11th Annual

Princess Margaret Cancer Centre

URO-ONCOLOGY DIALOGUE

Update on NMIBC PMH Trials

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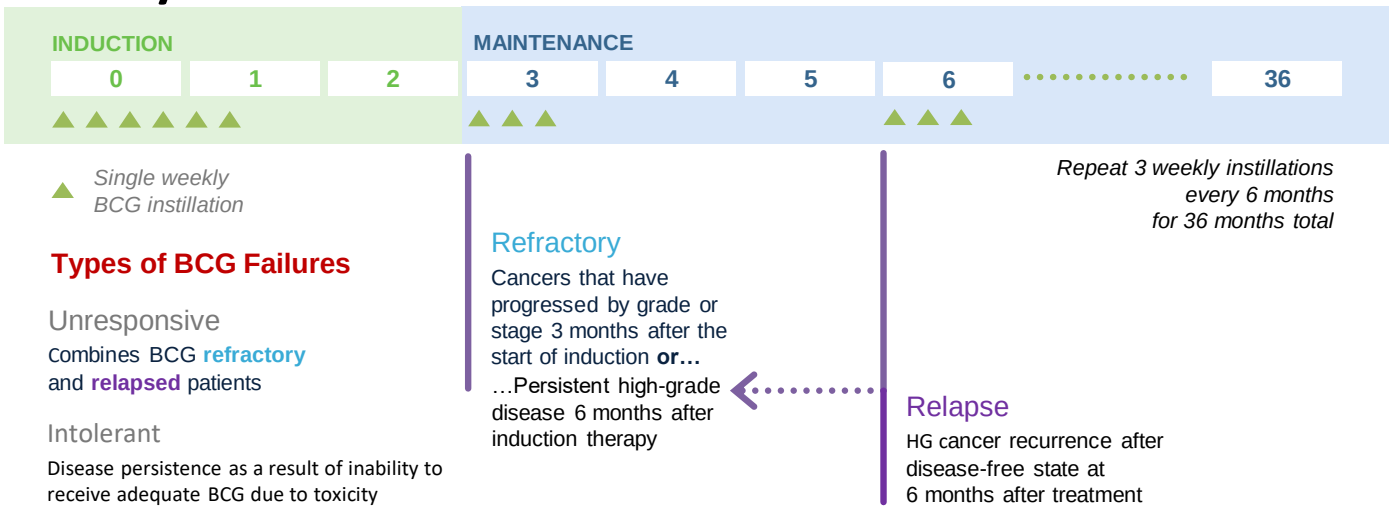
Disclosures

- Advisory Boards: Janssen, Merck, Roche, Ferring, Astellas, Theralase
- Grants/Honoraria: Abbvie, Sanofi, Ferring, TerSera
- Clinical Trials: Merck, Astra Zeneca, Bristol Myers Squibb, Theralase

Learning Objectives

- To gain awareness of the “BCG Unresponsive” bladder cancer state
- To become familiarized with alternative therapies for BCG Unresponsive NMIBC
- To be aware of clinical trials for NMIBC at PMH

SWOG regimen is the dosing schedule with the best efficacy evidence[1–4]



- BCG = Bacillus Calmette-Guerin; HG = high grade; I-O = immuno-oncology; NMIBC = non-muscle-invasive bladder cancer.
- **1.** TICE [package insert]. Whitehouse Station, NJ: Merck & Co Inc; 2016. **2.** Lamm DL, et al. *J Urol*. 2000;163(4):1124–1129. **3.** Kamat AM, et al. *Nat Rev Urol*. 2017;14(4):244–255. **4.** Kamat AM, et al. *J Clin Oncol*. 2016;34(16):1935–1944. 5. Plan A epidemiology report

FDA definition of **BCG unresponsive** defined as at last 1 of:

- Persistent or recurrent CIS alone or with recurrent Ta/T1 disease within 12 mo completion of adequate BCG therapy
- Recurrent high grade Ta/T1 disease within 6 mo of completion of adequate BCG therapy
- T1 high-grade disease at the first evaluation following an induction BCG course

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- Adequate defined as:
  - At least 5/6 doses initial induction + at least 2/3 doses maintenance
  - At least 5/6 doses initial induction + at least 2/6 doses of 2nd induction course

Management of BCG Failures

- **Radical cystectomy is the treatment of choice**
- 2nd induction BCG
  - 30-50% response rate
  - Cystectomy should be offered if BCG fails again
  - 3rd induction not recommended → 7% actuarial risk of progression with each additional course
- 2nd line intravesical agent options
  - IFN alpha, MMC, Gemcitabine, EMDA MMC BCG, combination chemo
- Clinical Trials

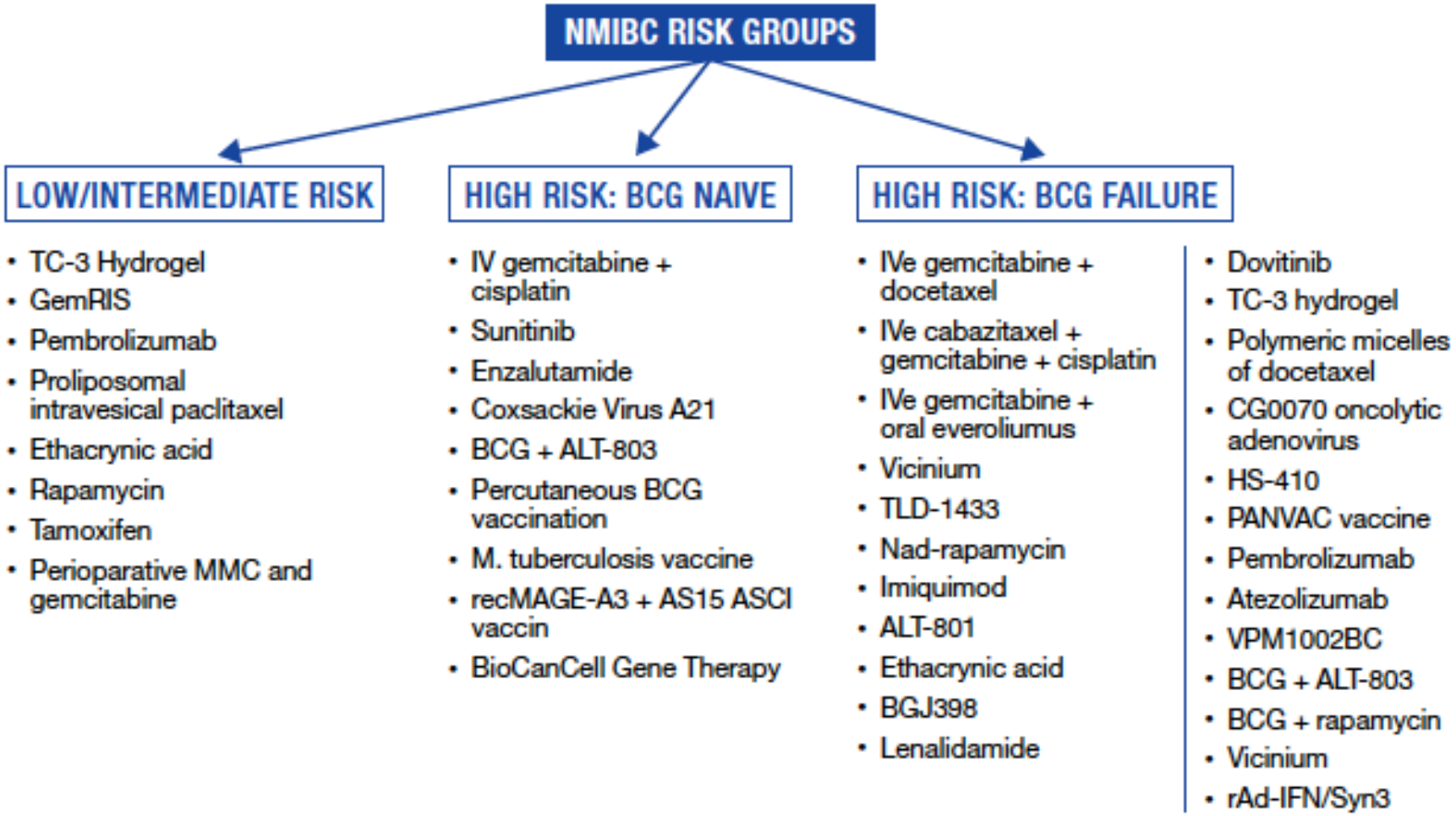
Novel Therapies and Trials I

TABLE 5-13 Novel Trials Involving Patients With Low- or Intermediate-Risk NMIBC

Trial name	Design	Primary endpoint(s)	NMIBC study population
NCT03167151 (PemBla)	Phase 1/2 randomized: intravesical vs. IV pembrolizumab	Safety and AEs at 90 days	Intermediate risk
NCT02075060 (IPOI vs. IPOP)	Phase 2 randomized: preoperative vs. postoperative MMC	PFS at 12 months	Low or intermediate risk
NCT03081858	Phase 1/2 cohort: proliposomal intravesical paclitaxel (TSD-001)	MTD and marker lesion response rates	Low or intermediate risk
NCT02852564	Phase 1 cohort: ethacrynic acid (Edecrin) oral	Urine concentrations of ethacrynic acid	Low, intermediate, or high risk
NCT03298958	Phase 3 randomized: oral sirolimus (rapamycin) vs. placebo	RFS at 2 years	Low, intermediate, or high risk
NCT02070120 (CALIBER)	Phase 2 randomized: TURBT vs. MMC	CR rate with chemoresection	Low or intermediate risk
NCT02197897 (BCTamoxifen)	Phase 2 cohort: tamoxifen	Marker lesion response	Low or intermediate risk
NCT03058757	Phase 2 randomized: preoperative MMC vs. standard of care	RFS	Low, intermediate, or high risk (not specified)
NCT02695771	Phase 3 randomized: postoperative MMC vs. postoperative gemcitabine vs. standard of care	Safety and AEs	Low, intermediate, or high risk (not specified)

