Radiofrequency-induced thermo-chemotherapy effect versus a second course of Bacillus Calmette-Guérin or institutional standard in patients with recurrence of non–muscle-invasive bladder cancer following induction or maintenance Bacillus Calmette-Guérin therapy (HYMN)

Tan, Wei Shen; Panchal, Anesh; Buckley, Laura; Devall, Adam J.; Loubiere, Laurence S.; Pope, Ann M.; Feneley, Mark R.; Cresswell, Jo; Issa, Rami; Mostafid, Hugh; Madaan, Sanjeev; Bhatt, Rupesh; McGrath, John; Sangar, Vijay; Griffiths, T. R.; Leyshon; Page, Toby; Hodgson, Dominic; Datta, Shibendra N.; Billingham, Lucinda J.; Kelly, John D.

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Radiofrequency-induced thermo-chemotherapy effect (RITE) versus a second course of bacillus Calmette-Guérin (BCG) or institutional standard in patients with recurrence of non-muscle invasive bladder cancer following induction or maintenance BCG therapy (HYMN): A phase III, open-label, randomised controlled trial

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ABSTRACT

Background

There is no effective intravesical second-line therapy for non-muscle invasive bladder cancer (NMIBC) when bacillus Calmette-Guérin (BCG) fails.

Objective

To compare disease-free survival time (DFS) between radiofrequency-induced thermo-chemotherapy effect (RITE) and institutional standard second-line therapy (control) in NMIBC patients with recurrence following induction/maintenance BCG.

Design, settings, and participants

Open-label, phase III randomised controlled trial accrued across 14 centres between May 2010 and July 2013 [HYMN (ClinicalTrials.gov: NCT01094964)].

Interventions

Patients were randomly assigned (1:1) to RITE (60min, 40mg mitomycin-C, 42±2°C) or control following stratification for CIS status (present/absent), therapy history (failure of previous induction/maintenance BCG) and treatment centre.

Outcome measurements and statistical analysis

Primary outcome measures were DFS and complete response (CR) at three months for the CIS at randomisation subgroup. Analysis was by intention-to-treat.

Results and limitations

A total of 104 patients were randomised (48 RITE: 56 control). Median follow-up for the 31 patients without a DFS event was 36 months. There was no significant difference in DFS between treatment arms (HR 1.33, [95% CI 0.84-2.10], p=0.23) or in three-month CR rate in CIS patients (n=71; RITE: 30% vs control: 47%, p=0.15). There was no significant difference in DFS between treatment arms in non-CIS patients (n=33; RITE: 53% vs control: 24% at 24 months, HR 0.50 [0.22-1.17], p=0.11). DFS was significantly lower in RITE compared to control in CIS with/without papillary patients (n=71; HR 2.06 [1.17-3.62], p=0.01; treatment-subgroup interaction p=0.007. Disease progression was observed in 4 patients in each treatment arm.
Adverse events and health-related quality-of-life between treatment arms were comparable.

**Conclusion**

DFS was similar between RITE and control. RITE may be a second line therapy for non-CIS recurrence following BCG failure although confirmatory trials are needed. RITE patients with CIS with/without papillary had lower DFS compared to control. HYMN highlights the importance of the control arm when evaluating novel therapies.

**Patient summary**

This study did not show a difference in bladder cancer outcomes between microwave heated chemotherapy and standard of care treatment. Papillary bladder lesions may benefit from microwave heated chemotherapy treatment, but more research is needed. Both treatments are similarly well tolerated.

Key words: bladder cancer, BCG failure, chemotherapy, device assisted therapy, hyperthermia, mitomycin-C, radiofrequency, randomised controlled trial, thermotherapy
1. INTRODUCTION

Non-muscle invasive bladder cancer (NMIBC) represents 75% of bladder cancer and adjuvant intravesical bacillus Calmette Guérin (BCG) is recommended for high risk NMIBC following transurethral resection (TUR) of papillary urothelial carcinoma or as ablative therapy for carcinoma in situ (CIS).

