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

Protocol Version & date	Version 6.0, 29 Jul 2014
OCTO Protocol No:	OCTO_015
REC Ref number:	10/H0604/59
EudraCT No.	2009-018153-23

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Interactive Web Response System (IWRS) – Randomisation and Drug Supply

https://www.cenduitsolutions.com

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2 Protocol Synopsis

Title of study:	A double blind randomised phase 2 trial of docetaxel with or without AZD6244 in wt *BRAF* advanced melanoma
Trial Name	DOC-MEK
Short Title	Docetaxel +/- AZD6244 in melanoma
Chief Investigator:	Professor Mark Middleton
Sponsor:	University of Oxford
OCTO Protocol No.	OCTO_015
EudraCT Number	2009-018153-23
REC Ref Number	
Aims:	To determine the efficacy and tolerability of the combination of the selective MEK inhibitor AZD6244 with docetaxel in patients with wild-type *BRAF* metastatic melanoma.
Scientific rationale	ERK1/2 is constitutively active in melanoma cells regardless of BRAF or NRAS status, presenting a potential target for treatment. Phosphorylated ERK is important for melanoma as it plays key roles in cell cycle entry, invasion and angiogenesis, as well as in resistance to apoptosis. AZD6244 is a highly selective allosteric inhibitor of MEK1/2. Treatment with AZD6244 leads to suppression of pERK levels in melanoma in a manner independent of BRAF and NRAS mutation status. Single agent therapy of melanoma with AZD6244 has been disappointing. In a phase 2 trial of AZD6244 6/104 patients achieved a partial response, including in a wt BRAF wt NRAS patient. AZD6244 and docetaxel have demonstrated synergy in a variety of animal xenograft models, including colorectal cancer (HCT-116, SW-620), NSCLC (A549) and melanoma (1025Lu).
Clinical rationale	Current treatment for metastatic melanoma is unsatisfactory. No agent has been shown to improve survival compared with supportive care, and classical cytotoxic agents produce responses in a minority (between 5 and 20%) of patients. Docetaxel has been evaluated in phase 2 trials in melanoma, producing response rates of 6-14%, in line with a number of cytotoxic agents. A phase 1 study of the combination of AZD6244 and docetaxel has recommended 75 mg BD of AZD6244 in combination with docetaxel 75 mg/m^2 q21 days for further study. Adverse events were consistent with the monotherapy toxicity profiles. To date the combination has been given to 12 patients with melanoma: 1 had a complete response; 1 a partial response; and 4 had stable disease beyond 6 cycles of treatment (18+ weeks) indicating clinical activity worthy of further study.
Primary Endpoint:	Progression free survival
Secondary Endpoints:	Objective response rate. Progression free survival at 6 months Safety of the AZD6244/docetaxel combination Overall survival.
Study Design:	A randomised, double-blind placebo controlled phase 2 trial. Randomisation 1:1 between treatment arms: either docetaxel 75mg/m^2 IV and placebo given bd, or AZD6244 75mg bd daily with docetaxel 75mg/m^2 IV. Docetaxel will be administered every 3 weeks for a maximum 6 cycles, but AZD6244/placebo may be continued beyond this, until disease progression.
Patient Numbers:	80 patients (40 per treatment arm) will be recruited to the study.
Target Population:	Chemonaive patients with metastatic cutaneous melanoma, with tumours wild type for BRAF.
Main eligibility / exclusion criteria	Inclusion Criteria • ≥ 16 years of age, written informed consent • Histologically confirmed, wild type BRAF, metastatic melanoma. • Unresectable Stage III or Stage IV metastatic melanoma. • Measurable disease as defined by modified RECIST criteria. • Eastern Cooperative Oncology Group (ECOG) Performance Score of 0-1. • Adequate haematological, hepatic and renal function.

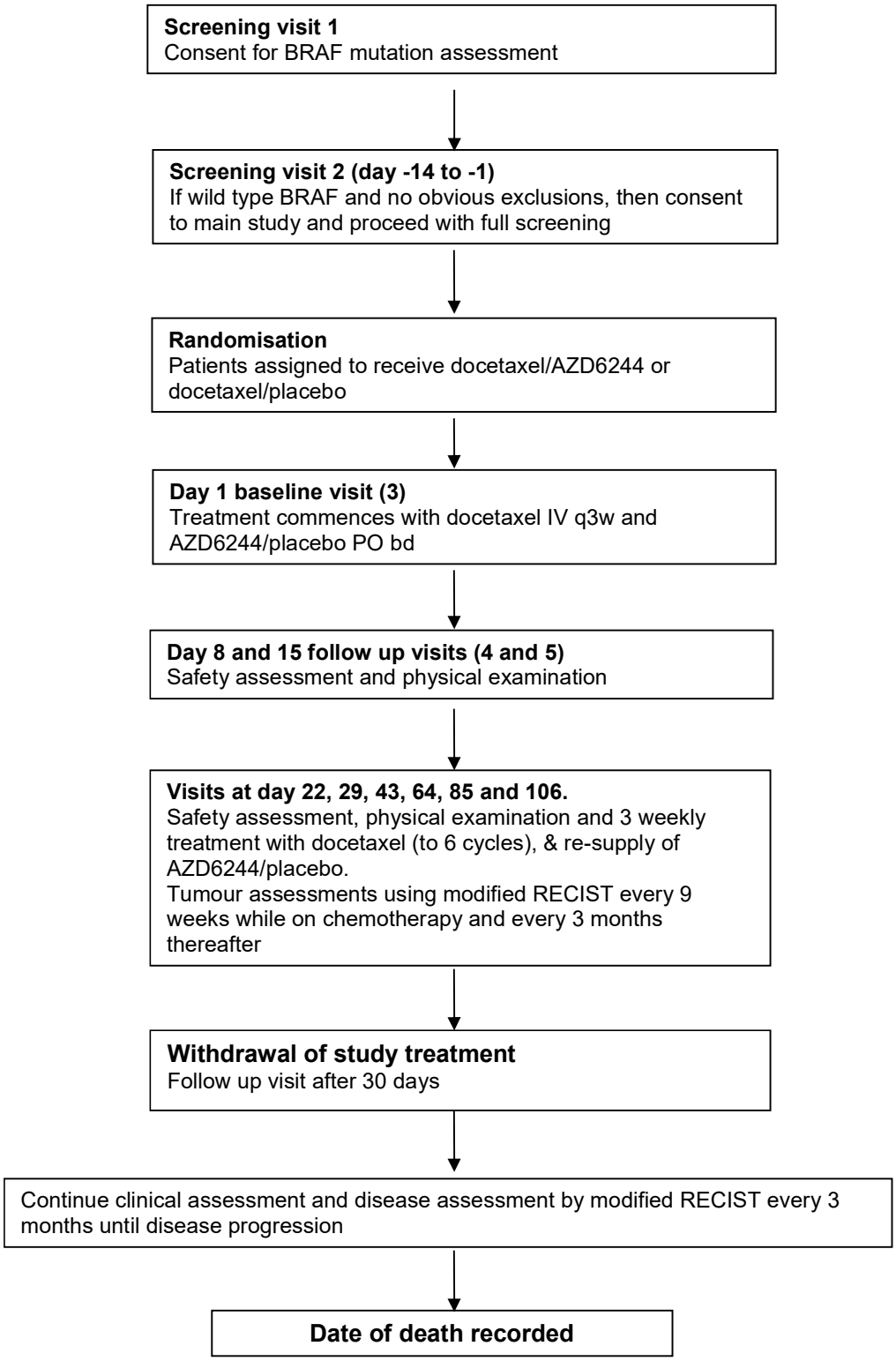
	• Adequate cardiac function (NYHA 0-1). • No evidence of brain metastases or treated brain metastasis with no evidence of relapse on cerebral MRI, or stable off treatment for 3 months. • Life expectancy > 12 weeks. • LDH ≤ 2xULN. Exclusion criteria • Radiotherapy or systemic melanoma therapy within 28 days prior to starting treatment. • Prior DNA damaging agents or BRAF or MEK inhibitors for metastatic melanoma • Pregnancy or breastfeeding woman • Grade ≥ 2 peripheral neuropathy at study entry • Known severe hypersensitivity to drugs formulated in polysorbate 80 • Ocular or mucosal malignant melanoma • Another active malignancy within the past five years • Clinically significant and uncontrolled major medical condition(s). • Refractory nausea and vomiting, chronic gastrointestinal diseases (eg, inflammatory bowel disease) or significant bowel resection that would preclude adequate absorption of AZD6244. • Taking medication known to interact significantly with CYP3A4.
Trial dose and administration	Docetaxel will be administered intravenously every 3 weeks at a dose of 75 mg/m^2. AZD6244 75mg or placebo will be given orally twice a day.
Duration on study	Patients will receive up to 6 cycles of docetaxel. Patients will receive AZD6244/placebo until disease progression or unacceptable toxicity.
Study Procedures and frequency	Complete physical examination at screening, on C1D1, C1D8, C1D15, C2D1, C2D8 and day 1 of every subsequent cycle. Blood for haematology and biochemistry will be taken at each of these visits. A 12 lead ECG will be performed at screening and day 1 of each cycle. Disease assessment by CT scanning using modified RECIST criteria at 9 and 18 weeks after randomisation, then every 3 months +/- 7 days until disease progression.
Criteria for evaluation	**Efficacy** Disease progression will be monitored by modified RECIST. **Safety** Safety and toxicity will be reported by using CTCAE (version 4). **Genotyping** BRAF mutation analysis will be performed on previously collected melanoma samples or on fresh biopsy specimens.
Statistical methods	The primary objective of this study will be to compare the efficacy of AZD6244 in combination with docetaxel, versus docetaxel alone, in first line patients with wt *BRAF* advanced cutaneous melanoma, by assessing progression free survival. Analysis will be performed when approximately 58 progression events have occurred. If the true Hazard Ratio (HR) is 0.57 (likely to correspond to a 75% prolongation of PFS), this analysis will have approximately 80% power to demonstrate a statistically significant difference for PFS, assuming a 1-sided 10% significance level.
Study Site(s)	Between 15 and 20 centres across the UK, under the auspices of the NCRI Melanoma Clinical Study Group
Duration of recruitment	Approximately 12 months
End of study	Last patient last visit
Funding:	The study will be funded according to the terms of the NCRN-AZ alliance, with AstraZeneca underwriting the excess treatment costs of docetaxel used in the study.

