A phase II trial of pembrolizumab in patients with non-small cell lung cancer and a performance status of 2

PROTOCOL version 6.0, 10th July 2018

UNIVERSITY OF BIRMINGHAM

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TRIAL CONTACTS

Chief Investigator:
Professor Gary Middleton, Professor of Medical Oncology
Institute of Immunology and Immunotherapy, University of Birmingham.
Tel: 0121 627 2000

Clinical Coordinators:
Professor Christian Ottensmeier, Professor of Experimental Medicine
University of Southampton and Southampton University Hospitals
Tel: 0238 120 5161 (PA, Miss Lynsey Block) Mobile 07879485676

Dr Yvonne Summers, Consultant Medical Oncologist
The Christie and University Hospital South Manchester
Tel: Christie 0161 446 8016; UHSM 0161 291 2829; Mobile 07776 144513

Dr Alastair Greystoke, Senior Lecturer and Honorary Consultant in Medical Oncology,
Sir Bobby Robson Clinical Trials Unit Freeman Hospital Newcastle upon Tyne
Tel: 0191 213 9224 or 0191 213 8476; Mobile 07738719014

Lead Biostatistician:
Professor Lucinda Billingham, Professor of Biostatistics, Cancer Research UK Clinical Trials Unit (CRCTU), Institute of Cancer and Genomic Sciences, University of Birmingham, B15 2TT

Trial Statistician:
Mr Kristian Brock, Senior Statistician, CRCTU, University of Birmingham.

Trial Coordinator:
Mr Rhys Mant, Early Drug Development (EDD) Team, CRCTU, University of Birmingham.

Senior Trial Manager:
Dr Joshua Savage, EDD Team Leader, CRCTU, University of Birmingham.

PePS2 Trial Office

Cancer Research UK Clinical Trials Unit, Institute of Cancer and Genomic Sciences, University of Birmingham, Edgbaston, Birmingham. B15 2TT

Enquiries:

☎ 0121 414 6788
🖷 0121 414 3529
✉ PePS2@trials.bham.ac.uk

Registration:

☎ 0121 414 6788 or 6754
(9.00 am till 5.00 pm Monday to Friday)

Serious Adverse Event Reporting:

🖷 0121 414 3529 (primary)
🖷 0121 414 7989 (secondary)

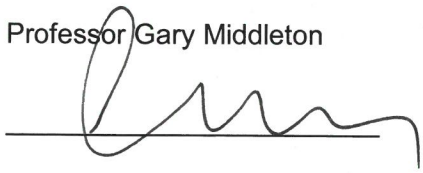
Sponsor:
University of Birmingham

SIGNATURE PAGE

PePS2 Trial Protocol vn 6.0, vd 10-Jul-2018

This protocol has been approved by:

Name: Professor Gary Middleton **Trial Role:** Chief Investigator

Signature:  **Date:** 13 / Jul / 2018

This protocol describes the PePS2 trial and provides information about procedures for patients taking part in the PePS2 trial. The protocol should not be used as a guide for treatment of patients not taking part in the PePS2 trial.

This protocol was written using CRCTU-PRT-QCD-001, version 1.0.

AMENDMENTS

The following amendments and/or administrative changes have been made to this protocol since the last submission.

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
1	07-Mar-2016	2.0	Substantial amendment	• Updated contact details • Addition of Safety follow-up visits to schedule of events, for 6 months after the last study dose. • Removal of Autoantibody collection from Schedule of Events • Statistical section has been redrafted for clarity • Correction of grammatical, formatting/ spelling errors • Addition of Safety follow-up visits in Sections 6.8: patient follow up, 6.11.3 Reporting requirements and 6.12.1.3 Events of Clinical Interest for 6 months after the last study dose.
	07-Jun-2016	2.0a	Non substantial amendment	• Stool sample instead of rectal swab • Correction of formatting and grammatical errors
2	30-Jan-2017	3.0	Substantial amendment	• Updated contact details • Correction of formatting and grammatical errors throughout • Eligibility: Updated Performance Status criterion • Clarified procedure for pre-registration screening • Eligibility: Amended requirements for obtainingPD-L1 status from archival tissue or a new biopsy if archival tissue is unavailable • Clarified patients with both PD-L1 positive and negative tumours are eligible. Patients who have had systemic therapy since the biopsy do not need to have a repeat biopsy. • Added that a newly obtained biopsy is mandatory at baseline (prior to Cycle 1/Day 1) for the assignment of PD-L1 status if an archival biopsy is not available and/or PD-L1 testing on the archival tissue is unsuccessful (see section 4.1 for more details). • Added slides of fresh cut sections from Formaldehyde Fixed Paraffin Embedded (FFPE) tissue block will

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
				be assessed by the site Pathologist for PD-L1 testing • Added if the PD-L1 status has already been obtained from a nationally recognised and MSD-approved laboratory, this will be acceptable and repeat PD-L1 staining will not be required • Added if a patient has had a repeat biopsy for the purpose of PD-L1 staining for the PePS2 trial but the biopsy failed to yield sufficient cells for PD-L1 status, this patient will still be eligible to enter the PePS2 trial but will be categorised as PD-L1 non-evaluable. • Added clearer definition of performance status of 2 in the inclusion and exclusion criteria. • Added flow chart of Treatment Assessments • Clarified assessments performed up to 28 and 7 days before treatment • Clarified procedure for registration • Added table for frequency of sample collection • Investigator brochure changed to Summary of Product Characteristics • Added another Event of Clinical interest and reference to immune-mediated AEs • Statistical considerations re-written and dose reduction removed.
5	14-Jun-2017	4.0	Substantial amendment	• Clarified trial objectives, outcomes measures and exclusion criteria in trial synopsis • Timing of some of the screening and week 0 assessments changed. • Additional measurments for cortisol and CRP added plus smoking history. • Clarified amount of time blood pressure and ECG to be performed. • To routine laboratory tests table added CRP and cortisol measurements and amended urinalysis. • Abbreviations table updated • Background and Rationale updated

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
				• Updated objectives and outcome measures, clarifying and sumarising primary objectives and secondary and exploratory outcome measures • Updated Trial Design • Amended Inclusion and Exclusion criteria • Amended Patient Registration to receive a copy of the ICF • Treatment assessments updated to reflect changes in addition of and time when samples collected. • Updated Dose Modification and Toxicity Management section • Changed prohibited concomitant medications so that systemic steroids can be taken by patients have started trial treatment but steroids can only be taken for a maximum of 2 weeks • Added patients who meet RECIST criteria for progressive disease (PD) may be continued on trial treatment if the treatment is tolerable and believed to be of clinical benefit to Patient Withdrawal section. • During reporting period, only details of all treatment-related AEs will be documented. • Amended Dose Modification and toxicity management section • Amended pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines table • Amended Statistical Considerations section
6	14th August 2017	5.0	Substantial amendment	• Updated contact details • Specified instructions for collection and freezing of stool sample. • Correction of formatting errors
7	10-Jul-2018	6.0	Substantial amendment	• Trial contact details updated. • Table 4 updated. • Section 15: Regualtory framework updated. • Section 16: Updated to include General Data Protection Regulations. • Minor spelling and formatting changes throughout.

TRIAL SYNOPSIS

Title

PePS2: A phase II trial of pembrolizumab in patients with non-small cell lung cancer and a performance status of 2

Trial Design

Multi-centre, single-arm phase II trial, testing pembrolizumab in a population of patients with non-small cell lung cancer (NSCLC) and an Eastern Cooperative Oncology Group (ECOG) performance status of 2

Trial Objectives

This is a phase II trial of programmed cell death protein 1 (PD-1) blockade in patients with programmed death ligand 1 (PD-L1) defined NSCLC and an ECOG performance status of 2 with the primary purposes:

- To determine that pembrolizumab is safe and tolerable at the selected dose
- To detect the durable clinical benefit in this population of patients treated with pembrolizumab that would justify further investigation

Secondary objective:

- To measure patient health related quality of life (HRQoL)

Exploratory objective:

- To discover possible biomarkers to predict for a response to pembrolizumab

Outcome Measures

Primary outcome measures:

- Toxicity defined as the occurrence of a treatment-related dose delay or treatment discontinuation due to an adverse event
- Durable Clinical Benefit defined as the occurrence of a complete response (CR), partial response (PR) or stable disease (SD) without prior progressive disease (PD) at or after the second scheduled CT scan (scheduled to occur at18 weeks).

Secondary outcome measures:

- Objective Response (OR)
- Progression-free survival time (PFS)
- Time to Progression (TTP)
- Overall survival time (OS)
- Health related quality of life (HRQoL)
- Duration of objective response (DOR) and duration of stable disease (DSD)

Patient Population

Patients with non-small cell lung cancer and an ECOG performance status of 2 (Appendix 1)

Sample Size

60 patients

Inclusion Criteria (not exhaustive - refer to section 4)

- Histologically confirmed PD-L1 status defined NSCLC.
- ECOG performance status 2 with no deterioration over the previous 2 weeks assessed by consenting physician.

- Patients must be ambulatory and capable of all self-care but unable to carry out any work activities
- Patients must be up and about more than 50% of waking hours

- Life expectancy > 12 weeks.
- Uni-dimensionally measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 (Appendix 2).
- Computerised Tomography (CT) scan of chest and abdomen within 28 days of starting pembrolizumab.
- Adequate haematological function:
  - Platelet count ≥100 x 10^9 /L
  - Neutrophils ≥1.5 x 10^9/L
  - Haemoglobin ≥ 90 g/L
- Adequate hepatic function:
  - Serum bilirubin ≤1.5 x upper limit of normal (ULN)
  - Serum transaminases ≤2.5 x ULN
- Adequate renal function
  - Creatinine clearance <1.5 times ULN concurrent with creatinine clearance >50 ml/min (calculated by Cockcroft and Gault equation – see Appendix 3). If this is ≤ 50 ml/min then an isotopic Glomerular Filtration Rate (GFR) may be carried out and must be > 50 ml/min
- Provision of signed and dated, written informed consent prior to any trial specific procedures, sampling and analyses.

Exclusion Criteria (not exhaustive - refer to section 4)

- Patients who do not meet the criteria of performance status = 2 on the ECOG Performance scale (Appendix 1), i.e. patients should not be:-
  - ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work.
- Untreated symptomatic brain or leptomeningeal metastatic disease.
- Medical or psychiatric conditions comprising informed consent.
- Any medical condition which in the opinion of the Investigator would compromise the ability of the patient to participate in the trial or which would jeopardise compliance with the protocol.
- Radiotherapy within 28 days of trial treatment.
- Active autoimmune disease that has required systemic treatment in past 2 years.
- Chronic usage of steroids or other immunosuppressant medication.
- Previous history of pneumonitis.
- Any evidence of clinical autoimmunity.

Trial Duration

4 years (1 year recruitment, 2 years trial treatment, 1 year patient follow up)

Trial Office Contact Details

PePS2 Trial Office

Cancer Research UK Clinical Trials Unit,Institute of Cancer and Genomic Sciences
University of Birmingham,Edgbaston,Birmingham,B15 2TT

