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European Association of Urology

## Platinum Priority – Bladder Cancer

Editorial by Christine V. Nikas and Angela B. Smith on pp. 699–700 of this issue

# Treatment of High-grade Non-muscle-invasive Bladder Carcinoma by Standard Number and Dose of BCG Instillations Versus Reduced Number and Standard Dose of BCG Instillations: Results of the European Association of Urology Research Foundation Randomised Phase III Clinical Trial “NIMBUS”

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**Abstract**

**Background:** Intravesical instillation of bacillus Calmette-Guérin (BCG) is an accepted strategy to prevent recurrence of non-muscle-invasive bladder cancer (NMIBC) but associated with significant toxicity.

**Objective:** NIMBUS assessed whether a reduced number of standard-dose BCG instillations are noninferior to the standard number and dose in patients with high-grade NMIBC.

**Design, setting, and participants:** A total of 345 patients from 51 sites were randomised between December 2013 and July 2019. We report results after a data review and safety analysis by the Independent Data Monitoring Committee based on the cut-off date of July 1, 2019.

**Intervention:** The standard BCG schedule was 6 wk of induction followed by 3 wk of maintenance at 3, 6, and 12 mo (15 instillations). The reduced frequency BCG schedule was induction at wks 1, 2, and 6 followed by 2 wk (wks 1 and 3) of maintenance at 3, 6, and 12 mo (nine instillations).

**Outcome measurements and statistical analysis:** The primary endpoint was time to first recurrence. Secondary endpoints included progression to  $\geq$ T2 and toxicity.

**Results and limitations:** In total, 170 patients were randomised to reduced frequency and 175 to standard BCG. Prognostic factors at initial resection were as follows: Ta/T1: 46/54%; primary/recurrent: 92/8%; single/multiple: 57/43%; and concomitant carcinoma in situ: 27%. After 12 mo of median follow-up, the intention-to-treat analysis showed a safety-relevant difference in recurrences between treatment arms: 46/170 (reduced frequency) versus 21/175 patients (standard). Additional safety analyses showed a hazard ratio of 0.40 with the upper part of the one-sided 97.5% confidence interval of 0.68, meeting a predefined stopping criterion for inferiority.

**Conclusions:** The reduced frequency schedule was inferior to the standard schedule regarding the time to first recurrence. Further recruitment of patients was stopped immediately to avoid harm in the reduced frequency BCG arm.

**Patient summary:** After surgical removal of the tumour, patients with high-grade non-muscle-invasive bladder cancer are treated with bacillus Calmette-Guérin to prevent recurrence and progression. This is associated with significant side effects. We report the results of a clinical trial showing a reduction in the number of instillations (from 15 to nine in total) being inferior to the standard protocol. From today's perspective, complete tumour resection and a standard number of instillations remain the standard of care.

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**1. Introduction**

Patients with high-grade non-muscle-invasive carcinoma of the bladder (NMIBC) show an increased risk of recurrence, progression, and metastases [1]. Instillation therapy with bacillus Calmette-Guérin (BCG) subsequent to transurethral resection (TUR) is considered the most effective form of treatment in these patients.

Following the initial landmark report demonstrating the efficacy of BCG [2], there has been little change in the empirical dose and schedule. The guidelines of the European Association of Urology (EAU) suggest 6-weekly instillations during an induction phase [3], followed by a maintenance schedule for optimal efficacy [4,5]. The Southwest Oncology Group (SWOG) found highly significant benefits regarding recurrence-free survival for a standard induction followed by a maintenance phase of BCG once weekly for 3 wks and at 3, 6, 12, 18, 24, 30, and 36 mo after BCG induction, as compared with BCG induction alone [6]. However, mainly due to significant toxicity, only 16% of the patients completed the treatment schedule.

Several attempts have been made to reduce BCG-associated toxicity. A trial by the European Organisation

for Research and Treatment of Cancer (EORTC 30962) [7] assessed noninferiority of 1 versus 3 yr of maintenance scheduled as applied by the SWOG [6], with either full or reduced (one-third) BCG doses. No differences in toxicity were observed between full and reduced BCG doses, but recurrence rates were increased with reduced doses, in both the 1- and the 3-yr maintenance arm. In high-risk patients, 3-yr maintenance was superior to 1-yr maintenance regarding recurrence, but did not show long-term benefits with respect to progression or survival. In a study by the Spanish Oncology Group (CUETO 98013), the standard BCG induction protocol with or without BCG maintenance comprising only one instillation every 3 mo for 3 yr was assessed [8]. However, the maintenance schedule seemed to be insufficient, as no significant decrease was observed in recurrence and progression rates compared with induction alone.

