END OF STUDY REPORT SUMMARY

Study Title: **A Phase II Study to Evaluate the Efficacy and Safety of PTK787 in Patients with Metastatic Cutaneous Melanoma**

Short Title: **PTK787 in advanced melanoma**

Date of first CA Authorisation: 24 February 2006

First Authorised in: United Kingdom

REC Reference Number: 06/MRE01/10

EudraCT Number: 2005-004710-33

ISRCTN191981

STUDY TITLE: A PHASE II STUDY TO EVALUATE THE EFFICACY AND SAFETY OF PTK787 IN PATIENTS WITH METASTATIC CUTANEOUS MELANOMA

TEST DRUG: PTK787/ZK222584 (Bayer Schering Pharma)

INDICATION: Advanced (metastatic) Melanoma

STUDY DESIGN: Investigator led, multi-centre, open label, uncontrolled, phase II

SPONSOR: Cambridge University Hospitals NHS Foundation Trust
R&D Department (Box 277), Addenbrooke's Hospital,
Hills Road, Cambridge CB2 0QQ

PROTOCOL CODE NUMBER: Camel 02

STUDY INITIATION DATE: 5th July 2006

STUDY COMPLETION DATE: 30th April 2009

COORDINATING INVESTIGATOR: Dr Pippa Corrie PhD FRCP, Consultant/Associate Lecturer, Oncology Centre, Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge CB2 0QQ

NAME OF SPONSOR SIGNATORY FOR REPORT: Dr Pippa Corrie, Oncology Centre, Addenbrooke's Hospital, Cambridge CB2 0QQ; Tel: 01223-216083 Fax: 01223-348071, Email: pippa.corrie@Addenbrookes.nhs.uk

THE STUDY WAS CONDUCTED ACCORDING TO THE PRINCIPLES OF GOOD CLINICAL PRACTICE

DATE OF REPORT: 30th April 2010

SYNOPSIS

Name of Sponsor/Company: Cambridge University Hospitals NHS Foundation Trust	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Vatalanib	Volume:	
Name of Active Ingredient: PTK787/ZK222584	Page:	

Title of Study:
A Phase II study to evaluate the efficacy and safety of PTK787 in patients with metastatic cutaneous melanoma

Investigators:
Dr Pippa Corrie (Chief Investigator and local Principal Investigator for Addenbrooke's Hospital, Cambridge) and Dr Anne Thomas (Principal Investigator at Leicester Royal Infirmary)

Study Centres:
Addenbrooke's Hospital, Cambridge and Leicester Royal Infirmary

Publication (reference):
A Phase 2 study of PTK787 in metastatic melanoma patients (submitted to BJC)

Study period:	**Phase of Development:**
From 5th July 2006 to 30th April 2009 (2 years + 10 months)	Phase II, open label, uncontrolled

Study Objectives:
Primary Objective: To determine the efficacy of PTK787 in patients with metastatic cutaneous melanoma in terms of Response Rate.
Secondary Objectives: 1) Time to progression; 2) Survival at 6 months and 1 year; 3)Overall survival; 4) Safety and toxicity; 5) Correlation of pharmacological and genetic markers to response; 6) Correlation of tumour vascularity and permeability to response.

Methodology:
Patients received an escalating dose of PTK787 over 15 days to reach the maximum dose of 1250mg daily. Each cycle of treatment was 28 days long; a minimum of two cycles was required to assess tumour status and the maximum period of therapy was 100 weeks. No dose adjustments for body surface or weight were made. In the case of unacceptable toxicity (assessed using NCI CTCAE version 3) the dose was reduced to 1000mg daily and further to 750mg daily.

Patients were assessed weekly during the first cycle and then after every subsequent cycle for adverse events. A complete blood count, biochemistry, physical examination, blood pressure measurement and urine analysis were assessed at each visit. Radiological assessment by CT scan was carried out every 8 weeks (2 cycles) in order to determine tumour response. In addition, plasma was collected for measurement of soluble markers of angiogenesis at baseline, after 4 weeks of treatment and then every 8 weeks of treatment until disease progression. Markers measured included Vascular Endothelial Growth Factor (VEGF), Vascular Endothelial Growth Factor Receptor 2 (VEGFR2), Hepatocyte Growth Factor (hepatocyte GF), Interleukin – 8 (IL-8), Lactate Dehydrogenase –A (LDH-A), and Placenta Growth Factor (PlGF).

