REQUEST FOR AUTHORISATION OF A CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE TO THE COMPETENT AUTHORITIES AND FOR OPINION OF THE ETHICS COMMITTEES IN THE COMMUNITY

For official use:

Date of receiving the request:	Date of request for additional information:	Grounds for non acceptance / negative opinion :
Date of request for information to make it valid:		Give date:
Date of valid application :	Date of receipt of additional / amended information :	Authorisation / positive opinion:
Date of start of procedure :		Give date:
Competent authority registration number :		Withdrawal of application :
Ethics Committee registration number :		Give date :

A: Trial identification

A1. National Competent Authority:

UK - MHRA

A2. European Clinical Trials Database (EudraCT) number:

2017-002329-39

A3. Full title of the trial:

Renal Adjuvant MultiPle Arm Randomised Trial (RAMPART): An international investigator-led phase III multi-arm multi-stage randomised controlled platform trial of adjuvant therapy in patients with resected primary renal cell carcinoma (RCC) at high or intermediate risk of relapse

A3-1. Title of the trial for lay people, in easily understood, i.e. non-technical, language

Can one drug (called durvalumab) or a combination of two drugs (called durvalumab and tremelimumab) stop kidney cancer coming back?

A3-2. Name or abbreviated title of the trial where available:

Renal Adjuvant MultiPle Arm Randomised Trial (RAMPART)

A4. Sponsor's protocol:

Number: RE06
Version: 1.0
Date: 03/10/2017

A5-1. ISRCTN number, if available :

ISRCTN53348826

A5-2. US NCT number:

NCT03288532

A5-3. Who Universal Trial Reference Number (UTRN)

A5-4. Other Identifiers:

Name	Identifier

A6. Is this a resubmission?

○ Yes ◉ No

A7. Is the trial part of a Paediatric Investigation Plan?

○ Yes ◉ No ○ Not Answered

B: Identification of the sponsor responsible for the request

B1. Sponsor

SP1
Contact person

Name of organisation	University College London
Given name	Mahesh
Family name	Parmar
Address	Institute of Clinical Trials & Methodology, MRC CTU at UCL
Town/city	London
Post code	WC1V 6LJ
Country	UNITED KINGDOM
Telephone	+44 020 76704700
Fax	+44 020 76704818
E-mail	m.parmar@ucl.ac.uk

B2.Legal representative in the European Economic Area for the purpose of this trial
A legal representative must be appointed for a clinical trial of an investigational medicinal product if the sponsor is not established within the European Economic Area (EEA) (see article 19 of Directive 2001/20/EC). If this applies, please enclose evidence that the legal representative is established within the EEA and has accepted the role of legal representative.

Legal Representative 1

Contact person

Name of organisation	
Given name	
Family name	
Address	
Town/city	
Post code	
Country	
Telephone	
Fax	
E-mail	

B3. Status of the sponsor: Non-Commercial

B.4 Source(s) of Monetary or Material Support for the clinical trial (repeat as necessary):

Name of organisation	Kidney Cancer UK
Country	UNITED KINGDOM
Name of organisation	AstraZeneca LTD UK
Country	UNITED KINGDOM

B.5 Contact point designated by the sponsor for further information on the trial:

Name of organisation	Institute of Clinical Trials & Methodology, MRC CTU at UCL, University College London
Functional name of contact point	Francesca Schiavone and Ben Smith
Street Address	90 High Holborn
Town/city	London
Post code	WC1V 6LJ
Country	UNITED KINGDOM
Telephone	+44 020 76704683
Fax	+44 020 7670-4818
E-mail	mrcctu.rampart@ucl.ac.uk

C: Applicant identification

C1. Request for the competent authority

C1-1. Who is responsible for the Clinical Trial Authorisation Application?

Sponsor

C1-4. Complete the details of the applicant below even if they are provided elsewhere on the form:

Contact person

Person or organisation name:	University College London
Contact person Given name	Mahesh
Contact person Family name	Parmar
Address	Institute of Clinical Trials & Methodology, MRC CTU at UCL
Town/city	London
Post code	WC1V 6LJ
Country	
Telephone	+44 020 76704700
Fax	+44 020 76704818
E-mail	m.parmar@ucl.ac.uk

C1-5. Do you want a xml file copy of the CTA form data saved on EudraCT?

○ Yes ○ No ◉ Not Answered

C2.Request for ethics commitee

C2-1. Who is responsible for the Clinical Trial Authorisation Application?

.....

C2-5. Complete the details of the applicant below even if they are provided elsewhere on the form

Person or organisation name:	.....
Title:	.....
Forename/Initials:	.....
Surname:	.....
Middlename:	.....
Address:	.....
Town/city:	.....
Post code:	.....
Country:	.....
Telephone:	.....
Fax:	.....
E-mail:	.....

