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Urothelial Cancer

Comparative Effectiveness of Bacillus Calmette-Guérin and Sequential Intravesical Gemcitabine and Docetaxel for Treatment-naïve Intermediate-risk Non–muscle-invasive Bladder Cancer

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Introduction

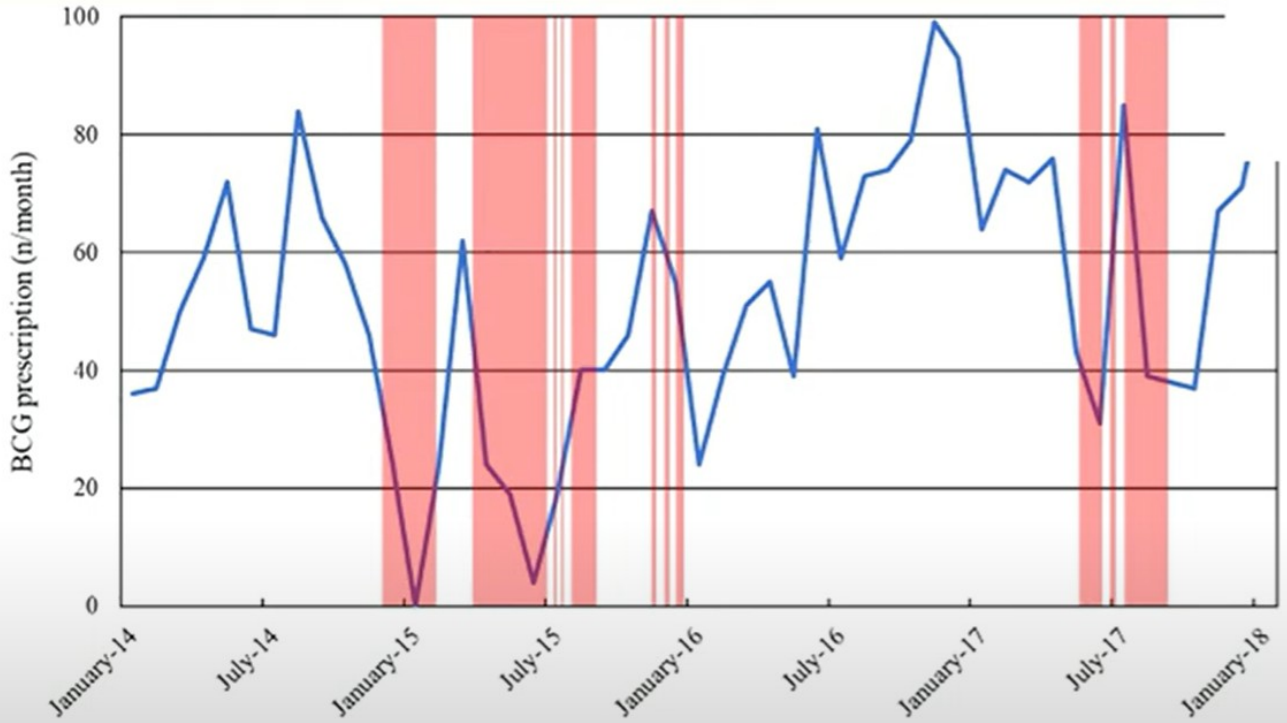
- IR-NMIBC across the American Urological Association(AUA) and European Association of Urology (EAU) guidelines For this heterogeneous patient group, the treatment recommended is adjuvant intravesical chemotherapy or bacillus Calmette-Guérin (BCG) [3,4].
- Current Gem/Doce regimens are associated with a 2-yr recurrencefree survival (RFS) rate of up to 69% for high-risk NMIBC
- Prior studies exploring the use of Gem/Doce in IR-NMIBC reported a 2-yr RFS rate of 70% [12,13].
- Of note, these studies primarily involved patients with low-grade (LG) Ta disease and used 2-yr maintenance regimens after induction therapy.

Risk Stratification

Low Risk	Intermediate Risk	High Risk
LG [a] solitary Ta ≤ 3cm	Recurrence within 1 year, LG Ta	HG T1
PUNLMP [b]	Solitary LG Ta > 3cm	Any recurrent, HG Ta
	LG Ta, multifocal	HG Ta, >3cm (or multifocal)
	HG [c] Ta, ≤ 3cm	Any CIS [d]
	LG T1	Any BCG failure in HG patient
		Any variant histology
		Any LVI [e]
		Any HG prostatic urethral involvement

[a]LG = low grade; [b]PUNLMP = papillary urothelial neoplasm of low malignant potential; [c]HG = high grade;
[d]CIS=carcinoma in situ; [e]LVI = lymphovascular invasion

United States now has 1 Supplier of BCG, with 3 Major Shortages in the past Decade



Numbers of Bacillus Calmette–Guerin (BCG) prescriptions per month. The shaded area represents BCG shortages identified through the [illegible]ical records.

