ORIGINAL ARTICLE

Erdafitinib or Chemotherapy in Advanced or Metastatic Urothelial Carcinoma

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ABSTRACT

BACKGROUND

Erdafitinib is a pan–fibroblast growth factor receptor (FGFR) inhibitor approved for the treatment of locally advanced or metastatic urothelial carcinoma in adults with susceptible *FGFR3|2* alterations who have progression after platinum-containing chemotherapy. The effects of erdafitinib in patients with *FGFR*-altered metastatic urothelial carcinoma who have progression during or after treatment with checkpoint inhibitors (anti–programmed cell death protein 1 [PD-1] or anti–programmed death ligand 1 [PD-L1] agents) are unclear.

METHODS

We conducted a global phase 3 trial of erdafitinib as compared with chemotherapy in patients with metastatic urothelial carcinoma with susceptible *FGFR3|2* alterations who had progression after one or two previous treatments that included an anti–PD-1 or anti–PD-L1. Patients were randomly assigned in a 1:1 ratio to receive erdafitinib or the investigator's choice of chemotherapy (docetaxel or vinflunine). The primary end point was overall survival.

RESULTS

A total of 266 patients underwent randomization: 136 to the erdafitinib group and 130 to the chemotherapy group. The median follow-up was 15.9 months. The median overall survival was significantly longer with erdafitinib than with chemotherapy (12.1 months vs. 7.8 months; hazard ratio for death, 0.64; 95% confidence interval [CI], 0.47 to 0.88; P=0.005). The median progression-free survival was also longer with erdafitinib than with chemotherapy (5.6 months vs. 2.7 months; hazard ratio for progression or death, 0.58; 95% CI, 0.44 to 0.78; P<0.001). The incidence of grade 3 or 4 treatment-related adverse events was similar in the two groups (45.9% in the erdafitinib group and 46.4% in the chemotherapy group). Treatment-related adverse events that led to death were less common with erdafitinib than with chemotherapy (in 0.7% vs. 5.4% of patients).

CONCLUSIONS

Erdafitinib therapy resulted in significantly longer overall survival than chemotherapy among patients with metastatic urothelial carcinoma and *FGFR* alterations after previous anti–PD-1 or anti–PD-L1 treatment. (Funded by Janssen Research and Development; THOR ClinicalTrials.gov number, NCT03390504.)

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*The THOR Cohort 1 Investigators are listed in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

Cisplatin-based chemotherapy is the standard treatment for newly diagnosed advanced and metastatic urothelial cancer.[1] However, more than 50% of patients with metastatic urothelial carcinoma are ineligible for cisplatin treatment, and those who receive chemotherapy typically have progression within a few months.[2,3]

Inhibitors of programmed cell death protein 1 (PD-1) and programmed death ligand 1 (PD-L1) are often used in patients who are ineligible for cisplatin, as maintenance therapy after platinum-based chemotherapy, or as second-line therapy for relapsed or refractory disease.[1] However, only approximately 30% of patients with metastatic urothelial cancer have a response to PD-1 or PD-L1 inhibitors.[4] Enfortumab vedotin is a standard drug that is given after platinum treatment and after PD-1 or PD-L1 inhibitor treatment; other options are sacituzumab govitecan and single-agent chemotherapy.[1] Coexisting conditions and residual toxic effects of previous therapy often prevent patients from receiving later-line treatments. In a real-world analysis, only approximately 30% of patients with metastatic urothelial cancer received anticancer treatment after discontinuation of PD-1 or PD-L1 inhibitors.[5] Additional treatment options are needed for patients after anti–PD-1 or anti–PD-L1 therapy.

Alterations in the gene encoding fibroblast growth factor receptor (*FGFR*) are observed in approximately 20% of advanced or metastatic urothelial cancers (and in approximately 36% of upper tract urothelial cancers)[6] and may function as oncogenic drivers.[7,8] Erdafitinib is an oral selective pan-FGFR tyrosine kinase inhibitor.[9] In a phase 2, single-group study (BLC2001) involving patients with locally advanced or metastatic urothelial cancer with susceptible *FGFR3|2* alterations who had progression after platinum-containing chemotherapy,[10,11] 40% of the patients who received erdafitinib had an objective response; the median progression-free survival was 5.5 months, and the median overall survival was 11.3 months.[11] On the basis of this study, erdafitinib was approved to treat locally advanced or metastatic urothelial carcinoma in adults with susceptible *FGFR3|2* alterations who have progression after platinum-containing chemotherapy.[12] THOR is a confirmatory, phase 3, randomized trial involving patients with previously treated metastatic urothelial carcinoma who were divided into two cohorts. In cohort 1, we assessed whether erdafitinib would improve survival over chemotherapy among patients with *FGFR*-altered metastatic urothelial carcinoma whose disease progressed after one or two previous treatments that included an anti–PD-1 or anti–PD-L1 agent. In cohort 2, we are examining erdafitinib as compared with pembrolizumab in patients who had not previously received an anti–PD-1 or anti–PD-L1 agent. Here, we present the results in cohort 1.