Kulkarni and Klaassen, Bladder Cancer: Joint SIU ICUD Consultation 2018

Novel Therapies and Trials II



Kulkarni and Klaassen, Bladder Cancer: Joint SIU ICUD Consultation 2018

Select Study Highlights

- Keynote 057
- VISTA
- Theralase I

Completed or Near Completion

- Theralase II
- POTOMAC
- KN 676
- CheckMate-9UT

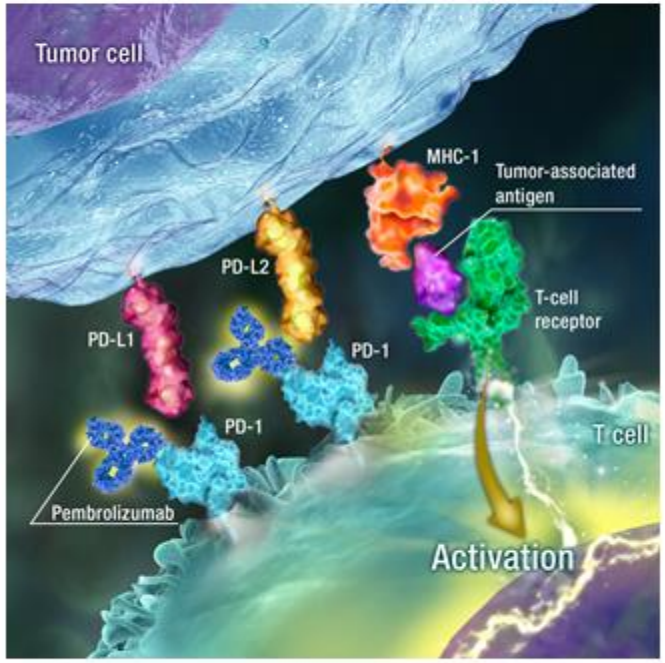
Newly opened

KEYNOTE 057
PEMBROLIZUMAB
MERCK
PHASE II TRIAL

de Wit KN057
ESMO 2018

NMIBC and the PD-1/L1 Pathway

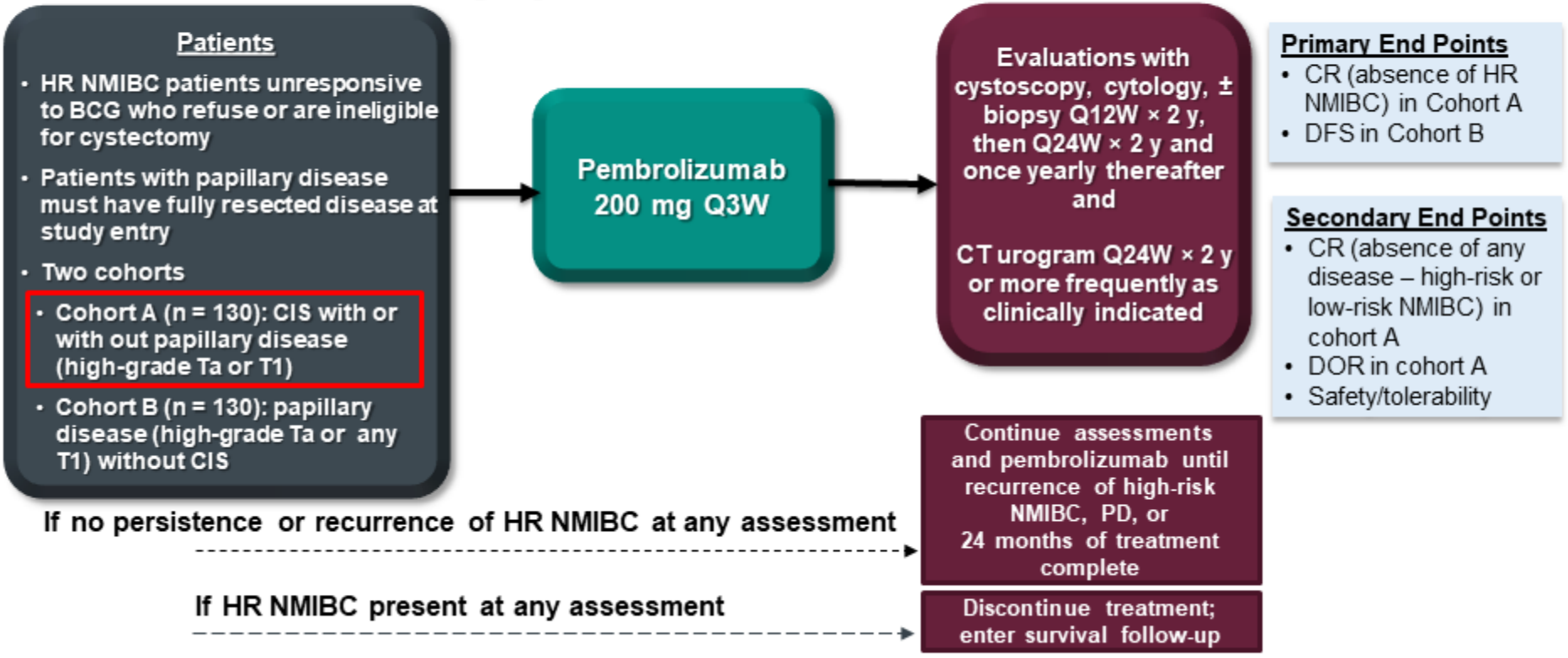
- Activation of the PD-1 pathway has been implicated in resistance to BCG therapy[1]
- The PD-1 inhibitor pembrolizumab has demonstrated significant antitumor activity in patients with metastatic urothelial carcinoma[2,3]
- Little is known about anti–PD-1 monotherapy for NMIBC



1. Fukumoto K et al. *Ann Surg Oncol.* 2018;25:2484-2491. 2. Balar AV et al. *Lancet Oncol.* 2017;18:1483-1492.3. Bellmunt J et al. *N Engl J Med.* 2017;376:1015-1026.

de Wit KN057
ESMO 2018

KEYNOTE-057: Single-Arm, Open-Label Phase 2 Study (NCT02625961)



Key Efficacy and Safety

Complete Response Rate at Month 3[a]

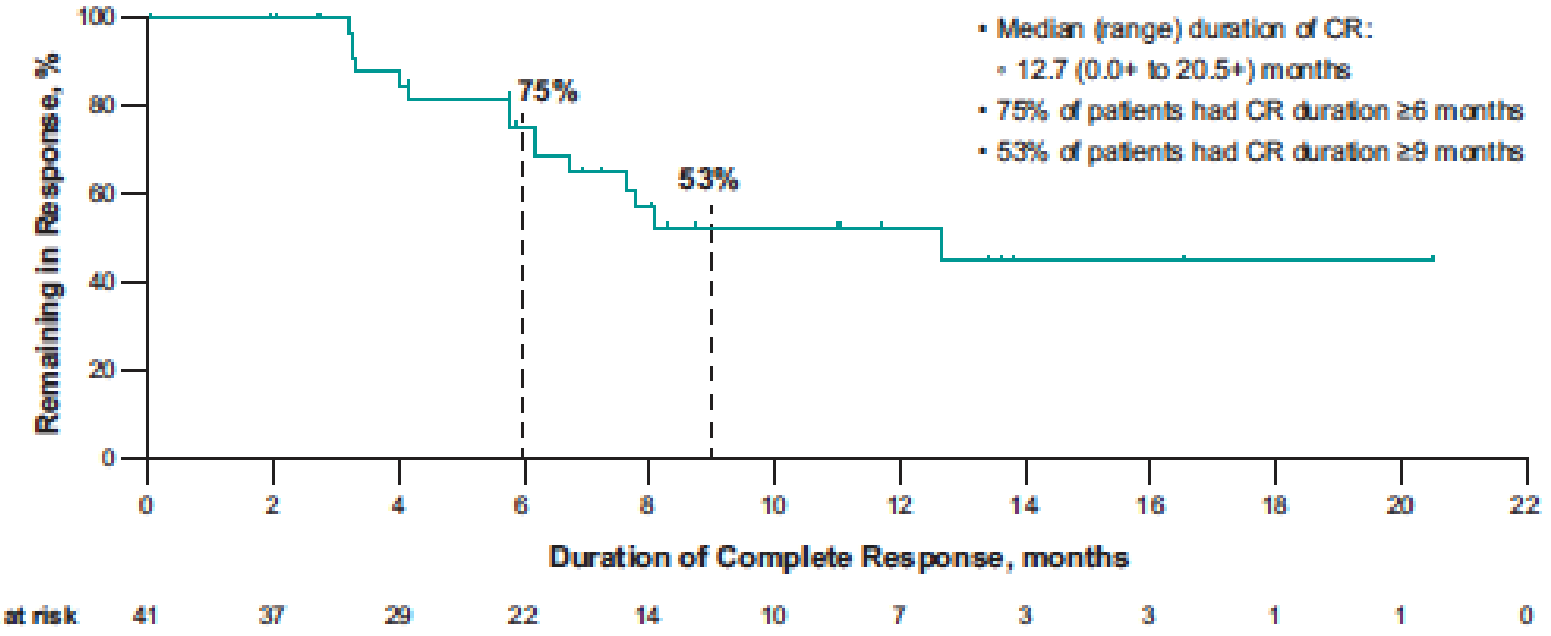
N = 102	Total Population		
	n	%	95% CI
CR	**41**	**40.2**	**30.6-50.4**
Non-CR	57	55.9	45.7-65.7
Persistent[b]	41	40.2	30.6-50.4
Recurrent[c]	6	5.9	2.2-12.4
NMIBC stage progression[d]	9	8.8	4.1-16.1
Non–bladder malignancy[e]	1	1.0	0.0-5.3
Progression to T2	0	0	NA-NA
Nonevaluable[f]	4	3.9	1.1-9.7

Adverse Event Summary

AE, n (%)	N = 102
≥1 AE	98 (96.1)
Treatment-related AE	66 (64.7)
Grade 3-5 AE	29 (28.4)
Grade 3/4 treatment-related AE	13 (12.7)
Serious AE	24 (23.5)
Serious treatment-related AE	8 (7.8)
Immune-mediated AE	19 (18.6)
Grade 3/4 immune-mediated AE	3 (3.0)
Death	2 (2.0)[g]
Death because of treatment-related AE	0 (0)
Discontinuation because of AE	8 (7.8)
Discontinuation because of treatment-related AE	8 (7.8)
Discontinuation because of serious AE	4 (3.9)
Discontinuation because of serious treatment-related AE	4 (3.9)

Duration of Response

Figure 4. Duration of Response for Patients Who Achieved Complete Response at Month 3[a,b]



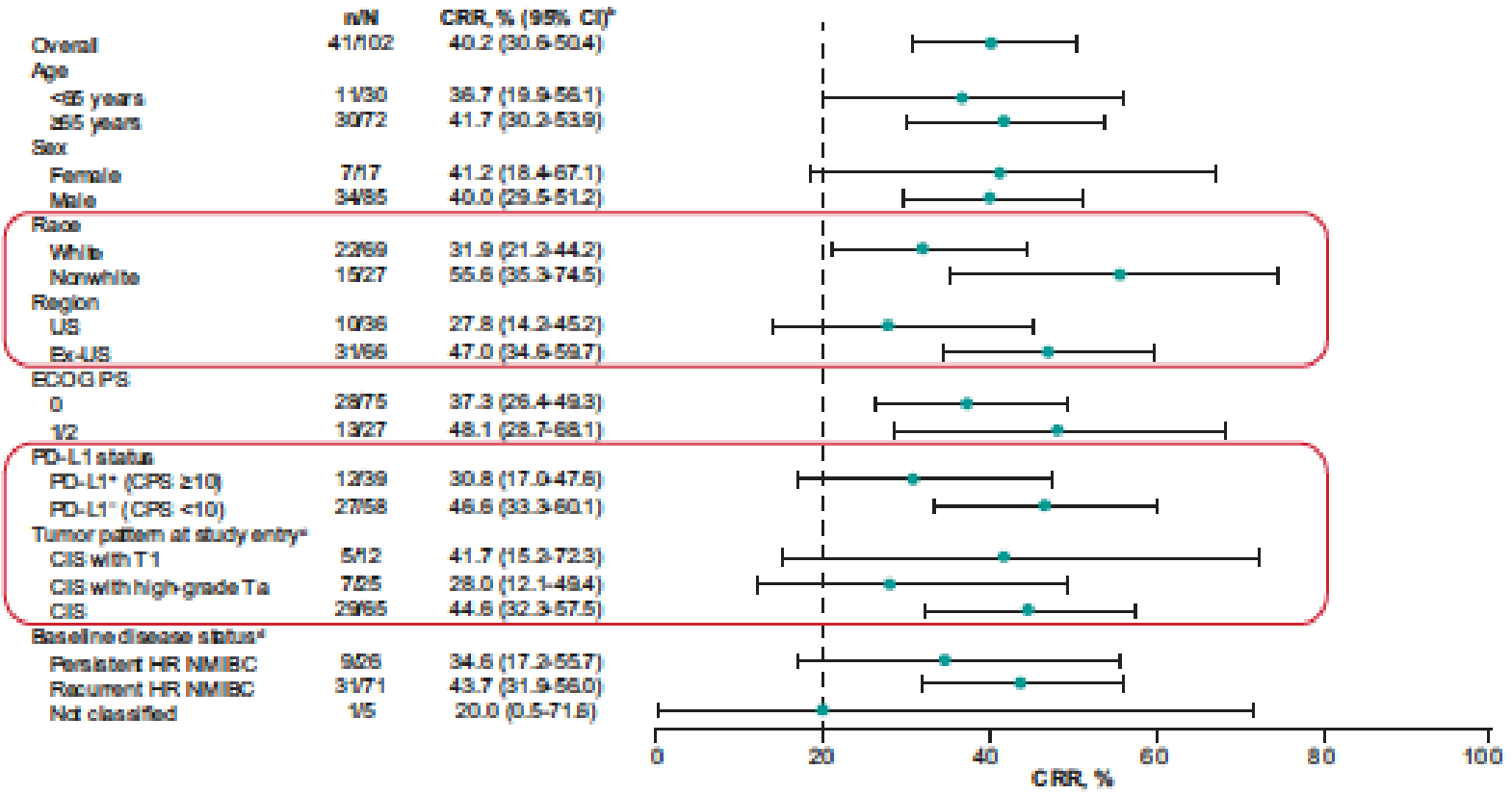
CR, complete response.

[a]1 month = 30.4367 days.

[b]Month 0 = time point when initial CR was achieved.

