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ORIGINAL ARTICLE

Multidisciplinary consensus document on the current treatment of bacille Calmette-Guérin-unresponsive non-muscle invasive bladder tumor

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Abstract Radical cystectomy is the current treatment of choice for patients with BCG-unresponsive non-muscle invasive bladder tumor (NMIBC). However, the high comorbidity of this surgery and its effects on the quality of life of patients require the investigation and implementation of bladder-sparing treatment options. These must be evaluated individually by the uro-oncology committee based on the characteristics of the BCG failure, type of tumor, patient preferences and treatment options available in each center. Based on FDA-required oncologic outcomes (6-month complete response rate for CIS: 50%; duration of response in responders for CIS and papillary: 30% at 12 months and 25% at 18 months), there is not currently a strong preference for one treatment over another, although the intravesical route seems to offer less toxicity. This work summarizes the evidence on the management of BCG-unresponsive NMIBC based on current scientific evidence and provides consensus recommendations on the most appropriate treatment.

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PALABRAS CLAVE
Bacilo de Calmette-Guérin *unresponsive*; Tratamiento intravesical; Tratamiento sistémico; Bacilo de Calmette-Guérin *unresponsive* ensayo clínico

Documento multidisciplinar de consenso sobre el tratamiento actual del tumor vesical no-músculo invasor que no responde al tratamiento con bacilo Calmette-Guérin

Resumen La cistectomía radical es el tratamiento actual de elección para el paciente con tumor vesical no-músculo invasor (TVNMI) no respondedor a la BCG. Si embargo, la elevada comorbilidad de esta cirugía y las secuelas que representa para la calidad de vida de los pacientes, requieren considerar la investigación e implementación de opciones terapéuticas de conservación vesical. Dichas opciones, deben evaluarse en comité uro-oncológico de forma individualizada en función de las características del fallo a la BCG, tipo de tumor, preferencias del paciente y opciones de tratamiento disponibles en cada centro. En función de los resultados oncológicos requeridos por la FDA (tasa de respuesta completa a 6 meses para CIS: 50%; duración de la respuesta en los respondedores para CIS y papilar: 30% a 12 meses y 25% a 18 meses), no existe en la actualidad una preferencia clara de un tratamiento sobre otro, si bien, la vía intravesical parece ofrecer una menor toxicidad. En este trabajo se resume la evidencia sobre el manejo del TVNMI que no responde a BCG en función de la evidencia científica actual y se aportan recomendaciones consensuadas sobre el tratamiento más adecuado.

Introduction

Adjuvant treatment with intravesical instillations of bacillus Calmette-Guérin (BCG) after transurethral resection (TUR) is recommended in high-risk NMIBC due to lower recurrence probability.[1] Regarding progression, despite discrepancies in the literature, it is considered that BCG could also provide benefit if maintenance therapy is completed.[1,2] The probability of 1- and 5-year recurrence after BCG treatment is 15%–61% and 31%–78%, respectively. In the case of progression, these values reach up to 17% and 45% at 1–5 years respectively.[3]

Patients can be considered BCG-unresponsive in cases of recurrent NMIBC after adequate treatment with BCG, and when continued BCG treatment is unlikely to provide benefit. The parameters of the definition require that it be a high-grade (HG) recurrence, consider the time of persistence/recurrence after completion of BCG therapy (refractory Ta-T1 within 6 months; CIS 12 within months), and at least 5 doses of an initial induction course plus at least 2 doses of a second induction course or maintenance therapy, the latter being the definition of ''adequate BCG treatment'' according to the United States Food and Drug Administration (FDA).[4]

In this scenario, the treatment of choice is radical cystectomy.[5] This surgery has a 5-year recurrence-free survival of 71.4%.[6] However, due to its high rate of postoperative complications (34.9%) and 90-day mortality (4.7%),[7] and that it is often performed in elderly patients with comorbidities who have already received previous treatments, bladder-sparing options have been recently developed for patients with BCG-unresponsive tumors.[8]

One of the main problems in developing clinical trials in this field has been the interpretation of the results, often based on complex definitions of BCG failure. According to current terminology, BCG failure comprises the following categories[5]:

- BCG-refractory tumor: high grade HG/T1G3 at 3 months; HG/TaG3 after 3 months and/or at 6 months after a second induction or initial maintenance course; Carcinoma in Situ (CIS) with no associated papillary tumor at 3 months and persistent at 6 months after second induction or initial maintenance course; HG tumor during maintenance treatment.
- BCG-relapsing tumor: Recurrence of HG/G3 tumor following completion of BCG maintenance despite an initial complete response.
- BCG-unresponsive tumor: HG/T1Ta tumor that recurs within 6 months of adequate BCG treatment, or CIS development within 12 months of completion of adequate BCG treatment.
- BCG-intolerance: Side effects that prevent the completion of adequate BCG treatment.
- In addition, the BCG-exposed category refers to patients with high-grade recurrence after BCG treatment that does not meet the criteria for BCG-unresponsive disease, and who may benefit from further treatment with more BCG. This category of high-risk patients includes[8,9]:
  1 BCG-resistant, defined as persistent or recurrent Ta or CIS HG NMIBC at 3 months after having received at least 5 of 6 doses of BCG induction.
  2 Delayed relapse after inadequate BCG therapy.
  3 Delayed relapse after adequate BCG therapy.

