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Erdafitinib Versus Chemotherapy in Advanced/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/metastatic urothelial carcinoma (mUC) in adults with susceptible *FGFR3/2* alterations (*alt*) who progressed after platinum-containing chemotherapy. Treatment with erdafitinib could address the unmet need in patients with *FGFR*-altered mUC with limited treatment options after progression on checkpoint inhibitors (anti–PD-[L]1).

METHODS

THOR Cohort 1 is a global phase 3 trial of erdafitinib versus chemotherapy in patients with mUC with susceptible *FGFR3/2alt* progressing after one/two prior treatments, including an anti–PD-(L)1. Patients were randomly assigned 1:1 to receive erdafitinib (8 mg per day with pharmacodynamically guided dose escalation to 9 mg) or investigator's choice of chemotherapy (docetaxel or vinflunine). The primary end point was overall survival.

RESULTS

8733 patients were screened for molecular eligibility in THOR; 1212 of 7293 patients had *FGFR* alterations as assessed via central screening (16.6% positivity rate) (Cohorts 1 and 2). In Cohort 1, 266 patients underwent randomization at the prespecified interim analysis; 136 to erdafitinib and 130 to chemotherapy. Median follow-up was 15.9 months. Overall survival was significantly longer with erdafitinib versus chemotherapy (median overall survival, 12.1 vs. 7.8 months; hazard ratio for death, 0.64; 95% confidence interval [CI], 0.47 to 0.88; P=0.005). Progression-free survival was also prolonged with erdafitinib (median progression-free survival, 5.6 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 3-4 treatment-related adverse events was similar in the two groups (45.9% in the erdafitinib group and 46.4% in the chemotherapy group). Fewer treatment-related adverse events leading to death (0.7% vs. 5.4%) were reported with erdafitinib than chemotherapy.

CONCLUSIONS

Erdafitinib significantly prolonged overall survival compared with chemotherapy in patients with mUC and *FGFRalt* after prior anti–PD-(L)1 treatment. (Funded by Janssen Research & Development; ClinicalTrials.gov number, NCT03390504.)

INTRODUCTION

Cisplatin-based chemotherapy is the standard of care 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 progress within a few months.[2,3] Programmed cell death protein and programmed death-ligand 1 (PD-[L]1) inhibitors are often used in first- (for cisplatin-ineligible patients or for maintenance therapy after platinum) or second-line post-platinum treatment.[1] However, only approximately 30% of patients with metastatic urothelial cancer respond to PD-(L)1 inhibitors.[4] Enfortumab vedotin is currently standard in patients who have progressed post-platinum and post-PD-(L)1 inhibitor treatment; other options are sacituzumab govitecan and single-agent chemotherapy.[1] Comorbidities and residual toxicity of prior therapy often prevent patients from receiving later-line treatments. In a real-world analysis, only ~30% of patients with metastatic urothelial cancer received subsequent anticancer treatment after PD-(L)1 inhibitor discontinuation.[5] There is a clear unmet need to extend treatment options for patients post–PD-(L)1 therapy.

Fibroblast growth factor receptor (*FGFR*) alterations are observed in ~20% of advanced or metastatic urothelial cancer (~36% in upper tract urothelial cancer)[6] and may function as oncogenic drivers.[7,8] Erdafitinib is an oral selective pan-FGFR tyrosine kinase inhibitor.[9] In the single-arm, phase 2 trial (BLC2001 NCT02365597) of erdafitinib in adult patients with locally advanced or metastatic urothelial cancer with susceptible *FGFR3/2* alterations who had progressed after platinum-containing chemotherapy,[10,11] erdafitinib showed clinical benefit with an overall response rate of 40%, a median progression-free survival of 5.5 months, and a median overall survival of 11.3 months.[11] Erdafitinib was granted approval in the United States

(accelerated approval) and 17 other countries to treat locally advanced or metastatic urothelial carcinoma in adults with susceptible *FGFR3/2alt* who have progressed after platinum-containing chemotherapy on the basis of this trial.[12] THOR is a confirmatory, randomized, phase 3 study in previously treated metastatic urothelial carcinoma composed of two cohorts designed to be evaluated separately. Cohort 2 examines erdafitinib versus pembrolizumab in patients naïve to anti–PD-(L)1 and will be reported separately. In Cohort 1 of the THOR trial reported here, we assessed whether erdafitinib improved survival over chemotherapy in patients with *FGFR*-altered metastatic urothelial carcinoma whose disease progressed after one or more prior treatments including a PD-(L)1 agent.

METHODS

STUDY DESIGN AND OVERSIGHT

This ongoing study was conducted in 121 sites in 23 countries/territories in North America, South America, Europe, Oceania, and Asia. It was designed by the sponsor, Janssen Research & Development, with input from the Protocol Steering Committee. Review boards at all participating institutions approved the study, which was conducted in accordance with the 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 patients provided written informed consent.

An independent data monitoring committee was commissioned to review safety data after at least 60 patients were enrolled and every 6 months afterwards, with a review of one pre-planned interim analysis to assess both efficacy and futility. Case report form data were captured via data entry by study center personnel in a sponsor database system.

The lead and senior authors and study sponsor authors accessed and verified the raw data. All authors had full access to all the data in the study, were involved in the investigation, data collection, data analysis, or interpretation of the study data, and the writing of the report and approval of the final version of the manuscript.

PATIENTS

Eligible patients were aged ≥18 years with metastatic or surgically unresectable urothelial cancer and select *FGFR*3/2 alterations (mutations/fusions), an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2, adequate organ function, progression on/after prior systemic therapy that included an anti-PD-(L)1 agent, and ≤2 prior lines of therapy. Molecular eligibility was confirmed using central laboratory screening or by local historical test results (from tissue or blood). Allowable local tests were next generation sequencing (NGS), direct digital counting methods, or the Qiagen Therascreen FGFR Rotor-Gene Q (RGQ) reverse transcription polymerase chain reaction test. Tumors were required to have one or more of the following *FGFR3* gene 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, FGFR3-BAIAP2L1*.

TREATMENT

Patients were randomized in a 1:1 ratio to receive 21-day cycles of oral erdafitinib (8 mg per day with pharmacodynamically guided uptitration to 9 mg on day 14) or investigator's choice of chemotherapy (docetaxel at a dose of 75 mg per square meter, administered intravenously over 1 hour, or vinflunine at a dose of 320 mg per square meter, administered intravenously over 20 minutes) every 3 weeks until disease progression or intolerable toxicity. Randomization was stratified according to ECOG performance status score (0 or 1 vs. 2), disease distribution

(presence vs. absence of visceral [lung, liver, or bone] metastases), and region (North America vs. the European Union vs. the rest of the world).

END POINTS

The primary end point was overall survival defined as the time from randomization to death due to any cause. Secondary end points included investigator-assessed progression-free survival (defined as the time from randomization to investigator-assessed disease progression Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST v1.1] or death), achievement of objective response as measured by the objective response rate (defined as the proportion of patients who achieved complete or partial response as assessed by RECIST v1.1 by investigator assessment), duration of response (defined as the 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 change from baseline in patient-reported outcomes (Functional Assessment of Cancer Therapy—Bladder Cancer, Patient-Global Impression of Severity, and the European Quality of Life – 5 Dimensions-5 Levels), which are planned to be reported separately.