It is generally considered that BCG therapy is immune dependent [9]. Animal studies suggest that fewer than the current number of instillations are sufficient to induce a proper immune response. NIMBUS was designed to demonstrate that such an approach results in similar clinical efficacy to the standard BCG therapy [10,11].

## 2. Patients and methods

NIMBUS is a randomised multicentre noninferiority trial (51 study sites) conducted in five countries (Germany, The Netherlands, France, Belgium, and Spain), to assess whether a reduced number of standard-dose BCG instillations are noninferior to the standard number and dose in patients with high-grade NMIBC (Supplementary material). Recruitment was between December 2013 and October 2019. Results are reported after a data review and safety analysis by the Independent Data Monitoring Committee (IDMC) based on the cut-off date of July 1, 2019. Thereupon, patient recruitment was stopped, and the trial will end once all patients have completed their visit at mo 6, wk 3 in April 2020.

The trial was approved by all relevant institutional review boards and independent ethics committees, and was conducted in compliance with the Declaration of Helsinki [12], Good Clinical Practice, and local regulatory requirements. Before entering the study, all patients voluntarily signed the informed consent.

### 2.1. Inclusion and exclusion criteria

BCG-naïve patients with high-grade (World Health Organization [WHO]/International Society of Urologic Pathologists classification [13]) Ta or T1, primary or recurrent, single or multiple urothelial papillary carcinoma of the bladder, with or without carcinoma in situ (CIS), were eligible for the study. The absence of high-grade papillary NMIBC after routine repeated TUR (re-TUR) and/or re-re-TUR had to be confirmed at histopathological examination. As per protocol amendment 5, dated May 2017, patients having Ta high-grade tumour could be included without re-TUR, in case muscle tissue was provided in a biopsy specimen confirming complete removal of the tumour.

Patients were excluded from study participation if they had previously received any systemic or multi-instillation intravesical chemotherapy within the past 3 mo or had any form of immunodeficiency, any tumours in upper urinary tract or prostatic urethra at any time, or another malignancy other than basal cell carcinoma of the skin or localised prostate cancer under active surveillance.

### 2.2. Randomisation and study interventions

Eligible patients were randomised to one of the following two treatment groups:

1. Standard frequency arm (SF arm): induction: once-weekly BCG instillations at wks 1–6; maintenance: once-weekly instillations at wks 1–3 at mo 3, 6, and 12 (15 instillations in total).
2. Reduced frequency arm (RF arm): induction: once-weekly BCG instillations at wks 1, 2, and 6; maintenance: instillations at wks 1 and 3 at mo 3, 6, and 12 (nine instillations in total).

Stratification factors were centre, Ta versus T1, concomitant CIS versus no CIS, type of BCG strain (Medac, Connaught, or Tice), and single versus multiple tumours. Randomisation was done by means of a validated randomisation programme as part of a web-based data management system. After entry of the stratification factors and some basic information, treatment allocation was displayed immediately on the screen. The randomisation programme used the minimisation method with a random element [14].

Lyophilised BCG (Medac:  $2 \times 10^8$ – $3 \times 10^9$  CFU, Connaught:  $1.8$ – $19.2 \times 10^8$  CFU, Tice:  $1$ – $8 \times 10^8$  CFU) was suspended in 50 ml of sterile physiological saline. After catheterising the bladder, the suspension was instilled. The catheter was withdrawn, and patients were requested to retain the liquid for 2 h.

Cystoscopy and urine cytology were performed every 3 mo during the first 2 yr and every 6 mo thereafter. Suspicion of disease recurrence

should be proved by histology. Local and systemic side effects were recorded continuously.

Patients concluded the study at first recurrence or after occurrence of new CIS, urothelial carcinoma in the upper tract or in the prostatic urethra, distant metastases, or necessity of systemic chemotherapy.

