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*Review / Derleme*

# Current intravesical therapies BCG-failure in non-muscle-invasive bladder cancer

## Kasa invaze olmayan BCG-refraktör mesane kanserinde güncel tedaviler

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**Özet**

Kasa invaziv olmayan mesane kanseri (Kİ-OMK) için birinci basamak tedavi intravezikal Bacillus Calmette-Guerin'dir (BCG). BCG'ye rağmen, tekrarlayan veya ilerleyen mesane kanseri için acilen alternatif tedavilere ihtiyaç vardır. BCG-refraktör Mesane kanserinde radikal sistektomi altın standart tedavidir. Hastaya bağlı nedenler ile(komorbidite, operasyon istememe gibi) sistektomi yapılamadığında diğer tedavilere başlanmalıdır. İntravezikal gemstabin, taksanlar, kombinasyon tedavileri , aşılar, gen terapisi gibi birçok klinik çalışma, bir sonraki adımı belirlemede kritik öneme sahiptir. Radikal sistektomiye alternatif, iyi tasarlanmış birçok yeni tedavi çalışması halen devam etmektedir. Yakın gelecekte rutin klinik uygulamaya girmesi beklenmektedir. Yeni tedaviler ile beraber mesane kanser tedavisinde önemli değişiklikler olacaktır.

**Anahtar Kelimeler:** Kasa invaze olmayan mesane kanseri, BCG-Refraktör, radikal sistektomi, intravezikal tedaviler.

**Abstract**

The first-line treatment for non-muscle invasive bladder cancer (NMIBC) is intravesical Bacillus CalmetteGuerin (BCG). Despite BCG, alternative treatments are urgently required for recurrent or progressive bladder cancer. Cystectomy is the gold standard treatment in BCG failure in bladder cancer. When cystectomy can not be performed for reasons related to the patient, other treatments should be started. Many clinical studies such as intravesical gemcitabine, taxanes or combination treatment, new therapeutic agents,..etc are critical in determining the next step. Alternative to radical cystectomy, well designed and many new treatment studies are still ongoing. They seem ready for routine clinical practice in the near future. We believe that NMIBC treatment modalities will change in the near future.

**Keywords:** Non-muscle invasive bladder cancer, BCG-refractory, radical cystectomy, intravesical teratments.

## INTRODUCTION

Bladder cancer (BCa) is the 9th widespread cancer type in the world (1). 75% of the patients are NMIBC, and 20% of new cases are high-grade T1 tumors. It is a heterogeneous cancer type, and therefore, it is important to identify patients with higher recurrence and progression and classify them according to the risk factors. In the long-term follow-up, progression risk ranges from 21-53% and cancer-related death risk from 14-34%(2). Disease recurrence and progression are tried to be predicted via multiple nomograms, and risk tables predict. With this, the most important risk factor for progression is NMBIC grade. According to European Association of Urology (EAU) guidelines for the NMIBC workgroup, all high-risk NMIBC (HRNMIBC) consists of stage T1, TaG3, primary, and concomitant cancer in situ of the bladder (CIS) and recurrent and large TaG1G2 tumours(3). The EAU definition of HRNMIBC is similar to that of the American Urological Association (AUA) stance on HNMIBC, except that all T1 tumors, regardless of grade, are defined as high-risk. The 5-year progression rate for patients with T1 ranges from 10 to 40%(4).

BCG treatment is the golden standard in NMIBC(3). Currently, the AUA and EAU recommend BCG induction (6 weeks) followed by 1–3 years of maintenance, depending on risk. Multiple studies have shown that BCG reduces recurrence and progression (3, 5). However, according to some studies, BCG's straight impact on diminishing progression, preventing metastasis, and cancer-specific survival (CSS) is still under discussion(6). In the study of Thiel et al., They stated that NMIBC did not affect the cancer-specific mortality(CSM) in patients receiving long-term BCG treatment, but it reduced recurrence and progression(7). Tumors with BCG failure present an essential progression and metastasis and thus a potentially life-threatening condition. This review will present recent information about BCG failure in NMIBC treatment.

