BJU Int 2020; **126:** 292–299 doi:10.1111/bju.15096

BJUI
BJU International

Original Article

A randomised Phase II trial of carboplatin and gemcitabine ± vandetanib in first-line treatment of patients with advanced urothelial cell cancer not suitable to receive cisplatin

Robert Jones[1], Simon Crabb[2], John Chester[3,4,5], Tony Elliott[6], Robert Huddart[7], Alison Birtle[8], Linda Evans[9], Jason Lester[4], Satinder Jagdev[5], Angela Casbard[10], Chao Huang[10,11], Tracie-Ann Madden[10] and Gareth Griffiths[2,10]

[1]Beatson West of Scotland Cancer Centre, University of Glasgow, Glasgow, [2]Southampton Clinical Trials Unit, University of Southampton, Southampton, [3]Cardiff University, [4]Velindre Cancer Centre, Cardiff, [5]St. James's University Hospital, Leeds, [6]Christie Hospital NHS Foundation Trust, Manchester, [7]Institute of Cancer Research, Sutton, [8]Royal Lancaster Infirmary, Lancaster, [9]Weston Park Hospital, Sheffield, [10]Centre for Trials Research, Cardiff University, Cardiff, and [11]Hull York Medical School, University of Hull, Hull, UK

Objectives

To assess the efficacy and tolerability of the dual epidermal growth factor receptor/vascular endothelial growth factor receptor inhibitor, vandetanib, in combination with carboplatin and gemcitabine in the first-line treatment of patients with advanced transitional cell carcinoma urothelial cancer (UC) who were unsuitable for cisplatin.

Patients and methods

From 2011 to 2014, 82 patients were randomised from 16 hospitals across the UK into the TOUCAN double-blind, placebo-controlled randomised Phase II trial, receiving six 21-day cycles of intravenous carboplatin (target area under the concentration versus time curve 4.5, day 1) and gemcitabine (1000 mg/m^2 days 1 and 8) combined with either oral vandetanib 100 mg or placebo (once daily). Progression-free survival (PFS; primary endpoint), adverse events, tolerability and feasibility of use, objective response rate and overall survival (OS) were evaluated. Intention-to-treat and per-protocol analyses were used to analyse the primary endpoint.

Results

The 82 patients were randomised 1:1 to vandetanib (n = 40) or placebo (n = 42), and 25 patients (30%) completed six cycles of all allocated treatment. Toxicity Grade ≥3 was experienced in 80% (n = 32) and 76% (n = 32) of patients in the vandetanib and placebo arms, respectively. The median PFS was 6.8 and 8.8 months for the vandetanib and placebo arms, respectively (hazard ratio [HR] 1.07, 95% confidence interval [CI] 0.65–1.76; P = 0.71); the median OS was 10.8 vs 13.8 months (HR 1.41, 95% CI 0.79–2.52; P = 0.88); and radiological response rates were 50% and 55%.

Conclusion

There is no evidence that vandetanib improves clinical outcome in this setting. Our present data do not support its adoption as the regimen of choice for first-line treatment in patients with UC who were unfit for cisplatin.

Keywords

carboplatin, gemcitabine, randomised controlled trial, tyrosine kinase inhibitor, urothelial carcinoma, vandetanib

Introduction

There are ~10 000 patients newly diagnosed with urothelial cancer (UC) in the UK [1] and 118 000 in Europe [2] per annum. Around 38% die within 1 year of diagnosis. The majority of UC deaths are caused by locally advanced or metastatic invasive bladder cancer. Advanced UC is a chemosensitive disease with response rates to cisplatin-containing regimens in previously untreated patients of ~55% and with a median overall survival (OS) in the region of 14 months [3,4]. However, cisplatin-based chemotherapy is not suitable for ~40% of patients [5], due to reasons such as

insufficient renal function, performance status or comorbidity. Much of the focus of clinical trials has been on improving outcomes in the cisplatin-fit population, but there is also a need to improve outcomes in the sizable minority of patients currently treated with non-cisplatin containing regimens.

For many of these patients, the standard of care is a combination gemcitabine plus carboplatin (GC) chemotherapy, giving a median progression-free survival (PFS) of between 4.8 and 5.3 months [6-9]. UC frequently expresses a variety of growth factor receptors, including epidermal growth factor receptors (EGFRs) and vascular endothelial growth factor receptors (VEGFRs) [10-12]. Over-expression of VEGF and its receptors in UC was associated with poor prognosis [13,14], suggesting a role for VEGF/VEGFRs in pathogenesis and potential clinical utility for molecularly targeted agents directed against these cell-surface receptors.

Vandetanib (ZD6474; Caprelsa®) is an oral tyrosine kinase inhibitor selective for VEGFR-1, VEGFR-2, VEGFR-3, and EGFR. Preclinical data have shown that vandetanib induced cell death *in vitro* at clinically meaningful concentrations in several UC cell lines, and that this effect was synergistic with platinum-containing chemotherapy agents [15]. *In vivo*, pharmacological inhibition of EGFR or VEGFR had anti-tumoral effects in carcinogen-induced and orthotopic models of bladder cancer, respectively [16,17]. Vandetanib has shown efficacy as a single agent in clinical trials for medullary thyroid cancer [18], and in combination with docetaxel in the second-line treatment of locally advanced or metastatic non-small cell lung cancer [19].