BCG-exposed patients and those with delayed relapses, beyond 24 months, may benefit from repeat treatment with BCG therapy.

In this regard, and with the aim of establishing common criteria for the inclusion of patients in clinical trials, a document has been drawn up for sponsors. It provides a consensus on the definition of unresponsive-BCG as the presence of at least one of the following criteria[10]:

- Persistent or recurrent CIS alone or with recurrent Ta/T1 disease within 12 months of completion of adequate BCG therapy.
- Recurrent high-grade Ta/T1 disease within 6 months of completion of adequate BCG therapy.

The following end points are applicable to BCG-unresponsive CIS and are the minimum thresholds recommended for the approval of novel agents:

- Complete response rate at 6 months: 50%.
- Duration of response in CIS and papillary responders: 30% at 12 months and 25% at 18 months.

Material and method

A group of 5 urology and oncology experts in this field elaborated and developed the thematic framework of contents. A literature search of the last 5 years (clinical trials in recruitment phase, published or with results reported at congresses, adequately designed

Table 1 Intravesical treatment options available and/or approved by the FDA.

	Valrubicin	Nadofaragene-Firadenovec	Gemcitabine-Docetaxel	HIVEC	RITE	EMDA
Schedule	wkly (800 mg) /6 wkly	1 trim. (75 mL/1 year)	1 g gem. /37,5 mg.doce.1 wkly/6 wkly 1 month/24 m.	1 wkly (40 mg.) /6—8 wkly	2sem(20 mg)/6 wkly 1/wkly −1 y 1/8 wkly −2 y	1 wkly (40 mg) /6 wkly 1 month/6 m
Tumor type	CIS	CIS	CIS/papillary		CIS/ papillary	CIS/ papillary
CR 3 m (%)		53,4				
CR 6 m (%)	21	40,8				
DR 1 y (%)	17	24,3	51 cis/70 pap.	62,9 (SLR)		
DR 2 y (%)			43 cis/47 pap.	36,8(SLR)	35(RFS)	61,5(3 a)
Local toxicity (1—2), (%)	90	70	48		81	23,1
Systemic toxicity (%)	ns	3,8	rare	rare	rare	11,5
Evidence	Phase III	Phase III	Retrospective	Retrospective	Phase III	Phase III
Author	Steinberg et al.[16]	Boorjian et al.[22]	Chevuru et al.[24]	Pignot et al.[26]	Tan et al.[27]	Racioppi et al.[28]

y: year; m. months; wkly: weekly; qtrly: quarterly; CIS: carcinoma in situ; pap: papillary; CR: complete response; DR: duration of response; ns. not stated; HIVEC: hyperthermic intravesical chemotherapy; RITE: radiofrequency-induced thermo-chemotherapy effect; EMDA: electromotive drug administration.

retrospective studies, prospective studies, and meta-analyses) was carried out in the Cochrane Library databases, Medline (PubMed), with the combination of the following keywords in the title or abstract: ''BCG Unresponsive'', ''BCG failure'' and ''BCG resistant'' ''clinical trials'' ''non-muscle invasive bladder cancer''. The clinical guidelines of the EAU, AUA, NCCN, ASCO, ESMO were also reviewed. Based on the selected articles, recommendations were formulated categorizing the specific grade of recommendation found by teleconference among all the authors participating in the document. For this purpose, the criteria described in the Grades of Recommendation Assessment, Development and Evaluation (GRADE) methodology were applied, transferring the results to a scale (strong, moderate, weak) for a better understanding of the recommendations.[11]

Adjuvant intravescal treatment options for BCG-unresponsive patients

The intravesical route has been the main method of administration of adjuvant treatments in NMIBC, mainly BCG and mitomycin C (MMC). In this regard, and in the setting of BCG-unresponsive disease, the search for intravesical alternatives has focused mainly on reducing the toxicity associated with systemic treatments, simplifying the administration of therapies, and achieving equal or better oncologic outcomes than those treatments (Table 1).

There are currently 2 FDA-approved intravesical agents for the treatment of BCG-unresponsive CIS (Valrubicin and Nadofaragene Firadenovec), neither approved by the European Medicines Agency (EMA). In BCG-unresponsive papillary NMIBC, there are no approvals yet. On the other hand, although not approved by regulatory agencies, there are published data on device-assisted chemotherapy or combinations of chemotherapeutic agents, mainly in patients refusing or who are not candidates for radical cystectomy.[12] Finally, there is a wide range of alternatives under study, which are discussed in other sections of this article.

