CLINICAL STUDY PROTOCOL

Full Study Title:	A randomised open-label phase III trial of Reduced Frequency pembrolizumab immuNothErapy for first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) utilising a novel multi-arm frequency-response optimisation design
Short Study title / Acronym:	REFINE-Lung
Product:	Pembrolizumab
Development Phase:	Phase III
Sponsor:	Imperial College London
Version no:	8.0
Protocol Date:	12th November 2024

This protocol has regard for the HRA guidance

RESEARCH REFERENCE NUMBERS

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This protocol describes the REFINE-Lung trial and provides information about procedures for enrolling patients to the trial. The protocol should not be used as a guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but centres enrolling patients for the first time are advised to contact the Clinical Trial Coordinator to confirm they have the most recent version. Problems relating to this trial should be referred, in the first instance, to the Clinical Trial Coordinator.

This trial will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the Data Protection Act 2018 and other regulatory requirements as appropriate.

ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
BMI	Body mass index
CCTS	Cancer Research UK Imperial Centre: Clinical Trials Section
CEAC	Cost Effectiveness Curve
CI	Chief Investigator
CR	Complete response
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
DoR	Duration of response
DSUR	Development Safety Update Report
EC	Database hosted by the Experimental Cancer Medicine Centre
ECMC	Experimental Cancer Medicine Centre
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EORTC	European Organisation for Research and Treatment of Cancer
FDG-PET	Fluorodeoxyglucose-Positron Emission Tomography
Hct	Haematocrit
Hgb	Haemoglobin
HRA	Health Research Authority
ICBRC	Imperial Cancer Biomarker Resource Centre
ICER	Incremental cost effectiveness ratio
ICHNT	Imperial College Healthcare NHS Trust
ICMJE	International Committee of Medical Journal Editors
ICTU	Imperial Clinical Trials Unit
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
ITT	Intention to Treat
IV	Intravenous
LDH	Lactate dehydrogenase
LFT	Liver function test

NETSCC	NIHR Evaluation, Trials and Studies Coordinating Centre
NIHR HTA	National Institute for Health Research: Health Technology Assessment Programme
NIMP	Non- Investigational Medicinal Product
NMB	Net monetary benefit
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PD	Progressive Disease
PFS	Progression free survival
PPIE	Patient and Public Involvement and Engagement
PR	Partial response
QA	Quality Assurance
QALY	Quality adjusted life year
QoL	Quality of life
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria in Solid Tumours
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable disease
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
T3	Triiodothyronine
T4	Thyroxine
TFT	Thyroid function test
TMG	Trial Management Group
TSC	Trial Steering Committee
TSH	Thyroid-stimulating hormone
ULN	Upper Limit of Normal
WBC	White blood cell

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TRIAL SUMMARY

TITLE	A randomised open-label phase III trial of REduced Frequency pembrolizumab immuNothErapy for first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) utilising a novel multi-arm frequency-response optimisation design
PRIMARY OBJECTIVE	To determine the optimal continuing dose frequency of pembrolizumab amongst patients with NSCLC who have benefited from and completed 6 months of standard therapy, defined as the longest dose interval non-inferior to standard therapy using 2 year survival as the primary outcome
SECONDARY OBJECTIVES	To assess quality of life (QoL), progression free survival (PFS), overall survival (OS), overall response rate (ORR), duration of response (DOR), safety and tolerability and cost effectiveness of the defined optimal dose frequency
EXPLORATORY OBJECTIVES	To collect archived tumour material, blood, imaging and PFS data from initiation of pembrolizumab. To use these data in separate studies to develop biomarkers of treatment sensitivity, toxicity and patient suitability for dose frequency de-escalation.
PHASE	III
DESIGN	Multi-centre randomised open-label, utilising novel multi-arm frequency- response optimisation
SAMPLE SIZE	1100 To assess the safety of this intervention, we will initially randomise patients 1:1 to 6 weekly (control) and 12 weekly arms. Once 150 patients are enrolled, an interim analysis will be performed. If the 12 weekly arm is not significantly less effective in terms of PFS, the remaining 9, 15 and 18 weekly reduced frequency arms will be opened. Simulation based sample size calculations indicate a requirement for 1100 patients (equally distributed across 5 arms) to identify whether either the 15 weekly or 18 weekly arm is non-inferior to control with 80% power at a one-sided alpha of 5%
STUDY POPULATION	Adults (≥18yrs) with pathologically confirmed advanced NSCLC who commenced first line treatment with pembrolizumab alone or in combination with chemotherapy as per NICE guidelines and remain progression free at 6 months and plan to continue treatment
INCLUSION CRITERIA SUMMARY	• Written informed consent prior to initiation of any study procedures and willingness and ability to comply with the study schedule • Any patient ≥18yrs who has received 6 months of pembrolizumab treatment, with or without chemotherapy, for advanced NSCLC who is planned to continue / move to immunotherapy every 6 weeks because of continued benefit.
EXCLUSION CRITERIA SUMMARY	• Disease progression or not tolerating treatment at 6 months into therapy • Any patient with a synchronous primary cancer. This includes any new cancer diagnoses or relapse of previously treated cancer since starting pembrolizumab treatment.

	• Clinician does not intend to continue immunotherapy • Any patient currently receiving an investigational agent and/or using an investigational device or has participated in a study of an investigational agent and/or used an investigational device within 28 days of randomisation.
TREATMENT, FOLLOW UP AND MAIN STUDY PROCEDURES	Patients will be registered into the study either at initiation of or during first-line pembrolizumab treatment. If registered at initiation, patients will be invited to enrol to a translational sub-study seeking to identify biomarkers of treatment response, resistance and suitability for dose frequency de-escalation. If a patient is progression free at 6 months, planned to continue pembrolizumab, has provided written informed consent and is eligible to participate they will be randomised on a 1:1 basis to one of two treatment arms: • 6 weekly pembrolizumab (control arm) • 12 weekly pembrolizumab Patients are permitted to receive 3 weekly pemetrexed chemotherapy as standard of care, where they have received this during the initial 6 months of treatment prior to randomisation. Once 150 patients are randomised (approximately 75 per treatment arm) and 37 PFS events have been observed in the control 6-weekly arm, an interim analysis will be performed. If the 12 weekly arm is not significantly less effective than the control arm in terms of PFS, the following treatment arms will be opened, and patients randomised accordingly: • 9 weekly pembrolizumab • 15 weekly pembrolizumab • 18 weekly pembrolizumab 1100 patients will be required with equal distribution (approximately 220 patients per arm) to identify whether the 15 weekly or 18 weekly arm is non-inferior to the control arm with 80% power at an alpha of 5%. Pembrolizumab will be given at a starting dose of 400mg IV in all treatment arms until confirmed disease progression, unacceptable adverse event/s or other protocol defined discontinuation criteria, and patients who progress on a reduced frequency treatment arm can be re-escalated the control arm of 6 weekly pembrolizumab. The exact schedule of assessments will vary according to the randomised treatment arm (see tables 3 to 7) with assessment of response to treatment according to RECIST v1.1 performed every 12 weeks. Following discontinuation of treatment there will be an end of treatment visit 28 days after the last dose of pembrolizumab, and

	patients will then be followed up every 12 weeks until 18 months from randomisation
PRIMARY ENDPOINT	Overall survival (OS) at 2 years, defined as from commencing pembrolizumab (18 months after randomisation) to death due to any cause or study termination.
SECONDARY ENDPOINTS	• OS, defined as from randomisation to death due to any cause or study termination • Progression free survival (PFS) as assessed by RECIST v1.1, defined as time from randomisation to first evidence of disease progression or death due to any cause • Overall response rate (ORR) as assessed by RECIST v1.1, defined as complete response (CR) or partial response (PR) • Duration of response (DoR) as assessed by RECIST v1.1, defined as time from randomisation to change in response from CR or PR to stable disease (SD) or progressive disease (PD) • Safety and tolerability as assessed by adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 • Quality of life (QoL) as assessed by EORTC QLQ-C30, EORTC QLQ-LC13 and EQ-5D-5L • Cost effectiveness as assessed by a decision analytic model providing an estimate of the incremental cost effectiveness ratio (ICER)/cost per quality adjusted life year (QALY), cost effectiveness acceptability curves (CEAC), deterministic sensitivity analysis and the net monetary benefit (NMB)
ESTIMATED RECRUITMENT PERIOD	4. 75 years / 56 months Within this there will be a feasibility/pilot period to enable interim analysis. Where 12 weekly pembrolizumab is not significantly less effective than the control arm in terms of PFS, the remaining 3 reduced frequency treatment arms will be opened. Similarly absolute and site averaged patient recruitment and randomisation rate (proportion of eligible patients recruited) will be evaluated during the feasibility/pilot period as tests of acceptability.
END OF TRIAL DEFINITION	The end of the trial is defined as collection of the last data point for the last patient
IMP	**Name**: Pembrolizumab **Formulation**: Concentrate for solution for infusion **Dose**: 400 mg starting dose in 6, 9, 12, 15 and 18 week frequencies depending on the treatment arm

	Route of administration: Intravenous (IV)

1. BACKGROUND AND RATIONALE

1.1 Introduction

Lung cancer is the most common cause of malignancy related death and over 85% of cases have non-small cell histology (NSCLC) [1]. Recently, outcomes have improved with immune checkpoint inhibiting (CPI) monoclonal antibodies such as pembrolizumab. In the first line setting, this drug significantly prolongs survival alone [2,3,4,5,6] and in combination with chemotherapy [7,8,9], by binding to and blocking the T cell inhibitory receptor, programmed death 1 (PD1), thereby enhancing T cell anti-tumour function. Pembrolizumab is given every 3 weeks at 200mg or every 6 weeks at 400mg for up to two years. However, pharmacological and clinical outcome data suggest standard regimens result in overtreatment, with important implications on cost, patient QoL and safety.

Here, we propose to address the question of whether pembrolizumab dosing frequency can be reduced in patients who respond to therapy, without compromising efficacy, utilising a novel multi-arm frequency optimisation design.

Recently, the landscape of NSCLC therapy has significantly stabilised. NICE has approved pembrolizumab monotherapy for all treatment-naïve patients with tumours ≥50% positive for programmed death ligand 1 (PDL1). Pembrolizumab is also approved in combination with chemotherapy irrespective of PDL1 positivity. Consequently, ~3600 patients/year in England with advanced NSCLC receive 1st line pembrolizumab alone or with chemotherapy every 3 or 6 weeks. No other immunotherapy agent significantly competes in the first line space and the numbers have remained overall stable in 2020 vs. 2019 despite a short-lived drop in approvals related to the first period of UK COVID19 lockdown restrictions (Figure 1). Our recent survey indicates many UK centres are adopting the new 6 weekly schedule to improve patient convenience and reduce administration costs, accelerated by efforts to reduce patient hospital exposure in the COVID19 era.

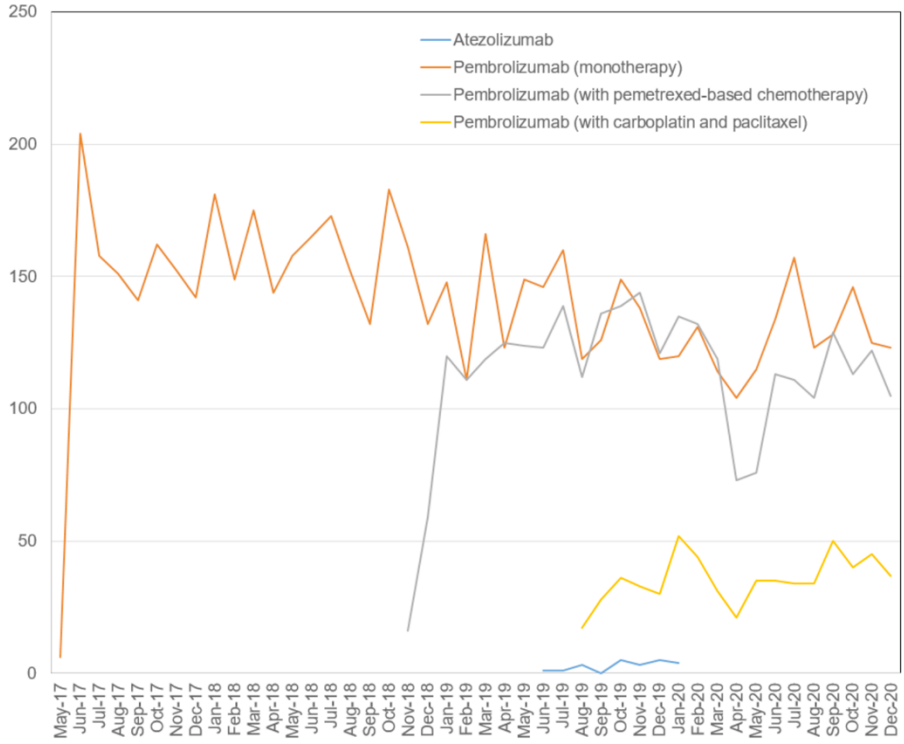


Figure 1. Monthly new prescriptions for 1st line pembrolizumab in England 2017-2020

Secondly, Prof. Max Parmar's team at the MRC Clinical Trials unit has developed a novel DURATIONS design to defining the optimal frequency of drug administration in a significant advance over traditional non-inferiority trials [10]. Patients are randomised to one of 5 or more arms across a range of dose frequencies, to estimate the relationship between frequency and efficacy over the entire range tested.

Crucially, this requires fewer patients than a multi-arm non-inferiority design and does not require an a priori hypothesis of which individual alternative dose frequency to test. To illustrate this, prior to adopting a DURATIONS design, we proposed a traditional non-inferiority study of control vs. 9 weekly therapy that required 1780 patients. Notably, the choice of 9 weekly treatment as the intervention arm was criticised by the NIHR panel prompting us to develop the current trial strategy as a highly efficient alternative to conventional designs.

Finally, 3 or 6 weekly pembrolizumab is now routinely used to treat melanoma, urological and head and neck cancers. Whilst trials of therapy discontinuation in responding patients with melanoma are underway [11], the potential to safely reduce dose frequency in any indication is unexplored. We expect our unique trial design to serve as a model for similar studies across multiple common cancer types and immunotherapy agents and we are currently designing a basket of trials based on this proposal.

1.2 Current immunotherapy dosing regimens may result in overtreatment

Several lines of evidence suggest current pembrolizumab dosing regimens may result in overtreatment. Pharmacodynamic data identify no relationship between pembrolizumab dose (0.3, 1, 3 or 10 mg/kg), serum levels (undetectable after 3 weeks) and occupancy of the target PD1 receptor on circulating T cells, with occupancy maintained at 60-80% at 80 days post dose [12]. Even 100 days after a single 10 mg/kg dose, receptor occupancy

remains between 60-100% of maximum. In vitro, 0.04 μg/ml of drug (one third of the minimum serum-detectable level) is sufficient to occupy >70% of PD1 molecules, suggesting plateau receptor occupancy at undetectable serum levels.

Consistent with these findings, there was no relationship between dose and efficacy in multiple clinical trials. In the phase 1 KEYNOTE-001 study, 550 patients with NSCLC were assigned to pembrolizumab 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks [8]. No evidence of a difference in clinical outcomes nor incidence of toxicity was seen between dose levels. In the phase 2/3 KEYNOTE-010 study that randomised 1034 previously treated patients with NSCLC to pembrolizumab 2 mg/kg, 10 mg/kg or docetaxel chemotherapy, there was no evidence of a difference in overall survival (OS) between the two pembrolizumab dose groups that were both superior compared to chemotherapy [13]. Similar lack of association between dose and efficacy have been reported in other tumour types with either pembrolizumab [14] or another anti- PD1 monoclonal antibody nivolumab [15].

Studies of responding NSCLC patients who stopped therapy as planned at 2 years or earlier because of toxicity reveal durable responses off treatment [8,9,16,17]. Thus, continued treatment up to 2 years may not be required. Similar results have been found in other cancer types including melanoma [18].

This data led to two early stopping trials currently open in melanoma as described in Section 1.4 below, but enthusiasm for such a trial in NSCLC was dampened by results of the Checkmate 153 study. In this trial, the primary endpoint was the safety of nivolumab administered every 2 weeks in older patients with NSCLC (>70 years) and individuals with poor performance status (PS 2). Additionally, an exploratory endpoint was included of efficacy amongst patients randomised at 1 year to stop or continue therapy for up to 2 years [19]. In the recently published final results [17], 174 patients who had not progressed were randomised, with retreatment allowed at progression in the discontinuation arm. Continuation resulted in superior progression free survival (PFS; HR 0.56, 95% CI 0.37-0.84) and overall survival (OS; HR 0.61, 95% CI 0.37-0.99). Notably, the arms were mismatched in terms of the proportion of patients with non-squamous histology (73.2 vs. 56.0% in favour of the continuous arm), which has previously been described to associate with superior OS outcomes in response to nivolumab compared to squamous disease [20,21].

