RISK STRATIFICATION, DEFINITIONS OF DISEASE STATES & BCG UNRESPONSIVE DISEASE

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Co-President, International Bladder Cancer Network (IBCN)
Risk Stratification
Risk Stratification: AUA/SUO

### TABLE 4: AUA Risk Stratification for Non-Muscle Invasive Bladder Cancer

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>LG(^a) solitary Ta ≤ 3cm</td>
<td>Recurrence within 1 year, LG Ta</td>
<td>HG T1</td>
</tr>
<tr>
<td>PUNLMP(^b)</td>
<td>Solitary LG Ta &gt; 3cm</td>
<td>Any recurrent, HG Ta</td>
</tr>
<tr>
<td>LG Ta, multifocal</td>
<td>HG Ta, &gt;3cm (or multifocal)</td>
<td>Any CIS(^d)</td>
</tr>
<tr>
<td>HG(^c) Ta, ≤ 3cm</td>
<td></td>
<td>Any BCG failure in HG patient</td>
</tr>
<tr>
<td>LG T1</td>
<td></td>
<td>Any variant histology</td>
</tr>
</tbody>
</table>

- **LG** = low grade; **PUNLMP** = papillary urothelial neoplasm of low malignant potential; **HG** = high grade; **CIS** = carcinoma *in situ*; **LVI** = lymphovascular invasion
## Risk Stratification: EAU

### Table 6.3: Risk group stratification

<table>
<thead>
<tr>
<th>Risk group stratification</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk tumours</td>
<td>Primary, solitary, Ta, G1* (PUNLMP, LG), &lt; 3 cm, no CIS</td>
</tr>
<tr>
<td>Intermediate-risk tumours</td>
<td>All tumours not defined in the two adjacent categories (between the category of low- and high-risk).</td>
</tr>
<tr>
<td><strong>High-risk tumours</strong></td>
<td>Any of the following:</td>
</tr>
<tr>
<td></td>
<td>• T1 tumour</td>
</tr>
<tr>
<td></td>
<td>• G3** (HG) tumour</td>
</tr>
<tr>
<td></td>
<td>• CIS</td>
</tr>
<tr>
<td></td>
<td>• Multiple and recurrent and large (&gt; 3 cm) Ta, G1G2 tumours (all conditions must be presented in this point)*</td>
</tr>
</tbody>
</table>
## Risk Stratification: EAU, 2021

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Risk</strong></td>
<td>A primary, single, Ta/T1 LG/G1 tumour &lt; 3 cm in diameter without CIS in a patient &lt; 70 years&lt;br&gt;• A primary Ta LG/G1 tumour without CIS with at most ONE of the additional clinical risk factors (see above*)</td>
</tr>
<tr>
<td><strong>Intermediate Risk</strong></td>
<td>Patients without CIS who are not included in either the low, high or very high-risk groups</td>
</tr>
<tr>
<td><strong>High Risk</strong></td>
<td>All T1 HG/G3 without CIS, EXCEPT those included in the very high-risk group&lt;br&gt;All CIS patients, EXCEPT those included in the very high-risk group</td>
</tr>
</tbody>
</table>

**Stage, grade with additional clinical risk factors:**
- Ta LG/G2 or T1 G1, no CIS with all 3 risk factors
- Ta HG/G3 or T1 LG, no CIS with at least 2 risk factors
- T1 G2 no CIS with at least 1 risk factor

**Very High Risk**
- Ta HG/G3 and CIS with all 3 risk factors
- T1 G2 and CIS with at least 2 risk factors
- T1 HG/G3 and CIS with at least 1 risk factor
- T1 HG/G3 no CIS with all 3 risk factors

*Additional clinical risk factors are:*  
- age > 70;  
- multiple papillary tumours;  
- tumour diameter > 3 cm.
## Updated EAU Prognostic Risk Factor