Despite maintenance BCG therapy, 55% of NMIBC patients develop recurrence and 20% progress to muscle invasive bladder cancer (MIBC) within 5 years [1]. Guidelines advocate early cystectomy or re-challenge with BCG following BCG failure [2-4]. Although early cystectomy is the standard of care, it remains a morbid procedure with a 90-day mortality of between 3.0-6.9% [5, 6]. Guidelines recommending re-challenging with BCG accept its limited efficacy and there is insufficient evidence to recommend the use of other intravesical agents [4, 7]. Radical radiotherapy is not effective for NMIBC [8].

Radiofrequency-induced thermo-chemotherapy effect (RITE) is a promising therapy for NMIBC. RITE delivers hyperthermia to the bladder wall potentiating chemotherapy cytotoxic effects and increases drug absorption by the formation of tunnelling microtubules [9, 10]. A recent randomised controlled trial (RCT) of BCG naïve NMIBC report a significantly higher 24-month RFS in RITE compared to BCG treated patients (82% vs 65%, p=0.02) in per-protocol analysis (PPA) consistent with previous studies [11, 12].

There has been no RCT comparing RITE to control in patients with recurrence of NMIBC following failure of induction/maintenance BCG. We report the results of HYMN, a phase III RCT comparing RITE to control defined as a second course of BCG or institutional standard in patients with NMIBC recurrence following induction or maintenance BCG (ClinicalTrials.gov: NCT01094964, CRUK/09/012).
2. METHODS

2.1 Trial design

HYMN is an open-label, two-arm, phase III RCT performed in accordance with the Declaration of Helsinki. Fourteen institutions throughout the UK participated in the trial (Supplementary Table 1). Appropriate ethical review board approved the trial protocol (v4.0) at all recruiting sites (IRAS 10306).

2.2 Patients

Patients with recurrence of intermediate or high risk NMIBC according to European Association of Urology (EAU) guidelines following induction/ maintenance BCG were eligible [2]. All patients had complete TUR of papillary lesions and in pT1 disease underwent re-resection to confirm the absence MIBC. Other inclusion criteria were age ≥18 years, WHO performance status ≤4 and patients unfit or unwilling to have radical cystectomy. All patients had imaging to exclude upper tract disease ≤12 months. Haematological and biochemical blood tests were within normal limits.

Key exclusion criteria included non-urothelial carcinoma, low grade NMIBC recurrence, treatment with intravesical chemotherapy ≤6 months (single post-TUR instillation allowed), prostatic urethra or upper tract disease, known mitomycin-C allergy, active/ intractable urinary tract infection, urethral stricture, small bladder capacity (<250 ml), significant urinary incontinence or history of pelvic radiotherapy.

2.3 Randomisation and masking

Patients were randomised (1:1 ratio) using a random treatment allocation sequence generated by the Cancer Research UK Clinical Trial Unit (CRCTU), University of Birmingham, which was concealed from participants and accessed by telephone using a central computerised randomisation service at CRCTU. Randomisation was stratified by CIS status (present/absent), therapy history (failure of previous induction/ maintenance BCG) and treatment centre. An independent Data Monitoring Committee (DMC) was appointed to oversee the safety and monitor the interim efficacy of treatment arms within the trial.

2.4 Interventions

Patients allocated to the experimental arm received six-weekly induction instillations of RITE using the Synergo® SB-TS 101 System [13, 14]. Treatment comprise of two
30-minute cycles, each with 20mg MMC (50 ml sterile water) at 42±2°C (40mg MMC in total) in accordance with the manufacturer’s guidance [15]. Dose reduction was not permitted. Patients disease-free three months after treatment commencement would proceed to maintenance RITE (one instillation of RITE every six weeks for year one and one instillation every eight weeks for year two).

Patients allocated to the control arm received either six consecutive weekly BCG instillations (50ml normal saline) followed by maintenance therapy (three consecutive weekly instillations at three, six, 12, 18 and 24 months) or institutional standard of care defined at randomisation. All patients were followed up for a minimum of 24 months at three monthly intervals comprising of physical examination, cystoscopy and urine cytology.

### 2.5 Outcomes

Co-primary outcome measures were disease-free survival time (DFS) for all patients and 3-month complete response (CR) for patients with biopsy-proven CIS at randomisation. DFS was determined as time from randomisation to earliest detection of histologically confirmed recurrence, positive urinary cytology or death. Three-month CR for patients with CIS was defined as absence of visible tumour at cystoscopy, negative urinary cytology and no CIS on random bladder biopsy.

