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 Inhibitors to reverse immunotherapy resistance

Strong and Broad IP
and Regulatory Exclusivity

Clinical trial collaboration
with big Pharma partner Merck

Companion Diagnostic
In development identifies patients most likely to respond

Short-Term Milestones
IND filing 3Q 2019; PI/PII initiation 3Q 2019

Solid Leadership and Scientific Team
Scientific founders co-inventors on first patents filed covering ETBR as a therapeutic target for cancer: NYU School of Medicine, 1997

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

ETBR: endothelin B Receptor

ENB Therapeutics snapshot

Founded in 2015

- Focused on cancer therapies to overcome drug resistance
- Technology originally developed at NYUSOM
- Based in NYC Alexandria Center for Life Science LaunchLabs incubator

Funding

- $500K friends and family
- Closed $1M Seed round 1Q 2018
- Closed $8M Series A 3Q 2018 to support Ph1 trials
- Raising $25M Series B to support Ph2

Management Team

- **Sumayah Jamal, MD-PhD, President, CSO, Co-founder:** 30 years research experience, 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, 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),
- CEO, CMO to be hired

Advisory Board

- **Sanjiv Agarwala, MD** Chief, Medical Oncology and Hematology, St. Luke's Cancer Center, world-recognized expert in cancer immunotherapy and melanoma
- **Jay Gibbs, PhD,** 30+ years in Pharma, expertise in oncology drug development, former Scientific Dir. At Astra Zeneca and Merck
- **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.
- **Adriann Sax,** 30 years pharma, Roche, BMS, Merck
- **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

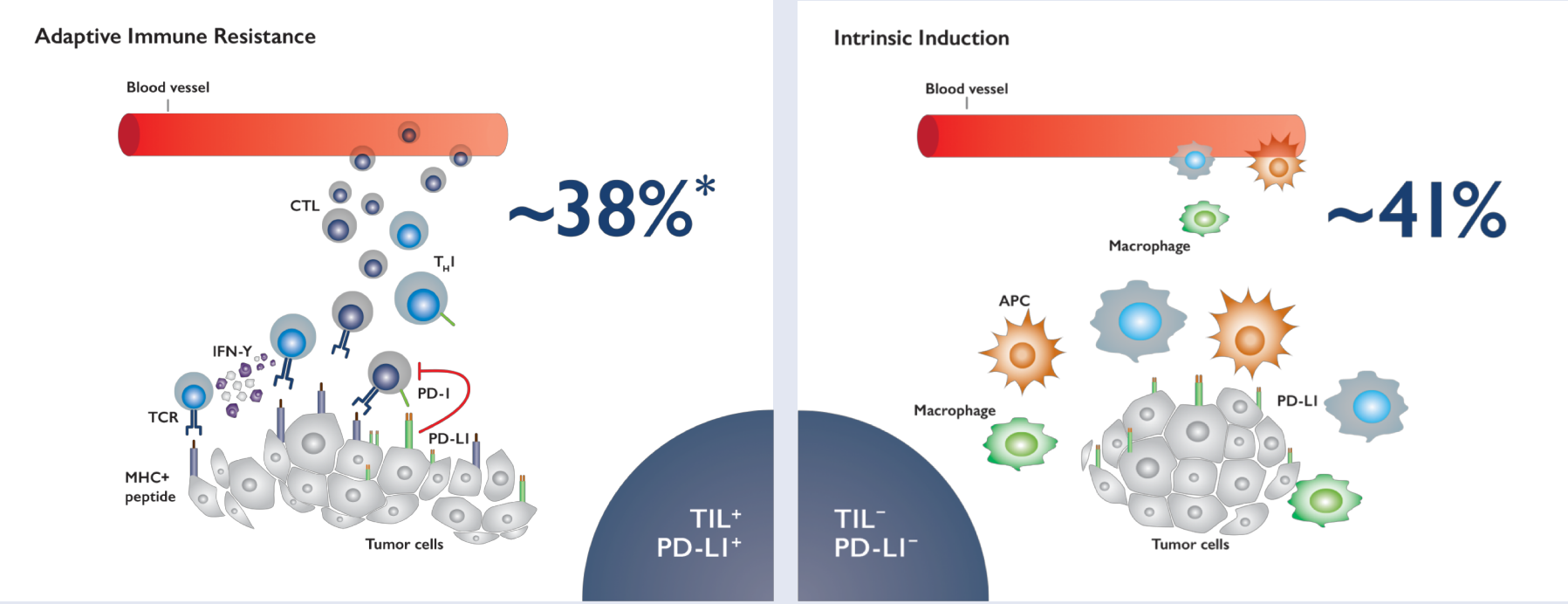
Consultants

- CMC-**Vincent Bille, PhD,** Founder Marble Pharma Consulting, 1990-2007 UCB/Lonza, expertise in synthetic peptide manufacturing
- Safety/tox: **Lesley Earl, PhD,** Assoc Dir. Non-clinical services, ERA consulting.25+ years industry experience in pre-clinical IND enabling study direction and management
- **Cello Health Bioconsultants**

The majority of cancer patients do 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
- 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

