



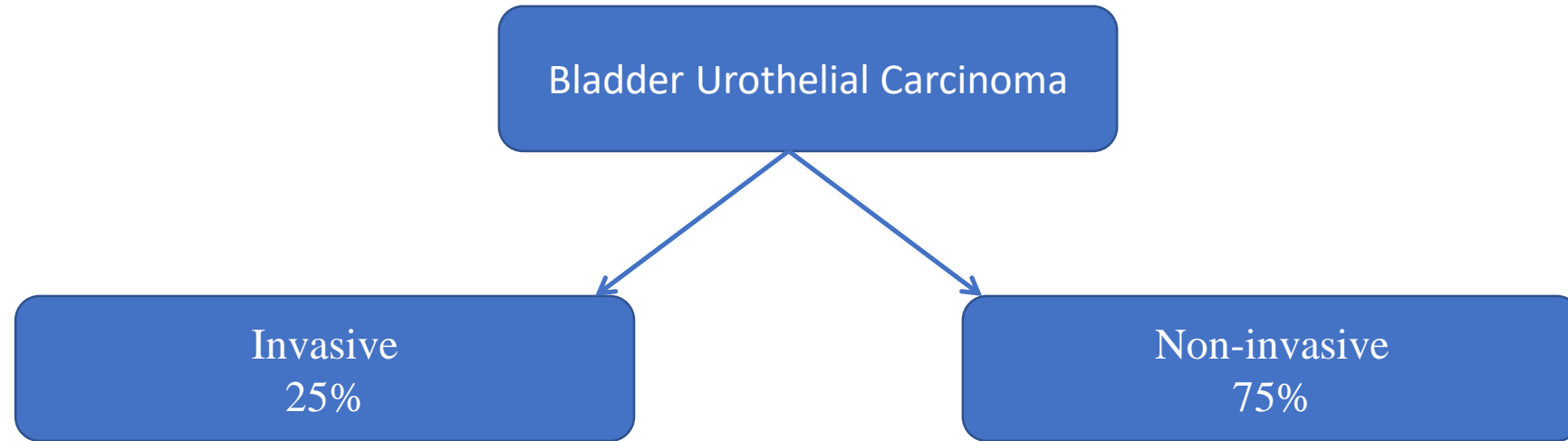
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University of Toronto

# TLD-1433 Photodynamic Therapy for BCG Unresponsive NMIBC: A Phase Ib Clinical Trial

# Disclosures

- **Advisory Board:** Merck, Roche, Theralase, Astellas, Janssen, Bayer, Sanofi
- **Clinical Trials:** Merck, Astra Zeneca, Theralase, BMS

# NMIBC: Unmet Needs

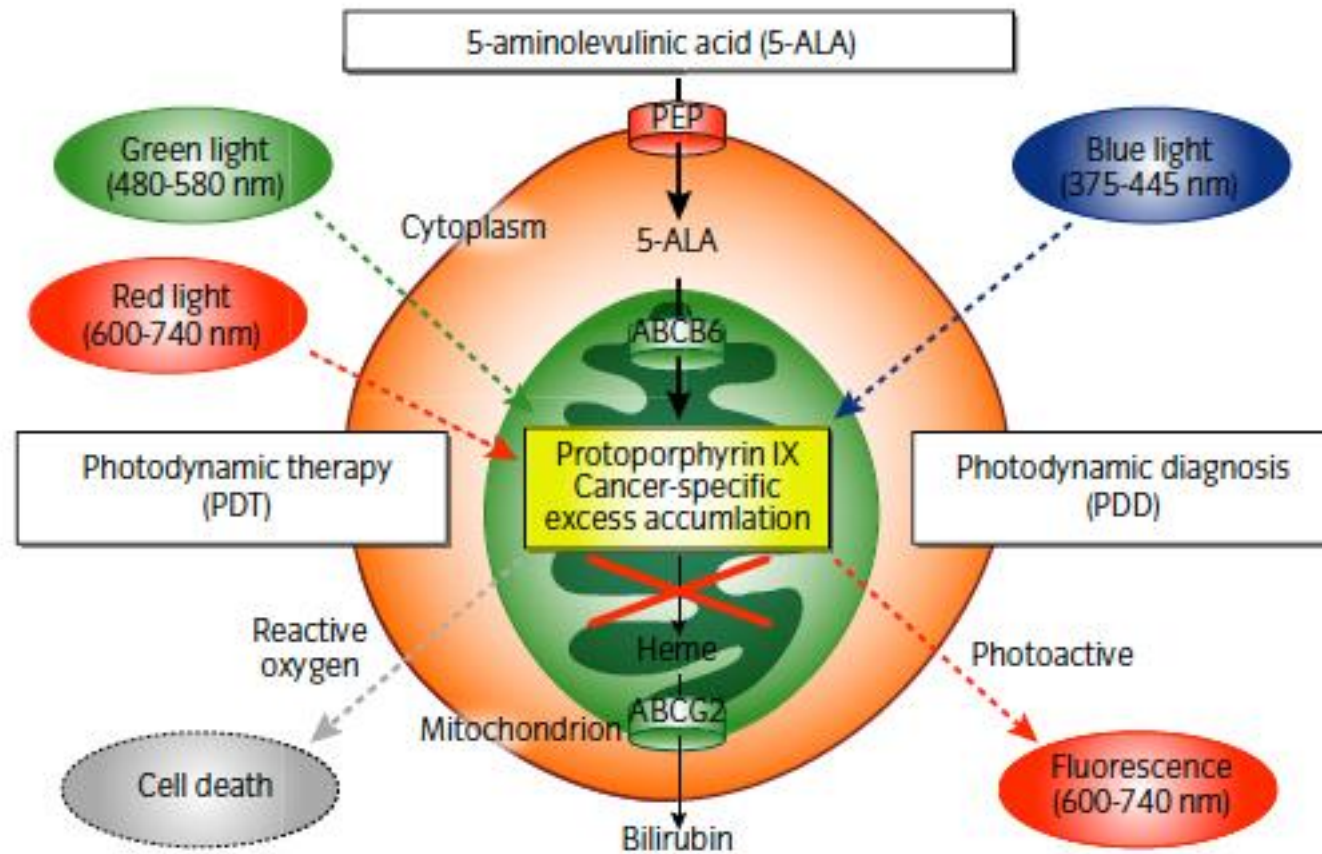


- Recurrence rates 60-70%
- Progression rates of 20-30%
- Only 3 drugs approved in the last 30+ years for NMIBC (by FDA or European Medicines Agency): BCG, Thiotepa, Valrubicin
- No standard therapies for BCG failures other than cystectomy

