Contemporary Clinical Trials 108 (2021) 106482

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

RAMPART: A phase III multi-arm multi-stage trial of adjuvant checkpoint inhibitors in patients with resected primary renal cell carcinoma (RCC) at high or intermediate risk of relapse

Bhavna Oza [a,*], Eleni Frangou [a], Ben Smith [a], Hanna Bryant [a], Rick Kaplan [a], Babak Choodari-Oskooei [a], Tom Powles [b], Grant D. Stewart [c], Laurence Albiges [d], Axel Bex [e,p], Toni K. Choueiri [f], Ian D. Davis [g,h,i], Tim Eisen [j], Alison Fielding [a], David Harrison [k], Anita McWhirter [l], Salena Mulhere [a], Paul Nathan [m], Brian Rini [n], Alastair Ritchie [a], Sarah Scovell [b], Clare Shakeshaft [a], Martin R. Stockler [i,o], Nat Thorogood [a], Mahesh K. B. Parmar [a], James Larkin [l], Angela Meade [a]

[a] MRC Clinical Trials Unit at UCL, Institute of Clinical Trials & Methodology, 2nd Floor 90 High Holborn, London WC1V 6LJ, UK
[b] St Bartholomew's Hospital, W Smithfield, London EC1A 7B, UK
[c] Department of Surgery, University of Cambridge, Cambridge Biomedical Campus, Cambridge CB2 0QQ, UK
[d] Institut Gustave Roussy, 114 Rue Edouard Vaillant, 94805 Villejuif, France
[e] Royal Free London NHS Foundation Trust UCL Division of Surgery and Interventional Science, Pond Street, London NW3 2QG
[f] Dana-Farber Cancer Institute, 450 Brookline Ave, Boston, MA 02215, United States
[g] Monash University Eastern Health Clinical School, Level 2, 5 Arnold Street, Box Hill, VIC 3128, Australia
[h] Department of Medical Oncology, Eastern Health, Melbourne, Australia
[i] ANZUP Cancer Trials Group, Sydney, Australia
[j] Department of Oncology, Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Cambridge Biomedical Campus Hill's Road, Cambridge CB2 0QQ, UK
[k] University of St Andrews, North Haugh, St Andrews KY16 9TF, UK
[l] Royal Marsden Hospital, 203 Fulham Rd, Chelsea, London SW3 6JJ, UK
[m] Mount Vernon Cancer Centre, Rickmansworth Rd, Northwood HA6 2RN, UK
[n] Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH, United States
[o] NHMRC Clinical Trials Centre, University of Sydney, Camperdown, NSW 2006, Australia
[p] Netherlands Cancer Institute, Amsterdam, the Netherlands

ARTICLE INFO

Keywords:
RAMPART
Renal cancer
Durvalumab
Tremelimumab
MAMS
Platform trial
Check-point inhibitor

ABSTRACT

Background: 20–60% of patients with initially locally advanced Renal Cell Carcinoma (RCC) develop metastatic disease despite optimal surgical excision. Adjuvant strategies have been tested in RCC including cytokines, radiotherapy, hormones and oral tyrosine-kinase inhibitors (TKIs), with limited success. The predominant global standard-of-care after nephrectomy remains active monitoring. Immune checkpoint inhibitors (ICIs) are effective in the treatment of metastatic RCC; RAMPART will investigate these agents in the adjuvant setting.

Methods/design: RAMPART is an international, UK-led trial investigating the addition of ICIs after nephrectomy in patients with resected locally advanced RCC. RAMPART is a multi-arm multi-stage (MAMS) platform trial, upon which additional research questions may be addressed over time. The target population is patients with histologically proven resected locally advanced RCC (clear cell and non-clear cell histological subtypes), with no residual macroscopic disease, who are at high or intermediate risk of relapse (Leibovich score 3–11). Patients with fully resected synchronous ipsilateral adrenal metastases are included. Participants are randomly assigned (3,2:2) to Arm A - active monitoring (no placebo) for one year, Arm B - durvalumab (PD-L1 inhibitor) 4-weekly for one year; or Arm C - combination therapy with durvalumab 4-weekly for one year plus two doses of tremelimumab (CTLA-4 inhibitor) at day 1 of the first two 4-weekly cycles. The co-primary outcomes are disease-free-survival (DFS) and overall survival (OS). Secondary outcomes include safety, metastasis-free survival, RCC

* Corresponding author at: Medical Research Council, Clinical Trials Unit at University College London, 90 High Holborn, London WC1V 6LJ, UK.
E-mail address: b.oza@ucl.ac.uk (B. Oza).

https://doi.org/10.1016/j.cct.2021.106482
Received 18 March 2021; Received in revised form 7 June 2021; Accepted 9 June 2021
Available online 16 September 2021
1551-7144/Crown Copyright © 2021 Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

specific survival, quality of life, and patient and clinician preferences. Tumour tissue, plasma and urine are collected for molecular analysis (TransRAMPART).
Trial registration: ISRCTN #: ISRCTN53348826, NCT #: NCT03288532, EUDRACT #: 2017–002329-39, CTA #: 20363/0380/001–0001, MREC #: 17/LO/1875, ClinicalTrials.gov Identifier: NCT03288532, RAMPART grant number: MC_UU_12023/25, TransRAMPART grant number: A28690 Cancer Research UK, RAMPART Protocol version 5.0.