Phone: 0121 414 6788
Fax: 0121 414 3529
E-mail: PePS2@trials.bham.ac.uk

Trial Schema

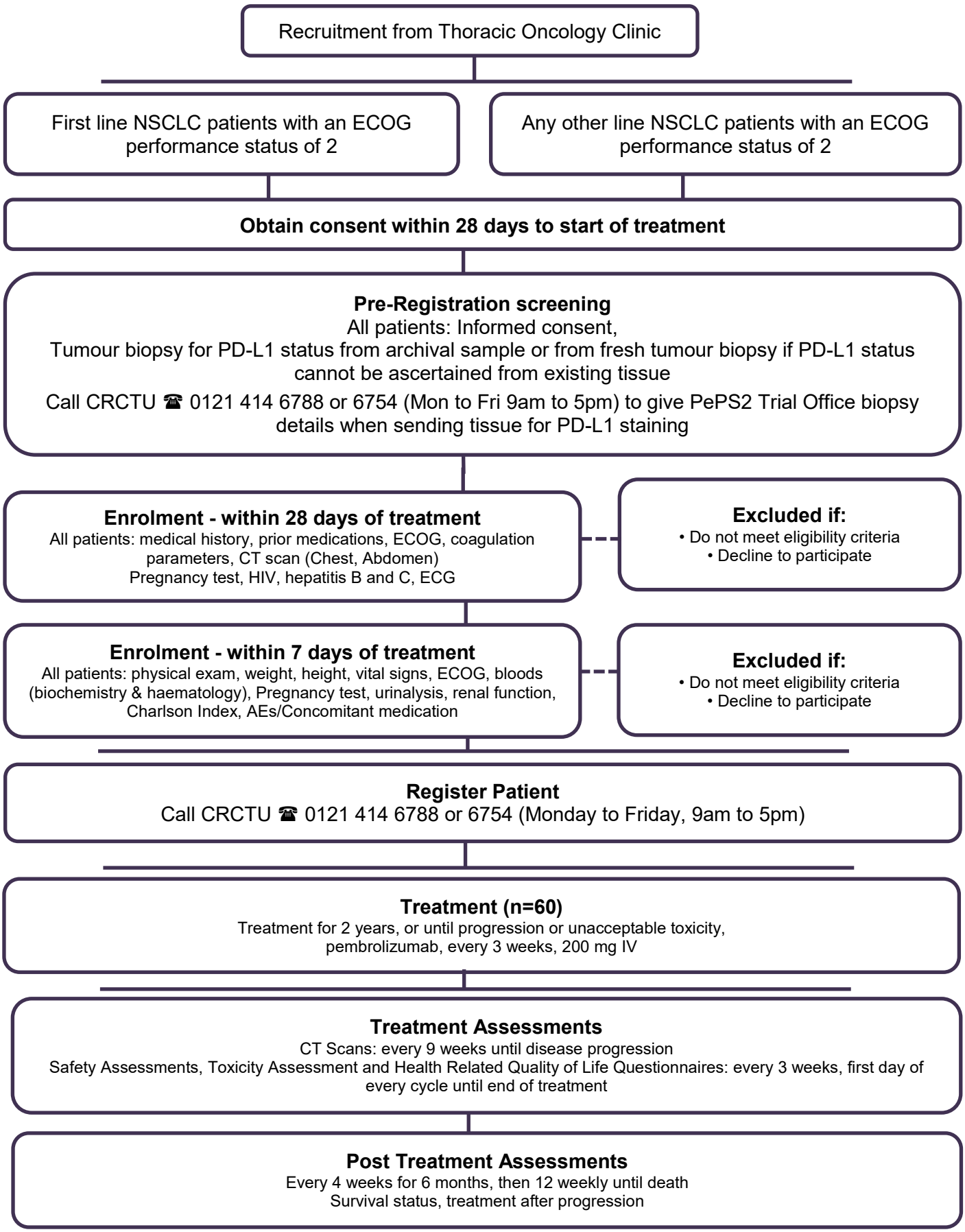


Table 1: Schedule of Events

	Screening		Treatment											Follow up		
	Within 28 days of entry	Within 7 days of treatment	Week/Cycle (21 Days ± 3 days)										Cycle 11-35 (21 Days ± 3 Days)	End of treatment	30 day Follow up	Long-term follow up Every 4 weeks for 6 months then 12 weekly until death
Week (approximate)			0	3	6	9	12	15	18	21	24	27	N			
Cycle			1	2	3	4	5	6	7	8	9	10	N			
Informed consent[1]	X															
Demographics / Medical History/Prior Medications[2]	X															
Charlson Index[3]		X														
HRQoL Questionnaire[4]			X	X	X	X	X	X	X	X	X	X	X	X		
Vital Signs[5]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination		X		X	X	X	X	X	X	X	X	X	X	X	X	
ECOG performance status[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG[7]	X															
Review Adverse Events and Concomitant Medications[8]		X	X	X	X	X	X	X	X	X	X	X	X	X	X*	X*
Full blood count (FBC)[9]		X		X	X	X	X	X	X	X	X	X	X	X	X	
Comprehensive serum chemistry panel[9]		X		X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis[9]		X				X			X			X	X*	X	X	
Coagulation parameters[10]	X														X	

	Screening		Treatment											Follow up		
	Within 28 days of entry	Within 7 days of treatment	Week/Cycle (21 Days ± 3 days)										Cycle 11-35 (21 Days ± 3 Days)	End of treatment	30 day Follow up	Long-term follow up Every 4 weeks for 6 months then 12 weekly until death
Week (approximate)			**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**N**			
Cycle			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**N**			
HIV, Hepatitis B and C[11]	X															
Pregnancy Test – Urine or Serum β-HCG[12]		X														
Renal function – GFR[13]		X														
Thyroid function and cortisol[14]		X		X		X		X		X		X	X[14]	X	X	
PBMC sample (60 ml blood)[15]			X	X	X (10ml)	X			X (10ml)			X (10ml)		X		
Stool sample [16]			X													
Cytokine/Chemokine Panel and proteomics[17]			X			X			X			X		X		
Germline DNA[18]			X													
ctDNA[19]			X			X			X			X		X		
Tumour Imaging with contrast[20]	X					X			X			X	X[20]		X[20]	X[20]
Study drug administration (30 minute infusion)			X	X	X	X	X	X	X	X	X	X	X			
Tumour biopsy (if archived tissue not available)[21]	X															

	Screening		Treatment											Follow up		
	Within 28 days of entry	Within 7 days of treatment	Week/Cycle (21 Days ± 3 days)										Cycle 11-35 (21 Days ± 3 Days)	End of treatment	30 day Follow up	Long-term follow up Every 4 weeks for 6 months then 12 weekly until death
Week (approximate)			**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**N**			
Cycle			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**N**			
Optional tumour biopsy from patients with durable clinical benefit post therapy[22]														X		
Survival assessment [23]																X

1.	Written informed consent must be obtained prior to performing any protocol specific procedure and within 28 days to starting treatment. Patient will need to be re-consented to PePS2 if over 28 days to treatment start.
2.	Includes smoking history, history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment, and best response to prior systemic treatments. Date of last prior cancer treatment must be documented.
3.	For Charlson Index see Appendix 4.
4.	QoL questionnaires include Functional Assessment of Cancer Therapy – Lung (FACT-L) questionnaire, EQ- 5D and patient generated subjective global assessment questionnaires, see Appendix 5. To be carried out prior to treatment.
5.	Vital signs to include: temperature, pulse, respiratory rate and blood pressure (average of 3 BP readings).
6.	For ECOG performance status criteria see Appendix 1.
7.	A standard 12-lead ECG will be performed, in triplicate if clinically abnormal rhythm detected, using local standard procedures once at screening. Clinically significant abnormal findings should be recorded as it should be reported as a concurrent condition. Additional time points may be performed as clinically necessary.
8.	Adverse Events (AEs) and laboratory safety measurements will be graded per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, Appendix 6. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness. *In addition to AE and Concomitant Medication review at each cycle, extra safety monitoring will be performed after the last trial dose monthly for up to 6 months.
9.	Routine laboratory tests (e.g., Full blood count (FBC); comprehensive serum chemistry panel; urinalysis) will be performed by the local trial site laboratory or their contract laboratory. Following cycle 13, urinalysis should be performed every 9 weeks*. FBC, serum chemistry and urinalysis may be collected up to 48 hours prior to any Cycle “X”, Day 1 dosing. Routine laboratory tests (serum chemistry; haematology) for screening should be performed within 7 days of first treatment.
10.	Prothrombin (PT) / International Normalised Ratio (INR) and partial thromboplastin (aPTT) should be collected at Screening and at the mandatory Safety Follow-up Visit after discontinuation of trial therapy. Coagulation parameters should be determined throughout the trial when clinically indicated.
11.	Testing will be performed by the local laboratory at Screening. Include Hepatitis C Virus (HCV) RNA (qualitative), Hepatitis B surface Antigen (HBsAg), and Human Immunodeficiency Virus (HIV) 1/2 antibodies.
12.	For women of reproductive potential, a urine pregnancy test will be performed within 72 hours of the first dose. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. See Section 4.3 (Contraception).
13.	Patients must have adequate renal function as defined by Creatinine clearance <1.5 x ULN concurrent with creatinine clearance >50 ml/min (calculated by Cockcroft and Gault equation – see Appendix 3, or as per institutional standard). If this is ≤50 ml/min then an

	isotopic GFR may be performed and must be ≥50 ml/min.
14.	Analysis of cortisol, T3, T4 and TSH (Thyroid Stimulating Hormone) will be performed by the local site laboratory. Following Cycle 2, testing will be performed every other cycle.
15.	60 ml blood collected before the start of infusion at cycle 1, cycle 2, cycle 4 and on termination of treatment and 10ml blood collected before the start of infusion at cycle 3, 7 and 10. Processing and storage of blood samples are to be carried out as described in the PePS2 Laboratory Manual.
16.	Collected before start of infusion 1. Processing and storage of the stool samples are to be carried out as described in Section 7.6.3.
17.	Collected before start of infusion at cycles 1, 4, 7, and 10. Processing and storage of blood samples are to be carried out as described in PePS2 Laboratory Manual. Analysis will be performed by a central laboratory.
18.	Collected before start of infusion at cycle 1. Analysis will be performed by a central laboratory. Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw). This sample should only be taken once from each subject.
19.	Collected before start of infusion at cycles 1, 4, 7, 10 and 13 and on termination of treatment. Analysis will be performed by a central laboratory. Processing and storage of blood samples are to be carried out as described in PePS2 Laboratory Manual.
20.	Tumour imaging by CT with contrast will be performed within 28 days prior to enrolment. The same imaging technique has to be used in a patient throughout the trial. Scans will be reported by RECIST 1.1 (Appendix 2). Tumour imaging will be performed every 9 weeks whilst the patient remains on trial therapy. CT scan results must be ready prior to cycle 4, 7, 10 etc. to allow the treating clinician to make decision about treatment continuation. Follow up CT scans will **only** be required every 9 weeks until progression or until commencement of another cancer treatment **for patients who come off treatment due to toxicity.** Response status will be assessed by the trial site.
21.	A newly obtained biopsy is mandatory during screening (prior to cycle 1/day 1) for the assignment of PD-L1 status if an archival biopsy is not available and/or PD-L1 testing on the archival tissue is unsuccessful (see sections 4.1 and 5.2.1.1 for more details). The biopsy may be either Endobronchial ultrasound (EBUS) or Computer-Tomography (CT)-guided. Refer to the PePS2 Laboratory Manual re: PD-L1 testing.
22.	One optional newly obtained biopsy for patients who were initially responsive but have relapsed on treatment may be taken at the end of treatment. The biopsy may be either Endobronchial ultrasound (EBUS) or Computer-Tomography (CT)-guided. Specific instructions for tissue collection and shipment are provided in the PePS2 Laboratory Manual.
23.	Follow up will be completed every 4 weeks for 6 months then every 12 weeks to record treatment after progression and death date.

Table 2: Routine Laboratory Tests

The laboratory tests listed below will be performed only by the local study trial site laboratory. Patient treatment and overall management decisions will be based on local laboratory data.

Haematology (Full blood count)	Biochemistry	Urinalysis	Other
Haematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Haemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate transferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Creatinine	Microscopic exam *(If any of the above are abnormal)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Lactate dehydrogenase (LDH)	Urine pregnancy test †	Free thyroxine (T4)
	Calcium		Thyroid stimulating hormone (TSH)
	Glucose		HBV antibody test
	Phosphorus		HCV RNA test
	Potassium		HIV antibody test
	Sodium		Blood for exploratory studies
	Magnesium		Stool sample for evaluation of gut microbiome
	Total Bilirubin		Cortisol
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		
	C-reactive protein (CRP)		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

ABBREVIATIONS

aPTT	Partial Thromboplastin Time
AE	Adverse Event
ALT	Alanine Aminotransferase
ABPI	Association of the British Pharmaceutical Industry
AST	Aspartate Transferase
BEBOP	Bayesian Evaluation of Binary Outcomes with Predictive variables
CR	Complete Response
CRCTU	Cancer Research UK Clinical Trials Unit
CRF	Case Report Form
CRN	Clinical Research Network
CRP	C-reactive protein
CR-UK	Cancer Research UK
CT	Computerised Tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumour DNA
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DKA	Diabetic Ketoacidosis
DoR	Duration of Response
DSD	Duration of stable disease
ECG	Electrocardiogram
ECI	Event of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
eQTL	Expression Quantitative Trait Loci
eRDC	Electronic Remote Data Capture
FACT-L	Functional Assessment of Cancer Therapy - Lung
FBC	Full Blood Count
FFPE	Formaldehyde Fixed Paraffin Embedded
FSH	Follicle-Stimulating Hormone
Gd	Grade
GFR	Glomerular Filtration Rate
GP	General Practitioner
HBsAg	Hepatitis B surface Antigen
HBV/HCV	Hepatitis B/C Virus
HRQoL	Health Related Quality of Life
HIV	Human Immunodeficiency Virus

IB	Investigator Brochure
IFN	Interferon
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
irRC	Immune related Response Criteria
ISF	Investigator Site File
ITIM	Immunoreceptor Tyrosine-based Inhibition Motif
ITSM	Immunoreceptor Tyrosine based Switch Motif
IV	Intravenous
KCO	Reduced transfer coefficient
LDH	Lactate Dehydrogenase
MHRA	Medicines and Healthcare products Regulatory Agency
MD-PS	Doctor assessed – Performance Status
MDSC	Myeloid-Derived Suppressor Cell
mOS	Median Overall Survival
NIHR	National Institute for Health Research
NK	Natural Killer
NSCLC	Non-Small Cell Lung Cancer
OR	Objective Response
OS	Overall Survival Time
OTC	Over The Counter
PBMC	Peripheral Blood Mononuclear Cell
PD	Progressive Disease
PD-1	Programmed cell Death protein 1
PD-L1	Programmed cell Death Ligand 1
PD-L2	Programmed cell Death Ligand 2
PFS	Progression Free Survival time
PK	Pharmacokinetic
PR	Partial Response
PS	Performance Status
PT	Prothrombin
REC	Research Ethics Committee
RECIST	Response Evaluable Criteria in Solid Tumours
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Stable Disease

SJS	Stevens-Johnson Syndrome
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1DM	Type 1 Diabetes Mellitus
T3	Total Thriiodothyronine
T4	Free Thyroxine
TEN	Toxic epidermal necrolysis
TIL	Tumour infiltrating lymphocyte
TNO	Patient Trial Number
TSH	Thyroid Stimulating Hormone
TTP	Time to Progression

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1 BACKGROUND AND RATIONALE

1.1 Background

Lung cancer is a devastating and very common healthcare problem. It is the most common cancer worldwide with 1.83 million new cases in 2012 (1). It is also the most common cause of cancer death worldwide with 1.69 million deaths in 2015 (2). In 2014 it was the most common cancer representing 13% of all cancers. There were 46, 400 new cases in the UK and the male to female ratio was almost equal at 12:10. Three quarter of cases are in people over the age of 65. Over the past 25 years the incidence has been steadily decreasing in Europe but in females has gone up by 70% in the same timeframe. The lifetime risk of developing lung cancer is 1 in 13 in men and 1 in 17 in women. The disease usually presents late with less than 25% having stage 1 or 2 disease. In the UK it accounts for 7% of all deaths. It is the most common cause of cancer death representing 22% of cancer death in 2014, where 35,900 people died of the disease. Mortality in men has been decreasing over the past 25 years but in Europe has gone up by 63% and still continues to increase in women.

