Efficacy and safety of erdafitinib in patients with locally advanced or metastatic urothelial carcinoma: long-term follow-up of a phase 2 study

*Arlene O Siefker-Radtke, Andrea Necchi, Se Hoon Park, Jesús García-Donas, Robert A Huddart, Earle F Burgess, Mark T Fleming, Arash Rezazadeh Kalebasty, Begoña Mellado, Sergei Varlamov, Monika Joshi, Ignacio Duran, Scott T Tagawa, Yousef Zakharia, Sydney Akapame, Ademi E Santiago-Walker, Manish Monga, Anne O'Hagan, Yohann Loriot, on behalf of the BLC2001 Study Group**

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*Members are listed in the appendix (pp 2–3)

Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA (Prof A O Siefker-Radtke MD); Vita-Salute San Raffaele University, IRCCS San Raffaele Hospital and Scientific Institute, Milan, Italy (Prof A Necchi MD); Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea (S H Park MD); Medical Oncology Department, Fundacion Hospital de Madrid and IMMA Medicine Faculty, San Pablo CEU University, Madrid, Spain (J García-Donas MD); Section of Radiotherapy and Imaging, Institute of Cancer Research and Royal Marsden NHS Foundation Trust, Sutton, UK (R A Huddart PhD); Medical Oncology Department, Levine Cancer Institute, Charlotte, NC, USA (E F Burgess MD); Medical Oncology Department, Virginia Oncology Associates, US Oncology Research, Norfolk, VA, USA (M T Fleming MD); Department of Medical Oncology, Norton Healthcare, Louisville, KY, USA (A Rezazadeh Kalebasty MD); Medical Oncology Department, Hospital Clinic Institut d'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Barcelona, Spain (B Mellado MD); Department of Urologic Oncology, Altai Regional Cancer Center, Barnaul, Russia (S Varlamov MD); Department

Summary

Background Erdafitinib, a pan-fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor, was shown to be clinically active and tolerable in patients with advanced urothelial carcinoma and prespecified *FGFR* alterations in the primary analysis of the BLC2001 study at median 11 months of follow-up. We aimed to assess the long-term efficacy and safety of the selected regimen of erdafitinib determined in the initial part of the study.

Methods The open-label, non-comparator, phase 2, BLC2001 study was done at 126 medical centres in 14 countries across Asia, Europe, and North America. Eligible patients were aged 18 years or older with locally advanced and unresectable or metastatic urothelial carcinoma, at least one prespecified *FGFR* alteration, an Eastern Cooperative Oncology Group performance status of 0–2, and progressive disease after receiving at least one systemic chemotherapy or within 12 months of neoadjuvant or adjuvant chemotherapy or were ineligible for cisplatin. The selected regimen determined in the initial part of the study was continuous once daily 8 mg/day oral erdafitinib in 28-day cycles, with provision for pharmacodynamically guided uptitration to 9 mg/day (8 mg/day UpT). The primary endpoint was investigator-assessed confirmed objective response rate according to Response Evaluation Criteria In Solid Tumors version 1.1. Efficacy and safety were analysed in all treated patients who received at least one dose of erdafitinib. This is the final analysis of this study. This study is registered with ClinicalTrials.gov, NCT02365597.

Findings Between May 25, 2015, and Aug 9, 2018, 2328 patients were screened, of whom 212 were enrolled and 101 were treated with the selected erdafitinib 8 mg/day UpT regimen. The data cutoff date for this analysis was Aug 9, 2019. Median efficacy follow-up was 24·0 months (IQR 22·7–26·6). The investigator-assessed objective response rate for patients treated with the selected erdafitinib regimen was 40 (40%; 95% CI 30–49) of 101 patients. The safety profile remained similar to that in the primary analysis, with no new safety signals reported with longer follow-up. Grade 3–4 treatment-emergent adverse events of any causality occurred in 72 (71%) of 101 patients. The most common grade 3–4 treatment-emergent adverse events of any cause were stomatitis (in 14 [14%] of 101 patients) and hyponatraemia (in 11 [11%]). There were no treatment-related deaths.

Interpretation With longer follow-up, treatment with the selected regimen of erdafitinib showed consistent activity and a manageable safety profile in patients with locally advanced or metastatic urothelial carcinoma and prespecified *FGFR* alterations.

Funding Janssen Research & Development.

Introduction

Until the past decade, after failure of platinum-based chemotherapy, second-line treatment options for patients with advanced urothelial carcinoma have been scarce, with poor activity and response rates that range from 10% to 20%.[1,2] Erdafitinib is a potent and selective pan-fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor[3] that has been approved in Brazil, Canada, Chile, Hong Kong, Israel, Jordan, Peru, Taiwan, Thailand, Saudi Arabia, Singapore, and the USA[4] to treat adults with locally advanced or metastatic urothelial carcinoma with *FGFR3/2* alterations who progressed during or after one or more lines of previous platinum-based chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-based chemotherapy. The National Comprehensive Cancer Network guidelines[5] for bladder cancer recommend erdafitinib as a second-line treatment option for patients with locally advanced or metastatic urothelial carcinoma following platinum-based therapy. The European Association of Urology guidelines[6] include FGFR inhibitors, such as erdafitinib, as promising therapies for second-line or later treatment of metastatic urothelial carcinoma and, although erdafitinib is not yet approved by the European Medicines Agency, it is included in the European Society for Medical Oncology guidelines.[7]

Research in context

Evidence before this study

We searched PubMed for clinical trials of fibroblast growth factor receptor (FGFR) inhibitors used to treat patients with urothelial cancer or bladder cancer, using the terms "bladder cancer" OR "urothelial cancer" AND "fibroblast growth factor receptor," published from Jan 1, 2010, to Jan 1, 2021, with limits for clinical trials and no language restrictions. At the time of the initial protocol approval for the phase 2 BLC2001 study of erdafitinib (Jan 19, 2015), our searches identified one published report of a clinical trial of an FGFR inhibitor (dovitinib in combination with gemcitabine plus cisplatin or carboplatin) in patients with advanced solid tumours, in which the combination was poorly tolerated. At that time, systemic treatment for metastatic urothelial carcinoma was generally unsatisfactory and had remained unchanged for several decades. More recently, approved anti-PD-(L)1 agents provided a small improvement in response rates over traditional chemotherapy and were accompanied by immune-related adverse events that were potentially serious and sometimes fatal. Differential responses to anti-PD-(L)1 agents have been observed in different bladder cancer subtypes based on gene expression and histopathology and their underlying immune microenvironment. The primary analysis of BLC2001 was published in 2019 and, on the basis of these data, erdafitinib was the first targeted therapy approved by the US Food and Drug Administration for treatment of patients with locally advanced or metastatic urothelial carcinoma and prespecified *FGFR* alterations. Erdafitinib is now included in the National Comprehensive Cancer Network and European Society for Medical Oncology guidelines as an option for second-line treatment of patients with locally advanced or metastatic urothelial cancer.

