BCG-unresponsive non-muscle-invasive bladder cancer: recommendations from the IBCG

Ashish M. Kamat[1], Marc Colombel[2], Debasish Sundi[1], Donald Lamm[3], Andreas Boehle[4], Maurizio Brausi[5], Roger Buckley[6], Raj Persad[7], Joan Palou[8], Mark Soloway[9] and J. Alfred Witjes[10]

Abstract | Intravesical immunotherapy with live attenuated BCG remains the standard of care for patients with high-risk and intermediate-risk non-muscle-invasive bladder cancer (NMIBC). Most patients initially respond, but recurrence is frequent and progression to invasive cancer is a concern. No established and effective intravesical therapies are available for patients whose tumours recur after BCG, representing a clinically important unmet need. Development and discovery of treatment options for BCG-unresponsive NMIBC is a high priority in order to decrease the morbidity, burden of health-care expenditures, and mortality related to bladder cancer. This Review of treatment options after BCG failure focuses on principles of optimal management emerging therapies, thus enabling a synthesis of recommendations for management for such patients.

The standard of care for intermediate-risk and high-risk non-muscle-invasive bladder cancer (NMIBC) after transurethral resection is intravesical immunotherapy with BCG[1,2] (BOX 1). Although the majority of patients are free from recurrence at 1 year after treatment[3], as many as 75% will develop a new tumour within 5 years[4] and a proportion of these patients will experience disease progression to muscle-invasive bladder cancer[5,6], which greatly affects their survival. When patients experience bladder cancer recurrence after BCG, nonsurgical options are limited. In fact, the FDA and EMA have approved only two additional agents for intravesical therapy of bladder cancer since 1959: thiotepa[7] and valrubicin[8], neither of which are truly effective salvage options. Here the International Bladder Cancer Group (IBCG) presents a Review of the existing and emerging treatment strategies for patients with bladder cancer who do not respond to BCG.

Definitions

The definition of what truly defines failure of BCG therapy is of critical importance when evaluating patients who have tumour recurrence after BCG immunotherapy, as the prognosis of patients who develop a new tumour after optimal treatment with BCG is different from that of patients who recur after suboptimal or inadequate therapy. Similarly, the prognosis of patients who recur with a low-grade papillary tumour is distinctly better than those who develop a high-grade tumour or T1 recurrence[9], which affects subsequent clinical management (BOX 1). A few principles must, therefore, be remembered when considering patient management. Firstly, BCG induction therapy must be followed by maintenance therapy to be considered optimal and/or adequate immunotherapy, especially in patients with high-risk disease. Several studies have shown that a 6-week induction course of BCG followed by 3-week BCG maintenance instillations at regular intervals is crucial for reducing recurrence and progression of bladder cancer[10–15]. The prototypical treatment course (as studied in SWOG 8507, EORTC 30911, and EORTC 30962) follows the 6-week induction course with three weekly intravesical instillations at 3, 6, 12, 18, 24, 30, and 36 months (maintenance)[10,15,16]. Other maintenance regimens (for example, monthly or quarterly instillations) have been studied and shown to be no better than induction alone[17–19]. Thus, contemporary guidelines recommend 1–3 years of maintenance with three weekly instillations based on tumour-specific recurrence and progression risks[20–22]. From a clinical trial design perspective, adequate BCG therapy can be defined as the receipt of ≥5 of six intended weekly induction treatments (one induction course) followed by at ≥2 additional weekly maintenance treatments (one maintenance course)[8,23] or a second re-induction instillation[23,24] in a 6-month time period.

Correspondence to A.M.K. Department of Urology, MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1373, Houston, Texas 77054, USA.
akamat@mdanderson.org

doi:10.1038/nrurol.2017.16
Published online 21 Feb 2017

Key points

- Intravesical immunotherapy in the form of BCG is the only effective adjuvant therapy for high-risk NMIBC (non-muscle-invasive bladder cancer) that reduces progression of disease
- Response to salvage therapies after BCG are highly dependent on pattern of tumour recurrence after BCG, especially with regards to dose, duration, and schedule of BCG administration and timing of tumour recurrence after BCG therapy
- For a patient to be considered BCG-unresponsive, they must have received ≥1 induction course (6 weeks) and one maintenance course (3 weeks) and either have refractory tumour (no disease-free interval) or have recurrence of high-grade tumour within 6 months of their last BCG exposure
- In true BCG-unresponsive patients, the only standard therapy is radical cystectomy
- No salvage medical or intravesical treatments have been shown to have durable efficacy in true BCG-unresponsive patients, although some show efficacy in select subgroups of patients
- Options presented to patients who have high-grade tumour recurrence after adequate BCG therapy should factor in the risk of invasive and metastatic disease, balanced with the potential benefit of bladder salvage

BCG intolerant
Scenario when a patient cannot receive BCG owing to treatment-related adverse effects.

BCG refractory
Presence of persistent high-grade cancer 6 months after the start of induction therapy, or cancers that have progressed by grade or stage 3 months after the start of induction therapy.

BCG relapse
Indicates cancer recurrence after achieving a disease-free state at 6 months after treatment.

Secondly, after understanding the definition of adequate BCG treatment, the different types of BCG failure must be defined (FIG. 1). The term "BCG intolerant" — an uncommon situation today, with contemporary understanding of the adverse effects of BCG[25] — indicates a scenario when a patient cannot receive BCG owing to treatment-related adverse effects[21]. "BCG refractory" indicates the presence of persistent high-grade cancer 6 months after the start of induction therapy, or cancers that have progressed by grade or stage[26] 3 months after the start of induction therapy. "BCG relapse" indicates cancer recurrence after achieving a disease-free state at 6 months after treatment. Among the relapsing patients, those whose tumour recurs within 6 months of the last BCG exposure seem to have as poor a prognosis as those who are BCG refractory, and the IBCG and Genitourinary American Society of Clinical Oncology (GU ASCO) Group have, therefore, adopted the term "BCG unresponsive" to denote this combined group of patients with BCG-refractory tumours and those who are BCG relapsing within 6 months of their last BCG exposure[8,23]. When evaluating the results of agents in single-arm studies, this group is the population of most interest, especially to regulatory bodies.

Thirdly, the definition of optimal clinical trial design and end points in studies evaluating BCG unresponsive patients is an important consideration. Previous trials can be considered limited owing to their heterogeneous inclusion criteria, but several clinical trials are active (TABLE 1). As of 2017, radical cystectomy is the only standard salvage therapy available for patients with BCG-unresponsive NMIBC. Thus, in light of the high risk of cancer progression in this setting, placebo comparators are unethical and single-arm trial designs are acceptable[8]. In turn, threshold response rates are necessary to differentiate positive from negative trials. Disease-free response rates of 30% and 25% at 12 months and 18 months, respectively, for papillary tumours (or complete response rates for carcinoma *in situ* (CIS)), have been proposed by the IBCG[8]. Prior recommendations from the AUA and FDA had suggested a threshold response rate of 30% at 18–24 months but these patients were not in the truly BCG-unresponsive group[24]. These target response rates are relevant to enable estimates of each respective outcome. Sample size calculations are based on expected event rates in the control arm and predetermined α (type I error), β (type II error, or false negative rate), and power (1- β) of the clinical trial[8].

A number of current recommendations for the optimal management of BCG-unresponsive disease have been made by guideline groups and expert panels (FIG. 2). The European Association of Urology (EAU) guidelines state that patients with BCG failure are unlikely to respond to further BCG therapy and that radical cystectomy is, therefore, the preferred option and that other treatment strategies are considered oncologically inferior[1]. However, the EAU does state that a repeat BCG induction course or intravesical chemotherapy are viable options for intermediate-risk tumours, because they are low-grade with a reduced risk of progression[21]. Joint recommendations from the EAU and International Consultation on Urologic Diseases (ICUD–EAU) state that the best option for BCG-refractory and BCG-relapsing disease might be a repeat induction BCG course, although radical cystectomy is also indicated in this setting. Although ICUD–EAU does not endorse salvage intravesical gemcitabine, valrubicin, or IFNα, the group states that hyperthermic chemotherapy is promising[27]. Guidelines from the American Urological Association (AUA) state that BCG-unresponsive patients should be offered radical cystectomy but not additional BCG. Patients with persistence or recurrence after a single induction course (in other words, inadequate BCG treatment) should be offered either a second induction course or maintenance BCG[22]. Inclusion in a clinical trial is an important alternative, given the dire need for effective new treatments in this scenario[8,22,27].

Author addresses

[1]Department of Urology, MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1373, Houston, Texas 77054, USA.
[2]Department of Urology, Claude Bernard University, Hôpital Edouard Herriot, Urologie — Pavillon V, 5 Place d'Arsonval, 69003 Lyon, France.
[3]Department of Surgery, University of Arizona and BCG Oncology, 3815 East Bell Road, Suite 1210, Phoenix, Arizona 85032, USA.
[4]Department of Urology, HELIOS Agnes Karll Hospital, Am Hochkamp 21, 23611 Bad Schwartau, Germany.
[5]Department of Urology, AUSL Modena, B. Ramazzini Hospital, Via G. Molinari, 1, 41012 Carpi-Modena, Italy.
[6]Department of Urology, North York General Hospital, 1333 Sheppard Avenue East, Suite 222, North York, Ontario M2J 1V1, Canada.
[7]Department of Urology/Surgery, Southmead Hospital & Bristol Urological Institute, Brunel Building, Southmead Road, Bristol BS10 5NB, UK.
[8]Department of Urology, Fundació Puigvert, Universitat Autònoma de Barcelona, Carrer de Cartagena, 340–350, 08025 Barcelona, Spain.
[9]Division of Urologic Oncology, Memorial Cancer Institute, Memorial Health System, 20801 Biscayne Boulevard, Suite 203, Aventura, Florida 33180, USA.
[10]Department of Urology, Radboud University Nijmegen Medical Centre, PO Box 9101, 6500 HGB, Nijmegen, Netherlands.