METHODS

TRIAL DESIGN AND OVERSIGHT

The THOR cohort 1 trial was conducted in 121 sites in 23 countries or territories in North America, South America, Europe, Oceania, and Asia. It was designed by the sponsor, Janssen Research and Development, with input from a protocol steering committee. The protocol is available with the full text of this article at NEJM.org. Review boards at all participating institutions approved the trial, which was conducted in accordance with the current Good Clinical Practice guidelines of the International Council for Harmonisation, applicable regulatory and country-specific requirements, and the principles of the Declaration of Helsinki. All the patients provided written informed consent.

An independent data monitoring committee was commissioned to review safety data after at least 60 patients had been enrolled and every 6 months afterwards, with a review of one prespecified interim analysis performed to assess both efficacy and futility. Data from case-report forms were captured through data entry by trial center personnel in a sponsor database system.

The first author, the last author, and the authors employed by the trial sponsor accessed and verified the raw data. All the authors had full access to all the data in the trial and were involved in the collection, analysis, or interpretation of the trial data; the writing of the manuscript; and approval of the final version of the manuscript. Writing assistance was funded by the sponsor.

PATIENTS

Eligible patients were 18 years of age or older with metastatic or surgically unresectable urothelial cancer and select *FGFR3|2* alterations (mutations or fusions); an Eastern Cooperative Oncology

Group (ECOG) performance-status score of 0, 1, or 2 (on a 5-point scale in which higher scores reflect greater disability); adequate organ function; and progression during or after previous systemic therapy that included an anti–PD-1 or anti–PD-L1 agent; patients had received no more than two previous lines of therapy. Molecular eligibility was confirmed with the use of central laboratory screening or local historical test results (from tissue or blood). Allowable local tests were next-generation sequencing, direct digital counting methods, or Qiagen Therascreen FGFR Rotor-Gene Q reverse-transcriptase–polymerase-chain-reaction assay. Tumors were required to have one or more of certain *FGFR3* mutations (R248C, S249C, G370C, or Y373C) or one or more of the following fusions (translocations): *FGFR2–BICC1*, *FGFR2–CASP7*, *FGFR3–TACC3_V1*, *FGFR3–TACC3_V3*, or *FGFR3–BAIAP2L1*.

TREATMENT

Patients were randomly assigned in a 1:1 ratio to receive 21-day cycles of oral erdafitinib (8 mg per day with a pharmacodynamically guided increase in the dose to 9 mg on day 14) or the investigator's choice of chemotherapy (docetaxel at a dose of 75 mg per square meter of body-surface area intravenously over a 1-hour period or vinflunine at a dose of 320 mg per square meter intravenously over a 20-minute period) every 3 weeks until the occurrence of disease progression or unacceptable toxic effects. Randomization was stratified according to the ECOG performance-status score (0 or 1 vs. 2), disease distribution (presence vs. absence of visceral [lung, liver, or bone] metastases), and geographic region (North America vs. Europe vs. the rest of the world).

END POINTS

The primary end point was overall survival, defined as the time from randomization to death from any cause. Secondary end points included investigator-assessed progression-free survival (time from randomization to investigator-assessed disease progression according to Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1, or death), objective response (complete or partial response according to RECIST, version 1.1, as assessed by the investigator), response duration (duration from the date of initial documentation of a response to first documented evidence of progressive disease or death), and safety. Secondary end points also included the change from baseline in patient-reported outcomes (Functional Assessment of Cancer Therapy–Bladder Cancer, Patient Global Impression of Severity, and the EuroQol Group 5-Dimension 5-Level questionnaire); results for these end points are not reported here.

ASSESSMENTS

Responses for solid tumors were assessed by the investigator according to RECIST, version 1.1, every 6 weeks for the first 6 months and every 12 weeks for the next 6 months and beyond. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Ophthalmologic examination at baseline included an Amsler grid test, optical coherence tomography (OCT), and ophthalmologic evaluation. An Amsler grid test was conducted at every cycle. Repeat OCT was performed as clinically indicated on the basis of the Amsler grid test or clinical assessment.

STATISTICAL ANALYSIS

The trial was designed to have at least 85% power to detect a hazard ratio for death of 0.65, corresponding to a 53% difference in median overall survival between the erdafitinib group and the chemotherapy group, with a two-sided type I error level of 0.05; one interim analysis of both efficacy and futility was planned at an information fraction of approximately 65% (approximately 136 of a total of 208 deaths). The enrollment of approximately 280 patients was sufficient to accrue the number of deaths required to provide the target statistical power. O'Brien–Fleming boundaries were applied and implemented by the Lan–DeMets spending function for a total type I error of 0.05. Early stopping for efficacy would be warranted if the two-sided P value at the interim analysis was less than 0.019 on the basis of the observed information fraction of 75% (i.e., 155 deaths) at the clinical cutoff date. Stopping for futility was possible if the hazard ratio at the interim analysis exceeded 1.0, given the totality of the data.

