ORIGINAL ARTICLE

Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma

Y. Loriot, A. Necchi, S.H. Park, J. Garcia-Donas, R. Huddart, E. Burgess, M. Fleming, A. Rezazadeh, B. Mellado, S. Varlamov, M. Joshi, I. Duran, S.T. Tagawa, Y. Zakharia, B. Zhong, K. Stuyckens, A. Santiago-Walker, P. De Porre, A. O'Hagan, A. Avadhani, and A.O. Siefker-Radtke, for the BLC2001 Study Group*

ABSTRACT

BACKGROUND

Alterations in the gene encoding fibroblast growth factor receptor (*FGFR*) are common in urothelial carcinoma and may be associated with lower sensitivity to immune interventions. Erdafitinib, a tyrosine kinase inhibitor of FGFR1–4, has shown antitumor activity in preclinical models and in a phase 1 study involving patients with *FGFR* alterations.

METHODS

In this open-label, phase 2 study, we enrolled patients who had locally advanced and unresectable or metastatic urothelial carcinoma with prespecified *FGFR* alterations. All the patients had a history of disease progression during or after at least one course of chemotherapy or within 12 months after neoadjuvant or adjuvant chemotherapy. Prior immunotherapy was allowed. We initially randomly assigned the patients to receive erdafitinib in either an intermittent or a continuous regimen in the dose-selection phase of the study. On the basis of an interim analysis, the starting dose was set at 8 mg per day in a continuous regimen (selected-regimen group), with provision for a pharmacodynamically guided dose escalation to 9 mg. The primary end point was the objective response rate. Key secondary end points included progression-free survival, duration of response, and overall survival.

RESULTS

A total of 99 patients in the selected-regimen group received a median of five cycles of erdafitinib. Of these patients, 43% had received at least two previous courses of treatment, 79% had visceral metastases, and 53% had a creatinine clearance of less than 60 ml per minute. The rate of confirmed response to erdafitinib therapy was 40% (3% with a complete response and 37% with a partial response). Among the 22 patients who had undergone previous immunotherapy, the confirmed response rate was 59%. The median duration of progression-free survival was 5.5 months, and the median duration of overall survival was 13.8 months. Treatment-related adverse events of grade 3 or higher, which were managed mainly by dose adjustments, were reported in 46% of the patients; 13% of the patients discontinued treatment because of adverse events. There were no treatment-related deaths.

CONCLUSIONS

The use of erdafitinib was associated with an objective tumor response in 40% of previously treated patients who had locally advanced and unresectable or metastatic urothelial carcinoma with *FGFR* alterations. Treatment-related grade 3 or higher adverse events were reported in nearly half the patients. (Funded by Janssen Research and Development; BLC2001 ClinicalTrials.gov number, NCT02365597.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Siefker-Radtke at the University of Texas M.D. Anderson Cancer Center, 1155 Pressler St., Unit 1374, Houston, TX 77030, or at asiefker@mdanderson.org.

*A list of investigators in the BLC2001 study is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2019;381:338-48.
DOI: 10.1056/NEJMoa1817323

Historically, treatment for patients with locally advanced and unresectable or metastatic urothelial carcinoma with second-line, single-agent chemotherapy with taxanes or vinflunine has resulted in an objective response rate of approximately 10% and a median overall survival of 7 to 9 months.[1-3] New agents such as the immune checkpoint inhibitors provide clinical benefit in some patients, with response rates of 13 to 21%[4-8] and improved survival (10.3 months) in one study.[5]

Gene-expression profiling suggests that urothelial carcinoma can be classified into several different subtypes,[9,10] which have distinct prognoses and benefit differently from chemotherapy[11] or immunotherapy.[8,12] The luminal I subtype, which has been associated with a poor response to immune checkpoint inhibitors,[8,12] has shown a relatively lower immune signature (the pattern of gene expression associated with immune response) and lower expression of programmed death ligand 1 (PD-L1) on tumor and infiltrating immune cells[13,14] than other subtypes and has a higher percentage of mutations in the gene encoding fibroblast growth factor receptor (*FGFR*).[13]

FGFRs induce signaling through networks that regulate cell proliferation, survival, migration, and differentiation.[15] Mutations and fusions in *FGFR2|3* are common in patients with urothelial carcinoma, particularly in the luminal I subtype, and can cause constitutive FGFR signaling that may contribute to carcinogenesis.[15] As many as 20% of patients with advanced urothelial carcinoma have *FGFR* alterations,[16] and such mutations are even more frequent (37%) in patients with upper tract urothelial carcinoma.[17] Thus, FGFR inhibition may be particularly appropriate in patients with luminal I subtype disease, in which immunotherapeutic approaches may be less effective.

Erdafitinib (JNJ-42756493), which was discovered by Janssen in collaboration with Astex Pharmaceuticals, is a potent tyrosine kinase inhibitor of FGFR1–4. The drug has shown antitumor activity in preclinical models of different solid tumors[18] and in a phase 1 study involving patients with urothelial carcinoma and other tumor types with *FGFR* alterations.[19-22] We initiated an uncontrolled, multicenter, open-label, phase 2 study (BLC2001) to assess the response in patients with locally advanced and unresectable or metastatic urothelial carcinoma with *FGFR* alterations.

METHODS

STUDY DESIGN AND OVERSIGHT

This ongoing study that included 126 sites in 14 countries was designed by the sponsor, Janssen Research and Development, with input from the first and last authors. Review boards at all participating institutions approved the study, which is being conducted in accordance with current Good Clinical Practice guidelines of the International Conference on Harmonisation, applicable regulatory and country-specific requirements, and the principles of the Declaration of Helsinki. All the patients have provided written informed consent.