Box 1 | **Risk classification of NMIBC and risk-adapted treatment algorithms**

Low-risk NMIBC

- Ta (papillary) tumour that is solitary AND low-grade AND primary
- Initial treatment with TURBT + single postoperative intravesical chemotherapy instillation

Intermediate-risk NMIBC

- Low-grade Ta tumours that are multiple and/or recurrent
- Enumerate risk factors
  - Multiple
  - Large (>3 cm)
  - Recur early (within 12 months)
  - Recur frequently (multiple per year)
- Initial treatment varies by number of risk factors
  - If 0: treat as a low-risk tumour
  - If 1–2: TURBT + intravesical chemotherapy + maintenance* or TURBT + induction BCG + maintenance* BCG
  - If 3–4: treat as a high-risk tumour

High-risk NMIBC

- T1 or high-grade or CIS
- Initial treatment with TURBT + induction BCG + maintenance BCG

CIS, carcinoma *in situ*; NMIBC, non-muscle-invasive bladder cancer; TURBT, transurethral resection of bladder tumour. *Full dose for 1 year.

Evaluating BCG-unresponsive disease

Before offering bladder-sparing therapies for patients with BCG-unresponsive disease, optimal staging of the patient's tumour must be confirmed. The IBCG, consistent with most experts, recommends evaluation of sanctuary sites, especially in patients with positive cytology and no visible tumour in the bladder. This evaluation includes evaluation (by biopsy) of the prostatic urethra and upper urinary tract (by imaging and selective cytological sampling), as these can be positive for cancer in up to half of cases[8,22,28]. Enhanced optical imaging of the bladder mucosa with blue light and/or narrow band imaging (NBI)[22] is also recommended, as it not only improves risk stratification but also provides an opportunity for more complete endoscopic resection.

Surgical options after BCG failure

The optimal salvage treatment after BCG failure is radical cystectomy. A retrospective series from Herr *et al.*[29] showed that, in patients with NMIBC who experienced disease recurrence or progression after BCG, those who underwent early cystectomy (within 2 years of initial BCG) had substantially longer disease-specific survival than those who underwent delayed surgery (and who more frequently had progressed to muscle-invasive disease). However, another retrospective study found that pathological and survival outcomes after radical cystectomy were not different between patients with NMIBC who had prior BCG or BCG plus salvage intravesical chemotherapy. Although this study did not detect a relationship between time to radical cystectomy and pathological upstaging or survival, it did find that the presence of T1 lesions after salvage intravesical chemotherapy (but not after BCG) was negatively associated with survival[30]. Taken together, these data suggest that immediate cystectomy after BCG failure is not mandatory, but rather that prudent and expeditious radical cystectomy after an attempt at salvage intravesical therapy can be an effective strategy. However, every attempt must be made to stage high-risk NMIBC properly: for example, in a multi-institutional analysis of 243 patients who had CIS only (refractory to prior intravesical therapies) and who underwent radical cystectomy, 36% were upstaged (≥pT1), 6% had lymph nodes with metastatic involvement, and 9% had pathological lymphovascular invasion, another adverse prognostic factor[31].

Radical cystectomy should not be undertaken lightly, owing to the morbidity and mortality associated with the procedure. For example, the 90-day major complication rate is 17%[32] and 90-day mortality after radical cystectomy has been reported to range from 2–10%[33–35], prompting clinicians to pursue less-invasive salvage treatments in the setting of BCG failure. Clinical considerations including the quality and duration of life must be considered, as must the desires of the patient.

Chemoradiation after BCG

Radiotherapy has historically had a limited role in the management of NMIBC. A historic series reported 42% 5-year recurrence-free survival (RFS) in 92 patients with T1 tumours using radiotherapy, although major late toxicities were common[36]. A randomized trial of radiotherapy versus conservative and intravesical adjuvant therapies for patients with high-grade T1 tumours showed no oncological benefit to radiation, leading the authors to conclude that radiotherapy is an inappropriate adjuvant therapy for NMIBC[37].

In 2016, combination chemoradiotherapy was studied[38]. In a nonrandomized trial of 141 patients, complete response rates of 88% were observed following chemoradiotherapy (platinum-based) with overall progression rates of 19% and 30% at 5 years and 10 years, respectively. Five-year disease-specific survival was 83%[38]. In a study of 18 patients with T1 tumours who progressed to T2 despite receiving BCG and were subsequently treated with chemoradiotherapy, 54% of patients were alive with intact bladders and were free of invasive recurrence at a median follow-up duration of 7 years[39] The authors concluded that chemoradiotherapy might be a viable alternative to immediate cystectomy in the management of patients with T1 recurrences after BCG.

However, radiation is not appropriate if extensive CIS is present[40]. The ongoing phase II trial RTOG 0926 (NCT00981656)[41] is evaluating the ability to preserve the bladder in patients treated with radiation therapy with cisplatin versus radiation therapy with 5-fluorouracil (5-FU) and mitomycin C (MMC) following BCG failure. Thus, chemoradiotherapy might emerge as a valid alternative for select BCG unresponsive patients who are unfit for radical cystectomy.

Chemotherapy after BCG failure

Intravesical chemotherapy after BCG failure has been attempted with several agents, either alone or in combination with each other or with BCG (TABLE 1). Although FDA-approved, intravesical thiotepa has been shown

BCG unresponsive
Denotes the group of patients with BCG-refractory tumours and those who are BCG-relapsing within 6 months of their last BCG exposure.

Type I error, α
Probability of incorrectly rejecting a true null hypothesis (false positive).

Type II error, β
Probability of incorrectly accepting a false null hypothesis (false negative).

Power, 1-β
The chance that a study will successfully demonstrate a true result.

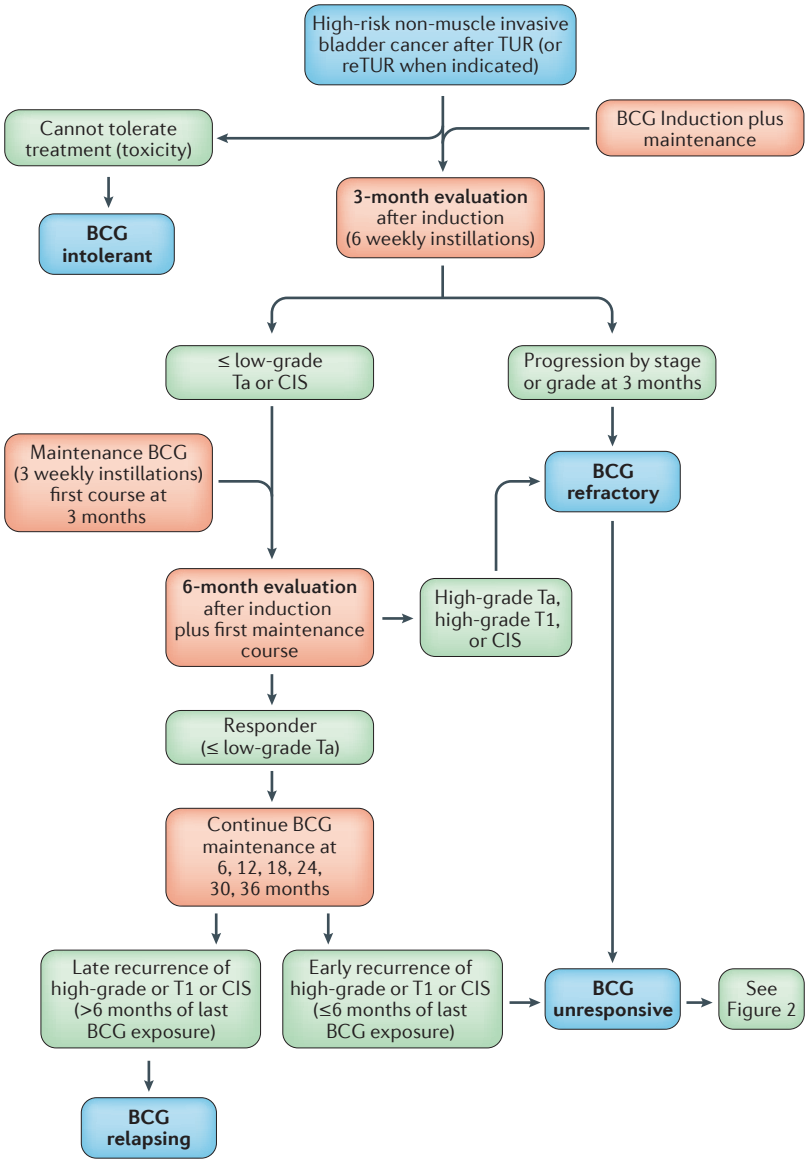

Figure 1 | **Classification of patients with high-risk NMIBC after intravesical BCG and types of BCG failure.** Distinct categories of clinical responses to BCG are determined by treatment duration/sequence, clinical response, and timing of clinical response, which are represented in the flowchart. CIS, carcinoma *in situ*; NMIBC, non-muscle-invasive bladder cancer; TUR, transurethral resection.

to be inferior to BCG for treatment-naive NMIBC[7]. Valrubicin is the only approved agent for intravesical use in BCG-refractory CIS when cystectomy is not an option — for example, if the patients refuses surgery or is medically unfit. A single-arm pivotal study of patients with BCG-failure (70% of whom had ≥2 prior BCG courses) treated with intravesical valrubicin was reported by Steinberg *et al.*[42], in which 81% of patients were classified as having a 3–24 month interval between the last intravesical treatment and starting valrubicin. Thus, what proportion of the study cohort was truly BCG-unresponsive is unclear. The primary outcome was disease-free response rate at 6 months, which was 21%[42]. However, updated outcomes from both this trial and an accompanying single-arm study showed that the 6-month response rate was lower, at 18%[43], and a multicentre retrospective analysis suggested that the 12-month response rate to valrubicin is even lower: just 16.4%[44]. Taken together, these data suggest that valrubicin is a suboptimal salvage therapy in the setting of BCG failure.

