Immunotherapy for non-muscle invasive bladder cancer

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Abstract

Supplies of intravesical Bacillus Calmette-Guerin (BCG), the first-line treatment for most intermediate- and high-risk non-muscle invasive bladder cancers (IR- and HR-NMIBC), have proven unreliable over the last decade. This review considers the evolution of BCG immunotherapy for NMIBC: from the discovery of the anti-tumour side-effects of Tuberculosis (TB) and subsequently the BCG vaccine, to recent advances in novel immunotherapeutic agents. We summarise the evidence for alternative options to standard intravesical BCG therapy regimens and describe the potential for immune response manipulating drugs in the treatment of NMIBC. These new agents, including immune checkpoint inhibitors, toll-like receptor agonists, and recombinant viral vectors, may provide better options in the management of NMIBC in the future.

Lay Abstract

Many patients with non-invasive bladder cancers may need treatments into the bladder, including one called Bacillus Calmette-Guerin (BCG). Unfortunately, the supplies of BCG have been interrupted and somewhat unreliable since 2012. Because of this, we have been forced to look at other means of treating our patients using drugs like BCG. This has made us think about how BCG treatment was first developed more than forty years ago, and how it has evolved as a treatment for bladder cancer. In this article, we review the current uses of BCG and other treatments for bladder cancer, and explore what the future may hold for bladder cancer treatments.

(Tweetable abstract – optional): This review explores the evolution of intra-vesical BCG therapy in IR- and HR-NMIBC. We also describe new and emerging immunotherapeutics in the management of NMIBC, which may become more important if the worldwide shortage of BCG continues.

Keywords

Bladder cancer, Bacillus Calmette-Guérin, BCG, Immunotherapy, Review

INTRODUCTION

Bladder cancer is the seventh most common cancer in Western society, with an annual global incidence of >430,000 cases(1). In the UK, we observe >10,000 new cases per year, with an estimated 70,000 patients living with bladder cancer at any one time. Greater than 90% are urothelial cell carcinomas (UCC) of the bladder (previously termed transitional cell carcinomas - TCC)(2).

Most patients in the UK (75-85%) present with non-muscle invasive bladder cancer (NMIBC: stages Ta/T1/Tis)(3); which represents a spectrum of disease from solitary small tumours with low-risks of recurrence or progression, to large multifocal disease with high-risks of early recurrence or progression to invasive or metastatic disease(4). Such progression to muscle-invasive bladder cancer (MIBC: stages ≥T2) occurs in up to 45% of NMIBC patients(4, 5), and is associated with worse outcomes than if the patient initially presented with MIBC, with a 5-year overall survival rate of only 27-50% despite radical therapies(6, 7). Intravesical Bacillus Calmette-Guérin (BCG) is central to the management of HR-NMIBC, and more recently IR-NMIBC, and has been used for over 40 years to reduce the risks of tumour recurrence and progression (rather than cure)(8). BCG thus represents one of the oldest immuno-oncology (IO) agents in current use. However, there has been a surge in the study and trial setting use of newer IO therapeutics for bladder cancers and other malignancies. In this review, we describe the history of BCG as an IO agent, the current use of BCG for bladder cancer, and the possible future of immunotherapy in bladder cancer.

BCG PAST: DISCOVERY, DEVELOPMENT & TREATMENT REGIMENS

Discovery & Development

The journey of discovery of the anti-tumour effects of tuberculosis (TB) to the development of intravesical BCG therapy is a fascinating series of linked events driving clusters of research, leading ultimately to the development of the BCG treatment regimes in use today.

In 1925, Dr Thomas Cherry noticed an inverse relationship between the incidence of cancers and tuberculosis (TB). Epidemiological data confirmed that as the incidence of TB declined, more people were dying from cancer(9). These findings were explored further by Dr Raymond Pearl in 1929, who conducted an autopsy series investigating TB lesions in two demographically matched patient groups. He concluded that active TB lesions were more than twice as likely to be present in the no malignancy 'control' group (16.3%) compared to the group with malignancies (6.6%)(10). From these findings stemmed the notion of the possible anti-tumour effects of TB.