Added value of this study

Our findings show that, with longer follow-up, erdafitinib treatment continues to show consistent clinical benefits for patients with locally advanced or metastatic urothelial cancer who have tumours with specific *FGFR* alterations, and that erdafitinib has a manageable safety profile.

Implications of all the available evidence

The long-term follow-up of this study confirms the benefit of erdafitinib, an FGFR inhibitor, for the treatment of patients with locally advanced or metastatic urothelial cancer and specific *FGFR* alterations. Further research, in a randomised, controlled, phase 3 study in patients with advanced urothelial cancer, is ongoing to evaluate erdafitinib as second-line monotherapy compared with a PD-1 inhibitor or chemotherapy. Another study is ongoing to evaluate erdafitinib in combination with a PD-1 inhibitor (cetrelimab) in first-line treatment of patients with metastatic urothelial carcinoma who are ineligible for cisplatin.

of Medicine, Penn State Cancer Institute, Hershey, PA, USA (M Joshi MD); **Department of Medical Oncology, Hospital Universitario Marqués de Valdecilla, Santander, Spain** (I Duran MD); **Division of Hematology and Medical Oncology, Weill Cornell Medical College, New York, NY, USA** (S T Tagawa MD); **Department of Internal Medicine, University of Iowa, Holden Comprehensive Cancer Center, Iowa City, IA, USA** (Y Zakharia MD); **Janssen Research & Development, Spring House, PA, USA** (S Akapame PhD, A E Santiago-Walker PhD, M Monga MD, A O'Hagan MPH); **Department of Cancer Medicine, INSERM U981, Gustave Roussy, Université Paris-Saclay, Villejuif, France** (Y Loriot MD)

Correspondence to:
Dr Arlene O Siefker-Radtke, Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
asiefker@mdanderson.org

See **Online** for appendix

Erdafitinib was approved by various regulatory authorities on the basis of the results of an open-label phase 2 study (BLC2001) in patients with locally advanced and unresectable or metastatic urothelial carcinoma and prespecified *FGFR3/2* alterations.[8] Participants had disease progression during or after one or more lines of previous chemotherapy or within 12 months after neoadjuvant or adjuvant chemotherapy.[8] On the basis of results from a planned interim analysis, the selected schedule of erdafitinib was once daily 8 mg/day continuously, with the possibility of pharmacodynamically guided uptitration to 9 mg (henceforth 8 mg/day UpT).[8] In the primary analysis, erdafitinib was associated with an investigator-assessed objective tumour response in 40 (40%; 95% CI 31–50) of 99 patients in the selected regimen group;[8] all responses were confirmed. Additionally, at a median follow-up of 11·2 months (IQR 8·2–15·6), median progression-free survival was 5·5 months (95% CI 4·2–6·0) and, at a median follow-up of 11·0 months (IQR 8·5–14·1), median overall survival was 13·8 months (95% CI 9·8–not reached [NR]).[8] Treatment-related adverse events of grade 3 or worse were reported in 45 (46%) of 99 patients at the time of the primary analysis.[8]

We aimed to assess the longer-term efficacy and safety of the selected regimen of erdafitinib among patients treated in the BLC2001 study.

Methods

Study design and participants

The open-label, non-comparator, phase 2, BLC2001 study was done at 126 medical centres in 14 countries across Asia, Europe, and North America (appendix pp 2–3). As described previously,[8] eligible patients were aged 18 years or older, with locally advanced and unresectable or metastatic urothelial carcinoma; measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; at least one *FGFR3* mutation or *FGFR2/3* fusion, as listed in a prespecified panel, identified by central laboratory testing using an RNA-based RT-PCR assay conducted at Almac Diagnostic Services, Craigavon, UK; a history of disease progression during or after one or more lines of previous systemic chemotherapy or within 12 months after neoadjuvant or adjuvant chemotherapy (chemotherapy-refractory patients) or were ineligible for cisplatin (due to impaired renal function or peripheral neuropathy) and chemotherapy-naive; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; and adequate bone marrow, liver, and kidney function (creatinine clearance rate ≥40 mL/min per 1·73 m²). Patients who had any number of previous lines of therapy or who had previously received immunotherapy (eg, immune checkpoint inhibitors) were eligible for enrolment. Patients were excluded if

they had received chemotherapy, targeted therapies, definitive radiotherapy, or treatment with an investigational anticancer agent within 2 weeks before the first administration of study drug; had persistent serum phosphate concentration greater than the upper limit of normal within 14 days of treatment that could not be resolved through medical management; or had a history of or current uncontrolled cardiovascular disease. Full exclusion criteria are listed in the appendix (p 4).

Review boards at all the participating institutions approved the study and all the protocol amendments; the study was performed according to the principles of the Declaration of Helsinki and guidelines for Good Clinical Practice and applicable regulatory requirements. Patients or their legally acceptable representatives provided written informed consent before participation.

Procedures

In the initial part of the study, patients were randomly assigned (1:1, with stratification by ECOG performance status, haemoglobin value, *FGFR* alteration type, previous treatment status, and disease distribution)[8] to once daily oral erdafitinib 10 mg/day intermittently (7 days on, 7 days off) or 6 mg/day continuously in 28-day cycles. On the basis of findings from an interim analysis and pharmacokinetic and pharmacodynamic modelling based on clinical data, the protocol was amended on Aug 9, 2016, to continue enrolment into a dosing schedule of 8 mg/day continuously with potential uptitration to 9 mg/day (UpT dose schedule) only, thereby converting the study to a single-group analysis.

In the selected 8 mg/day UpT regimen, uptitration to 9 mg/day continuous treatment was permitted on day 14 in patients who had not had adverse events that were considered related to treatment by the investigator, if patients had not reached the target serum phosphate level of 5·5 mg/dL (1·8 mmol/L), a level associated with an improved response rate in the phase 1 study.[8] Patients continued erdafitinib treatment at 8 mg/day if their serum phosphate levels on day 14 were within 5·5 to less than 7·0 mg/dL (2·3 mmol/L; target range).

Patients continued to receive erdafitinib until disease progression or unacceptable adverse events, as determined by the investigator. At the discretion of the investigator and the funder of the study, patients with investigator-assessed disease progression could continue erdafitinib treatment. Patients who interrupted treatment because of grade 1 adverse events reinitiated treatment at the same dose or at a lower dose. After resolution of grade 2 treatment-emergent adverse events, patients restarted treatment at the same dose or one dose lower (if necessary). For grade 3 adverse events, treatment was withheld; after resolution, treatment was resumed at one or two dose levels lower depending on the specific toxicity. In the case of grade 4 adverse events, treatment was interrupted or discontinued.

Efficacy was assessed using RECIST version 1.1 by CT or MRI of the chest, abdomen, and pelvis every 6 weeks for the first 3 months, every 12 weeks for the next 9 months, and every 4–6 months thereafter until disease progression. Objective responses were confirmed by an additional CT or MRI scan within 4–6 weeks after the first assessment when a response was recorded. After treatment discontinuation, patients were contacted every 12 weeks to assess survival outcomes. Efficacy results are reported for the 8 mg/day UpT regimen group only.