ASSESSMENTS

Assessment of responses for solid tumors were investigator-assessed by RECIST v1.1 and performed every 6 weeks for the first 6 months and then 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 scan (OCT), and ophthalmologic evaluation. An Amsler grid test was conducted at every cycle. Repeat OCT was done as clinically indicated based on the Amsler grid test or clinical assessment.

STATISTICAL ANALYSIS

The study was designed to have at least 85% power to detect a hazard ratio (HR) of 0.65, corresponding to a 53% increase in median overall survival for the erdafitinib group versus 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 approximately 65% information fraction (about 136 out 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, 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 based on the observed 75% information fraction (i.e., 155 deaths) at the clinical cutoff date. Stopping for futility was possible if the HR at the interim analysis exceeded 1.0, considering the totality of the data.

Key secondary end points were part of a hierarchical testing strategy to strongly control the overall family-wise Type I error rate at 0.05 (two sided). Descriptive subgroup analyses were conducted but with no adjustment for multiplicity. 95% confidence intervals (CIs) are presented but should not be used in place of a hypothesis test.

Efficacy analyses used the intention-to-treat population, comprising all patients randomized. Safety analyses used the safety population, comprising all patients who received at least one dose of study treatment. The distribution of overall survival and progression-free survival for each treatment arm was summarized using the Kaplan-Meier method and compared with a log-rank test. The estimated HR with 95% CI 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 risk with 95% CI.

RESULTS

PATIENTS

Of a total of 8733 patients screened for molecular eligibility in the THOR trial (Cohorts 1 and 2), 8396 had tumor samples available with any test results, 7293 had valid central laboratory test results; of patients with validated central test results, 1212 had *FGFR* alterations (positivity rate, 16.6%; **Fig. 1A** and **Fig. S1**). A total of 1324 patients with any test results had *FGFR* alterations detected, with 1212 based on central laboratory test results, 108 on local laboratory test results (patients with local results may also have had central results), and 64 transferred from other Janssen-sponsored studies (ANNAR [NCT03955913] and NORSE [NCT03473743]). The first patient enrolled in Cohort 1 on August 6, 2018. The clinical cutoff for this analysis was January 15, 2023. In Cohort 1, 266 patients were randomized, 136 to the erdafitinib group and 130 to the chemotherapy group (**Fig. 1B**). An imbalance was observed in those not treated between groups (one in the erdafitinib group and 18 in the chemotherapy group), largely due to 12 patients refusing treatment in the chemotherapy group. 99.2% of patients in Cohort 1 had *FGFR* alterations (two patients had *FGFR* alterations on central testing that were later identified as false positives after randomization due to an issue with specific central laboratory *FGFR* test kits identified by the kit manufacturer; these two patients did not have repeat central testing or prior local testing). In Cohort 1, 197 of 264 patients (74.2%) who had *FGFR* alterations were enrolled based on central test results; 67 patients were enrolled by local tests (tissue, n=60; blood, n=6; unspecified, n=1). 80.8% had *FGFR* mutations, 16.5% had *FGFR* fusions, and 1.9% had both *FGFR* mutations and fusions (**Table 1C** and **Table S2**). No patients had *FGFR2* alterations; the

FGFR3-S249C mutation was the most prevalent *FGFR* 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 across the erdafitinib and chemotherapy treatment groups (**Table 1** and **Table S3)**. Only one patient identified as Black; this was primary due to low enrollment in the United States and restrictions on reporting of race per local regulations on clinical practice (e.g., France). Most patients (89.7%) with PD-L1 results had low PD-L1 expression (combined positive score <10 [Dako PD-L1 IHC 22C3 assay, Labcorp]), with baseline PD-L1 expression not reported for some patients due to insufficient tumor availability.

All patients had prior treatment with an anti–PD-(L)1 therapy except three patients incorrectly assigned (**Table S4**). Over half of patients in both treatment groups received an anti–PD-(L)1 as a single agent in the second-line setting (erdafitinib, 55.9%; chemotherapy, 58.5%). One-third (33.1%) of patients in the erdafitinib group and one-quarter (25.4%) of patients in the chemotherapy group received one line of prior systemic therapy. Although not required by the study protocol, the majority of patients (89.1%) received at least one line of prior chemotherapy (50.8% had prior cisplatin; 29.3% had prior carboplatin).

EFFICACY

The median survival follow-up was 15.9 months (18.0 and 14.9 months in the erdafitinib and chemotherapy groups, respectively). At the interim analysis, a total of 155 deaths (~75% information fraction; 2-sided alpha of 0.019) had occurred (77 and 78 in the erdafitinib and chemotherapy groups, respectively). The median overall survival was 12.1 months in the erdafitinib group (95% CI, 10.3 to 16.4) and 7.8 months in the chemotherapy group (95% CI, 6.5 to 11.1), with an estimated HR of 0.64 (95% CI, 0.47 to 0.88; P=0.005; **Fig. 2A**). 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) in the erdafitinib group versus 66% (95% CI, 56 to 74) and 38% (95% CI, 28 to 47) in the chemotherapy group, respectively. The effect of erdafitinib was generally consistent across subgroups (**Fig. 2B**). Following the interim analysis, the independent data monitoring committee recommended to stop the study, unblind data, and allow crossover from chemotherapy to erdafitinib.

The median progression-free survival was 5.6 months (95% CI, 4.4 to 5.7) and 2.7 months (95% CI, 1.8 to 3.7) in the erdafitinib and chemotherapy groups, respectively, with an estimated HR of 0.58 (95% CI, 0.44 to 0.78; P<0.001; **Fig. 3A**). The objective response rate by investigator assessment was higher in the erdafitinib group (45.6%) (nine patients [6.6%] with complete response; 53 [39.0%] with partial response) than in the chemotherapy group (11.5%) (one [0.8%] with complete response; 14 [10.8%] with partial response) (relative risk [RR], 3.9; 95% CI, 2.4 to 6.6; P<0.001; **Fig. 3B**). The progression-free survival and objective response rate differences were generally consistent in the subgroups evaluated (**Fig. S2**). The disease control rate was also higher in the erdafitinib group (82.4%) than in the chemotherapy group (43.1%) (RR, 1.9; 95% CI, 1.6 to 2.4). The confirmed objective response rate by investigator assessment (≥2 consecutive assessments) was 35.3% in the erdafitinib group and 8.5% in the chemotherapy group (RR, 4.2; 95% CI, 2.3 to 7.6). 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 (34.6%) patients, with 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 received at least one dose of study treatment. The median duration of exposure was longer with erdafitinib compared 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 (77%) patients had dose up-titration from 8 to 9 mg, and 66 (48.9%) maintained ≥8 mg dose without dose reduction.

Adverse events of any cause occurred in 98.5% of patients in the erdafitinib group and 97.3% of patients in the chemotherapy group as shown in **Table 2** (overall safety in **Table S6**). Grade 3-4 treatment-related adverse events occurred in 45.9% of patients in the erdafitinib group and 46.4% of patients in the chemotherapy group. The most common (>5%) grade ≥3 treatment-related adverse events were palmar-plantar erythrodysesthesia syndrome (9.6%), stomatitis (8.1%), and onycholysis (5.9%) in the erdafitinib group and neutropenia (13.4%) and anemia (6.3%) in the chemotherapy group (**Table S7**).