Subgroup analyses: 3 month CR

Figure 5. Complete Reponse Rate at Month 3[a] by Subgroup Factors



VISTA TRIAL

VICINIUM

VIVENTIA → ELEVEN BIO → SESEN BIO

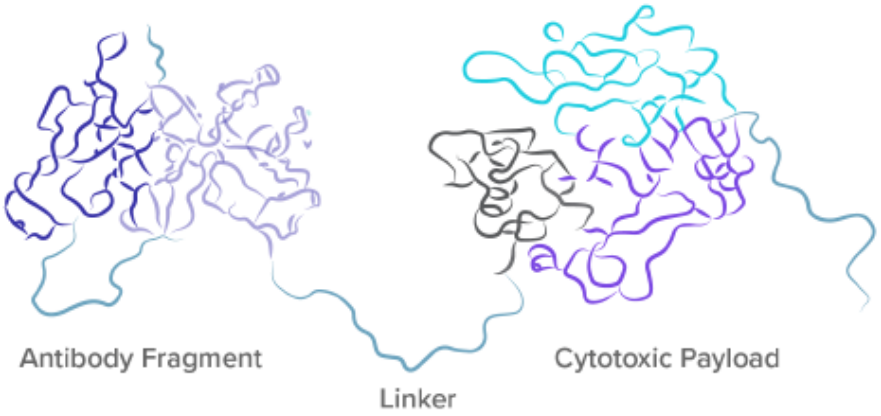
PHASE II TRIAL

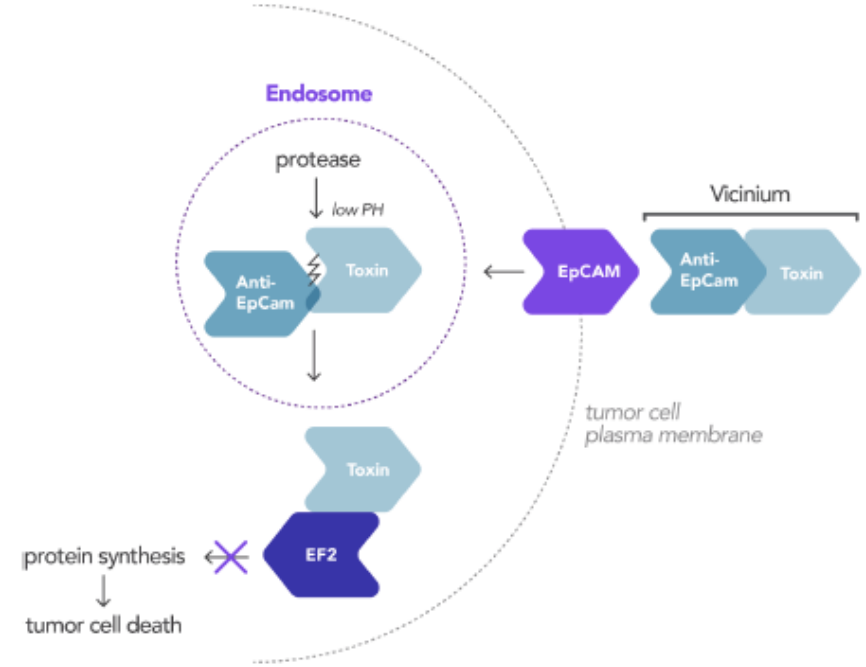
Vicinium: Fusion Protein

- Engineered as a single fusion protein comprising an antibody fragment, peptide tether and cytotoxic payload
- Peptide tether allows fusion protein to remain intact until internalized by cancer cell; avoiding normal tissue by bladder cancer cells
- Anti-EpCAM Ab fragment delivers toxin that kills tumor cells by blocking protein synthesis
  - Kills both rapidly proliferating and slower growing cancer cells
- EpCAM overexpressed in >98% of high grade NMIBCs*, minimal expression on healthy bladder tissue
- Potential to induce immunogenic cell death

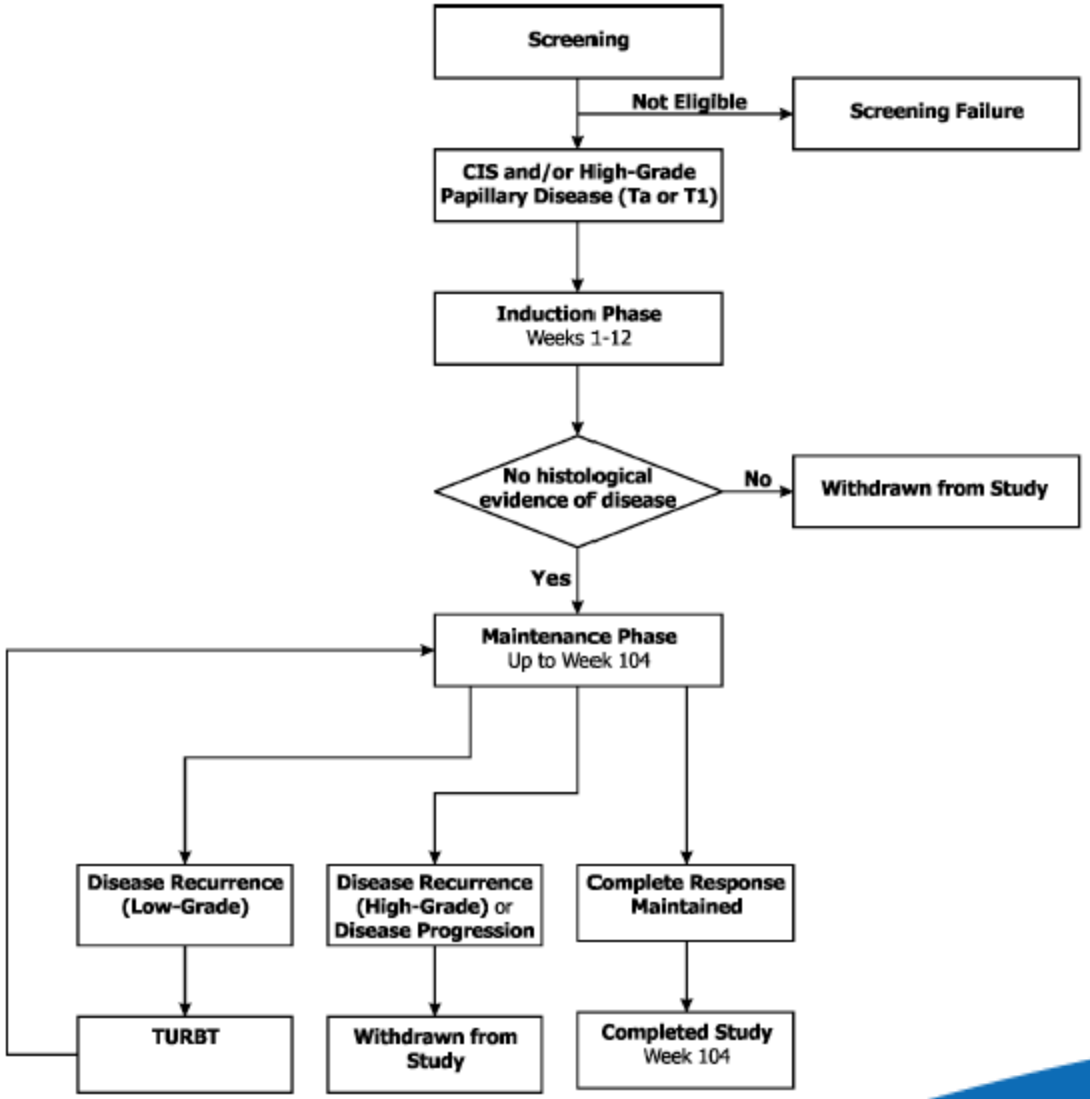
ETA: Pseudomonas exotoxin A
Potent: subpicomolar IC_{50}

* Data generated in prior Sesen BIO studies using internal antibody





Vicinium Trial Design



Vicinium Trial Design

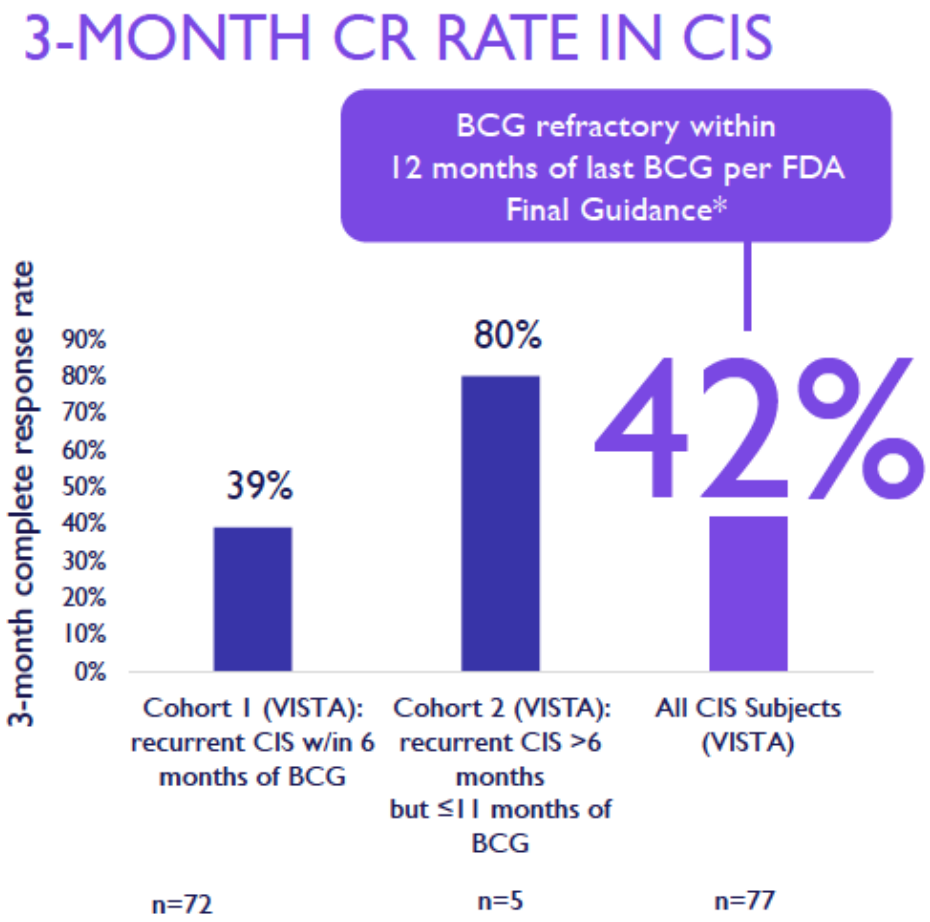
- 2 hr instillations, rotating every 15 min
- Induction Phase
  - 30mg of 50mL saline administered twice a week for weeks 1-6
  - 30mg of 50mL saline administered weekly for weeks 6-12
- Maintenance Phase
  - 30mg of 50mL saline administered every other week from week 14 – 104

Patients

CHARACTERISTICS	COHORT 1	COHORT 2	COHORT 3
	CIS that recurred within 6 months of BCG	CIS that recurred >6 months but ≤11 months of BCG	Papillary (without CIS) that recurred within 6 months of BCG
Total subjects enrolled	87	6	40
Evaluable subjects at 3-months*	72	5	34
Median age (current)	75	71	77
Males/Females	54/18	4/1	29/5
Median prior treatment for NMIBC			
BCG cycles	4 (range 2-14)		
Intravesical chemotherapy	1 (range 0-23)		
TURBT	4 (range 0-11)		

*Data as of 20 April 2018 cut-off

Early Results



Subjects (n=129)	Treatment-Emergent SAEs[4]	Treatment-Related SAEs
Any Serious AE	17 (13%)	4 (3%)
Acute kidney injury or renal failure	4	3
Hematuria	3	0
Cholestatic hepatitis	0	1

Phase III Complete Response Rate

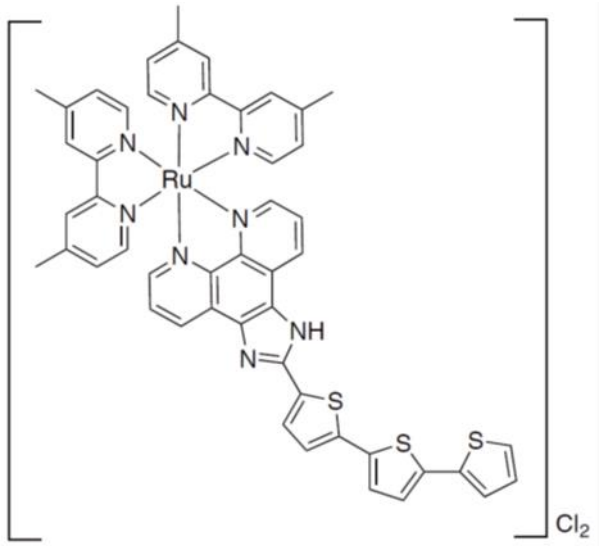
Cohort 1 (n=82) Complete Response Rate		
Time Point	Evaluable Patients	Complete Response Rate (95% Confidence Interval)
3-months	n=82	39% (28%-50%)
6-months	n=82	26% (17%-36%)
9-months	n=82	20% (12%-30%)
12-months	n=82	17% (10%-27%)

