Supercharging Cancer Immunotherapy

ENB Therapeutics

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.

Highly Differentiated Cancer Immunotherapy

Unlocks Immunotherapy

- Lead program, small molecule ENB-003, selectively targets Endothelin B, a key receptor implicated in PD-1 failures
- Blocks ETBR upstream of PD-1 inhibitors in the anti-tumor immunity cycle to induce immune cell infiltration, tertiary lymphoid organ formation, and reduce suppression of immune cells
- Highly differentiated mechanism of action versus T cell recruitment approaches

Validated Clinical Activity

- Disease-modifying activity in ENBOLDEN phase 1 trial in combination with Keytruda®
- **High objective response and disease control rates in patients not expected to respond to PD-1 (prior PD-1 failure without response and/or microsatellite (MS) stable)**
- Responses correlate with ETBR expression
- Upcoming Phase 2 trials: Pharma collaborations with Merck and Coherus; supported by MD Anderson Cancer Focus Fund and the Cancer Research Institute

Broad Market Potential

- Endothelin B expressed in ~40% of all solid tumors
- Difficult to treat indications (ovarian, melanoma, pancreatic) have highest percentage of patients with ETBR-Hi expression
- Blockbuster potential to expand market of immune checkpoint inhibitors

Pipeline Of Potent And Selective Endothelin B Inhibitors

ENB-003

Study number	Study arm	Primary indication	Preclinical	Phase 1	Phase 2	Partnership
NCT04918186	ENB-003 IV+ LOQTORZI	Platinum resistant ovarian cancer				Coherus Supply Agreement
NCT04205227	ENB-003 SC + KEYTRUDA	Platinum resistant ovarian cancer				MERCK Supply Agreement
NCT04205227	ENB-003 SC SINGLE AGENT	Platinum resistant ovarian cancer				
NCT04205227	ENB-003 SC+ KEYTRUDA	Solid Tumors				MERCK Supply Agreement

ENB-004,5,6 (oral small molecules)

Study number	Study arm	Primary indication	Preclinical	Phase 1	Phase 2	Partnership
		Solid Tumors				

Completed Upcoming

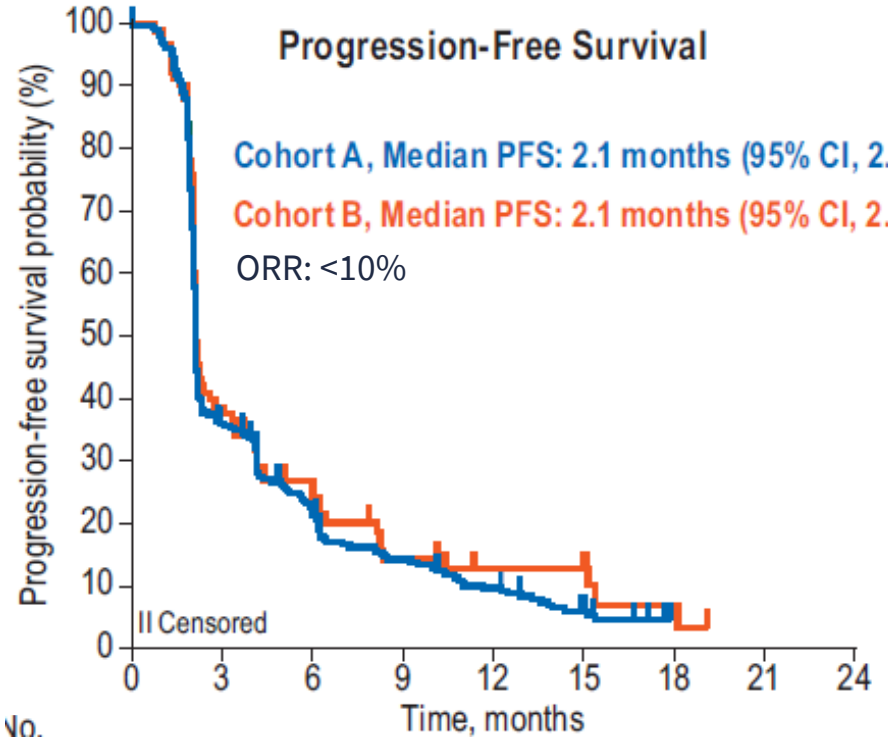
*All ENB assets are wholly owned by ENB

Checkpoint Inhibitors Have Been a Breakthrough in Oncology

Yet Effects Remain Limited to a Minority of Patients Due to Multiple Factors

Majority Of Patients *Do Not* Respond To Keytruda®

Keynote-100 study in advanced recurrent ovarian cancer



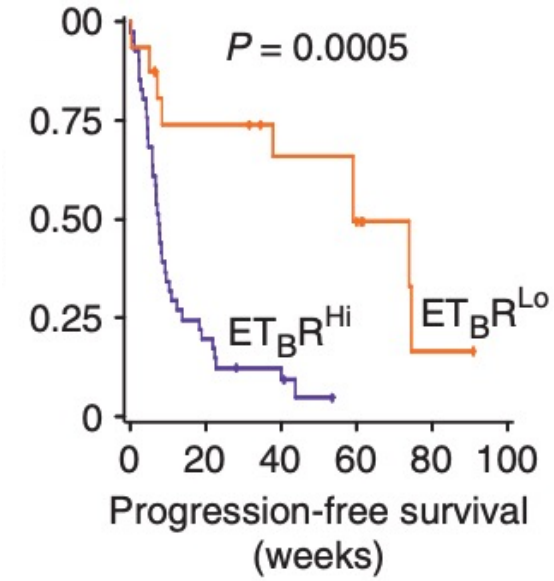
Limited utility and response due to:

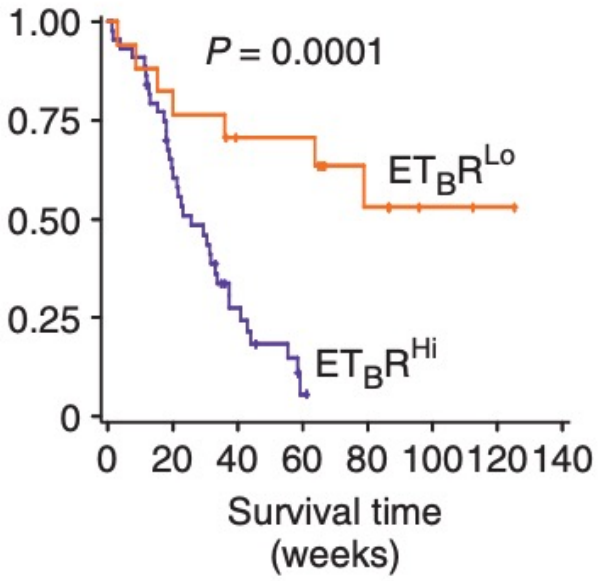
- Lack of PD-1/PD-L1 receptors
- Microsatellite (MS) Stable Disease
- Other factors, including endothelin B (“ETBR”) expression

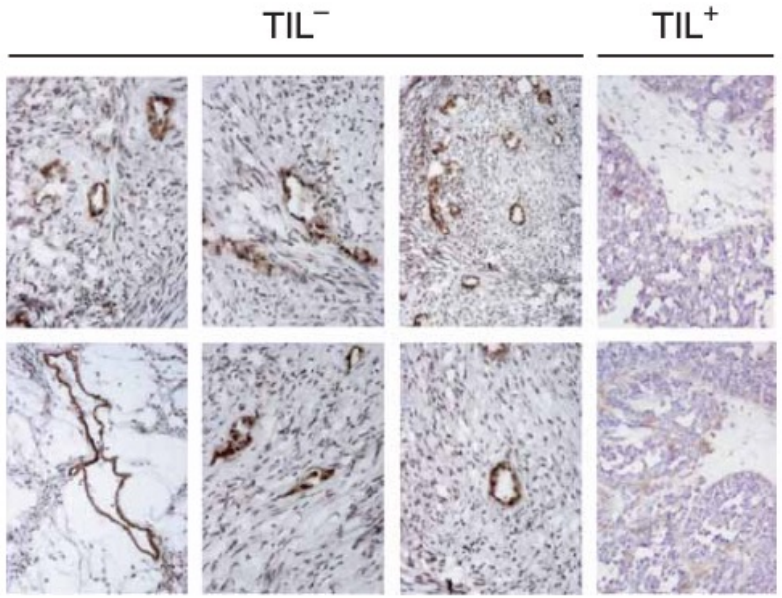
ETBR Status Correlates with Survival and TILs in Ovarian Cancer

Tumor Infiltrating Lymphocytes (TILs) Required for Immune Checkpoint Activity

- ~75% of ovarian cancer patients have high Endothelin B receptor expression
- Primary platinum resistant ovarian cancer (1º PROC) patients are typically excluded from clinical trials
- Vast majority are MS stable (MSS) and do not respond to anti-PD-1 (<10% ORR)
- ETBR-Hi status correlates with poor survival *AND* a lack of tumor infiltrating lymphocytes (TILs) which are required for anti-PD-1 to work