***% melanoma patients with anti-PD1 responder profile, lower responder rates observed in other cancers**

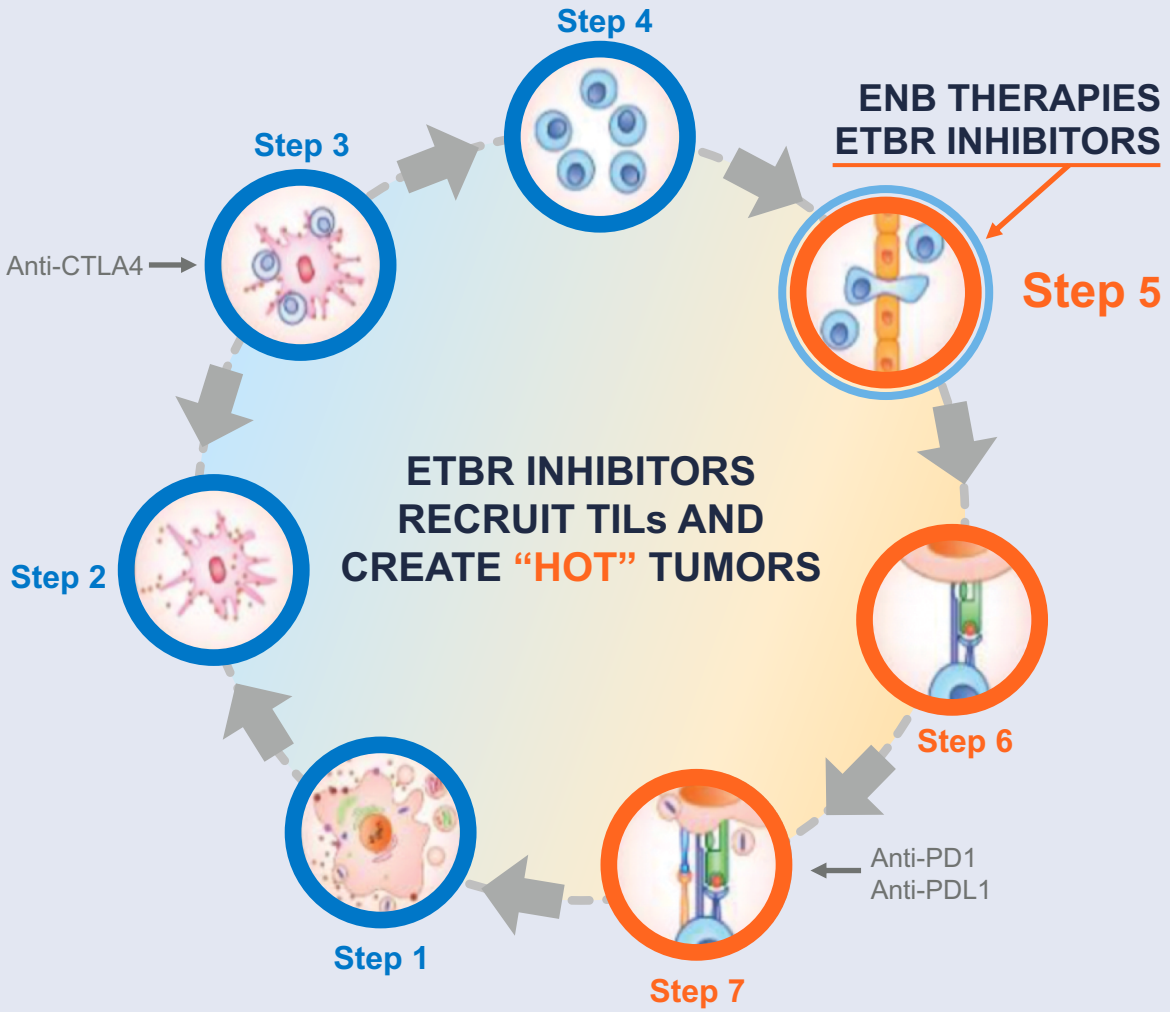


IO: Immunotherapy; **TIL:** Tumor infiltrating lymphocytes; **TME:** Tumor microenvironment

Source: Teng et al, *Cancer Research* 2015

Our therapies switch TIL- tumors to TIL+ tumors

- The ETBR is overexpressed in the TME in over 40% of all cancers and prevents TILs from infiltrating tumors
- Selective ETBR inhibitors switch TIL- "**cold**" tumors to TIL+ "**hot**" tumors in animal models and enhance efficacy of otherwise ineffective IO
- Intratumoral injection of ETBR inhibitors recruit TILs to skin cancers in human subjects
- B receptor selectivity required to convert TIL- tumors to TIL+ tumors
  - → A receptor blockade or A/B dual receptor blockade blocks TIL infiltration (see slide 25)
  - → No selective B receptor inhibitors have ever been tested in clinical trials for cancer

