PIVOT-006: A Phase-3, Randomized Study of Adjuvant Intravesical Cretostimogene Grenadenorepvec versus Surveillance for the Treatment of Intermediate-Risk NMIBC

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What is Cretostimogene Grenadenorepvec?

Conditionally replicating adenovirus

- Highly immunogenic

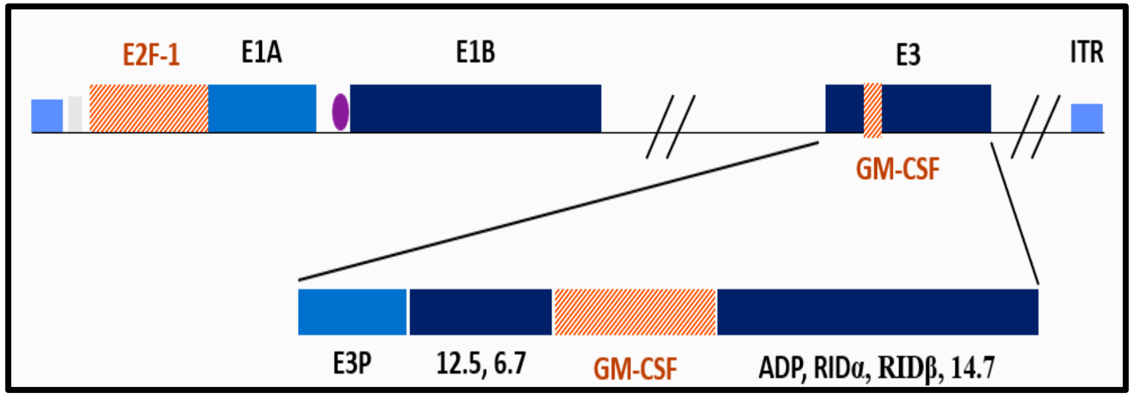
Oncolytic Immunotherapy

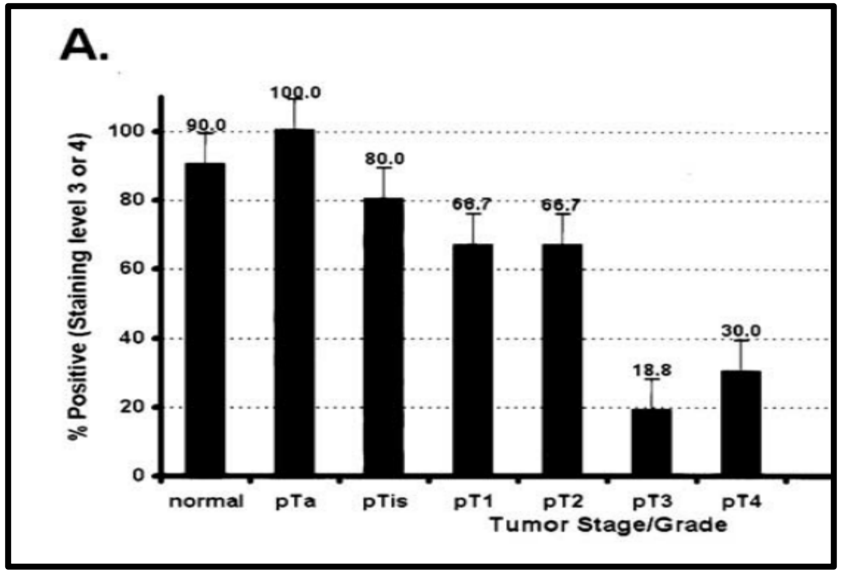
- Encodes GM-CSF
- Insertion of human E2F-1 promoter

Binds to Coxsackie Adenovirus Receptor (CAR)

- Robust expression in all stages of bladder cancer

Viral replication results in tumor lysis





CG Oncology proprietary illustration.
Sachs, et al. *Urology;* 2002
Burke, et al J Urol 2012

