RADVAN

Full title: A randomised double blind phase 2 trial of whole brain radiotherapy with or without vandetanib in metastatic melanoma with brain metastases

Short title: XRT +/- vandetanib in CNS melanoma

Clinical Study Report

Version 3.0 – 20 April 2016

Based on Protocol version 3.0 (08Aug2014)
Based on Statistical Analysis Plan version 1.0 (05Mar2015)

	Name	Title/Role	Affiliation	Signature	Date
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Study Initiation Date: 01 February 2012 (First patient registered)
Study Completion Date: 27 November 2014

A randomised, double blind, phase II trial of WBRT at 30 Gy in 10 fractions with vandetanib 100mg once daily or placebo for 21 days. The study was performed in compliance with Good Clinical Practice (GCP).

Contents

1. INTRODUCTION

This document details the analysis for the main paper(s) reporting results from the AstraZeneca-funded **randomised double blind phase 2 trial of whole brain radiotherapy with or without vandetanib in metastatic melanoma with brain metastases (RADVAN)**. The trial is included in the NCRN-AZ industry alliance. The results reported in these papers follow the strategy set out in the Statistical Analysis Plan (version 1.0, 05 March 2015). Exploratory analyses not pre-specified in the protocol and/or SAP will be expected to follow the broad principles laid down in the SAP and will be reported as post-hoc analyses in this report.

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

1.1 Key Personnel

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2. SYNOPSIS

Full Title of study:	A randomised phase 2 trial of whole brain radiotherapy with or without vandetanib in metastatic melanoma with brain metastases
Short Title:	XRT +/- vandetanib in CNS melanoma
Trial Acronym:	RADVAN
Name of Sponsor:	University of Oxford
Chief Investigator:	Professor Mark Middleton, Department of Oncology, Churchill Hospital, Oxford
Study centres:	Churchill Hospital, Oxford; Clatterbridge Centre for Oncology, Merseyside; Freeman Hospital, Newcastle upon Tyne; Mount Vernon Cancer Centre, Northwood; Norfolk & Norwich University Hospital, Norwich; St. Bartholomew's Hospital, London; Weston Park Hospital, Sheffield
Phase of development:	II
Studied period:	Date of first enrolment: 01 February 2012 Date of study completion: 27 November 2014
Objectives:	To compare WBRT with or without vandetanib in the treatment of patients with brain metastases from melanoma, in terms of progression free survival in the brain, with secondary end-points of progression free survival in the brain at 6 months, overall survival and safety and tolerability of vandetanib in combination with radiotherapy
Scientific rationale:	Vandetanib is an inhibitor of the VEGF, EGF and RET receptor tyrosine kinases, and a potent radiosensitiser. The effects of the drug on tumour vasculature and oxygenation are also predicted to enhance tumour responses to radiation
Clinical rationale:	The incidence of central nervous system (CNS) metastases in patients with metastatic melanoma ranges from 10% to 40% in clinical studies and is even higher in autopsy series, with as many as 72% having CNS involvement. Local control of brain metastases from melanoma is a significant problem and these contribute to death in >95% of patients diagnosed with them. Most patients are treated with radiotherapy, which has limited effectiveness, and their management represents a significant unmet medical need.
Primary Endpoint:	Progression free survival in brain
Secondary Endpoints:	Progression free survival in brain at 6 months, tolerability of vandetanib and WBRT, overall survival
Study Design:	Randomised double blind multi-centre phase 2 trial
Patient Numbers:	6 patients will be recruited to a non-randomised safety run in phase and 80 patients will be recruited to the randomised part of the study.
Early closure of recruitment	Recruitment to the trial closed on 30 Apr 2014 with 24 patients recruited (6 to the safety cohort and 18 to the randomised trial) following significant difficulties encountered in recruiting from this patient population. This decision was made by the TMG and agreed by IEPTOC following concerns that slow recruitment would lead to an inability to answer the research question in a timely manner.
Target Population:	Patients with unresectable metastatic melanoma with brain metastases
Main inclusion and exclusion criteria	Inclusion • ≥ 18 years of age, written informed consent • Histological confirmation of malignant melanoma • Unresectable Stage III or IV metastatic melanoma with brain metastases • Karnofsky Performance Score ≥70% • RTOG RPA score 1 or 2 • Measurable disease in the brain as defined by RECIST version 1.1 • Adequate haematological, hepatic and renal function • Adequate cardiac function (NHYA 0-1) • QTc <480msec Exclusion • Radiotherapy or systemic melanoma therapy within 28 days prior to starting treatment. • Prior whole brain irradiation

	• CNS melanoma where all detectable disease has been treated by neurosurgery or stereotactic irradiation • Presence of leptomeningeal disease • Pregnancy or breastfeeding women • Significant cardiovascular disease • Uncontrolled hypertension • Serum calcium, magnesium or potassium below the normal range despite supplementation • Requirement for medication that increases QTc and/or the risk of torsades de point • Requirement for medication that is a potent inducer of CYP3A4 function • Ocular malignant melanoma • Another active malignancy within the past five years • Clinically significant and uncontrolled major medical condition(s). • Any condition that would preclude adequate absorption of vandetanib.
Trial dose and administration:	Patients will receive three weeks of vandetanib 100mg once daily PO or placebo, starting 4 days (+/- 1 day) before whole brain radiotherapy (30 Gy in 10 fractions over 2 weeks)
Duration on study:	Patients will be on study until 12 months post randomisation or until progression the brain whichever is earliest. After this point patients will only be followed for survival data.
Study Procedures and frequency:	During treatment patients will be reviewed weekly. After completion of radiotherapy and study drug patients will be assessed clinically and radiologically at 30 days post-treatment and then at 2 month intervals, at which time performance status, disease status, steroid use and requirement for systemic therapy will be recorded. MRI head scan will be performed at these visits until intra-cranial progression is diagnosed.
Patient care post-trial:	After progression in the brain patients will be followed for survival only, and managed as per local standard practice
Criteria for evaluation	
Efficacy:	Progression free survival in brain will be measured by MRI scan using RECIST version 1.1
Safety:	The tolerability of vandetanib and radiotherapy will be evaluated using the NCI CTCAE (Version 4.0).
Histopathology:	No specific histopathology for the trial
Duration of study	Recruitment is anticipated to take 2 years, with a further 7 months for follow up to be completed.
End of study	Protocol defined as when all patients have at least 7 months follow-up from date of randomisation.
Publication policy	The results of this study will be published in a peer-reviewed scientific journal and used for other academic research purposes as agreed by the Investigators.
Summary – Conclusions	
Efficacy results:	On intention to treat analysis, median PFS in the brain was 3.25 months (90% confidence interval [CI]: 1.55-5.56) in those randomised to vandetanib, and 2.50 months (90% CI: 0.20-4.83) in those randomised to placebo; no statistically significant differences in PFS between the two treatment groups were found (p=0.339, Tarone-Ware test), although it must be noted that numbers were too small to accurately test for differences. The 6-month PFS rates were 20% and 13% respectively. There were 17 deaths recorded during the duration of the trial; median OS was 4.60 months [90% CI 1.55-6.28] in those randomised to vandetanib and 2.50 months [90% CI 0.20-7.20] in the placebo group (p=0.537, Tarone-Ware test). Two deaths in the placebo arm occurred within a week of the patients starting treatment, both due to progressive disease.
Safety results:	The most frequently occurring Adverse Events (AEs) were fatigue, confusion and alopecia. Of the total number of AEs, 14% were grade 3-4. In total, 11 Serious Adverse Events (SAEs) occurred; 2 experienced by 2 of 8 patients

	randomised to placebo (25%), 5 by 5 of 10 patients randomised to vandetanib (50%), and 4 by 3 of 6 patients in the safety run-in phase (50%). All deaths were disease related.
Conclusion:	The combination of WBRT 30 Gy in 10 fractions plus vandetanib 100mg OD is straightforward to administer and well tolerated in patients with melanoma brain metastases. Median PFS in brain was increased with the combination, but the low number of patients recruited and lack of statistical power to detect differences between treatment arms prevented adequate evaluation of the benefit of vandetanib in addition to radiotherapy. Study recruitment proved more challenging than expected, partly due to increased treatment options for such patients, and partly because many patients were not fit enough to start study treatment. These factors need to be carefully considered when designing future clinical trials for this patient population.
Date of report:	25 November 2015

3. ABBREVIATIONS

AE	Adverse Event
ADR	Adverse Drug Reaction
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
AST	Aspartate Transaminase
BST	British Summer Time
CI	Chief Investigator
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CT	Computerized Tomography
CTA	Clinical Trials Authorisation
CTCAE	Common Toxicity Criteria Adverse Events
CTRG	Clinical Trials and Research Governance
CTIMP	Clinical Trial of an Investigational Medicinal Product
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DSMC	Data & Safety Monitoring Committee
DSUR	Development Safety Update Report
ECG	Electrocardiogram
EGF	Epidermal Growth Factor
EGFR	Epidermal Growth Factor Receptor
EMEA	European Medicines Agency
EP	Early Progression
FBC	Full Blood Count
FDA	Food and Drug Administration
FCS	Fisher Clinical Services
GCP	Good Clinical Practice
GI	Gasto-Intestinal
GMP	Good Manufacturing Practices
GMT	Greenwich Mean Time
Gy	Gray
Hb	Haemoglobin
HCG	Human Chorionic Gonadotrophin
HDPE	High-density PolyEthylene
HIPAA	Health Information Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HTA	Human Tissue Act
IB	Investigator Brochure
IC_{50}	50% Inhibitory Concentration
ICH	International Conference on Harmonisation
IEPTOC	Independent Early Phase Trial Oversight Committee
ILD	Interstitial Lung Disease
IMP	Investigational Medicinal Product
IWRS	Interactive Web Response System
KDR	Kinase insert Domain-containing Receptor
KPS	Karnofsky Performance Score
LBBB	Left Bundle Branch Block
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
MHRA	Medicines and Healthcare products Regulatory Agency
MTD	Maximum Tolerated Dose
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute

NE	Not Evaluable
NHS	National Health Service
NIMP	Non-Investigational Medicinal Product
NRES	National Research Ethics Service
NSCLC	Non Small Cell Lung Cancer
NYHA	New York Heart Association
OCTO	Oncology Clinical Trials Office
OCTRU	Oxford Clinical Trials Research Unit
OD	Once Daily
ORB	Oxford Radcliffe Biobank
PD	Pharmacodynamic **or** Progressive Disease
PFS	Progression Free Survival
PK	Pharmacokinetic
PO	Per Os
PR	Partial Response
PVC	Premature Ventricular Contractions
QT	QT interval
QTc	Corrected QT interval
RCT	Randomised controlled trial
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria In Solid Tumours
RET	REarranged during Transfection
RPA	Recursive Partitioning Analysis
RTOG	Radiation Therapy Oncology Group
SAE	Serious Adverse Event
SD	Stable Disease
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
Tdp	Torsades De Pointes
TSC	Trial Steering Committee
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
WBC	White Blood Count
WBRT	Whole Brain Radiotherapy
XRT	Radiotherapy

4. ETHICS

OCTO and Principal Investigators have ensure that the RADVAN trial was conducted in compliance with the UK Clinical Trials Regulations[6], the principles of Good Clinical Practice (GCP) and the applicable policies of the Sponsoring Organisation. 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.

The study and any amendments were reviewed by an independent Research Ethics Committee (REC): NRES Committee South Central - Hampshire B, formerly NRES Committee South Central – Southampton B.

The Chief Investigator ensured that the protocol, patient information sheet, consent form and any other information that was presented to potential trial patients (e.g. advertisements or information that supports or supplements the informed consent) were reviewed and approved by an appropriately constituted, independent Research Ethics Committee (REC) and hosting organisation.

4.1 Informed Consent

Patients with brain metastases may potentially have reduced cognitive function and thus reduced ability to give informed consent for the study. Therefore capacity to give informed consent was formally assessed by the Investigator consenting the patient, using the following 2 criteria, as specified by the Mental Capacity Act (2005):

a. Is there an impairment of, or a disturbance in, the functioning of the person's mind or brain?
b. Is the impairment or disturbance sufficient to cause the person to be unable to make that particular decision?

At the time of consent, it must have been documented in the patient's notes that the Investigator consenting the patient had determined that he/she had the capacity to give informed consent, having applied the two-stage test above, as per local practice.

The participant must have personally signed and dated the latest approved version of the informed consent form before **any** study specific procedures were performed. The person who conducted the informed consent discussion must have also signed and dated the consent form and must have completed a 'Staff Contact Responsibilities Sheet' obtained from OCTO before taking on trial-related duties.

Written and verbal versions of the participant information and informed consent sheets were presented to the participants detailing no less than:

- the exact nature of the study
- the implications and constraints of the protocol
- the known side effects and any risks involved in taking part.

It was clearly stated that the participant is free to withdraw from the study at any time for any reason, without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant was allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Written informed consent was be obtained by means of participant dated signature and dated signature of the person who presented and obtained the informed consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent was given to the participants. The original signed form was retained at the study site, a copy kept in the patient's notes and a copy provided to a licenced Biobank as appropriate if a sample was being donated.

It was the Principal 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.

5. BACKGROUND AND STUDY DESIGN

The incidence of central nervous system (CNS) metastases in patients with metastatic melanoma ranges from 6% to 43% in clinical studies and is even higher in autopsy series, with as many as 74% having CNS involvement (Sampson *et al*, 1998). Local control of brain metastases from melanoma is a significant problem and these contribute to death in >95% of patients diagnosed with them. Current treatment for brain metastases from melanoma is unsatisfactory. No effective drug therapy exists and most trials of new agents exclude patients with active CNS disease. Most patients are treated with palliative Whole Brain Radiotherapy (WBRT). This provides symptomatic improvement in the majority of patients (Carella *et al*, 1980), but median survival following treatment is short, at around 3 to 4 months (Sampson *et al*, 1998).

Survival is predicted for by performance status, age and extra-cranial involvement, which together contribute towards the Radiation Therapy Oncology Group (RTOG) Recursive Partitioning Analysis (RPA) score. In a series at the Royal Marsden Hospital (Morris *et al*, 2004) patients with a RPA score of 1 (Karnofsky Performance score ≥70 and age <65) who underwent WBRT had a median survival of 5.0 months. Patients with RPA scores of 2 and 3 had a median survival of 2.3 and 0.7 months respectively. Further analysis identified a sub-group within patients with a RPA of 2, where the presence of leptomeningeal disease and/or involvement of multiple extra-cranial sites correlated with a very poor outcome and no benefit from WBRT. Thus the management of patients with melanoma brain metastases represents a significant unmet medical need.

Vandetanib is an orally bioavailable small molecule inhibitor of the VEGF, EGF and RET receptor tyrosine kinases, and a potent radiosensitiser. The effects of the drug on tumour vasculature and oxygenation are also predicted to enhance tumour responses to radiation. The aim of this study is to compare WBRT alone with WBRT and vandetanib in the treatment of patients with brain metastases from melanoma.

5.1 Research Hypotheses and Study Objectives

The main objective of the RADVAN study was to compare Whole Brain Radiotherapy (WBRT) with or without vandetanib in the treatment of patients with brain metastases from melanoma, in terms of progression free survival in the brain, with secondary end-points of progression free survival in the brain at 6 months, overall survival and safety and tolerability of vandetanib in combination with whole brain radiotherapy. Cognitive function was also originally a secondary end-point, but was removed from the protocol in 2012 as the tests were deemed to affect recruitment.

Primary Aim

- To assess the efficacy of vandetanib in combination with radiotherapy, compared with radiotherapy alone, in the treatment of patients with brain metastases from melanoma.

