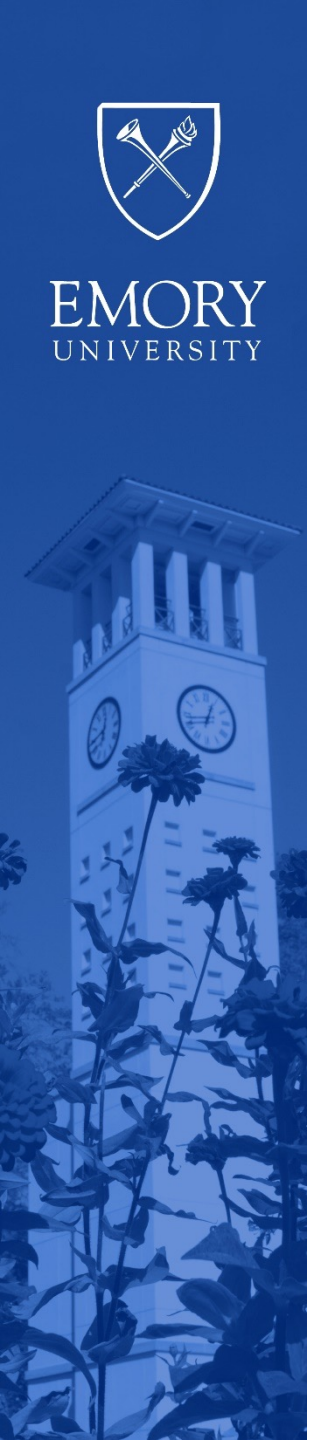


2024 Debates and Didactics in Hematology and Oncology

Current and Future Directions for NMIBC and MIBC

Presented by:

Shreyas Joshi, MD, MPH, FACS

Assistant Professor of Urology

Emory University Department of Urology

July 26, 2024

EMORY

Department of Urology

EMORY UNIVERSITY SCHOOL OF MEDICINE | Department of Urology

Disclosures

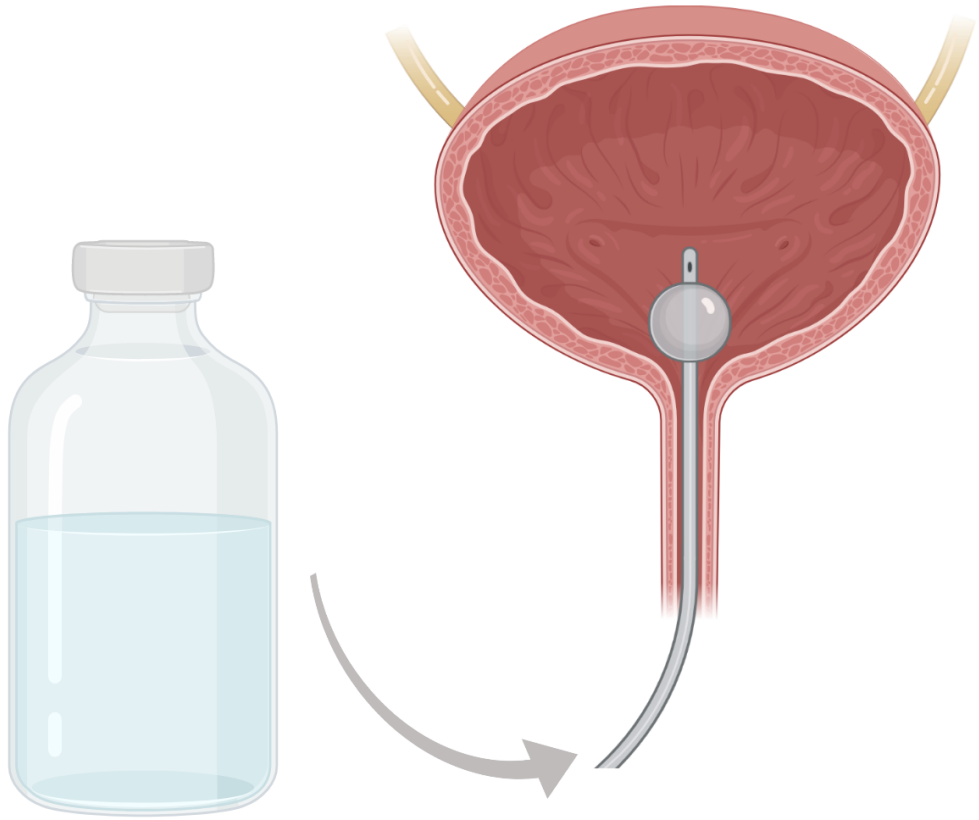
Consulting:

- CG Oncology
- enGene
- Photocure
- Blue Earth Diagnostics

Outline

- Background for NMIBC
- Latest advances in NMIBC
- Bladder preservation in MIBC
- Conclusions/Thoughts

Background



Prior to nadofaragene, only **four*** FDA-approved intravesical agents since 1959

- Thiotepa (1959)
- Doxorubicin (1974)
- **BCG (1989)**
- Valrubicin (1998)
- **Nadofaragene firadenovec (2022)**

Impact of BCG Shortage

Table 1 – Characteristics of treatment and disease recurrence according to study group.

	November 2011–September 2013 Control group			October 2013–December 2016 Study group (period of restricted supply)		
	Intermediate risk (n = 131; 68.6%)	High risk (n = 60; 31.4%)	Total (n = 191; 100%)	Intermediate risk (n = 140; 63.3%)	High risk (n = 71; 33.6%)	Total (n = 211; 100%)
Induction completed, n (%)	125 (95.4)	51 (85.0)	176 (92.1)		61 (85.9)	61 (28.9)
Consolidation completed, n (%)	112 (85.5)	50 (83.3)	162 (84.9)			
Maintenance ≥1 yr, n (%)	101 (77.0)	46 (76.7)	147 (77.0)			
Mitomycin C, n (%)				135 (96.4)		
Interruption for grade III toxicity	22 (16.8)	9 (15)	31 (16.2)	2 (1.5)	8 (11.3)	10 (4.8)
Recurrence, n (%)	17 (12.9)	14 (23.3)	31 (16.2)	61 (43.6)	38 (53.5)	99 (46.9)
New course of BCG, n (%)	16 (12.2)	10 (16.6)	26 (13.6)	28 (20.0)	20 (28.1)	48 (22.7)
New course of mitomycin C, n (%)	2 (6.4)		2 (1.0)	21 (15)	7 (9.8)	28 (13.2)
Cystectomy, n (%)		3 (5.0)	3 (1.5)	4 (2.8)	11 (15.5)	15 (7.1)