2.1 Schedule of Events

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			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).
[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.

2.2 Study Flow Chart



3 INTRODUCTION

In the developed world the incidence of melanoma has been increasing, with the highest noted in the southern hemisphere. In the UK, melanoma rates have risen more than any other cancer. Melanoma affects over 10,000 people every year and now represents the most common cancer in young adults. Early detection of melanoma leads to treatment in the form of surgical excision, but the disease metastasises in approximately 15% of patients. Current treatment for metastatic melanoma is unsatisfactory. No agent has been shown to improve survival compared with supportive care, and classical cytotoxic agents produce responses in a minority (between 5 and 13%) of patients. Despite these dismal figures dacarbazine remains the standard of care. Docetaxel has been evaluated in phase 2 trials in melanoma, producing response rates of 6-14% (Aamdal et al., Eur J Cancer 30A: 1061), in line with a number of cytotoxic agents.

One of the most important developments in melanoma has been the discovery that over 40% of patients harbour activating mutations in BRAF, principally V600E, an observation confirmed in a recent phase 2 clinical trial population (Board et al, Br J Cancer 101:1724). Recently, promising results have been observed with PLX4032, an agent targeting the activating V600E mutation in BRAF. In an early phase trial 25 of 38 patients with V600E BRAF responded to treatment at pharmacodynamically active doses (Chapman, European Journal of Cancer Supplements, Vol. 7, No 3, September 2009, Page 5). PLX4032 is now being evaluated in patients with metastatic melanoma harbouring mutated oncogenic BRAF in an international phase 3 trial.

New therapies are still needed for melanoma, as the utility of PLX4032 and related drugs remains uncertain until definitive trial results are available. Even if these bear out the early promise outlined above, effective therapy for the ~60% of patients without the V600E BRAF mutation will still be lacking.

3.1 Docetaxel mechanism of action

Docetaxel acts by promoting the assembly of tubulin into stable microtubules and inhibits their disassembly which leads to a marked decrease of free tubulin. Subsequent pathways to cell death are unclear and vary between cell types. In melanoma cells docetaxel induces apoptosis via pathways that are dependent on activation of caspase-2, which initiates mitochondrial dependent apoptosis by activation of Bax (Mhaidat et al., Mol Cancer Ther 6:752). Docetaxel induces activation of both JNK and ERK1/2, but not p38 mitogen-activated protein kinase or Akt kinases. Apoptosis is dependent on activation of JNK, which is required for phosphorylation and inactivation of bcl-2 and activation of Bax. Conversely, activation of ERK1/2 results in degradation of the BH3-only protein Bim and phosphorylation of Bad, inhibiting apoptosis (Mhaidat et al., Clin Cancer Res 13:1308). Taxane resistance can occur as a result of constitutive and/or drug-induced activation of the Ras-raf-MEK-ERK axis.

3.2 AZD6244 and ERK activation

ERK1/2 is constitutively active in melanoma cells regardless of their BRAF or NRAS status, presenting a potential target for treatment in this population. Phosphorylated ERK is important for melanoma because it plays key roles in cell cycle entry, invasion, and possibly angiogenesis, as well as in resistance to apoptosis (Smalley, Int J Cancer 104: 527). AZD6244 is a highly selective allosteric inhibitor of MEK1/2. Treatment with AZD6244 leads to suppression of pERK levels in melanoma in a manner independent of BRAF and NRAS mutation status (Haass et al., Clin Cancer Res, 14:230). Single agent therapy of melanoma with AZD6244 has been disappointing. In a phase 2 trial of AZD6244 6/104 patients achieved a partial response (Dummer et al., Proc ASCO 2008), including in a wt BRAF wt NRAS patient. A randomized phase 2 trial (NCRN063) is exploring AZD6244 in combination with dacarbazine in mutant BRAF melanoma.

3.3 AZD6244 and docetaxel

Our interest is in exploring the potential for MEK inhibition to overcome taxane resistance in melanoma. AZD6244 and docetaxel have demonstrated synergy in a variety of animal xenograft models, including colorectal cancer (HCT-116, SW-620 **figure 1**), NSCLC (A549) and melanoma (1025Lu **figure 2**) (Wilkinson et al., AACR 2008, abstract 4012).

Figure 1. Effect of AZD6244 and/or docetaxel in a SW620 colorectal cancer xenograft model

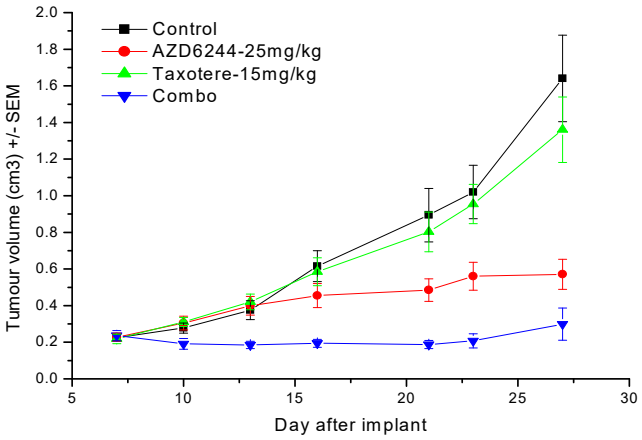
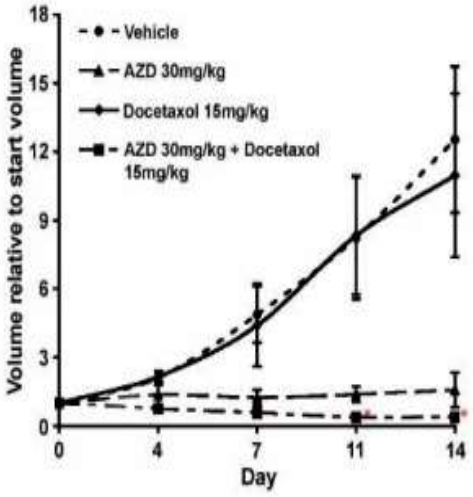


Figure 2. Effect of AZD6244 (30mg/kg daily po) and/or docetaxel (15mg/kg iv 3x per week) in a 1205Lu melanoma xenograft model (from Haass, ref above)



3.4 Justification for the doses to be used

A phase 1 study of the combination of AZD6244 and docetaxel has been conducted (AstraZeneca study D1532C00004). The 75 mg BD dose of AZD6244 in combination with docetaxel 75 mg/m^2 q21 days was recommended for further study. The most frequently reported adverse events were diarrhoea, fatigue, nausea, peripheral oedema, rash, vomiting, mucosal inflammation, neutropenia and constipation. Adverse events were consistent with the monotherapy toxicity profiles. To date the combination has been given to 12 patients with melanoma: 1 had a complete response; 1 a partial response; 4 had stable disease beyond 6 cycles of treatment (18+ weeks) indicating clinical activity worthy of further study.

4 Study Design

This is a randomised, double-blind, placebo-controlled multi-centre study. Eighty patients (forty in each of two arms) will be randomised with stratification for M stage (M1c vs M1a, M1b or M0) and performance status (0 vs 1). Patients will receive docetaxel with placebo or docetaxel with AZD6244.

Clinical study Objectives and Endpoints

Primary objective	Endpoints
To assess the efficacy of AZD6244 in combination with docetaxel, compared with docetaxel alone, in first line patients with wild type BRAF advanced malignant melanoma	Progression free survival
Secondary objective	**Endpoints**
To further assess the efficacy of AZD6244 in combination with docetaxel, compared with docetaxel alone, in first line patients with wild type BRAF advanced malignant melanoma	Overall survival (OS). Objective response rate (ORR) Progression free survival at 6 months (PFS)
To assess the safety and tolerability of AZD6244 in combination with docetaxel compared with docetaxel alone.	Adverse events using CTCAE v4.0 Vital signs and weight Biochemistry, haematology and urinalysis Physical examination ECG
Exploratory objectives	**Endpoints**
To assess the impact of tumour characteristics on response to docetaxel therapy with or without AZD6244	Immunohistochemistry of proteins in the MAPkinase pathway Genotyping of tumours

5 Patient Selection

The Investigator will determine patient eligibility based on the following criteria:

5.1 Screening for BRAF mutation

Patients will be eligible for screening for BRAF mutation status provided that:

1. They give written informed consent to screening for the BRAF mutation.
2. They are able to provide a tumour sample or are willing to have a fresh biopsy taken.
3. The Investigator anticipates that there is a reasonable expectation that they will satisfy the inclusion criteria in 5.2 below (NB formal screening for the main study should not be performed until the BRAF status of the patient is known).

Patients whose BRAF mutation status is already known through screening for, or participation in, previous studies, and who are known to be wt may proceed directly to screening for the main study. Otherwise mutation status will be assessed centrally in Oxford (see section 8.1).

5.2 Entry into the main study

5.2.1 Inclusion criteria

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

4. Aged ≥ 16 years
5. 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 section 8.1).
6. Unresectable stage 3 or 4, histologically proven cutaneous or unknown primary melanoma

7. At least 1 lesion, not previously irradiated, that can be accurately measured on CT or MRI as defined by modified RECIST criteria
8. ECOG performance score of 0 or 1.
9. Life expectancy of at least 12 weeks.
10. 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.
11. 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

5.2.2 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 appendix 3).

