Comparative Efficacy of Cabozantinib and Regorafenib for Advanced Hepatocellular Carcinoma

This video has been developed to accompany the *Advances in Therapy* article "Comparative efficacy of cabozantinib and regorafenib for advanced hepatocellular carcinoma" and is not intended for any other use.

This video will talk through the methods used in the recent matching-adjusted indirect comparison of cabozantinib versus regorafenib in patients with advanced hepatocellular carcinoma, HCC.

Matching-adjusted indirect comparisons are a way of estimating the likely comparative outcomes that treatments might achieve if used in the same patient population. They are increasingly used in health technology assessments where no direct comparative data are available, but they can also provide insights for clinicians who are trying to choose between treatment options with limited data available to guide treatment selection.

The authors carried out the analysis because there have been no head-to-head trials comparing cabozantinib and regorafenib for the second-line treatment of patients with advanced HCC.

In hepatocellular carcinoma, the CELESTIAL trial for cabozantinib and the RESORCE trial for regorafenib had similar overall designs, which made them potentially eligible for an indirect treatment comparison. Both were phase 3, double-blind, randomized, placebo-controlled trials of patients with advanced HCC who had received prior systemic therapy.

RESORCE, however, compared regorafenib to placebo in a second-line patient population after treatment with sorafenib. In contrast, CELESTIAL compared cabozantinib to placebo in a mixed second-and third-line patient population. Also, RESORCE excluded patients who were intolerant to sorafenib, whereas CELESTIAL did not.

To address these differences, the authors aligned the patient populations by limiting CELESTIAL to the group of patients who had progressed on, or after, prior sorafenib therapy, that is, to a "pure second-line" population.

However, there were still some differences between the patient characteristics of the CELESTIAL and RESORCE populations that could potentially influence the effect of treatment and bias a treatment comparison. These included differences in the ethnic mix and geographical origin of patients, as well as

differences in their ECOG performance status and duration of prior sorafenib treatment. Because of these differences, a standard indirect comparison would not have been valid, but a matching-adjusted indirect comparison was an appropriate methodology to compare both compounds.

Statistical adjustments were then applied to the CELESTIAL patient population to minimize any residual differences. This was achieved by weighting the baseline individual patient data from CELESTIAL to align them with the baseline summary statistics published for RESORCE.

While the matching and statistical adjustment procedures reduced the effective sample size and study power, they were successful in removing the reported effect-modifying differences between the trial populations. Treatment outcomes were then compared for the matching-adjusted populations.

Matching-adjusted indirect comparisons cannot account for all between-trial differences and they do not replace randomized controlled trials, but they do offer valuable estimates of the comparative outcomes of two treatments in the absence of direct trial data.

For more information, please see the full publication by Kelley et al.