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Focus on: Non-Muscle Invasive Bladder Cancer

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Question 1

In BCG-unresponsive CIS, what is your go-to?

A. Nadofaragene
B. Pembrolizumab
C. nogapedekin + BCG
D. Clinical trial

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Question 2

What is your preferred treatment for Ta HG papillary-only recurrence:

A. TAR-200
B. Gem/Doce
C. Early cystectomy
D. Repeat BCG

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Question 3

For a healthy patient with recurrent CIS+TaHG who refuses cystectomy, what is your recommended next treatment?

- A. Pembrolizumab
- B. Intravesical therapy
- C. Trial
- D. Surveillance

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NMIBC Overview

- High-risk NMIBC has high recurrence and progression risk.
- BCG remains standard initial therapy.
- Cystectomy still has its role

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Very high risk

- Variant (sarcomatoid, plasmacytoid, anaplastic, etc.)
- LVI
- Hydronephrosis

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Why New Therapies?

- BCG failure and shortages have driven innovation in intravesical and systemic therapies.

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INTERMEDIATE RISK

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Mitomycin reverse thermal gel

- Intermediate Risk-low grade
- ENVISION trial, FDA approved
- CR 79% (137/223) at 12 months

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FDA APPROVED FOR CIS +/-TA/T1HG

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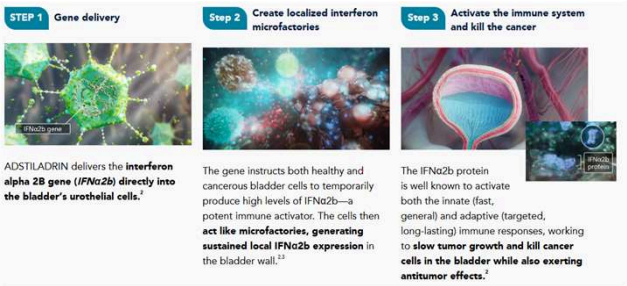
Nadofaragene Firadenovec

- Mechanism: Adenoviral IFNα gene therapy
- FDA Approved 2022, INSTILADRIN
- CR ~30% at 36 months



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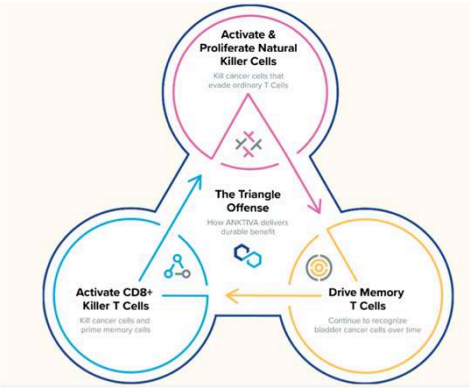
BCG+nogapedekin

- Mechanism: IL-15 agonist
- FDA Approved, Quilt-3.032
- Enhances immune activation with BCG
- CR 40% at 24months (N=19/77)



FDA package insert

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TAR-200

- Mechanism: Sustained gemcitabine delivery
- FDA Approved 2025, SUNRISE-1
- CR 51% (N=35/83) at 12 months

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Gemcitabine/Docetaxel

- Mechanism: Cytotoxic chemotherapy
- Not FDA approved combo
- Strong real-world outcomes
- CR ~40% at 2 years

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CISTO

Summary of 12-Month Outcomes

Favors BST	No Difference	Favors RC
Bowel health Sexual health	Physical functioning • Overall • By age Role functioning Social functioning Urinary health	Physical functioning • Patients w/ CIS • Unpartnered Cognitive functioning Mental health Financial health
Progression-free survival	Cancer-specific survival Overall survival	Recurrence-free survival

ONGOING TRIALS OR WITH THE FDA

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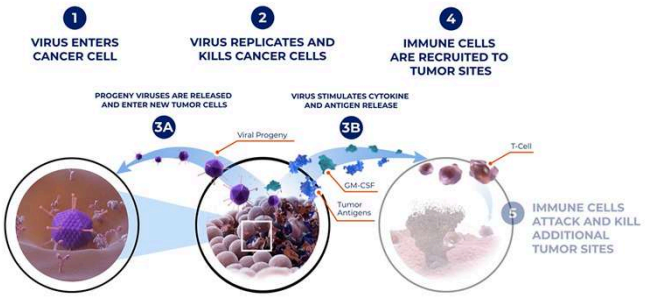
Cretostimogene

