Supplementary Table 1. Characteristics of the included studies

Study	Methods	Participants	Interventions	Outcomes	Funding sources	Declaration of interest	Notes
Di Stasi 2003	Study design: multicentre, prospective, randomised clinical trial Number of study centres: unclear Study dates: June 1994 to March 2001, follow-up 42–45 months Participants randomly assigned: 108 (36 in each group)	Inclusion criteria: - histologically confirmed multifocal Cis - concurrent pT1 papillary transitional cell carcinoma - adequate bone marrow reserve, normal renal function, normal liver function - Karnofsky performance score 50–100 Exclusion criteria: - prior carcinoma of the bladder or upper urinary tract, or both - other malignancies within 5 years of registration - pregnancy	Group A: MMC 40 mg with 960 mg excipient saline dissolved in 100 mL water instilled and retained in the bladder for 60 minutes Group B: 81 mg wet weight (mean 10.2, SEM 9.0×10^8 cfu) intravesical Pasteur BCG. Lyophilised BCG was suspended in 50 mL bacteriostatic-free saline 0.9% solution. Instillations retained for 120 minutes. Group C: MMC 40 mg with 960 mg excipient saline dissolved in 100 mL water instilled and retained in the bladder for 30 minutes with 20 mA pulsed electric current (600 mA minute) Procedure: - all groups were scheduled to receive an initial 6 intravesical treatments at weekly intervals commencing approximately 3 weeks after multiple biopsy/TUR procedures; - participants who had a complete response to the initial 6 weekly treatments underwent a further 10 monthly instillations; - if cancer persisted at 3 months, a second 6-week course was given. If disease persisted at 6 months, there was a cross-over to a 6-week second-line course of BCG for participants in the 2 MMC groups and electromotive MMC for participants in the BCG group.	Time to first recurrence, time to progression, time to death from any cause, adverse effects	Supported by grants Progetti di Ricerca di Ateneo ex 60% 1999–2000 and 2000–2001 from Tor Vergata University of Rome. Electromotive equipment provided by Physion Srl, Medolla, Italy.	No interest, except 1 coauthor, who reported financial interest with the company.	53 participants underwent cross-over: 25 with electromotive MMC and 15 with MMC switched to a 6-week BCG course; 13 with BCG failure switched to electromotive MMC. Here we only considered the MMC data with passive administration, not the electromotive MMC data. 1 of the study authors declared financial interest with the company providing the electromotive equipment.
Friedrich 2007	Study design: multicentre, prospective, randomised open-label clinical trial Number of study centres: unclear Study dates: 1995–2002, follow-up 2.9 years Participants randomly assigned: 495	Inclusion criteria: - histologically confirmed primary transitional cell carcinoma of the bladder or tumour recurrence after TUR without prior adjuvant therapy with intermediate-risk pTa G1 tumour (size > 3 cm, recurrent or multifocal tumour) or pTa G2 up to pT1 tumour (G1–3) - pT1 G3 tumours in case of a unifocal small tumour (diameter 2.5 cm) Exclusion criteria: - muscle-invasive tumour or a concomitant Cis - evidence of lymph node or distant metastasis - pT1 G3 tumour > 2.5 cm - pregnancy, mental disease, reduced kidney function or a second malignant disease	Group A: 6 weekly instillations of MMC 20 mg (MMC 6 week) Group B: 6 weekly instillations of BCG RIVM (BCG 6 week) Group C: 6 weekly instillations of MMC 20 mg followed by monthly instillations of MMC 20 mg for 3 years (MMC 3 years) Procedure: - instillation was performed with a volume of 20 mL after emptying the bladder; - participants received 20 mg of MMC or RIVM 2 10^8 cfu; - adjuvant intravesical therapy was started 4 weeks after TUR (after second TUR in case of a pT1 tumour). In case of recurrence, treatment was stopped.	Recurrence-free survival, adverse effects	Quote: "The work was supported in part by Fa. Medac GmbH, Wedel, Germany. Dr Pichlmeier is an employee of Medac GmbH."	Quote: "None of the authors will benefit financially from the publication of the manuscript."	Quote: "None of the authors will benefit financially from the publication of the manuscript. The work was supported in part by Fa. Medac GmbH, Wedel, Germany. Dr Pichlmeier is an employee of Medac GmbH." Our meta-analyses included groups A and B. Group C was considered in the sensitivity analyses.