Some 40 years earlier in the 1880s, Louis Pasteur successfully attenuated live strains of cholera and anthrax, and the rabies virus, creating non-virulent forms suitable for vaccination. In 1908, Albert Calmette and Camille Guérin adopted Pasteur's technique to create a successful vaccination against TB, known as Bacillus Calmette-Guérin or 'BCG'(11). Calmette and Guérin used isolated *Mycobacterium Bovis* from an infected cow; after 231 passages over 13 years, the bacterium was finally deemed innocuous, creating the live-attenuated BCG vaccine(12). The production of BCG vaccine provided a means for the therapeutic use of the anti-tumour effects of TB in a safer form.

Years later in 1959, Lloyd Old carried out the first study demonstrating the anti-tumour action of the BCG vaccine; mice with transplantable tumours given BCG vaccine demonstrated increased resistance to tumour growth compared to non-vaccinated control mice(13). These results supported Cherry's findings 30 years previously of the inverse relationship between the incidence of cancer and TB.

In 1966, Coe and Feldman investigated hypersensitivity responses in extracutaneous tissues of guinea pigs. They found that intra-vesical injection stimulated the greatest hypersensitivity response, and although not recognised at the time, this provided early evidence of the potential use for BCG in bladder cancer(14). Following this in 1971, a study by Zbar involving intralesional injections of BCG into hepatocarcinoma-induced guinea pigs, showed that animals injected with BCG did not develop metastases. For optimum effect, it was found that contact between the BCG and tumour cells was needed, and that tumours above a certain size were not effectively treated by BCG(15).

Results from these two studies formed the basis from which two concepts were derived:

1. The anti-tumour effect of BCG was better when restricted to one organ to maximise contact
2. The dose of BCG must be sufficient for the size of the tumour(s)

BCG was first used in the human bladder by deKernion *et al.* in 1975. A patient with an isolated metastasis of a malignant melanoma in the bladder underwent cystoscopic intra-lesional injection of BCG. Cystoscopy confirmed an active area of granulomatous inflammation, and subsequent excision did not identify any residual cancer(16).

Treatment Regimens

In 1976, the first intravesical instillation of BCG was performed by Morales. This was a small study of nine patients with a previous history of 22 tumour recurrences in 77 patient-months. Patients received 120mg BCG in 50ml saline for each of six instillations administered weekly; following BCG instillation only one recurrence was observed after 41 patient-months(17). Interestingly, this six-week regime arose because the Frappier BCG strain used was packaged in six vials, and because adverse side-effects of this strain diminished within one week, permitting weekly instillation(18). As identified previously by Zbar, a 'sufficient' dose of BCG was required for anti-tumour effects, so taking into account the added dilution from urine within the bladder, the 120mg dose was deemed suitable(18). Amid increasing scientific and clinical interest in BCG therapy for NMIBC, larger studies were undertaken that determined toxicity and efficacy. The US Food and Drug Administration (FDA) subsequently approved the use of intravesical BCG instillation for the treatment of NMIBC in 1990.

A meta-analysis conducted in 2002 concluded that BCG not only reduces recurrence of NMIBC but also reduces progression to MIBC(19). With an initial six-week course of BCG deemed safe and effective (what is now termed 'induction' BCG), attention then focused on prolonging the duration of intravesical BCG treatment ('maintenance') in the assumption that further treatment could improve oncological outcomes. Two early studies published in 1987 compared outcomes of patients receiving

maintenance therapy to induction alone. Interestingly, neither demonstrated significant differences in rates of tumour recurrence or progression between groups, initially suggesting maintenance therapy was not beneficial, yet increased patient side effects(20, 21). However, small sample sizes, the presence of macroscopic tumour in many cases, and heterogeneity in both the tumour types included and treatment schedules, may have confounded their results. Indeed, a subsequent larger trial with 550 patients was published by Lamm in 2000(22). Here, a more homogenous patient cohort with high-risk non-invasive papillary and carcinoma in situ, who were also macroscopically tumour free, were randomised to receive either induction BCG only or induction plus maintenance BCG (intravesical and percutaneous). The maintenance arm received BCG each week for three weeks at intervals of 3, 6, 12, 18, 24, 30, and 36 months after induction. This study revealed that the median recurrence-free survival was over twice as long for those receiving maintenance therapy (76.8 months) compared to those receiving induction only (35.7 months) ($p<0.0001$). Additionally, 5-year survival was 83% in the maintenance arm compared to 78% in the induction only arm confirming the patient benefits of maintenance BCG therapy. Furthermore, a 2003 meta-analysis concluded that toxicity did not differ between patients receiving maintenance therapy and those who do not(23). Therefore, despite increased healthcare costs and patient burden/morbidity, BCG maintenance therapy became incorporated into numerous international guidelines for the treatment of both high-risk, and more recently, intermediate-risk NMIBC(24).

