DOC-MEK

Short title: Docetaxel +/- AZD6244 in Melanoma

A double blind randomised phase 2 trial of docetaxel with or without AZD6244 in wt *BRAF* advanced melanoma

Statistical Analysis Plan
Version number 3.0 28th Feb2013

Based on protocol version 4.0, 24th Ju1 2012

REVIEW HISTORY		
Name	**Signature**	**Date**
Sharon Love (Trial Statistician)		
Mark Middleton (PI)		
Janet Dunn (DSMC Statistician)		

Centre for Statistics in Medicine

Sponsor Contact Address
Clinical Trials and Research Governance (CTRG), University of Oxford, Manor House, John Radcliffe Hospital, Headley Way, Headington, Oxford 0X3 9DU
Tel: +44 (0) 1865 222 672 Fax: +44 (0) 1865 222 648

OCTRU Oxford Clinical Trials Research Unit

UKCRC Registered Clinical Trials Units

OCTRU is a UKCRC Registered Clinical Trials Unit
OCTRU is a joint venture between the Centre for Statistics in Medicine (CSM) and the Oncology Clinical Trials Office (OCTO) both based at the University of Oxford

CONTENTS

1. INTRODUCTION

This document details the proposed presentation and analysis for the main paper reporting results from the *AstraZeneca-funded* double blind randomised phase 2 trial of docetaxel with or without AZD6244 in wt BRAF advanced melanoma ***(DOC-MEK)***. The results reported in these papers should follow the strategy set out here. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis (for example, to decide cut-points for categorisation of continuous variables), nor to prohibit accepted practices (for example, data transformation prior to analysis), but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the trial.

The analysis strategy will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of this analysis strategy; if reported, the source of the suggestion will be acknowledged.

Any deviations from the statistical analysis plan will be described and justified in the final report of the trial. The analysis should be carried out by an identified, appropriately qualified and experienced statistician, who should ensure the integrity of the data during their processing. Examples of such procedures include quality control and evaluation procedures.

1.1 Trial statistician(s): Ms Sharon Love
Senior Statistician and Head of Support
Cancer Research UK Medical Statistics Group
Centre for Statistics in Medicine
Wolfson College Annexe
Linton Road
Oxford, OX2 6UD

Email: sharon.love@csm.ox.ac.uk
Phone: 01865 284414
Fax: 01865 284424

Milensu Shanyinde
Same address as above

Email: milensu.shanyinde@csm.ox.ac.uk
Phone: 01865 284422

1.2 Chief Investigator: Professor Mark Middleton
Mark R. Middleton, PhD, FRCP
Professor of Experimental Cancer Medicine &
Consultant Medical Oncologist
Clinical Director, Oncology
Department of Oncology
Oxford University Hospitals NHS Trust
Churchill Hospital
Oxford, OX3 7LJ
UK

Tel +44 (0)1865 235315 (academic)
Tel +44 (0)1865 235272 (clinical)
Fax +44 (0) 1865 235981

Email mark.middleton@oncology.ox.ac.uk
Personal Assistant lindsey.bettison@oncology.ox.ac.uk
Clinical Secretary debra.sims@ouh.nhs.uk
Directorate PA chris.woodward@ouh.nhs.uk

1.3 Trials Unit Contact: Mrs Linda Collins

Oncology Clinical Trials Office (OCTO)
Department of Clinical Pharmacology
University of Oxford
Old Road Campus Research Building
Roosevelt Drive
Headington
Oxford
OX3 7DQ

Tel 01865 617089
Fax 01865 617010
Email linda.collins@clinpharm.ox.ac.uk

2. BACKGROUND INFORMATION

2.1 Aims of the Trial

The benefit of AZD6244 will be assessed using progression free survival (primary), objective response rate, overall survival and progression free survival at 6 months and the safety and tolerability will be assessed using several measures. A formal continuation into Phase II has been stated as the primary outcome being significant at $p \leq 0.1$ but the evidence from the other efficacy endpoints and from the safety and tolerability endpoints will also be taken into account when interpreting the result of the trial.

2.1.1 Primary aim

To determine the efficacy in terms of progression free survival of the combination of the selective MEK inhibitor AZD6244 with docetaxel compared to docetaxel alone in first line patients with wild-type *BRAF* advanced melanoma.

2.1.2 Secondary aims

To further assess the efficacy, safety and tolerability of AZD6244 in combination with docetaxel, compared with docetaxel alone, in first line patients with wild type BRAF advanced melanoma using overall survival, objective response rate, progression free survival at 6 months, adverse events using CTCAE v4.0, vital signs, weight, biochemistry, haematology and urinalysis, physical examination and ECG

2.1.3 Exploratory aim

To assess the impact of the tumour characteristics on response to docetaxel therapy with or without AZD6244 using immunohistochemistry of proteins in the MAPkinase pathway and by genotyping of tumours.

2.1.4 Exploratory aims known after start of trial

NRAS mutation status was not known before recruitment started. In light of recent findings, Colombino M et al (2012) recommended assessment of tumour mutations such as NRAS in patients with melanoma. Therefore we assessed the impact of NRAS mutation status on outcome.

Collection of Ipilimumab drug use status post DOCMEK treatment was not planned at start of the trial. Therefore we summarised IPI status after end of DOCMEK treatment.

