REduced Frequency ImmuNE checkpoint inhibition in cancers

A multi-arm phase II basket protocol testing reduced intensity immunotherapy across different cancers

Version: 5.0
Date: 03-Jan-2023

MRC CTU at UCL ID:	**RF01**
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GENERAL INFORMATION

This document was constructed using the MRC CTU at UCL Protocol Template Version 10.0. The CTU endorses the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) initiative. It describes the REFINE trial, coordinated by the Medical Research Council (MRC) Clinical Trials Unit (CTU) at University College London (UCL), and provides information about procedures for entering 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 trial team (email: mrcctu.REFINE@ucl.ac.uk) to confirm they have the most up-to-date version.

COMPLIANCE

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki 1996, the principles of Good Clinical Practice (GCP) as laid down by the ICH topic E6 (R2), the Commission Clinical Trials 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 2018 (DPA number: Z6364106), and the UK Policy Framework for Health and Social Care Research.

The trial will be conducted in accordance with the Clinical Trials Directive as implemented in the UK statutory instrument.

SPONSOR

UCL is the trial Sponsor and has delegated responsibility for the overall management of the REFINE trial to the MRC CTU at UCL. Queries relating to UCL sponsorship of this trial should be addressed to Professor Max Parmar, MRC CTU at UCL Director, MRC CTU at UCL, Institute of Clinical Trials & Methodology, 90 High Holborn 2nd Floor, London, WC1V 6LJ.

FUNDING

REFINE is funded by the Jon Moulton Charity Trust and the Medical Research Council (MC_UU_12023/28).

AUTHORISATIONS AND APPROVALS

This trial has been approved by the Research Ethics Committee and the Regulatory Authority in the UK.

TRIAL REGISTRATION

This trial is registered with the International Standard Randomised Controlled Trial Number (ISRCTN 79455488) Clinical Trials Register.

RANDOMISATIONS
To randomise, complete the required eCRFs on Open Clinica

SAE REPORTING
Please report all SAEs via the EDC system within 24 hours of becoming aware of an SAE

TRIAL ADMINISTRATION

Please direct all queries to the Trial Manager at the MRC CTU at UCL in the first instance. Clinical queries will be passed to the Chief Investigator (CI), Trial Physician or other members of the Trial Management Group (TMG) as appropriate.

COORDINATING SITE

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PPI COLLABORATORS

PPI Representative	Rose Woodward	Action Kidney Cancer, Manchester, UK
PPI Representative	Alison Fielding	Action Kidney Cancer, Manchester, UK

NB: throughout this document, "MRC CTU at UCL" is generally abbreviated to "CTU".

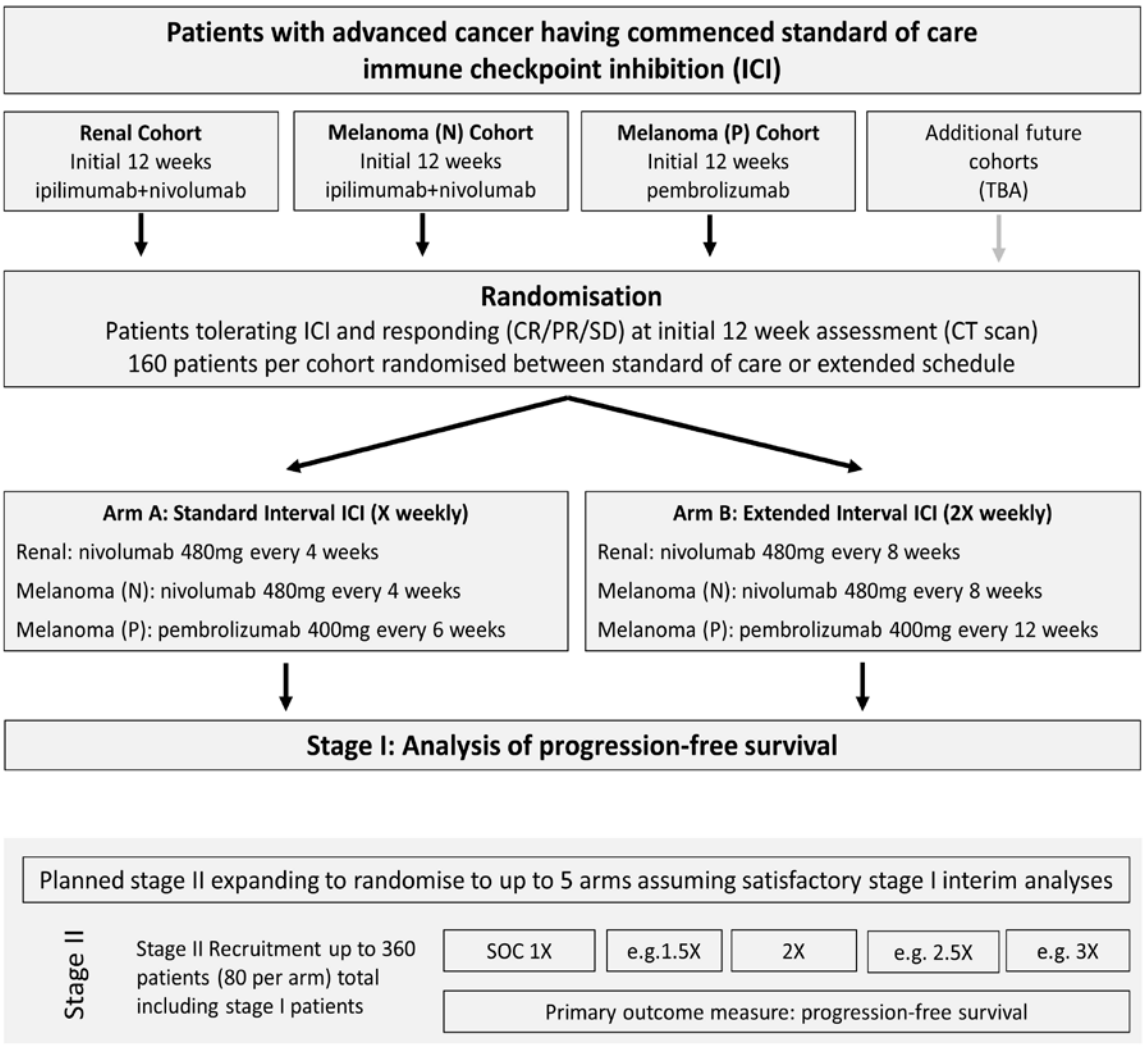
SUMMARY OF TRIAL

SUMMARY INFORMATION TYPE	SUMMARY DETAILS	
Acronym of trial	REFINE	
Long Title of Trial	REduced Frequency ImmuNE checkpoint inhibition in cancers: A multi-arm phase II basket protocol testing reduced intensity immunotherapy across different cancers	
Version	5.0	
Date	03-Jan-2023	
MRC CTU at UCL ID	RF01	
ISRCTN #	ISRCTN 79455488	
EudraCT #	2021-002060-47	
CTA #	CTA 31330/0008/001-0001	
MREC #	21/LO/0593	
Study Design	A randomised phase II, multi-stage, multi-arm (MAMS), basket trial investigating reduced intensity administration of immune checkpoint inhibition across multiple cancer types. The initial cohorts (baskets) will be patients with renal cancer receiving ipilimumab+nivolumab and patients with melanoma receiving ipilimumab+nivolumab and patients with melanoma receiving pembrolizumab. Patients responding to treatment after 12 weeks will be randomised to continue standard treatment or receive reduced intensity treatment.	
Setting	The trial will be run at NHS hospitals in the UK.	
Type of Participants to be Studied	Adults with locally advanced or metastatic cancer receiving immune checkpoint inhibitors as standard-of-care and responding to treatment (i.e. complete or partial response or stable disease) at 12 weeks in the UK.	
Ancillary Studies/Substudies	A number of studies are expected to be initiated whilst the trial is ongoing (subject to funding) including but not limited to a translational sub-study - blood samples will be prospectively collected for future translational projects.	
Sponsor	University College London (UCL) [coordinated by the MRC CTU at UCL]	
Interventions to be Compared	Standard-of-care immune checkpoint inhibition (ICI).	
	Stage I	Standard-of-care dose interval ('X' weekly) vs reduced intensity dosing (every 2 x 'X' weeks).
	Stage II	Up to 5 arms of different treatment intervals, subject to IDMC review of the first stage results.

SUMMARY INFORMATION TYPE	SUMMARY DETAILS	
Study Hypothesis	Extending the interval between doses of ICI in patients with advanced cancers maintains efficacy and disease control compared to standard intensity treatment, with patient and economic benefits.	
Primary Outcome Measure(s)	Stage I	Progression-free survival (time to event)
	Stage II	Progression-free survival (time to event)
Secondary Outcome Measure(s)	Overall survival	
	Quality-of-Life (QoL)	
	Treatment related toxicity	
	Mean incremental cost per patient Mean incremental QALYs per patient Cost-utility analysis assessing cost-effectiveness of reduced vs. standard frequency administration	
	Feasibility of recruitment to each cohort	
Randomisation	Patients will be randomised centrally through an interactive web-based system using minimisation (with a random element) with stratification by a small number of important stratification factors.	
Number of Participants to be Studied	Stage I	160 patients (80 per arm) for each cohort
	Stage II	360 patients for each indication/drug regimen
Duration	It is expected that recruitment to stage I will complete in approximately 12 months Analysis of disease control will be performed at approximately 6 months from completion of stage I recruitment. It is expected that recruitment to stage II will complete in a further 12 months. Analysis of disease control will be performed within 12 months of recruitment completion.	
Funder	Jon Moulton Charity Trust and Medical Research Council	
Chief Investigator	Dr Duncan Gilbert	

TRIAL SCHEMA

Figure 1: Trial Entry, Randomisation and Treatment



CR - complete response; PR - partial response; SD - stable disease; SOC – standard-of-care

TRIAL ASSESSMENT SCHEDULE – FLEXIBILITY AND TIMING

The trial assessment schedule for each cohort, detailed on subsequent pages, is aligned with standard practice as far as possible to ensure that the trial can be implemented easily. However, this is balanced with the need to ensure appropriate monitoring of patients on trial treatment and assessment of outcome measures.

Flexibility of Schedules and Follow-up:
To allow for variations in standard practice across sites:

- Informed consent can be taken by any member of the team appropriately trained and delegated to take consent on the trial delegation log.
- All assessments should be performed by appropriately qualified members of the team as per the trial delegation log.
- The CT scan schedule should not be amended in the event of dose delay and should remain as initially intended from randomisation date. Assessment can be +/- 1 week from expected date.
- The questionnaire schedule should not be amended in the event of dose delay and should remain as initially intended from randomisation date. Assessment can be +/- 1 weeks from expected date; questionnaires should be administered prior to infusions being given.

Table 1: Timing of Blood Tests: The table below shows the timelines in which blood samples need to be collected during the course of the trial:

Blood test	Timeframe prior to randomisation	Timeframe prior to follow up visit
Haematology	≤6 weeks[3]	≤5 days
Biochemistry	≤6 weeks[3]	≤5 days
Coagulation parameters (PT, PTT, International Normalised Ratio [INR])	≤6 weeks	Not required
Hepatitis serologies (hepatitis B surface antigen, hepatitis C antibody)	Up to 18 weeks (i.e. result prior to commencement of initial 12 weeks ICI result acceptable)	Not required
HIV antibodies	Up to 18 weeks (i.e. result prior to commencement of initial 12 weeks ICI result acceptable)	Not required
Blood sample for translational research	N/A	Immediately prior to each treatment administration

Table 2: Timing of Other Assessments: The table below shows the timelines in which other assessments need to be collected during the course of the trial:

Assessment	Timeframe prior to randomisation	Timeframe with respect to follow up visit
CT with contrast of chest, abdomen, and pelvis (alternatively PET-CT) and brain imaging – contrast CT/MRI – as appropriate.	8 weeks	+/- 1 week[1]
12-lead ECG	Up to 18 weeks (i.e. result prior to commencement of initial 12 weeks ICI result acceptable)	As clinically required
Serum HCG pregnancy test/Urine pregnancy test (women of childbearing potential only)[2]	Prior to treatment administration	Prior to each treatment administration

1 – The imaging schedule should not be amended in the event of dose delay remaining as initially intended from randomisation date.
2 – At screening a serum HCG pregnancy test must be performed, during follow-up a serum test is only required if there is any doubt over the urine test result.
3 – Haematology and biochemistry also required within 5 days of day 1 (if screening tests do not fall within this window).

TRIAL ASSESSMENT SCHEDULE – STAGE 1

Table 3: Nivolumab regimens (after combination ipilimumab+nivolumab) i.e. Renal and Melanoma (N)

	12 weeks Ipilimumab/Nivolumab with Clinical Response (CR/PR/SD)	Screening	Randomisation	1 Day 1	2 Week 4	3 Week 8	4 Week 12	5 Week 16	6 Week 20	7 Week 24	8 Week 28	9 Week 32	10 Week 36	11 Week 40	12 Week 44	13 Week 48	14 Week 52
Consent	Written Informed Consent	x[8]															
Randomisation	Randomisation[1]		x[8]														
Treatment	Arm A (SOC) Nivolumab 480mg			x[8]	x	x	x	x	x	x	x	x	x	x	x	x	x
	Arm B (Extended) Nivolumab 480mg			x		x		x		x		x		x		x	
Clinical Evaluation	Clinical History	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Physical Examination	x															
	ECG[2]	x															
	Weight	x		x	a	x	a	x	a	x	a	x	a	x	a	x	a
	Concomitant Medication	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x
	Adverse Events	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
Radiology	CT Scan/PET CT +/- brain imaging (MRI or CT)[3,5]	x					x			x			x			x	
Blood tests	Haematology[6]	x		x[10]	x	x	x	x	x	x	x	x	x	x	x	x	x
	Clinical Chemistry[6]	x		x[10]	x	x	x	x	x	x	x	x	x	x	x	x	x
	Coagulation parameters (PT, PTT, International Normalised Ratio [INR])	x															
	Hepatitis serologies (hepatitis B surface antigen, hepatitis C	x															
	HIV antibodies	x															
Pregnancy tests	Urine/Serum Pregnancy Test[4]	x		x	a	x	a	x	a	x	a	x	a	x	a	x	a
Patient Questionnaires	CSRI (health care resource use)[12]	x					x			x			x			x	
	EQ-5D-5L[12], QLQ-C30[5]	x					x			x			x			x	
Translational samples	Blood Sample[7]			x	a	x	a	x	a	x	a	x					

(a) Arm A (SOC) only.
1 – Randomisation occurs up to 8 weeks after last dose of first line immunotherapy.
2 – In case of clinically significant ECG abnormalities, including a QTcF value ≥450ms, 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 <450ms is confirmed.
3 – with stable disease or evidence of response.
4 – A serum HCG pregnancy test must be performed at screening, and should be performed at follow-up if there is any doubt over the results of the urine. Pregnancy tests must be undertaken at each scheduled treatment visit for participants who are WOCBP during the treatment period.
5 – 12 weekly contrast enhanced CT scans until disease progression and QLQ-C30 quality of life questionnaire every 12 weeks until disease progression.
6 – Haematology and Clinical Chemistry bloods are required at each visit. Where treatment is not being administered bloods can be taken at the GP or hospital phlebotomy. See section 6.2.4 for requirements. Blood tests are not required for patients who have discontinued treatment.
7 – Translational blood samples immediately prior to each treatment administration. Translational blood samples are not required for patients who have discontinued treatment.
8 – Screening, randomisation and day 1 may all occur on the same day.
9 – End of trial schedule visit occurs 8 weeks after last dose of trial treatment (where a participant does not wish to continue with follow-up) or after the completion of 1 year 9 months follow-up.
10 – If bloods at screening are taken within 5 days of day 1 the same results can be used.
11 – CT scan at End of Trial Schedule visit only performed if clinically indicated.
12 - EQ-5D-5L quality of life questionnaire and CSRI questionnaire at baseline and every 12 weeks until end of trial schedule.
13 – Trial visits should occur +/- 1 week as from the previous scheduled visit.

Table 3 continued:

	Ongoing Nivolumab, year 2	15	16	17	18	19	20	21	22	23	24	25
		Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Week 80	Week 84	Week 88	Week 92	End of Trial Schedule [9]
Treatment	Arm A (SOC) Nivolumab 480mg	x	x	x	x	x	x	x	x	x	x	
	Arm B (Extended) Nivolumab 480mg	x		x		x		x		x		
Clinical Evaluation	Clinical History	x	x	x	x	x	x	x	x	x	x	x
	Physical Examination											
	ECG[2]											
	Weight	x	a	x	a	x	a	x	a	x	a	x
	Concomitant Medication	x	x	x	x	x	x	x	x	x	x	x
	Adverse Events	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
Radiology	CT Scan/PET CT +/- brain imaging (MRI or CT)[3,5]		x			x			x			x[11]
Blood tests	Haematology[6]	x	x	x	x	x	x	x	x	x	x	x
	Clinical Chemistry[6]	x	x	x	x	x	x	x	x	x	x	x
	Coagulation parameters (PT, PTT, International Normalised Ratio [INR])											
	Hepatitis serologies (hepatitis B surface antigen, hepatitis C											
	HIV antibodies											
Pregnancy tests	Urine/Serum Pregnancy Test[4]	x	a	x	a	x	a	x	a	x	a	
Patient Questionnaires	CSRI (health care resource use)[12]		x			x			x			x
	EQ-5D-5L[12], QLQ-C30[5]		x			x			x			x
Translational samples	Blood Sample[7]											

(a) Arm A (SOC) only.
1 – Randomisation occurs up to 8 weeks after last dose of first line immunotherapy.
2 – In case of clinically significant ECG abnormalities, including a QTcF value ≥450ms, 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 <450ms is confirmed.
3 – with stable disease or evidence of response.
4 – A serum HCG pregnancy test must be performed at screening, and should be performed at follow-up if there is any doubt over the results of the urine. Pregnancy tests must be undertaken at each scheduled treatment visit for participants who are WOCBP during the treatment period.
5 – 12 weekly contrast enhanced CT scans until disease progression and QLQ-C30 quality of life questionnaire every 12 weeks until disease progression.
6 – Haematology and Clinical Chemistry bloods are required at each visit. Where treatment is not being administered bloods can be taken at the GP or hospital phlebotomy. See section 6.2.4 for requirements. Blood tests are not required for patients who have discontinued treatment.
7 – Translational blood samples immediately prior to each treatment administration. Translational blood samples are not required for patients who have discontinued treatment.
8 – Screening, randomisation and day 1 may all occur on the same day.
9 – End of trial schedule visit occurs 8 weeks after last dose of trial treatment (where a participant does not wish to continue with follow-up) or after the completion of 1 year 9 months follow-up.
10 – If bloods at screening are taken within 5 days of day 1 the same results can be used.
11 – CT scan at End of Trial Schedule visit only performed if clinically indicated
12 - EQ-5D-5L quality of life questionnaire and CSRI questionnaire at baseline and every 12 weeks until end of trial schedule.
13 – Trial visits should occur +/- 1 week as from the previous scheduled visit.