### BCG Refractory

Recurrence and progression in bladder cancer under BCG treatment is called "BCG refractory". In addition to the term BCG-refractory, terms such as BCG-unresponsible and BCG-failure may accompany. BCG-refractory in the relevant literature is defined as the recurrence of tumor after induction and maintenance. BCG-relapse refers to the recurrence of tumors after a disease-free status of 6 months. BCG-intolerance is the discontinuation of treatment due to side effects. In the European Organization for Research and Treatment of Cancer (EORTC) study in which 487 patients received 36 months of BCG, only 20% of the patients discontinued BCG due to local and/or systemic side effects(8). "Adequate BCG" is defined as at least five of the six instillations of subsequent two of the three during maintenance BCG. According to the EAU guideline, one of the following four items is to be present to label ''BCG refractory"(3).

1. Presence of T1G3/HG tumour in the first 3 months
2. Presence of TaG3/HG tumour after 3 months and/or at 6 months, after either re-induction or first course of maintenance
3. Presence of CIS (without concomitant papillary tumour) for3 months and persists for 6 months after either re-induction or first course of maintenance
4. Appearance of HG tumour during BCG maintenance therapy

BCG-refractory patient prognosis is worse compared to BCG-relapse. Shirakawa et al. reported a 10-year prognosis-free survival in 53,2% of the patients in the BCG refractory group, yet in 91,1% of the cases in the BCG-relapse group (9). The Herr HW et al. study revealed progression-free survival of 18 months in the BCG-refractory and 52 months in the BCG-relapse group. Half of the patients in the BCG-refractory group died of bladder cancer (8/17)(10). As conservative treatment is incapable of resulting in cancer-free status, immediate effective treatment should be started for BCG-refractory tumors and high-risk BCG-relapse tumors.

### Management of BCG-Refractory

The golden treatment of BCG failure in NIMBC is radical cystectomy (RC)(11). Time for RC is classified into 3. 1.Immediate cystectomy (HRNMIBC after

the first TUR), 2.Early cystectomy (after BCG failure), 3.Late cystectomy (after conservative treatments). Although RC treatment seems to be an aggressive modality, its advantage is higher due to the risk of morbidity and mortality. First of all, RC raises disease-free survival (DFS) up to 80-90% in the long term(11). It enables correct pathological staging in patients. The rise of the stage after RS varies between 25-50%(11). Performing lymphadenectomy with RC allows patients to detect metastatic lymph nodes (5-20%) (12, 13). In addition, post-RC follow-up protocol is easier than intravesical therapies. However, cystectomy was performed in only 4.7% of cases within 1 year after diagnosis of T1HG BCa (14)(Table 1).

**Table 1.** Summary disease-free and recurrence-free survival for current salvage therapies

| | Treatment | RFS |
|---|---|---|
| Standard of care: RC | 5-y CSS 80% | |
| Gemcitabine | 21%–28% RFS at 12 mo. | 21% RFS at 24 mo. |
| Docetaxel | 40% RFS at 12 mo. | |
| Valrubicin | 18%–21% RFS at 6 mo | 16% RFS at 12 mo. |
| Abraxane | 36% RFS at 12 mo. | |
| Gemcitabine/Docetaxel | 54% RFS at 12 mo. | 34% RFS at 24 mo. |
| Gemcitabine/MMC | 48% RFS at 12 mo. | 38% RFS at 24 mo. |
| BCG/INFa/IL-2/GM-CSF | 55% RFS at 12 mo. | 53% RFS at 24 mo. |
| Chemohyperthermia | 61-83% RFS at 12mo. | 59-61% RFS at 24mo. |

