Exploring Cretostimogene's Combination Potential in NMIBC Beyond Monotherapy

CG ONCOLOGY

Attacking Bladder Cancer for a Better Tomorrow™

Rebecca Tregunna, MD

Albert Institute Symposium
September 17, 2026

Agenda

- CORE-008 CX
- SWOG ARCIS
- XCEED

Efficacy and Safety of Intravesical Cretostimogene Grenadenorepvec Plus Gemcitabine in High-Risk BCG-Exposed Or BCG-Unresponsive Non-Muscle-Invasive Bladder Cancer

CORE-008 Cohort CX

Rationale for Novel Intravesical Combination Strategies in HR-NMIBC

- Published evidence supports efficacy and safety of cretostimogene monotherapy and in combination with pembrolizumab for HR BCG-UR NMIBC and nivolumab for MIBC.[1-3]
- Novel intravesical therapeutic approaches that leverage complementary mechanisms and immune-modulating synergy are still needed for HR NMIBC.
- Pre-clinical data supports mechanistic rationale for combining intravesical gemcitabine and cretostimogene.


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Article | Published: 06 June 2024

Oncolytic adenoviral therapy plus pembrolizumab in BCG-unresponsive non-muscle-invasive bladder cancer: the phase 2 CORE-001 trial

Roger Li, Paras H. Shah, Tyler F. Stewart, Jong Kil Nam, Trinity J. Bivalacqua, Donald L. Lamm, Edward M. Uchio, Daniel M. Geynisman, Joseph M. Jacob, Joshua J. Meeks, Rian Dickstein, Shane M. Pearce, Seok Ho Kang, Seung Il Jung, Ashish M. Kamat, James M. Burke, Kirk A. Keegan & Gary D. Steinberg

Nature Medicine **30**, 2216–2223 (2024) | Cite this article


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Oncolytic immunotherapy with nivolumab in muscle-invasive bladder cancer: a phase 1b trial

Roger Li, Nancy Y. Villa, Xiaoqing Yu, Joseph O. Johnson, Gustavo Borjas, Jasreman Dhillon, Carlos M. Moran-Segura, Youngchul Kim, Natasha Francis, Denise Dorman, John J. Powers, Wade J. Sexton, Philippe E. Spiess, Michael A. Poch, Logan Zemp, Scott M. Gilbert, Jingsong Zhang, Julio M. Pow-Sang, Alexander R. A. Anderson, Tingyi Li, Xuefeng Wang, G. Daniel Grass, James M. Burke, Colin P. N. Dinney, ... Jose R. Conejo-Garcia + Show authors

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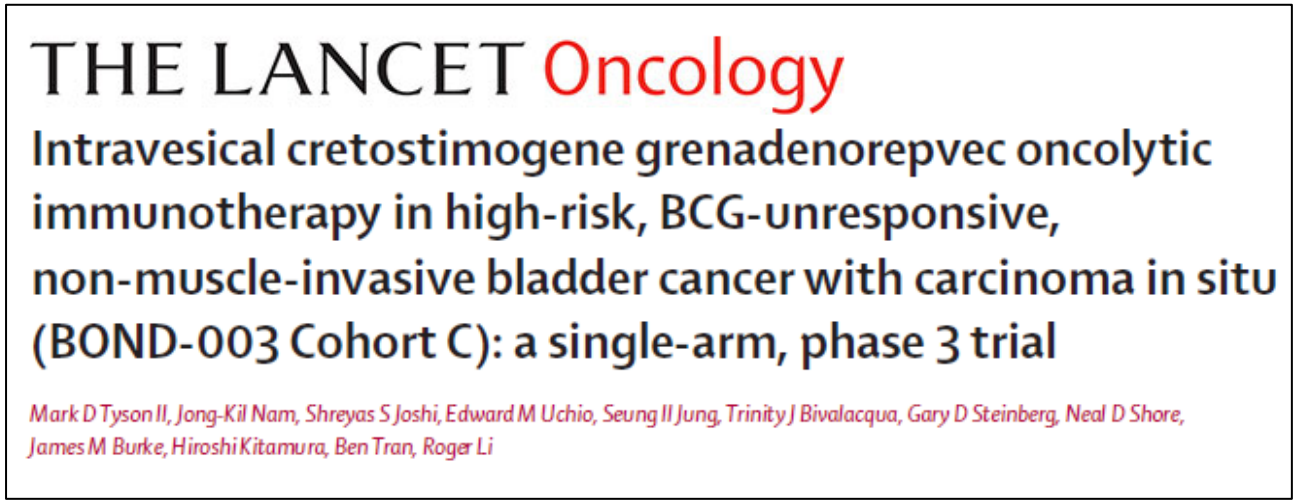
THE LANCET Oncology

Intravesical cretostimogene grenadenorepvec oncolytic immunotherapy in high-risk, BCG-unresponsive, non-muscle-invasive bladder cancer with carcinoma in situ (BOND-003 Cohort C): a single-arm, phase 3 trial

Mark D Tyson II, Jong-Kil Nam, Shreyas S Joshi, Edward M Uchio, Seung Il Jung, Trinity J Bivalacqua, Gary D Steinberg, Neal D Shore, James M Burke, Hiroshi Kitamura, Ben Tran, Roger Li

BCG: Bacillus Calmette-Guérin; BCG-UR: BCG-unresponsive; HR: high-risk; IVE: intravesical; MIBC: muscle-invasive bladder cancer; NMIBC: non-muscle-invasive bladder cancer

1. Tyson M, et al. *Lancet Oncology* 2026. 2. Li R, et al. *Nat Med* 2024;30(8):2216-2223 3. Li, R, et al. *Nat Med* 2025; 31(1):176-188