Secondary outcome measures include: progression-free survival time (PFS), overall survival time (OS) and disease-specific survival time (DSS) in all patients; recurrence-free survival time (RFS) in non-CIS patients and safety and tolerability of RITE. Adverse events were recorded according to the NCI Common Toxicity Criteria of Adverse Events v4.0. Health related quality of life (HRQoL) was assessed at trial entry and three months intervals for 12 months using EQ-5D [16].

### 2.6 Statistical analyses

Statistical analyses were based on intention-to-treat (ITT). PPA was defined as patients receiving ≥6 treatments. Kaplan-Meier method was used to assess time-to-event outcomes. As the primary analysis, treatment arms were compared using log-rank test with a univariable Cox regression model used to determine unadjusted hazard ratios (HR). Secondary analysis used multivariable Cox regression model with stratification factors (CIS status and therapy history) included as covariates to
give adjusted HRs and p-values as a sensitivity analysis. Pre-specified subgroup analysis was used to assess treatment effects separately within each stratification factor and they were compared using a treatment-subgroup interaction term alongside their individual terms in a multivariable Cox regression model. CR rates are compared using an odds ratio (OR) and Fishers Exact test for patients with CIS at randomisation.

The original sample size calculations anticipated that 242 patients with 81 events per arm would be required to detect an increase in DFS at 24 months from 45% to 60% (HR of 0.64) and in an embedded subgroup analysis of CIS patients, at least 27 patients per arm would be required to detect an increase in three-month CR from 40% to 80% (both 80% power, 5% two-sided significance). Statistical analysis was performed using Stata v14. Statistical significance was considered when p<0.05. The study conferred to CONSORT guidelines.
3. RESULTS

3.1 Patients

The HYMN trial closed prematurely on February 2014 following a joint decision by the independent DMC and trial steering committee (TSC) due to a higher than expected CIS recurrence in RITE treated patients. A total of 104 patients (48 RITE vs 56 control) were randomised between May 2010 and July 2013 (Figure 1). Follow-up ended on July 2017.

Baseline patient characteristics were well balanced across treatment arms (Table 1). There was a higher proportion of papillary disease with concurrent CIS randomised to RITE compared to control (25% vs 18%, p=0.38). There was no difference in patients who had random biopsies at 3 months between treatment arms. At trial conception, it was estimated that 22% of patients would have CIS at baseline. However, the actual proportion was 68% (n=71). High risk NMIBC was defined in 83% and 89% of the RITE and control arm respectively.

3.2 Efficacy

Disease-free survival analysis includes 73 events; 42 patients developed disease recurrence, 15 had recurrent CIS, 5 had disease progression and 11 patients died. Median follow-up time for the 31 patients without any of these DFS events was 36 months with only 4 patients less than 24 months follow-up. No significant overall benefit was observed in DFS when comparing RITE to control (Figure 2a) with 24-month DFS rate 35% versus 41% respectively (HR 1.33 [95% CI 0.84-2.10], p=0.23) (adjusted p=0.49). In the pre-planned co-primary analysis, there was no significant difference in the complete response rate of CIS at 3 months between RITE and control arms (30% vs 47%, OR 0.43 [95% CI 0.18-1.28], p=0.15). Pre-planned subgroup analysis showed that DFS of RITE treated patients were significantly lower than control in patients with baseline CIS (HR 2.06 [95% CI 1.17-3.62], p=0.01; Figure 2b). There was a non-significant higher DFS favouring RITE compared to control in non-CIS patients at baseline (HR 0.50 [95% CI 0.22-1.17], p=0.11; Figure 2c). This treatment-subgroup interaction was statistically significant (p=0.007, Figure 3). DFS in non-CIS patients at 24-months for RITE and control patients were 53% and 24% respectively.
The results for PPA were similar to ITT (Supplementary Figure 1). Subgroup analysis of previous BCG showed no significant treatment-subgroup interaction (Figure 3). Exploratory analysis of the effect of RITE on patients with CIS at baseline showed that the detrimental effect on DFS was marked in those with concurrent papillary and CIS disease (n=22) compared to those with CIS only (n=49) (Figure 3). There was no evidence of a differential treatment effect in CIS only patients (HR 1.53 [95% CI 0.77-3.05], p=0.22). No difference between RITE and control was observed in PFS (8 patients with progression, 24-month rates 83% vs 87%, p=0.16), OS (30 deaths, 24-month rates 85% vs 90%, p=0.18), and RFS (27 patients with disease recurrence in the 55 with papillary disease, 24-month rates 23% vs 40%; p=0.98) but a borderline difference in DSS (24-month rates 89% vs 96%; p=0.04) (Supplementary Table 2).