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Updated EAU</th>
<th>MD Anderson Cancer Center series (%)</th>
<th>Sylvester 2021 predicted (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1yr</td>
<td>5yr</td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
<td>136</td>
<td>1.5 (0.4-5.8)</td>
</tr>
<tr>
<td>High</td>
<td></td>
<td>313</td>
<td>4.3 (2.5-7.3)</td>
</tr>
<tr>
<td>Very high</td>
<td></td>
<td>118</td>
<td>9.7 (5.5-16.8)</td>
</tr>
</tbody>
</table>

- **MDACC Data:**
  - EAU Risk Calculator Overestimates Risk in BCG Treated Patients

Lobo...Kamat, *EUO, 2021 in press*
MDACC Data: All TaHG disease should be considered High Risk

Time to Progression on BCG (any stage/grade)

\[ p = 0.115 \]

Time to Progression to MIBC/Distant Metastatic Disease

\[ p = 0.363 \]
**Simplified Definition**

### International Bladder Cancer Group Risk Categories¹²

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Tumor Characteristics</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>Ta LG: Solitary, primary, ≤3 cm</td>
<td>Low risk of recurrence/progression</td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>Anything that falls between low risk and high risk</td>
<td>Recurrence is main concern</td>
</tr>
<tr>
<td>High Risk</td>
<td>Any HG (Ta, T1, CIS) Any T1</td>
<td>Progression is main concern</td>
</tr>
</tbody>
</table>

**All CIS is considered high risk by AUA, EUA, NCCN**

Intermediate risk tumors (low grade)

How many of the following 4 factors does the patient have?

- Multiple tumors
- Tumor size >3 cm
- Early recurrence (<1 year)
- Frequent recurrences (>1 per year)

0
TREAT SIMILAR TO LOW RISK:

1–2
TREAT AS INTERMEDIATE RISK:

≥3
TREAT AS HIGH RISK:

Stratification for Clinical Trials of Intermediate Risk Low Grade Tumors

Recognizing that the AUA and now EAU classifies TaHG tumors differently, the SITC-IBCG panel recommends that

For the purpose of clinical trials, all TaHG tumors (and TaG3 tumors if 3 stage grading is available) should be classified as high risk
Definitions of Disease States
Definition of BCG Unresponsive Disease

- Persistent or new T1 HG disease
  - at first evaluation (3 mos) following induction BCG

- Persistent or recurrent CIS
  - within 12 months of completion of adequate BCG therapy

- Recurrent HG Ta/T1 disease
  - within 6 months of completion of adequate BCG therapy

Adequate BCG therapy defined as:
- at least 5 of 6 doses of iBCG + at least 2 additional doses of mBCG

Kamat et al, JCO, 2016; Lerner et al, Bladder Cancer, 2016, FDA Guidance Document, 2018
Does “BCG unresponsive” define a worse prognosis HR NMIBC?

85 HG NMIBC: 55 recurred after BCG induction + first maintenance (= BCG unresponsive)
28 recurred after BCG induction only

BCG unresponsive showed worse prognosis: more cystectomies, HG recurrences & progression to MIBC in truly BCG unresponsive vs induction only BCG recurrent

Li R... Kamat A et al, Eur Urol 2019
What about reduced dose patients?
EORTC30962 – Full Dose vs Low Dose, 1 yr vs 3 yr

Four groups (5 year Disease Free Rates)

1 year @ 1/3rd dose: 54.5%
1 year @ full dose: 58.8%
3 year @ 1/3rd dose: 62.6%
3 year @ full dose: 64.2%

Oddens et al, Eur Urol, 2013
BCG Shortage: Dose Reduction

Package Insert

The freeze-dried BCG preparation is delivered in glass vials, each containing $1 \text{ to } 8 \times 10^8$ colony forming units (CFU) of TICE BCG which is equivalent to approximately 50 mg wet weight. Determination of \textit{in vitro} potency is achieved through colony counts derived from a serial dilution assay. A single dose consists of 1 reconstituted vial (see \textsc{DOSAGE AND ADMINISTRATION}).
BCG Shortage: Dose Reduction

**Package Insert**

The freeze-dried BCG preparation is delivered in glass vials, each containing 1 to $8 \times 10^8$ colony forming units (CFU) of TICE BCG which is equivalent to approximately 50 mg wet weight. Determination of *in vitro* potency is achieved through colony counts derived from a serial dilution assay. A single dose consists of 1 reconstituted vial (see DOSAGE AND ADMINISTRATION).

