Title of Research
Patient Reported Outcomes (PRO) As Prognostic Markers In Patients Treated With Targeted Therapies For Advanced Hepatocellular Carcinoma (PRO²-HCC)

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Summary of Research
Preservation or improvement of health-related quality of life (HR-QoL) is a major treatment goal for patients with advanced cancer in a palliative setting. In addition, quality of life may be a marker of disease aggressiveness. We will study whether patient-rated quality of life could replace an evaluation of general patient health status by a physician as a way to assess prognosis in hepatocellular carcinoma (HCC).

Various tools have been designed and validated to capture QoL, such as the EORTC QLQ-C30 and FACT scales. These are well established as primary or second or primary endpoints in oncology clinical trials. The EORTC QLQ-C30 has been translated into more than 100 languages, incorporating five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status/QoL scale, and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation and diarrhea) and perceived financial impact of the disease. Version 3.0 is the most recent.

HR-QoL scales are mostly used as a tool to compare the efficacy of different treatments. However, several studies have shown that Patient-Reported Outcomes (PRO), and especially measures of HR-QoL, can have a prognostic value. Various functional, symptom or global health status scales from the EORTC QLQ-C30 have been shown to be of predictive value across a wide range of cancers, including HCC. Moreover, in several studies, HR-QoL measures showed greater prognostic value than the clinician-rated Performance Status (PS). There may be several reasons for this: the qualitative nature of the WHO PS means that this provides less information than the continuous scoring used in QLQ-C30 scales; and there may be a lack of agreement between physician and patient assessments. Research suggests that physicians frequently underestimate symptom severity, especially for subjective symptoms such as fatigue, resulting in overestimating the overall health status of their patients.

Nevertheless, PS remains the most widely used and easiest way to evaluate the global health status of patients to inform treatment decision-making. Thus, PS is frequently used to determine eligibility and stratification for clinical trials, and is a component of widely-used prognostic scores such as the Barcelona Clinic Liver Cancer (BCLC) scale in HCC.

Some authors suggest that in HCC, it is possible to use HR-QoL scales instead of PS, especially for clinical research. However, the literature shows considerable heterogeneity between the various scales used to assess HR-QoL, and in the sub-scales of the EORTC QLQ-C30 shown to be of prognostic significance. Regarding the EORTC QLQ-C30 in HCC, the sub-scales most often reported as being prognostic are the Global Health (GH), the

Role Functioning (RF) and the Physical Functioning (PF) scales, and various symptoms sub-scales as fatigue, diarrhea and dyspnea. Moreover, no study has proposed a simple system for routine use of the EORTC QLQ-C30 as a prognostic indicator. To our knowledge, only one paper (Diouf *et al.*, 2015) has defined optimal cut-off points for QLQ-C30 subscales which could be useful for clinical trials and updates of existing prognostic systems. However, in our opinion, this remains difficult to use routinely. This is due to the complexity of the QLQ-C30 scoring process, and to the fact that it cannot replace the univariable and binary criteria, such as either "PS=0 vs PS>0" stratification criterion or PS < 2 eligibility criterion are often used in clinical trials.

Regarding studies of HR-QoL as a prognostic factor specifically for HCC, various dimensions have been shown to be associated with overall survival (OS). A comparison between functional scales – especially both RF and PF – with OMS PS could be useful. However, the literature does not define one specific parameter as the best to use for survival forecasting, and the feasibility of replacing PS with this unique parameter in existing classification systems has not been evaluated.

We performed a preliminary study in 81 patients treated with standard targeted therapy for advanced HCC, renal cell carcinoma (RCC) or melanoma, who completed the EORTC QLQ-C30 questionnaire when treatment was initiated, as part of their routine follow-up. We retrospectively analyzed the data from the questionnaires with the goal of defining an easy-to-use QoL criterion with prognostic value. In this preliminary study, we were able to define a RF score >75 (which is in line with the Diouf *et al.* 2015 cut-off of 66.67 in 271 patients) as being strongly prognostic, with median OS of 23.4 vs 6.0 months for those with a RF score <75 (Hazard Ratio (HR) = 0.26, p<0.001). RF score remained independently associated with OS even when adjusting for the PS. However, our data came from a small heterogeneous cohort from one center. Data from a large prospective trial could enable development of a robust HR-QoL parameter for self-evaluation of patient global health. We failed to show that patient self-reported RF could replace physician-reported PS.

We therefore aim to define a more appropriate HR-QoL score associated with overall survival, from a multinational cohort of more than 1,000 patients included in a phase 3 clinical trial; our final objective is to keep only one dimension by a binary score. Data from the BRISK-FL trial, especially HR-QoL elements, have already been published, comparing the results of treatment between the two arms, but not addressing the question of the baseline values as prognostic factors. We will not compare results of QoL between treatment arms, as we aim to define a prognostic parameter for use with any treatment. Also, we will not study the evolution of QoL parameters during treatment, focusing on baseline parameter.

We hypothesize that it is possible to provide a simple patient self-reported system adapted from the EORTC QLQ-C30 scales to provide accurate forecasting of overall survival. This might replace or improve evaluation of general health through clinician-reported activity of patients' daily living, with basic tools such as the WHO PS.

Study Design

This is a derivation and validation study of a new QoL-based scoring classification as a prognostic factor for patient survival in HCC. This is a retrospective cohort study based on re-analysis of data from the BRISK-FL clinical trial which randomized 1,150 patients with advanced HCC between the standard treatment (sorafenib), and an experimental treatment (brivanib). The trial failed to meet its primary objective of increasing OS with brivanib as compared with sorafenib, with the results showing very similar survival curves between the two arms. Baseline QoL data was available for 1,108 patients. The results of QoL analysis showed similar baseline characteristics, but higher decline of physical and role function subscales in the brivanib arm. No analysis of baseline QoL parameters as prognostic variables was done.

The primary objective of this study is to derive a clinically-efficient (i.e. ordinal or binary) prognostic score from the QLQ-C30 functional and/or symptom scales. Prognostic properties will be evaluated for overall survival, defined as the time from randomization in BRISK-FL study to death by any cause. Harrell's C-index, which

estimates the proportion of correct prediction, will be used to assess prognostic performance of the QoL-based categorized score.

Secondary objectives are to examine the association between QoL-based score, WHO PS and other existing prognostic classifications; and to validate QoL-based score as an independent pre-therapeutic prognostic factor in HCC, especially in association with existing prognostic classifications (i.e. BCLC).

Data collected for the present study will be anonymized, with the patients identified by a code that differs from the BRISK-FL study identification code, provided by the BRISK-FL sponsor. The correspondence table will be kept by the BRISK-FL sponsor. No date will be transmitted, but solely durations. Only aggregated results would be publically presented.

Study Population
The study population will consist of patients included and randomized in the BRISK-FL study, for whom the EORTC QLQ-C30 questionnaire was completed at baseline, within two weeks of the start of treatment.

Funding Source of Research
No specific funding is required for this analysis.

Requested Study
CA182-033 (NCT00858871): First Line Hepato Cellular Carcinoma (HCC) (BRISK FL)