Play (k)

BIOTECH AND PHARMA

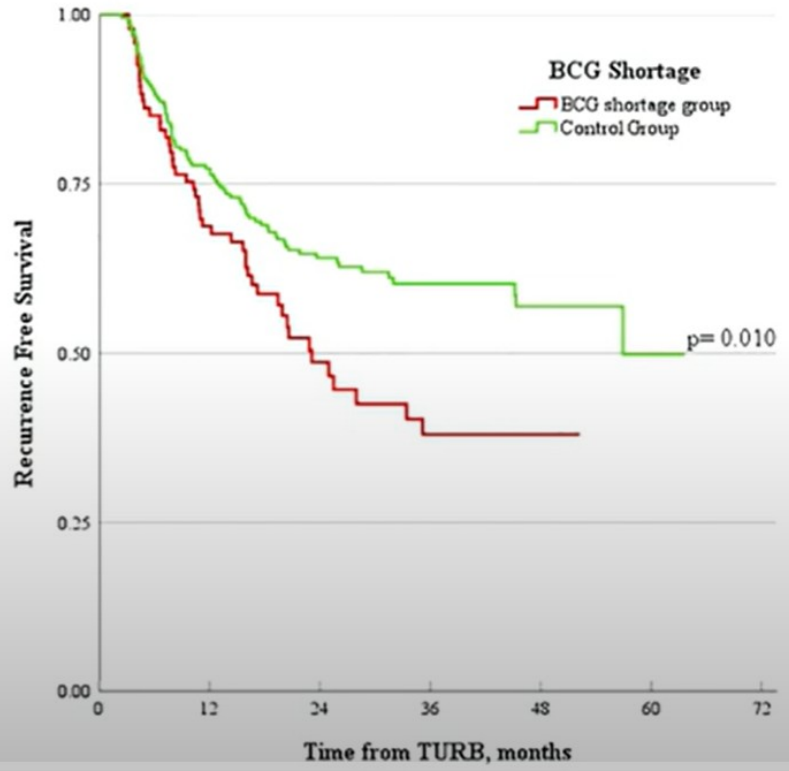
Mounting drug shortages delay treatments for patients with bladder cancer

Sections

The Washington Post
Democracy Dies in Darkness

Subscrib

Low prices of some lifesaving drugs make them impossible to get



Intermediate Risk, BCG Naïve

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2024 Bladder Cancer

Induction (Adjuvant) Intravesical Chemotherapy or BCG

- **Treatment option for NMIBC.**
- **The most commonly used agents are BCG, mitomycin, and gemcitabine.**
- **Initiated 3–4 weeks after TURBT with or without maintenance.**
- **Weekly instillations during induction are given for approximately 6 weeks**
- **Maximum of 2 consecutive cycle inductions without complete response.**

American Urological Association

Non-Muscle Invasive Bladder Cancer (NMIBC)

17. In an intermediate-risk patient a clinician should consider administration of a six-week course of induction intravesical chemotherapy or immunotherapy. (*Moderate Recommendation; Evidence Strength: Grade B*)

The available data supports the use of mitomycin C, doxorubicin, and epirubicin as choices for in patients with intermediate-risk NMIBC.

Jefferson Health

AUA Position Statement on BCG Shortage

The AUA recommends several management approaches to maintain high quality care for patients with Non-Muscle-Invasive Bladder Cancer (NMIBC). These recommendations may supersede the guideline statements found in the **Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Joint Guideline (2020)**. As always, these recommendations are subject to physician judgment in individual cases:

1. BCG should not be used for patients with low-risk disease.
2. Intravesical chemotherapy should be used as the first-line option for patients with intermediate-risk NMIBC. Patients with recurrent/multifocal low-grade Ta lesions who require intravesical therapy should receive intravesical chemotherapy such as mitomycin, gemcitabine, epirubicin, or docetaxel instead of BCG.
3. If BCG would be administered as second-line therapy for patients with intermediate-risk NMIBC, an alternative intravesical chemotherapy should be used rather than BCG in the setting of this BCG shortage.
4. For patients with high-risk NMIBC, high-grade T1 and CIS patients receiving induction therapy, they should be prioritized for use of full-strength BCG. If not available, these patients and other high-risk patients may be given a reduced 1/2 to 1/3 dose, if feasible.
5. If supply exists for maintenance therapy for patients with NMIBC, limit BCG dose to one year.
6. In the event of BCG supply shortage, maintenance therapy should not be given and BCG naïve patients with high-risk disease should be prioritized for induction BCG.
7. If BCG is not available, alternatives to BCG such as gemcitabine, epirubicin, docetaxel, valrubicin, mitomycin, or sequential gemcitabine/docetaxel or gemcitabine/mitomycin may also be considered with an induction and possible maintenance regimen.
8. Patients with high-risk features (i.e., high-grade T1 with additional risk factors such as concomitant CIS, lymphovascular invasion, prostatic urethral involvement or variant histology) who are not willing to take any potential oncologic risks with alternative intravesical agents, should be offered initial radical cystectomy, if they are surgical candidates.

Intravesical BCG during time of BCG shortage: NCCN Version 5 2024

- BCG induction and maintenance should be prioritized for patients at high risk for recurrence (eg, high-grade T1 and CIS), especially in theearly maintenance period (ie, 3 and 6 months post-induction).
- BCG maintenance for patients with intermediate-risk NMIBC can be risk adapted to prioritize patients with high-risk NMIBC
- BCG maint with high-risk NMIBC should be stopped at 1 year
- Consider induction with alternative agents if BCG is not available

  Alternative options: sequential gemcitabine/docetaxel, mitomycin, gemcitabine, epirubicin, valrubicin, docetaxel, or sequential gemcitabine/mitomycin.
- Consider a clinical trial if available
- If feasible, BCG may be split (1/3 or 1/2 dose) so that multiple patients may be treated with a single vial (for induction or high priority maintenance therapy).