Secondary Aims

- To further assess using other outcomes, the efficacy of vandetanib in combination with radiotherapy, compared with radiotherapy alone, in the treatment of patients with brain metastases from melanoma.
- To assess the safety and tolerability of vandetanib in combination with radiotherapy, compared with radiotherapy alone.

5.2 Study Design

RADVAN is a randomised, double-blind, placebo-controlled, multi-centre phase II trial. Eighty patients with brain metastases from melanoma (forty in each of two arms) were to be randomised 1:1 between radiotherapy with placebo or radiotherapy with vandetanib, with stratification for RPA score (2 levels; RPA 1 and RPA 2). Patients would receive three weeks of either vandetanib 100mg Once Daily (OD) or placebo, starting 4 days (+/- 1 day) before whole brain radiotherapy (30 Gy in 10 fractions). Patients continued to be reviewed on study until progression of brain metastases (by RECIST version 1.1) or at least 7 months post randomisation into study, whichever comes first, and thereafter would be followed up for survival alone.

The main study was preceded by a non-randomised safety run in phase (involving 6 patients) to confirm the tolerability of vandetanib 100mg once daily with radiotherapy at 30 Gy in 10 fractions in this patient group. Tolerability was defined as no study treatment related toxicity of grade 3 or more (CTCAE version 4.0) in at least 5 out of the 6 patients in the safety run in phase at 30 days post end of study treatment.

Date of start of recruitment:	Safety; Jan 2012, Randomisation; Apr 2013
Number to be recruited for safety run-in phase	6
Number to be recruited for randomisation:	80 (40 per arm)
Date of expected end of recruitment:	Safety; Apr 2013, Randomisation; Apr 2015*
Participating Centres:	Up to ten sites across the UK

** Recruitment was poor and so recruitment was stopped 30 April 2014.*

5.3 Participants

Eligible participants were adults aged 18 or over with histologically or cytologically proven malignant melanoma; unresectable stage III or IV metastatic melanoma with brain metastases (measurable disease as defined by RECIST v1.1). Participants had to have a Karnofsky performance score of ≥70%, a RTOG RPA score 1 or 2, adequate cardiac function and a life expectancy of at least 12 weeks. Participants were also willing and able to comply with the protocol for the duration of the study and scheduled follow-up visits and examinations; written informed consent had to be obtained before any study specific procedures are performed.
Patients who had received any radiotherapy or systemic melanoma therapy (except palliative radiotherapy) within 28 days prior to starting trial treatment were excluded. Patients were also ineligible for the trial if they had prior whole brain irradiation, CNS melanoma where all detectable disease had been treated by neurosurgery or stereotactic irradiation, or presence of leptomeningeal disease. Other exclusion criteria included pregnancy or breast-feeding, uncontrolled hypertension, or having had another active malignancy within the past five years.

5.4 Treatment Interventions

Safety run-in patients:
The safety run-in patients received vandetanib 100mg once daily (OD), starting 4 days (±1 day) before WBRT and continuing for 21 days in total.
Treatment with 100mg OD of vandetanib would have only proceeded if none or only one of the six patients in the safety run-in phase experienced a dose limiting toxicity (DLT). If any of the patients in the safety run-in phase experienced a DLT, the dose may have been modified as detailed in the protocol. If 2 or more patients experienced a DLT then the randomised phase of the trial would have proceeded with a reduced dose of 100mg vandetanib or placebo once every alternate day.

Randomised patients:
The randomised RADVAN patients received either vandetanib 100mg or placebo OD, starting 4 days (±1 day) before WBRT and continuing for 21 days in total. No study treatment was to be given beyond day 21, even if any doses were missed during this period.

The exposure to vandetanib was unchanged whether given in the fasted state or with food, and thus a restriction on dosing with food was not required. The dose of study drug (vandetanib or placebo) should have been repeated if emesis occurred within 30 minutes of taking the tablet. If the patient inadvertently did not take the dose in the morning, he or she could take that day's dose any time up to 10pm that same day. The study drug could therefore be taken before or after radiotherapy treatment. However, if a patient missed taking their scheduled dose and was unable to take the missed dose on the same day, he or she omitted the dose and should have taken the next scheduled dose as planned. Missed doses were not made up.

Summary Schedule of Events																
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**N/A**	**N/A**
Visit description	**Study screening**	**Start study drug**	**Start XRT D1**	**XRT D2**	**XRT D3**	**XRT D4**	**XRT D5**	**XRT D6**	**XRT D7**	**XRT D8**	**XRT D9**	**End of XRT D10**	**End of study drug**	**30 days post EOT**	**Every 2 months after Day 51 visit**	**At PD in brain[1]**
Day	**-14 to -1** N.B. No day 0	**1**	**5**	**8 (of study drug)**				**15 (of study drug)**				**19 (of study drug)**	**21 (of study drug)**	**51**	**-**	**-**
Visit window (days)	**N/A**	**N/A**	**+/- 1**	**+/- 2**				**+/- 2**				**+/- 2**	**+/- 2**	**+/- 7**	**+/- 7**	**N/A**
Study consent	X															
Demographics	X															
Medical History	X															
Concomitant Treatments	X	X			X				X				X	X	X	X
Karnofsky Performance Status	X	X			X				X				X	X	X	X
Physical Exam	X	X[2]			X				X				X	X	X	X
Clinical Disease Assess.	X	X			X				X				X	X	X	X
Need for systemic therapy															X	X
Vital Signs	X	X			X				X				X	X	X	X
Height	X															
Weight	X	X			X				X				X	X	X	X
Haematology and Biochemistry	X	X			X				X				X	X		
Urinalysis	X	X			X				X				X	X		
ECG[3]	X	X			X				X				X			
Pregnancy test	X															
Radiotherapy			- - - - - - - - - - 30 Gy in 10 fractions - - - - - - - - - -													
Vandetanib/placebo		- - - - - - - - - - - - - - - - - - Once daily dosing - - - - - - - - - - - - - - - - - -														
Adverse Events		X			X				X				X	X		
MRI head (with contrast)	Baseline													X	X	X
CT scan (body)	Baseline[4]															X
Blood sample[5]		X														

[1] After PD in brain, for follow up for survival only
[2] A physical examination is not required at baseline if the screening visit is within 3 days of commencing treatment
[3] A single 12-lead ECG must be performed at screening. Up to 3 ECGs may be obtained at screening, and the mean QTc value used to determine eligibility. On day 1 of vandetanib/placebo (visit 2), 12-lead ECGs must be performed pre-dose and 2 hours post dose (please see notes below). On subsequent visits, only a single pre-dose ECG is required, unless there is evidence of QT prolongation.
[4] Baseline CT scan of chest, abdomen and pelvis up to 28 days prior to commencing study treatment.
[5] Single 10mL blood sample (collected in EDTA) for DNA analysis (if consented to this optional sub study).

5.4.1 Dose modification and management of toxicity

Treatment with the study drug (vandetanib or placebo) was to be withheld if a patient developed significant QT interval prolongation or any CTCAE grade 3 or 4 toxicity considered related to study treatment (study drug or radiotherapy) that could not be adequately managed with optimal supportive care.
The study drug was not to be resumed once the toxicity improved to CTCAE grade 1 or baseline up to but not beyond day 21. If the toxicity was considered related to study treatment, study drug was to be restarted at a reduced dose of 100 mg once every **alternate day**. All medical events that resulted in a dose reduction had to be reported as Serious Adverse Events (SAEs).

If the randomised part of the study started with vandetanib 100mg every other day, then any dose reduction would have been to 100mg every third day.
Once a dose reduction was made, the dose was not to be increased again at a later stage. If the patient developed grade 3 or 4 toxicity considered related to study drug again, then the study drug would have been permanently discontinued.

5.5 Sample size

Six patients were recruited to the non-randomised safety run-in phase of the trial.

The original sample size calculated was 80 patients to be recruited to the randomised part of the trial. Analysis was to be performed when approximately 74 brain progression/death events had occurred, which was expected to be approximately 4 months after the 2 year recruitment period. The following is taken from the SAP:
If the true HR is 0.6 (likely to correspond to a 70% prolongation of PFS in the brain, i.e.: from a 10 week median PFS in brain to a 17 week median PFS in brain), this analysis will have approximately 80% power to demonstrate a statistically significant difference for brain PFS, assuming a 1-sided 10% significance level, a recruitment period of 2 years, and follow-up after last patient recruitment of 4 months. If a 1-sided $p<0.1$ is observed for the comparison of PFS in brain between vandetanib in combination with radiotherapy, versus radiotherapy alone, 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.

5.6 Randomisation

A screening log was kept of all patients considered for the study, including any that were subsequently excluded; the reason for exclusion is recorded on this form.

<u>Safety run-in patients:</u>
The first six patients were not randomised, and received radiotherapy with vandetanib as part of the safety run-in phase. These six patients received treatment and follow-up as per protocol.

<u>Randomised patients:</u>
Randomisation into the RADVAN study only began after the safety analysis of the first 6 patients (30 days post last treatment). Eligible patients were randomised 1:1 to receive radiotherapy with placebo or radiotherapy with vandetanib, stratifying for Recursive Partitioning Analysis (RPA) score (2 levels; RPA 1 and RPA 2).

Every effort should have been made to ensure that only eligible patients are randomised. If a patient was randomised in error, the study site should have contacted OCTO as soon as possible and, if necessary, treatment should have been stopped. Patients randomised in error should have been followed up for disease progression and for survival. For patients randomised in error who did not start study treatment, replacement patients would have been recruited and randomised.

Patients were randomised using an Interactive Web Response System (IWRS). Details on how to access and use the IWRS were provided in a separate User Guide.

5.7 Blinding

The trial was double-blinded, with patients and clinicians, site staff and trial office staff all kept blinded to the treatment allocation. Vandetanib and placebo were supplied as 100mg white film-coated tablets packed in high density polyethylene (HDPE) bottles by AstraZeneca and shipped to study sites by Fisher Clinical Services (FCS).
The randomisation codes were held by a separate company (Cenduit), and were only acquired by the trial statistician at the time of the final analysis.
The treatment code was to be broken at trial closure for all patients. In the rare event that a patient had a SUSAR and required an emergency code break, Investigators at site could have access to the unblinding function in the IWRS for emergency situations. If a patient was unblinded, the Investigator must have notified OCTO by contacting the RADVAN Clinical Trial Coordinator.
In the event of a SUSAR where the site had not yet unblinded the patient, if there was no clinical benefit to the site or patient of being unblinded, OCTO would unblind the patient for SUSAR reporting and not disclose the treatment allocation to the site.

5.8 Definition of Primary and Secondary Outcomes

5.8.1 Primary Outcome

Progression Free Survival in the brain
Progression Free Survival (PFS) in the brain was defined as the time from date of randomisation to date of disease progression in the brain (assessed by MRI scan using RECIST criteria version 1.1) or date of death (events) in the absence of RECIST progression. For patients without an event, the time from date of randomisation to date last known alive would be the censored PFS time.

5.8.2 Secondary Outcomes

Progression Free Survival in the brain at 6 months
This was defined as the time from randomisation until progression in the brain or death from any cause. Those who were not observed to progress or die during the course of the trial will be censored at their last known brain progression-free follow-up date. PFS rate at 6 months was defined as the percentage progression free at 6 months from the PFS Kaplan Meier curve. This allowed all patients randomised to be included.

Overall Survival
Overall Survival was defined as the time from randomisation to death (event), or the time from randomisation to date last known alive for censored patients.

5.8.3 Safety and Tolerability Outcomes

Adverse Events
Anticipated adverse events (AEs) with vandetanib, based on both pre-clinical and clinical data, including QT-prolongation, hypertension, skin toxicity and gastrointestinal toxicity (diarrhoea) were assessed using NCI CTCAE v4.0. Other AEs that may be related to vandetanib are detailed in the Investigator's Brochure for vandetanib, used as the trial Reference Safety Information.

Dose Limiting Toxicity (DLT)
A DLT is defined as significant QT interval prolongation or any CTCAE grade 3 or 4 toxicity considered related to study treatment (study drug or radiotherapy) that cannot be adequately managed with optimal supportive care. Significant QTc prolongation is defined as:

- A single QTc value of ≥501 msec or an increase of ≥60 msec from baseline or Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia (CTCAE grade 4)

OR

- Two consecutive QTc measurements, within 48 hours of one another, where either of the following criteria are met for both QTc values:

  - A QTc interval ≥501 msec (CTCAE grade 3) **OR**

  - An increase of ≥60 msec

Vital signs and weight
To be considered are; systolic and diastolic blood pressure (BP), pulse rate, weight and body surface area (BSA).

Biochemistry and haematology
The following were obtained at different timepoints throughout the trial:

- Haematology – Hb, white blood cells (WBC) with differential count (neutrophils and lymphocytes) and platelets
- Biochemistry – sodium, potassium, calcium, phosphate, urea, creatinine, total protein, albumin, bilirubin, alkaline phosphatase (ALP), ALT or AST and LDH
- Urinalysis

Analysis of routine blood samples for biochemistry and haematology during the trial were performed in the laboratories of the local hospital trust according to local procedures.

Physical examination
A complete physical examination must have been performed at screening within no more than 14 days before the patient received the first study dose, unless otherwise stated, and at other timepoints throughout the trial.

Electrocardiogram (ECG)

A single 12-lead ECG must have been performed at screening. Up to 3 ECGs may have been obtained at screening, and the mean QTc value used to determine eligibility. On day 1 of vandetanib/placebo (visit 2), 12-lead ECGs must have been performed pre-dose and 2 hours post dose. On subsequent visits, only a single pre-dose ECG was required, unless there was evidence of QT prolongation.

6. STUDY METHODS

6.1 Software employed

Analyses were undertaken using Stata version 13·1 (StataCorp, College Station, TX).

6.2 Data quality

Any calculations and derivation of variables have been checked by hand calculations for 5% of patients.

No missing data was planned to be imputed, and none was imputed.

A number of patients didn't comply with the full course of treatment (Section 5.4.1), or withdrew early (Section 5.4.2). A large number of patients also didn't have MRI scans at the timepoints specified in the protocol (Section 5.1.2).

6.3 Interim Analysis

The reason for the 6 patient safety sample was to confirm the tolerability of vandetanib 100mg OD with radiotherapy at 30 Gy in 10 fractions. All patients received the planned vandetanib arm of the randomised controlled trial (RCT). If at least 5/6 patients had no grade 3 toxicity then the trial would continue to randomise on a starting dose of 100mg per day. Otherwise, randomisation into the study would have started

with 100mg vandetanib on alternate days with a rewritten dose reduction, and the data would have been looked at after 12 randomised patients but without stopping recruitment to the trial.

An interim analysis of the safety patients' data took place in April 2013. A Trial Management Group (TMG) meeting took place on 10th April 2013; the TMG reviewed the safety data, concluded that there were 0/5* dose limiting toxicities (DLTs) and made a decision to proceed to the randomised trial 100mg vandetanib/placebo once daily with 30Gy of whole brain radiotherapy.

* One safety sample patient did not complete the course of IMP, and so was non-evaluable, hence the decision was made on 5 out of 6 patients.

6.4 Deviations from the statistical analysis plan

No deviations from statistical analysis plan.

6.5 Suggested Statistical Methods Section for Publication

The main study was preceded by a safety run-in phase to confirm the tolerability of the treatment combination in this patient group. 6 patients were recruited to this non-randomised safety run-in phase.