Krege 1996	Study design: multicentre, prospective, randomised clinical trial Number of study centres: 14 Study dates: August 1985 to September 1992, follow-up 20.2 months Participants randomly assigned: 327	Inclusion criteria: - histologically confirmed stage pTa/T1 grades 1–3 bladder cancer - complete resection of tumour, inconspicuous cystoscopy after 6 weeks - > 3,000/mL leukocytes; > 100,000/mL thrombocytes; serum creatinine < 2.0 mg Exclusion criteria: - primary stage pTa grade 1 tumours - metastasis, upper urinary tract tumour, hydronephrosis, other malignant disease or active tuberculosis - intravesical chemotherapy during the last 6 months or previous radiation - acute urinary infection	Group A: 112 participants randomised to TUR alone Group B: 113 participants randomised to TUR followed by intravesical MMC 20 mg in 50 mL saline Group C: 102 participants randomised to TUR followed by intravesical BCG 120 mg Connaught strain in 50 mL saline, plus concomitant subcutaneous BCG 0.5 mg. Procedure: - at 6 weeks after TUR, participants underwent subsequent urethrocystoscopy, and in case of residual tumour a second TUR was performed; - instillation was done only after complete resection of the tumour, 7 days after secondary resection at the earliest; - MMC was instilled via a catheter and kept in the bladder for 2 hours. Instillations were performed every 2 weeks during year 1 and once a month during year 2; - BCG was instilled intravesically for 1 hour. At the same time BCG 0.5 mg was applied subcutaneously. Therapy was continued once weekly for 6 weeks and once a month for 4 months; - in case of tumour recurrence TUR was repeated.	Time to recurrence, progression rate and adverse effects	Supported by a grant from the Ministry of Science and Technology, Germany.	No information reported.	Sample size calculations demanded the admission of 402 participants into the study. However, despite an extended recruitment phase to September 1992, only 337 participants were enrolled.

Supplementary Table 1. Continued

Study	Methods	Participants	Interventions	Outcomes	Funding sources	Declaration of interest	Notes
Lamm 1995	Study design: multicentre, prospective, randomised clinical trial Number of study centres: 65 institutions Study dates: not reported Participants randomly assigned: 447	Inclusion criteria: - histologically confirmed Ta or T1 transitional cell carcinoma at increased risk for tumour recurrence; - participants with stage Ta or T1 tumour with concurrent Cis were also eligible; - life expectancy ≥ 6 months, performance status of ≥ 2 according to Southwest Oncology Group criteria. Exclusion criteria: - tumours of stage T2 or higher; - concurrent treatment with chemotherapy or radiotherapy.	Group A: lyophilised Tice BCG 50 mg (5×10^8 cfu) diluted in 50 mL of sterile, preservative-free saline Group B: MMC 20 mg in 20 mL of sterile water Procedure: - treatment not sooner initiated than 1 week, and no later than 2 weeks, after tumour resection; - the suspensions were instilled into the bladder by gravity flow; - participants instructed to lie on their abdomen for 15 minutes and on their left, right and back for 15 minutes each and to retain the suspension, if possible, for 2 hours; - treatments were repeated weekly for 6 weeks and at 8 and 12 weeks, then monthly to 1 year.	Recurrence-free survival, worsening-free survival (progression to higher-stage disease), overall survival, adverse effects.	investigation was supported in part by the following PH.5 Cooperative Agreement grant numbers awarded by the National Cancer Institute, DHHS: CA46113, CA22433, CA13612, CA42777, C.446441, CA46282, CA13238, 'X45560, CA20319, C-427057, CA16385, 'X28862. CA35192, CA35431, CA12213, 'X22411, CA35090, CA32734, CA35178, C-435281, CA14028, CA35261, CA35117, CA45450, CA52420, CA37981, CA04919, CA36020. CA38926, CA32102, CA49957, CA21076.	No information on declaration of interests reported.	Trial of the Southwest Oncology Group. Early Trial Closure: quote: "The trial opened for accrual in December of 1988. The first planned interim analysis was performed in May 1992. It provided strong evidence of BCG arm superiority over the MMC arm with respect to prolonging the time to first recurrence in patients without Cis. Based primarily on the strength of this evidence the trial was closed by its data monitoring committee prior to the completion of planned accrual. The intent-to treat analysis presented in this article preserves the between arm comparability implemented through randomisation. However, because the trial was closed early with an indication of BCG superiority it is possible that patients randomised to MMC were switched to BCG treatment. If a large number of patients randomised to the MMC arm were switched to BCG treatment then the intent-to-treat analysis will underestimate the relative magnitude of the BCG effect size (as compared to MMC)."
