ENB Therapeutics

OVERCOMING IMMUNOTHERAPY RESISTANCE

Two unique mechanisms that target the tumor microenvironment

ENB-003 FIRST-IN-CLASS ENDOTHELIN B RECEPTOR ANTAGONIST

Blazing a trail that benefits patients and investors

Potential First and Best-in-Class
Selective ETBR Inhibitor ENB-003 to reverse immunotherapy resistance-novel approach to targeting the endothelin axis

Broad and Growing IP Portfolio
and Regulatory Exclusivity with Orphan Drug Designation granted

Clinical trial collaboration with Merck
For Ph1/Ph2 combination trial with lead product ENB-003 and pembrolizumab

Companion Diagnostic
In development with Roche Ventana

IND approved for Ph1/2 trials
Ph1 in progress, Ph2 anticipated Q1 2021

Experienced Leadership and Scientific Team
Endothelin pathway studies spanning over 20+ years

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

ETBR: endothelin B Receptor

ENB Therapeutics snapshot

Overview

- Clinical stage privately held company focused on cancer therapies to overcome immunotherapy resistance
- Ongoing Ph1/Ph2 combination trials with ENB-003 and Keytruda in platinum refractory/resistant ovarian, pancreatic cancer and anti-PD1-resistant melanoma
- Based in NYC Alexandria Center for Life Science LaunchLabs incubator
- Technology originally developed at NYUSOM- key patents unencumbered and 100% company-owned
- Small molecule lead product ENB-003 targets TME and tumor cells
- Discovery efforts for 2nd gen ETBR inhibitors ongoing
- Currently raising a $30M Series B to support our Phase 2 clinical trial

Senior Management Team

- **Sumayah Jamal, MD-PhD, President, CSO, Co-founder:** 30 years research experience, **20+ 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 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, Assoc. Dir. NYU Cancer Institute, 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)
- **Francois Wilhelm, MD-PhD, CMO:** 30+ years experience in R&D in oncology/hematology. Multiple IND and NDA submissions. Roche, J&J, P&G. 8 years biotech experience as CMO

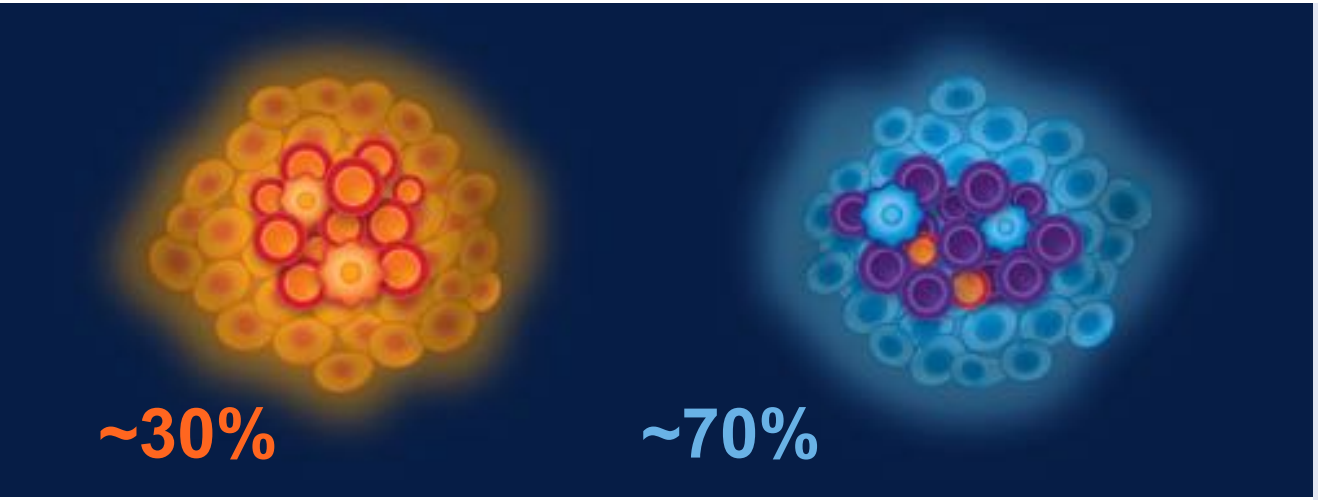
Scientific Advisors

- **Ryan Sullivan, MD** Dana Farber/ Harvard Cancer Center, leading melanoma investigator, member Center for Melanoma and Teermer Center for Targeted Therapy at MGH
- **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

Consultants

- **CMC: Vincent Bille, PhD; Regulatory: Diane Jackson-Matthews, PhD**

Unmet need: The majority of cancer patients do not respond to IO



Hot Tumors

- Have T-cells and cancer fighters
- Respond to checkpoint therapies

Cold Tumors

- Have immunosuppressive cells
- Have few or no T-cells
- Do not respond to checkpoints therapies

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

- 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

Checkpoint non-response in 60-90% of cases

TUMOR TYPE	% of checkpoint non-responders
MELANOMA	**~60%**
OVARIAN CANCER	**~92%**
PANCREATIC CANCER	**~100%**

Targeting immunotherapy resistance

Novel approach to targeting the endothelin axis

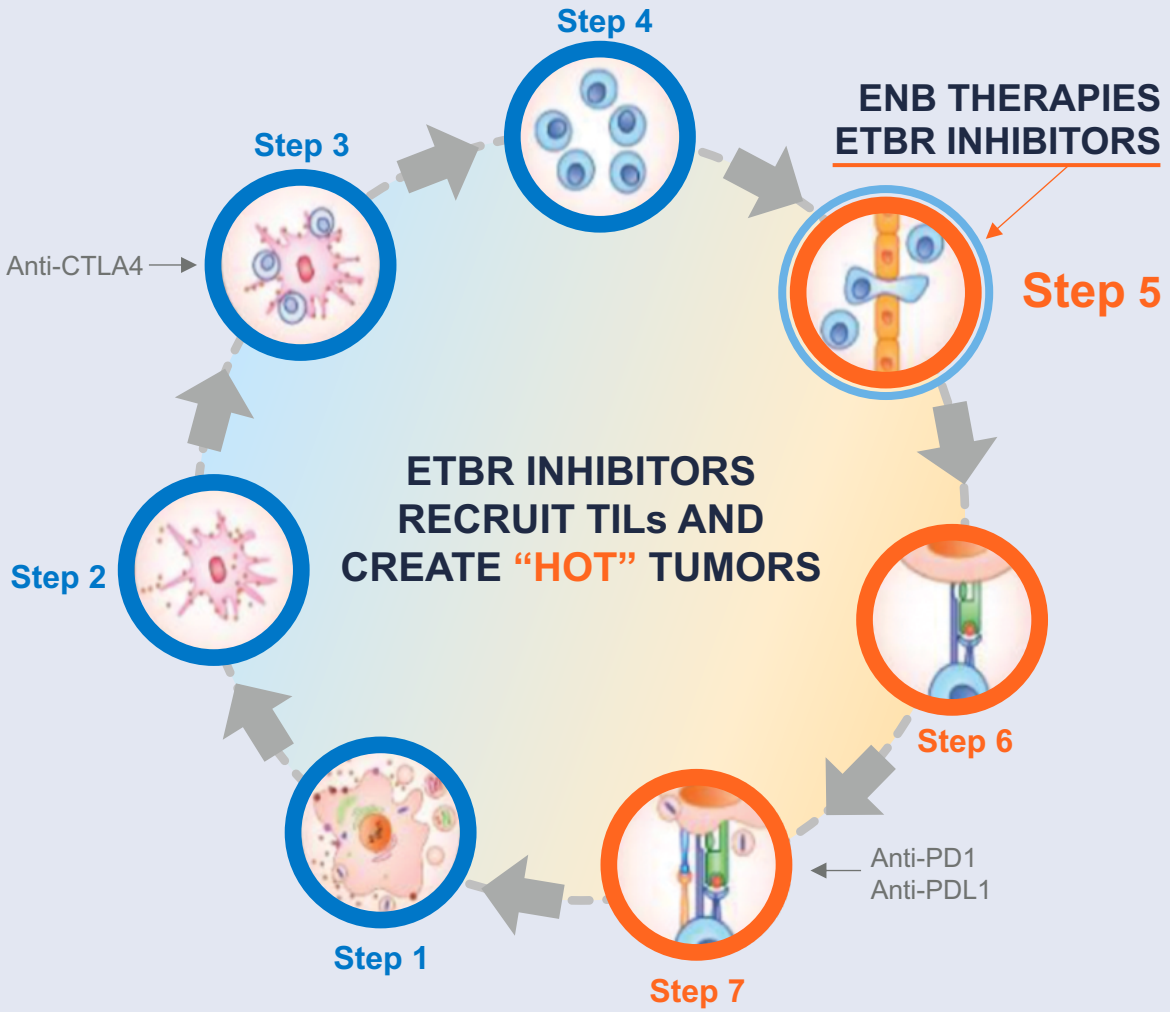
- We are the first group to bring a **selective Endothelin B receptor inhibitor** to clinical trial for cancer- B selectivity required to convert TIL- tumors to TIL+ tumors

  → Previous attempts to target the endothelin axis used A receptor inhibitors or A/B dual receptor inhibitors which block TIL infiltration (see slide 28)

- 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

ETBR: endothelin B receptor

Switching TIL- tumors to TIL+ tumors



~13,000

patients diagnosed with advanced disease annually[1]

~7,800

will be anti-PD1 resistant[2]

~7,000

addressable US patients estimated ETBR+

Target Indication: anti-PD1 resistant metastatic unresectable melanoma

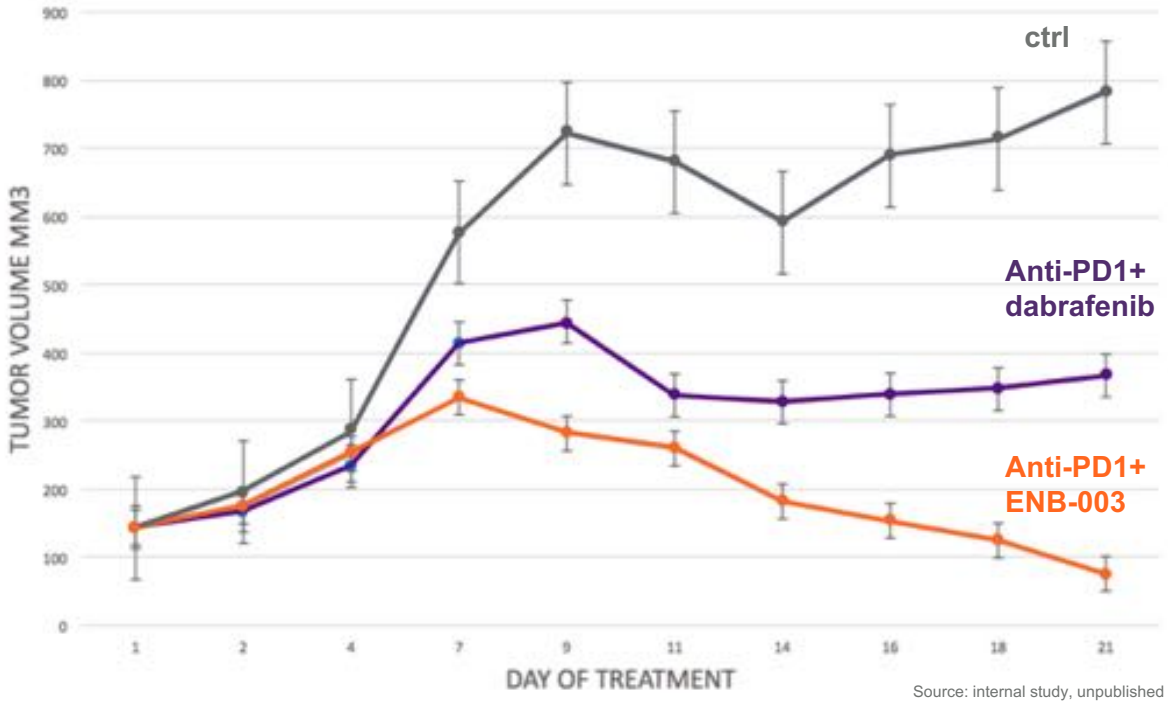
- ETBR is upregulated during melanoma progression[3]
- ETBRI stimulated TIL infiltration in melanoma clinical study[4]
- Retreatment with checkpoint inhibitors or chemotherapies post progression on anti-PD1 and BRAF/MEK: ORR: 4-10%[5,] OS ~7-8 months[6]

Market opportunity: ENB-003+anti-PD1 as 2L treatment for advanced ETBR+ melanoma patients who have failed anti-PD1 therapy (both wtBRAF and BRAFV600E).

May eventually become 1L if ETBR+ is predictive of anti-PD1 resistance

Notes:
1. SEERcancer.gov
2. Keynote-006
3. . Lahav et al. Cancer Research 64, 8945-8953; Dec. 15, 2004
4. Wouters et al The Oncologist 20: 1121 (2015)
5. CheckMate-37 Trial Results (ICC 10%), Keytruda label (4%)
6. Eur J Cancer. 2016; 65:182-184. J Clin Oncol. 2018; 36 (suppl: abstr e21588)

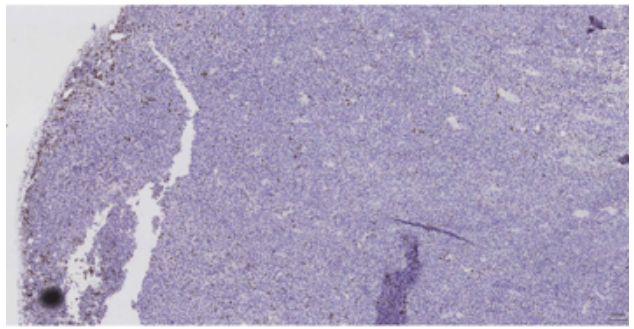
ENB-003 overcomes anti-PD1 resistance in a syngeneic melanoma model and eradicates tumors within 21 days: Previously tested SoC drug combinations using this model failed to shrink tumors and all resulted in eventual drug resistance (see slide 29)



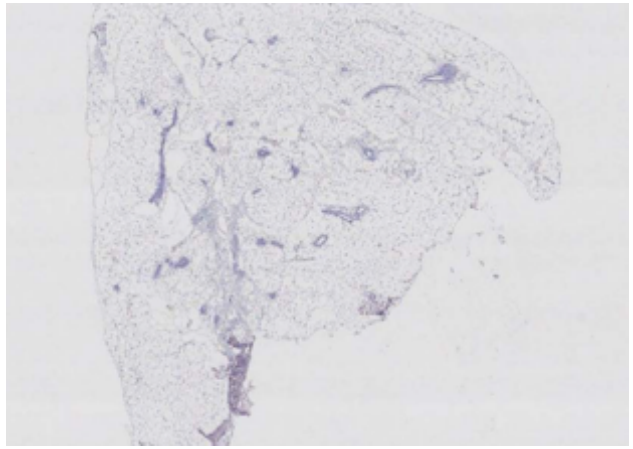
Source: internal study, unpublished

ENB-003 + anti-PD1 combination eradicates tumors, promotes intratumoral TLO ** formation: *A hallmark for IO responsiveness (see slides 39,40)*

Untreated control: paucity of TILs

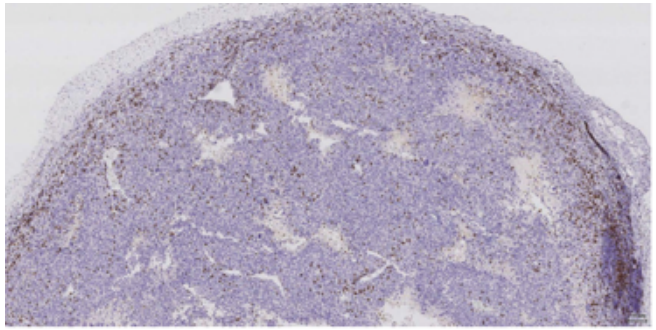


anti-PD1+ENB-003- No residual tumor

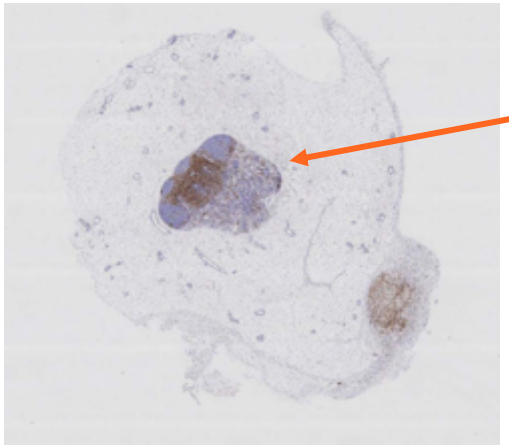


*brown stain

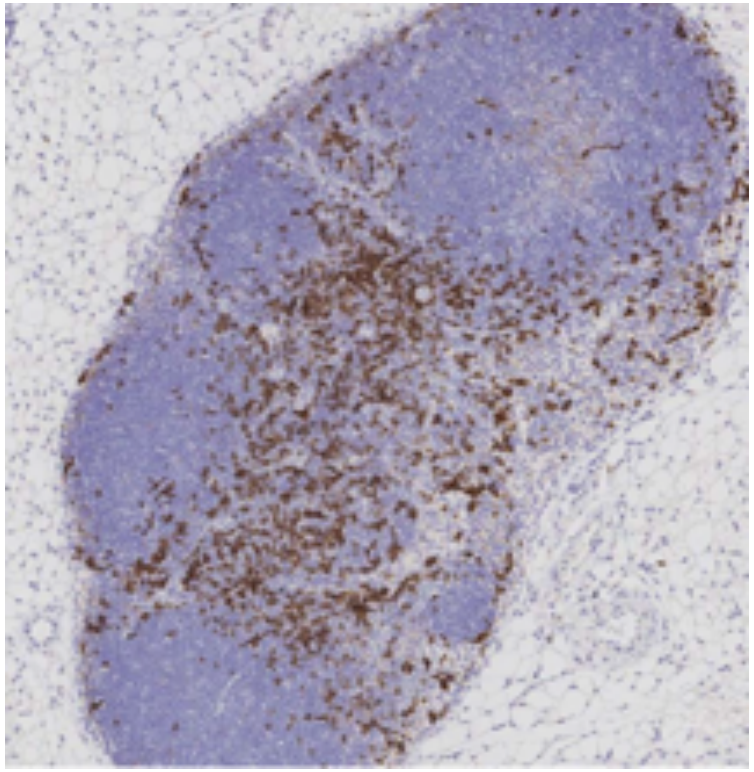
Anti-PD1+ dabrafenib: Increase in TILs, predominantly peripheral distribution



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



TLO (Hi mag)



** 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

~15,000

patients diagnosed with advanced disease annually[1]

~13,000

will be platinum refractory or resistant[2]

~9,900

addressable US patients estimated ETBR+[3]

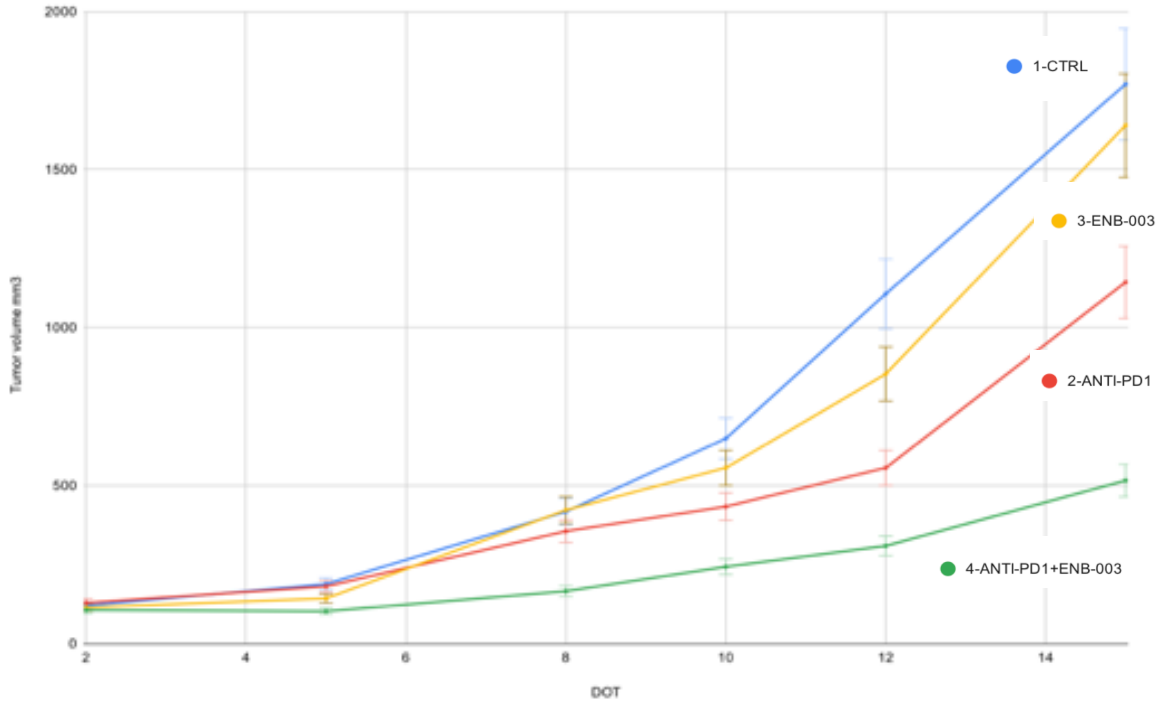
Target Indication: Platinum-refractory/ resistant epithelial Ovarian CA

- ETBR upregulation has been observed in ovarian cancer and predicts poor outcome and lack of TILs[3]
- Anti-PD-1 in advanced platinum resistant setting reported ORR 7%[4]
- Median OS of patients with platinum refractory/resistant disease is 12 mos[5]

Market opportunity: ENB-003+anti-PD1 as 2L treatment for ETBR+ platinum refractory/resistant ovarian cancer

If ETBR+ is predictive of platinum resistance then may become 1L for all advanced ETBR+ ovarian cancer

ENB-003 overcomes anti-PD1 resistance in a syngeneic ovarian cancer model: ENB-003 synergizes with anti-PD1 in effecting tumor growth inhibition



Notes:
1. seer.gov
2. Damia, et al. Cancers 2019, 11, 119; doi:10.3390/cancers11010119
3. Coukos et al, Nature Medicine Jan 2008; vol 147
4. Pembrolizumab, Matulonis, UA, ASCO 2018, 6/2/08, KEYNOTE-100
5. Pujade-Lauraine et al J. Clin. Oncol. 37⊗27): 2437 (20190

~46,000

patients diagnosed with unresectable disease annually[1,2]

~44,000

will be anti-PD1 resistant[3]

~26,000

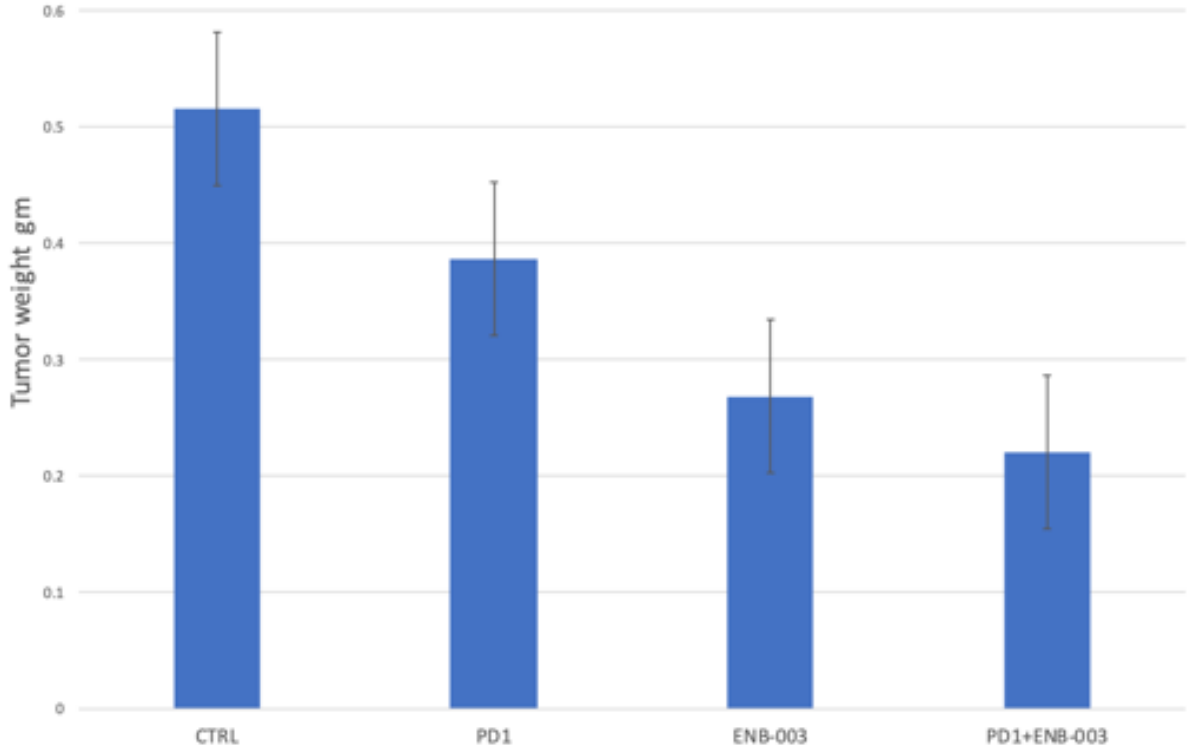
addressable US patients estimated ETBR+

Target Indication: unresectable Pancreatic CA

- 58% of pancreatic cancer tumors express high levels of ETBR (0%normal tissues[4])
- ETBRi inhibits PAC growth, TAM function and stellate cell function *vitro*[5]
- 5-year survival for distant stage disease is 3%[1]
- ORR to anti-PD1 is 0% (excluding excluding MSI-H or dMMR phenotype)

Market opportunity: ENB-003+anti-PD1 +/- chemo as 2L treatment for ETBR+ chemoresistant pancreatic cancer

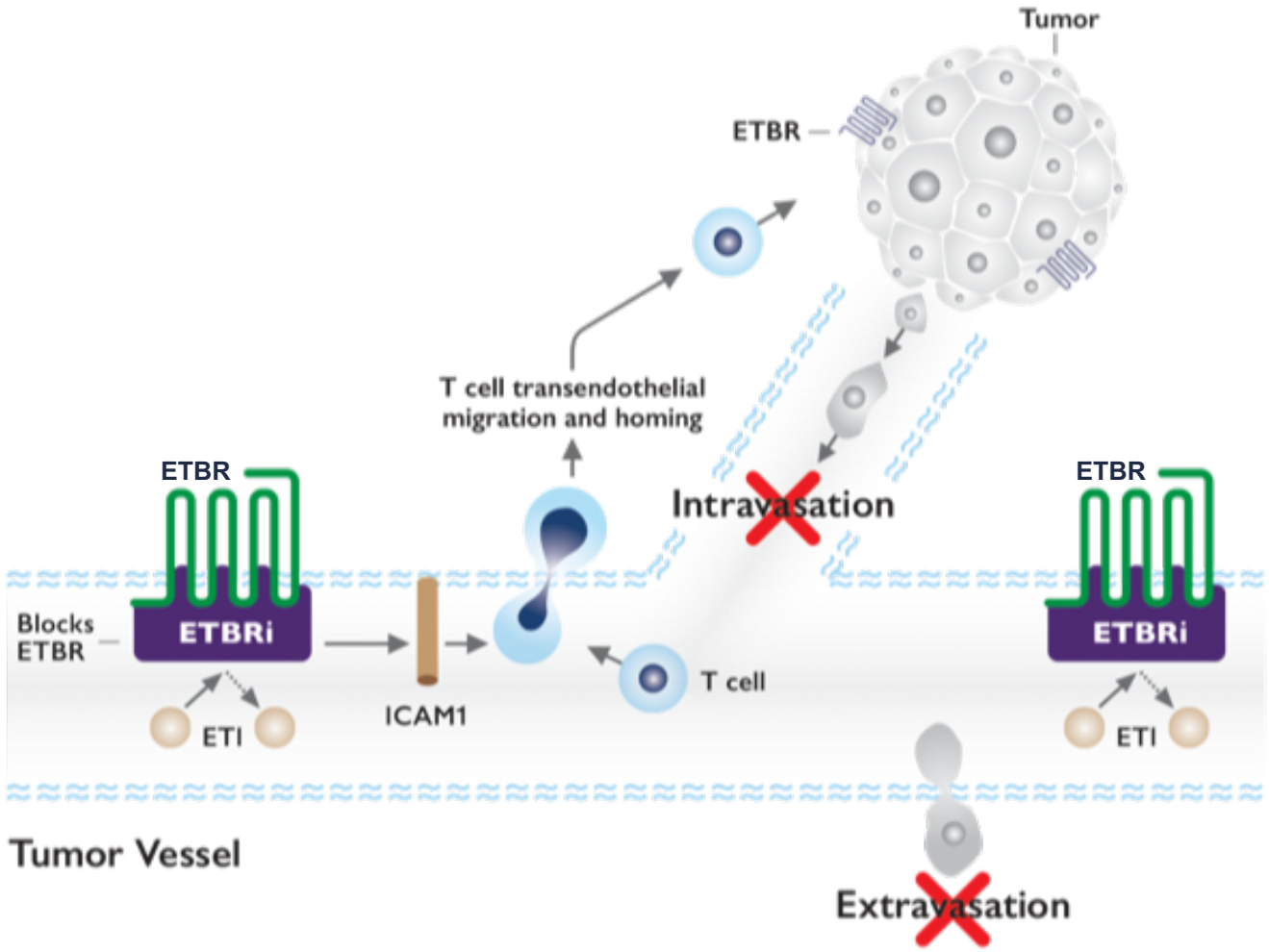
ENB-003 synergizes with anti-PD1 in a syngeneic orthotopic pancreatic cancer model:
ENB-003 with some single agent activity that is enhanced when combined with anti-PD1



Notes:
1. seer.gov
2. Malik et al J. Gastrointest. Oncol. 3(4): 326 (2012)
3. Pu et al J. Pancreatooguy 2(1): 6 (2019)
4. Soares et al J Immunother.38(1):1–11 (2015)
5. https://digitalcommons.unmc.edu/cgi/viewcontent.cgi?article=1207&context=etd

ETBRi MoA in cancer IO

- ENB-003 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

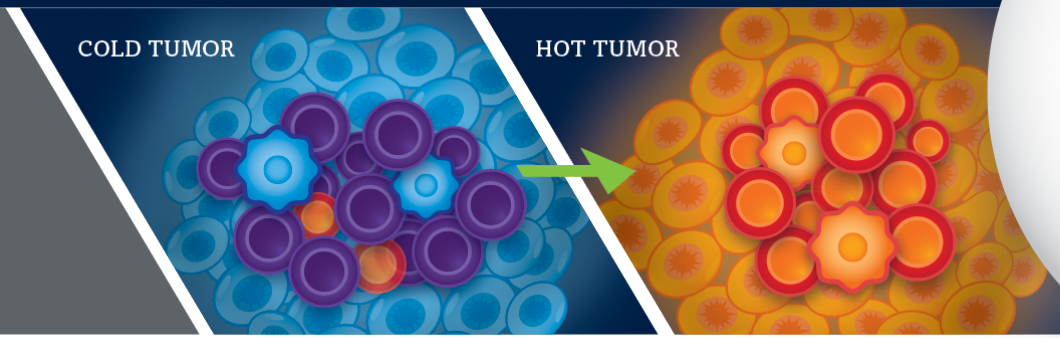


MoA: mechanism of action

Overcoming IO resistance across multiple cancer types

Selective ETBR inhibition targets the TME through two unique mechanisms

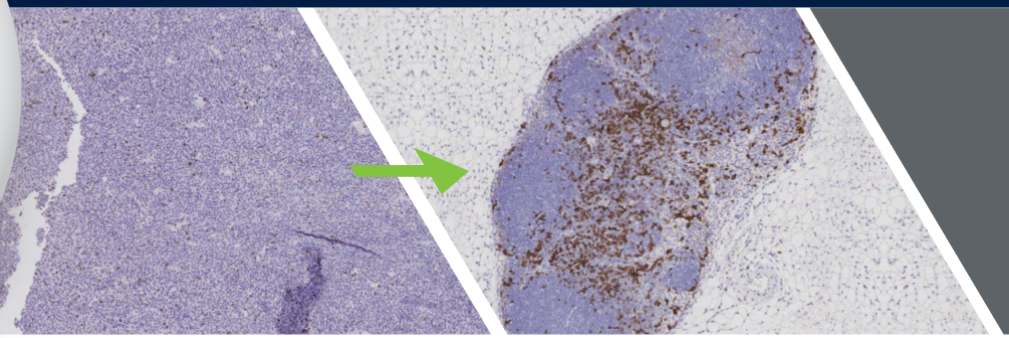
1. Switching immune-suppressed “cold” TMEs to “hot” TMEs, allowing TILs to infiltrate tumors



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

ENB Therapeutics

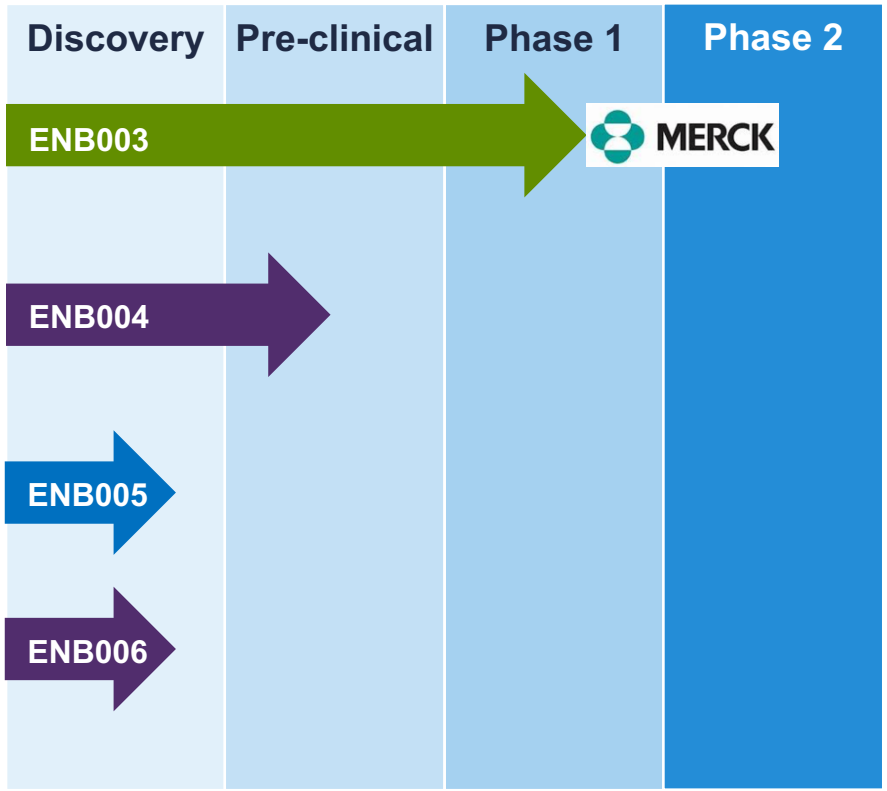
2. Creating new intra-tumoral TLOs that release T- and B-cells to destroy cancer cells



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 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
- ENB004: 2nd gen highly potent and selective orally bioavailable novel ETBRI with favorable PK properties
- ENB005: 2nd gen compound being developed to cross the BBB to target ETBR+ CNS malignancies such as glioblastoma, CNS lymphoma and melanoma that has metastasized to the brain
- ENB006: nanoparticle formulation of ENB003 being developed to enhance CNS penetration

BBB: Blood-brain barrier; **CNS:** Central nervous system; **NCE:** new chemical entity; **PK:** Pharmacokinetic

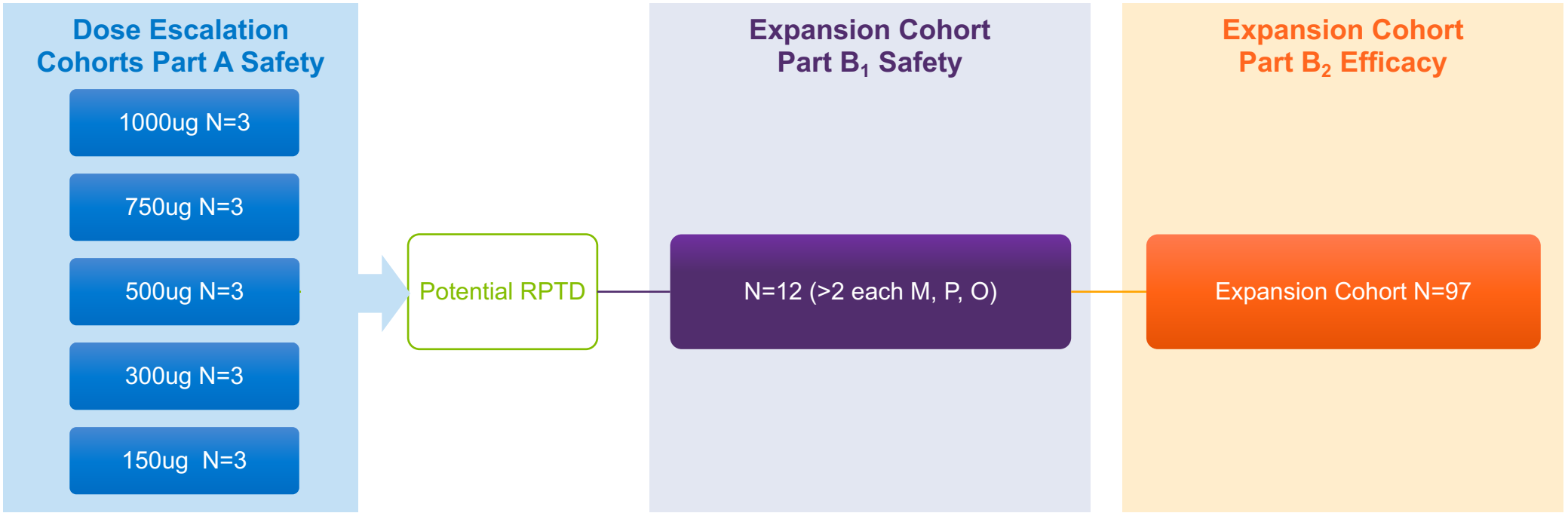
ENB003 with strong intellectual and regulatory exclusivity

All patents are 100% company-owned and unencumbered

Composition of Matter	**U.S. Patent 10,435,434: Issued; estimated expiration date: approx. 1/11/2039**
Method of Use	Combination of deuterated ETBRi with anti-PD1 U.S. Patent 10,435,434: Issued; estimated expiration date: approx. 1/11/2039; Combination of any ETBRi with any immune checkpoint inhibitor for cancers metastatic to brain- notice of allowance 6/2020
Companion diagnostic	IHC screen for ETBR and its ligands
Orphan drug designation	Awarded by FDA for melanoma in 2019: provides 7-year market exclusivity post FDA approval. Application for ovarian CA has been submitted

IHC: Immunohistochemistry

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. Pembro administered once per 21 day cycle, ENB-003 administered 3X per week for a total of 6 doses every other cycle. 18 patients, 3+3 design, dose escalation 22 days after initial Pembro administration.

Part B_1

Expansion cohort to confirm safety of RPTD (12 patients), no monotherapy run in.; Pembro administered once per 21 day cycle, ENB-003 administered 3X per week for a total of 6 doses every other cycle.

Part B_2

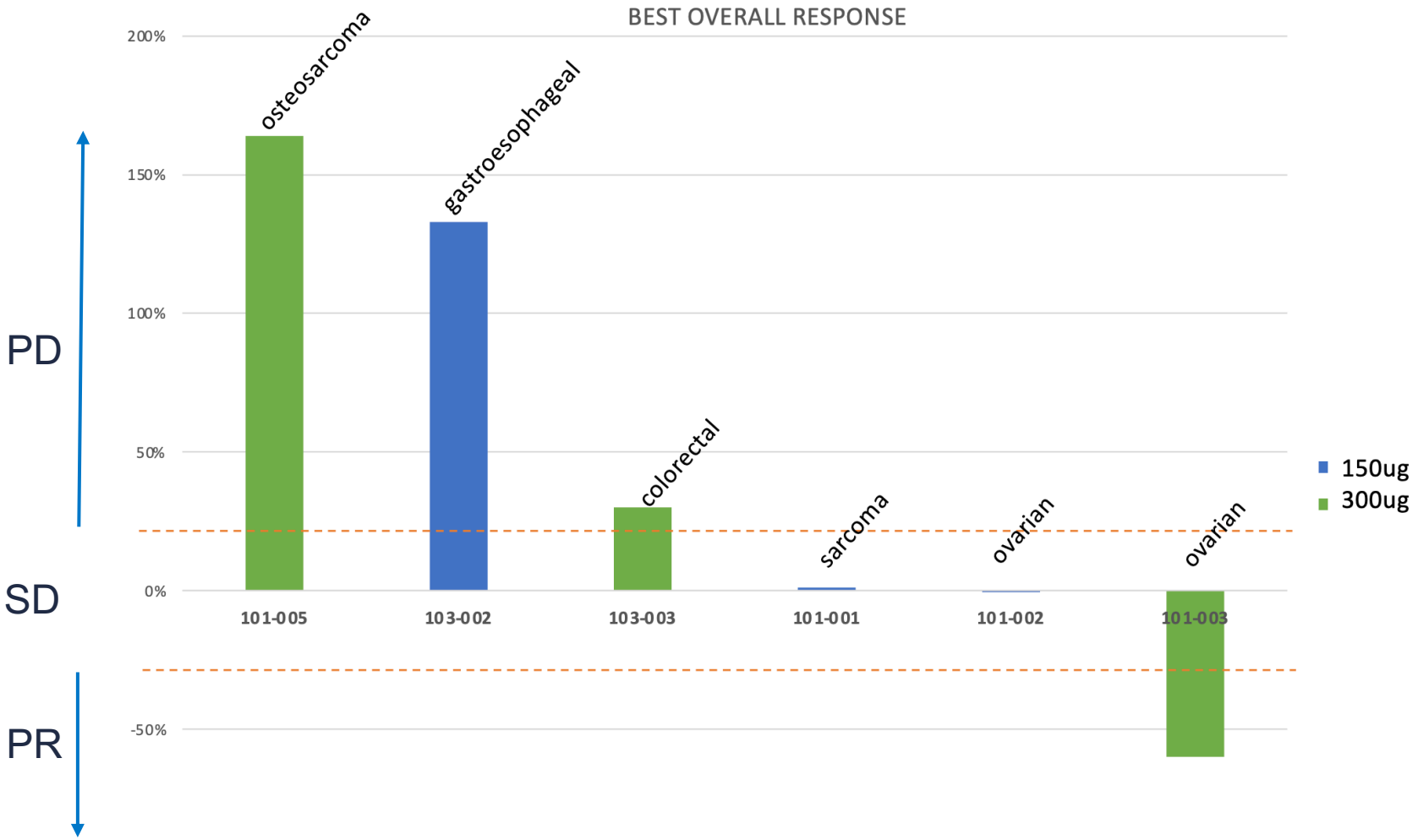
Expansion cohort at RPTD, N= 25 anti-PD1 resistant melanoma, 39 platinum-refractory/resistant ovarian cancer, 39 Pancreatic cancer, 6 Sarcoma (including Part B_1)

Pembro: pembrolizumab; **POC:** proof of concept; **RPTD:** recommended phase 2 dose

MERCK

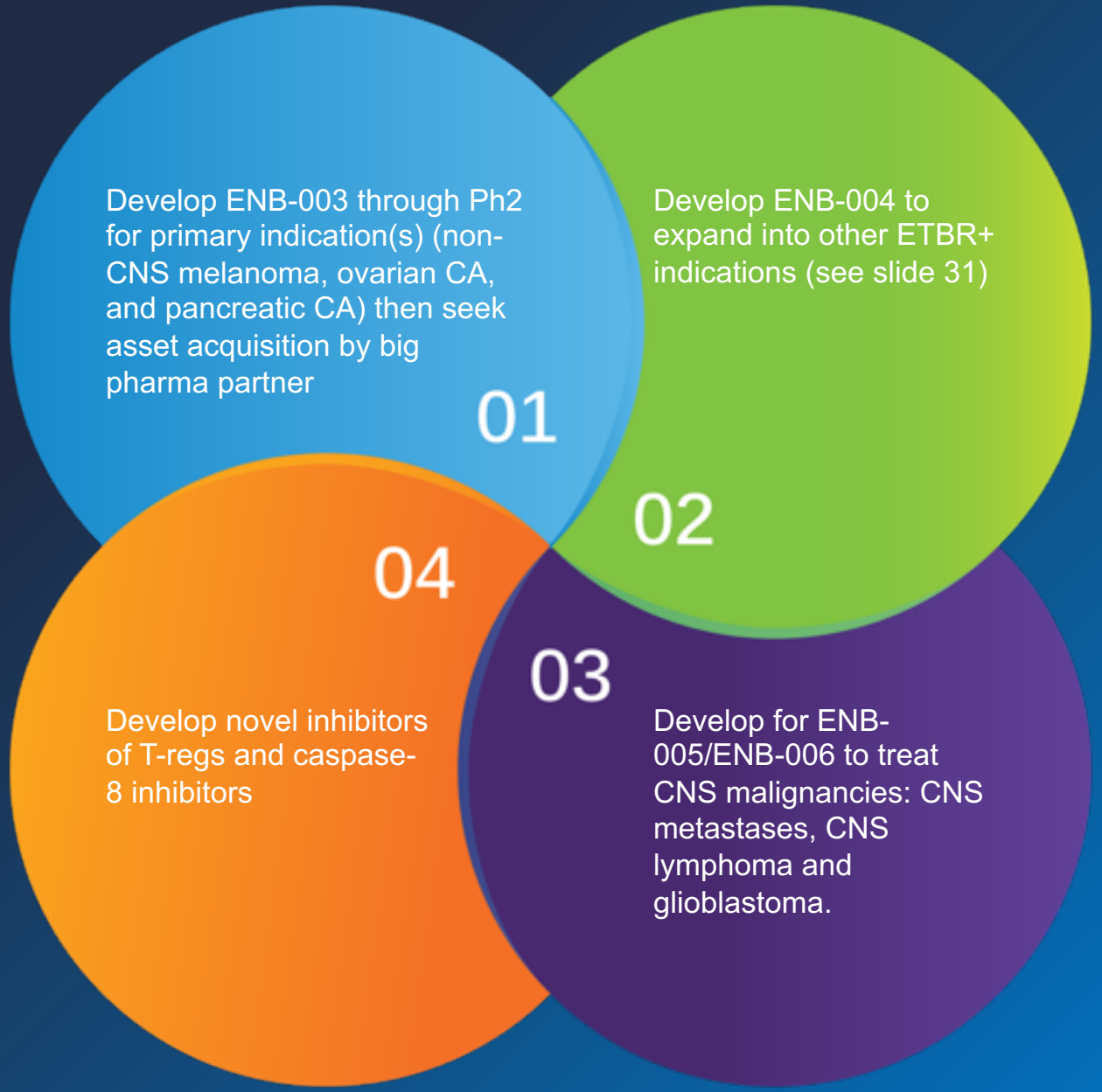
Best tumor response of primary target lesions to date show promise for ovarian cancer

- Tumor responses from 150ug and 300ug cohort
- The 150ug is subtherapeutic
- The 300ug dose is at the low end of the therapeutic window as extrapolated from animal models
- ***Best responses thus far are for ovarian cancer which is one of our target indications***



PD: progressive disease **SD**: stable disease **PR**: partial response

Business model



ENB's advantage

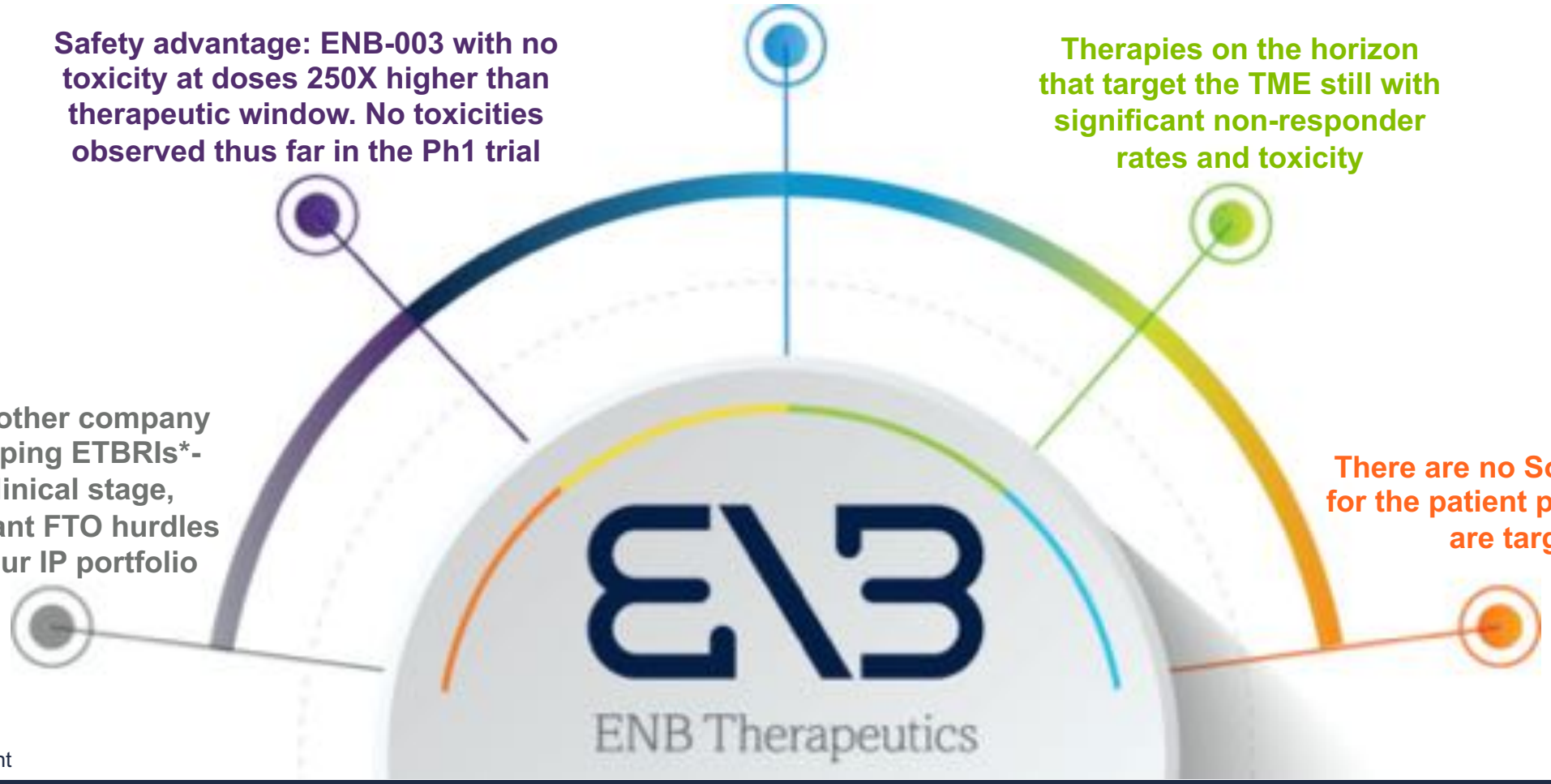
ETBRi therapy targets multiple players in TME unlike many single target therapies under investigation

Safety advantage: ENB-003 with no toxicity at doses 250X higher than therapeutic window. No toxicities observed thus far in the Ph1 trial

Therapies on the horizon that target the TME still with significant non-responder rates and toxicity

Only 1 other company developing ETBRIs*- preclinical stage, significant FTO hurdles from our IP portfolio

There are no SoC treatments for the patient populations we are targeting



* Lassogen

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 $30M Series B financing**
  - To support clinical development of ENB-003 through Phase 2
  - Preferred shares
  - **Use of proceeds:**
    - $20M clinical costs
    - $4M 4.5 FTEs x 2.25 years
    - $4M G&A
    - $2M preclinical studies

REMIGES VENTURES

Bio Advance

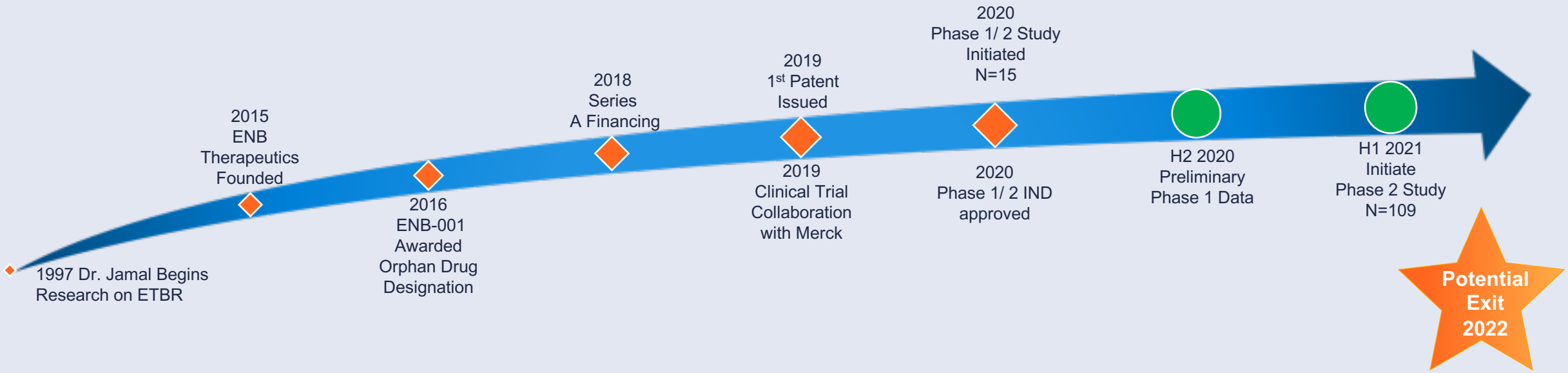
NEW YORK STATE OF OPPORTUNITY. | New York Ventures

pipeline ANGELS

ALEXANDRIA VENTURE INVESTMENTS

NY

ENB Therapeutics timeline



Active business/ corporate development discussions will continue with our partner Merck and be initiated with other strategic players

Thank You

Contact: sjamal@enbpharma.com