5.3 Patient screening and enrolment

Patients will be recruited from those referred to oncology services for management of advanced melanoma. Screening and study enrolment logs will be maintained by each site clinical study team. Before entering a patient onto the study the Principal Investigator or designated representative will confirm eligibility. If in any doubt the Oncology Clinical Trials Office must be consulted.

Patients will be randomised using an IWRS (see section 8.4)

5.4 Randomisation of patients

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). Every effort should be made to ensure that only eligible patients are randomised. If a patient is randomised in error, the study site should contact OCTO as soon as possible and if necessary treatment should be stopped. Patients randomised in error should be followed up for disease progression and for survival. For patients randomised in error, and who do not start study treatment, replacement patients will be recruited and randomised.

6 Investigational agents

The Investigational Medicinal Products in this trial are docetaxel, AZD6244 and Placebo. Docetaxel (Taxotere)[7] has a Marketing Authorisation for the treatment of several cancers (as described in the Summary of Product Characteristics) but is not authorised for use in melanoma. It is therefore being used as an IMP in this trial. AZD6244 is a new chemical agent developed by AstraZeneca, and is provided in capsule form. Placebo capsules are supplied by AstraZeneca.

6.1 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 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 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 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.

6.2 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 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

[7] Although Taxotere is listed in the protocol it is acceptable to use generic docetaxel now that it is available

up. Patients are permitted to continue to take AZD6244/placebo until they experience disease progression, in the absence of significant toxicity. If any patients are still on AZD6244/placebo at the time the final analysis is performed and the study is unblinded, any patients who are in the active arm will be offered the opportunity to continue on open label AZD6244. Any patients who are on placebo will be taken off IMP and offered standard care.

The end of study assessment will take place 30 days after the last AZD6244/placebo administration. If any adverse events attributable to either of the study drugs are still present, then the patient will be followed up appropriately until resolution or stabilisation of the AE(s), unless the patient starts another anti-tumour treatment.

If patients have not experienced disease progression at the time of the end of study assessment every effort should be made to follow them until disease progression, or the start of another anti-tumour therapy.

6.3 Criteria for Re-Treatment and Dose Reductions

Patients may receive second and subsequent doses of docetaxel on the scheduled day of treatment provided that they have an absolute neutrophil count >1.5x10^9/L and a platelet count >100x10^9/L, and no drug-related non-haematological toxicity of grade 3 or above.

6.3.1 Dose reduction of docetaxel.

Adverse events considered related to the administration of docetaxel are listed in the relevant product information sheet. A reduction in the dose of docetaxel should be considered if any of the following apply in the preceding cycle:

- Grade 3 or 4 neutropenia complicated by sepsis (temperature >38.5^{o}C or documented infection),
- Grade 4 neutropenia > 7 days duration,
- Grade 4 thrombocytopenia, or grade 3 thrombocytopenia complicated by haemorrhage,
- Grade 3 or 4 non-haematological toxicities that cannot be adequately controlled by optimization of supportive therapy (except fatigue of less that 2 weeks duration, changes in alkaline phosphatase and LDH, hyperglycaemia related to temporary steroid use and alopecia),
- Grade 3 or 4 peripheral sensory neuropathy of greater than 2 weeks duration.
- >2 week delay in re-treating with docetaxel

Treatment should not be reintroduced until the toxicity has resolved to grade 1 or less. Where there is a delay in re-treating with docetaxel subsequent visits will be defined by the start of each cycle of treatment (e.g. visit 9 would still be at the start of cycle 4, and later than the planned day 64). However scan times do not shift and continue in accordance with the randomisation date rather than cycles of treatment received.

In the case of neutropenic sepsis or grade 4 neutropenia greater than 7 days, docetaxel can be restarted at the full dose, when appropriate but with G-CSF support (centres should follow local guidelines). If neutropaenia recurs despite G-CSF, then the docetaxel should be reduced to 50 mg/m^2. If G-CSF support cannot be offered local policies for support will apply. If the neutropaenia then recurs then the docetaxel should be stopped.

In the case of other toxicities, a dose reduction in docetaxel to 50 mg/m^2 should be applied. No further dose reductions in docetaxel are permitted in the study.

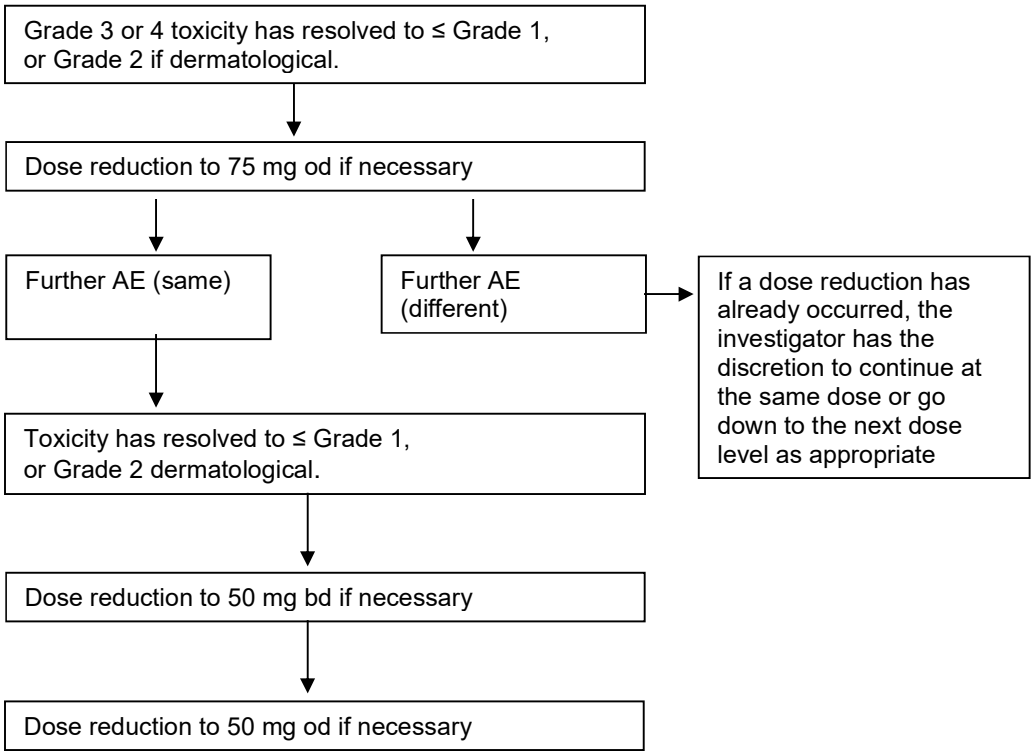
6.3.2 Dose reduction of AZD6244/placebo

Adverse events considered related to AZD6244 are fatigue, dermatitis (acne form), diarrhoea, nausea and periphery oedema. More detail can be found in the Investigator Brochure.

Treatment with AZD6244 should be withheld for any grade 3 or 4 (CTCAE criteria) or otherwise intolerable toxicity that cannot be adequately managed with optimal supportive care, if considered related to the study drug.

Treatment may be resumed once the toxicity improves to CTCAE grade 1 or baseline, or in the case of a skin rash to CTCAE grade 2. At the discretion of the Investigator, treatment can resume at the same dose: however if this is not likely to be tolerated then the dose should be reduced in the following stepwise manner, from 75mg b.d. to 75 mg o.d. to 50 mg b.d. to 50 mg o.d. If the drug is not tolerated at this level then the drug should be discontinued. The scheme for dose reductions is summarised overleaf.

NB once a dose reduction has occurred then the patient must remain at that dose and not be increased back to a previous dose level.



6.4 Concomitant medication and non-drug therapies

Concomitant therapies may be given as medically indicated, and will be documented at each follow up visit. However the following advice should be noted;

- Patients should avoid changing any drugs that may affect the metabolism of AZD6244 or docetaxel, particularly CYP3A4 and CYP1A2 inhibitors and inducers, unless considered to be in the best interests of the patient.
- Patients should avoid taking Vitamin E in doses that exceed 100% of the RDA (15mg).
- Patients on coumarin anticoagulants such as warfarin should have careful INR monitoring for the duration of the study.
- Patients should not have live attenuated or yellow fever vaccines. However, administration of the seasonal influenza and H1N1 ('swine flu') vaccines is not contraindicated.
- Patients should take care with sun exposure and take adequate precautions.

Steroid and anti-emetic premedication for administration of docetaxel should be given in line with local policy. ***For example****, dexamethasone 8mg twice a day may be given on the day before, day of and day after treatment with metoclopramide 10 mg to 20 mg tds.*

6.4.1 Conditions for palliative radiotherapy

The patient may have palliative radiotherapy while on study for symptomatic purposes providing that the AZD6244 is stopped for 3 days prior to and following treatment. The field should be as small as possible and not involve more than 20% of the bone marrow. The symptoms should be investigated to ensure that they do not constitute progressive disease. The lesions will no longer be evaluable for the purposes of the study, and if there is no longer disease that can be measured using modified RECIST following radiotherapy, then the patient should be followed for progression and overall survival only.

6.4.2 Prohibited medication

Patients should not be prescribed any other anti-cancer or investigational drugs while participating in this study

6.4.3 Management of overdose

To date, no subject has reported an overdose with AZD6244. There is currently no known antidote with AZD6244. Patients should be admitted for careful monitoring, and management should be supportive and tailored to symptoms as they arise.

If a patient does overdose, either accidentally or deliberately, this should be reported as an AE regardless of whether the patient experienced symptoms.

Overdosing with Docetaxel should be managed in line with local policy.

6.4.4 Management of hypersensitivity reactions

Hypersensitivity to docetaxel is a recognized complication, and may present with hypotension, facial flushing, back pain, dyspnoea, laryngeal and facial oedema and urticaria. Emergency management should be in line with local policy. The docetaxel should be stopped, and oxygen, adrenaline, hydrocortisone, antihistamines and appropriate ventilatory and circulatory support administered if necessary.