Our hypothesis was that co-targeting both EGFRs and VEGFRs may improve survival outcomes in patients with advanced UC who are not suitable to receive cisplatin as first-line treatment. The primary goal of the TOUCAN trial was to establish whether vandetanib combined with GC chemotherapy is safe and gives sufficient activity to warrant a future Phase III trial in this patient group.

Patients and methods

Study design

TOUCAN was a double-blind, parallel group, randomised screening Phase II trial approved by a UK multicentre research ethics committee (Ref:09/S0703/98) and the UK Medicine and Health care products Regulatory Agency (MHRA) [ClinicalTrials.gov Identifier: NCT01191892 and International Standard Randomised Controlled Trial Number (ISRCTN) 68146831]. The TOUCAN trial was funded by the AstraZeneca and the UK National Institute for Health Research (NIHR) Clinical Research Network (CRN):Cancer – Combinations Alliance, Cancer Research UK (CRUKE/09/024), and CRUK core funding to the Centre for Trials Research, Cardiff University . This was an academically sponsored clinical trial sponsored by Cardiff University.

Patients were eligible if they were aged ≥18 years; had histologically confirmed UC with TCC (pure or mixed histology); had radiologically measurable, locally advanced and/or metastatic disease [Response Evaluation Criteria In Solid Tumors (RECIST), version 1.1]; were not amenable to curative treatment with surgery or radiotherapy; and were not suitable for cisplatin. Unsuitability for cisplatin was defined as one or more of the following: (i) creatinine clearance <60 mL/min; (ii) Eastern Cooperative Oncology Group Performance Status (ECOG PS) =2 (N.B. patients are excluded if ECOG PS was >=3) ; (iii) clinically significant ischaemic heart disease; (iv) prior intolerance of cisplatin; (v) age >75 years; (vi) any other factor, which, in the opinion of the investigator indicated that cisplatin was not suitable. Patients were also ineligible for the trial if their creatinine clearance was <30 mL/min. All patients provided written informed consent.

The patients were randomly assigned (1:1) either to vandetanib or placebo in addition to GC with stratification by institution, ECOG PS (0–1 and 2) and renal function (creatinine clearance <60 vs ≥60 mL/min, calculated using the Cockcroft and Gault formula) using a central interactive web response system.

All patients received up to six 21-day cycles of carboplatin [target area under the concentration versus time curve (target AUC) 4.5] by intravenous infusion over 30–60 min on day 1 and gemcitabine (1000 mg/m^2) by intravenous infusion over 30 min, days 1 and 8, in combination with either vandetanib 100 mg or placebo once daily. The carboplatin dose was calculated using the Calvert formula {carboplatin dose (mg) = AUC × [GFR (mL/min) + 25]}. The corrected QT interval and laboratory safety parameters were measured every 21 days throughout the treatment phase.

Clinical and radiological response assessments were performed at weeks 9, 18, 26, 39 and 52 after the commencement of treatment, with radiological response assessed by comparison with baseline data, according to RECIST, version 1.1.

Endpoints

The primary endpoint was PFS, defined as the time from randomisation to disease progression and/or death. Those still alive and progression free were censored at the date last seen. Secondary endpoints included: safety, assessed via real-time serious adverse event (AE) reporting and at patients visits using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0; tolerability and feasibility of use of treatment, which was assessed by calculating the number of treatment reductions, delays and treatment withdrawals;

objective response, which was derived from radiological assessments and; OS, defined as the time from randomisation to death from any cause, censoring for those still alive at time last seen.

Statistical analysis

This was a placebo-controlled, randomised screening Phase II trial. The median PFS in patients with advanced UC not suitable for cisplatin was estimated to be ~5.3 months with chemotherapy. The sample size was calculated assuming 24-month recruitment, with 80% power and a one-sided α (type I error) of 0.2. Allowing a drop-out rate of 5%, 82 participants and 62 (PFS) events were required to demonstrate a hazard ratio (HR) of 0.65, based on the log-rank test. The data were analysed after 65 events were observed. A Phase III confirmatory trial was to be planned if there was statistical significance at the 10% level. In the event of statistical significance between 10.1% and 20%, a confirmatory trial was planned only if secondary endpoints indicated benefit.

At the end of the trial, analyses were performed on both intention-to-treat (ITT) and planned-per-protocol analysis (PPA) basis. The PPA excluded patients found to be ineligible or who did not start their trial medication during cycle 1.

Kaplan–Meier curves of PFS and OS were plotted and these were used to calculate the median PFS and OS for each arm. The Mantel–Cox version of the log-rank test (unadjusted) was used to assess the effect of vandetanib on PFS and OS. In addition, a planned adjusted analysis for the primary endpoint of PFS using a Cox proportional hazards model, including the stratification factors used in the randomisation, was performed (i.e., ECOG PS and renal function, with institution included in the model as a shared frailty). The secondary endpoints were presented as the proportion (and 95% CI) of patients in each treatment arm with: (i) an objective disease response (based on RECIST v1.1); (ii) Grade ≥3 toxicity; and (iii) a treatment reduction, delay and treatment withdrawal. No subgroup analyses were performed. There were no pre-defined early stopping guidelines.