A hierarchical testing strategy was used for key secondary end points to strongly control the overall familywise type I error rate at 0.05 (two-sided). Descriptive subgroup analyses were conducted without adjustment for multiplicity, and

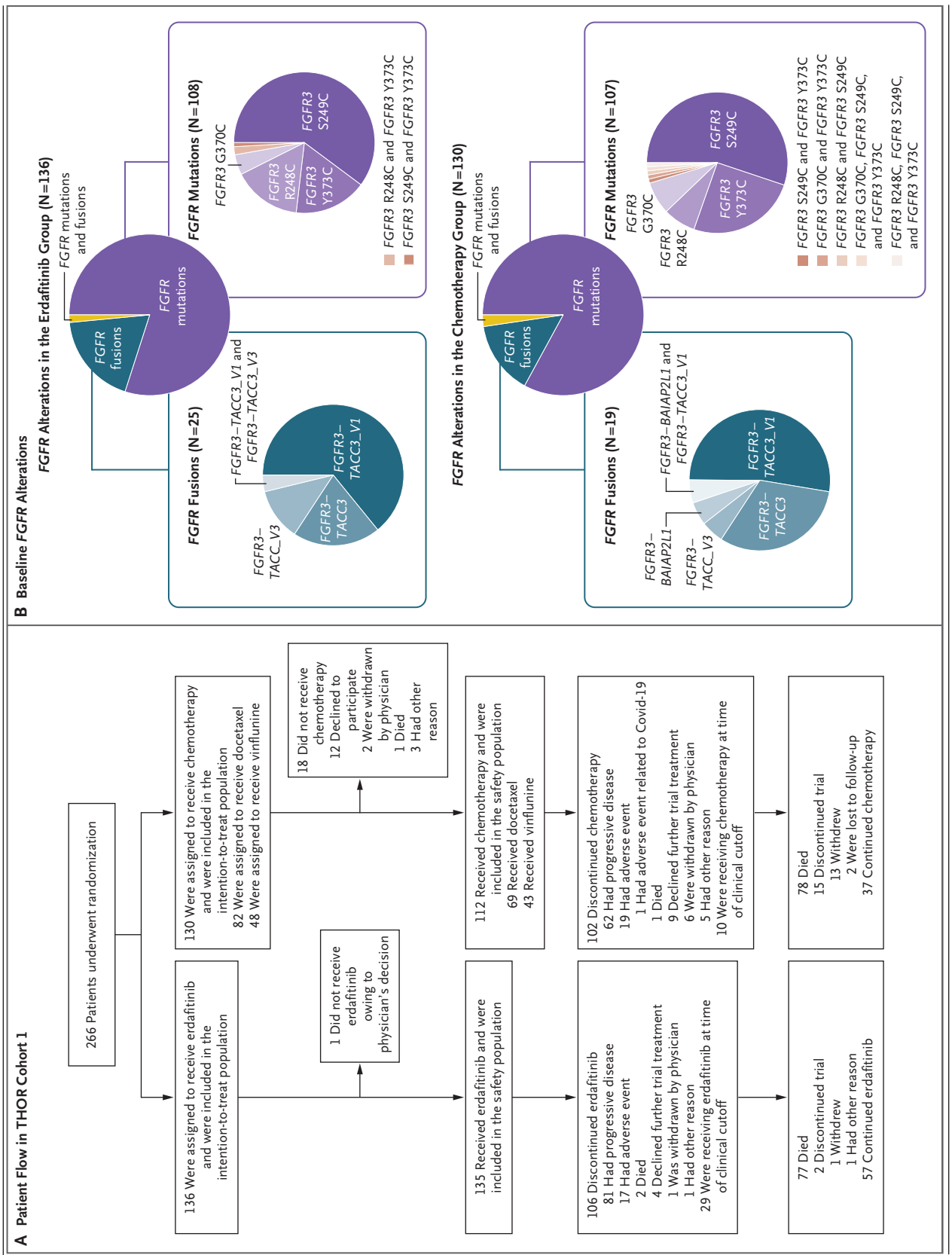


Figure 1 (facing page). Patient Flow and Baseline *FGFR* Alterations.

Three patients who had not previously received an anti–programmed cell death protein 1 (PD-1) or anti–programmed death ligand 1 (PD-L1) agent were incorrectly included in THOR cohort 1 (one patient in the erdafitinib group and two patients in the chemotherapy group). Owing to a global shortage of vinflunine during the trial, from June through December 2022, new patients who were assigned to the chemotherapy group could receive docetaxel only. Patients who received treatment with vinflunine in the trial continued to receive vinflunine. Paclitaxel was not included in the investigator's choice of chemotherapy options, because at the time that this trial was designed, docetaxel and vinflunine were the most commonly prescribed chemotherapy agents in participating countries. Panel B shows the baseline *FGFR* alterations. In the intention-to-treat population, two patients had false positive results (one in the erdafitinib group and one in the chemotherapy group) owing to an issue with specific central laboratory *FGFR* kits that was identified by the kit manufacturer. "*FGFR* fusions" indicates patients with *FGFR* fusions only, and "*FGFR* mutations" indicates patients with *FGFR* mutations only. *FGFR* alterations in patients with both mutations and fusions (two in the erdafitinib group and three in the chemotherapy group) are detailed in Table S2. Covid-19 denotes coronavirus disease 2019.

the 95% confidence intervals in these analyses should not be used in place of a hypothesis test.

