VGO NORTE INTERNATIONAL GU DEBATES

# NMIBC: What do I need to know to understand drug development in this setting?

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*Session 1 · Non-muscle invasive bladder cancer: are new treatments ready for prime time?*

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# Why NMIBC is unlike any other drug-development setting

1

## We treat after the tumour is gone

TURBT removes measurable disease. Outside CIS, efficacy means preventing recurrence, not shrinking tumour.

2

## The endpoint is a cystoscopy

Events are read by cystoscopy, cytology and biopsy – mostly open-label, investigator-assessed, schedule-driven.

3

## The comparator is scarce

BCG shortage, substrain differences and poorly documented 'adequate' exposure shape eligibility and control-arm performance.

4

## The exit is a cystectomy

Radical cystectomy is a competing event and a censoring mechanism – and bladder preservation is the value proposition.

**Plus a cultural split:** intravesical agents are urology-owned, systemic agents bring oncology toxicity currencies (irAEs) into a disease that rarely kills.

# Five disease states – five different regulatory questions

*The first question for any NMIBC trial: which state, and how exactly was it defined?*

| | Low-grade IR (recurrent) | High-risk BCG-naïve | BCG-exposed (after induction) | BCG-unresponsive CIS ± Ta/T1 | BCG-unresponsive papillary-only |
|---|---|---|---|---|---|
| **Clinical question** | Avoid repeat TURBT | Add to or replace BCG | Rescue before unresponsiveness | Bladder-sparing alternative to RC | Prevent recurrence after complete TURBT |
| **Control arm** | TURBT ± surveillance | BCG induction + maintenance | BCG re-induction | None (RC is SoC) | Intravesical gemcitabine / MMC |
| **Primary endpoint** | CR at 3 mo (ablative) / RFS (adjuvant) | EFS / DFS | EFS | CR any time + DoR | DFS / EFS |
| **Design accepted** | RCT preferred; single-arm approved once | Randomized | Randomized | Single-arm acceptable | Randomized |
| **Examples** | ENVISION (UGN-102), TAR-210 (FGFR+), PIVOT-006 | POTOMAC, CREST, KN-676, SunRISe-3, BRIDGE, COBRA, TRAIN, INTerpath-011 | KN-676 cohort A, CORE-008 | KN-057, nadofaragene, QUILT-3.032, SunRISe-1, BOND-003, LEGEND | SunRISe-5, MoonRISe-3 (FGFR+) |

RC, radical cystectomy; MMC, mitomycin C; CR, complete response; DoR, duration of response; EFS/DFS/RFS, event-/disease-/recurrence-free survival. FDA BCG-unresponsive guidance 2018; revised draft 08/2024.

# Definitions are the hidden variable

## Adequate BCG

≥5 of 6 induction + ≥2 of 3 maintenance instillations, or ≥5 of 6 induction + ≥2 of 6 second induction

## BCG-unresponsive (FDA / IBCG)

Persistent or recurrent CIS ± Ta/T1 within 12 months of adequate BCG

Recurrent high-grade Ta/T1 within 6 months of adequate BCG

High-grade T1 at the first evaluation after induction

## BCG-naïve

Often includes remote BCG: >2 years (KEYNOTE-676) or >3 years (SunRISe-3)

### Recurrent ≠ unresponsive

Late recurrence after adequate BCG may still respond to more BCG; unresponsive disease will not.

### Inclusion drift inflates CR

Enrolling BCG-exposed (not truly unresponsive) patients makes single-arm CR rates look better.

### The shortage creates orphans

Under-treated patients are neither naïve nor unresponsive – and qualify for neither trial type.

### Ask for the BCG log

Median instillations received tells you more than the eligibility box.

FDA Guidance BCG-unresponsive NMIBC (2018; revised draft Aug 2024); Kamat et al., J Clin Oncol 2016; Roumiguié et al., Eur Urol 2022.