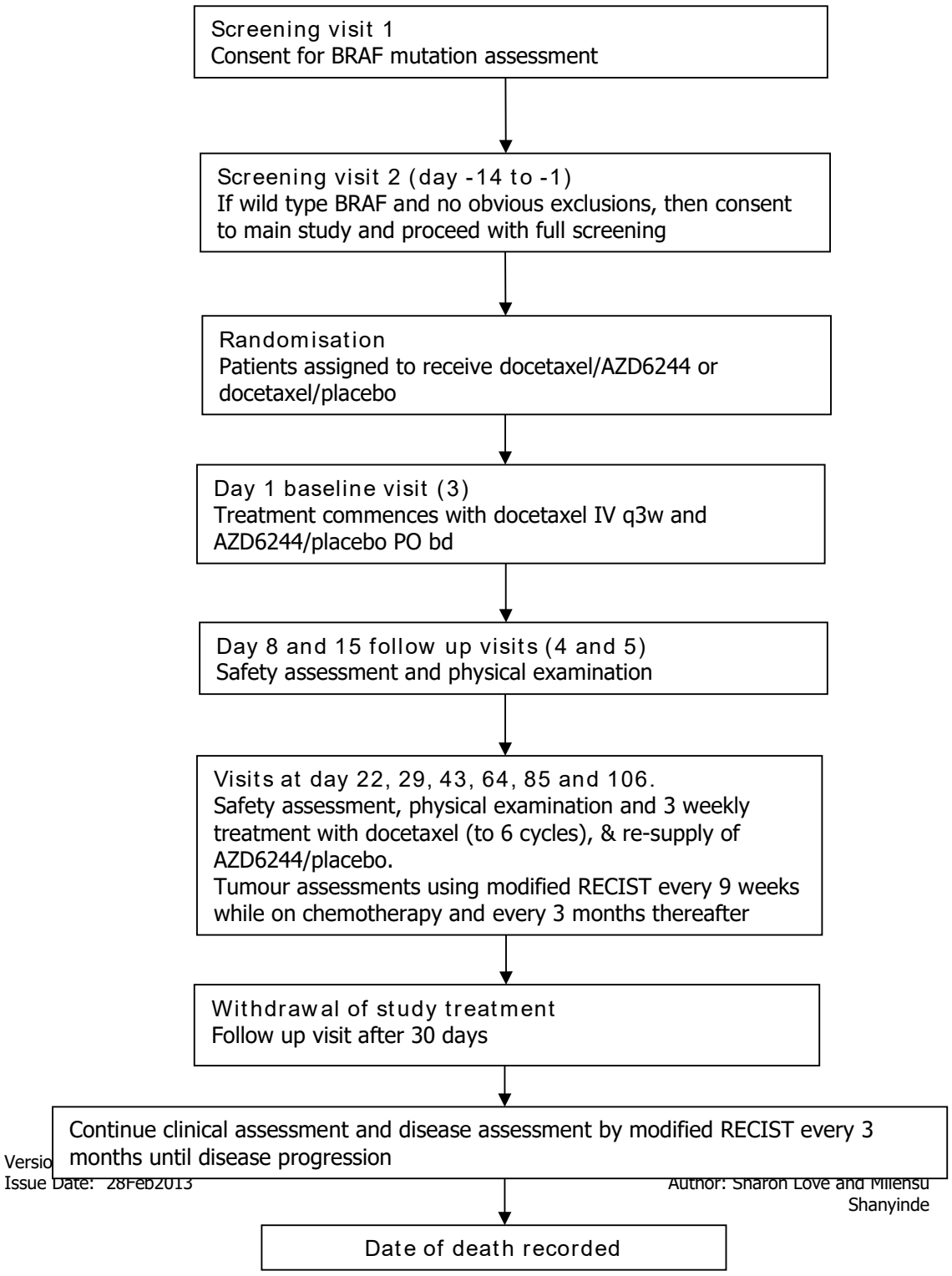
2.2 Study Design

DOC-MEK is a randomised, double-blind, placebo-controlled multi-centre study of patients with wild-type BRAF advanced melanoma. Eighty patients (forty in each of two arms) will be randomised to docetaxel with placebo or docetaxel with AZD6244 with stratification for M stage (M1c vs M1a, M1b or M0) and performance status (0 vs 1).

Date of start of recruitment:	26 October 2010
Number to be recruited:	80 (40 per arm)
Date of expected end of recruitment:	30April2012
Date of expected end of follow-up:	30August 2013

Participating Centres: 18 centres across the UK under the auspices of the NCRI Melanoma Clinical Study Group

2.2.1 Study Flowchart



2.3 Eligibility

2.3.1 Inclusion criteria

A patient will be eligible for inclusion in the main study if all of the following criteria apply:

1. Aged ≥ 16 years
2. Able to provide evidence from an accredited laboratory of wt BRAF status for their melanoma, or ascertainment of wt BRAF status from a sample of melanoma provided for mutational analysis in Oxford (see protocol v.4.0 24Jul2012 section 8.1).
3. Unresectable stage 3 or 4, histologically proven cutaneous or unknown primary melanoma
4. At least 1 lesion, not previously irradiated, that can be accurately measured on CT or MRI as defined by modified RECIST criteria
5. ECOG performance score of 0 or 1.
6. Life expectancy of at least 12 weeks.
7. The patient is willing to give consent to the main study and able to comply with the protocol for the duration of the study, including scheduled follow-up visits and examinations.
8. Haematological and biochemical indices within the ranges shown below.

Lab Test	Value required
Haemoglobin (Hb)	>10g/dL
White Blood Count (WBC)	> $3x10^9$/L
Platelet count	> 100,000/µL
Absolute Neutrophil count	> $1.5x10^9$/L;
Serum bilirubin	≤ 1.2 x ULN
AST (SGOT) or ALT	≤ 2.5 x ULN
LDH	≤ 2 x ULN
Creatinine clearance (Cockcroft-Gault)	>50 ml/min

2.3.2 Exclusion criteria

A patient will not be eligible for the trial if any of the following criteria apply:

1. Any anti-cancer therapy (including radiotherapy and participation in other clinical trials) within 28 days prior to Day 1.
2. Prior DNA damaging agents or cytotoxic chemotherapy for metastatic melanoma.
3. Any unresolved toxicity from prior anti-cancer therapy that is greater than CTCAE grade 2.
4. Pregnancy or breastfeeding women. Female patients must have a negative urinary or serum pregnancy test or have evidence of post-menopausal status (defined as absence of menstruation for > 12 months, bilateral oophrectomy or hysterectomy).
5. Grade ≥2 peripheral neuropathy at study entry.
6. Patients of reproductive potential who are not willing to use adequate contraceptive measures for the duration of the study (both male and female patients)
7. Known severe hypersensitivity reactions to docetaxel or other drugs formulated in polysorbate 80