# Photodynamic Diagnosis vs Therapy

**TREATMENT**

**DIAGNOSIS**



# History of Photodynamic Therapy

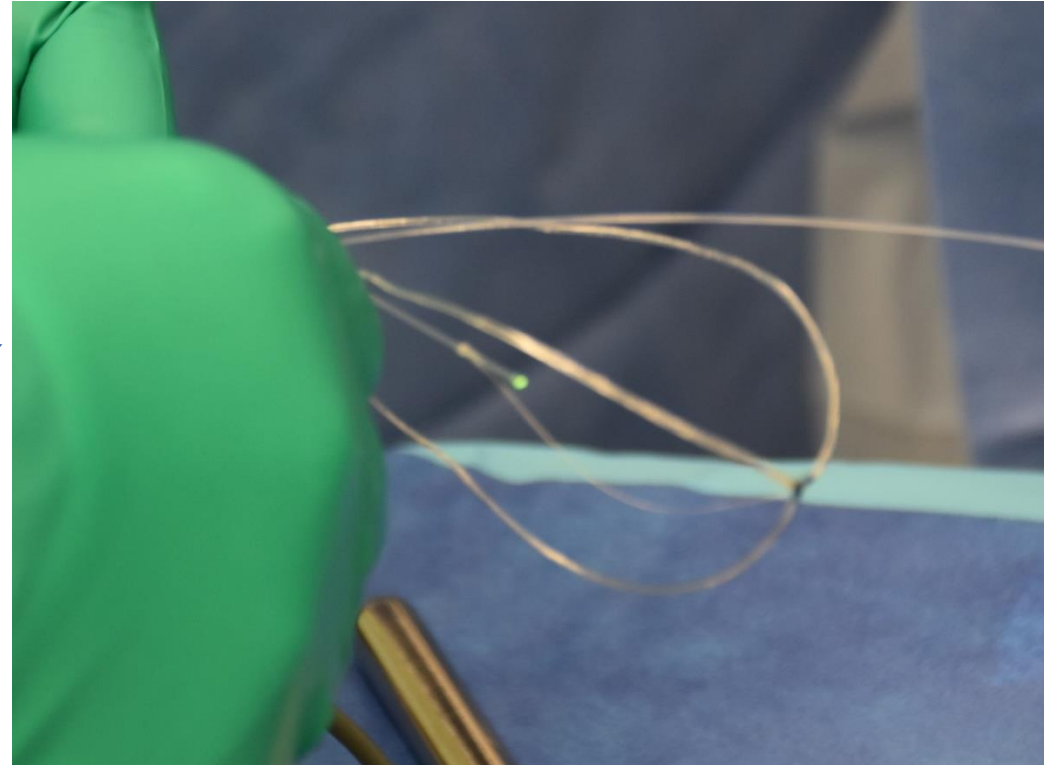
**Table 5.** Previous clinical studies of PDT for bladder cancer

References	No. Pts	Photosensitizer	Light Dose (J/cm <sup>2</sup> )	% Response		AEs
				Early	Late	
Nseyo et al <sup>10</sup>	22	Photofrin II	15-20	83.30	30 (complete)	Irritating LUTS, bladder shrinkage Bladder capacity loss Skin photosensitivity, transient bladder capacity decrease Asymptomatic reflux, bladder contraction, fibrosis Not applicable Bladder contracture Dysuria due to urinary tract infection, hematuria Transient frequency, urgency Vesicoenteric fistula Irritative bladder symptoms, infection, gross hematuria Irritative bladder symptoms, infection, hematuria
D'Hallewin and Baert <sup>25</sup>	18	Photofrin II	75, 100	Not applicable	60	
Uchibayashi et al <sup>26</sup>	23	Hematoporphyrin derivative		73.50	22	
Walther et al <sup>27</sup>	20	Photofrin II	5.1-25.6	45	20	
Nseyo et al <sup>17</sup>	58	Photofrin	10-60	75-84	53	
Manyak and Ogan <sup>28</sup>	34	Porfimer sodium		56	44	
Berger et al <sup>29</sup>	31	5-ALA	30-50	Not applicable	52 (2 yrs)	
Waidelich et al <sup>30</sup>	11	5-ALA	100	Not applicable	46 (18 mos)	
Lee et al <sup>11</sup>	5	Fotolon	10 (intravenous), 24 (intravesical)	80 (6 mos)	60	
Bader et al <sup>20</sup>	17	HAL	25 (PDT 1), 50 (PDT 2), 100 (PDT 3)	52.9 (6 mos)	11.8 (21 mos)	
Present series	34	Radachlorin	15	90.9 (1 yr)	64.4 (2 yrs)	