Table 4: Pembrolizumab (6 weekly monotherapy) i.e. Melanoma (P)

	12 weeks Pembrolizumab with Clinical Response (CR/PR/SD)	Screening	Randomisation	1	2	3	4	5	6	7	8	9	10
				Day 1	Week 6	Week 12	Week 18	Week 24	Week 30	Week 36	Week 42	Week 48	Week 54
Consent	Written Informed Consent	x[8]											
Randomisation	Randomisation[1]		x[8]										
Treatment	Arm A (SOC) Pembrolizumab 400mg			x[8]	x	x	x	x	x	x	x	x	x
	Arm B (Extended) Pembrolizumab 400mg			x		x		x		x		x	
Clinical Evaluation	Clinical History	x		x	x	x	x	x	x	x	x	x	x
	Physical Examination	x											
	ECG[2]	x											
	Weight	x		x	a	x	a	x	a	x	a	x	a
	Concomitant Medication	x		x	x	x	x	x	x	x	x	x	x
	Adverse Events	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
Radiology	CT Scan/PET CT +/- brain imaging (MRI or CT) [3,5]	x				x		x		x		x	
Blood tests	Haematology[6]	x		x[10]	x	x	x	x	x	x	x	x	x
	Clinical Chemistry[6]	x		x[10]	x	x	x	x	x	x	x	x	x
	Coagulation parameters (PT, PTT, International Normalised Ratio [INR])	x											
	Hepatitis serologies (hepatitis B surface antigen, hepatitis C	x											
	HIV antibodies	x											
Pregnancy tests	Urine/Serum Pregnancy Test[4]	x		x	a	x	a	x	a	x	a	x	a
Patient Questionnaires	CSRI (health care resource use)[12]	x				x		x		x		x	
	EQ-5D-5L[12], QLQ-C30[5]	x				x		x		x		x	
Translational samples	Blood Sample[7]			x	a	x	a	x	a	x			

(a) Arm A (SOC) only.
1 – Randomisation occurs up to 8 weeks after last dose of first line immunotherapy.
2 – In case of clinically significant ECG abnormalities, including a QTcF value ≥450ms, 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 <450ms is confirmed.
3 – with stable disease or evidence of response.
4 – A serum HCG pregnancy test must be performed at screening, and should be performed at follow-up if there is any doubt over the results of the urine. Pregnancy tests must be undertaken at each scheduled treatment visit for participants who are WOCBP during the treatment period.
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7 – Translational blood samples immediately prior to each treatment administration. Translational blood samples are not required for patients who have discontinued treatment.
8 – Screening, randomisation and day 1 may all occur on the same day.
9 – End of trial schedule visit occurs 8 weeks after last dose of trial treatment (where a participant does not wish to continue with follow-up) or after the completion of 1 year 9 months follow-up.
10 – If bloods at screening are taken within 5 days of day 1 the same results can be used.
11 – CT scan at End of Trial Schedule visit only performed if clinically indicated.
12 - EQ-5D-5L quality of life questionnaire and CSRI questionnaire at baseline and every 12 weeks until end of trial schedule.
13 – Trial visits should occur +/- 1 week as from the previous scheduled visit.

Table 4 continued:

	Ongoing Pembrolizumab, year 2	11	12	13	14	15	16	17
		Week 60	Week 66	Week 72	Week 78	Week 84	Week 90	End of Trial Schedule [9]
Consent	Written Informed Consent							
Randomisation	Randomisation[1]							
Treatment	Arm A (SOC) Pembrolizumab 400mg	x	x	x	x	x	x	
	Arm B (Extended) Pembrolizumab 400mg	x		x		x		
Clinical Evaluation	Clinical History	x	x	x	x	x	x	x
	Physical Examination							
	ECG[2]							x
	Weight	x	a	x	a	x	a	x
	Concomitant Medication	x	x	x	x	x	x	x
	Adverse Events	x	x	x	x	x	x	x
	WHO Performance Status	x	x	x	x	x	x	x
Radiology	CT Scan/PET CT +/- brain imaging (MRI or CT) [3,5]	x		x		x		x[11]
Blood tests	Haematology[6]	x	x	x	x	x	x	x
	Clinical Chemistry[6]	x	x	x	x	x	x	x
	Coagulation parameters (PT, PTT, International Normalised Ratio [INR])							
	Hepatitis serologies (hepatitis B surface antigen, hepatitis C							
	HIV antibodies							
Pregnancy tests	Urine/Serum Pregnancy Test[4]	x	a	x	a	x	a	
Patient Questionnaires	CSRI (health care resource use)[12]	x		x		x		x
	EQ-5D-5L[12], QLQ-C30[5]	x		x		x		x
Translational samples	Blood Sample[7]							

(a) Arm A (SOC) only.
1 – Randomisation occurs up to 8 weeks after last dose of first line immunotherapy.
2 – In case of clinically significant ECG abnormalities, including a QTcF value ≥450ms, 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 <450ms is confirmed.
3 – with stable disease or evidence of response.
4 – A serum HCG pregnancy test must be performed at screening, and should be performed at follow-up if there is any doubt over the results of the urine. Pregnancy tests must be undertaken at each scheduled treatment visit for participants who are WOCBP during the treatment period.
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8 – Screening, randomisation and day 1 may all occur on the same day.
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13 – Trial visits should occur +/- 1 week as from the previous scheduled visit.

LAY SUMMARY

Immune checkpoint inhibitors are a type of drug used to treat patients with a number of different types of advanced cancers. They help the body's immune system detect or find cancer cells. The immune system is important in fighting infections and cancer. Immune checkpoint inhibitors can stop cancers growing for many months or years.

Immune checkpoint inhibitors are given to patients through an injection into a vein every 3-6 weeks in a hospital or clinic. Blood tests are needed before each injection. This means that patients spend a lot of time (and money) on hospital visits. The drugs are also expensive costing many thousands of pounds per month and use a lot of hospital resource (e.g. cancer treatment teams).

It is likely that immune checkpoint inhibitors work for a longer period of time than originally thought. This means it may be possible to give the drugs less often and still have the same effect on the cancer.

The unwanted side-effects of these drugs are unlike those of traditional chemotherapy drugs as they may cause auto-immune problems. This means that the patients' immune system attacks their normal tissues. The relationship between dose of drug and side-effect is not clear but it is possible that giving the drugs less often might limit the side-effects experienced by patients.

REFINE is a clinical trial that tests whether patients can receive these drugs less often whilst getting the same benefit in terms of treating their cancer. The REFINE trial is an initial test of this idea and has the potential to develop into a larger trial. The REFINE trial aims to understand the benefits to patients and to the health service from this approach. REFINE will start by testing this in a group of patients with advanced kidney cancer or melanoma but will then test this approach in patients with a range of other tumour types.

CONTENTS

1 BACKGROUND 1
1.1 INTRODUCTION 1
1.2 IMMUNE CHECKPOINT INHIBITORS 1
1.2.1 Immunotherapy and Renal Cell Cancer 2
1.2.2 Immune Checkpoint Inhibition and Melanoma 3
1.3 REDUCING TREATMENT INTENSITY OF ICI 3
1.3.1 Reduced Treatment Duration 3
1.3.2 Extended Dosing interval 4
1.4 OBJECTIVE 4
1.5 REFINE DESIGN 5
1.5.1 Outcome Measures 6
1.6 STATISTICAL CONSIDERATIONS 6
1.7 HEALTH ECONOMIC CONSIDERATIONS 6
1.8 TRANSLATIONAL STUDIES 7

2 SELECTION OF SITES AND CLINICIANS 8
2.1 SITE AND INVESTIGATOR INCLUSION CRITERIA 8
2.1.1 PI's Qualifications & Agreements 8
2.1.2 Adequate Resources 9
2.1.3 Site Assessment 9
2.2 APPROVAL AND ACTIVATION 9
2.3 SITE MANAGEMENT 10

3 SELECTION OF PATIENTS 11
3.1 INCLUSION CRITERIA 11
3.1.1 GENERAL INCLUSION CRITERIA 11
3.1.2 COHORT SPECIFIC INCLUSION CRITERIA 12
3.2 PATIENT EXCLUSION CRITERIA 12
3.3 NUMBER OF PATIENTS 13

4 RANDOMISATION 14
4.1 RANDOMISATION 14
4.1.1 Informed Consent 14
4.1.2 Screening procedures 14
4.1.3 Timing of Randomisation 14
4.2 RANDOMISATION PRACTICALITIES 15
4.3 CO-ENROLMENT GUIDELINES AND REPORTING 15

5 TREATMENT OF PATIENTS 16
5.1 INTRODUCTION 16
5.1.1 Stage I 16
5.1.2 Treatment Arm A (SOC) 17
5.1.3 Treatment arms B (extended interval) 17
5.1.4 Dispensing 17
5.1.5 Products 17
5.1.6 Dose Modifications, Interruptions & Discontinuations 18
5.2 MANAGEMENT OF CASES OF TRIAL MEDICATION OVERDOSE 19
5.3 PROTOCOL TREATMENT DISCONTINUATION 19

5.3.1 Trial treatment discontinuation at patient request 20
5.3.2 Discontinuation criteria for adverse events 20
5.3.3 Trial treatment discontinuation for progression 21
5.3.4 Treatment Beyond Progression 21
5.4 ACCOUNTABILITY & UNUSED DRUGS/DEVICES 22
5.5 COMPLIANCE AND ADHERENCE 22
5.6 TREATMENT DATA COLLECTION 22
5.7 NON-TRIAL TREATMENT 22
5.7.1 Medications Permitted 23
5.7.2 Medications Not Permitted 23
5.7.3 Medications to be Used With Caution 24
5.7.4 Treatment After Trial Event 24
5.8 CONTRACEPTION 24
5.9 CO-ENROLMENT GUIDELINES 24

6 ASSESSMENTS & FOLLOW-UP 25
6.1 TRIAL ASSESSMENT SCHEDULES 25
6.1.1 Telephone Assessments 25
6.2 CLINICAL/SAFETY ASSESSMENTS 25
6.2.1 Physical Examination 25
6.2.2 Pregnancy Tests 25
6.2.3 Electrocardiograms 25
6.2.4 Laboratory Assessments 26
6.3 RADIOLOGICAL ASSESSMENTS OF RESPONSE AND DISEASE PROGRESSION 28
6.4 PROCEDURES FOR ASSESSING QUALITY OF LIFE 28
6.5 FOLLOW-UP 28
6.6 EARLY STOPPING OF FOLLOW-UP 28
6.7 PATIENT TRANSFERS 29
6.8 LOSS TO FOLLOW-UP 29

7 SAFETY REPORTING 30
7.1 DEFINITIONS 30
7.1.1 Medicinal Products 30
7.1.2 Adverse Events 31
7.1.3 Adverse events exempt from the expedited reporting timeframe (24 hours) 31
7.1.4 Other Study-specific Requirements 31
7.2 INVESTIGATOR RESPONSIBILITIES 32
7.2.1 Investigator Assessment 32
7.2.2 Notification Procedure 34
7.3 MRC CTU RESPONSIBILITIES 34

8 QUALITY ASSURANCE & CONTROL 36
8.1 RISK ASSESSMENT 36
8.2 CENTRAL MONITORING AT CTU 36
8.3 ON-SITE/REMOTE MONITORING 36
8.3.1 Direct Access to Patient Records 36
8.3.2 Confidentiality 36
8.4 SOURCE DATA 36

9 STATISTICAL CONSIDERATIONS 38
9.1 METHOD OF RANDOMISATION 38

9.2 OUTCOME MEASURES 38
9.2.1 Primary 38
9.2.2 Secondary 38
9.3 SAMPLE SIZE 38
9.3.1 stage 1 (each cohort) 38
9.3.2 stage 2 (each cohort) 39
9.3.3 Potential Phase 3 Extension 39
9.4 INTERIM MONITORING AND ANALYSES 40
9.4.1 Primary Outcome measures - stage 1 (each cohort) 40
9.4.2 Secondary outcomes measures – stage 1 40
9.4.3 progressing from stage I to stage II 40
9.4.4 Primary Outcome measures - stage 2 (Planned, each cohort) 41
9.4.5 Secondary outcomes measures – stage 2 41
9.4.6 Missing data and loss to follow-up 41

10 HEALTH ECONOMICS 43
10.1 OVERVIEW 43
10.1.1 QALYs 43
10.1.2 Resource Use and Costs 43
10.1.3 Time points for data collection 43
10.1.4 Analysis and reporting results 43
10.1.5 Lifetime modelling 44

11 ANCILLARY STUDIES 45
11.1 TRANSLATIONAL PROJECTS 45
11.1.1 Baseline tumour samples 45
11.1.2 Serial blood samples 45

12 REGULATORY & ETHICAL ISSUES 46
12.1 COMPLIANCE 46
12.1.1 Regulatory Compliance 46
12.1.2 Site Compliance 46
12.1.3 Data Collection & Retention 46
12.2 ETHICAL CONDUCT 46
12.2.1 Ethical Considerations 46
12.2.2 Favourable Ethical Opinion 47
12.3 COMPETENT AUTHORITY APPROVALS 48
12.4 OTHER APPROVALS 48
12.5 TRIAL CLOSURE 48

13 INDEMNITY 49

14 FINANCE 50

15 OVERSIGHT & TRIAL COMMITTEES 51
15.1 TRIAL MANAGEMENT GROUP (TMG) 51
15.2 TRIAL STEERING COMMITTEE (TSC) 51
15.3 INDEPENDENT DATA MONITORING COMMITTEE (IDMC]) 51
15.4 ROLE OF STUDY SPONSOR 51

16 PATIENT AND PUBLIC INVOLVEMENT 53
16.1 POTENTIAL IMPACT OF PPI 53
16.2 IDENTIFYING PPI CONTRIBUTORS 53
16.3 PPI IN THE ONGOING RUNNING OF STUDY 53

17 PUBLICATION AND DISSEMINATION OF RESULTS 54

18 DATA AND/OR SAMPLE SHARING 55

19 PROTOCOL AMENDMENTS 56
19.1 PROTOCOL 56
19.1.1 Amendment made to protocol version 1.0 07-Jul-2021 56
19.1.2 Amendment made to protocol version 2.0 19-Aug-2021 56
19.1.3 Amendment made to protocol version 3.0 05-Oct-2021 56
19.1.4 Amendment made to protocol version 4.0, 04-Mar-2022 56

20 REFERENCES 58

ABBREVIATIONS

ABBREVIATION	EXPANSION
ABPI	Association of the British Pharmaceutical Industry
AE	Adverse event
AR	Adverse reaction
bid	Bis in die (twice a day)
BNF	British National Formulary
BSA	Body surface area
CF	Consent form
CI	Chief Investigator
CI	Confidence interval
CLRN	Comprehensive Local Research Network
CNS	Central Nervous System
COM	Clinical Operations Manager
CPM	Clinical Project Manager
CR	Complete response
CRF	Case Report Form
CRN	Clinical Research Network
CSRI	Client Service Receipt Inventory
CT	Computed Tomography
CTA	Clinical Trials Authorisation
CTAAC	Clinical Trials Awards and Advisory Committee
CTIMP	Clinical trial of an investigational medicinal product
CTLA4	Cytotoxic T-lymphocyte associated protein 4
CTU	*See MRC CTU at UCL, below*
DCF	Data Clarification Form
DH	Department of Health

ABBREVIATION	EXPANSION
DM	Data Manager
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DPA	(UK) Data Protection Act
DSUR	Developmental Safety Update Report
ECG	Electrocardiogram
ECRIN	European Clinical Research Infrastructure Network
EDC	Electronic Data Capture
EFGCP	European Forum for Good Clinical Practice
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ERC	Endpoint Review Committee
EU	European Union
EudraCT	European Union Drug Regulatory Agency Clinical Trial
FBC	Full Blood Count
FDA	(US) Food and Drug Administration
FFPE	Formalin Fixed Paraffin Embedded
GCP	Good Clinical Practice
GP	General Practitioner
GSA	Group-specific appendix
HBV	Hepatitis B Virus
HBsAg	Hepatitis B surface Antigen
HBc	Hepatitis B core (antigen)
HCG	Human Chorionic Gonadotrophin
HE	Health economics
HEAP	Health economics analysis plan
HES	Hospital Episodes Statistics