### 2.3. Endpoints

The primary endpoint was time to first recurrence. Secondary objectives were rate of progression to muscle-invasive ( $\geq T2$ ) disease, identification of the number and grade of recurrent tumours, and identification of the incidence and severity of side effects, specifically the occurrence of treatment-related toxicity higher than grade 2 (according to WHO).

### 2.4. Statistical considerations

NIMBUS was a randomised nonblinded trial designed to establish noninferiority of a reduced versus a standard number of BCG instillations for high-grade NMIBC. Inferiority of the experimental arm was defined as the upper part of the confidence interval (CI, using one-sided 2.5% level of significance) being lower than a hazard ratio (HR; hazard experimental/hazard standard) of 0.75 for recurrence.

The sample size was calculated to be 500 patients per arm at a statistical power of 80%. Owing to BCG shortage, recruitment was delayed and statistical assumptions were redefined in amendment 4 from May 2016. Taking into account prolonged recruitment and follow-up times, patient numbers were reduced to 412 per arm maintaining statistical power. Safety analyses and IDMC evaluations were performed initially at yearly intervals, the past 2 yr at 6 mo intervals. According to the protocol, when inferiority was shown, further analyses were requested to check for biases and stopping the study needed to be considered.

The HR for time from randomisation to first recurrence was analysed in the intention-to-treat population, as well as the rate of progression to muscle-invasive disease, occurrence of distant metastasis, and survival. Time to first recurrence was estimated by means of the Kaplan-Meier method. A univariate Cox proportional hazard model was applied to assess treatment effects.

Patients who received at least one dose of study medication are hereinafter referred to as safety population and considered for reports concerning adverse events (AEs).

## 3. Results

Between December 2013 and July 1, 2019, 345 of the 824 patients planned in the current version of the study protocol were randomised, 170 to the RF arm and 175 to the SF arm. Thereof, 165 patients per arm received study medication (Fig. 1). Of the high-grade tumours, about half were Ta/T1 (45% vs 54%), and the majority were primary (92%) and without concomitant CIS (73%). There were 57% and 43% uni- and multifocal tumours, respectively. The vast majority of patients underwent routine re-TUR: 152 (89%) in the RF arm and 161 (92%) in the SF arm (Table 1).

The median follow-up time of this safety analysis was 12 mo for all patients and 14 mo for patients without recurrence.

### 3.1. Efficacy

Disease recurrence was observed in 67/345 patients: 46/170 in the RF arm and 21/175 in the SF arm. Thereof, two RF