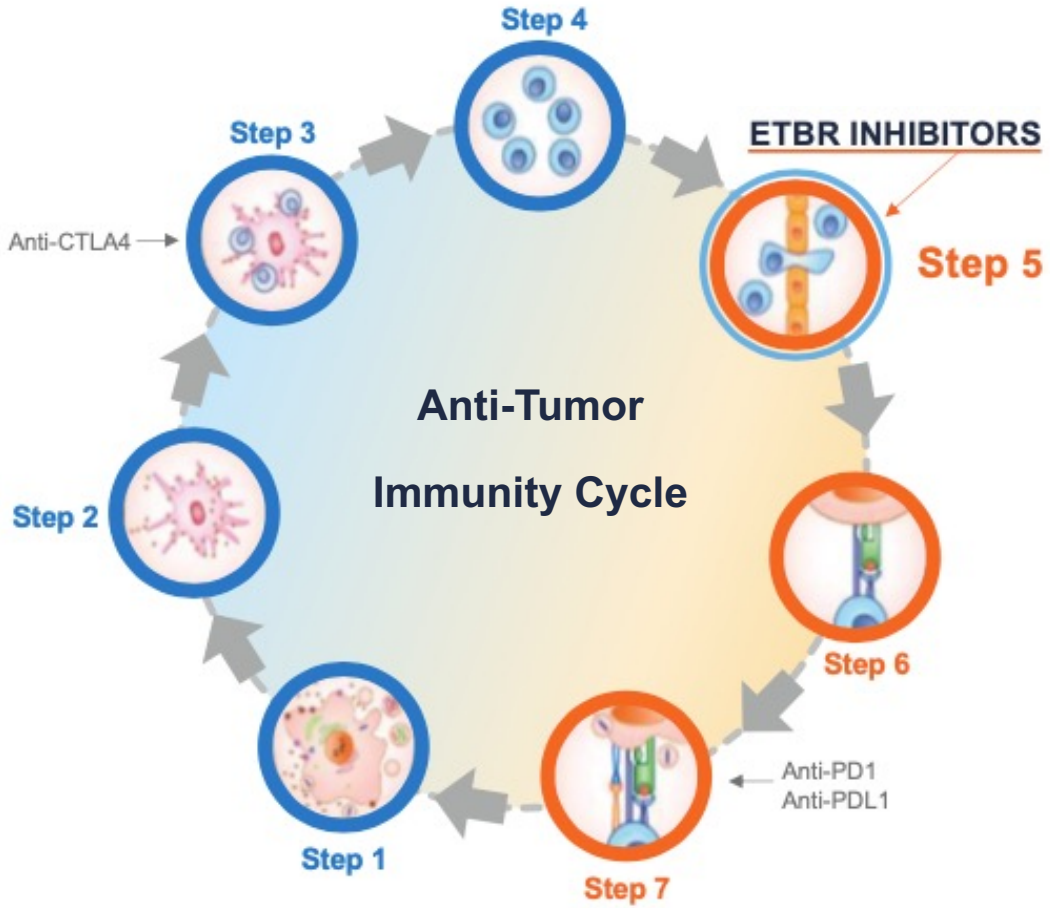


TIL- Tumor Infiltrating Lymphocytes

ETBR: Validated Target Affecting TIL Recruitment and Activation

Unlocks Broader PD-1 Potential by Acting Upstream of Checkpoint Target

- ETBR expression blocks the T cell trafficking step of the anti-tumor immunity cycle[1]
- ETBR expression correlates with poor survival across multiple solid tumors
- ~40% of all tumors express ETBR
- Higher ETBR expression rates are associated with more difficult to treat and resistant tumors



TIL- Tumor Infiltrating Lymphocytes

1. Clin Cancer Res 2009;15(14) July 15, 2009

ENB-003: A Highly Potent, Selective Inhibitor Of Endothelin B

Selectivity Is Key; Non-selective Inhibitors Lack Immunostimulatory Activity

Endothelin is a validated target with approved therapeutics, but approved non-selective inhibitors of endothelin A and B lack immunostimulatory effects

ENB-003 Profile

- **First-in-class, best-in-class**
- Small molecule
- Selective inhibitor of Endothelin B Receptor (ETBR)
- Low nanomolar potency against ETBR
- Good safety profile
- Intravenous and subcutaneous bioavailability
- Issued patents with 2039 expiry

ENB-003 IC_{50}	
Endothelin A (ETAR)	*
Endothelin B (ETBR)	66ng/ml

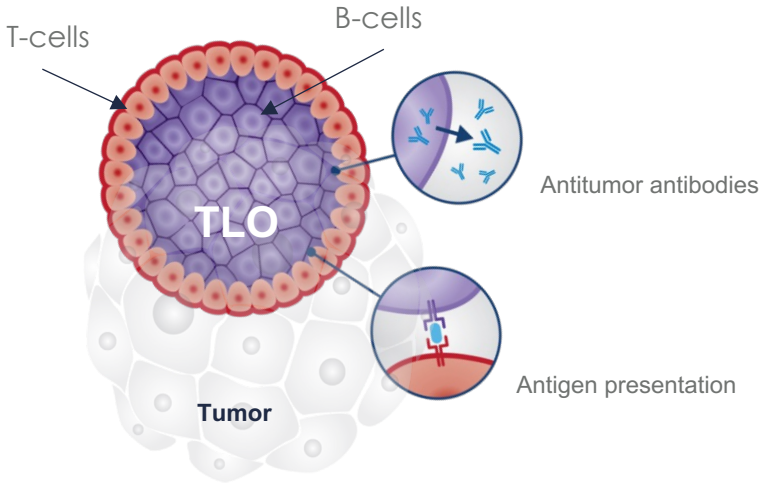
**Activity too low to calculate*

ENB-003 Acts Throughout the Tumor Microenvironment (TME)

Differentiated Mechanism of Action beyond Enabling TIL Infiltration and PD-1 Potentiation

Blood vessels

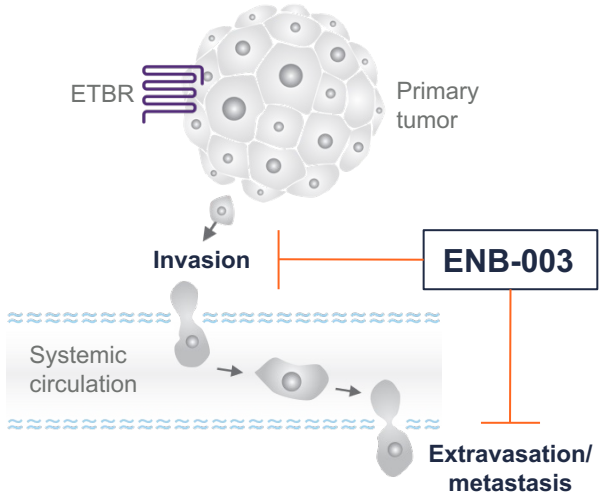
Restores expression of ICAM-1, stimulating T cell and B cell infiltration and induces intratumoral tertiary lymphoid organ (TLO) formation



TIL: Tumor infiltrating lymphocytes

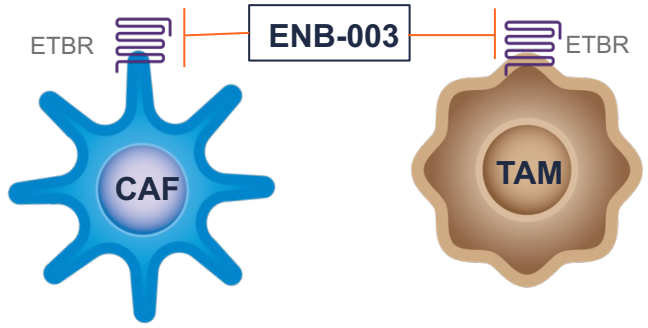
Tumor cells

Inhibits ETBR-mediated invasion and metastasis



Immunosuppressive cells

Blocks ETBR-mediated immunosuppressive functions of Cancer Associated Fibroblasts (CAFs) and Tumor Associated Macrophages (TAMs)

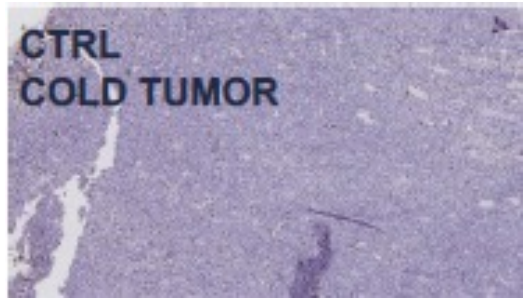


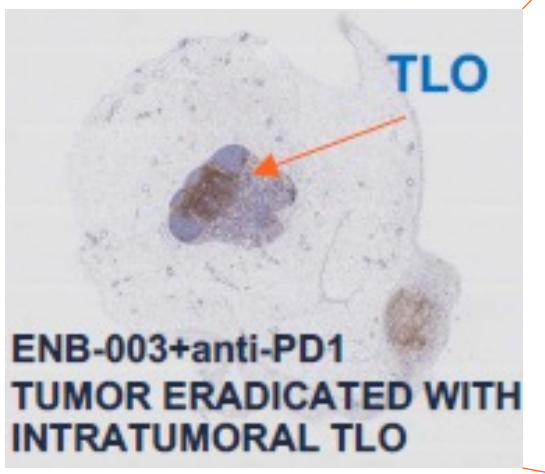
CAFs promote resistance to checkpoint inhibitors and block the function of immune cells required for anti-tumor activity (NK and cytotoxic T cells and dendritic cells)