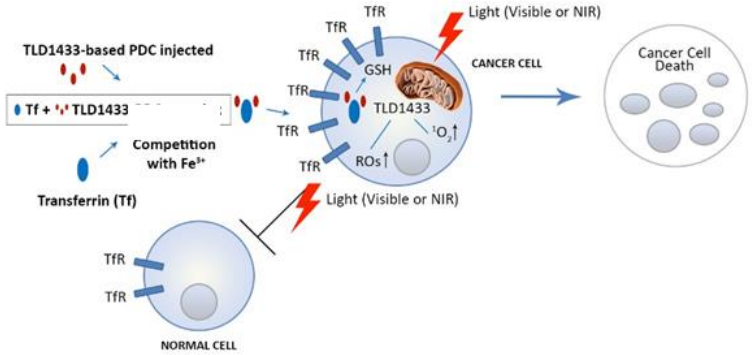
Cohort 2 (n=7) Complete Response Rate		
Time Point	Evaluable Patients	Complete Response Rate (95% Confidence Interval)
3-months	n=7	57% (18%-90%)
6-months	n=7	57% (18%-90%)
9-months	n=7	43% (10%-82%)
12-months	n=7	14% (0%-58%)

PHOTODYNAMIC THERAPY (PDT) TRIAL
TLD-1433
THERALASE
PHASE I TRIAL

Photodynamic Therapy Trial: Background Information

TLD1433





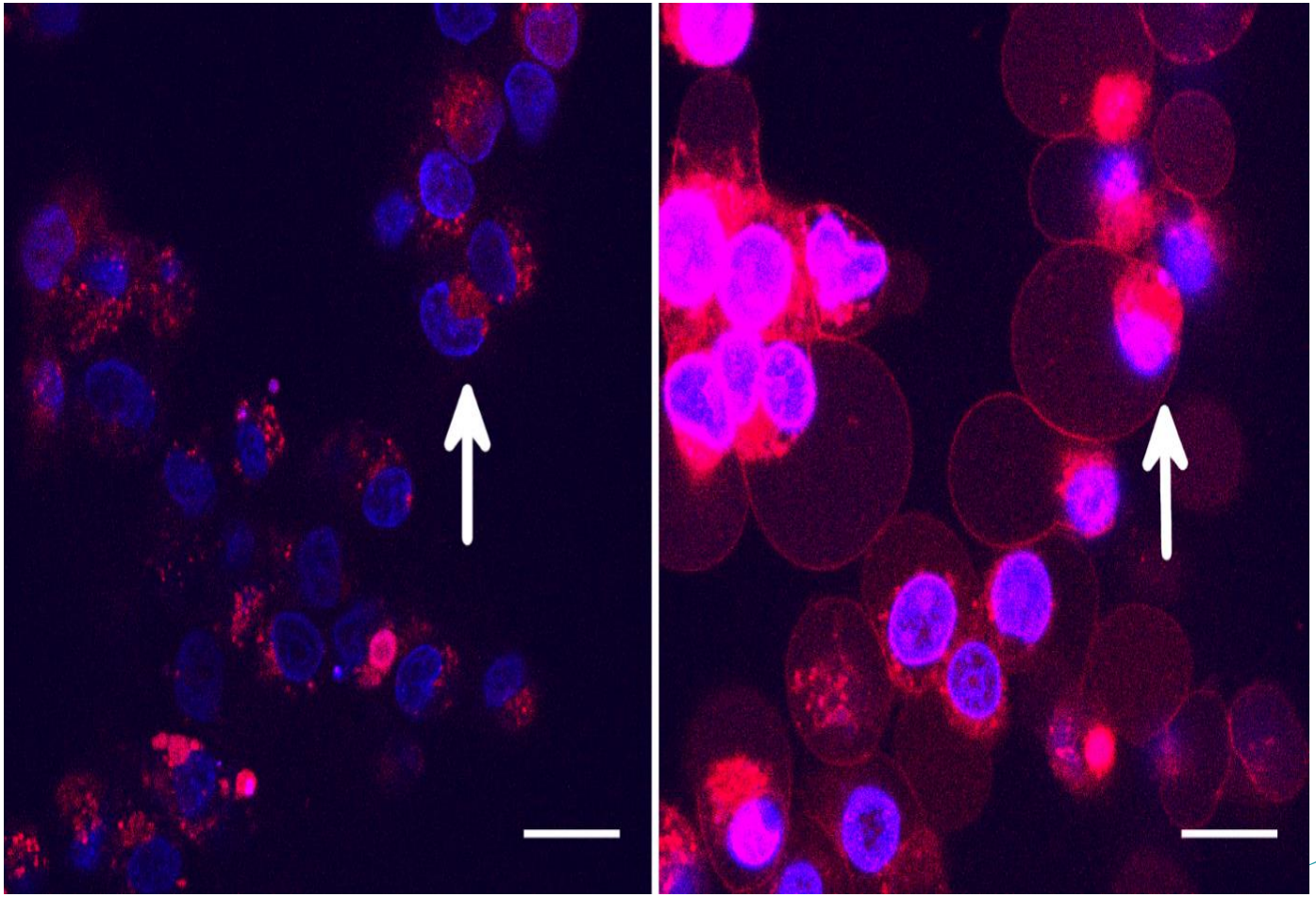
- Soluble and stable in water
- High quantum yield and ROS production
- Preferential bladder tumor accumulation
- Exceptional ability to ablate in vivo tumors across multiple animal models
- Safe in GLP pharmacology and toxicology studies

- 70 min instillation
- GA
- Exposure time calculated based

On power delivery (up to 60 min)

TLD-1433 Localization

TLD-1433 localizes in the cytoplasm of the cancer cell (mitochondria)



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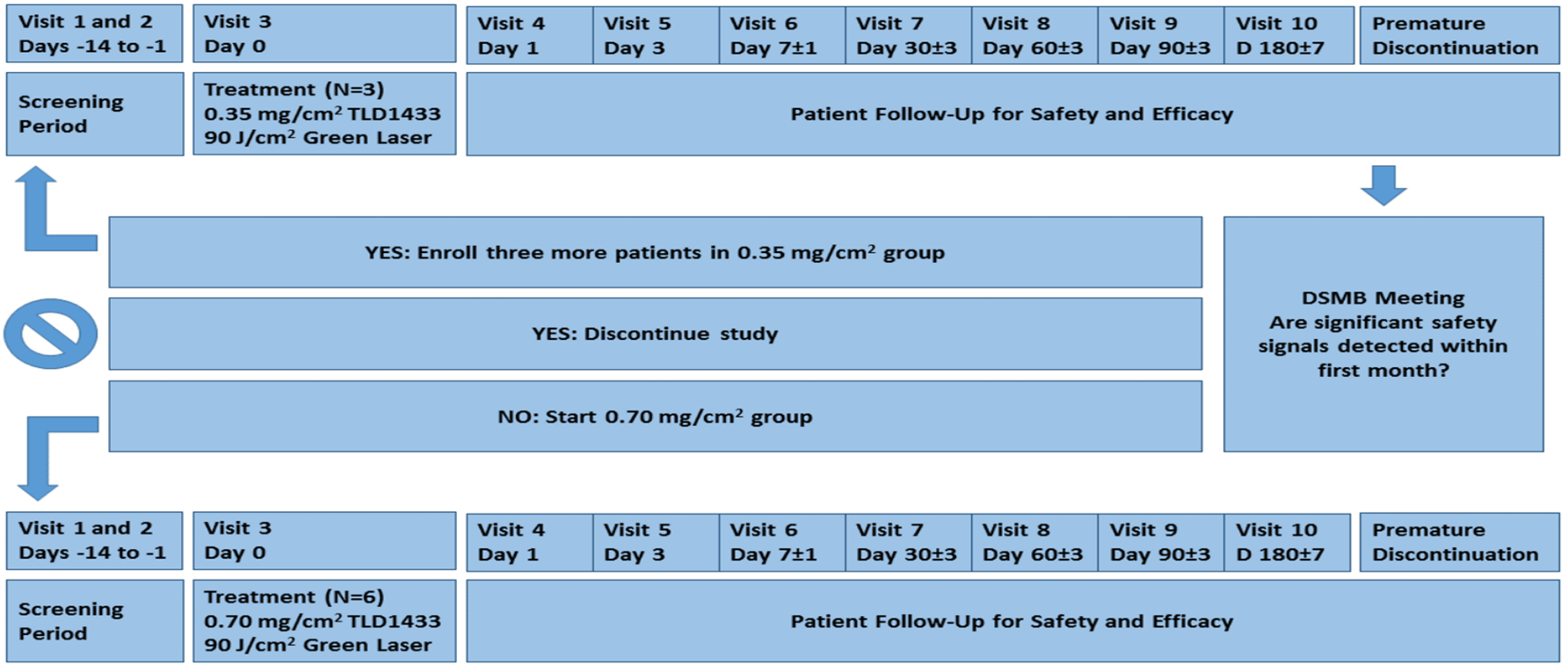
Overall Study Design & Plan

The study will consist of 2 phases. In the first phase, 3 subjects will receive PDT employing 0.35 mg/cm2 (maximum recommended starting dose) TLD-1433. If treatment with the maximum recommended starting dose does not raise significant safety concerns, an additional 6 subjects will receive PDT with 0.70 mg/cm2 (therapeutic dose) TLD-1433.



2.4.2 *The Probe*

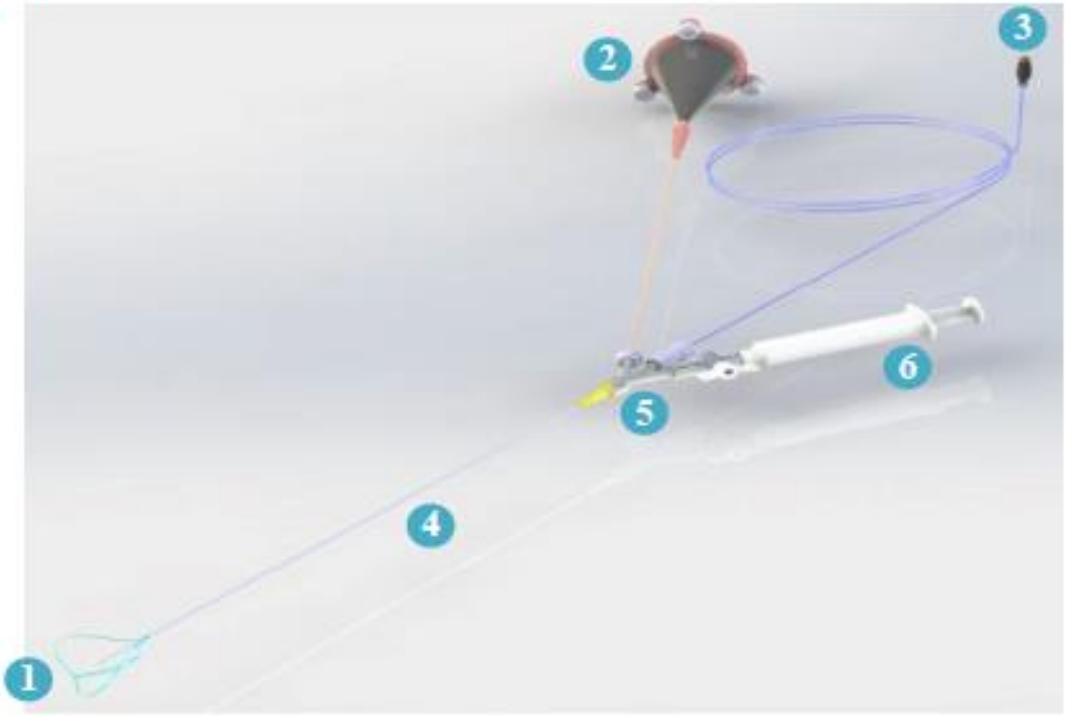


Figure 7: Laser Source Detector probe (TLC-34XX)

1. **The Cage:**
   A. Cage Arms with Detectors : 3 flat bundles of 4 optical fibers
   B. Emitter: a Spherical diffuser fibre movable relative to the detectors.
2. **Detector Plug:** 12 position detector fiber connector
3. **Emitter Connector:** Single position FC connector
4. **Catheter Tube:** This part of the probe is inside a catheter.
5. **Three way Y swivel:** 3 female and 1 male
6. **Syringe with a Stop cock:** This is the port used to inject USP water to open the bladder.(optional depending on the cystoscope to be use. If the cystoscope has a separate water irrigation channel.

