BC-819
RECOMBINANT DNA THERAPY FOR NMIBC

March 2017
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## Our Story on a Page

### Important Unmet Need in Bladder Cancer
- 570,000 prevalent cases of non-muscle invasive bladder cancer (NMIBC) in US; no drugs approved since 1998
- Significant recurrence rates and side effects associated with standard of care, intravesical Bacille Calmette-Guerin (BCG), in early disease

### Unique Plasmid-Based Cancer Gene Therapy Platform
- First-of-its-kind technology, first-in-class cancer therapy
- Guided by H19, highly expressed in bladder cancer but not normal tissues, to express lethal toxin in tumor

### BC-819 Program Underway
- Successfully completed in NMIBC:
  - Phase 1/2 and phase 2b monotherapy trials of BC-819
  - Phase 2 trial of combination of BC-819 with BCG
- Responses in heavily pretreated patients in all three studies; >45% and >30% durable responses at 1 and 2 years; safety profile favorable
- Recent FDA guidance and company interactions guide development program
- Two registration trials ready, each of which may support approval:
  - Phase 2 monotherapy in BCG-unresponsive patients
  - Phase 3 of combination with BCG, under SPA from FDA

### Significant Commercial Opportunity
- Projections: year-5 US sales up to $1.3B

### Robust Pipeline/IP Portfolio
- BC-821: second-generation plasmid with enhanced activity
- IP provides for product exclusivity for all programs beyond 2035

### Accomplished Global Team
- Experienced new management team with record of scientific innovation and successful global oncology product approval and commercialization
- Based in Cambridge and Jerusalem
At a Glance

Scientific and Medical
• Focus on discovering and developing therapies for patients with cancer in areas of unmet need
• Initial program: genetic therapy for early stage bladder cancer
• Utilizes technology licensed from Hebrew University

Corporate
• Based in Cambridge and Jerusalem
• New CEO (former Harvard faculty; Ariad chief medical officer) based in Cambridge, building U.S. team and infrastructure

Financial
• Market capitalization: approximately $28M (3/16/17).
• Publicly traded in Israel (TASE:BICL)
• 74 million outstanding shares, 80 million fully diluted
• $4.5 million cash at year-end, no debt
BIOCANCCELL’S SCIENCE

Exploiting H19: Gene Therapy to Target Bladder Cancer

BioCanCell’s founding discovery: H19 long non-coding RNA

- It is a controlling element for central malignant cell processes
- It is selectively and highly expressed in bladder cancer cells
- We have engineered H19 control elements into a targeted, recombinant DNA construct encoding lethal toxin, selectively expressed in tumors: BC-819

H19 in situ hybridization (ISH) of bladder tumor, showing H19 expression as black grains, and absence of expression in normal surrounding tissue

Normal tissue: H19 OFF

Malignant tumor: H19 ON

BC-819 recombinant H19-toxin gene: UNEXPRESSED

BC-819 recombinant H19-toxin gene: EXPRESSED and LETHAL
BC-819 IN NON-MUSCLE INVASIVE BLADDER CANCER

Ready for Registrational Trials

**LEAD CANDIDATE BC-819:**
Three studies complete; two pivotal trials ready to be initiated, either of which support approval

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Approval</th>
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<tbody>
<tr>
<td>204</td>
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**Phase 2 trial of BC-819**
In approx. 140 patients with BCG-unresponsive disease who are not a candidate for further BCG therapy

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Approval</th>
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<tr>
<td>301</td>
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</table>

**Phase 3 trial of BC-819 plus BCG**
In approx. 495 patients who have failed only initial BCG treatment; this trial was granted an **SPA** by the FDA
NON-MUSCLE-INVASIVE BLADDER CANCER: NMIBC

New Solutions Needed

In the United States

**4th** MOST COMMON CANCER IN MALES

570,000 PREVALENT CASES

77,000 NEW CASES/YEAR

Quality of Life Issues

Repeated recurrence
Repeated cystoscopy and surgery
Repeated drug treatment cycles
Lifelong cystoscopy follow-up

Worldwide

**9th** MOST COMMON CANCER

420,000 NEW CASES/YEAR

96,000 NEW CASES/YEAR IN EU ALONE

Quality of Life Issues

No New Drugs in 20 years

0 Drugs approved by FDA since 1998 for NMIBC

In the United States

570,000 PREVALENT CASES

77,000 NEW CASES/YEAR

Worldwide

420,000 NEW CASES/YEAR

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Quality of Life Issues

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No New Drugs in 20 years

0 Drugs approved by FDA since 1998 for NMIBC
NMIBC CLASSIFICATION AND EPIDEMIOLOGY

Most NMIBC Patients Present with Stage Ta Disease

- Noninvasive papillary urothelial carcinomas may arise via hyperplasia and are categorized as genetically stable tumors. Approximately 70% of patients with NMIBC present with stage Ta disease.
- Muscle-invasive urothelial carcinomas may originate from the progression of dysplasia or flat carcinoma in situ (CIS) and these tumors are categorized as genetically unstable.

