Manuscript title: 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)

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Abstract

Background

Non-muscle invasive bladder cancer (NMIBC) has a significant risk of recurrence despite adjuvant intravesical therapy.

Objective

To determine if celecoxib, a COX-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 years with intermediate or high risk NMIBC were accrued across 51 United Kingdom centres between 1st November 2007 and 23rd July 2012.

Interventions

Patients were randomised (1:1) to celecoxib 200 mg twice daily or placebo for two years. Patients with intermediate risk NMIBC were recommended to receive 6 weekly mitomycin C; high risk NMIBC cases received 6 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 months (IQR: 36-57), 3-year recurrence-free rate (RFR) (95% CI) was 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 (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 time to recurrence was longer in pT1 NMIBC patients treated with celecoxib compared to placebo (HR: 0.53, [0.30-0.94], interaction test p=0.04). The 3-year 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 placebo (1.7%) (difference +3.4% [-0.3%-7.2%], p=0.07).

Conclusion

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 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.

Key words: bladder cancer; chemoprevention; COX-2 inhibitor; randomised trial; cardiovascular events**.**

1. Introduction

Bladder cancer represents the 9th 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 years [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 NSAIDs had an a lower risk of developing bladder cancer (odds ratio 0.81, 95% CI: 0.68-0.96) compared to non- or irregular NSAID use patients [7]. Consistent with this, COX-2 is overexpressed in bladder cancer compared to 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, to placebo in high risk NMIBC recruited subjects 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 months 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 if celecoxib in combination with standard therapy is more effective in terms of reducing to 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 (EAU) guidelines (2002) were eligible for the trial [10]. Patients had complete transurethral resection of bladder tumour (TURBT) for histopathological staging and all pT1 disease underwent re-resection to confirm the absence of detrusor tumour invasion. Patients were ≥18 years old, with WHO performance status of ≤2 with no upper tract transitional cell carcinoma (TCC) confirmed by imaging within the past 36 months and had not received NSAIDs (other than low dose aspirin ≤150 mg daily) or celecoxib for a minimum of two months 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 contraindications to NSAIDs, pregnant or lactating women, adverse reactions to sulfonamides or NSAIDs, current or long-term use of NSAIDs and oral corticosteroids, malignancy within the past 2 years, patients with known or suspected congestive heart failure (II-IV NYHA), cardiovascular disease, blood pressure of >160/100mmHg and/ or patients with diabetes requiring insulin.

2.3 Randomisation and Masking

Following TURBT, randomisation was performed by telephone to the 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 cardiovascular safety data to advise in confidence the IDMC.

2.4 Interventions

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

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 (AE), 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, 12, 24 and 36 months. High risk patients also completed measures at 8 & 12 weeks and 6 months.

2.6 Sample size and power

Estimating a recurrence free rate at 3 years 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 non-compliance rates of 14.5% at 12 months and 28% at 24 months and that stopping trial treatment early halves the treatment effect, a revised target sample size of 475 patients (193 events) with 5% drop out and 80% power was selected.

2.7 Statistical analysis

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

Time-to-event endpoints were summarised using Kaplan Meier methods. Treatments were compared by the stratified log-rank test and effect 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 $\geq$3 grade and serious cardiovascular events were compared by Fisher's exact test.

Treatment effect on HRQOL were obtained from ANCOVA models. Only patients with paired baseline and timepoint data were analysed. A p-value of <0.01 (and related 99% confidence intervals) was deemed statistically significant to account for multiple comparisons.

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

3. Results

3.1 Patients

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

A total of 177 (75%) in the celecoxib arm and 189 (80%) patients in the placebo arm took the study drug for ≥12 months, with 120 (51%) and 144 (61%) respectively completing 24 months of study treatment (Table 2). In December 2013, the trial stopped for futility and given a small increased risk of cardiovascular 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 years median follow-up.