An independent safety committee reviewed the trial throughout; including formal safety reviews after the first 10 and 20 patients in each arm had been recruited.

Results

Baseline patient and tumour characteristics

The 82 patients were randomised from 16 hospitals across the UK, between April 2011 and December 2014. A Consolidated Standards of Reporting Trials (CONSORT) diagram is shown in Fig. 1. Baseline patient and tumour characteristics were similar in the two treatment arms and are presented in Table 1.

Treatment tolerability and feasibility of use

In all, 13 (33%) of the 40 participants assigned to receive vandetanib and 25 (60%) of the 42 assigned to placebo received all six cycles of GC. The median (interquartile range [IQR]) numbers of cycles received were 5 (3.5–6) and 6 (4–6), in the vandetanib and placebo arms, respectively. Patients received a median (IQR) of 88 (46–116) days of vandetanib and 105 (63–126) days of placebo. Eight (20%) of the 40 participants in the vandetanib arm received all six cycles of vandetanib; 22 (55%) failed to do so because of toxicity, three (8%) because of progression, three (8%) due to patient choice, two (5%) due to death, and two (5%) for unknown reasons. In all, 17 (41%) of the 42 patients in the placebo arm received all six cycles of placebo; 14 (33%) did not do so due to toxicity, seven (17%) due to disease progression, one (2%) by patient choice, one (2%) due to death, and two (5%) for unknown reasons.

Safety

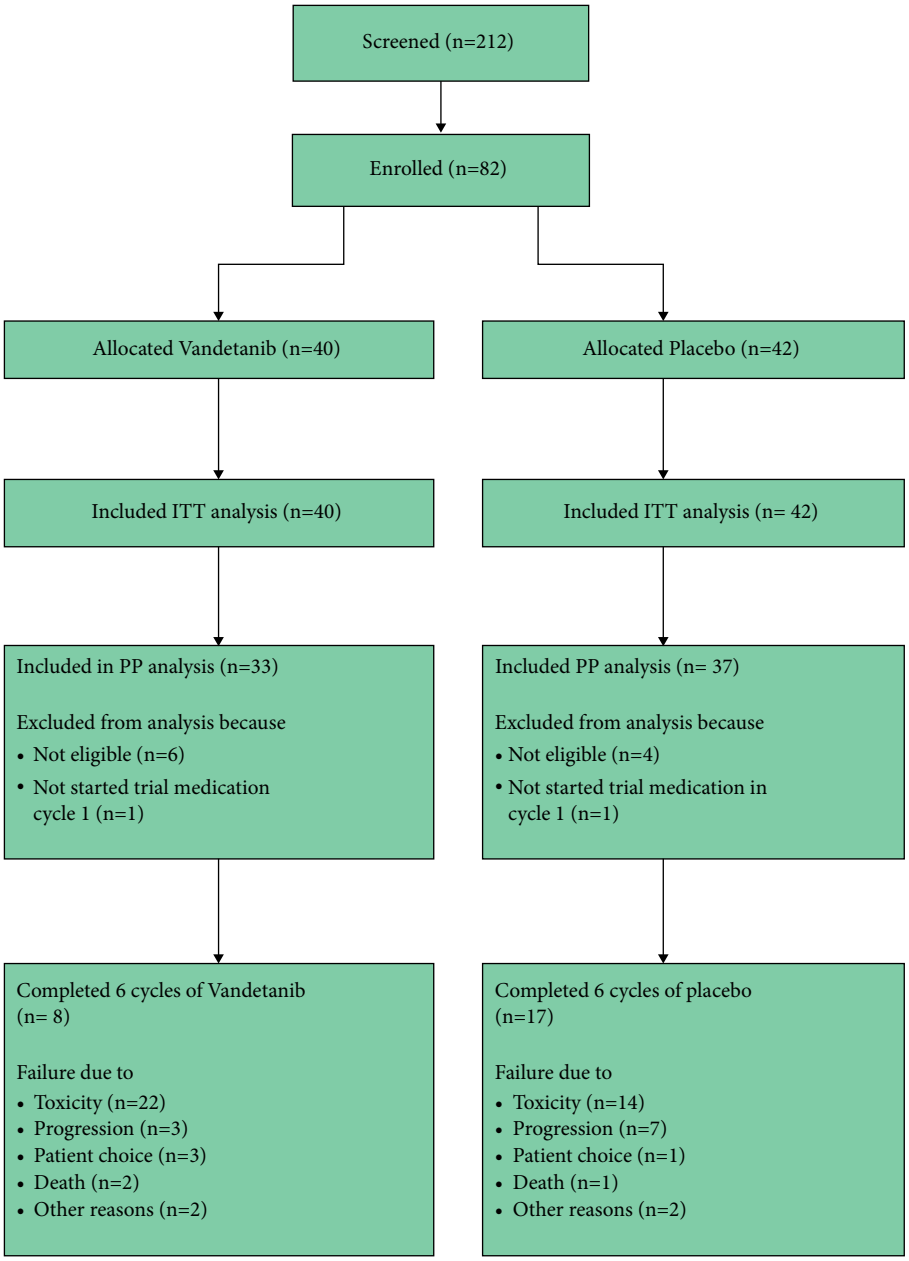
Similar rates of treatment-emergent AEs were seen in the two arms, with Grade 3–4 toxicities seen in 80% of patients in the vandetanib arm and 76% in the placebo arm. The commonly occurring toxicities are summarised in Table 2.

