Circulating tumour DNA guided Adaptive BRAF and MEK Inhibitor therapy (DyNAMIc)

DyNAMIc Protocol

V4.0, 27/03/2023

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Study Sponsor:

The Christie NHS Foundation Trust

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Chief Investigator:

Professor Paul Lorigan

Consultant Medical Oncology

The Christie NHS Foundation Trust

The funder of this research trial had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Protocol Approval

I, the undersigned, hereby approve this clinical study protocol:

Authorised by Chief Investigator:

Signature: _____ **Date:**

Professor Paul Lorigan

Consultant in Medical Oncology

The Christie NHS Foundation Trust

Authorised on behalf of The Sponsor:

Signature: _____ **Date:**

Dr Clare Griffin

Research Integrity and Governance Manager

Sponsor Representative

The Christie NHS Foundation Trust

Authorised on behalf of University of Liverpool:

Signature: _____ **Date:**

Dr Ashley Jones

Lead Statistician

University of Liverpool

General Information

For the purposes of clarity, use of the words ‘Study’ and ‘Trial’ are interchangeable synonyms and their usage will differ depending on the context in which they are used.

This document describes the DyNAMIc trial including detailed information about procedures and recruitment. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. Any amendments will be circulated to the investigators participating in the trial, but sites entering patients for the first time are advised to contact Liverpool Clinical Trials Centre (LCTC), the coordinating clinical trials unit, to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator, Professor Paul Lorigan, via the LCTC.

This protocol defines the participant characteristics required for study entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements. Waivers to authorise non-compliance are not permitted.

Incidence of protocol non-compliance whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations. These are monitored and reported to trial oversight committees.

The template content structure is consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013) and has regard for the Health Research Authority guidance. Regulatory and ethical compliance information is located in section 12.

The LCTC has achieved full registration by the UK Clinical Research Collaboration (www.ukcrc.org) as their standards and systems were assessed by an international review panel as reaching the highest quality. The LCTC has a diverse trial portfolio underpinned by methodological rigour, a GCP compliant data management system, and quality management system.

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Sponsor :	**Trial Management, Monitoring and Data Collection:**	**Statistics:**
The Christie NHS Foundation Trust Wilmslow Road Manchester M20 4BX ☎ 0161 918 7432 ✉ the-christie.sponsoredresearch@nhs.net	Liverpool Clinical Trials Centre University of Liverpool 1st Floor Block C Waterhouse Building 3 Brownlow Street Liverpool L69 3GL ☎ 0151 794 8929 ✉ Dynamic_study@liverpool.ac.uk	Liverpool Clinical Trials Centre University of Liverpool 1st Floor Block C Waterhouse Building 3 Brownlow Street Liverpool L69 3GL ☎ 0151 794 2000 ✉ Dynamic_study@liverpool.ac.uk
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Contact Details: Individuals		
Individual Authorised to Sign the Protocol and Protocol Amendments on behalf of the Sponsor:	**Chief Investigator (CI):**	**Trial Manager**
Clare Griffin The Christie NHS Foundation Trust Wilmslow Road Manchester M20 4BX ☎ 0161 918 7432 ✉ clare.griffin1@nhs.net	Prof. Paul Lorigan, MB, MD, FRCP The University of Manchester, and The Christie NHS Foundation Trust Wilmslow Road M20 4BX ☎ 0161 446 8002 ✉ Paul.Lorigan@nhs.net	Tony Coffey Liverpool Clinical Trials Centre University of Liverpool 1st Floor Block C Waterhouse Building 3 Brownlow Street Liverpool L69 3GL ✉ Dynamic_study@liverpool.ac.uk
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Additional Contacts:

The contact details for the trial oversight committee members and participating centres are detailed in documents supplementary to the protocol and stored in the Trial Master File.

Table of Contents

1. GLOSSARY

AE	Adverse Event
AR	Adverse Reaction
CBC	Cancer Biomarker Centre
cfDNA	Cell free DNA
ctDNA	Circulating tumour DNA
CI	Chief Investigator
CRF	Case Report Form
CRUK	Cancer Research UK
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumour DNA
CTIMP	Clinical Trial of an Investigational Medicinal Product
DNA	Deoxyribonucleic acid
ddPCR	Droplet digital PCR
ECG	Electrocardiograph
ECOG	Eastern Cooperative Oncology Group
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
FFPE	Formalin fixed paraffin embedded
GCP	Good Clinical Practice
GP	General Practitioner

HCP	Health Care Professional
HRA	Health Research Authority
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICO	Information Commissioner's Office
ISDMC	Independent Safety and Data and Monitoring Committee
IMP	Investigational Medicinal Product
ISF	Investigator Site File (part of the Trial Master File)
ISRCTN	International Standard Randomised Controlled Trials Number
IWRS	Interactive Web Response System
LCTC	Liverpool Clinical Trials Centre
LDH	Lactate dehydrogenase
MA	Marketing Authorisation
MHRA	Medicines and Health Care Products Regulatory Agency
MTA	Material transfer agreement
NHS	National Health Service
NIHR CRN	National Institute for Health Research Clinical Research Network
NRES	National Research Ethics Service
OS	Overall survival
PD	Progressive disease
PFS	Progression Free Survival
PI	Principal Investigator
PISC	Participant Information Sheet and Consent (form)

PR	Partial response
PSF	Pharmacy Site File
QA	Quality Assurance
QC	Quality Control
R&D	Research & Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria In Solid Tumours
RN	Research Nurse (Registered)
RSI	Reference Safety Information
RSO	Research Support Office
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Stable disease
SDV	Source Data Verification
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAB	Tumour activity and burden level (TAB; mutant copies of ctDNA/ml of plasma)
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

TTP	Time to progression
UAR	Unexpected Adverse Reaction
VAF	Variant allele frequency
WOCBP	Women of child bearing potential

2. PROTOCOL OVERVIEW

Full Title:	Circulating tumour DNA guided Adaptive BRAF and MEK Inhibitor therapy
Acronym:	DyNAMIc
Phase:	II
Target Population:	Patients in the United Kingdom, aged 18 years and over, with stage III unresectable, or IV, cutaneous melanoma with *BRAF* mutation and mutant ctDNA levels of BRAF VAF ≥15 copies/ml of plasma
Sample size:	40 patients
Trial Arms	ARM A: Standard of care: Continuous dosing of encorafenib 450mg once daily plus binimetinib 45mg twice daily. ARM B: Adaptive therapy: 4 weeks of encorafenib 450mg once daily plus binimetinib 45mg twice daily, followed by adaptive cycles based on ctDNA TAB level
Inclusion Criteria:	1. Written and informed consent obtained from participant and agreement of participant to comply with the requirements of the study 2. Histological confirmation of cutaneous melanoma 3. ≥ 18 years of age 4. Stage III un-resectable/ IV disease 5. Measurable disease on CT (thorax, abdomen and pelvis, ± neck if indicated) and/or PET-CT, and CT or MRI (brain) scan (RECIST v1.1) 6. *BRAF* p.V600E/K/R mutation confirmed (exact point mutation must be known) 7. BRAF ctDNA TAB level of ≥15 copies/ml of plasma 8. ECOG performance status 0/1/2 9. Prior radiotherapy or radiosurgery must have been completed at least 2 weeks prior to the first dose of study drugs 10. Adequate organ function as defined below: • Haemoglobin ≥ 9 g/dL • White blood count ≥ 2 x10^9/L

	• ANC[a] ≥ 1.2 x10^9/L • Platelet count ≥ 75 x10^9/L • Albumin ≥ 2.5 g/dL • Total bilirubin[b] ≤ 1.5 x ULN[a] • AST[a] or ALT[a] ≤ 3 x ULN[a] • Calculated creatinine clearance[c] ≥ 30ml/min • Left Ventricular Ejection fraction (LVEF) ≥ 50% or ≥LLN[a] by ECHO 11. Women of childbearing potential participating in the study (WOCBP see appendix B for definition) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to the start of study drug. 12. WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drugs plus at least 1 month following last dose of drug (either encorafenib or binimetinib), (see appendix B). 13. Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment plus 90 days (duration of sperm turnover) from last dose of drug (either encorafenib or binimetinib), (see appendix B). 14. Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, WOCBP participating in the study who are continuously not heterosexually active must still undergo pregnancy testing (as described in inclusion criterion 11). a. Abbreviations: ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; LLN = lower limit of normal; ULN = upper limit of normal. b. Except if the patient has Gilbert Syndrome or liver metastasis, in which case the bilirubin must be <3 x ULN c. Calculate creatinine clearance using standard Cockcroft-Gault formula (Appendix A).
Exclusion Criteria:	1. Prior systemic targeted BRAF/MEKi therapy for stage IV (metastatic) melanoma (treatment for stage III allowed as long as RFS ≥6 months

	following discontinuation of drugs) 2. BRAF wild-type malignant melanoma 3. Metastasis to the brain or leptomeninges 4. Any contraindication to treatment with Encorafenib or Binimetinib as per the local Summary of Product Characteristics 5. Hypersensitivity to the active substance or to any of the excipients of Encorafenib or Binimetinib 6. Current use of a prohibited medication as described in Section 8.9 7. History of another malignancy. **Exception:** Patients who have been disease-free for 3 years, (i.e. patients with second malignancies that are indolent or definitively treated at least 3 years ago), curatively treated in situ cancer of the cervix, ductal carcinoma in situ (DCIS); stage 1, grade I endometrial carcinoma, or patients with a history of completely resected non-melanoma skin cancer. No additional therapy should be required whilst the patient is on study. 8. Any serious or unstable pre-existing medical conditions (aside from malignancy exceptions specified above), psychiatric disorders, or other conditions that could interfere with the patient's safety, obtaining informed consent, or compliance with study procedures. 9. Known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection. 10. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption 11. Child Pugh B or C liver disease 12. Coronary syndromes (including myocardial infarction within 6 months or unstable angina) 13. A history or evidence of current ≥ Class II congestive heart failure as defined by the NYHA guidelines with an ejection fraction of <50% (see appendix C). 14. Treatment refractory hypertension defined as a blood pressure of systolic >150 mmHg and/or diastolic >95 mm Hg on >3 occasions which cannot be controlled by anti-hypertensive therapy; 15. Uncorrectable electrolyte abnormalities > CTCAE v5 Grade 1 (e.g. hypokalaemia, hypomagnesaemia, hypocalcaemia), long QT syndrome (baseline QTC interval ≥ 480msec) or taking medicinal products known

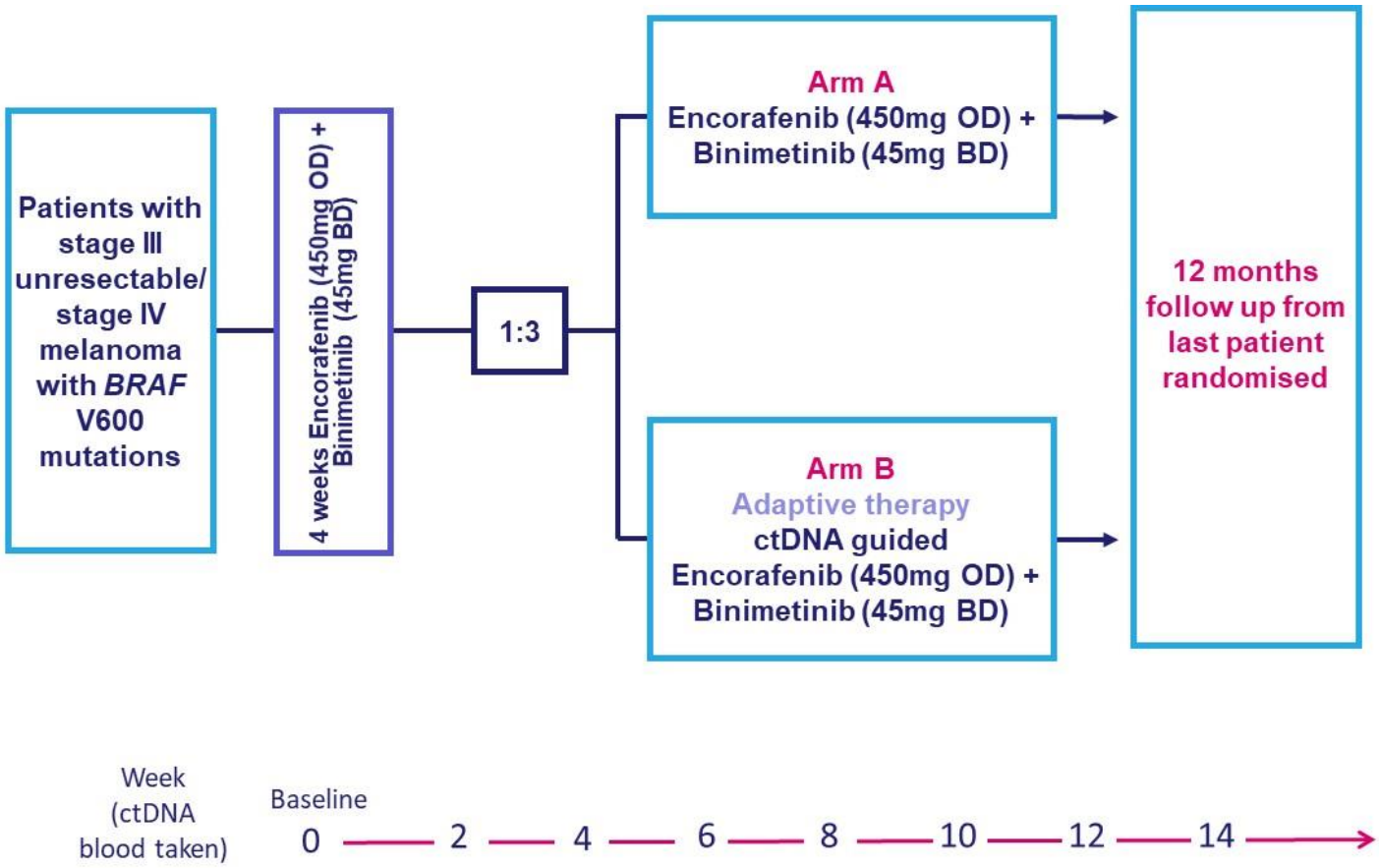
<table>
<tr><td></td><td>to prolong the QT interval.
16. A history or current evidence/risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR) including presence of predisposing factors to RVO or CSR (e.g., uncontrolled glaucoma or ocular hypertension, uncontrolled hypertension, uncontrolled diabetes mellitus, or a history of hyperviscosity or hypercoagulability syndromes);
17. Females who are pregnant or breast-feeding and are not able to stop breast-feeding prior to first dose of study drugs (see section 7.4);
18. Prisoners or patients who are involuntarily incarcerated.
19. Patients who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness.</td></tr>
<tr><td>Study Centres and Distribution:</td><td>Approximately 11 Secondary / Tertiary NHS Hospital sites across the UK</td></tr>
<tr><td>Patient Study Duration:</td><td>Duration of treatment:
All patients will be treated until progressive disease, unacceptable toxicity or withdrawal of patient consent, at which point their care will be managed as per standard of care.
Duration of follow-up:
A minimum follow-up of 12 months for all patients who do not experience disease progression.</td></tr>
<tr><td>Study Duration:</td><td>36 months</td></tr>
<tr><td rowspan="6">Investigational Medicinal Products (all arms)</td><td colspan="2">Encorafenib</td></tr>
<tr><td>Form:</td><td>Capsule</td></tr>
<tr><td>Dose:</td><td>450mg once daily</td></tr>
<tr><td>Route:</td><td>Oral</td></tr>
<tr><td colspan="2">Binimetinib</td></tr>
<tr><td>Form:</td><td>Tablet</td></tr>
<tr><td>Dose:</td><td>45 mg twice daily</td></tr>
</table>

	Route:	Oral
	Objectives:	
Primary:	1. To assess whether tumours respond to re-introduction of encorafenib plus binimetinib following the first "drug off" period, assessed by % decrease of tumour activity and burden level (TAB; mutant copies of ctDNA/ml of plasma).	
Secondary:	1. To optimise the thresholds of percentage reduction in TAB level in ctDNA as a measure of response to stop drugs and the percentage increase in TAB as a decision to restart drugs (see section 5.1 for further details). 2. To assess maximal response (complete response (CR)/partial response (PR)/stable disease (SD)/progressive disease (PD)) to therapy in Arm A vs. Arm B 3. To assess progression free survival (PFS) 4. To assess PFS at 6, 12 and 15 months in Arm A vs. Arm B 5. To assess overall survival 6. To assess number of adaptive therapy cycles completed by participants on Arm B 7. To assess median duration of adaptive therapy cycles 8. To assess whether ctDNA result can be provided within 5 working days from sample receipt into CBC 9. To assess quality of life of Arm A continuous vs. Arm B adaptive dosing 10. To assess toxicity (all grade adverse events) in Arm A continuous vs. Arm B adaptive dosing	
Exploratory/ Translational:	**<u>Exploratory objectives</u>** 1. To describe maximal reduction in TAB level for each adaptive cycle 2. To describe rise in TAB levels during drug off period for each patient 3. To examine clonal evolution during continuous vs. adaptive drug dosing 4. To explore the relationship between observing a rise in ctDNA levels of mutant *BRAF* copies/ml and progressive disease observed scheduled scan results in Arm A	

	Translational work Samples will be collected for research work including tumour biopsies and blood. Any translational studies using DyNAMIc samples must be authorised by the TMG. Due to the hypothesis-generating design of translational studies, these will not be performed to GCP standard, however will be conducted with scientific rigour in accordance with principles of respect for persons, beneficence and justice. Translational work aims will include but are not limited to: • Understanding of tumour evolution on targeted therapy which will include in depth genetic and epigenetic analysis of ctDNA • Understanding of response and resistance to therapy which can include analysis of DNA, RNA metabolites and proteins • Characterisation of stage IV/stage III unresectable melanoma which can include analysis of DNA, RNA metabolites and proteins Any leftover samples will be stored for up to 20 years in sponsor approved laboratories and will be available for research work authorised by the TMG.

2.1 Schematic of Study Design

Figure 1: DyNAMIc Schematic


Patients with stage III unresectable/ stage IV melanoma with *BRAF* V600 mutations
4 weeks Encorafenib (450mg OD) + Binimetinib (45mg BD)
1:3
Arm A
Encorafenib (450mg OD) + Binimetinib (45mg BD)
Arm B
Adaptive therapy
ctDNA guided
Encorafenib (450mg OD) + Binimetinib (45mg BD)
12 months follow up from last patient randomised
Week (ctDNA blood taken)
Baseline
0
2
4
6
8
10
12
14

3. ROLES AND RESPONSIBILITIES

3.1 Sponsor

The Christie NHS Foundation Trust is the sponsoring organisation and is legally responsible for the study. They will centrally manage the budget and allocate funding to collaborating organisations, and formally delegate specific sponsoring roles to the Chief Investigator and LCTC.

3.2 Funder

This study is funded by The Jon Moulton Charity Trust, a registered charitable organisation, via a £1.25 million grant to sponsor; the study will be run as a non-commercial investigator led clinical trial.

The funder has reviewed the proposal in line with their funding policies and will receive updates on progress as required by the terms and conditions of funding.

The funder can be contacted via Dr Helen Critchley, telephone number 020 3034 2645, or via email at helen@jpmfoundation.co.uk.

3.3 The Study Team

Chief Investigator:

Professor Paul Lorigan is the Chief Investigator and is an employee of The Christie NHS Foundation Trust, and is responsible for overall design and conduct of the trial in collaboration with other members of the study team.

Principal Investigators:

In each participating centre, a principal investigator will be identified to be responsible for identification, recruitment, data collection and completion of case report forms (CRF), along with follow-up of study patients and adherence to study protocol at site. They will also be responsible for safety reporting and processing any applicable safety information.

Clinical Trials Unit:

LCTC at the University of Liverpool, in collaboration with the Chief Investigator, will have overall management responsibility and will be responsible for trial management activities including (but not limited to) study planning, Trial Master File management, safety reporting, data management, randomisations, statistical analysis, coordination of participating sites.

LCTC will manage the budget allocated to UoL.

3.4 Oversight Committees

The DyNAMIc trial is subject to oversight from the following committees:

Trial Management Group (TMG):

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead Investigators (clinical and non-clinical), members of the LCTC and representation from the sponsor. The TMG is responsible for monitoring all aspects of the progress and conduct of the trial and will be responsible for the day-to-day running and management of the trial. The TMG will meet at least monthly at setup stage and then reduce at a reduced frequency throughout the trial unless more frequent meetings are required. See section 3.4 for further information.

Trial Steering Committee (TSC):

The Trial Steering Committee will consist of an independent chairperson, at least 2 independent experts, one must be in the field of melanoma and the other in ctDNA, an independent biostatistician and will include the CI, selected Principal investigators and observers as documented in the TSC Charter. The TSC will also include at least one lay patient representative member. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The decision for the continuation of the trial lies with the TSC.

The TSC will operate under the terms of their specific charters and members must disclose any conflicts of interest prior to any contribution. The TSC will meet at least annually, but as agreed in the TSC Charter. See section 3.4 for further information.

Independent Safety and Data Monitoring Committee (ISDMC):

The Independent Safety and Data Monitoring Committee (ISDMC) will consist of an independent chairperson, plus an independent member with clinical expertise in melanoma and ctDNA, and an independent biostatistician.

The ISDMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The ISDMC will first convene before the first patient is recruited and will then define frequency of subsequent meetings (at least annually). Details of the interim analysis and monitoring are provided in sections 6.4 and 12.3 respectively.

An ISDMC Charter, membership and member declarations will be drafted and agreed by the ISDMC in the first meeting. The ISDMC will provide a recommendation to the Trial Steering Committee concerning the continuation of the study. See section 3.4 for further information.

Molecular Tumour Board (MTB):

The Molecular Tumour Board will consist of (but is not limited to) the CI, one other clinician, a statistician, a representative from CBC and a mathematician.

The MTB will discuss each threshold in addition to a general overview of the data and kinetics of ctDNA levels. Features of any patients who have progressed clinically on scan without a corresponding rise in TAB level will also be discussed.

An MTB Charter, membership and member declarations will be drafted and agreed by the MTB in the first meeting. The MTB will immediately adjust the threshold levels as required and update the Trial Steering Committee retrospectively.

3.5 Protocol Contributors

The table below lists in alphabetical order (by surname) those who have substantively contributed to the design of the protocol:

Name	Affiliations	Contribution to protocol
Prof Trevor Graham	Barts Cancer Institute	Study design and input regarding tumour evolution and mathematical analyses.
Benita Hallewell-Goodwin	The Christie NHS Foundation Trust	Sponsor Review and Approval.
Dr Richard Jackson	Liverpool Clinical Trials Centre (University of Liverpool)	Lead on statistical input to study design and statistical analysis plan.
Dr Rebecca Lee	The University of Manchester, The Christie NHS Foundation Trust	Clinical input, study design, protocol review.
Prof Paul Lorigan	The Christie NHS Foundation Trust	Lead on clinical input, study design, protocol review and approval.
Alkesh Patel	The Christie NHS Foundation Trust	Lead on Pharmaceutical aspects of the study and pharmacy approval.
Ms Charlotte Rawcliffe	Liverpool Clinical Trials Centre (University of Liverpool)	Lead on trial management input to the study protocol.
Dr Dominic Rothwell	Cancer Biomarker Centre CRUK Manchester institute (MI)	Development of the ctDNA assays to GCP standards.
Mr Nigel Smith	Cancer Biomarker Centre CRUK MI	Development of the ctDNA assays to GCP standards.
Prof Andrea Sottoriva	Human Technopole	Study design and input regarding tumour evolution and mathematical analyses.
Dr Benjamin Werner	Barts Cancer Institute	Study design and input regarding tumour evolution and mathematical analyses.

4. INTRODUCTION

4.1 Background

Melanoma:

Melanoma has been increasing in incidence over the last two decades due to a number of environmental and social factors as well as increased surveillance (1). It is the 4th most common cancer in the United Kingdom with 13,348 new cases diagnosed in 2011 (2). The World Health Organisation (WHO) reported in 2012 approximately 130,000 new diagnoses worldwide, with 37,000 deaths (3). More recent data from Cancer Research UK (CRUK) report 2333 melanoma-related deaths between 2016-2018, accounting for 1% of total cancer deaths (4).

The majority of patients are diagnosed with stage I/II melanoma, however 9% will be diagnosed with stage III/IV disease (5). Whilst only a very small percentage of patients with stage I disease will relapse, a further 10-25% of patients with stage II disease will progress to stage IV disease (6). Although survival has significantly improved with the paradigm-shift of treatment type from chemotherapy to immune and targeted therapies, approximately 40-50% of patients with stage III unresectable or stage IV disease who receive treatment will not survive to 5 years (7). New strategies are therefore required to improve both progression free and overall survival for this group of patients.

Current standard treatment of stage IV melanoma:

With the growing understanding of genetic alterations in melanoma and immune modulation by checkpoint molecules, two new therapeutic approaches have become standard therapy in late stage melanoma, with both strategies improving overall survival (OS) in randomised trials.

Immune therapy:

One of the major mechanisms cancer cells use to avoid T cell mediated death is by up-regulation of immune checkpoints. In late stage melanoma, ipilimumab, a monoclonal antibody targeting CTLA-4, was the first checkpoint inhibitor to achieve improved OS in two randomised trials (8,9). The identification of the PD-L1/PD-1 axis as important for T cell responses to cancer cells (10), led to two therapies gaining FDA and NICE approval in melanoma: pembrolizumab and nivolumab. The Phase III Checkmate 066 trial randomised 418 treatment naïve, BRAF wild-type patients to receive either nivolumab (3mg/kg) or dacarbazine (11). It showed an objective response rate (ORR) of 40.0% (95% CI, 33.3 to 47.0) in the nivolumab group versus 13.9% (95% CI, 9.5 to 19.4) in the dacarbazine group (11). Median progression free survival (PFS) was 5.1 months in the nivolumab group versus 2.2 months in the dacarbazine group (HR=0.43; 95% CI, 0.34 to 0.56; P<0.001) (11). The 1 year OS rate was 72.9% (95% CI, 65.5 to 78.9) in the nivolumab group, as compared with 42.1% (95% CI, 33.0 to 50.9) in the dacarbazine group (HR 0.42; 99.79% CI, 0.25 to 0.73; P<0.001)

(11). Similar results were obtained in a Phase III trial of pembrolizumab with a response rate of 32.9% vs. 11.9% for ipilimumab and 1 year survival rate of 68.4% for pembrolizumab vs. 58.2% for ipilimumab (HR 0.69; 95% CI 0.52 to 0.90) (12).