Valrubicin

Valrubicin is a semi-synthetic anthracycline for intravesical administration, analog to Doxorubicin, but with more rapid cell membrane penetration and greater accumulation in the cell cytoplasm. Its FDA approval for BCG-unresponsive CIS occurred prior to the publication of their definitions of BCG failure. This is why its efficacy data do not meet the criteria for new approvals that were subsequently established. There are several studies carried out with this drug, including the phase III pivotal trial published in 2000.[13–16] In this study, 90 patients with BCG-unresponsive CIS received 6 weekly instillations of 800 mg of Valrubicin. One of its major limitations is that patients were eligible for inclusion in the study if they had received only one instillation of BCG. In fact, only 38% of the individuals had received at least 3 instillations. Complete response was defined as the absence of disease after 6 months of treatment initiation, being 21% and decreasing to 17% at one year. The difference between responders and non-responders with respect to the proportion of patients who preserved their bladder is noteworthy in this study. Within 2 years, 90% of initial responders had avoided cystectomy, compared to approximately 48% of non-responders. As for the safety profile, 90% of patients experienced any local adverse event, most of them mild or moderate, the most frequent being pollakiuria, urgency and dysuria. Only 3 of the 90 patients were unable to complete the full regimen due to toxicity. An update of these data was published in 2013 along with data on patients from another study yielding similar results.[17]

Nadofaragene firadenovec

The efficacy and tolerability of interferon alfa-2b in patients with tumors relapsing after BCG has been known for years. However, the duration of response is very limited, probably due to insufficient exposure to the protein with conventional instillations.[18] Nadofaragene-Firadenovec (rAd-IFNα/Syn3)

consists of two components: rAd-IFNα, a recombinant non-replicating adenovirus that transfers a copy of the interferon alpha-2b gene into urothelial cells (thus inducing endogenous interferon production), and Syn3, a polyamide that enhances viral transduction into cells. Preclinical studies have shown a significant increase in local interferon alpha-2b production without increasing systemic production, as well as significant tumor responses.[19–21]

In December 2022 the FDA approved its use for the treatment of patients with BCG-unresponsive CIS based on the results of the pivotal phase III trial that reported data from 151 patients (103 of them in the CIS cohort) in 2021.[22] In this case, the criteria for patient inclusion did meet the definitions required by the FDA. Treatment consisted of intravesical instillations of 75 mL of Nadofaragene Firadenovec (3×1011 viral particles/mL), with a regimen comprised of one instillation every 3 months (4 instillations in total). The primary endpoint of the study was the complete response rate at 3 months, being 53.4% and decreasing to 40.8% and 24.3% at 6 and 12 months, respectively. Regarding the safety profile, 70% of the patients presented a drug-related adverse event, mostly grade 1–2, the most frequent being discomfort during instillation, fatigue, bladder spasms and urinary urgency.

Gemcitabine/Docetaxel

For some years now, the role of sequential treatment with Gemcitabine and Docetaxel by intravesical route has been investigated, both in high-risk BCG-naïve NMIBC and in BCG-unresponsive tumors. Given the different mechanisms of action of both molecules, Gemcitabine is administered first as it requires active DNA synthesis, a process which might be hampered by the anti-mitotic effects of docetaxel. The treatment protocol consists of an instillation of 1 g of Gemcitabine in 50 mL of saline or sterile water, retained for 60–90 min, followed by an instillation of 37.5 mg of Docetaxel in 50 mL of saline or sterile water, retained for 60–120 min after catheter removal.

A retrospective multicenter US registry published in 2020 included 276 patients receiving Gemcitabine/Docetaxel, of whom 105 had BCG-unresponsive NMIBC.[23] Within this group, patients with BCG-unresponsive CIS obtained a 2-year high-grade disease-free rate of 50% (58% in the case of BCG-unresponsive papillary-only disease). All patients in this study were treated with an induction course of 6 weekly instillations, while maintenance was optional, consisting of a monthly instillation for 24 months. In this regard, the addition of a maintenance course was shown in the multivariate analysis to be significantly associated with a lower risk of disease recurrence. Regarding the safety profile, and with data from the entire series (276 patients), 40.6% suffered adverse events, and 9.4% of the patients underwent treatment changes due to toxicity. Only 3.3% of patients were unable to tolerate a full treatment course due to side effects.

The most recent retrospective single-center series was published in 2023. It reported the results of 97 patients with BCG-unresponsive NMIBC treated with Gemcitabine/Docetaxel between 2009 and 2017.[24] The treatment regimen consisted of 6 weekly instillations followed by monthly maintenance for up to 24 months. Seventy-one percent of patients had CIS (associated or not with papillary tumor), and the rest of the patients had papillary disease only. Recurrence-free survival in patients with CIS (with or without papillary tumor) was 51%, 43%, 32% and 18% at 1, 2, 3 and 5 years, respectively. In the case of papillary-only disease, these figures increased to 70%, 47%, 38% and 38% at the same follow-up durations. In the overall series, cancer-specific survival was 100% at 2 years and 92% at 5 years. Regarding tolerance, 48% of patients experienced some type of adverse event, all of them grade 1–2, and 13% presented symptoms that required changes in the treatment regimen. The most frequent adverse events were bladder spasms.