1.1.1 Pharmaceutical and Therapeutic Background

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumours to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Immunoglobulin (Ig) superfamily member related to CD28 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) which has been shown to negatively regulate antigen receptor signalling upon engagement of its ligands (PD-L1 and/or PD-L2) (3, 4). The structure of murine PD-1 has been resolved (5). PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signalling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signalling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signalling cascade (3, 6-8). The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signalling proteins (9, 10). PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer (NK) cells (11, 12). Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells (13). The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-haematopoietic tissues as well as in various tumours (9, 14-16). Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signalling motifs. Binding of PD-L1 or PD-L2 to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-haematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues (9). Although healthy organs express little (if any) PD-L1, a variety of cancers demonstrate abundant levels of this T-cell inhibitor. PD-L1 expression in tumour tissues can be upregulated by oncogenic activation (innate immune

resistance – ALK or PTEN loss can increase PD-L1 expression). In adaptive immune resistance Interferon-gamma (IFN-γ) produced by infiltrating T lymphocytes upregulate PD-L1 expression by tumour cells and thus act as a negative feedback mechanism to dampen an anti-tumour immune attack (17).

1.1.2 Pembrolizumab in Lung Cancer

Pembrolizumab is a high affinity humanized IgG4 PD-1 blocking antibody antagonising the effects of both PD-L1 (IC50 0.1-0.3nM) and PD-L2 (0.5-0.9 nM). It lacks antibody-dependent cell-mediated cytotoxicity (ADCC) and Complement-dependent cytotoxicity (CDC) activity and thus has no cytotoxic effect on PD-1 expressing T cells (18). In the PePS2 trial both untreated and previously treated patients will be eligible for treatment with MK-3475. Data on 495 patients with NSCLC treated with pembrolizumab have been published (19). Four hundred and ninety five patients were treated, 101 of these receiving pembrolizumab as first line therapy. Treatment was well tolerated with grade 3 or higher adverse events (AEs) being reported in 9.5%. Grade 3 or greater pneumonitis was reported in 1.8% with a death in 1 patient. The commonest immune-mediated AE was hypothyroidism (all grades 6.9%) easily managed with replacement therapy. Grade 3 or greater rash, transaminitis and diarrhoea was seen in only 0.2%, 0.6% and 0.6% respectively: all grade infusion reactions were 3% with only 1 patient having a severe infusion reaction. The overall response rate was 19.4%, 24.8% in first line patients and 18% in those who had received previous therapy. Stable disease rate was 21.8%. Median duration of response was 12.5 months, 23.3 months in those receiving pembrolizumab first line. There was no difference in response duration according to proportion of tumour cells expressing PD-L1 (proportion score). Of these, 23.2% of patients had a proportion score of at least 50%, 37.6% with a score 1 - 49% and 39.2% with a score <1%. The response rate in these 3 subsets was 45.2%, 16.5% and 10.7% respectively. Median survival and progression free survival curves were very similar for those with proportion scores of <1% or 1-49% and survival was less in these two groups compared with patients with proportion score $\geq$50%.
Subsequent randomised trials have demonstrated superior overall survival for patients who had received previous platinum-based chemotherapy, with PD-L1 expression >1% receiving pembrolizumab with the second line standard of care comparator docetaxel and improved survival when delivered as a first line agent compared to platinum chemotherapy in patients with >50% than cell PD-L1 expression (20-21). Thus, pembrolizumab has high-level activity in NSCLC with long durability of response in both first and subsequent line patients.

1.2 Trial Rationale

1.2.1 Rationale for Patient Population

Many patients with lung cancer have impaired performance status making them ineligible for trials of new therapies including anti PD-1: all of the trials reported thus far have been in patients with performance status (PS) 0-1. In the National Lung Cancer Audit Database, 18.2% of the PS2 patients had adenocarcinoma and 21.5% had squamous cell cancer (personal communication). In a large Polish series, 30.8% of patients were PS2 and the percentages for males and females were almost identical (22).

Clinical trials of standard-of-care therapy have been successfully performed in the PS2 only population. Overall survival and progression free survival was significantly better for PS2 patients treated with paclitaxel/carboplatin compared to erlotinib with median overall survival (mOS) of 9.7 months for chemotherapy patients. These patients had a 37% Grade 3/4 rate of adverse events (AEs) and there was a 6% rate of treatment-related death (23). In a separate PS2 only clinical trial, PS2 patients had significantly better survival with

pemetrexed/carboplatin compared with pemetrexed alone: again PS2 patients treated with doublet chemotherapy had median survivals of around 9 months (24). There was a 3.9% treatment-related death rate in the combination chemotherapy arm. These results show that chemotherapy can be delivered to PS2 patients but that the outcomes are modest and toxicity not insignificant. Importantly, they demonstrate the feasibility of performing clinical trials in this population.

Importantly for this trial, there is no reason why the good clinical tolerability or durable response rates for pembrolizumab should differ for PS2 patients when compared to their PS0-1 counterparts. This trial prospectively evaluates the clinical hypothesis with rigorous ascription of PS2 status.

1.2.2 Rationale for Design

This is an open label, multi-centre, single arm phase II trial registering 60 patients with NSCLC and an Eastern Cooperative Oncology Group (ECOG) performance status of 2. Patients are eligible for the trial irrespective of line of treatment and the design accounts for PD-L1 tumour status in order to assess the implication of treatment outcome according to PD-L1 status in this population and to ascertain accurate data on PD-L1 status in these patients.

The primary objectives are to characterise the safety profile and tolerability of pembrolizumab and to define durable clinical benefit (complete response (CR), partial response (PR) or stable disease (SD) ≥18 weeks).

The excellent therapeutic index of pembrolizumab makes its testing in PS2 NSCLC highly attractive. Essential to the success of this programme is the highly accurate ascription of PS in each patient entered. In particular, it is crucial that Investigators do not downgrade a patient who is truly PS1 to PS2 in order to offer them the trial. The question then becomes who is best placed to assess PS – physician or patient? Is a patient assessment less prone to manipulation in order to satisfy eligibility criteria? There are a number of publications pertinent to this. Dajczman and colleagues used a PS assessment tool designed for patient use derived from Box 4 of the validated patient-generated subjective global assessment scale and analysed congruency with physician assessed PS (MD-PS) on the ECOG scale (25). Patient-PS was not congruent with MD-PS in 54% of cases with 69% of the patients in this group rating themselves of poorer PS than the physician. Importantly, physicians seemed more accurate in distinguishing PS1 and PS2 – median survival of patient assessed PS1 and PS2 patients was virtually identical but there was a clear difference in survival for PS1 and PS2 patients assessed as such by the physician. Patients and physicians assessed whether they were eligible for a clinical trial requiring PS0/1. In 24/30 cases where there was disagreement on trial entry, the patient would have excluded themselves. However, these 24 patients had a median survival of 8.7 months numerically higher than the entire patient assessed PS1 cohort. These data strongly suggests that physicians are more discriminating in their ascription of PS. These data are very similar to those of Ando *et al.* who showed in univariate and multivariate analysis that assessment of PS 0, 1 and 2 by physicians successfully stratified survival whereas the patients failed to distinguish PS1 and PS2 survival (26). The Cox model including oncologist assessed PS best fitted the actual survival data. There was no significant difference in the assessment of nurses and oncologists. Thus, oncologist assessed PS appears to be most accurate and discriminatory and will be used here. Exact criteria for ascription of PS2 status will be recorded and checked at the PePS2 Trial Office as appropriately eligible. Patient-assessed PS will be recorded and correlations will be made between patient and physician PS.

1.2.3 Rationale for Choice of Treatment

Rationale for dose:
A population pharmacokinetic (PK) analysis has been performed using serum concentration time data from 476 patients. The population PK evaluation revealed that there was no significant impact of tumour burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for pembrolizumab, therefore a 200 mg flat dose has been selected.

Rationale for Q3W dosing schedule:
PK data analysis of pembrolizumab administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to Summary of Product Characteristics - SPC). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days).

2 OBJECTIVES AND OUTCOME MEASURES

2.1 Objectives

2.1.1 Primary Objectives

The first primary objective of this trial is to determine that pembrolizumab is safe and tolerable at the selected dose of 200 mg 3 weekly, in NSCLC patients with a physician scored ECOG PS of 2.

The second primary objective is to allow detection of durable clinical benefit to justify further investigation in subsequent studies.

2.1.2 Secondary Objectives

- Quality of life will be assessed using the FACT-L questionnaire and EQ-5D questionnaire
- All patients will be comprehensively assessed by the Charlson's co-morbidity score and the outcome analysed by the severity of any associated co-morbidities
- Progression free survival time, time to progression and overall survival time.

2.1.3 Exploratory Objectives

To discover possible biomarkers for the prediction of a response to treatment with pembrolizumab.

2.2 Outcome Measures

The trial includes two co-primary outcome measures of toxicity and efficacy (as defined below) and a set of secondary outcome measures (listed below).

2.2.1 Primary Outcome Measures

2.2.1.1 Toxicity

AEs will be recorded in relation to each cycle of treatment and graded according to Common Terminology Criteria for Adverse Events (CTCAE) criteria (see Appendix 6). The toxicity co-primary outcome measure for the trial is defined as the occurrence of a treatment-related dose delay or treatment discontinuation due to an adverse event.

2.2.1.2 Efficacy

Patients will have Computerised Tomography (CT) scans every 9 weeks from baseline until disease progression. On each occasion, overall tumour burden will be assessed using RECIST version 1.1 (see Appendix 2). The efficacy co-primary outcome measure for the trial is durable clinical benefit defined as the occurrence of
a complete response (CR), partial response (PR) or stable disease (SD) without prior progressive disease (PD) at or after the second scheduled CT scan (scheduled to occur at18 weeks).

2.2.2 Secondary Outcome Measures

2.2.2.1 Objective Response

Patients will have CT scans every 9 weeks from baseline until disease progression. On each occasion, overall tumour burden will be assessed using RECIST version 1.1 (see Appendix 2). Best overall response is the best response recorded over the whole period of assessment and could be CR, PR, SD, progressive disease (PD) or inevaluable for response (for which reasons such as early death due to disease or early death due to toxicity will be specified). Objective response (OR) is the occurrence of CR or PR as the best overall response. OR will be based on responses confirmed using the subsequent 9-weekly scan but OR based on unconfirmed responses will also be reported.

2.2.2.2 Health Related Quality of Life

This is defined as the functional effect of a medical condition and/or its consequent treatment upon a patient. The purpose of Health related quality of life (HRQoL) measurement is to quantify the degree to which the medical condition or its treatment impacts the individual's life in a valid and reproducible way. HRQoL will be assessed over time using FACT-L questionnaire and EQ-5D questionnaire (see Appendix 5).

2.2.2.3 Time to Progression

This is defined as the time from commencement of trial treatment to the date of CT scan when progressive disease is first recorded. Patients with no recorded progression at the time of analysis or who die without recorded progression will be censored at the date of the CT scan when they were last recorded with an evaluable measure that was not progression.

2.2.2.4 Progression-Free Survival Time

This is defined as the time from commencement of trial treatment to the date of CT scan when progressive disease first recorded or date of death without previously recorded progression. Patients who are alive with no recorded progression at the time of analysis will

be censored at the date of the CT scan when they were last recorded with an evaluable measure that was not progression.

2.2.2.5 Overall Survival Time

This is defined as the time from commencement of trial treatment to the date of death. Patients who are alive at the time of analysis will be censored at the date last seen alive.

