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1 **Manuscript title:** BOXIT – A randomised phase III placebo-controlled trial evaluating the
2 addition of celecoxib to standard treatment of transitional cell carcinoma of the bladder
3 (CRUK/07/004)

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31

32

33 **Abstract**

34 **Background**

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

37 **Objective**

38 To determine if celecoxib, a COX-2 inhibitor, reduces the risk of recurrence in NMIBC
39 patients receiving standard treatment.

40 **Design, Setting and Participants**

41 BOXIT (CRUK/07/004, ISRCTN84681538) is a double-blinded, phase III, randomised
42 controlled trial. Patients aged ≥ 18 years with intermediate or high risk NMIBC were accrued
43 across 51 United Kingdom centres between 1st November 2007 and 23rd July 2012.

44 **Interventions**

45 Patients were randomised (1:1) to celecoxib 200 mg twice daily or placebo for two years.
46 Patients with intermediate risk NMIBC were recommended to receive 6 weekly mitomycin
47 C; high risk NMIBC cases received 6 weekly Bacillus Calmette Guérin and maintenance
48 therapy.

49 **Outcome measurements and statistical analysis**

50 The primary endpoint was time to disease recurrence. Analysis was by intention to treat.

51 **Results and limitations**

52 A total of 472 patients were randomised (236:236). With median follow-up of 44 months
53 (IQR: 36-57), 3-year recurrence-free rate (RFR) (95% CI) was celecoxib: 68% (61%-74%)
54 versus placebo: 64% (57%-70%) (hazard ratio (HR) 0.82, [0.60-1.12], p=0.2). There was no
55 difference in high (HR 0.77 [0.52-1.15], p=0.2) or intermediate risk (HR 0.90 [0.55-1.48],
56 p=0.7) NMIBC. Subgroup analysis suggested time to recurrence was longer in pT1 NMIBC
57 patients treated with celecoxib compared to placebo (HR: 0.53, [0.30-0.94], interaction test
58 p=0.04). The 3-year progression rates in high risk patients were low: 10% (6.5%-17%) and
59 9.7% (6.0%-15%) in celecoxib and placebo arms respectively. Incidence of serious
60 cardiovascular events was higher in celecoxib (5.2%) than placebo (1.7%) (difference +3.4%
61 [-0.3%-7.2%], p=0.07).

62 **Conclusion**

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

66 **Patient summary**

67 Celecoxib was not shown to reduce the risk of recurrence in intermediate or high risk NMIBC
68 although celecoxib was associated with delayed time to recurrence in pT1 NMIBC patients.
69 The increased risk of cardiovascular events does not support the use of celecoxib.

70

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

73 **1. Introduction**

74 Bladder cancer represents the 9th most common cancer with 429,000 new cases per year
75 worldwide [1]. Over 75% of new cases are non-muscle invasive bladder cancer (NMIBC) and
76 following tumour resection, between 28-52% of patients will develop recurrence within 5
77 years [2]. Efforts to reduce recurrence of NMIBC include the use of intravesical
78 chemotherapy and Bacillus Calmette Guérin (BCG) [3, 4].

79 Cyclo-oxygenase (COX) enzyme controls a rate limiting step implicated in carcinogenesis by
80 regulating the conversion of arachidonic acid to prostaglandin E2 (PGE2) and inhibits
81 apoptosis by overexpressing Bcl-2 [5]. Inhibition of COX-2 results in cell cycle arrest
82 triggering apoptosis in *in vitro* studies [6]. A population-based case-controlled study
83 reported that patients taking regular NSAIDs had an a lower risk of developing bladder
84 cancer (odds ratio 0.81, 95% CI: 0.68-0.96) compared to non- or irregular NSAID use patients
85 [7]. Consistent with this, COX-2 is overexpressed in bladder cancer compared to normal
86 urothelium and COX-2 expression is associated with disease recurrence and progression [8].

87 A phase II randomised controlled trial (RCT) comparing celecoxib, a selective COX-2
88 inhibitor, to placebo in high risk NMIBC recruited subjects who received adjuvant BCG was
89 reported by Sabichi and colleagues [9]. It was powered to detect a large treatment effect of
90 53% relative reduction in recurrence at 12 months but failed to show a difference [9].
91 Further, the study did not assess health related quality of life (HRQOL). The BOXIT study
92 (ISRCTN84681538) sought to determine if celecoxib in combination with standard therapy is
93 more effective in terms of reducing to the risk of disease recurrence than standard therapy
94 alone for the treatment of intermediate or high risk NMIBC.