[Figure 1 –The evolution of BCG therapy.]

BCG PRESENT: SHORTAGES & TREATMENT EVOLUTION

Shortages

There have been several different strains of BCG available, including, but not limited to, Connaught, TICE, Pasteur, Danish, Moreau and Merck. Despite both a recent meta-analysis and review (25, 26) suggesting no superiority of one strain over another in the management of high-risk NMIBC, the Connaught strain appeared to be the most widely used. However, as of July 2012, there has been a worldwide shortage of BCG vaccine - the manufacturers of the BCG Connaught strain shut down temporarily following reports of US FDA regulatory breaches, and later stopped Connaught strain production indefinitely in 2016(27). There are several different strains of BCG available, but limited data comparing their relative efficacy(28). Many centres were forced to use Merck's TICE strain following the Connaught shortage, but a randomised controlled trial in 2014 suggested that TICE may be less effective than Connaught following induction. The Connaught strain was found to have 74% 5-year recurrence-free survival compared to 48% for TICE(28). An ongoing large-scale trial (the Southwest Oncology Group (SWOG) S1602), is further evaluating the efficacy of the Tokyo-172 BCG strain, after a smaller 2013 study suggested similar one-year recurrence-free survival to the Connaught strain, *i.e.* superior to TICE for both induction and maintenance(29). In addition, a 2016 retrospective study suggested that the Moreau strain had comparable efficacy to those more widely used, with 5-year recurrence-free survival of 65% and progression-free survival of 81%(30). Following this, a retrospective study in 2019 compared BCG TICE with BCG Moreau and found no difference between progression-free and recurrence-free survival, concluding BCG Moreau as an alternative effective substrain for the treatment of NMIBC in a time of shortage(31). SWOG S1602 is also evaluating potential benefit of priming with subcutaneous BCG prior to intravesical BCG to enhance T-cell entry into the bladder mucosa(32). It is clear that further studies are required to evaluate efficacy of alternative strains to help overcome the shortages of the currently-licensed and historically widely-used BCG strains. Notwithstanding, there is little incentive for companies to manufacture BCG - each dose is relatively cheap to purchase, but labour-intensive to produce (three

months of culturing and susceptibility to contamination)(33). Since one course of induction BCG therapy (6 instillations) exceeds the dose required to meet the UK's annual BCG vaccination requirements for one year, the shortages have caused major issues with continuing current BCG regimes as a first-line treatment for most IR- and HR-NMIBC(34).

For many years, the precise anti-tumour mechanism of BCG has remained unclear and is beyond the scope of this article. However, various recent mechanistic studies have improved our understanding(35, 36) which may prove helpful when investigating adjuncts to BCG use, that could improve efficacy and/or reduce toxicity.

Treatment Evolution

BCG shortages continue to impact clinical practice(37). It has therefore been important to investigate possible ways of reducing BCG use whilst maintaining clinical efficacy, specifically, the use of adjunct therapies (in combination with BCG), and modifications to the current standard BCG treatment regimes.

<u>Combination Therapy</u>

Mitomycin C (MMC) is a chemotherapeutic agent that was first found to reduce bladder cancer recurrence following intravesical instillation in 1988(38). Mitomycin C binds and crosslinks DNA through alkylation, preventing DNA synthesis(39). Electromotive drug administration (EMDA) is a recent innovation that enhances drug efficacy by the processes of iontophoresis, electro-osmosis and electroporation(40). When EMDA is utilised to deliver intravesical MMC it is thought that it can penetrate 4-7 times deeper into the bladder mucosa(41), thereby increasing the concentrations of MMC reaching cancer cells. Combinations of BCG and EMDA-MMC instillations have shown promise as an alternative to the full course of both BCG induction and maintenance therapy(42).

Adapting Treatment Regimens

As described by Lamm, the dose-response curve for BCG is bell-shaped, indicating that excessively high concentrations of BCG may worsen outcomes and may paradoxically enhance tumour growth(43). If this curve peak can be determined however, treatment regimes could be optimised further or tailored to each patient, with potentially improved outcomes. Unfortunately however, uncertainty persists over the length and frequency of instillations during maintenance therapy, thus the optimal schedule and length of the maintenance period remains an area of ongoing clinical investigation.

