Prof Geert Verbeke from the University of Hasselt opened the day. He showed that a discriminant analysis based on many outcomes, measured longitudinally, in an unbalanced design, in order to predict time-to-event outcomes, is technically possible. He illustrated his talk with an example on patients with kidney transplant between 1983 and 2000 at U.H.Leuven. A pattern-mixture approach was used. It was shown that allowing the longitudinal markers to be correlated considerably improves predictions and that various mixed models can be combined and fitted using pairwise fitting approach.

Prof Hein Putter provided the 2nd presentation of the day. In the first part of his talk, he illustrated the issue of immortal time bias in the study of the effect of response to chemotherapy on survival. Doing a landmark analysis at different time points can solve this issue. In the second part of this talk, Prof Putter showed the assets of using different landmark datasets at different time points for a dynamic prediction. He illustrated his talk with an example on survival in postmenopausal hormone-sensitive breast cancer patients (TEAM study).

Dr Yolanda Barbachano, Statistical Assessor at MHRA (PhD, Medical Statistics) provided his personal opinion regarding the current regulatory issues in Survival Analysis. She summarized her ideas in four points. She started with the summary statistics and showed us that we should use carefully the median, the hazard ratio, percentage of subjects event-free at time t. The best way to do is to always look at the curve and never use a summary statistic alone. After that point, she gave us tools to avoid issue when interim analyses are planned and when the study stops for success at interim. She drew also our attention to the fact that missing data are often overlooked and can really be issue in survival analysis (informative/non-informative censoring for example). Her last point was issues caused by switching treatments (Patients on control swap to investigational or patients on both treatments go to next line therapy as per local guidelines).

Kevin Carroll presented the topic “The use and utility of parametric AFT modeling in the analysis of time data”. Accelerated failure time analysis (Exponential, Log Normal and Weibull for example) represents a powerful and versatile alternative to traditional Cox PH approach. Weibull is the only AFT member that is simultaneously proportional. He explained us how the use of parametric survival models is not scary (Conceptually no different to MMRM for repeated measures or Negative Binomial for repeat events (e.g. COPD)). He showed us that Weibull analysis gives very similar results to Cox in terms of the HR, CI and p-value regardless of true underlying distribution of time to event. This method is versatile and offers greater range of inferences and deeper insight than conventional Cox analysis (E.g. Event time ratio, event rate estimates, median and CI estimated, maturation predication). He concluded saying that parametric AFT modeling should at least be used as a supportive analysis to a regular Cox analysis.

Caroline Mattin from Amgen presented the lessons learned from the EVOLVE study, a trial testing a treatment regimen for secondary hyperparathyroidism (HPT) including or not Cinacalcet. First, she introduced the study design, and the effect of drop-in and drop-out on observed treatment effect. Then, she presented the primary results (Time to a composite endpoint) which were not statistically significant. Some issues explained the non significance of the results: (1) baseline imbalance in age (an important prognostic endpoint), (2) the high drop-out rate, (3) the high rate of surgical procedures that modified the risk of event, and (4) the low event rate. For the first 3 issues, sensitivity analyses were performed to assess the impact on those issues. Those different sensitivity analyses appeared to be statistically significant. Caroline concluded with lessons learned from this trial.

Veerle de Pril from BMS presented the statistical challenges in immuno-oncology. She first summarized what cytotoxic agents, cytostatic agents and immunotherapies are, and the type of endpoints used in those types of agents or therapies. Then, the outlines what are the important

issues in the design and analysis in Immuno-oncology, and gave some examples. She gave the impact of long-term survival and delayed clinical effect on (1) study duration and power, (2) probabilities for stopping at interim analysis. She then presented some additional analysis considerations such as prediction of timing of analyses, and type of models and summary statistics to be used in the primary, and in case of long-term survival or delayed clinical effect. She concluded her talk by stressing the importance of understanding the disease characteristics and MOA of therapy on possible delayed clinical effect and long term survival, and its implication on study design and analyses.

In the 4th session, Nicola Schmitt (AstraZeneca) presented the topic "Missing data in survival analysis". First, she introduced censoring as a form of missing data, and gave examples of informative censoring, a kind of censoring that can be problematic to study's results since traditional survival techniques assume censor at random. She then presented a combine study that analyzed the effect of censoring rules by means of a metric which measures the degree of informative censoring. Conclusion of the work was that censoring lead to bias if both informative and not equally distributed in both arms. She finally concluded her talk by presenting some strategies to handle missing data and showed results from simulations that compare standard Cox analysis versus multiple imputations approach.

Jan Bogearts and Leen Slaets from EORTC presented together the last topic of the day "One-way optional cross-over: biases and analysis approaches". The issue behind this topic was the influence of later lines of treatment on the overall survival comparison, and in particular the one-way partial cross-over at time of progression from control arm to experimental drug. Both speakers agree that cross-over should be avoided as much as possible from the start of studies but know that it's not always avoidable due to all drugs already existing on the market. They simulated different methods to handle cross-over and to study the overall survival effect in absence of cross-over, and tried to show if we can assume that the lack of OS effect in the ITT population is completely due to cross-over or not.

A lively panel discussion closed the meeting.

Perrine Bamps, Sophie Dekeyser, Emmanuel Quinaux and Pierre Squifflet (IDDI)