Efficacy

At the time of final analysis, a total of 65 patients (79%) had progressed or died. Comparison of PFS between the two treatment arms using ITT gave an unadjusted HR of 1.07 (95% CI 0.65–1.76; one-sided $P = 0.71$; Fig. 2A). Corresponding adjusted analysis gave an HR of 1.04 (95% CI 0.63–1.71). The absolute difference in 1-year PFS was −1.9% (12.9% in the vandetanib arm and 14.7% in the placebo arm), 95% CI −11.3% to 13.9%. The median PFS for the vandetanib arm was 6.8 months (95% CI 4.6–8.5) and for the placebo arm was 8.8 months (95% CI 5.7–9.0). An unadjusted analysis using PPA gave a similar result with a HR of 1.00 (95% CI 0.59–1.70).

In all, 32 patients (80%) in the vandetanib arm and 38 (90%) in the placebo arm were evaluable for radiological response. On an ITT basis, responses (complete response + partial response) were seen in 20 of 40 patients (50%) in the vandetanib arm and 23 of 42 (55%) in the placebo arm. The change in size of measurable lesions at first protocol-mandated response assessment (week 9 after commencement of treatment; 64 evaluable patients) is presented as a waterfall plot in Fig. 3.

Fig. 1 CONSORT flow diagram of trial participants.



A total of 48 patients (58%) had died by the time of analysis: 42 deaths were disease related, two were treatment related, and four due to other reasons. The median OS for the vandetanib arm was 10.8 months (95% CI 8.0–13.0) and for the placebo arm was 13.8 months (95% CI 11.1–16.6). Comparison of OS gave an unadjusted HR of 1.41 (95% CI 0.79– 2.52; one-sided $P = 0.9$), using an ITT analysis, which represents a 41% increase in risk of death after the addition of vandetanib (Fig. 2B). There was a corresponding absolute reduction of 10.6% in the 1-year OS in the vandetanib arm (54.4% in the vandetanib arm vs 65.0% in the placebo arm) (95% CI 31.2–6.0%).

Discussion

The goal of this trial was to assess the safety and efficacy of vandetanib in combination with GC chemotherapy. Based on this trial, although this combination was found to be safe, there was no evidence that this combination improved clinical outcomes in this cohort of patients with advanced UC who were unsuitable for cisplatin. These data are consistent with a

Table 1 Patients' characteristics.

Characteristic	Vandetanib	Placebo
Total number of patients enrolled	40	42
Age, years, median (IQR)	73.5 (66–77)	73.5 (67–79)
Reason not suitable for cisplatin, *n* (%)		
Renal function GFR <60 mL/min	27 (69.2)	29 (69.1)
ECOG PS 2	10 (26.3)	10 (23.8)
Ischaemic heart disease	4 (10.3)	6 (14.3)
Prior intolerance to cisplatin	0 (0.0)	5 (11.9)
Age >75 years	13 (34.2)	23 (54.8)
Other	13 (34.2)	17 (40.5)
Sex, *n* (%)		
Male	32 (80.0)	35 (83.3)
Female	8 (20.0)	7 (16.7)
Location of primary disease, *n* (%)		
Bladder	28 (70.0)	34 (81.0)
Other	12 (30.0)	8 (19.1)
Stage, *n* (%)		
T4, T4a, T4b	9 (22.5)	5 (12.2)
N1, N2, N3	28 (70.0)	25 (59.5)
M1	22 (55.0)	18 (42.9)
Previous neoadjuvant chemotherapy, *n* (%)		
Yes	4 (10)	4 (9.5)
Metastasis, *n* (%)		
Lung	13 (32.5)	8 (19.0)
Liver	2 (5.0)	7 (16.7)
Nodes	25 (62.5)	25 (59.5)
Bone	2 (5.0)	4 (9.5)
Other	6 (15.0)	7 (16.7)
None	7 (17.5)	9 (21.4)
Bajorin Risk Group, *n* (%)		
0 (no visceral metastases and ECOG PS <2)	16 (41.0)	21 (50.0)
1 (visceral metastases or ECOG PS ≥2)	22 (56.4)	19 (45.2)
2 (visceral metastases and ECOG PS ≥2)	1 (2.6)	2 (4.8)

previous report that vandetanib does not improve efficacy when combined with docetaxel in patients receiving second-line treatment of advanced UC [20]. Our present results are in contrast to the small benefits seen with vandetanib in combination with docetaxel in non-small cell lung cancer [19] and with a recently reported randomised Phase III trial using another anti-VEGFR agent, ramucirumab (a fully human anti-VEGFR2 monoclonal antibody), which demonstrated improved PFS and response rates in combination with docetaxel for patients with UC in the second-line setting [21]. However, the data presented in the present study are consistent with other trials exploring the efficacy of drugs targeting the VEGFR pathways in UC [22], with most agents tested having been found to have insufficient activity to take to Phase III. Recent results of a randomised Phase III trial of gemcitabine plus cisplatin with or without bevacizumab in the first-line setting have shown an improvement in PFS with the addition of bevacizumab, but no improvement in the primary endpoint of OS (ClinicalTrials.gov Identifier: NCT00942331; www.clinicaltrials.gov) [23]. Similarly, EGFR-targeted therapies have shown insufficient activity in both biomarker-selected and -unselected patients with UC. Notably, a Phase III trial of the dual EGFR inhibitor, lapatinib (LaMB), in patients selected for EGFR and/or human epidermal growth factor receptor 2 (HER2) expression, failed to show activity in advanced UC following first-line chemotherapy [24].

