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 Inhibitors to reverse immunotherapy resistance

Strong and Broad IP and Regulatory Exclusivity

Soon-to-be Announced collaboration with big Pharma partner

Companion Diagnostic Identiﬁes ETBR and ET1 overexpression; patients most likely to respond

Short-Term Milestones
IND ﬁling 2Q 2019; PI/PII initiation 3Q 2019

Solid Leadership and Scientiﬁc Team
Scientiﬁc founders discovered the role of ETBR in metastatic spread of melanoma at NYU Medical Center in 1997

Capital and Time Efﬁcient Development Program
Clinical proof of concept within 12 months
# ENB Therapeutics snapshot

## Founded in 2015
- Focused on 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 1Q 2018
- Closed $8M Series A 3Q 2018 to support Ph1 trials
- Raising $25M 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 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

## Consultants
- **CMC-Vincent Bille, PhD,** Founder Marble Pharma Consulting, 1990-2007 UCB/Lonza, expertise in synthetic peptide manufacturing
- **Safety/Tox:** **Rashmi Sharma, PhD,** Camargo Pharm. Svcs. 16+ years industry experience in pre-clinical IND enabling study direction and management
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

IO: Immunotherapy; TIL: Tumor infiltrating lymphocytes; TME: Tumor microenvironment

Source: Teng et al, Cancer Research 2015
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
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
BQ788 (our parent compound) was originally developed as a research tool:

- **BQ788**: small molecule developed at Merck/Banyu in 1994 as a research tool (never commercialized)
- Compound has been safely administered in many human clinical trials to investigate endothelin axis in cardiovascular system
- Doses previously administered safely in humans are higher than anticipated therapeutic doses for cancer

Ishikawa et al, PNAS 1994
First-in-class ENB-001 and NCE ENB-003: 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

- **Orphan drug designation for melanoma awarded by FDA to ENB**

- **Low solubility, rapid plasma clearance**

**ENB003**
- Deuterium exchanged NCE derivative of BQ788
- COM filed 2018
- Enhanced PD profile
- Launch in initial target indications (non-CNS)

**ENB001**
- Nanoparticle formulation of BQ788-accelerated clinical path
- Strong IP- COM 2015
- ↑ Solubility, ↓ Plasma clearance
- Being developed to cross BBB for CNS malignancy

**BBB**: Blood-brain barrier; **CNS**: Central nervous system; **COM**: composition of matter; **CV**: Cardiovascular; **IP**: intellectual property; **NCE**: new chemical entity; **PD**: Pharmacodynamic
ETBR expression across multiple cancer types
The ETBR is a master regulator of melanoma progression

- ETBR is a melanoma tumor progression marker
  → Expression of ETBR, as well as ETBR-activating ligands ET-1/ET-3, increase during melanoma progression, forming an autocrine loop
- Promotes de-differentiation of melanoma cells
- Suppresses apoptosis by upregulating PARP-3 and BCL-2A1
- Activates intracellular kinases: MEK, RAF, AKT, FAK
- Upregulates key factors that promote melanoma progression: CXCL1, CXCL8, VEGF, MCAM, MMP-2, MMP-9, MTI-MMP, BCL21a, PARP-3, osteopontin, HIF-1 alpha, COX1/COX2, PGE2, GNAQ
- Downregulates factors that suppress melanoma invasion (e.g., E-cadherin)

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Source: Rosano et al, Nature Reviews Cancer 2013
ETBR is highly expressed on TAMs, PSCs and blood vessels in pancreatic cancer

**TAMs promote**
- Immune suppression
- Invasion/metastasis
- Vascular remodeling
- Chemotherapy resistance
- Tumorigenicity
- BQ788 blocks TAM function

**PSCs block**
- IO efficacy and cause desmoplasia, metastasis and chemoresistance
- PSC responsible for IO resistance in preclinical models of pancreatic cancer
- BQ788 blocks PSC function: and production of ECM and CTGF

**Grid map representation of ET-1, ETAR and ETBR expression in blood vessels**
- ETBR expressed on 31.5% of blood vessels in the TME

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CTGF: connective tissue growth factor; ECM: extracellular matrix; ETAR: endothelin receptor A; PCS: pancreatic stellate cell; TAM: tumor associated macrophage
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M. Jain, unpublished data, seminar video: https://youtu.be/e2yt_gJqZzk
ETBR blockade enhances IO efficacy and prolongs survival in preclinical models of lung and ovarian cancer by recruiting TILs

ETBRI stimulates T-cell infiltration and enhances IO efficacy in lung cancer model in mice

ETBRI stimulates T-cell infiltration and enhances IO efficacy in ovarian cancer model in mice

