RE06
RAMPART

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

Version: **4.0**
Date: **26-May-2020**

MRC CTU at UCL ID:	**RE06**
ISRCTN #:	**ISRCTN53348826**
NCT #:	**NCT03288532**
EUDRACT #:	**2017-002329-39**
CTA #:	**20363/0380/001-0001**
MREC #:	**17/LO/1875**

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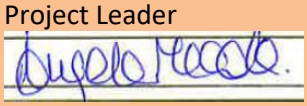
Signature:	
Date	26-May-2020

SUMMARY OF TRIAL

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Acronym and Short Title	RAMPART - Renal Adjuvant MultiPle Arm Randomised Trial
Long Title of Trial	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.
Version	4.0
Date	22-May-2020
MRC CTU at UCL ID	RE06
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NCT #	NCT03288532
EudraCT #	2017-002329-39
CTA #	20363/0380/001-0001
REC #	17/LO/1875
Study Design	RAMPART is a phase III Multi-Arm, Multi-Stage (MAMS), multi-centre, randomised controlled platform trial.
Type of Participants to be Studied	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 B** for details of Leibovich scoring system.
Setting	The trial will be run at hospitals in the UK, France, Australia, New Zealand and the US.
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).
Study Aims	The RAMPART platform trial has been designed to evaluate multiple treatments simultaneously, while adapting to a

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	changing 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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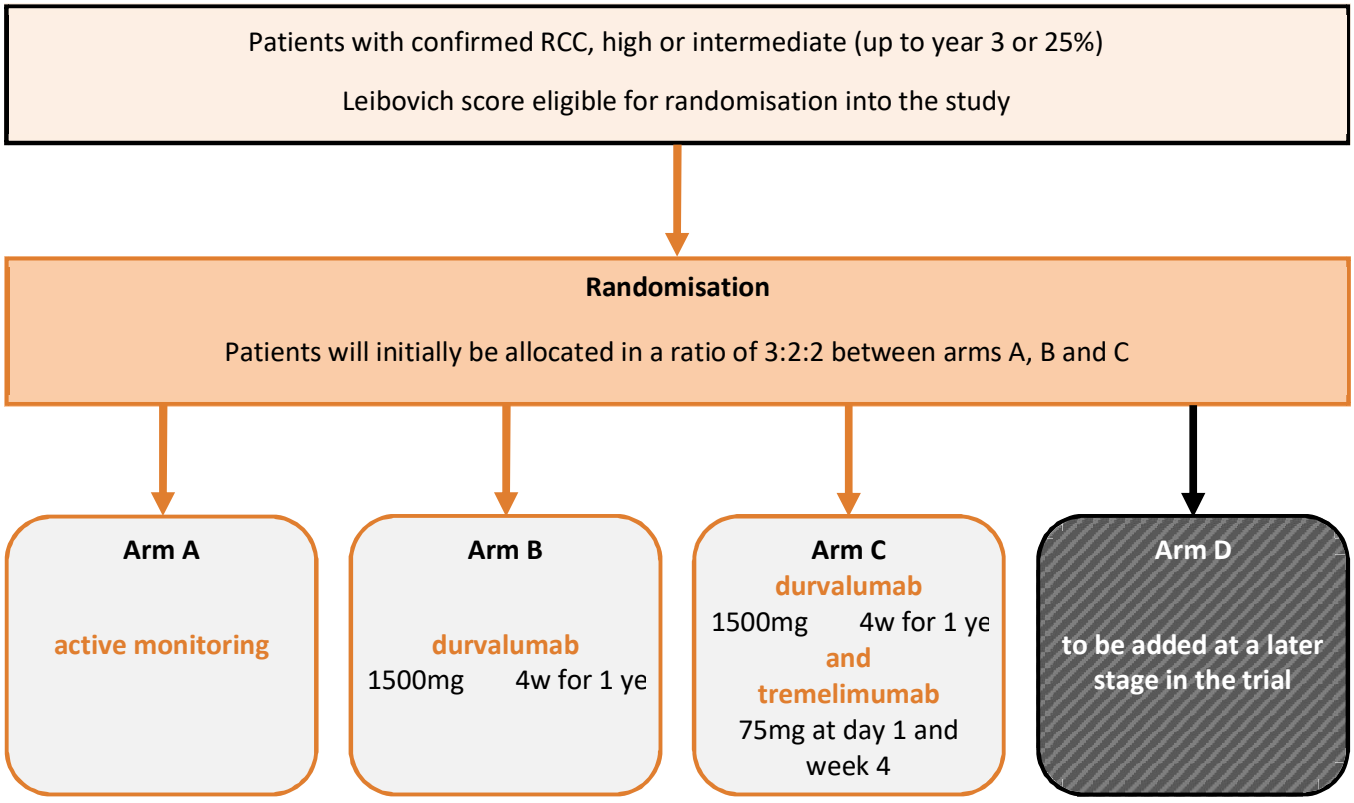
	• Arm C - 500 patients
Duration	The duration of treatment in each of research arms B and C is one year. Follow-up will continue until the primary outcomes have reached maturity. We anticipate reporting on the co-primary outcomes as follows (all times are from the start of recruitment): • DFS in the durvalumab tremelimumab combination arm (C) after approx. 6.25 years • DFS in the single-agent durvalumab arm (B) after approx. 10.5 years • OS in high-risk patients (Leibovich Score 6-11) in the durvalumab tremelimumab combination arm (C) after approx. 13.25 years • OS in high-risk patients (Leibovich Score 6-11) in the single-agent durvalumab arm (B) after approx. 20.5 years
Ancillary Studies/Sub studies	**Translational Sub-study** TransRAMPART (see **Section 6.7**) Baseline samples: • FFPE tissue samples (provision of at least one tumour block is mandatory) • Blood sample (provision of one EDTA baseline sample, collected prior to the first infusion is mandatory) *Note: Details on all TransRAMPART sub-studies and sample collection(s) will be included in the TransRAMPART protocol.* **Patient Reported Outcomes** (see **Section 1.11.2**) Preferences for adjuvant immunotherapy in RAMPART (PAIR) Quality of Life
Sponsor	The RAMPART trial is an investigator-led academic trial sponsored by UCL and co-ordinated by the MRC CTU at UCL.
Funders	Kidney Cancer UK (clinical trial grant award) AstraZeneca LP (educational grant and free-of-charge durvalumab and tremelimumab) Cancer Research UK (prospective sample collection award)
Trial Managers	Mr Ben Smith Ms anna Bryant
Chief Investigator	Prof James Larkin
MRC CTU at UCL Project Leader	Dr Angela Meade

