RAMPART: A model for a regulatory-ready academic-led phase III trial in the adjuvant renal cell carcinoma setting

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ABSTRACT

The development of therapeutics in oncology is a highly active research area for the pharmaceutical and biotechnology industries, but also has a strong academic base. Many new agents have been developed in recent years, most with specific biological targets. This has mandated the need to look at different ways to streamline the evaluation of new agents. One solution has been the development of adaptive trial designs that allow the evaluation of multiple agents, concentrating on the most promising agents while screening out those which are unlikely to benefit patients. Another way forward has been the growth of partnerships between academia and industry with the shared goal of designing and conducting high quality clinical trials which answer important clinical questions as efficiently as possible.

The RAMPART trial (NCT03288532) brings together both of these processes in an attempt to improve outcomes for patients with locally advanced renal cell carcinoma (RCC), where no globally acceptable adjuvant strategy after nephrectomy currently exist. RAMPART is led by the MRC CTU at University College London (UCL), in collaboration with other international academic groups and industry. We aim to facilitate the use of data from RAMPART, (dependent on outcomes), for a future regulatory submission that will extend the license of the agents being investigated. We share our experience in order to lay the foundations for an effective trial design and conduct framework and to guide others who may be considering similar collaborations.

Trial Registration:
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1. Background

Largescale phase III randomised controlled trials have evaluated various oral tyrosine kinase inhibitors (TKIs) after nephrectomy, for localised RCC. None have shown overall survival (OS) benefit in this setting [1–4]. Therefore, nephrectomy followed by active surveillance for relapse, remains the most common global standard of care. Patients with intermediate or high-risk RCC after surgical resection, as assessed by renal cancer specific prognostic scores, remain at significant risk of relapse and death [5]. An effective adjuvant strategy for all patients with locally advanced RCC remains an unmet clinical need.

Clinical trials of adjuvant therapies in RCC are a notoriously challenging and lengthy undertaking. They require a large network of collaborating groups and investigators to meet accrual targets and an inherently lengthy follow-up period owing to relatively distant outcome measures. At the MRC CTU at UCL, we have a rich experience of leading successful large, international collaborative trials in various disease types, including SORCE (NCT00492258) our previous trial in the adjuvant RCC setting [1]. We also have expertise in the development and evaluation of novel trial designs to streamline the evaluation of new therapies [6]. We have leveraged both of these capabilities to develop the RAMPART trial (NCT03288532); an international phase III randomised multi-arm, multi-stage (MAMS) platform trial of adjuvant immune checkpoint inhibitors (ICIs) in treatment of locally advanced RCC.

In this paper, we describe the clinical rationale behind the agents used in RAMPART. We outline the MAMS design and explain the choice of control arm, study population and primary outcome measures. We detail features influenced by collaboration with leading international academic groups, with industry partners (AstraZeneca AZ), and the scientific advice we received from the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) during the design phase. We do this to demonstrate the necessary steps for developing an efficient international academic led trial, ready to meet standards compatible with future regulatory submission. In doing so, we aim to accelerate the development of effective adjuvant treatments for patients with locally advanced RCC.

2. Rationale for a trial of adjuvant ICIs for locally advanced RCC

Types of ICI therapy include antibodies against cytotoxic T-lymphocyte associated antigen 4 (anti-CTLA-4) and programmed cell death protein 1 / programmed cell death protein ligand 1 (anti-PD-1/ PDL-1). In recent years, ICIs have revolutionized the treatment options available in both the adjuvant and advanced setting for patients with various cancers, including lung and melanoma [7–9]. In advanced RCC, promising results have been observed with combination ICI therapies - for example ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1) [9,10] as well as the combination of ICI therapies with tyrosine kinase inhibitors (TKIs) [11–13]. In this context, an investigation of ICIs in the setting of locally advanced RCC is justified.

