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.

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Date: 22-Nov-2017

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Date: 22-Nov-2017
GENERAL INFORMATION

This document was constructed using the MRC CTU at UCL Protocol Template Version 4.0. The MRC CTU at UCL endorses the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) initiative (1). It describes the trial, coordinated by the Medical Research Council (MRC) Clinical Trials Unit (CTU) at University College London (UCL), and provides information about procedures for entering patients/participants into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but sites entering patients for the first time are advised to contact the RAMPART Trial Team, MRC CTU at UCL, London, UK, to confirm they have the most up-to-date version.

Throughout this document the MRC Clinical Trials Unit at UCL, will either be referred to as ‘MRC CTU at UCL’ or ‘the unit’. In instances where neither read well in the sentence, ‘the CTU’ may be used.

COMPLIANCE

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki 1996 (2013, 7th revision), the principles of ICH Good Clinical Practice (GCP)*, Commission Directive 2005/28/EC with the implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act (DPA number: Z6364106), and the National Health Service Research Governance Framework for Health and Social Care (RGF).

International sites will comply with the principles of GCP* as laid down by the ICH topic E6 (Note for Guidance on GCP), Commission Directive 2005/28/EC [the European Directive 2001/20/EC (where applicable)] and applicable national regulations.

* RAMPART is an investigator-initiated academic platform trial. The trial will be initiated and conducted in compliance with the principles of GCP. However, sufficient elements will be put in place from the outset of the trial 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.

SPONSOR

UCL is the trial Sponsor and has delegated responsibility for the overall management of the trial to the MRC CTU at UCL. Queries relating to sponsorship should be addressed to Prof Max Parmar, MRC CTU at UCL Director, MRC CTU at UCL, 90 High Holborn, London, WC1V 6LJ or via the RAMPART Trial Management Team (TMT).

FUNDING

Non-commercial partner funding: Kidney Cancer UK

AstraZeneca LP (educational grant plus free-of-charge durvalumab and tremelimumab)

AUTHORISATIONS AND APPROVALS

UK: This trial has been approved by the NIHR Renal Clinical Studies Group and is funded and peer-reviewed by a NIHR non-commercial partner, it is therefore part of the NIHR Clinical Research Network portfolio.
International Collaborators: details on national approvals and authorisation will be added as new international collaborators join the trial.

TRIAL REGISTRATION

This trial has been registered with the ClinicalTrials.gov and ISRCTN registries, where it is identified as NCT03288532 and ISRCTN53348826 respectively.

RANDOMISATIONS

To randomise, call MRC CTU at UCL, Monday to Friday (between 9am and 5pm GMT/BST)
Tel: +44 (0) 20 7670 4777
National Coordinating Centres will randomise patients on behalf of international centres and in line with country-specific Group Specific Appendix (GSA)

TRIAL ADMINISTRATION

Please direct all queries to a RAMPART Trial Manager at MRC CTU at UCL in the first instance; clinical queries will be passed to the Chief Investigator and Trial Physician via the Trial Manager.

CONTACTS FOR OUT OF HOURS CLINICAL/EMERGENCY QUERIES

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FRANCE

To be confirmed

USA

To be confirmed
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<td>Acronym and Short Title</td>
<td>RAMPART - Renal Adjuvant Multiple Arm Randomised Trial</td>
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<tr>
<td>Long Title of Trial</td>
<td>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.</td>
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<td>17/LO/1875</td>
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<tr>
<td>Study Design</td>
<td>RAMPART is a phase III Multi-Arm, Multi-Stage (MAMS), multi-centre, randomised controlled platform trial.</td>
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<tr>
<td>Type of Participants to be Studied</td>
<td>Patients who have had their RCC resected and are classified as being at intermediate or high risk of recurrence (Leibovich score 3-11) are eligible for randomisation into RAMPART. At the start of recruitment patients with Leibovich score 3-11 will be eligible for randomisation. We will monitor accrual and stop recruiting intermediate risk patients (Leibovich Score 3-5) after three years or when intermediate risk patients contribute 25% of the total accrual target, whichever is earlier. Recruitment of patients with Leibovich Score 6-11 will continue until the accrual target is reached. See Appendix C – The Leibovich Risk Model for Prediction of Progression after radical nephrectomy for clear cell renal cell carcinoma for details of Leibovich scoring system.</td>
</tr>
<tr>
<td>Setting</td>
<td>The trial will be run at hospitals in the UK, France, Australia, New Zealand and the US.</td>
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| Interventions to be Compared | Patients will be randomly assigned in a ratio of 3:2:2 (A:B:C) to the following trial arms:  
  - Arm A - active monitoring for 1 year  
  - Arm B - durvalumab (1500mg) 4 weekly for 1 year (13 cycles maximum)  
  - Arm C - durvalumab (administered as per arm B, i.e. 13 cycles maximum) and tremelimumab (75mg) on day 1 and week 4 visits (i.e. 2 cycles). |
<p>| Study Aims               | The RAMPART platform trial has been designed to evaluate multiple treatments simultaneously, while adapting to a changing |</p>
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| landscape as data on different agents and combinations of agents emerges. The aims for the initial research comparisons are as follows:  
• Does treatment with either durvalumab alone or a combination of durvalumab and tremelimumab increase Disease Free Survival (DFS) compared with active monitoring (Arm B vs Arm A, and Arms C vs Arm A respectively)?  
• Does treatment with either durvalumab alone or a combination of durvalumab and tremelimumab increase Overall Survival (OS) compared with active monitoring in patients classified as Leibovich high-risk (Arm B vs Arm A, and Arms C vs Arm A respectively)?  |

**Study Hypothesis**  
Durvalumab is able to prevent tumour relapse by the inhibition of the programmed cell death 1 (PD-1)/programmed death ligand 1 (PD-L1) pathway, which plays a critical role in tumour immune evasion. Combination treatment with anti-CTLA4 agent tremelimumab increases immune response and anti-tumour activity.

**Co-Primary Outcome Measure(s)**  
DFS and OS  
• DFS is defined as the interval from randomisation to first evidence of local recurrence, new primary 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 (including RCC).

**Secondary Outcome Measure(s)**  
• 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  
• Toxicity  
• Patient preferences for adjuvant immunotherapy

**Exploratory Objective**  
To collect blood and tissue samples for defining biological responses to durvalumab and for identifying candidate markers (e.g. PD-L1 expression) that may correlate with likelihood of clinical benefit.

**Randomisation**  
Patients will be randomised centrally using block randomisation across a small number of important stratification factors.

**Number of Participants to be Studied**  
Approximately 1,750 patients will be recruited to the initial three arm design. As RAMPART is an adaptive, platform trial we plan to add at least one additional arm over time. Recruitment across the current three study arms will be:  
• Arm A - 750 patients  
• Arm B - 500 patients
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<td>Duration</td>
<td>The duration of treatment in each of research arms B and C is one year. Follow-up will continue until the primary outcomes have reached maturity. We anticipate reporting on the co-primary outcomes as follows (all times are from the start of recruitment):&lt;br&gt;• DFS in the durvalumab + tremelimumab combination arm (C) after approx. 6.25 years&lt;br&gt;• DFS in the single-agent durvalumab arm (B) after approx. 10.5 years&lt;br&gt;• OS in high-risk patients (Leibovich Score 6-11) in the durvalumab + tremelimumab combination arm (C) after approx. 13.25 years&lt;br&gt;• OS in high-risk patients (Leibovich Score 6-11) in the single-agent durvalumab arm (B) after approx. 20.5 years</td>
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<td>Ancillary Studies/Sub studies</td>
<td>Translational Sub-study&lt;br&gt;TransRAMPART (see Section 6.7)&lt;br&gt;Baseline samples:&lt;br&gt;• FFPE tissue samples (provision of at least one tumour block is mandatory)&lt;br&gt;• Blood sample (provision of one EDTA baseline sample, collected prior to the first infusion is mandatory)&lt;br&gt;Note: Details on all TransRAMPART sub-studies and sample collection(s) will be included in the TransRAMPART protocol.</td>
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<tr>
<td>Sponsor</td>
<td>The RAMPART trial is an investigator-led academic trial sponsored by UCL and co-ordinated by the MRC CTU at UCL.</td>
</tr>
<tr>
<td>Funders</td>
<td>Kidney Cancer UK (clinical trial grant award)&lt;br&gt;AstraZeneca LP (educational grant and free-of-charge durvalumab and tremelimumab)</td>
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<td>MRC CTU at UCL Project Leader</td>
<td>Dr Angela Meade</td>
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**TRIAL SCHEMA**

**Figure 1** Trial Entry, Randomisation and Treatment

Patients with confirmed RCC, high or intermediate (up to year 3 or 25%) Leibovich score eligible for randomisation into the study

**Randomisation**

Patients will initially be allocated in a ratio of 3:2:2 between arms A, B and C

Arm A
- active monitoring
  - for 1 year

Arm B
- durvalumab
  - 1500mg q4w for 1 year

Arm C
- durvalumab
  - 1500mg q4w for 1 year
- tremelimumab
  - 75mg at day 1 and week 4

Arm D
- to be added at a later stage in the trial
### Trial Assessment Schedule

#### Year 1
- Pre-surgery
- Day 1
- Wk 2
- Wk 4
- Wk 6
- Wk 8
- Wk 12
- Wk 16
- Wk 20
- Wk 24
- Wk 28
- Wk 32
- Wk 36
- Wk 40
- Wk 44
- Wk 48

#### Year 2
- M 15
- M 18
- M 21
- M 24
- M 27
- M 30
- M 33
- M 36
- M 42
- M 48
- M 54
- M 60
- M 72
- M 84
- M 96
- M 108
- M 120

#### Year 3
- Year 3
- Year 4
- Year 5
- Year 7
- Year 8
- Year 9
- Year 10

#### Year 4

#### Year 5

#### Year 7

#### Year 8

#### Year 9

#### Year 10

### Consent
- Written Informed Consent
- X

### Clinical Assessments

#### Clinical History
- X

#### Physical Examination
- X

#### Vital Signs
- X

#### Weight
- X

#### Height
- X

#### ECG
- X

#### Concomitant Medications
- X

#### AEs
- X

#### WHO Performance Status
- X

### Radiology

#### CT Scan
- X

### Laboratory Tests

#### Haematology
- X

#### Clinical Chemistry
- X

#### Hepatitis serologies
- X

### Pregnancy Tests

#### Urine or serum HCG pregnancy Test
- X

### Questionnaires

#### EQ-5D (optional)
- X

#### QLQ-C30 (optional)
- X

#### PAIR Questionnaire (optional)
- X

### TransRAMPART Samples

#### Blood Sample
- X

#### FFPE Tissue Block
- X

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*Serum HCG pregnancy test must be performed to exclude pregnancy at screening. Urine pregnancy test is acceptable after contraception has been established. A serum HCG pregnancy test should be performed if there is any doubt over the results of the urine test. *

* If DFS event occurring before M36

§ Sample taken at time of surgery and required to assess eligibility

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*DFS Event*
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<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>AESI</td>
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<td>Alkaline Phosphatase</td>
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<td>ALT</td>
<td>Alanine Aminotransferase</td>
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<td>Confidence Interval</td>
</tr>
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<td>$C_{\text{max}}$</td>
<td>Maximum Concentration</td>
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<tr>
<td>$C_{\text{min}}$</td>
<td>Minimum Concentration</td>
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<tr>
<td>CRF</td>
<td>Case Report Form</td>
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<td>Clinical Research Network</td>
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<td>Computed Tomography</td>
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<tr>
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<td>Clinical Trials Authorisation</td>
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<td>CTCAE</td>
<td>Common Terminology Criteria for Adverse Event</td>
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<td>CTLA-4</td>
<td>Cytotoxic T-Lymphocyte-Associated Protein 4</td>
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<td>Clinical Trials Unit</td>
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<td>Chest X-ray</td>
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<td>DFS</td>
<td>Disease-free Survival</td>
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<td>Expansion</td>
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<td>DMP</td>
<td>Data Management Plan</td>
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<td>(UK) Data Protection Act</td>
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<td>DSUR</td>
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<td>Electrocardiogram</td>
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<td>(US) Food and Drug Administration</td>
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<td>FFPE</td>
<td>Formalin Fixed Paraffin Embedded</td>
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<td>Hazard Ratio</td>
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<td>IB</td>
<td>Investigator’s Brochure</td>
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<td>ICH</td>
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<td>IL</td>
<td>Interleukin</td>
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<tr>
<td>IMP</td>
<td>Investigational Medicinal Product</td>
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<td>Expansion</td>
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<tr>
<td>INR</td>
<td>International Normalised Ratio</td>
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<tr>
<td>IV</td>
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<td>kg</td>
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<td>Lactate Dehydrogenase</td>
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<tr>
<td>mAb</td>
<td>Monoclonal Antibody</td>
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<td>MCH</td>
<td>Mean Corpuscular Haemoglobin</td>
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<td>MFS</td>
<td>Metastasis-Free Survival</td>
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<tr>
<td>mg</td>
<td>Miligrams</td>
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<td>Medicines and Healthcare products Regulatory Agency</td>
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<td>MRI</td>
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</tr>
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<td>ms</td>
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<td>NSCLC</td>
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<td>ORR</td>
<td>Objective Response Rate</td>
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<td>Preferences for Adjuvant Immunotherapy in RAMPART</td>
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<td>Patient Reported Outcomes</td>
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<tr>
<td>PT</td>
<td>Prothrombin Time</td>
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<tr>
<td>PTT</td>
<td>Partial Thromboplastin Time</td>
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<tr>
<td>PVC</td>
<td>Polyvinylchloride</td>
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<tr>
<td>QA</td>
<td>Quality Assurance</td>
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<tr>
<td>Q4W</td>
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<td>RBC</td>
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<td>Expansion</td>
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<td>RGC</td>
<td>Research Governance Committee</td>
</tr>
<tr>
<td>RGF</td>
<td>Research Governance Framework (for Health and Social Care)</td>
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<tr>
<td>RMST</td>
<td>Restricted Mean Survival Time</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAR</td>
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<td>SD</td>
<td>Stable Disease</td>
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<td>SPC</td>
<td>Summary of Product Characteristics</td>
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<td>sPD-L1</td>
<td>Soluble Programmed Death Ligand 1</td>
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<tr>
<td>SSIGN</td>
<td>Stage, Sign, Grade and Necrosis</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
</tr>
<tr>
<td>TKI</td>
<td>Tyrosine Kinase Inhibitor</td>
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<td>Trial Master File</td>
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<td>Trial Management Group</td>
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<td>Trial Steering Committee</td>
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<tr>
<td>TSH</td>
<td>Thyroid Stimulating Hormone</td>
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<td>TNM</td>
<td>Tumour Nodes Metastasis</td>
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<td>UAR</td>
<td>Unexpected Adverse Reaction</td>
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<tr>
<td>ULN</td>
<td>Upper Limit of Normal</td>
</tr>
<tr>
<td>WBC</td>
<td>White Blood Cell</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<td>WT</td>
<td>Weight</td>
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1 BACKGROUND

1.1 INTRODUCTION

Renal Cell Carcinoma (RCC) represents 2% to 3% of all cancers (excluding non-melanoma skin cancer) worldwide, with the highest incidence occurring in the more developed regions of the world (2). In 2012, the global incidence and mortality were 338,000 new cases and 143,405 deaths, respectively. Over the last 2 decades, the incidence of RCC has increased by approximately 2% both worldwide and in Europe. In the European Union, there were approximately 84,400 new cases of RCC and 34,700 deaths in 2012 (3). In the UK, the incidence was 9,123 people in 2014, making RCC the 8th most common cancer (Office for National Statistics 2016). In 2015, kidney and renal pelvis cancers were the 9th most common cancer in the US, with 61,560 new cases (3.7% of all new cancer cases) and 14,080 deaths. Significant RCC mortality is observed from the 4th decade of life onward (2). Age-specific mortality rates rise steadily from around the age of 40 to 44 years and more sharply from around the age of 65 to 69 years, with the highest rates in the ≥85 years old age group in both sexes. Overall, 50% patients who develop RCC will die from this disease. No adjuvant therapy is known to be effective.

The most recent generation of adjuvant trials in RCC tested tyrosine kinase inhibitors (TKIs) targeting the vascular endothelial growth factor receptor. Unfortunately, despite showing efficacy in advanced RCC, the results in the adjuvant setting, so far, are inconclusive.

The ASSURE trial (NCT00326898) of 1 year of sunitinib or sorafenib versus placebo showed no evidence of benefit of either drug over placebo (DFS HR 1.02 and 0.97 for sunitinib and sorafenib, respectively, with 97.5% CIs of 0.85–1.23 and 0.80–1.17, respectively) (4). There was modest evidence of a DFS benefit in the S-TRAC trial (NCT00375674) of 1 year of sunitinib when DFS events were subject to blinded review (HR 0.76; 95% CI 0.59–0.98; p=0.03) (5). The PROTECT trial (NCT01235962) also showed no evidence of a DFS benefit for 1 year of pazopanib over placebo (DFS HR 0.862; 95% CI 0.69–1.06; p=0.165) (6). The EVEREST trial (NCT01120249) comparing 54 weeks of everolimus with placebo in intermediate and high risk RCC patients has completed accrual but is not expected to report for a number of years.

There remains only a small possibility that 3 years of sorafenib (as tested in SORCE; NCT00492258) or 3 years of axitinib (as tested in ATLAS; NCT01599754) will prove beneficial. However, given the toxicity and cost associated with this type of treatment, especially for long duration, the benefit will have to be large for the current standard-of-care after nephrectomy to change.

The current global standard-of-care after nephrectomy for localised RCC therefore remains active monitoring (i.e., observation by clinical and radiological means). 30-40% patients with initially localised RCC develop metastatic disease following nephrectomy. Need for adjuvant therapy is most marked in the high-risk population where outcomes are predictably poor. However, the risk of recurrence in patients who are of intermediate risk of recurrence is not insignificant. An effective adjuvant therapy would prevent disease recurrence with the ultimate aim of prolonging survival.

1.2 IMMUNE CHECKPOINT INHIBITORS

Immuno-oncology is an approach to cancer therapy designed to modulate the body’s own immune system to promote tumour destruction. Immune checkpoint inhibitors work by targeting molecules that serve as checks and balances on immune responses. By blocking these inhibitory molecules or
activating stimulatory molecules, these treatments are designed to unleash or enhance pre-existing anticancer immune responses. Durvalumab and Tremelimumab are both immune checkpoint inhibitors.

1.2.1 RATIONALE FOR A TRIAL OF IMMUNE CHECKPOINT INHIBITORS IN ADJUVANT RCC

The first suggestion that kidney cancer might be a good target for immunotherapy came from the observation that patients with metastatic kidney cancer occasionally experienced spontaneous regressions after surgical removal of the primary tumour (7). Immunotherapies in the form of immune-stimulating chemicals called cytokines have been used for more than a decade to treat kidney cancer. The cytokines IL-2 and IFN-alpha cause kidney cancers to shrink in approximately 10% to 20% of patients and provide durable remissions in a subset of these patients. In the recent past, IL-2 was the most common first-line therapy for advanced kidney cancer, but because it can have serious side-effects, many doctors now only use it for cancers that are not responding to targeted therapies.

1.3 PD-1/PD-L1 INHIBITION - DURVALUMAB AND NIVOLUMAB

Programmed death ligand 1 (PD-L1; B7 homolog 1 [B7-H1], cluster of differentiation [CD] 274) is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. In normal tissue, PD-L1 is expressed on T-cells, B lymphocytes (B-cells), dendritic cells, macrophages, mesenchymal stem cells, bone marrow-derived mast cells, as well as various non-haematopoietic cells (8). The normal function of PD-L1 is to regulate the balance between T-cell activation and tolerance through interaction with 2 receptors, programmed cell death 1 (PD-1, CD279) and CD80 (B7-1). PD-L1 is also expressed by tumours and acts at multiple sites to help tumours evade detection and elimination by the host immune system. Interactions between the receptors and ligands results in reduced T-cell activation and fewer activated T-cells in the circulation. In the tumour microenvironment, PD-L1 expressed on tumour cells binds to PD-1 on activated T-cells reaching the tumour and this delivers an inhibitory signal to those T-cells, preventing them from killing the target tumour cells, and thus protecting the tumour from immune elimination (9).

Durvalumab is a human immunoglobulin G1 (IgG1) kappa mAb that blocks the interaction of PD-L1 (but not programmed cell death ligand-2) with PD-1 on T cells and CD80 (B7.1) on immune cells (IC) and is engineered to reduce antibody-dependent cell-mediated cytotoxicity. In vitro studies demonstrate that durvalumab antagonises the inhibitory effect of PD-L1 on primary human T cells, resulting in their restored proliferation and release of interferon gamma (IFNγ) (10).

PD-L1 is a member of the B7 family of ligands that inhibit T-cell activity through binding to the PD-1 receptor (8) and to CD80 (11). PD-L1 expression is an adaptive response that helps tumours evade detection and elimination by the immune system. Expression of PD-L1 protein on both tumour cells (TC) and tumour-infiltrating IC is induced by inflammatory signals that are typically associated with an adaptive immune response (eg, IFNγ). The binding of PD-L1 to PD-1 on activated T cells delivers an inhibitory signal to the T cells, protecting the tumour from immune elimination (9). PD-L1 may also inhibit T cells through binding to CD80, although the exact mechanism is still not elucidated (11, 12).

In vivo studies have shown that durvalumab inhibits tumour growth in xenograft models via a T-cell dependent mechanism (10). Based on these data, durvalumab was expected to stimulate the patient’s antitumor immune response by binding to PD-L1 and shifting the balance toward an anti-tumour response.
The current durvalumab Investigator Brochure (IB) provides a complete summary of the available non-clinical and clinical information including pharmacodynamics, pharmacokinetics, safety and efficacy.

Nivolumab is a monoclonal antibody which has a similar mechanism of action to durvalumab. It blocks PD-L1 from binding to PD-1, which then activates the T-cells to find and kill cancer cells. The rationale for the use of durvalumab in RAMPART comes from results observed in earlier phase trials of durvalumab in multiple tumour types alongside its similarity to nivolumab.