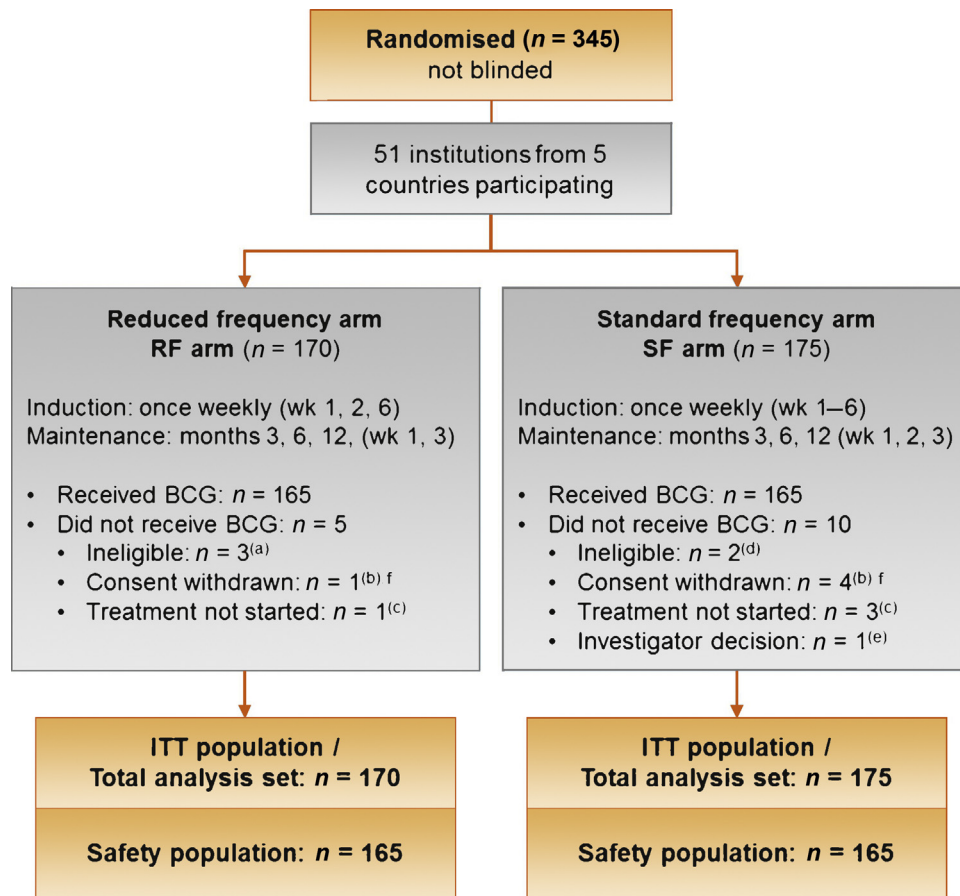


Fig. 1 – Consolidated Standard of Reporting Trials diagram.

BCG = bacillus Calmette-Guérin; ITT = intention to treat; RF = reduced frequency; SF = standard frequency.

<sup>a</sup>1 ×  $\geq$  T2, 1 × history of upper urinary tract tumour, 1 × laboratory abnormalities.

<sup>b</sup>consent withdrawn prior to start BCG treatment.

<sup>c</sup>randomised shortly before 1 July 2019.

<sup>d</sup>1 × upper urinary tract tumour, 1 × no re-re-TUR performed because patient opted for cystectomy.

<sup>e</sup>no further details available.

<sup>f</sup>Consent withdrawn: 14 in the SF arm versus three in the RF arm.

patients and one SF patient were considered to have recurrence, although their lesions were just coagulated without biopsy. A univariate Cox regression analysis revealed an HR of 0.40 (upper part of the one-sided 97.5% CI being 0.68) for first recurrence in favour of the SF-arm group. Furthermore, a subgroup analysis was performed for 298 patients who were (or could have been) observed for at least 6 mo since randomisation, as this time span was indicated for realisation of a planned interim analysis. Univariate Cox regression analysis indicated the HR for the first recurrence to be 0.39 (upper part of the one-sided 97.5% CI being 0.66), again favouring the SF arm. Kaplan-Meier survival estimates were calculated for both settings (Fig. 2). The median time to recurrence was not reached in any treatment arm.

One and six patients in the RF and the SF arm, respectively, progressed to muscle-invasive disease ( $\geq$ T2), and one additional patient treated with the standard therapy developed distant metastases. In total, 10 patients

died during the study, none related to the study drug (Table 2).

### 3.2. Treatment discontinuation

In the SF arm, 80 patients received the last planned treatment at mo 12, wk 3. Thereof, three patients missed one dose of BCG and one patient missed two doses of BCG during maintenance. In the RF arm, 69 patients received the last planned treatment at mo 12, wk 3. Thereof two patients missed two doses of BCG during maintenance. Thus, by the time of this analysis, 67 patients in the RF arm and 76 patients in the SF arm had completed all nine or 15 BCG instillations as per protocol (Table 3).

Fewer AEs were observed in the RF arm. Out of 330 patients in the safety population, for 249 a total of 2139 AEs have been reported. A total of 113/165 patients were affected with 670 AEs in the RF arm and 136/165 patients were affected with 1469 AEs in the SF arm. Notably,

**Table 1 – Baseline characteristics for patients and disease for reduced and standard frequency arms.**

	RF arm (n = 170)	SF arm (n = 175)
Male gender, n (%)	138 (81)	146 (83)
Type of cancer, n (%)		
Primary	156 (92)	161 (92)
Recurrent	14 (8.2)	14 (8.0)
Number of tumours, n (%)		
Single	95 (56)	102 (58)
Multiple	75 (44)	73 (42)
Highest tumour category, n (%)		
T0	0 (0)	3 (1.7) <sup>a</sup>
Ta	82 (48)	74 (42)
T1	87 (51)	98 (56)
≥T2	1 (0.6) <sup>b</sup>	0 (0)
Associated CIS, n (%)	44 (26)	48 (27)
BCG strain used, n (%)		
BCG Medac	153 (90)	159 (91)
BCG Tice	13 (7.6)	14 (8.0)
BCG Connaught	4 (2.4)	2 (1.1)

BCG = bacillus Calmette–Guérin; CIS = carcinoma in situ; RF arm = reduced frequency arm; SF arm = standard frequency arm.

