EUROPEAN UROLOGY 75 (2019) 593–601

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Bladder Cancer

Editorial by John L. Gore and Jonathan L. Wright on pp. 602–603 of this issue

BOXIT—A Randomised Phase III Placebo-controlled Trial Evaluating the Addition of Celecoxib to Standard Treatment of Transitional Cell Carcinoma of the Bladder (CRUK/07/004)

John D. Kelly [a,†,], Wei Shen Tan [a,†], Nuria Porta [b], Hugh Mostafid [c], Robert Huddart [b,d], Andrew Protheroe [e], Richard Bogle [f], Jane Blazeby [g], Alison Palmer [h], Jo Cresswell [i], Mark Johnson [j], Richard Brough [k], Sanjeev Madaan [l], Stephen Andrews [m], Clare Cruickshank [b], Stephanie Burnett [b], Lauren Maynard [b], Emma Hall [b],*

on behalf of the BOXIT Investigators

[a] *University College London, London, UK;* [b] *The Institute of Cancer Research, London, UK;* [c] *Royal Surrey County Hospital NHS Foundation Trust, Guildford, UK;* [d] *The Royal Marsden NHS Foundation Trust, London, UK;* [e] *Oxford University Hospitals NHS Foundation Trust, Oxford, UK;* [f] *Epsom and St Helier University Hospitals NHS Trust, Carshalton, UK;* [g] *University of Bristol, Bristol, UK;* [h] *Royal Free London NHS Foundation Trust, London, UK;* [i] *South Tees Hospitals NHS Foundation Trust, Middlesbrough, UK;* [j] *The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK;* [k] *Stockport NHS Foundation Trust, Stockport, UK;* [l] *Dartford and Gravesham NHS Trust, Dartford, UK;* [m] *Dorset County Hospital NHS Foundation Trust, Dorchester, UK*

Article info

Article history:
Accepted September 11, 2018

Associate Editor:
James Catto

Statistical Editor:
Andrew Vickers

Keywords:
Bladder cancer
Chemoprevention
Cyclo-oxygenase 2 inhibitor
Randomised trial
Cardiovascular events

Abstract

Background: Non–muscle-invasive bladder cancer (NMIBC) has a significant risk of recurrence despite adjuvant intravesical therapy.
Objective: To determine whether celecoxib, a cyclo-oxygenase 2 inhibitor, reduces the risk of recurrence in NMIBC patients receiving standard treatment.
Design, setting, and participants: BOXIT (CRUK/07/004, ISRCTN84681538) is a double-blinded, phase III, randomised controlled trial. Patients aged ≥18 yr with intermediate- or high-risk NMIBC were accrued across 51 UK centres between 1 November 2007 and 23 July 2012.
Intervention: Patients were randomised (1:1) to celecoxib 200 mg twice daily or placebo for 2 yr. Patients with intermediate-risk NMIBC were recommended to receive six weekly mitomycin C instillations; high-risk NMIBC cases received six weekly bacillus Calmette-Guérin and maintenance therapy.
Outcome measurements and statistical analysis: The primary endpoint was time to disease recurrence. Analysis was by intention to treat.
Results and limitations: A total of 472 patients were randomised (236:236). With median follow-up of 44 mo (interquartile range: 36–57), 3-yr recurrence-free rate (95% confidence interval) was as follows: celecoxib 68% (61–74%) versus placebo 64% (57–70%; hazard ratio [HR] 0.82 [0.60–1.12], $p = 0.2$). There was no difference in high-risk (HR 0.77 [0.52–1.15], $p = 0.2$) or intermediate-risk (HR 0.90 [0.55–1.48], $p = 0.7$) NMIBC. Subgroup analysis suggested that time to recurrence was longer in pT1 NMIBC patients

† These authors are joint first authors.
* Corresponding author. Division of Surgery and Interventional Science, University College London, 3rd floor Charles Bell House, 43-45 Foley Street, London W1W 7TS, UK. Tel. +44(0)20 76796490; Fax: +44(0)20 76796470.
E-mail address: j.d.kelly@ucl.ac.uk (J.D. Kelly).

https://doi.org/10.1016/j.eururo.2018.09.020

treated with celecoxib compared with those receiving placebo (HR 0.53 [0.30–0.94], interaction test $p = 0.04$). The 3-yr progression rates in high-risk patients were low: 10% (6.5–17%) and 9.7% (6.0–15%) in celecoxib and placebo arms, respectively. Incidence of serious cardiovascular events was higher in celecoxib (5.2%) than in placebo (1.7%) group (difference +3.4% [–0.3% to 7.2%], $p = 0.07$).

Conclusions: BOXIT did not show that celecoxib reduces the risk of recurrence in intermediate- or high-risk NMIBC, although celecoxib was associated with delayed time to recurrence in pT1 NMIBC patients. The increased risk of cardiovascular events does not support the use of celecoxib.

Patient summary: Celecoxib was not shown to reduce the risk of recurrence in intermediate- or high-risk non–muscle-invasive bladder cancer (NMIBC), although celecoxib was associated with delayed time to recurrence in pT1 NMIBC patients. The increased risk of cardiovascular events does not support the use of celecoxib.

1. Introduction

Bladder cancer represents the ninth most common cancer with 429 000 new cases per year worldwide [1]. Over 75% of new cases are non–muscle-invasive bladder cancer (NMIBC), and following tumour resection, 28–52% of patients develop recurrence within 5 yr [2]. Efforts to reduce recurrence of NMIBC include the use of intravesical chemotherapy and bacillus Calmette-Guérin (BCG) [3,4].

