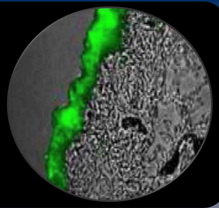
A Phase 2a Marker Lesion Study of Intravesical TSD-001 for Treatment of Low-Grade, Stage Ta, Non-Muscle Invasive Bladder Cancer

Neal Shore, Danny Huynh, Rian Dickstein, David Josephson, Karl Bean, and Michael G. Oefelein

Carolina Urological Research Clinic, Chesapeake Urology Associates Trovare Clinical Research, Tower Urology Research, LIPAC oncology



Introduction

TSD-001 is a third-generation formulation of paclitaxel specifically designed for intracavitary (e.g., urinary, peritoneal, intra-pleural) instillation. LIPAC's preclinical work established TSD-001's (proliposomal paclitaxel) potential to penetrate the urinary bladder's urothelium and persist for up to 48 hours in the urine. Systemic exposure and toxicity after TSD-001 intravesical exposure is minimal. Based on these and other preclinical work, LIPAC Oncology filed an IND with the Food and Drug Administration (FDA; December 2017) and began first in human investigation of TSD-001 to prevent recurrence and progression of NMIBC(May 2018)

Under IND 129419, the sponsor recently completed the treatment portion of an open-label, single-arm phase 1/2a study (Study TD-001) of a proliposomal paclitaxel formulation (TSD 001) administered intravesically to subjects with low grade, stage Ta NMIBC. The study consists of safety assessments, dose escalation (doses between 10 mg to 540 mg), pharmacokinetics (PK) assessments, marker lesion response rate, and surveillance of tumor recurrence.

Methods

TD-001 is a phase 1/2a study to evaluate the safety of TSD-001, the local and systemic paclitaxel PK concentrations after intravesical exposure to TSD-001, the RFS after TURBT and intravesical TSD-001, and the marker lesion response rate after TSD-001 treatment in subjects with low grade, stage Ta NMIBC (low to intermediate risk NMIBC). The study includes 3 parts; part 1 and part 2 are complete, but part 3 is currently ongoing:

TD-001 Part 1 (n=6): Part 1 was a phase 1 study. The primary objective for part 1 was to establish the MTD, which was defined as the dose immediately preceding the dose at which DLT occurred or when a MDD was reached. The severity and frequency of AEs were assessed in the weeks following TSD-001 administration using the NCI CTCAE Version 5.0 definitions.

The secondary objectives for part 1 was to determine the local (bladder urine) and systemic (peripheral blood) paclitaxel PK concentrations before and after intravesical exposure to TSD 001 at all doses. Blood and urine samples were collected 15 minutes (± 15 minutes) before and 2 hours (± 10 minutes) after each instillation.

Exploratory objectives for part 1 included evaluation of the change from baseline to the last post dose time point (Week 16) in urinary HR-QoL as measured by the IPSS (men only) and OAB-q scores.

TD-001 Part 2 (n=9): The primary objective for phase 2a, part 2, was to assess the marker lesion response rate using the MTD/MDD of TSD-001 established in part 1. Subjects in part 2, cohort 1 received once weekly doses of the MDD for 6 weeks (6 total doses), and subjects in part 2, cohort 2 received once weekly doses of the MDD for 8 weeks (8 total doses). For subjects in part 2, cohort 1, the marker lesion response rate assessment occurred at Week 12 (± 7 days). The marker lesion response rate assessment for subjects in part 2, cohort 2 was determined at Week 15 (± 7 days).

The secondary objectives of part 2 were to: 1) determine the systemic (peripheral blood) paclitaxel PK concentrations before and after the third intravesical exposure to TSD-001, and 2) characterize the severity and frequency of AEs following intravesical administration of TSD 001 at the MTD/MDD established in part 1, as defined according to NCI CTCAE Version 5.0.

Paclitaxel PK concentration measurements of peripheral blood during part 2 were obtained at the following time points: 1) 2 hours (± 10 minutes) after the first intravesical instillation, and 2) 15 minutes (± 15 minutes) before and 2 hours (± 10 minutes) after the third intravesical exposure of TSD-001 at the MTD/MDD.