Study Objectives

Primary: to evaluate the safety of PDT employing TLD1433 and controlled uniform laser light (TLC-3200 System)

Secondary: to evaluate the pharmacokinetics (PK) of TLD1433

Exploratory: to evaluate the efficacy of PDT employing TLD1433 and controlled uniform laser light (TLC-3200 System)

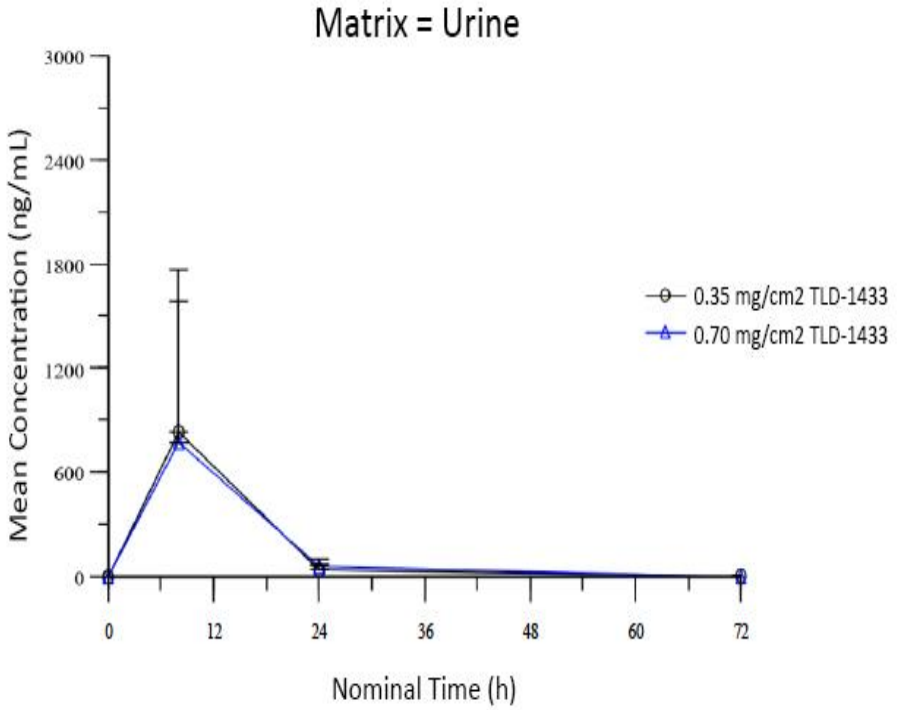
Phase Ib: Summary of Adverse Events

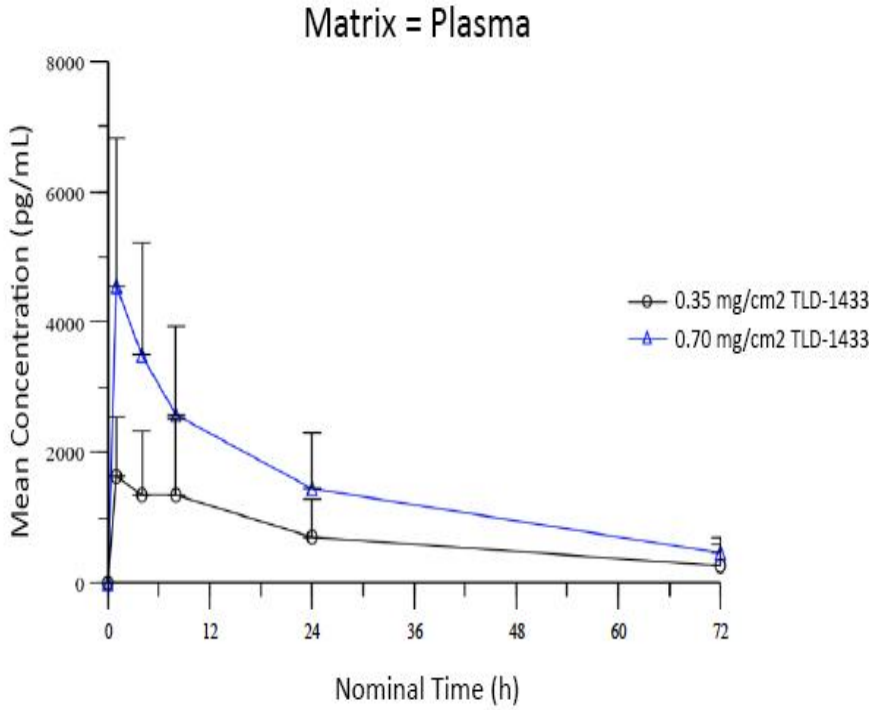
Adverse Event ("AE") Summary	Number of AEs (Description)	AE Grade
Severe, Life threatening or disabling, Death	0	3,4,5
Adverse Events	(Pain (eye, pelvic, low back, joint, right flank), urge incontinence, diarrhea, constipation, fatigue, urinary frequency / urgency, bladder spasm, hematuria, nocturia, dry skin)	1 to 2
Adverse Events (Not Completely Resolved within 180 Days)	(Urge Incontinence*, Urinary Frequency*, Dry Skin#) *Pre-existing condition #Not study drug related	2

Severity of Adverse Events

- Grade 1 = Mild
- Grade 2 = Moderate
- Grade 3 = Severe
- Grade 4 = Life-threatening or disabling
- Grade 5 = Death

PK Analysis of TLD-1433 (6 patients)





Data points represent average TLD-1433 concentrations per ml of samples (mean +/- standard deviations).

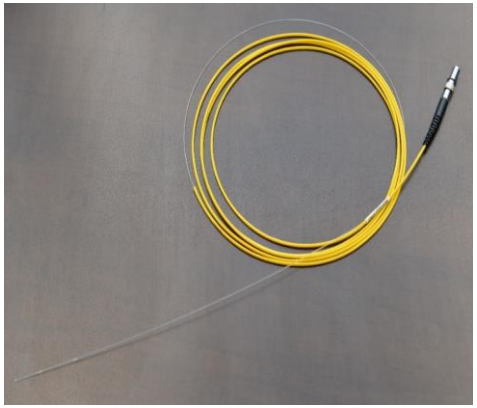
TLD-1433 is removed from the body via urine within 24 hours and via plasma within 72 hours.

Phase Ib: Exploratory - Efficacy[2]

Treatment Dose	Half-Dose 0.35mg/cm²			Full-Dose 0.70mg/cm²		
Subject	**001-001 (Patient 1)**	**001-002 (Patient 2)**	**001-003 (Patient 3)**	**001-004 (Patient 4)**	**001-005 (Patient 5)**	**001-006 (Patient 6)**
Safety	**No disease progression (180 days)**			**66% Complete Response (360 days)**		
Pathology	T1 HG w/ Cis (180 days)	T1 HG w/Cis (180 days)	Cis (180 days)	T1 HG w/ Cis Unrelated to Treatment (138 days)	**No clinical evidence of bladder tumour (360 days)**	**No clinical evidence of bladder tumour (360 days)**
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 (180 Days)	Solid mass in the right renal pelvis has enlarged in the interval (180 Days)	No definite evidence for abdominal pelvic disease. Plaque-like areas of calcification in the posterior bladder wall grossly similar (180 Days)	1) Vertebral metastases 2) Focus of density within the left upper pole renal calyx is likely intra -pelvis urothelial malignancy Patient removed from study (138 Days)	**No** evidence of metastatic disease in the abdomen or pelvis. **360 Day Cystoscopy: No clinical evidence of bladder tumour (360 Days)**	**No** evidence of metastatic disease in the abdomen or pelvis. **360 Day Cystoscopy: No clinical evidence of bladder tumour (360 Days)**

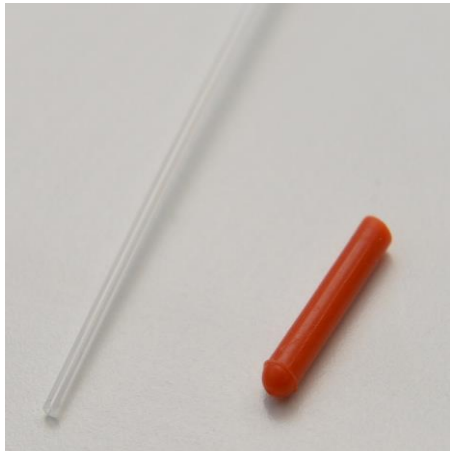
PHOTODYNAMIC THERAPY (PDT) TRIAL
TLD-1433
THERALASE
PHASE II TRIAL

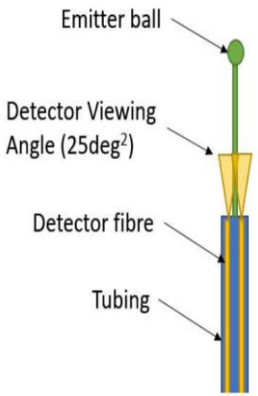
Emitter



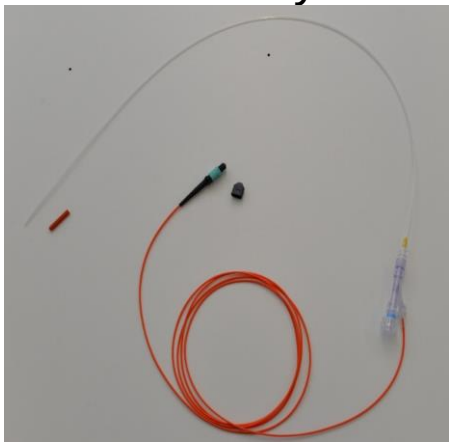
- Optimized UV epoxy for Spherical Diffuser
  (More secure attachment to Emitter)
  (Allows up to 4W operation)

Detector





- More accurate, repeatable and reliable optical detection
- Optical detection drives Emitter warning screens
- 2 mm diameter fits through working channel of flexible cystoscope
- More robust and easier to use in OR
- More easily sterilized



Phase II NMIBC Clinical Study

Phase II NMIBC Clinical Study

Multi-site (Approximately 20 sites), single-arm, open-label study

100 patients to be evaluated at Therapeutic Dose (0.70 mg/cm$^{2)}$

Key Inclusion Criteria

Have histologically confirmed NMIBC CIS with or without resected papillary disease (Ta, T1) (HG)

Patients with Ta or T1 disease have undergone complete TURBT

Considered BCG-Unresponsive

FDA guidelines (February 2018) for BCG-Unresponsive Non-Muscle-Invasive Bladder Cancer states that,

"In BCG-unresponsive NMIBC, a single-arm clinical trial with complete response rate and duration of response as the primary endpoint can provide primary evidence of effectiveness to support a marketing application" [3]

[3] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM529600.pdf

Phase II NMIBC Clinical Study Design

theraLASE® Healing at the Speed of Light®

Outcome Measures

Primary Outcome Measure

Evaluated by:

- Complete Response ("**CR**") at 90 days

  and

- Duration of CR at 360 days

CR defined as:

- -ve cystoscopy **&** -ve urine cytology
- +ve cystoscopy with biopsy-proven benign **or** low-grade NMIBC and -ve cytology
- -ve cystoscopy with malignant urine cytology if cancer is found in the upper tract or prostatic urethra and random bladder biopsies are -ve.