Six (4.4%) and seven patients (6.3%) in the erdafitinib and chemotherapy groups, respectively, had treatment-emergent adverse events that led to death (**Table S8**). Fewer investigator-assessed treatment-related adverse events that led to death occurred in the erdafitinib group (0.7% [n=1]; sudden death [n=1]) than in the chemotherapy group (5.4% [n=6]; atypical pneumonia [n=1], febrile bone marrow aplasia [n=2], febrile neutropenia [n=1], septic shock [n=2]).

Treatment-related serious adverse events occurred in 18 (13.3%) and 27 patients (24.1%) in the erdafitinib and chemotherapy groups, respectively (**Table S6**; treatment-emergent serious adverse events in **Table S9**).

Adverse events of any cause led to treatment discontinuation in 19 (14.1%) and 20 (17.9%) patients in the erdafitinib and chemotherapy groups, respectively (**Tables S10**). Fewer treatment-related adverse events led to treatment discontinuation in the erdafitinib group (8.1% vs. 13.4%).

Grade 3–4 adverse events of interest based on the known safety profile of erdafitinib included nail disorders (11.1%), skin disorders (11.9%), and central serous retinopathy (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; of those with ongoing events, 5 of 7 (71%) were grade 1.

DISCUSSION

Erdafitinib significantly prolonged median overall survival compared with chemotherapy in patients with advanced or metastatic urothelial carcinoma with *FGFR* alterations after prior treatment with anti–PD-(L)1 therapy, with a median overall survival of 1 year (HR = 0.64). The overall survival benefit favoring erdafitinib was consistent across subgroups. Erdafitinib provided significantly longer median progression-free survival and a greater objective response rate compared with chemotherapy. Erdafitinib toxicity was manageable with dose modifications and supportive measures. These phase 3 results demonstrate the clinical benefit of erdafitinib in patients with locally advanced or metastatic urothelial carcinoma with *FGFR* alterations after anti–PD-(L)1 treatment and validate the predictive value of the prespecified *FGFR3* alteration panel in patients with metastatic urothelial carcinoma. The THOR Cohort 1 data further support the recommendation for molecular testing in all patients with metastatic urothelial carcinoma to identify patients with *FGFR* alterations who may benefit from erdafitinib.

The overall survival benefit favoring erdafitinib was generally consistent across subgroups, acknowledging that the study was not designed to assess treatment effect in subgroups. These included subgroups of number of prior lines of therapy, presence or absence of prior platinum-based therapy, primary tumor location (lower or upper tract), presence of liver or lung metastases, type of chemotherapy (erdafitinib compared with docetaxel and vinflunine), and type of *FGFR* alteration (mutation or fusion or both). The overall survival benefit 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. Based on previous studies in patients with *FGFR*-altered urothelial carcinoma in which a partial exclusive relationship has been reported between luminal papillary tumors expressing *FGFR* and PD-(L)1–expressing non-luminal tumors,[13,14] the PD-(L)1–positive subgroup only represents a minority of patients enrolled. Given the small sample size of patients with PD-(L)1–positive tumors (erdafitinib, n=7; chemotherapy, n=11), it would be difficult to draw definitive conclusions in this subset of patients, but *FGFR3*-positive PD-(L)1–positive tumors might have a different biology compared with *FGFR3*-positive PD-(L)1–negative tumors.

The *FGFR* alteration subgroup analysis is limited by the absence of *FGFR2* alterations in the study population but is reflective of *FGFR2* alterations having a very rare occurrence in urothelial carcinoma. We also observed a generally consistent erdafitinib effect across subgroups for progression-free survival and objective response rate.

Current data show that erdafitinib was well tolerated compared with chemotherapy. In the erdafitinib group, 45.9% of patients had grade 3-4 treatment-related adverse events compared with 46.4% of patients in the chemotherapy group.. One treatment-related death occurred on

erdafitinib compared with six treatment-related deaths on chemotherapy. Discontinuation due to treatment-related adverse events was also lower with erdafitinib (8.1%) compared with chemotherapy (13.4%).

The erdafitinib safety profile was consistent with the prior BLC2001 study.[10,11] Ophthalmologic examinations were conducted to detect central serous retinopathy, a known adverse event of interest in patients treated with FGFR inhibitors. The protocol required post-baseline ophthalmologic examinations, including optical coherence tomography scans in patients with symptoms, an abnormal Amsler grid, or when otherwise clinically indicated. Most cases of central serous retinopathy resolved at the time of the clinical cutoff, and those that remained ongoing were grade 1. Non-central serous retinopathy eye disorders occurred in 42% of patients in the erdafitinib group, with the most frequent being dry eye and conjunctivitis at rates similar to that observed previously in BLC2001. Importantly, erdafitinib's safety profile differs from that of other options including antibody-drug conjugates (e.g., neuropathy, serious cutaneous adverse reactions, myelosuppression) and chemotherapy (myelosuppression).[15,16] Overall, erdafitinib had a favorable tolerability profile compared with standard single-agent chemotherapy.

Based on the current knowledge, *FGFR3* mutations/fusions are early events in urothelial carcinoma oncogenesis.[17] Testing samples from the primary tumor should be sufficient to detect *FGFR3* alterations. While the majority of the patients enrolled in this study provided primary tumors for testing, either primary or metastatic tumor samples can be used.

In conclusion, our findings demonstrate significant extension of survival for erdafitinib over standard-of-care chemotherapy for patients with advanced or metastatic urothelial carcinoma

with *FGFR* alterations after anti–PD-(L)1 treatment. The overall survival benefit of erdafitinib in patients with metastatic urothelial carcinoma with *FGFR* alterations supports molecular testing for *FGFR* alterations in all patients with metastatic urothelial cancer.

AUTHOR CONTRIBUTIONS

YL, NM, SHP, RAH, EFB, NH, SB, VG, JHK, BPV, BT, ST, YK, SA, KD, SM, NLS, and AOS supported the study. YL, ST, YK, SA, KD, SM, NLS, and AOS accessed and verified the raw data. All authors had full access to all the data in the study, were involved in the investigation, data collection, data analysis, or interpretation of the study, and the writing of the report and approval of the final version of the manuscript, and had final responsibility for the decision to submit for publication.

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 the Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

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Figure Legends

Figure 1. CONSORT Diagram. THOR Screening (Panel A) and THOR Cohort 1 (Panel B) Patient Flow (Panel C) Baseline *FGFR* alterations. Three patients who did not receive a prior anti–PD-(L)1 agent were incorrectly assigned to Cohort 1 (erdafitinib, n = 1; chemotherapy, n = 2). Due to global shortage of vinflunine during the study, from June to December 2022, new patients assigned to the chemotherapy group could only receive docetaxel. Patients who received treatment with vinflunine in the study continued to receive vinflunine. Paclitaxel was not included in the investigator choice of chemotherapy options, as at the time this study was designed, docetaxel and vinflunine were the most commonly prescribed chemotherapy agents in participating countries. Panel A footnote: *Only includes patients with positive and negative results from central testing. Panel C footnotes: *Intent-to-treat population (two patients were false positive for *FGFR* alterations [erdafitinib group, n=1; chemotherapy group, n=1] due to an issue with specific central laboratory *FGFR* kits identified by the kit manufacturer); †Patients with *FGFR* mutations only; ‡Patients with *FGFR* fusions only. §*FGFR* mutations and fusions (erdafitinib group, n=2; chemotherapy group, n=3) are delineated in **Table S2**.

