EUROPEAN JOURNAL OF CANCER 46 (2010) 2671–2673

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Short Communication

A phase 2 study of vatalanib in metastatic melanoma patients ☆

Natalie Cook [a], *Bristi Basu* [a], *Swethajit Biswas* [a], *Paula Kareclas* [a], *Colette Mann* [a], *Cheryl Palmer* [a], *Anne Thomas* [b], *Steve Nicholson* [b], *Bruno Morgan* [b], *David Lomas* [a], *Bhawna Sirohi* [a], *Adrian P. Mander* [d], *Mark Middleton* [c], *Pippa G. Corrie* [a,*]

[a] *Cambridge University Hospitals NHS Foundation Trust (Addenbrookes Hospital), Cambridge, UK*
[b] *Dept. of Cancer Studies and Molecular Medicine, University of Leicester, University Hospitals of Leicester NHS Trust (Leicester Royal Infirmary), Leicester, UK*
[c] *University of Oxford, Department of Medical Oncology, Churchill Hospital, Old Road, Headington, Oxford OX3 7LJ, UK*
[d] *MRC Biostatistics Unit Hub in Trials Methodology Research, Cambridge, UK*

ARTICLE INFO

Article history:
Received 25 June 2010
Received in revised form 13 July 2010
Accepted 14 July 2010
Available online 25 August 2010

Keywords:
NGR-hTNF
Vascular targeting agent
Colorectal cancer

ABSTRACT

Background: A phase 2 study of vatalanib (PTK787/ZK222584) an oral tyrosine kinase inhibitor of VEGFR 1, 2 and 3 was undertaken in patients with metastatic melanoma.
Methods: Adults with pathologically confirmed metastatic melanoma, WHO Performance status 0–2, and adequate haematological, hepatic and renal function, were treated with vatalanib until disease progression. The trial used Fleming's single stage design.
Results: Tumour control rate (CR + PR + SD) was 35% at 16 weeks, with objective response seen in only 1 patient. Median progression-free survival was 1.8 months (95% CI 1.8–3.7 months) and median overall survival was 6.5 months (95% CI 3.9–10.2 months).
Conclusion: Vatalanib stabilised disease in a proportion of patients, although overall survival was disappointing.

1. Introduction

Metastatic melanoma is highly resistant to conventional cancer treatments.[1] Systemic therapy with either biological agents or cytotoxics offers limited survival benefit; therefore novel therapeutic strategies are urgently needed. Angiogenesis is essential for tumours to invade and metastasise, and inhibitors of angiogenesis are now available to treat a variety of cancers. Clinical trials of anti-angiogenesis drugs in melanoma have proved disappointing to date.[2–4]

Vatalanib (PTK787/ZK22584) is an oral multitargeted tyrosine kinase inhibitor which blocks VEGFR-1, VEGFR-2 and VEGFR-3, with additional activity against PDGFR and c-kit.[5] Vatalanib showed clinical activity in phase 1 and 2 trials in patients with several types of cancer.[6–8]

☆ *Research Support*: This study was sponsored by Cambridge University Hospitals NHS Foundation Trust, adopted by the UK National Cancer Research Institute (NCRI), supported by grants from Bayer Schering Pharma and Addenbrooke's Charitable Trust. M.R.M. is supported by the NIHR Biomedical Research Centre, Oxford.

* *Corresponding author:* Address: Oncology Centre, Cambridge University Hospitals NHS Foundation Trust, Cambridge CB2 0QQ, UK. Tel.: +44 1223 274401; fax: +44 1223.
E-mail address: pippa.corrie@addenbrookes.nhs.uk (P.G. Corrie).

0959-8049/$ - see front matter
doi:10.1016/j.ejca.2010.07.014

2. Materials and methods

2.1. Study design and treatment

This phase 2 study of vatalanib was undertaken to evaluate efficacy and safety in patients with metastatic melanoma. The primary end-point was disease control rate. The vatalanib regimen used in this study was 1250 mg total daily dose, taken orally, 500 mg in the morning and 750 mg in the evening. Patients were assessed weekly during the first cycle and then after every subsequent cycle. Radiological assessment by CT scan was performed every 8 weeks during treatment to determine tumour status. Treatment continued until disease progression, development of unacceptable toxicity or until patient refusal.