Recurrence Rates: 319 % increase; Cystectomy Rates: 500 % increase

Emory University School of Medicine
Department of Urology

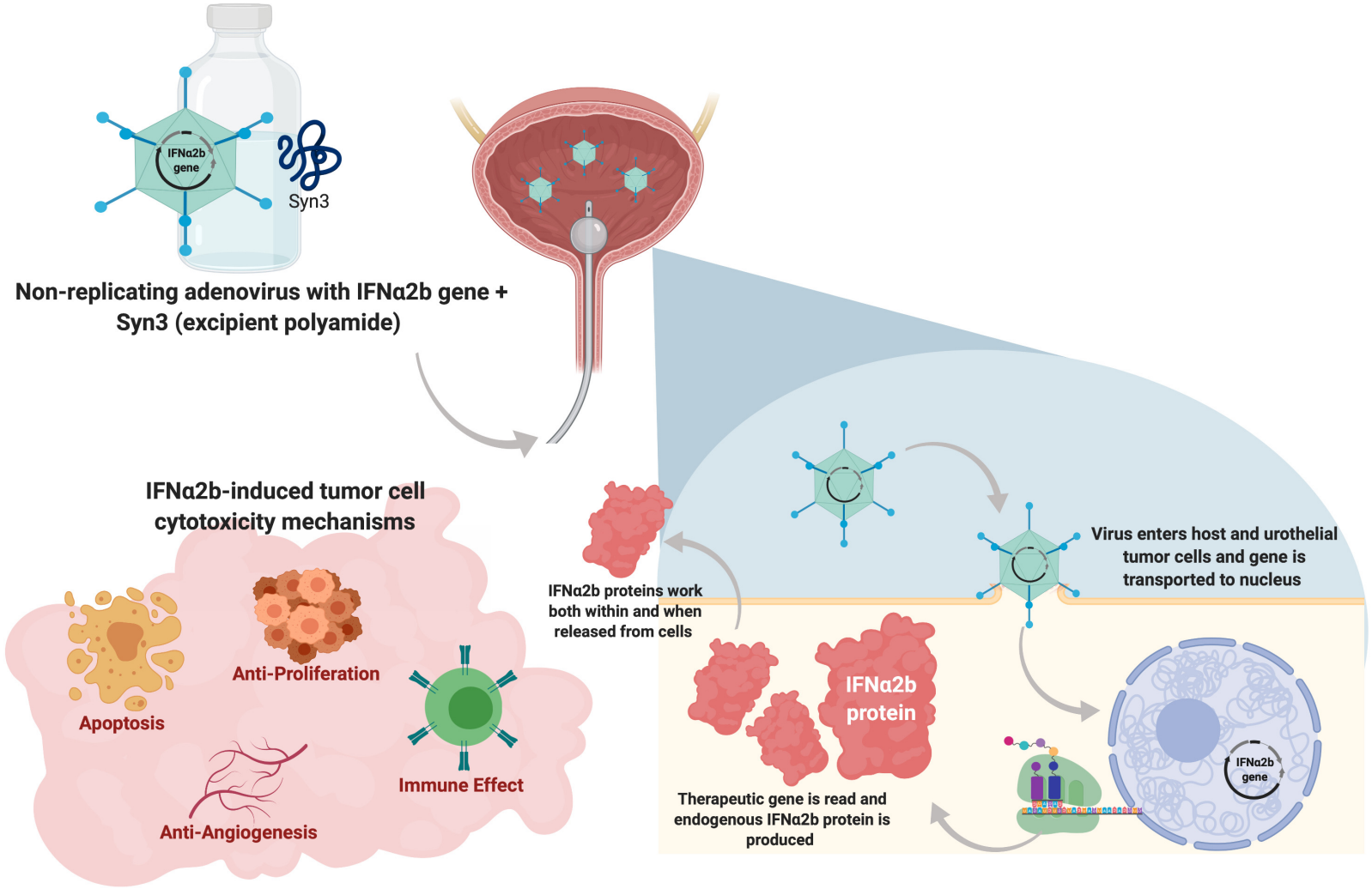
Ourfali et al *Eur Urol Focus* 2019

Gene therapy: Choosing a “gene” for bladder cancer

- Bladder cancer is an immunogenic tumor
- Choosing an agent that activates the immune system makes logical sense based on the success of BCG

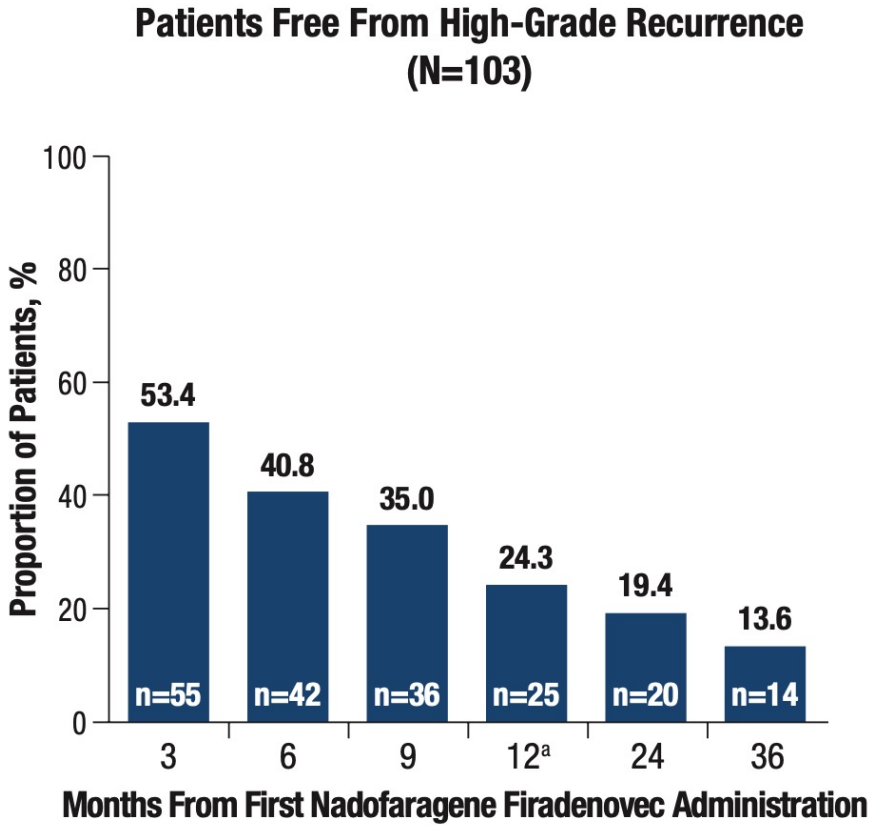
Targeting CIS based on the need for a “marker lesion” per FDA guidance