1. Introduction

Patients with intermediate or high-risk locally advanced renal cell cancer (RCC), as stratified by RCC specific prognostic scores, are at significant risk of relapse after surgical tumour resection. 20–30% of patients with intermediate risk and 40–60% of patients with high risk RCC develop metastatic disease following nephrectomy [1–3]. Between 1 and 4% of patients with RCC present with synchronous ipsilateral adrenal metastases that can be resected at the time of nephrectomy [4]. These patients are treated adjuvantly, and they are considered to behave similarly to patients with high risk RCC. An effective strategy for reducing the risk of recurrence or death for patients with locally advanced, fully resected RCC remains an unmet clinical need.

TKIs targeting the vascular endothelial growth-factor receptor are established in treating metastatic RCC and have been extensively tested in the adjuvant setting. Five TKI trials have produced results: ASSURE, PROTECT, S-TRAC, ATLAS and now SORCE [5–10]. These studies evaluated the effect of oral TKIs compared to placebo and none have shown a benefit of TKI on overall survival (OS) [10,11]. Only the S-TRAC trial showed a modest DFS benefit with 1 year of sunitinib (HR 0.76; 95% CI 0.59–0.98; $p = 0.03$) compared to placebo on blinded independent central review [7]. 63% of sunitinib treated patients experienced Grade ≥ 3 toxicities, with many patients unwilling or unable to complete treatment. On this basis, the Food and Drug Administration (FDA) approved sunitinib for the adjuvant treatment of patients with high risk RCC. However, given the toxicity and cost associated with sunitinib in this setting, the results have not been universally practice changing. Therefore, nephrectomy followed by active surveillance for relapse, remains the predominant standard of care globally.

Treatment with ICIs, either as a dual combination or in combination with TKIs have revolutionised the management of patients with advanced RCC. The combination of ipilimumab, a monoclonal antibody against human cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) with nivolumab, a monoclonal antibody against programmed cell death protein-1(PD-1) is now a first line treatment for patients with intermediate or poor risk advanced RCC, classified according to the International Metastatic Renal-Cell Carcinoma Database Consortium (IMDC) model [12]). This followed findings from CHECKMATE-214 [13], a phase III study showing an 18 month OS of 75% (95% CI; 70–78) for the combination ICI group versus 60% (95% CI; 55–65) for sunitinib [14]. In addition, single agent nivolumab, is routinely available in the second line setting for patients who have progressed on TKI therapy regardless of IMDC risk, based on a 5.6 month OS benefit of nivolumab over everolimus [15]. There are now a number of ICI and TKI combination strategies which have shown efficacy benefit over sunitinib in the first line setting, including axitinib (TKI) with avelumab (anti-programmed death-ligand 1 (PD-L1)), axitinib with pembrolizumab (anti-PD-1), pembrolizumab with lenvatinib (TKI) and nivolumab with cabozantinib (TKI) [16–19].

Durvalumab (anti PD-L1) and tremelimumab (anti-CTLA-4) are agents of the same class as other ICIs. Durvalumab is efficacious for patients with non-small-cell lung cancer who have completed definitive chemo-radiotherapy, showning a progression free survival (PFS) advantage of 11.2 months in patients receiving durvalumab compared with placebo [20]. Durvalumab in combination with tremelimumab has shown benefit to OS and PFS in the third-line treatment of patients with metastatic NSCLC, (in those with PD-L1 tumour cells $\geq$25%) and is being evaluated in the advanced setting in patients with various tumour types (NCT03298451), (NCT03994393) and (NCT02516241).

Therefore, the RAMPART trial, led by the MRC CTU at University College London (UCL) and working in partnership with AstraZeneca, is investigating the activity of durvalumab alone and in combination with tremelimumab after nephrectomy for patients with locally advanced RCC. There is also potential for adding additional research arms as the trial progresses.

2. Methods

2.1. Overview of design

RAMPART is a phase III, multi-arm multi-stage (MAMS) trial, initiated with a control (Arm A; active monitoring) and two research arms, (Arm B; durvalumab and Arm C; durvaumab with tremilimumab) (Fig. 1). Initially, participants with Leibovich scores 3 to 11 (intermediate and high risk) [21] are eligible to be randomised. Intermediate-risk participants (Leibovich scores 3–5) will be capped at 25% of the total accrual target or after four years of recruitment, whichever is earlier. Inclusion of intermediate risk participants acknowledges that they are at a substantial risk of relapse, although they tend to occur later than those at high risk. By including the intermediate-risk participants during the early years of the trial, there will be sufficient numbers, followed for long enough, to contribute to the disease-free survival (DFS) analysis. Recruitment of participants with Leibovich scores 6 to 11 will continue to the accrual target of 1750 participants. Participants with ipsilateral adrenal metastases that are completely resected at the time of nephrectomy are eligible for RAMPART, which was a mid-trial protocol change implemented in July 2021.

