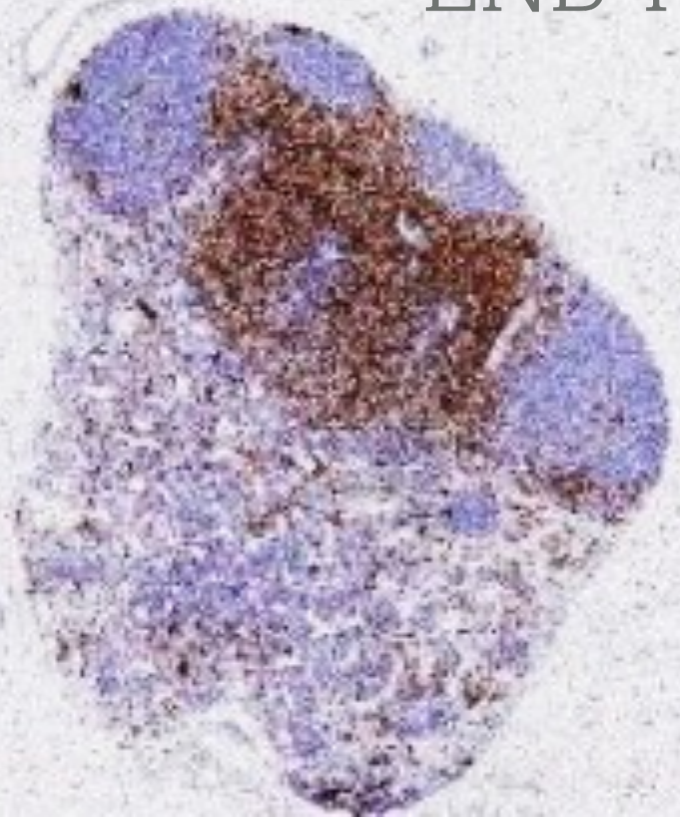
Reprogramming the Tumor Microenvironment

ENB Therapeutics

ENB-003

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

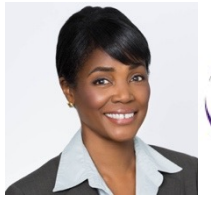


Strong team, strong IP, encouraging Phase 1 data

- Privately held clinical stage company focused on treating drug resistant cancers
- Lead program is **ENB-003** oncology platform molecule for multiple oncology indications
  - ❖ Issued composition of matter and method of use patents with 2039 expiry
- Validated by immunotherapy collaboration with **Merck** for Phase 1 and Phase 2 trials in chemo-resistant pancreatic cancer and ovarian cancer and anti-PD1-resistant melanoma (**ENB-003+Keytruda**)
- **In ongoing international Phase 1 dose finding study, clinical benefit observed to date in 40% of immunotherapy resistant patients despite not yet reaching optimal dose**

Our Senior Management Team:

