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

--Manuscript Draft--

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Abstract:	Background Erdafitinib, a pan-fibroblast growth factor receptor (FGFR) kinase inhibitor, was effective and tolerable in patients with advanced urothelial carcinoma and prespecified FGFR alterations in the primary analysis from the open-label, phase 2, non-comparator, BLC2001 study at median 11 months' follow-up. The aim of the current analysis was to assess long-term efficacy and safety for the selected regimen. Methods Eligible patients were ≥18 years with locally advanced and unresectable/metastatic urothelial carcinoma, had at least one prespecified FGFR alteration and an Eastern Cooperative Oncology Group performance status of 0–2. The selected regimen determined in the initial part of the study was 8 mg/day continuous 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 (ORR) according to Response Evaluation Criteria In Solid Tumors (RECIST) 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 the study (ClinicalTrials.gov number NCT02365597). Findings Between May 25, 2015, and August 9, 2018, 212 patients were enrolled and 101 patients were treated with erdafitinib 8 mg/day UpT . Data cutoff for this analysis was August 9, 2019. Median efficacy follow-up was 24·0 (interquartile range 22·7–26·6) months. Investigator-assessed ORR for patients treated with the selected erdafitinib regimen was 40% (95% CI 30%–49%). Interpretation With longer follow-up, treatment with the selected regimen of erdafitinib showed consistent efficacy and a manageable safety profile in patients with locally advanced/metastatic urothelial carcinoma and prespecified FGFR alterations. Funding Janssen Research & Development.

Dr Cheryl Reeves
Senior Editor
The Lancet Oncology

August 30, 2021

Dear Dr Reeves

On behalf of my co-authors, I would like to thank you and the editorial team for the positive feedback on our submitted manuscript, "Efficacy and safety of erdafitinib in patients with locally advanced or metastatic urothelial carcinoma: long-term follow-up of the pivotal phase 2 study." In response to this feedback, we have provided a revised manuscript and a point-by-point response below with answers to each point in a tabular format.

We do hope that the editorial team's queries have been addressed and hope that the manuscript will now be acceptable for publication in *The Lancet Oncology*. We look forward to hearing from you.

Yours sincerely,

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Response to Reviewer Comments:

Reviewer comments	Author response and changes made	Page number and paragraph in the revised, tracked paper where changes can be found
Editor's comments		
1. Please check with your co-authors, and confirm, that all names are spelt correctly, and affiliations listed correctly. We cannot guarantee that we will be able to correct names and affiliations after publication of your article.	We can confirm that all names are spelt correctly, and affiliations are listed correctly. No changes have been made	NA
2. Please supply (after author names on the title page) one preferred degree per author and indicate in the authorship if any authors are full professors.	We have updated the author list as requested: "Arlene O Siefker-Radtke MD (Prof), Andrea Necchi MD (Prof), Se Hoon Park MD, Jesús García-Donas MD, Robert A Huddart PhD, Earle F Burgess MD, Mark T Fleming MD, Arash Rezazadeh Kalebasty MD, Begoña Mellado MD, Sergei Varlamov MD, Monika Joshi MD, Ignacio Duran MD, Scott T Tagawa MD, Yousef Zakharia MD, Sydney Akapame PhD, Ademi E Santiago-Walker PhD, Manish	Page 1, paragraph 2

	Monga MD, Anne O'Hagan MPH, Yohann Loriot MD, on behalf of the BLC2001 Study Group"	
3. Please format the author affiliation list to Lancet style. Please list authors by full first name and last name; and then for affiliations, by including the author initial and full last name, followed by one degree, in brackets following the author institution.	We have updated the author affiliation list as requested: "Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, 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, Republic of South Korea (S H Park MD); Medical Oncology Department, Fundacion Hospital de Madrid, Madrid, Spain, IMMA, Medicine Faculty, San Pablo CEU University, Madrid, (J García-Donas MD); Section of Radiotherapy and Imaging, Institute of Cancer Research and Royal Marsden NHS Foundation Trust, Sutton, UK (R A Huddart MBBS, PhD); Medical Oncology Department, Levine Cancer Institute, Charlotte, North Carolina, USA (E F Burgess MD); Medical Oncology Department, Virginia Oncology Associates, US Oncology Research, Norfolk, Virginia, USA (M T Fleming MD); Department of Medical Oncology, Norton Healthcare, Louisville, Kentucky, USA (A Rezazadeh Kalebasty MD); Medical Oncology Department, Hospital Clinic Institut	Page 1, paragraph 3 and Page 2, paragraph 1

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4. As your author line includes a study group (eg, 'on behalf of the BLC2001 study group'), collaborators' names and affiliations may be listed in the appendix. Additionally, if you wish the names of collaborators within a study group to appear on PubMed, please upload with your revision a separate Word document with a list of names of the study group members presented as a two-column table. First and middle names or initials should be placed in the first column, and surnames in the second column. Names should be ordered as you wish	Please note that collaborators names are listed within the appendix under "List of BLC2001 investigators."	Appendix, pages 2-3

	them to appear on PubMed. The table will not be included in the paper itself – it's simply used to make sure that PubMed adds the names correctly. **We will not make changes to the collaborator list after publication so please ensure names are spelled correctly and first names and surnames are in the correct columns**		
5.	The Research in Context Panel: Added value of this study: Authors should summarise here how their findings add value to the existing evidence. IMPORTANT: Please do NOT reiterate the results (eg, do not include data) or describe your study approach (this is already covered by the abstract), but rather explain how the findings extend knowledge in the field. Implications of all the available evidence: Authors should state the implications for practice or policy and future research of their study combined with existing evidence.	We have modified the "Added value of this study" part of the "Research in Context Panel" so that it does not simply reiterate the results of the study. However, we hope that you understand that we are unable to remove all of the data, as this is the main point/value of the manuscript; we are providing longer-term data further supporting the use of erdafitinib for the treatment of patients with locally advanced or metastatic urothelial cancer whose tumours harbour specific *FGFR* alteration(s) "We show that, ~~at a median of 24 months'~~with longer follow-up, erdafitinib treatment continues to show consistent clinical ~~efficacy~~ benefits for patients with locally advanced or metastatic urothelial cancer whose tumours harbour specific *FGFR* alterations and that erdafitinib has a manageable safety profile. ~~With the longer follow-up, there was a consistent benefit in objective response rate, progression-free survival, and overall survival and, with a median treatment exposure of 5·4 months,~~	Page 6, paragraph 2

	~~the safety profile remained consistent with no new safety signals identified.~~	
6. If your paper reports results of a trial, please follow our formatting guidelines for these study types, available to download from www.thelancet.com/for-authors/forms ('RCT guidelines').	Please note that the manuscript reports data from an open-label phase 2 study and so RCT guidelines are not applicable. The non-comparator nature of the study has been clarified within the Abstract: "Background Erdafitinib, a pan-fibroblast growth factor receptor (FGFR) kinase inhibitor, was effective and tolerable in patients with advanced urothelial carcinoma and prespecified *FGFR* alterations in the primary analysis from the open-label, phase 2, non-comparator, BLC2001 study at median 11 months' follow-up. The aim of the current analysis was to assess long-term efficacy and safety for the selected regimen." And the Methods section of the manuscript: "The open-label, phase 2, non-comparator BLC2001 study (NCT02365597) in patients with locally advanced or metastatic urothelial carcinoma was conducted at 126 sites in 14 countries across Asia, Europe, and North America (see appendix p 2)."	Page 4, paragraph 1 Page 8, paragraph 3
7. Summary: Your abstract should conform to the guidelines for abstracts (http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(07)61835-2/fulltext), and must include: a. Background: It should end with a sentence indicating the aim of this study. b. Methods: A brief summary of the main patient characteristics (including age limit, disease status and histologies permitted,	The abstract has been adjusted following this guidance as follows: "**Background** Erdafitinib, a pan-fibroblast growth factor receptor (FGFR) kinase inhibitor, was effective and tolerable in patients with advanced urothelial carcinoma and prespecified *FGFR* alterations in the	Pages 4 and 5

performance status, and if second line or beyond, criteria regarding previous lines of treatment) c. Methods: Details of the regimens used (including route of administration). d. Methods: Details of how randomisation was done (eg, allocation concealment; nature of blinding, if any; how sequence was generated; stratification factors, etc) if any of the patients included in this follow up were initially randomised. e. Methods: An explicit description of the actual primary endpoint only. f. Methods: The nature by which analyses were done (eg, intention to treat, per protocol). g. Methods: The status of the trial – final analysis? h. Findings: exact dates of recruitment and median follow-up (IQR) for the analyses presented. i. Findings: Data for the primary endpoint only. Secondary outcomes cannot be selectively reported in the abstract, and space restrictions typically prevent all secondary outcomes from being included in the abstract. j. Interpretation: please do not just restate your findings. What do they mean, clinically? What are their implications? k. Please note that all results reported in the Summary need to be reported in the main text. l. See recent issues of the journal for examples. Accuracy and completeness are essential	primary analysis from the open-label, phase 2, non-comparator BLC2001 study at median 11 months' follow-up. ~~We report further data~~ The aim of the current analysis was to assess long-term efficacy and safety ~~at a median 24 months' follow-up~~ for the selected regimen. **Methods** Eligible patients were ≥18 years with locally advanced and unresectable/metastatic urothelial carcinoma, had at least one prespecified *FGFR* alteration and an Eastern Cooperative Oncology Group performance status of 0–2. The selected regimen determined in the initial part of the study was 8 mg/day continuous 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 (ORR) according to Response Evaluation Criteria In Solid Tumors (RECIST) 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 the study (ClinicalTrials.gov, number NCT02365597). **Findings** Between May 25, 2015, and August 9, 2018, 212 patients were enrolled, and 101 patients were treated with erdafitinib 8 mg/day UpT. Data cutoff for this analysis was August 9, 2019. Median efficacy follow-up was 24·0 (interquartile range 22·7–26·6) months.	

	Investigator-assessed ORR for patients treated with the selected erdafitinib regimen was 40% (95% CI 30%–49%). ~~Median DoR was 6·0 months (95% CI 4·2–7·5); 31% of patients had responses lasting 12 or more months. 12- and 24-month survival rates were 49% and 31%, respectively. Median PFS was 5·5 months (95% CI 4·3–6·0) and median OS was 11·3 months (95% CI 9·7–15·2). The safety profile remained similar to that in the primary analysis, with no new safety signals reported with longer follow-up.~~ **Interpretation** With longer follow-up, treatment with the selected regimen of erdafitinib showed consistent efficacy and a manageable safety profile in patients with locally advanced/metastatic urothelial carcinoma and prespecified FGFR alterations. **Funding** Janssen Research & Development."	
8. Please confirm that your study conforms to the CONSORT guidelines by completing and returning the checklist. CONSORT – for RCTs – http://download.thelancet.com/flatcontentassets/authors/tlo-consort-checklist.pdf	Please note that this is a non-randomised trial and so the CONSORT checklist is not applicable.	NA
9. Methods, Study design and participants. Please ensure that the following items are included: a. An indication of estimated life expectancy of eligible patients, if prespecified by protocol. b. Comorbidities permitted/not permitted.	To confirm, the estimated life expectancy of eligible patients was not prespecified by the study protocol. Patient exclusion criteria detailing any comorbidities have been added to the appendix (page 4). The following text has been added to signpost readers to this information:	Page 8, paragraph 3 and Appendix, page 4

	"Patient exclusion criteria are on appendix p 4."	
10. Methods: procedures. Please ensure that the following items are included: a. Planned route of administration. b. Criteria for a patient to be removed from the study. c. Details of permitted dose reductions/interruptions. d. Type and frequency of radiographic assessments. e. If applicable, whether or not the primary endpoint was centrally reviewed. f. Frequency and type of laboratory monitoring. g. Frequency and type of adverse event monitoring should be here not in the outcomes section. h. If you have included such data for a drug(s), please confirm that the dose, route, and frequency of administration (and the form: eg, a particular salt) are correct. i. Please give the manufacturer, city, and country for erdafitinib.	Please find below a list of where this information can be found in manuscript or where it has been added: a. The following information has been moved to the Procedures section: "In the initial part of the study, patients were randomly assigned (1:1, with stratification performed as previously described[8]) to oral erdafitinib (Janssen-Cilag SpA, Latina, Italy) at 10 mg/day intermittently (7 days on, 7 days off) or 6 mg/day continuously in 28-day cycles (appendix p 6). Based on findings from an interim analysis and pharmacokinetic/pharmacodynamic modelling based on clinical data, the protocol was amended to continue enrolment into the 8 mg/day UpT dose schedule..." b. "Patients continued to receive erdafitinib until disease progression or unacceptable AEs, as determined by the investigator. At discretion of the investigator and the sponsor, patients with investigator-assessed disease progression could continue erdafitinib treatment." c. The following text has been added: "Patients who interrupted treatment	Page 9, paragraph 3 Page 10, paragraph 2

	because of grade 1 events reinitiated treatment at the same or 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). Patients who interrupted treatment because of lower grade events reinitiated treatment at the same or a lower dose." d. This information has been moved from the Outcomes to the Procedure section: "Patients were assessed for efficacy using RECIST by computed tomography or magnetic resonance imaging 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." e. For the primary analysis, all disease evaluations in the selected-regimen group were also evaluated by an independent radiological review. These results were included in the primary publication (Loriot et al. *NEJM* 2019). Please note that no additional formal analysis by central review is provided for this final analysis. f. The following text has been moved to the Procedure section: "Safety was	Page 10, paragraph 2 Page 10, paragraph 3

	assessed by clinical laboratory testing, physical examination, electrocardiography, and ophthalmologic examination (frequency of these assessments is described on appendix p 15)." g. The following text has been moved to the Procedure section: "Investigators assessed and graded AEs and abnormalities according to National Cancer Institute CTCAE criteria (version 4.0) for the duration of the study." h. The dose, route, and frequency of administration have been moved to the Procedure section: "In the initial part of the study, patients were randomly assigned (1:1, with stratification performed as previously described[8]) to oral erdafitinib (Janssen-Cilag SpA, Latina, Italy) at 10 mg/day intermittently (7 days on, 7 days off) or 6 mg/day continuously in 28-day cycles (appendix p 6). Based on findings from an interim analysis and pharmacokinetic/pharmacodynamic modelling based on clinical data, the protocol was amended to continue enrolment into the 8 mg/day UpT dose schedule..." i. The manufacturer, city, and country for erdafitinib has been added to this section:	NA Page 10, paragraph 4 Page 10, paragraph 4

	"In the initial part of the study, patients were randomly assigned (1:1, with stratification performed as previously described[8]) to oral erdafitinib (Janssen-Cilag SpA, Latina, Italy)…"	Page 9, paragraph 3 Page 9, paragraph 3
11. Methods: Outcomes: Please ensure the following items are included. a. Definition of the primary endpoint. b. Definition of all secondary endpoints c. All prespecified primary and secondary outcomes specified in the protocol should be listed in the Methods and reported in the Results. If any outcomes prespecified in the protocol are not reported in the present paper, this should be stated in the Outcomes section with a full justification.	We have provided a list of where this information can be found in the Outcomes section of the manuscript or where it has been added: a. "The primary endpoint was confirmed objective response rate (ORR = % complete response [CR] + % partial response [PR]) among patients treated	Page 11, paragraph 1

d. Please ensure any prespecified exploratory endpoints are clearly described as such and move any post-hoc outcomes to the Statistical analysis section.	with the selected regimen; all CRs and PRs required confirmation within 4–6 weeks of first assessment of response, and were assessed by the investigators per RECIST v1.1; disease control rate (DCR [CR + PR + stable disease (SD)]) was also calculated." b. "Secondary endpoints were PFS (defined as time from the first dose of study drug until the first documented evidence of progressive disease [or relapse for patients who experienced CR during the study] or death, whichever occurred first), duration of response (DoR, defined as time from the initial documentation of a response to the first documented evidence of progressive disease [or relapse for patients who experienced CR during the study] or death), OS (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 (considered for publication by another journal)." c. We can confirm that all prespecified primary and secondary outcomes specified in the protocol have been	Page 11, paragraph 1

	included in the Methods and reported in the Results, except for response rate in biomarker-specific subgroups analysis as this has been reported in the primary publication (Loriot et al. *NEJM* 2019) and pharmacokinetics as this information is currently being considered for publication by another journal. d. We have updated the manuscript to clarify which outcomes are post-hoc.	Page 11, paragraph 1 Page 11, paragraph 1
12. Please clarify the secondary endpoint of ORR by biomarker subgroups. What are the biomarker subgroups? Where is this reported in the manuscript? Where is this specified in the protocol or SAP?	The secondary endpoint of response rate by biomarker subgroups has already been described in the Methods section. This is prespecified in section 2.1.2. of the protocol (p 39), but we have updated this sentence to specify the biomarker subgroups and state that these data were previously reported: "response rate in biomarker-specific	Page 11, paragraph 1

	subgroups (FGFR translocations *vs* mutations; previously reported[8])"	
13. Secondary endpoint PK is not reported – please add a justification to the outcomes section as to why these data are not reported and specify whether they will be reported elsewhere.	Please note that pharmacokinetics data are currently under consideration for publication by another journal. Therefore, this information is not included in this manuscript.	Page 11, paragraph 1
14. All subgroup analyses prespecified in the SAP must be described in the statistical section All pre-specified subgroups must be reported in full, or a justification given for why not. Any that are post hoc should be reported and described as such.	The following text about subgroup analysis has been moved from the Outcomes to the Statistical analysis section and expanded for clarifications: "Prespecified subgroup analysis included secondary efficacy endpoints of best objective response, DoR (among patients with a confirmed objective response by investigator assessment), PFS, and OS within the primary efficacy and chemorefractory population, and was assessed by *FGFR* alterations (mutations and/or fusions), presence of visceral metastases (lung, liver or bone), prior chemotherapy, and prior immunotherapy; subgroup best objective response data have been published.[8] Post hoc subgroup analysis included DoR, PFS, and OS within the primary efficacy and chemorefractory population assessed by preplanned subgroups based on primary tumour location (upper *vs* lower tract), and other patient demographic baseline characteristics." Please note that best objective response data were previously reported as part of the primary analysis (Loriot et al. *NEJM* 2019).	Page 12, paragraph 2

15. Are the subgroup analyses by age, sex, and most baseline disease characteristics, described in the results pre-specified. Please update the methods section to describe them as pre-specified or post-hoc.	We confirm that this analysis is prespecified. The Methods section has been updated accordingly.	Page 12, paragraph 2
16. The SAP states that- Subgroup analyses for the best objective response rate, PFS, DOR and OS, will be conducted (Section 2.9) within the PE population and chemo-refractory population, respectively. Please ensure this is added to the statistical section and all are reported in the results section.	The following amends were made to the Statistical analysis section for clarification: "Prespecified subgroup analysis included secondary efficacy endpoints of best objective response, DoR (among patients with a confirmed objective response by investigator assessment), PFS, and OS within the primary efficacy and chemorefractory population, and was assessed by *FGFR* alterations (mutations and/or fusions), presence of visceral metastases (lung, liver or bone), prior chemotherapy, and prior immunotherapy; subgroup best objective response data have been published.[8] Post hoc subgroup analysis included DoR, PFS and OS within the primary efficacy and chemorefractory population assessed by preplanned subgroups based on primary tumour location (upper *vs* lower tract), and other patient demographic baseline characteristics."	Page 12, paragraph 2
17. Was primary tumour location (upper versus lower tract) a prespecified subgroup analyses?	We confirm that while the subgroups by primary tumour location and baseline characteristics were preplanned for the primary analysis, the analyses of DoR, PFS, and OS in these subgroups in the current manuscript are post hoc. The Methods section has been updated accordingly.	Page 12, paragraph 2