<sup>a</sup> Patients had CIS only: 1 × treatment completed (15 instillations), patient included in follow-up, no recurrence; 1 × treatment completed (14 instillations), patient included in follow-up, first recurrence, and tumour in prostatic urethra at mo 36; 1 × consent withdrawn after six instillations, patient included in follow-up until that time point, no recurrence.

<sup>b</sup> Patient did not receive BCG and not included in follow-up.

more patients in the SF arm (14 patients) withdrew their consent than in the RF arm (three patients). A detailed analysis will be subject of the final study results.

#### 4. Discussion

Intravesical instillation of BCG is the standard of care in patients with high-grade NMIBC [15]. BCG was shown to be superior to intravesical chemotherapy in reducing the risk of recurrence and, possibly, progression [16,17]. The current state-of-the-art comprises an induction phase followed by further BCG instillations during a maintenance schedule for 1–3 yr [6,8,18]. Various doses, induction and maintenance schedules, and durations of BCG have been investigated, trying to decrease the severity and frequency of side effects while maintaining efficacy. However, dose reduction to one-third revealed to be less effective without reducing toxicity [7]. Furthermore, a maintenance phase comprising only one instillation of BCG every 3 mo was not sufficient to significantly decrease recurrence and progression rates over induction alone [8].

NIMBUS investigated whether an RF of instillations during induction and maintenance would result in clinical efficacy similar to standard BCG therapy. Ideally, this was expected to be accompanied by fewer side effects and inconvenience. Our approach was based on a recent animal study showing that BCG instillations at wks 1 and 6 induce only a predominately Th1-mediated cytokine response being equivalent to 6-weekly BCG instillations [10]. One extra instillation at wk 2 or 5 increased the Th2 cytokine response, being noteworthy, as BCG-induced Th1/Th2 cytokine ratio is associated with effective antitumour activity [11].

Therefore, the NIMBUS induction cycle with BCG instillations was scheduled at wks 1, 2, and 6. In line with

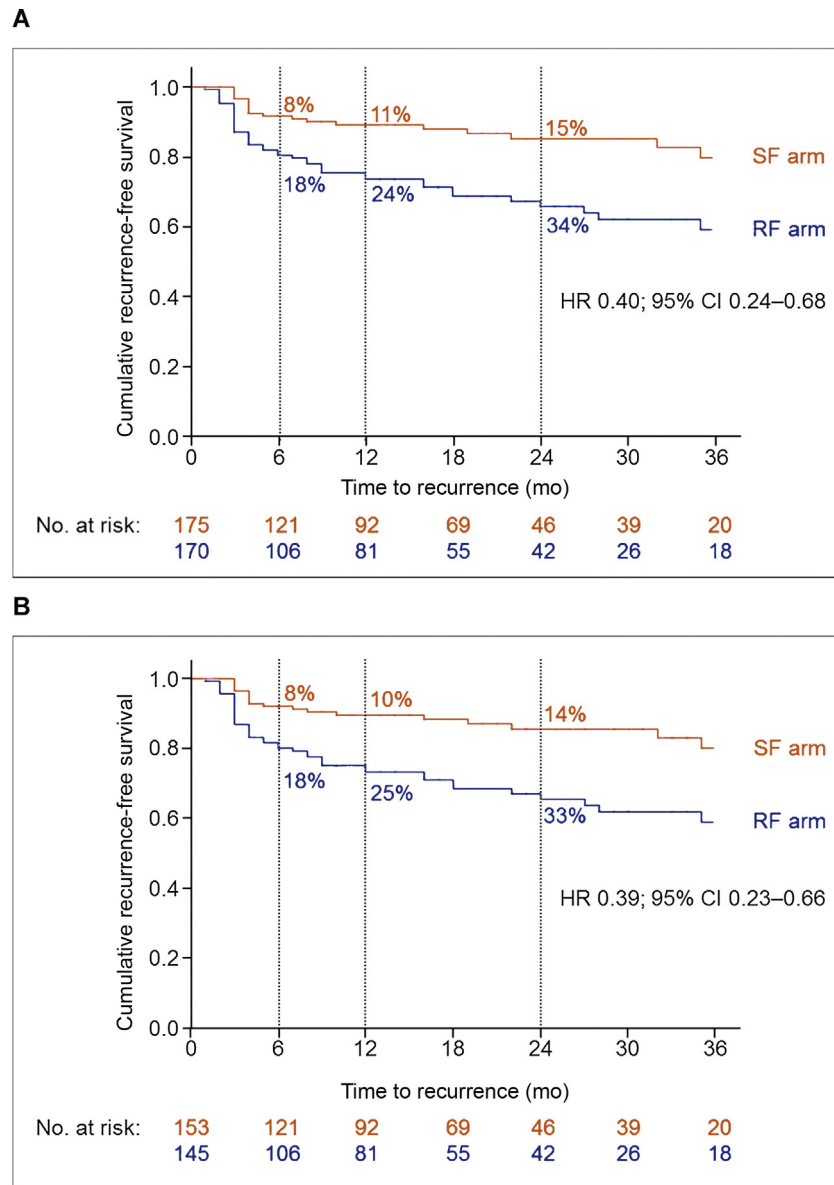
CUETO 98013 showing that one maintenance instillation is insufficient, BCG instillations were applied at wks 1 and 3 for maintenance in our study. One year of maintenance was applied, as this is considered the minimally required time span [4,5] and as 3 yr of maintenance has only a slight impact on recurrence but not on progression [7].