3.3 Safety

41 RITE patients and 48 control patients were included in the PPA. Five RITE patients did not complete ≥6 instillations due to adverse events: skin rash, urinary urgency and nocturia, inability to catheterise (n=2), haematuria, and patient refusal of treatment while five control arm patients were excluded due to the following adverse events: urinary urgency (n=2), persistent dysuria, haematuria, and patient refusal of treatment. Two patients in the RITE arm did not receive treatment: patient choice (n=1) and ineligibility post-randomisation (n=1). Three patients in the control arm were not treated: patient choice (n=2) and significant incontinence (n=2) after randomisation.

One or more adverse events occurred in 84 (81%) patients (42 RITE patients vs 42 control patients). No difference in adverse events between each treatment modality was observed (Table 2). Most adverse events were grade 1-2. There were two grade 4 toxicity in the control arm which was due to arthritis and the other BCG related sepsis resulting in death. No difference in health-related quality of life was observed between the two treatment arms although RITE patients rated their health status higher than controls at three, six and nine months follow-up (Figure 4).
4. DISCUSSION

The aim of the HYMN was to determine if RITE is superior to standard of care in patients with recurrence of NMIBC following BCG. HYMN was a pragmatic study and in the absence of standard of care for this patient cohort who refuse cystectomy, pre-planned treatment plan for control was determined by the local institution. HYMN remains the only RCT to test a novel therapy in this patient cohort. The trial showed no difference in DFS between RITE and standard therapy in all patients and three-month CR rate in CIS patients at baseline. Pre-planned subgroup analysis of DFS showed RITE was beneficial in non-CIS patients (RITE 53% vs control 24% at 24-months) although this was not statistically significant.

A post-hoc analysis shows a higher number of concurrent papillary and CIS tumours in the RITE arm compared to control (25% versus 18%, p=0.38). The presence of CIS with papillary disease is associated with an increased risk of disease recurrence and progression and genomic studies suggest that these patients are genotypically similar to MIBC [17, 18]. It is plausible that patients with concurrent papillary and CIS have a significant risk of disease progression regardless of treatment modality.

The rationale for hyperthermia follows *in vitro* and clinical studies which showed that increase in chemotherapy temperature can promote tissue permeation, promoting better drug absorption and synergistically increased tumour cell apoptosis [9]. Previous RCT data suggest a benefit for RITE compared to BCG or MMC in BCG naïve patients [11, 19]. In HYMN, we report that RITE treated non-CIS NMIBC patients had a lower DFS compared to control although this was not significant. In a predominantly non-CIS cohort (1.2% CIS), Colombo *et al*. reported that RITE had a higher 24-month RFS compared to MMC alone (83% vs 43%, p<0.001) and a durable response at 10-year RFS (53% vs 15%, p<0.001) [19, 20].

Arends *et al*. randomised 190 patients to either RITE or BCG, both with maintenance therapy [11]. The proportion of patients with high risk disease was 31% (57/184) and 23% (42/184) of patients had CIS at randomisation. In ITT analysis, Arends *et al*. reported a higher but non-significant 24-month RFS favouring the RITE compared to BCG (78% vs 65%, p=0.08) in non-CIS disease. A PPA showed a significant benefit favouring RITE compared to BCG (81% vs 65%, p=0.02) however outcome for CIS patients were not reported [11]. The non-CIS RITE treated patients in HYMN hints
towards similar results although there were only 33 patients in this pre-planned subgroup analysis.