Part D: Investigational Medicinal Products

D: Information on the IMPs

Information on each "bulk product" before trial-specific operations (blinding, trial specific packaging and labelling) should be provided in this section for each investigational medicinal product (IMP) being tested including each comparator, if applicable. If the trial is performed with several products please create a separate set of the following questions for each product. If the product is a combination product please give separate information for each active substance.

Click on the first row and enter details of the product in the following screens. When you have completed the details, click on the navigate button or the "See All" link and return to this section to enter details of the next product. When you have completed details of all products please move to question D7 using the navigation screen.

D. Investigational medicinal products

PR1 Durvalumab

PR2 Tremelimumab

D1. Indicate which of the following is described below then repeat as necessary for each:

This refers to the IMP number: **PR1**
Investigational medicinal product category:
Test IMP

D2. Status of the IMP ***If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to section D.2.2***

D2-1. Does the IMP to be used in the trial have a marketing authorisation?

◯ Yes ◉ No ◯ Not Answered

D2-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

In the protocol, is treatment defined only by active substance?
◯ Yes ◉ No ◯ Not Answered

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?
◯ Yes ◉ No ◯ Not Answered

The products to be administered as IMPs are defined as belonging to an ATC group
◯ Yes ◉ No ◯ Not Answered

Other :
◯ Yes ◉ No ◯ Not Answered

D2-3. IMPD submitted:

Full IMPD
◯ Yes ◉ No ◯ Not Answered

Simplified IMPD

◉ Yes ○ No ○ Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only

○ Yes ◉ No ○ Not Answered

D2-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

○ Yes ◉ No ○ Not Answered

D2-5. Has the IMP been designated in this indication as an orphan drug in the Community?

○ Yes ◉ No ○ Not Answered

D2-6. Has the IMP been the subject of scientific advice related to this clinical trial?

◉ Yes ○ No ○ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

◉ Yes ○ No ○ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

○ Yes ◉ No ○ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

D3. Description of IMP

D3-1.

D.3.1 Product name where applicable	Durvalumab
D.3.2 Product code where applicable	MEDI4736
D.3.3 ATC codes, if officially registered	L01XC28
D.3.4 Pharmaceutical form (use standard terms)	Concentrate and diluent for solution for infusion
D.3.4.1 Is this a specific paediatric formulation?	○ Yes ◉ No ○ Not Answered
D.3.5 Maximum duration of treatment of a subject according to the protocol	1 year maximum; 13 cycles in total. Cycle defined as 28 days with infusion on Day 1 of each cycle

D.3.6 Dose allowed

D.3.6.1 First dose for first-in-human clinical trial	
D.3.6.1 Specify per day or total:	○ per day ○ total ◉ Not Answered
D.3.6.1 Specify total dose (number and unit)	
D.3.6.1 Route of administration (relevant to the first dose):	
D.3.6.2 Maximum dose allowed	1500 mg per infusion 28 day cycle with infusion on day 1
D.3.6.2 Specify per day or total	◉ per day ○ total ○ Not Answered
D.3.6.2 Specify total dose (number and unit)	53.57 mg milligram(s)
D.3.6.2 Route of administration (relevant to the maximum dose):	Intravenous Use

D.3.7 Routes of administration for this IMP

Intravenous Use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

D3-8. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available):	Durvalumab
CAS number:	1428935-60-7
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C6502H10018N1742O2024S42
Chemical/biological description of the Active Substance	Human immunoglobulin (Ig) G1 kappa (IgG1κ) monoclonal antibody (mAb) that blocks the interaction of programmed cell death ligand 1 (PD-L1) (but not programmed cell death ligand-2) with programmed cell death 1 (PD-1) on T-lymphocyte (T-cells) and cluster of differentiation (CD)80 (B7.1) on immune cells (IC) and is engineered to reduce antibody-dependent cell-mediated cytotoxicity (ADCC).
Strength	
Concentration unit:	mg/ml milligram(s)/millilitre
Concentration type:	equal
Concentration number (only use both fields for range):	50

D3-11. Type of IMP

Does the IMP contain an active substance:

Of chemical origin?	○ Yes ◉ No ○ Not Answered
Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))	◉ Yes ○ No ○ Not Answered

Is this a:

