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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

Corporate

- Based in Cambridge and Jerusalem
- New CEO (former Harvard faculty; Ariad CMO; led two FDA approvals) based in Cambridge, building U.S. team and infrastructure

Financial

- Market capitalization: approximately $22M (end Q2 2017)
- Publicly traded in Israel (TASE:BICL)
- $5M cash (end Q2 2017)
- After Israel offering, 96 million outstanding shares, 108 million fully diluted
## Leadership

### Frank Haluska, MD, PhD
- **President and Chief Executive Officer**
- ARIAD Pharmaceuticals CMO, SVP of Clinical R&D
- Led development and approvals of two oncology drugs
- Harvard College BA, U. Penn MD, PhD, MIT post doc
- MGH residency, DFCI fellowship, Harvard Medical School faculty
- MGH: Physician and founder of the melanoma research programs
- Dana-Farber/Harvard Cancer Center: Skin cancer program leader

### Yan Moore, MD, MBA
- **Chief Medical Officer and Sr. Vice President of Clinical Development**
- ARIAD Pharmaceuticals: VP of Medical Affairs
- Sanofi: Associate Vice President, Global Medical/Clinical Lead
- GSK: Executive Director, Oncology R&D
- BMS: Global Indication Lead
- GPC Biotech: Senior Director, Head of Medical Affairs
- Oncura: Global Medical Director

### Jonathan Burgin, MBA, CPA
- **Chief Financial Officer and Chief Operating Officer**
- BioCanCell: former CEO
- Radcom, Ltd: CFO
- XLT Biopharmaceuticals: CFO
- Y.L.R. Capital Markets: CFO
- Kesselman & Kesselman (PWC): Senior Manager

### Michal Gilon, PhD
- **Vice President of Research and Development**
- Hebrew University of Jerusalem: R&D Project Manager, Researcher, Post-doctoral fellowship, PhD
- Europe Molecular Biology Organization (EMBO): Professor
- Hadassah Academic College: Professor

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4 | October 2017 | Company Presentation
BioCanCell’s founding discovery: H19 gene

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

H19 in situ hybridization (ISH) of bladder tumor, showing H19 expression as black grains, and absence of expression in normal surrounding tissue.
**Status of the Program: Ready for Registrational Trials**

**LEAD CANDIDATE BC-819:**
Three studies are complete; two pivotal trials, BC-204 and BC-301, are ready to be initiated, either of which will support approval.

**Phase I**

**Phase II**

**Approval**

**Phase 2 trial**
In approx. 140 patients with BCG-unresponsive disease who are not a candidate for further BCG therapy.

**Phase 3 trial**
In approx. 495 patients who have failed only initial BCG treatment; this trial was granted an SPA by the FDA.

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**BioCanCell**

6 | October 2017 | Company Presentation
NON-MUSCLE-INVASIVE BLADDER CANCER: NMIBC

New Solutions Needed

In the United States

<table>
<thead>
<tr>
<th>4th MOST COMMON CANCER IN MALES</th>
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<tbody>
<tr>
<td>570,000 PREVALENT CASES</td>
</tr>
<tr>
<td>77,000 NEW CASES/YEAR</td>
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</table>

Worldwide

<table>
<thead>
<tr>
<th>9th MOST COMMON CANCER</th>
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<tbody>
<tr>
<td>420,000 NEW CASES/YEAR</td>
</tr>
<tr>
<td>150,000 NEW CASES/YEAR IN EU ALONE</td>
</tr>
</tbody>
</table>

Quality of Life Issues

Repeated recurrence
Repeated cystoscopy, surgery and drug treatment cycles
Lifelong cystoscopy follow-up
Most expensive cancer to treat

No New Drugs in 20 years

0 Drugs approved by FDA since 1998 for NMIBC
Non-Muscle Invasive Bladder Cancer and BC-819

- Non-muscle invasive bladder cancers (NMIBC) have a low metastatic potential. They are resected and treated with adjuvant intravesical therapy. BC-819 is an experimental intravesical therapy.

- Muscle-invasive bladder cancers may originate from the progression of NMIBC, signify a greater risk of metastatic disease, and are treated with complete bladder resection. Prevention of progression is a key goal.

Sources:
BC-819 Designed to be Included in Early Treatment

**Diagnosis**

- Bladder cancer presents with early symptoms: hematuria, urgency, dysuria
- Diagnosed and treated by cystoscopy
- Tumors are removed by transurethral resection (TUR)
- Tumors then classified pathologically and treated according to their staging

**NMIBC treatment**

- After resection, adjuvant Bacille Calmette Guerin (BCG, attenuated tuberculosis bacteria) given into the bladder
- **BC-819** is being tested in patients for whom BCG fails
- Standard approach is well suited for BC-819 treatment, with instillation into the bladder allowing direct contact of high drug concentration without systemic exposure

Cystoscopic view of bladder lining with focus of bladder cancer
Magnitude of Need in NMIBC

