Intravesical Photo Dynamic Therapy for BCG-Unresponsive NMIBC CIS Patients - Phase II Clinical Study Interim Analysis

Kulkarni G.S., Richards K., Black P., Rendon R, Chin J., Shore N., Jayram G., Kramalowsky E., Saltzstein D., Agarwal P., Belkoff L., O'Donnell M., Kamat A., Mandel A., DuMoulin-White R.J., Roufaiel M., Kaspler P., Kassouf W.

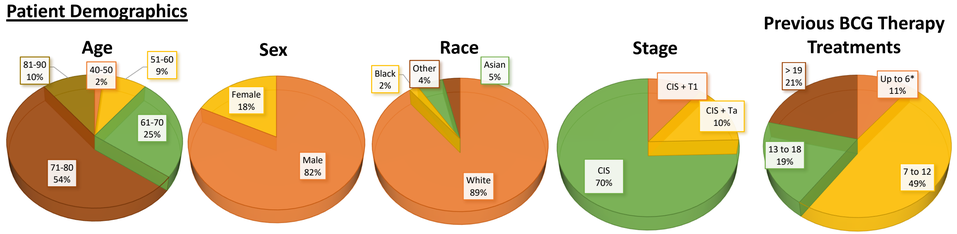
Introduction

Novel therapies are required for Bacillus Calmette-Guerin ("**BCG**")-Unresponsive, high-risk Non-Muscle Invasive Bladder Cancer ("**NMIBC**"). We report the interim results of a Phase II clinical study of Intravesical light-activated Ruvidar® in patients with BCG-Unresponsive Carcinoma In-Situ ("**CIS**") with or without resected Ta / T1 papillary disease.

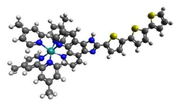
Methods

- Out of a planned 125 patients, 57 patients have been enrolled and provided the primary Study Treatment (46%).
- Study Treatments (Day 0) – intravesical instillation of the the Ruthenium-based photosensitizer Ruvidar® (0.70 mg/cm^2) followed by activation with a 520 nm intravesical laser under general anesthesia (Study Device TLC-3200) to a total of 90 J/cm^2 of laser light).
- An additional Study Treatment was delivered on Day 180 in the absence of progressive or metastatic disease.

Patient Demographics



Study Drug (Ruvidar®)



Study Device (TLC-3200)

Laser Emitter

Laser Detector

Objectives (In compliance with FDA's 2018 Guidance to Industry [1])

- **Primary** – Efficacy - Complete Response ("**CR**"), at any point in time
- **Secondary** - Duration of Efficacy (CR at 12 months, post initial CR)
- **Tertiary** - Safety - Incidence and severity of Adverse Events, Grade 4 or higher directly related to Study Drug and/or Study Device that do not resolve within 450 days post treatment

Notes

- The data analysis is interim in nature and represents the clinical data accrued to date.
- Patients with a negative cystoscopy and positive cytology were defined as Indeterminate Response ("**IR**"), as these patients remain under investigation for lower and/or upper tract urothelial carcinoma. Total Response ("**TR**") is defined as Complete Response ("**CR**") + Indeterminate Response ("**IR**").
- * Intolerant to BCG Therapy

Performance to Objectives

Interim analyses include 52 evaluable patients (patients assessed by a principal investigator) at the 90 day assessment and 12 evaluable patients at the 450 day assessment. Data for the primary and secondary outcomes are listed in the table:

Assessment Day	90	%	180	%	270	%	360	%	450	%
Complete Response ("CR")	28	54%	23	62%	15	56%	9	43%	8	67%
Indeterminate Response ("IR")	6	12%	8	22%	6	22%	2	10%	2	17%
Total Response (CR and IR)	34	65%	31	84%	21	78%	11	52%	10	83%
Evaluable Patients	52		37		27		21		12	

The interim clinical data demonstrates a 90 day CR of 54% and a sustained duration of response in 67% of patients, who remained in the study and were evaluated at 450 days.