# Know your comparator: modern BCG is a strong control arm

**85%**

**CR at any time in CIS**

BCG I+M alone – CREST control arm

**82%**

**DFS at 24 months**

BCG I+M alone – POTOMAC control arm

**77→67%**

**RFS at 1 → 5 years**

Ta/T1 + CIS on BCG (Matulay, J Urol 2021)

**6%**

**grade ≥3 TRAEs**

BCG I+M (any grade 70%) – CREST

| BCG trial | Question | Result | Consequence for drug development |
|---|---|---|---|
| **SWOG 8507** | Maintenance vs induction only | Maintenance improves RFS and progression | Only BCG induction + maintenance is an acceptable control |
| **NIMBUS** | 9 vs 15 instillations | Reduced frequency inferior (HR 0.40, standard vs reduced) | No 'BCG-light' control arms – dose-sparing costs efficacy |
| **SWOG S1602** | Tokyo-172 vs TICE; intradermal priming | Tokyo non-inferior (HR 0.82); priming no benefit (HR 1.0) | Substrains can be pooled; supply options widen |

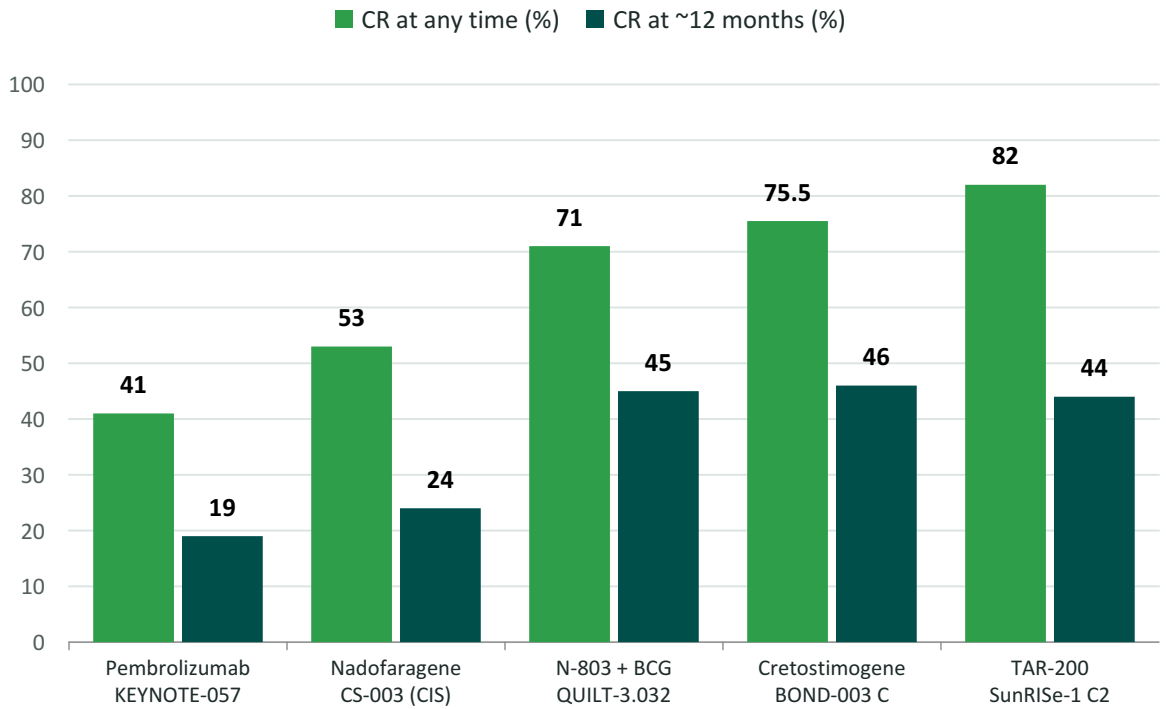
Lamm et al., J Urol 2000; Grimm et al., Eur Urol 2020; Svatek et al. (SWOG S1602, NCT03091660); Shore et al., AUA 2025 / Nat Med 2025; De Santis et al., Lancet 2025.