***RFS:*** *Recurrence Free Survival,* ***CSS:*** *Cancer Specific Survival,* ***RC:*** *Radical Cystectomy*

Postponed cystectomy is worsening possible treatment outcomes in patients with T1HG BCa. In the Harry et al. study in which 90 patients underwent cystectomy, they followed the patients for 96 months. Disease-free survival was present in 92% of patients who underwent an operation in 2 years and 56% of those who were performed 2 years later (15). Denzinger et al. proposed T1HG BC patients early cystectomy based on at least two of three risk factors (multiple tumors, tumor size> 3 cm, and CIS). 105 patients accepted early cystectomy (51%). CIS was related to aggravated DSS in patients who delayed cystectomy. In addition, 10-year cancer-free survival was 78% in patients undergoing early cystectomy and 51% in patients who delay cystectomy(16). The multicentric study of Gontero et al. with T1HG BC patients provides the most substantial data, though retrospectively, to evaluate the timing of cystectomy. In their studies, some patients with T1 underwent emergency cystectomy, while others underwent early and late cystectomy. RC (113) of 221 (9%) patients who died due to BC had RC performed. Perhaps the most important reason for it being more than expected was the delayed RC(17). In the multicenter studies of Fritsche HM et al., it is emphasized that 1/3 (35.5%) of T1 patients who underwent RC for more than 4 years died from metastatic disease (13). All of these studies underline that in cases with cystectomy in T1HG disease, radical treatment postponed results with sacrificed opportunities for total cure. Although the importance of early cystectomy is clear, urologists' surgical suggestions to the patient in daily practice are still controversial. A scarce amount, 1.8%, of the cases prefer immediate cystectomy and 66% after disease progression (11).

## Intravesical Treatments

### Second Course BCG

The AUA guideline for NMIBC suggests after the 1st BCG course for persistent or recurrent Ta or CIS BC patients, the 2nd course of BCG (except for T1). The AUA guideline suggests the failure of the 2nd BCG course RC. The number of studies is limited and has small patient series. Brake et al. presented the results of the 2nd course BCG (24/106) (18). Out of the 24, 19

(79%) had complete response (CR). Daniels et al. had the largest patient series in 2nd course BCG (19). They reported CR after 3 months 89% and after 36 months 65%. 3.4 % (4/106) reported progression. In conclusion, according to AUA retreatment with 2nd course, BCG is an effective treatment modality.

### Mitomycin

Mitomycin C (MMC) is an antineoplastic agent that cross-links synthesis that prevents DNA. MMC is also a urothelial tissue dryer that allows increased permeability to intravesical agents. It is most commonly used as a single dose applied for low-grade disease during transurethral resection of bladder tumor. In EAU and AUA guidelines, the first-line treatment is intravesical BCG (3, 20). Malmström and colleagues enrolled 261 patients in their HGTa or HGT1 study. Only 4 (19%) did not have any cancer diagnosis in the 3 years to follow (21). In another phase 3 study (ANZUP1301), BCG and BCG + MMC combination comparison revealed lower recurrence rate compared to BCG alone (42% vs. 58%) (22). MMC is currently not accepted as an alternative treatment for BCG failure.

### Valurobisin

Valrubicin is a semi-synthetic anthracycline and the only one treatment modality approved by the FDA in BCG resistant bladder cancer. In a single-arm study involving 90 BC cases with CIS or high-grade Ta and T1; (99% failed at least 2 intravesical treatments), 30 months follow-up; At 6 months, 18%-21% of patients and at 24 months 8% patients received CR (23). RC was performed in 56% of patients, and 15% of patients were pT3 or higher. Cancer related death occurred in patients who avoided cystectomy or experienced a CR. In their updated study, 80 patients with BCG refractor and BCR intolerance were included (24). The CR rate is 18%. In the retrospective cohort study when Valrubicin was regenerated in 2009, RFS (recurrence-free survival) in 100 patients (51% CIS); It was 51.6% at 3 months, 30.4% at 6 months, and 16.4% at 12 months (25). Considering the studies, despite the FDA approval in BCG failure patients, the authors do not recommend salvage therapy to Valurubicin because of low response rates.