One explanation for the lack of efficacy of vandetanib in the present trial might have been failure to select patients appropriately. Predictive markers for VEGF-targeted therapies have, to date, been elusive in other disease and valid predictive markers for EGFR-targeted therapies are not sufficiently prevalent in UC [25].

Despite the failure to demonstrate incremental benefit from vandetanib, the overall outcomes for patients in the present trial were better than expected. Notably, in both arms of the present study the median PFS (6.8 vs 8.8 months) and OS (10.8 vs 13.8 months) were better than seen in a previous Phase III trial of GC chemotherapy in a similar group of patients (PFS 5.8 months and OS 9.3 months) [6]. This may reflect patient selection, as patients needed to be considered suitable for combination treatment by investigators or could be due to the use of a wider definition of 'unsuitable for cisplatin'. We cannot be certain as to the reasons for the apparent trend towards poorer survival amongst those receiving vandetanib, but it could have been due to reduced exposure to chemotherapy seen in this arm. In addition, there were some imbalances in baseline characteristics between the arms.

After many years in which various combinations of small-molecule cytotoxic drugs and/or molecularly targeted drugs have failed to achieve substantial improvements in survival outcomes in advanced UC, significant interest has recently been generated in the use of immunotherapies, including a report of improved survival with the anti-programmed cell death-1 (PD-1) monoclonal antibody, pembrolizumab, as second-line therapy for metastatic UC [26]. Our response rate (50%) and OS data (median OS 10.8 months) in the vandetanib arm are not dissimilar to those seen in a trial of pembrolizumab in the same setting (first-line treatment of patients with metastatic UC unsuitable for cisplatin), which reported an objective response rate (ORR) of 24% and a median OS of 11.5 months [27] and with a single-arm trial of the anti-PD-L1 monoclonal antibody, atezolizumab, which demonstrated an ORR of 23% and a median OS of 15.9 months [28]. Several Phase III trials comparing GC with immunotherapy in the population unsuitable for cisplatin are currently unreported (ClinicalTrials.gov Identifier: NCT02516241; NCT02853305; NCT02807636; www.clinicaltrials.gov).

In conclusion, there is no evidence that the addition of vandetanib to GC chemotherapy improves clinical outcomes. Our present findings do not support a Phase III study or its use as first-line treatment in patients with UC who are unfit for cisplatin.

Table 2 Treatment-emergent AEs.

	Vandetanib (*N* = 40)		Placebo (*N* = 42)	
	Any, *n* (%)	≥3, *n* (%)	Any, *n* (%)	≥3, *n* (%)
	36 (90)	32 (80)	41 (98)	32 (76)
Blood and lymphatic system disorders				
Anaemia	26 (65)	6 (15)	25 (60)	8 (19)
Gastrointestinal disorders				
Abdominal pain	5 (13)	1 (3)	9 (21)	0 (0)
Constipation	6 (15)	0 (0)	11 (26)	0 (0)
Diarrhoea	15 (38)	1 (3)	10 (24)	0 (0)
Dyspepsia	4 (10)	0 (0)	2 (5)	0 (0)
Mucositis (oral)	7 (18)	0 (0)	7 (17)	0 (0)
Nausea	14 (35)	2 (5)	12 (29)	1 (2)
Vomiting	7 (18)	2 (5)	13 (31)	0 (0)
General disorders and administration site conditions				
Oedema of the limbs	3 (8)	0 (0)	7 (17)	0 (0)
Fatigue	24 (60)	1 (3)	30 (71)	1 (2)
Fever	3 (8)	1 (3)	5 (12)	2 (5)
Pain	14 (35)	1 (3)	15 (36)	3 (7)
Infections and infestations				
Infections	0 (0)	0 (0)	4 (10)	1 (2)
Lung	5 (13)	1 (3)	3 (7)	0 (0)
Investigations				
ALP	9 (23)	0 (0)	9 (21)	1 (2)
Neutrophil count decreased	15 (38)	12 (30)	15 (36)	8 (19)
ALT	13 (33)	0 (0)	12 (29)	2 (5)
AST	6 (15)	0 (0)	5 (12)	0 (0)
Creatinine increased	6 (15)	0 (0)	7 (17)	1 (2)
Lymphocyte count	18 (45)	2 (5)	12 (29)	2 (5)
Platelet count decreased	23 (58)	19 (48)	19 (45)	12 (29)
Weight	5 (13)	0 (0)	6 (14)	0 (0)
WBC	19 (48)	7 (18)	21 (50)	6 (14)
Metabolism and nutrition disorders				
Anorexia	11 (28)	0 (0)	8 (19)	0 (0)
Hyperglycaemia	2 (5)	0 (0)	4 (10)	1 (2)
Hyperkalaemia	2 (5)	1 (3)	2 (5)	0 (0)
Hypomagnesaemia	8 (20)	0 (0)	8 (19)	0 (0)
Hypophosphataemia	9 (23)	1 (3)	3 (7)	1 (2)
Hypokalaemia	7 (18)	1 (3)	2 (5)	0 (0)
Musculoskeletal and connective tissue disorders				
Back pain	5 (13)	0 (0)	2 (5)	1 (2)
Myalgia	4 (10)	0 (0)	0 (0)	0 (0)
Nervous system disorders				
Dizziness	4 (10)	0 (0)	5 (12)	0 (0)
Insomnia	6 (15)	0 (0)	3 (7)	0 (0)
Renal and urinary disorders				
Acute kidney injury	4 (10)	3 (8)	2 (5)	1 (2)
Proteinuria	6 (15)	2 (5)	4 (10)	0 (0)
Haematuria	10 (25)	3 (8)	8 (19)	2 (5)
UTI	6 (15)	5 (13)	4 (10)	1 (2)
Respiratory, thoracic and mediastinal disorders				
Cough	10 (25)	0 (0)	4 (10)	0 (0)
Dyspnoea	11 (28)	0 (0)	8 (19)	0 (0)
Epistaxis	4 (10)	1 (3)	2 (5)	0 (0)
Respiratory infection	4 (10)	2 (5)	1 (2)	1 (2)
Skin and subcutaneous tissue disorders				
Alopecia	3 (8)	0 (0)	5 (12)	0 (0)
PPE	7 (18)	0 (0)	1 (2)	0 (0)
Photosensitivity	6 (15)	3 (8)	0 (0)	0 (0)
Pruritus	3 (8)	2 (5)	4 (10)	0 (0)
Rash	19 (48)	5 (13)	11 (26)	0 (0)
Skin infection	2 (5)	2 (5)	4 (10)	3 (7)
Vascular disorders				
Hypertension	6 (15)	5 (13)	6 (14)	1 (2)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PPE, palmar-plantar erythrodysesthesia syndrome; WBC, white blood cell count. All AEs with ≥10% any grade incidence in either arm from initiation of study treatment.

