European Association of Urology

Bladder-sparing Therapy for Bacillus Calmette-Guérin–unresponsive Non–muscle-invasive Bladder Cancer: International Bladder Cancer Group Recommendations for Optimal Sequencing and Patient Selection

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BACKGROUND

- Recent surge in the development of agents for bacillus Calmette-Guérin–unresponsive (BCG-U) Non–Muscle-invasive bladder cancer (NMIBC).

- No RCT data on comparisons of these agents

- Practical recommendations for selection and sequencing of these agents in different subgroups of BCG-U NMIBC is the need of the hour.

Objectives

- To formulate recommendations for optimal selection of patients and therapies for bladder-sparing treatment (BST) options in BCG-U NMIBC.

Methodology

- Bladder cancer experts reviewed the literature and developed draft recommendations, which were then voted on by International Bladder Cancer Group (IBCG) members using a modified Delphi process.
- Final recommendations formulated during a live meeting in in August 2023.
- Final recommendations achieved >75% agreement during the meeting.

Defining a case

- Criteria for BCG U disease
- Optimal staging
- Standardized Pathology reports

Table 1 – Definition of BCG-unresponsive non–muscle-invasive bladder cancer [1]

At least one of the following:

1. Persistent or recurrent carcinoma in situ with or without non–muscle-invasive papillary disease within 12 mo of completion of adequate BCG therapy [a]
2. Recurrent high-grade Ta/T1 tumor within 6 mo of completion of adequate BCG therapy [a]
3. High-grade T1 disease at the first evaluation following BCG induction

BCG = bacillus Calmette-Guérin.

[a] Adequate BCG therapy is defined as at least five of six doses of an initial induction course with at least two additional doses (either as part of maintenance therapy or a second induction course).

Treatment options

- Chemotherapy based options
- Immune checkpoint inhibitors
- Gene based therapies
- Intravesical immunotherapy
- Targeted agents
- Miscellaneous therapies

Chemotherapy based options

- Single-agent chemotherapy
- MMC VS OPTIMISED MMC/ HYPERTHERMIC MMC :

Significantly better RFS at 5 yr(41% vs 25%)

Chemotherapy based options

- Single-agent GEMCITABINE

- VALRUBICIN : Not specifically indicated for BCG-U disease.
- Single-agent chemotherapy : May be considered for BCG-U papillary-only disease.
- SunRISe-1 study : TAR-200 Gemcitabine and Cetrelimab as monotherapies in BCG-U NMIBC

Chemotherapy based options

- Combination chemotherapy : GEMCITABINE + DOCETAXEL

IBCG : GEM/+DOCE with extended monthly maintenance

should be considered as the intravesical chemotherapy

option of choice

LONG TERM OUTCOMES
5-yr survival rates
28% for high-grade RFS
89% for PFS
74% for CFS
92% CSS
66% OS

Immune checkpoint inhibitors

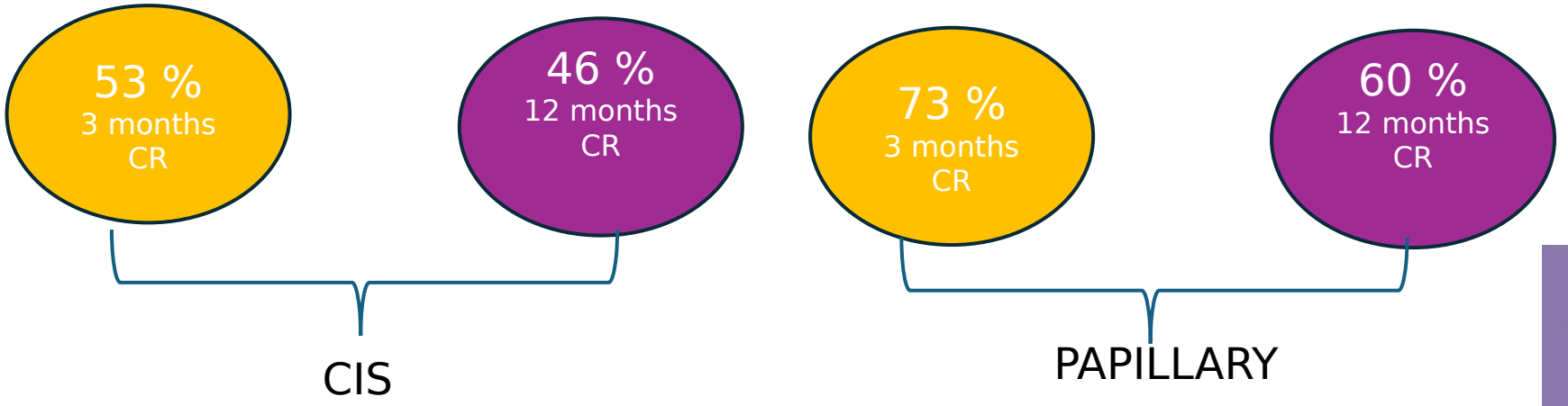
- KEYNOTE-057 trial : PEMBRO
- SWOG S1605 trial : Atezolizumab
- GU-123 STUDY : Atezolizumab + BCG