Whilst these results suggest caution for future early stopping trials of immunotherapy in NSCLC, the study was not powered for these efficacy analyses. Consequently, the question of whether early stopping of immunotherapy for NSCLC is safe, remains open. However, considering clinician and patient concern around early discontinuation, we propose a study to evaluate whether pembrolizumab dose frequency can be reduced without compromising efficacy amongst patients with proven benefit at 6 months. The hypothesis that dose frequency can safely be reduced is based on biological insights into long lasting PD1 receptor occupancy.

1.3 Retreatment after discontinuation can be effective

Presentation of this trial at two different PPIE forums revealed primary concerns around the management of patients who progress on a frequency reduced arm. Several reports suggest immunotherapy re-challenge can be effective in NSCLC, particularly amongst those who did not stop due to disease progression. In KEYNOTE-010, 14 patients who progressed after

discontinuing pembrolizumab following 24 months of therapy were retreated and 11 (79%) achieved PR or stable disease [9]. In a small retrospective study of 68 patients who discontinued immunotherapy due to toxicity, retreatment was associated with a significant improvement in overall survival (HR 0.45; 95% CI, 0.21–1.0, p=0.049) amongst those (n=48) who had not achieved a partial response prior to discontinuation. In a subsequent study of 144 patients with NSCLC retreated with immunotherapy, both PFS and OS after re-treatment were found to be most favourable amongst patients who discontinued due to toxicity or a clinical decision, compared to those who progressed [22]. Thus, in response feedback from our PPIE group and this data, we have incorporated re-escalation back to standard dosing frequency for patients progressing on the reduced frequency experimental arms.

1.4 Current trial landscape

The results outlined above indicate continued treatment up to 2 years may not be required and patients can effectively be retreated after discontinuation. Two studies are underway to determine whether immunotherapy can safely be discontinued in responding patients with advanced melanoma [11]. The Canadian Clinical Trials Group STOP GAP study (NCT02821013) is currently recruiting 550 patients, randomised 1:1 to standard of care anti-PD1 treatment for a maximum of 24 months or to stop treatment at radiologically defined maximum tumour response. In parallel, the UK NIHR portfolio DANTE trial (ISRCTN15837212) is currently recruiting 1208 patients, randomised 1:1 to standard of care anti-PD1 treatment or to stop treatment for patients who are progression free at 12 months. In both studies, patients in the early stopping arm will be retreated upon progression.
Crucially, there are no studies of immunotherapy dose frequency reduction in any cancer type.

1.5 Necessity for this research

According to NHSE data, there were ~3600 patients with NSCLC who commenced pembrolizumab monotherapy or in combination with chemotherapy in 2019 and this number seems very stable over time (see Figure 1 above). Approximately 50-60% of patients continue pembrolizumab after 6 months because of clinical benefit [5] and even at 2 years about 25% may still be receiving this agent 6 weekly [8,9]. We hypothesize that continued 6 weekly dosing beyond 6 months is unnecessary and that a reduced frequency would be equally effective. This trial will be of fundamental importance for the NIHR HTA remit, patients, carers and the NHS for the following reasons:

- Pembrolizumab related toxicity can occur at any time during treatment, and reduced dose intensity is expected to reduce toxic events.
- Reduced hospital visits are expected to significantly improve patient quality of life [28]
- Reducing dose intensity by up to two thirds the current standard as proposed here will achieve significant NHS cost savings (non-NHS discounted pembrolizumab costs £45,000/patient-year).

Our novel trial design proposed here will systematically and efficiently determine the optimal frequency of pembrolizumab administration in a manner applicable to the majority of cancer immunotherapy indications beyond our study. This trial therefore has the potential to dramatically alter the landscape of cancer immunotherapy trial conduct nationally and globally.

1.6 Translational objectives

Identification of biomarkers to stratify patients more effectively for therapy will revolutionise patient care. A major barrier to biomarker development has been lack of access to annotated samples from patients enrolled to phase III immunotherapy trials. To date, these trials have been industry led and biomarkers development has not been prioritised. Where sample data suitable for biomarker development have been collected, these are usually difficult or impossible to access. As the largest investigator led study of cancer immunotherapy to date, REFINE-Lung will generate a highly valuable resource to greatly accelerate biomarker development. We will incorporate a translational sub-study to collect archived tumour samples, blood, imaging and outcome data to drive basic and translational research aiming to explore fundamental aspects of the biology of cancer immunotherapy and develop novel biomarkers of response, resistance, toxicity and patient suitability for dose frequency de-escalation to guide management decisions and further reduce the risk of overtreatment.

2. OBJECTIVES AND ENDPOINTS

2.1 Primary Objective and Endpoint

Objective	Endpoint
To determine the optimal continuing dose frequency of pembrolizumab amongst patients with NSCLC who have benefited from and completed 6 months of standard therapy, defined as the longest dose interval non-inferior to standard therapy using 2 year survival as the primary outcome.	Overall survival (OS) at 2 years, defined as from commencing pembrolizumab (18 months from randomisation) to death due to any cause or study termination

2.2 Secondary Objectives and Endpoints

Objective	Endpoint
To assess overall survival in the defined optimal reduced dose frequency	OS, defined as from randomisation to death due to any cause or study termination
To assess progression free survival in the defined optimal reduced dose frequency	Progression free survival (PFS) as assessed by RECIST v1.1, defined as time from randomisation to first evidence of disease progression or death due to any cause
To assess overall response rate in the defined optimal reduced dose frequency	Overall response rate (ORR) as assessed by RECIST v1.1, defined as complete response (CR) or partial response (PR)
To assess duration of response in the defined optimal reduced dose frequency	Duration of response (DoR) as assessed by RECIST v1.1, defined as time from randomisation to change in response from CR or PR to stable disease (SD) or progressive disease (PD)
To assess safety and tolerability in the defined optimal reduced dose frequency	Safety and tolerability as assessed by adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0
To assess quality of life in the defined optimal reduced dose frequency	Quality of life (QoL) as assessed by EORTC QLQ-C30, EORTC QLQ-LC13 and EQ-5D-5L
To assess cost effectiveness in the defined optimal reduced dose frequency	Cost effectiveness as assessed by a decision analytic model providing an estimate of the incremental cost effectiveness ratio (ICER)/cost per quality adjusted life year (QALY), cost effectiveness acceptability curves (CEAC), deterministic sensitivity analysis and the net monetary benefit (NMB)

2.3 Exploratory Objectives and Endpoints

To collect archival cancer tissue, pre- and on treatment blood samples, Pre- and on treatment CT scans and Outcome data, from patients commencing 1st line pembrolizumab who register within the trial prior to starting treatment (6 months before randomisation). These data will be used to develop biomarkers of response, resistance, toxicity, and to guide decisions around dose frequency de-escalation.

To collect blood samples and CT scans from patients randomised within the study and to use these data to develop biomarkers of early recurrence.

3. STUDY DESIGN

3.1 Design

This is a multi-centre randomised open-label, utilising novel multi-arm frequency- response optimisation according to section 3.2 and Figure 1. The study will be performed at 27-35 investigational sites in the UK with the possibility to open additional sites pending confirmation of funding.

3.2 Treatment regimens

To begin with patients can be registered into the study either before or during first-line treatment with 6 weekly pembrolizumab. If a patient is progression free at 6 months, planned to continue pembrolizumab, has provided written informed consent and is eligible to participate they will be randomised on a 1:1 basis to one of two treatment arms:

- 6 weekly pembrolizumab (control arm)
- 12 weekly pembrolizumab

Patients are permitted to receive 3 weekly pemetrexed chemotherapy as standard of care, where they have received this during the initial 6 months of treatment prior to randomisation. Patients who progress on 12 weekly pembrolizumab can be re-escalated to 6 weekly treatment. The next cycle of treatment should commence as close as possible to 6 weeks from the previous cycle.

Once 150 patients are randomised (approximately 75 per treatment arm) and there have been at least 37 PFS events in the control arm, an interim analysis will be performed. If recruitment is slower than expected, at each Independent Data Monitoring Committee meeting, the number of events will be reviewed and if appropriate, the interim analysis brought forward, by a recommendation to the Trial Steering Committee. If the 12 weekly arm is not significantly less effective than the control arm in terms of PFS, the following treatment arms will be opened:

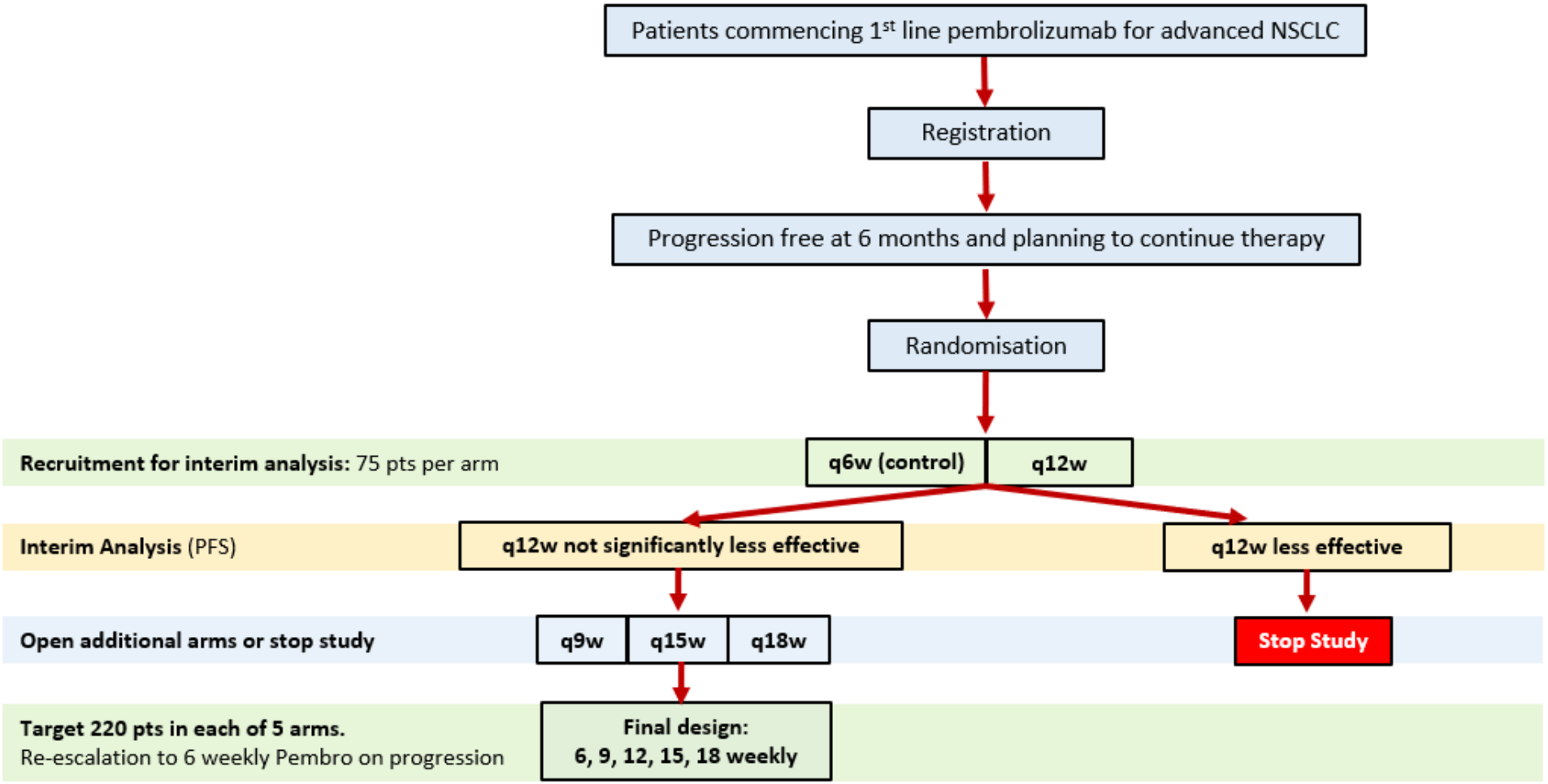
- 9 weekly pembrolizumab
- 15 weekly pembrolizumab
- 18 weekly pembrolizumab

Patients who progress on reduced frequency pembrolizumab can be re-escalated to 6 weekly treatment upon confirmation by RECIST v1.1. The next cycle of treatment should commence as close as possible to 6 weeks from the previous cycle.

Table 1: Summary of treatment arms

Treatment arm / frequency of 400mg pembrolizumab	Number of patients
6 weekly (control)	220
12 weekly	220
9 weekly	220
15 weekly	220
18 weekly	220
Total number of patients	1100

STUDY FLOWCHART (Figure 1)



3.3 Translational Sub-Study

The translational sub-study is optional and not all recruiting centres will take part. This is decided during set-up based on capacity and may change throughout the trial based on discussions between the trial team and site R&D departments.

In addition to the randomised treatment, patients may be approached to take part in optional translational aspects. Research blood samples will be collected during the initial cycles of randomised treatment. Research bloods will be collected before the first 3 cycles post randomisation, please refer to the REFINE-Lung Laboratory Manual for further details.

Furthermore, patients may be approached at initiation of first-line pembrolizumab, to take part in the optional translational sub-study. This is covered in a separate patient information sheet and informed consent form. The sub-study entails collection of data and research blood samples at baseline and during treatment prior to randomisation. If the participant does not go on to be randomised, data collection will stop after the initial 6 months of treatment. We will recruit all patients who are considered for this study into the translational aspects from all sites open to recruitment if they have capacity and capability to perform these optional aspects. An exact recruitment figure cannot be determined due to the dropout rate in the initial phase of treatment due to, for example, progression or toxicity. However, total recruitment may be greater than the 1750 patients included in the randomised treatment phase to allow for this dropout.

This exploratory research is funded by a combination of a North West London Pathology Research & Education Board Grant and the Lung Cancer Research charity. Additional funding may be secured in the future to increase sample collection.

4. PARTICIPANT ENTRY

4.1 Study setting and population

The study will recruit adults with pathologically confirmed advanced NSCLC who are receiving first-line treatment with pembrolizumab, progression free at 6 months and planned to continue treatment. Patients are permitted to receive 3 weekly pemetrexed chemotherapy as standard of care, where they have received this during the initial 6 months of treatment prior to randomisation. Recruitment, treatment and follow up will occur at participating NHS sites.

(i) Translational Sub-Study Inclusion criteria

1. Any patient ≥18yrs who is starting first line pembrolizumab treatment, with or without chemotherapy, for advanced NSCLC

(ii) Translational Sub-Study Exclusion criteria

1. Any patient with a synchronous primary cancer. This includes any new cancer diagnoses or relapse of previously treated cancer at the time of starting pembrolizumab treatment.
    - Patients with non-invasive cancer that has been completely excised e.g. basal cell or squamous cell skin cancer can be enrolled. This should be recorded as part of the participants medical history and discussed with the REFINE-Lung team prior to consent.

- Synchronous primary cancer is defined as any other type of cancer active at the time consenting and all cancer cases should be discussed with the REFINE-Lung team prior to consent.
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(iii)Randomisation Inclusion criteria

1. Written informed consent prior to initiation of any study procedures and willingness and ability to comply with the study schedule.
2. Any patient ≥18yrs who has received 6 months of pembrolizumab treatment, with or without chemotherapy, for advanced NSCLC who is planned to continue / move to immunotherapy every 6 weeks because of continued benefit i.e., progression free by CT criteria (within 6 weeks of entry) and not suffering significant toxicity.

(iv) Randomisation Exclusion criteria

1. Disease progression or not tolerating treatment at 6 months into therapy.
    - Imaging results showing a mixed response/pseudo-progression is not considered disease progression if the treating clinician is continuing pembrolizumab treatment and patients would be eligible.
2. Any patient with a synchronous primary cancer. This includes any new cancer diagnoses or relapse of previously treated cancer since starting pembrolizumab treatment.
    - Patients with non-invasive cancer that has been completely excised e.g. basal cell or squamous cell skin cancer can be enrolled. This should be recorded as part of the participants medical history and discussed with the REFINE-Lung team prior to randomisation.
    - Synchronous primary cancer is defined as any other type of cancer active at the time consenting to the trial and all cancer cases should be discussed with the REFINE-Lung team prior to randomisation.
3. Clinician does not intend to continue immunotherapy.
4. Any patient currently receiving an investigational agent and/or using an investigational device or has participated in a study of an investigational agent and/or used an investigational device within 28 days of randomisation.
    - Observational and sample collection studies are not included.
    - Patients in follow-up from other trials are eligible.