Jefferson SKCCC Ongoing BGC Shortage Plan

Intermediate Risk

- Clinical trial when open
- 1st Line - Intravesical chemo (single agent Gem/Mito or Gem/Doce) with 1 year of maint therapy
- 2nd Line – Alternate Intravesical chemotherapy

- *BCG + 1 yr maintenance an option reserved for intravesical chemotherapy failures if supply is available*

Retrospective Review of Patients with Bacillus Calmette-Guérin Naïve, High-Risk Nonmuscle-Invasive Bladder Cancer Treated with Gemcitabine/Docetaxel

After complete transurethral resection of bladder tumor (TURBT) for nonmuscle-invasive bladder cancer (NMIBC), adjuvant therapy with Bacillus Calmette-Guérin (BCG) is recommended to prevent relapse

However, BCG use is associated with:

- Availability
- Efficacy
- Intolerance

This study explored the outcomes of using a combination of gemcitabine/docetaxel (Gem/Doce) as an alternative adjuvant therapeutic regimen in patients with NMIBC

Retrospective review of patients with BCG naïve, high-risk NMIBC on a Gem/Doce regimen

107 patients

TURBT

6 weekly intravesical treatments

- **47** Carcinoma in situ
- **55** **T1** stage
- **1 gm** Gem + **37.5 mg** Doce

Surveillance carried out over 2 years

Measured outcomes and their results

Patient-reported adverse events	Intolerance	2-Year recurrence-free survival	Cancer progression events	2-Year cancer-specific survival
56%	3.7%	82%	0	100%
(Including 1 Grade 3 event)	(Patients did not complete full induction)	(High-grade recurrence-free survival: 84%)		

Sequential intravesical Gem/Doce could serve as an effective adjuvant therapeutic alternative following TURBT

Sequential Intravesical Gemcitabine and Docetaxel for Bacillus Calmette-Guérin Naïve, High-Risk Nonmuscle-Invasive Bladder Cancer

McElree *et al.* (2022) | DOI: 10.1097/JU.0000000000002740

THE JOURNAL of UROLOGY®

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Rob Svatek
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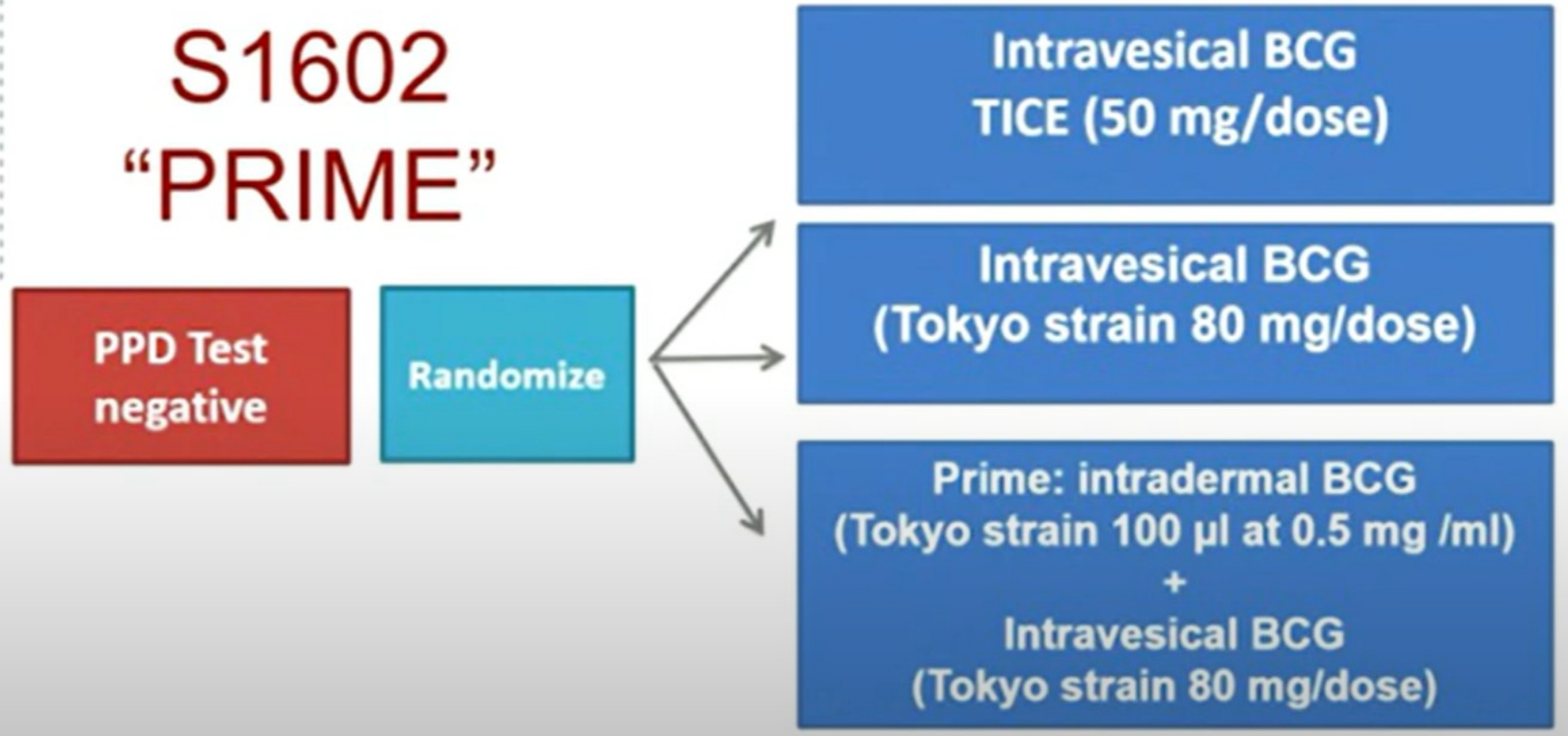


