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Investigating the duration of anti-PD1 monoclonal antibody treatment for metastatic melanoma

DANTE

A randomised phase III trial to evaluate the Duration of ANti-PD1 monoclonal antibody Treatment in patients with metastatic mElanoma

Sponsor: Sheffield Teaching Hospitals NHS Foundation Trust [STH19290]

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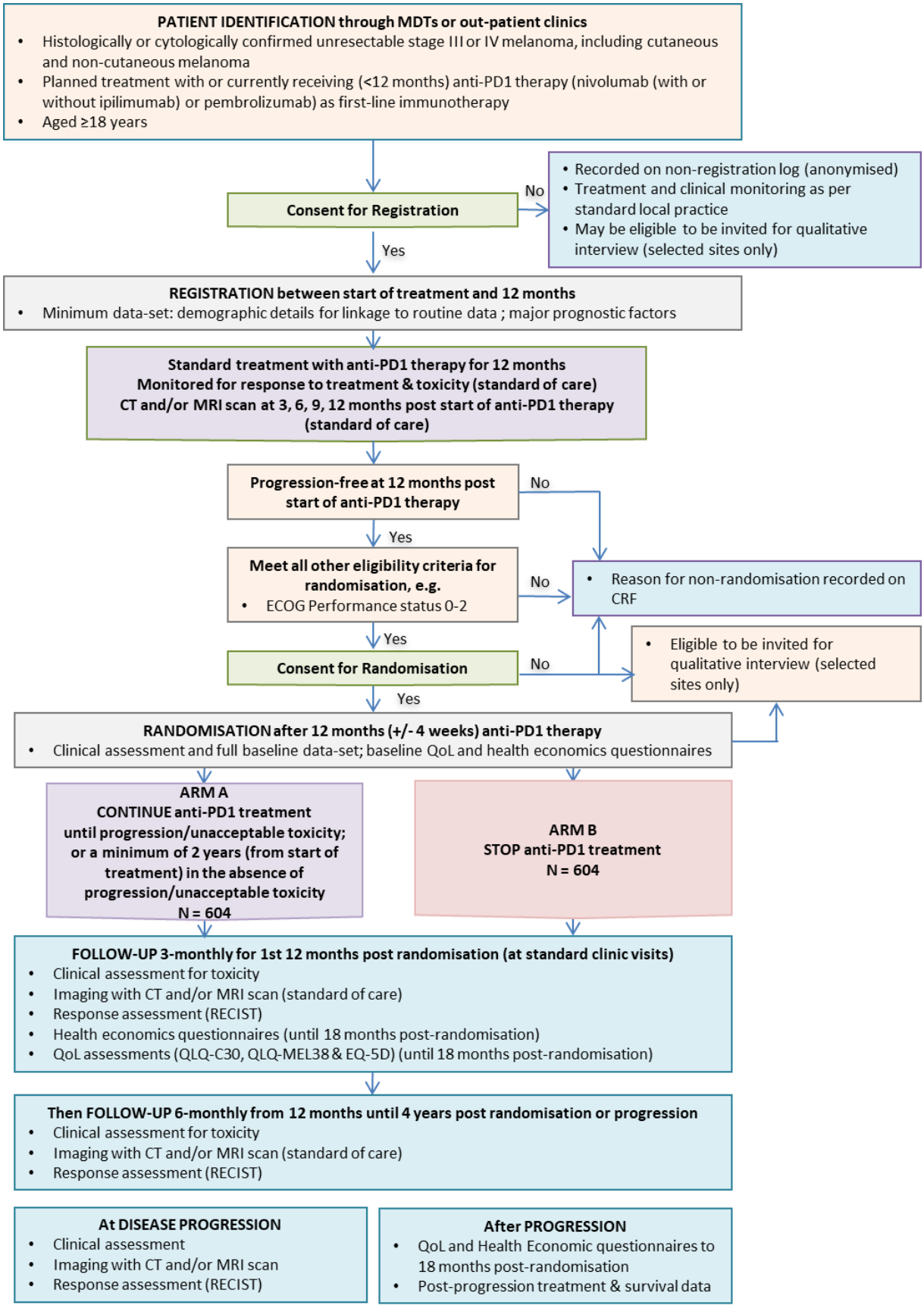
2 Table of Contents

3 Trial Summary

Title	A randomised phase III trial to evaluate the Duration of ANti-PD1 monoclonal antibody Treatment in patients with metastatic mElanoma
Acronym	DANTE
EudraCT no.	2017-002435-42
ISRCTN no.	15837212
IRAS ID:	230556
Sponsor	Sheffield Teaching Hospitals NHS Foundation Trust
Funder	National Institute for Health Research (NIHR), Health Technology Assessment Programme Grant Ref: 15/57/66
Population	Registered: Adults with advanced (unresectable stage III or stage IV (metastatic)) melanoma who are commencing or who have received less than 12 months of anti-PD1 therapy (nivolumab, with or without ipilimumab, or pembrolizumab) as their first-line immunotherapy treatment. Randomised: Adults with advanced (unresectable stage III or stage IV (metastatic)) melanoma who have received 12 months of anti-PD1 therapy (nivolumab, with or without ipilimumab, or pembrolizumab) as their first-line immunotherapy treatment and who are progression-free at 12 months.
Sample size	1208 patients over 5 years
Design	Multi-centre, randomised, controlled, multi-stage, non-inferiority trial (two arm trial)
Objectives	To evaluate whether 1st line anti-PD1 therapy of 12 months total duration can achieve and maintain as good an outcome in terms of efficacy and patient acceptance, and improves QoL, tolerability, safety and cost, as 1st line anti-PD1 therapy given until disease progression or unacceptable toxicity.
Intervention	Patients will be randomised to one of the two treatment arms: • Current standard practice: Anti-PD-1 therapy until disease progression or unacceptable toxicity; or a minimum of 2 years (from the start of treatment) in the absence of disease progression or unacceptable toxicity (control arm) or • 12 months of anti-PD-1 therapy (i.e. no further treatment following randomisation)
Follow-up	3-monthly imaging (CT and/or MRI) and clinical assessment until 12 months post randomisation, then 6-monthly CT and/or MRI until 4 years post randomisation.
Primary endpoint	• Progression-free survival (Time to progression will be assessed in a sensitivity analysis to the primary endpoint)
Secondary endpoints	• Quality of life (key secondary) • Overall survival • Objective response rate • Best tumour response rate • Duration of response • Cost effectiveness • Safety
Exploratory endpoints	• Biomarkers of treatment response and toxicity* *subject to a separate funding application and protocol amendment
Definition of end of trial	The end of the trial is defined as the date of the collection of the last participant data item.

Figure 3.1: Trial Schema



4 Abbreviations

Abbreviation	Definition
AE	Adverse event
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
APL	Authorised personnel log
AR	Adverse reaction
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
BRAF	A human gene that encodes a protein called B-Raf
CHI	Community Health Index
CI	Confidence Interval Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CSG	Clinical Studies Group
CT	Computerised tomography
CTA	Clinical Trial Authorisation
CTCAE	Common Toxicity Criteria for Adverse Events
CTRU	Clinical Trials Research Unit
CV	Curriculum vitae
CYP	Cytochrome P450
DANTE	A randomised phase III trial to evaluate the Duration of ANti-PD1 monoclonal antibody Treatment in patients with metastatic mElanoma
DMEC	Data Monitoring and Ethics Committee
DNA	Deoxyribonucleic acid
ECOG	Eastern Co-operative Oncology Group
eMC	electronic Medicines Compendium
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
EudraCT	European Clinical Trials Database
FBC	Full blood count

GCP	Good Clinical Practice
GP	General Practitioner
H&C	Health and care
HES	Hospital Episode Statistics
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRA	Health Research Authority
HTA	Health Technology Assessment
ICMJE	International Committee of Medical Journal Editors
ID	Identification
IMP	Investigational medicinal product
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention to treat
LDH	Lactate dehydrogenase
LFTs	Liver function tests
MAP	Mitogen-activated protein
MEK	Mitogen-activated protein kinase kinase
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NCRI	National Cancer Research Institute
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NSCLC	Non-small cell lung cancer
ONS	Office for National Statistics
ORR	Objective response rate
OS	Overall survival
PD1	Programmed cell death-1
PD-L1	Programmed death ligand 1
PFS	Progression-free survival

PI	Principal Investigator
PIN	Personal identification number
PIS	Patient information sheet
PPI	Patient and public involvement
QALY	Quality-adjusted life year
QoL	Quality of life
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria In Solid Tumours
RGF	Research Governance Framework
SACT	Systemic anti-cancer therapy
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SAR	Serious Adverse Reaction
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TA	Technology Assessment
TMG	Trial Management Group
TSC	Trial Steering Committee
TSH	Thyroid stimulating hormone
U&Es	Urea and electrolytes
UK	United Kingdom

5 Introduction

5.1 Melanoma

Melanoma is the most aggressive form of skin cancer. In the UK, incidence and mortality rates are doubling every 10-20 years with 15,419 new cases and 2,459 deaths in 2014[1]. In its early stages, melanoma can be cured by surgery. However, it can metastasise to nearby lymph nodes (stage III) or to other parts of the body (stage IV) and, without treatment, median life expectancy is 8 months. Until 2011, no anticancer drugs improved survival for advanced melanoma patients. Since then, two classes of novel agents, immune checkpoint inhibitors and, for those patients with BRAF mutant melanoma, MAP kinase pathway inhibitors, have improved outcomes, extending median survival to around 3 years. Both classes of drugs are approved by the National Institute for Health and Care Excellence (NICE) for routine use. Checkpoint inhibitors are a treatment option for metastatic melanoma patients, irrespective of genotype. Two classes are currently in clinical use: anti-CTLA4 and anti-programmed death receptor 1 (PD1) antibodies. Of these, the most active are anti-PD1 antibodies.

5.2 Immune checkpoint inhibition in cancer therapy

Immunotherapy is cancer treatment, which is designed to boost the body's own defences to fight cancer. 'Switching on the immune system' is a strategy that should work in melanoma because sometimes melanomas spontaneously regress, melanomas are often surrounded by inflammatory cells, and vitiligo has been associated with tumour regression.

CTLA4 is a protein receptor expressed on regulatory T cells, which inhibits early T cell activation. PD1 is expressed on antigen-stimulated T cells in the blood and induces downstream signalling that inhibits T-cell proliferation, cytokine release and cytotoxicity. Melanoma, and other cancers, suppress cytotoxic T-cell activity by expressing PD1 ligand (PDL1) on the cell surface. Antibodies targeting CTLA4, PD1 and PD-L1 can reverse T-cell suppression and induce long-lasting anti-tumour responses.

5.3 Immune checkpoint inhibitors in melanoma

There has been extensive evaluation of non-specific immunotherapies against melanoma, such as interferon (low and high dose) and interleukin, in both the adjuvant and metastatic setting. Whilst sustained responses have been seen in some cases, survival gains are limited so these cytokines have not become established as standard of care. More recent studies have investigated the efficacy and tolerability of specific immune checkpoint inhibitors.

5.3.1 Ipilimumab

Ipilimumab was the first checkpoint inhibitor to enter the clinic and the first non-surgical treatment to extend survival of metastatic melanoma patients. Ipilimumab is a highly selective humanised monoclonal antibody against CTLA4. Ipilimumab alone or in combination with gp100 is more active than gp100 in patients with melanoma who have progressed after previous systemic therapy[2]. This study showed a survival advantage of 3.5

months when comparing ipilimumab alone vs gp100 (overall survival of 10.1 versus 6.4 months; Hazard ratio (HR) for death, 0.66; p=0.003). The progression-free survival (PFS) was similar for all 3 groups at 12 weeks, but then the curves separated. Grade 3 or worse immune-mediated adverse events occurred in 10-15% of patients treated with ipilimumab compared with 3% treated with gp100 alone, with seven associated deaths (in 676 patients) from colitis and Guillain-Barre syndrome. The subsequent trial of ipilimumab+dacarbazine compared with dacarbazine as first line treatment also showed improved survival of 11.2 versus 9.1 months (HR 0.72; p<0.001) and reconfirmed the adverse event profile, although there were no drug attributable deaths as the oncology community was very proactive in treating immune-mediated toxicities[3]. NICE approved ipilimumab as first and second line therapy in 2014 and 2012, respectively[4 5].

5.3.2 Anti-PD1 therapy

Published data on the anti-PD1 therapies, pembrolizumab and nivolumab, show that these are more active than ipilimumab, with higher response rates, better tolerance and longer survival. Pembrolizumab and nivolumab have been approved by NICE as both first and second line therapy[6 7].

5.3.3 Clinical trials with pembrolizumab

Pembrolizumab was first tested in patients who progressed after ipilimumab. KEYNOTE-001[8 9] confirmed the dose of pembrolizumab and generally mild-moderate side-effects such as fatigue, rash, arthralgia and gastrointestinal disturbance. Immune-mediated adverse reactions included pneumonitis, colitis, thyroiditis, hepatitis and neuropathy. An expansion cohort of patients with advanced melanoma randomised 173 patients to pembrolizumab at 2 mg/kg or 10 mg/kg every 3 weeks until disease progression[10]. The objective response rate (ORR) was 26% with median PFS of 22 weeks (95% CI 12-36 weeks) in the 2 mg/kg dose group and 14 weeks (95% CI 12-24 weeks) with 10 mg/kg.

KEYNOTE-002[11] randomised 540 patients with ipilimumab-refractory melanoma to pembrolizumab (2mg/kg or 10mg/kg) or investigator choice chemotherapy. Pembrolizumab 2 mg/kg administered as a 3-weekly infusion significantly improved PFS (HR 0.57, 95% CI 0.45-0.73, p<0.0001) compared to chemotherapy, and this was also true for the pembrolizumab 10mg/kg arm. 6-month PFS was 34% (95% CI 27-41%) in the pembrolizumab 2 mg/kg group, 38% (31-45%) in the 10 mg/kg group, and 16% (10-22%) in the chemotherapy group. Treatment-related grade 3-4 adverse events occurred in 20 (11%) patients in the pembrolizumab 2 mg/kg group, 25 (14%) in the pembrolizumab 10 mg/kg group, and 45 (26%) in the chemotherapy group. The most common treatment-related grade 3-4 adverse event in the pembrolizumab groups was fatigue (two [1%] of 178 patients in the 2 mg/kg group and one [<1%] of 179 patients in the 10 mg/kg group, compared with eight [5%] of 171 in the chemotherapy group). Other treatment-related grade 3-4 adverse events with pembrolizumab included generalised oedema and myalgia (each in two [1%] patients) in those given pembrolizumab 2 mg/kg, and hypopituitarism, colitis, diarrhoea, decreased appetite, hyponatremia, and pneumonitis (each in two [1%]) in those given pembrolizumab 10 mg/kg. Median overall survival (OS), 18 month and 24 month OS rates were greater with pembrolizumab, but did not reach statistical significance[12], as patients could cross over on progression.

KEYNOTE-006[13] compared pembrolizumab (2 mg/kg every 2 or 3 weeks for up to 24 months) to ipilimumab in patients with advanced melanoma who had received no more than 1 prior systemic therapy. The trial randomised 834 patients, 66% of whom were treatment-naive. The estimated 6-month PFS rates were 47.3% for pembrolizumab every 2 weeks, 46.4% for pembrolizumab every 3 weeks, and 26.5% for ipilimumab (HR 0.58, p<0.001 for both pembrolizumab regimens versus ipilimumab; 95% CIs 0.46-0.72 and 0.47-0.72, respectively). Estimated 12-month survival rates were 74.1%, 68.4%, and 58.2%, respectively (HR for pembrolizumab every 2 weeks, 0.63, 95% CI 0.47-0.83, p=0.0005; HR for pembrolizumab every 3 weeks, 0.69, 95% CI 0.52-0.90, p=0.0036). The response rate was improved with pembrolizumab administered every 2 weeks (33.7%) and every 3 weeks (32.9%), as compared with ipilimumab (11.9%) (p<0.001 for both comparisons). The median time to response was similar in all groups: 86 days (range 32-212 days) and 85 days (range 36-251 days) with pembrolizumab every 2 and 3 weeks, and 87 days (range 80-250 days) with ipilimumab. Responses were ongoing in 89.4%, 96.7%, and 87.9% of patients, respectively, after a median follow-up of 7.9 months. Pembrolizumab was less toxic than ipilimumab: rates of grade 3-5 treatment-related adverse events were lower in the pembrolizumab groups (13.3% and 10.1%) than in the ipilimumab group (19.9%). Updated long-term results after a median follow-up of 33.9 months were presented at the 2017 ASCO Annual Meeting[14]. These showed that the 33-month OS rate was 50% with pembrolizumab (pooled analysis of both arms) vs. 39% with ipilimumab, and PFS rates were 31% and 14% respectively.

5.3.4 Clinical trials with nivolumab

Nivolumab was compared against chemotherapy in ipilimumab-refractory disease in CHECKMATE-037[15]. Patients had an ORR with nivolumab of 31.7% vs 10.6% for chemotherapy. Grade 3/4 drug-related toxicities occurred in 5% on nivolumab vs 9% on chemotherapy with no treatment-related deaths. Patients with BRAF wild type melanoma who had previous immunotherapy were enrolled into CHECKMATE-066[16] and randomised to receive nivolumab or standard dacarbazine chemotherapy. One-year survival was significantly higher for patients receiving nivolumab: 72.9% vs 42.1% (HR 0.42, 99.79% CI 0.25-0.73, p<0.01). Median PFS was 5.1 vs 2.2 months (HR 0.43, 95% CI 0.34-0.56, p<0.001), ORR 40.0% vs 13.9% (odds ratio 4.06, p<0.001), and severe toxicity 11.7% vs 17.6%. The survival benefit with nivolumab versus dacarbazine was observed across pre-specified subgroups, including subgroups defined by tumour expression of PD-L1.

In CHECKMATE-067[17], 945 previously untreated advanced melanoma patients were randomised to receive nivolumab alone, in combination with ipilimumab, or ipilimumab alone. Nivolumab alone or in combination resulted in significantly longer PFS than ipilimumab alone (6.9 vs 11.5 vs 2.9 months; HR 0.42 for nivolumab-ipilimumab compared to ipilimumab alone and 0.52 for nivolumab monotherapy versus ipilimumab; the study was not powered for a direct comparison between the combination arm and nivolumab alone). The combination arm was very toxic, with 55.0% of patients experiencing grade 3 or more adverse events compared with 16.3% of patients on nivolumab alone. Nivolumab alone had an ORR of 44% and disease stabilisation was seen in 11% of patients. Median time to response was similar between arms, and was 2.78 months (range 2.3-12.5 months) in the nivolumab alone arm. In the combination arm, the median number of doses of nivolumab was 4 (range 1-39) and only 47% of patients received more than 4 doses of nivolumab monotherapy after combination. 68.8% of patients who discontinued the combination therapy due to toxicity achieved either a

complete or partial response. Updated long-term results after a minimum follow-up of 60 months showed that the 5-year OS rates were 52% in the combination arm, 44% in the nivolumab alone arm, and 26% in the ipilimumab arm[18]. There were 2 treatment-related deaths in the combination arm and one each in the nivolumab and ipilimumab monotherapy arms.