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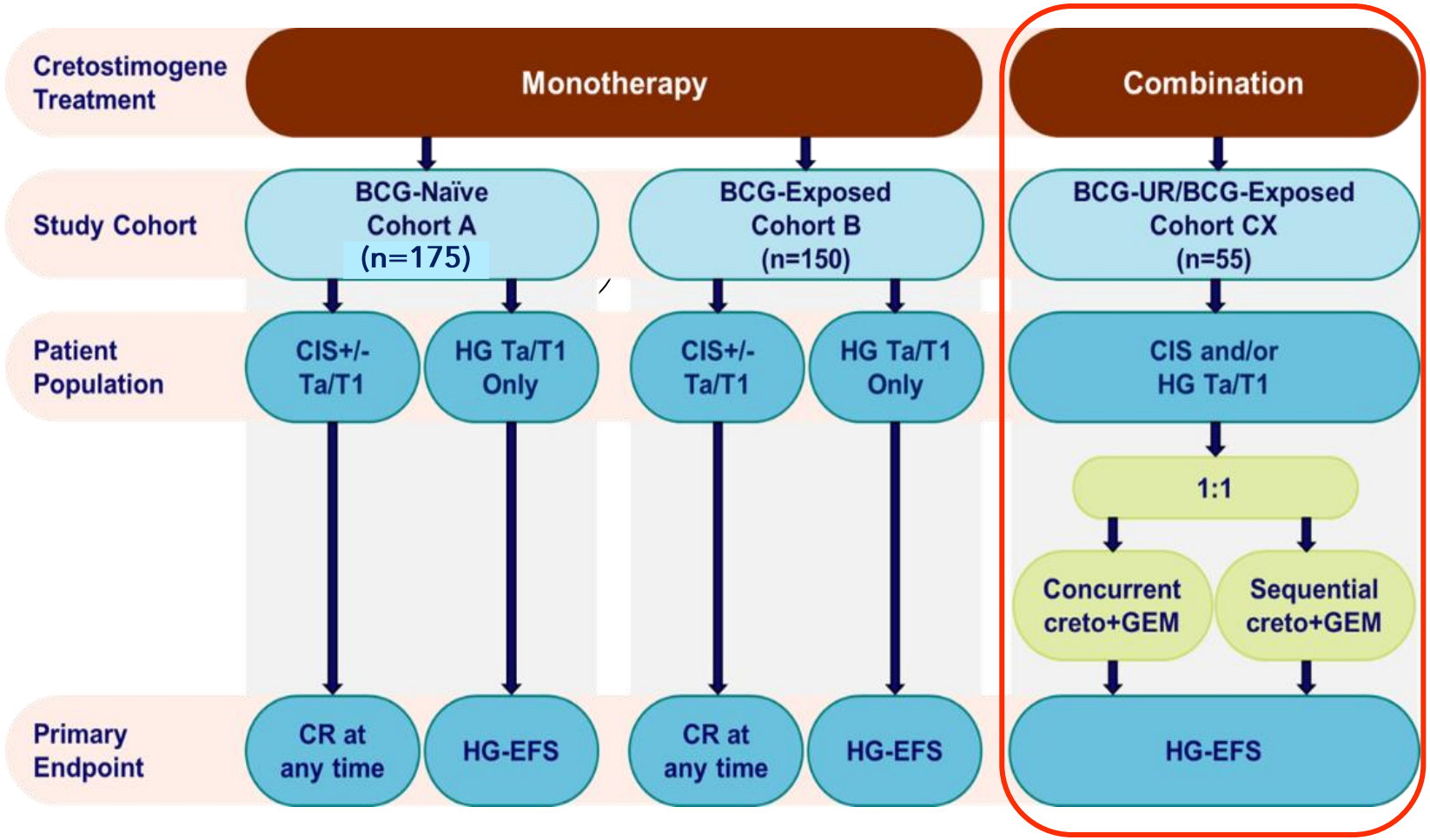
CORE-008 Phase 2/3, Multi-Cohort Trial in HR NMIBC



CIS= Carcinoma in Situ; CR=Complete Response; GEM= Intravesical Gemcitabine; HG-EFS= High-Grade Event-Free Survival
HG-EFS defined as High-grade recurrence/persistence, progression to T1, progression to T2+ and death from any cause
Concurrent: Same-day administration of cretostimogene (first) followed by gemcitabine throughout induction and maintenance.
Sequential: Two weekly cretostimogene instillations followed by one gemcitabine instillation (Weeks 1, 2, 4, 5 vs Weeks 3, 6), continued in maintenance.

BCG-Exposed

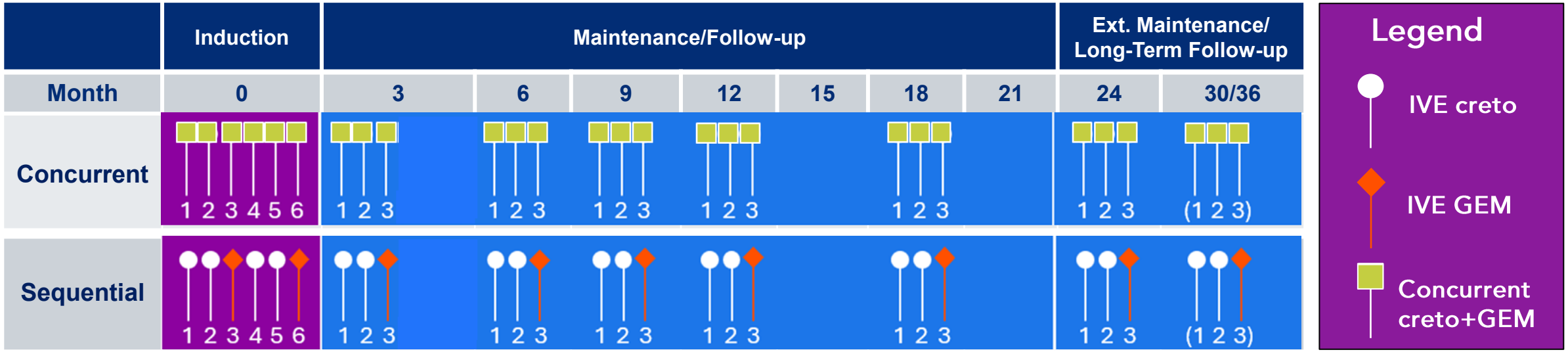
Patients who had prior BCG and either presented with CIS/HGTa recurrence at first evaluation (BCG-resistant), recurred outside of the BCG-unresponsive window following adequate BCG, or recurred within 24 months after inadequate BCG