A data review committee was commissioned by the sponsor to conduct interim analyses, monitor safety, review efficacy, and make recommendations regarding study conduct. Data for this report were transcribed by study personnel at each site from source documents into sponsor-prepared electronic case-report forms. All the authors assume responsibility for the completeness and accuracy of the data and for the fidelity of the study to the protocol (available with the full text of this article at NEJM.org). The first and last authors developed the first draft of the manuscript with editorial assistance funded by the sponsor. All the authors had full access to and participated in the interpretation of the data and reviewed and approved the manuscript before submission for publication.

PATIENTS

All the patients who were enrolled in the study had locally advanced and unresectable or metastatic urothelial carcinoma with measurable disease, according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.[23] The patients were required to have at least one *FGFR3* mutation or *FGFR2|3* fusion, as listed in a prespecified panel, according to the results of testing in a central laboratory. There was no specific selection of patients with any particular fusion or mutation on the list. We assessed RNA from formalin-fixed, paraffin-embedded tumor samples using a custom reverse-transcriptase–polymerase-chain-reaction assay, which is being developed as a companion diagnostic test (Qiagen).

Patients were also required to have a history of disease progression during or after at least one course of previous systemic chemotherapy or within 12 months after receiving neoadjuvant

or adjuvant chemotherapy. Patients who had received no previous chemotherapy could participate if they were ineligible to receive cisplatin, according to protocol criteria of the presence of a glomerular filtration rate of less than 60 ml per minute per 1.73 m^2 of body-surface area during 24-hour urine measurement or as calculated by the Cockcroft–Gault equation or the presence of peripheral neuropathy of grade 2 or higher, according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. All the patients were required to have a performance-status score of 2 or less on the Eastern Cooperative Oncology Group (ECOG) scale, which ranges from 0 (no disability) to 5 (death). There was no limit on the number of previous courses of treatment or on the previous receipt of immunotherapy (e.g., treatment with an immune checkpoint inhibitor).

Patients were required to have adequate bone marrow, liver, and kidney function (creatinine clearance, ≥40 ml per minute). Patients with phosphate levels persistently above the upper limit of the normal range despite medical management, uncontrolled cardiovascular disease, brain metastases, known hepatitis B or C infection, or known infection with the human immunodeficiency virus were excluded.

TREATMENT

At the time of study initiation, we randomly assigned patients in a 1:1 ratio to receive 28-day cycles of oral erdafitinib according to either an intermittent regimen (10 mg per day, with daily administration for 7 days and off for 7 days) or a continuous regimen (6 mg per day) until a regimen could be selected for further study (dose-selection phase) (Fig. S1 in the Supplementary Appendix, available at NEJM.org). Randomization was stratified according to the ECOG performance-status score (0 or 1 vs. 2), hemoglobin value (<10 g per deciliter vs. ≥10 g per deciliter), *FGFR* alteration type (mutation vs. fusion), previous treatment status (chemotherapy resistance vs. no previous chemotherapy), and disease distribution (presence vs. absence of liver, lung, or bone metastases). The selection of the starting dose was based on the efficacy and profile of treatment-related adverse events in a phase 1 study (see the Background section in the Supplementary Appendix).

A planned interim analysis of safety and efficacy was performed in June and July 2016. On the basis of observed data at that time and on pharmacokinetic and pharmacodynamic modeling of serum phosphate levels (a biomarker of FGFR inhibition), further enrollment to the intermittent-regimen group was halted. On August 9, 2016, the protocol was amended to increase the starting dose to 8 mg per day in a continuous regimen, thereby converting the study to a single-group analysis. The amendment further specified that on day 14, in patients with no adverse events that were considered by the investigator to be related to treatment, the daily dose of erdafitinib could be escalated to 9 mg with the use of a pharmacodynamically guided approach if the patients had not reached the target phosphate level of 5.5 mg per deciliter (1.8 mmol per liter), a level that had been associated with an improved response rate in the phase 1 study (see the Background section in the Supplementary Appendix). The patients continued to receive 8 mg once daily if their serum phosphate levels on day 14 were within the target range of 5.5 to less than 7.0 mg per deciliter (2.3 mmol per liter).

The treatment with erdafitinib continued until disease progression or unacceptable adverse events, as determined by the investigator. Patients who had investigator-assessed disease progression could continue to receive erdafitinib at the discretion of the investigator and the sponsor. Prophylactic measures to prevent adverse events are described in the Methods section in the Supplementary Appendix.

ASSESSMENTS

We used RECIST to assess patients for efficacy using computed tomography or magnetic resonance imaging of the chest, abdomen, and pelvis once every 6 weeks for the first 3 months, once every 12 weeks for the next 9 months, and then once every 4 to 6 months until disease progression. All objective responses required confirmation by an additional scan within 4 to 6 weeks after the first assessment. All disease evaluations in the selected-regimen group were also evaluated by an independent radiologic review committee. Patients were contacted every 12 weeks for survival assessment.

We evaluated safety using the results of clinical laboratory testing, physical examination, electrocardiography, and ophthalmologic examination. Adverse events and abnormalities were assessed by the investigators and graded according to the National Cancer Institute criteria.

END POINTS

The primary end point was the confirmed response rate among patients treated with the selected regimen. Secondary end points were progression-free survival, response duration, overall survival, safety, response rate in biomarker-specific subgroups, and pharmacokinetics. (Details regarding secondary end points are provided in the Methods section in the Supplementary Appendix.)