### Gemcitabine

Gemcitabine is a pyrimidine analog blocking DNA replication leading to apoptosis carcinoid cells. It was studied elaborately as an agent promising cancer treatment. As a non-vesicant chemotherapy option, it preserves tissue from injuries if intravesically administered.

Dalbagni et al. conducted the first phase 2 study. They included 30 patients who did not accept cystectomy with BCG refractor or BCG intolerance (20 patients received BCG therapy above 2 courses). Gemcitabine 2,000 mg/100 mL was administered for three subsequent weeks twice as an intravesical course with a one-week interval. Disease-free survival (DFS) was 21% at 12 months. Progression in the first year was 3,5%, and the first-year cystectomy rate was 20.5% (26). A multicenter phase 2 study conducted by the SWOG evaluated gemcitabine as a 6-week induction course with subsequent monthly maintenance throughout a year in high-risk patients (86% of the cohort) receiving 2 BCG courses previously. 28% RFS in the 1st and 21% in the 2nd year were observed. Disease progression was observed in two cases, and 32% of the patients had cystectomy, with 6% pT2 or higher pathology results (27).

Lorenzo et al. compared gemcitabine with BCG treatment failure cases. A group of patients was given gemcitabine induction and maintenance doses (2000 mg/50 mL, twice a week). The other group was given BCG again. Gemcitabine group recurrence response was better than BCG (52.3% vs. 87.5%). The risk of progression was above 35% in both groups, especially the T1 stage; it was close to 70% in the very high-risk group (28). Although heterogeneous groups have been compared in Gemcitabine studies, it may be an alternative treatment to BCG.

### Taxanes

Docetaxel is a microtubule depolymerization inhibitor with antimitotic tumor activity. Docetaxel protocol was applied for 33 patients. The mean DFS was 13.3 months. At 29 months of follow-up, 1st and 2nd year DFS was 45% and 32%, respectively. CR was generally 30% (11/33). Six patients received RC. The

most common drug-related side effect was dysuria and hematuria (29). Induction and monthly maintenance dose were given in 54 BCG refractory bladder cancer phase 2 studies (28 BCG, 20 BCG + interferon, 10 MMC + BCG). In 59% of the cases, CR rate was observed. 40% and 25% RFS rates were determined at 1 year and 3 years, respectively. RC was performed in 24% of the cases at a median two-year follow-up, and 28% progressed to T2 (30).

Abraxane, compared to docetaxel, is a nanoparticle albumin-bound version of paclitaxel. It has been considered to increase bioavailability and was also used in a phase II trial. In the 1st year, RFS was 36% in 28 patients. 9 patients underwent cystectomy (21%)(31). In the long-term revised study (mean 41 months) of the same study, the recurrence-free patient group was 18%, and the 5-year overall specific survival (OSS) and cancer-specific survival (CSS) were 56% and 91% (32). Cremophor-free and nanopolymer-based docetaxel, Docetaxel-PM, was employed in a phase 3 study (NCT02982395) to determine intravesical Docetaxel-PM efficacy and safety compared to MMC in BCG-refractory BC.

### Intravesical Combination Treatments

Combination chemotherapy regimens have like multi-agent intravenous therapy studied in-depth and described elaborately. The use of various drugs may result in elevated toxicity risk; however, gemcitabine and docetaxel, non-desiccant cytotoxic therapeutic drugs, combined with desiccant drugs, such as mitomycin, to enable these drugs to be infused after another and make use of the advantages of multiple action functions and highlight their effectiveness. Studies on combined intravesical chemotherapy have not been fully established due to various problems such as BCG unresponsive patients, poor tumor segregation, small patient series, retrospective studies, and limitations.