Figure 2. Overall Survival. Kaplan–Meier estimate of overall survival by treatment group (Panel A). Overall survival according to key subgroups (Panel B). The vertical dotted line represents the HR for the overall population for comparison purposes. CI, confidence interval; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

Figure 3. Key Secondary End Points. Kaplan–Meier estimate of progression-free survival by treatment group (Panel A). Objective response rate (Panel B).

Table 1. Demographics and Disease Characteristics of the Patients at Baseline.

Characteristic	Erdafitinib (N = 136)	Chemotherapy (N = 130)
Median age (range) — yr	66 (32–85)	69 (35–86)
Age subgroup — no. (%)		
<65	59 (43.4)	45 (34.6)
≥65	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 PS — no. (%)†		
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-(L)1 status — no. (%)‡	n = 96	n = 79
CPS <10	89 (92.7)	68 (86.1)
CPS ≥10	7 (7.3)	11 (13.9)
FGFR alterations — no. (%)		
Mutations	108 (79.4)	107 (82.3)
Fusions	25 (18.4)	19 (14.6)
Mutations and fusions	2 (1.5)	3 (2.3)
Prior lines of systemic therapy — no. (%)		
1	45 (33.1)	33 (25.4)
2	90 (66.2)	97 (74.6)
3	1 (0.7)	0

*Visceral metastases in lung, liver, and bone.

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

‡Based on patients with available data.

Table 2. Treatment-Emergent Adverse Events in the Safety Population.*

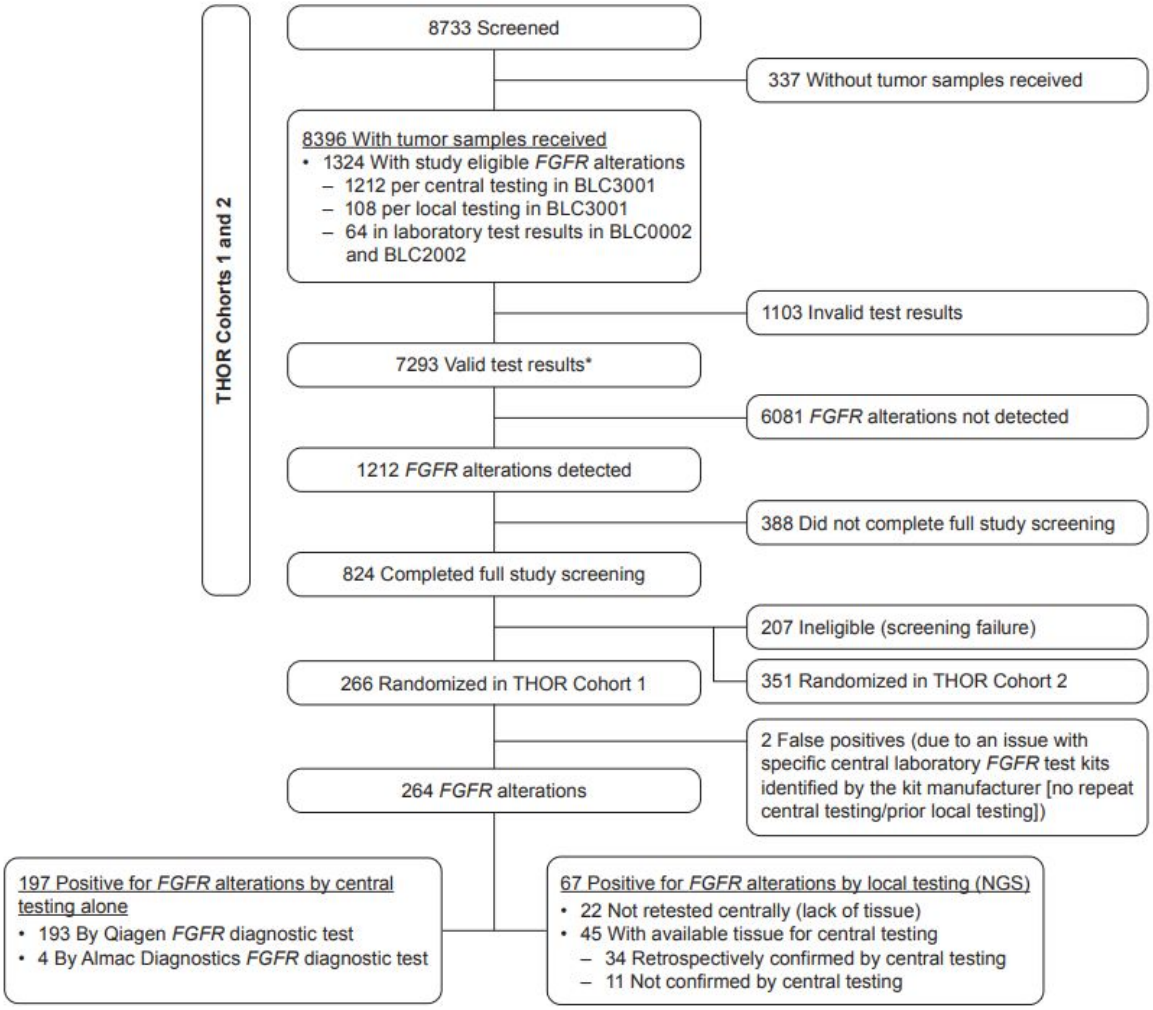
Adverse event — no. (%)	Erdafitinib (N = 135)				Chemotherapy (N = 112)			
	Any grade	Grade 1	Grade 2	Grade ≥3	Any grade	Grade 1	Grade 2	Grade ≥3
Hyperphosphatemia	108 (80.0)	70 (51.9)	31 (23.0)	7 (5.2)	0	0	0	0
Diarrhea	84 (62.2)	49 (36.3)	31 (23.0)	4 (3.0)	19 (17.0)	7 (6.3)	9 (8.0)	3 (2.7)
Stomatitis	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)	28 (20.7)	8 (5.9)	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 treatment-emergent adverse events of any cause by preferred term and worst toxicity grade that were reported in more than 15% of the patients in either treatment group.

Figure 1.

A



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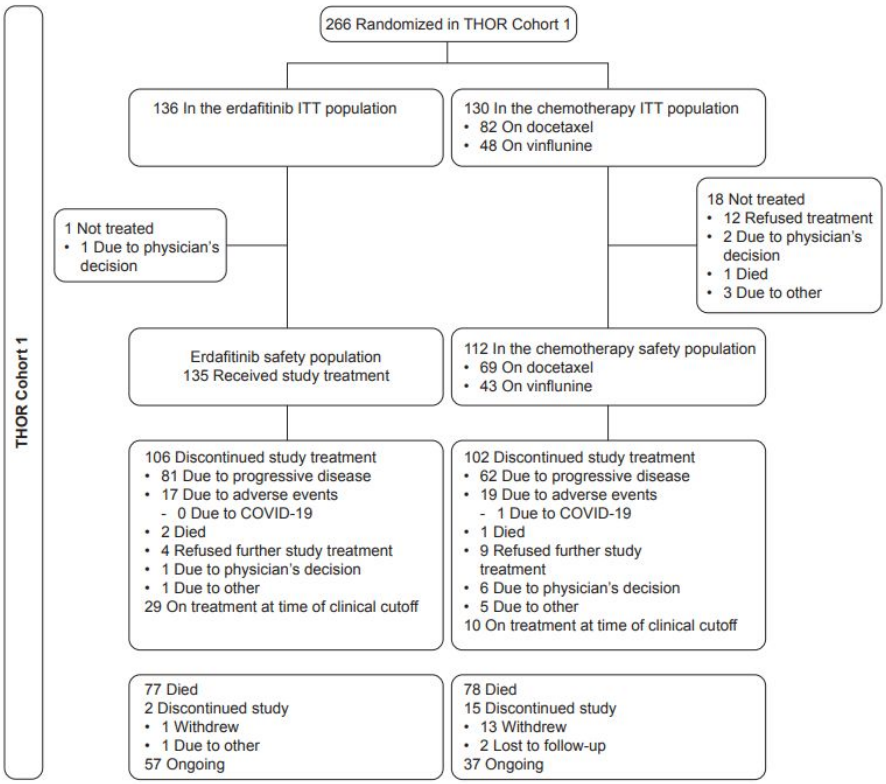