Treatment was given until progressive disease, unacceptable toxicity or patient withdrawal. Thereafter, patients continued to be followed up for survival data. Patients who had not progressed by the end of the treatment period continued to have CT scans at 3-monthly intervals until such time as there was evidence of progression.

Six patient with at least 1 liver metastasis of >4cm were offered Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI) prior to starting treatment and then 1 week and 4 weeks after starting treatment.

Number of patients (planned and analysed):
Thirty four patients were recruited to the trial (as required by trial protocol) between July 2006 and January 2008. Eight of these patients had received prior systemic therapy for advanced disease.

Diagnosis and main criteria for inclusion:
Adults with pathologically-confirmed metastatic melanoma, ECOG performance status of 0-2, and adequate haematological, hepatic and renal function, were recruited to the study.

Test product, dose and mode of administration, batch number:
PTK787/ZK22584 is manufactured by Bayer Schering Pharma in 250mg tablets and is a selective inhibitor of the VEGR receptor tyrosine kinases, VEGFR-1 and VEGFR-2. In order to minimise immediate drug-related toxicities, patients received an escalating dose of PTK787 orally over 15 days, starting at 250mg twice daily for days 1-7, then increased to 500mg twice daily for days 8-15 and if tolerated, continued on the full dose of 1250mg daily divided as 500mg in the morning and 750mg in the evening with doses approximately 12 hours apart.

All 34 patients recruited to this trial received PTK787 batch number M19401 manufactured on 23/02/2004

Duration of treatment:
Each cycle of treatment was 28 days (4 weeks) and patients continued with treatment until documented disease progression or unacceptable toxicity. Twelve patients completed one or less cycle and two patients completed 25 cycles. From the other twenty patients, 11 completed 2-4 cycles, 8 completed 5-8 cycles and 1 completed 14 cycles.

Reference therapy, dose and mode of administration, batch number: N/A

Criteria for Evaluation:
Efficacy: Primary endpoint was disease (cancer) control rate, defined as complete response (CR), partial response (PR) and stable disease (SD) as best response. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total representative of all involved organs were identified as target lesions and recorded and measured at baseline. The best response achieved from the start of treatment until disease progression was recorded for each patient. Objective tumour response was evaluated according to RECIST criteria with a minimum of two cycles of treatment required to assess tumour status. Time to disease progression was measured from the date of trial registration until the date of documented disease progression.

Safety: All adverse events were recorded during the trial using NCI CTCAE version 3 criteria.

Statistical methods:
The trial used Flemings single stage design. If the disease control rate was less than 5% there would be no further interest in pursuing the development of PTK787 in the context of melanoma. If the rate was greater than 20% this might be considered clinically significant. α was set to 0.05 and β to 0.1, thus 34 patients were needed.

SUMMARY-CONCLUSIONS
Efficacy Results: Thirty patients were assessable for tumour response (the other four were withdrawn from study before their tumour response could be assessed). The median Progression Free Survival (PFS) was 1.8 months and median overall survival was 6.5 months. The tumour control rate (CR+PR+SD) was 35% although there were no complete responses. There were 6 patients (18%) who had stable disease for over 3 months. The one patient with a partial response had an overall survival of 6.5 months.

Safety Results: Overall, PTK787 was well tolerated and the main grade 3-4 toxicities included elevated liver enzymes, fatigue, neutropenia, hypertension, vomiting and dizziness.

Conclusion: Although overall survival was disappointing, PTK787 stabilised disease in a considerable proportion of patients with manageable toxicities. High baseline levels of LDH-A were correlated with a worse prognosis.

ETHICS

Favourable Ethical opinion of the PTK787 study was given by the South East Multi-Centre Research Ethics Committee (Kent and Medway Stategic Health Authority, Preston Hall, Aylesford, Kent ME20 7NJ) on 13th February 2006 with Dr J.M. Lamberty as Chair. This REC also reviewed and approved all amendments to the study submitted between February 2006 and April 2009.

The Ethics favourable opinion was extended to the two participating Sites, Addenbrooke's Hospital, Cambridge and Leicester Royal Infirmary, following site-specific assessment by Cambridge Research Ethics Committee (on 15/02/2006) and Leicester Northamptonshire & Rutland Research Ethics committee 1 (on 01/08/2006) respectively.

ETHICAL CONDUCT OF STUDY

It is confirmed that the study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and according to the Medicines for Human Use (Clinical Trials) Regulations incorporating EU Directives 2001/20/EC and 2005/28/EC.