For the randomised part of the study, a 70% prolongation of progression-free survival (PFS) in the brain was considered clinically relevant (from a 10 week median brain PFS to a 17 week median brain PFS), corresponding to a hazard ratio (HR) of 0.6. With a one-sided significance level of 0.01, and power of 80% approximately 74 brain progression or death events and 80 patients were required to demonstrate a statistically significant difference in PFS in the brain between the two arms. It was estimated that this number of events would occur approximately 4 months after the planned two year recruitment period. However, following significant difficulties encountered in recruiting from this patient population, recruitment to the trial was closed early, with 24 patients recruited (6 to the safety cohort and 18 to the randomised trial), meaning that the previously calculated sample size target of 80 patients was not reached.

Patients were randomised 1:1 between radiotherapy with placebo or radiotherapy with vandetanib, with stratification for Recursive Partitioning Analysis (RPA) score (2 levels; RPA 1 and RPA 2). Patients were randomised using an Interactive Web Response System (IWRS).

All survival analyses were intention-to-treat (ITT) and involved all patients who were randomly assigned to the main study, irrespective of the treatment they received. The population for the safety and tolerability analysis was all patients who were randomised and received at least one dose of treatment drug. A per-protocol sensitivity analysis was also performed, including only data from patients who received 21 days of treatment drug and 10 fractions of radiotherapy, and MRI scans as per protocol.

Progression-free survival in the brain was defined as the time from date of randomisation to the date of disease progression in the brain (assessed by MRI scan using RECIST criteria version 1.1) or date of death. Patients without an event were censored at their date last known alive and brain progression free.
Overall Survival was defined as the time from randomisation until the date of death. Patients who were not observed to die within the course of the trial were censored at their date last known alive.

7. DESCRIPTIVE ANALYSES

7.1 Study participants

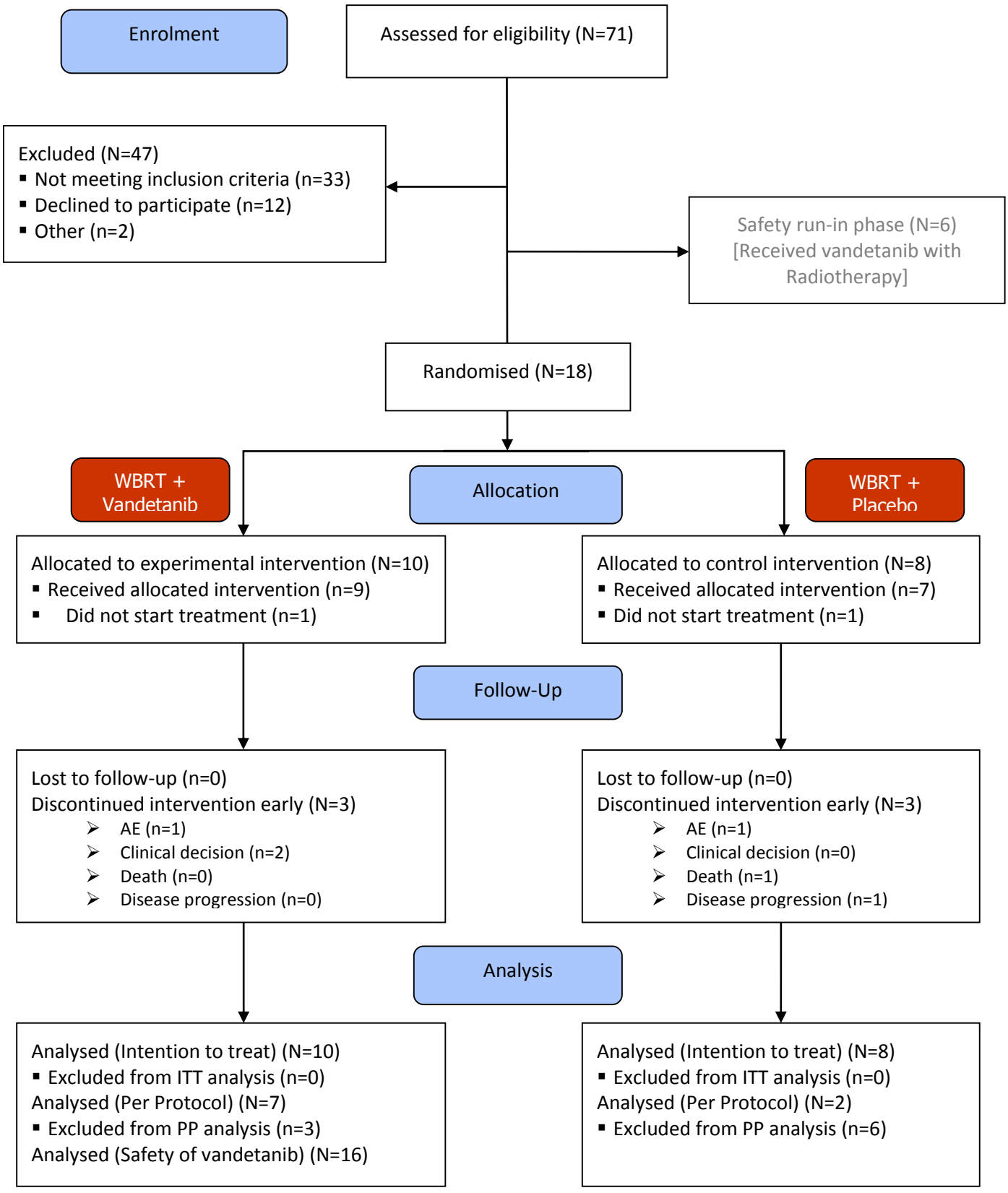


Table: Expansion of reasons for exclusion

Expansion of reason for exclusion	N	Subtotal reason for exclusion
>3 extra-cranial metastatic sites*	2	
Contraindicated concomitant medication	1	
Died in screening	2	
Inadequate cardiac function	1	
Leptomeningeal disease	2	
Life expectancy <12 weeks	3	
No brain metastases	2	
Not known	7	
Patient unable to comply with protocol	3	
Poor performance status	7	
Resectable brain metastases	2	
Systemic therapy within 28 days	1	
		Not meeting inclusion criteria n = 33
Patient chose alternative treatment	4	
Patient unable to travel	1	
Not known	7	
		Refused to participate n = 12
Unknown reason	2	
		Other reason n = 2
Total patients screened but not recruited	47	

* This was amended in 2012 to no longer be an exclusion criteria, so that more patients could be recruited to the trial.

7.1.1 Deaths

All deaths observed in the study were disease related.

7.1.2 Description of available data

Frequency of MRI scans:

MRI scan	Vandetanib + WRBT (n, %)	Placebo + WBRT (n, %)	All randomised patients (n, %)	All who received vandetanib* (n, %)
Baseline	9 (90%)	8 (100%)	17 (94.4%)	15 (93.8%)
30 days post end of study treatment	5 (50%)	3 (37.5%)	8 (44.4%)	10 (62.5%)
4 months	2 (20%)	2 (25%)	4 (22.2%)	5 (31.3%)
6 months	1 (10%)	1 (12.5%)	2 (11.1%)	2 (12.5%)
8 months	1 (10%)	1 (12.5%)	2 (11.1%)	3 (18.8%)
10 months	0	0	0	2 (12.5%)
12 months	0	0	0	2 (12.5%)
Progression in brain	3 (30%)	2 (25%)	5 (27.8%)	5 (31.3%)

* All patients in safety run-in or randomisation phase who were allocated to receive vandetanib: column added for safety of vandetanib analysis

7.1.3 Protocol deviations and violations

Trial No	Site	Date OCTO Aware	Deviation Description	Action Taken
RVS05	Churchill Hospital	24-Apr-13	Patient RVS05 is in follow up and due for visit and scans in early May. Patient decided to participate in another trial and has scans booked - MRI head and CT C/A/P. Can these scans be used for the RADVAN follow up so the patient is not rescanned shortly afterwards?	Brain MRIs in the protocol are done 2 monthly +/- 7 days from scheduled timepoint. MRM confirmed that as patient is not in randomised phase, can be more lenient than +/- 7 days with follow up scans. Advised to accept the deviation and use scans performed for other trial on this occasion.
RVS04	Clatterbridge Cancer Centre	17-Apr-14	The patient's baseline MRI Head was done at their local hospital (Wrexham) and the images were imported to the Clatterbridge electronic notes system. However no scan report accompanied the images and there is no record of this scan being reported to RECIST either by Clatterbridge or Wrexham. The Clatterbridge radiologist will not re-report the baseline scan to RECIST retrospectively. The first follow up MRI was reported to RECIST and this data has been entered into OpenClinica; however the assessment of response is not applicable if there are no baseline measurements for comparison.	OCTO confirmed with site that measurable disease in the brain and a baseline MRI of the head with lesions measured by RECIST 1.1 is essential for RADVAN eligibility and assessment of the primary endpoint. Site to ensure that the missing baseline scan measurements are annotated in the OpenClinica CRF and that the disease response on the first follow-up scan is updated to Not Evaluable. Confirmed with the Trial Statistician that as this patient was in the safety cohort rather than the randomised trial, the patient's data would not have contributed towards the final statistical analysis (refer to Protocol section 9.8.1). Therefore the deviation is minor rather than major.
RV015	Mount Vernon Cancer Centre	22-Nov-13	Patient RV015 started vandetinib/placebo treatment on 21 Nov 2013. Following first dose experienced a seizure related to their brain metastases.	Site informed OCTO & Prof Middleton advised that treatment should be interrupted and restarted 1 week later once the patient's fitting improved. Radiotherapy was also delayed while the drug was held for 6 days to give the same run in prior to the start of radiotherapy.
RV014	Norfolk & Norwich University Hospital	10-Jan-14	Patient unblinded by OCTO to report a SUSAR, site to remain blinded. The site unblinded the patient in Cenduit on 10 Jan 2014 in error.	Patient continues in trial follow up as per protocol. Site notified of the mistake, Chief Investigator, PVC and Statistician notified of unblinding.

7.2 Recruitment

6 eligible participants were recruited to the safety run-in phase of the trial between 1st February 2012 and 14th February 2013. One patient, however, did not complete the course of IMP and so was non-evaluable, leaving 5 evaluable patients.
In April 2013, the RADVAN Trial Management Group (TMG) reviewed the safety data of the 5 evaluable safety cohort patients, concluded that 0/5 Dose Limiting Toxicities (DLTs) had been observed, and hence decided to proceed to the randomised part of the trial. The corresponding safety report is included in Appendix 1 of this document.

Between 24th April 2013 and 17th April 2014, 18 eligible participants were recruited to the randomised phase of the trial.
The TMG met on 30 Apr 2014 and agreed to close the RADVAN trial early to recruitment with immediate effect. 24 of 86 patients had been recruited at this time and there was no indication from sites that the recruitment rate to the randomised trial (1.4 patients per month) would improve in the future. Therefore the TMG felt that the risk-benefit profile of the trial was such that closing the study to recruitment early was the most appropriate action and this decision was supported by the Independent Early Phase Trial Oversight Committee (IEPTOC), AstraZeneca and CTAAC. The TMG also agreed that the follow up period would be adjusted from 12 months from last randomisation to 7 months from last randomisation to enable the trial to close early. The trial closed in Nov 2014, at which point there was a median follow-up of 4.5 months on all patients.

7.3 Baseline Characteristics

Characteristic	Vandetanib + WRBT (n, %)	Placebo + WBRT (n, %)	All randomised patients (n, %)	All who received vandetanib* (n, %)
Age [years] (mean, SD)	57.3 (11.1)	63.7 (14.8)	60.1 (12.9)	61.7 (11.5)
Gender				
Male	5 (50%)	3 (37.5%)	8 (44.4%)	9 (56.3%)
Female	5 (50%)	5 (62.5%)	10 (55.6%)	7 (43.7%)
Karnofsky performance status				
100 – Normal; no evidence of disease	2 (20%)	1 (12.5%)	3 (16.7%)	3 (18.8%)
90 – Able to carry on normal activity; minor signs of disease	5 (50%)	5 (62.5%)	10 (55.6%)	7 (43.8%)
80 – Normal activity with effort; some signs of disease	2 (20%)	2 (25%)	4 (22.2%)	5 (31.3%)
70 – Cares for self; unable to carry on normal activity	1 (10%)	0	1 (5.6%)	1 (6.3%)
Smoking status				
Never	6 (60%)	2 (25%)	8 (44.4%)	9 (56.3%)
Ex-Smoker	3 (30%)	4 (50%)	7 (38.9%)	5 (31.3%)
Current-Smoker	1 (10%)	0	1 (5.6%)	1 (6.3%)
Unknown	0	2 (25%)	2 (11.1%)	1 (6.3%)
Past Medical History				
Prior surgical treatment for this disease	10 (100%)	7 (87.5%)	17 (94.4%)	16 (100%)
Prior medical treatment for this disease	6 (60%)	6 (75%)	12 (66.7%)	8 (50%)
Prior RT treatment for this disease	3 (30%)	1 (12.5%)	4 (22.2%)	5 (31.3%)
Significant medical or surgical history not related to current disease	7 (70%)	8 (100%)	15 (83.3%)	12 (75%)
Height [cm] (mean, SD)	170.3 (10.0)	169.8 (10.9)	170.1 (10.1)	171.3 (9.4)
Weight [kg] (mean, SD)	81.0 (13.6)	75.2 (17.2)	78.4 (15.1)	82.7 (14.3)
Ethnicity				
White British	9 (90%)	8 (100%)	17 (94.4%)	15 (93.7%)
Other White background	1 (10%)	0	1 (5.6%)	1 (6.3%)
Vital signs (mean, SD)				
Temperature	36.4 (0.6)	36.5 (0.5)	36.5 (0.5)	36.3 (0.5)
Pulse rate	77.2 (17.8)	73.3 (14.6)	75.4 (16.1)	73.8 (16.0)
Systolic blood pressure	131.7 (13.8)	135.3 (11.6)	133.3 (12.6)	136.8 (15.1)
Diastolic blood pressure	74.3 (7.8)	76.1 (8.7)	75.1 (8.0)	75.6 (11.9)
Biochemistry (n=freq. of patients with abnormal results)				
Sodium	2 (20%)	0	2 (11.1%)	3 (18.8%)
Potassium	0	0	0	0
Calcium	0	0	0	0
Phosphate	0	1 (12.5%)	1 (5.6%)	1 (6.3%)
Urea	4 (40%)	4 (50%)	8 (44.4%)	7 (43.8%)
Creatinine	2 (20%)	0	2 (11.1%)	2 (12.5%)
Total protein	2 (20%)	0	2 (11.1%)	1 (12.5%)
Albumin	0	0	0	0
Bilirubin	2 (20%)	1 (12.5%)	3 (16.7%)	4 (25%)
Alkaline phosphate (ALP)	0	0	0	0
ALT	2 (20%)	1 (12.5%)	3 (16.7%)	2 (12.5%)
AST	1 (10%)	3 (37.5%)	4 (22.2%)	1 (6.3%)
LDH	5 (50%)	4 (50%)	9 (50%)	10 (62.5%)
Haematology results (n=freq. of patients with abnormal results)				

Characteristic	Vandetanib + WRBT (n, %)	Placebo + WBRT (n, %)	All randomised patients (n, %)	All who received vandetanib* (n, %)
Haemoglobin	2 (20%)	0	2 (11.1%)	2 (12.5%)
White cell count	4 (40%)	7 (87.5%)	11 (61.1%)	7 (43.8%)
Neutrophils	4 (40%)	6 (75%)	10 (55.6%)	8 (50%)
Lymphocytes	4 (40%)	3 (37.5%)	7 (38.9%)	8 (50%)
Platelets	0	2 (25%)	2 (11.1%)	0
Urinalysis				
Normal	8 (80%)	7 (87.5%)	15 (83.3%)	14 (87.5%)
Abnormal but not clinically significant	1 (10%)	1 (12.5%)	2 (11.1%)	1 (6.3%)
Not done	1 (10%)	0	1 (5.6%)	1 (6.3%)
ECG				
Normal	8 (80%)	6 (75%)	14 (77.8%)	12 (75%)
Abnormal but not clinically significant	2 (20%)	2 (25%)	4 (22.2%)	3 (18.8%)
Not done	0	0	0	1 (6.3%)
Measurable disease at baseline				
Yes	10 (100%)	8 (100%)	18 (100%)	16 (100%)
No	0	0	0	0

* All patients in safety run-in or randomisation phase who were allocated to receive vandetanib: column added for safety of vandetanib analysis

7.3.1 Numbers analysed

Intention-to-treat (ITT) population: The primary analysis was intention-to-treat and involved all 18 patients who were randomly assigned, irrespective of the treatment they received.