STATISTICAL ANALYSIS

The study was designed to enroll approximately 180 patients with prespecified *FGFR* alterations. Of these patients, at least 88 were required to receive the selected regimen. The primary hypothesis was that the objective response rate to a daily regimen of 8 mg or 9 mg of erdafitinib would be more than 25%. 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%. We used the Kaplan–Meier method to estimate progression-free survival and overall survival. Data for patients who were progression-free and alive or with unknown status were censored at the time of the last tumor assessment. Efficacy end points were analyzed at the cutoff date for the primary analysis.

RESULTS

PATIENTS

Between May 25, 2015, and March 15, 2018, we assessed 2214 patients for eligibility (Fig. S1 in the Supplementary Appendix). Of 210 eligible patients, 33 were randomly assigned to the intermittent regimen and 78 to the continuous regimen. After amendment of the protocol on August 9, 2016, we assigned 99 patients to the selected-regimen group.

On March 15, 2018 (the cutoff date for the primary analysis), and after 40 deaths, the median follow-up duration for survival was 11.0 months (interquartile range, 0.7 to 17.4; 95% confidence interval [CI], 9.1 to 12.2) among the patients in the selected-regimen group. The median number of monthly cycles of erdafitinib was 5 (range, 1 to 18); the median treatment duration was 5.3 months. Of the 99 patients, 41 had an escalation in the daily dose of erdafitinib to 9 mg; 13 patients continued treatment for at least 4 weeks after disease progression, according to the protocol.

Table 1. Demographic and Clinical Characteristics of the 99 Patients in the Selected-Regimen Group at Baseline.*

Characteristic	Value
Age — yr	
Median	68
Range	36–87
ECOG performance-status score — no. (%)†	
0	50 (51)
1	42 (42)
2	7 (7)
Treatment history — no. (%)	
Progression or relapse after chemotherapy	87 (88)
No previous chemotherapy	12 (12)
Progression or relapse after immunotherapy	22 (22)
No. of previous treatments — no. (%)	
0	11 (11)
1	45 (45)
≥2	43 (43)
Visceral metastasis — no. (%)	
Present‡	78 (79)
Absent	21 (21)
Creatinine clearance rate — no. (%)	
<60 ml/min	52 (53)
≥60 ml/min	47 (47)

* The patients in the selected-regimen group received continuous daily treatment with 8 mg or 9 mg of erdafitinib until disease progression or unacceptable adverse events, as determined by the investigator. Percentages may not total 100 because of rounding.

† Scores on the Eastern Cooperative Oncology Group (ECOG) scale range from 0 (no disability) to 5 (death).

‡ Patients could have more than one site of visceral metastasis.

The demographic and clinical characteristics of the patients at baseline in the selected-regimen group are listed in Table 1, and in Table S1 in the Supplementary Appendix. The baseline characteristics of the patients who were treated during the randomized phase of the study are listed in Table S2 and the Results section in the Supplementary Appendix.

Across all regimens, 184 patients had previously received first-line platinum-based chemotherapy, 83 had received second-line chemotherapy, and 24 had received third-line chemotherapy before study enrollment. Across all regimens, the best response rates according to investigators' assessments were 35% (33 of 94 patients) among those who had received first-line gemcitabine plus cisplatin; 25% (15 of 59 patients) among those who had received first-line gemcitabine plus carboplatin; 23% (5 of 22 patients)

among those who had received first-line methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC); 17% (8 of 46 patients) among those who had received second-line docetaxel, vinflunine, or paclitaxel; and 15% (3 of 20 patients) among those who had received third-line docetaxel, vinflunine, or paclitaxel.

PRIMARY END POINT

In the selected-regimen group, the confirmed response rate was 40% (95% CI, 31 to 50), according to investigator assessment; the median time until the first assessment of a confirmed response was 1.4 months (Table 2). Because the lower boundary of the confidence interval was more than 25%, the primary end point was achieved. An additional 39 patients (39%) had stable disease in at least one disease evaluation (>36 days). Two patients did not undergo any disease evaluation after baseline.

Response rates were similar regardless of previous chemotherapy, the number of previous courses of treatment, the presence of visceral metastasis, or baseline characteristics such as age, sex, hemoglobin level, or renal function (Table 2 and Fig. 1A). Of the 97 patients who underwent at least one disease evaluation after baseline, 75 (77%) had a reduction in the sum of target-lesion diameters, and 48 (49%) had a maximum tumor reduction of 30 to 100% (Fig. S2 in the Supplementary Appendix). The response rate according to independent radiologic review was 34% (95% CI, 25 to 44), which resulted in a relative discordance rate of 16% in the primary efficacy population. Response rates among the patients who received the randomized intermittent and continuous regimens are listed in Table S3 in the Supplementary Appendix.

The response rate among the 74 patients with *FGFR* mutations in the selected-regimen group was 49% (Table 2). An additional 26 patients with *FGFR* mutations had stable disease for a median of 3.7 months (range, 0 to 13.6). Responses were not affected by the presence of a particular mutation. Among the 25 patients with *FGFR* fusions, the response rate was 16%. The most common fusion was *FGFR3:TACC3v1*, which was found in 11 patients (Table S1 in the Supplementary Appendix); of these patients, 4 (36%) had a response to treatment.

A total of 22 patients in the selected-regimen group had received immunotherapy before study enrollment (Table 1); among these patients, the confirmed response rate to erdafitinib was 59%. An exploratory analysis determined that only 1 of the 22 patients (5%) had a history of response to previous immunotherapy, according to investigators' assessments.

SECONDARY END POINTS

Among the 99 patients in the selected-regimen group, the median duration of response was 5.6 months (95% CI, 4.2 to 7.2) (Table 2). Approximately 30% of these responses were maintained for more than 12 months (Fig. 1B). Among the 39 patients with stable disease, 13 (33%) had disease stabilization that lasted for more than 6 months (Fig. S3 in the Supplementary Appendix). At the time of data cutoff, 21% of the patients were continuing to receive erdafitinib. Response durations for patients in the two randomized dose-investigation groups are provided in Table S3 in the Supplementary Appendix.