95

96 **2. Patients and Methods**

97 **2.1 Trial design**

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

102 **2.2 Patients**

103 All patients with primary or recurrent intermediate or high risk NMIBC according to
104 European Association of Urology (EAU) guidelines (2002) were eligible for the trial [10].
105 Patients had complete transurethral resection of bladder tumour (TURBT) for
106 histopathological staging and all pT1 disease underwent re-resection to confirm the absence
107 of detrusor tumour invasion. Patients were ≥ 18 years old, with WHO performance status of
108 ≤ 2 with no upper tract transitional cell carcinoma (TCC) confirmed by imaging within the
109 past 36 months and had not received NSAIDs (other than low dose aspirin ≤ 150 mg daily) or
110 celecoxib for a minimum of two months prior to entry. Haematological and biochemical
111 blood tests were within adequate levels.

112 Key exclusion criteria include non-TCC NMIBC, tumour involving prostatic urethra or upper
113 urinary tract, $\geq pT2$ TCC, known contraindications to NSAIDs, pregnant or lactating women,
114 adverse reactions to sulfonamides or NSAIDs, current or long-term use of NSAIDs and oral
115 corticosteroids, malignancy within the past 2 years, patients with known or suspected
116 congestive heart failure (II-IV NYHA), cardiovascular disease, blood pressure of
117 $>160/100$ mmHg and/ or patients with diabetes requiring insulin.

118 **2.3 Randomisation and Masking**

119 Following TURBT, treatment was allocated (1:1) using computer generated random
120 permuted blocks of size 6, stratified by treating centre and risk group. ICR-CTSU performed
121 the randomisation, and treatment allocation was blinded to participants and investigators.
122 The IDMC reviewed safety and efficacy of the trial blinded to treatment allocation. A
123 Cardiovascular Safety Committee (CVSC) was established to review unblinded cardiovascular
124 safety data to advise in confidence the IDMC.

125 **2.4 Interventions**

126 Patients were randomised to either celecoxib 200mg twice daily or placebo for two years. It
127 was recommended that all patients received standard of care single intravesical 40 mg in 40
128 ml of MMC (MMC1) instillation within 24 hours following TURBT unless contraindicated.
129 High risk patients received induction BCG (81 mg BCG, Connaught strain) comprising of 6
130 weekly instillations, and maintenance therapy (three weekly instillations at 4, 6, 12, 18, 24,
131 30, 36 months) was recommended. Study treatment was commenced before BCG induction
132 in high risk patients. It was recommended that intermediate risk patients received 6 weekly
133 instillations of 40mg MMC (MMC6). Disease recurrence was monitored by regular
134 cystoscopies as per guidelines [3]. A centrally reviewed baseline ECG was performed to
135 confirm eligibility, with follow-up ECGs at 12 and 24 months.

136 **2.5 Outcomes**

137 The primary endpoint was time to recurrence of bladder cancer which was defined as time
138 from randomisation to date of confirmation of cancer recurrence. Secondary efficacy
139 endpoints included NMIBC recurrence rate in intermediate risk patients, time to progression

140 to invasive disease in high risk patients, disease free survival and overall survival. For
141 disease-related events and survival, patients event free or alive at the time of analysis were
142 censored at their last available assessment.

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

147 HRQOL was assessed using the EORTC Quality of Life Questionnaire (EORTC QLQ-C30) [11]
148 and the EORTC QLQ-BLS24 [12]. Patients completed questionnaires at baseline, 12, 24 and
149 36 months. High risk patients also completed measures at 8 & 12 weeks and 6 months.

150 **2.6 Sample size and power**

151 Estimating a recurrence free rate at 3 years of 51% in the control arm, 206 patients per arm
152 were required to detect a difference of 15% with 85% power and two-sided alpha of 5%
153 (hazard ratio (HR) of 0.63). Assuming non-compliance rates of 14.5% at 12 months and 28%
154 at 24 months and that stopping trial treatment early halves the treatment effect, a revised
155 target sample size of 475 patients (193 events) with 5% drop out and 80% power was
156 selected.

157 **2.7 Statistical analysis**

158 Analyses of outcomes were on an intention to treat (ITT) basis, and according to treatment
159 received for safety and tolerability endpoints. Sensitivity analyses were performed on the
160 per protocol (PP) population (≥ 12 months of study drug or earlier if due to disease

161 progression, drug toxicity or death). Statistical significance was defined as p-value= 0.05 and
162 95% confidence intervals reported. Analyses were adjusted by risk group.

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

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

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

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

174

175 **3. Results**

176 **3.1 Patients**

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

181 A total of 177 (75%) in the celecoxib arm and 189 (80%) patients in the placebo arm took
182 the study drug for ≥ 12 months, with 120 (51%) and 144 (61%) respectively completing 24
183 months of study treatment (Table 2). In December 2013, the trial stopped for futility and
184 given a small increased risk of cardiovascular event in patients on celecoxib, the CVSC, IDMC
185 and TSC recommended halting recruitment of patients still on study treatment (6.8%
186 celecoxib, 7.6% placebo). Follow-up continued until maturity of data at 3 years median
187 follow-up.