Advanced Therapy IMP (ATIMP) [1]	○ Yes ◉ No ○ Not Answered
Combination product that includes a device, but does not involve an Advanced Therapy	○ Yes ◉ No ○ Not Answered
Radiopharmaceutical medicinal product?	○ Yes ◉ No ○ Not Answered
Immunological medicinal product (e.g. vaccine, allergen, immune serum)?	○ Yes ◉ No ○ Not Answered
Plasma derived medicinal product?	○ Yes ◉ No ○ Not Answered
Extractive medicinal product?	○ Yes ◉ No ○ Not Answered
Recombinant medicinal product?	○ Yes ◉ No ○ Not Answered
Medicinal product containing genetically modified organisms?	○ Yes ◉ No ○ Not Answered
Herbal medicinal product?	○ Yes ◉ No ○ Not Answered
Homeopathic medicinal product?	○ Yes ◉ No ○ Not Answered
Another type of medicinal product?	○ Yes ◉ No ○ Not Answered

Specify the mode of action for the active substance in this medicinal product
The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action. Durvalumab is a human immunoglobulin (Ig) G1 kappa (IgG1κ) monoclonal antibody (mAb) that blocks the
interaction of programmed cell death ligand 1 (PD-L1) (but not programmed cell death ligand-2) with programmed cell death 1 (PD-1) on T-lymphocyte (T-cells) and cluster of differentiation (CD)80 (B7.1) on immune cells (IC) and is engineered to reduce antibody-dependent cell-mediated cytotoxicity (ADCC).

Is it an IMP to be used in a first-in-human clinical trial?	○ Yes ◉ No ○ Not Answered

[1,2,3,4,5] Complete sections D.4, D.5, D.6. and D.7, as applicable
[2,3] As defined in Annex 1 part IV of Directive 2001/83/EC as amended
[4] As defined in Article 2(1)(b) of Regulation 1394/2007/EC
[6] Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

D1. Indicate which of the following is described below then repeat as necessary for each:

This refers to the IMP number: **PR2**
Investigational medicinal product category:
Test IMP

D2. Status of the IMP ***If the IMP has a marketing authorisation in the Member State concerned by this application but the trade name and marketing authorisation holder are not fixed in the protocol, go to section D.2.2***

D2-1. Does the IMP to be used in the trial have a marketing authorisation?

◯ Yes ◉ No ◯ Not Answered

D2-2. Situations where an IMP to be used in the CT has a MA in the MS concerned, but the protocol allows that any brand of the IMP with a MA in that MS be administered to the trial subjects and it is not possible to clearly identify the IMP(s) in advance of the trial start

In the protocol, is treatment defined only by active substance?
◯ Yes ◉ No ◯ Not Answered

In the protocol, do treatment regimens allow different combinations of marketed products used according to local clinical practice at some or all investigator sites in the MS?
◯ Yes ◉ No ◯ Not Answered

The products to be administered as IMPs are defined as belonging to an ATC group
◯ Yes ◉ No ◯ Not Answered

Other :
◯ Yes ◉ No ◯ Not Answered

D2-3. IMPD submitted:

Full IMPD
◯ Yes ◉ No ◯ Not Answered

Simplified IMPD
◉ Yes ◯ No ◯ Not Answered

Provide justification for using simplified dossier in the covering letter

Summary of product characteristics (SmPC) only
◯ Yes ◉ No ◯ Not Answered

D2-4. Has the use of the IMP been previously authorised in a clinical trial conducted by the sponsor in the Community?

◯ Yes ◉ No ◯ Not Answered

D2-5. Has the IMP been designated in this indication as an orphan drug in the Community?

◯ Yes ◉ No ◯ Not Answered

D2-6. Has the IMP been the subject of scientific advice related to this clinical trial?

◉ Yes ○ No ○ Not Answered

Please indicate source of advice and provide a copy in the CTA request:

From the CHMP?

◉ Yes ○ No ○ Not Answered

CHMP = Committee for Medicinal Products for Human Use

From a MS competent authority?

○ Yes ◉ No ○ Not Answered

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

D3. Description of IMP

D3-1.

D.3.1 Product name where applicable	Tremelimumab
D.3.2 Product code where applicable	CP-675,206 (formerly), MEDI1123
D.3.3 ATC codes, if officially registered	None
D.3.4 Pharmaceutical form (use standard terms)	Concentrate and diluent for solution for infusion
D.3.4.1 Is this a specific paediatric formulation?	○ Yes ◉ No ○ Not Answered
D.3.5 Maximum duration of treatment of a subject according to the protocol	2 cycles maximum; Cycle defined as 28 days with infusion on Day 1 of each cycle

D.3.6 Dose allowed

D.3.6.1 First dose for first-in-human clinical trial	
D.3.6.1 Specify per day or total:	○ per day ○ total ◉ Not Answered
D.3.6.1 Specify total dose (number and unit)	
D.3.6.1 Route of administration (relevant to the first dose):	
D.3.6.2 Maximum dose allowed	75 mg per infusion 28 days cycles with infusion on Day 1 2 cycles maximum
D.3.6.2 Specify per day or total	◉ per day ○ total ○ Not Answered
D.3.6.2 Specify total dose (number and unit)	2.67 mg milligram(s)
D.3.6.2 Route of administration (relevant to the maximum dose):	Intravenous Use

D.3.7 Routes of administration for this IMP

Intravenous Use

This is a sub-set of questions about each IMP. To return to the list of IMPs select "See all" at the top of the page or select "Navigate". To complete further questions about this IMP select "Next".