2.2. Outcome measures

There are two co-primary endpoints in RAMPART, DFS and OS. DFS is defined as the interval from randomisation to first evidence of local recurrence, new primary renal cell carcinoma (RCC), distant metastases, or death from any cause, whichever occurs first. OS is defined as all-cause mortality; the time from randomisation to death from any cause. An adjuvant trial focusing on DFS and OS independently would take up to fifteen to twenty years to report its results and would potentially deny many thousands of patients the opportunity to benefit from promising new treatments. Therefore, both DFS and OS were accepted, after regulatory and scientific review, as co-primary endpoints. OS will be examined conditional on seeing improvements in DFS. However, DFS is the primary outcome on which regulatory approval will be sought for durvalumab monotherapy and/or the combination of durvalumab and tremelimumab. Reporting both DFS and OS as co-primary endpoints will provide the complete picture and allow clinicians and regulators to make fully informed treatment decisions.

The following secondary outcome measures will be analysed:

- Safety
- Metastasis-free survival (MFS), defined as the interval from randomisation to first evidence of metastases or death from RCC;
- RCC specific survival time, defined as the time from randomisation to death from RCC;
- Quality of Life (EQ-5D, EORTC QLQ-C30)

- Preferences for Adjuvant Immunotherapy in RAMPART (PAIR) sub-study questionnaire at baseline, week 16 and after completing treatment at month 15.

2.3. Sample size

RAMPART is powered for both the DFS and OS outcomes. The sample size calculations and design characteristics for RAMPART were obtained using nstage (version 3.0.1, 10-Sep-2014). Specifically, the nstage program was used to obtain the 'ideal' target number of control arm events needed at each stage for each comparison and an approximate idea for the timing of the stages. Artpep (version 1.0.4 PR 05-Jul-2013) was then used to project a more realistic analysis timeline using accrual and time-to-event patterns based on the SORCE trial (ISRCTN: ISRCTN38934710, EUDRACT: 2006–006079-19; NCT00492258). ART (version 1.1.0, 10-Dec-2013) was used to determine the absolute differences in DFS and OS at relevant time points. All calculations were performed in Stata 14.1.

Using control arm data from the SORCE trial [9] we anticipate a 3-year DFS rate of 65% for the control arm of RAMPART. We plan to recruit 1750 participants (750 to Arm A, 500 to Arm B and 500 to Arm C) over approximately 5.5 years but will continue until the accrual target is reached.

2.4. Adjusting sample size estimates for multiple comparisons

We have adjusted the RAMPART sample size to allow for multiple comparisons. The overall type I error rate – i.e. the family-wise type I error rate (FWER) [19] - is strongly controlled at 2.5% for all the pairwise comparisons whether or not a new research arm is added. Simulations were used to find the final stage significance level that control the FWER across the three pairwise comparisons. We considered two different scenarios: 1) the trial starts (and possibly concludes) with two research arms B and C, 2) or a new research arm (Arm D) is added before accrual to the current 3-arm trial completes. We applied Dunnett's approach to calculate the FWER in both scenarios 1 and 2. The results showed that the final stage significance level of 0.0097 in all pairwise comparisons controls the overall FWER at 2.5% when Arm D is added later on. Our simulations also showed that the final stage significance level of the two original pairwise comparisons can be increased to 0.015 if the deferred arm is not added, to buy back the unspent type I error of the third pairwise comparison. The relevant methods to calculate the correlation structure are described in Choodari-Oskooei et al. (2020) [22].

2.5. Eligibility and participant recruitment

Participants entering the RAMPART trial have undergone potentially curative nephrectomy for RCC and must satisfy the eligibility criteria, summarised in Tables 1 and 2. The time window for entry (up to 12 weeks post nephrectomy) allows treatment to be started at the earliest opportunity to maximise the potential benefits, whilst also considering safety from a post-surgical perspective.

2.6. Site recruitment

RAMPART is open to hospitals throughout the United Kingdom (UK). Recruitment will commence in Australia, New Zealand, France and Spain in mid 2021 (other countries may join subsequently).

UK site recruitment has been organised in 'waves' of hospitals, grouped by geography and also by their accrual to SORCE. Doing this has enabled more individualised site support. Lessons learnt from opening successive waves helps with optimising and refining activation processes, training of hospital staff and the provision of more useful guidance documents. Given the novel nature of the treatments and concerns around potential toxicity, the trial management team have been able to keep a closer eye on safety with a smaller initial group of sites.

2.7. RAMPART and the COVID-19 pandemic

Recruitment of participants into RAMPART and the treatment of existing RAMPART participants was suspended on 23-Mar-2020 due to the COVID-19 pandemic as it was unknown whether durvalumab and/or tremelimumab would lead to an increased risk or severity of COVID-19 for RAMPART participants. AstraZeneca subsequently advised that there