Combination therapy results in increased depth of response compared to single agents. The Checkmate 067 study randomised 945 previously untreated patients to combination nivolumab and ipilimumab (N+I) vs. ipilimumab alone or nivolumab vs. ipilimumab (13). The study was not powered to detect a difference between N+I and nivolumab however descriptive analyses have been subsequently performed and showed N+I to have better efficacy especially in those patients with poor prognostic features (>3 sites disease, high LDH, M1c/d disease) at baseline (14). The overall response rate (ORR) was 45% (95% CI, 39-50) in the nivolumab group, 58% (95% CI, 53-64) in the N+I group, and 19% (95% CI, 15-24) in the ipilimumab group with time to objective response 2.8 months for all groups (13,15). At 5 years, median PFS was 11.5 months (95% CI, 8.7-19.3) with N+I, compared to 2.9 months (95% CI, 2.8 to 3.2) with ipilimumab (HR for death or disease progression, 0.42; 99.5% CI, 0.35 to 0.51; P<0.001), and 6.9 months (95% CI, 4.3 to 9.5) with nivolumab (HR compared to ipilimumab, 0.53; 99.5% CI, 0.44-0.64; P<0.001) (15). Overall survival at 5 years was 52% in the nivolumab-plus-ipilimumab group and 44% in the nivolumab group, as compared with 26% in the ipilimumab group (15). The median OS was more than 60.0 months (median not reached; 95% CI, 38.2 to not reached) in the N+I group, 36.9 months (95% CI, 28.2 to 58.7) in the nivolumab group, and 19.9 months (95% CI, 16.8 to 24.6) in the ipilimumab group (15). The HR of N+I vs. ipilimumab was 0.54 (0.44-0.67) and HR of nivolumab vs. ipilimumab was 0.65 (0.53-0.79) (15). A recent update with median follow-up of 6.5. years confirmed the ongoing benefits of both combination ipilimumab + nivolumab, with no new safety signals (16). The best outcomes were seen in patients with small volume disease, normal LDH and good performance status.

More recently, the RELATIVITY Phase III trial randomised 714 previously untreated patients with stage III unresectable or stage IV melanoma to nivolumab or nivolumab plus relatlimab; a LAG-3 blocking antibody (17). At a median follow-up of 13.2 months, the median PFS in the nivolmab plus relatlimab group was 10.1 months vs. 4.6 months for nivolumab (HR 0.75; 95% CI 0.6–0.9, P= 0.0055). PFS rates at 12 months were 47.7% (95% CI, 41.8–53.2) for nivolumab plus relatlimab vs. 36.0% (95% CI, 30.5–41.6) for nivolumab. Patients benefited from the combination irrespective of LAG-3 expression and therefore it is unlikely that it will be a clinically useful predictive biomarker. Incidence of grade 3/4 side effects was 18.9% for N+R vs. 9.7% for nivolumab with treatment discontinuation rates 14.6% vs. 6.7% respectively. Thus, in indirect comparisons with N+I, this combination is considerably better tolerated and is likely to become standard of care first line immune therapy at least in patients with lower risk disease.

Targeted therapy:

Activation of the mitogen-activated protein kinase (MAPK) pathway is crucial to the progression of melanoma (18). Approximately 35- 45% of patients diagnosed with melanoma harbour a mutation in *BRAF*, which results in increased kinase activity and downstream phosphorylation of MEK and ERK (19,20). Due to this reliance

of *BRAF* mutant melanomas on the MAPK pathway for their continued survival and proliferation, a number of treatments targeting elements crucial to its signalling have been developed (21–23). Initially, single agent BRAF inhibitors were reported to improve OS, resulting in a paradigm shift in melanoma management (21).

More recently, Phase III results combining BRAF and MEK inhibition have been reported (24–26). In the COMBI-D Phase III trial, ORR was 67% in the dabrafenib plus trametinib (D+T) group vs. 51% in the dabrafenib/placebo group in 423 randomised patients (24). After 301 events, median PFS was 11 months (95% CI 8.0-13.9) in the D+T arm vs. 8.8 months (95% CI 5.9–9.3) in the dabrafenib only group (HR 0.67, 95% CI 0.53-0.84; P=0.0004) (27). The COLUMBUS Phase III trial randomised patients 1:1:1 to encorafenib plus binimetinib (E+B), encorafenib or vemurafenib. ORR by central review was 63% (56-70) in the E+B group vs. 51% (43-58) in the encorafenib group vs. 77 (40%; 33-48) in the vemurafenib group (26). At a median follow-up of 16.6 months (95% CI 14.8-16.9), median PFS was 14.9 months (95% CI 11.0-18.5) in the encorafenib plus binimetinib group, and 7.3 months (5.6-8.2) in the vemurafenib group (HR 0.54, 95% CI 0.41-0.71; P<0.0001) (26). Updated results at 48.8 months revealed median OS was 33.6 months (95% CI, 24.4-39.2) for E+B, 23.5 months (95% CI, 19.6-33.6) for encorafenib and 16.9 months for vemurafenib (95% CI, 14.0-24.5) (28). E+B vs. vemurafenib decreased the relative risk of death by 39% (HR, 0.61; 95% CI, 0.48–0.79) (28). Further follow-up at a median of 70.4 months presented at ASCO 2021, reported the median OS (95% CI) and 5-year OS rate with E+B were 33.6 (95% CI 24.4–39.2) months and 34.7% (95% CI 28.0–41.5), respectively (29). The 5-year PFS rate was 22.9% for E+B vs.10.2% for vemurafenib; ORR (95% CI) was 64.1% (56.8–70.8) vs. 40.8% (33.8–48.2); and the median duration of response (DOR) was 18.6 in the E+B group vs. 12.3 months in the vemurafenib group (29). No new safety concerns were reported.

The Food and Drug Administration (FDA) approved vemurafenib/cobimetinib (V+C), D+T and encorafenib/binimetinib (E+B) for use in patients with metastatic *BRAF* V600E/K/R/D mutated melanoma on the basis of these phase III trials, however the National Institute for Clinical Excellence has not authorised V+C for use in the UK (21,23,25,26,30,31).

Newer agents such as next generation paradox-breaking BRAF inhibitors (e.g. PLX8394 (32)), which prevent RAF dimerization and ERK inhibitors (33), which target further down the MAPK pathway could potentially overcome some of the resistance mechanisms to BRAF and MEK inhibition, but have yet to be tested beyond Phase I/II trials.

Targeted vs. immune therapy and scheduling of therapy lines:

Whilst there have been no direct comparisons of targeted therapy and immunotherapy, a number of indirect comparisons have been carried out (7,34), and these show a clear benefit in terms of long term survival for immunotherapy over targeted therapy in the metastatic setting. The results of the DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing) trial examining dabrafenib and trametinib followed by ipilimumab and nivolumab or ipilimumab and nivolumab followed by dabrafenib and trametinib in patients with stage III-IV *BRAF* V600 melanoma (NCT02224781) are awaited. This trial switches patients on treatment progression rather than at response to either therapy.

An alternative approach is to switch patients when they are responding to targeted therapy as this can result in changes to the tumour and the microenvironment that facilitates immune response. Pre-clinical data has revealed that BRAF inhibition results in an environment that can enhance immune responses (35,36). Tumours responding to BRAF inhibitors have been shown to have increased T cell infiltration, improved T cell recognition of melanoma associated antigens and reduced production of immunosuppressive cytokines (36–39). Micropthalmia-associated transcription factor (MITF) is up-regulated following BRAF inhibition, resulting in increases in the expression of lineage antigens, such as gp100, melan-A, and tyrosinase-related proteins 1 and 2 (39,40). PD-L1 expression has also been shown to increase following 10-14 days of BRAF inhibitor therapy, which could enhance the effect of PD-1 inhibitors (40,41).

The SEquential COMBo Immuno and Targeted therapy (SECOMBIT; NCT02631447) study and the Immunotherapy With Ipilimumab and Nivolumab Preceded or Not by a Targeted Therapy With Encorafenib and Binimetinib (EBIN; NCT03235245) studies are both assessing whether a pre-specified period of induction targeted therapy (12 weeks for EBIN and 8 weeks for SECOMBIT) results in improved survival (42,43). Early results from SECOMBIT showed promising results for the induction arm of the trial (42). However, these strategies do not personalise treatment to the individual response of a patient and are at risk (particularly with 12 weeks of therapy) of patients already developing resistant clones which are more immune suppressive due to the length of the induction period. The CAcTUS (Circulating Tumour DNA gUided therapy Switch; NCT03808441) trial in *BRAF* mutant patients, uses circulating tumour DNA (ctDNA) to determine when patients are responding to targeted therapy in order to personalise the timing of the switch. All of these trials allow restart of targeted therapy upon progression on immune therapy, therefore even if these strategies are shown to be effective, optimising targeted therapy scheduling remains critical for these patients.

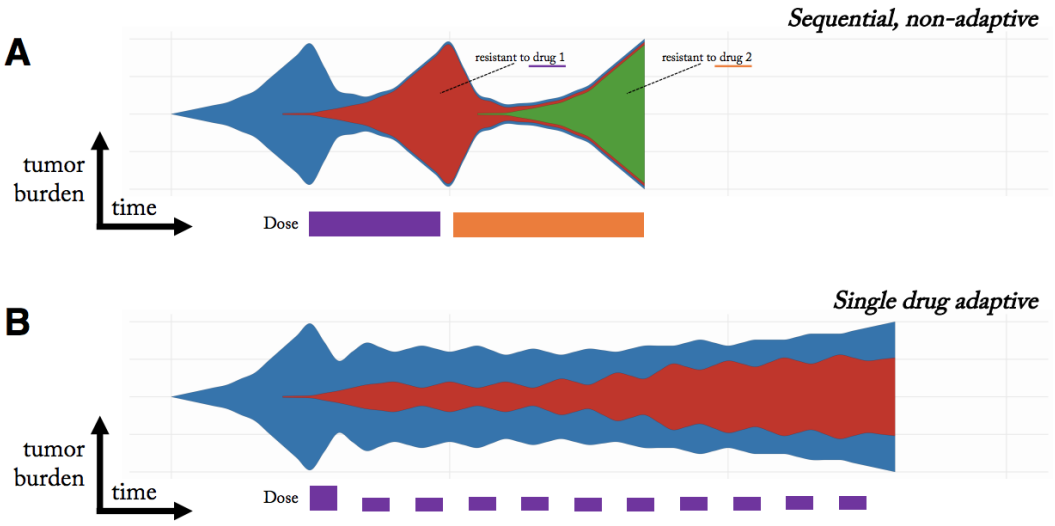
Combining targeted and immune therapy

Studies examining combination targeted and immune therapy have been largely negative with no significant PFS difference seen for combination of spartalizumab, dabrafenib and trametinib (D+T) vs. D+T in a phase III trial (44). Only a small benefit was seen for PFS as per investigator assessment from 10.6 months (95% CI 9.3–12.7) in the control group (vemurafenib plus cobimetinib) to 15.1 months (11.4–18.4) in the triplet group (atezolizumab, vemurafenib plus cobimetinib; HR 0.78; 95% CI 0.63–0.97; log-rank p=0.025 which was not confirmed by independent assessment (45). Neither trial compared triplet therapy with anti-PD-1 single agent or combination N+I which would be more in line with standard of care in this group of patients. Sub-group analysis of these trials is ongoing and may provide a signal as to which patients could benefit from this strategy; however, this would need confirming in further randomised trials.

Adaptive therapy:

Adaptive therapy relies on the competition between drug-sensitive and drug-resistant subclones to control overall tumour growth (Figure 2) (46,47). It aims to stabilise tumour burden by allowing a significant population of treatment sensitive cells to survive, which suppress proliferation of the less fit, resistant populations (46).

Figure 2. Conventional sequential therapy of two treatments selects for a clone resistant to treatment one (red) upon tumour relapse and subsequently a clone resistant to treatment two (green). B. Adaptive therapy maintains a stable tumour volume by introducing treatment holidays. Drug sensitive clones (blue) suppress the growth of less fit resistant clones (red). Adapted from West et al 2020.



Research has shown a reduction in drug resistant clones when targeted therapies are withdrawn. Mathematical analyses of tumour evolution have shown that continuous dosing selects for drug resistant clones, whilst an adaptive approach can control these (48,49). A number of models have been developed which have considered the proportion of resistant cells at start of therapy, the spatial constraints of tumours, the phenotypic switch of resistant cells with a tendency to result in slower growth rates, cell turnover rate, and velocity of evolution (47,49–55). A framework for considering how cancer evolves has been proposed based on 4 major components; the diversity of a cancer and how this changes over time (Evolutionary index) and the hazards impacting on clonal survival and resources available to neoplastic cells (Ecological index) (56). Adaptive therapy disrupts both the evolutionary and ecological indices in order to slow tumour growth.

To support these models in patients, a study with colorectal cancer revealed that resistant *KRAS* mutant clones identified in circulating tumour DNA (ctDNA) declined upon withdrawal of EGFR-specific antibodies (57). In addition, an adaptive therapy strategy has recently been tested in a pilot study treating patients with abiraterone in prostate cancer until a > 50% decline in their baseline levels of PSA pre-abiraterone was observed (46). Upon achieving this decline, abiraterone therapy was suspended and only restarted when the PSA increased to the baseline level (46). Preliminary data showed that all of the patients achieved PSA control when abiraterone was restarted and there was a signal that progression free survival (PFS) was improved compared to historical controls (46).

In melanoma, a number of models have shown that adaptive therapy could delay progression compared to continuous dosing. One study examined the differences in transcriptional states of melanoma cells *in vitro* using single cell analysis at baseline, when treated with vemurafenib and when drug was removed (58). They showed there was heterogeneity of these states, which mainly associated with levels of MITF, AXL and c-JUN, which have previously been associated with melanoma invasive/proliferative states (58–61). Different phenotypic states were associated with different growth kinetics and therefore they developed a two-compartment mathematical (ODE: ordinary differential equation) model to describe the competition between the sensitive and resistant states. The model was used to develop a personalised adaptive schedule, which was then tested in mice. This revealed that the adaptive therapy schedule delayed tumour progression in comparison with continuous or fixed intermittent schedules (58). The same group has subsequently examined the optimal timing of therapy and identified potential predictive factors as to which patients would likely benefit the most from an adaptive strategy (54). They compared two models; the first assumed genetically fixed drug-sensitive and resistant populations that competed for limited resource and the second considered phenotypic switching between drug-sensitive and resistant cells. They found that in both models adaptive therapy delayed time to progression by 6–25 months compared to continuous therapy. Factors predicting response to adaptive therapy included number of initial sensitive cells, competitive effect, switching rate from resistant to sensitive cells, and sensitive cell growth rate (54).

Further human-based data in melanoma supporting the potential benefit and safety of an adaptive strategy include a number of studies that have also shown that further responses can be seen to BRAF/MEK targeted therapy upon rechallenge following a drug holiday after progression or toxicity (62–65). An open-label phase II clinical trial showed that patients who had previously progressed on targeted therapy and had at least 12 weeks off treatment responded to rechallenge with 8/25 (32%) patients having a partial response and 10/25 (40%) having stable disease (63). Taken together, these studies suggest that melanoma resistance is plastic and can change following periods of treatment withdrawal.

Circulating tumour DNA (ctDNA):

An adaptive strategy requires precise and dynamic monitoring of changes in tumour activity and growth in order to be viable for use in the clinic. We have developed a number of assays based on circulating tumour DNA and have shown that it has potential to meet these criteria. Cell-free DNA (cfDNA) is DNA within the blood circulation, which is released from cells. Circulating tumour DNA (ctDNA) is DNA present in the bloodstream arising from cancer cells, which can be detected through identifying somatic mutations within it (66). Mandel and Métais first identified circulating nucleic acids in the blood stream in 1948, however it was not until 1994 that their potential utility as biomarkers for cancer detection and monitoring was realised (67). At that time, Sorenson *et al* showed the presence of mutated *KRAS* ctDNA sequences in the blood of patients with pancreatic cancer whose tumours also possessed mutated *KRAS* (68). The mechanisms behind the release of ctDNA are not completely understood, however it is thought it is produced by cell necrosis, apoptosis and secretion from macrophages that have phagocytosed cells (67,69). In addition circulating

tumour cells (CTCs) can also release nucleic acids into the blood, which can be detected through a variety of methods (70).

Many studies have examined the role of ctDNA as a “liquid biopsy” which can predict disease progression, monitor treatment response and reflect tumour resistance. CtDNA has been shown to reflect disease status and tumour burden whilst on treatment for a variety of cancers (71–73). CtDNA levels correlated with treatment response when compared to computerised tomography (CT) imaging in patients with metastatic breast cancer on treatment (74). Levels increased on average 5 months (range 2-9) before progressive disease was seen on imaging (74). In melanoma, baseline pre-treatment level of mutant *BRAF* in cfDNA has been shown to be a predictive biomarker of duration of therapy in patients treated with the BRAF/MEK inhibitors. In a pooled analysis from four clinical trials enrolling patients with tissue confirmed *BRAF* V600E/K mutant melanoma, copies of mutant *BRAF* were identified in 76% (V600E) and 81% (V600K) of 732 baseline plasma samples using BEAMing (beads, emulsion, amplification). Its presence was associated with lower response rates compared to those patients where mutant *BRAF* was undetectable (75). Furthermore, patients who had detectable mutant *BRAF* had a significantly shorter PFS and OS compared to those with undetectable levels (76). This remained significant in multivariable analysis comparing baseline factors including LDH and performance status in 3 out of 4 of the studies (76). More recently, a further validation study of patients treated in the COMBI-d and COMBI-MB trials of dabrafenib plus trametinib supported baseline detectable ctDNA as a predictor of PFS and OS on targeted therapy (72). Using a cut-off of 64 copies of ctDNA per millilitre pf plasma (determined using droplet digital PCR [ddPCR]) they stratified patients as high and low risk. Patients with low vs. high risk disease had a significantly longer PFS 12.7 vs. 6.5 months (HR 1.74; 95% CI 1.37–2.21, p<0.0001) and 35.1 vs. 13.4 months (HR 2.23; 95% CI 1.73–2.87, p<0.0001) (72).

There is also increasing evidence that ctDNA could be used to monitor patients on therapy, and that ctDNA changes may be detectable ahead of radiological or biochemical (LDH) change, giving an early indicator as to treatment efficacy or an early herald of disease progression. One study showed that progression in ctDNA was identified in 2 patients 86 and 120 days prior to radiological progression in patients treated with targeted therapy (77). A further study took longitudinal samples from 36 patients on targeted therapy, with 12 of these having detectable ctDNA levels prior to commencement of treatment (78). There was a significant decrease in ctDNA in all of the patients (p<0.01), with median time to becoming undetectable (n = 7) or <1 % (n = 5) of 13 days (range 6–40 days) (78). An increase in the *BRAF* V600 mutant ctDNA fraction was detected prior to the clinical diagnosis of PD in 12 out of 27 (44 %) patients and simultaneously with PD in 7 out of 27 (26 %) patients (78). These data were subsequently confirmed in another study, which showed ctDNA levels increased before radiological progression by a mean of 110 days (79).

Although one study did not support the use of ctDNA as an on-treatment biomarker of response to targeted therapy (78), larger studies have shown that it could be a useful tool (72,80). One study investigated whether ctDNA levels of 10 copies per ml of plasma or higher in the first plasma sample since treatment initiation were predictive of PFS. They found patients with undetectable ctDNA had a median PFS of 9 vs. 4 months in

patients with detectable ctDNA (HR, 4.05; 95% CI, 1.56 to 10.53). A large analysis of 224 patients from the COMBI-d trial, compared ctDNA levels in paired samples pre-treatment and at 4 weeks on dabrafenib plus trametinib (72). From the patients with paired samples, 201 (90%) had detectable ctDNA at baseline, and 121 (60%) still had detectable ctDNA following 4 weeks of treatment (72). All patients with conversion to undetectable levels had disease control (complete response, partial response, or stable disease) as their best overall response, compared with 103 (87%) of 118 patients with detectable ctDNA at week 4 (proportional odds likelihood ratio test for association P=0.0002) (72). In patients with high LDH only (above upper limit of normal), undetectable ctDNA at week 4 was significantly associated with PFS (HR 1.99; 95% CI 1.08–3.64, p=0.027) and OS (HR 2.38; 95% CI 1.24–4.54, p=0.0089) (72). Conversion to undetectable ctDNA at week 4 was independently associated with both PFS and OS in a Cox regression model that included clinical prognostic factors such as performance status and 3 or more organ sites with metastases (72). Taken together, these studies suggest that decreasing ctDNA levels on treatment are predictive of response to targeted therapy.

In addition, ctDNA can be used to detect mechanisms of resistance to therapy. In their seminal study, Murtaza *et al* demonstrated the proof of principle that circulating-free DNA (cfDNA) extracted from the plasma of patients over a course of treatment could be used to detect new mutations conferring resistance to therapy (71). Using whole exome sequencing (WES) of ctDNA, they demonstrated the emergence of an activating mutation in *PIK3CA* following treatment with paclitaxel in a patient with breast cancer and an *EGFR* T790M mutation on disease progression in a patient with lung cancer on gefitinib (71). In melanoma, studies have shown the development of mutations associated with resistance to targeted therapy, including *NRAS* and *PIK3CA* mutations (81,82). Thus, ctDNA can be used to not only assess tumour activity, but also clonal evolution during therapy, which can inform further models and future treatment strategies.

4.2 Rationale

Limitations of current treatments:

Despite the advances in melanoma management, patients with stage IV melanoma still die from their disease, with a 5 year survival of 39-70% depending on prognostic features such as number of disease sites, brain/liver/bone metastasis and raised lactate dehydrogenase (6). Combination BRAF and MEK inhibitor therapy has resulted in improved survival for patients (26). However resistance develops after a median of 12-15 months for the majority (24,26). Recently, combination anti-PD-1, BRAF and MEK inhibitors have been shown to be disappointing with COMBI-I not meeting its primary PFS endpoint and only a marginal improvement against targeted therapy (rather than immune therapy typically given as standard of care in the first line) seen for combination atezolizumab, vemurafenib and cobimetinib, which was not significant by independent committee review (45). New strategies are therefore required to prevent resistance occurring.

Adaptive therapy vs. intermittent therapy:

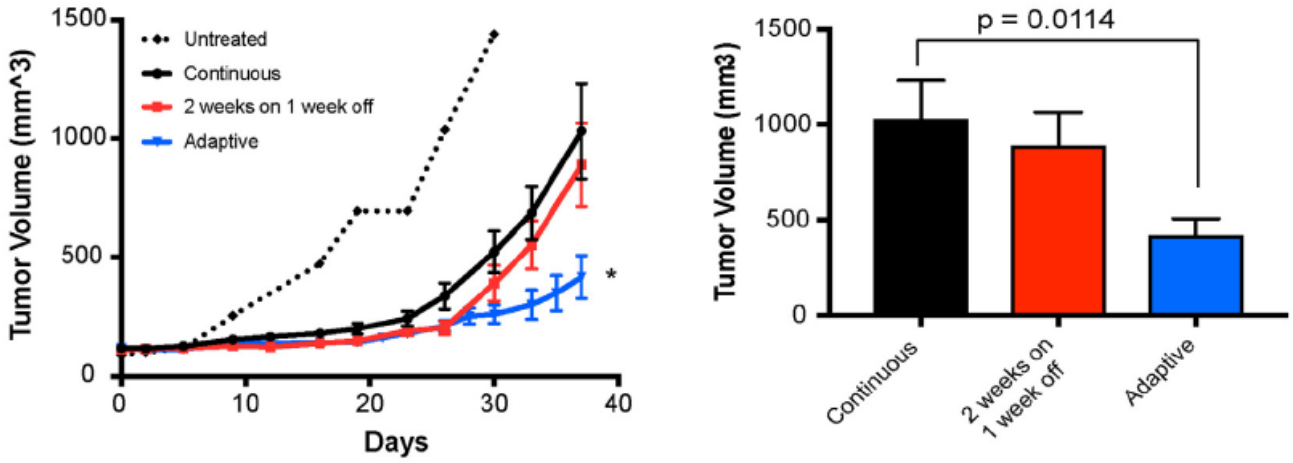
Preclinical studies in melanoma have shown a cell intrinsic fitness disadvantage when drug is withdrawn from targeted therapy resistant cells (83–85). The mechanism underlying this dependency of melanoma cells on the same therapeutic drugs to which they have acquired resistance or “drug addiction” phenotype is due to ERK2 hyperactivation, transcriptional re-programming, DNA damage and parthanatos-related cell death (84–86).

Based on these data, a number of clinical trials have examined alternative dosing strategies for targeted therapy in melanoma. Firstly, the INTERIM study (a randomised phase II feasibility study of INTERmittent versus continuous dosing of oral targeted combination therapy In patients with *BRAF* V600 mutant stage 3 unresectable or metastatic Melanoma NCT03352947) uses a fixed intermittent dosing compared to standard dosing of dabrafenib plus trametinib. Patients are treated with dabrafenib (150mg twice daily) on days 1 – 21 of a 28 day cycle and trametinib (2mg once daily), on days 1 – 14 of a 28 day cycle. The SWOG S1320 randomized phase II trial of intermittent versus continuous dosing of dabrafenib and trametinib in BRAFV600E/K mutant melanoma, compared intermittent dosing 5 weeks on, 3 weeks off schedule with continuous dosing after an initial 8 week continuous run-in of therapy. Continuous dosing was shown to have a statistically significant progression free survival compared with intermittent dosing (median 9.0 months versus 5.5 months, P = 0.064, pre-specified two-sided α = 0.2) (87). Although results are awaited for INTERIM and the scheduling is different, SWOG S1320 does not suggest that fixed intermittent dosing is a strategy to pursue further into Phase III studies. One of the possible reasons for this lack of efficacy may be due to the pharmacokinetics of trametinib in particular in humans vs. mice/*in vitro*. As the half-life of trametinib in humans is approximately 10 days (86), the potential pharmacodynamic impact of sudden drug removal seen *in vitro* and in mice where the half-life is much shorter, cannot be reproduced in humans. In addition, a fixed schedule does not account for intra-patient tumour heterogeneity, with individual patients experiencing different tumour kinetics. Therefore a personalised approach may be a better strategy.

As described above, adaptive therapy can personalise therapy to the kinetics of tumour growth and development of resistant clones vs. sensitive clones within each individual patient. When compared against continuous and fixed intermitted dosing *in vivo* a study showed a significant improvement in tumour control

with an adaptive strategy (Figure 3) (58). This was better than a fixed intermittent/metronomic schedule modelling SWOG S1320 or INTERIM, which was not significantly different from continuous therapy.

Figure 3. A. In vivo experiment treating WM164 cells with continuous vs. fixed intermittent dosing (2 weeks on 1 week off) vs adaptive PLX4720 treatment. **B.** Tumour volume at experiment end shows significant improvement with adaptive therapy vs continuous or fixed intermittent.