# History of Photodynamic Therapy

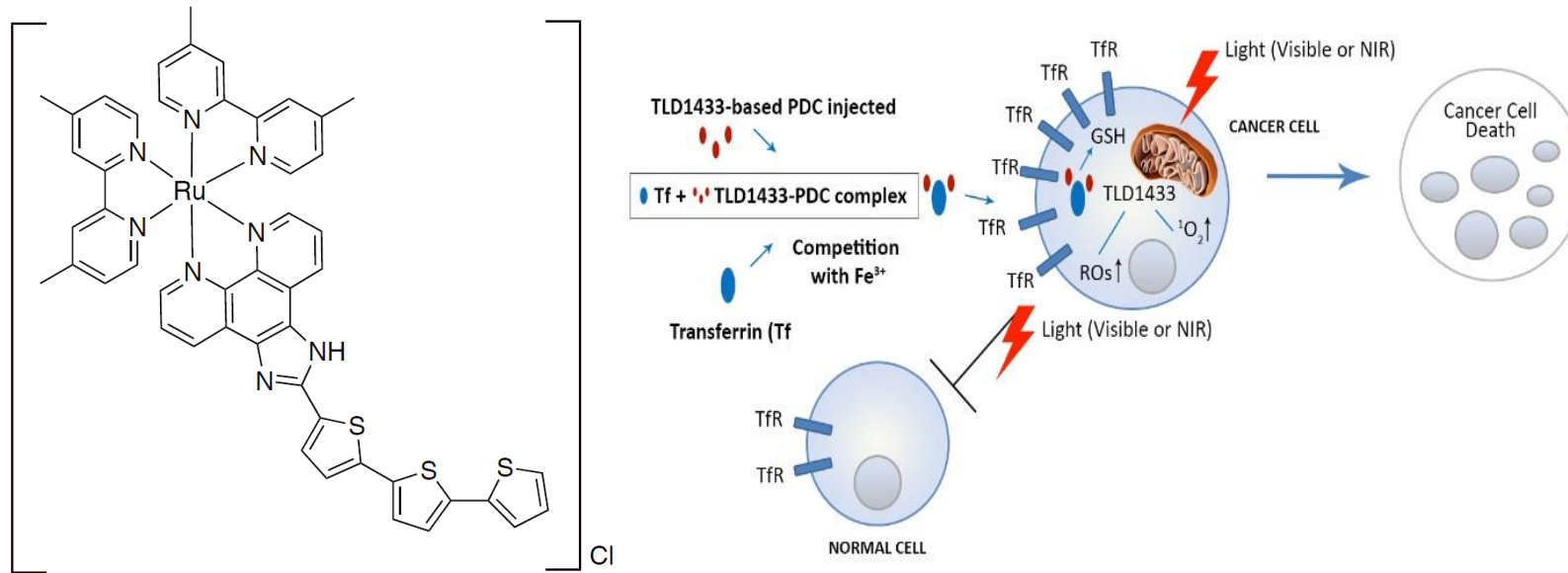
- Issue: “collateral damage”
- Remedies/Amelioration
  - Accurate measurement of light delivery
    - Bladder shape and volume
  - Account for reflected light
  - Increased cancer cell specificity