8. Ocular or mucosal malignant melanoma
9. Another active malignancy within the past five years.
10. Evidence of brain metastases, *unless* surgically resected/stereotactic radiosurgery treated brain metastasis with no evidence of relapse on cerebral MRI, or treated brain metastasis and stable off treatment, including steroids, for 3 months.
11. Clinically significant and uncontrolled major medical condition(s): such as active infection, bleeding diathesis.
12. Patients who are known to be serologically positive for Hepatitis B, Hepatitis C or HIV.
13. Cardiac conditions, including uncontrolled hypertension (BP>160/100 despite treatment), heart failure NYHA class 2 or above, prior or current cardiomyopathy, myocardial infarction within 6 months or angina requiring nitrate therapy more than once a week.
14. Previous treatment with EGFR, ras, raf or MEK inhibitors.
15. Inability to swallow capsules, refractory nausea and vomiting, chronic gastrointestinal diseases (eg, inflammatory bowel disease) or significant bowel resection that would preclude adequate absorption.
16. Taking medication that significantly induces or inhibits CYP3A4 (see protocol v.4.0 24Jul2012 appendix 3).

2.4 Treatment Interventions

2.4.1 Docetaxel

Patients will receive docetaxel 75 mg/m^2, rounded to the nearest 10 mg, based on the most recent body surface area, as a 1 hour (Intravenous) IV infusion in 250ml of either 5% glucose solution or 0.9% sodium chloride solution. Standard pre-medication with steroids should be given, consisting of dexamethasone 8 mg b.d. for 3 days starting 1 day prior to docetaxel administration. Treatment will be given on day 1 and every 3 weeks for up to 6 cycles. The dose of docetaxel may be reduced or delayed if necessary as described in see protocol v.4.0 24Jul2012 1 section 6.3.1. There will be no adjustments or dose capping for missing limbs and no dose capping for larger patients.

Patients should be observed closely for hypersensitivity reactions especially during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of docetaxel, thus facilities for the treatment of hypotension and bronchospasm should be available. If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require interruption of therapy. Hypersensitivity reactions should be managed according to local protocols, and docetaxel may be re-introduced according to the scheme described in protocol v4.0 24Jul2012 section 6.3.1. However, severe reactions, such as severe hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of docetaxel and appropriate therapy. Patients who have developed severe hypersensitivity reactions should not be re-challenged with docetaxel, but may continue with AZD6244/placebo within the study.

2.4.2 AZD6244/Placebo

Patients will be allocated AZD6244/placebo by bottle number. They will receive 75mg AZD6244 or placebo orally twice a day on a continuous schedule. The AZD6244/placebo will be supplied in white HDPE (High Density Polyethylene) bottles containing capsules of 25mg strength. At each visit, sufficient capsules will be provided for the period until the patient's next scheduled visit. It is not possible to specify capsules numbers in each bottle as availability of the AZD6244 and/or placebo may vary during the trial.

Capsules should be taken whole and not opened or crushed. They should be taken on an empty stomach (no food or drink for 2 hours before or 1 hour after treatment), with approximately 240ml of water. Doses should be taken approximately 12 hours apart. Wherever possible doses should not be missed but if a dose is missed then the next dose should be taken at the allotted time and the missed dose should not be made up. Patients are permitted to continue to take AZD6244/placebo until they experience disease progression, in the absence of significant toxicity.

2.5 End of Trial

The 'end of trial' is defined as the last visit of the last patient undergoing the trial.

2.6 Code break

The treatment code will be broken at trial closure for all patients.

2.7 Sample Size

Eighty patients will be recruited to the study. Analysis will be performed when approximately 58 disease progression/death events have occurred. The trial is planned to recruit for 12 months and follow-up all patients for at least 3 months after last patient recruitment. If the true Hazard Ratio (HR) is 0.57 (likely to correspond to a 75% prolongation of progression free survival (PFS)), this analysis will have approximately 80% power to demonstrate a statistically significant difference for PFS, assuming a 1-sided 10% significance level. If a 1-sided $p<0.1$ is observed for the comparison of PFS between AZD6244 in combination with docetaxel, versus docetaxel, the results will be regarded as promising (but not definitive) as there is a less than 1 in 10 probability that such a result could have been detected if there was truly no treatment effect.

The trial will be assessed on an intention-to-treat basis, being grouped according to the treatment they were assigned. Thus, all patients randomised to receive treatment within the study will be evaluable PFS and secondary endpoints (e.g response).

There is no pre-defined interim analysis or stopping rule.

2.8 Randomisation

Eligible patients will be randomised 1:1 to receive Docetaxel with Placebo or Docetaxel with AZD6244, stratifying for M status (M1c vs M1a or b or M0) and Performance Status (0 vs 1) and using a variable blocksize.

Randomisation is completed via an IWRS system: https://www.fisheracts.com

2.9 Definition of Primary and Secondary Outcomes

2.9.1 Primary outcome

Progression free survival. This is defined as time from date of randomisation to the first of date of progression (using CT scan and RECIST criteria) or date of death (events). For patients without an event, the time from date of randomisation to date last known alive will be the censored PFS time.
Note that the quality of this data will depend on the CT scans being carried out as scheduled. This will be described (see section 5.7) and a sensitivity analysis conducted (see section 7.6)

2.9.2 Secondary outcomes

Objective response rate. The objective response is defined as the best overall response recorded from the start date of treatment until disease progression. The numerator of the objective response rate is the number of patients achieving a CR or PR. The denominator is all patients randomised.