5. PROCEDURES AND MEASUREMENTS

5.1 Identification and recruitment of patients

Potential patients will be identified either by their direct clinical care team at a participating investigational site (i.e., PI and/or appropriately trained and delegated co-Investigator), or as the result of referral to the PI and/or co-Investigator by a clinician based within or outside of that investigational site. This will usually involve meetings of the multi-disciplinary team (MDT). Recruitment will take place as part of routine hospital surgical and oncology clinic visits at participating investigational sites.

Recruitment into the main, randomised trial will be in a 2-stage process of initial approach followed by randomisation at 6 months. At any point between treatment initiation and before 6 months of therapy, patients will be approached and invited to consent to the study. Ideally, we aim for the majority to be approached at initiation, particularly once recruitment is underway. Patients will be provided an information sheet introducing them to the trial and any patients who initially decline may be re-approached, see Figure 2. It is expected

research teams keep a record of approached patients in order to reapproach at the relevant time point. On advice of our PPIE advisory group, this approach has been adopted to give participants as much time as possible to consider randomisation. This will improve the acceptability of reduced frequency treatment. Additionally, this will enable collection of baseline disease response assessments prior to randomisation at 6 months post treatment initiation. Participants will be registered in the eCRF at the point of consent.

Consented patients will have a screening CT scan done +/- 6 weeks of the 6 month treatment landmark date. Patients who are progression free (according to local review) and planning to continue pembrolizumab will be eligible to be randomised.

5.1.1 Identification and recruitment of patients for translational sub-study

Patients who are yet to commence pembrolizumab will be invited to enrol to a translational sub-study to address our exploratory endpoints. As part of this, we will seek consent to collect archived tumour material, additional blood samples (up to 25ml) taken prior to starting pembrolizumab and at subsequent cycles. We will additionally seek consent to obtain treatment data, routine bloods and CT scan images generated before and during treatment along with clinical outcome data.

We aim for patients to be approached before starting pembrolizumab to be able to collect baseline samples see Figure 2.

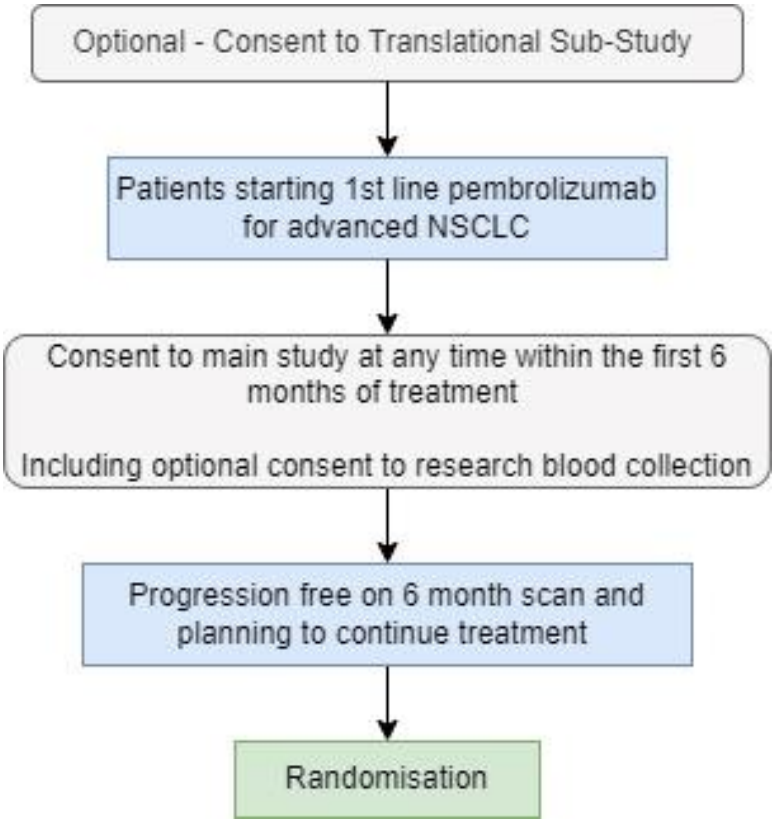

Figure 2: Flow chart describing when participants can be consented for the main study with optional research blood collection and optional translational sub-study

5.2 Sub-Study Visit Schedule

Table 2a: Optional Translational Sub-Study - 6 weekly Pembrolizumab Administration

Study Period →	6 Months prior to Randomisation					
Time-point → Assessments ↓	Baseline	Week 6	Week 12	Week 18	Week 24	At progression/ withdrawal
Translational Study Informed Consent	X					
Medical History & Demographics	X					
Tumour Histology	X					
Adverse Events[3,6]			X		X	X
Pembrolizumab Administration[5]	X	X	X	X	X	
Tumour Assessments[1]	X		X		X	X
Archival Tissue	X					
Research Bloods[4]	X	X	X			
Record of Progression Free Survival and Overall Survival[2]			X		X	X

1. CT scans assessed by RECIST V1.1 should be documented prior to initial dose of pembrolizumab and at the frequency of standard practice thereafter. An example of 3 monthly is given in the table above.
2. Survival should be recorded at each tumour assessment.
3. Haematology, biochemistry, LFTs and TFTs tests should be completed as per local practice prior to administering pembrolizumab. The result of each test does not need to be reported but any significant abnormalities resulting in adverse events should be reported at the above indicted timepoints.
4. Research bloods are to be collected at 6 weeks (i.e. pre-cycle 2 if on 6 weekly, pre-cycle 3 if on 3 weekly) and at 12 weeks (i.e. pre-cycle 3 / 5 respectively). For further details refer to the REFINE-Lung Laboratory Manual.
5. Pembrolizumab should be administered as per local procedures, only details of administration are required for the sub-study. This procedure is included above to align the sub-study schedule with the local treatment schedule
6. SAEs are not required to be reported for patients only consented to the sub-study. If a patient simultaneously/later consents to the main trial, SAEs related to randomised trial procedures are required to be reported from the date of consent to the main trial.

Table 2b: Optional Translational Sub-Study - 3 weekly Pembrolizumab Administration

Study Period →	6 Months prior to Randomisation									
Time-point → Assessments ↓	Baseline	Week 3	Week 6	Week 9	Week 12	Week 15	Week 18	Week 21	Week 24	At progression/ withdrawal
Translational Study Informed Consent	X									
Medical History & Demographics	X									
Tumour Histology	X									
Adverse Events[3,6]					X				X	X
Pembrolizumab Administration[5]	X	X	X	X	X	X	X	X	X	
Tumour Assessments[1]	X				X				X	X
Archival Tissue	X									
Research Bloods[4]	X		X		X					
Record of Progression Free Survival and Overall Survival[2]					X				X	X

1. CT scans assessed by RECIST V1.1 should be documented prior to initial dose of pembrolizumab and at the frequency of standard practice thereafter. An example of 3 monthly is given in the table above.
2. Survival should be recorded at each tumour assessment.
3. Haematology, biochemistry, LFTs and TFTs tests should be completed as per local practice prior to administering pembrolizumab. The result of each test does not need to be reported but any significant abnormalities resulting in adverse events should be reported at the above indicted timepoints.
4. Research bloods are to be collected at 6 weeks (i.e. pre-cycle 2 if on 6 weekly, pre-cycle 3 if on 3 weekly) and at 12 weeks (i.e. pre-cycle 3 / 5 respectively). For further details refer to the REFINE-Lung Laboratory Manual.
5. Pembrolizumab should be administered as per local procedures, only details of administration are required for the sub-study. This procedure is included above to align the sub-study schedule with the local treatment schedule
6. SAEs are not required to be reported for patients only consented to the sub-study. If a patient simultaneously/later consents to the main trial, SAEs related to randomised trial procedures are required to be reported from the date of consent to the main trial.

5.3 Screening and pre-randomisation evaluations

Written informed consent will be obtained before the patient undergoes any screening procedures. Consent may be taken at any point within the 6 months initial phase of treatment, providing the participant has been given significant time to consider the trial.

Each patient will undergo screening procedures and randomisation in the period +/- 6 weeks of the 6 month landmark date. The landmark date is exactly 6 months from the start of treatment e.g. if the first dose was the 1st January, the landmark date would be 1st July. Patients should receive the first dose of treatment on the study +/- 6 weeks from the landmark date. If more than one dose was planned within this 12 week window, the first study dose should be the one closest to the landmark date, given the CT result has been reported in order to confirm eligibility. If the CT result has not been reported before their dose closest to the landmark, the first study dose should be the next scheduled dose after the result is received and must be within +/- 6 weeks from the landmark date. If there is a delay to treatment around the landmark e.g. due to toxicity, the first trial dose may be outside of this window.

For eligibility purposes, the CT scan result is valid for 6 weeks +/- a few days at the discretion of the trial team and should be repeated if the first dose is more than 6 weeks after the scan, e.g. if there is a delay in treatment. Please discuss any cases where the CT is out of this window with the trial team. All other screening procedures should also be repeated if they fall outside of the 6 week screening period. The first treatment on study corresponds to week 0/C1 in the protocol visit schedules (Tables 3-7). The second dose on study should be given at the randomised frequency.

Data obtained as standard of care e.g. completion of CT scans, prior to written informed consent may be used for the study provided they comply with the protocol specified timelines.

Once written informed consent has been obtained the patient should be added to the electronic case report form (eCRF), where a unique Trial ID will be allocated, which should be used in all correspondence during the screening period and beyond.

Screening procedures and assessments are as follows:

- Collection of demographic data
- Locally reported CT scan showing no evidence of progression
- Site confirmation that the patient is clinically suitable to continue pembrolizumab at 6 months (completion of eligibility criteria)
- Review of medical history to include cancer history and treatment
- Tumour Histology including PDL-1 status

A complete record of all patients who are approached, enter screening for the study, and those who go on to be enrolled, must be maintained at each site. The site investigators are responsible for ensuring that this record includes the allocated ID as well as the patient identifiable data including name, hospital number and date of birth.

Eligible patients who take part in the study must meet all the listed inclusion criteria and none of the exclusion criteria (section 4.1).

As pembrolizumab is contraindicated in pregnancy, if there are concerns surrounding risks of pregnancy or screening of women of childbearing potential, local procedures regarding testing and exclusion of pregnancy should be followed. Contraception should be used for 4 months post the last dose of pembrolizumab for all women of childbearing potential.

5.4 Randomisation

Randomisation will initially be on a 1:1 basis between 6 weekly and 12 weekly pembrolizumab. Assuming the interim analysis is favourable, or at most 15 months since the trial started if the necessary events for the interim analyses have not been reached yet, trial patients will then be preferentially randomised into the remaining 9, 15 and 18 weekly pembrolizumab arms modifying the allocation ratio to ensure that all 5 arms will complete enrolment at a similar time. Randomisation will be stratified according to the following factors: squamous/non-squamous histology and prior chemotherapy treatment. Permuted block randomisation will be used, with blocks of size 4 for the first stage of the trial. The dimension of the blocks in the second stage will depend on the allocation ratio. The Trial Statistician will be responsible for holding the randomisation code securely until the final analysis of the study but also to enable the interim analysis.

After eligibility has been confirmed, patients will be randomised to the trial. Randomisation will be performed centrally by Imperial Clinical Trials Unit – Cancer using the eCRF; there is no option available for manual randomisation. Upon randomisation each patient will be allocated a unique subject ID which should be used in all future correspondence.

Please refer to the eCRF Completion Manual for further details on patient randomisation.

After randomisation is completed the available archival tissue should be retrieved and sent to ICTU. See section 5.9 xiv for further details.

5.5 Week 0 Pre-Treatment

After randomisation, each patient will undergo assessments prior to starting study treatment. The procedures should be completed in accordance with standard of care timelines prior to commencing the next cycle of treatment.

Week 0 pre-treatment procedures and assessments are as follows:

- Completion of quality of life questionnaires
- Record of vital signs (including height and weight)
- Physical examination
- Assessment of ECOG performance status
- Blood test for analysis of haematology, biochemistry, liver and thyroid function
- Assessment of adverse events
- Assessment of concomitant medications
- Collection of research bloods

5.6 Randomisation Visit Schedule

Please refer to the relevant tables as follows:

Table 3: 6 weekly pembrolizumab

Study Period →	Screening		Randomisation[15]	Treatment[16]							End of Treatment and Follow-Up	
Time-point → Assessments ↓	Any point within the initial 6 months	Up to 6 weeks prior to first study dose		Week 0 (C1)	Week 6 (C2)	Week 12 (C3)	Week 18 (C4)	Week 24 (C5)	Every 6 Weeks[1]	Every 12 Weeks [1]	28 day follow-up[2]	Every 12 Weeks until W78[17]
Informed Consent	X											
Demographics		X[14]										
Medical History		X[14]										
Vital Signs[3]				X	X	X	X	X	X		X	
Physical Exam[19]				X	X	X	X	X	X		X	
ECOG Performance Status				X	X	X	X	X	X		X	
Haematology[4]				X	X	X	X	X	X		X	
Biochemistry[5]				X	X	X	X	X	X		X	
LFTs[6]				X	X	X	X	X	X		X	
TFTs[7]				X		X		X		X		
Tumour Histology		X[14]										
Tumour Assessments[8,9]		X				X		X		X	X[10]	X[18]
Archival Tissue			X[14]									
Randomisation			X									
Pembrolizumab Administration[11]				X	X	X	X	X	X			
Adverse Events				X	X	X	X	X	X	X	X	X[21]
Concomitant Medications				X	X	X	X	X	X	X	X	
QOL Assessment[12]				X		X		X		X	X[13]	X[22]
Research Bloods[20]				X	X	X						
Record of further treatment and survival												X

1. Patients continue on pembrolizumab for 2 years (18 months from trial entry) or until disease progression, unacceptable toxicity or withdrawal.
2. 28 days +/- 28 days from last dose of pembrolizumab. This visit should be completed for all patients whether they discontinue before 2 years or complete the full schedule of treatment.
3. Vital signs include height, weight, blood pressure, pulse and temperature. Height only taken at screening visit.
4. Haematology includes white blood cell count (WBC) with differential, haemoglobin (Hgb), haematocrit (Hct), and platelet count.
5. Biochemistry includes: Chem 7 (sodium [Na], potassium [K] chloride [Cl], creatinine [Cr], glucose), calcium, phosphate, magnesium and U&Es
6. Liver function tests includes: ALT or AST (either or both as per local practice), alkaline phosphatase, albumin, LDH, total bilirubin.
7. Thyroid Function Tests include: TSH, free T3, free T4 and should be completed every 12 weeks whilst the patient is on treatment.
8. Tumour assessments must be conducted by CT chest and abdomen **and** of any other measurable disease sites as appropriate. The first scan should be an appropriate assessment of the whole body e.g. FDG-PET CT whole body, or CT Chest, abdomen, pelvis to determine measurable disease sites. All scans assessed by RECIST version 1.1.
9. Tumour assessments will be conducted every 12 weeks until disease progression or end of study (18 months from trial entry).
10. Tumour assessment at the end of treatment visit does not need to be repeated if performed within the previous 6 weeks.
11. Pembrolizumab will be administered 6 weekly until disease progression, unacceptable toxicity, withdrawal or end of study (18 months from trial entry).
12. QOL (EORTC QLQ C30, EORTC QLQ LC13 and EQ-5D-5L) assessments should be completed at the same visit as Tumour Assessments, i.e., every 12 weeks whilst the patient is on treatment.
13. QOL (EORTC QLQ C30, EORTC QLQ LC13 and EQ-5D-5L) assessments at the end of treatment visit do not need to be repeated if a scan is not performed at this visit.
14. If not already collected as part of the translational sub-study
15. Randomisation is not a fixed timepoint and should occur at any point within the screening period.
16. If there are delays to the treatment schedule, all assessments should be delayed except the CT scansand QOL questionnaires
17. If patients discontinue pembrolizumab prior to 2 years (18 months from trial entry) they should be followed up every 12 weeks +/- 28 days until 2 years. 12 weeks should be calculated from the end of treatment visit (28 days +/- 28 days post last dose) or when the decision was made to stop treatment if a visit did not occur.
18. CT scans should be documented as per standard practice during the follow-up period.
19. After baseline, a symptom directed physical exam should be performed as clinically indicated.
20. Research bloods will only be collected for sites open to the sub-study.
21. Only AEs related to the IMP are required to be reported in the follow-up period. AEs are required for up to 1 year after the end of treatment or up to end of trial whichever is sooner for the patient. This data can be obtained from the participants medical records.
22. QOL (EORTC QLQ C30, EORTC QLQ LC13 and EQ-5D-5L) assessments are required for up to 1 year after the end of treatment or up to end of trial whichever is sooner for the patient.