**TLC-3400 Dosimetry Fibre Optic Cage**



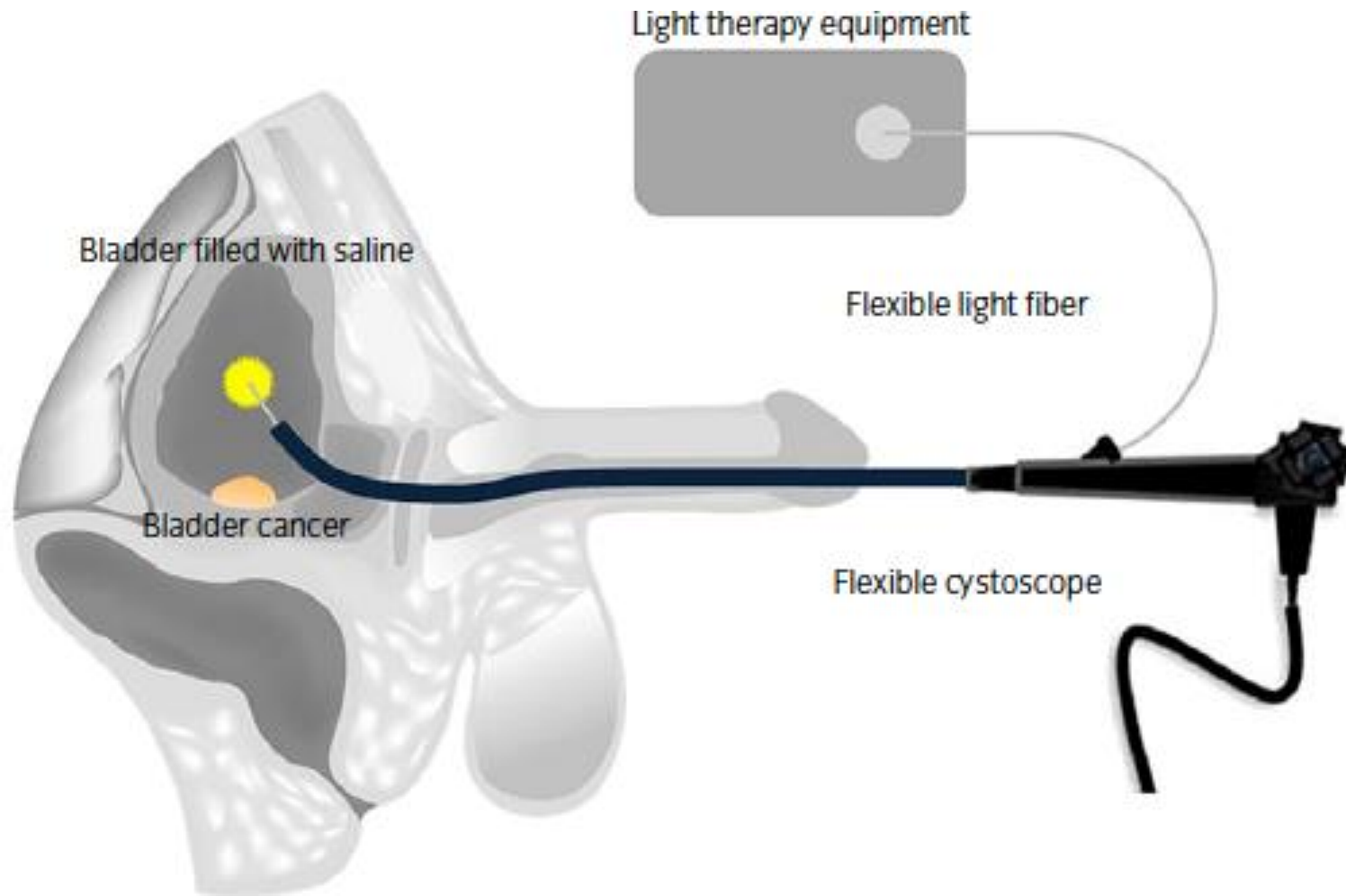
**TLD-1433**

# Compound: TLD-1433



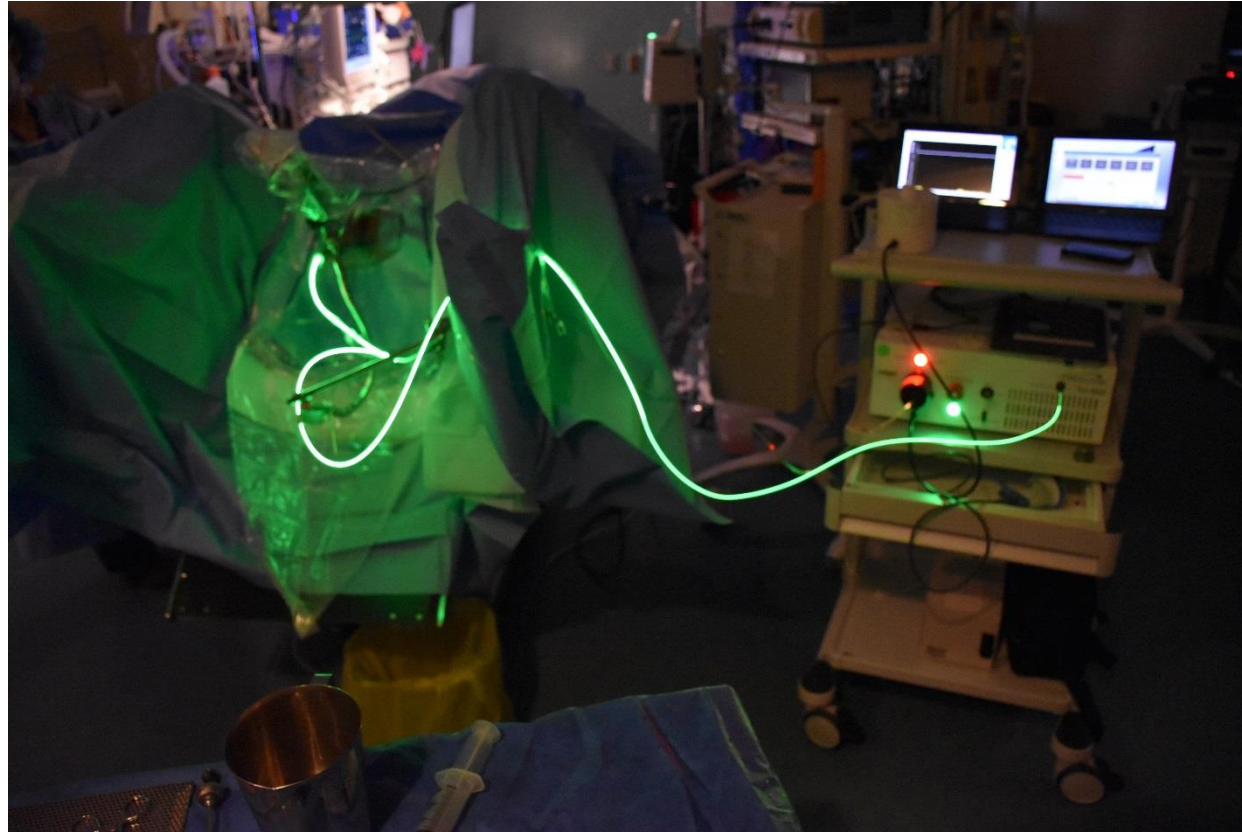
- Completely soluble and stable in water
- High quantum yield (conversion of light to ROS); hence high ROS production
- Preferential bladder tumor accumulation
- Exceptional ability to ablate in-vivo tumors across multiple animal models
- Proven safe in GLP (Good Laboratory Practice) pharmacology and toxicology studies
- Targeting via Transferrin Receptor (“**TfR**”)