Device-assisted chemotherapy

There are retrospective publications on the use of chemotherapy assisted by different devices in the treatment of BCG-unresponsive NMIBC. The main devices used are recirculant hyperthermic intravesical chemotherapy, radiofrequency-induced hyperthermia (RITE) and electromotive drug administration (EMDA). Below, we summarize the most relevant articles on each technology.

As for HIVEC therapy, which has preliminarily demonstrated comparable results to BCG in the initial treatment of high-risk NMIBC, it has also been used in patients with BCG-unresponsive disease.[25] The largest series includes 116 patients with both CIS and papillary disease from various French centers retrospectively analyzed. They were treated with 6–8 weekly instillations of 40 mg of MMC diluted in 50 cc of saline.[26] Recurrence-free survival was 62.9% and 36.8% at 1 and 2 years, respectively. Progression to muscle-invasive disease-free survival was 92.2% and 87.9% at 1 and 2 years, respectively. No patients had grade 3–5 adverse events, the most frequent being hypogastric pain, and 6.9% of patients were unable to complete treatment due to toxicity.

Regarding treatment with RITE, the most robust data come from a phase III trial involving 104 patients with intermediate- or high-risk disease with recurrence following BCG treatment.[27] Patients were randomly assigned to RITE plus MMC in the intervention group. Each course consisted of 2 instillations of 30 min with 20 mg of MMC diluted in 50 mL of sterile water, with an induction regimen of 6 weekly induction courses and maintenance with one instillation every 6 weeks during the first year and one every 8 weeks during the second year. The control group received BCG with a SWOG schedule for 2 years or the standard treatment of each institution (normothermic MMC or EMDA). Treatment with RITE yielded a disease-free survival of 35% at 2 years, compared to 41% in the control group. This trial closed recruitment earlier due to the high rate of disease recurrence in patients with CIS treated with RITE. Eighty-one percent of the patients in the study presented an adverse event, with no differences between the two arms. Of note with this device was the appearance of some grade 3–4 adverse events, such as pain, hematuria, fatigue, or skin rash.

Finally, there is only one prospective phase II trial with EMDA that included 26 patients.[28] The treatment regimen consisted of 40 mg of MMC diluted in 100 mL of sterile water retained in the bladder for 30 min with 20 mA pulsed elec-

Table 2 Systemic treatment options.

	Pembrolizumab	Atezolizumab	Erdafitinib
Schedule	1 inf (200 mg)/3 wkly–2 y	1 inf/1200 mg)/3 wkly–1 y	6 mg oral/day FGFR+
Tumor type	CIS/papillary	CIS/ papillary	CIS
CR 3 m (%)	41		100 (2 m)
CR 6 m (%)		27 CIS	75(5 m)
DR 1 y (%)	41 pap.		
DR 2 y (%)	28	49 (18 m.) pap.	
Local toxicity (1–2), (%)			
Systemic toxicity (%)	13	16	30
Evidence	Phase II	Phase II	Phase II
Author	Balar et al.[32] Necchi et al.[33]	Black et al.[34]	Catto et al.[36]
FDA	Approved	Not approved	Not approved

y: year; m: months; wkly: weekly; qtrly: quarterly; CIS: carcinoma in situ; pap: papillary; CR: complete response; DR: duration of response.

trical current, with 6 weekly instillations followed by a maintenance course of 6 monthly instillations. This study reports a high-grade disease-free rate of 61.5% at 3 years, with significantly worse results in patients with CIS. In terms of safety, 11.5% of patients with severe systemic adverse events (hypersensitivity to MMC), in whom treatment was discontinued, stand out. Local adverse events occurred in 23.1% of patients.

Systemic treatment options

In relation to systemic treatment, it can be confusing to justify this type of treatment in a disease that, in principle, is not muscle-invasive and presents a very low risk of dissemination, while exposing patients to the potential toxicity of systemic treatment (Table 2).

In the following sections we will review the main data on the various systemic treatment modalities that have been explored in NMIBC.

Systemic immunotherapy

Immunotherapy has demonstrated efficacy in the context of randomized phase III clinical trials in both metastatic and nonmetastatic muscle-invasive disease and is part of the standard treatment of this neoplasm.[29] Regarding NMIBC, we also have data to support a rationale for its use. We know that BCG-unresponsive NMIBCs have higher PD-L1 expression than those who respond to BCG,[30] and that BCG treatment can in turn increase PD-L1 levels.[31] Therefore, several trials have been conducted testing its use in different stages of NMIBC. In this section, we will focus on published data in BCG-unresponsive disease. Ongoing trials or trials without definitive results will be addressed in the next chapter.