Note that the quality of this data will depend on the CT scans being carried out as scheduled. This will be described (see section 5.7) and a sensitivity analysis conducted (see section 7.6)

Best overall response will be derived from Target Lesions (TL) measurements, overall assessment on Non-Target Lesions (NTL) and presence/absence of new lesions

Target lesions	Non-Target lesions	New Lesions*	Overall response
CR	CR (or NA)	No	**CR**
CR	IR/SD	No	**PR**
PR	CR, IR/SD (or NA)	No	**PR**
SD	CR, IR/SD (or NA)	No	**SD**
PD	Any	Yes or No	**PD**
Any	PD	Yes or No	**PD**
Any	Any	Yes	**PD**
NE	Non-PD	No	**NE**
Non-PD	NE	No	**NE**

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease
IR = incomplete response, NE = not evaluable, NA = not applicable, * = see criteria above

Progression free survival at 6 months. PFS at 6 months is defined as the percentage progression free survival at 6 months from the PFS Kaplan Meier graph. This would allow all patients randomised to be included.

Overall survival. This is defined as the time from randomisation to death (event) or time from randomisation to date last known alive (censored time).

Adverse events will be assessed using CTCAE v4.0

An adverse event or experience (AE) is defined as any untoward medical occurrence in a clinical investigation patient, temporally associated with the administration of an investigational medicinal product (IMP) or a comparator product, whether or not considered related to the IMP or a comparator product. An AE can therefore be any unfavourable and unintended sign, symptom, disease (new or exacerbated) and /or significant abnormal laboratory or physiological observation temporally associated with the use of a medicinal product.

Adverse event monitoring starts from the time the patient receives any of the research procedures until they complete the trial. The Investigator will assess and record in the case report form (CRF) any drug related adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course, duration and outcome, relationship of the adverse event to study drug, and any action(s) taken.

Vital signs and weight
Vital signs will be assessed using; temperature, pulse rate and blood pressure (BP).

Weight is measured in Kg.

Biochemistry, haematology and urinalysis
Analysis of routine blood samples for haematology and biochemistry during the trial will be performed in the laboratories of the local hospital trust according to local procedures.

Urinalysis will is assessed as normal or abnormal for every visit except in follow-up.

Physical examination
Physical examination will be assessed as normal or abnormal or not evaluated for each of the following body systems; General appearance, Skin, HEENT, Chest, Cardiovascular Abdomen, Lymph nodes, Extremities/Back, Musculoskeletal, Neurological and other if needed.

ECG is assessed as normal or abnormal on day 1 of each cycle prior to drug administration.

2.9.3 Exploratory outcomes

Immunohistochemistry of proteins in the MAPkinase pathway Genotyping of tumours

Genetic analysis will consist of evaluation of mutations deletions and insertions in genes other than BRAF that affect the function of the MAPkinase pathway. To date these include NRAS, PTEN, AKT, MEK, which will be the focus of initial analyses.

2.9.3.1 Post hoc outcomes: IPI and NRAS mutation status after start of trial

- Ipilimumab

During the course of DOCMEK study Ipilimumab started to be used after the failure of the DOCMEK treatment. Data on Ipilimumab drug use status was collected (in follow-up) and recorded as a binary variable (Yes/No) to indicate Ipilimumab drug use. If not known, reasons were recorded. We therefore describe Ipilimumab drug use in this study.

- NRAS

In light of external evidence of a non-randomised open label phase 2 study, Ascierto PA et al (2013) assessed the use of MEK162 in patients with NRAS-mutated or Val600 BRAF-mutated advanced melanoma. The study concluded that MEK162 is the first targeted therapy to show activity in patients with NRAS-mutated melanoma and might offer a new option for cancer with few effective treatments.

The potential importance of the NRAS mutational status was not known at the design phase of DOCMEK. However tumour tissues sample were stored so that new variables could be assessed. Therefore, the analysis of NRAS was only determined at the end of the DOCMEK study but it is motivated by external evidence rather than due to seeing the DOCMEK data.
NRAS mutational analysis for all patients has been done from archival melanoma tumour tissue samples and consent to use them was obtained at start of trial.
Data consisting of NRAS mutation status was collected after start of the trial (in follow-up), recorded as either Mutated or Wildtype (i.e. not mutated). If not known, reasons were recorded.
We therefore assessed the impact of NRAS mutation status on outcome (PFS and OS).

2.10 Outcomes Assessment Schedule

Visit	1	2	3	4	5	6	7	8	9	10	11	12+	Off Treatment Visits		
Cycle	0	0	1	1	1	2	2	3	4	5	6	7	N/A	N/A	N/A
Day	N/A	-14 to -1	1	8	15	22	29	43	64	85	106		N/A	30 days post Tx	Every 3 months
Visit description	Mutation Screening	Main study screening	Baseline	Treatment									Stop treatment	Post study visit	Follow up[1]
Visit window(days)	N/A		N/A	+/- 2	+/- 2	+/- 2	+/- 2	+/- 2	+/- 7	+/- 7	+/- 7	+/-7			
Mutation status consent	X														
Main study consent		X													
Demographics	X														
Medical History	X														
Concomitant Treatments		X	X	X		X		X	X	X	X	X	X	X	
ECOG PS		X	X	X		X		X	X	X	X	X	X	X	
Physical Exam		X	X[2]	X	X	X	X	X	X	X	X	X	X	X	
Clinical Disease Assess.		X	X	X		X		X	X	X	X	X	X	X	X
Vital Signs		X	X	X	X	X	X	X	X	X	X	X	X	X	
Height		X													
Weight		X				X		X	X	X	X	X	X	X	
Haematology and Biochemistry		X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG[3]		X	X												
Pregnancy test		X													
Docetaxel administration			X			X		X	X	X	X				
AZD6244/placebo			Twice daily dosing												
Urinalysis			X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X	
CT scan		Baseline[4]							X[5]			X			X[5]
Blood sample[6]	X														

[1] Survival status only may be recorded
[2] A physical examination is not required at baseline if the screening visit is within 3 days of commencing treatment
[3] ECG must be performed pre dose and 2 hours post dose on day 1 (visit 3). Otherwise a single pre-dose ECG is required.
[4] Baseline CT within 28 days of commencing treatment. This must include a contrast study of the head (an MRI head is acceptable as an alternative)
[5] Disease assessment by modified RECIST will be recorded at the end of cycles 3 & 6, and every 3 months thereafter until disease progression is recorded.
[6] Blood sample for genetic analysis may be taken at Main Study Screening if BRAF Mutation Screening not required.