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

193 **3.2 Recurrence free rate**

194 At median follow-up of 44 months (IQR: 36-57 months), 3-year recurrence free rate (RFR)
195 (95% CI) was celecoxib: 68% (61%-74%) versus placebo: 64% (57%-70%) (hazard ratio (HR):
196 0.82, [95% CI: 0.60-1.12], stratified log-rank $p=0.2$) (Figure 2A). When stratified by disease

197 risk, 3-year RFR was celecoxib: 75% (67%-81%) versus placebo: 68% (60%-74%) (HR: 0.77
198 [0.52-1.15], log-rank p=0.2) for high risk patients (Figure 2B) and 52% (40%-64%) versus 50%
199 (35%-63%) (HR: 0.90 [0.55-1.48], log-rank p=0.7) for intermediate risk patients (Figure 2B).
200 Exploratory subgroup analyses of the primary endpoint are shown in Figure 3. Time to
201 recurrence was longer in pT1 NMIBC patients in the celecoxib arm compared to placebo
202 (HR: 0.53, [95% CI: 0.30-0.94]); this effect was not seen in pTa patients (interaction p= 0.04).
203 Sensitivity analyses of the primary endpoint and disease free survival yielded similar results
204 (Supplement Figures 1-3).

205 **3.3 Progression rate and overall survival**

206 The 3-year rate of progression to invasive disease in high risk patients was low in both
207 groups: 10% (6.5%-17%) celecoxib versus 9.7% (6.0%-15%) placebo (log-rank p=0.8)
208 (Supplement Figure 4). Overall, there were 26 deaths in the celecoxib arm, and 21 in the
209 placebo arm. Deaths were due to bladder cancer (19), other malignancies (14), respiratory
210 causes (6), cardiovascular causes (3) or other (5). At 3 years, the overall survival in the
211 celecoxib arm was 92% (95% CI: 87-95) while in the placebo arm was 94% (90%, 97%) (HR:
212 1.21, [0.68-2.15], stratified log-rank p=0.5) (Supplement Figure 5).

213 **3.4 Safety and tolerability**

214 Worst CTC grade adverse events at any time are presented in Table 3. A total of 145 (32%)
215 patients (30% celecoxib versus 33% placebo) suffered grade 3-4 toxicity (p= 0.6). Only in 70
216 patients (15%) serious adverse events were reported with no differences between groups
217 (celecoxib 16%, placebo 14%, p=0.5). Incidence of CV events reported as serious while on

218 treatment was higher on celecoxib (5.2%) than placebo (1.7%) (absolute difference 3.4%
219 [95% CI: -0.3%-7.2%], p=0.07) (Supplement Table 2).

220 **3.5 HRQOL**

221 There was no significant difference in HRQOL assessed by QLQ-C30 and QLQ-NIMBC24
222 between treatments over the 36-month follow-up (Supplement Tables 3-4). At 6 months,
223 QLQ-C30 global health score was significantly worse than baseline in the celecoxib group
224 but not in the placebo group, although differences between groups were not statistically
225 significant. This deterioration in QL persisted at 24 months.

226

227 **4. Discussion**

228 The BOXIT trial did not show a difference in time to recurrence between the two treatment
229 arms. Exploratory subgroup analysis suggested time to recurrence was significantly longer in
230 pT1 NMIBC in the celecoxib arm compared to placebo. Cardiac events were more common
231 with celecoxib. Strengths of the study include its size and the use of patient reported quality
232 of life measures.

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

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

245 Targeting COX-2 inhibition in patients with high risk invasive (pT1) disease although
246 attractive for secondary prevention cannot be recommended because of CV toxicity. Pooled
247 analysis of 6 RCTs report that cardiovascular risk attributed to celecoxib is dependent on
248 dose and baseline cardiovascular risk [15]. The higher cardiovascular event rate in this study

249 compared to others may reflect the fact that bladder cancer patients are often older,
250 smokers and have had previous exposure to environmental hazards compared to the
251 general population despite excluding patients with a history of cardiovascular disease.

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

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

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

269 The results from BOXIT may point to an alternative strategy. A study of patients with Lynch
270 syndrome randomised to either aspirin or placebo showed a risk reduction of developing

271 colorectal carcinoma in patients with >2 years of aspirin therapy [22]. Furthermore the
272 benefit of aspirin is greatest in colorectal cancers which overexpress COX-2 (RR: 0.64; 95% CI
273 0.52-0.8) but not in tumours with a low or absent COX-2 expression [23]. It will be important
274 to understand whether non-selective COX-2 agents such as aspirin is an effective
275 chemoprevention option in high COX-2 expressing bladder cancers.

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

282 **5. Conclusions**

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

290

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328

329 **Figure legends**

330 Figure 1: Trial profile - CONSORT diagram

331

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

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

335

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

338

339

340

341 **Tables**

342 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)	N=236 66 (60-73)		N=236 68 (63-73)		N=472 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 \geq 140 and /or Diastolic \geq 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
\geq 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
\geq 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 ≥ 3 cm (n=45)", included in ≥ 3 cm category.