2.2.2.6 Duration of Objective Response and Duration of Stable Disease

Duration of objective response and duration of stable disease are defined as the time from commencement of trial treatment to the date of the subsequent CT scan when progressive disease is first confirmed or date of death without previously recorded progression. This outcome is calculated and reported separately for patients who achieve an OR or SD. Patients experiencing OR or SD who are alive with no recorded progression at the time of analysis will be censored at the date of the CT scan when they were last recorded with an evaluable measure that was not progression.

3 TRIAL DESIGN

The trial is a multi-centre single-arm phase II trial, testing pembrolizumab in a population of Eastern Cooperative Group (ECOG) performance status 2 patients with non-small cell lung cancer. It has co-primary outcome measures of toxicity and efficacy (as defined in Section 2.2.1). The trial will be an all-comers design and PD-L1 expression will be measured and included as an integral part of the trial design as a potentially predictive biomarker for response. In addition, whether or not patients are pre-treated will also be considered as a potentially predictive factor. We have used a bespoke design based on a Bayesian bivariate model (Brock *et al*.; to be submitted) and the target total recruitment is 60 evaluable patients. The trial will be a single stage design but will include interim monitoring of toxicity to ensure safety. The definition of an evaluable patient is given in Section 7.11. Details on the statistical basis behind this design are given in Section 13.

4 ELIGIBILITY

4.1 Inclusion Criteria

- Patients must have completed all standard of care therapy that the treating oncologist deems appropriate. All lines of therapy will be allowed.
- Histologically confirmed NSCLC and, if possible, confirmed PD-L1 status. Patients with both PD-L1 positive and negative tumours are eligible. Patients who have had systemic therapy since the biopsy do not need to have a repeat biopsy.
    - If the PD-L1 status has already been obtained from a nationally recognised and MSD-approved laboratory, this will be acceptable and repeat PD-L1 staining will not be required.
    - If a patient has had a repeat biopsy for the sole purpose of PD-L1 staining for the PePS2 trial but the biopsy failed to yield sufficient cells for PD-L1 status, this patient will still be eligible to enter the PePS2 trial but will be categorised as PD-L1 non-evaluable.

- Patients must have a performance status of 2 on the ECOG Performance scale (Appendix 1) with no deterioration over the previous 2 weeks assessed by consenting physician.
  - Patients must be ambulatory and capable of all self-care but unable to carry out any work activities.
  - Patients must be up and about more than 50% of waking hours.
- Life expectancy >12 weeks.
- CT scan of chest and abdomen within 28 days of starting pembrolizumab demonstrating uni-dimensionally measurable disease as per RECIST version 1.1 (Appendix 2).
- Demonstrate adequate haematological function:
  - Platelet count ≥100 x 10^9 /L
  - Neutrophils ≥1.5 x 10^9/L
  - Haemoglobin ≥ 90 g/L
- Demonstrate adequate hepatic function:
  - Serum bilirubin ≤1.5 x upper limit of normal (ULN)
  - Serum transaminases ≤2.5 x ULN
- Demonstrate adequate renal function
  - Creatinine clearance <1.5 times ULN concurrent with creatinine clearance >50 ml/min (calculated by Cockcroft and Gault equation – see Appendix 3). If this is ≤ 50 ml/min then an isotopic Glomerular Filtration Rate (GFR) may be carried out and must be > 50 ml/min
- Age ≥ 18 years.
- Provision of signed and dated, written informed consent prior to any trial specific procedures, sampling and analyses.
- Patients must agree to the use of contraception as detailed in section 4.3.

4.2 Exclusion Criteria

- Patients who do not meet the criteria of performance status = 2 on the ECOG Performance scale (Appendix 1) i.e. patients should not be ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work.
- Untreated symptomatic brain or leptomeningeal metastatic disease.
- Medical or psychiatric conditions compromising informed consent.
- Any medical condition which in the opinion of the Investigator would compromise the ability of the patient to participate in the trial or which would jeopardise compliance with the protocol.
- Patient who has had chemotherapy, radioactive or biological cancer therapy within 4 weeks prior to the first dose of trial therapy, or who has not recovered to CTCAE grade 1 or better from the Adverse Event (AE) due to cancer therapeutics administered more than 4 weeks earlier. Patient who has had erlotinib, gefitinib, afatinib, or crizotinib within 1 week prior to the first dose of trial therapy, or who has not recovered to CTCAE Grade 1 or better from the AE due to any of these drugs administered more than 1 week earlier. Patient who has had ipilimumab therapy may be enrolled if requirements specified in Inclusion Criterion are met.
- Active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
- Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid

replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

- Patient has risk factors for bowel obstruction or bowel perforation (examples include but not limited to a history of acute diverticulitis, intra-abdominal abscess and abdominal carcinomatosis).
- Patient has a known history of malignancy, unless the patient has undergone potentially curative therapy with no evidence of that disease for 3 years.
- Has a history of non-infectious pneumonitis requiring steroids or has active pneumonitis or significantly reduced transfer coefficient (KCO).
- Female patients of child bearing potential should be using adequate contraceptive measures, should not be breast feeding and must have a negative pregnancy test prior to start of dosing.
- Patient previously had a severe hypersensitivity reaction to treatment with another monoclonal antibody.
- Patient had prior treatment targeting PD-1: PD-L1 axis.
- Patient is positive for Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), active Hepatitis B (HBsAg reactive) or Hepatitis C (HCV RNA (qualitative) is detected); patients with negative Hepatitis C antibody testing may not need RNA testing.
- Known history of tuberculosis.
- Patient has an active infection requiring therapy.
- Has received a live vaccine within 30 days prior to the first dose of trial treatment.
- Patient is, at the time of signing informed consent, a regular user (including “recreational use”) of any illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol).
- Patients with symptomatic ascites or pleural effusion. A patient who is clinically stable following treatment for these conditions (including therapeutic thoraco- or paracentesis) is eligible.
- Any of the following cardiac criteria:
  - Mean resting corrected QT interval (QTc) >470 msec obtained from 3 consecutive ECGs
  - Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG e.g., complete left bundle branch block, third degree heart block
  - Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age or any concomitant medication known to prolong the QT interval.

4.3 Contraception

4.3.1 Women of childbearing potential

Women of childbearing potential are defined as women who have not had a hysterectomy and oophorectomy. Women with amenorrhea for <2 years will only be considered not to be of reproductive potential if they have a documented Follicle-Stimulating Hormone (FSH) value in the postmenopausal range.

Adequate contraception should be used from the time of screening, during the trial and for at least 90 days after completion of treatment**.**

Acceptable methods of contraception include total abstinence (if this is the patient’s usual and preferred lifestyle choice), tubal ligation, combined oral, transdermal or intra-vaginal hormonal contraceptives, medroxyprogesterone injections (e.g. Depo-provera), copper-

banded intra-uterine devices, hormone impregnated intra-uterine systems and vasectomised partners. All methods of contraception (with the exception of total abstinence) should be used in combination with the use of a condom by their male sexual partner for intercourse.

4.3.2 Males

Male patients with sexual partners who are pregnant or who could become pregnant (i.e. women of child-bearing potential) should use a condom during sexual intercourse during the trial and for at least 90 days after completion of treatment.

5 SCREENING AND CONSENT

5.1 Screening

Patients attending oncology clinic with a diagnosis of NSCLC and a PS2, and who in the Investigator's opinion would be potentially suitable for clinical trial entry will be screened for entry onto the trial. If informed consent is given, PD-L1 expression will be measured from either an archived biopsy if available, or a newly obtained biopsy. A repeat biopsy will not be required if the PD-L1 status has already been obtained from a nationally recognised and MSD-approved laboratory. Sites must send an anonymised copy of Pathology report to confirm PD-L1 testing during screening to the PePS2 Trial Office, before the patient can be registered.

The Investigator will also conduct a full screening evaluation to ensure that the patient satisfies all inclusion and exclusion criteria. Investigators must keep a pre-screening log of all patients who receive a Patient Information Sheet, a screening log of all patients who consent to the trial and a pre-registration screening log of all patients who have tumour tissue sent for PD-L1 testing for the PePS2 trial.

Patients' whose PD-L1 status was determined prior to the PePS2 trial will still need a screening number from the Pre-Registration Screening Log and will also need to complete the Pre-Registration Screening Form and enter date PD-L1 results obtained. Regular recruitment updates will be circulated to site staff.

5.2 Informed Consent

It is the responsibility of the Investigator or delegate specified on the Site Signature and Delegation Log to obtain written informed consent for each patient prior to performing any trial related procedure. Specific Patient Information Sheets are provided to facilitate this process. Investigators must ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial to the patient. The Investigator should also stress that the patient is completely free to refuse to take part or withdraw from the trial at any time. The patient should be given ample time to read the Patient Information Sheet and to discuss their participation with others outside of the site research team. The patient must be given an opportunity to ask questions which should be answered to their satisfaction. The right of the patient to refuse to participate in the trial without giving a reason must be respected.

If the patient expresses an interest in participating in the trial they should be asked to sign and date the latest version of the Informed Consent Form. The Investigator or delegate must then sign and date the form. A copy of the Informed Consent Form should be given to the patient, a copy should be filed in the hospital notes, and the original placed in the Investigator Site File (ISF). Informed consent should be obtained within 28 days of starting treatment; otherwise it will be necessary to re-consent the patient. Once the patient is entered into the

trial the patient's Trial Number (TNO) should be entered on the Informed Consent Form maintained in the ISF. In addition, if the patient has given explicit consent by signing the copy of the Informed Consent Form a copy of the signed Informed Consent Form must be sent in the post to the PePS2 Trial Office for review. Details of the informed consent discussions should be recorded in the patient's medical notes, this should include date of, and information regarding, the initial discussion, the date consent was given, with the name of the trial and the version number of the Patient Information Sheet and Informed Consent Form. Throughout the trial the patient should have the opportunity to ask questions about the trial and any new information that may be relevant to the patient's continued participation should be shared with them in a timely manner. On occasion it may be necessary to re-consent the patient, in which case the process above should be followed and the patient's right to withdraw from the trial respected.

Electronic copies of the Patient Information Sheet and Informed Consent Form are available from the PePS2 Trial Office and should be printed or photocopied onto the headed paper of the local institution.

Details of all patients approached about the trial should be recorded on the Patient Screening/Enrolment Log and with the patient's prior consent their General Practitioner (GP) should also be informed that they are taking part in the trial. A GP Letter is provided electronically for this purpose.

5.2.1 Screening Investigations

5.2.1.1 Histologically Confirmed PD-L1 status

As part of the pre-screening registration process, PD-L1 testing may be carried out on an archival biopsy sample if available or a newly obtained biopsy, at a nationally recognised MSD-approved laboratory for PD-L1 staining. Repeat biopsies are not required if the PD-L1 status is already known (see section 5.1).

Biopsies taken for PePS2 may be obtained by Endobronchial ultrasound (EBUS) or Computer-Tomography (CT)-guided. Five slides fresh cut sections from Formaldehyde Fixed Paraffin Embedded (FFPE) tissue will be assessed by the site Pathologist for PD-L1 testing with >50% tumour content and at least 50 viable neoplastic cells overall. These slides will then be shipped to an MSD-approved laboratory for PD-L1 testing and the Trial Office will inform sites of successful staining. The PD-L1 status of the patient must be known for patient to be eligible for the trial. The only exception to this will be patients who have submitted to a repeat biopsy for the explicit purpose of ascertaining the PD-L1 status in the PePS2 trial and where PD-L1 staining has failed on that repeat biopsy.

5.2.1.2 Screening Assessments

Please see Table 1 Schedule of Assessments, Table 2 Routine Laboratory Tests and the Treatment Assessments flowchart for detailed description of the procedures and tests.
After written informed consent is obtained, the following screening procedures must take place:-

Up to 28 days prior to trial treatment:

- Medical history – Radiographic studies performed prior to study trial entry may be collected for review by the Investigator.
- Prior Medications
- ECOG assessment

- Coagulation parameters
- CT scan with contrast (RECIST v1.1 reporting – Appendix 2)
- ECG
- HIV, Hepatitis B and C testing
- Tumour biopsy if archived tissue is not available

Up to 7 days prior to trial treatment

- Physical exam
- Charlson Index
- Vital signs
- Concomitant medications
- ECOG assessment
- Haematology
- Urinalysis
- Clinical chemistry
- Renal function - GFR
- Thyroid function and cortisol

Within 72 hours of first dose of pembrolizumab

- Pregnancy test if applicable

5.2.2 Patient Screening Log

The following details of all patients screened for participation in this trial will be collected:

- Screening number
- Date screened
- Date of Birth
- Sex
- Whether the patient was eligible and reasons for ineligibility
- Whether the patient gave written informed consent
- Whether the person was registered
- Reasons(s) patient was not registered

6 TRIAL ENTRY

Prior to recruitment of patients into the trial, the Principal Investigator for each site, or their delegate, should have returned all required documentation to the PePS2 Trial Office, and the site personnel involved with the trial must have received appropriate training from the Trial Coordinator.