# Procedure



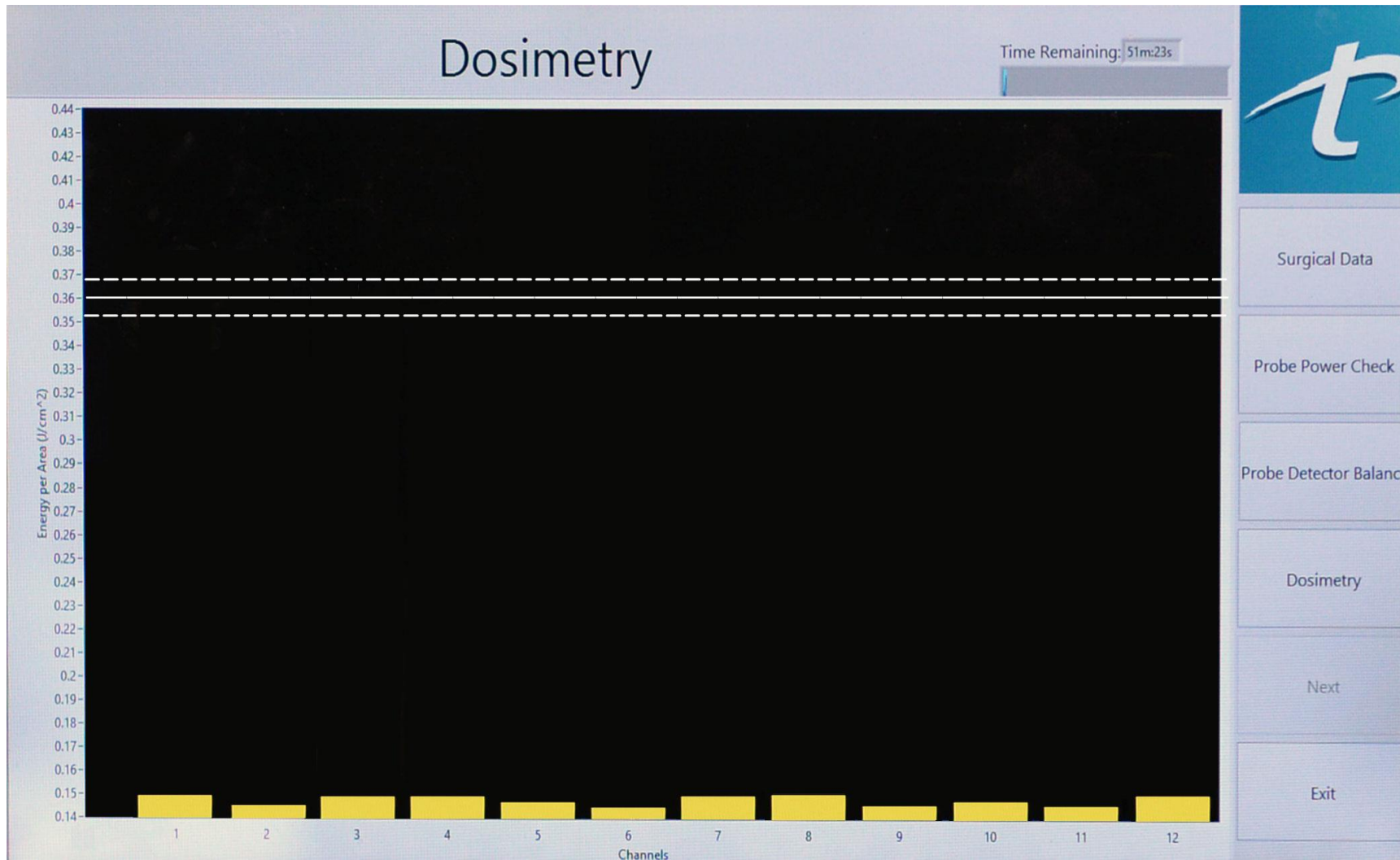


# Treatment Procedure

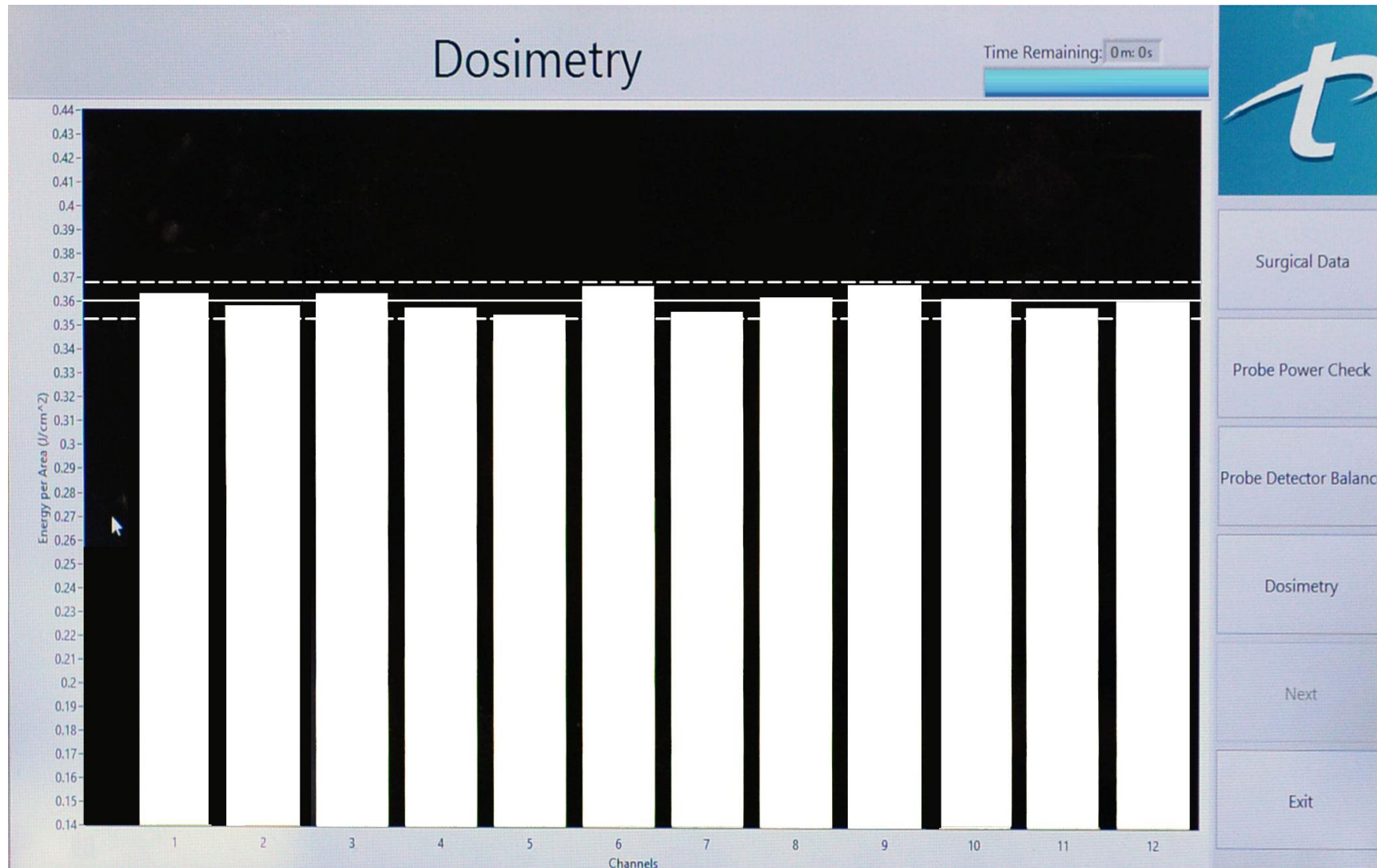


Bladder illuminated with green laser light (525nm) and treatment discontinued when TLC-3200 confirms delivery of approximately  $90\text{J}/\text{cm}^2$ . TLC-3200 measures light delivery in real time, ensuring that the final light dose delivery to the bladder remains at approximately  $90\text{ J}/\text{cm}^2$