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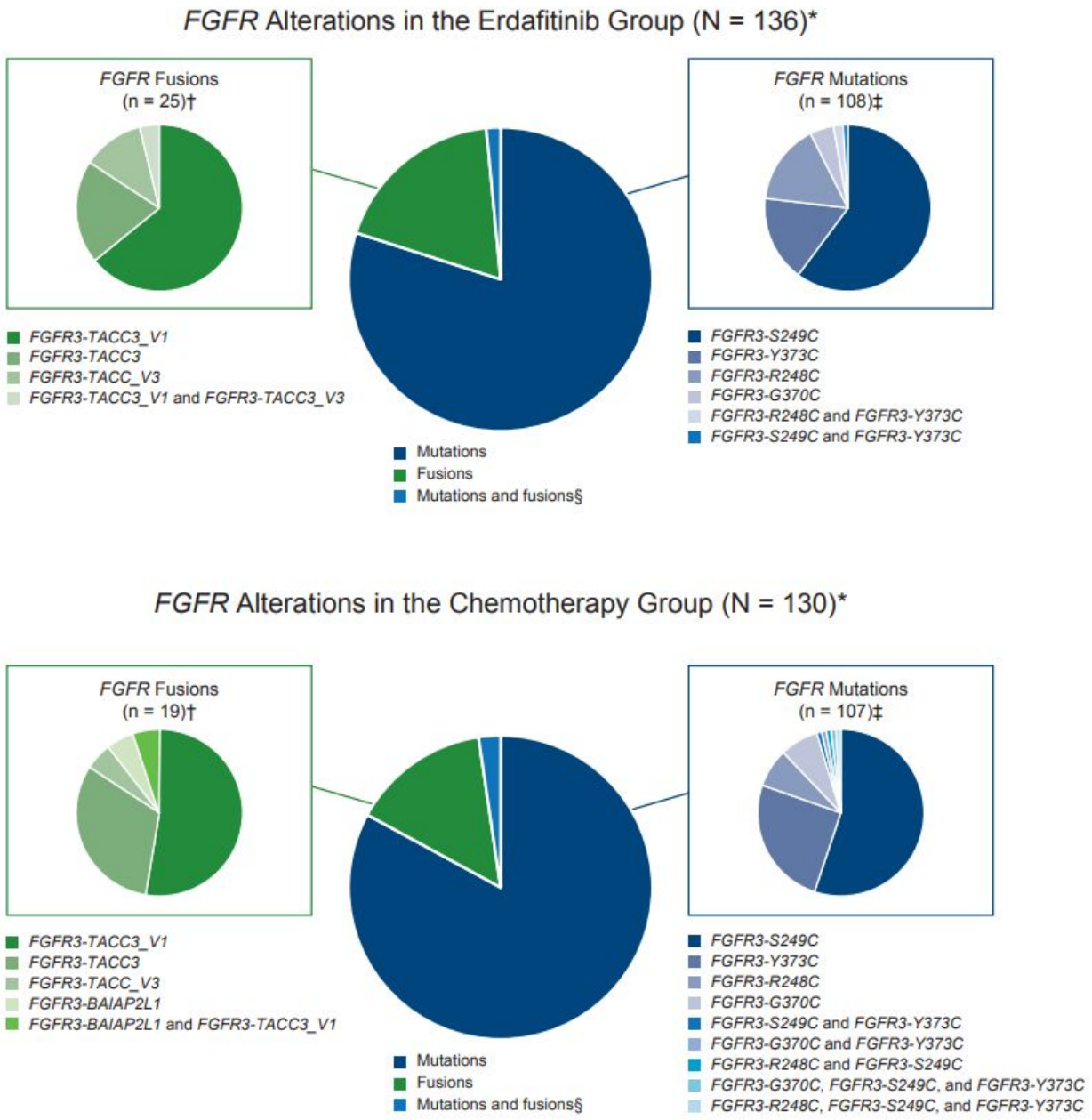
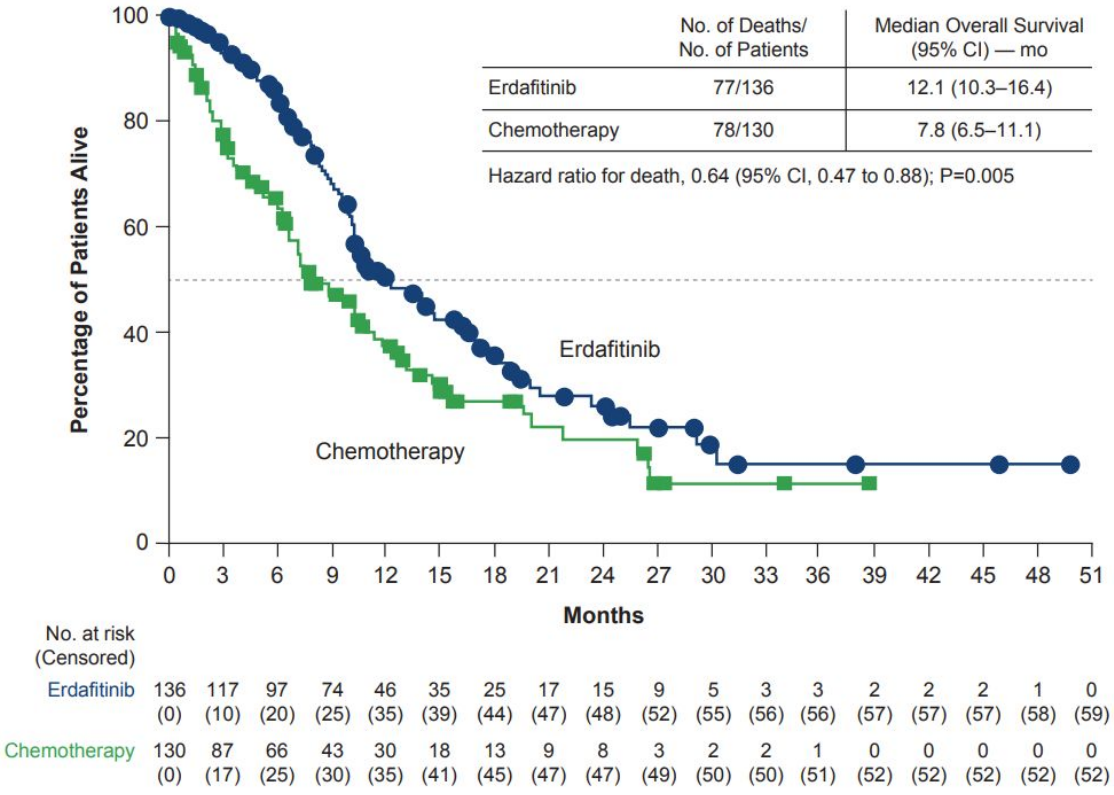