2.2. Patient eligibility

Inclusion criteria included histologically confirmed unresectable, metastatic cutaneous melanoma; the presence of measurable disease by RECIST; one prior treatment for metastatic disease was allowed as long as the outcome had been response to treatment or stable disease after a minimum of two cycles of planned treatment; ECOG performance status 0–2 and prior adjuvant therapy completed over 6 months previously. Patients were recruited from two United Kingdom institutions (Cambridge and Leicester). Ethics committee approval was obtained for each institution and written informed consent was obtained from all participants. The trial was conducted in accordance with the ICH-GCP standards and the Declaration of Helsinki.

2.3. Pharmacodynamic end-points

Patients with at least 1 liver metastasis of >4 cm were eligible for Dynamic Contrast Enhanced (DCE)-MRI scans at baseline, 2–6 d and 21–28 d after commencing treatment. Anonymised scan data were transferred to the University of Leicester for analysis. Scan and analysis protocols were as described previously.[9] Blood samples were taken for analysis of soluble angiogenesis markers.

2.4. Statistical design

Since response rates to systemic therapy are recognised to be extremely low in metastatic melanoma, and vatalanib is a cytostatic drug, the primary end-point for this study was disease control rate, defined as combining CR, PR and stable disease as the best response, measured at 8 weeks and maintained at 16 weeks, using RECIST. Using Fleming's single stage design, $\alpha = 0.05$ and $\beta = 0.1$, 34 patients were needed to obtain enough evidence to achieve a disease control rate of greater than 20% which might be of interest.

3. Results

3.1. Demographics

Thirty-four patients were recruited from August 2006 to January 2008. Baseline characteristics are summarised in Table 1

3.3. Toxicity and dose reductions

Forty-four percent of patients achieved the maximum daily dose for the duration of their treatment: 37% never achieved the maximum dose due to drug-related toxicity, while 19% required a dose reduction. Most common grade 3 adverse events included elevated liver enzymes (which were transient and reversible) and hypertension seen in 2 or more patients. The majority of dose modifications were for a combination of grade 2 toxicities, most commonly proteinuria, nausea, fatigue and dizziness.

3.4. Treatment efficacy

The tumour control rate (CR + PR + SD) was 35% for the 30 patients assessed. This was measured at 8 weeks and maintained at 16 weeks, using RECIST for response, although there was only 1 objective response (PR). The median PFS was 1.8 (95% CI 1.8, 3.7) months and median overall survival (OS) was 6.5 (95% CI 3.9, 10.2) months. Prior treatment did not significantly influence OS or PFS. Thirty-one patients had baseline LDH levels assessed and these appeared to correlate with overall survival. Baseline LDH over twice the upper limit of normal (>2×ULN) was associated with substantially worse outcomes: median survival was 2.3 months (95% CI 1, 3.9), compared with 9.0 months (95% CI 5.7, 14.4) for those with LDH levels <2×ULN (Cox proportional hazard ratio = 5.95, 95% CI 2.22, 19.95, p-value = 0.0013).

3.5. DCE-MRI analysis

Five patients underwent DCE-MRI studies. One case had a large tumour and visibly showed some new small areas of necrosis on treatment. The quantitative data showed a significant enhancement reduction (reduction in K^{trans} of >30%). A further case, for which no quantitative data were available, showed a reduction in enhancement on treatment which was estimated to result in a reduction in K^{trans} of >50%. No correlations were identifiable between soluble angiogenesis markers and patient outcomes, although complete datasets were available for only 8 patients.

4. Discussion

This phase 2 trial of vatalanib monotherapy in patients with metastatic melanoma revealed that the proposed twice-daily split-dose regimen remains difficult for patients to tolerate, with almost half the patients failing to achieve the maximum total daily dose of 1250 mg.

Vatalanib treatment achieved disease control in 35% of patients, one quarter of whom had received prior chemotherapy. Three patients continued on treatment for 12 months or more and 5 remain alive, but median PFS and OS were disappointing. Our attempts to identify pharmacological or functional markers predictive for better outcome with vatalanib were of limited value, in part due to limited data available to analyse. Evaluating DCE-MRI in patients with large liver metastases, vatalanib appeared to have a variable effect, with reduction in vascularity evident in 2 of 5 patients. DCE-MRI

Table 1 – Patient characteristics.