18. Methods: Statistical analysis. Please ensure the following items are included: a. Please clarify why the final analysis was done in the primary efficacy population when it states in the protocol/SAP that the final analysis will be done in the treated population. b. Please clarify whether the landmark analysis is prespecified. If not, please indicate that it is post-hoc in the methods and results. c. Rules for defining patients as not assessable. d. Statistical methods for analysis of the primary and secondary outcomes. e. Any sensitivity analyses, etc.	Please see answers to the points listed here below: a. The final analysis was performed in the treated population, which consists of all patients who received at least one dose of the study drug. Since the current manuscript reports on the 8-mg regimen, all relevant analyses are based on the primary analysis population, which includes all patients who received at least one dose of this regimen, as defined in the SAP, p 15. b. For clarity, the text relating to landmark analysis has been adjusted as follows: "A post hoc landmark analysis was performed to compare PFS and OS by responder status…" c. The following definition for response evaluable population has been included for clarity: "The response-evaluable population is defined as all patients who met all eligibility criteria, received at least one dose of study drug, had a baseline and at least one adequate post-treatment disease evaluation, have had clinical signs and/or symptoms of disease progression, or died prior to the first post-treatment disease evaluation. Adequate disease assessment is defined as having sufficient evidence	Page 12, paragraph 1 Page 13, paragraph 1 Page 12, paragraph 1

	to correctly indicate that progression has or has not occurred." Please note that only two patients were regarded as not assessable. This information is now included in the Results section: "Of the 101 patients who were treated with the 8 mg/day UpT regimen, two died due to progressive disease before the first postbaseline disease evaluation." d. Statistical methods for the analysis of primary and secondary outcomes are included as follows: "Data for patients who were progression-free and alive or with unknown status were censored at time of the last tumour assessment. The confidence intervals for median PFS, OS, and DoR were determined using complementary log-log transformation. For PFS and DOR, data from patients who were progression-free and alive or who had unknown status were censored at the last tumour assessment. For OS, 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." e. We confirm that no sensitivity analysis was performed for this final analysis.	Page 14, paragraph 1 Page 13, paragraph 1

	Sensitivity analysis was undertaken only for the primary analysis.	NA
19. Please explain any procedures or analyses that were done differently from their description in the protocol in the appropriate subsection in the Methods section. Please also mention if any protocol amendments affecting trial recruitment or conduct during the study were approved amendments.	On August 9, 2016, the protocol was amended to increase the starting dose to 8 mg/day in a continuous regimen, thereby converting the study to a single-group analysis. These amendments have now been clarified within the Procedures section of the manuscript: "Based on findings from an interim analysis and pharmacokinetic/pharmacodynamic modelling based on clinical data, the protocol was amended to continue enrolment into the 8 mg/day UpT dose schedule, thereby converting the study to a single-group analysis." Please note that the study and all protocol amendments were approved by the review boards: "Review boards at all participating institutions approved the study and all protocol amendments, which was performed	Page 9, paragraph 3

	according to principles of the Declaration of Helsinki and guidelines for Good Clinical Practice and applicable regulatory requirements. Patients or their legally acceptable representatives provided written consent before participation."	Page 9, paragraph 1
20. The Lancet journals are very supportive of protocol-based research and encourage authors to post the protocol document on a publicly accessible website; a margin link to the website will then be put in the paper. Would you like to do this for your protocol? If so, please provide the link in the Methods section of the main text. Please note that if you do wish to do this, the weblink must be permanent. Alternatively, please add the protocol to your appendix if you wish.	The protocol has been included within the appendix (p 18).	Appendix, page 18
21. The following points need to be addressed in the "Role of the funding source" statement: a. The role of the sponsors in the writing of the report. b. It is now required that all authors must have access to all the data reported in the study. This must be confirmed in the role of the funding source section of papers (by author initials). Those who had access to the raw data (by author initials). c. Please also add to this section (if true, or amend if not): "The corresponding author had full access to all of the data and the final responsibility to submit for publication."	This section has now been updated as follows: **Role of the funding source** The funder of the study, Janssen Research & Development, was involved in study design, data collection, data analysis, and data interpretation. Writing assistance was provided by Sally Hassan, PhD, Susan Neville, MSc, and Khalida Rizi, PhD, of Parexel, and was funded by Janssen Global Services, LLC. All investigators had access to the raw data for their individual sites. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.	Page 13, paragraph 3
22. Results: It is Lancet style to give actual numbers (numerator and denominator) together with percentages—eg, 'The confirmed investigator-assessed ORR was 40 (40%) of 101 (95% CI 30%–49%) among all patients'.	The numerators and denominators have been added were needed, for example: "The confirmed investigator-assessed ORR was 40%	Page 14, paragraph 4

	(40/101; 95% CI 30%–49%) among all patients receiving the 8 mg/day UpT regimen, consistent with the 40% ORR (40/99; 95% CI 31%–50%) at the time of primary analysis."	
23. Results: Please avoid the word 'trend'.	The text in question has been deleted to avoid duplication of data presented within the figures.	NA
24. Results: Please add number at risk and the number of patients censored in each group for each time point on your K-M curves. Please ensure both are cumulative and please use the format "number at risk (number censored)".	The number at risks and number censored have been added to the following K-M curves: Figure 2, Figure 4, Figure S3 and Figure S5	Pages 39 and 43 of the main manuscript, and pages 8 and 10 of the appendix
25. Results: Lancet style is to provide p values to 2 significant figures, unless p<0.0001 (please note four decimal places; if this is the case, then please revise to the latter). The exception is certain genetics studies, in which smaller p values can be reported exactly using scientific notation.	No changes needed.	NA
26. We do not allow the term "numerically". If it hasn't been statistically tested, it is OK to say something like "does/does not seem higher/lower".	Please note that the term "numerically" has been removed throughout as suggested: "Median time to response ~~was numerically~~ seemed longer for patients who had both liver and lung metastases (2·2 months [IQR 1·4–3·0) compared with those who had lymph node-only disease (1·4 months [IQR 1·4–1·4]), and those with liver (1·4 months [IQR 1·4–3·0]), lung (1·4 months [IQR 1·4–1·6]), bone (1·6 months [IQR 1·4–2·8]), and other metastases (1·4 months [IQR 1·3–1·4]). Similarly, median time to response ~~was~~	Page 15, paragraph 1

	~~numerically~~ appeared longer for patients with 2–3 sites of visceral disease compared with those who had 1 or no metastatic sites (2·0 [IQR 1·3–3·0] vs 1·4 [IQR 1·4–1·5] and 1·4 [IQR 1·3–1·4] months, respectively)." "Most patients had primary tumours in the lower tract (75% [76/101]) and 77% (78/101) had visceral metastases, but PFS and OS values ~~were numerically~~ seemed similar regardless of the primary tumour location, the presence/absence of visceral metastases, or the number of prior lines of therapy (figure 3 and appendix p 11)." "Additionally, while PFS and OS appeared ~~to be numerically~~ longer among chemotherapy-naïve patients compared with those who had received prior chemotherapy, multiple factors could have contributed to this finding, including potential differences in baseline disease characteristics in this small number of patients."	Page 16, paragraph 2 Page 19, paragraph 2
27. PFS, DOR, and OS seem to have been reported in the primary efficacy population – please clarify if this is correct, and explain why.	Please note that the manuscript reports data only on the 8-mg regimen, and as such all related analyses use the primary efficacy population (as defined in the SAP, p 15), ie, the treated population for the 8-mg regimen.	Page 12, paragraph 1
28. Please clarify why the timepoints of 12 and 24 months for OS have been reported – this does not seem to be prespecified in the protocol, please state if it is post-hoc if not in protocol.	Please note that the 12-month time point was prespecified since the final analysis was performed 12 months after the enrolment of	Page 15, paragraph 3

	the last patient. The 24-month analysis was carried out post hoc.	
29. DCR does not appear to be pre-specified in the protocol. Please specify as posthoc, and add to methods stats section as posthoc.	Please note that disease control rate has been calculated as a subset of objective response rates. This is now clarified within the Outcomes section: "The primary endpoint was confirmed objective response rate (ORR = % complete response [CR] + % partial response [PR]) among patients treated with the selected regimen; all CRs and PRs required confirmation within 4–6 weeks of first assessment of response and were assessed by the investigators per RECIST v1.1; disease control rate (DCR [CR + PR + stable disease (SD)]) was also calculated."	Page 11, paragraph 1
30. Results: Safety and tolerability data. Please ensure that the following items are included: a. Data regarding number of patients who required dose reductions. b. Data regarding number of patients who discontinued for drug-related toxicity and reasons. c. Data regarding drug-related serious adverse events and the most frequent in each treatment arm. d. Please state numbers and reasons for all deaths, irrespective of whether they were treatment-related.	Please see below detail of where this information can be found or has been added: a. "All patients experienced at least one treatment-emergent AE (TEAE; defined on appendix p 5) irrespective of dose uptitration, and 59·4% of patients (60/101) experienced TEAEs that led to dose reduction." b. "Of patients receiving 8 mg/day UpT, 15·8% (16/101) had AEs 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 (2·0%)	Page 17, paragraph 3 Page 18, paragraph 1

	reported the same TEAE leading to discontinuation (appendix p 16)." c. "Serious TEAEs occurred in 44·5% (45/101) of patients (see appendix p 14). The most common serious TEAEs were urinary tract infection and general physical health deterioration; 10·9% (11/101) were considered by the investigator to be related to erdafitinib, and no treatment-related deaths occurred." d. Grade 5 TEAEs are listed in Table 2. The following related footnote is also included: "*All TEAEs with the outcome of death (grade 5) were considered by the investigator to not be related to erdafitinib, and most events (7/8), including the two grade 5 events of asthaenia, occurred in the context of progressive disease."	Page 17, paragraph 1 Pages 35 to 37
31. Results: The adverse events table should be stratified by grades 1-2, 3, 4 and 5. For adverse events of grade 1 or 2, any occurring in ≥10% of patients should be reported. All grade 3, 4, and 5 events should be reported.	We have combined the data for grades 1 and 2 in Table 2 so adverse events are now stratified by grades 1–2, 3, 4, and 5, as suggested.	Pages 35 to 37
32. Forest plots – the x-axis should be on a log scale; please revise. Please ensure there is a row for the overall population.	Please note that forest plots (Figure 3 and Figure S4) have been modified as suggested.	Page 42 and appendix, page 9
33. If appropriate, please use SI units throughout the paper.	No changes are required.	NA

34. Please use rINNs for drug names.	Please note that rINNs are used throughout the manuscript. No changes are required.	NA
35. For genes and proteins, authors can use their preferred terminology so long as it is in current use by the community, but should provide the preferred human name from Uniprot (http://www.uniprot.org/uniprot/) for proteins and HUGO (http://www.genenames.org) for genes at first use to assist non-specialists.	No changes are required.	NA
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placed in the appendix rather than the main text, if possible and appropriate.	Figure 3 reporting on post hoc analyses of PFS and OS by response status to the appendix.	and page 8 of the appendix
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40. Please can you clarify whether figure 5 is a post-hoc analysis?	For clarity, the title of figure 5 has been amended as follows: "Figure 5: Post-hoc analysis of ~~C~~cumulative incidence of first-onset central serous retinopathy events by grade using the Kaplan–Meier method."	Page 32, paragraph 1
41. If you have claimed a first, please reword to: "To our knowledge… this is the first time...", since you can never be 100% sure.	No changes required.	
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	Employees of the sponsor, Janssen Research & Development, were involved in the study's design and the collection, analysis, and interpretation of data, in collaboration with the authors. Writing assistance was provided by Sally Hassan, PhD, Susan Neville, MSc, and Khalida Rizi, PhD, of Parexel, and was funded by Janssen Global Services, LLC. All investigators had access to the raw data at their individual sites. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.	
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author> et al to list my name in the acknowledgments section of their manuscript and I have seen a copy of the paper <full article title>"	~~Development.~~ The authors thank Dr Manu Sondhi MD, MPH, formerly of Janssen, for critical review of the manuscript draft. Writing assistance was provided by Sally Hassan, PhD, Susan Neville, MSc, and Khalida Rizi, PhD, of Parexel, and was funded by Janssen Global Services, LLC. The authors would like to thank patients who participated in this trial, their families, investigators, study coordinators, study teams, and nurses."	
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Efficacy and safety of erdafitinib in patients with locally advanced or metastatic urothelial carcinoma: long-term follow-up of the pivotal phase 2 study

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

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***Dr Monga worked at Janssen R&D when the study was conducted and analysed and has since left the company.**

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Abstract

Background Erdafitinib, a pan-fibroblast growth factor receptor (FGFR) kinase inhibitor, was effective and tolerable in patients with advanced urothelial carcinoma and prespecified *FGFR* alterations in the primary analysis from the open-label, phase 2, non-comparator, BLC2001 study at median 11 months' follow-up. The aim of the current analysis was to assess long-term efficacy and safety for the selected regimen.

Methods Eligible patients were ≥18 years with locally advanced and unresectable/metastatic urothelial carcinoma, had at least one prespecified *FGFR* alteration and an Eastern Cooperative Oncology Group performance status of 0–2. The selected regimen determined in the initial part of the study was 8 mg/day continuous 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 (ORR) according to Response Evaluation Criteria In Solid Tumors (RECIST) 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 the study (ClinicalTrials.gov number NCT02365597).

Findings Between May 25, 2015, and August 9, 2018, 212 patients were enrolled and 101 patients were treated with erdafitinib 8 mg/day UpT . Data cutoff for this analysis was August 9, 2019. Median efficacy follow-up was 24·0 (interquartile range 22·7–26·6) months. Investigator-assessed ORR for patients treated with the selected erdafitinib regimen was 40% (95% CI 30%–49%).

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

Funding Janssen Research & Development.

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 from Jan 1, 2010, to Jan 1, 2021. We used search terms “bladder cancer” OR “urothelial cancer” AND “fibroblast growth factor receptor,” with limits for clinical trials and no language preferences specified. At the time of the initial protocol approval for study BLC2001 (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 provide clinical benefit that is a small improvement in response rates over traditional chemotherapy and is accompanied by unique immune-related adverse events that are potentially serious and sometimes fatal. Differential response 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 the phase 2 study of erdafitinib (BLC2001) was published in 2019 and, based on 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 genetic 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

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

Implications of all the available evidence

Our research from longer 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 whose tumours harbour specific FGFR alteration(s). Further research, in a phase 3 randomised controlled 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 cisplatin-ineligible patients with metastatic urothelial carcinoma.

Introduction

Until recently, after failure of platinum-based chemotherapy, second-line treatment options for patients with advanced urothelial carcinoma have been limited, 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] approved in the United States,[4] Brazil, Canada, Thailand, Singapore, Peru, Israel, Taiwan, Hong Kong, and Saudi Arabia to treat adults with locally advanced or metastatic urothelial carcinoma with *FGFR3/2* alterations who progressed during or after one or more lines of prior platinum-containing chemotherapy, including within 12 months of (neo)adjuvant platinum-containing chemotherapy. The National Comprehensive Cancer Network guidelines for bladder cancer

recommend erdafitinib as a second-line treatment option for patients with locally advanced or metastatic urothelial carcinoma following platinum-based therapy.[5] The European Association of Urology guidelines include FGFR inhibitors such as erdafitinib as promising therapies for second-line or later treatment of metastatic urothelial carcinoma,[6] and, although erdafitinib is not approved by the European Medicines Agency, it is included in European Society for Medical Oncology guidelines.[7]

Erdafitinib was approved based on 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 chemotherapy or within 12 months after neoadjuvant/adjuvant chemotherapy.[8] Based on results from a planned interim analysis, the selected schedule of erdafitinib was set at 8 mg/day continuously, with the possibility of pharmacodynamically guided uptitration to 9 mg (henceforth 8 mg/day UpT [the selected-regimen group]).[8] In the primary analysis, erdafitinib was associated with an investigator-assessed objective tumour response in 40% (95% confidence interval [CI] 31%–50%) of patients in the selected-regimen group[8]; the confirmed response rate was also 40% among patients who progressed/relapsed after prior chemotherapy. Additionally, at a median follow-up of 11·2 months, median progression-free survival (PFS) was 5·5 months (95% CI 4·2–6·0) and, at a median follow-up of 11·0 months, median overall survival (OS) was 13·8 months (95% CI 9·8–not reached [NR]).[8] Treatment-related adverse events (AEs) of grade 3 or higher were reported in 46% of patients at the time of the primary analysis.[8]

We report longer-term efficacy, with 24·0 months' median follow-up, and safety outcomes from 5.4 months' median exposure (range: 0–31 months) among patients treated with the selected regimen of erdafitinib in BLC2001.

Methods

Study design and participants

The open-label, phase 2, non-comparator BLC2001 study (NCT02365597) in patients with locally advanced or metastatic urothelial carcinoma was conducted at 126 sites in 14 countries across Asia, Europe, and North America (see appendix p 2). As described,[8] eligible patients were ≥18 years, with locally advanced and unresectable or metastatic urothelial carcinoma; had 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, by central laboratory testing; a history of disease progression during or after one or more lines of previous systemic chemotherapy or within 12 months after neoadjuvant/adjuvant chemotherapy (chemotherapy-refractory patients) or were cisplatin ineligible (for impaired renal function/peripheral neuropathy) and chemotherapy naïve; an Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2; and adequate bone marrow, liver, and kidney function (creatinine clearance, ≥40 mL/min/1·73 m^2). Patients who had any number of prior lines of therapy or who previously received immunotherapy (eg, immune checkpoint inhibitors) were eligible for enrolment. Patient exclusion criteria are on appendix p 4.

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

Procedures

In the initial part of the study, patients were randomly assigned (1:1, with stratification performed as previously described[8]) to oral erdafitinib (Janssen-Cilag SpA, Latina, Italy) at 10 mg/day intermittently (7 days on, 7 days off) or 6 mg/day continuously in 28-day cycles (appendix p 6). Based on findings from an interim analysis and

pharmacokinetic/pharmacodynamic modelling based on clinical data, the protocol was amended to continue enrolment into the 8 mg/day UpT dose schedule, thereby converting the study to a single-group analysis.

In the selected 8 mg/day regimen, uptitration to 9 mg/day continuous treatment was permitted on day 14 in patients without AEs 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–<7·0 mg/dL (2·3 mmol/L; target range).

Patients continued to receive erdafitinib until disease progression or unacceptable AEs, as determined by the investigator. At discretion of the investigator and the sponsor, patients with investigator-assessed disease progression could continue erdafitinib treatment. Patients who interrupted treatment because of grade 1 events reinitiated treatment at the same or 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). Patients who interrupted treatment because of lower grade events reinitiated treatment at the same or a lower dose.

Efficacy was assessed using RECIST by computed tomography or magnetic resonance imaging 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 additional scan within 4–6 weeks after first assessment. After treatment discontinuation, patients were contacted every 12 weeks to assess survival.

Safety was assessed by clinical laboratory testing, physical examination, electrocardiography, and ophthalmologic examination (frequency of these assessments is described on appendix p 15). Investigators assessed and graded AEs and abnormalities according to National Cancer Institute CTCAE criteria (version 4.0) for the duration of the study.

Outcomes

The primary endpoint was confirmed objective response rate (ORR = % complete response [CR] + % partial response [PR]) among patients treated with the selected regimen; all CRs and PRs required confirmation within 4–6 weeks of first assessment of response and were assessed by the investigators per RECIST v1.1; disease control rate (DCR [CR + PR + stable disease (SD)]) was also calculated. Secondary endpoints were PFS (defined as time from the first dose of study drug until the first documented evidence of progressive disease [or relapse for patients who experienced CR during the study] or death, whichever occurred first), duration of response (DoR, defined as time from the initial documentation of a response to the first documented evidence of progressive disease [or relapse for patients who experienced CR during the study] or death), OS (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 (considered for publication by another journal).

Statistical analysis

The study had a power of 85% to reject the null hypothesis that the response rate was 25% or less, at a one-sided alpha level of 0·025, if the true response rate was 42% for the primary analysis.[8] All enrolled and treated patients in the selected-regimen group were included in the efficacy analysis (primary efficacy population). The response-evaluable population is defined as all patients who met all eligibility criteria, received at least one dose of study drug, had a baseline and at least one adequate post-treatment disease evaluation, have had clinical signs and/or symptoms of disease progression, or died prior to the first post-treatment disease evaluation. Adequate disease assessment is defined as having sufficient evidence to correctly indicate that progression has or has not occurred.