Estimated Enrollment: 969 patients

Background and Rationale: Historic Single Agent Chemotherapy vs BCG

Comparison	Bladder Ca Recurrence	Bladder Ca Progression	Overall Mortality
BCG vs MMC No. Trials RR (95% CI)	10 0.95 (0.81-1.11)	7 0.88 (0.66-1.17)	7 0.94 (0.83-1.06)
BCG vs Doxorubicin No. Trials RR (95% CI)	2 0.31 (0.16-0.6) 0.75 (0.64-0.88)	1 0.20 (0.02-1.72)	2 0.40 (0.01-12) 1.00 (0.71-1.37)
BCG vs Epirubicin No. Trials RR (95% CI)	5 0.54 (0.4-0.74)	5 0.6 (0.36-1.01)	3 0.72 (0.44-1.19)
BCG vs Gemcitabine No. Trials RR (95% CI)	3 1.67 (1.21-2.29) 0.53 (0.28-1.01) 0.76 (0.44-1.9)	2 1.11 (0.53-2.34) 0.52 (0.13-2.06)	1 1.2 (0.04- 34)

Multi-Institutional Retrospective GEMDOCE Series for BCG Unresponsive Disease

JOHNS HOPKINS MEDICINE

Retrospective Study of Gem/Doce Treatment
for Recurrent NMIBC Patients with History of BCG
June 2009 - May 2018

7 Institutions

276 Patients

MEDIAN
Age 73
Follow-up 22.9 months

Tolerance

9 Patients (3.3%)
unable to toleratate
full Gem/Doce course

Common Side Effects:

frequency/urgency,
dysuria

Survival Rates

Recurrence-Free

60% 1 Year

46% 2 Years

High Grade Recurrence-Free

65% 1 Year

52% 2 Years

Patient Outcomes

15.6%
43 of the 276 Patients
went on to cystectomy

4.0%
11 of the 43 Patients
had cancer muscle invasion

Muscle Invasion in 10 Patients

3.6%
via transurethral resection

Tidbit

Steinberg RL, Thomas LJ, Brooks N, et al. Multi-Institution Evaluation of Sequential Gemcitabine and Docetaxel as Rescue Therapy for Nonmuscle Invasive Bladder Cancer. J Urol. 2020;203(5):902-909. doi:10.1097/JU.0000000000000688

Infographic Designed By: Jessica Shah

Steinberg et al. Journal of Urology

- This contrasts with the AUA and EAU guidelines for IR-NMIBC, which recommend 1 yr of maintenance therapy after BCG induction. In this study, we explored the outcomes for patients with IR-NMIBC, primarily high-grade(HG) Ta, to determine the efficacy of BCG and Gem/Doce and the role of maintenance therapy in this unique population.

Patient and method

- Study setting, design, and population
- Single-center, Retrospective cohort study .
- Treatment Naïve –
- 2013.and 2023.
- IR categorization - AUA (n = 127) and EAU(n = 122) guidelines for NMIBC.
- Either treatment Induction course (5-6 cycles)→No evidence of recurrence →Maintenance therapy.

EXCLUSION -
Unifocal HG Ta > 3 cm,
Multifocal HG Ta,
Carcinoma in situ (CIS), HG T1 disease,
Lymphovascular invasion,
Prior BCG failure, variant histology,
Prostatic urethral involvement

BCG protocol

Joudi et al BCG protocol –

One vial (full strength) of TICE BCG (Organon Teknika, Jersey City, NJ, USA) in 50 ml of normal saline

Instilled – Induction – 5 to 6 cycles

60–90 min after instillation.

Maintenance regimens -

No recurrence

For 1 yr,

3, 6, and 12 month.

LUTS – BCG dose was halved (4 patient in the study

Gem/Doce protocol

Our Gem/Doce protocol has previously been described [15]. Two steps.

1. Gemcitabine
   - 1 or 2 g in 50 ml of normal saline per urethrally
   - Introduced → Voiding After 60 min.
2. Docetaxel
   - 37.5 mg of docetaxel in 50 ml of saline
   - Voiding 60 min

Maintainence Regimen

No Recurrence

Once a month for 1 year.

Refused - Close follow up with surveillance cystoscopies.

Postinduction surveillance and assessment

- Surveillance office cystoscopies - white-light cystoscope.
- The first surveillance cystoscopy was performed 6 wk after the last induction dose.
- Recurrence detected on in-office cystoscopy- triggered additional restaging procedures, including TURBT, urine cytology,and abdominal and pelvic imaging.
- Suspicious area - office cystoscopic fulguration of the suspicious site.
- Positive urine cytology but negative cystoscopy results, random bladder biopsies were performed

Covariates and study measures

- Baseline clinicopathological characteristics including

1. lesion size
2. pretreatment tumor pathology,
3. year of treatment, and
4. follow-up duration were collected.

Primary study measure - high-grade RFS in patients with primary high-grade IR-NMIBC.

- High-grade RFS was defined as freedom from high-grade recurrence after induction therapy.
- Time to recurrence was considered as the time from initiation of the induction course to the first recurrence.

- Other survival measures included any-grade RFS, and progression-free survival (PFS).