Compliance with standard of care treatments, by risk group and treatment arm are 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 months (IQR: 36-57 months), 3-year recurrence free rate (RFR) (95% CI) was celecoxib: 68% (61%-74%) versus placebo: 64% (57%-70%) (hazard ratio (HR): 0.82, [95% CI: 0.60-1.12], stratified log-rank p=0.2) (Figure 2A). When stratified by disease risk, 3-year RFR was 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 (Figure 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 (Figure 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 to placebo (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 (Supplement Figures 1-3).

3.3 Progression rate and overall survival

The 3-year rate of progression to invasive disease in high risk patients was low in both groups: 10% (6.5%-17%) celecoxib versus 9.7% (6.0%-15%) placebo (log-rank p=0.8) (Supplement Figure 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 (6), cardiovascular causes (3) or other (5). At 3 years, the overall survival in the celecoxib arm was 92% (95% CI: 87-95) while in the placebo arm was 94% (90%, 97%) (HR: 1.21, [0.68-2.15], stratified log-rank p=0.5) (Supplement Figure 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 versus 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 on celecoxib (5.2%) than placebo (1.7%) (absolute difference 3.4% [95% CI: -0.3%-7.2%], p=0.07) (Supplement Table 2).

3.5 HRQOL

There was no significant difference in HRQOL assessed by QLQ-C30 and QLQ-NIMBC24 between treatments over the 36-month follow-up (Supplement Tables 3-4). At 6 months, 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 QL persisted at 24 months.

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 significantly longer in pT1 NMIBC in the celecoxib arm compared to 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 a lower 5-year 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 chemopreventative 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 do 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 6 RCTs report that cardiovascular risk attributed to celecoxib is dependent on dose and baseline cardiovascular risk [15]. The higher cardiovascular event rate in this study compared

to others may reflect the fact that bladder cancer patients are often older, smokers and have had previous exposure to environmental hazards compared to the general population despite excluding patients with a history of cardiovascular 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 cardiovascular disease, it is not possible to predict a low risk group for whom 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 anti-tumour 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 check-point 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 reported a decline in global health following BCG induction therapy which improved to near baseline levels at 12 months [21]. 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 years of aspirin therapy [22]. Furthermore the benefit of aspirin is greatest in colorectal cancers which overexpress COX-2 (RR: 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 non-selective COX-2 agents such as aspirin is 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 suggest that COX-2 inhibition did not reduce recurrence risk in intermediate and high risk NMIBC, although time to recurrence was significantly longer in pT1 patients. While cardiovascular 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.

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Conflict of Interest Disclosures: *We declare no competing interests.*

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(1) / Mr Andrew Thompson (1) / Mr Bruce Montgomery (12) / Mr Colin Bunce (12) / Mr David Hrouda (1) / Mr Garrett Durkan & Mr Mark Johnson (34) / Mr Greg Boustead (3) / Mr Hugh Mostafid (22) / Mr James Catto (1) / Mr James Green (6) / Mr John Hetherington & Mr Matthew Simms (5) / Mr John McGrath (12) / Mr Jonathan McFarlane (2) / Mr Jorge Clavijo & Mr Laurence Coombs (3) / Mr Leyshon Griffiths (6) / Mr Matthew Perry (3) / Mr Nicholas Bryan (3) / Mr Noel Clarke (3) / Mr Owen Hughes (8) / Mr Param Mariappan (3) / Mr Paul Irwin (1) / Mr Paul McInerney (2) / Mr Philip Britton & Mr James Hicks (15) / Mr Philip Weston (14) / Mr Raj Persad & Mr Tim Whittlestone (22) / Mr Ralph Beard & Mr Barnaby Chappell (8) / Mr Richard Brough (61) / Mr Richard Parkinson (9) / Mr Roger Walker (2) / Mr Sanjeev Madaan (20) / Mr Seamus McDermott (2) / Mr Simon Hawkyard (7) / Mr Stephen Andrews (19) / Mr Stephen Thomas (14) / Mr Sunjay Jain (3) / Mr Tim Larner (4) / Mr Vijay Sangar (70) / Ms Rosemary Blades (2) / Prof Jayanta Barua (5) / Prof John Kelly (26) / Prof Peter Hoskin (9).