D3-8. Active substances

Complete all fields that currently apply to this Active Substance in this Product. If you have IMPs with different concentrations of the Active Substance complete a new Sub-section D for each.

Active Substance 1

Name of active substance (INN or proposed INN if available):	Tremelimumab
CAS number:	745013-59-6
Current sponsor code:	
Other descriptive name:	
Full Molecular formula	C6500H9974N1726O2026S52
Chemical/biological description of the Active Substance	Human IgG2 monoclonal antibody (mAb) directed against CTLA-4

Strength

Concentration unit:	mg/ml milligram(s)/millilitre
Concentration type:	equal
Concentration number (only use both fields for range):	20

D3-11. Type of IMP

Does the IMP contain an active substance:

Of chemical origin?	○ Yes	◉ No	○ Not Answered
Of biological / biotechnological origin?(other than Advanced Therapy IMP (ATIMP))	◉ Yes	○ No	○ Not Answered

Is this a:

Advanced Therapy IMP (ATIMP) (1)	○ Yes	◉ No	○ Not Answered
Combination product that includes a device, but does not involve an Advanced Therapy	○ Yes	◉ No	○ Not Answered
Radiopharmaceutical medicinal product?	○ Yes	◉ No	○ Not Answered
Immunological medicinal product (e.g. vaccine, allergen, immune serum)?	○ Yes	◉ No	○ Not Answered
Plasma derived medicinal product?	○ Yes	◉ No	○ Not Answered
Extractive medicinal product?	○ Yes	◉ No	○ Not Answered
Recombinant medicinal product?	○ Yes	◉ No	○ Not Answered
Medicinal product containing genetically modified organisms?	○ Yes	◉ No	○ Not Answered
Herbal medicinal product?	○ Yes	◉ No	○ Not Answered

Homeopathic medicinal product?	◯ Yes ◉ No ◯ Not Answered
Another type of medicinal product?	◯ Yes ◉ No ◯ Not Answered

Specify the mode of action for the active substance in this medicinal product
The mode of action should briefly describe the chemical, biochemical, immunological or biological means that the IMP uses to effect its pharmaceutical action.
Tremelimumab blocks the inhibitory signal resulting from CTLA-4
binding to CD80/86, leading to prolongation and enhancement of T-cell activation and expansion.

Is it an IMP to be used in a first-in-human clinical trial?	◯ Yes ◉ No ◯ Not Answered

(1,2,3,4,5) Complete sections D.4, D.5, D.6. and D.7, as applicable
(2,3) As defined in Annex 1 part IV of Directive 2001/83/EC as amended
(4) As defined in Article 2(1)(b) of Regulation 1394/2007/EC
(6) Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products. EMEA/CHMP/SWP/28367/2007

D8. Information on placebo *(if relevant; repeat as necessary)*

D8. Is there a placebo:

◯ Yes ◉ No ◯ Not Answered

D9. Sites responsible for final QP release for distribution to investigators.

D9-1. IMPs and placebos for which no responsible site needs to be identified.

This section is used to identify IMPs and placebos which:

- Have an MA in the EU **and**
- Are sourced from the EU market **and**
- Are used in the trial without modification (eg not overencapsulated) **and**
- The packaging and labeling is carried out for local use only as per article 9.2 of the Directive 2005/28/EC (GCP Directive).

If all the conditions above are met, then select below the IMPs and placebos to which this applies.

Index of Sites where the qualified person certifies batch release

In accordance with paragraph 38 of Annex 13 of Volume 4 of the Rules Governing Medicinal Products in the European Union

D9-2. Who is responsible in the Community for the certification of the finished IMP or placebo?
This section is dedicated to finished IMPs, i.e. medicinal products randomised, packaged, labelled and certified for use in the clinical trial. If there is more than one site or more than one IMP is certified, use extra pages and give each IMP its number from section D1 or D7 In the case of multiple sites indicate the product certified by each site.