3. QUALITY CONTROL AND DATA VALIDATION

OCTO is responsible for monitoring the trial in order to verify that (ICH GCP section 5.18):

- The rights and wellbeing of the human subjects are protected.
- The reported trial data are accurate, complete and verifiable from source documents.
- The conduct of the trial is in compliance with the approved protocol and GCP.

Monitoring will be performed in accordance with the applicable OCTO policies and guidelines. These may include activities designed to:

- Initiate the study and check progress periodically
- Review the essential trial documentation and study data collected.
- Conduct source document verification if required.
- Identify any issues and address their resolution
- Confirm proper closure of the clinical study site at the end of the clinical phase
- Monitor the study sample handling laboratories activities and facilities

The sponsor or OCTO may conduct quality assurance audit to assure compliance with protocol and ICH-GCP. The Regulatory agency may conduct a regulatory study inspection. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the Investigator and host institution(s) agree to allow auditors/inspectors direct access to all relevant documents and to allocate his/her time and the time of his/her staff to discuss findings and any relevant issues.

On a day-to-day basis forms are checked for compliance with the protocol, data consistency, missing data and timing and regular contact is maintained with site personnel to check on progress and deal with queries.

The randomisation has undergone a checking process with the company providing the randomisation service and will be checked by the statistician prior to analysis according to CSM Standard Operating Procedures.

4. DATA MONITORING COMMITTEE AND INTERIM ANALYSES

There is no DSMC and no planned interim analysis

POST NOTE; 17 November 2011
An independent DSMC convened to monitor aggregate safety data because there was a safety concern issue. In order to closely assess toxicity occurrence by treatment arm, all toxicity data and SAE's collected at OCTO were made available. Open and closed reports were presented to the DSMC. The open report included summaries of recruitment rate, protocol deviations and CRF return rates. The closed report included summaries of AE's and SAE's by treatment arm. The closed report was blinded and DSMC was unblinded verbally during the meeting.

After the meeting the DSMC recommended they review the data once more after 6 months following this safety analysis.

The DSMC will:

- Monitor data quality
- Monitor recruitment figures and loss to follow-up
- Monitor toxicity and SAEs

4.1 Data required for DSMC

The DSMC will receive the reports in advance for review before the meeting. Data will be presented in an Open and Closed report.

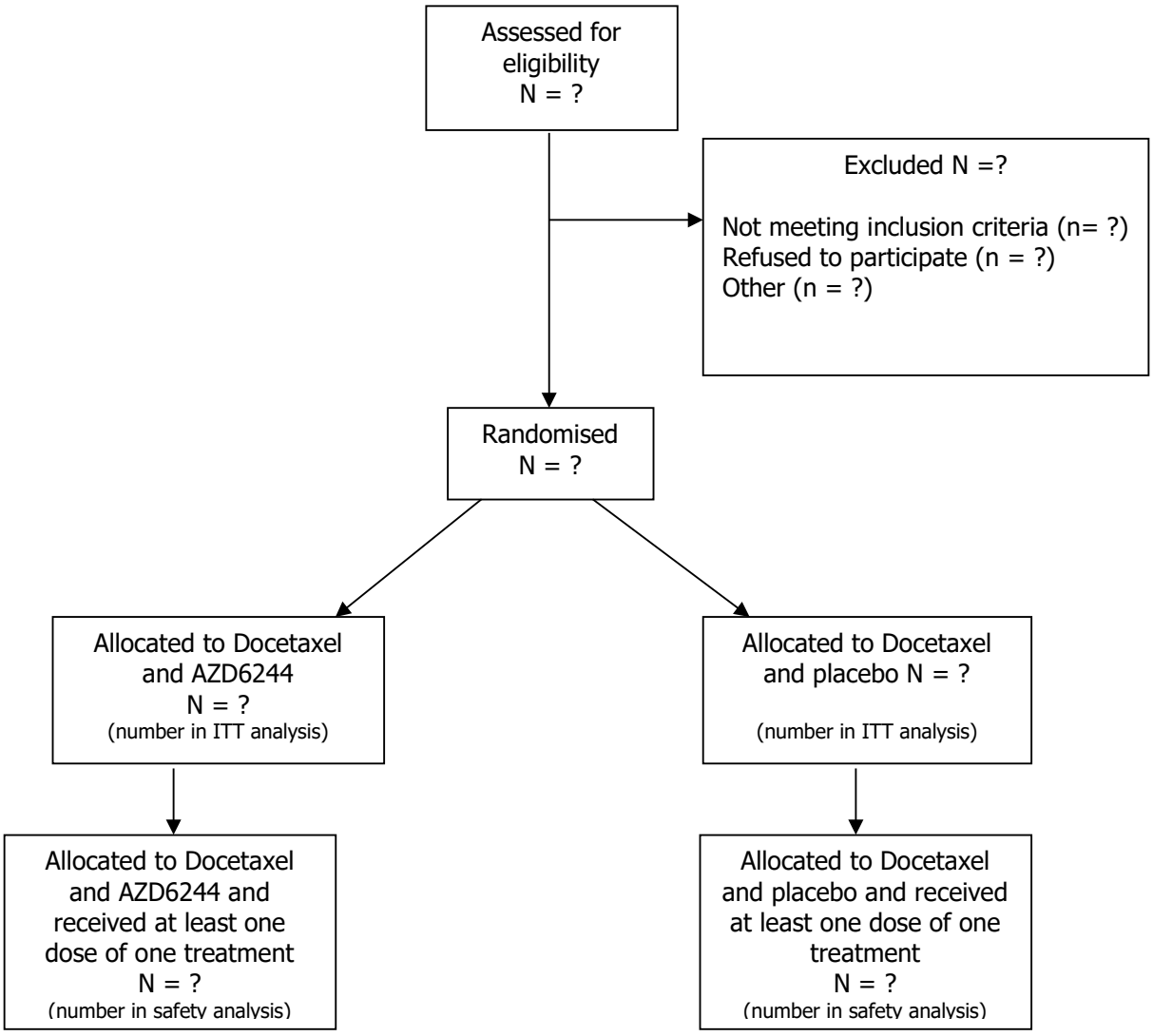
1. OCTO will be responsible for providing the following information in the open report;

