tests. For immunological tests such flow cytometry, immunology unit of SEROFO is able to carry out it. For genetic and epigenetic tests, foreign laboratory will be solicited.

Study Design

To assess hematogical, biochemical, immunohistological, epigenetical, genetical and neoantigenic predictive biomarkers in Malian BCLC stage C HCC cohort, we are going to conduct a national and multi-centre study with prospective data collection from patients with BCLC stage C HCC during the study period between January 1, 2024 to December 31, 2026, i.e. 3 years.

Sampling

This will be an exhaustive sampling of all patients with BCLC stage C HCC during the study period. All diagnosed liver cancer will be classified according to the Barcelona Clinic Liver Cancer staging system.

Sample size calculation

For the estimation of the prevalence rate of HCC in a national, multi-center, and prospective study, we will use the calculation of the minimum sample size using the following formula: $n = {}^{[z2*p(1-p)]}/_{e2}\,/\,{}^{2}/_{1+[z\ *p(1-p)]\,/\,e\ *N]}$. The confidence interval is 95%, i.e. Z= 1.96. The hospital prevalence of HCC in Mali is 5, 1% [17], which implies that $Z^2 = 0.95$. The population of Mali, i.e. 20,250,834 inhabitants. With a choice of margin of error at 5%, which is 0.05, a minimum sample size of 74, 4 was calculated. Attrition rate of 10% was incorporated in the calculation and sample size was estimated at 82 participants in each group.

Eligibility Criteria

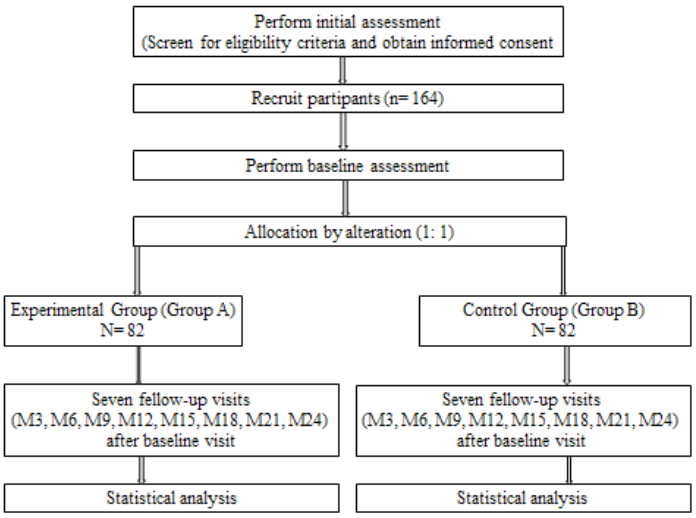
All consented patient with BCLC stage C HCC treated with sorafenib or ICIs in first line or second line therapy during a study period will be included. Will not be included in this study, others BCLC stage of HCC than BCLC stage C hepatocellular carcinoma; under others treatment regimens for BCLC stage C hepatocellular carcinoma other than sorafenib and ICIs; outside the study period; outside the study sites.

Recruitment and allocation

Potential participants will be screened for eligibility criteria and after obtaining well-informed written consent, it will be recruited as a participant. The participants will be distributed in 1: 1 manner into experimental group/group A (ICIs mono or combination therapy with first or second line) and control group/group B (Sorafenib in first line) (Figure 1). ICIs may be ipilimumab 5 milligrams per milliliter (Ipilimumab 3 mg/kg IV immediately following nivolumab 1 mg/kg IV on the same day, q3Weeks for 4 doses; after completing 4 doses of combination therapy, continue nivolumab as a single-agent until intolerable toxicity or disease progression) [18] and nivolumab 10 milligrams per milliliter (Nivolumab 1 mg/kg IV q3Weeks PLUS Ipilimumab 3 mg/kg IV on the same day for 4 doses; after completing 4 doses of combination therapy: Administer nivolumab 240 mg IV q2Weeks or 480 mg IV q4Weeks; continue until disease progression or unacceptable toxicity) [19]. Sorafenib 200 milligrams is indicated for unresectable hepatocellular carcinoma with

400 mg PO q12hr; if skin toxicity, discontinue/decrease dose frequency to qDay or every other day as recommended by Manufacturer [20].