Taken together, these data show that an adaptive therapy strategy can be used to overcome resistance to encorafenib plus binimetinib and in preclinical models of melanoma is superior to continuous or fixed intermittent dosing.

ctDNA as a measure of tumour activity and burden:

A dynamic marker of response and increasing tumour activity is required for an effective adaptive strategy. As discussed above, we have developed techniques using ctDNA in early and late stage melanoma, which are able to accurately monitor tumour burden and activity over time (88–91). By following tumour-specific mutations in the blood, we were able to show responses to treatment and detect disease progression prior to radiological relapse (91). We argue that ctDNA is not only a measure of tumour burden, but also tumour activity. This is supported by a study which analysed ctDNA and compared levels to tumour metabolic activity measured using FDG-PET in 52 patients who received systemic therapy for metastatic melanoma (92). Levels of ctDNA correlated with metabolic tumour activity seen on FDG-PET and early changes in ctDNA and metabolic disease burden were important indicators of treatment response (92). Thus, in DyNAMIc we refer to the tumour activity and burden level (TAB) level, which is equal to the number of mutant *BRAF* copies per millilitre (ml) of plasma.

ctDNA as an accurate biomarker of response dynamics vs. other biomarkers:

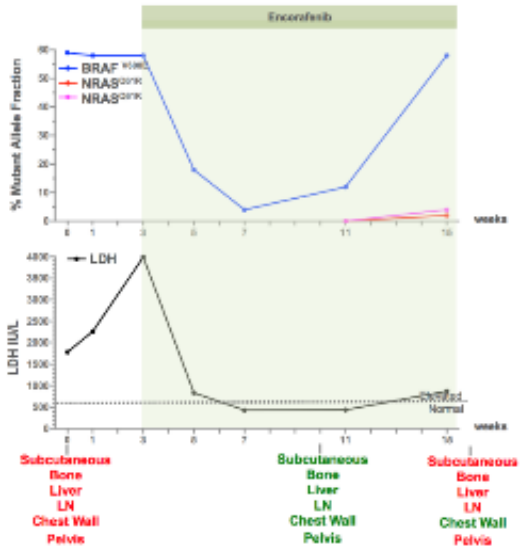


Figure 4. Progression in ctDNA is seen prior to progression on scan or rise in LDH

The "Adaptive BRAF-MEK inhibitor therapy for advanced BRAF mutant melanoma" trial (NCT03543969) is using participant's LDH levels, along with scans to decide when to hold or resume vemurafenib plus cobimetinib. However, we and others have shown that ctDNA is a better biomarker of tumour activity/burden than LDH (Figure 4) (81). Supporting our data, a small study of 6 patients with advanced melanoma treated with both targeted and immune therapies showed that longitudinal monitoring using ddPCR to detect BRAF/NRAS mutations in plasma was more accurate than LDH (93). A decrease in ctDNA levels corresponded with disease response (as early as one week into treatment) and a subsequent increase in levels corresponded with radiological progression (93). Similarly, another study compared ctDNA vs. LDH in identifying disease progression within 15 days of confirmed radiological progression in 26 patients. In 82% of patients ctDNA progression was detected vs. only 40% having an LDH rise, with a median difference in sensitivity of 42% (95% confidence interval, 27%–58%; $p < 0.001$ (77). Basing decisions to treat on ctDNA rather than LDH also enables us to include a greater number of patients as patients with normal LDH can still have detectable ctDNA. We therefore believe that using ctDNA enables more accurate monitoring of the disease, which increases the safety of an adaptive strategy.

Use of encorafenib plus binimetinib vs. other targeted therapy combinations:

There are currently two combination targeted therapy options available within the United Kingdom, dabrafenib plus trametinb and encorafenib plus binimetinib. Encorafenib has been shown to have increased potency and dissociation half-life, which translated into a superior overall response rate (51% vs. 40%) compared to vemurafenib another BRAF inhibitor (26,94). However, there have been no head-to-head randomised comparisons of D+T vs E+B. In their respective Phase III registration studies, median PFS was 11 months (95% CI 8.0-13.9) for D+T whilst for E+B it was 14.9 months (95% CI 11.0-18.5), but this could just be reflective of a different patient population. Encorafenib is an ATP-competitive BRAF inhibitor that suppresses the MAPK pathway in *BRAF* mutant tumour cells (V600E/V600D/V600K mutations), with a more than 10-times longer dissociation half-life (>30 hours) than either dabrafenib or vemurafenib, which enables sustained inhibition of the kinase (26). These preclinical data suggest that the encorafenib binimetinib combination will therefore enable more rapid control of sensitive clones when drug is resumed, making it a better therapy for an adaptive approach.

In addition, E+B and D+T have different toxicity profiles with D+T associated with pyrexia, skin rash and diarrhoea, whereas E+B is associated with nausea, vomiting and diarrhoea (28,95). One of the issues of the temperatures associated with dabrafenib (due to its metabolite) is that it can lead to multiple interruptions of therapy, which although has not been shown to impact outcomes in terms of survival, may cause issues with the logistics of an adaptive strategy, therefore we believe E+B may be a better option for this approach.

4.3 Risk and Benefits

Potential Risks:

This trial is categorised as Type B (somewhat higher than the risk of standard medical care) as per the risk-adapted approach to clinical trials adopted by the MHRA.

Disadvantages for participants include the extra visits and blood tests that will need to be made, side effects of the medication, CT scans and radioactive tracer used in PET-CT scans. They will be fully informed of these in the participant information sheet. The main risk however is that E+B does not control the cancer upon restarting drugs or that the ctDNA does not identify the cancer becoming active. Our extensive preclinical data and experience in the CAcTUS trial does not suggest that identification of the cancer becoming more active will be a problem as ctDNA is very accurate in identifying disease progression. The only scenario where ctDNA has been shown to be less effective in identifying disease progression is in the context of brain metastases, especially in isolated brain progression (77,96,97). This is likely due to the blood brain barrier reducing the variant allele frequency (VAF) of ctDNA in the blood. We have defined inclusion/exclusion criteria which only permits patients without brain metastases to enroll. We will monitor for development of brain metastasis throughout the study with regular scans. In addition, we plan to reassess outcomes and response to restart of drug has occurred following the first drug holiday for every 6 patients on Arm B of the study. This will enable us to assess the trajectory of the ctDNA copies/ml of plasma of each individual patient and the cohort to determine whether drug off or drug on thresholds should change or whether there are any safety signals regarding tumour control.

While all exposure to radiation carries a very low risk that it may itself cause cancer in the future, the majority of scans on this study would also be performed as part of standard treatment.

As with all medications, E+B both carry risks of side effects. The patient should be encouraged to familiarize themselves with the patient information leaflet that will be provided for each drug.

More information regarding management of risks associated with this trial will be detailed and assessed in a separate Risk Assessment, which will be reviewed and agreed by the Chief Investigator and sponsor as part of the over all trial set-up process.

Potential Benefits:

There are two main potential benefits for patients on the study. The first is that based on the preclinical findings discussed above, they may have a longer time before they would require their next treatment line with delayed clinical progression (whilst taking drug) using an adaptive strategy. This may also result in improved overall survival. In addition, an adaptive strategy may result in improved quality of life and reduction in side effects from treatment, especially during time off therapy.

4.4 Trial Hypothesis, Objectives and Outcomes

Research hypothesis:

- Patients will have ctDNA response upon re-introduction of encorafenib plus binimetinib following first drug holiday
- Encorafenib plus binimetinib therapy using adaptive scheduling based on ctDNA level will improve PFS, reduce toxicity and enhance quality of life compared to continuous dosing in patients with stage III unresectable or stage IV melanoma

Primary Objective:

1. To assess whether tumours respond to re-introduction of encorafenib plus binimetinib following the first “drug off” period, assessed by % decrease of tumour activity and burden level (TAB; mutant copies of ctDNA/ml of plasma).

Secondary Objective(s):

1. To optimise the thresholds of percentage reduction in TAB level in ctDNA as a measure of response to stop drugs and the percentage increase in TAB as a decision to restart drugs (see section 5.1 for further details).
2. To assess maximal response (complete response (CR)/partial response (PR)/stable disease (SD)/progressive disease (PD)) to therapy in Arm A vs. Arm B
3. To assess progression free survival (PFS)
4. To assess PFS at 6, 12 and 15 months in Arm A vs. Arm B
5. To assess overall survival
6. To assess number of adaptive therapy cycles completed

7. To assess median duration of adaptive therapy cycles
8. To assess whether ctDNA result can be provided within 5 working days from sample receipt into CBC
9. To assess quality of life of Arm A continuous vs. Arm B adaptive dosing
10. To assess toxicity (all grade adverse events) in Arm A continuous vs. Arm B adaptive dosing

Exploratory objectives:

1. To describe maximal reduction in TAB level for each adaptive cycle
2. To describe rise in TAB levels during drug off period for each patient
3. To examine clonal evolution during continuous vs. adaptive drug dosing
4. To explore the relationship between observing a rise in ctDNA levels of mutant *BRAF* copies/ml and progressive disease observed scheduled scan results in Arm A

Translational research:

Samples will be collected for research work including tumour biopsies and blood. Any translational studies using DyNAMIc samples must be authorised by the TMG. Due to the hypothesis-generating design of translational studies, these will not be performed to GCP standard, however will be conducted with scientific rigour in accordance with principles of respect for persons, beneficence and justice.

Translational work aims will include but are not limited to:

- Understanding of tumour evolution on targeted therapy which will include in depth genetic and epigenetic analysis of ctDNA
- Understanding of response and resistance to therapy which can include analysis of DNA, RNA metabolites and proteins
- Characterisation of stage IV/stage III unresectable melanoma which can include analysis of DNA, RNA metabolites and proteins

Any leftover samples will be stored for up to 20 years in sponsor approved laboratories and will be available for research work authorised by the TMG.

Primary Endpoint:

- Maximal reduction in percentage mutant copies/ml from baseline 2 TAB level upon restart of E+B following first drug off period.

Secondary Endpoints:

- Optimised thresholds of percentage reduction in ctDNA mutant BRAF copies/ml as a measure of response to stop drugs and the percentage and/or minimum increase in BRAF mutant copies/ml as a decision to restart drugs.
- Maximal radiological response (complete response (CR)/partial response (PR)/stable disease (SD)/progressive disease (PD)) to therapy in Arm A vs. Arm B
- PFS defined as time from randomisation to radiological (RECIST v1.1 and in Arm B defined as radiological progression whilst on targeted therapy unless stopped due to toxicity/choice) progression on Arm A vs. Arm B
- PFS defined as time from randomisation to radiological (RECIST v1.1 and in Arm B defined as radiological progression whilst on targeted therapy unless stopped due to toxicity/choice) progression at 6, 12 and 15 months on Arm A vs. Arm B
- Number of adaptive therapy cycles completed
- Median duration of adaptive therapy cycles
- Number and location of sites of disease progression
- Percentage of ctDNA results provided within 5 working days
- Incidence of CTCAE all grade adverse events in Arm A vs. Arm B
- Quality of life of Arm A vs. Arm B using EORTC QLQ-C30 and PRO-CTCAE questionnaires

Exploratory endpoints:

- Maximal reduction in ctDNA mutant BRAF copies/ml for each adaptive cycle
- Rise in ctDNA mutant BRAF copies/ml during drug off period for each patient

A summary table is on the next page.

Summary:

Objectives	Outcome Measures	Timepoint(s) of evaluation
Efficacy:		
Primary: Maximal reduction in percentage mutant copies/ml from baseline 2 TAB level upon restart of E+B following first drug off period.	ctDNA mutant *BRAF* copies/ml of plasma	Longitudinally throughout the study
Secondary: Optimised thresholds of percentage reduction in ctDNA mutant BRAF copies/ml as a measure of response to stop drugs and the percentage and/or minimum increase in BRAF mutant copies/ml as a decision to restart drugs.	ctDNA mutant *BRAF* copies/ml of plasma	Longitudinally throughout the study
Secondary: Maximal radiological response (complete response (CR)/partial response (PR)/stable disease (SD)/progressive disease (PD)) to therapy in Arm A vs. Arm B	Response rate using RECIST (v1.1) criteria	Baseline and 6 months follow-up
Secondary: PFS defined as time from randomisation to radiological (RECIST v1.1 and in Arm B defined as radiological progression whilst on targeted therapy unless stopped due to toxicity/choice) progression on Arm A vs. Arm B	Percentage of patients who have experienced disease progression or death	Continuously throughout the study
Secondary: PFS defined as time from randomisation to radiological (RECIST v1.1 and in Arm B defined as radiological progression whilst on targeted therapy unless stopped due to toxicity/choice) at 6, 12 and 15 months on Arm A vs. Arm B	Disease Progression or Death	Continuously throughout the study

Objectives	Outcome Measures	Timepoint(s) of evaluation
Efficacy:		
Secondary: Overall survival (OS) defined as time from randomisation until death in Arm A vs. Arm B	Death	Continuously throughout the study
Secondary: Number of adaptive therapy cycles completed	Completed adaptive therapy date	Longitudinally throughout the study
Secondary: Median duration of adaptive therapy cycles	Completed adaptive therapy date	Longitudinally throughout the study
Secondary: Number and location of sites of disease progression	Disease Progression or Death	Continuously throughout the study
Secondary: Percentage of ctDNA results provided within 5 working days from sample receipt into CBC	Percentage of ctDNA results reported within 5 days from sample receipt into CBC	Longitudinally throughout the study
Exploratory: Maximal reduction in ctDNA mutant BRAF copies/ml for each adaptive cycle	ctDNA mutant *BRAF* copies/ml of plasma	Longitudinally throughout the study
Exploratory: Rise in ctDNA mutant BRAF copies/ml during drug off period for each patient	ctDNA mutant *BRAF* copies/ml of plasma	Longitudinally throughout the study
Safety:		
Incidence of CTCAE all grade adverse events in Arm A vs. Arm B	Adverse Events and Serious Adverse Events defined by CTCAE version 5	Continuously throughout the study
Health Economics:		
None		
Other objectives:		
To assess quality of life of Arm A vs. Arm B	EORTC QLQ-C30 and PRO-CTCAE	Longitudinally throughout the study

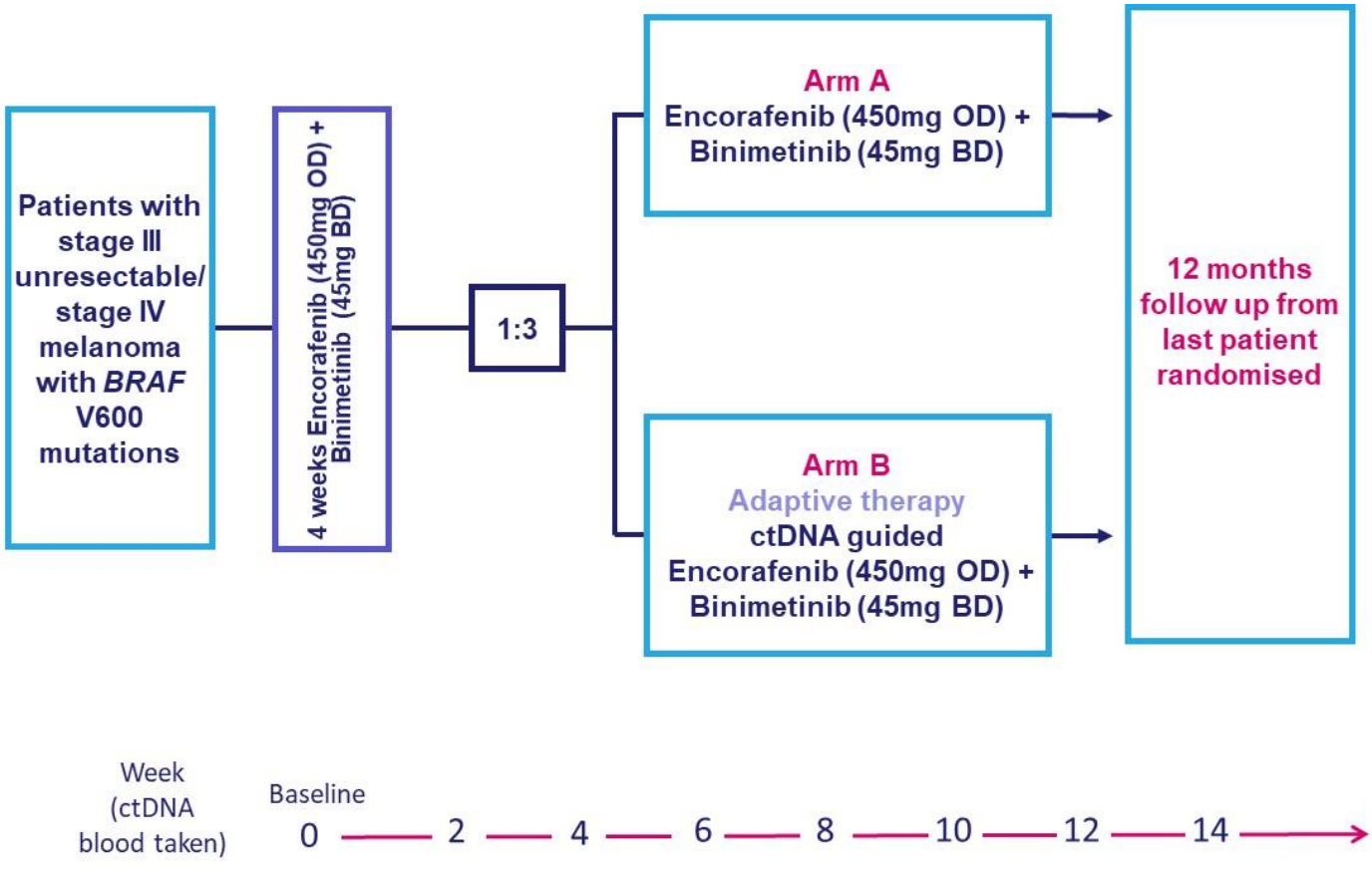
5. STUDY DESIGN

DyNAMIc is designed as a randomised, parallel arm proof-of-concept study to:

1. Test our hypothesis that tumours respond (measured by ctDNA mutant *BRAF* TAB level) to re-introduction of targeted therapy (following drug holiday).
2. Test the thresholds we have simulated based on our pre-clinical data are correct or whether they need refining based on response in patients examined prospectively.

Patients with stage III un-resectable or stage IV *BRAF* mutant metastatic melanoma eligible for the study will be randomised 1:3 (continuous:adaptive). All patients will commence encorafenib (E) 450mg once daily plus binimetinib (B) 45mg twice daily continuous dosing for 4 weeks. A baseline blood sample will be taken within 24 hours prior to commencing E+B to test for the level of ctDNA (Baseline TAB). At week 2 and week 4, further blood for ctDNA will be taken. Patients who meet the inclusion criteria will be randomised by week 2 of treatment. Patients will be stratified by ctDNA level at baseline. Patients will be treated until disease progression (RECIST v1.1) on scan whilst taking E+B, or stop due to patient choice/toxicity.

Figure 5 Trial Schema:



The study will recruit 10 patients into standard of care Arm A and 30 into the adaptive Arm B. As it is a pilot study, a balance is required to ensure the aims of the study are addressed in a timely way to move on to

further studies powered for efficacy endpoints whilst providing sufficient data to ensure that there is certainty regarding the optimal thresholds and that a signal is seen to support the concept. The aims of the study are to demonstrate a reduction in tumour burden through assessing drop in TAB upon restart of E+B. This will be demonstrated both within the adaptive arm and by comparison against the standard of care arm.

Sample size justifications are based on demonstrating that the adaptive approach can continue to induce a reduction in tumour burden when drugs are re-started. The aim is to show that this occurs both solely within the adaptive arm and by comparing the reduction against what is shown in the standard of care arm (which at that timepoint should be stable due to ongoing response or increasing if resistance emerging).

For comparisons within the adaptive arm only, the aim is to show that a reduction in TAB level given by a log fold change of 2 is observed. Analysis is based on estimation as opposed to demonstrating any pre-specified hypothesis. We expect the log-fold change in TAB level to have a standard deviation itself of 2 units. With 30 patients this will translate into 95% Confidence interval half length of 0.72 [e.g. if a log fold change of 2 is observed it will have an approximate 95% CI of (1.28 – 2.72)] which is sufficient precision to demonstrate a meaningful TAB reduction. Attrition bias will be minimised by analysing data based on the principle of intention-to-treat (ITT).

5.1 Molecular tumour board ongoing assessment of TAB levels

The DyNAMIc trial has 2 key decisions repeated for each adaptive cycle:

i. The TAB level to stop E+B

ii. The TAB level to restart E+B

The criteria for the stopping and restarting of treatment for participants on Arm B are subject to change. The initial threshold criteria are provided below.

- During the first drug withdrawal, the TAB level with be compared against the **baseline TAB** level (see Fig 6). If the ctDNA shows a rise in TAB level of ≥10% of **baseline TAB** or for patients with a **baseline TAB** of <200 copies/ml, a rise by the equivalent of 15 copies/10ml (depending on the volume of plasma used and subject to the limit of quantitation) or the scan shows disease progression (recist v1.1), the patient will restart E+B.
- Following the first period of drug withdrawal, upon restart of E+B, the TAB level will be compared to the **TAB baseline 2** level, which is the TAB level taken within 48 hours prior to E+B restart (see Fig 1). When the TAB level falls to ≤50% of **TAB baseline 2**, E+B are withdrawn.
- During the next period of drug withdrawal, E+B are restarted when the TAB level increases by ≥10% of **TAB baseline 2**, or for patients with a **baseline TAB** of <200 copies/ml, a rise by the equivalent of 15 copies/10ml (depending on the volume of plasma used and subject to the limit of quantitation), or the scan shows disease progression (recist v1.1).
- For each “on drug” targeted therapy cycle, when the TAB level falls to ≤50% of **TAB baseline 2**, E+B are withdrawn.

- For each “off drug” part of the adaptive therapy cycle E+B are restarted when the TAB level increases by ≥10% of **TAB baseline 2**, or for patients with a **baseline TAB** of <200 copies/ml, a rise by the equivalent of 15 copies/10ml (depending on the volume of plasma used and subject to the limit of quantitation), or the scan shows disease progression (recist v1.1).
- In addition, if the patient is “off drug” but the scan shows disease progression (RECIST v1.1) drug will be restarted.

We have determined these levels through our preclinical data tracking ctDNA levels in patients treated with targeted therapy and through analysis of baseline values of patients with stage IV *BRAF* mutant melanoma screened for the CAcTUS trial.

Throughout the trial, there will be ongoing monitoring of these thresholds by the molecular tumour board. They will meet after every 6th patient has re-commenced therapy following their first period of drug withdrawal on Arm B and will analyse and discuss the TAB levels for each individual on Arm B and for the cohort as a whole. Any changes to the thresholds must be agreed by the molecular tumour board and will be documented in “Circulating Tumour DNA Threshold Determination and Ongoing Evaluation”. For safety reasons, changes to ctDNA thresholds for the stopping and restarting of treatment will be implemented immediately.

The molecular tumour board will discuss 4 main aspects including an overview of the radiological and clinical response data and kinetics of ctDNA levels. Features of any patients who have progressed on scan without a corresponding rise in TAB level will also be discussed.

i. To assess what value the TAB rise during first drug withdrawal vs. TAB baseline (point 1 above) should be, given the data from patients on study.
ii. To assess what value the TAB rise vs. TAB baseline 2 level (point 2 above) should be, given the data from patients on study.
iii. To assess what value of TAB decrease compared to TAB baseline 2 should trigger a decision to withdraw drugs (point 3 above), given the data from patients on study.
iv. Whether these levels should be further adapted as patients complete more cycles of adaptive therapy or for different kinetics of TAB level. Rules may be further created based on mathematical modelling of patient data from DyNAMIc.

Figure 6 Adaptive treatment schedule on Arm B:

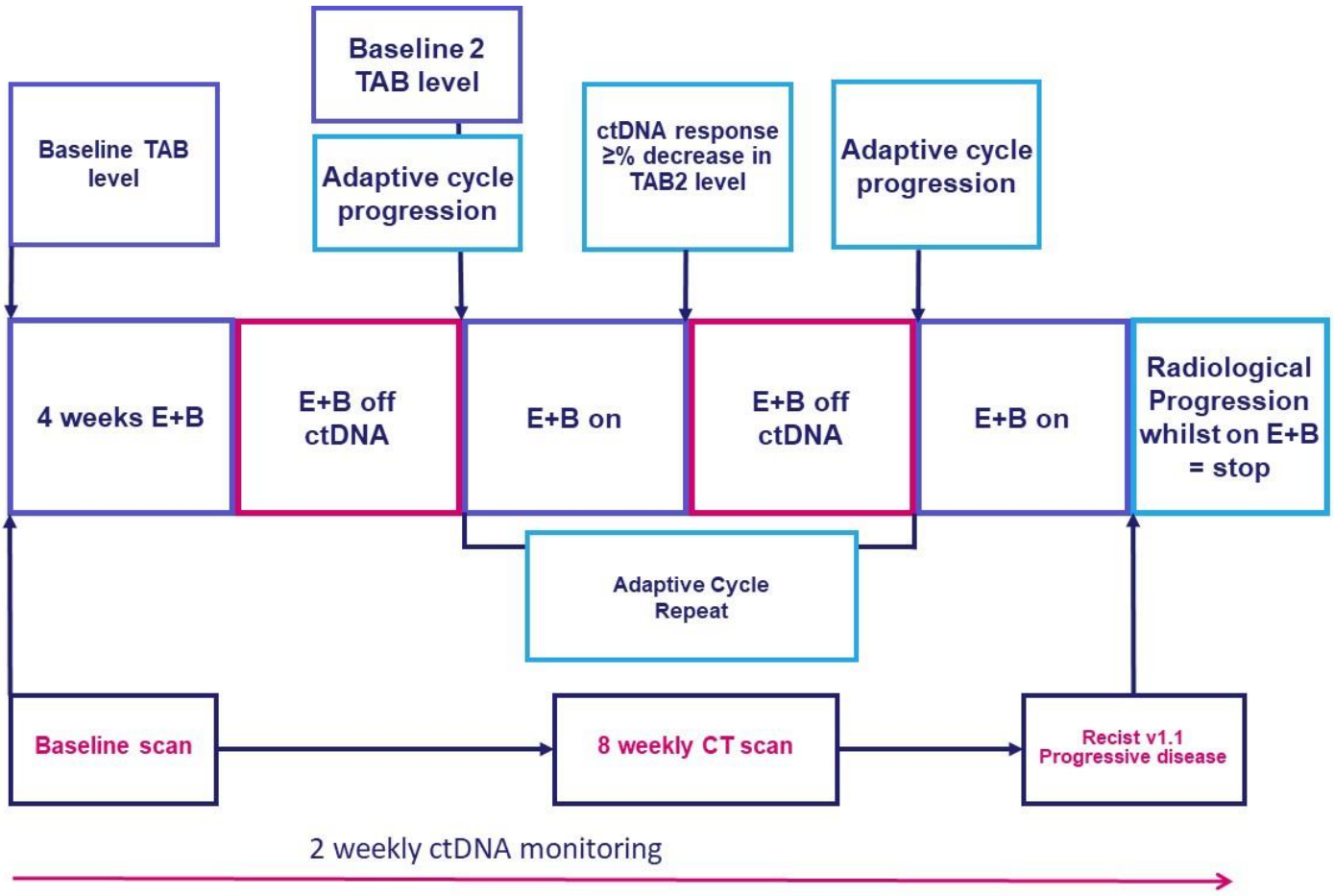


Figure. 6 Adaptive treatment schedule on Arm B. A baseline TAB level will be taken within 24 hours of taking first dose of study drugs. Patients will initially receive E+B continuously for 4 weeks before E+B are withdrawn. Whilst off E+B, TAB level will compared to baseline TAB and when criteria for drug restart are fulfilled, E+B will be restarted. Within 48 hours of the the first drug restart, a further TAB level will be taken, termed Baseline 2 TAB level. Further adaptive cycles will compare the TAB level to the baseline 2 TAB. When on E+B, if the criteria for drug withdrawal are fulfilled, E+B will be stopped. When off E+B the TAB level will be compared to TAB baseline 2 and if the criteria for drug restart are fulfilled, E+B will be restarted.