Efficacy analyses involved the intention-to-treat population, which included all the patients who underwent randomization. Safety analyses involved the safety population, which included all the patients who received at least one dose of trial treatment. The distribution of overall survival and progression-free survival for each treatment group was summarized with the use of the Kaplan–Meier method and compared with a log-rank test. The estimated hazard ratio with 95% confidence interval summarizing the magnitude of the benefit of erdafitinib relative to chemotherapy was derived from a Cox proportional-hazards model, with treatment as the sole independent variable. The Cochran–Mantel–Haenszel method was used to compare the distribution of objective response between treatment groups, including an estimate of the relative benefit with 95% confidence interval.

RESULTS

PATIENTS

A total of 8733 patients were screened for molecular eligibility (cohorts 1 and 2); 8396 had tumor samples available with any test results, and 7293 had valid central laboratory test results. Of the patients with validated central test results, 1212 had *FGFR* alterations (16.6% positivity) (Figs. S1 and S2 in the Supplementary Appendix, available at NEJM.org). A total of 1324 patients with any test results had *FGFR* alterations detected; the alterations were detected by central laboratory testing in 1212 patients, by local laboratory testing in 108 (patients with local results may have had central results), and in Janssen-sponsored studies in 64 (ClinicalTrials.gov numbers, NCT03955913 and NCT03473743).

The first patient was enrolled in cohort 1 on August 6, 2018, and the clinical cutoff date was January 15, 2023. A total of 266 patients underwent randomization: 136 were assigned to the erdafitinib group and 130 to the chemotherapy group (Fig. 1A). An imbalance between the two groups was observed in patients who did not receive the assigned regimen (1 in the erdafitinib group and 18 in the chemotherapy group), largely owing to 12 patients who declined treatment in the chemotherapy group.

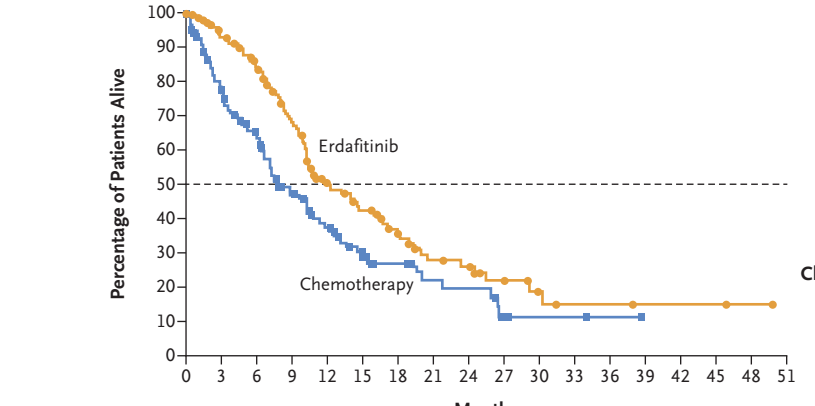
A total of 99.2% of the patients had *FGFR* alterations (2 patients had false positive results of central testing for *FGFR* alterations, identified after randomization owing to an issue with specific central laboratory *FGFR* test kits that was identified by the kit manufacturer; repeat central testing and previous local testing were not performed). A total of 197 of 264 patients (74.6%) with *FGFR* alterations were enrolled on the basis of central testing; 67 patients were enrolled on the basis of local testing (with tissue testing in 60 patients, blood testing in 6, and unspecified testing in 1). A total of 215 of 266 patients (80.8%) had *FGFR* mutations, 44 patients (16.5%) had *FGFR* fusions, and 5 patients (1.9%) had both *FGFR* mutations and fusions (Table 1, Fig. 1B, and Table S2). No patients had *FGFR2* alterations; the *FGFR3* S249C mutation was the most prevalent alteration (46.6%), followed by the *FGFR3* Y373C mutation (16.9%) and the *FGFR3–TACC3_V1* fusion (9.8%).

The demographic and clinical characteristics of the patients at baseline were balanced between the two treatment groups (Table 1 and Table S3). Only 1 patient identified as Black, owing to low enrollment in the United States and restrictions on the reporting of race according to local regulations. Most patients (157 of 175 [89.7%]) with PD-L1 results had low PD-L1 expression (com-

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Erdafitinib (N=136)	Chemotherapy (N=130)
Median age (range) — yr	66 (32–85)	69 (35–86)
Age group — no. (%)		
<65 yr	59 (43.4)	45 (34.6)
≥65 yr	77 (56.6)	85 (65.4)
Sex — no. (%)		
Male	96 (70.6)	94 (72.3)
Female	40 (29.4)	36 (27.7)
Race — no. (%)†		
White	81 (59.6)	63 (48.5)
Asian	37 (27.2)	40 (30.8)
Black	0	1 (0.8)
Multiple	0	1 (0.8)
Not reported	18 (13.2)	25 (19.2)
Geographic region — no. (%)		
North America	8 (5.9)	5 (3.8)
Europe	82 (60.3)	80 (61.5)
Rest of the world	46 (33.8)	45 (34.6)
Visceral metastasis — no. (%)		
Present‡	101 (74.3)	97 (74.6)
Absent	35 (25.7)	33 (25.4)
ECOG performance-status score§		
0	63 (46.3)	51 (39.2)
1	61 (44.9)	66 (50.8)
2	12 (8.8)	13 (10.0)
Primary tumor location — no. (%)		
Upper tract	41 (30.1)	48 (36.9)
Lower tract	95 (69.9)	82 (63.1)
PD-1 or PD-L1 status — no./total no. (%)¶		
CPS <10	89/96 (93)	68/79 (86)
CPS ≥10	7/96 (7)	11/79 (14)
FGFR alterations — no. (%)		
Mutation	108 (79.4)	107 (82.3)
Fusion	25 (18.4)	19 (14.6)
Mutation and fusion	2 (1.5)	3 (2.3)
False positive result	1 (0.7)	1 (0.8)
Previous lines of systemic therapy — no. (%)		
1	45 (33.1)	33 (25.4)
2	90 (66.2)	97 (74.6)
3	1 (0.7)	0