1.3.1 PD-1/PD-L1 INHIBITORS IN RCC

The Checkmate 025 phase III clinical trial (NCT01668784) compared nivolumab with the standard treatment, everolimus, in patients with advanced clear-cell RCC. It was the first trial to show an improvement in OS in patients with clear-cell RCC for any immune checkpoint inhibitor drug. The survival benefit was seen in patients, regardless of the extent of PD-L1 expression in their tumours. The median OS was 25 months (95% CI 21.8 to not estimable) with nivolumab and 19.6 months (95% CI 17.6–23.1) with everolimus. The HR for death with nivolumab versus everolimus was 0.73 (98.5% CI, 0.57–0.93; P=0.002), which met the pre-specified criterion for superiority (P≤0.0148). The objective response rate (ORR) was greater with nivolumab than with everolimus (25% vs 5%; odds ratio 5.98 [95% CI 3.68–9.72]; P<0.001). The median PFS was 4.6 months (95% CI 3.7–5.4) with nivolumab and 4.4 months (95% CI 3.7–5.5) with everolimus (HR 0.88; 95% CI 0.75–1.03; P=0.11). Grade 3 or 4 treatment-related AEs occurred in 19% of the patients receiving nivolumab and in 37% of the patients receiving everolimus; the most common event with nivolumab was fatigue (in 2% of the patients), and the most common event with everolimus was anaemia (in 8%) (13). In November 2015, nivolumab was approved by the FDA for patients with advanced RCC who have already received angiogenesis inhibitor therapy. In October 2016, the National Institute for Health and Care Excellence (NICE) approved nivolumab for use within the UK NHS for adults with previously treated advanced RCC, when the company (BMS) provides nivolumab with the discount agreed in the patient access scheme.
1.3.2 PD-1/PD-L1 INHIBITORS IN CANCERS OTHER THAN RCC

Durvalumab is being extensively tested in a number of tumour types.

In the PACIFIC trial (NCT02125461) 713 patients with stage III NSCLC who did not have progression after two or more cycles of platinum-based chemo-radiotherapy were randomised (2:1) to receive consolidation therapy with durvalumab or placebo. The co-primary outcome of PFS (by blinded central review) was reported in NEJM (14). At a median follow-up of 14.5 months median PFS was 16.8 months (95% CI 13.0 – 18.1) with durvalumab versus 5.6 months (95% CI, 4.6 – 7.8) with placebo (stratified HR for disease progression or death, 0.52; 95% CI 0.42 – 0.65, p<0.001). Safety was similar across the groups, G3 or 4 adverse events occurred in 29.9% of the patients who received durvalumab and 26.1% of those who received placebo; the most common G3 or 4 event was pneumonia (4.4% and 3.8%, respectively).

The efficacy and safety of durvalumab has recently been reported in a single-arm phase I/II trial in patients with locally advanced or metastatic urothelial carcinoma (NCT01693562). Data on 191 patients was reported; ORR was 17.8% (95% CI 12.7-24.0), including 7 complete responses. Median PFS and OS were 1.5 months (95% CI 1.4-1.9) and 18.2 months (95% CI 8.1-not estimable), respectively (15). Grade 3 or 4 treatment-related AEs occurred in 13 patients (6.8%); grade 3 or 4 immune-mediated AEs occurred in 4 patients (2.1%) and treatment-related AEs led to discontinuation in 3 patients (1.6%), 2 of whom had immune-mediated AEs that led to death (autoimmune hepatitis and pneumonitis). The data from this study was accepted for assessment by the Food and Drug Administration (FDA) for under priority review, leading to the approval of durvalumab on May 1st 2017 for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

The anti-PD-1 monoclonal antibody nivolumab received FDA approval in 2014 for the treatment of patients with advanced melanoma who have progressed after ipilimumab or ipilimumab and a BRAF inhibitor based on data from the phase III CheckMate 037 trial (NCT01721746) (16). In 2015 it was also FDA approved to treat patients with advanced non-small cell lung cancer (NSCLC) whose disease progressed during or after platinum-based chemotherapy based on results from the CheckMate 057 trial (NCT01673867) (17).

The Checkmate 238 trial (NCT02388906) (n=906 patients) compared nivolumab versus ipilimumab for adjuvant therapy in patients with resected advanced (stage IIIB, IIIC or IV) melanoma. At a median follow up of 18 months, the 12 month recurrence free survival (RFS) was 70.5% (95% CI 66.1 – 74.5) in the nivolumab group compared with 60.8% (95% CI 56.0 to 65.2) in the ipilimumab group (HR for disease recurrence or death, 0.65: 97.56% CI 0.51 to 0.83, p<0.001). A lower rate of treatment-related grade 3 or 4 adverse events was reported in the nivolumab group (14.4%) than in the ipilimumab group (45.9%) (18).

Pembrolizumab is a humanised anti-PD-1 antibody. In September 2014, it was approved by the FDA for use after treatment with ipilimumab, or after treatment with ipilimumab and a BRAF inhibitor in advanced melanoma patients who carry a BRAF mutation. In October 2015 it was also FDA approved for the treatment of metastatic NSCLC in patients whose tumours express PD-L1 and who have failed treatment with other chemotherapeutic agents (NCT01295827) (19).

The PD-L1 inhibitor, atezolizumab, has FDA approval for use in patients with bladder cancer who have failed on platinum-based treatment (NCT02108652) (20).
1.4 CTLA-4 INHIBITION – TREMELIMUMAB AND IPILIMUMAB

Cytotoxic T lymphocytes (CTLs) can recognise and destroy cancer cells. The CTL-associated protein 4 (CTLA-4, also known as CD152) is expressed on the surface of activated T lymphocytes. Binding of CTLA-4 to its target antigen-presenting cell (APC) ligands (B7-1 and B7-2) triggers intracellular transduction signals that antagonise the activation signals and terminates the T-cell response.

Tremelimumab is a human immunoglobulin (Ig)G2 monoclonal antibody (mAb) being investigated as a cancer immunotherapeutic agent. Tremelimumab is specific for human cytotoxic T lymphocyte-associated antigen 4 (CTLA-4; cluster of differentiation [CD]152), a cell surface receptor that is expressed primarily on activated T cells and acts to inhibit their activation. CTLA-4 delivers a negative regulatory signal to T cells upon binding of CD80 (B7.1) or CD86 (B7.2) ligands on antigen-presenting cells. Tremelimumab completely blocks the interaction of human CTLA-4 with CD80 and CD86, resulting in increased release of cytokines (interleukin [IL]-2 and interferon [IFN]-γ) from human T cells, peripheral blood mononuclear cells (PBMCs) and whole blood in the presence of activating stimuli.

The current tremelimumab Investigator Brochure (IB) provides a complete summary of the available non-clinical and clinical information including pharmacodynamics, pharmacokinetics, safety and efficacy.

Ipilimumab (mentioned above in numerous studies) is another fully human anti-CTLA-4 monoclonal antibody and therefore has a similar mechanism of action to tremelimumab. They differ in that ipilimumab is an IgG1 isotype while tremelimumab is an IgG2 isotype.

1.4.1 CTLA-4 INHIBITORS IN RCC

Ipilimumab has shown activity in advanced RCC; a phase II study was conducted in patients with metastatic RCC with a primary end point of response by RECIST criteria. Two sequential cohorts of patients received either 3 mg/kg followed by 1 mg/kg or all doses at 3 mg/kg Q3W (with no intention of comparing cohort response rates). Major toxicities were enteritis and endocrine deficiencies of presumed autoimmune origin. One of 21 patients receiving the lower dose had a partial response. Five of 40 patients at the higher dose had partial responses (95% CI for cohort response rate 4% to 27%) and responses were seen in patients who had previously not responded to IL-2. Thirty-three percent of patients experienced a grade 3 or 4 immune-mediated toxicity; enteritis and hypophysitis were the most frequent events. There was a highly significant association between autoimmune events (AEs) and tumour regression (response rate = 30% with AE, 0% without AE) (21).

1.4.2 CTLA-4 INHIBITORS IN CANCERS OTHER THAN RCC

In 2011, the FDA approved ipilimumab for the treatment of unresectable or metastatic melanoma. The approval was based on a Randomised Controlled Trial (RCT) in patients with unresectable or metastatic melanoma who had received at least 1 prior systemic treatment for melanoma. Patients were randomly assigned to receive either 3 mg/kg intravenous (IV) ipilimumab in combination with a gp100 peptide vaccine (n=403); ipilimumab plus vaccine placebo (n=137); or gp100 peptide vaccine with placebo (n=136). The median overall survival (OS) was 10.0 months among patients receiving ipilimumab plus gp100, as compared with 6.4 months among patients receiving gp100 alone (hazard ratio [HR] for death, 0.68; P<0.001). The median OS with ipilimumab alone was 10.1 months (HR for death in the comparison with gp100 alone, 0.66; P=0.003) (22). The recommended dose and
schedule for ipilimumab approved by the FDA was 3 mg/kg as an IV infusion every 3 weeks (Q3W), for a total of 4 doses.

In 2015, the FDA approved ipilimumab as adjuvant therapy in patients with resected stage III melanoma on the basis of Recurrence Free Survival (RFS) observed in the European Organisation for Research and Treatment of Cancer (EORTC) 18071 phase III trial (NCT00636168) (23). At a median of 5.3 years of follow-up, the 5-year OS rate was 11% higher in the ipilimumab arm (65.4%) than in the placebo arm (54.4%) (24). Quality-of-life analysis supported the benefit of ipilimumab treatment despite a rate of grade 3 or 4 immune-related adverse events of 42% (24, 25). However, as described earlier, longer RFS and a lower rate of grade 3 or 4 adverse events have been observed with nivolumab in this patient group (18).

Single agent CTLA4 inhibition in RCC is considered unattractive from existing data. Therefore, a tremelimumab monotherapy arm will not be included in the RAMPART trial.

1.5 COMBINATION OF PD-1/PD-L1 AND CTLA-4 INHIBITION

Targeting both PD-1/PD-L1 and CTLA-4 pathways may have additive or synergistic activity because the mechanisms of action of CTLA-4 and PD-1/PD-L1 are non-redundant. Drugs that block the PD-L1/PD-1 pathway act in the tumour microenvironment and prevent inhibition of T-cell function, whereas drugs that block the CTLA-4 pathway act in the lymphoid compartment to expand the number and repertoire of tumour-reactive T cells (26). Thus, combined blockade of both pathways targets both compartments.

The current durvalumab and tremelimumab IBSs provide a complete summary of the available non-clinical and clinical information including pharmacodynamics, pharmacokinetics, safety and efficacy.

1.5.1 COMBINATION OF PD-1/PD-L1 AND CTLA-4 INHIBITORS IN RCC

The first results from the phase III CheckMate 214 (NCT02231749) study of nivolumab plus ipilimumab versus sunitinib for treatment-naïve advanced RCC patients were presented at ESMO 2017 (Late Breaking Abstract 5) (27). With a median follow-up of 25.2 months, positive results were observed for all three co-primary outcome measures in patients with intermediate- and poor-risk disease classified according to the International Metastatic RCC Database Consortium (IMDC) model. The confirmed overall response rate (ORR) was 42% (95% CI 37-47) for ipilimumab plus nivolumab compared with 27% for sunitinib (95% CI 22-31), p<0.001. Median PFS was 11.5 months for the combination treatment group compared to 8.4 months for the sunitinib control group (HR 0.82; 99.1% CI 0.64-1.05, p=0.0331). Median OS was not reached for the ipilimumab and nivolumab combination (95% CI 28.2 – Not reached) and was 26.0 months (22.1 – Not Reached) in the control group [HR 0.63 (99.8% CI 0.44-0.89), p=0.0003]. The safety profile of the combination was manageable and consistent with previous studies.
1.5.2 COMBINATION OF PD-1/PD-L1 AND CTLA-4 INHIBITORS IN CANCERS OTHER THAN RCC

In the Checkmate 067 trial (NCT01844505) of previously untreated patients with metastatic melanoma, nivolumab alone or combined with ipilimumab resulted in significantly longer PFS than ipilimumab alone (28). The median PFS was 11.5 months (95% CI, 8.9–16.7) with nivolumab plus ipilimumab, as compared with 2.9 months (95% CI, 2.8–3.4) with ipilimumab (HR for death or disease progression, 0.42; 99.5% CI, 0.31–0.57; P<0.001), and 6.9 months (95% CI, 4.3–9.5) with nivolumab (HR for the comparison with ipilimumab, 0.57; 99.5% CI, 0.43–0.76; P<0.001). In patients with tumours positive for the PD-1 ligand (PD-L1), the median PFS was 14.0 months in the nivolumab plus ipilimumab group and in the nivolumab group, but in patients with PD-L1–negative tumours, PFS was longer with the combination therapy than with nivolumab alone (11.2 months [95% CI, 8.0 to not reached] vs 5.3 months [95% CI, 2.8–7.1]) (28). In June 2016, the National Institute for Health and Care Excellence (NICE) approved the combination of nivolumab and ipilimumab for use within the National Health Service (NHS) for patients with metastatic melanoma.

In an updated analysis of Checkmate 067, median OS had not been reached in the nivolumab plus ipilimumab group (95% CI 38.2 – NR) and was 37.6 months (95% CI 29.1 – NR) in the nivolumab group, and 19.9 months (95% CI 16.9 – 24.6) in the ipilimumab group. The HR for death with nivolumab plus ipilimumab versus ipilimumab was 0.55 (95% CI, 0.45 – 0.69, p<0.001) and with nivolumab versus ipilimumab was 0.65 (95% CI, 0.53 – 0.80, p<0.001). Treatment-related AEs of grade 3 or 4 occurred in 21% of the patients in the nivolumab group, 59% of those in the nivolumab-plus-ipilimumab group, and 28% of those in the ipilimumab group (29).

1.6 RATIONALE FOR RAMPART

Given the immunogenic nature of RCC and since agents of this class have shown activity in patients with advanced RCC and other tumour types, the RAMPART Trial Development Group believe it is timely to investigate the activity of durvalumab monotherapy and the combination of durvalumab and tremelimumab in the adjuvant RCC setting.

1.7 DURVALUMAB AND TREMELIMUMAB COMBINATION THERAPY DOSE RATIONALE

The dose of the anti-CTLA-4 agent, both as a single agent and in combination with PD-1 (PD-L1) agents, appears to be the main driver of toxicity; less toxicity is observed as the dose of the CTLA-4 agent is reduced. The dose of ipilimumab given for adjuvant melanoma is 10mg/kg, the dose with or without nivolumab in metastatic melanoma is 3mg/kg, and the dose with nivolumab in Checkmate 214 (NCT02231749) in advanced RCC is 1mg/kg.

The optimal number of cycles of combination therapy is unknown, although 4 cycles of combination therapy have been used in most trials to date. There is no strong scientific rationale for this duration being optimal. Data from previous melanoma trials suggest that activity still exists when fewer cycles are given (<4). Fewer cycles would reduce toxicity and improve tolerability, which is clearly important in the adjuvant setting. Therefore, in RAMPART, the combination arm (arm C) will consist of 2 cycles of the combination followed by single-agent durvalumab for the remainder of the year. This decision is based on the goal of selecting an optimal combination dose of durvalumab and tremelimumab that will yield sustained target suppression (sPD-L1), demonstrate promising efficacy, and have an acceptable safety profile in the adjuvant setting.
1.8 RATIONALE FOR FIXED DOSING

A population PK model was developed for durvalumab using monotherapy data from a Phase I study (study 1108; N=292; doses= 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumours). Population PK analysis indicated only minor impact of body weight (WT) on the PK of durvalumab (coefficient of ≤0.5). The impact of body WT-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40 to 120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-subject variability with fixed dosing regimen.

Similarly, a population PK model was developed for tremelimumab using data from Phase 1 through Phase 3 (N=654; doses= 0.01 to 15 mg/kg Q4W or Q90D; metastatic melanoma) (30). Population PK model indicated minor impact of body WT on PK of tremelimumab (coefficient of ≤0.5). The WT-based (1 mg/kg Q4W) and fixed dosing (75 mg/kg Q4W; based on median body WT of ~75 kg) regimens were compared using predicted PK concentrations (5th, median and 95th percentiles) using population PK model in a simulated population of 1000 patients with body weight distribution of 40 to 120 kg. Similar to durvalumab, simulations indicated that both body WT-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less between-subject variability with fixed dosing regimen.

Similar findings have been reported by others (31-34). Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (32). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-subject variability in PK and pharmacodynamics parameters (33).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar PK exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) and a fixed dose of 75 mg Q4W tremelimumab (equivalent to 1mg/kg Q4W) will be used in RAMPART.

1.9 IDENTIFIED AND POTENTIAL RISKS

Monoclonal antibodies directed against immune checkpoint proteins, such as PD-L1, PD-1 or CTLA-4, aim to boost endogenous immune responses directed against tumour cells. However, by stimulating the immune system, there is the potential for adverse effects on other tissues.

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. Potential risks are events with a potential inflammatory mechanism, which may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine replacement therapy. These risks include gastrointestinal AEs such as colitis and diarrhoea, pneumonitis, nephritis and acute renal failure; hepatic AEs such as hepatitis and liver enzyme elevations and dermatitis; and endocrinopathies such as hypo- and hyperthyroidism, hypophysitis, and adrenal insufficiency.
1.9.1 Durvalumab

Identified risks with durvalumab are diarrhoea, increases in transaminases, pneumonitis, and colitis. Potential risks include endocrinopathies (hypo and hyperthyroidism, hypophysitis, and adrenal insufficiency), hepatitis and hepatotoxicity, neurotoxicities, nephritis, pancreatitis, dermatitis, infusion-related reactions, anaphylaxis, hypersensitivity or allergic reactions, myocarditis and immune complex disease.

In monotherapy clinical studies, the AEs (all grades) reported very commonly (≥10% of patients) are fatigue, nausea, decreased appetite, dyspnoea, cough, constipation, diarrhoea, vomiting, back pain, pyrexia, abdominal pain, anaemia, arthralgia, peripheral oedema, headache, rash, and pruritus. Approximately 10% of patients experienced an AE that resulted in permanent discontinuation of durvalumab, and approximately 3.5% of patients experienced an SAE that was considered to be related to durvalumab by the study investigator.

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity. Toxicity Management Guidelines for durvalumab monotherapy are provided in Appendix B.

A detailed summary of durvalumab monotherapy AE data can be found in the current version of the durvalumab IB.

1.9.2 Durvalumab + Tremelimumab

The safety of durvalumab + tremelimumab combination therapy is being evaluated in numerous ongoing studies, and has shown a manageable safety and tolerability profile to date.

The potential risks with the combination of durvalumab + tremelimumab are similar to those for durvalumab and tremelimumab monotherapies. Emerging data from combinations of other agents in the same class indicate an increased frequency and/or severity of some potential immune-mediated toxicities.

In durvalumab + tremelimumab combination studies, the AEs (all grades) reported very commonly (≥10% of patients) are diarrhoea, fatigue, nausea, dyspnoea, pruritus, rash, increased amylase, decreased appetite, pyrexia, increased alanine aminotransferase (ALT), cough, colitis, and increased lipase.

Toxicity Management Guidelines for durvalumab + tremelimumab are provided in Appendix B. A detailed summary of durvalumab + tremelimumab combination AE data can be found in the current version of the durvalumab IB.

1.10 RAMPART Trial Design

RAMPART is a phase III multi-arm multi-stage randomised controlled platform trial, initiated with three arms.

1.10.1 Patient Population

At the start of recruitment, patients with Leibovich scores 3 to 11 will be eligible for randomisation. We will monitor accrual and stop recruitment of intermediate-risk patients (Leibovich scores 3-5) after 3 years or when intermediate-risk patients contribute 25% of the total accrual target, whichever is earlier. Intermediate-risk patients are still at a substantial risk of relapse (about 30%),
although relapses tend to be later; with a risk that high, these patients and their clinicians are anxious to understand if there is an adjuvant therapy relevant to them. By including the intermediate-risk patients during the early years of the trial, there will be enough of this group of patients, followed for long enough, that they will contribute events to the disease-free survival (DFS) analysis. Recruitment of patients with Leibovich scores 6 to 11 will continue until the accrual target is reached.

1.10.2 INTERVENTION

Patients will be randomised between the control arm and one of two research arms. Patients in the control arm (arm A) will not receive any adjuvant treatment but otherwise will be actively monitored according to the same schedule as patients randomised to the research arms. The research arms are (arm B) single-agent durvalumab, given as a flat 1500mg dose Q4W for 1 year, and (arm C) a combination of durvalumab for one year and tremelimumab on day 1 of the first two cycles of durvalumab treatment.

1.10.3 CHOICE OF CONTROL ARM

The current global standard-of-care after nephrectomy for localised RCC (i.e., the RAMPART population) remains active monitoring (i.e., observation by clinical and radiological means). The agents to be tested in this trial are administered via IV infusions. To minimise the burden to both patients and healthcare systems, an active monitoring control is proposed; consequently, treatment allocation will not be blinded.

An additional rationale for this approach is that DFS (starting from no evidence of disease) is inherently less subject to clinician bias than Progression Free Survival (PFS) (which is dependent on measurement of growth in lesions already present). The median time to a DFS event in the placebo arm of the ASSURE trial, which included a similar population of patients expected to accrue in RAMPART, was 6 years (4). Events will, therefore, typically accrue in the years after patients have completed their RAMPART protocol treatment. However, RAMPART employs a more frequent computed tomography (CT) scanning schedule in the first 2 years after randomisation than what has been used in the most recent adjuvant trials in this setting (e.g., SORCE or ASSURE); this approach will minimise any detection bias in relation to treatment assignment throughout the treatment period and after a year. Electronic copies of patients’ imaging scans will be collected and stored in a secure central repository to enable independent outcome review, blinded to treatment assignment, should the need arise. OS is, of course, not a subjective outcome measure. In the UK, OS dates can be cross-checked against national mortality registers.

Previous trials in the adjuvant RCC setting have tended to use placebo controls and blinding when the agents were administered in an oral formulation. In trials of agents administered by IV infusion, the choice of control arm has been mixed, either observation or placebo, usually observation when more than 1 agent was administered per research arm. The ongoing BR31 trial in adjuvant lung cancer is using a placebo control; however, it contains only 2 arms and the research arm includes just 1 agent (durvalumab) administered by IV infusion. In RAMPART, certain toxicities for both of the agents are expected, which will likely be more obvious in the combination arm. Patients and their doctors may, therefore, be able to distinguish between treatments even if placebo IV infusions (with their associated substantial inconvenience to patients and burden on healthcare resources) were included.