In RAMPART, we are investigating the PDL-1 inhibitor durvalumab as monotherapy (Arm B) and in combination with the CTLA-4 inhibitor tremelimumab (Arm C) after complete surgical excision of RCC.

3. Trial oversight and academic collaboration

At the very outset of planning a trial that might succeed SORCE, we developed a RAMPART Trial Management Group (TMG). The TMG brings together an international network of experts in the field of RCC, a number of patient representatives, and the trial team at the MRC CTU at UCL. This key collaboration has played the central role in shaping the design of RAMPART and has retained overall oversight as the trial has progressed.

UCL, as the host organisation for the MRC CTU at UCL, is the Sponsor of RAMPART. In order to extend RAMPART's reach internationally, UCL entered into collaborative agreements with the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP), University of Sydney, UNICANCER and Vall d'Hebron Institute of Oncology (VHIO). In order to develop a foundation for consistent trial conduct across countries, these agreements lay out the specific roles and responsibilities of the MRC CTU at UCL and those of each of our international collaborators.

RAMPART is currently the only international academic led multi-arm trial investigating ICIs in the adjuvant RCC setting; this is possible because of our unique multi-disciplinary international collaborations.

4. Collaboration and engagement with industry partners and regulators

UCL and AZ entered into early discussions outlining our respective requirements for a collaboration. As academic partners, we at UCL wanted overall Sponsorship of the trial and responsibility for the trial data. For the statistical analysis we requested that overall survival (OS) should be a co-primary outcome measure with disease free survival (DFS). There were also a number of trial conduct requests from UCL. We were keen to explore an ICI as monotherapy and separately, two ICIs in combination, within a single trial. We also wanted to be able to add an additional experimental arm, even one from another company, at some stage during trial conduct. AZ requested the development of a robustly designed trial, one that could be delivered within a suitable timeframe and had the potential to facilitate a future regulatory submission.

The team of senior statisticians and trial methodologists at the MRC CTU at UCL and the Chief Investigator entered into critical early discussions with AZ to ensure that both sets of needs were met. UCL and AZ entered into a start-up agreement, which provided critical initial funding to the MRC CTU at UCL to allocate staff and time to initiating the project. The start-up agreement facilitated a full collaboration agreement between UCL and AZ as the trial developed further.

In parallel, AZ applied for both a pre-Investigational New Drug Type B meeting with the FDA and also a request of Scientific Advice / Protocol Assistance to the EMA jointly on behalf of AZ and UCL as Sponsor. We worked in partnership with AZ on the briefing document that was submitted for review. Discussions with the agencies centred on the statistical analysis plan for RAMPART's MAMs design, including the approach to the interim analyses, the appropriateness of the co-primary outcomes of disease free survival (DFS) and overall survival (OS), the risk populations to include and the use of active monitoring as the control arm. We were able to discuss and agree the specific details of each of these features with our TMG in advance of discussions with the regulators. Our

experience of the discussions with regulators is that the FDA have a more overarching approach to trials and trialists whereas the EMA appoint rapporteurs from the different member states and so comments tend to be based on individual rather than organisational perspective.

Our strong working relationship with colleagues in AZ has been critical to the development and efficient conduct of RAMPART. Over time we have discussed and agreed a mutually acceptable data collection plan, we share relevant safety information with each other and we meet regularly to provide feedback on operational aspects of the trial. AZ review protocol amendments and any publications arising from the trial, but otherwise have no input into the day-to-day running of the trial. We would recommend this model of clear communication and a willingness to collaborate, including joint discussions with regulators, with others who are embarking on similar trial partnerships.

5. RAMPART trial design

5.1. The case for an adaptive MAMS platform trial in adjuvant RCC

At MRC CTU at UCL, we have rich experience of designing and running MAMS trials. The STAMPEDE trial in prostate cancer is the MRC CTU at UCL's flagship MAMS trial. Since the trials initiation in 2005, the STAMPEDE team have reported results on seven randomised comparisons (each of which could be considered a trial within a single overarching master protocol) [14–20] and will report on at least another four, with many more future comparisons under consideration.