Gemcitabine has been extensively studied as a salvage intravesical chemotherapeutic option. A phase I study of 18 patients with NMIBC who had failed ≥1 BCG courses showed an early (before 6 months) response rate of 39%[45]. In a phase II trial of 30 patients after BCG (20 of whom had undergone ≥2 prior BCG courses), the disease-free response rate at 12 months was 21%[46]. A multicentre phase II study including 58 patients who had undergone ≥2 prior BCG courses (SWOG S0353) demonstrated a 12-month disease-free rate of 28% and a 24-month disease-free rate of 21%[47]. Although the efficacy of gemcitabine for true BCG-unresponsive NMIBC is not known, additional trials have shown that intravesical gemcitabine might be better than additional BCG for NMIBC that recurs after a single course of BCG[48], and that patients with high-grade recurrences have improved disease-free survival when treated with gemcitabine as opposed to MMC[49].

Intravesical taxanes have also been studied in the BCG-unresponsive setting. Data in 18 patients with NMIBC who had failed at ≥1 BCG course and who enrolled in a phase I study of intravesical docetaxel, showed a 1-year disease-free rate of approximately 50% and 22% of patients were free from disease at 4 years[50]. Reporting updated outcomes from an expanded cohort, Barlow *et al.*[51] showed response rates of ~40% at 1 year and 25% at 3 years after treatment. In a similar patient population, nanoparticle albumin-bound paclitaxel (abraxane, thought to have increased intravesical bioavailability compared with docetaxel) as salvage intravesical chemotherapy demonstrated a disease-free response rate at 1 year of 36% in the 28 patients evaluated[52].

Thus, although intravesical chemotherapies have some activity after BCG, the overall consensus is that response rates are suboptimal and not durable. Furthermore, the trials are not entirely translatable to all patients with BCG-unresponsive disease, as many of those classified as 'BCG failures' might never have received adequate BCG in the first instance. Consequently, optimized chemotherapy or combination chemotherapies are being studied in this setting.

Combination chemotherapy

Combination chemotherapy has been used to treat metastatic disease for decades and is now being applied to NMIBC, especially in patients after failure of BCG treatment. Based on mechanisms of action, the combinations have evolved around sequential intravesical gemcitabine followed by intravesical docetaxel or MMC. In one series, 45 patients with recurrent NMIBC after BCG therapy were given intravesical gemcitabine 1 g/50ml for 1.5 h followed by intravesical docetaxel 37.5 mg/100ml for 2 h weekly for 6 weeks.

Table 1 | **Results of intravesical chemotherapy after BCG failure**

Agent	Outcomes	Studies
Valrubicin	18–21% disease free at 6 months	Steinberg *et al.*[42]
	16% disease free at 12 months	Dinney *et al.*[43]
Gemcitabine	21–28% disease free at 12 months	Dalbagni *et al.*[45]
	21% disease free at 24 months	Dalbagni *et al.*[46]
Docetaxel	40% disease free at 12 months	Laudano *et al.*[50]
Abraxane	36% disease free at 12 months	McKiernan *et al.*[52]

The regimen was well tolerated, and 89% of patients completed the treatment course[53]. At first cystoscopic evaluation, 66% of patients were free from disease and were given monthly maintenance. Disease-free rates were 54% at 1 year and 34% at 2 years. In Lamm's experience with 46 BCG-failure patients given hyperthermic gemcitabine (200 mg/10 cc with a warming balloon) and docetaxel 20 mg/10 cc, 49% of patients remained disease free at a median follow-up duration of 25 months (D. Lamm, unpublished work). Both tolerance and efficacy of the treatments were better than that of concurrently-treated patients who were managed with combination intravesical therapy with doxorubicin and/or MMC. A multi-institutional study of a patient cohort with high-risk NMIBC treated with sequential intravesical gemcitabine followed by MMC reported that 55% (26 of 47) of these patients had failed ≥2 BCG courses and RFS was 50% in such patients at 12 months[54]. However, these analyses were retrospective and remain to be validated in prospective studies.

Electromotive intravesical chemotherapy

Electromotive administration (EMDA) enables optimization and deep penetration of chemotherapeutics[55]. EMDA uses an intravesical electrode and grounding pad on the anterior abdominal wall and a 15–20 mA current applied for 20–30 min, causing the agent to be transported across the bladder urothelium and stroma via iontophoresis[56]. Contemporary translational work has shown that EMDA increases MMC penetration into superficial and deep tissue layers of human bladders with invasive bladder cancer, compared with conventional intravesical administration[57]. A three-armed prospective randomized trial in 398 patients with treatment-naive NMIBC who underwent either transurethral resection of bladder tumour (TURBT) alone, TURBT plus MMC, or EMDA/MMC plus TURBT demonstrated that EMDA/MMC plus TURBT was associated with significantly increased disease specific survival compared with the other groups (log-rank $P<0.001$), even in the subset of patients with high-risk NMIBC and multifocal disease[58].

A clinical trial by Di Stasi and colleagues[59] reported that sequential BCG + EMDA/MMC was more effective than BCG alone in patients with treatment-naive T1 NMIBC. However, information regarding the efficacy of EMDA/MMC or sequential BCG + EMDA/MMC in BCG-unresponsive patients is sparse (TABLE 2). One group reported 93% RFS with sequential BCG + EMDA/MMC at 2 years in patients with high-risk NMIBC, but some of the patients included in the study were treatment naive[60]. Thus, although a large body of emerging evidence suggests that EMDA is likely to be a useful tool in the armamentarium against NMIBC, its specific role in the BCG-unresponsive setting needs to be elucidated. To this end, another study evaluated outcomes of EMDA/MMC in 13 patients with high-risk recurrent NMIBC (pT1G3 and Tis) who had failed BCG. After a 6-week course of weekly EMDA/MMC, three patients (23%) remained recurrence-free at the 12-month assessment[61].

Chemohyperthermia

Hyperthermia is known to potentiate the effect of various chemotherapeutic agents and this strategy of chemohyperthermia (CHT) using local radiofrequency-induced hyperthermia has been used for intravesical chemotherapy with agents including MMC or epirubicin[62]. Various devices are available, but the most extensively studied is the Synergo system, which uses a 915 MHz intravesical microwave applicator located in the catheter to heat the bladder wall[63]. Typically, the treatment aims to achieve a bladder wall temperature >41 °C for at least two sessions of 20 min each, while circulating a solution of MMC.

The majority of studies with radiofrequency-induced CHT have been in patients who have undergone various different prior intravesical therapies —none, chemotherapy, or BCG. However, some studies with large proportions of patients with BCG-unresponsive disease (varying from 67% to 100%) have been performed[62,64–67]. In one retrospective report of 111 BCG-unresponsive patients with a median follow-up duration of 16 months (range 2–72 months), CHT was associated with 1-year and 2-year RFS of 85% and 56%, respectively; progression was seen in 3% of cases[64]. Another study including 38 patients with BCG-unresponsive tumours reported similar results for both recurrence and progression[65].

Witjes *et al.*[68] specifically reported on 49 patients with CIS treated with radiofrequency-induced CHT. In this patient population, an initial complete response rate (proven by both biopsy and cytology) was 92% at 6 months and an ongoing response rate was 51% at 27 months. No differences in patient response rates were observed between patients categorized as failing prior BCG treatment and those who were not categorized as such ($P=0.63$). A report of 56 patients with high-grade T1 tumours treated with CHT also showed similar efficacy among patients classified as BCG-failures and non-failures, with a 4-year recurrence rate of 46% and 44%, respectively[69]. Overall, 2-year recurrence rates after CHT for BCG-unresponsive patients vary between 25% and 53%[63,70]. Data regarding progression are scarce, but vary between 3% and 4% based on five studies[62,64–66,68], although progression was reported in up to 36% of patients in one study in which the definition of progression included initiation of any further treatment[67].

Only one publication is currently in existence comparing radiofrequency-induced CHT with BCG