**Dose**

- **Full**
  
  $1 \times 10^8$ to $8 \times 10^8$

Colony Forming Units (CFUs)
BCG Shortage: Dose Reduction

Package Insert

The freeze-dried BCG preparation is delivered in glass vials, each containing 1 to \(8 \times 10^8\) colony forming units (CFU) of TICE BCG which is equivalent to approximately 50 mg wet weight. Determination of in vitro potency is achieved through colony counts derived from a serial dilution assay. A single dose consists of 1 reconstituted vial (see DOSAGE AND ADMINISTRATION).

<table>
<thead>
<tr>
<th>Dose</th>
<th>CFU Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full</td>
<td>(1 \times 10^8) to (8 \times 10^8)</td>
</tr>
<tr>
<td>Half</td>
<td>(5 \times 10^7) to (8 \times 10^8)</td>
</tr>
<tr>
<td>One-Third</td>
<td>(3.3 \times 10^7) to (8 \times 10^8)</td>
</tr>
</tbody>
</table>
BCG Shortage: Dose Reduction

Package Insert

The freeze-dried BCG preparation is delivered in glass vials, each containing $1 \text{ to } 8 \times 10^8$ colony forming units (CFU) of TICE BCG which is equivalent to approximately 50 mg wet weight. Determination of in vitro potency is achieved through colony counts derived from a serial dilution assay. A single dose consists of 1 reconstituted vial (see DOSAGE AND ADMINISTRATION).

Dose

- **Full**: $1 \times 10^8$ to $8 \times 10^8$
- **Half**: $1 \times 10^8$ to $2.66 \times 10^8$
- **One-Third**: $3.3 \times 10^7$ to $8 \times 10^8$
Patients who have received reduced dose BCG should be included in trials for BCG Unresponsive Disease
BCG Exposed Disease State

International Bladder Cancer Group (IBCG) Consensus Statement on Clinical Trial Design for Patients with BCG-Exposed High Risk NMIBC

M. Roumiguié¹,² A.M. Kamat³, T.J. Bivalacqua⁴, S. Lerner⁵, W. Kassouf⁶, A. Böhle⁷, M. Brausi⁸, R. Buckley⁹, R. Persad¹⁰, M. Colombel¹¹, D. Lamm¹², J. Palou-Redorta¹³, M. Soloway¹⁴, Brothers K¹⁵, G. Steinberg¹⁶, Y. Lotan¹⁷, R. Sylvester¹⁸, A.J. Witjes¹⁹, P.C. Black¹,
BCG induction only

High grade T1
3 mo after start of BCG

High grade Ta/T1
≤6 mo after last dose BCG

CIS
≤12 mo after last dose BCG

BCG unresponsive

Adequate BCG

Inadequate BCG
NMIBC recurrence after BCG treatment

- BCG induction only
  - High grade Ta/CIS
  - 3 mo after start of BCG
  - BCG resistant

- Adequate BCG

- Inadequate BCG

BCG Exposed
NMIBC recurrence after BCG treatment

- **BCG induction only**
  - High grade Ta/CIS
  - 3 mo after start of BCG
  - BCG resistant

- **Adequate BCG**
  - Any high risk recurrence
    - 12 – 24 mo after last dose BCG
    - Late relapse after adequate BCG