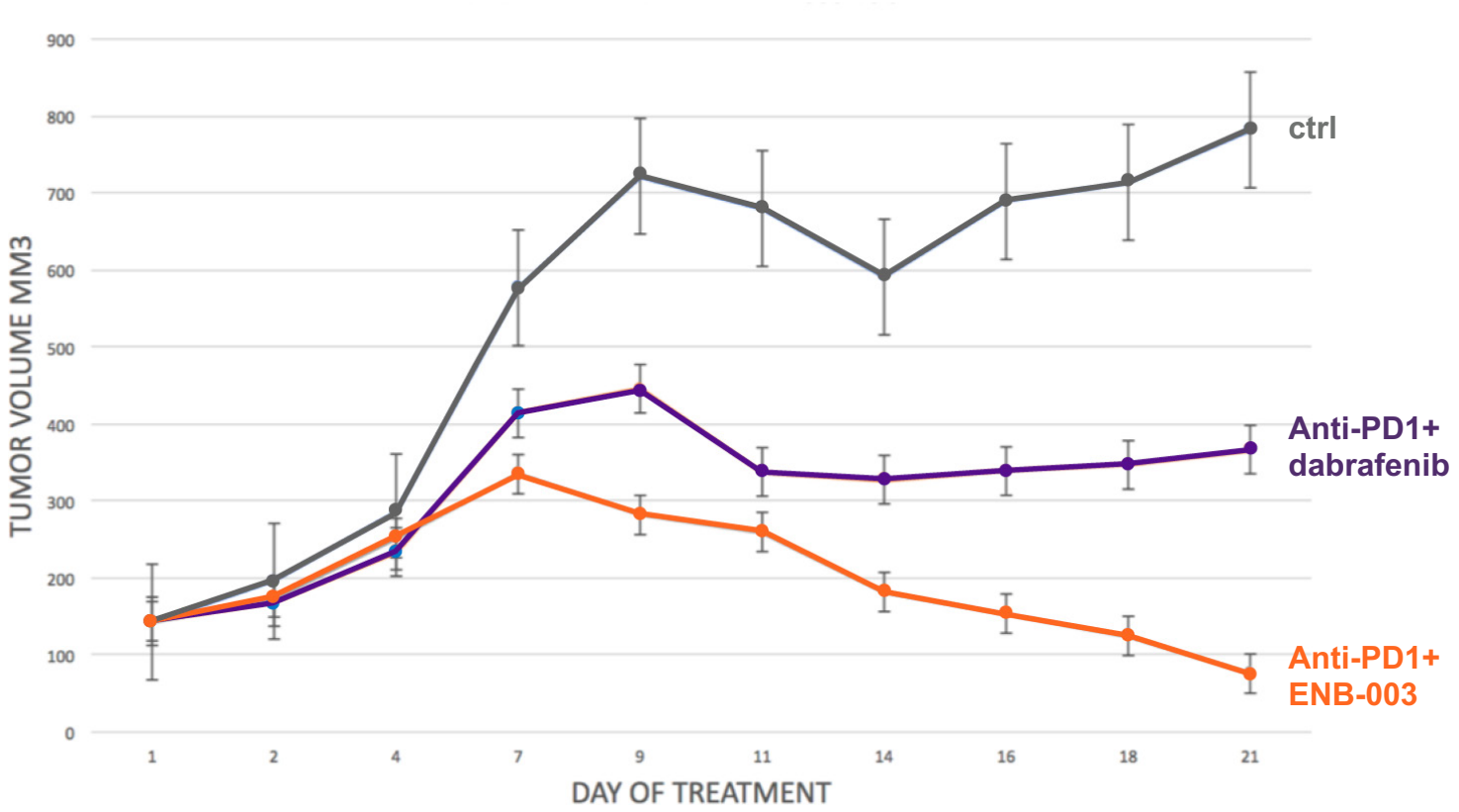


ETBR: endothelin B receptor, **TIL:** Tumor infiltrating lymphocytes, **TME:** Tumor microenvironment

ENB-003 overcomes anti-PD1 resistance in syngeneic melanoma model and eradicates tumors within 21 days

In vivo tumor growth curve: anti-PD1 resistant TIL- syngeneic melanoma model

- ENB-003 reversed anti-PD1 resistance, induced intratumoral TLO formation and eradicated tumors (see next slide)*
- Previously tested SoC drug combinations using this model failed to shrink tumors and all resulted in eventual drug resistance (see slide 24)



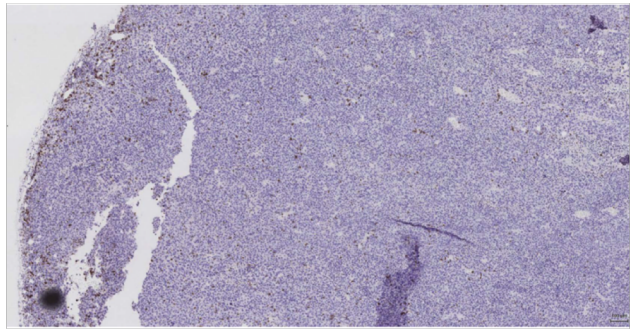
IV: Intravenous; **SoC**: standard of care

*Dosing regimen: 0.2mg/kg 3X per week IV, 6 doses total required for tumor eradication

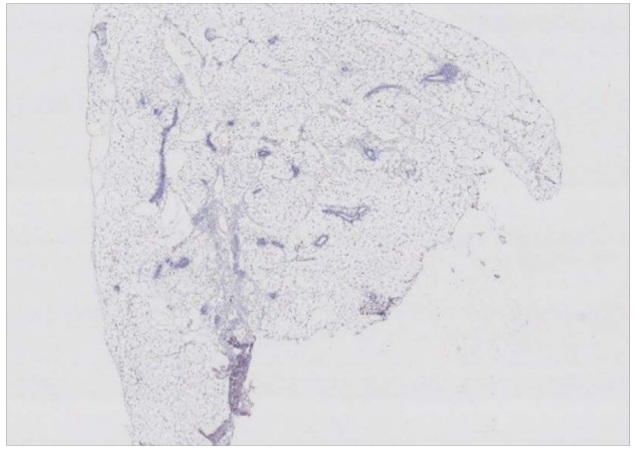
Source: internal study, unpublished

ENB-003 + anti-PD1 combination eradicates melanoma tumors in 21 days, promotes robust CD8+ TIL infiltration* and intratumoral TLO formation**