* Percentages may not total 100 because of rounding.
† Where recording of race was allowed by local law, race was reported by the patient.
‡ The patient had visceral metastasis in the lung, liver, or bone.
§ Scores on the Eastern Cooperative Oncology Group (ECOG) scale range from 0 (no disability) to 5 (death).
¶ The combined positive score (CPS) is the number of PD-L1–staining tumor cells, lymphocytes, and macrophages, divided by the total number of viable tumor cells, multiplied by 100. Results are for patients with available data.



	No. of Deaths/ No. of Patients	Median Overall Survival (95% CI)
		mo
Erdafitinib	77/136	12.1 (10.3–16.4)
Chemotherapy	78/130	7.8 (6.5–11.1)

Hazard ratio for death, 0.64 (95% CI, 0.47–0.88)
P=0.005

No. at Risk (no. with censored data)

Erdafitinib	136	117	97	74	46	35	25	17	15	9	5	3	3	2	2	2	1	0
	(0)	(10)	(20)	(25)	(35)	(39)	(44)	(47)	(48)	(52)	(55)	(56)	(56)	(57)	(57)	(57)	(58)	(59)
Chemotherapy	130	87	66	43	30	18	13	9	8	3	2	2	1	0	0	0	0	0
	(0)	(17)	(25)	(30)	(35)	(41)	(45)	(47)	(47)	(49)	(50)	(50)	(51)	(52)	(52)	(52)	(52)	(52)

Figure 2. Overall Survival.

Shown are Kaplan–Meier estimates of overall survival. Circles and squares indicate censored data in the erdafitinib group and chemotherapy group, respectively. Results for overall survival in key subgroups are provided in Figure S3.

bined positive score <10 [Dako PD-L1 IHC 22C3 assay, Labcorp]), with baseline PD-L1 expression not reported for some patients owing to insufficient tumor availability.

All the patients had previous treatment with an anti–PD-1 or anti–PD-L1 therapy, with the exception of three patients who had been assigned incorrectly (Table S4). More than half the patients in each treatment group had received an anti–PD-1 or anti–PD-L1 agent as a single agent for second-line therapy (55.9% in the erdafitinib group and 58.5% in the chemotherapy group). One third (33.1%) of the patients in the erdafitinib group and one quarter (25.4%) in the chemotherapy group had received one line of previous systemic therapy. Although not required by the trial protocol, the majority of patients (89.1%) had received at least one line of previous chemotherapy (cisplatin in 50.8% and carboplatin in 29.3%).

EFFICACY

The median duration of follow-up for survival was 15.9 months (18.0 months in the erdafitinib group and 14.9 months in the chemotherapy group). At the interim analysis, 155 deaths (information fraction of approximately 75%; two-sided alpha of 0.019) had occurred (77 in the erdafitinib group and 78 in the chemotherapy group). The median overall survival was 12.1 months in the erdafitinib group (95% confidence interval [CI], 10.3 to 16.4) and 7.8 months in the chemotherapy group (95% CI, 6.5 to 11.1), with an estimated hazard ratio for death of 0.64 (95% CI, 0.47 to 0.88; P=0.005) (Fig. 2). The estimated percentage of patients alive at 6 and 12 months was 85% (95% CI, 77 to 90) and 51% (95% CI, 41 to 60), respectively, in the erdafitinib group and 66% (95% CI, 56 to 74) and 38% (95% CI, 28 to 47), respectively, in the chemotherapy group. The results of the subgroup analysis are shown in Figure S3. After the interim analysis, the independent data monitoring committee made a recommendation to stop the trial, unblind the data, and allow crossover from chemotherapy to erdafitinib.