**BCG Exposed**
NMIBC recurrence after BCG treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Stage/grade of recurrence</th>
<th>Time to event</th>
<th>Disease state</th>
<th>BCG Exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG induction only</td>
<td>High grade Ta/CIS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 mo after start of BCG</td>
<td></td>
<td>BCG resistant</td>
<td></td>
</tr>
<tr>
<td>Adequate BCG</td>
<td>Any high risk recurrence</td>
<td>12 – 24 mo after last dose BCG</td>
<td>Late relapse after adequate BCG</td>
<td></td>
</tr>
<tr>
<td>Inadequate BCG</td>
<td>&lt; 24 mo after last dose BCG</td>
<td>&lt; 24 mo after last dose BCG</td>
<td>Late relapse after inadequate BCG</td>
<td></td>
</tr>
</tbody>
</table>
What’s next: Trials Earlier in NMIBC

**BCG “Exposed”**

Keynote 676

Similar Trials:
- Checkmate 7G8 with nivolumab
- ADAPT-Bladder durvalumab + RT

SITC Webinar, 101, Aug 2021 (Slide P. Black)
What’s next: Trials Earlier in NMIBC

**BCG “Exposed”**

- **High risk NMIBC**
  - Recurrence after induction BCG therapy only

  **BCG**
  - (N=550)
  - **1st endpoint: CR in patients with CIS**

  **BCG + Pembrolizumab**

**Similar Trials:**
- Checkmate 7G8 with nivolumab
- ADAPT-Bladder durvalumab + RT

**Keynote 676**

**BCG Naïve**

- **High risk NMIBC:**
  1. Any HG
  2. Any T1
  3. Low grade Ta if >3cm, recurrent + multifocal
  4. No prior BCG therapy

- **BCG Induction + Maintenance (24 months)**

**Similar Trials:**
- ALBAN with atezolizumab
- CREST with sasanlimab (subq)

**1st endpoint: DFS**

**Potomac**

SITC Webinar, 101, Aug 2021 (Slide P. Black)
Contemporary Outcomes of Patients with Nonmuscle-Invasive Bladder Cancer Treated with bacillus Calmette-Guérin: Implications for Clinical Trial Design

Justin T. Matulay, Roger Li, Patrick J. Hensley, Nathan A. Brooks, Vikram M. Narayan, H. Barton Grossman, Neema Navai, Colin P. N. Dinney and Ashish M. Kamat

Table 2. Survival analysis based on Kaplan-Meier estimates at 1, 3 and 5-year time points

<table>
<thead>
<tr>
<th></th>
<th>RFS-HG</th>
<th>PFS</th>
<th>CFS</th>
<th>OS</th>
<th>Median</th>
<th>Mos</th>
<th>Followup</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>81</td>
<td>76</td>
<td>74</td>
<td>97</td>
<td>93</td>
<td>92</td>
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<tr>
<td>EAU risk group</td>
<td></td>
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</tr>
<tr>
<td>Intermediate</td>
<td>95</td>
<td>92</td>
<td>86</td>
<td>100</td>
<td>100</td>
<td>100</td>
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<tr>
<td>High</td>
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<td>72</td>
<td>96</td>
<td>92</td>
<td>91</td>
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<tr>
<td>AUA NMIBC risk group</td>
<td></td>
<td></td>
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<tr>
<td>Intermediate</td>
<td>89</td>
<td>85</td>
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<tr>
<td>High</td>
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<td>71</td>
<td>96</td>
<td>94</td>
<td>93</td>
<td></td>
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<tr>
<td>Presence of CIS</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>LG Ta/T1 only</td>
<td>94</td>
<td>90</td>
<td>85</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>HG Ta/T1 only</td>
<td>81</td>
<td>77</td>
<td>75</td>
<td>97</td>
<td>93</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>CIS only</td>
<td>77</td>
<td>70</td>
<td>66</td>
<td>91</td>
<td>91</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>Ta/T1+CIS</td>
<td>77</td>
<td>68</td>
<td>67</td>
<td>96</td>
<td>92</td>
<td>89</td>
<td></td>
</tr>
</tbody>
</table>