At a median follow-up of 11.2 months, the median duration of progression-free survival according to investigators' assessments was 5.5 months (95% CI, 4.2 to 6.0) (Fig. 2A). At 12 months, the rate of progression-free survival was 19% (95% CI, 11 to 29). At a median follow-up of 11.0 months, the median duration of overall survival was 13.8 months (95% CI, 9.8 to not reached) (Fig. 2B). At 12 months, the rate of overall survival was 55% (95% CI, 43 to 66). The rates of progression-free survival and overall survival among patients in the randomized regimen groups are provided in Figure S4 and the Results section in the Supplementary Appendix.

Subsequent therapy was administered to 34 patients, of whom 25% received one subsequent course of treatment and 9% received two subsequent courses; 19 patients received chemotherapy, and 15 received immunotherapy as a first subsequent therapy. No patient had an objective response to the first subsequent course of chemotherapy; 1 patient had a partial response to the first subsequent course of immunotherapy.

SAFETY

All 99 patients in the selected-regimen group reported having an adverse event of any cause during treatment, as determined by investigators (Table 3). A total of 67% of such events were of grade 3 or 4; 46% of the patients reported having an adverse event of grade 3 or higher that was considered by investigators to be related to treatment (Table S6 in the Supplementary Ap-

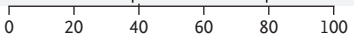
Table 2. Antitumor Activity of Erdafitinib in the 99 Patients in the Selected-Regimen Group.*

Variable	Value	Rate of Response (95% CI)
		percent
Response per investigator assessment — no. of patients†		
Any objective response	40	40 (31–50)
Complete response	3	3
Partial response	37	37
Stable disease	39	39
Progressive disease	18	18
Could not be evaluated or unknown	2	2
Median time to response — mo	1.4	
Median duration of response (95% CI) — mo	5.6 (4.2–7.2)	
Response per independent radiologic assessment — no. of patients†		
Objective response	34	34 (25–44)
Complete response	3	3
Partial response	31	31
Response according to previous treatment — no./total no.		
No chemotherapy	5/12	42
Progression or relapse after chemotherapy	35/87	40
Immunotherapy	13/22	59
Response according to number of previous systemic treatments — no./total no.		
0	4/11	36 (8–65)
1	17/45	38 (24–52)
2	11/29	38 (20–56)
3	6/10	60 (30–90)
≥4	2/4	50 (1–99)
Response according to presence or absence of visceral metastasis — no./total no.		
Present	30/78	38 (28–49)
Bone	10/21	48 (26–69)
Liver	7/20	35 (14–56)
Lung	23/57	40 (28–53)
Lymph node only	4/12	33 (7–60)
Upper tract disease‡	10/23	43 (23–64)
Lower tract disease§	30/76	39 (29–51)
Absent	10/21	48 (26–69)
Response according to daily dose of erdafitinib — no./total no.		
8 mg	20/58	34 (22–47)
8 mg with dose escalation to 9 mg	20/41	49 (34–64)
Response according to genetic alteration — no./total no.		
FGFR3 mutation	36/74	49 (37–60)
FGFR2/3 fusion	4/25	16 (2–30)

* FGFR denotes fibroblast growth factor receptor.
† The response in this category was confirmed on repeat imaging within 6 weeks after the initial observation of response.
‡ Upper tract disease occurred in the renal pelvis or ureter.
§ Lower tract disease occurred in the bladder, urethra, or prostatic urethra.

A Complete or Partial Response

Subgroup	Patients with Response (no./total no.)	Objective Response Rate (95% CI)
All patients	40/99	40 (31–50)
Age		
<65 yr	14/38	37 (22–52)
≥65 yr	26/61	43 (30–55)
<75 yr	32/83	39 (28–49)
≥75 yr	8/16	50 (26–75)
Sex		
Male	30/76	39 (29–51)
Female	10/23	43 (23–64)
Race		
White	31/74	42 (31–53)
Other	3/8	38 (4–71)
Geographic region		
United States	11/21	52 (31–74)
Other	29/78	37 (27–48)
Baseline ECOG score		
0 or 1	39/92	42 (32–53)
2	1/7	14 (0–40)
Baseline hemoglobin level		
<10 g/dl	8/15	53 (28–79)
≥10 g/dl	32/84	38 (28–49)
Baseline creatinine clearance		
<60 ml/min	20/52	38 (25–52)
≥60 ml/min	20/47	43 (28–57)
Previous systemic therapy		
None	4/11	36 (8–65)
1 Line	17/45	38 (24–52)
≥2 Lines	19/43	44 (29–59)
Immunotherapy	13/22	59 (39–80)