### Gemstabin + Mitomycin C Combination

In the first study, 27 patients with BCG failure in 2006 received positive results (20 months DFS) as a recovery therapy. Patients refusing cystectomy with BCG failure in the study of May bee et al. have been analyzed. Hereby, 24-month DFS was 37%, while progression was 3.7%. RC was performed in 19% of patients (33). Cockerill et al. studied combined GC and MMC weekly treatment. In 37% of the cases at 22.1 months of follow-up, durable responses were determined retrospectively (34). Another multi-centered study with 47 patients determined an initial CR of 68%. RFS rates of 48 % during the first and 38% at the second post-treatment year (35).

### Gemcitabine + Docetaxel Combination

Steinberg et al. were the first to describe sequential intravesical gemcitabine and docetaxel in BC treatment and reported 66% CR at the first control, 54% at 1st year, and 34% at the 2nd. In the patients who preferred cystectomy, no progression was seen (36).

### Gemcitabine, Cabazitaxel, and Cisplatin

A CR of 78% and minimal side effects were determined in a phase 1 study conducted in 2017 with 9 BCG refractory patients undergoing gemcitabine, cabazitaxel, and cisplatin (GCP) intravesical therapy (37). This trial was expanded to 18 BCG failures in 2019. Phase 1 study showed efficiency CR 94% and a DFS of 78% at 9.5 months (38). GCP's promising results have only been presented as an abstract form in AUA 2019 so far.

### Granulocyte-Macrophage Colony-Stimulating Factor

In BCG failure etiology, insufficient immunity was determined as an underlying factor. Granulocyte-macrophage colony-stimulating factor (GM-CSF) has been identified as a stimulatory cytokine in the proinflammatory BCG pathway (39). Hence, GM-CSF addition to intravesical treatment is considered to reinforce the proinflammatory response. Steinberg et al. reviewed retrospectively BCG-failure patients administered quadruple immunotherapy (reduced dose BCG, IFNa, interleukin (IL)-2, and GM-CSF)(40). A 53% DFS rate was reported in 24 months. T2 and higher stages were evident in cystectomy patients. This indicated the presence of an opportunity between BCG failure enabling

the exploration of salvage therapies without compromising curative surgery.

### BCG Derivatives: Mycobacterial Cell Wall Extract and Mycobacterial Cell Wall Nucleic Acid Complex

Shortly BCG was cheered as a success for the first time in BC patients; researchers began to try compounds with similar effects; yet, without exposing BC patients to the risks of using live attenuated bacteria. The first promising compound was mycobacterial cell wall extract (MCWE) from non-pathogenic Mycobacterium Phlei, developed by Morales et al. It was tested in various experimental animals in 1990, and since it had positive results, the first attempts of MCWE use in human bladder cancer was made by Morales et al. in 2001 with CIS cases. 61 patients in a single-arm study, 46% of patients had previously received BCG induction therapy. Although the CR rate was 62% in 3 months and 41% in 1 year, only 16 cases remained in 1 year (41). But the results were similar in patients with BCG refractory.

During experiments with MCWE, the researchers tried to increase their potency while reducing the adverse effects of MCWE. The outcoming compound was called the mycobacterial cell wall nucleic acid complex (MCNA). MCNA, such as MCWE, is an immunomodulatory agent derived from non-pathogenic M. Phlei mycobacterial cell wall fragments activated by nucleic acids. Therefore, it contains 5% to 10% M. Phlei DNA, which is thought to mediate its therapeutic effect. Immunomodulation similar to BCG and by direct cytotoxic effect different from BCG has simultaneously occurred during MCNA antitumor activity. It was also considered to have less potential toxic effects (42).

There are two important studies investigating MCN effectiveness. In 2009, Morales et al. presented two-arm studies comparing 4 mg and 8 mg MCNA in CIS patients. 85% of the whole cohort consisted of patients who received BCG induction therapy, and 35% and were of Ta / T1. Subsequent to 6-week 4 or 8 mg MCNA administration, patients received a 3-week maintenance dose at 3 and 6 months. In the first 3 months, CR was 62% (8 mg) with 40% (4 mg). The 1-year CR rate was 40% for 4 mg and 33% for the 8 mg group, and the results were successful. In their study, no follow-up evaluation was conducted, and only approximately 40% of the cases in the 8 mg MCNA cases were accessible 12-month post-treatment (43).