Per Protocol (PP) population: 9 patients were included in the per-protocol analysis and 9 patients were excluded as they did not did not receive 21 days of treatment drug (vandetanib/Placebo) and 10 fractions of radiotherapy.

Safety and tolerability analysis: 16 patients were randomised and received at least one dose of treatment drug (vandetanib/Placebo).

Safety of vandetanib analysis: 16 patients (including those 6 patients in the safety sample) were allocated to receive vandetanib.

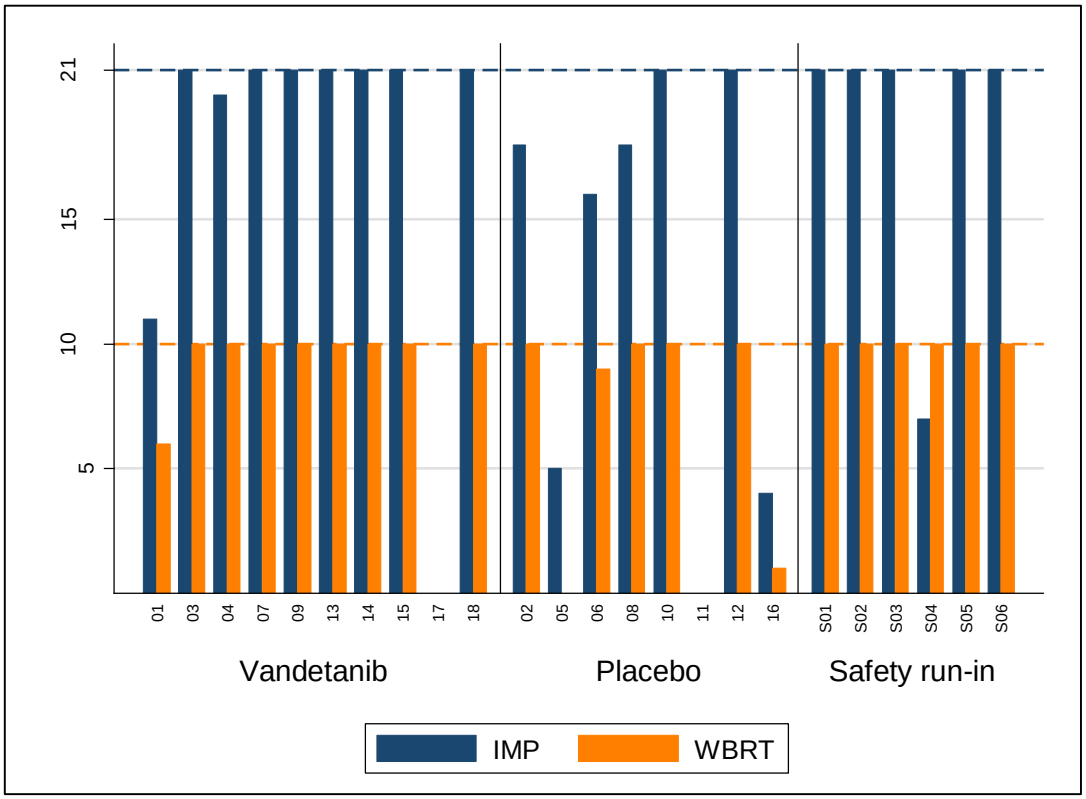
7.4 Compliance

7.4.1 Treatment compliance

Compliance	Vandetanib + WRBT (n, %)	Placebo + WBRT (n, %)	All randomised patients (n, %)	All who received vandetanib* (n, %)
IMP treatment (vandetanib or Placebo)				
Complete (21 days taken)	7 (70%)	2 (25%)	9 (50%)	12 (75%)
Incomplete but started	2 (20%)	5 (62.5%)	7 (38.9%)	3 (18.8%)
Did not start treatment	1 (10%)	1 (12.5%)	2 (11.1%)	1 (6.3%)
Mean number of days IMP taken	17.8	12.9	16.5	18.1
WBRT treatment				
Complete (10 days received)	8 (80%)	4 (50%)	12 (66.7%)	14 (87.5%)
Incomplete but started	1 (10%)	2 (25%)	3 (16.7%)	1 (6.3%)
Did not start treatment	1 (10%)	2 (25%)	3 (16.7%)	1 (6.3%)
Mean number of days WBRT received	8.6	6.3	8	9.1

* All patients in safety run-in or randomisation phase who received vandetanib: column added for safety of vandetanib analysis

The following graph displays the days of treatment received by each patient (IMP: vandetanib or Placebo, and Whole Brain Radiotherapy (WBRT)):



The following table displays the treatment compliance (both IMP & WBRT) of each patient, as well as the reasons their treatment was incomplete, if applicable.

Trial no	IMP dose reduction?	IMP treatment complete?	Days IMP taken	Reason IMP treatment incomplete	WBRT treatment complete?	Days WBRT received	Total Gy received	Reason WBRT treatment incomplete
RV001	Yes: day17	Incomplete but started	11	Days 10 - 16 QTc interval at unacceptable level. Restarted on 100mg alternate days and then taken off drug on 13th May due to deterioration in condition	Incomplete but started	6	18	Delay in radiotherapy due to SAE admitted with confusion. Patient restarted and then Dr decided for patient not to finish treatment due to deteriation of patients general condition.
RV002	No	Incomplete but started	18	Patient forgot to take tablets on 3 days. (2 days between 11 -15 May and on either 18 or 19th May).	Complete	10	30	
RV003	No	Complete	21		Complete	10	30	
RV004	No	Incomplete but started	20	Adverse event requiring discontinuation: patient admitted to hospital with haemorrhage of brain metastases	Complete	10	30	
RV005	No	Incomplete but started	5	Patient died	Did not start	0	0	Patient died
RV006	No	Incomplete but started	16	Adverse event requiring discontinuation: Patient developed a serious pleural effusion and so study treatment was temporarily stopped and later decided not to restart.	Incomplete but started	9	27	Significant deterioration in breathing on Day 8 of Radiotherapy treatment due to pleural effusion; decision made to give 27Gy over 9 fractions & transfer for a pleural drain.
RV007	No	Complete	21		Complete	10	30	
RV008	No	Incomplete but started	18	Patient reported missing 3 dosages in error, unknown which dates missed but reported that stopped drug on 03 October 2013	Complete	10	30	
RV009	No	Complete	21		Complete	10	30	

Trial no	IMP dose reduction?	IMP treatment complete?	Days IMP taken	Reason IMP treatment incomplete	WBRT treatment complete?	Days WBRT received	Total Gy received	Reason WBRT treatment incomplete
RV010	No	Complete	21		Complete	10	30	
RV011	Did not start	Did not start	0	Did not start treatment	Did not start	0	0	Did not start treatment
RV012	No	Complete	21		Complete	10	30	
RV013	No	Complete	21		Complete	10	30	
RV014	No	Complete	21		Complete	10	30	
RV015	No	Complete	21		Complete	10	30	
RV016	No	Incomplete but started	4	4 only taken as per SAE details: hospitalisation for confusion as result of disease progression.	Incomplete but started	1	3	Only one dose given due to disease progression reported in SAE.
RV017	Did not start	Did not start	0	Did not start treatment due to Abnormal ECG result- risk of increased QTc too great on study.	Did not start	0	0	
RV018	No	Complete	21		Complete	10	30	
RVS01	No	Complete	21		Complete	10	30	
RVS02	No	Complete	21	No doses missed but actually took an extra tablet so 22 taken in all. patient got confused when completing diary card.	Complete	10	30	
RVS03	No	Complete	21		Complete	10	30	
RVS04	No	Incomplete but started	7	As advised by consultant and SAE: Cognitive Disturbances	Complete	10	30	
RVS05	No	Complete	21		Complete	10	30	
RVS06	No	Complete	21		Complete	10	30	

7.4.2 Withdrawals from treatment

Reason for early treatment withdrawal	Vandetanib + WRBT (n, %)	Placebo + WBRT (n, %)	All randomised patients (n, %)	All who received vandetanib* (n, %)
Adverse event requiring discontinuation	1 (33.3%)	1 (33.3%)	2 (33.3%)	1 (25%)
Death	0	1 (33.3%	1 (16.7%)	0
Evidence of disease progression	0	1 (33.3%)	1	0
Unforeseen events: any event that in the judgement of the investigator makes further participation inadvisable	0	0	0	1 (25%)
Withdrawal by the investigator for clinical reasons not related to the study.	2 (66.7%)	0	2 (66.7%)	2 (50%)
Total	**3**	**3**	**6**	**4**

Further details of early treatment withdrawals are given in the table below:

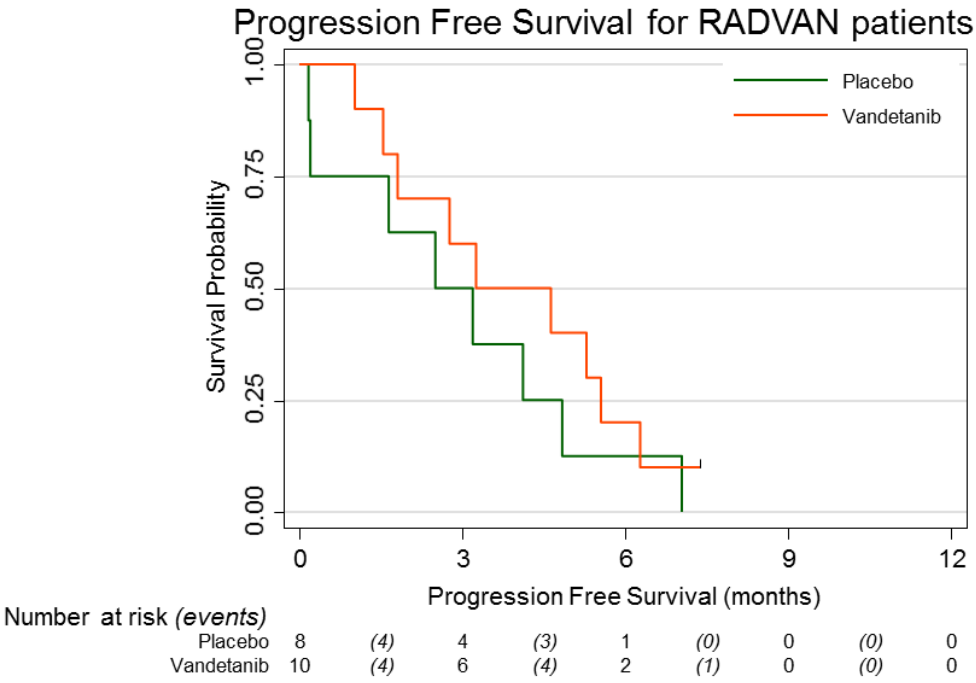
Trial no	Treatment arm	Reason for early treatment withdrawal	Details
RV001	Vandetanib + WBRT	Withdrawal by the investigator for clinical reasons not related to the study.	Dr decided inappropriate to continue due to deterioration in condition.
RV004	Vandetanib + WBRT	Adverse event requiring discontinuation	Patient admitted to hospital with haemorrhage of brain metastases
RV005	Placebo + WBRT	Death	Disease related death
RV006	Placebo + WBRT	Adverse event requiring discontinuation	Patient developed a serious pleural effusion and so study treatment was temporarily stopped and later decided not to restart.
RV011	Placebo + WBRT	Withdrawal by the investigator for clinical reasons not related to the study.	Did not start treatment: Blood work was out of limits post randomisation.
RV016	Placebo + WBRT	Evidence of disease progression	SAE - hospitalisation for confusion as result of disease progression
RV017	Vandetanib + WBRT	Withdrawal by the investigator for clinical reasons not related to the study.	Did not start treatment: Abnormal ECG result- risk of increased QTc too great on study.
RVS04	Safety (Vandetanib + WBRT)	Unforeseen events: any event that in the judgement of the investigator makes further participation inadvisable	SAE: Cognitive Disturbances

7.4.3 Unblinding

All 3 SUSAR were unblinded (through the Cenduit Sponsor's Unblinded Group) by Linda Collins (Trial Manager) for reporting. Each was assessed to see if anyone else should be unblinded and in each case the PI said that he didn't feel there was a clinical benefit to the site being unblinded. According to the protocol, patients who are unblinded should be continue to be followed up as per protocol. Unfortunately, for one SUSAR, Norfolk and Norwich University Hospital unblinded their patient in error. They confirmed that they were not intending to tell the patient their treatment allocation and it was agreed that this would not affect the data quality.

8. RESULTS: PRIMARY, SECONDARY AND EXPLORATORY

8.1 Primary Analysis Results: Progression Free Survival in brain (ITT analysis)

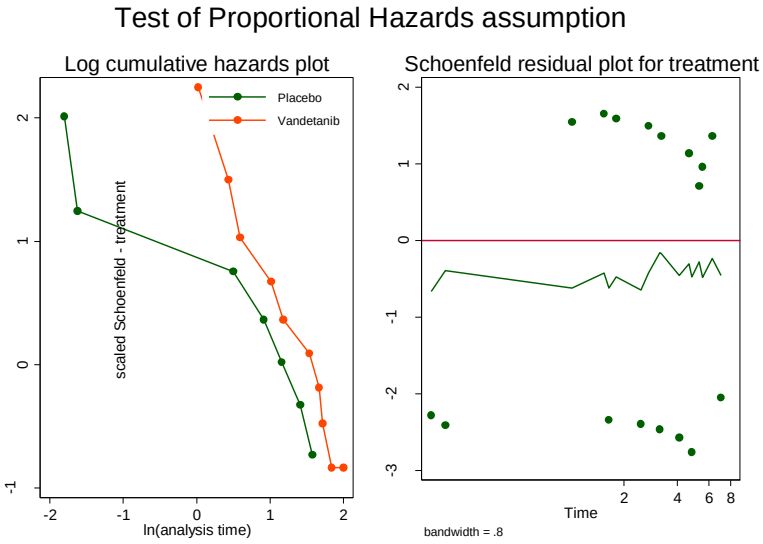


No statistically significant differences in PFS between treatment groups (p=0.3386, Tarone-Ware test).