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

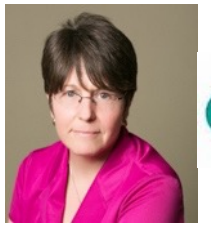


NYU School of Medicine

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

NYU School of Medicine

- Sandy Harm, MBA
  COO



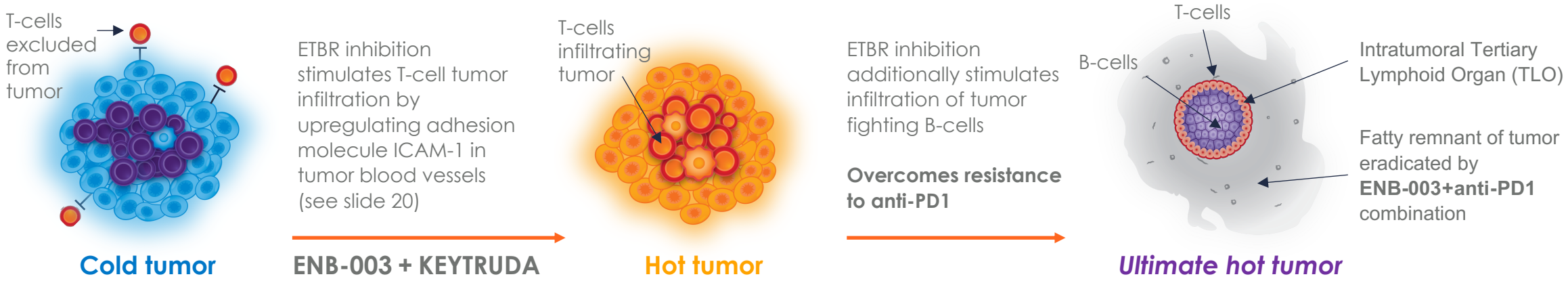
MERCK

- Mike Needle, MD
  CMO

Celgene

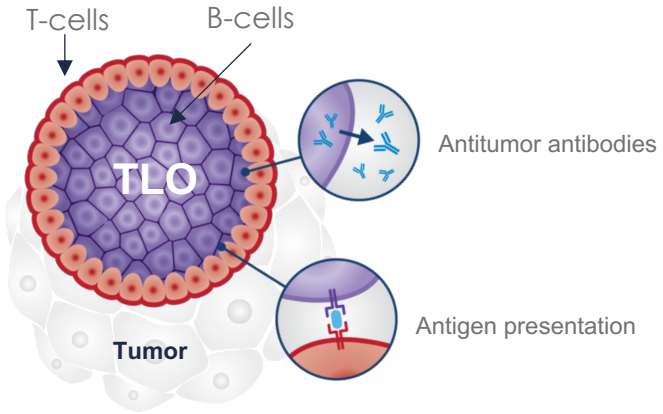
ENB-003 mechanism of action

- First-in-Class selective ETBR antagonist: Enhances immunotherapy efficacy in multiple cancer indications
  - Small molecule, received orphan drug designation from FDA for melanoma, applications pending for ovarian cancer and pancreatic cancer
- Inhibits ETBR (a cell surface receptor- **e**ndo**t**helin **B** **r**eceptor)
  - ETBR is highly expressed in over 40% of all cancers (slide 23), correlates with poor survival and tumors that lack T-cells (cold tumors)
  - ENB-003 increases sensitivity to anti-cancer agents by targeting multiple cell types in the tumor microenvironment
  - Potential synergy with multiple immuno-oncology platforms
- Creates the "ultimate hot tumor"
  - ENB-003 creates the ultimate hot tumor by not only stimulating T-cell infiltration but also stimulating the formation of new lymph nodes (TLOs) that contain tumor fighting T-cells and B-cells that eradicate tumors

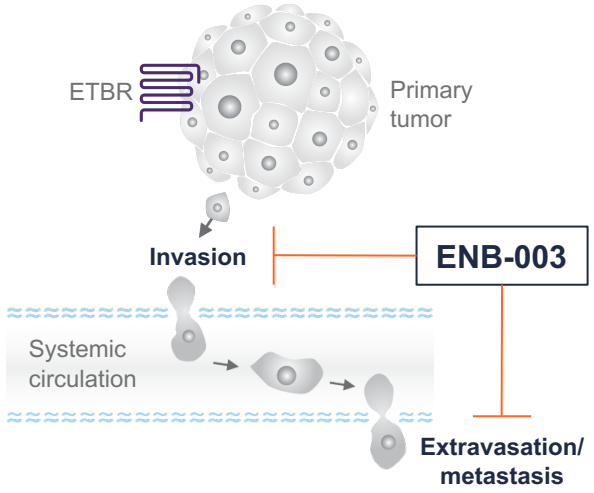


ENB-003 is unique in its multipronged effect on the tumor microenvironment despite very active clinical landscape around immune checkpoint combinations*

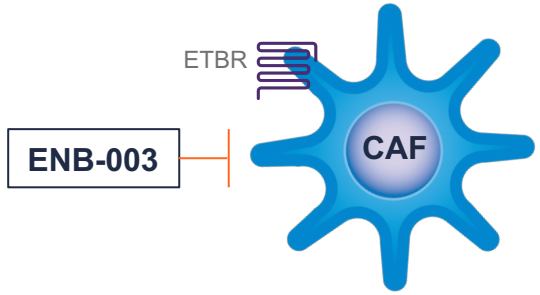
1 Creates the **ultimate hot tumor** by reprogramming the tumor microenvironment and inducing TLO formation