B Duration and Type of Response

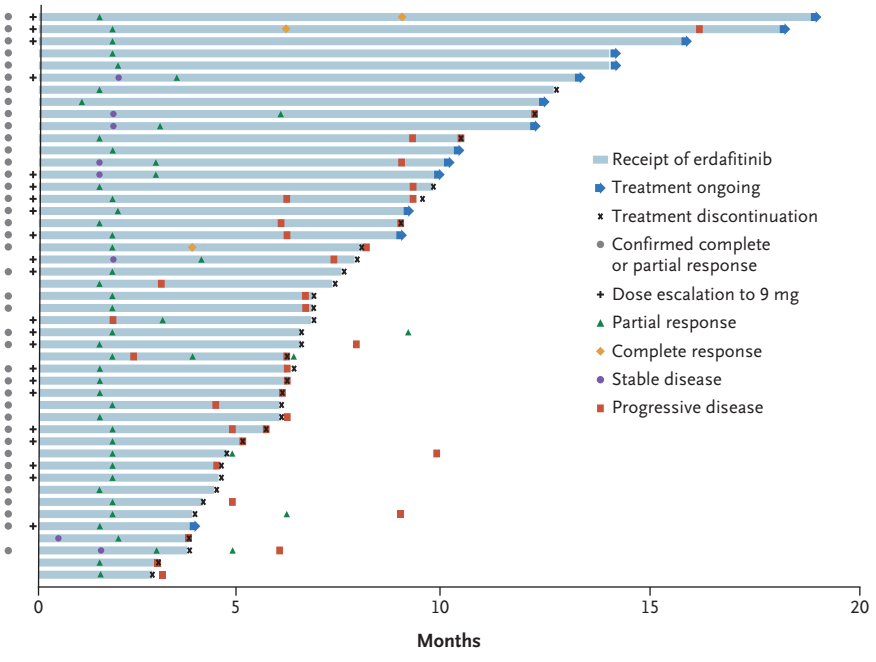
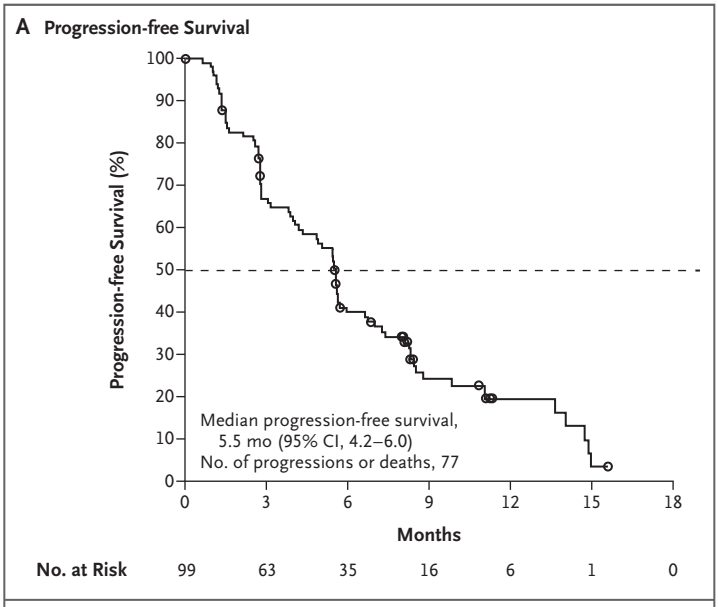


Figure 1 (facing page). Response to Treatment, According to Subgroup.

Panel A shows the rate of complete or partial response to continuous daily treatment with erdafitinib among patients in the selected-regimen group, according to subgroup. The safety profile allowed for a dose escalation from 8 mg to 9 mg of erdafitinib per day in 41 of the 99 patients who met target levels for serum phosphate. Panel B shows the duration and type of response in 47 patients, of whom 40 had a confirmed response (the primary end point) and 7 had an unconfirmed response. All objective responses required confirmation by an additional scan within 6 weeks after the first assessment. Race was reported by the patients. Scores on the Eastern Cooperative Oncology Group (ECOG) scale range from 0 (no disability) to 5 (death).

pendix). Common adverse events of grade 3 or higher were hyponatremia (11%), stomatitis (10%), and asthenia (7%). Serious adverse events were reported in 39 patients (Table S4 in the Supplementary Appendix). Disease progression was the most common reason for treatment discontinuation, which occurred in 62 patients (Fig. S1 in the Supplementary Appendix). Thirteen patients discontinued treatment because of adverse events, including detachment of the retinal pigment epithelium, hand–foot syndrome, dry mouth, and skin or nail events (in 2 patients each). A dose reduction was required in 55 patients. The most common adverse events leading to a dose reduction were stomatitis in 16 patients and hyperphosphatemia in 9 patients.

Among the 41 patients who had a dose escalation to 9 mg of erdafitinib per day, 24 (59%) required at least one dose reduction. The percentage of patients in the 9-mg group who had an adverse event of grade 3 or higher was similar to the percentage who had such an event in the overall population (68% and 66%, respectively). Common adverse events were similar among all the regimens (Tables S5, S6, and S7 in the Supplementary Appendix). One patient died from a myocardial infarction that was considered to be unrelated to treatment. Adverse events of special interest or clinical importance and their management are presented in Table S8 and the Results section in the Supplementary Appendix. Among the patients with central serous retinopathy events, 76% of the events resolved with a dose interruption or reduction or with the administration of a concomitant medication; all unresolved events were of grade 1 or 2.



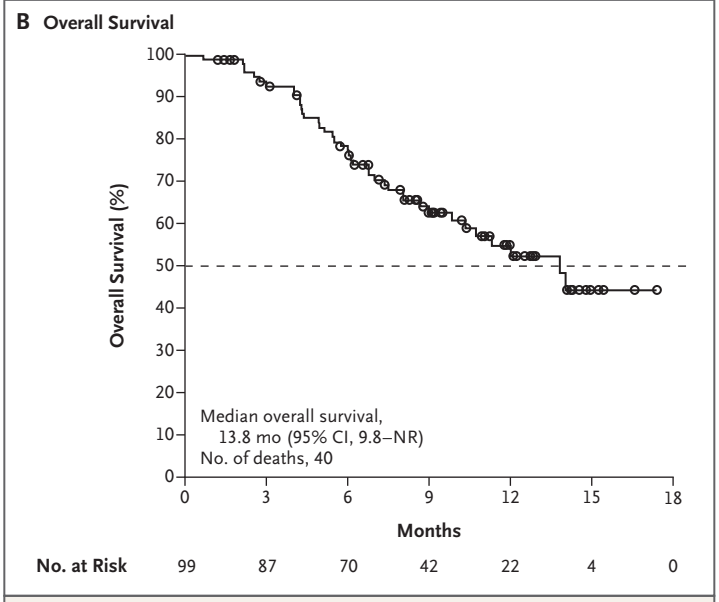


Figure 2. Progression-free Survival and Overall Survival.