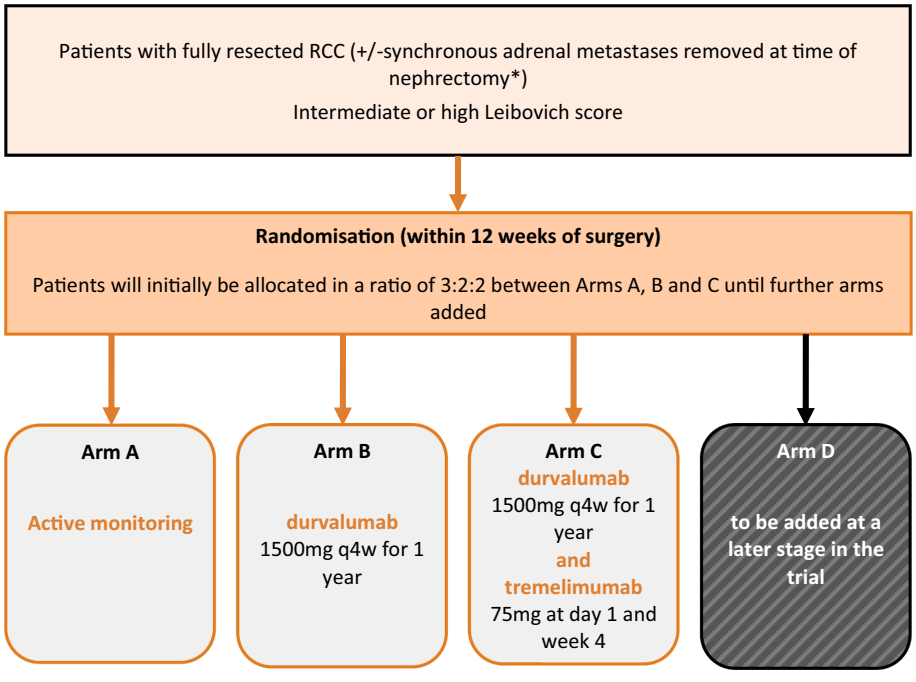

Fig. 1. Trial schema.

Table 1
Inclusion criteria (see protocol for more detailed list).

Inclusion Criteria
Histologically proven RCC all cell types except for pure oncocytoma, collecting duct, medullary and transitional cell cancer
Microscopically positive resection margins after **radical** nephrectomy at the nephrectomy bed, renal vein or inferior vena cava
Synchronous ipsilateral adrenal metastases, provided they are fully resected at the time of nephrectomy
No residual macroscopic disease on post-operative CT scan after resection of RCC
Leibovich Score 3-11
Nephrectomy 28-91 days prior randomisation
WHO PS 0-1
FFPE tissue available
Haemoglobin ≥9.0g/dL
Neutrophil count ≥1.5 x 10^9/L
Platelet count ≥100 x 10^9
Bilirubin ≤1.5 ULN
AST/ALT ≤2.5 ULN
Creatinine Clearance > 40mL/min
≥ 18 years of age
Following trial's contraception policy (see RAMPART protocol V5.0 for details)

WHO World Health Organisation; PS Performance status; FFPE Formalin-fixed paraffin embedded; AST aspartate aminotransferase; ALT alanine aminotransferase; ULN upper limit normal.

was no evidence linking participants treated with either drug or the combination to a higher risk or severity of COVID-19 infection. As the potential benefits of treatment in the RAMPART trial outweigh the risks overall, RAMPART was re-opened on 07-Jul-2020. Sites were advised to restart treatment of existing participants and recruit new participants as and when they could.

Significant changes have been made to the RAMPART protocol during the pandemic to optimise safety for participants in terms of minimising time spent in hospital. Sites are now permitted to complete the participant consent process via either video or phone, where it forms part of local policy to reduce patient exposure to COVID-19. For more details on the Remote Consent Policy see RAMPART protocol version 5.0 [23]. In addition, the COVID-19 pandemic has significantly impacted the way in which clinical assessments can be conducted by sites and is highlighted below. These changes have enabled the RAMPART trial to remain active through subsequent waves of the pandemic.

2.8. Randomisation

Participants are randomised centrally between Arm A and the research Arms B and C using stratified block randomisation in the ratio 3:2:2. Treatment allocation is not blinded. To decrease determinability, the stratification factors are not listed here but are described in the RAMPART Statistical Analysis Plan, which will be finalized and published prior to the first interim analysis. Participants randomised to Arms B and C start treatment within 14 days of randomisation.

2.9. Treatment schedule and assessments

Participants in Arm B receive a fixed dose of 1500 mg durvalumab via IV infusion every four weeks for up to 13 cycles. Participants in Arm C receive four weekly 1500 mg durvalumab IV for a total of 13 cycles and two doses of 75 mg tremelimumab IV with the first and second cycles of durvalumab.

Participants in the active monitoring arm (Arm A) receive no drug; however they are radiologically assessed at the same frequency as participants on the active treatment arms. Arm A participants are clinically assessed at weeks 16, 32 and 52. Participants in arms B and C are assessed at day 1, then on a 2 weekly basis until week 8, and then every 4 weeks until week 52.

Since the COVID-19 pandemic there is now a greater emphasis on remote clinical assessments and this approach is supported by patient groups. Therefore, where it is deemed appropriate by the investigator, the pre-treatment clinical assessments can be carried out remotely (via telephone or video). The laboratory tests may be completed at the participants GP or a local hospital. Once the assessments have been completed at week 52 all participants will move into follow-up phase.

Table 2
Exclusion criteria.