Table 4: 12 weekly pembrolizumab

Study Period →	Screening		Randomisation[15]	Treatment[16]						End of Treatment and Follow-Up	
Time-point → Assessments ↓	Any point within the initial 6 months	Up to 6 weeks prior to first study dose		Week 0 (C1)	Week 12 (C2)	Week 24 (C3)	Week 36 (C4)	Week 48 (C5)	Every 12 Weeks [1]	28 day follow-up[2]	Every 12 Weeks until W78[17]
Informed Consent	X										
Demographics		X[14]									
Medical History		X[14]									
Vital Signs[3]				X	X	X	X	X	X	X	
Physical Exam[19]				X	X	X	X	X	X	X	
ECOG Performance Status				X	X	X	X	X	X	X	
Haematology[4]				X	X	X	X	X	X	X	
Biochemistry[5]				X	X	X	X	X	X	X	
LFTs[6]				X	X	X	X	X	X	X	
TFTs[7]				X	X	X	X	X	X		
Tumour Histology		X[14]									
Tumour Assessments[8, 9]		X			X	X	X	X	X	X[10]	X[18]
Archival Tissue			X[14]								
Randomisation			X								
Pembrolizumab Administration[11]				X	X	X	X	X	X		
Adverse Events				X	X	X	X	X	X	X	X[21]
Concomitant Medications				X	X	X	X	X	X	X	
QOL Assessment[12]				X	X	X	X	X	X	X[13]	X[22]
Research Bloods[20]				X	X	X					
Record of further treatment and overall survival											X

1. Patients continue on pembrolizumab for 2 years (18 months from trial entry) or until disease progression, unacceptable toxicity or withdrawal. On progression patients can be re-escalated to 6 weekly pembrolizumab i.e., the control arm and remain in trial
2. 28 days +/- 28 days from last dose of pembrolizumab. This visit should be completed for all patients whether they discontinue before 2 years or complete the full schedule of treatment.
3. Vital signs include height, weight, blood pressure, pulse and temperature. Height only taken at screening visit.
4. Haematology includes white blood cell count (WBC) with differential, haemoglobin (Hgb), haematocrit (Hct), and platelet count.
5. Biochemistry includes: Chem 7 (sodium [Na], potassium [K] chloride [Cl], creatinine [Cr], glucose), calcium, phosphate, magnesium and U&Es
6. Liver function tests includes: ALT or AST (either or both as per local practice), alkaline phosphatase, albumin, LDH, total bilirubin.
7. Thyroid Function Tests include: TSH, free T3, free T4 and should be completed every 12 weeks whilst the patient is on treatment.
8. Tumour assessments must be conducted by CT chest and abdomen **and** of any other measurable disease sites as appropriate. The first scan should be an appropriate assessment of the whole body e.g. FDG-PET CT whole body, or CT Chest, abdomen, pelvis to determine measurable disease sites. All scans assessed by RECIST version 1.1.
9. Tumour assessments will be conducted every 12 weeks until disease progression or end of study (18 months from trial entry). On progression patients can be re-escalated to 6 weekly pembrolizumab i.e., the control arm and remain in trial.
10. Tumour assessment at the end of treatment visit does not need to be repeated if performed within the previous 6 weeks.
11. Pembrolizumab will be administered 12 weekly until disease progression, unacceptable toxicity, withdrawal or end of study (18 months from trial entry). On progression patients can be re-escalated to 6 weekly pembrolizumab i.e., the control arm and remain in trial.
12. QOL (EORTC QLQ C30, EORTC QLQ LC13 and EQ-5D-5L) assessments should be completed at the same visit as Tumour Assessments, i.e., every 12 weeks whilst the patient is on treatment..
13. QOL (EORTC QLQ C30, EORTC QLQ LC13 and EQ-5D-5L) assessments at the end of treatment visit do not need to be repeated if a scan is not performed at this visit.
14. If not already collected as part of the translational sub-study
15. Randomisation is not a fixed timepoint and should occur at any point within the screening period.
16. If there are delays to the treatment schedule, all assessments should be delayed except the CT scans and QOL questionnaires
17. If patients discontinue pembrolizumab prior to 2 years (18 months from trial entry) they should be followed up every 12 weeks +/- 28 days until 2 years. 12 weeks should be calculated from the end of treatment visit (28 days +/- 28 days post last dose) or when the decision was made to stop treatment if a visit did not occur.
18. CT scans should be documented as per standard practice during the follow-up period.
19. After baseline, a symptom directed physical exam should be performed as clinically indicated.
20. Research bloods will only be collected for sites open to the sub-study.
21. Only AEs related to the IMP are required to be reported in the follow-up period. AEs are required for up to 1 year after the end of treatment or up to end of trial whichever is sooner for the patient. This data can be obtained from the participants medical records.
22. QOL (EORTC QLQ C30, EORTC QLQ LC13 and EQ-5D-5L) assessments are required for up to 1 year after the end of treatment or up to end of trial whichever is sooner for the patient.

Table 5: 9 weekly pembrolizumab

Study Period →	Screening		Randomisation[15]	Treatment[16]								End of Treatment and Follow-Up	
Time-point → Assessments ↓	Any point within the initial 6 months	Up to 6 weeks prior to first study dose		Week 0 (C1)	Week 9 (C2)	Week 12	Week 18 (C3)	Week 24	Week 27 (C4)	Every 9 Weeks[1]	Every 12 Weeks[1]	28 day follow-up[2]	Every 12 Weeks until W78[17]
Informed Consent	X												
Demographics		X[14]											
Medical History		X[14]											
Vital Signs[3]				X	X		X		X	X		X	
Physical Exam[19]				X	X		X		X	X		X	
ECOG Performance Status				X	X		X		X	X		X	
Haematology[4]				X	X		X		X	X		X	
Biochemistry[5]				X	X		X		X	X		X	
LFTs[6]				X	X		X		X	X		X	
TFTs[7]				X	X		X		X	X			
Tumour Histology		X[14]											
Tumour Assessments[8,9]		X				X		X			X	X[10]	X[18]
Archival Tissue			X[14]										
Randomisation			X										
Pembrolizumab Administration[11]				X	X		X		X	X			
Adverse Events				X	X	X[20]	X	X[20]	X	X	X[20]	X	X[22]
Concomitant Medications				X	X	X[20]	X	X[20]	X	X	X[20]	X	
QOL Assessment[12]				X		X		X			X	X[13]	X[23]
Research Bloods[21]				X	X		X						
Record of further treatment and overall survival													X

1. Patients continue on pembrolizumab for 2 years (18 months from trial entry) or until disease progression, unacceptable toxicity or withdrawal. On progression patients can be re-escalated to 6 weekly pembrolizumab i.e., the control arm and remain in trial.
2. 28 days +/- 28 days from last dose of pembrolizumab. This visit should be completed for all patients whether they discontinue before 2 years or complete the full schedule of treatment.
3. Vital signs include height, weight, blood pressure, pulse and temperature. Height only taken at screening visit.
4. Haematology includes white blood cell count (WBC) with differential, haemoglobin (Hgb), haematocrit (Hct), and platelet count.
5. Biochemistry includes: Chem 7 (sodium [Na], potassium [K] chloride [Cl], creatinine [Cr], glucose), calcium, phosphate, magnesium and U&Es
6. Liver function tests includes: ALT or AST (either or both as per local practice), alkaline phosphatase, albumin, LDH, total bilirubin.
7. Thyroid Function Tests include: TSH, free T3, free T4.
8. Tumour assessments must be conducted by CT chest and abdomen **and** of any other measurable disease sites as appropriate. The first scan should be an appropriate assessment of the whole body e.g. FDG-PET CT whole body, or CT Chest, abdomen, pelvis to determine measurable disease sites. All scans assessed by RECIST version 1.1.
9. Tumour assessments will be conducted every 12 weeks until disease progression or end of study (18 months from trial entry). On progression patients can be re-escalated to 6 weekly pembrolizumab i.e., the control arm and remain in trial.
10. Tumour assessment at the end of treatment visit does not need to be repeated if performed within the previous 6 weeks.
11. Pembrolizumab will be administered every 9 weeks until disease progression, unacceptable toxicity, withdrawal or end of study (18 months from trial entry). On progression patients can be re-escalate to 6 weekly pembrolizumab i.e., the control arm and remain in trial.
12. QOL (EORTC QLQ C30, EORTC QLQ LC13 and EQ-5D-5L) assessments should be completed at the same visit as Tumour Assessments, i.e., every 12 weeks whilst the patient is on treatment.
13. QOL (EORTC QLQ C30, EORTC QLQ LC13 and EQ-5D-5L) assessments at the end of treatment visit do not need to be repeated if a scan is not performed at this visit.
14. If not already collected as part of the translational sub-study
15. Randomisation is not a fixed timepoint and should occur at any point within the screening period..
16. If there are delays to the treatment schedule, all assessments should be delayed except the CT scans and QOL questionnaires
17. If patients discontinue pembrolizumab prior to 2 years (18 months from trial entry) they should be followed up every 12 weeks +/- 28 days until 2 years. 12 weeks should be calculated from the end of treatment visit (28 days +/- 28 days post last dose) or when the decision was made to stop treatment if a visit did not occur.
18. CT scans should be documented as per standard practice during the follow-up period.
19. After baseline, a symptom directed physical exam should be performed as clinically indicated.
20. Where patients may not be seen by the research team, assessments can be completed remotely where possible.
21. Research bloods will only be collected for sites open to the sub-study.
22. Only AEs related to the IMP are required to be reported in the follow-up period. AEs are required for up to 1 year after the end of treatment or up to end of trial whichever is sooner for the patient. This data can be obtained from the participants medical records.
23. QOL (EORTC QLQ C30, EORTC QLQ LC13 and EQ-5D-5L) assessments are required for up to 1 year after the end of treatment or up to end of trial whichever is sooner for the patient.

Table 6: 15 weekly pembrolizumab

Study Period →	Screening		Randomisation[1][5]	Treatment[16]							End of Treatment and Follow-Up	
Time-point → Assessments ↓	Any point within the initial 6 months	Up to 6 weeks prior to first study dose		Week 0 (C1)	Week 12	Week 15 (C2)	Week 24	Week 30 (C3)	Every 15 Weeks [1]	Every 12 Weeks [1]	28 day follow-up[2]	Every 12 Weeks until W78[17]
Informed Consent	X											
Demographics		X[14]										
Medical History		X[14]										
Vital Signs[3]				X		X		X	X		X	
Physical Exam[19]				X		X		X	X		X	
ECOG Performance Status				X		X		X	X		X	
Haematology[4]				X		X		X	X		X	
Biochemistry[5]				X		X		X	X		X	
LFTs[6]				X		X		X	X		X	
TFTs[7]				X		X		X	X			
Tumour Histology		X[14]										
Tumour Assessments[8,9]		X			X		X			X	X[10]	X[18]
Archival Tissue			X[14]									
Randomisation			X									
Pembrolizumab Administration[11]				X		X		X	X			
Adverse Events				X	X[20]	X	X[20]	X	X	X[20]	X	X[22]
Concomitant Medications				X	X[20]	X	X[20]	X	X	X[20]	X	
QOL Assessment[12]				X	X		X			X	X[13]	X[23]
Research Bloods[21]				X		X		X				
Record of further treatment and overall survival												X

1. Patients continue on pembrolizumab for 2 years (18 months from trial entry) or until disease progression, unacceptable toxicity or withdrawal. On progression patients can be re-escalated to 6 weekly pembrolizumab i.e., the control arm and remain in trial.
2. 28 days +/- 28 days from last dose of pembrolizumab. This visit should be completed for all patients whether they discontinue before 2 years or complete the full schedule of treatment.
3. Vital signs include height, weight, blood pressure, pulse and temperature. Height only taken at screening visit.
4. Haematology includes white blood cell count (WBC) with differential, haemoglobin (Hgb), haematocrit (Hct), and platelet count.
5. Biochemistry includes: Chem 7 (sodium [Na], potassium [K] chloride [Cl], creatinine [Cr], glucose), calcium, phosphate, magnesium and U&Es
6. Liver function tests includes: ALT or AST (either or both as per local practice), alkaline phosphatase, albumin, LDH, total bilirubin.
7. Thyroid Function Tests include: TSH, free T3, free T4.
8. Tumour assessments must be conducted by CT chest and abdomen **and** of any other measurable disease sites as appropriate. The first scan should be an appropriate assessment of the whole body e.g. FDG-PET CT whole body, or CT Chest, abdomen, pelvis to determine measurable disease sites. All scans assessed by RECIST version 1.1.
9. Tumour assessments will be conducted every 12 weeks until disease progression or end of study (18 months from trial entry). On progression patients can be re-escalated to 6 weekly pembrolizumab i.e., the control arm and remain in trial.
10. Tumour assessment at the end of treatment visit does not need to be repeated if performed within the previous 6 weeks.
11. Pembrolizumab will be administered every 15 weeks until disease progression, unacceptable toxicity, withdrawal or end of study (18 months from trial entry). On progression patients can be re-escalated to 6 weekly pembrolizumab i.e., the control arm and remain in trial.
12. QOL (EORTC QLQ C30, EORTC QLQ LC13 and EQ-5D-5L) assessments should be completed at the same visit as Tumour Assessments, i.e., every 12 weeks whilst the patient is on treatment.
13. QOL (EORTC QLQ C30, EORTC QLQ LC13 and EQ-5D-5L) assessments at the end of treatment visit do not need to be repeated if a scan is not performed at this visit.
14. If not already collected as part of the translational sub-study
15. Randomisation is not a fixed timepoint and should occur at any point within the screening period..
16. If there are delays to the treatment schedule, all assessments should be delayed except the CT scans and QOL questionnaires.
17. If patients discontinue pembrolizumab prior to 2 years (18 months from trial entry) they should be followed up every 12 weeks +/- 28 days until 2 years. 12 weeks should be calculated from the end of treatment visit (28 days +/- 28 days post last dose) or when the decision was made to stop treatment if a visit did not occur.
18. CT scans should be documented as per standard practice during the follow-up period.
19. After baseline, a symptom directed physical exam should be performed as clinically indicated.
20. Where patients may not be seen by the research team, assessments can be completed remotely where possible.
21. Research bloods will only be collected for sites open to the sub-study.
22. Only AEs related to the IMP are required to be reported in the follow-up period. AEs are required for up to 1 year after the end of treatment or up to end of trial whichever is sooner for the patient. This data can be obtained from the participants medical records.
23. QOL (EORTC QLQ C30, EORTC QLQ LC13 and EQ-5D-5L) assessments are required for up to 1 year after the end of treatment or up to end of trial whichever is sooner for the patient.