Depending on the severity of the reaction, at the Investigator's discretion and with appropriate monitoring and availability of resuscitation equipment, the patient may be rechallenged with docetaxel following a hypersensitivity reaction. The following rechallenge schedule may be adopted

- Dexamethasone 20mg iv 3 hours before administration on the day of treatment and 20mg iv 30 minutes prior to docetaxel administration
- Ranitidine 50 mg iv 30 minutes prior to docetaxel
- Chlorphenamine 10mg iv stat 30 minutes prior to docetaxel.
- Docetaxel given at 10% of the rate ie 25 ml per hour for 2 hours. If no further reaction is seen, then the rate may be increased to 50 ml per hour for 1 hour, then 75 ml per hour, then 100 ml per hour to complete the infusion.

If less than 10% of the dose was administered initially, then rechallenge may take place with the full dose of docetaxel. If more than 10% was administered then the chemotherapy should be represcribed with an appropriate dose reduction. If the rechallenge is more than 72 hours after the initial dose, then haematology and biochemistry needs to be reassessed to determine suitability.

On subsequent cycles following a rechallenge the same schedule should be followed in line with local policy.

If hypersensitivity to docetaxel recurs despite full premedication then the docetaxel should be stopped.

6.4.5 Management of skin toxicity

The skin toxicity seen with AZD6244 has yet to be fully investigated. The management of skin toxicity is based on the consensus guidelines produced for other targeted agents thought to produce a similar pattern of skin toxicity.

Grade	Action
Grade 1	Regular emollients and oatmeal based creams eg Aveeno Topical steroids e.g. 1% hydrocortisone Topical antibiotics e.g. clindamycin gel Oral antihistamines for itch Avoid sun exposure
Grade 2	Continue above plus consider topical pimecrolimus Oral antibiotics i.e. doxycycline 100 mg bd
Grade 3	Stop AZD6244 and allow rash to resolve to grade 2 or better. Consider dose reduction as outlined in the algorithm in 6.3.2. Consider superinfection eg staph aureus, take swabs and consider oral antibiotics or topical mupirocin. Consider oral steroids, prednisolone 20mg daily in severe cases

6.5 Patient evaluability

All patients who receive at least one dose of docetaxel and/or AZD6244/placebo and who have post-dose data available will be evaluable for the safety analysis. Efficacy will be analysed on an intention-to treat-basis and therefore any patient who is randomized within the trial will be included in the analysis.

7 Pharmaceutical Information

7.1 IMP Supply

AZD6244/placebo will be supplied, appropriately labelled in accordance with all applicable regulatory requirements, by AstraZeneca to study sites and dispensed by the Pharmacy Department in the appropriate hospital trust. Docetaxel will be sourced locally in the same way as standard treatment and prescribed in accordance with local regulations.

A patient's first bottle will be allocated and shipped at randomisation. Resupplies will be managed through an Interactive Web Response System (IWRS). The web based system will facilitate randomisation to treatment, stratification and automated supply management of the AZD6244/placebo to the sites. Subsequent patient study medication assignment will also be managed through the IWRS.

Any patients who remain on active treatment once the final analysis has been performed will be allocated open label bottles of AZD6244. The open label bottles of AZD6244 will not be managed through the IWRS and will be dispensed by the Pharmacy Department in the appropriate hospital Trust in quantities determined by the Investigator. Sites will request re-supply of open label AZD6244 by contacting the trial team in OCTO.

The cost of Docetaxel will be reimbursed as detailed in the Clinical Trial Agreement between Sponsor and NHS Trust.

7.1.1 Handling and storage

Only patients enrolled in the trial may receive the trial drug supplies in accordance with this protocol and under the supervision of the Investigator. All supplies must be stored in a secure, limited access storage area.

7.2 Preparation

7.2.1 Formulation, Method of Reconstitution and stability

AZD6244/placebo will be supplied as 25 mg Hyd-Sulfate capsules in white high density polyethylene (HDPE) bottles. At each visit patients will receive sufficient capsules for treatment until the next scheduled visit.

Docetaxel is formulated as a concentrate for solution for infusion or as a concentrate and solvent for solution for infusion depending on the brand/generic form. The concentrate is a clear colourless,to pale yellow or pale yellow to brownish yellow solution depending on the brand/generic form.Docetaxel will be reconstituted in 250 ml of 0.9% Sodium Chloride or 5% glucose in line with local policies (refer to the instructions in the

SmPC for the particular brand/generic form being used at site). Once reconstituted, docetaxel to be handled as per local practice.

7.2.2 Labelling

The responsible Pharmacy will ensure that docetaxel supplies are appropriately labelled to give the following information and in accordance with all applicable regulatory requirements.

Batch number
Active medication strength
Dosing instructions
Storage instructions
Investigator contact address
Name of sponsor
“For clinical trial use only” and “Keep away from children”

Note that emergency contact details will be supplied to the patient separately.

7.2.3 Administration

AZD6244/placebo is administered orally as three 25 mg capsules in the morning and three 25 mg capsules in the evening. AZD6244/placebo must be taken on an empty stomach (no food or drink for 2 hours before or 1 hour after treatment) with 240 ml of water. Doses should be taken 12 hours apart where possible. The dose can be taken up to 3 hours after the scheduled time. If missed, the dose should be ignored and the next dose taken at the scheduled time.

Docetaxel is administered into a peripheral vein over 1 hour.

7.2.4 Vein Extravasation /Accidental Spillages and Occupational Safety

Vein extravasation and accidental spillages should be dealt with according to hospital policy. Docetaxel is an exfoliant cytotoxic agent and likely to cause inflammation and skin shedding but not deep tissue damage. The product is not expected to pose an occupational safety risk to site staff under normal conditions of use and administration.

7.3 Drug accountability

The Principal Investigator is responsible for investigational product accountability, reconciliation, and record maintenance throughout the course of the study. This responsibility may be delegated to designated pharmacy staff who must maintain accurate records of all trial drug receipts from the supplier, dispensing to trial patients, and the disposal of all unused drug. This inventory must be available for review by representatives of the sponsor, Regulatory Authority or Chief Investigator on request.

Empty or partially used vials or returned unused capsules will be properly disposed of by pharmacy in accordance with local practice.

On completion of the trial, the Chief Investigator (or designee) will instruct pharmacy in the arrangements for the destruction of any unused study drug.

8 Trial assessments and procedures

A summary of the study assessments and procedures is given in section 2.1. Details of all protocol evaluations and investigations will be recorded in the patient medical record for reconciliation with the study Case Record Folder.

8.1 BRAF mutation screening

The consent process will be conducted in a stepwise manner. Patients will be given two separate consent forms. The first will outline the principles and rationale of evaluating BRAF mutation status (Consent Form A). In order to limit the time that patients have to wait to obtain their mutation status, and in recognition that this usually involves sourcing archival biopsy material, they will be permitted to give consent to mutation

screening without the usual 24 hour period for consideration, if they so desire. At this visit patients will be asked to provide a 10mL blood sample (collected in EDTA) for genotyping (Consent Form B).

Patients submitting to mutation screening will be logged with the Oncology Clinical Trials Office in Oxford in order to obtain a screening number before a sample is sent. A sample from their tumour will be dispatched to:

DOC-MEK
Sample Handling Laboratory, Level 1
Oxford Cancer and Haematology Centre
Churchill Hospital
Oxford
OX3 7LE

The sample should be accompanied by a despatch note detailing the screening number, any local identifying numbers and source of the tissue.

If a BRAF mutation is not detected from initial testing because the sample is deemed by the laboratory to be of poor quality (defined as poor fixation, less than 1% cells in sample, less than 50 cells in sample or inadequate DNA preparation), then one further sample may be analysed. If the results remain inconclusive then the patient will not be eligible for randomisation to the trial.

Where patients already have knowledge of their BRAF mutation status they must be logged with the Oncology Clinical Trials Office in the normal way in order to obtain a screening number. The report detailing their mutation status as wt for BRAF must be provided to the Office to allow them to proceed to screening for the main trial.

8.2 Mutation screening procedures

Once the patient has consented to the BRAF mutation screening phase demographic information and medical and surgical history will be recorded, but no further study-specific investigations will be made until mutation status is known.

8.3 Further Main Study screening procedures

Once the BRAF mutation status is known and shown to be wild type, then the following screening procedures will be performed within 14 days of dosing unless otherwise stated.

- Main study informed consent (Consent Form C)
- Disease staging
- Concomitant medications and previous anti cancer therapy
- Smoking status
- Tumour evaluation according to RECIST guidelines: CT scan of the chest abdomen and pelvis and other imaging of known sites of disease if appropriate. Baseline imaging must be performed within 28 days of commencing treatment
- CT or MRI of the brain.
- Assessment of ECOG performance status
- Physical examination and vital signs
- Blood samples for haematology and clinical biochemistry, including LDH
- Urinalysis
- Pregnancy test, if applicable
- Single ECG
- Overall assessment of patient eligibility

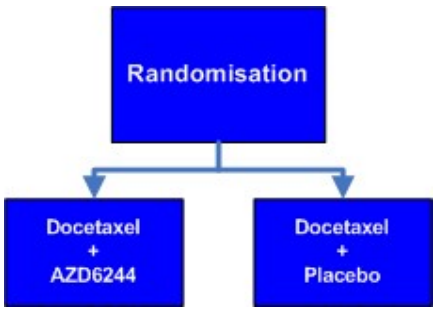
Collection of AEs commences after signing Consent Form C.

Eligible patients will then be randomised to the study.

8.4 Randomisation Procedures

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

Patients will be randomised to one of two arms as shown below:



Each patient will be assigned a unique identifying number and first bottle number for AZD6244/placebo.