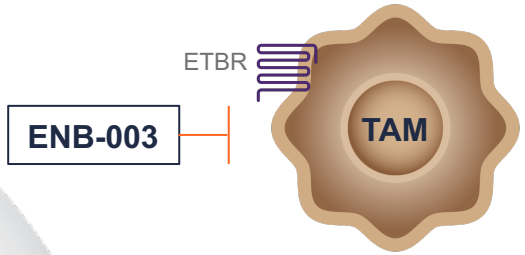
2 Blocks invasion and metastasis



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)

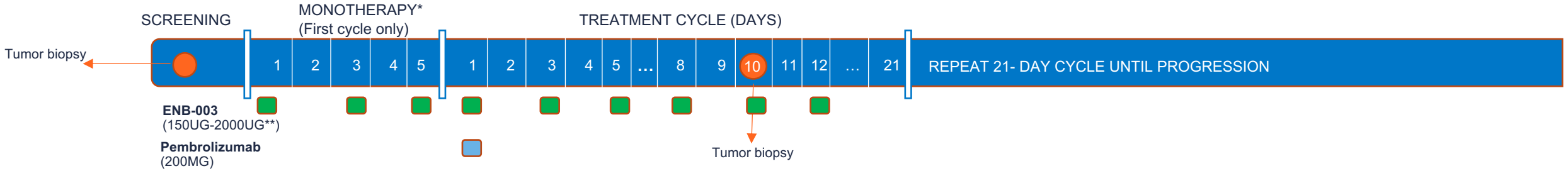


TAMs inhibit T-cell function and promote metastasis

*see slide 21 for more details

ENB Therapeutics

Immunotherapy collaboration with Merck



- Ongoing Phase 1B study to determine safety of ENB-003 in combination with Keytruda
  - ❖ Collaboration initiated by Merck who helped design our clinical trial and work closely with us
  - ❖ Enrolling up to 23 anti-PD1 resistant melanoma, chemoresistant pancreatic cancer and chemoresistqnt ovarian cancer
  - ❖ Endpoints: safety and tolerability, clinical response
  - ❖ Study start: April 2020, topline results expected March 2022
  - ❖ Multi-center-open label
  - ❖ 5 cohorts completed
  - ❖ Currently enrolling the final cohort

- Phase 2 study to determine efficacy and safety of ENB-003 in combination with Keytruda
  - ❖ Endpoints: clinical response, safety and tolerability
  - ❖ Anticipated study start: Q3 2022
  - ❖ Multi-center-open label
  - ❖ Enrolling 109 anti-PD1 resistant melanoma, chemoresistant pancreatic cancer and chemoresistqnt ovarian cancer
- Robust pre-clinical proof of concept for all 3 target indications

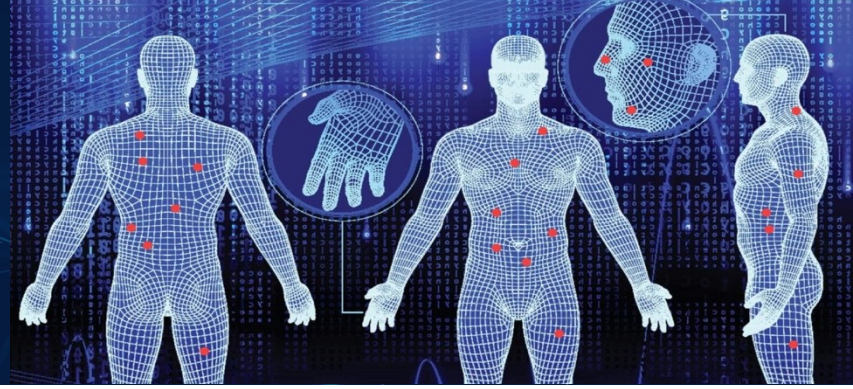
*Phase 1B only, **anticipated Phase 2 dose of ENB-003 is 2000ug