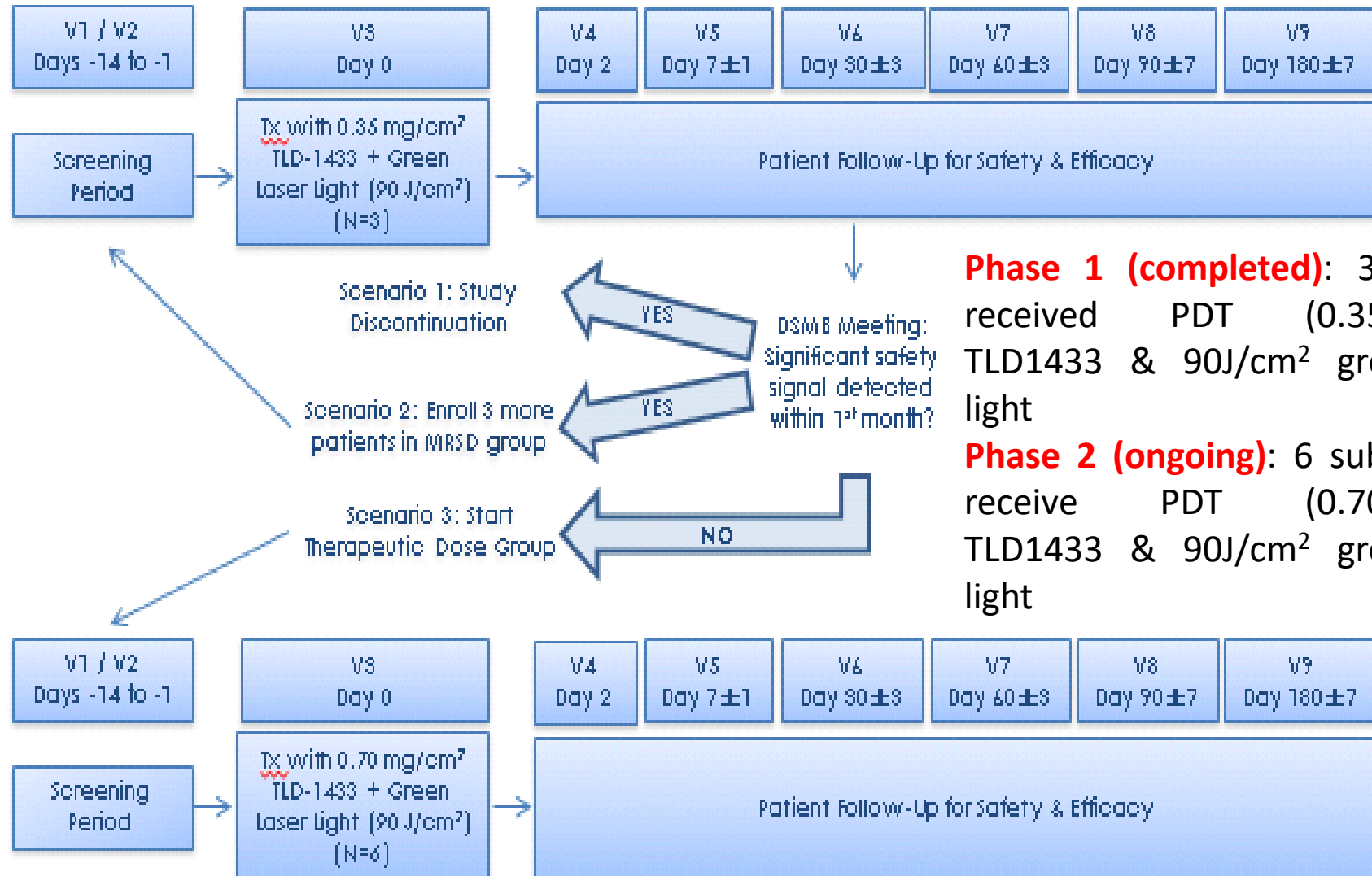
# Dosimetry Screen Prior to Treatment



# Dosimetry Screen Post Treatment



# Phase Ib Study Design: BCG Unresponsive



# Bladder Cancer History

001-001	001-002	001-003
<ul style="list-style-type: none"> <li>• TURBT February 2015 – T1 HG</li> <li>• Re-TURBT March 2015 – CIS</li> <li>• June 2015 - BCG x 6</li> <li>• Cystoscopy w/Bx January 2016 – Partially denuded urothelium w/ dysplasia</li> <li>• TURBT March 2016 – CIS</li> <li>• May 2016 – BCG x 5; developed R testicular mass</li> <li>• TURBT + R orchiectomy August 2016 – CIS, BCG orchitis</li> <li>• Refused further BCG, refused cystectomy, referred for trial</li> <li>• TURBT January 2017 – T1 HG re-TURBT Feb 2017 – T1 HG w/ Cis</li> </ul>	<ul style="list-style-type: none"> <li>• Cystoscopy w/ Biopsy – May 2016 – CIS</li> <li>• July 2016 – BCG x 6</li> <li>• Oct 2016 – BCG x 3</li> <li>• TURBT – Jan 2017 – T1HG + CIS</li> <li>• Re-TURBT – Feb 2017 – CIS</li> </ul>	<ul style="list-style-type: none"> <li>• TURBT– 2012 CIS</li> <li>• 2012 - BCG x 6</li> <li>• TURBT January 2015 – CIS</li> <li>• Feb 2015 – BCG x 6</li> <li>• April 2015 BCG x 3</li> <li>• TURBT Sept 2015 – CIS</li> <li>• Refused cystectomy, referred for trial</li> <li>• TURBT March 2016 – TaHG</li> <li>• April 2016 – BCG x 6</li> <li>• July 2016 – BCG x 3</li> <li>• TURBT – Sept 2016 – CIS</li> <li>• Oct 2016 – Feb 2017 – Merck Pembro trial</li> <li>• TURBT February 2017 – CIS</li> </ul>