188 ***[Table 1:*** *A summary of studies investigating different BCG regimens (D = dose, FD = full dose, AE = adverse events).]*

Oddens' 2013 RCT, summarised in **Table 1**, describes the potential to reduce the duration of BCG maintenance after comparing three years to one year maintenance(44). For HR-NMIBC patients, three years' full-dose BCG (maintenance) reduced tumour recurrences compared to one year full-dose, but did not reduce disease progression or overall mortality. This trial also evaluated using 1/3 dose BCG for both induction and maintenance; this appeared to have decreased efficacy but without reduced side-effects/toxicity, however, patient drop-out was lower than with higher dose and longer maintenance schedules. This suggests that current practice of three-year maintenance therapy with full-dose BCG could be reduced to improve patient compliance with a small trade-off in reduced efficacy. Furthermore, a reduced-dose regime would reduce financial costs and ensure BCG supplies last longer.

Following Oddens' findings, a 2015 CUETO group RCT investigated the efficacy of three year maintenance BCG (BCG instillation once every three months) versus BCG induction only (BCG once-weekly for six weeks)(45). This maintenance schedule reduced the number of BCG instillations from 27 (the standard SWOG regimen) to 18. Interestingly, this study suggested that recurrence and progression rates, and overall and cancer-specific survival, were no different between the induction only and induction plus maintenance arms(45). Furthermore, there was lower attrition due to toxicity/side-effects in the induction only arm compared to the maintenance arm (2.6% and 9.9%, respectively). These data suggest that for maintenance therapy to be more effective than induction alone, maintenance instillations must be more frequent than every three months.

The 2020 phase III NIMBUS RCT investigated different induction and maintenance BCG instillation frequencies(46). The reduced frequency group received three induction doses at weeks 1, 2 and 6, compared to standard regime of once-weekly dosing for six weeks, and fewer maintenance cycles at weeks one and three of months 3, 6 and 12, compared to the standard weekly dosing for three weeks at months 3, 6 and 12, for one year. Overall, the reduced frequency group received a total of nine BCG instillations, versus 15 for the standard/control group. Although the reduced frequency arm experienced fewer adverse events, the trial was closed early due to a 'safety-relevant difference' in

recurrences between treatment arms: 27.1% recurrences after 12 months' median follow-up, compared to 12.0% in the standard BCG arm.

Alternative Therapies

Bladder cancer is said to be 'BCG-unresponsive' when there is persistent or recurrent CIS and/or papillary tumour within 12 months, or recurrent high-grade Ta/T1 tumour within six months of adequate BCG treatment(47). Adequate BCG therapy is defined by at least five out of six induction doses with two out of three maintenance doses, or five induction doses plus two second course induction doses(47).

For patients who may not tolerate BCG or are BCG-unresponsive, a novel rescue therapy was proposed by Steinberg in 2015(48). This involved weekly intravesical instillations of gemcitabine immediately followed by docetaxel (Gem/Doce) for six weeks(48). Gemcitabine (a deoxycytidine nucleoside analogue) causes DNA synthesis inhibition, whilst docetaxel (an inhibitor of tubulin dis-assembly) disrupts the cell cycle(48). This combination acts synergistically and leads to apoptosis and reduced cell division, and ultimately tumour cell death.

Subsequently, a small clinical trial in 2017, suggested that this combination chemotherapy was safe and effective for patients with high-risk NMIBC who were BCG naïve(49). Steinberg *et al.* performed a retrospective review of patient records at multiple institutions examining the efficacy of Gem/Doce(50). Recurrence-free survival of high-risk disease was 65% at one year and 52% at 2 two years with only 3.3% of patients unable to complete the treatment course due to side-effects(50). This confirmed the potential for Gem/Doce as a rescue therapy following BCG failure, and highlighted the need for further (prospective) studies evaluating this combination therapy.

BCG FUTURE: BUILDING ON THE IMMUNOTHERAPY PARADIGM

The significant reduction in risk of recurrence and progression of NMIBC in patients receiving BCG, has highlighted the importance of immunotherapy for bladder cancer. As understanding of the molecular events and characteristics of various cancers improves(51), more targeted novel therapies are being developed.