Exclusion Criteria
Previous diagnosis of RCC
Metastatic or residual macroscopic disease (synchronous adrenal metastases which are fully resected at the time of nephrectomy are permitted).
Single pulmonary nodule ≥5mm (unless benign). multiple small, less than 5 mm nodules may be eligible if nodules are radiologically stable for at least 8 weeks
Prior anti-cancer treatment (other than nephrectomy) for RCC
Unresolved toxicity CTCAE v4.03 Grade ≥2 from previous anticancer therapy
Major surgical procedure within 28 days prior randomisation
Clinically significant pneumonitis or fibrosis
Concurrent enrolment in other RCT unless observational (non-interventional) or during follow-up period of an interventional study
Current or prior use of immunosuppressive therapy within 14 days prior to first dose of trial IMP
Active or prior autoimmune or inflammatory disorder
History of immunodeficiency syndrome
History of allogeneic organ transplant
Uncontrolled inter-current illness; congestive heart failure, unstable angina, uncontrolled cardiac arrhythmia, acute peptic ulcer/gastritis, acute bleeding, psychiatric illness that would limit study compliance
Active infection (participants who are exhibiting symptoms consistent with COVID-19, or who have tested positive, should not be randomised into the study until they are asymptomatic and at least 14 days after a positive test)
Live attenuated vaccine within 30 days prior to randomisation
Pregnant or breastfeeding
Patient has archival FFPE pathology tissue available, and agrees to provide at least one sample, as well as baseline CPDA and PAXgene blood samples for future translational research
Clinically significant pneumonitis or fibrosis

CTCAE Common Terminology Criteria for Adverse Events; RCT randomised controlled trial, FFPE Formalin-fixed paraffin embedded; CPDA citrate-phosphate-dextrose solution with adenine.

2.10. *Criteria for discontinuing allocated interventions*

An individual participant may stop treatment early for any of the following reasons.

- Disease progression
- Unacceptable toxicity, Inter-current illness or change in patient's condition that justifies discontinuation
- Any change in the patient's condition that in the clinician's opinion makes continuing investigational medicinal product a safety risk.
- Pregnancy or intent to become pregnant
- Grade $\geq$ 3 infusion reaction
- Initiation of alternative anticancer therapy including another investigational agent
- Withdrawal of consent for treatment by the patient
- Missing consecutive treatment visits[1].

[1] For treatment breaks due to COVID-19 infection, there is no specified maximum time between durvalumab infusions prior to restarting treatment. The second dose of tremelimumab for Arm C participants however, must be given within 12 weeks of starting trial treatment. Regardless of any administration delays, the maximum duration of durvalumab treatment must not exceed 1 year.

2.11. Participant follow-up

Participants on all arms who have not progressed are seen at week 52 (end of year one), and are followed-up on a three monthly basis until the end of year three. Initially, they have CT scans (with contrast) of the chest, abdomen and pelvis every six months. After year three, participants have annual clinical follow-up with a CT until year five. For the purposes of the trial, participants have a CT scan at either years seven or eight and a further CT scan at ten years. Follow-up assessments may be conducted in person or remotely (via telephone or video) if deemed appropriate. The trial follow-up schedule is described in Table 3.

2.12. Tumour assessment

The DFS outcome will be investigator-reported and must be based on thorough investigation and evidence such unequivocal radiological progression or biopsy. Site specific combined imaging and surgical review, followed by histopathological discussion (if relevant) at multidisciplinary team discussion is the routine way in which DFS events are classified.

2.13. Safety/toxicity management

ICIs aim to boost endogenous immune responses directed against tumour cells. This augmented immune response may lead to activation of autoreactive T-cells that damage host tissues. Immune-related adverse events (ir-AEs) can affect any body system. Combined PDL-1 plus CTLA-4 blockade is likely to trigger more ir-AEs than anti PD-1 alone. A comprehensive toxicity management guide is provided to all investigators to manage potential ir-AEs based on the severity of treatment-emergent toxicities graded per NCI CTCAE v4.03 [23]. It includes criteria for permanent discontinuation of study drug/study regimen based on CTCAE grade. In addition, study drug should be permanently discontinue for the following conditions:

- If an ir-AE results in missing consecutive treatment visits. Inability to reduce corticosteroid to a dose of $\leq$10 mg of prednisone per day (or equivalent) within 8 weeks after last dose of study drug/study regimen
- Grade $\geq$ 3 recurrence of an ir-AE following resumption of dosing
- Grade $\geq$ 3 infusion reaction

2.14. Monitoring

The monitoring plan for RAMPART is based on a formal risk assessment, initially undertaken during trial development. The plan is reviewed and updated as appropriate on at least an annual basis.

The RAMPART team conduct central and on-site monitoring checks to identify potential issues with consent, eligibility, treatment administration, drug supply and safety monitoring. Any issues identified will be raised and discussed with the local team.

Each participating site will have their first on-site monitoring visit within one year of randomising a patient to active treatment, (Arms B or C). The frequency of subsequent visits to sites will be determined by the outcomes of central monitoring. At times when site visits are difficult to conduct (e.g. COVID-19 pandemic), more central monitoring checks are performed to check site compliance.

2.15. Data management

Paper CRFs are used in RAMPART. Original copies of CRFs are retained at individual sites whilst copies are sent via secure email to the MRC CTU at UCL where they are stored securely. Key variable checks are performed on receipt of all RAMPART CRFs to ensure any potential safety issues are rapidly identified. Data is single entered onto a customised in-house database by trained staff. The database has many built

Table 3
Routine follow-up assessment schedule.