Prespecified subgroup analysis included secondary efficacy endpoints of best objective response, DoR (among patients with a confirmed objective response by investigator assessment), PFS, and OS within the primary efficacy and chemorefractory population, and was assessed by *FGFR* alterations (mutations and/or fusions), presence of visceral metastases (lung, liver or bone), prior chemotherapy, and prior immunotherapy; subgroup best objective response data have been published.[8] Post hoc subgroup analysis included DoR, PFS, and OS within the primary efficacy and chemorefractory population assessed by preplanned subgroups based on primary tumour location (upper *vs* lower tract), and other patient demographic baseline characteristics. The chemotherapy relapsed/refractory (R/R) subgroup within the efficacy population included patients treated with one or more doses of erdafitinib who had progressive disease on or after one or more lines of prior chemotherapy or who had progressed/relapsed within 12 months of their last dose of neoadjuvant/adjuvant chemotherapy. Patients who received at least one dose of the study drug were included in the safety analysis (safety population).

Data for patients who were progression-free and alive or with unknown status were censored at time of the last tumour assessment. The confidence intervals for median PFS, OS, and DoR were determined using complementary log-log transformation. For PFS and DOR, data from patients who were progression-free and alive or who had unknown status were censored at the last tumour assessment. For OS, 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. A post hoc landmark analysis was performed to compare PFS and OS by responder status (patients with a confirmed best objective response of CR or PR) and non-responders (patients with a confirmed best objective response of SD 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 as it allowed sufficient time for responses to be confirmed.

The BLC2001 study protocol (p 18) and statistical analysis plan (p 145) are in the appendix. 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, Janssen Research & Development, was involved in study design, data collection, data analysis, and data interpretation. Writing assistance was provided by Sally Hassan, PhD, Susan Neville, MSc, and Khalida Rizi, PhD, of Parexel, and was funded by Janssen Global Services, LLC. All investigators had access to the raw data at their individual sites. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

Between May 25, 2015, and August 9, 2018, 212 eligible patients were enrolled and treated with erdafitinib, and 101 patients were treated with the 8 mg/day UpT regimen (60 patients received 8 mg/day and 41 patients were uptitrated to 9 mg/day). Efficacy results are reported for the 8 mg/day UpT regimen group only. Of the 101 patients who were treated with the 8 mg/day UpT regimen, two died due to progressive disease before the first postbaseline disease evaluation.

At the clinical cutoff date (August 9, 2019), median follow-up for efficacy (estimated based on the time from first dose of study treatment to date of censoring for PFS using the reverse Kaplan–Meier method[9]) was 24·0 months (interquartile range [IQR] 22·7–26·6). Median treatment duration was 5·4 months (range: 0–31).

Two patients were enrolled into the 8 mg/day UpT regimen group after the clinical cutoff date for the primary analysis (March 15, 2018). Patient demographics and baseline characteristics are presented in table 1. Consistent with the primary analysis, progressive disease was the

most common reason for treatment discontinuation. At the analysis cutoff date, 24 patients (24%) in the 8 mg/day UpT group remained in the study.

The confirmed investigator-assessed ORR was 40% (40/101; 95% CI 30%–49%) among all patients receiving the 8 mg/day UpT regimen, consistent with the 40% ORR (40/99; 95% CI 31%–50%) at the time of primary analysis.[8] Of the 99 patients treated with 8 mg/day UpT who underwent at least one disease evaluation after baseline, 76 (77%) had a reduction in the sum of target-lesion diameters, and 48 (48%) had a maximum tumour reduction of 30–100% (appendix p 7). Further analyses of response revealed similar ORRs irrespective of the presence or absence of visceral metastases (33·3% [3/9], 35·0% [7/20], 40·4% [23/57], 34·8% [8/23], 40·0% [4/10], and 50·0% [7/14] for patients with lymph node-only disease, and those with liver, lung, bone, both liver and lung, and other metastatic disease, respectively). Median time to response seemed longer for patients who had both liver and lung metastases (2·2 months [IQR 1·4–3·0) compared with those who had lymph node-only disease (1·4 months [IQR 1·4–1·4]), and those with liver (1·4 months [IQR 1·4–3·0]), lung (1·4 months [IQR 1·4–1·6]), bone (1·6 months [IQR 1·4–2·8]), and other metastases (1·4 months [IQR 1·3–1·4]). Similarly, median time to response appeared longer for patients with 2–3 sites of visceral disease compared with those who had 1 or no metastatic sites (2·0 [IQR 1·3–3·0] *vs* 1·4 [IQR 1·4–1·5] and 1·4 [IQR 1·3–1·4] months, respectively). We note that these results are based on a limited number of responders per disease site.

Median DoR was 6·0 months (95% CI 4·2–7·5); 31% (31/101) of responders had a DoR that was maintained for ≥12 months (figure 1; of 101 patients, 40 had a confirmed response: PR in 36 [35·6%] and CR in 4 [4·0%]). Additionally, 41% of patients achieved a best response of SD for at least one disease evaluation period (>36 days), leading to an overall DCR of 80·2% (95% CI 72·4%–88·0%) for the primary efficacy population.

Median PFS was 5·5 months (95% CI 4·3–6·0) for all patients treated with the selected regimen (figure 2A). There had been 72 events in the 8 mg/day erdafitinib UpT group, and

median OS was 11·3 months (95% CI 9·7–15·2) (figure 2B). The 12-month survival rate was 49% and the 24-month survival rate 31%.

Based on a landmark analysis, at 3 months after treatment initiation, PFS was similar between responders and non-responders while OS improved for responders (appendix p 8). It is noted that any differences in PFS and OS observed between responders and non-responders are numerical and limited by small numbers.

PFS, OS, and DoR were not impacted by factors such as age, sex, and most baseline disease characteristics, including haemoglobin level and renal function (figure 3 and appendix p 9). Patients with an ECOG PS of 0–1 versus 2 had a longer median PFS (5·6 [95% CI 5·0–6·8] *vs* 3·2 [95% CI 1·0–4·9]) and a longer median OS (13·8 [95% CI 10·3–15·8] *vs* 5·1 [95% CI 3·0–8·0]).

Most patients (69% [70/101]) had mutations, 25% (25/101) had fusions, and 6% (6/101) had both mutation and fusion. The most common mutations were FGFR3-S249C (46% [45/99]), FGFR3-R248C (13% [13/99]) and FGFR3-Y373C (12% [12/99]), and the most common fusion was FGFR3-TACC3_V1 (11% [11/99]). PFS, DoR, and OS values seemed similar between patients with *FGFR* mutations and those with *FGFR* fusions (figure 3 and appendix p 9).

Most patients had primary tumours in the lower tract (75% [76/101]) and 77% (78/101) had visceral metastases, but PFS and OS values seemed similar regardless of the primary tumour location, the presence/absence of visceral metastases, or the number of prior lines of therapy (figure 3 and appendix p 11).

Most patients (88% [89/101]) had received prior chemotherapy (table 1). Similar to the ORR for all treated patients, confirmed ORR for the chemotherapy R/R population was 39·3% (95% CI 29·2%–49·5%). Additionally, overall DCR in the chemotherapy R/R population (79·8% [95% CI 71·4%–88·1%]) was similar to that in the all-treated population. Median

PFS among treated chemotherapy R/R patients (figure 3A; appendix p 10 and 11) was also similar to that among all treated patients. Median OS was 10·6 months (95% CI 9·0–14·7) for treated chemotherapy R/R patients (among whom 65 events occurred [figure 3B and appendix p 10 and 11]). For patients who had prior chemotherapy (appendix p 10 and 11) versus all treated patients (figure 2), median PFS and median OS were similar. For chemotherapy-naïve patients (n=12), median PFS was 14·9 months (95% CI 2·8, 26·7) and median OS was 20·8 months (8·9–NE).

Almost a quarter of patients who received the 8 mg UpT regimen had received prior immunotherapy (table 1), but PFS and OS were similar regardless of the number of lines of prior immunotherapy (figure 3). Median PFS for those who had received prior immunotherapy (5·7 months [95% CI 4·9–8·3]; figure 3A) was also similar to that for all treated patients. Median OS was 10·9 months (95% CI 8·0–21·1) for patients with prior immunotherapy (amongst whom 19 events were recorded [figure 3B]).

The safety profile of erdafitinib at a median treatment exposure of 5·4 months remained consistent with that in the primary analysis.[8] All patients experienced at least one treatment-emergent AE (TEAE; defined on appendix p 5) irrespective of dose uptitration, and 59·4% of patients (60/101) experienced TEAEs that led to dose reduction. Grade 3–4 TEAEs of any causality occurred in 71·3% (72/101) of patients, the most common (occurring in ≥10% of patients) being stomatitis and hyponatraemia (table 2 and appendix p 12); 52·4% (53/101) had grade 3 TEAEs that were considered related to erdafitinib 8 mg UpT. No grade 4 TEAEs were considered related to erdafitinib. No new treatment-related AEs were observed with longer follow-up (see appendix p 13). The most common TEAEs were hyperphosphataemia, stomatitis, diarrhoea, and dry mouth (table 2). Serious TEAEs occurred in 44·5% (45/101) of patients (see appendix p 14). The most common serious TEAEs were urinary tract infection and general physical health deterioration; 10·9% (11/101) were considered by the investigator to be related to erdafitinib, and no treatment-related deaths occurred. Of patients receiving 8

mg/day UpT, 15·8% (16/101) had AEs 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 (2·0%) reported the same TEAE leading to discontinuation (appendix p 16).

The proportion of patients with central serous retinopathy (CSR; a known class effect of FGFR inhibitors and a TEAE of special interest) was 26·7% in all treated patients (27/101; appendix p 14), 25·0% (15/60) in patients who received 8 mg/day and 29·3% (12/41) in those whose dose was uptitrated to 9 mg/day. Most of these events (85·2% [23/27]) were grade 1 or 2 (figure 4 and appendix p 14). At data cutoff, 63·0% (17/27) of CSR events had resolved (median [range] time to resolution 27 days [9–299]); all 10 unresolved events were grade 1 or 2 (appendix page 14). The median time to first onset of CSR was 53 days for any-grade AE and 94 days for grade 3 events (figure 4); 7.4% (2/27) occurred after 6 months. Among treated patients, dose reduction, dose interruption, and treatment discontinuation for CSR occurred in 12·8% (13/101), 7·9% (8/101), and 3·0% (3/101), respectively (see appendix p 5 for dose modification for most common TEAEs). Other select TEAEs are reported on appendix p 17, including among those who received 8 mg/day and those whose dose was uptitrated to 9 mg/day; rates of hyperphosphataemia were higher in the non-uptitrated group than in the uptitrated group (86·7% [52/60] *vs* 65·9% [27/41]); the incidences of stomatitis, nail events, non-CSR events, skin events, and diarrhoea were comparable between patients who received 8 mg/day and those who received 9 mg/day.

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 compared with the primary analysis

(median follow-up ~11 months).[8] There were no new safety signals with a median treatment exposure of 5·4 months. The confirmed investigator-assessed ORR was 40%; median PFS and OS were 5·5 and 11·3 months, respectively. Clinically meaningful treatment benefit with erdafitinib was observed in patients regardless of prior chemotherapy or immunotherapy and most baseline disease characteristics. Responses lasted a median of 6·0 months, and 31% lasted for 1 year or more. Patients with ECOG PS 0–1 versus 2 had a longer median PFS and OS, but there was no numerical difference in PFS and OS by presence/absence of visceral metastases, *FGFR* alteration type, or kidney function (baseline creatinine clearance < or ≥60 mL/min). Additionally, while PFS and OS appeared longer among chemotherapy-naïve patients compared with those who had received prior chemotherapy, multiple 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 nonrandomised study, and some subgroups contained small numbers of patients. This should be considered when interpreting the results.

The primary results from 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 may harbour *FGFR* alterations[11]; *FGFR3* alterations have been reported in ~22% of patients with urothelial bladder carcinoma at all stages in one study,[12] suggesting a role for wider implementation of *FGFR* testing, as patients with certain *FGFR* alterations may benefit from FGFR inhibition. Other FGFR inhibitors are also being investigated in metastatic urothelial carcinoma, including infigratinib and rogaratinib. In one study, the ORR for infigratinib (an FGFR1–3 inhibitor) was 24% in the second- and later-line setting for advanced/unresectable or metastatic urothelial carcinoma.[13] In an expansion cohort of a phase 1 study 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 prior lines of therapy, ORR was 24%.[14]

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 ORRs of 14% and 32%, respectively.[15] As second-line therapy, checkpoint blockade immunotherapies have demonstrated an ORR of ~20%.[16-21] The ORR reported for studies of antibody–drug conjugates as second-line treatment, were 40·6% for enfortumab vedotin (phase 3 study; median follow-up, 11·1 months)[22] and 31% for sacituzumab govitecan (phase 1/2 study).[23]

The PFS and OS seen in the current analysis of the BLC2001 study confirm the persistent benefit of erdafitinib 8 mg UpT. These median PFS and OS data are also, generally, comparable with 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 UpT in our study, 31% had responses lasting 12 months or more, and 12- and 24-month survival rates were 49% and 31%, respectively. Patients with objective responses to erdafitinib also had increased PFS and OS; PFS and OS were independent of most baseline disease characteristics. The durability of ORR, PFS, and OS noted in our study demonstrated 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 ctDNA, and the presence of *EGFR*, *CCND1*, and *BRAF* alterations at baseline correlated with shorter PFS, and *EGFR* with shorter OS.[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. CSR events, a known class effect of mitogen-activated protein kinase pathway inhibitors, including for FGFR,[28-30] occurred in approximately one quarter of patients, but were mostly grade 1 or 2 and the majority resolved at data cutoff.

The open-label, single-arm study design of BLC2001 is a limitation. Patients were selected based on the presence of nine prespecified *FGFR* alterations; because gene amplifications were not included among these alterations and whole genome sequencing was not performed, other mechanisms for constitutive activation or resistance were not assessed. The Kaplan–Meier curves for PFS and OS by responder status at the 3-month landmark (appendix p 8) and some of the subgroup analyses (figure 3) 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 recurring after treatment with bacillus Calmette-Guérin. Frequency of *FGFR* alterations is higher in early-stage urothelial carcinoma.[11]

In conclusion, in the BLC2001 study, at a median 24·0 months of follow-up, second-line erdafitinib treatment of patients with locally advanced or metastatic urothelial carcinoma and prespecified *FGFR* alterations demonstrated consistent, durable efficacy with a median OS of 11·3 months and almost one third of patients having responses lasting 12 months or longer; tolerability was comparable to that in the primary analysis. 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 prior platinum-containing chemotherapy, including within 12 months of (neo)adjuvant platinum-containing chemotherapy, and who have specific *FGFR* alterations. Erdafitinib is therefore being investigated in other treatment settings.

Author contributions

ASR, ASW, YL, AO, MJ, and AR were involved in the conceptualization and design of the study. SA, ID, JGD, RAH, MJ, STT, YZ, AN, BM, SHP, AO, AR, ASW, and ASR were involved in the investigation, data collection, data analysis, or interpretation of the study. All authors reviewed the data analyses, data interpretation, and writing the report, and approved the final version of the submitted manuscript.

Declaration of interest

EFB has received grants or contracts from Pfizer and Astellas Pharma; honoraria from Exelixis and Bayer; stock or stock options from Exelixis, Becton Dickinson, Calithera Biosciences, Gilead Sciences, Medtronic, Clovis Oncology, and Macrogenics, all outside 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, Pharamcyclics Janssen Oncology, and Novartis; honoraria from Bristol Myers Squibb, Ipsen, Roche/Genentech, Janssen Oncology, MSD Oncology,

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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 site, requests for study data access can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

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Figure Legends

Figure 1: **Swimmer's plot of duration and type of response for 101 patients treated with 8 mg/day erdafitinib with potential for uptitration to 9 mg/day**

Bars are coloured to show best response.

Responses that occurred or were maintained after treatment discontinuation due to adverse events but prior to the start of subsequent therapy are included in the display. One patient, shown as treatment ongoing, had a drug interruption at the data cut but had not discontinued erdafitinib.

Figure 2: **Investigator-assessed progression-free survival (A) and overall survival (B) for 8 mg/day erdafitinib with potential for uptitration to 9 mg/day**

Figure 3: **Estimated median (and associated 95% confidence interval) for progression-free survival (A) and overall survival (B) by subgroup**

*Upper tract includes renal pelvis and ureter. †Lower tract includes bladder, urethra and prostatic urethra. ‡Visceral metastases includes metastases into lung, liver, and bone. †Prior immunotherapy includes atezolizumab, pembrolizumab, nivolumab, durvalumab, avelumab, anti-csf1r antibody, tremelimumab. BL, baseline; CrCl, creatinine clearance; Hb, haemoglobin; IO, immunotherapy; NE, not evaluable; R/R, relapsed refractory. The bars represent the associated 95% confidence interval by selected subgroup. *FGFRm+f-= FGFR* mutation present and fusion absent. *FGFRm-F+=FGFR* mutation absent and fusion present. *FGFRm+f+=FGFR* mutation and fusion present. IO=immunotherapy. OS=overall survival. PFS=progression-free survival.

Figure 4: **Post hoc analysis of 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 no dose modification in another patient, and one patient had grade 3 detachment of retinal pigment

671 epithelium, which initially resolved but then recurred as a grade 2 event following dose
672 reduction (ultimately leading to discontinuation of erdafitinib in this patient).
673

Table 1: **Baseline characteristics**

Patients	**Erdafitinib 8 mg/day UpT n=101***
Age, median (range), years	67 (36–87)
ECOG PS	
0	51 (50%)
1	43 (43%)
2	7 (7%)
Pretreatment†	
Progressed or relapsed after chemotherapy	89 (88%)
Chemotherapy naive	12 (12%)
Prior immunotherapy	24 (24%)
Number of lines of prior treatment‡	
0	10 (10%)
1	48 (48%)
2	28 (28%)
≥3	15 (15%)
Visceral metastases§	
Present	78 (77%)
Liver	20 (20%)
Lung	57 (56%)
Bone	23 (23%)
Absent	23 (23%)
Lymph node only	9 (9%)
Other¶	14 (14%)
Haemoglobin level, g/dL	86 (85%)

Patients	Erdafitinib 8 mg/day UpT n=101*
≥10	15 (15%)
<10	
Tumour location	25 (25%)
Upper tract	76 (75%)
Lower tract	
Creatinine clearance rate	53 (52%)
<60 mL/min	48 (48%)
≥60 mL/min	
FGFR alteration#	
FGFRm+f-	70 (69%)
FGFRm-f+	25 (25%)
FGFRm+f+	6 (6%)

Data are n (%). *Two patients were added to the 8 mg/d UpT regimen after the cutoff date for the primary analysis (March 15, 2018). †The pretreatment groups are not mutually exclusive. ‡The chemo relapsed/refractory efficacy population (n=89) consists of all patients in the 8 mg daily regimen who were treated with ≥1 dose of erdafitinib and had progressed on or after ≥1 prior chemotherapy or progressed/relapsed within 12 months of 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, as 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 and/or other visceral metastases (not lung, liver or bone). #*FGFR* alteration (mutations [m] and/or fusions [f], analysed as present [+] or absent [-]).
ECOG PS=Eastern Cooperative Oncology Group. UpT=possibility of uptitration to 9 mg/day.