Immune Checkpoint Inhibitors

There are a plethora of clinical trials evaluating the efficacy of new and more established immune checkpoint inhibitors (ICIs) across multiple haematological and solid organ malignancies. Our understanding of ICIs is still in relative infancy but many are already showing great promise. For example, in the Keynote-057 trial, 101 BCG-unresponsive high-risk NMIBC patients received at least one dose of pembrolizumab during 24 months, or until tumour recurrence, or until dropout due to toxicity/side-effects(52). Keynote-057 found that 41% patients achieved a complete response (absence of recurrent high-risk NMIBC or disease progression) at three months(52), and 46% of those responding remained recurrence and progression free at 12 months(52). Furthermore, pembrolizumab treatment led to a 12-month progression-free survival of 83%(52). Despite inferiority in oncological outcomes compared to radical cystectomy, the use of pembrolizumab was approved by the FDA in 2017 following these promising data, and it is currently used in clinical practice. However, more studies are required to determine optimum treatment regimes. More recently, and for BCG-naïve high-risk NMIBC patients, the POTOMAC study assessed the efficacy of durvalumab (a PD-L1 inhibitor) in combination with BCG, compared to standard BCG therapy alone, in BCG-naïve high-risk NMIBC patients(53). It is anticipated that results from these and other clinical trials will lead to more options and greater success in the management of NMIBC, as stand-alone novel ICI therapy or in combination with BCG.

Toll-like Receptor Agonists

BCG immunotherapy is thought to act, at least in part, through interactions with three toll-like receptors (TLRs); TLR2, TLR4 and TLR9(54).

Toll-like receptors are a large family of cell membrane-spanning proteins that mediate multiple intracellular mechanisms and pathways vital to the innate immune system. Agonists of TLRs have been shown to possess anti-tumour activity across multiple malignancies(55), including, for example, the TLR7 agonist Imiquimod, already in clinical use for basal cell carcinoma and some penile cancers(56).

Importantly for bladder cancer, TLRs are present in urothelium, and although their expression may ~~be~~ decrease in bladder tumours, their activity has been shown to persist(54). Therefore, TLR agonists appear an attractive target in bladder cancer, and as such, agonists of TLR2, TLR4, TLR7 and TLR9 have been investigated for anti-tumour effects in in-vitro and in-vivo bladder models(54). A small first phase clinical trial of intravesical Imiquimod determined it was safe and had low systemic absorption and toxicity(57). However, further studies are required to establish the optimal TLR(s) to target for NMIBC, and thenceforth desired effects on bladder tumour recurrence or progression to MIBC.

An alternate TLR-mediated immunotherapy is the use of BCG cell wall skeleton (CWS). BCG-CWS is a component of the BCG cell wall that can be produced readily, and provides ligands for TLR2 and TLR4(54). Preliminary investigations have shown growth retardation of bladder tumours when administered intravesically in mice(56). The Morales group demonstrated that for patients who have failed standard BCG therapy, intravesical instillations of such a mycobacterial cell wall-DNA complex possessed anti-tumour activity without significant toxicity or patient side-effects(58). These studies highlight the promise and huge potential of immunotherapy, targeting Toll-Like Receptors, for the management of bladder cancer, whether alone or in combination with BCG.

Other Promising Immunotherapeutic Approaches

Interferon alpha-2b, a recombinant protein immune modulator, has been shown to induce bladder tumour regression in animal studies(59, 60). A subsequent clinical trial of different dosing regimes of Interferon alpha-2b in patients with BCG failure or BCG-unresponsive NMIBC, demonstrated good tolerability and suggested potential benefit in recurrence-free survival(61). This interferon was delivered in the form of a recombinant replication-deficient adenovirus gene vector 'Nadofaragene Firadenovec' (rAd-INFα/Syn3) which stimulates local urothelial INFα-2b production, leading to tumour regression(61). Consequently, a phase three trial recruited patients with BCG-unresponsive NMIBC, who received single intravesical doses of Nadofaragene Firadenovec, repeated at 3, 6 and 9 months, if there was no high-grade recurrence(62). Results were promising, with 53.4% of participants having a complete response (macroscopic tumour resolution) at month three, and 45.5% of patients were recurrence free at 12 months(62). This trial also demonstrated 91.9% 24-month overall survival for those receiving at least one dose, whilst significant side effects were only seen in 2% of patients(62). Therefore, Nadofaragene Firadenovec, as a novel and first-of-its-kind gene therapy, could be considered as a viable alternative for patients who fail to respond to BCG therapy (as an alternative to, or if unfit for, radical cystectomy), or even as a potential first-line treatment, for which further data are imminent.