TAMs inhibit T cell function and promote metastasis

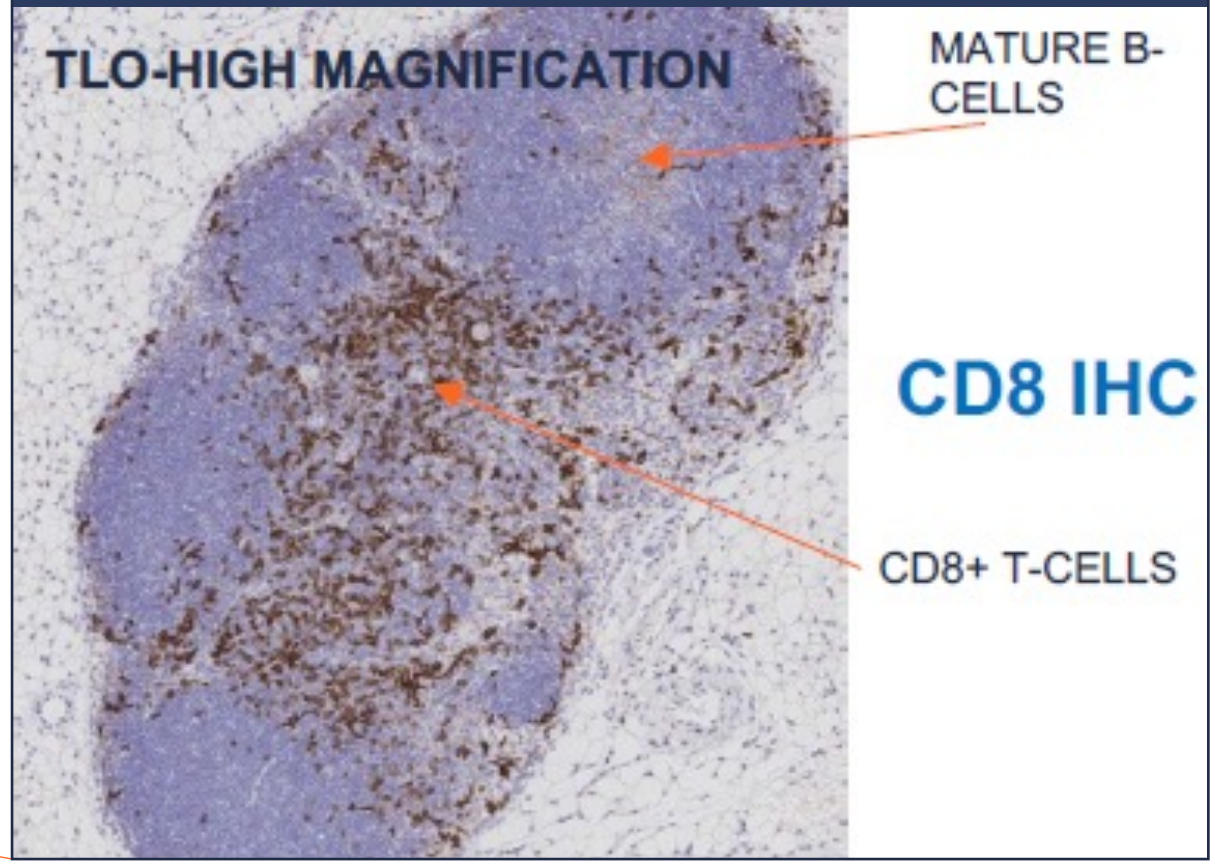
ENB-003 Induces Formation of Tertiary Lymphoid Organs (TLOs)

Antibody Super Factories Producing T and B Cells to Fight Cancer





TLOs: Antibody Super Factories providing long lasting anti-tumor immunity; Associated with favorable clinical prognosis



SM1 Syngeneic Melanoma model

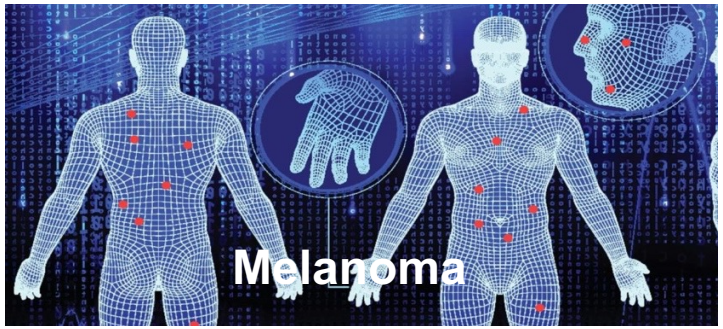
Tumor Biology Determines Key TME Compartment for ETBR Effect

Blood vessels

ETBR expression on blood vessels blocks T Cells from exiting bloodstream and entering tumor

: 75%-80% **(~10K patients annually in US**)

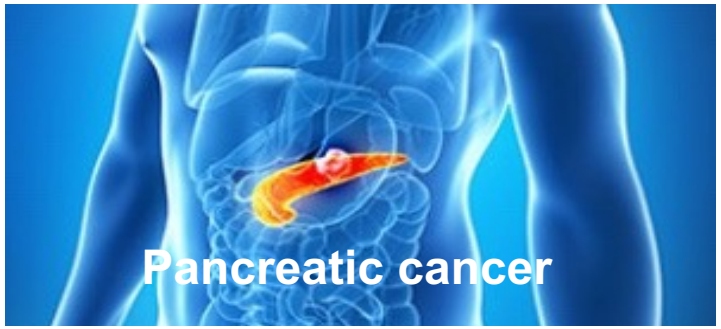
Tumor cells



ETBR drives proliferation, invasion and metastasis, and suppresses apoptosis of melanoma cells.

Patients eligible: 80%-90% **(~7K patients annually in US**)

Immunosuppressive cells



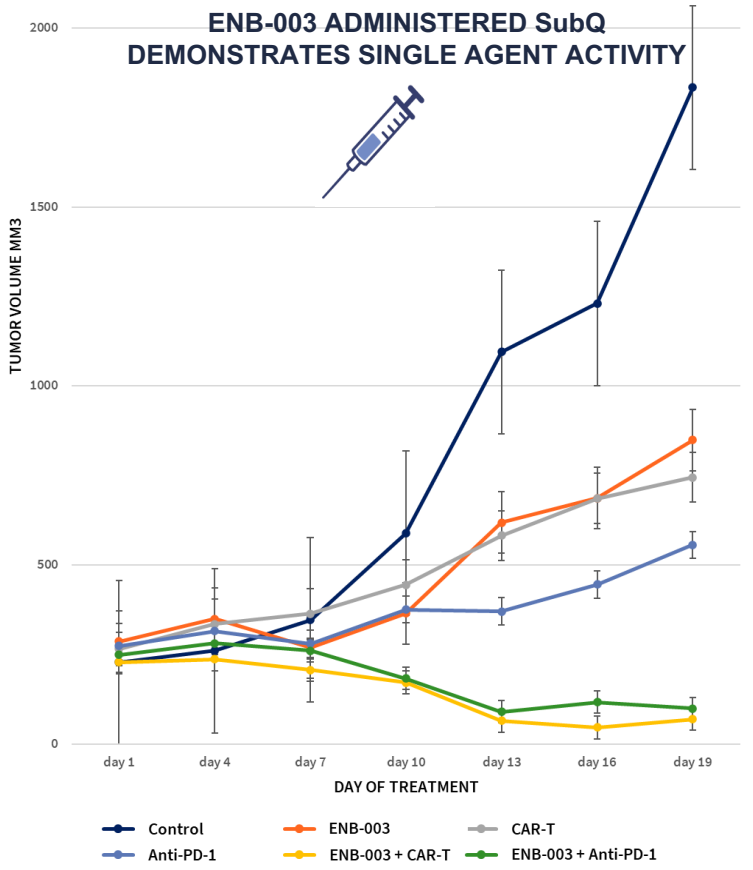
ETBR expressed on stellate cells that secrete fibrotic crust and block therapeutics

Patients eligible: ~25%-33% **(~11K-14K patients annually in US**)