Figure 1: Shows the study procedure in the form of a flow chart



Study procedure: Assessments and data collection

The study design and assessment plan is summarized in Figure 1. Part 1 of the study will permit to recruit, allocated participants, and to start follow-up with predictive biomarkers data collection, management and analysis from the 82 eligible subjects of each group during 1 years. Part 2 correspond of the end of recruitment and allocation and continuing follow-up until M24 from the last recruited participant. And this part 2 of the study will focus

on genetic, epigenetic and neoantigenic data management and analysis. It will last 2 years.

Both parts of the study follow the same planned protocol schedule consisting of a baseline visit followed by seven consecutive visits (Baseline visit, M3, M6, M9, M12, M15, M18, M21, and M24 visits), plus additional unscheduled visits in the event of HCC complications.

Sociodemographical and clinical assessments, sampling for laboratory assessments and therapeutic responses and evolutionary outcomes are to be performed at specified visits, as shown in table 1.

Table 1: Schedule of variable assessment during follow-up.

Assessments	Baseline visits	Follow-up
Sociodemographic data	X	
age	X	
sex	X	
profession	X	
ethnicity	X	
Clinical data	X	X
physiological personal history	X	
pathological personal and familial history	X	
physical examination findings	X	X
ECOG PS scale	X	
Child-Pugh scale	X	
BCLC findings	X	
others	X	X
Immuno-hematological data (hemogram or flow cytometry)	X	X
lymphocytes (CD4+, CD8+)	X	X
B Cells (CD20+)	X	X
lymphocytes (CD134+, CD137+, and FOXP3+)	X	X
natural killer cells (NKp46+)	X	X
peripheral blood absolute lymphocyte count	X	X
absolute eosinophil count; relative lymphocyte count	X	X
circulating tumor cells	X	X
number of activated T cells (CD134+, CD137+, and FOXP3+)	X	X
monocytes (CD16+ and CD68+)	X	X
CD8+PD-1hiCTLA-4hi and CD4+FOXP3-PD-1hi subpopulations	X	X
myeloid-derived suppressor cells	X	X
others	X	X
Biochemical data	X	X
LDH level	X	X
others	X	X
Immuno-histological data	X	X
tumor-infiltrating lymphocyte (CD4+, CD8+)	X	X
Basal level expression of PD-L1	X	X
IFN-γ signaling in CD8+ T cells	X	X
PD-L1 copy number gain	X	X
expression of IDO	X	X
Th1-associated markers	X	X
ICOS pathway	X	X
others	X	X
Mutational and Neoantigenic data	X	X
neoantigen-expressing tumor clones	X	X
clonal mutations in neoantigens	X	X
mismatch-repair deficiency	X	X
others	X	X
Genetic data	X	X
overexpression of IGK, GBP1, STAT1, IGLL5, and OCLN	X	X
overexpression of immune-related peptides expanding pre-existing T cells	X	X
copy number alterations (CAN) of PD-L1 and PD-L2	X	X
others	X	X
Epigenetical data	X	X
methylation pattern of PD-L1 and CTLA-4	X	X
serum levels of miRNA	X	X
others	X	X
TTherapeutic data	X	X
Regimen of first-line with Sorafenib or ICIs in monotherapy	X	X
Regimen of second-line with ICIs combination	X	X
Evolutionary data	X	X
Partial remission	X	X
Complete remission	X	X
ICIs related-adverses events	X	X
Sorafenib related-adverses events	X	X
progression-free survival	X	X
overall survival	X	X
relapsed cases	X	X
deaths	X	X

Definitions

Some conditions and outcomes are defined in the table 2**.**

Table 2: Definitions of conditions and outcomes.

Conditions/outcomes	Definitions
BCLC staging system in HCC	Advanced stage; preserved liver function; ECOG PS: 1 – 2; Child Pugh: A – B; macrovascular invasion or extrahepatic spread.
First-line therapy of BCLC stage C HCC	Tyrosine kinase inhibitors (sorafenib) or ICIs monotherapy (Ipilimumab + Nivomumab)
Second-line of BCLC stage C HCC	ICIs combination (Ipilimumab + Nivomumab) indicate if irAEs or non-responders to first-line therapy

Biosampling

Biosampling will take place at inclusion and after 12 and 24 months. Blood samples will be collected at these times. All samples will be processed immediately according to a standardized protocol. All samples will be frozen at −80°C and stored at the Liquid Biobank (LBB, www.biobankenbern.ch), Inselspital, Bern, until further analysis in batches. The following parameters will be examined: hematological, biochemical, immunohistochemical, and especially genetic, epigenetic and neoantigenic predictive biomarkers.