BCG-Unresponsive

Participants who received adequate BCG (5+2) and present with:

- HG T1 at first evaluation following induction course
- HG Ta/T1 within 6 mo
- CIS within 12 mo

CORE-008 Cohort CX Treatment and Assessment Schedule



- Re-induction allowed for patients with HG Ta and/or CIS at Month 3
- Assessments include: Cystoscopy & Cytology every 3 months; CT/MRU every 6 months
- Clinic-based instillation with flexibility to void at home after instillation during maintenance

Concurrent: Same-day administration of cretostimogene (first) followed by gemcitabine throughout induction and maintenance.
Sequential: Two weekly cretostimogene instillations followed by one gemcitabine instillation (Weeks 1, 2, 4, 5 vs Weeks 3, 6), continued in maintenance.
Efficacy assessments based on local pathology review.

Patient Demographics & Baseline Characteristics

Patients in Safety Dataset	N=55	%
Gender		
Male	43	78.2
Female	12	21.8
Age (Years)		
Mean (Range)	73.1 (54-88)	
Median (IQR)	75 (66-79)	
Age (Categories)		
< 65	10	18.2
≥ 65 and < 75	17	30.9
≥75	28	50.9
ECOG PS		
0	48	87.3
1	6	10.9
2	1	1.8
HR NMIBC T-Stage at Study Entry		
CIS +/- HG Ta/T1	28	50.9
HG Ta/T1	27	49.1
BCG History, n (%)		
Median BCG doses (IQR)	7.0 (6-13)	
BCG-Exposed	36	65.5
BCG-Unresponsive	19	34.5

- All patients enrolled from the U.S. across multiple sites of care
  - 80.0% community
  - 20.0% academic
- **Majority of patients are:**
  - Male (78.2%)
  - White (92.7%)
  - > 65 years (81.8%)
- **Cohort generally well-balanced across concurrent and sequential treatment arms**

Efficacy data cutoff as of 13MAR2026.