# The endpoint toolbox – and where each one misleads

| Endpoint | Where used | What it captures | Pitfall |
|---|---|---|---|
| **CR at any time** | BCG-unresponsive CIS | Ablative activity on non-resectable disease | Re-induction often allowed; says nothing about durability |
| **Landmark CR (12 mo) / DoR** | BCG-unresponsive CIS | Durable disease control | Crude vs Kaplan–Meier estimates; biopsy mandates differ |
| **EFS / DFS** | BCG-naïve, papillary-only | Prevention of high-risk events | Composite; open-label, investigator-assessed; components differ by trial |
| **RFS** | Intermediate risk | Recurrence burden | Low-grade recurrences: real burden, low lethality |
| **Progression (≥T2 / metastasis)** | All states | The event that matters most | Rare – trials are underpowered; stage-migration definitions vary |
| **Cystectomy-free survival** | BCG-unresponsive | Bladder preservation | Driven by physician and patient choice, not only disease |
| **Overall survival** | All states | Safety net | Not feasible as primary; immature at approval |

No validated surrogate links CR, EFS or DFS to progression or survival in NMIBC.

# Headline CR vs durable CR in BCG-unresponsive CIS




## Half to two-thirds of responders keep their response at one year.

IBCG benchmark for a meaningful agent: CR ≈30% at 12 months, ≈25% at 18 months.

**Cross-trial caveats:**

re-induction permitted, dosing duration (TAR-200 up to 24 mo), central vs local review, mandatory biopsy, depth of prior BCG.

12-month CR: KN-057 19% (18/96); nadofaragene 24% (25/103); QUILT-3.032 45% (37/82); BOND-003 46% (crude); TAR-200 ≈44% derived (82.4% × 52.9% of responders with DoR ≥12 mo). Compiled from R. Li, AUA 2024 and primary reports. Not head-to-head.

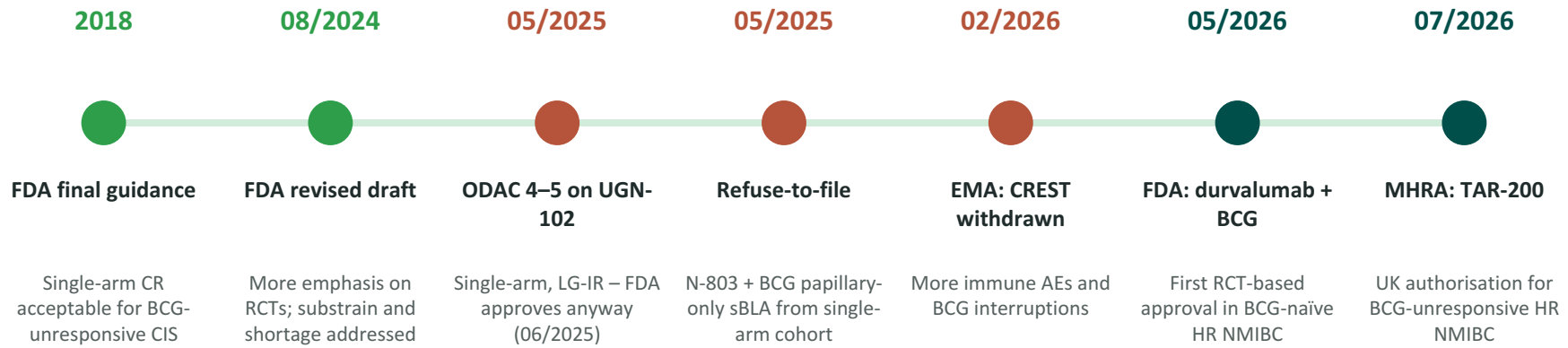
# BCG-unresponsive NMIBC: approvals, toxicity and price