Safety was assessed by clinical laboratory testing, physical examination, electrocardiography, and ophthalmological examination (for more details, see the protocol in the appendix). Investigators assessed and graded adverse events and abnormalities according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 for the duration of the study.

Outcomes

The primary endpoint was confirmed objective response rate (the proportion of patients with a complete response and those with a partial response) among patients treated with the selected dose regimen; all complete and partial responses required confirmation within 4–6 weeks of the first assessment of response and were assessed by the investigators using RECIST version 1.1. Secondary endpoints were progression-free survival (defined as time from the first dose of study drug until the first documented evidence of progressive disease [or relapse for patients who had complete response during the study] or death, whichever occurred first), duration of response (defined as time from the initial documentation of a response to the first documented evidence of progressive disease [or relapse for patients who had complete response during the study] or death), overall survival (defined as time from the first dose of study drug to death from any cause), safety, response rate in biomarker-specific subgroups (*FGFR* translocations *vs* mutations; previously reported[8]), and pharmacokinetics (to be published elsewhere).

Statistical analysis

The study had a power of 85% to reject the null hypothesis that the objective response rate was 25% or less, at a one-sided α level of 0·025, if the true response rate was 42% for the primary analysis.[8] A sample size of at least 88 patients was required to obtain 85% power. In this final analysis, all enrolled and treated patients in the selected regimen group were included in the efficacy analysis (primary efficacy population); no additional formal analysis by central review is provided. The response-evaluable population was defined as all patients who met all eligibility criteria, received at least one dose of study drug, had a baseline disease evaluation and at least one adequate assessment after treatment, had clinical signs or symptoms of disease progression previously, or died before the first post-treatment disease evaluation. Adequate disease assessment was defined as having sufficient evidence to correctly indicate that progression

had or had not occurred. The chemotherapy relapsed or chemorefractory subgroup population within the efficacy population included patients treated with one or more doses of erdafitinib who had progressive disease during or after one or more lines of previous chemotherapy or who had progressed or relapsed within 12 months of their last dose of neoadjuvant or adjuvant chemotherapy. Patients who received at least one dose of the study drug were included in the safety analysis (safety population).

Prespecified subgroup analyses were done for objective response rate and the secondary efficacy endpoints of duration of response (among patients with a confirmed objective response by investigator assessment), progression-free survival, and overall survival within the primary efficacy and chemotherapy relapsed or chemorefractory population, in subgroups based on ECOG performance status, haemoglobin concentration, type of *FGFR* alterations (mutations or fusions), presence or absence of visceral metastases (lung, liver, or bone), and previous chemotherapy; subgroup objective response rate data have been published previously.[8] Subgroup analyses within the chemorefractory population are not presented in this paper. Post-hoc subgroup analyses included duration of response, progression-free survival, and overall survival within the primary efficacy and chemorefractory population, in subgroups based on primary tumour location (upper *vs* lower urinary tract), previous immunotherapy, age, sex, and other patient demographic baseline characteristics (eg, renal function, previous lines of systemic therapy, and liver metastases). Objective response rate by subgroup was not included in the final analysis; only time to event endpoints were included. Because there was very minor changes to the objective response rate across the entire 8 mg regimen, it was thought that minimal changes would be observed in subgroups too and thus deemed not clinically meaningful to include objective response rate by subgroup in the final analysis.

Disease control rate (the proportion of patients with complete response, partial response, and stable disease) and time to response (time from start of treatment to the first response; including subgroup analysis in patients with visceral metastases) were post-hoc endpoints.

Median follow-up time was estimated based on the time from first dose of study treatment to date of censoring for progression-free survival using the reverse Kaplan-Meier method.[9] The 95% CIs for median progression-free survival, overall survival, and duration of response were determined using complementary log-log transformation. For progression-free survival and duration of response, data from patients who were progression-free and alive or who had unknown survival status were censored at the last tumour assessment. For overall survival, data from patients who were alive or whose vital status was unknown were censored at the date the patient was last known to be alive. Overall survival, progression-free survival, and duration of response were prespecified to be provided at selected landmark points (12 months and 24 months for overall survival; 12 months for progression-free survival and duration of response). A post-hoc landmark analysis was

	Participants (n=101)*
Age, years	67 (61–73)
ECOG performance status	
0	51 (50%)
1	43 (43%)
2	7 (7%)
Pretreatment†	
Progressed or relapsed after chemotherapy	89 (88%)
Chemotherapy-naive	12 (12%)
Previous immunotherapy	24 (24%)
Number of lines of previous treatment‡	
0	10 (10%)
1	48 (48%)
2	28 (28%)
≥3	15 (15%)
Visceral metastases§	
Present	78 (77%)
Absent	23 (23%)
Liver	20 (20%)
Lung	57 (56%)
Bone	23 (23%)
Lymph node metastases only	9 (9%)
Other metastases¶	14 (14%)
Haemoglobin concentration, g/dL	
≥10	86 (85%)
<10	15 (15%)
Primary tumour location	
Upper tract	25 (25%)
Lower tract	76 (75%)
Creatinine clearance rate	
<60 mL/min	53 (52%)
≥60 mL/min	48 (48%)
FGFR alteration	
FGFR mutation present and fusion absent	70 (69%)
FGFR mutation absent and fusion present	25 (25%)
FGFR mutation and fusion present	6 (6%)

Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group. UpT=possibility of uptitration to 9 mg/day. *Two patients were added to the selected 8 mg/day UpT erdafitinib regimen after the data cutoff date for the primary analysis (March 15, 2018). †The pretreatment groups are not mutually exclusive. ‡The chemotherapy relapsed or refractory efficacy population (n=89) consisted of all patients in the 8 mg/day UpT regimen who were treated with at least one dose of erdafitinib and had progressed on or after one or more lines of previous chemotherapy, or progressed or relapsed within 12 months of the last dose of neoadjuvant or adjuvant chemotherapy. §Per-protocol patients with visceral metastases included those with lung, liver, or bone lesions; the combined number of patients with metastases at different visceral sites exceeds the total number with visceral metastases present because some patients had metastatic disease in more than one site. ¶Patients who had any combination of lymph node plus soft tissue or visceral metastases that were not lung, liver, or bone, or soft tissue, or other visceral metastases (not lung, liver, or bone).

Table 1: **Baseline characteristics**

Figure 1: **Swimmer's plot responses in 101 patients treated with the selected 8 mg/day erdafitinib UpT regimen**

Bars are coloured to show best response achieved by each patient. Responses that occurred or were maintained after treatment discontinuation due to adverse events but before the start of subsequent therapy are included in the figure. UpT=potential for uptitration to 9 mg/day. *One patient, shown as treatment ongoing, had a drug interruption at the data cutoff but had not discontinued erdafitinib.

done to compare progression-free survival and overall survival in responding patients (patients with a confirmed best objective response of complete response or partial response) and non-responders (patients with a confirmed best objective response of stable disease or progressive disease, no measurable disease at baseline, or without a post-baseline tumour assessment) based on responses assessed at 3 months after the start of treatment. A 3-month landmark was considered sufficient for this exploratory analysis because it allowed sufficient time for responses to be confirmed. A post-hoc analysis of cumulative incidence of first-onset central serous retinopathy events was performed by grade using the Kaplan-Meier method.