Table 7: 18 weekly pembrolizumab

Study Period →	Screening		Randomisation[1] [5]	Treatment[16]							End of Treatment and Follow-Up	
Time-point → Assessments ↓	Any point within the initial 6 months	Up to 6 weeks prior to first study dose		Week 0 (C1)	Week 12	Week 18 (C2)	Week 24	Week 36 (C3)	Every 18 Weeks [1]	Every 12 Weeks [1]	28 day follow-up[2]	Every 12 Weeks until W78[17]
Informed Consent	X											
Demographics		X[14]										
Medical History		X[14]										
Vital Signs[3]				X		X		X	X		X	
Physical Exam[19]				X		X		X	X		X	
ECOG Performance Status				X		X		X	X		X	
Haematology[4]				X		X		X	X		X	
Biochemistry[5]				X		X		X	X		X	
LFTs[6]				X		X		X	X		X	
TFTs[7]				X		X		X	X			
Tumour Histology		X[14]										
Tumour Assessments[8,9]		X			X		X	X		X	X[10]	X[18]
Archival Tissue			X[14]									
Randomisation			X									
Pembrolizumab Administration[11]				X		X		X	X			
Adverse Events				X	X[20]	X	X[20]	X	X	X[20]	X	X[22]
Concomitant Medications				X	X[20]	X	X[20]	X	X	X[20]	X	
QOL Assessment[12]				X	X		X	X		X	X[13]	X[23]
Research Bloods[21]				X		X		X				
Record of further treatment and overall survival												X

1. Patients continue on pembrolizumab for 2 years (18 months from trial entry) or until disease progression, unacceptable toxicity or withdrawal. On progression patients can be re-escalated to 6 weekly pembrolizumab i.e., the control arm and remain in trial.
2. 28 days +/- 28 days from last dose of pembrolizumab. This visit should be completed for all patients whether they discontinue before 2 years or complete the full schedule of treatment.
3. Vital signs include height, weight, blood pressure, pulse and temperature. Height only taken at screening visit.
4. Haematology includes white blood cell count (WBC) with differential, haemoglobin (Hgb), haematocrit (Hct), and platelet count.
5. Biochemistry includes: Chem 7 (sodium [Na], potassium [K] chloride [Cl], creatinine [Cr], glucose), calcium, phosphate, magnesium and U&Es
6. Liver function tests includes: ALT or AST (either or both as per local practice), alkaline phosphatase, albumin, LDH, total bilirubin.
7. Thyroid Function Tests include: TSH, free T3, free T4.
8. Tumour assessments must be conducted by CT chest and abdomen **and** of any other measurable disease sites as appropriate. The first scan should be an appropriate assessment of the whole body e.g. FDG-PET CT whole body, or CT Chest, abdomen, pelvis to determine measurable disease sites. All scans assessed by RECIST version 1.1.
9. Tumour assessments will be conducted every 12 weeks until disease progression or end of study (18 months from trial entry). On progression patients can be re-escalated to 6 weekly pembrolizumab i.e., the control arm and remain in trial.
10. Tumour assessment at the end of treatment visit does not need to be repeated if performed within the previous 6 weeks.
11. Pembrolizumab will be administered every 18 weeks until disease progression, unacceptable toxicity, withdrawal or end of study (18 months from trial entry). On progression patients can be re-escalated to 6 weekly pembrolizumab i.e., the control arm and remain in trial.
12. QOL (EORTC QLQ C30, EORTC QLQ LC13 and EQ-5D-5L) assessments should be completed at the same visit as Tumour Assessments, i.e., every 12 weeks whilst the patient is on treatment.
13. QOL (EORTC QLQ C30, EORTC QLQ LC13 and EQ-5D-5L) assessments at the end of treatment visit do not need to be repeated if a scan is not performed at this visit.
14. If not already collected as part of the translational sub-study
15. Randomisation is not a fixed timepoint and should occur at any point within the screening period..
16. If there are delays to the treatment schedule, all assessments should be delayed except the CT scans and QOL questionnaires.
17. If patients discontinue pembrolizumab prior to 2 years (18 months from trial entry) they should be followed up every 12 weeks +/- 28 days until 2 years. 12 weeks should be calculated from the end of treatment visit (28 days +/- 28 days post last dose) or when the decision was made to stop treatment if a visit did not occur.
18. CT scans should be documented as per standard practice during the follow-up period.
19. After baseline, a symptom directed physical exam should be performed as clinically indicated
20. Where patients may not be seen by the research team, assessments can be completed remotely where possible.
21. Research bloods will only be collected for sites open to the sub-study.
22. Only AEs related to the IMP are required to be reported in the follow-up period. AEs are required for up to 1 year after the end of treatment or up to end of trial whichever is sooner for the patient.
23. QOL (EORTC QLQ C30, EORTC QLQ LC13 and EQ-5D-5L) assessments are required for up to 1 year after the end of treatment or up to end of trial whichever is sooner for the patient.

5.7 Treatment

Treatment visits, and their relevant assessments, will be conducted according to randomised treatment arm – please refer to tables 3-7. Procedures should be conducted in accordance with local standard of care timelines for pembrolizumab prior to commencing the next cycle of treatment. The next treatment cycle should be as close as possible to the randomised frequency, within reason, for example, allowing for public holidays. Assessments completed every 12 weeks, calculated from week 0 (tumour assessments andQoL) should be completed +/-14 days of the expected visit.

Patients are permitted to receive 3 weekly pemetrexed chemotherapy as standard of care, where they have received this during the initial 6 months of treatment prior to randomisation.

5.8 Follow-up

Wherever possible, patients will attend an end of treatment visit 28 days +/- 28 days after the last dose of pembrolizumab. If a patient completes 24 months of treatment (18 months from randomisation), no additional follow-up is required post the end of treatment visit and monitoring should be undertaken according to standard of care.

For patients that stop treatment early, for example due to progression or toxicity, survival data should be recorded every 12 weeks +/- 28 days. 12 weeks should be calculated from the end of treatment visit (28 days +/- 28 days post last dose) or when the decision was made to stop treatment if a visit did not occur.

If a patient is re-escalated from a reduced frequency to 6 weekly standard treatment, then they should remain in study provided they are happy to do so and follow the 6 weekly schedule whilst still benefiting. Patients should then enter the follow-up if treatment is stopped before 24months.

Assessments will be as follows, please also refer to tables 3-7 for full details.

<u>End of treatment visit</u>

- Record of vital signs
- Symptom directed physical examination
- Assessment of ECOG performance status
- Blood test for analysis of haematology, biochemistry and liver function
- Tumour assessment by RECIST v1.1 following CT chest and abdomen +/- additional measurable disease sites, if not completed in the previous 6 weeks.
- Assessment of adverse events
- Assessment of concomitant medications
- Completion of quality of life questionnaires

<u>Follow up visits</u>

- Record of further treatment and overall survival
- Record of any further tumour assessments if completed. These are not required to be reported as per RECIST V1.1.
- Collection of AEs **<u>related to the IMP only</u>** for up to 1 year after the end of treatment or up to end of trial whichever is sooner for the patient. This data can be obtained from the participants medical records.
- Collection of quality of life questionnaires for up to 1 year after the end of treatment or up to end of trial whichever is sooner for the patient.

5.9 Procedures, Assessments and Laboratory Evaluations

Procedures may be delivered away from the participating site where this is standard practice for pembrolizumab treatment at the site. This includes remote delivery of IMP, if available locally, where this is administered by adequately trained staff. Staff members performing remote procedures must be delegated to do so on the trial delegation log. Local SOPs regarding delivery of procedures and IMP administration remotely must be followed and shared with the sponsor.

Protocol assessments that are completed as standard of care for pembrolizumab administration (e.g. not QoL questionnaires) may be completed by any trained staff member at the participating site. The data must be available for the research team to enter into the eCRF.

(i) Demographic data

Patient date of birth will be collected at screening. For equality and diversity purposes, gender including gender reassignment; sexual orientation; marital status; disability; ethnicity, religion; geographical location and socioeconomic status and smoking status/history) will also be collected with all questions being optional to answer. NHS or CHI (Scotland participants only) number will be collected in order to access any missing endpoint data and long term outcomes from national databases if required.

(ii) Medical history to include cancer history and treatment

A medical history will be taken. This history will detail the patient's cancer, including details of prior anti-cancer therapies. Data from diagnostic imaging and from the initial 6 months of treatment, prior to randomisation, will also be collected. Any other relevant medical history and treatments will also be recorded. Use and type of antibiotics and steroids during the preceding 6 months and whilst on study should be recorded. Concurrent diseases, i.e., other medical conditions that are ongoing from the start of the study, will be documented as adverse events if they worsen.

(iii)Vital signs

Vital signs including height (screening only), weight, body temperature, pulse, blood pressure and BMI will be recorded as indicated in the Study Plan, tables 3-7. Vital signs may be assessed at any time during the visit, however pulse and blood pressure should be measured after at least 10 minutes rest.

(iv)Physical examination

A complete physical examination will be performed at Week 0. The following examinations should be undertaken: general appearance; skin; eyes, ears, nose, mouth and throat; head, neck and thyroid; chest; cardiovascular; abdomen; extremities; spine; musculoskeletal; lymph nodes; neurological; other. The outcome of the examinations will be assessed to include whether normal, abnormal (clinically significant or not clinically significant) or not done. Subsequent examinations should be symptom directed as indicated in the Study Plan, tables 3-7.

(v) ECOG performance status

ECOG performance status will be performed as indicated in the Study Plan, tables 3-7, and according to the criteria detailed in Appendix 1.

(vi) Laboratory evaluations

The following laboratory evaluations will be conducted as indicated in the Study Plan, tables 3-7, with collection and analysis according to standard practice at the relevant site.

- Haematology: white blood cell count (WBC) with differential, haemoglobin (Hgb), haematocrit (Hct) and platelet count;
- Biochemistry: Chem 7 (sodium [Na], potassium [K], chloride [Cl],
- creatinine [Cr], glucose), calcium, phosphate, magnesium, urea and electrolytes;
- Liver function tests (LFTs): ALT or AST (either or both as per local practice), alkaline phosphatase (ALP), albumin, lactate dehydrogenase (LDH) and total bilirubin;
- Thyroid function tests (TFTs): TSH, free T3, free T4;

(vii) Tumour assessment

Tumour assessment will be performed using a CT scan of the chest and abdomen +/- pelvis +/- additional measurable disease sites at screening and every 12 weeks until confirmed disease progression or 18 months from randomisation. Details of the screening scan result and all subsequent scans post randomisation, including the RECIST report will be collected in the eCRF database. Image files will be collected from the scan prior to any pembrolizumab treatment (baseline), and all subsequent scans for all patients who are screened and consented to be randomised into the study. Further details of the image transfer process are located in the Imaging manual. The first scan should be an appropriate assessment of the whole body e.g. FDG-PET CT whole body, or CT Chest, abdomen, pelvis to determine measurable disease sites.

Patient response to treatment will be assessed using RECIST v1.1. The RECIST v1.1 (January 2009) guidelines for measurable, non-measurable, target and non-target lesions and the objective tumour response criteria (complete response, partial response, stable disease or progression of disease) are detailed in Appendix 2. In the unlikely event that a centre cannot complete a RECIST assessment then the centre should contact the study coordinator to ascertain whether an alternative approach can be agreed.

(viii) Tumour histology

Tumour histology will be collected. This includes PDL-1 positivity and presence of specific driver mutations if available.

(ix) Assessment of adverse events

Adverse events (AEs) will be assessed as indicated in the Study Plan, tables 3-7, according to the data detailed in section 7.1.

Adverse events may be reported by any member of the research team, assuming they are trained and delegated to perform this task. However, causality assessments must be completed by a clinician.

AEs are required to be reported in the follow-up period for up to 1 year after the end of treatment or up to end of trial whichever is sooner for the patient. **Only AEs related to the IMP are required to be reported** in the follow-up period. This data can be obtained from the participants medical records.

(x) Assessment of concomitant medications

Concomitant medications will be assessed as indicated in the Study Plan, tables 3-7, with the following data recorded for each medication:

- Name
- Start date / whether ongoing / end date
- Indication
- Dosage
- Frequency
- Route of administration

All medications taken while the patient is on trial should be recorded.

If a COVID-19 vaccine is administered during treatment, this will be recorded as a concomitant medication, with each dose recorded separately. It is recommended that the vaccine is administered following current guidance on COVID-19 vaccines for patients receiving systemic anti-cancer therapy.

Localised radiation therapy is permitted e.g. for the treatment of symptoms related to metastases, and this should be recorded as a concomitant medication. One medication entry should be created per course of treatment with the number of grays over fractions/sessions detailed.

(xi) QOL assessment

Patients must be given the following validated questionnaires to complete as indicated in the Study Plan, table 3-7: QLQ-C30, QLQ-LC13 and EQ-5D-5L. Questionnaires may be posted to patients for completion remotely and return where required.

Questionnaires can also be provided in a number of additional languages other than English, which can be requested from the REFINE-Lung team as required.

(xii) Record of future treatment and overall survival

A record of future treatment and survival status must be kept during follow up every 12 weeks from the end of treatment visit (or when the decision was made to stop treatment if a visit did not occur), until 18 months from randomisation.

(xiii) Exploratory / Research samples

For patients enrolled to the translational sub-study, archived tumour material from cancer diagnosis, blood (up to 25ml) taken pre-initiation of pembrolizumab, 6 weeks and 12 weeks into treatment, and CT scan images generated pre-initiation of pembrolizumab and during treatment will be collected, see table 2.

For patients enrolled to REFINE-Lung, where a patient agrees to take part in the exploratory research aspects of the study, we will collect archived tumour materials (if not already obtained), blood (up to 25ml), and CT scan images generated pre-randomisation and during treatment will be collected, see tables 3-7. Research bloods will be collected before the first 3 cycles post randomisation, please refer to the REFINE-Lung Laboratory Manual for further details.

(xiv) Sample storage and analysis

Written informed consent which include the collection and use of specified biological samples and a full chain of custody will be maintained for all samples throughout the study.

PIs are responsible for maintaining full traceability of biological samples collected from patients while these are in storage at their site, until shipment to ICTU and from return to site and/or disposal. Any person(s) responsible for temporarily holding samples, e.g., sub-contracted service provider must keep full traceability of samples from initial receipt of sample to onward shipment, return or disposal as appropriate.

Samples shipped to ICTU will be stored and analysed according to this protocol, a separate study laboratory manual, and any additional documentation produced by ICTU as required.

Imperial College London, through ICTU, has oversight of each sample's lifecycle through internal procedures and monitoring of study sites.

Archival tissue blocks will be returned to the originating investigator site at the end of the study or earlier upon written request.

Samples retained for further use will be registered with the Imperial College Healthcare NHS Tissue Bank (ICHTB).

5.10 Incidental Findings

Incidental findings are defined as observations of potential clinical significance unexpectedly discovered in research participants and unrelated to the purpose of the study. These may include for example abnormal or unexpected findings from laboratory samples or from radiology images.

We would not expect many incidental findings to be identified during this study. However, any incidental findings that were discovered would be reported back by the Chief investigator and study team to the participant's treating oncologist and the participant themselves in writing. This may for example include any results from the translational analysis conducted.

If an incidental finding is observed during the study, and it is considered a significant abnormality, then the study team should report these to the PI who should take action accordingly. It is the PI's responsibility to ensure findings are communicated to the participant, GPs or other clinicians as appropriate. Incidental findings should be reported to the sponsor trials team.

6. TREATMENTS

6.1 Treatment arms

Pembrolizumab 25 mg/ml concentrate for solution will be dispensed from site specific hospital stock, for randomised treatment according to section 3.2 and table 1.

6.2 Investigational Medicinal Product Details

Pembrolizumab is an IMP for the purposes of this study.

Pembrolizumab monotherapy is licensed for all treatment-naïve patients with tumours ≥50% positive for programmed death ligand 1 (PDL1). Pembrolizumab is also licensed in

combination with chemotherapy irrespective of PDL1 positivity. However, pembrolizumab is not licensed for any frequency other than 3 or 6 weekly.

The Summary of Product Characteristics (SmPC) will be used as reference safety information (RSI) for the study, as submitted for CTA and amended where required during the trial e.g., when submitting DSURs, substantial amendment to study etc.

6.3 Labelling and Packaging

Packaging and labelling of pembrolizumab should be according to local practice. There are no trial-specific requirements.

6.4 Storage and Dispensing

Storage of pembrolizumab must be in line with the relevant SmPC.

Once the pembrolizumab has been diluted for infusion, it should ideally be used immediately. If not used immediately it should be refrigerated at 2-8^{o}C for a maximum of 96 hours (including up to 6 hours at ≤ 25^{o}C) and not frozen. If refrigerated, the vials and/or IV bags must be allowed to come to room temperature prior to use.

Dispensing will be according to local standard practice.

6.5 Dosage, Duration and Compliance

Dosage of pembrolizumab is 400mg at a frequency determined by randomisation i.e., 6 weekly (control), 9 weekly, 12 weekly, 15 weekly or 18 weekly. Treatment will be given until confirmed disease progression or 18 months from randomisation. Treatment will be given at outpatient clinics at the recruiting hospital, meaning that compliance can be monitored by the site and any problems reported as protocol deviations/violations in the eCRF (see section 9.7).

Patients who progress on reduced frequency pembrolizumab can be re-escalated to 6 weekly treatment. The next cycle of treatment should commence as close as possible to 6 weeks from the previous cycle. Patients should remain on 6 weekly study treatment for the remainder of the 18months, unless they progress further, then patients should go into the follow-up period.

Patients should be treated as per standard local practice following the completion of study treatment (18 months from randomisation). IMP will not be provided to patients post completion of the study as recommend in NICE guidelines of 2 years maximum treatment.

6.6 Accountability

The investigator and appropriately trained and delegated staff will document the receipt, dispensing, administration and destruction of pembrolizumab as per local policy.

Please refer to the IMP Handling Manual for further details.