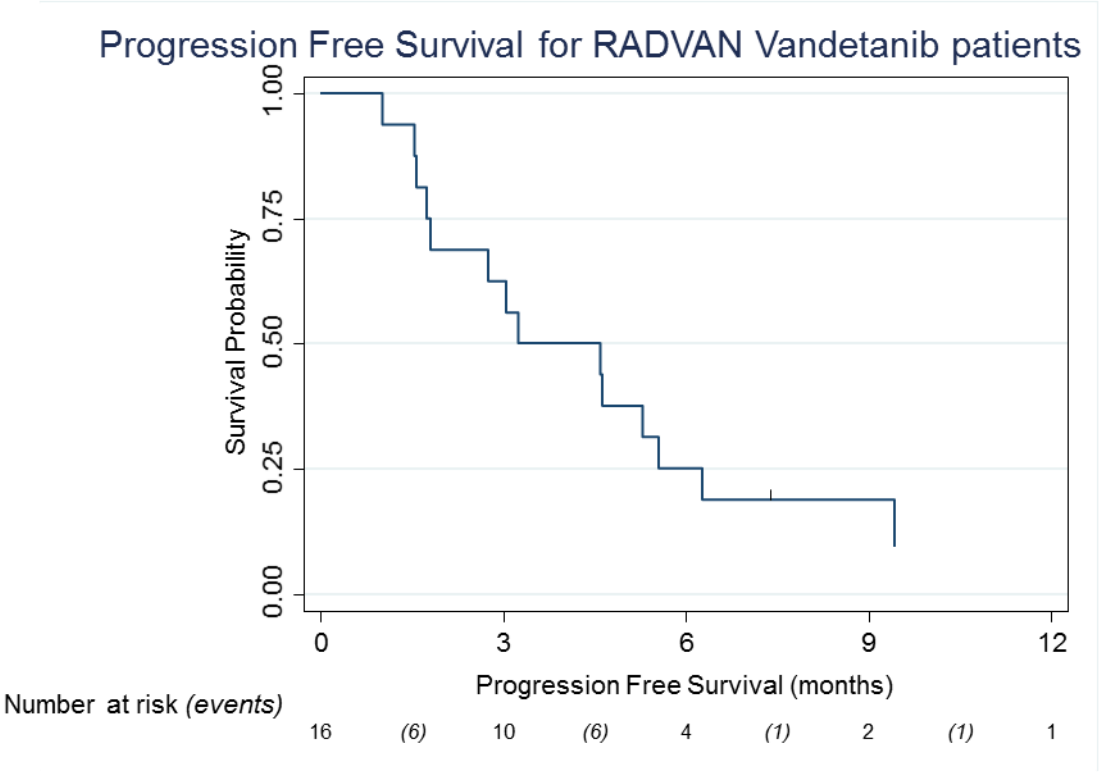
Progression-Free Survival Summary:

Treatment group	No. patients	No. events	Median PFS (90% CI) in months	Unadjusted HR (90% CI)
Placebo	8	8	2.50 (0.20, 4.83)	-
Vandetanib	10	9	3.25 (1.55, 5.56)	0.65 (0.29, 1.45)

Using the Log Cumulative Hazards Plot and the Schoenfield residuals plot (below) to assess the proportional hazards assumption suggests this assumption is violated, so the treatment effect has been obtained using a Weibull parametric proportional hazards model, and no significant difference in hazards was found.



Progression-Free Survival for all patients who received vandetanib (those randomised to the vandetanib arm and those in the safety cohort N=16):



Progression-Free Survival Summary:

Treatment group	No. patients	No. events	Median PFS (90% CI) in months
Vandetanib (randomised + safety cohort)	16	15	3.25 (1.81, 5.56)

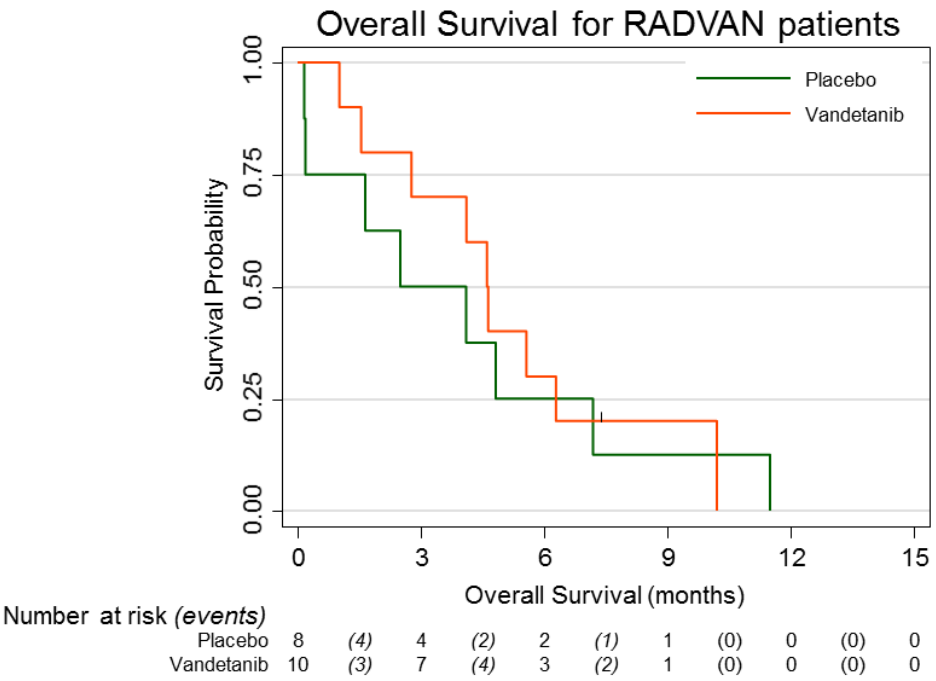
8.2 Secondary Analysis Results: Progression Free Survival in brain at 6 months

Treatment group	No. patients	PFS rate at 6 months %	Standard error	90% CI	Estimated difference in PFS rate % (90% CI)
Placebo	8	13	0.12	(1 to 37)	7 (-22 to 36) p=0.693
Vandetanib	10	20	0.13	(5 to 43)	

Progression Free Survival in brain at 6 months for all patients who received vandetanib:

Treatment group	No. patients	PFS rate at 6 months %	Standard error	90% CI
Vandetanib (randomised + safety cohort)	16	25	0.11	(10 to 44)

8.3 Secondary Analysis Results: Overall Survival (ITT analysis)

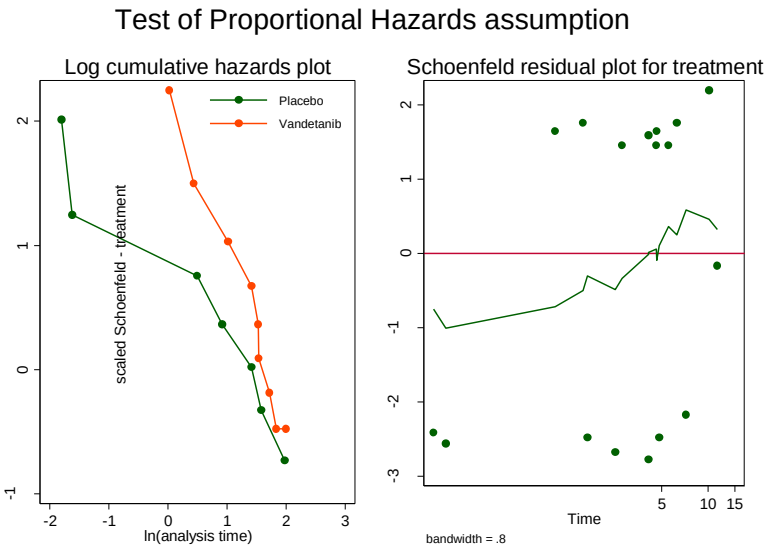


No statistically significant differences in OS between treatment groups (p=0.5366, Tarone-Ware test).

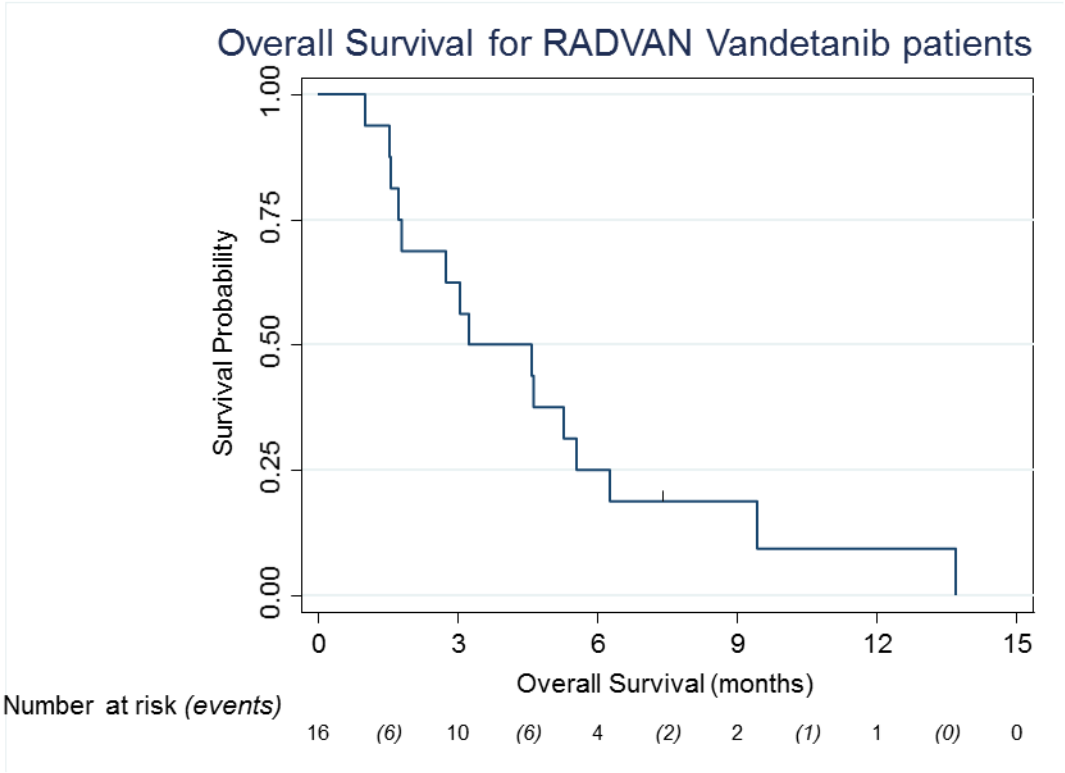
Overall Survival Summary:

Treatment group	No. patients	No. events	Median OS (90% CI) in months	Unadjusted HR (90% CI)
Placebo	8	8	2.50 (0.20, 7.20)	-
Vandetanib	10	9	4.60 (1.55, 6.28)	0.85 (0.37, 1.96)

Using the Log Cumulative Hazards Plot and the Schoenfield residuals plot (below) to assess the proportional hazards assumption suggests this assumption is violated, so the treatment effect has been obtained using a Weibull parametric proportional hazards model, and no significant difference in hazards was found.



Overall Survival for all patients who received vandetanib (those randomised to the vandetanib arm and those in the safety cohort; N=16):



Overall Survival Summary:

Treatment group	No. patients	No. events	Median OS (90% CI) in months
Vandetanib (randomised + safety cohort)	16	15	4.60 (1.55, 6.28)

8.4 Secondary Analysis Results: Safety

8.4.1 Adverse Events (AEs) – Graded by the NCI CTCAE Version 4.0

Table of frequency of all AEs, by treatment arm

AE event	Vandetanib + WRBT	Placebo + WBRT	All randomised	All who received vandetanib
	No.	No.	No.	No.
Alopecia	3	0	3	5
Confusion	2	0	2	5
Fatigue	5	4	9	9
Hypertension	0	0	0	0
QT-Prolongation	1	0	1	1
Skin toxicity	9	2	11	14
Gastrointestinal toxicity	7	2	9	13
Other toxicities	10	15	25	29
Total	**37**	**23**	**60**	**76**

Table of frequency of CTCAE ≥ grade 3 AEs, by treatment arm

AE event	Vandetanib + WRBT	Placebo + WBRT	All randomised	All who received vandetanib
	No.	No.	No.	No.
QT-Prolongation	1	0	1	1
Hypertension	0	0	0	0
Skin toxicity	0	0	0	0
Gastrointestinal toxicity	1	0	1	1
Other toxicities	4	4	8	8
Total	**6**	**4**	**10**	**10**

Table of frequency of all AEs per patient, by treatment arm

AE event	Vandetanib + WRBT	Placebo + WBRT	All randomised	All who received vandetanib
	No. of patients	No. of patients	No. of patients	No. of patients
QT-Prolongation	1	0	1	1
Hypertension	0	0	0	0
Skin toxicity	4	2	6	7
Gastrointestinal toxicity	5	2	7	8
Other toxicities	8	6	14	14
Any	**8**	**7**	**15**	**14**

Table of frequency of CTCAE ≥ grade 3 AEs per patient, by treatment arm

AE event	Vandetanib + WRBT	Placebo + WBRT	All randomised	All who received vandetanib
	No. of patients	No. of patients	No. of patients	No. of patients
QT-Prolongation	1	0	1	1
Hypertension	0	0	0	0
Skin toxicity	0	0	0	0
Gastrointestinal toxicity	1	0	1	1
Other toxicities	3	4	7	5
Any	**4**	**4**	**8**	**6**

Table of worst CTCAE grade AE per patient, by treatment arm

Worst CTCAE grade	Vandetanib + WRBT (N=10)	Placebo + WBRT (N=8)	All randomised (N=18)	All who received vandetanib (N=16)
	No. of patients (%)	No. of patients (%)	No. of patients (%)	No. of patients (%)
No AE reported	2 (20%)	1 (12.5%)	3 (16.7%)	2 (12.5%)
1	2 (20%)	0	2 (11.1%)	3 (18.8%)
2	2 (20%)	3 (37.5%)	5 (27.8%)	5 (31.3%)
3	4 (40%)	3 (37.5%)	7 (38.9%)	5 (31.3%)
4	0	1 (12.5%)	1 (5.6%)	1 (6.3%)

Table of frequency of AEs, by AE System and Term

AE System	AE Term	Vandetanib + WBRT	Placebo + WBRT	All randomised
Cardiac				
	Atrial Fibrillation	1	0	**1**
	Pericardial Effusion	1	0	**1**
Eye				
	Blurred vision	0	2	**2**
Gastrointestinal				
	Constipation	1	0	**1**
	Diarrhea	2	1	**3**
	Dysguesia	0	1	**1**
	Enterocolitis infectious	1	0	**1**
	Nausea	2	0	**2**
	Vomiting	1	0	**1**
General and administration site conditions				
	Fatigue	5	3	**8**
	Other - Headaches	0	1	**1**
Infections and Infestations				
	Infection	1	0	**1**
	Urinary tract infection	1	0	**1**
Investigations				
	QT-Prolongation	1	0	**1**
Musculoskeletal and connective tissue				
	Back pain	0	2	**2**
Nervous Systems				
	Ataxia	1	0	**1**
	Dysguesia	1	0	**1**
	Encephalopathy	1	0	**1**
	Headache	2	0	**2**
	Intracranial haemorrhage	1	0	**1**
	Other – Transient headaches	1	0	**1**
	Other – Transient Visual Disturbance	1	0	**1**
	Peripheral sensory neuropathy	0	1	**1**
Psychiatric				
	Confusion	2	0	**2**
	Other – migraines with shapes in eyes	0	1	**1**
Respiratory				
	Cough	1	2	**3**
	Dysphonia	0	1	**1**

AE System	AE Term	Vandetanib + WBRT	Placebo + WBRT	All randomised
	Dyspnoea	0	1	**1**
	Fatigue	0	1	**1**
	Pleural effusion	0	1	**1**
	Pneumonitis	0	1	**1**
	Sore throat	0	1	**1**
Skin & subcutaneous tissue				
	Alopecia	3	0	**3**
	Dry skin	1	0	**1**
	Other – cellulitis	1	0	**1**
	Pain of skin	1	0	**1**
	Rash maculo-papular	1	1	**2**
	Scalp pain	1	0	**1**
	Skin rash	0	1	**1**
	Skin reaction	1	0	**1**
Vascular				
	Thromboembolic event	0	1	**1**
	Total	**37**	**23**	**60**

8.4.2 AE Comparison

	Treatment Group		
	Vandetanib + WBRT	**Placebo + WBRT**	**Total**
Patients with at least one AE of CTCAE grade ≥3	6	4	10
Patients with no AEs of CTCAE grade ≥3	3	3	6
Total	9	7	16*

* Two patients did not receive any doses of treatment so they are not included in the safety analyses.