LIST OF TABLES ATTACHED

Table 1: Demographics of patients registered on PTK787
Table 2: Duration of PTK787 treatment
Table 3: Baseline characteristics of patients on PTK787
Table 4: Efficacy results
Table 5: Listing of most common grade 2 and all grade 3 and 4 Adverse Events that were possibly, probably or definitely related to PTK787 treatment.

Table 1: Demographics of patients registered on PTK787

Patient number	Date of Registration	Participating Centre	Sex	Age at registration (years)
1	01/08/2006	Cambridge	M	37
2	08/11/2006	Cambridge	M	23
3	08/11/2006	Cambridge	M	35
4	22/11/2006	Cambridge	F	76
5	13/12/2006	Cambridge	M	57
6	09/01/2007	Cambridge	M	67
7	24/01/2007	Cambridge	M	73
8	13/02/2007	Leicester	F	74
9	28/02/2007	Cambridge	M	45
10	07/03/2007	Cambridge	F	54
11	14/03/2007	Cambridge	M	57
12	27/03/2007	Cambridge	F	69
13	03/04/2007	Leicester	M	65
14	30/05/2007	Leicester	F	31
15	19/06/2007	Leicester	M	58
16	19/06/2007	Leicester	M	66
17	27/06/2007	Cambridge	M	71
18	03/07/2007	Cambridge	M	54
19	11/07/2007	Leicester	M	57
20	25/07/2007	Cambridge	F	74
21	01/08/2007	Cambridge	M	48
22	01/08/2007	Cambridge	F	56
23	01/08/2007	Cambridge	M	63
24	11/09/2007	Leicester	F	62
25	12/09/2007	Cambridge	F	65
26	28/09/2007	Leicester	F	49
27	17/10/2007	Cambridge	M	55
28	31/10/2007	Cambridge	F	35
29	07/11/2007	Cambridge	M	65
30	28/11/2007	Leicester	F	79
31	05/12/2007	Cambridge	M	66
32	13/12/2007	Leicester	M	69
33	03/01/2008	Cambridge	F	77
34	23/01/2008	Cambridge	M	62
		Average age		**58.6**
		Median age		**62**

Table 2: Duration of PTK787 treatment

Patient number	Number of cycles* completed	Reason for ending treatment	Max dose of PTK787 achieved (mg)	DCE-MRI
1	6	Disease Progression	1250	No
2	3	Disease Progression	1250	No
3	5	Disease Progression	1250	No
4	2	Toxicity	500	Yes
5	8	Disease Progression	1250	No
6	7	Disease Progression	1250	No
7	2	Disease Progression	500	No
8	25	Drug expiry	1250	No
9	0	Disease Progression	1000	Yes
10	0	Toxicity	500	No
11	24	Drug expiry	1250	No
12	2	Disease Progression	750	Yes
13	1	Disease Progression	1250	No
14	1	Disease Progression	1250	Yes
15	1	Disease Progression	1250	No
16	1	Disease Progression	1250	No
17	8	Disease Progression	1250	No
18	6	Disease Progression	1250	No
19	0	Brain tumour	500	No
20	1	Toxicity	500	No
21	2	Disease Progression	1250	No
22	4	Disease Progression	1000	No
23	4	Disease Progression	1250	No
24	0	Disease Progression	1250	No
25	4	Disease Progression	1000	No
26	2	Disease Progression	1250	No
27	0	Toxicity	500	No
28	1	Toxicity and Progression	1250	No
29	5	Needed surgery	1250	No
30	1	Toxicity	1250	No
31	14	Drug expiry	1250	No
32	2	Disease Progression	1250	Yes
33	2	Disease Progression	1250	Yes
34	5	Disease Progression	1250	No