However, the results clearly reveal an increased recurrence rate in the RF arm. The upper boundary of the one-sided 97.5% CI was 0.68, meeting the predefined stopping rule of NIMBUS of 0.75. After a median follow-up time of 12 mo, a relative risk reduction for recurrence of 60% in favour of SF-BCG was observed. Of the 46 recurrences in the experimental arm, 27 occurred during the first 6 mo, leading to early separation of the curves (Fig. 2) and suggesting that the reduced number of BCG instillations during the induction phase was detrimental to efficacy and therefore potentially harmful.

Urine samples were collected from 44 patients to evaluate cytokine response following BCG instillations. Their analyses are on-going and will enable investigation of cytokines induced by Th1- and Th2-mediated immune response.

In the RF arm, more often an abnormal cystoscopy or cytology showing suspicious or evidently malignant cells preceded an unscheduled TUR (78/82 vs 69/77). This goes along with the detection of a higher number of tumours in the RF arm. A diagnostic bias cannot be excluded as the interpretation of cystoscopy or cytology is subjective. However, this appears unlikely given the magnitude of difference between treatment arms.

NIMBUS is the first prospective trial using routine re-TUR prior to BCG induction in line with the current EAU guideline recommendation, which is, however, mainly based on retrospective analyses [19,20]. While re-TUR was initially required in all patients, it was later abandoned



**Fig. 2** – Kaplan-Meier survival analysis displaying time to recurrence (time between randomisation and date of first recurrence or last follow-up) in (A) all patients (intention-to-treat analysis) and (B) patients observed for at least 6 mo since their randomisation in the study. CI = confidence interval; HR = hazard ratio; RF = reduced frequency arm; SF = standard frequency.

for completely resected and histopathologically confirmed Ta tumours. Nevertheless, overall 91% of the patients underwent re-TUR prior to BCG induction therapy. This may have contributed to the very low recurrence rate in the standard BCG arm (estimated recurrence rates 11% and 15% at 12 and 24 mo, respectively). This is much lower than expected when considering both the EORTC risk tables based on patients without BCG maintenance and re-TUR [1] and the CUETO risk tables based on patients receiving maintenance but no routine re-TUR [21].

Regarding tumour progression, very few events were recorded, probably due to the short follow-up time. In general, we found an expected level of toxicity. Fewer patients were affected with fewer AEs in the reduced treatment arm than in the standard arm. The final analysis

of NIMBUS with longer follow-up will provide more mature information and allow a more detailed analysis.