8.5 Treatment Period

The following procedures will be performed throughout the treatment period. At each visit the Investigator will make an assessment of the clinical disease status of the patient to inform decision making, but objective radiological assessment will be as specified below:

Day 1 **Visit 3**	Physical Examination Vital signs Document Concurrent therapy Haematology – FBC Biochemistry* – to include: U&Es, LFTs and LDH Urinalysis Baseline AEs and performance status (PS) Administration of Docetaxel Dispensing of AZD6244/placebo ECGs pre dose and 2 hrs post dose
Day 8 **Visit 4**	Physical Examination, vital signs and PS Document Concurrent therapy Haematology – FBC Biochemistry* – to include U&Es, LFTs Urinalysis Record Adverse Events
Day 15 **Visit 5**	Physical Examination Vital signs Haematology – FBC Biochemistry* – to include U&Es, LFTs Urinalysis Record Adverse Events

Day 22 **Visit 6**	Physical Examination, vital signs and PS Document Concurrent therapy Weight Haematology – FBC Biochemistry* – to include: U&Es, LFTs and LDH Urinalysis Record Adverse Events Administration of Docetaxel Dispensing of AZD6244/placebo
Day 29 **Visit 7**	Physical Examination Vital signs Haematology – FBC Biochemistry – to include: U&Es, LFTs Urinalysis Record Adverse Events
Day 43 Visit 8 **Day 64 Visit 9** **Day 85 Visit 10** **Day 106 Visit 11**	Physical Examination, vital signs and PS Document Concurrent therapy Weight Haematology – FBC Biochemistry* – to include: U&Es, LFTs and LDH Urinalysis Record Adverse Events Administration of Docetaxel Dispensing of AZD6244/placebo Assessment of tumour response immediately before visit 9
Visit 12 +	Physical Examination, vital signs and PS Document Concurrent therapy Weight Haematology – FBC Biochemistry* – to include: U&Es, LFTs and LDH Urinalysis Record Adverse Events Dispensing of AZD6244/placebo
End of treatment	Physical Examination, vital signs and PS Document Concurrent therapy Weight Haematology – FBC Biochemistry* – to include U&Es, LFTs and LDH Urinalysis Record Adverse Events
30 days post treatment.	Physical Examination, vital signs and PS Document Concurrent therapy Weight Haematology – FBC Biochemistry* – to include U&Es, LFTs and LDH Urinalysis Record Adverse Events

* U and Es to include Sodium, Potassium, Calcium, Urea, Creatinine, Phosphate, and LFTs to include Bilirubin, Alkaline Phosphatase, ALT or AST, albumin, GGT and total protein.

8.6 Follow-up

Information will be sought on patient status at least every 3 months after cessation of all therapy and will be monitored for resolution of any toxicity including laboratory assessments as required. Disease assessment using modified RECIST will take place every 3 months until disease progression is documented. Once disease progression has occurred, then further clinical follow up is at the Investigator's discretion: for the purposes of the study survival status must be recorded every 3 months. Following unblinding and final analysis of the trial data, no further follow-up data will be collected for patients who have already been withdrawn from treatment.

If the patient reaches 12 months off treatment without evidence of disease progression by modified RECIST criteria, then CT and/or MRI scans can be performed according to local practice until disease progression is documented. Any patients who remain on active treatment following final analysis will be followed for adverse events only and no further data will be collected for the study. Sites will report any SAEs (apart from those that are exempt as per protocol) to OCTO until 30 days post last dose of treatment.

9 Early patient withdrawal

If a patient is withdrawn early the end of study assessments should be performed and recorded (as above) as soon as possible and ideally on the day the decision is made. Patients who withdraw from treatment without progressing should be followed until disease progression. The reasons for study withdrawal must be recorded in the medical records and CRF. Patients who are removed from study treatment due to AEs (clinical or laboratory) will be treated and followed according to accepted medical practice. All pertinent information concerning the outcome of such treatment must be recorded in the CRF.
The following are justifiable reasons for the Investigator to withdraw a patient from study:

- Unacceptable toxicity.
- Adverse event requiring discontinuation.
- Unforeseen events: any event that in the judgement of the Investigator makes further participation inadvisable.
- Withdrawal of consent.
- Serious violation of the study protocol (including persistent patient attendance failure and persistent non-compliance with the prescribed medication).
- Withdrawal by the Investigator for clinical reasons not related to the study.

With exception of withdrawal of consent (unless the patient agrees to the information being collected) patients should be followed for disease progression and overall survival.

Early patient withdrawal must be logged in the IWRS to ensure that drug resupplies are stopped.

9.1 Code break/Unblinding

The treatment code will be broken at trial closure for all patients. In the rare event that a patient requires emergency code break, site staff are to do the following;

During office hours (Monday to Friday, 9:00-17:00 - GMT/BST) contact OCTO on 0800 389 1629. The request will be reviewed by Chief Investigator (or his designee).

While waiting for a decision from the clinical review, treating clinicians should withhold the AZD6244/placebo and treat the medical problem in the most appropriate manner with all the supportive care required. It should always be assumed that the patient is on the active arm of the trial (i.e. receiving AZD6244).

If a codebreak is agreed OCTO staff will contact Fisher Clinical Services and obtain the relevant details. These will then be provided to the study site.

Patients who have had the treatment code broken will receive no further treatment in the study but will be followed up as per protocol. Code breaking should be avoided wherever possible.

10 Pharmacokinetic and Pharmacodynamic Assessments and correlative science

10.1 Pharmacokinetic (PK) Variable(s)

Pharmacokinetic assessments are not planned in this study.

10.2 Pharmacodynamic (PD) variables

Pharmacodynamic assessments are not planned in this study.

10.3 Tumour genotyping, protein analysis and germline genetics

Consent will be requested from patients to retain tumour samples for future research, once BRAF mutation status has been determined. This will not be a requirement for participation in the main study. In addition, patients will be asked to provide a specimen of whole blood for DNA extraction and future genetic analyses. 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.

Whole blood samples should be stored at -70^{O}C, and sent in batches as notified by OCTO to:

DOC-MEK, Sample Handling Laboratory, Level 1, Oxford Cancer and Haematology Centre, Churchill Hospital, Oxford, OX3 7LE.

11 Assessment of Safety

The Investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. 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. For serious adverse events not considered "probably related" to study drug, the Investigator will provide an "Other" cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded. All adverse events will be followed to a satisfactory conclusion.

Should an Investigator become aware of any drug-related SAEs following withdrawal from the study, these must also be reported as stated below.

All adverse events reported into OCTO will be processed following OCTO standard operating procedures.

11.1 Adverse Event Definitions

11.1.1 Adverse Event

An Adverse Event or experience (AE) is 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. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse. An AE includes but is not limited to:

- Significant or unexpected worsening or exacerbation of the condition/indication under study thought by the Investigator to indicate lack of the expected treatment efficacy. N.B. disease progression per se is not an AE.
- A clinically significant worsening of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either IMP or a concurrent medication (overdose per se, whether accidental or intentional should not be reported as an AE/SAE).
- Other reportable events that must be treated as AEs are as follows:
- Any pregnancy occurring in a patient or a patient's partner during occurring within six months of the last trial agent administration. These should be reported (even if the patient was withdrawn from the study) in the same timelines as a serious adverse event (SAE). The outcome of a pregnancy should be followed up carefully and any abnormal outcome of the mother or the child should be reported.
- Any newly identified malignancy, occurring after first administration of study agent in subjects participating in this clinical trial.
- Any SAE that could be related to the protocol procedures, and which could modify the conduct of the trial.

Examples of an AE do not include a/an:

- Medical / surgical procedure (e.g., endoscopy, appendectomy) being performed for a pre-existing condition which was planned prior to study entry
- Situations where an untoward medical occurrence did not occur (social and/or convenience hospital admission).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

11.1.2 Adverse Drug Reaction (ADR)

An Adverse Drug Reaction is an AE which is considered to be causally related to any dose of the IMP. This means that a causal relationship between the IMP and the AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. An adverse drug reaction, the nature or severity of which, is not consistent with applicable product information is said to be an unexpected adverse drug reaction.

11.1.3 Serious Adverse Events (SAEs)

A Serious Adverse Event (SAE) is any AE, regardless of dose, causality or expectedness, that:

- **Results in death**
- **Is life-threatening**

*[**NOTE**: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.]*

- **Requires in-patient hospitalisation or prolongs existing inpatient hospitalisation**

*[**Note**: In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether hospitalisation occurred or was necessary, the AE should be considered serious.]*

- **Results in persistent or significant incapacity or disability**

*[**Note**: this definition means a substantial disruption of a person's ability to conduct normal life functions. It does include experiences of relatively minor medical significance or accidental trauma (e.g. sprained ankle) which do not constitute a substantial disruption.]*

- **Is a congenital anomaly or birth defect**
- **Is any other medically important event**

*[**Note**: A medically important event is defined as an event that may jeopardise the patient or may require intervention to prevent one of the outcomes listed above. Any new primary cancer must be reported as an SAE.].*

11.1.4 Disease-Related Events or Outcomes not requiring expedited SAE reporting

An event that is part of the natural course of the disease under study (i.e., disease progression or admission for standard treatment) should not be reported as an SAE. However, if the progression of the underlying disease is greater than that which would normally be expected, or if the Investigator considers that there may be a causal relationship between the IMP or protocol design/procedures and the disease progression, then it must be reported as per section 11.2 below.

11.1.5 Clinical laboratory abnormalities and other abnormal assessments as AEs and SAEs

Abnormal laboratory findings (e.g., clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g., ECGs, X-rays and scans) that are judged by the Investigator as clinically significant will be recorded as AEs or SAEs if they meet the definitions given above. By definition, **all grade 4 laboratory abnormalities will be reported as SAEs**. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the Investigator as more severe than expected for the patients condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

11.1.6 Determining adverse event causality

The relationship of an AE to docetaxel or AZD6244/placebo will be determined as follows:

Probably
• Starts within a time related to the study drug administration and • Cannot be reasonably explained by known characteristics of the patient's clinical state.
*Possibly
• Starts within a time related to the study drug administration and • A causal relationship between the study drug and the adverse event is at least a reasonable possibility.
Unlikely
• The time association or the patient's clinical state is such that the study drug is not likely to have had an association with the observed effect.
Unrelated
• The AE is definitely not associated with the study drug administered

** Note that unless otherwise defined, the term 'drug-related' includes 'possibly'*

The Investigator must endeavour to obtain sufficient information to determine the causality of the adverse event (i.e. relation to surgery, study drug, other illness, progressive malignancy etc) and must provide his/her opinion of the causal relationship between each AE and study drug. This may require instituting supplementary investigations of significant AEs based on their clinical judgement of the likely causative factors and/or include seeking a further opinion from a specialist in the field of the AE.