Exploratory endpoints of part 2 included change from baseline to the end of the treatment in IPSS (men only) and OAB-q scores and paclitaxel levels in voided urine samples at 24, 48, and 72 hours after the third instillation of TSD-001.

Safety for parts 1 and 2 was evaluated by analyzing results of AEs, laboratory test, vital signs, electrocardiogram, and physical examination assessments.

Part 3: The primary objective of part 3 is to track recurrence-free survival after exposure to TSD-001.

Results

The intravesical instillation of TSD-001 delivers high urinary concentrations of paclitaxel which persistent for up to 48 hours post instillation. There were no detectable paclitaxel levels in the systemic circulation despite high and dose-proportional levels in the urinary bladder.

TSD-001 was safe when administered intravesically on a biweekly, or weekly schedule in 15 subjects. TSD-001 was also safely administered immediate post-TURBT in 7 patients, and weekly thereafter for up to 8 total intravesical administration. No dose limiting toxicity was observed over a dose range from 10 to 540 mg, and an exposure of 396 to 5036 mg hours and a total dose exposed 243-2880 mg. No SAE attributed to TSD-001 were observed. AEs were otherwise mild-moderate and not dose-limiting.

TSD-001 was well tolerated when intravesically administered on a biweekly or weekly schedule. Both the IPSS and the OAB-q demonstrated no reduction in urinary HRQOL in NMIBC patients after TURBT and repeated (biweekly or weekly) intravesical instillation of TSD-001. Please note that the neither the IPSS nor the OAB-q are specifically validated for NMIBC patients, however, the instruments do provide a general measure of voiding bother and QOL. The tolerability of TSD-001 compares favorably to the historical controls of MMC or BCG reported in SWOG 8795.

TSD-001 demonstrated a 1-year recurrence-free survival result of 83% in low-intermediate risk NMIBC patients when used adjuvant to TURBT. Compared to historical controls derived from the EORTC risk calculator, the expected 12-month RFS is 62-76% for low-intermediate risk patients with NMIBC when treated with incumbent therapies (e.g. Mitomycin C, BCG) after TURBT (www.eortc.be/tools/Bladdercalculator/). In addition, in highly recurrent and pretreated NMIBC patients, a 63% PP marker lesion response rate (56% MITT) was observed, which supports the potential for TSD-001 to reduce recurrences in Ta, low grade NMIBC.

Conclusions

In conclusion, the TSD-001 formulation delivers high and dose proportional paclitaxel levels to the urinary bladder, that demonstrate persistence up to 48 hours post instillation. The TSD-001 formulation was safe when dosed biweekly between 10 and 540 mg, or weekly at 360 mg. Unlike BCG or intravesical chemotherapy, which are associated with inflammatory or chemical cystitis, TSD-001 was well tolerated with no change in urinary HR-QOL as measured by the OAB-q and/or IPSS before, during and after intravesical dosing. Evidence of promising efficacy is demonstrated by both the 1-year RFS (83%) and the marker lesion response rates (63%) in highly recurrent and pretreated patients.

Bibliography

1. Calais da Silva, F., Denis, L., Bono, A., Bollack, C., & Bouffioux, C. (1988). Intravesical chemoresection with 4'-epi-doxorubicin in patients with superficial bladder tumors. Eur Urol, 14(3), 207-209. doi:10.1159/000472938.
2. Sylvester, R. J., van der Meijden, A. P., Oosterlinck, W., Witjes, J. A., Bouffioux, C., Denis, L., & Kurth, K. (2006). Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol, 49(3), 466-465; discussion 475-467. doi:10.1016/j.eururo.2005.12.031.
3. Woldu, S. L., Bagrodia, A., & Lotan, Y. (2017). Guideline of guidelines: non-muscle-invasive bladder cancer. *BJU Int, 119*(3), 371-380. doi:10.1111/bju.13760.
4. Roth, B. J., Dreicer, R., Einhorn, L. H., Neuberg, D., Johnson, D. H., Smith, J. L., . . . Loehrer, P. J. (1994). Significant activity of paclitaxel in advanced transitional-cell carcinoma of the urothelium: a phase II trial of the Eastern Cooperative Oncology Group. *J Clin Oncol, 12*(11), 2264-2270. doi:10.1200/JCO.1994.12.11.2264.