<table>
<thead>
<tr>
<th>Stage at Diagnosis</th>
<th>Percent of Total NMIBC Patients</th>
</tr>
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<tbody>
<tr>
<td>Ta</td>
<td>70%</td>
</tr>
<tr>
<td>T1</td>
<td>25%</td>
</tr>
<tr>
<td>Tis</td>
<td>5%</td>
</tr>
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</table>

BLADDER CANCER DIAGNOSIS AND TREATMENT

Early Diagnosis and Therapy are Central to Management

**Diagnosis**

- Typically presents with early symptoms: hematuria, urgency, dysuria
- Is diagnosed by cystoscopy
- Tumors are removed, a procedure called trans-urethral resection (TUR)
- Tumors are then classified pathologically and treated according to their staging

**NMIBC treatment**

- After resection, adjuvant chemotherapy or Bacille Calmette Guerin (BCG, attenuated tuberculosis bacteria) given into the bladder
- **BioCanCell’s BC-819 technology** being tested in patients for whom these therapies fail
- Standard approach well suited for BC-819 treatment, with instillation into the bladder allowing direct contact of high drug concentration without systemic exposure
Magnitude of Need in NMIBC¹

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Description</th>
<th>U.S. Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>75%</td>
<td>of prevalent bladder cancer cases are NMIBC</td>
<td>430,000 in U.S. alone</td>
</tr>
<tr>
<td>85%</td>
<td>are intermediate and high risk²</td>
<td>366,000 in U.S. alone</td>
</tr>
<tr>
<td>~80%</td>
<td>intermediate and high risk cases are treated with BCG³</td>
<td>293,000 in U.S. alone</td>
</tr>
<tr>
<td>70%</td>
<td>of NMIBC patients recur after BCG treatment</td>
<td>205,000 in U.S. alone</td>
</tr>
</tbody>
</table>

BioCanCell U.S. patient population: 205,000 recurrent NMIBC cases after BCG treatment

¹ All figures refer to NMIBC (non-muscle-invasive bladder cancer)
² Decision Resources
³ Source: IMS data 2011
FDA Fostering New Treatment Development

- FDA has recognized the need in NMIBC and has been exceptionally active in providing guidance
- 2014: Published guidelines for NMIBC development in collaboration with AUA
- 2016: Published Guidance for Industry with recommendations for patient populations, endpoints, trial design and development program as a pathway to approval
- Yet, poor progress to date in NMIBC underscores unmet need

The regulatory opportunity in NMIBC is clear; BioCanCell’s clinical development program has been formulated with FDA guidance
BC-819
Unique Technology, Potent Mechanism

A first-in-class, first-of-its-kind gene therapy

• Fundamental technology is targeted recombinant DNA-based gene construct for bladder cancer, engineered to express lethal toxin specifically in malignant cells

Plasmid based, highly targeted

• BC-819 is a 4.5 kb recombinant DNA plasmid containing 832 bp of H19 regulatory sequences driving expression of diphtheria toxin A chain only in malignant cells
• Complexed with polyethylenimine (PEI) to enhance transfection efficiency

Potent lethal payload

• Diphtheria toxin A (shown at right) an extraordinarily potent genetic payload: one molecule may kill a cell, binding NAD and EF2 and inhibiting protein translation
• Lack of the B chain prevents transfer of toxin between cells
BC-819 IN MALIGNANT CELLS
Driving Lethal Expression of Diphtheria Toxin

Preclinical data illustrate BC-819 mechanism of action regarding tumor cell entry, specificity and transcription of the lethal genetic payload

Exposure and tumor uptake of plasmid:
Analysis of BC-819-treated patients demonstrate persistence of plasmid 48 hrs in urine (A) and uptake in tumor (B)

Transcription of diphtheria toxin:
BC-819 treatment of orthotopic rat bladder cancer model demonstrates transcription of DTA

PCR of urine following BC-819 instillation at 2 hrs (lane 2), 24 hrs (3), 48 hrs (4) and 72 hrs (5) post-treatment. PCR of tumor biopsy 18 hrs post-treatment (lane 7). 100 bp ladder, lanes 1,6

RT-PCR of bladder (lane 2), liver (3), and kidney (4) RNA shows expression in bladder consequent to plasmid uptake and transcription specifically in malignant tissue. 100 bp ladder marker in lane 1
**BC-819 IN VIVO**

**Effective in Eliminating Experimental Bladder Cancer**

Animal model data demonstrate that intravesical instillation of BC-819 eliminates rat bladder cancers.