FGFR Alterations in the Erdafitinib Group (N = 136)*
FGFR Fusions (n = 25)†
FGFR Mutations (n = 108)‡
FGFR3-TACC3_V1
FGFR3-TACC3
FGFR3-TACC_V3
FGFR3-TACC3_V1 and *FGFR3-TACC3_V3*
FGFR3-S249C
FGFR3-Y373C
FGFR3-R248C
FGFR3-G370C
FGFR3-R248C and *FGFR3-Y373C*
FGFR3-S249C and *FGFR3-Y373C*
Mutations
Fusions
Mutations and fusions§
FGFR Alterations in the Chemotherapy Group (N = 130)*
FGFR Fusions (n = 19)†
FGFR Mutations (n = 107)‡
FGFR3-TACC3_V1
FGFR3-TACC3
FGFR3-TACC_V3
FGFR3-BAIAP2L1
FGFR3-BAIAP2L1 and *FGFR3-TACC3_V1*
FGFR3-S249C
FGFR3-Y373C
FGFR3-R248C
FGFR3-G370C
FGFR3-S249C and *FGFR3-Y373C*
FGFR3-G370C and *FGFR3-Y373C*
FGFR3-R248C and *FGFR3-S249C*
FGFR3-G370C, *FGFR3-S249C*, and *FGFR3-Y373C*
FGFR3-R248C, *FGFR3-S249C*, and *FGFR3-Y373C*
Mutations
Fusions
Mutations and fusions§

Figure 2

A



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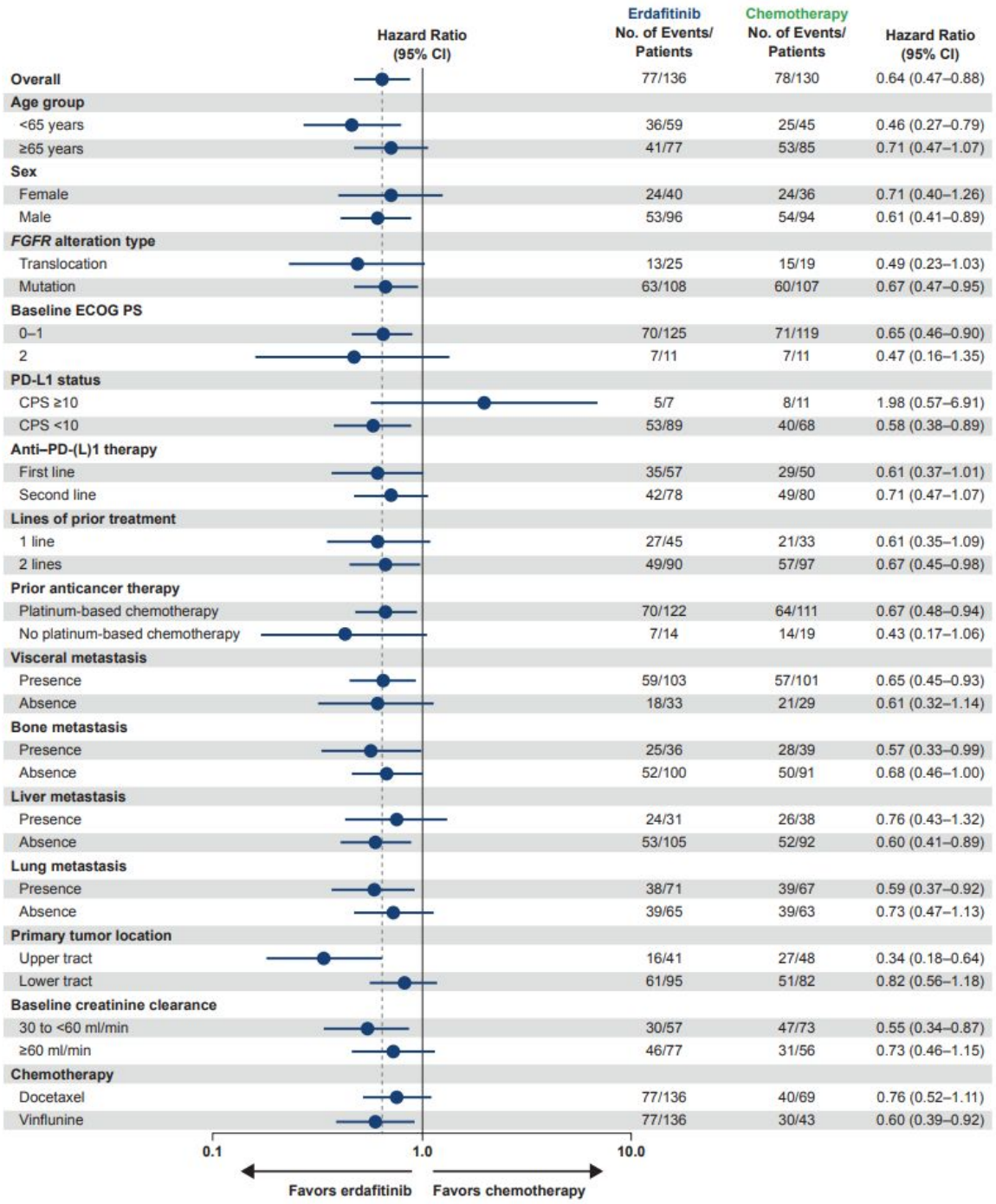
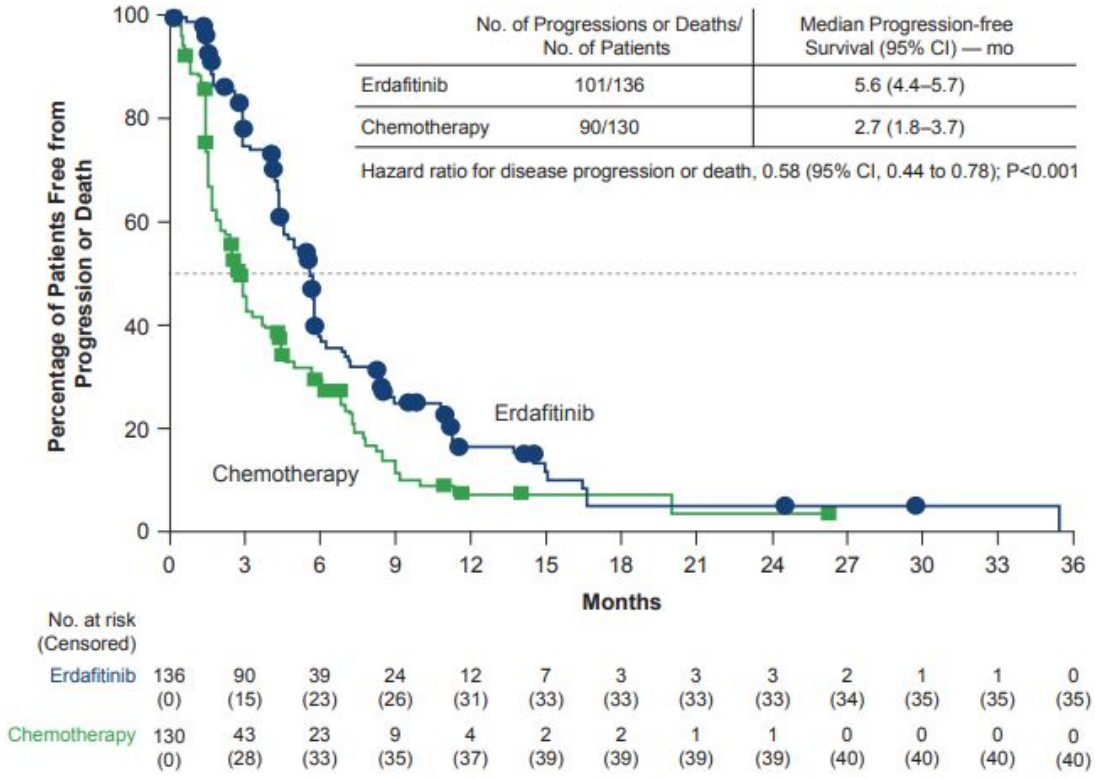
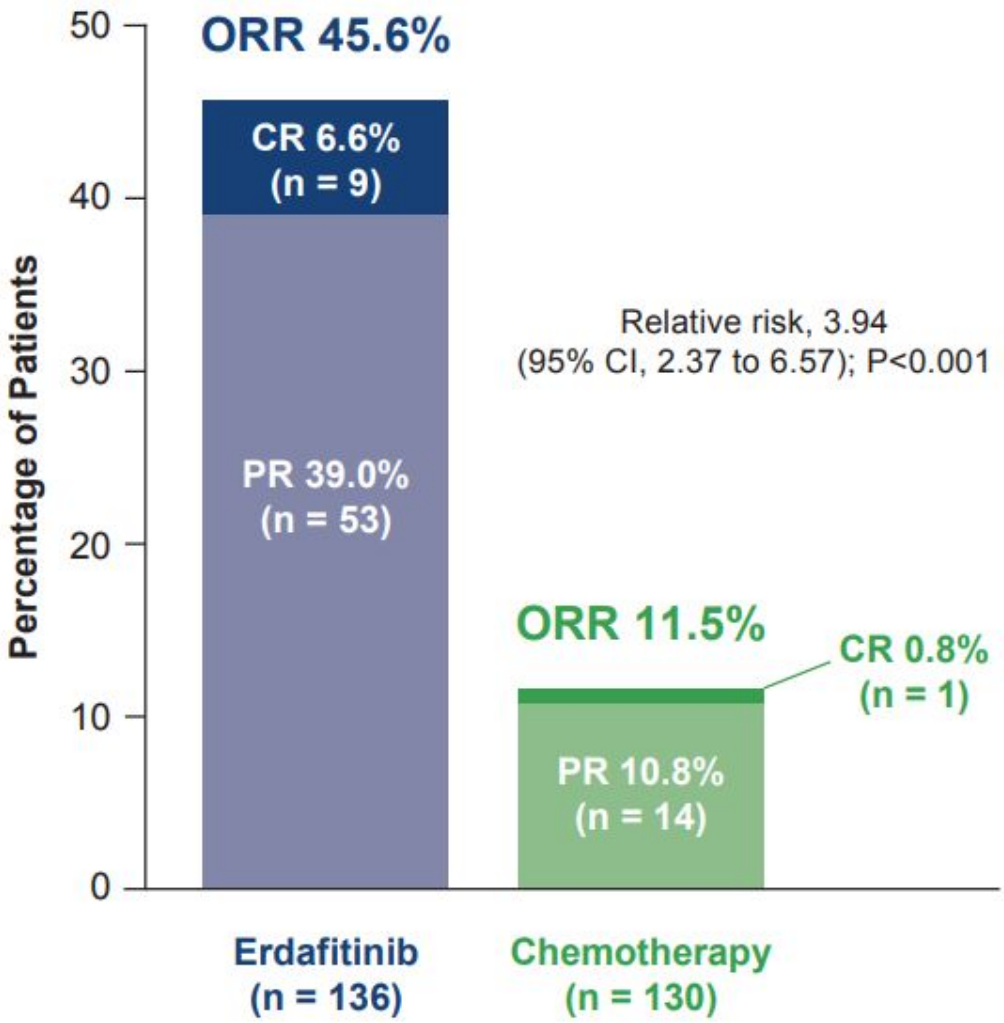