	Week 52	Month 15	Month 18	Month 21	Month 24	Month 27	Month 30	Month 33	Month 36	Month 42	Month 48	Month 54	Month 60	Month 84	Month 120	DFS Event	As clinically required
Clinical Assessments																	
Physical Examination																	X
Concomitant Medications	X	X															
Adverse Events	X	X															
WHO Performance Status	X	X	X	X	X	X	X	X	X		X		X	X	X		
Radiology																	
CT Scans	X		X		X		X		X		X		X	X	X	X	X
Laboratory Tests																	
Haematology	X	X															X
Clinical Chemistry	X	X															X
Questionnaires																	
EQ-5D *(optional)*		X							X							X	
QLQ-C30 *(optional)*		X							X							X	
PAIR *(optional)*		X															

WHO World Health Organisation; EQ-5D EuroQol- 5 Dimension Questionnaire; QLQ-C30 European Organisation for the ReseConcRadiologyomitant Medicationsarch and Treatment of Cancer Quality of Life Questionnaire version 3.0.

in validations (value ranges, date inconstancies, treatment administration) to help ensure the data is both accurate and correct. The RAMPART Data Management Plan provides a comprehensive breakdown of how data is to be acquired, handled and secured.

2.16. Statistical analysis plan

All efficacy analyses will be performed in the intention-to-treat population. The treatment effect for each of the initial two treatment comparisons and each of the two co-primary outcomes will be assessed using a stratified Cox model, stratifying for the factors used in randomisation. Data will be presented graphically using Kaplan-Meier plots. The Chi-squared test or Mann-Whitney test will be implemented for categorical data comparisons, including toxicity, as appropriate. Subgroup analyses will be conducted to assess consistency of treatment effect across potential or expected prognostic factors, including subgroup analyses by PD-L1 baseline expression status. Full details of all planned analyses are documented in the RAMPART Statistical Analysis Plan.

2.17. Interim analyses for disease-free survival (DFS)

As part of the MAMS design, one interim analysis is planned for the comparison of Arm C vs Arm A (combination vs control) and three interim analyses are planned for the comparison of Arm B vs Arm A (monotherapy vs control). Each one will consider both a lack-of-benefit and overwhelming benefit of treatment on DFS. Both sets of stopping boundaries are included in the RAMPART protocol [23].

Based on assumptions for accrual and survival distribution for the control arm, at the time of the trial design the first interim analyses were planned 4.75 years after the trial started. However, the exact timing of the interim analyses will be subject to change as they are time-to-event analyses. The most up-to-date information on the timeline for interim analyses can be found in the RAMPART protocol [23].

2.18. Primary DFS analysis

The primary DFS analysis of Arm C vs Arm A is planned when 276 control arm event events have been observed, The target HR for Arm C versus Arm A is 0.70, which translates to an absolute improvement in 3-year DFS of 9%, from 65% to 74%. This design gives 87.3% power to detect this difference at the 0.0097 one-sided significance level. If the DFS result at this time point is positive, OS will also be analysed using a closed test, even though the data will be not be fully mature, allowing for a more complete assessment of the DFS results.

2.19. Overall survival

The primary OS analysis is planned in high risk participants only (with Leibovich Score 6–11). With approximately 940 high-risk participants in the Arm C vs Arm A comparison, we will have 80% power to detect a HR of 0.7. This HR translates to an absolute difference in OS at 5 years of 6.5%, increasing survival from 76% to 82.5%.

With approximately 940 high-risk participants in the Arm B vs Arm A comparison, we will have 80% power to detect a HR of 0.75. This HR translates to an absolute difference in OS at 5 years of 5.4%, increasing survival from 76% to 81.4%.

2.20. Translational studies/sub-studies

2.20.1. TransRAMPART

TransRAMPART is the Cancer Research UK (CRUK) funded translational study linked to RAMPART. TransRAMPART is an expanded sample collection, building on the samples already obtained through RAMPART and supplementing them with additional sample types and collection time points. To ensure that all sites can contribute to the study, we have defined three participation levels (Bronze, Silver and Gold). For more details see TransRAMPART protocol [24] and the sample collection manual [25].

2.21. Safety and efficacy of the COVID-19 vaccines

There is little published prospective data on the safety of COVID-19 vaccines for participants receiving ICI therapy. In RAMPART we will be publishing the vaccinations our participants receive, any adverse events that they experience following administration of the vaccine as well as any subsequent COVID-19 infections. Relevant information for trial participants should be submitted on the COVID-19 case report form (CRF).

2.22. Regulatory and ethical considerations

The trial will be conducted in compliance with the approved protocol of the Declaration of Helsinki 2008, the principles of Good Clinical Practice (GCP), Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the EU General Data Protection Regulation (GDPR), and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF). International centres will comply with the principles of GCP as laid down by the ICH topic E6 R2 (Note for Guidance on GCP) and applicable national regulations.

Scientific advice on the clinical trial protocol has been obtained from both the European Medicines

Agency (EMA) and FDA. Sufficient elements are in place to enable compliance with ICH GCP (both retrospectively and prospectively) if it is decided at a later stage that trial data are to be submitted to regulatory authorities as part of a licensing application.