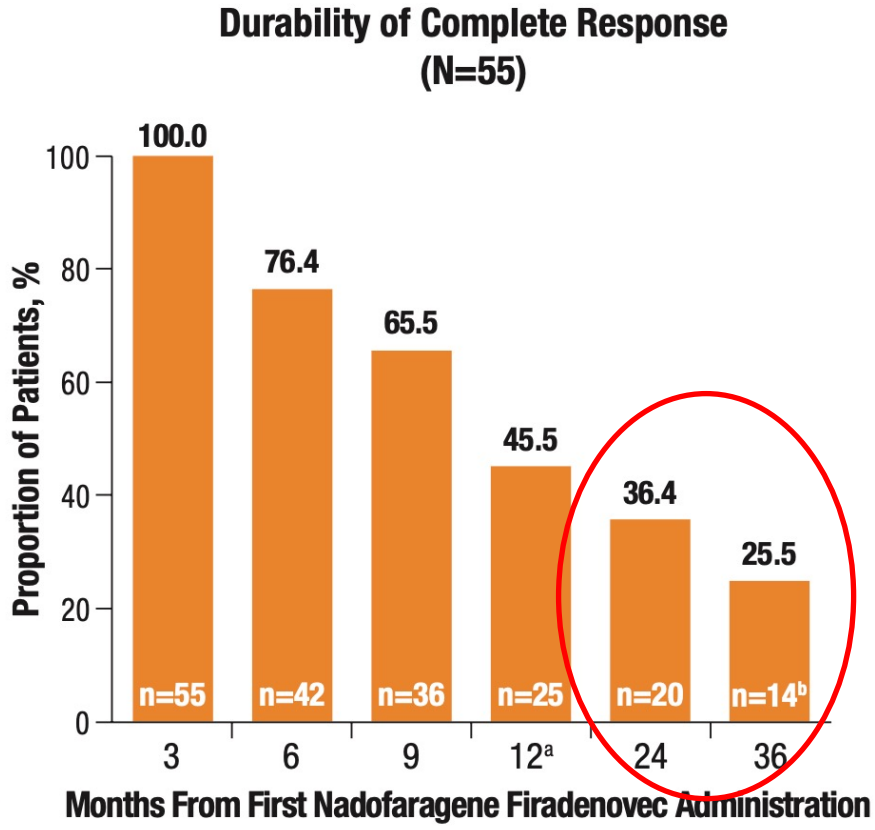
Nadofaragene firadenovec - Gene expression: Interferon



Narayan and Dinney, *Urol Clin N Am* 2020

36-Month Efficacy in Patients with CIS +/- Ta/T1





- In the overall CIS ± Ta/T1 cohort (N=103), the Kaplan–Meier estimated median (95% CI) duration of HGRFS was 6.0 months (3.4-8.3)
- At 36 months, 14/55 patients (25%) who had achieved a CR at 3 months remained HGRF
- Four patients (4%) experienced progression to muscle-invasive disease documented by TURBT at time of high-grade recurrence as documented in the electronic case report form

[a]At 12 months, response was assessed by mandatory 5-point biopsy.

[b]36/55 patients (65%) had high-grade disease recurrence and 5/55 patients (9%) had their last disease response assessment performed before month 36 with documented HGRFS.

Boorjian, Narayan…Dinney, et al SUO 2023

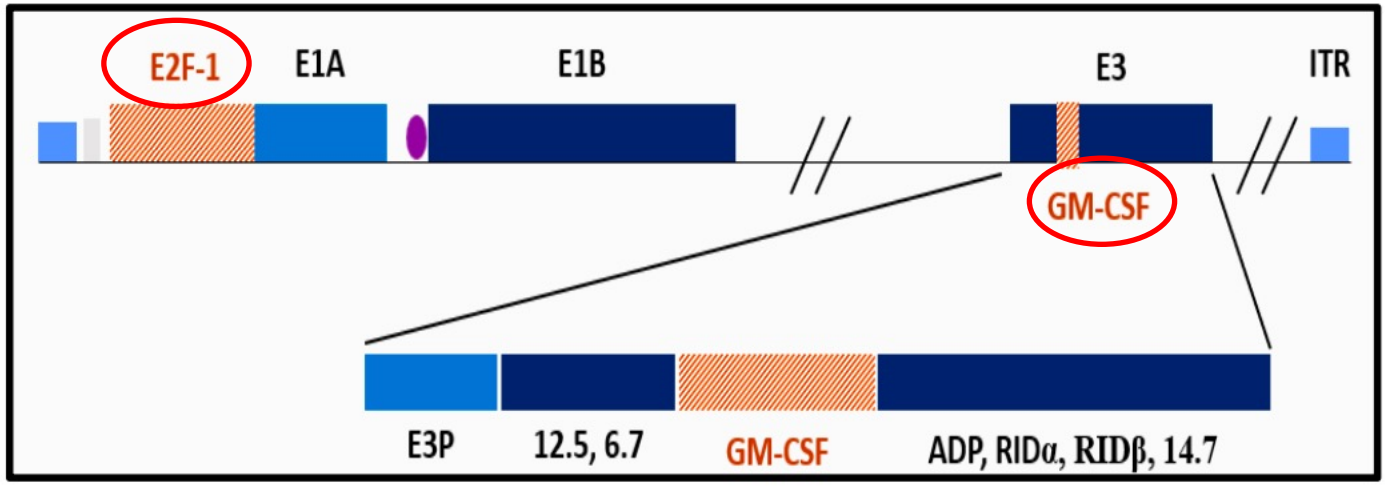
Cretostimogene Grenadenorepvec

Gene expression: GM-CSF

- Conditionally replicating adenovirus
- Binds to Coxsackie Adenovirus Receptor (CAR)
  - Robust expression in all stages of bladder cancer
- Viral replication results in tumor lysis

Tyson et al. (SUO 2023)