Untreated control: paucity of TILs

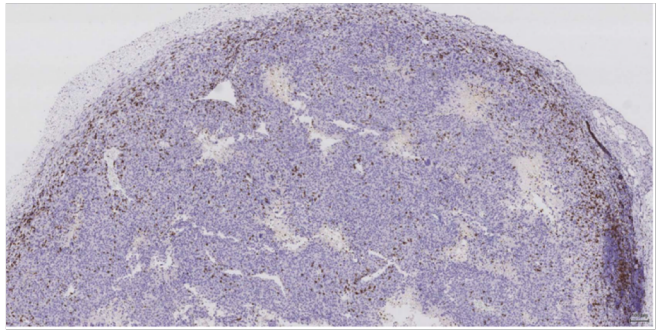


anti-PD1+ENB-003- No residual tumor

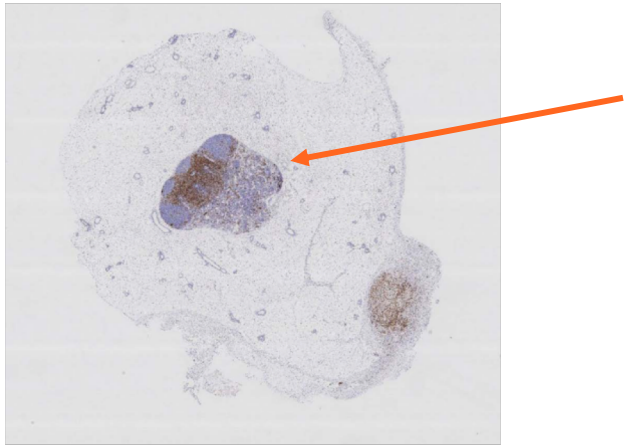


*brown stain

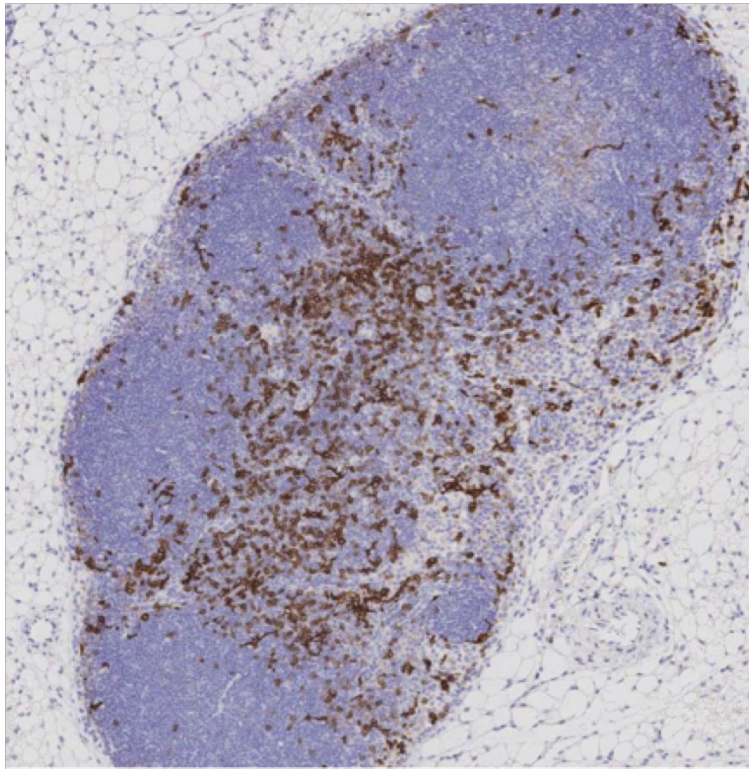
Anti-PD1+ dabrafenib: Increase in TILs, predominantly peripheral distribution



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



TLO (Hi mag)

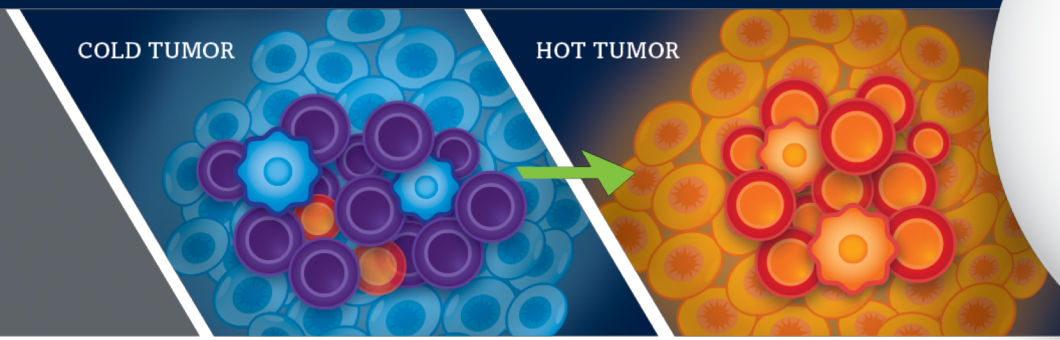


** TLOs are functionally equivalent to lymph nodes, produce tumor-specific T- and B-cells: **"antibody factories to fight cancer,"** induce long lasting anti-tumor immunity and are associated with favorable clinical prognosis in multiple cancers