The BLC2001 study protocol is provided in the appendix, together with the statistical analysis plan. SAS (version 9.4) was used for all statistical analyses. This study is registered with ClinicalTrials.gov, NCT02365597.

Role of the funding source

The funder of the study was involved in study design, data collection, data analysis, and data interpretation, and funded writing assistance provided by Parexel.

Results

Between May 25, 2015, and Aug 9, 2018, 2328 patients were screened, of whom 212 were enrolled and 101 were treated with the selected erdafitinib 8 mg/day UpT regimen (60 patients received 8 mg/day and 41 patients were uptitrated to 9 mg/day; appendix p 6, table 1). Of the 101 patients who were treated with the 8 mg/day UpT regimen, two died due to progressive disease before the first disease evaluation after the baseline assessment.

At the clinical cutoff date for this analysis (Aug 9, 2019), median follow-up for efficacy was 24·0 months (IQR 22·7–26·6). Median treatment duration was 5·4 months (IQR 2·8–9·0). Two patients were enrolled into the 8 mg/day UpT regimen group after the clinical cutoff date for the primary analysis (March 15, 2018). Consistent with the primary analysis, progressive disease was the most common reason for treatment discontinuation (appendix p 6). At the analysis cutoff date, 24 patients (24%) in the 8 mg/day UpT group remained in the study.

Among all patients who received the 8 mg/day UpT regimen, the proportion of patients with a confirmed investigator-assessed objective response was 40 (40%; 95% CI 30–49) of 101 patients, consistent with the objective response rate at the time of the primary analysis (40 [40%; 31–50] of 99 patients).[8] Among the 40 responding patients, 36 (36%) of 101 had a partial response and four (4%) had a complete response; figure 1). Additionally, 41 (41%) of 101 patients had a best response of stable disease for at least one disease evaluation period (>36 days), meaning that disease control was achieved in 81 of 101 patients, leading to an overall disease control rate (post-hoc endpoint) of 80% (95% CI 72–88) for the primary efficacy population. 76 (77%) of 99 patients treated with the 8 mg/day UpT regimen, who had at least one disease evaluation after baseline, had a reduction in the sum of target lesion diameters, and 48 (48%) had a maximum tumour diameter reduction of 30–100% (appendix p 7).

Prespecified subgroup analyses of objective response rate showed similar response rates irrespective of the presence or absence of visceral metastases (objective responses were recorded in three [33%] of nine patients

with lymph node only disease, seven [35%] of 20 with liver metastases, 23 [40%] of 57 with lung metastases, eight [35%] of 23 with bone metastases, four [40%] of ten with both liver and lung metastases, and seven [50%] of 14 with other metastatic disease). Objective response rate by subgroup was not included in the final analysis; only time to event endpoints were included.

Median duration of response in all 101 treated patients was 6·0 months (95% CI 4·2–7·5); 31 (31%) of 101 patients had a response that was maintained for at least 12 months.

Median progression-free survival was 5·5 months (95% CI 4·3–6·0) for all 101 patients treated with the selected regimen (figure 2A). The 12-month progression-free survival rate was 21% (95% CI 13–29). There were 72 overall survival events and 90 progression-free survival events in the 8 mg/day erdafitinib UpT group, and median overall survival was 11·3 months (95% CI 9·7–15·2; figure 2B). The 12-month overall survival rate was 49% (95% CI 39–59) and the 24-month survival rate was 31% (22–40).

Based on the post-hoc landmark analysis, at 3 months after treatment initiation, progression-free survival was similar between responders and non-responders whereas overall survival was improved for responders (appendix p 8); however, these findings are limited by the small numbers included.

In our prespecified subgroup analyses, compared with patients with an ECOG performance status of 2, patients with an ECOG performance status of 0–1 had longer median progression-free survival (5·6 months [95% CI 5·0–6·8] *vs* 3·2 months [1·0–4·9]) and longer median overall survival (13·8 months [10·3–15·8] *vs* 5·1 months [3·0–8·0]). Median duration of response was 6·0 months (95% CI 4·2–7·5) in patients with an ECOG performance status of 0–1 and 2·8 months (not evaluable [NE]–NE) in those with an ECOG performance status of 2.

78 (77%) of 101 patients had visceral metastases, but our prespecified subgroup analysis showed that duration of response, progression-free survival, and overall survival were similar regardless of the presence or absence of visceral metastases (figure 3, appendix p 9).

Most patients (70 [69%] of 101) had *FGFR* mutations, 25 (25%) had fusions, and six (6%) had both mutation and fusion. The most common mutations were *FGFR3* S249C (45 [46%] of 99 patients who had at least one disease evaluation after baseline), *FGFR3* R248C (13 [13%]), and *FGFR3* Y373C (12 [12%]), and the most common fusion was *FGFR3* TACC3v1 (11 [11%]). In our prespecified subgroup analysis of outcomes by *FGFR* alteration type, duration of response, and overall survival were generally similar between patients with *FGFR* mutations and those with *FGFR* fusions, although progression-free survival was shorter in patients with *FGFR* fusions than in those with *FGFR* mutations (figure 3, appendix p 9).

Median progression-free survival and overall survival were similar between patients who had baseline haemoglobin concentrations of less than 10 g/dL versus those who had haemoglobin concentrations of 10 g/dL or greater (figure 3). Duration of response was 6·0 months (95% CI 3·0–7·9) in patients with baseline haemoglobin concentrations of less than 10 g/dL and 5·8 months (4·2–13·4) in those with haemoglobin concentrations of 10 g/dL or greater.

In our post-hoc subgroup analyses, progression-free survival, overall survival, and duration of response were not affected by factors such as age and sex (appendix p 9) and most baseline disease characteristics, including haemoglobin level, primary tumour location, and renal function (figure 3, appendix p 9).