Another trial evaluating a recombinant fusion protein in BCG-unresponsive HR-NMIBC patients is VISTA. This phase III non-randomised trial uses Vicinium, a potent inhibitor of protein synthesis that ultimately induces irreversible cell death. Intravesical Vicinium is administered twice weekly for six weeks then weekly for six weeks (induction), then every two weeks for up to two years (maintenance). The three-month complete response was 42% in patients with CIS, and 68% in patients with HR-NMIBC without CIS. Given these promising early results, Vicinium is undergoing FDA licensing application as a potential alternative to radical cystectomy in BCG-unresponsive patients(63).

Cancer-specific vaccines have been trialled on a small-scale with intravesical immuno-stimulation by BCG with encouraging results: a non-randomised study investigated 24 NMIBC patients in three groups, receiving either vaccine injection (MAGE-A3) alone, or alongside one of two intravesical BCG combinations(64). All groups seroconverted after the vaccination schedule, and half the participants had detectable cancer-specific T-cells irrespective of group, yet only those receiving BCG had these same T-cells detected in urine. This suggests there may be an enhanced vaccine response via immune-stimulation which may help to localise cancer specific T-cells to the tumour.

Vγ9/Vδ2 T-cells are the main T-cell type in peripheral blood, and are involved in mediating immune responses to a variety of diseases(65). Vγ9/Vδ2 T-cells can be activated by pyrophosphate-containing phosphoantigens, and by specific prodrugs(65). Previously, pyrophosphate-containing phosphoantigen use has been limited due to their instability in serum, however, prodrugs have been synthesised that are much more stable in serum, and have also shown successful eradication of bladder cancer cells *in vitro*(65). If these findings can be replicated *in vivo* and in clinical trials, and new immunotherapy targets are identified, the management of NMIBC has a promising future.

CONCLUSIONS

Intravesical BCG immunotherapy remains invaluable, and the standard of care for most patients with intermediate- and high-risk NMIBC that do not need or want upfront radical cystectomy. However, with increasing pressure on availability, and treatment failure rates of up to 40%(66), BCG is not the best long-term solution for NMIBC. Fortunately, combination and novel immune- therapies are becoming more refined, with improved efficacy, reduced toxicity, and fewer side-effects. Such treatment options will be become ever more necessary due to the rising incidence of bladder cancer with an ageing population and continued BCG shortages. Therefore, ongoing trials of immunotherapeutic agents and novel means of delivering existing drugs (e.g. MMC) to improve

efficacy or decrease toxicity, are particularly important for the future of NMIBC management(42, 67, 68).

EXECUTIVE SUMMARY

History of BCG

- The current standard BCG regime of six weeks induction followed by maintenance was developed over the course of many years.

BCG Shortage and different BCG Strains

- There has been a worldwide shortage of BCG since 2012 (including crises in 2012 and 2014), with differing efficacy between available BCG strains.

Future directions of BCG treatment

- There is the potential to reduce or shorten BCG treatment schedules to decrease BCG usage in a time of continued shortage.
- BCG in combination with Mitomycin C, which may reduce BCG usage.
- Alternative therapies to BCG for those who are BCG-unresponsive.

Future of Immunotherapy in NMIBC

- Immune system targeting agents such as immune checkpoint inhibitors, toll-like receptor agonists, and cancer-specific vaccines, may prove useful as an adjunct to BCG or in BCG-unresponsive patients.

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Reference Annotations

9. *of interest: The inverse relationship between cancer and tuberculosis was recognised from epidemiological data. This was the basis for the anti-tumour function of TB.

17. *of interest: The first trial of intravesical instillation of BCG was performed. The findings from this small trial were the beginning for clinical development of BCG as a therapeutic agent.

22. **of considerable interest: This trial evaluated the efficacy of the maintenance period compared to induction therapy alone. The results showed that outcomes were greatly improved with maintenance therapy.

36. *of interest: This trial proved the efficacy of intravesical MMC. This drug has since been used to manage bladder cancer as an alternative to BCG for many years.

54. *of interest: This trial investigates the use a PD-1 inhibitor in combination with BCG or stand-alone.

59. *of interest: The Morales group showed that using components of BCG intravesically can still produce a response.