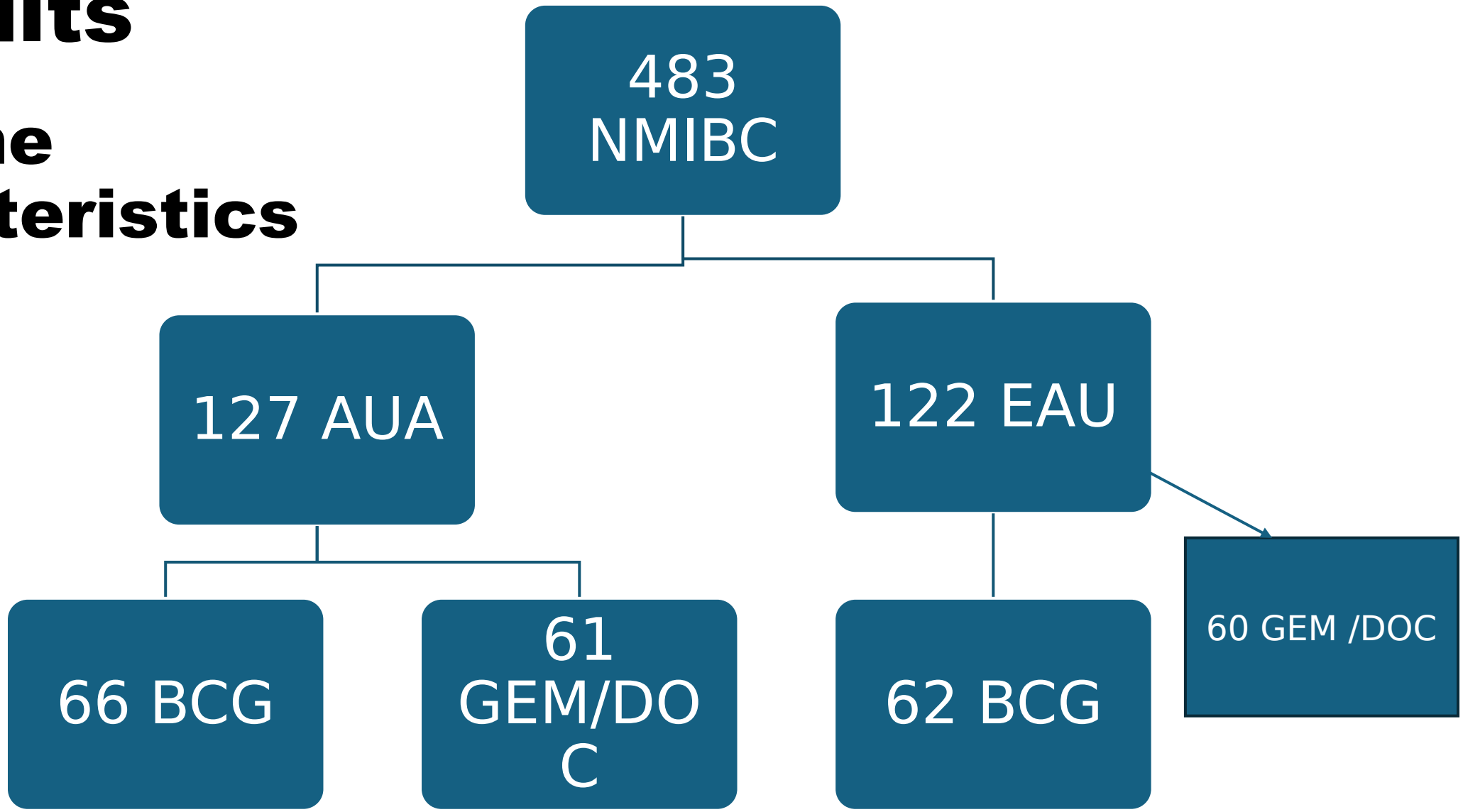
- Progression was defined as an increase in tumor stage and/or grade after induction treatment.

Statistical analysis

- Continuous variables - median with interquartile range (IQR) – Mann whitney U test
- Categorical variables are presented as absolute numbers with proportions- Fisher’s exact test
- Survival analysis - Kaplan-Meier method and the log-rank test.
- Initial univariable analysis - was performed to identify predictors associated with any-grade and high grade recurrence.
- Multivariate <odel - Predictors that demonstrated significant associations and were most clinically relevant were included in a multivariable model to control for confounders.
- Patients who were lost to follow-up were censored at their last known visit.
- Statistical significance was set at a two-sided p value of <0.05.
- All statistical analysis was performed using R version 4.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

- **Baseline characteristics**



Parameter	All patients (n = 127)	BCG (n = 66)	Gem/Doce (n = 61)	p value
Median age, yr (IQR)	70 (62 - 76)	69 (61.2–76)	72 (62–76)	0.83
Median body mass index, kg/m^2 (IQR)	27 (24.25 - 30)	27 (24–30.8)	27 (25.4–29.3)	0.91
Sex, n (%)				0.82
Male	102 (80.3)	52 (79)	50 (82)	
Female	25 (18.7)	14 (21)	11 (18)	
Race, n (%)				0.94
White	75 (59.1)	38 (57.6)	37 (60.7)	
African American	17 (13.4)	9 (13.6)	8 (13.1)	
Other	35 (27.6)	19 (28.8)	16 (26.2)	
Smoking status, n (%)				0.86
Never	51 (40.1)	28 (42.4)	23 (37.7)	
Current	14 (11)	7 (10.6)	7 (11.5)	
Former	62 (48.9)	31 (47)	31 (50.8)	
ASA score, n (%) [a]				0.12
1	2 (1.6)	0 (0)	2 (3.3)	
2	62 (48.8)	26 (39.4)	36 (59)	
3	53 (41.7)	32 (48.5)	21 (34.4)	
4	2 (1.6)	1 (1.5)	1 (1.6)	
Median lesion size, cm (IQR) [b]	1.35 (0.8–2.35)	1.3 (0.7–2.2)	1.5 (1–2.5)	0.24
Tumor size, n (%) **				0.12
≤3 cm	102 (80.3)	58 (87.9)	44 (72.1)	
>3 cm	20 (15.7)	7 (10.6)	13 (21.3)	
Pretreatment T stage, n (%)				0.41
Ta	122 (96.1)	62 (94)	60 (98.4)	
T1	5 (3.9)	4 (6)	1 (1.6)	
Pretreatment tumor grade, n (%)				0.89
Low grade	44 (34.6)	22 (33.3)	22 (36.1)	
High grade	83 (65.4)	44 (66.7)	39 (63.9)	
Pretreatment tumor pathology, n (%)				0.34
Low-grade Ta	39 (30.7)	18 (27.3)	21 (34.5)	
High-grade Ta	83 (65.4)	44 (66.7)	39 (63.9)	
Low-grade T1	5 (3.9)	4 (6)	1 (1.6)	
Multifocal disease, n (%)	23 (18.1)	9 (13.6)	14 (30)	0.26
Year of treatment, n (%)				<0.001
2013–2020	69 (54.3)	59 (89.4)	10 (16.4)	
2021–2023	58 (45.7)	7 (10.6)	51 (83.6)	
Eligible patients who received mTx, n/N (%)	40/90 (44.4)	21/47 (44.7)	19/43 (44.2)	>0.99
Median follow-up, mo (IQR)	31.7 (14.3–53.9)	53.1 (25.3–71.2)	20.2 (8.28–33.1)	<0.001