6.1 Patient Registration

Patients must be registered with the PePS2 Trial Office at Cancer Research UK Clinical Trials Unit (CRCTU) at the University of Birmingham.

- Prior to trial entry, sites should complete the first page of the Pre-Registration Screening Form and phone the Trial Office to
  - give the site-specific screening number from the pre-registration screening log
  - confirm and email an anonymised pathology report with PD-L1 results from an archived tissue or
  - confirm that slides from a newly obtained biopsy will be sent with the Pre-Registration Screening Form to an MSD-approved laboratory for PD-L1 staining.

- After all eligibility criteria have been met, participating sites must fax copies of the Eligibility Forms to the PePS2 Trial Office and the patient's eligibility will be confirmed at registration.
- Sites must then telephone the registration line with the details required on the Registration Form and the patient will be registered over the phone and allocated a Trial Number (TNO). The registration line will be open during office hours, 9am-5pm, Monday-Friday.
- A fax will be sent to the main site administrator and Pharmacy confirming the details of registration. Trial drug prescriptions must include the patient's TNO and dose.
- Sites should post a copy of the Informed Consent Form to the PePS2 Trial Office.

0121 414 6788 (Tel)
0121 414 3529 (Fax)
Or
PePS2@trials.bham.ac.uk

7 TREATMENT DETAILS

7.1 Details of Investigational Medicinal Product

Pembrolizumab is an Investigational Medicinal Product (IMP) for the purposes of this trial. Full details of the IMP are contained in the PePS2 Pharmacy Manual, which also lists the Pharmacist's responsibilities, details of labelling, record keeping for prescribing, dispensing, and accountability of the IMP. The PePS2 Pharmacy Manual will be sent to the responsible Pharmacist.

7.2 Investigational Medicinal Product Supply

Pembrolizumab will be supplied, packaged and delivered to sites by Almac. See the PePS2 Pharmacy Manual for further information.

7.3 Pembrolizumab Administration

Pembrolizumab will be administered as a 30 minute IV infusion, with a window of -5 and +10 minutes, at a flat dose of 200 mg. A dosing interval every 3 weeks (Q3W) will be employed. See the PePS2 Pharmacy Manual for further information about pembrolizumab.

Table 3: Dosing Instructions for pembrolizumab.

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	200 mg flat dose	Q3W	30 minute IV infusion	For 2 years or until progression	Experimental

7.4 Treatment Schedule

For details please refer to the Table 1: Schedule of Events (see page x) and the Treatment Assessments Schedule (see page 14).

Patients will be administered pembrolizumab for up to 2 years or until progression; each cycle being 21 days. Trial treatment should be administered on day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Schema. Trial treatment may be administered up to 3 days before or after the scheduled day 1 of each cycle due to administrative reasons. Trial treatments will be administered on an outpatient basis.
Patients with unacceptable toxic side effects from pembrolizumab will come off treatment until disease progression.

In the case of CR it is at the discretion of the Investigator to keep a patient on trial treatment or to discontinue trial treatment based on the following guidelines. This decision will be based on the clinical judgment of a patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Patients who have a confirmed complete response by two scans ≥4 weeks apart and who have been on pembrolizumab treatment for at least 6 months may discontinue pembrolizumab treatment at the discretion of the Investigator after receiving at least two doses beyond the initial determination of CR. Pembrolizumab may be resumed upon disease recurrence in these patients.

Treatment Assessments

(21 day cycles 1-10 & then repeated up to cycle 35)

Pre-treatment

- Vital signs/Weight/Physical exam
- ECOG PS
- FBC/serum chem. panel
- Tumour imaging/tumour biopsy
- ECG & urinalysis
- Thyroid/cortisol
- Demographics/Medical History/Prior Medications
- HIV/Hep B & C
- Pregnancy Test
- GFR/coagulation
- Charlson Index

Cycle 1/Day 1

- Vital signs/Weight
- ECOG PS/HRQoL
- AEs/Conmed. review
- FBC/serum chem. panel
- 60 ml blood for PBMC
- Plasma for cytokine/chemokine & proteomics
- Germline DNA/ctDNA
- Stool sample

Cycle 2 (± 3 days)

- Vital signs/Weight/Physical exam
- ECOG PS/HRQoL
- AEs/Conmed. review
- FBC/serum chem. panel
- Thyroid/cortisol/60 ml blood for PBMC

Cycle 3 (± 3 days)

- Vital signs/Weight/Physical exam
- ECOG PS/HRQoL
- AEs/Conmed. review
- FBC/serum chem. panel
- 10 ml blood for PBMC

Cycle 4 (± 3 days)

- Vital signs/Weight/Physical exam
- ECOG PS/HRQoL
- AEs/Conmed. review
- FBC/serum chem. panel
- AEs/Conmed. review
- Tumour imaging/Urinalysis
- Thyroid/cortisol/60 ml blood for PBMC
- Plasma cytokine/chemokine/proteomics
- ctDNA

Cycle 5 (± 3 days)

- Vital signs/Weight/Phys. exam
- ECOG PS/HRQoL
- AEs/Conmed. review
- FBC/serum chem. panel
- AEs/Conmed. review
- 10 ml blood for PBMC

Cycle 6 (± 3 days)

- Vital signs/Weight/Phys. exam
- ECOG PS/HRQoL
- AEs/Conmed. review
- FBC/serum chem. panel
- AEs/Conmed. review
- Thyroid/cortisol

Cycle 7 (± 3 days)

- Vital signs/Weight/Physical exam
- ECOG PS/HRQoL
- AEs/Conmed. review
- FBC/serum chem. panel
- Tumour imaging
- 10 ml blood for PBMC
- Plasma cytokine/chemokine/proteomics
- ctDNA

Cycle 8 (± 3 days)

- Vital signs/Weight/Phys. exam
- ECOG PS/HRQoL
- AEs/Conmed. review
- FBC/serum chem. panel
- Thyroid/cortisol

Cycle 9 (± 3 days)

- Vital signs/Weight/Physic. exam
- ECOG PS/HRQoL
- AEs/Conmed. review
- FBC/serum chem. panel
- AEs/Conmed. review

Cycle 10 (± 3 days)

- Vital signs/Weight/Physical exam
- ECOG PS/HRQoL
- AEs/Conmed. review
- FBC/serum chem. panel
- Urinalysis/ Tumour imaging
- Thyroid/cortisol/10 ml blood for PBMC
- Plasma cytokine/chemokine/proteomics
- ctDNA

7.5 Dose Modification and Toxicity Management

AEs associated with pembrolizumab exposure may represent an immunologic etiology. Immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 4.

Table 4: Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	AE management with corticosteroid[1, 4] and/or other therapies	Monitoring and Supportive Care
Pneumonitis	Grade 2	Withhold[2, 3]	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of pneumonitis • Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhoea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of enterocolitis (i.e. diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e. peritoneal signs and ileus). • Subjects with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Subjects with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4 or recurrent Grade 3	Permanently discontinue		
AST / ALT elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	AE management with corticosteroid[1, 4] and/or other therapies	Monitoring and Supportive Care
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for subjects with T1DM • Administer anti-hyperglycemic in subjects with hyperglycemia	• Monitor subjects for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids to treat secondary adrenal insufficiency and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold until improved to Grade <2 and if controlled with hormone replacement. Otherwise permanently discontinue		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g. propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold until recovery to Grade ≤1. Otherwise permanently discontinue		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (e.g. levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2mg/kg or equivalent) followed by taper.	• Monitor for changes of renal function
	Grade 3 or 4	Permanently discontinue		
Skin Reactions	Grade 3	Withhold	• Based on severity of AE administer corticosteroids	• Monitor for suspected severe skin reactions.
	Grade 4	Permanently discontinue		
Stevens-Johnson syndrome (SJS)	Suspected SJS or TEN	Withhold	• Refer to a specialist unit for assessment and treatment.	• Monitor for suspected servre skin reactions.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	AE management with corticosteroid[1, 4] and/or other therapies	Monitoring and Supportive Care
or toxic epidermal necrolysis (TEN) suspected	Confirmed SJS or TEN	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event[5]		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

Footnotes: General Instructions for management of irAE

1. *Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.*
2. *For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. For subjects with Grade 3 or 4 immune-related endocrinopathy, pembrolizumab may be resumed when AE improves to Grade 2 or lower and is controlled with hormonal replacement therapy.*
3. *For situation where pemborlizumab is withheld initially, pembrolizumab should be **permanently discontinued** if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks.*
4. *For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.*
5. *Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis*

***Note:** For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).*

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical/surgical events or logistical reasons not related to study therapy (e.g. elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should recommence trial therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the PePS2 Trial Office. The reason for interruption should be documented in the patient's medical notes and on the CRF.

7.6 Sample Collection

7.6.1 Blood Collections

Blood collection for safety evaluation assumes priority over other procedures. Whenever possible, pre-treatment blood samples should be obtained by fresh peripheral venepuncture. If a patient does not have peripheral access, the sample may be collected from a central catheter immediately after an initial withdrawal of at least 10 ml of blood; or preferably, after a series of other blood sample collections from the central catheter.

For details on sample collection and processings, please refer to the PePS2 Laboratory Manual.

7.6.2 Tissue Sample Collection

Where patients have given consent, a pre-registration, pre-treatment baseline biopsy will be taken for PD-L1 assessment. In addition, an optional end of treatment biopsy may be taken if patients have responded on treatment for 18 weeks but have now relapsed (maximum one per patient). Specific instructions for tissue collection and shipment are provided in the PePS2 Laboratory Manual.

7.6.3 Stool Sample

A stool sample will be obtainedonce onlyat any time post-registration, pre-treatment and before the start of the first infusion. A stool sample, no less than 20g, should be collected by the patient at home, frozen and stored in a stool sample container. The stool sample should be frozen at the point of collection.

Sites will be provided with stool sample containers, sample bags, silver freezer sheets and padded envelopes and should provide patients with the instructions and materials to freeze stool samples as follows:

a. In preparation for the collection of stool sample, soak the silver freezer sheet in fresh warm water for 10 mins.
b. Place the freezer sheet in freezer at home for at least 3 hours.
c. After collection of stool in stool sample container, place container in sample bag and wrap around in frozen freezer sheet.
d. Place the stool sample, bag and freezer pack in the padded envelope, seal and put in freezer.
e. At next hospital visit, take the padded envelope containing stool sample and hand to PePS2 Research Team.

Stool samples will remain frozen for up to 3h if left in padded envelope with freezer pack.
The stool sample should be immediately transferred to a -80°C freezer in the pre-labelled Stool Only freezer box. Specific instructions for labelling and shipment are detailed in the PePS2 Laboratory Manual.

Table 5: Frequency of sample collection

Time-point	Tumour biopsy	PBMC sample (60 ml)	Stool sample	Cytokine/ Chemokine Panel & Proteomics (plasma)	Germline DNA (whole blood)	ctDNA (plasma)
Post-registration, pre-treatment	✓*		✓			
Cycle 1		✓		✓	✓	✓
Cycle 2		✓				
Cycle 3		✓**				
Cycle 4		✓		✓		✓
Cycle 7		✓**		✓		✓
Cycle 10		✓**		✓		✓
End of treatment	✓***	✓		✓		✓

* pre-registration, pre-treatment baseline biopsy (fresh if no archive is available)
** only 10 ml required
*** optional newly obtained biopsy

7.7 Quality of Life Assessment

HRQoL questionnaires (Appendix 5) will be completed in order to establish how PS2 patients are coping with trial treatment. Patients will be asked to complete a questionnaire before every cycle of pembrolizumab. The Research Nurse should spend time with the patient going through the questionnaire and answering any questions patients might have at cycle 1. Thereafter the patient should then answer the questionnaire independently then return it the Research Nurse.

7.8 Treatment Compliance

Treatment compliance will be based on patient attendance to scheduled clinic visits as pembrolizumab will be administered in these sessions.

7.9 Concomitant Medication

7.9.1 Acceptable Concomitant Medications

Throughout the trial any concomitant medication or therapy deemed necessary to provide adequate supportive care may be prescribed and should be recorded within the Case Report Form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. The indication for the treatment should be recorded at the same time. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date will also be included on the CRF.

All concomitant medications received within 28 days of Trial Entry and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30

days after the last dose of trial treatment should be recorded for Serious Adverse Events (SAEs).

7.9.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Anti-cancer systemic chemotherapy or biological therapy within 28 days prior to the first dose of trial treatment and while participating in the trial.
- Immunotherapy not specified in this protocol.
- Chemotherapy not specified in this protocol.
- Investigational agents other than pembrolizumab.
- Radiation therapy
  - **Note:** Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with the Trials Office. Recommencement of trial treatment after radiation therapy will be at the discretion of the PI after consultation with the PePS2 Trial Office.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the PePS2 Trial Office.
- Whilst participating on the trial, patients may be given systemic steroids due to an acute medical situation but the steroids may only be given for a maximum of 2 weeks. During this period, trial treatment must stop and can be restarted when the steroid administration is complete. If the subject requires the continued use of steroid treatment for more than 2 weeks, they should be withdrawn from the trial.
- Any form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment and while participating on the trial. Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

Subjects who, on the assessment by the Investigator, require the use of any of the aforementioned treatments for clinical management should be withdrawn from the trial. Subjects may receive other medications that the Investigator deems to be medically necessary.