RS1

Both

Name of the organisation:	Fisher Clinical Services UK Limited
Address	Langhurstwood Road
Town/city	Horsham
Post code	RH12 4QD
Country	UNITED KINGDOM

Give the manufacturing authorisation number

18693

If no authorisation, give the reasons:

Select the relevant IMP(s) and Placebo(s) from the drop down lists.

IMP

PR1

IMP
PR2

E: Design of the Trial.

E.1 Medical Condition or Disease under Investigation

E1-1. Medical condition or disease under investigation (1)

Specify the medical condition(s) to be investigated (free text) :
Renal Cell Carcinoma

Medical condition in easily understood language
Cancer of the kidney

Identify the therapeutic area
Diseases [C] - Cancer [C04]

(1) In the case of healthy volunteer trials, the intended indication for the product under development should be provided.

E1-2. MedDRA information (2)

MR1

Version	14.0
Level	LLT
Classification Code	10067946
Term	Renal cell carcinoma
SOC	10029104 - Neoplasms benign, malignant and unspecified (incl cysts and polyps)

(2) Applicants are encouraged to provide the MedDRA lower level term (LLT) if applicable and classification code.

E1-3. Is any of the conditions being studied a rare disease? (3)

◯ Yes ◉ No ◯ Not Answered

(3) Refer to "Points to consider on the calculation and reporting of the prevalence of a condition for Orphan drug designation": COM/436/01 (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/09/WC500003773.pd

E2. Objective of the trial

E2-1. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

The RAMPART trial is aiming to address two research questions:

1. Does treatment with either durvalumab alone or a combination of durvalumab and tremelimumab delay the cancer from coming back compared with the current standard-of-care (active monitoring) in patients with kidney cancer who underwent surgery and are at intermediate or high risk of recurrence?

2. Does treatment with either durvalumab alone or a combination of durvalumab and tremelimumab increase life expectancy compared with current standard-of-care (active monitoring) in patients with kidney cancer who underwent surgery and are at intermediate or high risk of recurrence?

E2-2. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

There are a number of secondary research questions that the RAMPART trial is aiming to address:

1. Does treatment with either durvalumab alone or a combination of durvalumab and tremelimumab delay the cancer from spreading outside the kidneys?

2. Does treatment with either durvalumab alone or a combination of durvalumab and tremelimumab reduces the chances of dying from kidney cancer?

3. How does treatment with either durvalumab alone or a combination of durvalumab and tremelimumab affect the quality of life of patients?

4. What side effects are experienced in patients undergoing treatment with either durvalumab alone or a combination of durvalumab and tremelimumab?

5. What are patients' preferences when it comes to treatments affecting the immune system?

E2-3. Is there a sub-study?

(●) Yes ( ) No ( ) Not Answered

Give the full title, date and version of each sub-study and their related objectives:

All patients will be approached at the time of consent for the collection of a baseline EDTA blood sample and provision of an archival FFPE tumour sample for biomarker testing for PD-1/PD-L1 marker expression. PD-L1 testing has been requested by the Food and Drug Administration as a key aspect of the trial during the initial scientific advice consultation with the regulatory agency.

Several translational sub-studies are being considered by the by the Trial Development Group for future development; the full umbrella of translational research associated with the main study will be detailed in a separate protocol to be submitted to the Ethics Committee in a separate instance.

E3. Please list the principal inclusion criteria (list the most important, max 5000 characters).

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 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 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
7.Adequate normal organ and marrow function
a.Haemoglobin ≥9.0g/dL (transfusions will be allowed within 2 weeks of randomisation in order to achieve the entry criteria).
b.Absolute neutrophil count (ANC) ≥1.5 x 109/L (≥1500 per mm3).
c.Platelet count ≥100 x 109 (≥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
8.12-lead ECG on which QTcF must be <470 ms. In case of clinically significant ECG abnormalities, including a QTcF value ≥470 ms, two additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding.
9. Patient must weight ≥30Kg at the time of randomisation

10.Subjects must be ≥ 18 years in age.
11.Written Informed Consent obtained from the patient
12.Both men and women enrolled in this trial must use adequate contraception during the treatment phase of the study and for 6 months afterwards. Egg donation, sperm donation and breastfeeding must be avoided.
13. Evidence of post-menopausal status or negative urinary or serum 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).

E4. Please list the principal exclusion criteria (list the most important, max 5000 characters).

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.
7. History of leptomeningeal carcinomatosis.
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.
13. History of allogeneic organ transplant.
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.

E5-1. What is the primary outcome measure for the study?(max 5000 characters)

The RAMPART trial has two co-primary outcome measures
1. Disease Free Survival (DFS)
2. Overall Survival (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).