11.1.7 Expectedness

Expected AEs are AEs that have been assessed as expected events for the IMPs, based upon previous experience in man. AEs that are considered expected in this trial are based on data in humans. The list of expected AEs for the Investigational Medicinal Product(s) in this trial can be found in the protocol section 6.3.2 or the Summary of Product Characteristics (for docetaxel) and Investigator Brochure (for AZD6244).

11.1.8 Suspected Unexpected Serious Adverse Drug Reaction (SUSARs)

A SUSAR is a suspected, unexpected, serious adverse reaction. SUSARs therefore are suspected to be at least possibly related to the study agent and fulfil the definition of a SAE, the nature and severity of which are not consistent with the applicable product information. All SUSARs related to an IMP must be reported to the Medicines and Healthcare products Regulatory Agency (MHRA) and the Main REC within specified time periods.

In addition, other safety issues also qualify for expedited reporting where they might materially alter the current risk-benefit assessment of an IMP or be sufficient to change the IMP administration or the overall conduct of the trial. For instance:

- Single case reports of an expected serious adverse reaction with an unexpected outcome.
- An increase in the rate of occurrence 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 reported by the Investigator to the Sponsor.
- New event relating to the conduct of the trial or the development of the IMP likely to affect the safety of the subjects.
- In the event that a participant or his/her partner becomes pregnant whilst taking part in a clinical trial or during a stage where the fetus could have been exposed to the medicinal product (in the case of the active substance or one of its metabolites having a long half life). The pregnancy should be followed up by the Investigator (via the patient's healthcare professional) until delivery. If the pregnancy results in an abnormal outcome, which the healthcare professional considers might be due to the drug, this should be treated as an expedited report.

11.2 Expedited reporting of SAEs and SUSARs

The following SAE expedited reporting requirements apply regardless of the Investigator's assessment of the causality or expectedness of the SAE. All Serious AEs should be reported on the trial Serious Adverse Event Report Form (see SAE Report Form and completion guidelines).

Reports must be faxed within one working day of site staff becoming aware of event to:

The Oncology Clinical Trials Office (OCTO) - +44 (0) 1865 227038

Each separate episode must be recorded on a separate SAE Report Form. For example, if an AE resolves completely or resolves to baseline and then worsens again, this must be recorded as a separate AE. The NCI CTCAE Version 4.0 must be used to grade each AE, and the worst grade recorded.

The SAE Report Form must be completed as thoroughly as possible with all currently available details of the event and the Investigator's assessment of causality at the time of the initial report. The Investigator (or a medically qualified designee) must sign the form. To ensure the SAE report is forwarded within the designated time frames, the Investigator will not wait to receive additional information before sending the initial notification. The form will be updated when additional information is received.

If the SAE has not been reported within the specified timeframes, a reason for lateness must be added on the fax cover sheet when sending the SAE Report Form.
The Investigator team shall ensure that all SAE reports *(including follow-up reports of new information, responses to queries and changes to the assessment of expectedness or causality)* are transmitted to the trials office.

11.3 Safety reporting requirements and arrangements

The Annual Progress Report, as required by NRES, will be prepared by OCTO and submitted to the main REC within 30 days of the anniversary of ethical approval for the trial. Annual Safety Reports will be prepared by OCTO in collaboration with the Chief Investigator and submitted to the MHRA and main REC within 60 days of the anniversary of MHRA approval, as required.

Copies of the annual progress report and the annual safety report will be sent to the sponsor and to participating sites to forward to R and D as per local requirements.

11.3.1 Expedited Safety Reporting

OCTO is responsible for the identification and expedited reporting of SUSARs to the Medicines and Healthcare products Regulations Agency (MHRA) and the Main Research Ethics Committee (REC) as required under the applicable UK GCP legislation. Fatal or life-threatening SUSARs must be reported to the MHRA and the Main REC within 7 calendar days of the Sponsor receiving the report. Follow up information for fatal or life-threatening SUSARs must be reported to the MHRA and REC within 8 calendar days of submitting the initial report. All other SUSARs are reportable within 15 calendar days of receipt. Therefore expedited reporting of SAEs by the Investigator is crucial to the Sponsor meeting these timelines. The Chief Investigator will ensure that all Investigators are kept informed as new safety profile information becomes available.

11.3.2 Annual Progress and Safety Reports (ASRs)

The Oncology Clinical Trials Office is responsible for providing periodic trial progress reports as required to the Regulatory Authority, the Sponsor and Ethics Committee. Unless otherwise instructed, Annual Progress Reports will be submitted to the ethics within 30 days of the anniversary of the ethics favourable opinion and the ASR and Annual Safety Reports (ASR) will be submitted in parallel to the MHRA and responsible Research Ethics Committee within 60 days of the anniversary of the date of MHRA approval.

11.4 Recording adverse events at the study site

All reportable SAEs and ADRs (Adverse Drug Reactions) must be recorded on the patient CRF. All concomitant medications and any therapy used to treat the event must be recorded in the medical record. Copies of the original SAE Report Forms, together with the fax cover sheet and transmission confirmation (if available) will be filed in the Investigator Site File. Each SAE report must be entered into the SAE Log form held in the Investigator Site File.

11.5 Follow-up of serious adverse events

Follow up will continue until all the necessary safety data for the event has been gathered. Any serious adverse event that is ongoing when a subject completes his/her participation in the trial must be followed until any of the following occurs:

• The event resolves or stabilizes;

• The event returns to baseline condition or value (if a baseline value is available);

• The event is attributed to other agent(s) or to factors unrelated to study conduct.

If new or amended information on a previously reported SAE becomes available, the Investigator should report this to the Sponsor on a new SAE Report Form using the completion guidelines. In addition, the sponsor may make requests for further information to the study site at regular intervals. Requested follow-up information should be reported to in a timely manner and as soon as possible after receipt of the follow up request. For fatal or life-threatening SUSARs, follow-up information should be reported as soon as possible, as follow up for these cases is reportable to the MHRA and Main REC within eight calendar days of the initial report being sent.

12 Assessment of Efficacy

12.1 Measurement of disease

All patients must have at least 1 lesion that is measurable using RECIST in a field that has not previously been treated by radiotherapy. Disease must be measured according to modified RECIST given in Appendix 2.

12.2 Tumour assessment

A clinical and radiological evaluation of malignancy, as judged appropriate by the Investigator, and in line with the protocol, must be performed before starting the study treatment. The same methods that detect lesions at baseline will be used to follow these lesions throughout the study. To ensure compatibility, the radiological assessments used to assess response must be performed using identical techniques. Imaging based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumour effect of a treatment.

12.2.1 Baseline evaluations:

These will include radiological measurements of the extent of disease by CT scan, or MRI scan where applicable. Fluorescence angiography will be performed to evaluate the extent of any optical lesions. All areas of disease present must be mentioned (even if specific lesions are not going to be followed for response) and the measurements of all measurable lesions must be recorded on the scan reports. Any non-measurable lesions must be stated as being present. For clinical measurements, documentation by colour photography including a ruler to estimate the size of the lesion is recommended.

12.2.2 Evaluations during treatment and at off-study

Tumour assessment will be repeated as per the schedule given at sections 2.1 and 2.2, or more frequently if clinically indicated. All lesions measured at baseline must be measured at subsequent disease assessments, and recorded on the scan reports. All non-measurable lesions noted at baseline must be reported as present or absent.

The Principal Investigator must ensure that the radiologists are aware of the requirement to follow up and measure every target lesion mentioned at baseline and comment on the non-target lesions in accordance with modified RECIST criteria.

12.3 Tumour response

To be assigned a status of CR or PR, changes in tumour measurements must be confirmed by two consecutive observations. To be assigned a status of stable disease (SD), follow-up measurements must have met the SD criteria at least once and at least six weeks after study treatment is started.

Should rapid tumour progression occur before the completion of nine weeks treatment the patient will be classified as having early progression (EP).

Tumour response should be classified as “not evaluable” (NE), only when it is not possible to classify it under another response category, e.g., when baseline and/or follow-up assessment is not performed or not performed appropriately.

The applicable overall response category for each visit that includes disease assessment must be recorded in the medical record for inclusion in the CRF.

12.3.1 Other definitions of outcome

Toxic death:	Any death to which drug toxicity is thought to have a major contribution.
Early death:	Death during the first three weeks of treatment that is not a toxic death.
Progression free survival:	The interval from the day of randomisation until disease progression or death in the absence of RECIST progression.
Overall survival:	The interval between the day of randomisation and death.

13 Defining the End of Trial

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

It is the responsibility of the Chief Investigator to inform the Main REC, the Sponsor and the Regulatory Authority within 90 calendar days of the ‘end of the trial’ that the study has closed.

The sponsor and the Chief Investigator reserve the right to terminate the trial at any time. In terminating the study, they must ensure that adequate consideration is given to the protection of the patient’s best interests. In particular, where patients are still receiving AZD6244/placebo when the above conditions are met, consideration must be given to ensuring continued drug supply.

14 Statistical considerations

80 patients will be recruited to the study. A detailed statistical analysis plan will be drawn up prior to breaking of the blind. 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.