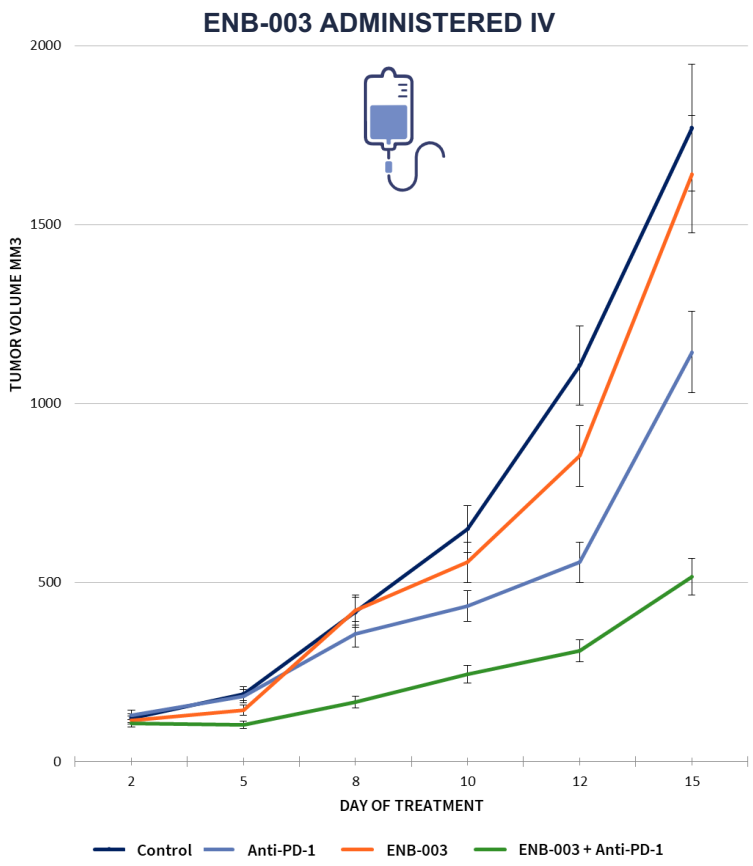
ENB-003 Mediated Tumor Inhibition and Regression In-Vivo

Activity Demonstrated Using SubQ & IV with Monotherapy and Combination Regimens

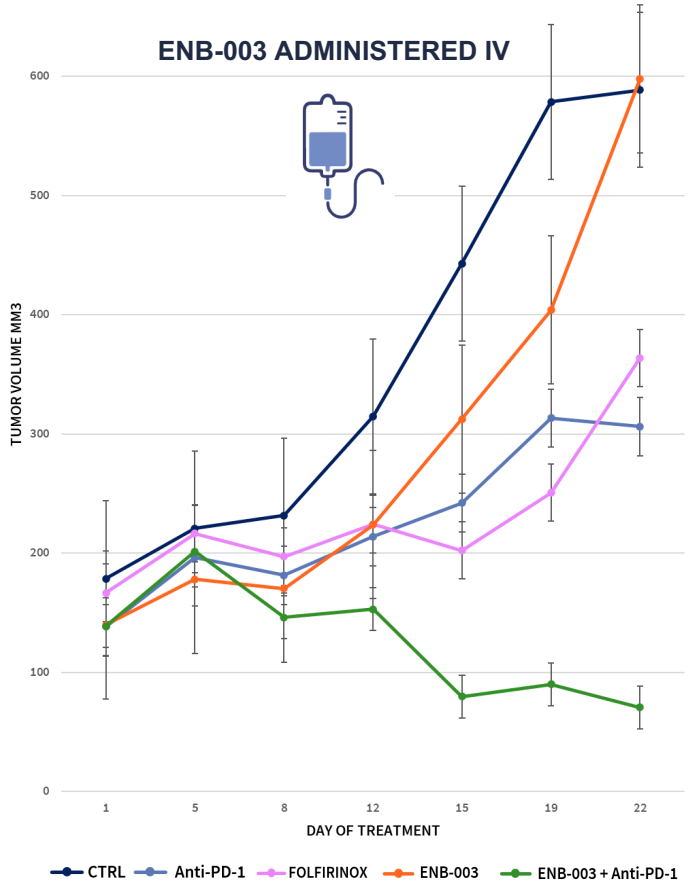
4T1 Triple Negative Breast Cancer



ID8-VEGF Ovarian Cancer



UNKC6141 Pancreatic Cancer



ENBOLDEN-101 Phase 1 Trial design: ENB-003+ Keytruda

Screening

- All tumor types
- PD-1 failure without a response, and/or microsatellite stable
- Cohort 1-5: ETBR Hi only
- Cohort 6: ETBR Hi and ETBR Lo/Zero

Tumor biopsy at baseline

Monotherapy Run in

Cohort 1-6: dose escalation (150, 300, 500, 750, 1000, 2000UG) ENB-003 IV Push

- Monotherapy run in for a total of 5 days
- Dosing for ENB-003 administered on Days 1, 3, & 5

Combination Treatment Cycle

Cohort 1-6: ENB-003 150-2000UG IV Push + Keytruda 200mg Q3w

- Dosing for ENB-003 administered on days 1, 3, 5, 8, 10, 12 of each cycle
- Treatment Cycle is a total of 21 days

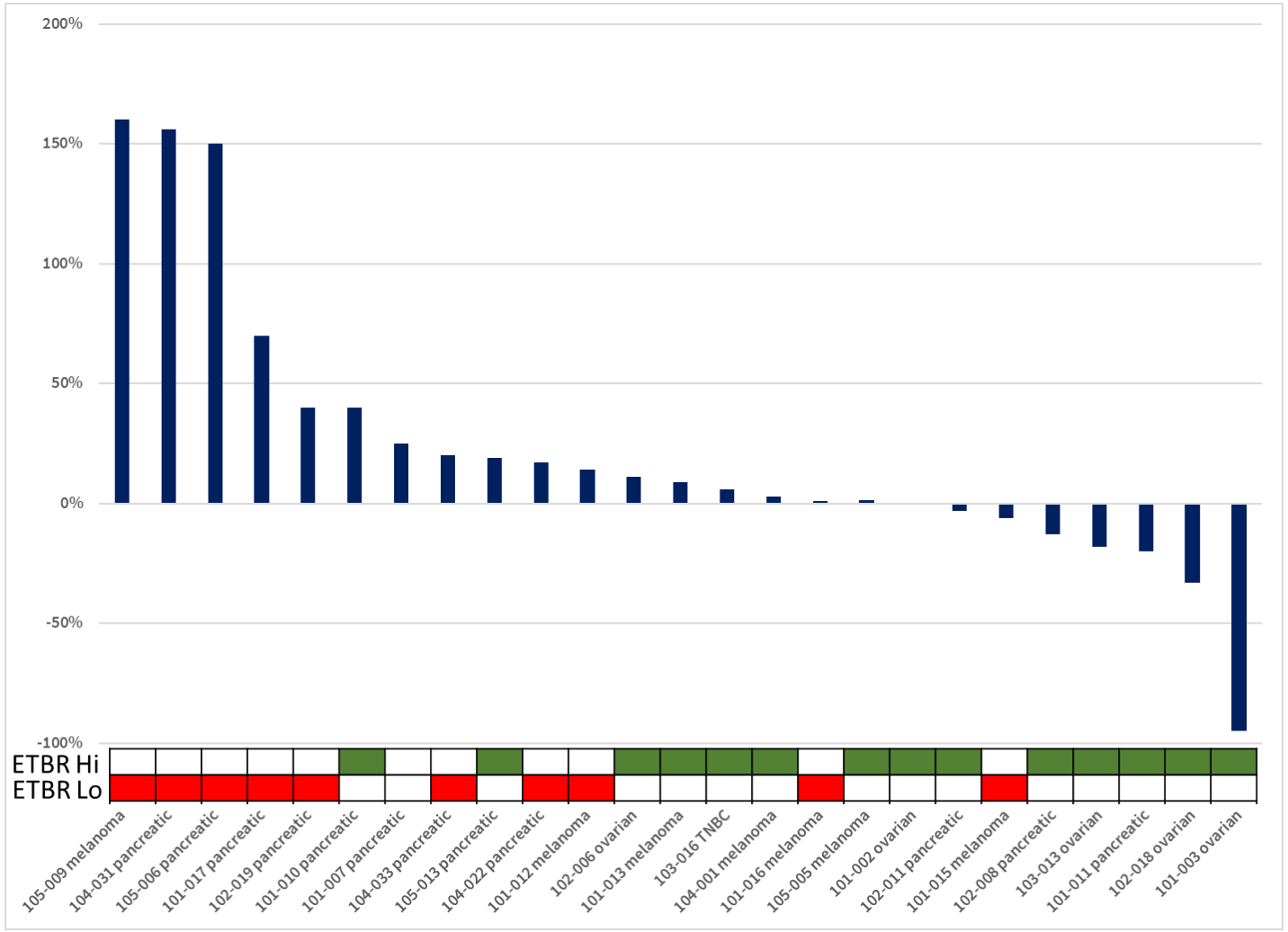
Repeat Treatment Cycles

- Treatment continues until progression or discontinuation
- Cohort 1-5: Combination Treatment Cycle repeats every other 21 days (every 42 days)
- Cohort 6: Combination Treatment Cycle repeats every 21 days
- 2000UG of IV ENB-003 is the recommended dose for Phase 2