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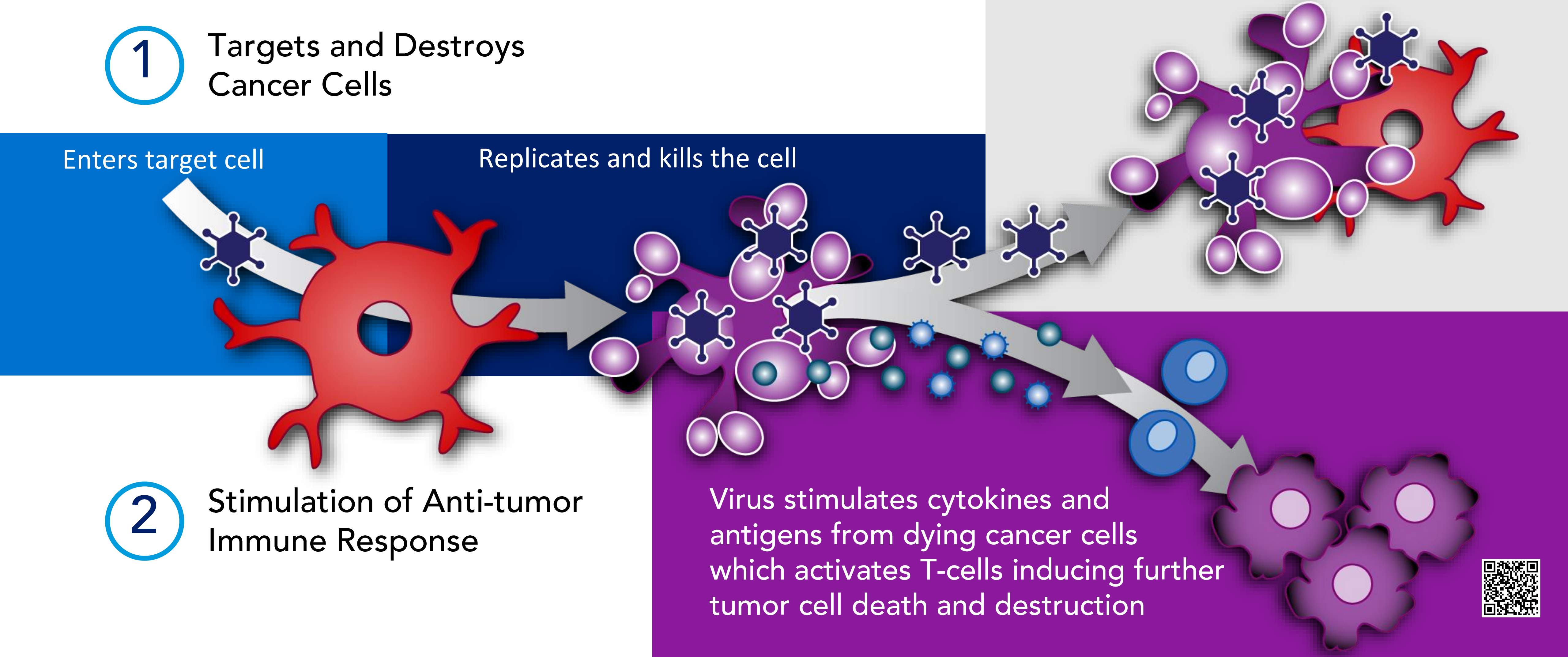
GM-CSF- Granulocyte-macrophage colony-stimulating factor; Rb- Retinoblastoma

Oncolytic Immunotherapy: Selective Oncolysis and Potent Anti-Tumor Immune Response