ABBREVIATION	EXPANSION
HIV	Human Immunodeficiency Virus
HRA	Health Research Authority
HR QoL	Health Related Quality of Life
IB	Investigator Brochure
ICER	Incremental Cost Effectiveness Ratio
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICI	Immune checkpoint inhibitor
IDMC	Independent Data Monitoring Committee
IFN	Interferon
IMDC	International Metastatic RCC Database Consortium
IMP	Investigational medicinal product
IO	Immuno-oncology
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention-to-treat
IUD	Intrauterine device
KPS	Karnofsky Performance Status
LFT	Liver Function Tests
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
MRC CTU at UCL	Medical Research Council Clinical Trials Unit at University College London (also generally abbreviated to “CTU”)
MREC	Multi-centre Research Ethics Committee
MRI	Magnetic Resonance Imaging
NCRI	National Cancer Research Institute
NCRN	National Cancer Research Network

ABBREVIATION	EXPANSION
NHS	National Health Service
NHSCR	National Health Service Central Register
NHS-IC	National Health Service Information Centre
NICE	National Institute for Health and Care Excellence
NIH	US National Institutes of Health
NIHR	National Institute for Health and Care Research
NIHR CSP	National Institute for Health and Care Research Co-ordinated System for gaining NHS Permission
NIMP	Non-investigational-medicinal product
NRES	National Research Ethics Service
NSCLC	Non-small cell lung cancer
OD	Once daily
ONS	Office of National Statistics
OS	Overall Survival
PALS	Patient Advice and Liaison Services
PD	Progressive Disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death ligand 1
PET	Positron Emission Tomography
PFS	Progression Free Survival
PI	Principal Investigator
PIS	Patient Information Sheet
PK	Pharmacokinetics
PR	Partial Response
PROM	Patient Reported Outcome Measure
PSSRU	Personal Social Services Research Unit
Q3wk	Every 3 weeks

ABBREVIATION	EXPANSION
Q4wk	Every 4 weeks
Q6wk	Every 6 weeks
Q8wk	Every 8 weeks
Q12wk	Every 12 weeks
Q16wk	Every 16 weeks
QALY	Quality Adjusted Life Year
QMAG	Quality Management Advisory Group
QoL	Quality-of-life
QP	Qualified Person
R&D	Research and Development
RCC	Renal Cell Carcinoma
RCT	Randomised controlled trial
REC	Research Ethics Committee
RGC	Research Governance Committee
RGF	Research Governance Framework (for Health and Social Care)
RSI	Reference Safety Information
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
SD	Stable Disease
SMT	Senior Management Team
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
SSA	Site-specific approval
SSG	Scientific Strategy Group
SSI	Site-specific information
SUSAR	Suspected unexpected serious adverse reaction

ABBREVIATION	EXPANSION
TFT	Thyroid function test
TM	Trial Manager
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
TSC	Trial Steering Committee
TSH	Thyroid Stimulating Hormone
U+E	Urea and Electrolytes
UAR	Unexpected adverse reaction
UKCRN	UK Clinical Research Network (now the NIHR CRN)
WHO	World Health Organization
WOCBP	Women of childbearing potential

1 BACKGROUND

1.1 INTRODUCTION

Immune checkpoint inhibitors (ICI) have revolutionised cancer treatment, resulting in durable responses and long-term survival in patient groups where previously responses were rare and survival was measured in months. ICIs are monoclonal antibodies that target immune checkpoints, such as the programmed cell death 1 receptor (PD-1) and programmed cell death receptor ligand 1 (PD-L1), which play a key role in physiological immune homeostasis. Inhibition of these checkpoints, through which cancer cells evade the immune system, unmasks the cancer from the host immune system, and enhances pre-existing anticancer immune responses.

In the setting of advanced disease, ICIs are routinely administered on a schedule of frequent intravenous administrations (typically every 3-6 weeks) for up to 2 years, until cancer progression or the development of intolerable side-effects. The lack of a dose-response relationship and the limited understanding of the role of predictive biomarkers to guide their use and ongoing treatment, gives an opportunity to reduce treatment intensity, potentially reducing side effects and drug costs.

Our aims are to understand better how to limit individual patient exposure whilst maintaining efficacy with the potential for major benefits in terms of patient quality-of-life and financial costs. The prolonged physiological activity of these drugs means that wider spacing between doses (reduced frequency of administration) should be possible without compromising outcomes. Current approaches to reduce treatment are testing early cessation in responding patients at a pre-defined, arbitrary endpoint (e.g. stopping treatment after one year in patients with metastatic non-small cell lung cancer or melanoma).

REFINE is a multi-arm, multi-stage (MAMS) adaptive trial using the durations design to investigate this approach of extending dosing intervals in patients with advanced cancers who experience an initial (radiological) response to ICI treatment. As a basket trial this approach will be tested in a number of different cancers and with differing drug regimens. The aim is to identify the optimal (longest) dose interval with the lowest acceptable loss of disease control. The initial two stages of this multi-stage project will refine and underpin a subsequent expansion to a phase III study which may establish a new standard-of-care. REFINE includes comprehensive participant involvement and health economic expertise alongside translational science to maximise the relevance and transferability of our results.

1.2 IMMUNE CHECKPOINT INHIBITORS

Immune manipulation to control cancers has been attempted for decades through the use of interferon or interleukin-2 (Il-2) but toxicities were frequent and, although complete responses were seen, they were infrequent and stochastic. Cancer cells have been demonstrated to evade immune clearance through the activation of immune checkpoints whose normal function is to keep the immune system in check and avoid auto-immune activation. The normal function of PD-L1 is to regulate the balance between T-cell activation and tolerance through interaction with its receptor, PD-1 which is expressed on the surface of immune effector cells (1). PD-L1 is also inappropriately expressed by tumours, helping tumours evade detection and elimination by the host immune system. In the tumour microenvironment PD-L1, inappropriately expressed on tumour cells, binds to PD-1 on activated anti-tumour T-cells within the tumour, delivering an inhibitory signal to those T-cells and preventing them from killing the target tumour cells and thus protecting the tumour from

immune elimination. Recent improved understanding of this important mechanism of tumour survival has been swiftly followed by therapeutic manipulation of these ligand: receptor interactions. Monoclonal antibodies which inhibit the PD-L1: PD-1 checkpoint (or similar ligand: receptor interactions involving the CTLA4 receptor) are now established as standards-of-care across several indications for recurrent or metastatic disease and are under investigation in potentially curable settings. A notable example is the transformation of outcomes for metastatic melanoma, where long-term outcomes from the combination of the immune checkpoint inhibitors (ICI) ipilimumab (anti-CTLA4) and nivolumab (anti-PD-1) have recently demonstrated a 5-year survival of 52% for patients with advanced disease (2) – a situation where previously a median survival of just 6 months would have been expected.

The use of ICI has expanded rapidly to multiple tumour types. It has been suggested that a higher frequency of gene mutations in certain cancers, exemplified by tumour mutational burden (TMB), increases the likelihood of recognition of tumours by the host immune system and, as such, a greater chance of an anti-tumour immune response (3). Despite intensive investigation, across a range of tumour types, success in identifying validated predictive biomarkers of response has been limited (4). There is an association between strong expression of PD-L1 on tumours and increased response to ICI, but this is not sufficient to allow selection of patients for treatment in most current indications. Currently therefore, ICI are typically offered to all patients within a certain indication, despite the expectation that – as with longer-established systemic anti-cancer therapies - only a minority of patients will benefit from treatment.

Clinical response to treatment with ICI identifies a group of responding patients across different tumour types that likely have more in common biologically (in the host: tumour interactions at least) than their tissue of origin. Importantly, responding patients currently remain on treatment indefinitely – regular intravenous administrations of monoclonal antibodies (every 4-weeks, for instance). This approach requires a major commitment of resources for individual patients and the health service alike. It is this group of patients whose tumours are responding that are the focus of REFINE, in particular those patients undergoing treatment with ICI in the setting of advanced/ metastatic cancers that are responding to treatment after their initial 12-weeks.

1.2.1 IMMUNOTHERAPY AND RENAL CELL CANCER

Kidney cancer accounts for 5% and 3% of all adult malignancies in men and women, respectively, representing the 7th most common cancer in men and the 10th most common cancer in women (5). The highest incidence of kidney cancers occurs in the higher income regions of the world. In the UK it affected 9,123 people in 2014, making RCC the 8th most common cancer overall (www.ons.gov.uk). Renal cell carcinoma (RCC) accounts for approximately 80% of all kidney cancers. Well-known risk factors for RCC include cigarette smoking, obesity and hypertension, but RCCs are also more common in patients with end-stage renal failure or acquired renal cystic disease, and in patients on dialysis, those who have had kidney transplantation or those with tuberous sclerosis syndrome (5).

Primary RCCs are typically treated with surgical resection. With respect to the management of patients with advanced disease, the combination of ipilimumab (anti-CTLA4) for 4 cycles (3-weekly) with nivolumab (anti-PD-1) followed by nivolumab alone resulted in improved overall survival as compared with the tyrosine kinase inhibitor (TKI), sunitinib (6, 7). As such the combination of ipilumumab+nivolumab is now considered a standard-of-care for intermediate and poor-risk advanced RCC. Similarly, the addition of pembrolizumab to another TKI, axitinib, also improved overall survival compared to sunitinib (standard-of-care), with responses seen in 59% of patients and a median progression-free survival of 15.1 months (8). The phase III Javelin Renal 101 trial reported a statistically significant progression-free survival benefit of another anti-PD-L1 ICI, avelumab, and

axitinib compared to sunitinib, with an objective response rate of 52% versus 27% respectively (9). Mature overall survival data are awaited.

In the UK, the current combination of ipilumumab+nivolumab is recommended as front-line/treatment-naïve therapy for advanced disease, in intermediate- or poor-risk RCC patients as defined in the IMDC criteria.

1.2.2 Immune Checkpoint Inhibition and Melanoma

Immunotherapy has dramatically improved outcomes for patients with metastatic melanoma. Of all solid tumours, melanoma has been shown to have some of the highest rates of response to ICI. Malignant melanomas typically have a high tumour mutational burden (TMB), owing to the mutagenic effects of ultraviolet light; high TMB is associated with increased response to ICI. (10).

Disseminated malignant melanoma was once a disease considered refractory to systemic therapy with a median overall survival of between 6-10 months. However, combination blockade of PD-1 and CTLA-4 for patients with metastatic melanoma in the first-line setting has led to 5-year survival rates of 52% (2) with responses independent of PD-L1 expression (11). Toxicity can be high with combination therapy, with grade 3 or 4 treatment-related adverse events occurring in almost 60%. Therefore, single agent treatment with the anti-PD-1 agent, pembrolizumab, remains an appropriate option in the first line setting for those not suited to combination therapy, with grade 3–4 treatment-related adverse events shown to occur in only 17% (11).

1.3 REDUCING TREATMENT INTENSITY OF ICI

1.3.1 Reduced Treatment Duration

On-going trials are investigating how to reduce exposure to ICI whilst maintaining efficacy, using the approach of early cessation - either at a single fixed time point or following maximal radiological response (with reintroduction of drug at progression).

Optimal duration of treatment with ICIs remains an open question. The CHECKMATE 153 study in advanced non-small cell lung cancer (NSCLC) is the only study to date specifically designed to address this question in this patient group (22). In this large community-based trial, patients with NSCLC with disease control (progression-free) after 12 months on nivolumab were randomised to either continuation of nivolumab (until progression or intolerable side-effects) or discontinuation, with re-challenge upon progression in the discontinuation group. A marked progression-free survival benefit was demonstrated for continuous nivolumab as compared with early cessation (HR=0.56, 95%CI 0.37-0.84 in preliminary results. Although the study was not powered for overall survival and follow-up is immature, the treatment effect on overall survival also favoured continued treatment (HR=0.62, 95%CI 0.42-0.92).

Two trials in the setting of metastatic melanoma are also currently testing the early cessation approach. The UK NIHR DANTE trial (ISCRTN15837212) is a non-inferiority trial that randomises patients receiving anti-PD-1 therapy who are progression-free at 12 months to either stop treatment (with re-challenge allowed on progression) or continue as per standard use.

The Canadian STOP-GAP trial (NCT02821013) is assessing intermittent versus continuous treatment with anti-PD-1 inhibitors, with patients randomised to either standard 2 years of treatment or treatment until maximal tumour response with subsequent re-treatment at the time of progression. It is therefore primarily evaluating the role of re-challenge rather than the specific question of

optimal treatment duration, with a primary outcome measure of overall survival and multiple quality-of-life and health economic secondary outcomes.

1.3.2 EXTENDED DOSING INTERVAL

Phamacokinetic studies in clinical trials have demonstrated the wide therapeutic margin of anti-PD-1 antibodies, with little evidence seen of a dose-response relationship (13), in contrast with cytotoxic chemotherapy. These results have since been supported in long-term follow-up studies, where increasing exposure to drug, at higher doses, has not correlated with overall survival (14). Furthermore, in early phase I trials of anti-PD-1 antibodies, physiologic efficacy (as measured by maximal receptor occupancy), was seen at much lower doses than those that became accepted standards of care (12).

Pharmacokinetic simulation studies have recently been used to amend the recommended dosing of the PD-1 inhibitor nivolumab to 240mg q2w or 480mg q4w (15, 16), although this remains significantly higher than the observed 0.1mg/kg minimal effective dose (12). Further work suggests that nivolumab could be effectively dosed q8-14w (after the first 2 doses), resulting in a potential 70% cost saving (17).

Pembrolizumab was first approved by the FDA for advanced melanoma in 2014 at a dose of 2mg/kg every three weeks. However, changes in dosing strategy have moved away from weight-based dosing to fixed doses, with 200mg 3-weekly now approved. Dosing patients with 400mg of pembrolizumab at 6-weekly intervals (excluding patients with a high clearance of drug, who have a low chance of clinical benefit and poorer prognosis) has been demonstrated to achieve similar trough concentration to current standard in virtually all patients, where trough concentration has previously been associated with overall survival. A reduced frequency of pembrolizumab dosing may therefore maintain efficacy. This is supported by pharmacodynamic studies, measuring T-cell responses to pembrolizumab, that show 95% target activation with a single dose of 1mg/kg (18) and reducing plasma clearance of pembrolizumab over time (19,20) associated with patients whose tumours are responding to ICI (21).

ICI are associated with an increased risk of autoimmune toxicities (colitis, pneumonitis, hypophysitis, thyroiditis etc). As with the relationship between dose and efficacy, that between drug concentrations and the likelihood of adverse events is also uncertain. It is possible therefore that less frequent dosing of ICI, with the associated lower plasma concentrations, may result in a reduction in both the incidence and duration of immune-related adverse events (15).

1.4 OBJECTIVE

The REFINE trial aims to determine optimum treatment intensity with immune checkpoint inhibitors. Through the basket trial design, REFINE aims to maintain efficacy outcomes for patients with a range of solid tumours and investigate a number of drug regimens.

REFINE will initially test this approach in a cohort of patients undergoing treatment with nivolumab (after combination ipilumumab+nivolumab) for advanced renal cancer, a cohort of patients with advanced malignant melanoma treated with the same regimen albeit different dosing (nivolumab after ipilumumab+ nivolumab) and also a cohort of patients with melanoma treated with pembrolizumab.

The REFINE trial as described in this protocol is initially a phase II assessment, looking for an initial indication of whether treatment can be delivered less often. Depending on the results, a larger,

definitive phase III assessment of the approach may be undertaken in the relevant cohorts within this same protocol.

REFINE is a parallel and complementary programme to REFINE-Lung, an initiative developed by the Lung Clinical Studies Group of the NCRI led by Prof Michael Seckl, Imperial College London, in collaboration with Prof Parmar of MRC CTU at UCL. REFINE-Lung assesses the optimal frequency of pembrolizumab administration in the context of treatment of metastatic NSCLC.

1.5 REFINE DESIGN

REFINE tests multiple schedules of administration, with the aim of determining the longest interval between doses that does not result in loss of disease control.

This is a multi-arm, multi-stage basket platform using the durations design. Each basket comprises a cohort defined by a specific tumour type and a specific ICI regimen. The first stage includes a randomisation between two arms in each cohort – one standard-of-care and one experimental arm testing a single frequency of reduced intensity treatment (i.e. an extended treatment interval) with 160 patients randomised to either standard (every 'X' weeks) or extended interval dosing (every 2 'X' weeks). Following analysis of these data, the second stage then tests additional experimental arms (with dosing intervals depending on the efficacy of the 2 'X' weekly schedule) in a second cohort of newly recruited patients, with the intervals informed by the results from the stage I patients. A substantial amendment will be submitted to the Medicines and Healthcare Products Regulatory Agency (MHRA) for approval prior to the commencement of stage II, and before the opening of enrolment in cohorts at reduced intensity treatment not already described in section 5 of this protocol.

Patients eligible for each of the cohorts within this trial are those responding to ICI (i.e. CR/PR/SD) after 12 weeks of treatment for advanced cancer, within specific indication (cancer type) and drug regimen cohorts.

The aim of this protocol is to demonstrate the feasibility of recruiting patients to this approach and investigate the first two stages of this MAMS design – initially investigating a single, extended dosing interval with a primary outcome measure of progression-free survival at 9 months from randomisation (12 months since starting ICI treatment). Assuming satisfactory recruitment and no reduction in PFS with altered dosing interval, the second stage tests a maximum of 3 further experimental arms to better understand the relationship between treatment interval and efficacy. The third stage will continue to a full phase III evaluation of appropriate cohorts.