NICE has approved the use of the combination ipilimumab + nivolumab regimen as a first line treatment[19]. However, the incremental gain in efficacy must be weighed against a substantially greater risk of severe, life threatening and life changing toxicities with a high rate of hospitalisation. This trade-off is particularly relevant in an ageing population and for those who are symptomatic at presentation. Therefore, although it is anticipated that the numbers of patients treated with the combination regimen will rise over time, the majority of patients are likely to continue to receive an anti-PD1 antibody as monotherapy as their first line treatment for the foreseeable future.

In summary, for both pembrolizumab and nivolumab given as first line immunotherapy, approximately 40% of patients with advanced melanoma are likely to have a reduction in tumour burden, with many responses being profound and durable, while a further 12-14% will experience stable disease. From the emerging data, over 50% of patients who achieve at least disease stabilisation initially remain progression-free, and thus on continuous treatment, for 2 years or more. However, presented data on both combination ipilimumab + nivolumab and single agent pembrolizumab has shown that patients who need to stop treatment for toxicity may have very durable responses[20 21], suggesting that continuous repeated infusions may not be biologically necessary.

5.4 Anti-PD1 therapy in routine clinical practice

Currently, two anti-PD1 therapies, pembrolizumab and nivolumab, are licensed for the first line treatment of advanced melanoma in adults in Europe. According to the Summary of Product Characteristics, the recommended duration of treatment is:

- Pembrolizumab - until disease progression or unacceptable toxicity
- Nivolumab (either as monotherapy or in combination with ipilimumab) – as long as clinical benefit is observed or until treatment is no longer tolerated by the patient

Following publication of the NICE technology appraisal guidance TA366[6], TA384[7],and TA400[19], nivolumab (with or without ipilimumab) or pembrolizumab have been recommended as a first-line immunotherapy option for patients with advanced (unresectable or metastatic) melanoma. In their consideration of the evidence, NICE noted that there was uncertainty about the optimum duration of treatment with both drugs, but that there was limited evidence to determine it, and so recommended treatment in line with the marketing authorisation. In practice, the anti-PD-1 inhibitors are given for as long as there is clinical benefit, for up to a total duration of 2 years.

5.5 Evidence for duration of immune checkpoint inhibition

Ipilimumab is administered over 12 weeks, as 4 x 3-weekly infusions. In contrast, pembrolizumab and nivolumab are licensed for continuous treatment until disease

progression. Clinical trials suggest that around 40% of patients are progression-free, and therefore can expect to continue treatment, beyond 2 years[13 22]. The question as to whether anti-PD1 therapy needs to be continuously administered to generate an immune response is taxing the global oncology community. There is no biological evidence that justifies continuous therapy. Continuous administration generates a significant burden to patients and the NHS.

Currently, there is no direct evidence to determine the optimal duration of anti-PD1 therapy in melanoma. Observations from completed clinical trials suggest that treatment may not need to be continuously administered until disease progression. Patients who discontinue treatment prior to progression, e.g. for toxicity, can achieve or maintain a good response without drug[13 20-22]. In the phase 1 trial of pembrolizumab (Keynote 001), melanoma patients who achieved a complete response were permitted to stop drug. 105/655 (17%) of patients had a complete response; 67/105 stopped pembrolizumab while still in complete response (most due to patient choice). The 24-month disease free survival rate from time of complete response was ~90% in both all 105 patients and the 67 who stopped treatment[23]. In Keynote-006, the planned duration of treatment with pembrolizumab was 24 months. Data presented at the 2017 ASCO Annual Meeting show that responses were maintained following treatment completion[14]. In that study, 104/556 (19%) patients completed the planned course of pembrolizumab. After a median follow-up of 9.0 months following completion of pembrolizumab, the PFS rate was 91% (95% CI 80-96%) in all 104 patients; 95% (95% CI 69-99%) in 24 patients in complete response, 91% (95% CI 74-97%) in 68 patients in partial response, and 83% (95% CI 48-96%) in the 12 patients with stable disease as their best response who had completed 24 months of treatment. These results suggest that disease control can be maintained without drug in patients who have had partial response or stable disease as their best response, as well as those who have had a complete response.

The CHECKMATE-153 study has compared treatment until progression with 12 months of nivolumab in advanced non-small cell lung cancer (NSCLC), and is the first randomised study evaluating duration of anti-PD1 therapy. In this study 220/1245 patients still on nivolumab after 12 months were randomised to continue until progression or stop treatment; patients in the discontinuation arm could re-start nivolumab at progression. Initial results were presented at the 2017 ESMO Congress[24] and reported better PFS with continuous vs. 12 months treatment, median PFS not reached vs. 10.3 months (95% CI 6.4-15.2), HR 0.42 (95% CI 0.25-0.71). Overall survival results were immature but did not currently show a statistically significant difference between the treatment arms, HR 0.63 (95% CI 0.33-1.20). The primary objective of CHECKMATE-153 was to investigate the safety of nivolumab in NSCLC (a stage IIIb/IV trial) in the whole trial population enrolled at the start of treatment. The number of patients who were still receiving anti-PD1 therapy at 12 months and eligible for this randomisation was small, and the results are immature. It is not clear whether these findings can be generalised to other tumour types. These data taken in context with the observations from trials of anti-PD1 therapy in melanoma described above support the need for additional randomised studies evaluating treatment duration in melanoma, and other tumour types.

The optimal duration of treatment with either pembrolizumab or nivolumab is now a major priority question to be addressed. A Canadian study (STOP GAP; NCT02821013) is currently assessing the potential to stop treatment after maximal tumour response. This

relatively small study primarily focuses on the role of rechallenge rather than the specific question of optimal duration of treatment. The DANTE trial is designed to evaluate whether, in those patients who are progression-free after 12 months of treatment, stopping treatment results in non-inferior clinical efficacy outcomes compared with continuing on treatment beyond 12 months. Consenting patients will be randomised to either stop or continue their treatment until progression/unacceptable toxicity or a minimum of 2 years (from the start of treatment) in the absence of disease progression/unacceptable toxicity, and the 2 arms will be compared in terms of efficacy, QoL, patient acceptance of randomisation, treatment tolerance, safety and health economics. Subject to separate funding applications, potential radiological and biological markers predictive of key efficacy and toxicity outcomes will also be assessed.

5.6 Rationale for study

Most responses to anti-PD1 antibodies occur within 6 months of starting treatment and there are multiple examples of patients continuing to respond when treatment has been stopped due to toxicities or patient choice. Treatment until progression represents a significant burden on patients and health service resources. We aim to show that reducing the length of treatment does not negatively impact survival and improves QoL for patients and cost effectiveness of these high cost drugs. We have chosen 12 months as the point to stop as most patients have achieved their best response by 1 year on treatment and the progression-free survival event rate slows after this time point[25]. It was therefore considered to be an acceptable time point for patients and clinicians to stop treatment.

DANTE is designed to compare reduced duration anti-PD1 therapy to standard practice. Therefore, we have been pragmatic in choice of the control arm, which is defined as treatment until progression/unacceptable toxicity in accordance with the Marketing Authorisation for both drugs, or a minimum of 2 years (from the start of treatment) in the absence of disease progression/unacceptable toxicity to reflect changing practice in response to data from the Keynote-006 trial[13 14].

This research is timely because anti-PD1 therapy for advanced melanoma has recently entered routine clinical practice both in the UK, following approval of both pembrolizumab and nivolumab for this indication by NICE[6 7 19](and pembrolizumab by the Scottish Medicines Consortium)[26], and internationally. There is no biological evidence that justifies continuous therapy, while patients who have discontinued therapy prior to progression may maintain a good response without drug. Uncertainty and lack of evidence of the required duration of therapy was noted by NICE in their guidance on both pembrolizumab and nivolumab[6 7]. The question of duration of anti-PD1 therapy is one that is currently taxing the global oncology community and any data generated into this question will be of interest worldwide. Anti-PD1 therapy is active against a large number of other cancer types so results from this trial will inform future use of these agents across the whole spectrum of cancer types.

We calculate that the cost of this trial will represent a saving of up to £39 million compared with patients receiving standard treatment off trial. If this trial demonstrates that 12 months of treatment is not inferior to treating until disease progression, this could represent a cost saving of £76 million per year for the NHS in advanced melanoma alone and may have an impact on use of checkpoint inhibitors in other cancer types.

5.7 Biomarkers of response and toxicity

Immune checkpoint inhibitors offer potentially life-saving treatment for some patients receiving these drugs. However, it is clear from multiple clinical trials that over half of patients receiving anti-PD1 antibody therapy[27] do not benefit and are therefore exposed to risks of toxicity unnecessarily. Currently, there are no early response biomarkers that can identify and predict those patients who will not respond to treatment, nor those patients who might be more likely to experience severe treatment-related toxicities, in whom treatment might best be avoided. Based on the receptor-ligand interaction, there has been much interest in evaluating the predictive value of tumour PD-L1 expression, but, its value remains uncertain. PD-L1 positivity is associated with improved overall response rate, PFS and OS, but around 10% of patients whose tumours are PD-L1 negative also benefit and achieve durable responses similar to PD-L1 positive cohorts[28]. Other groups have searched for genetic signatures that predict for outcomes. High tumour mutational load has been associated with, although not predictive of, improved survival[29], while circulating tumour DNA measured at baseline and within 12 weeks of starting anti-PD-1 therapy was recently reported to predict for response[30]. Other genomic and non-genomic features are likely also to contribute to response patterns[31]. Recent preclinical and clinical data suggest that the gut microbiota may influence response to and toxicity from melanoma immunotherapy[32 33]. Culturing and gene sequencing of gut flora in stool samples before and during treatment may be informative to generate predictive biomarkers as well as potential novel therapeutic interventions in the future. In this study, we will seek patient consent to access any archival tumour samples collected prior to study entry. Subject to a separate funding application and protocol amendment, we will take the opportunity to collect additional tumour tissue as well as blood and stool prior to, during and on stopping anti-PD1 therapy, in order to comprehensively study a variety of potential biomarkers predicting for treatment response, non-response and toxicity.

6 Aims and Objectives

6.1 Aims

The aim of this study is to evaluate whether patients with advanced melanoma receiving first line anti-PD-1 therapy can achieve and maintain as good an outcome if they receive 12 months total treatment duration compared with standard treatment duration, i.e. until disease progression or unacceptable toxicity, or a minimum of 2 years (from the start of treatment) in the absence of disease progression or unacceptable toxicity.

6.2 Primary objective

The primary objective is to determine whether reduced duration therapy is non-inferior to standard treatment in terms of progression-free survival (PFS).

6.3 Secondary objectives

The key secondary objective is to evaluate the different strategies' effect on patients' quality of life (QoL) and determine whether reduced duration therapy achieves superior QoL outcomes.

Other secondary objectives are:

- to determine whether overall survival (OS) is non-inferior when using reduced duration therapy
- to determine whether the proportion of patients who experience a response after randomisation, and the duration of response, are non-inferior when anti-PD-1 therapy is stopped at 12 months compared to current standard practice (continued until progression or unacceptable toxicity, or for a minimum of 2 years (from the start of treatment) in the absence of disease progression or unacceptable toxicity)
- to compare safety and toxicity of the two treatment strategies
- to evaluate the cost-effectiveness of the two strategies

6.4 Exploratory objectives

Subject to securing appropriate funding, radiological and biological predictive biomarkers of response and toxicity will be explored.

6.5 Objectives at specific stages of the trial

The trial has been designed with 3 interim stages, with the aim of identifying lack of feasibility of recruitment and efficacy early in the trial. Following the primary analysis of efficacy and safety (stage 4), there will be a further long-term follow-up stage (stage 5) with the aim of identifying any detriment to long-term survival with reduced duration treatment.

The objectives of the stages are:

- Stage 1 (internal pilot): To demonstrate an adequate rate of recruitment and patient acceptance of randomisation to reduced treatment duration
- Stage 2: To confirm feasibility of the recruitment target based on all centres
- Stage 3: To identify early evidence of lack of efficacy or even superiority of reduced treatment duration
- Stage 4 (primary analysis): To investigate the efficacy, impact on QoL, safety and cost-effectiveness of reduced treatment duration
- Stage 5 (long-term follow-up): To investigate the long-term efficacy and toxicity of reduced treatment duration

Prior to randomisation, there is a registration phase for which all patients who are commencing first line anti-PD1 therapy, or who have been on anti-PD1 therapy for less than 12 months, will be eligible. The main objectives of the registration phase are:

- to introduce the trial concept at initiation of therapy, with the aim of improving acceptance of randomisation
- to allow tracking of patients so randomisation reminders can be co-ordinated
- to allow patients who decline randomisation to be identified for the qualitative interviews within the internal pilot
- to establish a cohort of patients receiving anti-PD1 therapy with linked demographic, stage and outcome data, so that representativeness of the trial randomised population and generalisability of results can be determined
- to enable future large scale translational research studies to be undertaken in patients who have received first line anti-PD1 therapy

The registration phase of this protocol is not considered to be part of the clinical trial.

Patients who remain on anti-PD1 therapy and are progression-free at 12 months will be eligible for randomisation. The ‘clinical trial’ component of this protocol from a regulatory perspective commences from randomisation.

7 Design

7.1 Trial design

DANTE is a multicentre, prospective, randomised, controlled, 2-arm, parallel-group, multi-stage, unblinded, non-inferiority phase III trial. It is comparing 12 months of anti-PD1 therapy (the experimental arm) with standard duration, which is until progression or unacceptable toxicity, or a minimum of 2 years (from the start of treatment) in the absence of disease progression or unacceptable toxicity (the control arm). The anti-PD1 treatment is either nivolumab (with or without ipilimumab for the first few cycles pre-randomisation) or pembrolizumab (clinician/patient choice), for patients with advanced (unresectable or metastatic) melanoma who have not received prior systemic immunotherapy for advanced disease and who remain on anti-PD1 therapy and are progression-free after 12 months of treatment. Prior BRAF/MEK inhibitor treatment is allowed. The trial will include 1,208 randomised patients. The recruitment period is 5 years, with each patient being followed up for 4 years after randomisation.

To ensure that both feasibility of the intervention/trial design and any lack of efficacy are identified early in the trial, three intermediate stages have been incorporated into the trial design with stop/continuation rules depending on randomisation and recruitment rates (stages 1 and 2) and an interim assessment of efficacy (stage 3). Provided these conditions are met the trial will continue seamlessly, enabling the stage 4 primary and secondary study objectives to be attained in a timely manner. The stage 4 primary analysis will occur when all patients have completed 12 months of follow-up after randomisation. A long-term analysis (stage 5) will be conducted when all patients have completed 4 years of trial follow-up.

7.2 Intervention and comparator

Currently, two anti-PD1 therapies, pembrolizumab and nivolumab (monotherapy or in combination with ipilimumab), are licensed for the first line treatment of advanced (unresectable or metastatic) melanoma in adults in Europe until disease progression or unacceptable toxicity, and are recommended by NICE. The optimal duration of treatment with anti-PD1 drugs remains unknown.

Prior to randomisation, all trial participants will receive 12 months anti-PD1 treatment with nivolumab (+/- ipilimumab for the first few cycles) or pembrolizumab, as per standard practice. This initial period of treatment, pre-randomisation, is not considered to be part of the clinical trial.

The clinical trial component of this protocol starts from the point of randomisation, which is at 12 months (+/- 4 weeks) after the start of anti-PD1 therapy.

The control treatment arm in the trial therefore starts from the point of randomisation and is either pembrolizumab or nivolumab (according to investigator-choice of anti-PD1 therapy, made at the start of treatment) given until disease progression or unacceptable toxicity; or a minimum of 2 years (from the start of treatment) in the absence of disease progression or unacceptable toxicity, in accordance with standard practice. The experimental treatment arm

also starts from the point of randomisation and is to stop treatment at randomisation, i.e. no further treatment (until disease progression).

While the two anti-PD1 drugs have not been compared head-to-head, expert consensus is that they can be considered equivalent in terms of efficacy and toxicity. As the aim of this study is to determine whether duration of anti-PD1 therapy can be safely reduced rather than comparing the efficacy of different anti-PD1 therapies, investigator-choice of either drug, made at the start of treatment, is allowed. Choice of therapy is a stratification factor to ensure balance between the treatment arms. Any differences between the drugs will also be accounted for in the trial analysis. Other anti-PD1 therapies are in development at the present time; their progress will be monitored and stratification for further such drugs considered if needed.

7.3 Registration

To determine representativeness of the trial randomised population and hence to assess generalisability of the study results, there is an initial registration phase for which all patients commencing, or who are within 12 months of starting, anti-PD1 therapy as standard of care first line therapy will be eligible. Patients can be registered at any time within their first 12 months on therapy. At registration, patients will be asked to consent to the collection of basic demographic and disease-related data and to allow treatment and survival to be tracked via routine data sources. Other key aspects of the registration phase are that it will allow the trial concept to be introduced at the initiation of therapy and continue throughout the 12-month run-in period, with the aim of improving acceptance of randomisation. It will also allow patients who decline randomisation to be identified for the qualitative interviews, which will further add to improving randomisation rates where necessary.

Patients who remain on anti-PD1 therapy and are progression-free after 12 months of therapy will be eligible for randomisation.

The clinical trial component of this protocol starts from the point of randomisation.

7.4 Randomisation

Randomisation will occur after 12 months of treatment. Randomisation (1:1) will be by minimisation with a random element incorporating BRAF status (wildtype, mutation or unknown), prior BRAF/MEK inhibitor therapy for advanced disease (yes or no), prior (neo)adjuvant immunotherapy (yes or no), disease stage (III or IV), presence of brain metastases (yes or no), performance status (0/1 or 2), centre, choice of initial anti-PD1 treatment (pembrolizumab, nivolumab or ipilimumab-nivolumab), and response after the first 12 months of therapy (complete response, partial response or stable disease).

1,208 patients will be randomised between two treatment options: (i) to stop anti-PD1 therapy (i.e. 12 months in total) (experimental treatment); or (ii) to continue anti-PD1 therapy until disease progression or unacceptable toxicity, or a minimum of 2 years (from the start of treatment) in the absence of disease progression or unacceptable toxicity (control treatment). The doses and scheduling of the anti-PD1 therapy will be in accordance with current standard practice.