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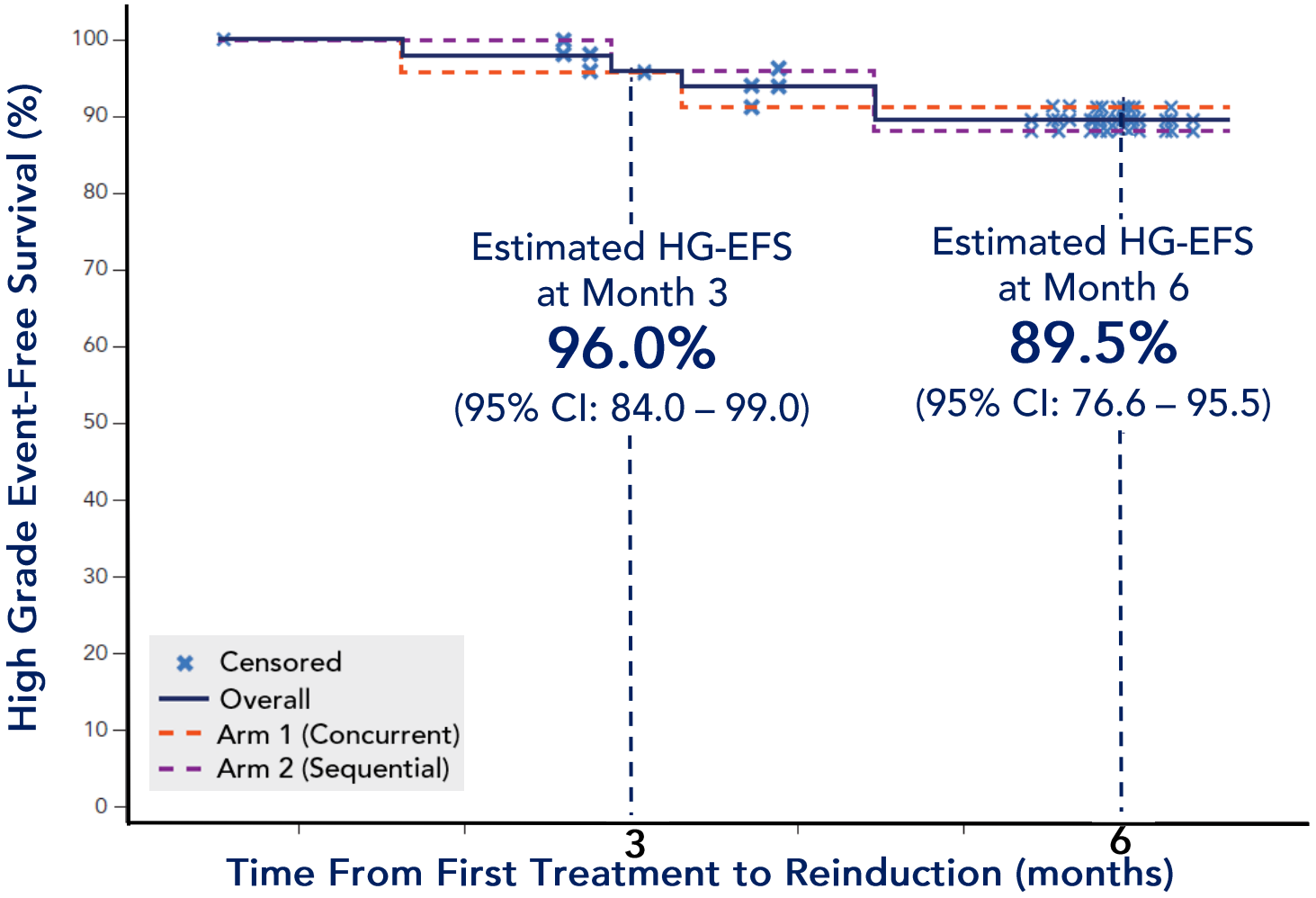
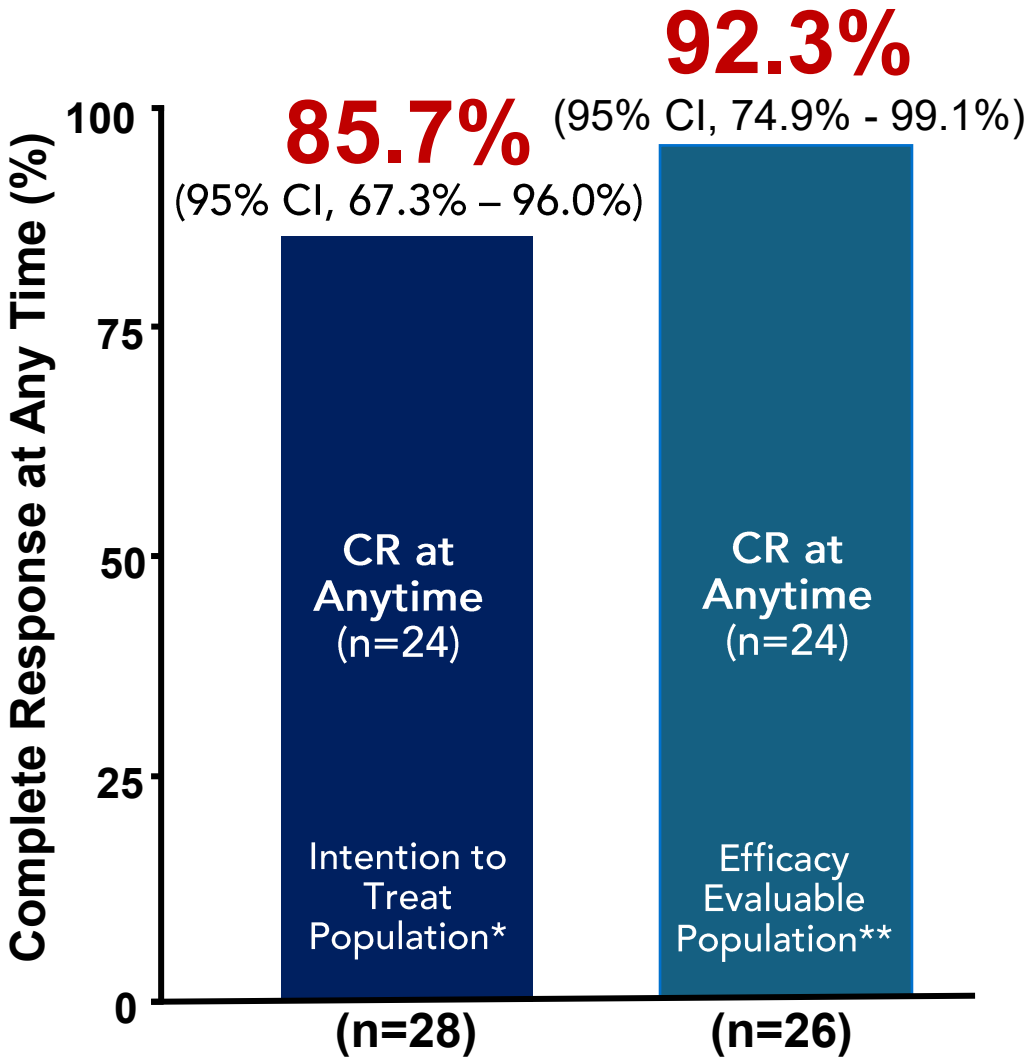
High-Grade Event-Free Survival at 3 and 6-Months From CORE-008 Cohort CX (ITT Population)



- Median follow-up: 6.6 months
- **No significant differences in HG-EFS by arm**
- **Consistent response among BCG-UR and BCG-exposed subgroups**
- No treatment-related progression to MIBC or mUC
  - 2 patients experienced NMIBC stage reclassification

BCG-UR= BCG-Unresponsive; CIS= Carcinoma in Situ; HG-EFS= High-Grade Event-Free Survival; MIBC= Muscle Invasive Bladder Cancer; mUC= Metastatic Urothelial Carcinoma; HG-EFS defined as high-grade recurrence/persistence, progression to T1, progression to T2+ and death from any cause; Efficacy data cutoff as of 13MAR2026; Efficacy assessments based on local pathology review; HG-EFS presented in intention to treat (ITT) population representative of all patients randomized on CORE-008 Cohort CX (Arm 1/Concurrent; Arm 2/Sequential). Two patients with CIS at baseline were found with HGT1 at Month 6.

High Complete Response Rates Within CIS-Containing Population



CR Rate	% (n/N)	95% Confidence Interval
Concurrent	83.3% *10 out of 12 patients*	(51.6, 97.9)
Sequential	87.5% *14 out of 16 patients*	(61.7, 98.5)

- Includes BCG-Exposed and BCG-Unresponsive patients
- High CR rates were achieved in both concurrent and sequential arms, with overlapping confidence intervals
- CR outcomes were directionally consistent with primary endpoint findings (HG-EFS)

CIS= Carcinoma in Situ; CR=Complete Response
CR defined as having negative cystoscopy, urine cytology, and biopsy (as indicated).
Efficacy data cutoff as of 13MAR2026. Efficacy assessments based on local pathology review.
* Intention to treatment (ITT) population includes all participants who are randomized in Cohort CX (Arm 1/Concurrent; Arm 2/Sequential).
** Efficacy evaluable population includes patients who have received at least four doses of cretostimogene, meet the definition of BCG-Unresponsive/BCG-Exposed and have completed a protocol-defined efficacy assessment at Month 3

