OVERCOMING IMMUNOTHERAPY RESISTANCE

Two unique mechanisms that target the tumor microenvironment
Blazing a trail that benefits patients and investors

Potential First and Best-in-Class
Selective ETBR Inhibitors to reverse immunotherapy resistance

Strong and Broad IP and Regulatory Exclusivity

Clinical trial collaboration with big Pharma partner Merck

Companion Diagnostic
In development identifies patients most likely to respond

Short-Term Milestones
IND approved P1/P2 initiation Q1 2020

Solid Leadership and Scientific Team
Scientific founders co-inventors on first patents filed covering ETBR as a therapeutic target for cancer: NYU School of Medicine, 1997

Capital and Time Efficient Development Program
Clinical proof of concept within 12 months

ETBR: endothelin B Receptor
ENB Therapeutics snapshot

Founded in 2015
- Focused on cancer therapies to overcome drug resistance
- Technology originally developed at NYUSOM
- Based in NYC Alexandria Center for Life Science LaunchLabs incubator

Funding
- $500K friends and family
- Closed $1M Seed round Q1 2018
- Closed $8M Series A Q3 2018 to support Ph1 trials
- Raising $25M Series B to support Ph2

Management Team
- Sumayah Jamal, MD-PhD, President, CSO, Co-founder: 30 years research experience, co-inventor on first patents filed covering the ETBR as a therapeutic target for cancer, work conducted as a PI at NYUSOM serves as the foundation for the company’s drug development programs
- Robert J. Schneider, Chair SAB, Co-founder: Assoc. Dean for Therapeutics Alliances at NYUSOM, co-founder of successful biotech companies (Imclone, Canji, PTC Therapeutics)
- Sandy Harm, COO: 24 years at Merck, oversaw development and launch of Keytruda as Oncology, Dir. Commercial Operations, last position Dir. Med. Affairs Strategy and Operations (entire US),
  - CEO, CMO to be hired

Advisory Board
- Sanjiv Agarwala, MD Chief, Medical Oncology and Hematology, St. Luke’s Cancer Center, world-recognized expert in cancer immunotherapy and melanoma
- Jay Gibbs, PhD, 30+ years in Pharma, expertise in oncology drug development, former Scientific Dir. At Astra Zeneca and Merck
- Dan Littman, MD-PhD, Recognized worldwide as a pioneer in the field of immunology. Helen L. and Martin S. Kimmel professor of molecular immunology in the Skirball Institute of Biomolecular Medicine at the New York University School of Medicine and is a Howard Hughes Medical Institute Investigator.
- Adriann Sax, 30 years pharma, Roche, BMS, Merck

Advisory Board
- Anthony Davenport, PhD, Dir. British Heart Foundation Group at Cambridge, UK, foremost expert in the field of endothelin biology and receptor antagonists, >100 peer reviewed publications and book chapters

Consultants
- CMC-Vincent Bille, PhD, Founder Marble Pharma Consulting, 1990-2007 UCB/Lonza, expertise in synthetic peptide manufacturing
- Safety/tox: Lesley Earl, PhD, Assoc Dir. Non-clinical services, ERA consulting, 25+ years industry experience in pre-clinical IND enabling study direction and management
- Cello Health Bioconsultants
The majority of cancer patients do not respond to IO

- Efficacy of IO requires TILs to infiltrate tumors
- Patients with TIL+ TME demonstrate the best response to IO (only 38% of melanomas) but the majority of patients have TIL- tumors and don’t respond to IO
- By targeting the TME and converting TIL- tumors to TIL+ tumors we can improve response rates in patients who would otherwise not respond to IO

*% melanoma patients with anti-PD1 responder profile, lower responder rates observed in other cancers

Source: Teng et al, Cancer Research 2015

IO: Immunotherapy; TIL: Tumor infiltrating lymphocytes; TME: Tumor microenvironment
Switching TIL- tumors to TIL+ tumors

- The ETBR is overexpressed in the TME in over 40% of all cancers and prevents TILs from infiltrating tumors
- Selective ETBR inhibitors switch TIL- tumors “cold” to TIL+ tumors “hot” in animal models and enhance efficacy of otherwise ineffective IO
- Intratumoral injection of ETBR inhibitors recruit TILs to skin tumors in human subjects
- B receptor selectivity required to convert TIL- tumors to TIL+ tumors
  → A receptor blockade or A/B dual receptor blockade blocks TIL infiltration (see slide 14)
  → No B selective inhibitors have ever been tested in clinical trials for cancer