# Bladder Cancer History

001-004	001-005	001-006
<ul style="list-style-type: none"> <li>• TURBT January 2012 – T1 HG urothelial carcinoma</li> <li>• Re-resection March 2012 – Negative for malignancy</li> <li>• BCG???</li> <li>• TURBT October 2012 – Ta LG</li>   <li>• TURBT February 2015 – TaHG</li> <li>• BCG x 6 – June/July 2015</li> <li>• TURBT December 2015 - Cis</li> <li>• BCG x 6 – March/April 2016</li> <li>• BCG x 3 – May/June 2016</li> <li>• BCG x 3 – August/September 2016</li> <li>• TURBT January 2017 – Cis</li> <li>• BCG x 6 – Feb/Mar 2017</li> <li>• TURBT May 2017 – T1 HG w/ Cis</li> <li>• Re-resection July 2017 negative</li> </ul>	<ul style="list-style-type: none"> <li>• TURBT July 2015 – T1 LG</li> <li>• TURBT August 2016 – T1 HG</li> <li>• TURBT December 2016 – Negative for Malignancy</li> <li>• BCG x 6 – Feb/Mar 2017</li> <li>• TURBT June 2017 – T1 HG</li> <li>• BCG x 6 - June/July 2017</li> <li>• TURBT Nov 2017 – T1 HG</li> </ul>	<ul style="list-style-type: none"> <li>• TURBT November 2012 – Cis</li> <li>• BCG x 6 – January 2013</li> <li>• TURBT June 2013 – Ta LG</li> <li>• TURBT May 2015 – Negative for malignancy</li> <li>• TURBT October 2016 - Cis</li> <li>• BCG x 6 – Nov/Dec 2016</li> <li>• BCG x 3 – March 2017</li> <li>• BCG x 3 - May 2017</li> <li>• TURBT December 2017 – Cis</li> </ul>

# First 3 Patient: PDT procedure

Subject	001-001	001-002	001-003
Treatment date	March 30 <sup>th</sup> , 2017	April 12 <sup>th</sup> , 2017	April 18 <sup>th</sup> , 2017
Drug instillation	9:03 – 10:03	8:37 – 9:37	7:10 – 8:10
O/R time	10:35 – 15:25 (170 min)	9:52 – 12:32 (160 min)	8:24 – 11:25 (181 min)
Laser activation	Multiple stops and starts in laser activation period		
	12:10 – 14:34	10:57 – 12:08	9:22 – 10:59
Discharge time	19:15	19:00	17:00

# Next 3 Patient: PDT procedure

Subject	001-004	001-005	001-006
Treatment date	July 20 <sup>th</sup> , 2017	January 10 <sup>th</sup> , 2018	February 7 <sup>th</sup> , 2018
Drug instillation	7:09 – 8:10	7:01 – 8:01	7:08 – 8:09
O/R time	8:22 – 10:46 (144 min)	7:48 – 10:36 (168 min)	8:03 – 10:30 (127 min)
Laser activation	Multiple stops and starts in laser activation period		
	9:15 – 10:27	9:17 – 9:31 Fibre tip dislodged 10:00 – 10:23	9:09 – 10:16
Discharge time	17:23	16:00	17:49



# Adverse Events

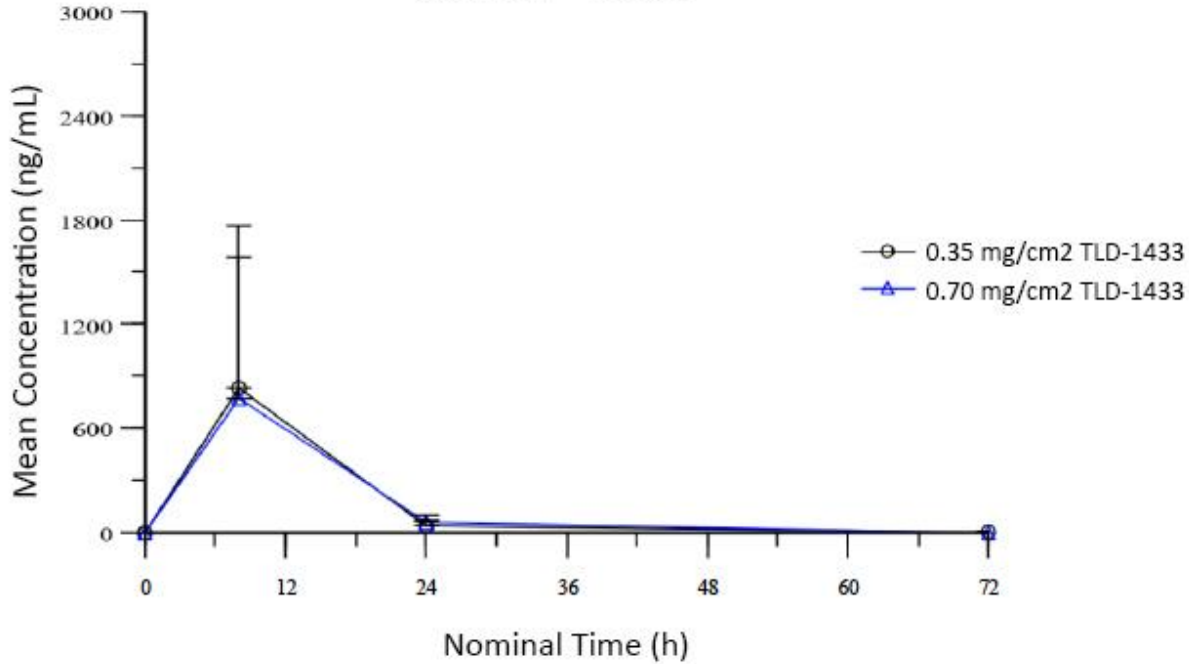
Subject	001-001	001-002	001-003
Pelvic Pain	1 – Mild (ongoing @ End of study)	2 – Moderate (resolved @ day 6)	nil
Bladder Spasms	2 – Moderate (resolved @ day 6); 1 – Mild on day 91 (resolved @ day 91)	2 – Moderate (ongoing @ end of study)	nil
Constipation	1 – Mild (resolved @ day 5)	1 – Mild (resolved @ day 6)	nil
Urge Incontinence	2 – Moderate (resolved @ day 6)	nil	nil
Fatigue	2 – Moderate (onset day 11, ongoing at end of study)	1 – Mild (ongoing @ end of study)	nil
Pain	nil	Joint: 2 – Moderate (onset @ day 13, resolved @ day 57) Low back: 1 – Mild (onset @ day 61, ongoing end of study)	Eye: 1 – Mild (resolved @ day 1)
Penile discomfort	1 – Mild (onset @ day 79, resolved @ day 84)	nil	1 – Mild (resolved @ day 5)
Urinary Frequency	nil	1 – Mild (resolved @ day 22)	1 – Mild (resolved @ day 6)
Other	nil	Hematuria: 1 – Mild (onset @ day 61, resolved @ day 168)	Nocturia: 1 – Mild (onset @ day 170, ongoing at end of study)