1. Targets and Destroys Cancer Cells

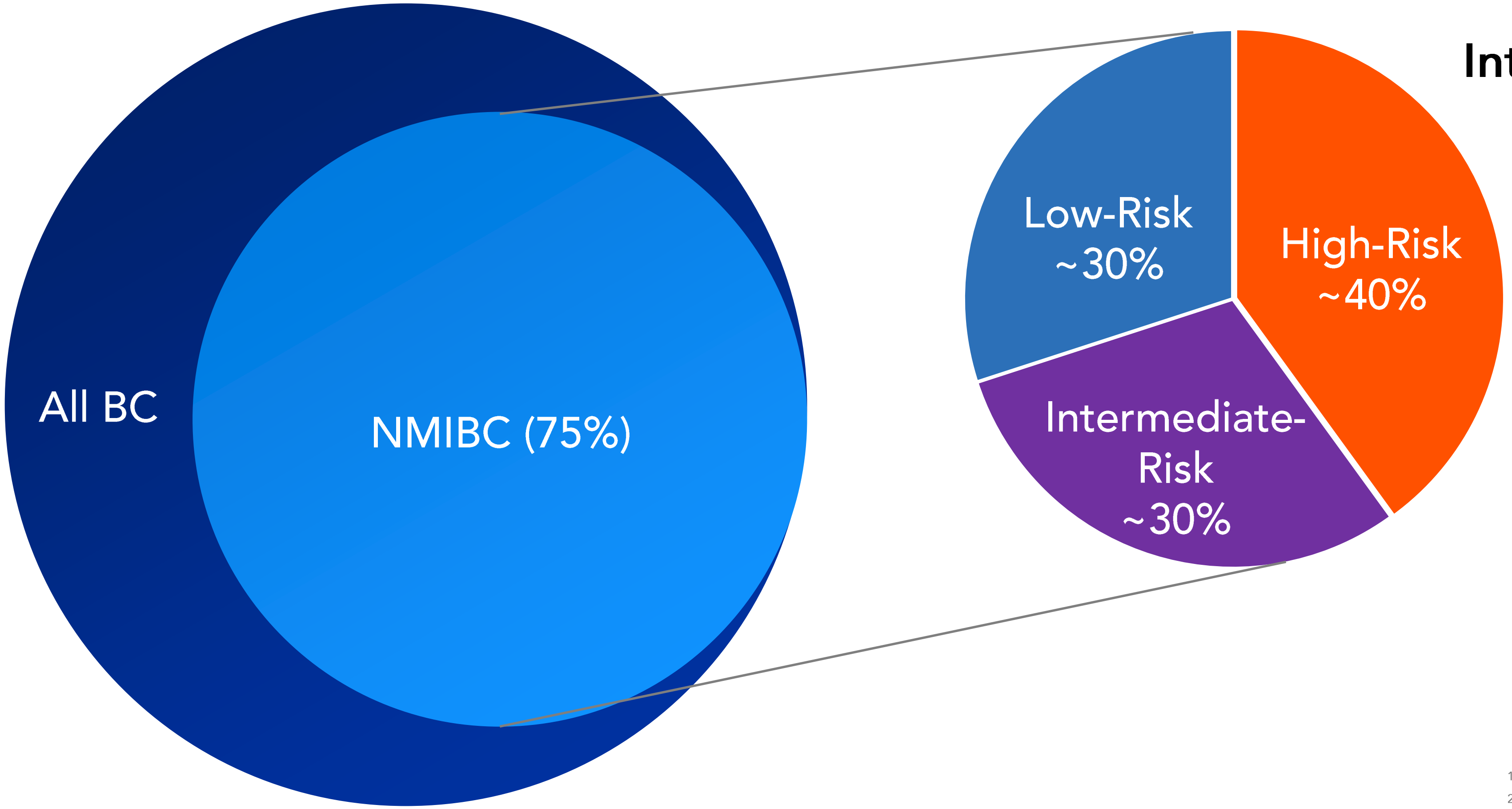
2. Stimulation of Anti-tumor Immune Response



Significant Unmet Need with High Prevalence of Intermediate-Risk NMIBC in the U.S.