- Mechanism: Oncolytic virus + GM-CSF
- Fast Track
- CR ~75%



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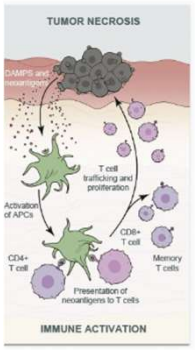
Belzupacap Sarotalocan

- Mechanism: Light-activated VDC
- Investigational
- Localized tumor destruction



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EG-70

- BCG Unresponsive CIS
- LEGEND trial, Phase II
- Non-viral genetic, localized gene therapy

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Relmada NDV-01

- Sustained release gem/doce, release up to 10 days
- Phase III
- Intermediate risk NMIBC, BOOST trial

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SYSTEMIC THERAPIES FOR HR NMIBC

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Pembrolizumab

- Mechanism: PD-1 inhibitor
- FDA Approved 2020, KEYNOTE-057
- Systemic option for BCG-unresponsive CIS

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Durvalumab+BCG

- Mechanism: PD-L1 inhibitor
- No new safety outcomes, POTOMAC

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Controversy: Best First Salvage?

- Nadofaragene vs Pembrolizumab vs BCG+nogapedekin
- No head-to-head trials
- Decision driven by patient + toxicity + logistics

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Treatment Sequencing

- No clear algorithm
- BCG reinduction thing of the past?
- Requires individualized decision-making

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Controversy: Systemic vs Intravesical

- Systemic: broader immune activation
- Intravesical: lower toxicity
- Patient selection critical

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Clinical Trials Importance

- Many therapies single-arm
- Trials guide future standards

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Case 1

65M, T1HG + CIS

Question: What is first-line therapy?

A. BCG induction
B. Pembrolizumab
C. TAR-200
D. Cystectomy

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Case 1

- Answer: BCG induction
- Pearl: BCG remains first-line for HR-NMIBC; early adequate induction is critical.

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Case 2

92F persistent CIS after BCG

Question: Best next treatment option?

A. Nadofaragene
B. Repeat BCG
C. Surveillance
D. TURBT only

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Case 2

- Answer: Nadofaragene firadenovec
- Pearl: Gene therapy with q3 month dosing.

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Case 3

68M BCG-unresponsive CIS + TaHG

Question: Preferred approach?

A. nogapedekin + BCG
B. Radiation
C. Antibiotics
D. Observation

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Case 3

- Answer: nogapedekin + BCG
- Pearl: Combination immunotherapy enhances response in CIS-containing disease.

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Case 4

75M BCG-unresponsive, refuses surgery

Question: Best systemic option?

A. Pembrolizumab
B. BCG reinduction
C. TURBT alone
D. None

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Case 4

- Answer: Pembrolizumab
- Pearl: Systemic therapy reserved for cystectomy-ineligible or refusing patients.

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Case 5

70F heart failure and 4L oxygen baseline, CIS+TaHG papillary-only recurrence after BCG

Question: Best therapy?

A. TAR-200
B. Cystectomy immediately
C. Radiation
D. Surveillance

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Case 5

- Answer: TAR-200
- Pearl: Sustained drug delivery improves exposure and convenience.

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Case 6

60M multiple TaHG recurrences post-BCG

Question: Reasonable salvage?

A. Gem/Doce

B. TURP

C. Antibiotics

D. None

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Case 6

- Answer: Gemcitabine/Docetaxel
- Pearl: Widely used salvage with strong retrospective efficacy.

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Case 7

66F fit, BCG-unresponsive CIS

Question: Best approach?

A. Trial
B. Do nothing
C. Repeat TURBT only
D. Radiation

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Case 7

- Answer: Clinical trial
- Pearl: Trials are critical given evolving landscape and lack of sequencing clarity.

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Controversy: When to Cystectomy?

- Early cystectomy improves oncologic control
- But overtreatment risk
- Balance biology vs patient preference

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Algorithm for HR-NMIBC

1. BCG-NAÏVE HIGH-RISK
→ Full-dose BCG induction + maintenance

2. BCG-UNRESPONSIVE, CIS ± papillary:
→ Nadofaragene OR nogapedekin + BCG OR TAR-200 OR gem/doce
→ Consider Pembrolizumab if systemic candidate

3. HIGH-RISK FEATURES (T1HG, LVI, variant)
→ Early cystectomy discussion

4. THROUGHOUT ALL STAGES
→ Clinical trial prioritization

5. PRINCIPLE
→ No fixed sequencing → personalize based on biology + patient goals

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Key Takeaways

- NMIBC landscape rapidly evolving
- Multiple FDA-approved options now available
- No defined sequencing strategy
- Shared decision-making is essential
- Clinical trials remain critical