Pembrolizumab *(KEYNOTE-057)*

The KEYNOTE-057 trial was the first study to lead to FDA approval of an immunotherapeutic agent -Pembrolizumab- in the setting of NMIBC. This is a non-randomized, single-arm phase II study including BCG-unresponsive patients who were ineligible for or declined radical cystectomy. They were treated with Pembrolizumab 200 mg every 3 weeks for up to 2 years or until progression or recurrence of NMIBC.

In cohort A of this trial, whose results were published in 2021,[32] its efficacy was analyzed in 96 patients with CIS with or without papillary tumors (Ta or high-grade T1). Forty-one percent had a complete response (CR) at 3 months, a median CR duration of 16.3 months, and 28% of CRs lasting longer than 2 years. Regarding the toxicity profile, 13% of patients had grade 3–4 treatment-related toxicity, and 22% had immune-mediated toxicity, mainly grade 1–2, primarily hypothyroidism.

The results obtained in cohort B were reported in 2023.[33] A total of 132 patients with papillary tumor (Ta or high-grade T1) without CIS had a median disease-free survival (DFS) of 6 months, with 12-month DFS of 41%, and a median progression-free survival (PFS) to worsening of grade, stage, or death of 44.5 months. No significant differences in toxicity were observed compared to what was previously reported for cohort A.

With these results, the FDA approved Pembrolizumab for the subgroup of patients represented in Cohort A, i.e., patients with CIS with or without papillary tumor (Ta or high-grade T1). Even so, the uncertainty of these results must be highlighted, as it is a non-comparative trial, and due to the potential occurrence of severe immune-mediated toxicity, which, although rare, can compromise the patient's life or cause medium- to long-term sequelae.

Atezolizumab *(SWOG S1605)*

This trial is also a single-arm phase II study conducted in a similar population to that of KEYNOTE-057: BCG-unresponsive patients ineligible for or declining radical cystectomy.[34] A total of 129 patients who were eligible for efficacy analysis were treated with Atezolizumab 1200 mg every 3 weeks for up to 1 year. Both CIS and non-CIS patients are allowed, although the primary endpoint of the trial is the 6-month response rate in the subgroup of patients with CIS. In this subgroup of 74 patients, the CR rate at 6 months is 27%, which is below the minimum level prespecified in the trial. The median duration of CR is 17

months, with 56% of CRs lasting more than 1 year. Out of all 129 patients in the study, 10 (9.3%) had progression to muscle-invasive or metastatic disease. Sixteen percent of patients had grade 3–5 treatment-related adverse events, including 3 treatment-related deaths (myasthenia gravis, sepsis, and myositis).

Although the activity of Atezolizumab may appear to be lower than that of Pembrolizumab in the KEYNOTE-057 trial and knowing that direct comparisons between clinical trials should be avoided, there are some differences to consider. In the S1605 trial, the primary endpoint of CR at 6 months is defined by a mandatory biopsy regardless of cystoscopy findings, whereas in the KEYNOTYE-057 trial biopsy was performed only in the case of cystoscopy and/or urinary cytology abnormalities. On the other hand, the investigators of S1605 discontinued treatment with Atezolizumab in some cases when CIS persisted at the 3-month evaluation, although the main endpoint of the trial was CR at 6 months; this may have prevented the detection of later responses to immunotherapy. In any case, and pending the results of other ongoing trials, for the time being Atezolizumab has no FDA-EMA indication for the treatment of NMIBC.

Targeted therapy

Regarding targeted therapy, we only have data on Erdafitinib at present. Erdafitinib is an inhibitor of the fibroblast growth factor receptor (FGFR). In the same way as immunotherapy, Erdafitinib has demonstrated efficacy in metastatic disease and the potential efficacy of the systemic and intravesical routes in NMIBC is being investigated. Activating FGFR mutations are frequent in NMIBC, present in up to 75% of low-grade tumors, but with lower frequency when the disease has become muscle-invasive or metastatic. Therefore, the use of FGFR inhibitors at earlier stages of the disease seems to have a clear biological rationale.[35]

The THOR-2 trial (BLC2003) is a randomized phase II trial comparing Erdafitinib versus the investigator's treatment of choice in patients with BCG-unresponsive NMIBC with FGFR alterations. The initial results of the trial have been presented in 2023, analyzing the first ten patients included in cohort 2 of the study (patients with CIS) treated with Erdafitinib.[36] At 2 months of treatment, CR of 100% was observed, and at 5 months, CR 75% was observed. However, responses generally seem to be of short duration, with a median response duration of 3 months. In addition, 3 patients (30%) presented grade 3–4 toxicity, mainly xerostomia, onycholysis and mucositis, a toxicity profile already known from its use in metastatic disease. We also have the results of the exploratory cohort 3[37] in patients with intermediate-risk NMIBC and FGFR alterations (n = 10). Again, response rates are high at 75% but of short duration (median 2.8 months). Due to the efficacy data of short duration and the unfavorable toxicity profile, FGFR inhibitors are being reoriented to intravesical use, aiming to avoid the systemic toxicity of their administration and to improve efficacy figures providing greater exposure of the tumor to the drug by the intravesical route.