Trial Registration NCT04205227

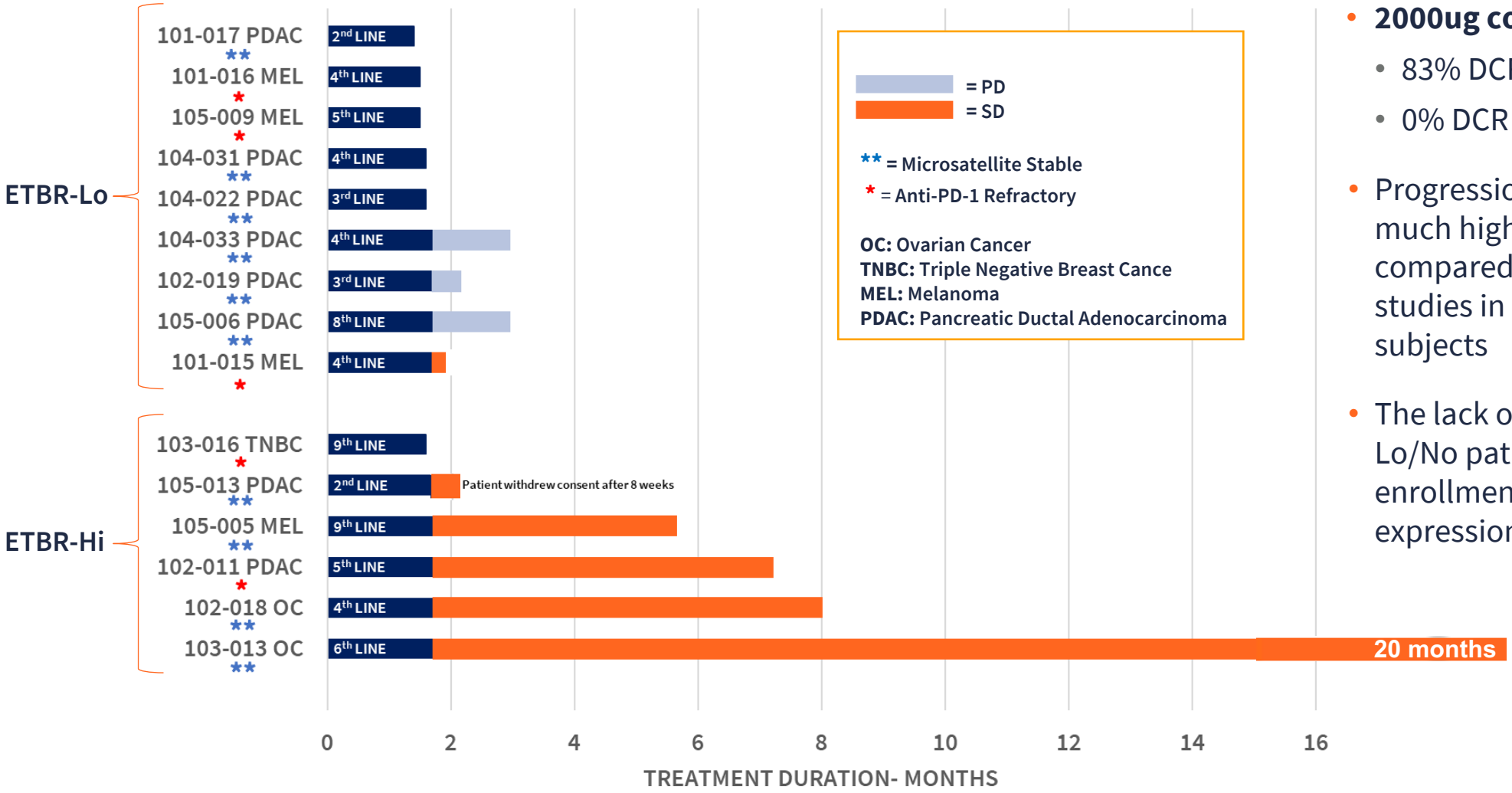
ENBOLDEN-101 Phase 1 Trial results: ENB-003+ Keytruda

Trend Towards Higher Activity With Increased Dose and Frequency



- Objective responses and disease control seen in both MS stable patients and PD-1 failures, neither of which would be expected to respond to PD-1 therapy
- Combination of ENB-003 and Keytruda was generally well tolerated
- 83% disease control rate for ETBR-Hi patients in cohort 6
- 33% disease control rate for ETBR-Hi patients in cohorts 1-5
- High response and disease control rates in difficult to treat tumors including platinum refractory/resistant ovarian, melanoma, and pancreatic

Disease Control Correlates with ETBR-HI Status in Highest Dose Cohort



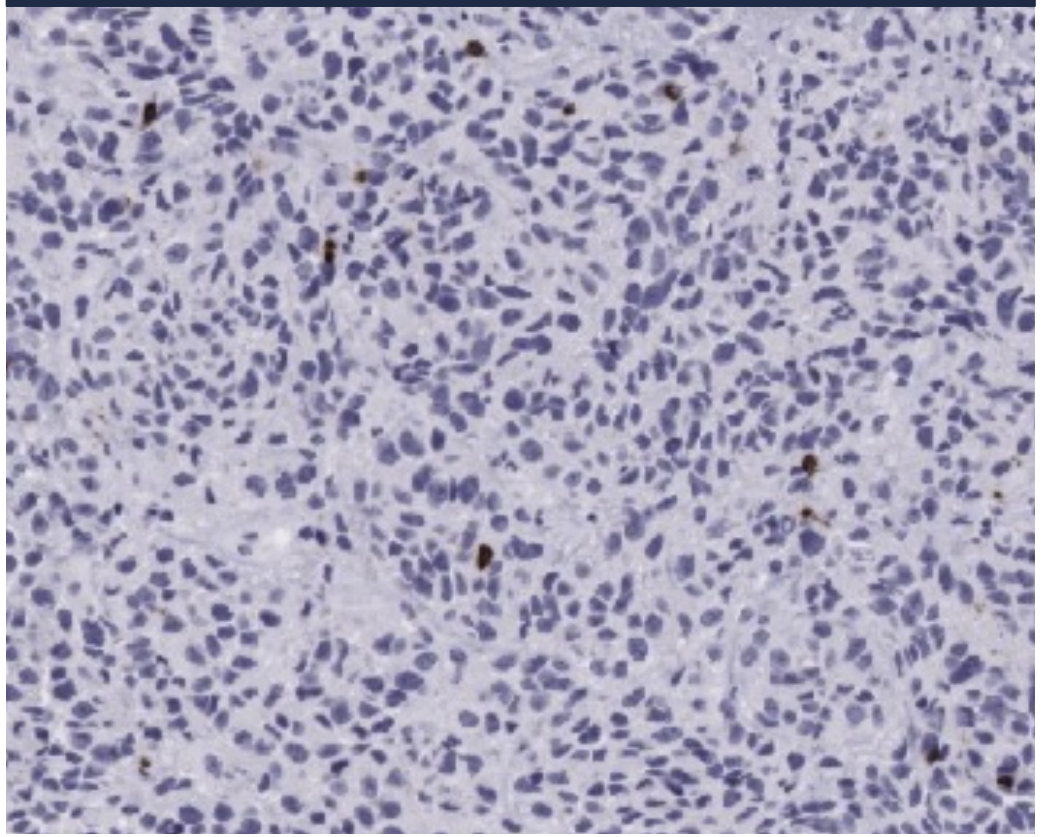
- **2000ug cohort:**
  - 83% DCR in ETBR-HI (N=6)
  - 0% DCR ETBR-LO/NO (N=9)
- Progression free survival and DCR much higher than expected when compared to historical Keytruda studies in PD-1 failures or MS Stable subjects
- The lack of responses in ETBR Lo/No patients confirms need for enrollment requirement for ETBR expression in Phase 2 trial

ENB-003 Dramatically Increases T-Cell Infiltration in Phase 1 study

T-Cells Within Tumor Microenvironment Required for Anti-PD-1 Therapies to be Effective