14.1 Safety

All patient receiving a study dose will be assessed for toxicity. Safety variables will be summarised by descriptive statistics, with patients grouped according to treatment received. SAEs and ADRs will be summarised by incidence rates and classified by the worst severity grade observed. Laboratory data will be presented by dose level at each observation time. Values outside normal limits will be identified and summarised by frequency distribution. Laboratory variables will be described using the NCI CTCAE (Version 4.0).

14.2 Patient evaluability

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 for response.

14.3 Analysis

The primary aim of PFS will be analysis by Cox Regression Analysis using the randomisation stratifying factors as covariates. A p value of ≤0.1 will be considered significant and worthy of a further trial.

14.4 Analysis timings

The primary aim will be analysed when we have all patients recruited, followed up for at least 3 months and 58 PFS events.
The final analysis of the secondary and post hoc aims will be completed as determined in the statistical report.

15 Trial Administration

15.1 Regulatory and ethical considerations

The Sponsor and Principal Investigator will ensure that this protocol will be conducted in compliance with the UK Clinical Trials Regulations[8], the ICH guidelines of Good Clinical Practice (GCP)[9] and the applicable policies of the University of Oxford. Together, these implement the ethical principles of the Declaration of Helsinki (1996) and the regulatory requirements for clinical trials of an investigational medicinal product under the European Union Clinical Trials Directive.

15.1.1 Ethical conduct of the trial and ethics approval

The Investigator will ensure that the protocol, patient information sheet, consent form, GP Letter and any other information that will be presented to potential trial patients (e.g. advertisements or information that supports or supplements the informed consent) are reviewed and approved by an appropriately constituted, independent Research Ethics Committee (REC).

8 The Medicines for Human Use (Clinical Trials) Regulations (S.I. 2004/1031) and any subsequent amendments to it.
9 ICH Harmonised Tripartite Guideline E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Step 5, adopted by CPMP July 1996.

15.1.2 NHS Research Governance and sponsorship

The Investigator is responsible for applying for local Trust management approval to conduct the trial in accordance with local arrangements and policies. Trust approval and indemnity must be confirmed in writing before patient recruitment commences at an Investigator site.

The University of Oxford will provide written confirmation of Sponsorship. The Chief Investigator will authorise the trial commencement once satisfied that all arrangements and approvals for the proper conduct of the trial are in place. A separate study delegation agreement, setting out the responsibilities of the Chief Investigator, the Oncology Clinical Trials Office and the Sponsor will be put in place between the parties.

15.2 Regulatory Authority approval

This study will be conducted under a UK Medicines and Healthcare Products Regulatory Agency (MHRA) Clinical Trials Authorisation (CTA). MHRA approval to conduct the study will be obtained prior to initiating the study.

15.2.1 Protocol amendments

Amendments are changes made to the research after a favourable ethical opinion has been given. A 'substantial amendment' is an amendment to the terms of the MHRA CTA application, the REC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of the investigational medicinal product(s) used in the trial.

Non-substantial amendments are those where the change(s) involve only minor logistical or administrative aspects of the study, such as a change in contact details.

The Chief Investigator shall determine whether an amendment is substantial with reference to current applicable guidance and policies. All substantial amendments will be submitted to the sponsor for approval. Once approval has been obtained from the sponsor the substantial amendments will be submitted to the responsible REC, the MHRA and the host (NHS) Trust for approval and/or for information as appropriate. Written documentation of the Ethics Committee 'favourable opinion' (and MHRA and Trust approval as deemed appropriate) must be received before a substantial amendment can be implemented. The only exceptions are for changes necessary to eliminate an immediate hazard to study patients.

It is the Chief Investigator's responsibility to update patients (or their authorised representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the patient's willingness to continue in the trial. The Chief Investigator must ensure this is documented in the patient's medical notes and the patient is re-consented.

15.2.2 Informed consent

It is the responsibility of the Investigator, or a person designated by the Investigator to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, anticipated benefits and potential hazards of the study. The content and process of obtaining informed consent will be in accordance with the applicable GCP Regulatory and ethical requirements. Consent will be obtained before any protocol specific procedures are performed.

Optional consent for additional research

Where suitable patients will be invited to allow their tumour biopsy sample to be used in future research and to provide whole blood for DNA extraction, but this will not be a requirement for participation.

15.3 Trial Monitoring and Quality Assurance

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.

15.4 Records retention

During the clinical trial and after trial closure the Investigator must maintain adequate and accurate records to enable the conduct of a clinical trial and the quality of the research data to be evaluated and verified. These essential documents (as detailed in Section 8 of the ICH GCP Guidelines) must be stored in such a way that ensures that they are readily available, upon request, to the sponsor or the Regulatory Agency, for the minimum period required by national legislation or for longer if needed. The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the host institution policy.

15.5 Patient confidentiality

All records identifying the patients will be kept confidential and to the extent permitted by the laws/regulations, will not be made publicly available. Only the patient number and patient initials will be recorded in the case report form. Before sending out any other document (e.g. a pathologist report, scan, copy medical record or study log) the Investigator site research team will check for and obliterate any information that could uniquely identify the patient. Study findings stored on a computer will be stored in accordance with local data protection laws. The Investigators will maintain a list to enable patients' records to be identified. The patients will be informed in writing that:

Members of the research team will need access to their records to collect information. Representatives of the sponsor, Chief Investigator, study monitors, Regulatory Agency and the Ethics Committee may inspect their medical records to verify information collected. All personal information made available will be handled in the strictest confidence and in accordance with local data protection laws. When the results of the study are published, the identity of the patients will remain confidential.

15.6 Completion of the Case Report Form (CRF)

A Case Report Form (CRF) will be completed for each patient enrolled into the trial. If a patient is withdrawn early, the reason will be noted on the CRF. If a patient is withdrawn from the study because of an AE, thorough efforts should be made to document the outcome. The CRF will not contain any source data. All appropriate laboratory data, summary reports and Investigator observations will be transcribed into the CRF from the relevant medical record(s).

OCTO staff will enter patient data into the database at regular intervals and raise data queries. Queries concerning the source data or medical interpretation will be resolved and documented by authorised members of the clinical study team. Corrections [whether to the source data or to data query listing for entry into the eCRF must only be made by striking out any errors, with a single stroke, and not by using correction fluid. The incorrect figure must remain visible and the correction should be initialled and dated by the person authorised by the Investigator to make the correction. A reason for the change or correction should be given as appropriate. This cycle will be repeated as necessary until the patient data are declared clean.

The Investigators (or their deputies) are responsible for ensuring the accuracy and completeness of the key trial data for their patients. They should sign the CRFs off prior to data lock and analysis. The Investigator approved CRFs will be archived with the trial master file.

15.7 Data and Safety Monitoring

An independent Data & Safety Monitoring Committee (DSMC) is now established for this trial, following a safety concern in another trial notified to us by AZ. The committee met soon after the safety concern was raised and 6 months later to assess the toxicity and SAE by treatment arm. The committee has endorsed the analysis plan outlined above.

15.8 Clinical study report

All clinical data will be presented at the end of the study on final data listings. The data manager and statistician will prepare a clinical study report based on the final data listings. The report will be submitted to the Investigator(s) for review and signature to confirm that it accurately represents the data collected during the course of the study. At this point the trial data will be locked for analysis and publication. The Chief Investigator will provide the Trial Steering Committee, sponsor, responsible Research Ethics Committee with a copy of the final clinical report once available.

15.9 Study funding

This trial is being organised by the Oncology Clinical Trials Office (OCTO) at the University of Oxford and is being funded by an educational grant from Astra-Zeneca. Any additional NHS clinical service support costs of patient care while on-study should be met by the host medical institution.

15.10 Indemnity

Arrangements for NEGLIGENT harm.
The University has arrangements in place to provide for harm arising from participation in the study for which the University is the Research Sponsor. NHS indemnity operates in respect of the clinical treatment which is provided.

Arrangements for NON-NEGLIGENT harm
The University has arrangements in place to provide for non-negligent harm arising from participation in the study for which the University is the Research Sponsor.

15.11 Publication policy

The Chief and Co-Investigators (the Investigators) will retain ownership of all data arising from this trial. The intention is to publish this research in a specialist peer reviewed scientific journal on completion of the study. The results may also be presented at scientific meetings and/or used for a thesis. The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the trial and retain final editorial control. Authors shall acknowledge the study sponsor and funding bodies as appropriate.

16 References

Aamdal et al 1994
Docetaxel (Taxotere) in advanced malignant melanoma: a phase II study of the EORTC Early Clinical Trials Group. Eur J Cancer 30A:1061-1064.

Board et al 2009
Detection of BRAF mutations in the tumour and serum of patients enrolled in the AZD6244 (ARRY-142886) advanced melanoma phase II study. Br J Cancer 101:1724-30.

Chapman et al 2009
Early efficacy signal demonstrated in advanced melanoma in a phase I trial of the oncogenic BRAF selective inhibitor PLX4032. Eur J Cancer 7(3) supplement page 5.

Dummer et al 2008

AZD6244 (ARRY-142886) vs temozolomide in patients with advanced melanoma: an open label, randomised, multi-centre phase II study. Presented at the 44th American Society of Clinical Oncology Annual Meeting, 30 May–3 June 2008. Abstract number 9033.

Haass et al 2008
The Mitogen-Activated Protein/Extracellular Signal-Regulated Kinase Kinase inhibitor AZD6244 (ARRY-142886) induces growth arrest in melanoma cells and tumor regression when combined with docetaxel. Clin Cancer Res 14:230-239.

Mhaidat et al 2007 (1)
Docetaxel-induced apoptosis in melanoma cells is dependent on activation of caspase-2. Mol Cancer Ther 6: 752-761.

Mhaidat et al 2007 (2)
Docetaxel-induced apoptosis of human melanoma is mediated by activation of c-Jun NH2-terminal kinase and inhibited by the Mitogen-Activated Protein Kinase Extracellular Signal-Regulated Kinase 1/2 pathway. Clin Cancer Res 13: 1308-1314.