Cyclo-oxygenase (COX) enzyme controls a rate-limiting step implicated in carcinogenesis by regulating the conversion of arachidonic acid to prostaglandin E2 (PGE2) and inhibits apoptosis by overexpressing Bcl-2 [5].COX-2 inhibition results in cell cycle arrest, triggering apoptosis in in vitro studies [6]. A population-based case-controlled study reported that patients taking regular nonsteroidal anti-inflammatory drugs (NSAIDs) had a lower risk of developing bladder cancer (odds ratio 0.81, 95% confidence interval [CI]: 0.68–0.96) compared with patients with non- or irregular NSAID use [7]. Consistent with this, COX-2 is overexpressed in bladder cancer compared with normal urothelium, and COX-2 expression is associated with disease recurrence and progression [8].

A phase II randomised controlled trial (RCT) comparing celecoxib, a selective COX-2 inhibitor, with placebo in recruited high-risk NMIBC patients who received adjuvant BCG was reported by Sabichi and colleagues [9]. It was powered to detect a large treatment effect of 53% relative reduction in recurrence at 12 mo but failed to show a difference [9]. Further, the study did not assess health-related quality of life (HRQOL). The BOXIT study (ISRCTN84681538) sought to determine whether celecoxib in combination with standard therapy is more effective in reducing the risk of disease recurrence than standard therapy alone for the treatment of intermediate- or high-risk NMIBC.

2. Patients and methods

2.1. Trial design

BOXIT (CRUK/07/004) is a multicentre, phase III, randomised, double-blind, placebo-controlled trial sponsored by the Institute of Cancer Research. It was approved by London Central Multicentre Research Ethics Committee, and overseen by independent Trial Steering (TSC) and Data Monitoring Committees (IDMC).

2.2. Patients

All patients with primary or recurrent intermediate- or high-risk NMIBC according to European Association of Urology guidelines (2002) were eligible for the trial [10]. Patients had complete transurethral resection of bladder tumour (TURBT) for histopathological staging, and all pT1 diseases underwent re-resection to confirm the absence of detrusor tumour invasion. Patients were ≥18 yr old, with WHO performance status of ≤2 with no upper tract transitional cell carcinoma (TCC) confirmed by imaging within the past 36 mo, and had not received NSAIDs (other than low-dose aspirin ≤150 mg daily) or celecoxib for a minimum of 2 mo prior to entry. Haematological and biochemical blood tests were within adequate levels.

Key exclusion criteria include non-TCC NMIBC, tumour involving prostatic urethra or upper urinary tract, ≥pT2 TCC, known contra-indications to NSAIDs, pregnant or lactating women, adverse reactions to sulphonamides or NSAIDs, current or long-term use of NSAIDs and oral corticosteroids, malignancy within the past 2 yr, patients with known or suspected congestive heart failure (II–IV NYHA), cardiovascular (CV) disease, blood pressure of >160/100 mmHg, and/or patients with diabetes requiring insulin.

2.3. Randomisation and masking

Following TURBT, randomisation was performed by telephone to the Institute of Cancer Research's Clinical Trials and Statistics Unit (ICR-CTSU). Treatment was then allocated (1:1) using computer-generated random permuted blocks of size 6, stratified by treating centre and risk group. Treatment allocation was blinded to participants and investigators. The IDMC reviewed safety and efficacy of the trial blinded to treatment allocation. A cardiovascular safety committee (CVSC) was established to review unblinded CV safety data to advise in confidence the IDMC.

2.4. Interventions

Patients were randomised to either celecoxib 200 mg twice daily or placebo for 2 yr. It was recommended that all patients received standard-of-care single intravesical 40 mg in 40 ml of mitomycin C (MMC1) instillation within 24 h following TURBT unless contraindicated. High-risk patients received induction BCG (81 mg BCG, Connaught strain) comprising six weekly instillations, and maintenance therapy (three weekly instillations at 4, 6, 12, 18, 24, 30, and 36 mo) was recommended. Study treatment was commenced before BCG induction in high-risk patients. It was recommended that intermediate-risk patients received six weekly instillations of 40 mg MMC (MMC6). Disease recurrence was monitored by regular cystoscopies as per guidelines [3]. Centrally reviewed baseline elctrocardiography (ECG) was performed to confirm eligibility, with follow-up ECGs at 12 and 24 mo.

2.5. Outcomes

The primary endpoint was time to recurrence of bladder cancer, which was defined as time from randomisation to date of confirmation of cancer recurrence. Secondary efficacy endpoints included NMIBC recurrence rate in intermediate-risk patients, time to progression to invasive disease in high-risk patients, disease-free survival, and overall survival. For disease-related events and survival, patients event free or alive at the time of analysis were censored at their last available assessment.

Safety and tolerability of celecoxib were assessed by treatment compliance and reporting of adverse events, graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCIC-CTCAE v3.0), and recoded using MedDRA (v14.0).

HRQOL was assessed using the EORTC Quality of Life Questionnaire (EORTC QLQ-C30) [11] and the EORTC QLQ-BLS24 [12]. Patients completed questionnaires at baseline and at 12, 24, and 36 mo. High-risk patients also completed measures at 8 and 12 wk and at 6 mo.

2.6. Sample size and power

Estimating a recurrence-free rate (RFR) at 3 yr of 51% in the control arm, 206 patients per arm were required to detect a difference of 15%, with 85% power and two-sided alpha of 5% (hazard ratio [HR] of 0.63). Assuming noncompliance rates of 14.5% at 12 mo and 28% at 24 mo and that stopping trial treatment early halves the treatment effect, a revised target sample size of 475 patients (193 events) with 5% dropout and 80% power was selected.

2.7. Statistical analysis

Analyses of outcomes were on an intention-to-treat basis, and according to treatment received for safety and tolerability endpoints. Sensitivity analyses were performed on the per protocol (PP) population (≥12 mo of study drug or earlier if due to disease progression, drug toxicity, or death). Statistical significance was defined as $p = 0.05$, and 95% CIs were reported. Analyses were adjusted by risk group.