There are no prohibited therapies during the post-treatment follow-up phase.

7.10 Patient Follow up

After a patient is discontinued from trial therapy, a mandatory safety follow-up visit should be performed 28 days after the last infusion of trial medication. Procedures and assessments

performed at the safety follow-up visit should follow the respective guidelines described in the Schedule of Events. The patient will be monitored for all AEs monthly for up to 6 months and then 12 weekly during long term follow up.

For patients who start another cancer therapy before 28 days after discontinuation of trial therapy, the safety follow-up visit should occur prior to the patient receiving another cancer therapy. Follow up calls will be made every 12 weeks to record treatment after progression and death date if applicable.

7.11 Patient Withdrawal

The Investigator will make every reasonable effort to keep each patient on trial. However, if the Investigator removes a patient from the trial treatment or if (s)he declines further participation final assessments will be performed, if possible. All the results of the evaluations and observations, together with a description of the reasons for trial withdrawal, must be recorded in the CRF. For patients withdrawing from trial treatment for reasons other than withdrawal of consent or due to disease progression then continue with RECIST 1.1 scans until documented progression as per protocol. For patients who have come off treatment due to unacceptable toxicity, CT scans will be performed every 9 weeks until disease progression or until the patient starts another anti-cancer treatment. CT scans are to be reported according to RECIST v1.1 criteria (see Appendix 2).

Following assessment by the Principal Investigator and discussion with the PePS2 Trial Office, patients who meet RECIST criteria for progressive disease (PD) may be continued on trial treatment if the treatment is tolerable and believed to be of clinical benefit. Documentation of continued clinical benefit should be recorded in the patient's medical notes by an Investigator.

In the event of a patient's decision to withdraw from the trial, the Investigator must ascertain from which aspects of the trial the patient wishes to withdraw, and record the details on the Withdrawal CRF. All patients will continue to be followed-up, and all information and tissue samples collected up until the point of withdrawal, will be retained and analysed.

Patients who withdraw from the trial due to AEs (clinical or laboratory) will be treated and followed according to accepted medical practice. All pertinent information concerning the outcome of such treatment must be recorded in the CRF.

The following are justifiable reasons for the Investigator to withdraw a patient from trial:

- Unacceptable toxicity
- Unforeseen events: any event which in the judgement of the Investigator makes further treatment inadvisable
- SAE requiring discontinuation of treatment
- Withdrawal of consent
- Serious violation of the trial protocol (including persistent patient attendance failure and persistent non-compliance)
- Withdrawal by the Investigator for clinical reasons not related to the trial drug treatment

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the Investigator should any untoward effect occur. In addition, a subject may be withdrawn by the Investigator or the Sponsor if enrolment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation are provided in Section 7.5.

An evaluable patient is a patient who receives treatment with pembrolizumab. Where a patient is withdrawn from the trial and is not evaluable, an additional patient will be recruited to replace them.

7.12 Expected Toxicity, Rescue Medications and Supportive Care

7.12.1 Management of Infusion Reactions

Pembrolizumab may cause severe or life threatening infusion-reactions. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 6.

Table 6: Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with:- Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

8 TRANSLATIONAL RESEARCH ASSOCIATED WITH THE PEPS2 TRIAL

Exploratory outcomes will be based on the identification of possible biomarkers predictive of response to pembrolizumab. We will analyse blood and stool samples to identify possible biomarkers of response. This will be a purely discovery analysis and new putative biomarkers would require prospective validation.

9 ADVERSE EVENT REPORTING

The collection and reporting of AEs will be in accordance with the Medicines for Human Use Clinical Trials Regulations 2004 and its subsequent amendments. Definitions of different types of AE are listed in Appendix 7. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the source data) with reference to the SPC.

9.1 Reporting Requirements

9.1.1 Adverse Events

All medical occurrences which meet the definition of an AE (see Appendix 7 for definition) should be reported. Please note this includes abnormal laboratory findings that are deemed clinically significant by the Investigator (abnormal laboratory findings that are not clinically significant are not AEs) or any pre-existing AEs that worsen by at least 1 CTCAE grade from baseline. If an AE changes grade, this should be reported as an individual AE.

9.1.2 Serious Adverse Events

Investigators should report AEs that meet the definition of an SAE (see Appendix 7 for definition) as detailed in Section 8.2.

9.1.2.1 Monitoring pregnancies for potential Serious Adverse Events

It is important to monitor the outcome of pregnancies of patients in order to provide SAE data on congenital anomalies or birth defects.

In the event that a patient or their partner becomes pregnant during the SAE reporting period please complete a Pregnancy Notification Form (providing the patient's details) and return to the PePS2 Trial Office as soon as possible. If it is the patient who is pregnant, provide outcome data on a follow-up Pregnancy Notification Form. Where the patient's partner is pregnant, consent must first be obtained and the patient should be given a Release of Medical Information Form to give to their partner. If the partner is happy to provide information on the outcome of their pregnancy they should sign the Release of Medical Information Form. Once consent has been obtained, provide details of the outcome of the pregnancy on a follow-up Pregnancy Notification Form. If appropriate also complete an SAE Form as detailed below.

9.1.3 Events of Clinical Interest

Selected non-serious AEs and SAEs are also known as Events of Clinical Interest (ECI). This also includes immune-mediated AEs (see Appendix 7 for more details). Events of clinical interest for this trial include:

1. An overdose of pembrolizumab. For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

* **Note:** These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

9.1.4 Reporting period

Details of all treatment-related AEs will be documented and reported from the date of patient registration until 6 months after the administration of the last treatment. SAEs that are judged to be at least possibly related to IMP must still be reported in an expedited manner irrespective of how long after IMP administration the reaction occurred.

9.2 Reporting Procedure

9.2.1 Site

9.2.1.1 Adverse Events

AEs should be reported on an AE Form (and where applicable on an SAE Form). An AE Form should be completed at each visit and returned to the PePS2 Trial Office.

AEs will be reviewed using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (see Appendix 6). Any AEs experienced by the patient but not included in the CTCAE should be graded by an Investigator and recorded on the AE Form using a scale of (1) mild, (2) moderate or (3) severe. For each sign/symptom, any changes in grade should be documented.

9.2.1.2 Serious Adverse Events

For more detailed instructions on Serious Adverse Event (SAE) reporting refer to the SAE Form Completion Guidelines contained in section 5 of the ISF.

AEs defined as serious and which require reporting as an SAE should be reported on an SAE Form. When completing the form, the Investigator will be asked to define the causality and the severity of the AE which should be documented using the CTCAE version 4.0.

On becoming aware that a patient has experienced an SAE, the Investigator (or delegate) must complete, date and sign an SAE Form. The form should be faxed together with a SAE Fax Cover Sheet to the PePS2 Trial Office using one of the numbers listed below as soon as possible and no later than 24 hours after first becoming aware of the event:

To report an SAE, fax the SAE Form with an SAE Fax Cover Sheet to:

0121 414 3529 (primary) or 0121 414 7989 (secondary)

On receipt the PePS2 Trial Office will allocate each SAE a unique reference number. This number will be transcribed onto the SAE Fax Cover Sheet which will then be faxed back to the site as proof of receipt. If confirmation of receipt is not received within 1 working day please contact the PePS2 Trial Office. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE. The SAE Fax Cover Sheet completed by the PePS2 Trial Office should be filed with the SAE Form in the ISF.

For SAE Forms completed by someone other than the Investigator, the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. The form should then be returned to the PePS2 Trial Office in the post and a copy kept in the ISF. Investigators should also report SAEs to their own Trust in accordance with local practice.

9.2.1.3 Events of Clinical Interest

ECI must be reported within 24 hours to the PePS2 Trial Office. For the time period beginning when the consent form is signed until treatment allocation, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the PePS2 Trial Office if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet or a procedure.

For the time period beginning at treatment allocation through 6 months following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to pembrolizumab, must be reported within 24 hours to the Trial Office.

9.2.1.4 Provision of Follow-up Information

Patients should be followed up until resolution or stabilisation of the Follow-up information should be provided on a new SAE Form (refer to the SAE Form Completion Guidelines for further information).

9.2.2 PePS2 Trial Office

On receipt of an SAE Form, seriousness and causality will be determined independently by a Clinical Coordinator. An SAE judged by the Investigator or Clinical Coordinator to have a reasonable causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). The Clinical Coordinator will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected (i.e. is not defined in the Reference Safety Information) it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

9.2.3 Reporting to the Competent Authority and Research Ethics Committee

9.2.3.1 Suspected Unexpected Serious Adverse Reactions

The PePS2 Trial Office will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the Medicines and Healthcare products Regulatory Agency (MHRA) and Research Ethics Committee (REC) within 7 days. Detailed follow-up information will be provided within an additional 8 days.

All other events categorised as SUSARs will be reported within 15 days.

9.2.3.2 Serious Adverse Reactions

The PePS2 Trial Office will report details of all SARs (including SUSARs) to the MHRA and main REC annually from the date of the Clinical Trial Authorisation, in the form of a Developmental Safety Update Report.

9.2.3.3 Adverse Events

Details of all AEs will be reported to the MHRA on request.

9.2.3.4 Other safety issues identified during the course of the trial

The MHRA and REC will be notified immediately if a significant safety issue is identified during the course of the trial.

9.2.4 Investigators

Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the ISF.

9.2.5 Trial Steering Committee

The Trial Steering Committee will review all SAEs.

9.2.6 Manufacturer of Investigational Medicinal Product

All SAEs will be reported to Merck, Sharp and Dohme, the manufacturer of the Investigational Medicinal Product, within an agreed timeframe from first awareness of the event of the PePS2 Trial Office during the reporting period.

10 DATA HANDLING AND RECORD KEEPING

10.1 Data Collection

10.1.1 Case Report Form (CRF)

The CRF will comprise a set of forms capturing details of eligibility, baseline characteristics, treatment and outcome details. This trial will use an electronic remote data capture (eRDC)

system which will be used for completion of CRF. Access to the eRDC system will be granted to individuals via the Trial Office. Pre-screening Registration, SAE reporting and Notification of Pregnancy will be paper-based.

The CRF must be completed by the Investigator or an authorised member of the site research team (as delegated on the Site Signature and Delegation Log) within specified timeframes (found in the CRF completion guidelines). The exceptions to this are the SAE Form, which must be co-signed by the Investigator and reported in an expedited manner.

Data reported on each form should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the form. All missing and ambiguous data will be queried. All sections are to be completed. CRF guidelines will be provided. In all cases it remains the responsibility of the Investigator to ensure that the CRF has been completed correctly and that the data are accurate.

The format and questions in the CRF may be amended by the Trial Office, as appropriate, throughout the duration of the trial. Whilst this will not constitute a protocol amendment, sites will be notified of new versions of the form when they are available in the eRDC system, and in the case of the SAE form, new versions of the form must be implemented by participating sites immediately on receipt.

10.2 Archiving

It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source records (e.g. signed Informed Consent Forms, Investigator Site Files, Pharmacy Files, patients' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 25 years after the end of the trial or following the processing of all biological material collected for research, whichever is the later. Do not destroy any documents without prior approval from the PePS2 Trial Office.

11 QUALITY MANAGEMENT

11.1 Site Set-up and Initiation

All sites will be required to sign a Clinical Trial Site Agreement prior to participation. In addition all participating Investigators will be asked to sign the necessary agreements and registration forms; and supply a current CV to the PePS2 Trial Office. All members of the site research team will also be required to sign the Site Signature and Delegation Log, which should be returned to the PePS2 Trial Office. Prior to commencing recruitment all sites will undergo a process of initiation. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, AE reporting, collection and reporting of data and record keeping. Sites will be provided with an Investigator Site File and a Pharmacy File containing essential documentation, instructions, and other documentation required for the conduct of the trial.

The PePS2 Trial Office must be informed immediately of any change in the site research team.

11.2 On-site Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the CRCTU Quality Management Plan. Additional on-site monitoring visits may be triggered for example by poor CRF return, poor data quality, low SAE reporting rates, excessive

number of patient withdrawals or deviations. If a monitoring visit is required the PePS2 Trial Office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the PePS2 trial staff access to source documents as requested.

11.3 Central Monitoring

Trial staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trial staff will check incoming data entered onto the PePS2 eRDC for compliance with the protocol, data consistency, missing data and timing. Sites will be sent electronic Data Clarification Forms requesting missing data or clarification of inconsistencies or discrepancies. Where a patient has given explicit consent sites are requested to send in copies of signed Informed Consent Forms for in-house review.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or good clinical practice (GCP), and/or poor recruitment. Any major problems identified during monitoring may be reported to the Trial Management Group and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the REC and MHRA.

11.4 Audit and Inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents.

Sites are also requested to notify the PePS2 Trial Office of any MHRA inspections.