Table 2: **Most common treatment-emergent adverse events and worst toxicity grade**

	Erdafitinib 8 mg/d UpT (n=101)	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 5***
Patients with any TEAE (worst toxicity grade)	101 (100·0%)	29 (28·7%)	58 (57·4%)	6 (5·9%)	8 (7·9%)
Hyperphosphataemia†	79 (78·2%)	77 (76·2%)	2 (2·0%)	0	0
Stomatitis	60 (59·4%)	46 (21·3%)	14 (13·9%)	0	0
Diarrhoea	55 (54·5%)	51 (50·4%)	4 (4·0%)	0	0
Dry mouth	46 (45·5%)	45 (44·5%)	1 (1·0%)	0	0
Decreased appetite	41 (40·6%)	40 (39·6%)	1 (1·0%)	0	0
Dysgeusia	41 (40·6%)	39 (38·6%)	2 (2·0%)	0	0
Alopecia	34 (33·7%)	34 (33·7%)	0	0	0
Dry skin	34 (33·7%)	34 (33·7%)	0	0	0
Fatigue	33 (32·7%)	31 (30·6%)	2 (2·0%)	0	0
Constipation	29 (28·7%)	28 (27·7%)	1 (1·0%)	0	0
Dry eye	28 (27·7%)	27 (26·7%)	1 (1·0%)	0	0

	Erdafitinib 8 mg/d UpT (n=101)	Grade 1–2	Grade 3	Grade 4	Grade 5*
Palmar-plantar erythrodysaesthesia syndrome	25 (24·8%)	20 (19·8%)	5 (5·0%)	0	0
Asthaenia	23 (22·8%)	15 (14·9%)	6 (5·9%)	0	2 (2·0%)
Anaemia	22 (21·8%)	17 (16·8%)	5 (5·0%)	0	0
Nausea	22 (21·8%)	21 (20·8%)	1 (1.0%)	0	0
Alanine aminotransferase increased	19 (18·8%)	17 (16·8%)	2 (2·0%)	0	0
Onycholysis	19 (18·8%)	17 (16·8%)	2 (2·0%)	0	0
Paronychia	19 (18·8%)	16 (15·8%)	3 (3·0%)	0	0
Urinary tract infection	18 (17·8%)	13 (12·9%)	5 (5·0%)	0	0
Vision blurred	18 (17·8%)	18 (17·8%)	0	0	0
Weight decreased	18 (17·8%)	17 (16·8%)	1 (1.0%)0	0	0
Nail dystrophy	17 (16·8%)	11 (10·9%)	6 (5·9%)	0	0

Data are n (%). Patients with one or more TEAE were counted only once for each AE and worst AE grade reported. TEAEs occurring in 15% or more patients are shown. No grade 4 AEs were considered to be related to erdafitinib. *All TEAEs with the outcome of death (grade 5) were considered by the investigator to not be related to erdafitinib, and most events (7/8), including the two grade 5 events of asthaenia, occurred in the context of progressive disease.

†Hyperphosphatemia was graded based on 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.
TEAE=treatment-emergent adverse event. TRAE=treatment-related adverse event. UpT=potential for uptitration to 9 mg/day.

Figure 1.

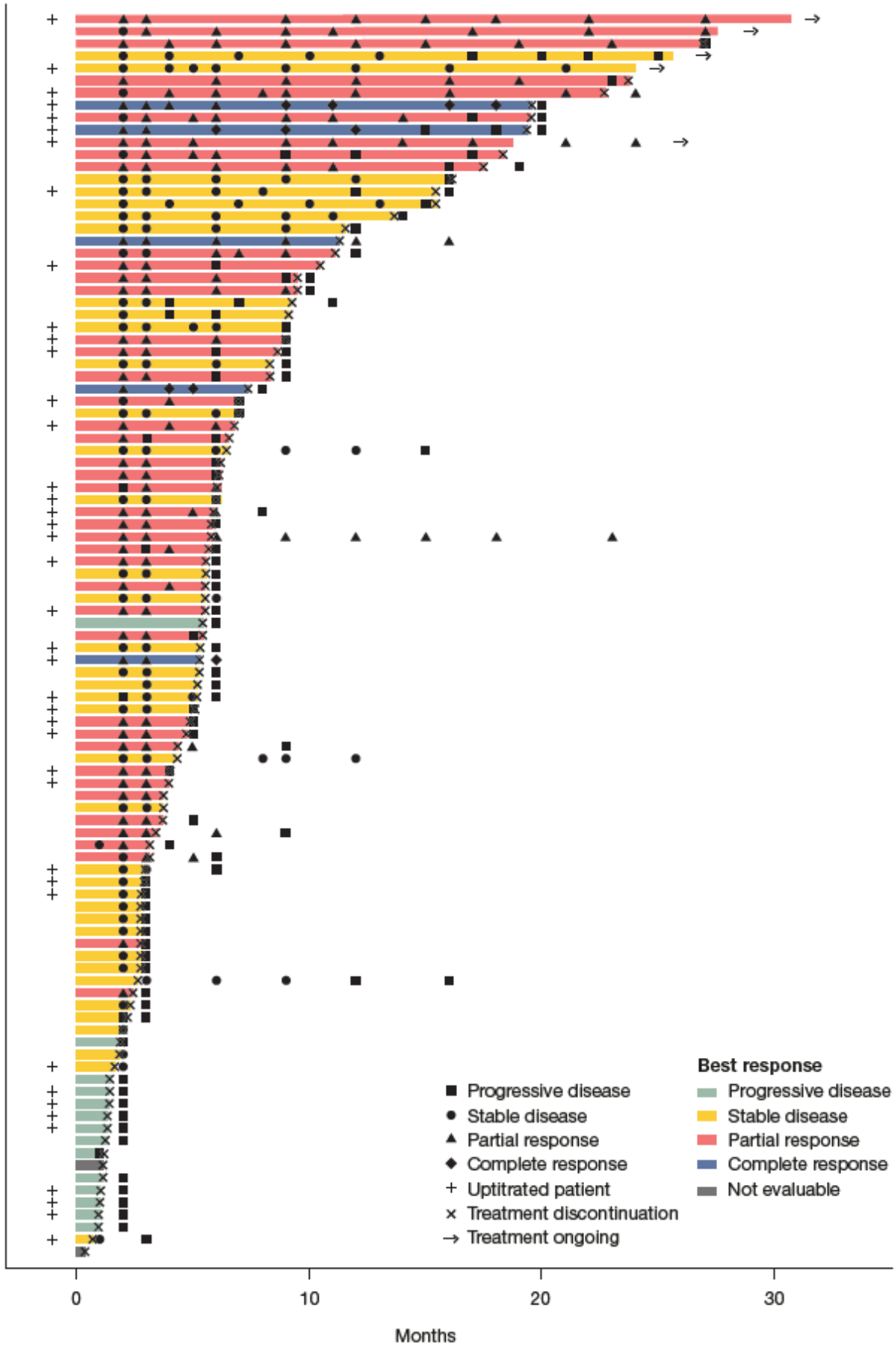

Progressive disease
Stable disease
Partial response
Complete response
Uptitrated patient
Treatment discontinuation
Treatment ongoing
Best response
Progressive disease
Stable disease
Partial response
Complete response
Not evaluable
0
10
20
30
Months

Figure 2.

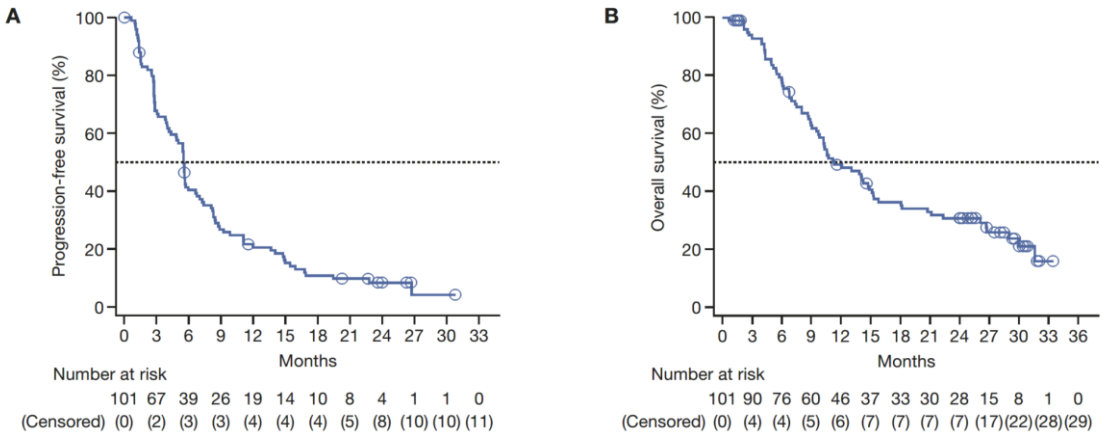


Figure 3.

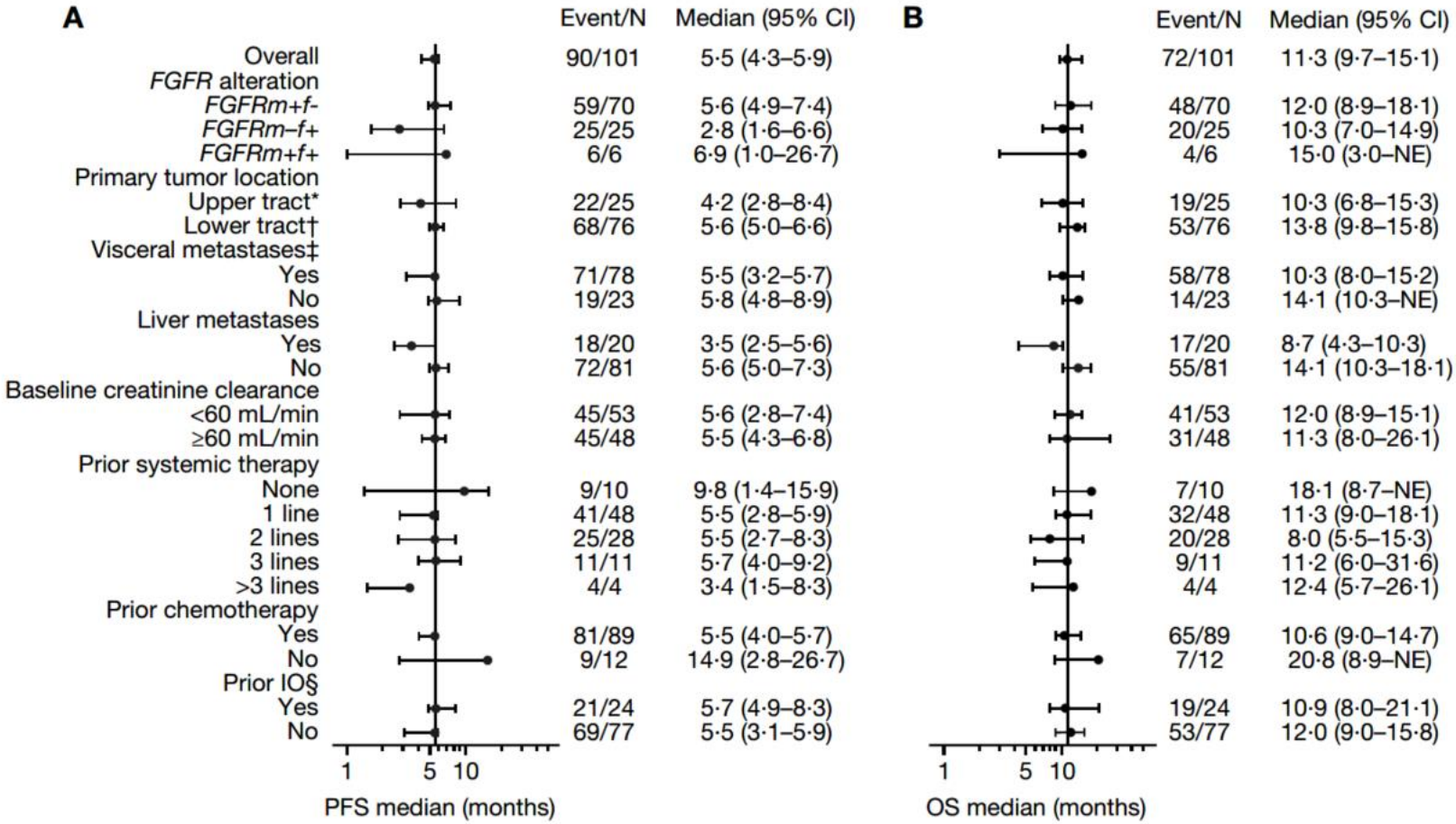
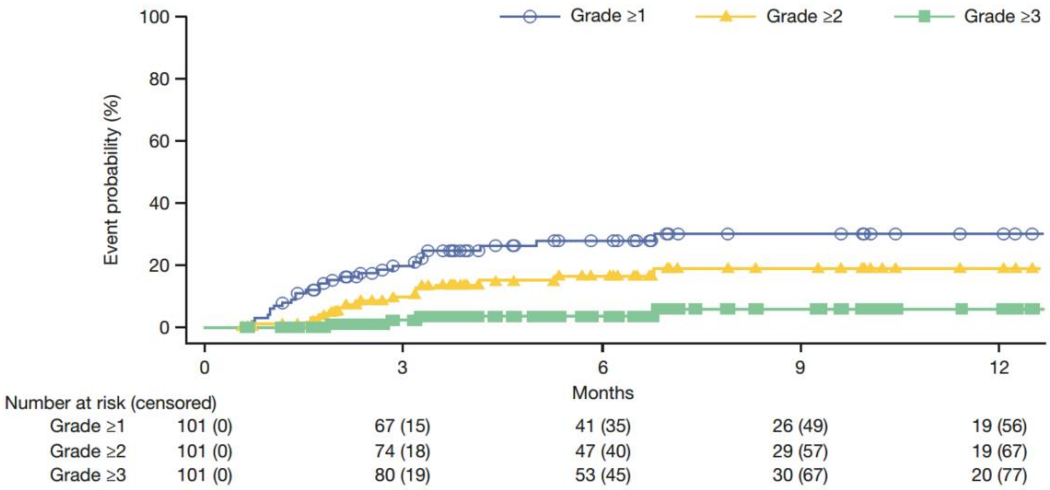

A
Event/N
Median (95% CI)
Overall 90/101 5·5 (4·3–5·9)
FGFR alteration
FGFRm+f- 59/70 5·6 (4·9–7·4)
FGFRm–f+ 25/25 2·8 (1·6–6·6)
FGFRm+f+ 6/6 6·9 (1·0–26·7)
Primary tumor location
Upper tract* 22/25 4·2 (2·8–8·4)
Lower tract† 68/76 5·6 (5·0–6·6)
Visceral metastases‡
Yes 71/78 5·5 (3·2–5·7)
No 19/23 5·8 (4·8–8·9)
Liver metastases
Yes 18/20 3·5 (2·5–5·6)
No 72/81 5·6 (5·0–7·3)
Baseline creatinine clearance
<60 mL/min 45/53 5·6 (2·8–7·4)
≥60 mL/min 45/48 5·5 (4·3–6·8)
Prior systemic therapy
None 9/10 9·8 (1·4–15·9)
1 line 41/48 5·5 (2·8–5·9)
2 lines 25/28 5·5 (2·7–8·3)
3 lines 11/11 5·7 (4·0–9·2)
>3 lines 4/4 3·4 (1·5–8·3)
Prior chemotherapy
Yes 81/89 5·5 (4·0–5·7)
No 9/12 14·9 (2·8–26·7)
Prior IO§
Yes 21/24 5·7 (4·9–8·3)
No 69/77 5·5 (3·1–5·9)
1 5 10
PFS median (months)
B
Event/N
Median (95% CI)
72/101 11·3 (9·7–15·1)
48/70 12·0 (8·9–18·1)
20/25 10·3 (7·0–14·9)
4/6 15·0 (3·0–NE)
19/25 10·3 (6·8–15·3)
53/76 13·8 (9·8–15·8)
58/78 10·3 (8·0–15·2)
14/23 14·1 (10·3–NE)
17/20 8·7 (4·3–10·3)
55/81 14·1 (10·3–18·1)
41/53 12·0 (8·9–15·1)
31/48 11·3 (8·0–26·1)
7/10 18·1 (8·7–NE)
32/48 11·3 (9·0–18·1)
20/28 8·0 (5·5–15·3)
9/11 11·2 (6·0–31·6)
4/4 12·4 (5·7–26·1)
65/89 10·6 (9·0–14·7)
7/12 20·8 (8·9–NE)
19/24 10·9 (8·0–21·1)
53/77 12·0 (9·0–15·8)
1 5 10
OS median (months)

Figure 4.



Number at risk (censored)					
Grade ≥1	101 (0)	67 (15)	41 (35)	26 (49)	19 (56)
Grade ≥2	101 (0)	74 (18)	47 (40)	29 (57)	19 (67)
Grade ≥3	101 (0)	80 (19)	53 (45)	30 (67)	20 (77)

~~Longer-term e~~Efficacy and safety of erdafitinib in patients with locally advanced or metastatic urothelial carcinoma: ~~24-month~~long-term follow-up of the pivotal phase 2 study

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Abstract

Background Erdafitinib, a pan-fibroblast growth factor receptor (FGFR) kinase inhibitor, was effective and tolerable in patients with advanced urothelial carcinoma and prespecified *FGFR* alterations in the primary analysis from the open-label, phase 2, non-comparator, BLC2001 study at median 11 months' follow-up. ~~We report further data~~The aim of the current analysis was to assess long-term efficacy and safety ~~at a median 24 months' follow-up~~ for the selected regimen.

Methods ~~We administered erdafitinib at three different dosing regimens to patients~~ Eligible patients were ≥18 years with locally advanced and unresectable/metastatic urothelial carcinoma, had at least ~~1~~one~~and~~ prespecified *FGFR* alteration and ~~had~~ an Eastern Cooperative Oncology Group performance status of 0–2.s~~.~~. The selected regimen determined in the initial part of the study was 8 mg/day continuous oral erdafitinib in 28-day cycles, with provision for pharmacodynamically~~-~~ guided uptitration to 9 mg/day (8 mg/day UpT)~~-~~. The ~~P~~primary endpoint was investigator-assessed confirmed objective response rate (ORR) according to Response Evaluation Criteria ~~i~~In Solid Tumors (RECIST) version 1.1. ~~; secondary endpoints were progression-free survival (PFS), duration of response (DoR), overall survival (OS), safety, predictive biomarker evaluation, and pharmacokinetics.~~ Efficacy and safety were analysed in all treated patients who received at least ~~1~~one dose of erdafitinib. This is the final analysis of the study ~~is registered with(~~ ClinicalTrials.gov~~,~~ number NCT02365597).

Findings ~~We enrolled 212 patients between~~ Between May 25, 2015, and August 9, 2018, 212 patients were enrolled and ~~treated~~ 101 patients were treated with erdafitinib 8 mg/day UpT ~~the 8 mg/day continuous erdafitinib regimen with potential for uptitration to 9 mg/day~~. Data cutoff for this analysis was August 9, 2019. Median efficacy follow-up was 24·0 (interquartile range 22·7–26·6) months. Investigator-assessed ORR for patients treated with the selected erdafitinib regimen was 40% (95% CI 30%–49%). ~~Median DoR was 6·0 months (95% CI 4·2–7·5); 31% of patients had responses lasting 12 or more months. 12- and 24-month~~

survival rates were 49% and 31%, respectively. Median PFS was 5·5 months (95% CI 4·3–6·0) and median OS was 11·3 months (95% CI 9·7–15·2). The safety profile remained similar to that in the primary analysis, with no new safety signals reported with longer follow-up.

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

Funding Janssen Research & Development.

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 from Jan 1, 2010, to Jan 1, 2021. We used search terms "bladder cancer" OR "urothelial cancer" AND "fibroblast growth factor receptor," with limits for clinical trials and no language preferences specified. At the time of the initial protocol approval for study BLC2001 (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 provide clinical benefit that is a small improvement in response rates over traditional chemotherapy and is accompanied by unique immune-related adverse events that are potentially serious and sometimes fatal. Differential response 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 the phase 2 study of erdafitinib (BLC2001) was published in 2019 and, based on 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 genetic 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

We show that, ~~at a median of 24 months'~~with longer follow-up, erdafitinib treatment continues to show consistent clinical ~~efficacy~~ benefits for patients with locally advanced or metastatic urothelial cancer whose tumours harbour specific *FGFR* alteration~~(s)~~ and that erdafitinib has a manageable safety profile. ~~With the longer follow-up, there was a consistent benefit in objective response rate, progression-free survival, and overall survival and, with a median treatment exposure of 5·4 months, the safety profile remained consistent with no new safety signals identified.~~

Implications of all the available evidence

Our research from longer 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 whose tumours harbour specific FGFR alteration(s). Further research, in a phase 3 randomised controlled 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 cisplatin-ineligible patients with metastatic urothelial carcinoma.