Overcoming IO resistance across multiple cancer types

Selective ETBR inhibition targets the TME through two unique mechanisms

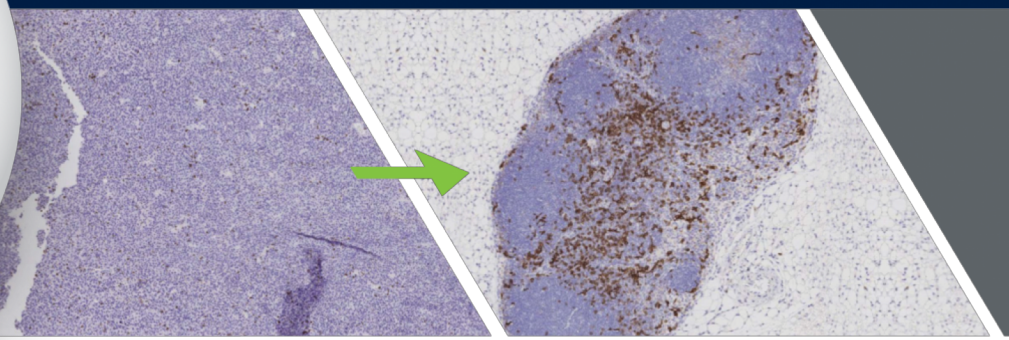
1. Switching immune-suppressed “cold” TMEs to “hot” TMEs, allowing TILs to infiltrate tumors



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

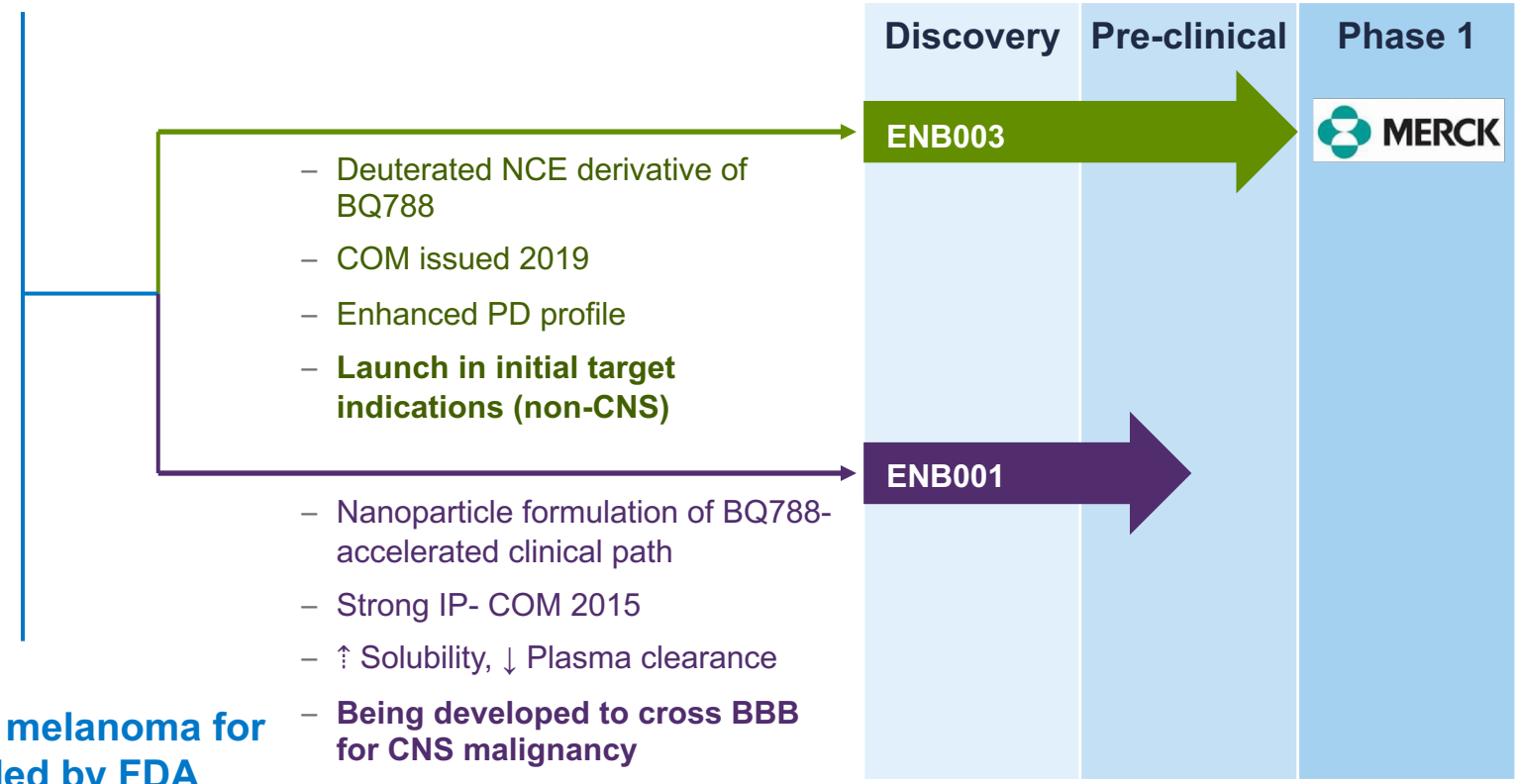


TLOs are new lymph nodes that form within tumors and eradicate them

ETBR: endothelin B receptor; **IO:** immunotherapy; **TLO**: tertiary lymphoid organ; **TME:** Tumor microenvironment

First-in-class NCE ENB-003 and ENB-001 : potential synergy with multiple immuno-oncology platforms