Favorable and Well-Tolerated Safety Profile

Preferred Term (MedDRA v.26.1)	Overall (n=55)	
	Grade 1-2 n (%)	Grade ≥ 3 n (%)
Patients with ≥ 1 TRAE	36 (65.5 %)	0 (0)
Treatment-Related AE reported in ≥ 10% patients		
Bladder Spasm	26 (47.3)	0 (0)
Dysuria	19 (34.5)	0 (0)
Pollakuria	14 (25.5)	0 (0)
Fatigue	10 (18.2)	0 (0)
Micturition Urgency	8 (14.5)	0 (0)
Hematuria	6 (10.9)	0 (0)

- **0% Grade ≥ 3 TRAEs, SAEs or deaths**
- 85.5% (47/55) completed all protocol-defined treatments
  - Arm 1 (Concurrent)- 71.4% (20/28)
  - Arm 2 (Sequential)- 100% (27/27)
- **No patients discontinued on Arm 2 (sequential) due to TRAE**
- 4 patients withdrew from Arm 1 (concurrent) for persistent grade 1-2 localized TRAEs
- No difference in the proportion of patients with AEs between arms

AE= adverse events; SAE= Serious adverse events; TRAE=treatment-related adverse events
Safety Data Cutoff Date 13MAR2026
Concurrent: Same-day administration of cretostimogene (first) followed by gemcitabine throughout induction and maintenance.
Sequential: Two weekly cretostimogene instillations followed by one gemcitabine instillation (Weeks 1, 2, 4, 5 vs Weeks 3, 6), continued in maintenance.

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CORE-008 Cohort CX: Summary and Conclusions

- The combination of cretostimogene and gemcitabine demonstrates **robust clinical efficacy and safety** in BCG-exposed and BCG-unresponsive NMIBC
- **Comparable efficacy** observed in both concurrent and sequential arms
- Sequential administration of intravesical cretostimogene and gemcitabine was **well-tolerated** and supports the feasibility of intravesical-only treatment strategies
- **Continued follow-up is underway** to further characterize longer-term outcomes

SWOG Trial S2611
A Randomized Comparison of Intravesical TherapieS (ARCIS)

A Phase 3 RCT evaluating GEM-DOCE versus CRETO-GEM for the treatment of High-Risk BCG-unresponsive NMIBC

Mark Tyson, Scott Delacroix, Sia Daneshmand, Seth Lerner, Cathy Tangen, Josh Meeks, Roger Li, Darrell Nakagawa

Rationale for ARCIS

- BCG unresponsive NMIBC
  - Durable bladder-sparing options needed
  - Gem-Doce: community standard, not randomized[1]
  - Creto-Gem: biologically rational combination[2]
  - CORE-008 Cohort CX data
  - NCI CTPM called for head-to-head evidence[4]
  - ARCIS: FDA-aligned Ph3 RCT

CORE-008 Cohort CX[3]

Endpoint	Estimate for BCG-Unresponsive CIS and Papillary-only
6 month EFS	**89.5%** (95% CI: 76.6 – 95.5)
CR Rate at Any Time (ITT)	**85.7%** (95% CI, 67.3 – 96.0)
Grade 3 TEAEs	**0%**
Discontinuation	**0%**

1. Steinberg 2020; 2. Dinney, et al., unpublished; 3. Bivalacqua et al., 2026; 4. Apolo et al., 2025

ARCIS: A Randomized Comparison of Intravesical TherapieS; BCG: Bacillus Calmette-Guérin; BCGu: BCG-unresponsive; NMIBC: non-muscle invasive bladder cancer; GEM-DOCE: gemcitabine + docetaxel; CRETO-GEM: cretostimogene + gemcitabine; NCI: National Cancer Institute; CTPM: Clinical Trials Planning Meeting; FDA: Food and Drug Administration; Ph3: Phase 3; RCT: randomized controlled trial; CIS: carcinoma in situ; Pap: papillary; CR: complete response; ITT: intent-to-treat; EFS: event-free survival; TEAE: treatment-emergent adverse event; CI: confidence interval

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ARCIS: A Randomized Comparison of Intravesical TherapieS (SWOG 2611)

Pre-treatment

FFPE Urine AI Path

Two-drug sequential instillation (G, D)

Induction						Maintenance	
D1	D8	D15	D22	D29	D35	Mo 3–9	Mo 12–24
G-D	G-D	G-D	G-D	G-D	G-D	Monthly maintenance	Monthly maintenance

Post-treatment
12 mo or at recurrence

FFPE Urine AI Path

Key Eligibility Criteria
BCG-unresponsive Ta/T1/Tis

RANDOMIZE [1]

ARM A
Gem/Doce[2]

ARM B
Creto/Gem[2]

post-induction assessment

Primary Endpoint
HG-EFS[3]

Optional Step 2:
Creto Mono

OFF Protocol
Treatment Follow-Up

Single drug instillation cycling C, C, G

Induction						Maintenance	
D1	D8	D15	D22	D29	D35	Mo 3–9	Mo 12–24
Creto	Creto	Gem	Creto	Creto	Gem	CCG Every 3 mo	CCG Every 3 mo

1. Stratified: CIS ± HG Ta/T1 vs. HG Ta/T1 alone
2. Mandatory biopsy at 12 months for patients with CIS on the qualifying biopsy entering the trial (not merely history of CIS)
3. Primary endpoint: High-grade event defined as HG recurrence, progression (including metastatic disease), or death

AI: artificial intelligence; BCG: Bacillus Calmette-Guérin; C/Creto: cretostimogene grenadenorepvec; CCG: Creto-Creto-Gem; CIS/Tis: carcinoma in situ; D/Doce: docetaxel; EFS: event-free survival; FFPE: formalin-fixed paraffin-embedded; G/Gem: gemcitabine; HG: high grade; mo: months; Ta/T1/Tis: non-muscle invasive tumor stages.