There is a concern that patients may be more likely to drop out of protocol follow-up if they know that they are not receiving active treatment. Since there are no alternative treatments known to be active in the adjuvant setting, nor a known rationale for delayed or late treatment after potentially curative surgery, we expect little dropout but will emphasise to all patients the importance of
compliance with follow-up schedules, both from the perspective of optimising their future care, as well as to maximise the integrity of the trial.

1.10.4 OUTCOME MEASURES
There are two co-primary outcome measures in RAMPART: DFS and OS. DFS is the standard primary outcome in adjuvant RCC trials and for many adjuvant trials in a range of cancers. It is the primary outcome on which AstraZeneca will seek regulatory approval of durvalumab monotherapy and/or the combination of durvalumab and tremelimumab. OS is also a key outcome measure, particularly for patients and healthcare providers. However, in the setting of renal cancer, an adjuvant trial focussing only on OS would take up to 15 to 20 years to report its results, potentially denying many thousands of patients the opportunity to benefit from what appear to be promising new treatments. For this reason, we have co-primary outcomes of DFS and OS.

1.10.5 LEIBOVICH RISK SCORE
Many factors relating to clinical, anatomical, pathological and molecular aspects of patients with renal cell carcinoma (RCC) have been proposed as prognostic factors. Experience has shown that disease stage has provided the most valuable information but that prognostic accuracy can be improved using scoring systems which include tumour grade, performance status, histological evidence of tumour necrosis and symptomatic status (35-38). Frank et al devised an outcome prediction model – the SSIGN score to predict OS (39). This model was modified and extended by Leibovich et al focussing on metastases-free survival (40). This algorithm has become known as the Leibovich or Mayo score and is now routinely used for stratification of follow-up of patients with clear cell RCC (ccRCC) following nephrectomy for localised disease as well as for selection of patients for trials of adjuvant therapy. The Leibovich score has subsequently been externally validated (41). Clinico-pathological scoring systems such as these are thought to have plateaued and further advances are likely to incorporate molecular characteristics such as have been described recently (42, 43).

Leibovich and colleagues analysed clinico-pathological details of 1671 ccRCC patients who underwent radical nephrectomy for clinically localised RCC between 1970 and 2000, demonstrated that by using a simple scoring system, involving TNM staging, nuclear grade and presence of necrosis, it was possible to identify a high-risk cohort (374 patients or 22% of the sample) who had a 3-year metastasis-free survival (MFS) of only 37%, and an intermediate risk cohort (608 patients or 36% of the sample) with a 3-year metastasis-free survival of 80%(40). One important benefit of this scoring system is that it represents very little extra work for the reporting pathologist, as all required elements are part of the standard pathological reporting system. The Leibovich score was used to guide trial entry in the MRC SORCE study and will be used in RAMPART.

1.10.6 PD-L1 EXPRESSION
The role of PD-L1 expression in predicting response to immune checkpoint inhibitors in renal cancer is unclear (44-46). For this reason all patients, irrespective of PD-L1 status will be enrolled onto RAMPART. This will allow for a robust biomarker component of the study which will utilise renal cancer tissue, germ-line material, circulating biomarkers and metagenome (from urine and blood). If data on the role of PD-L1 expression (or any other translational aspect) change during the course of RAMPART, the trial could be adapted to include treatment within a biomarker defined population.

1.10.7 THE NEED FOR AN ADAPTIVE MAMS PLATFORM TRIAL DESIGN
Clinical trials of adjuvant therapies are necessarily long-term and challenging and require a large network of international collaborating groups and investigators. Having gathered all the resources and funding to launch such trials and then pinning hopes on a single research question to the
exclusion of all others is not an ideal strategy. Building a clinical trial platform upon which evolving and new research questions may be addressed over the coming years is an efficient trial design in terms of both time and cost – saving tens of years and many millions of pounds – and gives us the greatest opportunity to fulfil that great unmet need of improving outcomes for patients with RCC as rapidly as possible. This is, of course, only appropriate when there are a reasonable number of new potential approaches to adjuvant treatment currently (or soon) available. This is the situation in renal cancer.

With the platform MAMS trial design, once effective agents or combinations have been identified (and assuming that our large international network of committed sites is recruiting well), we can make progress within the framework of one trial rather than starting a competing trial or waiting a number of years, often between 5 and 10, until the first trial reports. This is particularly important in the adjuvant RCC setting where it takes international collaboration and many years (more than 10 years) to develop, launch, and deliver a trial.

1.11 ANCILLARY STUDIES

1.11.1 TransRAMPART
The provision of at least one archival FFPE tumour sample and a baseline EDTA blood sample for future translational research is a prerequisite for randomisation into RAMPART. It is expected that the collection of further biological samples at baseline and follow-up visits will be introduced to the trial at a later date, pending a successful funding application. This sub-study is an important part of RAMPART and is called TransRAMPART (currently under development). Patients may be enrolled into TransRAMPART at the same time as they are randomised into RAMPART. Further information on TransRAMPART can be found in the TransRAMPART Sample Collection Manual.

1.11.2 Patient Reported Outcomes (PRO)
Preferences for Adjuvant Immunotherapy in RAMPART (PAIR) is an optional sub-study conducted in selected countries to determine the survival benefits trial participants judge necessary to make adjuvant immunotherapy worthwhile, and the factors influencing their preferences. The underlying goal of this sub-study is to improve multi-disciplinary communication, decision-making and care for future patients considering immunotherapy by revealing the judgments and attitudes of those who have been through this experience. PAIR questionnaires will be completed at baseline, week 16, and either at month 15, or approximately 3 months after the last dose for patients stopping treatment early. Further information on PAIR can be found in Appendix E– Preferences for adjuvant immunotherapy in RAMPART (PAIR).

Patient’s quality of life will be assessed through another optional sub-study using the QLQ-C30 and EQ-5D questionnaires. Questionnaires will be completed by patients at baseline, at week 16, month 15, month 36 and at progression (if progression occurs before month 36).

1.11.3 Pharmacokinetic (PK) and Anti-Drug Antibody (ADA) Testing
In the region of 5-7 UK sites will take part in a separate small PK and ADA testing study. Patients who have been randomised to arm B and C will be asked to provide additional consent for this sub-study; 100 patients are required in total, 50 from each arm. Details of the sampling schedule, sample collection and processing are under development and will be detailed in the RAMPART Site Manual.
2 SELECTION OF SITES AND INVESTIGATORS

2.1 SITE AND INVESTIGATOR INCLUSION CRITERIA

To participate in the RAMPART trial, investigators and clinical trial sites must fulfil a set of basic criteria that have been agreed by the Trial Management Group (TMG) and are defined below.

2.1.1 Principal Investigator’s (PI’s) Qualifications & Agreements

- The investigator should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial at their site and should provide evidence of such qualifications through an up-to-date curriculum vitae and/or other relevant documentation requested by the Sponsor, the REC, the IRB, and/or the regulatory authorities.

- The investigator should be thoroughly familiar with the appropriate use of the investigational products as described in this protocol and current IBs.

- The investigator should be aware of, and should comply with, the principles of GCP and the applicable regulatory requirements. RAMPART is an investigator-initiated academic platform trial. The trial will be initiated and conducted in compliance with the principles of GCP. However, sufficient elements will be put in place from the outset of the trial 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. A record of GCP training should be accessible for all investigators.

- The investigator and site should permit monitoring and auditing by the Sponsor, auditing by AstraZeneca, and inspection by the appropriate regulatory authorities.

- The investigator should maintain a delegation log of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

- The investigator should sign an Investigator Statement, which verifies that the site is willing and able to comply with the requirements of the trial. The investigator should also sign a Clinical Trial Agreement with the Sponsor.

2.1.2 Adequate Resources

- The investigator should be able to demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period (that is, the investigator regularly treats the target population).

- The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

- The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

- The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational products, and their trial-related duties and functions.
- The site should have sufficient data management resources to allow prompt data return to the MRC CTU at UCL. Sites that have previously participated in MRC CTU at UCL-coordinated trials should have a proven track record of good quality and timely data return.

2.1.3 SITE ASSESSMENT

Sites which meet the selection criteria must complete a Site Accreditation Form, which includes the Investigator Statement, Clinical Trial Agreement, Signature and Delegation of Responsibilities Log, Training Log, and staff contact details. Details on site activation and implementation of substantial amendments will be provided to sites by the RAMPART TMT.

The Investigator Statement and Clinical Trials Agreement verify that the site is willing and able to comply with the requirements of the trial. Each one is signed by the Principal Investigator at the site. In addition and in compliance with the principles of GCP, all site staff participating in the trial must complete the Signature and Delegation of Responsibilities Log and forward this to the MRC CTU at UCL. The MRC CTU at UCL must be notified of any changes to trial personnel and/or their responsibilities. An up-to-date copy of this log must be stored in the Investigator Site File (ISF) at the site and also at the Trial Master File (TMF) at the MRC CTU at UCL.

2.2 APPROVAL AND ACTIVATION (UK)

On receipt of the completed site accreditation documents at the MRC CTU at UCL, written confirmation will be sent to the PI. A Randomisation Pack will be provided to the site.

Each site’s pharmacist will also be informed of the site’s activation and an initial drug order will be dispatched to the named pharmacist in the site accreditation documents.

The site should conduct the trial in compliance with the protocol as agreed by the Sponsor, by the regulatory authorities, and which was given favourable opinion by the REC and/or IRB.

A list of activated sites will be available on the RAMPART website. Potential participants should only be approached when all approvals are in place and the site has been activated by the RAMPART TMT.

2.3 APPROVAL AND ACTIVATION (NON-UK)

Information regarding site approval and activation for non-UK sites is provided in a separate group-specific appendix for each country.
3 SELECTION OF PATIENTS

3.1 SURGERY GUIDELINES

All patients to be considered for entry into the study must undergo a full or partial nephrectomy (as per national guidelines) in order to remove the primary renal tumour(s). Open and laparoscopic excisional techniques are permissible.

Notes from the surgery should be used to complete Surgery CRF once a patient has been randomised.

3.2 POST-SURGERY PROCEDURES – CALCULATION OF LEIBOVICH SCORE

Once surgery has been performed a sample of the removed tumour is inspected by a pathologist who will calculate the patient’s Leibovich score. Further information on the Leibovich score and how to calculate it is given in Appendix C – The Leibovich Risk Model for Prediction of Progression after radical nephrectomy for clear cell renal cell carcinoma.

3.3 RAMPART ELIGIBILITY CRITERIA

There will be no exceptions to eligibility requirements at the time of randomisation. Questions about eligibility criteria should be addressed prior to attempting to randomise the participant.

The eligibility criteria are the standards used to ensure that only medically appropriate patients are considered for this trial. Patients not meeting the criteria should not join the study. For the safety of the patients, as well as to ensure that the results of this trial can be useful for making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the trial.

Participants will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

3.3.1 RAMPART INCLUSION CRITERIA

1. Histologically proven RCC (all cell types of RCC are eligible, except for pure oncocytoma, collecting duct, medullary and transitional cell cancer [TCC]); no evidence of residual macroscopic disease on post-operative CT scan after resection of RCC. Patients with treated bilateral synchronous RCCs are eligible.
2. At the start of recruitment patients with Leibovich score 3-11 will be eligible for randomisation. MRC CTU at UCL will monitor accrual and stop recruiting intermediate risk patients (Leibovich Score 3-5) after three years or when intermediate risk patients contribute 25% of the total accrual target, whichever is earlier. Recruitment of patients with Leibovich Score 6-11 will continue until the accrual target is reached.
3. Patients should have had surgery at least 28 days but no more than 91 days prior to their randomisation date.
4. Post-operative scans should be performed within 28 days prior to randomisation.
5. WHO Performance Status 0 or 1.
6. Patient has archival FFPE pathology tissue available, and agrees to provide at least one sample (FFPE tumour block from nephrectomy, or a minimum of 10 unstained slides), as well
as a baseline EDTA blood sample for future translational research (this is separate to providing consent for TransRAMPART; see Section 4.2.1).

7. Adequate normal organ and marrow function
   a. Haemoglobin ≥9.0g/dL (transfusions will be allowed within 2 weeks prior to randomisation in order to achieve the entry criteria).
   b. Absolute neutrophil count (ANC) ≥1.5 x 10^9/L (≥1500 per mm³).
   c. Platelet count ≥100 x 10^9 (≥100,000 per mm³).
   d. Bilirubin ≤1.5 x ULN (This will not apply to subjects with confirmed Gilbert’s syndrome (i.e., persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of haemolysis or hepatic pathology), who will be allowed only in consultation with their physician).
   e. AST/ALT ≤2.5 x ULN.
   f. Calculated Creatinine Clearance level >40mL/min by Cockcroft Gault formula (using actual body weight):
      \[ \text{Males:} \quad \text{Creatinine CL (mL/min)} = 1.23 \times \frac{\text{Weight (kg)} \times (140 - \text{Age})}{\text{serum creatinine (μmol/L)}} \]
      \[ \text{Females:} \quad \text{Creatinine CL (mL/min)} = 1.04 \times \frac{\text{Weight (kg)} \times (140 - \text{Age}) \times 0.85}{\text{serum creatinine (μmol/L)}} \]

8. 12-lead ECG on which QTcF must be <450 ms. In case of clinically significant ECG abnormalities, including a QTcF value ≥450 ms, two additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding. Patients are only eligible if a QTcF of <450ms is confirmed

9. Subjects must be ≥18 years of age.

10. Written informed consent obtained from the patient.

11. Both men and women enrolled in this trial must be in agreement with trial policy on contraception (Section 5.8.4) during the treatment phase of the study and 6 months afterwards. Egg donation, sperm donation and breastfeeding must be avoided.

12. Evidence of post-menopausal status or negative serum HCG pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrhoeic for 12 months without an alternative medical cause. The following age-specific requirements apply:
   a. Women <50 years of age will be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinising hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilisation (bilateral oophorectomy or hysterectomy).
   b. Women ≥50 years of age will be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilisation (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

### 3.3.2 RAMPART EXCLUSION CRITERIA

1. Previous diagnosis of RCC.
2. Metastatic or macroscopic residual disease.
3. Patients with a single pulmonary nodule ≥5mm diameter are not eligible unless the nodule has had a definite benign diagnosis. Patients with multiple small, less than 5 mm nodules may be eligible if nodules have been shown to be radiologically stable for at least 8 weeks.
4. Prior anticancer treatment (other than nephrectomy) for RCC.
5. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria
   a. Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
   b. Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or tremelimumab may be included only after consultation with the Study Physician.
6. History of another primary malignancy except for:
   a) Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence.
   b) Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
   c) Adequately treated carcinoma in situ without evidence of disease.
8. Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study.
9. Major surgical procedure (as defined by the Investigator) within 28 days prior to the start of treatment. Local surgery of isolated lesions for palliative intent is acceptable.
10. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.
11. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:
   a. Patients with vitiligo or alopecia
   b. Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
   c. Any chronic skin condition that does not require systemic therapy
   d. Patients without active disease in the last 5 years may be included but only after consultation with the RAMPART Trial Management Team
   e. Patients with coeliac disease controlled by diet alone
12. A history of immunodeficiency syndrome. Please consult the MRC CTU at UCL on an individual basis if there is any uncertainty.
14. Uncontrolled intercurrent illness including, but not limited to:
   a. Ongoing or active infection
   b. Symptomatic congestive heart failure
   c. Uncontrolled hypertension
   d. Unstable angina pectoris
   e. Uncontrolled cardiac arrhythmia
   f. Active peptic ulcer disease or gastritis
   g. Active bleeding diatheses
   h. Psychiatric illness or social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent.
15. Active infection including
   a. Tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice)
b. Hepatitis B (known positive HBV surface antigen (HBsAg) result)
c. Hepatitis C
d. Human immunodeficiency virus (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible.

*Note:* Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

16. Receipt of live attenuated vaccine within 30 days prior to the start of treatment.

*Note:* Patients, if enrolled, should not receive live vaccine while receiving investigational medicinal product and up to 30 days after the last dose of investigational medicinal product.

17. Pregnant or breastfeeding patients.

18. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.

19. Known allergy or hypersensitivity to durvalumab or tremelimumab, or any of their excipients.

20. Previous investigational medicinal product assignment in the present study.

### 3.4 NUMBER OF PATIENTS

Approximately 1,750 patients will be recruited to the initial three research arms of the trial (see Section 9 for details of sample size calculations).

Recruitment across the study arms will be as follows:
- Arm A - 750 patients
- Arm B - 500 patients
- Arm C - 500 patients

### 3.5 PRE-RANDOMISATION SCREENING PROCEDURES & INVESTIGATIONS

#### 3.5.1 INFORMED CONSENT

Written informed consent to enter into the trial and be randomised must be granted by participants after explanation of the aims, methods, benefits and potential hazards of the trial and before any trial-specific screening procedures are performed.

The trial should be introduced by the clinician responsible for the patient; however the informed consent process may then be completed by qualified, experienced nurses according to local practice. Any delegation of responsibilities should be clearly documented on the trial Delegation Log. Evidence of relevant training should be available in the local site file.

It must be made completely and unambiguously clear that the participant is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their treatment.

Signed consent forms must be kept by the investigator and a copy given to the participant or family. With consent, the GP Letter should be sent to the patient’s general practitioner informing them of the trial and the patient's involvement in it.
3.5.2 **SCREENING PROCEDURES**

Screening procedures will be performed up to 28 days before randomisation, unless otherwise specified. All patients must first read, understand, and sign and date the RAMPART Consent Form before any study-specific screening procedures are performed.

Procedures that are performed prior to the signing of the Consent Form and are considered standard-of-care may be used as screening assessments if they fall within the 28-day screening window.

The procedures that must be performed prior to randomisation are described in Table 2.

**Table 2  Screening Procedures**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>To be completed prior to randomisation within</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>28 days</td>
</tr>
<tr>
<td>Review of eligibility criteria</td>
<td>X</td>
</tr>
<tr>
<td>Medical history</td>
<td>X</td>
</tr>
<tr>
<td>Complete physical exam (Section 6.3.1)</td>
<td>X</td>
</tr>
<tr>
<td>Assess baseline symptoms</td>
<td>X</td>
</tr>
<tr>
<td>WHO Performance Status</td>
<td>X</td>
</tr>
<tr>
<td>Vitals signs (Section 6.3.3)</td>
<td>X</td>
</tr>
<tr>
<td>Weight and height</td>
<td>X</td>
</tr>
<tr>
<td>Review of prior and concomitant medications</td>
<td>X</td>
</tr>
<tr>
<td>12-lead ECG on which QTcF must be &lt;450 ms. In case of clinically significant ECG abnormalities, including a QTcF value ≥450 ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding. Patients are only eligible if a QTcF of &lt;450ms is confirmed</td>
<td>X</td>
</tr>
<tr>
<td>Post-operative imaging of disease by CT with contrast of chest, abdomen and pelvis</td>
<td>X</td>
</tr>
<tr>
<td>Haematology (see Table 3)</td>
<td></td>
</tr>
<tr>
<td>Clinical chemistry (see Table 4)</td>
<td></td>
</tr>
<tr>
<td>Coagulation parameters (PT, PTT, International Normalised Ratio [INR])</td>
<td></td>
</tr>
<tr>
<td>Hepatitis serologies (Hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody)</td>
<td></td>
</tr>
<tr>
<td>Serum HCG pregnancy test (women of childbearing potential only)</td>
<td></td>
</tr>
</tbody>
</table>
### Table 3  Haematology Assessments (Screening)

<table>
<thead>
<tr>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basophils</td>
</tr>
<tr>
<td>Eosinophils</td>
</tr>
<tr>
<td>Haematocrit</td>
</tr>
<tr>
<td>Haemoglobin</td>
</tr>
<tr>
<td>Lymphocytes</td>
</tr>
<tr>
<td>Mean corpuscular haemoglobin (MCH)</td>
</tr>
<tr>
<td>Mean corpuscular haemoglobin concentration (MCHC)</td>
</tr>
<tr>
<td>Mean corpuscular volume (MCV)</td>
</tr>
<tr>
<td>Monocytes</td>
</tr>
<tr>
<td>Neutrophils</td>
</tr>
<tr>
<td>Platelet count</td>
</tr>
<tr>
<td>Red blood cell count (RBC)</td>
</tr>
<tr>
<td>Total white cell count (WBC)</td>
</tr>
</tbody>
</table>

### Table 4  Clinical Chemistry Assessments (Screening)

<table>
<thead>
<tr>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
</tr>
<tr>
<td>Alkaline phosphatase (ALP)</td>
</tr>
<tr>
<td>Alanine aminotransferase (ALT) A</td>
</tr>
<tr>
<td>Amylase B</td>
</tr>
<tr>
<td>Aspartate aminotransferase (AST) A</td>
</tr>
<tr>
<td>Bicarbonate C</td>
</tr>
<tr>
<td>Calcium C</td>
</tr>
<tr>
<td>Chloride C</td>
</tr>
<tr>
<td>Creatinine</td>
</tr>
<tr>
<td>Creatinine clearance C</td>
</tr>
<tr>
<td>Gamma glutamyltransferase (GGT) C</td>
</tr>
<tr>
<td>Glucose</td>
</tr>
<tr>
<td>Hepatitis serologies (hep A antibody, hep B surface antigen, hep C antibody)</td>
</tr>
<tr>
<td>Lactate dehydrogenase (LDH)</td>
</tr>
<tr>
<td>Lipase B</td>
</tr>
<tr>
<td>Magnesium C</td>
</tr>
<tr>
<td>Potassium</td>
</tr>
<tr>
<td>Random cortisol</td>
</tr>
<tr>
<td>Sodium</td>
</tr>
<tr>
<td>Thyroid stimulating hormone (TSH) – if abnormal check free T3 and T4 D</td>
</tr>
</tbody>
</table>
A. Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥2 × upper limit of normal (and no evidence of Gilbert’s syndrome) then fractionate into direct and indirect bilirubin.

B. It is preferable that both amylase and lipase parameters are assessed. For sites where only 1 of these parameters is routinely measured then either lipase or amylase is acceptable.

C. Bicarbonate (where available), calcium, chloride, creatinine clearance, gamma glutamyltransferase, magnesium, testing are to be performed at screening, on Day 1 (unless screening laboratory assessments are performed within 3 days prior to Day 1), and if clinically indicated. Tests will need to be repeated on Day 1 if done more than 3 days prior.

D. Free T3 or free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system.
4 RANDOMISATION

4.1 RANDOMISATION PRACTICALITIES

Further details on the randomisation method can be found in Section 9.1.

