BACKGROUND

- Globally, about 270,000 cases of kidney cancer are diagnosed yearly and 116,000 people die from the disease.1
- HOPE 205: a phase II, multi-center study comparing LEN + EVE against EVE alone showed that the combination of LEN and EVE prolonged the PFS (14.6 months vs. 5.5 months; HR: 0.40; 95% CI: 0.24-0.68; p<0.001) and OS (25.5 months vs. 15.4 months; HR: 0.51; 95% CI: 0.30-0.88; p=0.040) as compared to EVE alone in RCC patients following progression after prior anti-vascular endothelial growth factor (VEGF)-targeted therapy.2
- The combination of LEN and EVE was approved by U. S. Food and Drug Administration in 2016, in combination with everolimus, for the treatment of advanced renal cell carcinoma following one prior anti-angiogenic therapy. It was also accepted for priority review by the European Medicines Agency (EMA) for the second line treatment of mRCC.

However, in the absence of randomized controlled trials involving a direct head-to-head comparison between the treatment arms, a bias is observed in the results of crossover.

OBJECTIVES & METHODS

- 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 correlation on OS and PFS 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% patient crossover, respectively. Hainsworth and PBO (30% pazoban vs sunitinib) and Hainsworth 201313 also allowed patient crossover (RPSFT adjusted).

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

- Scenario A: all comparators plus placebo versus EVE.
- Scenario B: all comparators versus placebo.
- Scenario C: LEN+EVE versus all comparators + placebo.

RESULTS

- Hazard ratios for OS in AXI vs EVE shifted from below null (0.98) to above null (1.17) and mortality risk (placebo vs. EVE) moved 51% further from null (1.15 vs. 1.67). A shift further away from the null suggests higher mortality risk.
- Scenario 9 showed a wide range of OS HR change after adjusting for crossover: -31.6% (PAZ vs EVE) to +45.2% (PBO vs EVE)
- Further, in “A”, three of the HR values increased (SOR, AXI, PBO) and two decreased (PAZ, SUN)

- Scenario B - EMA 2016 data cut

“Scenario B” shows all HR values for OS closer to null than 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)

- Scenario C - EMA 2016 data cut

“Scenario C” showed a wide range in change for HR values after crossover adjustment: -22.4% (LEN+EVE vs SOR) to +71.4% (LEN+EVE vs SUN)

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

CONCLUSIONS

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

REFERENCES

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