There have been nine Serious Adverse Events ("**SAEs**") identified (1 Grade I (sepsis), 2 Grade II (tachycardia, hematuria), 3 Grade III (acute kidney injury, cellulitis), 2 Grade IV (urosepsis, depression/anxiety) and 1 Grade V).

None of the SAEs were deemed to be directly related to the Study Drug or Study Device according to the Data Safety Monitoring Board.

Interim clinical data demonstrates a complete response rate in 54% of evaluable patients at 90 days (n=52) and a sustained duration of this response in 67% of evaluable patients at 450 days (n=12)

Based on the clinical data collected to date, Theralase®'s light-activated Ruvidar® represents a viable treatment option with an acceptable safety profile

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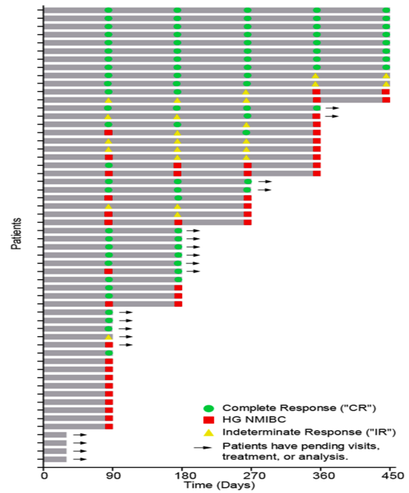
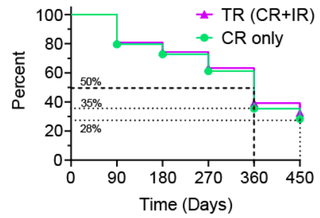
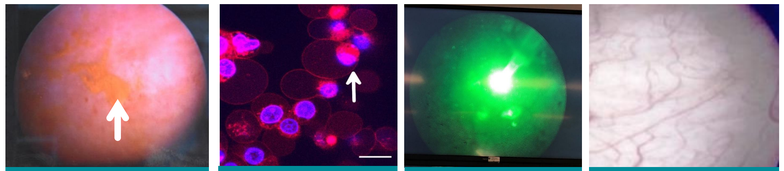
Swimmer's Plot



Kaplan Meier Curve



Study Treatment



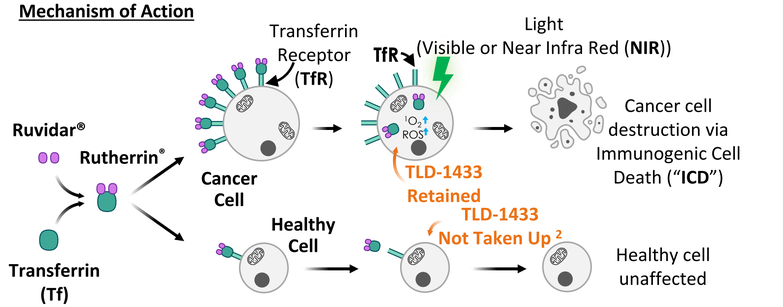
TLD-1433 instilled in bladder via catheter demonstrating absorption into CIS

TLD-1433 localizes preferentially inside bladder cancer cells

Green laser light activates TLD-1433 through fiber optics

Bladder cancer cells destroyed by singlet oxygen and / or Reactive Oxygen Species ("**ROS**")

Mechanism of Action



Future Directions for Research

- Completion of the Phase II NMIBC Clinical Study and submission for regulatory approval
- Clinical development of an injectable form of Ruvidar® (Ruvidar® + transferrin = Rutherrin®) to be administered intravenously for absorption into Non-Small Cell Lung Cancer ("**NSCLC**") and Glio Blastoma Multiforme ("**GBM**"), then activated with X-ray radiation.

[1] BCG-Unresponsive Nonmuscle Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment – Guidance for Industry" Dated: February 2018; www.fda.gov/media/101468/download

[2] Seymour GJ, Walsh MD, Lavin MF, Strutton G, Gardiner RA. Transferrin receptor expression by human bladder transitional cell carcinomas. Urol Res. 1987;15(6):341-4. doi: 10.1007/BF00265663. PMID: 3324443.