The median progression-free survival was 5.6 months (95% CI, 4.4 to 5.7) in the erdafitinib group and 2.7 months (95% CI, 1.8 to 3.7) in the chemotherapy group, with an estimated hazard ratio for progression or death of 0.58 (95% CI, 0.44 to 0.78; P<0.001) (Fig. 3A). The percentage of patients with an objective response according to investigator assessment was higher in the erdafitinib group than in the chemotherapy group (45.6% vs. 11.5%; relative benefit, 3.94;

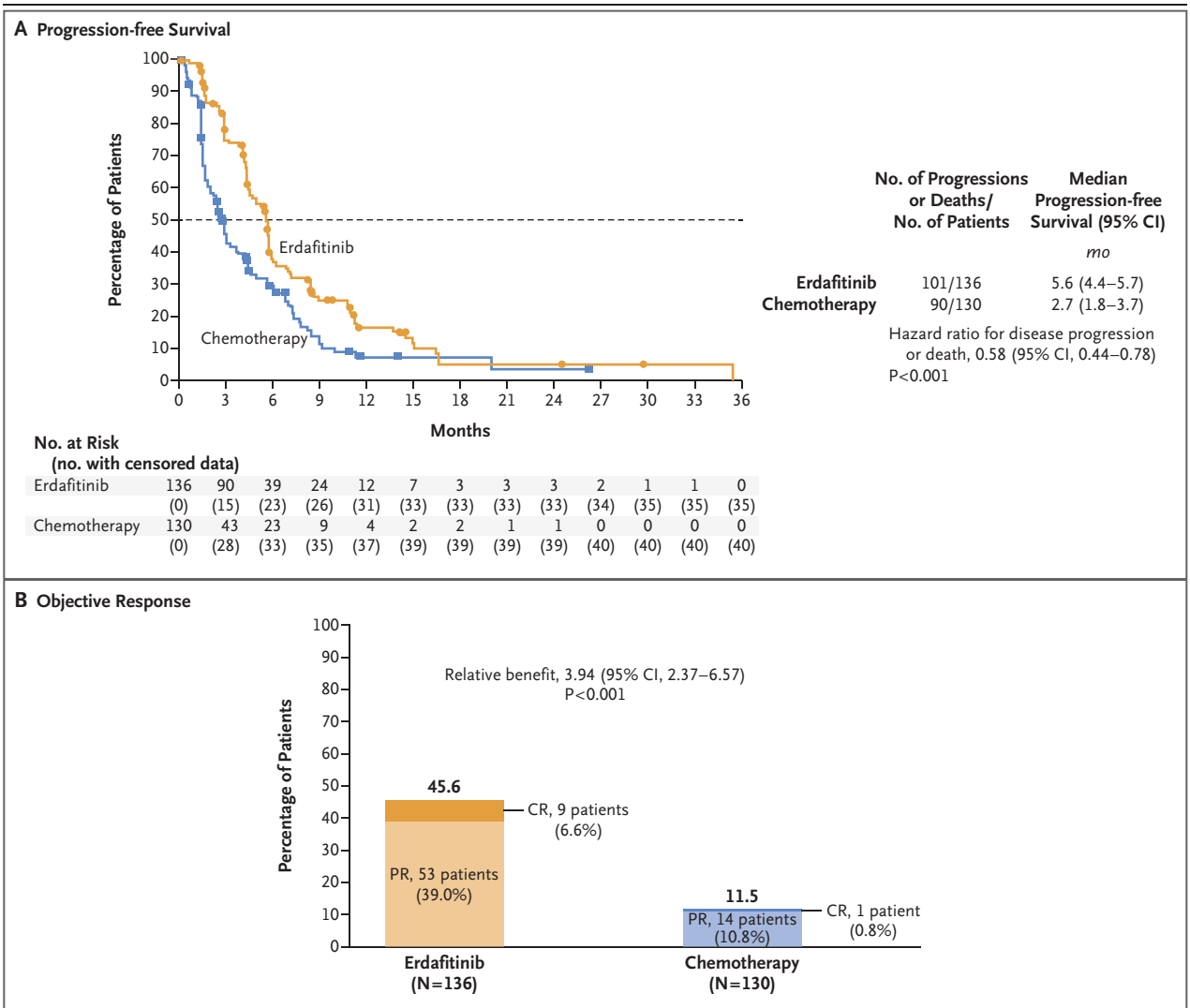


Figure 3. Key Secondary End Points.

Panel A shows Kaplan–Meier estimates of progression-free survival. Circles and squares indicate censored data in the erdafitinib group and chemotherapy group, respectively. Panel B shows the percentages of patients with an objective response. CR denotes complete response, and PR partial response.

95% CI, 2.37 to 6.57; P<0.001) (Fig. 3B). In the erdafitinib group, 9 patients (6.6%) had a complete response, and 53 (39.0%) had a partial response; in the chemotherapy group, 1 patient (0.8%) had a complete response, and 14 (10.8%) had a partial response. The results of subgroup analyses of progression-free survival and objective response are shown in Figure S3. The percentage of patients with a confirmed objective response by investigator assessment (two or more consecutive assessments) was 35.3% in the erdafitinib group and 8.5% in the chemotherapy group (relative benefit, 4.16; 95% CI, 2.27 to 7.64). The median duration of response was 4.9 months (95% CI, 3.8 to 7.5) in the erdafitinib group and 5.6 months (95% CI, 2.1 to 6.0) in the chemotherapy group. Subsequent anticancer therapy was received by 92 patients (34.6%), including 44 (32.4%) in the erdafitinib group and 48 (36.9%) in the chemotherapy group (Table S5).