The Medicines and Healthcare Products Regulatory Agency (MHRA) granted the Clinical Trials Authorisation on the 24th November 2018. The London Riverside Research Ethics Committee granted ethical approval on 8th January 2018.

2.23. Patient and public involvement

The RAMPART Trial Management Group (TMG) is committed to engaging with the public and involving patient representatives in all aspects of the trial. Patient Public Involvement (PPI) activities include commenting on grant applications, promotion of the trial at start-up, advising on strategies to aid patient recruitment and ongoing engagement with relevant patient groups and charities. Patient newsletters, information sheets and trial promotional videos have been developed by the trial management team with the support of PPI delegates.

Patient representatives are members of the RAMPART TMG while other patient representatives are members of the MRC CTU Genitourinary Trial Steering Committee (TSC) and therefore are actively involved in discussions on trial progress including IDMC recommendations.

2.24. Trial oversight

RAMPART is sponsored by UCL. The MRC CTU at UCL has overall responsibility for the study working closely with the Chief Investigator, all members of the TMG and all collaborators. The Trial Management Team (TMT) meet on a weekly basis to discuss all aspects of trial conduct, including for example site set-up, participant accrual and safety management. The TMT report to the TMG. The TMG is responsible for the running of the trial and meets at least six times a year. An Independent Data Monitoring Committee (IDMC) meet approximately annually to review safety, compliance with treatment and efficacy data (at pre-planned interim analyses). They are the only group who see the confidential, accumulating efficacy data for the trial. The IDMC advise the TSC. The TSC provides overall supervision of the trial and provides

advice and recommendations through its independent Chair. The ultimate decision for the continuation of the trial lies with the TSC.

2.25. Use of electronic health records (EHR)

We plan to incorporate the use of EHR to improve on follow-up of participants enrolled to RAMPART by charting their health status and survival, for example, from records maintained by NHS Central Registry or any applicable national registry.

3. Conclusion

RAMPART is an international, UK-led trial that will assess the benefit of ICIs in participants at intermediate and high risk of recurrence after surgical resection of locally advanced RCC. Participants with synchronous ipsilateral adrenal metastases, removed at the time of nephrectomy are included in RAMPART (implemented in July 2021).

The first patient was randomely assigned in October 2018. By the end of June 2021, 259 of the target of 1750 participants from 34 UK sites were recruited. Recruitment of intermediate risk participants continues, (25% cap has not been reached). After a short pause at the start of the COVID-19 pandemic, RAMPART has re-established recruitment in the UK and in mid 2021 opened in France, Australia and Spain. There have been no safety concerns highlighted in IDMC safety reviews to date.

RAMPART is a three arm adaptive MAMS platform trial upon which at least one new research arm (Arm D) can be added over the coming years. Importantly, the RAMPART trial design allows the control arm to be amended should the standard of care change. This will allow progress to be made in the treatment of locally advanced RCC within the framework of one trial rather than starting a competing trial or waiting a number of years, until the first trial reports. This is critical in the adjuvant setting in RCC where it takes international collaborations many years to develop, launch and deliver a trial. 'RAMPART: A Model for a regulatory ready academic led phase III trial in the adjuvant RCC setting' (Contemporary Clinical Trials [26]), outlines the pertinent lessons we have learnt during the process of trial design, development and conduct.

TransRAMPART is a unique scientific collaboration that will provide an opportunity to address unanswered issues for patients with locally advanced RCC including which patients are most in need of adjuvant ICIs. Research will also explore biomarkers that predict treatment response and those that might pre-empt the onset of significant toxicity. It is likely that the research conducted on the TransRAMPART samples will lead to tangible benefits for patients.

The full support of our UK and international collaborators is essential to meet our ambitious accrual target of 1750 participants in order to complete this important trial aimed at improving the adjuvant treatment of renal cell carcinoma.

An up-to-date version of the RAMPART protocol can be found at https://www.rampart-trial.org/.

Credit

Conceptualisation; TMG clinicians, Mahesh K B Parmar, Rick Kaplan, Angela Meade. Input from all members of the RAMPART TMG.

Writing - Original Draft and data curation; Bhavna Oza, Elena Frangou, Ben Smith, Hanna Bryant, Angela Meade

Visualization; Bhavna Oza, Angela Meade

Supervision; Angela Meade, Clare Shakeshaft

Project administration/Funding acquisition; Mahesh K B Parmar, Rick Kaplan, Angela Meade

Passive PSO reviewer- Eric Goluboff

Trial status

The trial is currently open to recruitment.

Abbreviations

Noted in text

Funding

AstraZeneca LP have provided an educational grant for the trial and free of charge durvalumab and tremelimumab. A small grant is also provided by Kidney Cancer UK. MRC CTU at UCL also provides funding for staff working on the trial. The TransRAMPART sample collection is being funded by a Prospective Sample Collection award from Cancer Research UK.

Availability of data and materials

N/A.

Author's contributors

N/A.

Ethics approval and consent to participate

The RAMPART trial was approved by the Riverside Research Ethics Committee and the Health Research Authority (HRA) and is part of the UK National Cancer Research Network (NCRN) portfolio. Reference number 17/LO/1875. The RAMPART trial is an investigator-led academic trial sponsored by UCL and co-ordinated by the MRC CTU at UCL. All participants signed an Informed Consent Form prior to entry into the study. A separate consent process will be employed for TransRAMPART sub-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.