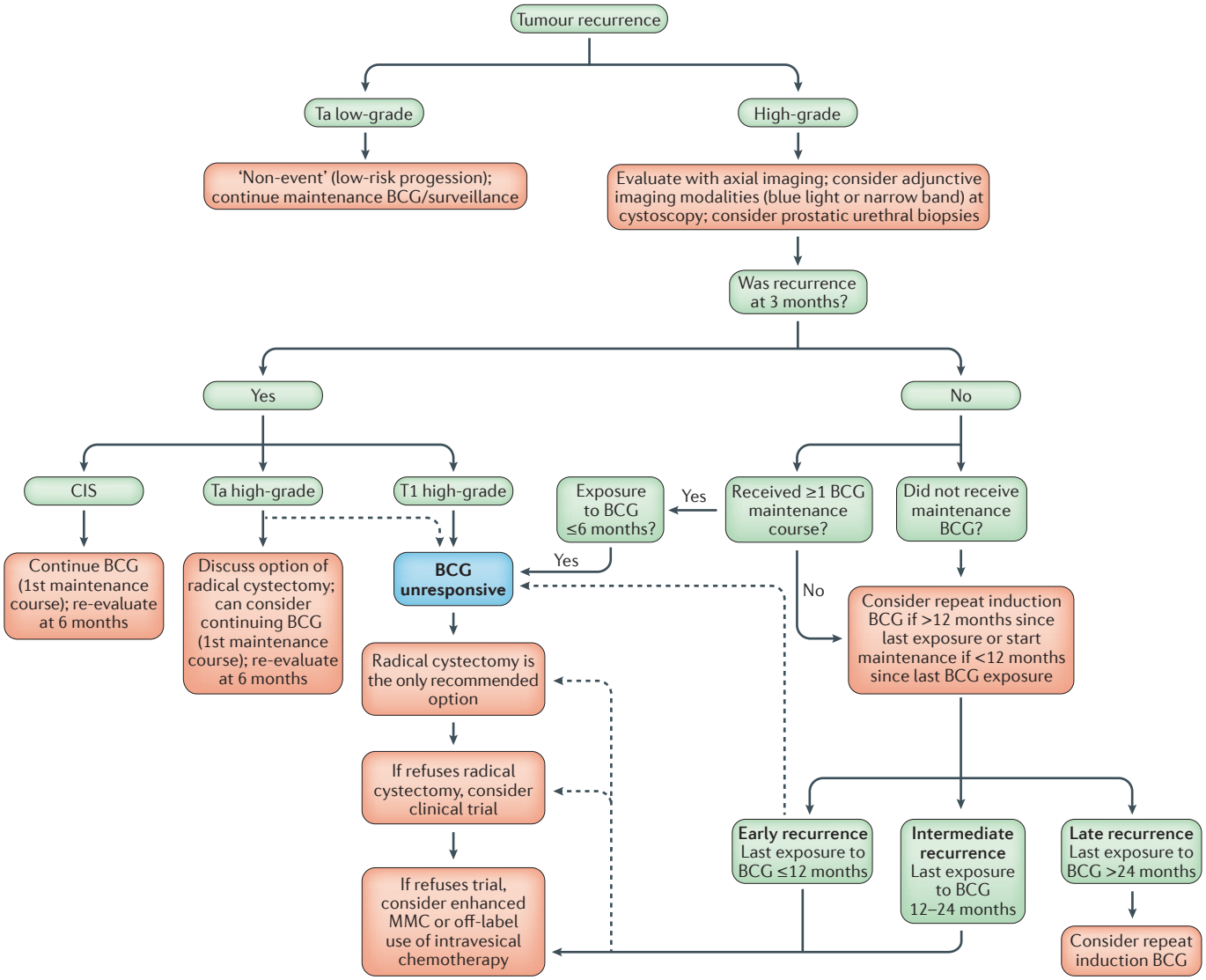

Figure 2 | **Recommendations for management of patients after BCG failure.** Management approaches for patients who do not respond to BCG or recur after BCG are determined by the timing and duration of prior BCG therapy as well as timing of clinical recurrence. CIS, carcinoma *in situ*; MMC, mitomycin C; NMIBC, non-muscle-invasive bladder cancer.

— a randomized controlled trial comparing 1 year of each treatment in 190 patients with intermediate-risk or high-risk NMIBC[71]. Although outcomes with both treatments were comparable for patients with CIS (complete response (CR) rates of 88.9% and 85.7% were reported for CHT and BCG, respectively (P >0.1) for papillary tumours), patients who received CHT achieved a 24-month RFS of 81.8% compared with 64.8% in the BCG-treated group. Progression was reported as <2% of patients in both groups. Although they are encouraging, these results should be interpreted with caution with regard to BCG-unresponsive patients, as a large proportion of papillary tumours were not high grade and prior BCG treatment within 48 months was an exclusion criterion of the study — in fact 95% of patients in this trial were BCG naive.

Immunotherapy after BCG failure

Repeat BCG

BCG and other immunotherapies have the potential to be effective for highly selected patients with NMIBC who fail initial BCG treatment. If a patient has persistent disease after a single induction course of BCG, a second induction course is associated with a 43–63% response rate[72–74]. However, additional (≥3 courses) are not recommended owing to toxic effects[75] and increased oncological risks; ≥3 induction courses are associated with only a 20% response rate and 80% rate of progression or metastatic cancer[72,73,76]. These data have been supported in subsequent studies; for example, for patients with persistent NMIBC despite ≥2 BCG courses, the hazard ratios for failure of additional BCG ranged from 1.54 to 2.74 depending the presence of papillary-only

Table 2 | **Studies of EMDA–MMC**

Publication	Study design	Treatment type	*n*	Included tumours
Brausi *et al.*[55]	Prospective phase II	MMC versus EMDA–MMC	28	Ta–T1
Riedl *et al.*[132]	Case series	EMDA–MMC	16	Ta–T1, CIS
Colombo *et al.*[133]	Prospective non-randomized	Therapeutic	80	Single recurrent low-grade Ta–T1
Di Stasi *et al.*[61]	Randomized controlled trial	MMC versus BCG versus EMDA–MMC	108	T1, CIS
Di Stasi *et al.*[59]	Randomized controlled trial	BCG versus sequential BCG + EMDA–MMC	212	CIS
Gan *et al.*[60]	Retrospective	Sequential BCG + EMDA–MMC	151	Ta–T1, CIS
Di Stasi *et al.*[58]	Randomized controlled trial	TURBT alone versus MMC versus EMDA–MMC	352	Ta–T1
Bachir *et al.*[134]	*Post hoc* cost effectiveness analysis of a prospective trial	BCG versus sequential BCG + EMDA–MMC	212	T1

CIS, carcinoma *in situ*; EMDA, electromotive drug administration; MMC, mitomycin C; TURBT, transurethral resection of bladder tumour.

NMIBC versus CIS[77]. Thus, if a patient is truly BCG-unresponsive and their high-grade bladder cancer persists after one or two courses of BCG, additional BCG is not recommended.

IFNα

IFNα has been shown to have a direct antitumour effect in preclinical models of bladder cancer[78], and a multicentre phase II trial has suggested that BCG plus IFNα might be effective in certain patients with prior BCG exposure, namely those who had not received more than just induction BCG[79]. Although this report had multiple design concerns — not least of which was the inclusion of BCG-naive patients — these data led to the clinical practice of using BCG + IFNα for BCG-relapsing NMIBC, particularly after a disease-free interval ≥12 months[80]. However, further data demonstrate that BCG + IFNα is not more effective than BCG alone[81]. Importantly, among truly BCG-unresponsive patients, the response rate to BCG + IFNα at 24 months is only 23%[82], which is similar to the historic BCG data. Thus, IFNα has a limited role in this setting at the current time.

Historical immunotherapies

Keyhole-limpet haemocyanin and bropirimine. Two immunotherapeutic agents are of historical importance: keyhole-limpet haemocyanin (KLH) and bropirimine. KLH is an immune stimulant that is intravesically and intracutaneously administered and has shown effectiveness in multiple preclinical mouse models[83]. However, in a randomized trial of 283 patients that compared KLH to MMC (including patients with intermediate-risk and high-risk NMIBC but excluding those with CIS), patients in the KLH treatment arm were found to have a significantly higher risk of cancer recurrence (adjusted HR 2.32, $P<0.001$)[84]. Bropirimine is an oral agent that induces type I interferon signalling. Initial studies suggested that its efficacy was equivalent to intravesical BCG in patients with treatment-naive CIS[85], but subsequent data failed to demonstrate any additive effect to BCG in these patients[86].

Emerging immunotherapies

BCG intradermal priming. One re-emerging therapy for BCG-unresponsive NMIBC involves BCG intradermal priming to augment response to BCG itself. BCG priming — essentially by intradermal injection of BCG vaccine, similar to what is done during vaccination for tuberculosis in many developing countries — leads to a BCG-specific memory T cell response that, in turn, leads to increased bladder infiltration by cytotoxic $CD8^+$ T cells upon repeated BCG exposure[87]. This observation parallels clinical data that suggest that, among patients with NMIBC, individuals with prior intradermal BCG vaccination benefit from improved response rates[87,88], although this observation is not uniform[89]. To formally test the hypothesis that prior BCG vaccination induces a memory T cell response that can increase the bladder specific T cell response to intravesical BCG, the randomized PRIME trial (NCT02326168)[90] will soon report 3-month response rates to BCG induction courses with or without intradermal BCG vaccination.

MCNA. Mycobacterium phlei cell wall–nuclei acid complex (MCNA) is derived from a nonpathogenic mycobacterium and has been shown to have direct antitumour and indirect cytokine-mediated effects against bladder tumours[91]. In a single-arm phase III trial including 129 patients BCG-refractory or BCG-relapsing disease treated with induction and maintenance MCNA, the disease-free response rate at 12 months after treatment was 25%[92]. However, MCNA is not currently approved for NMIBC.

Immune checkpoint blockade

Immune checkpoint blockade is rapidly gaining interest in many solid tumours, including bladder cancer. Atezolizumab, an anti-PD-L1 antibody, has been approved by the FDA for use in patients with cisplatin-resistant metastatic urothelial carcinoma[93,94]. Atezolizumab and other anti-PD-L1 antibodies are also being studied in early stages of bladder cancer, including BCG-unresponsive disease. For example, the KEYNOTE-057

Intradermal priming
Intradermal injection of BCG vaccine in order to induce BCG-specific memory T cells

trial (NCT02625961)[95] is evaluating the response rate to systemic administration of pembrolizumab, an anti-PD-1 antibody, in BCG-unresponsive patients who are not eligible for or refuse radical cystectomy[96].

Viral gene therapy

Viral gene therapy represents another frontier in immunotherapy for BCG-unresponsive NMIBC. CG00700 is an oncolytic adenovirus that expresses a *GMCSF* transgene and selectively replicates in retinoblastoma (Rb)-deficient cells. In a multicentre phase I trial including patients with BCG-refractory or BCG-relapsing disease, CG00700 treatment was associated with a 49% response rate at 10.4 months; patients with Rb-deficient tumours (assessed via Rb-phosphorylation) seemed to have even higher response rates[97]. A single-arm phase III study (NCT02365818)[98] is currently recruiting patients with NMIBC after BCG failure and will assess response rates at 18 months, as well as PD-1 and PD-L1 immunohistochemistry scores of tumour cells and infiltrating immune cells.

Instiladrin (rAd-IFNα/Syn3) is a replication-deficient adenovirus that expresses an IFNα transgene, and could also be used to treat BCG-unresponsive NMIBC[99]. rAd-IFNα/Syn3 was studied in a phase I trial of patients with BCG-unresponsive tumours and a complete response rate of 36% was noted at 12 months after treatment[100]. In a multicentre phase II trial, a similar 12-month response rate (35%) was noted[101], and emerging RNA sequencing data of patient tumours both before and after treatment suggest that up to one-third of patients with immune-depleted tumours demonstrate enrichment of infiltrating T cell markers and immune checkpoint molecules after therapy[102]. A single arm phase III trial (NCT02773849)[103] will evaluate response rates at 12 months and will also study tissue and urine genomic biomarkers associated with response.