In a post-hoc analysis, median time to response was 1·4 months (95% CI 1·2–8·5). Median time to response was longer in patients who had both liver and lung metastases (2·2 months [IQR 1·4–3·0]) than in those who had lymph node only disease (1·4 months [1·4–1·4]), and those with liver (1·4 months [1·4–3·0]), lung (1·4 months [1·4–1·6]), bone (1·6 months [1·4–2·8]), and other metastases (1·4 months [1·3–1·4]). Similarly, median time to response was longer in patients with two to three sites of visceral disease (2·0 months [IQR 1·3–3·0]) than in

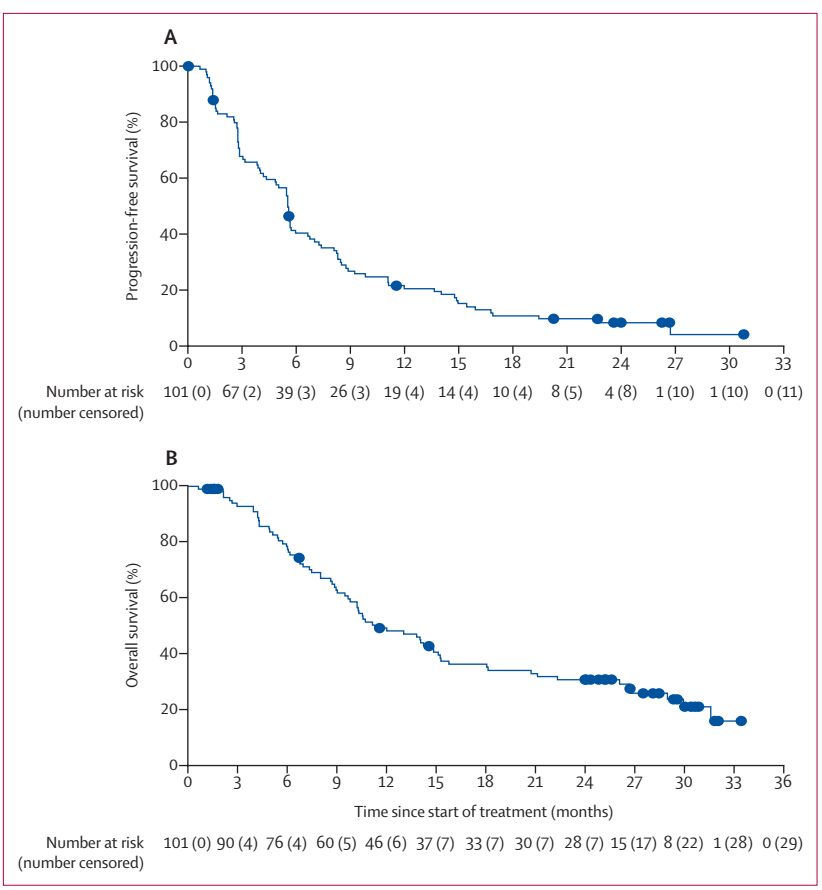


Figure 2: **Investigator-assessed progression-free survival and overall survival for patients treated with the selected 8 mg/day erdafitinib UpT regimen**
(A) Progression-free survival. (B) Overall survival. Dots denote censored patients. UpT=potential for uptitration to 9 mg/day.

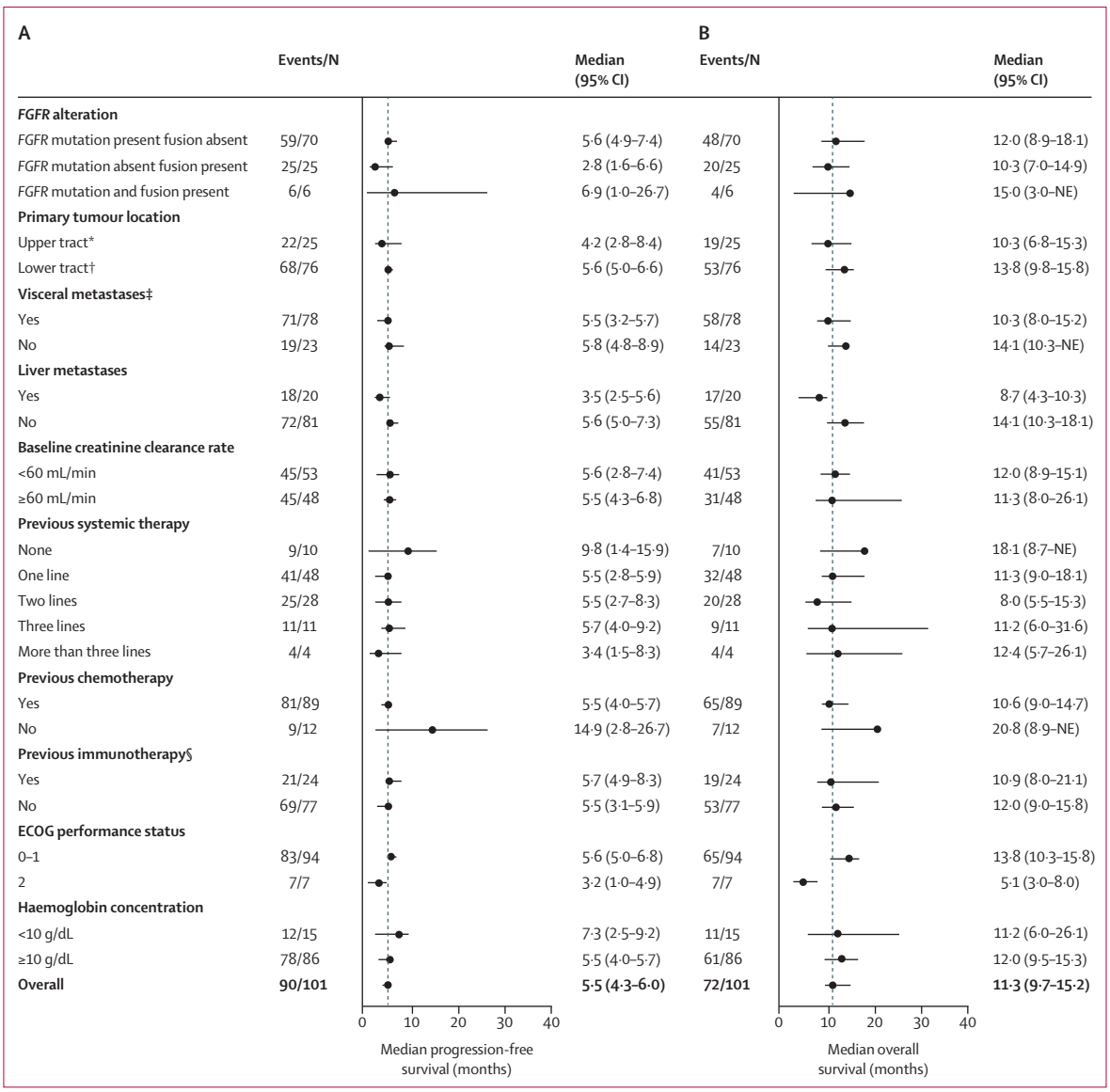


Figure 3: **Subgroup analysis of progression-free survival and overall survival**
(A) Progression-free survival. (B) Overall survival. Error bars represent the associated 95% CIs. Vertical dashed lines denote overall median progression-free survival and overall survival, respectively. NE=not evaluable. *Upper tract includes renal pelvis and ureter. †Lower tract includes bladder, urethra, and prostatic urethra. ‡Visceral metastases include metastases in lung, liver, and bone. §Previous immunotherapy includes atezolizumab, pembrolizumab, nivolumab, durvalumab, avelumab, anti-csf1r antibody, and tremelimumab.

those who had one (1·4 months [1·4–1·5]) or no metastatic sites (1·4 months [1·3–1·4]), but these results were based on a small number of responders per disease site.