The phase III trial of MCNA was the one-arm study of 129 patients treated with a 6-week induction course of 8 mg MCNA between Morales et al. between 2006 - 2011, subsequent 3-week maintenance induction cycles for 2 years (3, 6, 12, 18, and 24 monthly intervals). All patients have previously received BCG, and 83% recurred within 1 year after BCG therapy. Patients received an average of 12 MCNA vaccinations with a 99% compliance rate for scheduled vaccinations. Only 2 patients stopped treatment due to adverse effects. The Median follow-up of the whole group was 34.7 months. 30 patients 1-year RFS rate is 25% (5.7 months), 4 patients (13%) recurred within 1 year. Overall, the cancer progression rate was 22%. 43% underwent cystectomy, and 21% of them had pT2 disease (44). In general, although the findings do not have very high response rates, BCG has more than 20% RFS in first-year recovery regimens in unresponsive patients. The rate rises to 34% in patients with CIS (41, 44). In the literature, there are no comparative studies in BCG refractory patients with other agents. Still, it can be used as an alternative treatment in patients with BCG intolerance as the side effect profile is low.

### Chemohyperthermia

Chemohyperthermia (C-HT) is the combination of MMC with hyperthermia of the intravesical agent. Temperature increase up to 40 °C - 44°C is maintained in the bladder through hyperthermia in order to alter intracellular metabolism resulting in DNA damage and induced apoptosis. Moreover, an increase in blood perfusion and cell permeability, enabling enhanced uptake of intravesical agents, is also made possible through hyperthermia (45).

A multicenter prospective randomized control trial comparing C-HT with MMC versus conventional MMC in 83 NMIBC high-risk T1/Ta patients (35%–

39%) or recurrent NMIBC (60%– 65%) was conducted by Colombo et al. RFS in the C-HT with the MMC group was 82.9% versus 42.5% with the MMC group after a 24-month follow-up(46). Different results have been reported in various retrospective analyses of C-HT with MMC in a BCG-refractory group. RFS of 85% at first and 56% at the second year have been reported, lower in BCG-refractory patients with CIS with rates of 23% and 41% (47).

In general, recurrence rates are variable for patients who have previously had BCG refractories after C-HT. Although current data is limited, long-term studies are needed.

### Intraarterial Chemotherapy

One of the bladders-preserving treatment modalities is intraarterial chemotherapy. Zafu et al. reported in their retrospective study intraarterial chemotherapy in 62 patients refusing RC out of 238 in total and intravesical chemotherapy in 141 and immediate RC in 35 patients (48). In the bladder, preserving chemotherapies, cisplatin, and gemcitabine were administered. CSS and PFS are lower in the intravesical chemotherapy group compared to intraarterial chemotherapy and RC group. . However, in terms of PFS and OS, there were no statistically significant differences between RC and intraarterial chemotherapy groups. Further prospective studies are necessary to verify these findings.

### Trimodal Therapy

Despite the fact that chemo-radiotherapy is in practice for the treatment of MIBC, its practice in NMIBC is currently still under discussion. Weiss et al., the first study on chemo-radiotherapy use in NMBIC, enrolled 141 cases of high-risk T1 stage undergoing pelvic (50.4 Gy) and bladder (55.8 Gy) radiotherapy with subsequent cisplatin or carboplatin-based chemotherapy following TUR. 19% were the 5-year, and 30% were the 10-year progression rates and CR rate was 88% (49). Although the results are promising, it is a problem that the BCG refractor patient group is unclear in their studies. Despite BCG treatment, a small series of 18 patients of T1 stage progressing to T2 underwent chemo-radiotherapy, and 54% of the 7-year median follow-up did not progress. Although an alternative treatment is considered in BCG-refractor patients, it has been stated that especially RT is not suitable for patients with CIS.