ENB retains all rights to ENB-003 under a clinical trial collaboration with MERCK

~13,000
patients diagnosed with advanced disease annually

~7,800
will be anti-PD1 resistant

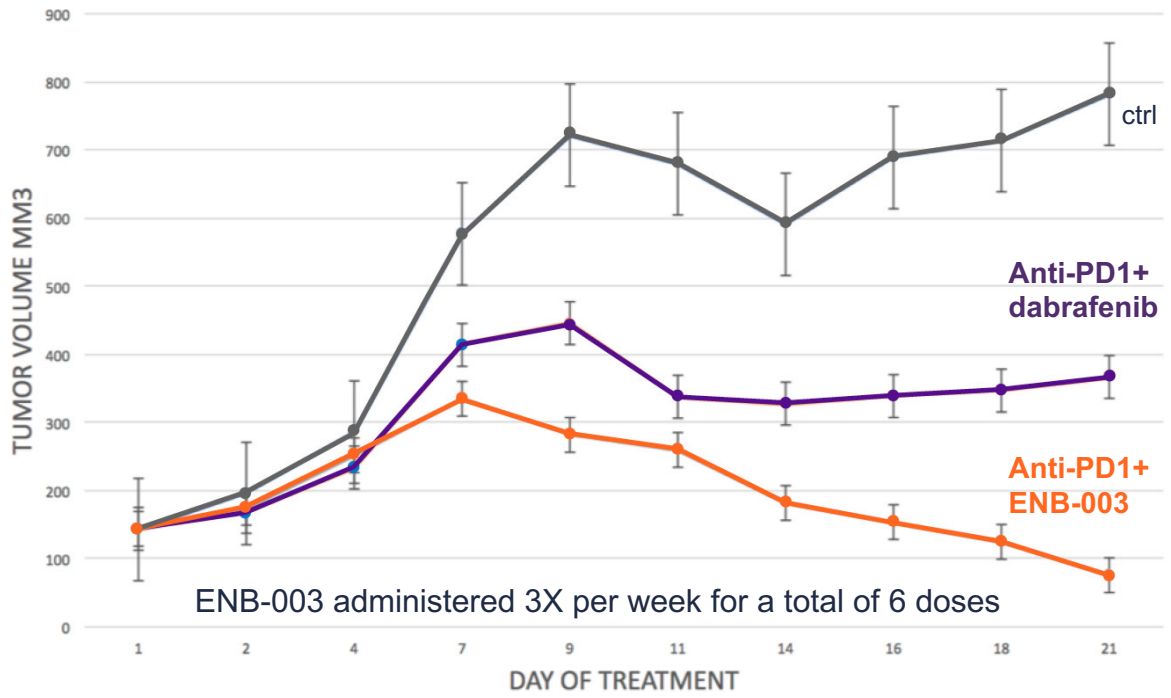
~7,000
addressable US patients estimated ETBR+



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

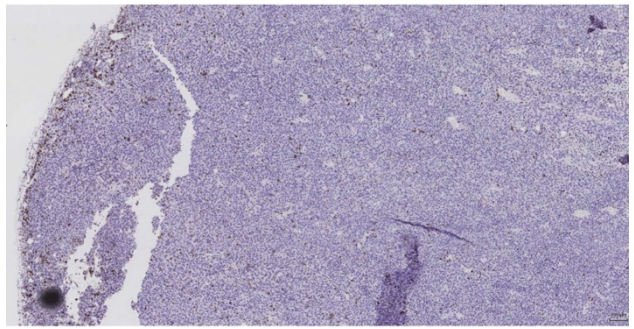
See next slide for Tertiary Lymphoid Organ (TLO) formation from this study