Patients will be randomised centrally using a computerised algorithm developed and maintained by the MRC CTU at UCL. Patients are eligible for randomisation when their eligibility has been confirmed by the consultant responsible for their care and when their written informed consent has been obtained.

<table>
<thead>
<tr>
<th>RANDOMISATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>To randomise, call MRC CTU at UCL, Monday to Friday (between 9am and 5pm GMT/BST) Tel: +44 (0) 20 7670 4777</td>
</tr>
<tr>
<td>National Coordinating Centres will randomise patients on behalf of international centres and in line with country-specific Group Specific Appendix (GSA)</td>
</tr>
</tbody>
</table>

4.2 CO-ENROLMENT GUIDELINES

Only patients who have experienced disease progression may join a new randomised controlled trial. Follow-up within RAMPART for the co-primary outcome measure of OS will still be required. Participants may join observational studies at any point during their participation to RAMPART but follow-up data must continue to be provided to the RAMPART TMT.

Questions regarding co-enrolment should be directed to a member of the RAMPART TMT.

4.2.1 BIOLOGICAL SAMPLES

Provision of at least one archival FFPE tumour sample and one EDTA blood sample is mandatory for all patients to allow for future translational research.

Patients should also be asked to consent to participate in TransRAMPART. A schedule of the additional samples to be collected in the TransRAMPART study can be found in the TransRAMPART Sample Collection Manual.

Details on collection, storage, and transportation of all samples collected as part of RAMPART or TransRAMPART can also be found in the TransRAMPART Sample Collection Manual.

In 5-7 UK sites, blood samples will be collected in both experimental arms (50 Arm B and 50 Arm C patients) for the purpose of PK and ADA analysis. Details on the sampling schedule, sample collection and processing can be found in the RAMPART Site Manual.

4.2.2 PATIENT REPORTED OUTCOMES (PRO)

Patients who have consented to participate in the PRO sub-studies should complete a baseline EQ-5D, QLQ-C30 and Preferences for Adjuvant Immunotherapy in RAMPART (PAIR) questionnaire prior to randomisation. All baseline questionnaires for the PRO sub studies will need to be completed before the patient has their first infusion. Please refer to Section 1.11.2 for more information on ancillary studies on PRO.
5 TREATMENT OF PATIENTS

5.1 INTRODUCTION

Patients will initially be randomly assigned in the ratio 3:2:2 to one of the following research arms:
- **Arm A** – active monitoring
- **Arm B** – single agent durvalumab
- **Arm C** – combination durvalumab and tremelimumab

Patients on Arm B and C must start treatment within 14 days of randomisation.

5.2 ARM A – ACTIVE MONITORING

Patients in the active monitoring arm will receive no IMP; however they will be followed-up radiologically in the same manner as patients on the active treatment arms. Please refer to Section 6.1 for details of the follow-up schedule.

5.3 ARM B – SINGLE AGENT DURVALUMAB

5.3.1 PRODUCTS

Durvalumab will be supplied by AstraZeneca as a 500 mg vial solution for infusion. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10mL. IMP vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. The vials should be protected from light by storing in an opaque container. Durvalumab must be used within the individually assigned expiry date on the label.

5.3.2 TREATMENT SCHEDULE

Patients in the durvalumab monotherapy group will receive a fixed dose of 1500 mg durvalumab via IV infusion Q4W for up to 13 cycles with the last administration on week 48. A cycle is defined as 28 days. Treatment delays beyond the 28 day cycle (beyond administrative delays for up to three days either side of the expected infusion date) should be discussed with the TMT.

If time between infusions exceeds 8 weeks then the treatment must be permanently discontinued; regardless any administration delays, the maximum duration of treatment must not exceed 1 year. In practice this means a patient may miss a single infusion before having to resume treatment at their next scheduled visit.

Pre-menopausal patients are required to have a negative urine HCG pregnancy test prior to the administration of the trial treatment. A serum HCG pregnancy test should be performed if there is any doubt over the results of the urine test.

Table 5  Arm B Dosing Schedule
5.3.3 **Durvalumab IV Preparation**

The dose of durvalumab for administration must be prepared using an aseptic technique.

Total time from needle puncture of the durvalumab vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

If in-use preparation and/or storage time exceeds these limits, a new dose must be prepared from new vials. Infusion solutions must be allowed to equilibrate to room temperature as per local guidance prior to commencement of administration.

No incompatibilities between durvalumab and polyvinylchloride (PVC) or polyolefin IV bags have been observed. A fixed dose of 1500mg durvalumab will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2 or 0.22 μm in-line filter.

Procedure: Remove 30.0 mL of IV solution from the IV bag prior to addition of durvalumab. Next, 30.0 mL of durvalumab (i.e., 1500 mg of durvalumab) is added to the IV bag such that final concentration is within 1 to 20 mg/mL (IV bag volumes 100 to 1000 mL). Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

5.3.4 **Durvalumab IV Administration**

Durvalumab will be administered at room temperature (approximately 25°C) by controlled infusion via an infusion pump into a peripheral or central vein. The entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2 or 0.22 μm in-line filter; less than 55 minutes is considered a deviation and should be detailed on the Treatment CRF.

If there are interruptions during the durvalumab infusion, the maximum time for IV bag infusion should not exceed 8 hours at room temperature. In the event that the infusion time exceeds the 8 hour time limit, a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

The IV line will be flushed with a volume of IV solution (0.9% [w/v] saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

If a patient’s weight falls to 30 kg or below the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q4W until their weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg Q4W.)
5.3.5 Monitoring of Dose Administration

Patients will be monitored before, during and after the infusion with assessment of vital signs. Patients are monitored (pulse rate, blood pressure and temperature) every 30 minutes during the infusion period (including times where infusion rate is slowed or temporarily stopped). Please refer to Section 6.3.3 for more information on vital signs monitoring.

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognise and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit subjects to an intensive care unit if necessary.

A 1 hour observation period is required after the first infusion of durvalumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator’s discretion (suggested 30 minutes after each durvalumab infusion).

In the event of a Grade ≤2 infusion-related reaction, the infusion rate of durvalumab may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For subjects with a Grade ≤2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Paracetamol and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion related reaction is Grade 3 or higher in severity, durvalumab will be permanently discontinued.

5.3.6 Toxicity Management During Treatment

Please refer to the RAMPART Toxicity Management Guidelines (Appendix B) for information on managing toxicities while patients are undergoing trial treatment.

5.4 Arm C – Combination Durvalumab and Tremelimumab

5.4.1 Products

See Section 5.3.1 for details on durvalumab.

Tremelimumab will be supplied by AstraZeneca as a 400mg vial solution for infusion. The solution contains 20mg/mL of tremelimumab, 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, and 0.27 mM disodium edetate dihydrate (EDTA); it has a pH of 5.5. The nominal fill volume is 20 mL. Investigational medicinal product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Tremelimumab must be used within the individually assigned expiry date on the label.

5.4.2 Treatment Schedule

Patients in the durvalumab and tremelimumab combination therapy group will receive 1500 mg durvalumab via IV infusion Q4W for 2 cycles and 75mg tremelimumab via IV infusion Q4W for 2 cycles. A cycle is defined as 28 days. Treatment delays beyond the 28 day cycle (beyond administrative delays for up to three days either side of the expected infusion date) should be discussed with the TMT. Patients will then continue 1500mg durvalumab Q4W, with the final dose administered at week 48 (13 total cycles).
If time between infusions exceeds 8 weeks then the treatment must be permanently discontinued; regardless any administration delays, the maximum duration of durvalumab treatment must not exceed 1 year.

Pre-menopausal patients are required to have a negative urine HCG pregnancy test prior to the administration of the trial treatment. A serum HCG pregnancy test should be performed if there is any doubt over the results of the urine test.

### Table 6  Arm C Dosing Schedule

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Day 1</th>
<th>Wk 2</th>
<th>Wk 4</th>
<th>Wk 6</th>
<th>Wk 8</th>
<th>Wk 12</th>
<th>Wk 16</th>
<th>Wk 20</th>
<th>Wk 24</th>
<th>Wk 28</th>
<th>Wk 32</th>
<th>Wk 36</th>
<th>Wk 40</th>
<th>Wk 44</th>
<th>Wk 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremelimumab (anti-CTLA4)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Durvalumab (anti-PDL1)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

**5.4.3 Durvalumab IV Preparation**

See Section 5.3.3 for details.

**5.4.4 Tremelimumab IV Preparation**

The dose of tremelimumab for administration must be prepared using an aseptic technique. Total time from needle puncture of the tremelimumab vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

It is recommended that the prepared final IV bag be stored in the dark at 2°C to 8°C (36°F to 46°F) until needed. If storage time exceeds these limits, a new dose must be prepared from new vials. The refrigerated infusion solutions in the prepared final IV bag should be equilibrated at room temperature as per local guidance prior to administration.

No incompatibilities between tremelimumab and polyvinylchloride or polyolefin IV bags have been observed. Doses of 75 mg tremelimumab will be administered using an IV bag containing 0.9% (w/v) saline, with a final tremelimumab concentration ranging from 0.1 mg/mL to 10 mg/mL, and delivered through an IV administration set with a 0.2 μm or 0.22 μm in-line filter.

Procedure: Remove 3.8 mL of IV solution from the IV bag prior to addition of tremelimumab. Next, 3.8mL of tremelimumab (i.e., 75 mg of tremelimumab) is added to the IV bag such that final concentration is within 0.1mg/mL to 10mg/mL (IV bag volumes 50 to 500 mL). Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

**5.4.5 Tremelimumab and Durvalumab Administration**

Tremelimumab will be administered first at room temperature (approximately 25°C) by controlled infusion via an infusion pump into a peripheral or central vein. The entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2 or 0.22 μm in-line filter; less than 55 minutes is considered a deviation. Please refer to Section 6.3.3 for more information on vital signs monitoring.

If there are interruptions during a tremelimumab infusion, the maximum time for IV bag infusion should not exceed 8 hours at room temperature. In the event that the infusion time exceeds the 8
hour time limit, a new dose must be prepared from new vials. Tremelimumab does not contain preservatives, and any unused portion must be discarded.

The IV line will be flushed with a volume of 0.9% (w/v) saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

On the first dosing occasion, the durvalumab infusion will start approximately 1 hour after the end of the tremelimumab infusion. A 1-hour observation period is also required after the first infusion of durvalumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent post-infusion observation periods can be at the Investigator’s discretion (suggested 30 minutes after each durvalumab and tremelimumab infusion).

Durvalumab will be administered at room temperature (approximately 25°C) by controlled infusion via an infusion pump into a peripheral or central vein. The entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2 or 0.22μm in-line filter; less than 55 minutes is considered a deviation.

If there are interruptions during durvalumab infusion, the maximum time for IV bag infusion should not exceed 8 hours at room temperature. In the event that the infusion time exceeds the 8 hour time limit, a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

The IV line will be flushed with a volume of IV solution (0.9% [w/v] saline equal to the priming volume of the IV bag used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

If a patient’s weight falls to 30kg or below the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q4W and 1mg/kg tremelimumab Q4W until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500mg plus tremelimumab 75 mg Q4W).

Table 7 Durvalumab and Tremelimumab Hold and Infusion Times

<table>
<thead>
<tr>
<th>PROCEDURE</th>
<th>MAXIMUM TIME</th>
</tr>
</thead>
<tbody>
<tr>
<td>From needle puncture to start of administration</td>
<td>4 hours at room temperature</td>
</tr>
<tr>
<td></td>
<td>24 hours at 2°C to 8°C</td>
</tr>
<tr>
<td>IV bag infusion, including interruptions</td>
<td>8 hours at room temperature</td>
</tr>
</tbody>
</table>

5.4.6 Monitoring of Dose Administration

Patients will be monitored before, during and after the infusion with assessment of vital signs. Patients are monitored (pulse rate, blood pressure and temperature) every 30 minutes during the infusion period (including times where infusion rate is slowed or temporarily stopped). Please refer to Section 6.3.3 for more information on vital signs monitoring.

A 1 hour observation period is required after the first infusion of durvalumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator’s discretion (suggested 30 minutes after each durvalumab infusion).
As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognise and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit subjects to an intensive care unit if necessary.

In the event of a Grade ≤2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For subjects with a Grade ≤2 infusion related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion related reaction is Grade ≥3 in severity, study drugs will be permanently discontinued.

5.4.7 TOXICITY MANAGEMENT DURING TREATMENT
Please refer to the trial’s Toxicity Management Guidelines (Appendix B) for information on managing toxicities while patients are undergoing trial treatment.

5.5 OVERDOSE OF TRIAL MEDICATION
Please refer to Section 7.2.2.

5.6 PROTOCOL TREATMENT DISCONTINUATION

In consenting to the trial, patients are consenting to trial treatment, trial follow-up and data collection. However, an individual patient may stop treatment early or have treatment stopped early for any of the following reasons:

- Disease progression
- Unacceptable toxicity Intercurrent illness that prevents further treatment
- Any change in the patient’s condition that justifies the discontinuation of treatment in the clinician’s opinion
- Patient is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational medicinal product might constitute a safety risk.
- Pregnancy or intent to become pregnant
- Grade ≥3 infusion reaction
- Initiation of alternative anticancer therapy including another investigational agent
- Withdrawal of consent for treatment by the patient

As the patient’s participation in the trial is entirely voluntary, they may choose to discontinue the trial treatment at any time without penalty or loss of benefits to which they are otherwise entitled outside of the trial. Although the patient is not required to give a reason for discontinuing their trial treatment, a reasonable effort should be made to establish this reason while fully respecting the patient’s rights.

Patients should remain in the trial for the purpose of follow-up and data analysis (unless the patient withdraws their consent from all stages of the trial). If a patient withdraws consent for follow-up, refer to Section 6.11.
5.7 ACCOUNTABILITY & UNUSED DRUGS

The dose of trial medication administered to each patient will be recorded on the Treatment CRF. Reasons for any dose delay, reduction, or missed doses will also be recorded in this CRF.

A complete dispensing log, including batch number and copies of the prescription form/charts, will be maintained by the site pharmacy for all trial medication.

Pharmacy will keep an accountability log for all trial medication. Any unused medication that has been accounted for may be destroyed by the site; a record of destruction must be maintained.

A Pharmacy Pack and Manual will be provided to all participating centres prior to activation.

5.8 NON-TRIAL TREATMENT

The doctor responsible for the patient’s care must be informed as soon as possible about any medication patients have taken from the time of screening until the end of the study treatment. Concomitant medications, including herbal preparations, which patients have taken during the study period, will be recorded on the Concomitant Medications CRF.

5.8.1 MEDICATIONS PERMITTED

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as “not permitted” in Section 5.8.2.

Table 8 Permitted Medications

<table>
<thead>
<tr>
<th>RESCUE, SUPPORTIVE MEDICATION OR CLASS OF DRUG</th>
<th>USAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant medications or treatments (e.g., acetaminophen or diphenhydramine) deemed necessary by the Investigator to provide adequate prophylactic or supportive care, except for those medications identified as “not permitted” as listed in Section 5.8.2.</td>
<td>To be administered as prescribed by the Investigator</td>
</tr>
<tr>
<td>Best supportive care (including antibiotics, nutritional support, growth factor support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy, other treatments as necessary])</td>
<td>Should be used when necessary for all patients</td>
</tr>
<tr>
<td>Opioids</td>
<td>Can be used with caution and under medical control after discussion with the Trial Physician</td>
</tr>
<tr>
<td>Inactivated viruses</td>
<td>Can be used when necessary for all patients</td>
</tr>
</tbody>
</table>

5.8.2 MEDICATIONS NOT PERMITTED

The medications listed in Table 9 are not permitted during the patient’s time on study treatment (unless otherwise indicated).

Table 9 Prohibitive Medications

<table>
<thead>
<tr>
<th>PROHIBITED MEDICATION OR CLASS OF DRUG</th>
<th>USAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any investigational anticancer therapy other than those under investigation in this study</td>
<td>Should not be given concomitantly whilst the patient is on study treatment</td>
</tr>
</tbody>
</table>
### PROHIBITED MEDICATION OR CLASS OF DRUG

<table>
<thead>
<tr>
<th>PROHIBITED MEDICATION OR CLASS OF DRUG</th>
<th>USAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study</td>
<td>Should not be given concomitantly whilst the patient is on study treatment</td>
</tr>
<tr>
<td>Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study</td>
<td>Should not be given concomitantly whilst the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [e.g., by local surgery or radiotherapy])</td>
</tr>
<tr>
<td>Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers.</td>
<td>Should not be given during the study. (Use of immunosuppressive medications for the management of durvalumab or tremelimumab related AEs or in patients with contrast allergies is acceptable. In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. Temporary uses of corticosteroids for concurrent illnesses [e.g., food allergies or CT scan contrast hypersensitivity] are acceptable upon discussion with the Trial Physician)</td>
</tr>
<tr>
<td>Drugs with laxative properties and herbal or natural remedies for constipation</td>
<td>Should be used with caution through to 90 days after the last dose of tremelimumab during the study</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Should not be given concomitantly or through 90 days after the last dose of tremelimumab (acute renal failure has been reported with combination therapy of tremelimumab and sunitinib)</td>
</tr>
<tr>
<td>Live attenuated vaccines</td>
<td>Should not be given through 30 days after the last dose of durvalumab or tremelimumab.</td>
</tr>
</tbody>
</table>

#### 5.8.3 TREATMENT AFTER DISEASE PROGRESSION

Treatment will be at the discretion of the doctor responsible for the patient’s care.

#### 5.8.4 CONTRACEPTION

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

**Female patient of childbearing potential**

Females of childbearing potential who are sexually active with a non-sterilised male partner must use at least one highly effective method of contraception (Table 10) from the time of screening and must agree to continue using such precautions for 180 days after the last dose of durvalumab and tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period; cessation of birth control after this point should be discussed with a responsible physician. Male partners of a female subject must use male condoms plus spermicide throughout this period. Abstinence is acceptable only if it is the preferred and usual lifestyle of the subject. Occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Female patients should refrain from breastfeeding throughout this period. Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal (defined 12 months with no menses without an alternative medical cause).

**Male patients with a female partner of childbearing potential**

Non-sterilised males who are sexually active with a female partner of childbearing potential must use male condoms plus spermicide from screening until 180 days after receipt of the final dose of durvalumab and tremelimumab combination therapy or 90 days after receipt of the final dose of...
durvalumab monotherapy, whichever is the longer time period. Male patients should refrain from sperm donation throughout this period.

Female partners of a male subject must also use a highly effective method of contraception throughout this period (see Table 10).

Table 10 Highly Effective Methods of Contraception for Women

<table>
<thead>
<tr>
<th>BARRIER OR INTRAUTERINE METHODS</th>
<th>HORMONAL METHODS</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Copper T intrauterine device</td>
<td>- Etonogestrel implants: e.g., Implanon or Norplan</td>
</tr>
<tr>
<td>- Levonorgesterel-releasing intrauterine system (e.g., Mirena)(^B)</td>
<td>- Intravaginal device: e.g., ethinylestradiol and etonogestrel</td>
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<td></td>
<td>- Medroxyprogesterone injection: e.g., Depo-Provera</td>
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<td></td>
<td>- Normal and low dose combined oral contraceptive pill</td>
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<tr>
<td></td>
<td>- Norelgestromin/ethinylestradiol transdermal system</td>
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<tr>
<td></td>
<td>- Cerazette (desogestrel)</td>
</tr>
</tbody>
</table>

A. Highly effective (i.e., failure rate of <1% per year)
B. This is also considered a hormonal method

5.8.5 Blood Donation

Subjects should not donate blood while participating in this study. Blood donations should not be made for at least 90 days following the last infusion of durvalumab, or 180 days after receipt of the final dose of durvalumab and tremelimumab combination therapy.
6 ASSESSMENTS & FOLLOW-UP

6.1 TRIAL ASSESSMENT SCHEDULE – ARM A ONLY

Patients in arm A are radiologically assessed at the same frequency as patients on arms B and C, however they do not need to be clinically assessed as frequently. Arm A patients will therefore be clinically assessed at weeks 16, 32 and 52 only. Please refer to Table 11 for a breakdown of the required assessments and Section 6.5 for a detailed breakdown on the blood tests required.

Any adverse events experienced since the last visit should be recorded on the Adverse Events CRF and any changes to existing or new con-medications should be updated on the Concomitant Medication CRF.

Once the assessments have been completed at week 52 the patient will move into follow-up phase. Please see Section 6.8 for details of the trial follow-up schedule.

Table 11 Trial Assessments During Year 1 – Arm A Only

<table>
<thead>
<tr>
<th>Clinical Assessments</th>
<th>Wk 16</th>
<th>Wk 32</th>
<th>Wk 52</th>
<th>DFS Event</th>
<th>As Clinically Required</th>
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</thead>
<tbody>
<tr>
<td>Physical Examination</td>
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<tr>
<td>Vital Signs</td>
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<td>ECG</td>
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<tr>
<td>Concomitant Medications</td>
<td>X</td>
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<tr>
<td>AEs</td>
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<tr>
<td>WHO Performance Status</td>
<td>X</td>
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</tbody>
</table>

Radiology

| CT Scan                       | X     | X     | X     | X         |                        |

Laboratory Tests

| Haematology                   | X     | X     | X     | X         |                        |
| Clinical Chemistry            | X     | X     | X     | X         |                        |

Questionnaires

| EQ-5D (optional)              | X     |       |       |           |                        |
| QLQ-C30 (optional)            | X     |       |       |           |                        |
| PAIR Study Questionnaire (optional) | X     |       |       |           |                        |

6.2 TRIAL ASSESSMENT SCHEDULE – ARMS B AND C

Patients in arms B and C will be assessed at day 1, then on a 2 weekly basis until week 8, and then every 4 weeks until week 52. Additional assessments may be conducted at the Investigators discretion.

At each visit (including weeks 2 and 6) a Treatment CRF should be completed. Any adverse events experienced since the last visit should be recorded on the Adverse Events CRF and any changes to existing or new con-medications should be updated on the Concomitant Medication CRF.
Clinical assessments and laboratory tests will be performed at all visits during the treatment phase to assess and ensure patient safety. Please refer to Table 11 for a breakdown of the required assessments and Section 6.5 for a detailed breakdown on the blood tests required.

Once the required dosing and assessments have been completed at week 48 the patient will end trial treatment and move into follow-up. Please see Section 6.8 for details of the trial follow-up schedule.