Cretostimogene Grenadenorepvec



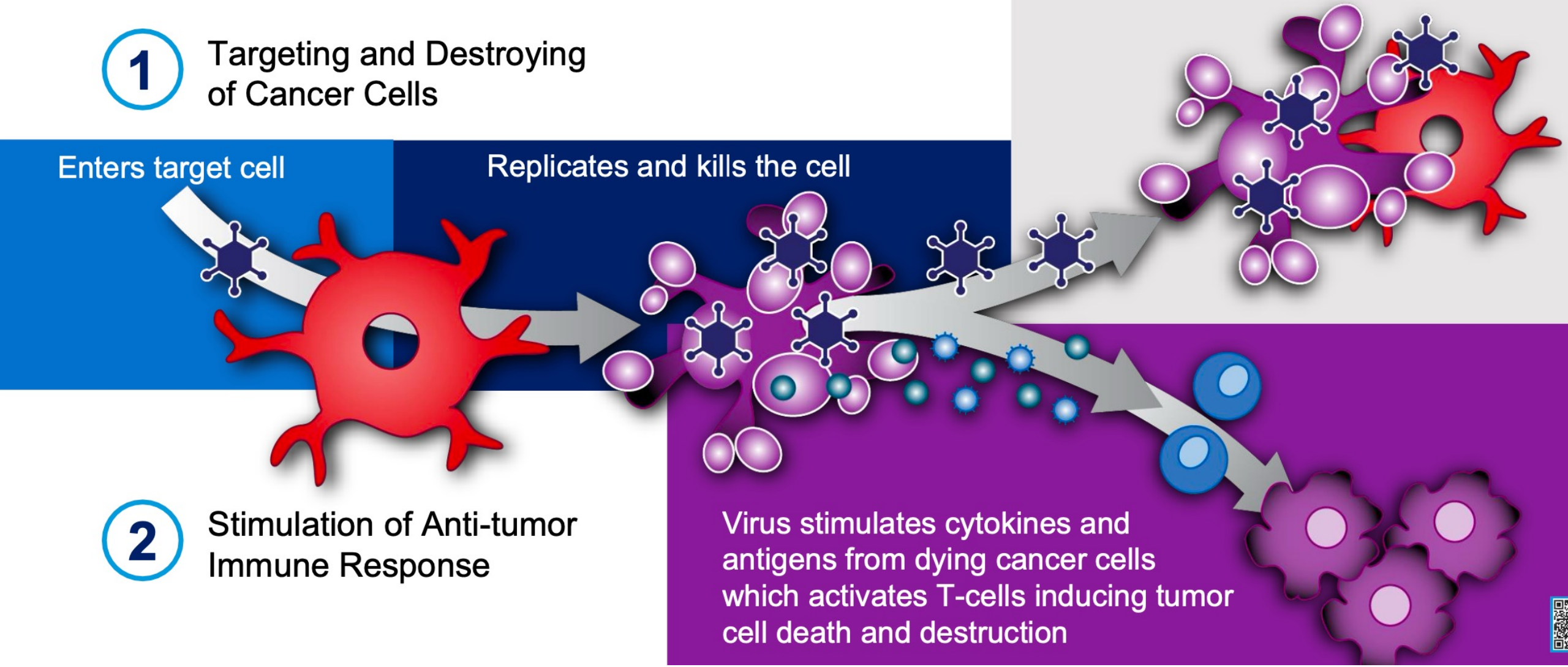
Oncolytic Immunotherapy: Selective Oncolysis and Potent Anti-Tumor Immune Response

1 Targeting and Destroying of Cancer Cells

Enters target cell

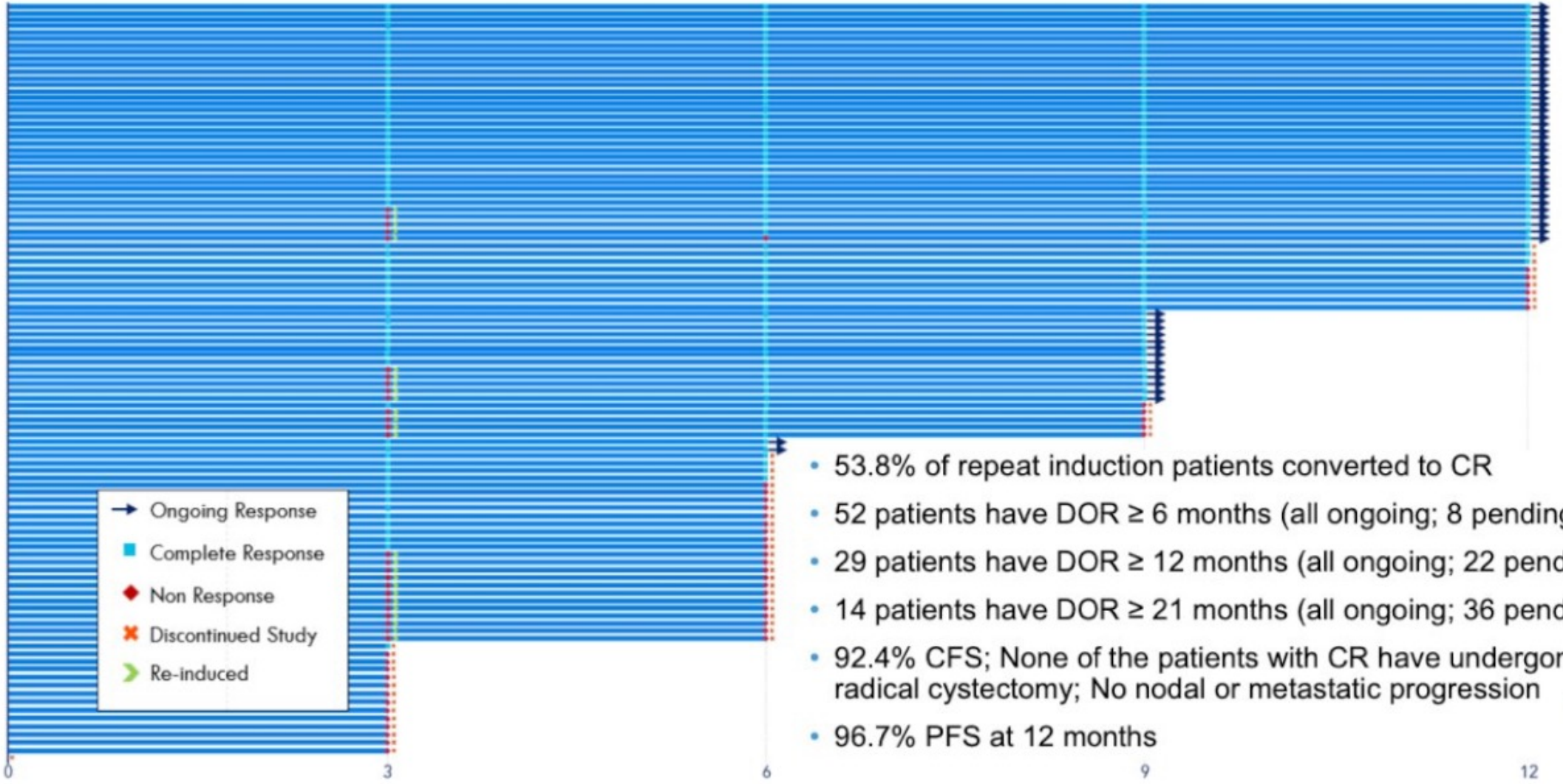
Replicates and kills the cell

Spreads to additional tumor cells inducing a chain reaction of killing cancer cells