Photodynamic therapy

Photodynamic therapy involves the activation of a photosensitizer agent administered to the patient using specific wavelengths of light applied topically (in this case in the bladder). PDT may also be called photoradiation therapy, phototherapy, or photochemotherapy. In a study of 24 patients with NMIBC who had failed ≥2 BCG courses and who received photodynamic therapy consisting of oral 5-aminolevulinic acid followed by 60 min of intravesical argon irradiation of the bladder using a cystoscopic approach, 50% of patients were disease free after a median follow-up duration of 11 months[104]. However, this treatment regimen proved to be excessively cardiotoxic, with 80% of patients experiencing hypotension or tachyarrhythmias. Another group reported results from 17 patients who underwent photodynamic therapy using intravesical instillation of hexaminolevulinic acid followed by photoactivation (60–120 min via cystoscopic xenon light)[105]. Only 12 of 17 patients had undergone prior BCG, yet the 12-month response rate was only 12%. These high levels of toxicity have meant that photodynamic therapy has not become widely used in bladder cancer. However newer agents with a higher therapeutic index and lower toxicity are being developed and could provide an effective salvage option for BCG-unresponsive NMIBC.

Future directions

Targeted therapies

Among the many targets for therapy in bladder cancer[106], most of the activity has been around inhibitors or antibodies against angiogenesis, epidermal growth factor receptor (EGFR), fibroblast growth factor receptor 3 (FGFR3), and mechanistic target of rapamycin (mTOR) pathways[107]. Whereas most of these studies are focused on the metastatic setting[108–110], others — such as a trial of dovitinib, a dual inhibitor of vascular–endothelial growth factor receptor 3 (VEGFR3) and FGFR3 (NCT01732107)[111] are also underway in patients with superficial tumours resistant to BCG therapy (TABLE 3).

The mTOR inhibitor RAD001 (everolimus) is being investigated in combination with intravesical gemcitabine in a phase I/II trial that includes patients with CIS who are BCG-intolerant, BCG-unresponsive, or BCG-relapsing (NCT01259063)[112] VB4-845 (vicinium), is a targeted intravesical therapy containing a pseudomonal exotoxin conjugated to a moiety that targets epithelial cell adhesion molecule (EpCAM). In a phase I trial of 64 patients with BCG-intolerant or BCG-relapsing NMIBC, the disease-free survival at 3 months was 39%[113]. A phase III trial of vicinium in BCG-unresponsive patients (NCT02449239)[114] is ongoing, and will evaluate disease-free response rate at 24 months as a primary outcome.

Other trials of targeted agents include oral sunitinib in patients with NMIBC that is recurrent after prior BCG exposure (NCT01118351)[115], which is completed but not yet reported[116]. ALT-801 — a p53-specific T cell receptor fused to IL-2 that has shown modest activity in patients with p53-expressing solid tumours[117] — is being trialled in combination with gemcitabine (both systemically administered) in NMIBC patients with BCG failure (NCT01625260)[118].

Other ongoing trials

A potential limitation of the effectiveness of intravesical therapy is short duration of drug exposure and contact with the urothelium. In order to overcome this obstacle, preclinical studies have investigated the possibility of increasing tissue cisplatin levels by intravesical delivery, for example, via a thermosensitive hydrogel[119]. MitoGel is a thermosensitive hydrogel containing MMC that is currently being investigated in upper tract urothelial carcinoma (NCT02701023)[120]. Taris GemRIS is an investigational intravesical drug delivery system that elutes gemcitabine and is also undergoing formal evaluation in a phase Ib trial for patients with low-risk and intermediate-risk NMIBC (NCT02720367)[121]. In this study, the GemRIS device is delivered cystoscopically and remains indwelling for the first week of treatment, is removed, and is then reinserted for another week after a week without treatment. Finally, GemRIS is removed at the time of TURBT. These agents have not been evaluated in the BCG-unresponsive setting but might warrant formal study.

Table 3 | **Active clinical trials for patients with NMIBC after BCG failure**

Trial name	Description	End point	Study population
RTOG 0926 (NCT00981656)[41]	RT + cisplatin versus RT + 5-FU + MMC	Freedom from radical cystectomy	BCG failure
PRIME (NCT02326168)[90]	BCG versus BCG + prior intradermal BCG vaccination	3-month CR rate	Intermediate-risk (≥1 risk factor from BOX 1) or high-risk NMIBC
KEYNOTE-057 (NCT02625961)[95]	Pembrolizumab (anti-PD-1)	CR, RFS	BCG-unresponsive
BOND2 (NCT02365818)[98]	CG00700 (GM-CSF expressing oncolytic adenovirus)	18-month CR rate	BCG failure
NCT02773849 (REF. 103)	rAd-IFNα/Syn3 (instiladrin)	12-month RFS	BCG-unresponsive
NCT01732107 (REF. 111)	Dovotinib (anti-FGFR3)	6-month CR rate	BCG-refractory
NCT02449239 (REF. 114)	VB4-845 (vicinium)	24-month RFS	BCG-unresponsive
NCT01259063 (REF. 112)	RAD001 (everolimus) + intravesical gemcitabine	12-month RFS	BCG failure
NCT02009332 (REF. 131)	ABI-009 (albumin-bound rapamycin nanoparticles)	3-month, 12-month CR rate	BCG failure
NCT01625260 (REF. 118)	ALT-801 (p53-specific TCR/IL-2 fusion protein) plus gemcitabine	RFS	BCG failure
NCT02015104 (REF. 126)	PANVAC ([oxviral vaccine expressing CEA, MUC-1, and immune co-stimulants) + BCG	RFS	BCG-refractory

5-FU, 5-fluourouracil; BCG, Bacille Calmette–Guerin; CEA, carcinoembryonic antigen; CR, complete response; FGFR3, fibroblast growth factor receptor 3; GM-CSF, granulocyte macrophage colony-stimulating factor; MMC, mitomycin C; NMIBC, non-muscle-invasive bladder cancer; PD-1, programmed cell death protein 1; RFS, recurrence free survival; RT, radiation therapy; TCR, T cell receptor.

Cancer vaccines are also under investigation in NMIBC. Vesigenurtacel-L is an intradermal vaccine composed of irradiated cancer cells that secrete the cellular heat shock protein gp96, which induces a tumour-specific memory T-cell response[122]. Vesigenurtacel-L in combination with BCG has been shown to induce T cell infiltration into tumours of patients with NMIBC, particularly in those who respond to therapy[123]. Early reported results of a phase I/II study suggest that addition of Vesigenuracel-L to BCG does not add to the response seen with BCG alone (NCT02010203)[124]. PANVAC is a poxviral vaccine that expresses transgenes for tumour antigens mucin-1 (MUC-1) and carcinoembryonic antigen (CEA), as well as a set of co-stimulatory molecules (B7.1, LFA-3, and ICAM-1) to enhance the antitumour T cell response[125]. A phase II trial (NCT02015104)[126] is ongoing to evaluate the effect of BCG versus BCG + PANVAC in BCG-refractory NMIBC (TABLE 3).

Novel molecules

Several novel agents that have shown promise in preclinical studies might become relevant for both investigational and routine clinical use in the future. Second mitochondria-derived activator of caspase (smac, also known as diablo homologue, mitochondrial) mimetics inhibit inhibitors of apoptosis proteins (IAP); these molecules have been shown to enhance bladder cancer cell death *in vitro* in the setting of gemcitabine chemotherapy[127] or inflammatory cytokines (such as tumour necrosis factor ligand superfamily member 10 (TRAIL))[128]. In addition, bladder tumours frequently express EGFR, and the targeted toxin construct DAB398EGF leverages this attribute in order to selectively deliver diphtheria toxin to cancer cells via toxin conjugation to EGF; this treatment has been shown to be effective when administered intravesically in an orthotopic mouse model[129]. Other investigators have demonstrated that cystoscopically delivered gold nanoparticles conjugated to an EGFR antibody can selectively bind and then heat-kill bladder cancer cells after activation by infrared light[130]. Further work is needed, however, before we can move these agents into the clinic for primetime use.

Conclusions

BCG-unresponsive NMIBC is a particularly high-risk disease state, defined as the presence of high-grade tumours that are either refractory to BCG treatment (cancer progression at 3 months or persistent high-grade disease at 6 months after initiation of induction BCG (with six instillations, given once a week) and one maintenance BCG dose of three instillations (given once a week for 3 weeks), or that relapse within 6 months of the most recent BCG exposure. Nonsurgical treatments for this disease state are needed, as radical cystectomy is currently the only effective salvage option for these patients, but is associated with considerable morbidities and mortality. Enhanced intravesical chemotherapy and immune treatments are promising developments. Widespread clinical acceptance and use of emerging therapies will require novel agents and well-designed trials to demonstrate meaningful oncological benefit, which has been defined by expert consensus as disease-free rates of >30% at 12 months and 25% at 18 months.