Standard-of-care ICI for patients with advanced RCC is currently 4-weekly (q4w) nivolumab after 12 weeks of combination ipilimumab+nivolumab. Stage I of REFINE will therefore randomise patients between 4-weekly (standard-of-care) and 8-weekly (experimental) administration of nivolumab, following completion of ipilimumab+nivolumab.

In advanced melanoma, regimens typically used are again ipilimumab+nivolumab (as per the Renal cohort albeit with different doses of each drug) or pembrolizumab administered 6-weekly. The Stage I REFINE Melanoma nivolumab (N) cohort will randomise patients between 4 and 8-weekly nivolumab (after 12 weeks of combination treatment), as for the Stage I RCC cohort, above. The Melanoma pembrolizumab (P) cohort will randomise patients not progressing at 12 weeks between 6- and 12-weekly pembrolizumab.

The ultimate objective in all 3 cohorts is to establish whether the extended dose interval has a disease control rate non-inferior to the control arm with a pre-specified margin. As opposed to the trials investigating whether a fixed duration of therapy is non-inferior to continuous treatment, the approach taken in REFINE with multiple arms testing numerous dosing intervals will generate a dose: frequency response (disease control) curve informing an optimal decision around scheduling treatment (23).

1.5.1 Outcome Measures

Analysis of progression-free survival will be performed at 3-6 months after stage I recruitment has completed and will inform the design of the second stage design.

Completion of the first two stages of REFINE will demonstrate the feasibility of recruiting to a trial testing extended dosing interval of administration of different ICIs in responding patients across multiple indications. We will demonstrate the extended intervals of therapeutic intervention across which efficacy is retained and be ready, subject to additional funding, to definitively establish a standard of care ICI with improved therapeutic index and cost effectiveness.

1.6 STATISTICAL CONSIDERATIONS

A key goal of REFINE is to inform a phase 3 design to establish the optimal dosing interval of ICI, similar to REFINE-Lung (ISRCTN70247820). In such a trial, a curve will be fitted to the data from the multiple arms, modelling the frequency-response relationship. Using this curve, estimates of the 2-year overall survival risk ratios for each extended frequency against the control will be obtained, together with the associated confidence intervals. These will be used to find the most reduced frequency non-inferior to control within a pre-specified non-inferiority margin.

REFINE will closely align with REFINE-Lung (assessing the optimal frequency of pembrolizumab administration in the context of treatment of patients with metastatic NSCLC) with a shared design and statistical analysis plan maximising the efficiency of this approach.

1.7 HEALTH ECONOMIC CONSIDERATIONS

We will calculate the mean change in cost per quality-adjusted life-year (QALY) gained of 2X-weekly (intervention arm) relative to X-weekly (standard of care arm) administration of nivolumab or pembrolizumab in each of the three cohorts (Renal Cancer, Melanoma (N), Melanoma (P)) over a 24-month time horizon in an initial trial-based analysis, from the perspective of the NHS and Personal Social Services, and this will be extended to a lifetime decision analytic model. Pairwise comparisons between arms within the same cohort will also be made using data collected in the second stage of REFINE, calculating net monetary benefit at a range of cost-effectiveness thresholds, if appropriate, when other treatment frequencies are trialled in stage 2.

The same methods will be applied to all three cohorts: QALYs will be calculated from the utility scores calculated from participant responses to the EQ-5D-5L (24), as the area under the curve (25), adjusting for baseline differences using regression analysis; costs will be calculated by multiplying resource use by standard unit cost information, and will be collected via a modified version of the participant-completed Client Service Receipt Inventory (CSRI) and from treatment and concomitant medication CRFs, including information on inpatient and outpatient hospital service use including ICI treatment costs, primary and community health and social care service contacts, and other medications (26). EQ-5D-5L and service use information will be collected from participants at

baseline, 12 and 24 weeks, and every 12 weeks thereafter, including after disease progression. Information on administration of ICI and concomitant medications will be collected as described in Table 1 and Table 2. Baseline costs for resource use including medications will be collected over the 12-week period preceding baseline.

Further details of these analyses are in section 10 below and will be described in the **Health Economics Analysis Plan (HEAP)**, which will form a chapter of the **Statistical Analysis Plan (SAP)**.

1.8 TRANSLATIONAL STUDIES

Serial biomarkers of immune recognition and activation will be applied through collaboration with multiple labs. Initially, serial blood will be collected from patients in each intensity arm for pharmacokinetic analysis of therapeutic drug levels and high dimensional flow cytometry to characterise T-cell immunophenotypes and PD-1 receptor occupancy to determine whether reduction in dose frequency has any effect on T-cell differentiation and activation states.

Please see the **REFINE Laboratory Manual for Sites** and **REFINE Laboratory Manual for Imperial** details on sample collection, preparation (serum, plasma) and storage.

REFINE will develop a separately funded translational programme to identify biomarkers associated with initial and ongoing response (again in collaboration with REFINE Lung).

2 SELECTION OF SITES AND CLINICIANS

The trial Sponsor has overall responsibility for site and investigator selection.

2.1 SITE AND INVESTIGATOR INCLUSION CRITERIA

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

Sites where a recent previous serious protocol breach has occurred for any MRC CTU run trial will be thoroughly reviewed before allowing participants to enter the trial.

Those centres that meet the criteria will be issued with the REFINE master file documentation for their Site-specific Approval (SSA) and CTU accreditation documents. Centres must complete the REFINE Accreditation Form at the same time as applying for their SSA.

2.1.1 PI'S QUALIFICATIONS & AGREEMENTS

1. The investigators 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 and/or the regulatory authorities.

2. The investigator should be thoroughly familiar with the appropriate use of the investigational product(s) as described in the protocol, in the product information and in other information sources provided by the Sponsor.

3. The investigator should be aware of, and should comply with, the principles of GCP and the applicable regulatory requirements. A record of GCP training should be accessible for all investigators.

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

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

6. The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.

7. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

8. The investigator should sign an investigator statement, which verifies that the site is willing and able to comply with the requirements of the trial.

2.1.2 ADEQUATE RESOURCES

1. 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).

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

3. 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.

4. The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, and their trial-related duties and functions.

5. The site should have sufficient data management resources to allow prompt data return to the CTU (refer to the **Data Management Plan** for timelines).

2.1.3 SITE ASSESSMENT

Each selected clinical trial site must complete the **REFINE Accreditation Form**, which includes the **Investigator Statement**, **Signature and Delegation of Responsibilities Log**, and staff contact details. The Investigator Statement verifies that the site is willing, and able to comply with the requirements of the trial. This will be 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 CTU. The CTU 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 Trial Master File (TMF) at the site and also at the CTU.

2.2 APPROVAL AND ACTIVATION

The Clinical Trial Authorisation (CTA) for the trial requires that the MHRA be supplied with the names and addresses of all participating site principal investigators. Trial staff at the CTU will perform this task; hence it is vital to receive full contact details for all investigators prior to their entering patients.

Site training will be performed prior to the activation of the site and will include all processes for the trial including but not limited to protocol training, data management procedures, procedures for handling of investigational medicinal product, adverse event reporting procedures, procedures for laboratory samples, and frequency and expectations for any monitoring visits. A log of attendees will be kept in the TMF as a record of participants present at all types of training events.

Before a site can open to recruitment, formal Sponsor Site Green light/Accreditation will be completed in order to document that the site has met all the requirements to participate in the trial. Written confirmation of site activation will be sent to the PI.

The site's pharmacist will also be informed of the site's activation.

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

The PI or delegate should document and explain any deviation from the approved protocol and communicate this with the trial team at the CTU.

A list of activated sites may be obtained from the Trial Manager.

2.3 SITE MANAGEMENT

All participating sites will be managed by the MRC CTU at UCL.

3 SELECTION OF PATIENTS

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.

These eligibility criteria are the standards used to ensure that only medically appropriate patients are considered for this study. Patients not meeting the criteria should not join the trial. For the safety of the patients and 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 study.***

Questions about eligibility criteria should be addressed prior to attempting to randomise the participant. Contact the MRC CTU trial team preferably by email at mrcctu.refine@ucl.ac.uk (or 0207 670 4744) for specific eligibility queries.

3.1 INCLUSION CRITERIA

3.1.1 GENERAL INCLUSION CRITERIA

1. Patients with locally advanced or metastatic cancers for which immune checkpoint inhibitors are standards-of-care and whose clinician has determined they are candidates for treatment with this approach (see also Cohort Specific Inclusion Criteria, below).
2. WHO Performance Status 0 or 1.
3. Patients aged ≥18years.
4. Adequate normal organ and marrow function:
    a. Haemoglobin ≥90g/L (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 mm^3).
    c. Platelet count ≥100 x 10^9/L (≥100,000 per mm^3).
    d. Bilirubin ≤1.5 x ULN or patients with confirmed Gilbert's syndrome (i.e. persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of haemolysis or hepatic pathology).
    e. AST/ALT ≤3 x ULN.
    f. eGFR >40mL/min by CKD-EPI formula .
5. Resting 12-lead ECG on which QTcF must be <450 ms. This will usually have been performed prior to commencement of the initial 12 weeks ICI.
6. Both men and women enrolled in this trial must be in agreement with trial policy on contraception (see Section 5.8) during the treatment phase of the study. Egg donation, sperm donation and breastfeeding must be avoided.
7. Evidence of post-menopausal status or negative serum HCG pregnancy test for female pre/peri-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).

3.1.2 COHORT SPECIFIC INCLUSION CRITERIA

In addition to the general inclusion criteria, the following cohort-specific eligibility criteria apply.

3.1.2.A Renal cohort specific inclusion criteria:

1. Patients with unresectable locally advanced or metastatic renal cell carcinoma (including clear cell and papillary histologies).
2. Intermediate or poor risk as defined in the International Metastatic Renal Cell Carcinoma Database Consortium criteria (prior to the initial 12 weeks treatment with ICI combination).
3. Patients have received at least one dose of induction ipilumumab and received nivolumab as first-line treatment as planned.
4. No evidence of progression on ipilimumab and nivolumab induction therapy and due to commence maintenance nivolumab (i.e. response or stable disease on cross sectional imaging on completion of initial 12 weeks treatment with ICI combination).

3.1.2.B Melanoma cohort specific inclusion criteria:

1. Patients with locally advanced (unresectable) or metastatic melanoma, including primary mucosal but not uveal melanoma.
2. No evidence of progression on ipilimumab and nivolumab induction therapy, have received at least one dose of induction ipilimumab and are due to commence maintenance nivolumab (i.e. response or stable disease on cross sectional imaging - including where present any brain metastases - on completion of initial 12 weeks treatment with ICI combination).

   Or

   Patients have received single agent pembrolizumab first line for 12 weeks, with no evidence of progression (i.e. response or stable disease - including where present any brain metastases) on cross sectional imaging 12 weeks after initiation of ICI, and due to continue pembrolizumab every 6 weeks.

3.2 PATIENT EXCLUSION CRITERIA

1. Patients who have received ICI in a prior line of treatment.
2. Patients who have undergone any prior systemic anti-cancer treatment (previous participation in adjuvant studies allowed, providing the patient was on the observation/ placebo arm – this may require un-blinding of the patient).
3. Patients where treatment is the combination of anti-PD-1 and tyrosine kinase inhibitor (e.g. pembrolizumab+axitinib) or the combination of traditional cytotoxic chemotherapy and anti-PD-1.
4. History of another previous malignancy, except for:
   a. Malignancy treated with curative intent and with no known active disease ≥5 years prior to the first dose of ICI.
   b. Adequately treated non-melanoma skin cancer without evidence of current, active disease.
   c. Adequately treated carcinoma in situ without evidence of current, active disease.
   d. Non-muscle invasive bladder cancer.

5. Concurrent enrolment in another interventional clinical study, unless in the follow-up period, except where approved by the CTU (see co-enrolment section for further details).
6. Current or prior use of immunosuppressive medication within 14 days of starting trial treatment, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10mg/day of prednisone, or an equivalent corticosteroid.
7. 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). 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.
    c. Hepatitis C. Note: Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
    d. Human immunodeficiency virus (positive HIV 1/2 antibodies).
8. Receipt of a live attenuated vaccine within 30 days prior to the start of treatment.
   Note: Patients, if enrolled, should not receive a live vaccine while receiving immune checkpoint inhibitor and up to 30 days after the last dose of immune checkpoint inhibitor.
9. Known allergy or hypersensitivity to immune checkpoint inhibitor.
10. Pregnant or breastfeeding patients.
11. Uncontrolled adrenal insufficiency.
12. Any serious or uncontrolled medical or psychiatric disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, interfere with participation and/or compliance in the trial, or interfere with the interpretation of study results.

3.3 NUMBER OF PATIENTS

The study intends to enrol 160 patients into stage I for each cohort (80 patients randomised to each arm). For statistical considerations and sample size calculations see Section 9.

Following analysis of these data, the second stage will then test multiple experimental arms (depending on the efficacy of the extended dosing interval). Stage II intends to enrol up to an additional 200 patients per cohort (see Trial Schema) dependent on stage I results.

4 RANDOMISATION

4.1 RANDOMISATION

4.1.1 INFORMED CONSENT

It is expected that participants will be introduced to the trial and provided with the Patient Information Sheet during the 12 weeks of standard of care treatment that precedes trial entry. Participants that meet all the inclusion criteria and none of the exclusion criteria for their cohort and wish to participate, should sign the **REFINE Informed Consent Form**.

Written informed consent to enter and be randomised in the trial must be obtained from participants after explanation of the aims, methods, benefits and potential hazards of the trial and before any trial-specific procedures (including blood draws) 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, delegated individuals 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. These participants will then be assigned a participant identification number via the trial database and then randomised.

Signed consent forms must be kept by the investigator and documented in the eCRF and a copy given to the participant. Remote monitoring of the completed consent forms may be utilised through the course of the trial. Following consent, a letter including the trial synopsis should be sent to the general practitioner informing him/her of the participant's involvement in the trial.

It must be made 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 affecting their care in any way.

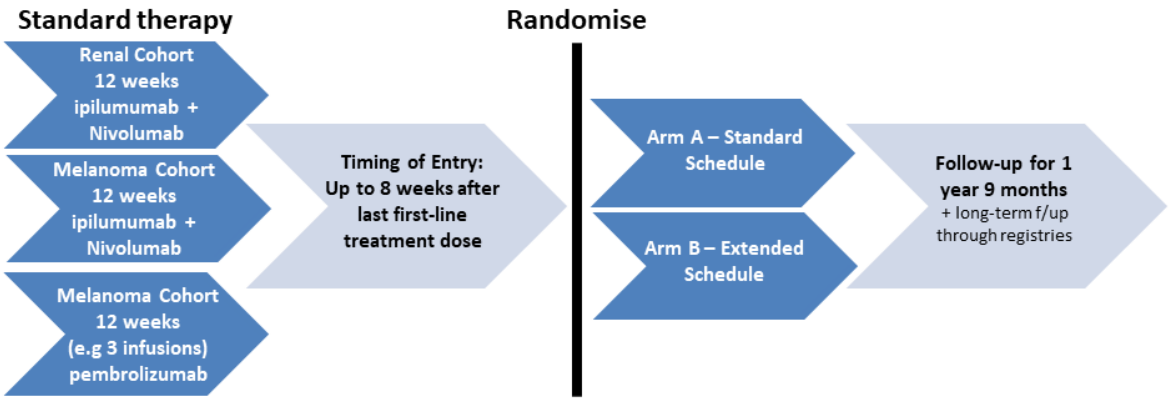
4.1.2 SCREENING PROCEDURES

All patients must first read, understand, sign and date the REFINE Informed Consent Form before any study-specific screening procedures are performed. Procedures that are performed prior to the signing of the REFINE Informed Consent Form and are considered standard-of-care may be used as screening assessments if they fall within the trial screening window (see the Trial Assessment Schedules for further details).

4.1.3 TIMING OF RANDOMISATION

All participants must receive 12 weeks of first-line immunotherapy prior to trial entry. Randomisation can occur anytime up to 8 weeks after the last dose of the first 12 weeks treatment. For ipilimumab+nivolumab regimens this is 8 weeks following the fourth ipilimumab infusion (or the fourth nivolumab if the ipilimumab component was stopped early); for pembrolizumab regimens this is 8 weeks following the third infusion of pembrolizumab.

Figure 2: Timing of Entry



4.2 RANDOMISATION PRACTICALITIES

Eligibility must be confirmed prior to randomisation. Central randomisation will be implemented using an interactive web-based system. 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. Trial treatment will be administered unblinded - "open label".

RANDOMISATIONS
To randomise, complete the required eCRFs on Open-Clinica.

4.3 CO-ENROLMENT GUIDELINES AND REPORTING

Patients previously enrolled in interventional trials may be eligible for recruitment into REFINE, as long as they have not received prior immunotherapy (i.e. remain eligible for immune checkpoint inhibitors as standard of care). If necessary, previous blinded treatments may need unblinding to ensure this is the case.

Interventional clinical trials: REFINE participants should not join any other interventional trial during treatment in REFINE, unless they have experienced a disease progression event within REFINE. Follow-up within REFINE for the outcome measure of PFS will still be required. Site investigators should check with the CTU prior to participants commencing any IMP within an interventional clinical trial to ensure there are no concerns about interactions with REFINE treatments. Overall survival is a secondary outcome measure of REFINE, therefore follow-up must continue after co-enrolment. Participation in interventional studies must be reported to CTU via the EDC system.

Non-interventional clinical trials: Co-enrolment in non-interventional studies for any indication is permitted at any time providing that it does not interfere with treatment or assessments in REFINE. Participation in non-interventional trials does not require reporting to CTU.