The multi-arm design of RAMPART (Fig. 1) allows the investigation of durvalumab (anti-PDL-1) as monotherapy (Arm B) and separately in combination with tremelimumab (anti-CTLA-4) (Arm C), within the scope of a single trial. Furthermore, the platform allows the addition of new research arms, involving promising agents or combinations within an already recruiting trial. Importantly the addition of one arm (Arm D) is embedded in the original statistical design assumptions [21]. In a multi-arm setting, there are two different measures of type I error rate: the pairwise type I error rate (PWER) and the family-wise type I error rate (FWER) [22]. In RAMPART, the overall type I error rate – i.e. the FWER [22], is strongly controlled at 2.5% for all the pairwise comparisons whether or not a new research arm is added. The PWER is the probability of incorrectly rejecting the null hypothesis for the primary outcome in a particular experimental arm, regardless of outcomes in the other experimental arms [22]. For each pairwise comparison in the RAMPART trial, we calculated the PWER both analytically and using simulations considering two scenarios: A) the trial starts (and possibly concludes) with two research arms; and B) a new research arm is added before accrual to the current 3-arm trial completes. The results from our simulations show that the final stage significance level of 0:0097 in all pairwise comparisons controls the overall FWER at 2.5% when the 3rd research arm is added later on (i.e. scenario B). Further simulation studies also showed that the final stage significance level of the two original pairwise comparisons can be increased to 0.014 if the deferred arm is not added (i.e., scenario A) to buy back the unspent type I error of the third pairwise comparison. We applied Dunnett's approach to empirically calculate the FWER in both scenarios A and B. By strongly controlling the FWER at 2.5% (one-sided), RAMPART is robustly designed for both eventualities. The relevant methods to calculate the correlation structure are described in Choodari-Oskooei et al. [22].

RAMPART's multi-stage design includes pre-planned, time-to-event driven interim analyses for both lack of benefit and overwhelming benefit. Lack of benefit analyses allow the cessation of recruitment to treatment arms where treatments offer no effect, which means participant accrual can be focused on the more promising research arms and the control arm. The planned overwhelming benefit analysis allows the reporting of results earlier if sufficient benefit is observed. In all comparisons, a constant stopping boundary (i.e. Haybittle-Peto type) is used at all interim stages for overwhelming efficacy. The overall type I error rate was adjusted for any multiplicity as a result of interim analysis. Importantly, it was agreed with regulators that interim data showing overwhelming benefit could support an early submission of licensing extension for durvalumab to include treatment of locally advanced RCC after nephrectomy. The timelines for all analyses and stopping guidelines as planned at the outset of the trial are described in detail in our trial protocol, currently version 5.0 [23].

An additional adaptive feature of the MAMS design is that the control arm can be altered if the recognised standard of care changes. If we were to change the control arm according to new standard of care treatments for patients with locally advanced RCC, we would revisit the design assumptions and recalculate the sample size to maintain the statistical integrity of the trial. We would be able to make this change as a protocol amendment rather than starting a new trial. RAMPART's MAMS design therefore gives us the greatest opportunity to fulfil the goal of improving outcomes for patients with RCC as rapidly and efficiently as possible.