2 Stimulation of Anti-tumor Immune Response

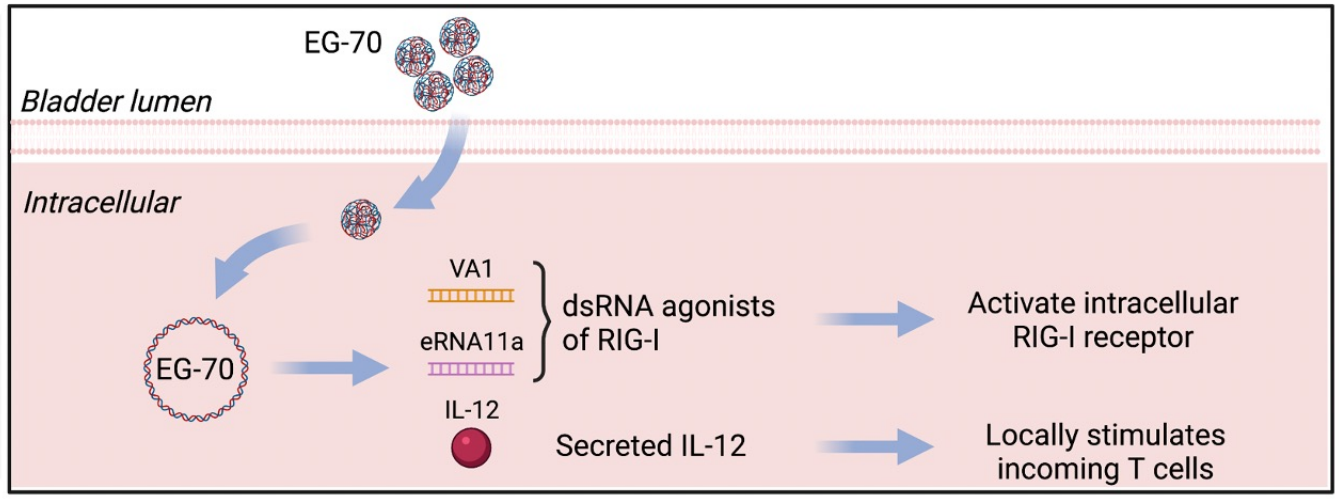
Virus stimulates cytokines and antigens from dying cancer cells which activates T-cells inducing tumor cell death and destruction



- 53.8% of repeat induction patients converted to CR
- 52 patients have DOR ≥ 6 months (all ongoing; 8 pending)
- 29 patients have DOR ≥ 12 months (all ongoing; 22 pending)
- 14 patients have DOR ≥ 21 months (all ongoing; 36 pending)
- 92.4% CFS; None of the patients with CR have undergone radical cystectomy; No nodal or metastatic progression
- 96.7% PFS at 12 months

Emory University School of Medicine
Department of Urology

Detalimogene Voraplasmid



RIG-I agonists:

- NK cell stimulation and suppressor cell attenuation promotes tumor killing environment
- Clinical data with innate immune activators support biological rationale
- Stimulate T cell recruitment and neo-antigen presentation

IL-12:

- Polarization, proliferation, and activation of T cells increases tumor killing
- Promotes immunological memory
- Strong efficacy in oncology with dose-limiting toxicities when systemically administered

Detalimogene Voraplasmid

- Phase 1 LEGEND study
  - 73% CR at any time
  - Excellent safety profile

- Pivotal Phase 2 currently enrolling

Comparing Outcomes

	EG-70 *	Nadofaragene *	Nogapendekin alfa inbakicept	Cretostimogene *	TAR-200	Pembrolizumab
MOA	Gene therapy IL-12 and RIG-1 agonists	Gene therapy IFNα2b	*Combination of IL-15 superagonist + BCG*	Oncolytic immunotherapy GM-CSF	Local delivery gemcitabine via "pretzel"	Immunotherapy PD-1 inhibitor
Stage	**Pivotal phase 2 enrolling**	**FDA-approved 2022**	*PDUFA April 2024*	**Phase 3 enrollment complete**	Phase 2 ongoing	FDA-approved 2020
Trial	LEGEND	Phase 3	*QUILT 3.032*	BOND-003	SunRISe-1	KEYNOTE-057
N	22	103	*82*	105	90	96
Age (median: yrs)	NR	72	*73*	72	71	73
Male	NR	89%	*87%*	76%	77%	84%
CR rate: any time	**73% (16/22)**	**51% (50/98)**	*71% (58/82)*	**75.2% (50/66)**	77% (23/30)	41% (39/96)
CR rate at 6 months	**45% (10/22)**	**41% (42/103)**	*56% (46/82)*	**64% (42/66)**	NR	NR
CR rate at 12 months	**NR**	**24% (25/103)**	*45% (37/82)*	**27.6%**	NR	NR
DOR ≥6 months	NR	NR	*NR*	74% (32/43)	100% (11/11)	NR
DOR ≥12 months	NR	46% (23/50)	*37% (30/82)*	NR	100% (6/6)	46% (18/39)
Safety	0% G3+ TRAE	4% G3+ TRAE	*20% G3 TEAE* *2% G4 TEAE* *1% G5 TEAE*	0% G3+ TRAE	7.4% G3+ TRAE	13% G3+ TRAE
Treatment-related discontinuation rate	NR	3%	*NR*	0%	3.7%	11%