Questions regarding co-enrolment should be directed to the REFINE TMT (mrcctu.refine@ucl.ac.uk).

5 TREATMENT OF PATIENTS

5.1 INTRODUCTION

It is the responsibility of the treating investigator to perform the relevant assessments to ensure the patient is fit to receive treatment safely, at each time point.

5.1.1 STAGE I

Patients with advanced disease receiving standard-of-care immune checkpoint inhibitor (ICI) with no evidence of progression after 12 weeks initial treatment (i.e. response or stable disease) who meet all of the inclusion and none of the exclusion criteria will be randomly assigned in the ratio 1:1 to one of the following research arms:

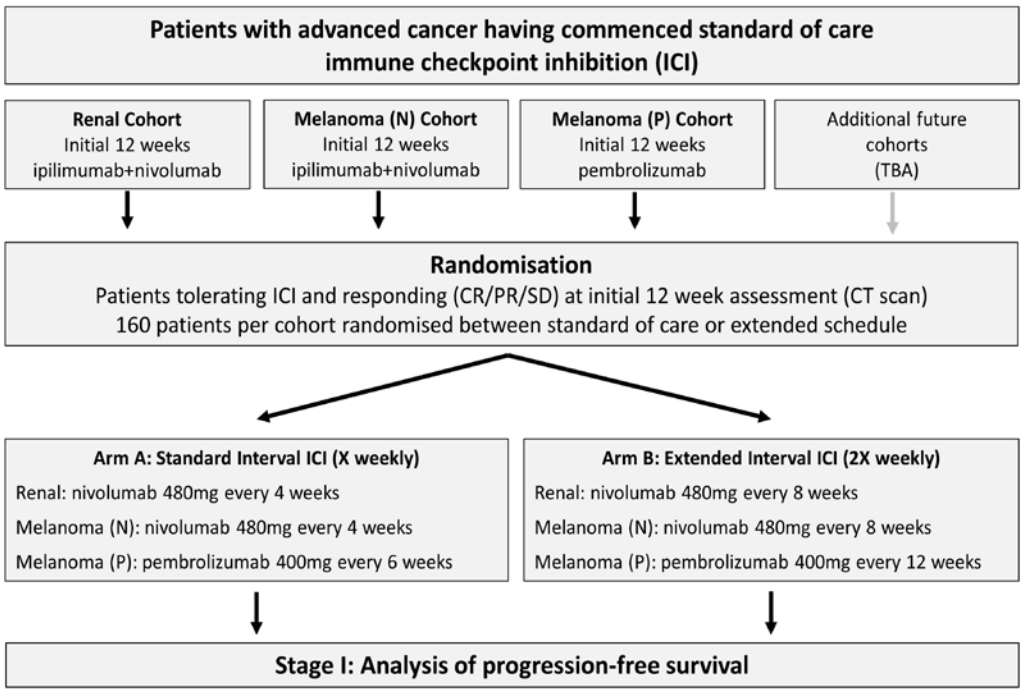
Arm A – standard-of-care interval ICI ('X' weekly)

Arm B – extended interval ICI (2 'X' weekly)

Treatment will be given as part of the trial until disease progression, toxicity that precludes further treatment, patient preference or for 1 year 9 months from start of randomised treatment (i.e. 2 years total treatment), whichever is sooner. Participants who are still responding to ICI treatment at 2 years will have the option to continue on treatment outside the trial as part of their normal care after the trial ends. It will be left to the discretion of the treating clinician if participants randomised to Arm B continue on the extended dosing interval or revert to standard of care.

Patients experiencing progression on the extended dosing interval (Arm B) will be offered treatment intensification (i.e. reverting to standard of care ICI dosing frequency, as per Arm A) at the patient and clinician's discretion.

Figure 3: Stage I REFINE



5.1.2 TREATMENT ARM A (SOC)

Patients in Arm A will receive standard-of-care interval ICI (4 weekly – q4w - for nivolumab after ipilimumab+nivolumab regimens, and 6 weekly – q6w – for pembrolizumab), commencing no more than 8 weeks after their last infusion (to facilitate any required steroid taper)They will be followed-up radiologically in the same manner as patients on Arm B. Please refer to the Trial Assessment Schedule for details of the follow-up schedule.

- REFINE (Renal) – Nivolumab (following induction ipilumumab+nivolumab) 480mg q4w
- REFINE (Melanoma - N) - Nivolumab (following induction ipilimumab+nivolumab) 480mg q4w
- REFINE (Melanoma – P) – Pembrolizumab 400mg q6w

5.1.3 TREATMENT ARMS B (EXTENDED INTERVAL)

Patients in Arm B will receive extended interval ICI, which in stage I is double the dosing interval of Arm A (standard dosing frequency). They will be followed-up radiologically in the same manner as patients on arm A. Please refer to the Trial Assessment Schedule for details of the follow-up schedule.

- REFINE (Renal) – Nivolumab (following induction Ipilumumab/Nivolumab) 480mg q8w
- REFINE (Melanoma – N) – Nivolumab (following induction Ipi/Nivo) 480mg q8w
- REFINE (Melanoma – P) – Pembrolizumab 400mg q12w

5.1.4 DISPENSING

All medication dispensed for the REFINE trial should be documented on a drug accountability log as per local procedures. At each site, a named trial pharmacist will be required to maintain complete records of all study medication dispensed.

Procedures for drug labelling, accountability and destruction will be detailed in the **Pharmacy Manual of Operations** and must be in compliance with applicable local regulations, GCP and the protocol. Staff from the MRC CTU will monitor drug accountability, either via remote monitoring or at site visits.

5.1.5 PRODUCTS

All immune checkpoint inhibitors used in REFINE will be supplied by local hospital sites, as per standard-of-care treatment and should be stored and prepared as per local guidelines and manufacturer's instructions. The Investigational Medicinal Products (IMP) within REFINE are nivolumab and pembrolizumab. Both IMPs will be handled in line with the manufacturers' recommendations, as per the current version of the relevant SPC.

Nivolumab will be administered as an approximate 60-minute IV infusion, as a flat dose of 480mg. Pembrolizumab will be administered as an approximate 60-minute IV infusion, as a flat dose of 400mg. Either may be diluted in 0.9% Sodium Chloride solution and administered using an infusion set and an in-line, sterile, non-pyrogenic, low protein binding filter (please refer to respective SPC for further details).

5.1.6 Dose Modifications, Interruptions & Discontinuations

Flat dosing schedules are used in all cohorts and all arms, as above. No dose modifications or dose reductions are permitted. Doses of immune checkpoint inhibitors may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment. Toxicities should be managed as per local and national/international guidelines. Please see section 5.1.6.B for toxicities that require treatment delays and section 5.3.2 for toxicities that require discontinuation.

5.1.6.A Dose Delay

If treatment is delayed for a period of less than 6 weeks treatment can recommence once appropriate, and the schedule will be restarted from the date of administration of the delayed dose.

If treatment is delayed for >6 weeks for any reason (other than the use of steroid tapers to manage drug related adverse events), the subject must be permanently discontinued from study therapy.

Dosing delays or interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed but prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the MRC CTU must be informed and will consult the CI. Tumour assessments (including imaging scheduling) should continue as per protocol even if dosing is interrupted or delayed.

5.1.6.B Adverse events which require treatment delays

Regardless of cohort and arm in which a participant is enrolled, immune checkpoint inhibitor administration should be delayed for the following:

- Skin AR Grade ≥3
- Fatigue Grade ≥3
- Any Grade ≥3 drug-related **laboratory** abnormality other than:
  - Grade 3 lymphopenia or leukopenia does not require dose delay.
  - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥2 toxicity.
  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥3 toxicity.
  - Subjects with combined Grade 2 AST/ALT and total bilirubin values meeting discontinuation parameters (see section 5.3.2) should have treatment permanently discontinued.
  - Any Grade ≥3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay. MRC CTU should be informed of all Grade ≥3 amylase or lipase abnormalities.
- All other AEs Grade ≥2
- Any AE, laboratory abnormality, or concurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Subjects who require delay of immune checkpoint inhibitor should be re-evaluated weekly or more frequently if clinically indicated and resume dosing when re-treatment criteria are met. In case of any uncertainties regarding AE management and/or treatment delay/resumption please contact the MRC CTU.

Criteria for permanent discontinuation are detailed in section 5.3.2.

5.1.6.C Criteria to Resume Treatment

Subjects may resume treatment with study drug when the AR(s) resolve to Grade ≤1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 skin AR may resume treatment in the presence of Grade 2 AR.
- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin.
- Drug-related pulmonary toxicity, diarrhoea, or colitis, must have resolved to baseline before treatment is resumed.
- Drug-related endocrinopathies adequately controlled with physiologic hormone replacement may resume treatment.

5.1.6.D Stopping Drug Early

Discontinuation criteria are considered in section 5.3.

5.2 MANAGEMENT OF CASES OF TRIAL MEDICATION OVERDOSE

An overdose is defined as a subject receiving a dose of ICI in excess of the protocol doses. Dosing information will be recorded on the eCRF.

If the overdose results in an AE or SAE, this must be recorded appropriately (see section 7).

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

5.3 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 be stopped early for any of the following reasons:

- Withdrawal of consent for treatment by the patient
- Disease progression, defined as the presence of any new lesion or 20% increase in existing tumour burden from time of initial measurement (see section 5.3.3 below)
- Unacceptable toxicity or adverse event
- Intercurrent illness that prevents further treatment
- Any change in the patient's condition which, in the clinician's opinion, justifies the discontinuation of treatment
- Inadequate compliance with the protocol treatment, in the judgement of the treating physician
- Pregnancy or intent to become pregnant
- Grade ≥3 infusion reaction
- Initiation of alternative anticancer therapy including another investigational agent
- Any dosing interruption lasting >6 weeks with the following exception:
    - Dosing delays or interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
    - MRC CTU must be informed prior to re-initiating treatment.
    - Tumour assessments should continue as per protocol even if dosing is interrupted or delayed.

Where participants discontinue treatment early they 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 early from follow-up, refer to section 6.6.

5.3.1 TRIAL TREATMENT DISCONTINUATION AT PATIENT REQUEST

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

It should be clear to the patient and recorded in the patient notes what aspect(s) of the trial the participant is discontinuing their participation. These could include:

- Withdrawal from further treatment
- Withdrawal from sample collections
- Withdrawal from questionnaires
- Withdrawal from further trial follow-up
- Withdrawal from electronic health record use.

Information on any level of patient discontinuation should be recorded on the relevant eCRF.

Data on patients who stop follow-up early will be kept and included in analysis.

5.3.2 DISCONTINUATION CRITERIA FOR ADVERSE EVENTS

Treatment with immune checkpoint inhibitor must be discontinued for any of the following, regardless of cohort:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting >7 days, including uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, and infusion reactions, with the following exceptions for drug-related laboratory abnormalities and endocrinopathies:
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except those noted below:
- Grade 3 drug-related thrombocytopenia >7 days or associated with bleeding requires discontinuation
- Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
  - AST or ALT >8 x ULN
  - Total bilirubin >5 x ULN
  - Concurrent AST or ALT >3 x ULN and total bilirubin >2 x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to Grade <4 within 1 week of onset.

- Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Grade 4 lymphopenia or leucopenia
- Grade 4 drug-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively.

5.3.3 TRIAL TREATMENT DISCONTINUATION FOR PROGRESSION

Progression is defined as the appearance of one or more new lesions, or at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10mm (except for pathological lymph nodes which must have a short axis of at least 15mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumour burden if the longest diameter increases to at least 10mm (except for pathological lymph nodes which must have a short axis of at least 15mm). In situations where the relative increase in total tumour burden by 20% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5mm. This includes brain metastases where appropriate.

PET-CT assessment is an accepted alternative to CT scans, for the melanoma cohorts in particular. Here progression is defined as an increase in SUV peak (normalised to lean body mass) of at least 30% (and at least 0.8 SUL units) of the target lesion, or an increase in size of the target lesion by 30%, the unequivocal progression of nontarget lesions or the development of at least one new lesion.

If the participant discontinues trial treatment due to disease progression, the follow up schedule should be followed, provided this is clinically appropriate.

5.3.4 TREATMENT BEYOND PROGRESSION

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease (PD). This might include patients experiencing progression at a single site who receive local therapy (surgical excision / ablation etc).

Therefore, subjects will be permitted to continue treatment beyond initial RECIST 1.1 or PERCIST 1.0 defined PD as long as they meet the following criteria determined by the investigator:

- Investigator-assessed clinical benefit;
- Tolerance of study drug;
- Stable performance status.

Patients on Arm B (extended interval immune checkpoint inhibition) who experience progression and are clinically fit to continue treatment may continue the extended interval dosing or will have the option to intensify their treatment (i.e. cross over back to Arm A regimen).

Treatment beyond progression must not delay an imminent intervention which may prevent serious complications of disease progression (e.g. CNS metastases).

Radiographic assessment (scans) should continue to as per the Trial Assessment Schedule, following initial investigator-assessed progression to determine whether there has been a decrease in the tumour size or continued PD. Tumour measurements should be compared to the progression scan, which should be considered as the new baseline. For the subjects who continue study therapy beyond disease progression, further progression is defined as presence of any new lesion (regardless of % increase in tumour burden) or an additional 10% increase in existing tumour burden from time of initial PD.

5.4 ACCOUNTABILITY & UNUSED DRUGS/DEVICES

The dose of trial medication administered to each patient will be recorded on worksheets and in the EDC system. Reasons for any dose delay, reduction, or missed doses will also be recorded in the EDC system.

Treatment in both arms uses NHS stock, and sites are responsible for documentation of drug dispensing and disposal of unused product. All medication dispensed for the REFINE trial should be documented on a drug accountability log as per local procedures.

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

5.5 COMPLIANCE AND ADHERENCE

Doses and dates of administration will be recorded on worksheets and in the electronic data capture (EDC) system. For the renal and melanoma-N cohorts, the planned administration date is 4 weeks (arm A) or 8 weeks (arm B) after the last administration, and for the melanoma-P cohort the planned administration date is 6 weeks (arm A) or 12 weeks (arm B) weeks after the last administration. A window of 1 week either side of this planned date is acceptable. Where doses are administered more than 1 week from planned administration date this will be considered a protocol deviation except in the case of AE related dose delay. The reason for the deviation will be recorded in the EDC system.

5.6 TREATMENT DATA COLLECTION

Refer to the trial assessment schedules for the assessments required. Investigations in this trial will use the results of local assessments, aside from the separate translational blood tests. Data will be collected in the EDC system of MRC CTU.

EDC must only be completed by personnel authorised to do so by the Principal Investigator, as recorded on the trial-specific Authorised Personnel Log.

5.7 NON-TRIAL TREATMENT

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 5.7.2. A list of medications to be used with caution is provided in section 5.7.3. Permitted supportive medications include transfusion of blood and blood products, treatment with antibiotics, anti-diarrhoeal medication, antiemetics, and analgesics.

Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if >10mg/day prednisone or equivalent. A brief (<2 weeks) course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

Palliative radiotherapy and palliative surgical resection are permitted during the study. Please discuss with the MRC CTU if such treatment is planned, as this may constitute disease progression.

5.7.1 Medications Permitted

Rescue, Supportive Medicine or Class of Drug	Usage
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 5.7.2.	To be administered as prescribed by the Investigator
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]	Should be used when necessary for all patients
Opioids	Can be used with caution and under medical control as prescribed by the Investigator
Inactivated viruses	Can be used when necessary for all patients
COVID-19 Vaccinations	It is expected that patients will have completed vaccination against COVID-19 prior to commencement of ICI but RNA and adenovirus vaccines may be used when necessary.

5.7.2 Medications Not Permitted

Prohibited Medication or Class of Drug	Usage
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10mg/day of prednisone or equivalent (except as stated in section 5.7 above), methotrexate, azathioprine, and tumour necrosis factor-α blockers **(except to treat an adverse reaction).**	Should not be given during the study. (Use of immunosuppressive medications for the management of ARs 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

5.7.3 MEDICATIONS TO BE USED WITH CAUTION

Caution should be used when using the following medication

- Drugs with laxative properties and herbal or natural remedies for constipation, due to the risk of diarrhoea on immune checkpoint inhibitors
- Drugs with a predisposition to hepatotoxicity should be used with caution due to the potential for hepatic toxicity from immune checkpoint inhibitors

5.7.4 TREATMENT AFTER TRIAL EVENT

Treatment will be at the discretion of the responsible physician.

5.8 CONTRACEPTION

Male participants must agree to use an acceptable method of contraception during sexual contact with a pregnant female or a woman of childbearing potential (WOCBP) while taking trial treatment, during dose interruptions and for at least 20 weeks after the last dose of trial treatment. Acceptable methods of contraception are listed in Appendix I.

WOCBP must agree to use a highly effective method of contraception while taking trial treatment and for at least 20 weeks after the last dose of trial treatment. Pregnancy tests must be undertaken at each scheduled treatment visit for participants who are WOCBP during the treatment period.

Further details of the definition of WOCBP and appropriate contraception can be found in Appendix I.

5.9 CO-ENROLMENT GUIDELINES

Co-enrolment in previous or future trials is considered in section 4.3.

6 ASSESSMENTS & FOLLOW-UP

6.1 TRIAL ASSESSMENT SCHEDULES

The frequency of follow-up visits and assessments are detailed in the Trial Assessment Schedule. As far as possible, trial follow-up visits and assessments have been aligned with standard practice. All assessments should be performed by appropriately qualified members of the team as per the trial delegation log.