Using Chi square test yields $X^2 = 0.15$, $p = 0.70$, therefore non-significant; any difference in safety profile between treatment groups is observed by chance.

8.4.3 Vital Signs, Physical Examination and Electrocardiogram (ECG)

DAY 1	Vandetanib + WRBT [N=10]	Placebo + WBRT [N=7]
Vital signs: Median (range)		
- Systolic BP - Diastolic BP - Pulse rate	132.5 (87-153) 68 (56-93) 80.5 (58-114)	128 (117-138) 72 (66-85) 69 (57-100)
Weight: Mean (SD)	79.7 (13.9)	76.9 (17.1)
Electrocardiogram (ECG)	**n (%)**	**n (%)**
Normal	8 (80%)	5 (71.4%)
Abnormal but not clinically significant	1 (10%)	2 (28.6%)
Abnormal and clinically significant	1 (10%)	0
Physical examination	**n (%) (n=Freq. of patients with abnormal results)**	**n (%) (n=Freq. of patients with abnormal results)**
General appearance	0	0
Lymph Nodes	4 (40%)	1 (14%)
Head and neck	1 (10%)	1 (14%)
Skin	4 (40%)	1 (14%)
Eyes	0	0
Abdomen	1 (10%)	0
Respiratory	1 (10%)	0
Cardiovascular	1 (10%)	1 (14%)
Neurological	0	0
Dermatological	2 (20%)	1 (14%)
Musculoskeletal	2 (20%)	0

DAY 8	Vandetanib + WRBT [N=9*]	Placebo + WBRT [N=6*]
Vital signs: Median (range)		
- Systolic BP - Diastolic BP - Pulse rate	137 (110-146) 75 (68-89) 76 (53-98)	132 (122-151) 79 (66-89) 68 (62-81)
Weight: Mean (SD)	78.2 (12.0)	76.9 (1.2)
Electrocardiogram (ECG)	**n (%)**	**n (%)**
Normal	6 (66.7%)	4 (66.7%)
Abnormal but not clinically significant	2 (22.2%)	0
Abnormal and clinically significant	1 (11.1%)	0
Not done	0	2 (33.3%)
Physical examination	**n (%) (n=Freq. of patients with abnormal results)**	**n (%) (n=Freq. of patients with abnormal results)**
General appearance	1 (11%)	0
Lymph Nodes	3 (33%)	0
Head and neck	0	0
Skin	5 (56%)	1 (17%)
Eyes	0	0
Abdomen	0	0
Respiratory	1 (11%)	2 (33%)
Cardiovascular	1 (11%)	0
Neurological	1 (11%)	0
Dermatological	3 (33%)	1 (17%)
Musculoskeletal	2 (22%)	0

*** Data was not collected for all patients**

DAY 15	Vandetanib + WRBT [N=9*]	Placebo + WBRT [N=5*]
Vital signs: Median (range)		
- Systolic BP - Diastolic BP - Pulse rate	141 (105-150) 78 (64-84) 80 (50-104)	132.5 (122-156) 84.5 (67-87) 70.5 (64-74)
Weight: Mean (SD)	79.9 (11.6)	72 (8.5)
Electrocardiogram (ECG)	**n (%)**	**n (%)**
Normal	6 (66.7%)	4 (80%)
Abnormal but not clinically significant	3 (33.3%)	0
Abnormal and clinically significant	0	0
Not done	0	1 (20%)
Physical examination	**n (%) (n=Freq. of patients with abnormal results)**	**n (%) (n=Freq. of patients with abnormal results)**
General appearance	1 (11%)	0
Lymph Nodes	2 (22%)	0
Head and neck	0	0
Skin	6 (67%)	1 (20%)
Eyes	0	0
Abdomen	0	0
Respiratory	1 (11%)	0
Cardiovascular	1 (11%)	0
Neurological	1 (11%)	0
Dermatological	3 (33%)	1 (20%)
Musculoskeletal	1 (11%)	0

*** Data was not collected for all patients**

DAY 21/End of Treatment	Vandetanib + WRBT [N=10]*	Placebo + WBRT [N=5]*
Vital signs: Median (range)		
- Systolic BP - Diastolic BP - Pulse rate	145.5 (104-156) 82 (65-93) 78 (50-97)	136.5 (109-152) 77.5 (68-88) 82 (68-94)
Weight: Mean (SD)	78.3 (11.9)	65.8 (8.1)
Electrocardiogram (ECG)	**n (%)**	**n (%)**
Normal	6 (60%)	4 (80%)
Abnormal but not clinically significant	2 (20%)	0
Abnormal and clinically significant	0	0
Not done	2 (20%)	1 (20%)
Physical examination	**n (%) (n=Freq. of patients with abnormal results)**	**n (%) (n=Freq. of patients with abnormal results)**
General appearance	0	0
Lymph Nodes	2 (20%)	0
Head and neck	0	0
Skin	5 (50%)	2 (40%)
Eyes	0	0
Abdomen	0	0
Respiratory	0	0
Cardiovascular	0	0
Neurological	1 (10%)	0
Dermatological	2 (20%)	1 (20%)
Musculoskeletal	1 (10%)	0

*** Data was not collected for all patients**

30 days post EOT	Vandetanib + WRBT [N=4]*	Placebo + WBRT [N=3]*
Vital signs: Median (range)		
- Systolic BP - Diastolic BP - Pulse rate	117 (99-133) 69 (59-77) 77.5 (64-101)	123 (119-152) 79 (66-90) 78 (75-82)
Weight: Mean (SD)	79.2 (10.5)	67.1 (9.7)
Electrocardiogram (ECG)	**n (%)**	**n (%)**
Normal	0	0
Abnormal but not clinically significant	1 (25%)	0
Abnormal and clinically significant	0	1 (33.3%)
Not done	3 (75%)	2 (66.7%)
Physical examination	**n (%) (n=Freq. of patients with abnormal results)**	**n (%) (n=Freq. of patients with abnormal results)**
General appearance	1 (25%)	0
Lymph Nodes	1 (25%)	0
Head and neck	0	0
Skin	1 (25%)	0
Eyes	0	0
Abdomen	0	0
Respiratory	1 (25%)	0
Cardiovascular	0	0
Neurological	0	0
Dermatological	2 (50%)	0
Musculoskeletal	0	0

*** Data was not collected for all patients**

8.4.4 Serious Adverse Events

Throughout the RADVAN trial, there were 5 SAEs experienced by vandetanib + WBRT randomised arm patients, 4 SAEs experienced by the safety run-in patients, and 2 SAEs experienced by Placebo + WBRT randomised arm patients.

Trial no.	Event diagnosis	CTCAE grade	Start date	Stop date	Ongoing?	SUSAR?	Seriousness
RV001	Confusion	3	03-May-13	13-May-13	No	No	3.In-patient hospitalisation or Prolongation of existing hospitalisation
RV004	Haemorrhage of brain metastases	3	06-Aug-13	09-Aug-13	No	No	3.In-patient hospitalisation or Prolongation of existing hospitalisation
RV006	Pleural effusion.	3	02-Aug-13	16-Aug-13	No	No	3.In-patient hospitalisation or Prolongation of existing hospitalisation
RV007	Confusion	3	27-Aug-13	04-Sep-13	No	Yes	3.In-patient hospitalisation or Prolongation of existing hospitalisation
RV010	Interstitial Pneumonitis	3	18-Nov-13		Yes	No	3.In-patient hospitalisation or Prolongation of existing hospitalisation
RV014	Diverticular Abscess/perforation (Colonic Perforation)	4	21-Dec-13	23-Dec-13	No	Yes	2.Life Threatening
RV015	Interstitial Pneumonitis	3	13-Jan-14	30-Jan-14	Yes	No	3.In-patient hospitalisation or Prolongation of existing hospitalisation
RVS02	Cerebral oedema	4	19-Jul-12	21-Jul-12	No	No	3.In-patient hospitalisation or Prolongation of existing hospitalisation
RVS04	Confusion/cognitive disturbance	3	28-Nov-12	31-Dec-12	No	Yes	3.In-patient hospitalisation or Prolongation of existing hospitalisation
RVS04	Cognitive Disturbances	3	04-Dec-12	31-Dec-12	No	Yes (concurrent with above SAE)	3.In-patient hospitalisation or Prolongation of existing hospitalisation
RVS06	Constipation	2	29-Mar-13	05-Apr-13	No	No	3.In-patient hospitalisation or Prolongation of existing hospitalisation

8.5 Exploratory Analysis Results: Systemic Therapy

6 patients (3 from the safety cohort, 3 from the main study) required systemic therapy after their completion of the RADVAN study treatment. Details of their systemic therapy are given in the table below:

Trial no.	Systemic Therapy	Start date	End date	Ongoing?
RV003	Temzolomide	01Oct13	Dec-13	No
RV013	Ipilimumab	15Jan14	19Feb14	No
RV018	Ipilimumab	20Jun14	22Aug14	No
RV018	MK3475	16Oct14	-	Yes
RVS02	Dacarbazine	06Sep12	-	Yes
RVS04	Vemurafenib	10Apr13	-	Yes
RVS05	Immunotherapy	01May13	Nov-13	No
RVS05	Ipilimumab	11Dec13	27Dec13	No

Systemic Therapy	Frequency of patients received
Dacarbazine	1
Immunotherapy	1
Ipilimumab	3
MK3475	1
Temzolomide	1
Vemurafenib	1

The RADVAN patients will have needed further systemic treatment as part of ongoing disease control after RADVAN, especially for disease outside the brain, as the RADVAN treatment can only be expected to provide local control of brain metastases. This could have affected the OS analysis of the study.

8.6 Exploratory Analysis Results: Objective Response Rate

Where response is defined as Complete Response (CR), Partial Response (PR) or Stable Disease (SD) using RECIST criteria v1.1, the objective response rate 30 days post end of treatment (Day 51) for RADVAN randomised patients is 6/18 (33%).

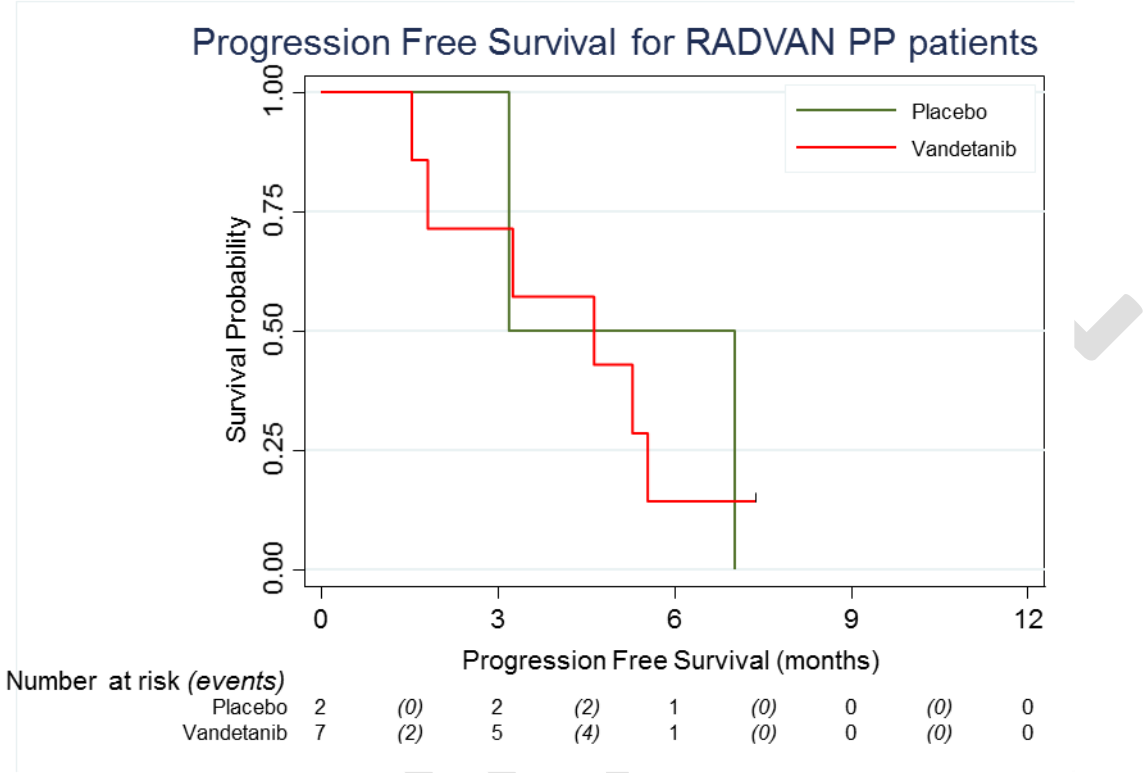
RECIST responses are recorded in the table below.

Trial no.	Timepoint at which response was measured					
	Day 51	4 Months	6 Months	8 Months	10 Months	12 Months
RV001	Progressive Disease					
RV002	Stable Disease	Stable Disease				
RV003	Stable Disease	Stable Disease				
RV004	Stable Disease					
RV005						
RV006						
RV007						

Trial no.	Timepoint at which response was measured					
	Day 51	**4 Months**	**6 Months**	**8 Months**	**10 Months**	**12 Months**
RV008						
RV009						
RV010	Stable Disease					
RV011						
RV012	Stable Disease	Stable Disease	Stable Disease	Progressive Disease		
RV013						
RV014						
RV015	Progressive Disease					
RV016						
RV017						
RV018	Partial Response	Partial Response	Partial Response	Partial Response		
Safety run-in phase patients						
RVS01	Stable Disease	Stable Disease				
RVS02						
RVS03	Stable Disease					
RVS04	Stable Disease	Stable Disease		Partial Response	Complete Response	Progressive Disease
RVS05	Stable Disease	Stable Disease	Stable Disease	Stable Disease	Stable Disease	
RVS06	Partial Response					

8.7 Sensitivity analysis: PFS in brain & PFS in brain at 6 months on per-protocol population

The following figure and table show Progression Free Survival and Progression Free Survival at 6 months in those patients who received 21 days of treatment drug (vandetanib/placebo) and 10 fractions of radiotherapy as per-protocol. As there were only 2 patients in the placebo arm who received their treatment as per-protocol, no formal tests have been carried out.



Progression-Free Survival Summary:

Treatment group	No. patients	No. events	Median PFS (90% CI) in months
Placebo	2	2	3.19 (3.19, .)*
Vandetanib	7	6	4.64 (1.55, 5.56)

* There is not enough information available in order for this to be calculated (only 2 patients).

Treatment group	No. patients	PFS rate at 6 months %	Standard error	90% CI
Placebo	2	50	0.35	(2 to 88)
Vandetanib	7	15	0.13	(1 to 41)

9. DISCUSSION

Failure to recruit patients was the main drawback to the RADVAN study. Unfortunately research teams across the country found it more difficult than expected to find patients who were suitable for the study and for whom the trial was the best treatment option for their cancer. The researchers recognised that recruitment was progressing slowly and tried to improve the recruitment rate by changing the eligibility criteria so that more people could join the study, and by removing some tests from the study to make clinic visits shorter. Recruitment targets were set but were, however, unfortunately not met.

