P0141

A Phase 2A/B, Multicenter, Open-Label Study Evaluating the Efficacy and Safety of Dabogratinib (TYRA-300) in Participants With Low-Grade Upper Tract Urothelial Carcinoma (SURF303)

Surena F. Matin,[1] Gautam Jayram,[2] Laura Bukavina,[3] Xin Huang,[4] Viraj Degaonkar,[4] Dinesh Ganapathy,[4] Erik Goluboff,[4] Morgan Rouprêt[5]

BACKGROUND

- UTUC is a relatively rare malignancy, representing 5%–10% of urothelial carcinomas[1,2], yet it is associated with diagnostic challenges[3], invasive disease[1,4], high recurrence rates[2,4,5], and treatment complexity[5]
- Low-grade UTUC is characterized by a high prevalence of *FGFR3* alterations, reported in approximately 80% and up to 96% of tumors across studies[5–8]
- Standard management includes endoscopic tumor ablation with or without intraluminal chemotherapy or radical nephroureterectomy (NU)[1,2,5,9,10]
- Intracavitary therapy is technically challenging due to upper tract anatomy,[11] is most effective in low-volume disease, and often results in NU as the default curative option for patients with multifocal or high-volume tumors[12]
- A recent preoperative phase 1b study of pan-FGFR inhibition demonstrated the potential for FGFR3 inhibition in UTUC, enabling renal preservation in a proportion of patients[5]
- Currently available FGFR inhibitors lack FGFR3 isoform specificity and are associated with off-target toxicities resulting from inhibition of FGFR1/2/4, including nail disorders, stomatitis, hyperphosphatemia, central serous retinopathy, and other class-related adverse events[13]
  - Dabogratinib is an oral, highly selective FGFR3 inhibitor designed to minimize off-target inhibition while maintaining activity against activating *FGFR3* (Table 1)[13]
  - In the Phase 1 portion of the SURF301 study for metastatic urothelial carcinoma, early clinical data demonstrated infrequent pan-FGFR-associated toxicities, including no hyperphosphatemia, and no dose reductions or discontinuations at 60 mg QD or below (n = 22; data cut off date, August 15, 2024)[14]
  - Dabogratinib is being evaluated in patients with low-grade UTUC in the global phase 2a/b SURF303 study (NCT07265947). 60mg QD is one of two planned doses in the SURF303 study[15]

Table 1. In Vitro FGFR Isoform Selectivity of Dabogratinib IC_{50} (nM)

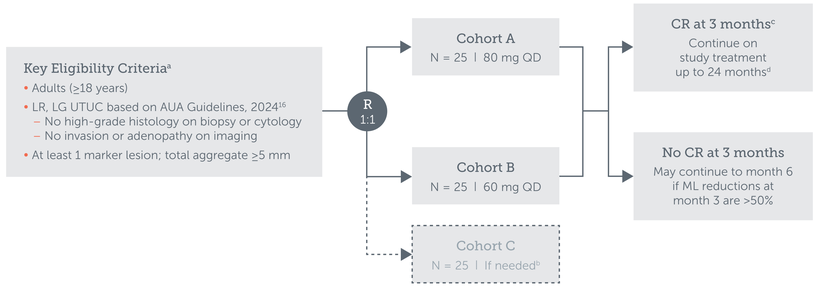
	FGFR3	FGFR1	FGFR2	FGFR4	FGFR1/ FGFR3
Dabogratinib	11	278	157	405	25
Erdafitinib	2.6	5.2	3.8	11	2

In engineered Ba/F3 cell assays, dabogratinib shows potent FGFR3 inhibition, with 25-fold selectivity over FGFR1 compared with 2-fold selectivity for erdafitinib. Half-maximal inhibitory concentration values are shown; lower values reflect stronger inhibition.

METHODS

- SURF303 (NCT07265947) is a phase 2a/b, multicenter, open-label, randomized study evaluating the efficacy and safety of oral dabogratinib QD in adults with low grade UTUC[15]
- Participants are enrolled in a biomarker-unselected population, with retrospective assessment of *FGFR3* alterations, and are stratified by aggregate baseline marker lesion size (<1.5 cm vs ≥1.5 cm)
- Phase 2a employs a parallel, randomized (1:1) design evaluating two dose cohorts
  - Dose cohort A: dabogratinib 60 mg QD
  - Dose cohort B: dabogratinib 80 mg QD
  - An optional third dose cohort may be opened if warranted based on emerging safety and/or efficacy data from cohorts A and B
- Following dose optimization, Phase 2b will enroll additional participants to further evaluate the efficacy, safety, pharmacokinetics, and therapeutic activity of dabogratinib at the selected dose (Figure 1)

Figure 1. Study Design of SURF303



Schematic representation of the study design, illustrating patient, randomization, study cohorts, and dabogratinib dosing assignments.
[a]Stratification by aggregate baseline ML size <1.5 cm vs. ≥1.5 cm.
[b]Cohort C may be initiated if needed following initial data review of the 60 mg QD and 80 mg QD cohorts.
[c]Participants with a reduction in marker lesion(s), as per Investigator assessment, at 3-month assessment will be allowed to continue treatment until Cycle 6 for an evaluation at 6 months.
[d]Assessments are conducted every 3 months through Month 18 and every 6 months thereafter.