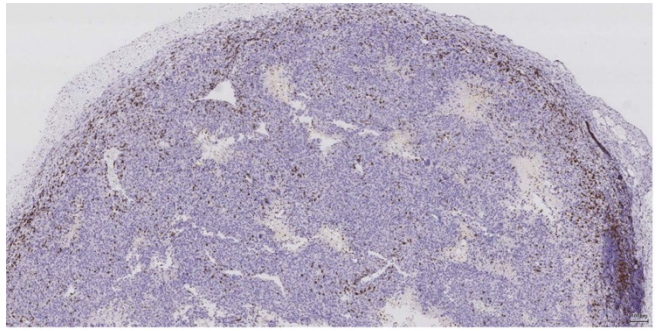
Source: internal study, unpublished

ENB-003 + anti-PD1 combination eradicates tumors, promotes intratumoral TLO ** formation: *A hallmark for IO responsiveness (see slides 30-35)*

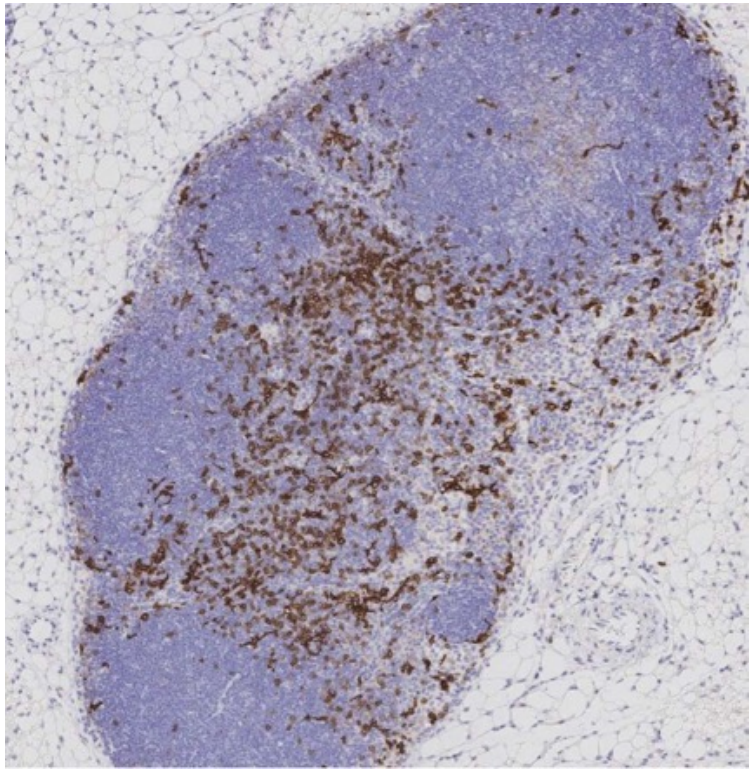
Untreated control: paucity of CD8+ T-cells (stain brown)



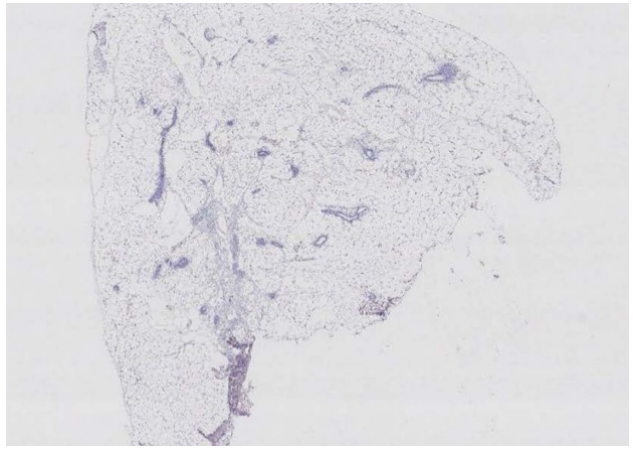
Anti-PD1+ dabrafenib: Increase in CD8+ T-cells, predominantly peripheral distribution



TLO (Hi magnification)