Table 2 – Patient-reported adverse events after intravesical treatment with BCG or sequential Gem/Doce

Adverse event	BCG (*n* = 66)		Gem/Doce (*n* = 61)	
	Events, *n* (%)	CTCAE grade	Events, *n* (%)	CTCAE grade
Urinary frequency	4 (6)	1	7 (11.5)	1
Urinary urgency	3 (4.5)	1	5 (8.2)	1
Nocturia	2 (3)	1	1 (1.6)	1
Abnormal body odor	0	–	1 (1.6)	1
Dysuria	5 (7.5)	2	3 (4.9)	2
Hematuria	1 (1.5)	2	0	–
Malaise/weakness	1 (1.5)	2	0	–
Infectious complications (fever/sepsis) [a]	1 (1.5)	3	1 (1.6)	2

BCG = bacillus Calmette-Guérin; Gem/Doce = gemcitabine/docetaxel; CTCAE = Common Terminology Criteria for Adverse Events.

[a] One patient in the BCG group developed sepsis and required admission.

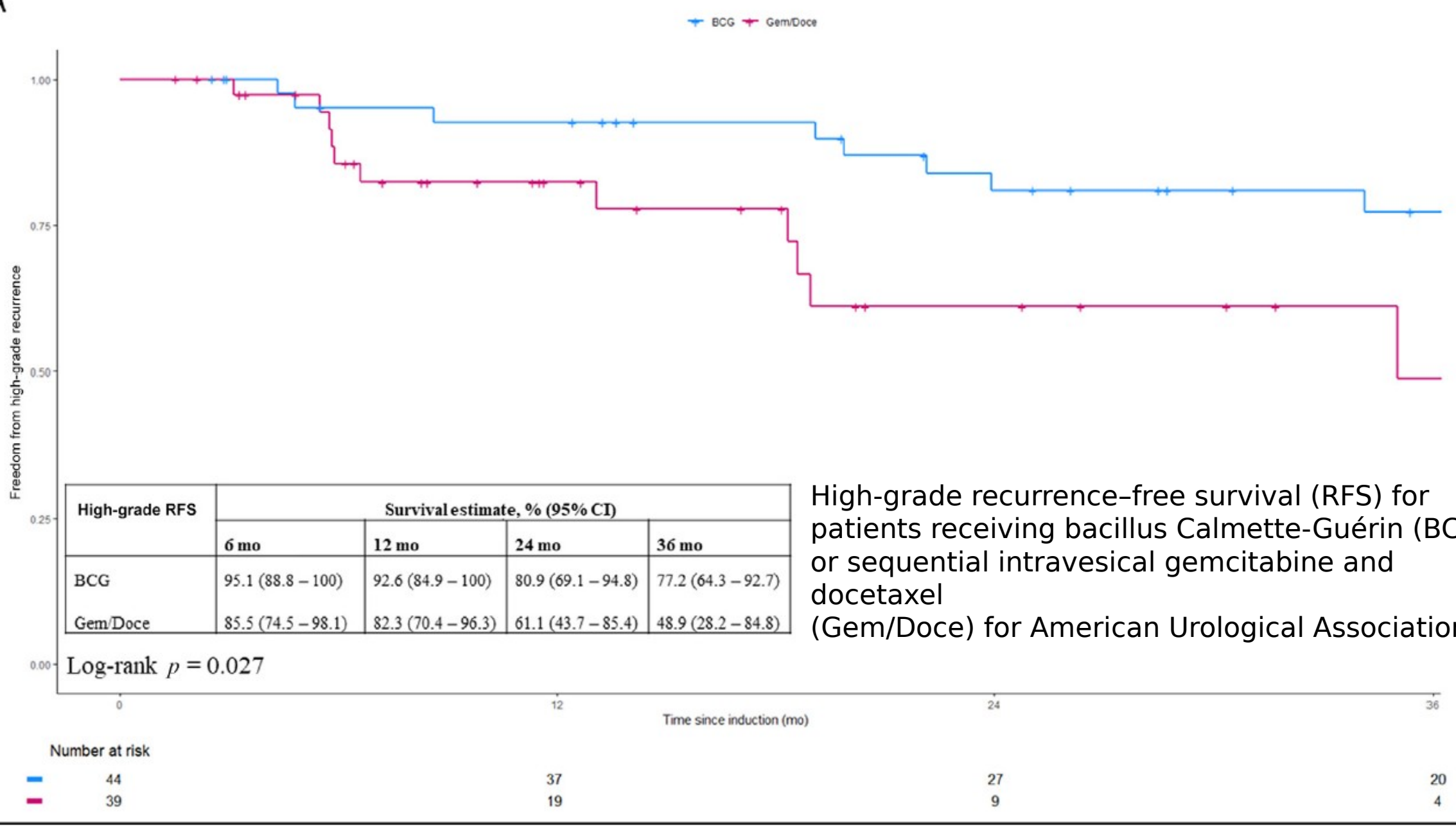
- 3.3. Survival outcomes

	BCG	GEM/doc	
Median follow up	53.1	20.2	
Recurrence	30(45.5)	31(50.8)	
High grade Recurrence	10(15.2)	11(18%)	
Disease progression	6(9.8%)	5(7.6%)	
Cystectomy	1	3	4
Metastatic disease	2	2	
1year RFS	92.6%	82.3	
2year RFS	80.6	61.1	
Any grade RFS 1st year 2nd Year	 68.6 59.8	 62.5 40.9	

