CLINICAL STUDY PROTOCOL

A Phase 1/2a Study of STM-416 Administered Intraoperatively to Patients Undergoing Transurethral Resection of Bladder Tumor (TURBT) for Recurrent High-Grade Papillary Bladder Cancer

Investigational Product: STM-416

Protocol Number: STM-416-01

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OBJECTIVES AND ENDPOINTS:

Objectives	Endpoints
Phase 1	
Primary	
• To evaluate the safety and tolerability of STM-416 in patients with a history of high-grade Ta or T1 NMIBC without CIS with recurrent papillary tumors undergoing TURBT.	• Incidence of dose-limiting toxicities; and • Incidence of AEs or SAEs.
Secondary	
• To evaluate the pharmacokinetic and pharmacodynamic data of resiquimod (R848) after administration of STM-416 in patients with a history of high-grade Ta or T1 NMIBC without CIS with recurrent papillary tumors undergoing TURBT.	• Quantitation of resiquimod (R848) in patient blood including C_{max}, $AUC_{0\text{-}last}$, and T_{max} for the single dose at several time points post-treatment; and • Measurement of pharmacodynamic parameters including urine cytokines.
Phase 2a	
Primary	
• To evaluate the effect of STM-416 on recurrence-free survival time in patients with a history of high-grade Ta or T1 NMIBC without CIS with recurrent papillary tumors undergoing TURBT. Recurrence will be evaluated by cystoscopy and urine cytology.	• Time to event Kaplan-Meier analysis for recurrence up to 2 years post-dosing.
Secondary	
• To evaluate the pharmacodynamic data of the 2 STM-416 doses under study administered immediately following TURBT.	• Measurement of pharmacodynamic parameters including urine cytokines.

AE = adverse event; $AUC_{0\text{-}last}$ = area under the concentration time curve from time 0 to the last measurable concentration; CIS = carcinoma in situ; C_{max} = maximum plasma concentration; NMIBC = non-muscle invasive bladder cancer; SAE = serious adverse event; T_{max} = time to reach the maximum plasma concentration; TURBT = transurethral resection of bladder tumor.

POPULATION:

Inclusion Criteria

All patients must meet the following criteria for inclusion:

1. Are aged 18 years or older;
2. Have a history of pathologically confirmed high-grade Ta or T1 non-muscle invasive bladder cancer (NMIBC) without carcinoma in situ (CIS) who have completed standard of care (SOC) previously, with recurrent papillary disease seen on cystoscopy, and who are undergoing TURBT without perioperative intravesical chemotherapy;
3. Are considered high risk for recurrence;
4. Have Eastern Cooperative Oncology Group Performance Status of 0, 1, or 2;
5. Have adequate organ and marrow function as defined below:
    - Hemoglobin ≥9.0 g/dL;
    - Absolute neutrophil count ≥1.0 × 10^9/L (>1000 per mm^3);
    - Platelet count ≥75 × 10^9/L (>75,000 per mm^3);
    - Serum bilirubin ≤1.5 × institutional upper limit of normal (ULN);
    - Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)/alanine aminotransferase (ALT) (serum glutamic-pyruvic transaminase) ≤2.5 × institutional ULN;
    - Urine protein (albumin) ≤ 30mg/g ; and
    - Creatinine clearance (CL) >45 mL/min by the Cockcroft-Gault formula or by 24-hour urine collection for determination of creatinine CL:
        - Males: Creatinine CL (mL/min) = Weight (kg) × (140 − Age)/(72 × serum creatinine (mg/dL)); or
        - Females: Creatinine CL (mL/min) = Weight (kg) × (140 − Age) × 0.85/(72 × serum creatinine (mg/dL)).
6. If sexually active men who have not had a vasectomy, must agree to use 2 acceptable methods of contraception throughout the study (eg, condom plus spermicidal gel) with partners of childbearing potential. Sperm donation is prohibited during the duration of participation in this study and for 21 days after STM-416 administration; and
7. Have an ability to understand and willingness to sign an Institutional Review Board-approved written informed consent document (or that of legally authorized representative, if applicable).