75% of prevalent bladder cancer cases are NMIBC

430,000 in U.S. alone

85% are intermediate and high risk²

366,000 in U.S. alone

~ 80% intermediate and high risk cases are treated with BCG³

293,000 in U.S. alone

70% of NMIBC patients recur after BCG treatment

205,000 in U.S. alone

BioCanCell U.S. patient population:

205,000 recurrent NMIBC cases after BCG treatment

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² All figures refer to NMIBC (non-muscle-invasive bladder cancer)
³ Decision Resources
³ Source: IMS data 2011
NMIBC

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, specifically 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, validated target**

- **Diphtheria toxin** (shown at right) an extraordinarily potent genetic payload: one molecule may kill a cell, binding NAD and EF2 and inhibiting protein translation. Lack of B chain prevents transfer between cells
- Unlike most cancer therapies, for BC-819 there is no need to validate a new target or pathway. DTA MOA is well understood
**EXPRESSION OF H19 IN NORMAL AND MALIGNANT CELLS**

**H19 is a Cancer-Specific Target**

**A**

H19 expression in a panel of 27 human tissue samples. Quantitative transcriptomics analysis (RNA-Seq) was used to classify the tissue-specific expression of genes across a representative set of all major human organs and tissues. These data were integrated with protein expression data. As shown, H19 expression is largely silent in adult tissues, with the exception of expression in placental tissues. Of note, there is little expression in bladder cancer (arrow). Fagerberg et al., Mol. Cell Proteomics 13: 397, 2014. See https://www.ncbi.nlm.nih.gov/gene/283120

**B**

In situ hybridization (ISH) of H19 in bladder cancer. Histopathology of bladder cancer stained to demonstrate H19 expression. Black grains (arrow) demonstrate abnormal expression. Normal tissue (top right of section) does not stain for H19.

**H19 is not normally expressed in adult tissues, but is expressed in a variety of human cancers**

Expression analysis in a large panel of human tissues demonstrates lack of normal adult expression, including in normal bladder (Fig. A, left)

In contrast, H19 expression has been identified broadly in human cancers, including especially bladder carcinoma (Fig B). Of note BCG therapy has been shown to upregulate H19 expression in bladder cancer (our unpublished results)

In our phase 2 study of BC-819, at entry 47 patients were tested for H19, and all 47 demonstrated H19 expression. H19 is expressed in all subtypes of NMIBC, including CIS
Quantitative analysis of plasmid uptake using fluorescent activated cell sorter (FACS) approaches demonstrates incorporation of multiple BC-819 copies into bladder cancer cells

FACS can isolate and sort the population of choice (Fig. A) after BC-819 transfection

85.2% of analyzed population demonstrates the presence of BC-819 after a single in vitro transfection (Fig. B)

Majority of the cell population express high levels of Cy3 (Fig. C) indicating uptake of multiple copies of BC-819

BC-819 uptake was determine using Cy3 detection by FACS. T24p bladder cancer cells were transfected with BC-819 (tagged with Cy3)/PEI complex and analyzed 24 hours post transfection. (A) Forward Scatter (FS) vs Side Scatter (SS) plot was used to identify live and dead cells. (B) using mCherry channel on gated live cells, cells expressing Cy3 were counted. 85.2% of live cells (60.2% of dead cells; 80% of all cells) express Cy3. (C) Relative expression of Cy3 was evaluated: X-axis (mCherry-A) is signal intensity; y-axis (Count) is cell number. Most of the population expresses high intensity, indicating uptake of multiple plasmid copies.

BioCanCell unpublished data
Driving Lethal Expression of Diphtheria Toxin A

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

**Transcription of diphtheria toxin A mRNA:**
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 bladder tumor biopsy 18 hrs post-treatment (lane 7). 100 bp ladder, lanes 1,6

RT-PCR of bladder cancer (lane 2), liver (3), and kidney (4) RNA shows expression in bladder cancer consequent to plasmid uptake and transcription specifically in malignant tissue. 100 bp ladder marker in lane 1
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>
</thead>
<tbody>
<tr>
<td>Phase 1/2 Monotherapy</td>
<td>Complete; N=18</td>
<td>22% Complete Responses</td>
</tr>
<tr>
<td>Phase 2 Monotherapy</td>
<td>Complete; N=47</td>
<td>46% Durable Responses at 1 year</td>
</tr>
<tr>
<td>Phase 2 Induction with BCG</td>
<td>Enrollment</td>
<td>19 month median time to recurrence</td>
</tr>
<tr>
<td></td>
<td>Complete; N=38</td>
<td></td>
</tr>
<tr>
<td>Phase 2 Monotherapy for Registration</td>
<td>FDA Approved to Initiate EU, Canada agreement</td>
<td>Ready for Initiation</td>
</tr>
<tr>
<td>Phase 3 Combination with BCG</td>
<td>FDA SPA, EU, Canada Agreement</td>
<td>Ready for Initiation</td>
</tr>
</tbody>
</table>
BC-819 MARKER STUDIES