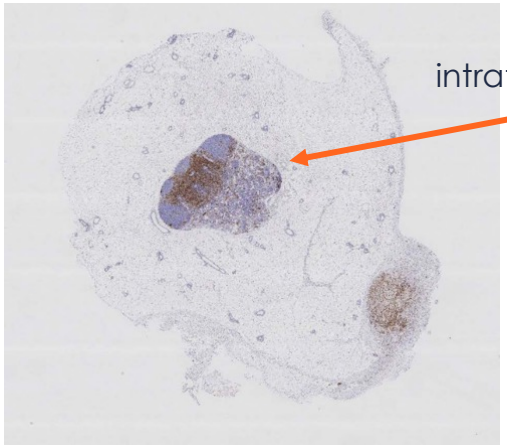


anti-PD1+ENB-003- No residual tumor



*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

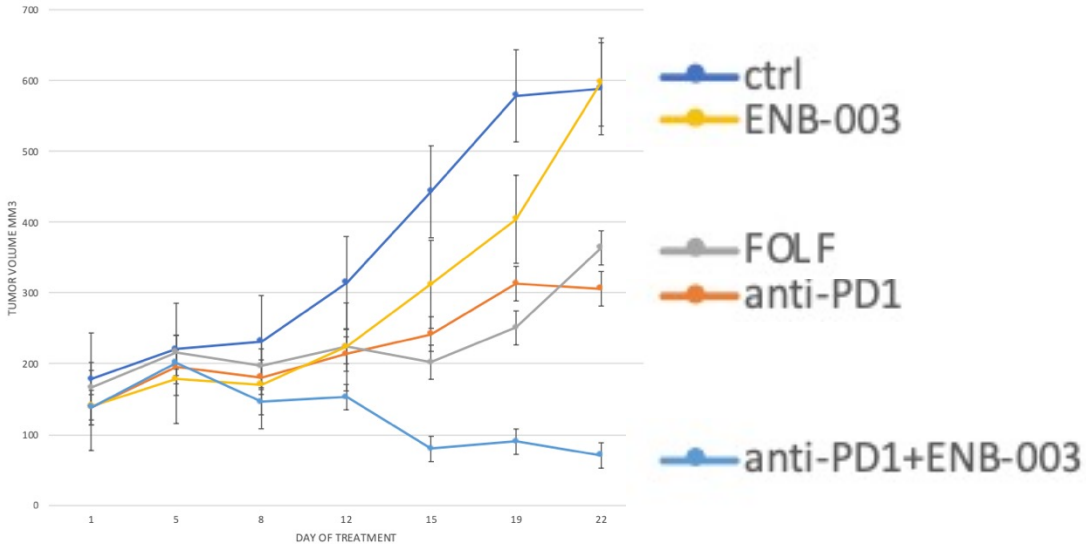
will be anti-PD1 resistant

~26,000

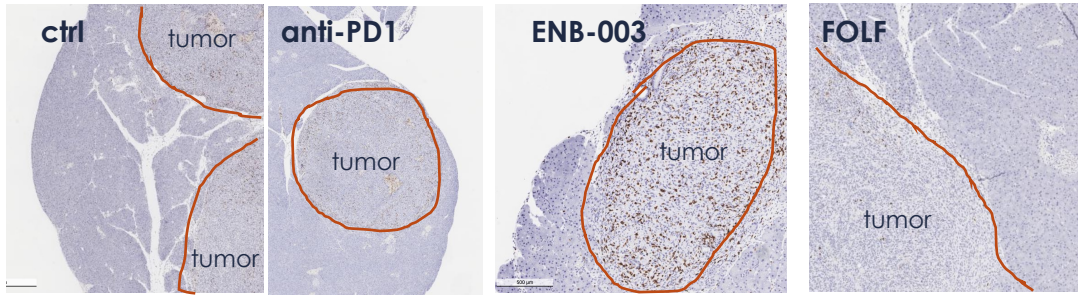
addressable US patients estimated ETBR+

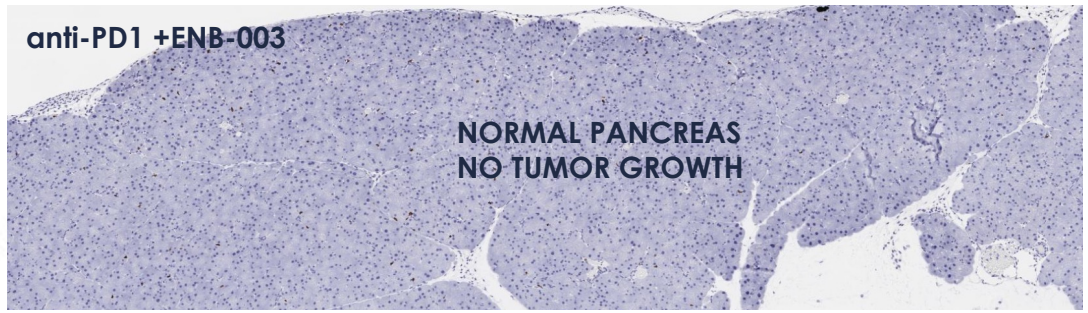
Target indication 2: chemoresistant unresectable Pancreatic CA