A nonrandomized phase II trial with high-grade NMIBC patients subsequent to BCG failure with RT+cisplatin following TUR or RT+5-fluorouracil is currently being conducted (NCT00981656) with cystectomy-free survival as the primary goal. Trimodaltherapy could be an alternative for suitable patients with BCG failure, unfit for RC, according to the preliminary findings.

### New Therapeutic Agents Ongoing with Phase II - III Clinical Trials

Recently, many new treatment agents such as immunotherapy, vaccines, and viral treatments are tried in muscle-invasive and non-muscle-invasive bladder cancer. Below are several trial studies in Phases II and III in the BCG-refractor population that will be highlighted (Table 2).

### Check-point Inhibitors

In the past few years, several immune checkpoint inhibitors proved to be useful in the treatment of BC, and as a result, monoclonal antibody therapies have been approved by the FDA. In BC, the increase in PD-L1 tumor expression levels leads to a worsening prognosis. Therefore, many phase ll/lll studies of anti-PD-1 (pembrolizumab, nivolumab) and anti-PD-L1 (atezolizumab, durvalumab, avelumab) agents have been initiated.

One of these studies is the pembrolizumab (NCT02625961) study. In BCG refractor cases, a 24-month evaluation of IV pembrolizumab injection at a three-week interval is being studied. Out of the 103 cases, three-month CR was 39% (40/103) and 14 months CR 30 % (29/103). Severe side effects were seen 13%. Early results of the treatment are currently expected.

### Vaccines,Gene Therapy,Interleukins

Vaccines are expected to enable immunity against tumor-related antigens in various cancer types. In theory, the monoclonal antibodies are along with the therapy of cancer also to prevent relapse and progres-

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**Table 2.** Clinical Trials of BCG-Failure in NMIBC

| Therapy type | Agent | Ref/Study ID | Phase | Study Design | Results / Primary Outcome |
|---|---|---|---|---|---|
| **Chemotherapy** | Cabazitaxel,Gemcitabine, and Cisplatin | NCT02202772 | 1 | Single arm, BCG-failure patients<br>Induction: 6 x weekly instillation | Active, NR /<br>1.Adverse Event 2 . CR |
| **Immunotherapy** | Pembrolizumab | NCT02625961 | 2 | Single arm, BCG-failure, Refused RC<br>Pembrolizumab 200 mg 3 week up to 24mo | Recruting, CR: 40/103 (39%), 3 mo / 1. CR ,2. RFS |
| | Atezolizumab | NCT 02844816 | 2 | Single arm, BCG-failure<br>Atezolizumab IV 3 wk; max 17 doses/51 week | Recruiting , NR /<br>1. CR , 2. RFS |
| **Gen Therapy** | CG0070 | NCT 02365818 | 2 | Single arm,BCG-failure, Refused RC<br>Induction: 6 x weekly instillation of $1 \times 10^{12}$ Vp CG0070,<br>Maintenance: same | Recruting CR: 13/57 (23%)<br>18.mo / 1.CR 2.RFS |
| | rAd-IFNα/Syn3 | NCT 02773849 | 3 | Single arm, BCG-failure<br>Maintenance: 3 week instillation up to 84 weeks Intravesical instillation 3 mo | Active, CR:14/40 (35%)<br>12.mo / 1.CR |
| **Vaccines** | PANVAC | NCT 02015104 | 2 | Randomize , BCG vs BCG+PANVAC , BCG-failure<br>6 x weekly instillation BCG starting at week 3; PANVAC-V2 x 108 pfu SQ at wk 0, PANVAC-F x 109 pfu SQ at wk 3,7,15 | Active, NR / 1.RFS |
| | ALT-801 | NCT01625260 | 1/2 | Single arm, BCG-failure<br>Induction: 2 cycles of IV ALT-801 (4 doses) + IV Gemcitabine 1000 mg/m$^2$ (2 doses) Maintenance: 1 cycle | Active, NR / 1. CR ,<br>2.Tolerability |
| | HS-410 | NCT02010203 | 1/2 | Single arm , BCG-failure<br>Randomized, placebo-controlled Arm 1: HS-410 Low-Dose + BCG<br>Arm 2: H2-410 High Dose + BCG<br>Arm 3: Placebo + BCG<br>Arm 4: If no BCG,<br>will receive high dose HS-410 | Active, NR/ 1.Safety and tolerability 2. RFS |
| **Drug delivery** | Docetaxel-PM | NCT 02982395 | 3 | Experimental: 75 mg/100 ml NS of intravesical docetaxel-PM ,<br>Comparator: 40 mg/100 ml NS of MMC | Recruiting , NR / 1. CR |
| | Albumin-bound Paclitaxel Nanoparticles | NCT03636256 | 3 | Single arm, BCG-Failure<br>NanoDoce instillation at 2.0 or 3.0 mg/m ,Induction: 6 x weekly instillation<br>Maintenance: 3 weekly instillation 3mo | Recruiting , NR /<br>1.CR , 2.RFS |
| **Chemoradiotion** | Trimodality Therapy | NCT00981656 | 2 | BCG-failure , Refused RC<br>Randomized – Arm 1. Radiation (61.2 Gy) + Cisplatin<br>Arm 2. Radiation (61.2 Gy) + MMC + 5-FU | Recruiting , NR /<br>1.CR 2.RFS |