6.1.1 TELEPHONE ASSESSMENTS

Patients in Arm B will have intermittent telephone assessments to align clinical/safety assessments with the standard-of-care schedule (Arm A). Clinical history, adverse events and performance status will be assessed at these time points. Centres may schedule a face-to-face visit where clinically indicated. Patients will also require haematology and clinical chemistry bloods (see Table 5 and Table 6) and WOCBP will require a pregnancy test at these assessments. These should be taken at the GP or hospital phlebotomy.

In certain circumstances it may be appropriate to replace other hospital visits with telephone consultations providing that it is still possible to collect all the necessary follow-up information. In these instances, it is acceptable to replace appointments with telephone consultations providing the required blood results and safety tests are available to the research team. All necessary information required to complete the Follow-up eCRF is still required. All details on the telephone consultation must be recorded in the participants' notes as per in person assessments.

6.2 CLINICAL/SAFETY ASSESSMENTS

6.2.1 PHYSICAL EXAMINATION

Routine physical examinations will be performed according to the assessment schedule. Weight and performance status will be performed at each assessment. 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.

6.2.2 PREGNANCY TESTS

Female patients of childbearing potential will undertake a urinary pregnancy test prior to administration of each cycle of ICI. Serum HCG pregnancy tests will be used if there is any doubt over the result from the urinary test.

6.2.3 ELECTROCARDIOGRAMS

Resting 12-lead ECGs will be recorded at screening, and as clinically required throughout the study. It is expected that the screening ECG will have been taken prior to the initiation of the initial 12 weeks treatment with ICI.

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 for randomisation if a QTcF of <450ms is confirmed.

6.2.4 LABORATORY ASSESSMENTS

Trial patients will be required to have the assessments listed in the following tables before each infusion in order to assess and ensure patient safety. Patients on the extended interval will also have these tests performed alongside each telephone assessment. The tests can be completed up to 5 days prior to the visit and results must be available prior to the patients receiving treatment.

Patients will undergo laboratory assessments at the same frequency as their dosing schedule.

Additional haematology and clinical chemistry tests can also be carried out during the trial period as clinically indicated.

Table 5: Haematological Assessments to be performed up to 5 days before the treatment visit

ASSESSMENT
Haemoglobin
Monocytes
Basophils
Eosinophils
Total white cell count (WCC)
Neutrophil
Lymphocytes
Platelet count

Table 6: Clinical Chemistry Assessments to be performed up to 5 days before the treatment visit

ASSESSMENT	PERFORMED AT ALL VISITS	PERFORMED AT SCREENING AND THEN AS CLINICALLY INDICATED THEREAFTER
Albumin	x	
Alkaline phosphatase (ALP)	x	
Alanine aminotransferase (ALT) [1]	x	
Aspartate aminotransferase (AST) [1]	x	
Bicarbonate [3]		x
Calcium	x	
Adjusted calcium	x	
Chloride [3]		x
Creatinine	x	
eGFR	x	
Gamma glutamyltransferase (GGT) [3]		x
Glucose	x	
Urine or serum HCG pregnancy test [5]	x	
Lactate dehydrogenase (LDH)	x	
Magnesium [3]		x
Potassium	x	
Random cortisol[6]	x	
Sodium	x	
Thyroid stimulating hormone (TSH) – if abnormal check free T3 and T4 [4]	x	
Total bilirubin [1]	x	
Total protein	x	
Urea or blood urea nitrogen (depending on local practice)	x	
Uric acid	x	

1. 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.
2. Bicarbonate (where available), chloride, gamma glutamyltransferase, magnesium, testing are to be performed at screening, on Day 1 (unless screening laboratory assessments are performed within 5 days prior to Day 1), and if clinically indicated. Tests will need to be repeated on Day 1 if done more than 5 days prior.
3. 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. 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.

5. If random cortisol is <LLN and the patient is not currently taking or has not taken a course of steroids within 14 days perform 9am cortisol. If the 9am cortisol is <LLN test pituitary profile (LH, FSH, Prolactin, GH, ACTH).

6.3 RADIOLOGICAL ASSESSMENTS OF RESPONSE AND DISEASE PROGRESSION

Cross sectional imaging assessment (typically CT with contrast of the chest, abdomen and pelvis though PET CT is an acceptable alternative where used in routine local practice and brain imaging with contrast CT or MRI should be included as appropriate) will be carried out at baseline (within 56 days prior to randomisation) and then every 12 weeks (+/-1 week) since the first treatment administered within the trial, regardless of whether treatment is delayed for toxicity or other medical reason. This will continue until disease progression or treatment discontinuation, whichever occurs later. The outcome of each of these scheduled assessments should be reported on worksheets and in the EDC system. Local reporting of scans must be according to RECIST V1.1 criteria (or PERCIST for PET-CT).

6.4 PROCEDURES FOR ASSESSING QUALITY OF LIFE

Extended frequency immunotherapy may be associated with favourable health-related quality-of-life (HR-QoL) in comparison to standard frequency dosing, due to reduced hospital attendance, and a hypothesised reduced toxicity. In order to evaluate treatment tolerability and its impact from a patient perspective, Patient-Reported Outcome Measures (PROM) to evaluate both overall HR-QoL and patient-reported AEs (physical symptoms of the cancer and side-effects of the treatments) will be collected. The severity and trajectory of AEs (symptoms or side-effects) of both treatment schedules will be reported, allowing comparison between clinician reported AEs (CTCAE V5.0) and patient-reported AEs using Patient Reported Outcome Methods (PROMs).

Participants will be asked to complete the EQ-5D and QLQ-C30 questionnaires at baseline, then at 12-week intervals (as per the treatment assessment schedules). If a progressive disease event occurs the EQ-5D should be continued every 12 weeks if deemed acceptable by the investigator and the patient. The QLQ-C30 can be stopped at disease progression.

Questionnaires completed at treatment visits should be done prior to the administration of any scheduled infusions. At screening questionnaires should be completed prior to the randomisation being completed.

6.5 FOLLOW-UP

Participants will have in-person clinical assessments with each scheduled treatment. Participants will be followed up for 1 year and 9 months from randomisation according to the trial assessment schedule, regardless of treatment status or progression. An end of trial schedule visit will take place 8 weeks after the last dose of trial treatment (where a participant does not wish to continue with follow-up) or after the completion of 1 year 9 months follow-up. Please refer to the trial assessment schedule. Longer term data including information on progression and survival will be collected on an annual basis until the end of the trial.

6.6 EARLY STOPPING OF FOLLOW-UP

In line with usual clinical care, cessation or alteration of regimens at any time will be at the discretion of attending clinicians or the participants themselves. If a patient chooses to discontinue their trial

treatment, they should always be followed up providing they are willing, that is, they should be encouraged to not leave the whole trial; if they do not wish to remain on trial follow-up, however, their decision must be respected and the patient will be withdrawn from the trial completely. The CTU should be informed of this via the appropriate eCRF. Patients stopping early have a negative impact on a trial's data.

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).

Patients may change their minds about stopping trial follow-up at any time and re-consent to participation in the trial, depending on the duration of cessation – please discuss these cases with the MRC CTU.

Patients who stop trial follow-up early will not be replaced.

6.7 PATIENT TRANSFERS

For participants moving away from the area and planning to transfer care, every effort should be made for the participant to be followed-up at another trial site. The participant will need to sign a new consent form at the new trial site. Once this has been done, the new trial site will take over responsibility for their ongoing participation in the trial.

To document the transfer process the main contact person at the current hospital should complete the appropriate eCRF. Any outstanding eCRFs and data queries for the participant should be completed prior to transfer.

Photocopies of the following documents may then be sent to the new hospital to complete the transfer and originals must also be retained at the original site for monitoring purposes:

- Consent form
- Completed Worksheets
- Any documentation relating to the participant's participation in REFINE (participant names must be removed from any documentation).

6.8 LOSS TO FOLLOW-UP

Before a patient can be confirmed as lost to follow-up, every effort should be made to contact them, including liaising with their general practitioner. A participant is considered lost to follow-up if they have not been seen for 6 months and the site has made at least 3 attempts to contact them and documented this in the medical notes.

7 SAFETY REPORTING

The principles of GCP require that both investigators and Sponsors follow specific procedures when notifying and reporting adverse events or reactions in clinical trials. These procedures are described in this section of the protocol. Section 7.1 lists definitions, section 7.2 gives details of the investigator responsibilities and section 7.3 provides information on CTU responsibilities.

7.1 DEFINITIONS

The definitions of the EU Directive 2001/20/EC Article 2 based on the principles of GCP apply to this trial protocol. These definitions are given in table 7.

Table 7: Definitions

TERM	DEFINITION
Adverse Event (AE)	▪ 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.
Adverse Reaction (AR)	▪ Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Unexpected Adverse Reaction (UAR)	▪ 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 Brochure (IB) for that product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	▪ 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***

*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.

*** 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.

7.1.1 MEDICINAL PRODUCTS

An investigational medicinal product is defined as the tested investigational medicinal product and the comparators used in the study. (EU guidance ENTR/CT 3, Apr-2006 revision). For REFINE these

are the immune checkpoint inhibitors nivolumab and pembrolizumab. (Ipilimumab is completed before joining the trial, so this is not an IMP).

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:

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

Adverse events do not include:

- Medical or surgical procedures; the condition that leads to the procedure is the adverse event
- 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)

Immune checkpoint inhibitors are associated with immune related adverse events. Treatment related toxicities should be reported via the eCRF.

7.1.3 ADVERSE EVENTS EXEMPT FROM THE EXPEDITED REPORTING TIMEFRAME (24 HOURS)

The following events, in the context of this trial, are exempt from the expedited reporting timeframe (24 hours), but must be reported within 30 days of the investigator's knowledge of the event, if they meet the seriousness criteria.

- Diagnosis of a new cancer
- Disease progression (including death due to primary cancer)
- Elective admissions (irrespective of the length of stay, e.g. 1 day admissions)

7.1.4 OTHER STUDY-SPECIFIC REQUIREMENTS

7.1.4.A Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures.

The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant and considered related to trial treatment
- any laboratory test result that meets the definition of an SAE
- any laboratory abnormality that required the participant to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy
- laboratory abnormalities that constitute potential drug-induced liver injury, defined as:

  1) ALT or AST elevation > 3 times upper limit of normal (ULN)

  And/or

  2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

and

3) No other immediately apparent possible causes of ALT or AST elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (e.g. anaemia versus low haemoglobin value).

7.1.4.B Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, the investigational product will be permanently discontinued in an appropriate manner.

The investigator must immediately notify MRC CTU within 24 hours using the EDC system.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the EDC system.

Any pregnancy that occurs in a female partner of a male study participant should be reported. Information on this pregnancy will be collected on the EDC system. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

If the outcome of the pregnancy either in a female participant or a female partner of a male participant meets a criterion for immediate classification as an SAE - spontaneous abortion (any congenital anomaly detected in an aborted foetus is to be documented), stillbirth, neonatal death, or congenital anomaly—the Investigator should repeat the procedures for expedited reporting of SAEs as outlined above.

7.2 INVESTIGATOR RESPONSIBILITIES

Specific treatment related Ars, AEs resulting in treatment interruption and specific laboratory abnormalities as defined in section 7.4.4.A should be recorded in the patient's medical notes and reported to the CTU via the EDC system. SAEs should be notified to the CTU within 24 hours after the investigator becoming aware of the event (see section 7.1.3 for those events exempt from expedited reporting).

Pregnancies should be notified to the MRC CTU at UCL within 24 hours after the investigator becoming aware of the event using the EDC system.

7.2.1 INVESTIGATOR ASSESSMENT

Adverse events will be recorded and graded according to the NCI CTCAE v5.0 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.

7.2.1.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 7. If the event is serious, then an SAE Form must be completed and the CTU notified within 24 hours (unless exempt from expedited reporting as per section 7.1.3).

7.2.1.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 scales in NCI CTCAE v5.0.

7.2.1.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 8. 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 8: Assigning Type of SAE through Causality

RELATIONSHIP	DESCRIPTION	SAE TYPE
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR
Possible	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).	SAR
Unlikely	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).	Unrelated SAE
Unrelated	There is no evidence of any causal relationship	Unrelated SAE

7.2.1.D Expectedness

The Sponsor has the overall responsibility for determination of expectedness. An unexpected adverse reaction is one not previously reported in the current Reference Safety Information (see trial website for current approved RSIs) or one that is more frequent or more severe than previously reported. The definition of an unexpected adverse reaction (UAR) is given in table 7. If a SAR is assessed as being unexpected, it becomes a SUSAR.

7.2.1.E Notification

MRC CTU should be notified of all SAEs within 24 hours of the investigator becoming aware of the event (see section 7.1.3 for those events exempt from expedited reporting).

Investigators should notify the MRC CTU of all SAEs occurring from the time of signature of the informed consent form until 19 weeks (approximately 5 half-lives of the IMPs), after the last protocol treatment administration. SARs and SUSARs must be notified to the CTU until trial closure. Any subsequent events that may be attributed to treatment should be reported to the MHRA using the yellow card system.

7.2.2 NOTIFICATION PROCEDURE

1. The SAE must be reported through the EDC system by an investigator (named on the Signature List and Delegation of Responsibilities Log, who is responsible for the patient's care; this will be either the Principal Investigator or another medically qualified person with delegated authority for SAE reporting). Due care should be paid to the grading, causality of the event, as outlined above. In the absence of the responsible investigator, the eCRF should be completed by a member of the site trial team (who are included in the delegation log). The responsible investigator should subsequently check the eCRF, make changes as appropriate, sign-off and then re-submit to the CTU as soon as possible. The minimum criteria required for reporting an SAE are the trial number, eCRF submitted by an identifiable person included in the delegation log, the event name and grade, and why it is considered serious.

2. Follow-up: 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. If extra information becomes available, the information recorded on the EDC system must be updated. Extra, annotated information and/or copies of test results may be provided separately and should be submitted via galaxkey. 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.

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

SAE REPORTING
Please report all SAEs via the EDC system within 24 hours of becoming aware of an SAE

7.3 MRC CTU RESPONSIBILITIES

The Chief Investigator, one of the cohort specific lead investigators, or a medically qualified delegate will review all SAE reports received. The causality assessment given by the local investigator at the hospital cannot be overruled; in the case of disagreement, both opinions will be provided in any subsequent reports.

The CTU is undertaking the duties of trial Sponsor and is responsible for the reporting of SUSARs and other SARs to the regulatory authority and the research ethics committees, as appropriate. All serious events will be MedDRA coded at clinical review. Fatal and life-threatening SUSARs must be reported to the competent authority within 7 days of the CTU becoming aware of the event; other SUSARs must be reported within 15 days.

The CTU will also keep all investigators informed of any safety issues that arise during the course of the trial.

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

8 QUALITY ASSURANCE & CONTROL

8.1 RISK ASSESSMENT

The Quality Assurance (QA) and Quality Control (QC) considerations have been 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 CTU's Research Governance Committee (RGC) and has led to the development of a **Data Management Plan**, **Safety Management Plan**, **IMP Management Plan** and **Quality Management and Monitoring Plan** which will be separately reviewed by the Quality Management Advisory Group (QMAG).

8.2 CENTRAL MONITORING AT CTU

MRC CTU staff will review EDC data for errors and missing data points.

Other essential trial issues, events and outputs will be detailed in the **Quality Management and Monitoring Plan** that is based on the trial-specific **Risk Assessment**.

8.3 ON-SITE/REMOTE MONITORING

The frequency, type and intensity for routine monitoring and the requirements for triggered monitoring will be detailed in the **Quality Management and Monitoring Plan**. This plan will also detail the procedures for review and sign-off.

Remote or self- monitoring will be utilised through the course of the trial. Site staff may be asked to scan and send anonymised sections of a participant's medical record to the CTU for remote verification or asked to complete a form to confirm compliance with protocol procedures.

8.3.1 DIRECT ACCESS TO PATIENT RECORDS

Participating investigators should agree to allow trial-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Patients' consent for this must be obtained.

8.3.2 CONFIDENTIALITY

We plan to follow the principles of the UK DPA.

8.4 SOURCE DATA

The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data are contained in source documents and are defined by EU guidelines as all information in original

records that are used for the reconstruction and evaluation of the clinical trial. Source documents are the first place where the source data are recorded. These can include hospital records (including worksheets which form part of the participant notes/records), clinical and office charts, laboratory notes, X-rays, participant completed questionnaires, and pharmacy dispensing records. For this trial, some participant completed questionnaire data elements may be recorded directly into eCRFs and therefore the eCRF will be regarded as source data in these cases.

Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail). Each data element should only have one source.

A source data plan/agreement will be put in place as part of the green light process with each site. This plan/agreement will define the source documents and the data therein, together with location of these source documents and any applicable plans for transmission of source data between the site and the Sponsor/delegated institution.

The following data should all be verifiable from source documents, as defined above:

- signed consent and (where applicable) assent forms
- dates of visits including dates any trial specimens were taken and processed in the laboratory
- eligibility and baseline values
- adverse events of any grade that lead to treatment modification and adverse events judged definitely/probably/possibly related to IMP
- severe (grade 3/4) adverse events
- serious adverse events
- dates IMP were drug dispensed and (if necessary) drugs returned
- Pharmacy or clinic IMP accountability and prescription logs

9 STATISTICAL CONSIDERATIONS

9.1 METHOD OF RANDOMISATION

Patients will be randomised centrally via a randomisation server, using minimisation including a random element, with stratification by a small number of key factors. To decrease determinability, the stratification factors are not listed here but can be found in the **REFINE Statistical Design Document**.

A manual randomisation list will be generated by the trial statistician and will be stored centrally at MRC CTU at UCL in a secure location, for use in the event that the randomisation server is unavailable.