*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



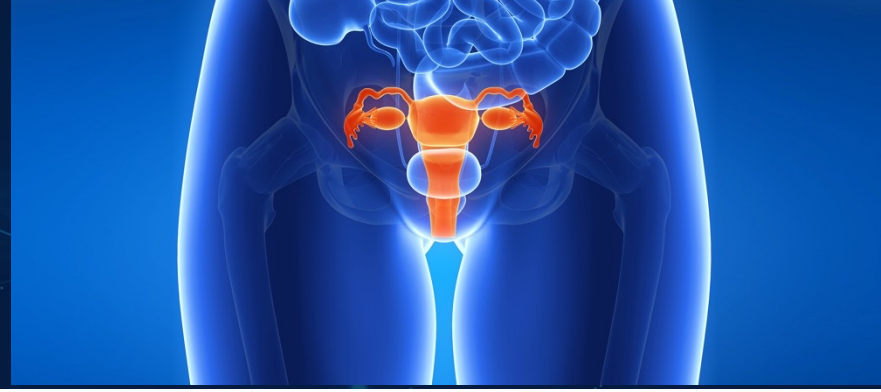


*The UN-KC-6141 model was derived from a pancreatic tumor of a Kras(G12D);Pdx1-Cre (KC) mouse at 50 weeks of age

~15,000
patients diagnosed with advanced disease annually

~13,000
will be platinum refractory or resistant

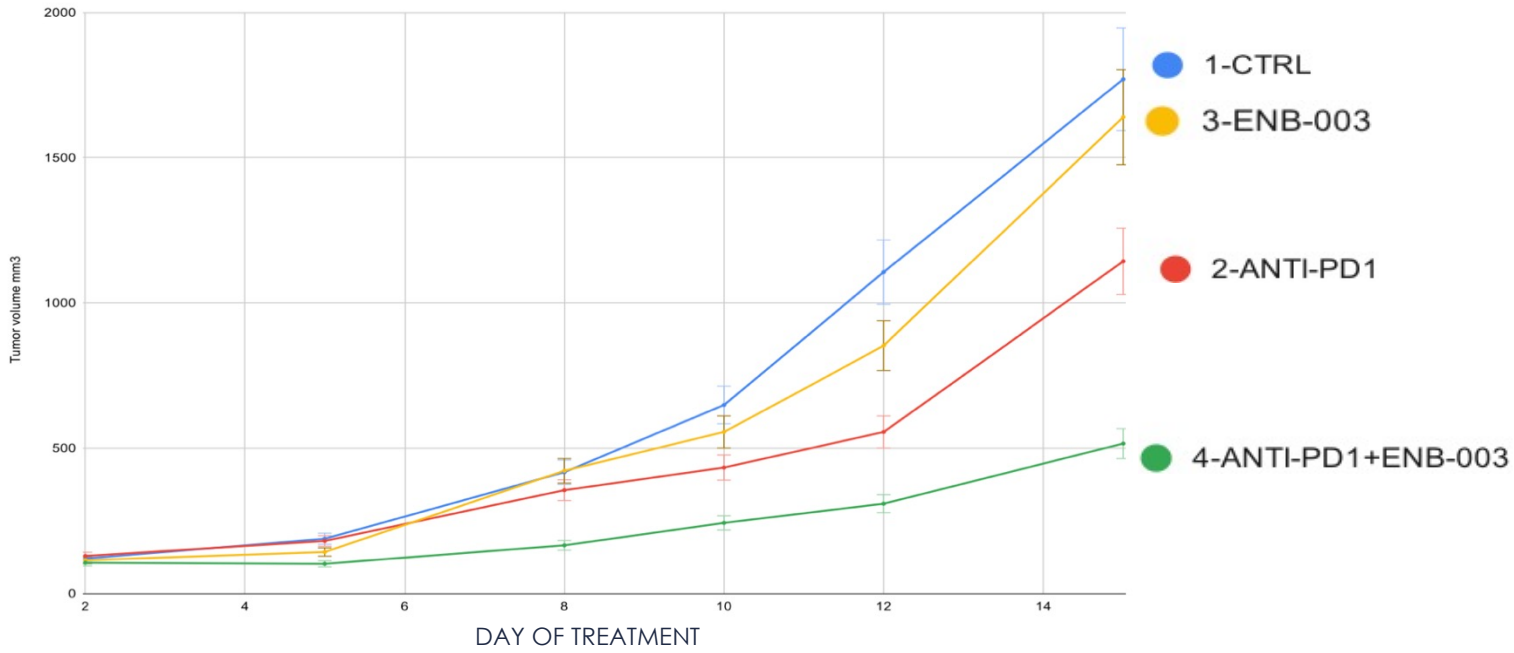
~9,900
addressable US patients estimated ETBR+