Outcomes

Primary Outcome Measures

Primary outcomes will be hematogical, biochemical, immunohistological, epigenetical, genetical and neoantigenic predictive biomarkers associated to clinical responses, ICIs

toxicities, and others evolutionary (partial remission, progression-free survival, overall survival, relapsed cases, and deaths) outcomes. These predictive biomarkers will be measured by hemogram, flow cytometry, biochemical test, immunohistochemical examination, exploring epigenetic, genetic and neoantigenic tests. A structured questionnaire on the clinical responses, ICIs toxicities and evolutionary outcomes will be administered.

Secondary Outcome Measures

Secondary outcomes will be the characterization the socio-demographic, clinical, therapeutic and evolutionary aspects and the novel predictive biomarkers of patients with BCLC stage C HCC identified because of cross-sectional analysis between these aspects and predictive biomarkers. A structured questionnaire on these aspects will be administered and predictive biomarkers measurement as stipulated below will be done.

Data Management and Analysis

Database

All data from this cohort study will be collected electronically using a dedicated central electronic data capturing system (REDCap). All structured questionnaires will be distributed as online surveys and directly entered electronically into the database.

Data Management

Data will be extracted under strict confidential measures, anonymised and will be accessible to only research supervisors during the data extraction process. The extracted data will be captured and saved into a password-protected Microsoft Access 2016 database with the password known to only persons responsible for data capturing and the principal investigators. Data capturing will be managed and coordinated by a dedicated data manager who checks all captured data for correctness. The finalised database will be stored in a secured electronic system and backed-up on a dual-core electronic processor. Then it will be exported into SPSS version 22 software for analysis.

Data Analysis

To detect a positive correlation between predictive biomarkers and clinical responses, irAEs and others outcomes, a cross-sectional analysis (comparison between patients and controls of data acquired during the follow-up) of continuous variables will be done with Student's t test or analysis of variance or in case of skewed distributions which cannot be normalized corresponding nonparametric tests will be used. Chi-squared and fisher's exact tests will be used for cross-sectional analysis of categorical variables. The relative risk (hazards ratios) will be calculated with their corresponding 95% confidence intervals and alpha level of 0.05 will be applied as the criterion for statistical significance. Quantitative data will be presented as means and standard deviation; and qualitative data will be expressed as numbers and percentages.

Ethical issues

The protocol will be submitted to the Faculty of Medicine, of Pharmacy and Odonstomatology ethics committee for approval. The anonymity of the patients will be guaranteed, the informed consent of all participants will be obtained.

Discussion

Among BCLC staging system, only the advanced stage (stage C) HCC patient is eligible for systemic treatments. Indeed, according to international guidelines, sorafenib and lenvatinib represent the standard-of-care options in the first-line treatment, the multikinase inhibitors regorafenib and cabozantinib or ramucirumab, the anti-vascular-endothelial growth factor-2 (VEGF-R2), are the main choices in the second-line setting but their poor tolerability have brought out the need for new therapeutic strategies. In this context, the immune checkpoint inhibitors (ICIs) might represent the most important novelty and the future perspective in the field of HCC. Therefore, the need to identify predictive biomarkers to select those patients who might actually benefit from ICIs-based treatment is urgently a challenge [4,9].

Detailed information on predictive biomarkers specifically in stage C HCC patients remains scarce. These data are often derived from outside Africa and are not multidimensional approaches notably assessing globally the predictive biomarkers in these patients.

This cohort study will the potential to make an important contribution to increase the knowledge on predictive biomarkers associated to therapeutic efficacy, IrEAs and others evolutionary outcomes in patient with HCC under ICIs. Our study will differ from previous studies by assessing globally the predictive biomarkers whose the well-conducted cross-sectional analysis could provide novel relevant predictive biomarkers, simplified therapeutic algorithm, and novel prognostic index development; and by holding in Africa particularly in Mali where predictive biomarkers especially in BCLC stage C HCC patient constitute almost virgin ground. To address the complexity of the study, this study will be supported by a large team of experts in different fields, and has national and international collaborations.

As this study addresses the evolution of stage C HCC patient under ICIs, a limitation will be the national recruitment, which does not allow generalization of our data. We are exploring a future study to fill this gap and to provide an additional multi-country study.

The results of this study are expected to change current therapeutic approach in BCLC stage C HCC patient by focusing on patient-specific choice of ICIs after assessing globally the predictive biomarkers, improve stage C HCC patient prognosis, provide novel predictive biomarkers, and to implement the biobank in Mali so that to pursue investigation for predictive biomarkers by others protocols or by others researcher.

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