

## Statement concerning the shortage of BCG vaccine from the EAU Guidelines Panel on Non-muscle-invasive Bladder Cancer

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### The current situation

The company Sanofi Pasteur has announced a suspension of the production of the BCG Connaught strain in June 2012. Unfortunately, the company was not able to reestablish the manufacturing and terminated BCG production in 2012. As the Connaught strain supplied a significant segment of the world market, the end of its production resulted in a global shortage of BCG in the treatment of non-muscle invasive bladder cancer (NMIBC). Although the situation is different in individual countries, it represents potential danger for patients and requires the attention of urologists.

Each urologist has an obligation to provide optimal treatment according to the current evidence for individual patients with NMIBC. This statement summarizes information which can help the urologist with treatment decisions in the absence of BCG or with a suboptimal supply of BCG on the market.

### Current role of BCG in the treatment of NMIBC and EAU guidelines recommendations

BCG intravesical immunotherapy is the most effective conservative management for patients with intermediate and high risk NMIBC after complete TURB (transurethral resection of the bladder), where it significantly reduces the recurrence rate and has an impact on the early progression rate.

According to EAU guidelines on NMIBC, BCG intravesical instillations are indicated in patients with intermediate- and high-risk tumours (see Table 1). For optimal efficacy, the induction course (6-weekly instillations) should be followed by at least one year of maintenance.

**Table 1: Risk group stratification**

Risk group stratification	Characteristics
Low-risk tumours	Primary, solitary, TaG1 (PUNLMP, LG*), < 3 cm, no CIS
Intermediate-risk tumours	All tumours not defined in the two adjacent categories (between the category of low- and high risk).
High-risk tumours	Any of the following: <ul style="list-style-type: none"> <li>• T1 tumour</li> <li>• G3 (HG**) tumour</li> <li>• carcinoma <i>in situ</i> (CIS)</li> <li>• Multiple, recurrent and large (&gt; 3 cm) TaG1G2 /LG tumours (all features must be present)*.</li> </ul>
	<b>Subgroup of highest risk tumours:</b> T1G3/HG associated with concurrent bladder CIS, multiple and/or large T1G3/HG and/or recurrent T1G3/HG, T1G3/HG with CIS in the

	prostatic urethra, some forms of variant histology of urothelial carcinoma, lymphovascular invasion.
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*Substratification of high-risk tumours for clinical purposes is addressed in Table 7.2.*

*\*Low grade is a mixture of G1 and G2.*

*\*\* High grade is a mixture of some G2 and all G3.*

### **Is the efficacy of different BCG strains comparable?**

Two smaller studies demonstrated some differences in efficacy between strains. As both these trials used induction BCG without any maintenance, this needs further confirmation in prospective trials. The published meta-analysis of prospective randomized trials did not suggest any difference in efficacy of the BCG strains (Pasteur, Frappier, Connaught, TICE, RIVM).

There are no data which provide information on whether switching from one BCG strain to another during the treatment schedule can have an impact on anti-tumour efficacy.

### **How long should the optimal BCG schedule be? When can BCG instillations be terminated without compromising efficacy?**

For optimal efficacy, the induction course of BCG should be followed with at least one year maintenance schedule as was confirmed by several meta-analyses. Many maintenance schedules have been used with a maximum of 27 instillations over 3 years.

The randomised controlled trial demonstrated that three years of application in high risk tumours brought additional reduction of recurrence rate but no difference in progression and overall survivals comparing of one year only. There were registered no differences in intermediate risk tumours.

Taking together, with the current shortage, BCG instillations can be safely terminated when the patient has completed one year of BCG treatment.

### **What is optimal number of induction and maintenance instillations?**

The EAU Guidelines recommend 6 weekly instillations in induction and 3 weekly instillations in each period of maintenance schedule. Whether the reduction of instillations (f.i 4 during induction and 2 during maintenance) compromises the efficacy is currently not known and this question may be answered by the ongoing NIMBUS trial which has been set up by the EAU Research Foundation.

### **What is the optimal dose of BCG? Can the dose be reduced?**

Data from prospective randomised trials suggest that one-third dose is associated with a higher recurrence rate. Moreover, the routine use of one-third dose BCG is complicated by potential technical difficulties such as preparing the reduced dose reliably given uneven distribution of colony-forming-units in the dry product formulation. For these reasons, EAU guidelines do not recommend a dose reduction during BCG treatment.

### **Can be BCG instillations be replaced by another treatment?**

In patients with tumours at intermediate risk, intravesical chemotherapy (multiple instillations for up to 12 months) represents an alternative treatment option to BCG immunotherapy. It has a higher risk of recurrence but a lower risk of side effects.

In patients with tumours at high risk, EAU guidelines provide two treatment options, intravesical BCG immunotherapy and radical cystectomy. Radical cystectomy represents an oncologically safe but more invasive treatment which should be discussed, particularly in patients with the highest-risk tumours (see table 1).

Some limited data have been presented about device-assisted chemotherapy instillations, microwave-induced hyperthermia (RITE) or electromotive drug administration (EMDA). RITE with intravesical MMC achieved promising efficacy in comparison with BCG and might replace BCG in patients with intermediate- and high-risk tumours. EMDA was used sequentially with BCG, which downgrades its value for BCG replacement.

### **Conclusions and recommendations:**

1. The efficacy of different BCG strains seems to be comparable
2. In the current situation of BCG shortages, instillations can be safely terminated when the patient has completed one year of BCG.
3. In patients with intermediate-risk tumours, adjuvant BCG treatment can be replaced by intravesical chemotherapy, which represents an alternative treatment option.
4. In patients with high-risk tumours, particularly in those with highest risk cases, an immediate radical cystectomy should always be considered. This should be underlined, particularly in the current situation with BCG shortages.
5. In patients with tumours at high risk who are unfit to or unwilling to undergo a cystectomy, there is no scientifically proven alternative to BCG treatment. Thus every effort should be made to obtain an available BCG strain. As an alternative, microwave induced hyperthermia (RITE) with chemotherapy seems to provide promising results and could be considered. Passive intravesical chemotherapy can achieve some responses in CIS, influence the recurrence rate in TaT1 tumours and thus provide some benefit for the patient. Urologists should not forget, however, that the effect of passive intravesical chemotherapy on tumour progression has never been confirmed.
6. It should be emphasized that the most important modality in the treatment of non-muscle invasive bladder cancer remains a complete and precisely performed TURB, independent of the availability of BCG on the market.
7. The Guidelines Panel seek the support of the European authorities and the industry to ensure that BCG production is safeguarded in the future, to be able to maintain the treatment results and quality of life of patients with NMIBC.