5.2. Choice of control arm

Previous trials in the adjuvant RCC setting tended to use placebo controls and blinding of patients to treatment arms when the agents were administered orally. In RAMPART, certain toxicities for both the ICI agents are expected, which will likely be more obvious in the combination arm. Therefore, to minimise the burden to both patients and healthcare systems, we decided not to include an intravenous placebo. Consequently, our control arm is 'active monitoring' and treatment allocation is not blinded. The results from ASSURE, PROTECT, STRAC and more recently the SORCE trial have shown no overall survival benefit for TKIs over placebo in the adjuvant RCC setting [1–4] giving us confidence that active monitoring by clinical and radiological means is the most appropriate control for RAMPART. All patients are
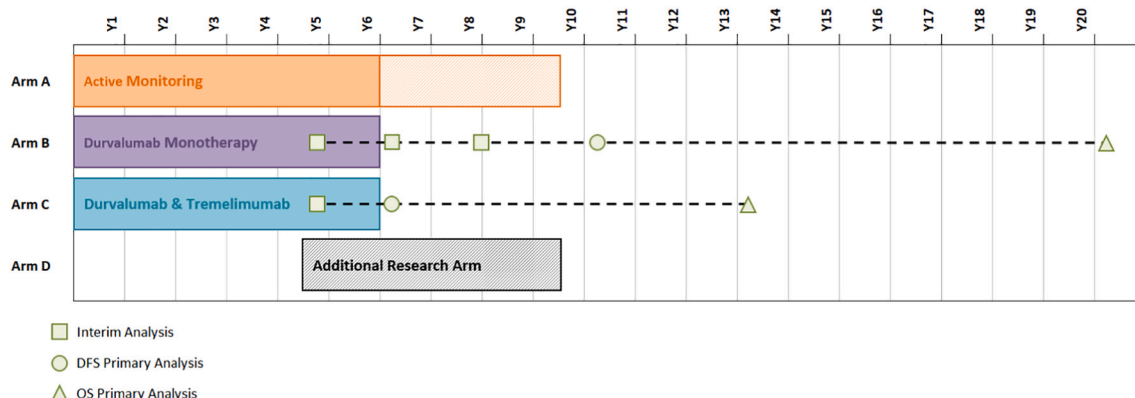

Fig. 1. RAMPART trial - adaptive design.

radiologically monitored at the same frequency to standardize follow-up of all arms thereby minimising bias in reporting disease relapse. To optimize compliance, we underline the importance of adhering to follow-up schedules in the information that we provide to patients and sites. In addition, where deemed appropriate by the investigator, there is a greater emphasis on providing remote clinical assessments since the COVID-19 pandemic, which improves upon flexibility for patients on all arms.

5.3. Choice of dosing schedule in the combination arm

As with all treatments, ICIs have recognised side-effects. The impact and risk of side-effects caused by treatments may be very different in an adjuvant setting where patients may already be surgically cured, and has been rigorously considered by the RAMPART TMG. The dose of the anti-CTLA-4 agent, both as a single agent and in combination with anti-PD-1/PD-L1 agents, appears to be the more dominant driver of toxicity. Although most trials to date have used four cycles of combination ICI therapy, there is no strong scientific rationale for this duration. In RAMPART, we have opted for two cycles of the anti-CTLA/anti-PD-L1 combination followed by single-agent durvalumab for the remainder of the year in the combination therapy arm (Arm C). This decision reflected our responsibility to select a treatment strategy that balances the optimal potential for efficacy with an acceptable safety profile for patients with locally advanced RCC. In line with comments from the regulators, we have given patients sufficient information regarding the potential benefits and risks of durvalumab and tremelimumab and we agreed to hold our Independent Data Monitoring Committee (IDMC) meetings every 6 months in the early years of the trial.

5.4. Choice of study population

A key challenge in any adjuvant trial relates to how to how best to characterise and stratify patients according to their risk of relapse for the purposes of trial eligibility. The Leibovich score [24] was a pragmatic choice by the RAMPART TMG as all component prognostic factors are required as part of routine pathology reporting in RCC, thus negating the need for additional expertise or training for its calculation. Furthermore, clinical markers such as patient's performance status or symptoms at baseline are not included, reducing the chance of subjective bias in its assessment.