Shown are Kaplan–Meier curves of progression-free survival (Panel A) and overall survival (Panel B) after continuous daily treatment with erdafitinib in the selected-regimen group. The dashed horizontal line indicates the median duration. NR denotes not reached.

DISCUSSION

This study met its primary objective, with a 40% confirmed response rate after continuous daily treatment with 8 mg or 9 mg of oral erdafitinib. These findings showed that among patients with locally advanced and unresectable or metastatic urothelial carcinoma with certain *FGFR*

Table 3. Adverse Events in the 99 Patients in the Selected-Regimen Group.*

Adverse Event	Any Grade	Grade 1	Grade 2	Grade ≥3
		number of patients (percent)		
Hyperphosphatemia	76 (77)	53 (54)	21 (21)	2 (2)
Stomatitis	57 (58)	21 (21)	26 (26)	10 (10)
Diarrhea	50 (51)	31 (31)	15 (15)	4 (4)
Dry mouth	45 (46)	34 (34)	11 (11)	0
Decreased appetite	38 (38)	18 (18)	20 (20)	0
Dysgeusia	37 (37)	23 (23)	13 (13)	1 (1)
Fatigue	32 (32)	12 (12)	18 (18)	2 (2)
Dry skin	32 (32)	24 (24)	8 (8)	0
Alopecia	29 (29)	23 (23)	6 (6)	0
Constipation	28 (28)	19 (19)	8 (8)	1 (1)
Hand–foot syndrome	23 (23)	6 (6)	12 (12)	5 (5)
Anemia	20 (20)	9 (9)	7 (7)	4 (4)
Asthenia	20 (20)	2 (2)	11 (11)	7 (7)
Nausea	20 (20)	13 (13)	6 (6)	1 (1)
Dry eye	19 (19)	14 (14)	4 (4)	1 (1)
Onycholysis	18 (18)	6 (6)	10 (10)	2 (2)
Alanine aminotransferase increased	17 (17)	13 (13)	2 (2)	2 (2)
Paronychia	17 (17)	3 (3)	11 (11)	3 (3)
Blurred vision	17 (17)	10 (10)	7 (7)	0
Nail dystrophy	16 (16)	5 (5)	5 (5)	6 (6)
Urinary tract infection	16 (16)	0	11 (11)	5 (5)
Vomiting	13 (13)	10 (10)	1 (1)	2 (2)
Hyponatremia	12 (12)	1 (1)	0	11 (11)
Hematuria	10 (10)	7 (7)	1 (1)	2 (2)
Dyspnea	8 (8)	4 (4)	2 (2)	2 (2)
Nail disorder	8 (8)	4 (4)	1 (1)	3 (3)
Acute kidney injury	6 (6)	2 (2)	2 (2)	2 (2)
Cataract	6 (6)	3 (3)	1 (1)	2 (2)
Colitis	5 (5)	1 (1)	2 (2)	2 (2)
General deterioration in physical health	5 (5)	0	1 (1)	4 (4)
Keratitis	5 (5)	0	2 (2)	3 (3)
Aphthous ulcer	4 (4)	2 (2)	0	2 (2)
Increase in γ-glutamyltransferase	3 (3)	1 (1)	0	2 (2)
Urosepsis	3 (3)	0	0	3 (3)

* Listed are all adverse events of any cause that were reported in more than 15% of the patients, along with adverse events of grade 3 or higher that were reported in more than 1 patient. Serious adverse events are reported in Table S4 in the Supplementary Appendix.

alterations, erdafitinib had promising antitumor activity. The response to erdafitinib was rapid and independent of the number of previous courses and types of therapy, the presence of visceral metastasis, or tumor location.

Among the patients in the selected-regimen group, the median duration of progression-free survival was 5.5 months and the median duration of overall survival was 13.8 months. Included in this analysis were patients with visceral metastasis and poor kidney function in whom multiple courses of therapy had failed. As allowed in

the protocol, 13 patients continued to receive treatment after disease progression, which included limited progression in a target lesion or the appearance of a small new lesion while the patient was assessed as having ongoing clinical benefit. The safety profile allowed for the continuous daily administration of 8 mg of erdafitinib, with a dose escalation to 9 mg daily guided by the serum phosphate level. Such dose escalation did not increase the severity of adverse events, with a similar percentage of events of grade 3 or higher in the two dose groups. Hyperphosphatemia, a known class effect of FGFR inhibitors,[24] was reported in 77% of the patients. The frequency of hyperphosphatemia decreased during the course of treatment without long-term sequelae, a reduction that may have been the result of compensatory mechanisms of phosphorus homeostasis. Ocular events including central serous retinopathy are known class effects of inhibitors of the mitogen-activated protein kinase pathway.[24-26] Although ocular adverse events were common with erdafitinib treatment, the events were mostly mild to moderate and resolved with dose interruption or reduction.