NMIBC Prevalence in U.S. [1]

NMIBC Risk Stratification



Intermediate-Risk NMIBC

- High Recurrence; 50-70%[2]
- Low Progression; < 5%[2]
- Common[2]
- Costly[3]
- Chronic[4]
- Risk of Anesthesia, Surgery[5]

BC- Bladder Cancer; NMIBC- Non-Muscle Invasive Bladder Cancer

[1] SEER Cancer Stat Facts: Bladder Cancer
[2] Babjuk, et al. *Eur Uro;* 2019
[3] Mossanen, et al. *World J Urol;* 2019
[4] Sharma, et al. *J Uro;* 2021, Suppl 3
[5] Erikson, et al. *Scand J Uro;* 2020

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MANAGEMENT PER NMIBC RISK GROUP

AUA RISK GROUP (SEE BL-2)		INITIAL MANAGEMENT	FOLLOW-UP
Low		Surveillance[o]	Follow-up (BL-E)
Intermediate		Intravesical therapy[p,q] (preferred) or Surveillance	Follow-up (BL-E)
High	Bacillus Calmette-Guérin (BCG) naïve → Very-high-risk features[n]	Cystectomy (preferred) or BCG[p]	Follow-up (BL-E)
High	Bacillus Calmette-Guérin (BCG) naïve → No very-high-risk features	BCG[p] (category 1, preferred) or Cystectomy	Follow-up (BL-E)
High	BCG unresponsive or BCG intolerant	Cystectomy[r] (preferred) or Intravesical chemotherapy[p,s] or Pembrolizumab (select patients)[t] or Nadofaragene firadenovec-vncg (select patients)[u]	Follow-up (BL-E)

Follow-up (BL-E)
If prior BCG, maintenance BCG[p] (preferred)

- Cytology positive
- Imaging negative
- Cystoscopy negative

→ BL-4

Cystoscopy positive → Reclassify AUA Risk Group and manage accordingly

Intermediate-Risk NMIBC Study Design Considerations

- No standard of care treatment is approved by the FDA for IR-NMIBC
- Surveillance as the control arm is appropriate
  - Low risk of progression[1]
  - Consistent with guideline-directed care[1-3]
- Low utilization of intravesical therapy for IR-NMIBC[2,4,5]
- Randomized data supports single dose, peri-operative intravesical chemotherapy[6]

IR- Intermediate Risk; NMIBC- Non-Muscle Invasive Bladder Cancer; TURBT- Transurethral Resection of Bladder Tumor

[1] Sylvester, et al. *Eur Urol* 2006
[2] Matulay, et al. Urol Oncol 2020
[3] NCCN Guidelines – Bladder Cancer V3.2024
[4] Mori, et al. Urol Oncol 2020
[5] Lewicki, et al. JAMA Open Network 2022
[6] Messing, et al. JAMA 2018

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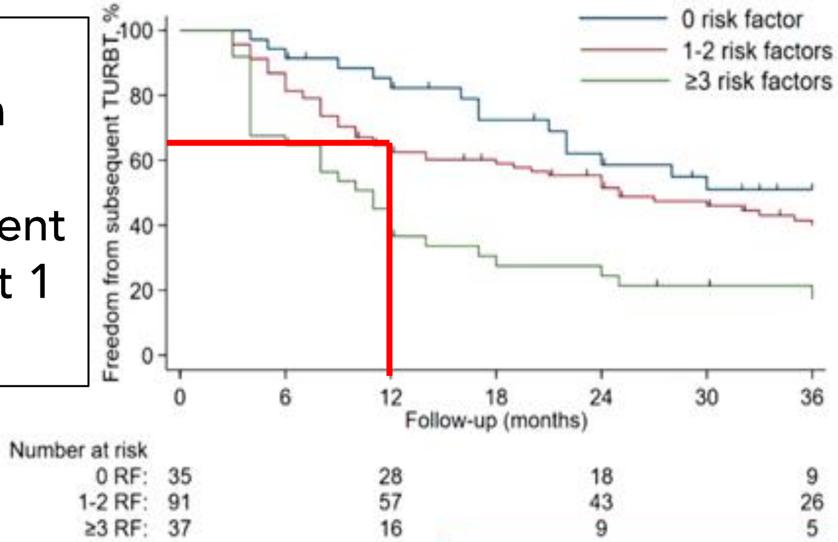
Results