343

344

345 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	%	
<i>N patients</i>	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
<i>Reasons for non-compliance:</i>										
<i>Disease progression</i>	21	13	25	14	0.1*	3	4.3	1	1.7	0.6*
<i>AE/tolerability</i>	26	16	16	8.9		10	15	4	7.0	
<i>Loss to follow-up</i>	0	0	0	0		0	0.0	1	1.7	
<i>Patient/clinician decision</i>	20	12	17	9.5		3	4.3	4	7.0	
<i>Early cessation IMP Dec 2013</i>	12	7.2	16	8.9		4	5.8	2	3.5	
<i>Other</i>	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	<i>not applicable</i>									
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	

346 MMC1= Single instillation post inge instillation of mitomycin C post transurethral resection; MM6= Maintenance
 347 mitomycin C; BCG= Bacillus Calmette Guérin (BCG); BCG6=BCG induction

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

349

350 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

351

352 **References**

353

354 [1] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer
355 incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN
356 2012. *International Journal of Cancer*. 2015;136:E359-E86.

357 [2] Cambier S, Sylvester RJ, Collette L, Gontero P, Brausi MA, van Andel G, et al. EORTC
358 Nomograms and Risk Groups for Predicting Recurrence, Progression, and Disease-specific
359 and Overall Survival in Non-Muscle-invasive Stage Ta-T1 Urothelial Bladder Cancer

- 360 Patients Treated with 1-3 Years of Maintenance Bacillus Calmette-Guerin. *European*
361 *Urology*. 2016;69:60-9.
- 362 [3] Tan WS, Rodney S, Lamb B, Feneley M, Kelly J. Management of non-muscle invasive
363 bladder cancer: A comprehensive analysis of guidelines from the United States, Europe and
364 Asia. *Cancer treatment reviews*. 2016;47:22-31.
- 365 [4] Sylvester RJ, van der MA, Lamm DL. Intravesical bacillus Calmette-Guerin reduces the
366 risk of progression in patients with superficial bladder cancer: a meta-analysis of the
367 published results of randomized clinical trials. *J Urol*. 2002;168:1964-70.
- 368 [5] Sheng H, Shao J, Morrow JD, Beauchamp RD, DuBois RN. Modulation of apoptosis and
369 Bcl-2 expression by prostaglandin E2 in human colon cancer cells. *Cancer research*.
370 1998;58:362-6.
- 371 [6] Grosch S, Tegeder I, Niederberger E, Brautigam L, Geisslinger G. COX-2 independent
372 induction of cell cycle arrest and apoptosis in colon cancer cells by the selective COX-2
373 inhibitor celecoxib. *FASEB Journal*. 2001;15:2742-4.
- 374 [7] Castelao JE, Yuan JM, Gago-Dominguez M, Yu MC, Ross RK. Non-steroidal anti-
375 inflammatory drugs and bladder cancer prevention. *British Journal of Cancer*. 2000;82:1364-
376 9.
- 377 [8] Kim SI, Kwon SM, Kim YS, Hong SJ. Association of cyclooxygenase-2 expression with
378 prognosis of stage T1 grade 3 bladder cancer. *Urology*. 2002;60:816-21.
- 379 [9] Sabichi AL, Lee JJ, Grossman HB, Liu S, Richmond E, Czerniak BA, et al. A randomized
380 controlled trial of celecoxib to prevent recurrence of nonmuscle-invasive bladder cancer.
381 *Cancer Prev Res*. 2011;4:1580-9.
- 382 [10] Oosterlinck W, Lobel B, Jakse G, Malmstrom PU, Stockle M, Sternberg C. Guidelines
383 on bladder cancer. *European Urology*. 2002;41:105-12.
- 384 [11] Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The
385 European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life
386 instrument for use in international clinical trials in oncology. *Journal of the National Cancer*
387 *Institute*. 1993;85:365-76.
- 388 [12] Blazeby JM, Hall E, Aaronson NK, Lloyd L, Waters R, Kelly JD, et al. Validation and
389 reliability testing of the EORTC QLQ-NMIBC24 questionnaire module to assess patient-
390 reported outcomes in non-muscle-invasive bladder cancer. *European Urology*. 2014;66:1148-
391 56.
- 392 [13] Lamm DL, Riggs DR, Shriver JS, vanGilder PF, Rach JF, DeHaven JI. Megadose
393 vitamins in bladder cancer: a double-blind clinical trial. *J Urol*. 1994;151:21-6.
- 394 [14] Czachorowski MJ, Amaral AFS, Montes-Moreno S, Lloreta J, Carrato A, Tardón A, et
395 al. Cyclooxygenase-2 Expression in Bladder Cancer and Patient Prognosis: Results from a
396 Large Clinical Cohort and Meta-Analysis. *PLoS One*. 2012;7:e45025.
- 397 [15] Solomon SD, Wittes J, Finn PV, Fowler R, Viner J, Bertagnolli MM, et al.
398 Cardiovascular risk of celecoxib in 6 randomized placebo-controlled trials. *Circulation*.
399 2008;117:2104-13.
- 400 [16] Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with
401 selective COX-2 inhibitors. *Jama*. 2001;286:954-9.
- 402 [17] Sharma S, Stolina M, Yang S-C, Baratelli F, Lin JF, Atianzar K, et al. Tumor
403 Cyclooxygenase 2-dependent Suppression of Dendritic Cell Function. *Clinical Cancer*
404 *Research*. 2003;9:961-8.
- 405 [18] Dovedi SJ, Kirby JA, Atkins H, Davies BR, Kelly JD. Cyclooxygenase-2 inhibition: a
406 potential mechanism for increasing the efficacy of bacillus calmette-guerin immunotherapy
407 for bladder cancer. *J Urol*. 2005;174:332-7.
- 408 [19] Atkins H, Davies BR, Kirby JA, Kelly JD. Polarisation of a T-helper cell immune
409 response by activation of dendritic cells with CpG-containing oligonucleotides: a potential