7.5 Target population and setting

The target randomised population is patients (18 years or older) with advanced (unresectable or metastatic) melanoma who have commenced first line immunotherapy with anti-PD1 therapy as standard treatment in the NHS who are progression-free after 12 months of treatment and who plan to remain on anti-PD1 therapy. Patients will be recruited from NHS cancer centres in the UK with expertise in the treatment of advanced melanoma. Participation may also be extended to other selected countries.

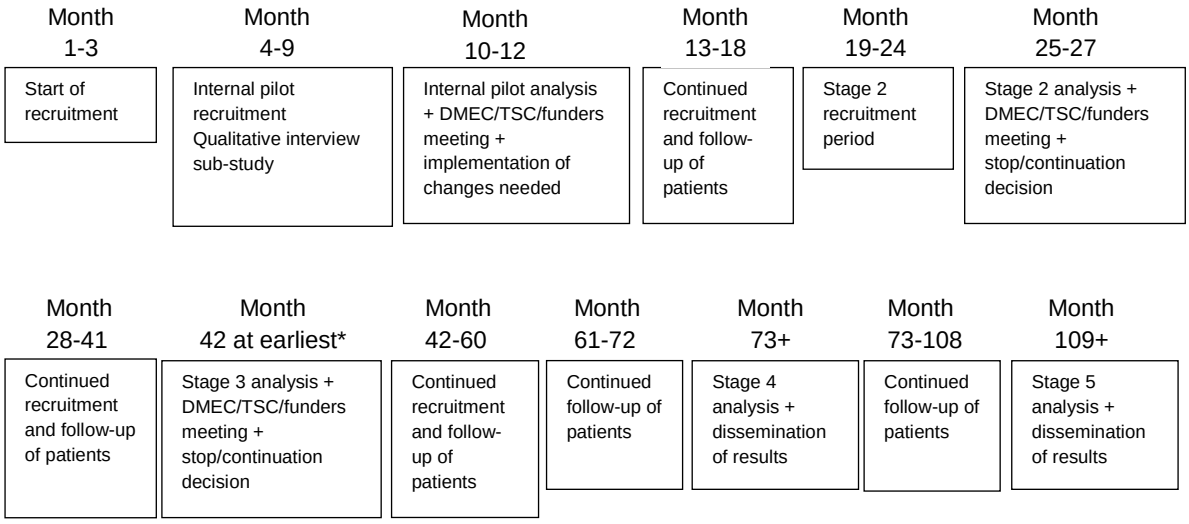
7.6 Assessment of outcome

All patients will be closely monitored for response to treatment and progression and to assess and manage toxicity. To avoid bias in the assessment of PFS, RECIST measurements will be conducted at the same time-points in both study arms. Assessment of measurable disease by RECIST will occur every 3 months up to 12 months after randomisation (i.e. 2 years after the start of anti-PD1 therapy), and then every 6 months to 4 years post-randomisation (i.e. 5 years after the start of anti-PD1 therapy). It is standard practice to continue to follow this schedule of assessment in patients continuing on anti-PD1 therapy and those who have stopped for toxicity (or other reasons prior to progression). Thus, no trial-specific CT or MRI scans will be conducted in this study. Imaging studies will be reported locally by site radiologists. Patients who are allocated to stop treatment at 12 months will be offered standard care if their disease progresses. This may involve a different immunotherapy, a BRAF inhibitor or another treatment. NHS England have agreed that if a patient in the experimental arm stops treatment at 1 year and then progresses by RECIST criteria, treatment options on progression can include restarting anti-PD1 antibody therapy. Similar confirmation has been received for patients in South East and South West Wales. Currently, patients in Scotland will need to be considered on an individual case basis. The position in North Wales and Northern Ireland remains unconfirmed at present.

Trial follow-up assessments will be performed at the same time-points in both arms, 3-monthly for the first 12 months after randomisation then 6 monthly up to 4 years (48 months) after randomisation. Data will be collected from standard of care clinical assessment and CT/MRI scans to assess for response or progression, and drug-related toxicity. Toxicity will be recorded using Common Toxicity Criteria for Adverse Events version 5.0 (CTCAE v5.0) according to the same schedule at standard clinic appointments. Trial-specific procedures will be the QoL and health economics questionnaires collected 3-monthly up to 18 months after randomisation. The trial visit schedule conforms to routine clinical follow-up and all data collection will be performed at standard clinic visits. However where possible, routinely collected data will be used to improve trial efficiency once patients are on 6-monthly follow-up. There is one additional quality of life/health economics questionnaire at 15 months post randomisation, which can be completed by post.

7.7 Multi-stage design

Figure 7.1: Timings of each stage of the trial



* Anticipated

7.7.1 Stage 1: Internal pilot to assess feasibility of recruitment and acceptance of randomisation

7.7.1.1 Aim

In the internal pilot, the main aim is to investigate the feasibility of the study by an early assessment of randomisation rates and recruitment achieved at 9 months after the start of the recruitment period. An important factor in the feasibility of this study is whether sufficient patients will accept randomisation to reduced duration therapy. Feasibility will therefore be assessed by targets for both the absolute number of patients randomised and for the registration-to-randomisation conversion rate.

There is evidence from other discontinuation studies that randomising at the point of treatment divergence, rather than at the start of treatment, can reduce acceptance of randomisation and recruitment[34]. Patient interviews are therefore included, which will explore the acceptability of randomisation, and methods being used to approach and inform patients about the study.

7.7.1.2 Timing and site selection

The internal pilot will run from month 4 to 9 of recruitment in at least 10 sites that are open to recruitment by the start of month 4 (i.e. so that sites will have been recruiting for at least 6 months by the end of the internal pilot to ensure that they have had time to become familiar with the trial). Based on previous experience with multi-centre cancer phase III trials at the Clinical Trials Research Unit (CTRU) and the Health Research Authority (HRA) approvals process, it is considered that it will be feasible to expect 10 sites to be open to recruitment by the start of month 4. It is not planned to restrict the number of sites opening during the pilot phase as all sites have an established research infrastructure and a proven track record of

recruiting to phase III trials in melanoma and all sites need to be open from month 19 of recruitment to allow 1,208 patients to be randomised in approximately 5 years. All sites will be experienced in the use of anti-PD1 therapy by the time the study opens to recruitment.

7.7.1.3 Outcome measures and targets

Outcome measures are:

- Percentage of eligible patients who agree to be randomised
- Number of patients randomised at 9 months

The primary outcome of interest in the internal pilot is the percentage of registered eligible patients who agree to be randomised, as that will allow acceptability of reduced duration therapy to be assessed. 'Green/amber/red' targets for this outcome measure have been set, where reaching the 'green' target should allow 1,208 patients to be randomised within 5 years; reaching the 'amber' target suggests that the trial could recruit to time with modifications to trial procedures; and failing to achieve the 'red' target means that the trial will not be able to randomise 1,208 patients in an acceptable timeframe, and that a rescue plan is needed.

From existing evidence, it is expected that around 75% of registered eligible patients will agree to be randomised[34]. A registration-to-randomisation conversion rate in eligible patients of around 60% should allow the recruitment target to be achieved (see Section 19.1.2; i.e. 1,208 out of 1,999 eligible patients are required to be randomised). With a registration-to-randomisation conversion rate of only 45%, approximately 900 patients would be expected to be randomised in 5 years with an extra 1.7 years of recruitment required to reach 1,208 patients.

In-depth interviews using a semi-structured topic guide (developed and adapted using patient and public involvement (PPI) advice) to ensure consistency of content will be undertaken with 18 patients, including 12 patients who agree to be randomised into the study across the two arms and 6 patients who choose not to be randomised. Interviews will be audio recorded with permission and will be 30-40 minutes in duration. Interviews may be conducted face to face or over the telephone. The data from the interviews of patients who choose to be randomised or who decline to be randomised will be used to support recruitment strategies in the trial. Data from this stage will also be used to provide insight about patients' views of discontinuing treatment and their reasons for taking up or declining this option.

Targets at 9 months are therefore:

- Green: If ≥60% of eligible patients are randomised, the trial will continue seamlessly to stage 2
- Amber: If 46-59% of eligible patients are randomised, findings from the patient interviews will be used to inform changes to trial processes, e.g. to patient documentation, informed consent processes, additional site training
- Red: If ≤45% of eligible patients are randomised, a rescue plan will be put in place following review by the trial independent Data Monitoring and Ethics Committee

(DMEC) and Trial Steering Committee (TSC) and discussion with the trial funder. This may include re-evaluation of the design including the timing of randomisation

To ensure that an adequate number of randomisations is being achieved, an overall target for the number of patients randomised at 9 months has been set. Data from the AVAST-M study[35] has been used to predict expected site performance, which is the most recent high volume national multi-centre academic melanoma study and recruited 1,343 patients to time and target. During this internal pilot stage, where recruitment is expected to be at its slowest whilst sites familiarise themselves with trial processes, an average of 3 randomised patients per site in 9 months is expected. Therefore the overall recruitment target at 9 months is at least 30 randomised patients from at least 10 sites.

In order to monitor the representativeness of the randomised population, baseline demographic details and disease characteristics of the registered and randomised populations at the end of the internal pilot will be assessed. Any required changes to the trial and associated documentation will be implemented between months 10-12 of recruitment and recruitment at 18 months (stage 2) reassessed.

7.7.2 Stage 2: Confirm feasibility of recruitment

To confirm feasibility of recruitment, recruitment from all sites between months 19 to 24 of recruitment will be assessed, with analysis and decisions about stop/continue made between months 25-27. It is expected all sites will be open by month 19. 'Green/amber/red' targets for recruitment between months 19-24 have been set, where reaching the 'green' target should allow 1,208 patients to be randomised within approximately 5 years; reaching the 'amber' target suggests that the trial could recruit to time with modifications to trial procedures or a short extension in recruitment time; and failing to achieve the 'red' target means that the trial will not be able to randomise 1,208 patients in an acceptable timeframe, and that a decision about stop/continuation is needed.

Based on an expected average of 6 randomised patients/site/year with 45 sites open for 6 months, 135 patients are expected to be randomised. This is the 'green' target and achievement of ≥135 patients randomised over the 6-month period from months 19-24 will be required to demonstrate that the recruitment target of 1,208 patients can be met. Achieving the stage 2 'green' recruitment target (i.e. at least 135 randomised patients in 6 months) and estimating the number of randomised patients in months 1-18 is likely to demonstrate that, assuming the expected average randomisation rate of 6 patients/site/year continues beyond stage 2, the recruitment target of 1,208 randomised patients can be met in approximately 5 years. This calculation uses recruitment data from months 1-11 (in that there were 22 randomised patients and 27 sites open to recruitment in this time period) and also assumes the following: approximately 100 patients will be randomised between months 12-18 (based on 2 new sites opening per month), 135 patients will be randomised in months 19-24, and 810 patients will be randomised in months 25-60 based on the expected average randomisation rate of 6 patients/site/year. Stage 2 will however allow for a more accurate estimation of future randomisations to confirm when the target of 1,208 randomised patients is expected to be reached and therefore whether a short extension in recruitment time is required.

The 'amber' target is ≥113 patients randomised between months 19-24 and is based on an average of 5 randomised patients/site/year with 45 sites open for 6 months. Recruitment at this rate would allow at least 675 patients to be randomised over Years 3-5. Using an estimate of approximately 122 patients randomised in total in months 1-18, recruitment at this rate would allow ≥75% of the recruitment target to be achieved by the end of Year 5 (≥910 patients) and the full sample size of 1,208 patients reached with a further 15 months of recruitment.

Targets at 24 months are therefore:

- Green: If ≥135 patients are randomised between months 19-24, the trial will continue with no changes
- Amber: If 113-134 patients are randomised, it is proposed that the trial should continue but options to boost recruitment will be considered in discussion with the TSC, DMEC and the funder, including opening additional UK sites, further trial publicity, or extension of recruitment if it is concluded that the shortfall can be achieved within a reasonable timescale
- Red: If <113 patients are randomised, ongoing recruitment will be discussed with the DMEC, TSC and funder. The consequence should be to stop the trial unless other options such as international collaboration indicate that the shortfall in patients can be addressed

This stop/continuation decision will be made by the NIHR HTA Programme, advised by the TSC chair.

In order to monitor the representativeness of the randomised population, baseline demographic details and disease characteristics of the registered and randomised populations at the end of stage 2 will be assessed. In addition, summaries of overall survival for both registered (for those patients who are alive and progression-free at 12 months) and randomised patients will be presented. Overall survival data for registered patients who are not randomised will be obtained from routine and/or translational study (where available) data.

7.7.3 Stage 3: Interim assessment of efficacy

One formal statistical interim analysis is planned to test for superiority ($p<0.005$) or inferiority ($p<0.05$) of the experimental arm against the control arm on PFS when at least half the required number of patients have been randomised and have completed 12 months of trial follow-up, and the study is at least 30 months into recruitment. Different alpha levels have been incorporated to reflect the relative importance of the interim analysis for superiority and inferiority claims.

7.7.4 Stage 4: Primary assessment of efficacy

In stage 4 the efficacy of reduced duration anti-PD1 therapy will be assessed. The outcome measures in stage 4 are:

- Primary: Progression-free survival

- Key secondary: Quality of life
- Secondary: Overall survival; objective response rate, best tumour response rate and duration of response; drug-induced toxicity; cost-effectiveness

The primary analysis will be time-driven[36] and occur when all patients have completed 12 months of follow-up after randomisation. Time to progression will also be assessed as a sensitivity analysis to the primary outcome measure.

7.7.5 Stage 5: Long-term assessment of efficacy

A long-term follow-up analysis (of PFS, OS and toxicity) is planned when all patients have completed 4 years of follow-up after randomisation. There is now up to 10-year follow-up data for clinical trials of ipilimumab in advanced melanoma with a pooled overall survival rate of approximately 20% in a recent meta-analysis[37]. Therefore, this analysis is considered to be an important component of the trial to ensure that there is no detriment to survival with reduced duration anti-PD1 therapy in the long-term. In addition, side-effects can come on months or even years[38] after these drugs are stopped and so this study will inform clinicians as to how delayed these toxicities can be and the potential reduction in toxicities as a result of shorter treatment duration.

8 Participating Sites and Investigators

8.1 Participating sites

Each participating site must be able to comply with the following, as applicable to the trial activities taking place at the site:

- Trial treatments, imaging, clinical care, follow-up schedules and all requirements of the trial protocol, including expertise in the management of toxicity in patients on anti-PD1 therapy/immune check-point inhibitors
- Requirements of the Research Governance Framework and amendments and the Medicines for Human Use (Clinical Trials) Regulations 2004 and all amendments
- Data collection requirements, including adherence to CRF submission timelines as per Section 14
- Collection, preparation and shipment of biological samples for future translational research (subject to future funding and protocol amendment)
- Monitoring requirements as outlined in Section 21.2

Participating sites will be required to complete a trial-specific feasibility questionnaire to confirm that they have adequate resources and experience to conduct the trial.

8.2 Principal investigators and co-investigators

Sites must have an appropriate Principal Investigator (PI) authorised by the site, and ethics committee and regulatory authority, to lead and coordinate the work of the trial on behalf of the site. Other investigators at site wishing to participate in the trial must be trained and approved by the PI. Investigators involved in the treatment and care of patients must be medical doctors and have experience of treating melanoma and giving immunotherapy.

8.3 Training requirements for site staff

All site staff must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site authorised personnel log (APL).

CVs for all staff must be kept up-to-date, signed and dated, and copies (or statement of their location) held in the Investigator Site File (ISF) held at site. An up-to-date, signed copy of the CV for the PI must be forwarded to the CTRU prior to site activation and upon request.

Good Clinical Practice (GCP) training is required for all staff responsible for trial activities. The frequency of repeat training may be dictated by the requirements of their employing institution, or 2 yearly where the institution has no policy, and more frequently when there have been updates to the legal or regulatory requirements for the conduct of clinical trials. Evidence of current GCP training for the PI must be forwarded to the CTRU prior to site activation and upon request.

8.4 Site initiation

Before a site is activated, the CTRU trial team will arrange a site initiation with the site which, as a minimum, the PI and research nurse must attend. The site will be trained in the day-to-day management of the trial. Essential documentation required for trial activation will be checked. Site initiation will normally be performed for each site by teleconference. On-site initiation visits will be conducted if deemed appropriate.

8.5 Essential documentation

The following documentation must be submitted by the site to the CTRU prior to site activation:

- Trial specific site feasibility questionnaire (identifying relevant local staff)
- All relevant institutional approvals (e.g. local NHS permission)
- A completed authorised personnel log that is initialled and dated by the PI (with all tasks and responsibilities delegated appropriately)
- A copy of the PI's current CV that is signed and dated
- A copy of PI's current GCP training certificate
- Signed PI declaration
- A signed Clinical Trial Site Agreement (model Non-commercial Agreement for UK sites) between the Sponsor and the relevant institution

Sites must inform the CTRU of any additional sites involved in the patient pathway. Recruiting sites which will be referring patients to a different site, for all or some of the trial activities, will not be activated until the relevant site involved is ready to be activated.

8.6 Site activation

Once the CTRU trial team has received all the required essential documentation, the site has received their investigator and pharmacy site files and the site has been initiated, a site activation email will be issued to the PI and other research staff by CTRU. **Sites must not approach any potential patients until they have received an activation email from CTRU.**

9 Patient Eligibility

Patients meeting all of the inclusion criteria, and none of the exclusion criteria, will be considered for participation in the trial. Eligibility waivers to any of the inclusion and exclusion criteria are not permitted. We have kept inclusion/exclusion criteria as broad as possible to allow all patients eligible to receive anti-PD1 therapy as standard treatment to potentially participate in the study. Any additional exclusion criteria are to clarify safety considerations.