63% Freedom from Subsequent TURBT at 1 Year



Median Time on AS	
0 RF	28 months (IQR 12-36)
≥ 3 RF	15 months (IQR 4-18)

Table 2. *Estimated Kaplan-Meier Survivor Function for Freedom of Subsequent Transurethral Resection of Bladder Tumor Stratified According to International Bladder Cancer Group Intermediate-risk Non-muscle Invasive Bladder Cancer Scoring System*

Variable	Overall (n=163)	0 RF (n=35)	1-2 RF (n=91)	≥3 RF (n=37)
6 mo, % (95% CI)	80 (73-85)	91 (76-97)	81 (72-88)	65 (47-78)
12 mo, % (95% CI)	61 (53-68)	82 (65-92)	63 (52-72)	37 (21-52)
24 mo, % (95% CI)	47 (39-55)	59 (39-74)	51 (41-61)	24 (12-40)
36 mo, % (95% CI)	37 (29-45)	51 (32-67)	40 (29-50)	17 (6-32)

R. Contieri

The International Bladder Cancer Group Intermediate-risk Non-muscle Invasive Bladder Cancer (IBCG IR-NMIBC) scoring system predicts the need for intervention fo patients on active surveillance.

Phase 3 Adjuvant Cretostimogene vs Surveillance for Intermediate-Risk NMIBC

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N = Up to 364

Regimen: Cretostimogene Induction and Maintenance

Design: Two arms, IVe cretostimogene after TURBT vs TURBT

Endpoints: RFS, RFS at 12-month and 24-month, PFS, & Safety

Trial Type: Open label

Exploratory: OS, Cancer Specific Survival, PROs, HRQoL, Biomarkers

Key Entry Criteria

- IR-NMIBC
  - Solitary LG Ta >3cm
  - Multifocal LG Ta
  - LG T1
  - LG Recurrent < 1 yr
  - HG Ta ≤ 3cm
- Adequate organ function
- ECOG 0-2

1:1 Randomization

Stratification: Perioperative Chemo, HG vs LG

Geography: North America

Arm A: Cretostimogene After TURBT

Disease Assessment:
Every 3 mos cystoscopy & cytology, for 2 years; then every 6 mos starting Year 3

Arm B: Complete TURBT Alone

Arm B patients offered Cretostimogene treatment following IR-NMIBC recurrence

HG- High Grade; IR- Intermediate Risk; IVE- Intravesical; LG- Low Grade; NMIBC- Non-Muscle Invasive Bladder Cancer; OS- Overall Survival; PFS- Progression Free Survival; PRO- Patient Reported Outcomes; RFS- Recurrence Free Survival; TURBT- Transurethral Resection of Bladder Tumor

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Exclusion Criteria

- Current or prior evidence of **HR-NMIBC** defined as:
  - HG T1
  - HG Ta > 3 cm that is recurrent or multifocal
  - Any *carcinoma in situ* (CIS)
  - Any variant histology
  - Any HG prostatic urethral involvement
  - Any LVI
  - Any BCG treatment failure in HG patient
- LR-NMIBC
  - A LG solitary, Ta ≤ 3 cm lesion that has recurred more than 12 mos after a previous IR-NMIBC diagnosis
- Has **IR-NMIBC** that **cannot be completely resected**
- Has hx of **MIBC**, Nodal or Metastatic disease