An important finding in HYMN is the efficacy of the control arm. A single arm study of Valrubicin in 90 cases of BCG-refractory CIS reported a 90-day CR rate of 21% which was sufficient evidence for FDA approval [21]. A Food and Drug Administration (FDA) public workshop and the International Bladder Cancer Group (IBCG) recommended that a single arm study design is sufficient to provide evidence of efficacy in the setting of recurrence following BCG therapy [22, 23]. Both the FDA-AUA workshop and IBCG felt that a six-month CR rate of 40-50% and a RFS of ≥25-30% at 18-24 months in BCG refractory-CIS would be clinically meaningful [22, 23]. Both RITE and control arm in HYMN achieved a 24-month DFS of 35% and 41% respectively, which was better than Valrubicin and above the recommended threshold for clinically meaningful effect although patients in HYMN would have a better prognosis as BCG relapsing and intolerant patients were included. We would caution that a control arm remains important for the design of studies to assess efficacy of novel agents in the setting of BCG failure NMIBC.

Study limitations include that HYMN closed early at interim analysis and did not reach its recruitment target. Patients treated with RITE had 40 mg MMC which was consistent with the dosage used in two previous RCTs [11, 19]. A single arm study of RITE with 80mg MMC to treat CIS report a DFS of 86% with a mean follow-up of 26 months suggest that a higher MMC dose might be more effective [24]. Up to 23% of patients in the control group received EMDA MMC which may be more effective than challenging to BCG although efficacy between these two treatments are similar in the randomised trial [25]. HYMN recruited a heterogenous group of BCG refectory, resistance and intolerance as this trial commenced before the FDA-AUA recommendations [23].
5. CONCLUSIONS

DFS was similar between RITE and control treated patients. HYMN suggest the potential for RITE as a second line therapy for non-CIS recurrence following BCG although confirmatory trials are needed. RITE treated patients with CIS with/without papillary had lower DFS compared to control. RITE is well tolerated compared to control. HYMN highlights the importance of the control arm when evaluating novel therapies.
HYMN primary analysis prepared for European Urology

Funding
Cancer Research UK, Medical Enterprises Europe, Kyowa Kirin Pharmaceutical Development Ltd.

Ethical approval of studies and informed consent
The trial received ethical approval from the UK Multicentre Research Ethics Committee and regulatory approval from the UK Medicines and Healthcare Regulatory Agency in October 2009. In addition, each participating centre obtained local institutional review board approval. Written consent was obtained from all study participants.

Declaration of intent and financial disclosures
John D Kelly is a consultant for Combat Medical outside submitted work. Wei Shen Tan has received travel support to attend conferences from Combat Medical and Medical Enterprises Europe B.V. Jo Cresswell reported personal fees from honorarium from ProStraken for a teaching course outside the submitted work. TR Leyshon Griffiths reported personal fees from Prostrakan, Combat Medical and Ipsen outside the submitted work. Lucinda Billingham reported personal fees from Astra Zeneca, Eli Lilly, Celgene, Pfizer and Roche outside the submitted work. All other authors report nothing to disclose.

Role of the Funder/Sponsor
This trial was clinician-initiated and led, sponsored by the University College London. Cancer Research UK funded the trial administration (trial number CRUK/09/012). Kyowa Kirin Pharmaceutical Development Ltd. provided funds which helped to fund the procurement and maintenance costs of the Synergo system. Medical Enterprises Europe B.V. supplied the Synergo system at a discounted rate and its associated disposables to the participating sites. None of the funders had a role in the study design, data collection, data analysis, data interpretation, writing of the report or the decision to submit the paper for publication.

Acknowledgment
We are indebted to all the patients who have participated in the HYMN trial and to many associates particularly other urologists, research nurses, pathologist and data manager for their assistance with this study. Acknowledgement and thanks go to
Jennifer Barnwell and Kathryn Paterson who were instrumental in the early
development and opening of the HYMN trial.
Figure 1: CONSORT diagram for the HYMN trial

Randomised N=104
Stratification based on treating centre, presence or absence of CIS and induction versus maintenance therapy