Malmström 1999	Study design: multicentre, prospective, randomised clinical trial Number of study centres: 12 Study dates: 1987–1992, follow-up of 10 years Participants randomly assigned: 261	Inclusion criteria: - people with stage Ta, grades 1–3 or stage T1, grades 1 and 2 tumours with ≥ 3 tumour effects during the prior 18 months - people with stage T1, grade 3 and people with primary or concomitant dysplasia or carcinoma Exclusion criteria: - previous or ongoing intravesical treatment with MMC, BCG or radiotherapy, chemotherapy during the prior 6 months - any secondary malignancy except treated Cis of the uterine cervix or basal cell carcinoma of the skin - ongoing corticosteroid therapy - leukocytes < 3,000/mL, thrombocytes < 100,000/mL - untreated urinary tract infection, urethral stricture preventing cystoscopy, active tuberculosis, pregnancy - Karnofsky performance index < 50	Group A: MMC 40 mg dissolved in 50 mL phosphate buffer (pH 7.4) Group B: BCG (Danish strain 1331) 120 mg containing 1×10^9 cfu, dissolved in 50 mL saline Procedure: - therapy begun 1–3 weeks after TUR or biopsies, and was given weekly for 6 weeks, then monthly for up to 1 year and every 3 months during year 2; - treatment cross-over for people with stage Ta, grades 1–3 or stage T1, grades 1 and 2 disease if tumour relapsed at 2 consecutive follow-up visits. Cross-over was performed at initial relapse in people with stage T1, grade 3 tumour, and if cytology and biopsies showed malignancy after 6 months of treatment in people with stage Cis disease or dysplasia.	Recurrence-free survival, progression-free survival, overall survival	No information on funding in the first study publication reported. The later publications referred to governmental funding sources.	No information on declaration of interests in the first study publication. In the publication of 1999, 1 author reported "financial interest and/or other relationship with Statens Serum Institute;" in the publication of 2007, the authors declared no conflicts of interests.	Supported by Grant 2323-Bg5-09XBB from the Swedish Cancer Society. First author declared financial interest or other relationship with Statens Serum Institute, or both.
Mangiarotti 2008	Study design: prospective, randomised clinical trial Number of study centres: 1 Study dates: recruitment period not reported, follow-up 12–108 months Participants randomly assigned: 92	Inclusion criteria: - histologically confirmed Ta-T1 G1-2 stage tumour Exclusion criteria: - no previous intravesical treatment	Group A: MMC 40 mg in 50 mL saline Group B: BCG Tice Procedure: - therapy started 1 month after TUR; - MMC once a week for 8 weeks, thereafter for once a month for 1 year; - BCG weekly for 6 weeks, thereafter once a month for 1 year.	Recurrence rate, recurrence-free survival, adverse effects	Not reported.	No information on interests reported.	Sample size estimation required 97 participants to allow a 5% dropout and 92 remaining participants (46 in each group). The article reported on the 92 participants and on the 46 per group.