Figure legends

Figure 1: Trial profile - CONSORT diagram

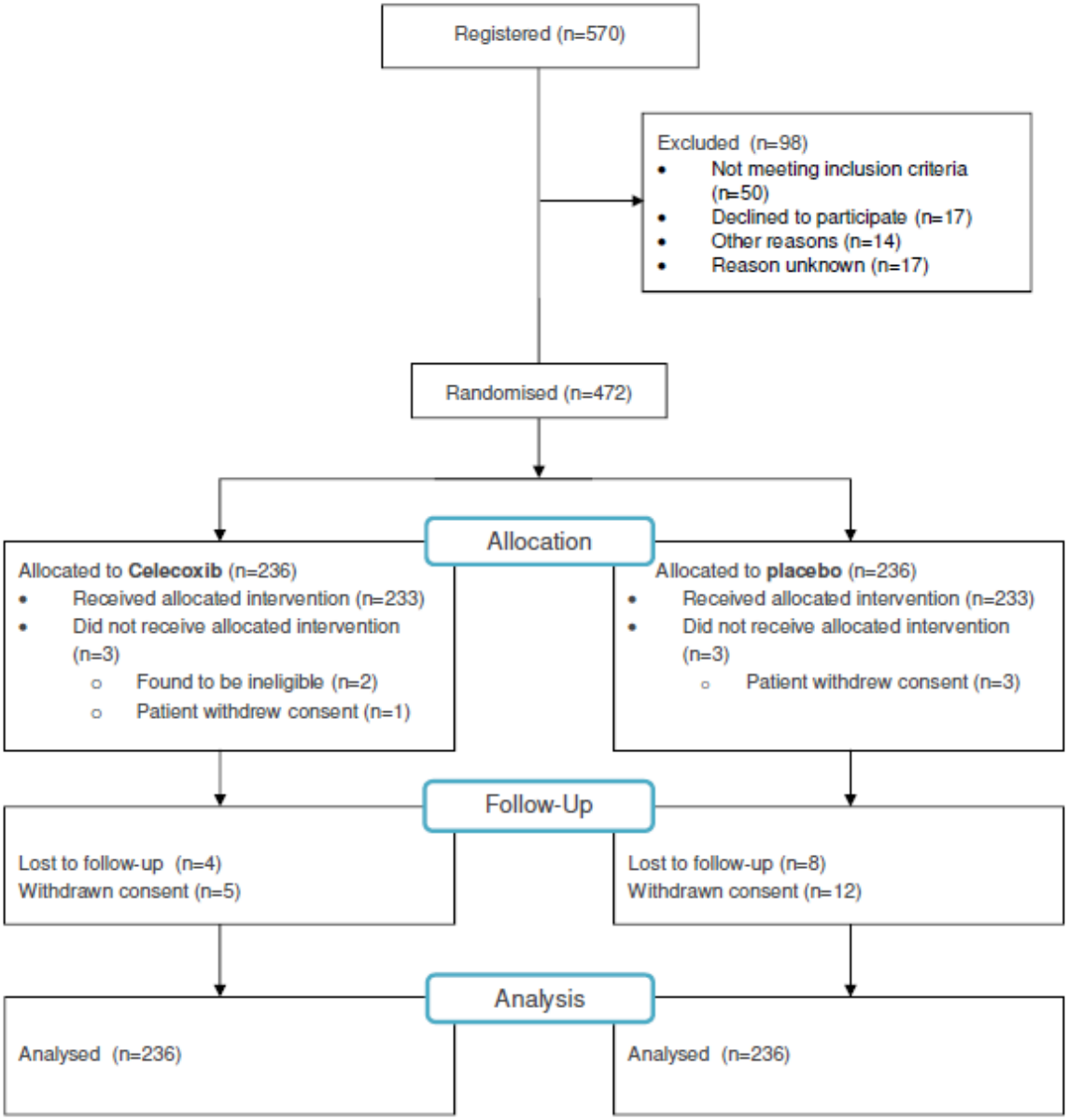
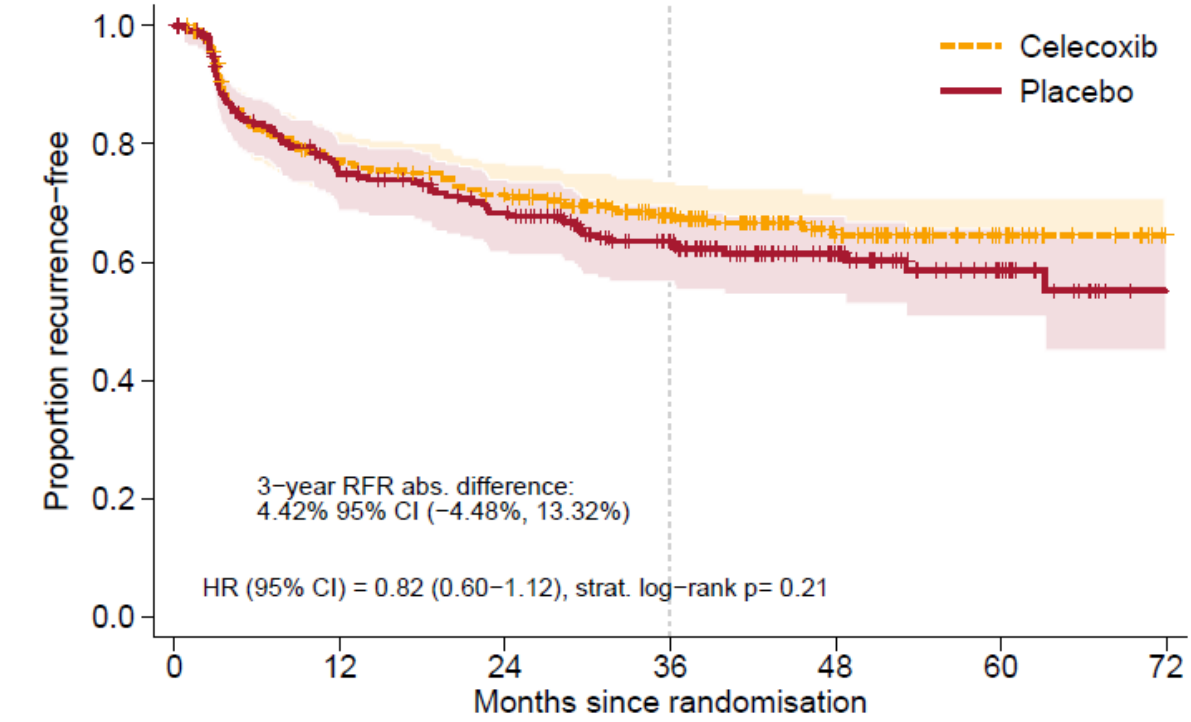