| Agent | Mechanism / route | Pivotal trial | Grade ≥3 AEs | Regulatory status (09/2026) | US cost / year* |
|---|---|---|---|---|---|
| **Pembrolizumab** | Anti-PD-1, IV | KEYNOTE-057 | 13% TRAE | FDA 01/2020 | $204,700 |
| **Nadofaragene firadenovec** | IFN-α2b gene therapy, intravesical | CS-003 | 4% TRAE | FDA 12/2022 | $244,000 |
| **Nogapendekin alfa + BCG** | IL-15 superagonist + BCG | QUILT-3.032 | ≈20% TEAE (all-cause) | FDA 04/2024; papillary sBLA refused 05/2025 | $528,300 |
| **TAR-200 (gemcitabine system)** | Continuous-release device | SunRISe-1 | ≈7% TRAE | FDA 09/2025; MHRA (UK) 07/2026 | $690,000 |
| **Cretostimogene** | Oncolytic adenovirus (GM-CSF) | BOND-003 | 0% TRAE | Rolling BLA; completion Q4 2026 | – |

**Approval ≠ access:** five modalities reached the market on single-arm CIS data – but HTA bodies (NICE, G-BA/IQWiG) ask for comparative benefit, which single-arm trials cannot provide.

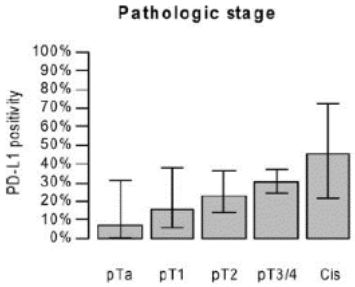
*Approximate US annual list prices (vs BCG ≈$1,800 and gem/doce ≈$3,300 per year), as compiled by B. Szabados 2026. AE definitions differ (TRAE vs TEAE); R. Li, AUA 2024.

# Where regulators draw the line on single-arm evidence




**Rule of thumb:** single-arm data convince only where the counterfactual is known (untreated CIS persists and progresses). Everywhere else – randomize, and expect toxicity to be weighed against a disease that rarely kills.

# IO + BCG: the rationale – and what phase 3 taught us

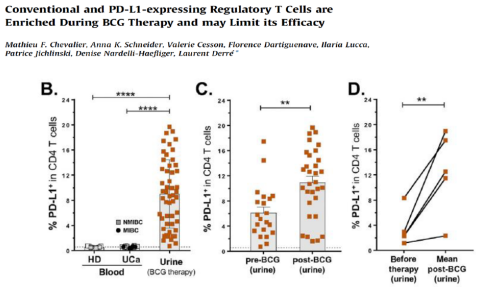



## PD-L1 is highest in CIS

≈5% of cells before BCG; 15–20× higher in CIS recurring after BCG

Strong PD-L1 in BCG-induced granulomata (11/12 recurrences)

*Inman et al., Cancer 2007*




## BCG induces its own brake

PD-L1+ conventional and regulatory CD4 T cells accumulate in urine during BCG

*Chevalier et al., Eur Urol 2018*

## The trials: IO amplifies BCG – it does not replace it

| | |
|---|---|
| **1.14** | POTOMAC – durvalumab + BCG induction only vs BCG I+M |
| **1.16** | CREST – sasanlimab + BCG induction only vs BCG I+M |
| **neg.** | ALBAN – atezolizumab + BCG vs BCG |

**Consequence:** benefit only with full BCG maintenance – so IO add-on does not solve the BCG shortage, and the right patient (PD-L1? very high risk?) is still undefined.