	No. (%)
No. of patients	34
Sex	
Male	21 (62)
Female	13 (38)
Median age, years (range)	62 (23–79)
AJCC Disease Stage	
IV	34 (100)
IV M1a	4 (12)
IV M1b	2 (6)
IV M1c	28 (82)
Prior therapy	
No prior therapy	26 (76)
Prior therapy	8 (24)
WHO performance status	
0	28 (82)
1	6 (18)
2	0 (0)
Baseline LDH	
<2×ULN	24 (71)
>2×ULN	7 (20)
Not determined	3 (9)

may be a potential tool for the assessment of early response to angiogenesis inhibitors, but more patients would be required to address this fully. As in previous metastatic melanoma studies, a negative association between OS and serum LDH was demonstrated.[10]

In summary, vatalanib does not have useful clinical activity in metastatic melanoma. Agents with similar mechanisms of action are being evaluated in earlier stage disease. It will be important to identify pharmacological and functional markers of outcome which could assist in identifying subgroups of patients more likely to benefit from such treatment.

Role of the funding source

This was an investigator-initiated study designed by the corresponding author. Addenbrookes Charitable Trust provided an educational grant. Bayer Schering Pharma provided vatalanib free of charge for trial participants. The study was sponsored by the Cambridge University Hospitals NHS Foundation Trust (UK) and adopted by the UK National Cancer Research Institute (NCRI). Data collection and other logistical aspects of the study were managed by the Cambridge Cancer Trials Centre.

Contributors

P.C. conceived and designed the study; P.C., N.C., S.B., B.B., C.P., A.T. and S.N. were involved in the provision of study patients and data; C.M. and P.K. were involved in the collection and verification of patient data; B.M. and D.M. were responsible for DCE-MRI studies and B.M. was responsible for data analysis; M.M. was responsible for analysis of patient serum for biomarker assays. P.C., P.K., A.M., S.B., B.B. and N.C. were involved in overall study data analysis and interpretation; P.C., N.C., S.B. and B.B. were involved in manuscript writing; all authors gave approval of the final manuscript.

Conflict of interest statement

None declared.

REFERENCES

1. Tsao H, Atkins MB, Sober AJ. Management of cutaneous melanoma. *N Engl J Med* 2004;**351**(10):998–1012.
2. Varker KA, Biber JE, Kefauver C, et al. A randomized phase 2 trial of bevacizumab with or without daily low-dose interferon alfa-2b in metastatic malignant melanoma. *Ann Surg Oncol* 2007;**14**(8):2367–76.
3. Eisen T, Ahmad T, Flaherty KT, et al. Sorafenib in advanced melanoma: a Phase II randomised discontinuation trial analysis. *Br J Cancer* 2006;**95**(5):581–6.
4. Fruehauf Jea. Axitinib (AG-013736) in patients with metastatic melanoma: a phase II study. *J Clin Oncol* 2008:26 [abstract 9006].
5. Wood JM, Bold G, Buchdunger E, et al. PTK787/ZK 222584, a novel and potent inhibitor of vascular endothelial growth factor receptor tyrosine kinases, impairs vascular endothelial growth factor-induced responses and tumor growth after oral administration. *Cancer Res* 2000;**60**(8):2178–89.
6. Gauler TCea. Phase II open-label study to investigate efficacy and safety of PTK787 orally administered once daily at 1250mg as second line monotherapy in patients with stage IIIB or IV non-small cell lung cancer. *Proc Am Soc Clin Oncol* 2006;**24**:274s [abstract 5075].
7. Thomas AL, Trarbach T, Bartel C, et al. A phase IB, open-label dose-escalating study of the oral angiogenesis inhibitor PTK787/ZK 222584 (PTK/ZK), in combination with FOLFOX4 chemotherapy in patients with advanced colorectal cancer. *Ann Oncol* 2007;**18**(4):782–8.
8. Conrad C. A phase I/II trial of single-agent PTK 787/ZK 222584 (PTK/ZK), a novel, oral angiogenesis inhibitor, in patients with recurrent glioblastoma multiforme (GBM). *J Clin Oncol* 2004;**22**(14s):1512.
9. Morgan B, Utting JF, Higginson A, et al. A simple, reproducible method for monitoring the treatment of tumours using dynamic contrast-enhanced MR imaging. *Br J Cancer* 2006;**94**(10):1420–7.
10. Agarwala SS, Keilholz U, Gilles E, et al. LDH correlation with survival in advanced melanoma from two large, randomised trials (Oblimersen GM301 and EORTC 18951). *Eur J Cancer* 2009;**45**(10):1807–14.