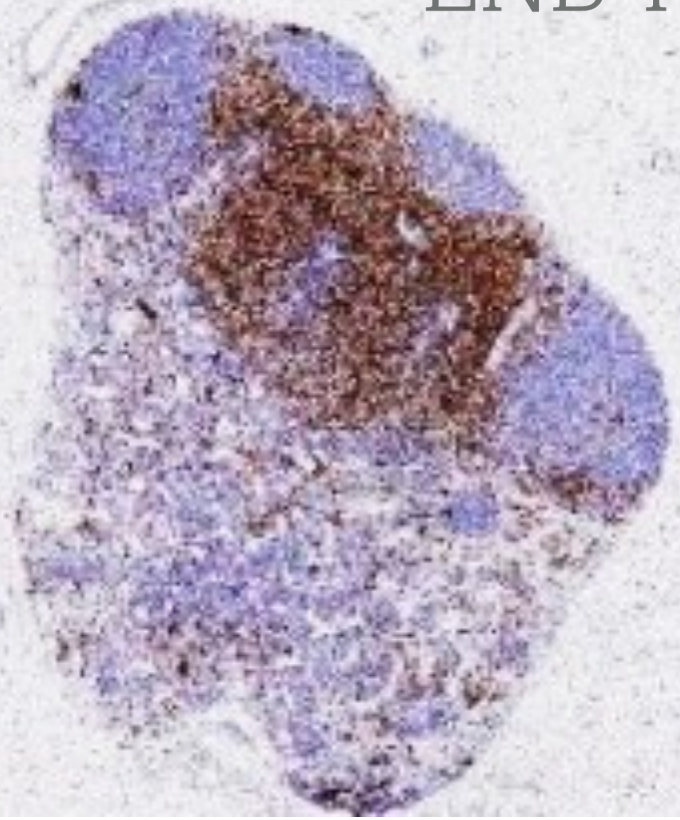
Reprogramming the Tumor Microenvironment

ENB Therapeutics

ENB-003

First-in class selective ETBR antagonist for treatment of drug resistant cancers



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

Encouraging clinical signals in Phase 1

in late line drug resistant patients, demonstrated safety of ENB-003 with no DLTs across the first 6 cohorts

Broad and Growing IP Portfolio

Technology 100% company-owned, **issued** COM & MOU patents with 2039 expiry. Orphan Drug Designation granted for 2 indications. 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 H1 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

NYU School of Medicine

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

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

NYU School of Medicine

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)

Sandy Harm, MBA
COO

MERCK

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)

Giovanni Selvaggi, MD
Acting CMO

Bristol-Myers Squibb

12+ years industry veteran Oncologist , immuno-oncology drug development, clinical trial design, strategic partnerships, FDA IND experience. Former GSK. Novartis (Global Cl. Dir. Onc.), BMS (program lead) 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

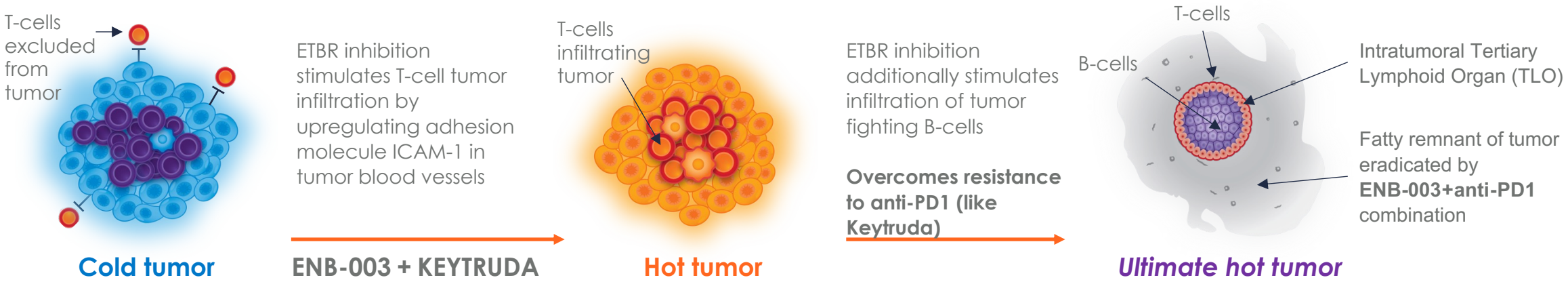
- Our therapeutic target, the ETBR, creates a barrier that prevents T-cells from infiltrating and killing tumors
- This barrier prevents immuno-oncology agents like Keytruda (pembrolizumab) from working
- ENB-003 allows agents like Keytruda to target indications that are currently untreatable
- ENB-003 + 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 multibillion market opportunity with these two indications alone__
- __Molecular target:__ *biomarker screen in development*