- IBCG : Single-agent ICI is currently most appropriate for patients for whom safer alternative treatment options have been exhausted.

GENE BASED THERAPIES

Nadofaragene firadenovec

The fundamental concept with gene delivery is to turn the bladder into a ‘protein bioreactor’ and produce high local levels of the therapeutic agent, which in turn has been theorized to increase therapeutic efficacy

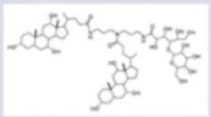


Non-replicating adenoviral vector-based gene therapy

FDA approval in December 2022

rAd-IFNα2b transmits the *IFNα2b* gene into the host nucleus for transcription, without inserting genes into the host chromosome After instillation, cells of the bladder wall produce and secrete IFNα2b protein over a sustained period (up to 10 days in phase 1 studies)

IFNα has several direct and indirect anti-tumor mechanisms and causes tumor cell death



Syn3 is synthetic analogue that disrupts the urothelial glycosaminoglycal (GAG) layer and enhances adenovirus-mediated β-galactosidase transduction of the urothelium and NMIBC

OTHER GENE BASED THERAPIES

CG0070 is a cancer selective replication competent adenovirus that preferentially replicates in retinoblastoma (Rb) pathway defective cells

Insertion of a gene that causes production of granulocyte-monocyte colony-stimulating factor (GM-CSF), with tumour toxicity.

ONGOING TRIALS :

- The BOND-03 trial is a single arm Phase III trial aiming to accrue 110 patients with BCG-unresponsive NMIBC and assess intravesical CG0070 response
- The CORE-01 trial is a Phase II study assessing the combination of Pembrolizumab with intravesical CG0070

Intravesical Immunotherapy-based agents

- Nogapendekin alfa inbakicept-pmln (NAI / N-803/ANKTIVA)
- Interleukin-15 superagonist : Enhances the immune-mediated effects of interleukin-15
- Boosts the immune response primed by BCG.
- In April 2024, the FDA approved NAI : BCG-unresponsive CIS +/- papillary NMIBC.

Phase 2/3 QUILT-3.032 trial

With 50 mg BCG intravesical for 6 consecutive weeks

QUILT-3.032 Update Cohort A: NMIBC CIS	NAI + BCG Efficacy
Complete Response (CR) Rate % (95% CI) N=100	71% (61.1, 79.6)
Duration of Complete Response N=71 (Evaluable Responders)	53+ Months & Ongoing (>4 Years)
Cystectomy Avoidance in Responders %	
Cystectomy-Free Rate at 12 months	96%
Cystectomy-Free Rate at 24 months	90%
Cystectomy-Free Rate at 36 mo	84%
Disease Specific Survival % (N=100)	
12 Months	100%
24 Months	99%
36 Months	99%

July 2024 data cutoff by KM

QUILT-3.032 Cohort B: NMIBC Papillary Without CIS	NAI + BCG Efficacy, N=80
Disease-Free Survival (DFS)	
12 Months (Primary Endpoint)	58% (46.6, 68.2)
24 Months	52% (40.3, 62.7)
Median Disease-Free Survival, Mo (95% CI)	25.3 Mo (9.8 - 40.1)
Cystectomy Avoidance Rate	
Cystectomy Free Rate at 12 Months	92%
Cystectomy Free Rate at 24 Months	88%
Cystectomy Free Rate at 36 Months	82%
Disease Specific Overall Survival %	
12 Months	99%
24 Months	96%
36 Months	96%

July 2024 data cutoff by KM, N=80

Only 3% grade 3 treatment-related adverse events (TRAEs) and no grade 4-5 TRAEs.