89 (88%) of 101 patients had received previous chemotherapy (table 1). A confirmed objective response was achieved by 35 of 89 patients in the chemotherapy relapsed or refractory population, giving an objective response rate of 39% (95% CI 29–50), which was similar to the objective response rate in the all-treated population. Median duration of response was 6·0 months (95% CI 4·2–7·5) in all treated patients versus 5·6 months (4·2–7·2) in the chemotherapy relapsed or refractory population. Additionally, the disease control rate (post-hoc endpoint) in the chemotherapy relapsed or refractory population (disease control in 71 of 89 patients; 80% [95% CI 71–88]) was similar to that in the all-treated population. Median progression-free survival in the treated chemotherapy relapsed or refractory population (81 events; median 5·5 months, 95% CI 4·0–5·7; figure 3A, appendix p 10) was also similar to that in the all-treated population. Median overall survival was 10·6 months (95% CI 9·0–14·7) for the treated chemotherapy relapsed or refractory population (among whom 65 deaths occurred; figure 3B, appendix p 10). In chemotherapy-naive patients

(n=12), median progression-free survival was 14·9 months (95% CI 2·8–26·7) and median overall survival was 20·8 months (8·9–NE; figure 3; appendix p 11). Five (42%; 95% CI 14–70) of 12 chemotherapy-naive patients had an objective response.

24 (24%) of 101 patients who received the 8 mg UpT regimen had received previous immunotherapy (table 1), but progression-free survival, overall survival, and duration of response were similar regardless of the number of lines of previous immunotherapy (post-hoc analysis; figure 3, appendix p 9).

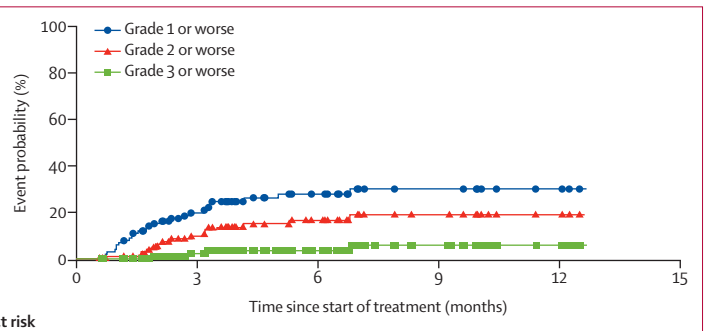
The safety profile of erdafitinib at a median treatment exposure of 5·4 months (IQR 2·8–9·0) remained consistent with that in the primary analysis.[8] All patients experienced at least one treatment-emergent adverse event (defined in appendix p 5) irrespective of dose uptitration, and 60 (59%) of 101 patients experienced treatment-emergent adverse events that led to dose reduction. Grade 3–4 treatment-emergent adverse events of any cause occurred in 72 (71%) of 101 patients; the most common (occurring in ≥10% of patients) were stomatitis (in 14 [14%] of 101 patients) and hyponatraemia [in 11 [11%]; table 2, appendix p 12). 53 (52%) of 101 patients had grade 3 treatment-emergent adverse events that were considered related to erdafitinib 8 mg UpT (appendix p 13). No grade 4 adverse events were considered related to erdafitinib. No new treatment-related adverse events were observed with longer follow-up (appendix p 13). The most common treatment-emergent adverse events (of any grade) were hyperphosphataemia, stomatitis, diarrhoea, and dry mouth (table 2). Serious treatment-emergent adverse events occurred in 45 (45%) of 101 patients (appendix p 14). The most common serious treatment-emergent adverse events were urinary tract infection and general physical health deterioration; serious treatment-emergent adverse events in 11 (11%) of 101 patients were considered by the investigator to be related to erdafitinib, and no treatment-related deaths occurred. Of patients receiving the 8 mg/day UpT regimen, 16 (16%) of 101 had adverse events considered related to erdafitinib that led to treatment discontinuation. The frequency of any one event leading to treatment discontinuation was low; no more than two patients (2%) reported the same adverse event leading to treatment discontinuation (appendix p 16).

The proportion of patients with central serous retinopathy (a known class effect of FGFR inhibitors and a treatment-emergent adverse event of special interest) was 27 (27%) of 101 in the all-treated population (post-hoc analysis; appendix p 15); 15 (25%) of 60 who received 8 mg/day and 12 (29%) of 41 whose dose was uptitrated to 9 mg/day. 23 [85%] of 27 events were grade 1–2 (figure 4, appendix p 15). At data cutoff, 17 (63%) of 27 central serous retinopathy events had resolved (median time to resolution 27 days [range 9–299]); all ten unresolved events were grade 1–2 (appendix p 15). The median time to first onset of central serous retinopathy was 53 days (IQR 32–100) for any grade event and 94 days (72–154) for grade 3 events

	Grade 1–2	Grade 3	Grade 4	Grade 5*
All treatment-emergent adverse events	29 (29%)	58 (57%)	6 (6%)	8 (8%)
Hyperphosphataemia†	77 (76%)	2 (2%)	0	0
Stomatitis	46 (21%)	14 (14%)	0	0
Diarrhoea	51 (50%)	4 (4%)	0	0
Dry mouth	45 (45%)	1 (1%)	0	0
Decreased appetite	40 (40%)	1 (1%)	0	0
Dysgeusia	39 (39%)	2 (2%)	0	0
Alopecia	34 (34%)	0	0	0
Dry skin	34 (34%)	0	0	0
Fatigue	31 (31%)	2 (2%)	0	0
Constipation	28 (28%)	1 (1%)	0	0
Dry eye	27 (27%)	1 (1%)	0	0
Palmar-plantar erythrodysaesthesia syndrome	20 (20%)	5 (5%)	0	0
Asthaenia	15 (15%)	6 (6%)	0	2 (2%)
Anaemia	17 (17%)	5 (5%)	0	0
Nausea	21 (21%)	1 (1%)	0	0
Alanine aminotransferase increased	17 (17%)	2 (2%)	0	0
Onycholysis	17 (17%)	2 (2%)	0	0
Paronychia	16 (16%)	3 (3%)	0	0
Urinary tract infection	13 (13%)	5 (5%)	0	0
Vision blurred	18 (18%)	0	0	0
Weight decreased	17 (17%)	1 (1%)	0	0
Nail dystrophy	11 (11%)	6 (6%)	0	0

Data are n (%). n represents number of patients. Patients with one or more treatment-emergent adverse events were counted only once for each adverse event and worst grade reported. Treatment-emergent adverse events that occurred in at least 15% of patients are shown. No grade 4 adverse events were considered to be related to erdafitinib. *All treatment-emergent adverse events with the outcome of death (grade 5) were considered by the investigator to be unrelated to erdafitinib, and most events (seven of eight), including the two grade 5 events of asthaenia, occurred in the context of progressive disease (death due to acute myocardial infarction was not in the context of progressive disease). †Hyperphosphataemia was graded on the basis of protocol-defined criteria: 5·5–6·9 mg/dL as grade 1; 7·0–8·9 mg/dL as grade 2; 9·0–10·0 mg/dL as grade 3; >10·0 mg/dL as grade 4.