1. Babjuk, M. *et al.* EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2016. *Eur Urol.* **71**, 447–461 (2016).
2. Kamat, A. M. *et al.* Defining and treating the spectrum of intermediate risk nonmuscle invasive bladder cancer. *J. Urol.* **192**, 305–315 (2014).
3. Shelley, M. *et al.* Intravesical bacillus Calmette–Guérin in Ta and T1 bladder cancer (review). *Cochrane Database Syst. Rev.* **4**, CD001986 (2000).
4. Sfakianos, J. P., Kim, P. H., Hakimi, A. A. & Herr, H. W. The effect of restaging transurethral resection on recurrence and progression rates in patients with nonmuscle invasive bladder cancer treated with intravesical bacillus Calmette–Guerin. *J. Urol.* **191**, 341–345 (2014).
5. Lamm, D. *et al.* Review article defining progression in nonmuscle invasive bladder cancer: it is time for a new, standard definition. *J. Urol.* **191**, 20–27 (2014).
6. Cambier, S. *et al.* EORTC nomograms and risk groups for predicting recurrence, progression, and disease-specific and overall survival in non-muscle-invasive stage Ta–T1 urothelial bladder cancer patients treated with 1–3 years of maintenance bacillus Guerin. *Eur. Urol.* **69**, 60–69 (2016).
7. Martínez-Piñeiro, J. A. *et al.* Bacillus Calmette–Guerin versus doxorubicin versus thiotepa: a randomized prospective study in 202 patients with superficial bladder cancer. *J. Urol.* **143**, 502–506 (1990).
8. Kamat, A. M. *et al.* Definitions, end points, and clinical trial designs for non-muscle-invasive bladder cancer: recommendations from the International Bladder Cancer Group. *J. Clin. Oncol.* **34**, 1935–1944 (2016).
9. Mmeje, C. O. *et al.* Papillary recurrence of bladder cancer at first evaluation after induction bacillus Calmette–Guerin therapy: implication for clinical trial design. *Eur Urol.* **70**, 778–785 (2016).
10. Lamm, D. L. *et al.* Maintenance bacillus Calmette–Guerin immunotherapy for recurrent Ta, T1, and carcinoma *in situ* transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. *J. Urol.* **163**, 1124–1129 (2000).
11. Bohle, A., Jocham, D. & Bock, P. Intravesical bacillus Calmette–Guerin versus mitomycin C for superficial bladder cancer: a formal meta-analysis of comparative studies of recurrence and toxicity. *J. Urol.* **169**, 90–95 (2003).
12. Malmström, P.-U. *et al.* An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus bacillus Calmette–Guerin for non-muscle-invasive bladder cancer. *Eur. Urol.* **56**, 247–256 (2009).
13. Hinotsu, S. *et al.* Maintenance therapy with bacillus Calmette–Guérin Connaught strain clearly prolongs recurrence-free survival following transurethral resection of bladder tumour for non-muscle-invasive bladder cancer. *BJU Int.* **108**, 187–195 (2010).
14. Zhu, S. *et al.* Optimal schedule of bacillus Calmette–Guerin for non-muscle-invasive bladder cancer: a meta-analysis of comparative studies. *BMC Cancer* **13**, 332 (2013).
15. Oddens, J. *et al.* Final results of an EORTC-GU cancers group randomized study of maintenance bacillus Calmette–Guerin rin in intermediate- and high- risk Ta, T1 papillary carcinoma of the urinary bladder: one-third dose versus full dose and 1 year versus 3 years of maintenance. *Eur. Urol.* **63**, 462–472 (2013).
16. Sylvester, R. J. *et al.* Long-term efficacy results of EORTC genito-urinary group randomized phase 3 study 30911 comparing intravesical instillations of epirubicin, bacillus Calmette–Guerin, and bacillus Calmette–Guerin plus isoniazid in patients with intermediate- and high-risk. *Eur. Urol.* **57**, 766–773 (2010).
17. Palou, J. *et al.* Control group and maintenance treatment with bacillus Calmette–Guerin for carcinoma in siute and/or high grade bladder tumors. *J. Urol.* **165**, 1488–1491 (2001).
18. Kamat, A. M. & Porten, S. Myths and mysteries surrounding bacillus Calmette–Guerin therapy for bladder cancer. *Eur. Urol.* **65**, 267–269 (2014).
19. Kamat, A. M. *et al.* Consensus statement on best practice management regarding the use of intravesical immunotherapy with BCG for bladder cancer. *Nat. Rev. Urol.* **12**, 225–235 (2015).
20. Gakis, G. *et al.* ICUD-EAU international consultation on bladder cancer 2012: radical cystectomy and bladder preservation for muscle-invasive urothelial carcinoma of the bladder. *Eur. Urol.* **63**, 45–57 (2013).
21. Babjuk, M. *et al.* EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2013. *Eur. Urol.* **64**, 639–653 (2013).
22. Chang, S. S. *et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO Guideline* [online] https://www.auanet.org/common/pdf/education/clinical-guidance/Non-Muscle-Invasive-Bladder-Cancer.pdf (2016).
23. Lerner, S. *et al.* Clarification of bladder cancer disease states following treatment of patients with intravesical BCG. *Bl Cancer* **1**, 29–30 (2015).
24. Jarow, J. P. *et al.* Clinical trial design for the development of new therapies for nonmuscle-invasive bladder cancer: report of a Food and Drug Administration and American Urological Association public workshop. *Urology* **83**, 262–265 (2013).
25. Shah, J. B. & Kamat, A. M. Strategies for optimizing bacillus Calmette–Guerin. *Urol. Clin. North Am.* **40**, 211–218 (2013).
26. Kamat, A. M., Cookson, M., Witjes, J. A., Stenzl, A. & Grossman, H. B. The impact of blue light cystoscopy with hexaminolevulinate (HAL) on progression of bladder cancer — a new analysis. *Bl Cancer* **2**, 273–278 (2016).
27. Burger, M. *et al.* ICUD-EAU international consultation on bladder cancer 2012: non-muscle-invasive urothelial carcinoma of the bladder. *Eur. Urol.* **63**, 36–44 (2013).
28. Birkha, D., Recker, F., Thalmann, G. N. & Giannarini, G. Bacillus Calmette–Guerin failure in patients with non-muscle-invasive urothelial carcinoma of the bladder may be due to the urologist's failure to detect urothelial carcinoma of the upper urinary tract and urethra. *Eur. Urol.* **65**, 825–831 (2014).
29. Herr, H. W. & Sogani, P. C. Does early cystectomy improve the survival of patients with high risk superficial bladder tumors? *J. Urol.* **166**, 1296–1299 (2001).
30. Haas, C. R. *et al.* The timing of radical cystectomy for bacillus Calmette–Guerin failure: comparison of outcomes and risk factors for prognosis. *J. Urol.* **195**, 1704–1709 (2016).
31. Tilki, D. *et al.* Characteristics and outcomes of patients with clinical carcinoma *in situ* only treated with radical cystectomy: an international study of 243 patients. *J. Urol.* **183**, 1757–1763 (2010).
32. Leow, J. J. *et al.* Propensity-matched comparison of morbidity and costs of open and robot-assisted radical cystectomies: a contemporary population-based analysis in the United States. *Eur. Urol.* **66**, 569–576 (2014).
33. Stimson, C. J. *et al.* Early and late perioperative outcomes following radical cystectomy: 90-day readmissions, morbidity and mortality in a contemporary series. *J. Urol.* **184**, 1296–1300 (2010).
34. Hounsome, L. S., Verne, J., Mcgrath, J. S. & Gillatt, D. A. Trends in operative caseload and mortality rates after radical cystectomy for bladder cancer in England for 1998–2010. *Eur. Urol.* **67**, 1056–1062 (2015).
35. Liberman, D. *et al.* Septuagenarian and octogenarian patients treated with radical cystectomy for urothelial carcinoma of the bladder. *Urology* **77**, 660–666 (2011).
36. Gospodarowicz, M. K. *et al.* Bladder cancer: long-term follow-up results of patients treated with radical radiation. *Clin. Oncol. (R. Coll. Radiol.)* **3**, 155–161 (1991).
37. Harland, S. J. *et al.* A randomized trial of radical radiotherapy for the management of pT1G3 NXM0 transitional cell carcinoma of the bladder. *J. Urol.* **178**, 807–813 (2007).
38. Weiss, C., Wolze, C., Engehausen, D. G., Ott, O. J. & Krause, F. S. Radiochemotherapy after transurethral resection for high-risk T1 bladder cancer: an alternative to intravesical therapy or early cystectomy? *J. Clin. Oncol.* **24**, 2318–2324 (2016).
39. Wo, J. Y. *et al.* The results of concurrent chemo-radiotherapy for recurrence after treatment with bacillus Calmette–Guérin for non-muscle-invasive bladder cancer: is immediate cystectomy always necessary? *BJU Int.* **104**, 179–183 (2008).
40. Shipley, W. *et al.* Full-dose irradiation for patients with invasive bladder carcinoma: clinical and histological factors prognostic of improved survival. *J. Urol.* **134**, 679–683 (2007).
41. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT00981656?term=00981656&rank=1 (2015).
42. Steinberg, G. *et al.* Efficacy and safety of valrubicin for the treatment of bacillus Calmette–Guerin refractory carcinoma *in situ* of the bladder. *J. Urol.* **163**, 761–767 (2000).
43. Dinney, C. P. N. *et al.* Intravesical valrubicin in patients with bladder carcinoma *in situ* and contraindication to or failure after bacillus Calmette-Guérin. *Urol. Oncol.* **31**, 1635–1642 (2013).
44. Cookson, M. S. *et al.* Use of intravesical valrubicin in clinical practice for treatment of nonmuscle-invasive bladder cancer, including carcinoma *in situ* of the bladder. *Ther. Adv. Urol.* **6**, 181–191 (2014).
45. Dalbagni, B. G. *et al.* Phase I trial of intravesical gemcitabine Calmette–Guerin-refractory transitional-cell carcinoma of the bladder. *J. Clin. Oncol.* **20**, 3193–3198 (2002).
46. Dalbagni, G. *et al.* Phase II trial of intravesical gemcitabine in bacille Calmette–Guérin-refractory transitional cell carcinoma of the bladder. *J. Clin. Oncol.* **24**, 2729–2734 (2006).
47. Skinner, E. C. *et al.* SWOG S0353: phase II trial of intravesical gemcitabine in patients with nonmuscle invasive bladder cancer and recurrence rin after 2 prior courses of intravesical bacillus Calmette–Guerin. *J. Urol.* **190**, 1200–1204 (2013).
48. Lorenzo, G. Di, Perdona, S. *et al.* Gemcitabine versus bacille Calmette–Guerin after initial bacille Calmette–Guerin failure in non-muscle-invasive bladder cancer: a multicenter prospective randomized trial. *Cancer* **116**, 1893–1900 (2010).
49. Addeo, R. *et al.* Randomized phase III trial on gemcitabine versus mytomicin in recurrent superficial bladder cancer: evaluation of efficacy and tolerance. *J. Clin. Oncol.* **28**, 543–548 (2010).
50. Laudano, M. A. *et al.* Long-term clinical outcomes of a phase I trial of intravesical docetaxel in the management of non-muscle-invasive bladder cancer. *Urology* **75**, 134–137 (2010).
51. Barlow, L. J., Mckiernan, J. M. & Benson, M. C. Long-term survival outcomes with intravesical docetaxel for recurrent nonmuscle invasive bladder cancer after previous bacillus Calmette–Guérin therapy. *J. Urol.* **189**, 834–839 (2013).
52. Mckiernan, J. M. *et al.* Phase II trial of intravesical nanoparticle albumin bound paclitaxel for the treatment of nonmuscle invasive urothelial carcinoma of the bladder after bacillus Calmette–Guerin treatment failure. *J. Urol.* **192**, 1633–1638 (2014).
53. Velaer, K. N., Steinberg, R. L., Thomas, L. J., O'Donnell, M. A. & Nepple, K. G. Experience with sequential intravesical gemcitabine and docetaxel as salvage therapy for non-muscle invasive bladder cancer. *Curr. Urol. Rep.* **17**, 1–5 (2016).
54. Lightfoot, A. J. *et al.* Multi-institutional analysis of sequential intravesical gemcitabine and mitomycin C chemotherapy for non-muscle invasive bladder cancer. *Urol. Oncol.* **32**, 35.e15–35.e19 (2014).
55. Brausi, M. *et al.* Intravesical electromotive administration of drugs for treatment of superficial bladder cancer: a comparative phase II study. *Urology* **51**, 506–509 (1998).
56. Chien, Y. & Banga, A. Iontophoretic (transdermal) delivery of drugs: overview of historical development. *J. Pharm. Sci.* **78**, 353–354 (1989).
57. Di Stasi, S. M. *et al.* Electromotive versus passive diffusion of mitomycin C into human bladder wall: concentration–depth profiles studies. *Cancer Res.* **59**, 4912–4918 (1999).
58. Di Stasi, S. M. *et al.* Electromotive instillation of mitomycin immediately before transurethral resection for patients with primary urothelial non-muscle invasive bladder cancer: a randomised controlled trial. *Lancet Oncol.* **12**, 871–879 (2011).
59. Di Stasi, S. M. *et al.* Sequential BCG and electromotive mitomycin versus BCG alone for high-risk superficial bladder cancer: a randomised controlled trial. *Lancet Oncol.* **7**, 43–51 (2006).
60. Gan, C. *et al.* Sequential bacillus Calmette–Guerin/electromotive drug administration of mitomycin C as the standard intravesical regimen in high risk nonmuscle invasive bladder cancer: 2-year outcomes. *J. Urol.* **195**, 1697–1703 (2016).
61. Di Stasi, S. M. *et al.* Intravesical electromotive mitomycin C versus passive transport mitomycin C for high risk superfical bladder cancer: a prospective randomized study. *J. Urol.* **170**, 777–782 (2003).
62. Arends, T. J., van der Heijden, A. G. & Witjes, J. A. Combined chemohyperthermia: 10-year single center experience in 160 patients with nonmuscle invasive bladder cancer. *J. Urol.* **192**, 708–713 (2014).