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xCEED (CORE-008 Cohort E): Phase 3 Randomized Trial of Cretostimogene + Gemcitabine vs Gemcitabine Monotherapy in BCG-Exposed HR NMIBC

xCEED: Phase 3 Randomized Trial of Cretostimogene + Gemcitabine vs Gemcitabine Monotherapy in HR BCG-Exposed NMIBC

- Rationale
  - Large, clinically relevant BCG-exposed population with limited randomized evidence
  - Designed to answer whether sequential intravesical cretostimogene + gemcitabine improves EFS vs gemcitabine monotherapy
  - Builds directly on CORE-008 Cohort CX feasibility, safety and early efficacy signal
  - Gemcitabine monotherapy
    - Ongoing BCG shortage
    - Real world USA evidence points to use of gemcitabine monotherapy[1]
    - Poor uptake of gem/doce in community practice[2]
    - Efficacy, safety and tolerability of gemcitabine demonstrated in HR NMIBC including in patients with BCG-exposed NMIBC[3,4]
    - Other studies in BCG-exposed NMIBC using chemotherapy monotherapy as control[5]

[1]Kulkarni, G.S., Cote, S., Kelleher, M., Yin, X., Lin, D. and Williams, S.B., 2025. IP02-26 REAL-WORLD TREATMENT PATTERNS IN PATIENTS WITH BCG-EXPOSED PAPILLARY ONLY HIGH-RISK NON-MUSCLE INVASIVE BLADDER CANCER. *Journal of Urology, 213*(5S), p.e109
[2]FDA Public Workshop: Contemporary Issues in Non-Muscle Invasive Bladder Cancer (NMIBC) Trial Design and Interpretation. 18 May 2026.
[3] Di Lorenzo G, Perdonà S, Damiano R, et al. Gemcitabine versus bacille Calmette-Guérin after initial bacille Calmette-Guérin failure in non-muscle-invasive bladder cancer: a multicenter prospective randomized trial. Cancer. 2010;116(8):1893-1900.
[4]Moyer, J.A., Ashraf, M., Mi, L., Zganjar, A.J., Lyon, T.D., Shah, P.H., Boorjian, S.A. and Tyson, M.D., 2026. Comparative effectiveness of intravesical gemcitabine versus sequential gemcitabine and docetaxel for high-risk non-muscle-invasive bladder cancer. Urologic Oncology, published online 13 July 2026
[5]Porten, S., Bhanvadia, S., Najmi, S., Sweiti, H., Maffeo, J., Stromberg, K., Gale, J. and Pradere, B., 2025, March. SunRISe-5: a phase 3, randomized, open-label study of TAR-200 compared with intravesical chemotherapy after bacillus Calmette-Guérin in recurrent high-risk non–muscle-invasive bladder cancer. In Urologic Oncology: Seminars and Original Investigations (Vol. 43, No. 3, pp. 54-55). Elsevier.

xCEED (CORE-008 Cohort E): Phase 3 Randomized Trial of Cretostimogene + Gemcitabine vs Gemcitabine Monotherapy in BCG-Exposed HR NMIBC

Key Eligibility Criteria

- HR BCG-Exposed NMIBC
  - CIS +/- Ta/T1 or HG T1/Ta
    - BCG-resistant
    - Delayed relapse after *adequate* BCG
    - Delayed relapse after *inadequate* BCG
- No history of BCG-unresponsive NMIBC
- ECOG PS 0-2

Stratification Factors

- Presence of CIS at baseline
- Time since last BCG dose

Disease Assessments

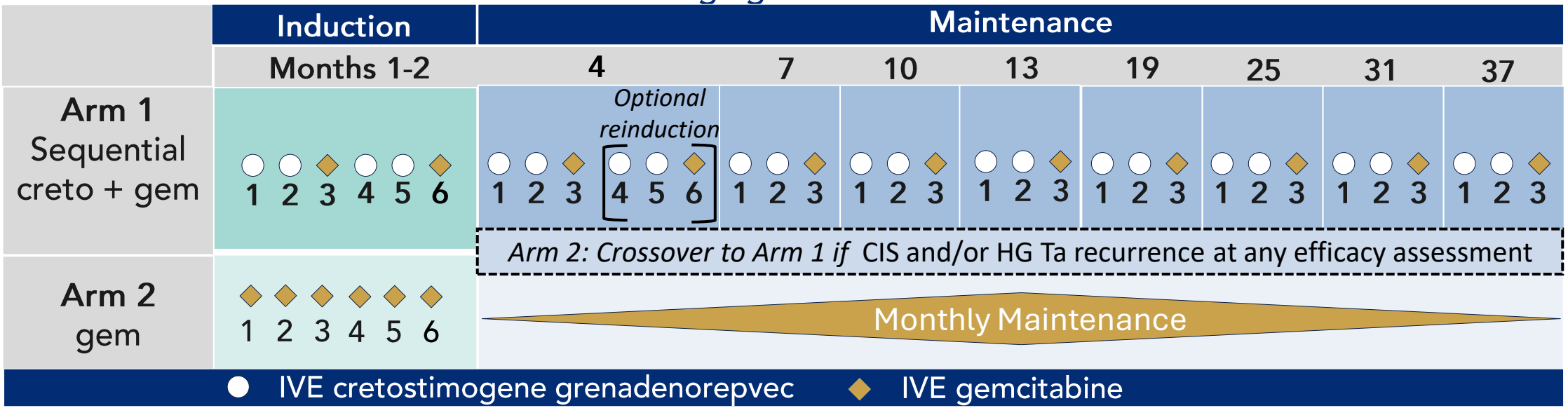
- Cystoscopy
- Urine cytology
- Biopsy for cause
- Imaging

Primary Endpoint

- EFS

Key Secondary Endpoints

- PFS
- CFS
- OS
- Safety
- DoR
- PROs



Reinduction is permitted in Arm 1 for biopsy-confirmed persistent high-grade Ta or CIS at the Month 3 efficacy assessment