ETBRI prolongs survival in ovarian cancer model in mice

ETBR blockade overcomes resistance to MAPK pathway inhibitors

ETBRi suppresses drug resistance to BRAFi

ETBRi prevents outgrowth of drug-resistant cells

ETBRi enhances cell death induced by BRAFi

BRAFi: BRAF inhibition

Smith et al, EMBO Molecular Medicine 2017
Immune escape due to ETBR overexpression in TME correlates with cold tumors and poor survival across multiple cancer types

**Ovarian cancer**  

**Squamous cell carcinoma**  
Tanaka et al, British Journal of Cancer 2014

**Pancreatic cancer**  
Jain M, unpublished data, seminar video: [https://youtu.Be/e2yt_gjzzk](https://youtu.Be/e2yt_gjzzk)

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*Note: The images show survival distribution functions and overall survival rates with different ETBR expression levels.*
Switching immune-suppressed “cold” TMEs to “hot” TMEs
ETBRi MoA in cancer IO

- Our products block ETBR on the luminal surface of tumor blood vessels, which allows the transendothelial migration and homing of T-cells from the vessel to the tumor.

- The molecular mechanism involves upregulation of ICAM-1, which is required for T-cells to leave the circulation and infiltrate the tumor. → Activated T cells are then able to infiltrate the tumor and kill it.

- Our products also block ETBR expressed on the tumor cells, preventing metastatic spread.

**MoA**: mechanism of action
ETAR blockade abolishes TIL recruitment by BQ788

- Dual ETAR/ETBR antagonist macitentan fails to recruit CD8+ TILs or upregulate ICAM-1
- Addition of ETAR antagonist BQ123 blocks BQ788 from recruiting TILs and upregulating ICAM-1
- ALL previous attempts to target the endothelin axis in clinical trials utilized ETAR blockade

Coffman et al, Journal of Cancer Biology & Therapeutics 2013
ETAR blockade abolishes TIL recruitment by BQ788

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Coffman et al, Journal of Cancer Biology & Therapeutics 2013
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 (slide 17)*

- Previously tested SoC drug combinations using this model failed to shrink tumors and all resulted in eventual drug resistance (see next slide)

* Dosing regimen: 0.2mg/kg 3X per week IV, 6 doses total required for tumor eradication

Source: internal study, unpublished
ENB-003 overcomes anti-PD1 resistance in syngeneic melanoma model and eradicates tumors within 21 days

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**IV**: Intravenous; **SoC**: standard of care

*Dosing regimen: 0.2mg/kg 3X per week IV, 6 doses total required for tumor eradication*
ENB-003 + anti-PD1 combination show superior response to previous anti-PD1 combination studies with SM1 melanoma cell lines

- Published studies demonstrate lack of efficacy of anti-PD1 as a single agent in the SM1 cell line
- Treatment initiated when tumor sizes were much smaller than in our study (14-65 mm3 vs 150 mm3)
- Resistance emerged in all trial arms by day 25 post-tumor inoculation with no tumor elimination noted in any arms with any combination

![Graph showing tumor volume over time for different treatments](image)

Figure 1. Enhanced *in vivo* antitumor activity with dabrafenib (D) + trametinib (T) combined with PD-1 checkpoint blockade against SM1 tumors. *In vivo* tumor growth curves. SM1 bearing C57BL/6 mice were treated when tumors were 3–5 mm with D 30 mg/kg and T 0.15 mg/kg combination via oral gavage daily, 4 doses of 200 μg of anti-PD-1 (PD-1), D + PD-1, T + PD-1, D + T + PD-1, D + T + anti-CD137 (CD137), PD-1 + CD137 or vehicle + isotype control Ab (4 mice in each group). This is representative graph of a three times repetition of this experiment.

Homet Moreno et al, *Oncoimmunology* 2015

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Creating intratumoral TLOs
TLO formation is associated with favorable clinical prognosis and response to IO therapy

“…within the tumor microenvironment of TLSs, whose presence has a positive impact on tumor prognosis. TLSs are transient ectopic lymphoid aggregates displaying the same organization and functionality as canonical secondary lymphoid organs, with T-cell-rich and B-cell-rich areas that are sites for the differentiation of effector and memory T cells and B cells”

– Germain et al, Frontiers in Immunology 2015

“TLSs present in human solid tumors are essential for the shaping of a favorable immune micro-environment to control tumor development in most cases. They represent a formidable school for T-cell priming, B cell activation, and differentiation into plasma cells and an exquisitely located factory for antibody production. The manipulation of TLS neogenesis and maintenance represents, therefore, an exciting task to set up efficient anti-cancer vaccine strategies leading to long lasting anti-tumor adaptive responses.”