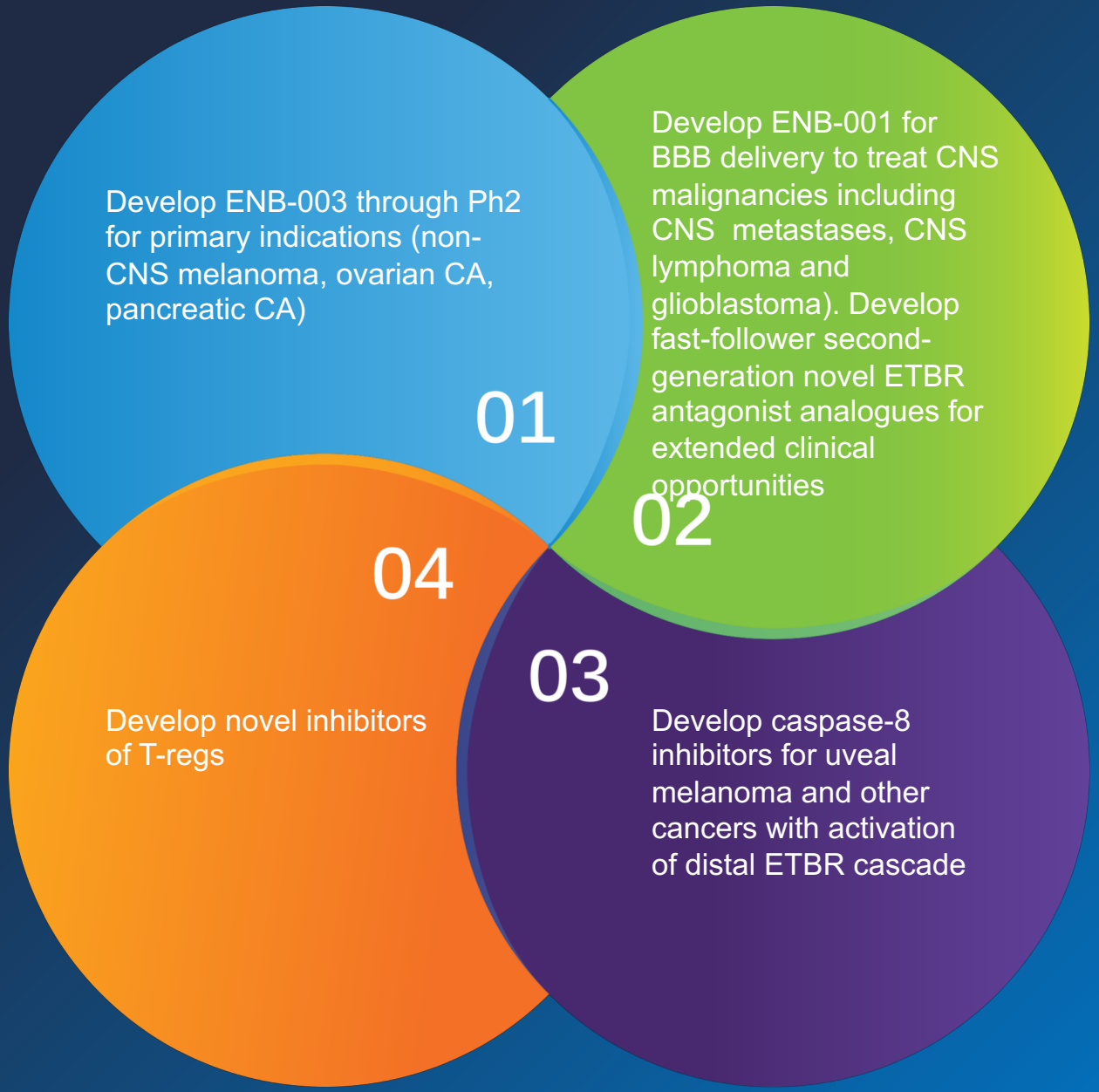
- **BQ788: Parent compound**
  - Off-patent research tool for CV disease
  - Established safety profile in >30 clinical studies (administered to 400+ patients)
  - Robust pre-clinical proof of concept across multiple cancers
  - Converts TIL- tumors to TIL+
  - Enhances immunotherapy efficacy
- **Low solubility, rapid plasma clearance**



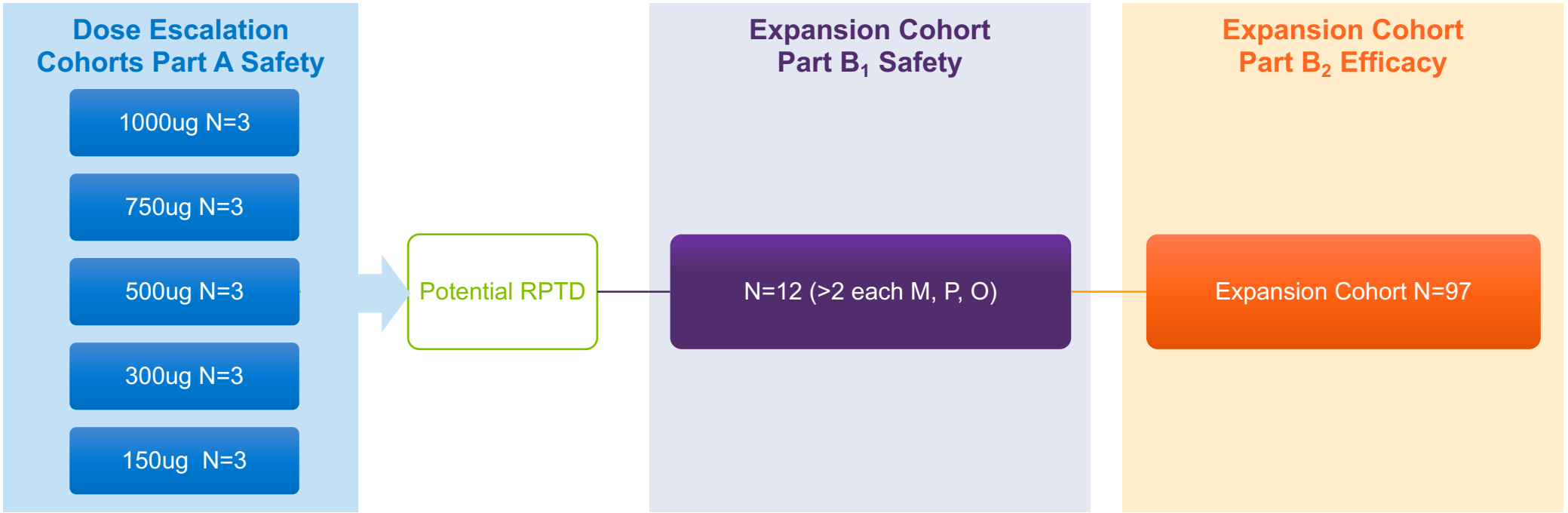
Orphan drug designation for melanoma for ENB-001 and ENB-003 awarded by FDA

BBB: Blood-brain barrier; **CNS:** Central nervous system; **COM**: composition of matter; **CV:** Cardiovascular; **IP:** intellectual property; **NCE:** new chemical entity; **PD:** Pharmacodynamic

Business model



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 x 1 21 day cycle, Pembro alone x 1 21 day 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 run in.; ENB-003+ Pembro, and Pembro alone in alternating 21 day cycles

Part B_2

Expansion cohort at potential RPTD, no run in with ENB-003, ENB-003+ Pembro, and Pembro alone in alternating 21 day cycles, N= 25 M, 39 O, 39 Part B_1)

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

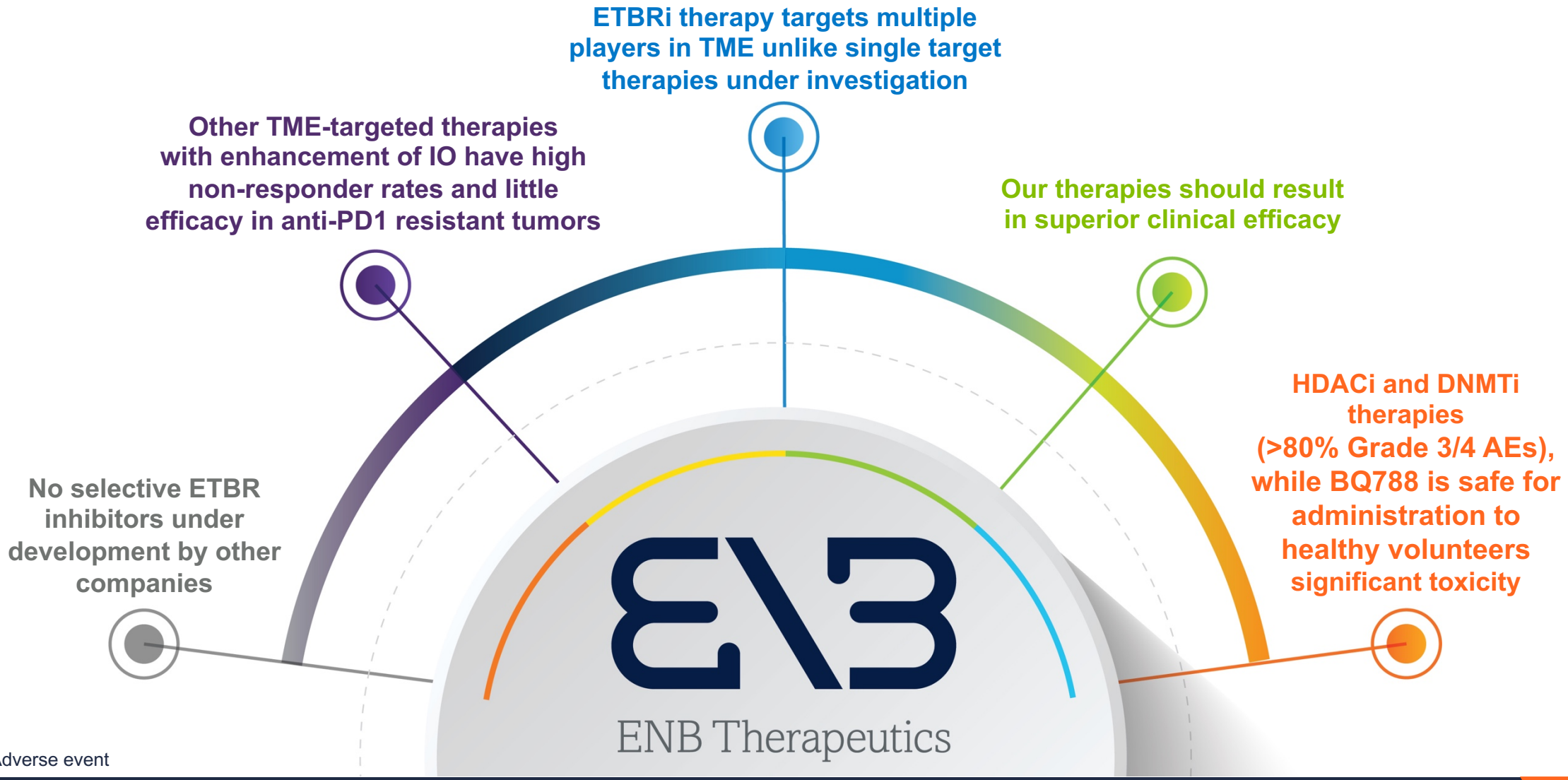
Strong intellectual and regulatory exclusivity