9.1 Inclusion for registration

- Histologically or cytologically confirmed unresectable AJCC stage III or stage IV (metastatic) melanoma, including cutaneous and non-cutaneous melanoma[39]
- Aged ≥ 18 years
- Planned or currently receiving (≤12 months + 4 weeks) treatment with first-line pembrolizumab or nivolumab (as monotherapy or with ipilimumab)
- Written informed consent for registration

9.2 Exclusion for registration

- Known active HIV, hepatitis B or C
- History of prior malignancy, other than melanoma,
    - *except* the following patients, who are eligible:
        - patients who have completed treatment for that malignancy and have been disease-free for at least 1 year prior to the start of anti-PD1 therapy,
        - or patients with a history of adequately treated Stage 1 or Stage 2 basal/squamous cell carcinoma of the skin,
        - or successfully treated in situ carcinoma.
- Prior systemic treatment for advanced melanoma within 5 years of starting the current/planned anti-PD1 therapy, other than BRAF and MEK inhibitors and the current or planned pembrolizumab, nivolumab or combination ipilimumab-nivolumab treatment. Prior adjuvant or neo-adjuvant therapy is allowed as long as it was completed at least 6 months prior to starting anti-PD1 therapy

9.3 Inclusion criteria for randomisation

- Registered in DANTE
- Progression-free by RECIST v1.1[31] criteria at 12 months (+/- 4 weeks) from the start of pembrolizumab or nivolumab (as monotherapy or with ipilimumab)[1]
- 12 months +/- 4 weeks from start of pembrolizumab or nivolumab (as monotherapy or with ipilimumab)
- Eastern co-operative oncology group (ECOG) performance status 0-2
- Considered fit by the treating clinician to continue to receive ongoing treatment with pembrolizumab or nivolumab
- Written informed consent for randomisation

9.4 Exclusion criteria for randomisation

- Severe co-morbidities, including severe auto-immune disease or pneumonitis
- Active infection requiring systemic therapy
- Known active HIV, hepatitis B or C
- History of prior malignancy, other than melanoma,
    - *except* the following patients, who are eligible:
        - patients who have completed treatment for that malignancy and have been disease-free for at least 1 year prior to the start of anti-PD1 therapy,
        - or patients with a history of adequately treated Stage 1 or Stage 2 basal/squamous cell carcinoma of the skin,
        - or successfully treated in situ carcinoma.
- Pregnant, breast-feeding or patients with reproductive potential (female and male) unwilling to use adequate contraception (Section 9.5) while receiving anti-PD1 therapy and for 6 months after the last dose. Women of reproductive potential are defined as: following menarche and until becoming post-menopausal, unless permanently sterile. Men of reproductive potential are defined as: post-pubescent and not sterile by vasectomy or bilateral orchidectomy.
- Prior systemic treatment for advanced melanoma within 5 years of starting the current anti-PD1 therapy, other than BRAF and MEK inhibitors, combination ipilimumab-nivolumab and the current pembrolizumab or nivolumab treatment. Prior adjuvant or neo-adjuvant therapy is allowed as long as it was completed at least 6 months prior to starting anti-PD1 therapy.

[1] Progression-free is defined as not meeting the criteria for disease progression by RECIST v1.1 when the 12-month pre-randomisation scan is compared to the pre-treatment baseline scan. Please see Appendix C for full details.

- Treated brain metastases with MRI evidence of progression and/or requirement for high doses of systemic corticosteroids that could result in immunosuppression (>10 mg/day prednisolone equivalents)
- Untreated brain metastases that are symptomatic and/or require local intervention (surgery, radiosurgery, corticosteroid therapy) or other systemic therapy.

9.5 Birth control

Female patients of childbearing potential should be advised to use adequate contraception[2] while receiving anti-PD1 therapy and for 6 months after the last dose. Male patients who are sexually active with a woman of childbearing potential should be advised to use barrier contraception while receiving anti-PD1 therapy and for 6 months after the last dose.

9.6 Prior and concurrent participation in other clinical trials

Participant eligibility for DANTE based on previous or concurrent participation in other clinical trials will be determined on a case-by-case basis and must be discussed with the CTRU prior to randomisation.

9.7 Eligibility and baseline assessments

Informed consent must be obtained (Sections 10.2, 10.4.1 and 10.5) prior to undertaking any trial-specific procedures, including non-routine screening investigations and assessments.

[2] Acceptable contraception is defined as one of the following: combined (oestrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal), progesterone only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomised partner, practicing true abstinence (when this is in line with the preferred and usual lifestyle of the participant).

10 Consent and Registration / Randomisation

10.1 Recruitment setting

The trial will be conducted at NHS Cancer Centres in the UK (England, Wales, Scotland and Northern Ireland) with expertise in treating patients with advanced melanoma with systemic anti-cancer therapy. It may also be conducted in other selected countries.

Research sites will be required to have obtained local management approval and undertaken a site initiation with the CTRU prior to the start of recruitment.

The trial aims to randomise 1,208 participants over 5 years.

10.2 Principles of informed consent

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their site. The PI must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised on the DANTE authorised personnel log, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki 1996. See Sections 10.4.1 and 10.5 for details of the staff who are permitted to take consent for registration and randomisation, respectively.

The right of the patient to refuse consent without giving reasons will be respected. Further, participants will be told that they remain free to withdraw from the trial at any time without giving reasons and without prejudicing any further treatment.

Informed consent must be obtained prior to the participant undergoing procedures specifically for the purposes of the trial which are out-with standard routine care at the participating site.

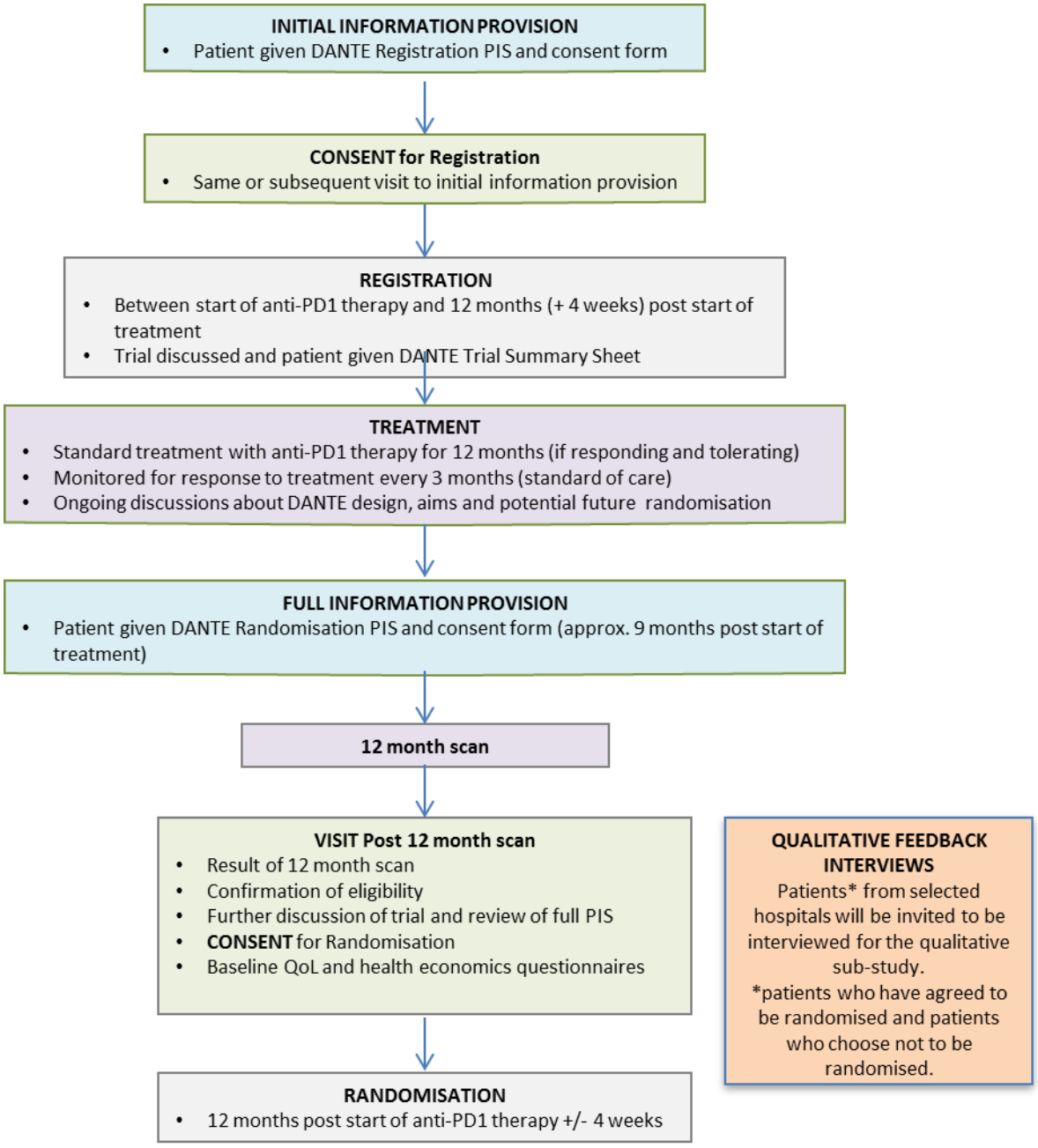
Where a participant is required to re-consent, or new information is required to be provided to a participant, it is the responsibility of the PI to ensure this is done in a timely manner and according to any timelines requested by the CTRU.

10.3 Recruitment processes

Patients will be identified through specialist melanoma multi-disciplinary teams (MDTs) and outpatient clinics.

This trial involves a 2-stage recruitment process: a registration stage and a subsequent randomisation stage (see Figure 10.1).

Figure 10.1: Overview of the information provision and registration / randomisation consent processes



10.4 Registration stage

All patients who are commencing the protocol-specified anti-PD1 therapy, or who have been on the protocol-specified anti-PD1 therapy for less than 12 months, will be eligible for registration. The main objectives of the registration stage are:

(i) to introduce the trial concept at initiation of therapy, with the aim of improving acceptance of randomisation after 12 months of treatment;

(ii) to allow tracking of patients so randomisation reminders can be co-ordinated;

(iii) to allow patients who subsequently decline randomisation to be identified for the qualitative interviews within the internal pilot;

(iv) to establish a cohort of all patients receiving anti-PD1 therapy with linked demographic, stage & outcome data, so that representativeness of the trial randomised population & generalisability of results can be determined;

(v) to establish a cohort of patients for large scale translational studies: all patients will be asked to give consent for any archival tumour samples to be accessed for future research. Subject to additional funding, additional patient samples may be collected in a future amended protocol.

10.4.1 Informed consent for registration

A verbal explanation of the trial and a short Registration Patient Information Sheet (Reg PIS) will be provided to the patient at a routine clinic appointment by the attending clinical team for the patient to consider. This can be done at any visit from the start of anti-PD1 therapy up to 12 months post start of treatment, but the earlier the better, in order to maximise the opportunity to educate patients about the trial concept during the first 12 months of treatment, with the aim of improving the acceptance of randomisation at 12 months.

Following information provision about registration, patients will have as long as they need to consider whether they would be willing to be registered, before they are formally consented. This can be less than 24 hours. Assenting patients will be invited to provide informed, written consent for registration at the same or a subsequent clinic visit. Consent for registration may be taken by an appropriately qualified member of the trial team (including nurse and other healthcare professionals) who has received GCP training and is authorised by the PI on the trial delegation log to take this consent. At the time of registration consent, or earlier, the patient will also be given a DANTE Trial Summary Sheet which will introduce them to the aims of the randomised component of the trial, in preparation for the randomisation stage which will occur, if eligible, 12 months after the start of treatment.

Site staff are responsible for:

- Checking that the correct (current approved) version of the Registration PIS and Consent Form is used
- Checking that information on the Registration Consent Form is complete and legible

- Checking that the patient has completed/initialled all relevant sections and signed and dated the form
- Checking that an appropriate member of staff has countersigned and dated the Consent Form to confirm that they provided information to the patient
- Checking that an appropriate member of staff has made dated entries in the patient's medical notes relating to the informed consent process (i.e. information given, consent signed, etc.)
- Making sufficient copies and filing the original consent form in the investigator site file, and filing a copy in the patient's medical notes.
- Giving the patient a copy of their signed Registration PIS/Consent Form and a DANTE Trial Summary Sheet.

Where a patient declines consent for registration, anonymised data will be recorded on a non-registration log (Section 10.7).

10.4.2 Registration process and timing

Informed written consent for registration must be obtained prior to registration, subject to the patient meeting all the eligibility criteria (Section 9.1). Consenting patients with advanced melanoma who are about to commence or are already receiving anti-PD1 therapy as standard of care first line therapy can be registered at any time within their first 12 months (+ 4 weeks) on therapy, but the earlier the better, in order to maximise the opportunity to educate patients about the trial concept during the first 12 months of treatment, with the aim of improving the acceptance of randomisation at 12 months. If it is known at the point of registration, that certain randomisation eligibility criteria cannot be fulfilled (e.g. if a 12-month scan has already been performed before registration and the patient shows progression as per RECIST v1.1), the patient should not be approached for registration and should be added to the non-registration log. Patients will also be asked for consent to access archived tumour samples; no samples will be collected until funding is confirmed and a protocol amendment is approved.

Registration will be performed centrally using the CTRU automated 24-hour registration system which can be accessed via the web or telephone. For the telephone system, a site code, staff authorisation code and Personal Identification Number (PIN) will be required. To register using the web, a staff email address, a site code and PIN will be required. Authorisation codes and PINs will be provided by the CTRU once all the necessary documentation has been received at CTRU and the site has been fully approved.

Participants may only be registered into the trial by an authorised member of staff at the trial research site, as detailed on the Authorised Personnel Log. The person telephoning or accessing the web address to register the participant must have completed the Registration Case Report Form (CRF) and have it available prior to accessing the 24-hour registration system. The following information will be required:

- Site code (assigned by CTRU) of the research site
- Name of person making the registration
- Participant details, including initials, date of birth and gender

- Confirmation of eligibility for registration
- Confirmation of date of written informed consent for registration
- Date of first treatment with anti-PD1 therapy

24hour registration:

Telephone: 0113 343 2290
or
Web: *https://lictr.leeds.ac.uk/webrand/*

Please ensure that you have completed the Registration Form before telephoning the registration line or accessing the web registration

Once registration is complete, the system will allocate the participant a unique 5 digit trial number. This number together with the centre number will form the participant ID number.

After registration, the site staff will:

- Add the unique participant ID number to the registration consent form and all CRFs
- Return a copy of the completed registration consent form to CTRU (by fax or secure file transfer – contact CTRU Data Manager for details), in line with the terms of the ethically approved consent form
- Return a copy of the completed Registration CRF by post to CTRU
- Record the patient details on the DANTE Patient ID Log.

After registration, the CTRU will:

- Email a Participant Registration Confirmation to the research site.

10.5 Informed consent for randomisation

Patients who are registered into DANTE, remain on anti-PD1 therapy and are progression-free at 12 months (+/- 4 weeks) post start of treatment will be eligible for randomisation (Sections 9.3 and 9.4).

Patients will have been approached for possible recruitment and given a DANTE Trial Summary Sheet at their registration visit. Investigators are encouraged to discuss the trial with the patient at regular intervals during their first 12 months of treatment, to educate them about the design and aims of the trial, in preparation for possible randomisation, if eligible.

As the patient is nearing the 12 month assessment point post start of anti-PD1 therapy, a verbal explanation of the trial and the Randomisation Patient Information Sheet (Rand PIS) will be provided by the attending medical staff (and/or nurse or other healthcare

professional) for the patient to consider. This will include detailed information about the rationale, design and personal implications of the trial. It is recommended that this information is given to the patient at approximately 9 months post the start of anti-PD1 therapy once the result of their 9-month routine re-assessment scan is known. Following information provision, patients will continue to receive treatment (if clinically appropriate) and attend routine clinic visits, and during this time, will have the opportunity to discuss the trial with their family and healthcare professionals.

At 12 months after the start of anti-PD1 therapy, the patient will have a CT and/or MRI scan to assess their disease status. At the next clinic visit, the patient will be told the results of their scan and will be formally assessed for eligibility for randomisation (Sections 9.3 and 9.4). If the patient is eligible, they will be invited to participate in the trial. Patients will have as long as they need to consider participation. If the patient and clinician considers that the patient has received sufficient information and has had adequate time to consider the trial over the preceding weeks since the trial was first introduced to them, they may be asked for informed consent at this visit. If the patient would like additional time to consider trial participation, they may come back to clinic to be consented at a later date, but this must be within the required time window for randomisation (12 months post start of anti-PD1 therapy +/- 4 weeks).

The formal assessment of eligibility and informed consent for randomisation may only be undertaken by the Principal Investigator (PI) or an appropriate medically qualified healthcare professional. The healthcare professional must have knowledge of the trial interventions and have received training in the principles of GCP and the Declaration of Helsinki 1996. He/she must be fully trained in the trial according to the ethically approved protocol and be authorised and approved by the PI to take informed consent for randomisation as documented in the trial Authorised Personnel Log.

Site staff are responsible for:

- Checking that the correct (current approved) version of the Randomisation PIS and Consent Form is used
- Checking that information on the Randomisation Consent Form is complete (including patient trial number) and legible
- Checking that the patient has completed/initialled all relevant sections and signed and dated the form
- Checking that an appropriate member of staff has countersigned and dated the Consent Form to confirm that they provided information to the patient
- Checking that an appropriate member of staff has made dated entries in the patient's medical notes relating to the informed consent process (i.e. information given, consent signed, etc.)
- Making sufficient copies and filing the original consent form in the investigator site file, and filing a copy in the patient's medical notes.
- Giving the patient a copy of their signed Consent Form and PIS

The participant will be provided with a local contact point where he/she may obtain further information about the trial.

Where a registered patient declines consent for randomisation, or is not randomised for any other reason, including not meeting the eligibility criteria, reasons for non-randomisation will be recorded on a non-randomisation CRF.

10.5.1 Randomisation process and timing

Informed written consent for randomisation must be obtained prior to randomisation, subject to the patient meeting all the eligibility criteria.

Randomisation must occur at 12 months (+/- 4 weeks) after the start of anti-PD1 therapy. **Note that participants must have completed their baseline QoL and health economics questionnaires prior to randomisation (Section 15) but after informed written consent has been obtained.**

Randomisation will be performed centrally using the CTRU automated 24-hour randomisation system which can be accessed via the web or telephone. For the telephone system, a site code, authorisation code and Personal Identification Number (PIN) will be required. To randomise using the web, a staff email address, a site code and PIN will be required. Authorisation codes and PINs will be provided by the CTRU. These codes will only be issued once a site has been fully approved and all the necessary documentation has been received at CTRU.

Participants may only be randomised into the trial by an authorised member of staff at the trial research site, as detailed on the Authorised Personnel Log. The person telephoning or accessing the web address to randomise the participant must have completed the Randomisation Case Report Form (CRF) and have it available prior to accessing the 24-hour randomisation system. The following information will be required:

- Site code (assigned by CTRU) of the research site
- Name of person making the randomisation
- Participant details, including initials and date of birth (which must match details provided at registration)
- Participant's unique trial number provided at registration
- Confirmation of eligibility for randomisation
- Confirmation of date of written informed consent for randomisation
- Confirmation of completion of baseline quality of life and health economics questionnaires

10.5.2 Treatment allocation

Patients will be randomised in a 1:1 allocation ratio to either continue on their prescribed anti-PD1 therapy (until disease progression or unacceptable toxicity, or a minimum of 2 years (from the start of treatment) in the absence of disease progression or unacceptable toxicity), or to stop anti-PD1 therapy. Randomisation will be by computer-generated minimisation incorporating a random element to ensure that treatment groups are well-

balanced for the following participant characteristics, details of which will also be required for randomisation:

- BRAF status (wildtype / mutation / unknown)
- Prior BRAF/MEK inhibitor therapy for advanced disease (yes / no)
- Prior (neo)adjuvant immunotherapy (yes / no)
- Disease stage (III / IV)
- Presence of brain metastases (yes / no)
- Performance status (0-1 / 2)
- Centre
- Treatment received within the last 12 months (pembrolizumab / nivolumab / ipilimumab-nivolumab)
- Response after 1st 12 months of therapy (complete response / partial response / stable disease)[3]

24hour randomisation:

Telephone: 0113 343 2290
or
Web: *https://lictr.leeds.ac.uk/webrand/*

Please ensure that you have completed the Randomisation Form before telephoning the randomisation line or accessing the web randomisation

Once randomisation is complete, the system will allocate a treatment arm for the participant (Section 10.5.2).