Figure 3

A


No. of Progressions or Deaths/ No. of Patients
Median Progression-free Survival (95% CI) — mo
Erdafitinib 101/136 5.6 (4.4–5.7)
Chemotherapy 90/130 2.7 (1.8–3.7)
Hazard ratio for disease progression or death, 0.58 (95% CI, 0.44 to 0.78); P<0.001
Percentage of Patients Free from Progression or Death
100
80
60
40
20
0
Erdafitinib
Chemotherapy
0 3 6 9 12 15 18 21 24 27 30 33 36
Months
No. at risk (Censored)
Erdafitinib 136 (0) 90 (15) 39 (23) 24 (26) 12 (31) 7 (33) 3 (33) 3 (33) 3 (33) 2 (34) 1 (35) 1 (35) 0 (35)
Chemotherapy 130 (0) 43 (28) 23 (33) 9 (35) 4 (37) 2 (39) 2 (39) 1 (39) 1 (39) 0 (40) 0 (40) 0 (40) 0 (40)

B



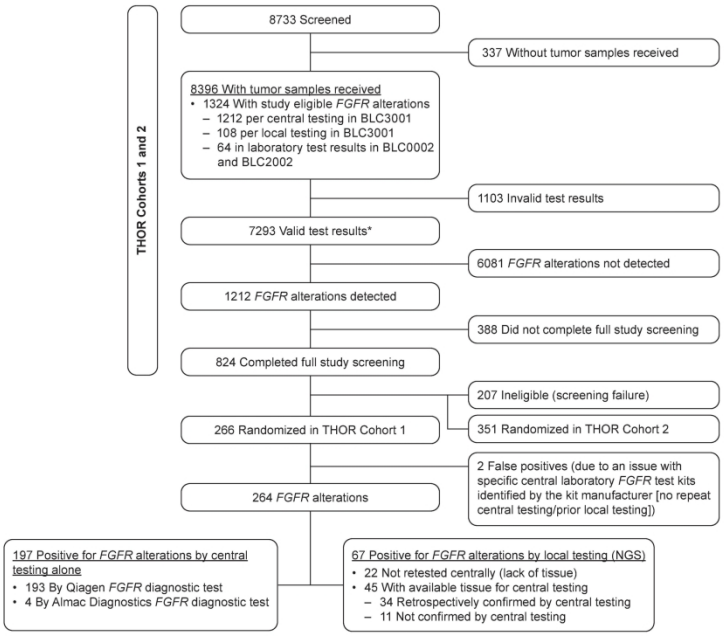


Fig. 1A

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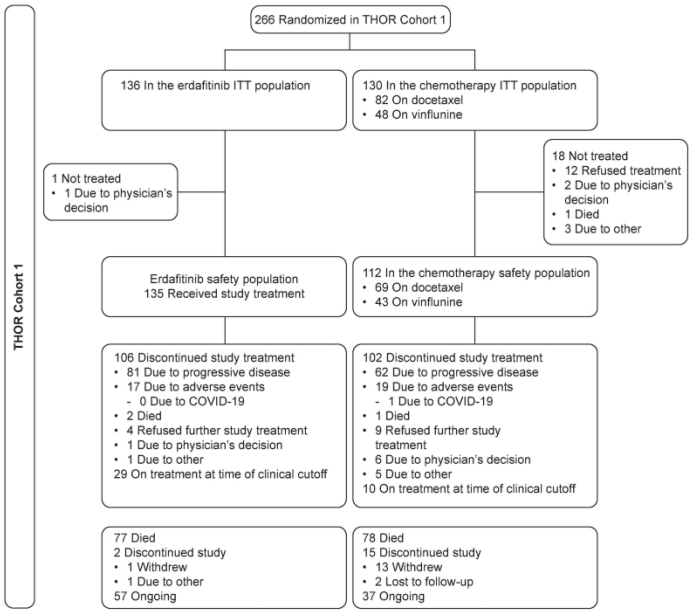

Fig. 1B

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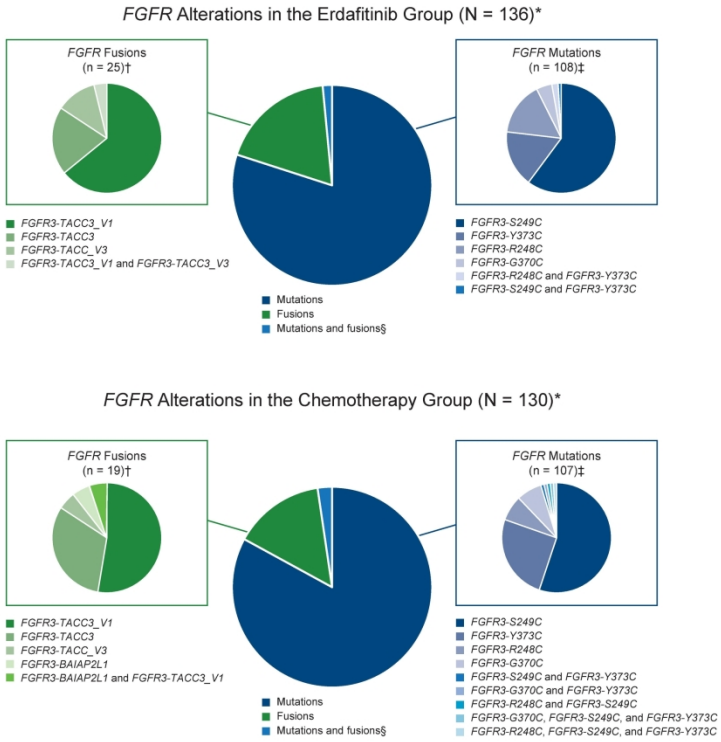

Fig. 1C

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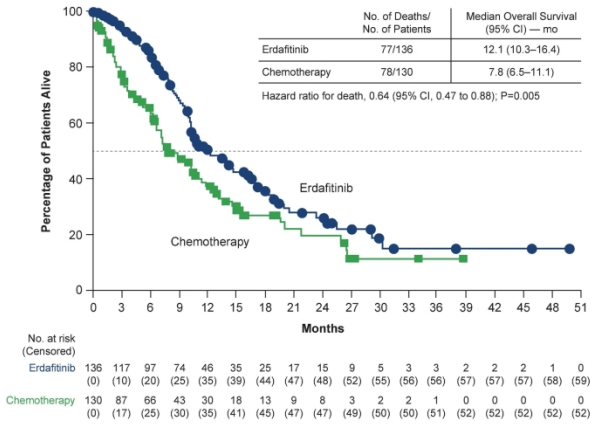

Fig. 2A

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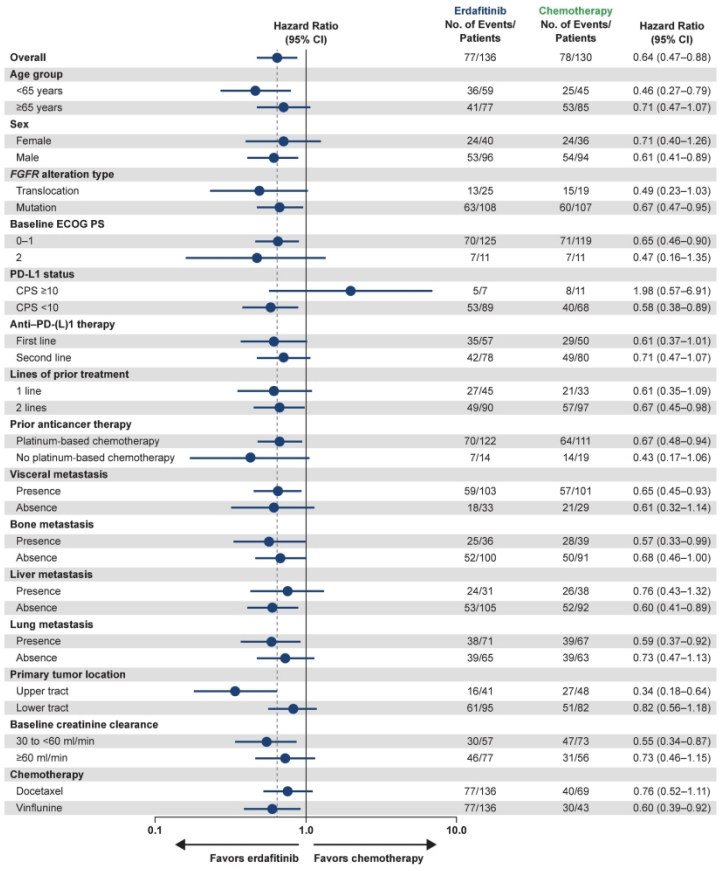

Fig. 2B

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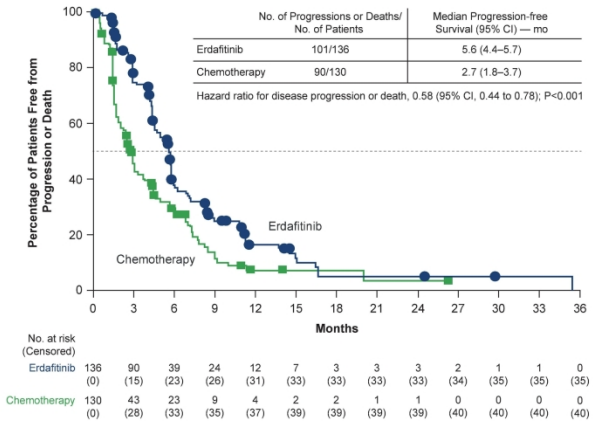

Fig. 3A

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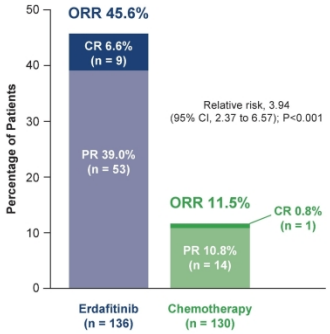

Fig. 3B

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