11.5 Notification of Serious Breaches

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments the Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of:

- The conditions and principles of GCP in connection with that trial or;
- The protocol relating to that trial, within 7 days of becoming aware of that breach

For the purposes of this regulation, a “serious breach” is a breach which is likely to effect to a significant degree:

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

Sites are therefore requested to notify the PePS2 Trial Office of a suspected trial-related serious breach of GCP and/or the trial protocol. Where the PePS2 Trial Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the PePS2 Trial Office in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action.

12 END OF TRIAL DEFINITION

The end of trial will be 6 months after the last data capture. This will allow sufficient time for the completion of protocol procedures, data collection and data input. The PePS2 Trial Office will notify the MHRA and REC that the trial has ended and will provide them with a summary of the clinical trial report within 12 months of the end of trial.

13 STATISTICAL CONSIDERATIONS

13.1 Definition and Calculation of Outcome Measures

13.1.1 Primary Outcomes

The trial design is based on two co-primary outcome measures representing toxicity and efficacy. The toxicity co-primary outcome measure for the trial is defined as the occurrence of a treatment-related dose delay or treatment discontinuation due to an adverse event.

Patients will have CT scans every 9 weeks from baseline until disease progression. On each occasion, overall tumour burden will be assessed using RECIST 1.1, according to the study protocol. The efficacy co-primary outcome measure for the trial is durable clinical benefit, defined as the occurrence of of a complete response (CR), partial response (PR) or stable disease (SD) without prior progressive disease (PD) at or after the second scheduled CT scan (scheduled to occur at18 weeks).

For example, a disease response of (CR / PR / SD) at 9 weeks, followed by a disease response of (CR / PR / SD) at 18 weeks would constitute efficacy. Likewise, (CR / PR / SD) at 9 weeks, missing data at 18 weeks, and (CR / PR / SD) at 27 weeks would also constitute efficacy. Patients for whom the primary efficacy outcome could not be determined will be taken as not experiencing durable clinical benefit.

13.1.2 Secondary Outcomes

13.1.2.1 Objective Response (OR)

Best overall response is the best response recorded over the whole period of assessment and could be complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) or inevaluable for response (NA, for which reasons such as early death due to disease or early death due to toxicity will be specified). Objective response (OR) is the occurrence of CR or PR as the best overall response. OR will be based on responses confirmed using the subsequent 9-weekly scan but OR based on unconfirmed responses will also be reported.

13.1.2.2 Health Related Quality of Life (HRQoL)

The purpose of HRQoL measurement is to quantify the degree to which the medical condition or its treatment impacts the individual's life in a valid and reproducible way. Health-related quality-of-life will be measured using the FACT-L and EQ-5D questionnaires, and a patient-generated subjective global assessment questionnaire, as identified in the protocol (see Appendix 5 for questionnaires). The FACT-L questionnaire generates 5 measures for analysis: physical well-being, social/family well-being, emotional well-being, functional well-being and the lung cancer subscale. The EQ5D questionnaire generates 2 measures for analysis: an EQ5D utility measure and an EQ5D Visual Analogue Scale. Questionnaires will be administered on day 1 of every cycle prior to receiving treatment and also at the end of treatment visit.

13.1.2.3 Time to Progression (TTP)

This is defined as the time from commencement of trial treatment to the date of CT scan when progressive disease is first recorded. Patients with no recorded progression at the time of analysis or who die without recorded progression will be censored at the date of the CT scan when they were last recorded with an evaluable measure that was not progression.

13.1.2.4 Progression-Free Survival Time (PFS)

This is defined as the time from commencement of trial treatment to the date of CT scan when progressive disease first recorded or date of death without previously recorded progression. Patients who are alive with no recorded progression at the time of analysis will be censored at the date of the CT scan when they were last recorded with an evaluable measure that was not progression.

13.1.2.5 Overall Survival Time (OS)

This is defined as the time from commencement of trial treatment to the date of death. Patients who are alive at the time of analysis will be censored at the date last confirmed alive.

13.1.2.6 Duration of Objective Response (DOR) and Duration of Stable Disease (DSD)

Duration of objective response and duration of stable disease are defined as the time from commencement of trial treatment to the date of the subsequent CT scan when progressive disease is first confirmed or date of death without previously recorded progression. This outcome will be calculated and reported separately for patients who achieve an OR or SD. Patients experiencing OR or SD who are alive with no recorded progression at the time of analysis will be censored at the date of the CT scan when they were last recorded with an evaluable measure that was not progression.

13.2 Methods of Analysis

13.2.1 Primary Outcomes

The co-primary outcomes will be summarised as toxicity rate and durable clinical benefit rate and analysed simultaneously using the BEBOP (Bayesian Evaluation of Binary Outcomes with Predictive variables) method, developed by Brock, *et al*. (publication forthcoming).

Each patient will have a PD-L1 proportion score and this will determine membership to one of three PD-L1 categories, shown in Table 7. These categories were validated to be predictive of response in Garon, et al (19). Additionally, each patient will be either previously treated or not previously treated. These two variables yield the six PePS2 cohorts shown in Table 8.

Table 7: A patient's PD-L1 category is inferred from their PD-L1 proportion score

Criteria on PD-L1 proportion score z	PD-L1 category
$z < 1\%$	Low
$1\% \leq z < 50\%$	Medium
$z \geq 50\%$	High

Table 8: PePS2 cohorts and corresponding vectors of predictive values, $x = (x_1, x_2, x_3)$

Cohort	Treatment status	PD-L1 category	x_1	x_2	x_3
1	Not pre-treated	Low	0	1	0
2	Not pre-treated	Medium	0	0	1
3	Not pre-treated	High	0	0	0
4	Pre-treated	Low	1	1	0
5	Pre-treated	Medium	1	0	1
6	Pre-treated	High	1	0	0

Let $\theta = (\alpha, \beta, \gamma, \zeta, \lambda, \psi)$ be a vector of parameters. We model the marginal probability of efficacy in patients with the predictive values $\boldsymbol{x} = (x_1, x_2, x_3)$ using the logit-model

$$\pi_E(\boldsymbol{x}, \theta) = \alpha + \beta x_1 + \gamma x_2 + \zeta x_3$$

and the marginal probability of toxicity using the logit-model

$$\pi_T(\boldsymbol{x}, \theta) = \lambda$$

Using these formulae, the probability of efficacy is different for each cohort. In contrast, the probability of toxicity is uniform across the cohorts. These assumptions are supported by data published on similar studies in performance status 0 and 1 patients.

Let a=1 for a given patient if they experience efficacy, and b=1 if they experience toxicity. The joint probability density of efficacy and toxicity events for this patient is modelled using the formula

$$\pi_{a,b} = \pi_E^a (1-\pi_E)^{(1-a)} \pi_T^b (1-\pi_T)^{(1-b)} + (-1)^{a+b} \pi_E (1-\pi_E) \pi_T (1-\pi_T) \frac{e^\psi - 1}{e^\psi + 1}$$

The fraction on the right-hand side, which ranges in value over (-1, 1) for $\psi \in (\infty, -\infty)$, models the association between efficacy and toxicity events.

Let $\boldsymbol{X} = \{(\boldsymbol{x}_1, a_1, b_1), \ldots, (\boldsymbol{x}_n, a_n, b_n)\}$ be the trial outcomes for n patients. The aggregate likelihood function is

$$L(\boldsymbol{X}, \theta) = \prod_{i=1}^{n} \pi_{a_i, b_i} (\boldsymbol{x}_i, \theta)$$

With prior f(θ), the posterior distribution, up to proportionality, is

$$f(\theta | X) \propto f(\theta) \; L(\boldsymbol{X}, \theta)$$

We use normal prior distributions for the elements of θ with means and variances given in Table 9. These give prior events rates of approximately 20% for efficacy and toxicity in each cohort. This can be verified by setting $\boldsymbol{X} = \{\}$ and estimating the 'posterior' probabilities of efficacy and toxicity. The prior event rates we use represent conservative extrapolations of those published in performance status 0 & 1 patients, where, if we were to anticipate a

difference compared to our performance status 2 population, the stronger PS=0/1 patients would be more likely to achieve response and less likely to experience toxicity.

Table 9: Parameters for normal prior distributions for the elements of θ

Parameter	Mean	Variance
α	-2.2	4
β	-0.5	4
γ	-0.5	4
ζ	-0.5	4
λ	-2.2	4
ψ	0	1

The EffTox software estimates the effective sample size of these priors to be equivalent to the outcomes of 1.32 patients, thus the priors may be considered to be weakly informative.

Given trial data $\boldsymbol{X}$, inferences on θ and functions of θ, such as $\pi_E(\boldsymbol{x}, \theta)$ and $\pi_T(\boldsymbol{x}, \theta)$, are made using the posterior probability measure. This requires solving integrals of dimension equal to the number of elements in θ. Generally, this is done numerically rather than analytically using software, described in the Statistical Analysis Plan (SAP).

Pembrolizumab will be considered successful in cohort *i* with the corresponding predictive vector x_i taken from Table 8 if

$$\Pr(\pi_E(\boldsymbol{x}_i, \theta) > 0.1 \mid \boldsymbol{X}) > 0.7$$

and

$$\Pr(\pi_T(\boldsymbol{x}_i, \theta) < 0.3 \mid \boldsymbol{X}) > 0.9$$

That is, we want to be 70% certain a-posteriori that the efficacy rate exceeds 10% and 90% certain that the toxicity rate is less than 30%, to approve the treatment in a given cohort. Separate decisions will be made for each cohort. The hurdle rates for efficacy and toxicity were chosen for their clinical relevance by considering the equivalent rates associated with alternative treatments that these patients might receive. The certainty rates were chosen to give good operating performance with the identified sample size, described in the SAP.

13.2.2 Secondary Outcomes

13.2.2.1 Time-to-event outcomes

Time-to-event outcomes (TTP, PFS, OS, DOR, DSD) will be analysed using the Kaplan-Meier method. Median time-to-event (and 90% CIs) will be presented for each outcome. Milestone events rates will be presented (with 90% CIs) for each outcome. Milestone rates will be presented at appropriate times, selecting from 3, 6, 12, 18 and 24 months. Note that 90% confidence intervals are appropriate in this single arm phase II trial.

13.2.2.2 Binary outcomes

Binary outcomes (OR) will be reported as a numerator, a denominator, a rate and a 90% confidence interval calculated using Wilson's method.

13.2.2.3 HRQoL outcomes

Descriptive longitudinal analyses of each quality of life score will be presented. If appropriate, the EQ5D utility score may be combined with the survival data to estimate quality-adjusted life years using the integrated quality-survival product (27).

The PePS2 SAP presents full details on the analysis method, including assessment of the BEBOP method by simulation study, and proposed exploratory analyses.

14 TRIAL ORGANISATIONAL STRUCTURE

14.1 Sponsor

The trial sponsor is the University of Birmingham.

14.2 Coordinating Centre

The trial is being conducted under the auspices of the Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham according to their local procedures.

14.3 Trial Management Group

A Trial Management Group (TMG) will be established and as a minimum will include the Chief Investigator, Co-Investigators, the Lead and Trial Statistician, Trial Management Team Leader and Trial Coordinator. Other key personnel may be invited to join the TMG as appropriate to ensure representation from a range of professional groups. Notwithstanding the legal obligations of the Sponsor and Chief Investigator, the TMG will be responsible for the day-to-day running and management of the trial and will meet by teleconference or in person as required.

14.4 Trial Steering Committe

The role of the Trial Steering Committee (TSC) is to provide oversight of the trial on behalf of the Sponsor (University of Birmingham) and to ensure that the trial is conducted to the rigorous standards set out in the GCP standards. In particular, the TSC will concentrate on progress of the trial, adherence to the protocol, patient safety and the consideration of new information of relevance to the research question(s). The safety and well-being of the trial participants are the most important considerations and should prevail over the interests of the science and society.

The TSC will provide advice, through its chair, to the Chief Investigator and the University of Birmingham on all appropriate aspects of the trial. The TSC will be asked to comment in detail on substantial changes to protocol. The TSC will meet at least once per year during recruitment.

14.5 Finance

This is an Investigator-initiated and Investigator-led trial funded by Merck, Sharp and Dohme.

The trial has been independently peer reviewed and has been adopted by the National Institute for Health Research (NIHR) Clinical Research Network (CRN) Portfolio.

15 ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html) (Appendix 8).

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research, the applicable UK Statutory Instruments, (which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments and the Data Protection Act 1998 and Human Tissue Act 2008) and GCP. This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations. The protocol will be submitted to and approved by the REC prior to circulation.

Before any patients are enrolled into the trial, the Principal Investigator at each site is required to obtain local R&D approval. Sites will not be permitted to enrol patients until written confirmation of R&D approval is received by the PePS2Trial Office.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

16 CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the General Data Protection Regulation 2016/679 and the Data Protection Act 2018. With the patient's consent, their full name, date of birth, hospital number, general practitioner details will be collected at trial entry to allow tracing through the Cancer Registries and the NHS Information Centre for Health and Social Care (service formally provided by the Office of National Statistics) and to assist with long-term follow-up via other health care professionals (e.g. patient's GP). Patients will be identified using only their unique Trial Number and initials on both electronic and paper CRF and correspondence between the PePS2 Trial Office and the participating site. However patients are asked to give permission for the PePS2 Trial Office to be sent a copy of their signed Informed Consent Form which will not be anonymised. This will be used to perform in-house monitoring of the consent process. The Investigator must maintain documents not for submission to the PePS2 Trial Office (e.g. Patient Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that patient confidentiality is protected.