Patients with *FGFR* mutations or fusions may be less likely to have a response to immunotherapy than are those without such alterations. In our study, only 1 of 22 patients (5%) had a history of response to previous immunotherapy; of these patients, 59% had a response to erdafitinib after failure of immunotherapy. This observation was also noted in a study of rogaratinib involving 10 patients, in whom 90% had a history of disease progression while receiving immunotherapy, whereas 30% had a response to rogaratinib.[27]

The 40% response rate to erdafitinib compares favorably with data from phase 1 and 2 studies of other FGFR inhibitors (which reported response rates of 0 to 25%[27-30]), phase 1 to 3 studies of immune checkpoint inhibitors (response rates of 13 to 21%[4-8]), phase 1 and 1–2 studies of antibody–drug conjugates such as enfortumab vedotin or sacituzumab govitecan (response rates of 33 to 34%[31,32]), and historical data regarding chemotherapy (response rates of approximately 10%[1-3]). Among the patients receiving erdafitinib, the median survival durations and the 12-month survival rate (55%) also compared favorably with those associated with pembrolizumab (progression-free survival, 2.1 months; overall survival, 10.3 months; and 12-month survival, 44%)[5] and atezolizumab (2.1 months, 11.1 months, and 46%, respectively).[6] The median duration of overall survival was similar to that in phase 1 and 1–2 studies after treatment with enfortumab vedotin and sacituzumab govitecan (12.5 months and 15.5 months, respectively).[31,32]

In conclusion, our findings indicate that the pan-FGFR inhibitor erdafitinib had measurable benefit in patients with advanced urothelial carcinoma with *FGFR* alterations.

Supported by Janssen Research and Development. Funding for editorial assistance with an earlier version of the manuscript was provided by Janssen Global Services.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients who volunteered to participate in this study and the investigators and staff members who cared for them; Anne-Gaelle Dosne, Ph.D., of Janssen Research and Development for analyses of the pharmacokinetics and pharmacodynamics of erdafitinib that contributed to the dose regimen selection; and Tamara Fink, Ph.D., of Parexel, for providing editorial assistance.

APPENDIX

The authors' full names and academic degrees are as follows: Yohann Loriot, M.D., Andrea Necchi, M.D., Se Hoon Park, M.D., Jesus Garcia-Donas, M.D., Robert Huddart, M.C.R.P., Earle Burgess, M.D., Mark Fleming, M.D., Arash Rezazadeh, M.D., Begoña Mellado, M.D., Sergey Varlamov, M.D., Monika Joshi, M.D., Ignacio Duran, M.D., Scott T. Tagawa, M.D., Yousef Zakharia, M.D., Bob Zhong, Ph.D., Kim Stuyckens, M.Sc., Ademi Santiago-Walker, Ph.D., Peter De Porre, M.D., Anne O'Hagan, M.P.H., Anjali Avadhani, M.D., and Arlene O. Siefker-Radtke, M.D.

The authors' affiliations are as follows: Gustave Roussy, INSERM Unité 981, Université Paris-Sud, Université Paris-Saclay, Villejuif, France (Y.L.); Fondazione IRCCS Istituto Nazionale dei Tumori, Milan (A.N.); Sungkyunkwan University Samsung Medical Center, Seoul, South Korea (S.H.P.); Genitourinary and Gynecological Cancer Unit, Centro Integral Oncológico Clara Campal, Madrid (J.G.-D.), Hospital Clinic Institut d'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Barcelona (B.M.), and Hospital Universitario Marques de Valdecilla, Santander (I.D.) — all in Spain; the Institute of Cancer Research, Sutton, London (R.H.); the Levine Cancer Institute, Atrium Health, Charlotte, NC (E.B.); Virginia Oncology Associates, US Oncology Research, Norfolk (M.F.); Norton Healthcare, Louisville, KY (A.R.); the Altai Regional Cancer Center, Barnaul, Russia (S.V.); the Penn State Cancer Institute, Hershey (M.J.), and Janssen Research and Development, Spring House (B.Z., A.S.-W., A.O., A.A.) — both in Pennsylvania; Weill Cornell Medical College, New York (S.T.T.); University of Iowa Hospitals and Clinics, Holden Comprehensive Cancer Center, Iowa City (Y.Z.); Janssen Research and Development, Beerse, Belgium (K.S., P.D.P.); and the University of Texas M.D. Anderson Cancer Center, Houston (A.O.S.-R.).