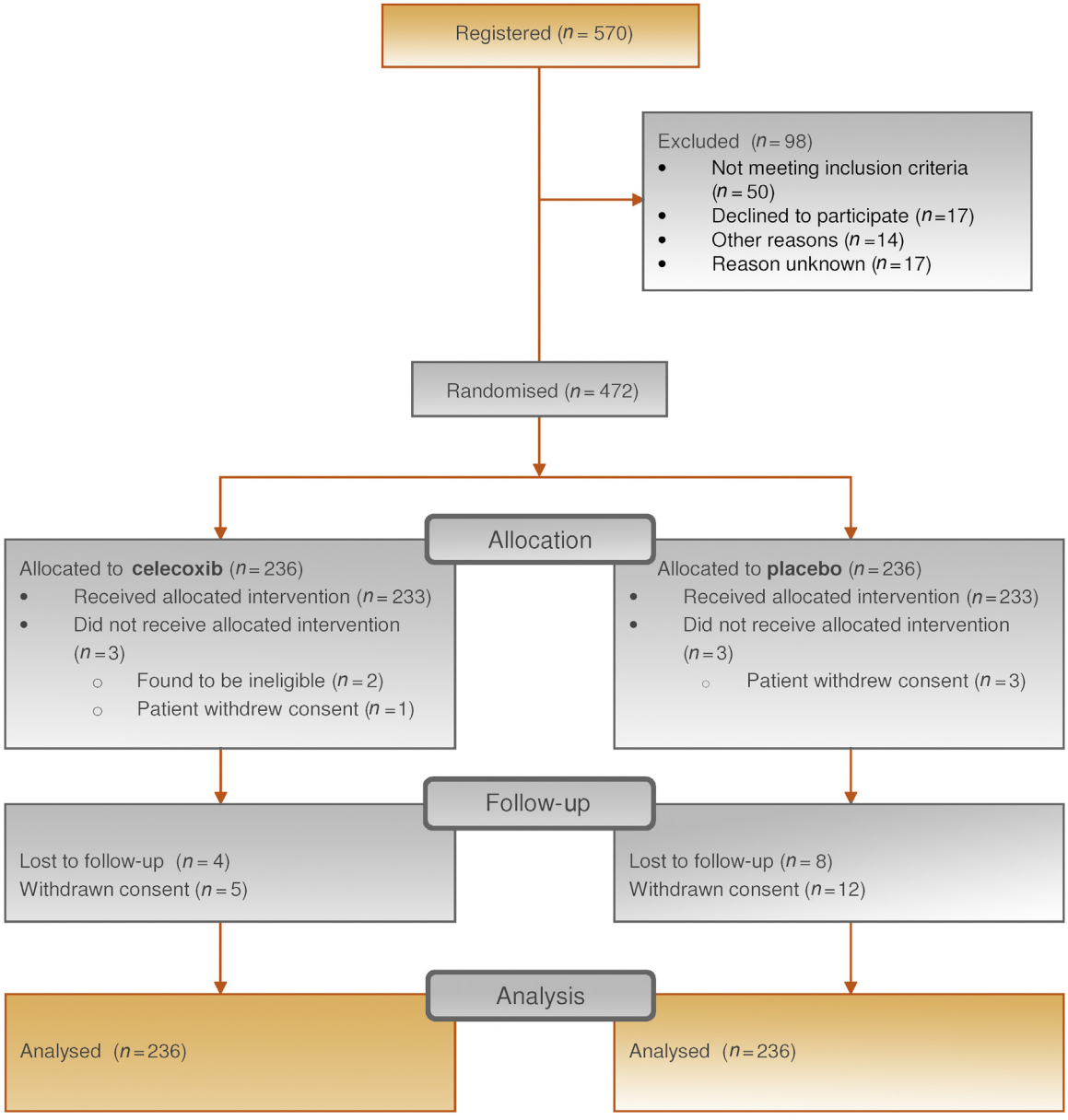

Fig. 1 – Trial profile—CONSORT diagram.

Time-to-event endpoints were summarised using Kaplan-Meier methods. Treatments were compared by the stratified log-rank test, and effect was estimated by stratified Cox models. Consistency of treatment effect was assessed in subgroup analyses. Proportional hazards were tested using Schoenfield residuals.

Worst CTCAE grade toxicities were summarised by treatment received. Incidence of ≥3 grade and that of serious CV events were compared by Fisher's exact test.

Treatment effect on HRQOL was obtained from analysis of covariance models. Only patients with paired baseline and time point data were analysed. A p value of <0.01 (and related 99% CIs) was deemed statistically significant to account for multiple comparisons.

Analyses were based on trial data up to 31 December 2014, and performed using STATA version 13.1 and R version 3.4.1.

3. Results

3.1. Patients

Between 1 November 2007 and 23 July 2012, 472 patients (236 celecoxib, 236 placebo) were recruited from 51 centres in the UK (Fig. 1). Demographics and clinical characteristics were evenly matched across treatment groups (Table 1). Additional baseline CV risk factors for both groups are reported in Supplementary Table 1.