Table 12 Trial Assessments During Treatment Phase – Arms B and C

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Wk 2</th>
<th>Wk 4</th>
<th>Wk 6</th>
<th>Wk 8</th>
<th>Wk 12</th>
<th>Wk 16</th>
<th>Wk 20</th>
<th>Wk 24</th>
<th>Wk 28</th>
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<th>Wk 36</th>
<th>Wk 40</th>
<th>Wk 44</th>
<th>Wk 48</th>
<th>Wk 52</th>
<th>DFS Event</th>
<th>As Clinically Required</th>
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</thead>
<tbody>
<tr>
<td><strong>Clinical Assessments</strong></td>
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<td><strong>Questionnaires</strong></td>
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</table>

* Serum HCG pregnancy test must be performed to exclude pregnancy at screening. Urine pregnancy test is acceptable after contraception has been established. A serum HCG pregnancy test should be performed if there is any doubt over the results of the urine test.

6.3 CLINICAL ASSESSMENTS

6.3.1 PHYSICAL EXAMINATION

Physical examinations will be performed according to the assessment schedule. Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at screening only. Targeted physical examinations are to be utilised by the Investigator on the basis of clinically
observed reported symptoms. Situations in which physical examination results should be reported as AEs are described in Section 7.1.

6.3.2 Electrocardiogram

Resting 12-lead ECGs will be recorded at screening, on day 1, and as clinically indicated throughout the study.

ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position.

At screening, a single ECG will be obtained on which QTcF must be <450 ms.

In case of clinically significant ECG abnormalities, including a QTcF value ≥450 ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding. Patients are only eligible if a QTcF of <450 ms is confirmed.

Situations in which ECG results should be reported as AEs are described in Section 7.1.

6.3.3 Vital Signs

Vital signs (blood pressure, pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules (see Table 12).

Supine BP will be measured using a semi-automatic BP recording device with an appropriate cuff size after the patient has rested for at least 5 minutes.

BP, pulse and temperature will be collected before, during, and after each infusion at the following times (based on a 60-minute infusion):
- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [i.e., the beginning of the infusion])
- Approximately 30 minutes after beginning infusion (halfway through infusion)
- At the end of the infusion (approximately 60 minutes ±5 minutes)

A 1 hour observation period is required after the first infusion of each agent. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator’s discretion (suggested 30 minutes after each durvalumab and tremelimumab infusion).

If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. The date and time of collection and measurement will be recorded on the Treatment Form. Additional monitoring with assessment of vital signs is at the discretion of the Investigator as per standard clinical practice or as clinically indicated.

Situations in which vital signs results should be reported as AEs are described in Section 7.1.

6.4 Radiology Assessments

During their first year on the study patients are assessed at 4 monthly intervals by CT scan (with contrast) of their chest, abdomen and pelvis (screening, week 16, week 32 and week 52). During years two and three CT frequency changes to 6 monthly (18, 24, 30 and 36 months). After year 3 (36 months), CT scans should be scheduled annually until five years. Patients who remain disease-free
should be scanned at either year 7 or 8 with a further CT scan at 10 years. A Disease Assessment CRF should be completed to report the outcome of each of these scheduled assessments.

Please see Section 6.10 for more information on tumour assessment.

### 6.5 LABORATORY TESTS

Trial patients will be required to have the assessments listed in the following tables (see Table 13 and Table 14) in order to assess and ensure patient safety.

Arm A patients will undergo laboratory assessments at weeks 16, 32 and 52 and as clinically indicated.

Patients in Arm B and C are required to have laboratory tests up to 120 days after last protocol treatment. This will be at Month 15 if treatment is completed as per protocol or sooner if treatment is discontinued early. Haematology and clinical chemistry tests can also be carried out after this period as clinically indicated.
### Table 13 Haematology Assessments (Treatment and Follow-up phase)

<table>
<thead>
<tr>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basophils</td>
</tr>
<tr>
<td>Eosinophils</td>
</tr>
<tr>
<td>Haematocrit</td>
</tr>
<tr>
<td>Haemoglobin</td>
</tr>
<tr>
<td>Lymphocytes</td>
</tr>
<tr>
<td>Mean corpuscular haemoglobin (MCH)</td>
</tr>
<tr>
<td>Mean corpuscular haemoglobin concentration (MCHC)</td>
</tr>
<tr>
<td>Mean corpuscular volume (MCV)</td>
</tr>
<tr>
<td>Monocytes</td>
</tr>
<tr>
<td>Neutrophils</td>
</tr>
<tr>
<td>Platelet count</td>
</tr>
<tr>
<td>Red blood cell count (RBC)</td>
</tr>
<tr>
<td>Total white cell count (WBC)</td>
</tr>
</tbody>
</table>

### Table 14 Clinical Chemistry Assessments (Treatment and Follow-up phase)

<table>
<thead>
<tr>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
</tr>
<tr>
<td>Alkaline phosphatase (ALP)</td>
</tr>
<tr>
<td>Alanine aminotransferase (ALT)</td>
</tr>
<tr>
<td>Amylase B</td>
</tr>
<tr>
<td>Aspartate aminotransferase (AST)</td>
</tr>
<tr>
<td>Bicarbonate C</td>
</tr>
<tr>
<td>Calcium C</td>
</tr>
<tr>
<td>Chloride C</td>
</tr>
<tr>
<td>Creatinine</td>
</tr>
<tr>
<td>Creatinine clearance C</td>
</tr>
<tr>
<td>Gamma glutamyltransferase (GGT)</td>
</tr>
<tr>
<td>Glucose</td>
</tr>
<tr>
<td>Urine or serum HCG pregnancy test</td>
</tr>
<tr>
<td>Lactate dehydrogenase (LDH)</td>
</tr>
<tr>
<td>Lipase B</td>
</tr>
<tr>
<td>Magnesium C</td>
</tr>
<tr>
<td>Potassium</td>
</tr>
<tr>
<td>Random cortisol</td>
</tr>
<tr>
<td>Sodium</td>
</tr>
<tr>
<td>Thyroid stimulating hormone (TSH) – if abnormal check free T3 and T4</td>
</tr>
<tr>
<td>Total bilirubin A</td>
</tr>
</tbody>
</table>
**Total protein**

**Urea or blood urea nitrogen (depending on local practice)**

**Uric acid**

A. Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥2 × upper limit of normal (and no evidence of Gilbert’s syndrome) then fractionate into direct and indirect bilirubin.

B. It is preferable that both amylase and lipase parameters are assessed. For sites where only 1 of these parameters is routinely measured then either lipase or amylase is acceptable.

C. Bicarbonate (where available), calcium, chloride, creatinine clearance, gamma glutamyltransferase, magnesium, testing are to be performed at screening, on Day 1 (unless screening laboratory assessments are performed within 3 days prior to Day 1), and if clinically indicated. Tests will need to be repeated on Day 1 if done more than 3 days prior.

D. Free T3 or free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system.

E. A urine HCG pregnancy test is required for pre-menopausal patients prior to each treatment administration; a serum HCG pregnancy test should be carried out if there is any doubt over the results of the urine HCG pregnancy test.

---

**6.6 PATIENT REPORTED OUTCOMES**

Participants will be asked to complete the EQ-5D and QLQ-C30 questionnaires at baseline, then at their week 16, month 15, and month 36 visits, and also at progression (if occurring before month 36). A window of one month either side of the year one and year three study visits is acceptable to enable good compliance.

Participants from countries taking part in the preferences for adjuvant immunotherapy in RAMPART (PAIR) sub-study will be asked to complete the preferences questionnaire at baseline, then at their week 16 visit and after completing treatment at the month 15 visit.

Questionnaires completed at treatment visits should be done prior to the administration of any scheduled infusions.

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**6.7 TRANSRAMPART**

Consenting patients will be asked to provide biological samples at baseline and follow-up visits. Further information on TransRAMPART can be found in the TransRAMPART Sample Collection Manual.

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**6.8 ROUTINE FOLLOW-UP OF PATIENTS**

An End of Treatment CRF should be completed after week 48 at the end of RAMPART trial treatment (Arm B and C only). An End of Treatment CRF should also be completed if the trial treatment is terminated early.

All patients (on all arms) who have not progressed will be seen at week 52, and will then continue to be followed-up on a 3 monthly basis until the end of year 3. During this time they will have CT scans (with contrast) of the chest and abdomen on a 6 monthly basis. A Post-treatment CRF should be completed at each of these follow-up visits.

After year 3, patients should have annual follow-up (and a Post-treatment CRF should be completed at each visit). For the purposes of the trial, patients should have a CT scan at either years 7 or 8 and a
further CT scan at 10 years. Please refer to Table 15, below, for a breakdown of the required follow-up assessments.

Please see Section 6.10 for long-term follow-up requirements.

### Table 15  Routine Follow-up Assessment Schedule

<table>
<thead>
<tr>
<th></th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Year 7</th>
<th>Year 10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wk 52</td>
<td>M 15</td>
<td>M 18</td>
<td>M 21</td>
<td>M 24</td>
<td>M 27</td>
<td>M 30</td>
</tr>
<tr>
<td><strong>Clinical Assessments</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Physical Examination</td>
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<td>X</td>
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<tr>
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<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>AEs</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>WHO Performance Status</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Radiology</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT Scan</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Laboratory Tests</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Haematology</td>
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<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
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<tr>
<td>Clinical Chemistry</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Questionnaires</strong></td>
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<td></td>
</tr>
<tr>
<td>EQ-5D (optional)</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>QLQ-C30 (optional)</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>PAIR Study Questionnaire (optional)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 6.9 FOLLOW-UP OF PATIENTS WHO STOP RAMPART TREATMENT EARLY (BEFORE 1 YEAR)

If a decision is made to stop treatment early, the relevant CRFs should be completed and returned to the RAMPART team; please refer to the Trial Manual and CRF Completion Guidelines for more information on CRF completion.

Patients should continue to be followed-up according to the original visit and scanning schedule (see Table 12) until the end of year 1. At each visit a Post-treatment CRF should be completed.

After year 1, the patient should be followed-up as per Section 6.8.

### 6.10 TUMOUR ASSESSMENT AND LONG-TERM FOLLOW-UP

DFS shall be measured from the day of randomisation until any of the following events: day of documented equivocal or definite local recurrence, new primary RCC, distant metastases or death from any cause.

The DFS outcome will be investigator-reported and must be based on thorough investigation and evidence such unequivocal radiological progression or biopsy. This is particularly important if recurrence is suspected within 6 months of starting study treatment, when pseudo-progression is most likely to occur, if at all.
Recurrences documented only on imaging evidence should be unequivocal and not attributable to different scanning technique or non-tumour (e.g., pulmonary adverse effects of drug therapy).

If a biopsy is not feasible, it is reasonable that patients with equivocal changes who are clinically stable should continue on the trial and be re-imaged at the next planned time or earlier if clinically indicated. If recurrence, distant metastases or new malignancy is confirmed, the DFS date is the date of the CT scan where equivocal changes were first described. For example, lung metastases may start as small abnormalities which are not definitively metastatic disease, but on repeat CTs continue to grow and meet the criteria for DFS. The DFS date would be the date of the CT scan in which the abnormality was first noted.

In rare instances where disease recurrence cannot be documented (as above) prior to initiation of new antineoplastic therapy, the patient will be considered to have had recurrence as of the day following the last prior imaging that did not show new definitive or equivocal findings.

Uncertainty about the status of disease progression must be discussed with the RAMPART Trial Management Team at the MRC CTU at UCL for referral to and discussion with the clinical members of the TMG.

6.11 EARLY STOPPING OF FOLLOW-UP

If a patient chooses to discontinue their trial treatment, they should be encouraged to continue with trial follow-up. Patients stopping follow-up early have a negative impact on trial’s data. If patients do not wish to remain on trial follow-up, however, their decision must be respected and they will be withdrawn from the trial completely.

If a patient objects to the provision of further follow-up data, site staff should inform the MRC CTU at UCL of this decision in writing. Patients may change their minds about stopping trial follow-up at any time and re-consent to participation in the trial. Patients who stop trial follow-up early will not be replaced.

If the medical data collected during the patient’s participation in the trial are kept for research and analysis purposes, they can be anonymised if necessary. Consent for future use of stored samples already collected can be refused when leaving the trial early (but this should be discouraged and should follow a discussion).

6.12 FOLLOW-UP TELEPHONE CONSULTATIONS

In certain circumstances it may be appropriate to replace hospital visits with telephone consultations providing that it is still possible to collect all the necessary follow-up information. Situations where this may be considered include at the point where patients would normally be discharged from oncology or urology services. In these instances, it is acceptable to alternate appointments with telephone consultations providing the required blood results are available to the research team.

All necessary information required to complete the relevant CRFs is still required and all details on the telephone consultation must be recorded in the patient’s notes as per in person assessments.
6.13 PATIENT TRANSFERS

If a patient moves, where feasible every effort should be made for the patient to be seen at another participating trial site. A Patient Transfer form should be signed by the PI at the both sites to confirm that they are happy with the arrangements. A copy of the patient’s CRFs should be provided to the new site and the patient will need to sign a new consent form. The transferring centre will need to ensure all data is current and up-to-date and that all queries raised up to the point of transfer have been resolved. Once this has been done, the new site will take over responsibility for the patient; until this has been done, responsibility for the patient lies with the original site.

6.14 CENTRAL COLLECTION AND RETENTION OF CT SCANS

Electronic copies of CT scans and accompanying reports should be anonymised and provided to MRC CTU at UCL for each trial participant. Further details of the process will be provided to sites upon their accreditation and detailed in the Site Manual.

The scans and reports will be stored in a secure central repository in case blinded review is required to support a regulatory submission at a future date.
ICH GCP requires that both investigators and Sponsors follow specific procedures when notifying and reporting AEs or reactions in clinical trials. These procedures are described in this Section 7.1 of the protocol.

7.1 DEFINITIONS

The definitions of the EU Directive 2001/20/EC Article 2 based on ICH GCP apply to this trial protocol. These definitions are given in Table 16.

Table 16 Event Definitions

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
<th>When and where to report it</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Event (AE)</td>
<td>Any untoward medical occurrence in a patient or clinical trial subject to whom a medicinal product has been administered including occurrences that are not necessarily caused by or related to that product.</td>
<td>From the time of consent and up to 120 days post-treatment visit via the AE CRF****</td>
</tr>
<tr>
<td>Adverse Reaction (AR)</td>
<td>Any untoward and unintended response to an investigational medicinal product related to any dose administered.</td>
<td>From the time of consent and up to 120 days post-treatment visit via the AE CRF****</td>
</tr>
<tr>
<td>Unexpected Adverse Reaction (UAR)</td>
<td>An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the Summary of Product Characteristics (SPC) or Investigator’s Brochure (IB) for that product.</td>
<td>From the time of consent and up to 120 days post-treatment visit via the AE CRF****</td>
</tr>
<tr>
<td>Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)</td>
<td>Respectively any adverse event, adverse reaction or unexpected adverse reaction that: Results in death Is life-threatening* Requires hospitalisation or prolongation of existing hospitalisation** Results in persistent or significant disability or incapacity Consists of a congenital anomaly or birth defect Is another important medical condition***</td>
<td>From the time of consent and within 24hrs of becoming aware of event via the SAE CRF</td>
</tr>
<tr>
<td>Adverse Event of Special Interest (AESI)</td>
<td>An adverse event of scientific and medical interest specific to the further understanding of the investigational medicinal product safety profiles that require close monitoring and rapid communication by the Investigator.</td>
<td>From the time of consent and up to 120 days post-treatment visit via the AE CRF****</td>
</tr>
</tbody>
</table>

*The term life-threatening in the definition of a serious event refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.*
Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, that has not worsened or for an elective procedure do not constitute an SAE.

Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. The following should also be considered serious: important AEs or ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above; for example, a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not result in hospitalisation or development of drug dependency.

Within a maximum of 4 weeks from the CRF due date

**7.1.1 MEDICINAL PRODUCTS**

An investigational medicinal product (IMP) is defined as the tested IMP and the comparators used in the study (EU guidance ENTR/CT 3, April 2006 revision).

Adverse reactions include any untoward or unintended response to drugs. Reactions to an IMP or comparator should be reported appropriately.

**7.1.2 ADVERSE EVENTS**

Adverse Events include:
1. An exacerbation of a pre-existing illness
2. An increase in frequency or intensity of a pre-existing episodic event or condition
3. A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
4. Continuous persistent disease or a symptom present at baseline that worsens following administration of the study treatment.

The term AE is used to include both serious and non-serious AEs.

**7.1.3 EXEMPTED ADVERSE EVENTS**

Adverse Events do not include:
- Disease progression or death as a result of disease progression (with no involvement of study drugs)
- Medical or surgical procedures; the condition that leads to the procedure is the AE
- Pre-existing disease or a condition present before treatment that does not worsen
- Hospitalisations where no untoward or unintended response has occurred, e.g., elective cosmetic surgery, social admissions.

**7.1.4 ADVERSE EVENTS OF SPECIAL INTEREST (AESI)**

AESIs of special interest (AESIs) are events of scientific and medical interest specific to the further understanding of the durvalumab and tremelimumab safety profiles and require close monitoring and rapid communication by the Investigator to the MRC CTU at UCL and subsequently to AstraZeneca. Durvalumab and tremelimumab AESIs may be serious or non-serious. The rapid reporting of these AESIs allows ongoing analysis of these events in order to characterise and understand them in association with the use of these IMPs. All AESIs should be reported on an Adverse Events CRF within 4 weeks of the occurrence.

AESIs for durvalumab and tremelimumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy.
These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-related adverse event (irAE) is defined as an AE that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate aetiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE. If the Investigator has any questions in regards to an AE being an irAE, the Investigator should promptly contact the Trial Management Team at the MRC CTU at UCL on page 2.

The AESIs are:
- Colitis or entereocolitis
- Diarrhoea
- ALT or AST increases, hepatitis and hepatotoxicity
- Hypersensitivity reactions, anaphylaxis or infusion reactions
- Neuropathy or neuromuscular toxicity (encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré and myasthenia gravis)
- Endocrinopathy (.e. events of hypophysitis, hypopituitarism adrenal insufficiency, diabetes insipidus, hyper- and hypothyroidism and type I diabetes mellitus)
- Dermatitis
- Renal failure or nephritis
- Pancreatitis or lab results suggestive of pancreatitis (raised serum lipase or amylase)
- Cardiac disorders (myocarditis)
- Other inflammatory responses that are rare with a potential immune-mediated aetiology include, but are not limited to, myocarditis, pericarditis, and uveitis.

Further information on these risks (eg, presenting symptoms) can be found in the current version of the durvalumab and tremelimumab IBs. More specific guidelines for their evaluation and treatment are described in detail in the RAMPART Toxicity Management Guidelines (Appendix B).

7.2 OTHER NOTABLE EVENTS

7.2.1 PREGNANCY

7.2.1.A Maternal Exposure
If a patient becomes pregnant during the course of the study, the IMPs should be discontinued immediately. Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP under study may have interfered with the effectiveness of a contraceptive medication.

A Pregnancy Monitoring CRF should be completed and sent to the MRC CTU at UCL within 24 hours of becoming aware of a pregnancy. The outcome of the pregnancy should be followed-up carefully and any abnormal outcome of the mother or the child should be reported within 24 hours of becoming aware of the event. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective terminations without complications should be reported on the Pregnancy Monitoring CRF.

7.2.1.B Paternal Exposure
Male patients should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of durvalumab and tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period.
Pregnancy of the patient’s partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 180 days after the last dose of durvalumab and tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period, should be followed up and documented.

Female partners of RAMPART patients will be asked to sign the Partner of RAMPART Patient Consent Form if conception occurs, to allow information about the outcome of the pregnancy to be collected. Once signed a Pregnancy Monitoring CRF should be completed and followed-up as per Section 7.3.1.A.

7.2.2 OVERDOSE
An overdose is defined as a subject receiving a dose of durvalumab and tremelimumab in excess of the protocol doses.

Any overdose of a study subject with durvalumab and tremelimumab, with or without associated AEs or SAEs, is required to be reported within 24 hours of knowledge of the event to the Sponsor. The Sponsor will subsequently notify AstraZeneca. If the overdose results in an AE, the AE must also be recorded as an AE (see Section 7.1). Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalisation, the event is serious and must be recorded and reported as an SAE (see Section 7.1).

There is currently no specific treatment in the event of an overdose of durvalumab or tremelimumab. The investigator will monitor for expected toxicity and use clinical judgment to treat any overdose.

7.2.3 HEPATIC FUNCTION ABNORMALITY (HY’S LAW)
Hepatic function abnormalities which meet the Hy’s Law criteria, with or without associated clinical manifestations, must be reported to the MRC CTU at UCL as a “hepatic function abnormality” notable event within 24 hours of the investigator becoming aware of the event. In order to meet the Hy’s Law criteria, the subject must fulfil the following:

$$\text{AST or ALT} \geq 3 \times \text{ULN}$$
$$\text{And}$$
$$\text{Bilirubin} \geq 2 \times \text{ULN}$$

The only exception would be if a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to the investigational product has been confirmed. Abnormalities that do not fit the Hy’s Law criteria should be reported as AESIs on the Adverse Event CRF.

Each reported notable event of hepatic function abnormality will be followed by the Investigator and evaluated by the Sponsor and AstraZeneca. Please refer to the Toxicity Management Guidelines (Appendix B) for further instruction on the management of hepatic function abnormalities.

7.3 INVESTIGATOR RESPONSIBILITIES

All non-serious AEs and ARs, whether expected or not, should be recorded in the patient’s medical notes and reported on the Adverse Events CRF and sent to the MRC CTU at UCL within one month of the CRF being due.
SAEs and Notable events should all be notified to the MRC CTU at UCL within 24 hours of the investigator becoming aware of the event.

### 7.3.1 Investigator Assessment

Adverse events will be recorded and graded according to the NCI CTCAE v4.03 guidelines using a recognised medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the local investigator for severity, relationship to the investigational product, possible aetiologies, and whether the event meets criteria of an SAE and therefore requires expedited notification to the MRC CTU at UCL.

#### 7.3.1.A Seriousness

When an AE or AR occurs, the investigator responsible for the care of the patient must first assess whether or not the event is serious using the definition given in Table 16. If the event is serious, then an SAE Form must be completed and the MRC CTU at UCL notified within 24 hours.

#### 7.3.1.B Severity or Grading of Adverse Events

The severity of all AEs and/or ARs (serious and non-serious) in this trial should be graded using the toxicity gradings in NCI CTCAE v4.03.

