

DR. STEVE P MCCOMBIE (Orcid ID : 0000-0002-3920-994X)

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**The BCG + Mitomycin trial for high risk non-muscle-invasive bladder cancer: Progress report and lessons learned**

Dickon Hayne <sup>1,2,3</sup>	dickon.hayne@uwa.edu.au
Martin Stockler <sup>1,4</sup>	martin.stockler@sydney.edu.au
Steve P. McCombie <sup>1,3</sup>	stevemccombie@ymail.com
Nicola Lawrence <sup>1,4</sup>	nicola.lawrence@ctc.usyd.edu.au
Andrew Martin <sup>1,4</sup>	andrew.martin@ctc.usyd.edu.au
Shomik Sengupta <sup>1,5,6,7</sup>	senguptaurology@gmail.com
Ian D. Davis <sup>1,8</sup>	ian.davis@monash.edu

Corresponding author: Dickon Hayne

<sup>1</sup> Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP)

<sup>2</sup> School of Surgery, University of Western Australia, Crawley, WA, 6009, Australia

<sup>3</sup> Fiona Stanley Hospital Urology, Murdoch, WA, 6150, Australia

<sup>4</sup> NHMRC Clinical Trials Centre, University of Sydney, NSW, 2050, Australia

<sup>5</sup> Department of Urology, Austin Health, Melbourne, VIC, 3084, Australia

<sup>6</sup> Austin Department of Surgery, University of Melbourne, Melbourne, VIC, 3010, Australia

<sup>7</sup> Ludwig Institute for Cancer Research, Austin Hospital, Melbourne, VIC, 3084, Australia

<sup>8</sup> Monash University Eastern Health Clinical School, Box Hill, VIC, 3128, Australia

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## **Trial overview**

The BCG + Mitomycin trial (ACTRN12613000513718; ClinicalTrials.gov NCT02948543; ANZUP 1301) is an ongoing randomised phase III trial aiming to compare the efficacy and safety of the addition of intravesical Mitomycin chemotherapy to standard intravesical BCG in patients with resected, high-risk non-muscle-invasive bladder cancer (NMIBC) [1]. Our meta-analysis suggested reduced rates of recurrence (relative risk (RR) 0.75; 95% CI 0.61 to 0.92,  $p < 0.01$ ) and progression (RR 0.45; 95% CI 0.25 to 0.81,  $p < 0.01$ ) with combination treatment as compared to treatment with BCG alone in patients with Ta or T1 disease, but not in those with pure carcinoma-in-situ (CIS) [2]. However, this remains unproven for all subgroups of high-risk NMIBC, or when treatment is delivered without electromotive delivery (as is usual), and requires corroboration in a definitive, large scale, randomised phase III trial.

Patients with high-risk NMIBC (high-grade Ta, or any-grade T1) are randomised 1:1 to either standard treatment (BCG) or experimental treatment (BCG + Mitomycin). As shown in Figure 1, standard treatment consists of induction (BCG once a week for six weeks) followed by maintenance (BCG once a month for ten months). Experimental treatment consists of induction (BCG or Mitomycin once a week for nine weeks) followed by maintenance (BCG or Mitomycin once a month for nine months).

This two-stage trial aims to recruit 130 participants for stage one and a further 370 participants for stage two (with final analysis based on the 500 participants). The primary outcome is treatment completion for stage one, and disease-free survival for stage two; secondary outcomes are disease activity, time to recurrence, time to progression, overall survival, adverse events, health-related quality of life, feasibility, and resource use. Full inclusion and exclusion criteria are outlined in the trial protocol [1], however most patients with high-risk NMIBC (except pure CIS) will be eligible as long as they have not had previous upper tract urothelial cancer, muscle-invasive bladder cancer, radiotherapy to the pelvis, or intravesical therapy (single post-operative doses are allowed). Importantly, potential participants need to be randomised within eight weeks of their initial resection (or within eight weeks of re-resection if this is required), and treatment is to start within four weeks of randomisation.

## **Recent literature**

Since the commencement of this trial the following pertinent studies have been published that strongly support our original rationale, hypothesis, and study protocol.

EORTC 30962 was a randomised trial of 1355 participants designed to clarify the effects of dose (full dose vs. one-third) and length of maintenance regime (12 months vs. 36 months) for BCG in the treatment of intermediate and high-risk NMIBC [3]. This trial found that the reduced dose did not affect toxicity, and that while 36 months of maintenance had a small benefit in reducing recurrence for high-risk patients it had no effect on progression or survival. Additionally, only 36% of participants were able to complete the planned 36 months of treatment. These results provide further support for the 12 month duration of intervention in the BCG + Mitomycin trial.

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Trials from the Finn bladder group failed to show much promise for Interferon alpha 2b [4], and provided further evidence that Mitomycin appears relatively ineffective in pure CIS, even when given in combination with BCG [5]. These trials provide further justification for our choice of intra-vesical agents, and the exclusion of patients with pure CIS from the BCG + Mitomycin trial.

CUETO 93009 was a trial of 407 participants with intermediate and high-risk NMIBC who were randomised to BCG (weekly for six weeks, followed by three further doses a fortnight apart), or BCG and Mitomycin (same schedule with the addition of intravesical Mitomycin a day before each BCG instillation) [6]. There was a significant improvement in disease-free interval with combination therapy compared with BCG alone (hazard ratio (HR) 0.57; 95% CI 0.39 to 0.83,  $p < 0.01$ ), the first trial to demonstrate this without using electromotive delivery. Unfortunately toxicity was significantly higher in the combination arm, a finding that does not appear to be eventuating in our BCG + Mitomycin trial based on early analysis. The toxicity and lack of an adequate maintenance schedule in CUETO 93009 means that this regimen is unlikely to become widely adopted.

### **Trial progress**

With funding from Cancer Australia, stage one of the BCG + Mitomycin trial opened for recruitment in December 2013. Unfortunately accrual lost momentum from August 2014 as a result of an unexpected international BCG shortage, which led to temporary suspension of recruitment and delays in opening new sites. However this shortage has since resolved and the trial is now accruing well. Recruitment to the trial was also adversely affected by the higher comparative cost to centres for participants in the combination arm. Financial support was sought from Omegapharm who is providing Mitomycin at a discounted cost to support the trial.

Despite these extraordinary circumstances the BCG + Mitomycin trial has made significant progress recruiting 99 participants from 11 Australian sites as of March 2017. It is anticipated that recruitment for stage one will be completed by the end of 2017 and a further 10 sites are expected to open for recruitment by the end of 2018. One significant hurdle in the opening of sites has been the relative lack of clinical trials infrastructure within urological departments. Solutions have included the reskilling of existing urology nursing staff and support from local medical oncology and clinical trials units have been crucial.

Collaboration between the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP) and the National Health and Medical Research Council (NHMRC) Clinical Trials Centre has been instrumental in the efficient progress of this trial. The BCG + Mitomycin trial is Australia's first large scale clinical trial for the treatment of NMIBC. Urologists are encouraged to support the trial by referring appropriate patients to currently active sites as listed in Table 1.

### **Conflict of interest**

IDD is supported by an NHMRC Practitioner Fellowship (APP1102604).

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<b>Victoria</b>
Austin Hospital
Epworth HealthCare (Richmond)
Footscray Hospital
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<b>New South Wales</b>
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NMIBC high Ta or any T1

