Title of Research
Joint Analysis of Health-Related Quality of Life Trajectories and Survival and Tumor Response Endpoints

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Data Sharing Agreement Date
January 20, 2016

Summary of Research
A growing number of oncology trials include patient-reported outcome (PRO) measures to evaluate treatment effects on health-related quality of life (HRQoL). However, PROs are rarely analyzed with the same rigor as traditional survival and tumor response endpoints. Conventional trial analyses evaluate the primary endpoint (typically overall survival or OS) and HRQoL endpoints separately, even though patient-reported symptoms and functioning constitute important indicators of treatment outcomes, particularly in advanced cancer. Analyses of PRO endpoints are also driven by descriptive hypotheses of average group-level change between two time points, which do not capture patient variability. Prior research has shown that analysis of PRO data along with key trial endpoints can yield more accurate and precise estimates of treatment effects.

Hepatocellular carcinoma (HCC), a primary malignancy of the liver, is the sixth most prevalent cancer and the third most frequent cause of cancer-related death worldwide. HCC is often diagnosed at an advanced stage, when most potentially curative therapies, chemotherapy, and radiation, offer limited efficacy. Sorafenib is the only systemic agent to demonstrate a benefit in overall survival as first-line therapy in advanced HCC.

BRISK-FL (A Randomized, Double-blind, Multi-center Phase III Study of Brivanib Versus Sorafenib as First-line Treatment in Patients With Advanced Hepatocellular Carcinoma) was a phase III trial of brivanib versus sorafenib for first-line treatment in advanced HCC. Though secondary efficacy endpoints, including time to progression (TTP), indicated similar anti-tumor activity between the two drugs, the trial did not meet its primary endpoint of overall survival noninferiority. BRISK-FL is an ideal setting for applying novel statistical methods, and HCC is a highly heterogeneous disease that lends itself well to examining individual variability in treatment outcomes.

This secondary analysis of BRISK-FL data will provide insights into treatment-related patterns of patient function and symptoms, and their associations with overall survival and time to progression, enabling more efficient evaluation of trade-offs between survival/tumor response and drug-related toxicities. These innovative methods could be applied to future trial analyses. The proposed research would also demonstrate the limitations of conventional trial analyses, and may help to advance statistical methodology by providing recommendations on the potential role of such analyses in different settings. A comprehensive understanding of differential disease impact and treatment effects on HRQoL and outcomes would better inform decision-making in clinical practice.

Study Design
This retrospective, longitudinal study will analyze patient-level data previously collected in the BRISK-FL trial.[1]

Joint modeling of longitudinal PRO and time-to-event data may address limits to conventional trial analyses by simultaneously estimating treatment effects on HRQoL and trial endpoints, as well as the association between the two outcomes. Three approaches to joint modeling – trajectory function, shared parameter, and joint latent

[1] https://clinicaltrials.gov/show/NCT00858871

class – would be applied to quantify treatment effects on patient-reported HRQoLs and key efficacy endpoints. Patient-reported function (physical, role) and symptom (abdominal pain, abdominal swelling, fever, jaundice) trajectories, along with survival and tumor responses, will be estimated. Physical and role function were assessed using the European Organization for the Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire [QLQ-C30]);[2] symptoms were measured by the HCC-specific module, QLQ- HCC18. Treatment effect estimates from joint models would be compared with estimates from conventional trial analyses.

Study Population

In the original BRISK-FL trial, 1,155 patients were randomized to receive either brivanib (n=577) or sorafenib (n=578); 1,150 patients were treated (n=575 in each arm). However, subjects randomized at sites in the People's Republic of China would be excluded from the proposed research due to ethical issues. Thus, the study sample comprises 456 subjects randomized to sorafenib and 476 subjects randomized to brivanib (N=932). Trial eligibility criteria, study procedures, and follow-up procedures are described in the BRISK-FL protocol.

Funding Source of Research

BMS Worldwide Health Economics and Outcomes Research (WWHEOR) Predoctoral Fellowship

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

[2] http://groups.eortc.be/qol/eortc-qlq-c30