After randomisation, site staff will:

- Provide the participant with a Trial ID card and inform them that it should be carried at all times and presented to medical staff should they be admitted to hospital during their time on trial.
- Notify the participant's GP (if the participant has consented to this) of their participation in the trial using the approved DANTE GP Letter.
- Return a copy of the completed randomisation consent form to CTRU (by fax or secure file transfer), in line with the terms of the ethically approved consent form.
- Return a copy of the completed Randomisation CRF by post to CTRU.

[3]Response and stable disease is defined according to RECIST v1.1 criteria and should be determined by comparing the 12-month pre-randomisation imaging and the pre-treatment baseline scan. See Appendix C.

- Complete the randomisation details on the DANTE Patient ID Log.

After randomisation, the CTRU will:

- Email a Participant Randomisation Confirmation to the research site, including pharmacy.

10.6 Loss of capacity following informed consent

Where valid informed consent is obtained from the participant and the participant subsequently becomes unable to provide ongoing informed consent by virtue of physical or mental incapacity, the consent previously given when capable remains legally valid.

Participants who lose capacity after informed consent has been obtained will continue with protocol treatment and assessments in consultation with the PI and participant's carer/family, with the participant's best interests foremost in the decision making process. Ongoing collection of safety and follow-up data will continue via the clinical care team for inclusion in the trial analysis in order to preserve the integrity of the trial's intention to treat analysis and fulfil regulatory requirements specifically for pharmacovigilance purposes.

10.7 Non-registration screening data

In order to determine the generalisability of the trial results, and for Consolidated Standards of Reporting Trials (CONSORT) requirements, participating research sites will be required to complete a Non-Registration log for all those patients who are commencing anti-PD1 therapy, or who have been on anti-PD1 therapy for less than 12 months, who are not registered into the trial. Anonymised data will be collected including:

- Age
- Gender
- Date screened
- Reason for non-registration:
    - The reason that a patient was not approached, or
    - The reason that a patient declined registration

However, the right of the patient to refuse consent for registration without giving reasons will be respected. This information will be requested from participating sites on a regular basis (at least 3 monthly) by the CTRU.

11 Patient Management Between Registration and Randomisation

After registration into DANTE, patients will receive anti-PD1 therapy (monotherapy or combination ipilimumab-nivolumab) and undergo clinical monitoring as per standard practice.

Treatment received during this period is not part of the clinical trial.

Investigators are encouraged to mention the DANTE trial to patients at regular intervals whilst they remain on treatment and progression-free.

The participant should be scheduled for a repeat CT/MRI scan every 3 months post start of anti-PD1 therapy, as per standard practice. Scans should be performed every 3 months, regardless of any delays or interruptions to treatment. It is therefore recommended that all scans are pre-booked as soon as possible following registration into DANTE, to ensure that appointments are available at the required times. This is important for all appointments, but it is particularly important that the 12-month scan occurs as close as possible to the 12 month anniversary after the start of treatment to ensure eligibility is confirmed and randomisation occurs 12 months (+/- 4 weeks) after the start of treatment.

Please see Section 14.3 for details of pre-randomisation assessments.

12 Trial Medicinal Product Management

12.1 Investigational medicinal product definition

Within the DANTE trial, only pembrolizumab and nivolumab are classed as Investigational Medicinal Products (IMPs). **The clinical trial component of this protocol starts from the point of randomisation. Pembrolizumab or nivolumab given to a registered patient prior to randomisation are not considered to be IMPs.**

12.2 Pembrolizumab and nivolumab composition

Pembrolizumab and nivolumab are humanised monoclonal anti-programmed cell death-1 (PD1) antibodies produced in Chinese hamster ovary cells by recombinant DNA technology.

- Pembrolizumab is commercially available as a 25mg/mL concentrate for solution for infusion or a 50mg powder for concentrate for solution for infusion
- Nivolumab is commercially available as a 10 mg/ml concentrate for solution for infusion.

For further details of composition of either IMP, refer to the current version of the manufacturer's Summary of Product Characteristics (SPC), which can be accessed via the electronic Medicines Compendium (eMC), website http://www.medicines.org.uk/emc.

12.3 IMP supply and handling

Both pembrolizumab and nivolumab are licensed in the UK and general 'off the shelf' supplies will be used. There is no requirement to ring-fence pembrolizumab or nivolumab for the DANTE trial. Both IMPs will be handled in line with the manufacturers' recommendations, as per the current version of the relevant SPC.

12.3.1 Use of 3rd party supply and delivery of IMP

IMP supply and delivery to a participant's home by 3rd party home healthcare companies is permitted if this is in accordance with routine NHS practice at the participating trial site. The trial does not require any additional actions beyond existing standard care practices. CTRU should be informed during the site set-up process, or if this is adopted during the life of the study. This arrangement must be documented in the model Non-Commercial Agreement between the Sponsor and participating site.

12.4 IMP formulation, storage and preparation

Pembrolizumab and nivolumab formulation, storage and preparation is in line with the manufacturers' recommendations, as per the current version of the relevant SPC.

12.5 IMP prescribing

As protocol treatment (if allocated to continue to receive anti-PD1 therapy) is a continuation of standard treatment given before randomisation, no trial-specific prescription is required. Sites will use their local standard prescriptions. A note of the location of completed prescriptions should be stored in the Pharmacy Site File.

12.6 IMP labelling

Pembrolizumab and nivolumab will be used in accordance with the conditions set out in Regulation 46 (2) of the Medicines for Human Use (Clinical Trials) Regulations 2004 (and amended in 2006). As both IMPs will be used within their licensed indication, no special trial labelling requirements apply and both pembrolizumab and nivolumab may be labelled in accordance with the requirements of Schedule 5 to the Medicines for Human Use (Marketing Authorisation etc.) Regulations 1994.

12.7 IMP accountability

No trial-specific accountability logs are required. Dispensing records will be in line with local standard practice and as a minimum will ensure that IMP is fully traceable by batch number. Treatment compliance is recorded by the Research Nurse on the Case Report Form; there is no requirement for compliance checks or routine monitoring to be performed within pharmacy.

13 Treatment Details

13.1 Regimens

This trial is designed to investigate reduced duration of anti-PD1 antibody therapy in the treatment of advanced melanoma. The regimens permitted for administration within the trial, i.e. after randomisation, are those approved by NICE for use in the treatment of metastatic or unresectable melanoma[6 7] and as per the current SPCs. These are currently:

Pembrolizumab	2mg/kg administered by intravenous infusion over 30 minutes every 3 weeks or 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes or As per current SPC

OR

Nivolumab	3mg/kg administered by intravenous infusion over 60 minutes every 2 weeks or 240 mg administered by intravenous infusion over 30 minutes every 2 weeks or 480 mg administered by intravenous infusion over 60 minutes every 4 weeks or As per current SPC

Any of these regimens is permitted within the trial. However, the agent to be used for each patient must be specified prior to randomisation and the same agent must be used for the whole duration of therapy. **Switching between anti-PD1 agents during trial treatment is not permitted.**

Participants will have received 12 months of standard therapy with the same anti-PD1 antibody prior to randomisation. Treatment prior to randomisation is not considered part of this clinical trial.

Following randomisation treatment within the trial is:

- **Arm A (standard therapy):** Continue anti-PD1 antibody until disease progression or unacceptable toxicity; or a minimum of 2 years (from the start of treatment) in the absence of disease progression or unacceptable toxicity

or

- **Arm B (investigational therapy):** Stop anti-PD1 antibody at randomisation

13.2 Treatment details post-randomisation: Arm A

13.2.1 Pre-treatment investigations

Participants should have a clinical assessment of toxicity and safety blood tests prior to administration of anti-PD1 therapy in accordance with usual local practice to allow safe administration of treatment in accordance with the SPC. See Section 14.4 for further information and Section 13.4 for guidance on managing toxicity.

13.2.2 Dosing

The dose of pembrolizumab and nivolumab should be calculated using actual body weight. Dose capping will not be used. Standard local practice for re-calculation of dose due to change in body weight and dose banding should be followed.

13.2.3 Administration

Pembrolizumab and nivolumab should be administered in accordance with instructions in the current version of the SPC for each drug.

13.2.4 Treatment modifications

13.2.4.1 Starting dose

The starting dose for all patients on trial should be as specified in Section 13.1. No modifications of the dose should be performed.

13.2.4.2 Dose reductions

No dose reductions should be performed. If treatment is interrupted for toxicity and then re-started, the dose of the anti-PD1 antibody does not change.

13.2.4.3 Dose delays

Treatment may be interrupted for toxicity for up to 12 weeks and then re-started. If toxicity has not adequately resolved within 12 weeks, anti-PD1 therapy should be discontinued. See Section 13.4 for guidance on managing toxicity.

Short treatment breaks for other reasons may be done at the discretion of the local Principal Investigator in accordance with usual local practice.

13.2.5 Concomitant medication

No formal pharmacokinetic interaction studies have been performed with either drug. Both are human monoclonal antibodies and are not metabolised by cytochrome P450 (CYP) enzymes or other drug metabolising enzymes, therefore no metabolic drug-drug interactions are expected.

13.2.5.1 Use of steroids and other immunosuppressants during anti-PD1 therapy

Systemic corticosteroids or other immunosuppressant drugs should be avoided prior to starting anti-PD1 antibody therapy because of their potential interference with the pharmacodynamic activity and efficacy of immune check-point inhibitors.

During therapy, systemic corticosteroids and other immunosuppressants may be used to treat immune-related adverse reactions as indicated by local guidelines and/or the SPC (see Section 13.4.2).

13.2.5.2 Concomitant anti-cancer therapies

Concomitant systemic anti-cancer treatments are not permitted.

13.2.6 Duration of treatment

All participants randomised to continue anti-PD1 therapy will continue to receive anti-PD1 therapy as per protocol:

- until disease progression (as defined by RECIST v1.1 criteria – see Appendix C) occurs whilst taking anti-PD1 therapy, or
- unacceptable toxicity, or
- participant chooses to stop protocol treatment, or
- clinician chooses to stop protocol treatment after a minimum of 2 years (from the start of treatment) in the absence of disease progression or unacceptable toxicity (if current standard practice).

13.2.7 Cessation of treatment

In line with usual clinical care, cessation or alteration of regimens at any time will be at the discretion of attending clinicians or the participants themselves. However all reasons for changes to treatment must be recorded. All participants who withdraw from protocol treatment or who are prescribed alternative treatment will remain in the trial for the purpose of follow-up and data analysis according to the treatment option to which they were allocated. Such patients will still attend for follow-up assessments, unless unwilling to do so, and CRFs will continue to be completed.

Reasons for discontinuation of treatment include:

- disease progression (as defined by RECIST v1.1 criteria – see Appendix C)
- unacceptable toxicity, in the opinion of the investigator or participant (Section 13.4.2)
- any Grade 3 immune-mediated adverse reaction that recurs (Section 13.4.2)
- any Grade 4 immune-mediated adverse reaction (except for endocrinopathies that are controlled with replacement hormones) (Section 13.4.2)
- participant decision (withdrawal of consent) (Section 14.11)
- pregnancy (Section 14.14)
- clinician decision to stop protocol treatment after a minimum of 2 years (from the start of treatment) in the absence of disease progression or unacceptable toxicity (if current standard practice).

13.2.8 Further therapy following cessation of treatment before progression

For patients in the control arm (Arm A), who stop anti-PD1 therapy before disease progression, it is anticipated that no further treatment for melanoma will be given until disease progression. In the event of further treatment being given, this must be reported on the relevant CRF.

13.2.9 Further therapy following disease progression

No specific recommendations are made regarding further treatment following disease progression. Treatment should be as per local policy. **Anti-PD1 antibody therapy can continue beyond progression at the investigator's discretion, but this would be outside the remit of this protocol and is not considered protocol treatment.**

13.3 Treatment details post randomisation: Arm B

Patients randomised to stop anti-PD1 therapy will receive no further treatment for their melanoma but will undergo regular monitoring and follow-up as per Section 14. It is important to note that patients may still experience toxicity following discontinuation of anti-PD1 therapy and recording of treatment-related toxicity occurring following randomisation to stop anti-PD1 therapy is part of trial procedures.

13.3.1 Further therapy following disease progression

If their disease progresses, patients will be offered standard treatment as per local policy. This may involve a different immunotherapy, a BRAF inhibitor or any treatment considered appropriate by the treating investigator. NHS England, and counterparts in South East Wales and South West Wales have confirmed that if a patient in the experimental arm (Arm B) stops treatment at randomisation and then progresses by RECIST v1.1 criteria, treatment options on progression can include restarting anti-PD1 antibody therapy. Currently, patients in Scotland will need to be considered on an individual case basis. The position in North Wales and Northern Ireland remains unconfirmed at present. **Anti-PD1 antibody therapy given after disease progression is outside the remit of this protocol and is not considered protocol treatment.**

13.4 Management of toxicity: Arm A and Arm B

13.4.1 Expected toxicity

Toxicity with anti-PD1 antibody therapy is characteristically immune-mediated. Both pembrolizumab and nivolumab have been reported to cause a wide range of immune-mediated adverse reactions. Expected toxicities of both agents are listed in the SPC.

These reactions can occur at variable times after initiation of therapy, with reports of reactions occurring within days after administration of the first dose to months after cessation of treatment.

Most adverse reactions are mild to moderate (CTCAE v5.0 Grade 1-2) and reversible, but severe and life-threatening reactions (Grade 3-4) can occur.

The most common side-effects (>10% incidence) of both agents are: fatigue, rash, pruritus, diarrhoea, nausea, decreased appetite (nivolumab) and arthralgia (pembrolizumab).

13.4.2 General principles

Toxicity management of immunotherapies is still evolving. It is recognised that investigators may refer to the ESMO guidelines on the management of toxicities from immunotherapy[40]

and UKON guidance[41], as well as the current version of the SPC for pembrolizumab and nivolumab, or local guidelines. Where there is conflicting advice in the different guidelines or SPCs, management of the toxicity is at the discretion of the local investigator. All sites must have local processes in place for management of toxicity in patients on anti-PD1 therapy/immune check-point inhibitors. These will be checked during the site approval process. Participants should be given a Patient Alert Card stating that they are on anti-PD1 therapy in accordance with standard practice.

Any participant with a suspected immune-mediated reaction should be adequately investigated to exclude other causes.

Most immune-mediated adverse reactions are reversible and depending on severity can be managed with interruptions of anti-PD1 therapy (if occurring during treatment), administration of systemic corticosteroids and/or supportive care.

If corticosteroids are started, they should continue until the toxicity has improved to Grade ≤1 severity. They should be tapered over at least 1 month.

If the immune-mediated reaction is not controlled with corticosteroids, addition of other systemic immunosuppressants should be considered. Supportive therapy including prophylactic antibiotics and anti-virals should be used as appropriate during immunosuppression.

Anti-PD1 therapy can generally be re-started once the adverse reaction has resolved to Grade ≤1 and the corticosteroid dose has been reduced to ≤10mg prednisolone or equivalent per day.

Anti-PD1 therapy must be permanently discontinued for any Grade 3 immune-mediated adverse reaction that recurs and for any Grade 4 immune-mediated adverse reaction, except for endocrinopathies that are controlled with replacement hormones.

13.5 Supportive care: Arm A and Arm B

Participants are permitted to receive supportive care throughout the trial, including transfusion of blood and blood products, treatment with antibiotics, anti-diarrhoeals, anti-emetics, analgesics etc, in accordance with local practice.

14 Trial Assessments and Data Collection

Participating sites will record trial participant data on trial-specific paper Case Report Forms (CRFs) and submit them to the CTRU. Missing and discrepant data will be flagged and additional data validations raised as appropriate by the CTRU data management team.

Participating sites will be expected to maintain a file of essential trial documentation (Investigator Site File (ISF)), which will be provided by the CTRU, and keep copies of all completed CRFs for the trial. The CRFs and participant-completed Quality of Life and health economics questionnaires will contain the participant's unique trial number, date of birth, and initials.

14.1 Schedule of events

The timing of interventions and assessments are summarised in Table 14.1.

14.1.1 Overview of visit schedule

Irrespective of their randomisation allocation, all participants will be seen for clinical assessment every 3 months for the first 12 months post randomisation, then every 6 months, as per standard practice.

Data collection for trial purposes via CRFs will occur at registration, randomisation, every 3 months for the first 12 months post randomisation, then 6-monthly during years 2-4 post randomisation, and at disease progression. Following progression, data collection will continue at the same time points for survival, selected toxicity and information on further treatment.

Quality of life and health economics questionnaires will be collected at randomisation, then every 3 months until 18 months post randomisation. Following progression, collection of these data continues at the same time points and patients should be encouraged to continue to complete the questionnaires.