ENB Therapeutics

* Excludes the MSI-H/dMMR phenotype

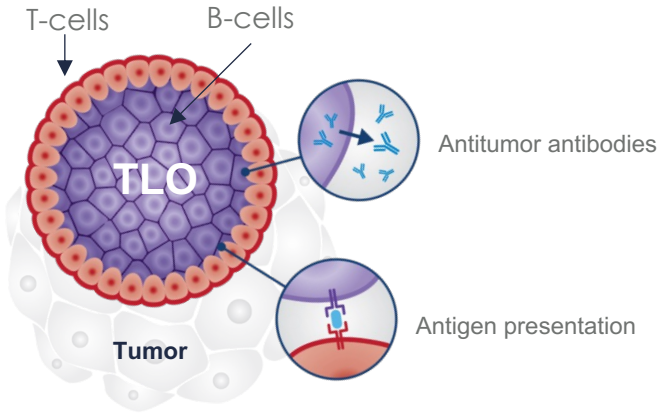
Overall, only ~15% of cancer patients achieve an objective response with IO therapies such as anti-PD1/PDL1

- ENB-003 is the key to unlock the full therapeutic potential of anti-PD1 and other IO 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

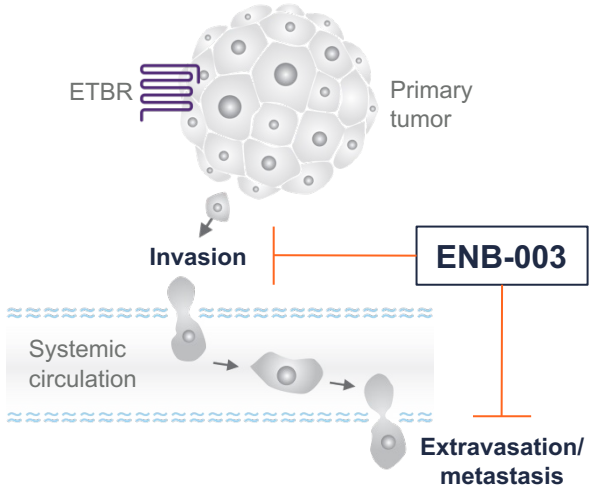


ENB-003 is unique in its multipronged effect on the tumor microenvironment despite very active clinical landscape around immune checkpoint combinations

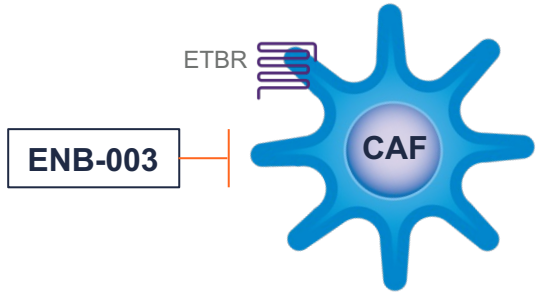
1 Creates the **ultimate hot tumor** by reprogramming the tumor microenvironment and inducing TLO formation



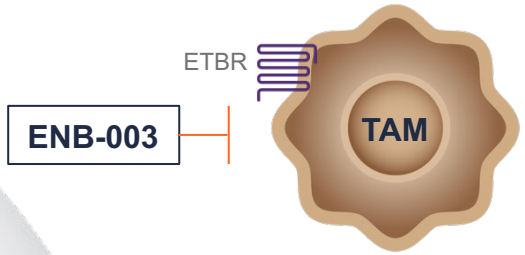
2 Blocks invasion and metastasis



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



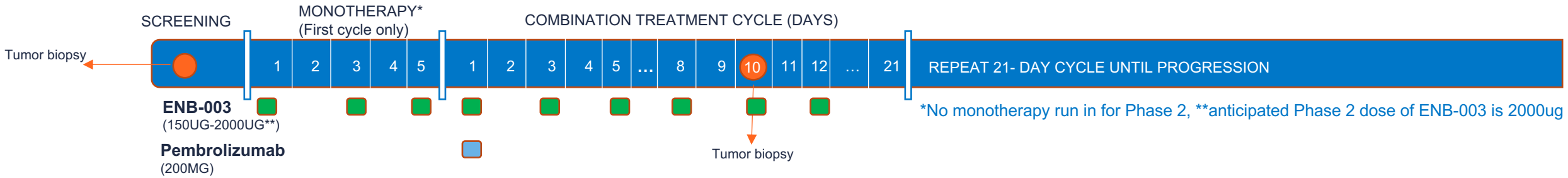
CAFs promote resistance to immune checkpoint inhibitors and chemotherapy, block the function of immune cells required for anti-tumor activity (NK and cytotoxic T cells and dendritic cells)