Conclusions/Thoughts

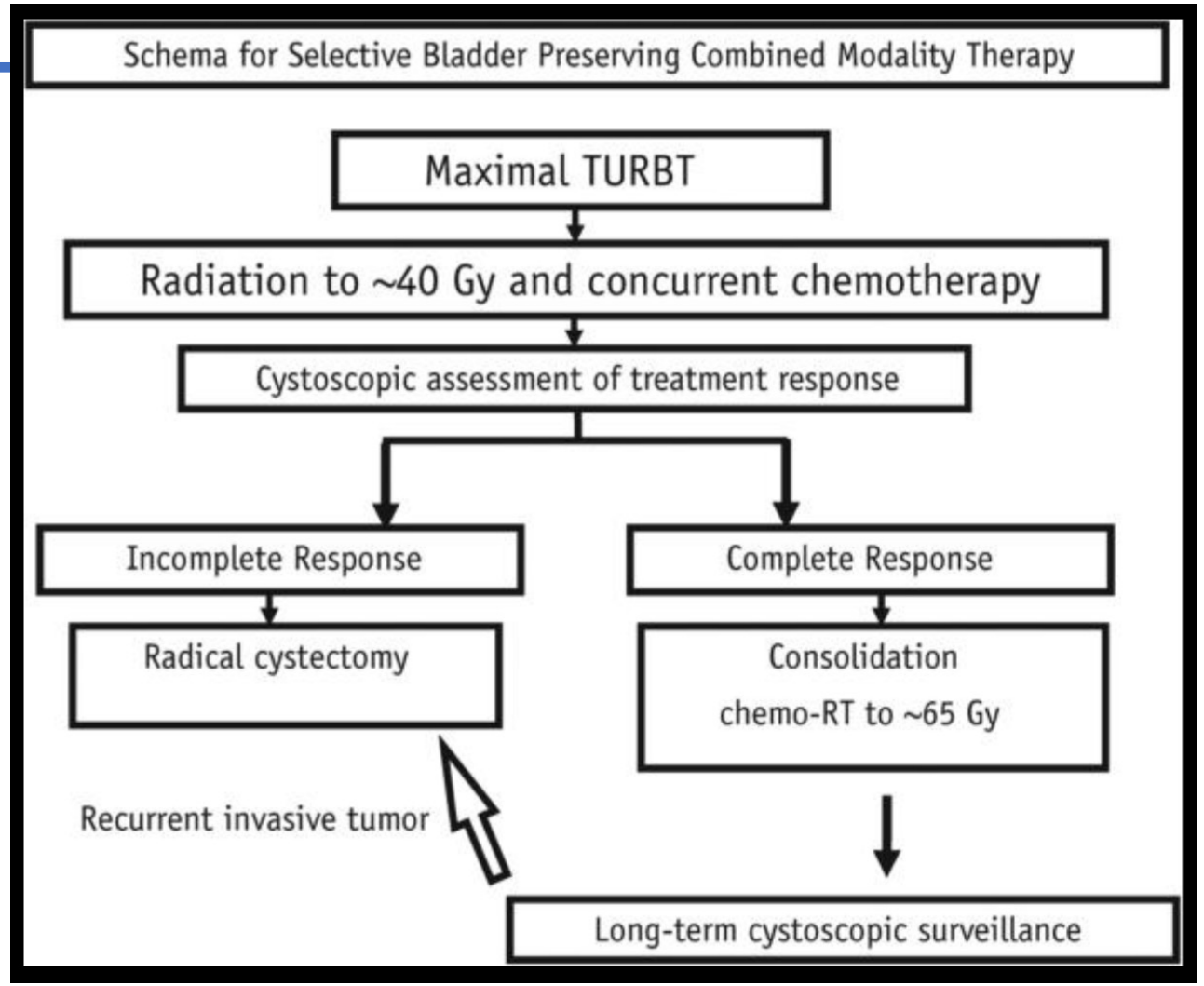
- 3 different intravesical gene therapies to watch in this space
  - Nadofaragene – nonreplicating adenoviral platform
  - Cretostimogene – conditionally replicating adenoviral platform
  - Detalimogene – nanopartical platform
- Promising efficacy in BCG salvage setting (CIS)
  - FDA approval of Nadofaragene
  - FDA fast track status of Cretostimogene
  - Pivotal Phase II study ongoing for Detalimogene
- Ease of use, excellent tolerability
- As the studies mature and real-world experience manifests, we will know more about how to incorporate these drugs for our patients

Muscle Invasive Bladder Cancer

- NAC + Cystectomy is gold standard
  - Trimodal Therapy appropriate in those who are poor surgical candidates or desire organ sparing approach
  - No head-to-head comparisons of NAC + Cystectomy vs. Trimodal Therapy

Trimodal Therapy

- Maximal TURBT + Chemoradiation
- No level 1 data comparing TMT to standard of care in prospective manner



Trimodal Therapy

- Contraindications
  - Multi-focal CIS
  - Large Tumor burden
  - Distant disease
  - Untreatable hydronephrosis caused by bladder cancer
  - Severe LUTS or Small bladder capacity
  - History of IBD
  - Previous pelvic radiation

Ideal TMT Patient: Small solitary T2 bladder tumor w/o CIS, hydronephrosis, or nodal involvement and good bladder function

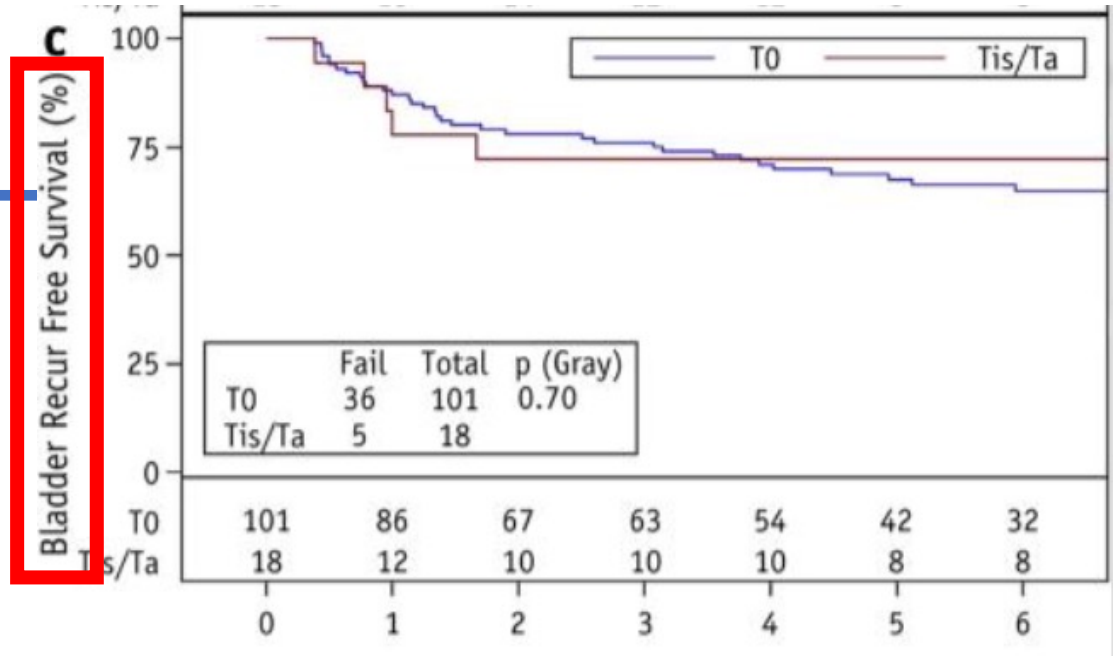
International Journal of Radiation Oncology*Biology*Physics
Volume 94, Issue 1, 1 January 2016, Pages 67-74