BCG: bacillus Calmette-Guérin; CFS: cystectomy free survival; CIS: carcinoma in situ; creto: cretostimogene; DoR: duration of response; ECOG PS: Eastern Cooperative Oncology Group performance status; EFS: event free survival; gem: gemcitabine; HG: high grade; HR: high risk; NMIBC: non-muscle invasive bladder cancer; OS: overall survival; PFS: progression free survival; PROs: patient reported outcomes

Conclusions and Next Steps

- CORE-008 Cohort CX: cretostimogene plus gemcitabine showed robust efficacy and safety in BCG-exposed and BCG-unresponsive NMIBC, with comparable results in the concurrent and sequential arms
- Sequential intravesical dosing was well tolerated, supporting intravesical-only treatment strategies; follow-up continues
- ARCIS (SWOG Phase 3) will provide the randomized head-to-head evidence of GEM-DOCE versus CRETO-GEM in BCG-unresponsive disease
- Focus now turns to xCEED (Cohort E): Phase 3 randomized trial of sequential cretostimogene + gemcitabine vs gemcitabine monotherapy in BCG-exposed HR NMIBC (N~314; primary endpoint EFS)
- Exciting TM plan ahead
- Future work with Dr Li on cretostimogene combination therapy in MIBC
  - SPARE-001

BCAN
20 Years of Impact

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Thank You

Bladder Cancer Patients and Their Families
Key Investigators, Study Coordinators, Nurses

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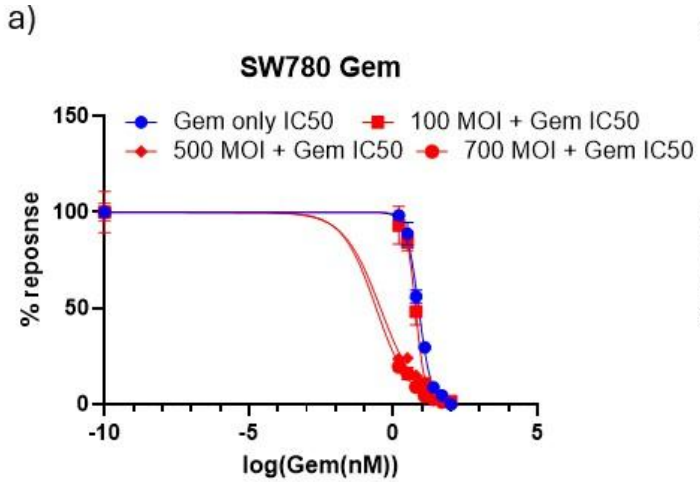
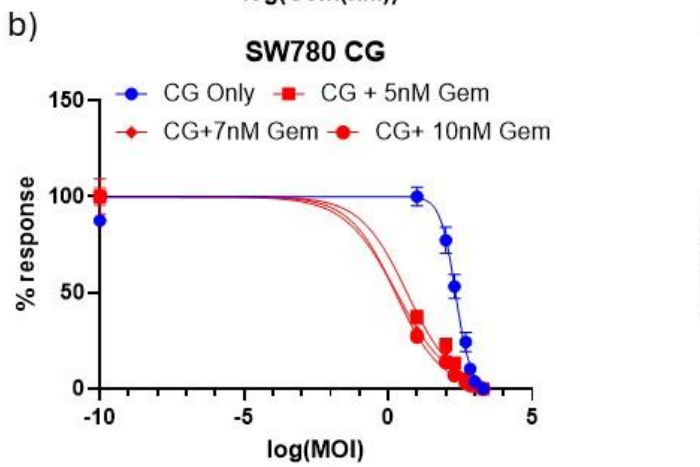
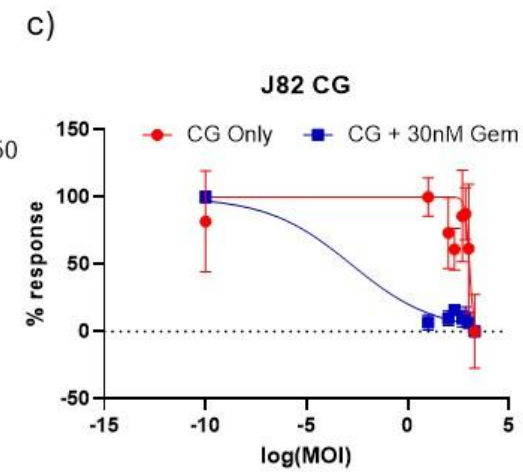
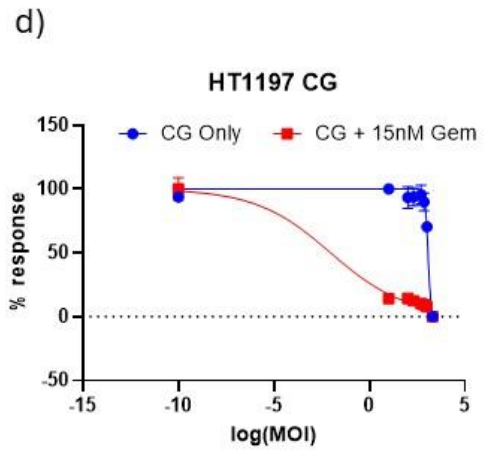
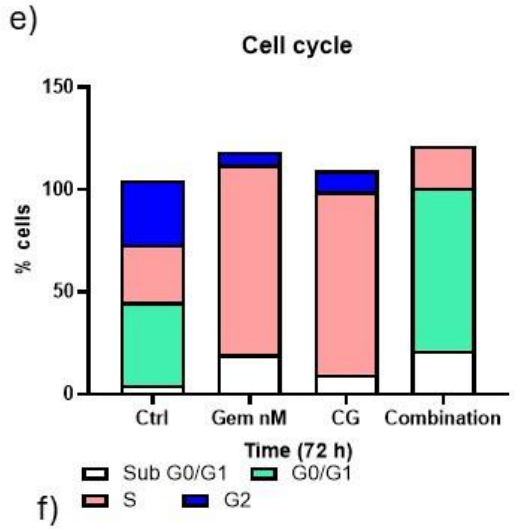
Gemcitabine Enhances the Anti-Tumor Activity of Cretostimogene