Table 2: **Most common treatment-emergent adverse events by worst toxicity grade in the safety population (n=101)**



Number at risk (number censored)						
Grade 1 or worse	101 (0)	67 (15)	41 (35)	26 (49)	19 (56)	..
Grade 2 or worse	101 (0)	74 (18)	47 (49)	29 (57)	19 (67)	..
Grade 3 or worse	101 (0)	80 (19)	53 (45)	30 (67)	20 (77)	..

Figure 4: **Post-hoc analysis of the cumulative incidence of first-onset central serous retinopathy events by grade using the Kaplan-Meier method**

Three patients had grade 3 central serous retinopathy events that resolved or lessened in severity to grade 1 following dose reduction or interruption in two patients and with no dose modification in another patient. One patient had grade 3 detachment of retinal pigment epithelium, which initially resolved but then recurred as a grade 2 event following dose reduction (leading to discontinuation of erdafitinib in this patient).

(figure 4); two (7%) of 27 events occurred after 6 months. 13 (13%) of 101 treated patients had a dose reduction, eight (8%) had a dose interruption, and three (3%) discontinued treatment for central serous retinopathy (see appendix p 5 for dose modifications for the most common treatment-emergent adverse events). Other select treatment-emergent adverse events are reported in the appendix (p 17). Rates of hyperphosphataemia were higher in the non-uptitrated group (52 [87%] of 60 patients) than in the uptitrated group (27 [66%] of 41); the incidences of stomatitis, nail events, non-central serous retinopathy events, skin events, and diarrhoea were similar between patients who received 8 mg/day and those who received 9 mg/day (appendix p 17).

Discussion

In this analysis of the BLC2001 study, with a median efficacy follow-up of 24·0 months, treatment with erdafitinib showed consistent efficacy in patients with locally advanced or metastatic urothelial carcinoma and *FGFR* alterations, in keeping with the primary analysis (median follow-up of about 11 months).[8] There were no new safety signals with a median treatment exposure of 5·4 months. The confirmed investigator-assessed objective response rate was 40% (95% CI 30–49), with promising progression-free and overall survival outcomes. Clinically meaningful treatment benefit with erdafitinib was observed in patients regardless of previous chemotherapy or immunotherapy and most baseline disease characteristics. Objective response lasted for a median of 6·0 months, and 31% of response lasted for 1 year or longer. Patients with an ECOG performance status of 0–1 had a longer median progression-free survival and overall survival than those with an ECOG performance status of 2, but there were no substantial differences in progression-free survival or overall survival by presence or absence of visceral metastases, *FGFR* alteration type, or kidney function (baseline creatinine clearance rate <60 mL/min or ≥60 mL/min). Although progression-free survival and overall survival seemed to be longer in chemotherapy-naive patients than in those who had received previous chemotherapy, several factors could have contributed to this finding, including potential differences in baseline disease characteristics in this small number of patients. Of note, all subgroup comparisons were exploratory in this non-randomised study, and some of the subgroups contained small numbers of patients, which should be taken into consideration when interpreting the results.

The results from the primary analysis of BLC2001 led to approval of erdafitinib by global health authorities, making it the first targeted therapy approved for patients with metastatic urothelial carcinoma.[10] As many as 32% of urothelial carcinomas might have *FGFR* alterations;[11] *FGFR3* alterations have been reported in about 22% of patients with urothelial bladder carcinoma at all stages in one study,[12] suggesting a role for the wider implementation of *FGFR* testing, since patients with particular *FGFR* alterations might benefit from FGFR inhibition. Other FGFR inhibitors are also being investigated in metastatic urothelial carcinoma, including infigratinib and rogaratinib. In one study,[13] the objective response rate for infigratinib (an FGFR1–3 inhibitor) was 24% in the second-line or later-lines setting for locally advanced or unresectable or metastatic urothelial carcinoma. In an expansion cohort of a phase 1 study[14] of another oral pan-FGFR kinase inhibitor, rogaratinib, in patients with advanced urothelial carcinoma (45% of whom had *FGFR* overexpression) with a median of two previous lines of therapy, the objective response rate was 24%.

A systematic review and meta-analysis of 22 studies involving single-agent chemotherapy and 24 studies including doublet chemotherapy in the second-line setting following platinum-based chemotherapy found objective response rates of 14% and 32%, respectively.[15] As second-line therapy, checkpoint blockade immunotherapies have shown an objective response rate of about 20%.[16–21] The objective response rate reported in studies of antibody–drug conjugates as second-line treatment were 40·6% for enfortumab vedotin (phase 3 study; median follow-up of 11·1 months)[22] and 31% for sacituzumab govitecan (phase 1/2 study).[23]

The progression-free survival and overall survival observed in the current analysis of the BLC2001 study confirm the persistent benefit of the selected erdafitinib 8 mg/day UpT regimen. These median survival data are also, generally, similar to those noted for second-line checkpoint inhibitors[16,18,19] and antibody–drug conjugates.[22,24] For many of the studies of these other agents, only short-term follow-up is currently available, and it will be important to see if those responses are durable. Additionally, owing to differences in patient populations, study design, and treatment regimens, it is difficult to make indirect cross-trial comparisons. Among patients treated with erdafitinib 8 mg/day UpT in this study, 31% had responses lasting 12 months or more, and 12-month and 24-month overall survival rates were 49% and 31%, respectively. Patients with objective responses to erdafitinib also had longer progression-free survival and overall survival than those who did not have objective responses; moreover, progression-free survival and overall survival were independent of most baseline disease characteristics. The durability of objective response rate, progression-free survival, and overall survival noted in this study shows the benefit of single-agent erdafitinib treatment in patients with metastatic urothelial carcinoma and prespecified *FGFR* alterations.

Data from other tyrosine kinase inhibitors suggest that primary and acquired resistance is an issue associated with FGFR inhibitors.[24–26] To identify markers of intrinsic resistance to FGFR inhibition, plasma samples from the BLC2001 study were tested using next-generation sequencing for circulating tumour DNA, and the presence of *EGFR*, *CCND1*, and *BRAF* alterations at baseline correlated with shorter progression-free survival, and the

presence of *EGFR* with shorter overall survival.[27] Further studies assessing the prognostic versus predictive value of these genes in patients with metastatic urothelial carcinoma and *FGFR3* alterations could provide additional insight.

In this analysis, based on a median 5·4 months' treatment exposure, the safety profile of erdafitinib in patients with locally advanced or metastatic urothelial carcinoma and *FGFR* alterations remained consistent with the primary analysis. Central serous retinopathy events, a known class effect of mitogen-activated protein kinase pathway inhibitors, including FGFR inhibitors,[28–30] occurred in approximately a quarter of patients but were mostly grade 1–2 and the majority of these events had resolved at data cutoff.

