Title of Research
An Objective Biomarker to Optimize Treatment Decisions in Advanced Hepatocellular Carcinoma after Sorafenib Failure

Lead Researcher
David Pinato

Primary Affiliation
Imperial College London, London, United Kingdom

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Summary of Research
Second-line therapies after sorafenib (SOR) failed efficacy testing partly due to suboptimal patient selection, given the dual influence of progressive malignancy and hepatic failure in determining outcome inadvanced hepatocellular carcinoma (aHCC). Whilst a number of adverse prognostic features—including elevated alfa-fetoprotein levels, high disease burden, and worse liver functional reserve—are known to impact survival after intolerance to or progression on SOR, there is a lack of standardized objective measures to improve the selection of patients for second-line therapies.

Current eligibility criteria for second-line studies are based on the presence of adequate organ function, preserved performance status, and an expected survival of at least 8–12 weeks following SOR cessation. These criteria are subjective and do not necessarily predict the natural course of the disease, which may often take an accelerated course to terminal liver failure or malignant dissemination in a significant proportion of patients, who might therefore be best suited to receive best supportive care as opposed to further lines of active anticancer treatments.

In a preliminary retrospective study, we derived a multicenter cohort of337 consecutive patients (Cohort A) from Europe (n=109, 32%) and Asia (n=230, 68%), 77% male, started on SOR within Barcelona Clinic Liver Cancer (BCLC) stage C (56%) or earlier (44%) after failure of locoregional therapies. At SOR initiation, 73%of patients were designated as Child-Pugh class A. We evaluated routinely available clinicopathologic factors at the moment of SOR discontinuation to construct an objective prognostic model to identify patients with shorter life expectancy post-SOR. Median overall survival (OS)was 9.6 (95%CI 6.5–12.7), whereas median post-SOR OS was 2.8 (95%CI 1.9–3.9),and median SOR durationwas5.0 months (95%CI 3.9–6.0). SOR cessation followed primarily radiologic progression (47%) or toxicity (34%).

Following multivariable screening of prognostic traits at SOR discontinuation, we constructed a complex model integrating determinants of liver reserve and malignant progression of the disease capable of stratifying individuals according to their post-SOR OS.

The overall aim of our study is therefore to validate the prognostic ability and accuracy of our multivariable predictive model of survival utilizing patients from the BRISK-FL study to further substantiate our initial retrospective findings.

Liver cancer is a common disease that can frequently be resistant to approved first-line chemotherapy agents such as sorafenib. This often leads to patients with liver cancer also failing second-line

chemotherapy, which is tried when the first ones do not work adequately. One reason why this occurs is because the patients most likely to benefit from second-line chemotherapy are not appropriately selected for treatment, since these patients can die not only of the cancer, but also from liver failure, which the chemotherapy cannot treat.

Current criteria for selecting patients who would benefit most from second-line chemotherapies are subjective and are not very accurate in predicting the course of either the cancer or subsequent liver failure. In a previous analysis, our group developed a model that could predict disease progression and survival in patients who had already been treated with sorafenib. In this analysis, we will test that model in the BRISK-FL study to validate its accuracy. BRISK-FL was a phase III randomized controlled trial comparing the efficacy and safety of brivanib versus sorafenib in patients with unresectable, advanced liver cancer. These findings could help physicians better select patients most likely to benefit from additional chemotherapy after having failed to respond effectively to sorafenib.

Study Design
This study is a retrospective, post-hoc sub-analysis of clinicopathologic features obtained from a subgroup of the per-protocol patient population who participated in the BRISK-FL study. For the purpose of this analysis, patients from the BRISK-FL study will be merged in a uniform cohort (Cohort B) that will serve to validate the findings from the retrospective cohort of patients we preliminary analyzed (Cohort A).We have previously developed a model to predict how patients fare after they have failed sorafenib treatment. However, that model was developed in patients who had been selected retrospectively. In this analysis, we will test the accuracy of this model in a prospectively enrolled clinical trial population.

Study Population
Cohort A (Retrospective Training Set): Dataset of 337 retrospectively collected patients as described in the summary.

Funding Source of Research
No specific funding is sought for this retrospective research project. Data analysis will be performed and sponsored by the investigators.

Requested Study
CA182-033 (NCT00858871): A Randomized, Double-Blind, Multi-Center Phase III Study of Brivanib Versus Sorafenib as First-Line Treatment in Patients With Advanced Hepatocellular Carcinoma