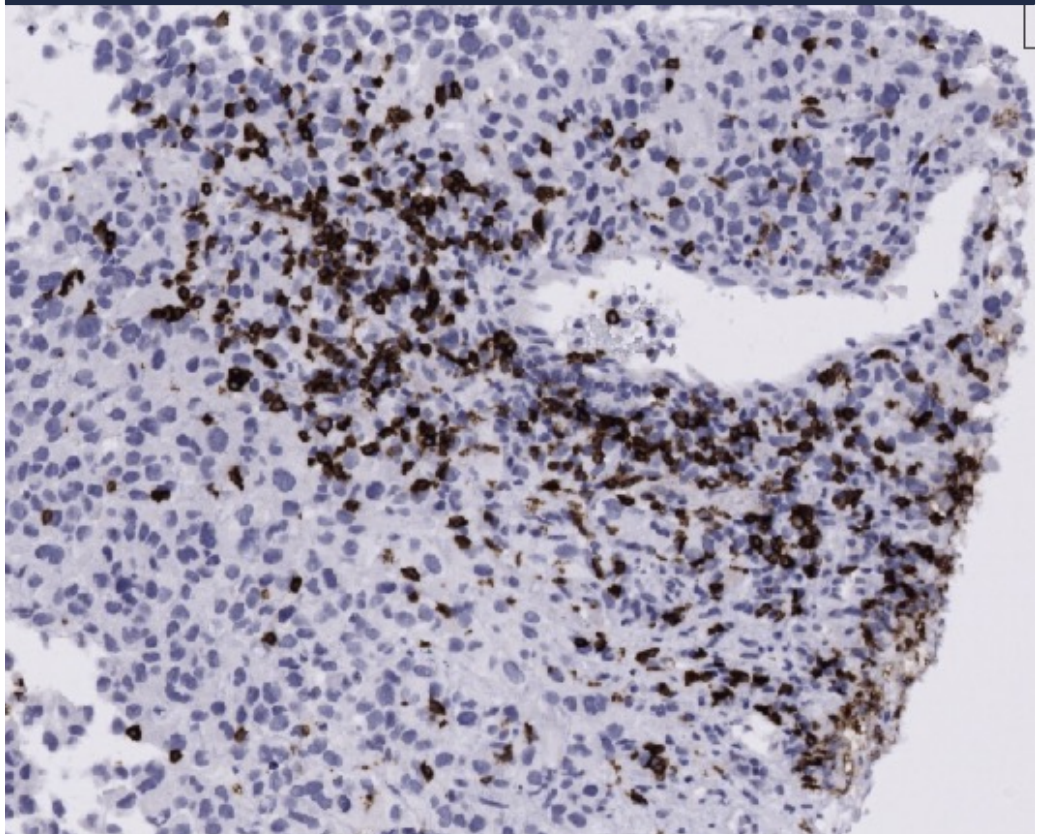
Baseline (pre dosing)

Little to no T-Cell Infiltration in Tumor



15 weeks Post Dosing

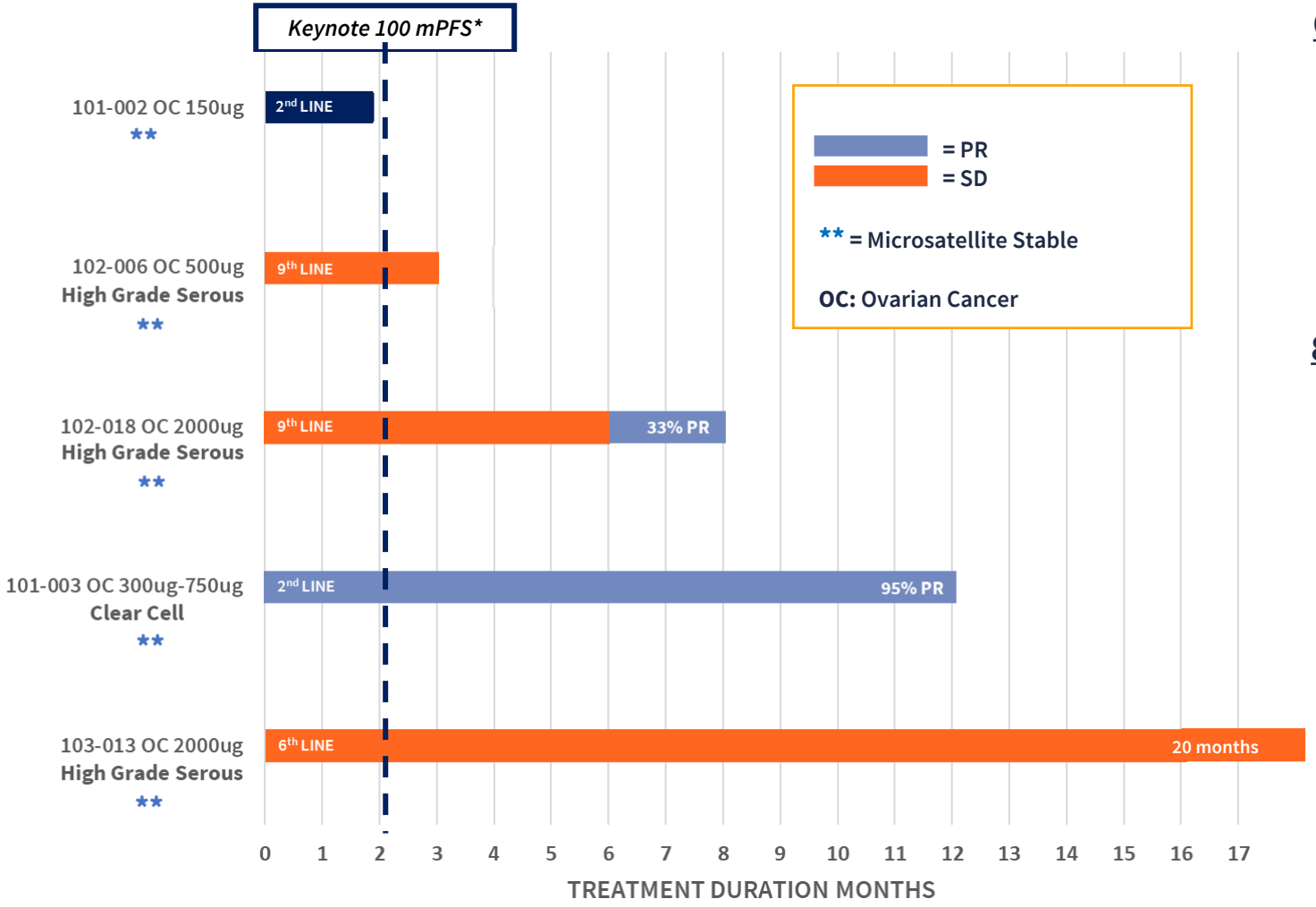
Significant T-Cell Infiltration in Tumor



Histopathology; melanoma subject, 5 prior lines including PD-1 failure, BRAF WT, high ETBR level in tumor, and <1% PD-L1 expression

40% Response Rate and 80% DCR in MS Stable Ovarian Cancer

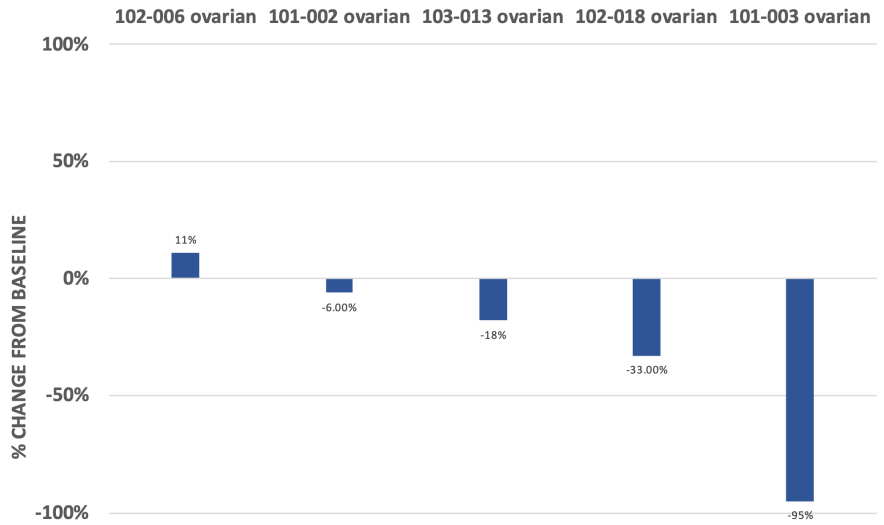
Compares Favorably to Expected ORR, DCR, and mPFS with Single Agent Pembrolizumab in Keynote 100 study



Ovarian Cancer Historical Benchmark Keynote 100

- Median Progression Free Survival (mPFS) rate at 2.1 months
- <10% Overall Response Rate (ORR)
- 37% Disease Control Rate (DCR)

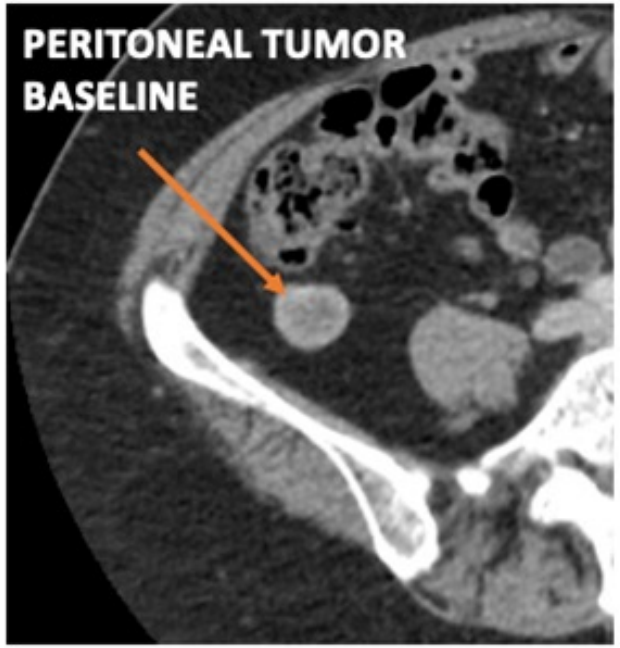
80% of OC Patients Show Shrinkage of Target Lesions