The open-label, single-arm study design of BLC2001 is a limitation of the trial. Patients were selected on the basis of the presence of nine prespecified *FGFR* alterations; because gene amplifications were not included among these alterations and whole-genome sequencing was not done, other mechanisms for constitutive activation or resistance were not assessed. The Kaplan-Meier curves for progression-free survival and overall survival by responder status at the 3-month landmark and some of the subgroup analyses are limited by small numbers; these are included here to offer clinical insights only. Erdafitinib is being investigated further in a phase 3, randomised, controlled study (NCT03390504) in patients with urothelial carcinoma as monotherapy versus immune checkpoint inhibitor (PD-1) or chemotherapy. Erdafitinib is also being investigated in the first-line, cisplatin-ineligible, metastatic urothelial carcinoma setting in combination with the PD-1 inhibitor cetrelimab (NCT03473743), and as monotherapy versus intravesical chemotherapy in a randomised, phase 2 study (NCT04172675) in high-risk non-muscle-invasive bladder cancer that recurred after treatment with bacillus Calmette-Guérin. The frequency of *FGFR* alterations is higher in early-stage urothelial carcinoma.[11]

In conclusion, in the BLC2001 study, at a median follow-up of 24·0 months, second-line erdafitinib treatment of patients with locally advanced or metastatic urothelial carcinoma and prespecified *FGFR* alterations showed consistent, durable clinical activity. Erdafitinib remains an important treatment option for patients with locally advanced or metastatic urothelial carcinoma who progressed during or after one or more lines of previous platinum-based chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-based chemotherapy, and who have specific *FGFR* alterations. Erdafitinib is therefore being investigated in other treatment settings.

Contributors

AOS-R, AES-W, YL, AO'H, MJ, and ARK were involved in the conceptualisation and design of the study. SA, ID, JG-D, RAH, MJ, STT, YZ, AN, BM, SHP, AO'H, AR, AES-W, YL, and AOS-R were involved in the investigation, data collection, data analysis, or interpretation of the study. AOS-R, AO'H and SA accessed and verified the raw data. All authors reviewed the data analyses, data interpretation, and writing of the report, and approved the final version of the submitted manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

EFB has received grants or contracts from Pfizer and Astellas Pharma; honoraria from Exelixis and Bayer; and stocks or stock options from Exelixis, Becton Dickinson, Calithera Biosciences, Gilead Sciences, Medtronic, Clovis Oncology, and Macrogenics, outside of the submitted work. ID has received grants or contracts from Roche/Genentech, AstraZeneca, and Astellas Pharma; consulting fees from Roche/Genentech, MSD Oncology, Bayer, Bristol Myers Squibb, Seattle Genetics, Pharmacyclics Janssen Oncology, and Novartis; honoraria from Bristol Myers Squibb, Ipsen, Roche/Genentech, Janssen Oncology, MSD Oncology, Astellas Pharma, and EUSA Pharma; and has been reimbursed for travel, accommodations, or expenses from Roche/Genentech, AstraZeneca Spain, and Ipsen, outside of the submitted work. MTF has received consulting fees from Janssen Oncology; honoraria from Genentech and Janssen Oncology; and has been reimbursed for travel, accommodations, or expenses from Medivation/Astellas and Genentech, outside of the submitted work. JG-D has received consulting fees from Bristol Myers Squibb and Clovis Oncology; honoraria from Roche, Bristol Myers Squibb, AstraZeneca, PharmaMar, GlaxoSmithKline, Amgen, Clovis Oncology, and Janssen-Cilag; and other financial or non-financial interests from Pfizer, Bristol Myers Squibb, Roche, AstraZeneca, Merck, GamaMabs Pharma, and InvitroCue, outside of the submitted work. RAH has received personal fees from Aspen Parkside Hospital, during the conduct of the study; consulting fees from Bristol Myers Squibb, Roche, Merck Sharp & Dohme, Janssen Oncology, Nektar, and Bayer; honoraria from Janssen Oncology; support for attending meetings or travel from Janssen Oncology, Roche/Genentech, MSD Oncology, and Nektar; other financial or non-financial interests from Merck Sharp & Dohme, Roche, Bristol Myers Squibb, and Janssen; has patents planned, issued, or pending from Janssen; and has a leadership or fiduciary role at Cancer Clinic London Limited Liability Partnership, outside of the submitted work. MJ has received consulting fees from Sanofi; and other financial interests from AstraZeneca and Pfizer, outside of the submitted work. YL has received consulting fees from Janssen, Astellas Pharma, Roche, AstraZeneca, MSD Oncology, Clovis Oncology, Seattle Genetics, and Bristol Myers Squibb; and has been reimbursed for accommodations or expenses from Astellas Pharma, Janssen Oncology, Roche, AstraZeneca, MSD Oncology, Clovis Oncology, Seattle Genetics, and Bristol Myers Squibb, outside of the submitted work. BM has received consulting fees from Pfizer, Roche, AstraZeneca, Bayer, Astellas Pharma, and Janssen, and for an immediate family member from Roche, Pfizer, and Amgen; support for attending meetings or travel from Janssen-Cilag and for an immediate family member from Roche; and other financial or non-financial interests from Roche, Janssen, and Bayer, outside of the submitted work. MM received personal fees from Janssen Oncology, during the conduct of the study. AN received personal fees from Bayer, during the conduct of the study; consulting fees from Merck Sharp & Dohme, Roche, Bayer, AstraZeneca, Clovis Oncology, Janssen, Seattle Genetics/Astellas, Bristol Myers Squibb, GlaxoSmithKline, and Ferring; honoraria from Roche, Merck, AstraZeneca, Janssen, Foundation Medicine, and Bristol Myers Squibb; support for attending meetings or travel from Roche, Merck Sharp & Dohme, AstraZeneca, Janssen, and Rainier Therapeutics; stocks or stock options for an immediate family member from Bayer; and other financial or non-financial interests from Merck Sharp & Dohme, AstraZeneca, and Ipsen, outside of the submitted work. AO'H received personal fees from Janssen, during the conduct of the study. AES-W received personal fees form Janssen, during the conduct of the study. AOS-R received support from the National Institutes of Health, Michael and Sherry Sutton Fund for Urothelial Cancer, Janssen, Takeda, Bristol Myers Squibb, BioClin Therapeutics, Nektar, Merck Sharp & Dohme, and Basilea; consulting fees from Janssen, Merck, National Comprehensive Cancer Network, Bristol Myers Squibb, AstraZeneca, Bavarian Nordic, Seattle Genetics, Nektar, Genentech, EMD Serono, Mirati Therapeutics, and Basilea; and has patents planned, issued, or pending related to molecular testing in muscle invasive bladder cancer, outside of the submitted work. STT has received consulting fees from Medivation, Astellas Pharma, Dendreon, Janssen, Bayer,

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Data sharing

Janssen Pharmaceutical Companies of Johnson & Johnson's data sharing policy is available at https://www.janssen.com/clinical-trials/transparency. As noted on this website, requests for study data access can be submitted through the Yale Open Data Access Project website at http://yoda.yale.edu.

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