The PePS2 Trial Office will maintain the confidentiality of all patients' data and will not disclose information by which patients may be identified to any third party other than those directly involved in the treatment of the patient and organisations for which the patient has given explicit consent for data transfer (e.g. Cancer Registries). Representatives of the PePS2 trial team may be required to have access to patient's notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times.

17 INSURANCE AND INDEMNITY

In terms of liability at a site, NHS Trust and non-Trust hospitals have a duty to care for patients treated, whether or not the patient is taking part in a clinical trial. Compensation is therefore available via NHS indemnity in the event of clinical negligence having been proven. University of Birmingham employees are indemnified by the University insurers for negligent harm caused by the design or co-ordination of the clinical trials they undertake whilst in the University's employment. The University of Birmingham cannot offer indemnity for non-negligent harm. The University of Birmingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation.

18 PUBLICATION POLICY

Results will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the TMG and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by Investigators must be reviewed by the TMG and Merck, Sharpe, Dohme. Manuscripts must be submitted in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of the University of Birmingham. Intellectual property rights will be addressed in the Clinical Trial Site Agreement between Sponsor and site.

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APPENDICES

Appendix 1: Eastern Cooperative Oncology Group Performance Status Criteria (28)

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Appendix 2: RECIST v1.1 criteria

RECIST version 1.1 will be used in this trial for assessment of tumour response. While either CT or MRI may be used, as per RECIST 1.1, CT is the preferred imaging technique in this trial.

The following contains excerpts from the RECIST version 1.1 plus trial specific instructions.
A free copy of the revised guidelines is available from http://www.eortc.be/Recist/documents/RECISTGuidelines.pdf (29)

Measurability of Tumour Lesions at Baseline

Only patients with measurable disease at baseline should be included. Measurable disease is defined by the presence of at least one measurable lesion. At baseline, tumour lesions will be categorised as follows:

- Measurable
- Non-measurable

Measurable lesions are those that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of 10 mm by CT scan (CT scan slice thickness no greater than 5 mm), 10 mm calliper measurement by clinical exam (lesions which cannot be accurately measured with callipers should be recorded as non-measurable) and 20 mm by chest X-ray. For malignant lymph nodes to be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by a CT scan (at baseline and during treatment, only the short axis will be measured and followed).

Non-measurable lesions are all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to >15 mm short axis) and truly non-measurable lesions.
Lesions considered to be truly non-measurable include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

Tumour lesions that are situated in a previously irradiated area are not considered measurable.
The term "evaluable" in reference to measurability is not recommended and will not be used because it does not provide additional meaning or accuracy.

All measurements should be recorded in metric notation using callipers (or a ruler) if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of treatment.

Specifications by Methods of Measurements

The same method of assessment and the same technique should be used to characterise each identified and reported lesions at baseline, during treatment and at the post-treatment assessment. Image-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumour effect of a treatment. CT is the best currently available and reproducible method for measuring target lesions selected for response assessment. Investigators should utilize the best available CT imaging technique available to them for determining response and PFS of patients participating in the PePS2 trial.

Tumour Response Evaluation

Baseline Documentation of "Target" and "Non-target" Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as “target” lesions and recorded and measured at baseline.

Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate, reproducible, repeated measurements.

A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as the reference by which to characterise the objective tumour response.

All other lesions (or sites of disease) should be identified as “non-target” lesions and should also be recorded at baseline. Measurements of these lesions are not required but these lesions should be followed as ‘present’, ‘absent’ or in rare cases ‘unequivocal progression’ and recorded.

Response Criteria

A. Evaluation of Target Lesions

Response Category	Description
Complete Response (CR)	Disappearance of all target lesions
Partial Response (PR)	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD)	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. In addition to this, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more lesion is also considered progression.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

B. Evaluation of Non-target Lesions

Response Category	Description
Complete Response (CR)	Disappearance of all non-target lesions
Incomplete Response/ Stable Disease (SD)	Persistence of one or more non-target lesion(s)
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions [1]

Notes:

1. To achieve “unequivocal progression” on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy.

C. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of treatment until disease progression In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

D. Overall Responses for all Possible Combinations of Tumour Responses in Target and Non-target Lesions With or Without the Appearance of New Lesions

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Complete response (CR)	CR	No	CR
Complete response (CR)	Non-CR/non-PD	No	PR
Complete response (CR)	Not evaluated	No	PR
Partial response (PR)	Non-PD	No	PR
Stable disease (SD)	Non-PD	No	SD
Not all evaluated	Non-PD	No	Not evaluable (NE)
Progressive disease (PD)	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective disease progression, even after discontinuation of treatment.

Frequency of Tumour Re-evaluations

For the PePS2 trial, clinical response rate, durable clinical benefit (CR+PR+SD≥18 weeks), PFS and duration of response will be evaluated radiologically by a CT scan of the chest and abdomen and other clinically relevant areas at baseline and at 9 weekly intervals and by clinical measurement at 3 weekly intervals until progression or discontinuation of trial medication. The final CT scan should be performed within 28 days of discontinuation of trial medication.
For patients who discontinue treatment prior to progression CT scans and clinical measurements should, where possible, continue to be performed in accordance with the relevant schedule of assessments.

Appendix 3: **Cockcroft and Gault equation**

Cockcroft and Gault creatinine clearance (CrCl):

$$\text{CrCl (mL/min)} = \frac{\text{N x [140-age (years)] x weight (kg)}}{\text{Serum creatinine (micromol/L)}}$$

Where N = 1.23 males, 1.04 females

Appendix 4: Charlson Index

The Charlson Index (30) will be used in this trial for the assessment of comorbiditiy.

Score	Condition
1	Myocardial infarction (history, not ECG changes only) Congestive heart failure Peripheral vascular disease (includes aortic aneurysm ≥6cm) Cerebrovascular disease: CVA with mild or no residua or TIA Dementia Chromic pulmonary disease Connective tissue disease Peptic ulcer disease Mild liver disease (without portal hypertension, includes chronic hepatitis) Diabetes without end-organ damage (excludes diet-controlled alone)
2	Hemiplegia Moderate or severe renal disease Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes) Tumour without metastasis (exclude if >5 years from diagnosis) Leukemia (acute or chronic) Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumour AIDS (not just HIV positive)
NOTE: For each decade >40 years of age, a score of 1 is added to the total score. Abbreviations: ECG, electrocardiogram; CVA, cerebrovascular accident; TIA, transient ischemic attack; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus	

Appendix 5: Quality of Life Questionnaires

A. Functional Assessment of Cancer Therapy – Lung (FACT-L)

*as available on www.facit.org

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	<u>PHYSICAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea.....	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain.....	0	1	2	3	4
GP5	I am bothered by side effects of treatment.....	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed.....	0	1	2	3	4

	<u>SOCIAL/FAMILY WELL-BEING</u>	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends.....	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness.....	0	1	2	3	4
GS5	I am satisfied with family communication about my illness.....	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
B1	I have been short of breath	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
L1	My thinking is clear	0	1	2	3	4
L2	I have been coughing	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
L3	I feel tightness in my chest	0	1	2	3	4
L4	Breathing is easy for me	0	1	2	3	4
Q3	Have you ever smoked? No ___ Yes ___ If yes:					
L5	I regret my smoking	0	1	2	3	4

B. EQ-5D Questionnaire

As available of www.euroqol.org (31)

C. Patient Generated Subjective Global assessment – Box 4

Box 4. Activities and Function: Over the past month I would generally rate my activity as:

0- Normal with no limitations
1- Not my normal self, but able to be up and about with fairly normal activities
2- Not feeling up to most things, but in bed or chair less than half the day
3- Able to do little activity and spend most of the day in bed or chair
4- Pretty much bedridden, rarely out of bed

Appendix 6: Common Terminology Criteria for Adverse Events (CTCAE), version 4.0

Toxicities will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The full CTCAE document is available on the National Cancer Institute (NCI) website, the following address was correct when this version of the protocol was approved: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Appendix 7: Adverse Event definition

Adverse Event
Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
Comment:
An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.

Adverse Reaction
All untoward and unintended responses to an IMP related to any dose administered.
Comment:
An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Serious Adverse Event
Any untoward medical occurrence or effect that at any dose:

- Results in death
- Is life-threatening*
- Requires hospitalisation** or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Or is otherwise considered medically significant by the Investigator***

Comments:
The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on patients/event outcome or action criteria.
* Life threatening in the definition of an SAE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
**Hospitalisation is defined as an unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Thus hospitalisation for protocol treatment (e.g. line insertion), elective procedures (unless brought forward because of worsening symptoms) or for social reasons (e.g. respite care) are not regarded as an SAE.
*** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs 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, should be considered serious.

Serious Adverse Reaction
An Adverse Reaction which also meets the definition of a SAE.

Suspected Unexpected Serious Adverse Reaction
A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information.
A SUSAR should meet the definition of an AR, UAR and SAR.

Unexpected Adverse Reaction
An AR, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator Brochure (IB) for an unapproved IMP or (compendium of) Summary of Product Characteristics (SPC) for a licensed product).
When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.

Events of Clinical Interest
Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicated a possible immune-related ECI then additional testing should be performed to rule out other etiologic causes. If no other cause was found, then it is assumed to be immune-related (ir).
An irAE is defined as a clinically significant AE of any organ that is associated with study drug exposure, is of unknown etiology, and is consistent with an immune -related mechanism. It is possible that irAEs other than those listed may be observed in subjects receiving pembrolizumab; therefore, all AEs of unknown etiology associated with drug exposure should be evaluated to determine if it is possibly immune related. This is meant to be a general guidance; therefore, recommendations in the current document might not be all inclusive. As such Investigators are encouraged to contact the PePS2 Trial Office as needed to discuss cases that warrant separate discussion outside of the scope of current guidelines. Permanent discontinuation of pembrolizumab due to irAE may be subject of discussion between the Trial Office and treating Investigator.
The most commonly reported immune-related adverse events across the dose schedules are hypothyroidism (7.2%), pneumonitis (2.9%), hyperthyroidism (2.2%), colitis (1.3%) and skin AEOSI (1.3% including all terms). Based on the mechanism of action of pembrolizumab and similar immunomodulatory agents, MSD is interested in potential irAEs, and encourages appropriate investigation of signs and symptoms suggestive of these. Consultation with the appropriate medical specialist should be considered when investigating a possible irAE. These events can occur after the first dose to several months after the last dose of treatment. Mild irAEs are usually treated symptomatically and do not require dosing delays or discontinuation. Higher grade and persistent lower grade irAEs typically necessitate withholding or discontinuing treatment and administration of systemic steroids or other immunosuppressive agents (such as tumor necrosis factor blockers), when systemic steroids are not effective. Early recognition of irAEs and initiation of treatment are critical to reduce the risk of complications, since the majority of irAEs are reversible with the use of steroids and other immune suppressants
Most immune-related adverse reactions occurring during treatment with pembrolizumab were reversible and managed with interruptions of pembrolizumab, administration of corticosteroids and/or supportive care. Immune-related adverse reactions have also occurred after the last dose of pembrolizumab.
For suspected immune-related adverse reactions, adequate evaluation to confirm aetiology or exclude other causes should be ensured. Based on the severity of the adverse reaction, pembrolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid taper should be initiated and continued over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered.
Pembrolizumab may be restarted within 12 weeks after last dose if the adverse reaction remains at Grade ≤ 1 and corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day.

Pembrolizumab must be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for any Grade 4 immune-related adverse reaction toxicity, except for endocrinopathies that are controlled with replacement hormones.
If an irAE does not resolve or improve to ≤ Grade 1 within 12 weeks after last administration of pembrolizumab, study therapy discontinuation should be considered after discussion with PePS2 Trial Office.

Appendix 8: WMA Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Recommendations guiding physicians in biomedical research involving human subjects
Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964
and amended by the
29th World Medical Assembly, Tokyo, Japan, October 1975
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly, Hong Kong, September 1989
and the
48th General Assembly, Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.
The Declaration of Geneva of the World Medical Association binds the physician with the words, "The Health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.
In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.
Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the Investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subject should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The Investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

Coordinating Trial Office

PePS2 Trial Office
Cancer Research UK Clinical Trials Unit
Institute of Cancer and Genomic Sciences
University of Birmingham
B15 2TT

Tel: 0121 414 6788
Fax: 0121 414 3529
Email: peps2@trials.bham.ac.uk

Patient Registration

Tel: 0121 414 6788 / 6754
Monday to Friday, 9:00am to 5:00pm

Serious Adverse Event Reporting

Fax SAE forms to:
0121 414 3529 or 0121 414 7989