TAMs inhibit T-cell function and promote metastasis

ENB Therapeutics

Immunotherapy collaboration with Merck*



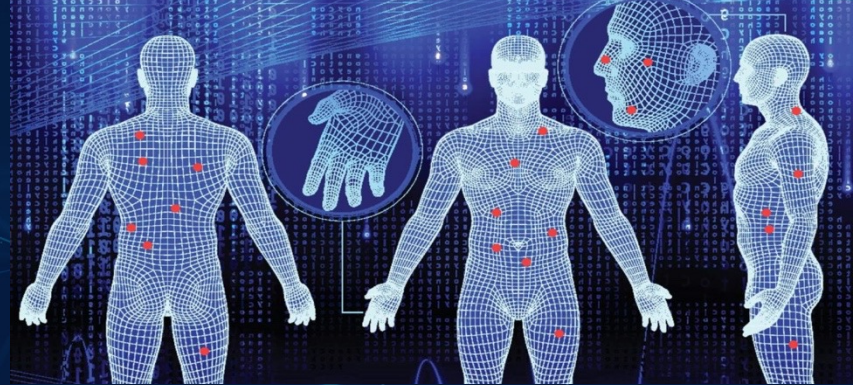
- Collaboration initiated by Merck who helped design our clinical trial and created a Joint Development Committee to guide our progress
- Ongoing **Phase 1B** study to determine safety of ENB-003 in combination with Keytruda in drug resistant cancers
  - ❖ Enrolling up to 30 subjects; all comers with 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 December 2022
- **Phase 2** study to determine efficacy and safety of ENB-003 in combination with Keytruda in drug resistant cancers
  - ❖ Enrolling up to 137 anti-PD1 resistant melanoma, chemoresistant pancreatic cancer and chemoresistant ovarian cancer, + exploratory basket: anti-PD1 resistant SCC of head and neck, TNBC
  - ❖ Endpoints: clinical response, safety and tolerability, anticipated start H1 2023
  - ❖ Anticipated response rate of selected patient population to single agent pembrolizumab is 0% for melanoma, pancreatic cancer, and platinum refractory ovarian cancer, 8% for platinum resistant ovarian cancer
- **Robust pre-clinical proof of concept for all target indications**

*ENB retains all rights to ENB-003 under the collaboration agreement
ENB is actively seeking other pharma partnerships

~13,000
patients diagnosed with advanced disease annually

~7,800
will be anti-PD1 resistant

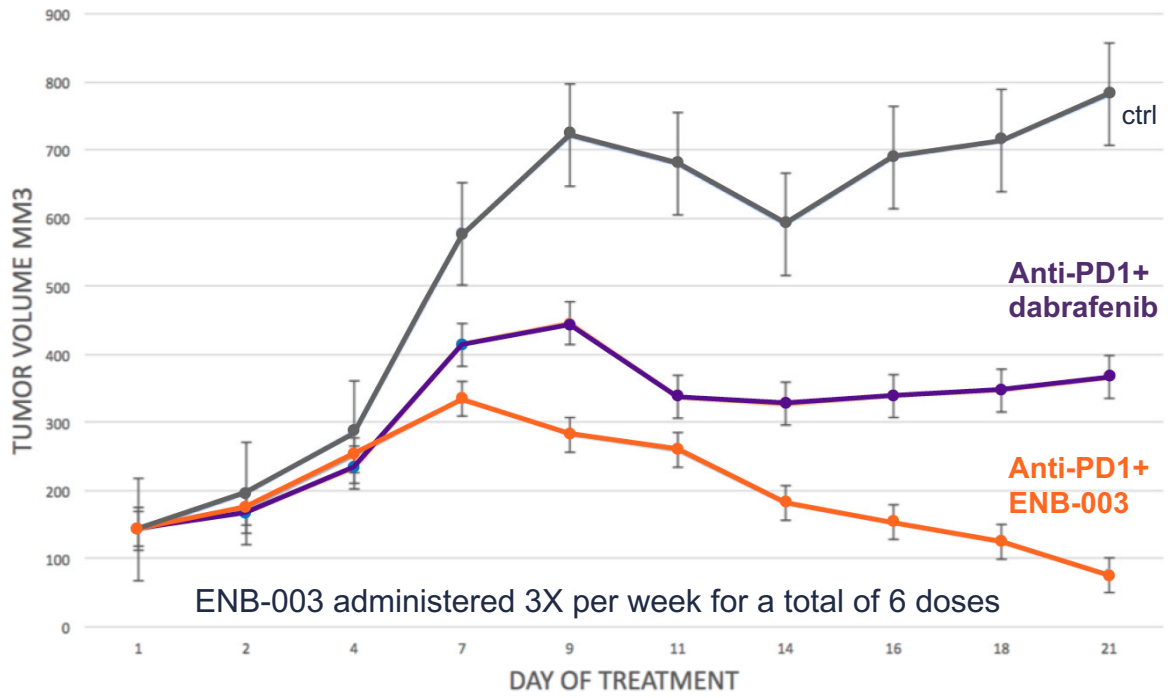
~7,000
addressable US patients estimated ETBR+