– Teillaud et al, Frontiers in Immunology 2017

TLS: Tertiary lymphoid structure
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

TLO (Hi mag)

anti-PD1+ENB-003- No residual tumor

** 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

*brown stain
High magnification reveals mature adipocytes, with no tumor cells evident in ENB-003- + anti-PD1-treated melanoma tumor
ENB-001 + anti-PD1 combination reproduces tumor eradication and TLO formation observed with ENB-003 in SM1 model

TLO formation observed with broad dosing range of ENB-001 and ENB-003

Source: Internal study, unpublished
Business model

Develop and launch ENB-003 for primary indication(s) (non-CNS melanoma, ovarian CA, or pancreatic CA).

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

Develop fast-follower second-generation novel ETBR antagonist analogues for extended clinical opportunities.

Develop caspase-8 inhibitors for uveal melanoma and other cancers with activation of distal ETBR cascade and category 2 cancers.

Develop novel inhibitors of T-regs.
## A platform for sequenced immuno-oncology growth opportunities

<table>
<thead>
<tr>
<th>CATEGORY 1 CANCER</th>
<th>CATEGORY 2 CANCER</th>
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<tbody>
<tr>
<td>ETBR+ CANCER CELL, ETBR+TME</td>
<td>ETAR+ CANCER CELL, ETBR+TME</td>
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<td>Melanoma*</td>
<td>Ovarian*</td>
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<td>Astrocytoma</td>
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<td>Pancreatic CA*</td>
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<td>Small cell lung</td>
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<td>Esophageal CA</td>
<td>Thyroid CA</td>
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<tr>
<td>Bladder CA</td>
<td>Gastric CA</td>
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<tr>
<td>Vulvar CA</td>
<td>CNS Lymphoma (ETBR+ TME)</td>
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</table>

| ENB-001 inhibits metastasis and recruits TILs | ENB-001 recruits TILs (Addition of caspase-8 inhibitor to block metastasis downstream of ETAR without causing immunosuppression) |

**CA**: Cancer

*First anticipated indications*
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

**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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<th>ENB-003</th>
<th>ENB-001</th>
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<tbody>
<tr>
<td>COM</td>
<td>Provisional COM patent filed 2018</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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<tr>
<td>Method of use</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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<tr>
<td>Orphan drug designation</td>
<td>Application for melanoma in preparation</td>
<td>Awarded by FDA for melanoma in 2016: provides 7-year market exclusivity post FDA approval</td>
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**IHC:** Immunohistochemistry
## Competitive landscape

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<tr>
<th>Drug Class</th>
<th>ETBRi</th>
<th>VEGFi</th>
<th>IDOi</th>
<th>CXCR4i</th>
<th>Adenosine Ri</th>
<th>HDACi</th>
<th>DNMTi</th>
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<tr>
<td>Drug name(s)</td>
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**CAF:** cancer-associated fibroblast; **DNMTi:** DNA methyltransferase inhibitor; **HDACi:** Histone deacetylase inhibitor; **IDOi:** Indoleamine inhibitor; **TAN:** tumor-associated neutrophil; **VEGFi:** vascular endothelial growth factor inhibitor
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 significant toxicity (>80% Grade 3/4 AEs), while parent compound BQ788 is safe for administration to healthy volunteers

AE: Adverse event
Milestones: Clinical development ENB-003

- **2018 1H**: Pre clin wrap-up
- **2018 2H**: cGMP production
- **2019 1H**: IND enabling studies
- **2019 2H**: Phase 1b N=18
- **2020 1H**: Phase 2 N=124: 3 indications
- **2020 2H**: Pre IND Meeting
- **2021 1H**: IND Submission
- **Capital**: $7 - $8M Series A, $25M Series B
- **Inflection Points**: Potential Exit
Funding

- **Funds raised to date**
  - $500K friends and family
  - $1M seed round closed 1Q 2018
  - Series A financing closed for $7M-$8M 3Q 2018

- **Seeking $25M Series B financing**
  - To support clinical development of ENB-003 through Phase 2
  - Preferred shares
Blazing a trail that benefits patients and investors

- Company founded to exploit the recent discovery that selective B receptor blockade is required for efficacy - all previous attempts to block endothelin axis failed due to non-selective A/B blockade
- Well understood MOA
- Robust preclinical efficacy across multiple cancers with tumor eradication
- Favorable clinical safety profile of parent compound
- Lead molecule, NCE ENB-003 ready for IND enabling studies
- Potentially synergistic with multiple immunotherapy platforms
- Block resistance to MAPK pathway inhibitors
- ENB-001 in development to deliver compounds across the BBB
- Only class of therapeutic known to induce intratumoral Tertiary Lymphoid Organ (TLO) formation for long term anti-cancer immunity
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Potential First and Best-in-Class Selective Endothelin B Receptor (ETBR) Inhibitors to reverse immunotherapy resistance

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Solid Leadership and Scientific Team Scientific founders who discovered role of ETBR in metastatic spread of melanoma at NYU Medical Center in 1997

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Contact: sjamal@enbpharma.com