Factors influencing any-grade and high-grade recurrence after intravesical therapy

- Following initial univariable analysis, multivariable analysis demonstrated that receipt of maintenance therapy (hazard ratio [HR] 0.4, 95% CI 0.22–0.72; p = 0.002) was predictive of lower any-grade recurrence, while induction Gem/Doce therapy was associated with higher risk of any-grade recurrence (HR 1.87, 95% CI 1.1–3.2; p = 0.035) (Table 3).
- For patients with high-grade primary disease, multivariable analysis revealed that induction Gem/Doce therapy was predictive of high-grade recurrence when compared to BCG (HR 3.4, 95% CI 1.27–9.1; p = 0.015).

A

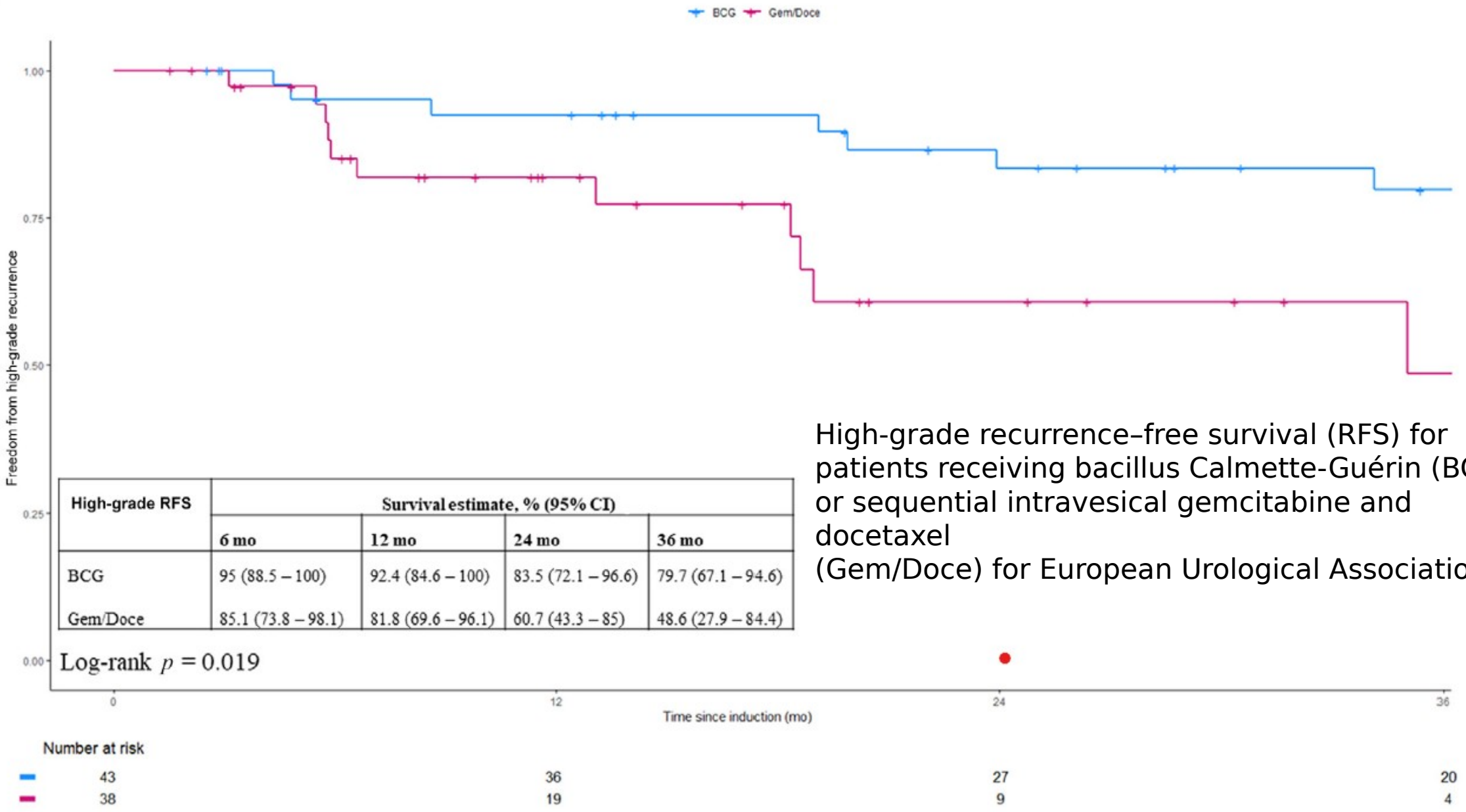


High-grade RFS	Survival estimate, % (95% CI)			
	6 mo	12 mo	24 mo	36 mo
BCG	95.1 (88.8 – 100)	92.6 (84.9 – 100)	80.9 (69.1 – 94.8)	77.2 (64.3 – 92.7)
Gem/Doce	85.5 (74.5 – 98.1)	82.3 (70.4 – 96.3)	61.1 (43.7 – 85.4)	48.9 (28.2 – 84.8)