6.7 Drug interactions / Precautions / Contraindications

Interactions

No formal pharmacokinetic drug interaction studies have been conducted with pembrolizumab. Since pembrolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.

Systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions. Corticosteroids can also be used as premedication, when pembrolizumab is used in combination with chemotherapy, as antiemetic prophylaxis and/or to alleviate chemotherapy-related adverse reactions.

Precautions
None. Management of specific adverse events is detailed in section 6.9.

Contraindications
Hypersensitivity to the active substance or to any of the excipients: L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate 80, water for injections.

6.8 Overdose of IMP

There is no information on overdose with pembrolizumab.
In case of overdose, patients must be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

6.9 Dose Modifications for Adverse Events

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic aetiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 8 below. Also see Section 6.9 for supportive care guidelines.

If a delay to treatment is required, all assessments in Section 5.6, Tables 3-7 should be delayed except those assessments on 12 weekly intervals – Tumour assessments and Quality of life questionnaires. These should remain at 12 weekly intervals regardless of the delays incurred to the treatment schedule.

Following standard NHS guidance, when a treatment break of more than 3 months beyond the randomised cycle length is needed, a standard treatment break approval form will be completed to restart treatment, including indicating as appropriate if the patient had an extended break because of Covid-19. This includes delays related to toxicity and any other reason for delays. This is not required to be shared with the trial team.

Table 8: Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Severity	Treatment modification
Pneumonitis	Grade 2	Withhold until adverse reactions recover to Grades 0-1*
	Grades 3 or 4, or recurrent Grade 2	Permanently discontinue
Colitis	Grades 2 or 3	Withhold until adverse reactions recover to Grades 0-1*
	Grade 4 or recurrent Grade 3	Permanently discontinue
Nephritis	Grade 2 with creatinine > 1.5 to ≤ 3 times upper limit of normal (ULN)	Withhold until adverse reactions recover to Grades 0-1*
	Grade ≥ 3 with creatinine > 3 times ULN	Permanently discontinue

Endocrinopathies	Grade 2 adrenal insufficiency and hypophysitis	Withhold treatment until controlled by hormone replacement
	Grades 3 or 4 adrenal insufficiency or symptomatic hypophysitis	Withhold until adverse reactions recover to Grades 0-1*
	Type 1 diabetes associated with Grade ≥ 3 hyperglycaemia (glucose > 250 mg/dL or > 13.9 mmol/L) or associated with ketoacidosis Hyperthyroidism Grade ≥ 3	For patients with Grade 3 or Grade 4 endocrinopathies that improved to Grade 2 or lower and are controlled with hormone replacement, if indicated, continuation of pembrolizumab may be considered after corticosteroid taper, if needed. Otherwise, treatment should be discontinued.
	Hypothyroidism	Hypothyroidism may be managed with replacement therapy without treatment interruption.
Hepatitis	Grade 2 with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 to 5 times ULN or total bilirubin > 1.5 to 3 times ULN	Withhold until adverse reactions recover to Grades 0-1*
	Grade ≥ 3 with AST or ALT > 5 times ULN or total bilirubin > 3 times ULN	Permanently discontinue
	In case of liver metastasis with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥ 50% and lasts ≥ 1 week	Permanently discontinue
Skin reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold until adverse reactions recover to Grades 0-1*
	Grade 4 or confirmed SJS or TEN	Permanently discontinue
Other immune-related adverse reactions	Based on severity and type of reaction (Grade 2 or Grade 3)	Withhold until adverse reactions recover to Grades 0-1*
	Grades 3 or 4 myocarditis Grades-3 or 4 encephalitis Grades-3 or 4 Guillain-Barré syndrome	Permanently discontinue
	Grade 4 or recurrent Grade 3	Permanently discontinue
Infusion-related reactions	Grades 3 or 4	Permanently discontinue
Note: toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0).		

* If treatment-related toxicity does not resolve to Grades 0-1 within 12 weeks after last dose of Pembrolizumab, or if corticosteroid dosing cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks, Pembrolizumab should be permanently discontinued.

6.10 Study drug administration

- Do not shake the vial.
- Equilibrate the vial to room temperature (at or below 25°C).
- Prior to dilution, the vial of liquid can be out of refrigeration (temperatures at or below 25°C) for up to 24 hours.
- Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. The concentrate is a clear to slightly opalescent, colourless to slightly yellow solution. Discard the vial if visible particles are observed.
- Withdraw the required volume up to 4 mL (100 mg) of concentrate and transfer into an intravenous bag containing sodium chloride 9 mg/mL (0.9%) or glucose 50 mg/mL (5%) to prepare a diluted solution with a final concentration ranging from 1 to 10 mg/mL. Each vial contains an excess fill of 0.25 mL (total content per vial 4.25 mL) to ensure the recovery of 4 mL of concentrate. Mix diluted solution by gentle inversion.
- From a microbiological point of view, the product, once diluted, should be used immediately. The diluted solution must not be frozen. If not used immediately, chemical and physical in-use stability of pembrolizumab has been demonstrated for 96 hours at 2°C to 8°C. This 96-hour hold may include up to 6 hours at room temperature (at or below 25°C). If refrigerated, the vials and/or intravenous bags must be allowed to come to room temperature prior to use. Translucent to white proteinaceous particles may be seen in diluted solution. Administer the infusion solution intravenously over 30 minutes using a sterile, non-pyrogenic, low-protein binding 0.2 to 5 µm in-line or add-on filter.
- Do not co-administer other medicinal products through the same infusion line.
- Pembrolizumab is for single use only. Discard any unused portion left in the vial.

6.11 Pre-medications / Non-IMP details

Where patients have received standard 3 weekly pemetrexed as chemotherapy in combination with pembrolizumab in the first 6 months of first-line therapy, pemetrexed may continue as a non-IMP during the study.

6.12 Permanent Discontinuation of Study Treatment and Withdrawal from Study

(i) Permanent discontinuation of study treatment

Patients may discontinue study treatment for the following reasons:

- Confirmed disease progression and/or death. Patients who progress on a reduced frequency can be re-escalated to 6 weekly pembrolizumab.
- At the request of the patient. Patients may also choose to re-escalate to 6 weekly pembrolizumab if they wish to discontinue with their randomised treatment; they will remain in the study.
- Adverse event/ Serious Adverse Event
- Allergic reaction to IMP
- Pregnancy
- If the investigator considers that a patient's health will be compromised due to adverse events or concomitant illness that develop after entering the study.

The primary reason for discontinuation must be recorded in the eCRF and the patient's medical records. Wherever possible the end of treatment visit should be conducted 28 days

after last dose of pembrolizumab and follow up conducted every 12 weeks until 18 months from randomisation for the purposes of recording further treatment and survival status. It is important wherever possible that participants continue into the follow-up period to ensure data for the primary endpoint is available.

(ii) Withdrawal from Study

Withdrawal from the study refers to discontinuation of study treatment and study procedures and can occur for the following reasons:

- Patient decision
- Investigator Decision
- Loss to follow-up
- Death

If a participant dies whilst participating in the study, a 'Statement of Death' eCRF must be completed. The following information will be collected: date of death, cause of death and if the death is related to the disease.

(iii)Procedures for Withdrawal from Study

In the event of a patient withdrawing from the study, no further visits or follow up will be conducted. The primary reason must be recorded in the eCRF and the patient's medical records. Any data and samples already collected will be retained and analysed.

If possible, the investigator should arrange for the end of study assessments to be completed. Where the patient has withdrawn due to an AE, the investigator should follow the procedures in section 7.0.

Where a patient has been lost to follow-up, this should be recorded on the eCRF with their last known contact date and survival status at the time.

7. PHARMACOVIGILANCE

7.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the trial medication, whether or not considered related to the IMP.

7.2 Disease Progression

Disease progression is a worsening of a patient's condition attributable to the disease for which the study medication is being given. This may be an increase in severity of the disease or increase in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. **Events that are unequivocally due to disease progression should not be reported as AEs during the study**.

7.3 New Cancers

The development of a new cancer should be regarded as an AE and reported accordingly. Generally, it will also meet at least one of the serious criteria.

7.4 Adverse Reaction (AR)

All untoward and unintended responses to an IMP related to any dose administered. All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions (Ars). The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

7.5 Unexpected Adverse Reaction

An AR, the nature or severity of which is not consistent with the applicable product information as set out in the Reference Safety Information (RSI) (in the investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected. Side effects documented in the RSI section of the SmPC/IB which occur in a more severe form than anticipated are also considered to be unexpected.
Expectedness assessment will be performed by the site PI.

7.6 Causality

The assignment of causality for adverse events should be made by the investigator responsible for the care of the participant using the definitions in the table below.

If any doubt about the causality exists, the local investigator should inform the study coordination centre who will notify the Chief Investigator. The pharmaceutical companies and/or other clinicians may be asked to advise in some cases.

In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the MHRA will be informed of both points of view.

Unrelated: No evidence of any causal relationship

Unlikely: There is little evidence to suggest there is a causal relationship (e.g., the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).

Possible: There is some evidence to suggest a causal relationship (e.g., because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the patient's clinical condition, other concomitant treatments).

Probable: There is evidence to suggest a causal relationship and the influence of other factors are unlikely.

Definite: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

7.7 Severity of Adverse Events

Severity of AEs will be assessed using the grading scales found in the National Cancer Institute CTCAE version 5.0 (27th November 2017), by attributing the most relevant CTCAE term. Where it is not possible to attribute a specific CTCAE term, a term may be attributed

by the investigator and assessed according to the introduction under Grades in CTAE version 5.0 i.e., grade 1=mild; grade 2=moderate; grade 3=severe; grade 4=life-threatening; grade 5= fatal.

CTCAE version 5.0 is accessible online here:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

7.8 Adverse Event recording

AEs will be collected from the point of consent to the main trial, until up to 1 year after the End of Treatment Visit (28 days post last dose) or up to end of study whichever is sooner for the patient. Patients will be followed up according to local practice until the event has stabilised or resolved, or the End of Study Visit, whichever is the sooner. SAEs will be recorded according to the same timeline. During the period between consent for the main trial and the first trial dose, only **events related to trial screening procedures** need to be recorded.

Any AEs which remain unresolved at the End of Study Visit should be followed up by the Investigator for as long as medically indicated, but without further recording in the CRF.

The following details will be collected in the CRF for each AE:

- AE term
- Onset date / whether ongoing / end date
- Severity i.e., CTCAE grade
- Causality to IMP
- Action taken
- Outcome
- Seriousness

7.8.1 Sub-Study Adverse Event Recording

AEs will collected from the point of consent while the patient remains on pembrolizumab treatment in the initial 6 months. Patients will be followed up according to local practice until the event has stabilised or resolved, or the End of Study Visit at the end of the initial 6 months, whichever is the sooner.

SAEs are not required to be reported for this period, **unless the patient has also consented to the main trial**. In this instance, SAEs would be required from the date of consent to the main trial, **if related to trial screening procedures**.

Any AEs which remain unresolved at the End of Study Visit should be followed up by the Investigator for as long as medically indicated, but without further recording in the CRF.

7.9 Abnormal Laboratory Test Results

All clinically important abnormal laboratory test results occurring during the study will be recorded as adverse events. The clinically important abnormal laboratory tests will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the investigator and the clinical monitor, or until a diagnosis that explains them is made.

7.10 Serious Adverse Events (SAE)

(i) Definition of SAE

An SAE is defined as any event that

- Results in death;
- Is life-threatening*;
- Requires hospitalisation or prolongation of existing inpatient's hospitalisation**;
- Results in persistent or significant disability or incapacity;
- Is a congenital abnormality or birth defect;

* "Life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

** "Hospitalisation" means any unexpected admission to a hospital department. It does not usually apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission).

Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/reactions that are not immediately life-threatening, or do not result in death or hospitalisation but may jeopardise a subject, or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

(ii) Reporting of SAEs

Rapid reporting of all SAEs i.e., within 24 hours, occurring during the study must be performed as detailed in the study-specific pharmacovigilance manual.

Active monitoring of participants after the end of the trial is not required, but if the investigator becomes aware of safety information that appears to be drug related, involving a participant who participated in the study, even after an individual participant has completed the study, this should be reported via the MHRA post-marketing yellow card system.

All SAEs will be reviewed by the Chief Investigator or a designated medically qualified representative to confirm expectedness and causality. Assessing SARs is not routinely completed centrally by the sponsor and is delegated to the Chief Investigator as detailed in the Delegation of Responsibilities agreement between Imperial College London, ICTU and the Chief Investigator for ICTU Portfolio studies. The CI or delegate will not downgrade the site's assessment of causality and expectedness but can advise accordingly on behalf of the sponsor.

Reporting of SAEs and review by the CI will be via the trial data collection system (CRF/eCRF). The study team will report all SAEs to Sponsor according to applicable standard operating procedures.

(iii) Definition of a Serious Adverse Reaction (SAR)

A SAR is defined as a SAE that is judged to be related to any dose of study drug administered to the participant.

(iv) Definition of Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any SAR that is NOT consistent with the applicable product information as set out in the Reference Safety Information (RSI) section of the Investigator Brochure (IB) or Summary of Product Characteristics (SPC).

(v) Reporting of SUSARs

SUSARs should be notified to the appropriate regulatory authority, the relevant REC and the Sponsor in accordance with regulatory requirements. SUSARs which are fatal or life-threatening will be reported not later than seven days after alerting the sponsor to the reaction. Any additional relevant information will be sent within eight days of the report.

A SUSAR which is not fatal or life-threatening will be reported within 15 days of first knowledge by the sponsor. The sponsor will inform all investigators about SUSARs occurring on the study.

Follow up of participants who have experienced a SUSAR should continue until recovery is complete or the condition has stabilised.

Contact details for reporting SAEs and SUSARs

REFINE-Lung@imperial.ac.uk
Tel: 020 7594 2180 (Mon to Fri 09.00 – 17.00)
rgit.ctimp@imperial.ac.uk

7.11 Developmental Safety Update Reports

Developmental Safety Update Reports (DSUR) will be submitted to the Sponsor, the Ethics Committee and Regulatory Authority in accordance with local / national regulatory requirements.

7.12 Pregnancy

Pembrolizumab is contraindicated in pregnancy and study treatment will be discontinued in patients who become pregnant. Pregnancy is not considered an SAE but where the patient gives their consent the pregnancy will be recorded and followed up in the eCRF to ensure a congenital abnormality does not occur.

7.13 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

8. STATISTICAL ANALYSES

8.1 Sample Size and power considerations

First stage (Interim Analysis)

For the interim efficacy analysis, we explored sample sizes needed with different possible design parameters. In particular, we varied the expected 6-month PFS in both the 6-weekly and 12-weekly arms, the power to detect inferiority of the 12-weekly arm and the significance level. First, we assumed PFS in the control arm to be 50% at 6 months post-randomisation, a conservative estimate based on available data. We then determined the number of

patients required to detect a hazard ratio significantly different from 1 with 80% power if the 12-weekly arm patients had a PFS ranging between 25% and 40% at 6 months. The lower bound of this range was based on an expected 6-month PFS with standard chemotherapy-only of about 20% from historical data [23, 5].

Figure 3 shows the sample size needed to detect inferiority of 12-weekly treatment with 80% power at varying significance cut-offs, given different expected PFS values. The black (PFS=25%) and blue (PFS=30%) lines were the only ones returning feasible sample sizes (within 50% of the total number of patients required for each arm) for an interim analysis, and amongst these two we selected the most conservative assumption (PFS=30%). The total sample size for the interim analysis was found to be 150 patients using a one-sided 5% significance level.