* Each cycle was 28 days

Table 3: Baseline characteristics of patients on PTK787

Patient No.	Site of primary	Breslow (mm)	Sites of metastasis	JCC staging	Baseline ECOG	Previous 1st line therapy?
1	lower limbs	5.0	lung, lymph node, abdomen	IV	0	Yes
2	head & neck	Not known	lung	IV M1b	0	No
3	lower limbs	5.7	lymph node, chest wall, lower limb	IV	0	No
4	unknown primary	Not known	liver	IV M1c	0	No
5	lower limbs	1.2	lung, liver, bone	IV	0	Yes
6	trunk	5.0	lung	IV M1b	0	Yes
7	head & neck	8.0	lung, lymph node, adrenals	IV	0	No
8	lower limbs	1.0	lymph node	IV M1a	0	No
9	unknown primary	Not known	liver, pancreatic tail, small bowel mesentery	IV	1	No
10	lower limbs	2.6	Lymph node	IV M1a	1	Yes
11	lower limbs	10.0	Lung, liver	IV	0	No
12	lower limbs	3.5	lung, liver, subcutaneous tissues	IV	1	Yes
13	trunk	2.0	lung, lymph node	IV	0	No
14	trunk	4.0	lung, lymph node	IV	0	No
15	trunk	0.4	lung, liver, lymph node	IV	0	No
16	upper limbs	0.9	lung, liver, bone, spleen	IV	0	No
17	ocular	Not known	lung, liver, bone, scalp, peritoneal deposits, right axilla	IV	0	Yes
18	right flank	2.3	lung, liver	IV	0	Yes
19	trunk	2.0	lung, liver, lymph node	IV	0	No
20	lower limbs	3.5	skin, lung, liver, lymph node	IV	0	Yes
21	trunk	Not known	liver, lymph node, spleen	IV	0	No
22	trunk	12.5	lung, liver	IV	1	No
23	trunk	Not known	lung, lymph node	IV	0	No
24	lower limbs	2.0	bone, lymph node	IV	1	No
25	lower	3.3	lung, lymph node, lytic	IV	0	No

	limbs		lesion L5			
26	lower limbs	2.3	lymph node	IV	0	No
27	trunk	7.5	lung, liver, left adrenal mass	IV	0	No
28	lower limbs	0.68	skin, lung, lymph node, pleural effusion, pelvis	IV	0	No
29	trunk	2.5	liver, small bowel, mediastinum	IV	0	No
30	trunk	5.0	lung, liver, lymph node, adrenal gland	IV	0	No
31	head & neck	4.0	lung, liver, lymph node, left neck	IV	0	No
32	trunk	13.5	liver, lymph node	IV	0	No
33	upper limbs	4.6	skin, lung, liver, artery & carpal tunnel nerve structures	IV	1	No
34	head & neck	7.0	skin, lung, lymph node	IV	0	No

Table 4: Efficacy results

Patient number	Overall survival (months) Cut off of 31/08/09	Time (months) to disease progression
1	11.1	3.5
2	5.7	1.6
3	11.3	1.8
4	15.9	5.8
5	14.4	7.2
6	9.9	4.2
7	6.5	1.8
8	25.1	25.1
9	1.3	0.7
10	1.5	Not determined
11	28.8	3.7
12	6.2	1.7
13	22.5	1.8
14	2.0	1.4
15	3.7	1.9
16	2.8	1.7
17	8.5	1.8
18	10.2	3.7
19	4.7	2.4
20	3.7	Not determined
21	9.0	1.8
22	8.3	1.8
23	14.6	3.6
24	1.0	Not determined
25	6.5	17.1
26	16.7	1.8
27	1.7	1.0
28	2.3	1.5
29	21.4	19.4
30	4.1	Not determined
31	20.0	11.8
32	3.9	1.7
33	3.6	1.8
34	6.6	3.7
Average	**9.3**	**4.6**
Median	**6.6**	**1.8**

Table 5: Listing of most common grade 2 and all grade 3 and 4 Adverse Events that were possibly, probably or definitely related to PTK787 treatment.

Toxicity	2		3/4*	
	No.	%	No.	%
Proteinuria	17	50	0	0
Elevated GGT	7	20.6	7	20.6
Elevated ALT	5	14.7	2	5.9
Fatigue	6	17.6	1	2.9
Hypertension	4	11.8	2	5.9
Nausea	6	17.6	0	0
Elevated Alk Phos	3	8.8	2	5.9
Dizziness	4	11.8	1	2.9
Vomiting	4	11.8	1	2.9
Elevated AST	2	5.9	1	2.9
Bilirubin in urine	2	5.9	1	2.9
Anorexia	3	8.8	0	0
Diarrhoea	2	5.9	0	0
Neutropenia	1	2.9	1	2.9
Leucopenia	2	5.9	0	0
Headache	2	5.9	0	0
Ataxia	1	2.9	1	2.9
Elevated T. Bili	0	0	1	2.9
Disorientation	0	0	1	2.9
Renal Colic	0	0	1	2.9

***All recorded toxicities were grade 3 with the exception of 2 (5.9%) grade 4 elevated GGT events**

SIGNATURE

Chief Investigator's Signature: PCC.....

Dr. P.G. CORRIE

Date 10/5/2010.....