TARGETED TREAMENT

- Oportuzumab monatox (OM; Vicineum)
- Erdafitinib : TAR-210 system
- Enfortumab vedotin (EV)
- ABI-009,an albumin-bound rapamycin (mTOR inhibitor)

MISCELANEOUS TREATMENT OPTIONS

- TURBT/fulguration : Not recommended
- Photodynamic therapy : PDT may be a viable option for BCG-U NMIBC in the future.
- Radiation-based treatment :
    - Ineligible for RC
    - No access to BST options
    - Cannot participate in a trial

General recommendations

- At the time of BCG-U diagnosis, BST may be offered as a safe alternative to RC in appropriately selected patients.
- Therapeutic failure for BST : High-grade urothelial carcinoma recurrence (Ta, T1, CIS) or clinical stage progression (T2, N+, M+) within 12 mo.
- Progression to muscle-invasive disease (cT2+) on BST should prompt evaluation in a multidisciplinary setting.

General recommendations

- At each tumor recurrence : restaging via TURBT, bimanual examination under anaesthesia, and cross-sectional imaging.
- Non–muscle-invasive therapeutic failure of BST (T1) and refuse or are ineligible for RC : Additional BCG-U clinical trials and BST on the basis of shared decision making.

General recommendations

Bladder-sparing therapy should be personalized according to

- Patient preferences
- Tumor characteristics
- Efficacy/toxicity profile of the treatment.

BCG-unresponsive carcinoma in situ

- Gemcitabine/docetaxel (GEM/DOCE)
- Nadofaragene firadenovec (NFF)
- Nogapendekin alfa inbakicept-pmln (NAI) + BCG

- Pembrolizumab is reserved for cases in which other treatments have been exhausted, because of its systemic toxicity,

Patients with BCG-unresponsive papillary-alone tumors

- GEM/DOCE, NFF
- NAI + BCG
- Single-agent chemotherapy
- Hyperthermic mitomycin C
- Pembrolizumab