Analysis of BC-819-treated rat bladders by ultrasound and at necropsy shows progression of experimentally induced tumor when treated with control vector (top) but tumor response when treated with BC-819 (bottom).

Wistar rats received N-butyl-N(4-hydroxybutyl) nitrosamine (BBN), a potent carcinogenic alkylating agent, in drinking water for 5-30 weeks. Tumors were evident by 10 weeks, with superficial invasion evident by 15 weeks and typically deep invasion by 20 weeks. At 19 weeks 100 ug of control luciferase vector (top) or BC-819 (bottom) was instilled weekly for 5 weeks intravesically.
### BC-819 CLINICAL STRATEGY

**A Linear Path to Approval Based on FDA Guidance**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Status</th>
<th>Result</th>
</tr>
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<tbody>
<tr>
<td><strong>Phase 1/2</strong></td>
<td>Complete; N=18</td>
<td>22% Complete Responses</td>
</tr>
<tr>
<td><strong>Phase 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>Complete; N=47</td>
<td>46% Durable Responses at 1 year</td>
</tr>
<tr>
<td>Combination with BCG</td>
<td>Enrollment Complete; N=38</td>
<td>Median Time to Progression Not Yet Reached</td>
</tr>
<tr>
<td><strong>Phase 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy for Registration</td>
<td>FDA Approved to Initiate EU, HC agreement</td>
<td>Ready for Initiation</td>
</tr>
<tr>
<td><strong>Phase 3</strong></td>
<td>SPA, FDA Approved, EU, HC Agreement</td>
<td>Ready for Initiation</td>
</tr>
<tr>
<td>Complete Responses Demonstrated</td>
<td></td>
<td></td>
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<tr>
<td>--------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Phase 1/2</strong></td>
<td><strong>Phase 2b</strong></td>
<td></td>
</tr>
<tr>
<td>Complete Responses:</td>
<td>22% (4/18)</td>
<td>33% (13/39)</td>
</tr>
<tr>
<td>Partial Responses:</td>
<td>22% (additional 4/18)</td>
<td>Not Assessed</td>
</tr>
<tr>
<td>Total Responses:</td>
<td>44% (8/18)</td>
<td>Not Assessed</td>
</tr>
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</table>

- Proof of concept requires ability to destroy macroscopic tumor
- Patients underwent complete resection of all existing lesions except a single marker tumor, assessed at 12 weeks
- **Complete responses observed in 17/57 patients (30%)** demonstrating activity against established cancer

D: Baseline: papillary tumor
E: 3 weeks following 6th instillation of BC-819: necrosis
### BC-819 THERAPY RESULTS

**Durable Remissions**

<table>
<thead>
<tr>
<th>Recurrence Free:</th>
<th>Phase 1/2</th>
<th>Phase 2b</th>
<th>Phase 2 Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At 3 months:</strong></td>
<td>56% (10/18)</td>
<td>64% (25/39)</td>
<td>77% (23/30)</td>
</tr>
<tr>
<td><strong>At 1 years:</strong></td>
<td>44% (8/18)</td>
<td>46% (18/39)</td>
<td>Ongoing</td>
</tr>
<tr>
<td><strong>At 2 years:</strong></td>
<td>29% (5/17)</td>
<td>33% (13/39)</td>
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- After responses, durability of remission the most important clinical parameter in patients undergoing adjuvant therapy after resection
- In the two monotherapy trials, twelve-month recurrence-free rates are **46%** (26/57)
- 24-month recurrence-free rates **32%** (18/56)
- Both compare favorably with historical 24-month experience of approximately **20%**
## BC-819 SAFETY PROFILE

**Results Suggests BC-819 Tolerability**

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication</th>
<th># of Patients</th>
<th># of Instillations</th>
<th>SAEs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BC-05-02</strong> (ph I/IIa)</td>
<td>Bladder cancer</td>
<td>18</td>
<td>432</td>
<td>4 unrelated, 1 possibly related</td>
</tr>
<tr>
<td><strong>BC-07-01</strong> (ph IIb)</td>
<td>Bladder cancer</td>
<td>39</td>
<td>936</td>
<td>6 unrelated, 1 possibly related</td>
</tr>
<tr>
<td><strong>BC-BLAD-01</strong> (combination)</td>
<td>Bladder cancer</td>
<td>38</td>
<td>224</td>
<td>1 unrelated</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>Bladder cancer</td>
<td>95</td>
<td>1592</td>
<td>11 unrelated, 2 possibly related</td>
</tr>
</tbody>
</table>