To achieve one of the main objectives of the trial, which is to establish the optimal thresholds to stop and start drugs based on TAB level, DyNAMIc will include assessment of these levels at regular intervals for each individual patient. This will also provide additional safety monitoring. Thus, after every 6th patient has re-commenced therapy following their first period of drug withdrawal on Arm B, a molecular tumour board will convene and will analyse and discuss the TAB levels for each individual on Arm B and for the cohort as a whole. Any revisions to the thresholds will be documented in a new version of “Circulating Tumour DNA Threshold Determination and Ongoing Evaluation”.

5.2 Blinding

This is an open label study with no blinding requirements. All researchers and participants know which treatment / intervention is being administered.

5.3 Study Setting

Participants will be identified and recruited from approximately 11 hospitals in the UK selected for their expertise in the treatment of melanoma and a track record in conducting clinical trials. Each of the centres must have the required research nurses, pharmacy support and laboratory equipment to undertake the study.

Selection of Participating Sites:

Criteria for the selection of centres will be determined by the Trial Management Group and will be described in a separate document 'DyNAMIc Site Feasibility Questionnaire' maintained in the Trial Master File (TMF).

Sites fulfilling the trial-specific criteria will be selected to be recruitment centres for the DyNAMIc trial and will be opened to recruitment upon successful completion of all global (e.g. REC and MHRA) and study-specific conditions (e.g. site personnel training requirements) and once all necessary documents have been returned to the LCTC. Initiation of sites will be undertaken in compliance with LCTC internal processes. Conditions and documentation required will be detailed on a LCTC Green Light Checklist maintained in the TMF and must be fully completed prior to opening sites to recruitment.

Selection of Principal Investigators:

Principal Investigators will be required demonstrate equipoise, relevant experience and commitment during early stage feasibility assessment. All investigators will have the particular medical expertise necessary to conduct the study in accordance to the protocol and all regulatory and ethical requirements. Written agreement to conduct research as such will be obtained prior to site initiation.

A suitable co-investigator should be identified at each site to deputise in case of PI absence.

6. STATISTICAL CONSIDERATIONS

6.1 Introduction

This Section details the statistical principles relating to the design and conduct of the DyNAMIc study. Please note that whilst an overview of the analytical techniques to be used are included here, a separate Statistical Analysis Plan (SAP) will be developed for evaluation of the primary and secondary outcomes. A separate SAP for exploratory work will also be produced.

6.2 Sample Size and Recruitment

Sample Size Calculation:

The **primary endpoint** is the Maximal reduction in percentage mutant copies/ml from baseline 2 TAB level upon restart of E+B following first drug off period. Whilst the study contains a randomised component, success of the study will depend on being able to demonstrate that at least 75% of patients randomised to the adaptive therapy can achieve a 50% reduction. From 30 patients, this success will be determined by ≥23 patients satisfying the endpoint criteria. Assuming a 'true' response rate of 85% the, based on exact binomial probabilities there is a 93% probability (Power) or observing this outcome. The probability of observing this result under varying assumptions of the 'true' success rates are provided in the table below.

'True' rate	60%	65%	70%	75%	80%	85%	90%
Pr (≥ 23 successes)	4%	12%	28%	51%	76%	93%	99%

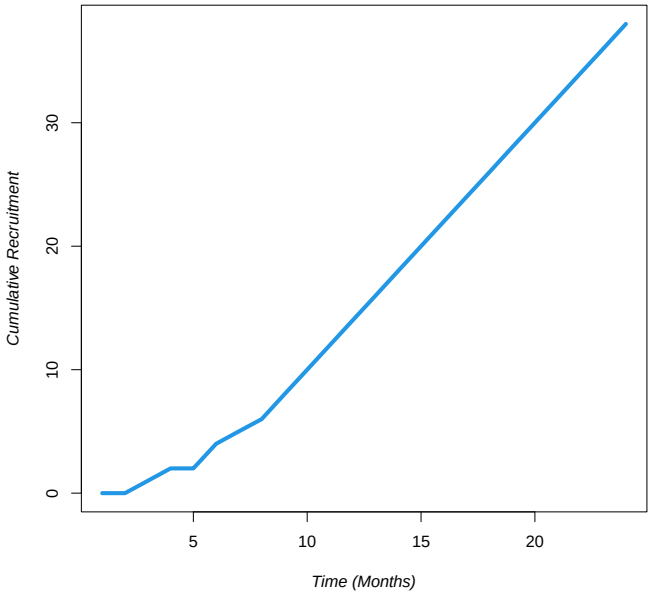
Precision of QoL Estimates as a key secondary endpoint:

Given the sample size of 40 patients and the large number of quality of life domains that can be observed from the EORTC QLQ-C30 and PRO-CTCAE then power calculations based on pre-set hypotheses are not provided. It is anticipated that overall scores such as the global health status will be of greatest interest. Here, based on previous studies a standard deviation of 12 units on the change in score between baseline and follow-up is reasonable. From a sample size of 40 patients, it is reasonable to expect data suitable for analysis on 32 patients. Based on these assumptions then a standard error of 2.12 will be observed. This will result in a 95% confidence interval half length of 4.16 being observed.

Feasibility of Sample Size:

Study recruitment is planned from 10 sites which will recruit at an average recruitment rate of 3 patients/year/site. Ensuring all sites are opened within 12 months then the a total of 24 months are required to obtain 40 patients.

Figure 7: Predicated recruitment curve:



6.3 Method of Randomisation

Allocation Sequence Generation:

Randomisation will be performed using a 1:3 allocation ratio. A pre-generated list produced on the principle of randomly permuted blocks will be used. Level of ctDNA will be included as the only stratification factor. It will have 3 levels; 15-50, 51-200 and >200 copies/ml of plasma. These are based on unpublished data from the CAcTUS trial.

Concealment and Implementation of Allocation Sequence:

Patient allocations will be irrevocably generated upon completion of the web-based registration form by a delegated member of the trial research team. Allocation concealment will be ensured as the service will not release the randomisation code until the patient has been recruited into the trial; this takes place after confirmation of ctDNA levels.

6.4 Interim Analyses

Interim analyses to assess the ctDNA response to restart of E+B will occur after every 6th patient has re-commenced therapy following their first period of drug withdrawal. The results will be discussed by a molecular tumour board specifically established to assess whether the levels of starting/stopping drugs determined by our preclinical data fit with our predictions. No formal stopping rules are included within the study design. Analyses of the accumulating data will also be performed at regular intervals (at least annually) for review by an ISDMC. These analyses will be performed at the LCTC. The ISDMC will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients or further follow-up. A decision to discontinue recruitment, in all patients or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians, including Principal Investigators, and the general clinical community.

6.5 Analysis Plan

Data Summaries:

Continuous data will be summarised as median (IQR) and categorical data will be presented as frequencies of counts with associated percentages. Summaries of the patient population will be reported by randomised group with Wilcox tests and Fisher tests (as appropriate) used to assess any differences.

Patient Groups for Analysis:

Analyses will be performed on an intention to treat principle, retaining all patients in the planned analyses irrespective of any protocol violations

Missing Data:

Missing data are assumed to be small and all analyses are planned on a complete case basis. If substantial missing data on outcome/other key data components are observed (>15%) then analyses will be conducted using multiple imputation.

Levels of Significance:

As assessment of the primary outcome is based on the observed count of successes, no pre-defined level of significance is required to demonstrate a successful study. All results will be presented alongside nominal 95% two-sided confidence intervals and a p-value use to determine statistical significance.

Analysis of the Primary Endpoint:

The primary endpoint is the number of patients to achieve a 50% maximal reduction in percentage mutant copies/ml of plasma from baseline 2 TAB level upon restart of E+B following first drug off period. This is measured as a binary endpoint and will be reported as a rate with associated 95% confidence intervals.

Further analyses will be performed on the TAB level over the course of the study. Here longitudinal regression techniques will be performed including random effects for the patient identifier.

Details on the analytical approaches for each secondary endpoint are included in the statistical analysis plan (SAP).

7. ELIGIBILITY CRITERIA

The DyNAMIc trial aims to recruit 40 patients based on sample size calculations described in Section 6.2. All patients must provide written, informed consent before any study procedures occur (see Section 9.2 for more information regarding informed consent processes) and must meet all eligibility criteria as described below before being randomised.

7.1 Inclusion Criteria

Patients eligible for the trial must comply with all of the following at randomisation:

1. Written and informed consent obtained from participant and agreement of participant to comply with the requirements of the study
2. Histological confirmation of cutaneous melanoma
3. ≥ 18 years of age
4. Stage III un-resectable/ IV disease
5. Measurable disease on CT (thorax, abdomen and pelvis, ± neck if indicated) and/or PET-CT, and CT or MRI (brain) scan (RECIST v1.1)
6. *BRAF* p.V600E/K/R mutation confirmed (exact point mutation must be known)
7. *BRAF* ctDNA TAB level of ≥15 copies/ml of plasma
8. ECOG performance status 0/1/2
9. Prior radiotherapy or radiosurgery must have been completed at least 2 weeks prior to the first dose of study drugs.
10. Adequate organ function as defined below:
    - Haemoglobin ≥ 9 g/dL
    - White blood count ≥ 2 $x10^9$/L
    - ANC[a] ≥ 1.2 $x10^9$/L
    - Platelet count ≥ 75 $x10^9$/L
    - Albumin ≥ 2.5 g/dL
    - Total bilirubin[b] ≤ 1.5 x ULN[a]
    - AST[a] or ALT[a] ≤ 3 x ULN[a]
    - Calculated creatinine clearance[c] ≥ 30ml/min
    - Left Ventricular Ejection fraction (LVEF) ≥ 50% or ≥LLN[a] by ECHO

11. Women of childbearing potential participating in the study (WOCBP see appendix B for definition) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to the start of study drug.
12. WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drugs plus at least 1 month following last dose of drug (either encorafenib or binimetinib), (see appendix B).
13. Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment plus 90 days (duration of sperm turnover) from last dose of drug (either encorafenib or binimetinib), (see appendix B).
14. Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, WOCBP participating in the study who are continuously not heterosexually active must still undergo pregnancy testing (as described in inclusion criterion 11).

a. Abbreviations: ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; LLN = lower limit of normal; ULN = upper limit of normal.

b. Except if the patient has Gilbert Syndrome or liver metastasis, in which case the bilirubin must be <3 x ULN

c. Calculate creatinine clearance using standard Cockcroft-Gault formula (Appendix A).

7.2 Exclusion Criteria

Any patient meeting any of the criteria listed below at baseline will be excluded from study participation:

1. Prior systemic targeted BRAF/MEKi therapy for stage IV (metastatic) melanoma (treatment for stage III allowed as long as RFS ≥6 months following discontinuation of drugs)
2. BRAF wild-type malignant melanoma
3. Metastasis to the brain or leptomeninges
4. Any contraindication to treatment with Encorafenib or Binimetinib as per the local Summary of Product Characteristics
5. Hypersensitivity to the active substance or to any of the excipients of Encorafenib or Binimetinib
6. Current use of a prohibited medication as described in Section 8.9
7. History of another malignancy. **Exception:** Patients who have been disease-free for 3 years, (i.e. patients with second malignancies that are indolent or definitively treated at least 3 years ago), curatively treated in situ cancer of the cervix, ductal carcinoma in situ (DCIS); stage 1, grade I endometrial carcinoma, or patients with a history of completely resected non-melanoma skin cancer. No additional therapy should be required whilst the patient is on study.
8. Any serious or unstable pre-existing medical conditions (aside from malignancy exceptions specified above), psychiatric disorders, or other conditions that could interfere with the patient's safety, obtaining informed consent, or compliance with study procedures.
9. Known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection.

10. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption
11. Child Pugh B or C liver disease
12. Coronary syndromes (including myocardial infarction within 6 months or unstable angina)
13. A history or evidence of current ≥ Class II congestive heart failure as defined by the NYHA guidelines with an ejection fraction of <50% (see appendix C).
14. Treatment refractory hypertension defined as a blood pressure of systolic >150 mmHg and/or diastolic >95 mmHg on >3 occasions which cannot be controlled by anti-hypertensive therapy;
15. Uncorrectable electrolyte abnormalities > CTCAE v5 Grade 1 (e.g. hypokalaemia, hypomagnesaemia, hypocalcaemia), long QT syndrome (baseline QTC interval ≥ 480msec) or taking medicinal products known to prolong the QT interval.
16. A history or current evidence/risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR) including presence of predisposing factors to RVO or CSR (e.g., uncontrolled glaucoma or ocular hypertension, uncontrolled hypertension, uncontrolled diabetes mellitus, or a history of hyperviscosity or hypercoagulability syndromes);
17. Females who are pregnant or breast-feeding and are not able to stop breast-feeding prior to first dose of study drugs (see section 7.4);
18. Prisoners or patients who are involuntarily incarcerated.
19. Patients who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

7.3 Co-enrolment Guidelines

Co-enrolment to other Clinical Trials of Investigational Medicinal Products (CTIMP) is not permitted.

To avoid potentially confounding issues, ideally participants should not be recruited into other non-CTIMP trials during their participation in DyNAMIc. Where recruitment into another non-CTIMP trial is considered to be appropriate and without having any detrimental effect on the DyNAMIc trial this must first be discussed with the LCTC who will contact the Chief Investigator (Prof. Paul Lorigan).

Individuals who have participated in a CTIMP within 30 days preceding screening will be ineligible for the DyNAMIc trial. Should patients wish to withdraw from DyNAMIc in order to take part in another CTIMP trial provisions for follow-up should be discussed with the CI and LCTC.

7.4 Lifestyle Restrictions

Meals and Dietary Restrictions:

Patients are not allowed to consume St John's Wort as part of herbal remedies as it could affect the efficacy of trial drugs. Grapefruit juice is contraindicated. No other meal/dietary restrictions apply.

Effects on Ability to drive and use machines:

Encorafenib and binimetinib have a minor influence on the ability to drive or use machines. Visual disturbances have been reported in some patients treated with encorafenib during clinical studies. Patients should be advised not to drive or use machines if they experience visual disturbances or any other adverse reactions that may affect their ability to drive and use machine

Contraception:

Women of childbearing potential must use effective contraception during treatment and for at least 1 month following the last dose (see appendix B). Combination treatment may decrease the efficacy of hormonal contraceptives. Therefore, female patients using hormonal contraception are advised to use an additional or alternative method such as a barrier method (e.g. condom) during treatment and for at least 1 month following the last dose.

During treatment and for at least 90 days following the last dose (duration of sperm turnover), males who are sexually active with WOCBP must use a male condom plus partner use of a suitable highly effective method of contraception (see appendix B).

Pregnancy and Breastfeeding:

It is unknown whether encorafenib or binimetinib, or their metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. For patient to be included they must have given birth/stopped breastfeeding 5 days prior to commencing treatment or they will be withdrawn from the trial.

In addition to those required as part of the study procedures, additional pregnancy testing of WOCBP is to be undertaken if clinically indicated according to the investigator criteria. This applies to both treatment arms and is regardless of whether a participant on Arm B is on or off treatment.

Fertility:

There are no data on the effects of encorafenib/binimetinib on fertility in humans. Based on findings in animals, the use of encorafenib may impact fertility in males of reproductive potential. As the clinical relevance of this is unknown, male patients should be informed of the potential risk for impaired spermatogenesis and local practice followed to address this. There are no animal data on the effect of binimetinib.

8. TRIAL TREATMENT/INTERVENTIONS

8.1 Introduction

Eligible patients will be randomised between Arm A continuous E+B and Arm B adaptive E+B. Patients in Arm A will receive encorafenib 450mg once daily plus binimetinib 45mg twice daily continuous dosing and patients in Arm B will receive encorafenib 450mg once daily plus binimetinib 45mg twice daily adaptive dosing.

Product	Storage	IMP status	Annex 13 Trial Labelling Required	Accountability	Supply Route	Funding
Encorafenib Arm A	**As per SmPC**	**IMP**	**No**	**Patient Diaries, CRF, Administration Records**	**To be supplied by sites from hospital stock**	**As per NHS funding**
Binimetinib Arm A	**As per SmPC**	**IMP**	**No**	**Patient Diaries, CRF Administration Records**	**To be supplied by sites from hospital stock**	**As per NHS funding**
Encorafenib Arm B	**As per SmPC**	**IMP**	**No – exemption from MHRA**	**Subject Level Accountability, Dispensation, Returns Patient Diaries**	**To be supplied by sites from hospital stock**	**As per NHS funding – agreed with NHS England**
Binimetinib Arm B	**As per SmPC**	**IMP**	**No – exemption from MHRA**	**Subject Level Accountability, Dispensation, Returns Patient Diaries**	**To be supplied by sites from hospital stock**	**As per NHS funding – agreed with NHS England**

Arm B Reserve Pack:

This study requires the use of “Reserve Packs” in Arm B, this is because patients will need to recommence treatment upon a phone call and therefore it may not be convenient for them to attend hospital to collect study drug. Patients in Arm B need to be dispensed a new 10 day reserve pack:

- At randomisation visit
- At each physical visit if the patients have taken any doses from the reserve pack
- If there has been a change to the dose of either Encorafenib or Binimetinib.

The schedule of events and figure 9 flowchart outline the timepoints at which a reserve pack should be dispensed.

The trial is fully open label and Encorafenib and Binimetinib are commercially available and should be sourced locally as per standard practice at the investigator sites using products that have a UK or EU license. Both encorafenib and binimetinib are still under a patent and will therefore only be available from current manufacturer Pierre Fabre Limited. The research sites will be responsible for using the most recent SmPC for products being used at site in the local pharmacy folder, or a file note that makes reference to the electronic source.

Descriptive information for the IMPs can be found in the respective package insert. IMPs will be used and stored as detailed on the product label and according to manufacturer’s instructions. There will be no re-imbursement to sites for the treatment as this is standard of care.

8.2 Treatment Name / Description

Encorafenib and Binimetinib will remain under patent for the duration of this trial, therefore only one brand of each, Braftovi and Mektovi respectively, are available for use.

All patients will commence encorafenib 450mg once daily plus binimetinib 45mg twice daily continuous dosing for 4 weeks. A baseline blood sample will be taken within 24 hours prior to commencing E+B to test for the level of ctDNA (Baseline TAB). Patients who meet the inclusion criteria will be randomised to Arm A continuous E+B vs. Arm B adaptive E+B. Patients will be stratified by ctDNA level at baseline. At week 2 and week 4, ctDNA will be taken. At week 4 the patient will commence the following depending on which arm they have been randomised to.

Arm A – Continuous encorafenib plus binimetinib targeted therapy

Standard of care (SOC) continuous dosing of encorafenib 450mg once daily plus binimetinib 45mg twice daily. Both drugs are administered as part of a 28 day cycle. Patients will have ctDNA testing every 2 weeks and clinical review every 4 weeks with scans every 8 weeks (+/- 1 week). Patients will be treated and undergo scans until confirmed disease progression on imaging (RECIST v1.1), significant toxicity or patient choice.

Arm B - Adaptive encorafenib plus binimetinib targeted therapy:

Trial treatment in this arm are given in cycles of 14 days, and commences only after one standard of care (SOC) cycle (i.e. 28 days) has been completed. Following the SOC cycle, patients will withhold encorafenib and binimetinib. They will undergo 2 weekly ctDNA monitoring for TAB level, with results returned within 5 working days from sample receipt at CBC (Figure. 8). If the ctDNA shows a prespecified rise in TAB level or the scan shows disease progression (RECIST v1.1), the patient will restart encorafenib 450mg once daily plus binimetinib 45mg twice daily. These values are based on our mathematical modelling of patients undergoing longitudinal ctDNA monitoring and data from the CAcTUS trial.

Patients will undergo a clinical review every 4 weeks with scans every 8 weeks (+/- 1 week). Patients will be treated and undergo scans until confirmed disease progression on imaging (RECIST v1.1), significant toxicity, patient choice or end of study at 3 years.

Reserve Pack

As patients on Arm B will need to restart treatment upon ctDNA and TAB level rises a reserve pack needs to be dispensed to the patients at randomisation to Arm B, see schedule of events.

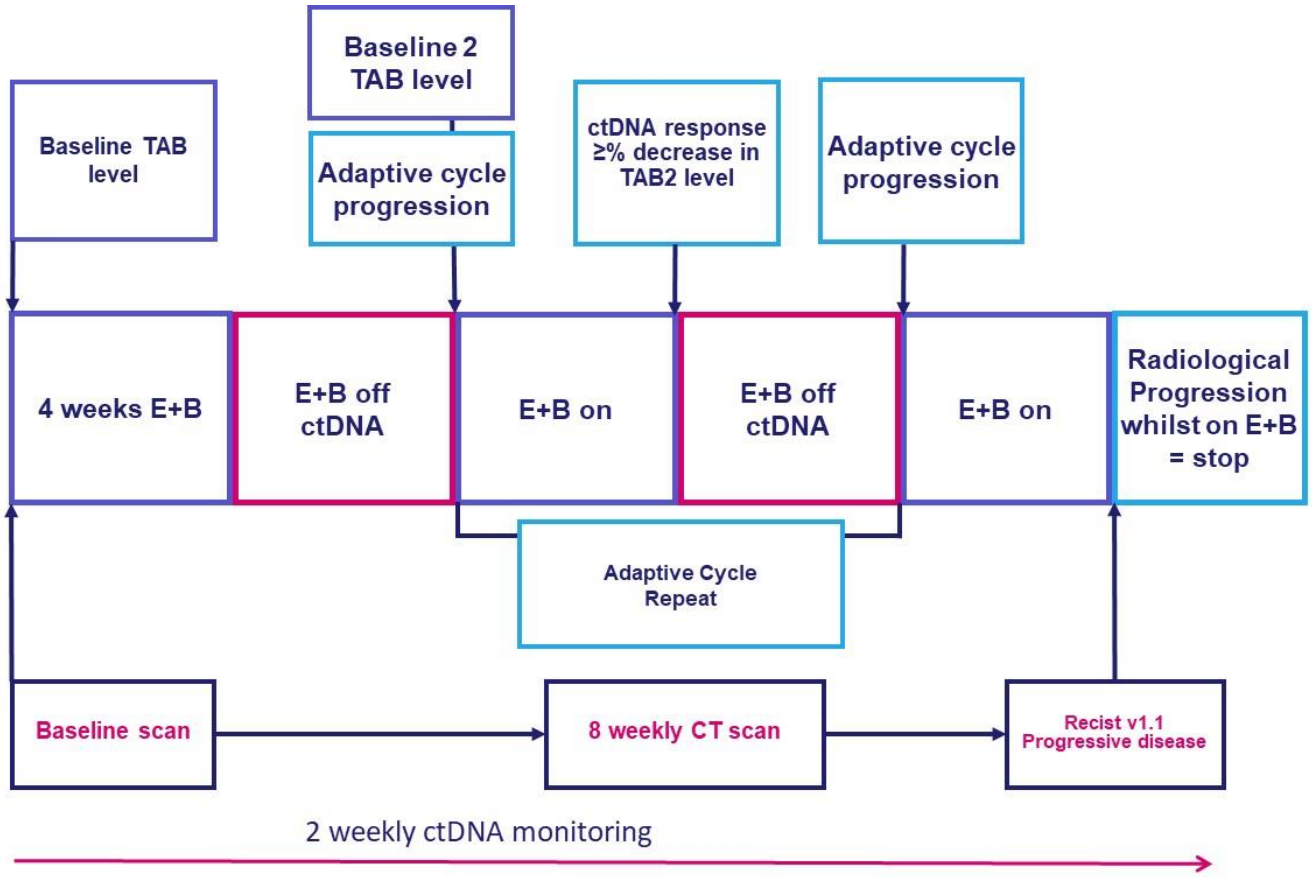


Figure. 8 Adaptive treatment schedule on Arm B. A baseline TAB level will be taken within 24 hours of taking first dose of study drugs. Patients will initially receive E+B continuously for 4 weeks before E+B are withdrawn. Whilst off E+B, TAB level will compared to baseline TAB and when criteria for drug restart are fulfilled, E+B will be restarted. Within 48 hours of the first drug restart, a further TAB level will be taken, termed Baseline 2 TAB level. Further adaptive cycles will compare the TAB level to the baseline 2 TAB. When on E+B, if the criteria for drug withdrawal are fulfilled, E+B will be stopped. When off E+B the TAB level will be compared to TAB baseline 2 and if the criteria for drug restart are fulfilled, E+B will be restarted.

Following the first period of drug withdrawal, at the time E+B are restarted, a new TAB level is taken, which will be the baseline for the rest of the adaptive cycles (called TAB baseline 2). Each time E+B are restarted following a drug holiday is defined as the start of the next targeted therapy adaptive 14 day cycle. For each targeted therapy cycle, when the TAB level falls by a pre-specified percentage of TAB baseline 2, E+B are withdrawn and they are restarted when the TAB level increases by a prespecified TAB level.

If patients have a dose limiting toxicity they will undergo dose reduction as per standard of care (see SmPC and section 8.5). If they require withdrawal of drug due to toxicity, this is allowed for a maximum of 6 weeks. If study drug is withdrawn due to toxicity for more than 6 weeks, the patient is to be withdrawn from treatment.

De-escalation and withdrawal of treatment will be proactively monitored in real time using the REACT system, managed by Digital Experimental Cancer Medicine Team.

The ctDNA level will continue to be taken at the same 2-weekly schedule, however will only be acted upon when they have re-started drug following toxicity. The schedule continues until there is disease progression (RECIST v1.1) seen on scan when the patient is taking E+B, or there is significant toxicity or patient choice to stop.

8.3 Manufacturing and Distribution

Regardless of its status as a standard of care treatment, Arm A in this study will be classed as an IMP due to the same products also being an experimental regimen within the same study.

Arm B in this study will be classed as IMP.

All IMP will be procured via the local supply chain at each participating hospital site. This study will fall under the exemption to Regulation 37 in Statutory Instrument 2004/1031. Meaning an exemption from the requirement to hold a manufacturing authorisation for investigational medicinal products (IMPs). The regulation specifically applies to “assembly” carried out in a hospital or health centre by a doctor, a pharmacist or a person acting under the supervision of a pharmacist.

To prevent accidental use, reserve packs need to be labelled as per the directions contained in the site dispensing section of the pharmacy manual.

Supply:

All drugs will be sourced from routine hospital stock and their handling and management will be subject to standard procedures of the pharmacy and the respective summary of product characteristics

Storage and dispensing:

Descriptive information for the drugs can be found in the patient information leaflet within each package. The study drugs should be stored in accordance with the environmental conditions (temperature, light, and

humidity) as determined by the manufacturer. If concerns regarding the quality or appearance of the drugs arise, the study drug should not be dispensed and the manufacturer informed immediately.