A total of 177 (75%) patients in the celecoxib arm and 189 (80%) in the placebo arm took the study drug for ≥12 mo, with 120 (51%) and 144 (61%), respectively, completing

Table 1 – Baseline demographics and clinical characteristics by randomised group

	Celecoxib (*N* = 236)		Placebo (*N* = 236)		Total (*N* = 472)	
	N	%	*N*	%	*N*	%
Risk group						
High risk	167	71	179	76	346	73
Intermediate risk	69	29	57	24	126	27
Gender						
Male	188	80	186	79	374	79
Age						
Median (Q1–Q3)	66 (60–73)		68 (63–73)		67 (61–73)	
Smoking status						
Current	42	18	27	11	69	15
Never	70	30	75	32	145	31
Previous	122	52	130	55	252	53
Missing	2	0.8	4	1.7	6	1.3
Hypertension (systolic ≥140 and/or diastolic ≥90)						
Yes	134	57	131	56	265	56
No	95	40	101	43	196	42
Missing	7	3.0	4	1.7	11	2.3
Diabetes						
Yes	23	9.7	19	8.1	42	8.9
No	213	90	216	92	429	91
Missing	0	0.0	1	0.4	1	0.2
Histological stage at baseline						
Ta	113	48	96	41	209	44
T1	83	35	95	40	178	38
Tis	24	10	28	12	52	11
Ta/Tis	5	2.1	10	4.2	15	3.2
T1/Tis	11	4.7	7	3.0	18	3.8
Histological grade at baseline						
G1	14	5.9	14	5.9	28	5.9
G2	93	39	73	31	166	35
G3	112	48	126	53	238	50
Unknown	13	5.5	15	6.4	28	5.9
Missing	4	1.7	8	3.4	12	2.5
Number of tumours at baseline [a]						
<3	156	66	156	66	312	66
≥3	76	32	71	30	147	31
Missing	4	1.7	9	3.8	13	2.8
Tumour size at baseline (cm) [a]						
<3	75	32	74	31	149	32
≥3	94	40	94	40	188	40
Not known	67	28	68	29	135	28
Previous recurrence in the last 2 yr						
No	165	70	166	70	331	70
Yes	69	29	67	28	136	29
Not known	2	0.8	3	1.3	5	1.1

Q1 = first quartile (25% percentile); Q3 = third quartile (75% percentile).

[a] Numbers from histological diagnosis were used where available. If not available, numbers from visual diagnosis were used. When tumour size was reported "estimated/assumed ≥3 cm (n = 45)", it was included in ≥3 cm category.

Table 2 – Compliance with trial and standard-of-care treatments, by risk group and treatment arm

	High risk (*N* = 346)					Intermediate risk (*N* = 126)				
	Celecoxib		Placebo		*p* value	Celecoxib		Placebo		*p* value
	N	%	*N*	%		*N*	%	*N*	%	
No. of patients	167	100	179	100		69	100	57	100	
Compliance with trial treatment										
Completed as planned (24 m)	76	46	102	57	0.03	44	64	42	74	0.2
Reasons for noncompliance										
Disease progression	21	13	25	14	0.1 [a]	3	4.3	1	1.7	0.6 [a]
AE/tolerability	26	16	16	8.9		10	15	4	7.0	
Loss to follow-up	0	0	0	0		0	0.0	1	1.7	
Patient/clinician decision	20	12	17	9.5		3	4.3	4	7.0	
Early cessation IMP Dec 2013	12	7.2	16	8.9		4	5.8	2	3.5	
Other	12	7.2	3	1.7		5	7.3	3	5.3	
Completed at least 12 mo of treatment	118	71	139	78	0.1	59	86	50	88	0.7
MMC1										
MMC1 given	89	53	98	55	0.8	37	54	33	58	0.6
MMC6										
Full MMC6 received	Not applicable					28	41	32	56	0.08
BCG induction										
Full BCG6 induction received	139	83	144	81	0.5	10	15	5	8.8	0.3
BCG (overall)										
None	12	7.2	13	7.3	0.9	59	86	52	91	0.6
Only Induction	19	11	23	13		0	0	0	0	
1–3 BCG maintenance courses	74	44	74	41		4	5.8	2	3.5	
4–7 BCG maintenance courses	62	37	69	39		6	8.7	3	5.3	

AE = adverse event; BCG = bacillus Calmette-Guérin; BCG6 = BCG induction; MMC1 = single instillation of mitomycin C after transurethral resection; MMC6 = maintenance mitomycin C.
[a] Chi = square test *p* value on noncompliant patients only.

24 mo of study treatment (Table 2). In December 2013, the trial stopped for futility, and given a small increased risk of CV event in patients on celecoxib, the CVSC, IDMC, and TSC recommended halting recruitment of patients still on study treatment (6.8% celecoxib, 7.6% placebo). Follow-up continued until maturity of data at 3 yr median follow-up.

Compliance with standard-of-care treatments, by risk group and treatment arm, is also shown in Table 2. The proportion of high-risk patients receiving BCG maintenance decreased with time from 61% at month 4 (65% celecoxib, 58% placebo) to 13% at month 36 (13% celecoxib, 12% placebo). Fifteen patients in the intermediate group (12%) received full BCG6 induction by physician choice.

3.2. *Recurrence-free rate*

At median follow-up of 44 mo (interquartile range [IQR]: 36–57 mo), 3-yr RFR (95% CI) was as follows: celecoxib 68% (61–74%) versus placebo 64% (57–70%; HR 0.82 [95% CI: 0.60–1.12], stratified log-rank $p = 0.2$; Fig. 2A). When stratified by disease risk, 3-yr RFR was as follows: celecoxib 75% (67–81%) versus placebo 68% (60–74%; HR 0.77 [0.52–1.15], log-rank $p = 0.2$) for high-risk patients (Fig. 2B), and 52% (40–64%) versus 50% (35–63%; HR 0.90 [0.55–1.48], log-rank $p = 0.7$) for intermediate-risk patients (Fig. 2B). Exploratory subgroup analyses of the primary endpoint are shown in Figure 3. Time to recurrence was longer in pT1 NMIBC patients in the celecoxib arm compared with that in the placebo arm (HR 0.53 [95% CI: 0.30–0.94]); this effect was not seen in pTa patients (interaction $p = 0.04$). Sensitivity analyses of the primary endpoint and disease-free survival yielded similar results (Supplementary Fig. 1–3).

