BACKGROUND

Globally, about 270,000 cases of kidney cancer are diagnosed yearly with 116,000 dying from the disease. 

HOPE 205 a phase II, multi-center study comparing lenvatinib (LEN) + everolimus (EVE) against EVE alone showed the combination of LEN + EVE prolonged progression free survival (PFS) (14.6 vs. 5.5 months; HR: 0.40; 95% CI: 0.24-0.68; p<0.001) and OS (25.5 vs. 15.4 months; HR: 0.51; 95% CI: 0.30-0.88, p=0.024) in renal cell carcinoma (RCC) patients following progression after 1 prior anti-vascular endothelial growth factor (VEGF) targeted therapy.

The combination LEN + EVE was approved by the US Food and Drug Administration in 2016 for the treatment of advanced renal cell carcinoma (mRCC) following the prior antiangiogenic therapy. It was also accepted for priority review by the European Medicines Agency (EMA) for the second line treatment of metastatic renal cell carcinoma (mRCC).

However, in the absence of randomized controlled trials involving a direct (head-to-head) comparisons of second line treatments for RCC, an indirect treatment comparison (ITC) involving LEN + EVE was conducted using networked data from HOPE 205, CHECKMATE-9ER, METASTAT (Mozer 2015, nibolimus vs everolimus), METEOR (Choueiri 2015, cabazitaxel vs axitinib), AXIOX (Mozer 2013, AXI, EVE), RECORD-1 (Motzer 2008, everolimus vs PBO) and TARGET (Escudier 2008; sarotentin vs PBO). The ITC incorporated adjustments for crossover and Hainsworth (2013) involving a direct (head-to-head) comparison of second line treatment of metastatic renal cell carcinoma (mRCC) was conducted using intention to treat (ITT) data versus adjusted data (placebo vs EVE) moved 45.2% further from null (1.15 (0.29-7.18) to 0.67 (0.29-1.54)).

LIMITATIONS

The current method assumes that for patients A and B, if both were to follow an alternative treatment in the crossover arm (e.g., LEN+EVE) then they would also have the same treatment effect. This is not true in practice and is a major limitation as previously observed in naive approaches to survival analysis in the crossover setting.

The model is based explicitly on the groups as randomized and estimates a treatment effect that is only statistically significant if the ITT analysis is statistically significant. In practice, based on the crossover study, the robustness of the crossover adjustment by applying other methods commonly used.

RESULTS

A follow-up analysis using updated HOPE 205 data (July 2015) with intention to treat (ITT) data versus adjusted-ITT data evaluated the impact of crossover on OS estimates and additionally explored potential bias due to the absence of adjustment. RECORD-1 (EVE vs PBO) and TARGET (SOR vs PBO) allowed 80% and 48% crossover patient respectively. Hainsworth (PAZ vs EVE) also allowed patient crossover (RPSST-adjusted).

Three ITC scenarios were analyzed using a frequentist ITC and the Bucher (1997) method with a two-sided 95% confidence interval. Epidemiological endpoints were evaluated in terms of hazard ratios for OS and PFS.

For the experimental arm.

REFERENCES

1. Bias was observed in naive approaches to survival analysis in the presence of crossover. Failure to account for this in clinical trials may have implications on the comparative effectiveness analysis and also on the cost-effectiveness results and may lead to inconsistent resource allocation decisions.

Scenarios C - (EMA data cut) 2016

Scenario C: showed a wide range in change for HR values after crossover adjustment.

Further, in C two of the values increased (PAZ, SUN) and three decreased (SOR, AXI, PBO).

Scenario B - EMA (2016) data cut

Scenario B shows, all ITT HR values for OS to closer than null with the crossover adjusted population.

Also, the direction of HR change is negative for all treatments and ranges from -10% (AXI vs EVE) to -53.0% (SUN vs PBO).

CONCLUSIONS

Bias was observed in naive approaches to survival analysis in the presence of crossover. Failure to account for this in clinical trials may have implications on the comparative effectiveness analysis and also on the cost-effectiveness results and may lead to inconsistent resource allocation decisions.