There will be no re-imbursement to sites for the drugs.

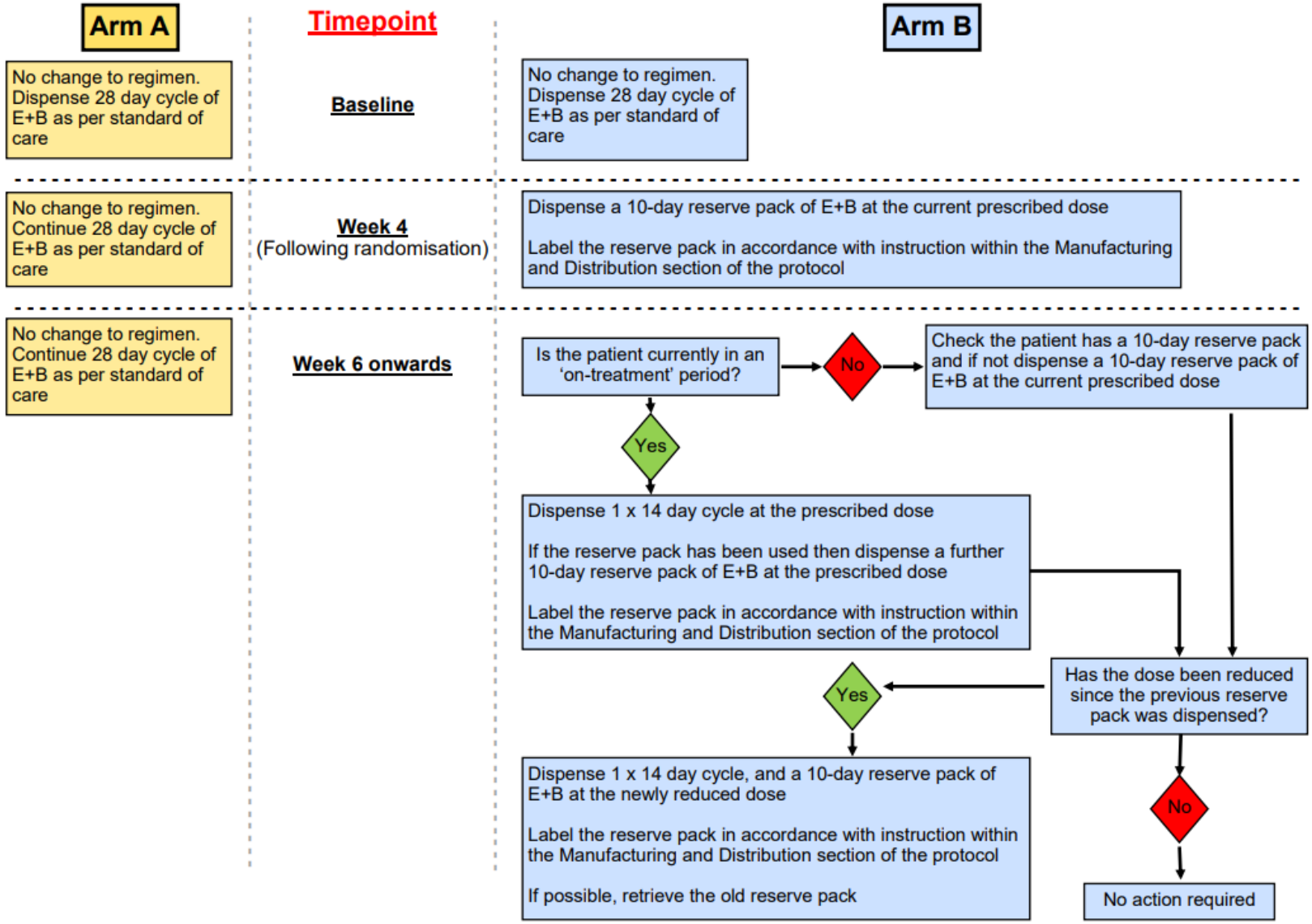
Study treatment should be dispensed according to the institutional standards at each site. Study treatment for Arm A is to be dispensed in cycles of 28 days. Study treatment for Arm B is to be dispensed in cycles of 14 days.

Participants on Arm B are to also be dispensed a further 10 day supply of medication, to be used as a 'reserve pack' if immediate recommencement of treatment is required following a ctDNA blood test. The reserve pack is to be replaced following its use, or if the dose is reduced. See figure 9, pharmacy dispensing diagram, below.

Product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes.

Please refer to the relevant SmPC for further information.

Figure 9: Pharmacy Dispensing Diagram:



8.4 Preparation and Administration

Preparation and administration of E+B will be according to the SmPC.

Note: If the patient vomits after the administration of either drug, dose(s) should not be re-taken and the next dose(s) taken as scheduled.

8.5 Treatment Modifications

After the patient has entered the trial, the clinician is free to give alternative treatment / intervention to that specified in the protocol, at any stage, if they feel it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the patient remains free to withdraw at any time from the protocol treatment and trial follow-up without giving reasons and without prejudicing further treatment.

If treatment-related toxicities occur on either arm, they are to be managed as per standard of care and in accordance with the dose modifications guidance within the current SmPC. Both treatments should be simultaneously dose reduced, interrupted or discontinued when possible. Refer to the current SmPC for information on exceptions where dose reductions to one IMP only are necessary.

8.6 Accountability Procedures

All E+B dispensed must have a sufficient ‘use by’ date.

A record of individual prescriptions will be maintained as per local practice. There will be reconciliation between doses recorded as dispensed and doses returned, inclusive of reserve packs.

8.7 Assessment of Compliance

Compliance is defined as at least 80% of the tablets taken. Non-compliance will be recorded as a protocol deviation.

In this trial, patient diaries and case report forms (CRF) will be used to capture information of IMPs dispensed/used. The sites will not be required to keep detailed accountability records of batch numbers and expiry dates of the IMPs dispensed. Participating patients will be provided with a patient diary to keep detailed record of all encorafenib capsules and binimetinib tablets taken by the patient during the trial. Study-site personnel will review dosing information with the patient (or legally authorised representative) on scheduled clinic visit days, providing instructions regarding dose, dose frequency and the number of tablets/capsules to be taken for each dose. Patients (or legally authorised representative) will be instructed to return all unused tablets/capsules and containers (empty, partially used, and/or unopened) for compliance check at the next

scheduled clinic visits. A compliance check and tablet/capsule count will be performed by study personnel during clinic visits. Study site personnel will record compliance information on the CRF.

A work instruction on the requirements for the compliance check will be provided to each participating site.

8.8 Product Recall

Hospital pharmacies are to have local policies in place for product recalls. If the need to recall either of the drugs used in this study is identified, the staff at site should inform the LCTC immediately.

The sponsor receives email alerts from MHRA. Should an alert regarding a product recall of either of the drugs be received, it will be relayed to sites immediately.

8.9 Concomitant Medications/Treatments and Specific Restrictions

Medications Permitted:

- Supportive care for disease-related and drug-related symptoms (anti-emetics, anti-diarrhoeals, and analgesics) may be offered to all participants on the trial including blood and blood products.
- Medications to manage co-morbidities apart from those listed below are permitted

Medications Not Permitted/ Precautions Required:

Please refer to the current SmPC for encorafenib and binimetinib. The following medications are **prohibited** within 28 days or 5 half-lives, whichever is shorter, prior to randomisation and during the study treatment period (unless to treat a drug-related adverse event):

- Any concurrent antineoplastic therapy (i.e., chemotherapy, hormonal therapy, immune therapy, non-palliative radiation therapy, or standard or investigational agents for treatment of cancer)
- Illicit drugs
- Antiretroviral drugs
- Herbal remedies (e.g., St. John's wort)

The following medications are **recommended to be stopped** within 28 days or 5 half-lives, whichever is shorter, prior to randomisation and during the study treatment period. If they must be continued then additional safety monitoring should be performed (please refer to SmPC for more details).

- CYP3A4 inhibitors (encorafenib is primarily metabolised by CYP3A4). Strong CYP3A4 inhibitors should be avoided (due to increased encorafenib exposure and potential increase in toxicity). Examples of strong CYP3A4 inhibitors include, but are not limited to, ritonavir, itraconazole, clarithromycin, telithromycin, posaconazole and grapefruit juice. In addition, CYP3A4 inducers should be avoided. Examples of moderate or strong CYP3A4 inducers include, but are not limited to

carbamazepine, rifampicin, and phenytoin. Alternative agents with no or minimal CYP3A induction potential should be considered.

- UGT1A1 inducers (such as rifampicin and phenobarbital) and inhibitors (such as indinavir, atazanavir, sorafenib) should be co-administered with caution as binimetinib is primarily metabolised through UGT1A1 mediated glucuronidation.

For further details regarding other drug interactions please refer to the SmPC.

Data on Concomitant Medication:

The investigator must be informed as soon as possible about any medication taken from the time of screening until 30 days after the last dose of study drugs.

Data on concomitant medication(s), including dietary supplements, taken during the study will not be collected for the study however the participant will be asked at each visit if they are taking any new medications in order to identify any non permitted medications..

8.10 Overdose

An overdose may be realised if informed by the patient, through diary cards, or via a check for compliance of treatment. An overdose for encorafenib is defined as the patient taking a dose of >450mg within 18 hours and for binimetinib a total dose of >90mg within 18 hours.

If an apparent overdose is observed, the site study time must establish from the patient if extra drug had been taken, or whether they had been, e.g. misplaced.

If an overdose is observed it must be recorded as an Adverse Event. Expedited reporting of overdose to LCTC is only required if the criteria of a Serious Adverse Event is met. Specific information on reporting adverse events can be found in section 10.

At doses of encorafenib between 600 to 800 mg once daily, renal dysfunction (Grade 3 hypercreatinaemia) was observed in 3 out of 14 patients. The highest administered dose occurred as a dosing error in one patient who took encorafenib at a dose of 600 mg twice daily for 1 day (total dose 1200 mg). Adverse reactions reported by this patient were Grade 1 events of nausea, vomiting and blurred vision; all subsequently resolved. The highest dose of binimetinib evaluated as single agent in clinical studies was 80 mg administered orally twice daily and was associated with ocular (chorioretinopathy) and skin toxicities (dermatitis acneiform).

Management:

There is no specific treatment for overdose of either drug.

If overdose occurs, the drugs should be interrupted and the patient should be treated supportively with appropriate monitoring as necessary.

Since both drugs are highly bound to plasma proteins, haemodialysis is likely to be ineffective in the treatment of overdose.

9. PARTICIPANT TIMELINES AND ASSESSMENTS

9.1 Identification and Screening

Potential participants will be identified from routine clinics, and their eligibility potential for the study assessed by the multi-disciplinary team responsible for their care. Only following review of the patient's hospital notes for eligibility will an appropriately qualified investigator or study nurse inform patients of the nature of the study and give relevant information, both verbally and in writing, about the objectives of the research, plus the benefits and risks.

Pseudonymised screening logs are to be completed for every patient considered as a potential participant for the trial, inclusive of those who are not registered as a participant. The screening log should ideally be updated in real time on a patient-by-patient basis. For monitoring purposes, all reasons for non-randomisation are to be recorded on the log.

A separate patient identification log which contains patient identifiers should be maintained at site. This document will link the screening log details to the patient. The patient identification log should be stored in a secure place, and separate to the screening log. It will be required for monitoring visits, but MUST never be sent outside of the site. Sites may use the DyNAMIc patient identification log template, or may create their own version.

The Informed Consent Form obtains permission from the patient for screening assessments to be conducted, including ctDNA testing, and must be signed before performing any protocol-related procedures that are not part of normal patient care. See section 9.2 for further details on informed consent.

To confirm eligibility, the screening visit should be performed **no more than 28 days** prior to randomisation. See Section 9.3 for list of trial assessments. If the patient's disease is rapidly progressing, or if the patient wants to start treatment immediately, screening can be performed during the first 2 weeks of treatment. In this scenario however, a baseline blood test for ctDNA must be obtained prior to commencing E+B, and the patient must be randomised within two weeks of commencing E+B.

9.2 Informed Consent

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Written informed consent is required for all patients participating in LCTC coordinated trials. The process should involve discussion between the potential participant and an individual knowledgeable about the research, the presentation of written material (e.g. information leaflet or consent document), and the opportunity for potential participants to ask questions and have these satisfactorily answered. In obtaining and documenting consent, the research team should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Informed consent should be regularly reaffirmed throughout the trial and

all discussions and consent should be documented appropriately. If a potential participant does not want to provide consent they do not have to give a reason.

A delegated member of the oncology team who is trained in obtaining informed consent will need to discuss the potential treatments and study pathway with the patient. The consent discussion will therefore occur during a routine clinic visit; the entire discussion should last for about 30-60 minutes. Written informed consent shall be obtained only when the patient has had sufficient time to consider the information.

Consent should not be discussed with, or requested from the patient until their potential participation has been discussed by the MDT responsible for their care, and their hospital notes checked for potential eligibility.

Essential trial information should be recorded in the patient's notes along with the date the informed consent was obtained. Informed consent must be obtained on currently approved version the DyNAMIc Informed Consent Form in use at the recruiting site, and signed on the same day by both the patient and the delegated member of the oncology team.

Informed Consent must be obtained before the performance of any protocol-related procedures that are not part of normal patient care, inclusive of screening assessments. An exception to commence treatment prior to the ctDNA results being known is available. See section 9.2. Any assessments that have already been conducted as part of standard care may be used instead of repeating the screening tests, but must fall within the screening period (up to 28 days before registration).

Prospective Informed Consent Process:

Written informed consent will be sought from patients who will be approached by the study team and invited to consider participation.

If there is a clinical indication, or if the patient wants to start treatment immediately and does not want to wait for the result of the screening ctDNA prior to randomisation, the patient should sign the section in the PISC entitled "Consent if commencing treatment immediately" and complete the confirmation of consent section once eligibility has been confirmed prior to randomisation.

A written information sheet that forms part of the ethically approved Participant Information Sheet and Consent (PISC) form will be provided. This includes a detailed explanation of the study and makes clear that the rights and welfare of the participants will be protected; it will be emphasised that consent may be declined or withdrawn at any time in the future without the quality of care being adversely affected. The research staff will facilitate verbal discussions about the research and the consent process, as well as providing answers to any questions that arise.

After verbal and written information has been provided, the individual seeking consent will ensure that the patient has fully understood all the information and will ask if they are happy to consent to participation in the trial.

Where this is the case, written informed consent will be obtained by means of a dated signature on the consent form. This should be countersigned and dated by the person who obtained informed consent i.e. the PI or other appropriately qualified member of the research team who has been delegated this responsibility.

The original signed document will be retained in the trial site's Investigator Site File (ISF) and copies will be made:

- One copy provided to the patients for their information,
- One copy transferred to the LCTC via a secure and encrypted method. The signed ICF (part of the PISC) must not be sent with any clinical data or completed pages from the CRF.
- One copy filed in the participant's medical records paper/electronic.

N.B. Details of the consent process (date, persons involved, version and type of information sheet and consent form used) must also be recorded directly into the participant's medical records.

Loss of capacity:

If the patient that has consented then becomes unable to give reaffirmed informed consent (as determined by the treating team), they will be immediately withdrawn from the trial, however previously obtained consent for the collection and use of data remains valid.

Attempts to elicit information regarding safety events (AE, SAE etc.) that may have occurred to the participant since their incapacitation should be made to the participant's family, chaperone etc.

Language Considerations:

If the patient does not have proficient English to provide informed consent, then a translator may be used to verbally translate the PISC according to local practice.

9.3 Screening (Eligibility) Assessment and Confirmation

Eligibility can only be confirmed by an appropriately qualified medical professional who is named on the delegation log and must not occur until fully informed consent is documented. Eligibility criteria are described in detail in Section 7.

Eligibility confirmation must be documented in the participant's medical notes. As a minimum, details must include who confirmed full eligibility, when this was confirmed, and when the participant was formally entered into the trial (e.g. date of randomisation).

The screening visit should be performed **no more than 28 days prior to randomisation** to confirm eligibility.

The following procedures will be performed at the patient's screening visit:

- Eligibility assessment

- Obtain written informed consent prior to any trial specific procedures being conducted.
- Medical history and physical examination, including height and weight, ECOG performance status and vital signs
- A complete list of all prior anti-cancer therapies will be recorded in the CRF.
- Retrieve primary tumour block and other tissue from cancer related surgeries
- Blood sampling for the following tests*
    - ctDNA (streck tube - inc. extra for research purposes)
    - Full blood count
    - Renal and liver function tests
    - Urea and electrolytes
    - LDH
- Is the patient is taking prohibited concomitant medication? If so, these should be stopped and/or alternatives found.
- Electrocardiograph (ECG)
- Echocardiogram (ECHO) - standard safety monitoring of patients receiving E+B, not a research requirement – please refer to SmPC. ECHO must however be done as part of screening and left ventricular function confirmed to be ≥LLN prior to randomisation, and must occur by week 2 of the first cycle of treatment (but not necessarily prior to commencing treatment)
- If participant has limb disease, a PET-CT (with contrast if no known allergy to it) is to be performed as clinically indicated in place of the CT scan.
- CT (with or without contrast if known allergy to it) of thorax, abdomen and pelvis, +/- neck if clinically indicated.
  Alternatively, as per local practice if known allergy to contrast, CT without contrast thorax (+/- neck), plus MRI without contrast of abdomen and pelvis.
- MRI of brain, CT is an acceptable alternative if required according to local practice (both with contrast if no known allergy to it)
  (Scans to be reported according to RECIST v1.1. See appendix D. It is imperative that the same modality of imaging is performed throughout the patient's time on the study in order for accurate RECIST reporting)
- Collect tissue from any surgically indicated surgical resection
- Pregnancy test for WOCBP
- Clinical disease assessment – must be measured. If also photographed, a ruler must be shown alongside to assess the scale of the measurements. (Images are retained by site as source documents)

***In addition:**

- BRAF status is to be confirmed to the trial team with exact point mutation
- *BRAF* ctDNA TAB level of ≥15 copies/ml of plasma **must be confirmed prior to randomisation from a blood test taken prior to commencing E+B**

IMPORTANT: If the patient is too unwell or wants to start targeted treatment without waiting for the screening result, then the screening ctDNA blood can be sent to CBC labs and the patient can start on targeted therapy prior to the screening tests, including the ctDNA bloods, being reported. Screening tests and the ctDNA result must be performed and reported prior to randomisation. The patient should however be counselled that they may still not be eligible to participate in the study, and will not be enrolled if they do not meet the eligibility criteria.

The day of or day before (-1 day) the start of targeted therapy is the baseline visit. It is essential that the ctDNA blood is taken on the day of this visit prior to treatment and that all the other baseline assessments should be performed within +/-7 days (see section 9.5).

If the patient does not start on targeted therapy on the day the screening ctDNA blood is sent, then a baseline ctDNA blood should be sent on the day of or day before (-1 day) the patient starts treatment (baseline visit). The week 2 ctDNA test will be compared to the ctDNA taken closest to when the patient commences targeted treatment i.e. the baseline.

Blood for ctDNA MUST be taken prior to commencing targeted therapy with E+B.

9.4 Registration

Patients who have given informed consent and have been found to comply with the required trial inclusion and exclusion criteria will be enrolled and registered onto the study, using a secure, 24 hour accessible, web-based system, by the research team at the recruiting site.

Registration should occur once:

a) Eligibility criteria have been fulfilled and confirmed (with the exception of the results from the ctDNA blood test)

b) Fully informed written consent has been obtained and appropriately documented

c) Baseline assessments have been completed.

d) Blood sample for ctDNA analysis has been taken

The patient will be given a unique study number by the system, which will also automatically generate a confirmation email which will be communicated to the LCTC trial team and all relevant members of the site staff and pharmacy, notifying them of the patient trial number.

This study number should then be filled in on each subsequent page of the patients CRF.

It is the responsibility of the delegated pharmacy staff to ensure there is sufficient supply of study drugs.

A personal login username and password, provided by the LCTC will be required to access the system. Designated research staff will be issued with their personal login and password upon completion of training

in the use of the system. This training will be coordinated by the LCTC and a 'Randomisation Instructions' document provided to site. These instructions will contain the web-link to the system.

System Failure:

Back-up systems/processes are in place to allow for continuity of randomisation in the event of internet failure at participating sites or main server failure at University of Liverpool.

In the very unlikely event of network failure at University of Liverpool, participating sites should contact the coordinating team at the LCTC to discuss options for the processing of a randomisation.

LCTC contact details are available from the 'LCTC Contact Details' document. This document is to be printed and filed in the Investigator Site File.

Back-up randomisation services are available Monday to Friday between 9:00 to 17:00 (excluding public or bank holidays, or University of Liverpool closed days, e.g. working days in between Christmas and New Year).

9.5 Baseline 1 Assessments

Baseline 1 refers to the assessments conducted prior to the initial commencement of standard of care treatment and is applicable to both arms. In order to accurately complete the Baseline CRF and collect the necessary information for the trial analyses, assessments should be completed as detailed below. *However, if the screening and baseline visits are done together (for participants who commence encorafenib/binimetinib immediately) then assessments for both visits will be performed at the same time. The baseline visit ctDNA blood* ***MUST*** *be taken on the day of, or day before (-1), commencing E+B. Other assessments need not be repeated as long as they were performed at a screening visit within 7 days of starting therapy.* ***Note – if Screening and Baseline visit is the same day, 8 x ctDNA tubes are to be taken.***

The following procedures will be performed at the participant's baseline visit:

- Confirmation that the patients still satisfies the eligibility criteria
- Blood tests
    - ctDNA (streck tube - inc. extra for research purposes)
    - Full blood count
    - Renal and liver function tests
    - Urea and electrolytes
    - LDH
    - CRP
- Is the patient is taking prohibited concomitant medication? If so, these should be stopped and/or alternatives found.
- Physical examination including ECOG performance status and vital signs.

- Pregnancy test for WOCBP
- Additional blood for research (EDTA tube)
- Clinical disease assessment – must be measured. If also photographed, a ruler must be shown alongside to assess the scale of the measurements. (Images are retained by site as source documents)
- Dispense initial 28 day supply of study medication
- Issue patient drug diary
- Optional research biopsy (see section 9.12). CT without contrast or ultrasound, as clinically indicated.
- Quality of life questionnaires (EORTC QLQ-C30 and PRO-CTCAE)

Routinely collected information e.g. medical history / vital signs / relevant blood test results etc. can be transcribed from the patient's medical notes into the CRF once appropriate consent has been obtained.

The patient can proceed to randomisation once the all baseline assessments have been completed and full eligibility is confirmed (see Section 7 for details).

9.6 Randomisation

Patients who start E+B immediately must be randomised within 2 weeks following the commencement of treatment, i.e. C1,D1. ONLY those patients who have been registered in accordance with section 9.4 are eligible for randomisation.

Eligibility will be finalised upon provision of confirmation from the CBC of the ctDNA result.. Should the result meet the eligibility criterion, the patient will be randomised. Patients will be randomised to receive either Arm A (Continuous Standard of Care therapy), or Arm B (Adaptive therapy) in a ratio of 1:3 (Arm A: Arm B).

Should the ctDNA analysis not be possible for any reason, the patient will be deemed ineligible for participation and will revert back to the local care pathway.

Once the randomisation is complete, an automated email confirmation will be sent to the Principal Investigator (PI) and other relevant research team members at the research site. Copies will also be sent to the trial email account and to the email address for management of blood kit supply.

Following allocation, participants should be notified of their allocation as soon as possible and then should have treatment adopted as described in Section 9.7

9.7 Intervention

Once the research team are made aware of the treatment arm allocated, the participants will have the treatment plan implemented. **All patients** will have a run-in of one complete standard of care cycle (i.e. 28

days) of E+B, then at that timepoint Arm A will continue on standard of care therapy and Arm B will withhold drug as described in Sections 9.8.4.

9.8 Schedule for Assessments and Follow-up – Arm A

Treatment assessments:

The procedures listed below are to be performed at the stipulated timepoints, and only for the treatment arm to which they apply.

Note that some assessments are independent of the treatment cycle schedule and are required at calendar timepoints (i.e. weeks or months) from the administration of treatment at cycle 1, day 1.

If two timepoints occur concurrently, the procedure needs to be completed only once, e.g. ctDNA blood.

Treatment Cycle 1, Day 15

- Blood tests
    - ctDNA (streck tube - inc. extra for research purposes)
    - Full blood count
    - Renal and liver function tests
    - Urea and electrolytes
    - LDH
- Is the patient is taking prohibited concomitant medication? If so, these should be stopped and/or alternatives found.
- Record and report any adverse events and/or toxicity assessments that have occurred since commencing initial treatment.
- Physical examination, including ECOG performance status and vital signs
- Additional blood for research (EDTA tube)
- Clinical disease assessment – must be measured. If also photographed, a ruler must be shown alongside to assess the scale of the measurements. (Images are retained by site as source documents)
- Pregnancy test for WOCBP (only if clinically indicated)

Treatment Cycle 2 (onwards), Day 1

- Blood tests
    - ctDNA (streck tube - inc. extra for research purposes)
    - Full blood count

- Renal and liver function tests
- Urea and electrolytes
- LDH

- Is the patient is taking prohibited concomitant medication? If so, these should be stopped and/or alternatives found.
- Record and report any adverse events and/or toxicity assessments that have occurred since commencing initial treatment.
- Physical examination, including weight, ECOG performance status and vital signs
- Electrocardiograph (ECG)
- Clinical disease assessment – must be measured. If also photographed, a ruler must be shown alongside to assess the scale of the measurements. (Images are retained by site as source documents)
- Pregnancy test for WOCBP (only if clinically indicated)
- Dispense supply of study medication
- Issue patient drug diary
- Compliance assessment – reconcile quantity of unused tablets.

Treatment Cycle 2 (onwards), Day 15

- Blood tests
  - ctDNA (streck tube - inc. extra for research purposes)
- Optional research biopsy (cycle 2 only) (see section 9.12). CT without contrast or ultrasound, as clinically indicated.
- Pregnancy test for WOCBP (only if clinically indicated)

Every 8 weeks from Cycle 1, Day 1

- Pregnancy test for WOCBP (only if clinically indicated)
- If participant has limb disease, a PET-CT (with contrast if no known allergy to it) can be performed as clinically indicated in place of the CT scan.
- CT (with or without contrast if known allergy to it) of thorax, abdomen and pelvis, +/- neck if clinically indicated.

  Alternatively, as per local practice if known allergy to contrast, CT without contrast thorax (+/- neck), plus MRI without contrast of abdomen and pelvis.

  (Scans to be reported according to RECIST v1.1. See appendix D. The same imaging modality, e.g. CT or PET-CT must be used throughout the study to enable RECIST comparison. Comparisons must not be made between PET and CT scans.)

Every 12 weeks from Cycle 1, Day 1

- Pregnancy test for WOCBP (only if clinically indicated)
- Quality of Life Assessments

Every 3 months from Cycle 1, Day 28 (e.g. months 4, 7, 10 etc.)