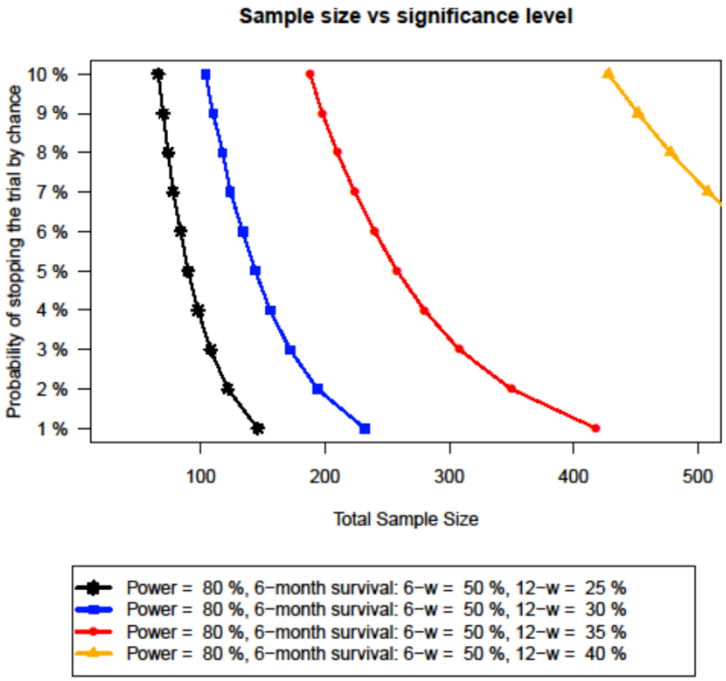

Figure 3: Sample size calculations

Thus, if the progression rate was also 50% in the 12-weekly arm, the probability of finding a significantly worse outcome amongst patients in the 12-weekly arm by chance alone, erroneously stopping the trial, was controlled at 5%. Under the assumption that 6 weekly pembrolizumab increases 6 month PFS from 20% to 50%, with the selected design parameters, we are well powered to stop the trial for lack of efficacy if halving pembrolizumab dose frequency reduces its effect by two thirds (i.e., 6 month PFS of 30%). As we are less well powered to detect smaller differences, assuming the trial proceeds to the second stage, the IDMC will review the data every 6 months to assess whether it is appropriate to continue randomising to all arms.

Second stage

For Stage 2, we determined the overall sample size using data sample size formula based on standard normal theory, assuming two year OS of ~65% based on available data from completed trials, whilst considering that patients are enrolled having already achieved 6 months treatment.

For the sample size calculation, we powered under the assumption that survival is the same irrespective of treatment frequency and that we would analyse the data fitting a FPLR model to estimate the frequency-response curve, using the fitted model to estimate a confidence interval around the risk ratio for each arm vs. control (experimental/control arm 2 year survival). We defined the margin of non-inferiority to be 0.88. Thus, an active arm can be declared non-inferior if the lower bound of the 95% CI for the 2 year survival risk ratio against 6-weekly is above 0.88 (Figure 4). With these design parameters, ~1000 patients equally distributed between 5 arms were enough to achieve 80% power to find that either the 15 weekly or the 18 weekly arm was non-inferior to 6 weekly, using a one-sided significance level of 5% (Figure 4). Allowing for ~10% attrition, the total sample size is 1100.

To address a previously raised concern that our study does not control type I error, we simulated a range of scenarios assuming 2 year survival drops linearly or nonlinearly across tested frequencies, from 65% to 57.2% (the boundary of non-inferiority), with 1000 patients. Unlike our previous Cox modelling approach, we found type I error was ≤5% for all modelled scenarios, comparing 18- and 6 weekly arms, indicating an acceptably low probability of falsely accepting the 18 weekly arm as noninferior.

8.2 Planned recruitment rate

We propose a internal pilot (n=150) to investigate whether 12 weekly treatment is significantly less effective than control, and additionally to investigate study feasibility by evaluating absolute and site averaged patient recruitment and randomisation rate (proportion of eligible patients recruited) as tests of acceptability.

Feasibility progression criteria have been set in line with the aim of randomising 1110 patients from approximately 35 sites. Additional sites may be opened if required and funding allows. Current NHS England data show that 3600 patients with NSCLC per year are treated with first-line pembrolizumab conservatively estimating 50% remain on treatment at 6 months, we expect 17000 patients per year to be eligible for randomisation. Looking at current recruitment data across sites, among sites open less than 9 months, we found that the average conversion rate (defined as the average proportion of the total monthly prescriptions of pembrolizumab that lead to a randomisation) was 10%. However, this increased to about 20%, for sites open since at least 9 months. Based on the available prescription figures across our open sites, under the assumption the conversion rate after all sites have been recruiting for 9 months will remain ~20%, we project we can achieve a steady state of 32 patients per month. This is under the assumption that average number of prescriptions in the sites yet to open will be roughly the same as the open sites.

In this pilot period if recruitment falls into the amber range of 50-99%, we will undertake and act upon additional analyses to resolve this, including opening additional sites (subject to funding), correspondence with the local CRN teams and undertaking patient/clinician interviews to determine barriers to recruitment. If recruitment falls into the red range of less than 50%, ongoing recruitment will be considered with the NIHR HTA Programme and TSC with a view to stopping the trial unless advised otherwise. See Table 9.

Table 9: Interim Analysis Progression criteria

RAG Rating	Red	Amber	Green
% Threshold	<50%	50-99%	≥100%

Total number of patients recruited	<75	75-149	≥150

8.3 Statistical analysis

Here we provide the key details of the planned statistical analysis. A separate, more comprehensive, statistical analysis plan will be prepared and finalised prior to database lock. Any deviation(s) from the final statistical plan in the final analysis will be described and justification given in the final report.

(i) Analysis populations

As our primary goal is to investigate the effectiveness of recommending a treatment strategy, the primary analysis population will be Intention to Treat (ITT). We will additionally consider the Per-Protocol population as a secondary objective, using inverse probability weighting methods to mitigate selection biases.

The Safety Population is defined as all patients receiving at least one dose of pembrolizumab within the trial.

(ii) Primary Endpoint Analysis

Interim analysis will be performed when approximately 37 PFS events have been observed in the control 6-weekly arm, which is expected to occur around 12-15 months from the start of recruitment. If by the time recruitment has started from 15 months this number of PFS events has not been reached, the 9-weekly, 15-weekly and 18-weekly frequency arms will be opened while waiting for the interim analysis results.

The analysis will consist of a Cox proportional hazards model, where the main covariate will be treatment, defined as standard-of-care (6-weekly frequency) or extended frequency (12-weekly frequency). The model will also adjust for the stratification variables and for any additional variable predictive of the outcome as specified in the statistical analysis plan. If there will be no statistical evidence of inferiority of the 12-weekly arm, i.e., if the whole confidence interval for the hazard ratio will not be above 1, the trial will proceed to the second stage.

For the second and final stage, data will be analysed by Fractional Polynomials Logistic Regression (FPLG) using 2 year survival as the primary outcome. On top of frequency, the model will be adjusted for any stratification variable and for trial stage. Additional adjustment variables will be described in the full statistical analysis plan. The number of powers selected in the fractional polynomial term will be a maximum of two. The risk ratio between the control 6-weekly arm and the other arms will be calculated using predictions from the fitted model. Uncertainty around these ratios will be estimated using bootstrap, by re-fitting the FPLG model within each bootstrap sample.

The furthest reduced frequency for which the whole confidence interval for risk ratio against 6-weekly is above the non-inferiority margin of 0.88 will be considered the optimal frequency. If this is not true for any of the active arms, 6-weekly will be considered the optimal frequency.

(iii)Secondary Endpoints Analysis

PFS will be analysed in the same framework as the primary outcome. Progression will be assessed longitudinally over time with 12 weekly imaging using RECIST v1.1 criteria to

enable calculation of the time to progression. Overall survival (OS), overall response rate (ORR) and duration of response (DOR) will additionally be evaluated.

QoL will be assessed 12 weekly, longitudinally over time. A linear mixed model will be used to obtain an estimate for the mean difference between treatment arms for continuous outcomes. Patients will be included as a random intercept and the model will include an arm, time-by-arm interaction and randomisation stratification variables as fixed effects. Model assumptions will be examined using residual analysis and examination of graphical displays such as normal quantile plots. Examination of subgroups will be specified *a priori* in the statistical analysis plan (SAP) and will be considered exploratory in nature.

(iv)Safety Analysis

Safety data analysis will be conducted on all subjects receiving at least one dose of pembrolizumab within the trial. The number and percentage of subjects experiencing an AE and the number of events will be summarized for each frequency reduced arm of the trial compared to the control 6 weekly arm. Information regarding severity will be examined with a focus on Grade 3-5 events using the Common Terminology Criteria for Adverse Events (CTCAE v5.0).

(v) Quality of life and health economic evaluation

A detailed analysis of the cost-effectiveness of this treatment will be undertaken using accepted methods applied to the trial data collection supplemented with estimates derived from the literature or expert opinion. We will analyse the cost-effectiveness using a short-term horizon (12 months) and construct a decision analytic model to calculate cost-effectiveness using a long-term horizon (expected lifetime of patients/long run model). The model will estimate costs of both alternatives from the NHS perspective. Cost components included in the analysis will be informed by the trial and will include consultant appointments, drug, pharmacy, drug administration, investigations (blood tests, CT scans) and costs to treat short- and long-term complications. Unit costs will be taken from standard sources (NHS payment by results, PSSRU-personal social services research unit, hospital data etc.). Quality adjusted life years (QALYs) will be measured using specific questionnaires for cancer (EORTC QLQ C30) and more specifically for lung cancer (EORTC QLQ LC13) as well as the EQ-5D-5L. We will estimate QoL values for each treatment frequency. The decision analytic model will provide an estimate of the incremental cost effectiveness ratio/cost per QALY (ICER) of the different reduced frequencies compared to the control 6 weekly treatment. Extensive sensitivity analysis will be performed to control for uncertainty in the data. Cost effectiveness acceptability curves will be constructed and extensive deterministic sensitivity analysis performed. The Net Monetary Benefit of the intervention and comparator will be assessed using the lower and upper threshold suggested by NICE.

(vi) Missing, Unused or Spurious Data

Any missing data in baseline covariates will be imputed with the mean if continuous and with the missingness indicator method if categorical.

Due to the way the outcome is defined, we do not expect many missing data in the outcome and any missingness will likely be driven by a mechanism unrelated to the outcome. Therefore, the primary analysis will only use patients with an observed outcome (Complete Case Analysis). Exploratory secondary analyses under different missingness assumptions and based on the use of Multiple Imputation will be considered and possibly described in the Statistical Analysis Plan.

We will also collect NHS, CHI or H&C number and date of birth from participants in order to access national databases such as NHS Digital to obtain data pertinent to the trial endpoints which is not available from the case report forms. As it currently stands this is not a service available for patients recruited in Northern Ireland but data will still be obtained in case this changes prior to the trial analysis.

9. REGULATORY, ETHICAL AND LEGAL ISSUES

9.1 Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformity with the 1964 Declaration of Helsinki and all subsequent revisions.

9.2 Good Clinical Practice

The study will be conducted in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 guidelines).

9.3 Research Ethics Committee (REC) Approval

(i) Initial Approval

Prior to the enrolment of patients, the REC must provide written approval of the conduct of the study at named sites, the protocol and any amendments, the Participant Information Sheet and Consent Form, any other written information that will be provided to the patients, any advertisements that will be used and details of any patient compensation.

(ii) Approval of Amendments

Proposed amendments to the protocol and aforementioned documents must be submitted to the REC for approval. Amendments requiring REC approval may be implemented only after a copy of the REC's approval letter has been obtained.

Amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented prior to receiving Sponsor or REC approval. However, in this case, approval must be obtained as soon as possible after implementation.

The sponsor trials team will make amendments and make the decision to amend the protocol and decide whether changes are substantial or non-substantial, with support from the Protocol Development Group where applicable. Changes will be communicated to stakeholders, including participating sites, electronically and be version controlled according to tracked changes and in accordance with the relevant standard operating procedures. The amended protocol will be reviewed by all members of the Protocol Development Group prior to finalising.

(iii) End of Trial Notification

The REC will be informed about the end of the trial, within the required timelines.

The end of trial notification will be submitted within 90 days of the end of trial definition being met. In the event of a premature halt of the trial, the timeframe is 15 days, and the reasons should be clearly explained in the notification.

9.4 Regulatory Authority Approval

The study will be performed in compliance with UK regulatory requirements. Clinical Trial Authorisation from the appropriate Regulatory Authority must be obtained prior to the start

of the study. In addition, the Regulatory Authority must approve amendments prior to their implementation (as instructed by the Sponsor), receive SUSAR reports and DSURs, and be notified of the end of the trial.

This study has a Clinical Trials Authorisation from the UK Competent Authority; MHRA. Reference: CTA 19174/0430/001

9.5 HRA approval

Health Research Authority (HRA) approval will be obtained prior to starting the study. Each participating site will confirm capacity and capability prior to commencing.

The HRA and all participating sites also need to be notified of all protocol amendments to assess whether the amendment affects the institutional approval for each site.

9.6 Other Required Approvals

The procedures are compliant with the Ionising Radiation (Medical Exposure) Regulations, and appropriate review by a Medical Physics Expert and Clinical Radiation Expert has been undertaken.

9.7 Non-Compliance and Serious Breaches

All protocol deviations and protocol violations will be reported via the eCRF and reviewed by the Chief Investigator and reported to the ICTU QA manager on a monthly basis. Protocol violations will be reported to the Sponsor. An assessment of whether the protocol deviation/violation constitutes a serious breach will be made.

A serious breach is defined as:
A breach of the conditions and principles of GCP in connection with a trial or the trial protocol, which is likely to affect to a significant degree:

- The safety or physical or mental integrity of the UK trial patients; or
- The overall scientific value of the trial

The Sponsor will be notified within 24 hours of identifying a likely Serious Breach. If a decision is made that the incident constitutes a Serious Breach, this will be reported to the MHRA and REC within 7 days of becoming aware of the serious breach.

9.8 Insurance and Indemnity and Sponsor

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

Imperial College London will act as the main Sponsor for this trial. Delegated responsibilities will be assigned to the NHS trusts taking part in the trial.

9.9 Trial Registration

The study will be registered on the following trial databases in accordance with requirements of the International Committee of Medical Journal Editors (ICMJE) regulations:

- Clinicaltrials.gov
- Cancer Research UK
- ISRCTN Registry

9.10 Informed Consent

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases, the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

If **written** informed consent is unable to be obtained, for example where the patient has full capacity to consent but is unable to write e.g. due to brain metastases/surgery, verbal consent may be used. Verbal consent is not permitted where the participant is able to sign the consent form.

An **impartial witness** should be present during the entire informed consent process and should complete their signature on the consent form on behalf of the patient. An impartial witness could be a family member, friend or another member of site staff **not involved** in the trial. If possible, with the participant's permission and resource available, documentation of the consent process using audio/video recording should be used.

The process should be documented thoroughly, including using **the REFINE-Lung witness statement template** in the participant's medical record. The participant should be provided with a copy of their witness signed consent form and witness statement along with the patient information sheet. Verbal consent will not affect the participants rights to withdraw from the trial.

If a participant was to lose the capacity to consent during their participation in the study, it would be the decision of the treating clinician as to whether they would continue treatment as per protocol. If the decision is to discontinue treatment, the participant would enter the follow-up period to collect data for the intention to treat (ITT) analysis. Consent to participate in the study is presumed to remain legally valid after loss of capacity (provided the protocol has not changed significantly since consent was obtained).

9.11 Contact with General Practitioner

It is the investigator's responsibility to inform the patient's General Practitioner (where applicable) by letter that the patient is taking part in the study provided the patient agrees to this, and information to this effect is included in the Participant Information Sheet and Informed Consent. A copy of the letter should be filed in the Investigator Site File.

9.12 Patient Confidentiality

The investigator must ensure that the patient's confidentiality is maintained. On the CRF or other documents submitted to the Sponsors, patients will be identified by a subject ID number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential file by the investigator.

The investigator shall permit direct access to patients' records and source documents for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor, NHS, Regulatory Authorities and RECs.

9.13 Data Protection and Patient Confidentiality

The investigators and study site staff will comply with the requirements of the Data Protection Act 2018 concerning the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

9.14 End of Trial

The end of the trial is defined as collection of the last data point for the last patient.

9.15 Study Documentation and Data Storage

The investigator must retain essential documents until notified by the Sponsor, and for at least ten years after study completion. Patient files and other source data (including copies of protocols, CRFs, original reports of test results, IMP dispensing logs, correspondence, records of written informed consent, and other documents pertaining to the conduct of the study) must be retained. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

9.16 Funding

The NIHR HTA Programme is funding this study. Funding allocated to sites is detailed in the participating site agreement. Requests and queries regarding payment should be sent to REFINE-Lung@imperial.ac.uk

10. DATA MANAGEMENT

10.1 Source Data

All original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial are classified as source data.

Source data are contained in source documents; these are defined as: original documents, data, and records e.g. hospital medical records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, radiological imaging, patient files, and records kept at the pharmacy, laboratories and any medico-technical departments involved in the clinical trial.

10.2 Language

CRFs will be in English. Generic names for concomitant medications should be recorded in the CRF wherever possible. All written material to be used by patients must use vocabulary that is clearly understood and be in the language appropriate for the study site. Patient information sheets, consent forms and quality of life questionnaires will be translated into a number of other languages used throughout the UK to ensure accessibility to all patients.