3.3. *Progression rate and overall survival*

The 3-yr rate of progression to invasive disease in high-risk patients was low in both groups: 10% (6.5–17%) in celecoxib versus 9.7% (6.0–15%) in placebo (log-rank $p = 0.8$) group (Supplementary Fig. 4). Overall, there were 26 deaths in the celecoxib arm and 21 in the placebo arm. Deaths were due to bladder cancer (19), other malignancies (14), respiratory causes (six), CV causes (three), or other causes (five). At 3 yr, overall survival in the celecoxib arm was 92% (95% CI: 87–95), while in the placebo arm it was 94% (90%, 97%; HR1.21 [0.68–2.15], stratified log-rank $p = 0.5$; Supplementary Fig. 5).

3.4. *Safety and tolerability*

Worst CTC grade adverse events at any time are presented in Table 3. A total of 145 (32%) patients (30% celecoxib vs 33% placebo) suffered grade 3–4 toxicity ($p = 0.6$). Only in 70 patients (15%) serious adverse events were reported with no differences between groups (celecoxib 16%, placebo 14%; $p = 0.5$). Incidence of CV events reported as serious while on treatment was higher in patients on celecoxib (5.2%) than in those on placebo (1.7%; absolute difference 3.4% [95% CI:–0.3% to 7.2%], $p = 0.07$; Supplementary Table 2).

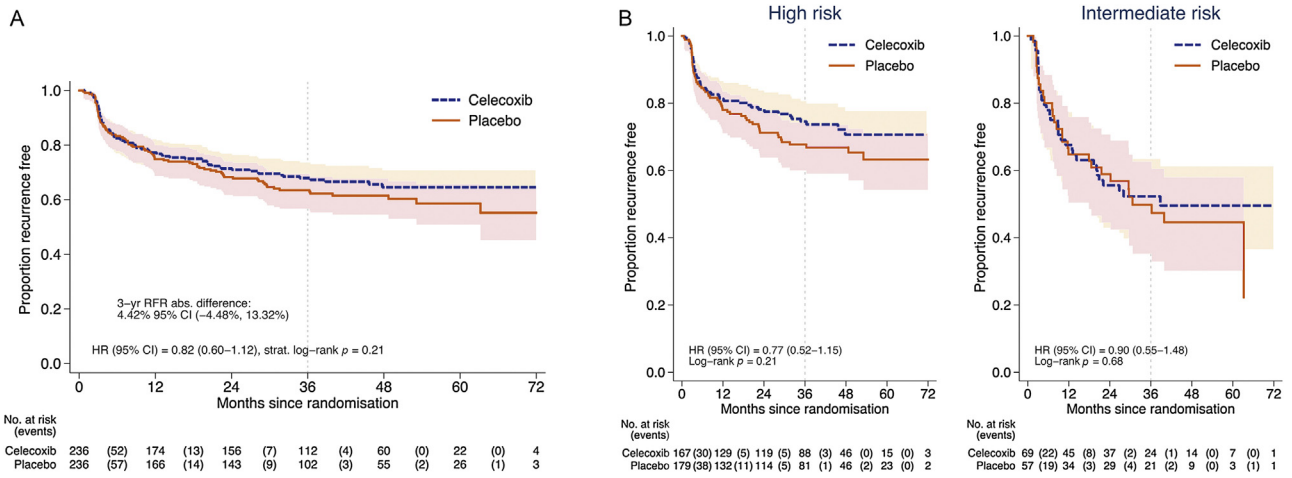

Fig. 2 – Kaplan-Meier estimates of recurrence-free rates (RFRs) (A) for all patients (ITT population) and (B) in high-risk (left) and intermediate-risk (right) patients. abs. diff = absolute difference; CI = confidence interval; HR = hazard ratio; strat = stratified.

