Themes and Sub-Themes

1.06 Design – Innovative designs

ADePT-DDR is a platform trial that aims to evaluate the safety and efficacy of different DNA Damage Repair (DDR) agents together with radiotherapy in patients with head and neck squamous cell carcinoma. The initial component of this trial is a single-arm dose-finding phase Ib/IIa trial.

The first agent to be used will be the DDR ATR inhibitor agent, AZD6738, in combination with radiotherapy alone. This will be assessed using a novel dose-escalation design known as the partial ordering time-to-event continual reassessment method (PO-TITE-CRM) to determine the maximum tolerated dose (MTD) of AZD6738, defined as the dose level closest to the level at which 25% of patients experience a dose-limiting toxicity.

The methodology adopted in this trial was first introduced in 2011 as an extension of the original continual reassessment method (CRM), a model-based approach to dose-finding trials. One of the key assumptions of the CRM is the monotonicity assumption which is that we assume that as the dosage of a drug increases so does the probability of toxicity. Nolan extended the CRM design to work in the presence of partial orders. Partial ordering occurs in the case where the monotonicity assumption does not hold and the ordering of doses in terms of toxicity is not fully known. This methodology was then further extended to include a time-to-event component that attempts to utilize data from partially observed patients throughout the trial to account for late-onset toxicities.

Due to the dose levels selected for investigation in this trial along with the long-term toxicities associated with the treatment an innovative solution was required to successfully run this trial. The novel methodology of PO-TITE-CRM was deemed an appropriate solution. We believe this is one of the first cases of the methodology being implemented in an actual trial.

We provide details of how the design works as well as insight into how it is applied in a trial setting. Multiple iterations of simulations were utilized to determine the optimal parameterization of the design. Simulation results from the optimal parameterization show the operating characteristics of the design perform well across a variety of scenarios.

Whilst being a very efficient design we highlight some of the difficulties and challenges that come with implementing such a design. As the issue of partial ordering may become more frequent we hope this account will be beneficial to those wishing to implement a design with partial orders.