The RADVAN TMG agreed to close the trial recruitment early after 24 of 86 patients had been recruited, and there was no indication from sites that the recruitment rate to the randomised trial (1.4 patients per month) would improve in the future. The group agreed that because patients couldn't be recruited quickly enough, the RADVAN team would not be able to fulfil the aim of the study with sufficient power, meaning that results from the study couldn't be obtained within a reasonable amount of time to allow the study to be useful for other patients in the future. Therefore the TMG felt that the risks to study participants of continuing with the study outweighed the possible benefits for participants and other cancer patients, hence they felt that the risk-benefit profile of the trial was such that closing the study to recruitment early was the most appropriate action. This decision was supported by the Independent Early Phase Trial Oversight Committee (IEPTOC), AstraZeneca and CTAAC. The TMG also agreed that the follow up period would be adjusted from 12 months from last randomisation to 7 months from last randomisation to enable the trial to close early. The trial closed in Nov 2014, at which point there was a median follow-up of 4.5 months on all patients.

On intention to treat analysis, median PFS in the brain was 3.25 months (90% confidence interval [CI]: 1.55-5.56) in those randomised to vandetanib, and 2.50 months (90% CI: 0.20-4.83) in those randomised to placebo; no statistically significant differences in PFS between the two treatment groups were found (p=0.339, Tarone-Ware test), although it must be noted that numbers were too small to accurately test for differences.
The 6-month PFS rates were 20% and 13% respectively. There were 17 deaths recorded during the trial and all were disease related; median OS was 4.60 months [90% CI 1.55-6.28] in those randomised to vandetanib and 2.50 months [90% CI 0.20-7.20] in the placebo group (p=0.537, Tarone-Ware test). This lack of significance may be due to no real difference but it might also be due to too few subjects and thus a lack of power to test it. Two deaths in the placebo arm occurred within a week of the patients starting treatment, both due to progressive disease.
For the safety analysis, all patients who received WBRT and vandetanib, in both the safety run-in phase and the randomised phase, were included. The most frequently occurring Adverse Events (AEs) were fatigue, confusion and alopecia. Of the total number of AEs, 14% were CTCAE grade 3-4. In total, 11 Serious Adverse Events (SAEs) occurred; 2 experienced by 2 of 8 patients randomised to placebo (25%), 5 by 5 of 10 patients randomised to vandetanib (50%), and 4 by 3 of 6 patients in the safety run-in phase (50%).. Common SAEs were confusion (experienced by 3 patients) and interstitial pneumonitis (experienced by 2 patients).

The combination of WBRT 30 Gy in 10 fractions plus vandetanib 100mg OD is straightforward to administer and tolerable in patients with melanoma brain metastases.
Median PFS in brain was increased with the combination, although this was not significant; the small number of patients recruited and lack of statistical power to detect differences between treatment arms prevented adequate evaluation of the benefit of vandetanib in addition to radiotherapy in melanoma patients.
Study recruitment proved more challenging than expected, partly due to increased treatment options for such patients, and partly because many patients were not fit enough to start study

treatment. These factors need to be carefully considered when designing future clinical trials for this patient population.

10. ABSTRACT

Abstract for NCRI 2015 conference

Theme: Diagnosis and Therapy

Authors: Avinash Gupta, Adelyn Wise, Matthew Goff, Linda Collins, Finn Tysoe, Sharon Love, Corran Roberts, Jenny Nobes, James Lester, Ernest Marshall, Carie Corner, Mark Middleton

Title: RADVAN: a randomised double blind phase 2 trial of whole brain radiotherapy with or without vandetanib in metastatic melanoma with brain metastases (ISRCTN20253034).

Background: The clinical incidence of brain metastases in patients with malignant melanoma ranges from 6% to 43%, and brain metastases contribute to death in >95% of cases. Until recently most patients were treated with whole brain radiotherapy (WBRT) with palliative intent and limited effectiveness. Vandetanib is an inhibitor of VEGF, EGF and RET receptor tyrosine kinases, and a potent radiosensitiser.

Method: Eligible patients with melanoma brain metastases were randomised (1:1) to radiotherapy with vandetanib or placebo. Patients received three weeks of either vandetanib 100mg once daily or placebo, starting 4 days (+/- 1 day) before WBRT (30 Gy in 10 fractions). The main study was preceded by a safety run-in phase with 6 patients to confirm regime tolerability. The main aim was to assess efficacy of vandetanib using the primary outcome of progression free survival in the brain (PFS brain) with secondary aims including safety and tolerability.

Results: From 71 patients screened, 6 patients were recruited to the safety run-in and a further 18 to the randomised phase which was then closed due to lack of accrual. At closure, in the randomised phase median PFS brain was 3.25 months 95%CI(1.0-5.6) in those randomised to vandetanib compared to 2.50 months 95%CI(0.2-4.8) in the placebo arm (p=0.339 Tarone-Ware test). There were 5 serious adverse events (SAEs) experienced by 5 patients in the arm randomised to vandetanib and 2 SAEs by 2 patients randomised to placebo.

Conclusions: The combination of WBRT plus vandetanib was found to be well tolerated in this patient population. Although median PFS brain was increased with the combination, this was not statistically significant due the lack of accrual. Study recruitment proved challenging due to the increased treatment options in this group of patients.

Acknowledgements: We would like to acknowledge the patients participating in the RADVAN study, study funding from NCRN-AZ alliance, study sponsorship from University of Oxford and site participation by Churchill Hospital, Clatterbridge Cancer Centre, Freeman Hospital, Mount Vernon Cancer Centre, Norfolk & Norwich University Hospital, St Bartholomew's Hospital, and Weston Park Hospital).

11. APPENDIX 1: RADVAN PRINCIPAL INVESTIGATORS

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Oxford Biomedical Research Centre

NHS National Institute for Health Research

UNIVERSITY OF OXFORD

RADVAN

Full title: A randomised double blind phase 2 trial of whole brain radiotherapy with or without vandetanib in metastatic melanoma with brain metastases

Short title: XRT +/- vandetanib in CNS melanoma

Safety Report

Version number 1.0 – 7th May2013

Based on protocol version 2.0 7thFeb2013, protocol decision plan version 2 1st Mar2013

Centre for Statistics in Medicine

REVIEW HISTORY		
Name	**Signature**	**Date**
Mark Middleton		
Sharon Love		

Sponsored by University of Oxford

octo Oncology Clinical Trials Office

OCTRU Oxford Clinical Trials Research Unit

UKCRC Registered Clinical Trials Units

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

CSM

Contents

1. INTRODUCTION

This document is for review by TMG. The document contains the safety information for patients in the safety cohort recruited into the trial who have received at least one dose of vandetanib therapy.

2. REPORT INFORMATION

This report includes a summary of the safety cohort which was originally planned as six patients. One patient did not complete the course of treatment (RVS04).They were not replaced.

Date of data-lock: 23Apr2013

Report prepared by: M Shanyinde, A Thomason, L Collins and S Love

Post-release note: clarifications have been added after review of the final CSR by AstraZeneca (December 2015 – February 2016), but no other changes have been made.

2.1 Protocol decision point

Incidence rates of grade 3 or more adverse events will be summarised in this safety cohort.

- If at least 5/6 patients have **no** grade 3 or more toxicity then start randomisation into the study on a starting dose of 100mg per day.

- Otherwise start on 100mg alternate days and check safety after 12 patients have been randomised.

Definitions specific to this decision point

Dose limiting toxicity:- Significant QT interval prolongation or any CTCAE grade 3 or 4 toxicity considered related to study treatment (study drug or radiotherapy) that cannot be adequately managed with optimal supportive care. Significant QTc prolongation is defined as:

- A single QTc value of ≥501 msec or an increase of ≥60 msec from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia (CTCAE grade 4)

OR

- Two consecutive QTc measurements, within 48 hours of one another, where either of the following criteria are met for both QTc values:

  - A QTc interval ≥501 msec (CTCAE grade 3) **OR**

  - An increase of ≥60 msec

Duration of treatment: - Patients in the safety run-in phase will receive vandetanib 100mg once daily starting 4 days (± 1 day) before whole brain radiotherapy and continuing for 21 days in total.

Toxicity rates: - Summarising incidence of grade 3 or more toxicity using CTCAE version 4.0. The number of toxicities of grade 3 or more, during treatment and for 30 days post study treatment will be summarised and listed in detail for the 6 patients (all of whom will receive vandetanib).

Tolerability will be defined as no study drug related toxicity of grade 3 or more (CTCAE version 4.0) in at least 5 out of the 6 patients in the safety run in phase at 30 days post end of study treatment.

3. BACKGROUND

3.1. Aims of the Trial

To compare Whole Brain Radiotherapy (WBRT) with or without vandetanib in the treatment of patients with brain metastases from melanoma, in terms of progression free survival in the brain.

Primary aim

- To assess the efficacy of vandetanib in combination with radiotherapy, compared with radiotherapy alone, in the treatment of patients with brain metastases from melanoma.

Secondary aims

- To further assess using other outcomes (progression free survival in brain at 6 months and overall survival), the efficacy of vandetanib in combination with radiotherapy, compared with radiotherapy alone, in the treatment of patients with brain metastases from melanoma.
- To assess the safety and tolerability of vandetanib in combination with radiotherapy, compared with radiotherapy alone.

3.2. Study Design

This is a randomised, double-blind, placebo-controlled, multi-centre Phase II trial. Eighty patients (forty in each of two arms) will be randomised 1:1 between radiotherapy with placebo or radiotherapy with vandetanib, with stratification for RPA score (2 levels; RPA 1 and RPA 2). Patients will receive three weeks of either vandetanib 100mg Once Daily (OD) or placebo, starting 4 days (+/- 1 day) before whole brain radiotherapy (30 Gy in 10 fractions). Patients will continue to be reviewed on study until progression of brain metastases (by RECIST version 1.1) or 12 months post randomisation into study, whichever comes first, and thereafter will be followed up for survival alone.

Safety run-in phase

The main study will be preceded by a non-randomised safety run in phase (involving 6 patients) to confirm the tolerability of vandetanib 100mg once daily with radiotherapy at 30 Gy in 10 fractions in this patient group. Tolerability will be defined as no study drug related toxicity of grade 3 or more (CTCAE version 4.0) in at least 5 out of the 6 patients in the safety run in phase at 30 days post end of study treatment.

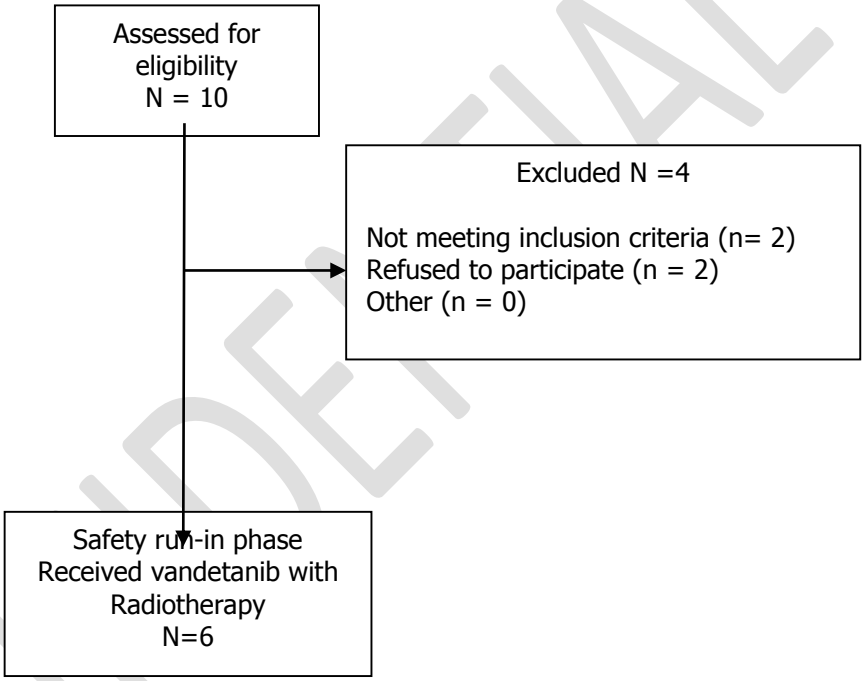
4. SUMMARY OF SCREENING LOGS

Site	Reason for inclusion/exclusion	N
Norfolk & Norwich	Eligible	3
	Recruited	3
	Declined	2
	Didn't want radiotherapy	1
	Unhappy to travel from distant local hospital	1
	Ineligible	1
	Due to more than 3 extra cranial metastases	1
Churchill	Eligible	2
	Recruited	2
	Ineligible	1
	Due to a concomitant medication exclusion	1
Clatterbridge	Eligible	1
	Recruited	1
Total		**10**
Not recruited		4
recruited		**6**

4.1 Recruitment summary

Site	Number of patients recruited
Norfolk & Norwich	3
Churchill	2
Clatterbridge	1

5. CONSORT FLOW DIAGRAM



6. BASELINE CHARACTERISTICS

The data below is a summary for all patients **excluding** RVS04

6.1 Demographic data

Characteristic	Number of patients
Gender, n Male Female	5 4 1
Age (yrs), n Mean(SD) Median (range)	5 71.6 (6.3) 73 (63-78)
Ethnicity, n White British	5 5
Smoking status, n Never Ex-smoker Current	5 3 2 0
Height (cm), n	5

Mean (sd) Median (range)	173.4 (8.9) 171.5 (161-185)

6.2 Disease staging

Characteristic	Number of patients
Histologically/cytologically proven malignant melanoma Yes	5 5
Controlled primary No Yes	5 2 3
Any extra cranial metastases Yes	5 5
Measurable disease(as per RECIST 1.1) Yes	5 5

6.3 Past medical history

Characteristic	Number of patients
Has patient received prior surgical treatment for this disease Yes	 5
Has patient received prior medical treatment for this disease No Yes	5 3 2
Has patient received any prior radiotherapy No Yes	5 4 1
Any significant medical or surgical history (not related to current disease) Yes	5 5

7. TREATMENT SUMMARY

7.1 IMP summary for each patient

Ptid	Starting Regime (ED = every day)	Did patient complete the study Tx	Date started-Date ended	Total duration of Tx (days)	Dose reduction
RSV01	100mg ED	Yes	02Feb2012-22Feb2012	21	No
RSV02	100mg ED	Yes	05Jul2012-26Jul2012	*21	No
RSV03	100mg ED	Yes	12Jul2012-02Aug2012	21	No
RSV04	100mg ED	No	22Nov2012-29Nov2012	7	No
RSV05	100mg ED	Yes	30Jan2013-19Feb2013	21	No
RSV06	100mg ED	Yes	14Feb2013-06Mar2013	21	No

*This patient had a note" *No doses missed but actually took an extra tablet so 22 taken in all. The patient got confused when completing diary card.*"

RVS04 experienced an SAE for confusion/cognitive disturbance which was reported as a SUSAR. The patient did not complete the study treatment and therefore was non-evaluable. See section 9, for more details.