410 therapeutic regime for bladder cancer immunotherapy. *British Journal of Cancer*.
411 2003;89:2312-9.

412 [20] Powles T, Eder JP, Fine GD, Braithel FS, Loriot Y, Cruz C, et al. MPDL3280A (anti-PD-
413 L1) treatment leads to clinical activity in metastatic bladder cancer. *Nature*. 2014;515:558-62.

414 [21] Gontero P, Oderda M, Mehnert A, Gurioli A, Marson F, Lucca I, et al. The impact of
415 intravesical gemcitabine and 1/3 dose Bacillus Calmette-Guerin instillation therapy on the
416 quality of life in patients with nonmuscle invasive bladder cancer: results of a prospective,
417 randomized, phase II trial. *J Urol*. 2013;190:857-62.

418 [22] Burn J, Bishop DT, Mecklin JP, Macrae F, Moslein G, Olschwang S, et al. Effect of
419 aspirin or resistant starch on colorectal neoplasia in the Lynch syndrome. *N Engl J Med*.
420 2008;359:2567-78.

421 [23] Chan AT, Ogino S, Fuchs CS. Aspirin and the Risk of Colorectal Cancer in Relation to
422 the Expression of COX-2. *New England Journal of Medicine*. 2007;356:2131-42.

423 [24] Cuzick J, Otto F, Baron JA, Brown PH, Burn J, Greenwald P, et al. Aspirin and non-
424 steroidal anti-inflammatory drugs for cancer prevention: an international consensus
425 statement. *The lancet oncology*. 2009;10:501-7.