Clinical trials and emerging treatments in high-risk NMIBC

This section will be dedicated to the review of treatments that are still under study and/or whose results have not yet been reported. Treatments are classified according to their mechanism of action.

Immune checkpoint inhibitors (PD-1/PD-L1 inhibitors)

Sasanlimab (PF-06801591)

A multicenter, non-randomized phase III trial (CREST; NCT 04165317) is currently investigating the role of Sasanlimab (subcutaneous PD-1 inhibitor) in high-risk NMIBC. The objective of this trial is to determine the safety and oncologic efficacy of Sasanlimab in patients with high-risk naive NMIBC (cohort A) or previously treated with BCG (cohort B).

In cohort A (enrollment closed), each participant was assigned to one of the three study treatment groups:

One group is given Sasanlimab and BCG (induction and maintenance).

The second group is given Sasanlimab and BCG (only induction).

The third group is given BCG only and does not receive Sasanlimab (control group).

In study cohort B, each new participant will be assigned to a study treatment group based on the type of their bladder tumor (CIS/non-CIS). Both groups will receive Sasanlimab. On August 31, 2022, the Sponsor announced the discontinuation of enrollment to cohort B. The decision to discontinue enrollment was not made for safety reasons.[38]

Durvalumab

Durvalumab (PD-L1 inhibitor) is currently being evaluated in a phase III trial (POTOMAC; NCT 03528694) in patients with BCG naïve NMIBC randomized to three groups:

Durvalumab (IV 1500 mg every 4 weeks/13 courses) and BCG induction and maintenance for 2 years.

Durvalumab (IV 1500 mg every 4 weeks/13 courses) and BCG induction only. BCG induction and maintenance for 2 years (control group). This study is now closed and has enrolled about 975 patients, with the primary endpoint being PFS.[39]

In the setting of BCG-unresponsive NMIBC, 12 patients received a combination of Durvalumab and Oportuzumab-Monatox, a fusion protein immunotoxin that binds to epithelial cell adhesion molecule (Ep-CAM)–positive tumor cells.

In an interim analysis, the authors reported that 41%, 33%, and 17% of the included patients were disease-free at 3-, 6-, and 12-months following treatment, respectively. Of the treatment-related side events, 8% were grade 3 or higher. Of note, Oportuzumab-Monatox has been studied separately in a Phase III trial of 89 patients, who had a CR of 40% at 3 months after instillation, of whom 52% remained disease-free at 1 year. The trial reported four treatment-related severe adverse events. However, the FDA did not approve the License Application for Oportuzumab Monatox.[39]

Nivolumab (CHECKMATE-9UT)

Finally, a randomized phase II study (CHECKMATE 9UT; NCT 02519256) is enrolling BCG-unresponsive patients to evaluate the safety of Nivolumab (PD-1 inhibitor), ±linrodostat mesylate (an indolamine 2,3-dioxygenase 1 [IDO1] inhibitor) or ±BCG. The investigators support the use of linrodostat because of the potential immunosuppressive role of IDO in NMIBC. The study includes patients with high-risk NMIBC with CIS, with or without papillary component who will be included in one of four treatment arms for monotherapy with Nivolumab or a combination of the aforementioned treatments.[40]

Bacteria- and virus-based therapies

TARA-002

TARA-002 is a lyophilized biological preparation containing cells of low virulence Streptococcus pyogenes treated with benzylpenicillin. It is manufactured using the same cell bank as OK-432, a group A Streptococcus genetically distinct from pyogenes, which has been used in Japan since 1975 for the treatment of lymphangioma.

TARA-002 is a broad immunopotentiator that activates both the innate and adaptive immune systems in the presence of tumor cells.

The Phase Ia/b (dose escalation/dose expansion) ADVANCE-1 study is currently open for patients who are unable to access BCG or have received at least one dose of BCG or intravesical chemotherapy. The study involves 6 weeks of treatment with intravesical instillation of TARA-002 and 6 weeks of subsequent follow-up. The objective is to determine the safety, tolerability, and preliminary efficacy of TARA-002 in patients with CIS or high-grade Ta. Of note, patients with a history of penicillin allergy are excluded from the study.[41]

Other emerging treatments

BCG re-challenge

Repeat BCG instillation or re-challenge has shown response rates in 40%–60% of patients who did not respond to the first course of BCG.[42] This approach is recommended by both the AUA Clinical Guidelines and the International Consultation on Urological Diseases (ICUD) for patients with BCG-refractory NMIBC.[43] For its part, although the AUA Clinical Guidelines recommend cystectomy for all BCG-refractory patients, in the case of persistence or recurrence after a single course of induction (inadequate BCG treatment), the guidelines recommend offering a second course of induction or maintenance of BCG. However, this will not be an option for BCG-intolerant patients, nor are further courses of BCG (after two or more BCG failures) recommended as tumor progression is highly likely and the chance of success is below 20%.[44]

