Questions and Answers after the Webinar of September 25, 2018

Assessing treatment benefit in immuno-oncology

1. Do you have examples of applying GPC to crossing survival curves?
Yes. In a published paper (Peron J, et al, JAMA Oncol 2016; 2:901-5), we have investigated GPC in a database that was simulated in order to resemble the IPASS trial, which compared gefitinib with chemotherapy in the first-line treatment of patients with adenocarcinoma of the lung (Mok TS, et al, N Engl J Med 2009; 361:947–57). In the overall population, the progression-free survival (PFS) curves crossed, likely due to the presence of a mixed population with regard to the predictive biomarker. In other words, there was an apparent early detriment from the use of gefitinib until around 11 months, with subsequent benefit. As a result, the assumption of proportional hazards was obviously violated, and the overall hazard ratio of 0.75 reported in the trial was not meaningful as well as potentially misleading. The analysis using GPC showed that, when any PFS difference was considered relevant, the net benefit (Δ) was negative. However when large PFS differences were considered, Δ was positive.

2. In delayed treatment effect situation, it is still a little counterintuitive to show patients that the chance of improving OS with threshold of m = 0 month is lower than the chance of improve with threshold of m = 6 months for example?
When there is a delayed treatment effect, patients may experience the event of interest early on (with equal probability on both treatments), or later (with lower probability on the new treatment). Hence the probability of the new treatment being better is smaller for a threshold of m = 0 because of the lack of treatment effect on early events.

3. What is the utility of GPC method in a pivotal trial setting? Will you advocate using it as a sensitivity analyses?
Yes. There is no regulatory experience with the GPC method, hence its use should be currently limited to sensitivity analyses for some other, well accepted, analysis method.

4. What's the regulatory acceptance of the generalized pairwise comparison?
At this point in time, we do not yet know, as there has been no specific case in which GPC was discussed with regulatory authorities. However, we anticipate there will be increasing interest on the part of regulatory authorities, because GPC can be a tool in the assessment of risk/benefit. Moreover, regardless of regulatory considerations, this novel method can be used to give the Sponsor a deeper insight into the benefits and risks of their new agents. The change of the net benefit over time is a very important information that is more easily quantified and interpreted with the net benefit than with other analysis methods.

5. Is the generalized pairwise comparison method similar to an extension of the Hodges Lehmann estimator for median differences? So we summarizing all possible pairwise comparisons between treatment and control? The extension to include both efficacy and safety endpoints seems very intuitively useful.
Yes, there is a tight connexion between the GPC method, the Wilcoxon-Mann-Whitney test, the Hodges-Lehmann estimator, and Harrell's c-index. The concept is surprisingly general and naturally leads to extensions that may be used in a variety of settings (multiple outcomes, whether prioritized or not, with or without thresholds of clinical relevance).