426

Figure 1

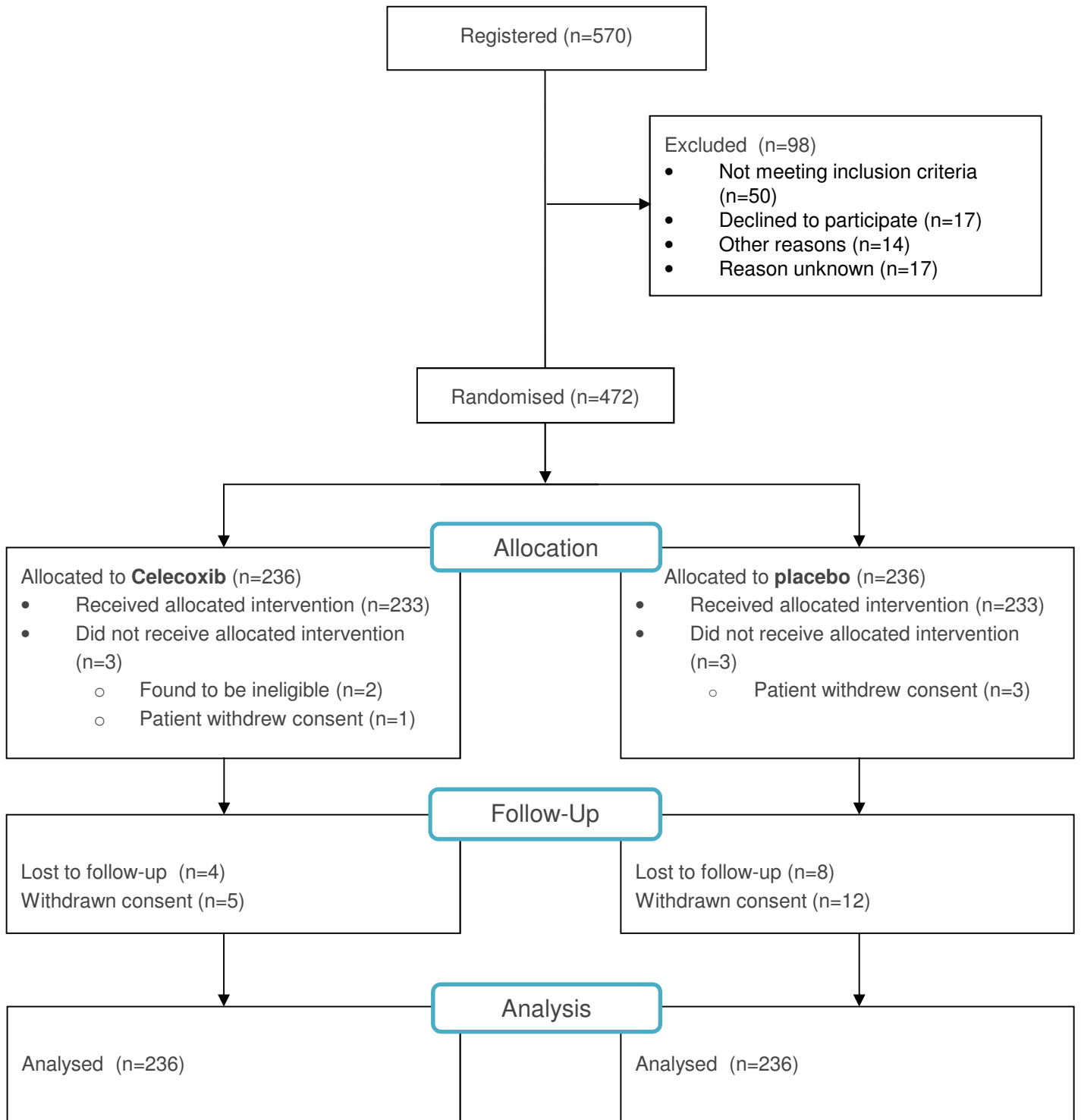
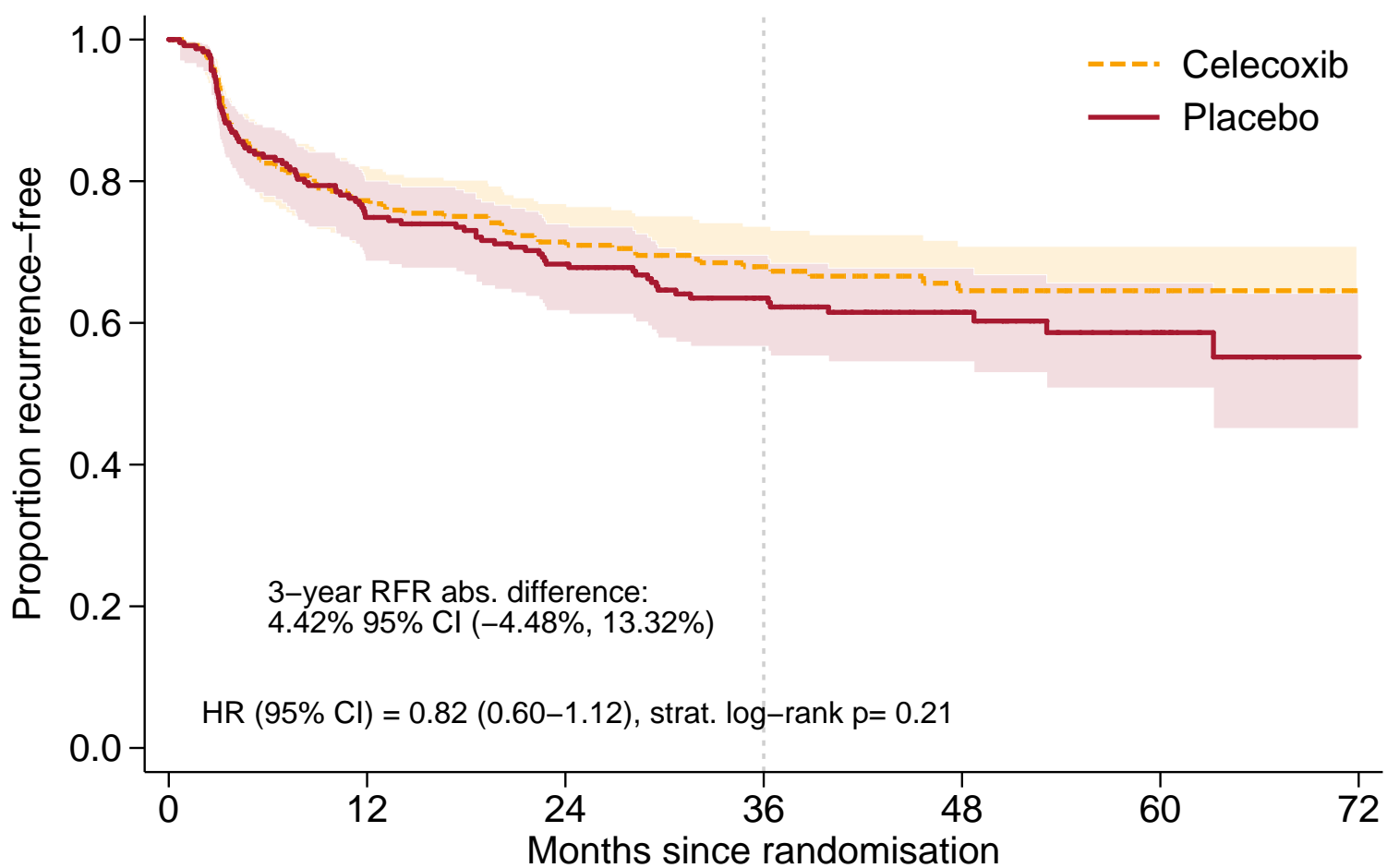
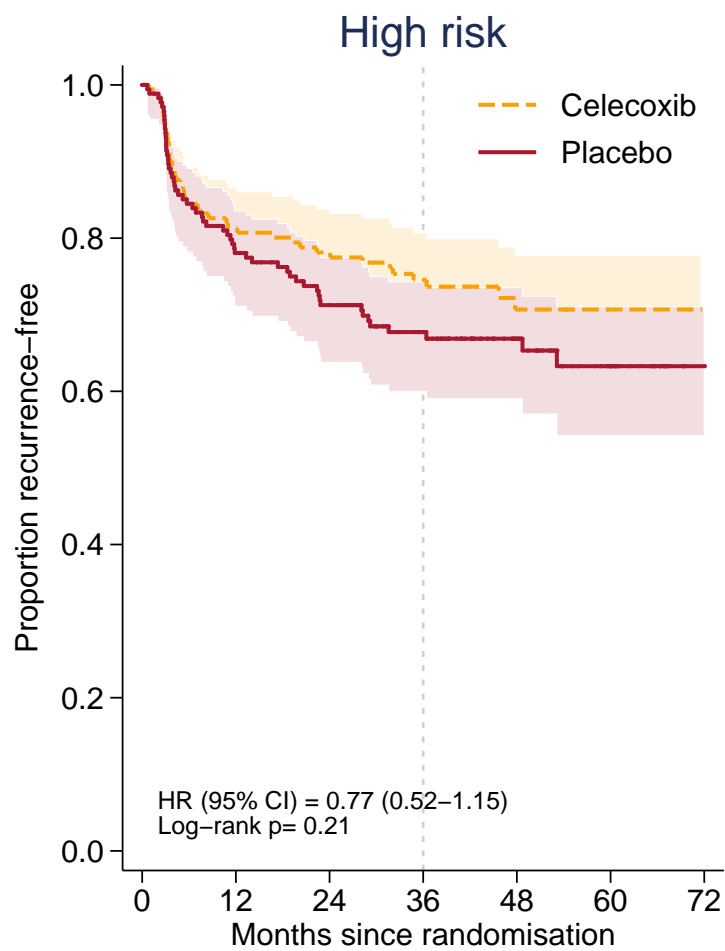