Secondary Outcome Measure

The incidence and severity of Adverse Events ("**AEs**") Grade 4 or higher not resolved in 360 days.

theraLASE® Healing at the Speed of Light®

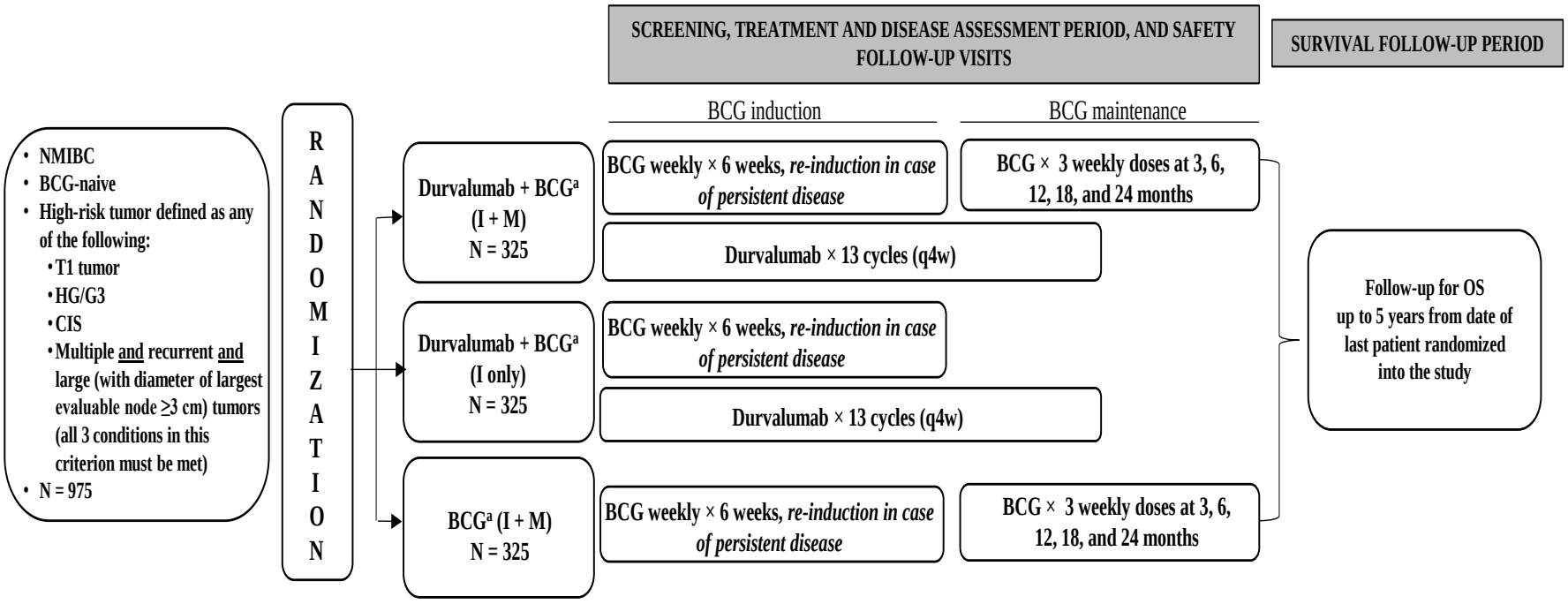
POTOMAC TRIAL
DURVALUMAB
ASTRA ZENICA
PHASE III

Geographical Distribution

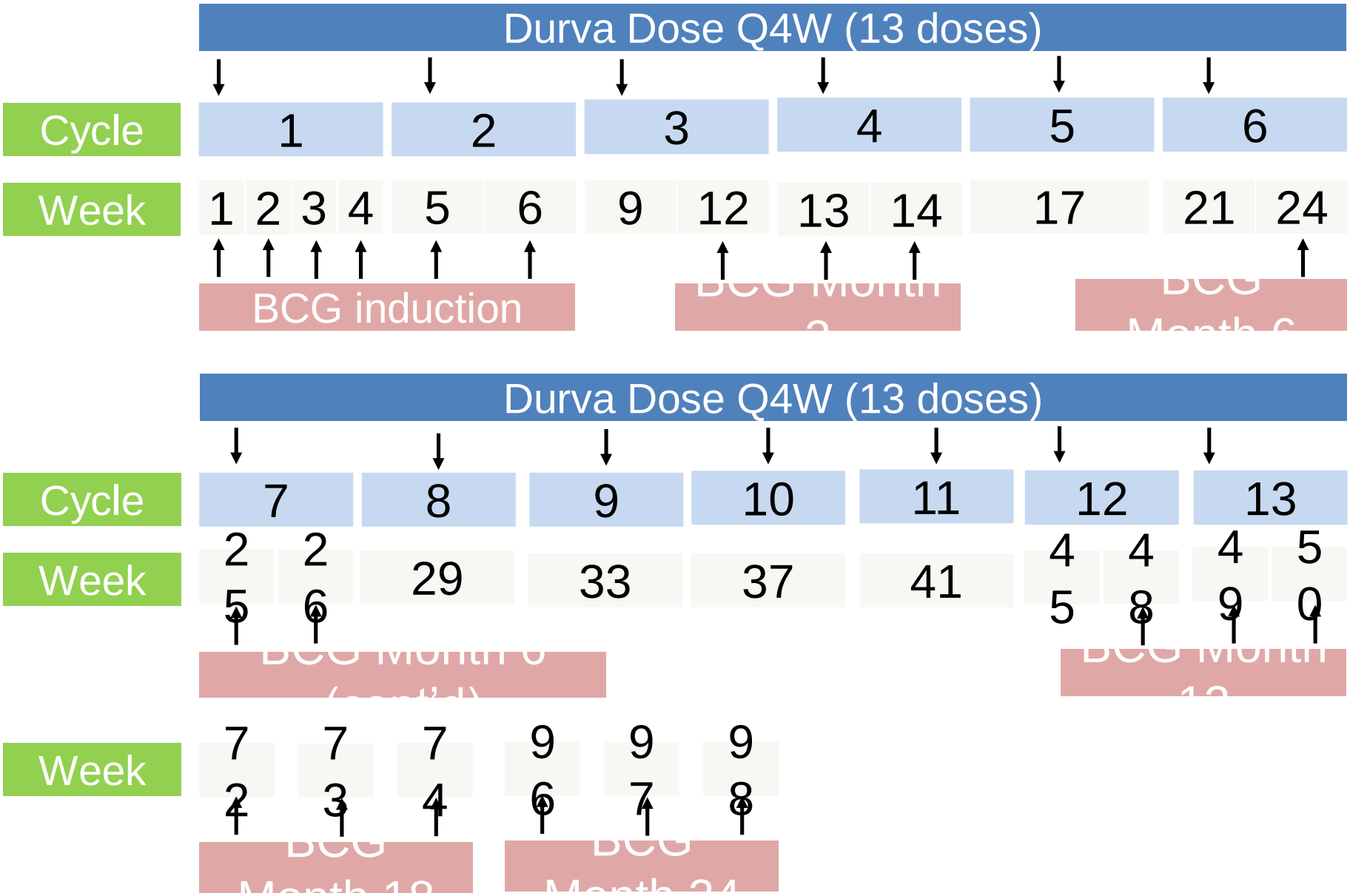
12 Countries - 115 Sites
975 Randomized subjects – 25% SF rate

Study Design: BCG naïve patients!!!

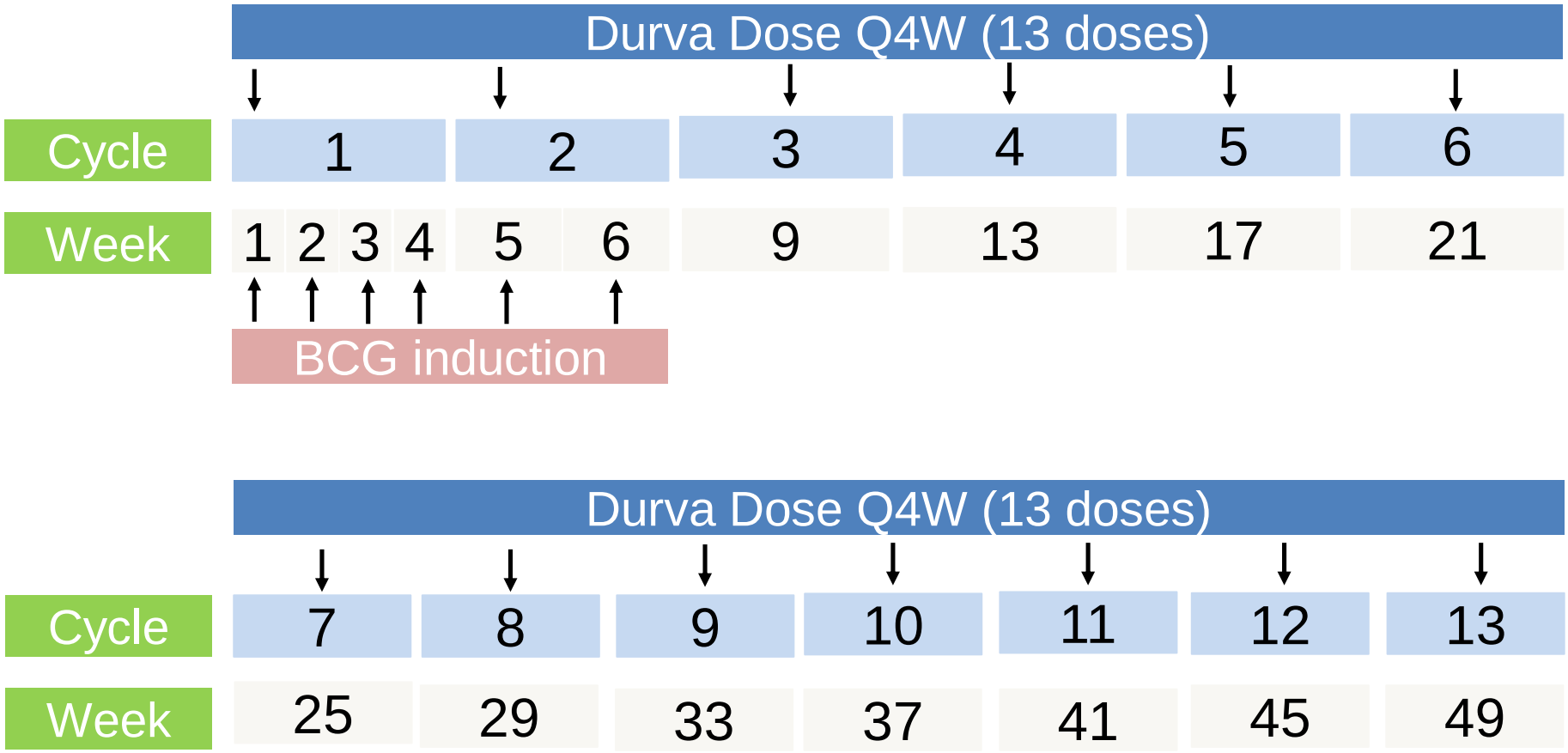
Stratified randomization factors:
1. Higher risk papillary disease (yes vs no) (meeting at least one of the following criteria will be "yes")
   - -T1G3, OR
   - -Multiple AND recurrent AND large (with diameter of largest evaluable node ≥3 cm) tumors
2. CIS (yes vs no)



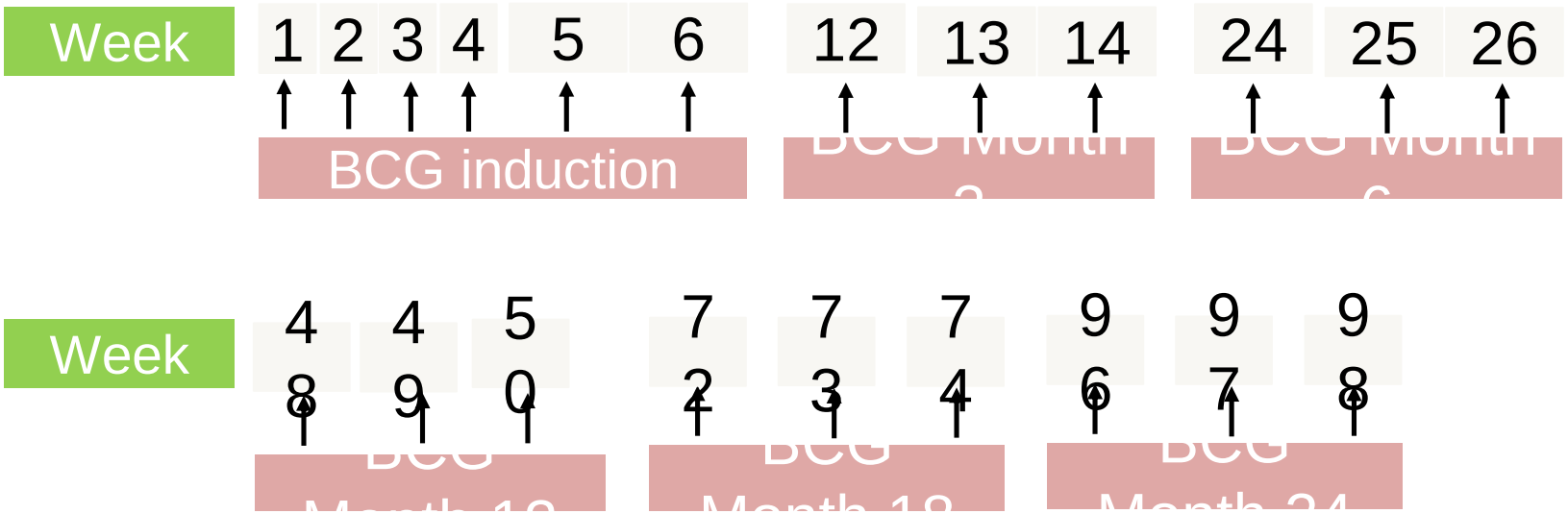
Study Treatment – Durva + BCG (ind + maint)