Introduction

Until recently, after failure of platinum-based chemotherapy, second-line treatment options for patients with advanced urothelial carcinoma have been limited, 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] approved in the United States,[4] Brazil, Canada, Thailand, Singapore, Peru, Israel, Taiwan, Hong Kong, and Saudi Arabia to treat adults with locally advanced or metastatic urothelial carcinoma with *FGFR3/2* alterations who progressed during or after one or more lines of prior platinum-containing chemotherapy, including within 12 months of (neo)adjuvant platinum-containing chemotherapy. The National Comprehensive Cancer Network guidelines for bladder cancer recommend erdafitinib as a second-line treatment option for patients with locally advanced or metastatic urothelial carcinoma following platinum-based therapy.[5] The European Association of Urology guidelines include FGFR inhibitors such as erdafitinib as promising therapies for second-line or later treatment of metastatic urothelial carcinoma,[6] and, although erdafitinib is not approved by the European Medicines Agency, it is included in European Society for Medical Oncology guidelines.[7]

Erdafitinib was approved based on 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 chemotherapy or within 12 months after neoadjuvant/adjuvant chemotherapy.[8] Based on results from a planned interim analysis, the selected schedule of erdafitinib was set at 8 mg/day continuously, with the possibility of pharmacodynamically guided uptitration to 9 mg (henceforth 8 mg/day UpT [the selected-regimen group]).[8] In the primary analysis, erdafitinib was associated with an investigator-assessed objective tumour response in 40% (95% confidence interval [CI] 31%–50%) of patients in the selected-regimen group[8]; the confirmed response rate was also 40% among patients who progressed/relapsed after prior chemotherapy. Additionally, at a median follow-up of 11·2 months, median progression-free

survival (PFS) was 5·5 months (95% CI 4·2–6·0) and, at a median follow-up of 11·0 months, median overall survival (OS) was 13·8 months (95% CI 9·8–not reached [NR]).[8] Treatment-related adverse events (AEs) of grade 3 or higher were reported in 46% of patients at the time of the primary analysis.[8]

We report longer-term efficacy, with 24·0 months' median follow-up, and safety outcomes from 5.4 months' median exposure (range: 0–31 months) among patients treated with the selected regimen of erdafitinib in BLC2001.

Methods

Study design and participants

The open-label, phase 2, non-comparator, BLC2001 study (NCT02365597) in patients with locally advanced or metastatic urothelial carcinoma was conducted at 126 sites in 14 countries across Asia, Europe, and North America (see appendix p 2). As described,[8] eligible patients were ≥18 years, with locally advanced and unresectable or metastatic urothelial carcinoma; had 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, by central laboratory testing; a history of disease progression during or after one or more lines of previous systemic chemotherapy or within 12 months after neoadjuvant/adjuvant chemotherapy (chemotherapy-refractory patients) or were cisplatin ineligible (for impaired renal function/peripheral neuropathy) and chemotherapy naïve; an Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2; and adequate bone marrow, liver, and kidney function (creatinine clearance, ≥40 mL/min/1·73 m^2). Patients who had any number of prior lines of therapy or who previously received immunotherapy (eg, immune checkpoint inhibitors) were eligible for enrolment. Patient exclusion criteria are on appendix p 4.

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

~~**Randomisation and masking**~~

Procedures

In the initial part of the study, patients were randomly assigned (1:1, with stratification performed as previously described[8]) to oral erdafitinib (Janssen-Cilag SpA, Latina, Italy) at 10 mg/day intermittently (7 days on, 7 days off) or 6 mg/day continuously in 28-day cycles (appendix p 564). Based on findings from an interim analysis and pharmacokinetic/pharmacodynamic modelling based on clinical data, the protocol was amended to continue enrolment into the 8 mg/day UpT dose schedule, thereby converting the study to a single-group analysis.

In the selected 8 mg/day regimen, uptitration to 9 mg/day continuous treatment was permitted on day 14 in patients without AEs 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–<7·0 mg/dL (2·3 mmol/L; target range).

Patients continued to receive erdafitinib until disease progression or unacceptable AEs, as determined by the investigator. At discretion of the investigator and the sponsor, patients with

investigator-assessed disease progression could continue erdafitinib treatment. Patients who interrupted treatment because of grade 1 events~~,~~ reinitiated treatment ~~was reinitiated~~ at the same or 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). Patients who interrupted treatment because of lower grade events~~,~~ reinitiated treatment at the same or a lower dose. ~~Patients were~~Efficacy was assessed ~~for efficacy~~ using RECIST by computed tomography or magnetic resonance imaging 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 additional scan within 4–6 weeks after first assessment. After treatment discontinuation, patients were contacted every 12 weeks to assess survival.

Safety was assessed by clinical laboratory testing ~~(blood samples for serum chemistry and haematology)~~, physical examination, electrocardiography, and ophthalmologic examination (frequency of these assessments is described on appendix p 15). Investigators assessed and graded AEs and abnormalities according to National Cancer Institute CTCAE criteria (version 4.0) for the duration of the study.

Outcomes

The primary endpoint was confirmed objective response rate (ORR = % complete response [CR] + % partial response [PR]) among patients treated with the selected regimen; all CRs and PRs required confirmation within 4–6 weeks of first assessment of response~~,~~ and were assessed by the investigators per RECIST v1.1; disease control rate (DCR [CR + PR + stable disease (SD)]) was also calculated. Secondary endpoints were PFS (defined as time from the first dose of study drug until the first documented evidence of progressive disease [or relapse for patients who experienced CR during the study] or death, whichever occurred first),

duration of response (DoR, defined as time from the initial documentation of a response to the first documented evidence of progressive disease [or relapse for patients who experienced CR during the study] or death), OS (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 (considered for publication by another journal).

~~In a subgroup analysis, secondary time-to-event efficacy endpoints of DoR (among patients with a confirmed objective response by investigator assessment), PFS, and OS were assessed by *FGFR* alterations (mutations and/or fusions), primary tumour location (upper versus lower tract), presence of visceral metastases (lung, liver or bone), prior chemotherapy, prior immunotherapy, and other patient demographic baseline characteristics.~~

Statistical analysis

The study had a power of 85% to reject the null hypothesis that the response rate was 25% or less, at a one-sided alpha level of 0·025, if the true response rate was 42% for the primary analysis.[8] All enrolled and treated patients in the selected-regimen group were included in the efficacy analysis (primary efficacy population). The response-evaluable population is defined as all patients who met all eligibility criteria~~;~~, received at least one dose of study drug, had a baseline and at least one adequate post-treatment disease evaluation, have had clinical signs and/or symptoms of disease progression, or died prior to the first post-treatment disease evaluation. Adequate disease assessment is defined as having sufficient evidence to correctly indicate that progression has or has not occurred.

Prespecified subgroup analysis included secondary efficacy endpoints of best objective response, DoR (among patients with a confirmed objective response by investigator assessment), PFS, and OS within the primary efficacy and chemorefractory population, and was assessed by *FGFR* alterations (mutations and/or fusions), presence of visceral metastases

(lung, liver or bone), prior chemotherapy, and prior immunotherapy; subgroup best objective response data have been published.[8] Post- hoc subgroup analysis included DoR, PFS, and OS within the primary efficacy and chemorefractory population assessed by preplanned subgroups based on primary tumour location (upper *vs* lower tract), and other patient demographic baseline characteristics. The chemotherapy relapsed/refractory (R/R) subgroup within the efficacy population included patients treated with one or more doses of erdafitinib who had progressive disease on or after one or more lines of prior chemotherapy or who had progressed/relapsed within 12 months of their last dose of neoadjuvant/adjuvant chemotherapy. Patients who received at least one dose of the study drug were included in the safety analysis (safety population).

Data for patients who were progression-free and alive or with unknown status were censored at time of the last tumour assessment. The confidence intervals for median PFS, OS, and DoR were determined using complementary log-log transformation. For PFS and DOR, data from patients who were progression-free and alive or who had unknown status were censored at the last tumour assessment. For OS, 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. A post- hoc landmark analysis was performed to compare PFS and OS ~~between responders~~by responder status (patients with a confirmed best objective response of CR or PR) and non-responders (patients with a confirmed best objective response of SD 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 as it allowed sufficient time for responses to be confirmed.

The BLC2001 study protocol (p 1418) and statistical analysis plan (p 15145) are in the appendix. 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, Janssen Research & Development, was involved in study design, data collection, data analysis, and data interpretation. Writing assistance was provided by Sally Hassan, PhD, Susan Neville, MSc, and Khalida Rizi, PhD, of Parexel, and was funded by Janssen Global Services, LLC. All investigators had access to the raw data at their individual sites. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

Between May 25, 2015, and August 9, 2018, 212 eligible patients were enrolled and treated with erdafitinib, and 101 patients were treated with the 8 mg/day UpT regimen (60 patients received 8 mg/day and 41 patients were uptitrated to 9 mg/day). Efficacy results are reported for the 8 mg/day UpT regimen group only. Of the 101 patients who were treated with the 8 mg/day UpT regimen, two died due to progressive disease before the first post-baseline disease evaluation.

At the clinical cutoff date (August 9, 2019), median follow-up for efficacy (estimated based on the time from first dose of study treatment to date of censoring for PFS using the reverse Kaplan–Meier method[9]) was 24·0 months (interquartile range [IQR] 22·7–26·6). Median treatment duration was 5·4 months (range: 0–31).

Two patients were enrolled into the 8 mg/day UpT regimen group after the clinical cutoff date for the primary analysis (March 15, 2018). Patient demographics and baseline characteristics are presented in table 1. Consistent with the primary analysis, progressive disease was the

most common reason for treatment discontinuation. At the analysis cutoff date, 24 patients (24%) in the 8 mg/day UpT group remained in the study.

The confirmed investigator-assessed ORR was 40% (40/101; 95% CI 30%–49%) among all patients receiving the 8 mg/day UpT regimen, consistent with the 40% ORR (40/99; 95% CI 31%–50%) at the time of primary analysis.[8] Of the 99 patients treated with 8 mg/day UpT who underwent at least one disease evaluation after baseline, 76 (77%) had a reduction in the sum of target-lesion diameters, and 48 (48%) had a maximum tumour reduction of 30–100% (appendix p 675). Further analyses of response revealed similar ORRs irrespective of the presence or absence of visceral metastases (33·3% [3/9], 35·0% [7/20], 40·4% [23/57], 34·8% [8/23], 40·0% [4/10], and 50·0% [7/14] for patients with lymph node-only disease, and those with liver, lung, bone, both liver and lung, and other metastatic disease, respectively). Median time to response ~~was numerically~~seemed longer for patients who had both liver and lung metastases (2·2 months [IQR 1·4–3·0) compared with those who had lymph node-only disease (1·4 months [IQR 1·4–1·4]), and those with liver (1·4 months [IQR 1·4–3·0]), lung (1·4 months [IQR 1·4–1·6]), bone (1·6 months [IQR 1·4–2·8]), and other metastases (1·4 months [IQR 1·3–1·4]). Similarly, median time to response ~~was numerically~~appeared~~–~~ longer for patients with 2–3 sites of visceral disease compared with those who had 1 or no metastatic sites (2·0 [IQR 1·3–3·0] *vs* 1·4 [IQR 1·4–1·5] and 1·4 [IQR 1·3–1·4] months, respectively). We note that these results are based on a limited number of responders per disease site. Median DoR was 6·0 months (95% CI 4·2–7·5); 31% (31/101) of responders had a DoR that was maintained for ≥12 months (figure 1; of 101 patients, 40 had a confirmed response: PR in 36 [35·6%] and CR in 4 [4·0%]). Additionally, 41% of patients achieved a best response of SD for at least one disease evaluation period (>36 days), leading to an overall ~~disease control rate (~~DCR ~~[CR + PR + SD])~~ of 80·2% (95% CI 72·4%–88·0%) for the primary efficacy population.

Median PFS was 5·5 months (95% CI 4·3–6·0) for all patients treated with the selected regimen (figure 2A). There had been 72 events in the 8 mg/day erdafitinib UpT group, and median OS was 11·3 months (95% CI 9·7–15·2) (figure 2B). The 12-month survival rate was 49% and the 24-month survival rate 31%.

Based on a landmark analysis, at 3 months after treatment initiation, PFS was similar between responders and non-responders while OS improved for responders (~~figure 3~~appendix p 8). It is noted that any differences in PFS and OS observed ~~in figure 3~~ between responders and non-responders are numerical and limited by small numbers.

PFS, OS, and DoR were not impacted by factors such as age, sex, and most baseline disease characteristics, including haemoglobin level and renal function (figure 34 and appendix p 6~~8~~9). Patients with an ECOG PS of 0–1 versus 2 had a longer median PFS (5·6 [95% CI 5·0–6·8] *vs* 3·2 [95% CI 1·0–4·9]) and a longer median OS (13·8 [95% CI 10·3–15·8] *vs* 5·1 [95% CI 3·0–8·0]).

Most patients (69% [70/101]) had mutations, 25% (25/101) had fusions, and 6% (6/101) had both mutation and fusion. The most common mutations were FGFR3-S249C (4~~5·5~~6% [45/99]), FGFR3-R248C (13~~·1~~% [13/99]) and FGFR3-Y373C (12~~·1~~% [12/99]), and the most common fusion was FGFR3-TACC3_V1 (11~~·1~~% [11/99]). PFS, DoR, and OS values ~~were numerically~~seemed similar between patients with *FGFR* mutations and those with *FGFR* fusions (figure 3 and appendix p ~~8~~9). ~~Median PFS, however, trended longer for patients with *FGFR* mutations (5·6 months [95% CI 4·9–7·4]) than for those with *FGFR* fusions (2·8 months [1·6–6·6]) (figure 4A). Median DoR was 6·0 (95% CI 4·2–7·5) months for patients with *FGFR* mutations and 6·2 (3·0–21·4) for those with *FGFR* fusions (figure 4B). Median OS was also similar between patients with *FGFR* mutations and those with *FGFR* fusions, but trended longer for patients with *FGFR* mutations (12·0 months [95% CI 8·9–18·1]) than for patients with *FGFR* fusions (10·3 months [95% CI 7·0–14·9) (appendix p 8).~~

Most patients had primary tumours in the lower tract (75% [76/101]) and 77% (78/101) had visceral metastases, but PFS and OS values ~~were numerically~~seemed similar regardless of the primary tumour ~~location or the~~location, the presence/absence of visceral metastases, or the number of prior lines of therapy (figure 3 and appendix p 11).

~~Almost half of patients had received one line of prior systemic therapy (chemotherapy and/or immunotherapy), and approximately one quarter had received two whilst approximately one sixth had received three or more prior lines of systemic therapy (table 1). PFS and OS were also not impacted by the number of prior lines of systemic therapy (figure 4). For patients who had received one, two, and three prior lines of therapy, median OS was 11·3 (95% CI 9·0–18·1), 8·0 (95% CI 5·5–15·3), and 11·2 months (95% CI 6·0–31·6), respectively (figure 4B).~~

Most patients (88% [89/101]) had received prior chemotherapy (table 1). Similar to the ORR for all treated patients, confirmed ORR for the chemotherapy R/R population was 39·~~·~~3% (95% CI 29·~~·~~2%–49·~~·~~5%). Additionally, overall DCR in the chemotherapy R/R population (79·8% [95% CI 71·4%–88·1%]) was similar to that in the all-treated population. Median PFS among treated chemotherapy R/R patients (~~5·5 months [95% CI 4·0–5·7];~~ figure ~~4A~~3A; appendix p ~~9~~10 and ~~8~~11) was also similar to that among all treated patients. Median OS was 10·6 months (95% CI 9·0–14·7) for treated chemotherapy R/R patients (among whom 65 events occurred [figure ~~4B~~ 3B and appendix p ~~7~~ ~~9~~10 and ~~8~~1~~0~~1]). ~~Median PFS, OS, and DoR in patients who had prior chemotherapy versus those who were chemotherapy naïve are presented in figure 4 and on appendix p 6 and 8.~~ For patients who had prior chemotherapy (appendix p ~~7~~ ~~9~~10 and ~~8~~1~~0~~1) versus all treated patients (figure 2), median PFS ~~(5·5 *vs* 5·5 months)~~ and median OS ~~(10·6 *vs* 11·3 months)~~ were similar. For chemotherapy-naïve patients (n=12), median PFS was 14·9 months (95% CI 2·8, 26·7) and median OS was 20·8 months (8·9–NE).

Almost a quarter of patients who received the 8 mg UpT regimen had received prior immunotherapy (table 1), but PFS and OS were similar regardless of the number of lines of prior immunotherapy (figure ~~4~~3). Median PFS for those who had received prior immunotherapy (5·7 months [95% CI 4·9–8·3]; figure ~~4A~~3A) was also similar to that for all treated patients. Median OS was 10·9 months (95% CI 8·0–21·1) for patients with prior immunotherapy (amongst whom 19 events were recorded [figure ~~4B~~3B]).

The safety profile of erdafitinib at a median treatment exposure of 5·4 months remained consistent with that in the primary analysis.[8] All patients experienced at least one treatment-emergent AE (TEAE; defined on appendix p 5) irrespective of dose uptitration, and 59·4% of patients (60/101) experienced TEAEs that led to dose reduction. Grade 3–4 TEAEs of any causality occurred in 71·3% (72/101) of patients, the most common (occurring in ≥10% of patients) being stomatitis and hyponatraemia (table 2 and appendix p ~~9~~11~~2~~); 52·~~·4~~3% (53/101) had grade 3 TEAEs that were considered related to erdafitinib 8 mg UpT. No grade 4 TEAEs were considered related to erdafitinib. No new treatment-related AEs were observed with longer follow-up (see appendix p ~~10~~13). The most common TEAEs were hyperphosphataemia, stomatitis, diarrhoea, and dry mouth (table 2). Serious TEAEs occurred in 4~~4·55~~% (45/101) of patients (see appendix p ~~11~~14). The most common serious TEAEs were urinary tract infection and general physical health deterioration; ~~11~~10·9% (11/101) were considered by the investigator to be related to erdafitinib, and no treatment-related deaths occurred. Of patients receiving 8 mg/day UpT, ~~16~~15·8% (16/101) had AEs considered related to erdafitinib that led to treatment discontinuation. The frequency of any one event leading to treatment discontinuation was low; no more than ~~three~~ two patients (~~2~~3·0%) ~~reported~~ reported the same TEAE leading to discontinuation~~.~~ (appendix p 16).

The proportion of patients with central serous retinopathy (CSR; a known class effect of FGFR inhibitors and a TEAE of special interest) was ~~27~~26·7% in all treated patients (27/101; appendix p ~~12~~14), 25·0% (15/60) in patients who received 8 mg/day and 29·3% (12/41) in

those whose dose was uptitrated to 9 mg/day. Most of these events (85·2% [23/27]) were grade 1 or 2 (figure 5 4 and appendix p 1214). At data cutoff, 63·0% (17/27) of CSR events had resolved (median [range] time to resolution 27 days [9–299]); all 10 unresolved events were grade 1 or 2 (appendix page 1214). The median time to first onset of CSR was 53 days for any-grade AE and 94 days for grade 3 events (figure 54); 7.4% (2/27) occurred after 6 months. Among treated patients, dose reduction, dose interruption, and treatment discontinuation for CSR occurred in 1312·8% (13/101), 87·9% (8/101), and 3·0% (3/101), respectively (see appendix p 3 5 for dose modification for most common TEAEs). Other select TEAEs are reported on appendix p 1317, including among those who received 8 mg/day and those whose dose was uptitrated to 9 mg/day; rates of hyperphosphataemia were higher in the non-uptitrated group than in the uptitrated group (8786·7% [52/60] *vs* 6665·9% [27/41]); the incidences of stomatitis, nail events, non-CSR events, skin events, and diarrhoea were comparable between patients who received 8 mg/day and those who received 9 mg/day.