Figure 2A

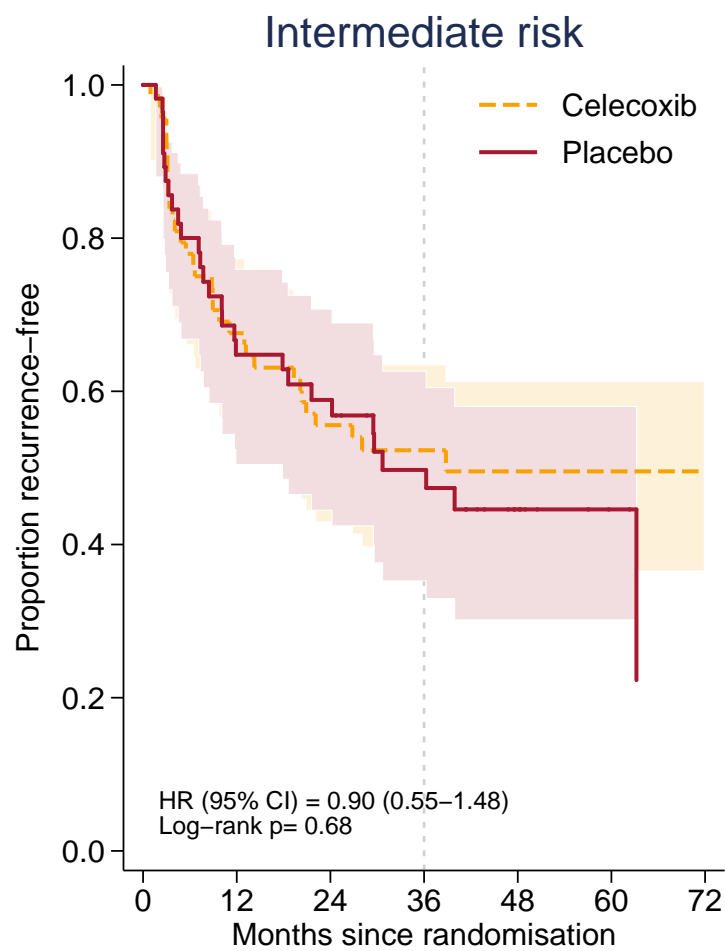


No. at risk (events)		0	6	12	18	24	30	36	42	48	54	60	66	72
Celecoxib	236	(52)	174	(13)	156	(7)	112	(4)	60	(0)	22	(0)	4	
Placebo	236	(57)	166	(14)	143	(9)	102	(3)	55	(2)	26	(1)	3	