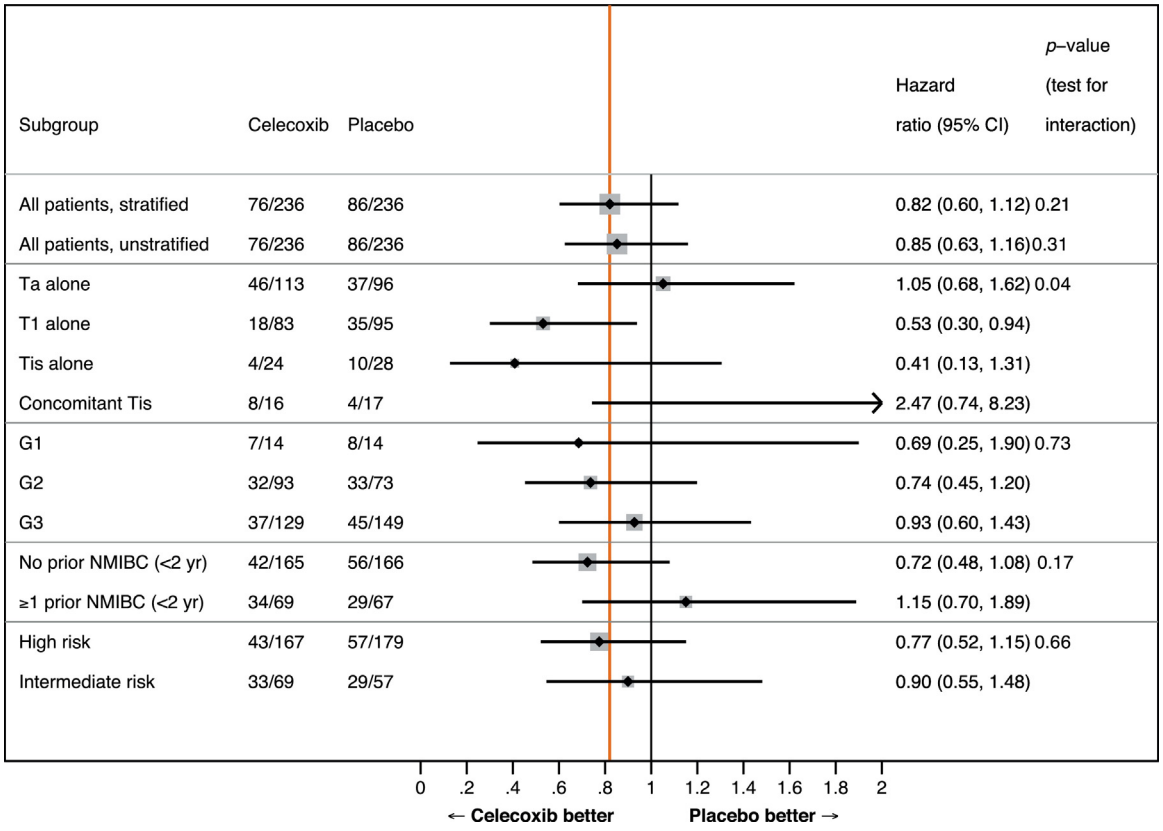

Fig. 3 – Subgroup analysis: hazard ratios for recurrence-free rate by tumour characteristics. CI = confidence interval; NMIBC = non–muscle-invasive bladder cancer.

3.5. *Health-related quality of life*

There was no significant difference in HRQOL assessed by QLQ-C30 and QLQ-NIMBC24 between treatments over the 36-mo follow-up (Supplementary Tables 3 and 4). At 6 mo, QLQ-C30 global health score was significantly worse than baseline in the celecoxib group but not in the placebo group, although differences between groups were not statistically significant. This deterioration in quality of life persisted at 24 mo.

4. Discussion

The BOXIT trial did not show a difference in time to recurrence between the two treatment arms. Exploratory subgroup analysis suggested time to recurrence was

Table 3 – Frequency of adverse events by randomised group

	Celecoxib (*N* = 228)		Placebo (*N* = 228)		Total (*N* = 456)	
	N	%	*N*	%	*N*	%
Worst CTCAE grade overall						
0	24	11	29	13	53	12
1	41	18	43	19	84	18
2	90	40	76	33	166	36
3	55	24	67	29	122	27
4	14	6.1	9	3.9	23	5.0
Ungraded	4	1.8	4	1.8	8	1.8
% G3–4	69	30	76	33	145	32
Grade 3–4 toxicities (>1% in either arm)						
Abdominal pain	6	2.6	5	2.2	11	2.4
Alveolitis allergic	3	1.3	0	0.0	3	0.7
Arthralgia	4	1.8	2	0.9	6	1.3
Back pain	3	1.3	2	0.9	5	1.1
Chills	3	1.3	0	0.0	3	0.7
Deep vein thrombosis [a]	0	0.0	7	3.1	7	1.5
Dyspepsia	5	2.2	4	1.8	9	2.0
Dyspnoea	0	0.0	4	1.8	4	0.9
Dysuria	3	1.3	7	3.1	10	2.2
Fatigue	4	1.8	4	1.8	8	1.8
Haematuria	2	0.9	3	1.3	5	1.1
Hypertension [a]	9	3.9	1	0.4	10	2.2
Insomnia	6	2.6	8	3.5	14	3.1
Micturition urgency	2	0.9	6	2.6	8	1.8
Pelvic pain	2	0.9	3	1.3	5	1.1
Prostatitis [a]	5	2.2	0	0.0	5	1.1
Rash	0	0.0	4	1.8	4	0.9
Tinnitus	4	1.8	0	0.0	4	0.9
Upper respiratory tract infection	4	1.8	4	1.8	8	1.8
Urinary frequency [a]	6	2.6	17	7.5	23	5.0
Urosepsis	3	1.3	1	0.4	4	0.9

CTCAE = National Cancer Institute's Common Terminology Criteria for Adverse Events v3.0.
Reported on *n* = 456 patients with at least one toxicity form completed. Groups compared by: two-sided Fisher's exact test comparing number with G3–4, except for worst grade overall with chi-square test for trend.
[a] All $p > 0.1$ except for deep vein thrombosis ($p = 0.02$), hypertension ($p = 0.02$), prostatitis ($p = 0.06$), and urinary frequency ($p = 0.03$).

significantly longer in pT1 NMIBC in the celecoxib arm compared with placebo. Cardiac events were more common with celecoxib. Strengths of the study include its size and the use of patient-reported quality of life measures.

Oral secondary prevention agents have been proposed in bladder cancer [13]. Sixty-four NMIBC patients receiving intravesical BCG were randomised to receive vitamins in the recommended daily allowance (RDA) or RDA multivitamins plus megadose vitamins, and showed lower 5-yr recurrence-free survival favouring patients treated with megadose vitamins [13]. The results of this study have not been validated, and to our knowledge, BOXIT is the only phase III trial to test an oral agent in NMIBC.

Despite data supporting a role of COX-2 inhibition in bladder cancer, our results do not support celecoxib as an effective chemopreventive agent for intermediate- and high-risk NMIBC. Similar findings were reported in a previous RCT on high-risk patients [9]. There was no duration dose response as evident in the PP analysis. The results show a significant benefit in cases with pT1 disease, and although not tested in the BOXIT study, studies demonstrate a clear correlation between the expression of COX-2 and tumour stage [14].

Targeting COX-2 inhibition in patients with high-risk invasive (pT1) disease, although attractive for secondary prevention, cannot be recommended because of CV toxicity. Pooled analysis of six RCTs report that CV risk attributed to celecoxib is dependent on dose and baseline CV risk [15]. The higher CV event rate in this study compared with others may reflect the fact that bladder cancer patients are often older, are often smokers, and have had previous exposure to environmental hazards compared with the general population despite excluding patients with a history of CV disease.