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 compared with the primary analysis (median follow-up ~11 months).[8] There were no new safety signals with a median treatment exposure of 5·4 months. The confirmed investigator-assessed ORR was 40%; median PFS and OS were 5·5 and 11·3 months, respectively. Clinically meaningful treatment benefit with erdafitinib was observed in patients regardless of prior chemotherapy or immunotherapy and most baseline disease characteristics. Responses lasted a median of 6·0 months, and 31% lasted for 1 year or more. Patients with ECOG PS 0–1 versus 2 had a longer median PFS and OS, but there was no numerical difference in PFS and OS by presence/absence of visceral

metastases, *FGFR* alteration type, or kidney function (baseline creatinine clearance < or ≥60 mL/min). Additionally, while PFS and OS appeared ~~to be numerically~~ longer among chemotherapy-naïve patients compared with those who had received prior chemotherapy, multiple 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 nonrandomised study, and some subgroups contained small numbers of patients. This should be considered when interpreting the results.

The primary results from 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 may harbour *FGFR* alterations[11]; *FGFR3* alterations have been reported in ~22% of patients with urothelial bladder carcinoma at all stages in one study,[12] suggesting a role for wider implementation of *FGFR* testing, as patients with certain *FGFR* alterations may benefit from FGFR inhibition. Other FGFR inhibitors are also being investigated in metastatic urothelial carcinoma, including infigratinib and rogaratinib. In one study, the ORR for infigratinib (an FGFR1–3 inhibitor) was 24% in the second- and later-line setting for advanced/unresectable or metastatic urothelial carcinoma.[13] In an expansion cohort of a phase 1 study 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 prior lines of therapy, ORR was 24%.[14]

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 ORRs of 14% and 32%, respectively.[15] As second-line therapy, checkpoint blockade immunotherapies have demonstrated an ORR of ~20%.[16-~~23~~ 21] The ORR reported for studies of antibody–drug conjugates as second-line treatment, were 40·6% for

enfortumab vedotin (phase 3 study; median follow-up, 11·1 months)[24,22] and 31% for sacituzumab govitecan (phase 1/2 study).[25,23]

The PFS and OS seen in the current analysis of the BLC2001 study confirm the persistent benefit of erdafitinib 8 mg UpT. These median PFS and OS data are also, generally, comparable with those noted for second-line checkpoint inhibitors[16,18,19,21] and antibody drug conjugates.[24,22,25,24] 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 UpT in our study, 31% had responses lasting 12 months or more, and 12- and 24-month survival rates were 49% and 31%, respectively. Patients with objective responses to erdafitinib also had increased PFS and OS; PFS and OS were independent of most baseline disease characteristics. The durability of ORR, PFS, and OS noted in our study demonstrated 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.[2,46-2,86] To identify markers of intrinsic resistance to FGFR inhibition, plasma samples from the BLC2001 study were tested using next-generation sequencing for ctDNA, and the presence of *EGFR*, *CCND1*, and *BRAF* alterations at baseline correlated with shorter PFS, and *EGFR* with shorter OS.[29,27] 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~~, with no new safety signals~~

~~identified~~. CSR events~~,~~ ~~are~~ a known class effect of ~~inhibitors of the~~ mitogen-activated protein kinase pathway inhibitors, ~~such as~~including for FGFR~~.~~,[30 28-32 30] occurred in ~~A~~approximately one quarter ~~(27%)~~ of patients ~~had CSR events~~, but ~~most (85%) of these~~ were mostly grade 1 or 2 ~~in severity and 63% (17/27)~~and the majority resolved at data cutoff~~; 37% (10/27) were unresolved~~.

The open-label, single-arm study design of BLC2001 is a limitation. Patients ~~in this study~~ were selected based on the presence of ~~9~~ nine prespecified *FGFR* alterations; because gene amplifications were not included among these alterations and whole genome sequencing was not performed, other mechanisms for constitutive activation or resistance were not assessed. The Kaplan–Meier curves for PFS and OS by responder status at the 3-month landmark (~~figure 3~~appendix p ~~7~~8) and some of the subgroup analyses (figure 3~~4~~) are limited by small numbers; these are included here to offer clinical insights only. ~~The activity of e~~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 recurring after treatment with bacillus Calmette-Guérin. Frequency of *FGFR* alterations is higher in early-stage urothelial carcinoma.[11]

In conclusion, in the BLC2001 study, at a median 24·0 months of follow-up, second-line erdafitinib treatment of patients with locally advanced or metastatic urothelial carcinoma and prespecified *FGFR* alterations demonstrated consistent, durable efficacy with a median OS of 11·3 months and almost one third of patients having responses lasting 12 months or longer~~.~~ ~~With a median treatment duration of 5·4 months,~~; tolerability was comparable ~~tolerability was~~

~~comparable~~ to that in ~~that at~~ the ~~time of the~~ primary analysis~~, with no new safety signals observed~~. 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 prior platinum-containing chemotherapy, including within 12 months of (neo)adjuvant platinum-containing chemotherapy, and who have specific *FGFR* alterations. Erdafitinib is therefore being investigated in other treatment settings.

Author contributions

ASR, ASW, YL, AO, MJ, and AR were involved in the conceptualization and design of the study. SA, ID, JGD, RAH, MJ, STT, YZ, AN, BM, SHP, AO, AR, ASW, and ASR were involved in the investigation, data collection, data analysis, or interpretation of the study. All authors reviewed the data analyses, data interpretation, and writing the report, and approved the final version of the submitted manuscript.

Declaration of interest

EFB has received grants or contracts from Pfizer and Astellas Pharma; honoraria from Exelixis and Bayer; stock or stock options from Exelixis, Becton Dickinson, Calithera Biosciences, Gilead Sciences, Medtronic, Clovis Oncology, and Macrogenics, all outside 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, Pharamcyclics 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, all outside 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

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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 site, requests for study data access can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

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Figure Legends

Figure 1: **Swimmer's plot of duration and type of response for 101 patients treated with 8 mg/day erdafitinib with potential for uptitration to 9 mg/day**

Bars are coloured to show best response.

Responses that occurred or were maintained after treatment discontinuation due to adverse events but prior to the start of subsequent therapy are included in the display. One patient, shown as treatment ongoing, had a drug interruption at the data cut but had not discontinued erdafitinib.

Figure 2: **Investigator-assessed progression-free survival (A) and overall survival (B) for 8 mg/day erdafitinib with potential for uptitration to 9 mg/day**

~~***Figure 3:*** **Investigator-assessed progression-free survival (A) and overall survival (B) for 8 mg/day erdafitinib with potential for uptitration to 9 mg/day based on response status at the 3-month landmark~~

~~CR=complete response. PR=partial response.~~

Figure 43: **Estimated median (and associated 95% confidence interval) for progression-free survival (A) and overall survival (B) by subgroup**

*Upper tract includes renal pelvis and ureter. †Lower tract includes bladder, urethra and prostatic urethra. ‡Visceral metastases includes metastases into lung, liver, and bone. †Prior immunotherapy includes atezolizumab, pembrolizumab, nivolumab, durvalumab, avelumab, anti-csf1r antibody, tremelimumab. BL, baseline; CrCl, creatinine clearance; Hb, haemoglobin; IO, immunotherapy; NE, not evaluable; R/R, relapsed refractory. The bars represent the associated 95% confidence interval by selected subgroup. *FGFRm+f-= FGFR* mutation present and fusion absent. *FGFRm-F+=FGFR* mutation absent and fusion present. *FGFRm+f+=FGFR* mutation and fusion present. IO=immunotherapy. OS=overall survival. PFS=progression-free survival.

Figure ~~54~~: Post- hoc analysis of ~~C~~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 no dose modification in another patient, and one patient had grade 3 detachment of retinal pigment epithelium, which initially resolved but then recurred as a grade 2 event following dose reduction (ultimately leading to discontinuation of erdafitinib in this patient).

Table 1: **Baseline characteristics**

Patients	**Erdafitinib 8 mg/day UpT n=101***
Age, median (range), years	67 (36–87)
ECOG PS	
0	51 (50%)
1	43 (43%)
2	7 (7%)
Pretreatment†	
Progressed or relapsed after chemotherapy	89 (88%)
Chemotherapy naive	12 (12%)
Prior immunotherapy	24 (24%)
Number of lines of prior treatment‡	
0	10 (10%)
1	48 (48%)
2	28 (28%)
≥3	15 (15%)
Visceral metastases§	
Present	78 (77%)
Liver	20 (20%)
Lung	57 (56%)
Bone	23 (23%)
Absent	23 (23%)
Lymph node only	9 (9%)
Other¶	14 (14%)
Haemoglobin level, g/dL	86 (85%)

Patients	Erdafitinib 8 mg/day UpT n=101*
≥10	15 (15%)
<10	
Tumour location	25 (25%)
Upper tract	76 (75%)
Lower tract	
Creatinine clearance rate	53 (52%)
<60 mL/min	48 (48%)
≥60 mL/min	
FGFR alteration#	
FGFRm+f-	70 (69%)
FGFRm-f+	25 (25%)
FGFRm+f+	6 (6%)

Data are n (%). *Two patients were added to the 8 mg/d UpT regimen after the cutoff date for the primary analysis (March 15, 2018). †The pretreatment groups are not mutually exclusive. ‡The chemo relapsed/refractory efficacy population (n=89) consists of all patients in the 8 mg daily regimen who were treated with ≥1 dose of erdafitinib and had progressed on or after ≥1 prior chemotherapy or progressed/relapsed within 12 months of 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, as 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 and/or other visceral metastases (not lung, liver or bone). #*FGFR* alteration (mutations [m] and/or fusions [f], analysed as present [+] or absent [-]).
ECOG PS=Eastern Cooperative Oncology Group. UpT=possibility of uptitration to 9 mg/day.

Table 2: **Most common treatment-emergent adverse events and worst toxicity grade**

	Erdafitinib 8 mg/d UpT (n=101)	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 5***
Patients with any TEAE (worst toxicity grade)	101 (100·0%)	29 (28·07%)	58 (57·4%)	6 (5·9%)	8 (7·9%)
Hyperphosphataemia†	79 (78·2%)	54 77 (5376·52%)	2 (2·0%)	0	0
Stomatitis	60 (59·4%)	21 46 (2021·83%)	14 (13·9%)	0	0
Diarrhoea	55 (54·5%)	34 51 (3350·74%)	4 (4·0%)	0	0
Dry mouth	46 (45·5%)	34 45 (3344·75%)	1 (1·0%)	0	0
Decreased appetite	41 (40·6%)	20 40 (1939·86%)	1 (1·0%)	0	0
Dysgeusia	41 (40·6%)	26 39 (2538·76%)	2 (2·0%)	0	0
Alopecia	34 (33·7%)	27 34 (2633·7%)	0	0	0

	Erdafitinib 8 mg/d UpT (n=101)	Grade 1–2	Grade 3	Grade 4	Grade 5*
Dry skin	34 (33·7%)	25 34 (2433·87%)	0	0	0
Fatigue	33 (32·7%)	13 31 (1230·69%)	2 (2·0%)	0	0
Constipation	29 (28·7%)	19 28 (1827·78%)	1 (1·0%)	0	0
Dry eye	28 (27·7%)	20 27 (1926·87%)	1 (1·0%)	0	0
Palmar-plantar erythrodysaesthesia syndrome	25 (24·8%)	5 20 (519·80%)	5 (5·0%)	0	0
Asthaenia	23 (22·8%)	3 15 (314·90%)	6 (5·9%)	0	2 (2·0%)
Anaemia	22 (21·8%)	8 17 (716·98%)	5 (5·0%)	0	0
Nausea	22 (21·8%)	14 21 (1320·98%)	1 (1.0%)	0	0

	Erdafitinib 8 mg/d UpT (n=101)	Grade 1–2	Grade 3	Grade 4	Grade 5*
Alanine aminotransferase increased	19 (18·8%)	14 17 (1316·98%)	2 (2·0%)	0	0
Onycholysis	19 (18·8%)	17 (16·98%)	2 (2·0%)	0	0
Paronychia	19 (18·8%)	4 16 (415·08%)	3 (3·0%)	0	0
Urinary tract infection	18 (17·8%)	13 (12·09%)	5 (5·0%)	0	0
Vision blurred	18 (17·8%)	9 18 (817·98%)	0	0	0
Weight decreased	18 (17·8%)	10 17 (916·98%)	1 (1.0%)0	0	0
Nail dystrophy	17 (16·8%)	6 11 (510·9%)	6 (5·9%)	0	0

Data are n (%). Patients with one or more TEAE were counted only once for each AE and worst AE grade reported. TEAEs occurring in 15% or more patients are shown. No grade 4 AEs were considered to be related to erdafitinib. *All TEAEs with the outcome of death (grade 5) were considered by the investigator to not be related to erdafitinib, and most events (7/8), including the two grade 5 events of asthaenia, occurred in the context of progressive disease.
†Hyperphosphatemia was graded based on 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.
TEAE=treatment-emergent adverse event. TRAE=treatment-related adverse event. UpT=potential for uptitration to 9 mg/day.

Figure 1.

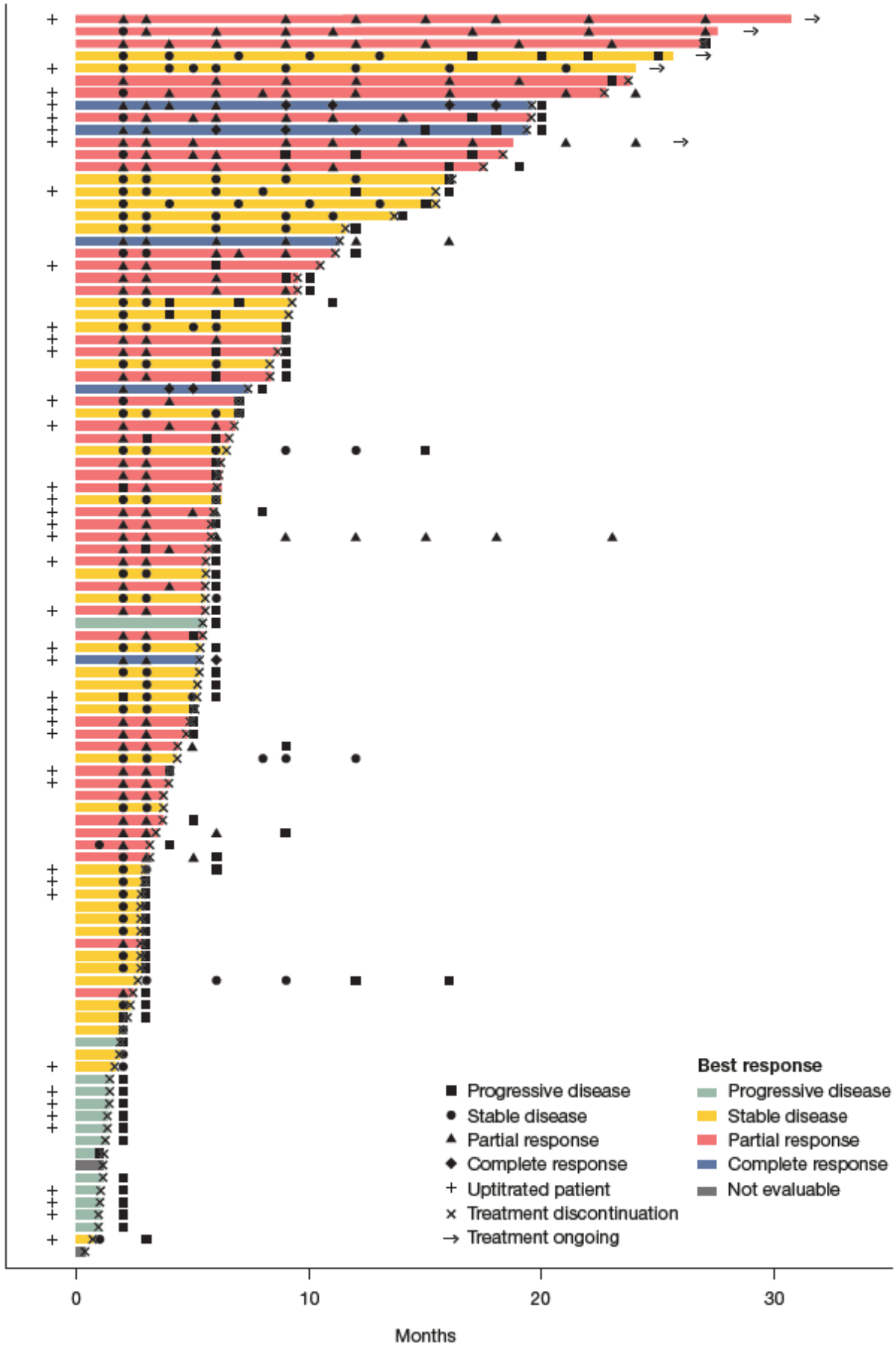
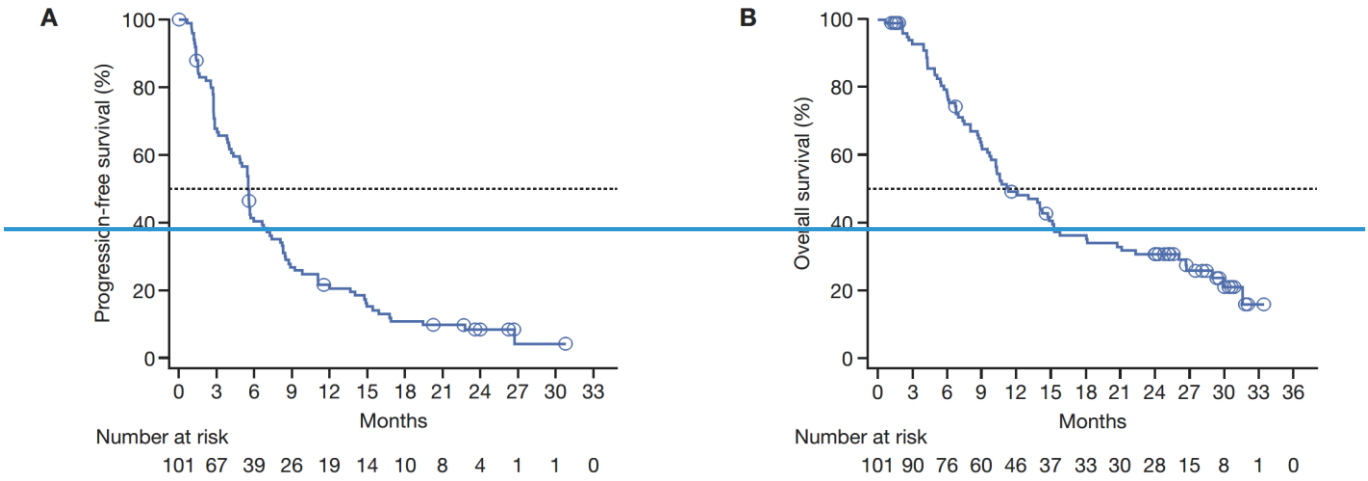
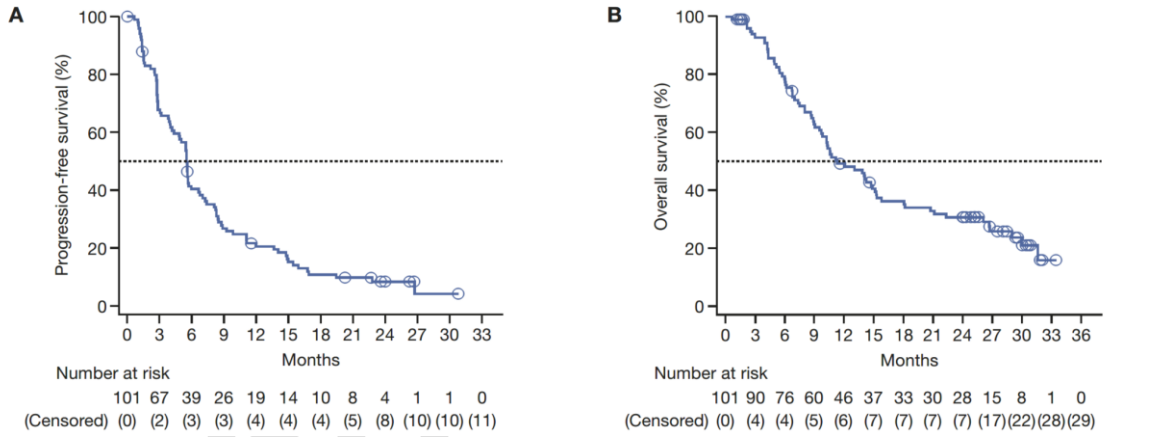

Progressive disease
Stable disease
Partial response
Complete response
Uptitrated patient
Treatment discontinuation
Treatment ongoing
Best response
Progressive disease
Stable disease
Partial response
Complete response
Not evaluable
0
10
20
30
Months

Figure 2.