- Pregnancy test for WOCBP (only if clinically indicated)
- Echocardiogram (ECHO) - standard safety monitoring of patients receiving E+B, not a research requirement – please refer to SmPC.

Every 6 months from Cycle 1, Day 1

- Pregnancy test for WOCBP (only if clinically indicated)
- MRI of brain, CT is an acceptable alternative if required according to local practice (both with contrast if no known allergy to it)
  (Scans to be reported according to RECIST v1.1. See appendix D)

At Disease Relapse

- Blood tests
  - ctDNA (streck tube - inc. extra for research purposes)
  - Full blood count
  - Renal and liver function tests
  - Urea and electrolytes
  - LDH
- Pregnancy test for WOCBP following five elimination half-lives of IMP with longest half-life, i.e. between 1-6 weeks following the end of *systemic* treatment (only required once at either relapse or end of treatment).
- Is the patient is taking prohibited concomitant medication? If so, these should be stopped and/or alternatives found.
- Physical examination, including weight, ECOG performance status and vital signs
- Collect tissue from any surgically indicated surgical resection
- Additional blood for research (EDTA tube)
- Clinical disease assessment – must be measured. If also photographed, a ruler must be shown alongside to assess the scale of the measurements. (Images are retained by site as source documents)
- Optional research biopsy (see section 9.12). CT without contrast or ultrasound, as clinically indicated.
- Quality of Life Assessments

Every 3 months following Disease Relapse

- Is the patient is taking prohibited concomitant medication? If so, these should be stopped and/or alternatives found.
- Record and report any adverse events and/or toxicity assessments
- Measure ECOG performance status

- Collect tissue from any surgically indicated surgical resection
- Record and report data on subsequent treatment(s), date(s) of disease progression of each, and survival status

End of Study and/or Withdrawal of Patient (excluding death)

- Is the patient is taking prohibited concomitant medication? If so, these should be stopped and/or alternatives found.
- Pregnancy test for WOCBP following five elimination half-lives of IMP with longest half-life, i.e. between 1-6 weeks following the end of *systemic* treatment (only required once at either relapse or end of treatment).
- Record and report any adverse events and/or toxicity assessments
- Physical examination, including ECOG performance status and vital signs
- Collect tissue from any surgically indicated surgical resection
- Clinical disease assessment – must be measured. If also photographed, a ruler must be shown alongside to assess the scale of the measurements. (Images are retained by site as source documents)
- Compliance assessment – reconcile quantity of unused tablets with treatment regimen.
- Record and report data on subsequent treatment(s), date(s) of disease progression of each, and survival status

Schedule of Assessments:

All assessments and follow-up are to be conducted in line with the Schedule of Assessment tables, below. The legend for the numerical caveats indicted in superscript is located in section 9.10.

ARM A	Pre-Treatment		Continuous Treatment			Fixed Timelines				Post-Treatment		
Study Procedures	Screening (up to 28 days prior to randomisation)	Baseline 1[9,10]	Cycle 1 D15	Cycle 2 onwards		Every 8 weeks from start of treatment	Every 12 weeks from start of treatment	Every 3 months following 1 month of treatment, e.g. months 4,7,10 etc.	Every 6 months from start of treatment	Disease relapse[17,18]	Follow-up after relapse Every 3 months	End of Study or Withdrawal
				D1	D15							
Window		-2/ +0d		+/- 2d		+/- 1w	+/- 2w	+/- 2w	+/- 1w		+/- 1w	+/- 1w
Eligibility check	x	x										
Written informed consent prior to any study procedure	x											
Medical history[1]	x											
Review of prior anti-cancer therapies	x											
Primary tumour block and any other tissue obtained through prior cancer-related surgery	x											
Haematology and Biochemistry[2,3]	x	x	x	x						x		
Blood for ctDNA (streck tube) including additional blood for research	x	x	x	x	x					x		

ARM A	Pre-Treatment		Continuous Treatment			Fixed Timelines				Post-Treatment		
Study Procedures	Screening (up to 28 days prior to randomisation)	Baseline 1[9,10]	Cycle 1 D15	Cycle 2 onwards D1	Cycle 2 onwards D15	Every 8 weeks from start of treatment	Every 12 weeks from start of treatment	Every 3 months following 1 month of treatment, e.g. months 4,7,10 etc.	Every 6 months from start of treatment	Disease relapse[17,18]	Follow-up after relapse Every 3 months	End of Study or Withdrawal
Window		-2/ +0d		+/- 2d		+/- 1w	+/- 2w	+/- 2w	+/- 1w		+/- 1w	+/- 1w
Concomitant/prohibited medication[4]	x	x	x	x						x	x	x
AE and toxicity assessment			x[13]	x							x[19,20]	x
ECOG	x	x	x	x						x	x	x
Weight	x			x						x		
Height	x											
ECG	x			x								
Echocardiogram	x							x				
CT scan (thorax, abdomen pelvis (+/- neck if clinically indicated) or MRI. PET-CT as clinically indicated	x					x						
CT or MRI brain	x								x			
Tissue Collection from surgical resection (only if clinically indicated see laboratory manual)[5]	x									x	x	x

ARM A	Pre-Treatment		Continuous Treatment			Fixed Timelines				Post-Treatment		
Study Procedures	Screening (up to 28 days prior to randomisation)	Baseline 1[9,10]	Cycle 1 D15	Cycle 2 onwards D1	Cycle 2 onwards D15	Every 8 weeks from start of treatment	Every 12 weeks from start of treatment	Every 3 months following 1 month of treatment, e.g. months 4,7,10 etc.	Every 6 months from start of treatment	Disease relapse[17,18]	Follow-up after relapse Every 3 months	End of Study or Withdrawal
Window		-2/ +0d		+/- 2d		+/- 1w	+/- 2w	+/- 2w	+/- 1w		+/- 1w	+/- 1w
Pregnancy test	x	x[11]	x[15]							x[16]		x[16]
Research blood sample (EDTA tube)		x	x							x		
Physical exam[6], vital signs and clinical disease assessment	x	x	x	x						x		x
Encorafenib plus binimetinib dispensed		x		x								
Research Biopsy[8]		x[12]			x[22]					x		
Quality of Life Assessments (EORTC QLQ-C30 and PRO-CTCAE)		x					x			x		
Issue patient drug diary		x		x								
Compliance assessment				x								x
Date of disease progression on each subsequent therapy											x	x
Subsequent treatment data											x	x
Survival status											x	x

9.9 Schedule for Assessments and Follow-up – Arm B

Treatment assessments

The procedures listed below are to be performed at the stipulated timepoints, and only for the treatment arm to which they apply.

Note that some assessments are independent of the treatment cycle schedule and are required at calendar timepoints (i.e. weeks or months) from the administration of treatment at cycle 1, day 1.

If two timepoints occur concurrently, the procedure needs to be completed only once, e.g. ctDNA blood.

Treatment Cycle 1, Day 15

- Blood tests
    - ctDNA (streck tube - inc. extra for research purposes)
    - Full blood count
    - Renal and liver function tests
    - Urea and electrolytes
    - LDH
- Is the patient is taking prohibited concomitant medication? If so, these should be stopped and/or alternatives found.
- Record and report any adverse events and/or toxicity assessments that have occurred since commencing initial treatment.
- Physical examination, including ECOG performance status and vital signs
- Pregnancy test for WOCBP (only if clinically indicated)
- Additional blood for research (EDTA tube)
- Clinical disease assessment – must be measured. If also photographed, a ruler must be shown alongside to assess the scale of the measurements. (Images are retained by site as source documents)

Treatment Cycle 1, Day 28

- Blood tests
    - ctDNA (streck tube - inc. extra for research purposes)
- Pregnancy test for WOCBP (only if clinically indicated)
- Dispense reserve pack supply of study medication and counsel participant on its use.
- Compliance assessment – reconcile quantity of unused tablets.
- Issue patient drug diary

During first period 'off-treatment'

2 weeks from day 1 'off-treatment'

- Optional research biopsy (see section 9.12). CT without contrast or ultrasound, as clinically indicated.
- Pregnancy test for WOCBP (only if clinically indicated)

Every 2 weeks from day 1 'off-treatment'

- Blood tests
    - ctDNA (streck tube - inc. extra for research purposes)
- Pregnancy test for WOCBP (only if clinically indicated)

Every 4 weeks from day 1 'off-treatment'

- Blood tests
    - ctDNA (streck tube - inc. extra for research purposes)
    - Full blood count
    - Renal and liver function tests
    - Urea and electrolytes
    - LDH
- Is the patient is taking prohibited concomitant medication? If so, these should be stopped and/or alternatives found.
- Record and report any adverse events and/or toxicity assessments that have occurred since commencing initial treatment.
- Physical examination, including weight, ECOG performance status and vital signs
- Pregnancy test for WOCBP (only if clinically indicated)
- Electrocardiograph (ECG)
- Clinical disease assessment – must be measured. If also photographed, a ruler must be shown alongside to assess the scale of the measurements. (Images are retained by site as source documents)
- Issue patient drug diary

During periods 'on-treatment'

Baseline 2

- Blood tests
    - ctDNA (streck tube - inc. extra for research purposes)
- Pregnancy test for WOCBP (only if clinically indicated)

Every 14 days (from day 1 of re-commencement)

- Blood tests
    - ctDNA (streck tube - inc. extra for research purposes)
- Pregnancy test for WOCBP (only if clinically indicated)
- Dispense 14 day supply of study medication, plus a replacement reserve pack
- Counsel participant on use of reserve pack
- Compliance assessment – reconcile quantity of unused tablets.

Every 28 days (from day 1 of re-commencement)

- Blood tests
    - ctDNA (streck tube - inc. extra for research purposes)
    - Full blood count
    - Renal and liver function tests
    - Urea and electrolytes
    - LDH
- Is the patient is taking prohibited concomitant medication? If so, these should be stopped and/or alternatives found.
- Physical examination, including weight, ECOG performance status and vital signs
- Pregnancy test for WOCBP (only if clinically indicated)
- Electrocardiograph (ECG)
- Dispense 14 day supply of study medication, plus a replacement reserve pack
- Counsel participant on use of reserve pack
- Compliance assessment – reconcile quantity of unused tablets.
- Clinical disease assessment – must be measured. If also photographed, a ruler must be shown alongside to assess the scale of the measurements. (Images are retained by site as source documents)
- Issue patient drug diary

Every 8 weeks from Cycle 1, Day 1

- Pregnancy test for WOCBP (only if clinically indicated)
- CT (with or without contrast if known allergy to it) of thorax, abdomen and pelvis, +/- neck if clinically indicated.
  Alternatively, as per local practice if known allergy to contrast, CT without contrast thorax (+/- neck), plus MRI without contrast of abdomen and pelvis.
  (Scans to be reported according to RECIST v1.1. See appendix D)

Every 12 weeks from Cycle 1, Day 1

- Pregnancy test for WOCBP (only if clinically indicated)
- Quality of Life Assessments

Every 3 months from Cycle 1, Day 28 (e.g. months 4, 7, 10 etc.)

- Pregnancy test for WOCBP (only if clinically indicated)
- Echocardiogram (ECHO) - standard safety monitoring of patients receiving E+B, not a research requirement – please refer to SmPC.

Every 6 months from Cycle 1, Day 1

- Pregnancy test for WOCBP (only if clinically indicated)
- MRI of brain, CT is an acceptable alternative if required according to local practice (both with contrast if no known allergy to it)
  (Scans to be reported according to RECIST v1.1. See appendix D)

At Disease Relapse

- Blood tests
  - ctDNA (streck tube - inc. extra for research purposes)
  - Full blood count
  - Renal and liver function tests
  - Urea and electrolytes
  - LDH
- Pregnancy test for WOCBP following five elimination half-lives of IMP with longest half-life, i.e. between 1-6 weeks following the end of systemic treatment (only required once at either relapse or end of treatment).
- Is the patient is taking prohibited concomitant medication? If so, these should be stopped and/or alternatives found.
- Physical examination, including weight, ECOG performance status and vital signs
- Collect tissue from any surgically indicated surgical resection

- Additional blood for research (EDTA tube)
- Clinical disease assessment – must be measured. If also photographed, a ruler must be shown alongside to assess the scale of the measurements. (Images are retained by site as source documents)
- Optional research biopsy (see section 9.12). CT without contrast or ultrasound, as clinically indicated.
- Quality of Life Assessments

Every 3 months following Disease Relapse

- Is the patient is taking prohibited concomitant medication? If so, these should be stopped and/or alternatives found.
- Record and report any adverse events and/or toxicity assessments
- Measure ECOG performance status
- Collect tissue from any surgically indicated surgical resection
- Record and report data on subsequent treatment(s), date(s) of disease progression of each, and survival status

End of Study and/or Withdrawal of Patient (excluding death)

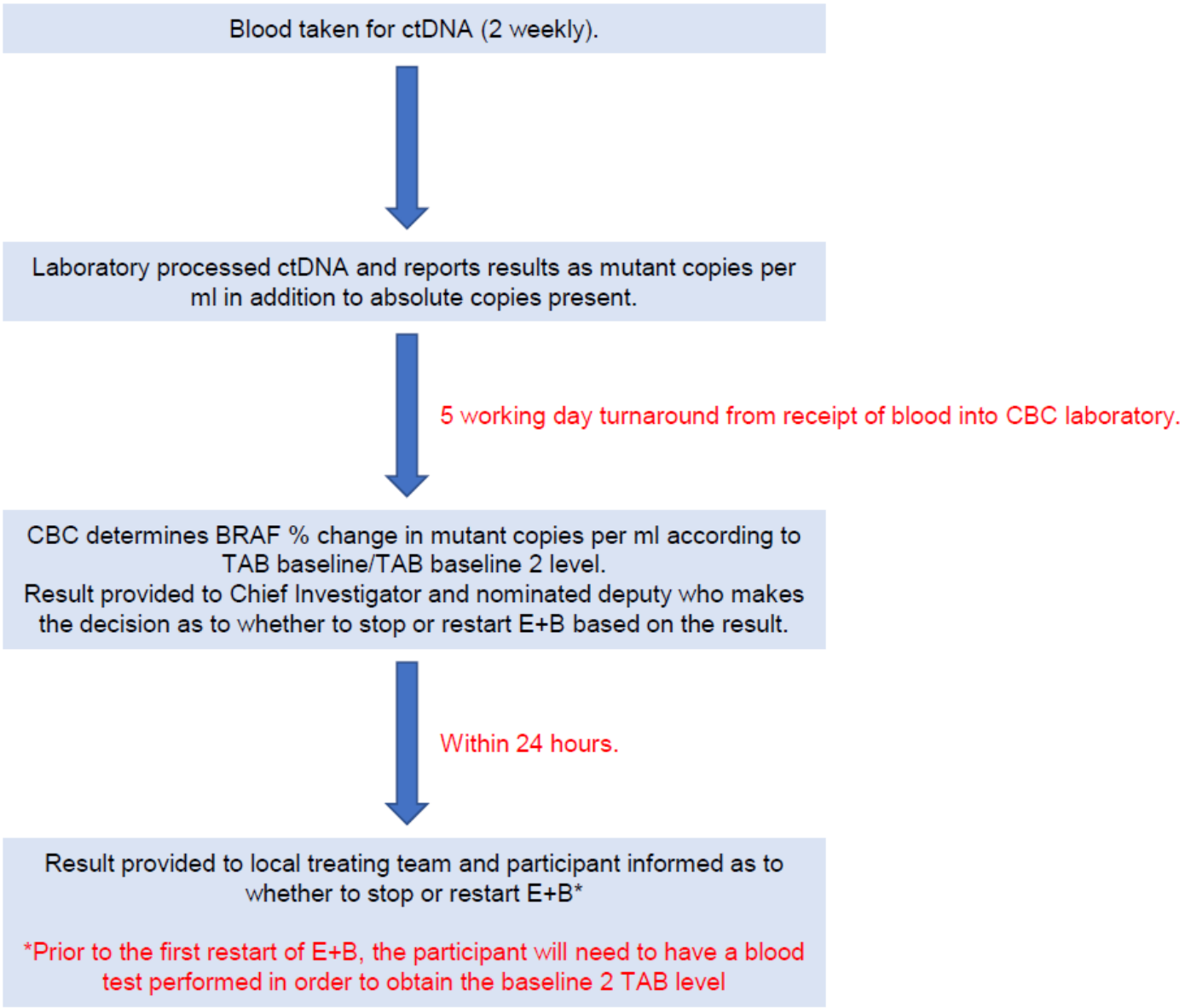
- Is the patient is taking prohibited concomitant medication? If so, these should be stopped and/or alternatives found.
- Pregnancy test for WOCBP following five elimination half-lives of IMP with longest half-life, i.e. between 1-6 weeks following the end of systemic treatment (only required once at either relapse or end of treatment).
- Record and report any adverse events and/or toxicity assessments
- Physical examination, including ECOG performance status and vital signs
- Collect tissue from any surgically indicated surgical resection
- Clinical disease assessment – must be measured. If also photographed, a ruler must be shown alongside to assess the scale of the measurements. (Images are retained by site as source documents)
- Compliance assessment – reconcile quantity of unused tablets with treatment regimen.
- Record and report data on subsequent treatment(s), date(s) of disease progression of each, and survival status

Arm B ctDNA real-time clinical decision making:

In order to determine when E+B should be “on” or “off”, blood for ctDNA will be taken at 2 weekly intervals and a clinical decision made based on the result. Please refer to laboratory manual for details regarding tubes. Details regarding the decision as to the thresholds of tumour activity and burden (TAB level) are found in section 5.1 and will be continuously reviewed by the trial team during the study. The decision as to whether

the patient should start or stop drug will be taken centrally and the site will be informed immediately. They will then inform the patient. Figure 10 shows the process of the blood being taken and actioning the result.

Figure 10 Flowchart of process of ctDNA being processed and patient being informed as to dosing of E+B



Schedule of Assessments:

All assessments and follow-up are to be conducted in line with the Schedule of Assessment tables, below. The legend for the numerical caveats indicted in superscript is located in section 9.10.

ARM B	Pre-Treatment				Off-Treatment		On-Treatment			Fixed Timelines				Post-treatment		
Study Procedures	Screening (up to 28 days prior to randomisation)	Baseline 1[9,10]	Cycle 1 D15 (SOC)	Cycle 1 D28 (SOC)	1st period of drug withdrawal: 2 weekly	1st period of drug withdrawal: 4 weekly	Baseline 2 (taken within 48 hours prior to first restart of E+ B) E+B)	Adaptive cycles onwards: 2 weekly	Adaptive cycles onwards: 4 weekly	Every 8 weeks from start of treatment	Every 12 weeks from start of treatment	Every 3 months following 1 month of treatment, e.g. months 4,7,10 etc.	Every 6 months from start of treatment	Disease relapse[17,18]	Follow-up after relapse Every 3 months	End of Study or Withdrawal
Window		-2/ +0d	+/- 2d	+/- 2d	+/- 2d			+/- 2d		+/- 1w	+/- 2w	+/- 2w	+/- 1w		+/- 1w	+/- 1w
Eligibility check	x	x														
Written informed consent prior to any study procedure	x															
Medical history[1]	x															
Review of prior anti-cancer therapies	x															
Primary tumour block and any other tissue obtained through prior cancer-related surgery	x															
Haematology and Biochemistry[2,3]	x	x	x			x			x					x		
Blood for ctDNA (streck tube) including additional blood for research	x	x	x	x	x[14]		x	x[14]						x		

ARM B	Pre-Treatment				Off-Treatment		On-Treatment			Fixed Timelines				Post-treatment		
Study Procedures	Screening (up to 28 days prior to randomisation)	Baseline 1[9,10]	Cycle 1 D15 (SOC)	Cycle 1 D28 (SOC)	1st period of drug withdrawal		Baseline 2 (taken within 48 hours prior to first restart of E+ B) E+B)	Adaptive cycles onwards		Every 8 weeks from start of treatment	Every 12 weeks from start of treatment	Every 3 months following 1 month of treatment, e.g. months 4,7,10 etc.	Every 6 months from start of treatment	Disease relapse[17,18]	Follow-up after relapse Every 3 months	End of Study or Withdrawal
					2 weekly	4 weekly		2 weekly	4 weekly							
Window		-2/ +0d	+/- 2d	+/- 2d	+/- 2d			+/- 2d		+/- 1w	+/- 2w	+/- 2w	+/- 1w		+/- 1w	+/- 1w
Concomitant/prohibited medication[4]	x	x	x			x			x					x	x	x
AE and toxicity assessment			x[13]			x									x[19,20]	x
ECOG	x	x	x			x			x					x	x	x
Weight	x					x			x					x		
Height	x															
ECG	x					x			x							
Echocardiogram	x											x				
CT scan (thorax, abdomen pelvis (+/- neck if clinically indicated) or MRI. PET-CT if clinically indicated	x									x						
CT or MRI brain	x												x			
Tissue Collection from surgical resection (only if clinically indicated see laboratory manual)[5]	x													x	x	x
Pregnancy test	x	x[11]	x[15]											x[16]		x[16]

ARM B	Pre-Treatment				Off-Treatment		On-Treatment			Fixed Timelines				Post-treatment		
Study Procedures	Screening (up to 28 days prior to randomisation)	Baseline 1[9,10]	Cycle 1 D15 (SOC)	Cycle 1 D28 (SOC)	1st period of drug withdrawal		Baseline 2 (taken within 48 hours prior to first restart of E+ B) E+B)	Adaptive cycles onwards		Every 8 weeks from start of treatment	Every 12 weeks from start of treatment	Every 3 months following 1 month of treatment, e.g. months 4,7,10 etc.	Every 6 months from start of treatment	Disease relapse[17,18]	Follow-up after relapse Every 3 months	End of Study or Withdrawal
					2 weekly	4 weekly		2 weekly	4 weekly							
Window		-2/ +0d	+/- 2d	+/- 2d	+/- 2d			+/- 2d		+/- 1w	+/- 2w	+/- 2w	+/- 1w		+/- 1w	+/- 1w
Research blood sample (EDTA tube)		x	x											x		
Physical exam[6], vital signs and clinical disease assessment	x	x	x			x			x					x		x
Encorafenib plus binimetinib, dispensed		x						x	x							
Reserve pack of E+B dispensed				x				x[7]	x[7]							
Counsel participant on use of reserve pack				x				x	x							
Research Biopsy[8]		x[12]			x[23]									x		
Quality of Life Assessments (EORTC QLQ-C30 and PRO-CTCAE)		x									x			x		
Issue patient drug diary		x		x		x			x							
Compliance assessment				x				x[21]	x							x
Date of disease progression on each subsequent therapy															x	x
Subsequent treatment data															x	x

ARM B	Pre-Treatment				Off-Treatment		On-Treatment			Fixed Timelines				Post-treatment		
Study Procedures	Screening (up to 28 days prior to randomisation)	Baseline 1[9,10]	Cycle 1 D15 (SOC)	Cycle 1 D28 (SOC)	1st period of drug withdrawal: 2 weekly	1st period of drug withdrawal: 4 weekly	Baseline 2 (taken within 48 hours prior to first restart of E+ B) E+B)	Adaptive cycles onwards: 2 weekly	Adaptive cycles onwards: 4 weekly	Every 8 weeks from start of treatment	Every 12 weeks from start of treatment	Every 3 months following 1 month of treatment, e.g. months 4,7,10 etc.	Every 6 months from start of treatment	Disease relapse[17,18]	Follow-up after relapse Every 3 months	End of Study or Withdrawal
Window		-2/ +0d	+/- 2d	+/- 2d	+/- 2d			+/- 2d		+/- 1w	+/- 2w	+/- 2w	+/- 1w		+/- 1w	+/- 1w
Survival status															x	x

9.10 Definitions of Assessments:

Schedule of Assessments – Legend:

1. See next page for details regarding medical history
2. Can be performed up to 48 hours prior to treatment apart from baseline (see section 9.5); see laboratory manual for details
3. See sections 9.8 or 9.9 for details regarding blood tests required
4. See section 8.9 for details on concomitant and prohibited medication
5. Tissue (FFPE and if possible a piece snap frozen) from any cancer-associated surgical procedure performed as part of routine care to be used for translational research. This can be at first and subsequent relapses following each line of treatment and prior to starting a new line of treatment (see laboratory manual for details).
6. Symptom guided, except at screening.
7. Only if a replacement is required due to usage or dose reduction
8. See laboratory manual for details
9. See section 9.5 for details regarding assessments at baseline 1
10. All procedures at this timepoint should be performed prior to commencing study treatment
11. Regardless of previous pregnancy tests, another must be done within 72 hours prior to commencing study treatment and have a negative result
12. Baseline biopsy can be performed within 6 weeks prior to start of study treatment
13. Only record events that occur after initial treatment has commenced
14. Required at every two and four week visit
15. Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivelant units of HCG) only required if clinically indicated.
16. Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) is required between 1-6 weeks after the last IMP dose. Testing is only required once, i.e. following relapse or end of study.
17. Within 28 days of confirmed relapse and prior to starting any new systemic therapy
18. See section 9.8 or 9.9 for details regarding assessments at relapse
19. SAE's should be proactively identified and reported for 90 days following the final administration of study treatment.
20. If site become aware outside of the 90 day post-treatment window of any SAE that has occurred (regardless of when it occurred) it is to be reported to the CTU. See section 10.6 for further details.

21. Only required for reserve pack compliance.
22. Required only once at cycle 2, day 15, +/- 5 days
23. Single occurrence only, two weeks into first 'off-treatment' period.

General assessments:

Medical History and Demographics:

Medical history should include the following:

- Sex and age
- History of presenting complaint including date first noted symptoms, date of original primary diagnosis and date of disease progression to stage III unresectable, or stage IV, disease
- Date of pathological diagnosis and copy of original pathology/genomics report (confirming melanoma and BRAF point mutation status)
- Date of previous -related surgeries
- Co-morbidities and past medical/surgical history
- Family history including history of cancers, and significant illnesses
- Social history including occupation, smoking history and ethnicity
- Review of all prior anti-cancer therapies

Checks should be made between the medical history and concomitant medication to ensure that all medical problems being treated have been included.

Concomitant Medications:

All concomitant medication including over-the-counter and herbal medications should be recorded and checked against prohibited medications (see section 8.9). If the patient is taking any prohibited medications these should be stopped and/or alternatives found, or the patient may be considered ineligible. Every effort should be made to collect complete data, at a minimum the drug name, dose, and the dates of administration are to be recorded. Patient notes should be used as source data. Information collected from the patient should be recorded in the patient notes. Missing information should be requested from any previous hospitals attended, or the patient's GP, and included within the hospital medical notes.

ECOG:

The Eastern Cooperative Oncology Group performance status should be assessed as summarised in Appendix E.