- BC-819 has shown an excellent safety profile.
- In 95 patients with bladder cancer treated with 1592 doses, 2 of 13 SAEs reported (micturition urgency; hematuria) were possibly drug related.
BC-819 CLINICAL DEVELOPMENT PROGRAM
Pathway to Registration

204
Phase 2 trial is a single-arm path to full approval

• FDA recommendations have been followed, and unmet need in these patients is high

301
Phase 3 trial is approved under SPA and will support a second indication

• Trial has been granted an SPA in this context
• This trial is complementary to the phase 2

These two trials provide independent routes to approval in two separate (but related) indications
BC-819 DURABILITY OF RESPONSE

Background for Phase 2

Monotherapy durability compared to historical experience:

- FDA/American Urological Association panel specified in CIS 30% recurrence-free rate at 18-24 months, excluding 20%, as being an approvable endpoint¹
- Historical experience 20% 24-month DFS, the basis for this shown in green
- The phase 2 data compare favorably to these specifications: 12-month timepoint demonstrates 46% recurrence free and this is the context for planned phase 2 trial; 18- and 24- month rates are >30%

¹ Jarow et al., J. Urology, 2014
BC-819 INITIAL REGISTRATIONAL STUDY PHASE 2 TRIAL 204

In Patients whose Disease is BCG-Unresponsive

Patients: High-risk NMIBC in pts with BCG-unresponsive disease; will require approximately 140 patients

- FDA agreement 2014: stated a single-arm study in this population could lead to approval
- Spanish, German and Canadian regulators also support study
BC-819 DURABILITY OF RESPONSE

Background for Phase 3 Trial

Combination therapy durability compared to historical experience:

- Historical average proportion of patients disease free at 24 months is 35%\(^1\) shown in green; median time to recurrence was 7 months in a CIS randomized trial\(^2\)
- Proposed Phase 3 endpoint is median time to recurrence:
  - Median time to recurrence of BC-819 combination not yet reached (with 10 months follow-up)
  - Median time to recurrence of historical control approximately 16 months
- These findings suggest combination therapy compares favorably with historical experience

2. De Lorenzo et al., Cancer 2010
In BCG Failure Patients Under SPA From FDA

Patients: Intermediate or high risk NMIBC after at least one failed course BCG; will require approximately 495 patients

- FDA reviewed, granted SPA, certifying it could meet condition for full approval
- Spanish, German and Canadian regulators support study as well
**NMIBC**

**A Robust Market**

- **50,000** patients eligible for BC-819 treatment, U.S.
- **100,000** patients eligible for BC-819 treatment, WORLDWIDE
- **13,500–21,500** projected year-5 U.S. patients treated
- **$540M–$1,290M** projected year-5 U.S. sales

- **366,000** prevalent NMIBC intermediate and high-risk patients
- **~20% (73,000)** of those patients are eligible for treatment each year
- **~70% (50,000)** of all treatable patients are eligible for BC-819 therapy
- Company-estimated market penetration at year 5:
  - BCG failure **25-40%**
  - BCG unresponsive and intolerant **30-50%** and **40-60%** respectively
- Assumes annual cost per patient per year of **$40,000–$60,000**
IN THE PIPELINE

Next-Generation Recombinant Plasmid

**BC-821:** Next-generation targeted plasmid

- Augments expression with IGF2-P4 promoter in addition to H19 promoter
- More potent in vitro and in vivo; IC50 (in green) approximately 4 times more potent than BC-819
# Intellectual Property and Exclusivity

**Key Granted Patents**
- BC-821: WO2009/053982: constructs containing multiple expression cassettes for cancer therapy

**Product Licenses**
- Exclusive worldwide license from the Hebrew University of Jerusalem for products arising out of patents in connection with the H19 and IGF2-P4 genes
- BioCanCell has the right to grant sub-licenses to third parties

**Expiration Dates**
- BC-819 patents (main patent US 6087164 A) will expire in the United States in 2017 and in 2018 for the rest of the world
- The Company filed new composition of matter IP in 2015 on the commercial formulation of BC-819, extending market exclusivity beyond 2035

**Marketing Exclusivity**
- BC-819 and BC-821 qualify as “biologicals” with marketing exclusivity of 12 years in the US and 8-11 years in the EU and Japan for new NCEs
Key Takeaways

Potential for first-of-its-kind DNA-directed cancer therapy in non-muscle invasive bladder cancer (NMIBC), a serious area of unmet need—**BC-819**

Preliminary data from development program and FDA agreement support direct path to approval with either of two trials

Potential of over $1 billion in sales in U.S. alone

Strong, newly expanding management team and global organization will facilitate program success

Promising pipeline and robust IP portfolio