10.3 Database
The electronic case report form (eCRF) is in OpenClinica.

The method of entry and validation, procedure for raising queries, and other core data entry aspects will be detailed in a separate Data Management Plan held by sponsor and in eCRF Completion Guidelines circulated to participating sites.

10.4 Data Collection
In compliance with GCP, the medical records/notes should be clearly marked and allow easy identification of a patient's participation in the clinical trial.

The Investigator (or delegated member of the site study team) must record all data relating to protocol assessments and procedures, laboratory, safety and efficacy data in the eCRF. Details of procedures for eCRF completion will be provided in eCRF Completion Guidelines circulated to participating sites.

10.5 Archiving
All trial documentation, including that held at participating sites and the trial coordinating centre, will be archived for a minimum of 10 years following the end of the study.

11. STUDY MANAGEMENT STRUCTURE

11.1 Trial Steering Committee
A Trial Steering Committee (TSC) will be convened including as a minimum an independent oncologist Chair, independent oncologist, independent statistician, PPIE representatives, the Chief Investigator, the trial coordinator and the trial operations manager. The role of the TSC is to provide overall supervision of trial conduct and progress. Details of membership, responsibilities and frequency of meetings will be defined in a separate Charter.

11.2 Trial Management Group
A Trial Management Group (TMG) will be convened including the Chief Investigator, key co-investigators and collaborators, trial statistician, health economist, a pharmacist, the trial coordinator and the trial operations manager. The TMG will be responsible for day-to-day conduct of the trial and operational issues. Details of membership, responsibilities and frequency of meetings will be defined in separate terms of Reference.

11.3 Independent Data Monitoring Committee
An Independent Data Monitoring Committee (IDMC) will be convened to include as a minimum an independent oncologist chair, an independent oncologist and an independent statistician. The role of the IDMC is advisory to the TSC to ensure the highest standard of patient safety and data integrity, to include the interim analysis. Details of membership, responsibilities and frequency of meetings will be defined in a separate Charter.

11.4 Early Discontinuation of the Study
If the interim analysis shows PFS in the 12 weekly arm to be significantly worse than the 6 weekly control arm, the trial will be terminated as this will indicate there is no space to reduce dose-frequency substantially without significantly affecting efficacy. Additional stopping criteria will be defined by the IDMC, including a required procedure for future visits/assessments if the study needs to be discontinued early.

11.5 Risk Assessment

A study-specific risk assessment will be performed prior to the start of the study to assign a risk category of 'low', 'medium' or 'high' to the trial. Risk assessment will be carried out by the ICTU QA Manager in collaboration with the Study Coordinator and the result will be used to guide the monitoring plan. The risk assessment will consider all aspects of the study and will be updated as required during the course of the study.

In addition, a COVID-19 risk assessment has also been performed to assess the study aspects against required procedures, visits and vaccine administration.

11.6 Monitoring

The study will be monitored periodically by trial monitors to assess the progress of the study, verify adherence to the protocol, ICH GCP E6 guidelines and other national/international requirements and to review the completeness, accuracy and consistency of the data.

Monitoring will incorporate central, remote and on-site elements.

Monitoring procedures and requirements will be documented in a Monitoring Plan, developed in accordance with the risk assessment.

11.7 Quality Control and Quality Assurance

Quality Control will be performed according to ICTU internal procedures. The study may be audited by a Quality Assurance representative of the Sponsor, Imperial College London and/or ICTU. All necessary data and documents will be made available for inspection.

The study may be subject to inspection and audit by regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd Edition).

11.8 Peer review

Independent peer review of the study has been conducted by the funder, the NIHR HTA Programme.

Internal review has been conducted by Imperial College London as follows:

- The Imperial Clinical Trials Unit (ICTU) Collaborators Committee;
- Cancer Research UK Imperial Centre: Clinical Trials Section (CCTS) Oversight Committee;
- The TMG, including external collaborators.

11.9 Public Involvement

This study will use a PPIE Group of approximately 6 members to ensure a wide range of views and perspectives. The PPIE Group will provide invaluable feedback with regards to participant priorities e.g., the realities of cancer and its treatment, as well as understanding of whether or not the study is acceptable.

A PPIE Expectations Agreement document (based on CRUK template) will be drafted with the group to clarify PPIE roles and expectations and ensure clarity about payment of expenses. Feedback of PPIE involvement is encouraged to enable discussion if changes need to be made to the study.

PPIE involvement in the various phases of the study is briefly outlined as follows, to be detailed in full in the PPIE Expectations Agreement:

- Design of the research – review of protocol and all patient facing documentation;
- Management and undertaking of the research – advising on recruitment strategies, contribution to TSC meetings to include standing PPIE items on the agenda;
- Dissemination of results – production of a plain English summary, advising on avenues for dissemination.

11.10 Publication and Dissemination policy

The Consort Guidelines and checklist should be reviewed prior to generating any publications for the trial to ensure they meet the standards required for submission to high quality peer reviewed journals etc. http://www.consort-statement.org/

Participants will be notified of the outcome of the trial, the format of the dissemination will be based on guidance from the PPIE Group at the time.

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The investigator may use this information for the purposes of the study only.

It is understood by the investigator that the Sponsor will use information developed in this clinical study in connection with the development of the IMP/device and, therefore, may disclose it as required to other clinical investigators and to Regulatory Authorities. In order to allow the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the Sponsor.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor.

Therefore, all information obtained as a result of the study will be regarded as CONFIDENTIAL, at least until appropriate analysis and review by the investigator(s) are completed.

Permission from the Executive/Writing Committee is necessary prior to disclosing any information relative to this study outside of the Trial Steering Committee. Any request by site investigators or other collaborators to access the study dataset must be formally reviewed by the TSC.

The results may be published or presented by the investigator(s), but the Funder will be given the opportunity to review and comment on any such results for up to 1 month before any presentations or publications are produced

A Clinical Study Report summarising the study results will be prepared and submitted to the REC within a year of the end of study. The results will also be submitted to the EudraCT results database in accordance with regulatory requirements.

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13. REVISION HISTORY

Version	Date	Summary of changes
1.0	12/01/2022	First version
2.0	21/02/2022	• Update to section 9.10 regarding patients who lose capacity to consent during their participation in the study
3.0	10/05/2022	• Clarification over CI review of SAE/SUSAR expectedness & causality on behalf of the sponsor and ability to overrule & advise in section 7.10. • Clarification over the use of contraception post last dose of IMP added to section 5.2 • Clarification over visit windows for treatment visits in section 5.6 • Removal of mandatory pelvic scans in sections 5.5, 5.7 and 5.8 vii.
4.0	05/07/2022	• Update to section 5.2 to clarify the timing of the screening period around the number of cycles received as standard treatment prior to randomisation • Update to section 5.5, tables 3, 5, 6 and 7 to clarify the 12 weekly procedures are a different frequency to the randomised arm • Update to section 5.5, tables 3 - 7, section 5.7 and section 5.8 (iv) to clarify the physical exam can be symptom directed after baseline. • Removal of mandatory ALT and AST test, changed to either or both if completed as part of standard practice in sections 5.8 (vi) and tables 3-7. • Removal of the second planned interim analysis. A single interim analysis will take place at 37 PFS events and stage 2 will open at 15months from the first patient.
5.0	19/10/2022	• Section 5.8 vii has been updated to clarify centres that cannot perform RECIST should discuss their local reporting method with the sponsor. • Section 5.2 updated to allow for extension to the screening window around the 6 month landmark date in some circumstances which should be discussed with the REFINE-Lung team prior to randomisation. • Tables 3-7, section 5.2 and 5.4 have been updated to streamline the procedures required at screening, randomisation and first study dose. • Updates throughout the protocol (section 3.3 and table 2, section 5.8 xiii) to reduce the number of research samples collected. • Update to tables 5-7 to clarify assessment of adverse events and concomitant medications can be performed remotely at certain visits. • Clarification that QoL questionnaires can be completed remotely in section 5.8 xi • Inconsistencies with CTCAE version updated in section 8.3 iv

6.0	10/03/2023	• Section 3.3 updated to include the funding details for the translational sub-study. • Section 5.2 updated to allow consent to be taken at any point after starting treatment, rather than in the 6 weeks prior to randomisation. • Tables 3-7 updated to reflect the change in consent timing. • Section 5.8 updated to allow for procedures to be completed away from the participating site where this is standard practice for pembrolizumab administration at the site. • Section 5.8 vi and footers in Tables 3-7 updated to remove mandatory bicarbonate testing. • Section 5.8 vii updated to confirm CT scan image files are also collected. • Section 4.1 exclusion criteria updated to clarify patients with synchronous primary cancers should not be enrolled.
7.0	26/01/2024	• Updates to research bloods for the translational sub-study post randomisation in tables 3-7 visit and section 3.3 and 5.9 xiii. There is a reduction in the number of samples required. • Clarification the sub-study is optional and not all recruiting centres will take part in section 3.3. • Clarification of screening timelines when radiology outcomes are delayed in section 5.3 • Clarification of exclusion criteria regarding mixed responses, synchronous cancers and other clinical trials in section 4.1 iii • Rewording of identification and recruitment of patients in the main trial (section 5.1) after consent window was changed in the previous protocol version as this was erroneously missed. • Sub-study visit schedule (Table 2) updated to 2A and 2B to clarify the data required for the sub-study. Incorrect CT scan collection also removed from week 6. Previously only trial required procedures were listed, all visits for data collection now listed. • Section 5 reordered and additional detail added to section headers for easier understanding • Visit window added to end of treatment visit 28 days post last dose and follow-up visits in section 5.8 and Tables 3-7 footers. • Clarification regarding end of treatment vs end of study when reporting adverse events in section 7.8 and 7.8.1 • Clarification regarding SAE reporting between consent and randomisation in section 7.8 and 7.8.1

		at the request of the MHRA in the previous protocol amendment • Addition of AE and QoL reporting in the follow-up period to collect late emerging toxicities. • Clarification localised radiation for symptoms is permitted and should be recorded as a concomitant medication. • Addition of the collection of NHS number and change of month/year of birth to date of birth to access NHS databases in sections 5.9i and 8.3vi. • ISRCTN added and EC Finder removed from trial registration list in section 9.9 • Trial Coordinator name change in contact list • Addition of new Co-Investigators • Clarification the IDMC has the ability to bring forward the interim analysis if recruitment is slower than expected. • Clarification in the footers of Tables 4-7 that re-escalation to standard of care is the control arm and patients can remain in the trial.
8.0	12/11/2024	• Updates to the trial summary to reflect changes throughout including the recruitment period. • Clarification that more sites will be opened if funding is available in section 3.1. • Changes to the sample size required in sections 3.2 and 8.1, flow chart (figure 1) updated. • Clarification how 12 weekly follow-up visits should be calculated in section 5.8 5.9 xii and footer 17 of tables 3-7. Section 5.8 also amended to clarify the EoT should be completed wherever possible to be consistent with section 6.12. • Removal of the requirement of follow-up CT scans to be reported via RECIST V1.1 in section 5.8 and footer 18 of tables 3-7 as this was an error. • Clarification that AEs in the follow-up period can be collected from medical records in section 5.8, 5.9 ix and footer 21 or 22 of tables 3-7. • Clarifications that protocol assessments that are SOC may be completed by any trained member of the site staff as long as the data is available for the research team for data entry in section 5.9. • Clarification that AEs can be assessed by any patient facing member of the delegated research team in section 5.9 ix. • Clarification that all concomitant medications the patient is taking must be recorded in section 5.9 x. • Addition of guidance regarding delays to cycles to align with NHS guidance for pembrolizumab administration in section 6.9.

		• Reminder added to section 6.12 regarding patients remaining in trial follow-up to obtain primary endpoint data. • Changes to record AEs and SAEs from first trial dose rather than randomisation in section 7.8. • Removal of references to APRs in 7.11 header and whole section 9.3 iii. • Changes to the planned recruitment rate in Section 8.2 • Changes to the statistical analysis plans in Section 8.3 • Addition of H&C number for Northern Ireland participants and clarification that currently access to NHS records in Northern Ireland is not possible but data will be collected in case this changes prior to analysis in section 8.3 vi. • Removal of reference to shipment of IMP in section 9.3 i. • Addition of verbal consent in section 9.10 for scenarios where written consent is not possible. • Changes to the frequency of thyroid function tests to align with other pre-cycle blood testing

SIGNATURE PAGE 1 (CHIEF INVESTIGATOR)

The signature below constitutes approval of this protocol by the signatory, on behalf of the Protocol Development Group, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: A randomised open-label phase III trial of REduced Frequency pembrolizumab immuNothErapy for first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) utilising a novel multi-arm frequency-response optimisation design

Protocol Number: C/41/2021

Signed: _____

Professor Michael Seckl
Professor of Molecular Cancer Medicine

Date: _____

SIGNATURE PAGE 2 (SPONSOR)

The signatures below constitute approval of this protocol by the signatory.

Study Title: A randomised open-label phase III trial of REduced Frequency pembrolizumab immuNothErapy for first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) utilising a novel multi-arm frequency-response optimisation design

Protocol Number: C/41/2021

Signed: _____

Name: _____
Head of Research Governance and Integrity
Imperial College London

Date: _____

SIGNATURE PAGE 3 (STATISTICIAN)

The signatures below constitute approval of this protocol by the signatory.

Study Title: A randomised open-label phase III trial of REduced Frequency pembrolizumab immuNothErapy for first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) utilising a novel multi-arm frequency-response optimisation design

Protocol Number: C/41/2021

Signed: _____

Dr Matteo Quartagno
Senior Research Fellow
Medical Research Council (MRC) Clinical Trials Unit

Date: _____

SIGNATURE PAGE 4 (PRINCIPAL INVESTIGATOR)

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: A randomised open-label phase III trial of REduced Frequency pembrolizumab immuNothErapy for first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) utilising a novel multi-arm frequency-response optimisation design

Protocol Number: C/41/2021

Address of Institution: _____

_____

_____

Signed: _____

Print Name and Title: _____

Date: _____

APPENDIX 1: ECOG PERFORMANCE STATUS

ECOG Grade		Performance Status
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 housework, 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

As published in Am J Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity and Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

APPENDIX 2: RECIST V1.1 CRITERIA

The following is taken from Eisenhauer et al, New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1), European Journal of Cancer, 45 (2009), 228-247.

At baseline, tumour lesions/lymph nodes will be categorised measurable or non-measurable as follows:

Measurable

Tumour lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

• 10 mm by CT scan (CT scan slice thickness no greater than 5 mm.

• 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

• 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

Non-measurable

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

• Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

• Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.

• Blastic bone lesions are non-measurable.

Cystic lesions:

• Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

• 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

• Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Specifications by methods of measurements

Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of assessment

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s)

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilisation of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumour markers: Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalise for a patient to be considered in complete response. Because tumour markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecological Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumour assessment for use in first-line trials in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumour has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Tumour response evaluation

Assessment of overall tumour burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the *overall tumour burden at baseline* and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. In studies where the primary endpoint is tumour progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as *target lesions* and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a *maximum* of two and four lesions respectively will be recorded). For evidence to support the selection of only five target lesions, see analyses on a large prospective database in the article by Bogaerts et al.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the *short* axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the *baseline sum diameters*. If lymph nodes are to be included in the sum, then as noted above, only the *short* axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Response criteria

Evaluation of target lesions:

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (*Note*: the appearance of one or more new lesions 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 diameters while on study.
Special notes on the assessment of target lesions:
Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.
Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (*Note*: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.
Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.
Evaluation of non-target lesions:
While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only *qualitatively* at the time points specified in the protocol.
Complete Response (CR): Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.
Progressive Disease (PD): *Unequivocal progression* of existing non-target lesions (*Note*: the appearance of one or more lesions is also considered progression).
Special notes on assessment of progression of non-target lesions:

The concept of progression of non-target disease requires additional explanation as follows: *When the patient also has measurable disease*. In this setting, 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. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression *solely* on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumour burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localised to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

New lesions:

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b) No FDG-PET at baseline and a positive FDG-PET at follow up:

If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing of the basis of the anatomic images, this is not PD.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.
Time point response:
It is assumed that at each protocol specified time point, a response assessment occurs.
Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.
Missing assessments and inevaluable designation:
When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.
Best overall response: all time points
The *best overall response* is determined once all the data for the patient is known.
Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.
Special notes on response assessment:
When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).
The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is

reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Table 1 – Patients with target (+/- non-target) disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Table 2 – Patients with non-target disease only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

a ‘Non-CR/non-PD’ is preferred over ‘stable disease’ for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.