Physical Examination, Vital Signs and Clinical Disease Assessment:

1. Full physical examination will include symptom-guided assessments of the cranial nerve, eye and skin examinations and neck nodes (if prior melanoma on the head), the respiratory, cardiovascular, abdominal, musculoskeletal, neurological, dermatological and lymph nodes systems.
2. Vital signs (heart rate, blood pressure, respiratory rate, oxygenation level) will also be evaluated. Height will be measured at screening only. Body weight will be observed in each examination.
3. Further targeted physical examinations are to be utilised by the Investigator on the basis of clinical observations and symptomatology.
4. Situations in which physical examination results should be reported as AEs are described in Section 10.7.
5. Efficacy Assessments

Imaging and clinical assessments:

1. Contrast enhanced CT scan of thorax, abdomen and pelvis every 8 weeks (+/- 1 week).
2. PET-CT as clinically indicated (patients with limb disease).
3. Contrast enhanced CT is the preferred modality for assessment. If patient is allergic to contrast, a non contrast CT of the thorax and MRI of liver and pelvis is an alternative.
4. CT of the neck to be included as clinically indicated.
5. In addition a CT or MRI of brain with contrast where possible should be performed every 6 months (+/- 1 week).
6. Tumour efficacy (RECIST) assessment dates are not affected by IMP dose delays and remain as originally scheduled, as they are based on the date of start of treatment.
7. Cutaneous lesions can be included for measurable disease if photographed with a ruler depicting clearly the size of target lesion(s). The same method will be used to assess response of the cutaneous lesions identified at baseline throughout the trial, that is, two tumour assessments (one for each method) will be performed at each planned assessment time if the ruler method is used.

Safety Assessments:

Laboratory Assessments – Haematology and Biochemistry:

Table 1 . Haematology Laboratory Tests

Haemoglobin	Mean corpuscular volume
Lymphocytes (ALC)	Platelet count
Eosinophils	Total white cell count
Neutrophils (ANC)	

Table 2 . Clinical Chemistry (Serum or Plasma) Laboratory Tests	
Albumin	Gamma glutamyltransferase
Alkaline phosphatase	Glucose
Alanine aminotransferase	Lactate dehydrogenase (hospital normal range should be provided)
Aspartate aminotransferase	Magnesium
Corrected Calcium	Phosphate
C-reactive protein[a]	Potassium
Creatinine	Sodium
Creatinine clearance[b]	Total bilirubin[a]
Creatinine kinase (CK)	Urea or blood urea nitrogen, depending on local practice

a. At baseline and on progression only

b. eGFR will be derived using Cockcroft-Gault equation (see Appendix A)

Pregnancy Test:

Women of childbearing potential (WOCBP) must have a serum or urine pregnancy test at screening and subsequently within 72 hours prior to commencing cycle 1 day 1 of therapy (minimum sensitivity 25 IU/L or equivalent units of HCG).

Echocardiogram:

This is a standard safety monitoring of patients receiving E+B, not a research requirement – please refer to SmPC. Echo must however be done as part of screening and left ventricular function confirmed to be ≥LLN

prior to randomisation, and must occur by week 2 of the first cycle of treatment (but not necessarily prior to commencing treatment).

- Following this, echo should be performed every 3 months (+/- 2 weeks) from the end of the first treatment cycle, i.e. from approximately 4 months after commencing treatment.

If grade 3-4 LVEF decrease or an absolute decrease of LVEF from baseline of ≥ 10% is observed then E+B should be discontinued and LVEF should be evaluated every 2 weeks until recovery.

ECG:

A single resting 12-lead ECGs will be recorded at screening (and every 28 days +/- 2 days throughout the study). ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position. The ECG should be monitored for any evidence of prolonged QT interval.

Quality of Life Assessments:

The following assessments will be performed every 12 weeks (with additional questionnaires performed at C2 D15 for patients on arm B when they are off targeted therapy):

- EORTC QLQ-C30 – global health status score. This will be calculated as per scoring instructions in the EORTC QLQ-C30 manual. A descriptive comparison will be made between the two arms for the change from baseline in global health status score at each timepoint between the standard and the experimental arms. In addition, comparisons will be made between patients who are on therapy with those off therapy during an adaptive therapy cycle (C2 D15).
- PRO-CTCAE – a patient reported outcome (PRO) measurement system developed to evaluate symptomatic toxicity. The questions selected will be based on anticipated adverse events observed in the Phase III Columbus study and the encorafenib and binimetinib SmPCs. A descriptive comparison will be made between the two arms for the change from baseline in global health status score at each timepoint between the standard and the experimental arms. In addition, comparisons will be made between patients who are on therapy with those off therapy during an adaptive therapy cycle (C2 D15).

9.11 Disease progression definition and procedures

Definition of disease progression:

Arm A – Disease progression is defined in accordance with RECIST v1.1 (2009) disease progression observed on imaging

Arm B – Disease progression is defined in accordance with RECIST v1.1 (2009) disease progression observed on imaging **when the patient is receiving** targeted therapy. If RECIST v1.1 disease progression observed when the patient is not on treatment, they should re-commence targeted therapy with a blood for ctDNA taken just prior to re-starting. If the next scan when on therapy shows further disease progression then they should stop treatment and that will be the disease progression event. If the next scan shows response then they will continue on adaptive treatment. The next ctDNA blood test taken should be compared against this one to determine ctDNA response as to whether drugs can be stopped again. This will be determined by the trial team in discussion with the site PI as to the clinical picture.

Procedures following disease progression:

The following should be performed when disease progression is confirmed:

- Blood tests
    - ctDNA
    - Full blood count
    - Renal and liver function tests
    - Urea and electrolytes
    - LDH
    - CRP
- Research bloods
- Optional research biopsy – ideally from a progressing lesion. Modality as clinically indicated. Biopsies will only be acquired if the lesions are considered to be safely accessible by the interventional radiologist or surgeon. Please refer to the lab manual for prioritising and initial processing of tissue samples.

Follow-up after progression:

Following progression patients are followed up remotely every 3 months until study completion/withdrawal or death, in order to capture the following data:

- Any subsequent anti-cancer therapy taken after study treatment discontinuation should be documented.
- Date of disease progression on each subsequent anti-cancer therapy should be documented.
- Survival data including data of death should be captured.

9.12 Sampling

Please refer to the DyNAMIc Laboratory Manual for detailed information and instructions

The following specimens may be collected as part of consent to the trial.

Due to the coronavirus pandemic, please refer to the laboratory manual which provides guidance on sample collection with regards to COVID-19.

Sample/collection procedures include:

- FFPE of primary tumour specimen
- Blood in EDTA tube for translational studies
- Blood for ctDNA analysis
- Fresh biopsy of easily accessible lesions (up to a maximum of three cores per procedure), at baseline when drug is removed on Arm B (C2 D15 +/-5 days) or when drug is present on Arm A (C2 D15 +/-5 days) and if progression on therapy. Patients may consent to any or all of these biopsies.
- If a surgical resection on study occurs for clinical reasons then provided the patient has consented this tissue should also be made available for translational research with collection as below

Sample Collection:

An outline for the collection, processing, storage and shipping of samples to are specified below. Please refer to the lab manual for more detailed instructions.

If ctDNA samples are missed, the patient will need to be re-called to clinic for a repeat sample to be taken.

If the ctDNA result does not pass quality control testing at the CRUK Cancer Biomarker Laboratory (CBC), or if the sample becomes exhausted prior to the result being known, then the translational sample will be used to repeat the test.

For other missed the samples, the reason and which sample/timepoint should be noted on the CRF

Tissue:

- Archival FFPE tumour tissue of the primary will be requested for all patients.
- Fresh biopsies (up to a maximum of three cores per procedure) will be obtained according to patient consent, as set out in the sample schedule. Biopsies will only be acquired if the lesions are considered to be safely accessible by the interventional radiologist or surgeon. Ideally the same site of disease should be biopsied on each occasion. Please refer to the lab manual for prioritising and initial processing of tissue samples. If insufficient material is available patients will not be subjected to an additional biopsy.

- If the patient undergoes a clinically indicated surgical procedure to remove cancer or biopsy of a lesion following consent, then samples will be obtained for translational research purposes. These include FFPE samples and if possible fresh frozen tissue. Please see laboratory manual for further details.

Blood:

- *Blood collected in Cell-Free DNA BCT Streck tubes for ctDNA analysis*
- At scheduled time points detailed in Sections 9.8 and 9.9 (schedules of trial treatments and assessments) 40-80 ml of blood will be collected in Cell-Free DNA BCT Streck tubes (provided by trial coordinators).
- Bloods collected in streck tubes must be sent by royal mail safe box system next day delivery, provided by the trial coordinator, on the day of taking – see lab manual for address.
- Samples taken at The Christie may be sent with the Cancer Research UK (CRUK)-Manchester Institute (MI) porters for transfer to CBC lab.
- *Blood collected in EDTA tubes for translational studies*
- At scheduled timepoints, 10ml blood will be collected in EDTA tubes – see schedule of assessments and laboratory manual for further details.

Sample Storage and Handling:

Please refer to the DyNAMIc laboratory manual for details regarding processing, handling and storage of biospecimens.

All collected biospecimens will be stored in designated and secure facilities within the CBC prior to analysis using a destructive test, or with the research team using secure sponsor approved facilities pending future use. Frozen tissue and plasma/blood pellet samples will be stored in temperature monitored, -80ºC freezers. To preserve patient confidentiality, samples will use only the patient trial ID number for identification and all samples will catalogued using a tracking system.

Custodianship:

The Chief Investigator will serve as custodian of samples for the duration of this study. Samples for ctDNA analysis will be stored short-term at the CBC laboratory or will be used for translational work, with other samples transferred to the research team for storage using sponsor approved facilities, pending future use. Sample usage will be under the control and jurisdiction of the Chief Investigator and Principal Investigators.

Samples will be stored at site as per the Lab Manual for a period of up to 24 months before being transferred by courier to the relevant laboratory. Clinical samples will be kept for up to 20 years and any surplus to the study requirements may be used for future translational research authorised by the trial management committee.

Disposal of biospecimens will be considered under certain circumstances including but not limited to use of the entire specimen; withdrawal of patient consent for storage and analysis of samples (obtained archival samples will be returned to original pathology lab) or reduced specimen integrity. Determination of the integrity of biospecimens is at the discretion of study personnel. Disposed samples will be logged within the tracking system (together with reason for disposal) and physically discarded according to institutional policy.

Sharing of samples with other centres:

Samples may be shared with other centres for research directly in connection with the existing protocol or for future translational work. This may include transfer of samples to collaborators in other countries. Where required, additional approvals will be sought to share samples and a Material Transfer Agreement will be put in place before samples are shared. This will be managed with the assistance of our human tissue governance team and R&D office.

9.13 Intervention Discontinuation and Participant Discontinuation/Withdrawal

In consenting to the trial, participants agree to all trial activities including administration of trial intervention and treatment and follow-up assessments / visits and data collection. Every effort should be made to facilitate the completion of these for every recruited participant. If it is not possible to complete these activities (or it is deemed inappropriate) the reasons why should be documented. The following sub-sections describe the different levels of discontinuation/withdrawal.

Premature Discontinuation of Trial Intervention

Participants may discontinue treatment for reasons including, but not limited to:

- Participant-led i.e. request by the participant
- Unacceptable toxicity (see Section 10 for safety reporting)
- Intercurrent illness preventing further treatment.
- Pregnancy
- Death
- Clinician-led:
    - Any change in the participant’s condition that justifies the discontinuation of treatment in the clinician’s opinion.

- Reasons of non-adherence or non-compliance with treatment or other trial procedures
- Participant meets an exclusion criterion (either newly developed or not previously recognised)
- Participant unable to receive E+B for >6 weeks

Discontinuation from study intervention does not mean discontinuation of the study altogether, and the remaining study procedures, follow-up assessment / visits and data collection should be completed as indicated in the protocol (unless consent is specifically withdrawn, see section 9.2). Data to be collected at the time of discontinuation will include the following:

- Confirmation of disease progression or deaths
- CtDNA

Patients who have discontinued treatment as per protocol will then be transferred into routine clinical care and will be treated as per local practice and guidelines.

Safety follow up is covered in section 10.6.

Participant Withdrawal from Follow-up:

Participants are free to withdraw from follow-up at any time without providing a reason, though a reason should be recorded if one is given. Those who wish to withdraw from further follow-up will have the data collected up to the point of that withdrawal included in the analyses, inclusive of data derived from the analyses of tissue samples. The participant will not contribute further data to the study and the LCTC should be informed via email to the LCTC and via completion of a Withdrawal CRF to be returned to the LCTC within 7 days.

If participants express a wish to withdraw from follow-up, participants should be given appropriate care under medical supervision for all ongoing adverse events until the symptoms resolve or the patient's condition becomes stable. Any SAEs will be notifiable to the LCTC via processes detailed in Section 10.10 even if a participant has withdrawn from follow-up.

If the participant withdraws their consent for any remaining samples to be to be included in analyses, all remaining samples originating from that patient will be destroyed. No remaining samples that are stored centrally will be returned to the treating hospital.

Participant Transfer:

If a participant moves from the area, every effort should be made for the participant to be followed-up at another participating trial centre and for this trial centre to take over responsibility for the participant or for follow-up via GP.

A copy of the participant CRFs should be provided to the new site. The patient remains the responsibility of the original site until the new site PI has signed the Transfer CRF.

Loss to Follow-up:

A participant will be considered lost to follow-up if s/he fails to return for four consecutive scheduled visits and is not contactable by the site research team. Methods of contact are detailed below.

If a participant fails to attend a required study visit the following actions must be taken and the efforts recorded in the patient medical notes.:

- One scheduled visit missed – Site to telephone participant to establish reasons for non-attendance, advise the participant on the importance of maintaining the assigned visit schedule, and attempt to re-arrange visit within allowed timelines.
- Two consecutive scheduled visits missed – Same as one scheduled visit being missed.
- Three consecutive visits missed – Same as one scheduled visit being missed. If, however, the participant cannot be contacted by telephone, the REC approved reminder letter is to be sent to their last known address.
- Four consecutive visits missed – Participant is classed as a loss to follow-up. Withdraw from study treatment and submit relevant CRF to LCTC.

9.14 End of Trial

The end of the trial is defined to be the date on which data for all participants is frozen and data entry privileges are withdrawn from the trial system. The trial may be closed prematurely by the Trial Steering Committee (TSC), on the recommendation of the Independent Safety and Data Monitoring Committee (ISDMC).

Site and closure activities will be centrally coordinated and conducted in accordance with LCTC processes regardless of whether the trial closes as planned or prematurely. This includes activities such as:

- End of Trial notification to REC and MHRA
    - Trial-related materials reconciled and returned/disposed of as appropriate. See pharmacy manual for further details on the destruction of medication.
    - All site data entered onto the study system, discrepancies raised and satisfactory responses received
    - Quality Control checks of the Investigator Site Files, Pharmacy Files and Trial Master File as appropriate.

10. Management of COVID-19

Patients who are COVID-19 positive at the time-point of a scheduled procedure should be advised to not attend hospital for their appointment, and the appointment re-scheduled for 7 days later. In this instance, procedures with a visit tolerance of less than seven days, e.g. bloods for ctDNA +/-2 days, will not be recorded as a protocol deviation.

For participants on Arm B, any changes to their adaptive treatment will also be deferred accordingly.

11. SAFETY REPORTING

Safety reporting in clinical trials is a legal and ethical requirement and it is imperative that all applicable requirements detailed here are followed during the trial.

11.1 Terms and Definitions

Adverse Event (AE):

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse Reaction (AR):

Any untoward and unintended response to an investigational medicinal product related to any dose administered.

Unexpected Adverse Reaction (UAR):

An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in the investigator's brochure (IB) or the Summary of Product Characteristics (SmPC), which may be referenced where the IMP in question is a product with a marketing authorisation.

Serious Adverse Event (SAE):

Any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, pregnancy, or is a congenital anomaly or birth defect.

Serious Adverse Reaction (SAR):

An adverse reaction which meets the definition of serious (see Section 10.2) is a Serious Adverse Reaction. A Serious Adverse Reaction event that has been assessed as ‘expected’ (see Section 10.5) according to the Reference Safety Information (see below) will remain classified as a Serious Adverse Reaction only, however some Serious Adverse Reactions that are considered ‘unexpected’ will be further classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR) (see below).

Suspected Unexpected Serious Adverse Reaction (SUSAR):

An adverse reaction that is classed in nature as serious and “unexpected” (i.e. not listed within the Reference Safety Information (RSI) approved for the trial by the MHRA and current at the time of onset of the SUSAR).

Reference Safety Information (RSI):

The information used for assessing whether an adverse reaction is expected (see section 10.5). This is contained in the Summary of Product Characteristics (SmPC) or Investigators Brochure (IB) for the product and must be approved for use by the MHRA. The RSI used to assess the expectedness of a SAR must be the current approved version at the time of onset of the SAR. The RSI for this trial is defined in section 10.5.

11.2 Assessment of Seriousness

The assessment of seriousness of safety events should be performed by an appropriately delegated, medically qualified member of the site research team.

A safety event / reaction is assessed as serious if it:

- Results in death;
- Is life threatening (i.e. the investigator considers the event places the subject at immediate risk of death from the experience as it occurred (this does not include an adverse experience that, had it occurred in a more severe form, might have cause death);
- Requires hospitalisation or prolongation of existing hospitalisation (hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE);
- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions);
- Consists of a congenital anomaly or birth defect (in offspring of subjects, or their partners, taking the IMP regardless of time of diagnosis);
- Other important medical events (these may not result in death, be life-threatening, overdose, secondary malignancy or require hospitalisation, but may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition).

11.3 Severity of Adverse Events

All adverse events should be assessed for severity. The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions in the table below:

Table 3: Severity Grading

Severity	Description
Mild	Does not interfere with routine activities.
Moderate	Interferes with routine activities.
Severe	Impossible to perform routine activities.
Life-Threatening	Life threatening at the time of the event, i.e. not *potentially* life-threatening.
Death	Caused by the event.

N.B. A distinction is drawn between **serious** and **severe** AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in Section 10.2. Hence, a severe safety event need not necessarily be a "serious" safety event.

11.4 Assessment of "Causality" - Relationship to Trial Treatment/Intervention

The assignment of the causality should be made using the definitions in the table below:

Table 4: Definitions of Causality:

Relationship	Description	Categorisation
Unrelated	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given	No reasonable possibility
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).	No reasonable possibility
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the	Reasonable possibility

Relationship	Description	Categorisation
	participant's clinical condition, other concomitant treatments).	
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Reasonable possibility
Almost certainly	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Reasonable possibility

Events that are assessed as being possibly, probably or almost certainly related will be reported as having a reasonable possibility of being related, and events assessed as unrelated or unlikely will be reported as having no reasonable possibility of being related.

Assessment of causality should be made based on known safety profiles of the SmPC and known risk profiles of other drugs in the same class. If any doubt about the causality exists, the local investigator should inform the LCTC who will notify the Chief Investigator. In the case of discrepant views on causality between the treating investigator and others, the opinion of the treating investigator will never be downgraded and the MHRA and REC will be informed of both points of view.

11.5 Assessment of "Expectedness"

The Chief Investigator and nominated Medical Reviewers for the DyNAMIc trial are responsible for determining whether a safety event is expected or unexpected, however the Chief Investigator or Medical Reviewer will not assess safety events for which they are the reporting clinician. There is no requirement for a reporting investigator to make an assessment of expectedness.

An event will be considered unexpected if it is not listed within the current and approved Reference Safety Information (RSI) (see section 10.5) for the study at the time of onset of the event. The nature, severity, or frequency of the event should be considered – if this is not consistent with that described for the type of event in the RSI the event should be assessed as unexpected.

Reference Safety Information / Information used to Assess Expectedness

The Reference Safety Information (RSI) to be used for this trial for each IMP is as follows. Versions of each are as approved via original application or subsequent amendment:

Summary of Product Characteristics Mektovi 15 mg film-coated tablets Section 4.8

Summary of Product Characteristics Braftovi 50 mg hard capsules Section 4.8

This will be updated as required and implemented only after approval from the appropriate regulatory authorities.

11.6 Time Period for Active Monitoring of Safety Events

IMPORTANT: Any safety events occurring after the end of the "active monitoring" period described below, and which meet the definition of serious (see section 11.2), and are observed for this study (see section 11.6) must continue to be reported by sites to the LCTC in accordance with the timeframes and procedures described in section 11.10. The same processes established for SAEs within the active monitoring period should be followed for these events.

Active monitoring of safety events experienced by trial participants will commence immediately following consent being provided by the participant, and continue until the definitive final administration of E+B. Care should be taken in establishing if SAEs for participants on Arm B meet the latter criterion. E.g. if an Arm B participant experiences an SAE on day 95 of being off-treatment, it still needs reporting to LCTC as it is not yet known if E+B will re-commence.

Safety events occurring outside the active monitoring period should be reported as per section 11.10 if the clinical team at the reporting site have established a causal link with the trial IMPs.

During the course of the study, all AEs and SAEs should be proactively followed up for each subject. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion. All unresolved SAEs and AEs must be followed up until resolution or death. Follow-up must be conducted by the Investigator for as long as medically indicated, and recording in source documents. The Sponsor retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary

Pregnancies will be followed up until at least until the outcome is known (see Section 11.8 for more information on reporting pregnancy).

11.7 Notes on Safety Event Recording

The following events must be recorded for the purposes of the trial:

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

- Laboratory abnormalities that require clinical intervention or further investigation (unless they are associated with an already reported clinical event).
- Abnormalities in physiological testing or physical examination that require further investigation or clinical intervention
- Injury or accidents
- A new cancer diagnosis
- Overdose of medication with signs or symptoms
- Pregnancy

Do not record:

The events below do not need recording as the trial is considered low risk:

- Medical or surgical procedures - the condition which leads to the procedure is the adverse event
- Pre-existing disease or conditions present before treatment that do not worsen
- Situations where an elective medical occurrence has occurred e.g. cosmetic surgery
- Overdose of medication **without signs or symptoms***
- The disease being treated or associated symptoms/signs unless more severe than expected for the patient's condition

[1] Note that although overdose of medication without signs or symptoms may be excluded from AE reporting it may still require investigation to ensure other protocol and regulatory requirements are met e.g. for IMP management and administration, or to ensure participant safety. If applicable, refer to appropriate part of Treatment section 8.10 (Overdose).

*N.B. If overdose occurred **with** resulting signs and symptoms that meet the protocol criteria for AE/AR/SAE/SAR/SUSAR then they should be reported accordingly (see section 11.10 for more information).

11.8 Reporting of Pregnancy

Pregnancies of participants, and where consent is obtained to do so partners of male participants, are to be reported to LCTC. If a participant becomes pregnant during the course of the study, the IMPs should be discontinued immediately.

If pregnancy occurs during either the intervention or specified follow-up period of the trial this must be notified to the LCTC using the Pregnancy Report Form, and within 24 hours of the research team becoming aware. The pregnancy must be followed up by the site research team until the outcome of the pregnancy and reported to LCTC.

Pregnancies of female participants are reportable if conception is assessed to have occurred within one month of the last administration of E+B. Pregnancies of partners of male participants are reportable if conception is assessed to have occurred within three months of the last administration of E+B (i.e. sperm regeneration cycle).

Any pregnancy outcomes which result in a safety event assessed as “serious” (e.g. birth defect) must also be reported separately on the appropriate Safety Event CRFs in accordance with processes described in section 11.10. All pregnancies and outcomes reported to LCTC will be notified to the study Sponsor and monitored by trial oversight committees.

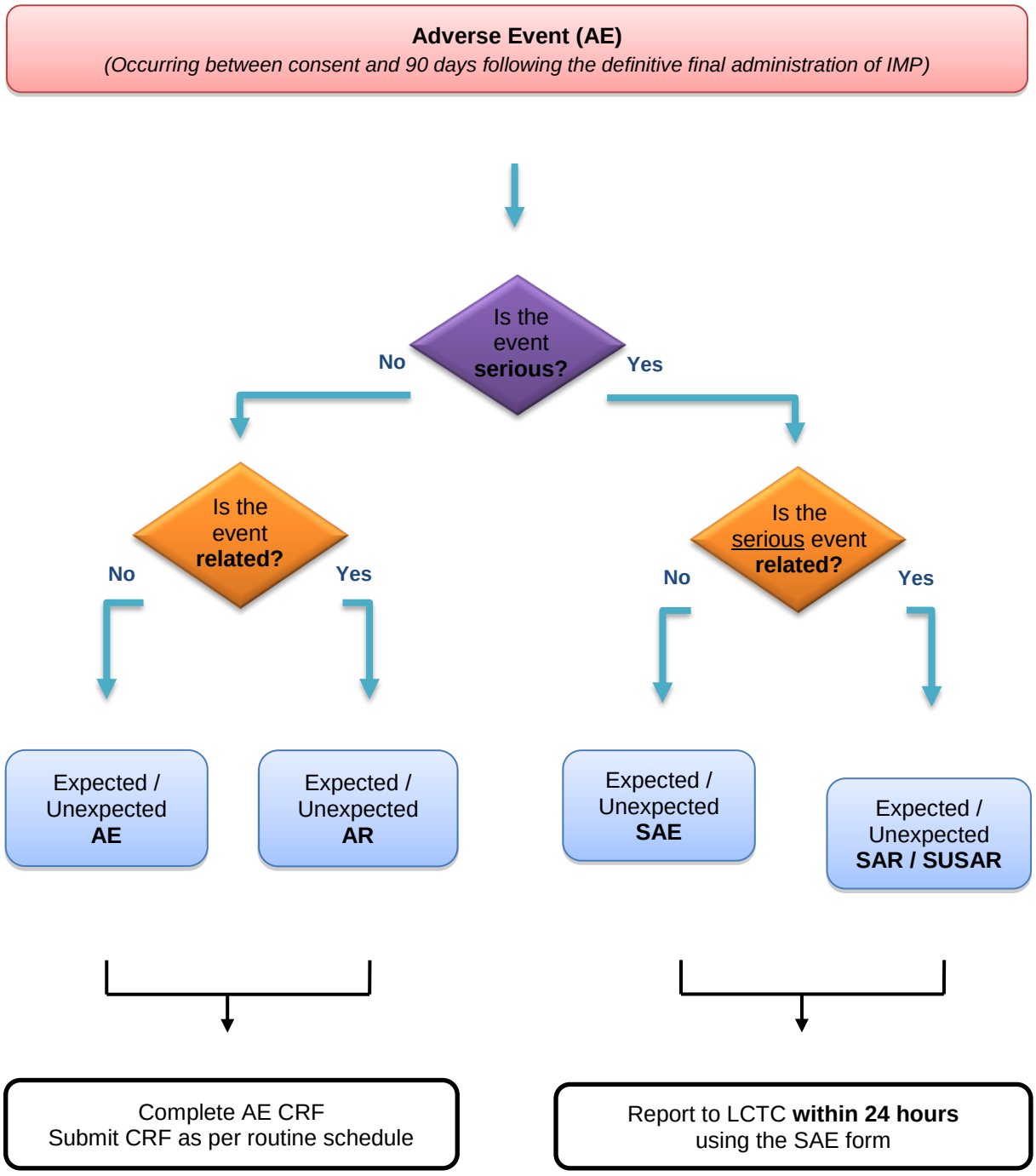
11.9 Notification of Deaths

If the research team become aware of the death of a participant (whether related to the trial or not) this should be notified to the LCTC using the appropriate CRF within 24 hours of becoming aware.