7.2 Radiotherapy administration summary

Ptid	Total Gy delivered	Date Started RT	Date stopped RT	Duration	Total Days received RT (days)
RSV01	30	06Feb2012	17Feb2012	11	10

RSV02	30	09Jul2012	23Jul2012	14	10
RSV03	30	16Jul2012	27Jul2012	11	10
RVS04	30	26Nov2012	13Dec2012	17	10
RVS05	30	04Feb2013	15Feb2013	11	10
TVS06	30	18Feb2013	01Mar2013	11	10

7.3 Radiotherapy treatment grid pattern up to data-lock

ptid	Week	Monday	Tuesday	Wednesday	Thursday	Friday	Total days recv'd RT
RSV01	1	√	√	√	√	√	10
	2	√	√	√	√	√	
	3	0	0	0	0	0	
RSV02	1	√	√	√	√	√	10
	2	√	√	√	0	√	
	3	√	0	0	0	0	
RSV03	1	√	√	√	√	√	10
	2	√	√	√	√	√	
	3	0	0	0	0	0	
RSV04	1	√	√	√	0	√	10
	2	√	0	0	0	√	
	3	0	0	0	0	0	
	4	√	√	√	√	0	
RSV05	1	√	√	√	√	√	10
	2	√	√	√	√	√	
	3	0	0	0	0	0	
RSV06	1	√	√	√	√	√	10
	2	√	√	√	√	√	
	3	0	0	0	0	0	

8. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Based on the 23Apr2013 data-lock, 37 AE's incidences have been reported in 5 patients. Distribution of the CTCAE grades are shown in table 8.1 and full details of each AE for each patient are summarised in table 8.3.

8.1 Summary of AEs

Ptid	Number of Adverse Events	CTCAE grade distribution *(Key:CTCAE grade x = n)*	Maximum CTCAE grade
RVS01	18	Grade 1 = 15 Grade 2 = 3	Grade 2
RVS02	6	Grade 2 = 4 Grade 3 = 1 Grade 4 = 1	Grade 4
RVS03	2	Grade 2 = 2	Grade 2
RVS04	0	0	-
RVS05	5	Grade 1 = 5	Grade 1
RVS06	6	Grade 1 = 1 Grade 2 = 5	Grade 2
Total	**37**	Grade 1 = 21 Grade 2 = 14 Grade 3 = 1 Grade 4 = 1	

8.2 Summary of SAEs

There are a total of four SAEs (includes RVS04) in three patients.

Ptid	SAE event	Number of SAE's	CTCAE grade distribution *(Key:CTCAE grade x = n)*
RVS02	Cerebral Oedema	1	Grade 4
RVS04	Confusion/Cognitive disturbance Cognitive disturbance	2	Grade 3 Grade 3
RVS06	Constipation	1	Grade 3
Total		**4**	**Grade 3 = 3** **Grade 4 = 1**

8.3 Adverse Event Description

Ptid	Adverse Event	CTCAE grade	AE start date	AE end date	Ongoing	Outcome	Causality
RVS01	Leg weakness	2	01/10/2011	-	Yes	Persisting	Malignant disease
	Leg numbness	1	01/10/2011	16/02/2012	No	Resolved	Malignant disease
	Lower back pain	1	01/10/2011	16/02/2012	Yes	Persisting	Not known
	Headaches	1	01/01/2012	-	Yes	Persisting	Malignant disease
	Blurred vision	1	01/01/2012	16/02/2012	Yes	Persisting	Not known
	Leg twitching	1	01/02/2012	01/02/2012	No	Resolved	Not known
	Fatigue	1	07/02/2012	17/02/2012	No	Worsened	Study drug
	Cough	1	01/02/2012	-	Yes	Persisting	Study drug
	Taste change	1	08/02/2012	-	Yes	Persisting	Study drug
	Rash forehead	1	14/02/2012	01/03/2012	No	Resolved	Study drug
	Nausea	1	02/02/2012	16/02/2012	No	Resolved	Not known
	Chilitis	1	04/02/2012	23/03/2012	No	Resolved	Study drug
	Fatigue	2	18/02/2012	-	Yes	Persisting	Study drug
	Hair loss	1	19/02/2012	23/03/2012	No	Resolved	Study drug
	Respiratory tract infection	2	09/03/2012	23/03/2012	No	Resolved	Other illness
	Left sided tremor	1	23/03/2012	-	Yes	Persisting	Malignant disease
	Seizure	1	12/05/2012	12/05/2012	No	Resolved	Malignant disease
	Left leg coldness - possible ischaemic limb	1	02/02/2012	16/02/2012	No	Resolved	Other illness
RVS02	Seizure	2	19/07/2012	19/07/2012	No	Resolved	Malignant disease
	Confusion	2	19/07/2012	19/07/2012	No	Resolved with sequelae	Malignant disease
	Gait Disturbance	2	19/07/2012	19/07/2012	No	Resolved with sequelae	Malignant disease
	Dizziness	3	19/07/2012	19/07/2012	No	Resolved with sequelae	Malignant disease
	Cerebral oedema	4	19/07/2012	27/07/2012	No	Improved	Malignant disease, study procedures
	Oral Candida	2	24/08/2012	-	Yes	Persisting	Malignant disease, Other illness
RVS03	Oral mucosal infection (fungal)	2	03/08/2012	-	Yes	Persisting	Other illness

Ptid	Adverse Event	CTCAE grade	AE start date	AE end date	Ongoing	Outcome	Causality
	Fatigue	2	29/07/2012	-	Yes	Persisting	Malignant disease
RVS05	Fatigue	1	04/02/2013	-	Yes	Persisting	Study procedures, study drug
	Rash (forehead)	1	16/02/2013	13/03/2013	No	Resolved	Study procedures, study drug
	Nausea	1	04/02/2013	19/02/2013	No	Resolved	Study procedures, study drug
	Dry mouth	1	13/02/2013	-	No	Resolved	Study procedures, study drug
	Insomnia	1	31/01/2013	-	Yes	Persisting	Study procedures, study drug
RVS06	Constipation - (with overflow)	2	29/03/2013	-	Yes	Improved	Other illness, study drug
	Epsitaxis (secondary to tight fitting RT mask)	1	20/02/2013	-	No	Resolved	Study procedures
	Alopecia	2	01/03/2013	-	Yes	Persisting	Study procedures
	Skin and subcutaneous tissue disorders - Other- Excoriated skin peri-anal area (secondary to overflow)	2	30/03/2013	-	No	Resolved	Study procedures
	Dry mouth	2	01/03/2013	-	Yes	Improved	Not known
	Mucosal infection - fungal	2	30/03/2013	05/04/2013	No	Resolved	Other illness

8.4 Serious Adverse Event description

SAE log number	Event Description	CTCAE Grade	SAE start date – SAE stop date	Seriousness	Causality
RVSSAE101 (RVS02)	Cerebral oedema "*Patient experiences a seizure yesterday 19th July at home precipitated by confusion, dizziness and decrease in mobility. Admitted to hospital for assessment, medication and physiotherapy*" Event unexpected = *No* Event outcome = *Resolved with sequelae* Event ongoing = *No*	4	19Jul2012 – 21Jul2012	In-patient hospitalisation or Prolongation of existing hospitalisation	Probably not related to vandetanib, Definitely related to the disease under study Definitely related whole brain radiotherapy, Not applicable for background standard therapy or other trial intervention
RVSSAE102 (RVS04)	Confusion/cognitive disturbance *"Patient developed mild confusion and delusional ideas 28 Nov 2012. Multifactorial. Increasing symptoms at home precipitated admission to local hospital. Observation and lorazepam. Vandetanib temporarily held."* Event unexpected = *Yes* Event outcome = *Recovered* Event ongoing = *No*	3	28Nov2012 – 31Dec2012	In-patient hospitalisation or Prolongation of existing hospitalisation	Possibly related to vandetanib, Possibly related to the disease under study Possibly related to whole brain radiotherapy, Not applicable for background standard therapy or other trial intervention

SAE log number	Event Description	CTCAE Grade	SAE start date – SAE stop date	Seriousness	Causality
RVSSAE103 (RVS04)	Cognitive disturbance *"Patient had become increasingly confused and irrational behaviour. Family finding it increasingly difficult to cope at home as a direct result of this. Admitted to observe"* Event unexpected = *Yes* Event outcome = *Recovered* Event ongoing = *No*	3	04Dec2012 – 31Dec2012	In-patient hospitalisation or Prolongation of existing hospitalisation	Possibly related to vandetanib, Possibly related to the disease under study Possibly related to whole brain radiotherapy, Not applicable for background standard therapy or other trial intervention
RVSSAE104 (RVS06)	Constipation *"Patient presented to A&E on 30 Mar 2013 with history of dark loose stools x3 episodes since 29 Mar 2013 and abdominal discomfort. To exclude bowel perforation or obstruction a plain abdominal x-ray was performed. Also presented with oral candida and the patient reported that she had found it difficult to eat because of discomfort caused by this. X-ray revealed no abnormality. Admitted to hospital for IV fluids and ?gastroenteritis. Reviewed and clinical examination performed - impression was constipation (with overflow of faeces as a result), no infective process involved. Prescribed enema and laxative with a view to being discharged*	2	29/03/2013 – 05/04/2013	In-patient hospitalisation or Prolongation of existing hospitalisation	Possibly related to vandetanib Definitely not related to whole brain radiotherapy Probably not related to disease under study Definitely not related to background standard Definitely not related to other trial intervention

SAE log number	Event Description	CTCAE Grade	SAE start date – SAE stop date	Seriousness	Causality
	by the end of the week. Bowels opened following enema. Follow up received 05 Apr 2013: Reviewed on ward - constipation improving, bowels opened, normal stool yesterday. Oral candida resolved and medication for this has stopped. Plan is to discharge home after the weekend with support as lives alone. Was given two glycerin suppositories rectally on 02 Apr 2013 with effect. Commenced on body was to prevent MRSA (octenisan) on 03 Apr 2013" Event unexpected = *No* Event outcome = *Recovered* Event ongoing = *Yes*				

8.5 SAE signs and symptoms

SAE log number	Signs and Symptom	SANDS CTCAE Grade	SANDS start date – SANDS stop date	SANDS outcome	Ongoing
RVSSAE101 (RVS02)	Seizure	2	19Jul2012 - 19Jul2012	Recovered	No
	Dizziness	3	19Jul2012 - 19Jul2012	Recovered	No
	Dizziness	1	20Jul2012 – 09Oct2012	Not recovered	Yes
	Confusion	2	19Jul2012 - 20Jul2012	Recovered	No
	Gait disturbance	2	19Jul2012 - 19Jul2012	Recovered	No
	Gait disturbance	1	20Jul2012 – 09Oct2012	Not recovered	Yes
	Confusion	1	20Jul2012 – 09Oct2012	Not recovered	Yes
RVSSAE102 (RVS04)	Confusion	3	28Nov2012-31Dec2012	Recovered	No
	Cognitive impairment	3	04Dec2012-31Dec2012	Recovering	No
RVSSAE104	Constipation	2	29Mar2013-?	Recovering	Yes

(RVS06)	Dyspepsia	2	29Mar2013-05Apr2013	Recovered	No

8.6 Summary of Radiotherapy treatment at time of SAE

SAE log number	Fraction	Total Gy's at SAE	Action taken
RVSSAE101	8	24	Dose not changed
RVSSAE102	3	9	Withdrawn temporarily
RVSSAE103	5	9	Withdrawn temporarily
RVSSAE104	Finished RT	30	Dose not changed

9 SUSAR

There has been one SUSAR to date.

The patient [RVS04] was hospitalised on 28 Nov 2012 for grade 3 cognitive disturbance (confusions and delusions) and discharged on 29 Nov 2012. The patient was readmitted with the same symptoms on 04 Dec 2012. The PI commented on Friday 07 Dec 2012 that the patient is settled and well; a follow up CT showed some increasing oedema and the patient appears to be responding to increased dexamethasone. The radiotherapy was halted but will now restart, but vandetanib has been withdrawn. The site does not believe the event is reversible posterior leukoencephalopathy syndrome which is listed in the vandetanib IB. The event is temporally related to IMP and the patient's condition has improved since they were withdrawn so the site feels an IMP causation is likely. The cognitive impairment resolved on 31 Dec 2012.

In summary RVS04 experienced an SAE for confusion/cognitive disturbance which was reported as a SUSAR. Oedema was found around their brain metastases, dexamethasone dosage was increased and IMP was withdrawn. There was a break in whole brain radiotherapy but the course was completed. The SAE was felt to be more likely related to radiotherapy and the oedema than to the IMP. The patient had no other adverse events to be reported and commenced systemic therapy on 10 Apr 2013.

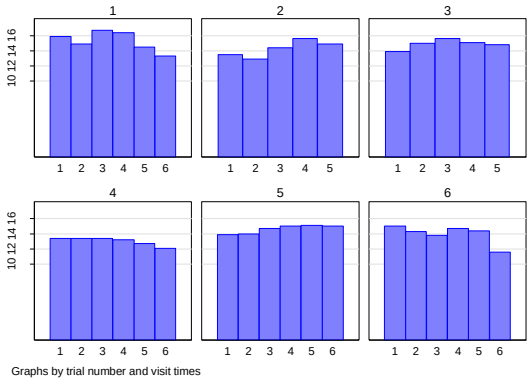
10 SUMMARY OF SAFETY RUN-IN PHASE

This study recruited six patients for the safety-run in phase. One patient RVS04 experienced an SAE reported as grade 3 confusion/cognitive disturbance which was reported as a SUSAR. RVS04 did not complete treatment and therefore was non-evaluable for the safety cohort, however safety data was collected. Another patient (RVS02) experienced an SAE reported as grade 4 cerebral oedema and IMP causality reported as probably not related to vandetanib. The patient did not miss any vandetanib and only missed one day of Radiotherapy. By definition of a DLT, the patient was adequately managed with optimal supportive care and therefore did not experience a DLT. This was confirmed with the clinician.

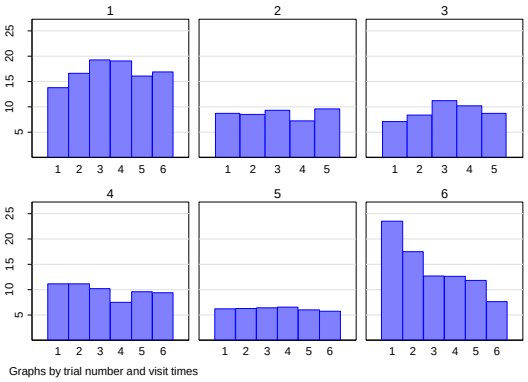
Therefore, our interpretation of the current data shows that no patients experienced a dose limiting toxicity in this safety cohort. The TMG agreed to proceed to the randomised phase of the trial of 100mg vandetanib/placebo once daily with 30Gy of whole brain radiotherapy.

11 HAEMATOLOGY: LABORATORY RESULTS

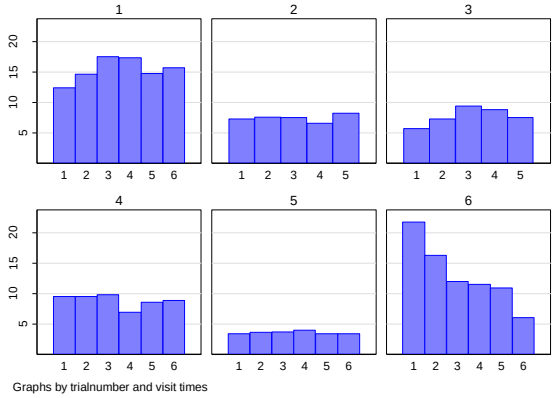
Haemoglobin



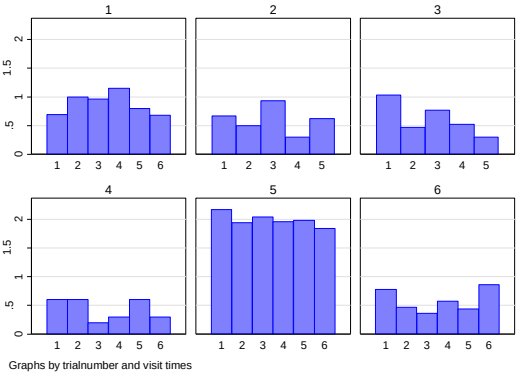
White blood cell count



Neutrophils



Lymphocytes



Platelets