TRIAL SCHEMA

Figure 1 Trial Entry Randomisation and Treatment



TRIAL ASSESSMENT SCHEDULE

Table 1 Trial Assessment Schedule

	Pre-surgery	Surgery	Eligibility	Randomisation ↓ 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 1 Wk 52	M 15	M 18	M 21	Year 2 M 24	M 27	M 30	M 33	Year 3 M 36	M 42	Year 4 M 48	M 54	Year 5 M 60	M 72	year 7 M 84	Year 8 M 96	Year 9 M 108	Year 10 M 120	DFS Event	As clinically required
Consent																																						
Written Informed Consent			X																																		
Clinical Assessments																																					
Clinical History	X		X																																		
Physical Examination	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Vital Signs			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X																				X
Weight			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X																				
Height			X																																		
ECG			X	X																																		X
Concomitant Medications			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X																		
AEs			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X																		
WHO Performance Status			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Radiology																																					
CT Scan	X		X							X				X					X		X		X		X		X		X		X		X			X	X
Laboratory Tests																																					
Haematology			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X																	X	X
Clinical Chemistry			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X																	X	X
Hepatitis serologies			X																																		
Pregnancy Test																																					
Urine or serum HCG pregnancy Test[Ж]			X	X		X		X	X	X	X	X	X	X	X	X	X	X																				
Questionnaires																																					
EQ-5D *(optional)*			X							X										X							X									X*	
QLQ-C30 *(optional)*			X							X										X							X									X*	
PAIR Questionnaire *(optional)*			X							X										X							X										
TransRAMPART Samples																																					
Blood Sample			X																																		
FFPE Tissue Block		X§																																			

Ж 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