TAR-200

TAR-200 is an intravesical drug delivery system for local continuous release of gemcitabine through a device placed inside the bladder. Nearly two-thirds of the drug load is released within 2 weeks as opposed to standard intravesical treatment where the dwell time is a maximum of 2 h. The TAR-200 device is placed using a bladder catheter and removed using a standard cystoscope. Currently, TAR-200 and cetrelimab (intravenous systemic PD-1 inhibitor) are under evaluation in the multicenter randomized phase IIb study in patients with BCG-unresponsive NNMIBC (SUNRISE-1)[45] and in BCG naïve patients (SunRISe-3). In 2023, the SunRISe-1 trial presented the first results of the ART-200 arm (23 patients) and Cetrelimab (24 patients) in monotherapy. The CR rate for the TAR-200 group was a promising 72.7% and for the Cetrelimab group 38.1%. TAR-200 was well tolerated and treatment-related adverse events greater than grade 3 were infrequent.

Using the same device, the preliminary results of the TAR-210 study for patients with NMIBC (cohorts 1 and 3) were recently presented at ESMO-2023. This study analyzes the efficacy and safety of intravesical Erdafitinib in patients with FGFR alterations. In the 11 patients of cohort 1 (BCG-unresponsive NMIBC) a recurrence free rate of 82% was observed and in cohort 3 (chemoablation in intermediate-risk NMIBC) 87% with very few adverse events.

N-803

N-803 is an Interleukin-15 superagonist complex that was developed to enhance the immune-mediated effects of interleukin-15 itself, enabling the activation and proliferation of natural killer and CD8+ T cells, without upregulation of T cells, thus potentiating the immune response caused by BCG. QUILT-3032 is a multicenter phase III clinical trial of intravesical BCG plus N-803 administered in standard induction and maintenance regimen for 160 patients with BCG-unresponsive NMIBC. The authors recently reported results in two cohorts: (1) CIS with or without papillary tumors (n = 83) and (2) papillary tumor only (n = 77). The complete response rate in the CIS cohort was 71% with a median duration of 24 months, whereas, in the papillary group, the disease-free rate was 57% and 48% at 1 and 2 years, respectively. Overall, 91% and 95% of patients in the CIS and non-CIS cohorts, respectively, avoided cystectomy. There were no treatment-related grade 4 or 5 adverse events. Following these positive results, the FDA accepted the Biologics License Application and granted breakthrough therapy to N-803 and fast-track designation when used in combination with BCG for BCG-unresponsive CIS.[46] Although the FDA previously declined its approval, the application was resubmitted on October 2023 and is currently being evaluated.

BCG plus Interferon-α2β

Interferon-α (IFN-α) is an immunomodulatory agent with anti-proliferative activity. Its potential synergism with BCG has justified the therapeutic combination of IFN-α plus BCG in patients with NMIBC after BCG failure. O'Donnell, et al.,[47] published in 2001 results of a retrospective study including 42 consecutive patients with NMIBC after BCG failure, with 29 patients with CIS (10 cases were pure CIS and 19 had CIS associated with papillary tumor). With a median follow-up of 30 months, the 12- and 14-month PFS rates were 63% and 53%, respectively. A multicenter randomized phase II trial, published by Joudi et al.,[48] evaluating the combination of IFN-α and BCG in 1007 patients, including 20% and 27% of CIS in the groups BCG naive and with BCG failure. With a median

Table 3 Recommendations based on available evidence.

Treatment indication	Strength rating
• To classify BCG failure according to the definitions and recommendations of the EAU guidelines and FDA document.	Strong
• Although radical cystectomy is the standard treatment, each case should be discussed individually in a uro-oncology committee to evaluate other conservative options depending on the type of tumor, options available at each center and patient preferences.	Strong
Intravesical treatment options	
• Study FGFR mutations.	Weak
• Consider participation of patients in ongoing clinical trials for BCG unresponsive.	Moderate
• For patients whose tumor has failed BCG and/or have not been able to complete adequate treatment due to toxicity, consider Gemcitabine-Docetaxel or HIVEC chemohyperthermia in case of CIS and/or papillary tumor, depending on the center's availability.	Weak
• For patients whose tumor has failed BCG and/or have not been able to complete adequate treatment due to toxicity, consider also treatment with EMDA in case of papillary tumor, depending on the center's availability.	Weak
• Nadofaragene Firadenovec has already been approved by the FDA. Consider its use based on approval by health authorities.	Strong
Systemic treatment options	
• Pembrolizumab has already been approved by the FDA. Consider its use based on approval by health authorities. Inform the patient of potential immune-mediated toxicity.	Strong
• Consider the participation of patients in ongoing clinical trials for BCG-unresponsive disease.	Moderate
• Study FGFR mutations.	Weak
New treatment options and clinical trials	
• Consider the participation of patients in ongoing clinical trials for BCG-unresponsive disease.	Moderate