- Number recruited
- Screening log summaries (reasons for exclusion)
- Protocol deviations
- Return rates on CRFs
- Any unblinding of randomised treatment prior to trial closure
- Any other additional data requested by the DSMC

2. The Centre for Statistics in Medicine will be responsible for the closed report and reviewing of the open report;
   - Summary of stratification variables by treatment arm
   - AEs and SAEs by treatment arm
   - Any other additional data requested by the DSMC

5. DESCRIPTIVE ANALYSES

5.1 Representativeness of Study Sample and Patient Throughput



5.2 Reasons for exclusions

Table: Expansion of reasons for exclusion

Reason for exclusion	N	Subtotal
		Not meeting inclusion criteria n=
		Refused to participate n=
		Other reason n=
Total patients screened but not recruited		

5.3 Protocol deviations

Protocol deviations will be reported.

5.4 Consent Withdrawal

Table: Consent Withdrawal

	Docetaxel + AZD6244	Docetaxel + Placebo
Patient withdrawn from further trial-related follow-up		

5.5 Baseline Comparability of Randomised Groups

A table showing characteristics of the two randomised groups at baseline will be presented to show comparability of the groups. Numbers (with percentages) for binary and categorical variables and means (with standard deviations), or medians (with lower and upper quartiles) for continuous variables will be presented; there will be no tests of statistical significance nor confidence intervals for differences between randomised groups on any baseline variable.

Variable	Docetaxel + AZD6244	Docetaxel + Placebo
Age		
Stage M1c M1a or M1b or M0		
ECOGPerformance Score 0 1		
Smoking status No Smoked in the past Never smoked		
Physical examination General		

Variable	Docetaxel + AZD6244	Docetaxel + Placebo
appearance Skin HEENT Chest Cardiovascular Abdomen Lymp nodes Extremities/back Musculoskeletal Neurological Other body system		
Vital signs Temperature Pulse rate Blood pressure Weight (kg)		
Height		
Biochemistry Phosphate (mmol/L) Calcium (mmol/L) Sodium (mmol/L) Potassium (mmol/L) Urea(mmol/L) Bilirubin (µmol/L) Alkaline (U/L) ALT (U/L) AST (U/L) Albumin (g/L) GGT (U/L) Total protein (g/L) LDH (U/L) Creatinine clearance ml/min		
Haematology results Haemoglobin (g/dL) White cell count ($x10^9$/L) Neutrophils ($x10^9$/L) Platelets ($x10^9$/L)		
ECG (at screening) Normal Abnormal Not done		
Urinalysis Normal Abnormal		
Other cancer treatment		
Other significant medical history		
Concomitant treatment		
Target lesion Sum LD		

5.6 Comparison of Losses to Follow-up

The numbers and pattern of losses to follow-up over the duration (expected to be 15 months) of the study will be reported and compared between the treatment groups. All patients will continue in follow-up until progression, death or until 3 months after the last patient is recruited.

5.7 Description of Available Data

For PFS and OS, events are recorded as and when they occur, and the analysis methods to be used are designed to deal with the problem of events not being observed. Median and range of follow-up will be reported for each arm, calculated by the reverse Kaplan-Meier method.

The frequency of CT scans needed for the PFS and Objective response rate will be described overall and within each treatment group. Responses without confirmatory response evidence from a CT scan will be described.

For safety and tolerability endpoints the patterns of availability of outcome data, from baseline to end of follow-up, will be summarised for the two arms.

The completeness of the data will be described but no missing data will be imputed.

5.8 Description of Compliance with Therapy

A summary of the treatment received by randomised group will be provided. This will include information in terms of cycle and dose of each drug received. Deviations from protocol including loss to follow-up, withdrawal by clinician and withdrawal of consent will be included.

5.8.1 Number of patients reaching each cycle by treatment group for Docetaxel

Maximum cycles reached	Docetaxel + AZD6244	Docetaxel + Placebo
1		
2		
3		
4		
5		
6		

5.8.2 Dose administered for Docetaxel is recorded at visit 3, 6, 8, 9, 10 and 11

Total dose delivered	Docetaxel + AZD6244	Docetaxel + Placebo
75		
…		

5.8.3 Withdrawal from Treatment

Reason for withdrawal from treatment	Docetaxel + AZD6244	Docetaxel + Placebo
e.g death		

5.8.4 Kaplan Meier plot to summarise time to stopping treatment

Docetaxel

For Docetaxel, time from start date of treatment (date of cycle 1, or visit 3 if unknown) to date of last dose administered

AZ/Placebo

For AZD6244/Placebo, time from start date of treatment (date of cycle 1, or visit 3 if unknown) to date of last dose administered

AZ/Placebo or Docetaxel (either treatments)

For either treatment, time from start date of treatment date of cycle 1, or visit 3 if unknown) to date of last dose administered

AZ/Placebo and Docetaxel (both treatments)

For both treatments, time from start date of treatment date of cycle 1, or visit 3 if unknown) to date of last dose administered

5.9 Unblinding of Randomised Treatments

Treatment code unblinding is expected to be rare. The independent Data and Safety Monitoring Committee will review unblinded summary data in the confidential closed report. Any unblinding with be listed and summarised. Patients who have had the treatment code broken will receive no further treatment in the study but will be followed up as per protocol.