Table 14.1: Assessment schedule

DANTE		T= -12mo to 0mo		T = 0	Post rand	Follow-up. Time from RANDOMISATION. Includes timepoints during treatment.											
	Pre-registration	Registration	Pre-randomisation	Randomisation	During treatment	3 mo	6 mo	9 mo	12 mo	15 mo	18 mo	2 years	2.5 years	3 years	3.5 years	4 years	At Progession
Histological or cytological confirmation of advanced melanoma	●																
Informed consent for registration	●																
Patient details		● (minimal)		●													
Registration		●															
Medical history			●[1]														
Clinical assessment			●[1]		●[5]	●	●	●	●		●	●	●	●	●	●	●
CT and/or MRI scan[6] (standard of care)	●[3, 4]		●[2, 3, 4]			●[4]	●[4]	●[4]	●[4]		●[4]	●[4]	●[4]	●[4]	●[4]	●[4]	●[4]
ECOG PS			●[1]														
FBC			●[1]		●[5]	●	●	●	●		●	●	●	●	●	●	●
U&E			●[1]		●[5]	●	●	●	●		●	●	●	●	●	●	●
LFTs			●[1]		●[5]	●	●	●	●		●	●	●	●	●	●	●
LDH			●[1]			●	●	●	●		●	●	●	●	●	●	●
Thyroid function tests (TSH as a minimum)			●[2]		●[5]												
Informed consent for randomisation			●														
Randomisation				●													
QoL questionnaires incl EQ5D (patient completed)			●[7] in clinic			● in clinic	● in clinic	● in clinic	● in clinic	● may be by post	● in clinic						
Health economics questionnaire (patient completed)			●[7] in clinic			● in clinic	● in clinic	● in clinic	● in clinic	● may be by post	● in clinic						
CTCAE toxicity monitoring				●[1]	●[5]	●	●	●	●		●	●	●	●	●	●	●
SAR monitoring and reporting				Monitor from randomisation until 5 months after the last protocol treatment dose													
Reason for non randomisation			●														

[1]within 14 days prior to randomisation

[2]within 28 days prior to randomisation (for CT scan, this is a recommendation only)

[3]results will be collected post randomisation for randomised patients only

[4]reported to RECIST v1.1 criteria (only applies if the patient is randomised)

[5]minimum of every 8 weeks whilst on treatment

[6]CT and/or MRI scan of the thorax, abdomen and pelvis, plus other known sites of disease that are assessable by imaging. Also CT and/or MRI of head pre-randomisation and at least 6 monthly in patients without known brain metastases at randomisation. The modality of imaging will be CT and/or MRI scans in accordance with standard clinical practice. Where possible, the same modality of imaging should be used to facilitate assessment of radiological response or progression.

[7]to be completed after consent and before randomisation

14.2 Pre-registration assessments (as per standard of care) and data collection

- Diagnostic biopsy
- Pre-treatment baseline imaging. This should be performed in accordance with standard practice at site. It is expected that imaging will usually comprise a CT scan of the thorax, abdomen and pelvis and a CT or MRI scan of the head, plus any other anatomic sites as indicated by symptoms or clinical examination findings. This imaging will need to be reported to RESIST v1.1 criteria for all patients who are formally assessed for eligibility for randomisation at 12 months (see Appendix C).

At registration, a minimum data-set will be collected (including demographic details, stage of disease, major prognostic factors, NHS[a]/CHI[b]/H&C[c] number ([a]England & Wales/ [b]Scotland/ [c]Northern Ireland)).

14.3 Pre-randomisation assessments

The following investigations and assessments will be carried out before randomisation, within the specified timeframes (existing assessments may be used if within the time specifications). **Written informed consent must be obtained before any assessments that are not part of standard care**.

- Medical history including concomitant medication (14 days)
- Clinical assessment including physical examination (14 days)
- Baseline toxicity assessment (14 days)
- ECOG Performance status (14 days)
- FBC, U&Es, LFTs, LDH (14 days)
- Thyroid function tests (TSH) (28 days)
- CT (or MRI) scan of the thorax, abdomen and pelvis plus other known sites of disease that are assessable by imaging, and CT or MRI scan of the head (timing to comply with the randomisation eligibility criteria Section 9.3, and ideally within 28 days before randomisation). Imaging will be assessed for response and progression in accordance with RECIST v1.1 compared to the pre-treatment baseline imaging. See Appendix C for details.

After consent, and before randomisation:

- Baseline QoL questionnaire
- Baseline health economics questionnaire

14.4 Treatment safety assessments post randomisation: Arm A only

Participants allocated to continue to receive anti-PD1 therapy should be assessed for safety in accordance with standard practice at site. It is expected that there should be no longer than 12 weeks between clinical safety assessments. As a minimum the following assessments will be undertaken:

- Physical examination
- Toxicity assessment
- FBC, U&Es, LFTs
- Thyroid function tests (TSH as a minimum)

Any other pre-treatment assessments performed as standard practice at trial sites should continue to be performed.

14.5 Follow-up assessments post randomisation (both arms)

Patients will be followed for response, progression, survival and toxicity at the same time points in both arms:

- 3-monthly (+/- 2 weeks) for 12 months after randomisation, then
- 6-monthly (+/- 2 weeks) up to 4 years (48 months) after randomisation

This visit schedule is in accordance with usual clinical practice.

The following assessments will be undertaken at each follow-up visit:

- Clinical assessment including physical examination
- Concomitant medication
- Toxicity assessment
- FBC, U&Es, LFTs, LDH

All randomised patients, regardless of treatment arm, will be assessed for toxicity of anti-PD1 therapy at each follow-up visit. It is important to note that side effects can occur following cessation of treatment so patients who stop treatment at randomisation (Arm B) may still develop new toxicity or continue to experience toxicity present at randomisation.

Toxicity will be assessed using CTCAE v5.0 and should be recorded at each follow-up visit.

Patients will be provided with a patient diary and should be encouraged to record symptoms experienced to act as an aide memoire for patients during follow-up visits to allow research staff at site to complete the follow-up CRFs. The diaries should not be returned to CTRU.

See Section 15 and Table 14.1 for details of timings of quality of life and health economics questionnaire administration.

14.6 Imaging assessments post randomisation

In accordance with standard of care, all randomised patients, regardless of treatment arm, will undergo imaging at the following time points until disease progression:

- 3-monthly (+/- 2 weeks) until 12 months post randomisation, and then
- 6-monthly (+/- 2 weeks) until 4 years post randomisation

The modality of imaging will be CT and/or MRI scans in accordance with standard clinical practice. Where possible, the same modality of imaging should be used to facilitate assessment of radiological response or progression.

Imaging of the chest, abdomen and pelvis is required at each time point plus any other known sites of disease that are assessable by imaging.

In patients without known brain metastases at randomisation, imaging of the head should be performed at least 6 monthly.

Imaging will be assessed for response and progression in accordance with RECIST v1.1. See Appendix C for details.

14.7 Assessments at disease progression

Progression on trial is defined according to RECIST v1.1; see Appendix C. If progression is suspected on clinical grounds (from symptoms or examination findings), this should be confirmed by imaging.

The following investigations and assessments will be undertaken at disease progression:

- Clinical assessment including physical examination
- Toxicity assessment
- Concomitant medication
- FBC, U&Es, LFTs, LDH

14.8 End of treatment

If a participant permanently discontinues DANTE protocol treatment, for any reason, an End of Treatment CRF must be faxed to CTRU within 7 days.

14.9 Follow-up after disease progression

Following progression, patients should continue to follow the trial visit schedule up to at least 18 months post-randomisation so that quality of life and health economics data can be collected at the planned time points, where possible.

Data on treatment administered post-progression, toxicity, and survival will be collected up to 4 years post randomisation at the planned time points via CRFs where possible (3-monthly for the first 12 months post randomisation then 6-monthly in years 2-4), and/or routine data sources (e.g. NHS Digital, ONS (Office for National Statistics) and SACT (Systemic Anti-Cancer Therapy data-set)).

14.10 Use of routine data sources

Consenting patients may be followed-up via routine data sources, including, but not limited to NHS Digital, ONS for survival and SACT for treatment information.

14.11 Withdrawal of consent

The PI or delegate should make every effort to ensure that the specific wishes of any participant who wishes to withdraw consent for further involvement in the trial are defined and documented using the Withdrawal CRF, in order that the correct processes are followed by the CTRU and site following the withdrawal of consent.

All participants who withdraw from protocol treatment or who are prescribed alternative treatment will remain in the trial for the purpose of follow-up and data analysis according to the treatment option to which they were allocated. Such patients will still attend for follow-up assessments, unless unwilling to do so, and CRFs will continue to be completed.

It should be made clear to any participant specifically withdrawing consent for further data collection that further data pertaining to safety will continue to be collected, for example the outcome of an event that was reported prior to withdrawal, and will be included in any safety analysis. In addition it is suggested that the participant is made aware of the fact that if any significant new information becomes available in regard to the treatment they have received in the trial it may be necessary to contact them in the future.

14.12 Assessment of efficacy

Progression and response will be assessed using RECIST v1.1[42] criteria (see Appendix C).

14.13 Deaths

All deaths occurring from the date of randomisation to the end of follow-up must be recorded on the Notification of Death CRF and sent to the CTRU within 7 days of the site team becoming aware of the death. It is important that the CRF is sent promptly so that any QoL questionnaire reminders sent by CTRU are stopped promptly.

14.14 Pregnancies

All pregnancies and suspected pregnancies in a trial participant, or their partner, occurring from the date of randomisation until six months after completion of protocol treatment[4] must be reported to the CTRU within 24 hours of the site becoming aware. All protocol treatment[4] must be stopped immediately if a pregnancy in a female participant occurs or is suspected.

The CTRU will report all pregnancies occurring during and within six months after completion of protocol treatment[4] to the Sponsor along with any follow-up information.

14.15 End of trial definition

The end of the trial is defined as the date of the collection of the last participant data item.

[4] Protocol treatment is defined as treatment given post randomisation as per the randomisation allocation, i.e. pregnancies occurring in patients in the stop treatment arm do not need to be reported.

15 Quality of Life and Health Economics

15.1 Data collection

Quality of life (QoL) and cost effectiveness will be assessed in all randomised patients via the following validated research questionnaires:

- the generic EORTC QLQ-C30 questionnaire[43]
- the melanoma-specific module EORTC QLQ-MEL38[44]
- EQ-5D-5L (EuroQol)[45]

In addition, resource use will be assessed using trial-specific health economic questionnaires.

QoL and health economic questionnaire packs will be administered to participants at the following time points, regardless of whether the patient is receiving treatment or not:

- Baseline, pre-randomisation (in clinic)
- 3 months post randomisation (+/- 2 weeks) (in clinic)
- 6 months post randomisation (+/- 2 weeks) (in clinic)
- 9 months post randomisation (+/- 2 weeks) (in clinic)
- 12 months post randomisation (+/- 2 weeks) (in clinic)
- 15 months post randomisation (+/- 2 weeks) (may be by post)
- 18 months post randomisation (+/- 2 weeks) (in clinic)

Research staff will provide the participant with the questionnaire packs in clinic (except the 15 month time point). Participants will be asked to complete the questionnaires in clinic. - If possible, all questionnaires should be completed prior to the participant's clinical consultation as this aids objectivity and compliance. Participants will seal the completed questionnaires in an envelope and hand it to the research staff. Research staff will then post the sealed envelopes to the CTRU.

The baseline questionnaires must be completed **after consent** has been obtained and **before randomisation**.

At the 15 month time point, unless the participant is being seen in clinic, the research team at site will post the questionnaire pack to the participant's home address, along with a stamped-addressed envelope (addressed to CTRU), for the patient to complete and post back.

15.2 Within trial cost-effectiveness

The within trial economic evaluation will estimate the incremental cost effectiveness ratio (ICER) for reduced duration anti-PD1 therapy compared to treatment until progression or unacceptable toxicity for patients with advanced melanoma from the perspective of the NHS and social care sector. A secondary analysis will be undertaken from the societal perspective. The analyses will use trial data collected to 18 months follow up.

The primary outcome measure of the trial is PFS. The trial economic evaluation will, for consistency, use the same primary outcome measure. However, as economic evaluations are designed to inform resource allocation decisions, evaluations will also be produced using overall survival and quality adjusted life years (QALYs) outcome measures. The estimation of QALYs requires the production of utility weights for each health state observed in the trial population. We will use the EQ-5D-5L (EuroQol) instrument[45] for this purpose.

Measurement of resource use: NHS resource use associated with each treatment modality will be collected. Data will also be collected on hospital admissions, extra outpatient visits, and use of supportive drugs to contribute to a health economics analysis of additional health costs related to treatment and the study. Data collection will be through trial CRFs (investigations, drugs, referrals for other services), patient completed health economic questionnaires (contact with patient, community and social care services) and use of hospital episode statistics (HES). Costs and outcomes will be discounted at 3.5% in line with current recommendations[46].

Incremental cost effectiveness ratios will be presented. Parameter uncertainty will be quantified using non-parametric bootstrapping techniques. Outputs will be presented as ICERs, cost effectiveness acceptability curves and expected net benefit.

As well as identifying the most cost-effective means of achieving a quality-adjusted life year (QALY), the NICE threshold of £20,000 per QALY will be applied. The impact of missing data will be examined using imputation methods. Sensitivity analyses will consider key cost drivers and factors that might affect the outcomes measured to explore uncertainty in the conclusions drawn[46].

15.3 Modelling long-term cost effectiveness

A long-term cost effectiveness analysis is required to capture the full impact of any therapy where it is possible that there is a difference in mortality between the interventions. The exact structure of the cost effectiveness model will be established in discussions with the clinicians on the study team and after analysis of the adverse event data observed in the trial. It is likely that the model will be a Markov or semi-Markov state model. As far as possible the transition rates for the model will be estimated from the clinical trial data – this will include PFS at 4 years follow up. For model parameters for which data could not be collected within the trial, e.g. longer term outcomes, recommended best practice will be followed in identifying and synthesising the best available evidence in the literature[47 48].

The long term cost effectiveness modelling will adopt the strategies for addressing issues of perspective and discounting as the within trial analysis.

The incremental cost effectiveness ratios will be estimated. To address uncertainty, probabilistic sensitivity analyses will be undertaken using Monte Carlo simulation techniques[48 49].

16 Qualitative research – patient feedback interviews

This trial will incorporate an integrated qualitative sub-study exploring patients' perceptions about the acceptability of randomisation.

In-depth interviews using a semi-structured topic guide (developed and adapted using PPI advice) to ensure consistency of content will be undertaken with 18 patients, including 12 patients who agree to be randomised into the study across the two arms and 6 patients who choose not to be randomised.

Interviews will be audio recorded with permission and will be 30-40 minutes in duration. Interviews may be conducted face to face or over the telephone. The data from the interviews of patients who choose to be randomised or who decline to be randomised will be used to support recruitment strategies in the trial. Data from this stage will also be used to provide insight about patients' views of discontinuing treatment and their reasons for taking up or declining this option.

This work will be undertaken under a separate ethically approved protocol.

17 Pharmacovigilance Procedures

17.1 General definitions

17.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product which does not necessarily have a causal relationship with this treatment.

17.1.2 Adverse Reaction (AR)

Adverse reactions (ARs) are all untoward and unintended responses to an investigational medicinal product related to any dose administered. This definition implies a reasonable possibility of a causal relationship which is supported by facts, evidence or arguments to suggest a causal relationship. This definition includes medication errors and uses outside what is foreseen in the protocol (i.e. if an AR occurs as a result of a medication error).

17.1.3 Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is any untoward medical occurrence or effect that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- consists of a congenital anomaly or birth defect
- jeopardised the subject or required intervention to prevent one of the above
- is otherwise considered medically significant by the Investigator

Medical and scientific judgement must be exercised in deciding whether an event is serious (see Section 17.4 for responsibilities). These characteristics / consequences must be considered at the time of the event and do not refer to an event which hypothetically may have caused one of the above.

17.1.4 Serious Adverse Reaction (SAR)

A Serious Adverse Reaction (SAR) is an SAE deemed to have been related to the investigational medicinal product. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Medical and scientific judgement must be exercised in deciding whether an event is serious (see Section 17.1.3 for definition of seriousness and Section 17.4 for responsibilities).

17.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product as set out in the Reference Safety Information (RSI) within the current approved version of the applicable SPC (Section 17.1.6). Severity describes the intensity of the event.

Medical and scientific judgement must be exercised in deciding whether an event is serious (see Section 17.1.3 for definition of seriousness and Section 17.4 for responsibilities).

17.1.6 Reference safety information

The Reference Safety Information (RSI) in this trial is defined as:

- Section 4.8 of the current approved version of the applicable SPC (pembrolizumab or nivolumab), supplied for use within the trial; (note this may not necessarily be the latest version of the SPC).

17.2 Monitoring period for toxicity and safety data

Toxicity will be monitored and reported (as per Section 17.3) for patients in both arms, from **randomisation until 4 years post randomisation**.[5] Toxicity will be recorded using Common Toxicity Criteria for Adverse Events version 5.0 (CTCAE v5.0) according to the same schedule as standard clinic appointments.

17.3 Operational safety recording and reporting requirements

As this trial is using IMPs which have a well-defined safety profile, and in line with standard practice and their marketing authorisation (or shorter duration), this trial will only collect the following:

For Arm A (standard therapy):

- Selected AEs related to anti-PD1 therapy administered before randomisation
- All ARs (any grade) related to anti-PD1 therapy administered after randomisation
- All SARs (any grade) related to anti-PD1 therapy administered after randomisation
- All SUSARs related to anti-PD1 therapy administered after randomisation

For Arm B (investigational therapy):

- Selected AEs related to anti-PD1 therapy administered before randomisation[6]

AEs related to anti-PD1 therapy administered before randomisation (Arm A and Arm B) and ARs (Arm A only) will be reported on the baseline and follow-up CRFs.

SARs and SUSARs (Arm A only) must be reported on the SAR or SUSAR CRF and faxed to CTRU **within 24 hours** of the trial site team becoming aware of the event. SARs and SUSARs will be actively monitored and reported **from randomisation until** 5 months after

[5] In addition to this, selected toxicity data related to anti-PD1 therapy administered before randomisation will be collected retrospectively at baseline – this is not part of the safety monitoring period.

[6] As Arm B participants do not receive any investigational medicinal products as part of this trial, by definition, no ARs, SARs and SUSARs will occur in these participants as part of this trial. However, adverse events related to anti-PD1 therapy administered before randomisation will be monitored for these participants from randomisation until 4 years post randomisation, just as for Arm A participants.

last protocol treatment dose and only for Arm A participants. If the site team becomes aware of any SARs or SUSARs after this active monitoring period, these should also be reported. (Arm B participants are not administered any investigational medicinal products as part of this trial (see Section 12.1), therefore SARs and SUSARs are not applicable to Arm B).

Non-serious or serious AEs not related to anti-PD1 therapy administered before or after randomisation will not be collected for trial purposes, but must still be recorded in the participants' medical notes.

See Table 17.1 for a summary of these requirements.

Table 17.1 Summary of safety reporting requirements

Event	Report on trial CRF	
	Arm A	Arm B
Selected Adverse Events (AEs) related to anti-PD1 therapy administered before randomisation (any grade)	✓	✓
Non-serious Adverse Events (AEs) not related to anti-PD1 therapy administered before or after randomisation (i.e. no causal relationship with trial treatment)	✘	✘
Serious Adverse Events (SAEs) not related to anti-PD1 therapy administered before or after randomisation (i.e. no causal relationship with trial treatment)	✘	✘
Adverse Reactions (ARs) (any grade) (i.e. related to anti-PD1 therapy administered after randomisation)	✓	✘
Serious Adverse Reactions (SARs) (any grade) (i.e. related to anti-PD1 therapy administered after randomisation)	✓	✘
Suspected Unexpected Serious Adverse Reaction (SUSAR) (i.e. related to anti-PD1 therapy administered after randomisation)	✓	✘

All of the events in the above table must be recorded in the patient notes even if they are not required to be reported on a trial CRF.