Figure 2: Kaplan- Meier estimates of recurrence-free rates (RFR) for (A) all patients (ITT population) and in (B) High Risk patients (left) and Intermediate Risk patients (right).

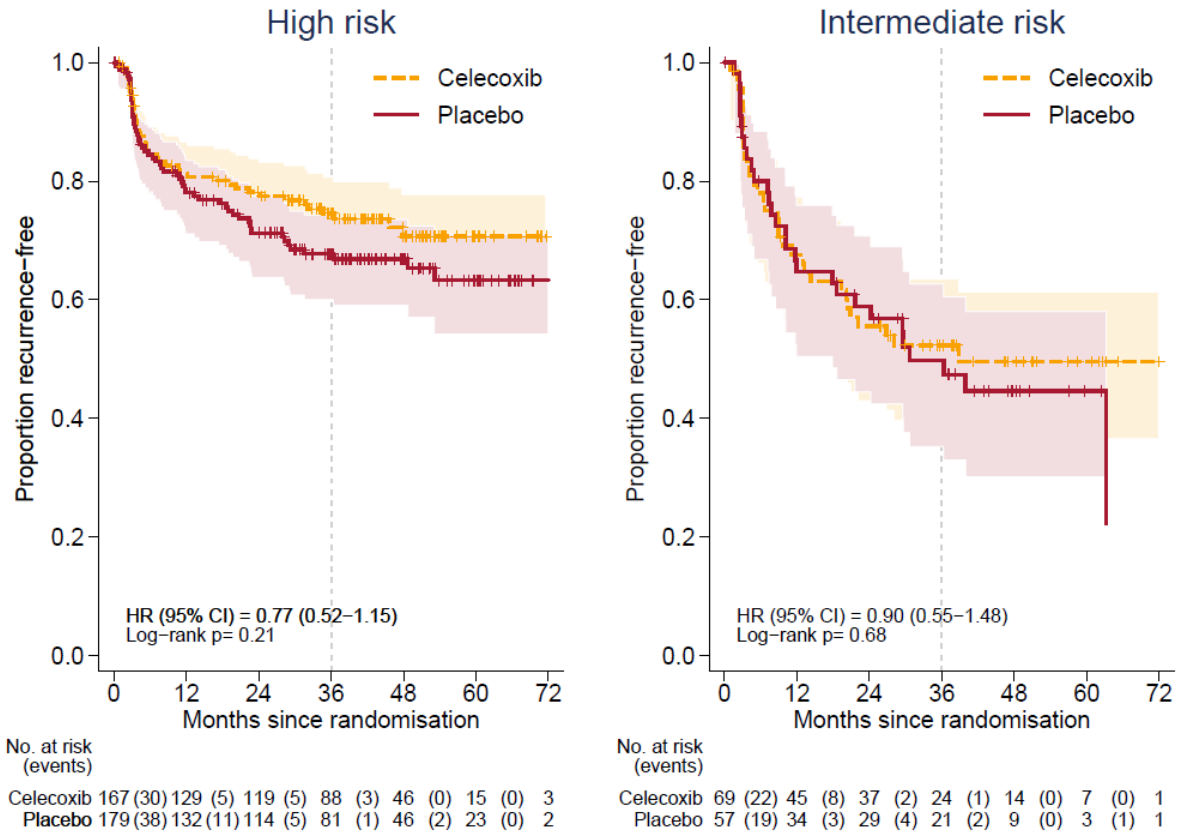
HR: Hazard Ratio; CI: confidence interval; abs. diff: absolute difference; strat: stratified