RITE N=48
Hyperthermia plus mitomycin (HM) followed by maintenance HM

N=2
Withdrawn before starting treatment

RITE N=46
Started treatment

N=2
Withdrawn before 3 months

RITE N=44
Reached 3 month surveillance

Control N=56
2nd course of BCG (BCG2) or Institutional Standard therapy

N=3
Withdrawn before starting treatment

Control N=53
Started treatment

Control N=53
Reached 3 month surveillance
Figure 2: Kaplan-Meier curves for disease-free survival time: (A) all randomised patients (n=104) [HR: 1.33, 95% CI: 0.84-2.10, p=0.23]; (B) Pre-planned subgroup analysis of all randomised patients with CIS at baseline (n=71) [HR: 2.06, 95% CI: 1.17-3.62, p=0.01]; (C) pre-planned subgroup analysis of all randomised patients without CIS at baseline (n=33) [HR: 0.50, 95% CI: 0.22-1.17, p=0.11].
HYMN primary analysis prepared for European Urology
Figure 3: Forest plot showing hazard ratios and 95% confidence intervals for disease-free survival time for pre-planned subgroup analysis of stratification factors (CIS status and previous BCG) and extended exploratory analysis of CIS status.
Figure 4: Mean EQ-5D score for RITE and control at baseline, 3, 6, 9 and 12 months
Table 1. Baseline characteristics of patients randomised

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RITE (n=48)</th>
<th>Control (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>34 (71%)</td>
<td>44 (79%)</td>
</tr>
<tr>
<td><strong>Age:</strong> Median (IQR)</td>
<td>77 (72-82)</td>
<td>76 (67-81)</td>
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<tr>
<td><strong>Smoking status:</strong></td>
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<tr>
<td>Never</td>
<td>15 (31%)</td>
<td>16 (29%)</td>
</tr>
<tr>
<td>Previous</td>
<td>28 (58%)</td>
<td>39 (70%)</td>
</tr>
<tr>
<td>Current</td>
<td>5 (10%)</td>
<td>1 (1.8%)</td>
</tr>
<tr>
<td><strong>Histology</strong>*:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papillary only</td>
<td>15 (31%)</td>
<td>18 (32%)</td>
</tr>
<tr>
<td>Ta G2</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Ta G3</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>T1 G2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>T1 G3</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Papillary and CIS</td>
<td>12 (25%)</td>
<td>10 (18%)</td>
</tr>
<tr>
<td>Ta G1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Ta G2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Ta G3</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>T1 G3</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>CIS Only</td>
<td>21 (44%)</td>
<td>28 (50%)</td>
</tr>
<tr>
<td>Previous BCG*</td>
<td>Institution Standard</td>
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<tr>
<td>--------------</td>
<td>----------------------</td>
<td></td>
</tr>
<tr>
<td>Induction only (≤6 instillations)</td>
<td>Induction plus maintenance (&gt;6 instillations)</td>
<td></td>
</tr>
<tr>
<td>18 (38%)</td>
<td>30 (63%)</td>
<td>19 (34%)</td>
</tr>
</tbody>
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<table>
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<tr>
<th>Institutional Standard</th>
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<tbody>
<tr>
<td>BCG alone</td>
</tr>
<tr>
<td>MMC alone</td>
</tr>
<tr>
<td>EMDA MMC</td>
</tr>
<tr>
<td>33 (59%)</td>
</tr>
<tr>
<td>10 (18%)</td>
</tr>
<tr>
<td>13 (23%)</td>
</tr>
</tbody>
</table>

*CIS status (present or absent) and previous BCG therapy (induction only or induction plus maintenance) used as stratification variables at randomisation.
Table 2: Reported adverse events stratified by treatment.

<table>
<thead>
<tr>
<th></th>
<th>All grades</th>
<th></th>
<th>Grades 3/4</th>
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<tbody>
<tr>
<td></td>
<td>RITE</td>
<td>Control</td>
<td>RITE</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>N=48</td>
<td>N=56</td>
<td>N=48</td>
<td>N=56</td>
</tr>
<tr>
<td>Pain</td>
<td>46%</td>
<td>56%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Dysuria</td>
<td>54%</td>
<td>59%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Increased frequency</td>
<td>52%</td>
<td>54%</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Increased urgency</td>
<td>42%</td>
<td>48%</td>
<td>0%</td>
<td>4%</td>
</tr>
<tr>
<td>Incontinence</td>
<td>23%</td>
<td>18%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Nocturia</td>
<td>33%</td>
<td>38%</td>
<td>0%</td>
<td>4%</td>
</tr>
<tr>
<td>Haematuria</td>
<td>48%</td>
<td>36%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>33%</td>
<td>38%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Fever</td>
<td>13%</td>
<td>25%</td>
<td>0%</td>
<td>0%</td>
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<tr>
<td>UTI</td>
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References