17.4 Responsibilities

Principal Investigator (PI):

1. Checking for ARs when participants attend for treatment and/or follow-up visits.
2. Using medical judgement in assigning seriousness and expectedness using the Reference Safety Information (Section 17.1.6) contained within the relevant Summary of Product Characteristics (pembrolizumab or nivolumab).
3. Ensuring that all SARs (including SUSARs) are recorded and reported to the CTRU within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SARs (including SUSARs) are chased with CTRU if a record of receipt is not received within 2 working days of initial reporting.
4. Ensuring that ARs are recorded and reported to the CTRU in line with the requirements of the protocol.

Chief Investigator (CI) / delegate or independent clinical reviewer:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning seriousness and expectedness of SARs where it has not been possible to obtain local medical assessment.
3. Immediate review of all SUSARs.
4. Review of specific SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.

CTRU:

1. Central data collection and verification of ARs, SARs and SUSARs according to the trial protocol onto a MACRO database.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
3. Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring & Ethics Committee (DMEC) and Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
4. Expedited reporting of SUSARs to the REC, MHRA and Sponsor within required timelines.
5. Notifying Investigators of SUSARs that occur within the trial which compromise participant safety.
7. Preparing Development Safety Update Reports (DSUR) for the MHRA and REC.

Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMEC regarding safety issues.

Data Monitoring & Ethics Committee (DMEC):

In accordance with the Trial Terms of Reference for the DMEC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

18 Endpoints

18.1 Primary endpoint

The primary endpoint is:

- Progression-free survival (PFS).

PFS will be calculated from the date of randomisation to the date of documented evidence of first progression or death (from any cause), or the date last known to be alive and progression-free for patients without a PFS event (non-inferiority endpoint). Please see Appendix C for assessment of progression after randomisation.

A sensitivity analysis to the primary endpoint will assess time to progression, where deaths without documented evidence of progression will be considered a competing risk event.

18.2 Secondary endpoints

The key secondary endpoint is:

- Quality of Life (QoL) measured using the participant self-report EORTC QLQ-C30[43] questionnaire and the melanoma-specific module QLQ-MEL38[44], and the EQ-5D-5L (EuroQol)[45]. The main QoL outcome of interest is the EORTC QLQ-C30 summary score[50] (superiority endpoint).

Other secondary endpoints are:

- Overall survival (OS), calculated from the date of randomisation to the date of death (from any cause), or the date last known to be alive for patients who are not known to have died (non-inferiority endpoint)
- Objective response rate, calculated as the proportion of patients achieving either a complete or partial response (non-inferiority endpoint)
- Best tumour response rate, calculated as the proportion of patients achieving each best response (complete response, partial response, stable disease or progressive disease)[42] (non-inferiority endpoint)
- Duration of response, calculated as the time from first tumour response (after randomisation) until disease progression (non-inferiority endpoint)
- Safety and anti-PD1 therapy-related toxicity. Toxicity will be recorded using CTCAE v5.0
- Cost-effectiveness of the two treatment strategies

The choice of primary endpoint was carefully considered given that patient-centred outcomes are very important in this context. However, it was also considered that to recommend reduced duration therapy, it is essential to demonstrate that survival is not detrimentally affected. This was supported by PPI representatives and in discussion with clinical colleagues. The primary outcome measure of the published trials demonstrating

efficacy of anti-PD1 therapies has been progression-free survival[51] and this has therefore been chosen as the primary endpoint.

Including QoL as a co-primary endpoint was also considered. However, an additional consideration is that so far there is little published data on QoL with anti-PD1 therapy. This is a new and evolving field, and to date none of the randomised controlled trials of anti-PD1 therapies in melanoma has published full QoL analyses. There is, therefore, a paucity of data for determination of (i) whether the measurements of those QoL components considered most relevant to be classed as a co-primary endpoint are sensitive to changes in a population treated with anti-PD1 therapy; (ii) appropriate clinically relevant differences and time-points; and (iii) calculation of sample size for QoL as a co-primary outcome measure. To highlight the importance of QoL in this study it has therefore been designated as the key secondary endpoint for the trial, and the EORTC QLQ-C30 summary score defined as the main QoL outcome of interest[50].

19 Statistical Considerations

19.1 Sample size and planned recruitment rates

19.1.1 Sample size

Although patients will be followed up for a total of 4 years after randomisation, based on clinical consensus, the primary time-point of PFS to base the sample size calculation on (and therefore the primary analysis) is at 12 months after randomisation (i.e. 2 years after the start of anti-PD1 therapy ('2-year PFS')).

In the CHECKMATE-067 trial[22] 43% of patients in the nivolumab only arm were alive and progression-free at 12 months after the start of treatment. The PFS rate at 24 months after the start of treatment was 37%. Given that 100% of our trial population will be alive and progression-free at 12 months after the start of anti-PD1 therapy (i.e. at the point of randomisation to the trial) and using a relative reduction between 43% and 37% (that is, (43-37)/43 = 14.0), then it is estimated that approximately 86% of our trial patients will be alive and progression-free at 24 months after the start of anti-PD1 therapy (i.e. 12 months after randomisation) in the control arm.

Therefore assuming the 2-year PFS rate in the control arm is 86% and defining non-inferiority as a reduction in 2-year PFS of no more than 6%, with 80% power and a one-sided significance level of 5%, 1,148 patients are required to test for this degree of non-inferiority using a one-sided log-rank test, assuming patients are followed for a fixed length of time (i.e. 12 months following randomisation). To account for a 5% drop-out rate, 1,208 patients (604 per arm) will be required in total. Since we are assessing inferiority and superiority of the experimental arm at the interim analysis and non-inferiority in the final analysis, no adjustment of the alpha levels of the confidence intervals at the final analysis is therefore required[52].

The non-inferiority margin has been defined following discussion with clinicians via the NCRI Skin Cancer Clinical Studies Group (CSG) and patient representatives. A 6% absolute difference is considered to be clinically acceptable. When considering the PFS rates 2 years after starting treatment, taking into account all patients who have progressed or died within the first 12 months of treatment, it is estimated that this 6% difference is equivalent to a difference of 2.6% i.e. the estimated PFS rate at 2 years after the start of treatment would be no worse than 34.4% (vs. 37%) in the experimental arm. This 2.6% difference is considered to be very small.

Given the change to the inclusion criteria in protocol version 6.0 to include patients receiving combination therapy (ipilimumab-nivolumab), the sample size was re-assessed to accommodate the inclusion of these patients. In the CHECKMATE-067 trial[22] the relative reduction between months 12 and 24 for patients on combination therapy was exactly the same as that for the nivolumab only arm (i.e. a relative reduction between 50% and 43% is 14%); hence it is also expected that approximately 86% of patients receiving ipilimumab-nivolumab to be alive and progression-free at 12 months post-randomisation for those randomised to the control arm. Therefore, the sample size will remain at 1,208 patients. To note, it is estimated that approximately 1/3rd of patients are on combination therapy; however

as the underlying assumption of the 2-year PFS rate in the control arm (86%) is not expected to be impacted by the proportions receiving monotherapy or combination therapy, the sample size will remain the same regardless of the distribution of randomised patients.

Patients currently receiving anti-PD1 therapy were surveyed during the design of DANTE to explore their perceptions around the benefits/risks of reduced duration therapy, including scenarios to understand what loss in efficacy patients consider acceptable when offset by the advantages of being free from treatment. Feedback from patients was that they recognised the advantages to being able to stop treatment after 1 year providing any detriment to disease control was minimal.

The non-inferiority margin of 6%, expressed as the difference in PFS rates at 12 months post-randomisation, corresponds to a non-inferiority margin of HR=1.48. It must be highlighted however that, although the primary endpoint in DANTE is a time-to-event endpoint, it is less appropriate to use a hazard ratio to define and demonstrate non-inferiority for trials assessing immune check-point inhibitors. As already noted, the timing of the primary assessment of efficacy is time-driven and will occur when all patients have completed 12 months of follow-up after randomisation; this time-point is considered to be the most clinically relevant time-point. In addition, the choice of a time-driven analysis is considered to be a pragmatic solution to the various challenges of designing a trial of immunotherapy. Current literature has proposed that for immune check-point inhibitors 'milestone survival' is an appropriate endpoint[36 53]. A milestone survival approach assesses the proportion of patients without a PFS event based on the Kaplan-Meier estimate at the time-point of interest.

Survival analyses are usually based on the exponential distribution assumption in which proportional hazards are assumed. For immune check-point inhibitors, although this assumption is not unreasonable, based on survival data for metastatic melanoma observed so far, it does not appear to correctly reflect the function of the curves. In addition, given the mechanisms of action of immunotherapies and our trial question, it is unclear as to when, if at all, separation of the survival curves will be seen in this trial. Therefore it should not be assumed that proportional hazards will definitely exist in our trial data and as such, a hazard ratio is unlikely to be an appropriate statistic to use to define non-inferiority.

With the current sample size, assuming questionnaire compliance is in line with that expected based on previous cancer clinical trials conducted at the CTRU, using the operational definitions by Cohen[54], there will be sufficient power to detect small changes in QoL using a 5% (2-sided) significance level.

19.1.2 Planned recruitment rates

The recruitment period is 5 years. This trial has been designed with 3 interim stages (described in detail in section 7.7), with the aim of the first two stages being to identify lack of feasibility of recruitment early in the trial. The overall recruitment target for stage 1 is at least 30 randomised patients during the first 9 months of recruitment from at least 10 trial sites. Stage 2 will run from months 19 to 24 and the recruitment target for this stage is at least 135 randomised patients.

As described in section 7.7.2, achieving the stage 2 'green' target and estimating the number of randomised patients in months 1-18 is likely to demonstrate that the recruitment target of

1,208 randomised patients can be met in approximately 5 years. This assumes the expected average randomisation rate of 6 patients/site/year continues beyond stage 2 (see section 7.7.2 for further details of this calculation). Stage 2 will however allow for a more accurate estimation of future randomisations to confirm when the target of 1,208 randomised patients is expected to be reached and therefore whether a short extension in recruitment time is required.

All proposed trial sites have proven track records in recruiting to interventional melanoma studies, as evidenced by data from the NCRI Skin Cancer CSG. Probable proportionate recruitment has been estimated from each site based on data from the AVAST-M study[35], which is the most recent UK-based academic trial of systemic therapy in melanoma. Treatment of melanoma is based in specialist centres and the proposed trial sites will give near complete geographic coverage. The potential patient population has been estimated from data prepared by Merck for NICE TA366[6], where the number of stage III and IV melanoma patients expected to receive anti-PD1 therapy per year from 2016-2020 was modelled using ONS data. This has been extrapolated to 2022 to cover the trial's recruitment period. Assuming 90% population coverage, it has been calculated that there will be an adequate number of potential patients (see Table 19.1). These data cover England and Wales only. Opening sites in Scotland and Northern Ireland will increase the population further.

Table 19.1: Estimate of potential patient population

Year	Max. no. of stage III or IV patients treated with anti-PD1 therapy per year	Assume 90% population coverage	Expect at least 43% eligible for randomisation[22]
2018	964	868	373
2019	998	898	386
2020	1033	930	400
2021	1068	961	413
2022	1103	993	427
Total	5166	4650	1999

20 Statistical Analysis

20.1 General considerations

Statistical analysis is the responsibility of the CTRU Statisticians, except for the health economic analysis which is the responsibility of the health economic TMG member. The analysis plan detailed below provides an overview of the analyses to be performed. A separate and fully detailed statistical analysis plan (SAP) will be written before any analyses are undertaken (separate DMEC, interim and final SAPs) and in accordance with CTRU standard operating procedures. Any changes to the finalised analysis plans, and reasons for changes, will be documented.

Analysis of the non-inferiority endpoints will be performed on both the intention-to-treat (ITT) and per-protocol (PP) populations, whilst analysis of the superiority endpoints will be performed on an ITT basis. Per-protocol analyses for the superiority endpoints will also be performed if there is a sufficient number of major protocol violators. For the superiority endpoints, the ITT analysis will be given primacy, however for the non-inferiority endpoints, equal weighting will be given to both the ITT and per-protocol analyses, as the ITT is likely to be the least conservative approach when testing for non-inferiority.

Safety and toxicity analyses will be performed on the safety population and the response endpoints will be analysed using the RECIST evaluable population. In addition, only participants in the RECIST evaluable population who have a response after randomisation will be included in the analysis of the duration of response endpoint.

The intention-to-treat population will consist of all participants randomised into the trial regardless of whether they were eligible and/or remained in the trial. In this population, participants will be grouped according to the treatment they were randomised to receive.

The per-protocol population will consist of participants who are not classed as major protocol violators, as defined in the statistical analysis plan. Participants will be summarised according to treatment received.

The safety population will include all participants who receive at least one dose of trial treatment (control group patients) and have at least one post-randomisation safety assessment. Analyses based on the safety population will also summarise participants according to treatment received.

The RECIST evaluable population will include all participants who had disease that was evaluable by RECIST v1.1 criteria at randomisation (the trial-defined ‘baseline’ measurement).

Hypothesis testing will be two-sided for superiority endpoints and one-sided for non-inferiority endpoints and use a 5% significance level, unless specified otherwise.

Sensitivity analyses may be performed for each endpoint, for example to take into account differing assumptions about missing data if there is a significant number of missing data, and will be detailed in the full statistical analysis plan.

20.2 Frequency of analysis

There will be 5 stages of analysis (see section 7.7 for full details). Stages 1-3 will be interim stages, with the aim of identifying lack of feasibility of recruitment and efficacy early in the trial. Stage 1 analysis and implementation of any required changes to the trial and associated documentation will take place between months 10-12 of recruitment. Stage 2 analysis and decision-making regarding continuation of the trial will take place between months 25-27 of recruitment. Stage 3 analysis will be conducted when at least half the required number of participants have been randomised and have completed 12 months of trial follow-up, and the study is at least 30 months into recruitment.

The primary analysis of efficacy and safety will be carried out at stage 4. Stage 4 analysis will occur when all participants have completed 12 months of follow-up after randomisation, which is anticipated to be 6 years from the start of recruitment. Stage 5 will be a long-term follow-up analysis with the aim of identifying any detriment to long-term survival with reduced duration treatment. Stage 5 analysis will take place when all participants have completed 4 years of follow-up after randomisation.

A DMEC will be set up to independently review interim data on efficacy, safety and recruitment. Interim reports will be presented to the DMEC in strict confidence, on at least yearly intervals. This committee, in light of the interim data and of any advice or evidence they wish to request, will advise the TSC if there is proof beyond reasonable doubt that one treatment is better.

20.3 Interim analyses (stages 1-3)

At stage 1 (internal pilot), feasibility of recruitment and acceptance of randomisation in sites that are open to recruitment by the start of month 4 will be assessed. The outcome measures will be (i) percentage of eligible patients who agree to be randomised within months 4 to 9 of recruitment and (ii) number of patients randomised at 9 months. Targets for (i) are:

- Green: ≥60% of eligible patients randomised
- Amber: 46-59% of eligible patients randomised
- Red: ≤45% of eligible patients randomised.

See section 7.7.1.3 for the implications of reaching the ‘green/amber/red’ targets. The target for (ii) is at least 30 randomised patients from at least 10 sites in the first 9 months of recruitment.

To confirm feasibility of recruitment, recruitment from all sites between months 19 to 24 of recruitment will be assessed at stage 2. Targets at stage 2 are:

- Green: ≥135 patients randomised
- Amber: 113-134 patients randomised
- Red: <113 patients randomised.

See section 7.7.2 for the implications of reaching the ‘green/amber/red’ targets.

In order to monitor the representativeness of the randomised population at an early stage in the trial, baseline demographics and disease characteristics of the registered and randomised populations in the internal pilot (stage 1) and stage 2 analyses will also be presented. In addition, as part of the stage 2 analysis a summary of overall survival for all registered patients who are alive and progression-free at 12 months (the intended patient population under study) and all randomised patients will be presented. Overall survival data for registered patients who are not randomised will be obtained from routine and/or translational study (where available) data.

One formal statistical interim analysis is also planned to test for superiority ($p<0.005$) or inferiority ($p<0.05$) of the experimental arm against the control arm on PFS (stage 3). Different alpha levels have been incorporated to reflect the relative importance of the interim analysis for superiority and inferiority claims. In the interim assessment of efficacy where inferiority or superiority of the experimental arm is being assessed, the analysis population will be the ITT population. PFS will be investigated using Kaplan-Meier survival curves. Participants without a PFS event at the time of analysis will be censored at the date they were last known to be alive and progression-free. If the proportional hazards assumption is met, Cox's Proportional Hazards model, adjusting for the minimisation factors, will be used to compare PFS between the treatment arms. If the proportional hazards assumption is not met, alternative methodology will be used (for example, restricted mean survival time).

20.4 Primary endpoint analysis (stages 4 and 5)

The primary endpoint is PFS. Interpretation of non-inferiority for PFS will be based on the 90% confidence interval (one-sided type I error rate of 5.0%) of the difference in PFS rates at 12 months post-randomisation determined from Kaplan-Meier estimates at this time-point; the 90% confidence interval of the hazard ratio (HR) will also be presented if appropriate. The upper limit of the 90% confidence interval of the difference in PFS rates at 12 months post-randomisation will be compared with the non-inferiority margin of 6%. If it is below this margin then the result will be taken as evidence that reduced duration therapy is not inferior to standard duration. If the upper limit is above the non-inferiority margin then non-inferiority will not have been demonstrated. PFS will be assessed using Kaplan-Meier survival curves. Participants without a PFS event at the time of analysis will be censored at the date they were last known to be alive and progression-free. Median PFS and corresponding 90% confidence intervals and PFS estimates at each year post-randomisation with corresponding 90% confidence intervals will also be presented for each treatment group and for the difference between groups. If the proportional hazards assumption is met, Cox's Proportional Hazards model, adjusting for the minimisation factors (and other prognostic factors in a secondary analysis), will be used to compare PFS between the treatment groups. If the proportional hazards assumption is not met, alternative methodology will be used (for example, restricted mean survival time). As this is a non-inferiority trial, in stages 4 and 5, analysis of PFS will be performed on both the ITT and per-protocol populations.

To obtain a current representation of PFS for the population of patients with unresectable stage III or stage IV (metastatic) melanoma who have not received prior systemic immunotherapy, a summary of PFS from the start of anti-PD1 therapy for all registered patients who are not randomised for any reason together with participants randomised to the control arm (standard duration) will be presented. PFS data for registered patients who are

not randomised for reasons other than progression or death will be obtained from routine and/or translational study (where available) data. Progression/death dates for registered patients who are not randomised due to progression/death within 12 months of starting anti-PD1 treatment will be collected on a non-randomisation CRF.