Timepoint(s) of evaluation of this end point (max 800 characters)
Estimated timelines for interim analyses: Disease Free Survival
C vs A and B vs A (Overwhelming Benefit) = 4.75 years
C vs A (Lack of Benefit) = 4.75 years
B vs A (Lack of Benefit) = 4.75 years
B vs A (Overwhelming Benefit)= 6.25 years
B vs A (Lack of Benefit)= 6.25 years
B vs A (Overwhelming Benefit)= 8 years

Estimated timelines for primary analyses
Disease Free Survival

Arm C vs A = 6.25 years
Arm B vs A = 10.5 years

Overall survival (high-risk patients only)
Arm C vs A = 13.25 years
Arm B vs A = 20.5 years

The protocol will usually identify a single primary end point but there may be a co-primary end point in some cases and/or a number of secondary end points.

E5-2. Secondary end point(s) (max 5000 characters)

1. Metastasis Free Survival (MFS) defined as the interval from randomisation to first evidence of metastases or death from RCC
2. RCC specific survival time
3. Quality of Life
4. Toxicity

Timepoint(s) of evaluation of this end point (max 800 characters)
Secondary outcomes will be analysed and reported at an appropriate time, which may be at the same time as the

analysis and reporting of the primary outcomes.

E6. What is the scope of the trial?

Diagnosis	○ Yes	◉ No	○ Not Answered
Prophylaxis	○ Yes	◉ No	○ Not Answered
Therapy	○ Yes	◉ No	○ Not Answered
Safety	◉ Yes	○ No	○ Not Answered
Efficacy	◉ Yes	○ No	○ Not Answered
Pharmacokinetic	○ Yes	◉ No	○ Not Answered
Pharmacodynamic	○ Yes	◉ No	○ Not Answered
Bioequivalence	○ Yes	◉ No	○ Not Answered
Dose Response	○ Yes	◉ No	○ Not Answered
Pharmacogenetic	○ Yes	◉ No	○ Not Answered
Pharmacogenomic	○ Yes	◉ No	○ Not Answered
Pharmacoeconomic	○ Yes	◉ No	○ Not Answered
Others	○ Yes	◉ No	○ Not Answered

Specify:

E7-1. Trial type and phase [1]

Human pharmacology (Phase I)	○ Yes	◉ No	○ Not Answered
Therapeutic exploratory (Phase II)	○ Yes	◉ No	○ Not Answered
Therapeutic confirmatory (Phase III)	◉ Yes	○ No	○ Not Answered
Therapeutic use (Phase IV)	○ Yes	◉ No	○ Not Answered

[1] The descriptions of the trial types provided are those recommended in preference to Phases. See page 5 of Community guideline CPMP/ICH/291/95. The development of a new indication after initial approval of a medicine should be considered as a new development plan.

E8. Design of the Trial.

E8-1. Is the trial design controlled?

◉ Yes ○ No ○ Not Answered

Specify:

Randomised	◉ Yes	○ No	○ Not Answered
Open	◉ Yes	○ No	○ Not Answered

Single blind	○ Yes	◉ No	○ Not Answered
Double blind	○ Yes	◉ No	○ Not Answered
Parallel group	○ Yes	◉ No	○ Not Answered
Cross over	○ Yes	◉ No	○ Not Answered
Other	○ Yes	◉ No	○ Not Answered

E8-2. If controlled, specify the comparator:

Other medicinal product(s)	○ Yes	◉ No	○ Not Answered
Placebo	○ Yes	◉ No	○ Not Answered
Other	◉ Yes	○ No	○ Not Answered

Specify the comparator
Active Monitoring (current standard-of-care)

Number of treatment arms in the trial
2

E8-3. Single site in the Member State concerned (see also section G):

○ Yes ◉ No ○ Not Answered

E8-4. Multiple sites in the Member State concerned (see also section G):

◉ Yes ○ No ○ Not Answered

Number of sites anticipated in Member State concerned
70

E8-5. Multiple Member States

◉ Yes ○ No ○ Not Answered

Number of sites anticipated in the Community.
20

E8-6. Trial being conducted both within and outside the EEA

◉ Yes ○ No ○ Not Answered

Trial conducted completely outside EEA

○ Yes ◉ No ○ Not Answered

Specify the countries in which trial sites are planned

FRANCE

Specify the number of sites anticipated outside of the EEA
0

E8-7. Will a data monitoring committee (DMC) be convened?

(●) Yes ( ) No ( ) Not Answered

E8-8.

Definition of the end of trial, and justification in the case where it is not the last visit of the last subject undergoing the trial.
If it is the last visit of the last subject, please enter "LVLS". If it is not LVLS provide the definition.
The trial will close when all patients have completed follow-up and all data queries have been resolved.