One limitation of NIMBUS is the lack of a central pathology review. This could have reduced the risk of inclusion of patients with minimal muscle-invasive disease or urothelial carcinoma with variant histology. A central review might have also led to a more objective discussion on the necessity of a radical cystectomy in certain patients with high-risk adverse clinical and/or pathological features such as the presence of lymphovascular invasion, larger tumour size, or a high number of tumours. Re-TUR could theoretically have influenced the course of the disease in both treatment arms, especially as fewer patients in the RF arm underwent re-TUR than in the SF arm. Another limitation is the unstratified use of photodynamic diagnostics (allowed

**Table 2 – Patient outcomes.**

	RF arm (n = 170)	SF arm (n = 175)
End of study	69	52
Recurrence	46	21
Progression to $\geq T2^a$	1	6
Distant metastases	0	1
Deaths	7 <sup>b</sup>	3 <sup>c</sup>

RF arm = reduced frequency arm; SF arm = standard frequency arm.

<sup>a</sup> At first recurrence.

<sup>b</sup> None related to study drug: one patient, autoimmune encephalitis or paraneoplastic syndrome; one patient, pulmonary embolism; one patient, sepsis; five patients, other reasons.

<sup>c</sup> None related to study drug: one patient, acute cardiac death; two patients, other reasons.

**Table 3 – Treatment duration at the time of analysis.**

Randomised Treatment received <sup>b</sup>	RF arm, n (%) <sup>a</sup> n = 170 n = 165	SF arm, n (%) <sup>a</sup> n = 175 n = 165
Induction wk 1	165 (100)	165 (100)
Induction wk 2	163 (99)	165 (100)
Induction wk 3	–	163 (99)
Induction wk 4	–	162 (98)
Induction wk 5	–	159 (96)
Induction wk 6	154 (93)	157 (95)
Maintenance mo 3 wk 1	117 (71)	137 (83)
Maintenance mo 3 wk 2	–	131 (79)
Maintenance mo 3 wk 3	112 (68)	125 (76)
Maintenance mo 6 wk 1	99 (60)	116 (70)
Maintenance mo 6 wk 2	–	112 (68)
Maintenance mo 6 wk 3	96 (58)	107 (65)
Maintenance mo 12 wk 1	72 (44)	85 (52)
Maintenance mo 12 wk 2	–	81 (49)
Maintenance mo 12 wk 3	69 (42)	80 (48)

BCG = bacillus Calmette-Guérin; RF arm = reduced frequency arm; SF arm = standard frequency arm.

SF arm: one patient missed induction at wk 3, one patient missed induction at wk 5, nine patients missed one dose of BCG, and one patient missed two doses of BCG during maintenance.

RF arm: one patient missed induction at wk 6, one patient missed one dose of BCG, and two patients missed two doses of BCG during maintenance.

<sup>a</sup> Percentage referred to patients treated at least once with BCG.

<sup>b</sup> At the time of analysis (July 1, 2019).

by investigator decision), which has been shown to decrease the risk of bladder cancer recurrence [22].

After reviewing the current data analysis, the IDMC advised stopping the study, as the upper limit of the one-sided 97.5% CI of the HR regarding recurrence fell below 0.75. The scientific committee immediately stopped patient recruitment, and study end was set to the time point of completion of the visit at mo 6, wk 3 for all patients. Patients were informed, and those still treated in the RF arm were given the opportunity to switch to the standard schedule.

## 5. Conclusions

The NIMBUS RF schedule was inferior to the standard schedule regarding time to first recurrence. In patients with high-grade NMIBC, this study supports the use of the

standard BCG regimen as recommended by the EAU guideline (6 wk of induction followed by 3 wk of maintenance at 3, 6, and 12 mo) after complete tumour resection.

**Author contributions:** Marc-Oliver Grimm had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Babjuk, Martínez-Piñero, Palou, Patel, Türkeri, Grimm, Witjes.

**Acquisition of data:** Grimm, van der Heijden, Colombel, Muilwijk, Martínez-Piñero, Babjuk, Türkeri, Palou, Patel, Bjartell, Witjes.

**Analysis and interpretation of data:** Grimm, Caris, Witjes.

**Drafting of the manuscript:** Grimm, Caris, Witjes.

**Critical revision of the manuscript for important intellectual content:** Grimm, van der Heijden, Colombel, Muilwijk, Martínez-Piñero, Babjuk, Türkeri, Palou, Patel, Bjartell, Caris, Schipper, Witjes.

**Statistical analysis:** Caris.

**Obtaining funding:** Witjes, Grimm, Colombel.

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**Supervision:** Witjes, Schipper, Grimm, Caris.

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