A sensitivity analysis to the primary endpoint will assess time to progression, where deaths without documented evidence of progression will be considered a competing-risk event. Time to progression will be investigated using cumulative incidence function curves. Participants without documented evidence of progression and who are not known to have died at the time of analysis will be censored at the date last known to be alive and progression-free. Participants who have died without evidence of progression will be censored at their date of death in the analysis estimating the treatment effect (i.e. Cox's Proportional Hazards model if appropriate) and classed as having a competing-risk event (i.e. not censored) in the analysis estimating the incidence of progressions (i.e. the cumulative incidence function curves). If the proportional hazards assumption is met, Cox's Proportional Hazards model, adjusting for the minimisation factors, will be used to compare time to progression between the treatment groups. If the proportional hazards assumption is not met, alternative competing-risk methodology where available will be used.

20.5 Secondary endpoints analysis (stages 4 and 5)

To note, only the secondary endpoints of OS and toxicity will be analysed at stage 5.

The main QoL outcome of interest is the summary score of the EORTC QLQ-C30. Quality of life, including the EORTC QLQ-C30 summary score, global QoL, functional scales and symptoms, will be summarised for each treatment arm at each post-randomisation time-point, using adjusted for baseline mean scores and 95% confidence intervals. These summaries and differences between treatment arms will be obtained and compared using a multi-level repeated measures model accounting for data at all post-randomisation time-points, assuming missing data at random and allowing for time, treatment, treatment-time interaction, and adjusting for baseline QoL and the minimisation factors (and other prognostic factors in a secondary analysis) [fixed effects] and for participant and participant-time interaction [random effects] where appropriate. Data will also be summarised descriptively using bar charts, box plots and summary tables. Missing data patterns will be examined carefully and alternative analyses using different missing data assumptions will be performed if appropriate (e.g. pattern mixture multi-level models). Analyses will be performed on the ITT population and also the per-protocol population if there is a sufficient number of participants who are classed as major protocol violators.

Overall survival will be investigated using Kaplan-Meier survival curves. Participants who are not known to have died at the time of analysis will be censored at the date they were last known to be alive. Median OS and corresponding 90% confidence intervals and survival estimates at each year post-randomisation with corresponding 90% confidence intervals will also be presented for each treatment group and for the difference between groups. If the proportional hazards assumption is met, Cox's Proportional Hazards model, adjusting for the minimisation factors (and other prognostic factors in a secondary analysis), will be used to compare OS between the treatment groups. If the proportional hazards assumption is not

met, alternative methodology will be used (for example, restricted mean survival time). Analysis of OS will be performed on both the ITT and per-protocol populations.

To obtain a current representation of OS for the population of patients with unresectable stage III or stage IV (metastatic) melanoma who have not received prior systemic immunotherapy, a summary of OS from the start of anti-PD1 therapy for all registered patients who are not randomised for any reason together with participants randomised to the control arm (standard duration) will be presented. OS data for registered patients who are not randomised for reasons other than death will be obtained from routine and/or translational study (where available) data. Death dates for registered patients who are not randomised due to death within 12 months of starting anti-PD1 treatment will be collected on a non-randomisation CRF.

Objective response rate will be summarised by the proportion of participants achieving either a complete or partial response, whilst best tumour response will be summarised by the proportion of participants achieving each best response (complete response, partial response, stable disease or progressive disease)[42]. The differences in rates between the treatment groups will be presented with corresponding 90% confidence intervals and compared using (i) logistic regression for objective response rates and (ii) ordered logistic regression for best tumour response, to adjust for the minimisation factors (and other prognostic factors in a secondary analysis). Sensitivity analyses will be conducted to allow for any deaths from causes other than melanoma, for whom no response status was observed. Analyses will be performed on the RECIST evaluable population; both an ITT and per-protocol analysis will be performed.

Duration of response will be assessed in only those participants in the RECIST evaluable population who have a response after randomisation; participants included in the analysis who die without documented evidence of disease progression will be considered a competing-risk event. Duration of response will be investigated using cumulative incidence function curves. Participants without documented evidence of progression and who are not known to have died at the time of analysis will be censored at the date last known to be alive and progression-free. Participants who have died without evidence of progression will be censored at their date of death in the analysis estimating the treatment effect (i.e. Cox's Proportional Hazards model if appropriate) and included as having a competing-risk event (i.e. not censored) in the cumulative incidence function curves. If the proportional hazards assumption is met, Cox's Proportional Hazards model, adjusting for the minimisation factors (and other prognostic factors in a secondary analysis), will be used to compare duration of response between the treatment groups. If the proportional hazards assumption is not met, alternative competing-risk methodology where available will be used. Both an ITT and per-protocol analysis will be performed.

Safety and toxicity (recorded using CTCAE v5.0) data will be reported descriptively and summarised using the safety population. In particular, SARs and SUSARs will be summarised by causality and body system.

Two sets of cost-effectiveness analyses will be undertaken for the health economics evaluation: within-trial analyses, comparing costs and outcomes between reduced and standard duration anti-PD1 therapy up to the 18-month post-randomisation follow-up time-point; and a decision analytic cost effectiveness model, which will extrapolate the results of

the trial to a lifetime horizon. Sensitivity analyses will be undertaken using recommended methods and discounting applied at the recommended rate (currently 3.5%). See section 15 for further details.

Subgroup analyses for the clinical randomisation factors and other baseline participant characteristics will be performed to investigate whether there is heterogeneity of treatment effect on outcomes.

An assessment of representativeness of the randomised population will also be included in the stage 4 (primary analysis) and stage 5 (long-term survival) analyses. Baseline demographics and disease characteristics of the registered and randomised populations in the stage 4 and stage 5 analyses will also be presented. In addition, summaries of overall survival and PFS (where possible) for all registered patients who are alive and progression-free at 12 months (the intended patient population under study) and all randomised patients will be presented. Overall and progression-free survival data for registered patients who are not randomised will be obtained from routine and/or translational study (where available) data. Overall survival for all registered patients who are not randomised for any reason together with participants randomised to the control arm (standard duration) will also be compared with national cancer registry data of all patients with advanced melanoma.

21 Trial Monitoring

Participating sites and PIs must agree to allow trial-related on-site monitoring, Sponsor audits and regulatory inspections by providing direct access to source data/documents as required. Patients are informed of this in the patient information sheet and are asked to consent to their medical notes being reviewed by appropriate individuals on the Consent Form.

CTRU will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

21.1 Data Monitoring and Ethics Committee

An Independent Data and Ethics Monitoring Committee (DMEC) will review the safety and ethics of the trial. Detailed un-blinded reports will be prepared by the CTRU for the DMEC at at-least yearly intervals. The DMEC will also review any other external information deemed relevant to the ethical running of the study.

21.2 Data Monitoring

Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until it is received, confirmed as not available or the trial is at analysis. However, missing data items will not be chased from participants (although missing questionnaires may be). The CTRU and Sponsor will reserve the right to intermittently conduct source data verification exercises on a sample of participants, which will be carried out by staff from the CTRU. Source data verification will involve direct access to patient notes at the participating hospital sites and the ongoing central collection of copies of consent forms and other relevant investigation reports. Central imaging review of selected cases may be conducted for quality assurance purposes to ensure consistency of reporting to RECIST v1.1 standards.

21.3 Clinical governance issues

To ensure responsibility and accountability for the overall quality of care received by participants during the study period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the Trial Steering Committee and, where applicable, to individual NHS Trusts.

22 Quality Assurance Processes

22.1 Quality assurance

The trial will be conducted in accordance with the principles of Good Clinical Practice (GCP) in clinical trials, as applicable under UK regulations, the NHS Research Governance Framework (RGF) and Scottish Executive Health Department Research Governance Framework for Health and Social Care 2006, and through adherence to CTRU Standard Operating Procedures.

22.2 Serious breaches

CTRU and Sponsor have systems in place to ensure that serious breaches of GCP or the trial protocol are picked up and reported. Investigators are required to promptly notify the CTRU of a serious breach (as defined in regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments) that they become aware of. A 'serious breach' is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial.

In the event of doubt or for further information, the Investigator should contact the Senior Trial Co-ordinator /Manager at the CTRU.

23 Ethical Considerations

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 48th World Medical Association General Assembly, 1996. Informed written consent will be obtained from the patients prior to registration and randomisation into the study. The right of a participant to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment.

23.1 Ethical approval

The trial will be submitted to and approved by a REC and the appropriate Site Specific Assessor for each participating centre prior to entering participants into the trial. The CTRU will provide the REC with a copy of the final protocol, patient information sheets, consent forms and all other relevant study documentation.

24 Confidentiality

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and electronically at the CTRU. The CTRU will comply with all aspects of the 2018 Data Protection Act and operationally this will include:

- consent from participants to record personal details including initials, date of birth, NHS/CHI/H&C number, hospital number.
- appropriate storage, restricted access and disposal arrangements for participant personal and clinical details.
- consent from participants for access to their medical records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to trial participation.
- consent from participants for the data collected for the trial to be used to evaluate safety and develop new research.
- copies of participant consent forms, which will include participant names, will be sent to the CTRU when a participant is registered and randomised into the trial. Participant NHS/CHI/H&C number will be collected at registration, but all other data collection forms that are transferred to or from the CTRU will be coded with a trial number and will include two participant identifiers, usually the participant's initials and date of birth.
- where central monitoring of source documents by CTRU (or copies of source documents) is required (such as scans or local blood results), the participant's name must be obliterated by site before sending.
- where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to CTRU.

If a participant withdraws consent for further trial treatment and / or further collection of data their data will remain on file and will be included in the final trial analysis.

25 Archiving

25.1 Trial data and documents held by CTRU

At the end of the trial, data and the Trial Master File will be securely archived by CTRU in line with the Sponsor's procedures for a minimum of 15 years.

25.2 Trial data and documents held by research sites

Site data and documents will be archived at the participating research sites. Following authorisation from the Sponsor, arrangements for confidential destruction will then be made.

25.3 Participant medical records held by research sites

Research sites are responsible for archiving trial participant medical records in accordance with the site's policy and procedures for archiving medical records of patients who have participated in a clinical trial. However, participant medical records must be retained until authorisation is received from the Sponsor for confidential destruction of trial documentation.

26 Statement of Indemnity

Sheffield Teaching Hospitals NHS Foundation Trust will be liable for negligent harm caused to participants treated in the UK that is caused by the design of the study. The NHS has a duty of care to patients treated in the UK, whether or not the patient is taking part in a clinical study, and the NHS remains liable for harm to UK patients due to clinical negligence under this duty of care.

27 Trial Organisational Structure

27.1 Responsibilities

27.1.1 Individuals and individual organisations

Chief Investigator (CI) – The CI is involved in the design, conduct, co-ordination and management of the trial. The CI will have overall responsibility for the design and set-up of the trial, and pharmacovigilance within the trial.

Trial Sponsor – The Sponsor is responsible for trial initiation management and financing of the trial as defined by Directive 2001/20/EC. These responsibilities are delegated to the CTRU as detailed in the trial contract.

Clinical Trials Research Unit (CTRU) – The CTRU will have responsibility for conduct of the trial as delegated by the Sponsor in accordance with relevant GCP standards and CTRU SOPs, and the GCP Conditions and Principles as detailed in the UK Medicines for Human Use (Clinical Trials) Regulations 2006, including randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data verification, monitoring schedule and statistical analysis for the trial. In addition the CTRU will support ethical approval submissions, any other site-specific approvals and clinical set-up, ongoing management including training, monitoring reports and promotion of the trial. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting and statistical analyses.

27.1.2 Oversight and trial monitoring groups

Trial Management Group (TMG) – The TMG, comprising the CI, CTRU team, other key external members of staff involved in the trial and a PPI representative will be assigned responsibility for the clinical set-up, on-going management, promotion of the trial, and for the interpretation and publishing of the results. Specifically the TMG will be responsible for (i) protocol completion, (ii) CRF development, (iii) obtaining approval from the REC and HRA and supporting applications for Site Specific Assessments, (iv) submitting a CTA application and obtaining approval from the MHRA, (v) completing cost estimates and project initiation, (vi) nominating members and facilitating the TSC and DMEC, (vii) reporting of serious adverse events, (viii) monitoring of screening, recruitment, treatment and follow-up procedures, (ix) auditing consent procedures, data collection, trial end-point validation and database development.

Trial Steering Committee (TSC) – The TSC, with an independent Chair, will provide overall supervision of the trial, in particular trial progress, adherence to protocol, participant safety and consideration of new information. It will include an Independent Chair, not less than two other independent members and a PPI representative. The CI and other members of the TMG may attend the TSC meetings and present and report progress. The Sponsor will be invited to TSC meetings. The Committee will meet annually as a minimum.

Data Monitoring and Ethics Committee (DMEC) – The DMEC will include independent membership and will review the safety and ethics of the trial by reviewing interim data during recruitment and the follow-up period. The Committee will meet annually as a minimum.

28 Publication policy

The trial will be registered with an authorised registry, according to the International Committee of Medical Journal Editors (ICMJE) Guidelines, prior to the start of recruitment.

The success of the trial depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributorship. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- conception and design, or acquisition of data, or analysis and interpretation of data,
- drafting the article or revising it critically for important intellectual content,
- and final approval of the version to be published,
- and that all these conditions must be met (www.icmje.org).

In light of this, the Chief Investigator and relevant senior CTRU staff will be named as authors in any publication. In addition, all collaborators will be listed as contributors for the main trial publication, giving details of roles in planning, conducting and reporting the trial.

To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the analysis of the primary endpoint, either for trial publication or oral presentation purposes, without the permission of the DMEC and TSC. In addition, individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the trial until the first publication of the analysis of the primary endpoint.

An electronic copy of peer-reviewed, published papers arising from this research will be deposited in the Europe PubMed Central database.

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Appendix A - ECOG Performance Status

GRADE	ECOG 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 house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair

Appendix B – National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE)

Toxicities will be assessed based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0, 27 November 2017.

A copy of NCI-CTCAE may be obtained at:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50

Appendix C – Evaluation of Progression and Response

Progression and response will be assessed according to RECIST v1.1[42]. This is in accordance with recent recommendations from the immune-RECIST working group that RECIST v1.1 should still be used to assess outcome measures in phase III trials of immunotherapy agents, with iRECIST criteria reserved for exploratory end-points[55].

Please see Section 14 for requirements on timing of scans, modality of imaging, and anatomic areas to be included.

(i) Assessment of eligibility for randomisation

Registered patients must be progression-free at 12 months after starting anti-PD1 antibody therapy to be eligible for randomisation (see Section 9.2).

To assess eligibility:

- The pre-treatment scan done at the start of anti-PD1 therapy is the baseline scan for the RECIST assessment
- It will be compared to the 12-month (pre-randomisation) scan, done at 12 months after commencing anti-PD1 therapy
- The response should be categorised according to RECIST as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) (see below for RECIST definitions)
- Patients with CR, PR or SD on this comparison are eligible for randomisation in the study. Patients with PD are not eligible

This means that sites must assess the pre-treatment scan of registered patients who are assessed for eligibility for randomisation to RECIST standards and also the 12-month scan. Other scans done during the registration period (at 3, 6 and 9 months after the start of anti-PD1 therapy) will not be used in the assessment of response or progression for trial purposes. Therefore, patients with apparent progression initially and delayed response will still be eligible for randomisation providing the comparison of the 12-month scan to the pre-treatment baseline is SD or better.

(ii) Assessment of progression and response after randomisation

Following randomisation:

- The 12-month (pre-randomisation) scan is the baseline for assessment of progression and response end-points. Target and non-target lesions must be defined from this scan
- All subsequent scans done on trial must be reported to RECIST standards with documented assessment of change in target and non-target lesions as defined on the pre-randomisation scan

(iii) RECIST v1.1 definitions

Measurable disease:

- Disease is classed as measurable if there is at least one lesion that can be accurately measured in at least one dimension (a target lesion)
- Target lesions should be selected on the basis of size and suitability for repeat measurement, up to a maximum of two measurable lesions per organ, and up to a maximum of five lesions in total. These should be representative of all involved organs
- Non-nodal lesions are classed as measurable if the longest diameter is ≥10 mm (assuming CT slice thickness is no greater than 5mm)
- Lymph nodes are classed as measurable if the short axis diameter is ≥15 mm (assuming CT slice thickness is no greater than 5mm)
    - Lymph nodes measuring >10 to <15mm are classed as non-measurable lesions
    - Lymph nodes ≤10mm are normal (i.e. not pathological)
- Clinical lesions (e.g. sub-cutaneous or cutaneous metastases) are only classed as measurable when they are superficial and ≥10 mm diameter as assessed using calipers. Documentation by colour photography including a ruler to estimate the size of the lesion is suggested. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken
- At baseline, report the *baseline sum diameter*. This is the reference by which tumour response will be measured and is calculated by adding:
    - the longest diameters of the non-nodal target lesions *plus*
    - the short axis diameters of nodal target lesions

Non-measurable disease:

- These are 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

Baseline documentation of "Target" and "Non-Target" lesions:

- All measurable lesions, up to a maximum of five in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline

- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically)
- All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up
    - Skin metastases that are only assessable by clinical examination and not classed as measurable should be classed as non-target lesions

Response definitions:

- **Complete response (CR):**
    - Disappearance of all lesions (i.e. all evidence of disease, not just the target lesions)
    - all lymph nodes must be non-pathological in size (<10mm short axis)
- **Partial response (PR):**
    - ≥30% decrease in the sum of diameters of target lesions compared to baseline, *with*
    - response or stable disease observed in non-target lesions, *and*
    - no new lesions
- **Stable disease (SD):**
    - Neither sufficient shrinkage to qualify for response or sufficient increase to qualify for progressive disease in target lesions, *with*
    - response or stable disease observed in non-target lesions, *and*
    - no new lesions
- **Progressive disease (PD):**
    - ≥20% increase in the sum of longest diameters of target lesions compared to smallest sum diameter recorded. In addition, the sum must also demonstrate an absolute increase of at least 5mm, *or*
    - unequivocal progression of non-target lesions (modest increases in the size of one or more non-target lesions is usually not sufficient), *or*
    - appearance of new lesions. New lesions must be unequivocal and not attributable to a different scanning technique or non-tumour. When in doubt continue treatment and repeat evaluation. If a scan shows a new lesion in an anatomical region which was not included in the baseline scans, this is still PD

NB. Response is always judged against baseline but progression is judged against the smallest sum diameter recorded

Time Point Response: Patients With Target (+/- Non-Target) Disease[42]

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	Not evaluable (NE)
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD