Reprogramming the Tumor Microenvironment to treat drug resistant cancers

Q3 2022
Forward looking statements

This presentation may contain forward-looking statements. These statements include but are not limited to words like "may", "expects", "believes", anticipates", “scheduled”, and "intends", and describe opinions about future events. These forward-looking statements involve known and unknown risks and uncertainties that may cause the actual results, performance or achievements of ENB Therapeutics to be materially different from any future results, performance or achievements expressed or implied by such forward-looking statements.
Company highlights

Privately held clinical stage company
Focused on treating drug resistant cancers

Potential First and Best-in-Class Lead program ENB-003: Selective ETBR Inhibitor, oncology platform molecule to overcome immunotherapy resistance in multiple oncology indications

Clinical trial collaboration with Merck
For Ph1/Ph2 trial with lead product ENB-003 in combination with pembrolizumab
Currently seeking other pharma partnerships

40% Clinical benefit in drug resistant patients in ongoing international Ph 1 dose finding trial

Broad and Growing IP Portfolio
Technology 100% company-owned, Issued COM & MOU patents with 2039 expiry, regulatory exclusivity with Orphan Drug Designation granted, Pipeline with novel 2nd gen compounds in development

Experienced Leadership and Scientific Team
Endothelin pathway studies spanning over 25+ years

Time Efficient Development Program
Ph2 initiation anticipated Q1 2023, clinical proof of concept within 12 months

ETBR: endothelin B Receptor; COM: composition of matter; MOU: method of use
Leadership

Sumayah Jamal, MD-PhD
President, CSO, Co-Founder

Robert J. Schneider, PhD
Co-Founder, Chair SAB

Sandy Harm, MBA
COO

Rita Laeufle, MD-PhD
CMO

25+ years focused on endothelin axis, co-inventor on first patents filed covering the ETBR as a therapeutic target for cancer, work conducted as a PI at NYU School of Medicine serves as the foundation for the company’s drug development programs

Senior scientist at NYU School of Medicine, Former Assoc. Dean for Therapeutics Alliances, Assoc. Dir. NYU Cancer Institute, co-founded multiple successful biotech companies (Imclone, Canji, PTC Therapeutics)

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)

18+ years industry veteran
Surgical oncologist, immuno-oncology drug development, clinical trial design, strategic partnerships, FDA IND experience. Former Genentech (Sr. Med. Dir. - GI cancers), Roche (Sr. Med. Dir. Avastin/ breast cancer), Novartis and biotech experience at CMO level.

Advisory Board

- **Ryan Sullivan, MD**, Leading melanoma investigator, Assoc. Dir Melanoma Program; member: Teermer Center for Targeted Therapy at MGH/Harvard Medical School
- **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.
- **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
- **Kim Nearing, MSc**, 20+ years biopharmaceutical experience- finance, operations, IR. Venture partner BVCF, Harvard trained, strong biotech fundraising track record, Board seats: Esthimos, BayHelix, others
- **Jay Gibbs, PhD**, 30+ years in Pharma, expertise in oncology drug development, former Scientific Dir. At Astra Zeneca and Merck
- **Adriann Sax**, 30 years pharma, Roche, BMS, Merck
ENB-003: A platform technology molecule creating new IO market opportunities

• Our therapeutic target, the ETBR, creates a barrier that prevents T-cells from infiltrating and killing tumors

• This barrier prevents immuno-oncology agents like Keytruda (pembrolizumab) from working

• ENB-003 allows Keytruda to target indications that are currently untreatable

• ENB-003 + Keytruda combination with encouraging preliminary clinical efficacy in drug resistant pancreatic cancer and drug resistant ovarian cancer which don’t respond to single agent Keytruda* => potential $7B market opportunity with these two indications alone

* Excludes the MSI-H/dMMR phenotype
The endothelin B receptor is a novel immune checkpoint inhibiting T-cell trafficking

- ETBR creates a barrier to immune cell trafficking resulting in "cold" tumors across multiple cancer types

- Immune therapies like anti-PD1 and CAR-T don’t work in solid tumors if T-cell infiltration is blocked

- Selective B receptor inhibitors restore the ability of T-cells to leave the circulation and infiltrate tumors

- This in turn enhances IO efficacy

- Approved non-selective endothelin inhibitors fail to stimulate T-cell infiltration (eg: Bosentan, Macitentan)
  - Only selective ETBR inhibitors enhance T-cell trafficking
  - We are the first to bring a selective ETBRi to the clinic
  - ENB-003 First-in-class ETBRi

**ETBRi**: endothelin B Receptor inhibitor; **TILs**: endothelin B Receptor inhibitor
Only 45% of cancer patients are eligible for anti-PD1/PDL1 therapy and of those, ~15% achieve an objective response

- ENB-003 is the key to unlock the full therapeutic potential of anti-PD1 and other IO agents in ETBR+ cancers
  - ETBR (endothelin B receptor) is a cell surface receptor highly expressed in over 40% of all cancers, expression correlates with poor survival and tumors that lack T-cells (cold tumors)
  - ENB-003 blocks ETBR and increases sensitivity to immuno-oncology agents by targeting multiple cell types in the tumor microenvironment
  - Small molecule, potential synergy with multiple immuno-oncology platforms
- Mechanism of action: ENB-003 Creates the “ultimate hot tumor”
  - Drugs like Keytruda don’t work in “cold” tumors that lack T-cells- ENB-003 when combined with anti-PD1 therapy, creates the ultimate hot tumor by not only stimulating T-cell infiltration but also stimulating B-cell infiltration and the formation of new lymph nodes (TLOs) that contain tumor fighting T-cells and B-cells that eradicate tumors
ENB-003 is unique in its multipronged effect on the tumor microenvironment despite very active clinical landscape around immune checkpoint combinations.

1. Creates the **ultimate hot tumor** by reprogramming the tumor microenvironment and inducing TLO formation.

2. Blocks invasion and metastasis.

3. Blocks the function of immunosuppressive cancer associated fibroblasts (CAFs) and tumor associated macrophages (TAMs).

- **ETBR**
- **CAFs** promote resistance to immune checkpoint inhibitors and chemotherapy, block the function of immune cells required for anti-tumor activity (NK and cytotoxic T cells and dendritic cells).
- **TAMs** inhibit T-cell function and promote metastasis.
Phase 1/2 clinical trial design

• **Ongoing Phase 1B** study to determine safety of ENB-003 in combination with pembrolizumab
  - Enrolling up to 23 subjects; all comers with minimum 3 each of anti-PD1 resistant melanoma, chemoresistant pancreatic cancer and chemoresistant ovarian cancer
  - Endpoints: safety and tolerability, clinical response; Multi-center open label, topline results expected July 2022

• **Phase 2** study to determine efficacy and safety of ENB-003 in combination with pembrolizumab
  - Enrolling up to 125 anti-PD1 resistant melanoma, chemoresistant pancreatic cancer and chemoresistant ovarian cancer, + 6 sarcoma patients
  - Endpoints: clinical response, safety and tolerability, anticipated start Q1 2023
  - Anticipated response rate to single agent pembrolizumab is 0% for eligible melanoma, pancreatic cancer, and platinum refractory ovarian cancer, 8% for platinum resistant ovarian cancer

• **Robust pre-clinical proof of concept for all 3 target indications**
\[\text{Target indication 1: anti-PD1 resistant unresectable metastatic melanoma}\]

\text{ENB-003 eradicates tumors in an anti-PD1-resistant syngeneic melanoma model within 21 days:} Previously tested standard of care drug combinations using this model failed to shrink tumors and all resulted in eventual drug resistance.

See next slide for Tertiary Lymphoid Organ (TLO) formation from this study.
ENB-003 + anti-PD1 combination eradicates tumors, promotes intratumoral TLO** formation: A hallmark for IO responsiveness

Untreated control: paucity of CD8+ T-cells (stain brown)

Anti-PD1+ dabrafenib: Increase in CD8+ T-cells, predominantly peripheral distribution

Anti-PD1+ENB-003- No residual tumor

TLO (Hi magnification)

**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
Target indication 2: chemoresistant unresectable Pancreatic CA

ENB-003 + anti-PD1 combination is superior to standard of care Folfirinox in a syngeneic pancreatic cancer model*

No tumor growth with ENB-003/anti-PD1 combination at 22 days of orthotopic study in pancreatic cancer model

*The UN-KC-6141 model was derived from a pancreatic tumor of a Kras(G12D);Pdx1-Cre (KC) mouse at 51 weeks of age.
Target indication 3: Platinum-refractory/ Platinum resistant epithelial Ovarian CA

anticipated response rate to single agent pembrolizumab: refractory/ resistant= 0%/8%

ENB-003 enhances anti-PD1 efficacy in a syngeneic ovarian cancer model*

~15,000 patients diagnosed with advanced disease annually

~13,000 will be platinum refractory or resistant

~9,900 addressable US patients estimated ETBR+

*ID8-VEGF model, ENB-003 administered 3X per week for a total of 6 doses,
Phase 1B clinical highlights: Encouraging responses in immunotherapy resistant patients with high unmet need

**ENB-003+Keytruda**

- **40% of patients with clinical benefit** in heavily pre-treated drug resistant patients despite not yet achieving IC50 for ENB-003
  - ETBR engagement confirmed via pharmacodynamic assays
- **No serious adverse events** caused by ENB-003
- **95% reduction in tumor burden** in a platinum refractory ovarian cancer patient durable out to a year (anticipated response rate to single agent Keytruda is 0%, other OC patients: mPFS ~ 2 mos, max PFS 6 mos)
- **7-month arrest of disease progression** in a tonsillar SCC patient who had previously failed anti-PD1
- **100% clinical benefit in ovarian cancer**
- **75% of pancreatic cancer patients with shrinkage of target lesions as best response**
- **100% of melanoma patients with stabilization of target lesions as best response**

**Serial CT scans from platinum refractory ovarian cancer patient with durable 100% response of peritoneal tumor**

*ENB retains all rights to ENB-003 under the collaboration agreement with Merck*
*We are actively seeking pharma partners*
First-in-class NCE ENB-003 and 2nd gen compounds: potential synergy with multiple immuno-oncology platforms

ENB’s growing pipeline of small molecule ETBRIs have the potential to enhance efficacy of multiple immune based therapies including but not limited to anti-PD1/anti-PDL1, CAR T, TIL therapy and cancer vaccines

- **ENB003**: Highly potent and selective ETBRi, ongoing Phase 1 trial to assess safety in combination with pembrolizumab in advanced ETBR+ solid tumors, COM and MOU patents issued with 2039 expiry, orphan drug designation for melanoma and pancreatic cancer

- **ENB004-6**: 2nd gen highly potent and selective orally bioavailable novel ETBRI with favorable PK properties

- Ongoing efforts in progress to develop compounds that can cross the BBB to treat CNS malignancies that express high levels of ETBR (e.g.: glioblastoma)

**BBB**: Blood-brain barrier; **CNS**: Central nervous system; **NCE**: new chemical entity; **PK**: Pharmacokinetic; **COM**: composition of matter; **MOU**: method of use
Competitive landscape with sparse in-class competition

Superior safety profile makes ENB-003 an ideal agent for combination therapy (far less toxic than anti-VEGF therapies)

Only 1 other company currently developing ETBRIs*-preclinical stage (target previously validated by Roche/Genentech’s ETBR-ADC)

Reprogramming the TME: multipronged targeting to elicit an immunodominant effect with TLO formation

Clinical trial with 3 shots on goal: multiple indications increase chance of success and potential valuation upon an exit

Potential to enhance efficacy multiple immune-based therapies: anti-PD1, anti-PDL1, anti-CTLA4, TIL therapy, CAR-T therapy, cancer vaccines

* Lassogen
AE: Adverse event
Milestones and timelines

*The 5 patient subsets that will be tested for futility are: 1) Chemoresistant pancreatic cancer; 2) anti-PD1-resistant melanoma, wt-Braf; 3) anti-PD1-resistant melanoma, mut-Braf; 4) Platinum refractory ovarian cancer; 5) Platinum resistant ovarian cancer.*
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