Target indication 1: anti-PD1 resistant unresectable metastatic melanoma

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

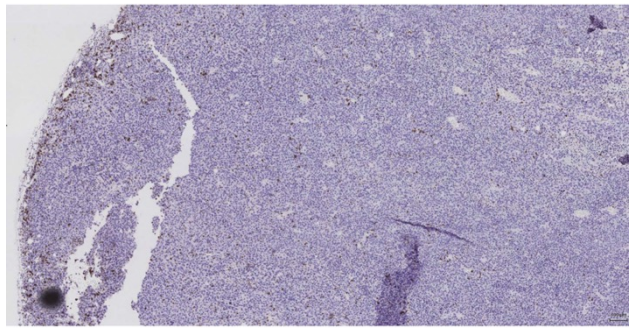
See next slide for Tertiary Lymphoid Organ (TLO) formation from this study



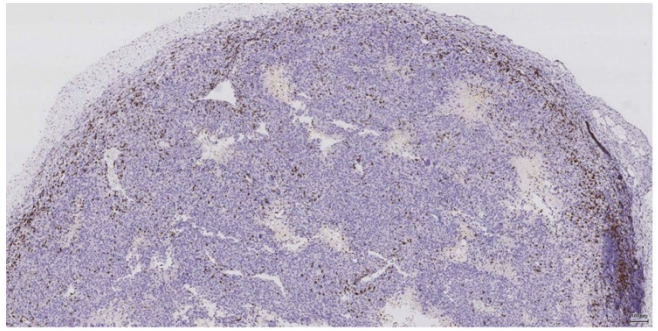
Source: internal study, unpublished

ENB-003 + anti-PD1 combination eradicates tumors, promotes intratumoral TLO ** formation: *A hallmark for IO responsiveness*

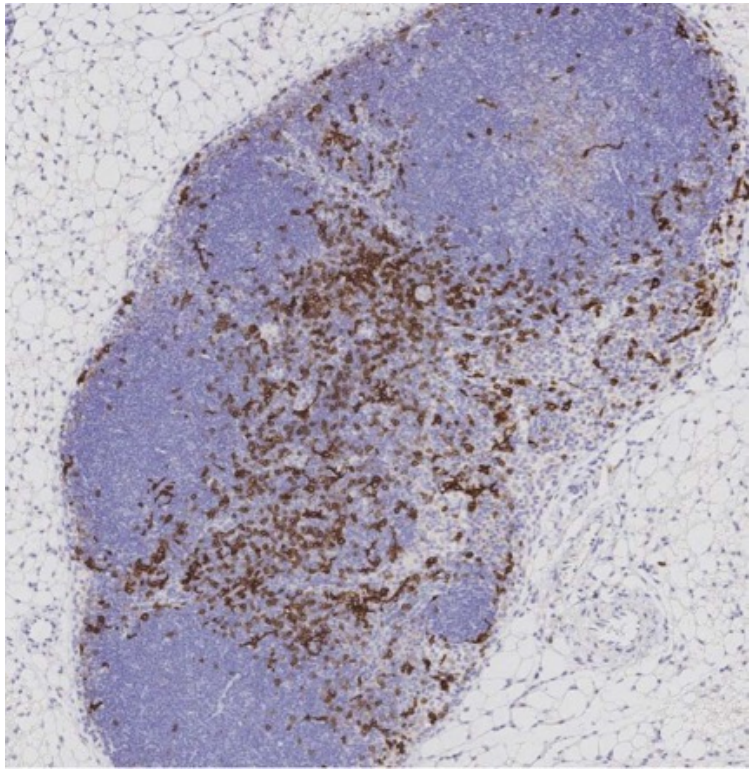
Untreated control: paucity of CD8+ T-cells (stain brown)



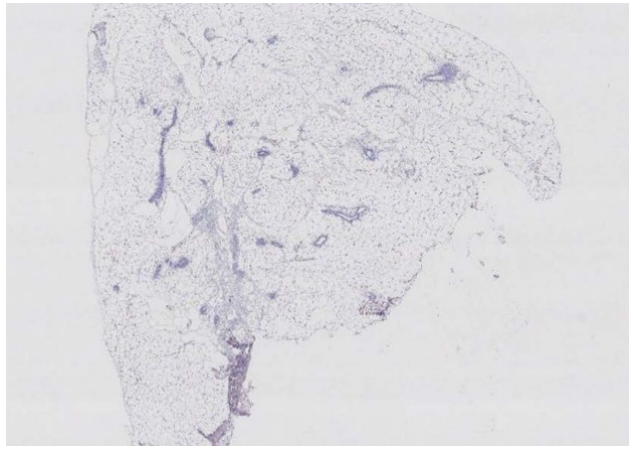
Anti-PD1+ dabrafenib: Increase in CD8+ T-cells, predominantly peripheral distribution



TLO (Hi magnification)

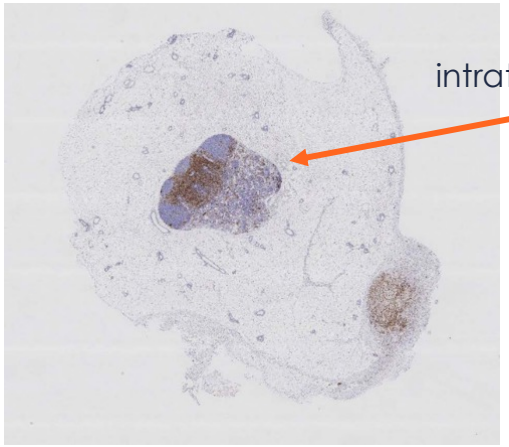


anti-PD1+ENB-003- No residual tumor



*brown stain

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

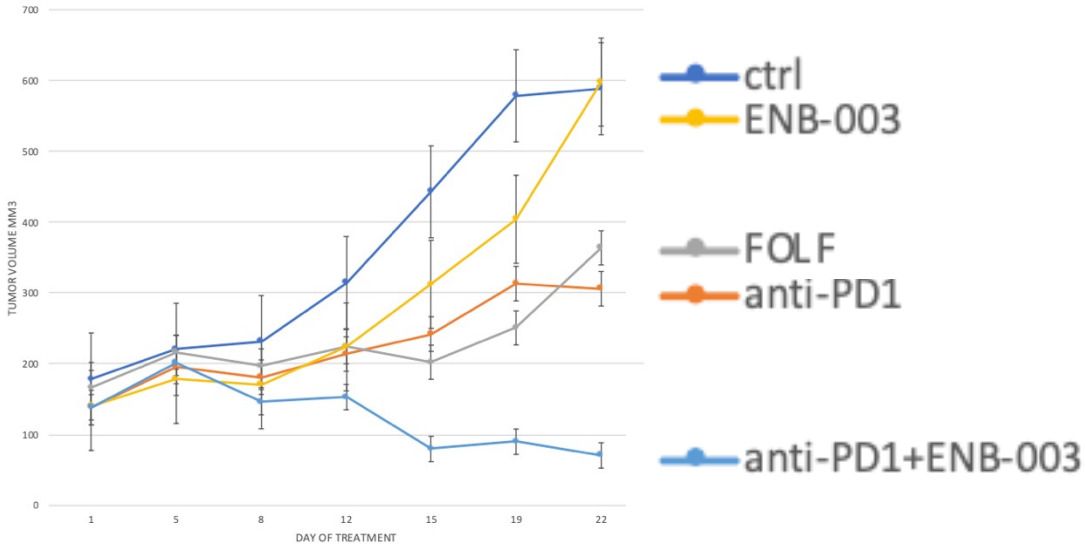
~46,000
patients diagnosed with unresectable disease annually

~44,000
will be anti-PD1 resistant

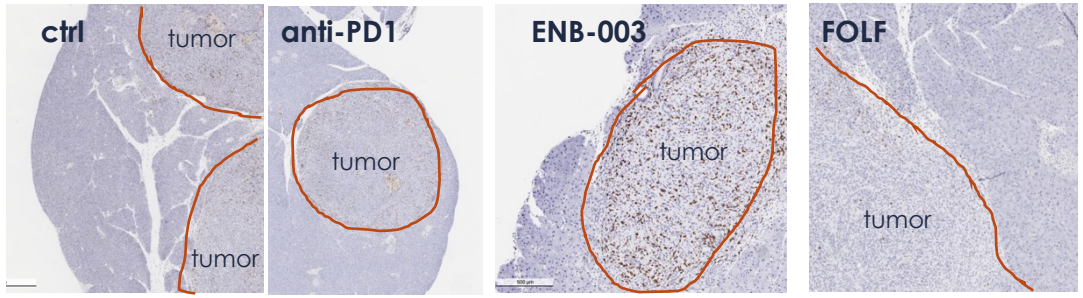
~26,000
addressable US patients estimated ETBR+

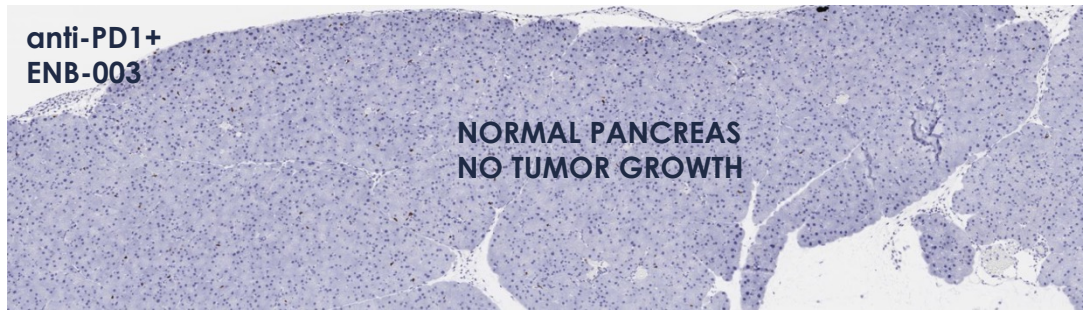
Target indication 2: chemoresistant unresectable Pancreatic CA

*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



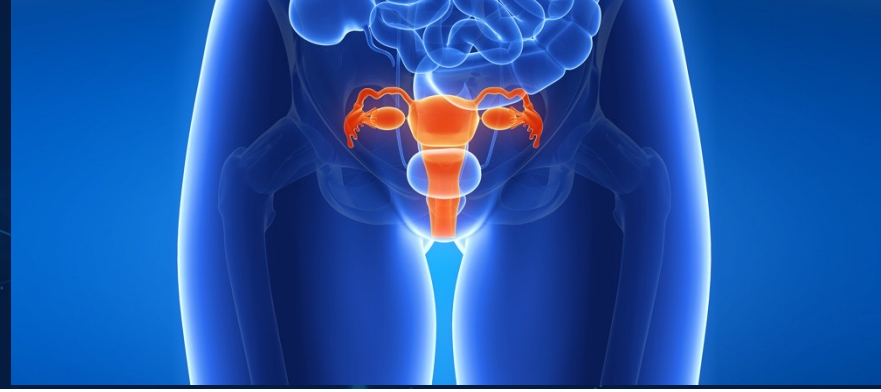


*The UN-KC-6141 model was derived from a pancreatic tumor of a Kras(G12D);Pdx1-Cre (KC) mouse at 50 weeks of age,

~15,000
patients diagnosed with advanced disease annually

~13,000
will be platinum refractory or resistant

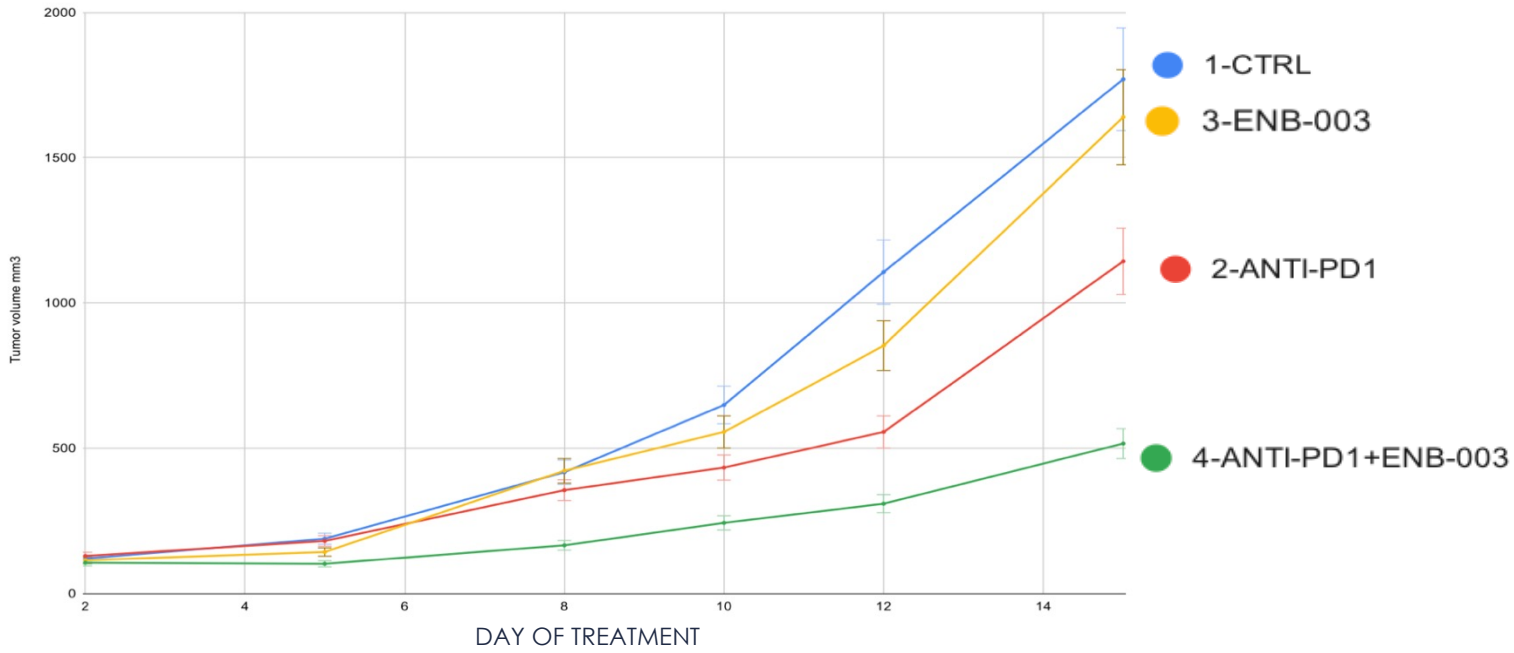
~9,900
addressable US patients estimated ETBR+



Target indication 3: Platinum-refractory/ Platinum resistant epithelial Ovarian CA

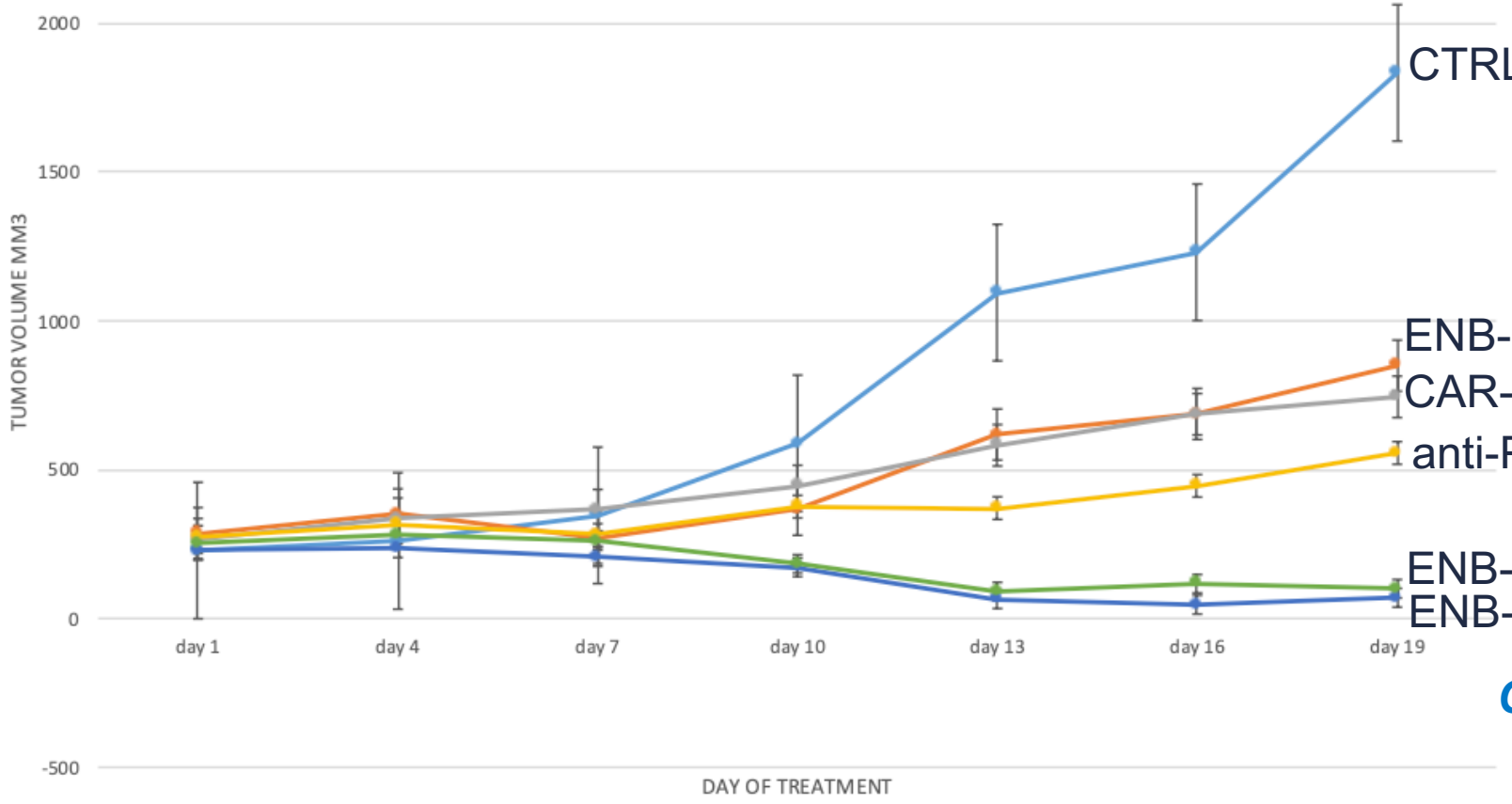
anticipated response rate to single agent pembrolizumab: refractory/ resistant= 0%/8%