11.10 Reporting Procedures

All safety events which are recorded for the study should be reported following the procedures detailed below. The occurrence of a safety event may come to the attention of research staff during routine study visits, from the participant’s notes, directly from the participant or by other means. Note that reporting procedures vary dependent on the nature of the incident (i.e. “serious” events are to be reported to LCTC in an expedited manner). Any questions concerning adverse event reporting should be directed to the LCTC in the first instance. A flowchart is given below to aid in determining reporting procedures for different types of adverse events

Flowchart for Site Reporting Requirements of Adverse Events:



Reporting Safety Events to the LCTC:

All safety events (whether or not assessed as serious / related / expected) should be recorded on an Adverse Event Form; multiple events can be recorded on one form. When documenting any adverse events the correct medical terminology **must** be used.

Safety events which are assessed as "serious" must **also** be recorded in more detail on Serious Safety Event Forms; a **single form** is used for each individual event (i.e. a single diagnosis), though multiple symptoms can be recorded. Each SAE should have a corresponding record on the participant's AE form. Where additional information is received by site after initial submission to LCTC, this should be provided on a follow-up form within 5 days. Serious Safety Event Forms collect data regarding the nature of event, date of onset, severity, corrective therapies given, outcome and causality; all serious events reported to LCTC will be reviewed by the Chief Investigator or Medical Reviewer, and assessed for causality and expectedness.

Follow-up After Adverse Events:

All reportable adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.

When reporting "serious" safety events the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes:

- resolved
- resolved with sequelae (specifying with additional narrative)
- not resolved/ongoing
- ongoing at final follow-up
- fatal or unknown.

11.11 Investigator Reporting Responsibilities

The PI is responsible for ensuring that all safety events which the local research team becomes of, and which requiring recording on this study of are reported to LCTC. It is the responsibility of the PI and other medically qualified doctors as recorded on the Delegation Log to assess the seriousness and causality of events.

All safety events must be recorded on the paper AE form, which is to be transferred to LCTC within 7 days following each update to it.

Unless the SAE is specified in the protocol as not requiring immediate reporting (see Section 11.7), safety events which meet the definition of "serious" must be reported in more detail to the LCTC on a paper SAE form and reported **immediately and in no circumstances later than 24 hours from becoming aware**, where they will be appropriately processed.

All safety reporting forms will be provided to sites as part of the greenlight procedure, and updated versions provided when implemented.

The SAE form should be completed by an appropriately delegated member of the research team; the assessments of seriousness and causality must be performed by an appropriately medically qualified person. Minimum reporting information must be provided in initial reports for all studies.

The minimum dataset required for a preliminary report should include the following:

Minimum information required for reporting:

- Sponsor study number
- One identifiable coded subject
- One identifiable reporter
- One event meeting the serious criteria
- One suspect IMP (including active substance name- code)
- A causality assessment

N.B. In the absence of a delegated medically qualified person, the form should be completed and signed by an alternative member of the research site trial team and submitted to the LCTC. As soon as possible thereafter, the responsible investigator should check the SAE form, make amendments as appropriate, sign and re-send to the LCTC. The initial report shall be followed by detailed follow-up reports as appropriate.

Safety events should be reported to the site R&D team in accordance with local policy.

Reporting an initial or follow-up SAE:

The investigator should ensure the actions below are completed for all reportable SAEs:

1. Research sites should telephone the appropriate trial co-ordinator / data manager on telephone number **0151 794 8929** to advise that an SAE report has been submitted as soon as possible.
2. **The SAE form should be transferred securely to LCTCSafe@liverpool.ac.uk (within 24 hours of becoming aware).**
3. The responsible investigator must notify their R&D department of the event (as per standard local governance procedures).
4. The patient must be identified by trial number, age and initials **only**. The patient's name **should not** be used on any correspondence.
5. SAEs must be subsequently followed up in line with the processes below:

a. Follow-up must continue until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised (see Section 11.6). N.B. Follow-up may continue after completion of protocol treatment if necessary.

b. Follow-up information is noted on a new SAE form to be transferred securely to the LCTC as soon as more information becomes available

c. Tick the appropriate box on the new SAE form to identify the type of report; this is dependent on resolution status of the SAE e.g. follow-up / final.

6. Extra, annotated information and/or copies of anonymised test results should only be submitted when requested by the medical reviewer via LCTC.

7. Blank Serious Adverse Event forms can be obtained from the LCTC by contacting the DyNAMIc Trial Coordinator. Contact details are available within the LCTC contacts document.

11.12 LCTC Responsibilities

The trial Sponsor, The Christie NHS Foundation Trust, have delegated to LCTC the duty of onward reporting of safety events to REC, regulatory authorities, the Sponsor and Pierre Fabre Ltd, the marketing authorisation holder for both encorafenib and binimetinib. LCTC SOPs will be followed to ensure appropriate reporting as detailed below.

All “serious” safety events will be forwarded to the Chief Investigator or Medical Reviewer by LCTC within 24 hours of receiving the minimum information from site. The CI (or delegate) will review information provided by site and for all events assessed as “related” will provide an assessment of “expectedness”.

Safety events which are assessed as serious, related and unexpected adverse events will be expedited to the REC and MHRA within the following timeframes (in accordance with Part 5 of the Medicines for Human Use (Clinical Trials) Regulations SI1031 (Sections 32-25)):

- SUSARs which are fatal or life-threatening – **as soon as possible and in any case no later than 7 days** after the LCTC is first aware of the event. If the initial report is incomplete, a complete report will be submitted within an additional 8 days.
- SUSARs that are not fatal or life-threatening – within **15 days** of the LCTC first becoming aware of the event.

A copy of the report will be emailed to the Sponsor in parallel with correspondence to the REC and MHRA. Additionally, SUSARs will be reported to the Principal Investigators of participating sites in line with the requirements of LCTC Standard Operating Procedures (SOP).

The LCTC will submit an Annual Safety Report to REC and a Development Safety Update Report to the MHRA on an annual basis.

The following safety issues should also be reported in an expedited fashion:

- An increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important.
- Post-study SUSARs that occur after the patient has completed a clinical trial and are notified by the Investigator to the LCTC.
- New events related to the conduct of the trial or the development of the IMPs and likely to affect the safety of the subjects, such as:
    a. A SAE which could be associated with the trial procedures and which could modify the conduct of the trial;
    b. A significant hazard to the subject population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease;
- Recommendations of the Independent Safety and Data Monitoring Committee where relevant for the safety of the subjects.

The PIs at all institutions participating in the trial will be notified of any SUSARs at a frequency defined by LCTC SOP.

Any concerns raised by the TSC or ISDMC or inconsistencies regarding safety reporting noted as part of central monitoring may prompt additional training at sites, with the potential for the LCTC to carry out site visits if there is suspicion of unreported AEs / ARs and SARs / SAEs in patient case notes. Additional training will also be provided if there are unacceptable delays in safety reporting timelines.

Patient safety incidents that take place in the course of research should be reported to the National Patient Safety Agency (NPSA) by each participating NHS Trust in accordance with local reporting procedures.

Maintenance of Blinding in Adverse Event Reporting:

Not applicable, open label study.

Safety Reports:

Safety reports will be generated during the course of the trial which allows for monitoring of safety event including reporting rates and safety events by site / arm. The LCTC will send annual developmental safety update reports (DSURs)/Annual Progress Reports (APRs) containing a list of all SAEs and SARs to the ISDMC, MHRA and main REC. If any safety reports identify issues that have implications for the safety of trial participants, the PIs at all institutions participating in the trial will be notified.

The DSUR will present a comprehensive annual review and evaluation of pertinent safety information collected during the reporting period relating to the Investigational Medicinal Products. It will cover the following 4 areas:

1. Examine whether the information obtained by the Sponsor during the reporting period is in accordance with previous knowledge of the investigational drugs' safety.
2. Describe new safety issues that could have an impact on the protection of clinical trial subjects.
3. Summarise the current understanding and management of identified and potential risks.
4. Provide an update on the status of the clinical investigation/development programme and study results have implications for the safety of trial participants, the PIs at all institutions participating in the trial will be notified.

Urgent Safety Measures (USMs):

An urgent safety measure (USM) is a procedure to protect clinical trial participants from any immediate hazard to their health and safety but has not previously been defined by the protocol. It can be put in place prior to authorisation by the REC and the MHRA.

The Sponsor/LCTC will notify the MHRA and REC immediately and, in any event, within 3 days that such a measure has been taken and the reasons why it has been taken. The initial notification to the REC and MHRA will be by telephone (ideally within 24 hours) and a notice in writing will be sent within 3 days, setting out the reasons for the USM and the plan for further action. After discussion with the REC and MHRA, further action will be agreed, which may include submission of a substantial amendment, a temporary halt, or permanent termination of the trial.

Following notification, if a substantial amendment is required this must be submitted as soon as possible to the REC and ideally within two weeks to the MHRA. If the study is temporarily halted it may not recommence until authorised to do so by the REC and MHRA. If the study is permanently terminated before the date specified for its conclusion (in the original applications to REC and MHRA), the Sponsor should notify the REC and MHRA within 15 days of the date of termination by submitting the formal End of Trial Notification.

11.13 Contact Details and Out-of-hours Medical Cover

As this is low risk e.g. IMP is standard NHS practice and both IMPs have a well established safety profile emergency and out-of-hours medical care will be in line with usual NHS arrangements and local standard practice; no special provision is required for DyNAMIc participants. All participants will be provided with a copy of the information sheet which includes information about their participation and contact details for the local research team who may be contacted if necessary. During office hours, the CI or delegate are able to provide medical advice in relation to participation using the contact details listed at the beginning of this document.

12. DATA MANAGEMENT AND TRIAL MONITORING

For the DyNAMIc trial the responsibilities for Data Management and monitoring are delegated to the LCTC. Separate Data Management and Trial Monitoring Plans have been developed which provide detail regarding the internal processes that will be conducted at the LCTC throughout the trial. Justification for the level of monitoring is provided within those documents and the trial-specific risk assessment. All data will be managed as per local LCTC processes and in line with all relevant regulatory, ethical and legal obligations.

12.1 Source Documents

The case report form (CRF) will be considered the source document for data where no prior record exists and which is recorded directly in the bespoke CRF, e.g. patient completed quality of life questionnaires. A DyNAMIc source document list will be produced for each site to be kept in the ISF and provide detail of what constitutes DyNAMIc-specific source data.

Date(s) of informed consent processes (including date of provision of participant information sheet(s), randomisation number and the fact that the patient is participating in a clinical trial (including possible treatment arms) should be added to the patient's medical record chronologically.

12.2 Data Collection Methods

The CRF is the primary data collection instrument for the study so all data requested on the CRF **must** be recorded and all missing data must be explained. A copy of all CRFs should be retained at site. Any corrections to wet ink CRFs should be made in accordance with GCP. Missing or inconsistent data will be queried by LCTC, the system will be updated based on the response. No corrections should be made to CRFs once submitted to LCTC to ensure a complete audit trail.

12.3 Monitoring

Monitoring is conducted to ensure protection of patients participating in the trial and all aspects of the trial (procedures, laboratory, trial intervention administration and data collection) are of high quality and conducted in accordance with sponsor and regulatory requirements.

A detailed Trial Monitoring Plan will be developed and agreed by the TMG and CI to describe who will conduct the monitoring, at what frequency monitoring will be done, and what level of detail monitoring will be conducted. This will be dependent on the documented risk assessment of the trial which determines the level and type of monitoring required for specific hazards. All processes may be subject to monitoring, e.g. enrolment, consent, adherence to trial interventions, accuracy and timeliness of data collection etc.

Trial Oversight Committees related to the monitoring of the trial are detailed in Roles and Responsibilities see section 3.4.

Central Monitoring:

There are a number of monitoring features in place at the LCTC to ensure reliability and validity of the trial data, to be detailed in the trial monitoring plan. Data will be entered into a validated system and during data processing there will be checks for missing or unusual values (range checks) and for consistency within participants over time. Other data checks relevant to patient rights and safety will also be regularly performed as per LCTC processes. Any suspect data will be returned to the site in the form of data queries. Data query forms will be produced at the LCTC from the trial system and sent either electronically or through the post to a named individual (as listed on the site delegation log). Sites will respond the queries providing an explanation/resolution to the discrepancies and return the data query forms to the LCTC. The forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the system.

Site monitoring visits may be 'triggered' in response to concerns regarding study conduct, participant recruitment, outlier data or other factors as appropriate.

Clinical Site Monitoring:

In order to perform their role effectively, the trial coordinator (or monitor) and persons involved in Quality Assurance and Inspection may need direct access to primary data, e.g. patient medical records, laboratory reports, appointment books, etc. Since this affects the participant's confidentiality, this fact is included on the PISC. In agreeing to participate in this study, a PI grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation. The purposes of site monitoring visits include, but are not limited to:

- assessing compliance with the study protocol;
- discussing any emerging problems that may have been identified prior to the visit;
- checking CRF and query completion practices.

12.4 Risk Assessment

In accordance with the LCTC SOPs, a risk assessment has been completed in partnership with:

- Representatives of the Trial Sponsors
- Representatives of CRUK Cancer Biomarker Centre
- CI and Co-Investigators
- Trial Coordinator

- Trial Statistician
- LCTC Head of Trial Management
- LCTC Informations Systems
- LCTC Data Management

In conducting this risk assessment, the contributors considered potential patient, organisational and study hazards, the likelihood of their occurrence and resulting impact should they occur.

The outcome of the risk assessment for a Clinical Trial of an Investigational Medicinal Product (CTIMP) is expressed as an overall risk level as set out below, assigned according to one of the following categories:

CTIMP Type A = Comparable to the risk of standard medical care

CTIMP Type B = somewhat higher than the risk of standard medical care

CTIMP Type C = markedly higher than the risk of standard medical care

The risk assessment resulted in a **CTIMP Type B.**

12.5 Confidentiality

This trial will collect personal data (e.g. participant names), including special category personal data (i.e. participant medical information) and this will be handled in accordance with all applicable data protection legislation. Data (including special category) will only be collected, used and stored if necessary for the trial (e.g. evidencing provision of consent, for data management and central monitoring, statistical analysis, regulatory reporting, etc.). At all times, this data will be handled confidentially and securely.

CRFs will be labelled with a unique trial screening and/or randomisation number. Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participant's signed informed consent forms being supplied to the LCTC by recruiting sites. This transfer of identifiable data is disclosed in the PISC.

N.B. Consent forms must be transferred separately to any other trial documentation to ensure the pseudonymisation of special category data is maintained.

Site-specific study-related information will be stored securely and confidentially at sites and all local relevant data protection policies will be adhered to.

The LCTC as part of The University of Liverpool will preserve the confidentiality of participants taking part in the study.

The data controller for this study is The Christie NHS Foundation Trust, which is also the sponsor, and is registered as a data controller with the Information Commissioners Office. The University of Liverpool and The University of Manchester are data processors and will preserve the confidentiality of participants taking part in the study.

Breaches of data protection principles or regulations identified by LCTC will be notified promptly to the trial Sponsor and The University of Liverpool's Data Protection Officer and appropriate processes followed.

12.6 **Quality Assurance and Control**

To assure protocol compliance, ethical standards, regulatory compliance and data quality, as a minimum, the following will occur:

- The PI and other key staff from each centre will attend initiation training, which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol.
- The TMG will determine the minimum key staff required to be recorded on the delegation log in order for the centre to be eligible to be initiated.
- The TC at the LCTC will verify appropriate approvals are in place prior to initiation of a centre and the relevant personnel have attended the trial specific training. A greenlight checklist will verify all approvals are in place prior to trial initiation at LCTC and the individual centre.
- The trial will be conducted in accordance with procedures identified in the protocol.
- The ISDMC and independent members of the TSC will provide independent oversight of the trial.
- The TMG will monitor screening, randomisation and consent rates between centres and compliance with the protocol.
- Data quality checks and monitoring procedures will be undertaken in line with the trial Data Management Plan.

12.7 **Records Retention**

The retention period for the DyNAMIc data and information is 20 years from the official End of Trial date (defined in section 9.14 above).

The PI at each investigational site must make arrangements to store the essential trial documents (as defined by ICH GCP guidelines) including the Investigator Site File, the applicable participant medical records and Pharmacy Site File, for the full length of the trial's retention period and will arrange for confidential destruction at the end of this period as instructed by the LCTC.

The PI is also responsible for archiving all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities). They must ensure the continued storage of the documents, even if they, for example, leave the clinic/practice or retire before the end of required storage period. Delegation of responsibility for this must be documented in writing.

All other persons and organisations involved in the trial will be responsible for storing and archiving the parts of the TMF relevant to their delegated duties (e.g. laboratories, IMP manufacturers and distributors, third-party vendors providing randomisation and IMP allocation systems, etc.).

The LCTC undertakes to archive as per their contractual requirements; documents will be archived in compliance with the principles of GCP. All electronic CRFs and trial data will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to secure premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

13. REGULATORY AND ETHICAL CONSIDERATIONS

13.1 Statement of Compliance

This study is designed to comply with the guideline developed by the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and will be conducted in compliance with the protocol, LCTC Standard Operating Procedures and the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004 and all subsequent amendments. Local sites must conduct research in compliance with the UK Policy Framework for Health and Social Care Research.

13.2 Ethical Considerations

The DyNAMIc trial will be conducted in accordance with, but not limited to, the UK Data Protection Act (DPA) 2018, Freedom of Information Act 2000 subject to the provisions of Sections 41 and 43 thereof, the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended), the Medicines Act 1968, the Human Tissue Act 2004, the principles of the World Medical Association Declaration of Helsinki 1996 and the UK Policy Framework for Health and Social Care Research, as amended from time to time.

Patients will be asked to consent that data are recorded, collected, stored and processed and may be transferred to other countries, in accordance with the UK DPA 2018 and UK General Data Protection Regulation (GDPR) and to allow a copy of their completed signed consent form to be sent to the LCTC.

This study may be terminated at the request of the CI, ISDMC, Independent Research Ethics Committee (REC) or the MHRA if, during the course of the study, concerns about the safety of further dosing emerge.

The CI will update the ethics committee of any new information related to the study drug when appropriate and this will also be disseminated to the Principal Investigators at each trial centre.

13.3 Approvals

The protocol, PISC and any proposed public-facing material will be submitted to an appropriate Research Ethics Committee (REC), MHRA, Health Research Authority (HRA) and host institution(s) for written approval.

Any substantial amendments to the original approved documents will be submitted and, where necessary, approved by the above parties before use.

13.4 Protocol Deviation and Serious Breaches

Deviations from, breaches or violations of, or non-compliance to either the protocol, the conditions or principles of GCP, and relevant regulatory and ethical e.g. MHRA and REC requirements are handled based on their nature and severity, thus:

Non-Serious breaches:

Protocol deviations and other non-serious breaches of GCP etc. will be managed according to local site and LCTC procedures as appropriate. They will be reported to trial oversight committees.

Serious breaches:

A breach of the protocol or GCP is 'serious' if it meets the definition of being "likely to affect to a significant degree the safety or physical or mental integrity of the trial participants, or the scientific value of the trial". This assessment can only be determined by the Sponsor.

If any persons involved in the conduct of the trial become aware of a potential serious breach, they must immediately report this to the LCTC who will in turn notify the Sponsor. The Sponsor will assess the breach and determine if it meets the criteria of a 'serious' breach.

The Sponsor may seek advice from medical expert members of the TMG and/or of the independent oversight committees (ISDMC and TSC) in determining whether or not the breach is likely to affect to a significant degree the safety, physical or mental integrity of participants.

The Sponsor may seek advice from the Trial Statistician in determining whether or not the breach is likely to significantly affect the scientific value of the trial. However, the Sponsor retains responsibility for the assessment of whether or not a breach meets the definition of 'serious' and is subject to expedited reporting to MHRA and REC.

Breaches confirmed as 'serious' will be reported to MHRA and REC within 7 days by the LCTC on behalf of the Sponsor and notified to the TMG, ISDMC and TSC at their next meeting.

Any requests for additional information from the Sponsor, TMG, TSC, ISDMC, MHRA or REC, will be promptly actioned by the relevant member(s) of the research team and open communication will be maintained to ensure appropriate corrective actions are taken and documented.

Incidents of protocol non-compliance will be recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

14. INDEMNITY

The Christie NHS Foundation Trust holds insurance against claims from participants for harm caused by their participation in this clinical study. However, the treating hospital continues to have a duty of care to the participant and the Sponsor does not accept liability for any breach in the hospital's duty of care, or any negligence of the part of hospital employees. In these cases, clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements.

15. PUBLICATION AND DISSEMINATION

15.1 Publication Policy

The results from different participating sites will be analysed together and published as soon as possible, maintaining participant confidentiality at all times. Individual clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group (TMG).

The TMG will form the basis of the writing committee and will advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants and if there are named authors these should include the trial's Chief Investigator Paul Lorigan and Sub investigator Rebecca Lee, representative (s) from CBC, Statistician(s) and Trial Manager(s) involved as a minimum. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial will be attached to any publications resulting from this trial and members of the TSC and ISDMC should be acknowledged.

Any publications arising from this research will be reviewed appropriately prior to publication.

Authorship:

Contributors to all four of (i) the design, conduct, data analysis and interpretation, (ii) writing, (iii) manuscript approval and (iv) accountability for the integrity of the work will, depending on their contribution and journal requirements, be included by name at the manuscript head or listed at the end in a by-line as members of the DyNAMIc trial management group which will also be named at the manuscript head.

15.2 Dissemination to Key Stakeholders

On completion of the research, a Final Trial Report will be prepared and submitted to the MHRA and REC. The results of DyNAMIc will be published regardless of the magnitude or direction of effect.

15.3 Data Sharing

At the end of the trial, after the primary results have been published, the anonymised individual participant data (IPD) and associated documentation (e.g. protocol, statistical analysis plan, annotated blank CRF) will be prepared in order to be shared with external researchers. All requests for access to the IPD will be reviewed by an internal committee at the LCTC and discussed with the Chief Investigator in accordance with the LCTC policy on data sharing.

16. CHRONOLOGY OF PROTOCOL AMENDMENTS

16.1 Version 1.0 (05/05/2022)

- Original Approved version

16.2 Version 2.0

- This version was never released. All changes are implemented into version 3.

16.3 Version 3.0 (28/11/2022)

- Expansion of exclusion criteria
- Removal of scans of the brain at every 8 weeks
- Re-classification of trial as a 'Type B'
- Addition of pregnancy tests for WOCBP following the end of systemic treatment and if clinically indicated
- Clarification that E+B are classed as IMP, regardless of the treatment arm
- Initial ctDNA thresholds for stopping and re-starting treatment included, along with a summary of how these will be monitored
- Update to co-enrolment guidelines
- Correction to inconsistencies in the timelines for the first re-start of treatment on Arm B
- Correction to timeline for the collection of data for adverse events
- Correction to inconsistencies in terminology, i.e. brain vs head and chest abdomen pelvis (CAP) vs thorax abdomen pelvis (TAP)

16.4 Version 4.0 (27/03/2023)

- Dose reduction tables removed and replaced with referene to the SmPC
- Elaboration to the proposed translational work on samples
- Formalisation of the Molecular Tumour Board as an Oversight Committee
- Requirement added to confirm consistency of scanning modality for the duration of a participants involvement, and that comparisons should not be made between images from differing modalities
- Removal of CRP blood test at all visits except baseline and progression
- Elaboration to the requirements for a physical examination of the head
- Update to advise translational blood sample will be used as a reserve for ctDNA analysis if required
- Section added on the ,anagement of patients with COVID-19
- Minor administrative changes

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18. DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL

Documents referenced within the protocol are separately maintained and version controlled. Any of the supplementary documents subject to MHRA or Research Ethics Committee review are submitted as separate version controlled documents.

19. APPENDICES

Appendix A: Cockroft-Gault formula:

Cockroft Gault Formula

C_{Cr}={((140–age) x weight)/(72xS_{Cr})} (x 0.85 if female)

Appendix B: Contraceptive Guidance:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

Contraception Requirements:

Male Participants:

Male participants with partners who are WOCBP are eligible to participate if they agree to one of the following during the protocol defined time frame outlined in Section 7.4:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 5 when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.
- Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 5 during the protocol-defined time frame outlined in Section 7.4.

Table 5 - Highly Effective Contraception Methods:

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*

• Combined (oestrogen- and progestogen- containing) hormonal contraception [b, c]
  ○ Oral
  ○ Intravaginal
  ○ Transdermal
  ○ Injectable

• Progestogen-only hormonal contraception [b, c]
  ○ o Oral
  ○ o Injectable

Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen- only contraceptive implant [b, c] • Intrauterine hormone-releasing system (IUS) [b] • Intrauterine device (IUD) • Bilateral tubal occlusion

- Vasectomized partner

A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

- Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Notes:

Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.

[a] Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly).

[b] If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 5 months, corresponding to time needed to eliminate study treatment after the last dose.

[c] If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Appendix C: NYHA Guidelines:

Functional Capacity:

Class I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Objective Assessment:

A	No objective evidence of cardiovascular disease.
B	Objective evidence of minimal cardiovascular disease.
C	Objective evidence of moderately severe cardiovascular disease.
D	Objective evidence of severe cardiovascular disease.

The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

Appendix D: Scans and RECIST criteria:

Scan modalities by anatomy

Colour legend

Gren = Required / Preferred	Amber = Acceptable alternative	Red = Not applicable

Anatomy	**Modality**			
	PET-CT	**CT only**	**MRI**	**Ultrasound**
Research Biopsy	N/A	Only if clinically indicated as per local practice.	N/A	Only if clinically indicated as per local practice.
Limbs (only if disease present)	Head to toe, with contrast if no known allergy.	N/A	N/A	N/A
Brain (if limb disease)	By default, if limb disease.	N/A	With contrast if no known allergy.	N/A
Brain (if no limb disease)	N/A	With contrast if no known allergy. Acceptable alternative to MRI, as per local practice	With contrast if no known allergy	N/A
Neck (if indicated)	By default, if limb disease.	With contrast if no known allergy.	N/A	N/A
Thorax	By default, if limb disease.	With contrast if no known allergy.	N/A	N/A
Abdomen & Pelvis	By default, if limb disease.	With contrast if no known allergy. If known allergy to contrast, MRI can be used as an alternative, as per local practice	Acceptable alternative to CT if known allergy to contrast, as per local practice.	N/A

For participants who have measurable disease at baseline, the table below provides a summary of the overall time point response: participants with target (+/- non-target) disease.

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

Legend:

CR = Complete Response,

NE = Not Evaluable,

PD = Progressive Disease,

PR = Partial Response,

SD = Stable Disease.

Missing Assessments and Not Evaluable Designation:

When no imaging/measurement is done at all at a particular time point, the participant is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response.

For full RECIST version 1.1 criteria please refer to:

https://ctep.cancer.gov/protocoldevelopment/docs/recist_guideline.pdf

Appendix E: ECOG performance status*:

Grade	ECOG 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
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group

Am J Clin Oncol. 1982;5:649-655