Fig. 2 Efficacy outcomes. Kaplan–Meier curves for (**A**) PFS and (**B**) OS.

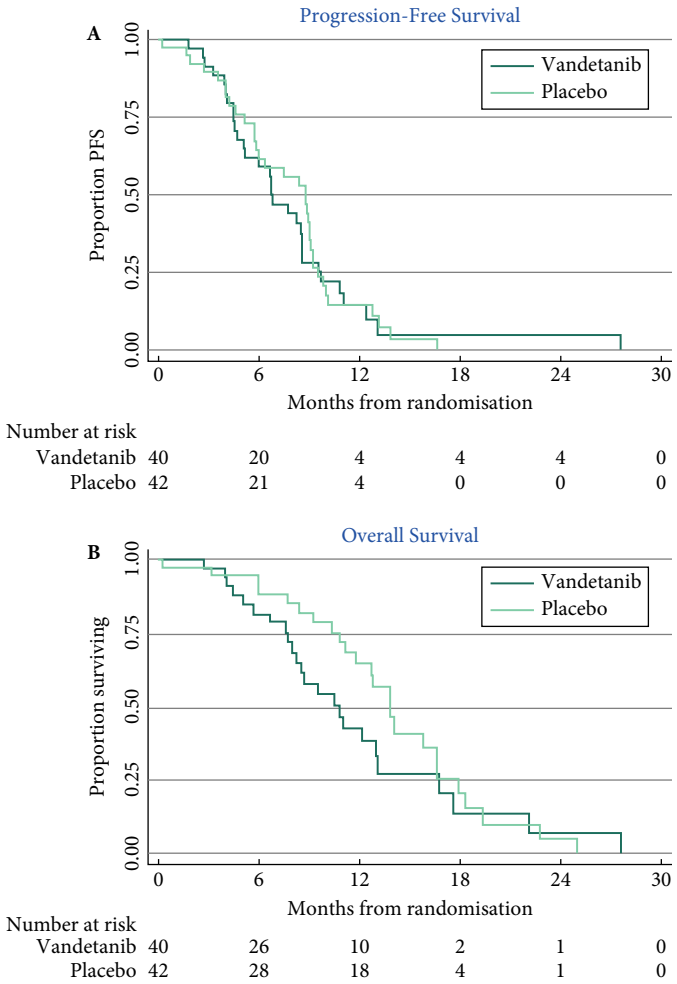
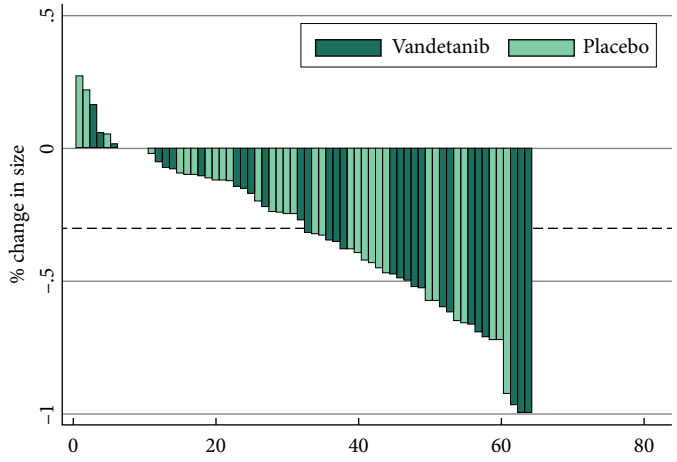


Fig. 3 Waterfall plots of change in size of measurable lesions. Absolute percentage reduction in size of sum of target lesions at week 9 compared with baseline scan. The dotted line is 30% reduction. Data from 64 patients, 18 patients were not assessable at this timepoint.