The next challenge was to choose the risk populations eligible for the trial. Confining the RAMPART population to Leibovich high risk (score 6 ≤) would limit patient recruitment but minimise the exposure of lower risk patients to potential drug toxicity. However, intermediate risk patients (scores 3–5) also have a substantial risk of relapse and death from RCC [24], highlighting the clinical dilemma if we were to exclude these patients entirely. Therefore, we included patients at intermediate risk of recurrence in RAMPART. We accounted for the treatment effect of the intermediate risk patients by entering them early to the trial, knowing that events are likely to occur later than in high risk patients and by capping their accrual at 25% of the total. Therefore, intermediate risk patients will contribute enough events to the primary DFS analysis and, should the trial yield a positive outcome, licensing may be extended to this cohort of patients.

5.5. Choosing co-primary outcome measures

We designed RAMPART to investigate two co-primary outcome measures: DFS and OS. DFS is the standard primary outcome in adjuvant trials, both in RCC and in a range of other cancers. New agents are often licensed based on this outcome.

OS remains a key survival outcome, particularly for patients and healthcare providers. However, in the setting of renal cancer, an adjuvant trial focussing only on OS would take up to 20 years to report its results, potentially denying thousands of patients the opportunity to

benefit from what may prove to be efficacious treatments. Pragmatically, we will analyse OS conditional on getting a signal in DFS. The primary OS analysis will include patients in the high-risk subgroup only to avoid the dilution of treatment effect due to high competing causes of death in the intermediate risk group. In response to comments from the regulators, we also updated the analysis plan to include an interim analysis of OS at the time of the interim and final DFS analyses.

5.6. Regulatory-future proofing –trial conduct

We have implemented sufficient elements from the outset of the trial to enable compliance with International Conference on Harmonisation – Good Clinical Practice (both retrospectively and prospectively). This will enable data from the RAMPART trial to be used as part of a licensing application. We have also put in place a number of notable future-proofing trial conduct features, which will facilitate a future regulatory submission.

Firstly, we have set up our clinical records database to be Clinical Data Interchange Standards Consortium (CDISC) compatible. This will help facilitate the submission of standardised data to the regulators and has the added benefit of facilitating data sharing with other organisations.

Secondly, we have built a CT scan repository to collect CT scans on an ongoing basis. In the first instance, sites are sending medical images to the MRC CTU at UCL for upload, but eventually trial sites will be able to remotely upload and anonymise medical images to the repository. This will allow CT scan images to be accessed at crucial time points should blinded central review be required.

Finally, we have implemented a risk-based quality management and monitoring plan for RAMPART including both central and on-site monitoring. As is appropriate for international trials, the oversight plan includes measures to ensure the appropriate and consistent conduct of RAMPART at all of our participating sites around the world. Our clear quality management plan gives us confidence in the integrity of the data as well as in the quality and consistency of trial conduct across all of our sites.

6. Conclusion

We have carefully designed and planned the RAMPART trial, drawing from the experience our unit offers in the development of MAMs trials and our experience leading the SORCE trial in the adjuvant RCC setting. We have built an international multidisciplinary, academic team to fine-tune an RCC specific adaptive platform. Finally, we sought the advice of both European and US regulators in designing our trial. We propose this model of working collaboratively from the outset with industry and regulatory bodies to shape trial design and conduct, in order to optimise futureproofing and ensure accountability for decision-making. Ultimately, we intend to show that efficient trial design and strategic collaborations between academia and industry partners can help patients get access to novel treatments sooner.

Fig. 1 shows the RAMPART trial design, including the timelines for analysis proposed at the outset of the trial. The option of adding a third research arm is accounted for in the trial design. The timing of when that arm might be added has not been decided. A contemporaneous control arm would continue for the duration of the trial.

Trial status

The trial is currently open to recruitment.

Abbreviations

Noted in text

Funding

Availability of data and materials

N/A

Author's contributors

N/A

Ethics approval and consent to participate

The RAMPART trial was approved in the UK by the Riverside Research Ethics Committee and the Health Research Authority (HRA). National approvals are also obtained in all participating countries. All participants signed an Informed Consent Form prior to entry into the study.

Consent for publication

N/A

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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