Matulay...Kamat, J Urol, 2021
Once BCG-Unresponsive, Always BCG-Unresponsive
Once BCG Unresponsive, Always BCG Unresponsive: An Open Letter to the FDA to Enhance Recruitment into Clinical Trials in Bladder Cancer

Ashish M. Kamat\textsuperscript{a,*}, Seth Lerner\textsuperscript{b}, Peter Black\textsuperscript{c}, Joaquim Bellmunt\textsuperscript{d}, Colin Dinney\textsuperscript{a}, Noah M. Hahn\textsuperscript{e}, Michael O'Donnell\textsuperscript{f} and Diane Z. Quale\textsuperscript{g}
Some Considerations for Clinical Trial Design
Bladder biopsies should be mandatory for high risk NMIBC trials

Mandatory biopsies of the bladder should be at 6 months
For patients with BCG unresponsive CIS, who have recurrence at 3 months

one additional course of treatment (until the 6 month evaluation) should be allowed
For patients enrolled in trials for high risk NMIBC—including BCG-unresponsive disease—prostatic urethral involvement is excluded in most trials.

The SITC-IBCG panel recommends patients be included, but stratified for randomization.
Patients with NMIBC undergoing cystoscopy may have this with white light or blue light depending on referral patterns.

There is no need to mandate blue light cystoscopy prior to study entry.
For patient with BCG-unresponsive disease, the FDA guidance document recommends single-arm studies. Despite recent developments, and currently available data, the SITC-IBCG panel (n=23) was split

51%: recommend best practice as control arm (eg Gem/Doce, Pembro, other …)

48%: continue to recommend single arm studies
Ashish M. Kamat, MD

Any CIS: 50% HG-RFS at 2 years

Papillary alone: 58% HG-RFS at 2 years

High grade bladder recurrence-free survival for BCG unresponsive cases

Steinberg, …, O’Donnell et al, J Urol, May 2020
Cystectomy as an Endpoint?

Drug X

Investigator’s choice therapy

BCG-Unresponsive, High-Risk NMIBC

Primary

EFS (recurrence of high-grade NMIBC, progression to MIBC, metastatic UC, or death)

Secondary

Time to cystectomy

POST-MARKETING REQUIREMENT
LONG TERM FOLLOW UP

Acute and Subacute Safety/Tolerability

Delayed Harm

TBC by Paul Kluetz in detail
KN57: Cystectomy Free Survival: 62.5% at 2 years

Non CR/Recurrent: 79 (82.3%)

- Radical Cystectomy: 36 (37.5%)
- No subsequent therapy received or unknown: 14 (14.6%)
- Local procedure (TURBT, biopsy, fulguration, radiation, PDT): 21 (21.9%)
- Intravesical therapy (BCG, chemotherapy, vicinium): 27 (28.1%)
- Systemic therapy (pembrolizumab): 3 (3.1%)

Total N=96

From ODAC Presentation, FDA Dec 2019
Nadofaragene: Cystectomy Free Survival: 65% at 2 years

No subsequent therapy received or unknown: ???

Radical Cystectomy: 43 (29%)

Local procedure (TURBT, biopsy, fulguration, radiation, PDT): ???

Intravesical therapy (BCG, chemotherapy, vicinium): ???

Systemic therapy (pembrolizumab, other): ???

Non CR/Recurrent: 78 (75.7%)

Total N=103

Data courtesy: Colin Dinney, 2021
Cystectomy Free Survival: Valid End Point?

• Important to patients – retain bladder (90+% of enrolled patients)

• Nebulous – hard to control
  - Indication for cystectomy (recurrence? Or progression?)
  - Timing of cystectomy (before or after progression?)
  - Patient/clinician preferences
  - Access to care

• Recommendation:
  - Important to collect and report the data
  - Not formally include it as a secondary endpoint