Acknowledgments

The trial was run independently at the Centre for Trials Research, Cardiff University on behalf of the National Cancer Research Institute (NCRI) Bladder (and renal) Clinical Studies Group. We thank AstraZeneca and latterly Genzyme/Sanofi for the provision of free vandetanib for use in the trial. We thank current and former staff of the Centre for Trials Research (previously the Wales Cancer Trials Unit) and Cardiff University for supporting the development and running of this trial (including Joanna Smith, Margherita Carucci, Loys Richards); members of the Trial Management Group including Dave Ardron and Harold Toone (patients' representatives), Sophia Cambell (nursing representative), Karen Pow (trial pharmacist), Tom Powles and John Kelly and members of the independent data monitoring committee and trial steering committee. Finally, we thank all patients who participated in the trial and the principal investigators at recruiting sites, their colleagues and the NIHR CRN:Cancer network and the Scottish Cancer Research Network for recruitment of patients.

Conflict of Interest

Robert Jones has received research grants from Astellas, Astrazeneca, Bayer, Exelixis and Roche, personal fees from Astellas, Astrazeneca, BMS, Bayer, Exelixis, Janssen, Ipsen, Merck Serono, MSD, Novartis, Pfizer, Roche, Sanofi Genzyme and EUSA and non-financial support from BMS, Bayer, Jassen, Ipsen and MSD. Simon Crabb has received research grants from Clovis Oncology, Astrazeneca, Astex Pharmaceuticals and personal fees from Roche, Janssen Cilag, MSD, Astellas, Bayer and Astrazeneca. Robert Huddart has received research grants from MSD and Roche, personal fees from MSD, Roche, Bayer, Nektar, Janssen, BMS, NICE and non-financial support from Roche, Nektar and Janssen and partnership funding from the cancer centre London. Gareth Griffiths has received research grants and other funding (teaching honoarium) from AstraZeneca. Angela Casbard has received grant funding from Astrazeneca and Cancer Research UK and non-financial support from Velindre NHS Trust. Jason Lester has received personal fees and non-financial support from Astrazeneca, Roche, BMS, Pfizer, Boehringer Ingelheim, Astellas, Sanofi Aventis and Novartis. Satinder Jagdev has received meeting sponsorship from Ipsen, Janssen, Astellas and personal fees from Novartis and BMS. Alison Birtle has received speaker fees from Roche, Sanofi Genzyme, MSD, Janssen, research funding from Sanofi genzyme with advisory board participation with Astrazeneca, Janssen and Roche. All remaining authors have declared no conflicts of interest.

References

1 **Cancer Research UK**. Bladder Cancer statistics reports for the UK, 2016. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer. Accessed January 2020

2 **Wong MC**, **Fung FD**, **Leung C, Cheung WW, Goggins WB, Ng CF**. The global epidemiology of bladder cancer: a joinpoint regression analysis of its incidence and mortality trends and projection. *Sci Rep* 2018; 8: 1129. DOI: 10.1038/s41598-018-19199-z.

3 **Von der Maase H**, **Hansen SW**, **Roberts JT et al**. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol* 2000; 18: 3068–77

4 **Loehrer PJ Sr**, **Einhorn LH**, **Elson PJ et al**. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. *J Clin Oncol* 1992; 10: 1066–73

5 **Egan PVB**, **Jones RJ**. Chemotherapy for bladder cancer: a United Kingdom practice survey. *J Clin Oncol* 2008; 26(Suppl.): 16078. DOI: 10.1200/jco.2008.26.15_suppl.16078

6 **De Santis M**, **Bellmunt J**, **Mead G et al**. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. *J Clin Oncol* 2012; 30: 191–9

7 **Bellmunt J**, **de Wit R**, **Albanell J**, **Baselga J**. A feasibility study of carboplatin with fixed dose of gemcitabine in "unfit" patients with advanced bladder cancer. *Eur J Cancer* 2001; 37: 2212–5

8 **Linardou H**, **Aravantinos G**, **Efstathiou E et al**. Gemcitabine and carboplatin combination as first-line treatment in elderly patients and those unfit for cisplatin-based chemotherapy with advanced bladder carcinoma: phase II study of the Hellenic Co-operative Oncology Group. *Urology* 2004; 64: 479–84

9 **Carles J**, **Nogue M**, **Domenech M et al**. Carboplatin-gemcitabine treatment of patients with transitional cell carcinoma of the bladder and impaired renal function. *Oncology* 2000; 59: 24–7

10 **Wu W**, **Shu X**, **Hovsepyan H, Mosteller RD, Broek D.** VEGF receptor expression and signaling in human bladder tumors. *Oncogene* 2003; 22: 3361–70

11 **Xia G**, **Kumar SR**, **Hawes D et al**. Expression and significance of vascular endothelial growth factor receptor 2 in bladder cancer. *J Urol* 2006; 175: 1245–52