~~Figure 3.~~

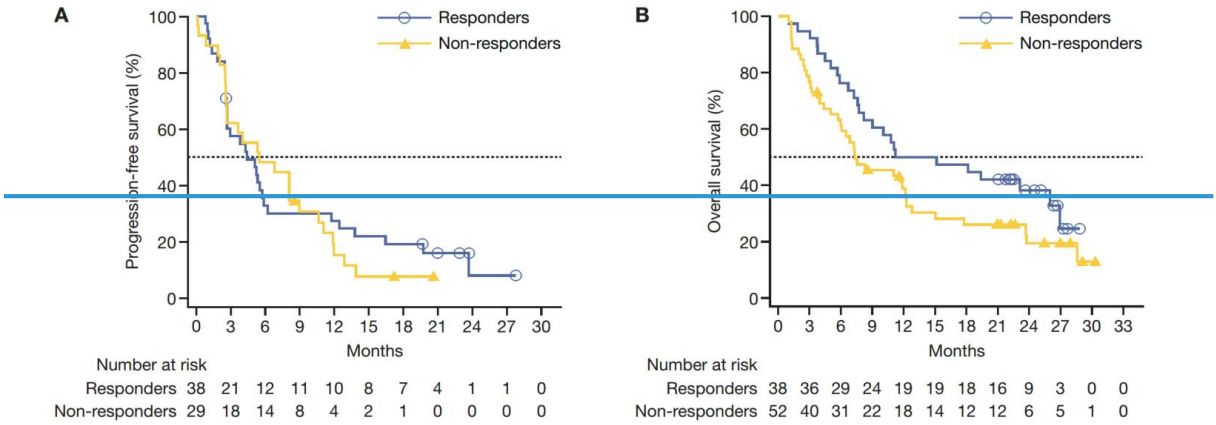
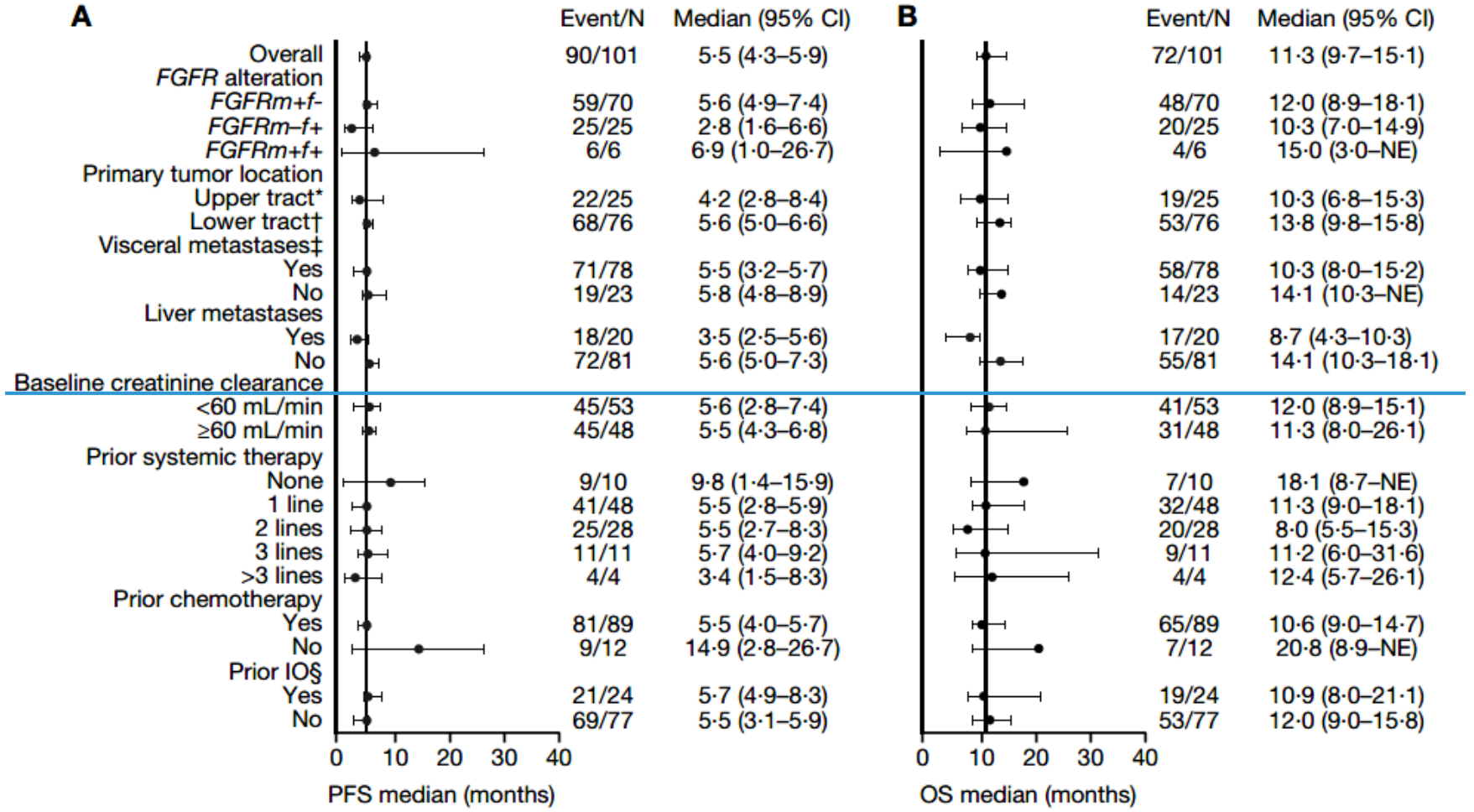
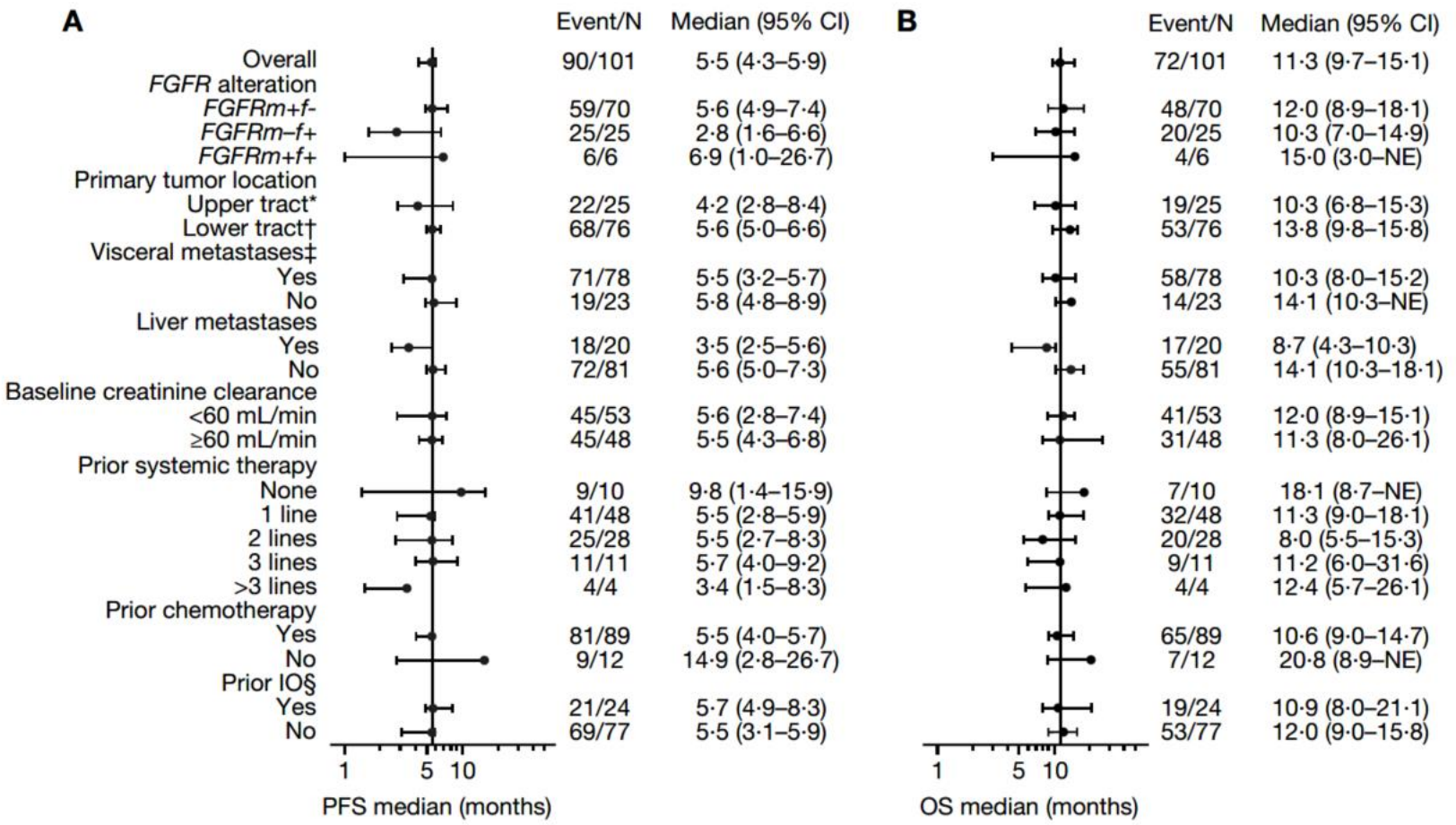


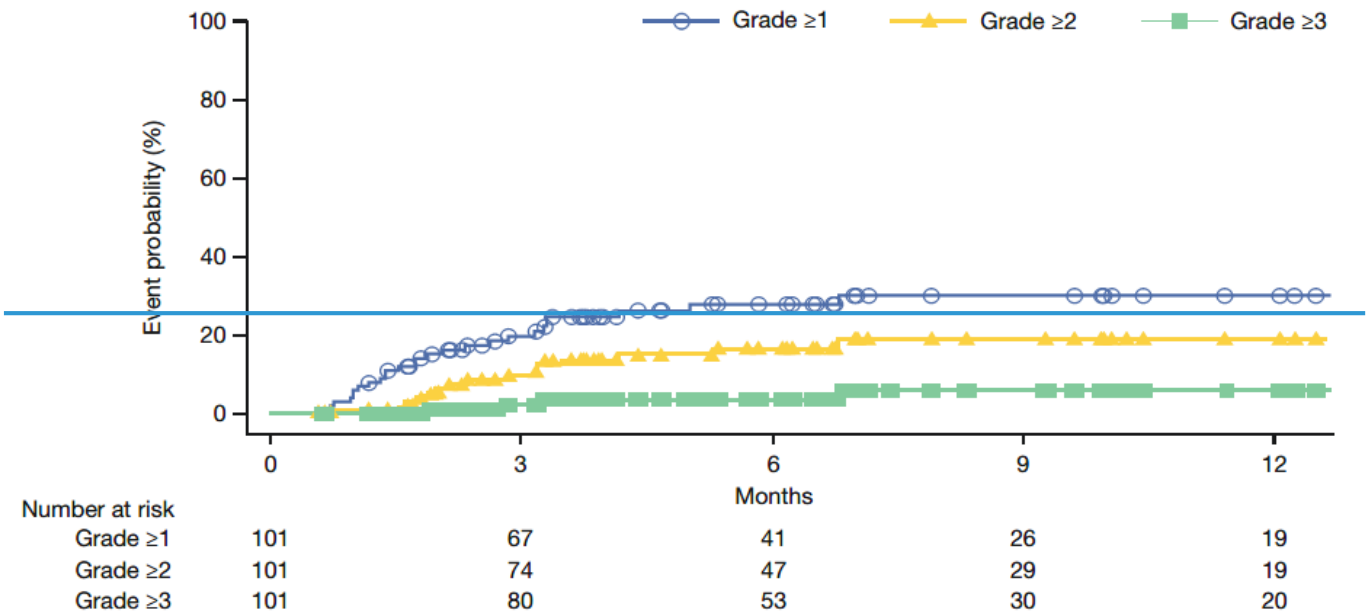
Figure 34.

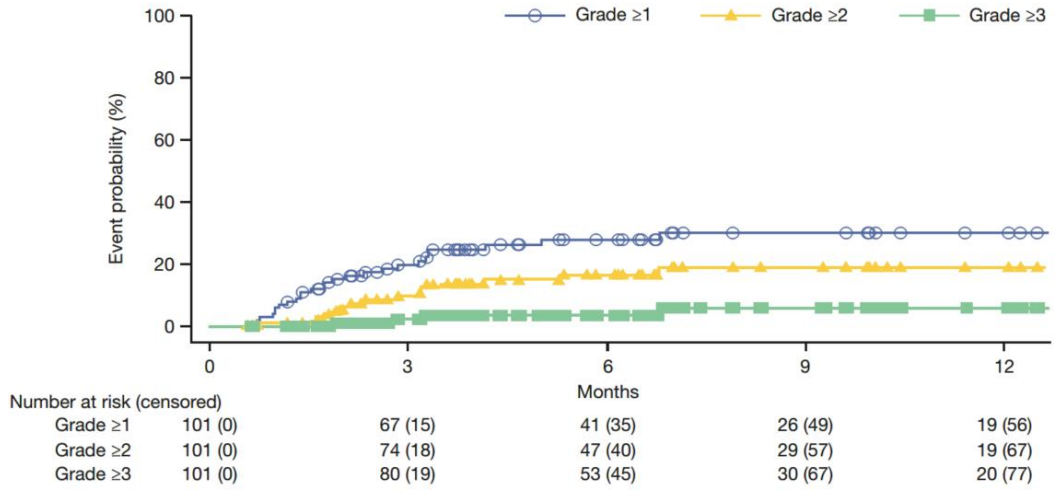

A
Event/N
Median (95% CI)
Overall
90/101
5·5 (4·3–5·9)
FGFR alteration
FGFRm+f-
59/70
5·6 (4·9–7·4)
FGFRm–f+
25/25
2·8 (1·6–6·6)
FGFRm+f+
6/6
6·9 (1·0–26·7)
Primary tumor location
Upper tract*
22/25
4·2 (2·8–8·4)
Lower tract†
68/76
5·6 (5·0–6·6)
Visceral metastases‡
Yes
71/78
5·5 (3·2–5·7)
No
19/23
5·8 (4·8–8·9)
Liver metastases
Yes
18/20
3·5 (2·5–5·6)
No
72/81
5·6 (5·0–7·3)
Baseline creatinine clearance
<60 mL/min
45/53
5·6 (2·8–7·4)
≥60 mL/min
45/48
5·5 (4·3–6·8)
Prior systemic therapy
None
9/10
9·8 (1·4–15·9)
1 line
41/48
5·5 (2·8–5·9)
2 lines
25/28
5·5 (2·7–8·3)
3 lines
11/11
5·7 (4·0–9·2)
>3 lines
4/4
3·4 (1·5–8·3)
Prior chemotherapy
Yes
81/89
5·5 (4·0–5·7)
No
9/12
14·9 (2·8–26·7)
Prior IO§
Yes
21/24
5·7 (4·9–8·3)
No
69/77
5·5 (3·1–5·9)
0 10 20 30 40
PFS median (months)
B
Event/N
Median (95% CI)
72/101
11·3 (9·7–15·1)
48/70
12·0 (8·9–18·1)
20/25
10·3 (7·0–14·9)
4/6
15·0 (3·0–NE)
19/25
10·3 (6·8–15·3)
53/76
13·8 (9·8–15·8)
58/78
10·3 (8·0–15·2)
14/23
14·1 (10·3–NE)
17/20
8·7 (4·3–10·3)
55/81
14·1 (10·3–18·1)
41/53
12·0 (8·9–15·1)
31/48
11·3 (8·0–26·1)
7/10
18·1 (8·7–NE)
32/48
11·3 (9·0–18·1)
20/28
8·0 (5·5–15·3)
9/11
11·2 (6·0–31·6)
4/4
12·4 (5·7–26·1)
65/89
10·6 (9·0–14·7)
7/12
20·8 (8·9–NE)
19/24
10·9 (8·0–21·1)
53/77
12·0 (9·0–15·8)
0 10 20 30 40
OS median (months)


A
Event/N
Median (95% CI)
Overall 90/101 5·5 (4·3–5·9)
FGFR alteration
FGFRm+f- 59/70 5·6 (4·9–7·4)
FGFRm–f+ 25/25 2·8 (1·6–6·6)
FGFRm+f+ 6/6 6·9 (1·0–26·7)
Primary tumor location
Upper tract* 22/25 4·2 (2·8–8·4)
Lower tract† 68/76 5·6 (5·0–6·6)
Visceral metastases‡
Yes 71/78 5·5 (3·2–5·7)
No 19/23 5·8 (4·8–8·9)
Liver metastases
Yes 18/20 3·5 (2·5–5·6)
No 72/81 5·6 (5·0–7·3)
Baseline creatinine clearance
<60 mL/min 45/53 5·6 (2·8–7·4)
≥60 mL/min 45/48 5·5 (4·3–6·8)
Prior systemic therapy
None 9/10 9·8 (1·4–15·9)
1 line 41/48 5·5 (2·8–5·9)
2 lines 25/28 5·5 (2·7–8·3)
3 lines 11/11 5·7 (4·0–9·2)
>3 lines 4/4 3·4 (1·5–8·3)
Prior chemotherapy
Yes 81/89 5·5 (4·0–5·7)
No 9/12 14·9 (2·8–26·7)
Prior IO§
Yes 21/24 5·7 (4·9–8·3)
No 69/77 5·5 (3·1–5·9)
1
5
10
PFS median (months)
B
Event/N
Median (95% CI)
72/101 11·3 (9·7–15·1)
48/70 12·0 (8·9–18·1)
20/25 10·3 (7·0–14·9)
4/6 15·0 (3·0–NE)
19/25 10·3 (6·8–15·3)
53/76 13·8 (9·8–15·8)
58/78 10·3 (8·0–15·2)
14/23 14·1 (10·3–NE)
17/20 8·7 (4·3–10·3)
55/81 14·1 (10·3–18·1)
41/53 12·0 (8·9–15·1)
31/48 11·3 (8·0–26·1)
7/10 18·1 (8·7–NE)
32/48 11·3 (9·0–18·1)
20/28 8·0 (5·5–15·3)
9/11 11·2 (6·0–31·6)
4/4 12·4 (5·7–26·1)
65/89 10·6 (9·0–14·7)
7/12 20·8 (8·9–NE)
19/24 10·9 (8·0–21·1)
53/77 12·0 (9·0–15·8)
1
5
10
OS median (months)