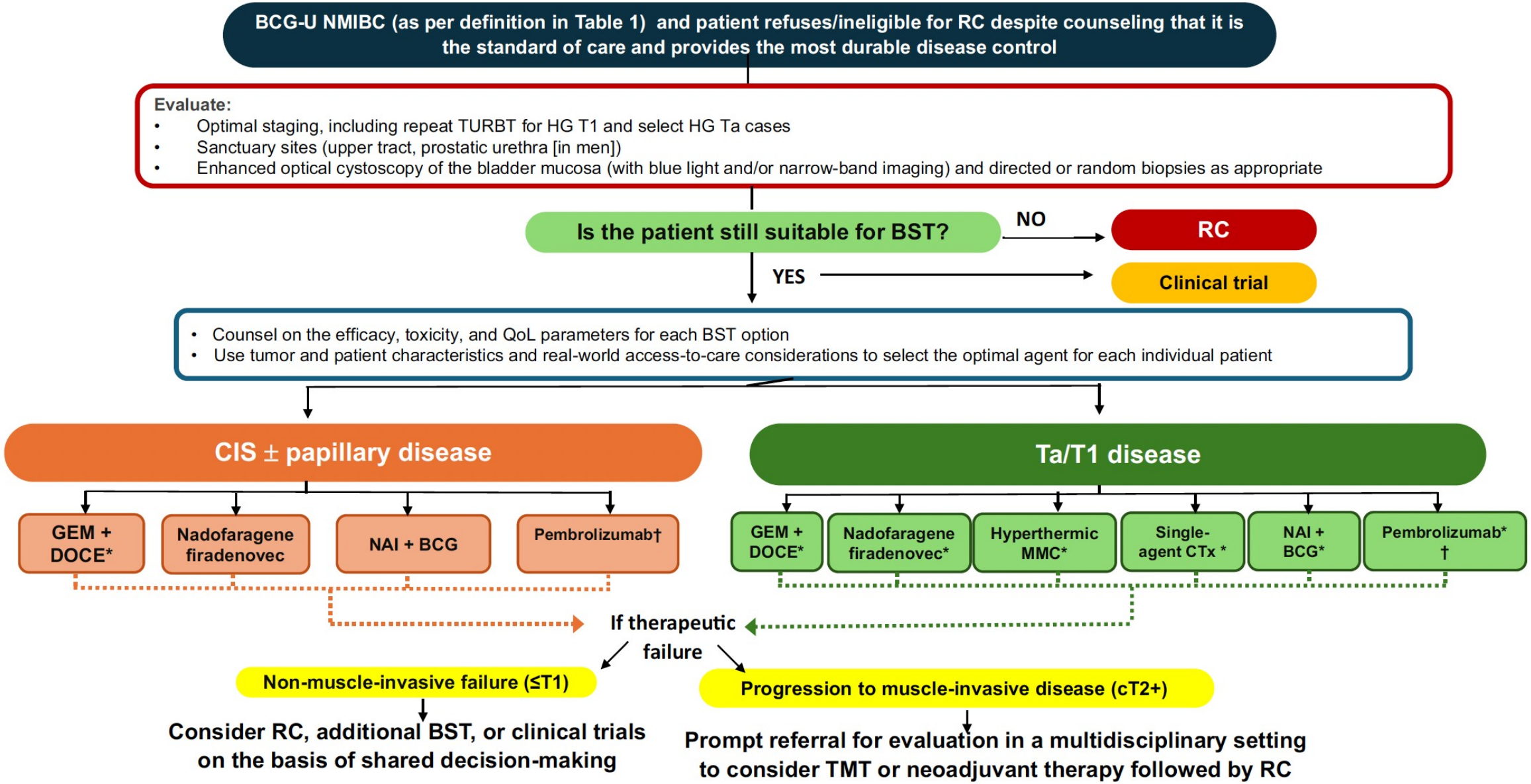

BCG-U NMIBC (as per definition in Table 1) and patient refuses/ineligible for RC despite counseling that it is the standard of care and provides the most durable disease control
Evaluate:
• Optimal staging, including repeat TURBT for HG T1 and select HG Ta cases
• Sanctuary sites (upper tract, prostatic urethra [in men])
• Enhanced optical cystoscopy of the bladder mucosa (with blue light and/or narrow-band imaging) and directed or random biopsies as appropriate
Is the patient still suitable for BST?
NO
RC
YES
Clinical trial
• Counsel on the efficacy, toxicity, and QoL parameters for each BST option
• Use tumor and patient characteristics and real-world access-to-care considerations to select the optimal agent for each individual patient
CIS ± papillary disease
GEM + DOCE*
Nadofaragene firadenovec
NAI + BCG
Pembrolizumab†
Ta/T1 disease
GEM + DOCE*
Nadofaragene firadenovec*
Hyperthermic MMC*
Single-agent CTx *
NAI + BCG*
Pembrolizumab* †
If therapeutic failure
Non-muscle-invasive failure (≤T1)
Consider RC, additional BST, or clinical trials on the basis of shared decision-making
Progression to muscle-invasive disease (cT2+)
Prompt referral for evaluation in a multidisciplinary setting to consider TMT or neoadjuvant therapy followed by RC

Table 4 – EAU-, AUA- and NCCN-recommended treatments for patients with BCG-U NMIBC who refuse or are ineligible for radical cystectomy

EAU 2023 guidelines [10]	AUA 2024 guidelines [12]	NCCN 2024 guidelines [11]
Any of the following (although administration within the context of a clinical trial is preferred): ■ Intravesical chemotherapy ■ Chemotherapy and microwave-induced hyperthermia ■ Electromotive administration of chemotherapy ■ Intravesical immunotherapy **Weak recommendation**	● Clinical trial enrollment ● Alternative intravesical therapy (ie, nadofaragene firadenovec) ● Alternative intravesical chemotherapies (ie, gemcitabine/docetaxel) ● Pembrolizumab (for patients with CIS within 12 mo of completion of adequate BCG therapy) **Conditional recommendation (evidence strength: grade C)**	● Intravesical chemotherapy ● Pembrolizumab for: ■ BCG-U CIS ± papillary tumors ■ BCG-U, high-risk NMIBC with high-grade papillary Ta/T1 only tumors without CIS **(category 2B)** ● Nadofaragene firadenovec for: ■ BCG-U CIS ■ High-grade papillary Ta/T1 only tumor without CIS **(category 2b)** **All recommendations are category 2a unless otherwise specified**

AUA = American Urological Association; BCG-U: bacillus Calmette-Guérin–unresponsive; CIS = carcinoma in situ; EAU = European Association of Urology; NCCN = National Comprehensive Cancer Network.

Conclusion

- Patients with BCG-U NMIBC treated with initial BST had similar outcomes to those for patients undergoing early RC, even for salvage RC after BST therapeutic failure

- BUT : Each failure increases rates of progression to MIBC/mUC

- Recent meta-analysis : Durability of response ??

Conclusion

- IBCG agreed that the optimal treatment should be personalized according to each patient's
  - Specific tumor characteristics (Grade, Stage)
  - Physiological makeup (ability/inability to hold an intravesical agent)
  - Real-world considerations (access to health care facilities, drug dosing, and costs).
- Further evidence from Randomized trial will guide future recommendations.