63. van Valenberga, H., Colombo, R. & Witjes, F. Intravesical radiofrequency-induced hyperthermia combined with chemotherapy for non-muscle-invasive bladder cancer. *Int. J. Hyperthermia* **32**, 351–362 (2016).
64. Nativ, O. *et al.* Combined thermo-chemotherapy for recurrent bladder cancer after bacillus Calmette–Guerin. *J. Urol.* **182**, 1313–1317 (2009).
65. Ayres, B., Connor, A., Corbishley, C. & Bailey, M. Radiofrequency hyperthermia and mitomycin C for the management of frail patients with high-risk non-muscle invasive bladder cancer who fail intravesical BCG treatment. *BJU Int.* **106** (Suppl. 1), 8, abstr.132 (2010).
66. Moskovitz, B., Halachmi, S., Moskovitz, M. & Nativ, O. 10-year single-center experience of combined intravesical chemohyperthermia for nonmuscle invasive bladder cancer. *Future Oncol.* **8**, 1041–1049 (2012).
67. Sooriakumaran, P. *et al.* Predictive factors for time to progression after hyperthermic mitomycin C treatment for high-risk non-muscle invasive urothelial carcinoma of the bladder: an observational cohort study of 97 patients. *Urol. Int.* **96**, 83–90 (2016).
68. Witjes, J. A., Hendricksen, K. & Nativ, O. R. O. Intravesical hyperthermia and mitomycin-C for carcinoma *in situ* of the urinary bladder: experience of the European Synergo® working party. *World J. Urol.* **27**, 319–324 (2009).
69. Halachmi, S. *et al.* Intravesical mitomycin C combined with hyperthermia for patients with T1G3 transitional cell carcinoma of the bladder. *Urol. Oncol.* **29**, 259–264 (2011).
70. Lammers, R. J. M., Witjes, J. A., Inman, B. A. & Leibovitch, I. The role of a combined regimen with intravesical chemotherapy and hyperthermia in the management of non-muscle-invasive bladder cancer: a systematic review. *Eur. Urol.* **60**, 81–93 (2011).
71. Arends, T. J. H. *et al.* Results of a randomised controlled trial comparing intravesical chemohyperthermia with mitomycin C versus bacillus Calmette–Guerin for adjuvant treatment of patients with intermediate- and high-risk non-muscle-invasive bladder cancer. *Eur. Urol.* **69**, 1046–1052 (2016).
72. Bui, T. & Schellhammer, F. Additional bacillus Calmette–Guerin therapy for recurrent transitional cell carcinoma after an initial complete response. *Urology* **49**, 687–691 (1997).
73. Dalbagni, G. & Herr, H. W. Current use and questions concerning intravesical bladder cancer group for superficial bladder cancer. *Urol. Clin. North Am.* **27**, 137–146 (2000).
74. Reijke, T. M.D. E. *et al.* Bacillus Calmette–Guerin versus epirubicin for primary, secondary, or concurrent carcinoma *in situ* of the bladder: results of a European organization for the research and treatment of cancer — Genitourinary Group phase III trial (30906). *J. Urol.* **173**, 405–409 (2005).
75. NCCN clinical practice guidelines in oncology: bladder cancer. *NCCN* [online] https://www.nccn.org/professionals/physician_gls/f_guidelines.asp org (2016).
76. Catalona, W., Hudson, M., Gillen, D., Andriole, G. & Ratliff, T. Risks and benefits of repeated courses of intravesical bacillus Calmette–Guerin therapy for superficial bladder cancer. *J. Urol.* **137**, 220–224 (1987).
77. Steinberg, R. L., Thomas, L. J., Mott, S. L. & O'Donnell, M. A. Bacillus Calmette–Guerin (BCG) treatment failures with non-muscle invasive bladder cancer: a data-driven definition for BCG unresponsive disease. *Bl Cancer* **2**, 215–224 (2016).
78. Papageorgiou, A. *et al.* Role of tumor necrosis factor-related apoptosis-inducing ligand in interferon-induced apoptosis in human bladder cancer cells. *Cancer Res.* **2004**, 8973–8979 (2004).
79. Joudi, F. N., Smith, B. J., & O'Donnell, M. A. Final results from a national multicenter phase II trial of combination bacillus Calmette–Guérin plus interferon alpha-2B for reducing recurrence of superficial bladder cancer. *Urol. Oncol.* **24**, 344–348 (2006).
80. Gallagher, B. L., Joudi, F. N., Maymí, J. L. & O'Donnell, M. A. Impact of previous bacille Calmette–Guérin failure pattern on subsequent response to bacille Calmette–Guerin plus interferon intravesical therapy. *Urology* **71**, 297–301 (2008).
81. Nepple, K. G. *et al.* Bacillus Calmette–Guérin with or without interferon alpha-2b and megadose versus recommended daily allowance vitamins during induction and maintenance intravesical treatment of nonmuscle invasive bladder cancer. *J. Urol.* **184**, 1915–1919 (2010).
82. Rosevear, H. M. *et al.* Factors affecting response to bacillus Calmette–Guérin plus interferon for urothelial carcinoma *in situ*. *J. Urol.* **186**, 817–823 (2011).
83. Rucker, F. & Rubin, H. Variation of the immunosystem by ciclosporin and keyhole-limpet hemocyanin — are there effects on chemically induced bladder carcinoma? *Urol. Int.* **44**, 77–80 (1989).
84. Lammers, R. J. M., Witjes, W. P. J., Janzing-Pastors, M. H., Caris, C. T. & Witjes, J. A. Intracutaneous and intravesical immunotherapy with keyhole limpet hemocyanin compared with intravesical mitomycin in patients with non-muscle-invasive bladder cancer: results from a prospective randomized phase III trial. *J. Clin. Oncol.* **30**, 2273–2279 (2012).
85. Witjes, W. P. *et al.* Results of a European comparative randomized study comparing oral bropirimine versus intravesical BCG treatment in BCG-naive patients with carcinoma *in situ* of the urinary bladder. European Bropirimine Study Group. *Eur. Urol.* **36**, 576–581 (1999).
86. Sarosdy, M. F. *et al.* A phase II clinical trial of oral bropirimine in combination with intravesical bacillus Calmette–Guérin for carcinoma *in situ* of the bladder: a Southwest Oncology Group study. *Urol. Oncol.* **23**, 386–389 (2005).
87. Biot, C. *et al.* Preexisting BCG-specific T cells improve intravesical immunotherapy for bladder cancer. *Sci. Transl Med.* **4**, 1–10 (2012).
88. Badalament, B. R. A. *et al.* A Prospective randomized trial of maintenance versus nonmaintenance intravesical bacillus Calmette–Guerin therapy of superficial bladder cancer. *J. Clin. Oncol.* **5**, 441–449 (1987).
89. Witjes, J. A., Fransen, M. P. H., van der Meijden, A. P. M., Doesburg, W. H. & Debruyne, F. M. J. Use of maintenance intravesical bacillus Calmette–Guérin (BCG), with or without intradermal BCG, in patients with recurrent superficial bladder cancer. Long-term follow-up of a randomized phase 2 study. *Urol. Int.* **51**, 67–72 (1993).
90. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT02326168?term = 02326168&rank = 1 (2015).
91. Filion, M. C., Lépicier, P., Morales, A. & Phillips, N. C. Mycobacterium phlei cell wall complex directly induces apoptosis in human bladder cancer cells. *Br. J. Cancer* **79**, 229–235 (1999).
92. Morales, A. *et al.* Efficacy and safety of MCNA in patients with nonmuscle invasive bladder cancer at high risk for recurrence and progression rin after failed treatment with bacillus Calmette–Guerin. *J. Urol.* **193**, 1135–1143 (2015).
93. Powles, T. *et al.* MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. *Nature* **515**, 558–562 (2014).
94. Rosenberg, J. E. *et al.* Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet* **387**, 1909–1920 (2016).
95. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT02625961?term = 02625961&rank = 1 (2017).
96. Kamat, A. M. KEYNOTE-057: phase 2 study of pembrolizumab for patients with BCG-unresponsive, high-risk non-muscle-invasive bladder cancer (NMIBC) [abstract]. *J. Clin. Oncol.* **34** (Suppl.), TPS4576 (2016).
97. Burke, J. M. *et al.* A first in human phase 1 study of CG0070, a GM-CSF expressing oncolytic adenovirus, for the treatment of nonmuscle invasive bladder cancer. *J. Urol.* **188**, 2391–2397 (2012).
98. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT02365818?term = 02365818&rank = 1 (2016).
99. Yamashita, M. *et al.* Syn3 provides high levels of intravesical adenoviral-mediated gene transfer for gene therapy of genetically altered urothelium and superficial bladder cancer. *Cancer Gene Ther.* **9**, 687–691 (2002).
100. Dinney, C. P. N. *et al.* Phase I trial of intravesical recombinant adenovirus mediated interferon-α2b formulated in Syn3 for bacillus Calmette–Guérin failures in nonmuscle invasive bladder cancer. *J. Urol.* **190**, 850–856 (2013).
101. Dinney, C. P. Emerging therapy for BCG unresponsive NMIBC. Presented at the Society of Urologic Oncology Winter Meeting (Washington, D.C.), SUO-CTC Scientific Session (2015).
102. Sundi, D. *et al. In vitro* effects of interferon alpha in bladder cancer: immune checkpoint expression and microRNA and mRNA genomic profiling [abstract MP83-12]. *J. Urol.* **195** (Suppl.), e1085 (2016).
103. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT02773849?term = 02773849&rank = 1 (2017).
104. Waidelich, R., Stepp, H., Baumgartner, R. & Weninger, E. Clinical experience with 5-aminolevulinic acid and photodynamic therapy for refractory superficial bladder cancer. *J. Urol.* **165**, 1904–1907 (2001).
105. Bader, M. J. *et al.* Photodynamic therapy of bladder cancer — a phase I study using hexaminolevulinate (HAL). *Urol. Oncol.* **31**, 1178–1183 (2013).
106. Kamat, A. M. *et al.* Bladder cancer. *Lancet* **388**, 2796–2810 (2016).
107. van Kessel, K., Zuiverloon, T., Alberts, A., Boormans, J. & Zwarthoff, E. Targeted therapies in bladder cancer: an overview of *in vivo* research. *Nat. Rev. Urol.* **12**, 681–694 (2015).
108. Choueiri, T. K. *et al.* Double-blind, randomized trial of docetaxel plus vandetanib versus docetaxel plus placebo in platinum-pretreated metastatic urothelial cancer. *J. Clin. Oncol.* **30**, 507–512 (2012).
109. Milowsky, M. I. *et al.* Final results of a multicenter, open-label phase II trial of dovitinib (TKI258) in patients with advanced urothelial carcinoma with either mutated or nonmutated FGFR3 [abstract]. *J. Clin. Oncol.* **31** (Suppl. 6), 255 (2013).
110. Hussain, M. H. A. *et al.* Trastuzumab, paclitaxel, carboplatin, and gemcitabine in advanced human epidermal growth factor receptor-2/neu–positive urothelial carcinoma: results of a multicenter phase II National Cancer Institute Trial. *J. Clin. Oncol.* **25**, 2218–2224 (2016).
111. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT01732107?term = 01732107&rank = 1 (2016).
112. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT01259063?term = 01259063&rank = 1 (2016).
113. Kowalski, M. *et al.* A phase I study of an intravesically administered immunotoxin targeting EpCAM for the treatment of nonmuscle-invasive bladder cancer in BCG-refractory and BCG-intolerant patients. *Drug Des. Devel. Ther.* **4**, 313–230 (2010).
114. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT02449239?term = 02449239&rank = 1 (2016).
115. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT01118351?term = 01118351&rank = 1 (2015).
116. Ahn, J. J. & Mckiernan, J. M. New agents for bacillus Calmette–Guerin-refractory bladder cancer. *Urol. Clin. North Am.* **40**, 219–232 (2013).
117. Fishman, M. N. *et al.* Phase I trial of ALT-801, an interleukin-2/T-cell receptor fusion protein targeting p53 (aa264-272)/HLA-A*0201 complex, in patients with advanced malignancies. *Clin. Cancer Res.* **17**, 7765–7776 (2011).
118. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT01625260?term = 01625260&rank = 1 (2017).
119. Chen, J., Leu, Y., Fang, C., Chen, C. & Fang, J. Thermosensitive hydrogels composed of hyaluronic acid and gelatin as carriers for the intravesical administration of cisplatin. *J. Pharm. Sci.* **100**, 655–666 (2011).
120. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT02701023?term = 02701023&rank = 1 (2016).
121. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT02720367?term = 02720367&rank = 1 (2016).
122. Binder, R. J., Han, D. K. & Srivastava, P. K. CD91: a receptor for heat shock protein gp96. *Nat. Immunol.* **1**, 151–155 (2000).
123. Steinberg, G. *et al.* Phase I/II study of patients with non-muscle invasive bladder cancer (NMIBC) treated with vesigenurtacel-L (HS-410) with or without bacillus Calmette–Guérin (BCG). Presented at the AACR 2016 Annu Meet [online] http://content.stockpr.com/heatbio/db/114/1119/file/AACR + 2016_HS-410_NMIBC_Phase1.pdf (2016).
124. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT02010203?term = 02010203&rank = 1 (2016).