Acknowledgments

The authors would like to acknowledge the efforts and contributions of all of our patient representatives, the trial investigators and research teams at sites. We would also like to show our gratitude to all the trial participants, without whom RAMPART would not be possible. All authors approved of the final version of the article, including the authorship list.

References

[1] S. Dabestani, et al., Long-term outcomes of follow-up for initially localised clear cell renal cell carcinoma: RECUR database analysis, Eur. Urol. Focus 5 (5) (2019) 857–866.

[2] S. Dabestani, et al., Renal cell carcinoma recurrences and metastases in primary non-metastatic patients: a population-based study, World J. Urol. 34 (8) (2016) 1081–1086.

[3] J.S. Lam, et al., Postoperative surveillance protocol for patients with localized and locally advanced renal cell carcinoma based on a validated prognostic nomogram and risk group stratification system, J. Urol. 174 (2) (2005) 466–472, discussion 472. (quiz 801).

[4] C.J. Weight, et al., The role of Adrenalectomy in renal Cancer, Eur. Urol. Focus 1 (3) (2016) 251–257.

[5] N.B. Haas, et al., Adjuvant treatment for high-risk clear cell renal Cancer: updated results of a high-risk subset of the ASSURE randomized trial, JAMA Oncol. 3 (9) (2017) 1249–1252.

[6] R.J. Motzer, et al., Randomized phase III trial of adjuvant Pazopanib versus placebo after nephrectomy in patients with localized or locally advanced renal cell carcinoma, J. Clin. Oncol. 35 (35) (2017) 3916–3923.
[7] A. Ravaud, et al., Adjuvant Sunitinib in high-risk renal-cell carcinoma after nephrectomy, N. Engl. J. Med. 375 (23) (2016) 2246–2254.
[8] M. Gross-Goupil, et al., Axitinib versus placebo as an adjuvant treatment of renal cell carcinoma: results from the phase III, randomized ATLAS trial, Ann. Oncol. 29 (12) (2018) 2371–2378.
[9] T. Eisen, et al., Adjuvant Sorafenib for renal cell carcinoma at intermediate or high risk of relapse: results from the SORCE randomized phase III intergroup trial, J. Clin. Oncol. 38 (34) (2020) 4064–4075.
[10] R.J. Motzer, et al., Adjuvant Pazopanib versus placebo after nephrectomy in patients with localized or locally advanced renal cell carcinoma: final overall survival analysis of the phase 3 PROTECT trial, Eur. Urol. 79 (3) (2021) 334–338.
[11] R.J. Motzer, et al., Adjuvant Sunitinib for high-risk renal cell carcinoma after nephrectomy: subgroup analyses and updated overall survival results, Eur. Urol. 73 (1) (2018) 62–68.
[12] D.Y. Heng, et al., Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor–targeted agents: results from a large, multicenter study, J. Clin. Oncol. 27 (34) (2009) 5794–5799.
[13] R.J. Motzer, et al., Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma, N. Engl. J. Med. 378 (14) (2018) 1277–1290.
[14] R.J. Motzer, et al., Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial, Lancet Oncol. 20 (10) (2019) 1370–1385.
[15] R.J. Motzer, et al., Nivolumab versus everolimus in advanced renal-cell carcinoma, N. Engl. J. Med. 373 (19) (2015) 1803–1813.
[16] B.I. Rini, et al., Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma, N. Engl. J. Med. 380 (12) (2019) 1116–1127.
[17] T.K. Choueiri, et al., Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma, N. Engl. J. Med. 384 (9) (2021) 829–841.
[18] R.J. Motzer, et al., Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma, N. Engl. J. Med. 380 (12) (2019) 1103–1115.
[19] R. Motzer, et al., Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma, N. Engl. J. Med. 384 (14) (2021) 1289–1300.
[20] S.J. Antonia, et al., Durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer, N. Engl. J. Med. 377 (20) (2017) 1919–1929.
[21] B.C. Leibovich, et al., Prediction of progression after radical nephrectomy for patients with clear cell renal cell carcinoma: a stratification tool for prospective clinical trials, Cancer 97 (7) (2003) 1663–1671.
[22] B. Choodari-Oskooei, et al., Adding new experimental arms to randomised clinical trials: impact on error rates, Clin. Trials 17 (3) (2020) 273–284.
[23] MRC CTU at UCL, Clinical Trial Protocol V5.0;Renal Adjuvant MultiPle Arm Randomised Trial (RAMPART): An International Investigator-Led Phase III Multi Arm Multi Stage Multi-Centre Randomised Controlled Platform Trial of Adjuvant Therapy in Patients with Resected Primary Renal Cell Carcinoma (RCC) at High or Intermediate Risk of Relapse, RE06; ISRCTN53348826; 2017–002329-39; NCT03288532, 2021.
[24] UCL, M.C.A, TransRAMPART protocol v1.0 24.08.2020, 2020.
[25] UCL, M.C.A, RAMPART Sample Collection Manual v3.0 17.08.2020, 2020.
[26] RAMPART: A Model for a regulatory ready academic led phase III trial in the adjuvant RCC setting, Contemporary Clinical Trials.