Figure 2B

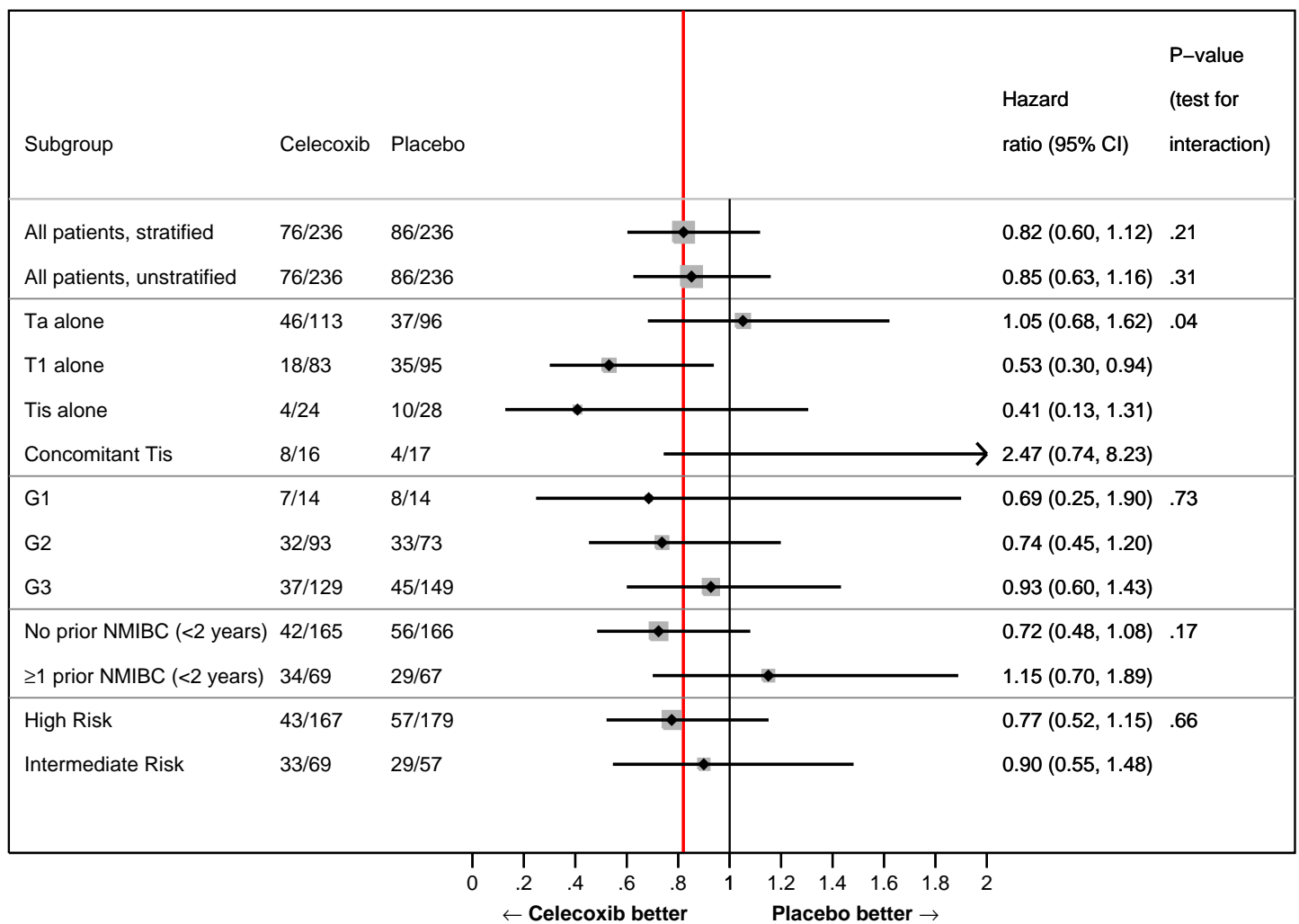


No. at risk (events)	0	12	24	36	48	60	72
Celecoxib	167 (30)	129 (5)	119 (5)	88 (3)	46 (0)	15 (0)	3
Placebo	179 (38)	132 (11)	114 (5)	81 (1)	46 (2)	23 (0)	2



No. at risk (events)	0	12	24	36	48	60	72
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

Figure 3



Take home message

Celecoxib did not reduce the overall risk of recurrence in intermediate or high risk non-muscle invasive bladder cancer. Sub-group analysis report that time to recurrence was significantly longer in pT1 patients treated with celecoxib although cardiovascular events were higher.

BOXIT Supplementary material

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