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



*ID8-VEGF model, ENB-003 administered 3X per week for a total of 6 doses

ENB-003* subcutaneous formulation with *single agent activity* in 4T1 breast cancer model, ***50% of tumors eradicated*** in combination with CAR-T or anti-PD1



54% tumor growth inhibition by single agent ENB-003

95% avg. tumor growth inhibition by ENB-003 +anti-PD1 or CAR-T

CAR-T was directed against HER2

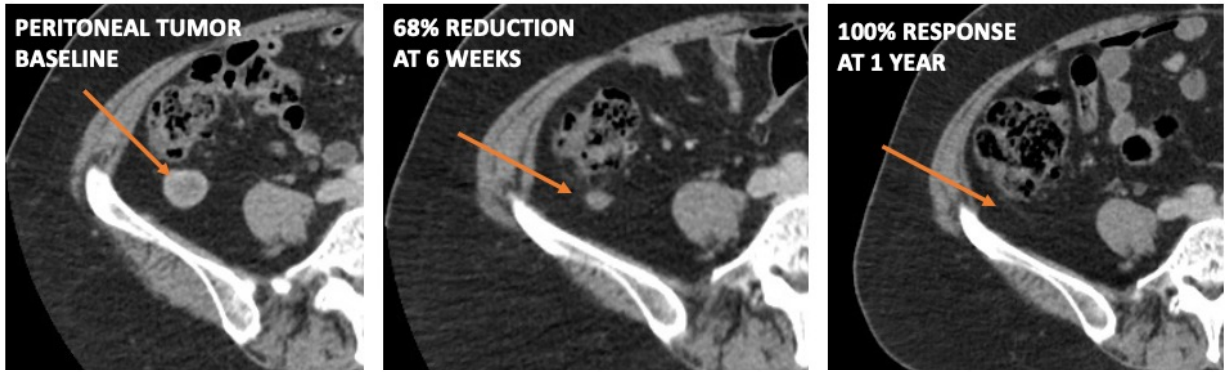
*ENB-003 was administered SC 3X per week x 8 doses, N= 6 per group

Phase 1 clinical data: Impressive 95% partial response in a platinum refractory ovarian cancer patient

- The patient was **negative for PD-L1** so response highly likely due to ENB-003 and not to pembrolizumab single agent activity
- Patient was **Microsatellite STABLE** – historically non-responder to single agent pembrolizumab
- Historical response rate of platinum refractory OC to single agent pembrolizumab is 0%
- Durable 12 – month progression free survival

  → : Historical PFS with single agent pembrolizumab in MSI-H/dMMR OC: mPFS ~ 2 mos, max PFS 6 mos
- 100% DCR in OC(vs 22% with single agent pembro), 33% ORR in ETBR+ subjects

Serial CT scans from platinum refractory ovarian cancer patient with durable 12-month progression free survival- 100% response of 2 of 3 target lesions and 88% response of remaining target lesion



CT SCAN	BASELINE	6 WEEKS	12 WEEKS	24 weeks	36 weeks	52 weeks
Target lesions mm	36 52 25	17 21 25	14 14 8	0 12 6	0 8 0	0 6 0
Sum (mm)	113	63 (-44%)	36 (-68%)	18 (-84%)	8 (-93%)	6 (-95%)
Non-target lesions mm	2	Non-CR Non-PD	Non-CR Non-PD	Non-CR Non-PD	Non-CR Non-PD	PD 1 of 2

Phase 1B clinical highlights: Encouraging responses in immunotherapy resistant patients with high unmet need

ENB-003+Keytruda

- ✓ **Encouraging clinical signals** in heavily pre-treated drug resistant patients despite not achieving IC50 for ENB-003 in first 5 cohorts (waterfall plot on slide 58)
  - ETBR engagement confirmed via pharmacodynamic assays
  - The vast majority of patients are PD-L1 negative so unlikely to respond to single agent pembrolizumab
- ✓ **No additional toxicity** caused by ENB-003 over known toxicity profile of pembrolizumab
- ✓ **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
- ✓ **4th line pancreatic cancer patient passed 7-month OS benchmark** in 6th cohort (mOS for 3rd line PAC is 3 months)
- ✓ **100% DCR in ovarian cancer and 33% ORR in ETBR+ patients**

*ENB retains all rights to ENB-003 under the collaboration agreement with Merck
We are actively seeking pharma partners

Competitive landscape with sparse in-class competition

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

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

Clinical trial with 5 shots on goal: multiple indications increase chance of success and potential valuation upon an exit

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

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