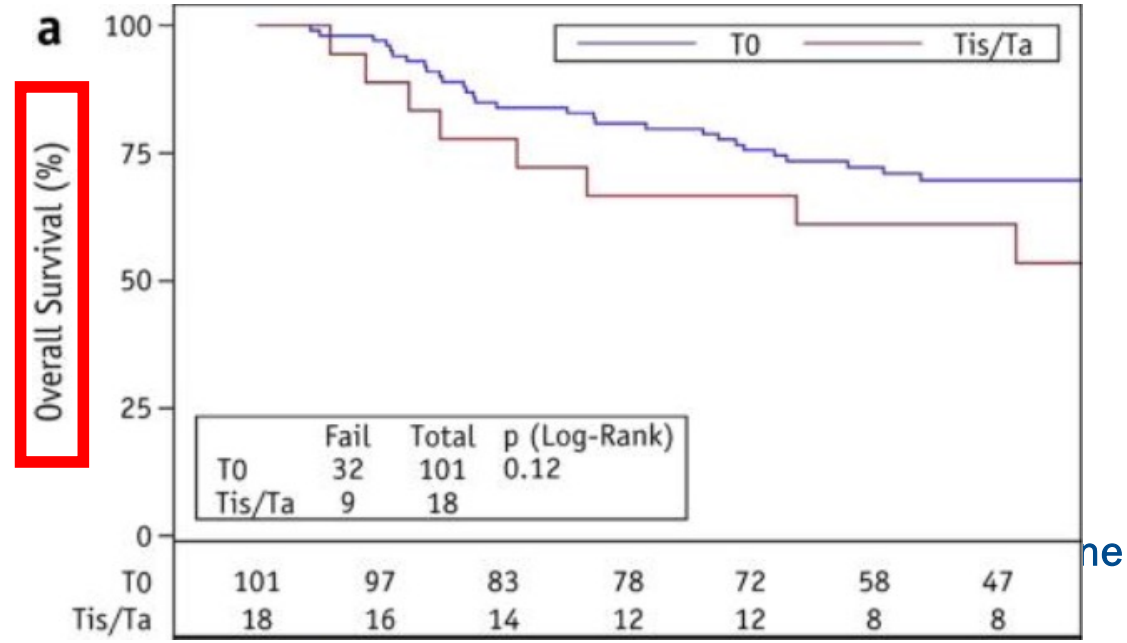
Clinical Investigation

Long-Term Outcomes Among Patients Who Achieve Complete or Near-Complete Responses After the Induction Phase of Bladder-Preserving Combined-Modality Therapy for Muscle-Invasive Bladder Cancer: A Pooled Analysis of NRG Oncology/RTOG 9906 and 0233

Timur Mitin MD *, Asha George MS †, Anthony L. Zietman MD ‡, Niall M. Heney MD ‡, Donald S. Kaufman MD ‡, Robert G. Uzzo MD §, Robert Dreicer MD ‖, H. James Wallace III MD ¶, Luis Souhami MD #, M. Chris Dobelbower MD **, Howard M. Sandler MD ††, William U. Shipley MD ‡

- No difference in DSS or OS between Complete and Partial Responders





Recurrence and Long-Term Outcomes

ELSEVIER

European Urology

Volume 66, Issue 1, July 2014, Pages 120-137

Collaborative Review – Bladder Cancer

Critical Analysis of Bladder Sparing with Trimodal Therapy in Muscle-invasive Bladder Cancer: A Systematic Review

Guillaume Ploussard [a b], Siamak Daneshmand [j], Jason A. Efstathiou [c], Harry W. Herr [d], Nicholas D. James [h], Claus M. Rödel [f], Shahrokh F. Shariat [e], William U. Shipley [c], Cora N. Sternberg [g], George N. Thalmann [i], Wassim Kassouf [a]

- Following TMT
  - Residual disease in 20-30%

Recurrence:

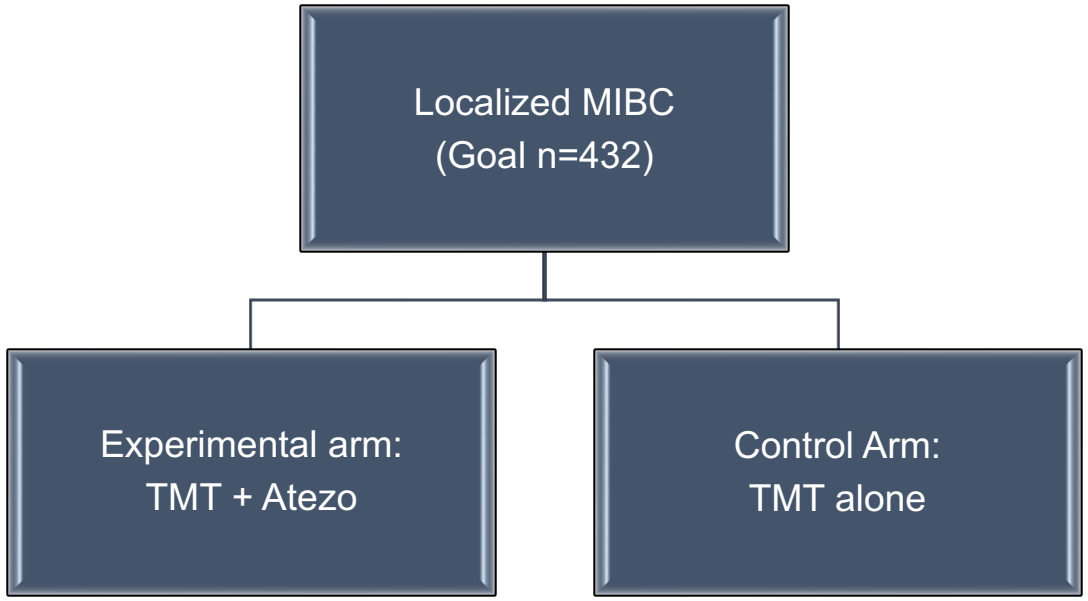
- 20-30% recurrence in complete responders (½ invasive, ½ superficial)

Outcomes:

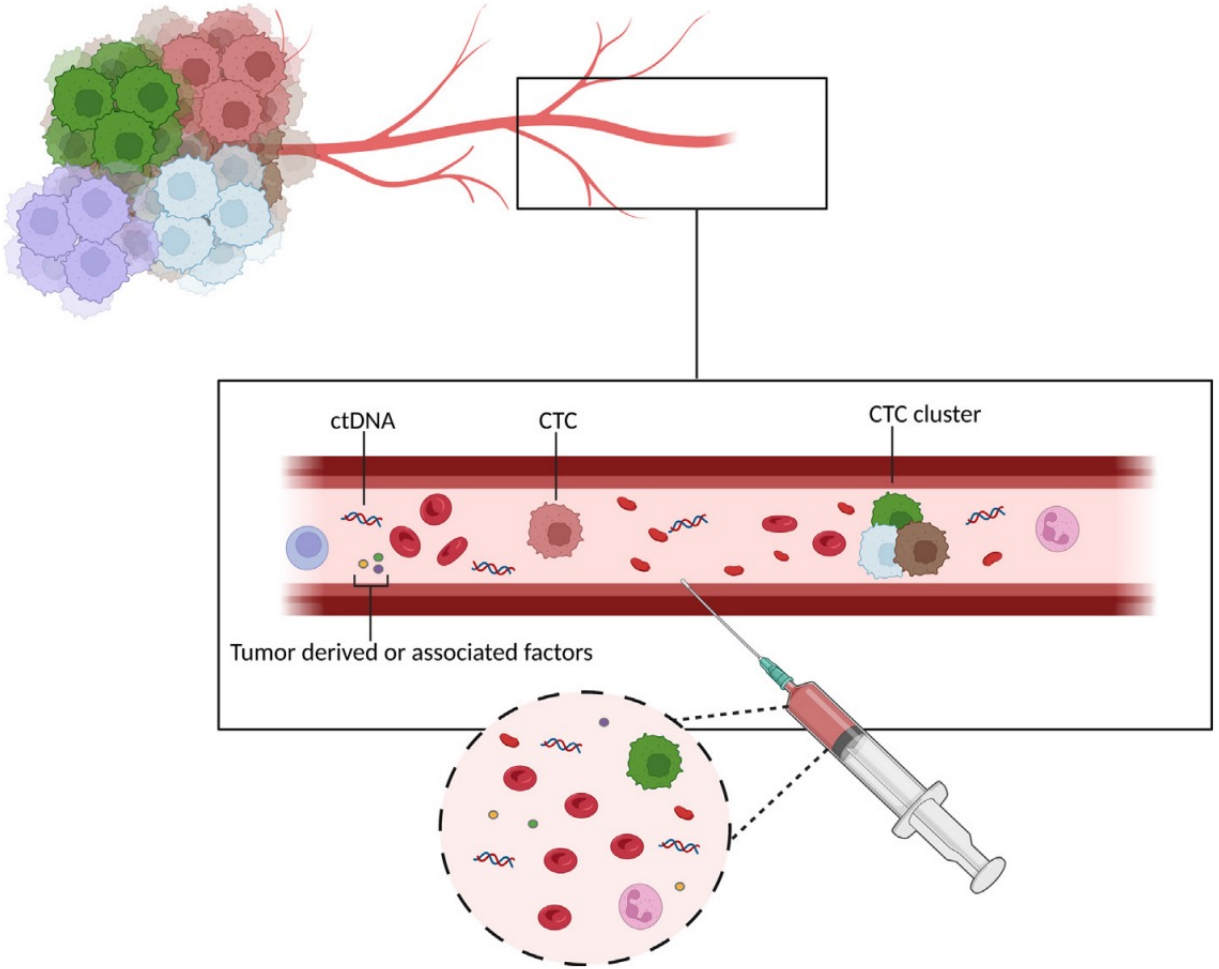
- 5-yr CSS: 50-82%
- 5-yr OS: 36-74%
- Salvage Cystectomy rates 25-30%

S1806

- Phase III randomized trial
- standard chemoradiation +/- atezolizumab in MIBC
- Atezo every 3 weeks for 6 months given with TMT vs TMT alone
- Pts with T2-T4a N0M0 bladder cancer



Circulating Tumor DNA (ctDNA)

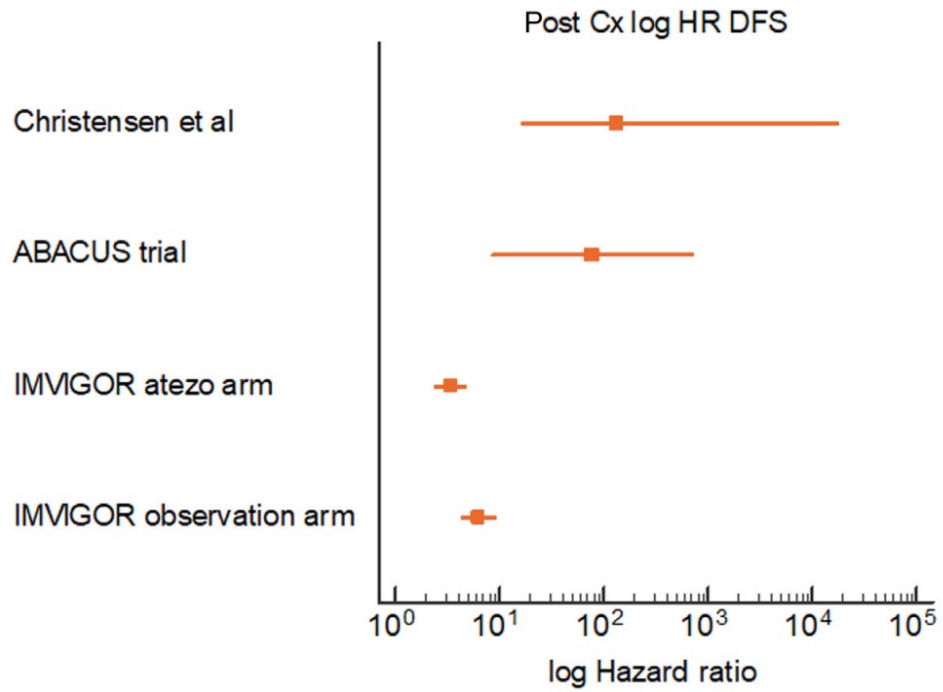


Crupi et al., European Urology Oncology 2024

Emory University School of Medicine
Department of Urology

ctDNA

- May have a role in predicting response to NAC, cystectomy, and adjuvant therapy
- May eventually help guide decision-making regarding the use of adjuvant therapies
- Current commercially available assay, though data on how to use the findings is limited



Study	Log HR	HR	low	High
Christensen et al .	2.12	131.3	16.6	1699.6
ABACUS trial	1.89	78.22	8.64	707.73
IMVIGOR atezo arm	0.53	3.36	2.44	4.62
IMVIGOR obs. arm	0.80	6.3	4.45	8.92

MIBC Conclusions

- TMT therapy is a viable option for patients with MIBC **in carefully selected patients** who desire a bladder sparing approach or those who cannot tolerate RC.

- **ctDNA** holds the most promise as a prognostic and risk-stratification tool during peri-treatment management of MIBC

Thank you!

Emory University School of Medicine
Department of Urology