CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2 Multicenter, Open-Label Study Evaluating the Efficacy and Safety of TYRA-300 in Participants with FGFR3 Altered Low Grade, Intermediate Risk Non-Muscle Invasive Bladder Cancer (SURF302)
Investigational Product Number:	TYRA-300
Investigational Product Name:	N/A
US IND Number:	IND 174439
EU CT/ Number:	**2025-521277-14-00**
Sponsor Name:	Tyra Biosciences, Inc. 2656 State Street Carlsbad, CA 92008, USA
Protocol Number:	TYR300-202
Phase:	2
Original Protocol (Version 0):	19 DEC 2024
Amendment #1	**24 Mar 2025**

5. Study Population

All participants must satisfy all the inclusion and exclusion criteria in this protocol to enroll in this study. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

1. Participants age ≥ 18 at the time of informed consent and willing and able to comply with all required study procedures
2. Able to understand and given written informed consent
3. Participants with histologically confirmed low-grade NMIBC within 6 weeks prior to randomization with prior diagnostic biopsy/TURBT to confirm stage and grade and with at least 3 mm and no more than 12 mm total (1/2 a resectoscope loop to 2 loops, refer to Section 8.1.5) residual visible tumor as a marker lesion(s) left behind:
    a. Ta low grade
    b. T1 low grade
4. Participants must have intermediate risk NMIBC, defined as having any of the following characteristics (AUA Guidelines, 2024)
    a. Recurrence within 1 year, LG Ta
    b. Solitary LG Ta >3cm
    c. LG Ta, multifocal
    d. LG T1
5. Documented activating FGFR3 mutation or fusion (Appendix 4)
6. Have undergone bladder mapping and identification of visible marker lesion(s) within 6 weeks prior to randomization (refer to Inclusion Criterion #3)
7. No evidence of urothelial carcinoma of the upper urinary tract (confirmed by imaging) or prostatic urethra within 6 months of randomization
8. No prior BCG administration within 1 year of date of consent.
9. No intravesical chemotherapy within 8 weeks prior to C1D1.
10. ECOG 0-1
11. Pathology consistent with pure urothelial carcinoma; if mixed histology, ensure that at least 80% of the sample is urothelial
12. Adequate bone marrow, liver, and renal function:
    b. Bone marrow function:
        i. Absolute neutrophil count (ANC) ≥1,500/mm3
        ii. Platelet count ≥75,000/mm3

iii. Hemoglobin ≥10.0 g/dL

e. Liver function:

i. Total bilirubin ≤ ULN

ii. Alanine aminotransferase (ALT) ≤ ULN

iii. Aspartate aminotransferase (AST) ≤ ULN

f. Renal function:

i. estimated glomerular filtration rate >60 mL/min calculated using the modification of diet in renal disease equation or CKD-EPI formula

ii. Serum Phosphate level ≤ ULN prior to starting treatment

g. Coagulation

i. International normalized ratio (INR) ≤1.5 × ULN

13. Ability to swallow tablets
14. Participants (male and female) of child-bearing potential (including females who are post-menopausal for less than 1 year) must be willing to practice effective contraception while on treatment and be willing and able to continue contraception for 3 months (males) and 6 months (females) after the last dose of study treatment. Potential male participants should consider the potential impact of TYRA-300 on their ability to father a child and discuss options with the site study staff.
15. Potential participants who are positive for human immunodeficiecy virus (HIV) must have a viral load below the limits of detection and on stable antiretroviral therapy for at least 3 months prior to C1D1. NOTE: some of the compounds in antiretroviral therapy may be on the prohibited medications list. Allowances will be made to ensure the participant's HIV treatment continues uninterrupted following a discussion with the Sponsor's medical monitor. A discussion of the impact of the antiretroviral therapy on TYRA-300 needs to be discussed with the potential participant prior to C1D1.
16. Potential participants with chronic heptatitis B virus (HBV) infection with active disease should be on a suppressive antiviral therapy prior to C1D1.
17. Potential participants patients with a history of hepatitis C virus (HCV) infection should have completed curative antiviral treatment and must have a HCV viral load below the limit of quantification.
18. Potential participants with a history of HCV infection and on current treatment must have a HCV viral load below the limit of quantification

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Presence of tumor in ureter or prostatic urethra
2. Current or previous history of muscle invasive bladder cancer
3. Current or previous history of lymph node positive and/or metastatic bladder cancer