12 **Parvin M**, **Sabet-Rasekh P**, **Hajian P**, **Mohammadi Torbati P.**, **Sabet-Rasekh P.**, **Mirzaei H.** Evaluating the prevalence of the epidermal growth factor receptor in transitional cell carcinoma of bladder and its relationship with other prognostic factors. *Iran J Cancer Prev* 2016; 9: e4022. https://doi.org/10.17795/ijcp-4022

13 **Kopparapu PK**, **Boorjian SA**, **Robinson BD et al**. Expression of VEGF and its receptors VEGFR1/VEGFR2 is associated with invasiveness of bladder cancer. *Anticancer Res* 2013; 33: 2381–90

14 **Crew JP**, **O'Brien T**, **Bradburn M et al**. Vascular endothelial growth factor is a predictor of relapse and stage progression in superficial bladder cancer. *Cancer Res* 1997; 57: 5281–5

15 **Flaig TW**, **Su LJ**, **McCoach C et al**. Dual epidermal growth factor receptor and vascular endothelial growth factor receptor inhibition with vandetanib sensitizes bladder cancer cells to cisplatin in a dose- and sequence-dependent manner. *BJU Int* 2009; 103: 1729–37

16 **Li Y**, **Yang X**, **Su LJ**, **Flaig TW**. VEGFR and EGFR inhibition increases epithelial cellular characteristics and chemotherapy sensitivity in mesenchymal bladder cancer cells. *Oncol Rep* 2010; 24: 1019–28

17 **Lubet RA**, **Lu Y**, **Bode AM et al**. Efficacy of the EGFr inhibitor Iressa on development of chemically-induced urinary bladder cancers: dose dependency and modulation of biomarkers. *Oncol Rep* 2011; 25: 1389–97

18 **Wells SA Jr**, **Robinson BG**, **Gagel RF et al**. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *J Clin Oncol* 2012; 30: 134–41

19 **Herbst RS**, **Sun Y**, **Eberhardt WE et al**. Vandetanib plus docetaxel versus docetaxel as second-line treatment for patients with advanced non-small-cell lung cancer (ZODIAC): a double-blind, randomised, phase 3 trial. *Lancet Oncol* 2010; 11: 619–26

20 **Choueiri TK**, **Ross RW**, **Jacobus S et al**. Double-blind, randomized trial of docetaxel plus vandetanib versus docetaxel plus placebo in platinum-pretreated metastatic urothelial cancer. *J Clin Oncol* 2012; 30: 507–12

21 **Petrylak DP**, **de Wit R**, **Chi KN et al**. Ramucirumab plus docetaxel versus placebo plus docetaxel in patients with locally advanced or metastatic urothelial carcinoma after platinum-based therapy (RANGE): a randomised, double-blind, phase 3 trial. *Lancet* 2017; 390: 2266–77

22 **Mazzola CR**, **Chin J**. Targeting the VEGF pathway in metastatic bladder cancer. *Expert Opin Investig Drugs* 2015; 24: 913–27

23 **Rosenberg JE**, **Ballman KV**, **Halabi S et al**. CALGB 90601 (Alliance): Randomised, double-blind, placebo-controlled phase III trial comparing gemcitabine and cisplatin with bevacizumab or placebo in ptients with metastatic urothelial cancer. *J Clin Oncol* 2019; 37(Suppl.): 4503. DOI: 10.1200/jco.2019.37.15_suppl.4503

24 **Powles T**, **Huddart RA**, **Elliott T et al**. A phase II/III, double-blind, randomized trial comparing maintenance lapatinib versus placebo after first line chemotherapy in HER1/2 positive metastatic bladder cancer patients. *J Clin Oncol* 2015; 33(Suppl.): 4505. https://doi.org/10.1200/jco.2015.33.15_suppl.4505

25 **Cancer Genome Atlas Research Network**. Comprehensive molecular characterization of urothelial bladder carcinoma. *Nature* 2014; 507: 315–22

26 **Bellmunt J**, **de Wit R**, **Vaughn DJ et al**. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med* 2017; 376: 1015–26

27 **Balar A**, **Bellmunt J**, **O'Donnell PH et al**. Pembrolizumab (pembro) as first-line therapy for advanced/unresectable or metastatic urothelial cancer: preliminary results from the phase 2 KEYNOTE-052 study. *Annal Oncol* 2016; 27(Suppl.): vi567. DOI: 10.1093/annonc/mdw435.25

28 **Balar AV**, **Galsky MD**, **Rosenberg JE et al**. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. *Lancet* 2017; 389: 67–76

Correspondence: Gareth Griffiths, Southampton Clinical Trials Unit, University of Southampton, Southampton, UK.

e-mail: gog1a13@soton.ac.uk

Abbreviations: AE, adverse event; target AUC, target area under the concentration versus time curve; CONSORT, Consolidated Standards of Reporting Trials; CRN, Clinical Research Network; CRUK, Cancer Research UK; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGF(R), epidermal growth factor (receptor); GC, gemcitabine plus carboplatin; HR, hazard ratio; ITT, intention-to-treat; NIHR, UK National Institute for Health Research; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death 1; PFS, progression-free survival; PPA, per-protocol analysis; RECIST, Response Evaluation Criteria In Solid Tumors; UC, urothelial cancer; VEGF(R), vascular endothelial growth factor (receptor).