Study Treatment – Durva + BCG (ind only)



Study Treatment – BCG (ind + maint)



Study Treatments

Durvalumab 1500 mg IV Q4W for 13 cycles

- Treatment until confirmed disease progression, unacceptable toxicity, or any discontinuation criterion are met
- Patients whose weight falls to ≤30 kg must receive weight-based dosing for durvalumab (as applicable) – equivalent to 20mg/kg of durvalumab until the weight improves to >30 kg, at which point the patient should resume taking the fixed dosing of durvalumab (1500mg)

BCG

- 1 vial of OncoTICE BCG or approved equivalent dose of local standard BCG strain administered intravesically weekly for 6 weeks (induction) and for 3 weekly doses at 3, 6, 12, 18, and 24 months (maintenance)

*Recurrence of low/intermediate risk disease post BCG induction should be removed by performing TURBT and the study treatment can continue

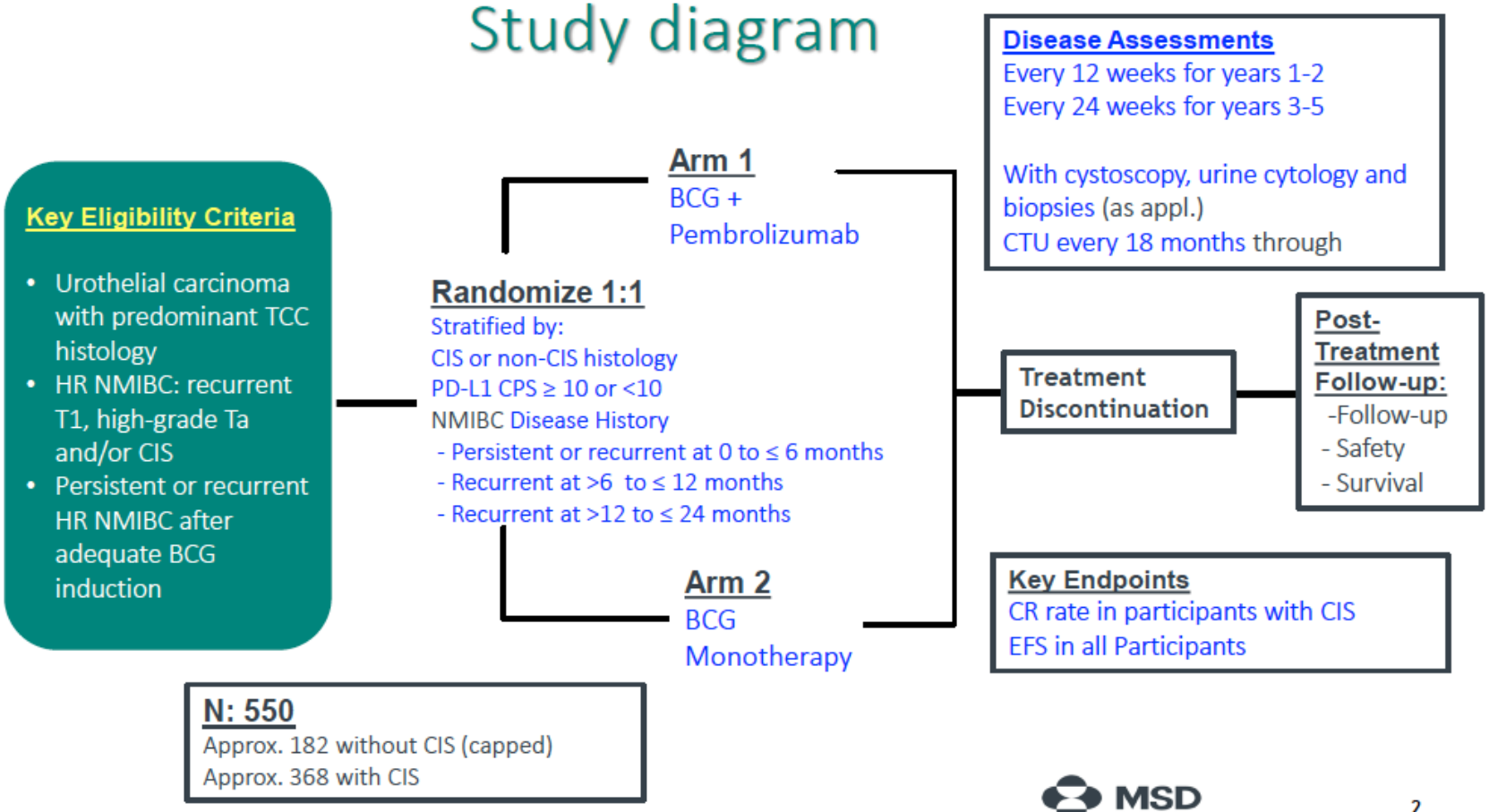
In order to minimize confounding of OS, patients randomized to BCG alone will not be allowed to cross over to the other treatment groups (BCG in combination with durvalumab)

Durvalumab and BCG may be administered on the same day; durvalumab would be administered first, followed by BCG

KEYNOTE 676
PEMBROLIZUMAB
MERCK
PHASE III

Trial Design

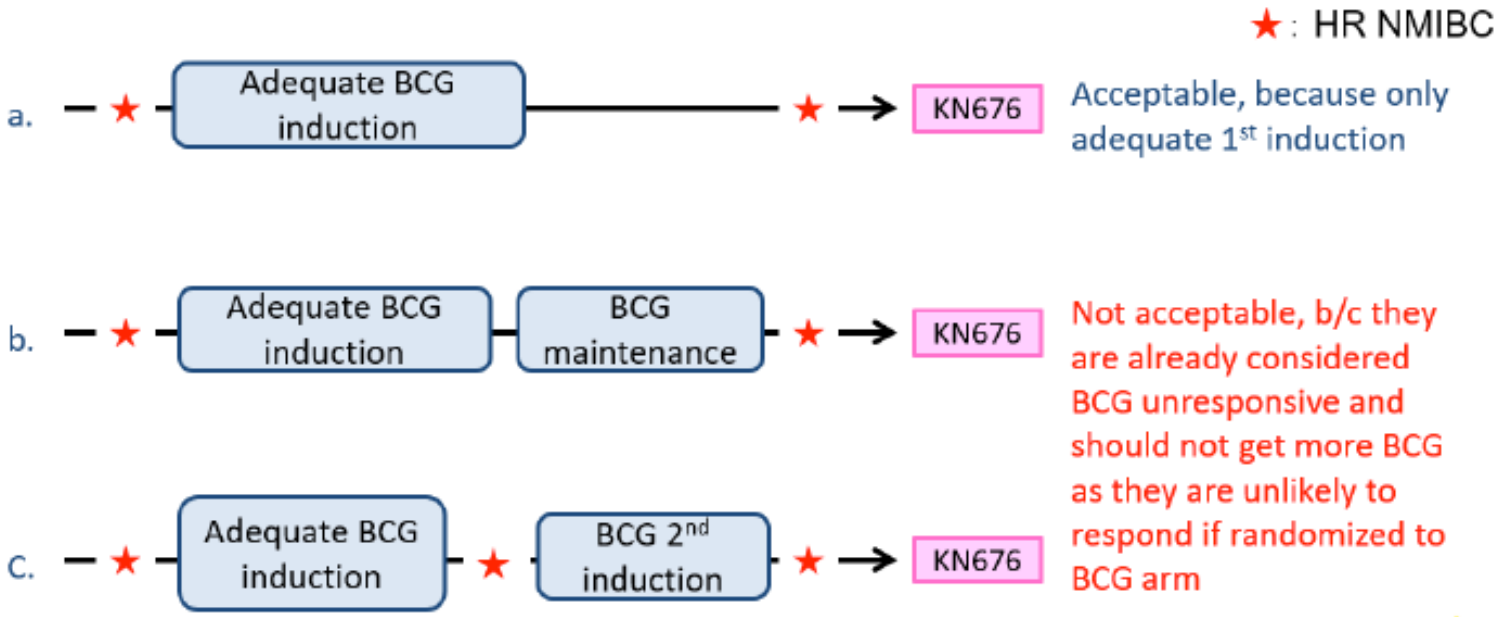
Study diagram



MSD INVENTING FOR LIFE

Inclusion

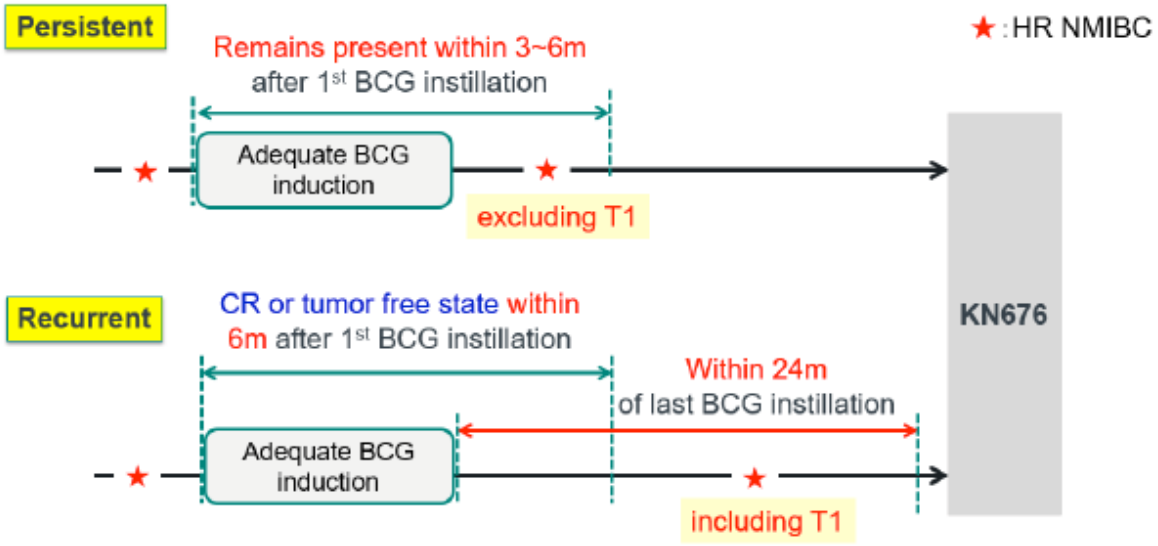
- Failed Adequate Induction BCG: 5 or 6 cycles all given within 10 weeks
- Cannot have received maintenance BCG



Persistent of Recurrent Disease

Following BCG induction therapy, must have persistent or recurrent HR NMIBC defined as

- High Risk NMIBC includes T1, high grade Ta and/or CIS
- Persistent: remains present within 3 months (-2 weeks) to 6 months (+4 weeks) after start of BCG induction (NOTE: persistent T1 not allowed), or
- Recurrent: reappearance of high risk NMIBC after achieving a CR or tumor-free state within 6 months (+ 4 weeks) after start of BCG induction. The recurrence must be within 24 months of last exposure to BCG [with up to an additional 56 days allowed to account for delays in the 24 month assessment]



CHECKMATE-9UT TRIAL
NIVOLUMAB + BMS-986205
BRISTOL-MYERS SQUIBB
PHASE II

A Phase 2, Randomized, Open-label Study of Nivolumab or Nivolumab/BMS-986205 Alone or Combined with Intravesical BCG in Participants with BCG-Unresponsive, High-Risk, Non-Muscle Invasive Bladder Cancer (**CA2099UT/CheckMate 9UT**)