Smalley 2003
A pivotal role for ERK in the oncogenic behaviour of malignant melanoma? Int J Cancer 104:527-532.

Therasse et al 2000
New guidelines to evaluate the response to treatment in solid tumors. J National Cancer Institute 2000;92:205-216.

Wilkinson et al 2008
Activity of the MEK 1/2 inhibitor AZD6244 (ARRY-142886) in combination with standard and approved therapies: impact of in vivo sequencing of drug administration. Presented at the 99th American Association for Cancer Research Annual Meeting, San Diego; 12-16 April, 2008. Abstract number 4012.

APPENDICES

APPENDIX 1: ECOG PERFORMANCE SCALE

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

APPENDIX 2: MEASUREMENT OF DISEASE - MODIFIED RECIST CRITERIA

This appendix details the implementation of **modified** RECIST guidelines for the DOC-MEK study for the assessment of tumour burden (Therasse et al., 2000 J National Cancer Institute 2000;92:205-216)
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Definition of measurable, non-measurable, target and non-target lesions

Only patients with measurable disease at baseline should be included in the study. Measurable disease is defined by the presence of at least one measurable lesion that has not been previously irradiated. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable:

- Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with spiral Computed Tomography (CT) scan or as ≥20 mm with conventional techniques (Conventional CT, Magnetic Resonance Imaging (MRI), and which have not previously been irradiated

- Exception applies to lymph nodes lesions: lymph node must be >15 mm in short axis when assessed by CT scan (slice thickness 5 mm).

Non-measurable:

- All other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan)

- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural / pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, cystic lesions.

- Previously irradiated lesions

- Brain metastasis.

Target lesions:

- A maximum of 10 measurable lesions (with a maximum of 5 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as target lesions (TL) at baseline.

Non-Target lesions:

- All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline.

Methods of measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

A summary of the methods to be used for modified RECIST assessment is provided below and those excluded from tumour assessments for this study are highlighted.

Table 1: Summary of methods of assessment

Target Lesions	Non-Target lesions and New Lesions
CT (preferred)	CT (preferred)
MRI	MRI
	Clinical examination
	X-ray, Chest X-ray
	Ultrasound
	Endoscopy and laparoscopy

CT and MRI
CT and MRI are generally considered to be the best currently available and reproducible methods to measure TL selected for response assessment and to assess NTL and new lesions. In the study it is recommended that CT examinations of the chest, abdomen and pelvis be used to assess tumour burden at baseline and follow-up time points. CT examination with intravenous (iv) contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For brain lesion assessment, MRI is the preferred method.

Clinical examination
Clinical examination will not be used as part of RECIST assessment for TL. Clinically detected lesions can be selected as target lesions if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

X-ray
Chest X-ray assessment will not be used as part of RECIST assessment for TL as they will be assessed by CT examination or MRI examination. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions. Plain X-ray may be used as a method of assessment for bone non-target lesions and for confirmation of new bone lesions.

Ultrasound
Ultrasound examination will not be used as part of RECIST assessment for TL as it is not a reproducible method and does not provide an accurate assessment of tumour size. Ultrasound examination can, however, be used to assess NTL and to identify the presence of new lesions.

Endoscopy and laparoscopy
Endoscopy and laparoscopy will not be used as part of RECIST assessment for TL as they are not validated in the context of tumour measurements. However, endoscopy and laparoscopy can be used for assessment of NTL and to identify the presence of new lesions.

Isotopic bone scan
Isotopic bone scans will not be used to assess bone lesions as part of RECIST assessment due to insufficient specificity. Bone lesions identified on an isotopic bone scan and confirmed by CT, MRI or X-ray at baseline should be recorded as NTL and followed by the same method as per baseline assessment. If new bone lesions or worsening bone symptoms occur and a bone scan is performed, then worsening of disease needs to be confirmed by CT, MRI or X-ray.

PET scan
PET scans will not be used for assessment of tumour response, as PET evaluations do not form part of the RECIST framework.

Tumour response evaluation

Schedule of evaluation
All baseline tumour assessments must adequately assess tumour burden and should be performed no more than 28 days before the start of study treatment and ideally should be performed as close as possible to the start of study of treatment. Any other sites at which new disease is suspected should also be adequately imaged at follow-up. Follow-up assessments will be performed at Week 9, Week 18, and every 12 weeks thereafter**. If an unscheduled radiological and/or clinical tumour assessment is performed, and the patient has not progressed, the next scheduled tumour assessment should still be performed at the planned time**. This schedule is to be followed in order to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

Target lesions (TL)

Documentation of target lesions
A maximum of 10 measurable lesions (with a maximum of 5 lesions per organ), representative of all lesions involved, should be identified as TL at baseline. Target lesions should be selected on the basis of their size

(lesions with the longest diameter) and their suitability for accurate repetitive measurements. **An exception will apply for lymph nodes assessment for which the short axis will be measured and followed at baseline and at follow-up time-points.** The site and location of each TL should be documented as well as the longest diameter (LD) of each TL. All measurements should be recorded in metric notation using a ruler, calipers, or electronic calipers etc. At baseline the sum of the LD for all TL will be calculated & reported as the baseline sum LD. At follow-up visits the sum of the LD for all TL will be calculated & reported as the follow-up LD.

Special cases:

- If a TL splits into two or more parts, then the sum of the LDs of those parts is recorded
- If two or more TL merge then the LD of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s)
- If a TL becomes too small to measure accurately, then an estimate as close to the size as possible should be provided. The minimum size that can be recorded for a single lesion is 5 mm
- If a TL cannot be measured accurately due to it being too large, provide as close an estimate as possible of the size of the lesion
- For TL measurable in 2 or 3 dimensions, always report the longest diameter
- When a TL has had any intervention eg, radiotherapy, embolisation, surgery etc., during the study, the size of the TL should still be provided where possible.

Evaluation of target lesions
This section provides the definitions of the criteria used to determine objective tumour visit response for TL at the investigational site.

Table 2: Overall visit response for target lesions

Complete Response (CR)	Disappearance of all TL since baseline
Partial Response (PR)	At least a 30% decrease in the sum of the LD of TL, taking as reference the baseline sum LD
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Progressive Disease (PD)	At least a 20% increase in the sum of the LD of TL, taking as reference the smallest sum LD recorded since the treatment started
Not Evaluable (NE)	Only relevant if any of the TL were not assessed or not evaluable or had a lesion intervention

Non-target lesions (NTL)

Evaluation of non-target lesions
All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

Table 3: Overall visit response for non-target lesions

Complete Response (CR)	Disappearance of all NTL since baseline
Incomplete Response (IR)/ Stable Disease (SD)	Persistence of one or more NTL
Progression (PD)	Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression must be clinically significant for the physician to consider changing (or stopping) therapy
Not Evaluable (NE)	Only relevant when one or some of the NTL have not been assessed and in the Investigator's opinion they are not able to

	provide an evaluable overall NTL assessment
Not Applicable (NA)	Only relevant if there are no NTL at baseline

New Lesions

Details of any new lesions will also be recorded with the date of assessment. Progression based on appearance of new lesions will be recorded if one of the following is applicable:

- New soft-tissue lesions measuring ≥10 mm in longest diameter
- For new lymph nodes lesions, the shorter axis should be above 15 mm to be classed as a new lesion.

If the Investigator is in doubt as to whether progression has occurred, particularly with response to NTL or the appearance of a new lesion, it is advisable to continue treatment until the next scheduled assessment or sooner if clinically indicated and reassess the patient's status. If the lesion is still present it should be recorded as a new lesion on the date it was first observed.

Evaluation of Date of Progression and Best Overall Response

The best overall response is the best response recorded from the start of treatment until disease progression. Date of progression and best overall response will be derived as part of the study analysis from TL measurements, overall assessment of NTL and presence/absence of new lesions.

Table 4: Overall visit response

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

Confirmation of response

In the DOC-MEK study, 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.

Specifications for radiological imaging

The following is recommended for use in DOC-MEK.

CT Scan

CT scans of the neck, thorax, abdomen, and pelvis should be contiguous throughout the anatomical region of interest. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. CT examination with IV contrast media administration is the preferred method. Contrast agent timing should be aimed at the portal-venous phase of the liver. In patients in whom the abdomen and pelvis have been imaged, oral contrast agents should be given to distinguish the bowel from other soft tissue masses. A consistent method should be used on subsequent examinations for any given patient.

If iodine contrast media is medically contraindicated at baseline, or at any time during the course of the study, then the recommended methods are: CT thoracic examination without contrast and abdominal and

pelvis MRI with contrast. If MRI cannot be performed then CT without iv contrast is an option for the thorax, abdomen and pelvis examination. For brain lesions assessment, MRI is the preferred method.

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not "selected" images of the apparent lesion.

MRI Scan

MRI is entirely acceptable and capable of providing images in different anatomical planes. It is important therefore that when it is used lesions must be measured in the same anatomical plane using the same imaging sequences on subsequent examinations. For a particular patient the same scanner should be used during the study assessment. However, CT is the imaging modality of choice.

APPENDIX 3: MEDICATIONS INTERACTING SIGNIFICANTLY WITH CYP3A4 AND CYP1A2

The following medications/foodstuffs are to be avoided during the course of the study. This list is not exhaustive, and advice should be sought from the trials office where there is doubt. The definition of a strong inhibitor used is one that causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance.

CYP3A4 Inhibitors	CYP3A4 Inducers
aprepitant clarithromycin diltiazem erythromycin fluconazole grapefruit juice indinavir itraconazole ketoconazole nefadozone nelfinavir ritonavir saquinavir telithromycin verapamil	barbiturates carbamazepine efavirenz glucocorticoids modafinil nevirapine phenobarbitol phenytoin pioglitazone rifabutin rifampin St John's wort troglitazone
CYP1A2 Inhibitors	**CYP1A2 Inducers**
fluvoxamine ciprofloxacin	