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Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.
How did you learn about the YODA Project?: Scientific Publication

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2026/07/sekino-COI.pdf
https://yoda.yale.edu/wp-content/uploads/2026/07/Takamori-COI.pdf
https://yoda.yale.edu/wp-content/uploads/2026/07/Yukihiro-COI.pdf
https://yoda.yale.edu/wp-content/uploads/2026/07/Shinsaku-Tasaka-IPD.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. NCT03390504 - 42756493BLC3001 - A Phase 3 Study of Erdafitinib Compared With Vinflunine or Docetaxel or Pembrolizumab in Subjects With Advanced Urothelial Cancer and Selected FGFR Gene Aberrations
2. NCT02365597 - 42756493BLC2001 - An Efficacy and Safety Study of Erdafitinib (JNJ-42756493) in Participants With Urothelial Cancer

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Clinical Outcomes by FGFR3 Mutation Subtype in Advanced Urothelial Carcinoma Treated with Erdafitinib: THOR and BLC2001 trials

Narrative Summary:

Advanced urothelial carcinoma is a serious form of bladder cancer that is often treated with erdafitinib when the tumor contains alterations in the FGFR3 gene. However, not all FGFR3 alterations are the same, and it is not known whether different FGFR3 mutation subtypes are associated with different treatment responses or survival outcomes. This study will combine individual patient data from the phase II BLC2001 trial and the phase III THOR trial to compare objective response rate, progression-free survival, and overall survival according to specific FGFR3 mutation subtypes. By identifying genomic factors associated with better or worse outcomes, this study aims to improve our understanding of which patients are most likely to benefit from erdafitinib and to support more personalized treatment strategies for patients.

Scientific Abstract:

Background:
Erdafitinib is an approved FGFR inhibitor for patients with locally advanced or metastatic urothelial carcinoma harboring FGFR2/3 alterations. However, FGFR3 mutations comprise multiple molecular subtypes, and it remains unclear whether treatment outcomes differ according to specific mutation subtypes.

Objective:
To evaluate the association between FGFR3 mutation subtypes and clinical outcomes in patients with advanced urothelial carcinoma treated with erdafitinib.

Study Design:
A pooled post hoc individual patient data (IPD) analysis of the phase II BLC2001 trial and the phase III THOR trial.

Participants:
Patients with locally advanced or metastatic urothelial carcinoma harboring FGFR3 alterations who received erdafitinib.

Primary and Secondary Outcome Measure(s):
The primary endpoint is objective response rate (ORR). Secondary endpoints include progression-free survival (PFS), overall survival (OS), duration of response (DoR), disease control rate (DCR), and safety. Outcomes will be compared according to FGFR3 mutation subtype.

Statistical Analysis:
ORR will be compared using logistic regression and Fisher's exact test. PFS, OS, and DoR will be analyzed using Kaplan--Meier estimates and Cox proportional hazards models. Multivariable analyses will adjust for clinically relevant covariates, and prespecified subgroup and sensitivity analyses will be performed.

Brief Project Background and Statement of Project Significance:

Patients with locally advanced or metastatic urothelial carcinoma (mUC) harboring susceptible FGFR2/3 alterations represent a distinct molecular subgroup for whom erdafitinib has become an established treatment option. The phase II BLC2001 trial demonstrated clinically meaningful antitumor activity of erdafitinib, and the phase III THOR trial subsequently confirmed its superiority over chemotherapy in previously treated patients with FGFR-altered mUC. These studies established FGFR inhibition as an important therapeutic strategy for this molecularly defined population.

Although activating FGFR3 mutations account for most FGFR alterations in mUC, they comprise several recurrent molecular subtypes, including S249C, Y373C, R248C, and G370C. Experimental studies have shown that these mutations differ in their structural location, receptor activation mechanisms, and downstream signaling properties, suggesting that they may not be biologically equivalent. However, clinical studies have generally evaluated patients according to the presence or absence of FGFR alterations, and it remains unknown whether individual FGFR3 mutation subtypes are associated with differences in response to erdafitinib or long-term clinical outcomes.

This study will perform a pooled individual patient data (IPD) analysis of patients treated with erdafitinib in the BLC2001 and THOR trials. By combining these complementary datasets, we will evaluate objective response rate, progression-free survival, overall survival, duration of response, and disease control rate according to specific FGFR3 mutation subtypes. We will also explore outcomes according to functional mutation domains and FGFR3 fusion status where appropriate. Multivariable analyses will be performed to account for clinically relevant prognostic factors and to determine whether mutation subtype independently predicts treatment outcomes.