ETBR: endothelin B receptor
ENB-003 overcomes anti-PD1 resistance in syngeneic melanoma model and eradicates tumors within 21 days

**In vivo tumor growth curve: anti-PD1 resistant TIL- syngeneic melanoma model**

- ENB-003 reversed anti-PD1 resistance, induced intratumoral TLO formation and eradicated tumors (see next slide)
- Previously tested SoC drug combinations using this model failed to shrink tumors and all resulted in eventual drug resistance (see slide 27)

**Notes:**
- IV: Intravenous; SoC: standard of care
- Source: internal study, unpublished
ENB-003 + anti-PD1 combination eradicates melanoma tumors in 21 days, promotes robust CD8+ TIL infiltration* and intratumoral TLO formation**

Untreated control: paucity of TILs

Anti-PD1+ dabrafenib: Increase in TILs, predominantly peripheral distribution

Anti-PD1+ENB-003- No residual tumor, intratumoral TLO

** TLOs are functionally equivalent to lymph nodes, produce tumor-specific T- and B-cells: "antibody factories to fight cancer," induce long lasting anti-tumor immunity and are associated with favorable clinical prognosis in multiple cancers
ETBRi overcomes anti-PD1 resistance in syngeneic bladder cancer model

**In vivo tumor growth curve: anti-PD1 resistant bladder cancer model**

- Parent compound BQ788* reversed anti-PD1 resistance
- Synergy observed with the anti-PD1+ BQ788 combination

* Similar results were obtained with lead product ENB-003

CTRL: Control; PD1: Anti-PD1; BQ: BQ788
ENB-003 overcomes anti-PD1 resistance in syngeneic ovarian cancer model

**In vivo tumor growth curve: anti-PD1 resistant ovarian cancer model**

- ENB-003 reversed anti-PD1 resistance
- Synergy observed with the anti-PD1+ ENB-003 combination

**CTRL:** Control; **PD1:** Anti-PD1; **BQ:** BQ788
ENB-003 enhances anti-PD1 efficacy in syngeneic pancreatic cancer model

Tumors harvested on day 10 of treatment

• ENB-003 with some single agent activity that is enhanced in the presence of anti-PD1 when administered at the 4.0ug dose

CTRL: Control ; PD1: Anti-PD1; BQ: BQ788
ENB-003 induces significant reduction in immunosuppressive cells in the TME of a syngeneic pancreatic cancer model.
Overcoming IO resistance across multiple cancer types

Selective ETBR inhibition targets the TME through two unique mechanisms

1. Switching immune-suppressed “cold” TMEs to “hot” TMEs, allowing TILs to infiltrate tumors

2. Creating new intra-tumoral TLOs that release T- and B-cells to destroy cancer cells

By converting TIL- tumors to TIL+ tumors we can improve response rates in patients who would otherwise not respond to IO

TLOs are new lymph nodes that form within tumors and eradicate them

ETBR: endothelin B receptor; IO: immunotherapy; TLO: tertiary lymphoid organ; TME: Tumor microenvironment
First-in-class NCE ENB-003 and ENB-001: potential synergy with multiple immuno-oncology platforms

**BQ788: Parent compound**
- Off-patent research tool for CV disease
- Established safety profile in >30 clinical studies (administered to 400+ patients)
- Robust pre-clinical proof of concept across multiple cancers
- Converts TIL- tumors to TIL+
- Enhances immunotherapy efficacy

**Low solubility, rapid plasma clearance**

Orphan drug designation for melanoma for ENB-001 and ENB-003 awarded by FDA

**Discovery**
- Deuterium exchanged NCE derivative of BQ788
- COM/MOU patent issued 2019
- Enhanced PD profile
- Launch in initial target indications (non-CNS)

**Pre-clinical**
- Nanoparticle formulation of BQ788- accelerated clinical path
- Strong IP- COM 2015
- ↑ Solubility, ↓ Plasma clearance
- Being developed to cross BBB for CNS malignancy

**Phase 1**

**BBB**: Blood-brain barrier; **CNS**: Central nervous system; **COM**: composition of matter; **CV**: Cardiovascular; **IP**: intellectual property; **NCE**: new chemical entity; **PD**: Pharmacodynamic
Business model