125. Gulley, J. L. *et al.* A pilot study to evaluate the safety and clinical outcomes of vaccination with recombinant CEA-MUC-1-TRICOM (PANVAC) poxviral-based vaccines in patients with metastatic carcinoma. *Clin. Cancer Res.* **14**, 3060–3069 (2008).
126. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT02015104?term=02015104&rank=1 (2017).
127. Lee, E. K. *et al.* A Smac mimetic augments the response of urothelial cancer cells to gemcitabine and cisplatin. *Cancer Biol. Ther.* **14**, 812–822 (2013).
128. Metwalli, A. R. *et al.* Smac mimetic reverses resistance to TRAIL and chemotherapy in human urothelial cancer cells. *Cancer Biol. Ther.* **10**, 885–892 (2010).
129. Yang, X. *et al.* Diphtheria toxin-epidermal growth factor fusion protein DAB389EGF for the treatment of bladder cancer. *Clin. Cancer Res.* **19**, 148–157 (2013).
130. Cho, S. *et al.* Functionalized gold nanorods for thermal ablation treatment of bladder cancer. *J. Biomed. Nanotechnol.* **10**, 1267–1276 (2014).
131. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT02009332?term=02009332&rank=1 (2016).
132. Riedl, C. R., Knoll, M., Plas, E. & Pfluger, H. Intravesical electromotive drug administration technique: preliminary results and side effects. *J. Urol.* **159**, 1851–1856 (1998).
133. Colombo, R. *et al.* Thermo-chemotherapy and electromotive drug administration of mitomycin C in superficial bladder cancer eradication: a pilot study on marker lesion. *Eur. Urol.* **39**, 95–100 (2001).
134. Bachir, B. G. *et al.* Contemporary cost-effectiveness analysis comparing sequential bacillus Calmette–Guerin and electromotive mitomycin versus bacillus Calmette–Guerin alone for patients with high-risk non-muscle-invasive bladder cancer. *Cancer* **120**, 2424–2431(2014).

Author contributions
All authors researched data for the article, made a substantial contribution to discussions of content, and wrote and reviewed or edited the manuscript before submission.

Competing interests statement
A.K. declares that he has acted as a consultant for Cepheid, Photocure,Telesta Therapeutics, Sanofi, Merck, Abbott Molecular, Theralase, Heat Biologics, Spectrum Pharmaceuticals, and Oncogenix. He has received grant support from FKD Industries, Photocure, Merck, and Heat Biologics, and he has a patent pending for a cytokine assay for BCG (CYPRIT) with the University of Texas MD Anderson Cancer Center. J.A.W. declares that he has acted as an adviser for MEL. J.P. declares clinical trial collaborations with Combat Medical and Presurgery. D.L. declares research collaborations with Vicinium and Cold Genesys-CG0070. R.B. declares that he has acted as a consultant for Sanofi. The other authors declare no competing interests.