Sponsored by: BMS

Bristol-Myers Squibb

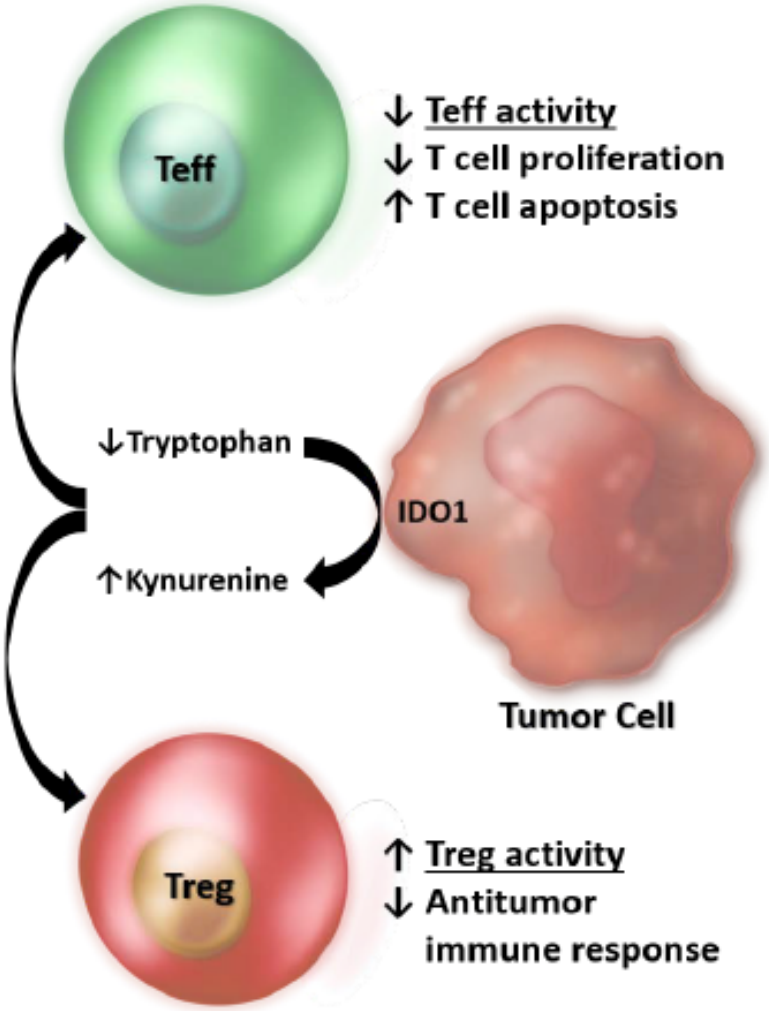
UHN Princess Margaret Cancer Centre

Trial Overview

- Global Phase 2b study, open-label, randomized
- Investigative agents:
  - BMS-986205 (IDO1 inhibitor) – indolamine 2,3 dioxygenase 1 inhibitor
  - Nivolumab (anti-PD1)
  - BCG
- Population: BCG unresponsive high-risk NMIBC
- Global Target: 436 randomized
- Local Target: 4 randomized
- Target time to completion: 5 years

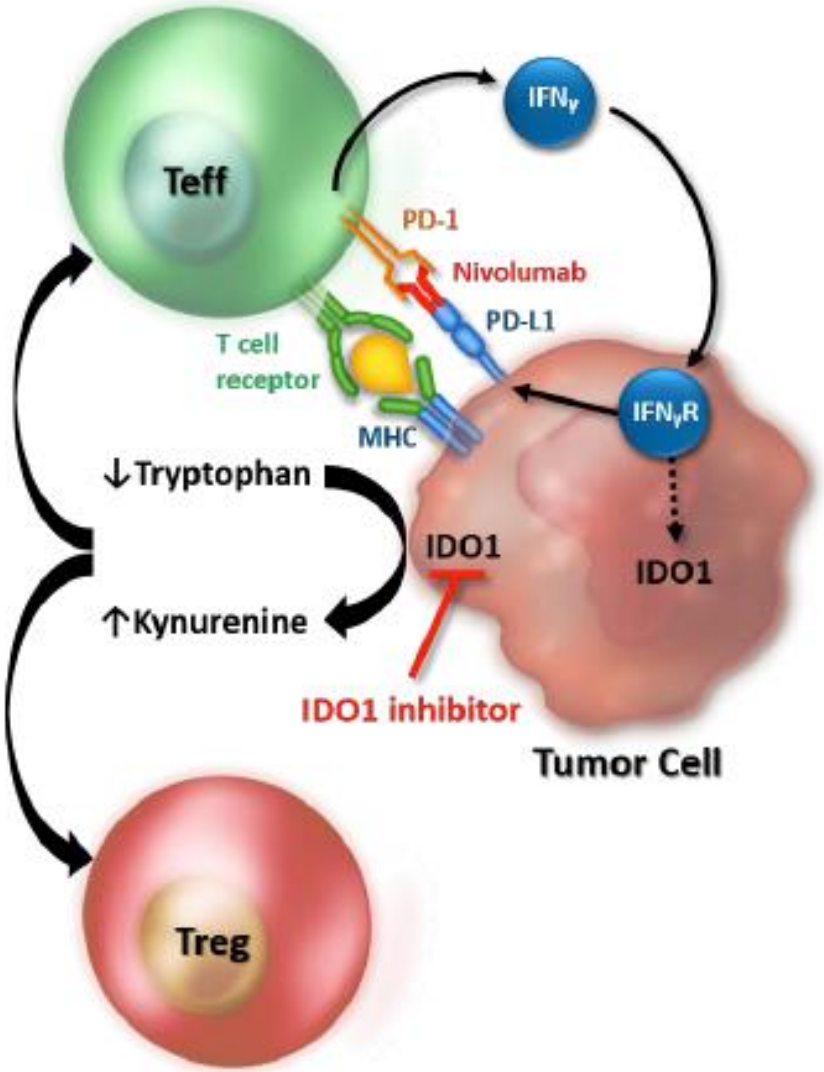
IDO1i in the Tumor Microenvironment

- IDO1 enzyme inhibits T-cell function through local depletion of tryptophan and production of immunosuppressive kynurenine
- High IDO1 expression is associated with a decrease in immune cell tumor infiltration and an increase in regulatory T cells (Tregs)
- IDO1 expression in tumors has also been associated with *poor prognosis, increased progression, and reduced survival*



Rationale for IDO1i + Anti-PD-1 Combination

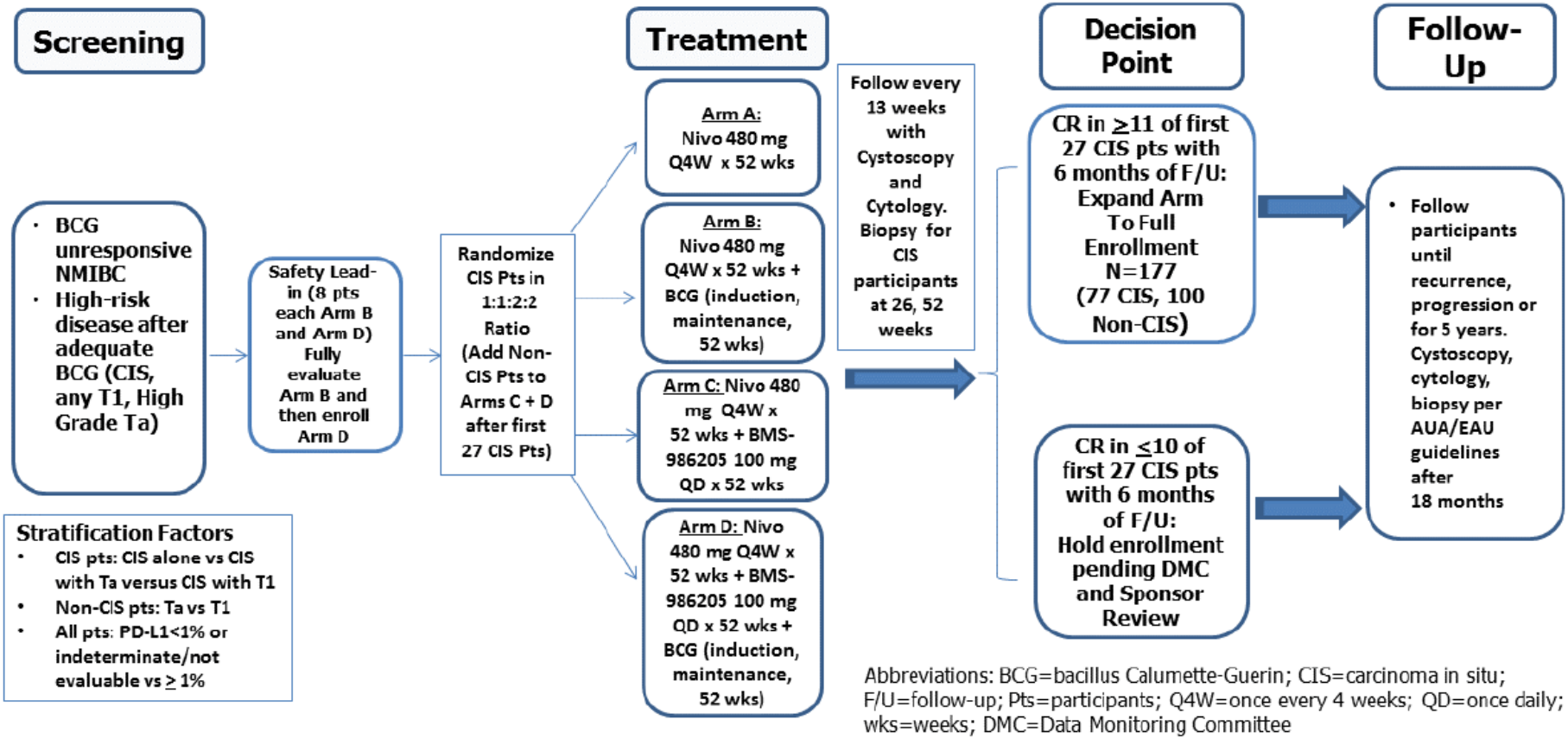
- IDO1 enzyme inhibits T-cell function through local depletion of tryptophan and production of immunosuppressive kynurenine
- High IDO1 expression is associated with a decrease in immune cell tumor infiltration and an increase in regulatory T cells (Tregs)
- IDO1 expression in tumors has also been associated with *poor prognosis, increased progression, and reduced survival*
- Anti-PD-1 treatment upregulates IDO1 expression in patients



Trial Design

- Treatment arms:
  - Arm A: Nivolumab only
  - Arm B: Nivolumab + BCG (safety lead-in arm 1)
  - Arm C: Nivolumab + BMS
  - Arm D: Nivolumab + BMS + BCG (safety lead-in arm 2)
- Safety Lead-In > Randomization Phase 1 > Phase 2 > Phase 3
- Current safety lead-in ending **May 15, 2019**
- **Phase 1**: Arms A + B + C open (1:1:2)
- **Phase 2**: CIS only (A + B + C + D; 1:1:2:2), Non-CIS (C + D; 1:1)
- **Phase 3**: Arms TBD by previous phases

Study Schematic



Abbreviations: BCG=bacillus Calumette-Guerin; CIS=carcinoma in situ; F/U=follow-up; Pts=participants; Q4W=once every 4 weeks; QD=once daily; wks=weeks; DMC=Data Monitoring Committee

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Study Treatment

- Nivolumab: 480mg, Q4W x 52 weeks
- BMS-986205: 100mg, QD x 52 weeks
- BCG: Induction, maintenance x 52 weeks

- Required assessments:
  - Cystoscopy: Every 13 weeks
  - Cytology (via bladder wash): Every 13 weeks
  - CIS patients: Random BBx at week 26 + 52
- Otherwise per standard clinical practice

Trial Objectives

Primary:

- Estimate complete response rate in CIS patients, event free survival for non-CIS patients per central lab evaluation

Secondary:

- Progression free survival
- Safety + tolerability of Nivo or Nivo + BMS alone or in combination with BCG

Updates

- Status of each trial
  - Keynote 057: recruiting non-CIS patients BCG unresponsive
  - VISTA: closed to accrual
  - Theralase I: closed to accrual
  - Theralase II: recruiting CIS patients
  - POTOMAC: recruiting BCG naïve high risk patients
  - KN 676: recruiting high risk patients having failed induction BCG
  - CheckMate-9UT: recruiting CIS patients BCG unresponsive

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QUESTIONS?