Supplementary Table 1. Continued

Study	Methods	Participants	Interventions	Outcomes	Funding sources	Declaration of interest	Notes
Michielsen 2013	Study design: prospective, randomised controlled clinical trial Number of study centres: 1 probably Study dates: not reported Participants randomly assigned: unclear	Inclusion criteria: - people with intermediate risk of non-muscle invasive urothelial carcinoma of the bladder Exclusion criteria: - not reported	Group A: MMC 40 mg in 50 mL 0.9% saline Group B: BCG full dose Procedure: - treatments weekly for 6 weeks, each group had a specific maintenance programme.	Disease-specific quality of life, measured with EORTC QLQ BLS24	No information reported.	No information reported.	Congress abstract available only.
NCT00974818	Study design: prospective, randomised clinical trial Number of study centres: 3 Study dates: September 2009 to March 2012 Participants randomly assigned: 50	Inclusion criteria: - pathologically confirmed Ta or T1 non-muscle invasive urothelial bladder tumours at intermediate risk Exclusion criteria: - any intravesical therapy within the past 6 months prior to current diagnosis - radiation treatment or surgery for the bladder or chemotherapy during the study	Group A: MMC 40 mg, dissolved in 20 mL sterile water Group B: BCG 81 mg, dissolved in 53 mL of diluent and saline Procedure: - MMC: induction course of 6 cycles of weekly intravesical therapy of MMC, followed by a maintenance schedule consisting of 3 weekly cycles of the same drug at 3, 6, 12, 18 and 24 months; - BCG: induction course of 6 cycles of weekly intravesical therapy of either BCG, followed by a maintenance schedule consisting of 3 weekly cycles of the same drug at 3, 6, 12, 18 and 24 months. Participants received 3 weekly cycles of intravesical BCG 27 mg 3, 6, 12, 18 and 24 months after the induction course.	Response to treatment (relapse rate), serious adverse effects, adverse effects	Sponsor was Memorial Sloan Kettering Cancer Center.	No information reported.	Study has been terminated due to lack of accrual. Only the trial entry is available: NCT00974818. Official name: mitomycin C versus Bacillus Calmette-Guérin in the intravesical treatment of non-muscle-invasive bladder cancer participants: a randomized phase III non-inferiority trial. Quote: "Due to a lack of patients accrued to the protocol the protocol was closed and the analysis of the 2 year relapse rates could not be compared."
Ojea 2007	Study design: multicentre, prospective, randomised clinical trial Number of study centres: unclear Study dates: March 1995 to May 1998, follow-up 52.6 months Participants randomly assigned: 430	Inclusion criteria: - intermediate-risk people with stages Ta G2 and T1 G1-2 tumours, without Cis Exclusion criteria: - Ta G1 tumours, high-risk tumours - concurrent or previous muscle-invasive disease, concurrent or previous tumour in the upper urinary tract or prostatic urethra - chronic urinary tract infection, cured or active tuberculosis - < 2 years of life expectancy, physical or psychic disability - any other malignancy except basal cell carcinoma of skin, previous pelvic irradiation - pregnancy or lactation - any other disease with immunodeficiency	Group A: low-dose BCG 27 mg Connaught strain Group B: very low-dose BCG 13.5 mg Connaught strain Group C: MMC 30 mg Procedure: - Instillations started 14–21 days after TUR with histological confirmation of bladder cancer and were repeated once a week for 6 weeks followed by another 6 instillations given once every 2 weeks for 12 weeks.	Disease-free interval, time to progression, overall survival, adverse effects	No information	The authors reported that they had nothing to disclose.	CUETO study 95011
Rintala 1991	Study design: multicentre, prospective, randomised clinical trial Number of study centres: unclear Study dates: 1984–1987, for a subgroup of participants there is a follow-up of 20 years Participants randomly assigned: 89	Inclusion criteria: - people with Cis grade 1–3 - frequently recurrent Ta-T1 papillary transitional cell cancer grade 1–3 - histologically confirmed malignancy or 3 consecutive malignant cytological findings, or both Exclusion criteria: - not reported.	Group A: BCG Pasteur Strain F, 75 mg Group B: MMC 20–40 mg (AUC method) Procedure: - instillations (for 2 hours) started 2 weeks after TUR. Weekly repetition during the first month, then once a month for 2 years.	Recurrence rate, recurrence index, overall mortality, progression, disease-specific mortality	Finnish Cancer Foundation, Academy of Finland Paolo Foundation and Research and Science Foundation of Farmos	No information reported.	FinnBladder I study group. Jarvinen reported 20-year follow-up data based on a subgroup of participants with TaT1 disease and without Cis (91/109 participants).