All patents are 100% company-owned and unencumbered

	ENB-003	ENB-001
COM	Patent office has issued notice of allowance for COM claims filed 2018- awaiting issuance of patent number	Formulation COM filed 2016-Nanoparticle formulation supports COM similar to NCE due to strict FDA guidelines regarding bioequivalence
Method of use	Patent office has issued notice of allowance for broad MOU claims filed 2018 for Combination of ETBRi with anti-PD1 and other IO therapies for the treatment of cancer-awaiting issuance of patent number	Combination with anti-PD1 and other IO therapies for the treatment of cancer
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 Bladder CA in preparation.	Awarded by FDA for melanoma in 2016: provides 7-year market exclusivity post FDA approval, Application for ovarian and bladder CA in preparation.

IHC: Immunohistochemistry

ENB's Advantage



AE: Adverse event

Funding

- **Funds raised to date**
  - $500K friends and family
  - $1M seed round closed 1Q 2018
  - Series A financing closed for $7M-$8M 3Q 2018
- **Seeking $25M Series B financing**
  - To support clinical development of ENB-003 through Phase 2
  - Preferred shares

REMIGES VENTURES

Bio Advance

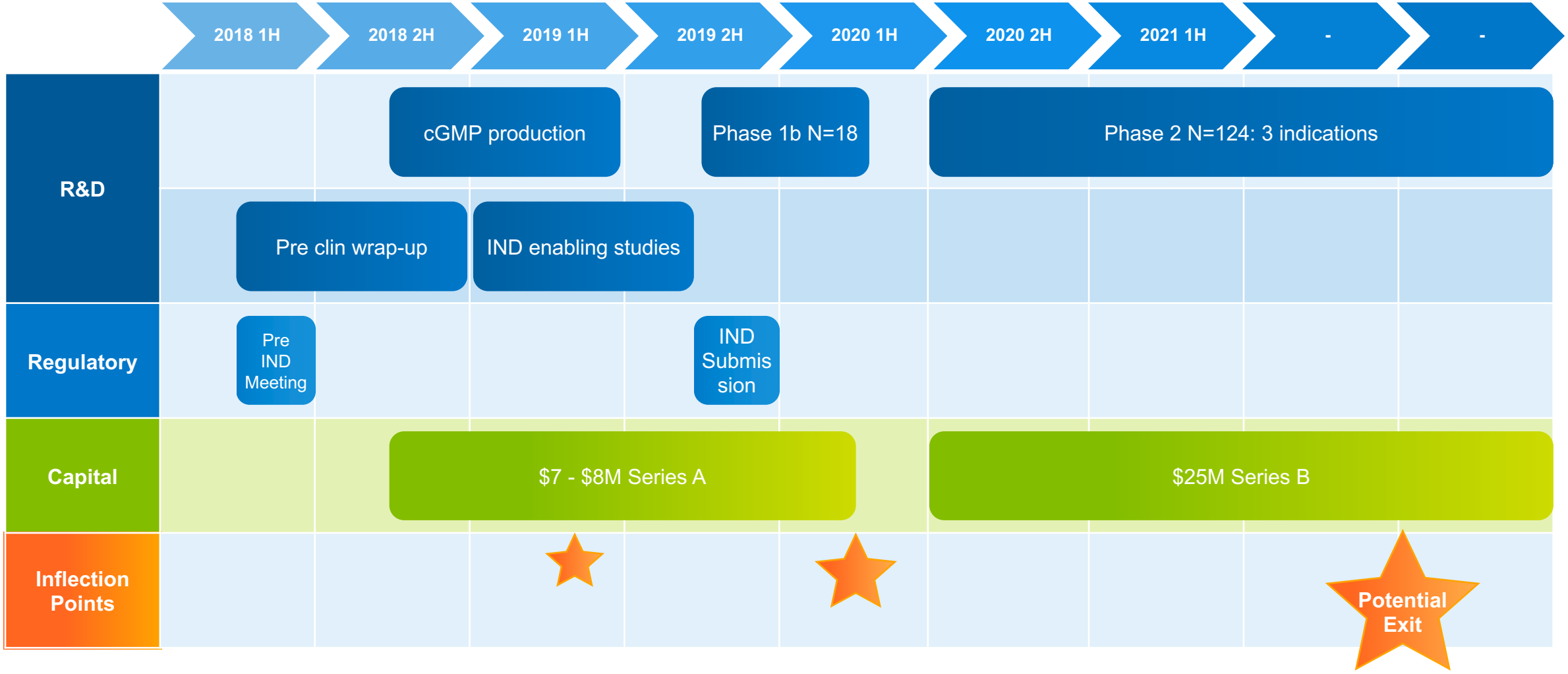
NEW YORK STATE OF OPPORTUNITY. | New York Ventures

pipeline ANGELS

ALEXANDRIA

NY

Milestones: Clinical development ENB-003



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Companion Diagnostic
Identifies ETBR and ET1 overexpression; Patients most likely to respond

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Solid Leadership and Scientific Team
Scientific founders who discovered role of ETBR in metastatic spread of melanoma at NYU Medical Center in 1997

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