Complete Responses Demonstrated

<table>
<thead>
<tr>
<th></th>
<th>Phase 1/2</th>
<th>Phase 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete Responses:</strong></td>
<td>22% (4/18)</td>
<td>33% (13/39)</td>
</tr>
<tr>
<td><strong>Partial Responses:</strong></td>
<td>22% (additional 4/18)</td>
<td>Not Assessed</td>
</tr>
<tr>
<td><strong>Total Responses:</strong></td>
<td>44% (8/18)</td>
<td>Not Assessed</td>
</tr>
</tbody>
</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 monotherapy</th>
<th>Phase 2 monotherapy</th>
<th>Phase 2 combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 3 months</td>
<td>56% (10/18)</td>
<td>64% (25/39)</td>
<td>89% (34/38)</td>
</tr>
<tr>
<td>At 1 year</td>
<td>44% (8/18)</td>
<td>46% (18/39)</td>
<td>68% (26/38)</td>
</tr>
<tr>
<td>At 2 years</td>
<td>29% (5/17)</td>
<td>33% (13/39)</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

- 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), and 24-month recurrence-free rates 32% (18/56)
- Both compare favorably with historical 24-month experience of approximately 20%\(^1\)

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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>BC-05-02 (ph 1/2)</td>
<td>Bladder cancer</td>
<td>18</td>
<td>432</td>
<td>4 unrelated 1 possibly related</td>
</tr>
<tr>
<td>BC-07-01 (ph 2)</td>
<td>Bladder cancer</td>
<td>39</td>
<td>936</td>
<td>6 unrelated 1 possibly related</td>
</tr>
<tr>
<td>BC-BLAD-01 (combination)</td>
<td>Bladder cancer</td>
<td>38</td>
<td>224</td>
<td>1 unrelated</td>
</tr>
<tr>
<td>Total</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
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 Registrational Trial

Monotherapy durability compared to historical experience:

- Phase 2 study demonstrates 46% recurrence free at 12 months; 18- and 24- month rates are >30% (right)
- 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
- Recent FDA trial approvals suggest 12-month DFS is an acceptable endpoint
- The registrational trial 204 endpoint will be 12-months DFS, and the phase 2 data compare favorably to these specifications

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

N = 140
Open Label
Two interim analyses
Primary endpoint: Durable responses at 12 months
BC-819 DURABILITY OF RESPONSE

Background for Phase 3 Registrational Trial

Induction combination therapy durability compared to historical experience:

• Combination study tested administering induction therapy of BC-819 plus BCG; patients followed up to 2 years after 6 or 12 week induction with combination
• Important to note that the study did not include BC-819 maintenance therapy post induction
• Combination therapy was feasible and well tolerated
• With median follow-up of approximately 15 months, Kaplan-Meier estimate of overall median time to recurrence is approximately 19 months (95% CI 17-21 months)
• Historical average proportion of patients disease free at 24 months is 35%\(^1\); median time to recurrence was 7 months in a CIS randomized trial\(^2\)
• Proposed Phase 3 combination therapy endpoint is median time to recurrence, and \textit{median time to recurrence in the BC-819/BCG induction study compares favorably with historical experience}

2. De Lorenzo et al., Cancer 2010
BC-819 SECOND REGISTRATIONAL STUDY: PHASE 3 COMBINATION TRIAL 301

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
COMMERCIAL MODELING OF NMIBC MARKET

A Robust Market

272,000
NMIBC PATIENTS ELIGIBLE FOR DRUG TREATMENT, US, EU AND JAPAN

60,000
PATIENTS ELIGIBLE FOR BC-819 TREATMENT, US, EU AND JAPAN

Approximately $500M
PROJECTED YEAR-5 US, EU AND JAPAN SALES

Approximately $1B
PROJECTED PEAK US, EU AND JAPAN SALES

- 257,000 new cases of bladder cancer in 2017 in US, EU, and Japan
- 73-81% of those patients present with NMIBC
- 272,000 incident and recurrent NMIBC are eligible for drug treatment
- ~60,000 of all drug treatable patients either failed or unresponsive are eligible for BC-819 therapy
- Company-estimated market penetration at year 5:
  - BCG failure 25-33%
  - BCG unresponsive 20-24%
- 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

![Graph showing relative luciferase activity](image)
FUNDRAISING OBJECTIVES AND TIMING

Clinical Trial Funding

• Plan to initiate clinical trial operations for both registrational studies by end of 2017
• This will enable enrolling first patients in the first half of 2018
• Funding for the trials will involve immediately raising up to approximately $15M either privately or via the TASE
• Following this round, the company plans to carry out a US IPO
**BIOCANCELL**

**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 “biologics” 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** |
|---|---|
| Strong, experienced management team and newly expanding global organization |
| Preliminary data from development program and FDA agreement support direct path to approval with either of two trials |
| Robust commercial potential serving large global population in need of new therapy |
| Promising pipeline and robust IP portfolio |