5.10 Reliability

The primary outcome of progression free survival is robust for the outcome of death. However progressions may be missed by not carrying out CT scans at appropriate times and the integrity of the PFS endpoint would be harmed by the CT scan frequency varying between the two treatment groups.

In the DOC-MEK study, response will be noted at the time of confirmation of response/ Confirmation of response (CR or PR) is determined by the study protocol to be performed at the next scheduled RECIST assessment following the date the criteria for response were first met. If a confirmation scan is performed earlier than the scheduled scan, every attempt should be made to perform the subsequent scans at their scheduled time points. In this way the assessment for progression should be similar in the two treatment groups and across all patients.

The scheduled scans are at times from randomisation +/- 3 days until 18 weeks and then every 3 months +/-7days to ensure similar scan frequency. If a scan is done at other times for patient symptoms, then the scheduled scan should still be done as well. The scan frequency will be summarised as described in section 5.7 of this statistical analysis plan and also checked per patient with any CT scan timing irregularities declared.

The checks for CT scans outlined in the paragraph above will also benefit the reliability of the objective response rate.

Calculations performed using a computer will be checked by hand calculations for a minimum of 5% or 20 patients, where appropriate.

6. PATIENT GROUPS FOR ANALYSIS

The primary analysis for this trial is based on the intention to treat (ITT) population, which is defined as all patients who were randomised. So if any patients are found to be ineligible and are replaced or if patients do not receive treatment they will still be analysed in the primary aim.

The safety and tolerability analysis will include all patients who were randomised and received at least one dose of one treatment.

Note also the sensitivity analysis described in section 7.6.

7. ANALYSES TO ADDRESS PRIMARY AIMS

All centres will be analysed together. It is expected that either STATA, SAS or SPLUS will be used for the analysis.

For the analysis of the primary outcome a P-value of 0.1 (10% level) one sided will be used to indicate statistical significance.

7.1 Statistical Methods Used for Analysis of Primary Outcome

The primary PFS analysis will be a Cox regression model using the randomisation stratifying factors as covariates and giving the hazard ratio for using AZD6244 with a 90% confidence interval. This will be presented alongside a Kaplan-Meier plot of all the data.

Results of an unadjusted (univariate) Cox model will also be presented in terms of a hazard ratio and 90% confidence interval.

The proportional hazard assumption will be assessed using plots of the log cumulative hazard function and Schoenfeld residuals. If the assumption is not appropriate and an accelerated failure time (AFT) pattern is discerned in the data this will be used instead of Cox to obtain effect size in terms of time ratios.

7.2 Adjustment of P values for Multiple Testing

No formal adjustment for multiple significance testing is intended. The benefit of AZD6244 will be assessed using PFS, ORR, OS and PFS at 6 months and the safety and tolerability will be assessed using several measures. A formal continuation into Phase III has been stated as the primary outcome being significant but the evidence from the other efficacy endpoints and from the safety and tolerability endpoints will also be taken into account.

7.3 Missing Data

Protocol deviations and withdrawals are included in any analysis for which they have data. For example, for the analysis of progression free survival (PFS), patients lost to follow-up are censored at the last date known alive. For the primary PFS analysis, all patients are included even if they missed a scheduled CT scan. Safety and tolerability data for such patients are included where available.

For PFS, known progression is analysed with CT scan schedule described as in 5.7 and a sensitivity analysis as in section 7.6.

For Objective Response Rate (ORR), the best known response is used with the CT scan schedule described as in 5.7 and a sensitivity analysis as in section 7.6.

For safety and tolerability data, available data is analysed. It is not always known if data is missing (eg a patient may not have had a particular adverse event or they may have experienced the event but the data not have been recorded) and we do not plan to impute data that is known to be missing

7.4 Pre-specified Subgroup Analysis

No subgroup analysis is planned except as sensitivity analysis (see section 7.6)

7.5 Treatment by Centre Interaction

Consistency of effect will be assessed across the 18 centres by informal examination of the within centre effects. There will be limited capacity to investigate these formally and it is noted that such centre effects are expected by chance.
Post recruitment note: Classifying centres for example by specialist centre versus others to assess consistency of effect because of the non-uniform distribution of patients recruited at each centre.

7.6 Sensitivity Analysis

An analysis of the
- PFS primary aim
- Objective response rate
- PFS at 6 months

using data only from those patients who have had CT scans as described in the protocol will be carried out as a sensitivity analysis.

An analysis of the primary aim using only data from patients taking AZD6244 as per protocol (section 6.2 version 4.0 24Jul2012) until end of cycle 3 for Docetaxel (IV on day 1 of each cycle) will be carried out as a sensitivity analysis.

8. ANALYSIS TO ADDRESS SECONDARY AIMS

The secondary aims of the study are to determine the effect of AZD6244 on overall survival (OS), objective response rate (ORR), progression free survival at 6 months, safety and tolerability.

8.1 Evaluation/ definition of Secondary Outcomes (where applicable)

These have been described in section 2.9.2.

8.2 Statistical Methods Used for Analysis of Secondary Outcomes

Overall Survival

For overall survival (OS) there will be fewer events than for the primary PFS outcome. Therefore the analysis of OS will be by logrank test with a p value of 0.1 considered significant. This will be presented alongside a Kaplan-Meier plot of all the data. The treatment hazard ratio and 90% confidence interval from an unadjusted (univariate) Cox model will also be presented.

