**Implementing the PO-TITE-CRM trial design into ADePT-DDR.**

**Introduction**

Worldwide there are approximately 600,000 new cases of Head and Neck Squamous Cell Carcinoma (HNSCC) each year \cite{stranskyMutationalLandscapeHead2011}. Of which, 12,000 occur in the UK with the most common forms of treatment being surgery, radiotherapy and/or chemotherapy \cite{cancerreaserchukHeadNeckCancers2017}. Radiotherapy is essential for the treatment of cancer. It has been estimated that more than 40\% of patients will receive radiotherapy at some point in their treatment \cite{roundRadiotherapyDemandActivity2013}. However, despite recent advancements in radiation techniques and the use of concomitant chemoradiotherapy, patients with solid tumours such as head and neck cancer have suboptimal cure rates \cite{cancerreaserchukHeadNeckCancers2017,cognettiHeadNeckCancer2008}. For those with advanced HNSCC primary radiotherapy with concurrent chemotherapy is often offered but, it has not been shown to improve survival in patients aged over 70 compared to radiotherapy alone \cite{pignonChemotherapyAddedLocoregional2000}. Therefore, any strategy to improve the efficacy of radiotherapy without increasing toxicity would have a significant impact on patient outcomes. DNA damage repair (DDR) inhibition is a potential technique which could be utilised as it potentiates the therapeutic effects of ionising radiation in cancer cells \cite{oconnorTargetingDNADamage2015}. Combining radiotherapy with DDR inhibition could improve clinical outcomes for these patients \cite{chalmersScienceFocusCombining2016}.

The ADePT-DDR trial is a platform trial which aims to evaluate the safety and efficacy of different DDR agents, or different immunotherapy agents and/or DDR and immunotherapy combinations, together with radiotherapy in patients with HNSCC. The initial component of this trial is a single-arm dose-finding trial investigating the ataxia telangiectasis and Rad3-related (ATR) inhibitor AZD6738 in combination with radiotherapy. ATR inhibitors not only stop DNA repair but impair the mechanism that allows for repairs to take place. Preclinical models have shown this double blocking to be effective in killing cancer cells \cite{meiAtaxiaTelangiectasiaRad3related2019}. The aim of this trial is to determine a maximum tolerated dose of AZD6738 in combination with radiotherapy.

The investigation of multiple-agent treatments, where the monotonicity assumption may not hold, is increasing in early phase trials. Finding the MTD in combinations of treatments, compared to single-agents, presents methodological challenges. Each drug individually may obey the monotonicity assumption we can refer to this as the doses being fully ordered. However, when multiple treatments are combined, the ordering of doses in terms of toxicity may not be fully apparent or may only be partially ordered. An order may be identified for a subset of the doses which would result in a partial order. Without a fully understood ordering it is uncertain which dose should be chosen in decisions of escalation and de-escalation and ultimately as the TD. This issue is not exclusively reserved for trials with multiple-agents. The monotonicity assumption may not hold for certain drugs in single-agent studies leading to partial orders of dose toxicity. For example, when dose and frequency of administration vary between dose levels. Monotonicity is a very strong assumption. It requires that probability of toxicity always increases - staying the same is not enough. At high enough doses, this assumption is almost surely violated for all interventions when the event probability reaches its maximum. Thus, even when total ordering is possible, the monotonicity assumption could be violated \cite{brockMoreBetterAnalysis2020}. This can occur in scenarios where multiple parameters of the treatment schedule are altered for each dose level. For example, either dose or treatment duration could be increased and even if patients receive an equal dose it would remain unclear as to if prolonged exposure to a lower dose is more toxic than short exposure to a higher dose, which implies a partial ordering of toxicity probabilities. This is the case for the proposed dose levels in ADePT-DDR.

Further methodological challenges revolve around the issue of late-onset toxicities. Typically, early phase trials implement a short window to observe DLTs. This works well in situations where toxicities are likely to occur rapidly after treatment. However, this is not optimal for treatments that could cause late-onset toxicities such as radiotherapy. The aim with ADePT-DDR would be to incorporate a larger observation window to account for potential late-onset toxicities from radiotherapy whilst also minimising the trial duration.

The continual reassessment method for partial orders (PO-CRM) developed by Wages et al. \cite{wagesContinualReassessmentMethod2011} extends the CRM design by relaxing the assumption of monotonicity and by modelling different potential orders. Wages et al. \cite{wagesContinualReassessmentMethod2011, wagesUsingTimetoeventContinual2013} further developed their work on the PO-CRM to deal with late-onset toxicities by implementing a TITE component. This trial design, referred to as the time-to-event continual reassessment method in the presence of partial orders (PO-TITE-CRM) by the authors, was chosen to be used in ADePT-DDR. We aim to provide insight into the methodology of PO-TITE-CRM through application in a real-world scenario.

**Methods**

**The PO-TITE-CRM-Design**

Wages et al. \cite{wagesUsingTimetoeventContinual2013} introduced the PO-TITE-CRM design which builds directly upon the PO-CRM design by incorporating a TITE component into the dose toxicity model. The aim of which is to determine the target dose for combinations of drugs where the monotonicity assumption does not hold, in a setting where late-onset toxicities are possible.

Using the notation of Wages et al. \cite{wagesContinualReassessmentMethod2011,wagesUsingTimetoeventContinual2013}, let denote the number of possible orders and be an indicator of a toxicity event. Then for a trial investigating combinations, , the dose for the th patient, , = 1,..., can be thought of as random . For a specific ordering , the toxicity probability is modelled by

for a weighted dose response model where . The weight, as defined by Cheung and Chappel \cite{cheungSequentialDesignsPhase2000}, is a function of the time-to-event of each patient and is incorporated linearly with the dose toxicity model so that . Each patient is followed for a fixed amount of time . Let represent the time-to-toxicity of patient . Then for ,

For simplicity we will refer to the weight function as . The weight function will have to be decided upon by the trials team, dependent on the scenario, a simple linear function or a more complex adaptive weights function could be utilised. There are also several working dose models which could be used for , Wages et al. \cite{wagesUsingTimetoeventContinual2013} present their design with the power parameter model given by

Here are the prior estimates of toxicity probabilities, or skeleton, for each potential ordering. Furthermore, prior probabilities are assigned to each order to account for any prior information regarding the plausibility of each model such that, , where and . When all orders are equally likely or there is no prior information available on possible orderings the prior is discretely uniform and would be .

A Bayesian framework is used and a prior probability distribution is assigned to the parameter . The ordering with the largest prior probability is selected as the starting ordering, in the scenario where all priors are equal an ordering is selected at random, subsequently a starting dose is also chosen. After patients have been entered into the trial data is collected in the form of . A weighted likelihood for the parameter is used to establish running probabilities of toxicity for each treatment combination. The weighted likelihood under ordering , is given by

which can be used to generate a summary value for each ordering. With the likelihood and the data , the posterior density for can be calculated using

This can then be used to establish posterior probabilities of the orderings given the data as

We select the single ordering, , with the largest posterior probability along with its associated working model and generate toxicity probabilities for each dose level. Once the th patient has been included the posterior probability of DLT can be calculated for so that

In turn, the dose level assigned to the ()th patient is the dose, , which minimises

where is the target toxicity rate.

**PO-TITE-CRM in ADePT-DDR**

Results