SAFETY

A total of 135 patients in the erdafitinib group and 112 patients in the chemotherapy group re-

Table 2. Adverse Events in the Safety Population.*

Event	Erdafitinib (N=135)				Chemotherapy (N=112)			
	Any Grade	Grade 1	Grade 2	Grade ≥3	Any Grade	Grade 1	Grade 2	Grade ≥3
	number (percent)							
Hyperphosphatemia	108 (80.0)	70 (51.9)	31 (23.0)	7 (5.2)	0	0	0	0
Diarrhea	84 (62.2)	49 (36.3)	31 (23.0)	4 (3.0)	19 (17.0)	7 (6.2)	9 (8.0)	3 (2.7)
Stomatitis	65 (48.1)	22 (16.3)	32 (23.7)	11 (8.1)	14 (12.5)	4 (3.6)	8 (7.1)	2 (1.8)
Dry mouth	53 (39.3)	45 (33.3)	8 (5.9)	0	4 (3.6)	4 (3.6)	0	0
Palmar–plantar erythrodysesthesia syndrome	41 (30.4)	6 (4.4)	22 (16.3)	13 (9.6)	1 (0.9)	0	1 (0.9)	0
Dysgeusia	37 (27.4)	28 (20.7)	8 (5.9)	1 (0.7)	8 (7.1)	5 (4.5)	3 (2.7)	0
Alanine aminotransferase increased	37 (27.4)	24 (17.8)	9 (6.7)	4 (3.0)	4 (3.6)	2 (1.8)	1 (0.9)	1 (0.9)
Constipation	36 (26.7)	24 (17.8)	12 (8.9)	0	31 (27.7)	13 (11.6)	16 (14.3)	2 (1.8)
Decreased appetite	36 (26.7)	18 (13.3)	14 (10.4)	4 (3.0)	23 (20.5)	10 (8.9)	10 (8.9)	3 (2.7)
Anemia	35 (25.9)	10 (7.4)	15 (11.1)	10 (7.4)	36 (32.1)	8 (7.1)	19 (17.0)	9 (8.0)
Alopecia	34 (25.2)	29 (21.5)	4 (3.0)	1 (0.7)	27 (24.1)	16 (14.3)	11 (9.8)	0
Dry skin	31 (23.0)	23 (17.0)	6 (4.4)	2 (1.5)	5 (4.5)	4 (3.6)	1 (0.9)	0
Onycholysis	31 (23.0)	9 (6.7)	14 (10.4)	8 (5.9)	1 (0.9)	0	1 (0.9)	0
Weight decreased	30 (22.2)	12 (8.9)	15 (11.1)	3 (2.2)	3 (2.7)	3 (2.7)	0	0
Aspartate aminotransferase increased	29 (21.5)	21 (15.6)	5 (3.7)	3 (2.2)	3 (2.7)	2 (1.8)	1 (0.9)	0
Onychomadesis	28 (20.7)	9 (6.7)	17 (12.6)	2 (1.5)	2 (1.8)	1 (0.9)	1 (0.9)	0
Nail discoloration	24 (17.8)	16 (11.9)	7 (5.2)	1 (0.7)	2 (1.8)	1 (0.9)	1 (0.9)	0
Dry eye	23 (17.0)	20 (14.8)	3 (2.2)	0	2 (1.8)	1 (0.9)	1 (0.9)	0
Asthenia	20 (14.8)	6 (4.4)	12 (8.9)	2 (1.5)	28 (25.0)	9 (8.0)	15 (13.4)	4 (3.6)
Nausea	20 (14.8)	10 (7.4)	8 (5.9)	2 (1.5)	27 (24.1)	15 (13.4)	10 (8.9)	2 (1.8)
Neutropenia	0	0	0	0	22 (19.6)	1 (0.9)	5 (4.5)	16 (14.3)
Fatigue	20 (14.8)	12 (8.9)	8 (5.9)	0	21 (18.8)	13 (11.6)	4 (3.6)	4 (3.6)

* Listed are adverse events (of any cause) that emerged or worsened during treatment, according to preferred term and highest grade, and that were reported in more than 15% of the patients in either treatment group.

ceived at least one dose of trial treatment. The median duration of exposure was longer with erdafitinib than with chemotherapy (4.8 months [range, 0.2 to 38.2] vs. 1.4 months [range, 0.03 to 27.0]). In the erdafitinib group, 104 patients (77.0%) had an increase in the dose from 8 to 9 mg, and 66 (48.9%) maintained a dose of 8 mg or more without a dose reduction.

Adverse events of any cause occurred in 98.5% of the patients in the erdafitinib group and 97.3% of those in the chemotherapy group (Table 2 and Table S6). Grade 3 or 4 treatment-related adverse events occurred in 45.9% of the patients in the erdafitinib group and 46.4% of those in the chemotherapy group. The most common treatment-related adverse events of grade 3 or higher were palmar–plantar erythrodysesthesia syndrome (9.6%), stomatitis (8.1%), onycholysis (5.9%), and hyperphosphatemia (5.2%) in the erdafitinib group and neutropenia (13.4%) and anemia (6.2%) in the chemotherapy group (Table S7).