***CR:*** *Complete Respons* , ***RFS:*** *Recurrence Free Survival* , ***NR:*** *Not Reported*

sion. There are currently three BCG-refractor vaccine studies (ALT-801, PANVAC ve HS-410). According to the preliminary results of HS-410's SUO 2016 annual meeting, the 1-year RFS is 84.6%(50).

Instiladrin (rAd-IFNa/Syn3) is a non-replicating adenovirus, including the human IFNa 2b gene. The preliminary results of Phase I-II studies have reported CR of 35% (14/40) within a year(50).CG0070 is an oncological adenoviirus increasing GM-CSF production and thus enabling selective viral replication in tumor cells and targeting the retinoblastoma tumor suppressor pathway. Packiam et al. (NCT02365818) have reported in BCG failure, or RC was refusing 57 cases a CR of 23 % during an 18-month follow-up (13/57)(50).

BCG impact is seen through increased immuno-response, and the addition of other agents such as interleukins and immunomodulators are still under discussion. ALT-803 is an IL-15 complex. In a Phase 1b study combined with BCG CR is achieved within 12 months (NCT02138734).

## CONCLUSION

The risk of recurrence, progression or even metastasis is high if NMIBC is not treated, especially in BCG failure. Currently, radical cystectomy is still the golden standard treatment modality. However, cystectomy-related morbidity is raising concerns for both urologists and patients. It is not possible to compare clinical studies with radical cystectomy pragmatically and to expect similar results in treatments. The underlying reasons are that these studies are of retrospective nature, the existence of scarce patient series in prospective studies, the inability to make reasonable comparisons due to the presence of heterogeneous groups, and pending studies on new agents. However, the preliminary findings of several Phase ll and lll studies, along with vaccines and gene therapies, have promising outcomes in future BCG failure. In the years to come, treatment modalities in urogenital cancers, particularly bladder cancer, will change the most frequently.

### Conflict of Interest

All authors declared that there is no conflict of interest.

### Financial Disclosure

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### Author Contributions

Conception and design; YEG, Data acquisition; YEG, Data analysis and interpretation; YEG, Drafting the manuscript; YEG, Critical revision of the manuscript for scientific and factual content; YEG, HHT, Supervision; YEG, HHT.

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