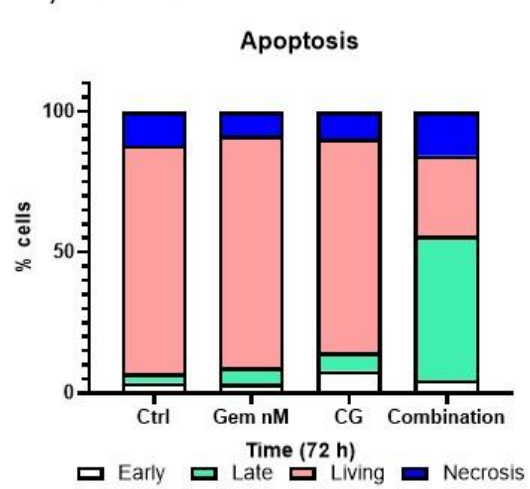












- Enhanced in-vitro response to cretostimogene when combined with gemcitabine.
- Increased G0/G1 cell-cycle arrest and apoptosis.

Steinmetz, Tholmier, Martini, and Mokkapati, 2025 (unpublished data).

Agenda

ARCIS Questions / Discussion

Statistics & Funding

- Parameters
  - GEM/DOCE
    - EFS at 2 yrs = 40 %
  - CRETO/GEM
    - EFS at 2 years = 55 %
  - One-sided alpha = 0.023
  - Power = 0.87
  - HR = 0.65
- Sample size
  - 308 total
  - 140 per arm
  - 10% cushion
- Interim Analysis
  - 25%, 50%, and 75% of expected EFS events
- Funding:
  - Drug & logistics support: CG Oncology (cretostimogene)

Q1: Clarify CORE-008 evaluable denominators and CIS responder counts

Overall Cohort Cx

- 55 enrolled
- 50 efficacy evaluable
- 24/26 efficacy evaluable CIS achieved CR at any time

Q5. BCG Unresponsive CIS / Pap

- Efficacy evaluable = 15
- 6 month CR = 14/15 (93.3%)

Q2: Role of Step 2 Cretostimogene Monotherapy Cohort

- Committee questioned value/statistical role of CRETO monotherapy cohort
- Not part of primary phase III comparison
- Nested phase II estimation cohort
  - Evaluates cretostimogene after recurrence on GEM-DOCE
  - Primary objective: estimate 12-month EFS
  - Secondary: CIS CR rate, DoR, safety
- Anticipated n≈70 provides ~±12% precision for 12-month EFS
- Generates prospective sequence-specific efficacy/safety data

Q3: Step 2 Cretostimogene Cohort: Eligibility and Bias Mitigation

- Committee concern: Step 2 eligibility may be heterogeneous and bias GEM-DOCE conduct
- Step 2 is not available before a primary EFS event
  - Patients cannot stop GEM-DOCE simply to receive cretostimogene
  - Step 2 occurs only after pathologically confirmed HG recurrence/persistence
- Primary phase III endpoint remains unaffected
- Eligibility will be tightened
  - Completion of induction, unless stopped for treatment-limiting toxicity
- Not a separate trial: designed to answer a prospective sequencing question

Q4: Quantitative Rationale for 2-Year EFS Assumption

- Committee asked for added support for assumed 2-year EFS of 55% with CRETO-GEM
- Assumption is not based on CORE-008 6-month data alone
- CORE-008 BCG-unresponsive CIS subset:
  - 6-month HG event-free: 10/11 = 90.9%
- GEM-DOCE benchmark in BCG-unresponsive CIS:
  - 6-month HG recurrence-free: ~75% (95% CI, 63–84)
- Durability support:
  - BOND-003 and CORE-001: ~90% of 12-month CRs remain in CR at 24 months
- Cross-study comparison limitations acknowledged

Q6: Maintenance Treatment Intensity and EFS Interpretation

- Committee asked whether maintenance schedule differences could affect EFS interpretation
- Clarification: no intended residual difference in maintenance intensity
  - Both arms: 9 maintenance treatments after induction in year 1
  - Both arms: 12 maintenance treatments in year 2

Q7: Rb-E2F Pathway Analyses

- Committee asked whether Rb-E2F analyses can be prespecified
- Not proposed as a formal named exploratory efficacy objective at this time
- Rationale:
  - No validated, commercially available Rb-E2F assay for this setting
  - Expected stratum sizes cannot be reliably estimated

Q8: Operational Role of Interim Analyses

- Committee asked about late interim analyses when accrual is 88–100% complete
- Interim analyses are not primarily accrual-stopping tools
- Primary value: potential earlier answer to the phase III question
  - Efficacy or futility result could emerge more than 2 years before final analysis
- DSMC/CTEP recommendations would depend on data maturity and result

Q9: Access and Scalability Considerations

- Committee asked about payer, access, and scalability if CRETO-GEM is superior
- ARCIS is not designed as a formal cost-effectiveness study
- Trial will generate implementation-relevant data
- GEM-DOCE implementation barriers are acknowledged
- CRETO-GEM may reduce some operational barriers, but still requires intravesical treatment infrastructure
- Future access will depend on regulatory status, guidelines, reimbursement, acquisition cost, and total value of care

Q10: CG Oncology Drug Supply Agreement

- Committee asked whether drug supply support is finalized
- CG Oncology has confirmed readiness to proceed to final agreement
- Final drug supply agreement will be executed with SWOG

Q11: Interim Analysis and Futility Rule

- Committee requested more detail on interim analyses and futility stopping
- Interim analyses planned at approximately:
  - 25%, 50%, and 75% of expected EFS events
- First interim: futility only
- Second and third interim: futility and efficacy
- EFS analyzed using Cox regression
- Futility target: alternative hypothesis HR=0.65