#### 7.3.1.C Causality

The investigator must assess the causality of all serious events or reactions in relation to the trial therapy using the definitions in Table 17. There are five categories: unrelated, unlikely, possible, probable, and definitely related. If the causality assessment is unrelated or unlikely to be related, the event is classified as an SAE. If the causality is assessed as possible, probable or definitely related, then the event is classified as an SAR.

**Table 17 Assigning Type of SAE Through Causality**

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Description</th>
<th>SAE Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated</td>
<td>There is no evidence of any causal relationship</td>
<td>Unrelated SAE</td>
</tr>
<tr>
<td>Unlikely</td>
<td>There is little evidence to suggest that there is a causal relationship (for example, the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (for example, the patient’s clinical condition, other concomitant treatment).</td>
<td>Unrelated SAE</td>
</tr>
<tr>
<td>Possible</td>
<td>There is some evidence to suggest a causal relationship (for example, because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (for example, the patient’s clinical condition, other concomitant treatments).</td>
<td>SAR</td>
</tr>
<tr>
<td>Probable</td>
<td>There is evidence to suggest a causal relationship and the influence of other factors is unlikely.</td>
<td>SAR</td>
</tr>
<tr>
<td>Definitely</td>
<td>There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.</td>
<td>SAR</td>
</tr>
</tbody>
</table>
7.3.1.D Expectedness

If there is at least a possible involvement of the trial treatment, the investigator should make an initial assessment of the expectedness of the event, however the Sponsor has the final responsibility for determination of expectedness. An unexpected adverse reaction (UAR) is one not previously reported in the current IB or one that is more frequent or more severe than previously reported. The definition of an UAR is given in Table 16. If a SAR is assessed as being unexpected, it becomes a SUSAR.

7.3.1.E Notification

The MRC CTU at UCL should be notified of all SAEs within 24 hours of the investigator becoming aware of the event.

Investigators should notify the MRC CTU at UCL of all SAEs occurring from the time of consent until 120 days after the last protocol treatment administration (Arms B and C). For Arm A patients, SAEs should be notified from the time of consent up to Month 15 of trial participation or until disease progression, whichever is sooner.

SARs and SUSARs for all patients across all trial arms (Arm A, B and C) must be notified to the MRC CTU at UCL until trial closure. Any subsequent events that may be attributed to treatment should be reported to the MHRA using the yellow card system.

7.3.2 Notification Procedure

1. The SAE CRF must be completed by the investigator (the consultant named on the Signature List and Delegation of Responsibilities Log who is responsible for the patient’s care), with due care being paid to the grading, causality and expectedness of the event as outlined above. In the absence of the responsible investigator, the form should be completed and signed by a member of the site trial team and faxed or emailed as appropriate. The responsible investigator should subsequently check the SAE Form, make changes as appropriate, sign and then re-fax to the MRC CTU at UCL as soon as possible. The initial report must be followed by detailed, written reports as appropriate.

The minimum criteria required for reporting an SAE are the trial number and date of birth, name of investigator reporting, the event, why it is considered serious, causality and expectedness.

2. Follow-up of SAEs: patients must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised. Follow-up should continue after completion of protocol treatment if necessary. A further SAE CRF, indicated as “Follow-up” should be completed and faxed or emailed to the MRC CTU at UCL as information becomes available. Extra, annotated information and/or copies of test results may be provided separately. The patient must be identified by trial number, date of birth and initials only. The patient’s name should not be used on any correspondence and should be deleted from any test results.

Staff should follow their institution’s procedure for local notification requirements.

SAE REPORTING

Within 24 hours of becoming aware of an SAE, SAR, or notable event, please fax a completed SAE form to the MRC CTU at UCL on:
Fax: +44 (0) 20 7670 4653 or email information to mrcctu.rampart@ucl.ac.uk
7.4 MRC CTU AT UCL RESPONSIBILITIES

Medically-qualified staff at the MRC CTU at UCL and/or the Chief Investigator (or a medically-qualified delegate, e.g., Trial Physician) will review all SAE reports received. The causality assessment given by the local investigator at the hospital can be changed with agreement but cannot be overruled; in the case of disagreement, both opinions will be provided in any subsequent reports, where relevant.

The MRC CTU at UCL is undertaking the duties of trial Sponsor and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA and competent authorities of other European member states and any other countries in which the trial is taking place) and the research ethics committees, as appropriate. Fatal and life-threatening SUSARs must be reported to the competent authorities within 7 days of the MRC CTU at UCL becoming aware of the event; other SUSARs must be reported within 15 days.

The MRC CTU at UCL, as Sponsor, will submit Annual Safety Reports in the form of a Developmental Safety Update Report (DSUR) to Competent Authorities (Regulatory Authority and Ethics Committee).

The MRC CTU at UCL will also keep all investigators informed of any safety issues that arise during the course of the trial. An Annual Safety Report for Investigators will be circulated at the same time as the DSUR is submitted. A line listing of all SUSARs will be circulated to all investigators every six months.

MRC CTU at UCL will notify AstraZeneca of all reportable (serious and unexpected and treatment-related or unknown relationship) events occurring in patients on the investigational arms (arm B and C). MRC CTU at UCL will also provide AstraZeneca with a copy of the Annual Safety Reports that are provided to investigators and the Competent Authorities (i.e., the DSUR). AstraZeneca retains the right to request additional information for any subject randomised to one of the investigational arms with ongoing AEs and/or SAEs at the end of the study, if judged necessary.

An Independent Data Monitoring Committee (IDMC) will review the accumulating data at regular intervals. The first meeting of the IDMC will be held after approx. 70 patients have been recruited to the trial and have received at least one cycle of treatment or after 6 months of patient accrual (whichever occurs first). The IDMC will subsequently meet at least annually, at a frequency they agree.
8 QUALITY ASSURANCE & CONTROL

8.1 RISK ASSESSMENT

The Quality Assurance (QA) and Quality Control (QC) considerations are based on a formal Risk Assessment, which acknowledges the risks associated with the conduct of the trial and how to address them with QA and QC processes. QA includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled. This Risk Assessment has been reviewed by the MRC CTU at UCL Research Governance Committee (RGC) and has led to the development of a Data Management Plan (DMP), Safety Reporting Plan and Monitoring Plan which will be separately reviewed by the internal Quality Management Advisory Group (Q MAG).

8.2 CENTRAL MONITORING AT MRC CTU AT UCL

MRC CTU at UCL staff will review CRF data for errors and missing data points.

Other plans for central monitoring will be detailed in the Quality Management and Monitoring Plan (QMMP).

8.3 ON-SITE MONITORING

On-site monitoring will be performed. The frequency, type and intensity for both routine and triggered monitoring visits will be detailed in the QMMP. This plan will also detail the procedures for review and sign-off.

8.3.1 DIRECT ACCESS TO PATIENT RECORDS

Participating investigators must agree (by signing the Investigator Statement) to allow trial-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Patient consent for this will be obtained as part of the general trial consent process.

8.3.2 CONFIDENTIALITY

The principles of the UK Data Protection Act will be followed regardless of the countries that the trial is being conducted in.
9 STATISTICAL CONSIDERATIONS

9.1 METHOD OF RANDOMISATION

Patients will be randomised centrally using stratified block randomisation. The randomisation list will be generated by the trial statistician and will be stored centrally at MRC CTU at UCL in a secure location.

Patients will initially be allocated to one of arms A, B and C in the ratio 3:2:2 using randomised blocks over a small number of stratification factors. To decrease determinability, the stratification factors are not listed here but can be found in the RAMPART Statistical Design Document.

9.2 OUTCOME MEASURES

9.2.1 CO-PRIMARY OUTCOMES - DEFINITIONS

Disease-free survival (DFS) and overall survival (OS) are co-primary outcome measures.

- DFS is defined as the interval from randomisation to first evidence of local recurrence, new primary 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 (including RCC).

9.2.2 SECONDARY OUTCOMES

The following secondary outcome measures will be explored:

- Metastasis-free survival (MFS), i.e., the interval from randomisation to first evidence of metastases or death from Renal Cell Carcinoma (RCC)
- RCC specific survival time, i.e., the time from randomisation to death from RCC
- Quality of Life
- Toxicity

9.3 TRIAL DESIGN

RAMPART is a phase III multi-arm, multi-stage (MAMS), multi-centre, randomised controlled platform trial. Full details of the methodology underlying the trial design are given by Royston et al (47, 48). The design allows several agents or combinations of agents to be assessed simultaneously against a single contemporaneous control group thereby accelerating treatment evaluation.

RAMPART will be initiated with a three-arm parallel design. We plan to add at least one further research arm to the platform over time, before any formal interim analyses on the initial two research comparisons are reported. In order to allow for the addition of an arm during recruitment to the current three arm design, we have used a one-sided alpha of 0.0097 at the primary DFS analysis stage, for each pairwise comparison of each research arm against the control arm. This design gives over 83% power to detect the targeted difference for each of these pairwise comparisons and strongly conserves the one-sided family-wise significance level at 2.5%. We conserve the type 1 error for the OS analysis by defining a closed test procedure, and only formally testing OS for those arms for which we see a positive result for DFS.
Should we not add an arm, we shall relax the one-sided alpha at the final stage to 0.014 for the two pairwise comparisons and report the definitive DFS and OS results slightly earlier in terms of calendar time.

Interim analyses of each research arm against control will be performed both for lack of benefit and for overwhelming benefit as described in 1.5.2 below.

9.4 SAMPLE SIZE

RAMPART is powered for both DFS and OS.

The sample size calculations and design characteristics for the RAMPART design were obtained using nstage (version 3.0.1, 10-Sep-2014). Specifically, the nstage program was used to obtain the 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). ART (version 1.1.0, 10-Dec-2013) was used to determine the absolute differences in DFS and OS at relevant timepoints. All calculations were performed in Stata 14.1.

Using the control arm data from the SORCE trial, we anticipate a 3 year DFS rate of 65% for the control arm of RAMPART. We plan to recruit 1,750 patients (750 to Arm A, 500 to Arm B and 500 to Arm C) over approximately 5.5 years. At the start of recruitment, patients with Leibovich score 3-11 will be eligible for randomisation. We will monitor accrual and stop recruiting intermediate risk patients (Leibovich Score 3-5) after three years or when intermediate risk patients contribute 25% of the total accrual target, whichever is earlier. Intermediate risk patients will only be included in the early years of the trial so that the majority of recurrences from intermediate risk patients will be expected to contribute to the DFS analysis. Recruitment of patients with Leibovich Score 6-11 will continue until the accrual target is reached.

9.5 INTERIM MONITORING & ANALYSES

An Independent Data Monitoring Committee (IDMC) will be convened. A charter will be drawn up that describes the membership of the IDMC, relationships with other committees, terms of reference, decision-making processes, the timing and frequency of interim analyses, and a description of stopping rules and/or guidelines.

9.6 PLANNED ANALYSES

9.6.1 SAFETY ANALYSIS

The first meeting of the IDMC will be held after approximately 70 patients have been recruited to the trial and those randomised to the research arms have completed at least one cycle of treatment or after 6 months of patient accrual (whichever occurs first). The group will subsequently meet on at least an annual basis.

9.6.2 DISEASE-FREE SURVIVAL

9.6.2.A Combination durvalumab and tremelimumab versus control (Arm C vs Arm A)

The primary DFS analysis of Arm C vs Arm A is planned when we have 276 control arm event events, which is estimated to happen approximately 6.25 years after recruitment starts (close to the end of
treatment for the last patient randomised to the trial). This timeline, which is illustrative, assumes that all of the research arms continue to this point. 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 and reported, even though the data will be not be fully mature, with only 46 control arm OS events expected. This will allow a more complete assessment of the DFS results.

One interim analysis is planned for the comparison of Arm C vs Arm A. This interim analysis will consider both a lack-of-benefit and overwhelming benefit on disease free survival. It will be performed when we have observed 197 control arm events (anticipated approximately 4.75 years after accrual starts). At this time, an observed HR of more than 0.831 for Arm C compared to control (Arm A) will be taken as an indication that there is insufficient benefit from the combination therapy. The stopping guideline for overwhelming benefit is to observe a p-value of less than 0.001 (one-sided).

9.6.2.B Durvalumab monotherapy versus control (Arm B vs Arm A)

The primary DFS analysis of Arm B versus Arm A is planned when we have 416 control arm events, which is estimated to happen approximately 10.75 years after recruitment starts. This timeline, which is illustrative, assumes that all of the research arms continue to this point. The target HR for Arm B versus Arm A is 0.75 which translates to an absolute improvement in 3-year DFS of 7.4%, from 65% to 72.4%. This design gives 83.5% 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 and reported, even though the data will be not be fully mature, with only 190 control arm OS events expected. This will allow a more complete assessment of the DFS results.

Three interim analyses are planned for the comparison of Arm B vs Arm A. Each interim analysis will consider both a lack-of-benefit and overwhelming benefit on disease free survival. The first interim analysis will be performed when we have observed 198 control arm events (anticipated approximately 4.75 years after accrual starts). At this time, an observed HR of more than 0.887 for Arm B compared to control (Arm A) will be taken as an indication that there is insufficient benefit from durvalumab monotherapy. The stopping guideline for overwhelming benefit is to observe a p-value of less than 0.001 (one-sided).

A second interim analysis will be performed when we have observed 277 control arm events (anticipated approximately 6.25 years after accrual starts). At this time, an observed HR of more than 0.864 for Arm B compared to control (Arm A) will be taken as an indication that there is insufficient benefit from durvalumab monotherapy. The stopping guideline for overwhelming benefit is to observe a p-value of less than 0.001 (one-sided).

A third interim analysis will be performed when we have observed 332 control arm events (anticipated approximately 8 years after accrual starts). At this time, an observed HR of more than 0.854 for Arm B compared to control (Arm A) will be taken as an indication that there is insufficient benefit from durvalumab monotherapy. The stopping guideline for overwhelming benefit is to observe a p-value of less than 0.001 (one-sided).
### Table 18 Estimated Timeline of Primary Analyses in RAMPART

<table>
<thead>
<tr>
<th>TIME FROM RECRUITMENT START</th>
<th>ALPHA</th>
<th>POWER</th>
<th>CONTROL ARM DFS EVENTS</th>
<th>CONTROL ARM OS EVENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.25 years Arm C vs A</td>
<td>0.0097 (one-sided)</td>
<td>87.3%</td>
<td>276</td>
<td>86</td>
</tr>
<tr>
<td>10.5 years Arm B vs A</td>
<td>0.0097 (one-sided)</td>
<td>83.5%</td>
<td>416</td>
<td>190</td>
</tr>
</tbody>
</table>

**DISEASE FREE SURVIVAL**

<table>
<thead>
<tr>
<th>TIME FROM RECRUITMENT START</th>
<th>ALPHA</th>
<th>POWER</th>
<th>CONTROL ARM DFS EVENTS</th>
<th>CONTROL ARM OS EVENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.25 years Arm C vs A (high risk patients only)</td>
<td>0.0097 (one-sided)</td>
<td>80%</td>
<td></td>
<td>238</td>
</tr>
<tr>
<td>20.5 years Arm B vs A (high risk patients only)</td>
<td>0.0097 (one-sided)</td>
<td>80%</td>
<td></td>
<td>344</td>
</tr>
</tbody>
</table>

**OVERALL SURVIVAL**

<table>
<thead>
<tr>
<th>TIME FROM RECRUITMENT START</th>
<th>COMPARISON AND TYPE OF ANALYSIS</th>
<th>ALPHA</th>
<th>POWER</th>
<th>STOPPING GUIDELINE</th>
<th>CONTROL ARM DFS EVENTS</th>
<th>CONTROL ARM OS EVENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.75 years</td>
<td>C vs A and B vs A Overwhelming Benefit</td>
<td>0.001 (one-sided)</td>
<td>82%</td>
<td>p&lt;0.001</td>
<td>197</td>
<td>46</td>
</tr>
<tr>
<td>4.75 years</td>
<td>C vs A Lack of Benefit</td>
<td>0.05  (one-sided)</td>
<td>91.7%</td>
<td>HR &gt; 0.831</td>
<td>198</td>
<td>46</td>
</tr>
<tr>
<td>4.75 years</td>
<td>B vs A Lack of Benefit</td>
<td>0.143 (one-sided)</td>
<td>91.7%</td>
<td>HR &gt; 0.887</td>
<td>197</td>
<td>46</td>
</tr>
<tr>
<td>6.25 years</td>
<td>B vs A Overwhelming Benefit</td>
<td>0.001 (one-sided)</td>
<td>83.8%</td>
<td>p&lt;0.001</td>
<td>277</td>
<td>86</td>
</tr>
<tr>
<td>6.25 years</td>
<td>B vs A Lack of Benefit</td>
<td>0.062 (one-sided)</td>
<td>91.7%</td>
<td>HR &gt; 0.864</td>
<td>277</td>
<td>86</td>
</tr>
<tr>
<td>8 years</td>
<td>B vs A Overwhelming Benefit</td>
<td>0.001 (one-sided)</td>
<td>83.5%</td>
<td>p&lt;0.001</td>
<td>332</td>
<td>131</td>
</tr>
</tbody>
</table>

### 9.6.3 OVERALL SURVIVAL

Conditional on getting a signal in DFS, we will analyse OS using a closed test. The primary OS analysis will be in patients with Leibovich Score 6-11. The rationale for targeting OS in higher risk patients as the primary OS analysis is because competing causes of death in the intermediate risk group (Leibovich Score 3-5) are very likely to be large enough to dilute any treatment effect in this group of patients.

#### 9.6.3.A Combination durvalumab and tremelimumab versus control (Arm C vs Arm A)

With approximately 940 high-risk patients in the Arm C vs Arm A comparison, we will have 80% power to detect an HR of 0.7 around 13.25 years after the trial commences. This HR translates to an absolute difference in OS at 5 years of 6.5%, increasing survival from 76% to 82.5%.
9.6.3.B Durvalumab monotherapy versus control (Arm B vs Arm A)
With approximately 940 high-risk patients in the Arm B vs Arm A comparison, we will have 80% power to detect an HR of 0.75 approximately 20.5 years after the trial commences. This HR translates to an absolute difference in OS at 5 years of 5.4%, increasing survival from 76% to 81.4%.

For both comparisons, we use a one-sided significance level of 0.0097 as we assume that an additional arm will be added to RAMPART before the initial three arms complete accrual. If an additional arm is not added we can change the one-sided significance level to 0.014 and report the OS results for each comparison slightly earlier.

9.7 ANALYSIS PLAN (BRIEF)
The primary outcome analyses will be performed on an intention-to-treat basis.

The process for evaluating and analysing the co-primary outcomes of disease-free and OS will follow a slightly amended version of that proposed by Royston and Parmar (Stat. in Med. 2011), and will use the following steps:

1. The treatment effect for each of the two comparisons and each of the two outcomes will be assessed using a stratified Cox model (one-sided with a significance level of 0.0097, stratifying for the factors used in randomisation). Data will be presented graphically using Kaplan-Meier plots.
2. The proportional hazards assumption will be tested using the Grambsch-Therneau test. Additionally, the HR over time will be plotted, as estimated from a flexible parametric model with a time dependent treatment effect. The model will utilise 5 degrees of freedom for the baseline distribution, and 5 degrees of freedom for the time-dependent treatment effect.
3. If there is no clear evidence of non-proportional hazards, an HR and 95% CIs will be presented.
4. If there is evidence of non-proportional hazards, the restricted mean survival time (RMST) will also be calculated using the same flexible parametric model as described in step 2. The RMST analysis for DFS will use a t* of 6 years for the comparison of Arm C vs Arm A and a t* of 10 years for the comparison of Arm B vs Arm A.

If the proportional hazard assumption is not rejected, Cox regression analysis adjusting for additional important baseline covariates will be performed to assess the robustness of the results. This analysis will include the assessment of interactions between baseline covariates and treatment allocation. If the proportional hazards assumption is rejected then we shall use the flexible parametric model to undertake these analyses.

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. Included will be a subgroup analyses by PD-L1 baseline expression status.

Full details of all planned analyses will be documented in the RAMPART Statistical Analysis Plan.
9.7.1 Controlling the Family-wise Error Rate in RAMPART

In RAMPART, the family-wise error rate (FWER) is strongly controlled at 2.5% (one-sided) by applying Dunnett’s approach to the pairwise comparisons of each of the experimental arms to the control arm. The Dunnett approach is more efficient than a simple Bonferroni correction as it takes into account the correlation between the pairwise test statistics because of the shared control arm events between the pairwise comparisons, whereas the Bonferroni correction assumes their independence. For each pairwise comparison, we estimated the pairwise type I error rate (PWER) both analytically and using simulations. These estimates take into account the interim stage lack-of-benefit and overwhelming benefit stopping rules. Since the design incorporates the stopping boundaries for lack of benefit, the actual estimates of the PWER for each pairwise comparison are slightly smaller than the design significance level at the final stage, i.e. 0.0097, if a new research arm is added before the current three-arm design completes accrual. If a further arm is not added we can reclaim some of the unspent type I error. In the latter case, the final stage pairwise significance level that achieves the overall FWER of 2.5% (one-sided) is estimated at 0.014.

To estimate the FWER, we considered two different scenarios: A) the trial starts (and possibly concludes) with 2 research arms; and B) a new research arm is added before accrual to the current 3-arm trial completes. We applied Dunnett’s approach to numerically estimate the FWER in both scenarios A and B. For scenario B, the Dunnett approach can be amended to accurately estimate the FWER.

Full details of all planned analyses will be documented in the RAMPART Statistical Analysis Plan.
10 REGULATORY & ETHICAL ISSUES

10.1 COMPLIANCE

10.1.1 REGULATORY COMPLIANCE

The trial complies with the principles of the 1996 version of the Declaration of Helsinki.

RAMPART is an investigator-initiated academic platform trial. The trial will be initiated and conducted in compliance with the approved protocol, the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with the implementation in national legislation in the UK by Statutory Instrument 2004/1031 (The Medicines for Human Use [Clinical Trials] Regulations 2004) and subsequent amendments, the UK Data Protection Act (DPA number: Z5886415), and the NHS Research Governance Framework for Health and Social Care (RGF).

Sufficient elements will be put in place from the outset of the trial to enable compliance with full ICH GCP guidelines (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.

Scientific advice on the clinical trial protocol has been obtained from both the European Medicines Agency (EMA) and Food and Drug Administration (FDA).

