Novel therapeutic strategies for NMIBC

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I have the following financial interests or relationships to disclose:

<table>
<thead>
<tr>
<th>Disclosure code</th>
<th>Astellas, Janssen, Merck, Roche, Bayer, Sanofi, Lilly, Spectrum, Sitka, Cubist, BioCancell, AbbVie, Ferring</th>
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<tr>
<td>C</td>
<td>New B Innovation, iProgen, GenomeDx</td>
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<td>S</td>
<td>Roche, Sitka, BioCancell</td>
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<tr>
<td>Clinical Trial Investigator</td>
<td>Roche, Sitka, BioCancell</td>
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State of the art treatment of NMIBC in 2016

<table>
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<tr>
<th>Single dose intravesical chemotherapy</th>
<th>Adjuvant intravesical chemotherapy (± device)</th>
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<tbody>
<tr>
<td>Adjuvant intravesical BCG</td>
<td>Salvage intravesical chemotherapy (e.g. docetaxel, valrubicin, gemcitabine)</td>
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(± PDD/NBI)
Novel intravesical therapy
**NMIBC – Disease States**

<table>
<thead>
<tr>
<th></th>
<th>low grade</th>
<th>high grade T1/Tis</th>
<th>high grade T1</th>
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</thead>
<tbody>
<tr>
<td><strong>2nd recurrence</strong></td>
<td>intravesical BCG/chemo</td>
<td>cystectomy</td>
<td></td>
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<tr>
<td><strong>1st recurrence</strong></td>
<td>intravesical chemo/BCG</td>
<td></td>
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<tr>
<td><strong>primary</strong></td>
<td>single dose peri-op chemo</td>
<td></td>
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<tr>
<td><strong>first line high risk</strong></td>
<td>intravesical BCG</td>
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<tr>
<td><strong>BCG unresponsive</strong></td>
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</tbody>
</table>

- **BCG unresponsive**
- **first line high risk**
Consensus definition of BCG-unresponsive patient cohort and outline of trial design for FDA registration pathway.


Clarification of Bladder Cancer Disease States Following Treatment of Patients with Intravesical BCG

Lerner S, Dinney C, Kamat A, Bivalacqua T, Nielsen M, O’Donnell M, Schoenberg M, Steinberg G
“BCG unresponsive NMIBC”

- Any high grade recurrence after induction + 1\textsuperscript{st} round maintenance, or 2 rounds induction
  
  - \textbf{Exception:} high grade T1 disease at 3 months (after induction BCG only) is considered “unresponsive”

- For patients who achieve complete response on induction/maintenance BCG: any high grade recurrence within 6 months of last dose of BCG

- Recurrent low grade Ta disease is not considered unresponsive in this context
BCG Naïve
A Randomized Trial to Evaluate the Influence of BCG Strain Differences and T Cell Priming for BCG-Naïve High-Grade Non-Muscle Invasive Bladder Cancer

PI: Robert S. Svatek, MD, MSCI
UT San Antonio
Pre-existing BCG-specific immunity improves anti-tumor response in patients

Patients with high-risk bladder tumor → PPD test → Surgery → BCG therapy → Clinical outcome?

Graph showing recurrence-free survival (%): PPD + (n=23) vs PPD - (n=32) with censored data.

Step 1 (Registration)
PPD Test
Step 2 (Randomize)

Prime: intradermal BCG
(Tokyo strain 100 µl at 0.5 mg/ml)
+ Intravesical BCG induction and maintenance
(Tokyo strain 80 mg/dose)

Intravesical BCG induction and maintenance
TICE (50 mg/dose)

Intravesical BCG induction and maintenance
(Tokyo strain 80 mg/dose)
Re-tooling BCG – VPM1002BC

- now in phase 1/2 trial for NMIBC (post-BCG)

Swiss Group for Clinical Cancer Research (NCT02371447)
Interleukin 15 superagonist complex (ALT-803)

- Phase Ib/II, open-label, dose-finding, multicenter study of intravesical BCG plus ALT-803 in NMIBC
  - BCG-naïve and BCG failure
  - phase II: compare to BCG alone
BCG unresponsive
What are options for 2\textsuperscript{nd} line intravesical therapy?

- repeat BCG
- BCG + IFN
- mitomycin (± hyperthermia/electromotive)
- gemcitabine
- docetaxel
- valrubicin
- epirubicin
SWOG S0353 Phase II trial of intravesical maintenance gemcitabine for BCG failures

28% RFS at 1 yr
20% RFS at 2 yr

Skinner et al, J Urol, 2013
Phase 2 trial of **Atezolizumab** in BCG-unresponsive NMIBC

- **BCG unresponsive Ta/T1/Tis (TURBT)**
  - Atezolizumab q 3 weeks
  - q 3 weeks
  - cysto cytol
  - 9 weeks*
  - • registration within 6 weeks of TURBT
  - • start therapy within 5 days of registration

- **cysto cytol**
  - Atezolizumab q 3 weeks
  - cysto biopsy cytol
  - CR @ 21 weeks*
  - (=6 months post TURBT)

- **surveillance for 18 months**
  - Atezolizumab maintenance q3wks for 9 cycles
  - RFS @ 18 months

* time is relative to first dose of atezolizumab

Black, Singh, Lerner
KEYNOTE-057 – Phase II Study of Pembrolizumab in High Risk Non Muscle Invasive Bladder Cancer

Patients with BCG-unresponsive HR NMIBC N = 260

Primary Endpoint: CR / DFS
Up to 2 year of treatment with 1 year of post-treatment follow-up
Pembrolizumab 200 mg IV solution for infusion
rAD-IFN α 2b (Instiladrin™)
CG0070 Oncolytic Virus

1. CG0070 virus attaches to cancer host cell.
2. Virus injects DNA into cell. E2F attaches to viral DNA & both enter the nucleus.
3. Viral DNA uses the host cell's machinery to make more copies of viral DNA & GM-CSF cytokines.
4. New viral DNA are packaged into viruses.
5. The cancer cell eventually lyses, releasing viruses that can infect other cancer cells.

- Phase III BCG-unresponsive NMIBC (BOND2) - NCT02365818
BioCancell

H19 Promoter

DTA Plasmid

Diphtheria Toxin sequence

BC819
Drug solubilized by hydrophobic interactions.

Docetaxel (size relative to HPG)

Hyper-Branched Polyglycerol

Sitka Biopharma
Randomize to activated arms (some arms may activate earlier than others)

Noah Hahn
Novel therapy for NMIBC

- numerous novel agents going to trial simultaneously
- focus on BCG-unresponsive NMIBC, but lots of room to expand into earlier disease states
  - little activity currently in intermediate risk, first line
- each has the potential to be at least an incremental advance
  - different mechanisms of action suggest potential for sequential and/or combination therapy in future
- critical to enroll patient into clinical trials!!!