Supplementary Table 1. Continued

Study	Methods	Participants	Interventions	Outcomes	Funding sources	Declaration of interest	Notes
Witjes 1996	Study design: multicentre, prospective, randomised clinical trial Number of study centres: 27 Study dates: 1987–1990, follow-up 36 months (2–81 months) Participants randomly assigned: 437	Inclusion criteria: - histologically confirmed primary or recurrent papillary transitional cell carcinoma stage Ta or T1 after complete TUR; - people with primary or concomitant Cis were also eligible. Exclusion criteria: - previously treated with intravesical or systemic cytotoxic agents or radiotherapy - recurrent severe bacterial urinary tract infections - bladder cancer other than transitional cell carcinoma or with a second primary malignancy (exception of basal cell or squamous cell carcinoma of the skin)	Group A: MMC 30 mg in 50 mL saline Group B: BCG-RIVM 5×10^8 bacilli in 50 mL saline Group C: BCG-Tice 5×10^8 bacilli in 50 mL saline Procedure: - MMC instilled once a week for 1 month (weeks 1–4) and thereafter once a month for 6 months; - BCG was administered once a week for 6 weeks. Treatments start 7–20 days after TUR; - if a recurrence was detected in the MMC group, complete resection was carried out and the MMC treatment continued monthly for another 3 months; - if disease recurred within 6 months in the BCG treatment group, a second course of 6 weekly instillations was administered after complete tumour resection; - if a recurrence was observed after completion of intravesical treatment or if the T category increased to T2 or higher, participants went off the study; - further treatment was left to the discretion of the individual urologist.	Recurrence-free survival, progression-free survival, adverse effects	No information reported.	No information reported.	Dutch South East Cooperative Trial. 1 pathologist determined stage and grade.
Witjes 1998	Study design: prospective, randomised clinical trial Number of study centres: 24 Study dates: January 1985 to October 1986, median follow-up 7.2 years Participants randomly assigned: 344	Inclusion criteria: - people with primary or recurrent pTa and pT1 bladder tumours, including Cis Exclusion criteria: - not reported	Group A: MMC 30 mg in 50 mL saline Group B: BCG-RIVM 5×10^8 bacilli in 50 mL saline Procedure: - intravesical therapy was started 7–15 days after resection; - MMC was given weekly for 4 consecutive weeks and thereafter monthly for 5 months; - BCG was given weekly for 6 consecutive weeks; - in case of a recurrence at 3 months, a complete resection was performed, where after in BCG-treated participants a second course was given and in MMC-treated participants instillations were continued; - in case of a recurrence at or after 6 months, or in case of progression to muscle invasion, the participant was withdrawn from the study.	Time to first recurrence, time to progression, adverse effects	This work was supported by grants 5U10 CA11488-26 and 5U10 CA11488-27 from the National Cancer Institute, Bethesda, MD.	No information reported.	Joint effort of the European Organisation for Research and Treatment of Cancer (EORTC) Genito-Urinary Tract Cancer Collaborative Group and the Dutch South East Cooperative Urological Group (protocol 30845).