10.1.2 SITE COMPLIANCE

UK sites will comply with the above. International collaborators shall be responsible for the operational management of RAMPART at their participating Clinical Sites and shall do so in compliance with the principles of Good Clinical Practice (GCP) as laid down by the ICH topic E6 (Note for Guidance on GCP), Commission Directive 2005/28/EC (the European Directive 2001/20/EC [where applicable]) and in accordance with applicable local laws or national regulations. An agreement will be in place between the collaborating organisations and the MRC CTU at UCL, setting out respective roles and responsibilities.

UK sites and international collaborators will inform the MRC CTU at UCL as soon as they are aware of a possible serious breach of compliance, so that the trial team can report this breach if necessary within 7 days as per the UK regulatory requirements. For the purposes of this regulation, a “serious breach” is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects in the trial, or
- The scientific value of the trial

10.1.3 DATA COLLECTION & RETENTION

CRFs, clinical notes and administrative documentation should be kept in a secure location (for example, locked filing cabinets in a room with restricted access) and held for a minimum of 15 years after the end of the trial. In some instances, documents may need to be retained for longer; refer to the UCL Records Retention Schedule for more detailed guidance. During this period, all data should be accessible to the competent or equivalent authorities, the Sponsor, and other relevant parties in accordance with the applicable regulations with suitable notice. The data may be subject to an audit by the competent authorities. Medical files of trial participants should be retained in accordance with the maximum period of time permitted by the hospital, institution or private practice.
10.1.4 Ethical Conduct of the Study

Before initiation of the trial at each clinical site, the protocol, all informed consent forms, and information materials to be given to the prospective participant will be submitted to all required ethics committees for approval. Any further amendments will also be submitted and approved all required ethics committees.

The rights of the participant to refuse to participate in the trial without giving a reason must be respected. After the participant has entered into the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the participant. The reason for doing so, however, should be recorded and the RAMPART Trial Management Team notified; the participant will remain within the trial for the purpose of follow-up and for data analysis by the treatment option to which they have been allocated. Similarly, the participant must remain free to change their mind at any time about the protocol treatment and trial follow-up without giving a reason and without prejudicing their further treatment.

10.2 Competent Authority Approvals

This protocol will be reviewed by the national competent or equivalent authority as appropriate in each country where the trial will be conducted.

This is a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC. Therefore, a CTA is required in the UK as are other country specific clinical trial authorisations as appropriate.

The EUdraCT number for the trial is 2017-002329-39.

The progress of the trial and safety issues will be reported to the competent authority, regulatory agency or equivalent in accordance with local requirements and practices in a timely manner.

Safety reports, including expedited reporting and SUSARS will be submitted to the competent authorities in accordance with each authority’s requirements in a timely manner.

10.3 Other Approvals

The protocol will be submitted by those delegated to do so to the relevant R&D department of each participating site or to other local departments for approval as required in each country. A copy of the HRA approval (or other relevant approval as above) and of the PIS and Consent Form (CF) on local headed paper should be forwarded to the MRC CTU at UCL before patients are entered.

Each participating site receiving funding or support from the US government will obtain a Federal Wide Assurance (FWA).

10.4 Trial Closure

The trial will close when all patients have completed follow-up and all data queries have been resolved.
11 INDEMNITY

The sponsor of the trial is the University College London (UCL). RAMPART is co-ordinated by the MRC CTU at UCL.

UCL holds insurance against claims from participants for injury caused by their participation in this clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial.

UCL does not accept liability for any breach in the hospital’s duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise. Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of UCL or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the UCL’s Insurers, via the UCL office.

Hospitals selected to participate in RAMPART must provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary can be provided on request.
12 FINANCE

RAMPART will be sponsored by UCL and co-ordinated by the MRC CTU at UCL in London. The trial is funded by Kidney Cancer UK (KCUK) and by an educational grant from AstraZeneca. AstraZeneca are also providing free durvalumab and tremelimumab.

The MRC CTU at UCL will have agreements with collaborating clinical organisations nationally and internationally. The agreements will set out the obligations of the parties, their respective roles and responsibilities and cover arrangements for budgets and financial transfers and reporting.

Participating institutions will be given payments per patient to cover the cost of additional tests and procedures associated with the implementation of the trial and management of the patients enrolled.
13 OVERSIGHT & TRIAL COMMITTEES

There are a number of committees involved with the oversight of the trial. These committees are detailed below, and the relationship between them expressed in Figure 2.

13.1 TRIAL MANAGEMENT GROUP (TMG)

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical), members of the MRC CTU at UCL trial team, PPI delegates and representatives from each international collaborative group. The TMG will be responsible for the day-to-day running and management of the trial and will meet approximately six times a year at least one of which will be in-person. The full details can be found in the TMG Charter.

13.2 TRIAL STEERING COMMITTEE (TSC)

The Trial Steering Committee (TSC) has membership from the TMG plus independent members, including the Chair. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chair. The ultimate decision for the continuation of the trial lies with the TSC. Further details of TSC functioning are presented in the TSC Charter.

13.3 INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

An Independent Data Monitoring Committee (IDMC) will be formed. The IDMC will be the only group who sees the confidential, accumulating data for the trial.

A statistician familiar with MRC CTU at UCL systems, the trial, and the trial database, but not involved in trial management or decision-making, will conduct the interim analyses and present them to the IDMC.

The IDMC will consider data using the statistical analysis plan and will advise the TSC. The IDMC can recommend premature closure or reporting of the trial, or that recruitment to any research arm is discontinued.

Further details of IDMC functioning and the procedures for interim analysis and monitoring are provided in the IDMC Charter.

13.4 ROLE OF STUDY SPONSOR

RAMPART is sponsored by UCL. The MRC CTU at UCL will have overall responsibility for the study design; obtaining and complying with the requirements of the relevant regulatory bodies; collection, management, analysis, and interpretation of data; writing of any reports; the decision to submit reports for publication, including who will have ultimate authority over each of these activities. It will work closely with the Chief Investigator, all members of the TMG, and all collaborators.
Figure 2  Relationship Between Trial Committees
14 PATIENT AND PUBLIC INVOLVEMENT (PPI)

The RAMPART Trial Management Group is committed to engage with the public and involve patient representatives in the development and conduct of the trial. For example, as part of the introduction to the TMG, new patient representatives might receive an overview on the trial to reflect on practice and assess strategies for trial-specific PPI activities.

The RAMPART trial has undergone scientific peer-review by Kidney Cancer UK which supports and endorses patient engagement in all parts of clinical research.

All patient representatives involved in RAMPART TMG activities are required to sign a Charter and disclose any potential conflict of interest. Signed charters are collated in the RAMPART TMF.

14.1 POTENTIAL IMPACT OF PPI

Continuous engagement with consumer group representatives will be a key aspect in the conduct of the trial. The novel nature of the investigational products being investigated requires vigilance on safety not only from a clinical perspective but also from a patient one. A key role will also be the promotion of the trial at start-up and ongoing engagement with relevant patient groups and charities that might wish to know about trial progress.

14.2 PPI IN THE ONGOING RUNNING OF THE TRIAL

Patient representatives will form part of the Trial Management Group membership and will be invited to attend all TMG meetings/teleconferences. The PPI delegates will be actively involved in discussions focusing on the progress and conduct of the trial.

PPI delegates will also form part of the MRC CTU Genitourinary TSC and will be invited to attend all TSC meetings/teleconferences and will be actively involved in discussions on trial progress and IDMC recommendations.

14.3 INTERPRETING AND PLANNING DESEMINATION OF TRIAL RESULTS

PPI delegates will be actively involved in the discussion of results emerging from the trial, and will be involved in reviewing the communications plan. Patient roadshows, results summaries and newsletters may also be developed by the trial management team with the support of PPI delegates.
15 PUBLICATION

The results for each comparison within RAMPART will be analysed separately when appropriate and according to pre-defined criteria developed from the MAMS design. The results from RAMPART analyses will be published when appropriate and possible. Individual clinicians must not publish data concerning their patients that are directly relevant to questions being addressed in RAMPART until the TMG has published its final report. The TMG will form the basis of the writing committee and decide on the nature of the publications.

All publications shall include a list of investigators (participating clinicians, nurses, pathologists etc) and if there are named authors, these should include at least the Chief Investigator, Project Lead, Statisticians and Trial Managers. If there are no named authors (i.e., group authorship) then a writing committee that includes at least the Chief Investigator and Trial Management Group members will be identified that would usually include these people.

The ISRCTN number ISRCTN53348826 that has been allocated to this trial should be attached to any publications resulting from this trial. Acknowledgement of funding along with any disclaimers required by the funding bodies must also be added to any publications.

The members of the TSC and IDMC should be listed with their affiliations in the Acknowledgements or Appendix of the main publication.
16 PROTOCOL AMENDMENTS

Not yet applicable.
APPENDIX A - COMPARATIVE TABLE OF SYMPTOMS REPORTED BY PATIENTS TREATED WITH DURVALUMAB AND TREMELIMUMAB

The table below details known adverse reactions as reported in the IBs for durvalumab and tremelimumab.

Adverse reactions listed using the following convention:
1. Very common (>1/10)
2. Common (>1/100, <1/10)
3. Uncommon (>1/1,000, <1/100)
4. Rare (>1/10,000, <1/1,000)
5. Very rare (<1/10,000)

<table>
<thead>
<tr>
<th>BODY SYSTEM</th>
<th>SYMPTOM</th>
<th>DURVALUMAB</th>
<th>TREMELIMUMAB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system</td>
<td>Anaemia</td>
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<td>Uncommon</td>
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<td>Acute coronary syndrome</td>
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<td>Cardiac failure congestive</td>
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<td>Myocardial infarction</td>
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<td>Ventricular arrhythmia</td>
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<td>Adrenal insufficiency</td>
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<td>Symptom</td>
<td>Durvalumab</td>
<td>Tremelimumab</td>
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<td>Body System</td>
<td>Symptom</td>
<td>Durvalumab</td>
<td>Tremelimumab</td>
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<td>Haematuria</td>
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<td>Productive cough</td>
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<td>Bronchial infection</td>
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<td>Skin</td>
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<td>Alopecia</td>
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<td></td>
<td>Rash maculo-papular</td>
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<tr>
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<td>Rash pruritic</td>
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<td>Blister</td>
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<td>Pruritus</td>
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<td>Dry skin</td>
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<td>Dermatitis</td>
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<td>Erythema</td>
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<td>Vascular disorders</td>
<td>Night sweats</td>
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<td>Hypertension</td>
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<td>Flushing</td>
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<td>SYMPTOM</td>
<td>DURVALUMAB</td>
<td>TREMELIMUMAB</td>
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</tr>
<tr>
<td></td>
<td>Pulmonary embolism</td>
<td>Uncommon</td>
<td>Rare</td>
</tr>
</tbody>
</table>
## General Considerations

### Dose Modifications

Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03. In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions:

- Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** after last dose of study drug/study regimen
- Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>No dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2</td>
<td>Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilises to Grade ≤1 after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions:</td>
</tr>
<tr>
<td></td>
<td>The event stabilizes and is controlled.</td>
</tr>
<tr>
<td></td>
<td>The patient is clinically stable as per Investigator or treating physician’s clinical judgement.</td>
</tr>
</tbody>
</table>

### Toxicity Management

It is recommended that management of irAEs follows the guidelines presented in this table:

- It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines.
- Whether events are noted specifically in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative aetiology (e.g., disease progression, concomitant medications, and infections).
- In the absence of a clear alternative aetiology, all events should be considered potentially immune related.
- Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events.
- For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.
- Some events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Discuss these events with the study physician, and promptly pursue subspecialty consultation.
- If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement.

---

| Grade 3 | Hold study drug/study regimen dose until Grade 3 resolution to Grade ≤1. If toxicity worsens, then treat as Grade 4. Study drug/study regimen can be resumed once event stabilises to Grade ≤1 after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: |
|         | The event stabilizes and is controlled. |
|         | The patient is clinically stable as per Investigator or treating physician’s clinical judgement. |

| Grade 4 | Hold study drug/study regimen dose until Grade 4 resolution to Grade ≤1. If toxicity worsens, then treat as Grade 5. Study drug/study regimen can be resumed once event stabilises to Grade ≤1 after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: |
|         | The event stabilizes and is controlled. |
|         | The patient is clinically stable as per Investigator or treating physician’s clinical judgement. |

| Grade 5 | Hold study drug/study regimen dose until Grade 5 resolution to Grade ≤1. If toxicity worsens, then treat as Grade 6. Study drug/study regimen can be resumed once event stabilises to Grade ≤1 after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: |
|         | The event stabilizes and is controlled. |
|         | The patient is clinically stable as per Investigator or treating physician’s clinical judgement. |

---

### Table: Toxicity Management Guidelines

<table>
<thead>
<tr>
<th>Grade</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>No dose modification</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilises to Grade ≤1 after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions:</td>
</tr>
<tr>
<td></td>
<td>The event stabilizes and is controlled.</td>
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<tr>
<td></td>
<td>The patient is clinically stable as per Investigator or treating physician’s clinical judgement.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Hold study drug/study regimen dose until Grade 3 resolution to Grade ≤1. If toxicity worsens, then treat as Grade 4. Study drug/study regimen can be resumed once event stabilises to Grade ≤1 after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions:</td>
</tr>
<tr>
<td></td>
<td>The event stabilizes and is controlled.</td>
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<td></td>
<td>The patient is clinically stable as per Investigator or treating physician’s clinical judgement.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Hold study drug/study regimen dose until Grade 4 resolution to Grade ≤1. If toxicity worsens, then treat as Grade 5. Study drug/study regimen can be resumed once event stabilises to Grade ≤1 after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions:</td>
</tr>
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<td></td>
<td>The event stabilizes and is controlled.</td>
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<td></td>
<td>The patient is clinically stable as per Investigator or treating physician’s clinical judgement.</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Hold study drug/study regimen dose until Grade 5 resolution to Grade ≤1. If toxicity worsens, then treat as Grade 6. Study drug/study regimen can be resumed once event stabilises to Grade ≤1 after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions:</td>
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<tr>
<td></td>
<td>The event stabilizes and is controlled.</td>
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<td></td>
<td>The patient is clinically stable as per Investigator or treating physician’s clinical judgement.</td>
</tr>
<tr>
<td>Grade 6</td>
<td>Hold study drug/study regimen dose until Grade 6 resolution to Grade ≤1. If toxicity worsens, then treat as Grade 7. Study drug/study regimen can be resumed once event stabilises to Grade ≤1 after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions:</td>
</tr>
<tr>
<td></td>
<td>The event stabilizes and is controlled.</td>
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<tr>
<td></td>
<td>The patient is clinically stable as per Investigator or treating physician’s clinical judgement.</td>
</tr>
</tbody>
</table>
### GENERAL CONSIDERATIONS

<table>
<thead>
<tr>
<th>DOSE MODIFICATIONS</th>
<th>TOXICITY MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doses of prednisone are at ≤10 mg/day or equivalent.</td>
<td>of symptoms, then resume corticosteroid tapering at a slower rate (&gt;28 days of taper).</td>
</tr>
<tr>
<td><strong>Grade 3</strong> Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below.</td>
<td><strong>Grade 4</strong> Permanently discontinue study drug/study regimen.</td>
</tr>
<tr>
<td><strong>Note:</strong> For Grade ≥3 asymptomatic amylase or lipase levels, hold study drug/study regimen and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed. <strong>Note:</strong> For Grade 3 and above asymptomatic amylase or lipase levels hold study drug/study regimen and if complete work up shows no evidence of pancreatitis, may continue or resume study drug/study regimen. <strong>Note:</strong> Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids.</td>
<td><strong>Note:</strong> More potent immunosuppressives such as TNF inhibitors (e.g., infliximab) (also refer to the individual sections of the irAE for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids.</td>
</tr>
<tr>
<td><strong>Note:</strong> Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids.</td>
<td><strong>With long-term steroid and other immunosuppressive use, consider need for pneumocystis jirovecii pneumonia (PJP, formerly known as pneumocystis carinii pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring.</strong></td>
</tr>
<tr>
<td><strong>Discontinuation of study drug/study regimen is not mandated for Grade 3 inflammatory reactions attributed to local tumour response (e.g., inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit-risk analysis for that patient.</strong></td>
<td><strong>Discontinuation of study drug/study regimen is not mandated for Grade 3 inflammatory reactions attributed to local tumour response (e.g., inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit-risk analysis for that patient.</strong></td>
</tr>
</tbody>
</table>

AE Adverse event; CTC Common Toxicity Criteria; CTCAE Common Terminology Criteria for Adverse Events; irAE Immune-related adverse event; IV intravenous; NCI National Cancer Institute; PO By mouth.
### SPECIFIC IMMUNE-MEDIATED REACTIONS

<table>
<thead>
<tr>
<th>ADVERSE EVENTS</th>
<th>SEVERITY GRADE OF THE EVENT (NCI CTCAE VERSION 4.03)</th>
<th>DOSE MODIFICATIONS</th>
<th>TOXICITY MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis/ILD</td>
<td>Any Grade</td>
<td>General Guidance</td>
<td>For Any Grade:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below.</td>
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<td></td>
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<td>- Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high-resolution CT scan.</td>
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<tr>
<td></td>
<td>Grade 1: (asymptomatic, clinical or diagnostic observations only; intervention not indicated)</td>
<td>No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other aetiologies.</td>
<td>For Grade 1 (radiographic changes only):</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>- Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated.</td>
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<tr>
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<td></td>
<td></td>
<td>- Consider pulmonary and infectious disease consult.</td>
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<tr>
<td></td>
<td>Grade 2: (symptomatic; medical intervention indicated; limiting instrumental ADL)</td>
<td>Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1.</td>
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<tr>
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<td></td>
<td>- If toxicity worsens, then treat as Grade 3 or Grade 4.</td>
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<tr>
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<td></td>
<td>- If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician’s clinical judgment and after completion of steroid taper.</td>
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<td>For Grade 2 (mild to moderate new symptoms):</td>
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<tr>
<td></td>
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<td>- Monitor symptoms daily and consider hospitalization.</td>
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<td></td>
<td>- Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent).</td>
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<td>- Reimage as clinically indicated.</td>
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<td></td>
<td>- If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started</td>
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<td></td>
<td></td>
<td>- If still no improvement within 3 to 5 days despite IV methylprednisone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is</td>
</tr>
</tbody>
</table>
**Diarrhea/Enterocolitis**

| Grade 3 or 4: (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) | Permanently discontinue study drug/study regimen. | For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):
- Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent.
- Obtain pulmonary and infectious disease consult.
- Hospitalize the patient.
- Supportive care (e.g., oxygen).
- If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks’ dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab.
- Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).a

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**Grade 3 or 4:**

- (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated)
- (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [e.g., tracheostomy or intubation])

**Diarrhea/Enterocolitis**

<table>
<thead>
<tr>
<th>Any Grade</th>
<th>General Guidance</th>
</tr>
</thead>
</table>
| - Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus).
- Patients should be thoroughly evaluated to rule out any...
alternative aetiology (e.g., disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc.
- Steroids should be considered in the absence of clear alternative aetiology, even for low-grade events, in order to prevent potential progression to higher grade event.
- Use analgesics carefully; they can mask symptoms of perforation and peritonitis.

| Grade 1: (stool frequency of <4 over baseline per day) | No dose modifications. | - Monitor closely for worsening symptoms.
- Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician’s clinical judgment. |

| Grade 2: (stool frequency of 4 to 6 over baseline per day) | - Hold study drug/study regimen until resolution to Grade ≤1
- If toxicity worsens, then treat as Grade 3 or Grade 4.
- If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper. | - Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide.
- Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.
- If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started.
- If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeks. Caution: it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab.
- Consult study physician if no resolution to Grade ≤1 in 3 to 4 days.
- Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-
<table>
<thead>
<tr>
<th>Grade 3 or 4: (Grade 3: stool frequency of ≥7 over baseline per day; Grade 4: life threatening consequences)</th>
<th>Grade 3 or 4: Permanently discontinue study drug/study regimen.</th>
<th>Grade 3 or 4:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent.</td>
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<tr>
<td>• Monitor stool frequency and volume and maintain hydration.</td>
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<tr>
<td>• Urgent GI consult and imaging and/or colonoscopy as appropriate.</td>
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<tr>
<td>• If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (e.g., infliximab at 5 mg/kg once every 2 weeks). <strong>Caution:</strong> Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab.</td>
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<tr>
<td>• Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).^a</td>
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</tr>
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</table>

**Hepatitis (elevated LFTs)**

Infliximab should not be used for management of immune-related hepatitis.

<table>
<thead>
<tr>
<th>Any Grade</th>
<th>General Guidance</th>
<th>PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1: (AST or ALT &gt;ULN and ≤3.0×ULN and/or TB &gt; ULN and ≤1.5×ULN)</td>
<td>• No dose modifications.</td>
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<tr>
<td></td>
<td>• If it worsens, then treat as Grade 2 event.</td>
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<td></td>
<td>Continue LFT monitoring per protocol.</td>
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<tr>
<td>Grade 2: (AST or ALT &gt;3.0×ULN and ≤5.0×ULN and/or TB &gt;1.5×ULN and ≤3.0×ULN)</td>
<td>• Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1.</td>
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<tr>
<td></td>
<td>• If toxicity worsens, then treat as Grade 3 or Grade 4.</td>
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<tr>
<td></td>
<td>• If toxicity improves to Grade</td>
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</tr>
<tr>
<td></td>
<td>Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until elevations of these are improving or resolved.</td>
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<td></td>
<td>• If no resolution to Grade ≤1 in 1 to 2 days, discuss with study physician.</td>
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<tr>
<td></td>
<td>• If event is persistent (&gt;3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.</td>
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</table>
≤1 or baseline, resume study drug/study regimen after completion of steroid taper.

- If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day.
- If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (mycophenolate mofetil). Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
- Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).

For Grade 3 or 4:
- Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent.
- If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
- Perform hepatology consult, abdominal workup, and imaging as appropriate.
- Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).