Log-rank $p = 0.027$

High-grade recurrence–free survival (RFS) for patients receiving bacillus Calmette-Guérin (BCG) or sequential intravesical gemcitabine and docetaxel
(Gem/Doce) for American Urological Association

B



High-grade RFS	Survival estimate, % (95% CI)			
	6 mo	12 mo	24 mo	36 mo
BCG	95 (88.5 – 100)	92.4 (84.6 – 100)	83.5 (72.1 – 96.6)	79.7 (67.1 – 94.6)
Gem/Doce	85.1 (73.8 – 98.1)	81.8 (69.6 – 96.1)	60.7 (43.3 – 85)	48.6 (27.9 – 84.4)

High-grade recurrence–free survival (RFS) for patients receiving bacillus Calmette-Guérin (BCG) or sequential intravesical gemcitabine and docetaxel
(Gem/Doce) for European Urological Association

Discussion

- Survival analysis revealed that both high-grade RFS for patients with highgrade primary tumors (log-rank p = 0.027) and any-grade RFS (log-rank p = 0.0036) were superior with BCG in comparison to Gem/Doce.
- Interestingly, the any-grade RFS curves appear to separate after the 1-yr maintenance protocol was completed for both groups. Approximately 45% of patients who were eligible for maintenance therapy actually received maintenance therapy in both groups. Reasons for not receiving maintenance therapy were BCG shortage, loss to follow-up, or patient refusal because of adverse effects of intravesical treatment.
- Multivariable Cox regression analysis revealed that Gem/Doce receipt was associated with higher risk of any-grade recurrence (HR = 1.87) and of high-grade recurrence of high-grade primary tumors (HR = 3.4), while receipt of maintenance therapy for 2 yr

Discussion

- **McElree et al [13]** explored outcomes for 77 patients with IR-NMIBC who received Gem/Doce and found a 2-yr RFS rate of 71%. This study was also primarily included patients with LG Ta disease who received 2-yr maintenance therapy. In our study, the Gem/Doce group had 2-yr RFS rates of 61.1% for high-grade recurrence and 40.9% for any-grade recurrence.
- The lower any-grade RFS rate in this study may be attributed to the fact that 65% of patients in this study had HG Ta disease, and that patients received maintenance therapy for just 1 yr.
- Followed by AUA and EAU guidelines recommend 1-yr maintenance with BCG, we followed a similar protocol for Gem/Doce.
- Patients receiving Gem/Doce require maintenance therapy to prevent disease recurrence.
- Ben-David et al [15] demonstrated higher RFS with maintenance therapy after Gem/Doce in comparison to induction therapy alone (2-yr any-grade RFS 87% vs 31%; log-rank $p < 0.0001$). The role of prolonged Gem/Doce maintenance therapy can possibly be attributed to its mechanism of action. Gem/Doce has a direct cytotoxic effect on tumor cells in the local environment[17,18] and the response is subject to attrition over time in the absence of regular intravesical instillations of Gem/Doce, which increased the risk of tumor recurrence.
- On the contrary, BCG induces sustained activation of the immune system [19]. This is reflected in our study, as patients who received BCG fared better than those who received Gem/Doce after the scheduled 1-yr maintenance therapy.
- BCG shortages have led to prioritization of its use for patients with high-risk NMIBC, HG T1 disease, and CIS. As a result, the use of alternative intravesical therapies such as Gem/Doce has increased

- This trend was also observed in our study, given that patients after 2020 were more likely to receive Gem/Doce for NMIBC. Despitethe widespread adoption of alternative intravesical chemotherapy for NMIBC, level 1 evidence demonstrating the noninferiority of these regimens in comparison to BCG has not yet been established.
- Randomized controlled trials (RCTs) such as BRIDGE (NCT05538663) evaluating outcomes of BCG and Gem/Doce in high-risk, treatment naïve NMIBC are ongoing [20].
- With the increasing use of Gem/Doce for IR-NMIBC, there is a growing need for standardization of Gem/Doce regimens for this heterogeneous group of patients.
- Establishment of routine therapeutic protocols for Gem/Doce in IR-NMIBC is an area of future research that must consider the efficacy and cost of prolonged maintenance therapy.

THIS study limitations.

1. The retrospective nature may have introduced selection bias.
2. we noted a significant difference in follow-up times between the two groups, as Gem/Doce therapy was initiated in 2019.
3. To truly ascertain the oncological outcomes for the two treatment groups, larger, multi-institutional studies with similar follow-up durations for BCG and Gem/Doce are necessary.

Future RCTs are necessary to truly ascertain the comparative effectiveness of BCG and Gem/Doce for IR-NMIBC.

GemDoce- Summary of Prospective Trials

- Phase 2 demonstrates promising 12 month efficacy (88%) in a high risk NMIBC population.
- Grade 3 Toxicities appear comparable to BCG but need to be assessed in head to head format.
- Phase 3 EA8212 BRIDGE- RCT of BCG vs GEMDOCE is ongoing

Conclusions

- For patients with IR-NMIBC, intravesical BCG resulted in superior any-grade RFS over Gem/Doce.

- Patients with high-grade primary tumors had worse high-grade RFS with Gem/Doce than with BCG.
- Maintenance therapy protocols appear to be important in determining long-term outcomes with Gem/Doce.
- Before adopting Gem/Doce as an alternative for treatment-naïve patients with IR-NMIBC, standardization of treatment protocols and maintenance regimens is necessary.
- The preliminary findings of the study were presented at the 2024 American Urological Association meeting (MP 16- 19), San Antonio, TX, USA.


D·CRAIG