A

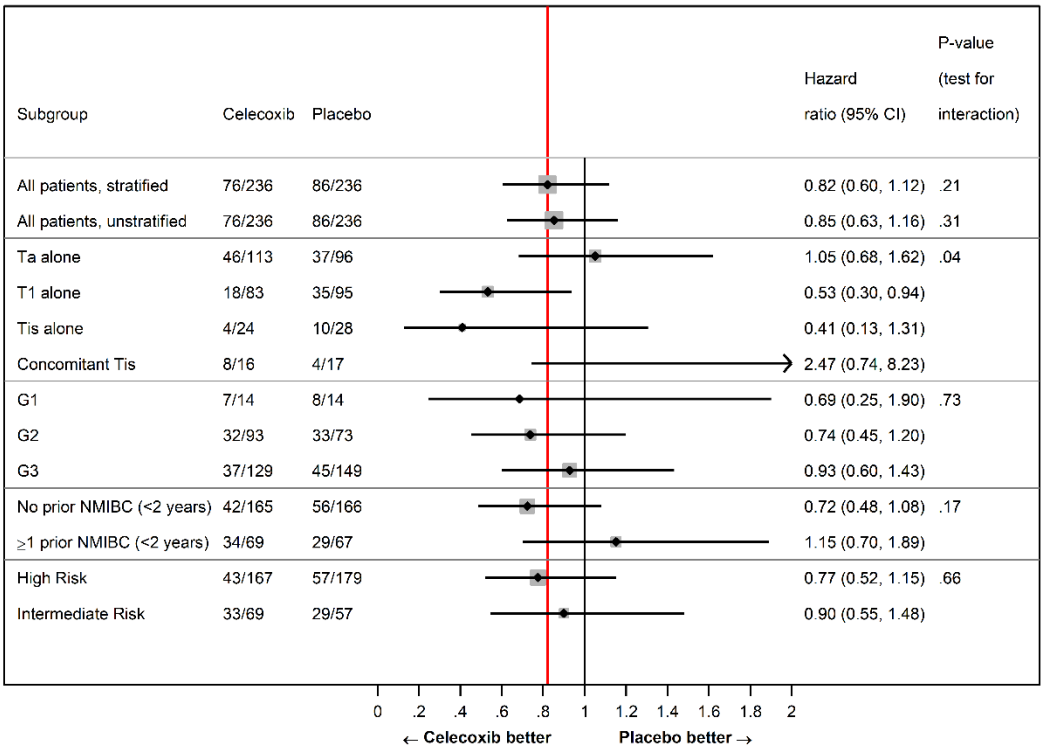


No. at risk (events)													
Celecoxib	236	(52)	174	(13)	156	(7)	112	(4)	60	(0)	22	(0)	4
Placebo	236	(57)	166	(14)	143	(9)	102	(3)	55	(2)	26	(1)	3

B


High risk
Celecoxib
Placebo
Proportion recurrence−free
1.0
0.8
0.6
0.4
0.2
0.0
HR (95% CI) = 0.77 (0.52−1.15)
Log−rank p= 0.21
0
12
24
36
48
60
72
Months since randomisation
No. at risk
(events)
Celecoxib 167 (30) 129 (5) 119 (5) 88 (3) 46 (0) 15 (0) 3
Placebo 179 (38) 132 (11) 114 (5) 81 (1) 46 (2) 23 (0) 2
Intermediate risk
Celecoxib
Placebo
Proportion recurrence−free
1.0
0.8
0.6
0.4
0.2
0.0
HR (95% CI) = 0.90 (0.55−1.48)
Log−rank p= 0.68
0
12
24
36
48
60
72
Months since randomisation
No. at risk
(events)
Celecoxib 69 (22) 45 (8) 37 (2) 24 (1) 14 (0) 7 (0) 1
Placebo 57 (19) 34 (3) 29 (4) 21 (2) 9 (0) 3 (1) 1

361 Figure 3: Subgroup analysis: hazard ratios for recurrence-free rate (RFR) by tumour
362 characteristics



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Tables

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	N=236		N=236		N=472	
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*						
<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*						
<3cm	75	32	74	31	149	32
>=3cm	94	40	94	40	188	40
Not known	67	28	68	29	135	28
Previous recurrence in the last 2 years						

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)

*Numbers from histological diagnosis used where available. If not available, numbers from visual diagnosis used. When tumour size reported "Estimated/assumed >=3cm (n=45)", included in >=3cm category.

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371 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			Celecoxib		Placebo		
	N	%	N	%	p-value	N	%	N	%	p-value
N patients	167	100	179	100		69	100	57	100	
Compliance with trial treatment										
Completed as planned (24 months)	76	46	102	57	0.03	44	64	42	74	0.2
Reasons for non-compliance:										
Disease progression	*21*	*13*	*25*	*14*		*3*	*4.3*	*1*	*1.7*	
AE/tolerability	*26*	*16*	*16*	*8.9*		*10*	*15*	*4*	*7.0*	
Loss to follow-up	*0*	*0*	*0*	*0*	*0.1**	*0*	*0.0*	*1*	*1.7*	*0.6**
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 months 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	*not applicable*									
Full MMC6 received						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	

372 MMC1= Single instillation post ingle instillation of mitomycin C post transurethral resection; MM6= Maintenance
373 mitomycin C; BCG= Bacillus Calmette Guérin (BCG); BCG6=BCG induction

374 *Chi2 test p-value on non-compliant pts only.

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376 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*		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*		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*		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*		6	2.6	17	7.5	23	5.0
Urosepsis		3	1.3	1	0.4	4	0.9

Reported on n=456 patients with at least 1 toxicity form completed. Groups compared by: 2-sided Fisher's exact test comparing number with G3-4, except for worst grade overall with X2 test for trend. All p-values >0.1 except for *Deep vein thrombosis (p=0.02) , hypertension (p=0.02), prostatitis (p=0.06) and urinary frequency (p=0.03).
CTCAE= National Cancer Institute's Common Terminology Criteria for Adverse Events v3.0

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