Objective response rate

The objective response rate will be compared between the treatment groups using a chi square test. A p value of 0.1 will be considered significant. Odds ratios and 90% confidence interval will be given. If there are enough events to make it meaningful, a logistic regression analysis for objective

response rate using the randomisation stratifying factors as covariates giving the OR with 90% confidence interval will also be presented.

PFS at 6 months

PFS at 6 months will be compared between the treatment groups using the Kaplan-Meier estimate and error for each treatment group. A p-value, estimate of the difference and a 90% confidence interval for the estimate will be given.

Adverse events

All evaluable patients will be assessed for toxicity. Toxicity levels will be described using the NCI CTCAE (Version 4.0). SAEs and AEs will be summarised by incidence rates and classified by the worst severity grade observed by treatment arm.

Example table of all categorised AE's by treatment arm

	Docetaxel + AZD6244 (n= XX)		Docetaxel + Placebo (n= XX)	
	All	Grade ≥3	All	Grade ≥3
Event All Adverse events	No	%	No	%
	Vandetanib + WRBT (n= XX)		Placebo + WBRT(n= XX)	
AE (grade ≥3)	No	%	No	%
Diarrhoea Vomiting ……..				

Example table of CTCAE Worst Grade AE per patient by treatment group

CTCAE Worst grade	Docetaxel + AZD6244 (n= XX)	Docetaxel + Placebo (n= XX)	TOTAL
1	x	x	x
2	x	x	x
3	x	x	x
4	x	x	x
No AE reported	x	x	x
Total	XX	XX	XX

Example table of frequency of CTCAE Grade 3 or more AE per patient by treatment group

CTCAE grade ≥3	Docetaxel + AZD6244 n (%)	Docetaxel + AZD6244 n (%)	TOTAL
No	x (xx)	x (xx)	x (xx)
Yes	x (xx)	x (xx)	x (xx)
No AE reported	x (xx)	x (xx)	x (xx)
Total	XX	XX	XX

9. ANALYSIS OF OTHER AIMS

The exploratory outcomes are defined in 2.9.3. Analysis not done by CSM

9.1 Additional Exploratory Analysis Not Specified Prior to Receiving Data

Any analyses not specified in the analysis plan will be exploratory in nature and a significance level of 0.05 will be used to declare statistical significance. 95% confidence intervals will be presented. The exploratory nature of the analysis and the indication for carrying out the analysis will be described in any publication or presentation.

9.2 Statistical methods used for the post hoc analysis of IPI and NRAS mutation status

- Ipilimumab

During the course of the DOCMEK study Ipilimumab started to be used after the failure of the DOCMEK treatment. Hence we need to describe its use.

Ipilimumab drug use will be summarised for each treatment arm.

- NRAS

The main analysis for NRAS will include the per-protocol (PP) sample. Since the NRAS is not available on all randomised, an analysis on the ITT sample is not relevant. A sensitivity analysis will be done on the PP sample minus those found to have a BRAF mutation on retesting.
Baseline characteristics will be described for both treatment arms. A Kaplan Meier plot by NRAS mutation status for PFS and OS will be presented. Six month PFS and OS estimates will be obtained from the KM plot and presented with a 95% confidence interval.

The prognostic impact of NRAS mutation status on PFS and OS will be assessed by adding an interaction term with treatment in the Cox model adjusting for stratification variables.
The hazard ratio for the treatment effect will be obtained from the interaction model and will be presented with a 95% confidence level. Significance level of 0.05 will be used to declare statistical significance. A Kaplan Meier plot by NRAS mutation status and treatment for PFS and OS will be presented.

The proportional hazards assumption will be assessed using Schoenfeld residuals and log cumulative hazard plot.

10. SERIOUS ADVERSE EVENTS

Any adverse event occurring from randomisation until the calendar time point 3 months post the last patient recruitment will be recorded.
Serious adverse events are defined as those that are fatal, life threatening, disabling or require hospitalisation or prolongation of hospitalisation. A comparison of serious adverse events between the AZD6244 treated and placebo groups will be assessed by examination of 95% confidence intervals for the difference in incidence. An overall category for any serious adverse event will also be compared. The analysis will be conducted in the intention to treat population. A comparison of adverse events will be made as part of the safety and tolerability secondary aim (see section 8.2)

Example table of summary table of incidence rates categorised SAE's by treatment arm

SAE Event description	Docetaxel + AZD6244 (n=xx)	Docetaxel + Placebo (n= xx)	TOTAL
e.g Febrile Neutropenia			
Total			

Example table of detailed summary of SAE's by treatment arm

Docetaxel + AZD6244 (n=xx)				Docetaxel + Placebo (n= xx)			
SAE log number	SAE Event description	Severity	Outcome	SAE log number	SAE Event description	Severity	Outcome
SAEXXXX				SAEXXXX			
Total							

11. REFERENCES

1. Ascierto PA et al. (2013). MEK162 for patients with advanced melanoma harbouring NRAS or Val600 BRAF mutations:a non-randomised, open-label pahse 2 study. Lancet. S1470-2045(13)

12. DOCUMENT HISTORY

Ver	Date	Who	Comments
0.1	25 Nov 2010	SBL	First version
0.2	5 Jan 2011	SBL	Second version. Sent to Linda Collins, Cheng Han and Mark Middleton
0.3	21Feb2012	MS	Updated some sections with tracked changes
0.3	26Mar2012	MS	Updated section 4
0.3	11April2012	MS	Clean version of SAP, for SBL review
0.4	20April2012	MS	SBL reviewed 0.3 manually MS updated new version 0.4, with SBL comments.
0.5	30May2012	MS	Update the rest of SBL's comments
1.0	01June2012	MS	Updated
1.1	20June2012	MS	Updated following SBL's comments highligted in Yellow.
2.0	13Aug012	MS	Updated inline with protocol v4.0 24Jul2012
2.1	16Aug2012	MS	MS sent to MM, and asked to update contact details, now updated
2.2	30Jan2013	MS	Added new sections; 2.1.4 and 2.9.4 re NRAS analysis