<table>
<thead>
<tr>
<th>Grade 3: (AST or ALT &gt;5.0×ULN and ≤20.0×ULN and/or TB &gt;3.0×ULN and ≤10.0×ULN)</th>
<th>For Grade 3: For elevations in transaminases ≤8 × ULN, or elevations in bilirubin ≤5 × ULN:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline</td>
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<tr>
<td>- Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper.</td>
<td></td>
</tr>
<tr>
<td>- Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days For elevations in transaminases &gt;8 × ULN or elevations in bilirubin</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 4: (AST or ALT &gt;20×ULN and/or TB &gt;10×ULN)</th>
<th>For Grade 3 or 4:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent.</td>
<td></td>
</tr>
<tr>
<td>- If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate mofetil is not available. <strong>Infliximab should NOT be used.</strong></td>
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<tr>
<td>- Perform hepatology consult, abdominal workup, and imaging as appropriate.</td>
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<tr>
<td>- Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).</td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>Grade 1: (Serum creatinine &gt; 1 to 1.5 × baseline; &gt; ULN to 1.5 × ULN)</td>
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<tr>
<td>------------------------------------------------</td>
<td>---------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Nephritis or renal dysfunction (elevated serum creatinine) | No dose modifications.                                               | Any Grade | - Consult with nephrologist.  
- Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria).  
- Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression or infections).  
- Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event. |
|                                                |                                                                     |           | - Monitor serum creatinine weekly and any accompanying symptoms.  
- If creatinine returns to baseline, resume its regular monitoring per study protocol.  
- If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4.  
- Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. |
| Grade 2: (serum creatinine >1.5 to 3.0 × baseline; >1.5 to 3.0 × ULN) | Hold study drug/study regimen until resolution to Grade ≤1 or baseline.  
• If toxicity worsens, then treat as Grade 3 or 4.  
• If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper. | • Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.  
• Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted.  
• Consult nephrologist and consider renal biopsy if clinically indicated.  
• If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.  
• If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started.  
• Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).  
• When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol. |
| Grade 3 or 4: (Grade 3: serum creatinine >3.0 × baseline; >3.0 to 6.0 × ULN;  
Grade 4: serum creatinine >6.0 × ULN) | Grade 3 or 4: Permanently discontinue study drug/study regimen. | For Grade 3 or 4:  
• Carefully monitor serum creatinine on daily basis.  
• Consult nephrologist and consider renal biopsy if clinically indicated.  
• Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.  
• If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started.  
• Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).
| Rash (excluding bullous skin formations) | Any Grade: (refer to NCI CTCAE v 4.03 for definition of severity/grade depending on type of skin rash) | General Guidance | • Monitor for signs and symptoms of dermatitis (rash and pruritus).
• If there is any bullous formation, the study physician should be contacted and study drug discontinued. |
| --- | --- | --- | |
| Grade 1 | No dose modifications. | Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream). | |
| Grade 2 | For persistent (>1 to 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline.  
• If toxicity worsens, then treat as Grade 3.  
• If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper. | • Obtain dermatology consult.  
• Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream).  
• Consider moderate-strength topical steroid.  
• If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, discuss with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent.  
• Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs. | |
| Grade 3 or 4 | **For Grade 3:**  
Hold study drug/study regimen until resolution to Grade ≤1 or baseline.  
If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days, then permanently discontinue study drug/study regimen.  
| **For Grade 3 or 4:**  
• Consult dermatology.  
• Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent.  
• Consider hospitalization.  
• Monitor extent of rash [Rule of Nines].  
• Consider skin biopsy (preferably more than 1) as clinically feasible.  
• Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti- |
| Endocrinopathy (e.g., hyperthyroidism, hypothyroidism, hypopituitarism, and adrenal insufficiency) | For Grade 4:  
Permanently discontinue study drug/study regimen. | PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).
- Discuss with study physician. |
| --- | --- | --- |
| Any Grade:  
(depending on the type of endocrinopathy, refer to NCI CTCAE v4.03 for defining the CTC grade/severity) | General Guidance | • Consult endocrinologist.  
- Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behaviour changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension, and weakness.  
- Patients should be thoroughly evaluated to rule out any alternative aetiology (e.g., disease progression including brain metastases, or infections).  
- Monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine labs depending on suspected endocrinopathy.  
- If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing. |
| Grade 1 | No dose modifications. | For Grade 1 (including those with asymptomatic TSH elevation):
- Monitor patient with appropriate endocrine function tests.  
- If TSH < 0.5 × LLN, or TSH >2 × ULN or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider endocrinology consult. |
| Grade 2 | Endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until patient is clinically stable. If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes | For Grade 2 (including those with symptomatic endocrinopathy):
- Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids.  
- Initiate hormone replacement as needed for management.  
- Evaluate endocrine function, and as clinically indicated, consider pituitary scan. |
and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions:

1. The event stabilizes and is controlled.
2. The patient is clinically stable as per investigator or treating physician’s clinical judgement.
3. Doses of prednisone are ≤10 mg/day or equivalent.

- For patients with abnormal endocrine work up, except for those with isolated hypothyroidism, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., levothyroxine, hydrocortisone, or sex hormones).

- Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).

- For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.

<table>
<thead>
<tr>
<th>Grade 3 or 4</th>
<th>Endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Consult endocrinologist.</td>
</tr>
<tr>
<td></td>
<td>- Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids.</td>
</tr>
<tr>
<td></td>
<td>- Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent</td>
</tr>
<tr>
<td></td>
<td>- Administer hormone replacement therapy as necessary.</td>
</tr>
<tr>
<td></td>
<td>- For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity.</td>
</tr>
<tr>
<td></td>
<td>- Once the patient is improving, gradually taper immunosuppressive steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).</td>
</tr>
<tr>
<td></td>
<td>• Discuss with study physician.</td>
</tr>
</tbody>
</table>

- For patients with abnormal endocrine workup, except for those with isolated hypothyroidism, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., levothyroxine, hydrocortisone, or sex hormones).

- Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).
| **Neurotoxicity**
| (to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre) |
| **Any Grade:**
| (depending on the type of neurotoxicity, refer to NCI CTCAE v4.03 for defining the CTC grade/severity) |
| **General Guidance** |
| • Patients should be evaluated to rule out any alternative aetiology (e.g., disease progression, infections, metabolic syndromes, or medications). |
| • Monitor patient for general symptoms (headache, nausea, vertigo, behaviour change, or weakness). |
| • Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). |
| • Perform symptomatic treatment with neurological consult as appropriate. |

| **Grade 1** |
| No dose modifications. |
| See “Any Grade” recommendations above. |

| **Grade 2** |
| For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1. For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or 4. Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of steroid taper. |
| • Discuss with the study physician. |
| • Obtain neurology consult. |
| • Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). |
| • Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. |
| • If no improvement within 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (e.g., IV IG). |

| **Grade 3 or 4** |
| For Grade 3: Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 irAE does not resolve to Grade ≤1 within 30 days. |
| For Grade 3 or 4: |
| • Discuss with study physician. |
| • Obtain neurology consult. |
| • Consider hospitalization. |
| • Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. |
| • If no improvement within 3 to 5 days despite IV corticosteroids, |
### Grade 4

**For Grade 4:**

- Permanently discontinue study drug/study regimen.
- Consider additional workup and promptly treat with additional immunosuppressants (e.g., IV IG).
- Once stable, gradually taper steroids over ≥28 days.

### General Guidance

- The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability.

- Patients should be evaluated to rule out any alternative aetiology (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult.

- Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and “repetitive stimulation” if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation.

- It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.

### Any Grade

**Peripheral neuromotor syndromes**

(such as Guillain-Barre and myasthenia gravis)

### Grade 1

**No dose modifications.**

- Discuss with the study physician.
- Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above.
- Obtain a neurology consult unless the symptoms are very minor.
| Grade 2      | Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. | • Discuss with the study physician.  
• Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above.  
• Obtain a neurology consult  
• Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine).  
**MYASTHENIA GRAVIS:**  
 o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist.  
 o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient.  
 o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis.  
**GUILLAIN-BARRE:**  
 o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective.  
 o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG. |
| Grade 3 or 4 | For Grade 3: Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 irAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. | For Grade 3 or 4:  
• Discuss with study physician.  
• Recommend hospitalization.  
• Monitor symptoms and obtain neurological consult.  
**MYASTHENIA GRAVIS:**  
 o Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting.
of respiratory insufficiency or autonomic instability.

**For Grade 4:**
Permanently discontinue study drug/study regimen.

under supervision of a consulting neurologist.
- Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG.
- If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis.

**GUILLAIN-BARRE:**
- It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective.
- Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.

### Myocarditis

<table>
<thead>
<tr>
<th>Any Grade</th>
<th>General Guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Guidance</strong></td>
<td></td>
</tr>
</tbody>
</table>
- The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function.
- Discuss with the study physician.
- Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures.
- Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed.
- Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications,
<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2: Symptoms with mild to moderate activity or exertion</th>
<th>Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated</th>
<th>Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.</td>
<td>Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician’s clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently discontinue study drug/study regimen.</td>
<td>Permanently discontinue study drug/study regimen.</td>
<td>Permanently discontinue study drug/study regimen.</td>
</tr>
</tbody>
</table>

**For Grade 1 (no definitive findings):**
- Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated.
- Consider using steroids if clinical suspicion is high.

**For Grade 2:**
- Monitor symptoms daily, hospitalize.
- Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy.
- Supportive care (e.g., oxygen).
- If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.
- Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).

**For Grade 3-4:**
- Monitor symptoms daily, hospitalize.
- Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy.
- Supportive care (e.g., oxygen).
- If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.
- Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).

\(^{a}\text{a}^{\text{a}}\)
AChE Acetylcholine esterase; ADL Activities of daily living; AE Adverse event; ALP Alkaline phosphatase test; ALT Alanine aminotransferase; AST Aspartate aminotransferase; BUN Blood urea nitrogen; CT Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; ILD Interstitial lung disease; irAE Immune-related adverse event; IG Immunoglobulin; IV Intravenous; GI Gastrointestinal; LFT Liver function tests; LLN Lower limit of normal; MRI Magnetic resonance imaging; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; PJP Pneumocystis jirovecii pneumonia (formerly known as pneumocystis carinii pneumonia); PO By mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.
<table>
<thead>
<tr>
<th>Severity Grade of the Event (NCI CTCAE Version 4.03)</th>
<th>Dose Modifications</th>
<th>Toxicity Management</th>
</tr>
</thead>
</table>
| Any Grade                                           | General Guidance   | • Manage per institutional standard at the discretion of investigator.  
|                                                    |                    | • Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnoea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia). |
| Grade 1 or 2                                        | For Grade 1:       | For Grade 1 or 2:    |
|                                                    | The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. | • Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator.     |
|                                                    | For Grade 2:       | • Consider premedication per institutional standard prior to subsequent doses. |
|                                                    | The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. | • Steroids should not be used for routine premedication of Grade ≤2 infusion reactions. |
|                                                    | Subsequent infusions may be given at 50% of the initial infusion rate. | |
| Grade 3 or 4                                        | Permanently discontinue study drug/study regimen. | Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid). |

CTCAE Common Terminology Criteria for Adverse Events; IM Intramuscular; IV Intravenous; NCI National Cancer Institute.
<table>
<thead>
<tr>
<th>Severity Grade of the Event (NCI CTCAE Version 4.03)</th>
<th>Dose Modifications</th>
<th>Toxicity Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade</td>
<td>Note: Dose modifications are not required for AEs not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.</td>
<td>Treat accordingly, as per institutional standard.</td>
</tr>
<tr>
<td>Grade 1</td>
<td>No dose modifications.</td>
<td>Treat accordingly, as per institutional standard.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.</td>
<td>Treat accordingly, as per institutional standard.</td>
</tr>
</tbody>
</table>
| Grade 3                                             | • Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.  
• For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen. | Treat accordingly, as per institutional standard. |
| Grade 4                                             | Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator’s clinical judgment, and consultation with the Sponsor.). | Treat accordingly, as per institutional standard. |

Note: As applicable, for early phase studies, the following sentence may be added: “Any event greater than or equal to Grade 2, please discuss with Study Physician.”

AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.
APPENDIX C – THE LEIBOVICH RISK MODEL FOR PREDICTION OF PROGRESSION AFTER RADICAL NEPHRECTOMY FOR CLEAR CELL RENAL CELL CARCINOMA

This model is derived from the clinical outcome of 1671 patients with clinically localised, unilateral clear cell RCC who underwent radical nephrectomy between 1970 and 2000. A large number of clinical and pathological features were assessed. Metastases-free survival was estimated using the Kaplan-Meier method. A multivariate Cox proportional hazards regression model was used to determine associations between the clinical and pathological features and distant metastases. The median follow-up was 5.4 years. Metastases occurred in 479 patients at a median of 1.3 years after nephrectomy. Multivariate analysis showed that the features in the table below were associated with progression to metastases (P<0.001 for all). The Leibovich score has subsequently been adopted within routine clinical practice worldwide and undergone independent validation (49). Although Leibovich score has only been validated in clear cell RCC it will also be employed to risk stratify patients with non-clear cell RCC.

**RISK SCORING**

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathological T category of primary tumour</td>
<td></td>
</tr>
<tr>
<td>pT1a</td>
<td>0</td>
</tr>
<tr>
<td>pT1b</td>
<td>2</td>
</tr>
<tr>
<td>pT2</td>
<td>3</td>
</tr>
<tr>
<td>pT3a-4</td>
<td>4</td>
</tr>
<tr>
<td>Regional lymph node status</td>
<td></td>
</tr>
<tr>
<td>pNx or pN0</td>
<td>0</td>
</tr>
<tr>
<td>pN1-pN2</td>
<td>2</td>
</tr>
<tr>
<td>Tumour size</td>
<td></td>
</tr>
<tr>
<td>&lt;10cms</td>
<td>0</td>
</tr>
<tr>
<td>10cms or more</td>
<td>1</td>
</tr>
<tr>
<td>Nuclear grade</td>
<td></td>
</tr>
<tr>
<td>1 or 2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Histological tumour necrosis</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
</tr>
</tbody>
</table>

**RISK GROUPS**

<table>
<thead>
<tr>
<th>SCORES</th>
<th>GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>Low-risk</td>
</tr>
<tr>
<td>3-5</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>6 or more</td>
<td>High-risk</td>
</tr>
</tbody>
</table>

Pathologists should inspect kidneys removed for cancer and record the following:

- Tumour size
- Direct spread to the adrenal gland or presence of adrenal metastasis
- Invasion into the renal vein or its segmental branches.

Following inspection of the specimen, specific areas for histological examination are selected to collect clinically relevant data. The following items are required for calculating the Leibovich score:

- Local staging
• Regional lymph node status (N category) including number involved relative to total
• Maximum diameter of tumour (cm)
• Nuclear Grade
• Histological tumour necrosis (see below)

Other items that are routinely recorded (according to current WHO classification): histological sub-type, nucleolar grade, microvascular invasion and margin status.

HISTOLOGICAL TUMOUR NECROSIS

Histological tumour necrosis is defined as the presence of any microscopic, coagulative tumour necrosis and is distinguished from degenerative changes such as hyalinisation, haemorrhage and fibrosis.

TUMOUR GRADING

The grading system is slightly different to the current UK recommendations of concurrent use of Fuhrman and ISUP nucleolar grade, and is therefore provided below (50) The overall grade is the highest present if it occupies at least one high power field (0.55 mm at x400 magnification). Adequate sampling is essential, taking care to include all areas with different macroscopic appearances and areas adjacent to foci of necrosis.

SYSTEM USED TO DEFINE NUCLEAR GRADE

<table>
<thead>
<tr>
<th>GRADE</th>
<th>FUHRMAN GRADE</th>
<th>ISUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Small nuclei (10 microns) with round uniform nuclei, inconspicuous nucleoli</td>
<td>tumours were defined as having inconspicuous or absent nucleoli at x400 magnification</td>
</tr>
<tr>
<td>2</td>
<td>Larger nuclei (15 microns) slightly irregular and with small nucleoli visible at x400.</td>
<td>nucleoli should be distinctly visible at x400, but inconspicuous or invisible at x100 magnification;</td>
</tr>
<tr>
<td>3</td>
<td>Larger nuclei (20 microns) with irregular outlines and large prominent nucleoli at x100</td>
<td>nucleoli should be distinctly visible at x100 magnification.</td>
</tr>
<tr>
<td>4</td>
<td>Pleomorphic nuclei, e.g., polylolated</td>
<td>tumours with extreme nuclear pleomorphism and those showing rhabdoid or sarcomatoid differentiation</td>
</tr>
</tbody>
</table>

Microvascular invasion is not part of the algorithm, but has been associated with increased risk. As a potential confounder therefore, it should be recorded.

SAMPLING PARAFFIN SECTIONS

Local protocols should be modified if necessary to ensure that the presence or absence of relevant features are documented, selecting blocks for maximum efficiency and clearly labelling their site of origin, in order to microscopically type, stage and grade the tumour:

• Tumour blocks (at least 1 per cm), including all areas with a different gross appearance
• Tumour and adjacent necrosis (often areas of high-grade)
• Tumour and its interface with:
  o normal parenchyma
o renal sinus (the renal sinus should be adequately sampled even if the tumour is distant from it, for microvascular invasion)
o perinephric fat, to include the closest surgical margin and the adrenal gland if adjacent
o renal pelvis

- The renal vein to confirm involvement if seen grossly and also a section of the renal vein margin.
- Nodal masses in the hilar region
- The adrenal gland (if not adjacent to the tumour, for metastatic spread)
- The ureteric surgical margin

### TNM PATHOLOGICAL STAGING (7TH EDITION, UICC)

<table>
<thead>
<tr>
<th>PRIMARY TUMOUR (pT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pTx</td>
</tr>
<tr>
<td>pT0</td>
</tr>
<tr>
<td>pT1</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>pT2</td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td>pT3</td>
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<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>pT4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>REGIONAL LYMPH NODES (pN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pNx</td>
</tr>
<tr>
<td>pN0</td>
</tr>
<tr>
<td>pN1</td>
</tr>
</tbody>
</table>
## APPENDIX D– WHO PERFORMANCE STATUS

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Able to carry out all normal activity without restriction.</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out light work.</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.</td>
</tr>
<tr>
<td>3</td>
<td>Capable only of limited self-care; confined to bed or chair more than 50% of waking hours.</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled; cannot carry out any self-care; totally confined to bed or chair.</td>
</tr>
</tbody>
</table>
APPENDIX E– PREFERENCES FOR ADJUVANT IMMUNOTHERAPY IN RAMPART (PAIR)

BACKGROUND AND RATIONALE

RAMPART will determine the effectiveness of adjuvant immunotherapy with durvalumab and tremelimumab in high and intermediate risk renal cell carcinoma. Preference studies determine the benefits that patients judge sufficient to make a treatment worthwhile (51-54). The minimum benefits judged sufficient to make adjuvant therapy worthwhile are usually small. For example, 50-70% of women having adjuvant chemotherapy for early breast cancer judged a 1% improvement in 5 year survival rate sufficient to make it worthwhile (54) There are no published studies of preferences for immunotherapy in cancer.

AIM

To determine the survival benefits judged sufficient to make adjuvant immunotherapy worthwhile (preferences), and factors associated with these preferences.

OBJECTIVES

The PAIR study will look to determine the:

**PRIMARY**
1. Preferences of patients experiencing adjuvant immunotherapy.
2. Baseline characteristics associated with patients’ preferences.
3. Differences in preferences after experiencing immunotherapy.

**SECONDARY**
4. Differences in preferences according to treatment group.
5. Differences in preferences between patients and doctors.

**TERTIARY**
6. Differences in preferences between RAMPART and SORCE trials.
7. Differences in preferences among cohorts with renal, lung, breast and colon cancers.

HYPOTHESES

The minimum benefit judged sufficient will be:

1. Modest for patients (median absolute benefits of 5% or less in survival rate and 12 months or less in survival time).
2. Smaller for patients with dependants or who feel better supported.
3. Similar before and after experiencing immunotherapy.
4. Larger after treatment with durvalumab and tremelimumab than with durvalumab alone.
5. Smaller for patients allocated observation than immunotherapy.
6. Larger for doctors than for patients.
7. Smaller for medical oncologists than urologists.
8. Smaller for patients treated with immunotherapy than sorafenib.
9. Similar for patients with renal cancer considering adjuvant immunotherapy to patients considering adjuvant chemotherapy for either breast or colorectal cancer.
10. Smaller for patients with renal cancer than for patients with lung cancer treated with adjuvant immunotherapy.
**POPULATION AND SETTING**

It will be offered to all English-speaking patients and doctors in selected countries participating but participation is optional.

**OUTCOMES AND MEASURES**

The preferences questionnaire is based on time trade-off questions using standardised, hypothetical scenarios considering adding either extra months to a given baseline survival time, or extra percentage points to a given baseline survival rate.

**STUDY DESIGN**

Observational study nested within an RCT.

**STUDY PROCEDURES**

English-speaking participants from selected countries in RAMPART complete a preferences questionnaire after consent but before randomisation, and at 3 months and 15 months after randomisation. Patients’ preferences questionnaires are administered together with the other patient-rated outcome measures used in RAMPART. English-speaking doctors participating in RAMPART complete the doctors’ preferences questionnaire when their site is initiated, and 2-3 years later.

**STATISTICAL CONSIDERATIONS**

A target sample size of 400 participants per treatment group provides 95% CIs no wider than +/-5% for estimating the primary measure of effect: the estimated proportion considering adjuvant immunotherapy for a given benefit. It also provides over 80% power to detect a true absolute difference of 10% between the proportions of participants in each of two treatment groups judging a given benefit sufficient to make adjuvant chemotherapy worthwhile.

**SIGNIFICANCE**

Data on the benefits participating patients and doctors judge sufficient to make adjuvant immunotherapy worthwhile will complement the trial findings, aid in their interpretation, and facilitate their application in making clinical decisions and formulating health policy.

**SCHEDULE OF ASSESSMENTS**

<table>
<thead>
<tr>
<th>FORM</th>
<th>BASELINE</th>
<th>FOLLOW-UP</th>
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<tbody>
<tr>
<td>Participant’s Preferences</td>
<td>After consent, before randomisation</td>
<td>3 month visit</td>
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<tr>
<td>Questionnaire</td>
<td></td>
<td>15 month visit</td>
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<tr>
<td>Doctor’s Preferences Questionnaire</td>
<td>Within 2 months of site activation</td>
<td>2-3 years after site activation</td>
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(CheckMate 037): a randomised, controlled, open-label, phase 3 trial. The Lancet Oncology. 2015;16(4):375-84. Epub 2015/03/22.


27. Escudier B ea. CheckMate 214: Efficacy and safety of nivolumab + ipilimumab (N+I) vs sunitinib (S) for treatment-naïve advanced or metastatic renal cell carcinoma (mRCC), including IMDC risk and PD-L1 expression subgroups. ESMO; Madrid2017.