HIVEC: hyperthermic intravesical chemotherapy; EMDA: electromotive drug administration; FGRC: **fibroblast growth factor receptors**.

follow-up of 24 months, the PFS rates in BCG naive patients and in patients with BCG failure were 59% and 45%, respectively ($P = .0001$). In a recent systematic review including 5 randomized trials with a total of 1231 patients with NMIBC, no clear difference was observed between BCG plus IFN-α and BCG alone in terms of recurrence (mean RR 0.76, 95% confidence interval [CI] 0.44–1.32). (RR average 0.26, 95% CI 0.04–1.87; two randomized trials; 219 participants; low-quality evidence).[3,49]

Mycobacterial cell wall-DNA complex (MCC)

In 2009, Morales et al. published the results of a first efficacy and safety trial with MCC in patients with NMIBC. Of the 55 patients, 52 were Cis (with or without associated papillary tumor) and 44 had previously received BCG or BCG and chemotherapy. These patients were treated with induction and maintenance, receiving weekly instillations of MCC, at doses of 4 mg (n = 25) or 8 mg (n = 30). In the intent-to-treat population, the complete response rate was 27.3% and 46.4% at 12 and 26 weeks with 4 mg and 8 mg, respectively.[50]

The NCT00406068 trial started in November 2006. It is a Multicenter Phase II/III trial evaluating the efficacy and safety of CCM in the treatment of patients with high-risk NMIBC refractory to BCG. With a three-phase design, induction, maintenance and long-term follow-up, patients start treatment with a course of 6 weekly instillations of intravesical MCC 8 mg. After evaluation with cystoscopy, cytology and biopsies at 3 months, disease-free patients will go on to receive 3 weekly instillations of MCC, maintenance regimen, at months 3, 6, 12, 18 and 24. Patients with residual non-muscle invasive disease at 3 months are considered for re-induction with an additional course of 6 instillations. The study was completed in July 2011, having enrolled 129 patients, of whom 94 (68 Cis with or without papillary tumor, and 26 papillary tumors without associated Cis) were subsequently re-analyzed, based on the new definition of refractory BCG. Overall, PFS was 48.9% at 6 months, 34.8% at 1 year, and 28.3% at 2 years from induction. The PFS rates at 6, 12 and 24 months were 61.2%, 61.2% and 50.1% in papillary tumors, compared to 44.8%, 26.5% and 16.6% in Cis, respectively.[2,3,51,52]

CORE1: CG0070+Pembrolizumab

Cretostimogene Grenadenorepvec (CG0070) is an oncolytic adenovirus that has shown good oncological outcomes when combined with Pembrolizumab in a phase II clinical trial designed for BCG-unresponsive patients (with CIS). All patients (n = 35) received a weekly CG0070 induction (1×1012 vp/mL) for 6 weeks, followed by a second weekly induction for 3 weeks in responders and 6 weeks in non-responders. Subsequently, all patients received weekly maintenance instillations for 3 weeks. Patients simultaneously received pembrolizumab every 6 weeks (as opposed to the customary 3 weeks) at a dose of 400 mg for 2 years. The overall complete response rate was 85% and at 12 months was 68%, as presented in AUA 23.[53]

Finally, in the context of phase I studies, the safety and preliminary efficacy results of Durvalumab in combination with BCG or radiotherapy in BCG-unresponsive patients have been published. The complete response rate at 3 months was 85% and 50% in the Durvalumab + BCG and Durvalumab + radiotherapy groups, respectively. These were 73% and 33% at one year, respectively. The study showed an adequate safety profile in the 22 patients included.[54]

Conclusions

Due to the fact that radical cystectomy provides the best oncologic outcomes, it remains being the first treatment option in the setting of BCG-unresponsive NMIBC. However, given its high morbidity rate, the evaluation of bladder sparing options within the framework of a multidisciplinary committee and on a case-by-case basis (patient preferences and tumor characteristics) is of paramount importance. According to the FDA definitions and criteria for BCG-unresponsive patients, intravesical treatment options fulfill the requirements in terms of oncologic outcomes, with acceptable toxicity rates (Table 3). Regarding systemic therapy as monotherapy, it does not seem to achieve such outcomes in a consistent manner, although the results of successive updates of clinical trials seem to approach this efficacy threshold. The low, but not negligible, risk of acute immune-mediated toxicity must also be considered. Therefore, the risk-benefit balance of each patient must be assessed on an individual basis when considering systemic treatment in this scenario. The inclusion of these patients in clinical trials is crucial to shed light on this stage of the disease.

Conflict of interest

The authors have stated that they have no conflict of interest.

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Further reading

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