BCG- Bacillus Calmette Geurin; HG- High Grade; HR- High Risk; IR- Intermediate Risk; IVE- Intravesical; LG- Low Grade; LR- Low Risk; LVI- Lymphovascular Invasion; MIBC- Muscle Invasive Bladder Cancer; NMIBC- Non-Muscle Invasive Bladder Cancer

Efficacy Assessments

Efficacy Assessments

- Visit, cystoscopy, biopsy for cause, cytology
  - Q3mo, first 2 years
  - Q6mo, 3rd year

  Imaging
  - Q12mo
- Mapping biopsy/imaging for isolated positive cytology
- Central pathology review

Recurrence Free Assessment

- Without recurrence or progression in the bladder
- Upper tract or prostatic urethra

Experience with Cretostimogene

- Familiar and convenient instillation process/schedule for practices
- Administered by allied healthcare professionals (MAs, RNs)
- Well-tolerated regimen
- Streamlined instillation process for future cohorts and studies

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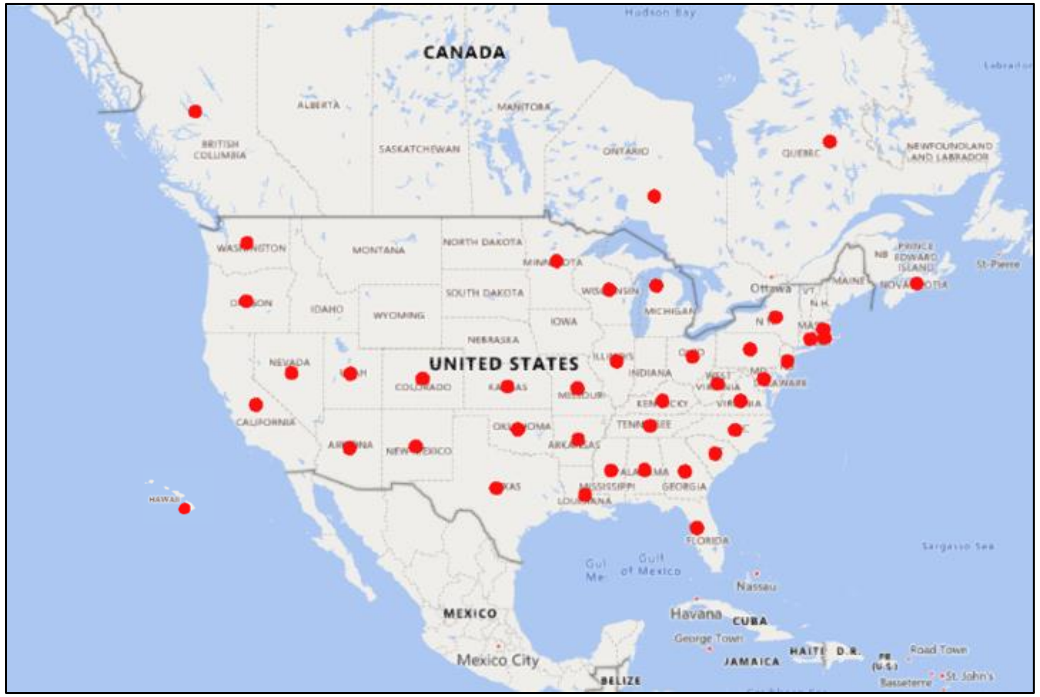
SUO-CTC Trial: PIVOT-006 Phase-3 Adjuvant Cretostimogene vs Surveillance in IR-NMIBC



- Over 90 North American sites participating
- First enrollments January 2024
  - Carolina Urologic Research Center, Neal Shore, M.D.
- Expected enrollment period – 30 Months
- At least 1 year of follow-up
- NCT06111235

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Acknowledgements

All Bladder Cancer Patients and Their Families

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SUO CTC Society of Urologic Oncology Clinical Trials Consortium, Inc.

BCAN Bladder Cancer Advocacy Network Leading the way to awareness and a cure

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QUESTIONS?

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