The proposed study addresses an important unmet need in precision oncology. If clinically meaningful differences in efficacy are identified among FGFR3 mutation subtypes, these findings could improve patient stratification, refine biomarker-driven treatment selection, and provide new insights into the biological heterogeneity of FGFR3-altered urothelial carcinoma. Even if no significant differences are observed, the study will provide valuable evidence supporting the use of erdafitinib across different FGFR3 mutation subtypes. The results will contribute to a better understanding of genomic determinants of response to FGFR inhibition and may inform the design of future clinical trials and translational studies investigating mechanisms of sensitivity and resistance.

References

Loriot Y, Necchi A, Park SH, et al. Erdafitinib in locally advanced or metastatic urothelial carcinoma. N Engl J Med. 2019.
Powles T, et al. THOR: Phase III trial of erdafitinib versus chemotherapy in patients with FGFR-altered advanced urothelial carcinoma.
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Specific Aims of the Project:

The primary objective of this study is to determine whether clinical outcomes following erdafitinib treatment differ according to specific FGFR3 mutation subtypes in patients with locally advanced or metastatic urothelial carcinoma. Using pooled individual patient data from the BLC2001 and THOR trials, we will compare objective response rate (ORR), progression-free survival (PFS), overall survival (OS), duration of response (DoR), and disease control rate (DCR) among patients with different FGFR3 mutation subtypes.

Secondary objectives are to evaluate treatment outcomes according to functional mutation domains (extracellular, transmembrane, and kinase domains) and FGFR3 fusion status, and to determine whether FGFR3 mutation subtype is independently associated with treatment efficacy after adjustment for established clinical prognostic factors.

We hypothesize that recurrent FGFR3 mutation subtypes differ in their sensitivity to erdafitinib because of distinct biological and structural properties. We further hypothesize that specific FGFR3 mutation subtypes are associated with superior or inferior clinical outcomes and that mutation subtype may serve as a predictive biomarker for response to FGFR-targeted therapy.

Study Design:

Individual trial analysis

What is the purpose of the analysis being proposed? Please select all that apply.

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

Individual patient data from the phase II BLC2001 trial and the phase III THOR trial will be used. The study population will include all patients who received erdafitinib and have available information on FGFR3 alteration status and clinical outcomes. Patients will be included if they have locally advanced or metastatic urothelial carcinoma with susceptible FGFR3 mutations or fusions and received at least one dose of erdafitinib.

Patients without available FGFR3 mutation subtype information or without evaluable efficacy data for the primary endpoint will be excluded from analyses requiring these variables. No additional demographic or clinical exclusion criteria will be applied. For analyses of specific FGFR3 mutation subtypes, patients will be categorized according to recurrent mutations (e.g., S249C, Y373C, R248C, G370C, and other mutations), functional mutation domains, or FGFR3 fusion status, depending on data availability.

Individual patient data from BLC2001 and THOR will be pooled and analyzed using a common statistical analysis plan. All analyses will be conducted within the approved secure data-sharing platform provided for the requested datasets.

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

Primary Outcome Measure:
The primary outcome will be objective response rate (ORR), defined as the proportion of patients achieving a complete response (CR) or partial response (PR) according to RECIST version 1.1, as assessed in the original clinical trials. ORR will be compared across individual FGFR3 mutation subtypes.

Secondary Outcome Measures:
Secondary outcomes will include progression-free survival (PFS), defined as the time from initiation of erdafitinib treatment to radiographic disease progression or death; overall survival (OS), defined as the time from treatment initiation to death from any cause; duration of response (DoR), defined among responders as the time from first documented response to disease progression or death; disease control rate (DCR), defined as the proportion of patients achieving CR, PR, or stable disease; and safety, assessed using the incidence of treatment-related adverse events, when available.

Patients will be categorized according to individual FGFR3 mutation subtypes (e.g., S249C, Y373C, R248C, G370C, and other mutations). Exploratory analyses will also evaluate outcomes according to functional mutation domains and FGFR3 fusion status.

No changes to the primary or secondary outcome measures are anticipated between this proposal and the final study report.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

The primary independent variable is FGFR3 mutation subtype. Patients will be categorized according to recurrent FGFR3 mutations, including S249C, Y373C, R248C, G370C, and other less common mutations, based on the genomic data available in the BLC2001 and THOR trials. Where appropriate, additional analyses will classify mutations according to their functional domains (extracellular, transmembrane, or kinase domain) and compare mutation-positive tumors with FGFR3 fusion-positive tumors.