E8-9. How long do you expect the study to last? (1)

In all countries concerned by the trial
Years: 20 Months: 0 Days: 0

In the MS concerned
Years: 20 Months: 0 Days: 0

(1) From the first inclusion until the last visit of the last subject.

E8-10. Recruitment start date

Recruitment start date in MS
02/01/2018
In any country
01/06/2018

(1) If not provided in the protocol.

F: Population of Trial Subjects

F1. What is the age span of the trial subjects?

Less than 18 years	○ Yes ◉ No ○ Not Answered	Approx no of participants: 0
Adult (18-64 years)	◉ Yes ○ No ○ Not Answered	Approx no of participants: 1600
Elderly (geater than 65 years)	◉ Yes ○ No ○ Not Answered	Approx no of participants: 150

The number of participants will be initial estimates. Applicants will not be required to update this information nor do they constitute an authorisation or restriction on the inclusion of these numbers of patients in the trial.

F2. What is the gender of the trial subjects?

Female	◉ Yes ○ No ○ Not Answered
Male	◉ Yes ○ No ○ Not Answered

F3. Please select the categories of the trial subjects:

Healthy volunteers	○ Yes ◉ No ○ Not Answered
Patients	◉ Yes ○ No ○ Not Answered
Specific vulnerable populations	○ Yes ◉ No ○ Not Answered

F4. Planned number of subjects to be included:

In the member state 1175

For a multinational trial:

In the European community: 200

In the whole clinical trial: 1750

F5. Plans for treatment or care after a subject has ended his/her participation in the trial. ***If it is different from the expected normal treatment, please specify:***

Study participants will undergo experimental treatment for a maximum of 1 year or until progression. Patients who present with disease progression will be able to access first line therapies for metastatic renal carcinoma as recommended by NICE.

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- (●) National coordinating investigator
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Street address	ST. JAMES'S UNIVERSITY HOSPITAL
Town/city	BECKETT STREET
Post Code	LS9 7TF
Country	UNITED KINGDOM
Telephone	
Fax	

E-mail	n.vasudev@nhs.net

IN41

Given name	Ashraf
Family name	Azzabi
Qualification (MD...)	MD, MBBCh
Institution name	CITY HOSPITALS SUNDERLAND NHS FOUNDATION TRUST
Institution department name	
Street address	SUNDERLAND ROYAL HOSPITAL
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Post Code	SR4 7TP
Country	UNITED KINGDOM
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Fax	
E-mail	ashraf.azzabi@nuth.nhs.uk

IN42

Given name	Tom
Family name	Waddell
Qualification (MD...)	MBChB, MRCP, MD
Institution name	THE CHRISTIE NHS FOUNDATION TRUST
Institution department name	
Street address	550 WILMSLOW ROAD
Town/city	WITHINGTON
Post Code	M20 4BX
Country	UNITED KINGDOM
Telephone	
Fax	
E-mail	Tom.Waddell@christie.nhs.uk

IN43

Given name	Jorg
Family name	Michels
Qualification (MD...)	MD, PhD, MRCP
Institution name	TORBAY AND SOUTH DEVON NHS FOUNDATION TRUST
Institution department name	
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Town/city	TORBAY HOSPITAL
Post Code	TQ2 7AA
Country	UNITED KINGDOM
Telephone	
Fax	
E-mail	jorg.michels@nhs.net

IN44

Given name	Jim
Family name	Barber
Qualification (MD...)	MRCP, FRCP, MBBS

Institution name	Velindre Cancer Centre
Institution department name	Velindre NHS Trust
Street address	
Town/city	
Post Code	
Country	UNITED KINGDOM
Telephone	
Fax	
E-mail	Jim.Barber@wales.nhs.uk

IN45

Given name	Janet
Family name	Brown
Qualification (MD...)	MBBS, BSc, FRCP, MD
Institution name	SHEFFIELD TEACHING HOSPITALS NHS FOUNDATION TRUST
Institution department name	
Street address	NORTHERN GENERAL HOSPITAL
Town/city	HERRIES ROAD
Post Code	S5 7AU
Country	UNITED KINGDOM
Telephone	
Fax	
E-mail	j.e.brown@sheffield.ac.uk

IN46

Given name	Pasquale
Family name	Innominato
Qualification (MD...)	MD, PhD
Institution name	Ysbyty Gwynedd/Bangor Hospital
Institution department name	
Street address	
Town/city	
Post Code	
Country	UNITED KINGDOM
Telephone	
Fax	
E-mail	Pasquale.Innominato@wales.nhs.uk

IN47

Given name	Anthony
Family name	Maraveyas
Qualification (MD...)	MD, PhD, MRCP, FRCP
Institution name	HULL AND EAST YORKSHIRE HOSPITALS NHS TRUST
Institution department name	
Street address	HULL ROYAL INFIRMARY
Town/city	ANLABY ROAD
Post Code	HU3 2JZ
Country	UNITED KINGDOM
Telephone	

Fax	
E-mail	anthony.maraveyas@hey.nhs.uk

For multi-centre trials where the CI is also a local PI, please list the CI as a PI at G2 (single-centre).