Whilst selective inhibition of COX-2 was initially thought to be advantageous due to a reduced risk of gastrointestinal ulceration, it is apparent that COX-2 plays an important role in the vasculature, leading to reduced tendency towards atherothrombosis [16]. However, since many acute coronary events occur in people without a previous history of CV disease, it is not possible to predict a low-risk group for which prolonged COX-2 therapy would be appropriate.

In BOXIT, celecoxib was commenced prior to the start of BCG therapy. COX-2 induces PGE2 to alter tumour cytokine microenvironment and dendritic cell antigen presentation [17]. In the preclinical setting, BCG activates dendritic cells resulting in a mixed cytokine response and COX-2 inhibition–suppressed PGE2 levels, polarising dendritic cells towards an antitumour Th1 response [18,19]. Altering the cytokine response to BCG therapy with COX-2 inhibition represents an attractive area for future research, given the interest in checkpoint inhibitors in the NMIBC setting [20].

There is a paucity of HRQOL patient-reported outcomes in NMIBC. In one other RCT of 120 patients, Gontero and colleagues [21] reported a decline in global health following BCG induction therapy, which improved to near baseline levels at 12 mo. Further exploration of HRQOL patterns and changes over time in BOXIT is planned.

The results from BOXIT may point to an alternative strategy. A study of patients with Lynch syndrome randomised to either aspirin or placebo showed a risk reduction of developing colorectal carcinoma in patients with >2 yr of aspirin therapy [22]. Furthermore, the benefit of aspirin is greatest in colorectal cancers, which overexpress COX-2 (relative risk: 0.64; 95% CI: 0.52–0.8) but not in tumours with a low or absent COX-2 expression [23]. It will be important to understand whether nonselective COX-2 agents such as aspirin are an effective chemoprevention option in high COX-2–expressing bladder cancers.

Limitations include a low uptake of patients treated with MMC6, and induction and maintenance BCG in intermediate- and high-risk patients, respectively, despite recommendation. This was not mandatory to minimise any differences in local practice to enhance patient recruitment. Further, baseline COX-2 expression was not determined in this trial. It is possible that selecting only patients overexpressing COX-2 may benefit from COX-2 inhibition.

5. Conclusions

BOXIT suggests that COX-2 inhibition did not reduce recurrence risk in intermediate- and high-risk NMIBC patients, although time to recurrence was significantly longer in pT1 patients. While CV risk precludes the use of celecoxib for secondary prevention, international consensus supports the use of aspirin due to its efficacy as well as safety profile [24]. Ongoing trials such as Add-Aspirin (NCT02804815), a prospective RCT investigating the role of aspirin in secondary prevention of breast, colorectal, stomach/oesophagus, and prostate cancer, will help inform the development of novel trials in NMIBC.

Author contributions: John D. Kelly 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: Kelly, Mostafid, Huddart, Protheroe, Bogle, Blazeby, Palmer, Cresswell, Johnson, Madaan, Hall.
Acquisition of data: Kelly, Mostafid, Huddart, Protheroe, Cresswell, Johnson, Brough, Madaan, Andrews.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: Tan, Porta, Kelly, Hall.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Porta, Maynard, Hall.
Obtaining funding: Kelly, Hall.
Administrative, technical, or material support: None.
Supervision: Kelly, Hall.
Other: None.

Financial disclosures: John D. Kelly certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Emma Hall—grant holder for Cancer Research UK—Clinical Trials Project Grant to host institution (ICR) to support central trial running costs at ICR-CTSU; Clinical Trials Unit programmatic grant funding to host institution to provide support to UCR-CTSU.

***Funding/Support and role of the sponsor*:** Central trial management costs were funded by Cancer Research UK (C8262/A5669). The BOXIT trial is supported by Cancer Research UK (CRUK/07/004). Alliance Pharma plc (formerly Cambridge Laboratories Limited) and Kyowa Hakko UK Limited provided educational grants to ICR to support central trial costs at ICR-CTSU. Pfizer Inc, under an investigator-initiated research agreement, provided treatment drug (celecoxib and placebo). Trial recruitment and on-going patient follow-up were facilitated within centres by the National Institute for Health Research (NIHR) Cancer Research Network. All funders played no role in the study design, data collection, analysis, interpretation, writing of the report, or the decision to submit the manuscript for publication.

Acknowledgements: Grateful thanks are due to all the patients who have participated in this study, all involved staff at the participating centres, and trials unit staff at ICR-CTSU, particularly the current trial manager Steve Penegar. We also acknowledge on-going contributions of colleagues in the BOXIT Trial Management Group, Trial Steering Committee, and Independent Data Monitoring Committee. Grateful thanks to the contributing principal investigators listed in alphabetical order (no. of patients recruited): Dr. Andrew Protheroe (30), Dr. Robert Huddart (five), Miss Joanne Cresswell (36), Miss Jyoti Shah (one), Miss Ling Keim Lee (five), Mr. Alister Campbell (two), Mr. Alvan Pope (one), Mr. Andrew Thompson (one), Mr. Bruce Montgomery (12), Mr. Colin Bunce (12), Mr. David Hrouda (one), Mr. Garrett Durkan and Mr. Mark Johnson (34), Mr. Greg Boustead (three), Mr. Hugh Mostafid (22), Mr. James Catto (one), Mr. James Green (six), Mr. John Hetherington and Mr. Matthew Simms (five), Mr. John McGrath (12), Mr. Jonathan McFarlane (two), Mr. Jorge Clavijo and Mr. Laurence Coombs (three), Mr. Leyshon Griffiths (six), Mr. Matthew Perry (three), Mr. Nicholas Bryan (three), Mr. Noel Clarke (three), Mr. Owen Hughes (eight), Mr. Param Mariappan (three), Mr. Paul Irwin (one), Mr. Paul McInerney (two), Mr. Philip Britton and Mr. James Hicks (15), Mr. Philip Weston (14), Mr. Raj Persad and Mr. Tim Whittlestone (22), Mr. Ralph Beard and Mr. Barnaby Chappell (eight), Mr. Richard Brough (61), Mr. Richard Parkinson (nine), Mr. Roger Walker (two), Mr. Sanjeev Madaan (20), Mr. Seamus McDermott (two), Mr. Simon Hawkyard (seven), Mr. Stephen Andrews (19), Mr. Stephen Thomas (14), Mr. Sunjay Jain (three), Mr. Tim Larner (four), Mr. Vijay Sangar (70), Ms. Rosemary Blades (two), Professor Jayanta Barua (five), Professor John Kelly (26), and Professor Peter Hoskin (nine).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.09.020.