# BCG-naïve high-risk NMIBC: the randomized era

| Trial | Experimental arm | Control | Primary EP / size | Result | Regulatory / status |
|---|---|---|---|---|---|
| **POTOMAC** | Durvalumab IV + BCG I+M (or I only) | BCG I+M | DFS; n = 1,018 | **HR 0.68** (I+M); I only 1.14 | FDA 05/2026; NICE appraisal from 03/2027 |
| **CREST** | Sasanlimab SC + BCG I+M (or I only) | BCG I+M | EFS; n = 1,055 | **HR 0.68** (I+M); I only 1.16 | EMA MAA withdrawn 02/2026 |
| **ALBAN** | Atezolizumab + BCG | BCG | RFS | **Negative** | – |
| **KEYNOTE-676** | Pembrolizumab + BCG | BCG | CRR / EFS | *Pending* | – |
| **INTerpath-011** | Intismeran (mRNA neoantigen) + BCG I+M | BCG I+M | Phase 2; n = 278 | *Pending* | Ongoing |
| **SunRISe-3** | TAR-200 ± cetrelimab (no BCG) | BCG | EFS; n ≈ 1,050 | *Pending* | – |
| **BRIDGE** | Gemcitabine / docetaxel | BCG | EFS (non-inferiority); n = 870 | *Pending* | – |
| **COBRA (UK)** | Gemcitabine / docetaxel | BCG I+M | n = 520 | *Recruiting* | Opened 07/2026 |
| **TRAIN (UK)** | Radiotherapy with radiosensitisation | BCG | n = 328 | *Recruiting* | – |

**Two strategies compete:** intensify BCG (IO, vaccine) vs replace BCG (device, chemotherapy, radiotherapy) – only the latter answers the shortage.

I+M, induction + maintenance. De Santis et al., Lancet 2025; Shore et al., AUA 2025; EMA withdrawal assessment (Zumrad) 2026; NICE ID5080.

# Reading positive trials: POTOMAC and CREST side by side

**0.68 | 0.68**

**DFS / EFS hazard ratio**

POTOMAC | CREST

**≈5% | ≈7%**

**absolute gain**

DFS 24 mo 86.5 vs 81.6 | EFS 36 mo 82.1 vs 74.8

**21 | 29%**

**grade 3–4 TRAEs**

vs 4% and 6% with BCG alone

**1.14 | 1.16**

**HR with BCG induction only**

No benefit without maintenance

## What is solid

Two independent RCTs (>1,000 patients each), identical effect size

POTOMAC: 60.7 months median follow-up; consistent in papillary, T1 and CIS subgroups

BCG exposure balanced; no signal of OS detriment

## What to question

CREST benefit driven by high-grade recurrence (26 vs 53 events); progression 18 vs 22, MIBC 7 vs 7

CIS: CR at any time 89.8% vs 85.2% (difference not significant)

Open-label, investigator-assessed; OS immature (HR 0.80 | 1.13)

Very-high-risk subgroup HR 0.34 (CREST, n = 58) – a selection hypothesis, not proof

De Santis et al., Lancet 2025 (POTOMAC); Shore et al., AUA 2025 / EMUC 2025 (CREST).

# Eight questions for the next NMIBC trial you read

1. **Which disease state?**
   Definition used, and how BCG adequacy was documented

2. **What is the control?**
   Full BCG induction + maintenance? (NIMBUS: fewer instillations, more recurrences)

3. **Single-arm or randomized?**
   Is the counterfactual known (CIS) or not (papillary)?

4. **Which endpoint components?**
   Persistent CIS, low-grade events, death – counted or not?

5. **How were events detected?**
   Mandatory biopsy, central pathology, blinded review

6. **Durable or headline?**
   12-month CR / 24-month DFS, not only CR at any time

7. **What about progression and RC?**
   Reported with denominators, not just 'no signal'

8. **What does it cost?**
   Toxicity, visits, catheterisations, price – and who manages irAEs

# Take-home messages

1. **Disease state first.** The same drug means different things in BCG-naïve, BCG-exposed and BCG-unresponsive disease.
2. **Know the comparator.** Modern BCG induction + maintenance is strong – absolute gains will be small.
3. **Single-arm is a privilege of CIS.** Everywhere else, regulators and HTA bodies want randomized, comparative data.
4. **Read the landmark, not the headline.** 12-month CR, absolute DFS/EFS gain and the event table carry the meaning.
5. **Weigh benefit against toxicity and price.** IO needs full BCG, adds irAEs – in a disease that rarely kills.

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**THANK YOU!**

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