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**



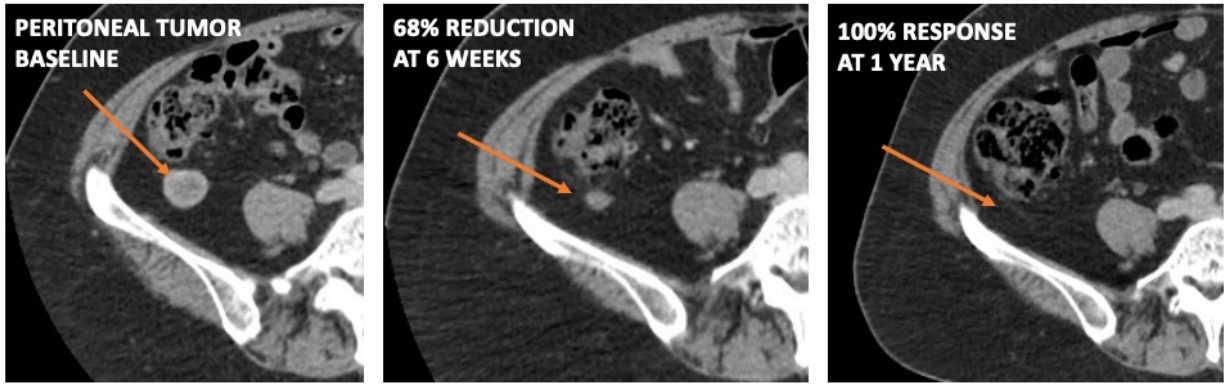
*ID8-VEGF model, ENB-003 administered 3X per week for a total of 6 doses

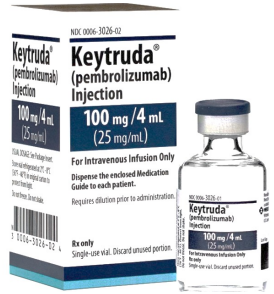
Phase 1B clinical highlights: Encouraging responses in immunotherapy resistant patients with high unmet need

ENB-003+Keytruda

- ✓ **40% clinical benefit** in heavily pre-treated drug resistant patients despite not yet achieving IC50 for ENB-003 (see slide 43 for waterfall plot)
  - 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%)
- ✓ **7-month arrest of disease progression** in a tonsillar SCC patient who had previously failed anti-PD1
- ✓ **100% clinical benefit in ovarian cancer**
- ✓ 50% 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 lesion





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

Only 1 other company developing ETBRIs*- preclinical stage,

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

AE: Adverse event