1. Develop ENB-003 through Ph2 for primary indication(s) (non-CNS melanoma, ovarian CA, and pancreatic CA)

2. Develop ENB-001 for BBB delivery to treat CNS malignancies including CNS metastases, CNS lymphoma and glioblastoma. Develop fast-follower second-generation novel ETBR antagonist analogues for extended clinical opportunities

3. Develop caspase-8 inhibitors for uveal melanoma and other cancers with activation of distal ETBR cascade

4. Develop novel inhibitors of T-reg

ENB Therapeutics
### ENB-003 Phase 1/2 POC clinical plan: 3 tumor basket trial

#### Part A
All comers with minimum 3 each of melanoma, pancreatic CA, ovarian CA: 1 week run-in with ENB-003 monotherapy followed by, ENB-003 + Pembro x 1 21 day cycle, Pembro alone x 1 21 day cycle (18 patients); 3+3 design, dose escalation 22 days after initial Pembro administration.

#### Part B₁
Expansion cohort to confirm safety of RPTD (12 patients), no run in.; ENB-003+ Pembro, and Pembro alone in alternating 21 day cycles

#### Part B₂
Expansion cohort at potential RPTD, no run in with ENB-003, ENB-003+ Pembro, and Pembro alone in alternating 21 day cycles, N= 25 M, 39 O, 39 Part B₁

### Dose Escalation Cohorts Part A Safety
- 1000ug N=3
- 750ug N=3
- 500ug N=3
- 300ug N=3
- 150ug N=3

### Expansion Cohort Part B₁ Safety
- N=12 (>2 each M, P, O)

### Expansion Cohort N=97

**Pembro**: pembrolizumab; **POC**: proof of concept; **RPTD**: recommended phase 2 dose
## Strong intellectual and regulatory exclusivity

All patents are 100% company-owned and unencumbered

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<thead>
<tr>
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<th>ENB-003</th>
<th>ENB-001</th>
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<tbody>
<tr>
<td>COM</td>
<td>U.S. Patent 10,435,434: Issued; estimated expiration date: approx. 1/11/2039</td>
<td>Formulation COM filed 2016-Nanoparticle formulation supports COM similar to NCE due to strict FDA guidelines regarding bioequivalence</td>
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<td>Method of use</td>
<td>Combination of ETBRi with anti-PD1 U.S. Patent 10,435,434: Issued; estimated expiration date: approx. 1/11/2039</td>
<td>Combination with anti-PD1 and other IO therapies for the treatment of cancer</td>
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<td>Companion diagnostic</td>
<td>IHC screen for ETBR and its ligands</td>
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<td>Orphan drug designation</td>
<td>Awarded by FDA for melanoma in 2019: provides 7-year market exclusivity post FDA approval, Application for Bladder CA and ovarian CA in preparation.</td>
<td>Awarded by FDA for melanoma in 2016: provides 7-year market exclusivity post FDA approval, Application for ovarian and bladder CA in preparation.</td>
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IHC: Immunohistochemistry
ENB's Advantage

**No selective ETBR inhibitors under development by other companies**

**Other TME-targeted therapies with enhancement of IO have high non-responder rates and little efficacy in anti-PD1 resistant tumors**

**ETBRi therapy targets multiple players in TME unlike single target therapies under investigation**

Our therapies should result in superior clinical efficacy

HDACi and DNMTi therapies with significant toxicity (>80% Grade 3/4 AEs), while BQ788 is safe for administration to healthy volunteers

AE: Adverse event
Funding

- **Funds raised to date**
  - $500K friends and family
  - $1M seed round closed 1Q 2018
  - Series A financing closed for $8M 3Q 2018

- **Seeking $25M Series B financing**
  - To support clinical development of ENB-003 through Phase 2
  - Preferred shares
### Milestones: Clinical development ENB-003

<table>
<thead>
<tr>
<th>Timeframe</th>
<th>R&amp;D</th>
<th>Regulatory</th>
<th>Capital</th>
<th>Inflection Points</th>
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<tbody>
<tr>
<td>2018 1H</td>
<td>cGMP production</td>
<td>Pre IND Meeting</td>
<td>$7 - $8M Series A</td>
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<tr>
<td>2018 2H</td>
<td>Pre clin wrap-up</td>
<td>IND Submis</td>
<td>Potential Exit</td>
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<td>2019 1H</td>
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<td>2019 2H</td>
<td>Phase 1b N=18</td>
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<td>2020 1H</td>
<td>Phase 2 N=109: 3 indications</td>
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Thank You

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