REFERENCES

1. Bellmunt J, Théodore C, Demkov T, et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. J Clin Oncol 2009;27:4454-61.
2. McCaffrey JA, Hilton S, Mazumdar M, et al. Phase II trial of docetaxel in patients with advanced or metastatic transitional-cell carcinoma. J Clin Oncol 1997;15:1853-7.
3. Vaughn DJ, Broome CM, Hussain M, Gutheil JC, Markowitz AB. Phase II trial of weekly paclitaxel in patients with previously treated advanced urothelial cancer. J Clin Oncol 2002;20:937-40.
4. Apolo AB, Infante JR, Balmanoukian A, et al. Avelumab, an anti-programmed death-ligand 1 antibody, in patients with refractory metastatic urothelial carcinoma: results from a multicenter, phase Ib study. J Clin Oncol 2017;35:2117-24.
5. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 2017;376:1015-26.
6. Powles T, Durán I, van der Heijden MS, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2018;391:748-57.
7. Powles T, O'Donnell PH, Massard C, et al. Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma: updated results from a phase 1/2 open-label study. JAMA Oncol 2017;3(9):e172411.
8. Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. Lancet Oncol 2017;18:312-22.
9. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of urothelial bladder carcinoma. Nature 2014;507:315-22.
10. Robertson AG, Kim J, Al-Ahmadie H, et al. Comprehensive molecular characterization of muscle-invasive bladder cancer. Cell 2017;171(3):540-556.e25.
11. McConkey DJ, Choi W, Shen Y, et al. A prognostic gene expression signature in the molecular classification of chemotherapy-naive urothelial cancer is predictive of clinical outcomes from neoadjuvant chemotherapy: a phase 2 trial of dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin with bevacizumab in urothelial cancer. Eur Urol 2016;69:855-62.
12. Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016;387:1909-20.
13. McConkey DJ, Choi W, Ochoa A, Siefker-Radtke A, Czerniak B, Dinney CP. Therapeutic opportunities in the intrinsic subtypes of muscle-invasive bladder cancer. Hematol Oncol Clin North Am 2015;29:377-94.
14. Siefker-Radtke A, Curti B. Immunotherapy in metastatic urothelial carcinoma: focus on immune checkpoint inhibition. Nat Rev Urol 2018;15:112-24.
15. Haugsten EM, Wiedlocha A, Olsnes S, Wesche J. Roles of fibroblast growth factor receptors in carcinogenesis. Mol Cancer Res 2010;8:1439-52.
16. Knowles MA, Hurst CD. Molecular biology of bladder cancer: new insights into pathogenesis and clinical diversity. Nat Rev Cancer 2015;15:25-41.
17. Li Q, Bagrodia A, Cha EK, Coleman JA. Prognostic genetic signatures in upper tract urothelial carcinoma. Curr Urol Rep 2016;17:12.
18. Perera TPS, Jovcheva E, Mevellec L, et al. Discovery and pharmacological characterization of JNJ-42756493 (erdafitinib), a functionally selective small-molecule FGFR family inhibitor. Mol Cancer Ther 2017;16:1010-20.
19. Soria J, Italiano A, Cervantes A, et al. Safety and activity of the pan-fibroblast growth factor receptor (FGFR) inhibitor erdafitinib in phase 1 study patients with advanced urothelial carcinoma. Presented at the European Society for Medical Oncology (ESMO) 2016 Congress, Copenhagen, October 7–11, 2016. abstract.
20. Tabernero J, Bahleda R, Dienstmann R, et al. Phase I dose-escalation study of JNJ-42756493, an oral pan-fibroblast growth factor receptor inhibitor, in patients with advanced solid tumors. J Clin Oncol 2015;33:3401-8.
21. Siefker-Radtke AO, Necchi A, Rosenbaum E, et al. Efficacy of programmed death 1 (PD-1) and programmed death 1 ligand (PD-L1) inhibitors in patients with *FGFR* mutations and gene fusions: results from a data analysis of an ongoing phase 2 study of erdafitinib (JNJ-42756493) in patients (pts) with advanced urothelial cancer (UC). J Clin Oncol 2018;36:Suppl 6:450. abstract (https://ascopubs.org/doi/10.1200/JCO.2018.36.6_suppl.450).
22. Loriot Y, Necchi A, Park SH, et al. Erdafitinib (ERDA: JNJ-42756493), a pan-fibroblast growth factor receptor (FGFR) inhibitor, in patients (pts) with metastatic or unresectable urothelial carcinoma (mUC) and *FGFR* alterations (FGFRa): phase 2 continuous versus intermittent dosing. J Clin Oncol 2018;36:Suppl 6:411. abstract (https://ascopubs.org/doi/10.1200/JCO.2018.36.6_suppl.411).
23. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
24. Chae YK, Ranganath K, Hammerman PS, et al. Inhibition of the fibroblast growth factor receptor (FGFR) pathway: the current landscape and barriers to clinical application. Oncotarget 2017;8:16052-74.
25. Renouf DJ, Velazquez-Martin JP, Simpson R, Siu LL, Bedard PL. Ocular toxicity of targeted therapies. J Clin Oncol 2012;30:3277-86.
26. Stjepanovic N, Velazquez-Martin JP, Bedard PL. Ocular toxicities of MEK inhibitors and other targeted therapies. Ann Oncol 2016;27:998-1005.
27. Joerger M, Cassier PA, Penel N, et al. Rogaratinib in patients with advanced urothelial carcinomas prescreened for tumor FGFR mRNA expression and effects of mutations in the FGFR signaling pathway. J Clin Oncol 2018;36:Suppl 15:4513. abstract (https://ascopubs.org/doi/10.1200/JCO.2018.36.15_suppl.4513).
28. Pal SK, Rosenberg JE, Hoffman-Censits JH, et al. Efficacy of BGJ398, a fibroblast growth factor receptor 1-3 inhibitor, in patients with previously treated advanced urothelial carcinoma with *FGFR3* alterations. Cancer Discov 2018;8:812-21.
29. Necchi A, Pouessel D, Leibowitz-Amit R, et al. Interim results of fight-201, a phase II, open-label, multicenter study of INCB054828 in patients (pts) with metastatic or surgically unresectable urothelial carcinoma (UC) harboring fibroblast growth factor (FGF)/FGF receptor (FGFR) genetic alterations (GA). Ann Oncol 2018;29:Suppl 8:900P. abstract (https://academic.oup.com/annonc/article/29/suppl_8/mdy283.109/5140623).
30. Milowsky MI, Dittrich C, Durán I, et al. Phase 2 trial of dovitinib in patients with progressive FGFR3-mutated or FGFR3 wild-type advanced urothelial carcinoma. Eur J Cancer 2014;50:3145-52.
31. Rosenberg JE, Sridhar SS, Zhang J, et al. Updated results from the enfortumab vedotin phase 1 (EV-101) study in patients with metastatic urothelial cancer (mUC). J Clin Oncol 2018;36:Suppl:4504. abstract (https://ascopubs.org/doi/10.1200/JCO.2018.36.15_suppl.4504).
32. Tagawa ST, Faltas B, Lam E, et al. Sacituzumab govitecan (IMMU-132) for patients with pretreated metastatic urothelial cancer (UC): interim results. Ann Oncol 2017;28:Suppl 5:858P. abstract.