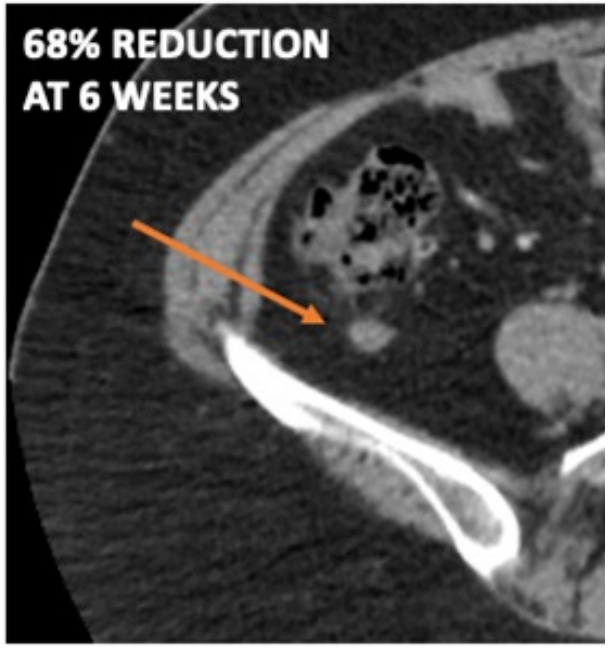
Near CR In Platinum Refractory Ovarian Cancer

Patient 101-003: PD-L1 Negative, MS Stable Subject Not Expected To Respond

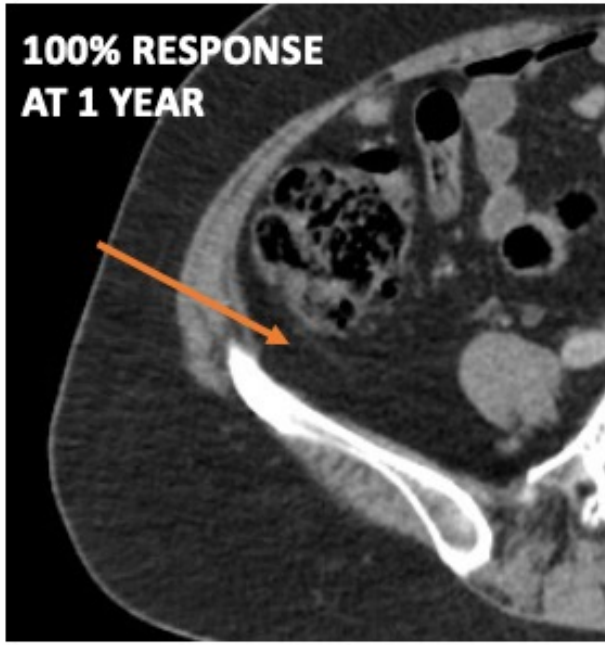
Baseline



6 Weeks



1 Year



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-

20-Month Progression Free Survival in 6th Line Platinum Resistant Ovarian Cancer Patient

Patient 103-013: PD-L1 <1%, MS Stable Subject Not Expected To Respond

- Heavily pre-treated: 6th line of therapy
- Relapse after each of 3 courses of platinum therapy
- Last Tx with carboplatin/peg liposomal doxorubicin- 6 mos
- 90% decrease in CA125 after treatment initiation

ENB-003+Keytruda Combination Well Tolerated

No Dose Limiting Toxicities or Significant Immune Related Adverse Events

TREATMENT EMERGENT ADVERSE EVENTS OCCURRING IN 10% OR MORE SUBJECTS IRRESPECTVE OF GRADE OR CAUSALITY (n=46)	n (%)	GRADE 3 OR HIGHER	POSSIBLY RELATED TO ENB-003 AND/OR PEMBROLIZUMAB
FATIGUE	13 (28.2%)	0	4
CONSTIPATION	12 (26.1%)	0	2
ABDOMINAL PAIN	12 (26.1.%)	4	1
NAUSEA	11 (23.9%)	0	0
ANEMIA	8 (17.4%)	1	1
DIARRHEA	8 (17.4%)	0	3
DYSPNEA	7 (15.2%)	3	3
HYPONATREMIA	6 (13.0%)	2	0
ASCITES	5 (10.9%)	1	0
RASH	5 (10.9%)	0	2
Vomiting	5 (10.9%)	1	1

ENB-003+Keytruda: A Promising Therapy For MSS/PD-1 Failures

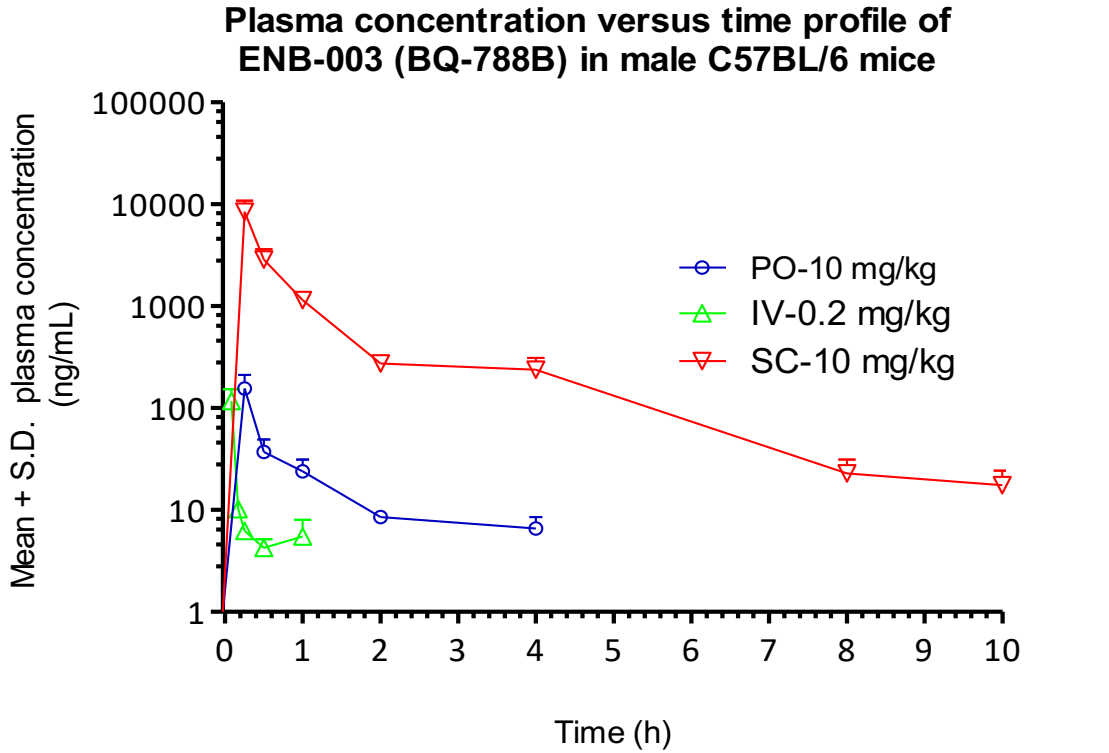
Initial Phase 2 study to be Conducted in Platinum Resistant Ovarian Cancer

- 40% ORR and 80% DCR in MSS primary platinum resistant ovarian cancer
  - ORR is <10% and DCR is 37% with single agent Keytruda (KN100)
- ~30% of OC population is primary platinum resistant; typically excluded from trials
- Favorable safety profile in Phase 1, no dose limiting toxicities
  - Recommended phase 2 dose: 2000ug
- Opportunity to explore single agent activity of subcutaneous formulation
- Candidate predictive biomarker
- Phase 2 initiation Q1 2025
  - Potential to expand into other cancer indications