Exclusion Criteria

Patients are to be excluded from the study if they meet any of the following criteria:

1. Have a history of CIS or muscle invasive bladder cancer;
2. Are receiving any other investigational agents;

3. Have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to resiquimod (R848), or excipients used in STM-416 including poloxamer 407 and sodium hyaluronate;
4. Have an uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements. Urinary tract infections are not exclusionary unless they are National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade 3 or higher;
5. Are a woman of childbearing potential regardless of contraceptive use;

   Note: Women of childbearing potential are only to be excluded in Phase 1 and Phase 2a to avoid bias due to the low prevalence of NMIBC in this population. However, they will be included in subsequent Phase 2/3 studies.
6. Have evidence of non-bladder urothelial (transitional cell) carcinoma by biopsy, cytology, or radiological imaging within the past 2 years of treatment (eg, upper tract or urethral transitional cell carcinoma, urethral urothelial carcinoma);
7. Have hydronephrosis, except for those patients where hydronephrosis has been longstanding (ie, predates the diagnosis of the CIS, Ta, or T1 by more than 2 years) and diagnostic evaluation at Screening shows no evidence of tumor causing the hydronephrosis;
8. Have received any other anticancer therapy (eg, chemotherapy, biologic therapy, immunotherapy, targeted therapy, endocrine therapy, radiation therapy, intravesical therapy, investigational agent) within 28 days (Phase 1) and 90 days (Phase 2a) of the study treatment;
9. Have a diagnosis of another malignancy within 2 years before the first dose of study treatment (except for superficial skin cancer; localized prostate cancer on active surveillance; or localized solid tumors deemed cured by surgery or radiation, and not treated with systemic anticancer therapy and not expected to require anticancer therapy in the next 2 years);
10. Have a history of current or prior use of immunosuppressive medication within 28 days before STM-416 treatment, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid;
11. Have active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, Guillain-Barre syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:
    - Patients with vitiligo or alopecia;
    - Patients with hypothyroidism stable on hormonal replacement (defined as no change in medications for 4 months);
    - Patients without active disease in the last 5 years may be included; and
    - Patients with celiac disease controlled by diet alone.
12. Have a history of primary immunodeficiency;

13. Have a QTc interval of >470 ms at Screening;
14. Have a history of allogeneic organ transplant;
15. Have a history of hypersensitivity to imiquimod or resiquimod (R848) or any excipient;
16. Have a known active infection with the following:
    - Tuberculosis (clinical evaluation that includes clinical history, physical examination, radiographic findings, and purified protein derivative testing if indicated);
    - Hepatitis B virus (HBV) or hepatitis C virus (HCV): Patients with active HBV infection or active HCV infection are ineligible. However, patients with a history of HBV infection who have undetectable or low levels of HBV DNA and normal ALT are eligible. Patients with chronic HBV infection who meet the criteria for anti-HBV therapy are eligible if they have initiated anti-HBV therapy prior to treatment with STM-416. Patients with a history of HCV infection are eligible if they have completed curative antiviral treatment and have a viral load that is below the limit of detection; or
    - Human immunodeficiency virus (HIV): Patients living with HIV infection are ineligible only if they have a CD4 count less than 350 cells/μL and a history of an acquired immunodeficiency syndrome (AIDS)-defining infection within the last 12 months. Patients with a CD4 count greater than 350 cells/μL or who have not had an AIDS-defining infection within the last 12 months are eligible. Eligible patients living with HIV should maintain effective anti-retroviral therapy.
17. Have any condition that, in the opinion of the Investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results;
18. Have uncontrolled seizures;
19. Have any unresolved NCI-CTCAE Grade ≥2 toxicity from previous anticancer therapy with the exception of alopecia, and vitiligo;
20. Have Grade ≥2 neuropathy, which will be evaluated on a case-by-case basis after consultation with the Principal Investigator; or
21. Are taking any of the following drugs, or other strong CYP1A2 inhibitors or inducers:
    - Fluvoxamine;
    - Abiraterone;
    - Midostaurin;
    - Enoxacin;
    - Ciprofloxacin;
    - Zafirlukast;
    - Technetium Tc-99m ciprofloxacin;
    - Furafylline;
    - Rofecoxib;
    - Quinidine;
    - Clinafloxacin;
    - Amiodarone; or
    - Viloxazine.