During stage I, patients will be allocated (1:1) to either arm A (standard interval) or B (extended interval). The exact allocation ratio for stage II will be determined once the number of available arms are confirmed, but it is anticipated that more patients will be allocated to the added arms than to the existing stage I arms.

It is expected that there will be a 3-to-6 month period between completing stage I recruitment and stage I results being available. As the results of stage I will inform which arms are included in stage II during this time randomisations will be paused.

9.2 OUTCOME MEASURES

9.2.1 PRIMARY

Progression-free survival (PFS) is the primary outcome measure for the first and second stages of REFINE.

PFS is defined as the interval from randomisation to first evidence of local recurrence, new renal primary cancer, distant metastases (new or progression of existing metastases), or death from any cause, whichever occurs first.

9.2.2 SECONDARY

Overall Survival (OS) is a secondary outcome measure and is defined as all-cause mortality, the time from randomisation to death from any cause (including cancer).

Further secondary outcome measures are the feasibility of recruiting patients and randomising them to extended interval treatment, Cancer-Specific Survival (CSS), i.e., the time from randomisation to death from cancer, Quality-of-life and Toxicity.

9.3 SAMPLE SIZE

9.3.1 STAGE 1 (EACH COHORT)

A target 160 patients will be randomised into stage I of each cohort, with equal numbers in each of the two arms. The sample size calculations were performed with function sizeCT.default from the powerSurvEpi R package, which implements the method proposed by Freedman (33) and were recalculated using the ART package within Stata (34).

For the Renal cohort, expected outcomes based on the long-term data with ipilimumab+nivolumab followed by nivolumab (6, 7) suggest a PFS at 9-months post-randomisation (i.e. 1 year since commencement of treatment) of approximately 70%, among patients progression-free at 12 weeks. The previous standard of care (sunitinib) demonstrated a 9-month PFS rate of approximately 50%.

For the Melanoma cohorts, the expected 9-months PFS rate (i.e. 1 year on treatment) from either regimen (N or P) is around 65% (2, 28). The prior standard of care (ipilimumab single agent) was reported to result in a PFS of ~45%.

Recruiting approximately 160 patients into each cohort during stage I will provide 80% power at a 5% one-sided significance level to detect an absolute reduction of 20% in the 9-month PFS rate. This number of patients would also be sufficient to demonstrate non-inferiority of the extended frequency arm, using a 20% non-inferiority margin.

For the renal cohort, a non-inferiority margin of 20% (reduction from 70% to 50%) represents a hazard ratio of 1.94, and for the melanoma cohorts a 20% margin (reduction from 65% to 45%) represents a hazard ratio of 1.85. In all analysis, the absolute reduction of 20% will be maintained as the non-inferiority margin, with the target hazard ratio being adjusted according to the observed control arm event rate.

The non-inferiority margin used in the design of REFINE is believed to be appropriate for an initial phase II evaluation of administering treatment less often. It is anticipated that a later phase III trial would need to employ a small non-inferiority margin.

For all cohorts, stage I analysis will be performed when approximately 30 PFS events have been observed in the control arm, which is expected to occur around six months after the completion of recruitment.

9.3.2 STAGE 2 (EACH COHORT)

The exact arms to be included in stage II will be decided based on the results of the stage I analyses, but it is anticipated that up to 5 arms will be included: the original arms from stage I (SOC and 2'X'), plus three new arms added (for example 1.5'X', 2.5'X' and 3'X').

It is anticipated that at least 50 patients would be recruited to each of the new arms, plus at least an additional 25 to each of the existing arms. Based on the same assumptions made for the stage 1 sample size calculations, this will provide around 80% power to demonstrate the non-inferiority relative to the control arm using a 20% non-inferiority margin. Stage II analyses will follow a conditional approach, with the most extended arm being analysed first, and less extended arms only being analysed if non-inferiority is not shown.

9.3.3 POTENTIAL PHASE 3 EXTENSION

Depending on the results seen in stages 1 and 2 in REFINE, it is anticipated that a larger phase 3 evaluation will take place. The exact design of, and arms to be included in a phase 3 trial will be determined once the stage 2 results are available and will also take into account any emerging external evidence. It is expected that a smaller non-inferiority margin would be use than in the current phase 2 assessment.

9.4 INTERIM MONITORING AND ANALYSES

An IDMC Charter will be drawn up that describes the membership of the IDMC, relationships with other committees, terms of reference, decision-making processes, and the timing and frequency of interim analyses (with a description of stopping rules and/or guidelines, if any).

The analyses will be described in detail in a full **Statistical Analysis Plan**. This section summarises the main issues. REFINE uses a multistage, multi-arm approach to test reduced frequency immune checkpoint inhibition across a range of solid cancers.

9.4.1 PRIMARY OUTCOME MEASURES - STAGE 1 (EACH COHORT)

The analysis will consist of a Cox proportional hazards model, where the main covariate will be treatment, defined as standard-of-care (Arm A – standard interval) or extended interval (Arm B – experimental) ICI. The model will also adjust for the stratification variables.

Each cohort will be analysed separately, using a 5% one-sided significance level. All patients will be included and analysed by their schedule allocation (intention to treat – ITT). The primary outcome measure will also be analysed using a per-protocol population: this is a subset of the ITT population, excluding any patients who did not begin treatment, and any who were randomised but later found to be ineligible.

9.4.2 SECONDARY OUTCOMES MEASURES – STAGE 1

Overall survival will be analysed in the same framework as the primary outcome measure.

Quality-of-life will be assessed 12-weekly, longitudinally over time. A more detailed description of our health-economic outputs can be found in section 10. A linear mixed model will be used to obtain an estimate for the mean difference between treatment arms for continuous outcomes. Participants will be included as a random intercept and the model will include an arm, time-by-arm interaction and randomisation stratification variables as fixed effects. Model assumptions will be examined using residual analysis and examination of graphical displays such as normal quantile plots. Examination of subgroups will be specified a priori in the **Statistical Analysis Plan** (SAP) and will be considered exploratory in nature.

Safety data analysis will be conducted on all subjects receiving at least one dose of study medication. The number and percentage of subjects experiencing an AE and the number of events will be summarized by arm. Information by severity will be examined with a focus on Grade 3-5 events using the Common Terminology Criteria for Adverse Events (CTCAE v5.0).

Feasibility of recruitment will be assessed by accessing screening logs from participating centres. The proportion of approached patients who agree to take part in the trial will be presented. The speed of recruitment will also be used to assess feasibility, with the time taken to complete stage 1 recruitment compared to the target of one year used in design considerations.

9.4.3 PROGRESSING FROM STAGE I TO STAGE II

The decision whether to proceed to stage II, and which arms to include, will be informed by the results of the primary and secondary analyses of stage I data, and following discussion with relevant oversight committees (TMG, IDMC, TSC). Strict statistical rules are not in place but will follow the guidance offered below.

If the stage I analysis shows that the extended interval arm (2'X') is significantly inferior to the standard interval arm (1'X'), i.e. the confidence interval for the hazard ratio lies entirely above 1, recruitment is likely not to be continued in the 2'X' arm, and no arms with further extended intervals (2.5'X' or 3'X') are likely to be opened. The trial committees will discuss whether there is any scientific merit in opening the intermediate interval (1.5'X') arm.

If the extended frequency arm is not shown to be significantly inferior, an assessment of non-inferiority will be made. If non-inferiority is shown, i.e. the confidence interval for the hazard ratio excludes the non-inferiority margin, then stage II is likely to proceed as planned, opening up arms with further extended intervals (2.5'X' and 3'X'). The trial committees will further discuss whether there is merit in adding the intermediate interval (1.5'X') arm at this stage.

In the event that the stage I results show neither clear inferiority or non-inferiority of the extended frequency arm, i.e. the confidence interval for the hazard ratio includes both 1 and the non-inferiority margin, the trial committees will determine which arms will be available in stage II. Safety and quality of life data will be considered alongside the efficacy data, as well as any emerging external evidence, including information from other REFINE cohorts.

Decisions will be made separately for each cohort, and as such not all cohorts may continue to stage II, and different arms may be introduced in each cohort.

9.4.4 Primary Outcome measures - stage 2 (Planned, each cohort)

Analysis of PFS in stage II will be performed as described for stage I, comparing an extended frequency arm to the standard frequency arm. The estimand will be the fully adjusted hazard ratio and the test will be performed at 5% (one-sided) significance level.

Analysis will begin by assessing the non-inferiority of the most extended frequency arm. If that arm demonstrates non-inferiority, no further arms are compared, and all arms can be considered for the phase III expansion of REFINE. If non-inferiority is not demonstrated, the next most extended frequency arm is assessed in the same manner, and so on until either an arm demonstrates non-inferiority, or all arms have been assessed.

9.4.5 Secondary outcomes measures – stage 2

Secondary outcomes within the second stage of REFINE will mirror those in stage I and be analysed in the same way. If stage II compromises of 4-5 arms, an additional secondary outcome will be to assess the feasibility of randomising to multiple arms, to support extending the multi-arm randomisation to a large phase III evaluation. This will involve looking at the proportion of potential patients who go on to be randomised.

9.4.6 Missing data and loss to follow-up

As planned analyses of primary and secondary outcome measures only include covariate adjustment using randomisation stratification factors, missing data are expected to be confined to the outcome variables.

For time to event analyses, patients without an observed event will be censored at the date of their last assessment. It is anticipated that the majority of censoring will be administrative censoring at the time of analysis, therefore the assumption of non-informative censoring should be valid. Patterns of censoring will be assessed and if necessary, for example if a high proportion of patients are lost to follow-up, sensitivity analyses may be performed to assess the robustness of results.

For quality-of-life analyses, initial analyses will use a complete case approach, without imputation of any missing data. Levels and patterns of missing data will be assessed, and if necessary, sensitivity analyses will be conducted using multiple imputation techniques.

10 HEALTH ECONOMICS

10.1 OVERVIEW

We will calculate the mean change in cost per quality-adjusted life-year (QALY) gained of 2'X'-weekly (intervention arm) vs 'X'-weekly (standard of care arm) administration of Nivolumab or Pembrolizumab in each of the three cohorts (Renal N, Melanoma N, Melanoma P). We will use data from participants in the first stage of REFINE, over a 24-month time horizon in an initial trial-based analysis in stage 1, from the perspective of the NHS and Personal Social Services, i.e. the perspective preferred by NICE, and this will be extended to a lifetime decision analytic model. Pairwise comparisons between pairs of arms within the same cohort will also be made using data collected in the second stage of REFINE, or joint multi-arm comparisons calculating net monetary benefit at a range of cost-effectiveness thresholds, if appropriate, when other treatment frequencies are trialled in stage 2.

10.1.1 QALYs

The same methods will be applied to all cohorts: QALYs will be calculated from the utility scores calculated from participant responses to the EQ-5D-5L (24), as the area under the curve, adjusting for baseline differences using regression analysis (27).

10.1.2 Resource Use and Costs

Resource use will be collected via a modified version of the participant-completed Client Service Receipt Inventory (CSRI (28)) and from treatment and concomitant medication data, and will include information on inpatient and outpatient hospital service use including ICI treatment costs, primary and community health and social care service contacts, and other medications. The modified CSRI will be drafted by the health economists in collaboration with other members of the core trial team, including clinicians and PPI collaborators.

Published NHS Reference Costs or Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care will be applied to service use information, and British National Formulary costs used where required for medications, with secondary analyses using any available information on patient access scheme discounts. The cost of administering the ICI, including medication costs and appointments etc., will be captured and included in both arms.

10.1.3 Time points for data collection

EQ-5D-5L and service use information will be collected from participants at baseline, 12 and 24 weeks, and every 12 weeks thereafter, including after disease progression. Information on administration of ICI and concomitant medications will be collected as described in trial assessment schedule. Baseline costs will be collected over the 12-week period preceding baseline.

10.1.4 Analysis and reporting results

Both costs and QALYs will be adjusted for baseline values, and for any other site, disease or patient confounding variables specified in the main clinical analysis. Mean incremental costs and QALYs and 95% confidence intervals will be jointly estimated with bootstrapping for the initial trial analysis (29, 30). Joint probabilistic sensitivity analysis will be used in the lifetime decision model. Cost-effectiveness acceptability curves and cost-effectiveness planes (31) will be reported from the bootstrapped or probabilistic results in each analysis to represent the probability that the intervention is cost-effective compared to the control arm for a range of values of the cost-effectiveness threshold of cost per QALY gained. We will conduct and report a range of sensitivity

analyses for any assumptions made. Missing data and adjustment for covariates will be handled in the same way as the main statistical analysis plan, using multiple imputation if appropriate. Costs and QALYs will be discounted at the standard 3.5% rate annually after the first year.

10.1.5 LIFETIME MODELLING

We plan to collect both EQ-5D-5L and resource use data including ICI and concomitant medications from baseline until after progression and for as long as possible for each participant, but if the lifetime models require additional later information not available from the trial data, then the published literature or expert opinion will used to provide this information.

Further details of these analyses will be described in the **Health Economics Analysis Plan (HEAP)**, which will form a chapter of the **Statistical Analysis Plan (SAP)**.

11 ANCILLARY STUDIES

11.1 TRANSLATIONAL PROJECTS

11.1.1 BASELINE TUMOUR SAMPLES

Patients will be offered the opportunity to consent to the use of their prior tumour biopsy (formalin fixed and paraffin embedded – FFPE) for future work (subject to separate funding). Amongst other questions, this aims to understand response to treatment with immune checkpoint inhibitors, both in terms of understanding differences in how individual patients experience treatment and also whether there are any predictive biomarkers to treatment response or dose frequencies.

11.1.2 SERIAL BLOOD SAMPLES

A sub-study within REFINE aims to better understand both the pharmacokinetics of immune checkpoint inhibitors and also the pharmacodynamics with respect to target efficacy between different frequencies of administration. Patients may be offered enrolment into a program of taking additional research blood samples. These will take the form of a 10ml EDTA tube and a 10ml clotted tube to be taken immediately prior to administration of drug as per the trial assessment schedule, in order to ascertain trough plasma concentrations of drug and similarly minimal T-cell receptor occupancies. Please refer to the **Sample Handling Manual** for further information.

12 REGULATORY & ETHICAL ISSUES

12.1 COMPLIANCE

12.1.1 REGULATORY COMPLIANCE

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki 1996 (32),the principles of Good Clinical Practice (GCP) as laid down by the ICH topic E6 (R2), Commission Clinical Trials Directive 2005/28/EC* with the implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, General Data Protection Regulation and the UK Data Protection Act 2018 (DPA number: Z6364106), and the UK Policy Framework for Health and Social Care Research.

*Until the Clinical Trials Regulation EU No 536/2014 becomes applicable, the trial will be conducted in accordance with the Clinical Trials Directive as implemented in the UK statutory instrument. When the directive is repealed on the day of entry into application of the Clinical Trial Regulation the trial will work towards implementation of the Regulation (536/2014) following any transition period.

12.1.2 SITE COMPLIANCE

An agreement will be in place between the site and MRC CTU, setting out respective roles and responsibilities.

The site will inform the Trials Unit as soon as they are aware of a possible serious breach of compliance, so that the Trials Unit 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

12.1.3 DATA COLLECTION & RETENTION

Clinical notes and administrative documentation including trial worksheets should be kept in a secure location (for example, locked filing cabinets in a room with restricted access) and held for a minimum of 25 years after the end of the trial. During this period, all data should be accessible, with suitable notice, to the competent or equivalent authorities, the Sponsor, and other relevant parties in accordance with the applicable regulations. 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.

12.2 ETHICAL CONDUCT

12.2.1 ETHICAL CONSIDERATIONS

12.2.1.A Randomisation

This is a randomised trial therefore neither the participants nor their physicians will be able to choose the participants' treatment. Treatment will be allocated randomly using a computer-based algorithm. This is to ensure that the groups of participants receiving each of the different treatments are as similar as possible.

12.2.1.B Evaluation of Novel Treatment Schedule

Potentially, extending the interval of treatment may have advantages over standard treatment, but this is not confirmed. This trial will follow a group of people who have been randomly allocated to either the standard treatment or the novel treatment schedule in order to measure the benefits of these approaches. All participants will be followed-up for toxicity and safety issues, so that any benefits can be weighed against any negative aspects, including the impact treatments have on other aspects of medical health as well as quality-of-life and value for money (health economic analysis).

12.2.1.C Facilitating Participant Feedback From Investigations and Additional Analyses

For participants who choose to take part in additional sub-studies, biological samples will be used in research projects. These projects will enable the study of genetic factors and other biomarkers that can help identify individuals who serve to benefit most from the treatments tested, and to further understand why and how treatment resistance develops. All samples will remain anonymised and only made accessible to approved collaborators granted access by the REFINE oversight committees. We will make every effort to protect the confidentiality of this information and make sure personal identities are protected.

12.2.1.D Considering the Impact of Emerging Data

If new information emerges during the course of the trial which may affect the treatment or follow-up of participants all Principal Investigators (PIs) will be informed of this and required to inform trial participants.

12.2.1.E Electronic health records

Participants are requested to provide consent to permit linkage of trial data to other sources of electronic health data to improve the reliability of long-term follow-up data. Explicit consent is requested for the CTU to store direct identifiers (name and NHS number) securely and separately from anonymised trial data. This is to permit verification of the information held by others and received by the CTU, ensuring that the trial database is only updated with accurate information.

12.2.2 Favourable Ethical Opinion

Following Main REC favourable opinion and Health Research Authority (in England) approvals and 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 each Trust's Research and Development (R&D) office. In Wales, Scotland and Northern Ireland, the R&D office will be asked to give approval. In England, the R&D office will be asked to confirm capacity and capability. Any further substantial amendments will be submitted and approved by the Main REC and HRA.