23

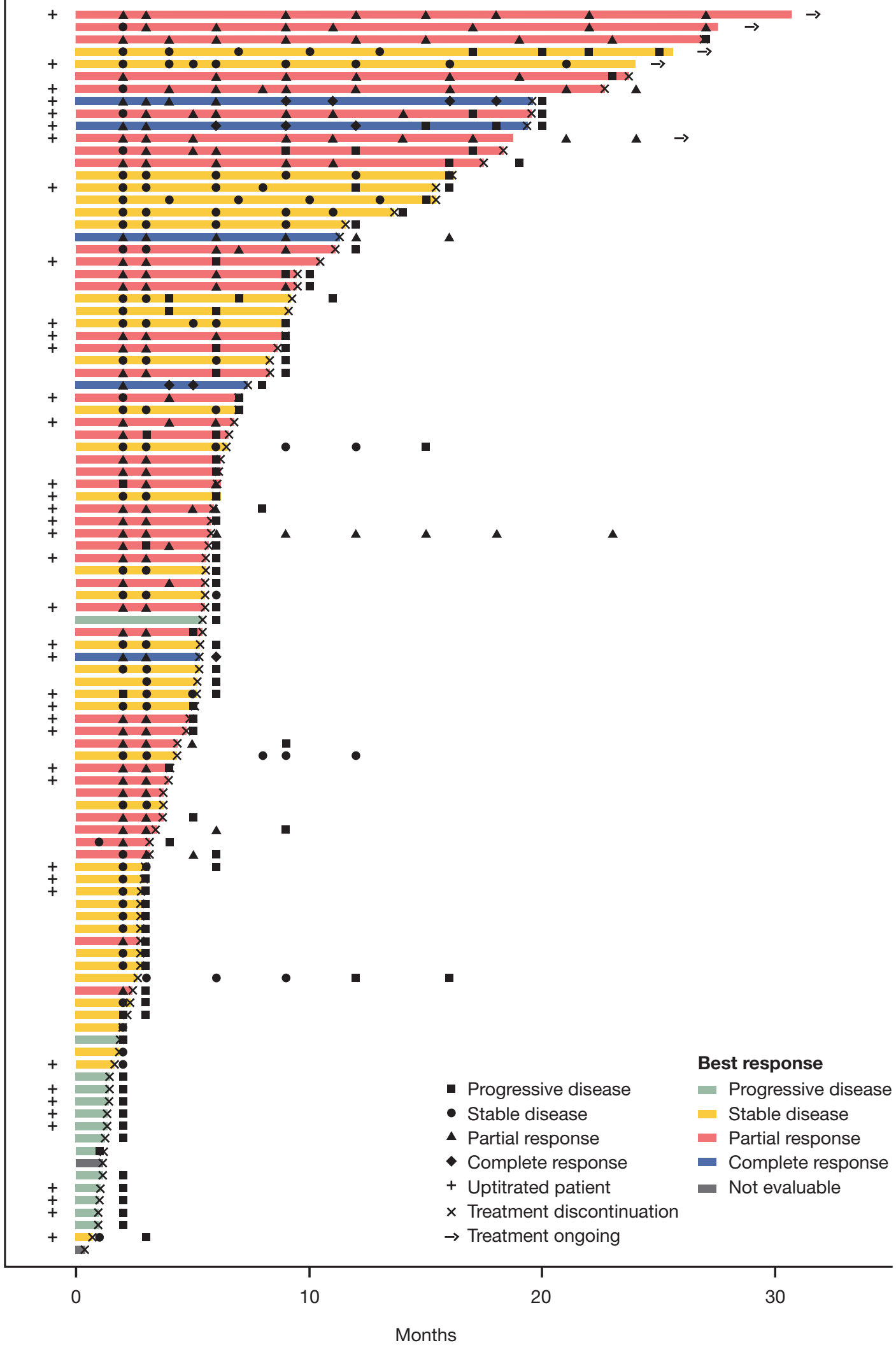
Figure 54.

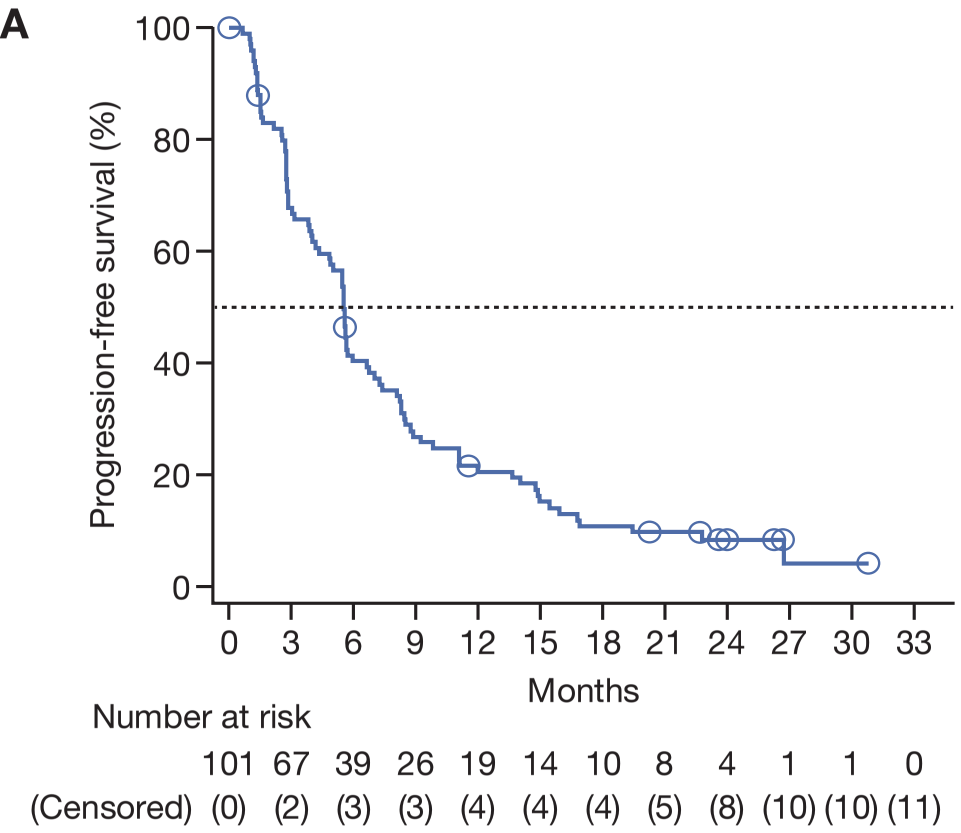

Grade ≥1
Grade ≥2
Grade ≥3
Event probability (%)
100
80
60
40
20
0
0
3
6
9
12
Months
Number at risk
Grade ≥1 101 67 41 26 19
Grade ≥2 101 74 47 29 19
Grade ≥3 101 80 53 30 20

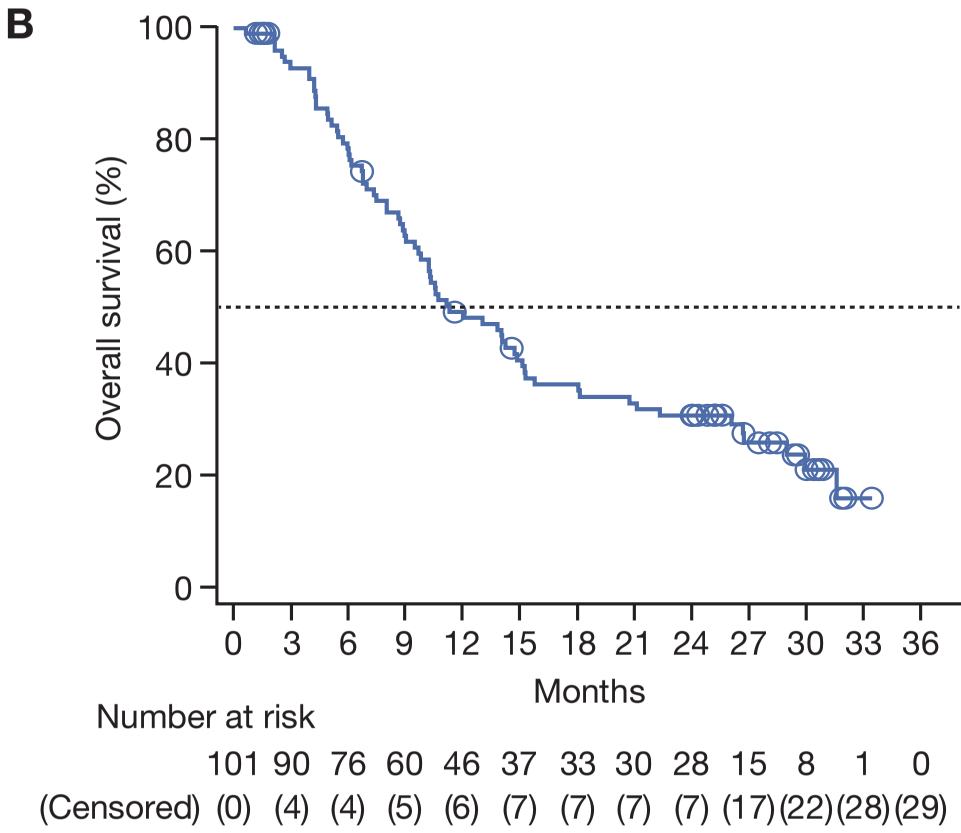

Grade ≥1
Grade ≥2
Grade ≥3
Event probability (%)
100
80
60
40
20
0
0
3
6
9
12
Months
Number at risk (censored)
Grade ≥1 101 (0) 67 (15) 41 (35) 26 (49) 19 (56)
Grade ≥2 101 (0) 74 (18) 47 (40) 29 (57) 19 (67)
Grade ≥3 101 (0) 80 (19) 53 (45) 30 (67) 20 (77)

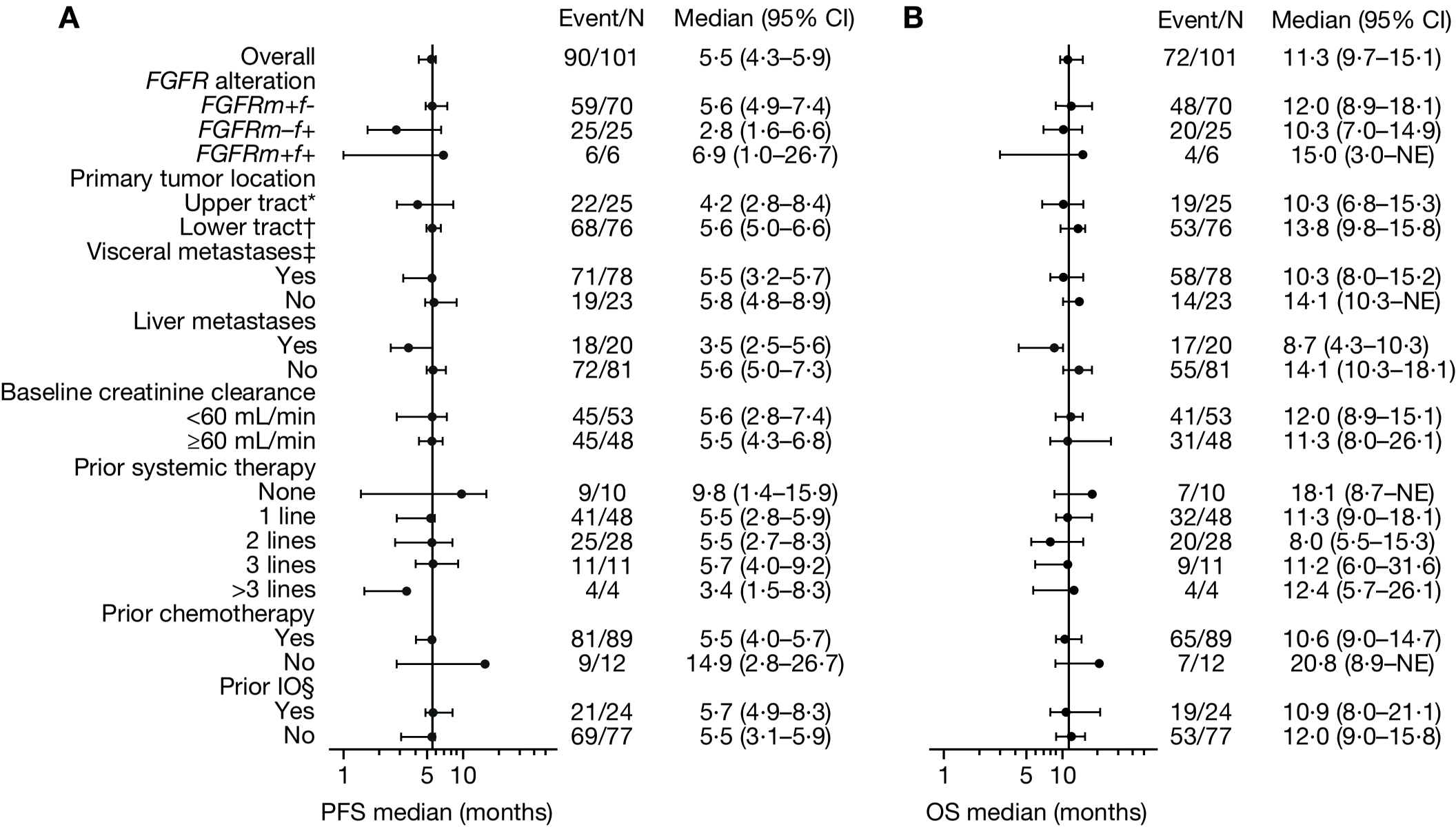
Supplementary File

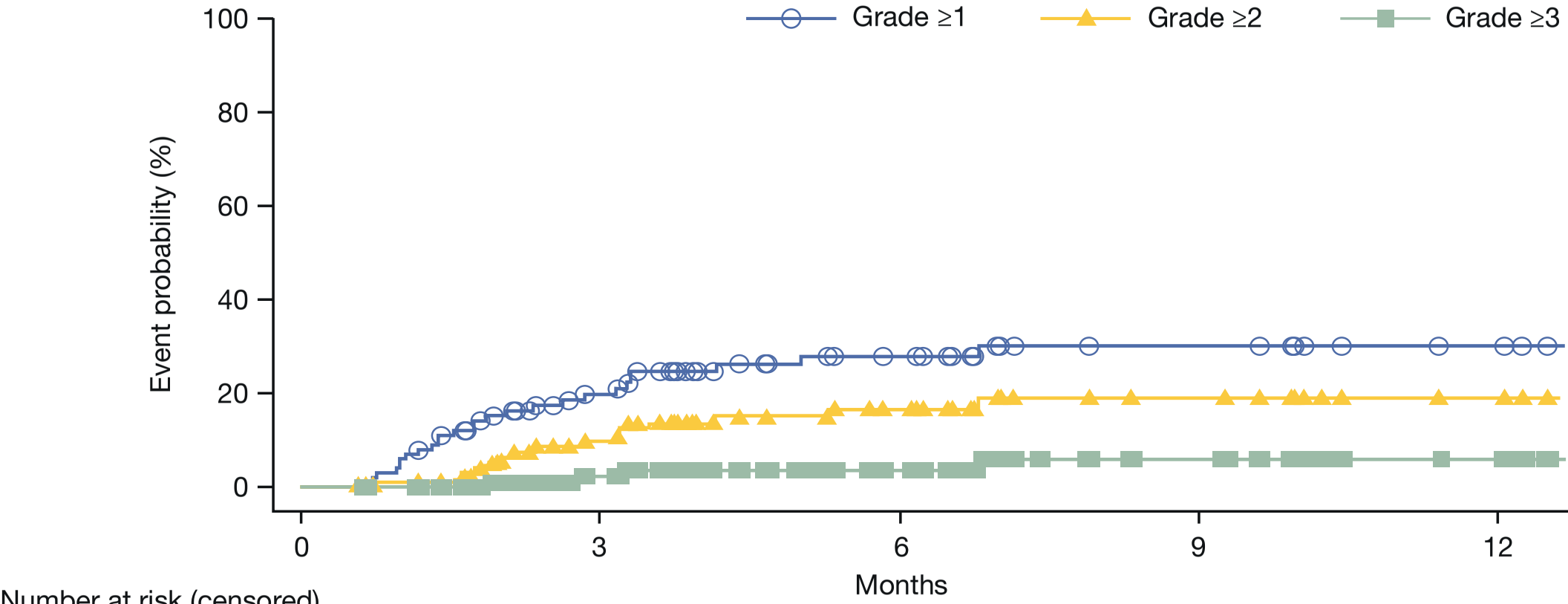
Figure 1


0
10
20
30
Months
Progressive disease
Stable disease
Partial response
Complete response
Uptitrated patient
Treatment discontinuation
Treatment ongoing
Best response
Progressive disease
Stable disease
Partial response
Complete response
Not evaluable


A
Progression-free survival (%)
100
80
60
40
20
0
0 3 6 9 12 15 18 21 24 27 30 33
Months
Number at risk
101 67 39 26 19 14 10 8 4 1 1 0
(Censored) (0) (2) (3) (3) (4) (4) (4) (5) (8) (10) (10) (11)


B
Overall survival (%)
100
80
60
40
20
0
0 3 6 9 12 15 18 21 24 27 30 33 36
Months
Number at risk
101 90 76 60 46 37 33 30 28 15 8 1 0
(Censored) (0) (4) (4) (5) (6) (7) (7) (7) (7) (17) (22) (28) (29)


A
Event/N
Median (95% CI)
Overall
90/101
5·5 (4·3–5·9)
FGFR alteration
FGFRm+f-
59/70
5·6 (4·9–7·4)
FGFRm–f+
25/25
2·8 (1·6–6·6)
FGFRm+f+
6/6
6·9 (1·0–26·7)
Primary tumor location
Upper tract*
22/25
4·2 (2·8–8·4)
Lower tract†
68/76
5·6 (5·0–6·6)
Visceral metastases‡
Yes
71/78
5·5 (3·2–5·7)
No
19/23
5·8 (4·8–8·9)
Liver metastases
Yes
18/20
3·5 (2·5–5·6)
No
72/81
5·6 (5·0–7·3)
Baseline creatinine clearance
<60 mL/min
45/53
5·6 (2·8–7·4)
≥60 mL/min
45/48
5·5 (4·3–6·8)
Prior systemic therapy
None
9/10
9·8 (1·4–15·9)
1 line
41/48
5·5 (2·8–5·9)
2 lines
25/28
5·5 (2·7–8·3)
3 lines
11/11
5·7 (4·0–9·2)
>3 lines
4/4
3·4 (1·5–8·3)
Prior chemotherapy
Yes
81/89
5·5 (4·0–5·7)
No
9/12
14·9 (2·8–26·7)
Prior IO§
Yes
21/24
5·7 (4·9–8·3)
No
69/77
5·5 (3·1–5·9)
1
5
10
PFS median (months)
B
Event/N
Median (95% CI)
72/101
11·3 (9·7–15·1)
48/70
12·0 (8·9–18·1)
20/25
10·3 (7·0–14·9)
4/6
15·0 (3·0–NE)
19/25
10·3 (6·8–15·3)
53/76
13·8 (9·8–15·8)
58/78
10·3 (8·0–15·2)
14/23
14·1 (10·3–NE)
17/20
8·7 (4·3–10·3)
55/81
14·1 (10·3–18·1)
41/53
12·0 (8·9–15·1)
31/48
11·3 (8·0–26·1)
7/10
18·1 (8·7–NE)
32/48
11·3 (9·0–18·1)
20/28
8·0 (5·5–15·3)
9/11
11·2 (6·0–31·6)
4/4
12·4 (5·7–26·1)
65/89
10·6 (9·0–14·7)
7/12
20·8 (8·9–NE)
19/24
10·9 (8·0–21·1)
53/77
12·0 (9·0–15·8)
1
5
10
OS median (months)



Number at risk (censored)

Grade ≥1	101 (0)	67 (15)	41 (35)	26 (49)	19 (56)
Grade ≥2	101 (0)	74 (18)	47 (40)	29 (57)	19 (67)
Grade ≥3	101 (0)	80 (19)	53 (45)	30 (67)	20 (77)