Subcutaneous Delivery Significantly Increases Time Above IC_{50}

Route to be examined in Phase 2

Pharmacokinetic Comparison by Route

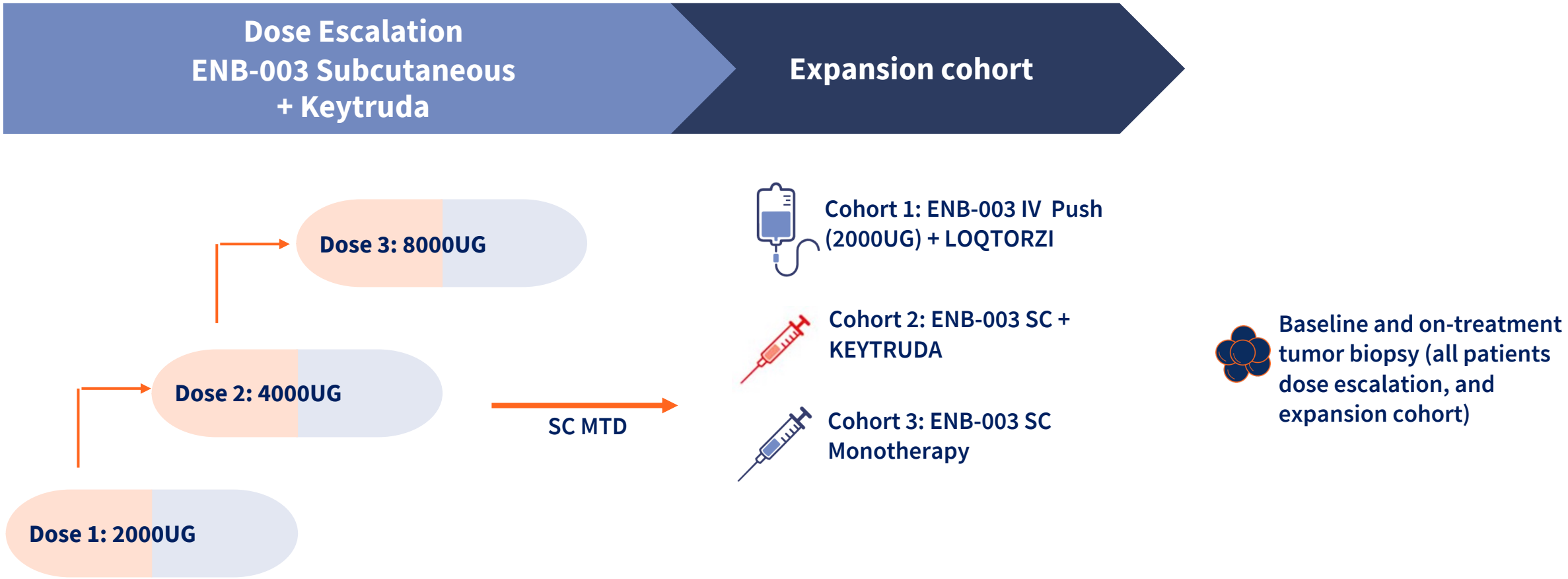


Demonstrated single agent activity comparable to immune checkpoint inhibitors using subcutaneous formulation

Subcutaneous toxicology demonstrates lack of toxicity at 50x the dose equivalent to the 2000ug IV dose used in the Phase 1 ENBOLDEN study

Discovery made during ENBOLDEN Phase 1 IV Trial

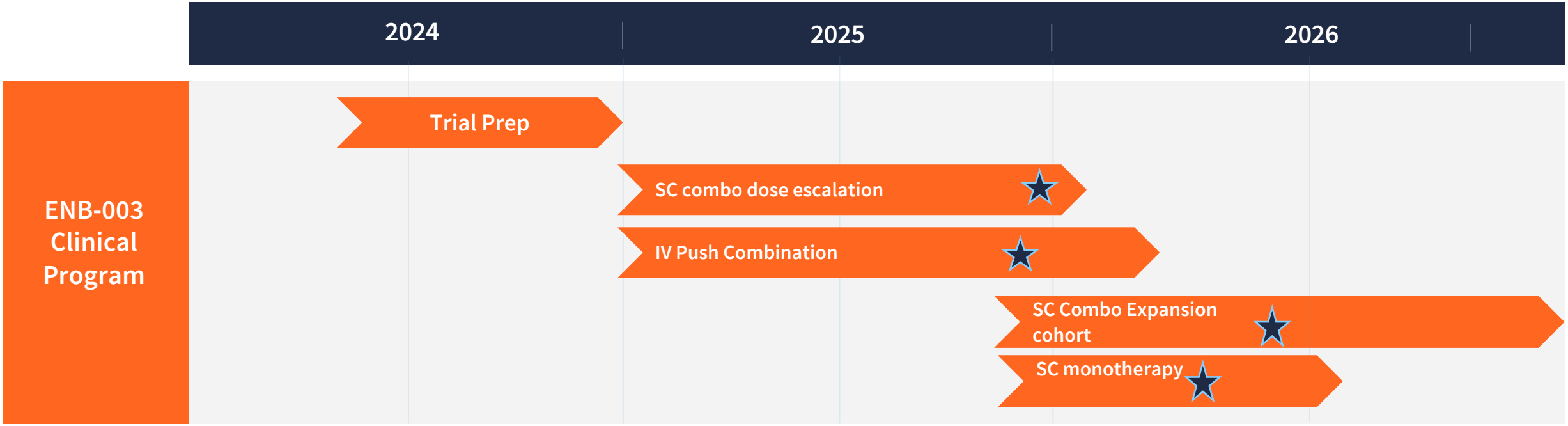
ENBOLDEN-202 Phase 2 Trial Design- MS stable PROC*



*Will enroll platinum refractory and primary PROC (progression within 6 months of initial treatment with platinum)

PROC: platinum resistant ovarian cancer

Phase 2 Trial Milestones



★ = 3 month ORR Readout (Primary Endpoint)

Experienced Leadership and Drug Developers

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CEO/CSO, Co-Founder

NYU School of Medicine

Sam Backenroth
CFO

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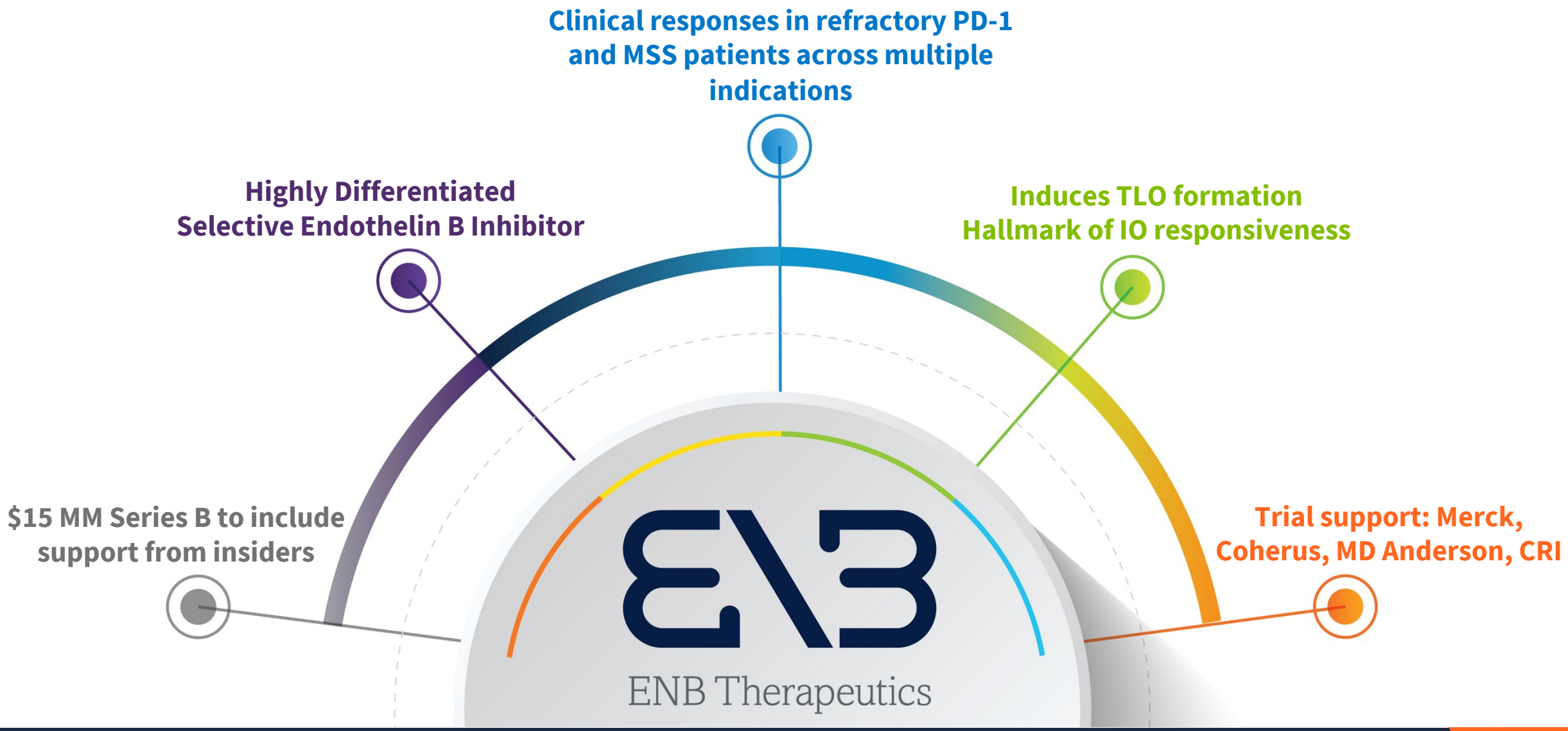
British Heart Foundation

The Opportunity



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