The study has been developed with Patient and Public Involvement (PPI) to ensure that its design is feasible and acceptable to potential participants, and to ensure its outcomes and potential impact are relevant to the population who may benefit from its results. PPI also helps to ensure transparency and accountability throughout this research. PPI activity will continue for the duration of the study, including dissemination of study results.

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; 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 his/her further treatment.

12.3 COMPETENT AUTHORITY APPROVALS

This protocol has been approved by the national competent body (MHRA).

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.

The EudraCT number for the trial is 2021-002060-47.

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 authority in accordance with its requirements in a timely manner.

12.4 OTHER APPROVALS

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

12.5 TRIAL CLOSURE

The end of trial will be when all participants have completed follow-up, all data have been obtained and the database has been locked.

13 INDEMNITY

The sponsor of the trial is the University College London (UCL). REFINE 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 REFINE 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.

14 FINANCE

The REFINE trial is funded by the Jon Moulton Charity Trust and the Medical Research Council (MRC).

Immune checkpoint inhibitors (IMP) are used as standard-of-care indications in all enrolled trusts, and therefore there is no drug cost.

REFINE is included in the NCRN portfolio and support will be available for participating UK centres in the usual way

15 OVERSIGHT & TRIAL COMMITTEES

There are a number of committees involved with the oversight of the trial. These committees are detailed below.

15.1 TRIAL MANAGEMENT GROUP (TMG)

The Trial Management Group (TMG) comprises the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the MRC Clinical Trials Unit (CTU) and PPI contributors (representing each tumour cohort and more generally the population of patients with advanced cancers being treated with immune checkpoint inhibition). The TMG will be responsible for the day-to-day running and management of the trial. It will meet approximately three times a year at least. The full details can be found in the TMG Charter.

15.2 TRIAL STEERING COMMITTEE (TSC)

The Trial Steering Committee (TSC) is made up of independent members, including the Chair and PPI contributors. 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. The TSC also has a role in reviewing data release requests. Further details of TSC functioning are presented in the **TSC Charter**.

15.3 INDEPENDENT DATA MONITORING COMMITTEE (IDMC])

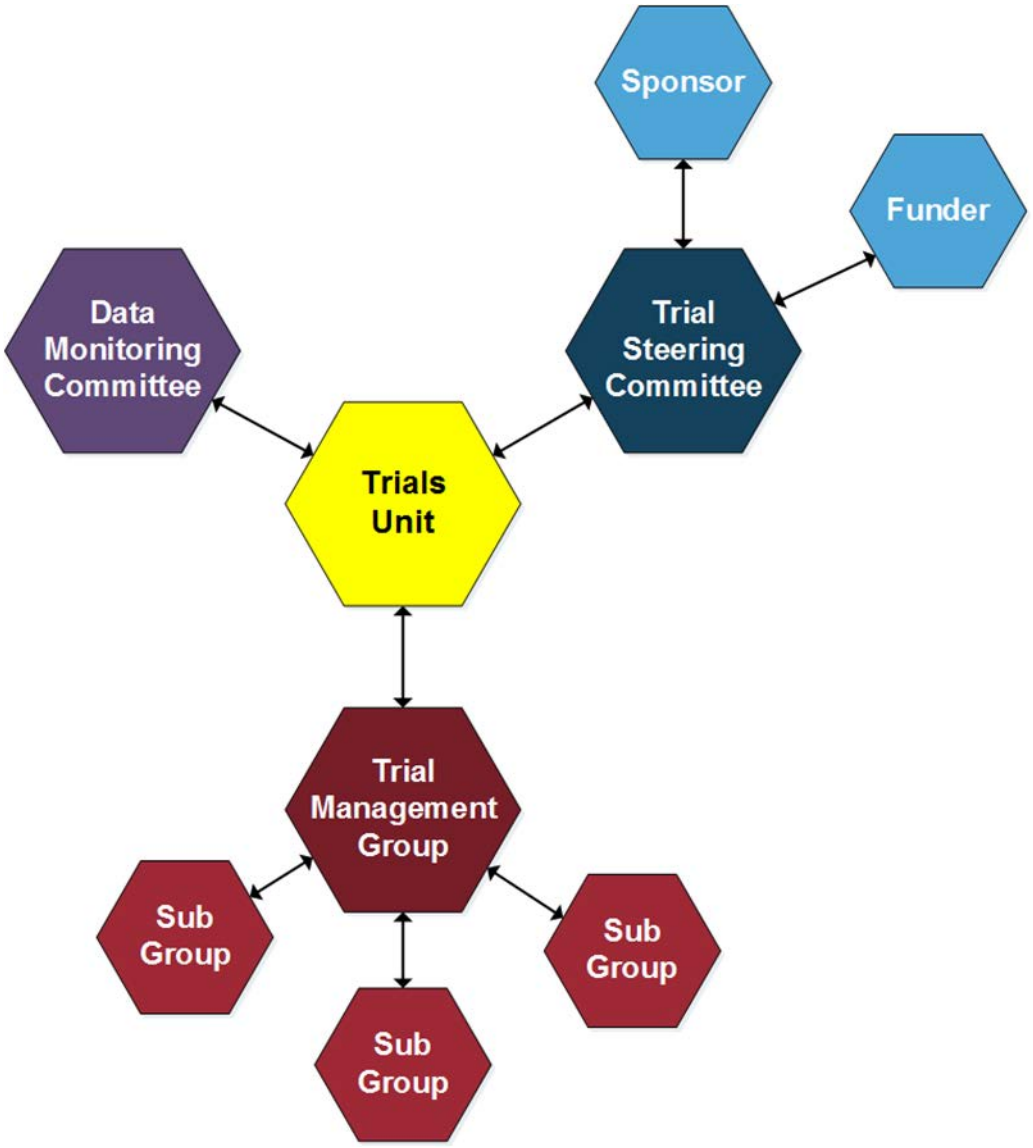
An Independent Data Monitoring Committee (IDMC) will be formed. The IDMC will be the only group who sees the confidential, accumulating data for the trial. Reports to the IDMC will be produced by the CTU statisticians. The IDMC will meet within 6 months after the trial opening to recruitment; the frequency of meetings will be dictated in the **IDMC Charter**. The IDMC will consider data using the statistical analysis plan (see section 9) and will advise the TSC. The IDMC can recommend premature closure or reporting of the trial, or that recruitment to any research arm be discontinued.

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

15.4 ROLE OF STUDY SPONSOR

The sponsor of the trial is University College London, as employer of the staff coordinating the trial at the MRC CTU at UCL.

Figure 4: Relationship and organisation of trial oversight committees



16 PATIENT AND PUBLIC INVOLVEMENT

Patient and Public Involvement (PPI) in research is defined by the NIHR as research being carried out 'with' or 'by' members of the public rather than 'to', 'about' or 'for' them. INVOLVE (the national advisory group funded supporting PPI in the NHS) intends 'public' to include patients, potential patients, carers and other users of health and social care services, as well as people from organisations that represent people who use services. In REFINE this includes PPI representatives having been involved in the trial design, development and ongoing management groups.

16.1 POTENTIAL IMPACT OF PPI

PPI has been important in REFINE trial design, underpinning the primary questions to be asked within REFINE and the details at each stage. PPI was central to the development of the patient facing materials (PIS and Consent) and the refinement of the health economic and Quality-of-life approach taken.

16.2 IDENTIFYING PPI CONTRIBUTORS

PPI representatives within REFINE were identified through an advert placed in the consumer forum of the National Clinical Research Institute (NCRI). Opportunities for PPI involvement in REFINE were also sent directly to the relevant support charities (Action Bladder Cancer, International Kidney Cancer Coalition - an independent international network of patient organisations that focus exclusively, or include a specific focus, on kidney cancer).

16.3 PPI IN THE ONGOING RUNNING OF STUDY

PPI representatives are active members of the trial management group and trial steering committee and will be directly involved in the analysis of results and presentation of trial data and subsequent publication.

17 PUBLICATION AND DISSEMINATION OF RESULTS

The results from the initial stage of REFINE will be published as soon as possible in peer-reviewed journals, as well as being presented at national and/or international conferences. Individual groups and clinicians must not publish data concerning their participants that are directly relevant to questions posed by the study until the TMG has published its report. The TMG (including PPI members) will form the basis of the Writing Committee and will advise on the nature of all publications.

There are expected to be a number of resulting publications and the authorship will vary for each. Individual authors are likely to include relevant members of the TMG and collaborators, as well as high-recruiting Investigators. All participating centres and corresponding PIs and co-PIs in the relevant cohort will be acknowledged in all relevant publications, along with members of the IDMC and TSC. The extensive PPI membership of REFINE will help shape and publicise the findings of the trial. This will include via NCRI and cancer specific charity communication channels reflecting the expertise of the PPI representatives.

Results from the primary analyses of the different tumour site-specific studies may be available at different times, as will results from the sub-studies. In order not to jeopardise the integrity of the ongoing trials, careful consideration (in discussion with the IDMC and TSC, as appropriate) will be given to the data to be released from each analysis for presentation/publication. Similarly, if at any point it is felt to be justified and appropriate to release specific data from an interim analysis, this would require discussion and agreement from the IDMC, who would be asked to provide guidance regarding the data to be released and how widely they should be disseminated.

18 DATA AND/OR SAMPLE SHARING

Data will be shared according to the CTU's moderated access approach, based on the following principles:

- No data should be released that would compromise an ongoing trial or study.
- There must be a strong scientific or other legitimate rationale for the data to be used for the requested purpose.
- Investigators who have invested time and effort into developing a trial or study should have a period of exclusivity in which to pursue their aims with the data, before key trial data are made available to other researchers.
- The resources required to process requests should not be under-estimated, particularly successful requests which lead to preparing data for release. Therefore adequate resources must be available in order to comply in a timely manner or at all, and the scientific aims of the study must justify the use of such resources.
- Data exchange complies with Information Governance and Data Security Policies in all of the relevant countries.

Researchers wishing to access REFINE data should contact the Trial Management Group in the first instance.

19 PROTOCOL AMENDMENTS

This is version 5.0 of the protocol.

19.1 PROTOCOL

19.1.1 AMENDMENT MADE TO PROTOCOL VERSION 1.0 07-JUL-2021

1. Throughout – version and date updated to v2.0, 19-Aug-2021
2. Section 1.5 – clarification regarding process for moving from stage I to stage II.

19.1.2 AMENDMENT MADE TO PROTOCOL VERSION 2.0 19-AUG-2021

1. Throughout – version and date updated to v3.0, 05-Oct-2021
2. Throughout – minor typographical corrections and amendments for consistency and clarity.
3. Addition of CTA and REC reference numbers.
4. Trial assessment schedules and flexibility – clarifications regarding visit windows, pregnancy testing requirements, and Quality of Life questionnaires.
5. Section 1.7 and 10.1 – clarification regarding health economics calculation.
6. Section 3.1.1 and section 6.3, table 6 – change from calculated creatinine clearance to estimated GFR using the CKD-EPI formula.
7. Section 5.8 and Appendix 1 – addition of acceptable methods of contraception (including acceptable contraception for male participants).
8. Section 6.3 – update to table 6 to clarify lab tests required at all visits vs those required at screening and as clinically indicated, and addition of footnote 6.
9. Section 9.2.1 – clarification regarding the trial definition of PFS.
10. Section 11.1.2 – clarification regarding the translational blood samples required.

19.1.3 AMENDMENT MADE TO PROTOCOL VERSION 3.0 05-OCT-2021

1. Throughout – version and date updates to v4.0, 04-Mar-2022
2. Throughout – minor typographical corrections and amendments for consistency and clarity.
3. Section 3.1.2.A – clarification of inclusion relating to IDMC.
4. Section 3.2 – removal of exclusion criteria relating to immune-related adverse events – intention is that those fit to treat as per standard of care will be eligible as already noted in section 5.1.
5. Section 6.4 – amendment to text relating to questionnaires for consistency with schedule of assessments.
6. Section 6.7 – clarification of process around patient transfers.
7. Section 7.1.4.A – section moved.
8. Appendix 2 – addition of TNM staging version 8.

19.1.4 AMENDMENT MADE TO PROTOCOL VERSION 4.0, 04-MAR-2022

1. Throughout – version and date updates to v5.0, 03-Jan-2023.
2. Throughout – formatting, spelling punctuation and grammar changes.
3. On cover page - addition of current UK Research and Innovation and MRC CTU badge.
4. Throughout - addition of ISRCTN number.
5. On Page ii - changes to MRC CTU at UCL staff.
6. On Page iii - changes to list of Co-Investigators and addition of PPI representatives.
7. On page viii Table 2 - Timing of Other Assessments.
8. On page ix Table 3 - Trial Assessment Schedule stage 1.
9. On page xi Table 4 - Pembrolizumab (6 weekly monotherapy) i.e. Melanoma (P).

10. Updated Glossary of Terms.
11. Section 3.1.2.A - Change to Renal cohort specific inclusion criteria to at least one dose of induction ipilumumab and received nivolumab as first-line treatment.
12. Section 3.1.2.B - Confirmation that Melanoma cohort specific inclusion criteria includes advanced unresectable Melanoma, with addition of primary mucosal but not uveal Melanoma.
13. Section 3.1.2.B - Change to Melanoma cohort specific inclusion criteria to include patients who have received at least one dose of induction ipilimumab or due to continue pembrolizumab. Confirmation that brain metastases are responsive or stable on cross sectional imaging in patients who have received at least one dose of induction ipilimumab.
14. Section 3.2 - Removed from Patient Exclusion Criteria Untreated brain metastases or brain metastases treated only with whole brain radiotherapy.
15. Section 4.1.3 - Change to Randomisation anytime up to 8 weeks after the last dose of the first 12 weeks treatment.
16. Section 5.1.2 - Clarification to Treatment Arm A (SOC)
17. Section 5.3.3 - Addition of PET-CT assessment as accepted alternative to CT scans and guidance on progression based on PET-CT assessment. Confirmation that brain metastases must also show an absolute increase of at least 5mm to be considered new lesions.
18. Section 5.3.4 - Added example of minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease guidance. Addition of PERCIST for assessing response criteria from PET scans. Removed guidance that immune checkpoint inhibitor treatment should be discontinued permanently upon documentation of further progression.
19. Table 6 - Removed requirement for Amylase and Lipase tests at any time during trial.
20. Section 6.3 - Addition of PET CT as acceptable alternative to CT scan where used in routine local practice and brain imaging with contrast CT or MRI included, as appropriate.
21. Section 10.1.4 - Confirmation that costs and QALYs will be discounted at the standard 3.5% rate annually after the first year of the trial.
22. Section 12.3 - Confirmation that protocol has been approved by the national competent body (MHRA).

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APPENDIX I – WOCBP AND HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Women of Childbearing Potential

For the purpose of this document, a woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

For the purpose of this document, a man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Highly Effective Methods of Contraception

For the purpose of this trial, methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation[1]
  - Oral
  - Injectable
  - implantable
- intrauterine device (IUD)[2]
- intrauterine hormone-releasing system (IUS)[2]
- bilateral tubal occlusion[2]
- vasectomised partner[2,3]
- sexual abstinence[4]

Acceptable Methods of Contraception

- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- male or female condom with or without spermicide[5]
- cap, diaphragm or sponge with spermicide[5]

Please see (35) for further guidance.

1 Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.
2 Contraception methods that in the context of this guidance are considered to have low user dependency.
3 Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

4 In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.
5 A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

APPENDIX II – TNM STAGING VERSION 8 FOR RENAL CELL CARCINOMA

Table 9: TNM Staging

T —primary tumour	TX	Primary tumour cannot be assessed
	T0	No evidence of primary tumour
	T1 T1a T1b	Tumour 7 cm or less in greatest dimension, limited to the kidney Tumour 4 cm or less Tumour more than 4 cm but not more than 7 cm
	T2 T2a T2b	Tumour more than 7 cm in greatest dimension, limited to the kidney Tumour more than 7 cm but not more than 10 cm Tumour more than 10 cm, limited to the kidney
	T3 T3a T3b T3c	Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia Tumour extends into the renal vein or its segmental branches, or tumour invades the pelvicalyceal system or tumour invades perirenal and/or renal sinus fat (peripelvic) fat but not beyond Gerota fascia Tumour extends into vena cava below diaphragm Tumour extends into vena cava above the diaphragm or invades the wall of the vena cava
	T4	Tumour invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)
N - regional lymph nodes	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	Metastasis in regional lymph node(s)
M—distant metastasis	M0	No distant metastasis
	M1	Distant metastasis

Table 10: RCC Staging

Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T3 N0 M0 T1, T2, T3 N1 M0
Stage IV	T4 Any N M0 Any T Any N M1

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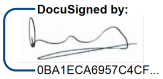
Duncan Gilbert duncan.gilbert@ucl.ac.uk Security Level: Email, Account Authentication (Optional)	DocuSigned by:  0BA1ECA6957C4CF... Signature Adoption: Uploaded Signature Image Using IP Address: 208.127.197.114	Sent: 25 January 2023 | 10:37 Viewed: 25 January 2023 | 10:38 Signed: 25 January 2023 | 10:39

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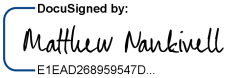
Matthew Nankivell m.nankivell@ucl.ac.uk Security Level: Email, Account Authentication (Optional)	DocuSigned by:  E1EAD268959547D... Signature Adoption: Pre-selected Style Using IP Address: 144.82.114.236	Sent: 25 January 2023 | 10:37 Resent: 01 February 2023 | 18:53 Viewed: 02 February 2023 | 07:34 Signed: 02 February 2023 | 07:34

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