# Adverse Events

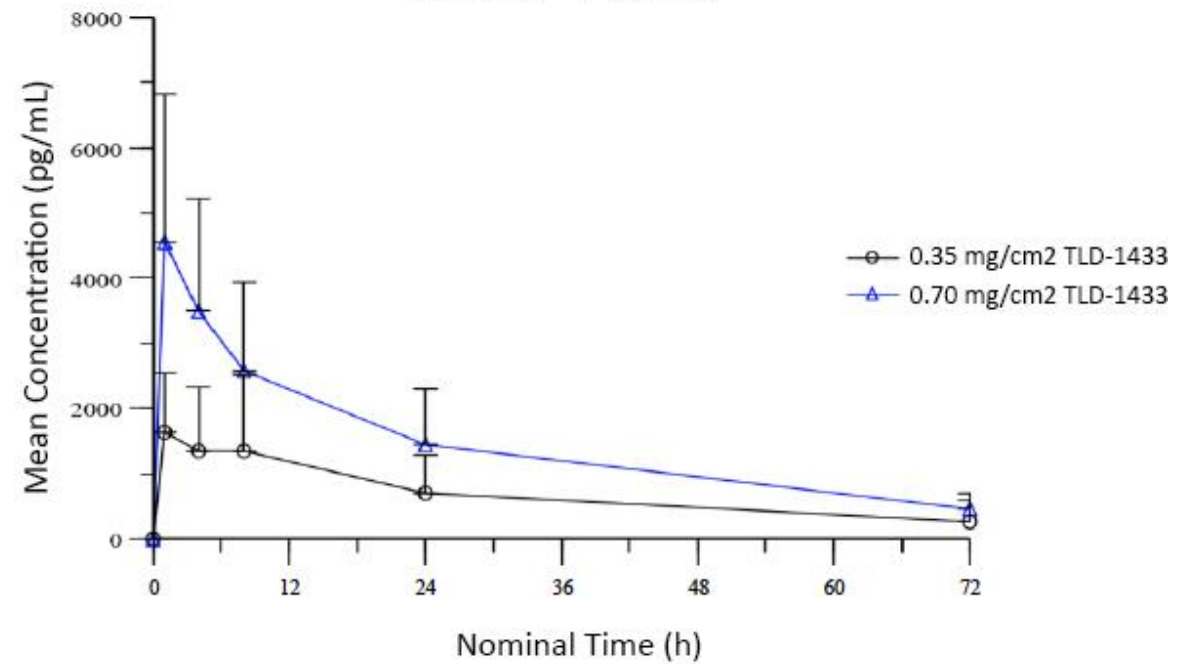
Subject	001-004	001-005	001-006
Urinary Tract Pain	1 – Mild (ongoing at end of study)	1 – Mild (resolved @ day 17)	2 – Moderate (resolved @ day 35)
Bladder Spasms	nil	1 – Mild (resolved @ day 2)	nil
Constipation	1 – Mild (resolved @ day 3)	nil	nil
Urinary Urgency	2 – Moderate (ongoing at end of study)	2 – Moderate (resolved @ day 17) 1 – Mild (onset @ day 38, resolved @ day 40)	ni
Urge Incontinence	nil	2 – Moderate (resolved @ day 17)	2 – Moderate (ongoing @ day 60)
Fatigue	nil	nil	1 – Mild (ongoing @ day 60)
Hematuria	1 – Mild (ongoing at end of study)	1 – Mild (resolved @ day 17)	1 – Mild (resolved @ day 26)
Urinary Frequency	2 – Moderate (ongoing at end of study)	2 – Moderate (resolved @ day 17)	2 – Moderate (ongoing @ day 60)
Other	Right flank pain: 1 – Mild (onset @ day 2, resolved @ day 14) Back pain: 2 – Moderate (onset @ day 127, ongoing at end of study)	Dry skin: 1 – Mild (onset @ day 79, ongoing @ day 90)	Diarrhea: 1 – Mild (onset @ day 43, resolved @ day 57)

# PK Analysis of TLD-1433 (6 patients)

Matrix = Urine



Matrix = Plasma



Data points represent average TLD-1433 concentrations per ml of samples (mean +/- standard deviations).  
TLD-1433 is removed from the body via urine within 24 hours and via plasma within 72 hours.

# End of Study

Subject	001-001	001-002	001-003	001-004	001-005	001-006
Pathology	T1 HG w/ Cis	Cis	Cis	T1 HG w/ Cis (indeterminate for involvement of muscularis propria)	NED	NED
Imaging	Increased lymphadenopathy. Generalized bladder wall thickening, and dilation of the right greater than left ureter again seen. Again noted is an area of ureteric thickening and narrowing on the right side.	Solid mass in the right renal pelvis has enlarged in the interval.	No definite evidence for abdominal pelvic disease. Plaque-like areas of calcification in the posterior bladder wall grossly similar.	(1) Recurrence of bladder cancer with worsening bilateral hydroureteronephrosis (2) Vertebral metastases. (3) Focus of density within the left upper pole renal calyx is likely intra -pelvis urothelial malignancy.	Pending – July 2018  <b>180 Day Cystoscopy:</b> No evidence of bladder tumor	Pending – August 2018  <b>180 Day Cystoscopy:</b> No evidence of bladder tumour

# Phase II Design

- 100 CIS+, BCG-unresponsive patients
- Multicentre – 20 in total
- Open at University of Toronto

# Acknowledgments

- Medical Advisory Board
  - Michael Jewett
  - Ashish Kamat
  - Michael O'Donnell
- Medical Biophysics
  - Dr. Lothar Lilge
- Research Coordinator
  - Michael Nesbitt



THERALASE TECHNOLOGIES INC.  
TEAM

- Roger White
- Arkady Mandel
- Wayne Embree

**PATIENTS!!!**