References

[1] Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359–86.

[2] Cambier S, Sylvester RJ, Collette L, et al. EORTC nomograms and risk groups for predicting recurrence, progression, and disease-specific and overall survival in non-muscle-invasive stage Ta-T1 urothelial bladder cancer patients treated with 1–3 years of maintenance bacillus Calmette-Guerin. Eur Urol 2016;69:60–9.

[3] Tan WS, Rodney S, Lamb B, Feneley M, Kelly J. Management of non-muscle invasive bladder cancer: a comprehensive analysis of guidelines from the United States, Europe and Asia. Cancer Treat Rev 2016;47:22–31.
[4] Sylvester RJ, van der MA, Lamm DL. Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. J Urol 2002;168:1964–70.
[5] Sheng H, Shao J, Morrow JD, Beauchamp RD, DuBois RN. Modulation of apoptosis and Bcl-2 expression by prostaglandin E2 in human colon cancer cells. Cancer Res 1998;58:362–6.
[6] Grosch S, Tegeder I, Niederberger E, Brautigam L, Geisslinger G. COX-2 independent induction of cell cycle arrest and apoptosis in colon cancer cells by the selective COX-2 inhibitor celecoxib. FASEB J 2001;15:2742–4.
[7] Castelao JE, Yuan JM, Gago-Dominguez M, Yu MC, Ross RK. Non-steroidal anti-inflammatory drugs and bladder cancer prevention. Br J Cancer 2000;82:1364–9.
[8] Kim SI, Kwon SM, Kim YS, Hong SJ. Association of cyclooxygenase-2 expression with prognosis of stage T1 grade 3 bladder cancer. Urology 2002;60:816–21.
[9] Sabichi AL, Lee JJ, Grossman HB, et al. A randomized controlled trial of celecoxib to prevent recurrence of nonmuscle-invasive bladder cancer. Cancer Prev Res 2011;4:1580–9.
[10] Oosterlinck W, Lobel B, Jakse G, Malmstrom PU, Stockle M, Sternberg C. Guidelines on bladder cancer. Eur Urol 2002;41:105–12.
[11] Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.
[12] Blazeby JM, Hall E, Aaronson NK, et al. Validation and reliability testing of the EORTC QLQ-NMIBC24 questionnaire module to assess patient-reported outcomes in non-muscle-invasive bladder cancer. Eur Urol 2014;66:1148–56.
[13] Lamm DL, Riggs DR, Shriver JS, vanGilder PF, Rach JF, DeHaven JI. Megadose vitamins in bladder cancer: a double-blind clinical trial. J Urol 1994;151:21–6.
[14] Czachorowski MJ, Amaral AFS, Montes-Moreno S, et al. Cyclooxygenase-2 expression in bladder cancer and patient prognosis: results from a large clinical cohort and meta-analysis. PLoS One 2012;7:e45025.
[15] Solomon SD, Wittes J, Finn PV, et al. Cardiovascular risk of celecoxib in 6 randomized placebo-controlled trials. Circulation 2008;117:2104–13.
[16] Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA 2001;286:954–9.
[17] Sharma S, Stolina M, Yang S-C, et al. Tumor cyclooxygenase 2-dependent suppression of dendritic cell function. Clin Cancer Res 2003;9:961–8.
[18] Dovedi SJ, Kirby JA, Atkins H, Davies BR, Kelly JD. Cyclooxygenase-2 inhibition: a potential mechanism for increasing the efficacy of bacillus Calmette-Guerin immunotherapy for bladder cancer. J Urol 2005;174:332–7.
[19] Atkins H, Davies BR, Kirby JA, Kelly JD. Polarisation of a T-helper cell immune response by activation of dendritic cells with CpG-containing oligonucleotides: a potential therapeutic regime for bladder cancer immunotherapy. Br J Cancer 2003;89:2312–9.
[20] Powles T, Eder JP, Fine GD, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature 2014;515:558–62.
[21] Gontero P, Oderda M, Mehnert A, et al. The impact of intravesical gemcitabine and 1/3 dose bacillus Calmette-Guerin instillation therapy on the quality of life in patients with nonmuscle invasive bladder cancer: results of a prospective, randomized, phase II trial. J Urol 2013;190:857–62.
[22] Burn J, Bishop DT, Mecklin JP, et al. Effect of aspirin or resistant starch on colorectal neoplasia in the Lynch syndrome. N Engl J Med 2008;359:2567–78.
[23] Chan AT, Ogino S, Fuchs CS. Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. N Engl J Med 2007;356:2131–42.
[24] Cuzick J, Otto F, Baron JA, et al. Aspirin and non-steroidal anti-inflammatory drugs for cancer prevention: an international consensus statement. Lancet Oncol 2009;10:501–7.