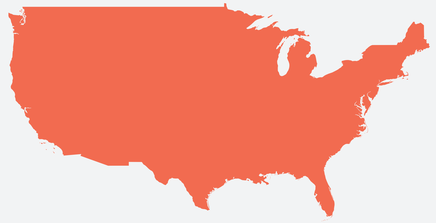
Participant Criteria[15]

Key Inclusion Criteria	Key Exclusion Criteria
• Adults ≥18 years of age • Histologically confirmed low-risk, low-grade upper tract urothelial carcinoma • Both favorable and unfavorable defined by AUA criteria 2024[16] • Presence of residual visible marker lesion(s) ≥5 mm identified within 8 weeks prior to randomization following diagnostic biopsy • Participants must have previous genomic report or archival/fresh tissue and urine samples for retrospective genomic testing • If synchronous NMIBC is present, disease must be fully resected and low-grade Ta or T1 • ECOG PS 0-2 • No evidence of prostatic urethral disease • No prior BCG within 1 year and no intravesical or intracavitary chemotherapy within 8 weeks • Pathology consists of pure UC • Adequate bone marrow, hepatic, and renal function	• High-grade UTUC or any features suggestive of high-grade disease • History of carcinoma in situ • History of prostatic urethra involvement • Current or prior muscle-invasive, lymph-node–positive, or metastatic bladder cancer • Evidence of squamous cell carcinoma, adenocarcinoma or undifferentiated carcinoma or small cell carcinoma of the bladder • Currently receiving systemic cancer therapy or systemic immunotherapy within 6 months of randomization • Current or prior history of pelvic external beam radiotherapy for bladder cancer • Prior treatment with an intravesical or intracavitary agent within 8 weeks of cycle 1, day 1 • Prior treatment with an FGFRi • Current evidence of central serous retinopathy or retinal pigmented epithelial detachment of any grade • Use of prohibited CYP3A inhibitors or inducers

Study Endpoints[15]

Primary Endpoint	Secondary Endpoints
• Complete response rate within 6 months in participants with *FGFR3*-altered low-grade UTUC	• Complete response rate within 6 months in all participants with low-grade UTUC • Duration of response among participants achieving a complete response (up to 36 months) • Complete response rate at 12 and 24 months • Safety and tolerability (up to 2 years) • Rate of renal preservation (up to 2 years) • Change from unresectable UTUC to resectable UTUC (up to 2 years)

SURF303 PROPOSED SITE LIST



UNITED STATES

- Loma Linda, CA
- Los Angeles, CA
- Tampa, FL
- Atlanta, GA
- Maywood, IL
- Jeffersonville, IN
- Greenwood, IN
- Plymouth, MA
- Royal Oak, MI
- Ann Arbor, MI
- St. Louis, MO
- Sewell, NJ
- Albany, NY
- New York, NY
- Syracuse, NY
- Columbus, OH
- Cleveland, OH
- Hershey, PA
- Philadelphia, PA
- Radnor, PA
- Mount Pleasant, SC
- Nashville, TN[a]
- Austin, TX
- Houston, TX
- Dallas, TX
- Seattle, WA

[a]The study is enrolling in the United States with additional site activations planned globally.

ISRAEL

- Holon
- Tel Aviv-Yafo
- Kefar Sava
- Ramat Gan
- Jerusalem

FRANCE

- Lille
- Paris
- Saint-Étienne

SPAIN

- Madrid
- Cadiz
- Valencia

BULGARIA

- Sofia
- Plovdiv

Abbreviations

AUA, American Urological Association; BCG, bacillus Calmette-Guérin; CYP3A, cytochrome P450 3A; ECOG PS, Eastern Cooperative Oncology Group performance status; FGFR, fibroblast growth factor receptor; FGFRi, fibroblast growth factor receptor inhibitor; GI, gastrointestinal; IC_{50}, inhibitory half-maximal concentration; IR, intermediate-risk; LG, low-grade; NMIBC, non–muscle-invasive bladder cancer; NU, nephroureterectomy; QD, once daily; R, randomization; TRAE, treatment-related adverse event; TURBT, transurethral resection of bladder tumor; ULN, upper limit of normal; UTUC, upper tract urothelial carcinoma.

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Author Affiliations

[1]MD Anderson Cancer Center, Houston, TX, USA; [2]Urology Associates, PC, Nashville, TN, USA; [3]Cleveland Clinic Glickman Urologic Institute, Cleveland, OH, USA; [4]Tyra Biosciences, Inc., Carlsbad, CA, USA; [5]Sorbonne University, Paris, France

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Sponsor Contact Information

TyraClinicalTrials@tyra.bio | Tyra Biosciences, Inc. | Carlsbad, CA, USA

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