G3. Central Technical Facility Details

G3. Central technical facilities to be used in the conduct of the trial. *Laboratory or other technical facility, in which the measurement or assessment of the main evaluation criteria are centralised.*

Organisation

Central technical facility organisation name	
Central technical facility organisation department	
Contact person Given name	
Contact person Family name	
Street address	
Town/city	
Post code	
Country	
Work Telephone	
Fax	
E-mail	

Enter the details of any duties subcontracted to this central technical facility in this trial:

Routine clinical pathology testing	○ Yes ◉ No ○ Not Answered
Clinical chemistry	○ Yes ◉ No ○ Not Answered
Clinical haematology	○ Yes ◉ No ○ Not Answered
Clinical microbiology	○ Yes ◉ No ○ Not Answered
Histopathology	○ Yes ◉ No ○ Not Answered
Serology / endocrinology	○ Yes ◉ No ○ Not Answered
Analytical chemistry	○ Yes ◉ No ○ Not Answered
ECG analysis / review	○ Yes ◉ No ○ Not Answered
Medical image analysis/ review - X-ray, MRI, ultrasound, etc.	○ Yes ◉ No ○ Not Answered
Primary/ surrogate endpoint test	○ Yes ◉ No ○ Not Answered
Other	○ Yes ◉ No ○ Not Answered

Network organisation details

G4. Network organisation details

Organisation
Contact person Given name
Contact person Middle name
Contact person Family name
Street address
Town/city
PostCode
Country
Telephone number
Fax number
E-mail

Activities carried out by the network

G5. Organisations to whom the sponsor has transferred trial related duties and functions

G5. Subcontractor organisations.
Enter details of central CRO facilities supplying services for at least this Member State.

Organisation
Department
Contact person Given name
Contact person Family name
Street address
Town/city
PostCode
Country
Telephone number
Fax
E-mail

Enter the details of any duties/ functions subcontracted to this sponsor's subcontractor facility in this trial

All tasks of the sponsor:	○ Yes ○ No ◉ Not Answered
Monitoring:	○ Yes ○ No ◉ Not Answered
Regulatory (e.g. preparation of applications to CA and Ethics Committee):	○ Yes ○ No ◉ Not Answered
Investigator recruitment:	○ Yes ○ No ◉ Not Answered
IVRS(1) - treatment randomisation:	○ Yes ○ No ◉ Not Answered
Data management:	○ Yes ○ No ◉ Not Answered
E-data capture:	○ Yes ○ No ◉ Not Answered
SUSAR reporting:	○ Yes ○ No ◉ Not Answered
Quality assurance auditing:	○ Yes ○ No ◉ Not Answered
Statistical analysis:	○ Yes ○ No ◉ Not Answered

Medical writing:	◯ Yes ◯ No ◉ Not Answered
Other duties subcontracted:	◯ Yes ◯ No ◉ Not Answered

H: Ethics Committee

H1-1. Type of application
Please tick the Ethics Committee box and give information of the Ethics committee concerned.

Ethics committee ☑

H2-1. Name and address of ethics committee:

Organisation	London - Riverside Research Ethics Committee
Work Address	London
PostCode	
Country	
Fax	

H2-2. Date of submission:

13/10/2017

H2-3. Current status of Ethics Committee Opinion at the time of submission to the National Competent Authority:

○ To be requested ◉ Pending ○ Given

I: Signature Of The Applicant In The Member State

I1. I hereby confirm that /confirm on behalf of the sponsor (tick which is applicable) that:

- [x] The information provided is complete;
- [x] The attached documents contain an accurate account of the information available;
- [x] the clinical trial will be conducted in accordance with the protocol;
- [x] The clinical trial will be conducted, and SUSARs and result-related information will be reported, in accordance with the applicable legislation.

I2. Applicant of the request for the competent authority (as stated in section C.1):

This section was signed electronically by Prof M Parmar on 16/10/2017 10:45.

Job Title/Post:

Organisation:

Email:

J: Checklist

J3. ***For details of the documents required for applications to the MHRA in the UK please see*** ***http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Applyingforaclinicaltrialauthorisation/Whattosend/index.htm***