FGFR3 mutation subtype will be evaluated as the primary predictor of objective response rate (ORR), progression-free survival (PFS), overall survival (OS), duration of response (DoR), and disease control rate (DCR). Multivariable analyses will adjust for established clinical prognostic factors, including ECOG performance status, prior systemic therapy, prior immune checkpoint inhibitor exposure, visceral metastases, primary tumor location, and trial, to assess the independent association between FGFR3 mutation subtype and clinical outcomes.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

The following variables will be included to characterize the study population and, where appropriate, as covariates in multivariable analyses: age, sex, ECOG performance status, primary tumor location (bladder vs upper urinary tract), disease stage, presence of visceral metastases (including liver metastases), prior systemic therapy, prior platinum-based chemotherapy, prior immune checkpoint inhibitor exposure, line of erdafitinib treatment, and trial (BLC2001 or THOR).

Tumor-related variables will include FGFR alteration type (mutation or fusion), functional mutation domain, and PD-L1 expression status, if available. Additional baseline clinical characteristics available within the trial datasets may also be summarized descriptively.

Continuous variables will be analyzed as continuous or categorized according to clinically relevant cutoffs, as appropriate. Categorical variables will be analyzed using the classifications defined in the original trial datasets. Variables included in multivariable models will be selected based on clinical relevance and data availability.

Statistical Analysis Plan:

Descriptive statistics will be used to summarize baseline demographic, clinical, and molecular characteristics. Continuous variables will be presented as means with standard deviations or medians with interquartile ranges, as appropriate, and compared using Student's t-test or the Wilcoxon rank-sum test. Categorical variables will be summarized as frequencies and percentages and compared using the chi-square test or Fisher's exact test.

The primary endpoint, objective response rate (ORR), will be compared among FGFR3 mutation subtypes using Fisher's exact test and multivariable logistic regression. Odds ratios (ORs) and 95% confidence intervals (CIs) will be estimated after adjustment for clinically relevant covariates.

Progression-free survival (PFS), overall survival (OS), and duration of response (DoR) will be estimated using the Kaplan--Meier method and compared using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals will be estimated using Cox proportional hazards regression

models. The proportional hazards assumption will be evaluated using Schoenfeld residuals. If the assumption is violated, restricted mean survival time (RMST) analyses will be performed as sensitivity analyses.

Multivariable analyses will adjust for clinically relevant baseline variables, including age, sex, ECOG performance status, primary tumor location, visceral metastases, prior platinum-based chemotherapy, prior immune checkpoint inhibitor exposure, line of therapy, and trial (BLC2001 or THOR), depending on data availability. Trial will also be included as a stratification factor or covariate to account for differences in study design and patient populations.

Exploratory analyses will compare outcomes according to individual FGFR3 mutation subtypes, functional mutation domains (extracellular, transmembrane, and kinase domains), and FGFR3 fusion status. Where sample size permits, interaction analyses will evaluate whether the association between FGFR3 mutation subtype and treatment outcomes differs across clinically relevant subgroups.

Sensitivity analyses will assess the robustness of the findings by excluding rare mutation subtypes, restricting analyses to patients with recurrent hotspot mutations, and performing separate analyses within each trial. All statistical tests will be two-sided, and a p-value <0.05 will be considered statistically significant. Because this is an exploratory post hoc analysis, no formal adjustment for multiple comparisons is planned, and all findings will be interpreted as hypothesis-generating.

Software Used:

R

Project Timeline:

The anticipated project start date is October 2026, following approval of the data request and execution of the Data Use Agreement. Data cleaning, harmonization, and statistical analyses are expected to be completed by March 2027. Additional sensitivity and subgroup analyses will be finalized by May 2027. Preparation of the first manuscript is anticipated to be completed by July 2027, with submission to a peer-reviewed journal by August 2027. Any required revisions will be addressed following peer review. Study findings and publication details will be reported to the YODA Project upon manuscript submission and again following publication, in accordance with the Data Use Agreement. The project is expected to be completed within the initial 12-month data access period.

Dissemination Plan:

The findings of this study will be disseminated through presentation at national and international scientific meetings and publication in a peer-reviewed journal. The primary product will be an original research manuscript describing the association between FGFR3 mutation subtypes and clinical outcomes following erdafitinib treatment in patients with advanced urothelial carcinoma. Target journals include European Urology Oncology, BJU International, Clinical Genitourinary Cancer, and Cancer Medicine, depending on the scope and impact of the final results. Study findings will also be shared with the scientific and clinical communities through conference presentations and reported to the YODA Project in accordance with the Data Use Agreement. The results are expected to improve understanding of genomic predictors of response to FGFR-targeted therapy and support future biomarker-driven treatment strategies.

Bibliography:

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- Powles T, Rosenberg JE, Sonpavde GP, et al. Erdafitinib versus chemotherapy in previously treated patients with advanced urothelial carcinoma and selected FGFR alterations (THOR): a phase 3, randomized, open-label trial. *N Engl J Med.* 2024.

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- van Rhijn BWG, Mertens LS, Mayr R, et al. FGFR3 alterations in bladder cancer: biological and clinical implications. *European Urology.* 2020.
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