Six patients (4.4%) in the erdafitinib group and seven patients (6.2%) in the chemotherapy group had adverse events that emerged or worsened during treatment and led to death (Table S8). Treatment-related adverse events that led to death occurred in fewer patients in the erdafitinib group than in the chemotherapy group (1 patient [0.7%], owing to sudden death, vs. 6 patients [5.4%],

including 2 each with febrile bone marrow aplasia and septic shock and 1 each with atypical pneumonia and febrile neutropenia).

Treatment-related serious adverse events occurred in 18 patients (13.3%) in the erdafitinib group and 27 patients (24.1%) in the chemotherapy group (Table S6). Serious adverse events of any cause that were reported in more than 2% of the patients in either group are shown in Table S9.

Adverse events of any cause led to treatment discontinuation in 19 patients (14.1%) in the erdafitinib group and 20 patients (17.9%) in the chemotherapy group (Table S10). Treatment-related adverse events that led to treatment discontinuation occurred in fewer patients in the erdafitinib group than in the chemotherapy group (8.1% vs. 13.4%).

Grade 3 or 4 adverse events that were of interest on the basis of the known safety profile of erdafitinib included skin disorders (in 11.9% of patients), nail disorders (in 11.1%), central serous retinopathy (in 2.2%), and other eye disorders (in 2.2%) (Table S11). In 16 of 23 patients (70%) with central serous retinopathy of any grade, events were resolved by the clinical cutoff date; among the 7 patients with ongoing events, the events in 5 were grade 1.

DISCUSSION

Erdafitinib therapy resulted in significantly longer median overall survival than chemotherapy among patients with advanced or metastatic urothelial carcinoma with *FGFR* alterations after previous treatment with anti–PD-1 or anti–PD-L1 therapy (12.1 months vs. 7.8 months; hazard ratio for death, 0.64). Erdafitinib was also associated with a significantly longer median progression-free survival and a greater likelihood of objective response than chemotherapy. Toxic effects that were observed during erdafitinib therapy were occasionally serious and even fatal in a few patients, although the occurrence of these adverse events with fatal outcomes appears similar to that observed with chemotherapy. These phase 3 results show the clinical benefit of erdafitinib in patients with locally advanced or metastatic urothelial carcinoma with *FGFR* alterations after anti–PD-1 or anti–PD-L1 treatment. These data further support the recommendation for molecular testing in patients with metastatic urothelial carcinoma to identify those with *FGFR* alterations who may benefit from erdafitinib.

Overall survival appeared to be longer with erdafitinib than with chemotherapy in a variety of subgroups (Fig. S3), including those defined according to previous lines of therapy, the presence or absence of previous platinum-based therapy, primary tumor location (lower or upper tract), the presence or absence of liver or lung metastases, chemotherapy type, and *FGFR* alteration type. The possible overall survival benefit that was observed with erdafitinib in patients with upper tract urothelial cancer may be clinically important but should be interpreted cautiously because of the small number of patients. Multiple previous reports have shown that *FGFR*-altered urothelial tumors are mostly luminal 1 tumors with few T-cell infiltrates and low PD-L1 expression.[13,14] This fact may explain why the percentage of patients with PD-L1 expression in this *FGFR*-selected cohort was lower than in overall populations of patients with urothelial cancer. Given the small sample of patients with tumors positive for PD-1 or PD-L1, definitive conclusions cannot be made in this subgroup of patients, but *FGFR3*-positive PD-1– or PD-L1–positive tumors might have different biologic features than *FGFR3*-positive PD-1– or PD-L1–negative tumors. In addition, the underrepresentation of Black patients complicates extrapolation of the results to that subgroup.

The safety profile of erdafitinib was consistent with that in the previous BLC2001 study.[10,11] Ophthalmologic examinations were conducted to detect central serous retinopathy, an adverse event of interest in patients treated with FGFR inhibitors. Most cases of central serous retinopathy were resolved by the clinical cutoff date; those that remained were grade 1. Eye disorders other than central serous retinopathy occurred in 42.2% of the patients in the erdafitinib group, with the most frequent being dry eye and conjunctivitis; the percentages of patients with these conditions were similar to those observed in the BLC2001 study. The safety profile of erdafitinib differs from that of other options such as antibody–drug conjugates (which can cause neuropathy, serious cutaneous adverse reactions, and myelosuppression) and chemotherapy (which can cause myelosuppression).[15,16]

The analysis of subgroups defined according to *FGFR* alteration is limited by the absence of *FGFR2* alterations in the trial population but is reflective of the fact that *FGFR2* alterations are rare in urothelial carcinoma. According to current knowledge, *FGFR3* mutations and fusions are early

events in the oncogenesis of urothelial carcinoma.[17] The testing of samples from the primary tumor should be sufficient to detect *FGFR3* alterations. Although the majority of the patients enrolled in this trial had primary tumor samples available for testing, samples from either primary or metastatic tumors can be used.

In this trial, erdafitinib resulted in significantly longer overall survival than standard chemotherapy among patients with advanced or metastatic urothelial carcinoma with *FGFR* alterations after anti–PD-1 or anti–PD-L1 treatment. The overall survival benefit of erdafitinib in patients with metastatic urothelial carcinoma with *FGFR* alterations supports molecular testing for *FGFR* alterations in patients with metastatic urothelial cancer.

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APPENDIX

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